NOVEL FREE RADICAL PROTOCOLS FOR THE SYNTHESIS OF HETEROCYCLES

By

William R S Barton BSc (Hons)

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ABBREVIATIONS

ACCN	azobiscyclohexylcarbonitrile
AIBMe	dimethyl azobisisobutyrate
AIBN	azobisisobutyronitrile
AMBN	azobismethylbutyronitrile
Ar	aryl
BOC	*t*-butoxycarbonyl
bp	boiling point
Bu	butyl
Bn	benzyl
CAN	ceric ammonium nitrate
CSA	(±)-camphorsulfonic acid
d	doublet
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DMF	dimethylformamide
DMFDMA	dimethylformamide dimethylacetal
DMSO	dimethyl sulfoxide
EDCI	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide
Et	ethyl
equiv	equivalent
GC	gas chromatography
h	hour(s)
IR	infra-red
LCMS	liquid chromatography mass spectrometry
lit.	literature
m	multiplet
MAS-NMR	magic angle spinning nuclear magnetic resonance
Me	methyl
min	minute(s)
Ms	mesyl
NCPS	non-crosslinked polystyrene

NMR	nuclear magnetic resonance
NPSP	*N*-(phenylselenyl)phthalimide
Ph	phenyl
PMHS	polymethylhydrosiloxane
ppm	parts per million
PS	polystyrene
q	quartet
rt	room temperature
s	singlet
SEM	scanning electron microscopy
SPOS	solid phase organic synthesis
t	triplet
TBDMS	*t*-butyldimethylsilane
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TTF	tetrathiafulvalene
TTMSS	tris(trimethylsilyl)silane
Ts	tosyl
p-TSA	*p*-toluenesulfonic acid
UV	ultraviolet

ABSTRACT

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WILL BARTON

PH.D. 2002

The tributyltin hydride/AIBN combination used to mediate radical cyclisations has become a common protocol in organic chemistry. This system which allows good substrate flexibility is a useful complement to ionic annulation reactions. However, the tin residues are highly toxic and difficult to separate from reaction mixtures. In this project, alternatives to tin have been used with varying success and a SPOS approach was adopted to minimise the problems associated with tin.

Acyl radical addition to 2- and 3-substituted electron deficient pyrroles was used to construct a variety of interesting bicyclic compounds including pyrrolizine alkaloids nordanaidone and hydroxydanaidol. Acyl radical reduction was retarded by slow syringe-pump addition of tributyltin hydride in cyclohexane to the acyl selenide and AIBN in acetonitrile as a two-phase solvent system. Carbon monoxide saturation of the reaction vessel and solution was also necessary to inhibit decarbonylation in slow cyclisations.

The first reported examples of alkyl radical cyclisations onto 3- and 4-substituted pyrazoles were successfully carried out. Electron withdrawing groups or conjugate stabilisation of the cyclised radical product were essential to promote cyclisation in these systems. Withasomnine, a root extract found in herbal remedies, was synthesised in good overall yield from 4-bromopyrazole (27% unoptimised).

Cyclisation of quadragel bound alkyl and acylselenides has been carried out in analogy to solution phase phenyl selenides. Homolytic cleavage of the resin supported selenides results in the traceless liberation of the radical centre from the support following which it can undergo homolytic aromatic substitution onto the heteroarene. A major benefit is the binding of toxic tin residues to the solid support improving handling and purification, although cleavage protocols require improvement.

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CHAPTER 1 INTRODUCTION

PROJECT OBJECTIVE

A shortcoming of many radical syntheses is the continued reliance on triorganostannanes as the chain carrier in radical chain propagation (scheme 1). Triorganostannanes are widely used in spite of the well-documented problems of toxicity, separation from reaction mixtures, purity and stability because they are more efficient in radical chain processes than many alternatives.

This project seeks to eliminate several of the problems associated with the use of triorganostannanes by the design of a SPOS strategy. Solution phase protocols were to be drafted and developed based on the progression of recent work within the Bowman group involving the synthesis of novel and interesting heterocyclic compounds *via* 'oxidative' carbon-centred radical addition to aromatic rings.

Solution phase protocols were then to be adapted to a SPOS to provide a robust and general method for the synthesis of suitable precursors for applications in radical cyclisations and related synthetic chemistry. Selected natural products were to be synthesised to show the application and specificity of the methodology to a given target.

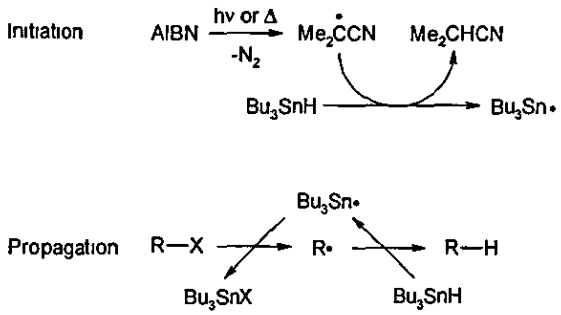
The ambiguity surrounding oxidative rearomatisation of the homolytic aromatic substitutions was also to be investigated in tandem with the development of solution phase protocols in order to provide a better understanding. Particular emphasis was based on the role of azo initiators in oxidative rearomatisation.

By way of introduction to the project, the following discussion relates the extensive work on solution phase synthesis of arenes and heteroarenes using group 14 metal mediated radical methodologies to the more limited research on SPOS involving radical synthesis. The oxidative rearomatisation also requires some discussion because it is integral to the success of many of the cyclisations within the project.

1.1 FREE-RADICAL CYCLISATIONS IN SOLUTION

In keeping with the current research interests of the Bowman group this brief review of recent solution phase free-radical synthesis will be confined largely to radical chain processes involving carbon-centred radicals in which the key step was a ring forming radical reaction using group 14 chain propagating species. Particular emphasis will be made in cases actively involving aryl

moieties because this is directly relevant to the body of research outlined in the following chapters.



Scheme 1: *Radical chain propagation involving tributyltin hydride*

A radical chain process involves initiation, propagation and termination. Azo initiators such as AIBN are frequently employed as radical chain initiators (Scheme 1). Di-*tert*butyl peroxide and dibenzoyl peroxide also fragment homolytically under thermolysis or photolysis for radical initiation purposes.

The first radical of the chain process depicted in Scheme 1 is generated by S_H2 abstraction of hydrogen from tributyltin hydride by initiator fragments to yield a triorganotin radical. The initiator is thus consumed at the expense of generating a stannyl radical, however radical chain propagation is continued by a series of ensuing elementary radical reactions.

As each radical transformation leads to the generation of a new radical centre, the radicals formed during propagation can perform one or more of a number of elementary unimolecular or bimolecular radical reactions. The simplest bimolecular reaction is radical addition to an alkene and key unimolecular processes include fragmentation, rearrangement, ring-opening and cyclisation. The radical chain will eventually terminate by radical-radical combination or disproportionation.

Knowledge of relative reaction rates and careful retrosynthetic analysis is required for sequential combination of these elementary processes, although the results of extended radical sequences and cascade cyclisations can rarely be rivalled using alternative synthetic strategies

Importantly, the role of the chain carrier is essentially the same for all commonly used group 14 propagating species, although premature reduction of the radical centre can be problematic for

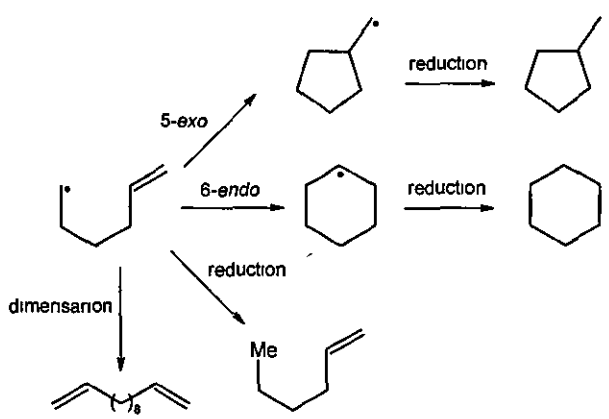
triorganometal hydride reactions. This can be overcome by using homolytic fission of the relatively weak Sn-Sn bond of hexaorganoditin compounds by photolysis or thermolysis. The radical precursors must be able to withstand more rigorous initiation conditions though.

Both techniques of generating stannyl radicals will be considered together because this project is more concerned with the nature of the chain carrier and ultimately the two methods generate similar species. Systems involving germanium and silicon will be discussed in more detail in section 1.2 in conjunction with improving radical cyclisation methodologies as less toxic alternatives to triorganotin mediated reactions.

1.1.1 Radical Cyclisation onto Alkenes and Alkynes

Intramolecular addition of a radical to an alkene can be readily achieved in the creation of small and large ring structures. In addition to broader guidelines to cyclisations such as Baldwin's rules,[1] detailed studies of radical cyclisations in the formation of small and medium ring structures have been carried out.

The cyclisation shown in Scheme 2 is typical of a large body of research that is now well documented whereby a carbon-centred radical undergoes intramolecular addition to an unsaturated bond in either an *exo* or *endo* fashion.[2] The product of 5-*exo* cyclisation was consistently isolated as the major product with trace amounts of 6-*endo* cyclisation observed. In this brief overview important regioselectivity and reactivity issues relating to alkyl radical addition to aromatic species will be introduced by analogy to these systems, albeit with some limitations.



Scheme 2: *The cyclisation of 5-hexenyl radical*

As radicals are neutral species, efficient electronic overlap is key to the advent of radical cyclisation because no charge-charge interactions exist. The geometry and conformation of the radical centre (Figure 1) will influence the cyclisation transition state and may determine if the required 109° angle of approach can be achieved.

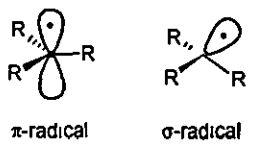


Figure 1: *Structure of π- and σ-radical centres*

The transition state of alkyl radical addition to an alkene depicted in Figure 2 shows an increase in *s*-character as the new bond forms. The radical centre can be stabilised by conjugation/ mesomerism, hyperconjugation and captodative stabilisation; the greater the π-character the more stable the radical centre. Hence, the electronic nature of the unsaturated bond and the radical centre are important to successful cyclisation.

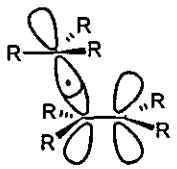
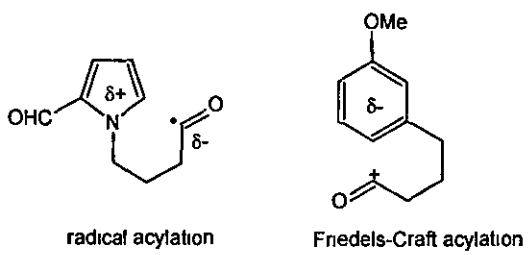


Figure 2: *Early transition state of radical addition to an alkene*

Radical chemistry has found increased use because the reactions are affected very little by solvent effects or hindered environments and have excellent functional group tolerances. Radicals may display electrophilic or nucleophilic tendencies based on their high electron affinity or low ionisation potential respectively, in addition to which the centres may also be hard or soft. Radical cyclisations thus offer a valuable synthetic alternative to many ionic C-C bond-forming reactions, because the reactivities are typically reversed (Scheme 3).

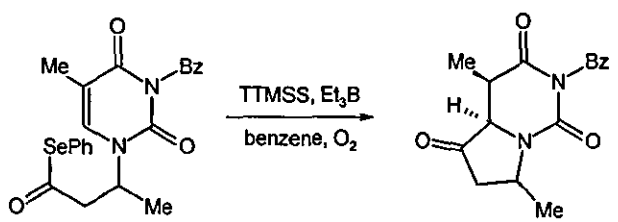


Scheme 3: *Comparative reactivities of radical and ionic acylations*

Baldwin's rules described the relative efficiency of competing cyclisation modes. However, as with all guidelines there are exceptions, particularly in the realm of radical annulation chemistry. For example, acyl radicals have been shown to have a greater propensity for 6-*endo* over 5-*exo* cyclisation.[3] This is presumably due to the predisposition for a favoured transition state over stability of the radical addition product unlike ionic pathways, hence the geometry required for good orbital alignment of the σ-type acyl radical and the alkene yields a 6-*endo* product.

Fortunately, the unpredictability and poor reaction control that plagued early synthetic radical chemistry is now under greater control due to the large volume of reactivity and kinetic studies. As such the design of a successful cyclisation should be based on the electronic nature of the radical centre and radicophile in addition to the reversibility and stability of the addition product and transition state.

This powerful bond forming procedure has found wider application in the synthesis of interesting heterocycles[4] inevitably extending the use of free radical mediated cyclisation methodology firmly into the heart of many natural product syntheses.[5] Recently, radical cyclisations are also being performed with greater consideration for stereocontrol, for example 5-*exo* acyl radical cyclisation shown in Scheme 4[4] gave rise to the azabicyclic product in 81% yield with good diastereocontrol (>19:1 diastereomeric ratio), a result of reduction of the more accessible face following cyclisation.



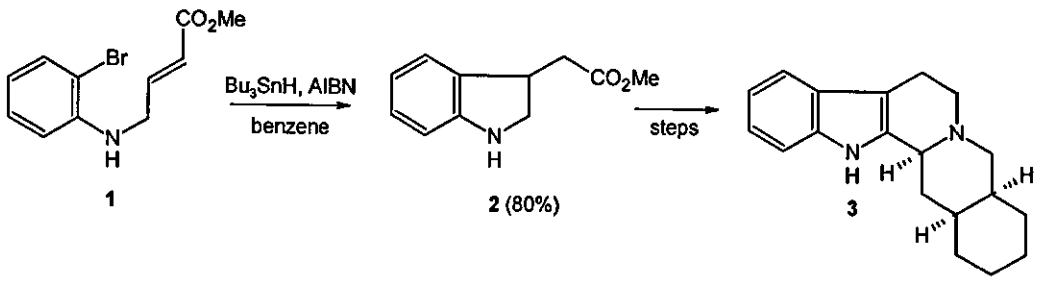
Scheme 4: *Acyl radical cyclisations in the synthesis of novel azabicycles*

Having established some of the principles and models used in accounting for several behavioural aspects in radical cyclisations, the remainder of this section will highlight recently published syntheses involving arenes and heteroarenes actively in the radical annulation reaction.

1.1.2 Aryl Radical Addition to Alkenes and Alkynes

Construction of bicyclic and polycyclic structures incorporating an aromatic core is readily achieved by intramolecular aryl radical addition to unsaturated bonds. As with alkyl radical cyclisations to unsaturated bonds competing *exo* and *endo* modes of cyclisation exist with

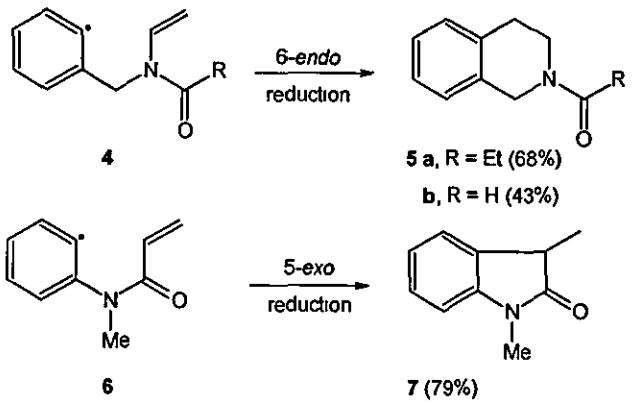
typically high *exo*·*endo* ratio in the formation of small and medium rings, although this is not always the case.[6,7] For example, the aryl radical generated from 2-bromo aniline derivative **1** gave exclusive 5-*exo* reductive cyclisation to yield (2,3-dihydro-1H-indol-3-yl)-acetic acid methyl ester **2** in good yield as a key intermediate early in the synthesis of (±)-alloyohimbane **3** (Scheme 5).[8] The potentially high yield of such transformations has led to an increasing use of radical cyclisation chemistry earlier in the synthesis of such natural products because the radical step need no longer be the final step.



Scheme 5: *Aryl radical cyclisation in the construction of (±)-alloyohimbane natural product*

If the radical centre resulting from 6-*endo* cyclisation is stabilised in some way, 6-*endo* cyclisation can dominate in the presence of a favourable 5-*exo* cyclisation pathway (Scheme 6).[6] The *N*-group attached to enamides **4** and **6** can have a marked effect on the cyclisation product, 6-*endo* cyclisation of **4** (**a**, CHO or **b**, COEt) results in a stabilised radical giving rise to largely 6-*endo* cyclisation (**5a** and **5b**). It is possible that enamide **6** (Me) has less stabilisation for 6-*endo* cyclisation or a less favoured transition state and 5-*exo* cyclisation dominates yielding isoindolinone **7** as the major product in high yield (79%).[9]

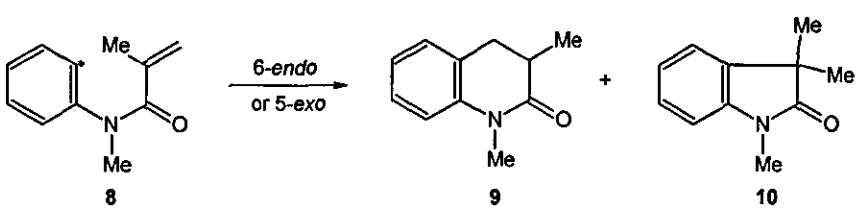
Neophyl type transformations to form the 6-*endo* products have been ruled out as being the major pathway because the rearrangement resulting from addition of the 5-*exo* cyclised radical to the aromatic ring usually requires an ortho stabilising group. Additionally, rearrangement *via* addition to the carbonyl group would also give the wrong isomer indicating the *N*-group stabilisation to be the dominant factor. This electronic fine-tuning of cyclisations makes radical cyclisation chemistry unique because the mode of addition is influenced by electronic effects but affected very little by steric bulk. Such variables are important in the retrosynthetic analysis of a target molecule.



Scheme 6: *Stabilised and non-stabilised 6-endo cyclisation*

Temperature and concentration effects can also be evident in dictating the outcome of closely competing reactions as the cyclisation of the aryl radical **8** illustrates (Scheme 7).[7] The radical species **8** can undergo 5-*exo* and 6-*endo* cyclisation to form oxindole **10** and dihydroquinolone **9** respectively, the ratio of these products (**10**:**9**) was found to be dependent on both temperature and concentration.

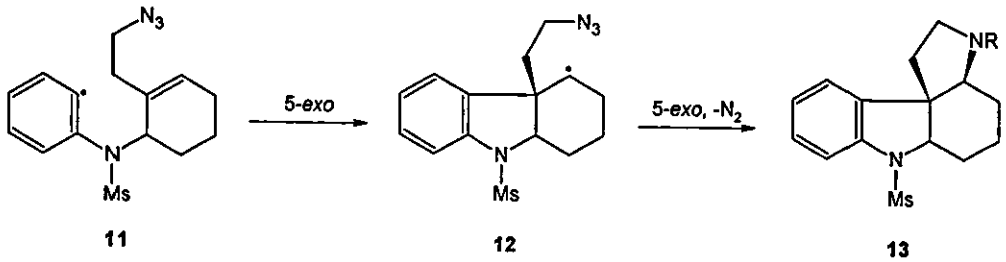
The cyclisation of **8** performed at 60 °C yielded a ratio of 1:6 in favour of the oxindole. An increase in temperature to 169 °C yields a 5:1 ratio now favouring the dihydroquinolone, this is due largely to thermally promoted rearrangements of the more facile 5-*exo* cyclisation radical product to the more stable 6-*endo* radical product. A 100-fold increase in the tributyltin hydride concentration at 169 °C results in domination of the oxindole again (1:6). This can be explained because the radical product of 5-*exo* cyclisation has the thermal activation energy to rearrange to the dihydroquinolone product, but the lifetime of the oxindole radical is diminished due to the increased concentration of triorganotin hydride. The reaction in scheme 7 shows either **9** or **10** can be isolated as the major product depending on the conditions, hence the synthetic chemist requires knowledge of relative rates and concentrations in the design of a radical cyclisation process.



Scheme 7: *Competing 5-exo and 6-endo cyclisation*

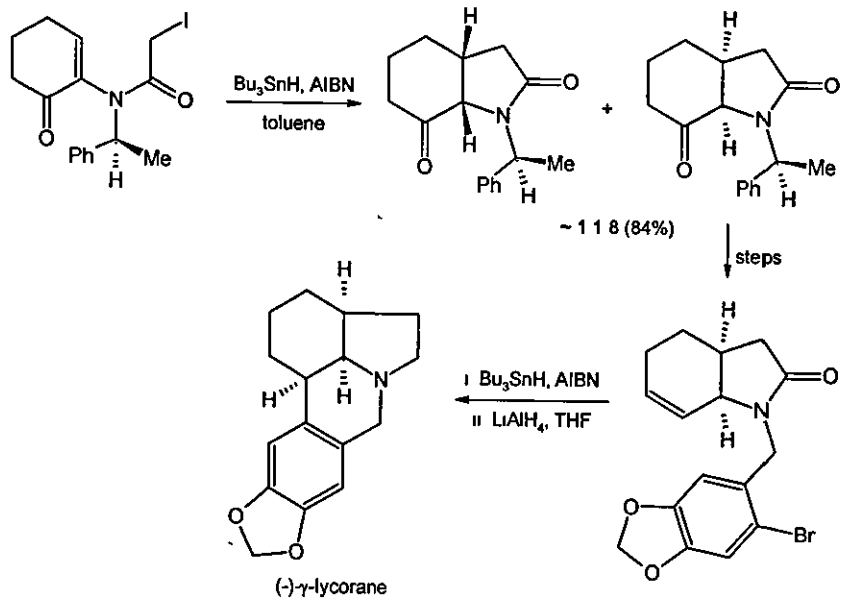
These competing modes of cyclisation can lead to the construction of interesting spirocyclic compounds[10] and have been used in the synthesis of spiro-dilactones as found in altenuic acid[11] in addition to interesting spirolactones.[12]

Multiple rings can be constructed from a single radical species because the radical centre formed following cyclisation can be used to perform a second cyclisation and so on. For example, formation of aryl radical **11** (Scheme 8) from the iodo precursor in the presence of TTMSS and AIBN results in a cascade 5-*exo*, 5-*exo* tandem cyclisation sequence.[13] Following 5-*exo* cyclisation of the aryl radical **11** onto the alkene, the cyclohexyl radical **12** can undergo a second 5-*exo* cyclisation onto the azide resulting in the extrusion of nitrogen gas. The resultant aminyl radical is reduced and silylated with the tris(trimethylsilyl)silyl halide resulting from aryl radical formation. The silyl group is cleaved post cyclisation under aqueous conditions to give the tetracyclic aspidospermine skeleton **13** in good yield (80%, R = H) with the desired *cis*-stereochemistry.



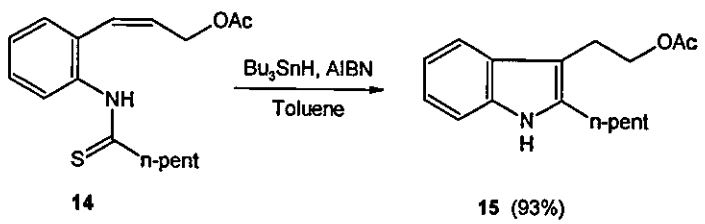
Scheme 8: *Synthesis of the core tetracycle of aspidosperma alkaloids*

Scheme 8 is indicative of the use of cascade radical cyclisation chemistry in the synthesis of natural products, although the construction of two or more rings does not need to be done in a cascade fashion. For example, polycyclic (-)-γ-lycorane was synthesised using two separate radical cyclisation steps (Scheme 9).[14] The first cyclisation required a chiral auxiliary and captodative stabilising group to enhance stereoselectivity and cyclisation yield respectively. Following a number of other chemical transformations, the penultimate step of the synthesis was 6-*exo* aryl radical addition onto an alkene giving the pentacyclic structure in 52% yield with the desired stereochemistry.



Scheme 9: *Synthesis of (-)-γ-lycorane*

Medium and large rings can also be constructed although *endo* cyclisation becomes more prevalent because the reaction is barely influenced by the cyclisation transition state and the reaction is more bimolecular in nature. For example, the 3-benzazepine structure present in many alkaloids can be prepared by intramolecular 7-*endo* addition of an aryl radical to an enamide double bond in 40 to 85% yield.[15]



Scheme 10: *Synthesis of indoles from 2-alkenylthioanilides*

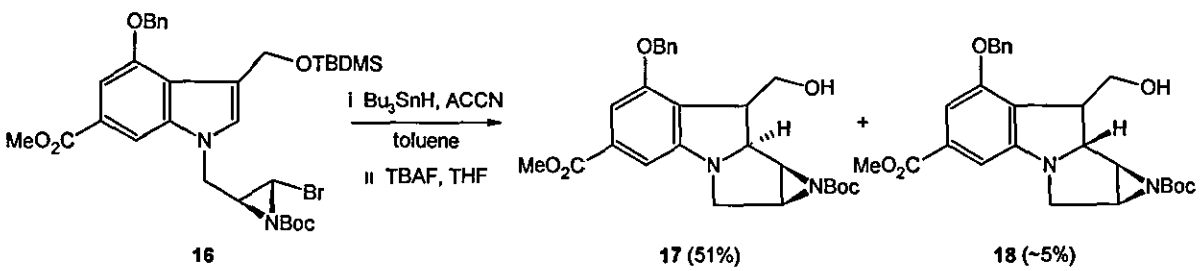
There are also many reported examples of aryl radicals in the synthesis of benzo derived arenes as shown in Scheme 10. The construction of the pyrrole section of 2,3-disubstituted indole **15** from 2-alkenylthioanilide **14** is one more example of the varied approaches available in radical synthesis.[16] Although the construction of the arene or heteroarene core from acyclic or benzo derivatives is a procedure common to radical cyclisation chemistry, the remainder of the introduction to solution phase radical cyclisations will concentrate on radical addition to aromatic groups.

1.1.3 Radical Cyclisations onto Aromatic Species

A benefit of radical disconnection strategies is the number of possible ways in which the ring may be constructed. An alternative disconnection route to benzo and heteroaromatic bicycles to that presented in the previous section involves radical addition to arenes. This section is key to introducing the final and more important concepts relevant to this project and will conclude the discussion of solution phase cyclisations.

Substantial research has been published on the intramolecular addition of radicals to heteroarenes resulting in synthetic elegance not feasible with ionic procedures. Regioselectivity and modes of cyclisation are usually more predictable than aryl additions to unsaturated bonds. The field of synthetic free radical cyclisation chemistry has obvious importance to the pharmaceutical industry and in many natural product syntheses. This section of radical chemistry is reviewed on a regular basis[5,17] and the importance of actively including a heteroarene in the synthetic scheme is reflected by the large number of examples reported.

A brief examination of contemporary literature shows an increasing use of this powerful C-C bond forming procedure as the key step in the construction of complex natural products and polycyclic structures[18,19,20,21] as highlighted by the cyclisation of the aziridinyl radical formed from **16** (Scheme 11).[20] Reductive 5-*exo* cyclisation onto the 3-substituted indole was used in a novel approach to mitomycin C with the desired stereochemistry to give mitomycin analogue **17** in good yield exemplifying the synthetic usefulness of radical mediated cyclisations.

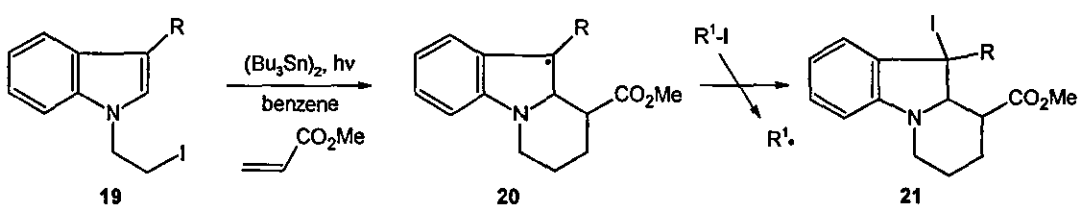


Scheme 11: *Synthesis of mitomycin C analogues using 5-exo aziridinyl radical cyclisation*

Scheme 11 presents an example of reductive cyclisation, a feature common to radical addition to normal unsaturated bonds, but not always observed in radical addition to aromatic species. Synthesis of heterocycles by radical addition to unsaturated non-aromatic bonds typically results in reduction of the newly formed radical centre, however radical addition to aromatic compounds is often accompanied by an oxidation step resulting in loss of a proton and an electron resulting in rearomatisation.

Reaction conditions involving tributyltin hydride and AIBN exclude oxygen and are performed in a weakly reducing matrix ruling out obvious oxidation pathways, yet countless examples of radical addition to arenes result in aromatisation of the addition product. There is, therefore, a distinct necessity to improve the understanding of this contentious mechanism[22] due to the increasing synthetic importance of homolytic aromatic substitutions.[5] Scheme 12 depicts *N*-ethylindole radicals formed from **19** in a conjugate radical addition to an electron poor alkene followed by cyclisation to yield radical alkyl iodide **20**. The benzylic radical does not reduce under these reaction conditions and the final product is that of 'oxidative' cyclisation with respect to the initial radical species.

It was tentatively suggested by the authors that rearomatisation could be the result of HI elimination of the atom-transfer product **21**.[22] However, the author concedes that empirical data contradicts such a sequence because the reaction would then be catalytic with respect to triorganotin but it was found not to be. Radical cyclisations performed within the Bowman group have shown that tributyltin hydride/AIBN are required in slight excess for homolytic aromatic subtitution to proceed efficiently. The participation of a disproportionation reaction is also ruled out by the observed product mixture; S_H2 abstraction by the stabilised benzylic radical would result in the formation of a less stable alkyl radical and is thermodynamically unfavourable.

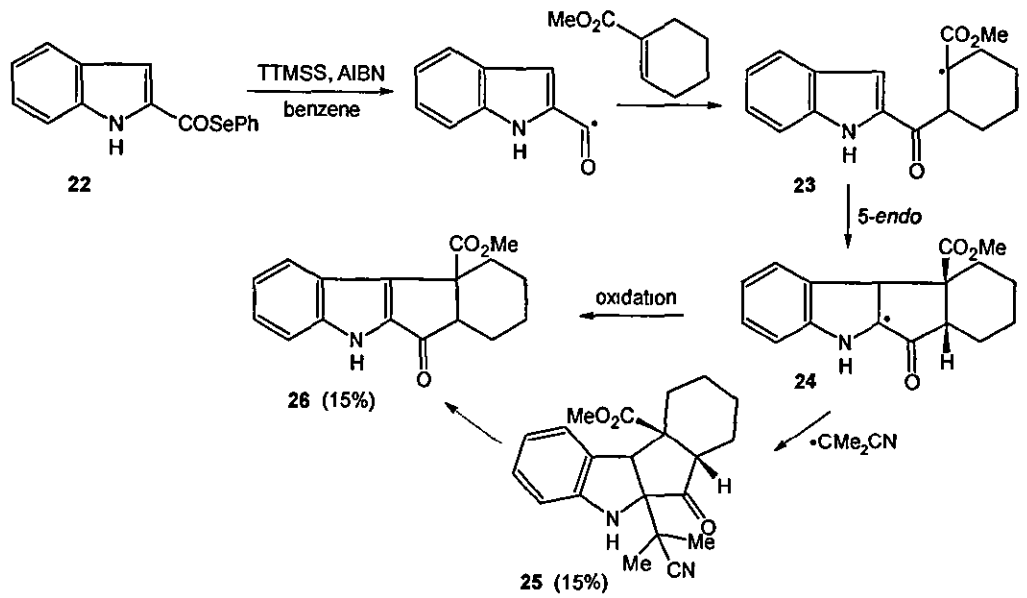


Scheme 12: *Atom transfer pathway in oxidative rearomatisation*

Scheme 13 proposes an alternative elimination pathway that accounts for the requirement of excess reagents for oxidative rearomatisation.[19] Following acyl radical addition to the alkene in similar Michael fashion, the alkyl radical can then perform a 5-*endo* cyclisation. The resulting radical intermediate **24** can potentially abstract a hydrogen to yield the reduced indoline product or the radical intermediate may be rearomatised by the loss of a proton and an electron.

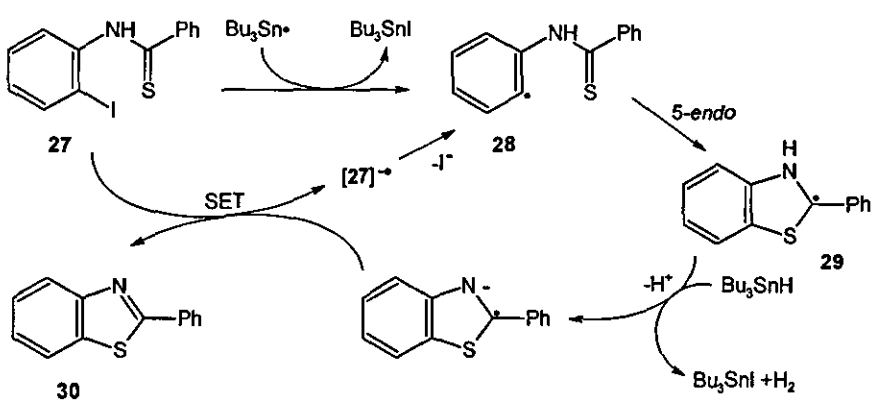
In this case, the oxidation product **26** (15%) was isolated in addition to a curious compound **25** (15%) resulting from radical-radical combination with a fragmented initiator radical. Although the isolation of such a compound is an interesting discovery, the radical-radical termination process is unlikely to occur efficiently enough under high dilution conditions necessary for

successful cyclisation to be the dominant path of rearomatisation, in addition to which the necessary elimination to rearomatise is not very favourable. A number of other compounds incorporating fragmented AIBN have also been reported.[23]



Scheme 13: *Isolation of a product from radical-radical combination*

Proposed mechanisms from previous work within the Bowman group suggest the mechanism may proceed *via* a pseudo $S_{RN}1$ mechanism (Scheme 14) due to direct analogies to $S_{RN}1$ substitutions.[24] Following the S_H2 abstraction of the iodine from **27** to form the aryl radical **28** the cyclisation proceeds as normal to form the radical species **29** stabilised by delocalisation onto the sulfur and the aromatic ring. Additionally, the dihydro products of many of these arenes are stable. Hence reductive cyclisation followed by oxidation during workup can be ruled out.

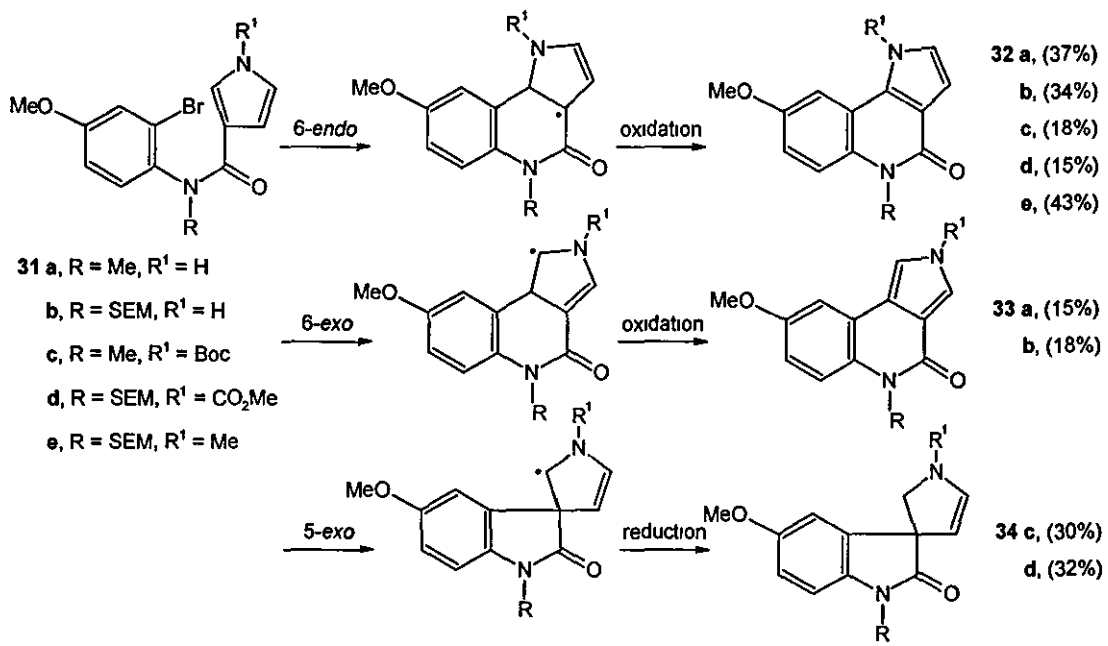


Scheme 14: *Pseudo $S_{RN}1$ mechanism in oxidative rearomatisation*

It is possible that tributyltin hydride may also act as a base in these reactions, in which case the mechanism involves a radical anion intermediate which may then undergo a single electron transfer to a molecule of starting material to yield the radical anion species $[27]^{\bullet}$. However, studies have yet to corroborate the necessary evolution of hydrogen gas despite many attempts. Recent work has cast some doubt over the pseudo $S_{RN}1$ mechanism, although no other mechanism has been provided. Slight variations on this mechanism have been proposed in work published involving radical addition to triazoles.[25]

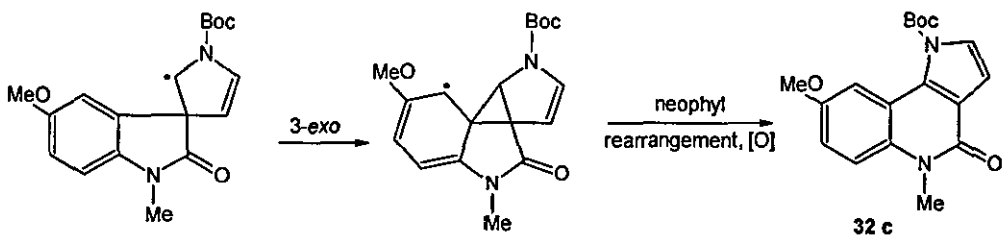
Alternative proposed mechanisms based on the role of the azo initiator in the oxidative rearomatisation[26,27] will be discussed in Chapter 3 in relation to the work carried out in this research. The discussion and direction of research stem from a set of experiments by Dr Emma Mann relating the stoichometry of azo initiator, tributyltin hydride and radical precursor required for successful cyclisation, confirming the need for an excess of initiator and chain carrier.[28]

The cyclised radicals are non-aromatic species but may be stabilised by π-electron delocalisation or captodative stabilisation leading to an extended lifetime that permits a variety of subsequent reactions or rearrangements to occur, one of which is oxidative rearomatisation.[29] Aryl radical addition to pyrroles can lead to reduced products under standard tributyltin hydride/AIBN conditions.[30,31] Scheme 15 shows how the electronic and steric nature of the pyrrole protecting group can promote reductive cyclisation to an interesting spiro compound.[30]



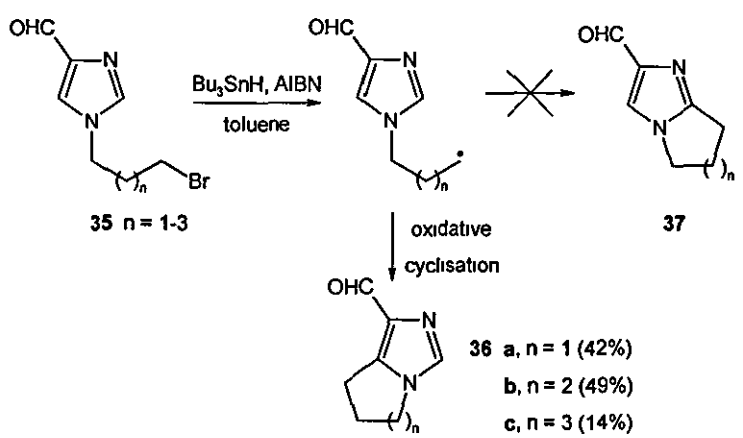
Scheme 15: *Protecting group effects in attempted 6-endo cyclisations*

There may be a destabilising effect on the product of 5-*exo* cyclisation onto pyrrole-1-carboxylates that causes a more rapid reduction, because this intermediate can potentially rearrange to the 6-*endo* product as depicted in Scheme 16. Both 6-*endo* and 5-*exo* pathways can ultimately lead to the pyrrole products **32a-e** by involvement of a neophyl type rearrangement of the intermediate alkoxy radical species following a 3-*exo* cyclisation. Products **32c** and **34c** are, therefore, both accessible from a common radical intermediate from 5-*exo* cyclisation.



Scheme 16: *Possible involvement of neophyl rearrangement*

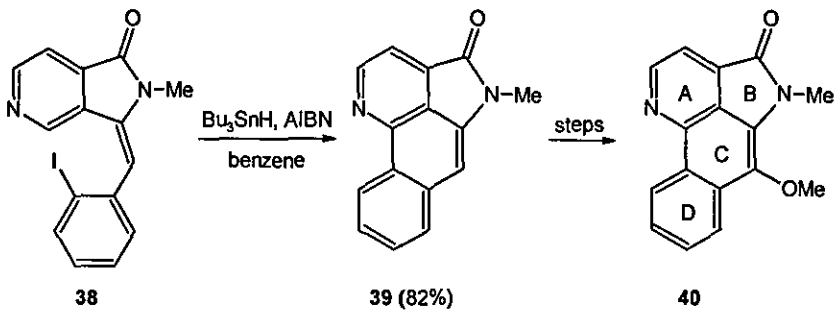
Alkyl radical cyclisations onto 5-membered heterocycles including pyrroles,[32,33] imidazoles,[34] pyrazoles[35] and 1,2,4-triazoles[36] have all been carried out successfully and are of important synthetic merit due to the occurrence of such fused bicyclic motifs in biologically active molecules. Work within the Bowman group has included alkyl radical cyclisations onto imidazoles of the type shown in Scheme 17. Conjugative stabilisation by the acyl group and the higher electrophilicity of the 5-position ensure complete regioselectivity is observed.[33] Reduced alkyl products were isolated in slower cyclisations, (n = 1 and 3; 10 and 8% respectively).



Scheme 17: *Regioselectivity in alkyl radical addition to 1,3-diazoles*

Other heterocycles including pyridine have also received attention, tethering of the A and D rings of natural product eupolauramine **40** has been accomplished by aryl radical addition to pyridine (Scheme 18).[18] Pyridones have also been used in radical cyclisation chemistry.[37]

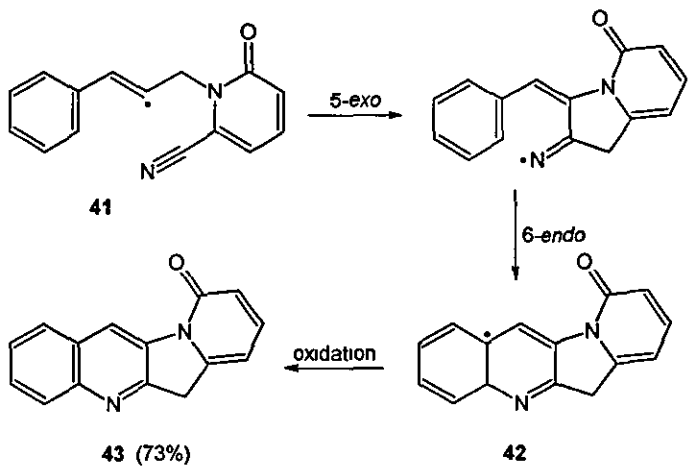
Although pyridones are less aromatic than pyridine, homolytic aromatic substitution has been accomplished using phenyl and pyridyl radicals in the construction of novel pyridone tricycles in modest yield.[38]



38 39 (82%) 40

Scheme 18: *Aryl radical addition to pyridine in the synthesis of eupolauramine*

Radical additions are governed by the electronic nature of the two reacting species, and hence can be predicted with some confidence allowing their usage in more demanding systems. For example, vinyl radicals have been used in tandem cyclisation sequences (Scheme 19).[37] The construction of the tetracycle **43** found in camptothecin analogues involves the tethering of rings A and D by the radical cascade formation of rings B and C. The 5-*exo* vinyl radical addition of **41** to the nitrile group followed by a 6-*endo* cyclisation and oxidation results in the desired tetracycle in good yield, although the success of the final cyclisation is strongly dependent on the nature of the aryl group.

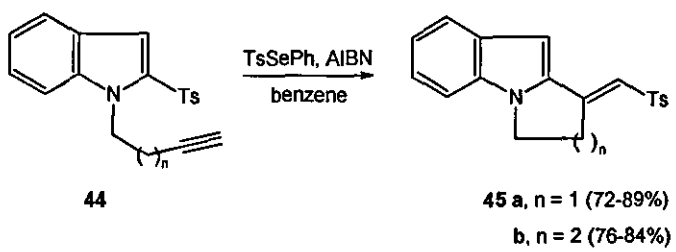


41 43 (73%) 42

Scheme 19: *Synthesis of camptothecin analogues by tandem cyclisation*

There are also a number of regioselectivity issues resulting from rearrangements and competing modes of cyclisation within the construction of this complex polycyclic structure; these could potentially be overcome by the introduction of a radical leaving group.

Ipso displacement of a suitable radical leaving group can be used to facilitate rapid rearomatisation or control cyclisation regioselectivity (Scheme 20).[39] The mechanism of rearomatisation is now more apparent than for unsubstituted arenes, because the radical displacement of a sulfonate is favourable by β-fragmentation of the cyclised intermediate, whereas the loss of hydrogen is not. The overall reaction constitutes an aromatic homolytic substitution and ensures the recovery of aromaticity. The 5- and 6-*exo* vinyl radical additions were achieved in good yield affording indoles **45 a-b** (72-89%) as the only reported product from the corresponding alkyne moieties. There was no evidence of 7-*exo* (n = 3) cyclisation despite repeated attempts. This procedure works equally well with alkenes and introduces the tosyl group selectively in the absence of tributyltin hydride.

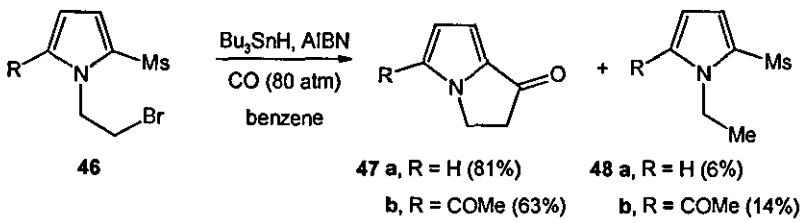


44 **45 a**, n = 1 (72-89%)
b, n = 2 (76-84%)

Scheme 20: *Homolytic aromatic substitution of tosyl group*

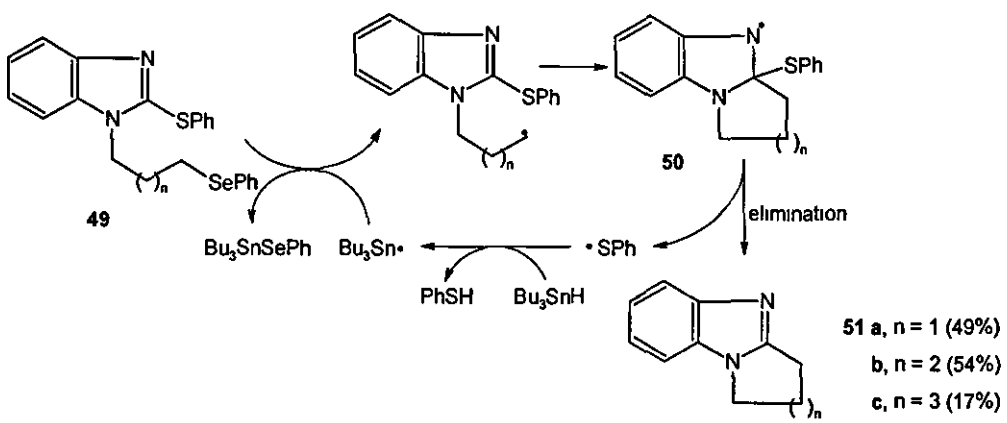
In addition to safeguarding rearomatisation, radical leaving groups are also used in slow cyclisations to enhance reactivity and regioselectivity.[40] The use of a methylsulfonyl radical leaving group greatly enhanced the acyl radical addition to the electron rich pyrrole nucleus **46** to yield the cyclised product **47** in 81% yield (Scheme 21). In the absence of the mesyl group the only product isolated under the same conditions was that of acyl radical reduction to the aldehyde (60%). Curiously none of the aldehyde product was isolated in the *ipso* displacement, but the reduced alkyl product **48a** was isolated in low yield.

The use of an electron withdrawing displacement group does not guarantee regioselectivity and attempts to perform the analogous 6-*exo* cyclisation resulted in *ipso* displacement of the mesyl group as the major product (54%) but also addition at the 5-position, resulting in oxidative cyclisation whilst maintaining the mesyl group. Also noteworthy is the lower yield where an acetyl group is present in place of hydrogen to yield the functionalised pyrrolizine **47b**. This may be in part due to competition from the acetyl group displacement noted in 6-*exo* cyclisation.



Scheme 21: *Ipso displacement of mesylate to increase reactivity*

Radical addition to benzimidazoles was also improved by use of aryl sulfonyl and aryl sulfanyl groups (Scheme 22).[41] Aryl sulfanyl and aryl sulfonyl leaving groups can be readily introduced to the 2-position of benzimidazole although aryl sulfonyl leaving groups facilitate cyclisation onto imidazoles in greater yield than the aryl sulfanyl groups. This is presumably due to the greater electron withdrawing potential of the sulfonyl group promoting alkyl radical attack at the 2-position.



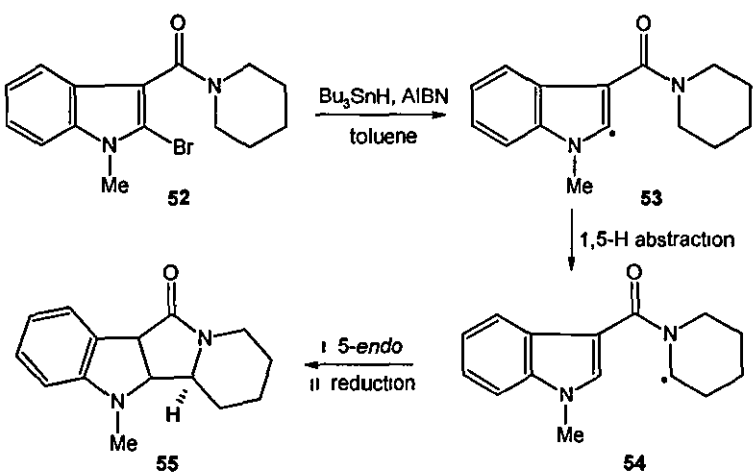
Scheme 22: *Ipso displacement to increase reactivity*

2-(Phenylsulfanyl)-benzimidazole precursors **49** were found to be suitably reactive for cyclisation possibly due to the lower aromaticity of the imidazole portion of the benzimidazole allowing radical attack at the 2-position. A β-fragmentation of intermediate radical **50** facilitates rearomatisation and elimination of a thiyl radical. The yields of cyclisation to **51a-c** are good and vary by ring size depending on ring strain and entropy effects.

Radical cyclisations can thus be enhanced or directed in troublesome cyclisations. However, radical translocation can provide alternative cyclisation routes. A˙ radical centre can intramolecularly abstract a suitably placed hydrogen in the absence of competing reactions, giving rise to a new radical centre; this translocation of the radical centre to a new position

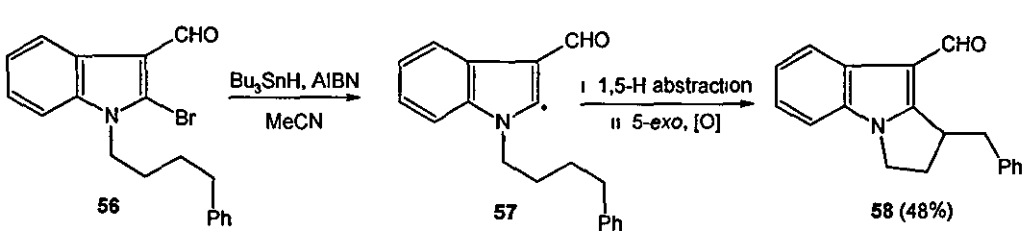
within the molecule can be of great synthetic use. For example, the introduction of a radical leaving group adjacent to a heteroatom can be problematic but the radical centre may still be generated in the absence of a radical leaving group by this type of intramolecular radical translocation. Such radical translocations must be considered in retrosynthetic analysis and the wide applicability has been recently reviewed.[42]

For example, an alternative route to the formation of the aziridinyl radical required in Scheme 11 could be envisaged by translocation of the radical centre from the aryl species to the aziridine side chain *via* 1,5-hydrogen abstraction. An example depicted in Scheme 23 shows the synthesis of 5-methyl-octahydro-5,10a-diaza-indeno[2,1-a]inden-10-one **55** by radical translocation methodology.[43] The indole radical **53** was able to abstract a hydrogen from the side chain and the newly formed radical species **54** can perform the cyclisation. In this case the cyclisation was reductive (54%) although aromaticity was restored by treatment of indoline **55** with DDQ (50%).



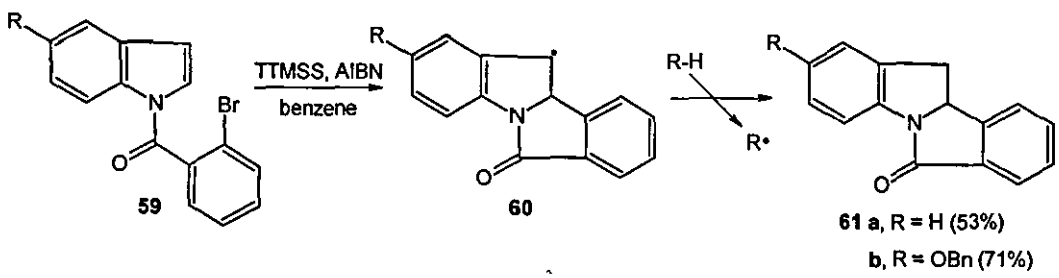
Scheme 23: *1,5-H Abstraction to facilitate 5-endo cyclisation*

A 1,5-hydrogen abstraction was also the unexpected side reaction in the attempted intramolecular addition of 2-indolyl radical **57** to the side chain aryl ring (Scheme 24).[44] The radical translocation permitted intramolecular cyclisation of the side chain radical to the indole ring in 5-*exo* fashion to yield the tricyclic indoline **58** in 48% yield.



Scheme 24: *Undesirable radical translocation in an attempted biaryl coupling*

It is evident from many of the examples presented that radical cyclisations onto aromatic species need not be oxidative, as highlighted in the previous two cases. α-Addition to indoles results in reduction in many cases, presumably due to the lower aromaticity of the heterocyclic portion compared to pyrrole alone (Scheme 25).[45] Cyclisation of aryl radicals liberated from bromo precursors **59** (R = H and OBn) was achieved with reduction of the benzylic radical intermediate **60** to yield **61 a** and **61 b** in reasonable yield (53 and 71% respectively).



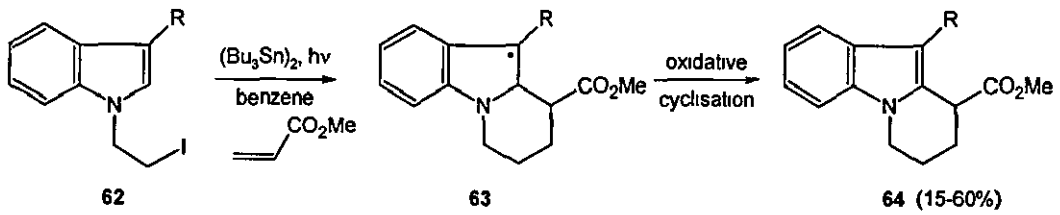
Scheme 25: *Reductive cyclisation involving indole*

Indoles are one of the most prominent heterocycles to feature in this field presumably due to the ease of β-substitution, the lack of cyclisation regioselectivity issues over five membered heterocycles and the high success of the cyclisations particularly with reference to mitomycin analogues.[46,20]

A further extension of the intramolecular radical cyclisation procedures was to incorporate a second component into the cyclisation whereby the radical centre undergoes addition to a suitable receptor that is then able to cyclise. For example, acyl radical addition to alkenes has been used in [3+2] homolytic aromatic substitution onto indoles (Scheme 13). Yields of up to 71% were achieved when methyl crotonate was present in excess, although cyclic and heterocyclic activated alkenes also give reasonable yields.[19] Reduction was observed in slow cyclisations even without a hydrogen donor present. Interestingly there is no mention of reduction or decarbonylation of the acyl radical. Finally, use of a hydrogen donor such as tributyltin hydride (Table 1) results in an increase in reduction of the electrophilic radical resulting from addition product **23**, a useful synthetic protocol in itself.[47]

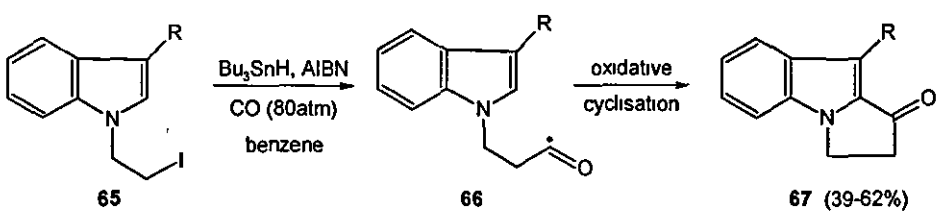
As discussed earlier in relation to oxidative rearomatisation, indole *N*-ethyl radicals derived from alkyl iodide **62** have been shown to undergo [4+2] cyclative addition to an electron deficient alkene if the latter is present in excess.[22] The resultant radical can then perform a 6-*exo* oxidative cyclisation onto the α-position of the indole ring in yields of up to 60% (R = CO_2Me) in this

instance (Scheme 26). As expected electron deficient groups enhance reactivity, the lowest yield was achieved where R = H. Interestingly, the reduced ethyl product was isolated in appreciable yield in one case (R = CHO, 31%) even in the absence of an obvious hydrogen donor. This compound may have been involved in the redox cycle of the rearomatisation.



Scheme 26: *Two component radical cyclisation reaction*

Radical mediated [4+1] cyclisations are also possible, involving radical addition to a carbene source. Radical addition to carbon monoxide yielding an acyl radical has only recently become synthetically useful,[48] however such additions are still troublesome because they must be carried out at high CO pressures and rule out syringe pump addition of tributyltin hydride. Acyl radical additions to pyrroles and indoles **65** have been performed in this manner with some success (Scheme 27).[49] The most favoured cyclisation occurs when R = CHO as might be predicted for the cyclisation of the nucleophilic acyl radical centre. Interestingly the reduced alkyl products are obtained in reasonable yield (22-34%) whereas the aldehyde products are not isolated at all in some cases confirming a facile acyl radical cyclisation following its formation.



Scheme 27: *Alkyl radical addition to carbon monoxide to form an acyl radical*

Such radical procedures can be applied to the synthesis of complex structures. Curran's synthesis of the potent anticancer agent (20S)-camptothecin utilises bimolecular aryl radical addition to phenyl isonitrile.[21] The resultant imidoyl radical then performs a 5-*exo-dig* cyclisation yielding a terminal vinyl radical which can then undergo oxidative cyclisation onto the phenyl ring to furnish the desired camptothecin core.

Many of the above schemes include organotin compounds as the radical propagating species in spite of the obvious problems associated with them. The following section will address reported methods of improving the experimental procedures involved in radical chemistry with emphasis on SPOS approaches.

1.2 Free-Radical Synthesis using Solid Supported Chemistry

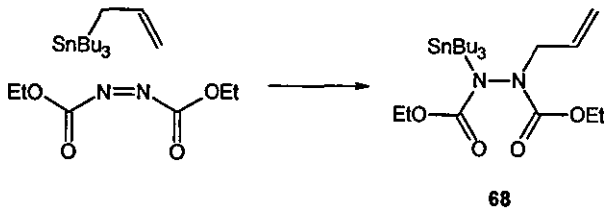
The benefits of SPOS have been well documented since the initial advent of solid supported construction peptides and oligonucleotides. Improvements in purification by simply washing away excess and spent reagents and the ability to drive reactions to completion lend themselves to radical chemistry because the aforementioned synthetic transformations use stoichiometric triorganotin in addition to selenium in many cases, which are both cumulative neurotoxins.

Although many approaches have been devised for removing organotin waste from reaction mixtures[50] there is no robust method available. In view of the difficulties involved in removing triorganotin waste from the reaction a generalised SPOS procedure could, therefore, present the solution.

The question arises whether it is necessary to develop a SPOS system in view of relatively new organotin-free chain carriers. Additionally, laborious method development and the requirement for excessive linker functionality plagues many SPOS procedures. The search for a chain carrier with applicability as general as tributyltin hydride is still ongoing although alternatives such as TTMSS and Bu_3GeH have found wide usage.[50] Triorganotin removal procedures and alternative chain carriers need some consideration first to evaluate whether a SPOS approach is beneficial to overcome the problems of organotin.

1.2.1 Alternatives to SPOS in the Improvement of Synthetic Free Radical Chemistry

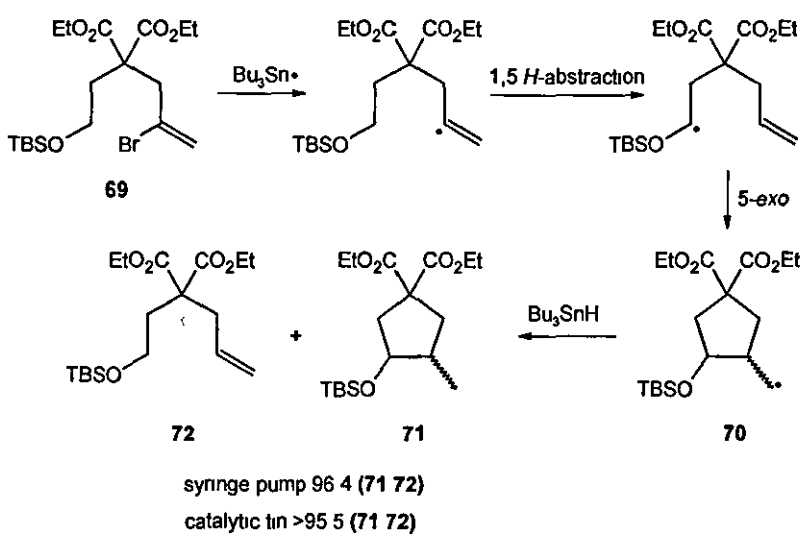
Triorganostannanes have taken a strong foothold in homolytic disconnection strategies because they have ideal characteristics for radical chain processes. Unfortunately organotin compounds are toxic and difficult to remove from the reaction mixture. Various procedures have been devised to remove organotin residues from the crude reaction mixture,[50] however many are excessively time consuming or of limited applicability. For example, a fused mixture of powdered CsF:CsOH (2:1) has been used to remove triorganotin halides from reaction mixtures with some success,[51] more specifically DEAD will remove excess allyl triorganotin present in the reaction mixture by the formation of **68**, but was of limited use (Scheme 28) [52]



Scheme 28: *Removal of excess allyltin residues*

Alternatively an acetonitrile solution of the reaction mixture can be washed with hexane to remove a large proportion of organotin residues although the separation is not complete. Improved separation can be achieved by using polyfluorinated organotin compounds under a similar premise, because the crude reaction product can be separated with relative ease by partitioning between dichloromethane and an immiscible fluorous phase such as perfluorocyclohexane to remove the fluorinated organotin waste.[53]

Minimisation of triorganostannane used in the transformation can be achieved by catalytic recycling of triorganotin hydride from a triorganotin halide in the presence of a reducing agent (Scheme 29). The use of deactivated sodium borohydrides in *t*-butanol has been successful but has limitations due to the still potent reducing capability. For example, cyclisation of the vinyl bromide **69** using standard slow addition of tributyltin hydride by syringe pump gave a similar ratio of the reduced material **72** to cyclised **71** to the reaction performed under catalytic tributyltin hydride recycling.[54] PMHS has found some use as the secondary hydride source but will only reduce tin alkoxides efficiently, although PMHS combined with KF was capable of regenerating the triorganotin hydride from a triorganotin halide for use in radical chain processes.[55]



Scheme 29: *Catalytic recycling of triorganotin hydride*

There has been a continuous effort from many groups to provide less toxic alternatives to triorganostannanes, many of which have found increased usage and are now well documented.[56] However the alternatives are generally not as efficient as triorganostannanes due in part to the higher hydride bond strength (Table 1). Tris(trimethylsilyl)silane (TTMSS)[57] has been the most widely used alternative because it is less toxic than triorganotin hydrides but has a similar level of applicability.

Hydrogen source	BDE
Et_3Si-H	95 1
$(Me_3Si)_3Si$-H	84.0
Bu_3Ge-H	88 6
Bu_3Sn-H	78 6

Table 1: *Stabilities evaluated by bond dissociation energy, BDE (kcal mol^{-1})*

The small difference in M-H bond strength between TTMSS and tributyltin hydride can have a significant influence on the reaction rate. TTMSS can be introduced directly into the initial reaction mixture in stoichiometric amount in favoured reactions because the rate of hydrogen abstraction is diminished (Table 2). Standard tributyltin hydride methodologies require slow syringe pump addition of the triorganotin solution to prevent premature reduction of the radical species.

Radical	Bu_3GeH	$(TMS)_3SiH$	Bu_3SnH
Ph•		3×10^8	$7\,8 \times 10^8$
t-BuO•	$9\,2 \times 10^7$	1.1×10^8	$2\,0 \times 10^8$
RCH_2•	9.5×10^4	3.9×10^5	$2\,5 \times 10^6$
$PhC(Me)_2OO$•	19	66	2.0×10^3

Table 2: *Hydrogen atom transfer rates of group 14 hydrides*

The weak *Sn-H* bond in tributyltin hydride does often yield reduced material and the problems of toxicity of triorganotin compounds and purification of reaction mixtures have already been established, hence avoiding the use of group 14 metal hydrides in radical sequences is

advantageous. TTF has been used in radical-polar crossover reactions to provide triorganotin free carbon-carbon bond formation.[58] Aryl diazonium salts accept single electron donation from TTF with subsequent extrusion of nitrogen. The resultant aryl radical can then undergo cyclisation. The cyclised radical combines with $TTF^{+\bullet}$ and hydrolysis of the sulfonium salt yields a bicyclic alcohol and recycled TTF.

A water soluble TTF derivative has been used in the synthesis of benzopyrans and indolines through radical-polar crossover reactions in aqueous media.[59] The TTF sulfonate salt (Figure 3) can be used catalytically and accommodates the use of water as a co-solvent depending on substrate solubility. Although its use was limited to aryl diazonium salts it is less toxic than triorganotin compounds and can be separated *via* simple aqueous extraction

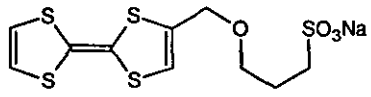
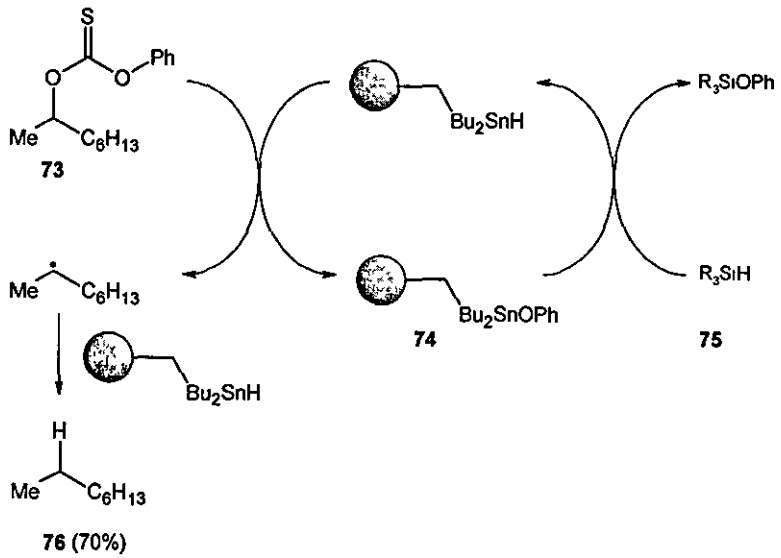


Figure 3: *Water soluble TTF for radical-polar crossover reactions*

The search for a comprehensive replacement for triorganotin hydrides is still on going within the Bowman group and many others, but so far the alternatives are unable to knock organotin from its pedestal based largely on generality. SPOS mediated radical chemistry may be able to provide alternative solutions as discussed in the following section.

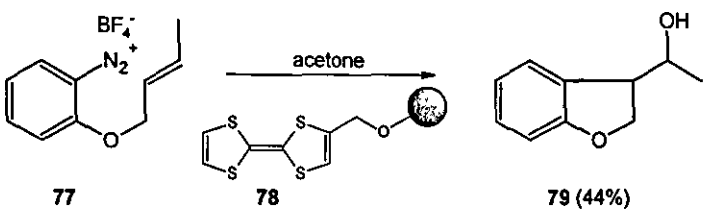
1.2.2 Solid Supported Radical Reagents

Solid phase organic synthesis (SPOS) can potentially eradicate many of the problems associated with triorganotin mediated radical reactions. Recent trends in general SPOS have made increasing use of solid supported reagents as opposed to the more traditional SPOS utilising the supported substrate. The most apparent solution was attachment of triorganotin hydride to solid support enabling recycling of triorganotin waste in addition to improved handling and removal.[60,61,62,63,64] Unfortunately the preparative route to solid-supported triorganotin hydrides was troublesome and the polymer was still prone to leaching of organotin waste. Barton-McCombie deoxygenation of solution phase substrates such as **73** has been carried out in good yield using resin bound organotin hydrides, although the reactivity was somewhat diminished over the related solution-phase reaction (Scheme 30).



Scheme 30: *Barton-McCombie deoxygenation of alcohols using supported organotin hydride*

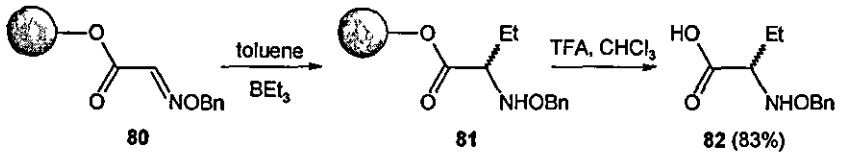
Solid supported TTF **78** has also been used in radical-polar crossover reactions to generate aryl radicals by one electron reduction of aryl diazonium salts such as **77** by TTF (Scheme 31).[65] Following radical cyclisation, the new radical centre was oxidised by $TTF^{+\bullet}$ allowing nucleophile addition; water present in the acetone quenched the carbocation to yield **79**. However substrate specificity limits the scope of reactions and reactivity was again slightly diminished.



Scheme 31: *Solid supported TTF in radical cyclisations of diazonium salts*

Similar principles have been applied to attaching transition metal catalysts for atom transfer radical cyclisations.[66] Yields of 75-96% were reported in favourable cyclisations of *N*-allyl-2-haloacetamides to yield functionalised pyrrolidine rings.

Although the general trend of contemporary SPOS is to use supported reagents to perform the synthetic transformation on the substrate in the solution phase, radical synthetic chemistry benefits greatly from carrying out the reaction on a solid support substrate as shown in scheme 32.[67] Ethyl radical addition to resin bound oxime ether **80** allows rigorous cleansing of hydroxylamine **81** prior to cleavage of the ester linkage to yield 2-benzyloxyamino-butyric acid **82** in 83% yield.



Scheme 32: *Alkyl radical addition to oxime ethers on solid support*

The traditional benefits of simply washing away excess and spent reagents could be instrumental to the success of triorganotin mediated radical reactions and will be considered in greater detail.

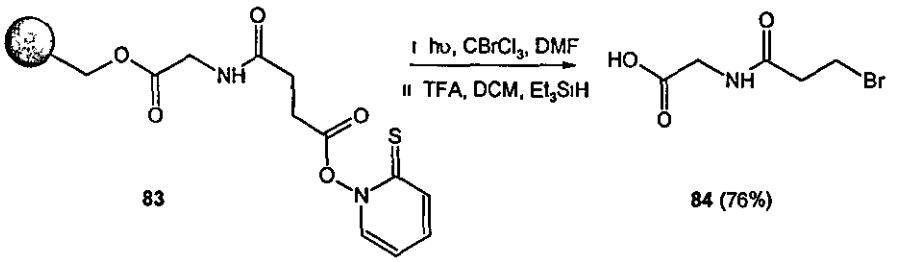
1.2.3 Radical Synthesis Performed on Solid Supports

The discipline of solid supported radical synthesis is still in its infancy and consequently the number of ring forming reactions is limited although several reviews have been published on solid supported radical reactions.[68,69] The scope of this discussion will therefore be broad, encompassing several facets of recent synthetic radical chemistry performed on solid supports with emphasis on more relevant heterocyclic synthesis reported in the literature.

A common drawback of standard SPOS is that of poor kinetics relative to the analogous solution phase reaction. Radical reactions are diffusion controlled, hence less likely to suffer the problems encountered in SPOS reactions with appreciable activation energy. In fact the pseudo-dilution effect the polymer has on the reaction kinetics can be a distinct benefit in the presence of competing side reactions.

Radicals are not influenced greatly by solvation effects and the solvent can thus be selected primarily for its ability to swell the resin, allowing neutral radical species to readily penetrate swollen polymer matrices. Linkers are employed in many cases and can play a significant role in the solubilisation of the tethered substrate; a number of commercially available resins have been used for SPOS radical reactions although typically the reasons for the choice of resin are rarely reported.

Analytical and spectroscopic determination of resin bound molecules is sufficiently advanced that a resin bound reaction product can be categorically identified qualitatively and quantitatively with a similar level of confidence as any other organic compound.[70,71,72,73] The latter is of great importance to the success of radical chemistry performed on solid supports because product mixtures can often be complex and cleavage is not always complete.



Scheme 33: *Radical decarboxylation of supported PTOC esters*

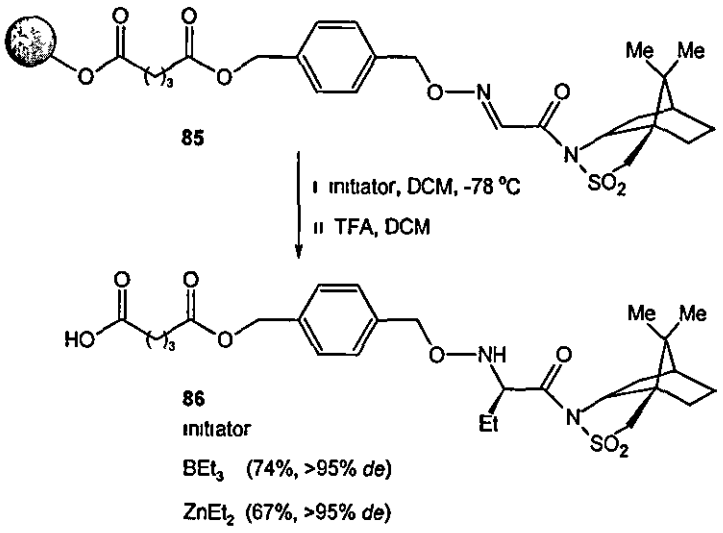
The reaction products must be readily cleaved in high yield at any point during the synthesis to gather information on the synthetic viability of each step. For example, Barton radical decarboxylation has been used in the solid supported modification of amino acids for peptide synthesis.[74] Photolytic cleavage of the PTOC ester **83** and decarboxylation yields an alkyl radical which can then be quenched with a bromine source such as $CBrCl_3$. The alkyl bromide can then be further functionalised on resin and the success of the often troublesome decarboxylation reaction was tested by cleaving a small amount from the resin to yield (3-bromo-propionylamino)-acetic acid **84** in 76% yield (Scheme 33).

The radical centre generated by decarboxylation was also used to capture electron deficient alkenes and as shown earlier in solution phase examples, the alkene was required in vast excess lending itself to this type of solid phase reaction because excess reagents can be washed away following the completion of the reaction. The use of PTOC esters has good synthetic value but the precursor synthesis was temperamental and was not a suitable general approach to radical cyclisation chemistry and further systems require consideration.

Performing a radical reaction on solid support and washing away all excess starting materials has obvious benefits, particularly for systems using triorganotin reagents or those requiring excessive amounts of initiator such as triethylborane initiated sequences. Initiation utilising the reaction of triethylborane in the presence of oxygen at low temperature is used in many stereocontrolled or thermolytically unstable reactions. However, large amounts of the initiator are typically required because the liberated ethyl radical required for radical initiation is rapidly consumed. Such procedures can potentially be improved by SPOS chemistry.

The use of triethylborane and diethyl zinc in radical alkylation of oxime ethers **85** derived from Oppolzer's camphorsultan could be achieved with excellent stereocontrol at low temperature (Scheme 34).[75] The radical reaction required oxygen/BEt_3 or $ZnEt_2$ to generate an ethyl radical

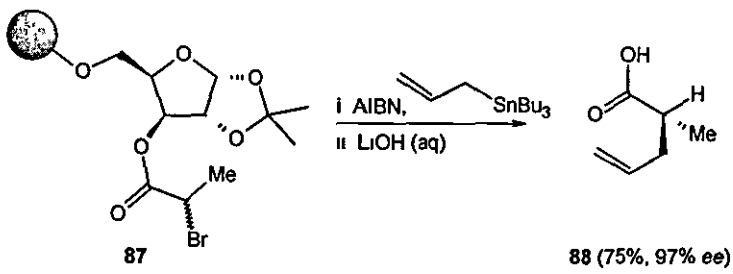
species that could undergo addition to the oxime ether or perform an atom transfer with a suitable alkyl iodide to generate a new radical centre for radical addition.



Scheme 34: *Stereospecific radical addition to supported oxime ethers*

Addition of an ethyl radical to resin bound oxime ether **85** and subsequent ester cleavage with TFA gave good yields of the hydroxylamine **86** (67-74%) with d.e.'s in excess of 95%. However, in order to minimise competing addition of the ethyl radical in atom transfer reactions the examples involving alkyl iodides were performed at 0 °C instead of –78 °C with obvious consequences on d.e.'s. The *i*-propyl and *c*-hexyl radical additions were accomplished with yields between 41-69% with good d.e. (90-92%). The reduced reactivity of the solid phase precursors resulted in better d.e.'s than the solution phase mimics although some unexplained problems were encountered during cleavage from the resin; a common complaint of SPOS.

Radical allylation of substituted α-bromo esters has been performed in good yield (58-76%) with allyltributyl stannane under free-radical conditions.[76] Functionalised allyl stannanes were also used in similar fashion with yields up to 95%. The authors reported enantioselective variants to be underway, although radical allylation has also been performed on NCPS and carbohydrate linked NCPS supported derivatives **87** with good stereocontrol affording the allylated product, 2-methyl-pent-4-enoic acid **88** in 75% with good enantiocontrol (97% *ee*) (Scheme 35).[77] The protected D-xylose linker attached to NCPS served as a suitable chiral auxiliary and derivatisation on the resin was accomplished readily. However, the procedure still requires a functional linkage to the solid-support giving rise to undesirable functionality in the cleavage product.



Scheme 35: *Stereocontrolled radical allylation on solid support*

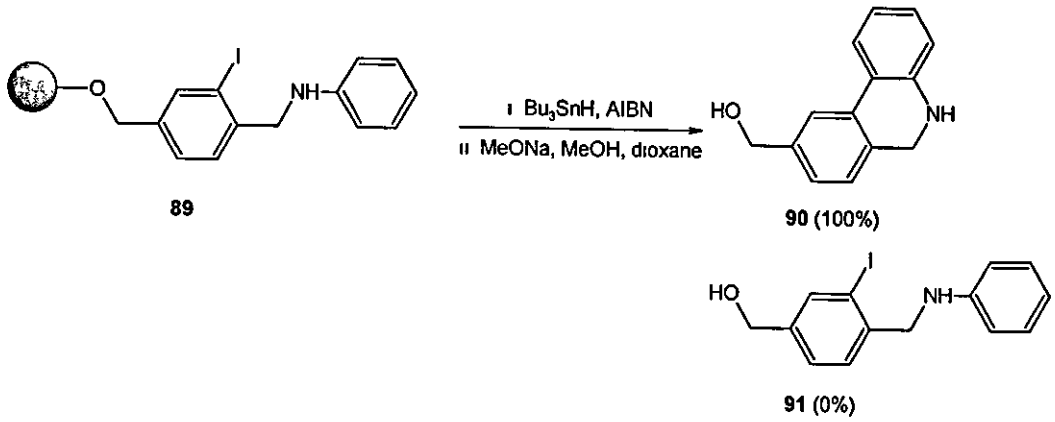
Versatile approaches to two component systems are available with SPOS because either the radical, or the component for radical addition, can be bound to the resin. Capture of radical species onto Wang supported dehydro-*N*-acetyl-α-amino acids from solution has been achieved *via* conjugate radical addition onto the electron deficient alkenes.[78] Following unsuccessful attempts to perform the additions under standard tributyltin hydride/AIBN/benzene conditions, the modification of supported dehydroamino acids was performed with *i*-propyl-, *t*-butyl- and *c*-hexyl-mercury halides in reasonable isolated yield following acid cleavage (49, 49 and 60% respectively).[79]

Alternatively the alkene component of the two component mixture may be present in the solution phase. This approach has been reported as the mechanism for loading an alkene substrate to the solid support by thiyl radical addition.[80] Both methods offer great versatility and the problem of removing excess starting materials from two component radical reactions was no longer an issue. The success of two component mixtures was encouraging with respect to potentially performing cyclisations on solid supports; a number of examples are discussed herein to conclude the introduction to solid phase radical chemistry.

The same principles are in operation for radical cyclisations on solid support as those in solution although consumption of the radical propagating species by the solid support and the observations highlighted in previous sections should be taken into consideration. Radical cyclisation followed by cleavage from the resin is the most common procedure to feature in SPOS radical cyclisation chemistry, although there are still limited examples.

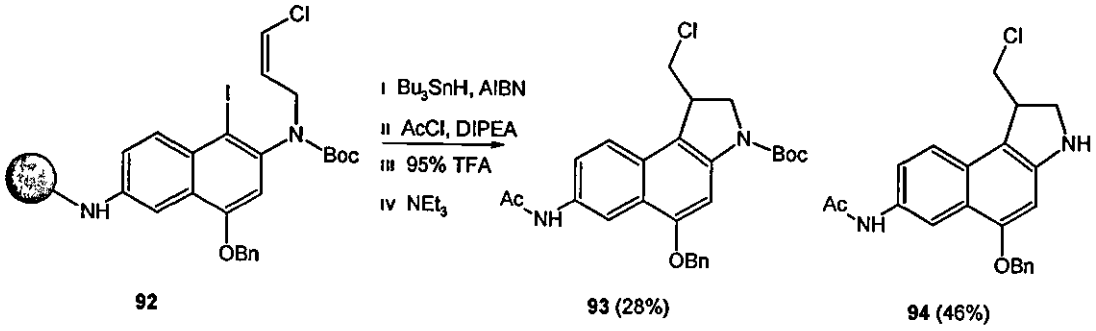
An example of homolytic aromatic substitution on bead was reported whereby a phenyl radical generated from resin bound aryl iodides such as **89** (Scheme 36) cyclise in good yield to a pendant aryl group.[81] The cyclisation product **90** was obtained as the sole product following treatment of **89** with 16 equivalents of tributyltin hydride; 4 equivalents of tributyltin hydride yielded unreacted **91** in 74% with only 26% of **90**. Similarly aryl radical cyclisations onto *O*- and

N-allylated phenols and anilines gave rise to dihydrobenzofurans and indolines respectively, although yields were variable.[82]



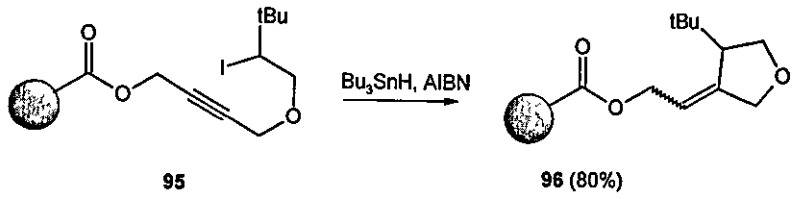
Scheme 36: *Aryl radical cyclisations on solid support*

Aryl radical cyclisation onto vinyl chlorides was performed in 5-*exo* fashion as a key step in the proposed SPOS construction of cyclopropyl indole antitumour antibiotics (Scheme 37).[83] Cyclisation of **92** was monitored by cleavage from the solid support prior to further functionalisation. As with many solid phase syntheses, an apparently trivial transformation (Boc deprotection using TFA) did not go to completion giving a mixture of **93** and **94**, thus emphasising the need for reliable qualitative and quantitative information on the integrity of the solid supported compounds.



Scheme 37: *Aryl radical cyclisation on solid support*

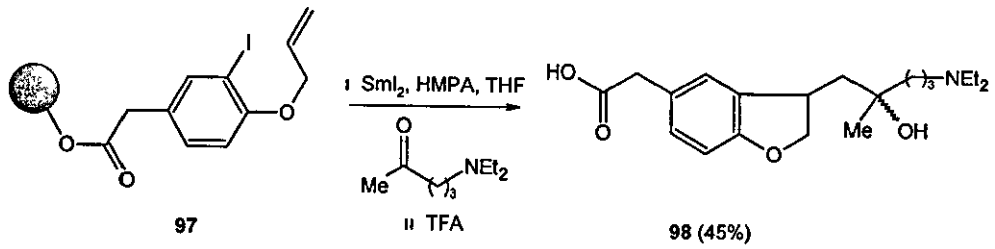
Phenyl radical cyclisations have also been used in the construction of dihydrobenzofurans on the solid support.[84,85] Cyclisations utilising acyclic and cyclic alkyl radicals have been used in the formation of THF rings on solid support as shown in Scheme 38.[84] Addition of the alkyl radical generated from the iodo precursor **95** to the pendant acetylene in a 5-*exo* manner gives rise to the supported THF **96** following the quenching of the vinyl radical.



95 96 (80%)

Scheme 38: *Radical mediated synthesis of THF rings on solid support*

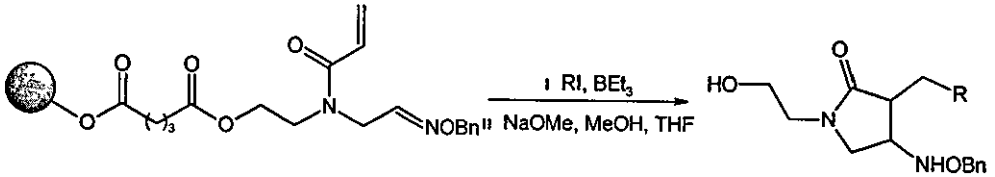
Dihydrobenzofurans can also be prepared using SmI_2 to generate the aryl radical from *O*-allylphenols such as **97** (Scheme 39).[86,87] The benefit of this technique was the ability to introduce a second component into the reaction mixture with greater efficiency than standard triorganotin hydride techniques. Following 5-*exo* aryl radical cyclisation generated by oxidation of samarium (II to III) the primary alkyl radical is reduced to the carbanion by electron donation from a second samarium diiodide equivalent. Carbanion attack at the ketone was then quenched to yield **98**.



97 98 (45%)

Scheme 39: *Samarium diiodide mediated cyclisation-addition reaction*

A further extension to the bimolecular radical additions to oxime ethers as outlined earlier in this section was that of intramolecular cyclisation onto oxime ethers.[88,89] 1,4-Conjugate radical addition to the supported oxime ether **99** (Scheme 40) facilitates cyclisation of the newly formed secondary alkyl radical to the pendant oxime ether, giving rise to pyrrolidinones **100a-d** in moderate yield (54-69%) following cleavage.



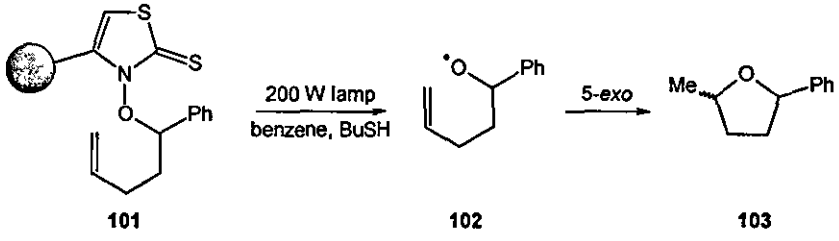
99

100 a, R = ^{i}Pr (69%)
b, R = c-hexyl (54%)
c, R = c-pentyl (59%)
d, R = ^{s}Bu (55%)

Scheme 40: *Radical addition-cyclisation onto supported oxime ethers*

The cyclisations discussed hitherto have been performed on solid supported precursors and the linker has been passive in the radical reaction, alternatively the radical cyclisation may be performed in solution and the radical may be captured by the solid support.[90]

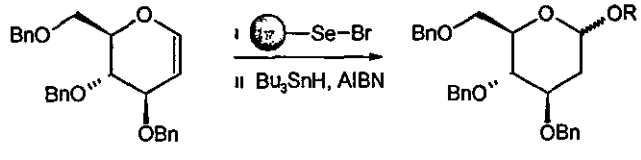
Perhaps a more elegant approach is a one-step cleavage/cyclisation protocol. Traceless homolytic cleavage has been performed using photolytic degradation of the solid supported *N*-hydroxythiazole-2(3)-thione **101** (Scheme 41). The resultant alkoxyl radical **102** underwent reductive 5-*exo* cyclisation to form a tetrahydrofuran ring **103**.[91] However, photolytic procedures often suffer from poor stability of the precursors.



101 **102** **103**

Scheme 41: *Traceless photolytic cleavage of N-hydroxythiazole-2(3)-thione linker*

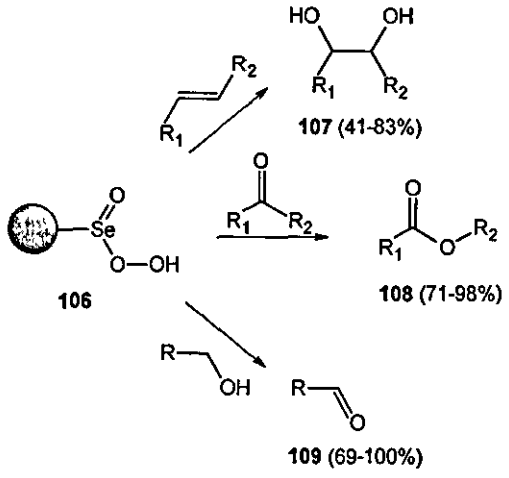
Completely traceless SPOS procedures are rare due to the requirement of a suitably selective labile linker, however, the relatively recent advent of polymer bound selenium reagents highlights the potential for not only for an ideal free radical SPOS approach (Scheme 42)[92] but also for a great improvement in the handling of selenium reagents required for a wide range of chemical transformations (Scheme 43).[93]



104 **105**

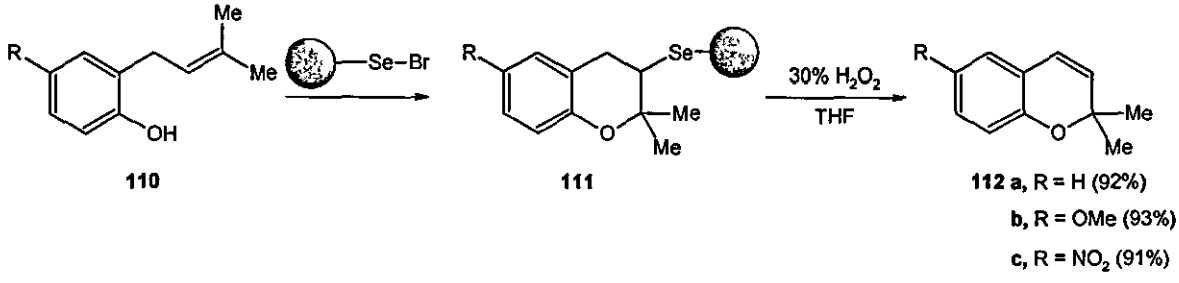
Scheme 42: *Traceless homolytic cleavage from solid-phase selenyl linker*

Attachment of selenium moieties to the solid support allows a large number of synthetic transformations accessible *via* selenium chemistry and the handling and stability of the selenium reagents was improved. Scheme 43 illustrates the use of resin bound selenium reagent **106** in the oxidation of alkenes to give dihydroxylated compounds **107**, Baeyer-Villiger oxidation of ketones to esters and oxidation of alcohols to aldehydes. Each transformation was achieved in good yield benefiting from the ease of purification.



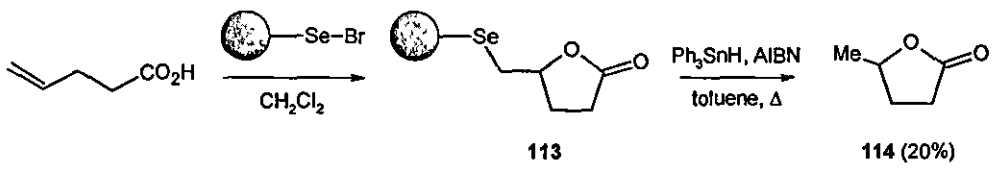
Scheme 43: *Useful selenium mediated transformations adapted to solid support*

The polymer bound selenium bromide has found most use in the non-radical cyclo-addition of *o*-prenylated phenols to the support followed by hydrogen peroxide mediated oxidative cleavage to form benzopyrans (Scheme 44).[94,95,96,97,98,99]



Scheme 44: *Synthesis of benzopyrans via a cyclo-addition/oxidative cleavage procedure*

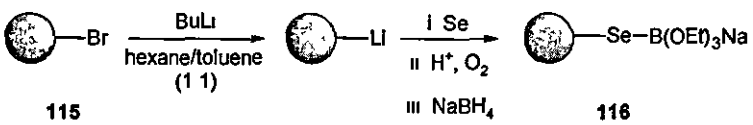
Polymer bound selenocyanates[100] and selenyl bromides[101] have been used in supported selenolactonisation-deselenation procedures. The latter involved reductive radical cleavage of the lactone into solution as well as the more commonly used oxidative method (Scheme 45). The linker used unfortunately participates in the reaction.



Scheme 45: *Selenolactonisation with reductive homolytic cleavage from solid support*

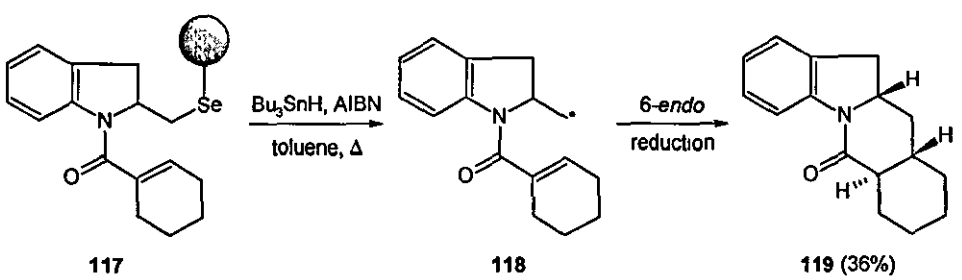
The selenolactonisation/cleavage procedure can be carried out with catalytic amounts of polymer bound selenocyanates if oxidative cleavage was used with yields ranging 20-83% reported.[100] PS bound selenosulfonates derived from Nicolaou's PS bound selenyl bromide have been used in the preparation of acetylenic sulfones by addition across the alkyne and oxidative cleavage of the vinyl selenide product.[102]

Radical cleavage of alkyl selenides derived from sodium PS-seleno(triethyl)borates (Scheme 46) has been performed.[103] The author does not mention problems associated with complete bromine-lithium exchange on the resin[104] or with the mixture of products following quenching with metallic selenium.



Scheme 46: *Synthesis of sodium PS-seleno(triethyl)borates*

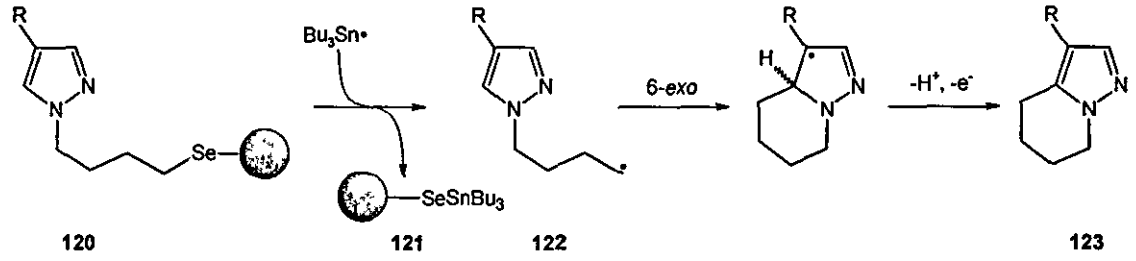
Solid phase synthesis involving resin bound selenides renders the resultant selenide product more stable, easier to handle, less toxic and obtainable in high purity. Much of the chemistry has involved simple oxidative cleavage of the selenyl group, however one of the few examples to utilise radical chemistry was the traceless homolytic cleavage of indolines (Scheme 47).[105] Attachment of the allyl anilides was accompanied by a cyclisation to form the indoline precursor **117**. Standard radical generation can provide a traceless cleavage to yield the alkyl radical **118**, which was suitably placed to perform a reductive cyclisation to form the tetracycle **119** in low yield. Unfortunately this method also makes use of volatile and highly toxic methyl selenides.



Scheme 47: *Traceless homolytic cleavage of supported selenide resulting in cyclisation*

Monitoring the reactions using the PS without a linker is troublesome because NMR spectroscopic analysis will yield poor data. A linker may be required to improve characterisation and kinetics of the resin bound selenides.[103]

This project seeks to expand and improve the range of radical chemistry performed on solid supports. The objective of the initial solution phase work will be the study of novel cyclisation systems requiring the use of phenyl selenyl radical leaving groups in order to form the basis of the SPOS system depicted in Scheme 48. The study of homolytic aromatic substitutions onto pyrazoles and pyrroles will constitute the majority of the research and these cyclisations will be adapted to the solid-phase approach.



Scheme 48: *Proposed SPOS approach for project*

The SPOS procedure should provide the most benefits to the desired cyclisation system Homolytic cleavage of resin bound selenides **120** will liberate a carbon centred radical **122** whilst the tin remains bound to the resin; the tin-selenide complex **121** can be removed by simple filtration whereas the cyclised material **123** remains in solution.

CHAPTER 2 ALKYL RADICAL CYCLISATIONS ONTO PYRAZOLES

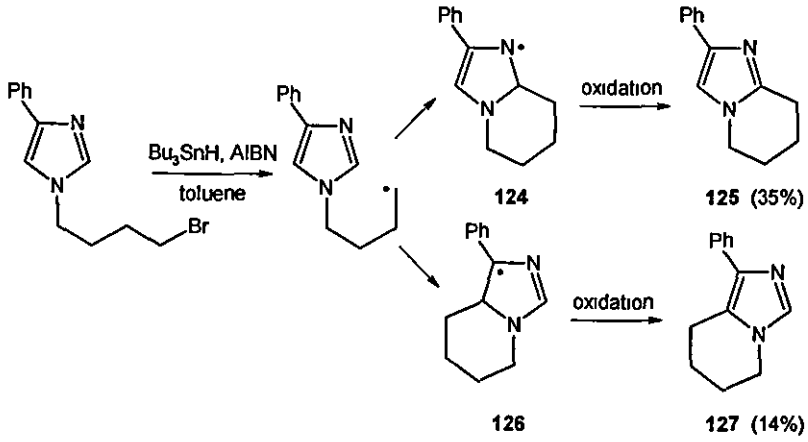
2.1 INTRODUCTION

Radical cyclisation of alkyl, aryl, acyl and other carbon centred radicals to arenes has become a widely expanding area of synthetic radical chemistry. The reason is obvious when the benefits are considered. For example, radical cyclisations are not strongly dependent on solvent effects, can be performed with predictable regiochemistry and crucially exhibit umpolung reactivity to common ionic procedures. Hence protocols not available *via* standard ring forming reactions are possible.

Consequently, aromatic homolytic substitution onto heteroarenes has entered the realm of complex natural product syntheses with great success. In addition to pyrroles and indoles, diazoles have received attention because they are important structures in numerous drug molecules and natural products.[106] Many examples feature a fused bicyclic structure accessible by radical annulation protocols.

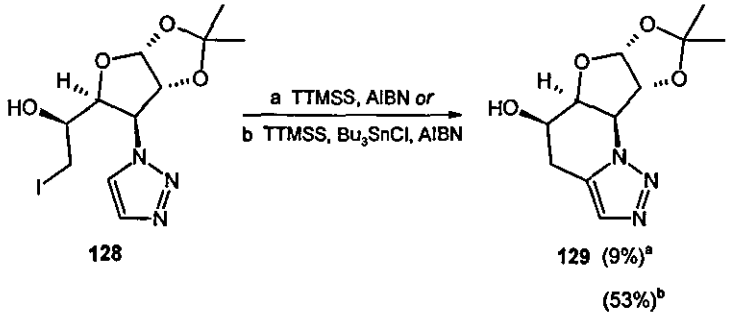
The study of alkyl and acyl radical systems is perhaps of most benefit to radical synthesis due to the host of excellent transition metal coupling procedures for unsaturated and aryl moieties from similar precursors. As discussed in Chapter 1, radical addition to aromatic species is often accompanied by rearomatisation by the loss of a proton and an electron. The overall process can therefore be considered aromatic homolytic substitution.

Synthesis of bicyclic imidazoles has been achieved using radical cyclisation of alkyl radicals onto 1,3-diazole (imidazole) moieties. In the absence of a blocking group at the 2-position, the regioselectivity was determined as portrayed below on 1,3-azoles (Scheme 49).[34] The π-radical intermediates **124** and **126** were stabilised by delocalisation, although curiously the additional stabilisation of benzylic radical **126** does not enhance cyclisation at the 5-position giving a low yield of the tetrahydro-imidazo[1,5-*a*]pyridine **127** (14%). In fact, the dominant cyclisation was that of 6-*exo* addition to the 2-position giving tetrahydro-imidazo[1,2-*a*]pyridine **125** in moderate yield (35%). Electron withdrawing groups at the 4-position have been shown to promote radical cyclisation at the 5-position (Scheme 17).



