Nitrogen-Directed Free Radical Rearrangements

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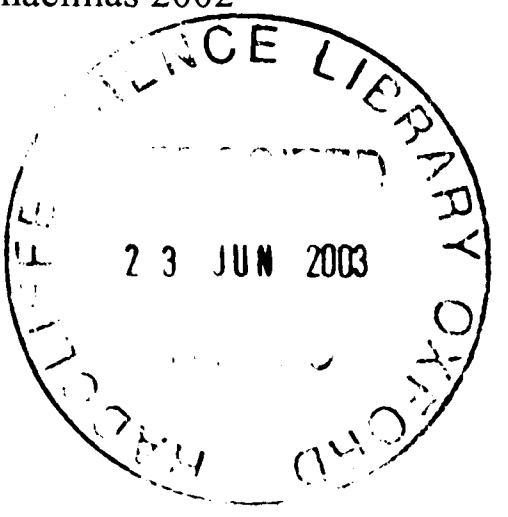

"I intend to reserve the field for myself"

- Moses Gomberg upon identifying the triphenylmethyl radical, 1900

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My parents have been a constant source of encouragement, and have always supported me in my aspirations - thank you both.

Last but by no means least I would like to thank Agnès, whose companionship has become an important part of my life.

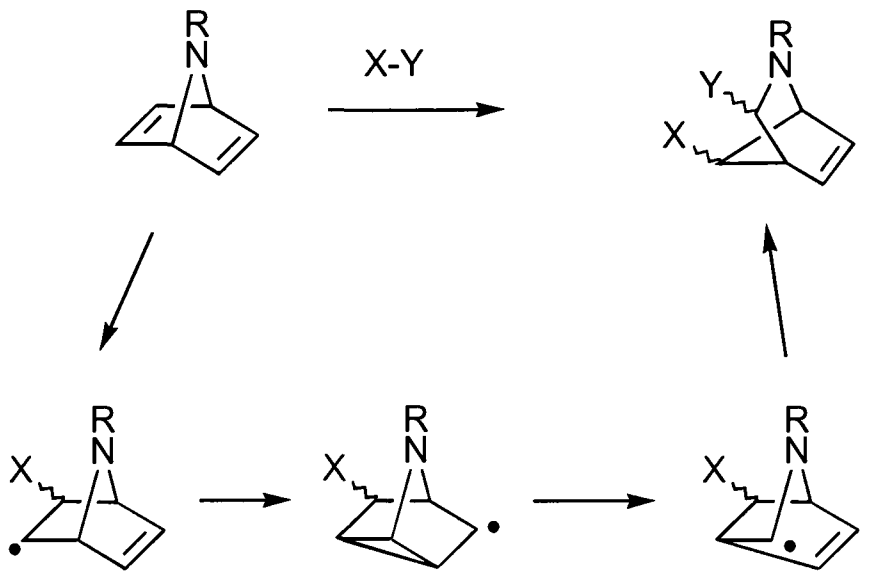
List of Abbreviations

1D	One-dimensional
9-BBN	9-Borabicyclo[3.3.1]nonane
AIBN	Azobis(isobuytronitrile)
R-BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl (Phenyl methyl)
Boc	*tert*-Butoxycarbonyl
COD	1,5-Cyclooctadiene
Cp	Cyclopentadienyl
DCCI	Dicyclohexyl Carbodiimide
R,R-DIOP	2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMAP	4-(*N,N*-Dimethylamino)pyridine
DMDO	dimethyl dioxirane
DMSO	Dimethyl sulfoxide
EDTA	Ethylene diamine tetraacetic acid
ee	Enantiomeric Excess
EPR	Electron Paramagnetic Resonance
EWG	Electron-Withdrawing Group
HMPA	Hexmethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
LDA	Lithium diisopropylamide

LUMO	Lowest Unoccupied Molecular Orbital
*m*CPBA	*meta*-Chloro-perbenzoic acid
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
nOe	nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
PTOC	2-pyridinethione oxycarbonyl
rac	Racemic
SET	Single Electron Transfer
SOMO	Singly-Occupied Molecular Orbital
TBAF	Tetra(n-butylammonium) Fluoride
TBTH	Tributyltin hydride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Tri(isopropyl)silyl
TMSCl	Trimethylsilyl chloride
Tol	*p*-Tolyl (*p*-methylphenyl)
TosMIC	Tosylmethyl isocyanide
Ts	Tosyl (*p*-toluenesulfonyl)
TTMSS	Tris(trimethylsilyl)silane

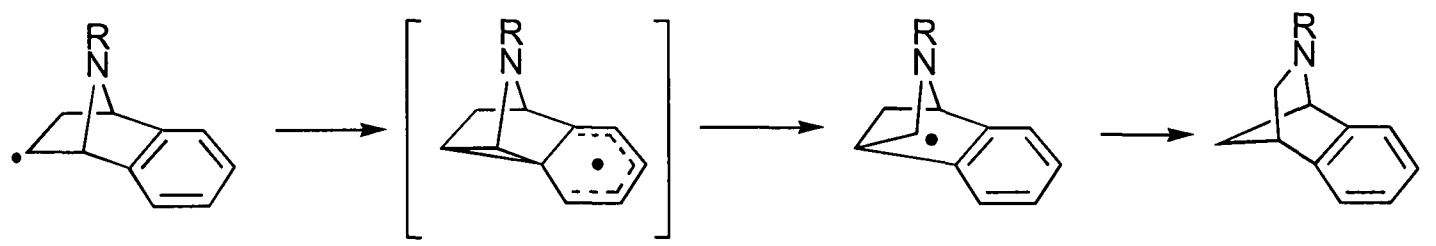
Abstract

This thesis describes efforts to develop new methods for the synthesis of bridged azacycles using nitrogen-directed free radical rearrangements. Free radical addition to 7-azanorbornadienes were carried out to give 7-substituted 2-azanorbornenes (Scheme a.1, X-Y = RS-H or PhSe-H).



Scheme a.1 Nitrogen-directed homoallylic radical rearrangement *via* intermolecular radical addition.

A conceptually novel and theoretically interesting nitrogen-directed neophyl rearrangement (Scheme a.2) was developed into a synthesis of 2-azabenzonorbornanes **2**.



1 **2**

Scheme a.2 Nitrogen-directed neophyl-like rearrangement to 2-azabenzonorbornanes.

In this case the radical **1** was generated by Barton deoxygenation of 7-azabenzonorbornanols. The effect on rearrangement of bicyclic core substitution and of aromatic ring electronics was probed in some detail, and the process was synthetically useful for a wide range of substrates.

Variation of the protecting group on nitrogen was investigated and the product profiles from neophyl-like rearrangement were consistent with a process driven by the stability of a radical α to nitrogen as a result of SOMO-lone pair orbital interaction.

The kinetics and mechanism of these processes are examined where appropriate, leading to estimates of rate constants for the rearrangements.

Stereochemical Abstract

The absolute sense of induction for the enantioselective reactions presented in Chapter Five is not known. Dashed and bold bonds are used to indicate relative stereochemistry only. A positive value of the ee is given when the first enantiomer to elute in chiral HPLC is in excess.

Introduction

This thesis is primarily concerned with synthesis of bridged nitrogen heterocycles. However, it is important at this point to introduce in general terms some of the processes that predominate in the free radical chemistry presented, and also to illustrate their use in synthesis, where applicable. Particular attention is paid to radical deoxygenation of alcohols, widely used in the project, and also to the emergence of radical methods using transition metals, an area of considerable current interest.

1.1 Overview of Free Radical Chemistry

Free radical chemistry has developed over the last century from a purely academic curiosity into a mainstream method for the construction of organic molecules.[1] In 1900, Moses Gomberg was the first to describe a free radical species, namely triphenylmethyl. Subsequently a number of organic reaction mechanisms came to be understood in terms of free radical intermediates, culminating in a seminal review by Hey and Waters,[2] which described all the common free radical reaction types. At this time, free radicals were not thought to be of use in organic synthesis, since they were considered too reactive to show selectivity in their reactions. Several discoveries were made in the 1970s which showed that this was not the case, with the development of radical deoxygenation of alcohols and the emergence of tributyltin hydride(TBTH)-mediated processes being of particular note.[3]

Following these advances, free radical chemistry was used increasingly to construct complex organic molecules. Beckwith's application[4] of Baldwin's rules[5] to explain the stereoselectivity of free radical cyclisations combined with an increasing understanding of free radical kinetics[6] allowed vastly improved selectivity. Curran's

classic synthesis of hirsutene[7] was one of the first to use free radical chemistry in the key step of a total synthesis. The mild reaction conditions and high reactivity meant that these processes were of great use in constructing the highly functionalised frameworks often encountered in natural product chemistry. The fact that radical intermediates are not highly solvated means that reactions are applicable to hindered systems and to the construction of quaternary centres. By the 1990s free radical methods were part of the mainstream of synthetic organic chemistry, and one of the more recent developments has been the emergence of transition metal-promoted radical reactions, with Mn(III),[8] Sm(II)[9] and latterly Ti(III)-based reagents[10,11] finding synthetic applications.

1.2 Tin Hydrides and their Analogues in Free Radical Chemistry

1.2.1 Radical Chain Mechanisms

Tributyltin hydride is still the most widely used mediator of free radical reactions.[12] It is very reactive towards carbon-centred radicals, since the thermodyamics favours the homolytic cleavage of the weak Sn-H bond and the formation of the stronger C-H bond. In order to design a free radical process such that it provides the desired products, a knowledge of the rates of the possible reactions that can occur is essential. Illustrated below are the steps for a typical TBTH-mediated radical chain reaction (Scheme 1.1):

Initiation: $In\text{-}In \rightarrow 2 \times In\bullet$ (k_{In})

Propagation 1: $In\bullet + Bu_3SnH \rightarrow InH + Bu_3Sn\bullet$ (k_1)

Propagation 2: $Bu_3Sn\bullet + AX \rightarrow Bu_3SnX + A\bullet$ (k_2)

Addition: $A\bullet + B \rightarrow A\text{-}B\bullet$ (k_{add})

Propagation 3: $A\bullet + Bu_3SnH \rightarrow AH + Bu_3Sn\bullet$ (k_3)

Propagation 4: $A\text{-}B\bullet + Bu_3SnH \rightarrow A\text{-}BH + Bu_3SnH$ (k_4)

Termination: A• or B• → non-radical products (k_t)

Scheme 1.1 A typical tin hydride-mediated radical chain mechanism for intermolecular radical addition.

In this example, the initiator is typically a peroxide or diazo- compound that fragments homolytically under the reaction conditions, either thermally or through photolysis. H-atom abstraction then generates the desired tributyltin radical, which in turn reacts with the precursor AX for the carbon-centred radical to give A•. AX is often an alkyl bromide or iodide, and step 2 is therefore driven by formation of a strong Sn-X bond at the expense of a weaker C-X bond. A• can now add to some acceptor species B, which is nearly always an unsaturated acceptor such as an acrylic ester. Both A• and A-B• can then be subject to H-atom transfer to give the final products. If a useful yield of the addition product A-BH is required, the addition of A• to B must be faster than formation of AH and also the termination step i.e. $k_{add} > k_3$ and $k_{add} > k_t$.

1.2.2 Polar effects

It is useful at this point to highlight the important role of polar effects in free radical chemistry, and their profound consequences for the rate constants mentioned above.[13] Although organic free radicals are neutral species, they still possess nucleophilic or electrophilic character, depending on their substituents. The polar character of a free radical species depends on the energy level of the Singly-Occupied Molecular Orbital (SOMO). Radicals with high energy SOMOs interact more favourably with LUMOs (Lowest Unoccupied Molecular Orbitals) of unsaturated radical acceptor molecules so they have nucleophilic character, and conversely those with low energy SOMOs interact better with HOMOs (Highest

Occupied Molecular Orbitals) of radical acceptors so they have electrophilic character (Fig. 1.1).

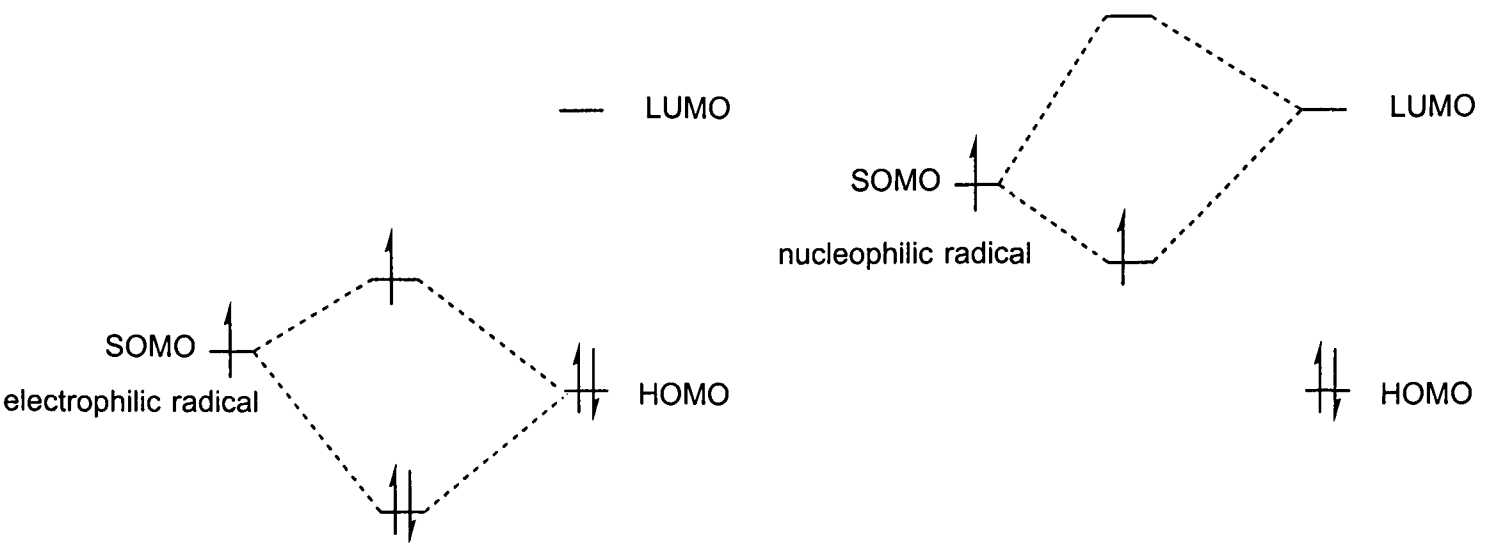
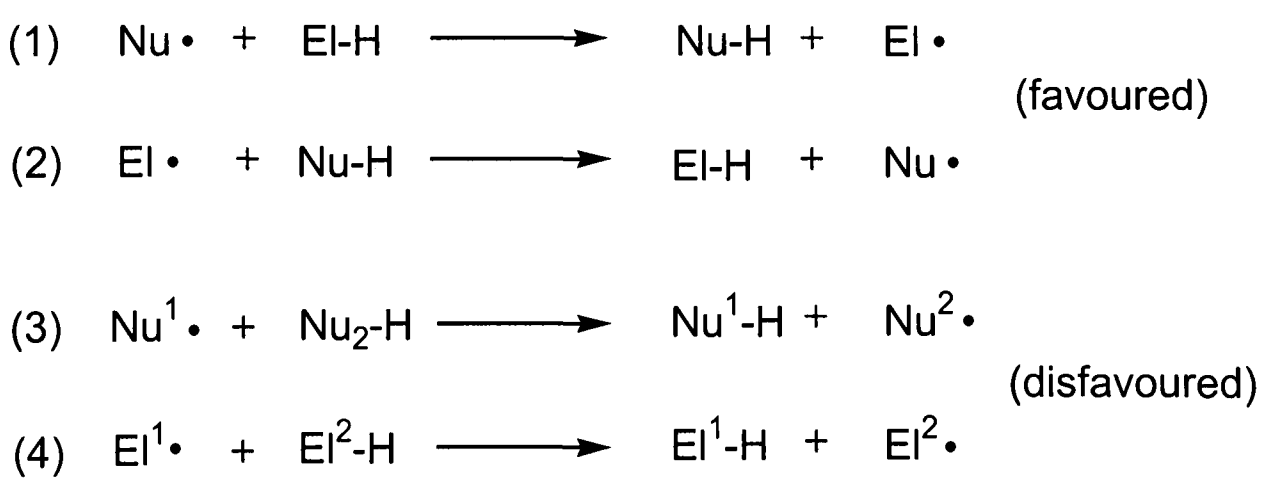


Fig. 1.1 MO interactions for radicals with electrophilic and nucleophilic character with unsaturated radical acceptors.

Polar effects are also used to explain the reactivity of radicals towards different H-atom donors in an analogous way to their rates of addition to unsaturated acceptors. Nucleophilic radicals (Nu•, Scheme 1.2) react more rapidly with H-atom donors (El-H) which give rise to electrophilic radicals, and vice-versa. Conversely, H-atom transfer to a radical that produces another radical with similar electronic characteristics is disfavoured (Scheme 1.2, equations 3 and 4).[14] This is shown by the equations below:



Scheme 1.2 Reactions of nucleophilic and electrophilic radicals with different H-atom transfer agents.

Once again this can be understood in terms of frontier orbitals, with the low energy SOMO of an electrophilic radical interacting more strongly with the high

energy σ orbital of the H-atom donor (NuH), whereas the high energy SOMO of a nucleophilic radical interacts more favourably with the low energy σ* orbital of the H-atom donor (El-H) (Fig. 1.2, below):

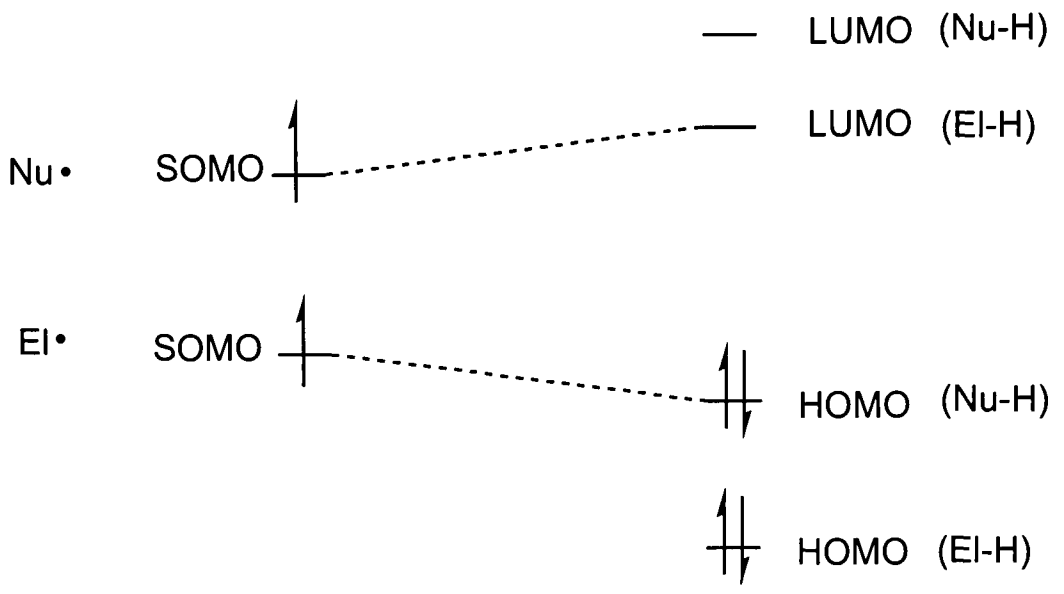
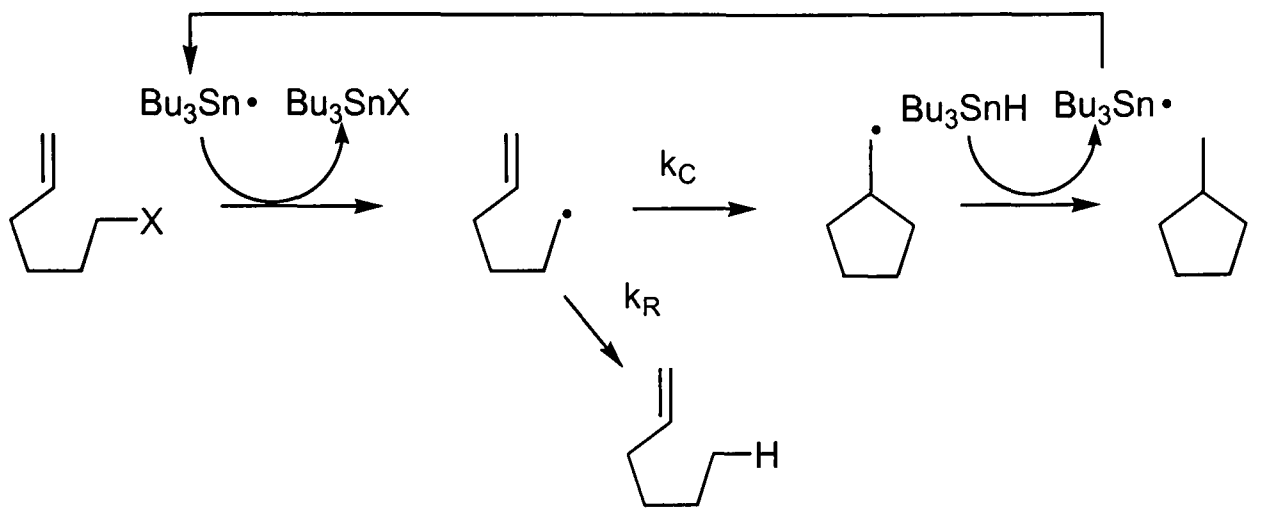


Fig. 1.2 Frontier orbital interactions for H-atom abstraction.