Scheme 49: *Regioselectivity in alkyl radical cyclisations onto imidazole*

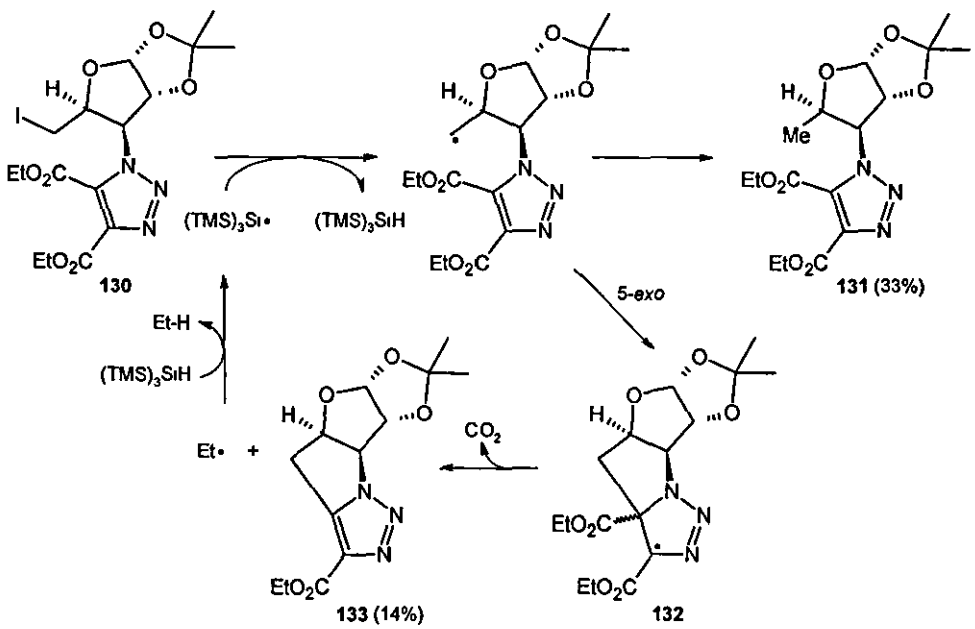
In similar fashion, alkyl radical cyclisation onto 1,2,3-triazoles have recently been performed in the synthesis of potential glycosidase inhibitors.[107,25] Scheme 50 depicts the homolytic aromatic substitution of D-allofuranose derived radical cyclisation precursor **128** to yield the tetracyclic triazole **129** with complete regioselectivity. Initially, yields were poor using TTMSS/AIBN (conditions a) to generate the desired radical. The cyclised triazole **129** was obtained in low yield (9%) in addition to 29% recovery resulting from radical reduction. Using tributyltin chloride in the presence of TTMSS (conditions b) dramatically increased cyclisation yields to 53% and the reduced material was also obtained in higher yield (34%). TTMSS should lower radical reduction rates and render the reaction mixture less toxic and easier to purify. Unfortunately, triorganotin compounds were still required to propitiate the troublesome cyclisation and must be rigorously removed prior to any biological testing



Scheme 50: *Alkyl radical cyclisation onto 1,2,3-triazoles*

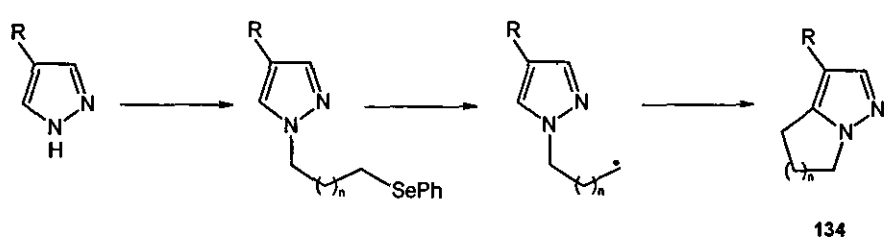
This protocol may, therefore, profit from being adapted to solid supported synthesis because the compounds can be rigorously purified by ablution of the resin prior to cleavage. Removal of toxic triorganotin residues is of particular importance for samples to be used in biological assays such as these.

As with many radical cyclisations onto aromatic rings the cyclisation was accompanied by an oxidation step as discussed in section 1.1.3. However, cyclisation onto the 1,2,3-triazole in the 4,5-diethoxy carbonyl derivative **130** may not appear to favour aromatic homolytic substitution due to the lack of suitable leaving groups (Scheme 51). The reduced compound **131** was isolated as expected in addition to the product of homolytic aromatic substitution **133.** The mechanism proposed by the authors was that of decarboxylation of the intermediate radical **132** to yield the cyclised material **133** (14%) and an ethyl radical which can then participate in the cycle.



Scheme 51: *Decarboxylative rearomatisation of triazoles*

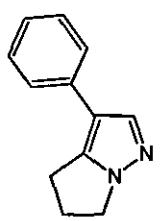
As with 1,2,3-triazoles, radical cyclisations onto 1,2-diazoles (pyrazoles) should proceed with greater selectivity than 1,3-diazoles because the pyrazole N-2 should not participate and cyclisation should proceed exclusively at the 5-position. As there are no general procedures for the synthesis of [1,2-*b*]-fused bicyclic pyrazoles **134**, it was envisaged that a homolytic aromatic substitution approach might provide a useful synthetic route to such structures (Scheme 52).[47] Surprisingly, prior to our research into radical cyclisations onto pyrazoles there were no reported examples and we were keen to explore the potential cyclisations.



Scheme 52: *Proposed synthesis of bicyclic pyrazoles by radical cyclisation*

Although [1,2-*b*]-Fused bicyclic pyrazoles can be prepared in a number of ways including [2+3] dipolar addition to cyclic systems[108] and condensation procedures involving acyclic precursors, [109] many of the reported protocols suffer from regioselectivity problems or poor overall yields. The radical addition protocol proposed will not suffer from regioselective ambiguity, because the cyclisation should occur exclusively at the 5-position with the pyrazole ring functionality already in place. This ensures regioselectivity of the functionalisation of the bicyclic structure is unambiguous in the final product.

In order to test the validity of intended SPOS protocols it is standard practice to perform a series of solution phase test reactions first. In accordance with the resin bound selenide approach to be adopted in this research (Scheme 48) a suitable solid phase mimic for the cyclisation precursors will be to use the phenyl selenyl radical leaving group. The phenyl selenyl functionality should mimic the polystyrene bound selenide prepared by Nicolaou[105] and the precursors are accessible from commercially available materials. These novel bicyclic structures could then provide the basis for further SPOS studies along with other heterocyclic examples performed within the Bowman group.



135

Figure 4: *Withania somnifera root extract withasomnine*

The controlled synthesis of one of the few pyrazole containing natural products was also to be performed in order to demonstrate the rational synthesis of a given target and show the applicability of the procedure. Plant extract withasomnine **135** (Figure 4) was first isolated from *Withania somnifera* 26 years ago[110] and features a 5,5-[1,2-*b*]-fused bicyclic pyrazole structure accessible using the proposed radical cyclisation methodology. The natural product has since been synthesised with a number of novel approaches,[108,109,111,112] and this would be the first reported example using radical protocols.

2.2 Synthesis of Bicyclic Pyrazoles

Prior to attempting the synthesis of withasomnine, cyclisation onto electron deficient pyrazoles was to be performed to determine the potential for cyclisation. Information about the oxidation level of the cyclised material would also be available, i.e. does cyclisation result in reduction of

the cyclised radical or does homolytic aromatic substitution occur in the absence of a suitable leaving group?

Alkyl radical cyclisation will occur preferentially onto electron deficient heteroarenes due to the nucleophilic nature of the alkyl radical, hence selected pyrazole targets for cyclisation require functionality with good electron withdrawing potential, ability to stabilise/delocalise the radical centre and be inert to tributyltin hydride/AIBN reaction conditions. Aromatic aldehyde and ester functionalities have been shown to provide these prerequisites in previous alkyl radical cyclisations performed within the Bowman group and are versatile functionalities for pre- and post-cyclisation manipulation.

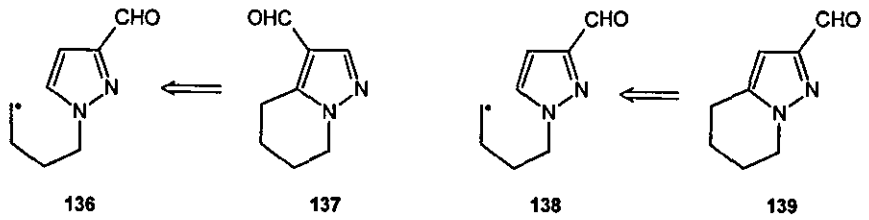
There are few commercially available or affordable pyrazoles with suitable functionality for this study although there are suitable preparative procedures in the literature. Standard heterocyclic chemistry applies to the construction of pyrazoles, commonly employing the condensation of hydrazine with a diketo equivalent to yield 3,5-disubstituted pyrazoles.

2.2.1 Synthesis of Cyclisation Precursors

Pyrazoles are unable to undergo the host of useful acylation procedures available to pyrroles and indoles. However, literature procedures exist for the synthesis of 3-[di(methoxy)methyl]-1*H*-pyrazole[113,114] and ethyl pyrazole-4-carboxylate[115,116] which could be used directly to give cyclisation precursors or converted to the desired radical cyclisation precursors containing an aldehyde (Scheme 53). Pyrazole-3-carbaldehyde and pyrazole-4-carbaldehyde were selected as the most suitable precursors to study the cyclisations onto pyrazole because the aldehyde is more electron withdrawing than the ester or dimethoxy acetal and will stabilise the product of radical addition when placed in conjugation (pyrazole-4-carbaldehyde but not pyrazole-3-carbaldehyde).

Synthesis of 3- and 4-substituted pyrazoles

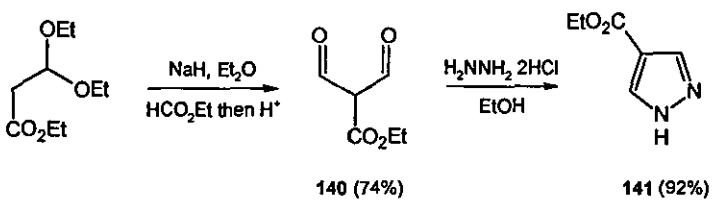
Cyclisation onto many of these heterocyclic systems containing aromatic aldehydes typically causes a slight downfield shift in the ^{1}H NMR spectrum of the aldehyde. The relative abundance of cyclised compound can thus be readily ascertained from the crude mixture even in the presence of multiple aryl and aliphatic peaks that accompany such reactions prior to purification. The 6-*exo* cyclisation of the identified precursors was of particular interest because this mode of cyclisation is commonly high yielding in homolytic aromatic substitution giving rise to novel tetrahydro-pyrazolo[1,5-*a*]pyridine aldehydes **137** and **139** (Scheme 53).



Scheme 53: *Synthesis of pyrazole-3-carbaldehyde and pyrazole-4-carbaldehyde derivatives*

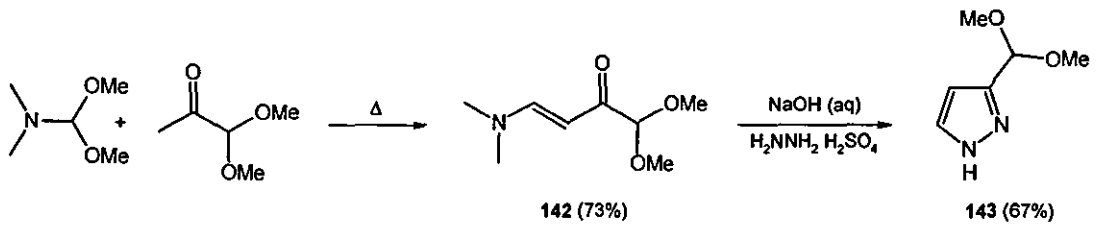
Radical intermediates **136** and **138** were to be generated from the corresponding selenide to facilitate homolytic aromatic substitution. As neither pyrazole aldehyde is commercially available pyrazole-4-carbaldehyde was to be prepared from 4-cyanopyrazole or alkyl pyrazole-4-carboxylates and pyrazole-3-carbaldehyde from the dimethoxyacetal protected aldehyde. Simple alkylation of these substrates would then yield the desired precursors for the synthesis of tetrahydro-pyrazolo[1,5-*a*]pyridine aldehydes **137** and **139**.

The synthesis of ethyl pyrazole-4-carboxylate **141** (Scheme 54) was performed with minor alterations to the reported procedure.[115,116] Isolation of ethyl pyrazole-4-carboxylate **141** was repeatedly achieved in good yield over two steps (68%), with the synthesis culminating in acid catalysed condensation of (ethoxycarbonyl)malondialdehyde **140** with hydrazine. Overall yields were comparable to those reported in the literature (71%) with no requirement for column chromatography.



Scheme 54: *Synthesis of ethyl pyrazole-4-carboxylate*

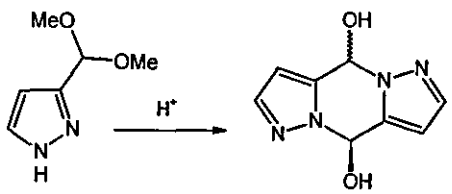
Pyrazole-3-carbaldehyde is not commercially available although 3-[di(methoxy)methyl]-1*H*-pyrazole **143** is; unfortunately the dimethylacetal is cost prohibitive and a synthetic route was required. A suitable method has been reported in good yield over two steps from commercially available materials.[113,114] Heating DMF-DMA neat in methylglyoxal-dimethylacetal yields the required enamine **142** for condensation with hydrazine (Scheme 55). Following distillation of enamine **142** the condensation with hydrazine sulfate was achieved in moderate yield (67%), although the role of the dimethoxyacetal in potential synthesis of pyradizinones was not investigated. The desired heteroarene **143** could be isolated in 49% overall yield, which was again in keeping with reported yields.



142 (73%) 143 (67%)

Scheme 55: *Synthesis of 3-[di(methoxy)methyl]-1H-pyrazole*

Acid catalysed hydrolysis of 3-[di(methoxy)methyl]-1*H*-pyrazole **143** should give rise to pyrazole-3-carbaldehyde. However, the major product of acetal hydrolysis was that of the dimer **144** shown in Scheme 56. It was therefore prudent to perform alkylations on the protected aldehyde **143** and then hydrolyse.

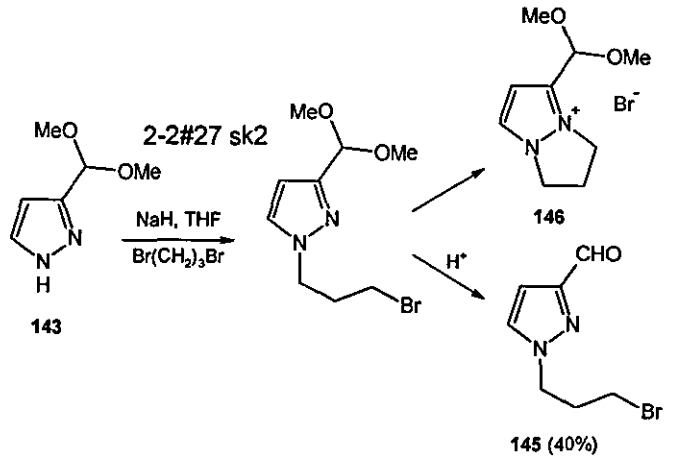


143 144

Scheme 56: *Dimerisation of pyrazole-3-carbaldehyde*

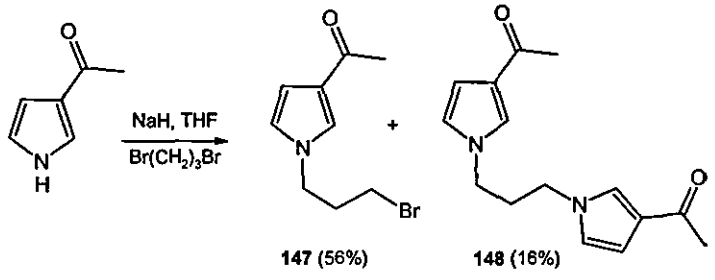
Preparation of suitable alkyl radical precursors can be achieved in a number of ways because there are a number of good radical leaving groups, however as a mimic for the PS selenyl reagents the phenyl selenyl group was to be used. This choice is of particular importance to radical cyclisations onto heterocycles containing basic nitrogens because it is a poor leaving group for nucleophilic displacement relative to more commonly used halides. The nucleophilicity of pyrazole N-2 is weakened by the presence of the α-nitrogen, but it is still aligned well for intramolecular attack on a pendant alkyl halide as shown in Scheme 57.

1-(3-Bromopropyl)-1*H*-pyrazole-3-carbaldehyde **145** was prepared in 40% yield by alkylation of pyrazole **143** with 1,3-dibromopropane followed by immediate hydrolysis of the acetal. The hydrolysis was required immediately because the pyrazole N-2 interfered yielding the pyrazolium salt **146**, but conversion to the aldehyde **145** with CSA inhibited this cyclisation. However, this route was not deemed suitable for radical cyclisation precursors due to the potential for ionic cyclisation and alternative procedures were used.



Scheme 57: *Intramolecular bromide displacement by pyrazole nitrogen*

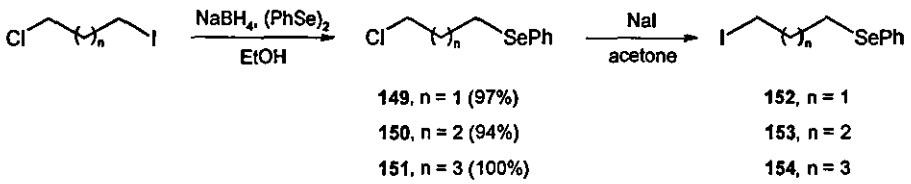
Another common side product observed was that of dialkylation with dihaloalkanes, although this was more commonly observed as a problem when heating was employed; i.e. in addition to the required cyclisation precursor **147** the dialkylated product **148** was also isolated (Scheme 58).[117] The presence of the basic nitrogen will also complicate matters further if heating is employed because there is the potential for dialkylation and various quaternisation pathways in the presence of alkyl bromides. Accordingly the use of potassium hydroxide in aprotic solvents such as DMF at room temperature was the chosen alkylation procedure because it was reasonably mild but sufficient to deprotonate the majority of pyrazoles.



Scheme 58: *Dialkylation product using dihaloalkanes*

Nucleophilic displacement of a suitable leaving group with phenyl selenyl anion can be utilised to introduce the radical leaving group and can be accomplished in a number of ways Sodium phenylselenolate can be prepared by reduction of diphenyl diselenide with hydrazine in the presence of base,[118] sodium metal[119] or sodium hydride[120] in THF and sodium borohydride in ethanol.[119] The latter technique is synthetically simple and robust producing a sodium selenoborate complex. The complexation results in a slight reduction in nucleophilicity although the phenylselenolate is sufficiently nucleophilic to displace bromides and iodides readily.

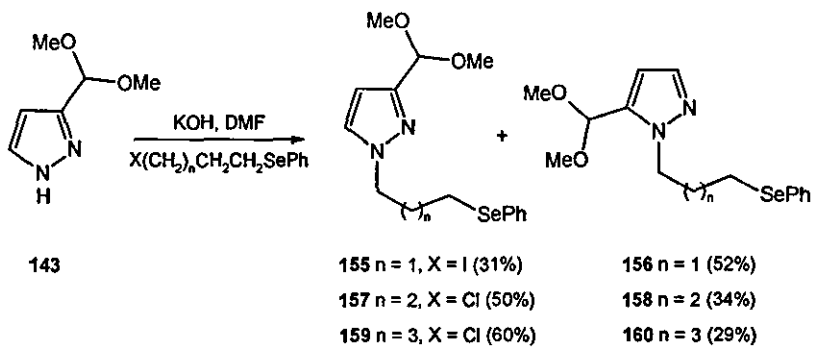
The preparation of phenyl selenyl building blocks **149-151** and **152-154** for the synthesis of radical precursors can be achieved in high yield utilising the methodology developed previously in the Bowman group (Scheme 59).[34] The sodium selenoborate complex reacts rapidly with alkyl iodides and bromides but does not react with alkyl chlorides. Hence the iodochloroalkanes allow the introduction of one selenide group to the chain but the less labile chloride was still available for nucleophilic displacement under different conditions. The building blocks can be used in the preparation of a number of precursors and will not dialkylate unlike dihaloalkanes.



Scheme 59: *Leaving group selection*

Although the chloro alkylselenides **149-151** can be converted to the more reactive iodo alkylselenides **152-154** in high yield, the halogen exchange can be performed during alkylation with potassium or sodium iodide *in situ.*

Alkylation of 4-substituted pyrazoles can be performed without regioselectivity issues, because the tautomers are identical. 3-Substituted pyrazoles will alkylate to give two regioisomers; both regioisomers 3-(dimethoxymethyl)-1-[*n*-(phenylselenyl)alkyl]-1*H*-pyrazole **155, 157, 159** and 5-(dimethoxymethyl)-1-[*n*-(phenylselenyl)alkyl]-1*H*-pyrazole **156, 158, 160** were obtained following alkylation (Scheme 60), although the desired isomer **155, 157, 159** was isolated in greater yield on several occasions.

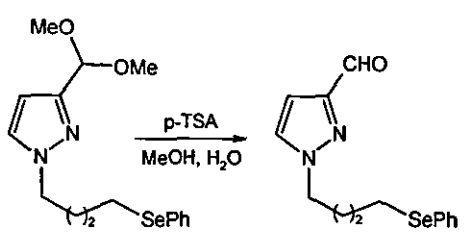


Scheme 60: *Alkylation of 3-[di(methoxy)methyl]-1H-pyrazole*

The two isomers were separated readily by column chromatography and the isomers were identified by the nOe interaction or lack of interaction between the *N*-methylene and the pyrazole 5-H in the ^{1}H NMR spectra. The elution order and NMR spectra of each isomer were sufficiently different to allow immediate identification thereafter.

Initially, the iodo precursors **152-154** were used in the alkylation reaction to increase the rate of nucleophilic displacement, although this step could be circumvented by use of the chloro precursor **149-151** in the alkylation reaction in the presence of excess potassium or sodium iodide. Hence the Finkelstein halogen exchange could be performed *in situ* to generate the iodide. In fact *in situ* halogen exchange gives higher yields of the desired isomer **157** and **159**.

This may be due to the slower formation of the anion using potassium hydroxide, hence the iodide was suitably activated to displacement with the pyrazole N-2. Additionally, the undesired isomers **156, 158** and **160** can provide additional stabilisation of the anion due to the proximity of the dimethoxy acetal lone pairs ability to co-ordinate the base cation. The more stable anion would react slowly with the chloro species, in which case complete removal of the iodide source should yield a higher still proportion of the desired isomer.

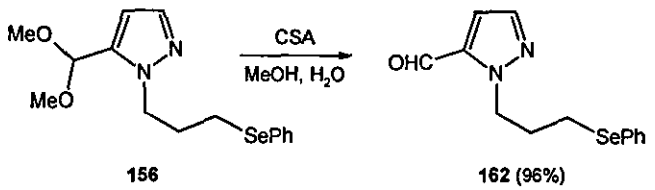


157 **161** (91%)

Scheme 61: *Acid catalysed acetal hydrolysis*

3-(Dimethoxymethyl)-1-[4-(phenylselenyl)butyl]-1*H*-pyrazole **157** could be readily converted to the aldehyde **161** by acidic hydrolysis (Scheme 61). Hydrolysis of 3-[di(methoxy)methyl]-1*H*-pyrazole **143** leads to significant dimerisation (Scheme 56) and was not considered as a viable option although it would allow greater flexibility.

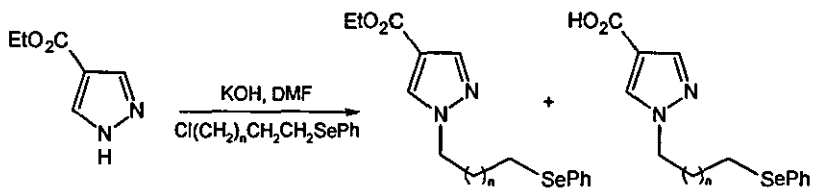
5-(Dimethoxymethyl)-1-[3-(phenylselenyl)propyl]-1*H*-pyrazole **156** could be converted to the aldehyde as shown in Scheme 62, although the potential for cyclisation of aldehyde **162** was not known.



156 162 (96%)

Scheme 62: *Acid catalysed acetal hydrolysis*

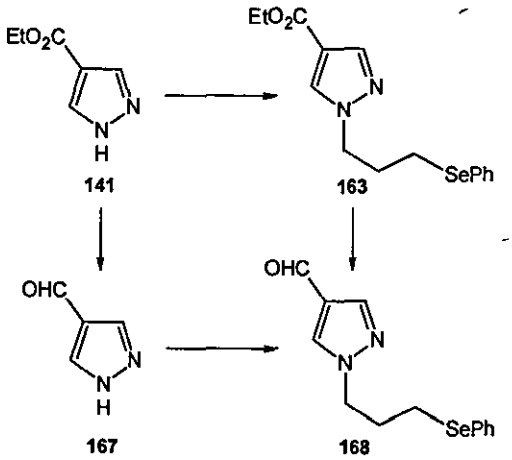
Alkylation of ethyl pyrazole-4-carboxylate **141** was achieved in low yield (**163-165**, 45-55%) presumably due to significant ester hydrolysis to yield carboxylic acids **166** (n = 1-3)observed by LCMS under the potassium hydroxide alkylation conditions (Scheme 63). Alternative alkylation conditions were not sought, because there was sufficient material to proceed with the radical cyclisation investigation. The yields could be improved simply by changing the base to sodium ethoxide or sodium hydride. Potassium hydroxide is highly activated in polar aprotic solvents leading to hydrolysis of the ester. Any attack of the ester in the presence of sodium ethoxide would lead to the desired product.



141 163, n = 1 (45%) 164, n = 2 (55%) 165, n = 3 (45%) 166

Scheme 63: *Alkylation of ethyl pyrazole-4-carboxylate*

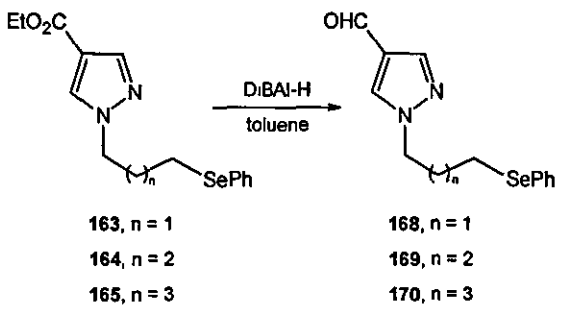
Electrophilic substitution was considered to introduce the formyl group and Vilsmeier-Haack formylation conditions were attempted on pyrazole. Unfortunately the Vilsmeier reagent failed to react with pyrazole following heating under reflux for 24 h in DCM. Although pyrazole-4-carbaldehyde precursors were accessible from ethyl pyrazole-4-carboxylate derivatives (Scheme 64), the formylation route would have provided a more concise preparation. DiBAl-H reduction of ethyl pyrazole-4-carboxylate **141** required 2.5 equivalents of the reducing agent because deprotonation of the pyrazole occurred. Cautious addition of the reducing agent still resulted in 1:1 mixture of the ester **141** and aldehyde **167** in addition to the alcohol.



Scheme 64: *Synthesis of pyrazole-4-carbaldehyde derivatives*

The preparation of the pyrazole-4-carbaldehyde precursors was performed by Nigel Jones as part of a final year project for Prof. W. R. Bowman and W. R. S. Barton. The synthesis of pyrazole-4-carbaldehyde **167** can be achieved from ethyl pyrazole-4-carboxylate **141** in a number of ways. Partial reduction of the ester using DIBAl-H at low temperature will provide the aldehyde in one step (Scheme 65), although yields were variable typically due to the quality of commercially available DIBAl-H.

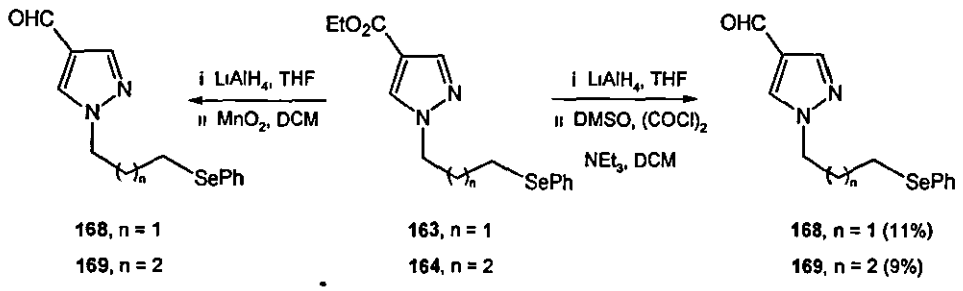
The uncertainty surrounding the exact concentration of the reductant in solution was problematic. Early attempts confirmed this because no reduction was observed even at room temperature and pyrazole-4-carbaldehydes **168-170** were not recovered. Although the reagent had been ordered specifically for the project further investigation of the solution indicated a significantly lower concentration of DiBAl-H than that stated.



Scheme 65: *Partial reduction of ethyl esters using DiBAl-H*

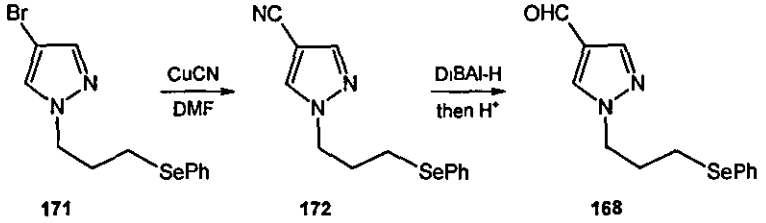
The failure of the partial reduction protocol resulted in the use of reduction to the alcohol followed by oxidation to the aldehyde. Reduction of the ester to the alcohol was achieved readily with lithium aluminium hydride (n = 1, 79%; n = 2, 70%) offering the possibility of a host of

highly selective partial oxidation procedures (Scheme 66). Oxidation of the alcohol using manganese dioxide failed to give adequate yields of pyrazole-4-carbaldehydes **168** and **169** and so the Swern oxidation was identified as the most robust procedure. The Swern oxidation is typically high yielding, but the aldehyde could only be isolated in surprisingly low yield (**168**, 11%; **169**, 9%) with no apparent explanation for the failure.



Scheme 66: *Synthesis of pyrazole-4-carbaldehyde derivatives*

An alternative route to the aldehyde may involve partial reduction and hydrolysis of 4-cyanopyrazoles. The starting material should be readily available from copper mediated coupling of copper cyanide and 4-bromo-1-(3-phenylselenyl-propyl)-1*H*-pyrazole **171** followed by DiBAl-H reduction of the cyano group to yield the desired aldehyde **168** (Scheme 67), although this was not attempted at the time.



Scheme 67: *Putative synthesis of pyrazole-4-carbaldehyde derivatives*

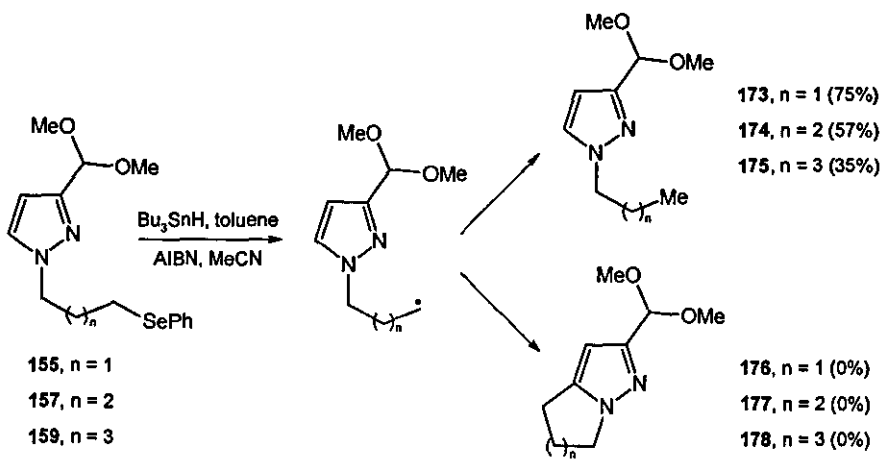
The precursors could thus be prepared in variable yields due to a number of unforeseen issues. Cyclisation of the selenides was attempted and the product mixtures were inspected for the occurrence of predicted products of radical reduction, reductive cyclisation at the 2- and 5-position and homolytic aromatic cyclisation.

2.2.2 Radical Cyclisation onto 3- and 4-Substituted Pyrazoles

The outcome of attempted radical cyclisation onto 3-[di(methoxy)methyl]-1*H*-pyrazole was likely to be that of dominating reduction due to the potentially unfavourable cyclisation. This cyclisation is likely to be unfavourable because there is a polarity incompatibility of the

nucleophilic alkyl radical and the electron rich heteroarene (the strong electron donation of the oxygen lone pairs (+M) of the acetal). However, the dimethoxy acetal is out of conjugation and may be sufficiently electron withdrawing (-I) to allow cyclisation to occur.

AIBN was added portion wise to a solution of 3-(dimethoxymethyl)-1-[*n*-(phenylselenyl)alkyl]-1*H*-pyrazole **155-157** in acetonitrile under reflux to maintain constant source of radical initiation throughout the reaction. Tributyltin hydride concentration was limited and controlled by slow syringe pump addition as a toluene solution to prevent premature reduction of the radical centre. Toluene was used in the addition as tributyltin hydride is poorly soluble in acetonitrile.



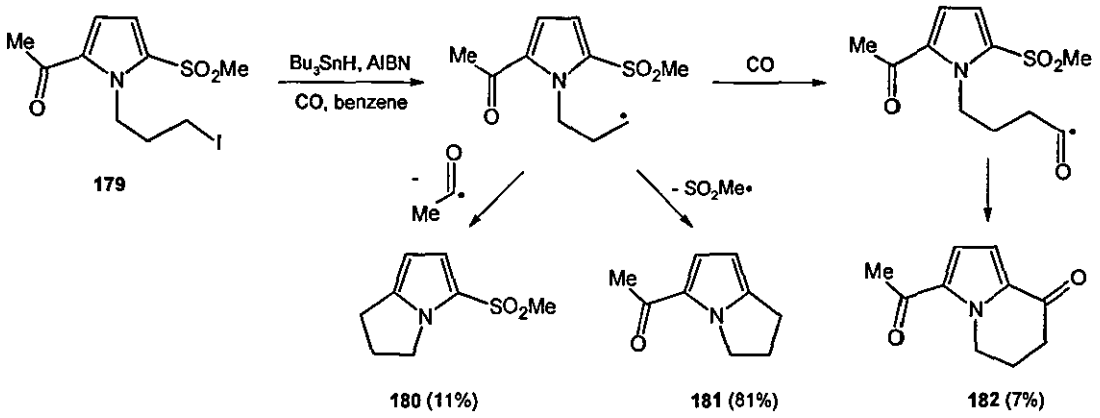
Scheme 68: *Attempted cyclisation of dimethoxyacetal precursors*

Unfortunately, reduction was observed in all cases as the major product, giving rise to 3-(dimethoxymethyl)-1-alkyl-1*H*-pyrazoles **173-175** in yields of 35-75%. No products associated with the anticipated cyclisations **176-178** were observed (Scheme 68) and the yields of reduction were also lower than expected in some cases. In the absence of cyclisation it might be expected that reduction would occur quantitatively, unfortunately unidentified side products accompanied each reaction. The reaction of 3-(dimethoxymethyl)-1-[5-(phenylselenyl)pentyl]-1*H*-pyrazole **159** in particular was accompanied by a large amount of an unknown compound.

We considered that lowering the temperature might lead to increased cyclisation although this can only be achieved with alternative initiators. Triethylborane was used to facilitate radical chain initiation at room temperature, because the controlled reaction with oxygen liberates highly reactive ethyl radicals. The use of triethylborane was problematic because the ethyl radical was highly reactive and large excesses of the initiator were commonly required. TTMSS was used in order to slow down radical reduction. Unfortunately, attempts to cyclise the potentially most

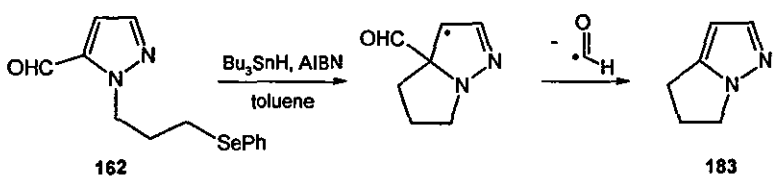
favourable 6-*exo* system, 3-(dimethoxymethyl)-1-[4-(phenylselenyl)butyl]-1*H*-pyrazole **157** also failed. Again the reduced compound **174** was the major product in 57% yield.

Acidic hydrolysis of the dimethoxy acetal derivatives yields the corresponding aldehydes in excellent yield and these precursors can then be used in radical cyclisations. Although the formyl group is not a good leaving group similar systems have resulted in cyclisation with the loss of ester (Scheme 51) and acetyl functionalities (Scheme 69).[40] The loss of the acetyl group in the presence of the methyl sulfonyl is testimony to the lability of such groups in radical cyclisation reactions. Although the methyl sulfonyl group was displaced following 5-*exo* alkyl radical cyclisation affording pyrrolizine **181** as the major product (81%), loss of the acetyl group to yield pyrrolizine **180** (11%) was isolated in greater yield than the desired **182** carbonylated material (7%). Yields of **180** were increased to 23% in the absence of a CO atmosphere.



Scheme 69: *Loss of acetyl group following radical addition*

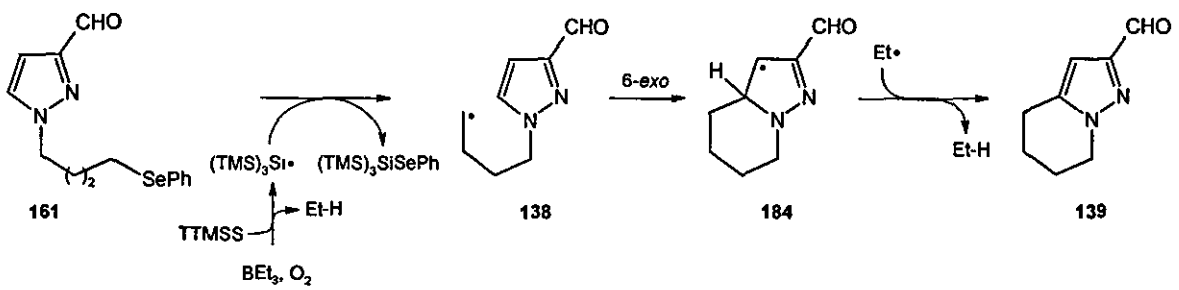
Syringe pump addition of tributyltin hydride to the pyrazole-5-carbaldehyde **162** in toluene was thus performed in the presence of AIBN. Unfortunately, attempted cyclisation of 1-[3-(phenylselenyl)propyl]-1*H*-pyrazole-5-carbaldehyde did not yield any identifiable cyclisation product either by reductive cyclisation to the 2- or 5-position or by homolytic aromatic substitution at the 5-position with the loss of the formyl radical (Scheme 70). These systems were not studied further due to the complex product mixture even in the absence of cyclisation.



Scheme 70: *Attempted cyclisation of pyrazole-5-carbaldehyde derivatives*

Homolytic aromatic substitution onto pyrazole-3-carbaldehyde at the 5-position was achieved in moderate yield as identified by spectroscopic analysis using triethylborane initiation in the presence of TTMSS (Scheme 71). The tetrahydro-pyrazolopyridine **139** was identified as the main reaction product along with unreacted starting material **161** in 2:3 ratio. This cyclisation indicates the formyl group was acting largely as a simple electron-withdrawing group to promote cyclisation because there was no additional resonance stability provided to the π-radical intermediate. The 4-isomer presents the possibility of captodative and resonance stabilisation and these factors may account for the slightly higher yield (Scheme 74).

The putative rearomatisation mechanism for cyclisations performed with triethylborane initiation is also described. The ethyl radical generated from the reaction of triethylborane and oxygen is a highly reactive species and is the most likely source for hydrogen abstraction of radical intermediate **184** to furnish cyclised product **139**. The requirement for an excess of triethylborane is possibly due to its rapid consumption in other processes besides rearomatisation due to its reactive nature.



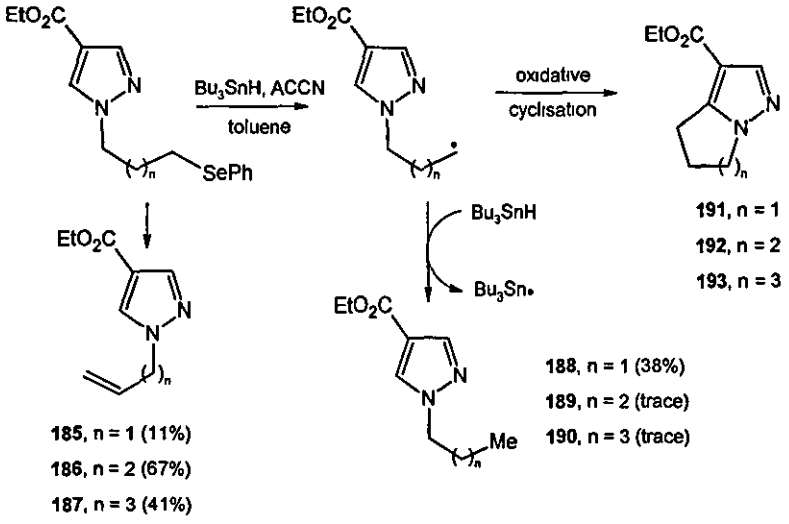
Scheme 71: *6-exo Alkyl radical cyclisation onto pyrazole-3-carbaldehyde*

The 5,6-fused bicycle **139** was the only analogue prepared for the pyrazole-3-carbaldehyde series due to time constraints. No optimisation was carried out because the precursor was limited and insufficient time remained to prepare any more. Yields were expected to be improved in the absence of triethylborane initiation because it is likely a proportion of the ethyl radicals undergo addition to the aldehyde, however the question then remains whether the selenide elimination would then dominate (Scheme 72). In the event of a successful SPOS program other analogues were going to be investigated and optimised, unfortunately the SPOS protocols proved more time consuming than initially expected.

Homolytic aromatic substitution onto ethyl pyrazole-4-carboxylate derivatives **163-165** was attempted under the premise that addition should occur readily due to the nature of conjugate

addition of radical to the heteroarene (Scheme 72). However under 'normal' tributyltin hydride conditions there was limited cyclisation and bicyclic pyrazoles **191-193** were identifiable by LCMS as a trace amount. The major product isolated in initial cyclisation attempts of **164** and **165** was that of apparent selenide elimination yielding the terminal alkene product **186** and **187** (67 and 41% respectively) in addition to small amounts of reduction identified by LCMS.

Reduction of the alkyl radical derived from homolytic cleavage of alkyl selenide **163** was also achieved in 38% yield accompanied by 11% of alkene **185,** but again no cyclisation product **191** was isolated. Similar terminal alkenes have been noted previously in a number of imidazole systems although not in pyrroles and it was apparent these conditions were not conducive to cyclisation and triethylborane systems were used.

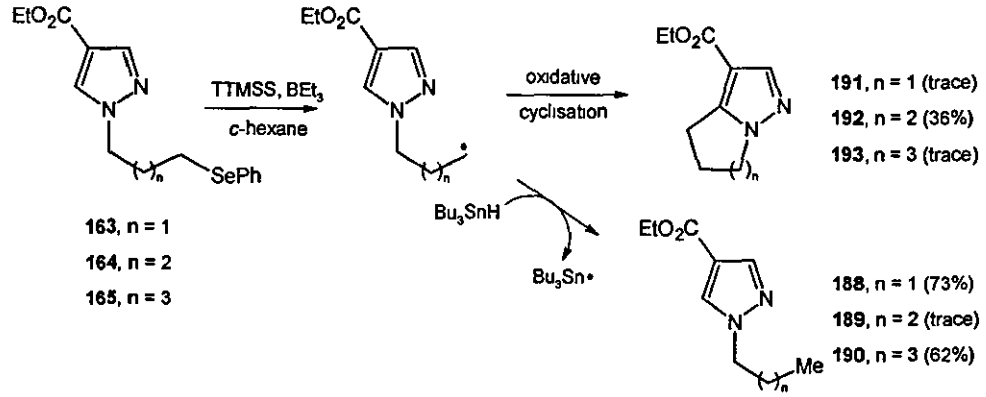


Scheme 72: *Attempted cyclisation of ethyl pyrazole-4-carboxylate derivatives*

The formation of alkene products **185-187** was eliminated from the reaction mixture by performing the reactions at lower temperature. The radical reaction was successfully accomplished by using a low temperature initiator triethylborane. Tris(trimethylsilyl)silane was used in place of tributyltin hydride in the low temperature reactions to reduce alkyl radical reduction (Scheme 73).

LCMS analysis of the crude reaction mixtures from precursors **163** and **165** indicated minor amounts of cyclisation products **191** and **193,** although neither compound was isolated. The reduced radical products ethyl alkylpyrazole-4-carboxylate **188** and **190** were the only compounds resulting from each mixture in yields of 73 and 62% respectively. Following attempted 6-*exo* cyclisation of precursor **164** a 3:2 ratio cyclised:reduced was observed by

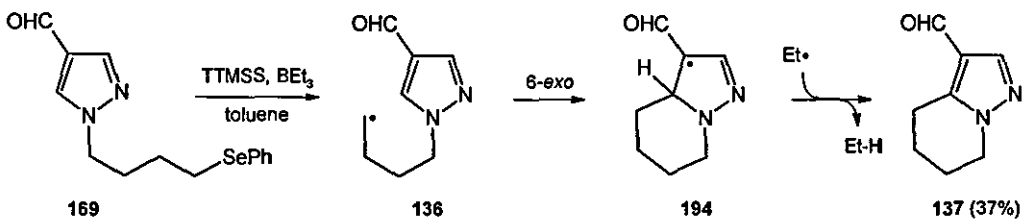
LCMS analysis, although no reduced product **189** was isolated following chromatographic purification. The small scale and poor chromophore associated with these heteroarenes limits detection thresholds and the cyclised material ethyl 4,5,6,7-tetahydropyrazolo[1,5-*a*]pyridine-3-carboxylate **192** was isolated in 36% yield as the only product.



Scheme 73: *Triethylborane initiated reaction of ethyl pyrazole-4-carboxylate series*

The radical resulting from addition to the heteroarene may also experience a captodative stabilisation due to the presence of the nitrogen lone-pair and the electron withdrawing acyl group. This commonly results in a net stabilisation of the radical centre, allowing a sufficiently long lived radical to facilitate oxidative rearomatisation. Destabilisation of the cyclised radical centre may only promote rearomatisation by the β-fragmentation with regeneration of the initial alkyl radical.

Cyclisation onto pyrazole-4-carbaldehyde was also achieved from the alkyl selenide **169** although yields were again moderate, with a slight improvement on the ester and pyrazole-3-carbaldehyde system (Scheme 74). The crude ^{1}H NMR spectrum had indicated a superior yield because the cyclised product **137** was the only immediately identifiable compound. The poor chromophore and small reaction scale were probably partly responsible for the poor recovery of cyclised material. This was the only cyclisation of this series to be performed again due to time constraints, because it was deemed more constructive to develop a suitable SPOS approach.



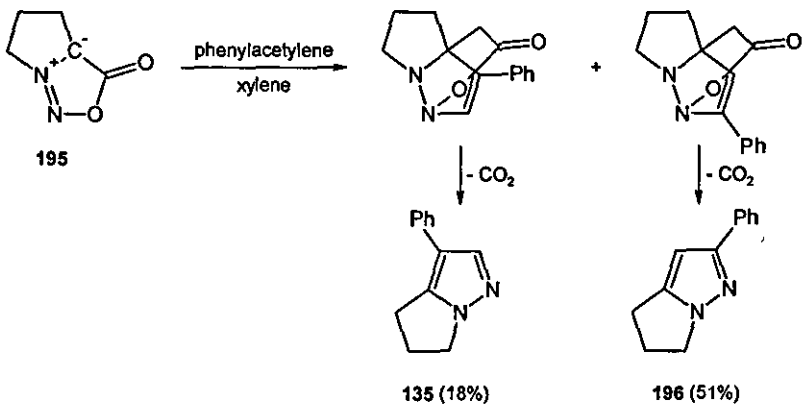
Scheme 74: *Cyclisation onto pyrazole-4-carbaldehyde*

The cyclisation onto electron deficient pyrazoles was performed with some success, although the necessary use of an inferior radical initiation technique (triethylborane) to eliminate the formation of the alkene by-products is regrettable. The absence of any cyclisation from the dimethoxyacetal series was not surprising, although the yields of addition to pyrazole aldehydes was lower than might be expected with reference to the imidazole systems explored previously in the Bowman group. Encouragingly for future endeavours into the synthesis of withasomnine, The cyclisation was regiospecific and the pyrazole aromaticity was intact following cyclisation.

2.3 Synthesis of Withasomnine and Derivatives

In contrast to many other nitrogen containing heteroarenes there is only a handful of natural products containing pyrazoles; withasomnine and analogues contain a [1,2-*b*]-fused bicyclic pyrazole structural motif and have been isolated from natural sources. Withasomnine **135** (Figure 4) was first isolated in 1966 from the roots of *withania somnifera* Dun. (*Solanaceae*), a plant indigenous to Mediterranean regions, South Africa and India.[110] Prior to this isolation the only reported alkaloid to contain a pyrazole ring system was β-1-pyrazolylalanine.[121]

Withasomnine **135** is used in alternative medicine and is inevitably claimed to cure a large number of ailments. The roots themselves were traditionally sold as an aphrodisiac and a tonic in southern India, although the renewed desire for natural remedies means that the extract can now be purchased over the Internet.



Scheme 75: *[2+3] Dipolar addition in the synthesis of withasomnine*

In the absence of a standard preparative procedure to [1,2-*b*]-fused bicyclic pyrazoles, alkyl radical cyclisation onto pyrazole provides a novel route to these structures. An example of earlier synthetic routes to withasomnine is depicted in Scheme 75. The meso-ionic structure **195** was

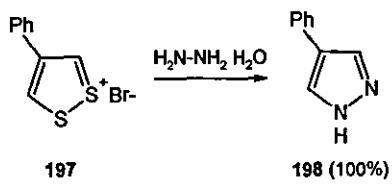
prepared from L-proline and subjected to phenylacetylene in xylene under reflux to perform the necessary [3+2] cycloaddition. Thermal decarboxylation afforded withasomnine **135** and *iso*-withasomnine **196** in combined 69% yield. Unfortunately, *iso*-withasomnine was isolated as the major addition product (51%) and withasomnine was obtained in 18% yield.

Of the previous syntheses of withasomnine none have made use of radical chemistry, although the natural product structure is potentially accessible by 5-*exo* alkyl radical cyclisation onto 4-phenylpyrazole. In light of the partial success of previous substrates, alkyl radical cyclisation onto 4-phenylpyrazole was to be performed because the regioselectivity of ring closure is now known and the phenyl group can be introduced with complete regioselectivity.

2.3.1 Synthesis of 4-Phenylpyrazole

The preparation of withasomnine **135** via alkyl radical cyclisation initially requires the synthesis of 4-phenylpyrazole because the phenyl group should be in place prior to cyclisation so that the substitution pattern is verified, in addition the phenyl group will promote cyclisation by stabilisation of the π-radical intermediate.

The synthesis of 4-phenylpyrazole **198** was not as straightforward as it at first appears because reported syntheses based on the construction of the pyrazole ring give at best moderate yields and have limited selectivity. For instance, the synthesis of 4-phenylpyrazole **198** can be achieved in 46% yield over four steps culminating in the reaction of hydrazine hydrate and 4-phenyl-1,2-dithiolium bromide **197** (Scheme 76).[122] Unlike many other procedures, the transformation can be carried out with completely regioselectivity and does not require chromatographic purification at any point. Unfortunately four steps were required and the yields were only moderate overall.

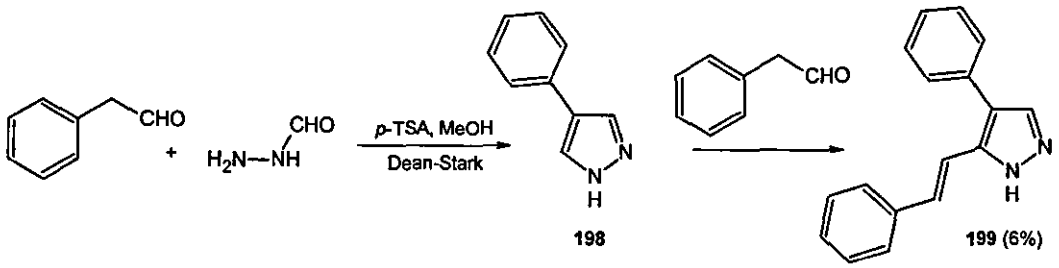


197 **198 (100%)**

Scheme 76: *Synthesis of 4-phenylpyrazole from 1,2-dithiolium salts*

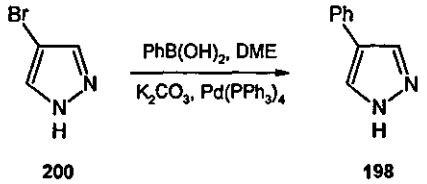
Synthesis of the pyrazole ring *via* condensation (Scheme 77) and alternative dipolar addition methodologies was attempted by a previous Bowman group member Emma Mann. The example shown indicates the desired biaryl compound **198** was formed initially but underwent further transformations to yield **199** as the only identifiable product in low yield (6%). Various other

approaches failed to yield any of the desired 4-phenylpyrazole **198** without additional ring functionalisation. This is indicative of the absence of versatile procedures for the synthesis of monosubstituted pyrazoles, although arylation of halogenated pyrazoles should be readily achieved due to the abundance of reliable biaryl couplings.



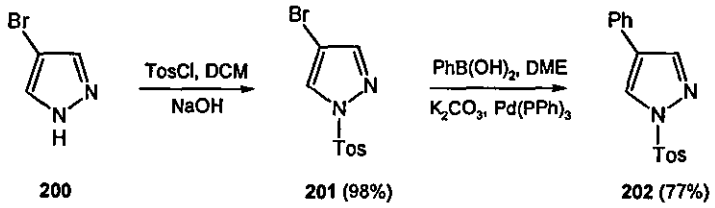
Scheme 77: *Attempted synthesis of 4-phenylpyrazole*

The use of biaryl coupling may attain notable improvements in the preparation of 4-phenylpyrazole. Although many biaryl coupling techniques exist, transition metal catalysed couplings are highly specific and palladium mediated aryl-aryl coupling procedures are typically high yielding and robust. Suzuki coupling facilitates the palladium catalysed tethering of an aryl boronic acid and an aryl halide. Unfortunately standard Suzuki coupling of phenylboronic acid and 4-bromopyrazole **200** did not yield any of the arylated pyrazole (Scheme 78). The interference may be due to deprotonation of 4-bromopyrazole **200** by potassium carbonate.



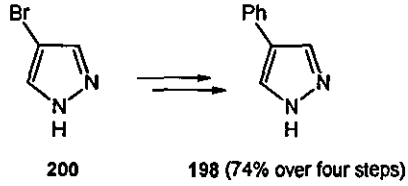
Scheme 78: *Attempted synthesis of 4-phenylpyrazole*

Palladium catalysed Grignard additions were also attempted using phenylmagnesium bromide and 4-bromopyrazole **200** although this procedure also gave rise to a complex inseparable mixture. As the interference was probably due to the presence of an available *N-H*, a nitrogen protecting group was thus introduced (Scheme 79). Tosyl protection of the pyrazole nitrogen of 4-bromopyrazole **200** was performed using sodium hydroxide in DCM to yield 4-bromo-1*H*-pyrazol-1-yl(4-methylphenyl)sulfone **201** in excellent yield.



Scheme 79: *Suzuki coupling of protected 4-bromopyrazole*

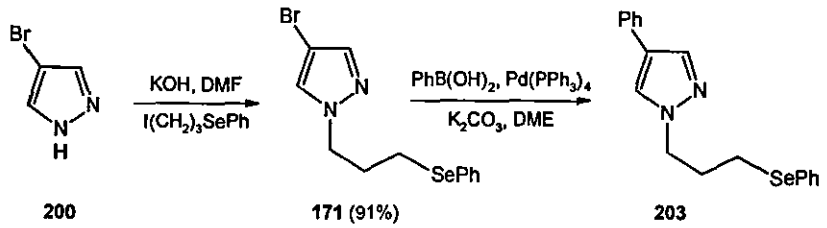
Protection of the pyrazole nitrogen prevented the previous problems and the Suzuki coupling was performed affording 1-[(4-methylphenyl)sulfonyl]-4-phenyl-1*H*-pyrazole **202** in 77% yield (Scheme 79). However, the reaction was performed once; optimisation of the conditions was never attempted although it should be possible to significantly increase the yields of an apparently straightforward palladium mediated coupling (Scheme 80). For example, 4-iodopyrazole can be prepared readily from pyrazole and iodine in the presence of CAN[123] and should significantly increase the rate of oxidative insertion of palladium.



Scheme 80: *Preparation of 4-phenylpyrazole by Suzuki coupling*

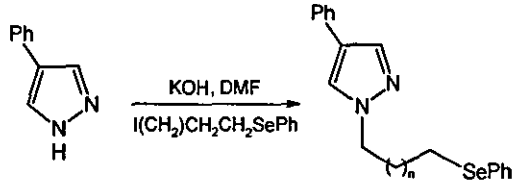
It is likely that yields could be improved for the Suzuki coupling, hence this approach represents a facile route to monoarylated pyrazoles as the unprotected 4-phenylpyrazole **198** was obtained in 74% overall yield following basic deprotection of 1-[(4-methylphenyl)sulfonyl]-4-phenyl-1*H*-pyrazole **202**.

In order to eliminate possibly unnecessary protection/deprotection steps, attempts were made to perform the Suzuki coupling on 4-bromo-1-(3-phenylselenyl-propyl)-1*H*-pyrazole **171** (Scheme 81), thus removing the tosylation/hydrolysis steps required in the initial synthesis. The use of the alkyl selenide chain as a *N*-protecting group eliminates two simple but time-consuming transformations at the expense of substrate flexibility. The reaction failed to yield 4-phenyl-1-(3-phenylselenyl-propyl)-1*H*-pyrazole **203** possibly as a result of strong chelation of the pyrazole N-2 and selenium to the palladium source and possibly due to the potential for oxidative insertion into the *C-Se* bond.



Scheme 81: *Attempted Suzuki coupling*

Alkylations of 4-phenylpyrazole **198** were performed in good yield using the iodo and chloro building blocks because there were no base sensitive functionalities present unlike earlier pyrazole systems (Scheme 82). Iodo derivatives **152-154** gave higher yields, although the use of the chloro derivatives eliminates the need for the additional Finkelstein halogen exchange because the sodium iodide is present to perform halogen exchange *in situ*.



Scheme 82: *Alkylation of 4-phenylpyrazole*

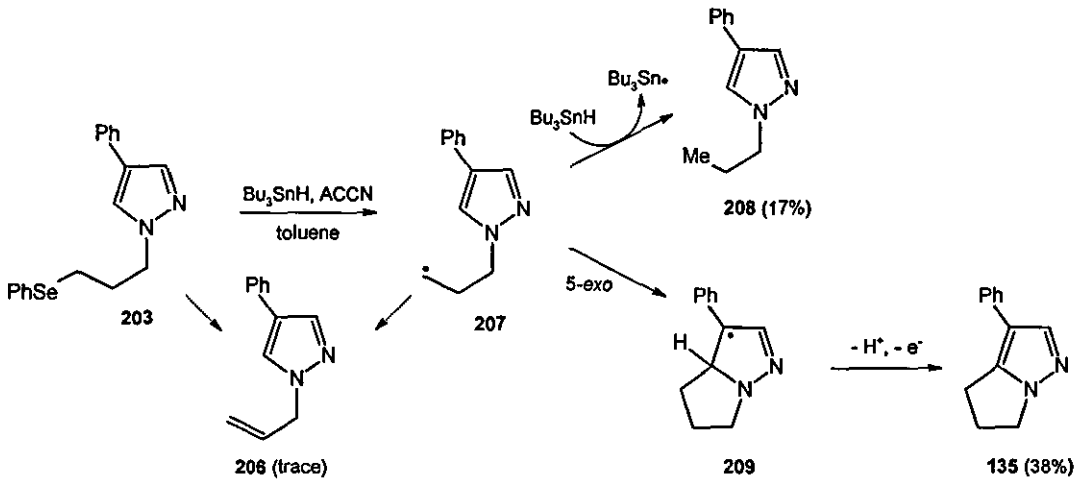
Preparation of the desired 4-phenylpyrazole precursors was achieved in good overall yield and was encouraging for an efficient synthesis of withasomnine and the larger ring homologues. The cyclisations were predicted to be favoured because the phenyl ring is suitably placed to delocalise and stabilise the product of radical addition and lower the cyclisation transition state energy. With this in mind, radical cyclisations were attempted.

2.3.2 Radical Cyclisation of 4-Phenylpyrazole Derivatives

The synthesis of withasomnine **135** was attempted by 5-*exo* cyclisation of alkyl radical **207** onto 4-phenylpyrazole. Generation of alkyl radical **207** was facilitated by syringe pump addition of tributyltin hydride in toluene to a toluene solution of 4-phenyl-1-(3-phenylselenyl-propyl)-1*H*-pyrazole **203** under reflux with portion wise addition of AIBN. As with the previous examples, no cyclisation onto the nitrogen was observed. However, a number of unknown side products were observed in addition to cyclised product **135** (withasomnine)(Scheme 83).

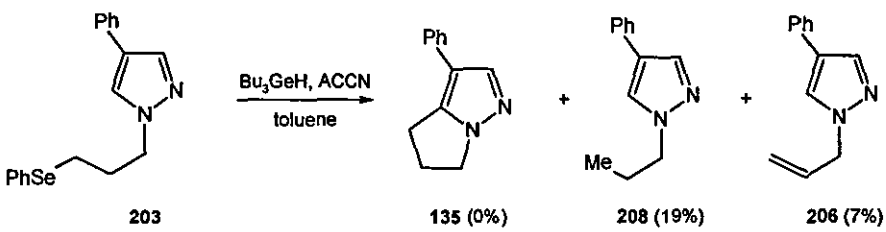
The absence of appreciable amounts of the alkene **206** under these conditions was encouraging. It appears that the alkene formation may be detrimental to radical cyclisation because cyclised product was only observed in low amounts if the alkene product was formed and vice versa.

5-*exo* Alkyl radical cyclisation onto 4-phenylpyrazole was achieved in moderate yield (38%) in addition to reduction of the radical centre **208** in 17% yield. The additional stabilisation of the π-radical intermediate **209** by the presence of the phenyl group must be considerably more than that of the ester or aldehyde functionality. Thus it appears that stability of the addition product may be more important than electron deficiency to cyclisation rate in these pyrazole systems.



Scheme 83: *Synthesis of withasomnine*

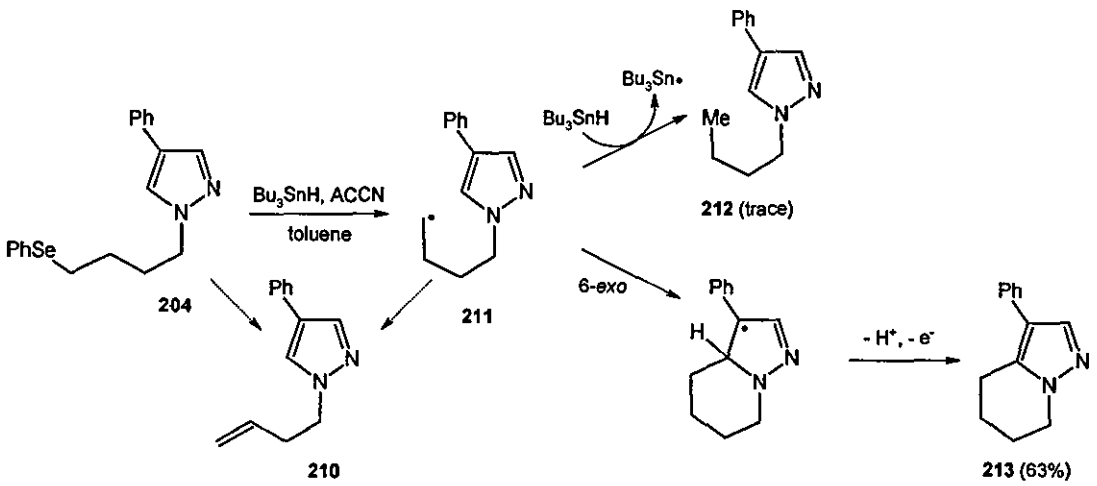
Withasomnine **135** was synthesised with complete regioselectivity throughout in an overall 28% yield from 4-bromopyrazole **200**. The low yield of cyclisation could be overcome with further optimisation and the issues of the diminished yield of the Suzuki coupling could also be addressed. Several unidentified products accompany this reaction, although the compounds were not always the same and vary in amount. They do not appear to be the direct results of addition to the nitrogen or of reductive cyclisation.



Scheme 84: *Attempted tributylgermanium hydride mediated cyclisation*

The elimination product **206** was again observed by LCMS although the amounts were not as significant as those identified during ethyl pyrazole-4-carboxylate series of alkyl radical cyclisations. However, the withasomnine system developed above was attempted with a less toxic and more stable tributyltin hydride substitute, namely tributylgermanium hydride, as part of Sussie Krintel's Ph.D. project.

The study showed the syringe pump addition of tributylgermanium hydride to ACCN and 4-phenyl-1-(3-phenylselenyl-propyl)-1*H*-pyrazole **203** in toluene under reflux failed to yield any cyclised material, but gave rise to unreacted selenide **203** (47%), reduction **208** (19%) and elimination product **206** (7%). The yield of elimination **206** was increased to 30% when ACCN was added portionwise; the only other compound noted under these conditions was unreacted starting material **203** (70%).

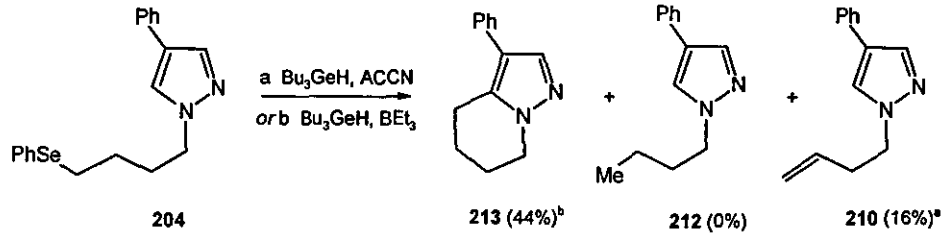


Scheme 85: *6-exo Cyclisation onto 4-phenylpyrazole*

Cyclisation of the 4-phenyl-1-(4-phenylselenyl-butyl)-1*H*-pyrazole **204** was higher yielding as expected in homolytic aromatic substitution and was the highest yielding cyclisation onto pyrazole yielding 3-phenyl-4,5,6,7-tetrahydropyrazolo[1-5-*a*]pyridine **213** in 63% yield (Scheme 85). The reduced compound **212** was again identified in LCMS analysis but none was isolated following chromatographic purification. Cyclisation using TTMSS in cyclohexane with triethylborane initiation did not improve yields in this cyclisation giving approximately a 2:1 ratio of cyclised **213**:reduced **212** by LCMS analysis

In an attempt to reduce the amounts of radical reduction tributylgermanium hydride was again used in this system by Sussie Krintel. Portion wise addition of ACCN again gave rise to elimination product **210** as the only product (16%) and unreacted starting material, 4-phenyl-1-

(4-phenylselenyl-butyl)-1*H*-pyrazole **204** (52%). To circumvent the elimination, triethylborane initiation was used with tributylgermanium hydride and the cyclised material **213** was then isolated in moderate yield (44%).

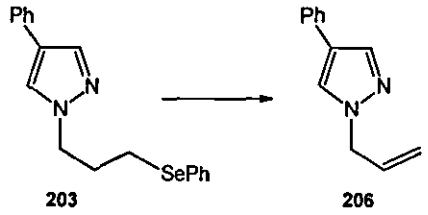


Scheme 86: *Attempted cyclisation using tributylgermanium hydride*

The lower yield reported in this alternative study may be a reflection of the radical stabilities as deduced from the bond dissociation energies (Table 1, p. 1-24). The stronger metal hydride bond of tributylgermanium hydride makes it ideal for certain systems because hydrogen abstraction is less pronounced. This has been used in Sussie Krintels project with great effect in reductive alkyl radical cyclisation and radical decarboxylation procedures. However, it would appear it was not sufficiently active in this case because generation of the germanium radical was proving difficult and large quantities of starting material being recovered.

The tributylgermanium hydride mediated cyclisations were also accompanied by the alkene products **206** and **210**, similar to those observed in the cyclisations onto ethyl pyrazole-4-carboxylate (Scheme 72). The exact mechanism of formation is not known although a limited time was spent investigating the reaction.

The yields of elimination show no apparent trend relating to chain length although the product was always a terminal alkene. The comparison of yields of alkene and reduced material imply disproportionation, if in operation, was not the only route, particularly because the alkene has been isolated in >50% yield in some cases. The alkene **206** was also determined not to be the product of thermal elimination because heating 4-phenyl-1-(3-phenylselenyl-propyl)-1*H*-pyrazole **203** in toluene under reflux for 24 h yielded no elimination and starting material **203** was recovered (Scheme 87). Incidentally, the formation of PhSeH is likely to inhibit any radical chain reaction though because the weak *Se-H* bond is an excellent hydrogen donor. The alkene formation was also not the product of Lewis acid (trialkylstannanes) promoted elimination, because heating 4-phenyl-1-(3-phenylselenyl-propyl)-1*H*-pyrazole **203** in the presence of tributyltin chloride gave none of the desired alkene.

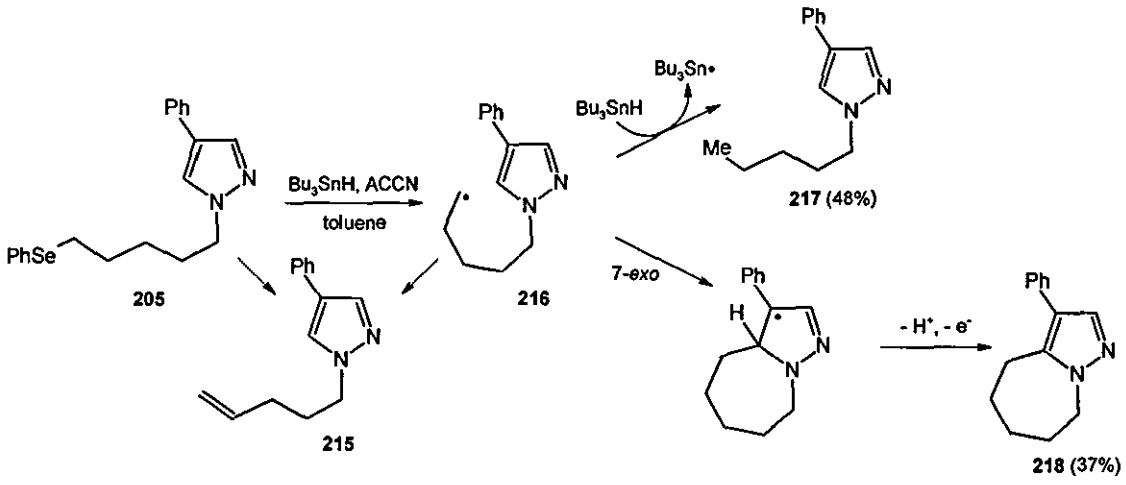


Scheme 87: *Possible elimination pathways*

It was plausible that the selenide may attack the azo initiator to facilitate intramolecular proton abstraction and 4-phenyl-1-(3-phenylselenyl-propyl)-1*H*-pyrazole **203** was heated in toluene in the presence of DIAD to investigate this possibility (DIAD was chosen as it is a non radical generating azo compound). This reaction also failed to produce the unsaturated compound.

The elimination reaction of alkylselenides was also observed in a number of reactions performed by other members of the Bowman group using TTMSS, tributyltin hydride and tributylgermanium hydride. This rules out the potential for oxygen transfer from triorganotin oxide impurities to form the selenoxide, which will then undergo a rapid elimination because TTMSS and triorganogermanium compounds are less susceptible to oxygenation.

The only conclusion drawn at this point is that the mechanism is either thermally promoted or relies on the azo initiator and is likely to be radical due to the conditions of elimination. The common factor observed during the formation of the alkenes is the presence of a basic nitrogen on the heterocycle. The phenomenon has not been observed with (phenylselenyl)alkyl chains attached to aromatic rings not containing nitrogen. The elimination was inhibited by the use of lower temperature initiation with triethylborane and TTMSS as the radical propagating species.



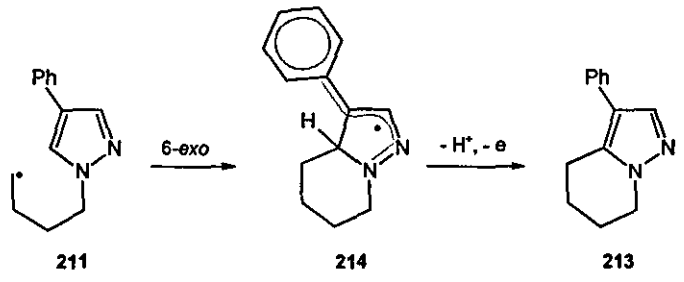
Scheme 88: *7-exo Cyclisation onto 4-phenylpyrazole*

The final cyclisation of the 4-phenylpyrazole series was that of the tetrahydropyrazolo[1,5-*a*]azepine. Alkyl radical cyclisation onto 4-phenylpyrazole in 7-*exo* fashion using 4-phenyl-1-(5-phenylselenyl-pentyl)-1*H*-pyrazole **205** was performed in moderate yield, **218** (37%) along with the reduced material **217** (48%) under 'normal' tributyltin hydride conditions (Scheme 88).

The high proportion of reduced material may also be due to a potential 1,5 H-abstraction of alkyl radical **216** to form a radical stabilised by the pyrazole nitrogen. The new radical centre has little alternative other than reduction. However, the 7-*exo* mode of cyclisation is entropically less favourable than the 5- and 6-*exo* cyclisation, hence the slower cyclisation also results in an increased proportion of reduction.

Tributylgermanium hydride propagated radical cyclisation of 4-phenyl-1-(5-phenylselenyl-pentyl)-1*H*-pyrazole **205** yielded alkene **215** in substantial yield (62%) with no other compounds reported. It would appear that formation of the alkene in some way inhibits radical cyclisation because either can be isolated in reasonable yield although not simultaneously.

It is apparent that radical cyclisation onto electron deficient pyrazoles yielded bicyclic products in moderate yield whereas cyclisations onto 4-phenylpyrazole was on average higher. Although the aforementioned problems of detection limits were lessened by the presence of the phenyl group, this result may be due to the greater stability of the product of radical addition because it is benzylic and stabilised by greater delocalisation (Scheme 89). This stabilisation should lead to a lowering in the transition state energy of cyclisation. Single crystal X-ray structure determination of withasomnine (appendix A) shows the 5,5-fused bicyclic product **135** to be almost entirely planar indicating a high degree of orbital overlap onto the phenyl ring facilitating radical stabilisation.



211 214 213

Scheme 89: *Delocalisation of radical cyclisation product*

The two aromatic rings of 4-phenylpyrazole have been shown to be essentially coplanar in the solution phase,[124] hence the product of radical addition will be delocalised onto the phenyl ring. Our ^{1}H NMR spectroscopic analysis and structure determination studies of the cyclised material **135** confirm this to be the case for the 5,5-fused ring system because the *ortho* protons were significantly deshielded. This deshielding was presumably due to the fixed anti relationship of the α-methylene having only a small influence. The 6,5- and 7,5-fused ring systems display noncoplanarity of the aromatic rings because the phenyl signals were present as a broad single signal in the ^{1}H NMR spectrum and the *ortho* protons were not significantly deshielded.

2.4 Conclusion

We have shown that alkyl radical cyclisation onto pyrazoles can be performed in a highly regioselective manner. The methodology also shows that bicyclic pyrazoles without excessive functional enhancements can be prepared. However, yields were variable and further work is required to optimise the conditions and reduce alkene formation. The more favourable examples will be studied in SPOS investigation and the results compared to the polymer bound analogues.

The cyclisation modes were again shown to occur with the general trend exhibited by previous research in the Bowman group and other research groups as the cyclisation rate diminishes in the order 6-*exo* > 5-*exo* > 7-*exo*. The 7-*exo* mode becomes entropically less favoured than 5- and 6-*exo* because the reaction is more bimolecular character.

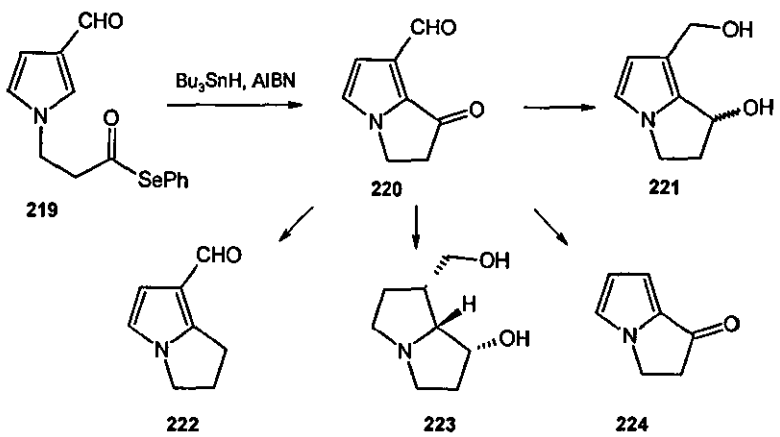
This sequence holds true for many alkyl radical cyclisations onto aromatic species when the overall reaction is homolytic substitution. The order differs from that of reductive cyclisations because the addition to an alkene requires a less demanding transition state. The product of 5-*exo* cyclisation is highly strained hence lowering the rate of cyclisation. Interestingly, the C(3)-C(3A)-C(4) bond angle of withasomnine **135** is high (143.81°) indicating immense strain in the fused ring system. Typically 5-*exo* cyclisation was facile and achieved in high yield; it was apparent that the reduction in yield compared to analogous 6-*exo* cyclisation can be attributed to the strain involved in these ring systems.

The formation of the alkene by-product was overcome by altering the radical generation procedure to lower temperature triethylborane initiation. The elimination was most prevalent in the ethyl pyrazole-4-carboxylate series, although parallel studies using tributylgermanium hydride have resulted in significant amounts of alkene isolated from the 4-phenylpyrazole series.

CHAPTER 3 ACYL RADICAL CYCLISATION ONTO PYRROLES

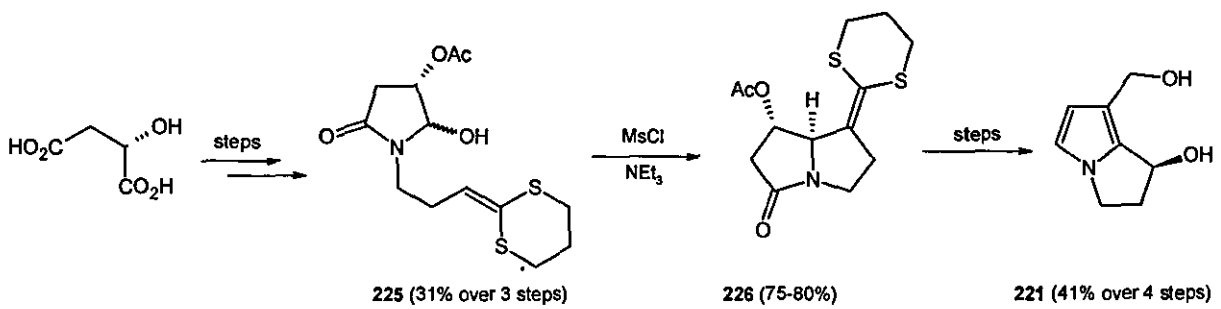
3.1 INTRODUCTION

In contrast to pyrazole there are many interesting fused bicyclic natural products accessible from pyrrole, including nordanaidone **224**, danaidal **222** and platynecine **223** (Scheme 90). A versatile intermediate pyrrolizine 1-oxo-2,3-dihydro-1*H*-pyrrolizine-7-carbaldehyde **220** can potentially be prepared using similar methodologies to those developed in the Chapter 2 using acyl selenides **219** because many of the natural product targets require functionalisation of the radical centre.



Scheme 90: *Potential synthesis of pyrrolizine and pyrrolizidine alkaloids*

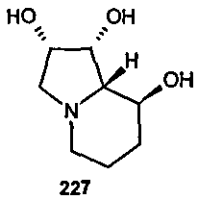
Alkaloids such as those shown in Scheme 90 have been synthesised in a variety of ways[125,126] but prior to our research none have used radical annulation procedures. An example of the novel ring forming chemistry used in the synthetic construction of these molecules is shown in Scheme 91. The principal ring forming reaction is performed with ketene dithioacetal **225** derived from malic acid.[126] The acetoxy group directs cyclisation onto an intermediate acyliminium species yielding pyrrolizidinone **226**, a precursor to the synthesis of a range of pyrrolizine and pyrrolizidine natural products including (+)-hydroxydanaidol (dehydroheliotridine) **221**.



Scheme 91: *Synthesis of (+)-hydroxydanaidol (dehydroheliotridine)*

The proposed radical synthesis shown in Scheme 90 also utilises a common intermediate **220** for the potential transformation to a number of pyrrolizine and pyrrolizidine alkaloids. The proposed intermediate and annulation strategies are different although intermediate **226** (Scheme 91) can access a similar range of natural products to our proposed intermediate **220** and was used in the synthesis of seven naturally occurring pyrrolizidine diols.

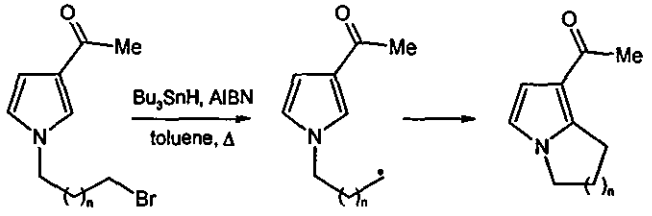
In addition to the pyrrolizine alkaloids, 6-*exo* acyl radical cyclisation at the 2-position of pyrrole could also lead to a number of indolizine and indolizidine natural products such as swainsonine (Figure 5), although these were not under investigation.



227

Figure 5: *Indolizidine structure of swainsonine*

The core structure of many of the [1,2-*a*]-fused pyrrole natural products requires substitution at the 3-positions of the pyrrole. A radical cyclisation approach would thus require cyclisation of a *N*-(ω-acyl)-radical at the 2-position of a 3-substituted pyrrole in order to introduce the required functionality. There is some precedent to suggest the cyclisation will occur as suggested in Scheme 90, because the regioselectivity of alkyl radical addition to 3-acetyl pyrrole was determined to be as demonstrated in Scheme 92 using 1-(ω-bromoalkyl)-3-acetylpyrrole precursors **228**. The presence of the acyl group at the β-position serves to stabilise the radical addition product by delocalisation and promotes cyclisation by drawing electron density from the 2-position yielding the fused bicyclic pyrroles **229-231** in good yield (46-54%).[34]

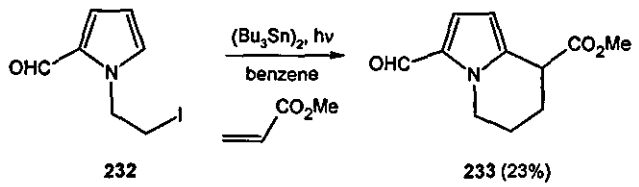


228 (n = 1-3)

229, n = 1 (46%)
230, n = 2 (45%)
231, n = 3 (54%)

Scheme 92: *Alkyl radical cyclisation onto 3-acetyl pyrrole*

The 6,5-fused bicyclic motif in swainsonine could be built in a bimolecular radical addition/cyclisation protocol as shown in Scheme 93.[22] The electron withdrawing potential and stabilising effect of the ester functionality enhances the rate of the initial alkyl radical addition. The radical chain can now enable cyclisation and the tetrahydroindolizine **233** was isolated in 23% yield from 1-(2-iodo-ethyl)-1H-pyrrole-2-carbaldehyde **232.**

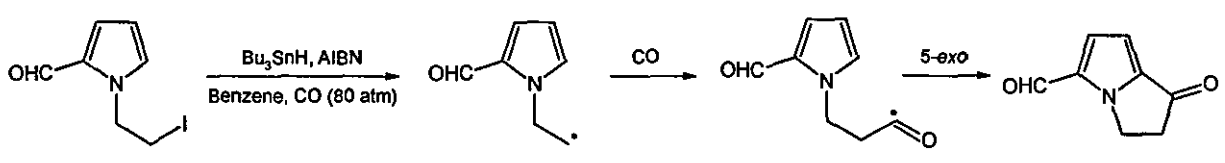


232 **233 (23%)**

Scheme 93: *2-Component cyclisation in the synthesis of indolizines*

In similar fashion, acyl radical addition to electron deficient alkenes has also been performed. The bimolecular reaction again results in cyclisation by conjugate addition to the electron deficient alkene.[19] The above examples were encouraging for the commencement of the proposed work. Acyl radicals have found increasing usage in the synthesis of unsymmetrical ketones[127] because they exhibit a reversal of reactivity over ionic acylation procedures. The low ionisation potential of the acyl radical leads to nucleophilic tendencies and hence the umpolung reactivity.

During our studies, examples of acyl radical addition to pyrroles were published. The research made use of alkyl radical addition **234** to carbon monoxide yielding acyl radical species **235** for cyclisation onto a suitable heterocycle (Scheme 94).[49] Alkyl radicals readily undergo addition to carbenes under suitable conditions, unfortunately this methodology suffers from the requirement for a high CO pressure, which is thus difficult to work with and impractical for slow addition of tributyltin hydride. The acyl radicals formed do undergo cyclisation in moderate yield though.



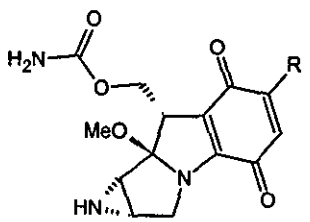
232 **234** **235** **236 (30%)**

Scheme 94: *Alkyl radical addition to CO source*

Acyl selenides offer a more attractive alternative to the generation of acyl radicals and can be prepared readily from carboxylic acids and acyl chlorides. By far the most common group used

is the phenylselenyl group because it can be introduced from a variety of commercially available sources (NPSP, PhSeBr, diphenyl diselenide). Methyl selenides have been used to a lesser extent because they are less active in the radical chain process and the starting materials are more troublesome. However, there are a small number of additional procedures available for the introduction of methyl selenides.[128]

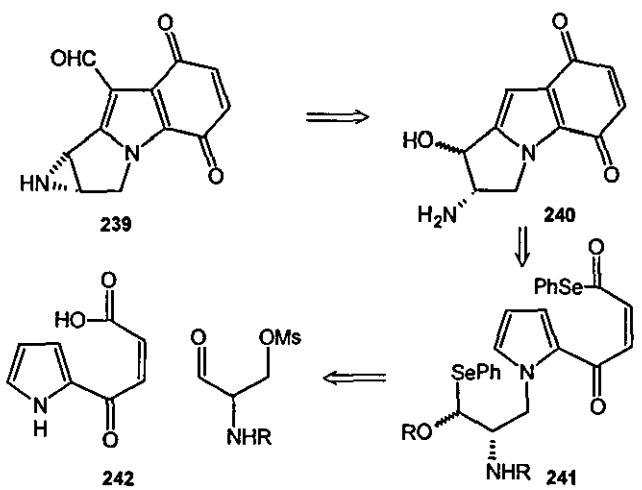
A number of radical cyclisations have been reported in the literature involving addition to pyrrole[34] although even more examples comprising of an indole core exist.[39] Many of the examples involving indole have been carried out in order to target analogues of mitomycin A **237** and C **238** because 5-*exo* cyclisation onto indole proceeds exclusively onto the 2-position yielding the required polycycle for the mitomycin core (Figure 6).



237 (R = OMe)
238 (R = NMe_2)

Figure 6: *Mitomycin A and C*

There have been no attempts reported of a tandem cyclisation approach, although there was little reason to suggest the retrosynthesis shown in Scheme 95 will not prove useful to the synthesis of new mitomycin and mitocene analogues **239** by extension of the acyl radical additions to pyrrole. The ring functionality can potentially be introduced at various stages offering good versatility.

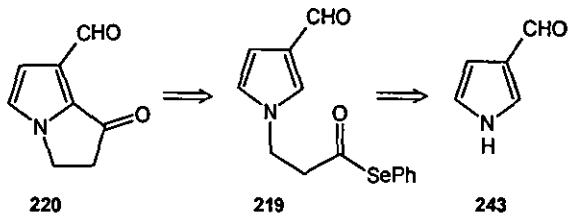


Scheme 95: *Retrosynthesis of mitocene tetracycle*

Alkylation of a suitable pyrrolo acid **242** with a Garner's aldehyde derivative can potentially lead to cyclisation precursor **241**. The tricyclic product **240** following tandem radical cyclisation could be further modified to incorporate the aziridine and ring substituents present in mitomycin A **237** and C **238**.

3.2 Synthesis of Pyrrolizine Alkaloids

A large number of pyrrolizine and pyrrolizidine alkaloids are accessible from a common precursor 1-oxo-2,3-dihydro-1*H*-pyrrolizine-7-carbaldehyde **220** using acyl radical cyclisations onto pyrrole (Scheme 90). The highly selective introduction of the oxygenated functionalities into the molecule can be achieved readily with radical cyclisation onto 3-substituted pyrroles derived pyrrole-3-carbaldehyde **243** (Scheme 96).



Scheme 96: *Retrosynthesis of pyrrolizine 1-oxo-2,3-dihydro-1H-pyrrolizine-7-carbaldehyde*

Suitable protection of pyrrole should allow selective functionalisation of the β-positions. In order to investigate the prospect of successful acyl radical cyclisation onto pyrrole-3-carbaldehyde, systems incorporating pyrrole-2-carbaldehyde **244** were examined, because the heterocyclic portion is commercially available and any difficulties experienced in subsequent cyclisations can be minimised.

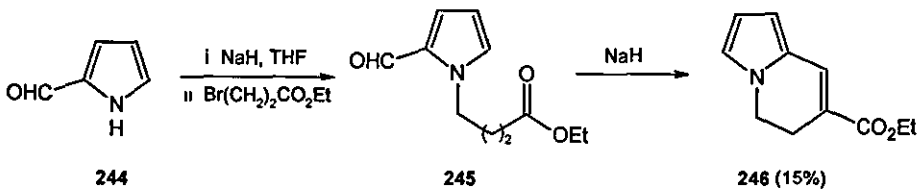
3.2.1 Radical Addition to Pyrrole-2-carbaldehyde

We considered that pyrrole-2-carbaldehyde **244** would provide a good test substrate for the proposed cyclisation onto pyrrole-3-carbaldehyde, overall following the same retrosynthesis as that shown in Scheme 96. Fortunately the starting material is commercially available unlike pyrrole-3-carbaldehyde **243** and alkylation followed by conversion to the acyl selenide and cyclisation should provide the desired products.

Synthesis of Acyl Selenide Precursors

The alkylating agents used were bromoalkyl esters because the propyl, butyl and pentyl chains were all available. Alternative routes may have involved ring opening butyrolactone[129] or Michael addition to suitable substrates with the sodium salt of pyrrole-2-carbaldehyde **244**. Initially the alkylations were performed in THF at reflux with a slight excess of sodium hydride

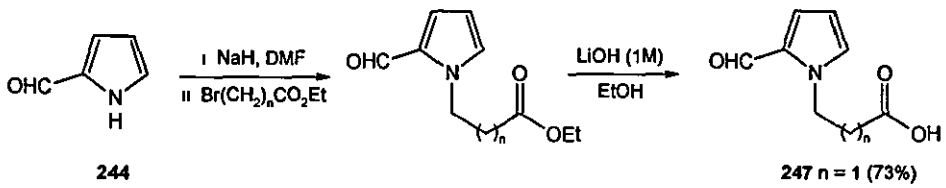
and yields were surprisingly low. Close examination of the reaction mixture indicated the alkylation was not a problem, however the excess sodium hydride and heating resulted in an unwanted cyclisation product **246** (Scheme 97).



244 **245** **246 (15%)**

Scheme 97: *Base mediated cyclisation/dehydration*

Alkylation of pyrrole-2-carbaldehyde **244** could be achieved in excellent yield with a slight excess of sodium hydride in DMF at room temperature. The mixture resulting from aqueous workup of the alkylation reaction could be used crude in the hydrolysis step, eliminating tedious chromatographic purification (Scheme 98). The pyrrolo carboxylic acids **247-249** were obtained sufficiently pure following basic extraction from the crude mixture to be used in selenations.

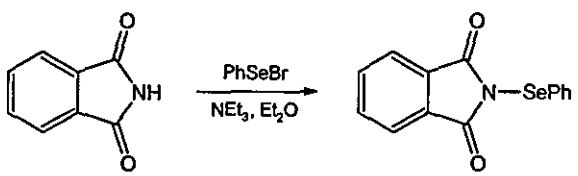


244

247 n = 1 (73%)
248 n = 2 (95%)
249 n = 3 (100%)

Scheme 98: *Alkylation of pyrrole-2-carbaldehyde*

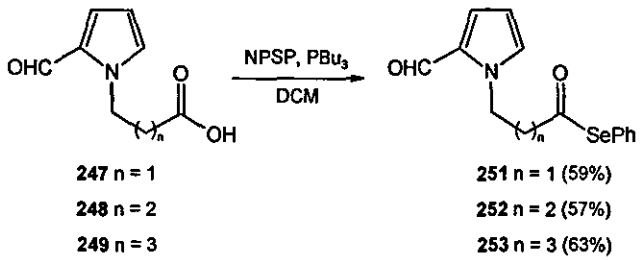
Selenations were performed with diphenyl diselenide or NPSP **250**.[130] Diphenyl diselenide is commercially available, thus avoiding the need for synthesis. We realise that it is advisable to purify the commercially available material by repeated recrystallisation because the presence of mono- and triselenides can hinder the success of some facets of selenium chemistry. NPSP **250** is also commercially available but it is relatively expensive. Preparation of NPSP **250** is straightforward and can be prepared in multigram quantities (Scheme 99).



250 (85%)

Scheme 99: *Preparation of NPSP*

Diphenyl diselenide and NPSP **250** behave similarly in the selenation reactions[131] (Scheme 100) although NPSP **250** reaction mixtures were less troublesome to handle due to the lower equivalents of selenium used. Tributylphosphine was used in all selenation reactions due to the greater reactivity over many common trisubstituted phosphines such as triphenylphosphine. The required acyl selenides **251-253** were achieved in moderate yield (57-63%), somewhat lower than reported selenation examples.[3] The stability of many of the acyl selenides was surprisingly good in the absence of acid. Storage at 4 °C was sufficient for over 1 year, although some minor purification was required. With the acyl selenide precursors in hand the substrates were subjected to tributyltin hydride and AIBN radical cyclisation conditions.



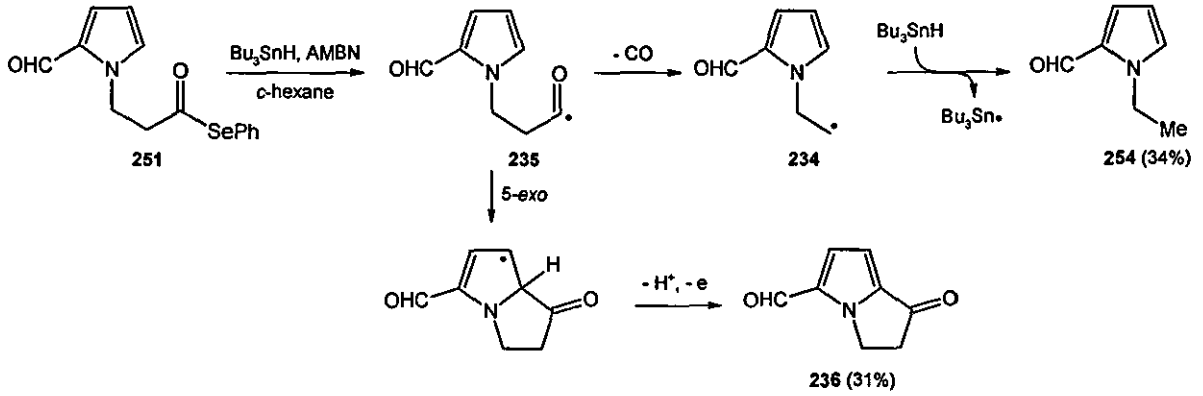
247 n = 1
248 n = 2
249 n = 3

251 n = 1 (59%)
252 n = 2 (57%)
253 n = 3 (63%)

Scheme 100: *Tributylphosphine mediated synthesis of acyl selenides 251-253*

ACYL RADICAL CYCLISATION ONTO PYRROLE-2-CARBALDEHYDE

Unexpected hindrances to the pyrazole alkyl radical cyclisations indicated some method development was likely in the study of new radical cyclisation systems. Treatment of phenyl 3-(2-formyl-1*H*-pyrrol-1-yl)propaneselenoate **251** to standard syringe pump addition of tributyltin hydride resulted in low yields of cyclisation affording 1-oxo-2,3-dihydro-1*H*-pyrrolizine-5-carbaldehyde **236** in 31% yield, in addition to the product of decarbonylation followed by radical reduction, *N*-ethyl pyrrole-2-carbaldehyde **254** (34%) in addition to unidentified side products (Scheme 101).

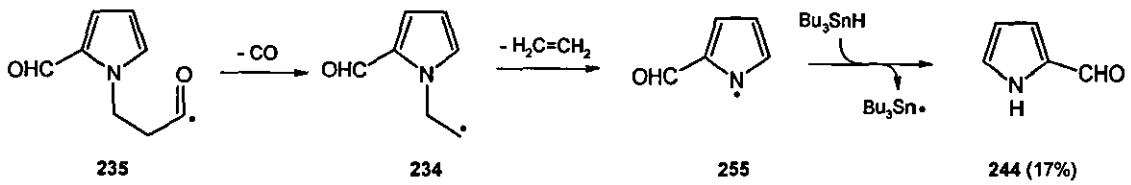


251 **235** **234** **254** (34%)

236 (31%)

Scheme 101: *5-exo Radical cyclisation onto pyrrole-2-carbaldehyde*

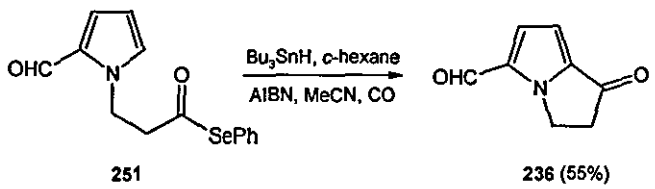
The poor recoveries and complex mixtures for this potentially facile cyclisation were initially attributed to possible interference from oxygen. In order to eliminate all oxygen from the solution, nitrogen was passed through the solution resulting in the isolation of complex mixture containing pyrrole-2-carbaldehyde **244** in 17% yield (Scheme 102). Presumably this was the product of decarbonylation and subsequent loss of ethene to yield the aryl radical **255**.



Scheme 102: *Loss of ethene from N-(ethyl)pyrrole-2-carbaldehyde radical*

It was apparent the key problems were loss of carbon monoxide to the alkyl radical **234** and reduction to *N*-ethyl pyrrole-2-carbaldehyde **254**. Performing radical reactions in acetonitrile with syringe pump addition of tributyltin hydride in cyclohexane can reduce the problems of radical reduction because the two solvents are immiscible. This is important when the relative solubility's are considered; tributyltin hydride is soluble in cyclohexane, however acetonitrile will only accommodate limited amounts of triorganotin compounds, hence $[Bu_3SnH]_{MeCN}$ is reduced but $[RCOSePh]_{MeCN}$ and $[AIBN]_{MeCN}$ remain high.

This solvent system is commonly used for separation of tributyltin hydride from the reaction mixture as a purification procedure following reaction, but not as the reaction solvent system. By retarding reduction, the two-phase solvent allows alkyl radicals such as *N*-ethyl pyrrole-2-carbaldehyde radical **234** an increased chance of carbonylation or cyclisation (long chain homologues).



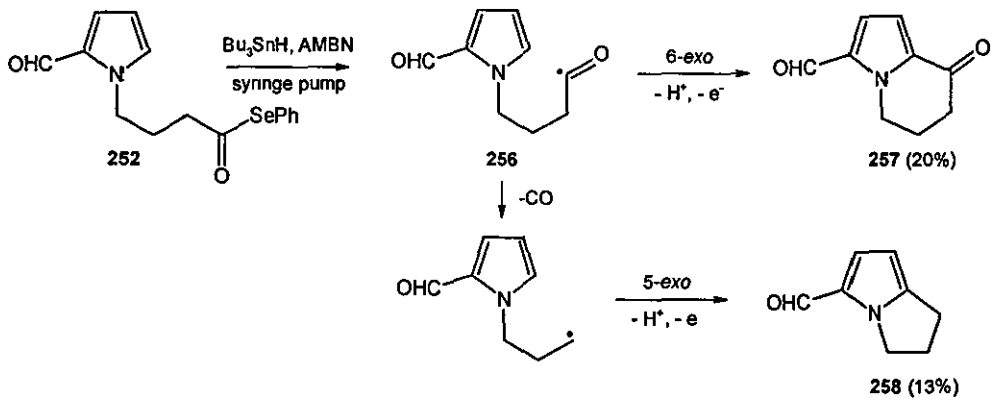
Scheme 103: *Two-phase solvent system and CO saturation to increase acyl radical cyclisation*

Additionally, saturation of the solution and reaction vessel with carbon monoxide was performed to decrease the rate of decarbonylation. Freeze/thaw evacuation techniques allowed the removal of oxygen from the reaction matrix and replacement with a carbon monoxide atmosphere. These new reaction conditions involving CO saturation and the two-phase solvent mixture resulted in

an improved yield of 1-oxo-2,3-dihydro-1*H*-pyrrolizine-5-carbaldehyde **236** (55%) (Scheme 103). It was interesting to note that in related research published during our studies, alkyl addition to CO at high CO pressure resulted in lower yield of 1-oxo-2,3-dihydro-1*H*-pyrrolizine-5-carbaldehyde **236** (30%) due to competing reduction of the radical centre.[49]

Catalytic triorganotin hydride generation was attempted using ^{t}BuOH, AIBN, 10% Bu_3SnCl, $Na(CN)BH_3$. However, the product mixture was complex and deemed unsuitable due to the problems of reduction with the borohydride source. In retrospect the reaction mixture should have been treated with a second equivalent of sodium borohydride following cyclisation to reduce all partially reduced products to obtain just the pyrrolizine diol from **236**.