Appropriate choice of H-atom donor, or a combination of two donors with different properties has recently led to the development of polarity-reversal catalysis.[14]

1.2.3 Free Radical Reaction Design

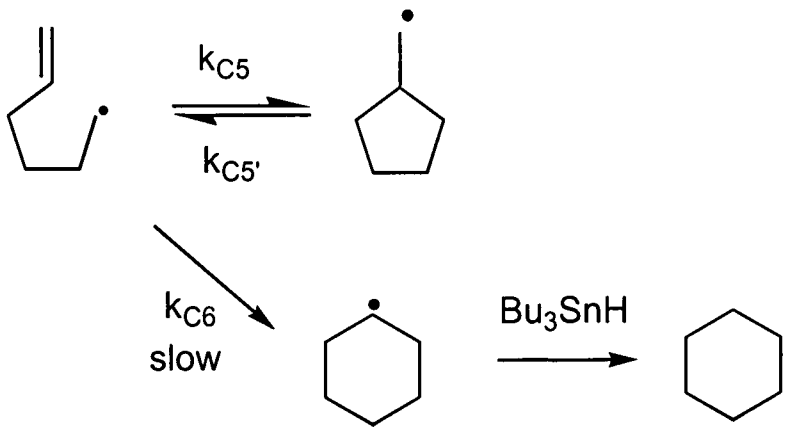
Intramolecular free radical reactions are relatively straightforward to design, since the tin hydride concentration can be altered such that the reaction, *e.g.* cyclisation or fragmentation, occurs competitively with reduction. The intramolecularity serves to accelerate any such reaction compared to its intermolecular equivalent, as the entropy of activation is much less negative in this case. It also considerably simplifies the mathematics, since the radical precursor and acceptor are part of the same molecule and the concentration of the acceptor need not be considered as a separate variable. The classic example of an intramolecular radical reaction is a 5-*exo* trig cyclisation using a suitable radical precursor group X tethered to an alkene (Scheme 1.3, overleaf).



Scheme 1.3 5-*exo* trig radical cyclisation.

In practice, 5-*exo* trig cyclisation is kinetically preferred over the alternative 6-*endo*, although both are stereoelectronically favoured under Baldwin's rules.[5] As long as cyclisation is appreciably faster than direct H-atom transfer to the first-formed radical ($k_C > k_R$), good yields of the cyclised product can be obtained. The value of k_R is readily found from the product of the second order H-atom transfer rate for TBTH (k_H) and the concentration of TBTH, i.e. $k_R = k_H[TBTH]$. The concentration of the tin hydride can be varied, e.g. using syringe pump techniques, such that cyclisations with different rates can occur, and the product profile can be carefully controlled. There is a lower limit to tin hydride concentration (about 0.001 M), since a radical species will ultimately decompose to non-radical products by other pathways if not trapped by the TBTH, which include H-atom transfer from the solvent. This means that the chain mechanism cannot be sustained. In practice, the rate constant k_C should be greater than $10^3 s^{-1}$ to avoid competition from bimolecular reduction by TBTH ($k_H = 2 \times 10^6$ $M^{-1}s^{-1}$ at 25 °C).[12] Typical rate constants for cyclisation are in the range $k_C = 10^4$-10^5 s^{-1}, depending on the sterics and electronics of the system in question. There are other caveats, however, in that if 5-*exo* cyclisation is reversible, the cyclohexyl radical arising from slower but

thermodynamically favoured 6-*endo* cyclisation can predominate, leading to a different product (Scheme 1.4).



Scheme 1.4 Thermodynamic 6-*endo*-trig cyclisation.

Extensions of this method to formation of polycyclic systems have now been developed, and this represents one of the most powerful ways of assembling these systems. [15]

As another example of the application of these kinetic principles, an intermolecular radical conjugate addition is shown below (Scheme 1.5):

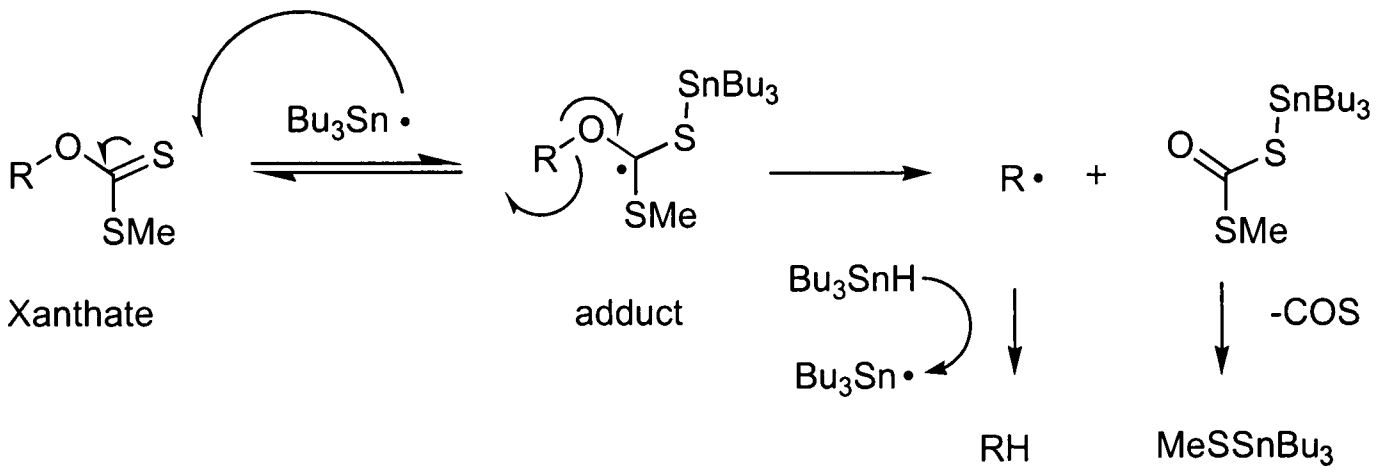
Scheme 1.5 conjugate radical addition to an alkyl acrylate.

Simple alkyl radicals are nucleophilic in character - they react more rapidly with electron-deficient unsaturated systems (e.g. enones and acrylates) than with simple olefins.[13] Despite this, several equivalents of the ester are normally required to prevent H-atom transfer directly to R•. Following the addition, the adduct radical is electrophilic in character and reacts more rapidly with TBTH than it does with another molecule of acrylate, preventing polymerisation. This demonstrates the

importance of kinetics and choice of radical acceptor in designing a free-radical process.

1.2.4 Barton deoxygenation of Xanthates

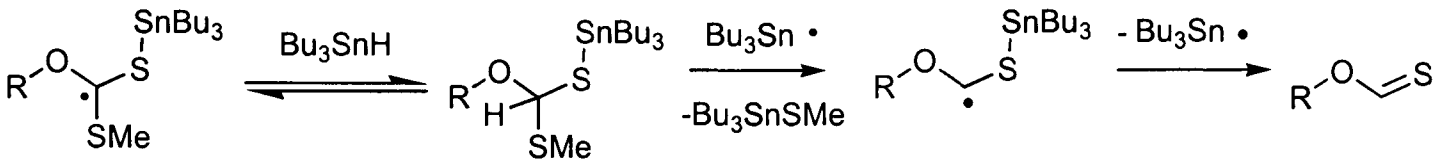
The Barton deoxygenation of secondary alcohols was one of the first synthetically useful free radical processes.[16] It was designed initially to overcome the problems of many ionic deoxygenations, which led to skeletal rearrangements of carbocations under acidic conditions. The reaction is also found to be applicable to hindered systems, such as nucleotides. Since that time it has become a common method for radical generation on an oxygenated substrate. The proposed mechanism is shown below, and was elucidated as a result of considerable investigation by Barton and others: [17]



Scheme 1.6 Mechanism of Barton-McCombie deoxygenation.

The tributyltin radical reversibly attacks the thiocarbonyl sulfur atom, cleaving the weak C-S π-bond and giving an adduct which then fragments to give the alkyl radical R•. This step is driven by the formation of a very stable carbonyl group. The more stable R• is, the more smoothly the fragmentation occurs. The radical R• can then undergo other chemistry, such as addition to an acceptor or rearrangement, prior to H-atom transfer from TBTH. In practice, the original Barton procedure is best suited to derivatives of secondary alcohols. Tertiary xanthates are

unstable to Chugaev elimination to give alkenes,[1] and primary xanthates tend to form thioformates in the reaction, which ultimately are hydrolysed to starting alcohol.[16] (Scheme 1.7).



Scheme 1.7 Formation of thioformates in Barton deoxygenation.

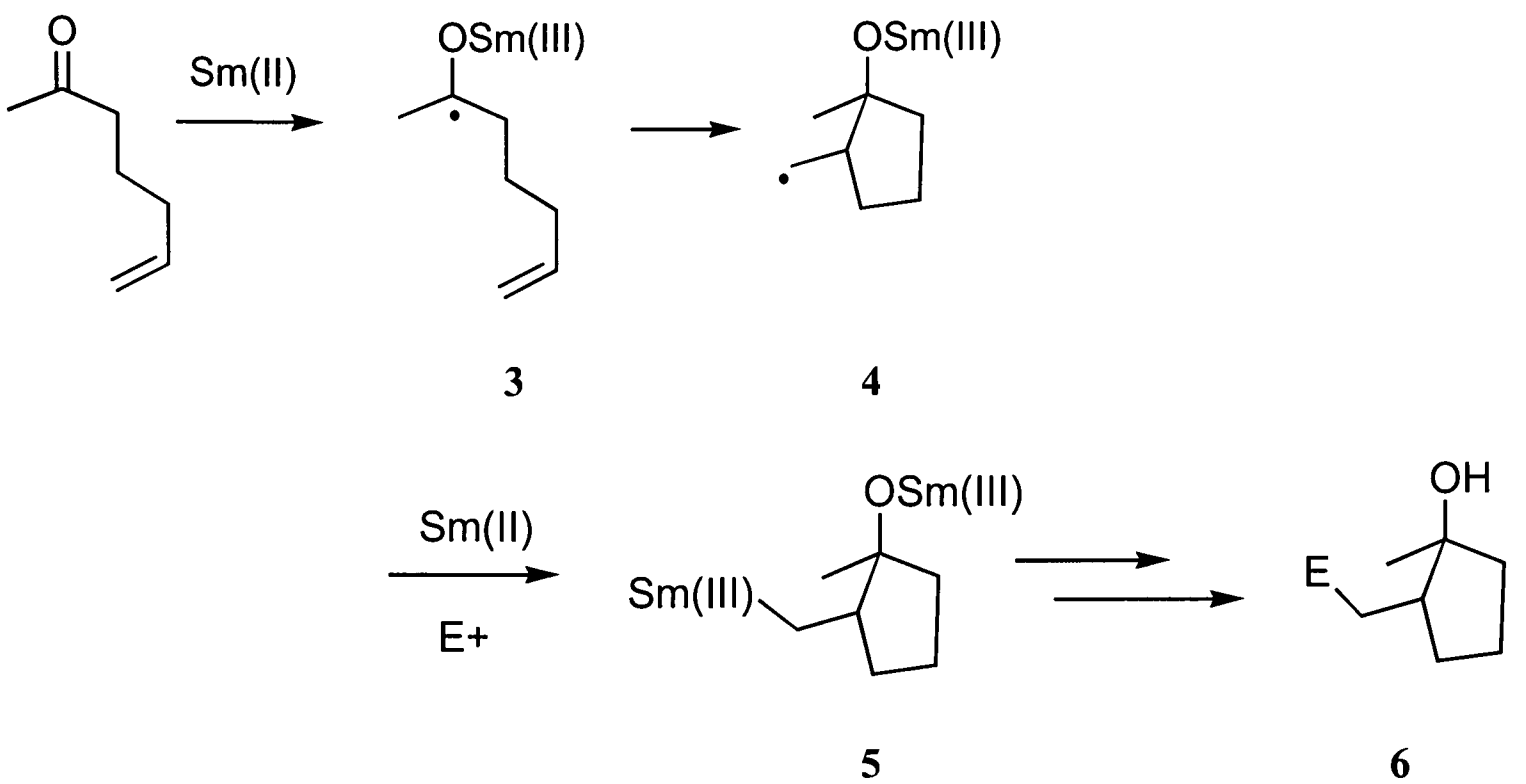
Special procedures have been developed by Barton[18] and others[19] to effect deoxygenation of tertiary alcohols. The reaction is compatible with most of the commonly-encountered functional groups in organic chemistry, and as such has found wide use in natural product synthesis.[16] A number of other thiocarbonyl derivatives are now known to undergo the reaction, and the use of tin hydride substitutes such as tris(trimethylsilyl)silane (TTMSS)[20] instead of TBTH has overcome the problem of removing toxic tin-containing by-products from reaction residues.[21] This difficulty has also been overcome by catalytic use of tin hydride[22] and by development of special procedures for removal of tin residues during work-up. [23, 24]

1.3 Free radical reactions involving transition metals

Whilst there has been considerable interest in development of substitutes for TBTH in recent years,[25, 26] it has been discovered that transition metals can be made to generate organic free radicals. Frequently, the chemistry is not accessible from the use of TBTH and its analogues, and so new reactivity can be developed.

1.3.1. Reductive radical generation with Samarium(II) Iodide

SmI_2 is a powerful reducing agent and its usefulness is derived from the ability of samarium to coordinate well to oxygen.[27] Treatment of a ketone with SmI_2 results in reduction to the alcohol.

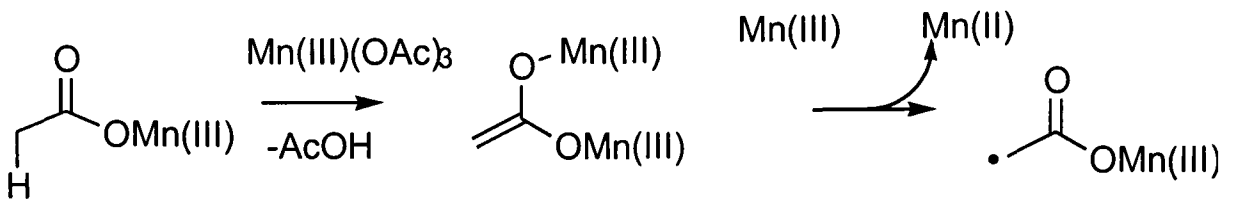


Scheme 1.8 Generalised radical generation and trapping with SmI_2.

Electron transfer from the metal into the carbonyl group of an unsaturated ketone gives rise to a Sm(III)-bound radical anion **3** (Scheme 1.8), which can then be trapped by a pendant double bond to give **4**. Further reduction leads to the formation of an organosamarium intermediate **5**, which can be trapped by reactive electrophiles to give **6** on work-up. This also demonstrates the considerable power of sequenced reactions in synthesis.[9] It is a characteristic of transition metal-based free radical processes that ionic processes can occur subsequently, depending on whether oxidative or reductive conditions are used.

1.3.2 Oxidative Radical Generation with Mn(III) salts

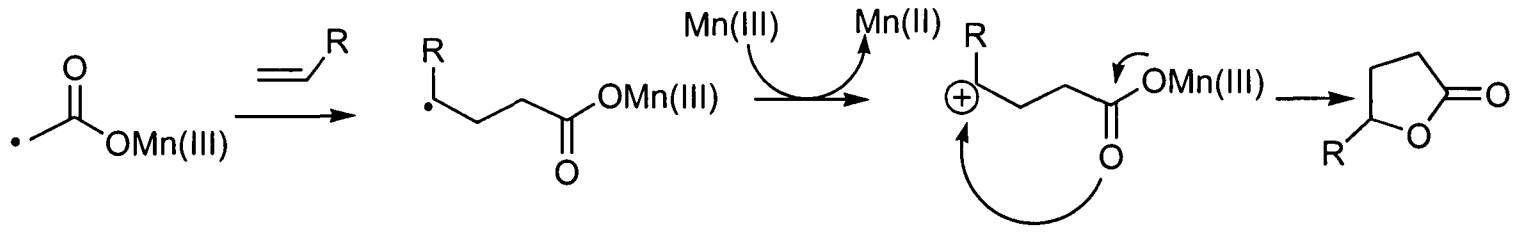
Manganese(III) salts have also been used to generate radicals from mono- and dicarbonyl compounds.[8] The mechanism of radical generation is similar, although not identical in both cases. Presented below is a general scheme:



7 **8** **9**

Scheme 1.9 Oxidative radical generation by Mn(III).

Lewis-acid promoted enolisation of a bound acetate ligand leads to enolate **8**, which undergoes a rapid SET to Mn(III) to give the radical intermediate **9**. In the presence of an alkene, intermolecular radical addition occurs (Scheme 1.10), followed by further oxidation of the resultant nucleophilic radical leading to lactone **10**:



9 **10**

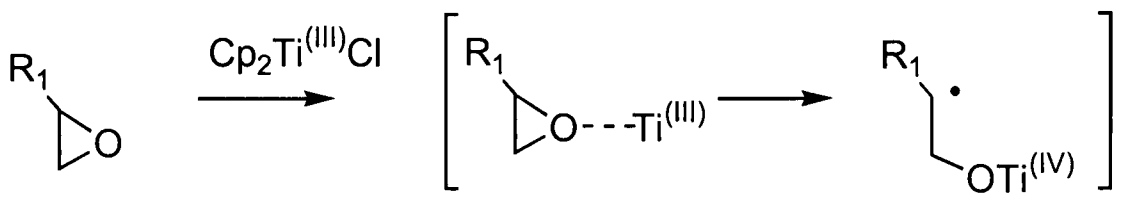
Scheme 1.10 Lactone formation with Mn(III).

The Mn(III) and Sm(II) methods are therefore contrasting in the radicals generated from carbonyl functionalities - Mn(III) produces electrophilic α-carbonyl radicals, and Sm(II) leads to nucleophilic ketyl radical species. This allows construction of diverse organic building blocks from carbonyl compounds using free radical chemistry, in addition to classical chemistry such as enolate generation or nucleophilic attack at carbonyl carbon. The metal-promoted radical chemistry is in

fact complimentary to the ionic carbonyl group chemistry, as umpolung species are produced by the use of free radicals.

1.3.3 Reductive ring opening of Epoxides with Ti(III)

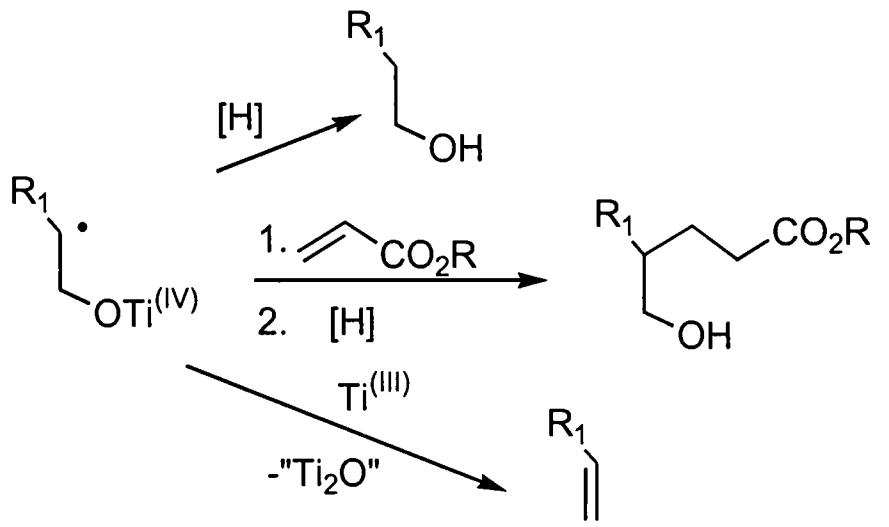
Whereas the previous two metal-promoted methods allow radical generation from carbonyl functionalities, the use of Ti(III) enables radical generation from epoxides,[10] which are readily available by simple oxidation of alkenes, or by connective methods such as addition of sulfur ylides to aldehydes.[28] Radical generation occurs by reductive ring opening of the epoxide **11** to give a radical β to a Ti(IV) alkoxide (Scheme 1.11):



11 **12**

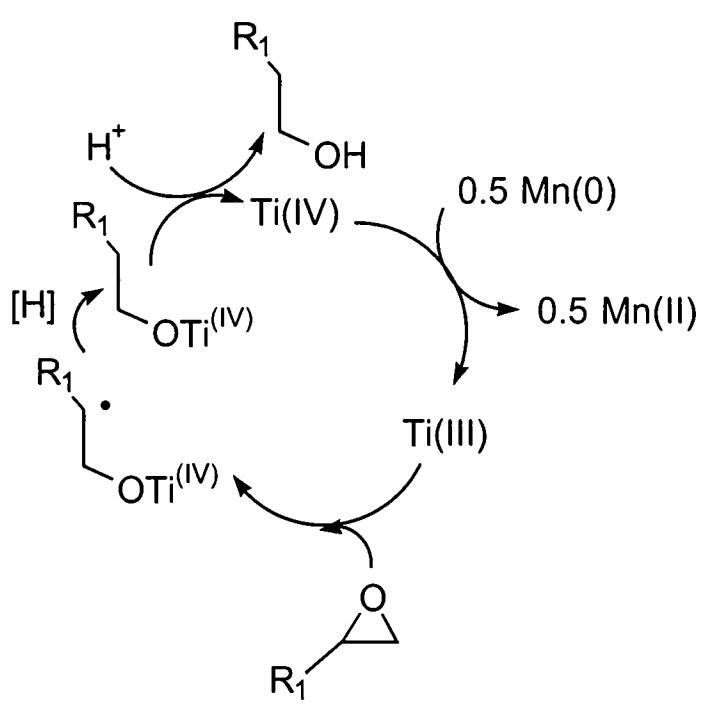
Scheme 1.11 Radical generation with Ti(III).