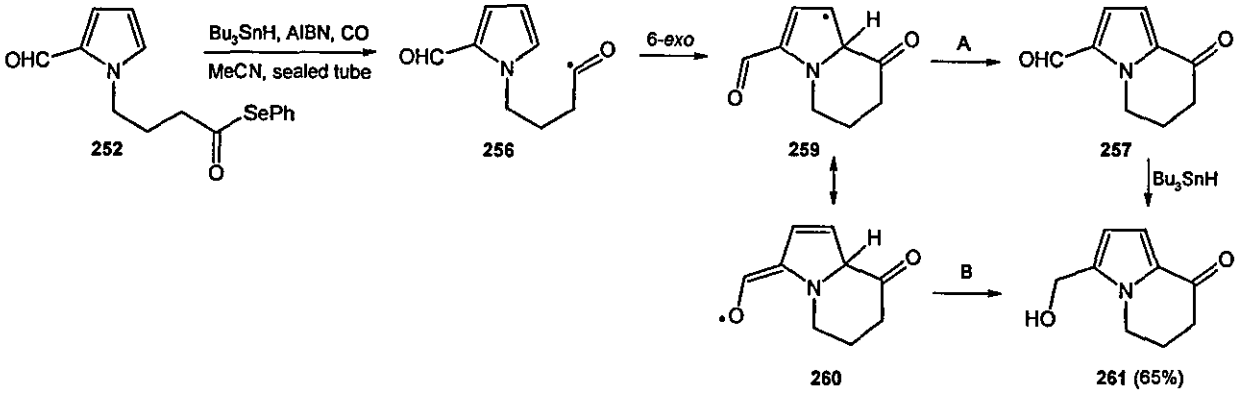
Treatment of phenyl 4-(2-formyl-1*H*-pyrrol-1-yl)butaneselenoate **252** to 'standard' tributyltin hydride/syringe pump conditions gave only low yields of the cyclised products **257** (20%) and **258** (13%) (Scheme 104) in part due to the extensive purification because the ^{1}H NMR spectra of the crude mixture had been encouraging but two chromatographic purifications were required.



Scheme 104: *Cyclisation of acyl selenides under standard tributyltin hydride conditions*

Decarbonylation was identified as the main problem in 6-*exo* acyl radical cyclisation, in addition to a number of unexplained side products in the crude ^{1}H NMR spectrum. CO saturation was again used to reduce decarbonylation and the reaction conditions were further modified to include a sealed vessel. A Schlenk tube was used because practically it is easier to saturate *via* freeze/thaw methodologies and it can maintain a sufficiently high CO pressure. However, the sealed system presented the practical limitation of a singular addition of tin hydride at the beginning, which may result in preferential reduction. In addition, the tube dimensions limited the reactions to small scale preparations, not desirable when high dilution conditions were required.

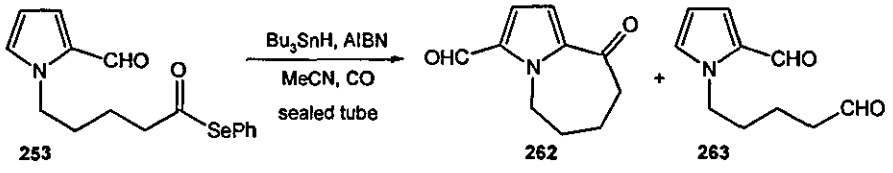
To some extent, the problems of premature radical reduction with tributyltin hydride can be overcome by two separate additions to the sealed tube. However, this exposes the reaction mixture to oxygen and requires stopping and cooling the reaction halfway through. The two-phase mixture could potentially be further adapted to use in the sealed tube systems to inhibit radical reduction. The two-phase solvent system might allow sufficiently slow crossover that the sealed tube reactions can be performed without multiple additions of tributyltin hydride.



Scheme 105: *Sealed tube reaction for 6-exo cyclisation*

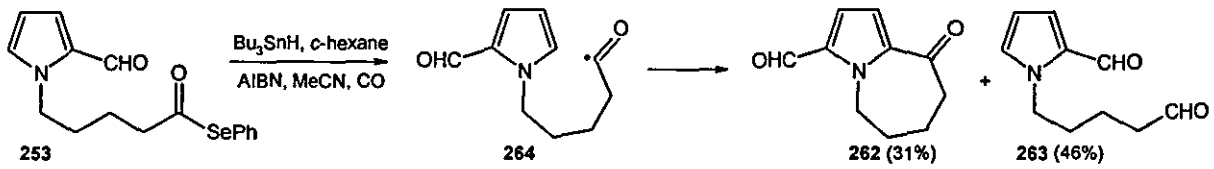
The only product isolated from the Schlenk tube reaction was the reduced cyclised material, 3-(hydroxymethyl)-5,6,7,8-tetrahydroindolizin-8-one **261** although the cyclised product **257** was observed by ^{1}H NMR spectral analysis. The reduction of the aldehyde was not expected in such high yield, although this does account for the curious product mixtures previously observed.

The slow 7-*exo* acyl radical cyclisation was expected to lead to dominating decarbonylation and reduction, hence sealed tube protocols were also attempted for this system (Scheme 106). Slow addition of tributyltin hydride was not possible using sealed tube protocols, hence portion wise addition was required. A singular addition of tributyltin hydride to acyl selenide **253** yielded the reduction product **263** almost quantitatively as observed by ^{1}H NMR spectroscopy. Addition in two portions resulted in the identification of the cyclised material **262** in approximately 20% yield (by ^{1}H NMR spectroscopy). The reduced compound **263** was again the major compound.



Scheme 106: *Sealed tube reaction under CO*

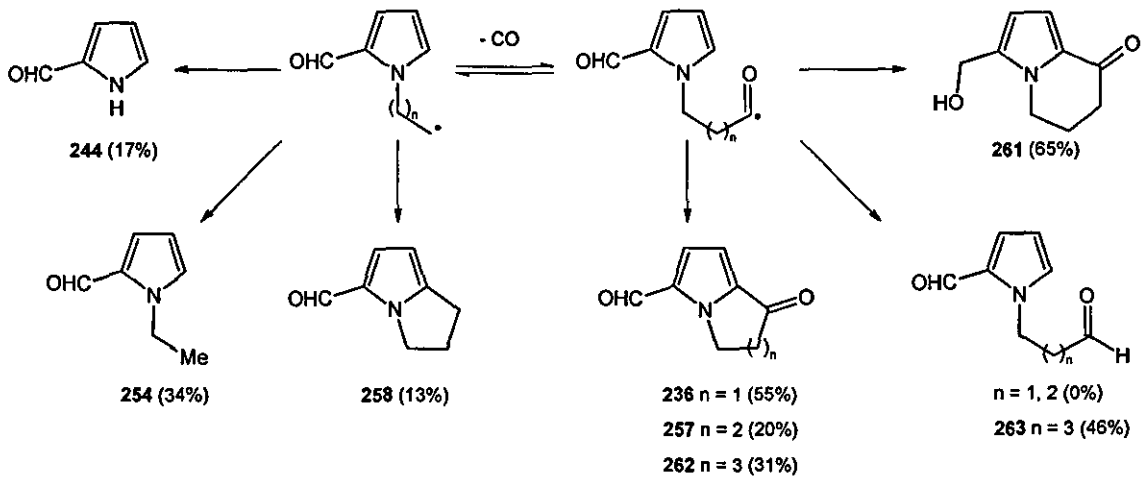
In light of the apparently slower decarbonylation, standard reaction vessels were used in order to minimise reduction of the acyl radical centres by slow addition of tributyltin hydride. Syringe pump addition of a cyclohexane solution of tributyltin hydride to an acetonitrile solution of the acyl selenide and azo initiator under CO was performed. This facilitates slow crossover of the tributyltin hydride into the acetonitrile layer, where the initiator and acyl selenide will reside preferentially, hence radical reduction was limited due to the low concentration of tributyltin hydride (Scheme 107).



Scheme 107: *Acyl radical cyclisation under CO*

The cyclisation product 9-oxo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carbaldehyde was isolated in a slightly increased yield (31%) by dual syringe pump of the trialkyltin hydride and AIBN separately. The 7-*exo* mode of cyclisation was not very favourable, and the yield could possibly be improved by slower syringe pump addition because reduction was dominating. Interestingly there was no evidence of decarbonylation and aldehyde **263** was isolated in 46% yield.

This section of work has yielded a number of interesting results as summarised in Scheme 108. Cyclisation of the acyl radical precursors was competing with decarbonylation and/or radical reduction. Decarbonylation was reduced by the use of CO saturation of the reaction vessel, this could also be used in conjunction with sealed tube methodologies to allow higher CO pressure.



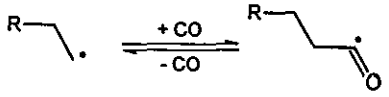
Scheme 108: *Summary of radical additions to pyrrole-2-carbaldehyde*

Reduction of acyl and alkyl radicals was inhibited by slow syringe pump addition of the tributyltin hydride and an immiscible two-phase solvent system. 6-*Exo* cyclisation proved to be the most facile mode although 5-*exo* acyl radical cyclisation proved to be high yielding also. It was apparent from various reaction mixtures that reductive cyclisation (Scheme 105) or reduction of the conjugated diketone was occurring during the reaction.

The apparently slower rate of decarbonylation of the 7-*exo* precursors was not clear, as the acyl radical reduction in the shorter chain homologues was less favourable than decarbonylation. The studies of this system have proved a useful basis for the synthesis of the pyrrolizine alkaloids discussed at the beginning of this chapter.

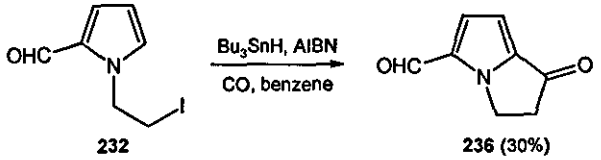
ALKYL RADICAL ADDITIONS TO CARBENES

Alkyl radicals can undergo addition to carbenes with the formation of a new radical centre and a one-carbon extension to the chain (Scheme 109). Carbon monoxide is a suitable carbene-like source and the radical addition protocol has been performed successfully in radical cyclisation chemistry yielding cyclic ketones from acyclic alkyl halides.



Scheme 109: *Carbonylation of an alkyl radical*

The published data confirms that the process is thermodynamically favourable because the rate of carbonylation of a primary radical is 6.3×10^{-5} $M^{-1}s^{-1}$ at 80 °C and the rate of decarbonylation to yield a primary alkyl radical is 2.0×10^{-5} $M^{-1}s^{-1}$ at 80 °C.[127] The possibility arises that the acyl radical species generated from acyl selenides may be possible from alkyl radicals also, thus introducing an additional functionalised centre into the cyclisation.

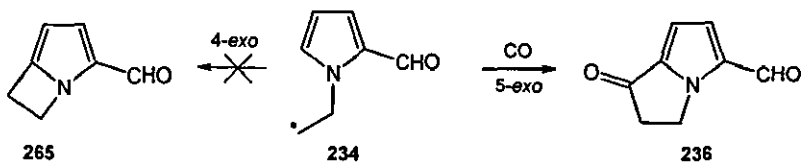


232 236 (30%)

Scheme 110: *Alkyl radical addition to CO*

During our research into acyl radical systems related cyclisations were reported featuring alkyl radical addition to carbon monoxide under high CO pressure to perform acyl radical cyclisations onto pyrroles.[49] This presents obvious practical problems of handling high CO pressure (80 atm)

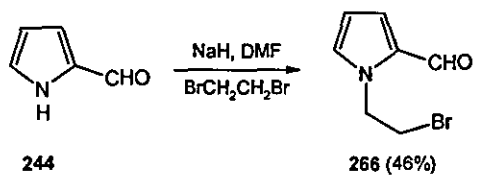
and the inability to syringe pump triorganotin hydride into reaction mixture. The results were variable; an example related to our own studies is shown in Scheme 110.



Scheme 111: *Acyl versus alkyl radical cyclisation onto pyrrole-2-carbaldehyde*

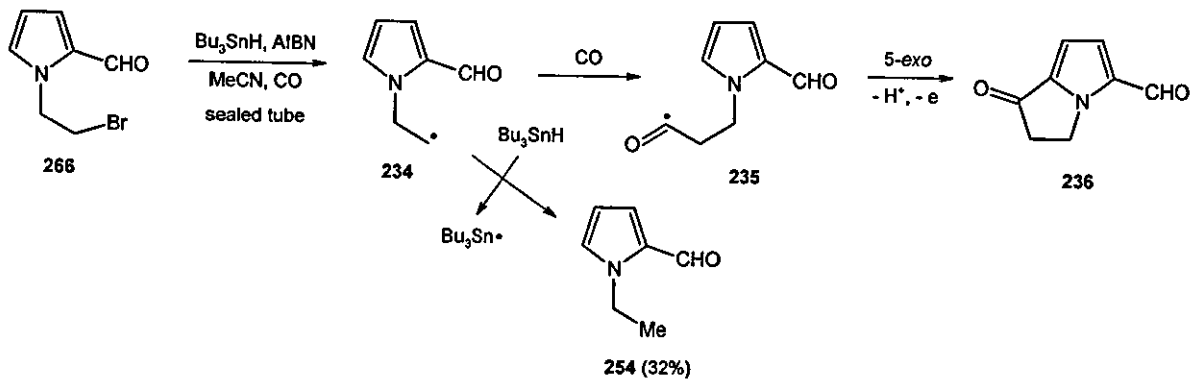
The thermodynamic data indicates that 80 atm of CO may be excessive and alkyl radical addition to CO should occur readily under moderate CO pressure, hence if the cyclisation of the acyl radical is rapid then reduced alkyl products will be limited if [Bu_3SnH] is kept low. The alkyl radical precursor chosen should be unable to undergo cyclisation as the alkyl radical, but the addition to CO would create a favoured cyclisation (Scheme 111).

The desired alkyl radical precursor for cyclisation of **266** was isolated in fair yield from alkylation of pyrrole-2-carbaldehyde **244** with 1,2-dibromoethane (Scheme 112).



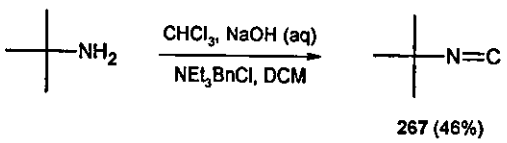
Scheme 112: *Alkylation of pyrrole-2-carbaldehyde*

The thermodynamic data appear to favour carbonylation indicating high pressures may not be required in favourable cyclisations. The bromo precursor **266**, AIBN and tributyltin hydride in acetonitrile (sealed tube) was subjected to three freeze/thaw cycles, replacing the atmosphere with CO and heated. However, the reaction shown in Scheme 113 failed with mild CO pressure and gave exclusively the reduced alkyl product. There was no evidence of cyclisation by ^1H NMR spectral analysis.



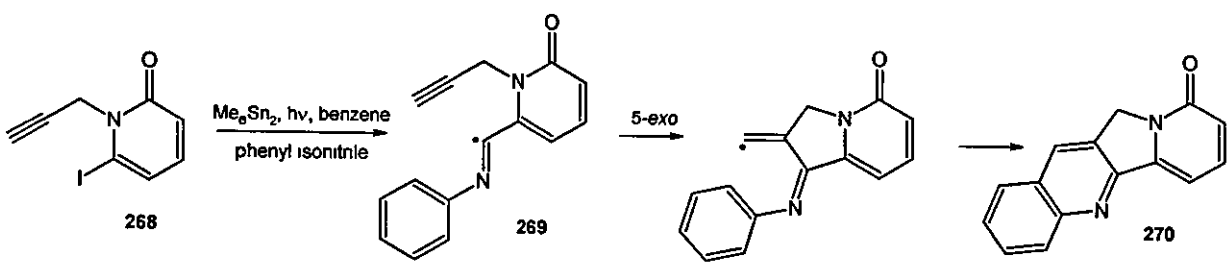
Scheme 113: *Attempted CO addition to an alkyl radical*

Alternative systems were then sought to test the methodology. In addition to CO, isonitriles were to be used. Isonitriles can be treated as a CO source because they are suitably prone to hydrolysis following inclusion into the structure and can be readily prepared from primary amines (Scheme 114).[132] The benefits of using the isonitrile in place of the CO include the greater ease of handling and accurate measurement, no requirement for sealed systems or specific equipment and the greater abundance in the reaction mixture.



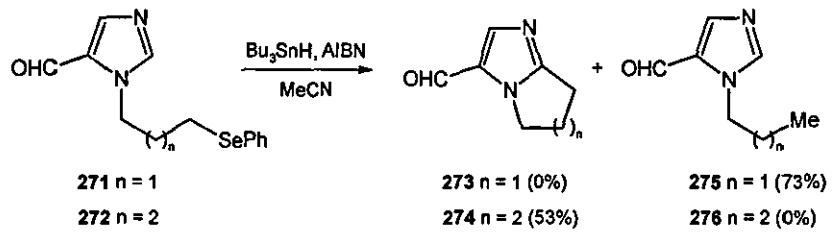
Scheme 114: *Preparation of t-butyl isonitrile*

Perhaps the most impressive use of radical addition to carbenes was that of Curran's research on camptothecin (Scheme 115).[133] Photolytic cleavage of hexamethylditin yields the trimethyltin radical which facilitates the pyridone radical from the iodo precursor **268**. Addition to phenyl isonitrile yields iminyl radical species **269** which was then able to undergo 5-*exo*, 6-*exo* cyclisation to yield the tetracyclic core of camptothecin **270** in 80% overall yield.



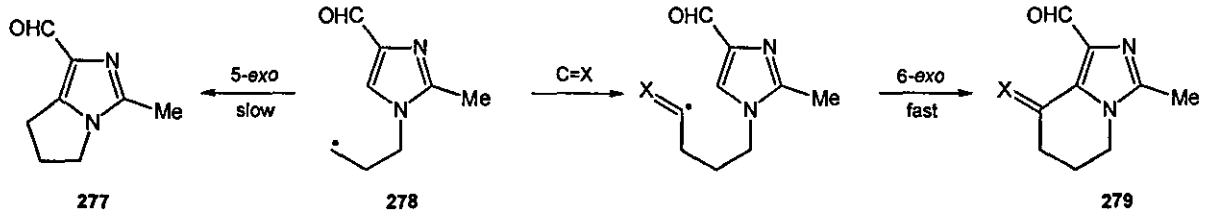
Scheme 115: *Phenyl isonitrile in the synthesis of camptothecin*

6-*exo* Alkyl radical cyclisation onto imidazoles have been performed in good yield previously in the Bowman group. 5-*exo* Cyclisations have been shown to be considerably less favourable in some cases (Scheme 116).[134] In which case, could addition to a carbene followed by 6-*exo* cyclisation occur more rapidly than 5-*exo* alkyl radical cyclisation or reduction? The yields of 5-*exo vs.* 6-*exo* cyclisation to yield imidazole **273** and **274** were encouraging because no 5-*exo* cyclisation was observed whereas 6-*exo* alkyl radical cyclisation was achieved in good yield.



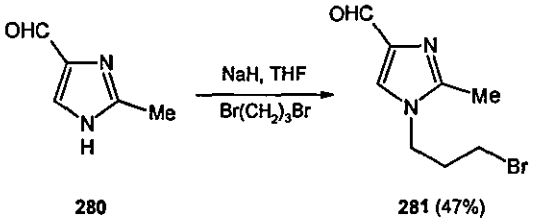
Scheme 116: *Alkyl radical 5- and 6-exo cyclisation to imidazoles*

A [5+1] cyclisation procedure should, therefore, be more feasible than in the pyrrole case and the alkyl radical addition to a carbene source was investigated using an imidazole alkyl radical system studied previously by Emma Mann (Scheme 117).



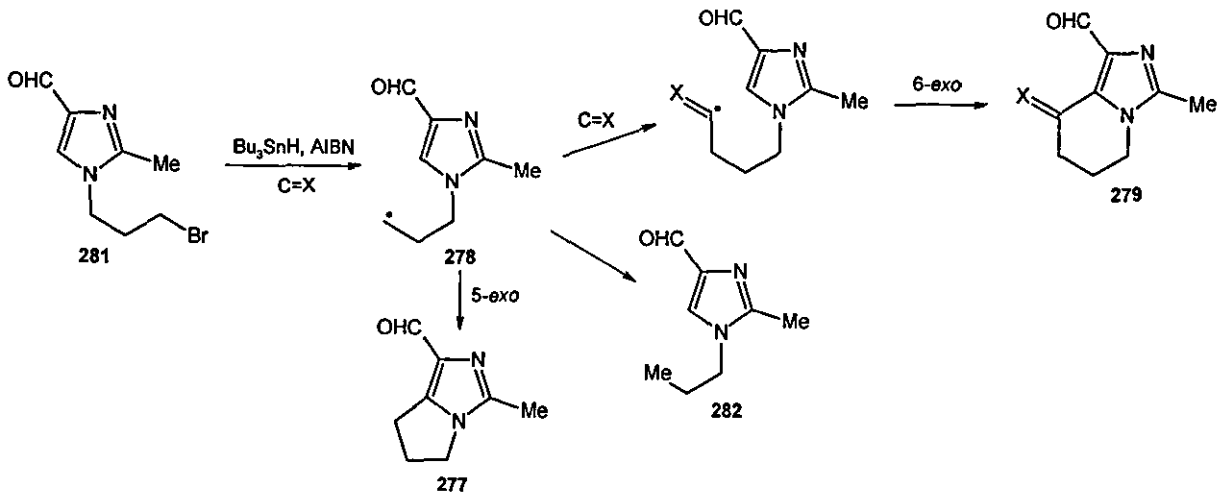
Scheme 117: *Potential [5+1] alkyl radical/carbene addition*

The 1-(3-bromopropyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **281** was prepared in a moderate 47% yield from 2-methyl-1*H*-imidazole-4-carbaldehyde **280** (Scheme 118). The alkylation of imidazoles was typically low due to the formation of dialkylated products, alkylation of the pyrazole N-2 and the regioselectivity issue.



Scheme 118: *Precursor for carbene addition protocol*

Syringe pump addition of tributyltin hydride to a CO saturated acetonitrile solution of 1-(3-bromopropyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **281** failed to give the desired product cyclised product **279** (Scheme 119, X = O). It was apparent that CO saturation of standard reaction vessels was insufficient to provide the desired acyl radical species in appreciable amounts, as two facile cyclisations have now failed. Cyclisation **277** and reduction **282** of the alkyl radical centres was noted in small amount from the crude ^{1}H NMR spectra.



Scheme 119: *Attempted [5+1] carbene addition/cyclisation*

In an attempt to introduce the isonitrile moiety **267** into the cyclisation (X = N-*t*Bu) two-phase addition of tributyltin hydride in cyclohexane to 1-(3-bromopropyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **281** and AIBMe in acetonitrile under reflux was employed in the presence of excess *t*-butyl isonitrile (Scheme 119). Unfortunately the crude ^{1}H NMR spectra indicated that the cyclised **277** and reduced alkyl products **282** were obtained, in addition to which, a terminal alkene product was identified.

Column chromatographic purification only yielded low amounts of each compound. Combination of a number of mixed fractions yielded starting material **281**, alkyl reduction **277** and the terminal alkene product were in a 7:5:6 ratio in 19% yield. The cyclised material **277** was isolated in 6% yield. The compound structures were verified by comparison of ^{1}H NMR spectra and TLC analysis of authentic samples.

The poor recovery and mixture of compounds present indicated this was unlikely to be a viable route to [5+1] cycloadditions and it was likely that the tributyltin hydride may be a contributing factor to the poor cyclisation yields. Hexamethyl ditin systems were to be investigated to

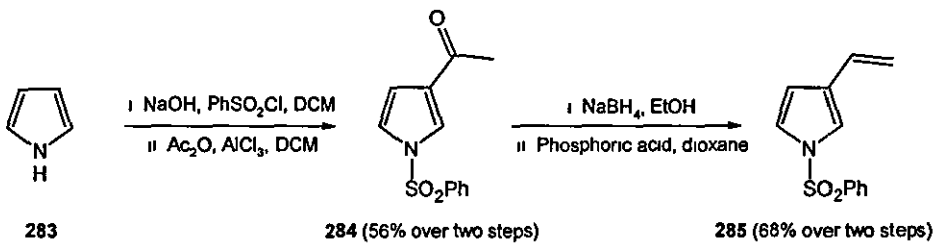
eradicate possible interference from the *Sn-H* bond although more promising activities were explored.

3.2.2 Radical Addition to Pyrrole-3-carbaldehyde

Pyrrole-3-carbaldehyde **243** was identified as the key pyrrole system for the synthesis of a variety of pyrrolizine and pyrrolizidines alkaloids. The formyl group and methyl alcohol was present in a number of the natural products and should promote cyclisation to the 2-position.

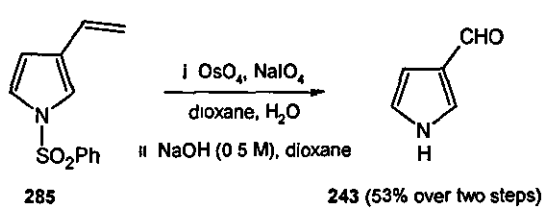
Synthesis of Acyl Selenide Precursors

There are few commercially available pyrrole systems with a single substitution at the 3-position. Fortuitously due to the importance of pyrroles in natural product synthesis and biologically active molecules there has been a large volume of research solely on the substitution of pyrroles. Initially, pyrrole-3-carbaldehyde **243** was synthesised from 3-acetyl pyrrole. The acetyl functionality could be introduced *via* selective aluminium trichloride catalysed Friedel-Crafts acylation of *N*-(phenylsulfonyl)pyrrole **293** with acetic anhydride, yielding 1-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]ethan-1-one **284** in good yield (93%) (Scheme 120).[135]



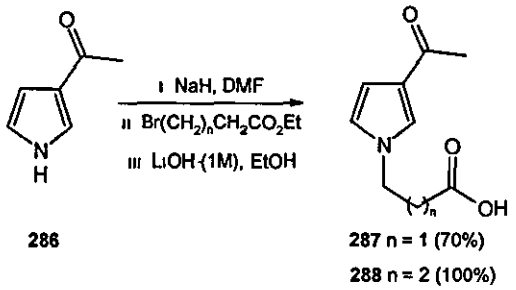
Scheme 120: *Synthesis of pyrrole-3-carbaldehyde*

The acetyl functionality was reduced and acid catalysed alcohol elimination yielded 3-vinylpyrrole in good yield, which could be oxidatively cleaved in a number of ways.[136] Johnson-Lemieux cleavage was employed during the original research and our results were equally good (Scheme 121). However, the overall scheme was very labour intensive for a simple molecule.



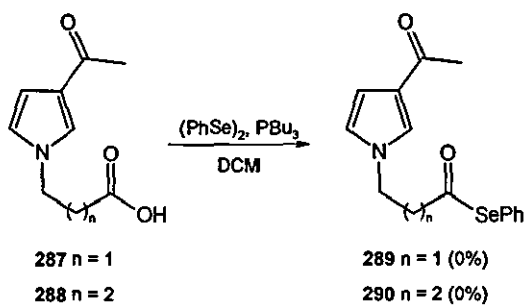
Scheme 121: *Johnson-Lemieux oxidative diol cleavage*

In order to investigate the regioselectivity of the acyl radical cyclisation we decided that the 3-acetylpyrrole systems would also be investigated because they could be prepared readily in excellent overall yield and could provide valuable information prior to the use of the more valuable pyrrole-3-carbaldehyde **243**. Basic hydrolysis of 1-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]ethan-1-one **284** yielded the required pyrrole **286** in high yield and in turn this could be converted to the necessary precursors **287** and **288** for selenation using the same alkylation procedures as previously described (Scheme 122).



Scheme 122: *Alkylation of 3-acetylpyrrole*

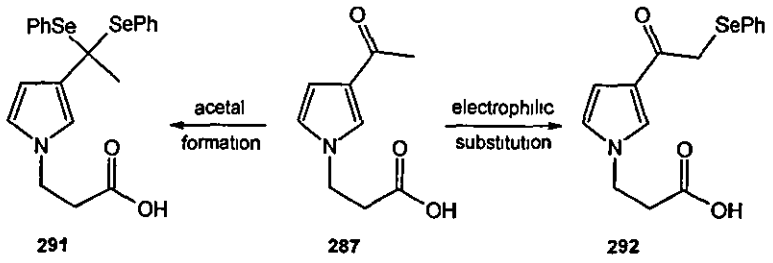
No *C*- or *O*-alkylation was observed and the desired acids **287** and **288** were isolated in good yield (70 and 100%). Unfortunately, there were significant problems encountered in the attempted conversion of the carboxylic acids **287** and **288** to the corresponding acyl selenide **289** and **290** (Scheme 123). It is known that ketones will undergo ready electrophilic substitution in the α-position with a suitable selenide source to form compounds of the type **292** shown in Scheme 124.[137] There is also some ^{1}H NMR spectral evidence implicating the formation of selenoacetals **291** from pyrrole-2-carbaldehyde derivatives because the pyrrole heterocycle is still intact although the aldehyde functionality has been consumed.



Scheme 123: *Attempted formation of 3-acetylpyrrole acyl selenides*

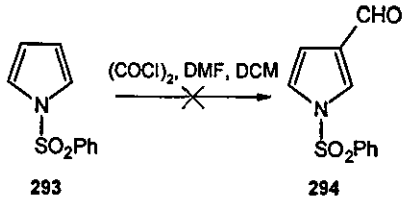
Attempts to selenate 3-(3-acetyl-1*H*-pyrrol-1-yl)propanoic acid and 4-(3-acetyl-1*H*-pyrrol-1-yl)butanoic acid have not given any of the desired product using previously successful

techniques. However, there was complete consumption of the selenating agent indicating possible preferential reaction with the methyl ketone functionality.



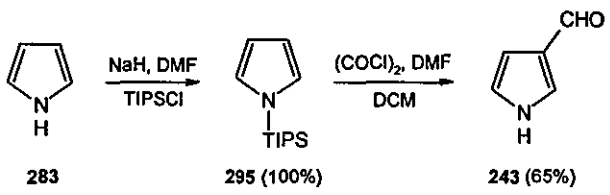
Scheme 124: *Possible formation of diselenoacetals and electrophilic substitutions*

The undesirable interference of the acetyl group was not investigated any further because the research was then concentrated more towards the 3-formyl derivatives. The directing effect of the phenyl sulfonyl group implied that Vilsmeier formylation of sulfonyl protected pyrrole **293** should yield the desired pyrrole-3-carbaldehyde **243** following hydrolysis (Scheme 125). The reaction was attempted with freshly prepared Vilsmeier reagent and was heated in DCM under reflux for 24 h without any reaction.



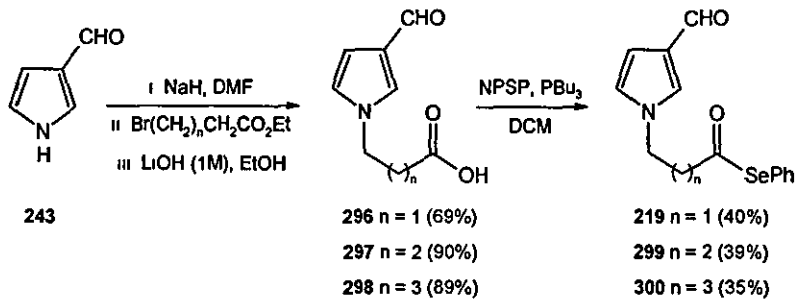
Scheme 125: *Attempted Vilsmeier formylation of N-(phenylsulfonyl)pyrrole*

Vilsmeier formylation of silyl protected pyrroles was possible because the silyl group does not influence the electronics of the ring; triisopropylsilane was found to be the ideal blocking group for the α-positions of pyrrole giving an excellent selectivity (Scheme 126).[138] The HCl generated *in situ* was also sufficient to desilylate during the course of the reaction and the unprotected pyrrole-3-carbaldehyde **243** could be isolated in good yield following chromatographic purification.



Scheme 126: *Vilsmeier formylation of triisopropylsilyl protected pyrrole*

The acyl selenide precursors were prepared in much the same manner as the pyrrole-2-carbaldehyde derivatives. Alkylation of pyrrole-3-carbaldehyde **243** and hydrolysis of the crude product was again achieved in good yield (Scheme 127).



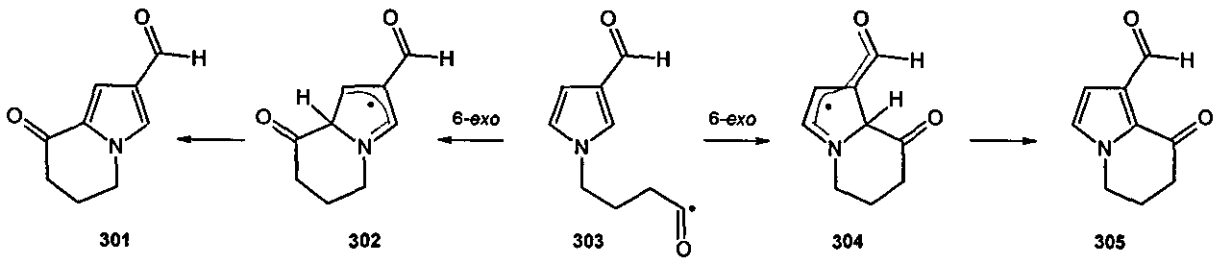
Scheme 127: *Alkylation of pyrrole-3-carbaldehyde*

The selenation were performed on carboxylic acids **296-298** using NPSP and diphenyl diselenide. Yields were lower for the pyrrole-3-carbaldehyde series although NPSP mediated selenations were consistently slightly higher affording acyl selenides **219, 299, 300** in 35-40 % yield.

ACYL RADICAL CYCLISATION ONTO PYRROLE-3-CARBALDEHYDE

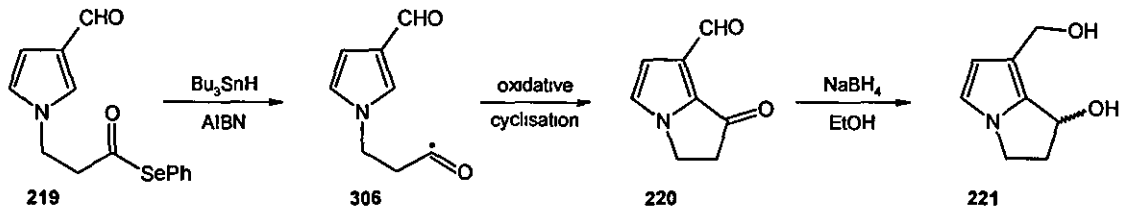
Cyclisation onto 3-substituted pyrroles leads to a versatile potential intermediate **220** in the synthesis of an array of pyrrolizine and pyrrolizidine natural products (Scheme 90). Hydroxydanaidol **221** and nordanaidone **224** were of particular interest because they were directly accessible from the cyclisation product 1-oxo-2,3-dihydro-1H-pyrrolizine-7-carbaldehyde **220** by reduction and transition metal catalysed decarbonylation respectively. Many of the related alkaloids have been made in a number of ways utilising novel ring forming chemistry,[139,140] although this was the first procedure using radical cyclisation protocols.

However, the regioselectivity of the cyclisation was not known for these systems although addition to the 2-position could be predicted with some confidence because it is the most electrophilic position accessible to the nucleophilic acyl radical (Scheme 128). The formyl group is also in conjugation with the radical following cyclisation at the 2-position and acyl radicals readily undergo conjugate addition.



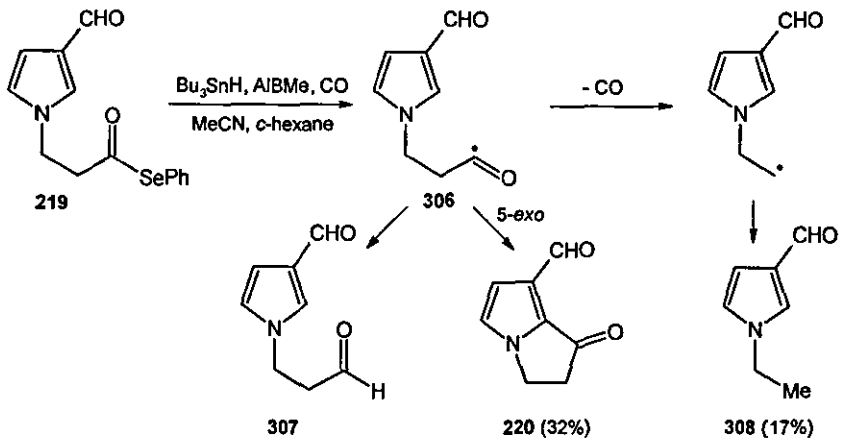
Scheme 128: *Potential pathways of acyl radical addition to pyrrole-3-carbaldehyde*

On the basis that the radical addition would proceed as expected, the synthesis of the pyrrolizine alkaloid precursor 1-oxo-2,3-dihydro-1*H*-pyrrolizine-7-carbaldehyde **220** was envisaged using 5-*exo* acyl radical addition to pyrrole-3-carbaldehyde to yield 1-oxo-2,3-dihydro-1H-pyrrolizine-7-carbaldehyde **220**. Reduction of the diketo product **220** should yield hydroxydanaidol **221** (Scheme 129).



Scheme 129: *Reduction of 1-oxo-2,3-dihydro-1H-pyrrolizine-7-carbaldehyde*

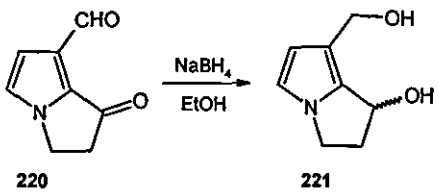
Using the methodologies developed previously for the pyrrole-2-carbaldehyde series, yields of cyclisation were reasonable (Scheme 130). The propaneselenoate **219** solution (acetonitrile) was saturated with CO and was subjected to dual syringe pump addition of AIBMe in acetonitrile and tributyltin hydride in cyclohexane to facilitate both additions slowly. The yield of cyclised material, 1-oxo-2,3-dihydro-1*H*-pyrrolizine-7-carbaldehyde **220** was 32% for isolated material although repeated chromatographic separation due to co-elution problems seriously hampered the yield. No acyl radical reduction **307** was observed although reduction of the decarbonylation product, 1-ethylpyrrole-3-carbaldehyde **308** was isolated in 17% yield.



Scheme 130: *5-exo Acyl radical cyclisation onto pyrrole-3-carbaldehyde*

Under the same conditions a separate reaction was performed and an impure fraction appeared to contain reduced cyclised material by ^{1}H NMR spectral analysis. The compound could not be purified, but the spectral data implied that the aldehyde functionality was still intact and the chemical shifts and splitting pattern of the pyrrole and aliphatic ring protons suggested reduction of the pyrrolizidone ring had occurred. Assuming this was the correct structure it was isolated in 17% yield (impure). Investigation of several ^{1}H NMR spectra from previous reactions, peaks could be identified corresponding to ketone and aldehyde reduction.

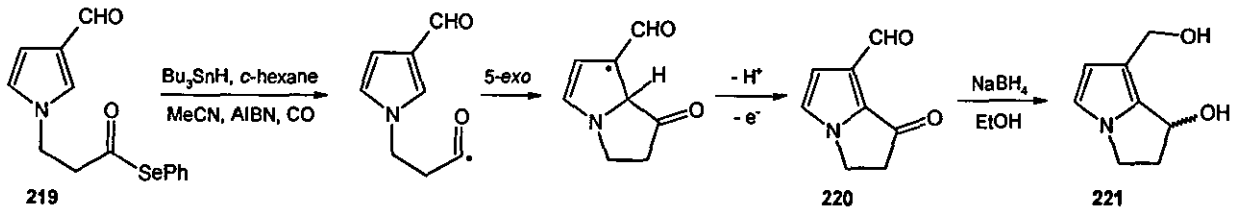
Isolation of the fully reduced hydroxydanaidol **221** was problematic though (Scheme 131); initially the sodium borohydride reduction itself was considered a problem and L-selectride was used at - 78°C in THF although this also failed to yield any product after several attempts. The main problem identified was the rapid decomposition and oligomerisation of the compound on exposure to acid during the reaction quench, presumably *via* the same mechanism as the acid catalysed construction of porphyrins.



Scheme 131: *Attempted synthesis of (±)-hydroxydanaidol*

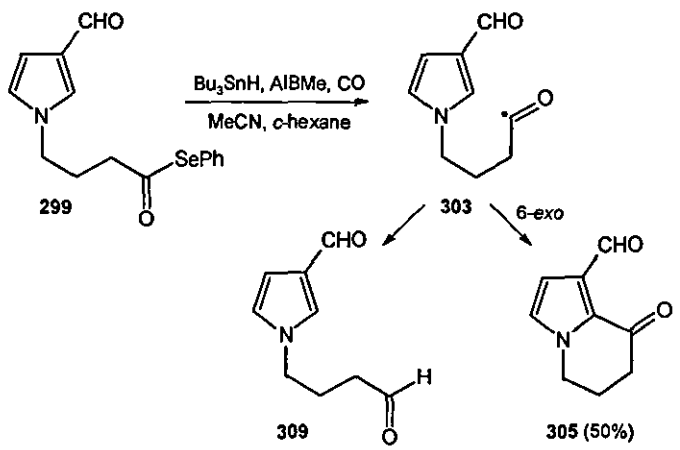
Treatment of the crude mixture following cyclisation was deemed the best method for isolation because ^{1}H NMR spectra of the crude cyclisation mixture had indicated that some reduction had already occurred presumably by hydrostannylation or reductive cyclisation. The reaction was

performed as before, and the crude reaction mixture was evaporated to dryness and treated with sodium borohydride in ethanol to yield hydroxydanaidol **221** in 17% yield (by ^{1}H NMR spectral analysis) over the two steps (Scheme 132).



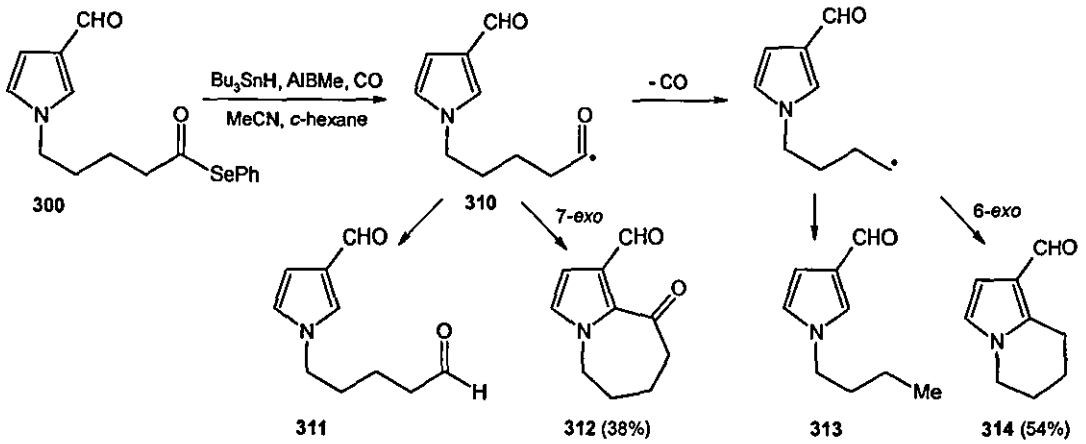
Scheme 132: *Synthesis of hydroxydanaidol*

Cyclisation of phenyl 4-(3-formyl-1*H*-pyrrol-1-yl)butaneselenoate **299** was achieved in good yield (Scheme 133). Phenyl 4-(3-formyl-1*H*-pyrrol-1-yl)butaneselenoate **299** solution (acetonitrile) was saturated with CO and subjected to dual syringe pump addition of AIBMe in acetonitrile and tributyltin hydride in cyclohexane to facilitate both additions slowly. The only compound isolated from the reaction under these conditions was the desired cyclisation to yield 8-oxo-5,6,7,8-tetrahydroindolizine-1-carbaldehyde **305** in 50% yield.



Scheme 133: *6-exo Cyclisation onto pyrrole-3-carbaldehyde*

The phenyl 5-(3-formyl-1*H*-pyrrol-1-yl)pentaneselenoate **300** solution (acetonitrile) was saturated with CO and was subjected to dual syringe pump addition of AIBMe in acetonitrile and tributyltin hydride in cyclohexane to facilitate both additions slowly. The potentially slow 7-*exo* cyclisation onto pyrrole-3-carbaldehyde was performed affording **312** in 38% yield in addition to the decarbonylated cyclised material **314** also in good yield (54%). A trace of starting material was also recovered indicating a very favourable system for cyclisation of both alkyl and acyl radicals because neither reduced products **311** or **313** were recovered.

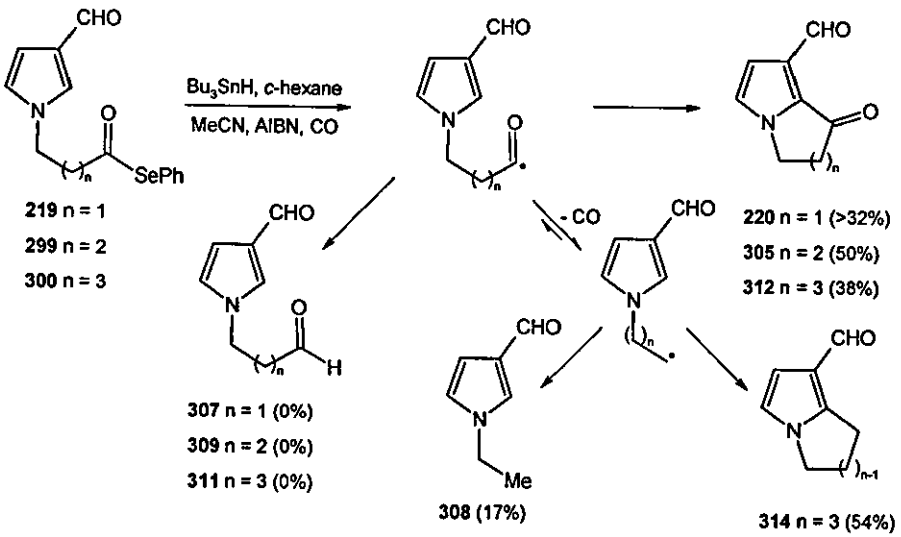


Scheme 134: *7-exo Acyl radical cyclisation onto pyrrole-3-carbaldehyde*

The CO saturation was required for this 7-*exo* acyl radical cyclisation. The analogous pyrrole-2-carbaldehyde system indicated a slower rate of decarbonylation for the 7-*exo* homologues.

As discussed previously, substitution in the 3-position of pyrrole presents a regioselectivity issue as the acyl radical can add at the 2- or 5-position (Scheme 128). Although spectral data indicated cyclisations had occurred exclusively at the 2-position, the regiochemistry was confirmed by X-ray crystallographic structure determination of the 6- and 7-*exo* cyclisation products (appendix A).

The key problem for acyl radicals under standard conditions was that of decarbonylation not reduction. Unfortunately optimisation of one set of conditions affects the other. For example, decarbonylation dominates slow 7-*exo* cyclisations. A sealed tube was utilised to maintain high CO pressure. The inability to add tributyltin hydride slowly to sealed tubes results in reduction of the acyl radical. A standard reaction vessel was thus used with two-phase solution to prevent reduction but again decarbonylation was prevalent.



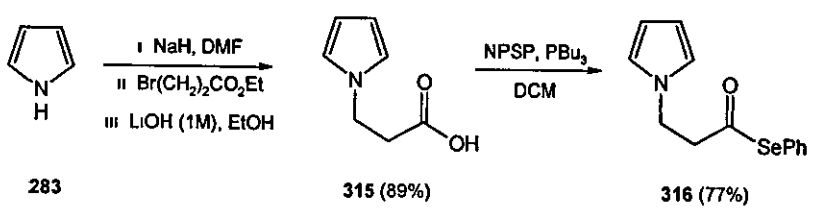
Scheme 135: *Summary of acyl radical addition to pyrrole-3-carbaldehyde*

The summary of acyl cyclisation onto pyrrrole-3-carbaldehyde (Scheme 135) shows that no reduced acyl radical product was isolated from any reaction. Reduction of the alkyl radical centre was only observed when cyclisation was very strained under the current conditions.

3.2.3 Acyl Radical Addition to Pyrrole

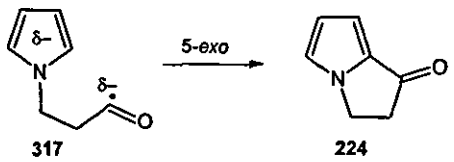
The selection of pyrrolizine and pyrrolizidine alkaloids presented in the previous section require functionalisation of the pyrrole nucleus at the 3-position prior to cyclisation. The use of an aldehyde enhances cyclisation and provides a versatile functionality for further manipulation. Nordanaidone **224** is a pyrrolizine natural product accessible by acyl radical addition to an unsubstituted pyrrole.

Nordanaidone **224** and other pyrrolizine alkaloids are important in the sexual selection of male moths and butterflies. The alkaloids are sequestered from plant material and excretion during courtship enhances the larvae survival chance because the compounds are both bitter and toxic. This protection mechanism encourages courtship with a suitable male. This natural product was synthesised using a radical cyclisation approach during the course of our investigation.[40]



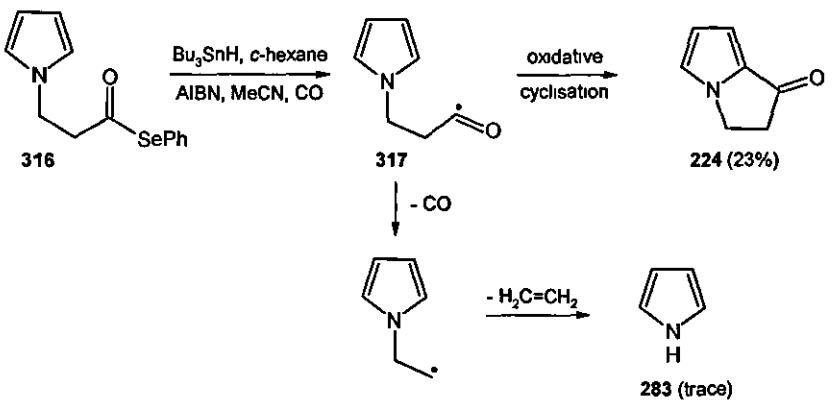
Scheme 136: *Selenation of N-substituted pyrrole derivative*

The alkylation of pyrrole was again highly successful and it was encouraging to note the increased yield of selenation in the absence of any other acyl functionalities (Scheme 136). The yields for selenation in the absence of an activated aldehyde were improved, which supports the suggested formation of diselenoacetals during the selenation reaction.



Scheme 137: *Unfavourable acyl radical attack*

Under 'normal' conditions, the nucleophilic acyl radical was not expected to readily undergo cyclisation onto pyrrole readily in the absence of an activating or leaving group as the pyrrole is too electron rich (Scheme 137). The procedure reported in the literature involving alkyl radical addition to CO failed to give any desired cyclised product **224** and reduction of the alkyl radical product dominated due to the high concentration of tributyltin hydride present. In order to facilitate cyclisation, a methyl sulfonyl group was introduced for homolytic displacement. The yield of cyclisation **224** was then 81%.



Scheme 138: *Acyl radical cyclisation onto pyrrole*

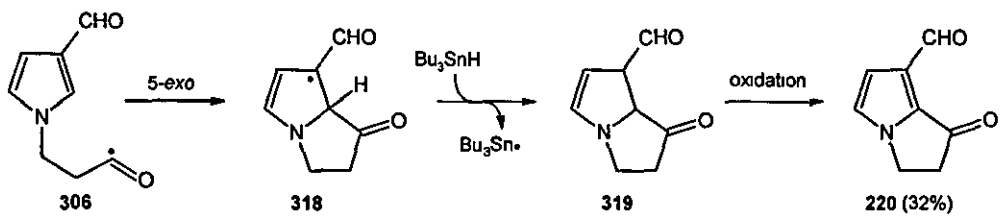
Surprisingly, 5-*exo* acyl radical cyclisation did occur onto the 1-substituted pyrrole **317** albeit in low yield (23%), affording nordanaidone (Scheme 138). The yield of cyclisation was rather low, but the radical annulation protocol presents a concise and selective synthesis of nordanaidone. Yields of cyclisation might be improved if a radical leaving group were employed although this has since been carried out.[40]

3.3 Oxidative Rearomatisation

The mechanism of oxidative rearomatisation following radical addition to an aromatic species in the presence of tributyltin hydride/AIBN is still unclear although several factors are essential for efficient cyclisation.[141] The reactions require a slight excess of both initiator and tributyltin hydride, implicating the radical chain is either very short or the reagents are consumed by other pathways.

3.3.1 Homolytic Aromatic Substitution

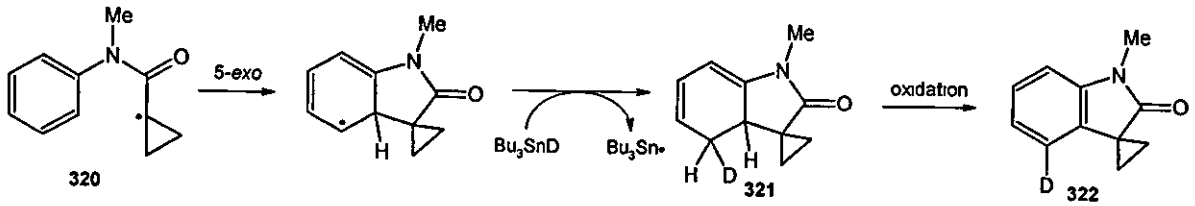
Various proposed mechanisms have been put forward for the curious oxidative rearomatisation that accompanies many radical additions to aromatic rings. Reductive cyclisation followed by oxidation *in situ* or during workup is considered by many to be unlikely. It is apparent that oxygen was not playing a leading role in the oxidation of reduced cyclised material **319** because the reaction vessels were deoxygenated (Scheme 139). Although traces of oxygen do remain after passing nitrogen through the solution, it is unlikely the amount present would be sufficient to give complete rearomatisation.[142]



Scheme 139: *Oxidation of reductive cyclisation products*

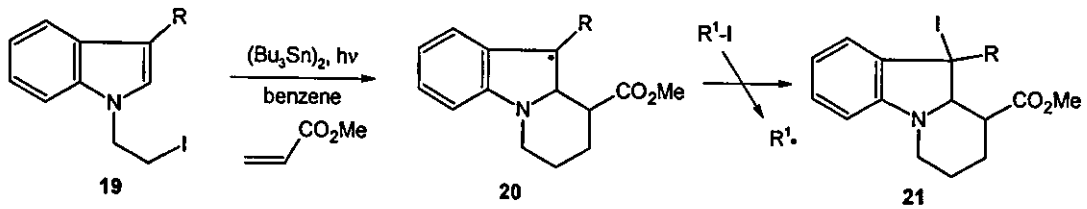
Disproportionation of **318** can be ruled out as the key mechanism as many cyclisation yields are greater than 50% and although oxidation of **319** during workup is feasible, many of the dihydro intermediates are relatively air-stable.

It was reported that in order to study the possible intermediacy of dihydro derivatives such as **219** attempted deuterium labelling was employed by cyclisation of radical **320** using tributyltin deuteride/AIBN propagation (Scheme 140).[141] Careful analysis of the reaction mixture failed to identify any deuterated aryl derivative **322** by ^{2}H NMR spectroscopy. Theoretically a statistical mixture of deuterated **322** and non-deuterated material should exist if oxidation proceeds *via* this pathway (assuming 6-*exo* and not 6-*endo* cyclisation occurs); the absence of any deuterated material indicates an alternative rearomatisation pathway.



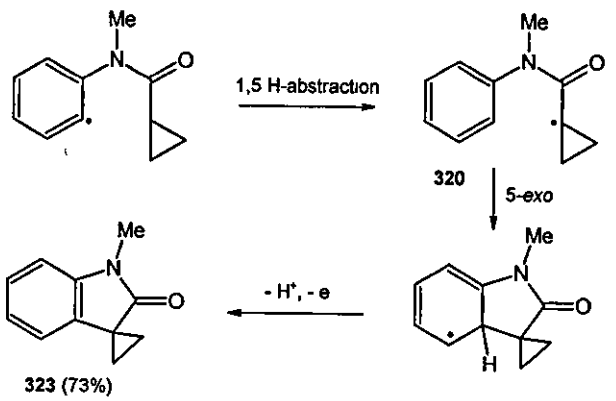
Scheme 140: *Deuterium inclusion from tributyltin deuteride*

The next most obvious recourse was the study of atom transfer pathways. Atom transfer/elimination mechanisms as shown in Scheme 141[22] would require only catalytic amounts of tributyltin hydride and substoichometric initiator amounts, however experimental data from the Bowman group amongst others contradicts this suggestion. The transfer is also thermodynamically unfavourable as this mechanism would require transfer of iodide onto a stable benzylic radical yielding a less stable primary radical.



Scheme 141: *atom transfer in oxidative rearomatisation*

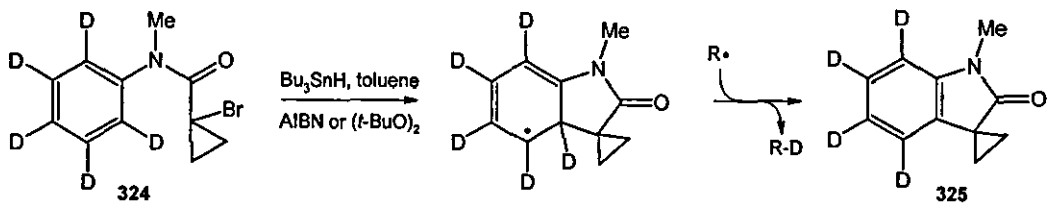
A radical anion intermediate was suggested as the key intermediate in a *pseudo* $S_{RN}1$ mechanism (Scheme 14). This mechanism has long been accepted by many, although the absence of detectable hydrogen gas has ruled out tributyltin hydride as the base.[134] The enhancement in reaction yield in the presence of DABCO[143] supports the *pseudo* $S_{RN}1$ mechanism, although experimental issues are in contradiction with the proposal.



Scheme 142: *Liberation of sub-stoichometric amounts of nitrogen*

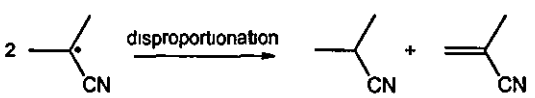
Following the homolytic aromatic substitution of cyclopropyl radical **320** (Scheme 142) incomplete homolytic decomposition of AIBN was noted although the cyclisation was successful yielding indoline **323** in 73% yield. Although only 0.3 equivalents of N_2 was detected, 1.2 equivalents of AIBN were used in the cyclisation, therefore, 0.9 equivalents of the azo initiator have been otherwise consumed.

Further studies were reported within the research and extension of the earlier deuteration experiments led to the preparation of pentadeuterobenzene derivative **324** on the premise that the 'culprit' performing the oxidation may be identified by ^2H NMR spectroscopy. The isolation of deuterated initiator fragments shown in Scheme 143 indicate one of the pathways by which oxidation was occurring, but not the only one because the yields are too low. Cyclisation using tributyltin hydride and AIBN lead to the formation of deuterated AIBN fragments (Me_2CDCN) identified by GCMS and ^2H NMR spectroscopy in 23% yield. When (t-BuO)$_2$ initiation was used, both *tert*-BuOD and tributyltin deuteride were isolated implicating both initiator and propagator as the 'oxidant'. [141]



Scheme 143: *Isolation of deuterated initiator fragments*

The necessity for deuterated substrates allows selective NMR spectral identification and eliminates confusion over the amount attributed to the disproportionation reaction shown in Scheme 144.[144] Thus the isolation of the deuterated initiator fragments clearly implies their role in rearomatisation.

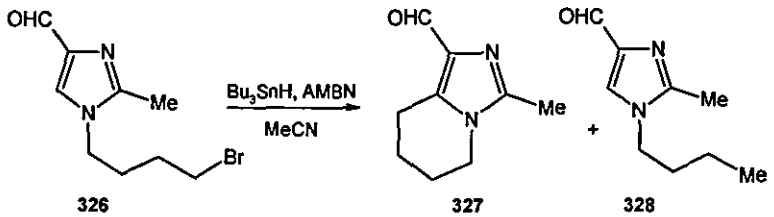


Scheme 144: *Disproportionation of initiator fragments*

It is therefore apparent that the oxidative rearomatisation directly involves the initiator fragments and possibly the triorganotin species in some way, although these may not be the sole route of aromatisation and it is apparent that several mechanisms may be simultaneously in operation.

3.3.2 The Role of AIBME

The overall mechanism must involve either derivatives of the initiator (AIBN) or propagator (Bu_3SnH) or a combination of both. Curran proposed that the initiator might play a key role in the rearomatisation of the aryl moiety, hence the requirement for stoichometric amounts of initiator.[145] Studies within the Bowman group have verified a dependence of radical cyclisation (Scheme 145) success rate on the amount of the azo initiator introduced in the presence of a given amount and concentration of tributyltin hydride (Table 3).



326 327 328

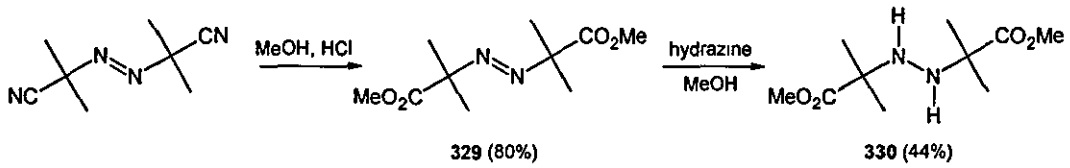
Scheme 145: *Alkyl radical cyclisation performed under variable initiator amounts*

The role of the initiator would evidently require reduction of the initiator in some way in order to facilitate the oxidative rearomatisation. It would be difficult to determine the role of AIBN directly because the absence of suitable spectroscopic markers and the poor stability towards mass spectral analysis meant that the exact species present would be difficult to ascertain. However, AIBMe can be derived from AIBN and has a similar decomposition profile (AIBN $t_{½}$ 10 h at 65 °C; AIBMe $t_{½}$ 10 h at 66 °C). The reduced compounds are potentially more stable though (early attempts to prepare reduced AMBN and AIBN by Emma Mann[146] indicated poor stability) and are spectroscopically identifiable, hence identification of any reduced compounds should be feasible.

AMBN	Cyclised **327** (%)	Reduced **328** (%)	Starting material **326** (%)
Excess	88	0	12
1 equiv.	92	0	0
0.75 equiv.	25	0	53
0.5 equiv.	43	0	53
0.25 equiv.	8	0	92
trace	0	0	74

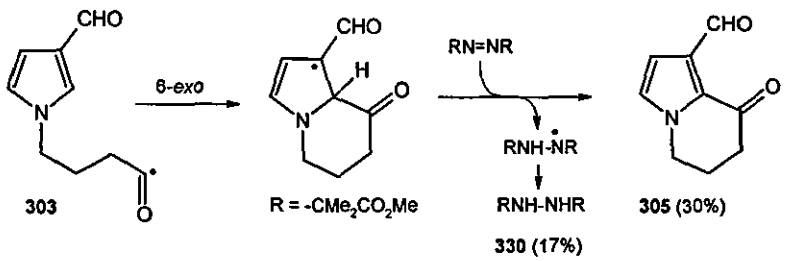
Table 3: *Dependence of cyclisation success on initiator amount*

The azo initiator AIBMe was thus derived from AIBN by treatment with hydrogen chloride in methanol (Scheme 146).[147] The reduction of the azo group of AIBMe could be accomplished using hydrazine in the presence of oxygen in order to provide confirmation of the reduced compound. The diimide formed from the reaction of hydrazine and oxygen was the active oxidant and its formation was greatly enhanced by the presence of copper (I) salts. This has been suggested to aid the formation of the *cis*-diimide and possibly to catalyse the synchronous delivery of two hydrogens.[148] The data for the reduced compound was sufficiently distinctive to allow identification by ^{1}H NMR spectroscopy. Unfortunately the compound was not stable to EI or FAB mass spectral analysis and so identification *via* this technique was not possible.



Scheme 146: *Synthesis of AIBMe and reduction to the hydrazine derivative*

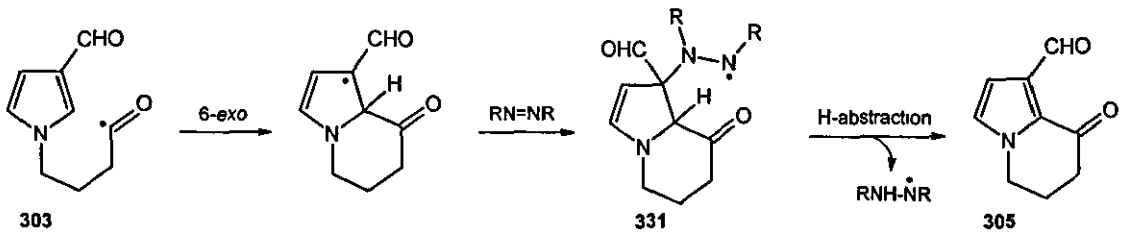
The freshly prepared AIBMe was used in a number of radical cyclisations and attempts were made to isolate any reduced hydrazine derivatives corresponding to **330.** The decomposition profile of AIBMe is similar to that of AIBN and should behave similarly in the reaction. Scheme 147 shows the isolation of the reduced material from an oxidative cyclisation in low yield (17%).



Scheme 147: *Isolation of reduced AIBMe from oxidative cyclisation*

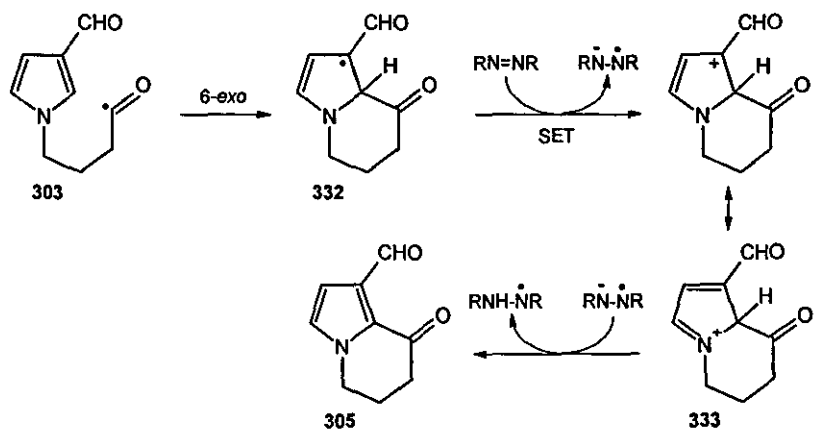
The azo initiator may abstract the hydrogen directly from the π-radical intermediate to facilitate rearomatisation as depicted by Scheme 147. Alternatively the π-radical intermediate may undergo radical addition to the intact azo initiator[149] followed by 1,4 H-abstraction and elimination of the hydrazyl radical (Scheme 148). A hydrazyl radical would result from either mechanism and will be stabilised by the presence of the adjacent nitrogen. The hydrazyl radical may then be responsible for a second direct *H*-abstraction from another π-radical intermediate or from tributyltin hydride.

This mechanism may account for the fact that although many of the reactions require a slight excess equivalence of AIBN, the reactions are finished before the theoretical decomposition of AIBN was complete. It also accounts for the dependence of reaction success on the amount of initiator and propagator. The hydrazyl radical was formed as the reaction proceeds and this in turn can liberate a stannyl radical, hence the chain rate is independent of the rate of AIBN decomposition following initiation but dependent on the concentration of tributyltin hydride and AIBN.



Scheme 148: *Possible radical addition/elimination of the azo initiator*

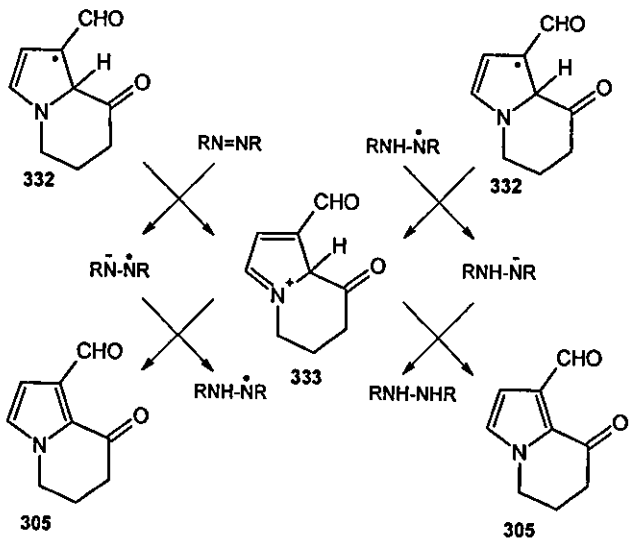
The mechanism may not require direct intervention of the initiator immediately, because it is possible that a single electron transfer occurs following cyclisation between the π-radical intermediate and the initiator (Scheme 149). This constitutes the most likely mechanism given all the data. The formation of this cation is stabilised by the nitrogen lone pair although proton loss resulting in rearomatisation is likely to be rapid. The presence of a suitable base such as DABCO would thus enhance the rate of rearomatisation as has been noted in other studies. The ability to perform SET in this and many other cases will be enhanced by the stabilisation from nitrogen.



Scheme 149: *Proposed single electron transfer during rearomatisation*

The fate of the hydrazyl radical then depends on many variables. It is weakly electrophilic in nature, therefore, it is quite plausible that this species is then the acceptor of a second SET from

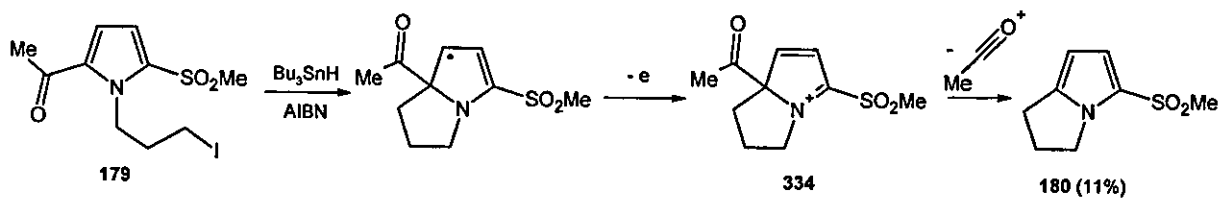
the π-radical **332** due to the high electron affinity. Hence the fully reduced hydrazine derivative **330** might be yielded following the rearomatisation of two equivalents of π-radical **332** (Scheme 150).



Scheme 150: *Consumption of hydrazyl radical species from initiator*

Although unlikely, this mechanism may also be related to that of the curious alkene product observed in the attempted cyclisation of pyrazoles and imidazoles. The formation of the alkene products has already been discussed in Chapter 2, although the mechanism proposed could not provide a good explanation.

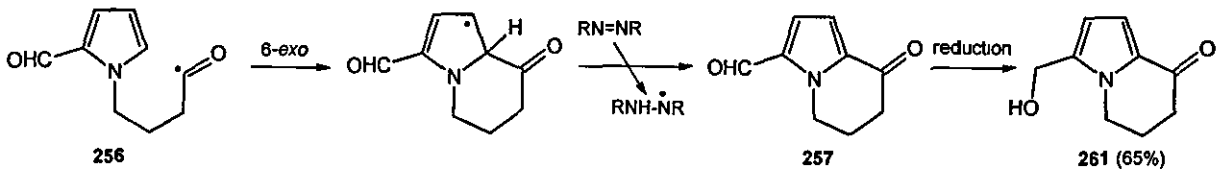
This mechanism can also provide a rational explanation for the loss of acyl groups discussed previously because the acylium cation would be a more stable leaving than the acyl radical (Scheme 151). Many of the leaving groups utilised in radical cyclisation chemistry have a low ionisation potential and would thus favour leaving as a cationic species.



Scheme 151: *Loss of an acylium cation during rearomatisation*

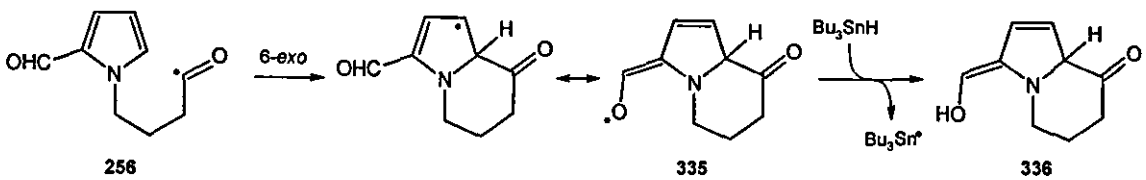
Due to the high yield of 6-*exo* cyclisation of acyl radical **256** onto pyrrole-2-carbaldehyde the same procedure was to be performed on these systems to determine the importance of the

initiator in the attempt to isolate reduced AIBMe **330** from the intermediate hydrazyl radical (Scheme 152).



Scheme 152: *Reductive cyclisation onto pyrrole-2-carbaldehyde*

Acidic workup to separate the hydrazine derivative from the reaction mixture was performed. Interestingly following extraction of the neutralised aqueous fraction the product of reductive cyclisation **261** (10%) was isolated and not the hydrazine derivative **330** (Scheme 153). Although there was also cyclised material **261** and **257** (20% by ^{1}H NMR spectral analysis) in the original organic layer, the presence of any pyrrole from the acidic extraction was perplexing. This raises a number of questions relating to the radical cyclisation.

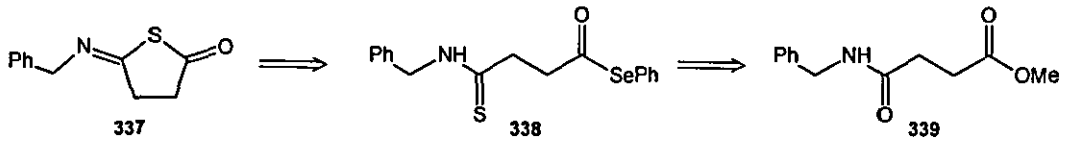


Scheme 153: *Reductive 6-exo cyclisation*

It must be concluded that the cyclisation appears to be reductive because the pyrrole compound is not basic but the cyclised compound **261** was extracted into acid following the reaction, possibly as the tautomer **336**. The selective reduction of the aldehyde in the presence of a strained ketone also implies a tautomerism of **336** occurred later in the workup rather than direct reduction with tributyltin hydride as reduced compounds identified previously occurred on the cyclic ketone. Disproportionation can again be ruled out, as in other cases, because the yield of reduced cyclised material is too high in previous cases relative to the expected cyclised material **257**.

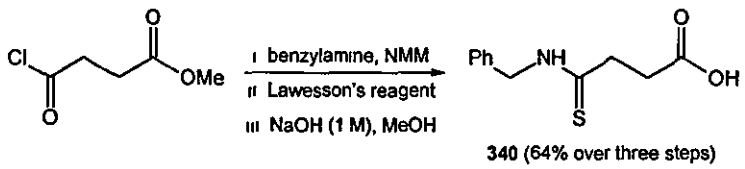
3.3.3 Oxidation of Thioamides

In many cases radical addition to thioamides results in oxidation. In order to ascertain whether the mechanisms are related and to establish if the reaction may be more suitable to a study into the mechanism a synthetic scheme as illustrated in Scheme 154 was undertaken. The study would also show if acyl radicals could undergo addition to thioamides.



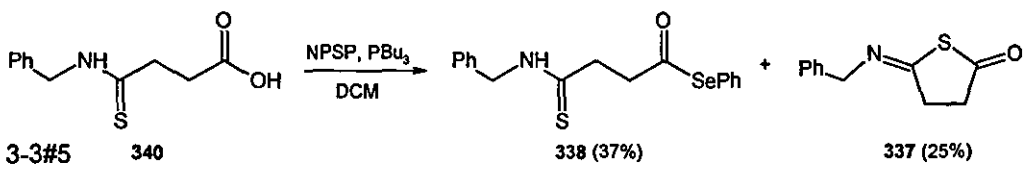
Scheme 154: *Proposed synthesis of thioamides suitable for acyl radical cyclisation*

The precursors were readily available from commercial sources. The amide coupling, thionation and hydrolysis furnished the required compound **340** under standard conditions in good yield (Scheme 155). The thionation was also readily achieved in high yield by the treatment of the amide with a slight excess of Lawesson's reagent in refluxing toluene. The slightly diminished yield is likely to be the result of thionation of the ester carbonyl because all starting material was consumed and the second compound present by TLC was not isolated following basic hydrolysis.



Scheme 155: *Synthesis of thioamide with Lawesson's reagent*

Selenation of the carboxylic acid **340** in the presence of the thioamide proved problematic though because the acyl selenide was prone to intramolecular attack from sulfur even at low temperature (Scheme 156). The phenylselenyl group is not a good leaving group in nucleophilic susbtitutions. However, the nucleophilicity and alignment of the thioamide is such that although isolation by column chromatography of the acyl selenide was feasible, the speed of the reaction was such that these precursors were not suitable for the proposed exploration of acyl radical addition and oxidation.

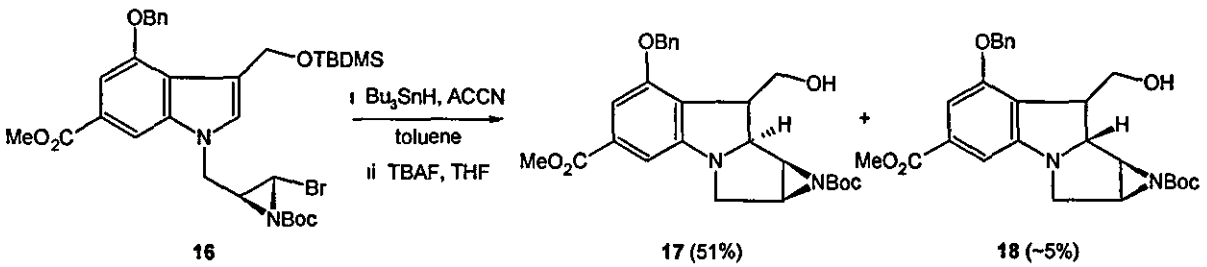


Scheme 156: *Attempted isolation of acyl selenide*

Unfortunately, the study of acyl radical addition to thioamides was not possible due to the premature cyclisation depicted in Scheme 156.

3.4 TOWARDS MITOMYCIN

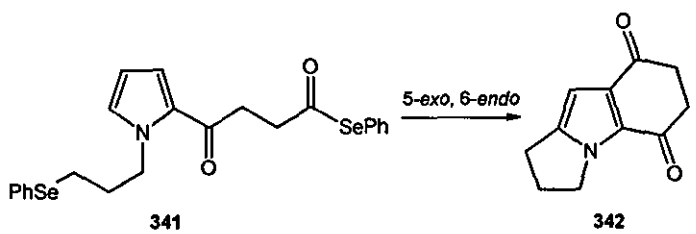
We considered whether methodologies could be developed towards a tandem cyclisation approach to the core structure of mitomycin A and C the indole analogues. Although a number of formal syntheses of mitomycin have been performed, few have included the use of free radical chemistry and none provide the construct from pyrrole. A tandem cyclisation approach onto pyrrole may be able to provide a suitable synthetic route from simple starting materials. Cyclisations onto indole commonly occur with reduction because the indoline ring is less susceptible to oxidation due to the reduced aromaticity of the second ring. Approaches using indole derivatives are numerous because the systems lend themselves to radical annulation procedures. An example of the cyclisation approaches is shown in Scheme 157.[20] Alternatively tandem cyclisation methodologies can be applied to the synthesis of the 5,3-fused ring system *via* intramolecular carbene addition to unsaturated systems.[150]



16 17 (51%) 18 (~5%)

Scheme 157: *Radical cyclisations in the synthesis of mitomycin skeletons.*

In order to test the validity of the proposed scheme, basic tricyclic systems were to be constructed based on the mitomycin and mitocene A and C skeleton (Scheme 158). Cyclisation of the aziridinyl radical or a derivative would ideally be the objective if the tandem cyclisation protocol proved worthy; this would doubtless require the development of new procedures because there is only limited research on aziridinyl radicals.[151]



341 342

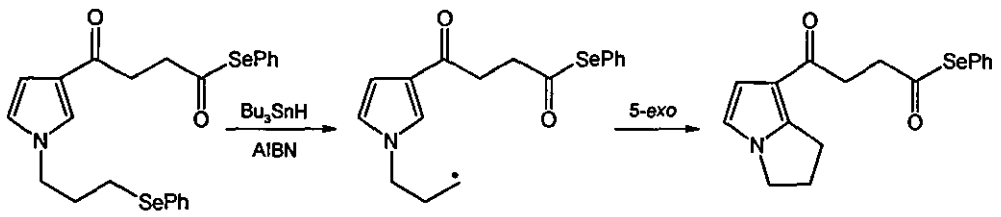
Scheme 158: *Proposed tandem radical cyclisation onto pyrrole*

The most likely problem to be encountered is whether two separate radical additions to pyrrole could be performed in one procedure and the question remains whether both would result in

rearomatisation. *N*-Alkyl radicals have been shown to undergo 5-*exo* addition to α-acylated pyrroles readily and the previous acyl radical protocols could theoretically be adapted to an alternative intramolecular cyclisation pathway as shown in Scheme 158.

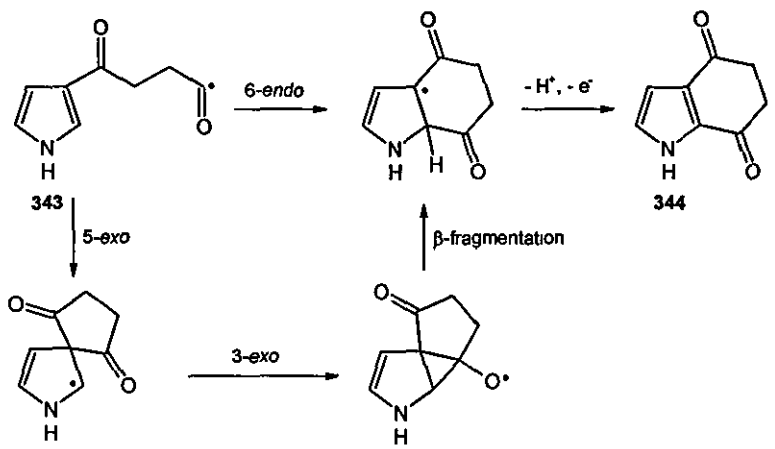
3.4.1 Acyl Radical Addition to Pyrrole

The tandem cyclisation approach was designed to make use of two separate radical additions to the pyrrole core as shown in Scheme 158. 3-Acylated pyrroles such as the 1,3-disubstituted pyrrole shown in Scheme 159 would provide obvious regioselectivity problems for the first cyclisation because the acyl radical and the *N*-alkyl radical would both be expected to undergo addition at the 2-position preventing the desired tandem cyclisation from occurring (Scheme 159).



Scheme 159: *Regioselectivity problem of β-acylated tandem cyclisation precursors*

However, the initial investigation into this research was based on the 6-*endo* cyclisation of radical species **343** derived from the corresponding β-substituted pyrrolo acyl selenide (Scheme 160). Analysis of the crude ^{1}H NMR spectrum indicated cyclisation had occurred to yield diketo indoline **344** and the possibility of a tandem procedure was investigated (Scheme 158).

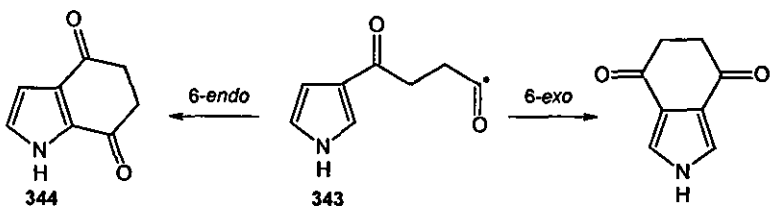


Scheme 160: *6-endo Cyclisation onto pyrrole*

The cyclisation shown in Scheme 160 also presents the possibility for a neophyl rearrangement *via* 5-*exo* cyclisation onto pyrrole and 3-*exo* cyclisation onto the carbonyl. β-Fragmentation of

the alkoxy radical would lead to the same intermediate radical from 6-*endo* cyclisation in this case. However, the presence of additional functionality adjacent to an acyl group would result in a scrambling of the functional group regiochemistry following cyclisation because the 3-*exo* cyclisation can occur onto either carbonyl.

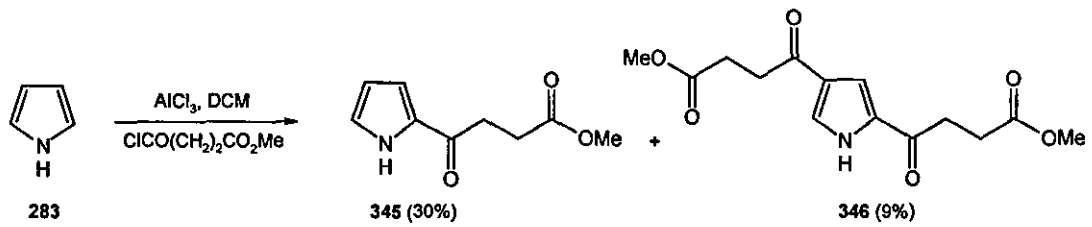
The regioselectivity of the acyl radical addition of the 3-isomer was not known (Scheme 161) although the superior electrophilicity and conjugate addition effect of the 2-position should enhance cyclisation suitably, and cyclised compound **344** was expected to dominate.



Scheme 161: *Regiochemistry of acyl radical cyclisation*

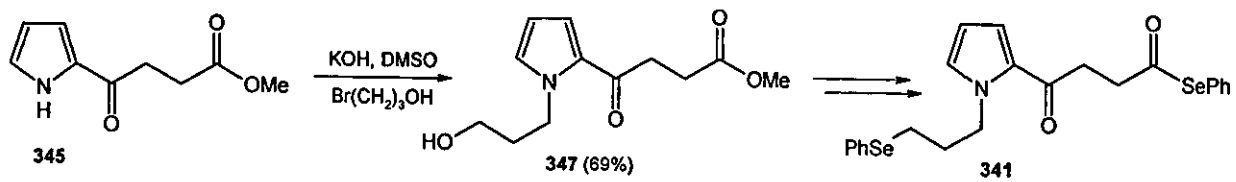
Ultimately the procedure requires the use of 2-acylated pyrroles to prevent any regioselectivity issues during radical cyclisation. The presence of the acyl group should serve to promote radical cyclisation as an electron-withdrawing group and stabilise the cyclised radical.

The 2- and 3-acylated pyrroles were readily available from common starting materials. Electrophilic substitution at the 2-position of pyrrole is a facile procedure, however, treatment of pyrrole **283** with methyl 4-chloro-4-oxobutyrate using aluminium trichloride catalysis yields the desired ester **345** in only 30% yield. This was probably due in part to the diacylation of pyrrole to yield a 2,4-disubstituted pyrrole **346** (Scheme 162). Hydrolysis of the diacid **346** was performed in 86% yield to give the corresponding dicarboxylic acid with a view to tandem cyclisation, although research into other areas took precedence.



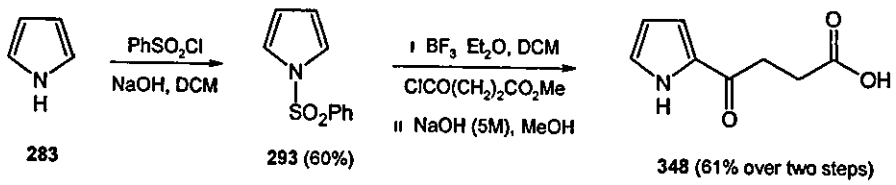
Scheme 162: *Synthesis of methyl 4-oxo-4-(pyrrol-2-yl)butanoate including diacylation*

The methyl ester **345** was left intact in order to prevent interference during alkylation of the pyrrole nitrogen. Alkylation using crushed potassium hydroxide in DMSO was effective in the introduction of the necessary propyl alcohol yielding pyrrolo ester **347** (Scheme 163). Hydrolysis to liberate the carboxylic acid and one-pot tandem selenation of the alcohol and the acid would provide the diselenyl precursor **341** for the construction of the mitomycin skeleton shown in Scheme 158.



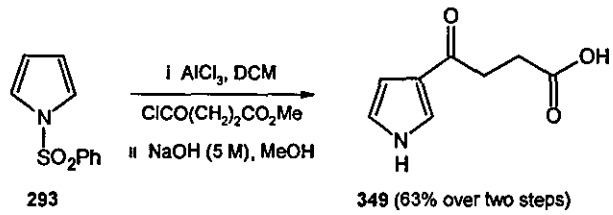
Scheme 163: *Alkylation of methyl 4-oxo-4-(pyrrol-2-yl)butanoate*

The diselenyl precursor for tandem radical cyclisation **341** could theoretically be obtained by a one-pot conversion of the corresponding acid of methyl ester **347**. However, because there were many variables in this cyclisation system, test substrates were prepared to study each of the tandem cyclisation components individually. The 5-*exo* cyclisation onto 2-acyl pyrroles is well known, hence our investigations commenced into the unknown acyl radical cyclisation. Radical cyclisation onto the β-position of pyrrole should be feasible from acyl selenides derived from pyrrolo carboxylic acid **348**.



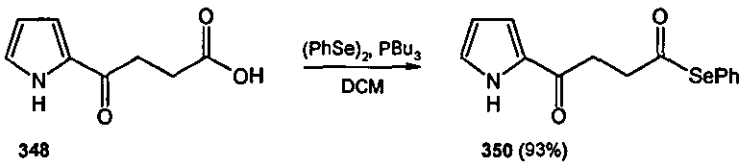
Scheme 164: *Friedel-Crafts acylation at the 2-position of pyrrole*

Yields of α-acylation of pyrrole were significantly improved by the use of a protecting group and a softer Lewis acid to control the acylation because *N*-(phenylsulfonyl)-1*H*-pyrrole **293** is a less active system (Scheme 164). The acylation proceeds in moderate yield (61%) although hydrolysis to the acid **348** was carried out in quantitative yield. Interestingly, there was no difference in yield between acylations performed in the historically favoured DCE and the DCM employed in the majority of our research, eliminating the use of the potential carcinogen.



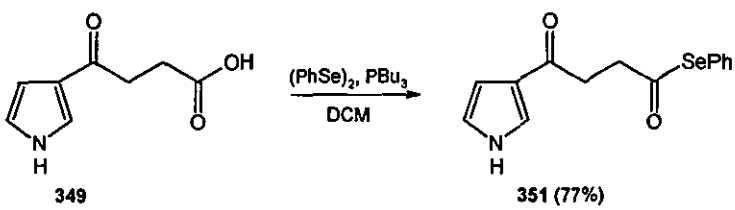
Scheme 165: *Regioselective β-acylation of pyrrole*

3-Substituted pyrroles were synthesised in order to ascertain whether there would be any enhancements in cyclisation reactivity over the 2-isomers. Differences in Lewis acidity can be used to influence the reactivity of pyrroles in order to control the direction of substitution (Scheme 165).[152,153] The stronger Lewis acid ($AlCl_3$) gave rise to an improved 89% yield of β-acylation over the boron trifluoride catalysed α-acylation. However, relatively poor yields for hydrolysis rendered the overall yield of 4-oxo-4-(1*H*-pyrrol-3-yl)butanoic acid **349** only slightly better than the 2-isomer **348**.



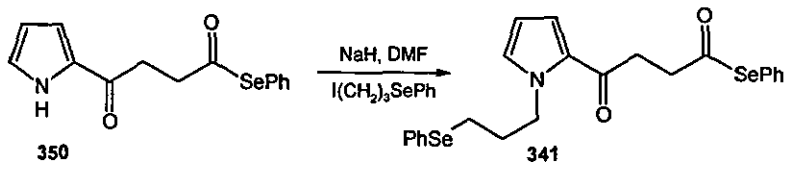
Scheme 166: *Synthesis of 2-pyrrolo-acyl selenides*

The formation of the acyl selenide precursors could be achieved in good yield for both 4-oxo-4-(1*H*-pyrrol-2-yl)butanoic acid **348** and 4-oxo-4-(1*H*-pyrrol-3-yl)butanoic acid **349** giving rise to phenyl 4-oxo-4-(1*H*-pyrrol-2-yl)butaneselenoate **350** and phenyl 4-oxo-4-(1*H*-pyrrol-3-yl)butaneselenoate **351** in 93 and 77% respectively (Scheme 166 and Scheme 167). The selenation yields were very good for both isomers compared to previous pyrrole systems; the participation of the formyl group in the previous systems was thus implicated further.



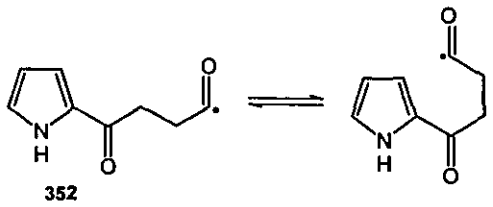
Scheme 167: *Synthesis of 3-pyrrolo-acyl selenides*

Attempts to install the *N*-alkyl selenide chain failed giving only a complex mixture containing large quantities of oligomerisation (Scheme 168).



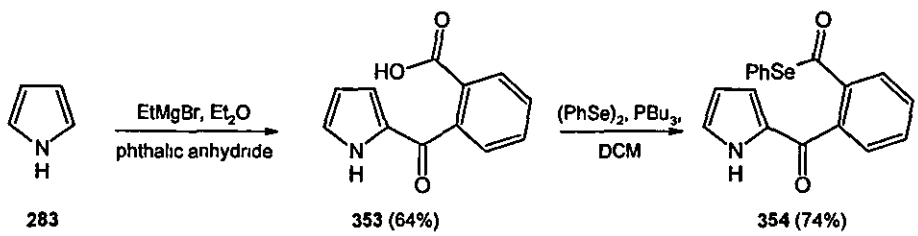
Scheme 168: *Attempted synthesis of mitomycin precursors*

Acyl selenides containing a more rigid conformation were also sought to promote a more favourable cyclisation transition state as the saturated derivatives phenyl 4-oxo-4-(1*H*-pyrrol-2-yl)butaneselenoate **350** and phenyl 4-oxo-4-(1*H*-pyrrol-3-yl)butaneselenoate **351** can potentially adopt an open chain conformation not conducive to cyclisation **352** (Scheme 169).



Scheme 169: *Open chain conformation acyl selenides*

Synthesis of acyl selenides having a more rigid geometry could be performed adequately from the benzoic acid derivative[154] shown in Scheme 170. Unfortunately the acyl selenides proved to be unstable and decomposed readily. 2-(1*H*-Pyrrole-2-carbonyl)-selenobenzoic acid *Se*-phenyl ester **354** was particularly prone to hydrolysis in the presence of mild acid and during silica gel chromatography, however rapid elution afforded the required acyl selenide in reasonable yield (74%).



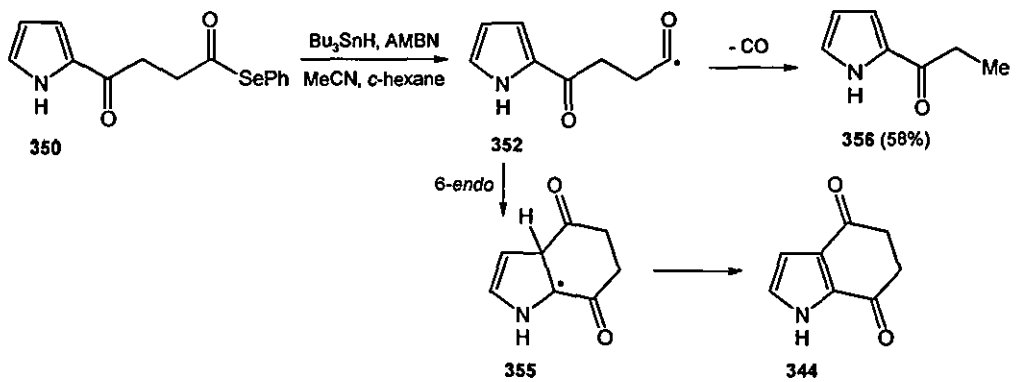
Scheme 170: *Synthesis of conformationally restricted acyl selenides*

The unsaturated precursors such as 2-(1*H*-pyrrole-2-carbonyl)-selenobenzoic acid *Se*-phenyl ester **354** were potentially more useful to mitomycin A and C because the cyclisation of phenyl 4-oxo-4-(1*H*-pyrrol-2-yl)butaneselenoate **350** would lead to 5,6-dihydro-1*H*-indole-4,7-dione and not the desired 2,3-dihydro-1*H*-indole-4,7-dione structure present in mitomycin A and C.

ACYL RADICAL CYCLISATION ONTO PYRROLE

Pattenden has shown 6-*endo* acyl radical cyclisation onto alkenes to be a facile process[3] and on the basis of our own findings of acyl radical additions to pyrroles, it was predicted these cyclisations would yield useful results with obvious uses in the synthesis of mitomycin A and C analogues. The initial target molecule 5,6-dihydro-1H-indole-4,7-dione was surprisingly poorly represented in the literature.[155]

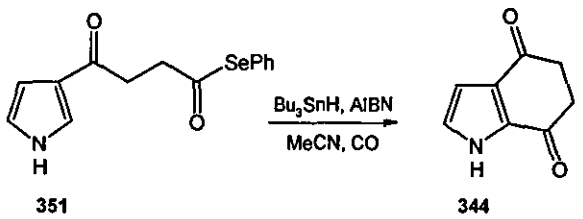
Syringe pump addition of tributyltin hydride to phenyl 4-oxo-4-(1*H*-pyrrol-2-yl)butaneselenoate **350** and AMBN liberates the acyl radical **352** (Scheme 171). Unfortunately, the 2-isomer failed to yield appreciable quantities of the cyclised material **344** and was identified as a minor product in an impure fraction following attempted chromatographic purification. The major product isolated was that of decarbonylation followed by reduction, 1-(1*H*-pyrrol-2-yl)-propan-1-one **356** in 58% yield. The reaction did yield an unidentifiable α-substituted pyrrole compound in appreciable quantity.



Scheme 171: *Attempted acyl radical cyclisation onto pyrrole*

The attempted cyclisation of phenyl 4-oxo-4-(1*H*-pyrrol-2-yl)butaneselenoate **350** was performed in a sealed tube under CO to prevent decarbonylation. In order to inhibit reduction the two-phase solvent system was utilised. ^{1}H NMR spectral analysis of the reaction mixture indicated one major compound relating to pyrrole. The compound remains unidentified, but was not starting material **350** or the cyclised material **344** or 1-(1*H*-pyrrol-2-yl)-propan-1-one **356** or the reduced acyl radical product or the unidentified product observed under the previous conditions. Interestingly, LCMS analysis indicates a mass ion present associated with reduction products, although no aldehyde peak is observed in the ^{1}H NMR spectrum. This mass ion might, therefore, be related to products of reductive cyclisation.

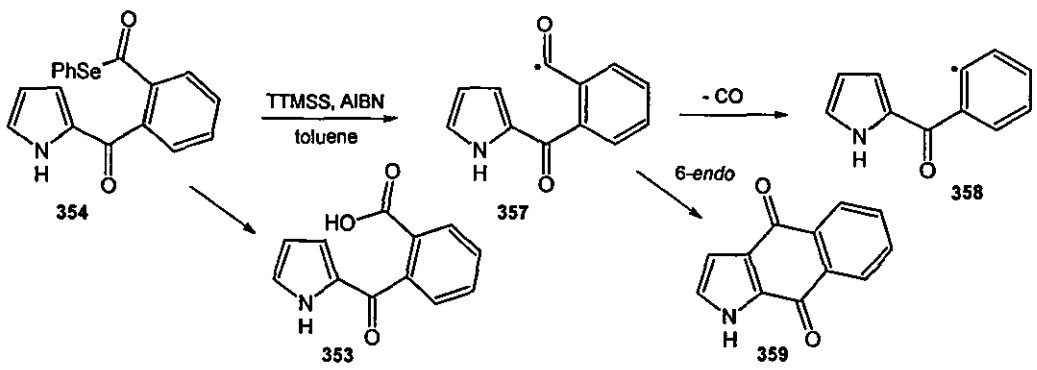
Attempted cyclisation of the 3-isomer **351** was performed under standard radical cyclisation protocols (Scheme 172). Evidence for cyclisation was found following ^{1}H NMR spectral analysis of impure fractions isolated from chromatographic purification, but the compound was present in low yield and could not be obtained pure.



Scheme 172: *Attempted cyclisation of 3-acylated pyrroles*

Attempts to improve the cyclisation involved the previously discussed two-phase solvent system (cyclohexane-acetonitrile) although the reaction afforded the decarbonylated reduced material 1-(1*H*-pyrrol-3-yl)-propan-1-one (4%) in addition to unreacted starting material **351** (25%) and no other identifiable products.

Our attention focussed on potentially more rigid systems to allow cyclisation. The acyl selenide was freshly prepared or purified prior to attempted cyclisation, however under the conditions developed during the previous acyl radical cyclisations there was no evidence of cyclisation (Scheme 173). Decarbonylation of aromatic acyl radicals **357** is less favoured than simple saturated acyl radicals and the geometry is now locked to encourage cyclisation, but the cyclisation did not occur under the conditions used.



Scheme 173: *Attempted aryl acyl radical cyclisations*

The only compound isolated following chromatographic purification was that of the benzoic acid **353**. The cyclisation products are 12 electron and as a result may exhibit some instability due to potential anti-aromatic nature.

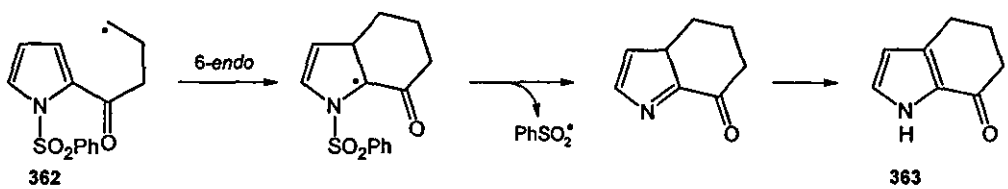
The failing of this potentially useful system was curious because various literature examples and our own work indicated the cyclisations should have been favourable. The influence of the decarbonylation on cyclisation was tested using alkyl radical systems. If the rate of decarbonylation was greater than expected in these systems, alkyl radical cyclisation might be possible from related alkyl bromides.