Initial formation of a σ complex by coordination of Ti(III) to the epoxide oxygen gives formally a metal-centred radical α to a 3-membered ring, which opens with relief of ring strain to give the radical **12**. This intermediate can then be trapped by H-atom donors e.g. 1,4-cyclohexadiene, electron-deficient alkenes or by another molecule of Ti(III). In the latter case, elimination then gives an alkene (Scheme 1.12, overleaf):



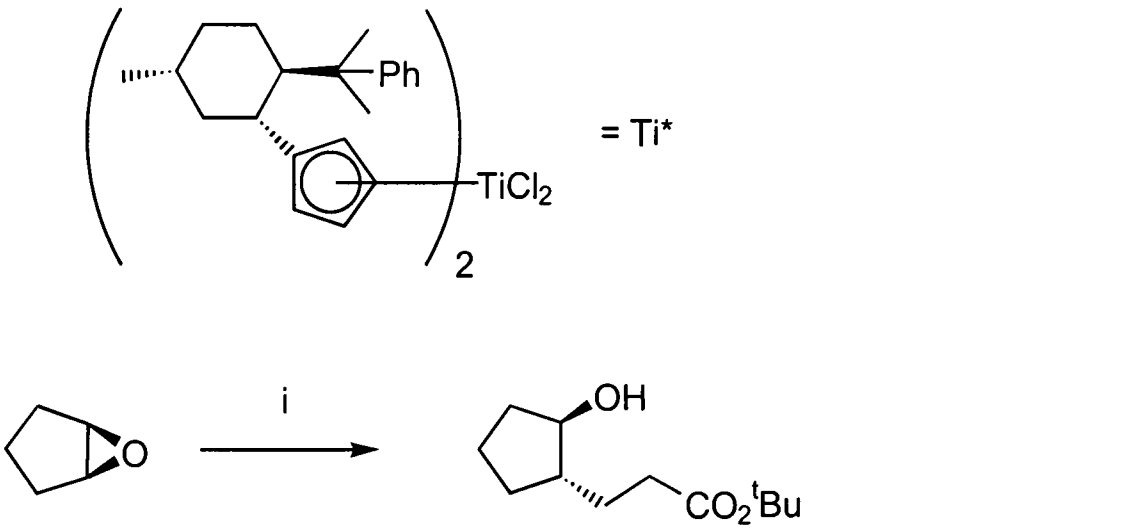
Scheme 1.12 Possible fates of radicals generated in Ti(III) chemistry.

Gansauer [11,29] has developed a version of this reaction which is catalytic in titanium. In the catalytic process manganese is used as the stoichiometric reductant and collidine hydrochloride protonates the Ti-O bond to regenerate Ti(IV):



Scheme 1.13 Catalytic cycle for Gansauer's Ti(III)-mediated reductive ring-opening of epoxides.

A procedure using a titanium complex with chiral cyclopentadienyl ligands (Ti*, Scheme 1.14) has led to a new method for the desymmetrisation of *meso*-epoxides in good *ee*.[30] This chemistry appears to have considerable potential, as it combines an asymmetric ring-opening with carbon-carbon bond formation in the presence of an acrylate (Scheme 1.14).



68%, 74% *ee*, *trans* : *cis* = 97 : 3

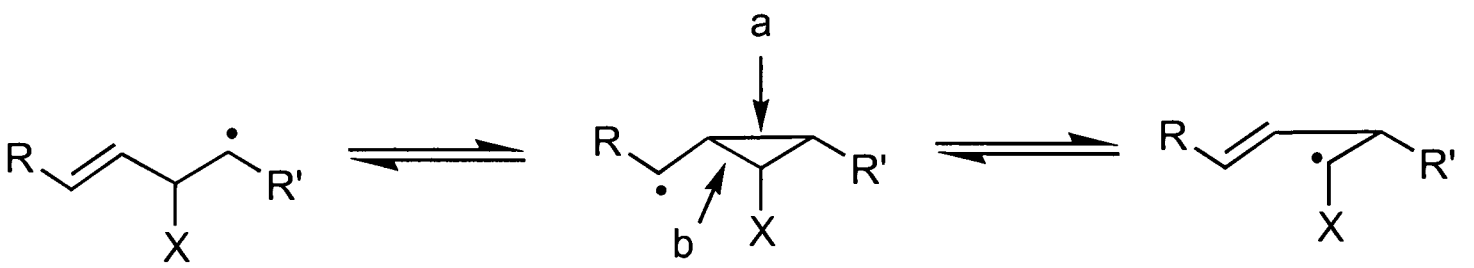
Scheme 1.14 Ti(III)-mediated enantioselective ring-opening of *meso*-epoxides. *Reagents and conditions*: i, 5 mol% Ti*, *tert*-butyl acrylate, 1,4-C_6H_8, Zn, collidine hydrochloride, THF, 48 h.

In addition, it is applicable to epoxides derived from bicyclic alkenes, many of which are incompatible with Jacobsen's asymmetric ring openings using activation with chiral Lewis acids.[31]

1.4 Radical Rearrangements

1.4.1 The homoallyl-cyclopropylmethyl rearrangement

A common free radical process of importance to the project is that of homoallylic rearrrangement. A generalised example is shown below:



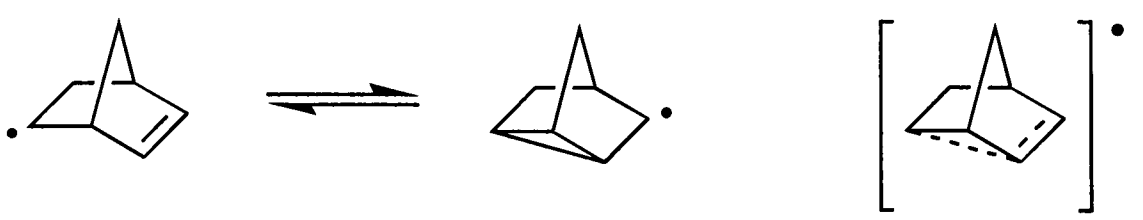
Scheme 1.15 Generalised homoallylic rearrangement

Generation of a homoallyl radical **13** leads to kinetically easy 3-*exo* trig ring closure to give **14**, which then opens with relief of ring strain to return to **13** or alternatively **15** depending which cyclopropane bond (a or b, Scheme 1.14) is

cleaved. The reaction has been extensively studied by mechanistic organic chemists, such that its kinetics and the stereoelectronic factors that govern its selectivity are now well understood.[32] The ring opening of **14** is usually faster than the ring closure step (~10^8 s^{-1} for ring opening *vs* ~10^4 s^{-1} for ring closure for R = R' = X = H),[33] which means that **14** is often present only in small amounts in the reaction mixture. Substitution can markedly affect the relative rates of ring opening and ring closure and hence the proportion of homoallyl and cyclopropyl methyl radicals present at equilibrium, but the equilibrium very often favours the ring-opened form. Selectivity for ring-opened radical **15** can be achieved if group X serves to stabilise the adjacent radical or guide ring opening to give **15** for stereoelectronic reasons.

1.4.2 The norbornenyl-nortricyclyl rearrangement

An analogous process in a bridged system is the rearrangement of norbornenyl radicals to nortricyclyl radicals. This reaction was also the subject of considerable interest throughout the 1950s and 1960's, again from those interested in probing mechanisms and the nature of radical species. The rearrangement of an unsubstituted system is shown below:

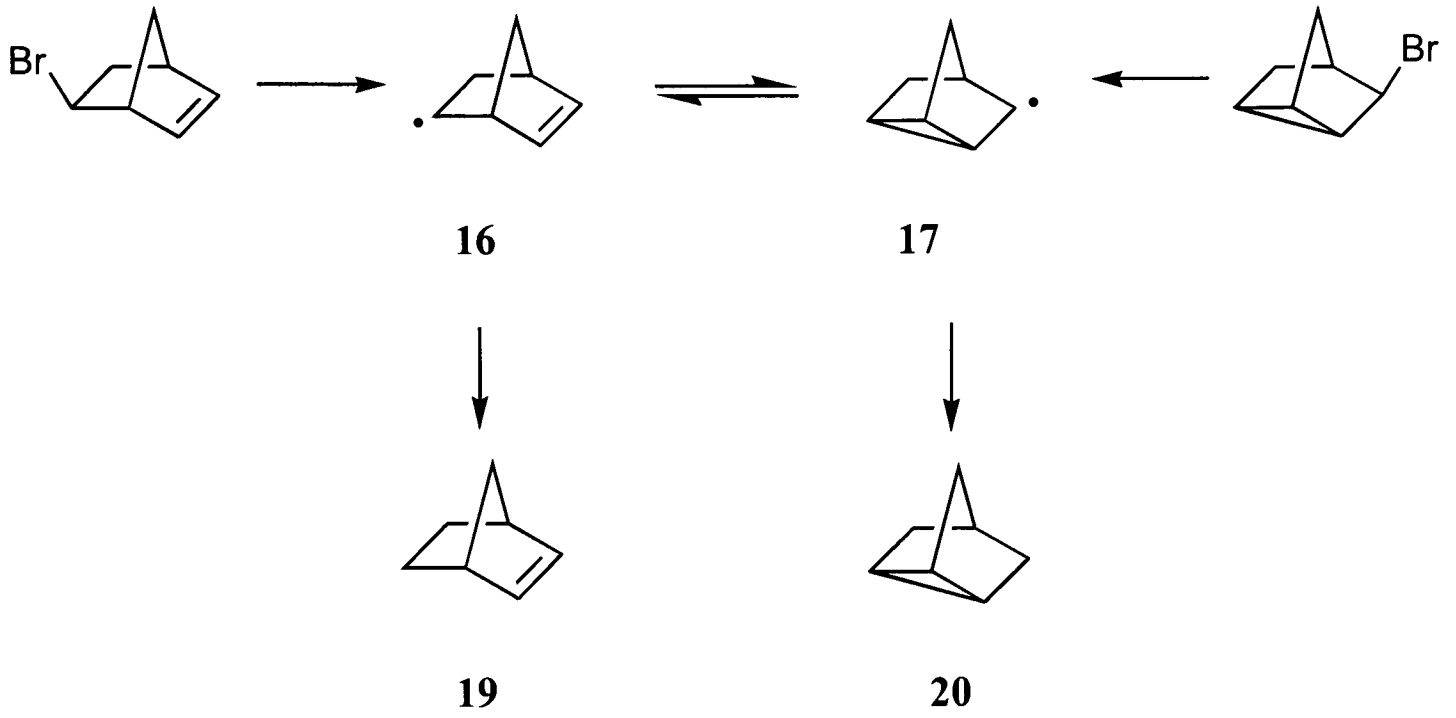


16 **17** **18**

Scheme 1.16 Norbornenyl-Nortricyclyl Rearrangement.

Of particular interest was the question of whether the rearrangement involved a pair of classical radicals **16** and **17** or a single non-classical species **18**, by analogy with carbocation chemistry (Scheme 1.16).[34,35] The results obtained from TBTH reduction of norbornenyl and nortricyclyl bromides at different

concentrations gave varying proportions of norbornene **19** and nortricyclane **20** (Scheme 1.17).[35] This confirms that classical intermediates **16** and **17** are involved, rather than non-classical **18**.



16 **17**

19 **20**

Scheme 1.17 Products from reduction of norbornenyl and nortricyclyl bromides.

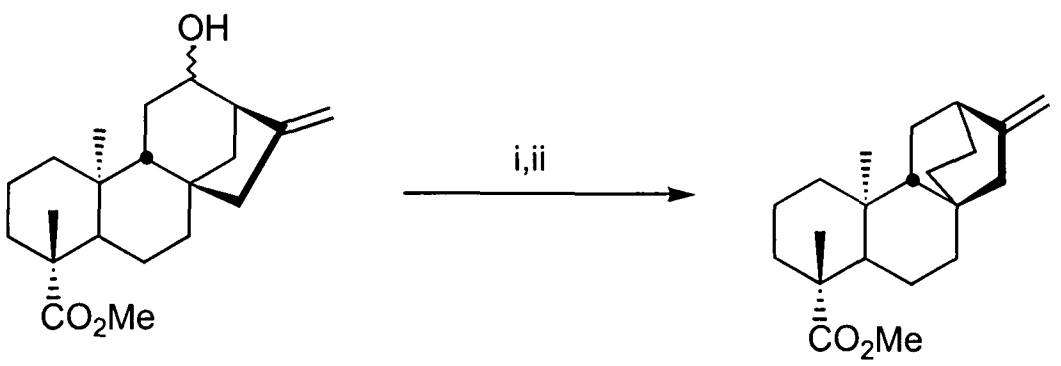
In an analogous mechanism to that shown in Scheme 1.15 (p.24), direct generation of radical **16** gives rise to an equilibrium of radicals **16** and **17**, leading to products **19** and **20** (~1:1 ratio) respectively. It has been shown that direct generation of radical **17** from a tricyclic radical precursor gives the same ratio of final products **19** and **20** in sufficiently dilute solution, i.e. suggesting that both reactions proceed through common intermediates (Scheme 1.17).[35,36] Note that, in this unsubstituted system, ring opening of the cyclopropane ring in **17** gives rise to radical **16** or *ent*-**16**, depending on which bond is cleaved.

The kinetics of the reaction are significantly different from the acyclic case, as the rates of ring-opening and ring closure are similar (both about 10^7 s^{-1}).[37] Ring-opening of the cyclopropylmethyl radical **14** (Scheme 1.15, p.x) is more entropically favourable than is ring-opening of **17** (Scheme 1.17, p.x), since radical **16** is a much more rigid, and therefore more ordered species than either of the

radicals **13** or **15**. This results in a decreased rate of ring-opening for **17** compared to **14**. Application of the same idea can explain why ring closure of **16** is faster than that for **13** or **15**. The radical centre in **16** is well disposed to cyclisation by the nature of the rigid bicyclo[2.2.1]heptenyl framework, whereas a number of conformations are available for homoallyl radicals **13** and **15**. Cyclisation should therefore be more favourable for **16** on entropic grounds. In addition, the increase in strain is not so marked for cyclisation of **16** as for **13** because the ring system is already quite strained in the bicyclic case, and further distortion upon cyclisation is not as important as for the acyclic system. Some other results related to this process will be discussed in more detail in Chapter 3.

1.4.3 Synthetic Applications of Homoallylic Rearrangements

There are now a number of reports of the use of homoallylic rearrangements in synthesis, including in bicyclic systems.[32] Recently Toyota and co-workers[38] employed a homoallylic rearrangement to construct the core of atisirene (Scheme 1.18, below):

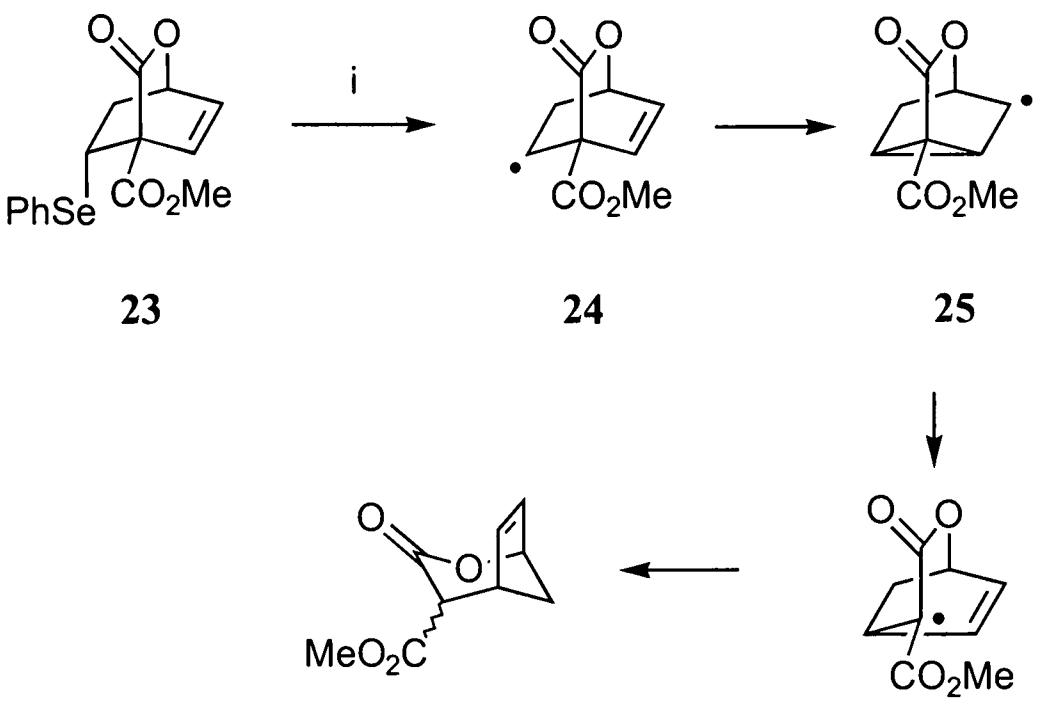


21 **22** (68%)

Scheme 1.18 *Reagents and conditions*: i, $Im_2C(=S)$, DMAP, $Cl(CH_2)_2Cl$; ii, Bu_3SnH, AIBN, toluene, reflux.

The product **22** is derived from the thermodynamically favoured homoallyl radical. The methylene-substituted cyclopentane ring in **21** is strained, so relief of this ring strain is probably the driving force for this transformation.

Radical delocalisation is also an effective driving force for directed homoallylic rearrangement, as demonstrated by the work of Marko,[39] who serendipitously discovered a useful rearrangement of bicyclic lactones (Scheme 1.19):

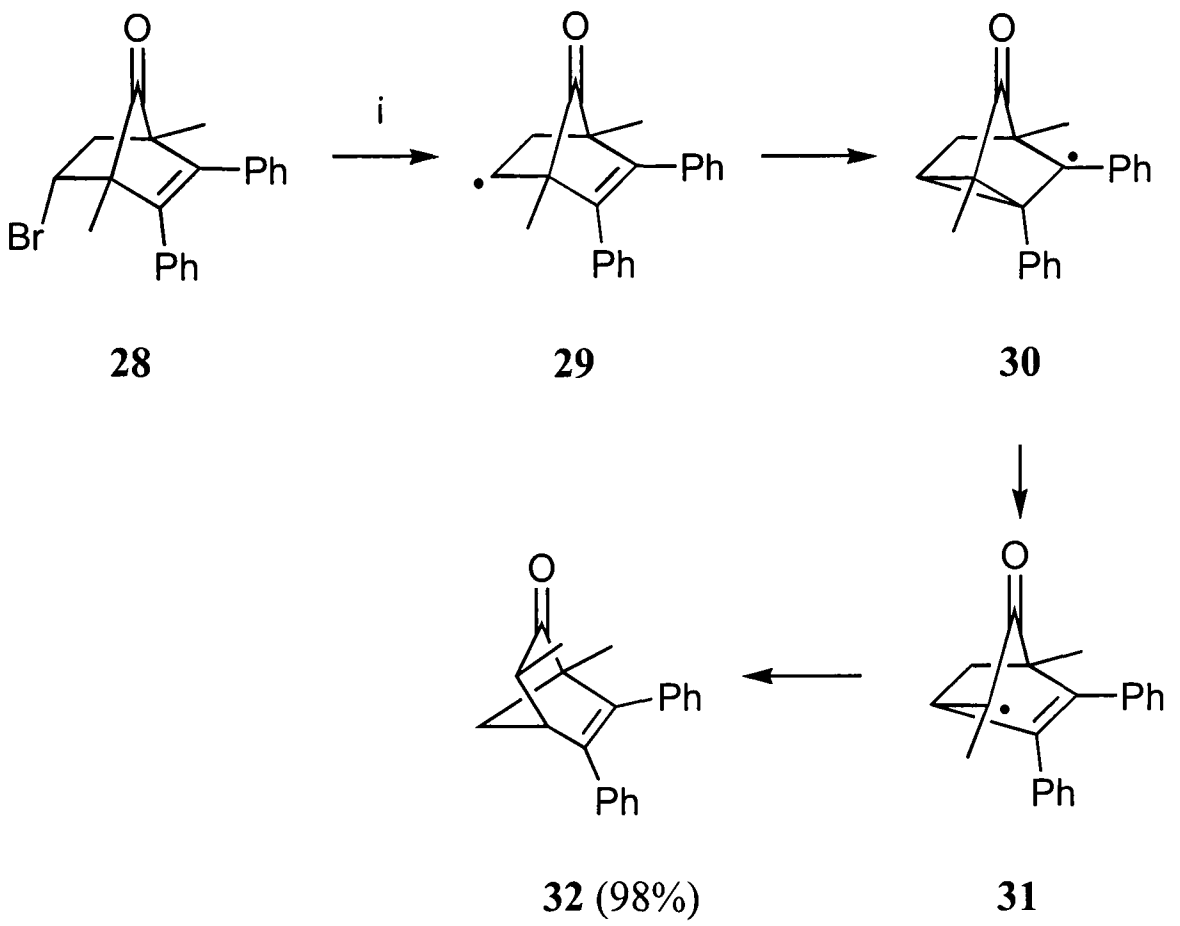


23 **24** **25** **26** **27** (87%)

Scheme 1.19 Homoallylic rearrangement of bicyclic lactones. *Reagents and conditions*: i, TTMSS, AIBN, toluene, reflux.

The first-formed radical **24** cyclises onto the transannular double bond, and then ring-opening leads ultimately to the rearranged product **27**. Radical **26** is presumably stabilised by delocalisation into the β-dicarbonyl functionality. Ring-opening to give **26** is probably also promoted by the electron-withdrawing carbonyl groups, which serve to lower the C-C σ* orbital energy of the adjacent cyclopropyl bonds and increase the interaction with the SOMO of the nucleophilic secondary alkyl radical.