3.4.2 Alkyl Radical Addition to Pyrrole

Cyclisation of alkyl radical precursors was attempted to facilitate a more favourable 6-*endo* cyclisation because decarbonylation was no longer an issue (Scheme 174). Alkyl bromide precursors **360** should be readily converted to the alkyl radical and cyclised in 6-*endo* fashion to yield indolones **361**. The ketone functionality was again in place to activate the pyrrole to nucleophilic radical approach and stabilise the radical addition product.

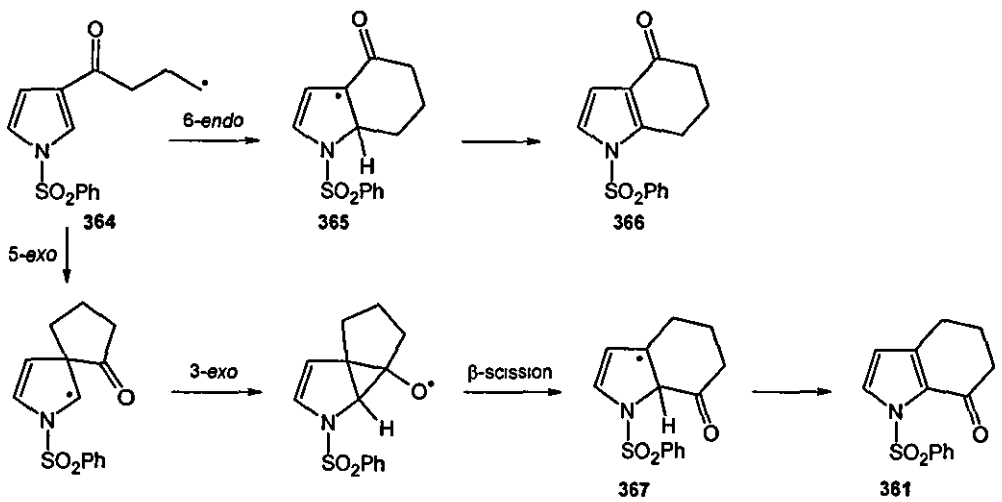
Scheme 174: *Alkyl radical cyclisation onto pyrrole*

Although the results could not be directly compared to the acyl radical results due to the presence of a further electron-withdrawing group, it did introduce an interesting possibility for oxidative rearomatisation. The phenyl sulfonyl group is known to enhance oxidative rearomatisation in such reactions because it is a far better radical leaving group than hydrogen. The phenyl sulfonyl radical may be lost following 6-*endo* cyclisation of radical **362** to yield the unprotected indolinone product **363** (Scheme 175).



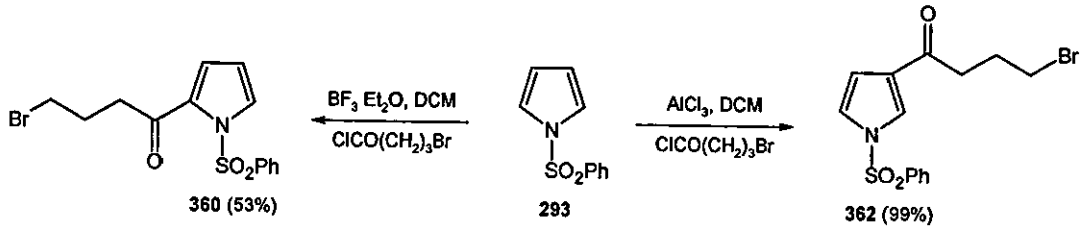
Scheme 175: *Oxidative rearomatisation by loss of phenyl sulfonyl group*

The alkyl radical cyclisations also have the potential for neophyl type rearrangements in the same manner as the acyl radicals discussed in the previous section. However, the alkyl radical cyclisations potentially give rise to two products, hence the rearrangement could be identified (Scheme 176). In competition with 6-*endo* cyclisation was a facile 5-*exo* cyclisation; this cyclisation would lead to scrambling of the acyl group regiochemistry in this system. Cyclisation of the 5-*exo* product in a 3-*exo* manner onto the ketone followed by β-fragmentation of the alkoxy radical yields radical **367**. The regiochemistry of the acyl group now differs from that of the 6-*endo* cyclisation radical **365**. Rearomatisation would yield 1-(phenylsulfonyl)-1,5,6,7-tetrahydro-indol-4-one **366** and 1-(phenylsulfonyl)-1,4,5,6-tetrahydro-indol-7-one **361** from the same initial radical species **364**. The potential cyclisation pathways available to the alkyl radical were intriguing although may lead to inseparable mixtures if the competing rates of cyclisation are closely matched.



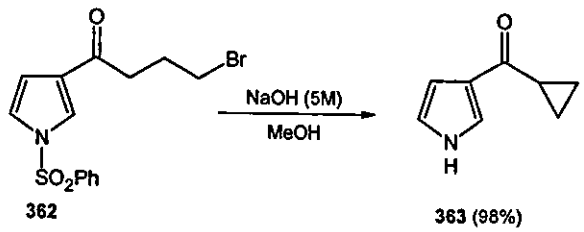
Scheme 176: *Possible neophyl type rearrangement*

The 2- and 3-substituted pyrrole precursors 4-bromo-1-[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl]butan-1-one **360** and 4-bromo-1-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]butan-1-one **362** could be prepared selectively by controlled Friedel-Crafts acylations in similar fashion to the acyl radical precursors in the previous section (Scheme 177). Interestingly, no Lewis acid mediated alkylation and a limited amount of cyclisation product was identified because the acyl chloride is significantly more activated towards Lewis acid mediated electrophilic substitution than the alkyl halide. The cyclisation is also unfavourable following acylation due to the deactivation of the pyrrole ring.



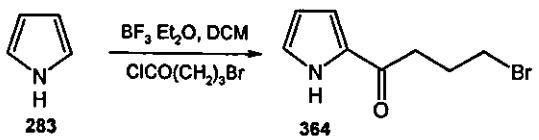
Scheme 177: *Friedel-Crafts acylation of N-(phenylsulfonyl)pyrrole*

Deprotection could not be performed on these systems because treatment of the bromo precursor with aqueous sodium hydroxide yielded quantitative conversion to the cyclopropanone in addition to the required deprotection yielding **363** in high yield (Scheme 178).



Scheme 178: *Basic deprotection and cyclopropanation*

The phenylsulfonyl group was not considered essential to the proposed route, although the synthesis of the unprotected pyrrole **364** was briefly investigated. Attempts to acylate the unprotected pyrrole **283** proved fruitless, resulting in oligomerisation of the pyrrole units (Scheme 179). Alternative protecting groups were considered although the possible rate enhancements of the sulfonyl group were seen more as a benefit.



Scheme 179: *Attempted acylation of pyrrole*

With the cyclisation precursors in hand the examination of their behaviour under radical conditions was performed with particular interest in the competing 6-*endo*, 5- and 6-*exo* modes of cyclisation.

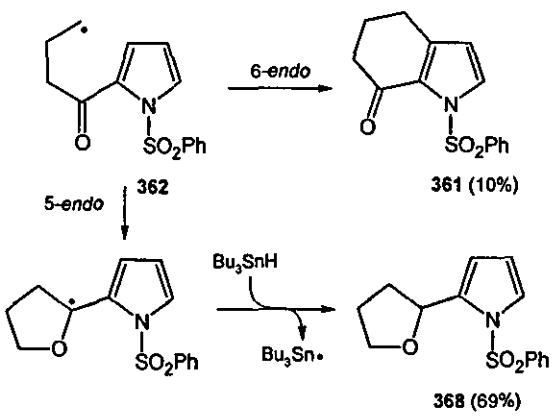
ALKYL RADICAL ADDITION TO PYRROLE

Encouraging to nucleophilic radical attack, phenyl sulfonyl group has been shown to inhibit orbital controlled electrophilic substitutions due to the reduced electron density at the α-

positions. Additionally the presence of the aromatic ketone will reduce electron density and stabilise the radical addition product.

The cyclisation was attempted using syringe pump addition of tributyltin hydride in toluene to an acetonitrile solution of 4-bromo-1-[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl]butan-1-one **360** under reflux in the presence of AIBN initiation. The reaction mixture was analysed by ^{1}H NMR spectroscopy indicating two identifiable compounds present one of which was the desired cyclised material **361**. The second major compound could not be identified because the spectral data did not correspond to alkyl radical reduction or the alternative regioisomer **366** and the pyrrole ring was still 1,2-disubstituted.

The phenyl sulfonyl group failed to enhance cyclisation onto the pyrrole ring and alkyl radical cyclisation had occurred onto the carbonyl oxygen instead. Reduction of the radical centre yields 1-phenylsulfonyl-2-(tetrahydro-furan-2-yl)-1*H*-pyrrole **368** as the major product in 69% yield (Scheme 180). Although 5-*endo* cyclisation is typically not a facile process; this 5-*endo* cyclisation does invoke a radical centre stabilised by both the adjacent oxygen and benzylic stabilisation. However, the result of this reaction was not predictable in the presence of historically more favourable cyclisation modes 5-*exo* and 6-*endo*.

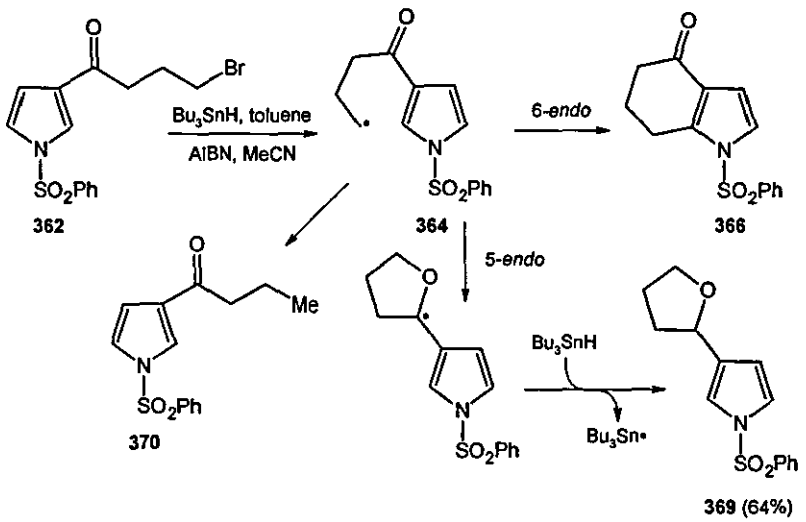


Scheme 180: *5-endo Cyclisation onto aryl ketone*

The cyclised material 1-(phenylsulfonyl)-1,4,5,6-tetrahydro-indol-7-one **361** was identified by correlation of the ^{1}H NMR spectral data with reported values in 10% yield by ^{1}H NMR spectral analysis. Attempted chromatographic purification resulted in co-elution of cyclised products **361** and **368**.

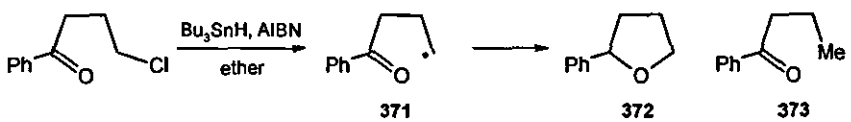
The unlikely result from this investigation indicates how unfavourable homolytic aromatic substitutions can be because the 5-*endo* cyclisation dominated in the presence of a suitably activated aromatic ring with a potential radical leaving group to provide rapid rearomatisation (phenyl sulfonyl group).

Interestingly, this result was reflected in the cyclisation of 4-bromo-1-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]butan-1-one **362** under the same conditions. A small amount of unreacted starting material **362** (17%) was also isolated, but the 5-*endo* cyclisation to yield 1-phenylsulfonyl-3-(tetrahydro-furan-2-yl)-1*H*-pyrrole **369** was the sole reaction product isolated in 64% yield (Scheme 181). There was no evidence of radical reduction **370** or 6-*endo*, 5- or 6-*exo* cyclisation onto the pyrrole ring.



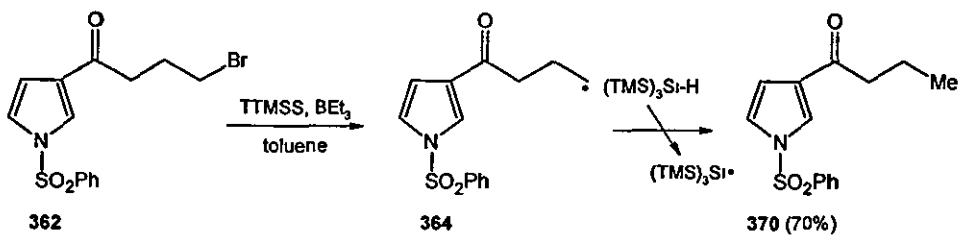
Scheme 181: *5-endo Cyclisation of 4-bromo-1-[1-(phenylsulfonyl)pyrrol-3-yl]butan-1-one*

Although 5-*endo* cyclisation is deemed unfavourable[156] there are a number of other examples reported in the literature involving radical cyclisations.[157] For example, Scheme 182 shows the 5-*endo* cyclisation of alkyl radical **371** onto the aromatic ketone and not onto the aryl group. The furan product **372** and the reduced product were obtained in 65% combined yield in 4:1 ratio respectively.



Scheme 182: *5-endo Cyclisation onto carbonyl moiety*

The reaction of 4-bromo-1-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]butan-1-one **362** with TTMSS under triethylborane initiation resulted in almost complete reduction of the radical centre to yield [1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]butanone **370** (70%) as the sole product isolated (Scheme 183). Although a small amount of the desired cyclisation product was observed in the ^{1}H NMR spectrum, none was isolated following chromatographic purification. This result was mirrored by the 2-isomer, yielding a small amount of cyclisation identifiable only by ^{1}H NMR spectroscopy.



Scheme 183: *Use of TTMSS in attempted radical cyclisation*

This was somewhat unexpected because TTMSS is a poor hydrogen donor relative to tributyltin hydride and reduction was not expected to dominate. However, TTMSS was introduced entirely at the beginning of the reaction and hence allowed reduction to occur. This result also demonstrates a possible requirement of thermal excitation for 5-*endo* cyclisation to occur, because none of the tetrahydrofuranyl derivative **369** was isolated.

The surprising isolation of the 5-*endo* cyclisation product from alkyl radical cyclisation onto aromatic ketones demonstrates the fickle nature of radical annulation protocols. The radical cyclisations were designed to study the competing homolytic aromatic substitutions. However, addition to the ketone oxygen was observed in high yield instead.

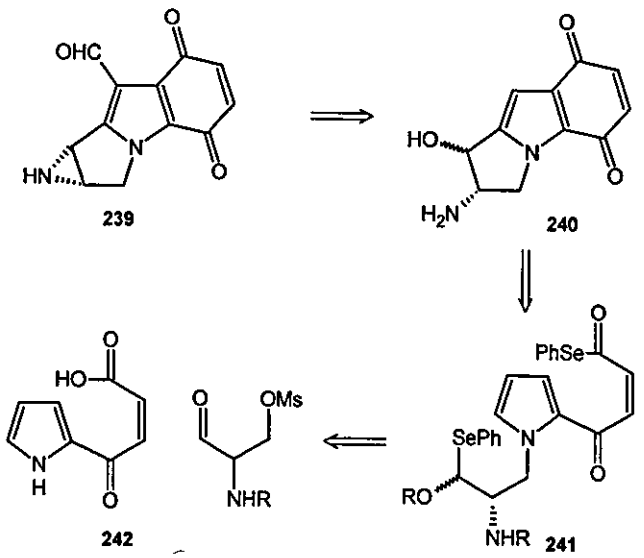
3.5 Conclusion

The synthesis of two pyrrolizine alkaloids was achieved in moderate yield by acyl radical addition to pyrroles. Further examples were possible although sufficient time had already been spent developing the procedures for use on solid support.

Although 5-*exo* homolytic substitution onto the heteroarene was typically higher yielding than 7-*exo*, the latter typically provides a 'cleaner' reaction with fewer unknown by-products. This was also noted in the alkyl radical cyclisations onto pyrrole.

Unfortunately the tandem cyclisation approach did not progress beyond the early cyclisation studies although many avenues of exploration were planned. The addition of silylselenides

across an aldehyde derived from Garner's aldehyde[158] and α-acylated pyrrole carboxylic acids should yield α-silyloxyselenides[159] **241** suitable for the tandem cyclisation protocols shown in Scheme 184. Tandem cyclisation of the α-silyloxy and acyl radical centres was predicted to give rise to a suitable precursor for conversion to the aziridine **240**. If the rate of cyclisation can be increased then these proposals may be explored later. Reduction of the ketone should offer greater chain flexibility increasing the likelihood of cyclisation onto the pyrrole in mind.



Scheme 184: *Putative synthesis of functionalised tricyclic skeletons*

Following the partial success of the solution phase work, the procedures were then adapted to a solid supported approach in the acyl radical cyclisation onto pyrrole-2 and 3-carbaldehydes`.

CHAPTER 4 SOLID PHASE ORGANIC SYNTHESIS

4.1 INTRODUCTION

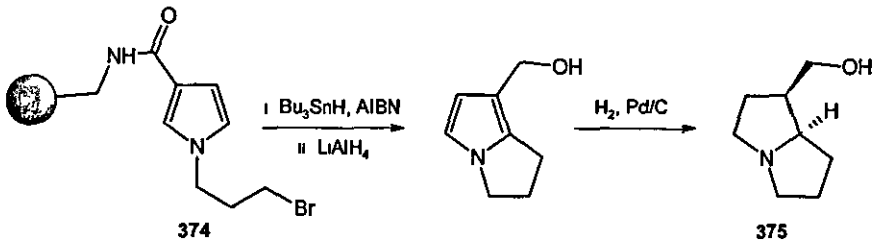
Many of the problems associated with synthetic radical cyclisation chemistry can potentially be improved by use of SPOS methodologies discussed in Chapter 1. There are four approaches of relevance to this project and the research interests of the Bowman group. These were categorised as follows; solid supported radical propagating species, tethered cyclisation substrates using 'traditional' linkers such as amide and ester linkages, traceless cleavage by homolytic *ipso* displacement of the resin linker during cyclisation and homolytic traceless cleavage of the substrate with subsequent cyclisation in the solution phase.

The first of these methodologies involves immobilised reagents such as PS bound organotin and organogermanium reagents. This approach is in keeping with current trends in SPOS as discussed in Chapter 1 and the attachment of organogermanium hydride propagating species is currently being studied within the Bowman group by Sussie Krintel.

Tethering radical propagating species to the solid support is of obvious benefit for toxic triorganotin reagents because they can be removed from the crude reaction mixture following the reaction.[64] Drawbacks associated with this approach are the troublesome syntheses of the supported triorganotin hydride and the problems of leaching of the organotin residues from the resin. The resin is also required to perform two steps in a chain sequence, hence initiation and propagation rely on typically poor kinetics of the solid supported reagent diminishing reactivity.

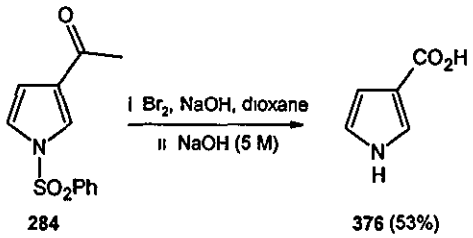
Alternative procedures utilise more traditional SPOS approaches whereby the radical cyclisation is performed on a resin bound substrate and the excess toxic reagents are washed away before the product is cleaved. Unfortunately this general procedure is not traceless and problems are often encountered during cleavage from solid supports. However, the benefit of complete removal of triorganotin waste prior to cleavage makes the procedure attractive and a small investigation into possible alkyl radical cyclisations onto pyrrole was undertaken.

Alkyl radical cyclisations have already been shown to undergo regioselective addition to 3-substituted pyrroles in similar systems in Chapter 3. We envisaged pyrrolizine and pyrrolizidine **375** compounds would be accessible by cyclisation of resin bound precursors such as the 3-substituted pyrrole **374** followed by reductive cleavage from the solid support (Scheme 185).



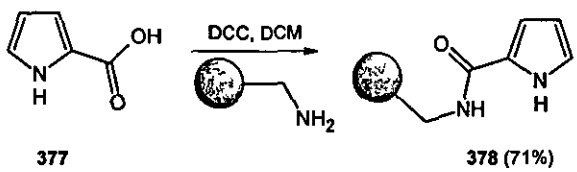
Scheme 185: *Possible solid supported radical cyclisation precursors*

An amide linkage was chosen to attach the heterocycles to solid support due to the number of high yielding amide coupling reactions, selective cleavage and the availability of pyrrole acids. Heterocyclic precursors pyrrole-3-carboxylic acid **376** (Scheme 186), pyrrole-2-carboxylic acid **377** and 4-oxo-4-(1*H*-pyrrol-3-yl)butanoic acid **349** (Scheme 165) were obtained and loading to aminomethylated polystyrene (1% crosslinked with DVB, Novabiochem, 1.13 $mmol.g^{-1}$, 100-200 mesh) was attempted.



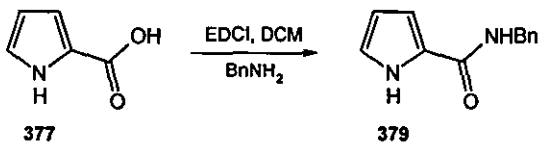
Scheme 186: *Synthesis of pyrrole-3-carboxylic acid*

Attempts to load pyrrole-2-carboxylic acid **377** and 4-oxo-4-(1*H*-pyrrol-3-yl)butanoic acid **349** as the respective acid chloride to aminomethylated PS proved unsatisfactory due to degradation of the polymer, although recovery yields of the polymer were encouraging. Attempted DCC and EDCI coupling of pyrrole-2-carboxylic acid **377** and the amino methylated PS (Scheme 187) resulted in incomplete reaction (71%). Problems were also encountered for the attempted coupling of 4-oxo-4-(1*H*-pyrrol-3-yl)butanoic acid **349** with coupling reagents DCC and EDCI, although yields were encouraging there was significant degradation of the PS support.



Scheme 187: *Loading of pyrrolo acids to aminomethylated PS*

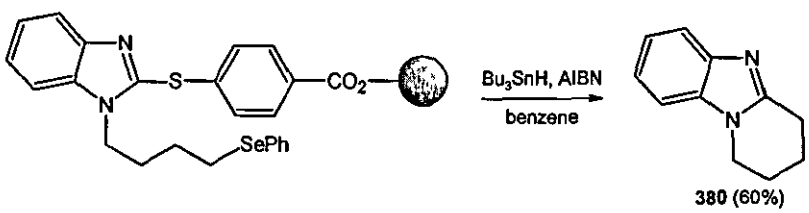
The incomplete reactions and polymer degradation observed for the amide couplings on solid support was very disconcerting and the solution phase analogues were attempted. Amidation of pyrrole-2-carboxylic acid **377** with benzylamine using EDCI could be achieved readily to give the pyrrole amide **379** in high yield (99%) giving no indication for the failure of the aminomethylated PS compounds (Scheme 188). It is likely that inexperience with the handling of resins was contributing to the poor yields and degradation. However, this program of work was not continued because more attractive traceless solid phase approaches were investigated as a higher priority.



377 **379**

Scheme 188: *Amidation of pyrrole-2-carboxylic acid*

Studies within our group by Rehana Karim have shown that homolytic traceless cleavage by *ipso* displacement of the resin linker can be achieved with suitable sulfur linkages (Scheme 189).[160] Homolytic aromatic substitution by the alkyl radical derived from the resin bound benzimidazole yields the cyclised product 1,2,3,4-tetrahydro-benzo[4,5]imidazo[1,2-*a*]pyridine **380** in 60% yield. Homolytic aromatic substitution was thus the only product from the radical reaction because products of radical reduction and unreacted starting material remain bound to the solid support. However, because the reaction matrix contains triorganotin selenide impurities there are still difficulties associated with separation of triorganotin waste from the cyclised material.

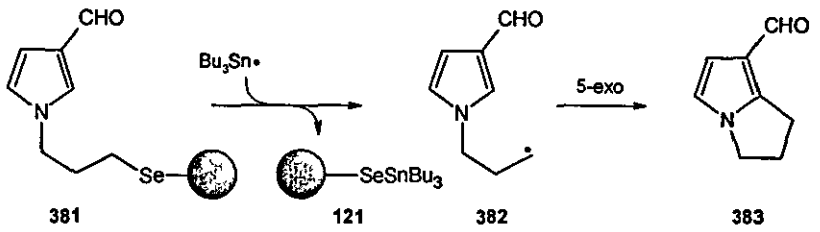


380 (60%)

Scheme 189: *Traceless cleavage of sulfur linkages*

The final SPOS approach, homolytic traceless cleavage of the cyclisation substrate, differs to the previous approach subtly by the position of the cleavage site (Scheme 190). The radical propagating species performs homolytic cleavage of the resin bound substrate **381** and remains bound to the solid support **121** improving the workup and handling. Theoretically this is the ideal system for homolytic aromatic substitutions because the resin is required only during cleavage.

The poor kinetics associated with SPOS and the diffusion zone away from the polymer should serve to enhance cyclisation of radical species **382** over reduction. This pseudo-dilution effect has been the downfall of many SPOS approaches but will be a major benefit to this system.



Scheme 190: *Traceless cleavage of supported alkyl selenides*

With this in mind the chalcogens seemed the most obvious method of linking. Due to the higher efficiency and softer nature of selenium in radical chemistry it appeared to be the ideal linkage for solid supported radical chemistry.

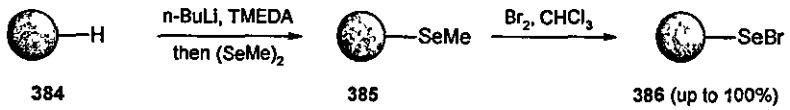
4.2 Synthesis of Polystyrene Bound Selenyl Bromide

Although toxic in high doses, selenium is a unique essential element for humans, although the therapeutic window of selenium levels is small. Selenium participates in vital biochemistry in the guise of various selenoproteins responsible largely for antioxidant and redox functions, particularly in the protection and development of the male reproductive system and muscle tissue.

The toxic effects of selenium on mammals from natural sources of Se-accumulating plants are well documented, hence attachment of selenium reagents to solid support should prevent unnecessary exposure of the chemist to high levels of selenium, in addition to the proposed improved removal of toxic triorganotin waste. In spite of the toxicity of selenium, it has found use in many commercial applications including diodes, photoelectric cells and metallurgy and the array of selenium chemistry is gaining wider appeal and so the requirement for cleaner synthetic methodologies is apparent.

Synthetically useful polystyrene bound selenide reagents were available directly from polystyrene according to the procedure published by Nicolaou.[161] We carried out a synthesis of PS selenyl bromide **386** according to Nicolaou's procedure in order to attach heterocyclic radical cyclisation precursors to PS support (Scheme 191). The method involves lithiation of PS solid support **384** (1% crosslinked with DVB, 100-200 mesh, Aldrich) and quenching with dimethyl diselenide to furnish PS methylselenide **385**. The methylselenide **385** can be readily converted to

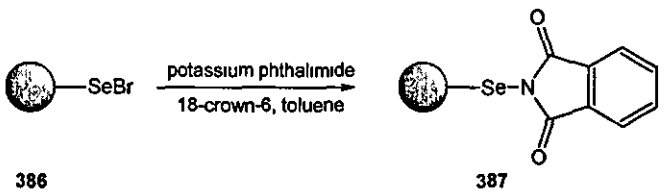
PS selenyl bromide **386** by brief exposure to bromine followed by thermally induced methyl bromide elimination.



Scheme 191: *Synthesis of PS bound selenyl bromide*

The procedure was amenable to scale-up but the dependence of the procedure on the volatile and highly toxic dimethyl diselenide makes the synthesis hazardous and unpleasant due to the strong odour of the methylselenides present. The success of each step was ascertained by mass change of the dried resins and could be inferred from standard elemental analysis although yields were variable. Elemental analysis of selenium and bromine was not possible within our department and was cost prohibitive on a regular basis. For example, Warwick Analytical Services charge £50 and £27 respectively per sample. Qualitative analysis of the PS selenyl bromide **386** shows that a darker red-brown colour was indicative of successful reaction. The bromination of aryl methylselenides was facile hence failure or incomplete reaction can be attributed to the failure of PS lithiation.

The selenyl bromide is a versatile functionality although alternative protocols were available to *N*-PS-selenylphthalimide (NPSSP) **387**, which could be prepared directly from the PS selenyl bromide **386** (Scheme 192). Yields were variable for this reaction although alternative procedures were not sought.

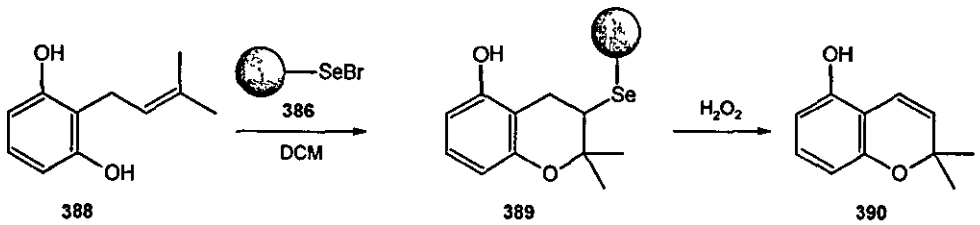


Scheme 192: *Synthesis of NPSSP*

The solution phase protocols developed earlier in the research could potentially be put into practice on solid support. Attachment of alkyl halide chains analogous to chloro alkylselenides **149-151** should be accomplished readily, hence the loading of heterocyclic radical cyclisation precursors was attempted.

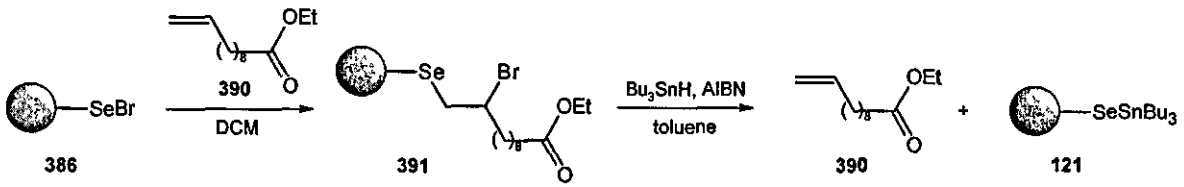
4.2.1 Synthesis of Polystyrene Bound Alkyl and Acyl Selenides

A great deal of the reported research of PS selenylbromides **386** relates to the synthesis of benzopyrans **390** by cyclisation of *o*-prenylated phenols **388** followed by oxidative cleavage of the resin bound dihydrobenzopyran **389** (Scheme 193).[94] The oxidative cleavage can be achieved cleanly and efficiently (95% pure) although this methodology may not be using the full scope of benefits the resin offers. It was our view that the improved handling of triorganotin selenide waste has a great deal to offer synthetic radical chemistry.



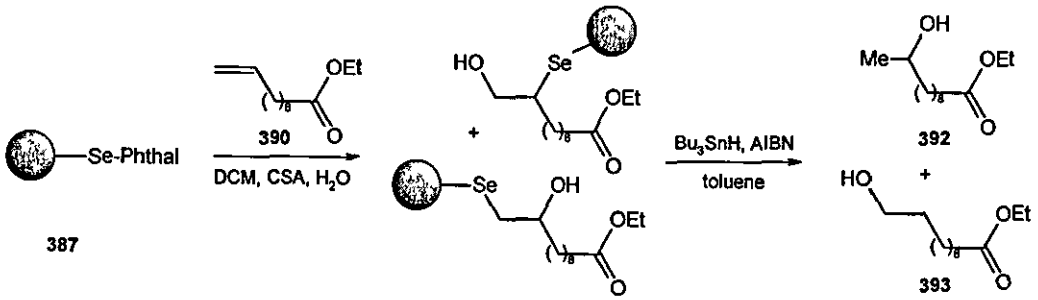
Scheme 193: *Cyclisation loading and oxidative cleavage in the synthesis of benzopyrans*

In order to examine the reactivity of the resin bound selenium reagents **386** and **387**, a selection of radical cleavage reactions included in the original communication were investigated.[92] We performed the loading of alkene **390** to PS selenyl bromide **386** followed by cleavage of the resultant alkyl selenide **391** under radical conditions in comparable yield to the published data, recovering 98% of alkene **390** based on yields recorded by mass change of the polymer (Scheme 194).



Scheme 194: *Addition/cleavage of ethyl undecylenate to PS selenyl bromide*

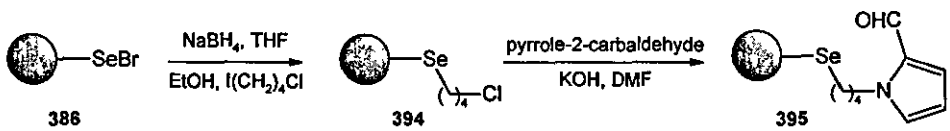
We then studied the capabilities of NPSSP **387**. In the presence of acid and water NPSSP **387** was expected to undergo addition across the alkene as shown in Scheme 195 yielding the two PS β-hydroxy alkylselenides products. The loading yields were typically low and homolytic cleavage did not provide adequate yields of either alcohol **392** and **393**. Further analysis of the NPSSP **387** indicated that although a colour and mass change was observed during the reaction of PS selenyl bromide **386** and potassium phthalimide (Scheme 192), the reaction had only been partially successful. The failure to perform this reaction to the standard reported in the literature was concerning, although the experimental details were sparse.



Scheme 195: *Addition of ethyl undecylenate to N-(PSselenyl)phthalimide*

Our attention focussed on adapting solution phase procedures used previously within the Bowman group to the solid support in the attempt to prepare heterocyclic radical cyclisation precursors related to this project using PS selenyl bromide **386**. Treatment of PS selenyl bromide **386** swollen in THF/ethanol with lithium borohydride and 4-iodo-1-chlorobutane appeared to have yielded the desired alkyl selenide **394** by observed mass and colour changes of the resin (Scheme 196). However, ^{1}H and ^{13}C NMR spectroscopy could not substantiate complete reaction because the spectral lines were broad.

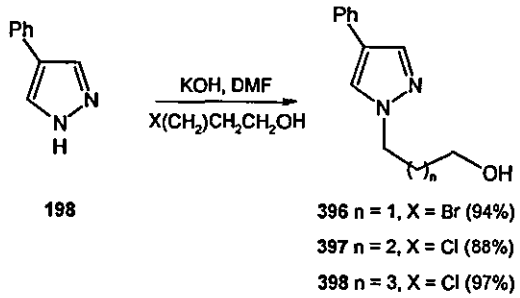
Nucleophilic displacement of the alkyl halide was not possible in appreciable yield without deterioration of the polymer. Neither pyrrole-2-carbaldehyde **244** or 2-methyl-4-formylimidazole could be attached under various conditions. Solution phase protocols gave rise to high yields of alkylation in the presence of lower equivalents of the heterocycle and base, consequently the solid phase approach had been expected to succeed.



Scheme 196: *Loading of heterocyclic radical cyclisation precursors*

Because direct alkylation of the alkyl halide was not possible without degradation of the polymer, alternative loading mechanisms were sought. An alcohol can be converted readily to the corresponding alkyl selenide under mild reaction conditions using trisubstituted phosphines and a selenide attached to a suitable nucleophilic leaving group. The pyrazole alcohols **396-398** shown in Scheme 197 were chosen for the attempted loading to PS selenyl bromide **386** due to the lack of oxygenated functionalities and hence lower potential for interference from tributylphosphine or the selenide source as discussed relating to the synthesis of acyl selenides in

Chapter 3. 4-Phenylpyrazole was alkylated in good yield (88-94%) with a range of chloro and bromo alcohols in the presence of potassium hydroxide.

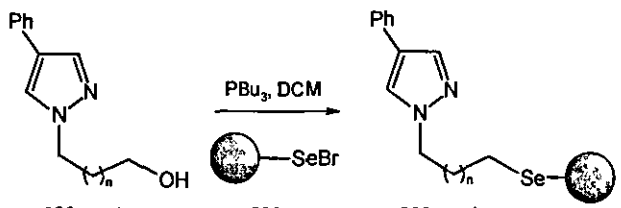


198

396 n = 1, X = Br (94%)
397 n = 2, X = Cl (88%)
398 n = 3, X = Cl (97%)

Scheme 197: *Synthesis of pyrazole derived alcohols*

The tributylphosphine mediated coupling of 4-phenylpyrazole alcohols **396-398** was attempted using PS selenyl bromide **386** (Scheme 198). The strong P=O bond was the driving force for the reaction and should allow the ready conversion of the alcohols to the desired alkyl selenides **399-401.** Unfortunately a decreased mass following reaction was consistently observed under a variety of conditions (alteration of time, temperature and addition order). Standard elemental analysis also confirmed that the desired reaction had not occurred. However, the decreased mass and colour change of the resin indicated consumption of the selenyl bromide functionality had occurred.



396 n = 1
397 n = 2
398 n = 3

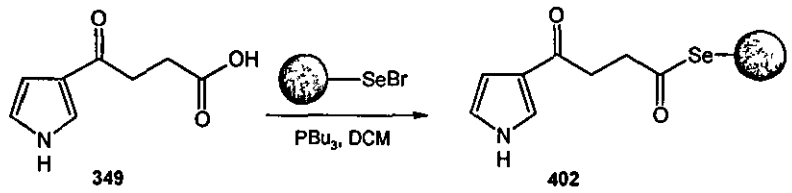
386

399 n = 1
400 n = 2
401 n = 3

Scheme 198: *Attempted tributylphosphine mediated loading of alcohols*

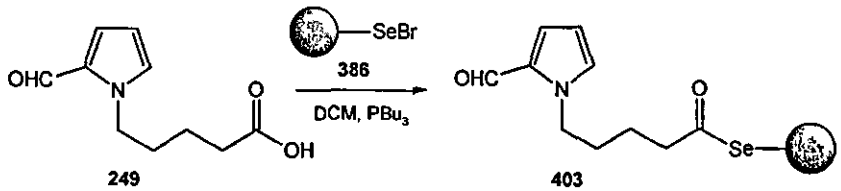
The failure to load alcohols to PS selenyl bromide **386** was not encouraging for the proposed attachment of carboxylic acids because the mechanism of acyl selenide formation is essentially the same. The first substrate attempted was related to our studies towards mitomycin (Chapter 3). 4-Oxo-4-(1*H*-pyrrol-3-yl)butanoic acid **349** was chosen because the acyl selenide was obtained in high yield in the solution phase studies.

The cyclisation of the solution phase acyl selenide analogue **351** derived from 4-oxo-4-(1*H*-pyrrol-3-yl)butanoic acid **349** has been shown to be unfavourable and decarbonylation dominates (Scheme 172). The *pseudo*-dilution effect of the resin during cleavage may help prevent radical reduction, hence the cyclisation could be carried out under high CO pressure in a sealed tube to inhibit decarbonylation as no slow syringe pump addition is required.



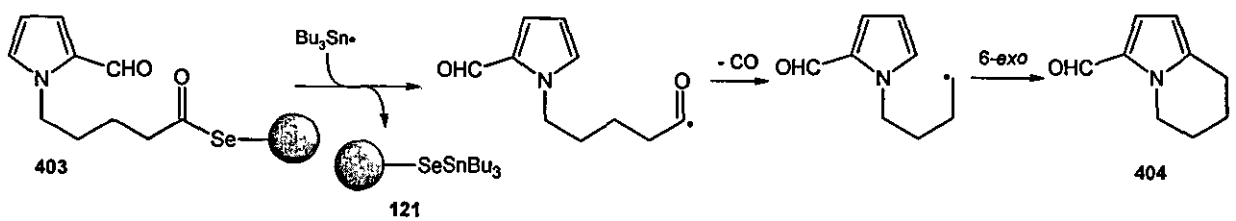
Scheme 199: *Attempted loading of acyl selenides to PS support*

Attempts to load 4-oxo-4-(1*H*-pyrrol-3-yl)butanoic acid **349** to solid support failed to give adequate loadings of the acyl selenide **402** (~0.06 mmol.g^{-1}) under selenation conditions used successfully during the solution phase investigations outlined in the previous chapter (Scheme 199). Several other heterocyclic carboxylic acids were equally unsuccessful. However, attachment of 5-(2-formyl-1*H*-pyrrol-1-yl)pentanoic acid **249** as the acyl selenide **403** shown in Scheme 200 was partially successful, although the resin loading was low (0.13 mmol.g^{-1}).



Scheme 200: *Attachment of acyl selenide precursors*

Homolytic cleavage of the resin bound acyl selenide **403** was achieved using tributyltin hydride and AIBN in toluene under reflux. The 'normal' tributyltin hydride conditions (i.e. absence of CO) resulted in cyclisation of the decarbonylated alkyl radical to yield **404** as the only compound identified by ^{1}H NMR spectroscopy.



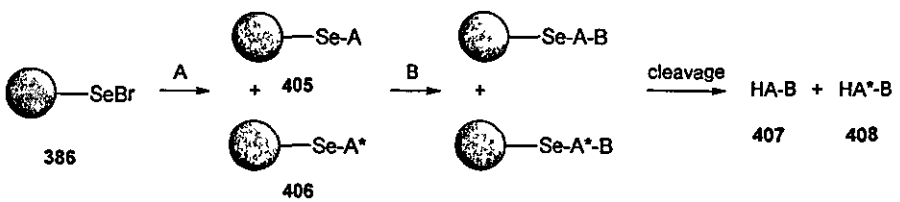
Scheme 201: *Traceless cleavage of PS bound acyl selenide*

The unexplained failure to load heterocyclic substrates to the PS selenyl bromide support in adequate yield had to be addressed. The resin characteristics also required improving to allow better spectroscopic analysis, hence a new solid supported selenium system was developed

4.3 Synthesis of Quadragel Bound Selenyl Bromide

The preparation of a new resin bound selenium reagent was an attractive proposal because the previous method had a number of drawbacks. The necessity to use dimethyl diselenide was a principal flaw because it was volatile and had a particularly foul smell, in addition to which it was expensive for large-scale preparations and highly toxic. Alternative resin bound selenium reagents exist but suffer similar drawbacks,[162] although recent advances have been published during our studies.[163] The new route, therefore, had to make use of less expensive materials that were more suitable to handle on a regular basis.

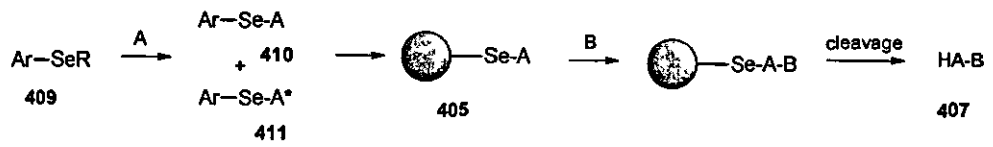
The use of dimethyl diselenide also gave rise to versatility limitations. For example, if a given reaction scheme utilises selenium chemistry (step A) to form the resin bound selenide **405** is accompanied by a side product **406**, this mixture must be carried through the sequence using the original PS methylselenide approach (Scheme 202). If step B or the cleavage from the resin were the only steps to benefit from solid supported chemistry, then the product following cleavage will contain an undesirable mixture of products **407** and **408**. Following a solution phase approach the impurity following the loading step could have been removed from the mixture. The question then arises whether attaching the substrate to the solid support has been beneficial as the separation of **407** and **408** must still be performed following cleavage.



Scheme 202: *Problems associated with direct attachment of methyl selenide to solid support*

Ideally the resin should incorporate greater latitude to perform the selenium chemistry and any subsequent problematic steps in solution phase followed by loading to the solid support of the purified precursor. In the theoretical scenario displayed in Scheme 203 step A was performed in solution-phase, purified and aryl selenide **410** was attached to the resin so that only the desired resin bound substrate **405** reaps the rewards of the solid supported chemistry. Unlike the

previous example (Scheme 202) the product of cleavage no longer contains artefacts of the impurity **411** such as compound **408**. The design of a new resin bound selenium reagent should allow greater flexibility such as this in the loading strategies.

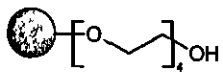


Scheme 203: *Flexible approach to selenide attachment*

Spectroscopic properties of the resin also required improvement. The peak broadening exhibited by gel-phase samples in NMR spectroscopy can be reduced by the use of MAS-NMR spectroscopy using sophisticated NMR instrumentation. The instrumentation is expensive and not available to the majority of chemists. In addition the parameters to reduce chemical shift anisotropy require significant optimisation to decrease line broadening and increase signal strength.

The selenium functionalities under study were linked directly to the PS backbone, hence NMR spectroscopic analysis was not possible using the standard 400 MHz NMR spectrometer available during the research. Improved analysis is required because the attempted loading of heterocyclic substrates to PS selenyl bromide **386** inexplicably failed to yield adequate results. In the absence of suitable spectroscopic analysis the problems encountered during the reaction remained unsolved. A suitable linker can allow the examination of resin bound samples using standard NMR spectroscopic techniques by allowing the substrate more mobility in the solution phase.

The new resin design, therefore, has to render the aryl selenide functionality more homogeneous in solution phase reactions. Consequently the addition of the selenium reagent must be selective to the linker functionality to give complete regioselective addition, ruling out the previous direct lithiation of the polymer backbone. A resin system matching the prerequisites was kindly donated by AstraZeneca, Alderley Park based on tetraethyleneglycol attached to hydroxylated PS 1% crosslinked with DVB and is sold as Quadragel **412** (Figure 7). Similar systems such as Tentagel make use of PEG linkers but are more susceptible to mechanical breakdown and the PEG unit length is not controlled.



412

Figure 7: *Quadragel resin developed by Astrazeneca*

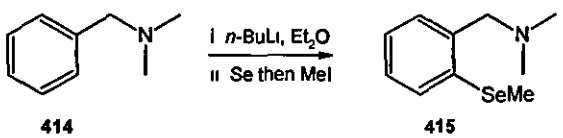
The selenide reagent must be tethered to an aryl moiety in order to provide suitable selectivity during homolytic cleavage. Conversion of the terminal alcohol of quadragel **412** to a suitable leaving group should allow the introduction of a phenoxide nucleophile containing the selenium functionality required for the quadragel bound selenyl reagent **413** (Scheme 204). Phenols are relatively acidic and the corresponding phenoxide can be generated under relatively mild basic conditions.

412 413

Scheme 204: *Putative synthesis of quadragel bound selenides*

Selenyl bromides will not tolerate the basic conditions required for attaching the phenoxide, hence a protected selenide must be attached to the resin. To yield clean conversion to the selenyl bromide the corresponding 4-methylselenyl-phenol should be attached to the solid support. Synthesis of the desired selenide could be envisaged *via* a number of routes, although close examination of many reported procedures indicates the yields are poor when either fragment is not aromatic.[164,165] These procedures were of little use to this project and the more limited scope of alkyl arylselenides must be examined.

Quenching aryl anions with metallic selenium is a common procedure for the synthesis of aryl selenides and stabilisation of the lithium salt of **414** can enhance reaction rates (Scheme 205).[166] The presence of the suitably disposed nitrogen lone pair results in regioselective lithiation and the selenium was thus directed. This technique has been used recently in the synthesis of a novel PS selenyl reagent.[167] However, for simplification of the resin NMR spectrum a *para*-substituted system was sought.



414 415

Scheme 205: *Heteroatom-directed aromatic lithiation for the synthesis of aryl selenides*

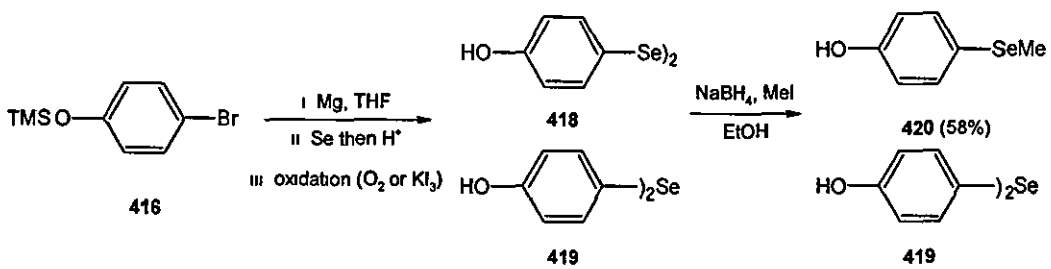
Initially, copper (I) mediated couplings were attempted with 4- bromo(phenoxy)trimethylsilane **416** and sodium phenylselenolate as a test substrate.[168] Unfortunately, these failed to yield any of the biaryl selenide **417** (Scheme 206). Although the sodium selenolates are potent nucleophiles, attempts to perform S_NAr substitutions in the absence of copper (I) iodide also failed.

416 **417**

Scheme 206: *Attempted copper (I) iodide catalysed selenation*

Halogen-lithium exchange was also attempted by the slow addition of *n*-BuLi to 4-bromo(phenoxy)trimethylsilane **416** in THF at –78 °C and quenching the resultant aryl lithium compound with dimethyl diselenide as identification of the desired methyl selenide would be readily achieved. If the conditions proved synthetically useful metallic selenium was going to be used in place of dimethyl diselenide followed by conversion to the methylselenide. However, all variations in the starting material equivalents resulted in a complex mixture of products.

Addition of powdered selenium to the aryl Grignard reagent derived from treatment of 4-bromo(phenoxy)trimethylsilane **416** with magnesium afforded the unprotected diselenide **418** upon oxidative workup, which was methylated to yield the desired 4-methylselenyl-phenol **420** for attachment to quadragel (Scheme 207). Unfortunately, the selenation reaction not only affords the required diselenide **418** but also other products such as the biaryl selenide **419** even in the absence of light, external heat source and oxygen.



416 **418** **419** **420 (58%)** **419**

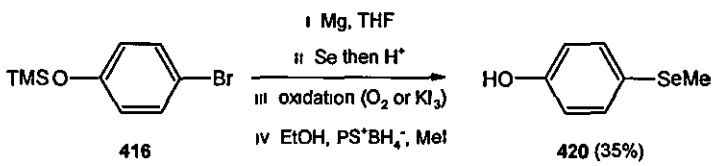
Scheme 207: *Synthesis of methyl with in situ desilylation*

The biarylselenide **419** was consistently identified as the major by-product and the mixture of **418** and **419** was isolated in 74% combined yield. This unwanted side product co-elutes with the diselenide **418** although separation of 4-methylselenyl-phenol **420** from the biarylselenide **419** was straight forward using column chromatographic purification. Hence the mixed product of the

diselenide **418** and biaryl selenide **419** was subjected to sodium borohydride in alcohol followed by methyl iodide because only the diselenide **418** could be reduced.

Initially the biaryl selenide **419** and diselenide **418** were separated from the reaction mixture although this was not necessary because the methylation can be performed on the crude product directly. 4-Methylselenyl-phenol **420** was prepared in a slightly increased overall yield of 51% compared to the 45% yield from the 'purified' diselenide **418** starting material. The final yields were slightly disappointing, but this approach benefits from the *in situ* deprotection presumably during the acidic quench of the Grignard reaction. However, the overall yield was good considering the number of chemical transformations, i.e. conversion of the TMS protected 4-bromophenol **416** to the Grignard reagent, selenation, protonation, oxidation to the diselenide, conversion of the diselenide to the sodium salt and methylation to yield 4-methylselenyl-phenol **420**. It is our suggestion that any future synthesis should perform the methylation directly following selenation to prevent the formation of mono- and triselenides during the oxidative workup.

In further efforts to improve workup, solid-phase borohydrides have also been used in the reduction of the diselenide **418** in the synthesis of 4-methylselenyl-phenol **420** (35%) in slightly diminished yield (Scheme 208).[165] Although workup was moderately improved there were not sufficient improvements to warrant the additional cost.

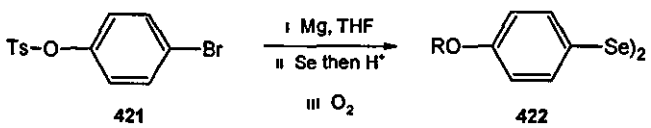


Scheme 208: *Solid supported borohydride reagent in reduction of diselenide*

4-Bromo(phenoxy)trimethylsilane **416** used in the original preparation of 4-methylselenyl-phenol **420** is commercially available but costly and routes to the compound involve the use of other expensive silylating agents. To produce a viable route to the synthesis of a supported reagent the costs need to be minimised because the loading procedures often involve an excess of reagents.

The same methodology to the synthesis of 4-methylselenyl phenol **420** was attempted with tosyl protected 4-bromophenol **421** because the starting materials were significantly cheaper. The

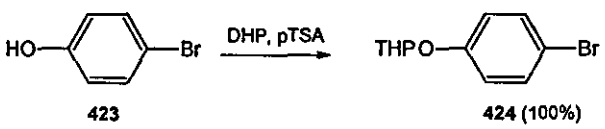
tosyl protection was achieved in moderate yield (60%) by rapid stirring of sodium hydroxide in DCM with 4-bromophenol and tosyl chloride, allowing for a rapid and efficient aqueous workup. Unfortunately, attempts to form the aryl anion by halo-lithium exchange and by formation of the Grignard failed to give any of the desired product **422** (Scheme 209). This was unfortunate because the tosyl group would deactivate the aryl ring and hopefully retard the formation of the biaryl selenide **419**. The tosyl group would also be insensitive to the mildly acidic conditions used and should, therefore, remain attached following selenation possibly allowing separation from the biaryl selenide **419** at that point.



Scheme 209: *Attempted selenation of tosylated 4-bromophenol*

We considered that 'protection' of 4-bromophenol as the sodium phenoxide might be possible by deprotonation with sodium hydride. Unfortunately, treatment of the sodium phenoxide with magnesium failed to yield any product. The synthesis had, therefore, to be based on a new protection strategy compatible with the reaction conditions and removed with a mild cleavage procedure.

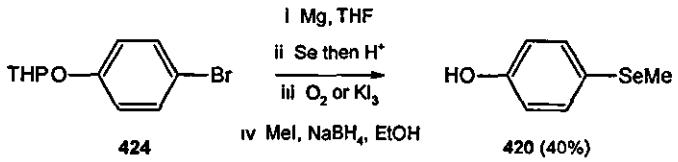
Based on the cost of starting materials, mild cleavage conditions and ease of preparation THP protected 4-bromophenol **424** was identified as the ideal starting material. THP protection of 4-bromophenol **423** can be achieved quantitatively in the presence of neat DHP and catalytic tosic acid (Scheme 210).[169] The THP protected material **424** was isolated following aqueous workup and sufficiently pure to proceed with the outlined route used for TMS protected material. The procedure was amenable to scale-up and does not require solvent, ideal for large-scale preparations.



Scheme 210: *THP protection of 4-bromophenol*

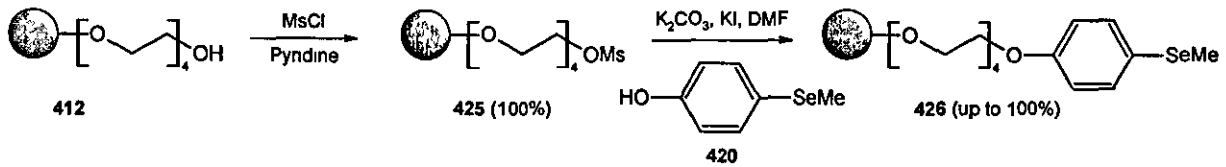
Treatment of the THP protected material to the same selenation, oxidation and methylation conditions as for the TMS protected material yielded the same unprotected methyl selenide **420**

(40%) in diminished yield (Scheme 211). However, the procedure was significantly cleaner and more reproducible affording the biarylselenide **419** and 4-methylselenyl-phenol **420** almost exclusively from the reaction mixture. Fortuitously, the THP group was also removed during workup, thereby eliminating the need for an additional deprotection step. However, any future usage of this procedure should examine the effect of performing the reactions in diethyl ether in place of THF. The proportion of diarylmagnesium compounds (Ar_2Mg) defined by the Schlenk equilibrium present in aromatic Grignard solutions is increased in THF relative to ether,[170] thus hindering the reaction.



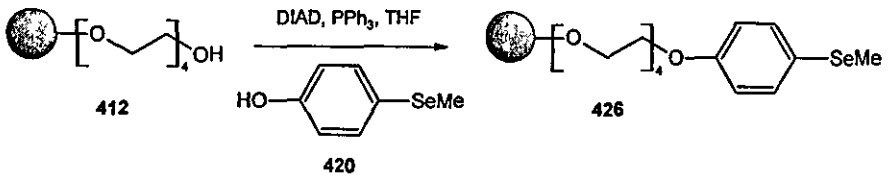
Scheme 211: *THP protected 4-bromophenol in selenation reactions*

Coupling 4-methylselenylphenol **420** to the resin could potentially be achieved in a number of ways. In the first method the quadragel **412** was converted to the corresponding mesylate **425** followed by displacement with the phenoxide anion to yield quadragel methylselenide **426** in good yield (Scheme 212). The yields of the mesylate displacement were variable though.



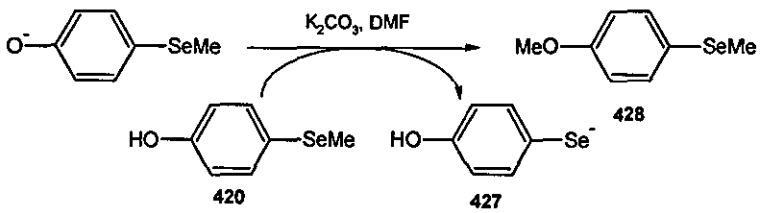
Scheme 212: *Mesylation and loading of the phenoxide*

We also attempted an alternative route to the required quadragel methyl selenide **426** was *via* Mitsunobu coupling of 4-methylselenyl-phenol **420** and quadragel **412** (Scheme 213). Although the mass change following reaction matched the theoretical mass change it was evident from ^{1}H and ^{13}C NMR spectroscopy that the desired transformation had not occurred entirely. The additional mass was accounted for by the apparent incorporation of the azo compound into the matrix as the ^{1}H NMR spectrum indicated. However, the unforeseen complications involving the DIAD, resulted in the use of the mesylate displacement procedure.



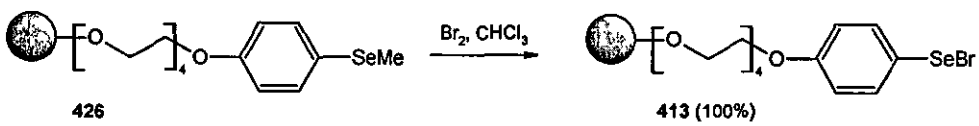
Scheme 213: *Mitsunobu coupling of 4-methylselenyl-phenol*

Use of Mitsunobu coupling of 4-methylselenyl phenol **420** to quadragel **412** could have eliminated the mesylation step on the resin, in addition to the potential demethylation of the methyl selenide (Scheme 214).[171] Some evidence for demethylation was obtained following the attempted isolation of unreacted methylselenide **420** from the mesylate displacement reactions. Demethylation of 4-methylselenyl phenol by the phenoxide renders the dimethylated product **428** useless in the alkylation reaction. Additionally, the selenolate **427** may attack the quadragel mesylate **425** resulting in a mixture of compounds attached to quadragel.



Scheme 214: *Demethylation of methylselenides*

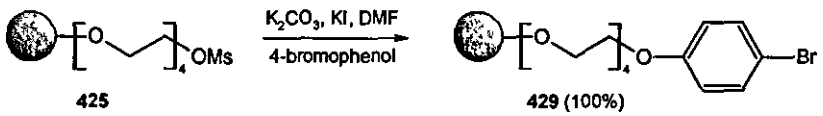
Quadragel methylselenide **426** was converted to the desired quadragel selenyl bromide **413** in quantitative yield with bromine (Scheme 215). This procedure was efficient and robust because the methyl selenide has a high affinity for bromine and the elimination of methyl bromide was rapid and essentially irreversible in an open system at elevated temperature. Quadragel selenyl bromide resin **413** is a highly versatile precursor for use in all areas of selenium chemistry and has been prepared without the use of highly toxic or volatile alkylselenides. We believe our resin provides a useful alternative to that reported by Nicolaou.



Scheme 215: *Bromination of quadragel methylselenide*

Although no attempts have been made to prepare the Grignard reagent on solid support, some attempts were made to perform halogen-lithium exchange on supported quadragel phenoxy

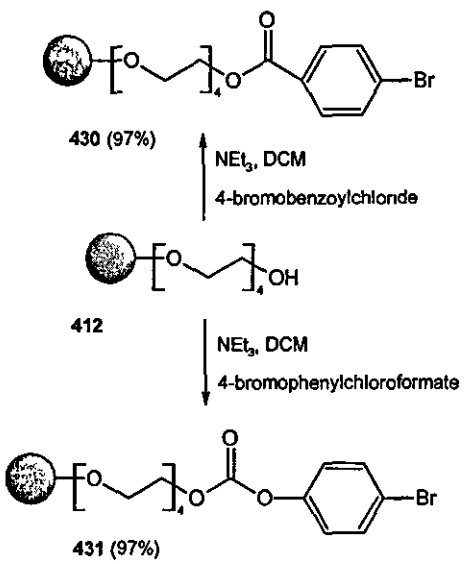
bromides **413** (Scheme 216) to facilitate the selenation on the solid support. The analogous solution phase reaction indicated a large mixture of products. The by-products were likely to be directly derived from reaction of the excess of *n*-butyllithium with the selenium electrophile. We rationalised that removal of the excess butyllithium by decanting would remove many of the problems associated with solution phase protocol because the lithiated quadragel could be swollen in fresh solvent and quenched with selenium metal.



Scheme 216: *Quadragel supported aryl bromides*

Initial studies made use of dimethyldiselenide because the resin had been fully characterised and the success of the reaction could be determined by standard ^{1}H NMR spectroscopy (δ_H 2.30 ppm). Unfortunately, lithiation of 4-bromophenoxy quadragel **429** and quenching with dimethyl diselenide failed to yield quadragel methylselenide **426**. Consequently, ester **430** and carbonate **431** linkages were investigated due to the high yield of loading and the ability to stabilise the anion (Scheme 217).

Unfortunately treatment of both the ester and carbonate resins with *n*-BuLi resulted in exclusive cleavage at the linkage site even at low temperature. As a result of these failures, attempts to introduce the selenium functionality directly onto the polymer support were ceased and the direct attachment of 4-methylselenyl-phenol **420** to the resin was used.

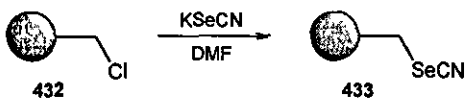


Scheme 217: *Ester and carbonate linked aryl bromides*

Having prepared a suitable solid supported selenium functionality the task was in hand to study the reactivity and limitations of this new quadragel selenide reagent. The preparation of heterocyclic precursors was to be attempted for homolytic cleavage, although firstly the reactivity in standard selenium chemistry was investigated.

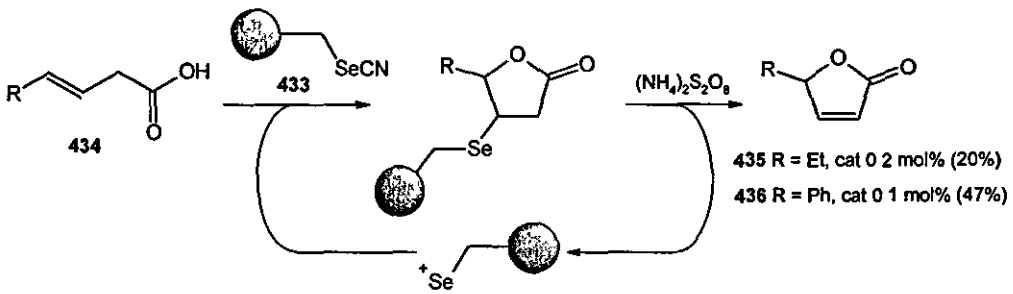
4.3.1 SELENOLACTONISATION

In order to study the efficiency of the quadragel bound selenyl bromide in non-radical synthesis the resin was used as the catalyst for a selenolactonisation protocol using ammonium sulfate in the presence of a suitable unsaturated carboxylic acid.[100] The reported procedure made use of supported selenocyanides **433** derived from the halide displacement of Merrifield resin **432** (4.3 $mmol.g^{-1}$, crosslinked with 2% DVB) with potassium selenocyanide (Scheme 218). As the resin had no linker and was significantly crosslinked, the only method of identification available was that of IR spectroscopy by analysis of the bond stretch of the cyano group. Elemental analysis indicated almost complete conversion.



Scheme 218: *Synthesis of PS selenocyanides from Merrifield resin*

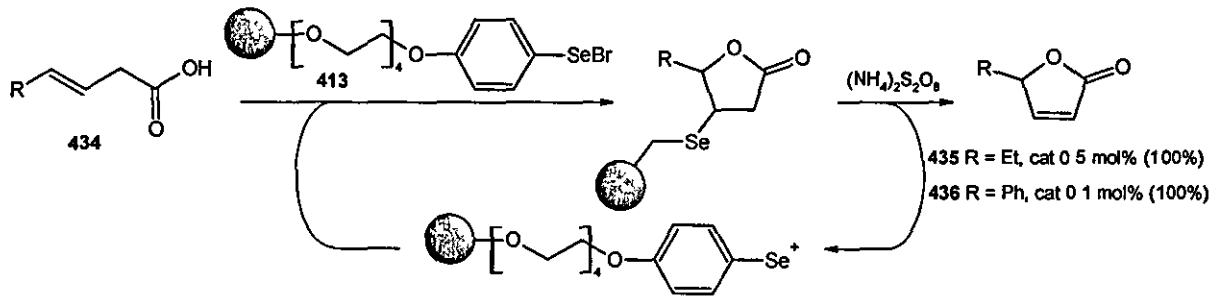
The authors reported the use of PS selenocyanide **433** in catalytic selenolactonisations using low catalyst loadings of 0.1-0.2mol%, although yields were reasonably low (Scheme 219). Solution phase phenyl selenyl bromide performed better giving 5-phenyl-5*H*-furan-2-one **436** in 81% yield from (*E*)-4-phenyl-but-3-enoic acid **434** (R = Ph) but only 31% of 5-ethyl-5*H*-furan-2-one **435** from *trans*-3-hexenoic acid **434** (R = Et).



Scheme 219: *Catalytic selenolactonisation using PS selenocyanide*

Initially the selenolactonisation of (*E*)-4-phenyl-but-3-enoic acid **434** (R = Ph) was performed with 0.5 mol% of quadragel selenyl bromide **413** catalyst due to the moderate yields of the

previous work. However, the reaction was found to have gone to completion and so 0.1 mol% of the quadragel selenyl bromide **413** was used, again resulting in quantitative conversion to the lactone (Scheme 220). Selenolactonisation of *trans*-3-hexenoic acid was also performed to yield 5-ethyl-5*H*-furan-2-one **435** quantitatively with 0.5 mol%; lower loadings were not investigated.



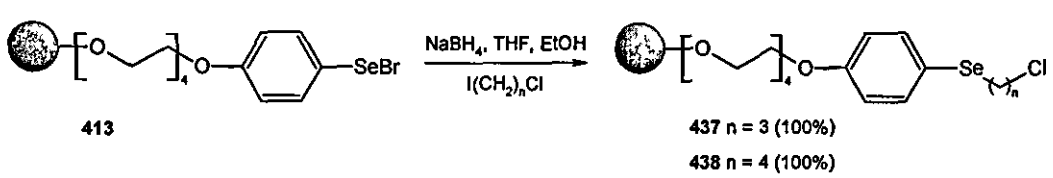
Scheme 220: *Selenolactonisation using Quadragel bound selenyl bromide*

We have shown a significant enhancement in selenolactonisation procedures using quadragel selenylbromide **413**, presumably due to the stabilisation of the selenium electrophiles by the *para*-oxygen. Much of the work published by Nicolaou on PS bound selenides makes use of oxidative cleavage in the synthesis of benzopyran systems (Scheme 193). It was our aim to develop a catalytic system of cyclisation onto solid support and oxidative cleavage, unfortunately time constraints did not allow this.

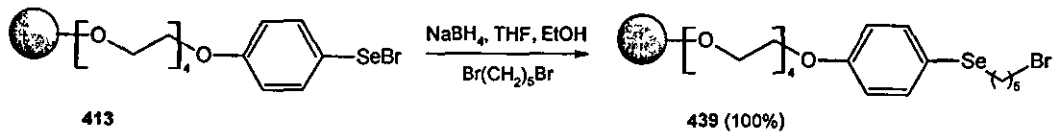
4.3.2 Synthesis of Quadragel Bound Alkyl and Acyl Selenides

The possibility of increased versatility in the selenide attachment has been discussed earlier in this chapter. We have devised four routes for the loading of the selenide precursors to the solid support. Each of the four routes has distinct benefits and drawbacks but offers flexibility.

The first route reflects the approach taken by Nicolaou[94] as we attached an aryl methylselenide to quadragel with subsequent conversion to the quadragel selenyl bromide. Conversion of the quadragel bound selenyl bromide **413** to the required alkyl selenides **437**, **438** and **439** was successfully achieved by treatment of the resin with sodium borohydride in methanol-THF in the presence of a suitable alkylating agent (Scheme 221 and Scheme 222).

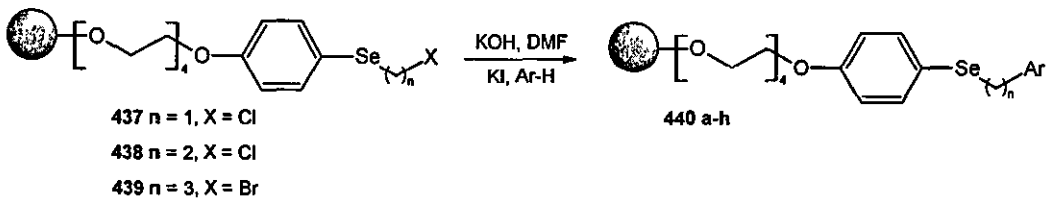


Scheme 221: *Synthesis of halo-propyl and -butyl selenides*



Scheme 222: *Synthesis of bromo-pentyl selenides*

The quadragel bound alkyl halides **437, 438** and **439** underwent conversion to suitable radical cyclisation precursors by displacement of the halide with a heterocycle to yield the cyclisation precursors **440a-h** (Scheme 223). A number of heterocyclic 5-, 6- and 7-*exo* homolytic aromatic substitution systems as described in Table 4 were synthesised based on the success of their solution phase counterpart.



Scheme 223: *Attachment of heterocycles to quadragel bound selenides*

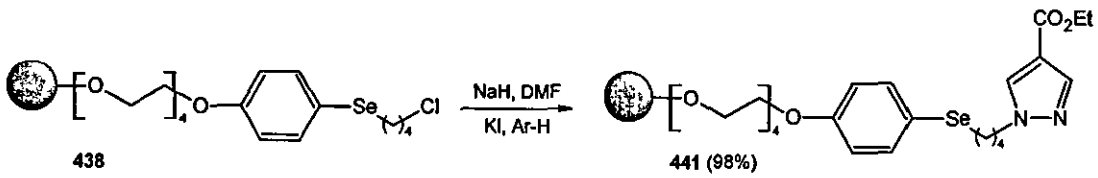
This technique allows the synthesis of a number of precursors from common intermediates quadragel selenyl bromide **413** and the alkyl halide derivatives **437-439**. Unfortunately, in contrast to the analogous solution phase protocols the procedure requires a number of equivalents to force the reaction to completion.

STARTING RESIN	HETEROCYCLE	YIELD
437	Pyrrole-2-carbaldehyde	100%, **440a**
437	4-Phenylpyrazole	100%, **440b**
437	Indole-3-carbaldehyde	100%, **440c**
438	Pyrrole-2-carbaldehyde	98%, **440d**
438	2-Chlorobenzimidazole	98%, **440e**
438	Indole-3-carbaldehyde	97%, **440f**
438	3-Acetylpyrrole	99%, **440g**
439	Pyrrole-2-carbaldehyde	100%, **440h**

Table 4: *Loading yields of heterocycles to quadragel alkyl selenides*

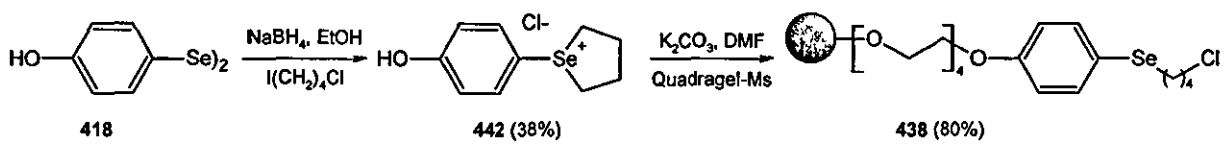
Yields of heterocycle alkylation calculated by mass change of the dried resin were slightly ambiguous because yields of >100% were occasionally obtained. Conversely yields calculated from standard elemental analysis of the resins were lower than the predicted yield, possibly because the measured nitrogen content was typically lower in resin samples due to incomplete combustion. Quantification using ^{77}Se NMR spectroscopy was to be investigated but time limitations did not allow this course of action.

Due to the incompatibility of ethyl pyrazole-4-carboxylate **141** with alkylation conditions based on potassium hydroxide in DMF, sodium hydride was used to facilitate the loading to the quadragel selenide **438** in high yield (Scheme 224).



Scheme 224: *Loading of ethyl pyrazole-4-carboxylate*

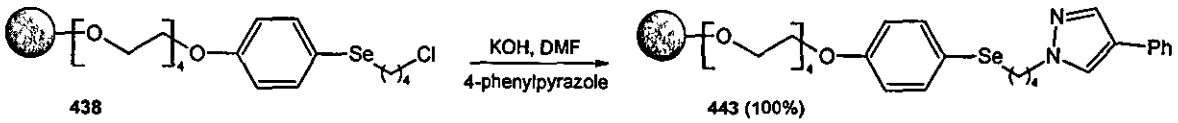
The second, less versatile approach was carried out for the synthesis of a functionalised aryl selenide **442**, which can be attached to solid support for further derivatisation (Scheme 225). Interestingly, the increased electron density of the aryl ring facilitates intramolecular attack of the selenide onto the alkyl halide producing tetrahydro-selenophenium chloride **442**. Yields were comparable to the related synthesis of 4-methylselenylphenol **420**, however the procedure benefits from the poor solubility of the selenide salt because the compound can be recrystallised from methanol in the presence of the biaryl side product **419**, eradicating chromatographic purification.



Scheme 225: *Synthesis and loading of phenolic alkyl selenide to quadragel*

There was some ambiguity about the nature of the counterion because either iodide or chloride can participate, although elemental analysis and ^{13}C NMR spectroscopy indicates that the chloride anion was present. ^{13}C NMR spectroscopy of resin **438** also indicates that the selenide bound to the resin may be present largely as the open chain form as shown in Scheme 225, rather

than the tetrahydro-selenophenium salt. The same selenide precursor **438** as the first procedure was thus possible from solution-phase preparations and attachment to the resin in similar overall yield. The benefits of improved purification and fewer reaction steps in addition to the lack of ambiguity surrounding the compound attached to the resin make this an attractive procedure.
The selenide precursor **438** was further functionalised in a similar manner to the previous route by nucleophilic displacement of the halide with 4-phenylpyrazole **198** to yield the desired selenyl precursor **443** in good yield (Scheme 226).

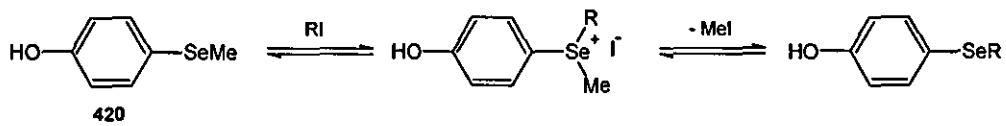


438 443 (100%)

Scheme 226: *Synthesis of quadragel N-(butyl)4-phenylpyrazole*

Alternatively, a third route resulted from the serendipitous discovery of the facile addition of alkyl halides across this phenolic selenide as shown in Scheme 227. This introduces the potential for a novel, clean and potentially efficient route to alkyl selenides directly from an alkyl halide and a methyl selenide.

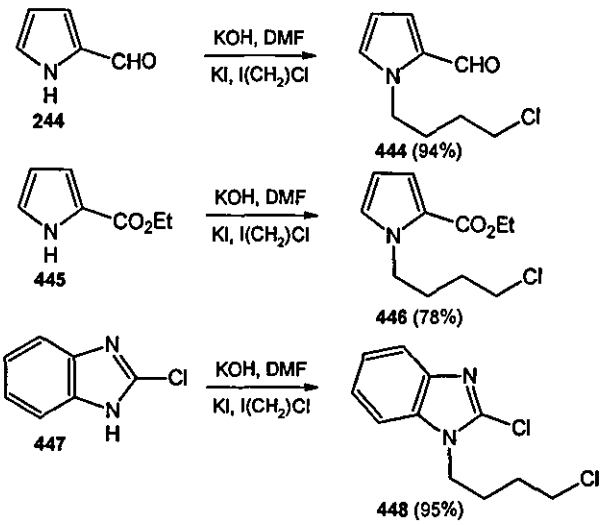
An equilibrium exists between the aryl methylselenide **420** and the trisubstituted selenonium. The resultant trisubstituted selenonium is also in equilibrium with the aryl alkylselenide (Scheme 227). As methyl iodide is highly volatile, thermal activation should result in an increased formation of the aryl alkylselenide as the methyl iodide will be removed from the second equilibrium equation.



420

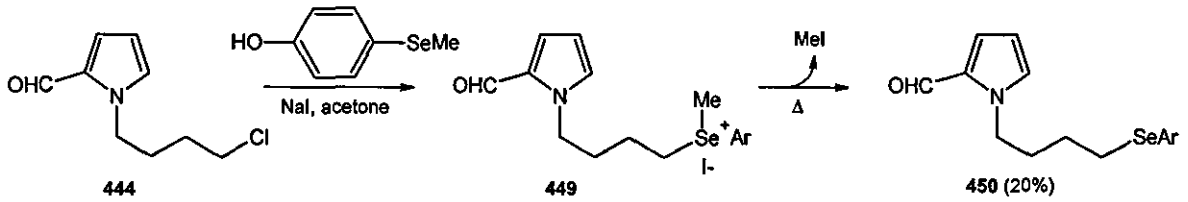
Scheme 227: *Addition of alkyl iodides to aryl methylselenides*

Heterocyclic precursors pyrrole-2-carbaldehyde **244**, ethyl pyrrole-2-carboxylate **445** and 2-chlorobenzimidazole **447** were alkylated with 4-iodo-1-chlorobutane to yield alkylchlorides **444**, **446** and **448** in good yield (Scheme 228) with a view to attaching to a solution phase or quadragel bound methyl selenide via the mechanism shown in Scheme 227.



Scheme 228: *Synthesis of alkyl halides for attachment to quadragel*

Addition of the alkyl halide to the methyl selenide was expected to lead to the selenonium salt **449** with subsequent loss of the volatile methyl iodide, thus shifting the equilibrium. Treatment of the alkyl halide **444** with sodium iodide in acetone under reflux in the presence of the methyl selenide **430** yielded the desired alkyl selenide **450** in low yield (20% by ^{1}H NMR) and unreacted starting material (Scheme 229).

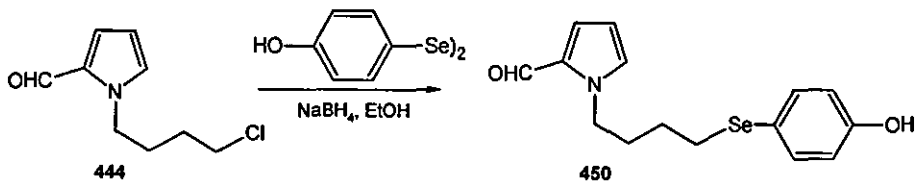


Scheme 229: *Synthesis of alkyl selenides from methylselenyl phenol*

Attempts to improve this by application of high vacuum to remove methyliodide rapidly resulted in a neat mixture that did not react any further. The reaction also failed completely for the benzimidazole derivative **448**. This protocol needs considerable work to improve it, but it could potentially provide a clean and efficient route to the synthesis of aryl alkyl selenides.

The final route investigated for the attachment of aryl alkylselenides to solid support is the least flexible methodology, but was potentially the most reliable because all but the loading and cyclisation/cleavage step can be performed in solution (Scheme 230). The specificity of the route does limit the applicability in the systems being studied, but there was no reason to suggest functional diversity could not be introduced later in solution or on-bead. Additionally there was

no methyl selenide group for removal (Scheme 214), the material was already alkylated and direct attachment would yield the cyclisation precursor or allows further on-bead manipulations.



Scheme 230: *Use of the diselenide to prepare precursors in solution-phase*

Attempts to synthesise aryl alkylselenide **450** from the alkyl chloride **444** failed due to the poor reactivity of the alkyl chloride toward the quadragel selenoborate complex. No product was observed in the reaction of alkyl chlorides **444, 446, 448** even in the presence of sodium iodide. It is apparent the alkyl bromide or alkyl iodides must be used directly in these reactions.

The resin loading procedures require significant optimisation but we have presented a more flexible approach to the synthesis of resin bound alkyl selenides. This approach can also accommodate the use of chemistry involving multiple products prior to attachment to the solid support as the compounds can be loaded to the resin at different points during the synthesis.

Another issue this procedure wanted to address was that of characterisation. PS selenides were not amenable to spectroscopic analysis, whereas quadragel linker allows clear IR spectroscopy. ^{13}C NMR Spectroscopic analysis in particular was superior to PS derivatives (Figure 8).

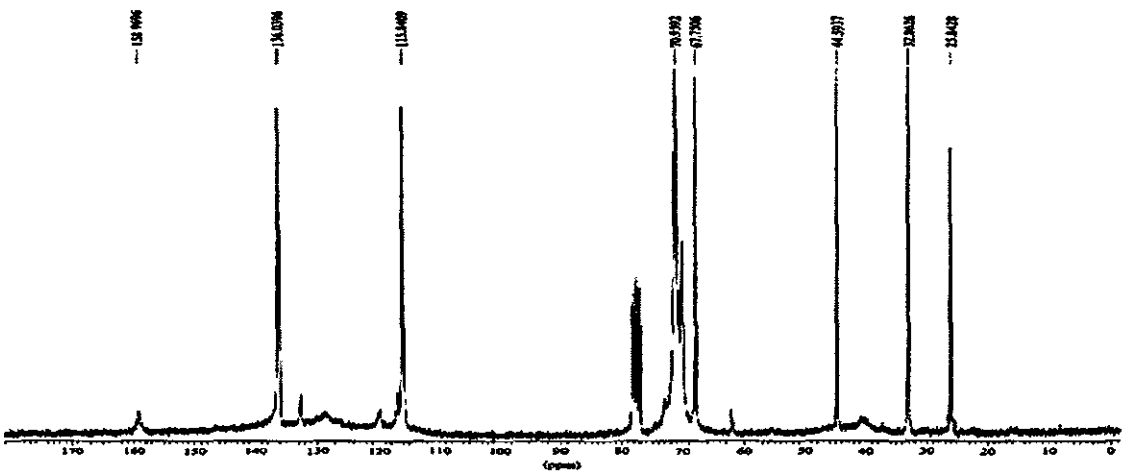


Figure 8: *^{13}C NMR spectrum of Quadragel chloro-propylselenide*

^{1}H MAS-NMR spectral analysis was performed successfully by Richard Lewis during my placement at Astrazeneca. Standard ^{1}H NMR spectroscopy renders identification of most functional groups difficult with the exception of aldehyde and alkenes due to the broad PS and PEG peaks.Standard KBr pellets of the ground resin were sufficient to provide good infrared spectra (Figure 9) because ATR spectra of the compressed swollen resins was poor.

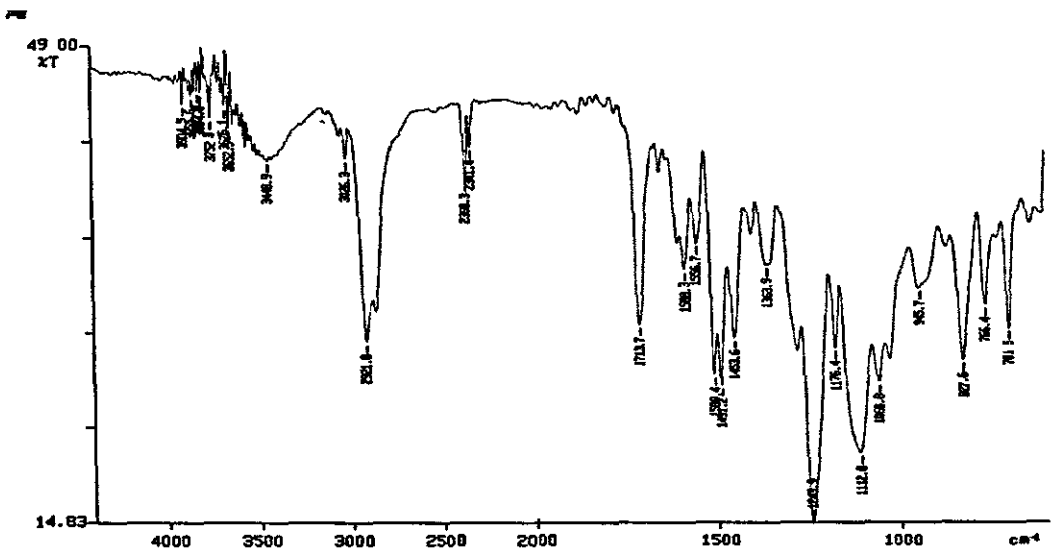
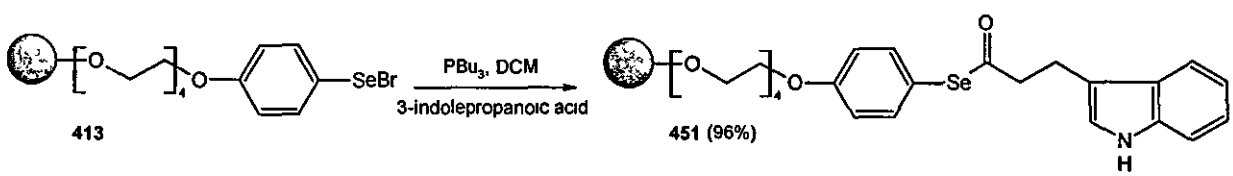
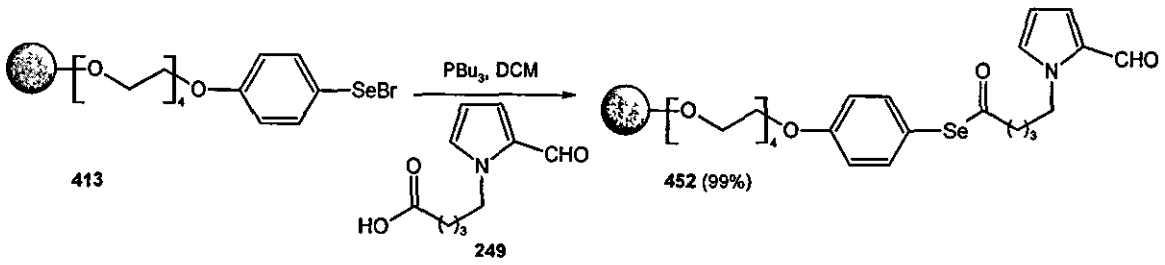


Figure 9: *Infra-red spectrum of N-butyl-ethyl(pyrazole-4-carboxylate)*

The synthesis of acyl selenides from PS selenyl bromide **413** was accomplished with partial success in one case due to an unknown side reaction interfering with a loss in mass and colour change observed. Similar conditions were used for the synthesis of acyl selenides from quadragel selenyl bromide **413** with greater success (Scheme 231 and Scheme 232). Unfortunately, cleavage to yield the indole acyl radical is unlikely to yield cyclisation because alkyl radical cyclisation onto indoles in this manner is not high yielding, even in more favoured systems.[19]



Scheme 231: *Attachment of 3-indolepropanoic acid to quadragel*

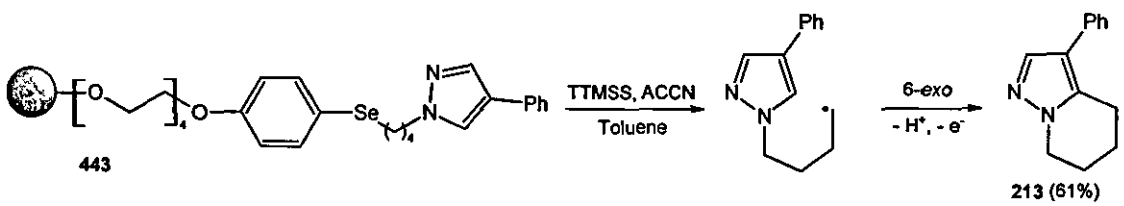


Scheme 232: *Attachment of 5-(2-formyl-1H-pyrrol-1-yl)pentanoic acid to quadragel*

From our initial studies into the quadragel resin chemistry it is abundantly clear that this approach is more suited to the attachment of heterocyclic radical annulation precursors. The effect of the *para*-oxygen on the reactivity of the selenide in radical reactions is not clear, although the oxygen has been shown to enhance reactions involving electrophilic selenium (selenolactonisation), additionally the quadragel bound selenolate anion has performed well in in alkylations and acyl selenide reactions.

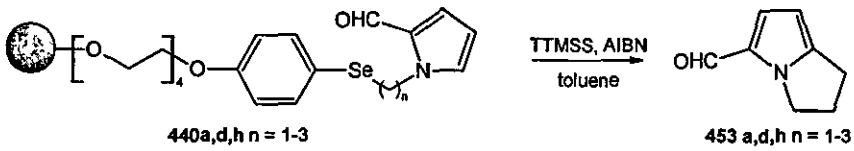
4.3.3 Reactions of Quadragel Bound Alkyl and Acyl Selenides

The quadragel alkylselenides **440a-h**, **441**, **443** and quadragel acyl selenides **451-452** can potentially facilitate a traceless cleavage protocol whereby the radical chain propagating species remains bound to the quadragel and the radical centre generated is released into solution. Cleavage conditions are more limited than the analogous solution phase reactions because the procedure relies on the ability of the solvent to swell the resin for efficient reaction. Cleavage from the support was achieved for the 4-phenylpyrazole derivative **443** yielding 3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine **213** as the only product in 61% yield by ^{1}H NMR spectrscopic analysis (Scheme 233).



Scheme 233: *Homolytic cleavage of N-butyl-4-phenylpyrazole*

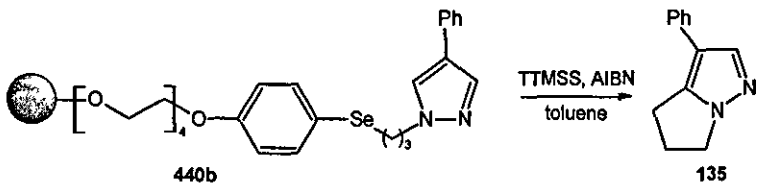
Heterocyclic systems **440a-h** and **441** (Scheme 234-Scheme 239) were also cleaved under the previous conditions. The cyclisation material was identified in the majority of cases by LCMS and ^{1}H NMR spectral analysis. However, the impure reaction mixtures were complex and disappointingly further purification and quantification was not possible in the limited time remaining.



Scheme 234: *Putative homolytic cleavage of pyrrole-2-carbaldehyde series*

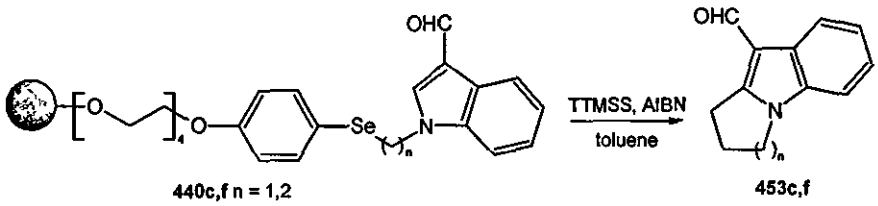
Cleavage of pyrrole-2-carbaldehyde precursors **440a,d,h** using TTMSS/AIBN was carried out in toluene giving rise to compounds associated with reduction of the aldehyde functionality as identified by ^{1}H NMR spectral analysis. The identification of peaks associated with cyclisation products were also identified in each case. This indicates that cyclisation has occurred and compounds **453a,d,h** have been reduced by TTMSS in solution. However, the compounds were only present in low concentration and conclusive identification was not possible.

Unfortunately, as was the case with all the homolytic cleavage reactions carried out, products associated with radical addition of initiator or TTMSS to toluene were identified in large quantities. This resulted in difficulties in analysis of the cleavage products by ^{1}H NMR spectroscopy and LCMS. Although toluene is a good solvent for the swelling of resins and is suitable for radical reactions, any future work involving these systems should seek an alternative solvent for homolytic cleavage.



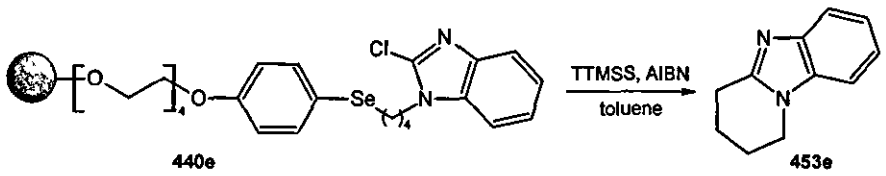
Scheme 235: *Putative solid supported synthesis of withasomnine*

Following the success of the 6-*exo* cyclisation onto 4-phenylpyrazole (Scheme 233) there was expected to be a similar success for the 5-*exo* cyclisation (Scheme 235). However, ^{1}H NMR spectral analysis and LCMS failed to conclusively identify the cyclised product **135**.



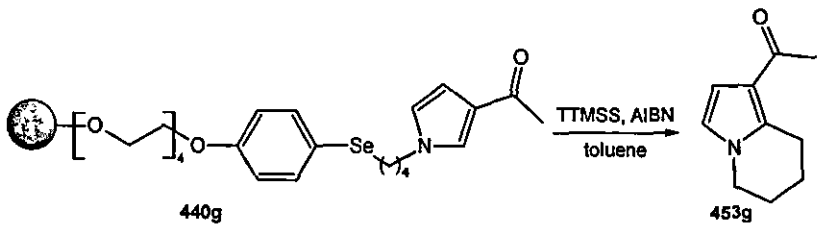
Scheme 236: *Putative homolytic of indole-3-carbaldehyde series*

Homolytic aromatic substitution products were identified for the indole-3-carbaldehyde systems **440c,f.** In this case the cyclisation appeared to have occurred without reduction of the aldehyde by ^{1}H NMR spectral analysis and LCMS yielding 5- and 6-*exo* cyclisation products **453c** and **453f** respectively. The LCMS chromatogram was again not clear and purification would be required to quantify cyclisation products **453c,f.**



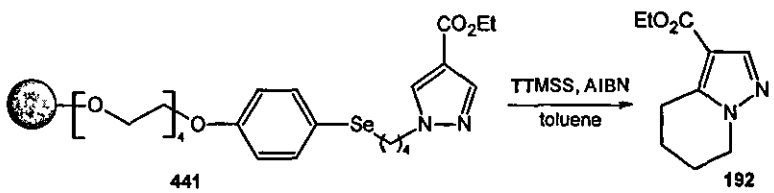
Scheme 237: *Putative homolytic cleavage/cyclisation of benzimidazole derivatives*

Homolytic cleavage of cyclisation precursor **440e** was found to contain cyclised material **453e** as the only compound identifiable by ^{1}H NMR spectroscopy by comparison to spectral data of an authentic sample (Scheme 237). The presence of tolyl and silyl waste again prevented accurate quantification.



Scheme 238: *Putative homolytic cleavage/cyclisation of 3-acetylpyrrole precursors*

The 3-acetylpyrrole precursor **440g** was cleaved using TTMSS/AIBN and cyclisation product **453g** was identified by ^{1}H NMR spectral comparison to that of an authentic sample. Further purification was required to fully characterise and quantify.

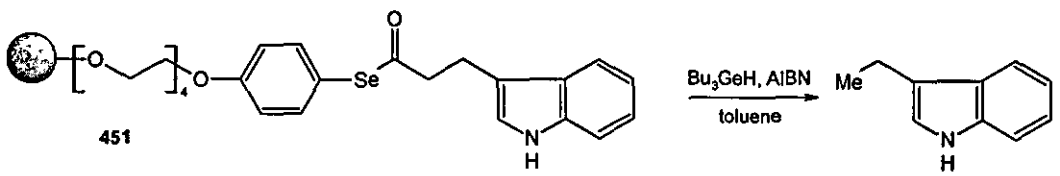


Scheme 239: *Putative homolytic*

The pyrazole precursor **441** was cleaved to yield ethyl 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-3-carboxylate **192** as the major product by ^{1}H NMR spectral analysis. Interestingly, in

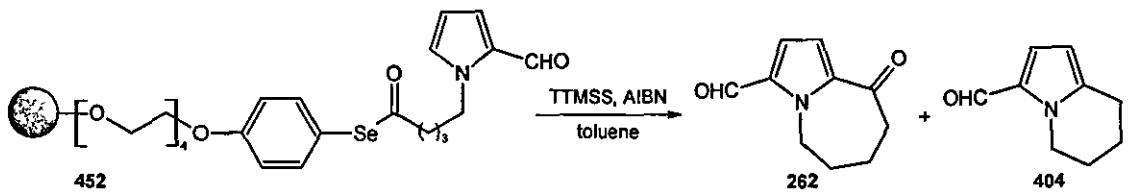
contrast to the analogous solution phase protocol, no alkene products associated with selenide elimination were identified in the reaction mixture.

Cleavage of acyl selenides was also attempted. Tributylgermanium hydride was used in place of TTMSS for the first attempted cleavage because it is a poor hydrogen donor and the cyclisation of the indole acyl radical was expected to be slow. No identifiable products were isolated from the cleavage reaction though.



Scheme 240: *Putative cleavage of acyl selenides*

Homolytic cleavage of **452** yielded the acyl radical cyclisation products **262** and **404** identified by mass spectral analysis. The ^{1}H NMR spectrum was too complex and saturated with impurities to make any identification.



Scheme 241: *Homolytic cleavage of quadragel bound acyl selenides*

We have shown that homolytic cleavage of alkyl and acyl selenides can be achieved using quadragel selenides. Unfortunately there were time constraints during the last section of work involving the homolytic cleavage and no purification of the cyclisation mixtures was performed. This resulted in only qualitative identification of the cyclisation products by LCMS and ^{1}H NMR spectral analysis. The conditions of cleavage require optimisation because the current procedure results in significant amounts of impurities in the reaction mixture.

4.3 4 Towards Suaveoline – A SPOS Approach (Future Work)

In order to demonstrate the uses of the quadragel selenyl bromide, suaveoline analogues (Figure 10) were the proposed target of a cyclisation-loading technique followed by traceless cleavage/cyclisation to install the two aliphatic rings utilising the resin reagent.

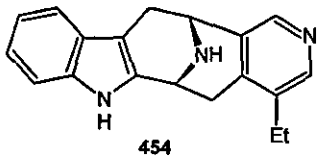
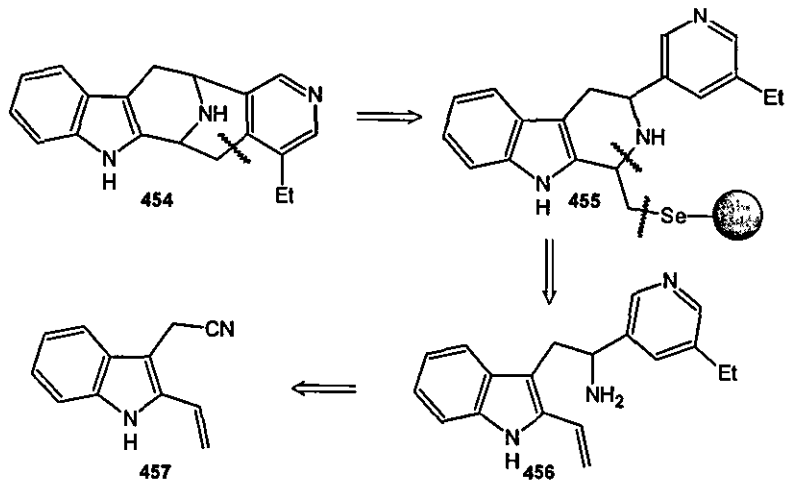


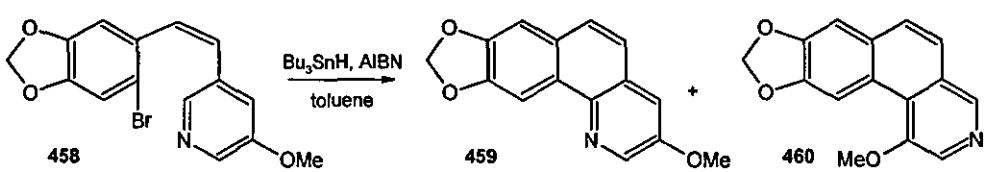
Figure 10: *Suaveoline*

Suaveoline has been synthesised from L-tryptophan *via* Pictet-Spengler cyclisation and Thorpe cyclisation,[172] but not using radical cyclisation methodologies. Retrosynthetic analysis indicates the most preferable disconnection to be as shown in Scheme 242 starting with a vinyltryptamine derivative **457**. The ability to perform the cyclisation/loading of anilines to alkenes in the presence of resin bound selenyl bromides is known.[94] Homolytic cleavage of **455** should result in 6-*exo* alkyl radical cyclisation onto the pyridine ring furnishing the suaveoline skeleton.



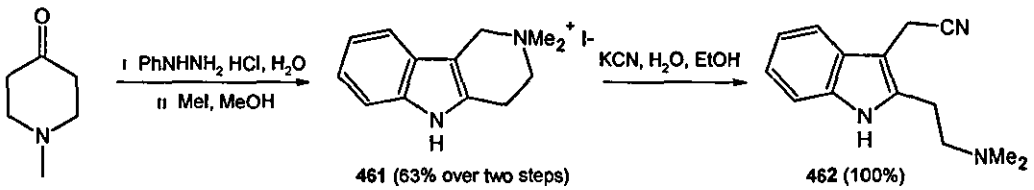
Scheme 242: *Retrosynthesis of suaveoline analogues*

The pyridine ring substituent may be required to direct cyclisation to the 4-position over the 2-position. Radical cyclisation onto 5-methoxypyridine derivatives **458** under standard tin hydride conditions gives a 1:1 mixture of the benzoisoquinolines **459** and **460** (Scheme 243),[173] whereas the introduction of a suitable directing group may promote the desired cyclisation. The benzo[*h*]-isoquinoline **459** was demethylated to yield the first reported synthesis of toddaquinoline. The reaction medium has been shown to affect the cyclisation regioselectivity of protonated pyridines and cyclisation to the 4-position can be enhanced.[17]



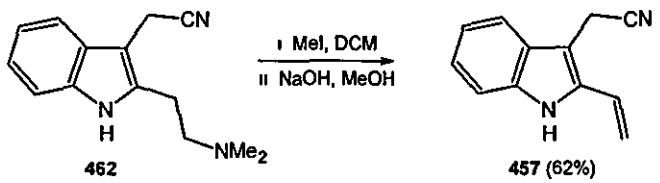
Scheme 243: *Radical cyclisation onto pyridine*

The vinyl indole structure shown in Scheme 245 was readily prepared in a number of simple transformations (Scheme 244).[174] The yields for the Fischer synthesis were disappointing when compared to those reported in the literature procedure. However, difficulties were experienced during workup and the reaction was not repeated. Methylation of the indole intermediate with methyl iodide was performed in high yield to afford 2,2-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-2-ium iodide **461** (92%). Treatment of 2,2-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-2-ium iodide **461** with potassium cyanide in ethanol furnished 2-(2-dimethylamino-ethyl)-1*H*-indole-3-carbonitrile **462** in quantitative yield. It was envisaged that Hoffman degradation of **462** followed by aryl addition to the nitrile and reduction would yield the proposed intermediate **456.**



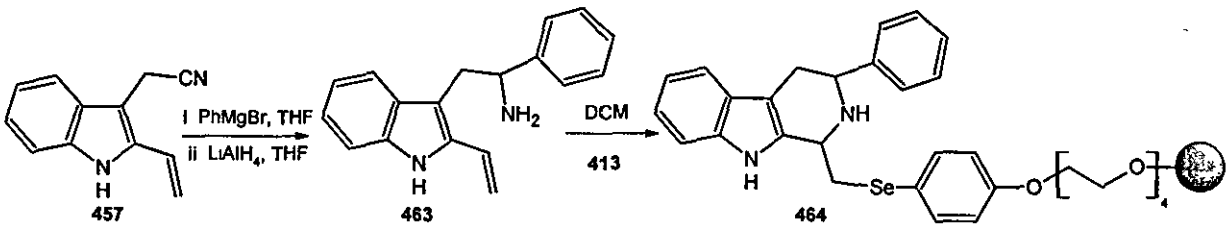
Scheme 244: *Synthesis of2-(2-dimethylamino-ethyl)-1H-indole-3-carbonitrile*

Fortunately, the oft troublesome Hoffman degradation was not required and following quaternisation of amine **462,** base mediated elimination was carried out to yield 2-vinyl-1*H*-indole-3-carbonitrile **457** in 62% yield.



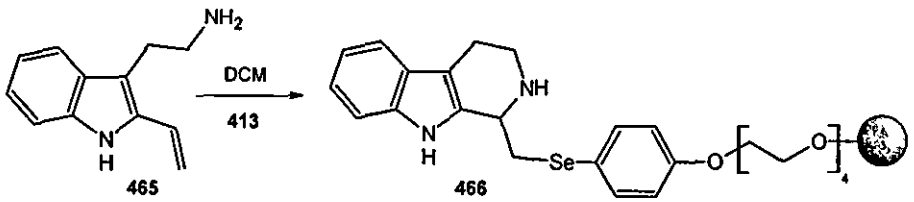
Scheme 245: *Synthesis of 2-vinyl-1H-indole-3-carbonitrile*

The foremost benefit of this cyclisation loading technique is that of the sequestration of the unstable vinyl tryptamine moieties as shown in Scheme 246. Subsequent to Grignard addition and *in situ* reduction[175] to the vinyl tryptamine, the resin is added to the crude mixture in solution and is able to selectively remove the compound from solution *via* a cyclative loading procedure onto the quadragel selenide support **413.**



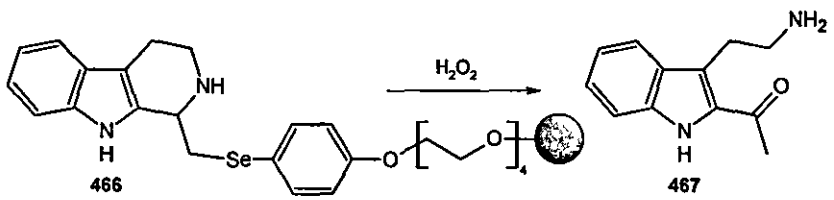
Scheme 246: *Cyclative loading of vinyl tryptamine derivatives to solid support*

Initially attempts were made using phenyl magnesium bromide addition to 2-vinyl-1*H*-indole-3-carbonitrile **457** followed by reduction with $LiAlH_4$ to yield vinyl tryptamine derivative **463** (Scheme 246). The quadragel selenyl bromide **413** was added to the reaction mixture containing the proposed structure **463**, which in turn should yield the resin bound substrate **464**.



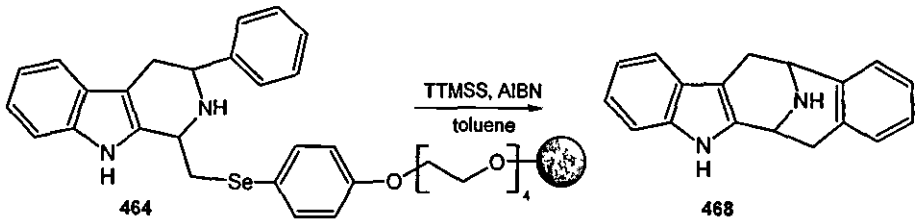
Scheme 247: *Cyclisation loading of amine to quadragel*

The mass and colour change indicated the reaction had occurred. However, yields were slightly lower than the predicted values. Grignard addition to nitriles does not always occur in high yield, in which case the primary amine **465** may have been the main product of the reaction giving rise to the resin bound selenide **466** (Scheme 247).



Scheme 248: *Oxidative cleavage of resin bound selenide*

In order to ascertain the loading and structure of the product on the solid support the quadragel resin was cleaved under oxidative conditions (Scheme 248), and the indole structure **467** was tentatively assigned by analysis of the ^1H NMR spectrum. Hence more rigorous procedures for the aryl addition are required.



Scheme 249: *Homolytic cleavage/cyclisation of suaveoline precursors*

The proposed radical cleavage/cyclisation was not achieved due to lack of time (Scheme 249). However, this system potentially provides a unique approach to the polycyclic analogues of suaveoline. Encouragingly, the amino cyclisation appeared to have occurred, albeit in the absence of the desired aryl group (Scheme 247).

4.4 Conclusion

Our studies into PS selenyl bromides reported in the literature produced variable results. The PS support failed to provide the correct attributes for our studies and so a new resin system was sought. Quadragel selenyl bromide **413** was successfully prepared in moderate overall yield in a regioselective manner. This new resin system was highly successful in catalytic selenolactonisations. Additionally, alkyl and acyl selenide radical cyclisation precursors were loaded in good yield.

The issues of reagent cost, resin homogeneity, improved spectroscopic analysis and loading versatility have all been addressed from the PS selenyl bromide approach reported by Nicolaou. The use of toxic dimethyl diselenide and non-regioselective selenide addition have also been eliminated. Our quadragel selenyl bromide **413** thus provides a useful alternative to those reported in the literature, although the procedure for homolytic cleavage needs to be refined.

CHAPTER 5 EXPERIMENTAL

REACTION SCHEME INDEX

General Experimental

Infrared spectra were obtained using a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer, thin film spectra were acquired using sodium chloride plates and resin spectra were obtained as a compressed film or ground and pressed to a potassium bromide pellet.

^{1}H and ^{13}C NMR spectra were measured at 250 and 100 MHz (unless stated otherwise), using a Bruker AC 250 and 400 MHz spectrometer respectively. The solvent used for NMR spectroscopy was $CDCl_3$ (unless stated otherwise) using TMS (tetramethylsilane) as the internal reference. Chemical shifts are given in parts per million (ppm) and *J* values given in Hertz (Hz).

The mass spectra were recorded using a Jeol SX-104 instrument utilising electron impact (E.I.) unless otherwise stated. Mass spectra determined by ESI were performed by the EPSRC national mass spectrometry service at the University of Wales, Swansea. Analysis by GCMS utilised a Fisons GC 8000 series (AS 800), using a 15 m x 0.25 mm DB-5 column and an electron impact low resolution mass spectrometer.

Chromatographic manipulations used Merck Kiesel 60 H silica gel as the absorbent and eluant mixtures of light petroleum and ethyl acetate unless otherwise stated. Reactions were monitored using thin layer chromatography (TLC) on aluminium backed plates with Merck Kiesel 60 F254 silica gel. TLC visualised by UV light and potassium permanganate or iodine. Melting points were recorded using an Electrothermal 9100 melting point instrument and are uncorrected.

The reactions requiring anhydrous conditions were carried out using glassware dried overnight at 150 °C. All reactions were performed under a nitrogen atmosphere unless otherwise stated. Reaction solvents were obtained commercially dry, except light petroleum (40-60 °C) which was distilled from calcium chloride, ethyl acetate, methanol and dichloromethane from calcium hydride and THF from sodium/benzophenone.

Sodium hydride was obtained as 60% dispersion in mineral oil and was washed with light petroleum prior to use. Reaction solutions were dried with magnesium sulfate during work up unless otherwise reported. Reaction solvent, initiator solutions and tributyltin hydride solutions were deoxygenated for a minimum of 30 min prior to selenation and radical reactions by bubbling nitrogen through the solution. Phthalimide was precipitated and removed from crude reaction mixture of NPSP selenation reactions prior to column chromatography. Hydrochloric acid used was 5 M.

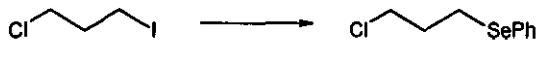
Resin agitation was by rotation using an adapted rotary evaporator for all PS and aminomethylated PS reactions, quadragel mesylation and mesyl displacement experiments to prevent the degradation caused by stirring (Appendix B). All other quadragel loading reactions were agitated by flat-bed rolling on threaded rollers and reaction vessels were flushed with nitrogen before sealing. Cleavage from quadragel under radical conditions was performed with standard stirring. The polymer supports used were PS 1% crosslinked with DVB, 100-200 mesh, available from Aldrich; aminomethylated PS, 1.13 $mmol.g^{-1}$, PS 1% crosslinked with DVB, 100-200 mesh, available from Novabiochem; quadragel, 2.14 $mmol.g^{-1}$, PS 1% crosslinked with DVB. PS samples were washed thoroughly before use.[176] Selenium and bromine elemental analysis were submitted to Warwick Analytical Service.

5.1 Experimental for Chapter 2

Alkyl Radical Addition to Pyrazoles

5.1.1 Alkyl Chains

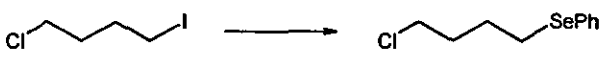
Synthesis of (3-chloro-propylselenyl)-benzene 149[41]



149

Sodium borohydride (1.00 g, 26.4 mmol) was added slowly to a stirred solution of diphenyl diselenide (3.70 g, 11.9 mmol) in ethanol (600 cm^3) at 0 °C. The solution was stirred for 30 min and 1-chloro-3-iodo-propane (4.85 g, 23.7 mmol) added and stirring was maintained at 0 °C for 1 h. The reaction mixture was stirred at room temperature for 16 h, evaporated to dryness and treated with hydrochloric acid (2 M, 50 cm^3). The aqueous layer was extracted three times with diethyl ether, washed with aqueous sodium carbonate and brine, dried and evaporated to dryness, yielding (3-chloro-propylselenyl)-benzene **149** (7.23 g, 97%) as a yellow oil; (Found: M^+, 233.9714. $C_9H_{11}ClSe$ requires 233.9714); υ_{max}(thin film)/cm^{-1} 2932 (C-H), 1577, 1281, 1072 and 734 (aromatic o.o.p. deformations); δ_H(400 MHz) 2.07-2.14 (2 H, m, 2-H), 3.02 (2 H, t, *J* 7.0, 1-H), 3.63 (2 H, t, *J* 5.0, 3-H), 7.24-7.28 (3 H, m, phenyl 3-5-H) and 7.49-7.51 (2 H, m, phenyl 2,6-H); δ_C 24.53 (2-C), 32.59 (1-C), 44.27 (3-C), 127.09 (phenyl 4-C), 129.05 (phenyl 3,5-C), 129.49 (phenyl 1-C) and 132.72 (phenyl 2,6-C); *m/z* 234 (M^+, 96%), 158 (100) and 77 (95).

Synthesis of (4-chloro-butylselenyl)-benzene 150[41]

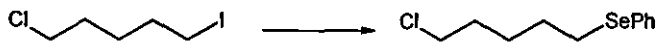


150

Sodium borohydride (1.22 g, 32.0 mmol) was added slowly to a stirred solution of diphenyl diselenide (4.00 g, 12.8 mmol) in ethanol (500 cm^3) at 0 °C. The solution was stirred for 30 min and 1-chloro-4-iodo-butane (5.58 g, 25.6 mmol) added and stirring was maintained at 0 °C for 1 h. The reaction mixture was stirred at room temperature for 20 h, evaporated to dryness and treated with hydrochloric acid (2 M, 75 cm^3). The aqueous layer was extracted three times with diethyl ether, washed with aqueous sodium carbonate and brine, dried and evaporated to dryness, yielding (4-chloro-butylselenyl)-benzene **150** (5.98 g, 94%) as a brown oil; (Found: M^+, 247.9871. $C_{10}H_{13}ClSe$ requires 247.9869); υ_{max}(thin film)/cm^{-1} 2932 (C-H), 1577, 1281, 1072 and 734 (aromatic o.o.p. deformations); δ_H 1.81-1.92 (4 H, m, 2,3-H), 2.92 (2 H, t, *J* 6.9, 1-H),

3.52 (2 H, t, *J* 6.2, 4-H), 7.24-7.28 (3 H, m, phenyl 3-5-H) and 7.47-7.49 (2 H, m, phenyl 2,6-H); δ_C 26.97 (2-C), 27.28 (3-C), 32.41 (1-C), 44.33 (4-C), 126.91 (phenyl 4-C), 129.08 (phenyl 3,5-C), 130.05 (phenyl 1-C) and 132.66 (phenyl 2,6-C); *m/z* 248 (M^+, 44%), 158 (67), 91 (100) and 78 (54).

Synthesis of (5-chloro-pentylselenyl)-benzene 151[41]

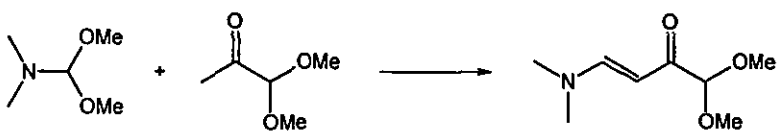


151

Sodium borohydride (0.61 g, 16.0 mmol) was added slowly to a stirred solution of diphenyl diselenide (2.00 g, 6.4 mmol) in ethanol (250 cm^3) at 0 °C. The solution was stirred for 30 min and 1-chloro-5-iodo-pentane (2.98 g, 12.6 mmol) added and stirring was maintained at 0 °C for 1 h. The reaction mixture was stirred at room temperature for 16 h, evaporated to dryness and treated with hydrochloric acid (2 M, 50 cm^3). The aqueous layer was extracted three times with diethyl ether, washed with aqueous sodium carbonate and brine, dried and evaporated to dryness, yielding (5-chloro-pentylselenyl)-benzene **151** (3.3 g, 100%) as a yellow oil; δ_H 1.53-1.58 (2 H, m, 3-H), 1.69-1.79 (4 H, m, 2,4-H), 2.91 (2 H, t, *J* 6.9, 1-H), 3.50 (2 H, t, *J* 6.2, 5-H), 7.23-7.26 (3 H, m, phenyl 3-5-H) and 7.47-7.50 (2 H, m, phenyl 2,6-H); δ_C 27.26 (3-C), 27.64 (2-C), 29.42 (4-C), 32.04 (1-C), 44.79 (5-C), 126 71 (phenyl 4-C), 129.03 (phenyl 3,5-C), 130.30 (phenyl 1-C) and 132.59 (phenyl 2,6-C). NMR spectroscopic data matched those from an authentic sample.

5.1.2 PYRAZOLES

Synthesis of (*E*)-4-(dimethylamino)-1,1-di(methoxy)but-3-en-2-one 142[114]

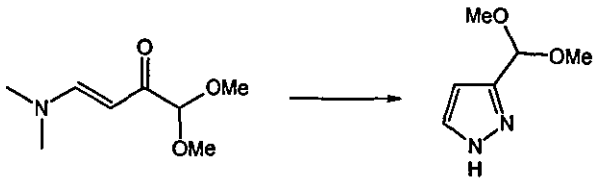


142

Dimethylformamide-dimethylacetal (23.83 g, 200 mmol) and methylglyoxal-dimethylacetal (23.63 g, 200 mmol) were stirred together at 66 °C for 30 h. The reaction mixture was cooled to room temperature and the crude brown oil was evaporated to dryness. Distillation under reduced pressure afforded (*E*)-4-(dimethylamino)-1,1-di(methoxy)but-3-en-2-one **142** (25.38 g, 73%) as a colourless oil; bp_{40} 127-129 °C; (Found: M^+, 173.1053. $C_8H_{15}NO_3$ requires 173.1052); υ_{max}(thin film)/cm^{-1} 2932 (C-H), 1651 (C=O) and 1574 (C=C); δ_H 2.96 (6 H, b, NMe_2), 3.40 (6 H, s, OMe), 4.52 (1 H, s, 1-H), 5.32 (1 H, d, *J* 12.8, 3-H) and 7.69 (1 H, d, *J* 12.8, 4-H); δ_C 37.51

(NMe_2), 45.33 (1-C), 54.39 (OMe), 104.52 (3-C), 154.70 (4-C) and 191.38 (2-C); *m/z* 173 (M^+, 13%), 98 (100) and 75 (27).

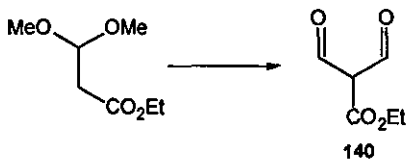
Synthesis of 3-[di(methoxy)methyl]-1*H*-pyrazole 143



142 143

(*E*)-4-(Dimethylamino)-1,1-di(methoxy)but-3-en-2-one **142** (17.21 g, 85.5 mmol) was added to a stirred solution of hydrazine sulphate (11.06 g, 85.5 mmol) in 10% aqueous sodium hydroxide (75 cm^3). After 2 h stirring, the reaction mixture was left to stand overnight at room temperature. The aqueous solution was exhaustively extracted with diethyl ether, dried (Na_2SO_4) and evaporated to dryness to yield 3-[di(methoxy)methyl]-1*H*-pyrazole **143** (10.50 g, 67%) as a colourless oil which solidified at reduced temperature to a colourless solid, mp 102-103 °C (lit.,[113] 94-96°C); (Found: M^+, 142.0740. $C_6H_{10}N_2O_2$ requires 142.0742); υ_{max}(thin film)/cm^{-1} 1573 (C=C); δ_H(400 MHz) 3.37 (6 H, s, OMe), 5.56 [1 H, s, C*H*(OMe)$_2$], 6.33-6.33 (1 H, m, pyrazole 4-H) and 7.55-7.55 (1 H, m, pyrazole 5-H); δ_C 52.69 (OMe), 98.94 [*C*H(OMe)$_2$], 103.61 (pyrazole 4-C), 133.61 (pyrazole 5-C) and 146.10 (pyrazole 3-C); *m/z* 142 (M^+, 10%), 111 (100) and 75 (10).

Synthesis of (ethoxycarbonyl)malondialdehyde 140[115]

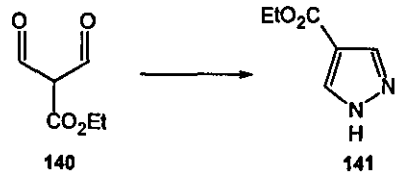


140

Sodium hydride (2.24 g, 56.0 mmol) was placed in a 250 cm^3 3-neck flask fitted with a reflux condenser and diethyl ether (50 cm^3) added to it. The suspension was stirred at 0 °C and ethyl formate (38.0 cm^3, 470 mmol) was added in one portion followed by the slow addition of ethyl (diethoxy)propionate (9.0 cm^3, 46.5 mmol) in ether (25 cm^3) over 2 h. The mixture was stirred at 0 °C for 4 h and warmed to room temperature for a further 24 h. The reaction was poured onto ice-water (100 cm^3) and washed three times with ether. The aqueous layer was acidified to pH 3 with concentrated hydrochloric acid and extracted with dichloromethane (3 x 50 cm^3), dried and evaporated to dryness to yield (ethoxycarbonyl)malondialdehyde **140** (4.93 g, 74%) as a pale yellow oil; (Found: M^+, 144.0423. $C_6H_8O_4$ requires 144.0423); υ_{max}(thin film)/cm^{-1} 3438, 1723

(C=O) and 1246; δ_H(400 MHz) 1.33 (3 H, t, *J* 7.0, Me), 4.29 (2 H, q, *J* 7.2, C*H*$_2$Me), 9.14 (2 H, s, C*H*O) and 13.10 (1 H, s, C*H*CO$_2$Et); δ_C 14.23 (Me), 60.64 (CH_2), 109.45 (CH), 174.81 (CO_2Et) and 186.39 (CHO); *m/z* 144 (M^+, 22%), 99 (93), 88 (81) and 70 (96).

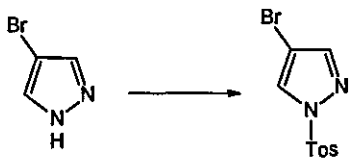
Synthesis of ethyl pyrazole-4-carboxylate 141[116]



140 141

(Ethoxycarbonyl)malondialdehyde **140** (4.80 g, 33.3 mmol) in ethanol (100 cm^3) was added to a vigorously stirred suspension of hydrazine dihydrochloride (4.00 g, 38.1 mmol) in ethanol (60 cm^3) in one portion. The reaction mixture was stirred at 0 °C for 2 h and at room temperature for 30 h. The reaction mixture was evaporated to dryness and partitioned between aqueous sodium bicarbonate and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate and the combined organic extracts washed with brine, dried and evaporated to dryness to yield ethyl pyrazole-4-carboxylate **141** (4.52 g, 92%) as a coloured solid; (Found: M^+, 140.0586. $C_6H_8N_2O_2$ requires 140.0586); υ_{max}(thin film)/cm^{-1} 1718 (C=O) and 1561 (C=C); δ_H(400 MHz) 1.36 (3 H, t, *J* 7.2, Me), 4.32 (2 H, q, *J* 7.2, C*H*$_2$Me) and 8.09 (2 H, s, pyrazole 3,5-H); δ_C 14.34 (CH_2CH_3), 60.37 (CH_2CH_3), 115.11 (pyrazole 4-C), 136.47 (pyrazole 3,5-C) and 163.25 (CO_2Et); 140 (M^+, 47%), 112 (100) and 95 (100).

Synthesis of 4-bromo-1*H*-pyrazol-1-yl(4-methylphenyl)sulfone 201

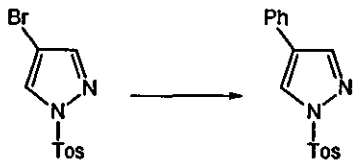


200 201

4-Bromopyrazole **200** (2.87 g, 19.5 mmol) was added to a stirred suspension of sodium hydroxide (2.34 g, 58.5 mol) in dichloromethane (150 cm^3). The reaction mixture was cooled to 0 °C and the reaction mixture was stirred for 10 min and tosyl chloride (8.92 g, 46.8 mmol) was added over 20 min. After 30 min at 0 °C the reaction mixture was allowed to warm to room temperature and stirring was maintained overnight. The reaction was quenched with water and extracted with dichloromethane and the combined extracts washed until neutral, dried and evaporated to dryness. Purification by column chromatography (light petroleum:dichloromethane, 3:1) yielded 4-bromo-1*H*-pyrazol-1-yl(4-methylphenyl)sulfone **201**

(5.78 g, 98%) as a white solid, mp 102-103 °C (lit.,[177] 96-97 °C); (Found: M^+, 299.9571. $C_{10}H_9BrN_2O_2S$ requires 299.9568); (Found: C, 39.8; H, 2.95; N, 9.1. $C_{10}H_9BrN_2O_2S$ requires: C, 39.9; H, 3.0; N, 9.3%); υ_{max}(KBr disc)/cm^{-1} 1594 (C=C) and 1384, 1174 (SO_2); δ_H(400 MHz) 2.43 (3 H, s, Me), 7.35 (2 H, d, *J* 8.0, tosyl 3,5-H), 7.65 (1 H, s, pyrazole 3-H), 7.89 (2 H, d, *J* 8.0, tosyl 2,6-H) and 8.10 (1 H, s, pyrazole 5-H); δ_C 21.76 (Me), 97.45 (pyrazole 4-C), 128.36 (tosyl 3,5-C), 130.20 (tosyl 2,6-C), 130.41 (pyrazole 3-C), 133.41 (tosyl 1-C), 145.61 (pyrazole 5-C) and 146.43 (tosyl 4-C); *m/z* 300 (M^+, 7%), 236 (31) and 91 (100).

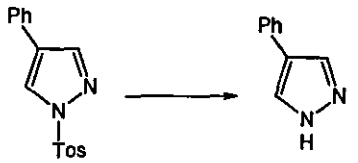
Synthesis of 1-[(4-methylphenyl)sulfonyl]-4-phenyl-1*H*-pyrazole 202



201 **202**

4-Bromo-1*H*-pyrazol-1-yl(4-methylphenyl)sulfone **201** (1.00 g, 3.4 mmol) and phenyl boronic acid (0.47 g, 3.8 mmol) were dissolved in 1,2-dimethoxyethane (DME) (20 cm^3) and aqueous potassium carbonate (2 M, 15 cm^3) was added. The reaction mixture was deoxygenated by passing a stream of nitrogen through the solution for 30 min and palladium tetrakis(triphenylphosphine) (0.40 g, 0.3 mmol) was added. The reaction mixture was heated at reflux for 24 h and the DME removed under reduced pressure. The crude reaction mixture was partitioned between water and dichloromethane, the aqueous layer was extracted with three portions of dichloromethane, dried and evaporated to dryness. The crude material was purified by column chromatography using light petroleum:dichloromethane, 2:1 as the eluant to afford 1-[(4-methylphenyl)sulfonyl]-4-phenyl-1*H*-pyrazole **202** (0.76 g, 77%) as a white solid, mp 117-118 °C; (Found: M^+, 298.0776. $C_{14}H_{14}N_2O_2S$ requires 298.0776); υ_{max}(KBr disc)/cm^{-1} 1595 (C=C) and 1379, 1174 (SO_2); δ_H(400 MHz) 2.42 (3 H, s, Me), 7.29-7.40 (5 H, m, phenyl-H), 7.47 (2 H, d, *J* 8.0, tosyl 3,5-H), 7.93 (2 H, d, *J* 8.0, tosyl 2,6-H), 7.98 (1 H, s, pyrazole 3-H) and 8.31 (1 H, s, pyrazole 5-H); δ_C 21.73 (Me), 125.80 (pyrazole 4-C), 126.04 (phenyl 2,6-C), 126.85 (phenyl 4-C), 127.85 (pyrazole 3-C), 128.21 (tosyl 3,5-C), 129.08 (phenyl 3,5-C), 130.10 (tosyl 2,6-C), 130.30 (tosyl 1-C), 133.99 (phenyl 1-C), 143.18 (pyrazole 5-C) and 146.00 (tosyl 4-C); *m/z* 298 (M^+, 63%), 234 (62) and 91 (100).

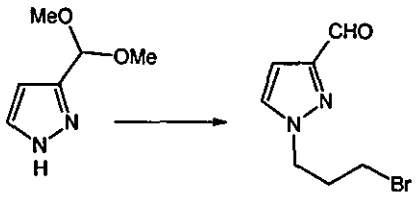
Synthesis of 4-phenyl-1*H*-pyrazole 198



202 198

1-[(4-Methylphenyl)sulfonyl]-4-phenyl-1*H*-pyrazole **202** (0.57 g, 1.9 mmol) was treated with 5 M sodium hydroxide (10 cm^3) and methanol (10 cm^3) and heated under reflux for 5 h. The methanol was removed under vacuum and the aqueous reaction mixture was diluted with water (50 cm^3), extracted with dichloromethane, dried and evaporated to dryness to yield 4-phenyl-1*H*-pyrazole **198** (0.27 g, 98%) as a white solid, mp 236-238 °C (lit.,[122] 236-237°C); (Found: M^+, 144.0689. $C_9H_8N_2$ requires 144.0688); υ_{max}(nujol mull)/cm^{-1} 3110 (aromatic C-H stretch) and 1458 (C=C); δ_H 7.14-7.18 (1 H, m, phenyl 4-H), 7.30-7.34 (2 H, m, phenyl 3,5-H), 7.54-7.56 (2 H, m, phenyl 2,6-H), 7.93 (2 H, b, pyrazole 3,5-H) and 12.65 (1 H, b, pyrazole 1-H); δ_C 121.08 (pyrazole 4-C), 125.02 (phenyl 2,6-C), 125.26 (pyrazole 3-C), 125.74 (phenyl 4-C), 128.66 (phenyl 3,5-C), 132.85 (phenyl 1-C) and 136.09 (pyrazole 5-C); *m/z* 144 (M^+, 100%).

Synthesis of 1-(3-bromopropyl)-1*H*-pyrazole-3-carbaldehyde 145

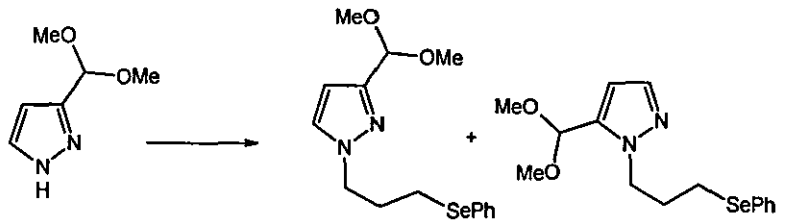


143 145

3-[Di(methoxy)methyl]-1*H*-pyrazole **143** (1.50 g, 8.1 mmol) was added to a stirred suspension of sodium hydride (0.21 g, 8.9 mmol) and 18-crown-6 (2.14 g, 8.1 mmol) in THF (50 cm^3) and the reaction mixture was stirred at room temperature for 30 min. Dibromopropane (8.18 g, 40.5 mmol) was added in one portion and stirring was maintained for 1 h at room temperature after which time the reaction mixture was heated at 50 °C for 3 h. The reaction mixture was cooled to room temperature and the crude mixture evaporated to dryness and purified by column chromatography initially yielding only the alkylated product. When left to stand overnight at 4 °C, it was apparent the compound was undergoing cyclisation onto the pyridine nitrogen. The isolated yield could be dramatically improved by direct hydrolysis of the crude material to the aldehyde as this prevents cyclisation. The remaining material was dissolved in methanol (50 cm^3), CSA (70 mg, 0.3 mmol) was added and the solution was stirred overnight. The crude

material was evaporated to dryness and partitioned between aqueous sodium bicarbonate and dichloromethane, the organic layer was removed. The aqueous layer was further extracted with dichloromethane and the combined organic layers were dried and evaporated to dryness. Purification by column chromatography yielded 1-(3-bromopropyl)-1*H*-pyrazole-3-carbaldehyde **145** (0.70 g, 40%) as a colourless oil. Yields could be improved if cyclisation is restricted. (Found: M^+, 215.9904. $C_7H_9BrN_2O$ requires 215.9898); υ_{max}(thin film)/cm^{-1} 1697 (C=O); δ_H(400 MHz) 2.43-2.50 (2 H, m, 2-H), 3.35 (2 H, t, *J* 4.0, 3-H), 4.41 (2 H, t, *J* 6.5, 1-H), 6.81 (1 H, d, *J* 2.3, pyrazole 4-H), 7.51 (1 H, d, *J* 2.3, pyrazole 5-H) and 9.97 (1 H, s, CHO); δ_C 29.63 (2-C), 32.46 (3-C), 50.61 (1-C), 106.01 (pyrazole 4-C), 132.08 (pyrazole 5-C), 151.99 (pyrazole 3-C) and 186.30 (CHO); *m/z* 216 (M^+, 5%), 136 (100) and 109 (63).

Synthesis of 3-(dimethoxymethyl)-1-[3-(phenylselenyl)propyl]-1*H*-pyrazole 155



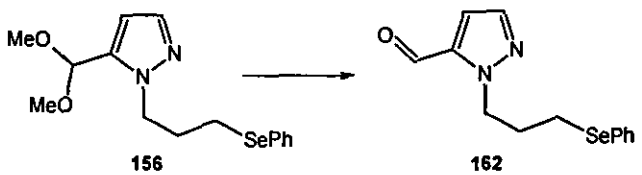
143 155 156

3-(Dimethoxymethyl)-1*H*-pyrazole **143** (0.43 g, 3.0 mmol) was added to a stirred suspension of crushed potassium hydroxide (0.51 g, 9.0 mmol) in DMF (20 cm^3) at 0 °C and the reaction mixture was stirred for 30 min. (3-Iodo-propylselenyl)-benzene **152** (1.08 g, 3.3 mmol) was added to the stirred suspension and the mixture was allowed to warm to room temperature and the reaction mixture was stirred for 36 h. The crude mixture was poured onto ice-water and extracted twice with ethyl acetate. The combined organic extracts were washed with water and twice with brine, dried and evaporated to dryness to yield a pale yellow oil. Purification by column chromatography yielded 3-(dimethoxymethyl)-1-[3-(phenylselenyl)propyl]-1*H*-pyrazole **155** (0.32 g, 31%) as a colourless oil in addition to the other isomer 5-(dimethoxymethyl)-1-[3-(phenylselenyl)propyl]-1*H*-pyrazole **156**. 3-(Dimethoxymethyl)-1-[3-(phenylselenyl)propyl]-1*H*-pyrazole **155**; (Found: M^+, 340.0696. $C_{15}H_{20}N_2O_2Se$ requires 340.0690); υ_{max}(thin film)/cm^{-1} 1578 (C=C), 1054 (C-O) and 738, 692 (aromatic o.o.p. deformations); δ_H 2.18-2.25 (2 H, m, 2-H), 2.80 (2 H, t, *J* 7.2, 3-H), 3.37 (6 H, s, OMe), 4.22 (2 H, t, *J* 6.7, 1-H), 6.27 (1 H, d, *J* 2.4, pyrazole 4-H), 7.21-7.28 (3 H, m, phenyl 3-5-H), 7.29 (1 H, d, *J* 2.4, pyrazole 5-H) and 7.43-7.48 (2 H, m, phenyl 2,6-H); δ_C 24.24 (3-C), 30.44 (2-C), 51.28 (1-C), 52.92 (OMe), 99.67 [CH(OMe)$_2$], 103.76 (pyrazole 4-C), 127.07 (phenyl 4-C), 129.14 (phenyl 3,5-C), 129.49

(pyrazole 3-C), 130.12 (phenyl 1-C), 132.72 (phenyl 2,6-C) and 150.08 (pyrazole 3-C); *m/z* 340 (M^+, 20%), 183 (100), 151 (100), 137 (100) and 109 (100).

3-[di(methoxy)methyl]-1*H*-pyrazole **143** (1.00 g, 5.4 mmol) was added to a vigorously stirred suspension of ground potassium hydroxide (0.90 g, 16 mmol) in DMF (50 cm^3). The reaction vessel was covered with aluminium foil to omit light from the reaction and after stirring for 30 min, 1-iodo-3-(phenylseleno)propane **152** (3.52 g, 10.8 mmol) was added in one portion. The reaction was stirred in the absence of light for 24 h, partitioned between ethyl acetate and water and the organic layer was removed. The organic extract was washed with water followed by brine, dried and evaporated to dryness yielding a mixture 5-(dimethoxymethyl)-1-[3-(phenylselenyl)propyl]-1*H*-pyrazole and starting material. Purification by column chromatography afforded 5-(dimethoxymethyl)-1-[3-(phenylselenyl)propyl]-1*H*-pyrazole **156** (0.96 g, 52%) as a colourless oil; (Found: M^+, 340 0696. $C_{15}H_{20}N_2O_2Se$ requires 340.0690); υ_{max}(thin film)/cm^{-1} 1054 (C-O) and 736, 691 (aromatic o.o.p. deformations); δ_H 2.16-2.28 (2 H, m, 2-H), 2.88 (2 H, t, *J* 7.2, 3-H), 3.28 (6 H, s, OMe), 4.26 (2 H, t, *J* 6.7, 1-H), 6.30 (1 H, d, *J* 1.9, pyrazole 4-H), 7.21-7.28 (3 H, m, phenyl 3-5-H), 7.43 (1 H, d, *J* 1.9, pyrazole 3-H) and 7.45-7.48 (2 H, m, phenyl 2,6-H); δ_C 24.38 (3-C), 30.40 (2-C), 49.35 (1-C), 52.88 (OMe), 97.40 [*C*H(OMe)$_2$], 106.17 (pyrazole 4-C), 126.90 (phenyl 4-C), 129.08 (phenyl 3,5-C), 129.84 (phenyl 1-C), 132.63 (phenyl 2,6-C), 138.21 (pyrazole 3-C) and 138.76 (pyrazole 5-C); *m/z* 340 (M^+, 9%), 309 (5) and 183 (100).

Synthesis of 1-[3-(phenylselenyl)propyl]-1*H*-pyrazole-5-carbaldehyde 162

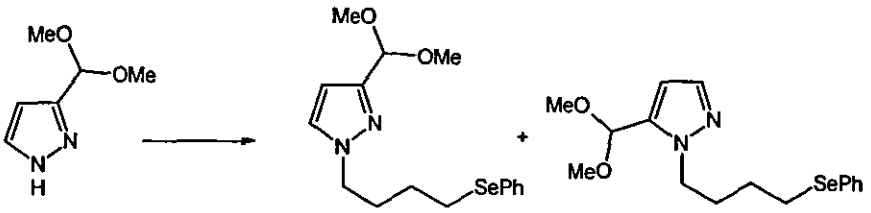


156 162

5-(Dimethoxymethyl)-1-[3-(phenylselenyl)propyl]-1*H*-pyrazole **156** (0.70 g, 2.1 mmol) was dissolved in methanol (50 cm^3) and CSA (120 mg, 0.5 mmol) was added and the solution was stirred overnight. The crude material was evaporated to dryness, partitioned between aqueous sodium bicarbonate and dichloromethane and the organic layer removed. The aqueous layer was further extracted with dichloromethane and the combined organic layers evaporated to dryness. Purification by column chromatography afforded 1-[3-(phenylselenyl)propyl]-1*H*-pyrazole-5-carbaldehyde **162** (0.58 g, 96%) as a colourless oil; (Found: M^+, 294.0271. $C_{13}H_{14}N_2OSe$ requires 294.0269); υ_{max}(thin film)/cm^{-1} 1682 (C=O) and 737,692 (aromatic o.o.p. deformations); δ_H 2.16-2.25 (2 H, m, 2-H), 2.85 (2 H, t, *J* 7.4, 3-H), 4.64 (2 H, t, *J* 6.8, 1-H), 6.89 (1 H, d, *J* 1.9, pyrazole 4-H), 7.23-7.27 (3 H, m, phenyl 3-5-H), 7.45-7.48 (2 H, m, phenyl

2,6-H), 7.55 (1 H, d, *J* 1.9, pyrazole 3-H) and 9.83 (1 H, s, CHO); δ_C 24.06 (3-C), 30.73 (2-C), 51.49 (1-C), 115.30 (pyrazole 4-C), 127.00 (phenyl 4-C), 129.10 (phenyl 3,5-C), 129.72 (phenyl-1-C), 132.78 (phenyl 2,6-H), 138.68 (pyrazole 5-C), 138.84 (pyrazole 3-C) and 179.55 (CHO); *m/z* 294 (M^+, 68%), 157 (53), 137 (100) and 109 (100).

Synthesis of 3-(dimethoxymethyl)-1-[4-(phenylselenyl)butyl]-1*H*-pyrazole 157



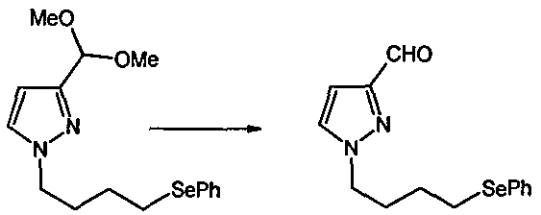
143 157 158

3-(Dimethoxymethyl)-1*H*-pyrazole **143** (0.43 g, 3.0 mmol) was added to a stirred suspension of crushed potassium hydroxide (0.51 g, 9.0 mmol) in DMF (20 cm^3) at 0 °C and the reaction mixture was stirred for 30 min. (4-Chloro-butylselenyl)-benzene **150** (0.89 g, 3.6 mmol) was added to the stirred suspension and the mixture was allowed to warm to room temperature and the reaction mixture was stirred for 28 h. The crude mixture was poured onto ice-water and extracted twice with ethyl acetate. The combined organic extracts were washed with water and twice with brine, dried and evaporated to dryness to yield a pale yellow oil. Purification by column chromatography yielded 3-(dimethoxymethyl)-1-[4-(phenylselenyl)butyl]-1*H*-pyrazole **157** (0.53 g, 50%) as a colourless oil in addition to 5-(dimethoxymethyl)-1-[4-(phenylselenyl)butyl]-1*H*-pyrazole **158** (0.36 g, 34%) as a colourless oil. 3-(Dimethoxymethyl)-1-[4-(phenylselenyl)butyl]-1*H*-pyrazole **157**; [Found: $(M+H)^+$, 354.0841. $C_{16}H_{23}N_2O_2Se$ requires 354.0847]; υ_{max}(thin film)/cm^{-1} 1578 (C=C), 1054 (C-O) and 737, 692 (aromatic o.o.p. deformations); δ_H 1.64-1.72 (2 H, m, 3-H), 1.94-2.01 (2 H, m, 2-H), 2.88 (2 H, t, *J* 7.0, 4-H), 3.37 (6 H, s, OMe), 4.10 (2 H, t, *J* 7.0, 1-H), 5.47 (1 H, s, C*H*), 6.27 (1 H, d, *J* 2.4, pyrazole 4-H), 7.22-7.27 (3 H, m, phenyl 3-5-H), 7.28 (1 H, d, *J* 2.4, pyrazole 5-H) and 7.42-7.48 (2 H, m, phenyl 2,6-H); δ_C 27.11 (3-C), 27.40 (2-C), 30.40 (4-C), 51.58 (1-C), 52.90 (OMe), 99.67 [$CH(OMe)_2$], 103.79 (pyrazole 4-C), 126.86 (phenyl 4-C), 129.04 (phenyl 3,5-C), 129.60 (pyrazole 5-C), 129.99 (phenyl 1-C), 132.63 (phenyl 2,6-C) and 149.76 (pyrazole 3-C); *m/z* 354 [$(M+H)^+$, 14%], 197 (100), 165 (100), 151 (100) and 111 (54).

The other isomer, 5-(dimethoxymethyl)-1-[4-(phenylselenyl)butyl]-1*H*-pyrazole **158**; [Found: $(M+H)^+$, 354.0849. $C_{16}H_{23}N_2O_2Se$ requires 354.0847]; υ_{max}(thin film)/cm^{-1} 1578 (C=C), 1053 (C-O) and 787, 737, 692, 668 (aromatic o.o p. deformations); δ_H 1.67-1.75 (2 H, m, 3-H), 1.95-2.01 (2 H, m, 2-H), 2.91 (2 H, t, *J* 7.2, 4-H), 3.29 (6 H, s, OMe), 4.15 (2 H, t, *J* 7.2, 1-H), 5.48 (1

H, s, C*H*), 6.30 (1 H, d, *J* 2.0, pyrazole 4-H), 7.21-7.25 (3 H, m, phenyl 3-5-H), 7.42 (1 H, d, *J* 2.0, pyrazole 5-H) and 7.44-7.50 (2 H, m, phenyl 2,6-H); δ_C 27.12 (3-C), 27.22 (2-C), 30.11 (4-C), 49.23 (1-C), 52.80 (OMe), 97.36 [$CH(OMe)_2$], 106.13 (pyrazole 4-C), 126.74 (phenyl 4-C), 128.97 (phenyl 3,5-C), 130.12 (phenyl 1-C), 132.58 (phenyl 2,6-C), 138.00 (pyrazole 3-C) and 138.45 (pyrazole 5-C); *m/z* 354 [$(M+H)^+$, 7%), 197 (100), 165 (27), 123 (49) and 111 (100).

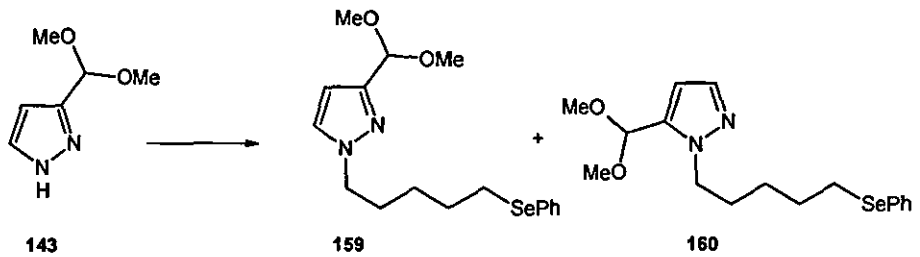
Synthesis of 1-(4-phenylselenyl-butyl)-1*H*-pyrazole-3-carbaldehyde 161



157 161

3-(Dimethoxymethyl)-1-[4-(phenylselenyl)butyl]-1*H*-pyrazole **157** (0.36 g, 1.0 mmol) was dissolved in ethanol (30 cm^3) and pTSA (19 mg, 0.1 mmol) was added and the solution was stirred overnight. The crude material was evaporated to dryness, partitioned between aqueous sodium bicarbonate and dichloromethane and the organic layer removed. The aqueous layer was further extracted with dichloromethane and the combined organic layers evaporated to dryness to yield 1-(4-phenylselanyl-butyl)-1*H*-pyrazole-3-carbaldehyde **161** (0.28 g, 91%) as a colourless oil; (Found: M^+, 308.0428. $C_{14}H_{16}N_2OSe$ requires 308.0432); υ_{max}(thin film)/cm^{-1} 2936, 2827 (C-H), 1693 (C=O), 1578 (C=C) and 760, 737 (aromatic o.o p. deformations); δ_H 1.66-1.75 (2 H, m, 3-H), 1.99-2.10 (2 H, m, 2-H), 2.90 (2 H, t, *J* 7.2, 4-H), 4.20 (2 H, t, *J* 7.0, 1-H), 6.77 (1 H, d, *J* 2.4, pyrazole 4-H), 7.22-7.27 (3 H, m, phenyl 3-5-H), 7.37 (1 H, dd, *J* 2.4, 0.8, pyrazole 2,6-H), 7.44-7.48 (2 H, m, phenyl 2,6-H) and 9.94 (1 H, d, *J* 0.8, CHO); δ_C 26.94 (3-C), 27.00 (2-C), 30.11 (4-C), 52.42 (1-C), 106.02 (pyrazole 4-C), 127.07 (phenyl 4-C), 129.12 (phenyl 3,5-C), 129.75 (phenyl 1-C), 131.11 (pyrazole 5-C), 132.82 (phenyl 2,6-C), 151.46 (pyrazole 3-C) and 186.38 (CHO); *m/z* 308 (M^+, 17%), 155 (17), 151 (100), 109 (46) and 97 (22).

Synthesis of 3-(dimethoxymethyl)-1-[5-(phenylselenyl)pentyl]-1*H*-pyrazole 159

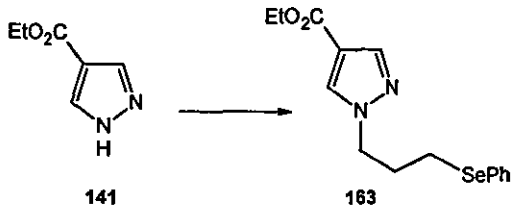


143 159 160

3-(Dimethoxymethyl)-1*H*-pyrazole **143** (0.43 g, 3.0 mmol) was added to a stirred suspension of crushed potassium hydroxide (0.51 g, 9.0 mmol) in DMF (20 cm^3) at 0 °C and the reaction mixture was stirred for 30 min. (5-Chloro-pentylselenyl)-benzene **151** (0.94 g, 3.6 mmol) and sodium iodide (0.045g, 0.3 mmol) were added to the stirred suspension and the mixture was allowed to warm to room temperature and the reaction mixture was stirred for 40 h. The crude mixture was poured onto ice-water and extracted twice with ethyl acetate. The combined organic extracts were washed with water and twice with brine, dried and evaporated to dryness to yield a pale yellow oil. Purification by column chromatography yielded 3-(dimethoxymethyl)-1-[5-(phenylselenyl)pentyl]-1*H*-pyrazole **159** (0.66 g, 60%) as a colourless oil, in addition 5-(dimethoxymethyl)-1-[5-(phenylselenyl)pentyl]-1*H*-pyrazole **160** (0.32 g, 29%) was also isolated as a colourless oil. 3-(Dimethoxymethyl)-1-[5-(phenylselenyl)pentyl]-1*H*-pyrazole **159**; (Found: M^+, 368.0998. $C_{17}H_{24}N_2O_2Se$ requires 368.1003); υ_{max}(thin film)/cm^{-1}1578 (C=C), 1053 (C-O) and 787, 692 (aromatic o.o.p. deformations); δ_H 1.36-1 43 (2 H, m, 3-C), 1.67-1.74 (2 H, m, 4-H), 1.81-1.89 (2 H, m, 2-H), 2.87 (2 H, t, *J* 7.2, 5-H), 3.38 (6 H, s, OMe), 4.08 (2 H, t, *J* 7.4, 1-H), 5.47 (1 H, s, C*H*), 6.28 (1 H, d, *J* 2.0, pyrazole 4-H), 7.20-7.28 (3 H, m, phenyl 3-5-H), 7.30 (1 H, d, *J* 2.0, pyrazole 5-H) and 7.43-7.49 (2 H, m, phenyl 2,6-H); δ_C 26.69 (3-C), 27.52 (4-C), 29.56 (2-C), 29.88 (5-C), 52.03 (1-C), 52.93 (OMe), 99.73 [$CH(OMe)_2$], 103.63 (pyrazole 4-C), 126.76 (phenyl 4-C), 129.00 (phenyl 3,5-C), 129.63 (pyrazole 5-C), 130.24 (phenyl 1-C), 132.54 (phenyl 2,6-C) and 149.73 (pyrazole 3-C); *m/z* 368 (M^+, 2%), 211 (100), 137 (12), 111 (19) and 75 (18).

The other isomer, 5-(dimethoxymethyl)-1-[5-(phenylselenyl)pentyl]-1*H*-pyrazole **160**; (Found: M^+, 368.1011. $C_{17}H_{24}N_2O_2Se$ requires 368.1003); υ_{max}(thin film)/cm^{-1} 1578 (C=C), 1055 (C-O) and 764, 692 (aromatic o.o.p. deformations); δ_H 1.15-1.27 (2 H, m, 3-H), 1.69-1.76 (2 H, m, 4-H), 1.81-1.97 (2 H, m, 2-H), 2.91 (2 H, t, *J* 7.4, 5-H), 3.30 (6 H, s, OMe), 4.12 (2 H, t, *J* 7.4, 1-H), 5.45 (1 H, s, C*H*), 6.30 (1 H, d, *J* 1.6, pyrazole 4-H), 7.19-7.27 (3 H, m, phenyl 3-5-H), 7.42 (1 H, d, *J* 1.6, pyrazole 5-H) and 7.43-7.49 (2 H, m, phenyl 2,6-H); δ_C 26.84 (3-C), 27.55 (4-C), 29.58 (2-C), 29.69 (5-C), 49.70 (1-C), 52.76 (OMe), 97.34 [*C*H(OMe)$_2$], 106.07 (pyrazole 4-C), 126.68 (phenyl 4-C), 128.98 (phenyl 3,5-C), 130.36 (phenyl 1-C), 132.49 (phenyl 2,6-C), 137.97 (pyrazole 3-C) and 138.41 (pyrazole 5-C); *m/z* 368 (M^+, 5%), 211 (70), 179 (100), 165 (89) and 137 (61).

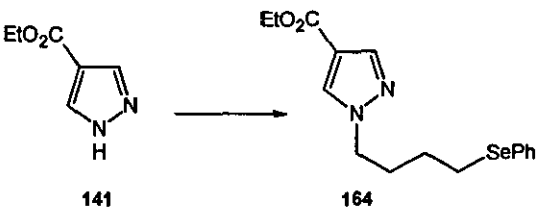
Synthesis ethyl 1-[3-(phenylselenyl)propyl]-1*H*-pyrazole-4-carboxylate 163



141 163

Ethyl pyrazole-4-carboxylate **141** (1.00 g, 7.14 mmol) was added to a stirred suspension of sodium hydride (0.45 g, 10.61 mmol) in DMF (20 cm^3) at 0 °C and the reaction mixture was stirred for 30 min. (3-Chloro-propylselenyl)-benzene **149** (2.51 g, 10.71 mmol) and sodium iodide (3.21 g, 21.2 mmol) was added to the stirred suspension and the mixture was allowed to warm to room temperature and the reaction mixture was stirred for 24 h. The crude mixture was poured onto ice-water and extracted twice with ethyl acetate. The combined organic extracts were washed with water and twice with brine, dried and evaporated to dryness to yield a pale yellow oil. Purification by column chromatography yielded ethyl 1-[3-(phenylselenyl)propyl]-1*H*-pyrazole-4-carboxylate **163** (1.09 g, 45%) as a colourless oil; (Found: M^+, 338 0540. $C_{15}H_{22}N_2O_2Se$ requires 338.0534); υ_{max}(thin film)/cm^{-1} 1718 (C=O), 1554 (C=C), 1220 and 1025 (C-O); δ_H 1.34 (3 H, t, *J* 7.2, CH_3), 2.20-2.27 (2 H, m, 2-H), 2.83 (2 H, t, *J* 6.8, 3-H), 4.22-4.31 (4 H, m, 1-H and CO_2CH_2), 7.23-7.28 (3 H, m, phenyl 3-5-H), 7.46-7.51 (2 H, m, phenyl 2,6-H), 7.80 (1 H, s, pyrazole 5-H) and 7.90 (1 H, s, pyrazole 3-H); δ_C 14.37 (Me), 24.08 (2-C), 30.03 (3-C), 51.56 (1-C), 60.13 (CO_2CH_2), 114.98 (pyrazole 4-C), 127.27 (phenyl 4-C), 129.00 (phenyl 1-C), 129.21 (phenyl 3,5-C), 132.78 (phenyl 2,6-C), 132.99 (pyrazole 5-C), 141.23 (pyrazole 3-C) and 162.94 (CO_2Et); *m/z* 338 (M^+, 27%), 293 (12), 181 (100), 153 (100), 135 (61), 95 (39) and 77 (30).

Synthesis of ethyl 1-[4-(phenylselenyl)butyl]-1*H*-pyrazole-4-carboxylate 164

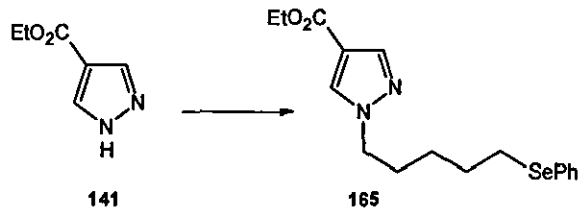


141 164

Ethyl pyrazole-4-carboxylate **141** (0.20 g, 1.3 mmol) was added to a stirred suspension of crushed potassium hydroxide (0.22 g, 3.9 mmol) in DMF (10 cm^3) at 0 °C and the reaction mixture was stirred for 30 min. (4-Iodo-butylselenyl)-benzene **150** (0.50 g, 1.5 mmol) was added to the stirred suspension and the mixture was allowed to warm to room temperature and the

reaction mixture was stirred for 28 h. The crude mixture was poured onto ice-water and extracted twice with ethyl acetate. The combined organic extracts were washed with water and twice with brine, dried and evaporated to dryness to yield a pale yellow oil. Purification by column chromatography yielded ethyl 1-[4-(phenylselenyl)butyl]-1*H*-pyrazole-4-carboxylate **164** (0.25 g, 55%) as a colourless oil; [Found: $(M+H)^+$, 353.0770. $C_{16}H_{21}N_2O_2Se$ requires 353.0768]; υ_{max}(thin film)/cm^{-1} 1714 (C=O) and 1555 (C=C); δ_H 1.34 (3 H, t, *J* 7.2, CH_3), 1.63-1.71 (2 H, m, 3-H), 1.97-2.02 (2 H, m, 2-H), 2.89 (2 H, t, *J* 7.2, 4-H), 4.11 (2 H, t, *J* 6.8, 1-H), 4.29 (2 H, q, *J* 7.2, CO_2CH_2), 7.21-7.28 (3 H, m, phenyl 3-5-H), 7.43-7.48 (2 H, m, phenyl 2,6-H), 7.82 (1 H, s, pyrazole 5-H) and 7.88 (1 H, s, pyrazole 3-H); δ_C 14.37 (Me), 26.86 (3-C), 26.99 (2-C), 29.93 (4-C), 51.95 (1-C), 60.11 (CO_2CH_2), 114.99 (pyrazole 4-C), 126.96 (phenyl 4-C), 129.07 (phenyl 3,5-C), 129.79 (phenyl 1-C), 132.33 (phenyl 2,6-C), 132.76 (pyrazole 5-C), 140.99 (pyrazole 3-C) and 162.97 (CO_2Et); *m/z* 353 [$(M+H)^+$, 30%] and 195 (100).

Synthesis of ethyl 1-[5-(phenylselenyl)pentyl]-1*H*-pyrazole-4-carboxylate 165

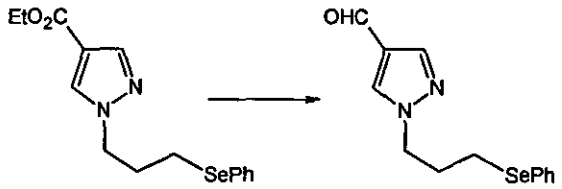


141 165

Ethyl pyrazole-4-carboxylate **141** (0.60 g, 4.3 mmol) was added to a stirred suspension of sodium hydride (0.27 g, 6.4 mmol) in DMF (20 cm^3) at 0 °C and the reaction mixture was stirred for 30 min. (5-Chloro-pentylselenyl)-benzene **151** (1.69 g, 6.4 mmol) and sodium iodide (1.93 g, 12.9 mmol) was added to the stirred suspension and the mixture was allowed to warm to room temperature and the reaction mixture was stirred for 24 h. The crude mixture was poured onto ice-water and extracted twice with ethyl acetate. The combined organic extracts were washed with water and twice with brine, dried and evaporated to dryness to yield a pale yellow oil. Purification by column chromatography yielded ethyl 1-[5-(phenylselenyl)pentyl]-1*H*-pyrazole-4-carboxylate **165** (1.09 g, 45%) as a colourless oil; (Found: M^+, 366.0848. $C_{17}H_{22}N_2O_2Se$ requires 366.0847); υ_{max}(thin film)/cm^{-1} 1715 (C=O), 1554 (C=C) and 1025 (C-O); δ_H 1.34 (3 H, t, *J* 7.0, Me), 1.37-1.43 (2 H, m, 3-H), 1.68-1.75 (2 H, m, 4-H), 1.82-1.90 (2 H, m, 2-H), 2.86 (2 H, t, *J* 6.6, 5-H), 4.08 (2 H, t, *J* 7.0, 1-H), 4.29 (2 H, q, *J* 7.0, CO_2CH_2), 7.20-7.27 (3 H, m, phenyl 3-5-H), 7.45-7.49 (2 H, m, phenyl 2,6-H), 7.84 (1 H, s, pyrazole 5-H) and 7.89 (1 H, s, pyrazole 3-H); δ_C 14.37 (Me), 26.52 (3-C), 27.40 (4-C), 29.47 (2-C), 29.52 (5-C), 52.37 (1-C), 60.09 (CO_2CH_2), 114.89 (pyrazole 4-C), 126 80 (phenyl 4-C), 129.02 (phenyl 3,5-C), 130.16

(phenyl 1-C), 132.49 (phenyl 2,6-C), 132.58 (pyrazole 5-C), 140.95 (pyrazole 3-C) and 163.02 (CO_2Et); *m/z* 366 (M^+, 14), 209 (100), 181 (36) and 153 (45).

Synthesis of [1-(3-phenylselenyl-propyl)-1*H*-pyraz-4-yl]carbaldehyde 168

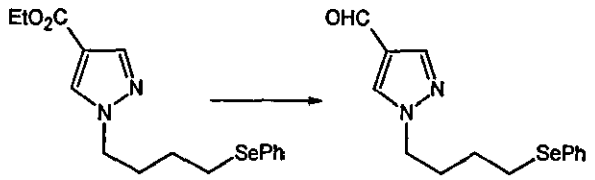


163 168

Lithium aluminium hydride (1 M, 6.0 cm^3) was added to ethyl 1-[3-(phenylselenyl)propyl]-1*H*-pyrazole-4-carboxylate **163** (0.80 g, 2.40 mmol) in THF at 0 °C over 10 min. The reaction was quenched after 4 h with ethanol and hydrochloric acid (2 M, 10 cm^3) was added. The aqueous layer was neutralised after 10 min and extracted with ethyl acetate, dried and evaporated to dryness to yield [1-(3-phenylselenyl-propyl)-1*H*-pyraz-4-yl]methanol (0.56 g, 79%) as coloured oil; δ_H 2.12-2.19 (2 H, m, 2-H), 2.72 (2 H, t, *J* 6.5, 3-H), 4.07 (2 H, t, *J* 6.5, 1-H), 5.22 (2 H, s, CH_2OH), 7.17-7.20 (3 H, m, phenyl 3-5-H), 7.21-7.24 (2 H, m, phenyl 2,6 -H) and 7.40 (2 H, s, pyrazole 3,5-H).

The crude alcohol was sufficiently pure to use directly in the oxidation. DMSO (0.35 g, 4.48 mmol) in DCM was cooled to –78 °C and oxalyl chloride (0.34 g, 2.70 mmol) was added slowly over 8 min and stirred for a further 30 min. [1-(3-Phenylselenyl-propyl)-1*H*-pyraz-4-yl]methanol (0.66 g, 2.24 mmol) in DCM (5 cm^3) was added slowly to the solution at –78 °C and stirred for 2 h. Triethylamine (1.13 g, 11.20 mmol) was added and the reaction was allowed to warm slowly to room temperature. The solution was treated with sodium bicarbonate solution and extracted with DCM, dried and evaporated to dryness to yield a coloured oil. Column chromatography afforded the desired [1-(3-phenylselenyl-propyl)-1*H*-pyrazol-4-yl]carbaldehyde **168** (72 mg, 11%) as a coloured oil; υ_{max}(thin film)/cm^{-1} 2928, 2852 (C-H), 1681 (C=O) and 1542 (C=C); δ_H 2.23-2.31 (2 H, m, 2-H), 2.82 (2 H, t, *J* 7.1, 3-H), 4.29 (2 H, t, *J* 6.6, 1-H), 7.26-7.29 (3 H, m, phenyl 3-5-H), 7.47-7.81 (2 H, m, phenyl 2,6-H), 7.81 (1 H, s, pyrazole 5-H), 7.96 (1 H, s, pyrazole 3-H) and 9.82 (1 H, s, CHO).

Synthesis of [1-(4-phenylselenyl-butyl)-1*H*-pyraz-4-yl]carbaldehyde 169

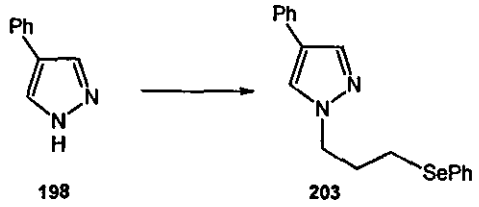


164 169

Lithium aluminium hydride (1 M, 2.9 cm^3) was added to ethyl 1-[4-(phenylselenyl)butyl]-1*H*-pyrazole-4-carboxylate **164** (0.40 g, 1.13 mmol) in THF at 0 °C over 10 min. The reaction was quenched after 4 h with ethanol and hydrochloric acid (2 M, 10 cm^3) was added. The aqueous layer was neutralised after 10 min and extracted with ethyl acetate, dried and evaporated to dryness to yield [1-(4-phenylselenyl-butyl)-1*H*-pyraz-4-yl]methanol (0.23 g, 70%) as coloured oil; δ_H 1.65-1.71 (2 H, m, 2-H), 1.95-2.01 (2 H, m, 3-H), 2.89 (2 H, t, *J* 7.2, 4-H), 4.08 (2 H, t, *J* 7.2, 1-H), 4.56 (2 H, s, CH_2OH), 7.23-7.24 (3 H, m, phenyl 3-5-H), 7.26-7.33 (2 H, m, phenyl 2,6 -H) and 7.44-7.47 (2 H, m, pyrazole 3,5-H).

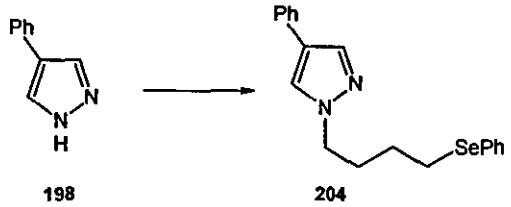
The crude alcohol was sufficiently pure to use directly in the oxidation. DMSO (0.40 g, 5.18 mmol) in DCM was cooled to –78 °C and oxalyl chloride (0.39 g, 3.11 mmol)was added slowly over 8 min and stirred for a further 30 min. [1-(4-Phenylselenyl-butyl)-1*H*-pyraz-4-yl]methanol (0.80 g, 2.59 mmol) in DCM (5 cm^3) was added slowly to the solution at –78 °C and stirred for 2 h. Triethylamine (1.31 g, 12.90 mmol) was added and the reaction was allowed to warm slowly to room temperature. The solution was treated with sodium bicarbonate solution and extracted with DCM, dried and evaporated to dryness to yield a coloured oil. Chromatographic purification afforded the desired [1-(4-phenylselenyl-butyl)-1*H*-pyrazol-4-yl]carbaldehyde **169** (70 mg, 9%) as a coloured oil; υ_{max}(thin film)/cm^{-1} 2931 and 2852 (C-H), 1681 (C=O) and 1543 (C=C); δ_H 1.68 (2 H, m, 2-H), 1.97 (2 H, t, *J* 7.1, 3-H), 2.89 (2 H, t, *J* 7.2, 4-H), 4.09 (2 H, t, *J* 7.2, 1-H), 7.22-7.24 (3 H, m, phenyl 3-5-H), 7.43-7.48 (2 H, m, phenyl 2,6-H), 7.82 (1 H, s, pyrazole 3-H), 7.88 (1 H, s, pyrazole 5-H) and 9.82 (1 H, s, CHO); δ_C 27.33 (3-C), 27.45 (2-C), 30.33 (4-C), 52.67 (1-C), 127.58 (phenyl 4-C), 129.64 (phenyl 3,5-C), 132.93 (pyrazole 5-C), 133.32 (phenyl 2,6-C), 141.37 (pyrazole 5-C) and 184.53 (CHO);

Synthesis of 4-phenyl-1-(3-phenylselenyl-propyl)-1*H*-pyrazole 203



4-Phenylpyrazole **198** (0.15 g, 1.0 mmol) was added to a stirred suspension of crushed potassium hydroxide (0.17 g, 3.0 mmol) in DMF (15 cm^3) and stirring was continued for 30 min. (3-Iodo-propylselenyl)-benzene **152** (0.65 g, 2.0 mmol) was added slowly to the stirred suspension and stirring was continued overnight. The crude reaction mixture was partitioned between water and ethyl acetate and the aqueous layer separated and extracted with ethyl acetate. The combined organic extracts were washed twice with water and twice with brine, dried and evaporated to dryness. The crude off-white oily solid was purified by column chromatography to yield 4-phenyl-1-(3-phenylselenyl-propyl)-1*H*-pyrazole **203** (0.34 g, 100%) as a white solid, mp 48-50 °C; [Found: $(M+H)^+$, 343.0717. $C_{18}H_{19}N_2Se$ requires 343.0713]; υ_{max}(KBr)/cm^{-1} 1607 (C=C) and 760, 693 (aromatic o.o.p. deformations); δ_H 2.23-2.37 (2 H, m, 2-H), 2.91 (2 H, t, *J* 7.1, 3-H), 4.31 (2 H, t, *J* 6.5, 1-H), 7.24-7.32 (4 H, m, phenyl-H), 7.37-7.52 (6 H, m, phenyl-H), 7.53 (1 H, s, pyrazole 3-H) and 7.77 (1 H, s, pyrazole 5-H); δ_C 24.36 (2-C), 30.42 (3-C), 51.31 (1-C), 122.88 (pyrazole 4-C), 125.48 (phenyl 2,6-C), 125.72 (pyrazole 3-C), 126.36 (phenyl 4-C), 127.14 (Se-phenyl 4-C), 128.83 (phenyl 3,5-C), 129.19 (Se-phenyl 3,5-C), 129.54 (Se-phenyl 1-C), 132.54 (phenyl 1-C), 132.85 (Se-phenyl 2,6-C) and 136.95 (pyrazole 5-C); *m/z* 343 [$(M+H)^+$, 29%] and 187 (100).

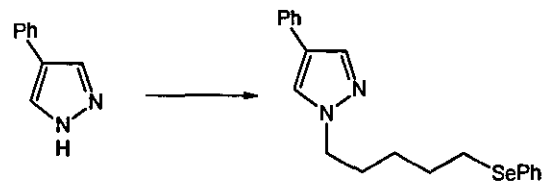
Synthesis of 4-phenyl-1-(4-phenylselenyl-butyl)-1*H*-pyrazole 204



4-Phenylpyrazole **198** (37 mg, 0.26 mmol) was added to a stirred suspension of crushed potassium hydroxide (44 mg, 0.78 mmol) in DMF (5 cm^3) and stirring was continued for 30 min. (4-Iodo-butylselenyl)-benzene **153** (175 mg, 0.52 mmol) was added slowly to the stirred suspension and stirring was continued overnight. The crude reaction mixture was partitioned between water and ethyl acetate and the aqueous layer was separated and extracted with ethyl acetate. The combined organic extracts were washed twice with water and twice with brine,

dried and evaporated to dryness. The crude off-white oily solid was purified by column chromatography to yield 4-phenyl-1-(3-phenylselenyl-propyl)-1*H*-pyrazole **204** (0.34 g, 100%) as a white solid, mp 44-45 °C; υ_{max}(KBr)/cm^{-1} 1607 (C=C) and 760, 692 (aromatic o.o.p. deformations); δ_H(400 MHz) 1.69-1.76 (2 H, m, 3-H), 1.99-2.07 (2 H, m, 2-H), 2.91 (2 H, t, *J* 7.2, 4-H), 4.14 (2 H, t, *J* 6.9, 1-H), 7.21-7.23 (4 H, m, phenyl-H), 7.30-7.37 (2 H, m, phenyl-H), 7.45-7.47 (4 H, m, phenyl-H), 7.57 (1 H, s, pyrazole 3-H) and 7.75 (1 H, s, pyrazole 5-H); δ_C 27.10-27.19 (2,3-C), 30.32 (4-C), 51.76 (1-C), 122.97 (pyrazole 4-C), 125.51 (phenyl 2,6-C), 125.88 (pyrazole 3-C), 126.34 (phenyl 4-C), 126.93 (Se-phenyl 4-C), 128.84 (phenyl 3,5-C), 129.07 (Se-phenyl 3,5-C), 129.98 (Se-phenyl 1-C), 132.66 (phenyl 1-C), 132.77 (Se-phenyl 2,6-C) and 136.70 (pyrazole 5-C).

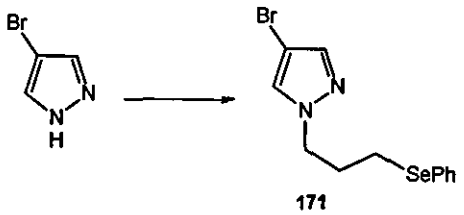
Synthesis of 4-phenyl-1-(5-phenylselenyl-pentyl)-1*H*-pyrazole 205



198 205

4-Phenylpyrazole **198** (0.30 g, 2.1 mmol) was added to a stirred suspension of crushed potassium hydroxide (0.35 g, 6.3 mmol) in DMF (25 cm^3) and stirring was continued for 30 min. (5-Iodo-pentylselenyl)-benzene **154** (0.88 g, 2.5 mmol) was added slowly to the stirred suspension and stirring was continued overnight. The crude reaction mixture was partitioned between water and ethyl acetate and the aqueous layer separated and extracted with ethyl acetate. The combined organic extracts were washed twice with water and twice with brine, dried and evaporated to dryness. The crude off-white oily solid was purified by column chromatography to yield 4-phenyl-1-(5-phenylselenyl-pentyl)-1*H*-pyrazole **205** (0.76 g, 98%) as a white solid, mp 36-37 °C; (Found: M$^+$, 370.0943. $C_{20}H_{22}N_2Se$ requires 370.0948); υ_{max}(KBr)/cm^{-1} 1607 (C=C) and 760, 736, 693, 666 (aromatic o.o.p. deformations); δ_H(400 MHz) 1.16-1.26 (2 H, m, 3-H), 1.66-1.75 (2 H, m, 4-H), 1.83-1.90 (2 H, m, 2-H), 2.86 (2 H, t, *J* 7.6, 5-H), 4.07 (2 H, t, *J* 7.0, 1-H), 7.18-7.25 (4 H, m, phenyl-H), 7.31-7.36 (2 H, m, phenyl-H), 7.42-7.48 (4 H, m, phenyl-H), 7.55 (1 H, s, pyrazole 3-H) and 7.76 (1 H, s, pyrazole 5-H); δ_C 26.75 (3-C), 27.53 (4-C), 29.65 (2-C), 29.84 (5-C), 52.16 (1-C), 122.70 (pyrazole 4-C), 125.48 (phenyl 2,6-C), 125.96 (pyrazole 3-C), 126.31 (phenyl 4-C), 126.78 (Se-phenyl 4-C), 128.86 (phenyl 3,5-C), 129.05 (Se-phenyl 3,5-C), 130.15 (Se-phenyl 1-C), 132.56 (phenyl 1-C), 132.70 (Se-phenyl 2,6-C) and 136.62 (pyrazole 5-C); *m/z* 370 (M$^+$, 6%), 213 (100), 157 (100), 157 (100), 145 (29) and 103 (23).

Synthesis of 4-bromo-1-(3-phenylselenyl-propyl)-1*H*-pyrazole 171

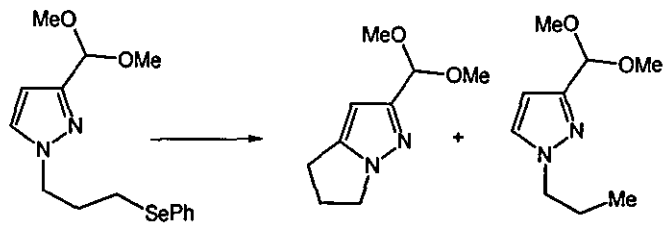


171

4-Bromopyrazole **200** (0.10 g, 0.7 mmol) was added to a stirred suspension of crushed potassium hydroxide (0.12 g, 2.1 mmol) in DMF (10 cm^3) and stirring was continued for 30 min. (3-Iodo-propylselenyl)-benzene **154** (0.46 g, 1.4 mmol) was added slowly to the stirred suspension and stirring was continued overnight. The crude reaction mixture was partitioned between water and ethyl acetate and the aqueous layer separated and extracted with ethyl acetate. The combined organic extracts were washed twice with water and twice with brine, dried and evaporated to dryness. The crude off-white oily solid was purified by column chromatography to yield 4-bromo-1-(3-phenylselenyl-propyl)-1*H*-pyrazole **171** (0.22 g, 91%) as a white solid; υ_{max}(thin film)/cm^{-1} 1578 (C=C) and 736, 691 (aromatic o.o.p. deformations); δ_H 2.13-2.24 (2 H, m, 2-H), 2.80 (2 H, t, *J* 6.9, 3-H), 4.18 (2 H, t, *J* 6.5, 1-H), 7.25-7.29 (4 H, m, phenyl 3-5-H and pyrazole 3-H) and 7.45-7.47 (3 H, m, phenyl 2,6-H and pyrazole 5-H); δ_C 24.09 (2-C), 30.19 (3-C), 51.67 (1-C), 97.69 (pyrazole 4-C), 127.14 (pyrazole 3-C), 129.15 (phenyl 3,5-C), 129.35 (phenyl 1-C), 129.45 (phenyl 4-C), 132 83 (phenyl 2,6-H) and 139.84 (pyrazole 5-C).

5.1.3 Alkyl Radical addition to Pyrazoles

Attempted synthesis of 2-(dimethoxymethyl)-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole 176

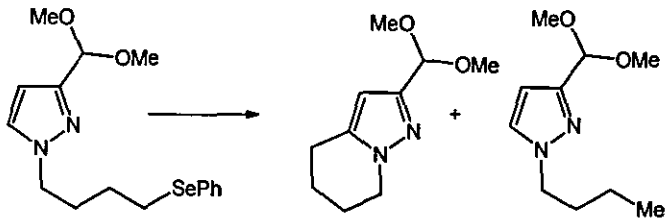


155 176 173

A solution of tributyltin hydride (0.12 cm^3, 0.38 mmol) and ACCN (0.20 g, 0.58 mmol) in toluene (50 cm^3) was added to a deoxygenated solution of 3-(dimethoxymethyl)-1-[3-(phenylselenyl)propyl]-1*H*-pyrazole **155** (0.12 g, 0.29 mmol) in acetonitrile (200 cm^3) heated under reflux for 5 h. The reaction mixture was heated at reflux for a further 30 min following complete addition, cooled to room temperature and evaporated to dryness. Purification by column chromatography gave the reduced product, 3-(dimethoxymethyl)-1-propyl-1*H*-pyrazole

173 (40 mg, 75%) as a colourless oil; (Found: M^+, 184.1209. $C_9H_{16}N_2O_2$ requires 184.1212); υ_{max}(thin film)/cm^{-1} 1056 (C-O) and 766 (aromatic o.o.p deformations); δ_H 0.90 (3 H, t, *J* 7.4, 3-H), 1.83-1.93 (2 H, m, 2-H), 3.38 (6 H, s, OMe), 4.08 (2 H, t, *J* 7.2, 1-H), 5.48 [1 H, s, C*H*(OMe)$_2$], 6.29 (1 H, d, *J* 2.2, pyrazole 4-H) and 7.34 (1 H, d, *J* 2.2, pyrazole 5-H); δ_C 11.03 (3-C), 23.74 (2-C), 52.89 (1-C), 53.84 (OMe), 99.75 [*C*H(OMe)$_2$], 103.52 (pyrazole 4-C), 129.60 (pyrazole 5-C) and 149.59 (pyrazole 3-C); *m/z* 184 (M^+, 1%), 153 (100), 111 (14) and 75 (9).

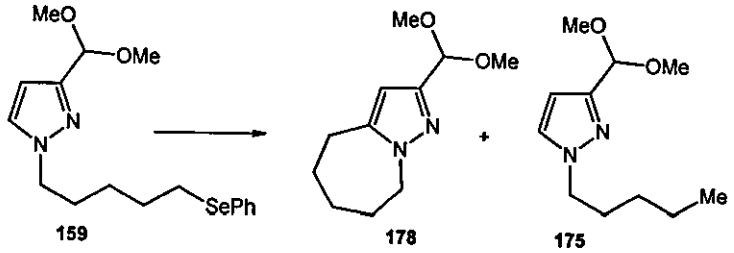
Attempted synthesis of 2-(dimethoxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine 177



157 **177** **174**

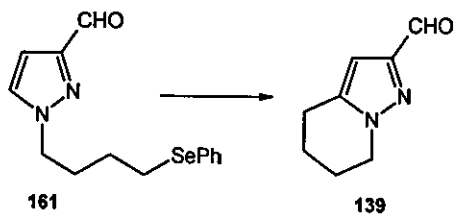
TTMSS (33 mg, 0.13 mmol) was added to a solution of 3-(dimethoxymethyl)-1-[4-(phenylselenyl)butyl]-1*H*-pyrazole **157** in cyclohexane at room temperature, the flask was fitted with a rubber septum and exposed to air *via* a needle. Triethyl borane in hexane (0.2 cm^3, 0.20 mmol) was added and stirring maintained at room temperature for 8 h. TTMSS (33 mg, 0.13 mmol) and triethylborane in hexane (0.2 cm^3, 0.20 mmol) were added and stirred for a further 12 h after which time a further portion of TTMSS (33 mg, 0.13 mmol) and triethyl borane in hexane (0.2 cm^3, 0.20 mmol) was added and stirred for 8 h. The reaction mixture was evaporated to dryness and purified by column chromatography yielding 3-(dimethoxymethyl)-1-butyl-1*H*-pyrazole **174** (11 mg, 57%) as a colourless oil; δ_H 0.93 (3 H, t, *J* 7.4, 4-H), 1.29-1.36 (2 H, m, 3-H), 1.80-1.90 (2 H, m, 2-H), 3.38 (6 H, s, OMe), 4.11 (2 H, t, *J* 7.2, 1-H), 5.48 [1 H, s, C*H*(OMe)$_2$], 6.28 (1 H, d, *J* 2.6, pyrazole 4-H) and 7.33 (1 H, d, *J* 2.6, pyrazole 5-H); δ_C 13.58 (4-C), 19.80 (3-C), 32.46 (2-C), 52.04 (1-C), 52.96 (OMe), 99.81 [*C*H(OMe)$_2$], 103.56 (pyrazole 4-C), 129.53 (pyrazole 5-C) and 149.89 (pyrazole 3-C).

Attempted synthesis of 2-(dimethoxymethyl)-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*]azepine 178



A solution of tributyltin hydride (0.11 cm^3, 0.38 mmol) and ACCN (0.15 g, 0.56 mmol) in toluene (50 cm^3) was added to a solution of 4-phenyl-1-(5-phenylselenyl-pentyl)-1*H*-pyrazole **159** (0.11 g, 0.29 mmol) in toluene (250 cm^3) heated under reflux for 4 h. The reaction mixture was heated at reflux for a further 30 min following complete addition, cooled to room temperature and evaporated to dryness. Purification by column chromatography yielded an unidentified product (42 mg) and the reduced product, 3-(dimethoxymethyl)-1-pentyl-1*H*-pyrazole **175** (21 mg, 35%) as a colourless oil; (Found: M^+, 212.1525. $C_{11}H_{20}N_2O_2$ requires 212.1528); υ_{max}(thin film)/cm^{-1} 1057 (C-O) and 764 (aromatic o o p. deformations); δ_H 0.88 (3 H, t, *J* 7.0, 5-H), 1.21-1.39 (4 H, m, 3,4-H), 1.82-1.87 (2 H, m, 2-H), 3.38 (6 H, s, OMe), 4.10 (2 H, t, *J* 8.0, 1-H), 5.48 [1 H, s, C*H*(OMe)$_2$], 6.28 (1 H, d, *J* 2.0, pyrazole 4-H) and 7.34 (1 H, d, *J* 2.0, pyrazole 5-H); δ_C 13.88 (5-C), 22.16 (4-C), 28.71 (3-C), 30.11 (2-C), 52.27 (1-C), 52.90 (OMe), 99.77 [*C*H(OMe)$_2$], 103.54 (pyrazole 4-C), 129.51 (pyrazole 5-C) and 149.56 (pyrazole 3-C); *m/z* 212 (M^+, 1%), 181 (100), 165 (14) and 111 (14).

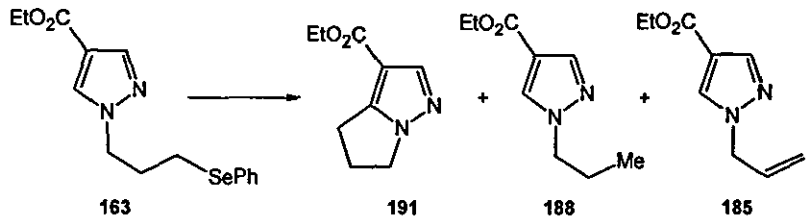
Synthesis of 4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridine-2-carbaldehyde 139



[1-(4-Phenylselenylbutyl)-1*H*-pyrazol-3-yl]carbaldehyde **161** (59 mg, 0.19 mmol) was dissolved in cyclohexane (20 cm^3) and the solution was deoxygenated and the reaction vessel sealed with a septum. The septum was pierced with a needle to allow airflow and TTMSS (84 mg, 0.38 mmol) in cyclohexane (10 cm^3) and triethylborane in hexane (1.0 M, 0.8 cm^3) were added independently to the solution in four equal amounts over 2 h. The reaction was quenched after 6 h with dil. hydrochloric acid (5 cm^3), neutralised with sodium bicarbonate solution and the

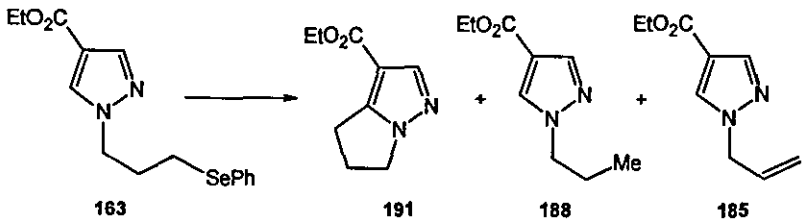
aqueous layer extracted with DCM. The combined organic layers were dried and evaporated to dryness to yield 4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridine-2-carbaldehyde **139** in addition to starting selenide **161** in a 2:3 ratio.

Attempted synthesis of ethyl 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole-3-carboxylate 191 (Bu_3SnH, ACCN)



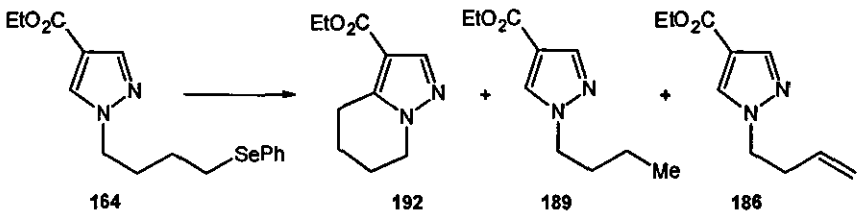
A solution of tributyltin hydride (0.07 cm^3, 0.26 mmol) and ACCN (80 mg, 0.40 mmol) in toluene (50 cm^3) was added to a solution of ethyl 1-[3-(phenylselenyl)propyl]-1*H*-pyrazole-4-carboxylate **163** (0.67 mg, 0.20 mmol) in toluene (200 cm^3) heated under reflux over 4 h. The reaction mixture was heated at reflux for a further 30 min following complete addition, cooled to room temperature and evaporated to dryness. Purification by column chromatography yielded he elimination product, ethyl 1-allyl-1*H*-pyrazole-4-carboxylate **185** and ethyl 1-propyl-1*H*-pyrazole-4-carboxylate **188** (14 mg, 38%) as a colourless oil; (Found: M^+, 182.1055. $C_9H_{14}N_2O_2$ requires 182.1055); υ_{max}(thin film)/cm^{-1} 2969, 1878, 1716 (C=O), 1555 (C=C), 1027 (C-O) and 769 (aromatic o.o.p. deformations); δ_H 0.92 (3 H, t, *J* 7.4, 3-H), 1.35 (3 H, t, *J* 7.0, CH_3), 1.86-1.95 (2 H, m, 2-H), 4.09 (2 H, t, *J* 7.0, 1-H), 4.29 (2 H, q, *J* 7.0, CO_2CH_2), 7.88 (1 H, s, pyrazole 5-H) and 7.90 (1 H, s, pyrazole 3-H); δ_C 10.99 (3-C), 14.37 (Me), 23.39 (2-C), 54.23 (1-C), 60.09 (CO_2CH_2), 114.82 (pyrazole 4-C), 132.35 (pyrazole 5-C), 140.91 (pyrazole 3-C) and 163.09 (CO_2Et); *m/z* 182 (M^+, 39%), 153 (69), 137 (100) and 95 (98). The elimination product, ethyl 1-allyl-1*H*-pyrazole-4-carboxylate **185** (4 mg, 11%); δ_H 1.34 (3 H, t, *J* 7.0, CH_3), 4.29 (2 H, q, *J* 7.0, CO_2CH_2), 4.74-4.77 (2 H, m, 1-H), 5.24-5.35 (2 H, m, 3-H), 5.97-6.07 (2 H, m, 2-H), 7.90 (1 H, s, pyrazole 5-H) and 7.92 (1 H, s, pyrazole 3-H).

Attempted synthesis of ethyl 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole-3-carboxylate 191 (TTMSS, BEt_3)



TTMSS (30 mg, 0.12 mmol) was added to a solution ethyl 1-[3-(phenylselenyl)propyl]-1*H*-pyrazole-4-carboxylate **163** (41 mg, 0.12 mmol) in cyclohexane (25 cm^3) at room temperature, the flask was fitted with a rubber septum and exposed to air *via* a needle. Triethyl borane in hexane (0.18 cm^3, 0.18 mmol) was added and stirring maintained at room temperature for 8 h. TTMSS (30 mg, 0.12 mmol) and triethylborane in hexane (0.18 cm^3, 0.18 mmol) were added and stirred for a further 12 h after which time a further portion of TTMSS (30 mg, 0.12 mmol) and triethyl borane in hexane (0.18 cm^3, 0.18 mmol) was added and stirred for 8 h. The reaction mixture was evaporated to dryness and purified by column chromatography yielding ethyl 1-propyl-1*H*-pyrazole-4-carboxylate **188** (16 mg, 73%) as a colourless oil.

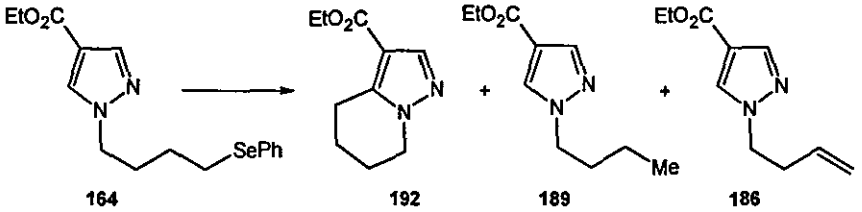
Attempted synthesis of ethyl 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-3-carboxylate 192 (Bu_3SnH, ACCN)



A solution of tributyltin hydride (0.07 cm^3, 0.26 mmol) and ACCN (80 mg, 0.40 mmol) in toluene (50 cm^3) was added to a solution of ethyl 1-[3-(phenylselenyl)propyl]-1*H*-pyrazole-4-carboxylate **164** (70 mg, 0.20 mmol) in toluene (250 cm^3) heated at reflux over 4 h. The reaction mixture was heated at reflux for a further 30 min following complete addition, cooled to room temperature and evaporated to dryness. Purification by column chromatography yielded the elimination product, ethyl 1-(but-3-enyl)-1*H*-pyrazole-4-carboxylate **186** (26 mg, 67%); (Found: M^+, 194.1053. $C_{10}H_{14}N_2O_2$ requires 194.1055); υ_{max}(thin film)/cm^{-1} 1713 (C=O), 1555 (C=C), 1028 (C-O) and 770 (aromatic o.o.p. deformations); δ_H 1.35 (3 H, t, *J* 7.2, Me), 2.59-2.65 (2 H, m, 2-H), 4.19 (2 H, t, *J* 7.0, 1-H), 4.28 (2 H, q, *J* 7.2, CO_2CH_2), 5.04-5.09 (2 H, m, 4-H), 5.68-

5.78 (2 H, m, 3-H), 7.87 (1 H, s, pyrazole 5-H) and 7.90 (1 H, s, pyrazole 3-H); δ_C 14.36 (Me), 34.21 (2-C), 52.06 (1-C), 60.11 (CO_2CH_2), 114.87 (pyrazole 4-C), 118.12 (5-C), 132.53 (pyrazole 5-C), 133.47 (4-C), 141.05 (pyrazole 3-C) and 163.05 (CO_2Et); *m/z* 194 (M^+, 42%), 193 (48), 166 (30), 153 (63), 144 (100) and 95 (36).

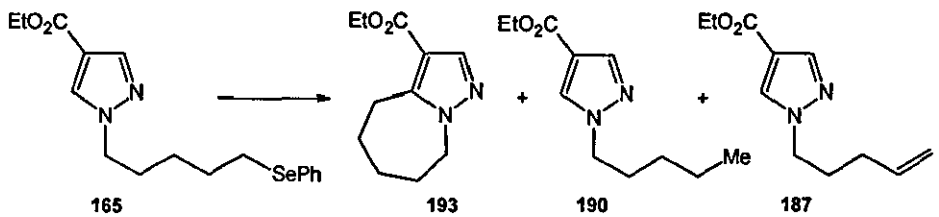
Synthesis of ethyl 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-3-carboxylate 192 (TTMSS, BEt_3)



164 192 189 186

TTMSS (33 mg, 0.13 mmol) was added to a solution of ethyl 1-[3-(phenylselenyl)propyl]-1*H*-pyrazole-4-carboxylate **164** (35 mg, 0.10 mmol) in cyclohexane (25 cm^3) at room temperature, the flask was fitted with a rubber septum and exposed to air *via* a needle. Triethyl borane in hexane (0.2 cm^3, 0.20 mmol) was added and stirring maintained at room temperature for 8 h. TTMSS (33 mg, 0.13 mmol) and triethylborane in hexane (0.2 cm^3, 0.20 mmol) were added and stirred for a further 12 h after which time a further portion of TTMSS (33 mg, 0.13 mmol) and triethyl borane in hexane (0.2 cm^3, 0.20 mmol) was added and stirred for 8 h. The reaction mixture was evaporated to dryness and purified by column chromatography yielding ethyl 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-3-carboxylate **192** (7 mg, 36%) as a colourless oil; (Found: M^+, 194.1056. $C_{10}H_{14}N_2O_2$ requires 194.1055); υ_{max}(thin film)/cm^{-1} 1709 (C=O), 1556 (C=C), 1050 (C-O) and 776 (aromatic o.o.p. deformations);. δ_H 1.34 (3 H, t, *J* 7.2, Me), 1.86-1.92 (2 H, m, 5-H), 2.01-2.06 (2 H, m, 6-H), 3.06 (2 H, t, *J* 6.4, 4-H), 4.15 (2 H, q, *J* 6.2, 7-H), 4.27 (2 H, q, *J* 7.2, CO_2CH_2) and 7.86 (1 H, s, 2-H); *m/z* 194 (M^+, 49%), 165 (51) and 149 (100).

Attempted synthesis of ethyl 5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*]azepine-3-carboxylate 193 (Bu_3SnH, ACCN)

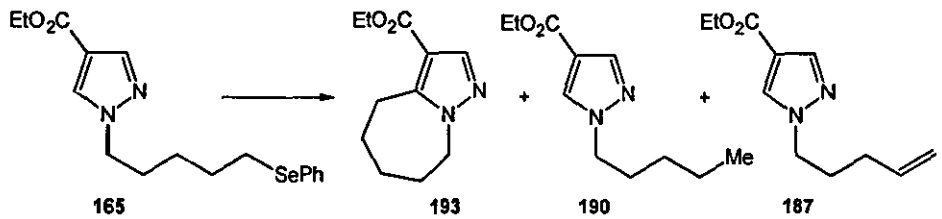


165 193 190 187

A solution of tributyltin hydride (0.07 cm^3, 0.26 mmol) and ACCN (80 mg, 0.40 mmol) in toluene (50 cm^3) was added to a solution of ethyl 1-[5-(phenylselenyl)pentyl]-1*H*-pyrazole-4-

carboxylate **165** (73 mg, 0.20 mmol) in toluene (250 cm^3) heated under reflux over 4 h. The reaction mixture was heated at reflux for a further 30 min following complete addition, cooled to room temperature and evaporated to dryness. Purification by column chromatography yielded the elimination product, ethyl 1-pent-4-enyl-1*H*-pyrazole-4-carboxylate **187** (17 mg, 41%) as a colourless oil; (Found: M^+, 208.1212. $C_{11}H_{16}N_2O_2$ requires 208.1212); υ_{max}(thin film)/cm^{-1} 3131; δ_H 1.35 (3 H, t, *J* 7.0, CH_3), 1.95-2.09 (4 H, m, 2,3-H), 4.13 (2 H, t, *J* 6.8, 1-H), 4.29 (2 H, q, *J* 7.0, CO_2CH_2), 5.02-5.08 (2 H, m, 5-H), 5.73-5.83 (2 H, m, 4-H), 7.87 (1 H, s, pyrazole 5-H) and 7.91 (1 H, s, pyrazole 3-H); 14.35 (Me), 28.95 (2-C), 30.33 (3-C), 51.75 (1-C), 60.09 (CO_2CH_2), 114.88 (pyrazole 4-C), 115.98 (5-C), 132.46 (pyrazole 5-C), 136.71 (4-C), 140.99 (pyrazole 3-C) and 163.06 (CO_2Et); 208 (M^+, 26), 207 (64), 180 (46), 163 (47), 153 (100) and 95 (59).

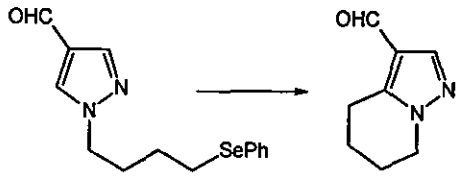
Attempted synthesis of ethyl 5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*]azepine-3-carboxylate 193 (TTMSS, BEt_3)



165 193 190 187

TTMSS (33 mg, 0.13 mmol) was added to a solution of ethyl 1-[5-(phenylselenyl)pentyl]-1*H*-pyrazole-4-carboxylate **165** in cyclohexane (25 cm^3) at room temperature, the flask was fitted with a rubber septum and exposed to air *via* a needle. Triethyl borane in hexane (0.2 cm^3, 0.20 mmol) was added and stirring maintained at room temperature for 8 h. TTMSS (33 mg, 0.13 mmol) and triethylborane in hexane (0 2 cm^3, 0.20 mmol) were added and stirred for a further 12 h after which time a further portion of TTMSS (33 mg, 0.13 mmol) and triethyl borane in hexane (0.2 cm^3, 0.20 mmol) was added and stirred for 8 h. The reaction mixture was evaporated to dryness and purified by column chromatography yielding ethyl 1-pentyl-1*H*-pyrazole-4-carboxylate **190** (13 mg, 62%)as a colourless oil; υ_{max}(thin film)/cm^{-1} 2951, 2894, 1701 (C=O) and 1244; δ_H 0.93 (3 H, t, *J* 7.4, 5-H), 1.20-1.36 (7 H, m, 3,4-H and CH_3), 1.82-1.92 (2 H, m, 2-H), 4.06 (2 H, t, *J* 7.0, 1-H), 4.25 (2 H, q, *J* 7.0, CO_2CH_2), 7.88 (1 H, s, pyrazole 5-H) and 7.89 (1 H, s, pyrazole 3-H); 13.82 (5-C), 14.34 (Me), 22.10 (4-C), 28.56 (3-C), 29.72 (2-C), 52.61 (1-C), 60.12 (CO_2CH_2), 114.78 (pyrazole 4-C), 132.35 (pyrazole 5-C), 140.86 (pyrazole 3-C) and 163.16 (CO_2Et).

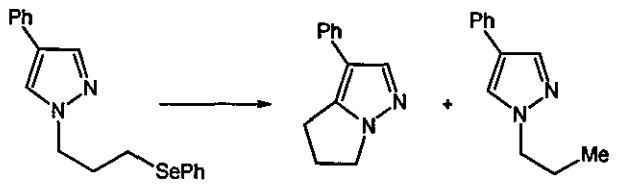
Synthesis of 4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridine-3-carbaldehyde 137



169 137

[1-(4-Phenylselenylbutyl)-1*H*-pyrazol-4-yl]carbaldehyde **169** (59 mg, 0.19 mmol) was dissolved in cyclohexane (20 cm^3) and the solution was deoxygenated and the reaction vessel sealed with a septum. The septum was pierced with a needle to allow airflow and TTMSS (84 mg, 0.38 mmol) in cyclohexane (10 cm^3) and triethylborane in hexane (1.0 M, 0.8 cm^3) were added independently to the solution in four equal amounts over 2 h. The reaction was quenched after 6 h with dil. hydrochloric acid (5 cm^3), neutralised with sodium bicarbonate solution and the aqueous layer extracted with DCM. The combined organic layers were dried and evaporated to dryness. Gradient elution column chromatography yielded 4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridine-3-carbaldehyde **137** (10.5 mg, 37%) as a colourless oil; (Found: M^+, 150.0794. $C_8H_{10}N_2O$ requires 150.0793); υ_{max}(thin film)/cm^{-1} 2884 (C-H), 1670 (C=O), 1562 (C=C) and 782 (aromatic o.o.p. deformations);. δ_H(400 MHz) 1.89-1.96 (2 H, m, 5-H), 2.04-2.11 (2 H, m, 6-H), 3.10 (2 H, t, *J* 6.4, 4-H), 4.18 (2 H, q, *J* 6.0, 7-H), 7.89 (1 H, s, 2-H) and 9.86 (1 H, s, CHO); *m/z* 150 (M^+, 84%), 149 (100) and 121 (19).