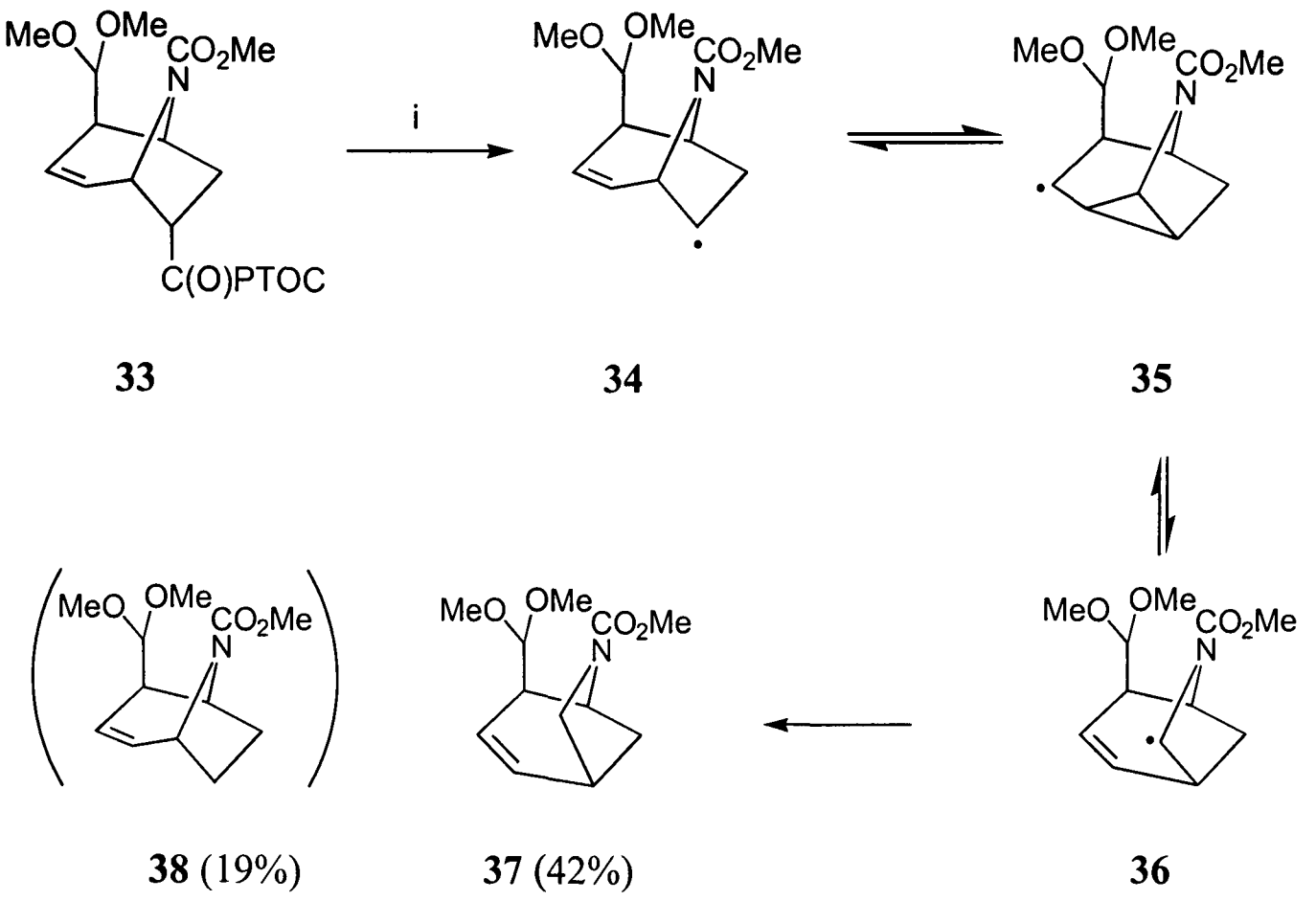
A homoallylic rearrangement in bicyclo[2.2.1]heptene ring system driven by delocalisation was reported by Srikrishna et al.[40] (Scheme 1.20, overleaf).



Scheme 1.20 *Reagents and conditions*: TBTH, AIBN, toluene, reflux, 3.5 h.

Reaction of the analogous substrate to **28** protected as the ketal produced a small amount of the ring-closed product in addition to the rearranged compound, showing that the presence of the carbonyl group had a definite, but not exclusive role in directing the rearrangement. It is interesting to note that although radical **30** is stabilised by the phenyl group adjacent to the radical centre, clean ring opening to **31** is still observed. This is probably due to relief of ring strain of the substituted cyclopropane.

An early example of a nitrogen-directed homoallylic radical rearrangement appeared in 1996.[41] Photolysis of the Barton ester **33** gives a radical **34** that can rearrange to give preferentially **36** at low concentration and ultimately **37** (Scheme 1.21, overleaf):



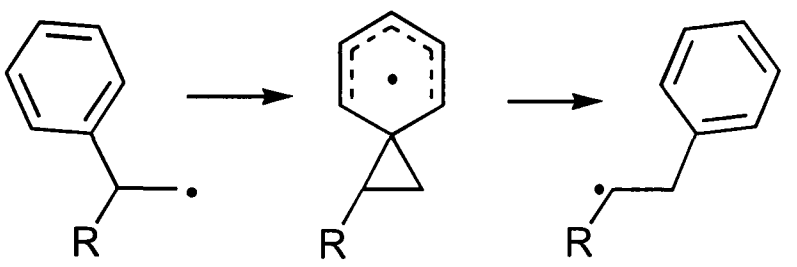
Scheme 1.21 *Reagents and conditions*: i, hν, Bu^{t}SH [0.15M], THF.

Varying amounts of directly reduced product **38** were also isolated, depending on the thiol concentration. The driving force for rearrangement was not fully explored by these workers, but the issue of radical stabilisation α to nitrogen will be addressed in some depth for related chemistry in chapters 4 and 6.

These examples highlight the feasibility of directed homoallylic radical rearrangements. The fact that in each case a different chemical principle drives rearrangement suggests that this idea could be of broad scope.

1.4.4 Neophyl Rearrangements

A third related free radical process is the 1,2-migration of an aryl group adjacent to a radical centre (Scheme 1.22, overleaf):



39 **40** **41**

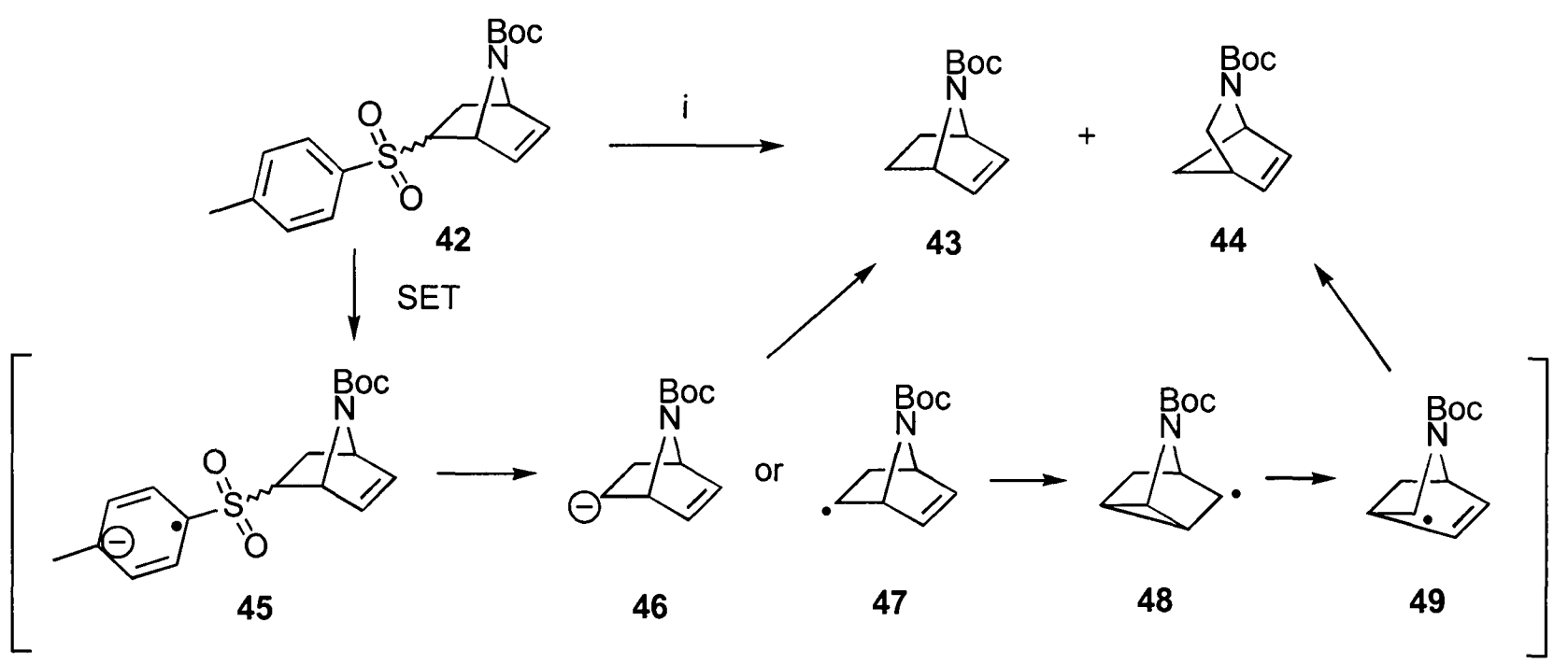
Scheme 1.22 Radical neophyl rearrangement.

This reaction was discovered by Kharasch in 1944,[42] and subsequently many other similar ones have been reported, but often as side products from other free radical processes.[43] Neophyl rearrangements have attracted interest as radical clocks for the measurement of other reactions. Despite considerable investigation, it is not known whether **40** is a discrete intermediate or simply the transition state for the reaction. Radical **40** (R = H) has been generated unambiguously by H-atom abstraction and its rapid decay to the neophyl radical observed by UV spectroscopy,[44] but this does not prove that **40** is an intermediate in the neophyl rearrangement.

The neophyl rearrangement of **39** → **41** is several orders of magnitude slower ($k = 1100\ s^{-1}$ at 25 °C when R = H)[43] than the homoallylic rearrangement of **13** to **15**, presumably because the disruption of aromaticity in the former process raises the activation energy compared to cleavage of a double bond in the latter. The slow rate of the neophyl rearrangement has meant that to date it has had very few applications in synthesis.

1.5 Recent Developments in the Hodgson Group

Much of the precedent for the work presented in future chapters was carried out by C. R. Maxwell, a former student in these laboratories.[45] Whilst examining possible routes to the frog alkaloid epibatidine,[46] it was discovered that desulfonylation of **42** gave a significant proportion of **44** (18%) in addition to the expected alkene **43** (62%) (scheme 1.23, below):

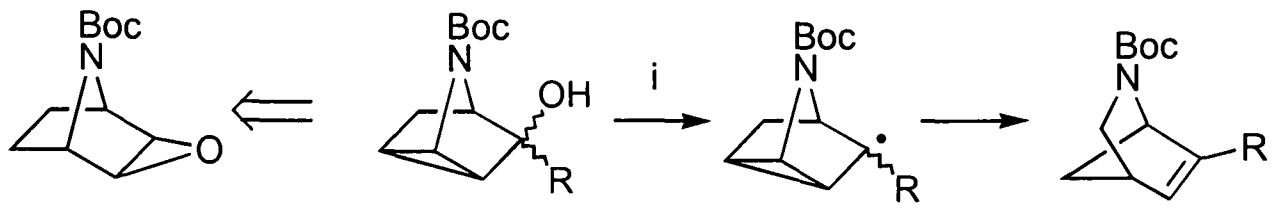


Scheme 1.23 Rearrangement during desulfonylation. *Reagents and conditions*: i, Na-Hg, NaH_2PO_4 buffer, MeOH, 0 °C, 6 h.

Following this result a mechanism was proposed to explain the formation of the rearranged product. Single-electron transfer (SET) gives radical anion **45**, which then fragments to give anion **46** or radical **47**. Anion **46** has a high energy barrier for rearrangement, so likely captures a proton to give the directly reduced 7-azabicyclo[2.2.1]hept-2-ene **43**. Radical **47** can cyclise onto the transannular double bond to give **48**, which in turn ring-opens to give **49**. A second SET and proton transfer then gives the 2-azabicyclo[2.2.1]hept-5-ene **44**.

To test the validity of this hypothesis, it was decided to generate azatricyclic radicals like **48** independently. Tricyclic alcohols **51** were found to be readily

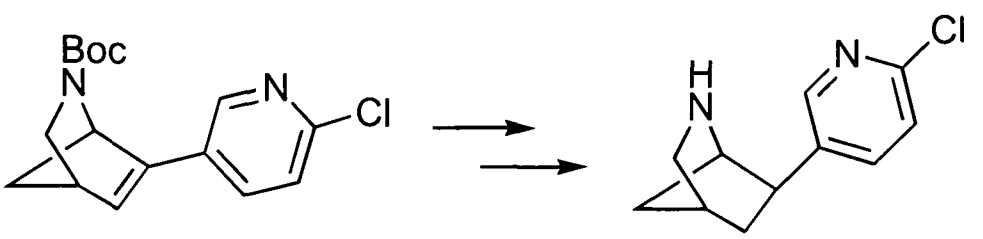
available from 7-azabicyclic epoxide **50** using deprotonation chemistry[45] and were deoxygenated according to the procedure of Dolan and MacMillan:[19]



50 **51** (R = H, Bu^n, Aryl) **52** **53** (63-64%)

Scheme 1.24 Deoxygenation of tricyclic alcohols. *Reagents and conditions*: i, MeOC(O)C(O)Cl, DMAP, 25 °C, MeCN; ii, Bu_3SnH, AIBN, toluene, reflux.

Deoxygenation gave only the 2-azabicyclic alkenes **53**, even when R would be expected to stabilise the radical **52**. This ring-opening strategy was used to prepare 2-azabicyclic analogues of epibatidine by hydrogenation and deprotection e.g. to give **55**.



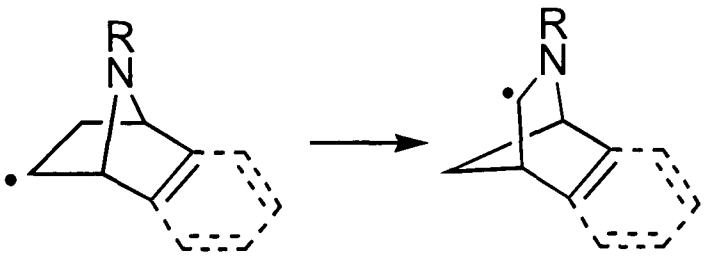
54 **55**

Scheme 1.25 A 2-azabicyclic analogue of epibatidine.

It was not apparent at this point why the ring opening was selective for the formation of the radical α to nitrogen. Two possibilities were suggested at the time - either the interaction of the lone pair with the radical centre had a stabilising effect, and/or the increased C-N-C bond angle in the rearranged product promoted amide-type resonance, thus conferring additional stability upon that structure. These results suggested for the first time that the 2-azabicyclo[2.2.1]hept-5-ene framework could be accessible from the much more readily available 7-azabicyclo[2.2.1]hept-2-ene skeleton,[47] which can be synthesised by cycloadditions with pyrroles and activated dienophiles.

1.6 Initial Aims of the Project

The first objective was to develop a route to a suitable substrate for generating the 7-azabicyclo[2.2.1]hept-2-enyl radicals **56**. Rearrangement to the 2-azabicyclo[2.2.1]hept-5-enyl radicals **57** would then be investigated, without the need to prepare the intermediate azatricyclic radical precursor (Scheme 1.24, p. 33).



56 **57**

Scheme 1.26 Generalised nitrogen-directed radical rearrangement.

Radicals like **56** were envisaged to be available from site-specific radical generation methods, such as Barton deoxygenation or titanium(III)-mediated epoxide opening (Scheme 1.11, p.22). Another possibility was to generate **56** by free radical addition to an appropriate azabicyclic alkene.

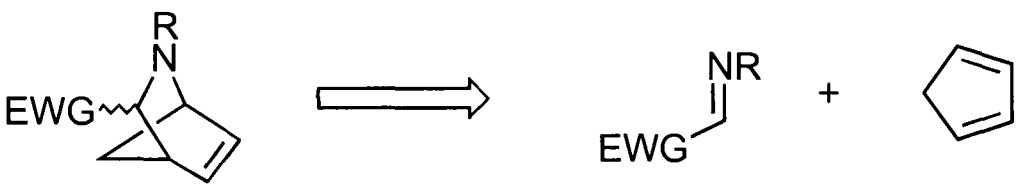
It was hoped that the methodology could then be extended to other ring systems and directing atoms or functionality other than nitrogen. Another important aim was to resolve the issue of what was driving the rearrangement by altering the electronics of the protecting group on nitrogen. This would hopefully be of use in optimising the reaction conditions and developing other free radical processes.

Chapter 2 : Initial Attempts to Induce Homoallylic Rearrangement

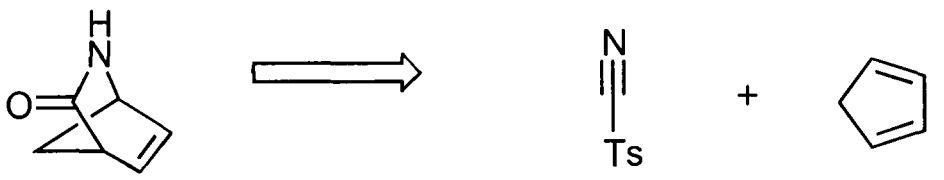
Before detailing the chemistry undertaken to prepare radical precursors for a nitrogen-directed radical rearrangement, it is useful to examine some previous routes to the target compounds for a comparison with our proposed methods.

2.1 Previous routes to 2-azabicyclo[2.2.1]heptenes

Nitrogen functional groups are abundant in natural products and pharmaceuticals. Consequently, new methods for synthesis of azacycles are highly sought after. Many of the free radical methods described above have been used effectively in making both saturated and unsaturated nitrogen heterocycles.[48] The 2-azabicyclo[2.2.1]hept-5-ene framework (shown below) has been the subject of some interest:[49]



58



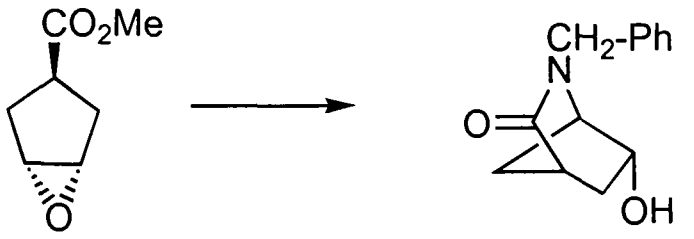
59

Scheme 2.1 Hetero-Diels-Alder disconnection of 2-azabicyclo[2.2.1]heptenes.

The most obvious disconnection, to cyclopentadiene and a C-N dienophile, is effective for the preparation of systems such as **58**. Usually a mixture of *endo* and *exo* products is obtained. The electron-withdrawing group (EWG) is often necessary for the preparation of stable dienophiles and also has an activating effect. At its simplest, the reaction can occur using an iminium species generated from NH_4Cl and formaldehyde. Vince's lactam **59** has been prepared by hydrolysis of the

hetero-Diels-Alder adduct of tosyl cyanide and cyclopentadiene.[50] This compound was a key intermediate in a route to carbocyclic aminonucleosides. Although cleavage of the double bond in these two examples could lead to substituted pyrrolidines[51] and thence to biologically active non-proteogenic amino acids, the scope of the Diels-Alder method is ultimately limited. Use of a substituted cyclopentadiene results in mixture of products, since 1,5-sigmatropic H-atom shifts[52] often isomerise the diene faster than the cycloaddition can take place.

These ring systems are also available by more conventional methods, such as amide formation and epoxide ring-opening to give **60**:[49]

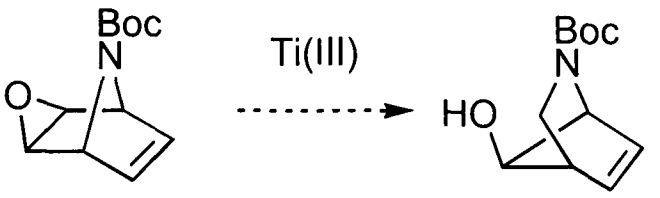


60

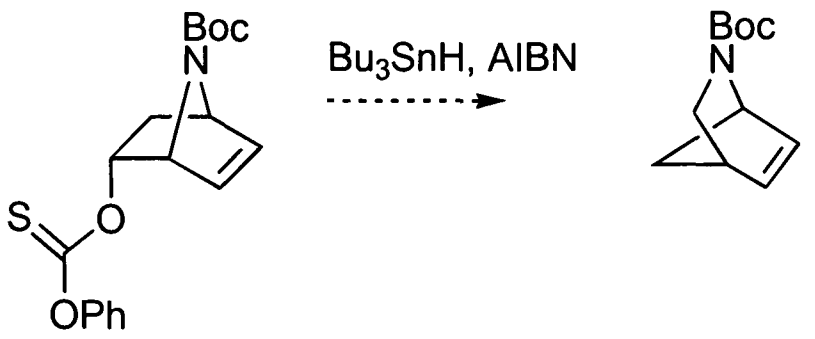
Scheme 2.2 Ring closing approach to a 2-azabicyclo[2.2.1]heptanol.

2.2 Choice of precursors

This chapter details the preparation of radical precursors **61** and **63**, in anticipation that treatment with an appropriate radical source would lead to the desired rearranged products **62** and **44** (Scheme 2.3, below and overleaf):



61 **62**

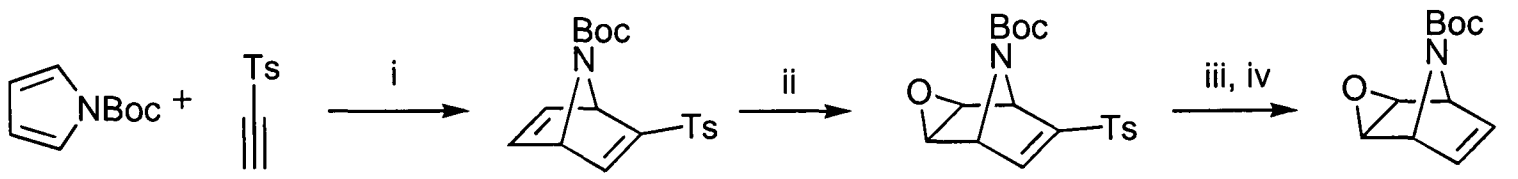


63 **44**

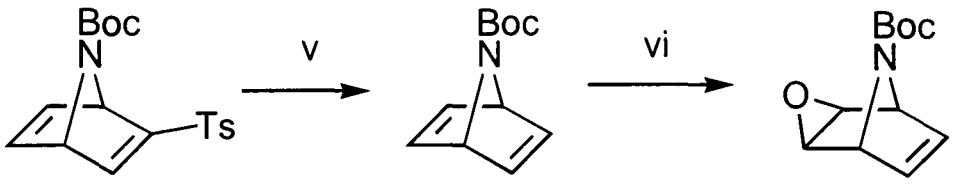
Scheme 2.3 Target radical precursors.