Synthesis of 3-phenyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole (withasomnine) 135



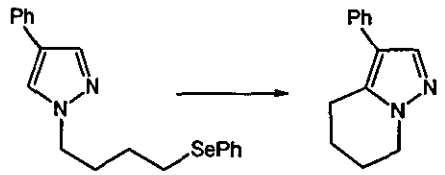
203 135 208

A solution of tributyltin hydride (0.11 cm^3, 0.38 mmol) and ACCN (0.15 g, 0.58 mmol) in toluene (50 cm^3) was added to a solution of 4-phenyl-1-(3-phenylselenyl-propyl)-1*H*-pyrazole **203** (0.10 g, 0.29 mmol) in toluene (200 cm^3) heated under reflux over 4 h. The reaction mixture was heated at reflux for a further 30 min following complete addition, cooled to room temperature and evaporated to dryness. The mixture was partitioned between 2 M hydrochloric acid and light petroleum and the aqueous layer was washed with light petroleum a further five times. The aqueous layer was neutralised and basified to pH 9 and extracted with dichloromethane three times, dried and evaporated to dryness to yield the crude cyclised material

(18 mg) in low yield as a colourless oily solid. LC-MS analysis of the light petroleum washings indicated a large amount of 3-phenyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole **135** present; recombination of all organic extracts followed by purification by column chromatography yielded 3-phenyl-5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole **135** (19 mg, 38%) as a white solid; (Found: M^+, 184.1000. $C_{12}H_{12}N_2$ requires 184.1005); υ_{max}(thin film)/cm^{-1} 2937, 1607, 1470, 1356, 762 and 694; δ_H 2.66-2.73 (2 H, m, 5-H), 3.10 (2 H, t, *J* 7.2, 4-H), 4.18 (2 H, t, *J* 7.4, 6-H), 7.14-7.21 (1 H, m, phenyl 4-H), 7.34-7.38 (phenyl 3,5-H), 7.42-7.46 (2 H, m, phenyl 2,6-H) and 7.81 (1 H, s, 2-H); δ_C 23.84 (5-C), 26.40 (4-C), 47.56 (6-C), 116.30 (3-C), 125.02 (phenyl 2,6-C), 125.61 (phenyl 4-C), 128.79 (phenyl 3,5-C), 130.90 (phenyl 1-C), 133.85 (3a-C) and 140.91 (2-C); *m/z* 184 (M^+, 100%), 128 (15) and 159 (18).

The reduced product, 3-phenyl-1-propyl-1*H*-pyrazole **208** (9 mg, 17%) was isolated as a colourless oil; (Found: M^+, 186.1154. $C_{12}H_{14}N_2$ requires 186.1157); υ_{max}(thin film)/cm^{-1} 3131; δ_H 0.95 (3 H, t, *J* 7.4, Me), 1.89-1.98 (2 H, m, 2-H), 4.11 (2 H, t, *J* 7.2, 1-H), 7.19-7.25 (1 H, m, phenyl 4-H), 7.34-7.38 (phenyl 3,5-H), 7.47-7.49 (2 H, m, phenyl 2,6-H), 7.63 (1 H, s, pyrazole 3-H) and 7.78 (1 H, s, pyrazole 5-H); δ_C 11.14 (3-C), 23.71 (2-C), 54.03 (1-C), 122.65 (pyrazole 4-C), 125.44 (phenyl 2,6-C), 125.89 (pyrazole 3-C), 126.23 (phenyl 4-C), 128.79 (phenyl 3,5-C), 132.75 (phenyl 1-C) and 136.54 (pyrazole 5-C); *m/z* 186 (M^+,87%), 157 (100) and 144 (64).

Synthesis of 3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine 213

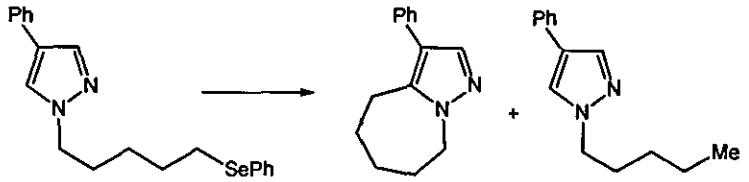


204 **213**

A solution of tributyltin hydride (0.105 cm^3, 0.29 mmol) and ACCN (0.15 g, 0.58 mmol) in toluene (50 cm^3) was added to a solution of 4-phenyl-1-(4-phenylselenyl-butyl)-1*H*-pyrazole **204** (0.10 g, 0.29 mmol) in toluene (200 cm^3) heated under reflux over 4 h. The reaction mixture was heated at reflux for a further 30 min following complete addition, cooled to room temperature and evaporated to dryness. Purification by column chromatography yielded 3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine **213** (47 mg, 63%) as a white solid; (Found: M^+, 199.1233. $C_{13}H_{14}N_2$ requires 199.1235); υ_{max}(thin film)/cm^{-1} 1602 (C=C) and 764, 699 (aromatic o.o.p. deformations); δ_H 1.84-1.90 (2 H, m, 5-H), 2.04-2.12 (2 H, m, 6-H), 2.95 (2 H, t, *J* 6.2, 4-H), 4.20 (2 H, t, *J* 7.0, 7-H), 7.20-7.28 (1 H, m, phenyl 4-H), 7.34-7.41 (4 H, m, phenyl 2,3,5,6-H) and 7.43 (1 H, s, 2-H); δ_C 20.55 (5-C), 23.12 (6-C), 23.15 (4-C), 48.18 (7-C), 118.49 (3-C),

125.75 (phenyl 4-C), 126.76 (phenyl 2,6-C), 128.61 (phenyl 3,5-C), 133.67 (phenyl 1-C), 135.79 (3a-C) and 137.25 (2-C); *m/z* 199 (M^+, 100%).

Synthesis of 3-phenyl-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*]azepine 218



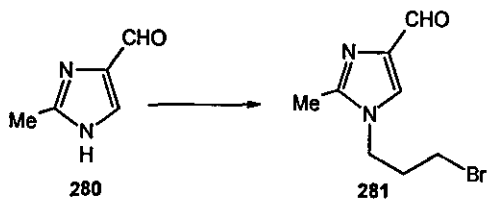
A solution of tributyltin hydride (0.130 cm^3, 0.49 mmol) and ACCN (0.21 g, 0.76 mmol) in toluene (50 cm^3) was added to a solution of 4-phenyl-1-(5-phenylselenyl-pentyl)-1*H*-pyrazole **205** (0.14 g, 0.38 mmol) in toluene (250 cm^3) heated under reflux over 4 h. The reaction mixture was heated at reflux for a further 30 min following complete addition, cooled to room temperature and evaporated to dryness. Purification by column chromatography yielded 3-phenyl-5,6,7,8-tetrahydro-4*H*-pyrazolo[1,5-*a*]azepine **218** (30 mg, 37%) as a colourless oil; (Found: M^+, 213.1396. $C_{14}H_{17}N_2$ requires 213.1392); υ_{max}(thin film)/cm^{-1} 1606 (C=C) and 765, 701 (aromatic o.o.p. deformations); δ_H 1.67-1.75 (2 H, m, 6-H), 1.79-1.89 (4 H, m, 5,7-H), 2.86-2.89 (2 H, m, 4-H), 4.31-4.33 (2 H, m, 8-H), 7.26-7.40 (5 H, m, phenyl-H) and 7.43 (1 H, s, 2-H); δ_C 24.39 (6-C), 26.80 (5-C), 28.00 (7-C), 30.93 (4-C), 53.34 (8-C), 120.99 (3-C), 126.12 (phenyl 4-C), 128.33 (phenyl 2,6-C), 128.55 (phenyl 3,5-C), 134.12 (phenyl 1-C), 136.53 (2-C) and 140.70 (3a-C); *m/z* 213 (M^+, 100%) and 177 (51).

The reduced product, 1-pentyl-4-phenyl-1*H*-pyrazole **217** (39 mg, 48%) was isolated as a colourless oil; (Found: M^+, 215.1548. $C_{14}H_{19}N_2$ requires 215.1546); υ_{max}(thin film)/cm^{-1} 1606 (C=C) and 763, 700 (aromatic o.o.p. deformations); δ_H 0.90 (3 H, t, *J* 7.0, 5-H), 1.26-1.42 (4 H, m, 3,4-H), 1.85-1.93 (2 H, m, 2-H), 4.12 (2 H, t, *J* 7.2, 1-H), 7.19-7.23 (1 H, m, phenyl 4-H), 7.33-7.37 (2 H, m, phenyl 3,5-H), 7.46-7.49 (2 H, m, phenyl 2,6-H), 7.61 (1 H, s, pyrazole 3-H) and 7.77 (1 H, s, pyrazole 5-H); δ_C 13.91 (5-C), 22.22 (4-C), 28.76 (3-C), 30.09 (2-C), 52.41 (1-C), 122.72 (pyrazole 4-C), 125.44 (phenyl 2,6-C), 125.83 (pyrazole 3-C), 126.24 (phenyl 4-C), 128.81 (phenyl 3,5-C), 132.76 (phenyl 1-C) and 136.47 (pyrazole 5-C); *m/z* 215 (M^+, 100%), 157 (17) and 145 (14).

5.2 EXPERIMENTAL FOR CHAPTER 3

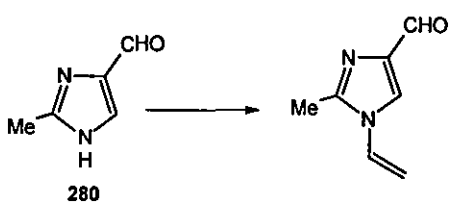
5.2.1 IMIDAZOLES

Synthesis of 1-(3-bromopropyl)-2-methyl-1*H*-imidazole-4-carbaldehyde 281



2-Methyl-1*H*-imidazole-4-carbaldehyde **280** (4.00 g, 36.0 mmol) was added to a stirred solution of sodium hydride (0.94 g, 39.0 mmol) in THF (200 cm^3) at room temperature and the reaction mixture was stirred for 10 min. The solution was heated under reflux for 20 min and 1,3-dibromopropane (21.9 cm^3, 216.0 mmol) was added in one portion. The reaction mixture was heated at reflux for 2.5 h and allowed to cool to room temperature, passed through a celite bed and evaporated to dryness. The crude reaction mixture was partitioned between light petroleum and hydrochloric acid (2 M) and the aqueous layer washed twice with light petroleum. The aqueous layer was neutralised with saturated sodium bicarbonate solution and basified to pH 10 with aqueous sodium hydroxide (1 M). The basic solution was extracted with dichloromethane, dried (Na_2SO_4) and evaporated to dryness, yielding 1-(3-bromopropyl)-2-methyl-1*H*-imidazole-4-carbaldehyde **281** (3.90 g, 47%) as a pale yellow oil; (Found: M^+, 136.0634. $C_7H_8N_2O$ requires 136.0637); υ_{max}(thin film)/cm^{-1} 1682 (C=O); δ_H(400 MHz) 2.29-2.35 (2 H, m, 2-C), 2.48 (3 H, s, Me), 3.39 (2 H, t, *J* 5.9, 3-C), 4.15 (2 H, t, *J* 6.7, 1-C), 7.65 (1 H, s, imidazole 5-H) 9.78 (1 H, s, CHO); δ_C 13.14 (Me), 29.02 (2-C), 32.74 (3-C), 44.48 (1-C), 126.15 (imidazole 5-C), 140.59 (imidazole 4-C), 147.12 (imidazole 2-C) and 185.20 (CHO); *m/z* 230 (M^+, 17%) and 98 (100).

Synthesis of 1-(eth-1-enyl)-2-methyl-1*H*-imidazole-4-carbaldehyde



2-Methyl-1*H*-imidazole-4-carbaldeyde **280** (4.00 g, 36.0 mmol) was added to a stirred solution of sodium hydride (0.94 g, 39.0 mmol) in THF (200 cm^3) at room temperature and the reaction mixture was stirred for 30 min. The solution was heated under reflux and 1,2-dibromoethane (15.5 cm^3, 180.0 mmol) was added in one portion. The reaction mixture was heated at reflux for

3 h and allowed to cool to room temperature, passed through a celite bed and evaporated to dryness. The crude reaction mixture was partitioned between light petroleum and hydrochloric acid (2 M) and the aqueous layer washed twice with petroleum. The aqueous layer was neutralised with saturated sodium bicarbonate solution and basified to pH 10 with aqueous sodium hydroxide (1 M). The basic solution was extracted with dichloromethane, dried (Na_2SO_4) and evaporated to dryness, affording the unsaturated compound 1-(eth-1-enyl)-2-methyl-1*H*-imidazole-4-carbaldehyde as the major product. Treatment of the crude mixture with aqueous sodium hydroxide overnight lead to complete conversion to the alkene, yielding 1-eth-1-enyl-2-methyl-1*H*-imidazole-4-carbaldehyde (1.47 g, 30%) as a colourless oil; (Found: M^+, 136.0634. $C_7H_8N_2O$ requires 136.0637); υ_{max}(thin film)/cm^{-1} 1682 (C=O); δ_H(400 MHz) 2.49 (3 H, s, Me), 5.13 (1 H, dd, *J* 2.0, 8.8, CH_{trans}), 5.40 (1 H, dd, *J* 2.0, 15.6, CH_{cis}), 6.89 (1 H, dd, *J* 8.8, 15.6, C*H*=CH_2), 7.82 (1 H, s, imidazole 5-H) and 9.84 (1 H, s, CHO); δ_C 13.40 (Me), 105.90 (1-C), 121.40 (2-C), 128.34 (imidazole 5-C), 140.84 (imidazole 4-C), 146.46 (imidazole 2-C) and 185.63 (CHO); *m/z* 136 (M^+, 100%) and 108 (29).

Synthesis of *tert*-butyl isocyanide 267[132]

267

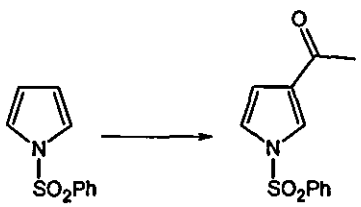
Sodium hydroxide (60.0g, 1.5 mol) was added in portions to water (60 cm^3) with vigorous stirring. Upon complete dissolution of sodium hydroxide, t-butylamine (40.7 cm^3, 0.39 mol), chloroform (15.7 cm^3, 0.20 mol) and benzyltriethylammonium chloride (0.40 g, 1.8 mmol) in dichloromethane (60 cm^3) was added slowly to the solution, maintaining vigorous stirring. The solution began to reflux and stirring was maintained for 3.5 h, after which time no more heat was evolved and the reaction was quenched with ice-water (150 cm^3). The organic layer was removed and the aqueous layer was extracted with dichloromethane (50 cm^3) and the combined organic extracts were dried. The crude filtrate was purified by fractional distillation, yielding *tert*-butyl isocyanide **267** (7.60 g, 46%) as a colourless oil (in low yield as a second distillation was required); bp 89-91 °C; (Found: M^+, 83.0735. C_5H_9N requires 83.0735); υ_{max}(thin film)/cm^{-1} 2986 (C-H) and 2145 (:C=N); δ_H 1.45 (9 H, t, $J_{N\text{-}H}$ 2.1, Me); δ_C 38.35 (Me), 61.78 (t, $J_{N\text{-}C}$ 5.0, *C*Me_3) and 160.13 (t, $J_{N\text{-}C}$ 4.0, *C*=NtBu); *m/z* 83 (M^+, 50%) and 57 (100).

Synthesis of *N*-(phenylsulfonyl)-1*H*-pyrrole 293

283 293

Pyrrole **283** (18.7 cm^3, 0.29 mol) was added to a stirred suspension of sodium hydroxide (34.6 g, 1.30 mol) in dichloromethane (200 cm^3). The reaction mixture was cooled to 0 °C, stirred for 10 min and benzene sulfonyl chloride (44.1 cm^3, 0.35 mol) was added over 20 min. After 30 min at 0 °C the reaction mixture was allowed to warm to room temperature and stirring was maintained overnight. The reaction was quenched with water, extracted with dichloromethane and the combined extracts washed until neutral, dried and evaporated to dryness, yielding *N*-(phenylsulfonyl)-1*H*-pyrrole **293** (35.8 g, 60%) as an off-white solid, mp 86-88 °C (lit.,[152] 87-88 °C); (Found: M^+, 207.0359. $C_{10}H_9NO_2S$ requires 207.0354); υ_{max}(KBr disc)/cm^{-1} 3136 (O-H), 1376, 1170 (SO_2) and 733 (aromatic o.o.p. deformations); δ_H(400 MHz) 6.29-6.31 (2 H, m, pyrrole 3,4-H), 7.15-7.18 (2 H, m, pyrrole 2,5-H), 7.47-7.52 (2 H, m, phenyl 3,5-H), 7.56-7.61 (1 H, m, phenyl 4-H) and 7.84-7.87 (2 H, m, phenyl 2,6-H); δ_C 113.69 (pyrrole 3,4-C), 120.84 (pyrrole 2,5-C), 126.77 (phenyl 3,5-C), 129.37 (phenyl 4-C), 133.80 (phenyl 2,6-C) and 139.18 (phenyl 1-C); *m/z* 207 (M^+, 44%), 141 (28) and 77 (100).

Synthesis of 1-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]ethan-1-one 284[135]

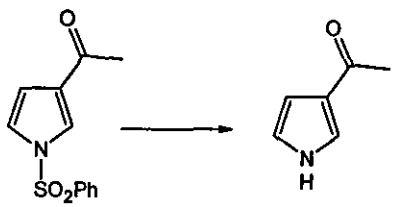


284

Acetic anhydride (5.7 cm^3, 60 mmol) was added dropwise over 5 min to a stirred solution of anhydrous aluminium chloride (16.0 g, 120 mmol) in dichloromethane (250 cm^3) and the reaction mixture was stirred at room temperature for 30 min. *N*-(Phenylsulfonyl)-pyrrole (6.2 g, 30 mmol) was added gradually and the reaction mixture was left to stir for 3 h before quenching with ice-water. The aqueous layer was extracted with dichloromethane, dried and evaporated to dryness. Recrystallisation of the residue from ethyl acetate/light petroleum yielded 1-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]ethan-1-one **284** (6.7 g, 93%) as an off-white solid, mp 96-97 °C (lit.,[135] 97-99 °C); (Found: M^+, 249.0458. $C_{12}H_{11}NO_3S$ requires 249.0450); υ_{max}(nujol

mull)/cm^{-1} 1664 (C=O), 1376, 1174 (SO_2) and 729 (aromatic o.o.p. deformations); δ_H 2.41 (3 H, s, CH_3), 6.68-6.70 (1 H, m, pyrrole 5-H), 7.14-7.16 (1 H, m, pyrrole 4-H), 7.53-7.59 (2 H, m, phenyl 3,5-H), 7.64-7.67 (1 H, m, pyrrole 2-H), 7.72-7.73 (1 H, m, phenyl 4-H) and 7.92-7.94 (2 H, m, phenyl 2,6-H); δ_C 27.37 (CH_3), 112.60 (pyrrole 5-C), 121.76 (pyrrole 4-C), 124.66 (pyrrole 2-C), 127.23 (phenyl 3,5-C), 129.82 (phenyl 2,6-C), 134.68 (phenyl 4-C) and 192.88 (C=O); *m/z* 249 (M^+, 30%), 234 (51), 141 (24) and 77 (100).

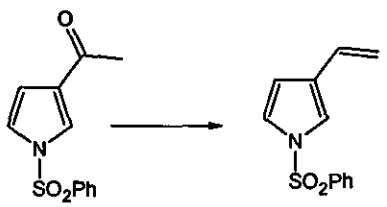
Synthesis of 1-(1*H*-pyrrol-3-yl)ethan-1-one 286



284 **286**

1-[1-(Phenylsulfonyl)-1*H*-pyrrol-3-yl]ethan-1-one **284** (6.7 g, 28 mmol) was treated with sodium hydroxide (5 M, 200 cm^3) and heated under reflux for 12 h. The reaction mixture was cooled and the product extracted with ethyl acetate, dried and evaporated to dryness to yield 1-(1*H*-pyrrol-3-yl)ethan-1-one **286** (3.7 g, 100%) as an off-white solid, mp 109-111 °C (lit.,[135] 112-114 °C); (Found: M^+, 109.0528. C_6H_7NO requires 109.0528); υ_{max}(nujol mull)/cm^{-1} 3193 (N-H) and 1633 (C=O); δ_H 2.44 (3 H, s, CH_3), 6.67 (1 H, m, pyrrole 5-H), 6.80 (1 H, m, pyrrole 4-H) and 7.43 (1 H, m, pyrrole 2-H); δ_C 26.85 (CH_3), 107.77 (pyrrole 5-C), 119.39 (pyrrole 4-C) and 123.66 (pyrrole 2-C); *m/z* 109 (M^+, 60%) and 94 (100).

Synthesis of 3-(eth-1-enyl)-1*H*-pyrrol-1-yl phenyl sulfone 285[136]

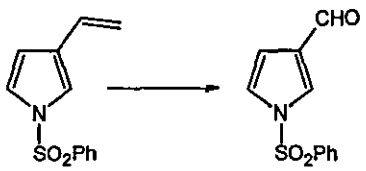


284 **285**

Sodium borohydride (3.0 g, 80 mmol) was added to a stirred solution of 1-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]ethan-1-one **284** (10.0 g, 40 mmol) in ethanol (250 cm^3) and the reaction mixture was stirred at room temperature for 2.5 h. The reaction was quenched with water and extracted with dichloromethane, the combined organic extracts were washed with saturated sodium bicarbonate solution followed by brine, dried and evaporated to dryness. The crude alcohol was dissolved in 1,4-dioxane (250 cm^3) and phosphoric acid (10.0 g, 102 mmol) in 1,4-dioxane (250

cm^3) added. The reaction mixture was heated at 120 °C for 16 h, after which time the solution was cooled to room temperature and partitioned between water and dichloromethane, the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with saturated sodium bicarbonate solution, brine and water, dried and evaporated to dryness to yield a dark brown oil. Purification by column chromatography afforded 3-(eth-1-enyl)-1*H*-pyrrol-1-yl phenyl sulfone **285** (6.30 g, 68% over 2 steps) as a pale yellow viscous oil, (Found: M^+, 233.0510. $C_{12}H_{11}NO_2S$ requires 233.0511); υ_{max}(thin film)/cm^{-1} 1639 (C=C), 1370, 1175 (SO_2) and 727, 684 (aromatic o.o.p. deformations); δ_H 5.10 (1 H, dd, *J* 1.4, 10.6, CH_{trans}), 5.44 (1 H, dd, *J* 1.4, 17.6, CH_{cis}), 6.43-6.55 (2 H, m, pyrrole 3-H, C*H*=CH_2), 7.11-7.12 (2 H, m, pyrrole 2,5-H), 7.44-7.52 (2 H, m, phenyl 3,5-H), 7.54-7.61 (1 H, m, phenyl 4-H) and 7.83-7.87 (2 H, m, phenyl 2,6-H); δ_C 111.04 (1-C), 113.58 (2-C), 118.48 (pyrrole 4-C), 121.71 (pyrrole 5-C), 126.79 (phenyl 3,5-C), 128.05 (pyrrole 3-C), 128.28 (pyrrole 2-C), 129.41 (phenyl 2,6-C), 133.89 (phenyl 4-C) and 138.92 (phenyl 1-C); *m/z* 233 (M^+, 42%), 144 (28) and 77 (100).

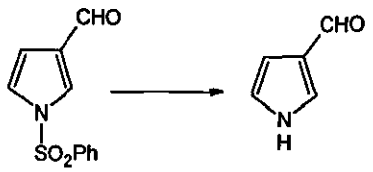
Synthesis of 1-(phenylsulfonyl)pyrrole-3-carbaldehyde 294[136]



285 294

3-(Eth-1-enyl)-1*H*-pyrrol-1-yl phenyl sulfone **285** (6.0 g, 25.7 mmol) was dissolved in 1,4-dioxane (400 cm^3) and water (120 cm^3). Osmium tetraoxide (65 mg, 0.26 mmol) and sodium periodate (11.3 g, 52.7 mmol) were added. The reaction mixture was stirred at room temperature and after 8 h diluted with water and extracted with dichloromethane, the organic extracts were dried and evaporated to dryness yielding a pale brown oil. The oil was purified by column chromatography (dichloromethane) to yield 1-(phenylsulfonyl)pyrrole-3-carbaldehyde **294** (4.2 g, 70%) as a clear oil; (Found: M^+, 235.0303. $C_{11}H_9NO_3S$ requires 235.0303); υ_{max}(thin film)/cm^{-1} 1684 (C=O), 1377, 1176 (SO_2) and 727, 684 (aromatic o.o.p. deformations); δ_H(400 MHz) 6.71-6.72 (1 H, m, pyrrole 4-H), 7.19-7.20 (1 H, m, pyrrole 5-H), 7.55-7.59 (2 H, m, phenyl 3,5-H), 7.66-7.68 (1 H, m, phenyl 4-H), 7.78-7.79 (1 H, m, pyrrole 2-H), 7.92-7.94 (2 H, m, phenyl 2,6-H) and 9.82 (1 H, s, CHO); δ_C 111.05 (pyrrole 4-C), 122.43 (pyrrole 5-C), 127.24 (phenyl 3,5-C), 128.00 (pyrrole 2-C), 129.83 (phenyl 2,6-C), 134.79 (phenyl 4-C), 137.95 (phenyl 1-C) and 185.03 (CHO); *m/z* 235 (M^+, 27%), 141 (27) and 77 (100).

Synthesis of pyrrole-3-carbaldehyde 243 (phenylsulfonyl hydrolysis)



294 243

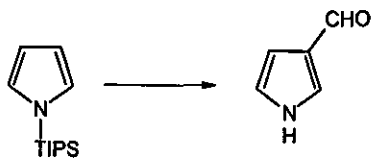
1-(Phenylsulfonyl)pyrrole-3-carbaldehyde **294** (4.0 g, 17.0 mmol) was dissolved in 1,4-dioxane (70 cm^3) and treated with aqueous sodium hydroxide (0.5 M, 70 cm^3). The reaction mixture was heated to 80 °C for 5 h, cooled to room temperature, extracted with ethyl acetate, dried and evaporated to dryness to yield pyrrole-3-carbaldehyde **243** (1.24 g, 76%) as an off-white solid, mp 65-66 °C (lit.,[138] 63-65 °C); (Found: M^+, 95.0372. C_5H_5NO requires 95.0371); υ_{max}(KBr disc)/cm^{-1} 3245 (N-H) and 1660 (C=O); δ_H 6.65-6.68 (1 H, m, pyrrole 4-H), 6.83-6.85 (1 H, m, pyrrole 5-H), 7.45-7.48 (1 H, m, pyrrole 2-H) and 9.79 (1 H, s, CHO); δ_C 107.19 (pyrrole 4-C), 120.88 (pyrrole 5-C), 126.53 (pyrrole 3-C), 127.95 (pyrrole 2-C) and 186.28 (CHO); *m/z* 95 (M^+, 100%) and 66 (55%).

Synthesis of *N*-(triisopropylsilyl)pyrrole 295[138]

283 295

Pyrrole **283** (5.0 cm^3, 72 mmol) was added dropwise to a stirred solution of sodium hydride (1.90 g, 79 mmol) in DMF (120 cm^3) and the reaction mixture was stirred for 1 h. The suspension was cooled to 0 °C and triisopropylsilyl chloride (15.3 cm^3, 72 mmol) added over 5 min. The reaction mixture was stirred at 0 °C for 3 h, after which time the reaction was quenched with water and extracted with diethyl ether. The organic extract was washed with water, dried and evaporated to dryness yielding *N*-(triisopropylsilyl)pyrrole **295** (15.4 g, 100%) as a yellow oil, (Found: M^+, 223.1763. $C_{13}H_{25}NSi$ requires 223.1756); υ_{max}(thin film)/cm^{-1} 3100 (sp^2 C-H), 2945 (sp^3 C-H), 1675 (C=C) and 1463 (sp^3 C-H deformations); δ_H 1.10 (18 H, *J* 7.4, CH_3), 1.45 (3 H, sept, *J* 7.4, CH), 6.31 (2 H, m, pyrrole 3,4-H) and 6.80 (2 H, m, pyrrole 2,5-H); δ_C 11.78 (CH), 17.63 (CH_3), 110.10 (pyrrole 3,4-C) and 124.02 (pyrrole 2,5-C); *m/z* 223 (M^+, 52%), 180 (100), 152 (45) and 110 (41).

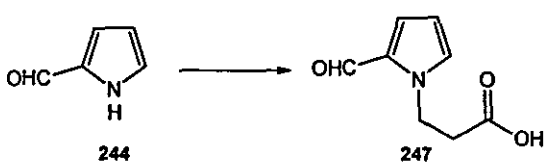
Synthesis of pyrrole-3-carbaldehyde 243 (Vilsmeier formylation)[138]



295 243

To a stirred solution of oxalyl chloride (12.0 cm^3, 137 mmol) in dichloromethane (500 cm^3) at 0 °C, was added a dry solution of *N,N*-dimethylformamide (11.6 cm^3, 150 mmol) in dichloromethane (25 cm^3). After stirring for 20 min at 0 °C, a solution of *N*-(triisopropylsilyl)pyrrole **295** (29.0 g, 130 mmol) in dichloromethane (25 cm^3) was added rapidly and the cooled solution was placed directly into a preheated oil bath at 60 °C. The solution was heated under reflux for 30 min, cooled to room temperature, stirred for 30 min and treated directly with aqueous sodium hydroxide (2 M, 500 cm^3) with vigorous stirring for 6 h. The aqueous phase was separated and exhaustively extracted with dichloromethane, dried over potassium carbonate and evaporated to dryness to yield a coloured oil. Purification by column chromatography afforded pyrrole-3-carbaldehyde **243** (8.0 g, 65%) as an off white solid, mp 64-66 °C (lit.,[138] 63-65 °C); (Found: M^+, 95.0372. C_5H_5NO requires 95.0371); υ_{max}(KBr disc)/cm^{-1} 3245 (N-H) and 1660 (C=O); δ_H 6.65-6.68 (1 H, m, pyrrole 4-H), 6.83-6.85 (1 H, m, pyrrole 5-H), 7.45-7.48 (1 H, m, pyrrole 2-H) and 9.79 (1 H, s, CHO); δ_C 107.19 (pyrrole 4-C), 120.88 (pyrrole 5-C), 126.53 (pyrrole 3-C), 127.95 (pyrrole 2-C) and 186.28 (CHO); *m/z* 95 (M^+, 100%) and 66 (55).

Synthesis of 3-(2-formyl-1*H*-pyrrol-1-yl)propanoic acid 247

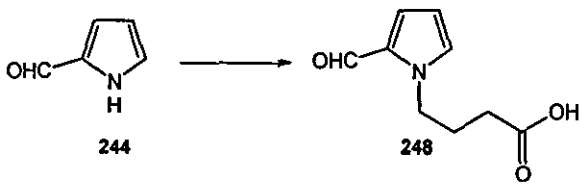


244 247

Pyrrole-2-carbaldehyde **244** (1.45 g, 15.0 mmol) was added to a stirred solution of sodium hydride (0.40 g, 16.5 mmol) in DMF (35 cm^3) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0°C, ethyl 3-bromopropanoate (3.1 cm^3, 24 mmol) was added dropwise over 2 min and the resulting mixture stirred for 2 h. The solution was allowed to slowly warm to room temperature and the reaction mixture was stirred for a further 24 h. The crude mixture was partitioned between water and ethyl acetate and the organic layer separated and washed twice with brine. The organic layer was dried and evaporated to dryness yielding a brown oil (2.81 g, 96%). The ester (2.81 g, 14.4 mmol) was sufficiently

pure to hydrolyse and was treated with aqueous LiOH solution (1 M, 100 cm^3), ethanol was added until a homogeneous mixture was achieved and the resulting solution stirred at room temperature for 2 h. The reaction mixture was washed with ethyl acetate and the aqueous layer acidified to pH 1 with dilute hydrochloric acid and extracted with ethyl acetate. The organic extracts were combined, washed with water, dried and evaporated to dryness, yielding 3-(2-formyl-1*H*-pyrrol-1-yl)propanoic acid **247** (1.75 g, 73%) as a dark red solid; mp 96-98 °C; (Found: M^+, 167.0584. $C_8H_9NO_3$ requires 167.0582); υ_{max}(KBr disc)/cm^{-1} 3500 (O-H), 1725 (C=O) and 1200 (C-O); δ_H 2.89 (2 H, t, *J* 6.3, 2-H), 4.57 (2 H, t, *J* 6.3, 3-H), 6.20-6.23 (1 H, m, pyrrole 4-H), 6.95-6.96 (1 H, m, pyrrole 3-H), 7.04-7.05 (1 H, m, pyrrole 5-H) and 9.52 (1 H, s, CHO); δ_C 35.74 (2-C), 44.77 (3-C), 110.15 (pyrrole 4-C), 126.21 (pyrrole 5-C), 131.09 (pyrrole 2-C), 133.10 (pyrrole 3 -C), 176.55 (CO_2H) and 179.83 (CHO); *m/z* 167 (100%), 122 (64) and 94 (38).

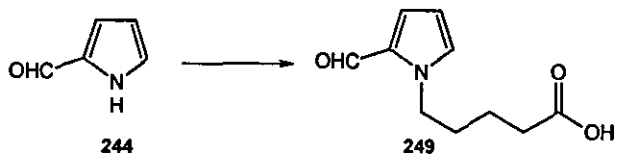
Synthesis of 4-(2-formyl-1*H*-pyrrol-1-yl)butanoic acid 248



Pyrrole-2-carbaldehyde **244** (1.45 g, 15.0 mmol) was added to a stirred solution of sodium hydride (0.40 g, 16.5 mmol) in DMF (35 cm^3) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0 °C and ethyl 4-bromobutanoate (3.5 cm^3, 24 mmol) was added dropwise over 2 min and the reaction mixture was stirred for 2 h. The solution was allowed to slowly warm to room temperature and the reaction mixture was stirred for a further 24 h. The crude mixture was partitioned between ethyl acetate and water and the organic layer separated and washed twice with brine. The organic layer was dried and evaporated to dryness yielding a pale yellow oil (4.0 g, 100%). The ester (4.00 g, 15.0 mmol) was sufficiently pure to hydrolyse and was treated with aqueous LiOH (1 M, 100 cm^3), ethanol was added until homogeneity was achieved and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was washed with ethyl acetate and the aqueous layer was acidified to pH 1 with dilute hydrochloric acid and extracted with ethyl acetate. The organic extracts were combined and washed with water, dried and evaporated to dryness yielding 4-(2-formyl-1*H*-pyrrol-1-yl)butanoic acid **248** (2.62 g, 95%) as a dark red oil; (Found: M^+, 181.0741. $C_9H_{11}NO_3$ requires 181.0739); υ_{max}(neat)/cm^{-1} 3239 (O-H), 1702 (C=O), 1654 (C=O) and 1207 (C-O); δ_H(400 MHz) 1.60 (2 H, m, 3-H), 2.29 (2 H, t, *J* 6.0, 2-H), 4.41 (2 H, t, *J* 6.0, 4-H), 6.21-6.23 (1 H, m, pyrrole 4-H), 6.96-6.99 (1 H, m, pyrrole 3-H), 7.19 (1 H, m, pyrrole 5-H) and 9.50

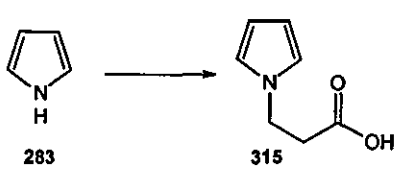
(1 H, s, CHO); δ_C 27.88 (3-C), 31.26 (2-C), 49.20 (4-C), 111.00 (pyrrole 4-C), 126.26 (pyrrole 5-C), 132.77 (pyrrole 2-C), 133.19 (pyrrole 3-C), 180.40 (CHO) and 208.02 (CO_2H); *m/z* 163 (30%), 122 (48), 66 (100) and 39 (59).

Synthesis of 5-(2-formyl-1*H*-pyrrol-1-yl)pentanoic acid 249



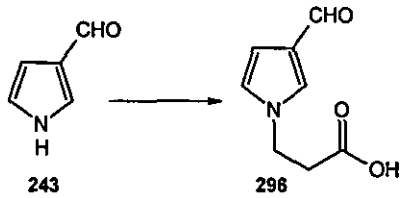
Pyrrole-2-carbaldehyde **244** (2.90 cm^3, 30.0 mmol) was added to a stirred solution of sodium hydride (0.80 g, 33 mmol) in DMF (80 cm^3) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0 °C and ethyl 5-bromovalerate (7.6 cm^3, 48 mmol) was added dropwise over 2 min. The reaction mixture was stirred at 0 °C for 2 h and at room temperature overnight. The crude mixture was partitioned between ethyl acetate and water and the organic layer separated and washed twice with brine. The organic layer was dried and evaporated to dryness, yielding a brown oil. The ester was sufficiently pure to hydrolyse and was treated with aqueous lithium hydroxide (1 M, 200 cm^3) and ethanol, until a homogeneous mixture was achieved and the resulting solution was stirred at room temperature for 4 h. The reaction mixture was washed with ethyl acetate and the aqueous layer acidified to pH 1 with hydrochloric acid, extracted with ethyl acetate, washed with water, dried and evaporated to dryness, yielding 5-(2-formyl-1*H*-pyrrol-1-yl)pentanoic acid **249** (5.95 g, 100%) as a red solid, mp 78-80 °C (ethanol); (Found: M^+, 195.0898. $C_{10}H_{13}NO_3$ requires 195.0895); υ_{max}(KBr disc)/cm^{-1} 2944 (O-H) and 1718, 1613 (C=O); δ_H 1.59-1.68 (2 H, m, 3-C), 1.76-1.88 (2 H, m, 4-C), 2.37 (2 H, t, *J* 7.3, 2-C), 4.33 (2 H, t, *J* 7.0, 5-C), 6.21-6.24 (1 H, m, pyrrole 4-H), 6.93-6.95 (2 H, m, pyrrole 3,5-H) and 9.51 (1 H, s, CHO); δ_C 21.56 (3-C), 30.63 (4-C), 33.41 (2-C), 48.67 (5-C), 109.74 (pyrrole 4-C), 125.20 (pyrrole 5-C), 131.28 (pyrrole 2-C), 131.45 (pyrrole 3-C), 178.78 (CHO) and 179.44 (CO_2H); *m/z* 195 (M^+, 100%), 136 (31), 122 (88), 108 (60), 94 (57) and 81 (45).

Synthesis of 3-(1*H*-pyrrol-1-yl)propanoic acid 315



Pyrrole **283** (1.04 cm^3, 15.0 mmol) was added to a stirred solution of sodium hydride (0.40 g, 16.5 mmol) in DMF (40 cm^3) and the reaction mixture was stirred at room temperature for 30 min. Ethyl 3-bromopropanoate (2.9 cm^3, 23 mmol) was added dropwise over 2 min and the reaction mixture was stirred for 10 h. The crude mixture was partitioned between ethyl acetate and water and the organic layer separated and washed twice with brine. The organic layer was dried and evaporated to dryness, yielding a coloured oil. The ester was sufficiently pure to hydrolyse and was treated with aqueous lithium hydroxide (1 M, 100 cm^3) and ethanol, until a homogeneous mixture was achieved and the resulting solution was stirred at room temperature for 4 h. The reaction mixture was washed with ethyl acetate and the aqueous layer acidified to pH 1 with hydrochloric acid and extracted with ethyl acetate, washed with water, dried and evaporated to dryness, yielding a pale brown viscous oil. Purification by column chromatography yielded 3-(1*H*-pyrrol-1-yl)propanoic acid **315** (1.85 g, 89%) an off-white solid, mp 60-62 °C; (Found: M^+, 139.0638. $C_7H_9NO_2$ requires 139.0633); υ_{max}(KBr disc)/cm^{-1} 2938 (O-H) and 1703 (C=O); δ_H 2.84 (2 H, t, *J* 6.9, 2-C), 4.21 (2 H, t, *J* 6.9, 3-C), 6.14-6.16 (2 H, m, pyrrole 3,4-H) and 6.67-6.68 (2 H, m, pyrrole 2,5-H); δ_C 36.22 (2-C), 44.49 (3-C), 108.64 (pyrrole 3,4-C), 120.54 (pyrrole 2,5-C) and 176.76 (CO_2H); *m/z* 139 (M^+, 95%), 94 (50) and 80 (100).

Synthesis of 3-(3-formyl-1*H*-pyrrol-1-yl)propanoic acid 296

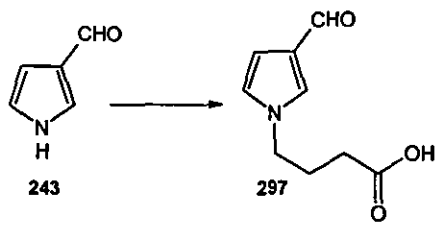


243 296

Pyrrole-3-carbaldehyde **243** (2.50 g, 26.0 mmol) was added to a stirred solution of sodium hydride (0.70 g, 29.0 mmol) in DMF (100 cm^3) at 0 °C and the reaction mixture was stirred for 1 h. Ethyl 3-bromopropanoate (4.3 cm^3, 39 0 mmol) was added dropwise over 5 min and the reaction mixture was stirred for 2 h at 0 °C. The solution was allowed to slowly warm to room temperature and the reaction mixture was stirred overnight. The crude mixture was partitioned between ethyl acetate and water and the organic layer separated and washed twice with brine. The organic layer was evaporated to dryness, yielding a pale brown oil. The ester was sufficiently pure to hydrolyse and was treated with aqueous lithium hydroxide (1 M, 100 cm^3), ethanol was added until a homogeneous mixture was achieved and the resulting solution was stirred at room temperature for 4 h. The reaction mixture was washed with ethyl acetate and the aqueous layer acidified to pH 1 with hydrochloric acid, extracted with ethyl acetate, washed with

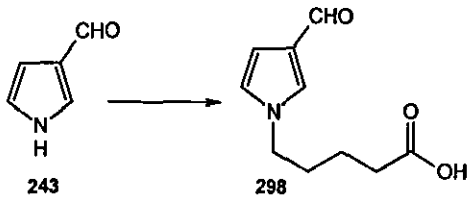
water, dried and evaporated to dryness to yield 3-(3-formyl-1*H*-pyrrol-1-yl)propanoic acid **296** (2.95 g, 69%) as an off-white solid, mp 111-113 °C; (Found: M^+, 167.0629. $C_8H_9NO_3$ requires 167.0633); υ_{max}(KBr disc)/cm^{-1} 3420 (O-H), 1716, 1622 (C=O), 1400 (O-H bend) and 1212 (C-O); δ_H 2.77 (2 H, t, *J* 6.0, 2-H), 4.18 (2 H, t, *J* 6.0, 3-H), 6.42-6.43 (1 H, m, pyrrole 4-H), 6.93-6.94 (1 H, m, pyrrole 5-H), 7 63-7.64 (1 H, m, pyrrole 2-H) and 9.62 (1 H, s, CHO); δ_C 35.66 (2-C), 45.42 (3-C), 107.23 (pyrrole 4-C), 124.36 (pyrrole 5-C), 126.22 (pyrrole 3-C), 130.92 (pyrrole 2-C), 172.47 (CO_2H) and 185.15 (CHO); *m/z* 167 (M^+, 84%), 166 (100) and 94 (42).

Synthesis of 4-(3-formyl-1*H*-pyrrol-1-yl)butanoic acid 297



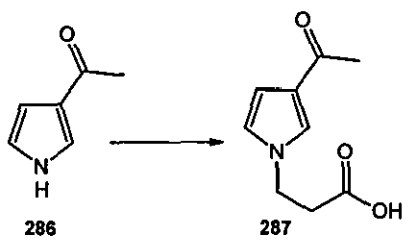
Pyrrole-3-carbaldehyde **243** (2.00 g, 21.0 mmol) was added to a stirred solution of sodium hydride (0.55 g, 23.0 mmol) in DMF (70 cm^3) at 0 °C and the reaction mixture was stirred for 1 h. Ethyl 4-bromobutanoate (4.9 cm^3, 34.0 mmol) was added dropwise over 5 min and the reaction mixture was stirred for 2 h at 0 °C. The solution was allowed to slowly warm to room temperature and the reaction mixture was stirred overnight. The crude mixture was partitioned between ethyl acetate and water and the organic layer separated and washed twice with brine. The organic layer was evaporated to dryness, yielding a coloured oil. The ester was sufficiently pure to hydrolyse and was treated with aqueous lithium hydroxide (1 M, 100 cm^3), ethanol was added until a homogeneous mixture was achieved and the resulting solution was stirred at room temperature for 4 h. The reaction mixture was washed with ethyl acetate and the aqueous layer acidified to pH 1 with hydrochloric acid, extracted with ethyl acetate, washed with water, dried and evaporated to dryness to yield 4-(3-formyl-1*H*-pyrrol-1-yl)butanoic acid **297** (3.40 g, 90%) as a coloured solid, mp 88-90 °C; (Found: M^+, 181.0742. $C_9H_{11}NO_3$ requires 181.0739); (Found: C, 59.5; H, 5.95; N, 7.65. $C_9H_{11}NO_3$ requires: C, 59.65; H, 6.1; N, 7.75%); υ_{max}(KBr disc)/cm^{-1} 3123 (O-H), 1716, 1634 (C=O) and 1348 (O-H bend); δ_H(400 MHz; DMSO-d6) 1.74-1.80 (2 H, m, 3-H), 1.99 (2 H, t, *J* 7.4, 2-H), 3.80 (2 H, t, *J* 7.0, 4-H), 6.26-6.27 (1 H, m, pyrrole 4-H), 6.74-6.75 (1 H, m, pyrrole 5-H), 7.46-7.47 (1 H, m, pyrrole 2-H) and 9.45 (1 H, s, CHO); δ_C(DMSO-d6) 26.41 (3-C), 30.82 (2-C), 48.78 (4-C), 107.26 (pyrrole 4-C), 124.34 (pyrrole 5-C), 126.23 (pyrrole 2-C), 130.97 (pyrrole 3-C), 174.09 (CO_2H) and 185.20 (CHO); *m/z* 181 (M^+, 100%), 94 (57) and 109 (33).

Synthesis of 5-(3-formyl-1*H*-pyrrol-1-yl)pentanoic acid 298



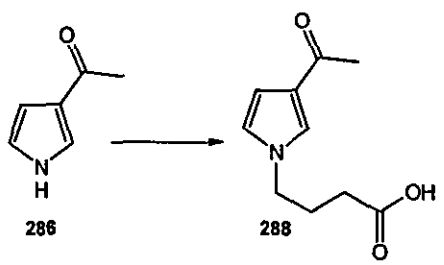
Pyrrole-3-carbaldehyde **243** (1.61 g, 16.8 mmol) was added to a stirred solution of sodium hydride (0.44 g, 18.5 mmol) in DMF (50 cm^3) at 0 °C and the reaction mixture was stirred for 1 h. Ethyl 5-bromovalerate (4.3 cm^3, 26.9 mmol) was added dropwise over 5 min and the reaction mixture was stirred for 2 h at 0 °C. The solution was allowed to slowly warm to room temperature and the reaction mixture was stirred overnight. The crude mixture was partitioned between ethyl acetate and water and the organic layer separated and washed twice with brine. The organic layer was evaporated to dryness yielding a coloured oil. The ester was sufficiently pure to hydrolyse and was treated with aqueous lithium hydroxide (1 M, 100 cm^3), ethanol was added until a homogeneous mixture was achieved and the resulting solution was stirred at room temperature for 4 h. The reaction mixture was washed with ethyl acetate and the aqueous layer acidified to pH 1 with hydrochloric acid, extracted with ethyl acetate, washed with water, dried and evaporated to dryness to give 5-(3-formyl-1*H*-pyrrol-1-yl)pentanoic acid **298** (2.93 g, 89%) as an off-white solid, mp 80-81 °C; (Found: M^+, 195.0897. $C_{10}H_{13}NO_3$ requires 195.0895); (Found: C, 61.3; H, 6.7; N, 7.05. $C_{10}H_{13}NO_3$ requires: C, 61.5; H, 6.7; N, 7.2%); υ_{max}(KBr disc)/cm^{-1} 3115 (O-H), 1723, 1644 (C=O) and 1333 (O-H bend); δ_H 1.58-1.70 (2 H, m, 3-H), 1.82-1.93 (2 H, m, 4-H), 2.39 (2 H, t, *J* 7.2, 2-H), 3.95 (2 H, t, *J* 6.9, 5-H), 6.62-6.68 (2 H, m, pyrrole 4,5-H), 7.29-7.30 (1 H, m, pyrrole 2-H) and 9.72 (1 H, s, CHO); δ_C 21.66 (3-C), 30.35 (4-C), 33.17 (2-C), 49.92 (5-C), 108.71 (pyrrole 4-C), 123.20 (pyrrole 5-C), 126.53 (pyrrole 3-C), 128.75 (pyrrole 2-C), 178.10 (CO_2H) and 185.59 (CHO); *m/z* 195 (M^+, 100%), 109 (64) and 94 (44).

Synthesis of 3-(3-acetyl-1*H*-pyrrol-1-yl)propanoic acid 287



1-(1*H*-Pyrrol-3-yl)ethan-1-one **286** (1.45 g, 15.0 mmol) was added to a stirred solution of sodium hydride (0.40 g, 16.5 mmol) in DMF (35 cm^3) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0 °C, ethyl 3-bromopropanoate (2.9 cm^3, 23 mmol) was added dropwise over 2 min and the reaction mixture was stirred for 2 h at 0 °C. The solution was allowed to slowly warm to room temperature and the reaction mixture was stirred for a further 4 h. The crude mixture was partitioned between ethyl acetate and water and the organic layer washed twice with brine. The organic layer was dried and evaporated to dryness, yielding a brown oil. The crude ester was sufficiently pure to hydrolyse and was treated with aqueous lithium hydroxide (1 M, 100 cm^3) and ethanol, until a homogeneous mixture was achieved and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was washed with ethyl acetate and the aqueous layer was acidified to pH 1 with hydrochloric acid and extracted with ethyl acetate. The organic layer was dried and evaporated to dryness to yield 3-(3-acetyl-1*H*-pyrrol-1-yl)propanoic acid **287** (1.89 g, 70%) as a pale brown oil; υ_{max}(KBr disc)/cm^{-1} 2926 (O-H), 1720 (acid C=O), 1654 (C=O), 1386 (O-H) and 1202 (C-O); δ_H 2.27 (3 H, s, CH_3), 2.76 (2 H, t, *J* 4.3, 2-C), 4.14 (2 H, t, *J* 4.3, 3-C), 6.40-6.41 (1 H, m, pyrrole 4-H), 6.84-6.85 (1 H, m, pyrrole 5-H) and 7.57-7.58 (1 H, m, pyrrole 2-H); δ_C 26.83 (CH_3), 35.42 (2-C), 44.95 (3-C), 108.17 (pyrrole 4-C), 122.83 (pyrrole 5-C), 125.28 (pyrrole 3-C), 126.96 (pyrrole 2-C), 172.17 (C=O) and 191.91 (CO_2H).

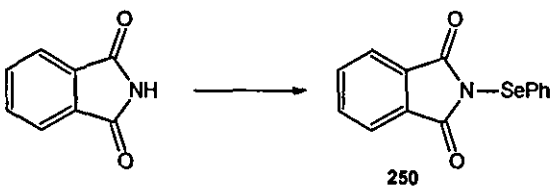
Synthesis of 4-(3-acetyl-1*H*-pyrrol-1-yl)butanoic acid 288



1-(1*H*-Pyrrol-3-yl)ethan-1-one **286** (1.64 g, 15.0 mmol) was added to a stirred solution of sodium hydride (0.40 g, 16.5 mmol) in DMF (35 cm^3) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0 °C and ethyl 4-bromobutanoate (3.5 cm^3, 24 mmol) was added dropwise over 2 min and the reaction mixture was stirred for 2 h. The solution was allowed to slowly warm to room temperature and the reaction mixture was stirred for a further 24 h. The crude mixture was treated with ethyl acetate and washed with water and brine. The organic layer was dried and evaporated to dryness, yielding the crude ester. The ester was sufficiently pure to hydrolyse and was treated with aqueous LiOH (1 M, 100 cm^3), ethanol was added until a homogeneous mixture was achieved

and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was washed with ethyl acetate and the aqueous layer was acidified to pH 1 with dilute hydrochloric acid and extracted with ethyl acetate. The organic extracts were combined and dried and evaporated to dryness, yielding 4-(3-acetyl-1*H*-pyrrol-1-yl)butanoic acid **288** (2.94 g, 100%) as a brown oil, (Found: M^+, 195.0892. $C_{10}H_{13}NO_3$ requires 195.0895); υ_{max}(thin film)/cm^{-1} 3410 (O-H), 1715, 1634 (C=O) and 1204 (C-O); δ_H 2.03-2.10 (2 H, m, 3-H), 2.36 (2 H, t, *J* 6.9, 2-H), 2.39 (3 H, s, CH_3), 3.97 (2 H, t, *J* 6.9, 4-H), 6.57-6.62 (2 H, m, pyrrole 4,5-H) and 7.30-7.31 (1 H, m, pyrrole 2-H); δ_C 26.10 (3-C), 26.90 (2-C), 48.98 (4-C), 109.85 (pyrrole 5-C, 122.46 (pyrrole 4-C, 125.86 (pyrrole 3-C), 126.41 (pyrrole 2-C) and 194.76 (C=O); *m/z* 195 (M^+, 49%), 180 (75), 94 (100) and 43 (100).

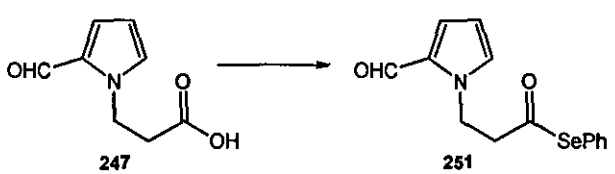
Synthesis of *N*-(phenylselenyl)phthalimide 250



250

Phenylselenyl bromide (3.00 g, 12.7 mmol) was dissolved in diethyl ether (100 cm^3) and added dropwise over 20 min to a stirred suspension of phthalimide (1.25 g, 8.5 mmol) in triethylamine (5.85 cm^3, 42.0 mmol) at room temperature. The reaction mixture was stirred for a further 30 min and the ammonium precipitate was removed by filtration. The ether solution was evaporated to dryness to yield *N*-(phenylselenyl)phthalimide **250** (2.19 g, 85%) as a yellow solid, mp 180-184 °C (lit.,[178] 181-184 °C); υ_{max}(KBr disc)/cm^{-1} 1774 (C=O) and 733 (aromatic o.o.p. deformations); δ_H 7.24-7.29 (3 H, m, phenyl 3,4,5-H), 7.59-7.63 (2 H, m, phenyl 2,6-H), 7.74-7.78 (2 H, m, ArCH) and 7.86-7.89 (2 H, m, ArCH); δ_C 30.73 (ArCH), 133.69 (ArCH), 135.63 (ArCH), 136.82 (ArCH), 137.15 (ArCH), 138.18 (ArC), 138.95 (ArCH), 139.39 (ArCH), 140.75 (ArC), 141.86 (ArCH) and 177.04 (C=O).

Synthesis of phenyl 3-(2-formyl-1*H*-pyrrol-1-yl)propaneselenoate 251

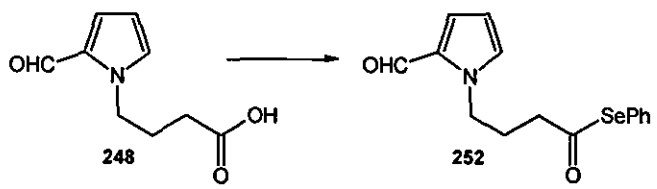


247 **251**

Diphenyl diselenide (2.40 g, 7.5 mmol) was stirred in dichloromethane (100 cm^3) at room temperature and tributylphosphine (2.5 cm^3, 10 mmol) was added dropwise over 2 min. The reaction mixture was stirred for a further 5 min and 3-(2-formyl-1*H*-pyrrol-1-yl)propanoic acid

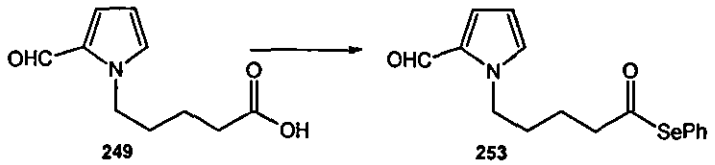
247 (0.80 g, 5.0 mmol) was added. The reaction mixture was stirred for 4 h, washed with water and brine and back extracted with dichloromethane. The organic layers were combined, dried and evaporated to dryness. The crude material was purified by column chromatography to yield phenyl 3-(2-formyl-1*H*-pyrrol-1-yl)propaneselenoate **251** (0.90 g, 59%) as a coloured solid, mp 59-61 °C; [Found $(M+H)^+$, 308.0195. $C_{14}H_{14}NO_2Se$ requires 308.0190]; υ_{max}(KBr disc)/cm^{-1} 3056 (ArCH), 1716, 1661 (C=O) and 739, 689 (aromatic o.o.p. deformations); δ_H(400 MHz) 3.21 (2 H, t, *J* 6.0, 2-H), 4.55 (2 H, t, *J* 6.0, 3-H), 6.20 (1 H, m, pyrrole 4-H), 6.94-6.97 (3 H, m, pyrrole 3,5-H), 7.33-7.39 (3 H, m, phenyl 3,4,5-H), 7.42-7.45 (2 H, m, phenyl 2,6-H) and 9.52 (1 H, s, CHO); δ_C 44.57 (2-C), 48.04 (3-C), 109.75 (pyrrole 4-C), 125.39 (pyrrole 5-C), 125.89 (phenyl 1-C), 129.09, 129.16 (phenyl 2,6-C), 129.40 (phenyl 3,5-C), 130.95 (pyrrole 2-C), 132.57 (pyrrole 3-C), 135.71 (phenyl 4-C), 179.30 (CHO) and 198.72 (COSePh).

Synthesis of phenyl 4-(2-formyl-1*H*-pyrrol-1-yl)butaneselenoate 252



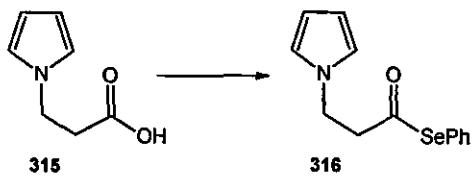
Tributylphosphine (6.8 cm^3, 26.0 mmol) was added to a solution of diphenyl diselenide (4.04 g, 13.0 mmol) in DCM (120 cm^3) over 2 min. After 5 min stirring 4-(2-formyl-1*H*-pyrrol-1-yl)butanoic acid **248** (1.95 g, 10.8 mmol) was added in one portion and the reaction mixture was stirred overnight at room temperature. The reaction mixture was washed with water and brine and the aqueous layers extracted with dichloromethane. The organic extracts were dried and evaporated to dryness. Purification by column chromatography yielded phenyl 4-(2-formyl-1*H*-pyrrol-1-yl)butaneselenoate **252** (1.98 g, 57%) as a brown oil; [Found: $(M+NH_4)^+$, 339.0610. $C_{15}H_{15}NO_2Se.NH_4$ requires 339.0612]; υ_{max}(neat)/cm^{-1} 3056 (ArCH), 1712, 1662 (C=O) and 737 (aromatic o.o.p. deformations); δ_H 2.11-2.19 (2 H, m, 3-H), 2.68 (2 H, t, *J* 7.2, 2-H), 4.37 (2 H, t, *J* 6.6, 4-H), 6.22-6.25 (1 H, m, pyrrole 4-H), 6.94-6.99 (2 H, m, pyrrole 3,5-H), 7.38-7.46 (3 H, m, phenyl 3,4,5-H), 7.52-7.59 (2 H, m, phenyl 2,6-H) and 9.53 (1 H, s, CHO); δ_C 26.74 (3-C), 43.96 (2-C), 47.71 (4-C), 109.96 (pyrrole 4-C), 125.28 (phenyl 1-C), 127.83 (pyrrole 5-C), 129.12, 129.16 (phenyl 2,6-C), 129.40 (phenyl 3,5-C), 131.62 (pyrrole 5-C), 131.72 (pyrrole 3-C), 135.91 (phenyl 4-C) and 179.34 (CHO).

Synthesis of phenyl 5-(2-formyl-1*H*-pyrrol-1-yl)pentaneselenoate 253



Tributylphosphine (4.1 cm^3, 16.6 mmol) was added dropwise over 2 min to a stirred solution of 5-(2-formyl-1*H*-pyrrol-1-yl)pentanoic acid **249** (1.25 g, 6.4 mmol) and NPSP (2.5 g, 8.3 mmol) in dichloromethane (60 cm^3) and stirring was maintained for 6 h at room temperature. The reaction mixture was diluted with dichloromethane and washed with water followed by brine, the combined aqueous layers were back extracted with dichloromethane. The combined organic extracts were dried and evaporated to dryness to yield an orange oily solid. Purification by column chromatography afforded phenyl 5-(2-formyl-1*H*-pyrrol-1-yl)pentaneselenoate **253** (1.35 g, 63%) as a viscous yellow oil, [Found: $(M+H)^+$, 336.0499. $C_{16}H_{17}NO_2Se$ requires 336.0502]; υ_{max}(thin film)/cm^{-1} 1720 and 1660 (C=O); δ_H 1.25-1.72 (2 H, m, 3-H), 1.76-1.85 (2 H, m, 4-H), 2.70 (2 H, t, *J* 7.2, 2-H), 4.30 (2 H, t, *J* 6.7, 5-H), 6.20-6.22 (1 H, m, pyrrole 4-H), 6.91-6.93 (2 H, m, pyrrole 3,5-H), 7.34-7.39 (3 H, m, phenyl 3,4,5-H), 7.46-7.51 (2H, m, phenyl 2,6-H) and 9.52 (1 H, s, CHO); δ_C 22.14 (3-C), 30.38 (4-C), 46.80 (2-C), 48.53 (5-C), 109.69 (pyrrole 4-C), 124.98 (pyrrole 5-C), 126.35 (phenyl 1-C), 128.89 (pyrrole 3-C), 129.33 (phenyl 3,5-C), 131.27 (phenyl 4-C), 135.76 (phenyl 2,6-C), 179.29 (CHO) and 199.94 (COSePh).

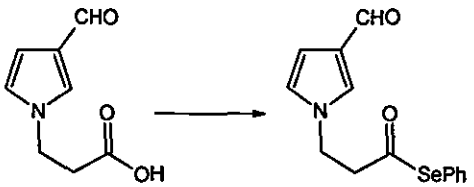
Synthesis of phenyl 3-(1*H*-pyrrol-1-yl)propaneselenoate 316



Tributylphosphine (2.1 cm^3, 8.6 mmol) was added dropwise over 2 min to a stirred solution of 3-(1*H*-pyrrol-1-yl)propanoic acid **315** (0.40 g, 2.9 mmol) and NPSP (1.12 g, 3.7 mmol) in dichloromethane (30 cm^3) and stirring was maintained for 4 h at room temperature. The reaction mixture was diluted with dichloromethane and washed with water followed by brine and the aqueous layer was back extracted with dichloromethane. The combined organic extracts were dried and evaporated to dryness to yield an orange oily solid. Purification by column chromatography yielded phenyl 3-(1*H*-pyrrol-1-yl)propaneselenoate **316** (0.62 g, 77%) as a white solid, mp 72-74 °C; [Found: $(M+H)^+$, 280.0239. $C_{13}H_{14}NOSe$ requires 280.0240]; (Found: C, 56.05; H, 4.6; N, 4.95. $C_{13}H_{13}NOSe$ requires: C, 55.95; H, 4.7; N, 5.0%); υ_{max}(KBr disc)/cm^{-1}

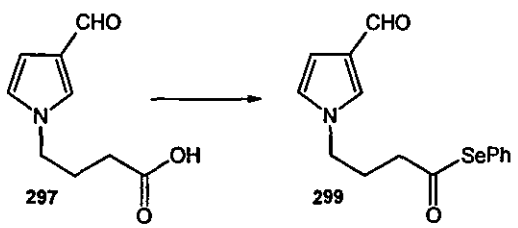
1694 (C=O) and 733, 688 (aromatic o.o.p. deformations); δ_H 3.14 (2 H, t, *J* 6.7, 2-H), 4.21 (2 H, t, *J* 6.7, 3-H), 6.14-6.15 (2 H, m, pyrrole 3,4-H), 6.62-6.64 (2 H, m, pyrrole 2,5-H), 7.37-7.42 (3 H, m, phenyl 3,4,5-H) and 7.45-7.47 (2 H, m, phenyl 2,6-H); δ_C 44.66 (2-C), 48.99 (3-C), 108.70 (pyrrole 3,4-C), 120.62 (pyrrole 2,5-C), 125.95 (phenyl 1-C), 129.20 (phenyl 4-C), 129.49 (phenyl 3,5-C), 135.79 (phenyl 2,6-C) and 198.32 (C=O); *m/z* 154 (65%), 124 (100), 96 (50) and 94 (45).

Synthesis of phenyl 3-(3-formyl-1*H*-pyrrol-1-yl)propaneselenoate 219



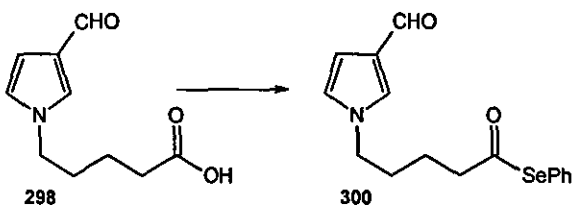
3-(3-Formyl-1*H*-pyrrol-1-yl)propanoic acid **296** (1.00 g, 6.0 mmol) and NPSP **250** (2.36 g, 7.8 mmol) were dissolved in dichloromethane (100 cm^3) and upon full dissolution, tributylphosphine (4.4 cm^3, 18.0 mmol) was added dropwise over 2 min. The reaction mixture was stirred for 4 h at room temperature, diluted with dichloromethane and washed with water followed by brine. The aqueous layers were combined and extracted with dichloromethane, the organic layers were combined, dried and evaporated to dryness to yield an orange oil. Purification of the crude material using gradient elution column chromatography yielded phenyl 3-(3-formyl-1*H*-pyrrol-1-yl)propaneselenoate **219** (0.73 g, 40%) as a white solid, mp 70-72 °C; [Found: $(M+NH_4)^+$, 325.0454. $C_{14}H_{13}NO_2Se.NH_4$ requires 325.0455]; υ_{max}(KBr disc)/cm^{-1} 1705, 1666 (C=O) and 741, 680 (aromatic o.o.p. deformations); δ_H 3.17 (2 H, t, *J* 8.0, 2-H), 4.25 (2 H, t, *J* 8.0, 3-H), 6.62-6.65 (2 H, m, pyrrole 4,5-H), 7.26-7.28 (1 H, m, pyrrole 2-H), 7.39-7.48 (5 H, m, phenyl-H) and 9.73 (1 H, s, CHO); δ_C 45.17 (2-C), 48.19 (3-C), 108.83 (pyrrole 4-C), 123.31 (pyrrole 5-C), 125.58 (pyrrole 3-C), 127.03 (phenyl 1-C), 129.01 (pyrrole 2-C), 129.43 (phenyl 4-C) 129.62 (phenyl 3,5-C), 135.78 (phenyl 2,6-C), 185.32 (CHO) and 198.13 (1-C).

Synthesis of phenyl 4-(3-formyl-1*H*-pyrrol-1-yl)butaneselenoate 299



4-(3-Formyl-1*H*-pyrrol-1-yl)butanoic acid **297** (2.92 g, 16.0 mmol) and NPSP **250** (7.25 g, 24.0 mmol) were dissolved in dichloromethane (100 cm^3) and the solution was deoxygenated for 30 min. Tributylphosphine (7.4 cm^3, 30.0 mmol) was added dropwise over 2 min. The reaction mixture was stirred for 6 h at room temperature, diluted with dichloromethane and washed with water followed by brine. The aqueous layers were combined and extracted with dichloromethane, the organic layers were combined, dried and evaporated to dryness to yield an orange oil. Crude phenyl 4-(3-formyl-1*H*-pyrrol-1-yl)butaneselenoate **299** (2.01 g) was purified by gradient elution column chromatography; [Found: $(M+NH_4)^+$, 339.0611. $C_{15}H_{15}NO_2Se.NH_4$ requires 339.0612]; υ_{max}(KBr disc)/cm^{-1} 1720, 1670 (C=O); δ_H(400 MHz) 2.11-2.18 (2 H, m, 3-H), 2.67 (2 H, t, *J* 7.0, 2-H), 3.98 (2 H, t, *J* 7.0, 4-H), 6.63-6.65 (2 H, m, pyrrole 4,5-H), 7.25-7.26 (1 H, m, pyrrole 2-H), 7.38-7.40 (3 H, m, phenyl 3-5-H), 7.48-7.51 (2 H, m, phenyl 2,6-H) and 9.72 (1 H, s, CHO); δ_C 26.48 (3-C), 43.52 (2-C), 48.71 (4-C), 108.73 (pyrrole 4-C), 123.18 (pyrrole 5-C), 125.96 (pyrrole 3-C), 126.79 (phenyl 1-C), 128.75 (pyrrole 2-C), 129.19 (phenyl 4-C) 129.49 (phenyl 3,5-C), 135.77 (phenyl 2,6-C), 185.30 (CHO) and 199.60 (1-C).

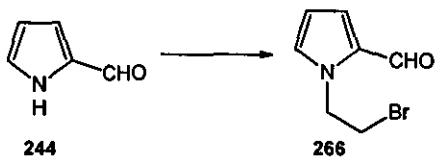
Synthesis of phenyl 5-(3-formyl-1*H*-pyrrol-1-yl)pentaneselenoate 300



5-(3-Formyl-1*H*-pyrrol-1-yl)pentanoic acid **298** (2.28 g, 11.7 mmol) and NPSP **250** (4.59 g, 15.2 mmol) were dissolved in dichloromethane (75 cm^3) and the solution was deoxygenated for 30 min and the solution cooled to 0 °C. Tributylphosphine (5.8 cm^3, 23.4 mmol) was added dropwise over 2 min. The reaction mixture was stirred for 4 h at 0°C, diluted with dichloromethane and washed with water and brine. The aqueous layers were combined and extracted with dichloromethane, the organic layers were combined, dried and evaporated to dryness to yield a yellow oil. Purification by gradient elution column chromatography yielded phenyl 5-(3-formyl-1*H*-pyrrol-1-yl)pentaneselenoate **300** (1.36 g, 35%) as a yellow oil, [Found: $(M+H)^+$, 336.0507. $C_{16}H_{18}NO_2Se$ requires 336.0502]; υ_{max}(thin film)/cm^{-1} 1718, 1668 (C=O); δ_H(400 MHz) 1.66-1.71 (2 H, m, 3-H), 1.83-1.88 (2 H, m, 4-H), 2.72 (2 H, t, *J* 7.0, 2-H), 3.92 (2 H, t, *J* 7.0, 5-H), 6.62-6.65 (2 H, m, pyrrole 4,5-H), 7.25-7.27 (1 H, m, pyrrole 2-H), 7.37-7.40 (3 H, m, phenyl 3-5-H), 7.48-7.50 (2 H, m, phenyl 2,6-H) and 9.73 (1 H, s, CHO); δ_C 22.27 (3-C), 30.13 (4-C), 46.53 (2-C), 49.85 (5-C), 108.62 (pyrrole 4-C), 123.11 (pyrrole 5-C), 126.15 (pyrrole 3-C), 126.67 (phenyl 1-C), 128.51 (pyrrole 2-C), 129.06 (phenyl 4-C) 129.43 (phenyl

3,5-C), 135.71 (phenyl 2,6-C), 185.30 (CHO) and 199.85 (1-C); *m/z* 336 (MH^+, 8%), 167 (68) and 150 (100).

Synthesis of 1-(2-bromoethyl)-1*H*-pyrrole-2-carbaldehyde 266

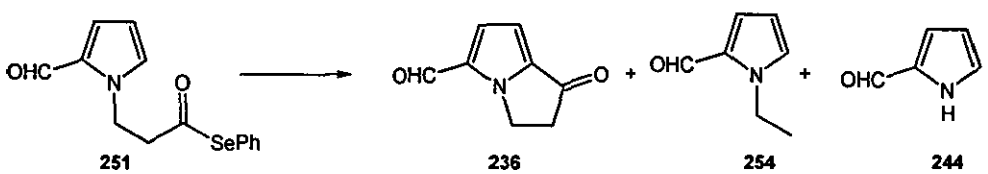


244 266

Pyrrole-2-carbaldehyde **244** (1.52 g, 16.0 mmol) was added to a stirred solution of sodium hydride (0.42 g, 17.5 mmol) in DMF (50 cm^3) and the reaction mixture was stirred at room temperature for 30 min. 1,2-Dibromoethane (4.1 cm^3, 48.0 mmol) was added dropwise over 5 min and stirring was maintained at 30 °C overnight. The crude mixture was partitioned between ethyl acetate and water and the organic layer washed twice with brine. The organic layer was dried and evaporated to dryness, yielding a brown oil. Purification by column chromatography afforded 1-(2-bromoethyl)-1*H*-pyrrole-2-carbaldehyde **266** (1.50 g, 46%) as a colourless oil, [Found: $(M+H)^+$, 200.9794. C_6H_8NOBr requires 200.9789]; υ_{max}(thin film)/cm^{-1} 1659 (C=O) and 765 (aromatic o.o.p. deformations); δ_H 3.68 (2 H, t, *J* 6.0, CH_2Br), 4.66 (2 H, t, *J* 6.0, NCH_2), 6.26 (1 H, dd, *J* 2.6, 3.9, pyrrole 4-H), 6.99-7.03 (2 H, m, pyrrole 3,5-H) and 9.53 (1 H, d, *J* 0.9, CHO); δ_C 31.80 (2-C), 50.75 (1-C), 109.68 (pyrrole 4-C), 125.67 (pyrrole 3-C), 130.96 (pyrrole 2-C), 132.60 (pyrrole 5-C) and 179.48 (CHO); *m/z* 201 (M^+, 15%), 122 (100) and 94 (30).

5.2.3 Acyl Radical Cyclisations onto Pyrroles

Synthesis of 1-oxo-2,3-dihydro-1*H*-pyrrolizine-5-carbaldehyde 236 (under N_2)



251 236 254 244

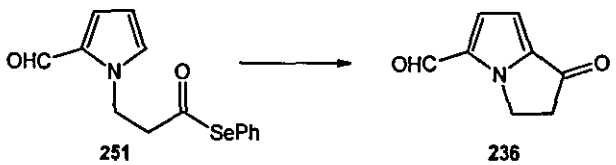
Tributyltin hydride (1.54 g, 5.3 mmol) in cyclohexane (50 cm^3) was added over 5 h to a solution of phenyl 3-(2-formyl-1*H*-pyrrol-1-yl)propaneselenoate **251** (0.72 g, 2.4 mmol) in cyclohexane (600 cm^3) heated under reflux and AMBN initiator was added at regular 30 min intervals. The reaction mixture was heated under reflux for 12 h after which time it was cooled to room temperature and evaporated to dryness. Purification by gradient elution column chromatography yielded the desired cyclised product 1-oxo-2,3-dihydro-1*H*-pyrrolizine-5-carbaldehyde **236**[49] (0.11 g, 31%) as a coloured oil; (Found: M^+, 149.0478. $C_8H_7NO_2$ requires 149.0477); υ_{max}(thin

film)/cm^{-1} 1711 (C=O); δ_H 4.35 (2 H, t, *J* 6.0, 2-H), 4.58 (2 H, t, *J* 6.0, 3-H), 6.70 (1 H, d, *J* 5.0, 7-H), 7.10 (1 H, d, *J* 5.0, 6-H) and 9.70 (1 H, s, CHO); δ_C 38.78 (2-C), 43.91 (3-C), 107.26 (7-C), 125.12 (6-C) and 186.83 (CHO); *m/z* 150 [(M+H$^+$), 100%], 122 (100) and 80 (100).

In addition to cyclisation, decarbonylation followed by reduction of the radical centre to form the volatile 1-ethyl-1*H*-pyrrole-2-carbaldehyde **254** (0.10g, 34%) was identified by correlating ^{1}H NMR spectra to dehalogenated 1-(2-bromoethyl)-1*H*-pyrrole-2-carbaldehyde **266**, δ_H 1.30 (3 H, m, Me), 4.34 (2 H, q, *J* 7.2, N-CH$_2$), 6.24-6.30 (1 H, m, pyrrole 4-H), 6.89-6.94 (1 H, m, pyrrole 3-H), 6.98-7.02 (1 H, m, pyrrole 5-H) and 9.47 (1 H, d, *J* 0.8, CHO).

Loss of ethene also occurs following decarbonylation to yield pyrrole-2-carbaldehyde **244** (17%) under more vigorous conditions, i.e. fast flow of nitrogen directly into reaction mixture. Under these conditions, very little cyclisation appeared to have occurred by analysis of the ^{1}H NMR spectrum and the major product isolated was that of the hydrolysed starting material (34%).

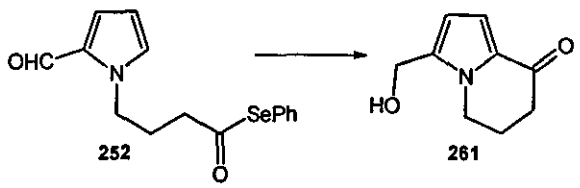
Synthesis of 1-oxo-2,3-dihydro-1*H*-pyrrolizidine-5-carbaldehyde 236 (under CO)



251 236

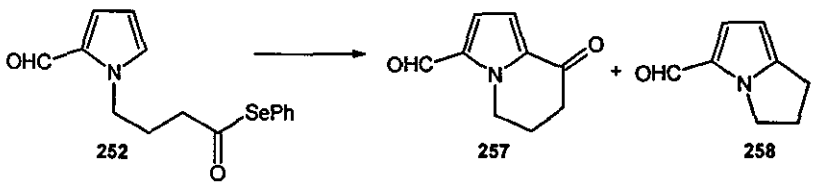
Phenyl 3-(2-formyl-1*H*-pyrrol-1-yl)propaneselenoate **251** (122 mg, 0.40 mmol) and AIBN (130 mg, 0.80 mmol) were dissolved in acetonitrile (50 cm^3) and following and the reaction vessel was subjected to the standard method for CO saturation and was fitted with a 3-way tap linked independently to a high vacuum source and a balloon of carbon monoxide. The vessel was subjected to liquid nitrogen temperatures and upon complete freezing was evacuated for 10 min, after which time the evacuated flask was allowed to fill with carbon monoxide and warmed to room temperature with the CO balloon attached. The freeze/thaw technique was repeated a further 2 times. The reaction mixture was warmed slowly to room temperature, placed in an oil bath at 80 °C and a solution of tributyltin hydride (0.16 cm^3, 0.60 mmol) in cyclohexane (20 cm^3) was added dropwise over 2 h. Heating was maintained overnight. The reaction mixture was cooled to room temperature, evaporated to approximately 30 cm^3 total volume and washed with light petroleum. The crude material was purified by gradient elution column chromatography to yield 1-oxo-2,3-dihydro-1*H*-pyrrolizidine-5-carbaldehyde **236** (33 mg, 55%) as the major product; (Found: M$^+$, 149.0478. $C_8H_7NO_2$ requires 149.0477); υ_{max}(neat)/cm^{-1} 1711 (C=O); δ_H 3.13 (2 H, t, *J* 6.1, 2-H), 4.63 (2 H, t, *J* 6.1, 3-H), 6.73 (1 H, d, *J* 4.4, 7-H), 7.12 (1 H, d, *J* 4.4, 6-H) and 9.75 (1 H, s, CHO); δ_C 38.78 (2-C), 43.91 (3-C), 107.26 (7-C), 125.12 (6-C) and 186.83 (CHO); *m/z* 150 (MH$^+$, 100%), 122 (100) and 80 (100).

Synthesis of 3-(hydroxymethyl)-5,6,7,8-tetrahydroindolizin-8-one 261 (under CO, sealed tube)



Tributyltin hydride (90 mg, 0.30 mmol), AIBN (50 mg, 0.30 mmol) and phenyl 4-(2-formyl-1*H*-pyrrol-1-yl)butaneselenoate **252** (48 mg, 0.15 mmol) were dissolved in acetonitrile (10 cm^3) in a 20 cm^3 Schlenk tube and was deoxygenated by passing a stream of nitrogen through the solution for 30 min. The tube was sealed and the solution saturated using the standard CO freeze/thaw technique. The tube vapour pressure was allowed to equilibrate at room temperature with the CO balloon attached and the tube was sealed and heated overnight at 95°C. After complete cooling, a stream of nitrogen was passed through the solution to remove CO. The reaction mixture was washed directly with light petroleum, evaporated to dryness and purified by column chromatography yielding 3-(hydroxymethyl)-5,6,7,8-tetrahydroindolizin-8-one **261** (16 mg, 65%) as a clear oil; (Found: M^+, 165.0787. $C_9H_{11}NO_2$ requires 165.0790); υ_{max}(thin film)/cm^{-1} 3387 (O-H), 1641 (C=O), 1341 (O-H bend) and 1180 (C-O); δ_H 2.27-2.32 (2 H, m, 6-H), 2.57-2.62 (2 H, m, 7-H), 4.14-4.19 (2 H, m, 5-H), 4.67 (2 H, s, CH_2OH), 6.21 (1 H, d, *J* 4.0, 2-H) and 6.96 (1 H, d, *J* 4.0, 1-H); δ_C 23.38 (6-C), 36 05 (7-C), 42.53 (5-C), 56.72 (CH_2OH), 110.19 (2-C), 113.29 (1-C), 131.85 (3-C), 136.52 (8a-C) and 187.58 (8-C); *m/z* 165 (M^+, 90%), 148 (100) and 57 (55).

Synthesis of 8-oxo-5,6,7,8-tetrahydroindolizine-5-carbaldehyde 257 (under N_2)

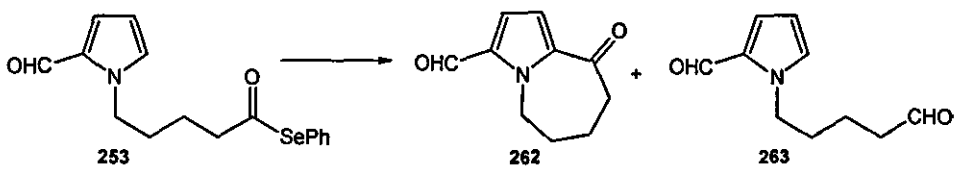


Tributyltin hydride (1.75 cm^3, 6.6 mmol) in cyclohexane (50 cm^3) was added at a rate of 8.3 cm^3/hour over 6 h to a solution of the phenyl 4-(2-formyl-1*H*-pyrrol-1-yl)butaneselenoate **252** (0.95 g, 3.0 mmol) in cyclohexane (500 cm^3) heated under reflux and AMBN initiator was added at regular 30 min intervals. The reaction mixture was evaporated to dryness and purified by column chromatography using gradient elution to yield 8-oxo-5,6,7,8-tetrahydroindolizine-5-carbaldehyde **257** (0.08 g, 20%) in addition to cyclised decarbonylated material **258** (0.05 g,

13%). The ^{1}H NMR spectrum of the crude reaction product indicated better yields but purification required two difficult chromatographic separations, thus losing significant amounts of material. The major reaction product was identified as 8-oxo-5,6,7,8-tetrahydroindolizine-5-carbaldehyde **257**; (Found: M^+, 163.0631. $C_9H_9NO_2$ requires 163.0633); υ_{max}(neat)/cm^{-1} 3282 (O-H), 1726 (C=O) and 1652 (C=O); δ_H 2.28-2.36 (2 H, m, 7-H), 2.66 (2 H, t, *J* 6.0, 6-H), 4.57 (2 H, t, *J* 4.4, 8-H), 6.94-7.00 (2 H, m, 2,1-H) and 9.75 (1 H, s, CHO); δ_C 23.24 (7-C), 36.52 (6-C), 44.72 (8-C), 113.11 (1-C), 122.25 (2-C) and 181.77 (C=O).

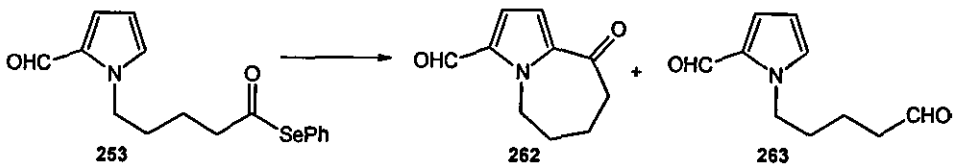
Cyclised product following decarbonylation, 2,3-dihydro-1*H*-pyrrolizine-5-carbaldehyde, was identified by the ^{1}H NMR spectrum correlation the to known compound **258**,[34] υ_{max}(neat)/cm^{-1} 1652 (C=O); δ_H 2.47-2.57 (2 H, m, 2-H), 2.86 (2 H, t, *J* 7.4, 1-H), 4.29 (2 H, t, *J* 7.2, 3-H), 5.97-5.99 (1 H, m, 7-H), 6.93-6.95 (1 H, m, pyrrole 6-H) and 9.38 (1 H, s, CHO).

Synthesis of 9-oxo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-a]azepine-3-carbaldehyde 262 (under CO)



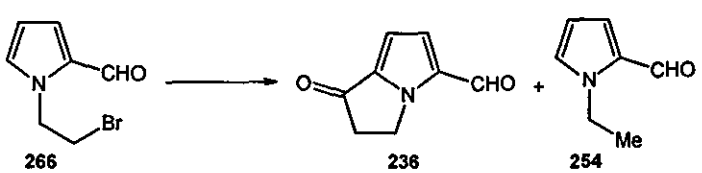
Phenyl 5-(2-formyl-1*H*-pyrrol-1-yl)pentaneselenoate **253** (0.817 g, 2.44 mmol) was dissolved in acetonitrile (50 cm^3) and was deoxygenated by passing a stream of nitrogen through the solution for 30 min and the solution was saturated with CO by freeze/thaw methodology. The reaction mixture was warmed to 80 °C and solutions of tributyltin hydride (0.98 cm^3, 3.66 mmol) in cyclohexane (50 cm^3) and AIBN (0.60 g, 3.66 mmol) were added independently by syringe pump over 5 h. Heating was maintained overnight. The reaction mixture was cooled to room temperature, evaporated to dryness and purified by gradient elution column chromatography. The acyl radical reduction product, 1-(5-oxopentyl)-1*H*-pyrrole-2-carbaldehyde **263** (200 mg, 46%) was obtained as a coloured oil and 9-oxo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-a]azepine-3-carbaldehyde **262** (133 mg, 31%) was obtained as a white solid, mp 79-81 °C; (Found: M^+, 177.0794. $C_{10}H_{11}NO_2$ requires 177.0790); υ_{max}(KBr disc)/cm^{-1} 1663 (C=O); δ_H 1.88-1.96 (2 H, m, 7-H), 2.03-2.10 (2 H, m, 6-H), 2.78-2.82 (2 H, m, 8-H), 4.80-4.85 (2 H, m, 5-H), 6.89-6.93 (2 H, m, 1,2-H) and 9.71 (1 H, s, CHO); δ_C 19.46 (7-C), 26.07 (6-C), 39.95 (8-C), 44.30 (5-C), 115.23 (1-C), 122.91 (2-C), 133.79 (9a-C), 141.29 (3-C), 181.83 (CHO) and 194.10 (9-C); *m/z* 177 (M^+, 73%) and 148 (42).

Synthesis of 9-oxo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-a]azepine-3-carbaldehyde 262 (under CO, sealed tube)



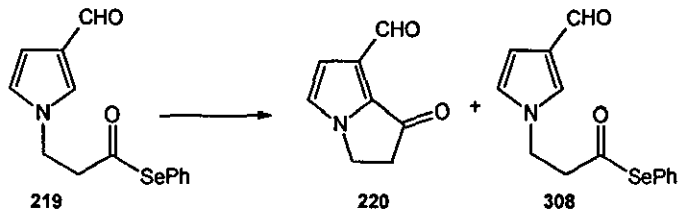
Phenyl 5-(2-formyl-1*H*-pyrrol-1-yl)pentaneselenoate **253** (50 mg, 0.15 mmol), tributyltin hydride (20 mg, 0.06 mmol) and AIBN (50 mg, 0.30 mmol) were dissolved in acetonitrile (10 cm^3) in a 20 cm^3 Schlenk tube and was deoxygenated by passing a stream of nitrogen through the solution for 30 min. The reaction tube was treated as before using standard CO saturation methodology. The tube vapour pressure was allowed to equilibrate at room temperature with the balloon attached. The tube was sealed and heated for 2 h at 90°C. The solution was cooled slowly to room temperature, frozen using liquid nitrogen and tributyltin hydride (40 mg, 0.12 mmol) was added. The tube was evacuated, purged with CO, sealed and warmed to room temperature. The tube was heated for a further 6 h at 90°C. The reaction mixture was washed with light petroleum, evaporated to dryness and purified by column chromatography yielding the reduction product(1-(5-oxopentyl)-1*H*-pyrrole-2-carbaldehyde **263** as the major compound and 9-oxo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-a]azepine-3-carbaldehyde **262** (20% by ^{1}H NMR spectral analysis). Characterisation data for 1-(5-oxopentyl)-1*H*-pyrrole-2-carbaldehyde **263**; (Found: M^+, 179.0945. $C_{10}H_{13}NO_2$ requires 179.0946); υ_{max}(thin film)/cm^{-1} 1722 and 1661 (C=O); δ_H(400 MHz) 1.60-1.65 (2 H, m, 3-H), 1.78-1.82 (2 H, m, 2-H), 2.47 (2 H, t, *J* 8.0, 4-H), 4.33 (2 H, t, *J* 8.0, 1-H), 6.20-6.23 (1 H, m, pyrrole 4-H), 6.92-6.94 (2 H, m, pyrrole 3,5-H), 9.52 (1 H, s, pyrrole CHO) and 9.75 (1 H, s, 5-C); δ_C 18.90 (3-C), 30.75 (2-C), 43.29 (4-C), 48.86 (1-C), 109.71 (pyrrole 4-C), 125.03 (pyrrole 5-C), 131.28 (pyrrole 3-C), 179.35 (CHO) and 201.84 (5-C); *m/z* 179 (M^+, 20%), 150 (100), 134 (45), 122 (91), 108 (52), 94 (57) and 80 (50).

Attempted synthesis of 1-oxo-2,3-dihydro-1*H*-pyrrolizidine-5-carbaldehyde 236 (under CO, sealed tube)



A solution of 1-(2-bromoethyl)-1*H*-pyrrole-2-carbaldehyde **266** (50 mg, 0.25 mmol), tributyltin hydride (150 mg, 0.50 mmol) and AIBN (82 mg, 0.50 mmol) in acetonitrile (10 cm^3) was prepared in a Schlenk tube and the solution was subjected to freeze/thaw with CO using standard methodology. The reaction mixture was heated overnight at 90 °C and at the end of the reaction the solvent was evaporated to dryness yielding a brown semi-solid. The crude material was purified by column chromatography yielding two closely related compounds. Halo-reduction to 1-ethyl-1*H*-pyrrole-2-carbaldehyde **254** (12 mg, 32%) was isolated as a colourless oil. A second compound closely related in structure was also isolated (10 mg), but has yet to be identified. 1-Ethyl-1*H*-pyrrole-2-carbaldehyde **254**; (Found: M^+, 123.0684. C_7H_9NO requires 123.0682); υ_{max}(thin film)/cm^{-1} 2935, 2980 (aliphatic C-H) and 1667 (C=O); δ_H 1.20 (3 H, m, Me), 4.36 (2 H, q, *J* 7.2, N-CH_2), 6.22 (1 H, dd, *J* 2.6, 3.9, pyrrole 4-H), 6.93 (1 H, dd, *J* 1.6, 3.9, pyrrole 3-H), 6.97 (1 H, m, pyrrole 5-H) and 9.54 (1 H, d, *J* 0.9, CHO); *m/z* 123 (M^+, 85%), 122 (100) and 94 (29).

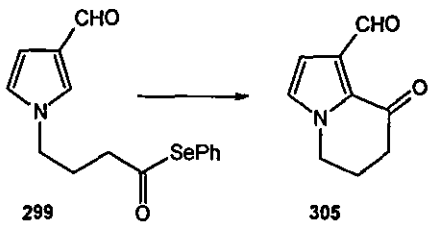
Synthesis of 1-oxo-2,3-dihydro-1*H*-pyrrolizine-7-carbaldehyde 220 (under CO)



Solutions of tributyltin hydride (524 mg, 1.8 mmol) in cyclohexane (50 cm^3) and AIBN (261 mg, 1.6 mmol) in acetonitrile (20 cm^3) were added independently over 7 and 5 h respectively to a CO saturated solution of phenyl 5-(3-formyl-1*H*-pyrrol-1-yl)pentaneselenoate **219** (527 mg, 1.6 mmol) and AIBN (261 mg, 1.6 mmol) in acetonitrile (250 cm^3) at 85°C. The reaction mixture was heated for a total of 16 h before being allowed to cool to room temperature, during cooling a stream of nitrogen was passed through the solution to remove CO. The reaction mixture was evaporated to dryness and purified by column chromatography yielding 1-oxo-2,3-dihydro-1*H*-pyrrolizine-7-carbaldehyde **220** (>32%, mixed fraction to be purified contains large amount of cyclised material) as a white solid and decarbonylated reduced product **308** (31 mg, 17%) as a colourless oil. 1-Oxo-2,3-dihydro-1*H*-pyrrolizine-7-carbaldehyde **220**; (lit.,[179] 95-97°C); (Found: M^+, 150.0554. $C_8H_7NO_2$ requires 150.0555); δ_H 3.18 (2 H, t, *J* 6.0, 2-H), 4.43 (2 H, t, *J* 6.0, 3-H), 7.00-7.04 (2 H, m, 5,6-H) and 10.20 (1 H, s, CHO); δ_C 39.69 (2-C), 43.63 (3-C), 116.09 (6-C), 123.55 (5-C), 126.42 (7-C), 135.54 (7a-C), 187.17 (C=O) and 187.31 (1-C); *m/z* 150 (M^+, 100%) and 107 (33).

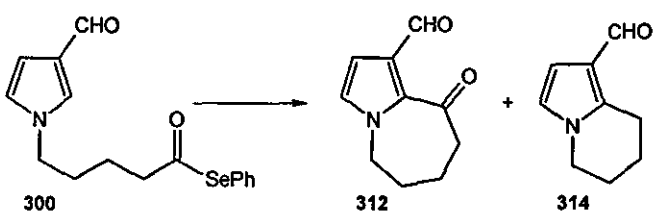
1-Ethyl-1*H*-pyrrole-3-carbaldehyde **308**, (Found: M^+, 123.0684. C_7H_9NO requires 123.0682); υ_{max}(thin film)/cm^{-1} 2935, 2980 (sp^3 C-H) and 1667 (C=O); δ_H 1.45 (3 H, t, *J* 7.3, C*H*$_3$), 3.96 (2 H, q, *J* 7.3, C*H*$_2$), 6.59-6.61 (1 H, m, pyrrole 4-H), 6.66-6.68 (1 H, m, pyrrole 5-H), 7.29-7.30 (1 H, m, pyrrole 2-H) and 9.70 (1 H, s, CHO); δ_C 16.60 (*C*H$_3$), 45.27 (*C*H$_2$), 108.73 (pyrrole 4-C), 123.20 (pyrrole 5-C), 126.81 (pyrrole 3-C), 128.59 (pyrrole 2-C) and 185.73 (*C*HO); *m/z* 123 (M^+,85%), 122 (100) and 94 (29).

Synthesis of 8-oxo-5,6,7,8-tetrahydroindolizine-1-carbaldehyde 305 (under CO)



Solutions of tributyltin hydride (0.77 g, 2.63 mmol) in cyclohexane (50 cm^3) and AIBMe (0.55 g, 2.41 mmol) in acetonitrile (20 cm^3) were added independently over 7 and 5 h respectively to a CO saturated solution of phenyl 4-(3-formyl-1*H*-pyrrol-1-yl)butaneselenoate **299** (700 mg, 2.20 mmol) and AIBMe (0.55 g, 2.41 mmol) in acetonitrile (250 cm^3) at 85°C. The reaction mixture was heated for a total of 10 h before being allowed to cool to room temperature, during cooling a stream of nitrogen was passed through the solution to remove CO. The reaction mixture was evaporated to dryness and purified by column yielding 8-oxo-5,6,7,8-tetrahydroindolizine-1-carbaldehyde **305** (180 mg, 50%) as a colourless solid, (Found: M^+, 163.0636. $C_9H_9NO_2$ requires 163.0633); υ_{max}(nujol mull)/cm^{-1} 1734, 1654 (C=O); δ_H 2.25-2.31 (2 H, m, 6-H), 2.62-2.65 (2 H, m, 7-H), 4.09-4.12 (2 H, m, 5-H), 6.72-6.75 (2 H, m, 2,3-H) and 10.45 (1 H, s, CHO); δ_C 22.13 (6-C), 36.00 (7-C), 44.58 (5-C), 108.64 (2-C), 124.34 (3-C), 128.14 (1-C), 130.49 (8a-C), 187.17 (8-C) and 187.31 (C=O); *m/z* 163 (M^+, 100%), 106 (37) and 79 (50).

Synthesis of 9-oxo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-1-carbaldehyde 312 (under CO)

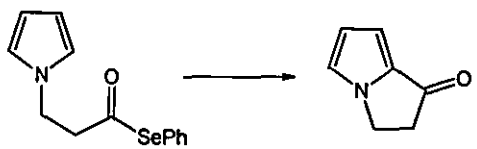


Solutions of tributyltin hydride (559 mg, 1.9 mmol) in cyclohexane (50 cm^3) and AIBMe (255 mg, 1.8 mmol) in acetonitrile (20 cm^3) were added independently over 7 and 5 h respectively to a

CO saturated solution of phenyl 5-(3-formyl-1*H*-pyrrol-1-yl)pentaneselenoate **300** (527 mg, 1.55 mmol) and AIBMe (255 mg, 1.8 mmol) in acetonitrile (250 cm^3) at 85 °C. The reaction mixture was heated for a total of 16 h before being allowed to cool to room temperature, during cooling a stream of nitrogen was passed through the solution to remove CO. The reaction mixture was evaporated to dryness and purified by gradient elution column chromatography yielding 9-oxo-6,7,8,9-tetrahydro-*5H*-pyrrolo[1,2-*a*]azepine-1-carbaldehyde **312** (90 mg, 38%) as a colourless semi-solid and decarbonylated cyclisation product **314** (150 mg, 54%) as a colourless oil. 9-Oxo-6,7,8,9-tetrahydro-*5H*-pyrrolo[1,2-*a*]azepine-1-carbaldehyde **312**, (Found: M^+, 177.0790. $C_{10}H_{11}NO_2$ requires 177.0790); υ_{max}(thin film)/cm^{-1} 1738, 1667 (C=O); δ_H 1.96-1.99 (2 H, m, 7-H), 2.09-2.13 (2 H, m, 6-H), 2.82-2.85 (2 H, m, 8-H), 4.25-4.28 (2 H, m, 5-H), 6.71-6.72 (2 H, m, 2,3-H) and 10.28 (1 H, s, CHO); δ_C 20.44 (7-C), 26.72 (6-C), 48.96 (8-C), 52.61 (5-C), 109.06 (2-C), 127.47 (3-C), 131.11 (1-C), 136.73 (9a-C), 188.75 (CHO) and 193.71 (9-C); *m/z* 177 (M^+, 100%), 120 (78) and 93 (42).

The decarbonylated cyclised material **312** was identified by close correlation to analogous acetyl compound, (Found: M^+, 149.0841. $C_9H_{11}NO$ requires149.0843); υ_{max}(thin film)/cm^{-1} 1660 (C=O); δ_H 1.85-2.02 (4 H, m, 6,7-H), 3.09 (2 H, t, *J* 6.4, 8-H), 3.95 (2 H, t, *J* 6.0, 5-H), 6.48-6.50 (2 H, m, 2-H), 6.55-6.56 (1 H, m, 3-H) and 9.79 (1 H, s, CHO); δ_C 19.87 (7-C), 22.66 (6-C), 23.00 (8-C), 45.42 (5-C), 109.30 (2-C), 120.96 (3-C), 121.66 (8a-C), 129.19 (1-C) and 185.10 (CHO); *m/z* 149 (M^+, 100) and 120 (61).

Synthesis of 2,3-dihydro-1*H*-pyrrolizidin-1-one; nordanaidone 224 (under CO)

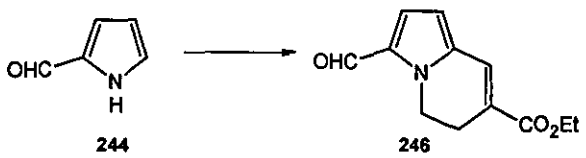


316 224

Phenyl 3-(1*H*-pyrrol-1-yl)propaneselenoate **316** (320 mg, 1.15 mmol) and AIBN (377 mg, 2.30 mmol) were dissolved in acetonitrile (250 cm^3) and was deoxygenated by passing a stream of nitrogen through the solution, the reaction mixture was saturated with CO using the standard technique; the freeze/thaw technique was repeated a two times. The reaction mixture was warmed slowly to room temperature and placed in an oil bath at 80 °C. A solution of tributyltin hydride (0.47 cm^3, 1.7 mmol) in cyclohexane (50 cm^3) was added dropwise over 4 h. Heating was maintained for a further 3 h and the reaction mixture was cooled to room temperature and evaporated to dryness. The oily solid was purified by gradient elution column chromatography yielding 2,3-dihydro-1*H*-pyrrolizidin-1-one **224**[40] (32 mg, 23%) as a clear semi-solid, (Found:

M^+, 121.0529. C_7H_7NO requires 121.0528); υ_{max}(thin film)/cm^{-1} 1697 (C=O); δ_H 3.09 (2 H, t, *J* 6.2, 2-H), 4.34 (2 H, t, *J* 6.2, 3-H), 6.51-6.54 (1 H, m, 6-H), 6.73-6.75 (1 H, m, 7-H) and 7.05 (1 H, m, 5-H); δ_C 39.44 (2-C), 42.11 (3-C), 107.59 (6-C), 116.97 (7-C), 122.83 (5-C) and 130.26 (7a-C); *m/z* 121 (M^+, 81%) and 93 (100).