2.3 Synthetic routes to 2,3-Epoxy-7-azabicyclo[2.2.1]hept-5-ene 61

The epoxide **61** had previously been prepared by Maxwell[45] *via* the routes shown below in low yield:



64 **65** (up to 81%) **66** (67%, lit.[53]70%) **61**(24%)

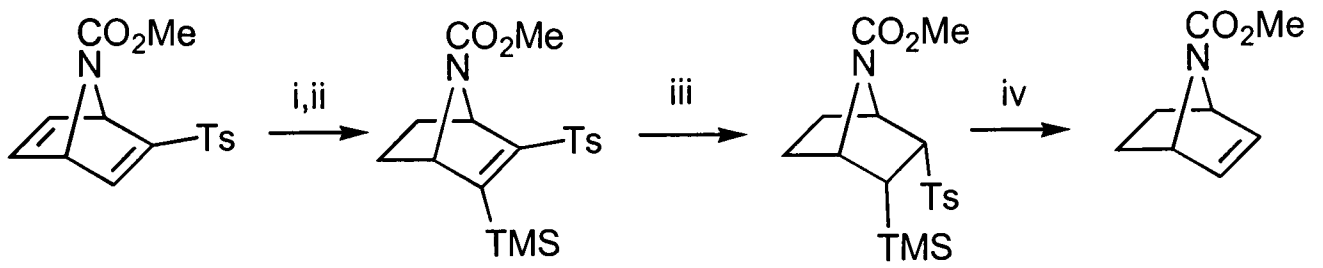


65 **67** (24%) **61** (60-70%)

Scheme 2.4 Maxwell's syntheses of epoxide **61**. *Reagents and conditions*: i, 85 °C, 24 h, neat; ii, mCPBA, CH_2Cl_2, 25 °C, 48 h; iii, Bu_3SnH, AIBN, toluene, 100 °C, 2 h; iv, TBAF, THF, 1 h, 25 °C; v, Na-Hg, NaH_2PO_4, Na_2HPO_4, MeOH, 0 °C, 6 h; vi, AcOOH, CH_2Cl_2, 24 h.

The stannylation route *via* **66** was not adopted, since **61** could not be isolated in sufficient purity for further reaction due to contamination by tin-containing products. The low yield of desulfonylation step (v) is clearly a weakness in the method that was finally chosen. It was felt worth trying to improve the route to **61** at this stage, since this material was likely to be used in quite large quantities. An examination of the work of Kaufmann[54] suggested an alternative route to the

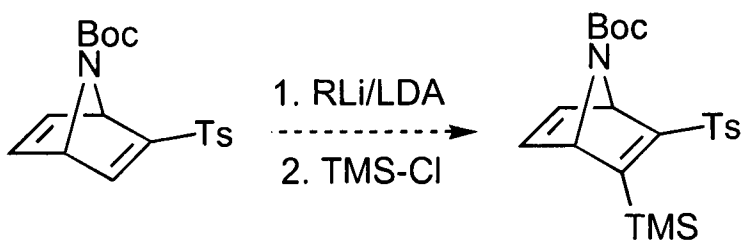
desired epoxide. Kaufmann had prepared the alkene **71** successfully *via* a lithiation and anion trapping strategy, followed by reduction and elimination:



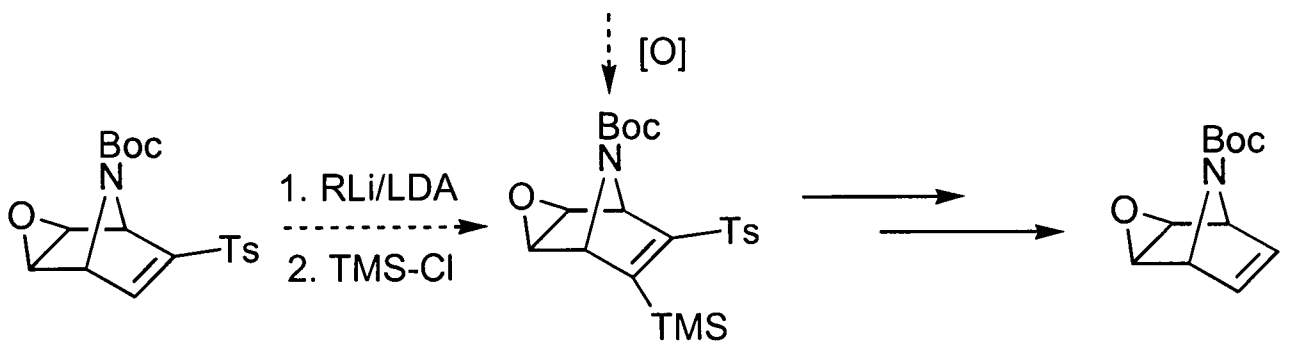
68 **69** (93%) **70** (99%) **71** (99%)

Scheme 2.5 Kaufmann's route to alkene **71**.[54] *Reagents and conditions*: i, H_2(1 equiv.), Pd/C, MeOH; ii, LDA, –78 °C, THF, 1 h then TMS-Cl → 25 °C, overnight; iii, diimide, 25 °C, 1 h; iv, TBAF, THF, 25 °C, 1 h.

It was proposed to apply this lithiation chemistry directly to **65** or **66**, thereby avoiding the use of the TBTH:



65 **72**

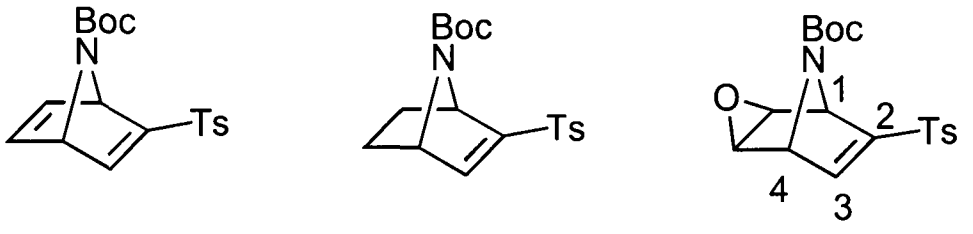


66 **73** **61**

Scheme 2.6 Proposed alternative route to epoxide **61**.

It was thought that if the anion derived from **65** or **66** could be trapped, a route to **61** containing reduction and elimination steps similar to those of Kaufmann could be developed. Unfortunately, all attempts to create and trap the anion of **65** or **66**, using Bu^nLi, LDA or Bu^tLi (1-2 h, –78 °C, THF then TMS-Cl) led to complete decomposition of starting material and a complex mixture of unidentifiable

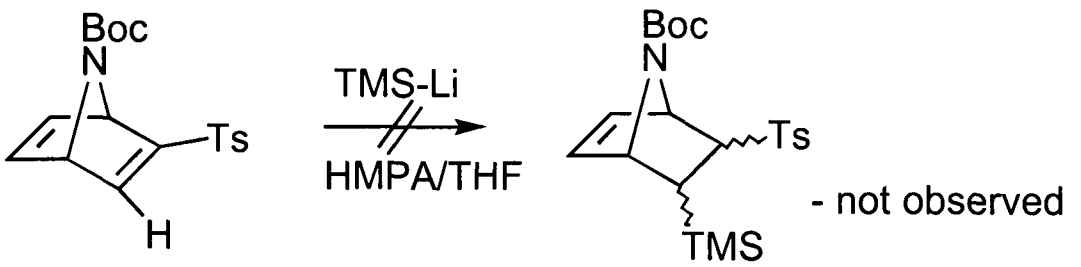
products. Inverse addition of a solution of **65** or **66** to a solution of LDA, or performing the quench (MeOH) at −78 °C made no difference to the outcome. The failure of this chemistry given its success in making **69** is hard to explain, but is consistent with the findings of Simpkins.[55] It is possible that transannular interaction of the filled π-orbitals in **65** raises the energy of the transition state for deprotonation compared to the reduced compound **74**, leading to competitive lithiation of the tosyl group.



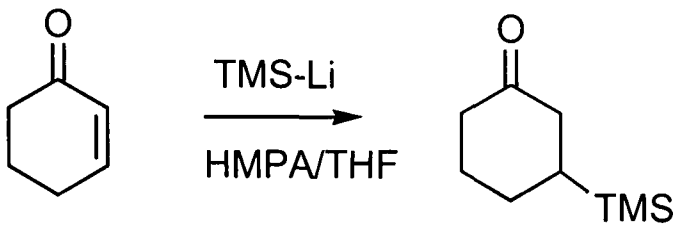
65 **74** **66**

Fig. 2.1 Substrates for lithiation-trapping.

For **66**, lithiation of the epoxide could compete with the desired deprotonation at C3. Attempted addition of the known trimethylsilyl lithium[56] into **65** also gave an unidentifiable mixture. As a test reaction, addition of TMS-Li to cyclohex-2-enone **75** gave a 57% yield of the Michael adduct **76**:



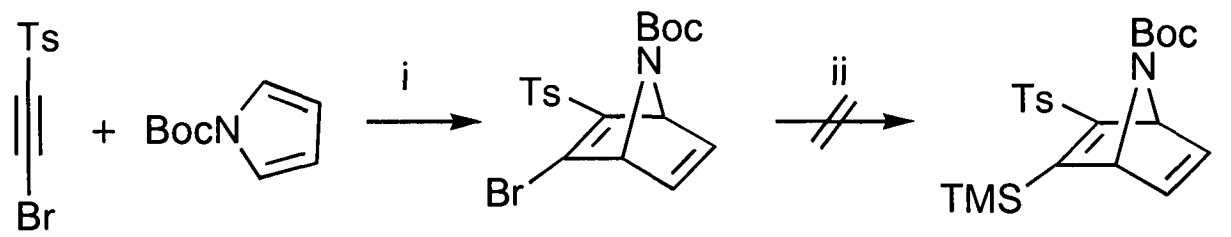
65



75 **76** (57%, lit.[57] 99%)

Scheme 2.7 Reactions with TMS-Li.

The final effort to synthesise **72** was an attempted lithium-halogen exchange reaction using the cycloadduct **78**[58] and then trapping with TMS-Cl. This also led to an unidentifiable mixture.



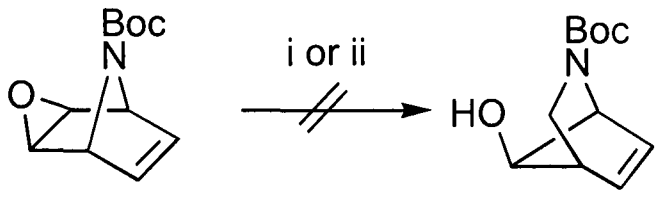
77 **78** (55%, lit.[58] 78%) **72**

Scheme 2.8 Attempted Li-Br exchange reaction. *Reagents and conditions*: i, 85 °C, neat, 24 h; ii, Bu^{t}Li (2 equiv.), THF, -78 °C, 1h, then TMS-Cl, –78 °C → 25 °C overnight.

At this point it was decided to return to the stannylation route to **61** (Scheme 2.4, p.37). The final stannyl radical addition was complicated by difficulty in removing tin residues. However, it was found that a treatment of the reaction mixture with 1 M NaOH[24] was useful in purifying the final product, and the yield after chromatography improved, albeit to a still modest 30%. The material obtained in this way was, however, sufficiently pure for use in subsequent reactions. Carrying out the rearrangement chemistry was keenly anticipated.

2.4 Attempted Rearrangement of 61 using Titanium Chemistry

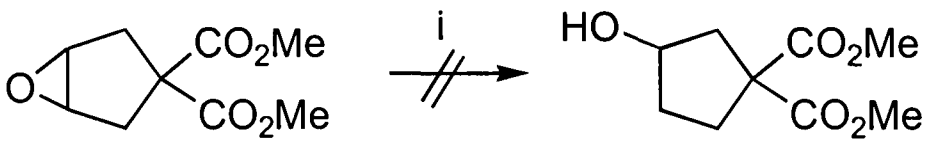
After a number of months optimising a route to **61**, with limited success, sufficient quantity had been obtained to test the reductive epoxide ring-opening chemistry.



61 **62**

Scheme 2.9 Proposed Ti(III)-mediated rearrangement. *Reagents and conditions*: i, Cp_2TiCl, 1,4-C_6H_8, THF, 25 °C, up to 2 h; ii, Mn, Cp_2TiCl_2 (5-10 mol%), 1,4-C_6H_8, collidine hydrochloride, THF, 25 °C.

Disappointingly, treatment of **61** under stoichiometric[10] or catalytic[11] conditions, with or without H-atom donors present, gave only unidentifiable mixtures. Literature reactions with stoichiometric amounts of Ti(III) reagent (*e.g.* on **79**) were unsuccessful, and led only to the recovery of starting material.

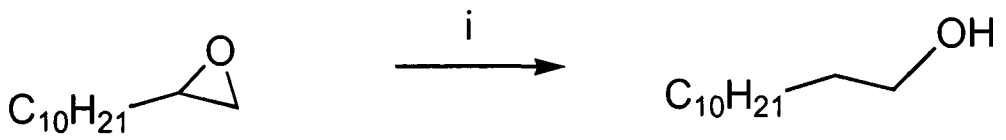


79 **80** (lit. [10] 72%)

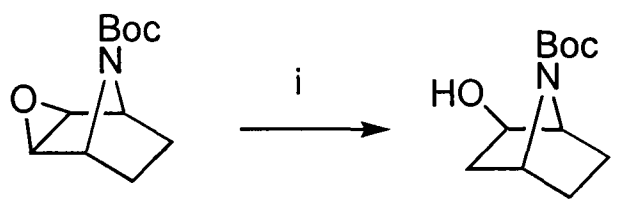
Scheme 2.10 Unsuccessful epoxide ring opening.

This chemistry originally had been carried out in a drybox, and the failure of the repeats led to the conclusion that the generation of the reagent from Cp_2TiCl_2 and activated zinc could not be achieved cleanly without this apparatus.

A reaction from the work of Gansauer[11] could be reproduced; treatment of **81** under catalytic Ti(III) conditions gave 37% of 1-dodecanol **82**. A sample of saturated epoxide **50** was converted to 50% of the known alcohol **83** (Scheme 2.11, overleaf).[59]



81 **82** (37%, lit.[11] 56%)



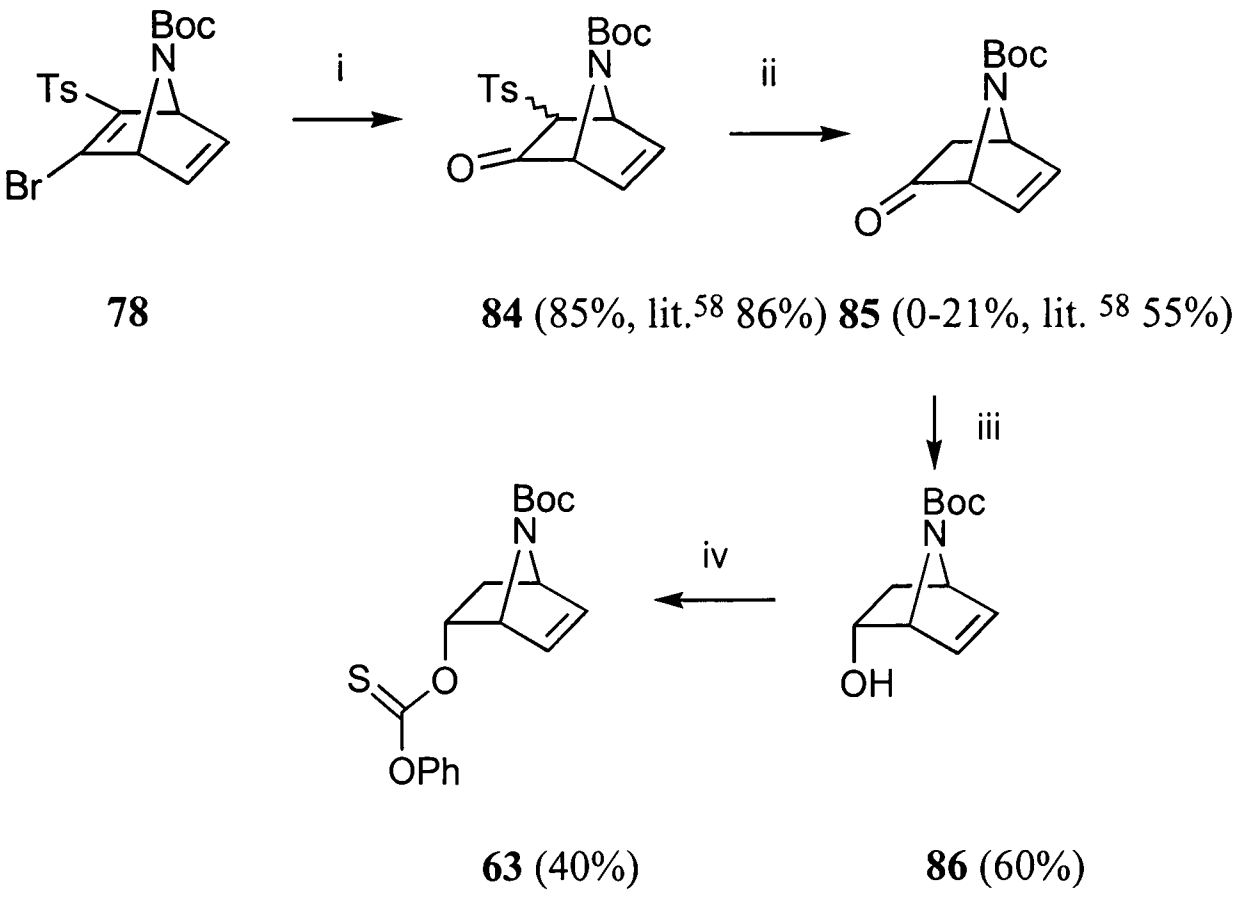
50 **83** (50%)

Scheme 2.11 Test reactions for titanium(III) chemistry. Reagents and conditions: i, Mn, Cp_2TiCl_2, 1,4-C_6H_8, collidine hydrochloride, THF, 25 °C, 24 h.

Given these results, it was concluded that the titanium chemistry was incompatible with the radical rearrangement we wished to investigate. It is possible that SET into the double bond occurs, giving a radical anion and fragmentation to a complex mixture. It was decided to abandon the titanium chemistry at this point in order to examine alternative radical sources.

2.5 Synthesis of a Barton deoxygenation precursor 63

Attention next turned to a substrate that would produce the desired 7-azabicyclo[2.2.1]hept-enyl radical under Barton deoxygenation conditions, i.e. **63** (Scheme 2.3, p.36-7). Following reports from Trudell[58] that 1-tosyl-2-bromoacetylene **77** (Scheme 2.8, p.40) could be used as a ketene equivalent in Diels-Alder reactions with pyrroles, it was thought that **63** could be readily synthesised by reduction of ketone **85** and then derivatisation of the alcohol **86** (Scheme 2.12, overleaf):



78 **84** (85%, lit.[58] 86%) **85** (0-21%, lit. [58] 55%)

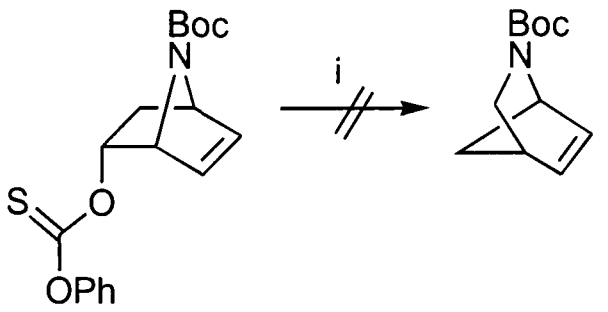
63 (40%) **86** (60%)

Scheme 2.12 Synthesis of Barton precursor **63**. *Reagents and conditions*: i, Et_3N, Et_2NH, MeCN, 25 °C, 30 min. then 2 M aq. HCl; ii, Al-Hg, Na_2HPO_4, THF-H_2O 9:1, 80 °C, 100 min.; iii, $NaBH_4$, MeOH, −10 °C, 90 min.; iv, PhOC(S)Cl, DMAP, MeCN, 25 °C, 18 h.

Following cycloaddition to give **78**, enamine formation and hydrolysis gave an epimeric mixture of sulfonyl ketones **84**. Removal of the sulfone with Al-Hg proved to be problematic, leading to inconsistent and low yields of ketone **85**. Despite contacting the authors for advice with this step, scale-up of the reaction served only to push the yield even lower, leading in some cases to complete decomposition of starting material and recovery of a complex mixture. Eventually, enough material was obtained to proceed with reduction of the ketone to give *endo*-alcohol **86**, assigned as such by comparison of the ^{1}H NMR spectrum with that of the known *exo* epimer obtained from hydroboration of diene **67** (Scheme 2.4, p.37).[45] Derivatisation to the thiocarbonate[16] occurred in modest yield, and finally the synthesis of alternative precursor **63** had been accomplished.

2.6 Attempted Rearrangement by Barton Deoxygenation

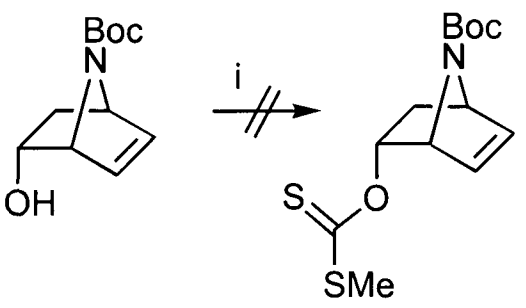
Treatment of **63** with Bu_3SnH and AIBN in toluene gave an unidentifiable mixture (Scheme 2.13, below):



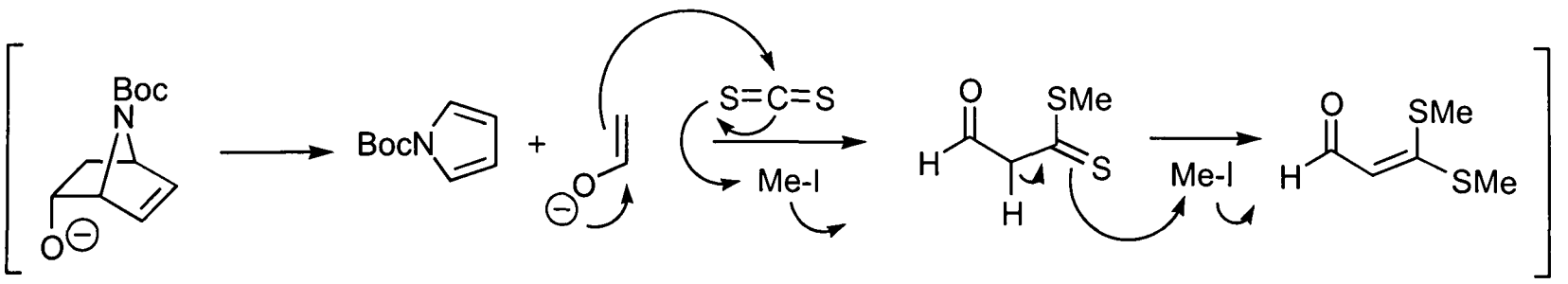
63 **44**

Scheme 2.13 *Reagents and conditions*: i, Bu_3SnH, AIBN, toluene, 75 °C, 3 h, then 1 M NaOH, 25 °C, 1 h.

It is not clear why this reaction failed to produce any of the desired alkene **44**. Possibly the product is unstable to the reaction conditions, but this seems unlikely, as isolated double bonds are not usually susceptible to attack by nucleophilic tributyltin radicals.[1] Maxwell[45] observed a retro-Diels-Alder reaction during attempted preparation of xanthate **87** from alcohol **86**, (Scheme 2.14):



86 **87**



Scheme 2.14 Retro-Diels-Alder reaction during xanthate preparation. *Reagents and conditions*: KH, CS_2, MeI, THF, 0 °C, 30 min.

Although this reaction occurred under ionic rather than free radical conditions, it does demonstrate the tendency of these systems to form the aromatic

N-Boc pyrrole. Thermal fragmentation would be more likely at higher temperatures, where the process would be entropically favoured. Since the desulfonylation step in the synthesis of **63** proved unreliable, this strategy for generating the radical on the azabicyclic ring was abandoned and an alternative was sought.

2.7 Conclusions and Recommendations

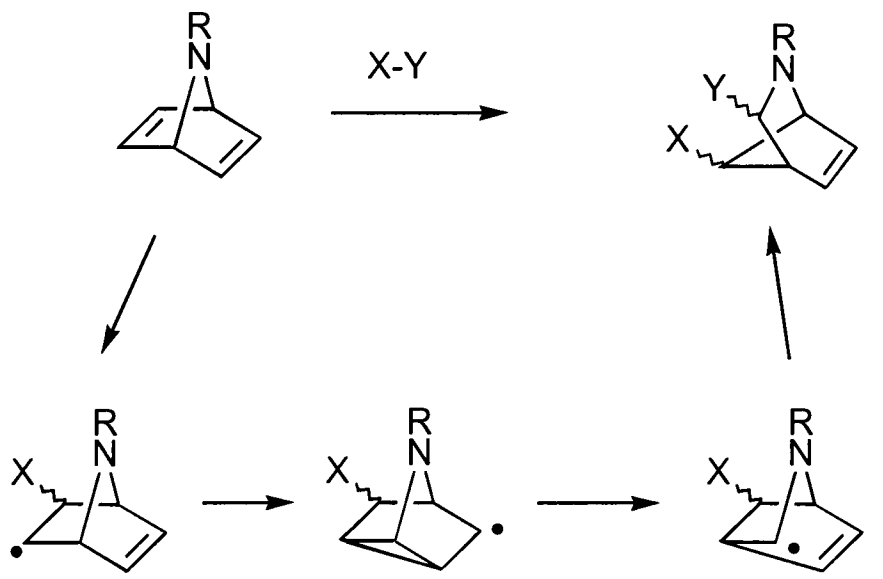
Attempts to initiate the desired free radical homoallylic rearrangement by titanium or thiocarbonyl chemistry have failed. The reason for the failure of the titanium chemistry is most likely due to electron transfer to the double bond of **61**, given its partial success with an otherwise identical saturated epoxide. The outcome of the Barton deoxygenation is harder to explain, and further investigation was hampered by the low-yielding desulfonylation.

Another possibility would be to treat ketone **85** with SmI_2, assuming a synthetically useful route could be found to the substrate. This could also enable C-C bond forming to take place after rearrangement, leading to a more functionalised product.

Currently under investigation within the group are radical additions-rearrangements using cycloadduct **65** (Scheme 2.1, p.35), which have led to a synthesis of functionalised pyrrolidines.[60] This avenue appears to offer a promising route to some useful targets.

Chapter 3: Radical Additions to 7-Azanorbornadienes

Following the failure of two different attempts to generate the 7-azabicyclo[2.2.1]heptenyl radical, another approach was required. This chapter details efforts to develop a tandem free radical addition – homoallylic rearrangement method to give 7-substituted 2-azanorbornenes (Scheme 3.1, below), in addition to a new examination of radical addition to norbornadiene.



Scheme 3.1 Generalised Radical addition to 7-azanorbornadienes.

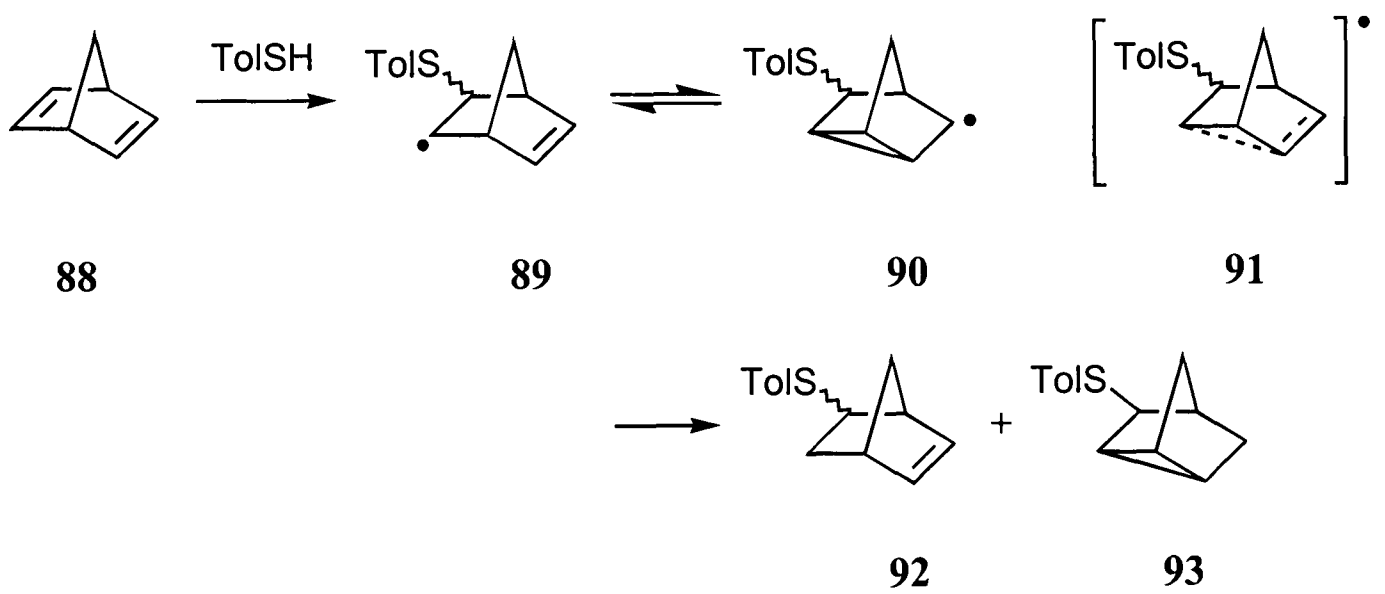
3.1 Choice of Radical Source

Thiols are known to add to alkenes *via* a free radical mechanism.[61] Experimentally the reactions are straightforward to carry out – the thiol is simply added to a solution of the alkene and stirred at the appropriate temperature, which is room temperature in the case of aromatic thiols. It was thought that if X-Y above could be RS-H, this would represent a convergent approach to 7-substituted 2-azabicyclo[2.2.1]hept-5-enes. Mechanistically, the reaction is simpler than a TBTH-mediated process. Generation of a carbon-centred radical using TBTH/AIBN always carries the danger that the radical could be reduced by TBTH before the desired process can occur (be it addition or rearrangement, for example). H-atom transfer to a thiyl radical from a thiol molecule simply reproduces the same thiyl radical, so reduction of the adding radical is not a complication. For these

reasons it was decided to investigate whether the addition of thiols to 7-azanorbornadienes could lead to the desired rearrangement.

3.2 Thiol Radical Additions to Norbornadiene

Radical additions of a number of species to norbornadiene have been extensively studied.[62] Cristol investigated the addition of *p*-thiocresol to norbornadiene **88**.[34] The product profile **92/93** was found to vary with concentration, leading to the conclusion that norbornenyl radicals **89** and nortricyclyl radicals **90** were discrete intermediates rather than a "non-classical" free radical **91** (Scheme 3.2):

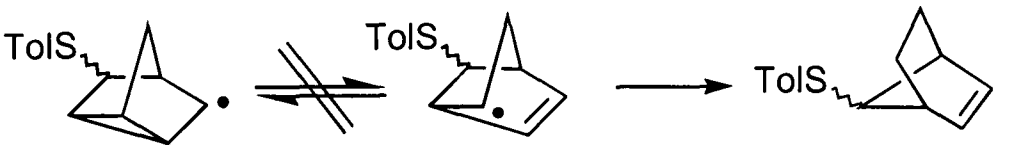


88 **89** **90** **91**

92 **93**

Scheme 3.2 Addition of *p*-thiocresol to norbornadiene.

In most cases, the tricyclic compound **93** was the major product. It is noteworthy that ring opening of **90** to give radical **94** and then formation of *meso*-sulfides **95** is not observed (Scheme 3.3). This is presumably due to a stabilising effect of the sulfur substituent, promoting the formation of **89** over **94**.



90 **94** **95**

Scheme 3.3 Selectivity in thiol addition to norbornadiene.

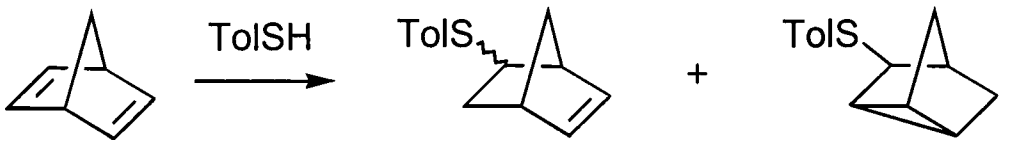
Some aspects of the norbornenyl-nortricyclyl rearrangement remained unexplained, particularly the fact that the ratio of bi- and tricyclic products seems to

differ markedly between radical reduction of norbornenyl bromide (Scheme 1.17, p.26) and the addition of *p*-thiocresol to norbornadiene: in the former case, a small excess of norbornene **19** (60%) over **20** is found under various dilution and temperature conditions;[35,36] whereas in the latter, tricyclic product **93** predominates, particularly at low thiol concentration (<0.5 M).[34] The thiol is a superior H-atom donor compared with TBTH,[6] so at similar concentration (TBTH was mixed neat with norbornenyl bromide, as was *p*-thiocresol with norbornadiene), more of the first-formed radical should be trapped before cyclisation. By this rationale the ratio **92** : **93** should be greater than **19** : **20** (Scheme 1.17, p.26). The product profiles clearly do not reflect this simple analysis.

Davies[62] offers two explanations for the product profile of the thiol addition, based on results available to him at the time (1970): first, that H-atom transfer to **90** happens faster than the equilibrium can be set up with **89**; or second, that the equilibrium lies very heavily towards **90** and the intermediates are quenched at a similar rate. In the second case, at high thiol concentration, **89** would be trapped to give **92**. As the reaction progressed, the thiol concentration would decrease and the equilibrium would be established leading to trapping of **90**. These models are consistent with no formation of products derived from **94**, but cannot be applied to explain the roughly equal ratio of **19** : **20** obtained from both norbornenyl and nortricyclyl radical precursors in the work of Kuivila.[36] Davies assumes that both possible ring-openings of **90** to give **89** or **94** are equally likely, but offers no reasoning in support of this.

For this reason, it was decided to repeat some of the early work to clear up some of these ambiguities. Addition of *p*-thiocresol to norbornadiene (an equimolar mixture) as one portion at 25 °C gave the following proportions of products (Table

3.1), as judged by ^{1}H NMR spectroscopy of the crude reaction mixtures. Data for both epimers of **92** were previously available,[63] and simple integration of the olefinic (~6.1 to 6.4 ppm) and aromatic signals (~7.3 ppm) gave the ratio of bicyclic to tricyclic products:

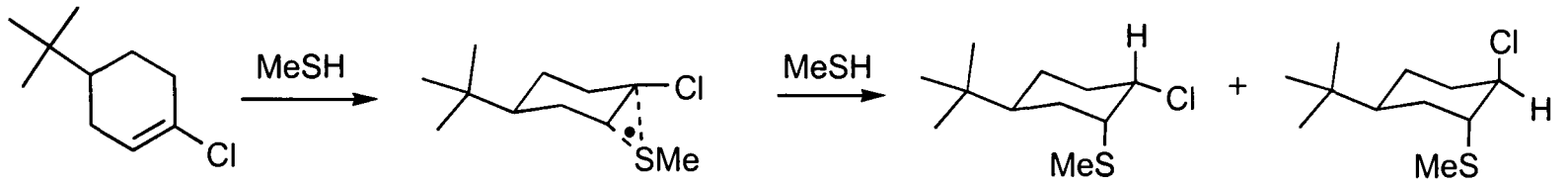


88 **92** (*exo* : *endo*, 5:1)[a] **93**

Initial [Thiol]/mol dm^{-3}	Ratio **92** : **93**
5.0 (neat)	40 : 60
2.0 (in toluene)	26 : 74
1.0	17 : 83
0.1	14 : 86

Table 3.1 Addition of thiols to norbornadiene at varying thiol concentration (average of two runs).
[a] C(H)-S (*exo*) had δ = 3.04 ppm; C(H)-S (*endo*) had δ = 3.67.

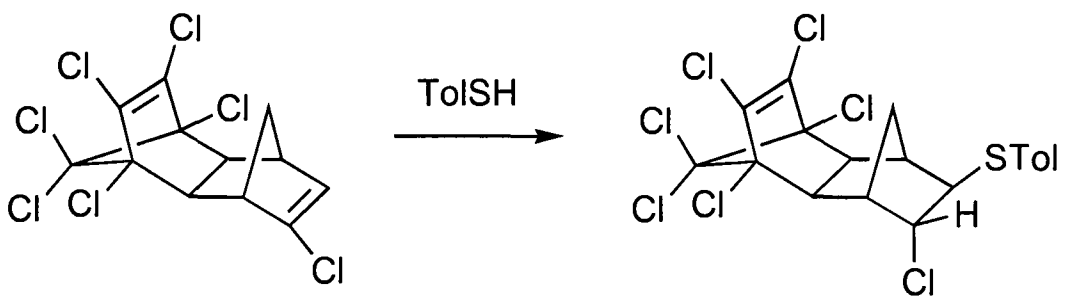
More dilute experiments ([Thiol] ≤ 0.05 M) gave rise to side reactions and a more complex mixture of products, although the proportion of alkene present appeared to remain constant. The results indicate that equilibrium has been attained between radicals **89** and **90** (Scheme 3.2). Given that **95** is not found, an explanation must be found to account for the selective ring-opening of **90** back to **89**. An obvious explanation is that the sulfur substituent has a stabilising effect on the radical **89**, which lowers the transition state energy for ring-opening. A bridged intermediate of the type **97** shown below has been invoked to explain the *trans* addition of methanethiol to 1-chloro-4-*t*-butylcyclohexene **96**:[64]



96 **97** **98** (88%) **99** (2%)
(+ 10% products from equatorial attack of thiyl radical)

Scheme 3.4 Bridged intermediate in thiol additions to a substituted cyclohexene.

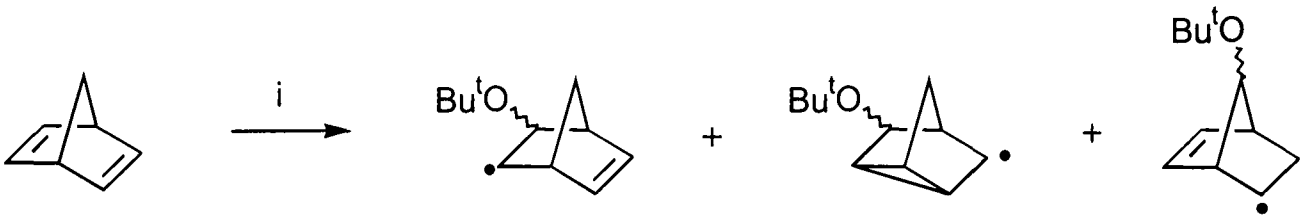
However, it is difficult to propose an intermediate similar to **97** for thiol addition to norbornadiene, since Cristol[65] showed that addition of *p*-thiocresol to 6-chloroaldrin **100** occurred exclusively in a *cis* fashion to give **101**:



100 **101** (85%)

Scheme 3.5 Addition of *p*-thiocresol to 6-chloroaldrin.

A bridged intermediate would be expected to give predominantly *trans* addition, so another explanation must be sought for radical stabilisation β to sulfur. An EPR study by Griller[66] revealed for the first time a rearrangement to give a 7-substituted norbornenyl radical **104**:



102 **103** **104**

Scheme 3.6 Addition of *t*-butoxyl to norbornadiene. *Reagents and conditions*:(t-BuO)$_2$, hν, propane/cyclopropane.

At −150 °C **103** is the predominant species, but at −70 °C **104** is formed and **102** is not observed. This result suggests that **102** is not significantly stabilised by

the presence of the oxygen substituent. The reason for the selective formation of **104** is not clear, although perhaps this is for steric reasons, as interactions of the *tert*-butoxyl group with the bicyclic core may be minimised for a 7-substituent compared to a 2-substituent.

Results of the additions of thiyl and butoxyl radicals give different product profiles, and the fact that radical stabilisation seems not to occur for **102**, but does for **89** suggests that the difference lies in the chemistries of oxygen and sulfur. Cristol[65] has effectively ruled out a bridged intermediate, but possibly the SOMO in **89** can interact favourably with the orbitals of the C-S bond in a way that is not possible for the orbitals of a C-O bond. Radicals interact favourably with both filled and empty orbitals, and the weakness of the C-S bond means a high energy σ orbital and a low energy σ* orbital, either of which could interact with the radical centre (Fig. 3.1, overleaf). The C-O bond is very strong, and the bonding and antibonding orbitals are much more disparate in energy, which could mean that they do not interact with the radical centre:

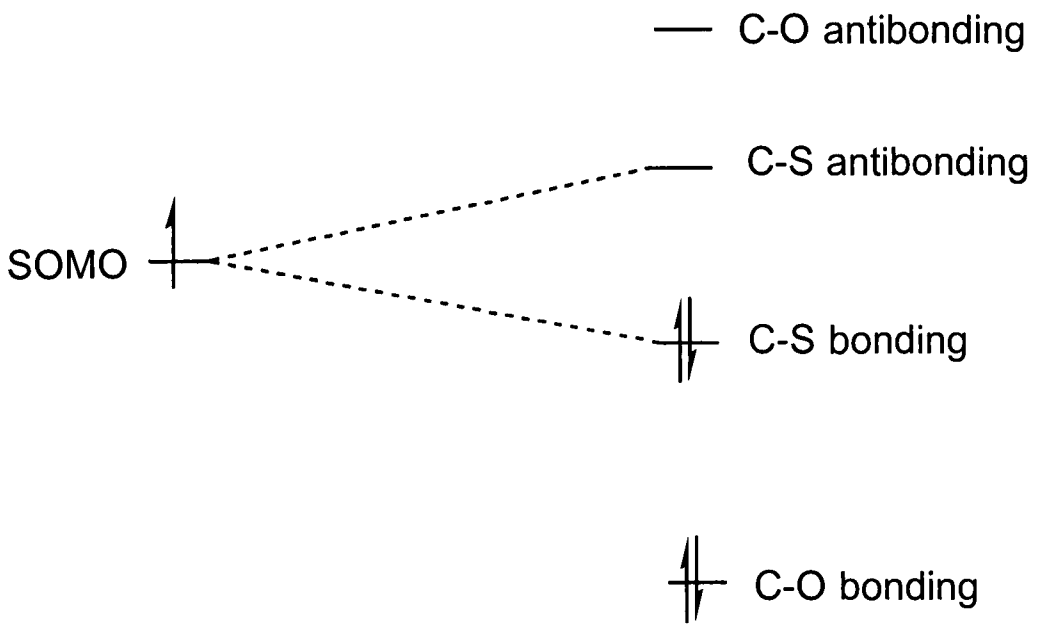
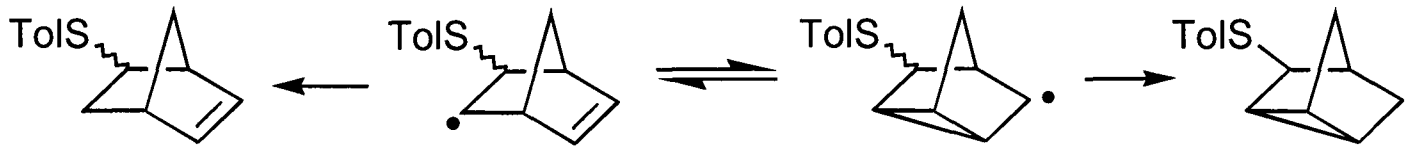


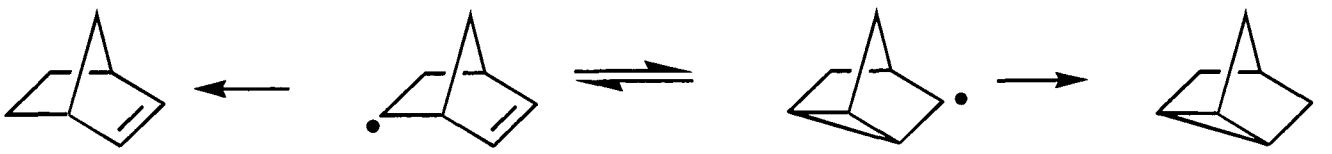
Fig. 3.1 Possible interactions of a radical centre with adjacent C-S and C-O orbitals.