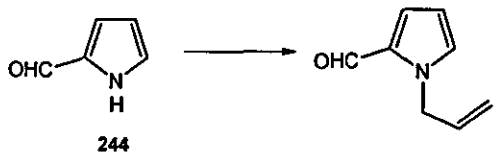
Synthesis of ethyl 5,6-dihydroindolizine-7-carboxylate 246



Pyrrole-2-carbaldehyde **244** (1.52 g, 16 mmol) was added to a stirred solution of sodium hydride (0.48 g, 20 mmol) in THF (200 cm^3) and heated to reflux. Ethyl 4-bromobutanoate (3.5 cm^3, 24 mmol) was added in one portion and heated under reflux overnight. The cooled crude mixture was passed through celite and the solvent removed yielding a brown oil. The crude material was purified by column chromatography yielding ethyl 5,6-dihydroindolizine-7-carboxylate **246** (0.46 g, 15%) as an orange oil, (Found: M^+, 191.0946. $C_{11}H_{13}NO_2$ requires 191.0946); υ_{max} (neat)/cm^{-1} 1694 (C=O) and 1256 (C-O); δ_H 1.33 (3 H, t, *J* 7.0, CH_3), 2.79 (2 H, t, *J* 7.3, 6-H), 4.01 (2 H, t, *J* 7.3, 5-H), 4.23 (2H, q, *J* 7.0, CH_2), 6.19-6.21 (1 H, m, 2-H), 6.34-6.35 (1 H, m, 8-H), 6.73 (1 H, m, 1-H), 7.47 (1 H, m, 3-H); δ_C 13.97 (6-C), 23.25 (CH_2), 43.56 (5-C), 109.32 (2-C), 111.40 (8-C), 118.90 (8a-C), 123.51 (1-C), 127.58 (3-C), 166.72 (CO_2Et).

5.2.4 Mitomycin Derivatives

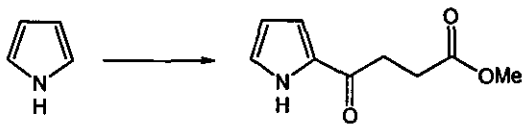
Synthesis of 1-prop-2-enyl-1*H*-pyrrole-2-carbaldehyde



Pyrrole-2-carbaldehyde **244** (1.43 g, 15.0 mmol) was added to a vigorously stirred suspension of ground potassium hydroxide (2.52 g, 45.0 mmol) in DMF (50 cm^3). After 30 min at room temperature, allylbromide (3.9 cm^3, 45.0 mmol) was added in one portion and the reaction mixture was stirred for 24 h. The reaction was quenched with water and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with water followed by brine, dried and evaporated to dryness to yield a pale yellow oil. Purification by column chromatography afforded 1-prop-2-enyl-1*H*-pyrrole-2-carbaldehyde as a colourless oil; (Found: M^+, 135.0684.

C_8H_9NO requires 135.0684); υ_{max}(thin film)/cm^{-1} 1664 (C=O); δ_H 4.96-5.05 (3 H, m, 1-H, CH_{trans}), 5.14-5.19 (1 H, m, CH_{cis}), 5.92-6.07 (1 H, m, C*H*=CH_2), 6.24-6.27 (1 H, m, pyrrole 5-H), 6.94-6.96 (2 H, m, pyrrole 3,4-H) and 9.55 (1 H, s, CHO); δ_C 50.92 (1-C), 109.88 (2-C), 117.13 (3-C), 124.59 (pyrrole 4-C), 130.98 (pyrrole 3-C), 131.39 (pyrrole 2-C), 134.03 (pyrrole 5-C) and 179.37 (CHO); *m/z* 135 (M^+, 89%), 118 (100) and 106 (42).

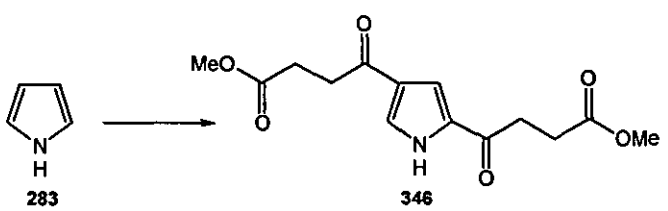
Synthesis of methyl 4-oxo-4-(1*H*-pyrrol-2-yl)butanoate 345



283 345

Methyl 4-chloro-4-oxo-butyrate (2.5 cm^3, 20.0 mmol) was added to a stirred suspension of anhydrous aluminium trichloride (5.30 g, 40.0 mmol) in dichloromethane (80 cm^3) and stirring was maintained at 0 °C until complete dissolution was achieved. Pyrrole **283** (1.40 cm^3, 20.0 mmol) in dichloromethane (20 cm^3) was added over 20 min. Approximately 30 min following complete addition, the reaction mixture was warmed to room temperature and the reaction mixture was stirred for 4 h. The reaction was quenched with ice-water (100 cm^3), the organic layer separated and the aqueous phase extracted further with dichloromethane. The combined organic extracts were washed with saturated sodium bicarbonate solution, water, dried (Na_2SO_4) and evaporated to dryness to yield methyl 4-oxo-4-(1*H*-pyrrol-2-yl)butanoate **345** (1.10 g, 30%) as an off-white solid, mp 52-54 °C; (Found: M^+, 181.0737. $C_9H_{11}NO_3$ requires 181.0739); υ_{max}(KBr disc)/cm^{-1} 1720, 1642 (C=O); δ_H 2.72 (2 H, t, *J* 6.8, 2-H), 3.15 (2 H, t, *J* 6.8, 3-H), 3.67 (3 H, s, Me), 6.22-6.26 (1 H, m, pyrrole 4-H), 6.95-6.98 (1 H, m, pyrrole 3-H), 7.02-7.05 (1 H, m, pyrrole 5-H) and 10.64 (1 H, b, pyrrole 1-H); δ_C 28.31 (2-C), 32.51 (3-C), 51.76 (Me), 110.51 (pyrrole 4-C), 116.83 (pyrrole 5-C), 125.49 (pyrrole 3-C), 131.36 (pyrrole 2-C), 173.48 (1-C) and 188.65 (4-C); *m/z* 181 (M^+, 36%), 150 (17) and 94 (100).

Synthesis of methyl 4-{4-[4(methyloxy)-4-oxobutanoyl]-1*H*-pyrrol-2-yl}4-oxobutanoate 346

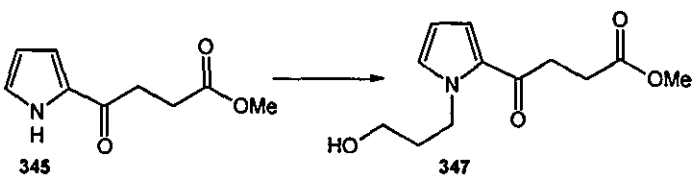


283 346

Methyl 4-chloro-4-oxo-butyrate (7.4 cm^3, 60.0 mmol) was added to a stirred suspension of anhydrous aluminium trichloride (16.00 g, 120.0 mmol) in dichloromethane (200 cm^3) and

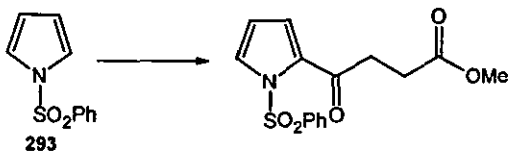
stirring was maintained at 0 °C until complete dissolution was achieved. Pyrrole **283** (2.8 cm^3, 40.0 mmol) in dichloromethane (50 cm^3) was added over 20 min and 30 min following complete addition, the reaction mixture was warmed to room temperature and the reaction mixture was stirred for 4 h. The reaction was quenched with ice-water (100 cm^3), the organic layer separated and the aqueous phase extracted further with dichloromethane. The combined organic extracts were washed with saturated sodium bicarbonate solution, water, dried (Na_2SO_4) and evaporated to dryness to yield methyl 4-{4-[4(methyloxy)-4-oxobutanoyl]-1*H*-pyrrol-2-yl}4-oxobutanoate **346** (1.01 g, 9%) as an off-white solid; (Found: M^+, 295.1055. $C_{14}H_{17}NO_6$ requires 295.1056); υ_{max}(KBr disc)/cm^{-1} 3314 (N-H) and 1721, 1674 (C=O); δ_H 2.75 (4 H, t, *J* 6.8, 2-H), 3.11-3.18 (4 H, m, 3-H), 3.70 (6 H, s, Me), 7.37-7.38 (1 H, m, pyrrole 3-H) and 7.62-7.63 (1 H, m, pyrrole 5-H); δ_C 27.87 (2-C), 32.53 (3-C), 34.20 (3-C), 51.86 (Me), 114.96 (pyrrole 3-C), 126.77 (pyrrole 4-C), 127.32 (pyrrole 5-C), 132.11 (pyrrole 2-C), 173.04 (1-C), 173.44 (1-C), 189.10 (4-C) and 193.17 (4-C); *m/z* 295 (M^+, 24%), 264 (22), 208 (100) and 176 (73).

Synthesis of methyl 1-(3-hydroxypropyl)-4-oxo-4-(1*H*-pyrrol-2-yl)butanoate 347



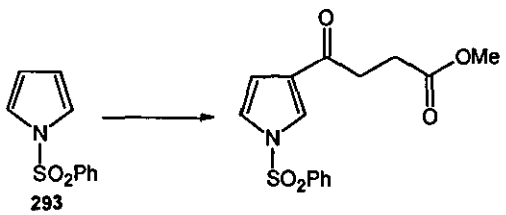
Methyl 4-oxo-4-(1*H*-pyrrol-2-yl)butanoate **345** (0.70 g, 3.9 mmol) was added to a vigorously stirred suspension of ground potassium hydroxide (0.65 g, 11.6 mmol) in DMSO (30 cm^3), stirred for 30 min and 1-bromo-propan-3-ol (0.52 cm^3, 5.8 mmol) was added in one portion. The reaction was stirred for 24 h, partitioned between ethyl acetate and water and the organic layer was removed. The organic extract was washed with water followed by brine, dried and evaporated to dryness yielding methyl 1-(3-hydroxypropyl)-4-oxo-4-(1*H*-pyrrol-2-yl)butanoate **347** (0.64 g, 69%) as a colourless oil; (Found: M^+, 239.1158. $C_{12}H_{17}NO_4$ requires 239.1158); υ_{max}(thin film)/cm^{-1} 3450 (O-H) and 1736, 1648 (C=O); δ_H 1.92-1.98 (2 H, m, $CH_2CH_2CH_2OH$), 2.70 (2 H, t, *J* 6.8, 2-H), 3.18 (2 H, t, *J* 6.8, 3-H), 3.52 (2 H, t, *J* 5.6, $CH_2CH_2CH_2OH$), 3.69 (3 H, s, OMe), 4.46 (2 H, t, *J* 6.6, $CH_2CH_2CH_2OH$), 6.17-6.18 (1 H, m, pyrrole 4-H), 6.91-6.92 (1 H, m, pyrrole 3-H) and 7.04-7.06 (1 H, m, pyrrole 5-H); δ_C ; *m/z* 239 (M^+, 50%), 208 (39), 124 (100) and 94 (63).

Synthesis of methyl 4-oxo-4-[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl]butanoate



Methyl 4-chloro-4-oxo butyrate (3.7 cm^3, 30.0 mmol) was added to a stirred solution of boron trifluoride etherate (7.40 cm^3, 60.0 mmol) in dichloromethane (50 cm^3). Stirring was maintained at room temperature for 10 min and *N*-(phenylsulfonyl)-1*H*-pyrrole **293** (2.14 cm^3, 10.0 mmol) in dichloromethane (10 cm^3) was added over 20 min and the reaction mixture was stirred for 4 days. The reaction was quenched with ice-water (100 cm^3) and the aqueous phase was extracted with further portions of dichloromethane. The combined organic extracts were washed with sodium hydroxide solution (0.1 M), water and dried (Na_2SO_4). Evaporation of solvent yielded methyl 4-oxo-4-[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl]butanoate (1.95 g, 61%) as a white solid; (Found: M^+, 321.0671 $C_{15}H_{15}NO_5S$ requires 321.0671); (Found: C, 56.0; H, 4.7; N, 4.4. $C_{15}H_{15}NO_5S$ requires: C, 56.1; H, 4.7; N, 4.35); υ_{max}(KBr disc)/cm^{-1} 1736, 1681 (C=O) and 1356, 1166 (SO_2); δ_H 2.62 (2 H, t, *J* 7.1, 2-H), 3.03 (2 H, t, *J* 7.1, 3-H), 3.61 (3 H, s, Me), 6.34-6.37 (1 H, m, pyrrole 4-H), 7.12 (1 H, dd, *J* 1.6, 3.9, pyrrole 3-H), 7.47-7.62 (3 H, m, phenyl 3-5-H), 7.80 (1 H, dd, *J* 1.6, 3.0, pyrrole 5-H) and 7.96-7.99 (2 H, m, phenyl 2,6-H); δ_C 27.96 (2-C), 33.86 (3-C), 51.74 (Me), 110.55 (pyrrole 4-C), 123.67 (pyrrole 5-C), 128.16 (phenyl 3,5-C), 128.72 (phenyl 2,6-C), 130.27 (pyrrole 3-C), 132.81 (pyrrole 2-C), 133.65 (phenyl 4-C), 138.85 (phenyl 1-C), 173.02 (1-C) and 186.21 (4-C); *m/z* 321 (M^+, 29%), 234 (95), 160 (60) and 141 (55).

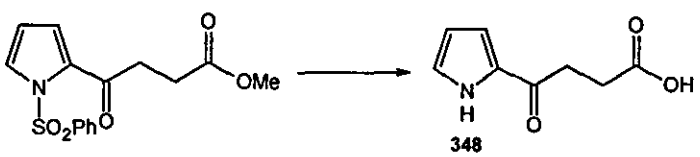
Synthesis of methyl 4-oxo-4-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]butanoate[152]



Methyl 4-chloro-4-oxo butyrate (6.10 g, 40.6 mmol) was added to a stirred suspension of anhydrous aluminium trichloride (10.80 g, 81.0 mmol) in dichloromethane (150 cm^3) and stirring was maintained at 0 °C until complete dissolution was achieved. *N*-(Phenylsulfonyl)-1*H*-pyrrole **293** (5.60 g, 27.1 mmol) in dichloromethane (50 cm^3) was added over 20 min. Approximately 30 min following complete addition the reaction mixture was warmed to room temperature and the

reaction mixture was stirred for 4 h. The reaction was quenched with ice-water (300 cm^3), the organic layer separated and the aqueous phase extracted further with dichloromethane. The combined organic extracts were washed with saturated sodium bicarbonate solution, water and dried (Na_2SO_4). Evaporation of solvent yielded methyl 4-oxo-4-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]butanoate (7.75 g, 89%) as an off-white solid, mp 66-68 °C (lit.,[152] 74-76 °C); (Found: M^+, 321.0672. $C_{15}H_{15}NO_5S$ requires 321.0671); (Found: C, 56.0; H, 4.55; N, 4.4. $C_{15}H_{15}NO_5S$ requires: C, 56.1; H, 4.7; N, 4.35); υ_{max}(KBr disc)/cm^{-1} 1736, 1678 (C=O) and 729, 687 (aromatic o.o.p. deformations); δ_H 2.70 (2 H, t, *J* 6.6, CH_2CO_2Me), 3.08 (2 H, t, *J* 6.6, $COCH_2$), 3.68 (3 H, s, Me), 6.70 (1 H, dd, *J* 1.6, 3.2, pyrrole 4-H), 7.15 (1 H, dd, *J* 2.4, 3.2, pyrrole 5-H), 7.54-7.58 (2 H, m, phenyl 3,5-H), 7.65-7.68 (1 H, m, phenyl 4-H), 7.78-7.79 (1 H, m, pyrrole 2-H) and 7.91-7.93 (2 H, m, phenyl 2,6-H); δ_C 27.69 (2-C), 34.30 (3-C), 51.83 (Me), 112.40 (pyrrole 4-C), 121.64 (pyrrole 5-C), 124.28 (pyrrole 2-C), 127.20 (phenyl 3,5-C), 128.63 (pyrrole 3-C), 129.76 (phenyl 2,6-C), 134.63 (phenyl 4-C), 138.15 (phenyl 1-C), 173.27 (1-C) and 192.97 (4-C); *m/z* 321 (M^+, 27%), 234 (100) and 141 (65).

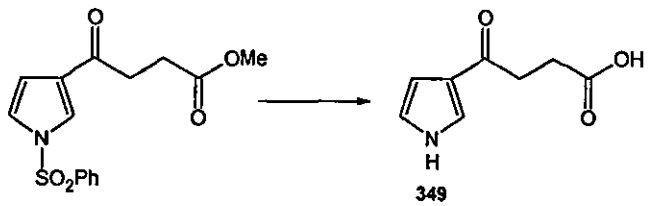
Synthesis of 4-oxo-4-(1*H*-pyrrol-2-yl)butanoic acid 348



348

Methyl 4-oxo-4-[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl]butanoate (1.90 g, 5.9 mmol) was dissolved in methanol (20 cm^3) and aqueous sodium hydroxide (5 M, 20 cm^3) was added. The reaction mixture was heated under reflux for 5 h and cooled to room temperature, acidified to pH 3 with hydrochloric acid and thoroughly extracted with dichloromethane. The organic layers were washed with water, dried and evaporated to dryness to give 4-oxo-4-(1*H*-pyrrol-2-yl)butanoic acid **348** (0.99 g, 100%) as an off-white solid, (Found: M^+, 167.0580. $C_8H_9NO_3$ requires 167.0582); υ_{max}(KBr disc)/cm^{-1} 3322 (N-H), 2960 (O-H) and 1714, 1643 (C=O); δ_H[400 MHz, $CO(CD_3)_2$] 2.67 (2 H, t, *J* 8.0, 2-H), 3.10 (2 H, t, *J* 8.0, 3-H), 6.22-6.24 (1 H, m, pyrrole 4-H), 7.01-7.03 (1 H, m, pyrrole 3-H) and 7.10-7.12 (1 H, m, pyrrole 5-H); δ_C 28.31 (2-C), 33.08 (3-C), 110.61 (pyrrole 4-C), 116.52 (pyrrole 5-C), 125.24 (pyrrole 3-C), 132.64 (pyrrole 2-C), 174.14 (1-C) and 188.57 (4-C); *m/z* 167 (M^+, 60%), 100 (73) and 94 (83).

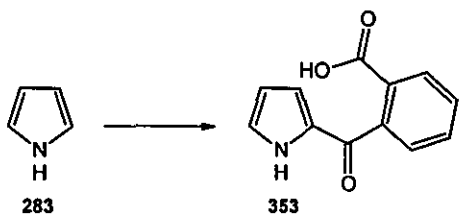
Synthesis of 4-oxo-4-(1*H*-pyrrol-3-yl)butanoic acid 349



349

Methyl 4-oxo-4-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]butanoate (2.41 g, 7.5 mmol) was dissolved in methanol (40 cm^3) and aqueous sodium hydroxide (5 M, 80 cm^3) was added. The reaction mixture was heated under reflux for 3 h and cooled to room temperature, acidified to pH 3 with hydrochloric acid and thoroughly extracted with diethyl ether. The organic layers were washed with water, dried and evaporated to dryness to give 4-oxo-4-(1*H*-pyrrol-3-yl)butanoic acid **349** (0.89 g, 71%) as an off-white solid, mp 92-93 °C (lit.,[180] 104-106 °C); (Found: M^+, 167.0583. $C_8H_9NO_3$ requires 167.0582); (Found: C, 57.8; H, 5.3; N, 7.85. $C_8H_9NO_3$ requires: C, 57.5; H, 5.45; N, 8.4%); υ_{max}(KBr disc)/cm^{-1} 3379 (N-H), 1728 (C=O) and 1620 (C=O); δ_H 2.46 (2 H, t, *J* 6.6, 2-H), 2.94 (2 H, t, *J* 6.6, 3-H), 6.42 (1 H, dd, *J* 2.5 and 4.1, pyrrole 4-H), 6.79 (1 H, dd, *J* 2.5 and 4.4 pyrrole 5-H), 7.54-7.57 (1 H, m, pyrrole 2-H) and 11.40 (1 H, br, pyrrole 1-H); δ_C 27.98 (2-C), 33.48 (3-C), 107.46 (pyrrole 4-C), 119.70 (pyrrole 5-C), 123.91 (pyrrole 2-C), 174.05 (1-C) and 193.10 (4-C); *m/z* 167 (M^+, 22%) and 94 (100).

Synthesis of 2-(1*H*-pyrrole-2-carbonyl)-benzoic acid 353[154]



283 **353**

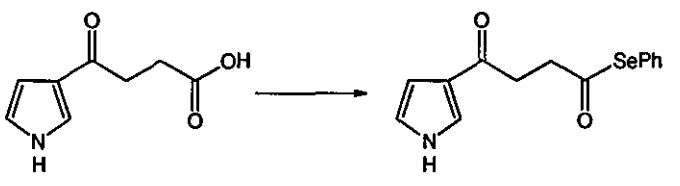
Crushed phthalic anhydride (2.96 g, 20 mmol) was stirred in diethyl ether (50 cm^3) and pyrrole **283** (1.34 g, 20 mmol) was added. Ethereal ethylmagnesium bromide (3 M, 40 mmol, 13.3 cm^3) was added to the stirred suspension at a rate of 26.6 cm^3/h for 15 min followed by 15.96 cm^3/h for 25 min. The crude reaction mixture was heated under reflux for 30 min and the solid formed upon cooling was collected and its solution in ice-water was filtered and washed twice with diethyl ether, acidified with dilute sulphuric acid and extracted four times with diethyl ether. The organic extracts were evaporated to dryness. The crude solid was heated at reflux in aqueous sodium hydroxide (2 M, 200 cm^3) for 2 h and the cooled solution was washed with dichloromethane, acidified with dilute hydrochloric acid and extracted with dichloromethane, dried and evaporated to dryness to yield 2-(1*H*-pyrrole-2-carbonyl)-benzoic acid **353** (2.75 g,

64%) as a pale brown amorphous solid; (Found: $[M+H]^+$, 216.0654. $C_{12}H_{10}NO_3$ requires 216.0661); υ_{max}(KBr disc)/cm^{-1} 3252 (N-H) and 1695 (C=O); $\delta_H(CD_3COCD_3)$ 6.19-6.20 (1 H, m, pyrrole 4-H), 6.38-6.39 (1 H, m, pyrrole 3-H), 7.19-7.20 (1 H, m, pyrrole 5-H), 7.50-7.52 (1 H, m, phenyl 6-H), 7.62-7.68 (phenyl 4,5-H) and 7.98-8.00 (1 H, m, phenyl 3-H); δ_C 110.82 (pyrrole 4-C), 118.98 (pyrrole 5-C), 125.95 (pyrrole 3-C), 128.95 (phenyl 4-C), 130.27 (phenyl 5-C), 130.77 (phenyl 3-C), 131.38 (pyrrole 2-C), 132.47 (phenyl 6-C), 142.65 (phenyl 1-C), 167.73 (*C*O_2H) and 185.66 (Ar*C*O); *m/z* 215 (M^+, 19%) and 94 (100).

Synthesis of phenyl 4-oxo-4-(1*H*-pyrrol-2-yl)butaneselenoate 350

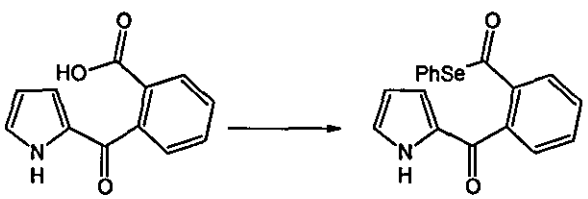
4-Oxo-4-(1*H*-pyrrol-2-yl)butanoic acid **348** (1.00 g, 6.0 mmol) and diphenyl diselenide (2.80 g, 9.0 mmol) were stirred in dichloromethane (25 cm^3) at –30 °C and tributylphosphine (2.2 cm^3, 9.0 mmol) was added dropwise over 5 min. The reaction mixture was stirred at –30 °C for 30 h after which time the reaction mixture was diluted with dichloromethane, washed with water and brine and back extracted with dichloromethane. The organic layers were combined, dried and evaporated to dryness. Purification by column chromatography using gradient elution yielded phenyl 4-oxo-4-(1*H*-pyrrol-2-yl)butaneselenoate **350** (1.70 g, 93%) as a white solid, mp 94-95°C; [Found (ESI): $(M+H)^+$, 308.0184. $C_{14}H_{14}NO_2Se$ requires 308.0189]; υ_{max}(KBr disc)/cm^{-1} 3295 (N-H), 1720, 1636 (C=O), 1403, 1107 and 1042; δ_H 3.12-3.19 (4 H, s, 2,3-H), 6.26-6.27 (1 H, m, pyrrole 4-H), 6.94-6.94 (1 H, m, pyrrole 3-H), 7.02-7.03 (1 H, m, pyrrole 5-H), 7.36-7.37 (3 H, m, phenyl 3-5-H)and 7.51-7.54 (2 H, m, phenyl 2,6-H); δ_C 32.52 (2-C), 41.58 (3-C), 110.82 (pyrrole 4-C), 116.45 (pyrrole 5-C), 124.87 (pyrrole 3-C), 126.26 (phenyl 1-C), 128.95 (phenyl 3,5-C), 129.36 (phenyl 4-C), 131.22 (pyrrole 2-C), 135.88 (phenyl 2,6-C), 187.39 (4-C) and 199.42 (1-C).

Synthesis of phenyl 4-oxo-4-(1*H*-pyrrol-3-yl)butaneselenoate 351



Diphenyl diselenide (2.22 g, 7.1 mmol) was stirred in dichloromethane (50 cm^3) at room temperature and tributylphosphine (1.8 cm^3, 7.1 mmol) was added dropwise over 2 min. The reaction mixture was stirred for a further 5 min and 4-oxo-4-(1*H*-pyrrol-3-yl)butanoic acid **349** (0.79 g, 4.7 mmol) was added. The reaction mixture was stirred for 6 h, diluted with dichloromethane, washed with water and brine and back extracted with dichloromethane. The organic layers were combined, dried and evaporated to dryness. The crude material was purified by column chromatography using gradient elution to yield phenyl 4-oxo-4-(1*H*-pyrrol-3-yl)butaneselenoate **351** (77%) as an off-white solid, mp 84-86°C; [Found: $(M+H)^+$, 308.0196. $C_{14}H_{14}NO_2Se$ requires 308.0189]; υ_{max}(KBr disc)/cm^{-1} 3222 (N-H), 1720, 1624 (C=O) and 741, 687 (aromatic o.o.p. deformations); δ_H 3.15 (4 H, s, 2,3-H), 6.65-6.68 (1 H, m, pyrrole 4-H), 6.75-6.78 (1 H, m, pyrrole 5-H), 7.34-7.39 (3 H, m, phenyl 3-5-H), 7.42-7.44 (1 H, m, pyrrole 2-H) and 7.51-7.55 (2 H, m, phenyl 2,6-H); δ_C 34.17 (2-C), 41.65 (3-C), 108.83 (pyrrole 4-C), 119.44 (pyrrole 5-C), 123.06 (pyrrole 2-C), 125.31 (phenyl 1-C), 126.41 (pyrrole 3-C), 128.90 (phenyl 4-C), 129.33 (phenyl 3,5-C), 135.90 (phenyl 2,6-C), 192.78 (4-C) and 199.94 (1-C).

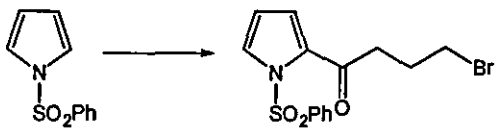
Synthesis of 2-(1*H*-pyrrole-2-carbonyl)-selenobenzoic acid *Se*-phenyl ester 354



2-(1*H*-Pyrrole-2-carbonyl)-benzoic acid **353** (0.32 g, 1.5 mmol) and diphenyl diselenide (0.70 g, 2.2 mmol) were stirred in dichloromethane (10 cm^3) at –30 °C and tributylphosphine (0.55 cm^3, 2.2 mmol) in dichloromethane (5 cm^3) was added dropwise over 5 min. The reaction mixture was stirred at –30 °C for 30 h after which time the reaction mixture was diluted with dichloromethane, washed with water and brine and the aqueous washings extracted with dichloromethane. The combined organic layers were dried and evaporated to dryness. Purification by column chromatography using gradient elution yielded 2-(1*H*-pyrrole-2-carbonyl)-selenobenzoic acid *Se*-phenyl ester **354** (0.39 g, 74%) as an off-white solid; υ_{max}(KBr disc)/cm^{-1} 3353 (N-H), 2925 1763 (C=O), 1611, 1466, 1095, 736 and 691; δ_H 6.17-6.20 (1 H, m, pyrrole 4-H), 6.27 (1 H, s, pyrrole 3-H), 6.89 (1 H, s, pyrrole 5-H), 7.04-7.10 (2 H, m, phenyl 5,6-H), 7.21-7.25 (3 H, m, Se-phenyl 3-5-H), 7.35-7.41 (1 H, m, phenyl 4-H), 7.49-7.52 (1 H, m, phenyl 3-H), 7.67-7.76 (2 H, m, Se-phenyl 2,6-H) and 8.79 (1 H, b, N-H); δ_C 107.80 (pyrrole 4-C), 109.14 (phenyl 4-C), 120.08 (pyrrole 5-C), 123.49 (pyrrole 3-C), 124.89 (phenyl 5-C), 124.98 (phenyl 2-C), 126.59 (*Se*-phenyl 4-C), 127.00 (pyrrole 2-C), 128.72 (*Se*-phenyl 3,5-C),

129.29 (*Se*-phenyl 4-C), 129.55 (phenyl 3-C), 134.21 (phenyl 6-C), 137.45 (*Se*-phenyl 2,6-C), 149.96 (phenyl 1-C) and 167.76 (Ar*C*O).

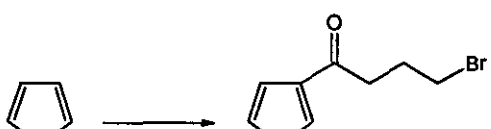
Synthesis of 4-bromo-1-[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl]butan-1-one 360



293 360

4-Bromobutyryl chloride (2.8 cm^3, 24.0 mmol) was added to a stirred solution of boron trifluoride etherate (3.0 cm^3, 24.0 mmol) in dichloromethane (50 cm^3). Stirring was maintained at room temperature for 10 min and *N*-(phenylsulfonyl)-1*H*-pyrrole **293** (2.48 cm^3, 12.0 mmol) in dichloromethane (10 cm^3) was added over 20 min and the reaction mixture was stirred for 4 days The reaction was quenched with ice-water (100 cm^3), the aqueous phase was extracted with further portions of dichloromethane. The combined organic extracts were washed with sodium hydroxide solution (0.1 M), water and dried (Na_2SO_4). Evaporation of solvent yielded 4-bromo-1-[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl]butan-1-one **360** (2.25 g, 53%) as a white solid, mp 68-69 °C; (Found: M^+, 354.9884. $C_{14}H_{14}BrNO_3S$ requires 354.9878); υ_{max}(thin film)/cm^{-1} 1676 (C=O) and 1364, 1174 (SO_2); δ_H 2.07-2.18 (2 H, m, 2-H), 2.88 (2 H, t, *J* 7.0, 3-H), 3.37 (2 H, t, *J* 6.4, 1-H), 6.35-6.37 (1 H, m, pyrrole 4-H), 7.11-7.12 (1 H, m, pyrrole 3-H), 7.50-7.54 (2 H, m, phenyl 3,5-H), 7.59-7.61 (1 H, m, phenyl 4-H), 7.81-7.83 (1 H, m, pyrrole 5-H) and 7.97-8.00 (2 H, m, phenyl 2,6-H); δ_C 27.02 (2-C), 33.25 (3-C), 37.13 (1-C), 110.54 (pyrrole 4-C), 123.74 (pyrrole 5-C), 128.11 (phenyl 3,5-C), 128.74 (phenyl 2,6-C), 130.40 (pyrrole 3-C), 133.05 (pyrrole 2-C), 133.69 (phenyl 4-C), 138.85 (phenyl 1-C) and 187.09 (4-C); *m/z* 355 (M^+, 4%), 234 (100), 185 (38), 141 (65), 94 (46) and 77 (100).

Synthesis of 4-bromo-1-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]butan-1-one 362

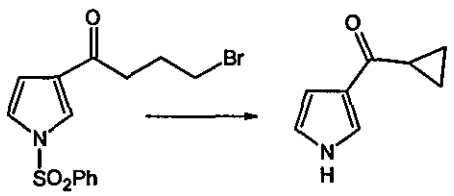


293 362

4-Bromobutyryl chloride (1.4 cm^3, 12.0 mmol) was added to a stirred suspension of anhydrous aluminium trichloride (1.60 g, 12.0 mmol) in dichloromethane (25 cm^3) and stirring was maintained at 0 °C until complete dissolution was achieved. *N*-(Phenylsulfonyl)-1*H*-pyrrole **293** (1.24 g, 6.0 mmol) in dichloromethane (5 cm^3) was added over 20 min. Approximately 30 min

following complete addition the reaction mixture was warmed to room temperature and the reaction mixture was stirred for 1 h. The reaction was quenched with ice-water (100 cm^3), the organic layer separated and the aqueous phase extracted further with dichloromethane. The combined organic extracts were washed with sodium hydroxide solution (0.1 M), water and dried (Na_2SO_4) and evaporated to dryness giving 4-bromo-1-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]butan-1-one **362** (2.11 g, 99%) as a coloured viscous oil; (Found: M^+, 354.9870. $C_{14}H_{14}BrNO_3S$ requires 354.9878); υ_{max}(thin film)/cm^{-1} 3131 (aromatic C-H), 1675 (C=O) and 1376, 1176 (SO_2); δ_H 2.20-2.27 (2 H, m, 2-H), 2.94 (2 H, t, *J* 7.0, 3-H), 3.49 (2 H, t, *J* 6.4, 1-H), 6.70 (1 H, dd, *J* 1.6, 3.2, pyrrole 4-H), 7.16 (1 H, dd, *J* 2.4, 3.2, pyrrole 5-H), 7.56-7.60 (2 H, m, phenyl 3,5-H), 7.65-7.68 (1 H, m, phenyl 4-H), 7.78-7.79 (1 H, m, pyrrole 2-H) and 7.92-7.94 (2 H, m, phenyl 2,6-H); δ_C 26.76 (2-C), 33.50 (3-C), 37.54 (1-C), 112.39 (pyrrole 4-C), 121.71 (pyrrole 5-C), 124.29 (pyrrole 2-C), 127.20 (phenyl 3,5-C), 128.94 (pyrrole 3-C), 129.77 (phenyl 2,6-C), 134.64 (phenyl 4-C), 138.13 (phenyl 1-C) and 193.82 (4-C); *m/z* 355 (M^+, 12 %), 249 (81), 234 (100), 141 (69) and 77 (100).

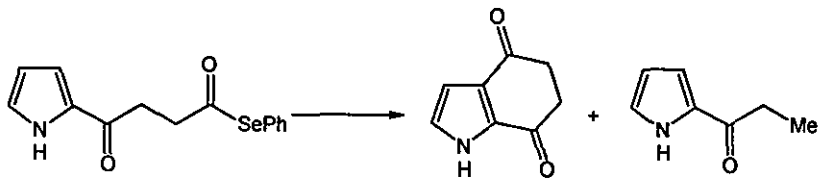
Synthesis of cyclopropyl(1*H*-pyrrol-3-yl)methanone 363



362 363

4-Bromo-1-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]butan-1-one **362** (1.88 g, 5.3 mmol) was dissolved in methanol (20 cm^3) and aqueous sodium hydroxide (5 M, 20 cm^3) was added. The reaction mixture was heated under reflux for 12 h and cooled to room temperature, acidified to pH 3 with hydrochloric acid and thoroughly extracted with dichloromethane. The combined organic layers were washed with water, dried and evaporated to dryness to give cyclopropyl(1*H*-pyrrol-3-yl)methanone **363** (0.70 g, 98%) as an off-white solid; (Found: M^+, 135.0685. $C_8H_9NO_3$ requires 135.0684); υ_{max}(KBr disc)/cm^{-1} 3205 (N-H) and 1617 (C=O); δ_H(400 MHz) 0.89-0.94 (2 H, m, C-H_{cis}), 1.15-1.18 (2 H, m, C-H_{trans}), 2.37-2.42 (1 H, m, C-*H*), 6.70-6.72 (1 H, m, pyrrole 4-H), 6.77-6.80 (1 H, m, pyrrole 5-H) and 7.48-7.50 (1 H, m, pyrrole 2-H); δ_C 10.35 (CH_2), 17.98 (*C*-H), 108.60 (pyrrole 4-C), 119.55 (pyrrole 5-C), 123.06 (pyrrole 2-C), 126.61 (pyrrole 3-C) 196.42 (C=O); *m/z* 135 (M^+, 43%) and 94 (100).

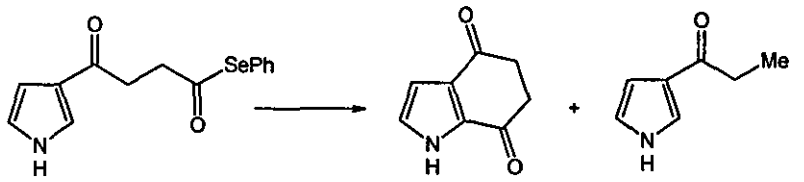
Attempted synthesis of 5,6-dihydro-1*H*-indole-4,7-dione 344 (under N_2)



350 344 356

Tributyltin hydride (0.75 cm^3, 2.8 mmol) and AMBN (0.88 g, 4.6 mmol) in cyclohexane (20 cm^3) was added over 7 h to a solution of phenyl 4-oxo-4-(1*H*-pyrrol-2-yl)butaneselenoate **350** (0.70 g, 2.3 mmol) in acetonitrile (250 cm^3) heated under reflux. The reaction mixture was heated under reflux for 9 h after which time it was cooled to room temperature and evaporated to dryness. Purification using gradient elution column chromatography yielded 1-(1*H*-pyrrol-2-yl)-propan-1-one **356** (0.164 g, 58%) as a colourless oil; υ_{max}(thin film)/cm^{-1} 3287 (N-H) and 1640 (C=O); δ_H(400 MHz) 1.22 (3 H, t, *J* 7.5, Me), 2.82 (2 H, q, *J* 7.5, COC*H*$_2$), 6.26 (1 H, ddd, *J* 2.5, 3.8, 2.5, pyrrole 4-H), 6.92 (1 H, ddd, *J* 3.8, 2.5, 1.3, pyrrole 3-H) and 7.04 (1 H, ddd, *J* 2.5, 2.9, 1.3, pyrrole 5-H).

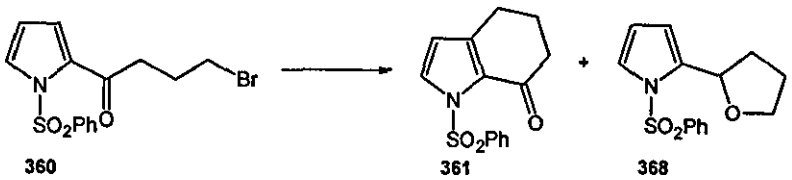
Attempted synthesis of 5,6-dihydro-1*H*-indole-4,7-dione 344 (under N_2)



351 344

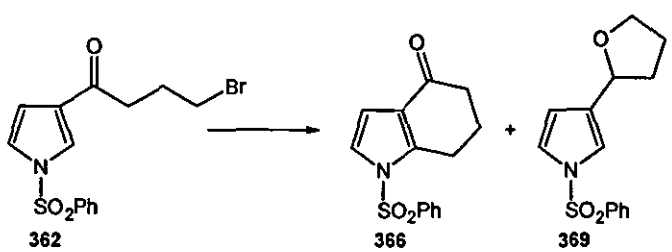
Tributyltin hydride (0.13 cm^3, 0.43mol) in cyclohexane (20 cm^3) and AIBN (0.14 g, 0.86 mmol) in acetonitrile were added over 7 h to a solution of phenyl 4-oxo-4-(1*H*-pyrrol-3-yl)butaneselenoate **351** (0.12 g, 0.39 mmol) in acetonitrile (50 cm^3) heated under reflux. The reaction mixture was heated under reflux for 9 h after which time it was cooled to room temperature and evaporated to dryness. Purification using gradient elution column chromatography yielded an unidentified monosubstituted pyrrole and 1-(1*H*-pyrrol-3-yl)-propan-1-one **356** (9 mg, 4%) as a colourless oil; δ_H 1.20 (3 H, t, *J* 7.5, Me), 2.80 (2 H, q, *J* 7.5, COC*H*$_2$), 6.68 (1 H, m, pyrrole 4-H), 6.78 (1 H, m, pyrrole 5-H) and 7.43 (1 H, m, pyrrole 3-H).

Synthesis of 1-(phenylsulfonyl)-1,4,5,6-tetrahydro-indol-7-one 361



Tributyltin hydride (0.59 cm^3, 2.2 mmol) and AIBN (0.36 g, 4.6 mmol) in toluene (50 cm^3) was added over 7 h to a solution 4-bromo-1-[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl]butan-1-one **360** (0.39 g, 1.1 mmol) in acetonitrile (250 cm^3) heated under reflux. The reaction mixture was heated under reflux for 9 h after which time it was cooled to room temperature and evaporated to dryness. Purification using gradient elution column chromatography yielded 1-(phenylsulfonyl)-1,4,5,6-tetrahydro-indol-7-one **361** (10% by ^1H NMR spectral correlation to reported data) and 1-phenylsulfonyl-2-(tetrahydro-furan-2-yl)-1*H*-pyrrole **368** (0.210 g, 69%) as a colourless oil; (Found: M^+, 277.0763. $C_{14}H_{15}NO_3S$ requires 277.0773); υ_{max}(thin film)/cm^{-1} 1368 and 1178 (SO_2); δ_H(400 MHz) 1.60-1.66 (1 H, m, 4-H), 1.92-1.96 (2 H, m, 3-H), 2.24-2.29 (1 H, m, 4-H), 3.77-3.81 (1 H, m, 5-H), 3 87-3.90 (1 H, m, 5-H), 5.27-5.28 (1 H, m, 2-H), 6.22-6.26 (2 H, m, pyrrole 3,4-H), 7.26-7.28 (1 H, m, pyrrole 5-H), 7.46-7.49 (2 H, m, phenyl 3,5-H), 7.55-7.57 (1 H, m, phenyl 4-H) and 7.80-7.82 (2 H, m, phenyl 2,6-H); δ_C 25.46 (3-C), 32.80 (4-C), 68.15 (5-C), 73.54 (2-C), 111.66 (pyrrole 4-C), 112.02 (pyrrole 5-C), 123.36 (pyrrole 3-C), 126.80 (phenyl 3,5-C), 129.22 (phenyl 2,6-C), 133.66 (phenyl 4-C), 137.04 (pyrrole 2-C) and 139.54 (phenyl 1-C).

Attempted synthesis of 1-(phenylsulfonyl)-1,5,6,7-tetrahydro-indol-4-one 366

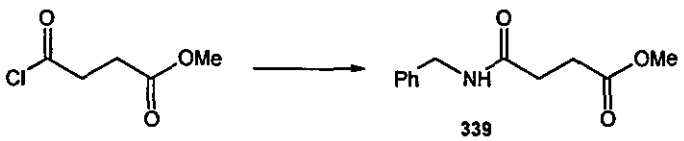


Tributyltin hydride (0.59 cm^3, 2.2 mmol) and AIBN (0.36 g, 4.6 mmol) in toluene (50 cm^3) was added over 7 h to a solution 4-bromo-1-[1-(phenylsulfonyl)-1*H*-pyrrol-3-yl]butan-1-one **362** (0.39 g, 1.1 mmol) in acetonitrile (250 cm^3) heated under reflux. The reaction mixture was heated under reflux for 9 h after which time it was cooled to room temperature and evaporated to dryness. Purification using gradient elution column chromatography yielded 1-phenylsulfonyl-3-(tetrahydro-furan-2-yl)-1*H*-pyrrole **369** (0.193 g, 64%) as a colourless oil; (Found: M^+,

277.0775. $C_{14}H_{15}NO_3S$ requires 277.0773); υ_{max}(thin film)/cm^{-1} 1370 and 1175 (SO_2); δ_H(400 MHz) 1.73-1.76 (1 H, m, 4-H), 1.88-1.93 (2 H, m, 3-H), 2.11-2.14 (1 H, m, 4-H), 3.74-3.80 (1 H, m, 5-H), 3.89-3.94 (1 H, m, 5-H), 4.72-4.74 (1 H, m, 2-H), 6.25-6.26 (1 H, m, pyrrole 4-H), 7.11-7.13 (2 H, m, pyrrole 2,5-H), 7.41-7.45 (2 H, m, phenyl 3,5-H), 7.51-7.54 (1 H, m, phenyl 4-H) and 7.82-7.84 (2 H, m, phenyl 2,6-H); δ_C 25.79 (3-C), 32.90 (4-C), 68.00 (5-C), 74.68 (2-C), 112.40 (pyrrole 4-C), 117.26 (pyrrole 5-C), 121.33 (pyrrole 2-C), 126.42 (phenyl 3,5-C), 129.38 (phenyl 2,6-C), 131.37 (pyrrole 3-C), 133.86 (phenyl 4-C) and 138.90 (phenyl 1-C); *m/z* 277 (M^+, 33%), 276 (26), 234 (22), 141 (37), 136 (57), 94 (42) and 77 (100).

5.2.5 THIOAMIDES

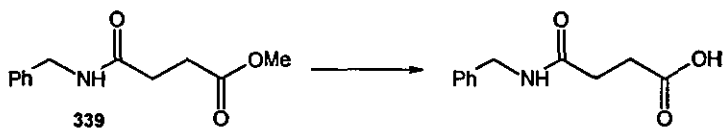
Synthesis of methyl 4-oxo-4-[(phenylmethyl)amino]butanoate 339



339

Benzylamine (2.0 cm^3, 18.2 mmol) was added over 2 min to a stirred solution of *N*-methyl morpholine (2.0 cm^3, 18.2 mmol) and methyl 4-chloro-4-oxo butyrate (2.0 cm^3, 16.5 mmol) in dichloromethane (20 cm^3) at 0 °C. The reaction was stirred at 0 °C for 1 h and quenched with hydrochloric acid (1 M, 20 cm^3). The aqueous layer extracted with dichloromethane and the combined organic extracts were washed with water, dried and evaporated to dryness, affording methyl 4-oxo-4-[(phenylmethyl)amino]butanoate **339** (3.45 g, 95%) as a white solid, mp 67-68 °C (lit.,[181] 57-58 °C); (Found: M^+ 221.1055. $C_{12}H_{15}NO_3$ requires 221.1052); (Found: C, 65.0; H, 6.95; N, 6.45. $C_{12}H_{15}NO_3$ requires: C, 65.2; H, 6.85; N, 6.35%); υ_{max}(KBr disc)/cm^{-1} 3306 (N-H), 1728, 1643 (C=O) and 698 (aromatic o.o.p. deformations); δ_H 2.50 (2 H, t, *J* 6.8, 3-C), 2.69 (2 H, t, *J* 6.8, 2-C), 3.67 (3 H, s, Me), 4.42 (2 H, *J* 6.0, PhC*H*$_2$) and 7.24-7.34 (5 H, m, phenyl-H); δ_C 29.72 (3-C), 31.36 (2-C), 44.04 (PhCH$_2$), 52.20 (Me), 127.85 (phenyl 4-C), 128.12 (phenyl 2,6-C), 129.06 (phenyl 3,5-C), 138.62 (phenyl 1-C), 171.62 (4-C) and 173.83 (1-C); *m/z* 221 (M^+, 20%), 189 (100), 160 (100), 104 (95) and 91 (72).

Synthesis of 4-oxo-4-[(phenylmethyl)amino]butanoic acid



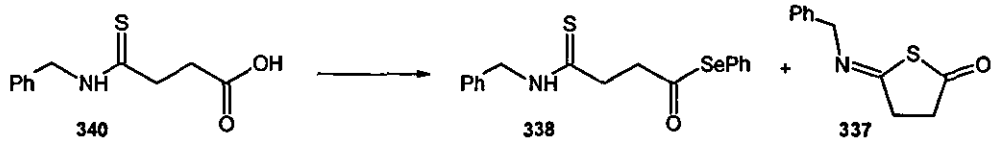
339

Methyl 4-oxo-4-[(phenylmethyl)amino]butanoate **339** (1.6 g, 7.2 mmol) was dissolved in methanol (25 cm^3) and treated with aqueous sodium hydroxide (1 M, 25 cm^3), the reaction mixture was heated at reflux for 4 h and cooled to room temperature. The methanol was removed by rotary evaporation and the aqueous layer acidified with hydrochloric acid (1 M), extracted with ethyl acetate, dried and evaporated to dryness to yield 4-oxo-4-[(phenylmethyl)amino]butanoic acid (1.20 g, 81%) as a white solid, mp 129-131 °C; (Found: M^+, 207.0895. $C_{11}H_{13}NO_3$ requires 207.0895); υ_{max}(KBr disc)/cm^{-1} 3302 (N-H), 3063 (O-H), 1713, 1643 (amide C=O) and 694 (aromatic o.o.p. deformations); δ_H 2.38-2.42 (2 H, m, 2-C), 2.45-2.49 (2 H, m, 3-C), 4.27 (2 H, d, *J* 5.6, PhCH_2), 7.21-7.33 (5 H, m, phenyl-H) and 8.34 (1 H, t, *J* 5.8, N-H); δ_C 29.48 (2-C), 30.34 (3-C), 42.37 (PhCH_2), 127.00 (phenyl 4-C), 127.47 (phenyl 2,6-C), 128.55 (phenyl 3,5-C), 139.93 (phenyl 1-C), 171.34 (4-C) and 174.19 (1-C); *m/z* 207 (M^+, 67%), 160 (84), 106 (100) and 91 (100).

Synthesis of 4-[(phenylmethyl)amino]-4-thioxobutanoic acid 340

Methoxyphenylthionophosphine sulfide dimer (Lawessons reagent, 4.38 g, 10.9 mmol) and methyl 4-oxo-4-[(phenylmethyl)amino]butanoate **339** (3.21 g, 15.5 mmol) were heated at 90 °C in dry toluene for 2 h. The reaction mixture was cooled to room temperature and the solvent evaporated. The crude reaction mixture was purified by column chromatography using dichloromethane eluent on neutral alumina. The ester was isolated and hydrolysed with aqueous sodium hydroxide (1 M, 20 cm^3) and methanol (10 cm^3) at 0 °C for 3 h. The methanol was removed by rotary evaporation and the reaction mixture diluted with water, acidified to pH 1 and extracted into ethyl acetate. The organic layers were washed with water, dried and evaporated to dryness to yield 4-[(phenylmethyl)amino]-4-thioxobutanoic acid **340** (2.14 g, 67% over 2 steps) as an off-white solid, mp 93-95 °C (lit.,[182] 100-102 °C); (Found: M^+, 223.0665. $C_{11}H_{13}NO_2S$ requires 223.0667); υ_{max}(KBr disc)/cm^{-1} 3241 (N-H), 1703 (C=O), 1542 (amide II) and 1262 (amide I); δ_H(400 MHz; DMSO-d6) 2.71-2.81 (4 H, m, 2,3-C), 4.80 (2 H, d, *J* 4.0, PhCH_2), 7.27-7.36 (5 H, m, phenyl-H) and 10.47 (1 H, b, m, N-H); δ_C(DMSO-d6) 33.16 (2-C), 48.67 (3-C), 127.46 (phenyl 4-C), 127.98 (phenyl 2,6-C), 128.67 (phenyl 3,5-C), 137.49 (phenyl 1-C), 173.78 (1-C) and 203.38 (4-C); *m/z* 223 (M^+, 77%) and 91 (100).

Synthesis of 4-[(phenylmethyl)amino]-4-thioxobutaneselenoate 338

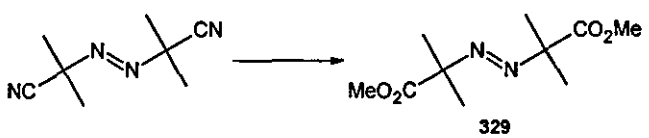


Tributylphosphine (1.05 cm^3, 4.25 mmol) was added dropwise over 5 min to a stirred solution of 4-[(phenylmethyl)amino]-4-thioxobutanoic acid **340** (0.50 g, 2.24 mmol) in dichloromethane (15 cm^3) at 0 °C. NPSP **250** (1.02 g, 3.36 mmol) was added in one portion and the reaction was stirred at 0 °C for 4 h. The reaction was quenched with water and the organic layer was diluted with dichloromethane. The organic layer was separated and the aqueous layer was extracted again with dichloromethane, the organic extracts were combined and washed with brine, dried and evaporated to dryness to yield an orange solid. Purification by column chromatography (dichloromethane/methanol) afforded 4-[(phenylmethyl)amino]-4-thioxobutaneselenoate **338** (295 mg, 37%) and the cyclised material, 5-[(phenylmethyl)imino]tetrahydrothiophen-2-one **337** (113 mg, 25%). 4-[(Phenylmethyl)amino]-4-thioxobutaneselenoate **338**; υ_{max}(thin film)/cm^{-1} 1720 (C=O) and 1651 (thioamide II); δ_H(400 MHz) 2.53 (2 H, t, *J* 6.0, 3-C), 3.12 (2 H, t, *J* 6.0, 2-C), 4.42 (2 H, d, *J* 6.0, CH_2Ph), 5.87 (1 H, b, N-H), 7.25-7.38 (6 H, m, phenyl-H), 7.49-7.52 (2 H, m, phenyl-H) and 7.76-7.85 (2 H, m, phenyl-H); δ_C 31.04 (2-C), 42.71 (PhCH_2), 43.79 (3-C), 126.12 (phenyl 1-C), 127.57 (benzyl-1-C) 127.80 (benzyl-2,6-C), 128.73 (benzyl-3,5-C), 129.05 (phenyl 4-C), 129.41 (phenyl 3,5-C), 135.90 (phenyl 2,6-C) and 138.03 (benzyl-1-C); MS analysis of the compound was not possible due to degradation.

The cyclised material; 5-[(phenylmethyl)imino]tetrahydrothiophen-2-one **337**; (Found: M^+, 205.0564. $C_{11}H_{13}NOS$ requires 205.0561); υ_{max}(DCM)/cm^{-1} 1747 (C=O); δ_H(400 MHz) 2.68-2.71 (2 H, m, CH_2CO), 3.09-3.12 (2 H, m, CH_2CH_2CO), 5.06 (2 H, s, PhCH_2), 7.24-7.30 (3 H, m, phenyl-H) and 7.40-7.43 (2 H, m, phenyl-H); δ_C 28.76 (CH_2C=NBzl), 38.81 (CH_2CO), 45.45 (PhCH_2), 127.94 (phenyl 4-C), 128.46 (phenyl 2,6-C), 129.07 (phenyl 3,5-C), 178.66 (*C*=NBzl) and 210.39 (C=O); *m/z* 205 (M^+, 100%), 148 (33) and 91 (28).

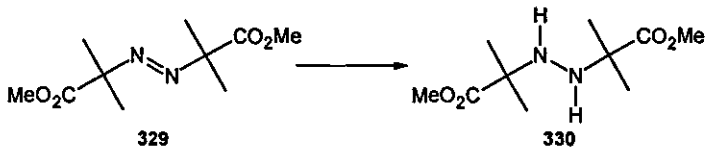
5.2.6 Oxidation Mechanism

Synthesis of dimethyl azobisisobutyrate 329[147]



The reaction flask was fitted with an aqueous sodium hydroxide scrubbing train and empty Dreschel bottle and dry HCl gas was passed through a stirred slurry of azobisisobutyronitrile (10.0 g, 60.9 mmol) in dry methanol (150 cm^3) at –5 °C *via* a glass pipette. Immediately the flask was cooled further to –20 °C to maintain a constant reaction temperature <10 °C. After 1 h the HCl source was removed and the reaction vessel equilibrated to 0 °C and the reaction mixture was stirred overnight. The reaction mixture was cooled to –80 °C and allowed to stand at this temperature for 30 min, after which time the solid was rapidly removed by vacuum filtration. The precipitate was stirred into ice-water and upon complete dissolution of organic matter the solution was filtered to remove particulate matter, extracted into dichloromethane, dried (Na_2SO_4) and evaporated to dryness to yield dimethyl azobisisobutyrate **329** (11.24 g, 80%) as a colourless oil; υ_{max}(thin film)/cm^{-1} 2989, 2952 (sp^3 hybridised C-H), 1742 (C=O) and 1466 (N=N); δ_H 1.42 (12 H, s, Me) and 3.68 (6 H, s, CO_2Me); δ_C 22.98 (Me), 52.37 ($CO_2\mathit{Me}$) and 173.89 ($\mathit{C}O_2Me$). Spectral analysis matched published data for authentic compound.[147]

Synthesis of dimethyl hydrazinobisisobutyrate 330



Hydrazine hydrate (0.26 g, 4.4 mmol) in ethanol (10 cm^3) was added to a stirred solution of dimethyl azobisisobutyrate **329** (0.25 g, 1.1 mmol) in ethanol (20 cm^3) and the reaction was stirred in air for 24 h at room temperature (Cu(I)I accelerates reaction rate, addition of catalytic quantities gives complete reaction in minutes). The white precipitate was removed and the reaction mixture evaporated to dryness. The resulting colourless oil was partitioned between ethyl acetate and hydrochloric acid (2 M), the organic layer was separated and the aqueous layer extracted again with ethyl acetate. The aqueous layer was basified to pH 9 with aqueous sodium hydroxide (2 M) and extracted with ethyl acetate. The combined organic layers were dried and evaporated to dryness to yield dimethyl hydrazinobisisobutyrate **330** (0.119 g, 47%) as a pale brown oil; (Found: M^+, 232.1423. $C_{10}H_{20}N_2O_4$ requires 232.1423); υ_{max}(thin film)/cm^{-1} 3435 (N-H) and 1728 (C=O); δ_H(400 MHz) 1.24 (12 H, s, Me) and 3.71 (6 H, s, CO_2Me); δ_C 23.86 (Me), 51.91 ($CO_2\mathit{Me}$), 61.34 ($\mathit{C}Me_2CO_2Me$) and 177.57 ($\mathit{C}O_2Me$); *m/z* 232 (M^+, 17%), 113 (65) and 102 (100).

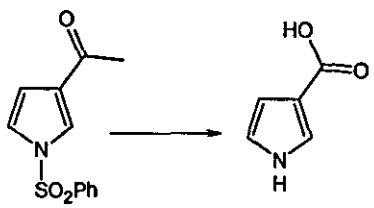
5.3 EXPERIMENTAL FOR CHAPTER 4

Synthesis of pyrrole-2-carboxylic acid 377

377

Ethyl pyrrole-2-carboxylate (2.0 g, 18 mmol) was dissolved in tetrahydrofuran (40 cm^3) and treated with aqueous lithium hydroxide (0.5 M, 40 cm^3). Stirring was maintained for 6 h and the reaction mixture diluted with water, washed with ethyl acetate and acidified to pH 3 with 20% citric acid solution. The aqueous mixture was extracted with ethyl acetate, dried and evaporated to dryness to yield pyrrole-2-carboxylic acid **377** (1.60 g, 84%) as an off-white solid; (Found: M^+, 111.0322. $C_5H_5NO_2$ requires 111.0320); (Found: C, 54.25; H, 4.55; N, 12.35. $C_5H_5NO_2$ requires: C, 54.05; H, 4.55; N, 12.6%); υ_{max}(KBr disc)/cm^{-1} 3364 (O-H) and 1654 (C=O); δ_H(DMSO-d6) 6.13-6.14 (1 H, m, 4-H), 6.72-6.73 (1 H, m, 3-H), 6.94-6.96 (1 H, m, 5-H); δ_C(DMSO-d6) 109.61 (4-C), 115.00 (3-C), 123.25 (2-C), 123.70 (3-C) and 162.22 (CO_2H); *m/z* 111 (M^+, 100%), 93 (92) and 65 (44).

Synthesis of pyrrole-3-carboxylic acid 376

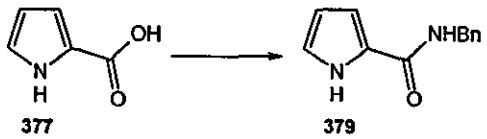


284 376

Bromine (3.55 cm^3, 69 mmol) was added to 12% sodium hydroxide solution (100 cm^3) in 1,4-dioxane (20 cm^3) and the resulting sodium hypobromite solution was cooled to 0 °C. 1-[1-(Phenylsulfonyl)-1*H*-pyrrol-3-yl]ethan-1-one **284** (3.74 g, 15.0 mmmol) was dissolved in 1,4-dioxane (200 cm^3) and water (50 cm^3) and the stirred solution was cooled to 0 °C; the cold sodium hypobromite solution was added dropwise over 15 min. After 1.5 h at 0 °C the reaction was quenched with acetone (45 cm^3) and acidified to pH 1 with hydrochloric acid, the aqueous solution was extracted with dichloromethane and the combined organic extracts were washed with water and brine, dried and evaporated to dryness to yield a pale brown solid. The crude acid was treated with aqueous sodium hydroxide solution (5 M, 200 cm^3) for 2.5 h at room temperature and acidified to pH 4 with 20% citric acid solution. The aqueous solution was extracted with ethyl acetate, dried and evaporated to dryness to yield pyrrole-3-carboxylic acid

376 (0.89 g, 53%) as a pale yellow solid, mp; (Found: M^+, 111.0323. $C_5H_5NO_2$ requires 111.0320); υ_{max}(KBr disc)/cm^{-1} 3352 (N-H), 3257 (O-H), 1654 (C=O) and 1158 (C-O); δ_H(DMSO-d6) 7.53 (1 H, m, 4-H), 7.56-7.59 (1 H, m, 5-H), 7.81-7.85 (1 H, m, 2-H).

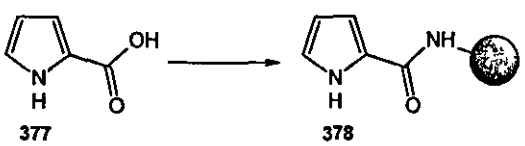
Synthesis of *N*-2-phenylmethyl-1*H*- pyrrole-2-carboxamide 379



377 379

Benzylamine (0.50 cm^3, 4.5 mmol) was added to a stirred solution of pyrrole-2-carboxylic acid **377** (1.00 g, 9.0 mmol) and *N*-methylmorpholine (1.00 cm^3, 9.0 mmol) in dichloromethane (15 cm^3) at 0 °C. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.72 g, 9.0 mmol) was added portionwise over 10 min and stirring was maintained for 30 min at 0 °C. The suspension was warmed to room temperature and the reaction mixture was stirred for a further 30 min, quenched with hydrochloric acid (1 M, 15 cm^3) and extracted with dichloromethane. The organic layers were combined and washed with aqueous sodium hydroxide (1 M, 15 cm^3), dried and evaporated to dryness to yield *N*-2-phenylmethyl-1*H*-pyrrole-2-carboxamide **379** (0.90 g, 99%) as a white solid, mp 122-124 °C; (Found: M^+, 200.0952. $C_{12}H_{12}N_2O$ requires 200.0950); υ_{max}(KBr disc)/cm^{-1} 1636 (C=O); δ_H 4.59 (2 H, d, *J* 3.8, PhCH_2), 6.18-6.19 (1 H, m, pyrrole 4-H), 6.40 (1 H, br, N-H), 6.56-6.58 (1 H, m, pyrrole 3-H), 6.84-6.86 (1 H, m, pyrrole 5-H), 7.26-7.32 (2 H, m, phenyl-H) and 10.20 (1 H, br, pyrrole 1-H); δ_C 43.36 ($PhCH_2$), 109.20, 109.64 (pyrrole 3,5-C), 121.95 (pyrrole 4-C), 125.69 (pyrrole 2-C), 127.48 (phenyl 4-C), 127.71 (phenyl 3,5-C), 128.71 (phenyl 2,6-C), 138.48 (phenyl 1-C) and 161.34 (C=O); *m/z* 200 (100%), 105 (61) and 94 (48).

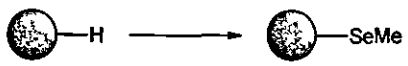
Synthesis of PS pyrrole-2-amide 378



377 378

Amino methylated PS (1.000 g, 1.13 mmol g^{-1} loading) was swollen in dichloromethane (25 cm^3) for 30 min and pyrrole-2-carboxylic acid **377** (251 mg, 2.26 mmol) followed by DCC (700 mg, 3.39 mmol) were added. The reaction mixture was agitated by rotation of the reaction vessel for 24 h and the polymer beads removed by filtration. The beads were treated with dichloromethane, methanol and water several times. The polymer beads were dried at the pump, followed by 6 h at 50 °C under vacuum, yielding the polymer bound pyrrole **378** (1.075 g, 71%).

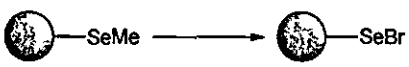
Synthesis of PS methylselenide 385[183]



384 385

Washed polystyrene (22.0 g) was suspended in cyclohexane (200 cm^3) and TMEDA (31.4 cm^3, 196 mmol) followed by the slow addition of 1.6 M *n*-butyllithium (166.9 cm^3, 267 mmol). The reaction mixture was heated to 65 °C for 5.5 h, after which time the reaction mixture was cooled and the liquid removed by decanting. The polymer was washed twice with cyclohexane and suspended in THF (250 cm^3). The lithiated polystyrene was quenched with dimethyl diselenide (4.16 cm^3, 44 mmol). After stirring for 1 h at room temperature the polymer was removed and washed rigorously with dichloromethane, methanol and toluene, the polymer was dried overnight under vacuum, yielding the PS methyl selenide **385** (27.60 g, 100%) as a yellow resin. The theoretical loading accounting for the change in mass was 1.68 $mmol.g^{-1}$.

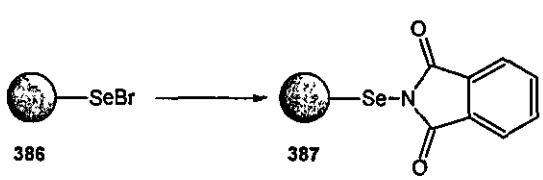
Synthesis of PS selenyl bromide 386[104,184]



385 386

PS methyl selenide **385** (26.40 g, 44.0 mmol loading) was swollen in chloroform (100 cm^3) and the suspension was stirred at 0 °C for 30 min. A solution of bromine (2.26 cm^3, 44.0 mmol) in chloroform (15 cm^3) was added in one portion and the reaction mixture was stirred for 10 min at 0 °C. The polymer was removed, washed with methanol and dichloromethane under vacuum and heated at reflux in ethanol for 1 h. The red polymer was removed and dried briefly at the pump before being transferred to dry fully under vacuum, giving PS selenyl bromide **386** (29.11 g, 95%) as a deep red polymer. The theoretical loading accounting for the change in mass was 1.45 $mmol.g^{-1}$.

Synthesis of *N*-(PSselenyl)phthalimide 387[161]

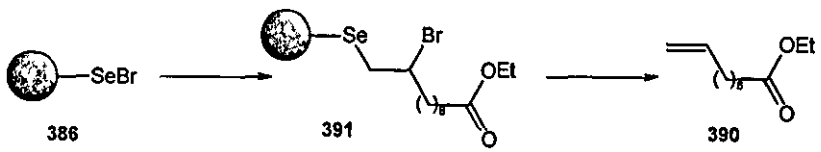


386 387

PS selenyl bromide **386** (11.00 g, 13.75 mmol) was swollen in a toluene solution (250 cm^3) containing potassium phthalimide (3.82 g, 20.6 mmol) and 18-crown-6 (5.45 g, 20.6 mmol) and

the reaction mixture was stirred for 16 h at room temperature. The polymer was removed and washed rigorously with toluene, dichloromethane and light petroleum yielding *N*-(PSselenyl)phthalimide **387** (11.90 g, >95%) as a pale yellow resin. The mass change indicated the reaction had occurred, elemental analysis and subsequent reactions proved the reaction was incomplete.

Synthesis of ethyl undecylenate 390

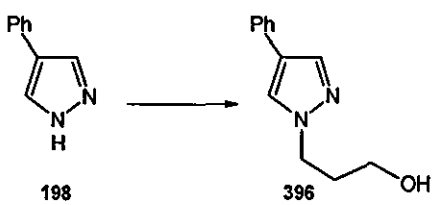


386 391 390

Ethyl undecylenate **390** (0.076 g, 0.39 mmol) was added to a suspension of pre-swollen PS selenyl bromide **386** (0.31 g, 0.39 mmol) in dichloromethane (15 cm^3). The suspension was agitated for 45 min, and the polymer removed. The polymer was washed with dichloromethane and light petroleum before being dried under vacuum. The resultant pale yellow polymer was dried under vacuum to yield the desired alkyl selenide **391** (0.32 g). The theoretical selenide loading accounting for mass change is 0.99 $mmol.g^{-1}$, although the recovery was lower than expected, this may be due to loss of material; υ_{max}(KBr disc)/cm^{-1} 2919 (C-H), 1734 (C=O) and 1028 (C-O).

A suspension of the PS bound ester (0.189 g, 0.19 mmol) in toluene (25 cm^3) was deoxygenated for 30 min, and AIBN (2 mg) and tributyltin hydride (0.72 g, 2.48 mmol) was added to it. The reaction mixture was heated at reflux for 4 h, cooled to room temperature and the polymer washed with dichloromethane, light petroleum and methanol. The crude reaction mixture was evaporated to dryness and purified by column chromatography to yield the crude olefin (0.187 mmol, ~98% by NMR). ^{1}H NMR spectrum and TLC matched that of an authentic sample.

Synthesis of 3-(4-phenyl-1*H*-pyrazol-1-yl)-1-propanol 396

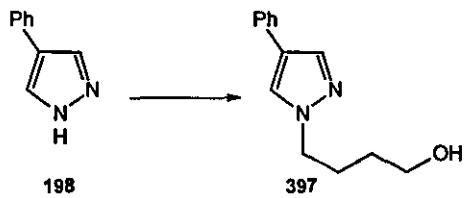


198 396

4-Phenyl-1*H*-pyrazole **198** (0.30 g, 2.1 mmol) was added to a vigorously stirred suspension of potassium hydroxide (0.35 g, 6.3 mmol) in DMF (15 cm^3) at 0 °C and the reaction mixture was stirred for 30 min. 3-Bromopropan-1-ol (0.23 cm^3, 2.5 mmol) was added in one portion and stirring was maintained for 45 min. The reaction mixture was poured onto ice-water and

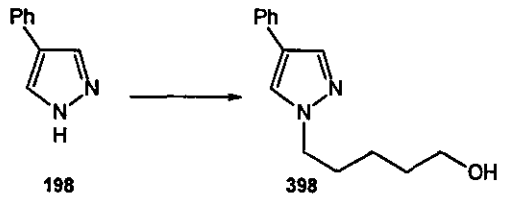
extracted twice with ethyl acetate. The combined organic extracts were washed with water and twice with brine, dried and evaporated to dryness to yield 3-(4-phenyl-1*H*-pyrazol-1-yl)-1-propanol **396** (0.40 g, 94%) as a white solid, mp 116-117 °C; (Found: M^+, 202.1105. $C_{12}H_{14}N_2O$ requires 202.1106); υ_{max}(KBr disc)/cm^{-1} 3349 (O-H), 1606 (C=C) and 1062 (C-O); δ_H(400 MHz) 2.06-2.13 (2 H, m, 2-H), 3.06 (1 H, b, OH), 3.62 (2 H, b, 3-H), 4.32 (2 H, t, *J* 6.4, 1-H), 7.20-7.25 (1 H, m, phenyl 4-H), 7.33-7.37 (2 H, m, phenyl 3,5-H), 7.45-7.48 (2 H, m, phenyl 2,6-H), 7.65 (1 H, d, *J* 0.8, pyrazole 3-H) and 7.77 (1 H, d, *J* 0.8, pyrazole 5-H); δ_C 32.84 (2-C), 49.22 (1-C), 59.35 (3-C), 123.00 (pyrazole 4-C), 125.48 (phenyl 2,6-C), 126.37 (phenyl 4-C), 126.56 (pyrazole 3-C), 128.85 (phenyl 3,5-C), 132.43 (phenyl 1-C) and 136.77 (pyrazole 5-C); *m/z* 202 (M^+, 37%), 157 (100) and 144 (29).

Synthesis of 4-(4-phenyl-1*H*-pyrazol-1-yl)-1-butanol 397



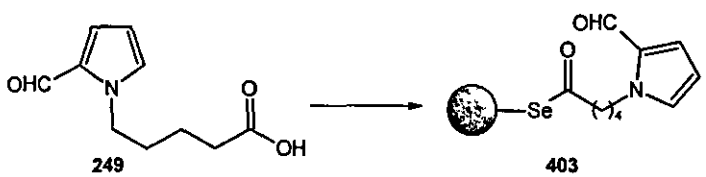
4-Phenyl-1*H*-pyrazole **198** (0.30 g, 2.1 mmol) was added to a vigorously stirred suspension of potassium hydroxide (0.35 g, 6.3 mmol) in DMF (15 cm^3) at 0 °C and the reaction mixture was stirred for 30 min. 4-Chlorobutan-1-ol (0.25 cm^3, 2.5 mmol) was added in one portion and stirring was maintained for 45 min. The reaction mixture was poured onto ice-water and extracted twice with ethyl acetate. The combined organic extracts were washed with water and twice with brine, dried and evaporated to dryness to yield 4-(4-phenyl-1*H*-pyrazol-1-yl)-1-butanol **397** (0.40 g, 88%) as a white solid, mp 84-86 °C; (Found: M^+, 216.1264. $C_{13}H_{16}N_2O$ requires 216.1263); υ_{max}(KBr disc)/cm^{-1} 3363 (O-H), 1607 (C=C), 1071 (C-O) and 761 (aromatic o.o.p. deformations); δ_H(400 MHz) 1.56-1.60 (2 H, m, 3-H), 1.98-2.03 (2 H, m, 2-H), 3.67 (2 H, t, *J* 6.4, 4-H), 4.19 (2 H, t, *J* 6.8, 1-H), 7.19-7.24 (1 H, m, phenyl 4-H), 7.32-7.38 (2 H, m, phenyl 3,5-H), 7.43-7.47 (2 H, m, phenyl 2,6-H), 7.63 (1 H, s, pyrazole 3-H) and 7.77 (1 H, s, pyrazole 5-H); δ_C 26.93 (2-C), 29.52 (3-C), 52.02 (1-C), 61.99 (4-C), 122.90 (pyrazole 4-C), 125.45 (phenyl 2,6-C), 126.06 (pyrazole 3-C), 126.38 (phenyl 4-C), 128.83 (phenyl 3,5-C), 132.56 (phenyl 1-C) and 136.56 (pyrazole 5-C); *m/z* 216 (M^+, 33%) and 144 (100).

Synthesis of 5-(4-phenyl-1*H*-pyrazol-1-yl)-1-pentanol 398



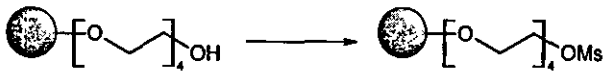
4-Phenyl-1*H*-pyrazole **198** (0.30 g, 2.1 mmol) was added to a vigorously stirred suspension of potassium hydroxide (0.35 g, 6.3 mmol) in DMF (15 cm^3) at 0 °C and the reaction mixture was stirred for 30 min. 5-Chloropentan-1-ol (0.31 g, 2.5 mmol) was added in one portion and stirring was maintained for 45 min. The reaction mixture was poured onto ice-water and extracted twice with ethyl acetate. The combined organic extracts were washed with water and twice with brine, dried and evaporated to dryness to yield 5-(4-phenyl-1*H*-pyrazol-1-yl)-1-pentanol **398** (0.47 g, 97%) as a white solid, mp 61-63 °C; (Found: M^+, 230.1419. $C_{14}H_{18}N_2O$ requires 230.1419); υ_{max}(KBr disc)/cm^{-1} 3357 (O-H), 1607 (C=C) and 760, 695 (aromatic o.o.p. deformations); δ_H(400 MHz) 1.35-1.42 (2 H, m, 3-H), 1.55-1.62 (2 H, m, 4-H), 1.87-1.94 (2 H, m, 2-C), 3.61 (2 H, t, *J* 6.4, 5-H), 4.12 (2 H, t, *J* 7.2, 1-H), 7.18-7.24 (1 H, m, phenyl 4-H), 7.32-7.36 (2 H, m, phenyl 3,5-H), 7.42-7.45 (2 H, m, phenyl 2,6-H), 7.60 (1 H, s, pyrazole 3-H) and 7.76 (1 H, s, pyrazole 5-H); δ_C 22.87 (3-C), 30.10 (2-C), 32.07 (4-C), 52.21 (1-C), 62.19 (5-C), 122.81 (pyrazole 4-C), 125.43 (phenyl 2,6-C), 126.05 (pyrazole 3-C), 126.33 (phenyl 4-C), 128.83 (phenyl 3,5-C), 132.58 (phenyl 1-C) and 136.48 (pyrazole 5-C); *m/z* 230 (M^+, 28%), 199 (20), 157 (100), 144 (84) and 84 (71).

PS bound phenyl 5-(2-formyl-1*H*-pyrrol-1-yl)pentaneselenoate 403



5-(2-Formyl-1*H*-pyrrol-1-yl)pentanoic acid **249** (0.53 g, 2.7 mmol) was added to a stirred suspension of PS selenyl bromide **386** (0.50 g, 1.8 mmol/g) in dichloromethane (15 cm^3) at –30 °C. Tributylphosphine (0.44 cm^3, 1.8 mmol) in dichloromethane (5 cm^3) was added over 5 min directly into the suspension. The suspension was stirred slowly for 48 h and the polymer was collected by filtration. The polymer was washed twice alternately with dichloromethane and ethyl acetate. The PS bound acyl selenide **403** was dried under vacuum. Elemental analysis indicated lower yield than anticipated.

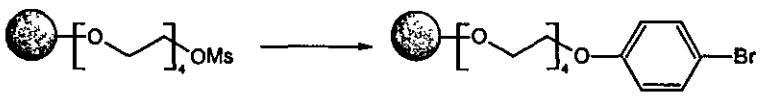
Synthesis of quadragel mesylate 425



412 425

Quadragel **412** (0.974 g, 2.0 mmol) was swollen in pyridine (20 cm^3) and cooled to 0 °C. Mesyl chloride (0.78 cm^3, 10.0 mmol) was added over 5 min and the agitated suspension was allowed to warm to room temperature. The reaction was quenched with aqueous THF after 2 h and the resin removed by filtration and washed with aqueous THF, THF and methanol. The resin was dried in vacuo overnight to yield quadragel mesylate **425** (1.125 g, 100%) as an off-white polymer; (Found: C, 62.9; H, 7.05; S, 6.75%); υ_{max}(thin film)/cm^{-1} 2925, 2853 (C-H), 1609 (C=C), 1353, 1174 (SO_2) and 1109 (C-O); δ_H 1.36-2.05 (b, PS-CH_n), 3.04 (3 H, s, b, SO_2*Me*), 3.66-4.02 (b, OCH_2), 4.35 (2 H, b, CH_2OMs) and 6.56-7.04 (b, phenyl-H); δ_C 37.55 (SO_2*Me*), 39.43-44.32 (phenyl-CH_n), 67.18 (CH_2OMs), 68.87-70.48 (OCH_2), 113.91 (phenyl 2,6-C) and 125.53-127.92 (phenyl *C*H).

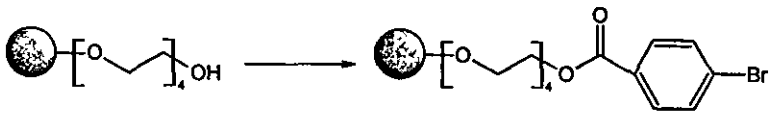
Synthesis of quadragel 4-bromo phenyl ether 429



425 429

Quadragel mesylate **425** (0.910 g, 1.70 mmol) was swollen in DMF (20 cm^3) and 4-bromophenol (1.25 g, 7.2 mmol), potassium iodide (1.20 g, 7.2 mmol) and potassium carbonate (1.00 g, 7.2 mmol) were added and the suspension was heated at 60 °C for 48 h. The reaction was quenched with aqueous THF and the resin was washed with DMF, water, aqueous THF, THF/DCM/Methanol alternately with a final washing of DCM. The resin was dried under vacuum to give quadragel 4-bromo phenyl ether **429** (1.01 g, 100%) as a pale brown resin (1.60 mmol g^{-1}); υ_{max}(thin film)/cm^{-1} 2920 (C-H), 1608 (C=C), 1111 (C-O) and 826 (aromatic o.o.p. deformations); δ_H 1.56-1.79 (b, PS-CH_n), 3.71-3.95 (b, OCH_2), 4.30 (2 H, b, CH_2OPhBr) and 6.78-7.76 (b, phenyl-H); δ_C 39.73-44.58 (phenyl-CH_n), 67.48 (phenyl'-OCH_2), 67.88 (phenyl'-OCH_2CH_2), 69.86-70.90 (OCH_2), 113.21 (phenyl'4-C), 114.32 (phenyl 4-C), 116.70 (phenyl' 2,6-C), 128.40 (phenyl *C*H), 132.46 (phenyl' 3,5-*C*) and 158.13 (phenyl' 1-*C*).

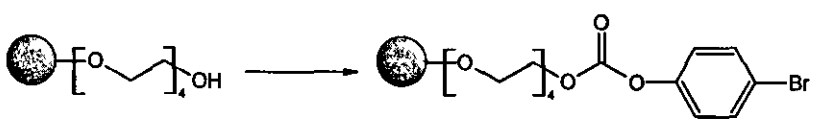
Synthesis of quadragel bound 4-bromobenzoate 430



412 430

Quadragel **412** (2.00 g, 4.2 mmol) was swollen in dichloromethane (20 cm^3) and triethylamine (1.2 cm^3, 8.4 mmol) was added. 4-Bromobenzoylchloride (1.84 g, 8.40 mmol) was added and the mixture was agitated for 2 h, filtered and washed with aqueous THF and THF/DCM/methanol alternately. The washed resin was dried under vacuum to yield the resin bound 4-bromobenzoate **430** (2.66 g, 97%) as a colourless resin (1.58 $mmol.g^{-1}$); υ_{max}(thin film)/cm^{-1} 2920 (C-H), 1721 (C=O), 1609 (C=C), 1245, 1104 (C-O) and 829 (aromatic o.o.p. deformations); δ_H 1.34-1.84 (b, PS-CH_n), 3.67-4.00 (b, OCH_2), 4.45 (2 H, b, CH_2OCOPhBr), 7.55 (phenyl 3,5-H) and 7.90 (b, phenyl 2,6-H).

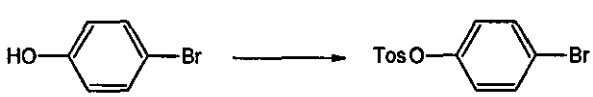
Synthesis of quadragel bound 4-bromophenol *via* carbonate linker 431



412 431

Quadragel **412** (2.00 g, 4.2 mmol) was swollen in dichloromethane (20 cm^3) and triethylamine (1.2 cm^3, 8.4 mmol) was added. 4-Bromophenylchloroformate (1.98 g, 8.40 mmol) was added and the mixture was agitated for 2 h, filtered and washed with aqueous THF and THF/DCM/methanol alternately. The washed resin was dried under vacuum to yield the resin bound 4-bromobenzoate **431** (2.800 g, 97%) as a colourless resin (1.48 $mmol.g^{-1}$); υ_{max}(thin film)/cm^{-1} 2920 (C-H), 1766 (C=O), 1608 (C=C), 1244, 1110 (C-O) and 827 (aromatic o.o.p. deforamtions); δ_H 1.37-1.85 (b, PS-CH_n), 3.42-3.68 (b, OCH_2), 4.38 (2 H, b, CH_2OCO$_2$PhBr), 7.06 (phenyl 3,5-H) and 7.47 (b, phenyl 2,6-H); δ_C 39.53-40.35 (phenyl-CH_n), 61.57-72.71 (OCH_2), 114.12 (phenyl 4-C), 122.85 (phenyl 2,6-C), 128.04 (phenyl *C*H) and 132.50 (phenyl 3,5-C).

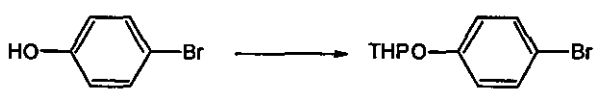
Synthesis of toluene-4-sulfonic acid 4-bromo-phenyl ester 421



423 421

4-Bromophenol **423** (25.00 g, 145 mmol) was added to a stirred suspension of sodium hydroxide (23.2 g, 0.58 mol) in dichloromethane (200 cm^3). The reaction mixture was cooled to 0 °C, stirred for 10 min and tosyl chloride (29.74 g, 156 mmol) was added over 20 min. After 30 min at 0 °C the reaction mixture was allowed to warm to room temperature and stirring was maintained overnight. The reaction was quenched with water, extracted with dichloromethane and the combined extracts washed until neutral, dried and evaporated to dryness, yielding toluene-4-sulfonic acid 4-bromo-phenyl ester **421** (35.8 g, 60%) as an off-white solid, (Found: M^+, 325.9617. $C_{13}H_{11}BrO_3S$ requires 325.9612); υ_{max}(KBr disc)/cm^{-1} 1654, 1481, 1376 and 1157; δ_H(400 MHz) 2.45 (3 H, s, Me), 6.84-6.88 (2 H, m, phenyl 2,6-H), 7.37 (2 H, s, br, tolyl 2,6-H), 7.38-7.42 (2 H, m, phenyl 3,5-H) and 7.68-7.71 (2 H, m, tolyl 3,5-H); δ_C 21.72 (Me), 120.56 (phenyl 4-C), 124.16 (phenyl 2,6-C), 128.52 (tolyl 3,5-C), 129.87 (tolyl 2,6-C), 132.03 (tolyl 1-C), 132.71 (phenyl 3,5-C), 145.66 (tolyl 4-C) and 148.62 (phenyl 1-C); *m/z* 326 (M^+, 16%), 155 (68) and 91 (100).

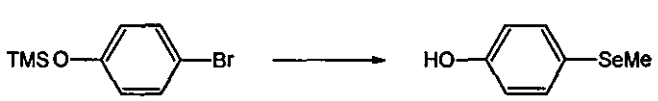
Synthesis of 2-(4-bromo-phenoxy)tetrahydropyran 424[169]



423 424

4-Bromophenol **423** (90 g, 520 mmol) and a catalytic amount of tosic acid (2-3 small crystals) were added to an excess of dihydropyran (400 cm^3) at room temperature and the reaction mixture was stirred for 2 h. The reaction was quenched by the addition of 5% aqueous sodium hydroxide solution (300 cm^3) and extracted with ether. The combined organic layers were washed twice with water, dried (Na_2SO_4) and evaporated to dryness to yield 2-(4-bromo-phenoxy)tetrahydropyran **424** (134.5 g, 100%) as a white solid; (Found: M^+, 256.0097. $C_{11}H_{13}BrO_2$ requires 256.0099); υ_{max}(KBr)/cm^{-1} 2945, 2870 (C-H) and 1238, 1116 (C-O); δ_H(400 MHz) 1.58-1.69 (3 H, m, 4,5-H), 1.82-1.85 (2 H, m, 3,4-H), 1.97-2.04 (1 H, m, 3-H), 3.56-3.60 (1 H, m, 6-H), 3.83 (1 H, m, 6-H), 5.35-5.36 (1 H, m, 2-H), 6.91-6.95 (2 H, m, phenyl 2,6-H) and 7.33-7.37 (2 H, m, phenyl 3,5-H); δ_C 19.04 (4-C), 25.53 (5-C), 30.64 (3-C), 62.36 (6-C), 96.87 (2-C), 114.20 (phenyl 4-C), 118.70 (phenyl 2,6-C), 132.58 (phenyl 3,5-C) and 156.58 (phenyl 1-C); *m/z* 256 (M^+, 9%), 174 (40), 172 (40), 145 (10) and 85 (100).

Synthesis of 4-methylselenyl-phenol 420



416 420

(4-Bromophenoxy)trimethylsilane **416** (10.00 g, 40.8 mmol) was dissolved in THF (20 cm^3) and 2 cm^3 was added to magnesium (1.27 g, 52.4 mmol) in a three necked flask fitted with reflux condenser and potassium hydroxide scrubbing train. A single crystal of iodine was added to the stirred suspension and heated gently until reflux was self-sustaining, the remainder of the THF solution was added dropwise to maintain reflux. The suspension was heated under reflux for 45 min, cooled to room temperature and grey selenium powder (3.06 g, 38.8 mmol) was added in one portion. The dark suspension was then heated under reflux for a further 3 h, cooled to 0 °C and quenched cautiously with saturated ammonium chloride solution. The mixture was filtered through celite and the solid was washed with saturated ammonium chloride and ether, the ether layer was separated and the aqueous layer extracted twice with ether, washed with brine, dried and evaporated to dryness to yield a viscous orange oil (6.21 g) which solidified on standing. NMR spectroscopic analysis indicated noticeable desilylation had occurred.

Sodium borohydride (74 mg, 1.96 mmol) was added slowly to a stirred solution of the crude diselenide (0.40 g) in ethanol (50 cm^3) at 0 °C. The solution was stirred for 30 min and iodomethane (0.23 g, 1.62 mmol) was added, stirring was maintained at room temperature for 16 h, evaporated to dryness and treated with hydrochloric acid (2 M, 10 cm^3). The aqueous layer was extracted three times with diethyl ether, washed with aqueous sodium carbonate and brine, dried and evaporated to dryness, yielding 4-methylselenyl phenol **420** (0.25 g, 51%) as an off-white solid; (Found: M^+, 187.9741. C_7H_8OSe requires 187.9740); υ_{max}(KBr disc)/cm^{-1} 3386 (O-H), 2950 (C-H), 1251 (C-O) and 817 (aromatic o.o.p. deformations); δ_H 2.30 (3 H, s, Me), 4.88 (1 H, s, OH), 6.73-6.78 (2 H, m, phenyl 2,6-H) and 7.34-7.39 (2 H, m, phenyl 3,5-H); δ_C 8.72 (Me), 116.27 (phenyl 2,6-C), 121.70 (phenyl 4-C), 133.66 (phenyl 3,5-C) and 154.69 (phenyl 1-C); *m/z* 188 (M^+, 71%), 173 (71) and 151 (100).

Synthesis of 4-(tetrahydroselenophen-1-yl)-phenol chloride 442

416 442

(4-Bromophenoxy)trimethylsilane **416** (9.00 g, 36.7 mmol) was dissolved in THF (20 cm^3) and 2 cm^3 was added to magnesium (1.14 g, 47.0 mmol) in a three necked flask fitted with reflux condenser and potassium hydroxide scrubbing train. A single crystal of iodine was added to the stirred suspension and heated gently until reflux was self-sustaining, the remainder of the THF solution was added dropwise to maintain reflux. The suspension was heated under reflux for 45 min, cooled to room temperature and grey selenium powder (2.75 g, 34.9 mmol) was added in

one portion. The dark suspension was then heated under reflux for a further 3 h, cooled to 0 °C and quenched cautiously with saturated ammonium chloride solution. The mixture was filtered through celite and the solid was washed with saturated ammonium chloride and ether, the ether layer was separated and the aqueous layer extracted twice with ether, washed with brine, dried and evaporated to dryness to yield a viscous orange oil (6.70 g) which solidified on standing.

Sodium borohydride (0.74 g, 19.6 mmol) was added slowly to a stirred solution of the crude diselenide (4.00 g) in ethanol (250 cm^3) at 0 °C. The solution was stirred for 30 min and 1-chloro-4-iodobutane (4.28 g, 19.6 mmol) was added, stirring was maintained at room temperature for 16 h and treated with hydrochloric acid (2 M, 10 cm^3). The reaction mixture was concentrated to a viscous slurry and the solid was collected, washed with ether and dried under vacuum to yield 4-(tetrahydroselenophen-1-yl)-phenol chloride **442** (0.81 g, 38%) as an off-white solid; (Found: M^+, 229.0129. $C_{10}H_{13}OSe$ requires 229.0132); υ_{max}(KBr disc)/cm^{-1} 1592 (C=C), 1277 (C-O) and 826 (aromatic o.o.p. deoformations); δ_H 2.37-2.50 (4 H, m, $SeCH_2CH_2$), 3.55-3.65 (2 H, m, $SeCH_2$), 3.79-3.90 (2 H, m, $SeCH_2$), 6.97-7.03 (2 H, m, phenyl 2,6-H) and 7.60-7.66 (2 H, m, phenyl 3,5-H); δ_C 32.26 ($SeCH_2CH_2$), 48.69 ($SeCH_2$), 117.36 (phenyl 4-C), 119.20 (phenyl 2,6-C), 133.19 (phenyl 3,5-C) and 163.35 (phenyl 1-C); *m/z* 229 (M^+, 100%).

Synthesis of methylselenyl quadragel 426 (mesylate displacement)

420 426

Quadragel mesylate **420** (1.383 g, 2.60 mmol) was swollen in DMF (30 cm^3) and 4-methylselenylphenol (0.80 g, 4.3 mmol), sodium iodide (1.30 g, 8.7 mmol) and potassium carbonate (1.20 g, 8.7 mmol) were added and the suspension was heated at 60 °C for 30 h. The reaction was quenched with aqueous THF and the resin was washed with DMF, water, aqueous THF, THF/DCM/Methanol alternately with a final washing of DCM. The resin was dried under vacuum to give methyl quadragel **426** (1.69 g, 100%) as a colourless resin (1.54 $mmol.g^{-1}$); υ_{max}(thin film)/cm^{-1} 2916 (C-H) and 1243, 1094 (C-O); δ_H 2.26 (SeMe), 3.32-3.80 (CH_2O) and 7.63-8.19 (phenyl-H); δ_C 8.56 (SeMe), 67.49-71.92 (CH_2-O), 115.53 (phenyl 2,6-C), 116.27 (phenyl 4-C) and 133.23 (phenyl 3,5-C).

Synthesis of quadragel 4-phenoxyselenyl bromide 413

426 413

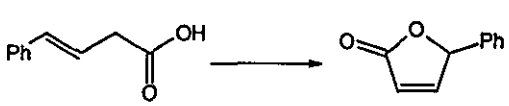
4-Methylselenylphenoxy quadragel **426** (2.55 g, 3.9 mmol) was swollen in chloroform (50 cm^3) and cooled to 0 °C. Bromine (0.67 g, 3.9 mmol) was added in chloroform (2 cm^3) and the mixture was agitated for 10 min, warmed to room temperature and the resin was collected by filtration. Some of the resin beads were already turning dark red/brown following the elimination of methyl bromide. The resin was swollen in ethanol and heated at reflux for 1 h. The resultant dark red resin was collected by filtration and washed with water/THF (1:1), THF, DCM and methanol. The resin was dried at the pump prior to drying overnight under vacuum to yield quadragel 4-phenoxyselenyl bromide **413** (2.806 g, 100%) as a dark red resin (1.40 $mmol.g^{-1}$); (Found: Br, 10.5; Se, 8.4%) elemental analysis indicates approximately 1.25 $mmol.g^{-1}$; υ_{max}(thin film)/cm^{-1} 2920 (C-H) and 1247, 1108 (C-O); δ_H 3.71 (CH_2O) and 6.89-7.81 (phenyl-H); δ_C 62.11-71.06 (*C*H_2-O), 116.16 (phenyl 2,6-C) and 139.54 (phenyl 3,5-C).

Synthesis of 5-ethyl-5*H*-furan-2-one 435

435

trans-3-Hexenoic acid (3.42 g, 30 mmol) was dissolved in acetonitrile (35 cm^3) and ammonium persulfate (13.69 g, 60 mmol) and quadragel 4-phenoxyselenyl bromide (0.10 g, 0.14 mmol) was added. The reaction was stirred at 65 °C for 72 h and cooled to room temperature. The crude reaction mixture was filtered through celite and evaporated to dryness to yield 5-ethyl-5*H*-furan-2-one **435** (3.40 g, 100%) as a colourless oil; (Found: M^+, 112.0522. $C_8H_8O_2$ requires 112.0524); υ_{max}(thin film)/cm^{-1} 2974, 2939 (C-H), 1747 (C=O), 1462 and 1165; δ_H 1.02 (3 H, t, *J* 7.5, CH_2CH_3), 1.71-1.89 (2 H, m, CH_2CH_3), 5.01-5.05 (1 H, m, 5-H), 6.13 (1 H, dd, *J* 5.7. 2.1, 3-H) and 7.49 (1 H, dd, *J* 5.7, 1.4, 4-H); δ_C 7.12 (CH_2CH_3), 24.36 (*CH2*CH3), 82.55 (5-C), 119.79 (3-C), 154.35 (4-C) and 171.46 (2-C); *m/z* 112 (M^+, 8%) and 83 (100).

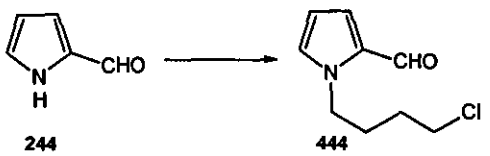
Synthesis of 5-phenyl-5*H*-furan-2-one 436



436

trans-Styrylacetic acid (4.87 g, 30 mmol) was dissolved in acetonitrile (35 cm^3) and ammonium persulfate (13.69 g, 60 mmol) and quadragel 4-phenoxyselenyl bromide (0.02 g, 0.03 mmol) was added. The reaction was stirred at 65 °C for 72 h and cooled to room temperature. The crude reaction mixture was filtered through celite and evaporated to dryness to yield 5-ethyl-5*H*-furan-2-one **436** (4.87 g, 100%) as a colourless oil; (Found: M^+, 160.0525. $C_{10}H_8O_2$ requires 160.0524); υ_{max}(thin film)/cm^{-1} 1753 (C=O), 1159, 1030, 853 and 701 (aromatic o.o p deformations); δ_H 6.01-6.02 (1 H, m, 5-H), 6.22 (1 H, m, 3-H), 7.25-7.29 (2 H, m, phenyl-H), 7.37-7.40 (3 H, m, phenyl-H) and 7.54 (1 H, m, 4-H); δ_C 82.57 (5-C), 119.02 (3-C), 124.66 (phenyl 2,6-C), 126.94 (phenyl 3,5-C), 127.18 (phenyl 4-C), 132.31 (phenyl 1-C), 154.16 (4-C) and 171.37 (2-C); *m/z* 160 (M^+, 59%), 131 (94), 115 (40), 105 (100) and 77 (64).

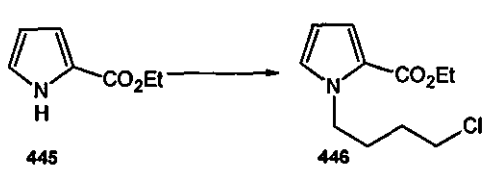
Synthesis of 1-(4-chlorobutyl)-1*H*-pyrrole-2-carbaldehyde 444



244 444

Pyrrole-2-carbaldehyde **244** (0.30 g, 3.2 mmol) was added to a vigorously stirred suspension of potassium hydroxide (0.54 g, 9.6 mmol) in DMF (15 cm^3) at 0 °C and the reaction mixture was stirred for 30 min. 1-Chloro-4-iodobutane (1.40 g, 6.4 mmol) was added in one portion and stirring was maintained for 10 h. The reaction mixture was poured onto ice-water and extracted twice with ethyl acetate. The combined organic extracts were washed with water and twice with brine, dried and evaporated to dryness to yield a coloured oil. Purification by column chromatography yielded 1-(4-chlorobutyl)-1H-pyrrole-2-carbaldehyde **444** (0.54 g, 94%) as a pale yellow oil; (Found: M^+, 185.0606. $C_9H_{12}ClNO$ requires 185.0607); υ_{max}(KBr disc)/cm^{-1} 1666 (C=O); δ_H(400 MHz) 1.74-1.80 (2 H, m, 3-H), 1.88-1.94 (2 H, m, 2-H), 3.52 (2 H, t, *J* 6.4, 4-H), 4.34 (2 H, t, *J* 7.0, 1-H), 6.22-6.24 (1 H, m, pyrrole 4-H), 6.92-6.96 (2 H, m, pyrrole 3,5-H) and 9.53 (1 H, d, *J* 0.9, CHO); δ_C 28.77 (3-C), 29.47 (2-C), 44.39 (4-C), 48.24 (1-C), 109.76 (pyrrole 4-C), 125.01 (pyrrole 5-C), 131.20 (pyrrole 2-C), 131.35 (pyrrole 3-C) and 179.34 (CHO); *m/z* 185 (M^+, 63%), 156 (39), 122 (100), 108 (53) and 94 (54).

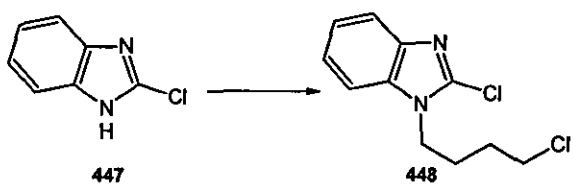
Synthesis of 1-(4-chlorobutyl)-1*H*-pyrrole-2-carboxylic acid ethyl ester 446



445 446

Ethyl pyrrole-2-carboxylate **445** (0.45 g, 3.2 mmol) was added to a vigorously stirred suspension of potassium hydroxide (0.54 g, 9.6 mmol) in DMF (15 cm^3) at 0 °C and the reaction mixture was stirred for 30 min. 1-Chloro-4-iodobutane (1.40 g, 6.4 mmol) was added in one portion and stirring was maintained for 10 h. The reaction mixture was poured onto ice-water and extracted twice with ethyl acetate. The combined organic extracts were washed with water and twice with brine, dried and evaporated to dryness to yield a coloured oil. Purification by column chromatography yielded 1-(4-chlorobutyl)-1*H*-pyrrole-2-carboxylic acid ethyl ester **446** (0.60 g, 78%) as a pale yellow oil. (Found: M^+, 229.0873. $C_{11}H_{16}ClNO_2$ requires 229.0870); υ_{max}(KBr disc)/cm^{-1} 1698 (C=O); δ_H(400 MHz) 1.34 (3 H, t, *J* 7.2, $CO_2CH_2CH_3$), 1.74-1.80 (2 H, m, 3-H), 1.89-2.04 (2 H, m, 2-H), 3.52 (2 H, t, *J* 6.5, 4-H), 4.27 (2 H, q, *J* 7.2, $CO_2CH_2CH_3$), 4.34 (2 H, t, *J* 6.9, 1-H), 6.11-6.13 (1 H, m, pyrrole 4-H), 6.82-6.83 (1 H, m, pyrrole 3-H) and 6.95-6.96 (1 H, m, pyrrole 5-H); δ_C 14.44 ($CO_2CH_2CH_3$), 29.03 (3-C), 29.67 (2-C), 44.48 (4-C), 48.34 (1-C), 59.79 ($CO_2CH_2CH_3$), 108.04 (pyrrole 4-C), 118.19 (pyrrole 5-C), 121.19 (pyrrole 2-C), 128.49 (pyrrole 3-C) and 161.13 (CO_2); *m/z* 229 (M^+, 40%), 194 (91), 184 (31), 156 (100), 124 (56) and 94 (64).