While the diagram above is largely conjecture, it is well known that C-S bonds can be cleaved by tributyltin radicals with nucleophilic character,[1] so an orbital interaction with a carbon-centred radical (also with nucleophilic character) seems plausible. This would explain the selectivity for ring-opening of **90** to give **89**, and suggests that Davies' assumption that ring-opening of **90** cannot be selective is not correct.

The issue of the different product profiles from the thiol additions[34] and the reductions of bromides to give **19** and **20** must now be addressed. The addition of *p*-thiocresol to norbornadiene at low concentration (Table 3.1) suggests that equilibrium is established between **89** and **90** (Scheme 3.7, below).



92 (14%) **89** **90** **93** (86%)



19 (approx 60%) **16** **17** **20** (approx 40%)

Scheme 3.7 equilibria in the norbornenyl-nortricyclyl system.

If the rates of H-atom transfer to **89** and **90** were equal, then the ratio **92** : **93** would reflect the proportion of **89** and **90** at equilibrium. It is likely that H-atom transfer to **16** and **17** from TBTH happens at very similar rates,[6] as both are unfunctionalised secondary radicals. Having previously argued that **89** is stabilised, we would then expect a larger ratio **92** : **93** than **19** : **20**, since **16** cannot be subject to the same stabilising effect as **89**. This is not what is observed experimentally, but can be explained if H-atom transfer to **89** is slower than H-atom transfer to **92**, and hence the ratio **92** : **93** does not reflect the ratio **89** : **90** at equilibrium. In most

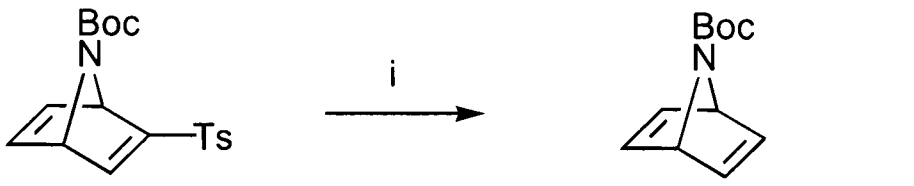
cases, the *p*-tolylthio- substituent is in the *exo* orientation. This is in accordance with the findings of Van Auken, whose results suggest a kinetic preference for *exo* attack of the thiyl radical.[67] Given Cristol's evidence that thiol additions to norbornenes show a preference for *cis* addition,[65] it is likely that approach of the H-atom donor (another molecule of *p*-thiocresol) to **89** is *exo*. This requires approach of the thiol *syn* to the *p*-tolylthio substituent, leading to steric interactions which could conceivably slow the rate of H-atom transfer. Approach to **90** is not subject to this hindrance, so H-atom transfer from an aromatic thiol to a secondary alkyl radical would occur at the 'normal' rate.[68] This would then result in proportionately more of **90** being trapped than **89**, and explain the difference in observed product profile derived from the equilibria shown in scheme 3.7.

In summary, a model has been proposed that accounts for the following:

- the absence of 7-substituted products in thiol additions to norbornadiene
- differing ratios of bicyclic and tricyclic products resulting from two different radical rearrangements involving norbornenyl/nortricyclyl radical equilibria.

3.3 Thiol additions to 7-Azanorbornadienes

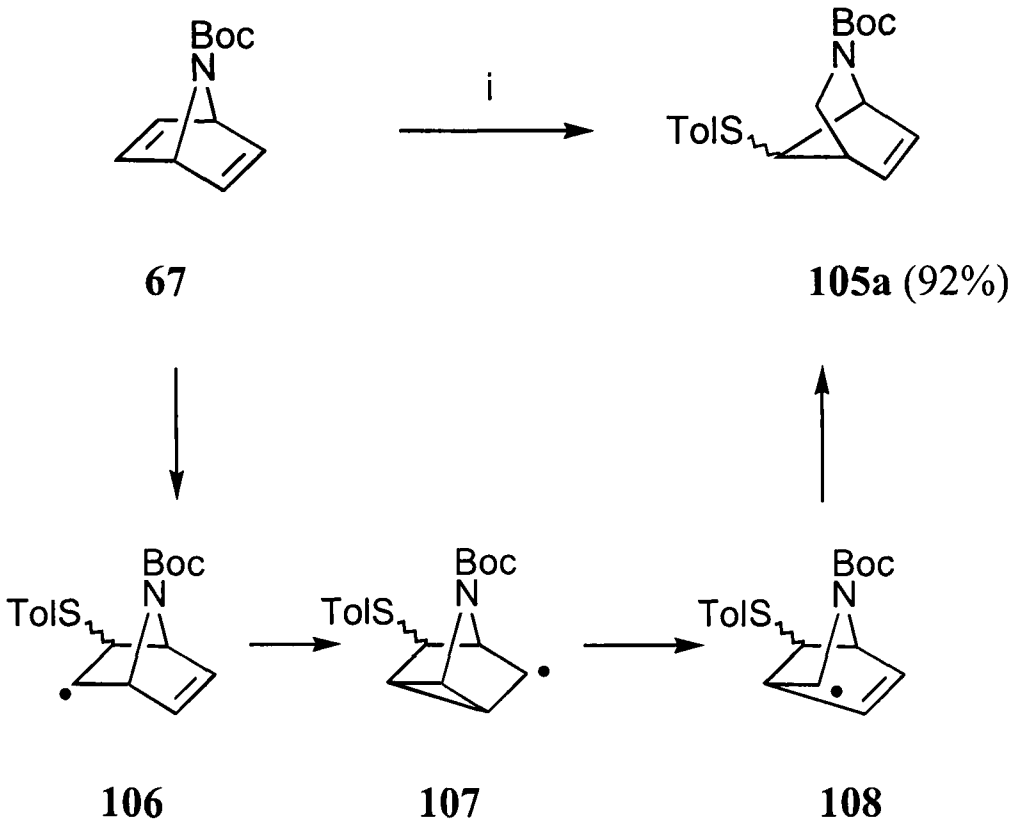
Encouraged by a better understanding of the radical addition in the all-carbon system, attention turned to the crux of the project – development of new rearrangement methods for the synthesis of azabicycles – based on the preliminary results of Maxwell.[45] Boc-protected 7-azanorbornadiene **67** was synthesised in modest yield from desulfonylation of Diels-Alder adduct **65**, as detailed in chapter two:



65 **67** (24%, lit. 24%[45])

Scheme 3.8 Synthesis of 7-Boc-7-azanorbornadiene. *Reagents and conditions*:i, Na-Hg, Na_2HPO_4, NaH_2PO_4, MeOH, 0 °C, 6 h.

It was found that addition of 0.9 equivalents of *p*-thiocresol to a solution of **67** in dry toluene at 20 °C under argon gave exclusively the desired rearranged product **105a** as a 3 : 1 mixture of epimers. Leaving the reaction for 2-3 h initially gave yields of 30-50% with substantial recovered starting material, but increasing the reaction time to 24 h gave a pleasing 92% yield of **105a** (Scheme 3.9, overleaf).[69] To our knowledge this is the first example of a synthetically useful intermolecular free radical addition-homoallylic rearrangement process.



Scheme 3.9 Addition-rearrangement of 7-azanorbornadiene.

The stereochemistry of the major epimer was confirmed by a 1D nOe experiment. Irradiation at the frequency of both sets of olefinic protons showed enhancement of only one of the signals of the protons α to the sulfur atom (Fig. 3.2). NOe enhancement was observed only for the major isomer. This confirms that the major product has the thio- group *syn* to nitrogen derived from expected initial *exo* attack of the thiyl radical on **67**.

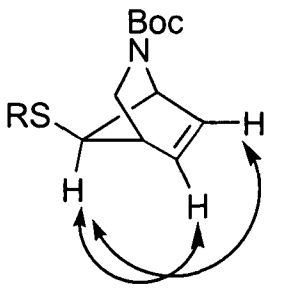
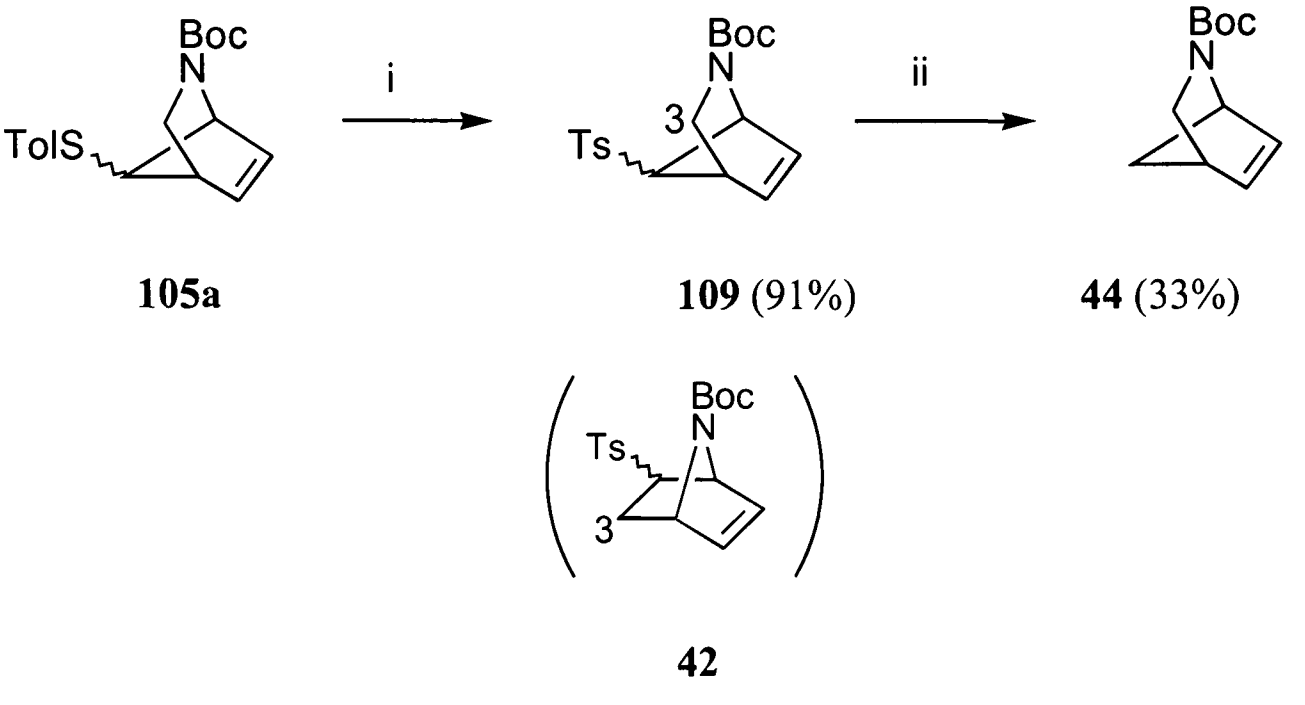


Fig. 3.2 nOe enhancements for *syn*-**105a** (R = Tol).

The structure of the product was confirmed by oxidation of **105a** to epimeric sulfones **109**, which had different spectral characteristics from known sulfones **42**.[70] In particular, the methylene protons attached to C3 possess very different NMR chemical shifts in **109** compared to **42** (δ = 3.7 (1 H) and 2.5 (1 H)

for **109** vs 1.8 ppm (2 H) for **42**). As further evidence, subsequent desulfonylation gave known alkene **44**[71] as the sole product (Scheme 3.10):

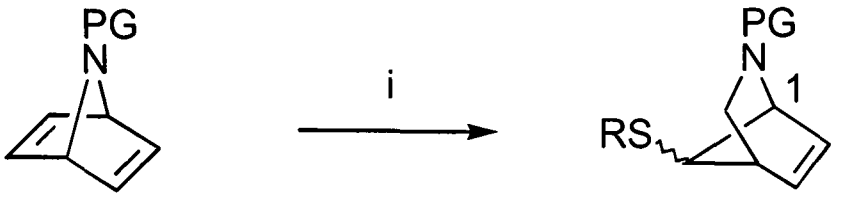


105a **109** (91%) **44** (33%)

42

Scheme 3.10 Confirmation of product structure. *Reagents and conditions*: i, AcOOH (6 equiv), NaOAc, Na_2HPO_4, CH_2Cl_2, 25 °C, 18 h; ii, Na-Hg, Na_2HPO_4, MeOH, 12 h, 0 °C-25 °C.

Diene **67** was found to react with a range of aromatic thiols at 20 °C in good to excellent yield (Table 3.2, below). Aliphatic thiols required higher temperature for reaction and the yields were more modest, possibly because polymerisation could compete with the slower H-atom transfer[6] compared to aromatic thiols. The major isomer was assigned as having *syn* stereochemistry by analogy with entry **a** (Table 3.2): the ^{1}H NMR chemical shift of the H-atom attached C1 was consistently ~0.2 ppm lower for the major isomer in all the examples shown overleaf.



105a-g

Scheme 3.11 Thiol additions to 7-azanorbornadienes. Reagents and conditions: RSH (0.9 equiv.), toluene or benzene (initial [thiol] = 0.1 M).

Entry	R	PG	T/°C	t/h	Yield/%	**105** syn : anti
a	*p*-Tol	Boc	20	24	92	3 : 1
b	*p*-Tol	MeOC(O)	20	4	66	4 : 1
c	Ph	Boc	20	24	92	4 : 1
d	2,6-DiMeC_6H_3	Boc	20	24	90	4 : 1
e	4-$NO_2C_6H_4$	Boc	20	72	50	7 : 1
f	4-$MeOC_6H_4$	Boc	20	24	59	2.5 : 1
g	Bu^n	Boc	80	6	59	2 : 1
h	Bu^t	Boc	80	24	48	5 : 1
i	HO-$(CH_2)_3$	Boc	80	14	56	3 : 1

Table 3.2 Thiol additions to 7-azanorbornadienes.[69]

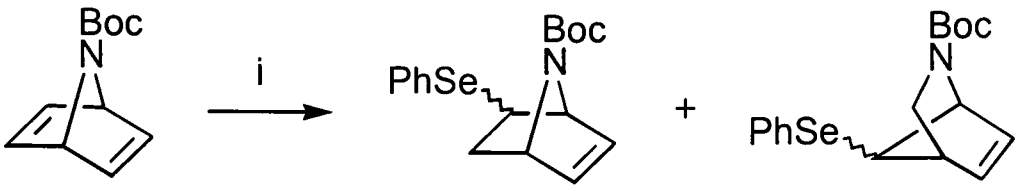
The results in table 3.2 show modest selectivity for the *syn* product derived from *exo* attack of the thiyl radical. There appears to be a correlation between selectivity for the *syn* product and the electronic nature of the thiol. The *p*-nitrobenzenethiol (entry **e**, table 3.2) gives the highest selectivity for *exo* attack; the *p*-methoxy substituent leads to the lowest selectivity, and the others lie between these extremes. Additional resonance stabilisation of the *p*-nitrobenzenethiyl radical may confer additional stability on that species compared to the other aromatic thiyl radicals. This suggests a less exothermic radical addition to the diene, a later transition state for the reaction and therefore more steric influence on the energy of the transition states for *endo* and *exo* addition, leading to higher selectivity for *exo* attack in this case. An alternative possibility is that electrostatic interaction between

the pi-orbitals of the Boc-carbonyl group and those of the electron-deficient aromatic ring helps to guide the approaching radical in from the *exo* face. More hindered thiols appear to increase the selectivity to some extent (entries **a** and **d**, and **g** and **h**), but the effect is not a strong one. Alteration of the protecting group (entries **a** and **b**) to *N*-methoxycarbonyl[72] by TFA deprotection and then reprotection according to the procedure of Corey[73] did not have a great effect on selectivity either.

Given the results with norbornadiene, complete selectivity for *exo* attack would not be expected, since azadiene **67** possesses a more hindered *exo* face. The product profile is most likely explained by kinetic preference for the *exo* face, rather than reversible attack by the thiyl radical and a thermodynamic product distribution.[67] Extrusion of the thiyl radical to regenerate **67** would be an endothermic step, as it would involve formation of a strained double bond. The minimal variation of selectivity with alteration of the steric or electronic properties of the thiols is consistent with an early transition state for an exothermic radical addition[1] and the formation of a long C-S bond.

3.4 Radical Addition of Benzeneselenol

In order to probe the kinetics of the rearrangement further, it was decided to treat diene **67** with benzeneselenol,[69] which reacts an order of magnitude faster in H-atom transfer to carbon-centred radicals.[6] Under identical conditions to the thiol additions presented above, a small amount of the product of simple addition to one double bond **110** was isolated in addition to the expected rearranged product **111** (Scheme 3.12, overleaf):



67 **110** (12%) (*exo* : *endo* 1:6) **111** (81%) (*syn* : *anti*, 3 : 1)

Scheme 3.12 Addition of benzeneselenol to 7-Boc-7-azanorbornadiene. *Reagents and conditions*: PhSeH (0.9 equiv), benzene, 25 °C, 24 h.

Selenide **110** was easily identified from its ^{1}H NMR spectrum - the two bridghead protons were clearly both α to nitrogen (δ ≈ 5 ppm). This material was analysed comprehensively by NMR spectroscopy. Interestingly, a NOESY experiment suggested that the major isomer had the selenyl substituent on the *endo* face: An nOe enhancement was observed between the olefinic protons and the C-3 proton *trans* to the proton attached to C-2:

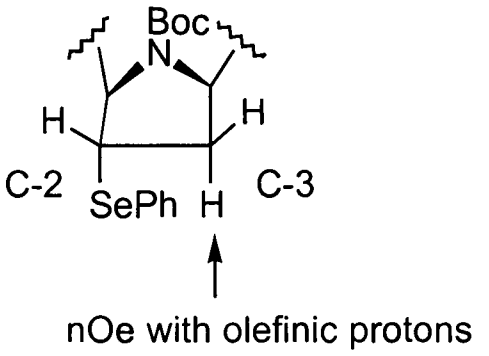


Fig 3.3 A portion of **110** illustrating relevant nOe's.

This can be explained if H-atom transfer from the *exo* face to the radical resulting from *endo* addition **113** (Fig. 3.4, overleaf) is faster than H-atom transfer to the more hindered radical resulting from *exo* addition **112**, which would result in proportionately more of the radical **113** being trapped before rearrangement could occur, and hence an excess of *endo* **110**.

112 **113**

Fig. 3.4 Radicals resulting from *exo* and *endo* attack on **67**.

Alternatively, **113** may cyclise more slowly than **112**, which also would lead to a greater proportion of *endo* **110**. Currently it is not possible to distinguish between these possiblities.

3.5 Interpretation of Kinetics

The result from the benzeneselenol addition allows an estimation of the rate constant for the rearrangement **106** → **108** (Scheme 3.9, p.56). Since none of the product of simple addition is observed in the reactions of aromatic thiols and a small amount of **110** is isolated in the reaction with benzeneselenol, rearrangement must occur at a rate that is 1 or 2 orders of magnitude greater than the initial H-atom transfer rate from the thiol. A value of 10^8 dm^3 $mol^{-1}s^{-1}$ for the second order H-atom transfer rate constant[6] and an initial thiol concentration of 0.1 mol dm^{-3} suggests the value of the first order rate constant for the rearrangement is 10^8-$10^9 s^{-1}$. This is faster than the ring opening and ring closure steps in the norbornenyl-nortricyclyl rearrangement, which are both ≈ 10^7 s^{-1}.[66] The effect of the sulfur substitutent on these rates has not been determined, although the results with the benzeneselenol addition presented herein suggest that adduct radicals resulting from *exo* and *endo* attack on 7-azanorbornadienes (Fig. 3.4, above) cyclise and are trapped at different rates, which may also be the case in the all carbon system. This implies that the observed *exo*/*endo* ratio of **92** (Table 3.1, p.50) and indeed of **105a-i** may not reflect the proportion of initial *exo* thiyl radical attack.

The difference between the product profiles in the thiol additions to norbornadiene and the 7-azanorbornadiene derivatives is striking. There are conceivably three reasons why the rearrangement leads to 2-azabicyclo[2.2.1]hept-5-enes:

1) Interaction of the radical centre with the lone pair on the nitrogen atom is strongly stabilising (Fig. 3.5) [74] and so the ring opening step **107** → **108** is accelerated by the stabilisation of the developing radical α to nitrogen.