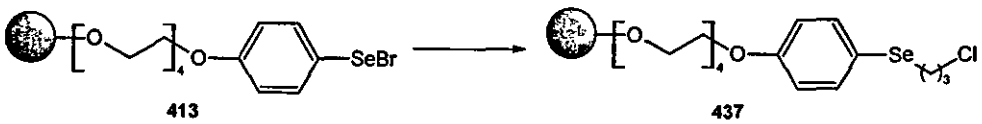
Synthesis of 2-chloro-1-(4-chlorobutyl)-1*H*-benzimidazole 448



447 448

2-Chlorobenzimidazole **447** (0.48 g, 3.2 mmol) was added to a vigorously stirred suspension of potassium hydroxide (0.54 g, 9.6 mmol) in DMF (15 cm^3) at 0 °C and the reaction mixture was stirred for 30 min. 1-Chloro-4-iodobutane (1.40 g, 6.4 mmol) was added in one portion and stirring was maintained for 10 h. The reaction mixture was poured onto ice-water and extracted twice with ethyl acetate. The combined organic extracts were washed with water and twice with brine, dried and evaporated to dryness to yield a coloured oil. Purification by column chromatography yielded 2-chloro-1-(4-chlorobutyl)-1*H*-benzimidazole **448** (0.74 g, 95%) as a colourless oil. (Found: M^+, 229.0873. $C_{11}H_{16}ClNO_2$ requires 229.0870); υ_{max}(KBr disc)/cm^{-1} 2955 (C-H), 1470 (C-H deformations), 1377, 745 (aromatic o.o.p. deformations); δ_H(400 MHz) 1.81-1.86 (2 H, m, 3-H), 1.98-2.03 (2 H, m, 2-H), 3.54 (2 H, t, *J* 6.2, 4-H), 4.22 (2 H, q, *J* 7.1, 1-H), 7.26-7.31 (3 H, m, aromatic-H) and 7.68-7.71 (1 H, m, aromatic-H); δ_C 27.09 (3-C), 29.84 (2-C), 44.13 (4-C), 44.47 (1-C), 109.72 (benzimidazole 7-C), 119.95 (benzimidazole 6-C), 123.14 (benzimidazole 5-C), 123.63 (benzimidazole 4-C), 135.29 (benzimidazole 3a-C), 140.77 (benzimidazole 7a-C) and 142.15 (benzimidazole 2-C); *m/z* 242 (M^+, 59%), 165 (100), 152 (20) and 129 (21).

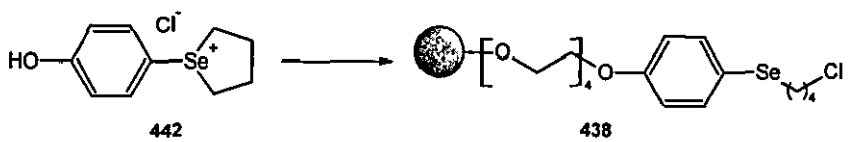
Synthesis of 4-(3-chloropropylselenyl)phenoxy quadragel 437



413 437

Quadragel 4-phenoxyselenyl bromide **413** (0.50 g, 0.70 mmol) was swollen in ethanol/THF (1:4, 25 cm^3) and sodium borohydride (0.12 g, 3.20 mmol) was added. The reaction mixture was agitated for one hour and 1-chloro-3-iodopropane (0.65 g, 3.20 mmol) was added. The reaction was agitated for 24 h and quenched by the addition of water, the resin was collected by filtration and washed with aqueous THF, THF, DCM and methanol. The resin was dried at the pump for 30 min and then thoroughly dried under vacuum overnight to yield 4-(3-chloropropylselenyl)phenoxy quadragel **437** (0.50 g, 100%) as a yellow resin (1.40 $mmol.g^{-1}$); υ_{max}(thin film)/cm^{-1} 2915 (C-H) and 1245, 1105 (C-O); δ_C 25.97 (2-C), 32.99 (1-C), 44.73 (3-C), 67.87-70.05 (CH_2-O), 115.96 (phenyl 2,6-C) and 136.16 (phenyl 3,5-C).

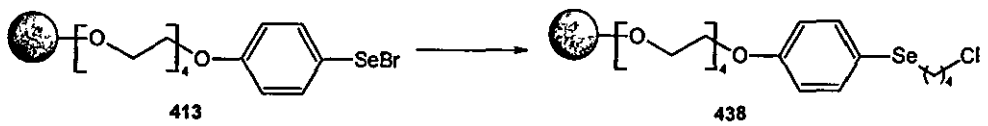
Synthesis of 4-(4-chlorobutylselenyl)phenoxy quadragel 438 (mesylate method)



442 438

Quadragel mesylate **425** (0.800 g, 1.47 mmol) was swollen in DMF (10 cm^3) and 4-tetrahydroselenoniumphenol chloride **442** (0.66 g, 2.50 mmol) and potassium carbonate (0.69 g, 5.00 mmol) were added and the suspension was heated at 60 °C for 48 h. The reaction was quenched with aqueous THF and the resin was washed with DMF, water, aqueous THF and THF/DCM/methanol alternately with a final washing of DCM. The resin was dried under vacuum to give 4-(4-chlorobutylselenyl)phenoxy quadragel **438** (1.16 g, 100%) as a colourless resin (1.38 $mmol.g^{-1}$). Slightly greater mass than expected indicates some ion exchange may have occurred; υ_{max}(KBr disc)/cm^{-1} 2925 (C-H) and 1243, 1111 (C-O); δ_H 1.84 (4 H, b, 2,3-H), 2.85 (2 H, b, 1-H), 3.72-4.33 (b, PEG and 4-H), 6.78 (2 H, b, phenyl 2,6-H) and 7.45 (2 H, b, phenyl 3,5-H); δ_C 26.66 (2-C), 28.57 (3-C), 29.11 (1-C), 44.37 (4-C), 115.29 (phenyl 2,6-C), 119.71 (phenyl 4-C), 135.60 (phenyl 3,5-C) and 158.62 (phenyl 1-C).

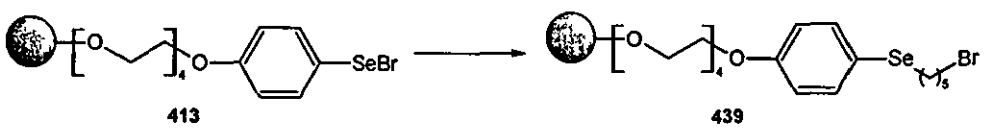
Synthesis of 4-(4-chlorobutylselenyl)phenoxy quadragel 438 (from selenyl bromide)



413 438

Quadragel 4-phenoxyselenyl bromide **413** (1.27 g, 1.8 mmol) was swollen in ethanol/THF (1:1, 40 cm^3) and lithium borohydride (2.0 M, 4.0 cm^3) was added. The reaction mixture was agitated for one hour and 1-chloro-4-iodobutane (2.18 g, 10 mmol) was added. The reaction was agitated for 24 h and quenched by the addition of water, the resin was collected by filtration and washed with aqueous THF, THF, DCM and methanol. The resin was dried at the pump for 30 min and then thoroughly dried under vacuum overnight to yield 4-(4-chlorobutylselenyl)phenoxy quadragel **438** (1.24 g, 95%) as a pale yellow resin (1.38 $mmol.g^{-1}$); data matched that of the alternate synthetic route.

Synthesis of 4-(5-bromopentylselenyl)phenoxy quadragel 439



413 439

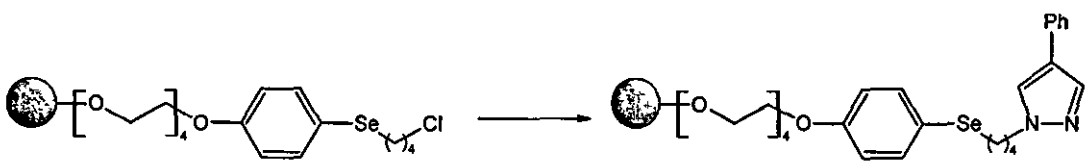
Quadragel 4-phenoxyselenyl bromide **413** (0.50 g, 0.70 mmol) was swollen in ethanol/THF (1:1, 40 cm^3) and sodium borohydride (0.12 g, 3.2 mmol) was added. The reaction mixture was agitated for one hour and 1,5-dibromopentane (0.74 g, 3.2 mmol) was added. The reaction was agitated for 24 h and quenched by the addition of water, the resin was collected by filtration and washed with aqueous THF, THF, DCM and methanol. The resin was dried at the pump for 30 min and then thoroughly dried under vacuum overnight to yield 4-(5-bromopentylselenyl)phenoxy quadragel **439** (0.55 g, 100%) as a yellow resin (1.27 $mmol.g^{-1}$); υ_{max}(KBr disc)/cm^{-1} 2924 (C-H) and 1244, 1126 (C-O); δ_H 1.54 (b, CH_2), 3.35 (b, PEG) and 6.96 (b, phenyl-H); δ_C 28.61 (3-C), 29.01 (2-C), 29.69 (4-C), 32.62 (1-C), 34.12 (5-C), 115.88 (phenyl 2,6-C) and 136.00 (phenyl 3,5-C).

Synthesis of quadragel *N*-propyl-4-phenylpyrazole 440b

437 440b

4-(3-Chloropropylselenyl)phenoxy quadragel **437** (0.46 g, 0.64 mmol) was swollen in DMF (15 cm^3) and 4-phenylpyrazole (0.22 g, 1.5 mmol) and crushed potassium hydroxide (0.09 g, 1.5 mmol) was added. The polymer was agitated for 15 min and potassium iodide (0.17 g, 1.5 mmol) was added. The polymer was agitated at room temperature for 24 h and the resin was collected by filtration, washed with aqueous THF, methanol, THF and DCM. The resin was dried at the pump for 15 min and dried overnight under vacuum to yield the quadragel bound pyrazole **440b** (0.51 g, 100%); (Found: C, 61.7; H, 5.9; N, 1.9%); υ_{max}(KBr disc)/cm^{-1} 2916 (C-H), 1606 (C=C), 1244, 1105 (C-O) and 826 (aromatic o.o.p. deformations); δ_C 25.76 (2-C), 30.91 (3-C), 51.64 (1-C), 67.84-71.09 (CH_2O), 116.03 (phenol 2,6-C), 123.17 (pyrazole 4-C), 125.86 (pyrazole 3-C, phenyl 2,6-C), 126.84 (phenyl 4-C), 129.32 (phenyl 3,5-C), 132.58 (phenyl 1-C), 136.18 (phenol 3,5-C), 137.09 (pyrazole 5-C) and 158.00 (phenol 1-C).

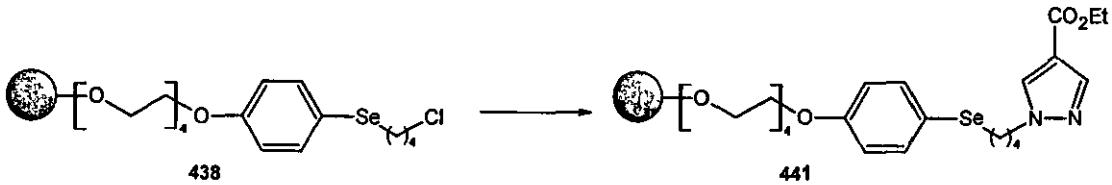
Synthesis of quadragel *N*-butyl-4-phenylpyrazole 443



438 443

4-(4-Chlorobutylselenyl)phenoxy quadragel **438** (1.083 g, 1.50 mmol) was swollen in DMF (15 cm^3) and 4-phenylpyrazole (0.48 g, 3.30 mmol) and crushed potassium hydroxide (0.28 g, 5.0 mmol) was added. The polymer was agitated for 15 min and sodium iodide was added. The polymer was agitated at room temperature for 24 h and the resin was collected by filtration, washed with aqueous THF, methanol, THF and DCM. The resin was dried at the pump for 15 min and dried overnight under vacuum to yield the quadragel bound pyrazole **443** (1.32 g, 100%) as a yellow resin (1.24 mmol.g^{-1}); (Found: C, 62.1; H, 6.5; N, 2.15%); υ_{max}(KBr disc)/cm^{-1}; δ_H 1.82 (4 H, b, 2,3-H), 2.84 (2 H, b, 4-H), 3.66-4.28 (b, PEG and 1-H), 6.76 (2 H, b, phenyl 2,6-H), 7.44 (3 H, b, phenyl 3,5-H and pyrazole 3-H) and 7.76 (pyrazole 5-H); δ_C 26.66 (2-C), 28.57 (3-C), 29.11 (4-C), 51.72 (1-C), 115.27 (phenol 2,6-C), 119.68 (phenol 4-C), 122.82 (pyrazole 4-C), 125.42 (phenyl 2,6-C), 125.85 (pyrazole 3-C), 126.26 (phenyl 4-C), 128.80 (phenyl 3,5-C), 132.61 (phenyl 1-C), 135.59 (phenol 3,5-C), 136.58 (pyrazole 5-C) and 158.66 (phenol 1-C).

Synthesis of quadragel *N*-butyl-ethyl(pyrazole-4-carboxylate) 441



Ethyl pyrazole-4-carboxylate **438** (0.31 g, 2.40 mmol) was added to sodium hydride (0.07 g, 1.8 mmol) in DMF (15 cm^3). The polymer was agitated for 15 min and 4-(4-chlorobutylselenyl)phenoxy quadragel (0.50 g, 0.70 mmol) and potassium iodide (0.30 g, 1.80 mmol) was added. The polymer was agitated at room temperature for 24 h and the resin was collected by filtration, washed with aqueous THF, methanol, THF and DCM. The resin was dried at the pump for 15 min and dried overnight under vacuum to yield the quadragel bound pyrazole **441** (0.56 g, 98%) as a yellow resin (1.22 $mmol.g^{-1}$); (Found: C, 61.85; H, 6.15; N, 1.5%); υ_{max}(KBr disc)/cm^{-1} 2922 (C-H), 1716 (C=O), 1245, 1111 (C-O) and 827 (aromatic o.o.p. deformations); δ_H 1.23-1.92 (m, CH_3 and CH_2), 3.70-4.03 (m, CH_2O and CH_2N) and 7.87-7.98 (m, aromatic-H); δ_C 14.92 (Me), 27.23 (3-C), 28.41 (2-C), 30.25 (4-C), 52.36 (1-C), 60.53 (CO_2CH_2), 67.84-71.15 (CH_2O), 115.96 (pyrazole 4-C, phenol 2,6-C), 132.89 (pyrazole 5-C), 136.06 (phenol 3,5-C), 141.35 (pyrazole 3-C) and 163.35 (CO_2Et).

Synthesis of quadragel *N*-propyl-pyrrole-2-carbaldehyde 440a

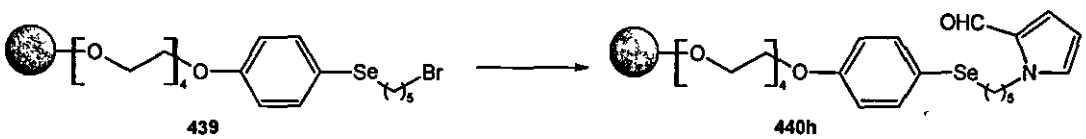
4-(3-Chloropropylselenyl)phenoxy quadragel **437** (0.512 g, 0.72 mmol) was swollen in DMF (15 cm^3) and pyrrole-2-carbaldehyde **244** (0.36 g, 3.75 mmol) and crushed potassium hydroxide (0.21 g, 3.75 mmol) was added. The polymer was agitated for 15 min and potassium iodide (0.62 g, 3.75 mmol) was added. The polymer was agitated at room temperature for 24 h and the resin was collected by filtration, washed with aqueous THF, methanol, THF and DCM. The resin was dried at the pump for 15 min and dried overnight under vacuum to yield quadragel *N*-propyl-pyrrole-2-carbaldehyde **440a** (0.56 g, 100%) as a pale yellow resin; (Found: C, 61.5; H, 6.05; N, 1.15%); υ_{max}(KBr disc)/cm^{-1} 2924, 2852 (C-H), 1648 (C=O) and 1239, 1121 (C-O); δ_C 25.50 (2-C), 31.48 (3-C), 48.58 (1-C), 67.72-70.99 (CH_2O), 109.90 (pyrrole 4-C), 115.80 (phenol 2,6-C), 125.22 (pyrrole 5-C), 131.79 (pyrrole 3-C), 135.72 (phenol 3,5-C) and 179.40 (CHO).

Synthesis of quadragel *N*-butyl-pyrrole-2-carbaldehyde 440d

438 440d

4-(4-Chlorobutylselenyl)phenoxy quadragel **438** (0.506 g, 0.70 mmol) was swollen in DMF (20 cm^3) and potassium iodide (0.66 g, 4.0 mmol), potassium hydroxide (0.22 g, 4.0 mmol) and pyrrole-2-carbaldehyde **244** (0.38 g, 4.0 mmol) was added. The reaction was agitated for 18 h and the resin was collected by filtration and washed with aqueous THF, THF, DCM and methanol. The resin was dried at the pump for 30 min and dried thoroughly overnight under vacuum to yield quadragel *N*-butyl-pyrrole-2-carbaldehyde **440d** (0.544 g, 98%) as a pale yellow resin; (Found: C, 63.9; H, 6.5; N, 0.80%); υ_{max}(KBr disc)/cm^{-1} 2924, 2852 (C-H), 1648 (C=O) and 1239, 1121 (C-O); δ_H 1.67-1.81 (m, CH_2), 2.82 (m, CH_2), 3.72-4.14 (m, OCH_2 and NCH_2), 6.37 (m, pyrrole 4-H), 6.90 (m, pyrrole 3,5-H) and 9.55 (C*H*O); δ_C 28.53 (3-C), 29.93 (2-C), 32.81 (4-C), 50.03 (1-C), 69.06-72.27 (*C*H_2O), 111.26 (pyrrole 4-C), 117.05 (phenol 2,6-C), 126.56 (pyrrole 5-C), 132.90 (pyrrole 3-C), 137.36 (phenol 3,5-C) and 180.85 (CHO).

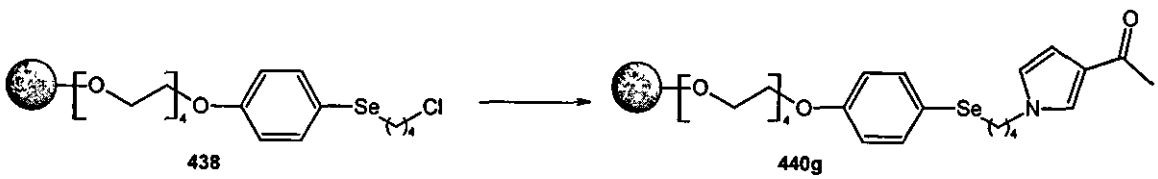
Synthesis of quadragel *N*-pentyl-pyrrole-2-carbaldehyde 440h



439 440h

4-(5-Bromopentylselenyl)phenoxy quadragel **439** (0.384 g, 0.49 mmol) was swollen in DMF (20 cm^3) and potassium iodide (0.42 g, 2.5 mmol), potassium hydroxide (0.14 g, 2.5 mmol)) and pyrrole-2-carbaldehyde **244** (0.24 g, 2.5 mmol) was added. The reaction was agitated for 18 h and the resin was collected by filtration and washed with aqueous THF, THF, DCM and methanol. The resin was dried at the pump for 30 min and dried thoroughly overnight under vacuum to yield quadragel *N*-pentyl-pyrrole-2-carbaldehyde **440h** (0.39 g, 100%) as a pale yellow resin; (Found: C, 62.05; H, 6.2; N, 0.6%); υ_{max}(KBr disc)/cm^{-1} 2926 (C-H), 1653 (C=O) and 1244, 1106 (C-O); δ_H 1.62 (m, CH_2), 4.11 (m, b, CH_2), 6.20 (m, pyrrole 4-H), 6.92 (m, pyrrole 3,5-H) and 9.53 (C*H*O); δ_C 27.81 (3-C), 30.00 (4-C), 31.05 (2-C), 32.07 (5-C), 50.20 (1-C), 68.76-72.03 (*C*H_2O), 110.89 (pyrrole 4-C), 116.81 (phenol 2,6-C), 126.25 (pyrrole 5-C), 132.70 (pyrrole 3-C), 133.50 (pyrrole 2-C), 136.85 (phenol 3,5-C) and 180.52 (CHO).

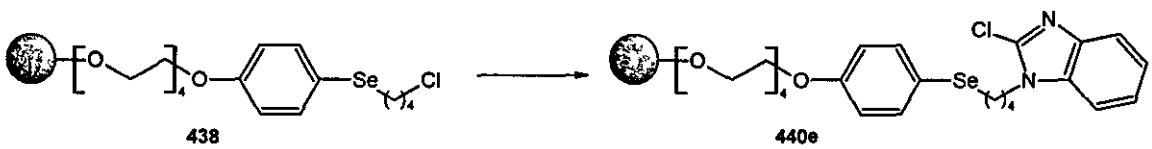
Synthesis of quadragel *N*-butyl-3-acetylpyrrole 440g



438 440g

4-(4-Chlorobutylselenyl)phenoxy quadragel **438** (0.50 g, 0.70 mmol) was swollen in DMF (20 cm^3) and potassium iodide (0.30 g, 1.8 mmol), potassium hydroxide (0.10 g, 1.8 mmol) and 3-acetylpyrrole (0.20 g, 1.8 mmol) was added. The reaction was agitated for 18 h and the resin was collected by filtration and washed with aqueous THF, THF, DCM and methanol. The resin was dried at the pump for 30 min and dried thoroughly overnight under vacuum to yield quadragel *N*-butyl-pyrrole-2-carbaldehyde **440g** (0.548 g, 99%) as a pale yellow resin; (Found: C, 64.9; H, 6.35; N, 0.9%); υ_{max}(KBr disc)/cm^{-1} 2920, 2867 (C-H), 1652 (C=O), 1607 (C=C), 1245, 1107 (C-O) and 826 (aromatic o.o.p. deformations); δ_H 2.27 (m, CH_3), 3.57 (m, CH_2) and 6.75-7.00 (m, aromatic-H); δ_C 27.32 (Me), 27.54 (3-C), 28.53 (2-C), 31.22 (4-C), 49.87 (1-C), 67.87-71.03 (CH_2O), 109.66 (pyrrole 5-C), 115.93 (phenol 2,6-C), 122.69 (pyrrole 4-C), 126.25 (pyrrole 2-C), 136.12 (phenol 3,5-C), 159.29 (phenol 1-C) and 193.72 (C=O).

Synthesis of quadragel *N*-butyl-2-chlorobenzimidazole 440e

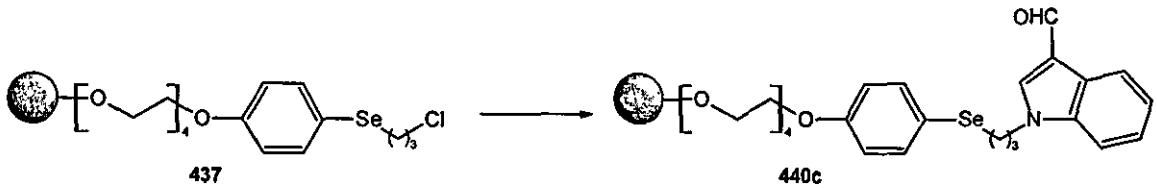


438 440e

4-(4-Chlorobutylselenyl)phenoxy quadragel **438** (0.498 g, 0.70 mmol) was swollen in DMF (20 cm^3) and potassium iodide (0.66 g, 4.0 mmol), potassium hydroxide (0.22 g, 4.0 mmol) and 2-chlorobenzimidazole (0.61 g, 4.0 mmol) was added. The reaction was agitated for 18 h and the resin was collected by filtration and washed with aqueous THF, THF, DCM and methanol. The resin was dried at the pump for 30 min and dried thoroughly overnight under vacuum to yield quadragel *N*-butyl-2-chlorobenzimidazole **440e** (0.580 g, 98%) as a pale yellow resin; (Found: C, 61.0; H, 6.15; N, 1.45%); υ_{max}(KBr disc)/cm^{-1} 2929 (C-H), 1455 (C-H deformations) and 1243, 1106 (C-O); δ_H(400 MHz) 1.83 (m, 2,3-H), 2.79 (m, 4-H), 3.72-4.07 (m, OCH_2 and NCH_2) and 6.17-7.30 (m, aromatic-H); δ_C 28.79 (3-C), 29.95 (2-C), 30.93 (4-C), 45.83 (1-C), 69.33-72.52 (OCH_2 and NCH_2), 111.41 (benzimidazole 7-C), 117.36 (phenol 2.6-C), 121.30 (benzimidazole 6-C), 124.57 (benzimidazole 5-C), 125.07 (benzimidazole 4-C), 136.84 (benzimidazole 3a-C),

137.82 (phenol 3,5-C), 142.31 (benzimidazole 7a-C), 143.56 (benzimidazole 2-C) and 160.48 (phenol 1-C).

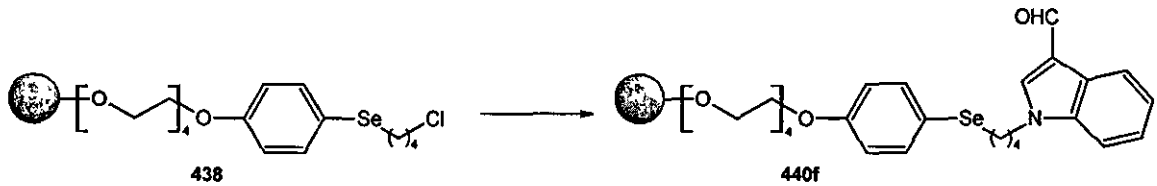
Synthesis of quadragel *N*-propyl-indole-3-carbaldehyde 440c



437 440c

4-(3-Chloropropylselenyl)phenoxy quadragel **437** (0.46 g, 0.64 mmol) was swollen in DMF (15 cm^3) and potassium iodide (0.17 g, 1.5 mmol), potassium hydroxide (0.08 g, 1.5 mmol) and indole-3-carbaldehyde (0.22 g, 1.5 mmol) was added. The reaction was agitated for 18 h and the resin was collected by filtration and washed with aqueous THF, THF, DCM and methanol. The resin was dried at the pump for 30 min and dried thoroughly overnight under vacuum to yield quadragel *N*-propyl-indole-3-carbaldehyde **440c** (0.502 g, 100%) as a pale yellow resin; (Found: C, 61.45; H, 5.8; N, 0.8%); υ_{max}(KBr disc)/cm^{-1} 2920, 2868 (C-H), 1655 (C=O), 1244, 1106 (C-O) and 826 (aromatic o.o.p. deformations); δ_C 25.53 (2-C), 29.96 (3-C), 46.62 (1-C), 67.20-72.92 (CH_2O), 110.60 (indole 7-C), 116.11 (phenol 2,6-C), 118.54 (indole 3-C), 122.47 (indole 6-C), 123.34 (indole 4-C), 124.43 (indole 5-C), 132.68 (3a-C), 136.19 (phenol 3,5-C), 137.48 (indole 7a-C), 139.20 (indole 2-C) and 184.93 (CHO).

Synthesis of quadragel *N*-butyl-indole-3-carbaldehyde 440f

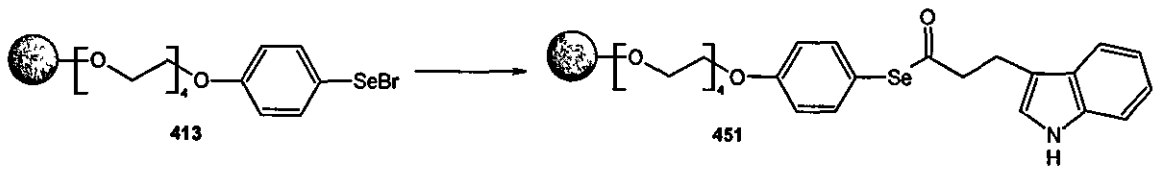


438 440f

4-(4-Chlorobutylselenyl)phenoxy quadragel **438** (1.010 g, 1.41 mmol) was swollen in DMF (25 cm^3) and potassium iodide (1.06 g, 6.40 mmol), potassium hydroxide (0.36 g, 6.40 mmol) and indole-3-carbaldehyde (0.92 g, 6.40 mmol) was added. The reaction was agitated for 18 h and the resin was collected by filtration and washed with aqueous THF, THF, DCM and methanol. The resin was dried at the pump for 30 min and dried thoroughly overnight under vacuum to yield quadragel *N*-butyl-indole-3-carbaldehyde **440f** (1.13 g, 97%) as a pale yellow resin; (Found: C, 62.4; H, 5.85; N, 0.75%); υ_{max}(KBr disc)/cm^{-1} 2914 (C-H), 1654 (C=O) and 1244, 1041 (C-O); δ_C 25.25 (3-C), 26.35 (2-C), 27.59 (4-C), 44.92 (1-C), 65.73-68.96 (CH_2O), 108.49 (indole 7-C), 113.77 (phenol 2,6-C), 116.23 (indole 3-C), 120.42 (indole 6-C), 121.17 (indole 4-

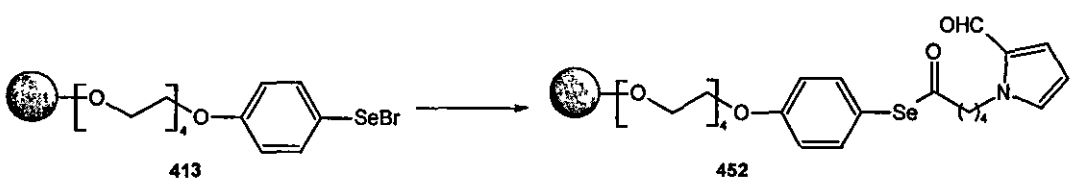
C), 122.30 (indole 5-C), 123.67 (3a-C), 134.11 (phenol 3,5-C), 135.41 (indole 7a-C), 136.85 (indole 2-C), 156.58 (phenol 1-C) and 182.85 (CHO).

Synthesis of quadragel-3-indolepropaneselenoate 451



3-Indolepropanoic acid (0.67 g, 3.5 mmol) was dissolved in DCM (5 cm^3) and triethylamine (0.48 cm^3, 3.5 mmol) was added, the crude mixture was evaporated to dryness and dissolved in THF and added dropwise to a suspension of quadragel 4-phenoxyselenyl bromide **413** (0.75 g, 1.05) and tributylphosphine (0.86 cm^3, 3.5 mmol) at 0 °C. The reaction mixture was agitated at 0 °C for 10 h. The resin was collected by filtration and washed with THF/water (1:1), THF, DCM and methanol. The resin was dried at the pump and further dried under vacuum overnight to yield quadragel-3-indolepropaneselenoate **451** (0.814 g, 96%) as a pale yellow resin; (Found: C, 65.8; H, 6.5; N, 0.9%); υ_{max}(KBr disc)/cm^{-1} 2923, 2854 (C-H), 1653 (C=O) and 1244, 1097 (C-O); δ_H 2.66-3.70 (CH_2), 6.90-7.53 (aromatic-H) and 8.62 (N-H);δ_C 21.84 (CH_2CH_2CO), 48.65 (CH_2CO), 68.19-71.45 (CH_2O), 112.25 (indole 7-C), 114.30 (indole 3-C), 116.50 (phenol 2,6-C), 119.35 (indole 6-C), 119.84 (indole 4-C), 122.67 (ındole 5-C), 127.98 (indole 3a-C), 136.12 (indole 7a-C), 137.14 (indole 2-C), 138.19 (phenol 3,5-C), 160.05 (phenol 1-C) and 201.99 (C=O).

Synthesis of quadragel 5-(3-formyl-1*H*-pyrrol-1-yl)pentaneselenoate 452

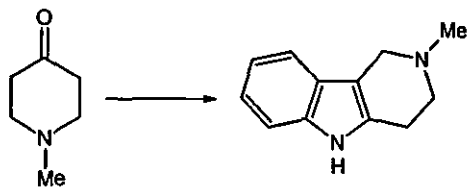


5-(2-Formyl-1*H*-pyrrol-1-yl)pentanoic acid **249** (0.68 g, 3.5 mmol) was dissolved in DCM (5 cm^3) and triethylamine (0.48 cm^3, 3.5 mmol) was added, the crude mixture was evaporated to dryness and dissolved in THF and added dropwise to a suspension of quadragel 4-phenoxyselenyl bromide **413** (0.75 g, 1.05 mmol) and tributylphosphine (0.86 cm^3, 3.5 mmol) at 0 °C. The reaction mixture was agitated at 0 °C for 10 h. The resin was collected by filtration and washed with THF/water (1:1), THF, DCM and methanol. The resin was dried at the pump and further dried under vacuum overnight to yield quadragel 5-(3-formyl-1*H*-pyrrol-1-yl)pentaneselenoate **452** (0.841 g, 99%) as a pale yellow resin; (Found: C, 64.9; H, 6.5; N,

0.6%); υ_{max}(KBr disc)/cm^{-1} 2925 (C-H), 1653 (C=O) and 1247, 1120 (C-O); δ_H 1.28-1.83 (m, C*H*$_2$), 4.19 (m, b, C*H*$_2$), 6.99 (m, aromatic-H) and 9.56 (C*H*O); δ_C 22.55 (3-C), 30.81 (4-C), 46.96 (2-C), 48.94 (5-C), 67.87-71.12 (*C*H$_2$O), 110.16 (pyrrole 4-C), 116.14 (phenol 2,6-C), 125.41 (pyrrole 5-C), 131.80 (pyrrole 3-C), 137.79 (phenol 3,5-C) and 179.71 (CHO).

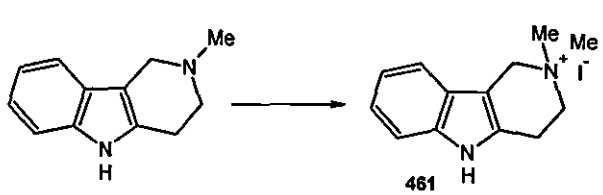
5.3.1 SUAVEOLINE

Synthesis of 2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole[185]



Phenyl hydrazine hydrochloride (8.34 g, 55.7 mmol) was stirred in water at room temperature and 1-methyl-4-piperidone (7.91 g, 69.9 mmol) was added in one portion. The reaction was quenched with excess potassium carbonate after 18 h stirring and the biphasic mixture was triturated to yield a white precipitate. Filtration afforded the hydrazone as a white solid which was used without further purification. The hydrazone was dissolved in sulphuric acid/water (1:4, 300 cm^3) and heated under reflux for 1 h. The cooled reaction mixture was basified with sodium hydroxide and treated with ethyl acetate. When complete dissolution of the organic material was achieved, the mixture was cooled to 0 °C and any insoluble materials removed by filtration. The aqueous phase was further extracted with ethyl acetate, dried and evaporated to dryness to yield 2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (7.10 g, 68%) as an off-white solid; (Found: M$^+$, 186.1158. $C_{12}H_{14}N_2$ requires 186.1157); υ_{max}(KBr disc)/cm^{-1} 3400 (N-H), 1625 (C=C) and 738 (aromatic o.o.p. deformations); δ_H 2.56 (3 H, s, NMe), 2.81-2.88 (4 H, m, 3,4-H), 3 67 (2 H, s, 1-H), 7.05-7.13 (2 H, m, 7,8-H), 7.27 (1 H, d, *J* 6.4, 6-H), 7.40 (1 H, d, *J* 7.6, 9-H) and 7.89 (1 H, s, broad, 5-H); δ_C 23.86 (4-C), 45.81 (NMe), 51.69 (3-C), 52.42 (1-C), 108.85 (9b-C), 110.53 (6-C), 117.51 (9-C), 119.26 (7-C), 121.13 (8-C), 126.08 (9a-C), 131.74 (4a-C) and 136.04 (5a-C); *m/z* 186 (M$^+$, 27%) and 143 (100).

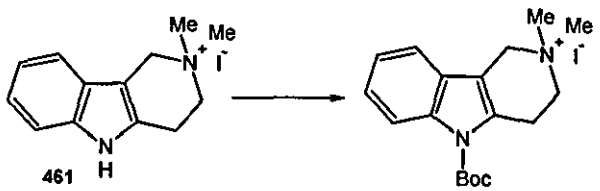
Synthesis of 2,2-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-2-ium iodide 461[174]



461

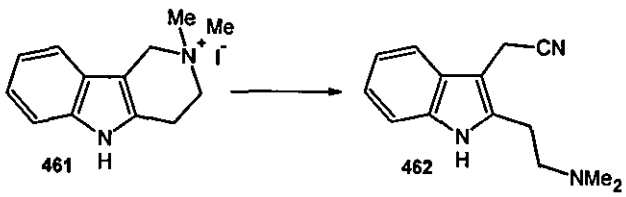
Methyl iodide (32.94 g, 108 mmol) was added to 2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (6.70 g, 36.0 mmol) in methanol (70 cm^3) at room temperature. The reaction mixture was stirred at room temperature for 30 min and the solution was concentrated to approximately 50 cm^3 total volume and diethyl ether (30 cm^3) was added. Trituration at 0 °C yielded 2,2-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-2-ium iodide **461** (10.90 g, 92%) as an off-white solid; [Found: M^+(ESI), 201.1391. $(C_{13}H_{17}N_2)^+$ requires 201.1392); υ_{max}(thin film)/cm^{-1} 3131; δ_H 3.27 (2 H, t, *J* 6.2, 4-H), 3.30 (6 H, s, NMe_2), 3.84 (2 H, t, *J* 6.2, 3-H), 4.73 (2 H, s, 1-H), 7.04-7.08 (1 H, m, 8-H), 7.14-7.18 (1 H, m, 7-H), 7.35-7.38 (1 H, m, 6-H) and 7.42 (1 H, d, J 8.0, 9-H); δ_C 20.71 (4-C), 52.12 (Me), 61.49 (3-C), 62.02 (1-C), 101.80 (9b-C), 112.43 (6-C), 118.36 (9-C), 120.84 (7-C), 123.45 (8-C), 126.45 (9a-C), 129.05 (4a-C) and 138.40 (5a-C); *m/z* 201 (M^+, 100%).

Synthesis of 5-(*tert*-butoxycarbonyl)-2,2-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-2-ium iodide



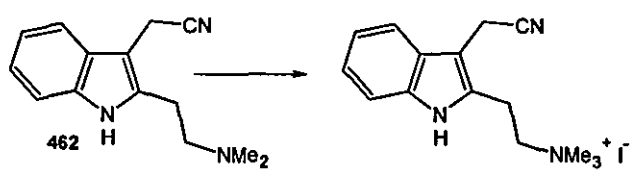
Di-*tert*-butyl dicarbonate (1.40 g, 6.4 mmol) and DMAP (37 mg, 0.3 mmol) were added to a stirred suspension of 2,2-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-2-ium iodide **461** (2.00 g, 6.1 mmol) in acetonitrile (10 cm^3). Complete dissolution was achieved after 10 min stirring at room temperature, the solution was stirred overnight at room temperature and diethyl ether (20 cm^3) was added. The suspension was cooled to 0 °C for 10 min and the precipitate was collected by filtration to afford 5-(*tert*-butoxycarbonyl)-2,2-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-2-ium iodide (2.56 g, 98%) as a beige solid; [Found: M^+ (ESI), 301.1916. $(C_{18}H_{25}N_2O_2)^+$ requires 301.1917]; υ_{max}(thin film)/cm^{-1} 1734 (C=O), 1623 (C=C) and 760 (aromatic o.o.p. deformations); δ_H 1.71 (9 H, s, ^{t}Bu), 3.34 (6 H, s, NMe_2), 3.54 (2 H, t, *J* 6.1, 4-H), 3.85 (2 H, t, *J* 6.1, 3-H), 4.76 (2 H, s, 1-H), 7.26-7.30 (1 H, m, 8-H), 7.33-7.38 (1 H, m, 7-H), 7.47 (1 H, d, *J* 7.6, 9-H) and 8.18 (1 H, d, J 8.4, 6-H); δ_C 23.78 (4-C), 28.48 [$C(CH_3)_3$], 52.36 (Me), 55.60 (3-C), 61.32 (1-C), 86.27 [$C(CH_3)_3$], 105.87 (9b-C), 116.84 (6-C), 118.83 (9-C), 124.42 (7-C), 126.19 (8-C), 127.69 (9a-C), 130.84 (4a-C), 137.72 (5a-C) and 155.27 ($CO_2{}^t$Bu); *m/z* 301 (M^+, 100%).

Synthesis of 2-(2-dimethylamino-ethyl)-1*H*-indole-3-carbonitrile 462



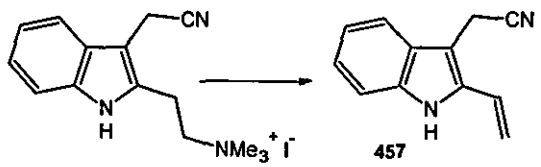
2,2-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indol-2-ium iodide **461** (2.00 g, 6.1 mmol) was dissolved in ethanol (30 cm^3) and a solution of potassium cyanide (1.98 g, 30.5 mmol) in water (10 cm^3) was added to it. The reaction was heated under reflux for 24 h and concentrated under vacuum. The aqueous solution was diluted and basified to pH 13, extracted exhaustively with ether and the combined layers were washed with water, dried and evaporated to dryness to yield 2-(2-dimethylamino-ethyl)-1*H*-indole-3-carbonitrile **462** (1.40 g, 100%) as a pale yellow solid; (Found: M^+, 227.1422. $C_{14}H_{17}N_3$ requires 227.1423); υ_{max}(thin film)/cm^{-1} 3131; δ_H 2.37 (6 H, s, NMe_2), 2.69 (2 H, t, *J* 5.8, ArCH_2), 2.92 (2 H, t, *J* 5.8, CH_2NMe_2), 3.76 (2 H, s, CH_2CN), 7.11-7.20 (2 H, m, 5,6-H), 7.34-7.37 (1 H, m, 7-H), 7.53-7.57 (1 H, m, 4-H) and 10.40 (1 H, s, b, N-H); δ_C 12.81 (CH_2CN), 22.34 (ArCH_2), 45.16 (NMe_2), 58.20 (CH_2NMe_2), 98.61 (3-C), 111.10 (7-C), 117.26 (4-C), 118.27 (CN), 119.68 (6-C), 121.53 (5-C), 126.90 (3a-C), 134.96 (2-C) and 137.18 (7a-C); *m/z* 227 (M^+, 81%), 169 (64), 143 (48) and 115 (60).

Synthesis of 2-(2-trimethylammonium-ethyl)-1*H*-indole-3-carbonitrile iodide[174]



2-(2-Dimethylamino-ethyl)-1*H*-indole-3-carbonitrile **462** (1.10 g, 4.80 mmol) was dissolved in DCM (60 cm^3) and methyl iodide (1.38 g, 9.60 mmol) in ethyl acetate (15 cm^3) was added. The reaction mixture was heated under reflux for 2 h, evaporated to dryness and the solid was washed with ether and dried under vacuum to yield 2-(2-trimethylammonium-ethyl)-1*H*-indole-3-carbonitrile iodide; [Found: M^+ (ESI), 242.1653. $(C_{15}H_{20}N_3)^+$ requires 242.1657]; υ_{max}(thin film)/cm^{-1} 3131; δ_H 3.20 (9 H, s, NMe_3), 3.30-3.34 (2 H, m, ArCH_2), 3.52-3.62 (2 H, m, CH_2NMe_3), 4.13 (2 H, s, CH_2CN), 7.05-7.16 (2 H, m, 5,6-H), 7.39 (1 H, d, *J* 8.0, 7-H), 7.50 (1 H, d, *J* 8.0, 4-H) and 11.23 (1 H, s, b, N-H); δ_C 12.56 (CH_2CN), 20.06 (ArCH_2), 52.80 (CH_2NMe_3), 64.35 (CH_2NMe_3), 101.62 (3-C), 111.51 (7-C), 118.16 (4-C), 119.59 (CN), 119.66 (6-C), 122.07 (5-C), 127.09 (3a-C), 131.59 (2-C) and 135.73 (7a-C); *m/z* 242 (M^+, 100%).

Synthesis of 2-vinyl-1*H*-indole-3-carbonitrile 457



2-(2-Trimethylammonium-ethyl)-1*H*-indole-3-carbonitrile iodide (1.27 g, 3.44 mmol) was dissolved in methanol and 5% sodium hydroxide solution was added. The reaction mixture was stirred for 2 h at room temperature and concentrated under vacuum, the crude residue was heated at 80 °C for 15 min and cooled to room temperature. The aqueous solution was extracted three times with DCM, dried (Na_2SO_4), evaporated to dryness and recrystallised from ether to yield 2-vinyl-1*H*-indole-3-carbonitrile **457** (0.38 g, 62%) as a white solid; (Found: M^+, 182.0843. $C_{12}H_{10}N_2$ requires 182.0844); υ_{max}(thin film)/cm^{-1} 3131; δ_H 3.73 (2 H, s, CH_2CN), 5.30 (1 H, d, *J* 11.6, CH_{trans}), 5.50 (1 H, d, *J* 17.6, CH_{cis}), 6.70 (1 H, dd, *J* 11.6, 17.6, $CH{=}CH_2$), 7.06-7.09 (1 H, m, 5-H), 7.13-7.16 (1 H, m, 6-H), 7.22-7.24 (1 H, m, 7-H), 7.50-7.52 (1 H, m, 4-H) and 8.36 (1 H, s, b, N-H); δ_C 13.26 (CH_2CN), 103.17 (C-3), 111.43 (C-7), 114.77 ($C{=}CH_2$), 118.24 (CN), 118.71 (4-C), 120.86 (6-C), 124.14 (5-C), 124.61 ($C{=}CH_2$), 127.78 (3a-C), 133.77 (2-C) and 136.28 (7a-C); *m/z* 182 (M^+, 90%), 155 (37) and 127 (12).

APPENDIX A - X-RAY CRYSTALLOGRAPHY

Structural determination by single crystal X-ray crystallography of withasomnine. Light petroleum was added carefully to sample tube containing a concentrated dichloromethane solution of the compound to maintain two phases. The tube was sealed and stored at room temperature. Small crystals had formed after 48 h and these were left to develop for a further 24 h before submitting for analysis.

Table 1: *Crystal data and refinement for withasomnine*

Temperature	150(2) K
Radiation, wavelength	MoKα, 0.71073 Å
Crystal system, space group	monoclinic, P2(1)/c
Unit cell parameters	a = 18.357(4) Å α = 90°
	b = 7.9639(17) Å β = 94.016(3)°
	c = 6.6560(14) Å γ = 90°
Cell volume	970.7(4) $Å^3$
Z	4
Calculated density	1.261 $g.cm^{-3}$
Absorption coefficient μ	0.076 mm^{-1}
F(000)	392
Crystal colour and size	colourless, 0.40 x 0.31 x 0.15 mm^3
Data collection method	Bruker SMART 1000 CCD diffractometer
	ω-rotation with narrow frames
θ range for data collection	2.22 to 25.00
Index ranges	h –21 to 21, k –9 to 9, l –7 to 7
Completeness to θ = 26.00°	99.9%
Reflections collected	5898
Independent reflections	1709 (R_{int} = 0.0234)
Absorption correction	multiscan
Min. and max. transmission	1.0000 and 0.8968
Structure solution	direct methods

Refinement method	full-matrix least-squares on F^2
Data / restraints / parameters	1709 / 0 / 127
Final R indices [I>2σ(I)]	R1 = 0.0372, wR2 = 0.0843
R indices (all data)	R1 = 0.0498, wR2 = 0.0912
Goodness-of-fit on F^2	1.058
Largest diff. peak and hole	0.217 and –0.206 e $Å^{-3}$

Table 2: *Atomic coordonates and equivalent isotropic displacement parameters ($Å^2$)*

U_{eq} is defined as one third of the trace of the orthogonalised U^{ij} tensor

	x	y	z	U_{eq}
N(1)	975(1)	6153(2)	5518(2)	29(1)
C(2)	1634(1)	6211(2)	6508(2)	28(1)
C(3)	2184(1)	5405(2)	5477(2)	24(1)
C(3A)	1805(1)	4825(2)	3731(2)	24(1)
C(4)	1889(1)	3955(2)	1770(2)	32(1)
C(5)	1090(1)	3720(2)	911(2)	33(1)
C(6)	613(1)	4891(2)	2091(2)	30(1)
N(7)	1106(1)	5288(2)	3836(2)	25(1)
C(8)	2962(1)	5231(2)	6138(2)	26(1)
C(9)	3271(1)	6233(2)	7691(2)	35(1)
C(10)	4001(1)	6093(2)	8336(3)	42(1)
C(11)	4442(1)	4953(2)	7443(2)	41(1)
C(12)	4145(1)	3948(2)	5905(3)	39(1)
C(13)	3415(1)	4081(2)	5255(2)	32(1)

Table 3: *Bond lengths (Å)*

N(1)-C(2)	1.3363(18)	C(5)-C(6)	1.533(2)
N(1)-N(7)	1.3496(16)	C(6)-N(7)	1.4569(18)
C(2)-C(3)	1.414(2)	C(8)-C(9)	1.395(2)
C(3)-C(3A)	1.391(2)	C(8)-C(13)	1.395(2)
C(3)-C(8)	1.471(2)	C(9)-C(10)	1.384(2)
C(3A)-N(7)	1.3415(18)	C(10)-C(11)	1.379(2)
C(3A)-C(4)	1.495(2)	C(11)-C(12)	1.381(2)
C(4)-C(5)	1.548(2)	C(12)-C(13)	1.383(2)

Table 4: *Bond angles (°)*

C(2)-N(1)-N(7)	102.66(11)	C(3A)-N(7)-N(1)	114.22(11)
N(1)-C(2)-C(3)	113.39(13)	C(3A)-N(7)-C(6)	116.20(12)
C(3A)-C(3)-C(2)	102.94(12)	N(1)-N(7)-C(6)	129.44(12)
C(3A)-C(3)-C(8)	129.53(13)	C(9)-C(8)-C(13)	117.68(14)
C(2)-C(3)-C(8)	127.52(13)	C(9)-C(8)-C(3)	120.23(13)
N(7)-C(3A)-C(3)	106.78(12)	C(13)-C(8)-C(3)	122.09(13)
N(7)-C(3A)-C(4)	109.34(12)	C(10)-C(9)-C(8)	121.26(15)
C(3)-C(3A)-C(4)	143.81(13)	C(11)-C(10)-C(9)	120.28(16)
C(3A)-C(4)-C(5)	103.00(11)	C(10)-C(11)-C(12)	119.27(15)
C(6)-C(5)-C(4)	107.34(12)	C(11)-C(12)-C(13)	120.73(15)
N(7)-C(6)-C(5)	101.25(11)	C(12)-C(13)-C(8)	120.78(15)

Table 5: *Anisotropic displacement parameters (Å x 10^3)*

The displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(1)	29(1)	28(1)	31(1)	-5(1)	6(1)	0(1)
C(2)	32(1)	24(1)	27(1)	-4(1)	3(1)	-2(1)
C(3)	29(1)	18(1)	25(1)	2(1)	3(1)	-1(1)
C(3A)	25(1)	19(1)	27(1)	3(1)	4(1)	1(1)
C(4)	34(1)	34(1)	30(1)	-5(1)	2(1)	4(1)
C(5)	36(1)	34(1)	27(1)	-3(1)	1(1)	-2(1)
C(6)	27(1)	29(1)	33(1)	1(1)	-2(1)	-4(1)
N(7)	25(1)	22(1)	27(1)	-1(1)	3(1)	-2(1)
C(8)	29(1)	24(1)	25(1)	5(1)	2(1)	-1(1)
C(9)	34(1)	37(1)	32(1)	-4(1)	-1(1)	1(1)
C(10)	39(1)	50(1)	35(1)	-5(1)	-7(1)	-5(1)
C(11)	28(1)	56(1)	39(1)	8(1)	-5(1)	1(1)
C(12)	32(1)	44(1)	42(1)	1(1)	4(1)	8(1)
C(13)	32(1)	33(1)	32(1)	-3(1)	2(1)	1(1)

Table 6: *Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$)*

	x	y	z	U_{eq}
H(2)	1723	6741	7780	33
H(4A)	2138	2859	1979	39
H(4B)	2169	4653	864	39
H(5A)	1044	4007	-539	39
H(5B)	936	2539	1070	39
H(6A)	472	5911	1307	36
H(6B)	167	4315	2487	36
H(9)	2974	7026	8319	42
H(10)	4200	6787	9399	50
H(11)	4944	4859	7880	49
H(12)	4446	3157	5287	47
H(13)	3220	3380	4194	38

Table 6: *Torsion angles (°)*

N(7)-N(1)-C(2)-C(3)	0.40(15)	C(2)-N(1)-N(7)-C(6)	-176.00(13)
N(1)-C(2)-C(3)-C(8)	-0.20(16)	C(5)-C(6)-N(7)-C(3A)	11.22(15)
N(1)-C(2)-C(3)-C(8)	-179.70(13)	C(5)-C(6)-N(7)-N(1)	-173.32(13)
C(2)-C(3)-C(3A)-N(7)	-0.10(15)	C(3A)-C(3)-C(8)-C(9)	164.66(14)
C(8)-C(3)-C(3A)-N(7)	179.39(13)	C(2)-C(3)-C(8)-C(9)	-16.0(2)
C(2)-C(3)-C(3A)-C(4)	176.17(19)	C(3A)-C(3)-C(8)-C(13)	-15.3(2)
C(8)-C(3)-C(3A)-C(4)	-4.3(3)	C(2)-C(3)-C(8)-C(13)	164.12(14)
N(7)-C(3A)-C(4)-C(5)	-9.47(16)	C(13)-C(8)-C(9)-C(10)	0.0(2)
C(3)-C(3A)-C(4)-C(5)	174.33(19)	C(3)-C(8)-C(9)-C(10)	-179.89(14)
C(3A)-C(4)-C(5)-C(6)	16.06(16)	C(8)-C(9)-C(10)-C(11)	0.2(3)
C(4)-C(5)-C(6)-C(7)	-16.28(15)	C(9)-C(10)-C(11)-C(12)	-0.3(3)
C(3)-C(3A)-N(7)-N(1)	0.37(16)	C(10)-C(11)-C(12)-C(13)	0.2(3)
C(4)-C(3A)-N(7)-N(1)	-177.29(12)	C(11)-C(12)-C(13)-C(8)	0.0(2)
C(3)-C(3A)-N(7)-C(6)	176.52(12)	C(9)-C(8)-C(13)-C(12)	-0.1(2)
C(4)-C(3A)-N(7)-C(6)	-1.14(16)	C(3)-C(8)-C(13)-C(12)	179.84(14)
C(2)-N(1)-N(7)-C(3A)	-0.47(15)		

Structural determination by single crystal X-ray crystallography of 8-oxo-5,6,7,8-tetrahydroindolizine-1-carbaldehyde. A sealed flask holding light petroleum was allowed to diffuse into a sample tube containing a concentrated dichloromethane solution of the compound at room temperature. Small crystals had formed after 4 days and these were left to develop for a further 48 h before submitting for analysis.

Table 1: *Crystal data and refinement for 8-oxo-5,6,7,8-tetrahydroindolizine-1-carbaldehyde*

Temperature	150(2) K
Radiation, wavelength	MoKα, 0.71073 Å
Crystal system, space group	orthorhombic, $Pna2_1$
Unit cell parameters	a = 6.9368(4) Å α = 90°
	b = 9.4151(6) Å β = 90°
	c = 11.9119(7) Å γ = 90°
Cell volume	777.97(8) $Å^3$
Z	4
Calculated density	1.392 $g.cm^{-3}$
Absorption coefficient μ	0.100 mm^{-1}
F(000)	344
Crystal colour and size	pale yellow, 0.34 x 0.24 x 0.08 mm^3
Reflections for cell refinement	4867 (θ range 2.75 to 28.52°)
Data collection method	Bruker SMART 1000 CCD diffractometer
	ω-rotation with narrow frames
θ range for data collection	2.76 to 28.56
Index ranges	h –9 to 8, k –11 to 12, l –15 to 15
Completeness to θ = 26.00°	100.0%
Intensity decay	0%
Reflections collected	6218
Independent reflections	1819 (R_{int} = 0.0124)
Reflections with $F^2>2\sigma$	1768
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.967 and 0.992
Structure solution	direct methods

Refinement method	full-matrix least-squares on F^2
Weighting parameters a, b	0.0459, 0.0767
Data / restraints / parameters	1819 / 1 / 110
Final R indices [$F^2>2\sigma$]	R1 = 0.0271, wR2 = 0.0733
R indices (all data)	R1 = 0.0282, wR2 = 0.0743
Goodness-of-fit on F^2	1.104
Absolute structure parameter	-0.1(9)
Extinction coefficient	0.0023(19)
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.235 and –0.197 e $Å^{-3}$

Table 2: *Atomic coordonates and equivalent isotropic displacement parameters ($Å^2$)*

U_{eq} is defined as one third of the trace of the orthogonalised U^{ij} tensor

	x	y	z	U_{eq}
C(1)	0.82404(16)	1.19813(11)	0.58546(10)	0.0223(2)
C(2)	076963(15)	1.16920(11)	0.69752(11)	0.0243(2)
C(3)	0.74191(15)	1.29812(11)	0.74995(11)	0.0238(2)
N(4)	0.77791(12)	1.40373(9)	0.67467(8)	0.0217(2)
C(5)	0.75824(15)	1.55625(11)	0.69646(12)	0.0270(2)
C(6)	0.89322(18)	1.63774(12)	0.61939(11)	0.0308(3)
C(7)	0.85932(17)	1.59662(12)	0.49707(11)	0.0298(3)
C(8)	0.86801(16)	1.43796(13)	0.47631(10)	0.0269(2)
O(1)	0.90212(15)	1.38924(11)	0.38374(8)	0.0403(2)
C(8A)	0.82721(15)	1.34681(11)	0.57294(10)	0.0217(2)
C(9)	0.87231(16)	1.09536(13)	0.49881(11)	0.0275(2)
C(2)	0.85662(13)	0.96684(9)	0.50961(9)	0.0361(2)

Table 3: *Bond lengths (Å)*

C(1)-C(8A)	1.4080(15)	C(1)-C(2)	1.4136(18)
C(1)-C(9)	1.4539(16)	C(2)-C(3)	1.3786(16)
C(3)-N(4)	1.3620(14)	N(4)-C(8A)	1.3684(15)
N(4)-C(5)	1.4657(13)	C(5)-C(6)	1.5192(17)
C(6)-C(7)	1.5259(19)	C(7)-C(8)	1.5153(16)
C(8)-O(1)	1.2175(16)	C(8)-C(8A)	1.4634(15)
C(9)-O(2)	1.2218(14)		

Table 4: *Bond angles (°)*

C(8A)-C(1)-C(2)	107.20(10)	C(8A)-C(1)-C(9)	125.66(11)
C(2)-C(1)-C(9)	127.13(10)	C(3)-C(2)-C(1)	107.18(10)
N(4)-C(3)-C(2)	108.60(11)	C(3)-N(4)-C(8A)	110.06(9)
C(3)-N(4)-C(5)	125.56(10)	C(8A)-N(4)-C(5)	124.32(9)
N(4)-C(5)-C(6)	109.29(10)	C(5)-C(6)-C(7)	110.73(10)
C(8)-C(7)-C(6)	113.57(10)	O(1)-C(8)-C(8A)	121.94(11)
O(1)-C(8)-C(7)	121.80(11)	C(8A)-C(8)-C(7)	116.23(10)
N(4)-C(8A)-C(1)	106.96(10)	N(4)-C(8A)-C(8)	121.01(10)
C(1)-C(8A)-C(8)	132.02(11)	O(2)-C(9)-C(1)	124.32(12)

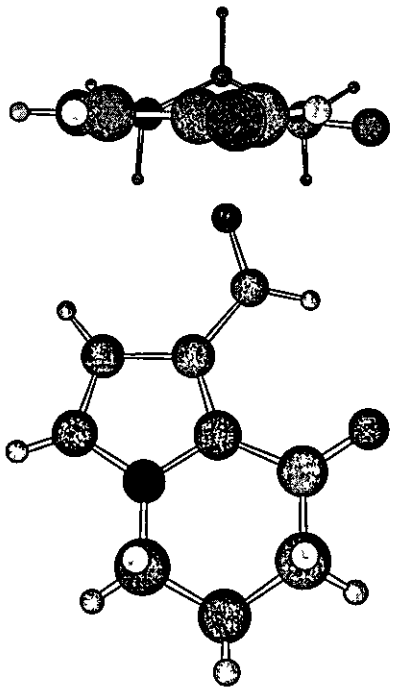
Table 5: *Anisotropic displacement parameters (Å)*

The displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	0.0196(5)	0.0232(5)	0.0239(5)	0.0013(5)	-0.0029(4)	-0.0014(4)
C(2)	0.0229(5)	0.0247(5)	0.0252(5)	0.0047(5)	-0.0030(4)	-0.0019(4)
C(3)	0.0231(5)	0.0275(5)	0.0208(5)	0.0051(4)	-0.0007(4)	-0.0015(4)
N(4)	0.0208(4)	0.0215(4)	0.0227(5)	0.0027(4)	-0.0011(3)	0.0000(3)
C(5)	0.0298(5)	0.0220(5)	0.0290(5)	-0.0010(5)	-0.0006(5)	0.0020(4)
C(6)	0.0315(6)	0.0222(5)	0 0386(6)	0.0051(5)	-0.0028(5)	-0.0028(4)
C(7)	0.0313(6)	0.0262(5)	0.0321(7)	0.0109(5)	-0.0001(5)	-0.0014(4)
C(8)	0.0241(5)	0.0309(6)	0.0256(6)	0.0080(4)	0.0000(4)	-0.0004(4)
O(1)	0.0543(6)	0.0426(5)	0.0241(4)	0 0056(4)	0.0087(4)	0.0008(4)
C(8A)	0.0194(4)	0.0233(5)	0.0223(5)	0.0006(4)	-0.0014(4)	-0.0009(4)
C(9)	0.0259(5)	0.0306(6)	0.0260(6)	-0.0029(5)	-0.0035(4)	-0.0002(4)
O(2)	0.0420(5)	0.259(4)	0.0405(5)	-0.0050(4)	-0.0044(4)	0.0013(4)

Table 6: *Hydrogen coordinates and isotropic displacement parameters ($Å^2$)*

	x	y	z	U
H(2)	0.7549	1.0780	0.7305	0.029
H(3)	0.7040	1.3111	0.8259	0.029
H(5A)	0.7905	1.5768	0.7758	0.032
H(5B)	0.6235	1.5863	0.6829	0.032
H(6A)	1.0285	1.6169	0.6401	0.037
H(6B)	0.8715	1.7410	0.6288	0.037
H(7A)	0.7313	1.6322	0.4735	0.036
H(7B	0.9576	1.6439	0.4498	0.036
H(9)	0.9192	1.1305	0.4292	0.033



Structural determination by single crystal X-ray crystallography of 9-oxo-6,7,8,9-tetrahydro-*5H*-pyrrolo[1,2-*a*]azepine-1-carbaldehyde. A sealed flask holding light petroleum was allowed to diffuse into a sample tube containing a concentrated dichloromethane solution of the compound at room temperature. Small crystals had formed after 4 days and these were left to develop for a further 48 h before submitting for analysis.

Table 1: *Crystal data and refinement for 9-oxo-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-1-carbaldehyde*

Temperature	150(2) K
Radiation, wavelength	MoKα, 0.71073 Å
Crystal system, space group	orthorhombic, $P2_12_12_1$
Unit cell parameters	a = 6.7750(5) Å α = 90°
	b = 7.4820(5) Å β = 90°
	c = 16.7802(12) Å γ = 90°
Cell volume	850.60(10) $Å^3$
Z	4
Calculated density	1.384 $g.cm^{-3}$
Absorption coefficient μ	0.097 mm^{-1}

F(000)	376
Crystal colour and size	colourless, 0.86 x 0.42 x 0.23 mm^3
Reflections for cell refinement	6051 (θ range 2.43 to 28.61°)
Data collection method	Bruker SMART 1000 CCD diffractometer
	ω-rotation with narrow frames
θ range for data collection	2.43 to 28.58
Index ranges	h –8 to 8, k –10 to 9, l –21 to 22
Completeness to θ = 26.00°	99.9%
Intensity decay	0%
Reflections collected	7232
Independent reflections	1988 (R_{int} = 0.0159)
Reflections with $F^2>2\sigma$	1947
Absorption correction	semi-empirical from equivalents
Min. and max. transmission	0.921 and 0.978
Structure solution	direct methods
Refinement method	full-matrix least-squares on F^2
Weighting parameters a, b	0.0449, 0.1739
Data / restraints / parameters	1988 / 0 / 119
Final R indices [$F^2>2\sigma$]	R1 = 0.0290, wR2 = 0.0781
R indices (all data)	R1 = 0.0296, wR2 = 0.0786
Goodness-of-fit on F^2	1.060
Absolute structure parameter	0.3(10)
Extinction coefficient	0.0016(4)
Largest and mean shift/su	0.001 and 0.000
Largest diff. peak and hole	0.217 and –0.206 e $Å^{-3}$

Table 2: *Atomic coordonates and equivalent isotropic displacement parameters ($Å^2$)*

U_{eq} is defined as one third of the trace of the orthogonalised U^{ij} tensor

	x	y	z	U_{eq}
C(1)	0.78578(17)	0.19546(15)	1.00602(6)	0.0208(2)
C(2)	0.78041(19)	0.05717(17)	0.94861(7)	0.0260(3)
C(3)	0.80644(19)	-0.10145(17)	0.98840(7)	0.0253(3)
N(4)	0.82480(14)	-0.06676(12)	1.06823(6)	0.0202(2)
C(5)	0.87836(18)	-0.19860(15)	1.12910(7)	0.0230(2)
C(6)	0.71007(18)	-0.23241(15)	1.18758(7)	0.0250(2)
C(7)	0.61763(18)	-0.05932(15)	1.21923(7)	0.0226(2)
C(8)	0.76971(18)	0.08924(16)	1.23360(6)	0.0218(2)
C(9)	0.82271(17)	0.19814(15)	1.16008(7)	0.0206(2)
O(1)	0.86598(15)	0.35581(11)	1.16647(5)	0.0295(2)
C(9A)	0.81245(16)	0.11425(14)	1.08054(6)	0.0193(2)
C(10)	0.76552(17)	0.38652(16)	0.99059(7)	0.0240(2)
O(2)	0.76912(15)	0.45271(13)	0.92441(6)	0.0324(2)

Table 3: *Bond lengths (Å)*

C(1)-C(9A)	1.4019(15)	C(1)-C(2)	1.4142(16)
C(1)-C(10)	1.4592(16)	C(2)-C(3)	1.3731(18)
C(3)-N(4)	1.3700(14)	N(4)-C(9A)	1.3725(14)
N(4)-C(5)	1.4656(14)	C(5)-C(6)	1.5255(16)
C(6)-C(7)	1.5334(16)	C(7)-C(8)	1.5347(16)
C(8)-C(9)	1.5214(16)	C(9)-O(1)	1.2202(14)
C(9)-C(9A)	1.4766(15)	C(10)-O(2)	1.2162(15)

Table 4: *Bond angles (°)*

C(9A)-C(1)-C(2)	107.09(10)	C(9A)-C(1)-C(10)	126.51(10)
C(2)-C(1)-C(10)	126.40(11)	C(3)-C(2)-C(1)	107.32(10)
N(4)-C(3)-C(2)	108.87(10)	C(3)-N(4)-C(9A)	109.18(10)
C(3)-N(4)-C(5)	125.19(10)	C(9A)-N(4)-C(5)	125.05(9)
N(4)-C(5)-C(6)	112.02(10)	C(5)-C(6)-C(7)	112.83(9)
C(6)-C(7)-C(8)	113.07(10)	C(9)-C(8)-C(7)	114.76(9)
O(1)-C(9)-C(9A)	120.11(10)	O(1)-C(9)-C(8)	120.21(10)
C(9A)-C(9)-C(8)	119.62(10)	N(4)-C(9A)-C(1)	107.53(10)
N(4)-C(9A)-C(9)	123.55(10)	C(1)-C(9A)-C(9)	128.91(10)
O(2)-C(10)-C(1)	123.99(12)		

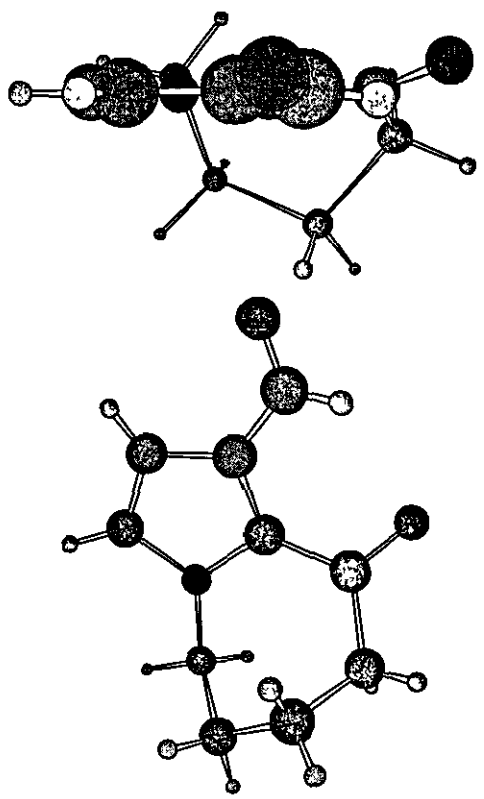
Table 5: *Anisotropic displacement parameters (Å)*

The displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \ldots + 2hka^*b^*U^{12}]$

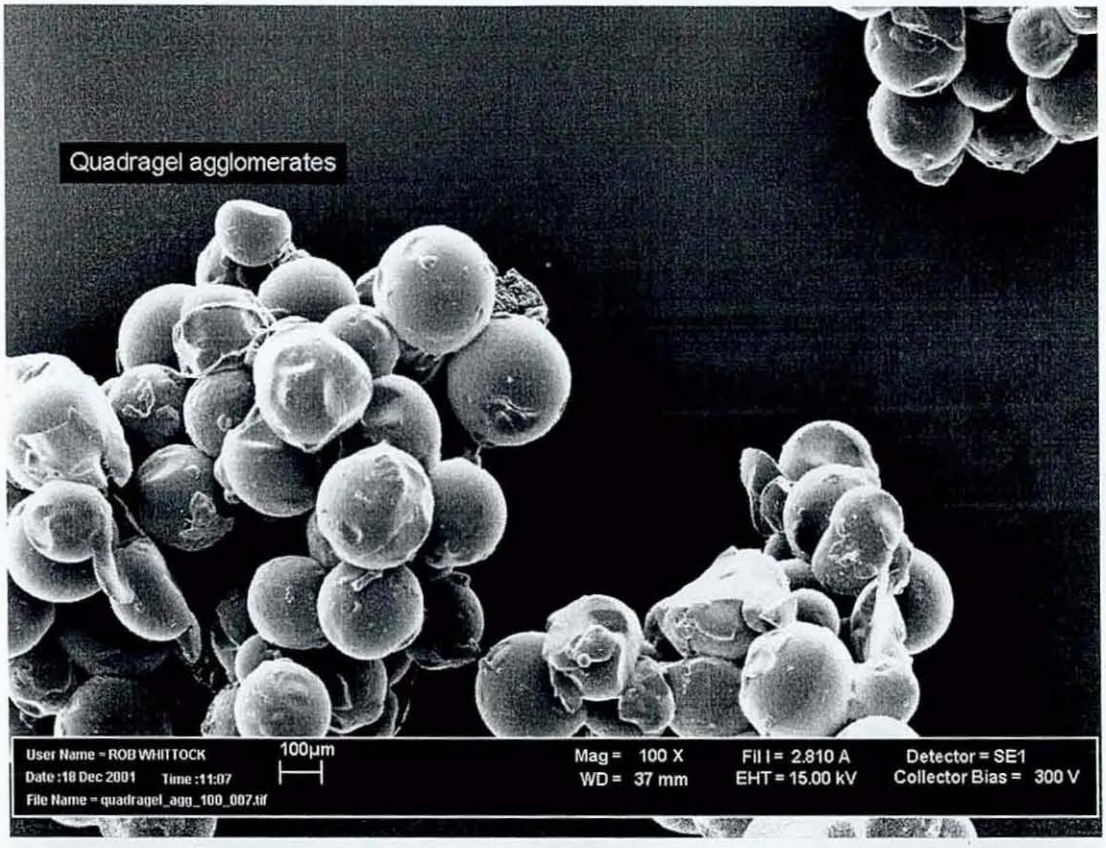
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	0.0182(5)	0.0226(6)	0.0217(5)	0.0016(4)	0.0007(4)	-0.0013(4)
C(2)	0.0273(6)	0.0293(6)	0.0214(5)	-0.0005(4)	0.0014(4)	-0.0016(5)
C(3)	0.0275(6)	0.0247(6)	0.0236(5)	-0.0044(4)	0.0018(5)	-0.0021(5)
N(4)	0.0206(4)	0.0171(4)	0.0228(4)	-0.0002(3)	0.0011(3)	-0.0007(4)
C(5)	0.0250(6)	0.0164(5)	0.0274(6)	0.0023(4)	0.0007(5)	0 0023(4)
C(6)	0.0269(6)	0.0208(5)	0.0273(5)	0.0025(4)	0.0015(5)	-0.0031(5)
C(7)	0.0214(5)	0.0237(5)	0.0227(5)	0.0015(4)	0.0013(4)	-0.0018(5)
C(8)	0.0238(5)	0.0213(5)	0.0202(5)	-0.0004(4)	-0.0019(4)	0.0000(4)
C(9)	0.0188(5)	0.0188(5)	0.0240(5)	-0.0003(4)	-0.0011(4)	0.0008(4)
O(1)	0.0392(5)	0.0192(4)	0 0302(4)	-0.0022(3)	-0.0013(4)	-0.0043(4)
C(9A)	0.0174(5)	0.0174(5)	0.0232(5)	0.0006(4)	0.0007(4)	-0.0005(4)
C(10)	0.0192(5)	0.0235(6)	0.0294(5)	0.0038(4)	-0.0006(4)	-0 0003(4)
O(2)	0.0303(5)	0.0321(5)	0.0349(5)	0.0134(4)	0.0019(4)	0.0008(4)

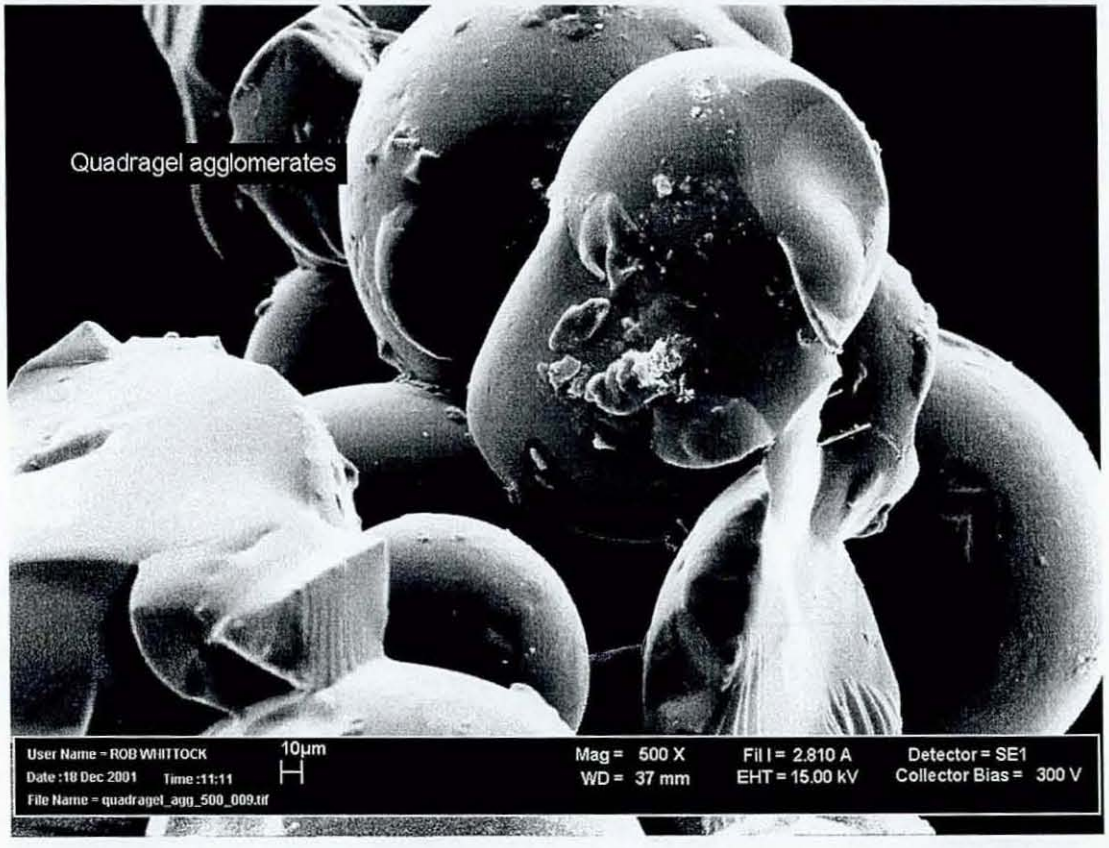
Table 6: *Hydrogen coordinates and isotropic displacement parameters ($Å^2$)*

	x	y	z	U
H(2)	0.7622	0.0714	0.8928	0.031
H(3)	0.8110	-0.2165	0.9645	0.030
H(5A)	0.9953	-0.1554	1.1588	0.028
H(5B)	0.9144	-0.3124	1.1028	0.028
H(6A)	0.7606	-0.3032	1.2331	0.030
H(6B)	0.6067	-0.3041	1.1608	0.030
H(7A)	0.5484	-0.0853	1.2699	0.027
H(7B)	0.5181	-0.0163	1.1805	0.027
H(8A)	0.7174	0.1713	1.2748	0.026
H(8B)	0.8917	0.0346	1.2550	0.026
H(10)	0.7485	0.4639	1.0349	0.029



APPENDIX B - SCANNING ELECTRON MICROGRAPHS OF QUADRAGEL





The scanning electron micrographs above show the degradation of the quadragel following stirring for 12h.

Appendix C - Publications and Presentations

Publications

S. M. Allin, W. R. S. Barton, W. R. Bowman and T. McInally, *Tetrahedron Lett.*, 2001, **42**, 7887.

S. M. Allin, W. R. S. Barton, W. R. Bowman and T. McInally, *Tetrahedron Lett.*, 2002, **43**, 4191.

Presentations

Medicinal Chemistry Seminar, AstraZeneca, 2001

SCI Meeting, Reading University, 2001

AstraZeneca Postgraduate Symposium, 2002

Poster Presentations

Gomberg 2000: 100 years of Radical Chemistry, University of Michigan, Ann Arbor, June 2000

RSC Heterocyclic Group, 15th Lakeland Symposium, Grasmere, Cumbria, May 2001

RSC East Midlands Meeting, April 2001, 2002

RSC Organic Free Radicals - Euchem, University of York, York, July 2002

REFERENCES

[1] J. E. Baldwin, *J Chem. Soc., Chem Commun.*, 1976, 734.

[2] G. F. Mejis, J. F. Bunnett and A. L. J. Beckwith, *J. Am. Chem. Soc.*, 1986, **108**, 4899.

[3] P. Double and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2005.

[4] P. A. Evans and T. Manangan, *Tetrahedron Lett*, 2001, **42**, 6637.

[5] W. R. Bowman, M. O. Cloonan and S. L. Krintel, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2885.

[6] H. Ishibashi, I. Kato, Y. Takeda, M. Kogure and O. Tamura, *Chem. Commun.*, 2000, 1527.

[7] K. Jones, S. A. Brunton and R. Gosain, *Tetrahedron Lett.*, 1999, **40**, 8935.

[8] S. M. Sparks and K. J. Shea, *Tetrahedron Lett*, 2000, **41**, 6721.

[9] K. Jones, M. Thompson and C. Wright, *J. Chem. Soc., Chem. Commun*, 1986, 115.

[10] A. A. Ponaras and Ö. Zaim, *Tetrahedron Lett.*, 2000, **41**, 2279.

[11] W. Zhang, *Tetrahedron Lett.*, 2000, **41**, 2523.

[12] W. Zhang and G. Pugh, *Tetrahedron Lett.*, 1999, **40**, 7595.

[13] M. Kizil, B. Patro, O. Callaghan, J. A. Murphy, M. B. Hursthouse and D. Hibbs, *J. Org. Chem.*, 1999, **64**, 7856.

[14] M. Ikeda, S. Ohtani, T. Sato and H. Ishibashi, *Synthesis*, 1998, 1803.

[15] M. M. Cid, D. Domínguez, L. Castedo and E. M. Vázquez-López, *Tetrahedron*, 1999, **55**, 5599.

[16] H. Tokuyama, T. Yamashita, M. T. Reding, Y. Kaburagi and T. Fukuyama, *J Am. Chem Soc.*, 1999, **121**, 3791.

[17] A. Studer and M. Bossart, *Radicals in Organic Synthesis*, eds. P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001, 62.

[18] C. Hoarau, A. Couture, H. Cornet, E. Deniau and P. Grandclaudon, *J. Org. Chem*, 2001, **66**, 8064.

[19] M.-L. Bennasar, T. Roca, R. Griera and J. Bosch, *J. Org. Chem.*, 2001, **66**, 7547.

[20] F. E. Ziegler and M. Belema, *J. Org. Chem.*, 1997, **62**, 1083.

[21] H. Josien, S.-B. Ko, D. Bom and D. P. Curran, *Chem Eur. J.*, 1998, **67**, 4.

[22] L. D. Miranda, R. Cruz-Almanza, M. Pavón, Y. Romero and J. M. Muchowski, *Tetrahedron Lett*, 2000, **41**, 10181.

[23] D. Nanni, P. Pareschi, C. Rizzoli, P. Sgarabotto and A. Tundo, *Tetrahedron*, 1995, **51**, 9045.

[24] W. R. Bowman, H. Heaney and B. M. Jordan, *Tetrahedron Lett.*, 1991, **47**, 10119.

[25] J. Marco-Contelles and M. Rodríguez-Fernández, *Tetrahedron Lett*, 2000, **42**, 381.

[26] D. P. Curran, H. Yu and H. Liu, *Tetrahedron*, 1994, **50**, 7343.

[27] S. M. Allin, W. R. S. Barton, W. R. Bowman and T. McInally, *Tetrahedron Lett*, 2001, **42**, 7887.

[28] W. R. Bowman, E. Mann and J. Parr, *J. Chem. Soc, Perkin Trans. 1*, 2000, 2991; W. R. Bowman and E. Mann, unpublished results.

[29] D. C. Harrowven, B. J. Sutton and S. Coulton, *Tetrahedron Lett.*, 2001, **42**, 9061.

[30] C. Escolano and K. Jones, *Tetrahedron Lett.*, 2000, **41**, 8951.

[31] K. Jones, T. C. T. Ho and J. Wilkinson, *Tetrahedron Lett*, 1995, **36**, 6743.

[32] T. C. Tim, K. Jones and J. Wilkinson, *Tetrahedron Lett.*, 1995, **36**, 6743.

[33] P. A. Dobbs, K. Jones and K. T. Veal, *Tetrahedron*, 1997, **53**, 8287.

[34] F. Aldabbagh, W. R. Bowman, E. Mann and A. M. Z. Slawin, *Tetrahedron*, 1999, **55**, 8111.

[35] S. M. Allin, W. R. S. Barton, W. R. Bowman and T. McInally, *Tetrahedron Lett.*, 2002, **43**, 4191.

[36] K. B. Hansen, S. A. Springfield, R. Desmond, P. N. Devine, E. J. J. Grabowski and P. J. Reider, *Tetrahedron Lett*, 2001, **42**, 7353.

[37] W. R. Bowman, C. F. Bridge, P. Brookes, M. O. Cloonan and D. C. Leach, *J. Chem Soc., Perkin Trans. 1*, 2002, 58.

[38] A. Nadin and T. Harrison, *Tetrahedron Lett*, 1999, **40**, 4073.

[39] S. Caddick, C. L. Shering and S. N. Wadman, *Tetrahedron*, 2000, **56**, 465.

[40] L. D. Miranda, R. Cruz-Almanza, A. Alvarez-García and J. M. Muchowski, *Tetrahedron Lett.*, 2000, **41**, 3035.

[41] F. Aldabbagh and W. R. Bowman, *Tetrahedron*, 1999, **55**, 4109.

[42] J. Robertson, J. Pillai and R. K. Lush, *Chem Soc. Rev*, 2001, **30**, 94.

[43] G. W. Gribble, H. L. Fraser and J. C. Badenock, *Chem Commun*, 2001, 805.

[44] A. Fiumana and K. Jones, *Tetrahedron Lett*, 2000, **41**, 4209.

[45] W. Zhang and G. Pugh, *Tetrahedron Lett*, 1999, **40**, 7591.

[46] C. J. Moody and C. L. Norton, *J Chem. Soc, Perkin Trans. 1*, 1997, 2639.

[47] M.-L. Bennasar, T. Roca, R. Griera and J. Bosch, *Org. Lett.*, 2001, **3**, 1697.

[48] I. Ryu, K. Kusano, N. Ogawa, N. Kambe and N. Sonoda, *J Am Chem. Soc.*, 1990, **112**, 1295.

[49] L. D. Miranda, R. Cruz-Almanza, M. Pavón, E. Alva and J. M. Muchowski, *Tetrahedron Lett.*, 1999, **40**, 7153.

[50] P. A. Baguley and J. C. Walton, *Angew. Chem., Int. Ed.*, 1998, **37**, 3072.

[51] B. S. Edelson, B. M. Stoltz and E. J. Corey, *Tetrahedron Lett*, 1999, **40**, 6729.

[52] J.-C. Blazejewski, P. Diter, T. Warchol and C. Wakselman, *Tetrahedron Lett.*, 2001, **42**, 859.

[53] D. P. Curran and S. Hadida, *J. Am. Chem. Soc.*, 1996, **118**, 2531.

[54] D. P. Curran and W. Shen, *J. Am. Chem. Soc.*, 1993, **115**, 6051.

[55] I. Terstiege and R. E. Maleczka, *J. Org. Chem.*, 1999, **64**, 342.

[56] A. Studer and S. Amrein, *Synthesis*, 2002, 835.

[57] C. Chatgilialoglu, *Acc. Chem Res.*, 1992, **25**, 188.

[58] O. Callaghan, C. Lampard, A. R. Kennedy and J. A. Murphy, *J. Chem. Soc, Perkin Trans. 1*, 1999, 995.

[59] B. Patro, M. C. Merrett, S. D. Makin, J. A. Murphy and K. E. B. Parkes, *Tetrahedron Lett.*, 2000, **41**, 421.

[60] M. Gerlach, F. Jördens, H. Kuhn, W. P. Neumann and M. Peterseim, *J. Org Chem.*, 1991, **56**, 5971.

[61] U. Gerigk, M. Gerlach, W. P. Neumann, R. Vieler and V. Weintritt, *Synthesis*, 1990, 448.

[62] G. Ruel, N. K. The, G. Dumartin, B. Delmond and M. Pereyre, *J. Organomet. Chem*, 1993, 444.

[63] Y. Ueno, K. Chino, M. Watanabe, O. Moriya and M. Okawara. *J. Am. Chem. Soc.*, 1982, **104**, 5564.

[64] P. Boussaguet, B. Delmond, G. Dumartin and M. Pereyre, *Tetrahedron Lett.*, 2000, **41**, 3377.

[65] B. Patro, M. Merrett, J. A. Murphy, D. C. Sherrington and M. G. J. T. Morrison, *Tetrahedron Lett*, 1999, **40**, 7857.

[66] A. J. Clark, R. P. Filik, D. M. Haddleton, A. Radigue, C. J. Sanders, G. H. Thomas and M. E. Smith, *J. Org Chem.*, 1999, **64**, 8954.

[67] H. Miyabe, Y. Fujishima and T. Naito, *J. Org Chem.*, 1999, **64**, 2174.

[68] R. E. Sammelson and M. J. Kurth, *Chem. Rev.*, 2001, **101**, 137.

[69] A. Ganesan, *Radicals in Organic Synthesis*, Ed. P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001, **2**, 80.

[70] B. Yan, *Acc. Chem Res*, 1998, **31**, 621.

[71] W. L. Fitch, G. Detre and C.P. Holmes, *J. Org. Chem.*, 1994, **59**, 7955.

[72] F. Lorgé, A. Wagner and C. Mioskowski, *J. Comb. Chem.*, 1999, **1**, 25.

[73] M. J. Shapiro and J. S. Gounarides, *Prog Nucl. Magn Reson Spectrosc.*, 1999, **35**, 153.

[74] M. E. Attardi and M. Taddei, *Tetrahedron Lett.*, 2001, **42**, 3519.

[75] H. Miyabe, C. Konishi and T. Naito, *Org. Lett.*, 2000, **2**, 1443.

[76] M. P. Sibi and S. V. Chandramouli, *Tetrahedron Lett.*, 1997, **38**, 8929.

[77] E. J. Enholm, M. E. Gallagher, S. Jiang and W. A. Batson, *Org. Lett.*, 2000, **2**, 3355.

[78] A.-M. Yim, Y. Vidal, P. Viallefont and J. Martinez, *Tetrahedron Lett* , 1999, **40**, 4535.

[79] X. Zhu and A. Ganesan, *J Comb. Chem.*, 1999, **1**, 157.

[80] Z. Timár and T. Gallagher, *Tetrahedron Lett* , 2000, **41**, 3173.

[81] S. Berteina, S. Wendeborn and A. De Mesmaeker, *Synlett*, 1998, 1231.

[82] S. Berteina, S. Wendeborn and A. De Mesmaeker, *Synlett*, 1999, 1121.

[83] G. Jia, H. Iida and J. W. Lown, *Synlett*, 2000, 603.

[84] A. Routledge, C. Abell and S. Balasubramanian, *Synlett*, 1997, 61.

[85] S. Berteina and A. De Mesmaeker, *Tetrahedron Lett.*, 1998, **39**, 5759.

[86] X. Du and R. W. Armstrong, *J. Org Chem.*, 1997, **62**, 5678.

[87] X. Du and R. W. Armstrong, *Tetrahedron Lett.*, 1998, **39**, 2281.

[88] H. Miyabe, H. Tanaka and T. Naito, *Tetrahedron Lett.*, 1999, **40**, 8387.

[89] H. Miyabe, K. Fujii, H. Tanaka and T. Naito, *Chem Commun.*, 2001, 831.

[90] G.-H. Jeon, J.-Y. Yoon, S. Kim and S. S. Kim, *Synlett*, 2000, 128.

[91] L. De Luca, G. Giacomelli, G. Porcu and M. Taddei, *Org Lett.*, 2001, **3**, 855.

[92] K. C. Nicolaou, J. Pastor, S. Barluega and N. Winssinger, *Chem Commun.*, 1998, 1947.

[93] R. T. Taylor and L. A. Flood, *J. Org. Chem.*, 1983, **48**, 5160.

[94] K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G.-Q. Cao, S. Barluenga and H. J. Mitchell, *J. Am Chem. Soc* , 2000, **122**, 9939.

[95] K. C. Nicolaou, J. A. Pfefferkorn and G.-Q. Cao, *Angew. Chem. Int. Ed* , 2000, **39**, 734.

[96] K. C. Nicolaou, G.-Q. Cao and J. A. Pfefferkorn, *Angew. Chem Int. Ed* , 2000, **39**, 739.

[97] K. C. Nicolaou, N. Winssinger, R. Hughes, C. Smethurst and S. Y. Cho, *Angew Chem Int. Ed* , 2000, **39**, 1084.

[98] K. C. Nicolaou, J. A. Pfefferkorn, S. Barluenga, H. J. Mitchell, A. J. Roecker and G.-Q. Cao, *J Am. Chem. Soc.*, 2000, **122**, 9954.

[99] K. C. Nicolaou, J. A. Pfefferkorn, H. J. Mitchell, A. J. Roecker, S. Barluenga, G.-Q. Cao, R. L. Affleck and J. E. Lillig, *J Am Chem. Soc* , 2000, **122**, 9968.

[100] K.-I. Fujita, H. Taka, A. Oishi, Y. Ikeda, Y. Taguchi, K. Fujie, T. Saeki and M. Sakuma, *Synlett*, 2000, 1509.

[101] K.-I. Fujita, K. Watanabe, A. Oishi, Y. Ikeda and Y. Taguchi, *Synlett*, 1999, 1760.

[102] H. Qian and X. Huang, *Tetrahedron Lett* , 2002, **43**, 1059.

[103] T. Ruhland, K. Anderson and H. Pederson, *J. Org Chem.*, 1998, **63**, 9204.

[104] M. J. Farrall and M. J. Fréchet, *J. Org Chem* , 1976, **41**, 3877

[105] K. C. Nicolaou, A. J. Roecker, J. A. Pfefferkorn and G.-Q. Cao, *J. Am. Chem. Soc.*, 2000, **122**, 2966.

[106] S.-A. Aladesanmi, R. Nia, C. Fontaine and M. Pais, *Phytochemistry*, 1995, **35**, 1053.

[107] J. Marco-Contelles and M. Rodríguez-Fernández, *J. Org. Chem.*, 2001, **66**, 3717.

[108] D. Ranganthan and S. Bamezai, *Synth. Commun.*, 1985, **15**, 259.

[109] A. Guzmán-Pérez and L. A. Maldonado, *Synth. Commun.*, 1991, **21**, 1667.

[110] H.-B. Schröter, D. Neumann, A. R. Katritsky and F. J. Swinbourne, *Tetrahedron*, 1966, **22**, 3180.

[111] J. K. Shen, H. Katayama, N. Takatsu and I. J. Shiro, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2087.

[112] S. Takano, Y. Imamura and K. Ogasawara, *Heterocycles*, 1982, **19**, 1223

[113] H. Bredereck, R. Sell and F. Effenberger, *Chem. Ber* , 1964, **97**, 3407.

[114] G. Maury, J.-P. Paugam and R. Paugam, *J. Heterocyclic Chem* , 1978, **15**, 1041.

[115] S. H. Bertz, G. Dabbagh and P. Cotte, *J. Org. Chem* , 1982, **47**, 2216.

[116] W. Holzer and G. Seiringer, *J. Heterocyclic Chem* , 1993, **30**, 865.

[117] E. Mann, *Ph.D Thesis*, 2001.

[118] L. Henriksen and N. Stuhr-Hansen, *J. Chem. Soc , Perkin Trans. 1*, 1999, 1915.

[119] D. Liotta, W. Markiewicz and H. Santiesteban, *Tetrahedron Lett.*, 1977, **50**, 4365.

[120] P. Dowd and P. Kennedy, *Synth Commun.*, 1981, **11**, 935.

[121] F. F. Noe and L. Fowden, *Nature*, 1959, **184**, 69.

[122] E. Klingsberg, *J Am. Chem Soc.*, 1961, **83**, 2934.

[123] M. I. Rodríguez-Franco, I. Dorronsoro, A. I. Hernández-Higueras and G. Antequera, *Tetrahedron Lett.*, 2001, **42**, 863.

[124] L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, 1966, **31**, 1878.

[125] C. L. Willis and M. R. Wills, *Organic Synthesis, Oxford University Press*, 74.

[126] A. R. Chamberlin and J. Y. L. Chung, *J Org. Chem.*, 1985, **50**, 4425.

[127] C. Chatgilialoglu, D. Crich, M. Komatsu and I. Ryu, *Chem Rev.*, 1999, **99**, 1991.

[128] J. Quirante, X. Vila, C. Escolano and J. Bonjoch, *J. Org Chem* , 2002, **67**, 2323.

[129] M. Banwell, A. Edwards, J. Smith, E. Hamel and P. Verdier-Pinard, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1497.

[130] K. C. Nicolaou, D. A. Claremon, W. E. Barnette and S. P. Seitz, *J. Am. Chem. Soc.*, 1979, **101**, 3704.

[131] K. C. Nicolaou, N. A. Petasis and D. A. Claremon, *Tetrahedron*, 1985, **41**, 4835

[132] G. W. Gokel, R. P. Widera and W. P. Weber, *Org Synth* , 232.

[133] H. Liu, *Ph.D. Thesis, University of Pittsburgh*, 1994.

[134] F. Aldabbagh, W. R. Bowman and E. Mann, *Tetrahedron Lett* , 1997, **38**, 7937.

[135] J. Rokach, P. Hamel and M. Kakushima, *Tetrahedron Lett.*, 1981, **22**, 4901.

[136] D. Xiao and D. M. Ketcha, 1995, **27**, 503.

[137] K. B. Sharpless, R. F. Lauer and A. Y. Teranishi, *J. Am. Chem Soc.*, 1973, **95**, 6137.

[138] B. L. Bray, P. H. Mathies, R. Naef, D. R. Solas, T. T. Tidwell, D. R. Artis and J. M. Muchowski, *J. Org. Chem.*, 1990, **55**, 6317.

[139] C. Ortiz and R. Greenhouse, *Tetrahedron Lett.*, 1985, **26**, 2831.

[140] S. H. Kang, G. T. Kim and Y. S. Yoo, *Tetrahedron Lett.*, 1997, **38**, 603.

[141] A. L. J. Beckwith, W. R. Bowman, E. Mann, J. Parr and J. M. D. Storey, article in preparation.

[142] W. K. Busfield, I. D. Jenkins and P. Van Le, *Polymer Bulletin*, 1997, **38**, 149.

[143] G. A. Russell, P. Chen, B. H. Kim and R. Rajaratnam, *J. Am. Chem Soc.*, 1997, **119**, 8795.

[144] E. S. Lewis and K. Ogino, *J. Am Chem Soc* , 1976, **98**, 2260.

[145] D. P. Curran, H. Yu and H. Liu, *Tetrahedron*, 1994, **50**, 7343.

[146] E. Mann, *PhD Thesis, Loughborough University*, 2001.

[147] G. A. Mortimer, *J Org. Chem.*, 1965, **30**, 1632

[148] E. J. Corey, D. J. Pasto and W. L. Mock, *J Am Chem. Soc.*, 1961, **83**, 2957

[149] B. D. Baigrie, J. I. G. Cadogan and J. T. Sharp, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1065.

[150] G. B. Jones, C. J. Moody, A. Padwa and J. M. Kassir, *J. Chem. Soc., Perkin Trans 1*, 1991, 1721.

[151] J. J. Li, *Tetrahedron*, 2001, **57**, 1.

[152] A. Zelikin, V. R. Shastri and R. Langer, *J Org. Chem.*, 1999, **64**, 3379.

[153] D. Xiao, J. A. Schreier, J. H. Cook, P. G. Seybold and D. M. Ketcha, *Tetrahedron Lett* , 1996, **37**, 1996.

[154] J. Cornforth and D. Ming-Hui, *J Chem. Soc. Perkin Trans. 1*, 1990, 1463.

[155] G. Malesani, G. Rigatti and G. Rodrhiero, *Tetrahedron Lett.*, 1969, **48**, 4173.

[156] J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman and R. C. Thomas, *J. Chem Soc., Chem Commun.*, 1976, 736.

[157] H. Ishibashi, T. Sato and M. Ikeda, *Synthesis*, 2002, **6**, 695.

[158] P. Garner and J. M. Park, *J Org Chem.*, 1987, **52**, 2361.

[159] G. E. Keck and A. M. Tafesh, *Synlett*, 1990, 257.

[160] R. Karim and W. R. Bowman, unpublished results.

[161] K. C. Nicolaou, D. A. Claremon, W. E. Barnette and S. P. Seitz, *J. Am. Chem. Soc.*, 1979, **101**, 3480.

[162] X. Huang and W. Xu, *Tetrahedron Lett.*, 2002, **43**, 5495.

[163] L. Uehlin and T. Wirth, *Org Lett.*, 2001, **3**, 2931.

[164] L. Engman and P. Eriksson, *Heterocycles*, 1996, **43**, 861.

[165] C. Millois and P. Diaz, *Org Lett.*, 2000, **2**, 1705.

[166] G. Mugesh and H. B. Singh, *Acc. Chem Res.*, 2002, **35**, 226.

[167] L. Uehlin and T. Wirth, *Chimia*, 2001, **55**, 65.

[168] W. R. Bowman, H. Heaney and P. H. G. Smith, *Tetrahedron Lett.*, 1984, **25**, 5821.

[169] P. C. Ruenitz, C. S. Bourne, K. J. Sullivan and S. A. Moore, *J. Med Chem.*, 1996, **39**, 4853.

[170] D. F. Evans and V. Fazakerley, *Chem. Commun.*, 1968, 974.

[171] M. Tiecco, L. Testaferri, M. Tingoli, D. Chianelli and M. Montanucci, *J. Org Chem*, 1983, **48**, 4289.

[172] P. D. Bailey and K. M. Morgan, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3578.

[173] D. C. Harrowven, M. I. T. Nunn, N. J. Blumire and D. R. Fenwick, *Tetrahedron*, 2001, **57**, 4447.

[174] J. Sapi, Y. Grébille, J-Y. Laronze and J. Lévy, *Synthesis*, 1992, 383.

[175] A. Pohland and H. R. Sullivan, *J. Am. Chem. Soc.*, 1953, **75**, 5898.

[176] M. J. Farrall and M. J. Frechet, *J. Org. Chem*, 1976, **41**, 3877.

[177] G. Heinisch, W. Holzer, O. Wolfgang and C. Obala, *Monatsch Chem*, 1988, **119**, 253.

[178] Aldrich Chemical Catalogue, 2000.

[179] Castillo et al., *Tetrahedron Lett.*, 1970, **15**, 1219.

[180] M. Kakushima, P. Hamel, R. Frenette and J. Rokach, *J. Org. Chem*, 1983, **48**, 3214.

[181] Y. Kita, H. Maeda, K. Omori, T. Okuno and Y. Tamura, *J. Chem. Soc, Perkin Trans. 1*, 1993, **23**, 2999.

[182] R. J. Cremlyn, *J. Chem. Soc.*, 1961, 5549.

[183] C. Lambert, M. Hilbert and L. Christiaens, *Syn. Commun.*, 1991, **21**, 85.

[184] L. Laitem, P. Thibaut and L. Christiaens, *J. Heterocyclic Chem.*, 1976, **13**, 469.

[185] A. H. Cook and K. J. Reed, *J. Chem. Soc.*, 1945, 402.