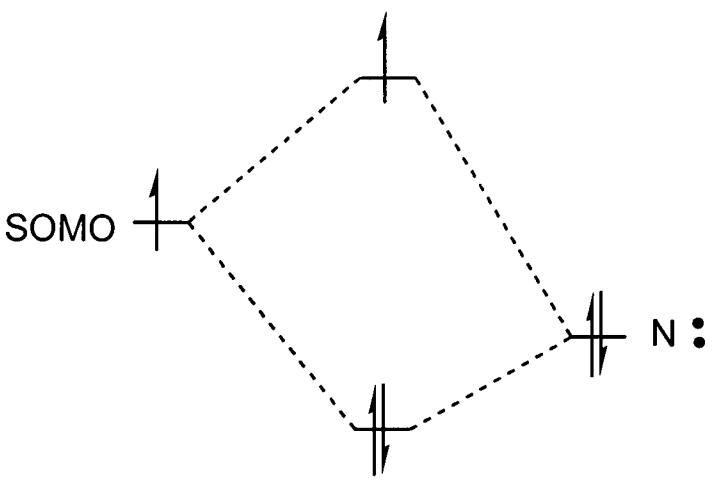


Fig. 3.4 Lone pair - SOMO interaction.

2) A larger C-N-C bond angle in the radical **108** than in **106** leads to more sp^2 character at nitrogen in **108** and therefore a more stabilising contribution from amide resonance in the product radical.

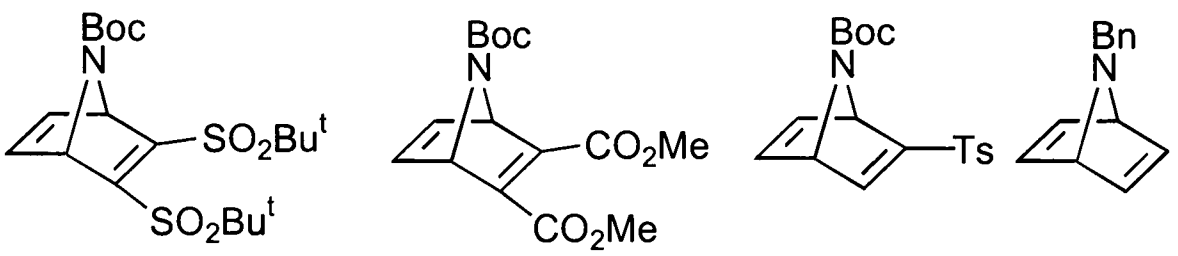
3) H-atom transfer from the thiol/selenol is significantly faster to **108** than for **106**. This is plausible if the orbital interaction described above is operating - it raises the energy of the SOMO, making it in theory more nucleophilic and therefore better at abstracting hydrogen from the thiol to give an electrophilic radical. This is in accordance with the analysis of polar effects presented in chapter one.

Of these possible explanations, (3) does not explain the original results of Maxwell,[45] who observed radical rearrangement during desulfonylation of **42** (Scheme 1.23, p.32) and selective ring opening during deoxygenations of tricyclic

alcohols. [75, 76] Both of these processes occurred without an electrophilic H-atom donor present, although it is likely that H-atom transfer does occur at different rates for **106** and **108**. At this point it is not possible to distinguish between (1) and (2), but this will be discussed at length in a later chapter.

3.6 Alternative substrates

Thiol additions were attempted without success on the substrates shown below. Substrates **114**[55,77] and **115**[78] shown below (Scheme 3.13) were synthesised by literature methods. Compound **116** was synthesised by TFA deprotection of diene **65** and alkylation with benzyl bromide in 38% overall yield.[79]



114 **115** **65** **116**

Scheme 3.13 Alternative substrates for thiol additions.

Diene **114** was unreactive towards *p*-thiocresol, whereas **115** and **65** gave complex mixtures, which appeared to result from addition to both double bonds. Reaction of *p*-thiocresol with **116** appeared to give a product assigned as arising from the expected rearrangement (one bridgehead α to nitrogen at $\delta \approx 4.0$ ppm in the ^{1}H NMR spectrum), but attempts at chromatography did not lead to its isolation.

3.7 Conclusions and Recommendations

Thiol additions to norbornadiene have been repeated which have led to a better understanding of the rearrangement processes involved, including a model which explains the different product profiles observed for thiol additions and the reduction of norbornenyl and nortricyclyl bromides.

A procedure has been developed for the intermolecular radical addition of thiols and selenols to carbamate protected 7-azanorbornadienes to give 2-azanorbornene derivatives in good yields *via* nitrogen-directed homoallylic rearrangement. The study has enabled an estimate of the rate of reaction, and possible explanations have been suggested for the selectivity of the rearrangement.

The process currently suffers from a lack of substrate generality, the solution to which may be the use of nucleophilic carbon-centred radicals in additions to 7-azanorbornadienes which are conjugated to electron-withdrawing groups. This has been pursued with some success within the group.[60]

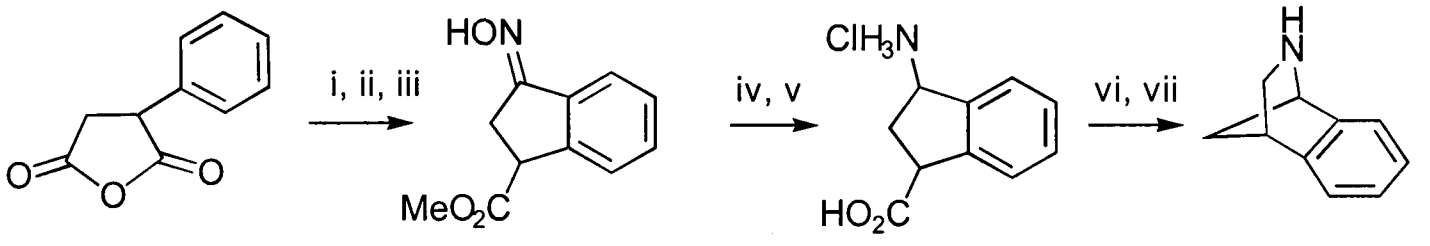
Other possible extensions to this method include rearrangements in other bicyclic ring systems. A key issue to be resolved is to discover what electronic or structural characteristics of the radicals involved drive the rearrangement.

Chapter Four: Development of Nitrogen-directed Neophyl-like Rearrangements

This chapter is concerned with synthesis of 2-azabenzonorbornanes *via* nitrogen-directed neophyl rearrangements. Previous syntheses of these amines are examined for comparison below.

4.1 Synthetic routes to 2-azabenzonorbornanes

These compounds are not readily accessible, to the extent that only a few reports have appeared in the literature in the last fifteen years. The route to the parent amine, developed by Grunewald et al.[80] and shown below, uses some conventional chemistry to access the amine **120**:



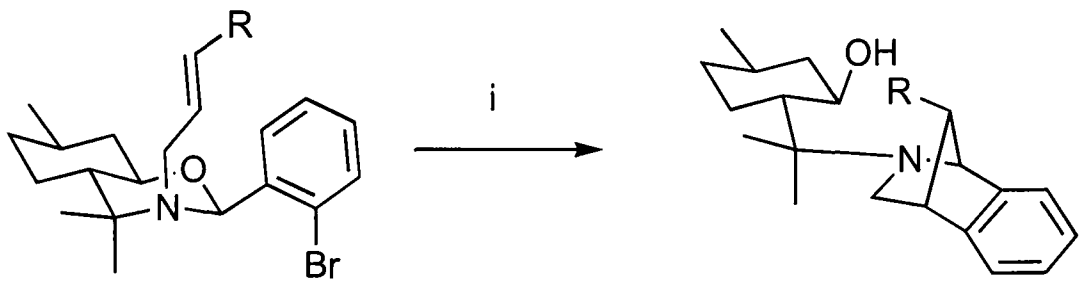
117 **118** **119** **120**

Scheme 4.1 Stepwise route to 2-azabenzonorbornane. *Reagents and conditions*: i, $AlCl_3$, $Cl(CH_2)_2Cl$; ii, MeOH, cat. H_2SO_4, reflux, 72% over 2 steps; iii, $H_2NOH.HCl$, NaOAc, H_2O/EtOH, 93%; iv, 50 psi H_2, Pd/C, MeOH/$CHCl_3$, 92%; v, 4 N HCl, reflux, 86%; vi, pyridine, DCCI, MeCN, reflux, 66%; vii, $LiAlH_4$, THF, 0 °C, 89%.

A Friedel-Crafts reaction with phenylsuccinic anhydride **117**, followed by esterification and condensation of the resultant ketone with hydroxylamine hydrochloride gives oxime **118**. Hydrogenation and formation of the HCl salt leads to **119**, then a DCCI-mediated coupling and $LiAlH_4$ reduction gives the desired amine **120**. The route is quite long, although efficient, but it is not easily amended to give more substituted products, either on the benzene ring or the bicyclic core.

A more innovative approach was adopted by Pedrosa and Andres,[81] in which lithiation of a bromobenzene **121** derivative leads to a double ring closure. A

chiral *N,O*-acetal guides the diastereoselectivity. Subsequent elimination then gives enantiopure 2-azabenzonorbornanes (Scheme 4.2, below):



R = 2-(OMe)Ph

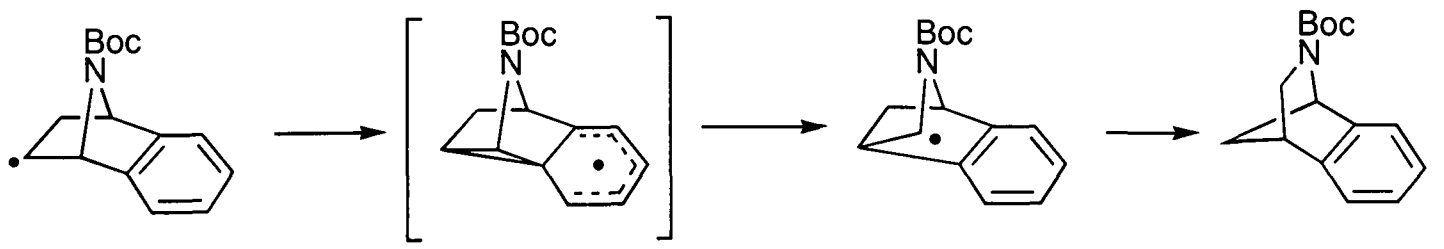
121 **122**

Scheme 4.2 Pedrosa's double cyclisation strategy for the synthesis of 2-azabenzonorbornanes. *Reagents and conditions*: i, *t*-BuLi, TMEDA, Et_2O, -90 °C to 25 °C, 95%.

The reaction occurs by a 6-*exo* cyclisation of the lithiated aromatic onto the alkene. The new alkyllithium then displaces the alkoxide to give **122** on work-up. This is a significant advancement over the original route, since it allows control of substitution, is diastereoselective and reaches the target compounds in only 3 steps from (–)-8-aminomenthol and *o*-bromobenzaldehyde.

4.2 Concept of Nitrogen-directed Neophyl-like Rearrangement

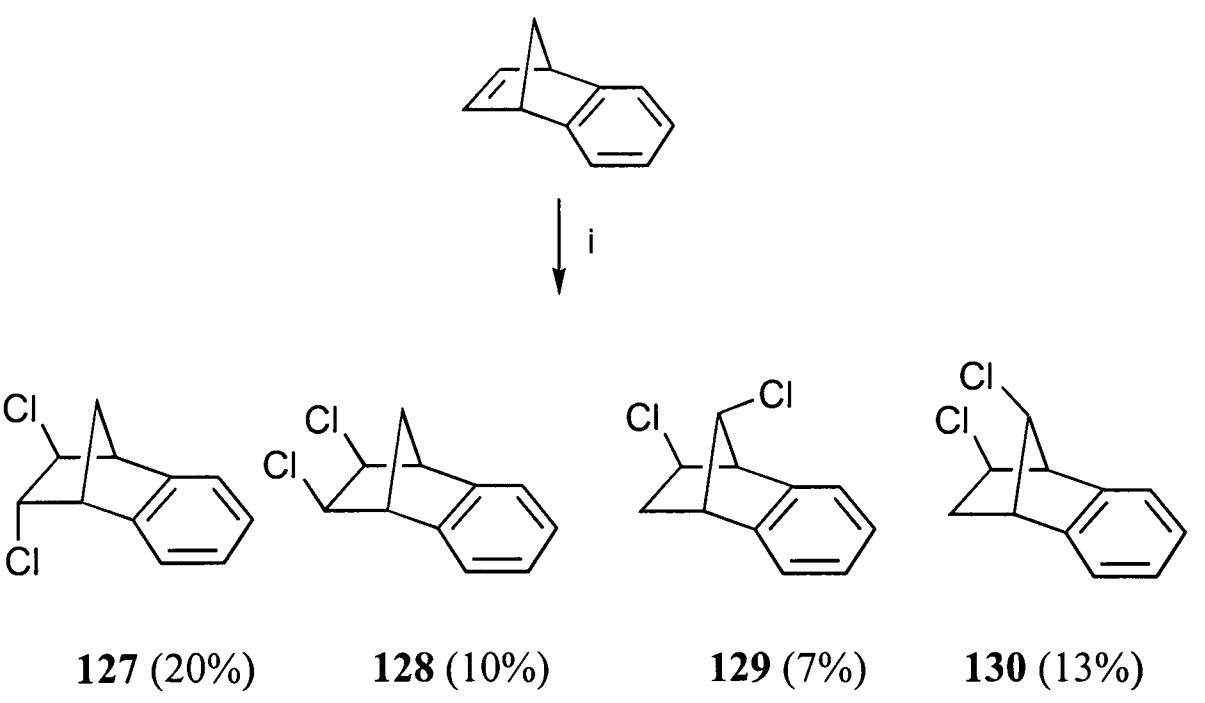
Given that routes to 2-azabenzonorbornanes were so scarce, it was concieved that an attractive entry to these systems would be *via* a radical 1,2-aryl shift (neophyl rearrangement) of a 7-azabenzonorbornanyl radical (**123** → **125**, Scheme 4.3 below). The challenge of inducing a radical neophyl-type rearrangement to give 2-azabenzonorbornane **126** was considerable.



123 **124** **125** **126**

Scheme 4.3 Proposed nitrogen-directed neophyl rearrangement.

Two main problems had to be overcome if this was to be a viable method for the synthesis of 2-azabenzonorbornanes such as **126**. First, that of generating the radical **123**, and secondly, creating conditions under which **123** would rearrange, presumably *via* **124** to the 2-azabenzonorbornanyl radical **125**. In contrast to the rearrangements presented in chapter three, this process involves a temporary disruption of aromaticity rather than cyclisation onto a double bond, thus raising the energy of the transition state. Before these studies, it was not known whether the rearrangement **123** → **125** would occur, as there are very few examples in the literature of neophyl-type rearrangements in the all-carbon system. Cristol added sulfuryl chloride (SO_2Cl_2) to benzonorbornadiene[82] to give the product distribution shown below (Scheme 4.4):

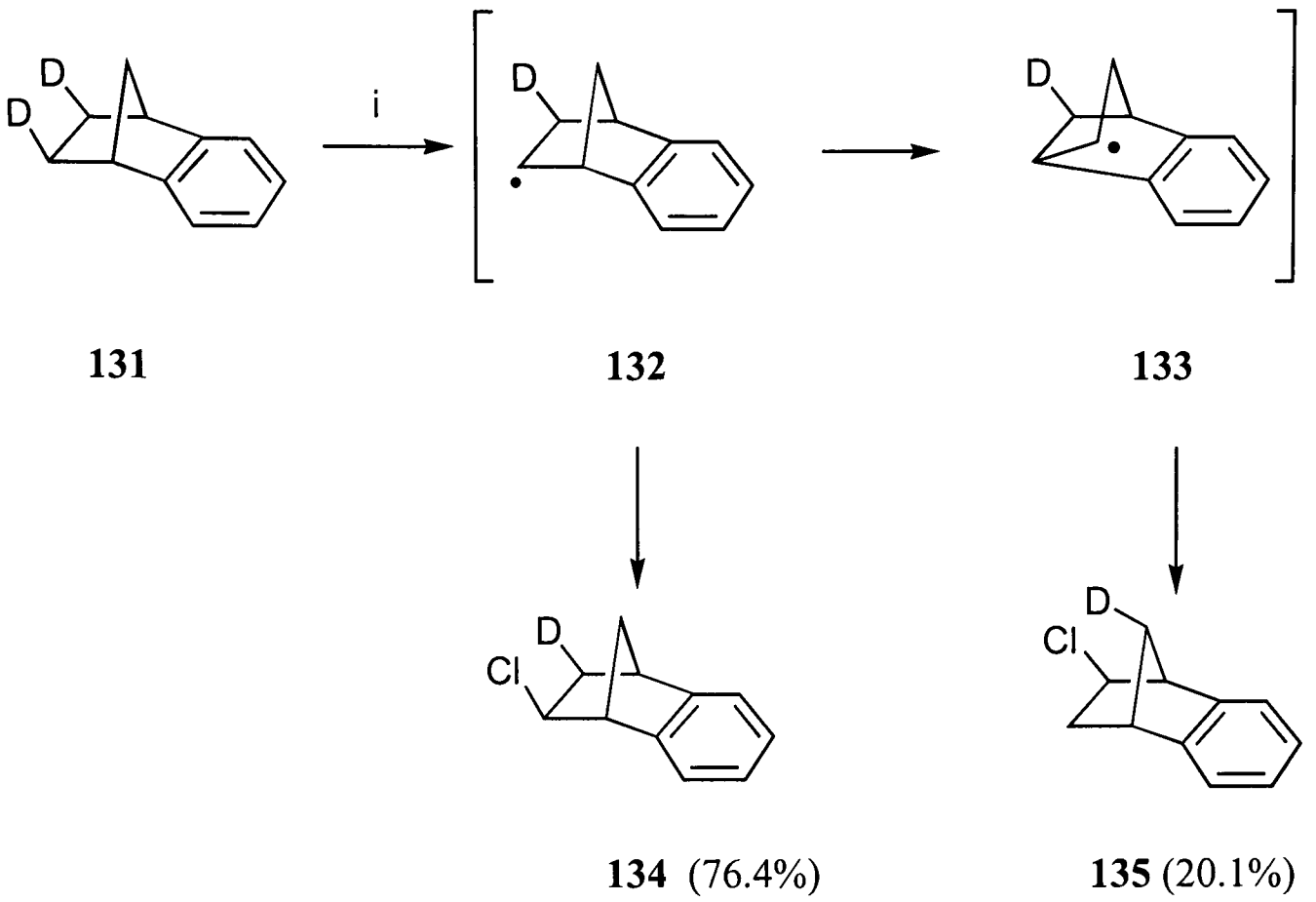


127 (20%) **128** (10%) **129** (7%) **130** (13%)

Scheme 4.4 Addition of sulfuryl chloride to benzonorbornadiene. *Reagents and conditions*: i, SO_2Cl_2, hν, CCl_4, 0-5 °C, 3 h.

The presence of *exo/syn* dichloride **129** was attributed to a small fraction of initial *endo* attack by a chlorine radical, then neophyl-like rearrangement and *exo* trapping from another molecule of sulfuryl chloride. Compound **129** was not detected in ionic addition using chlorine gas, and it was presumed that the radical reaction would be less selective for *exo* attack than the analogous ionic process.

This was the first suggestion that a 1,2-aryl shift could occur in a benzo-fused system, but is not conclusive proof. Deuterium scrambling was noted from D-atom abstraction from *exo*-dideuteriobenzonorbornene **131**:[83]



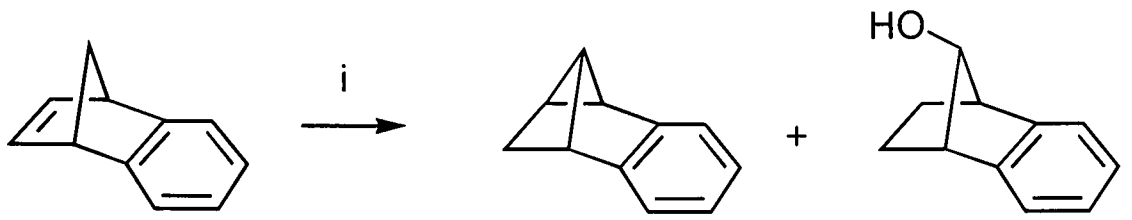
131 **132** **133**

134 (76.4%) **135** (20.1%)

Scheme 4.5 H-atom abstraction - chlorine radical trapping of **131**. *Reagents and conditions:* SO_2Cl_2, hν, CCl_4.

The product **135** was thought to arise from a similar rearrangement to that observed previously (Scheme 4.5).

Sonawane[84] reported the first example of a neophyl-like radical rearrangement in a benzo-fused system that gave a majority of the rearranged product (Scheme 4.6). Photolysis of H_2O_2 in the presence of benzonorbornadiene gave a mixture of **136**, the product of di-π-methane rearrangement and **137**, arising from addition of hydroxyl radical and then neophyl-like rearrangement. No other products were isolated, and the reason for the selectivity for the rearranged product is not clear.



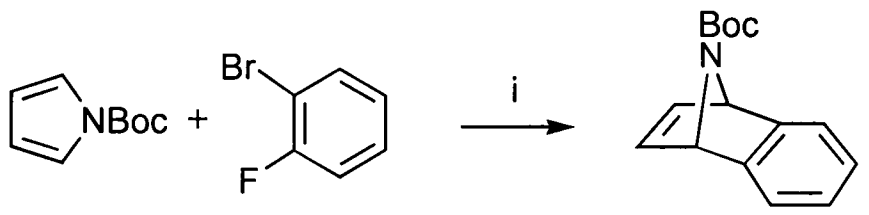
136 (14%) **137** (26%)

Scheme 4.6 Photolysis of H_2O_2 in the presence of benzonorbornadiene. *Reagents and conditions*: H_2O_2 (0.1 equiv.), hν, MeCN, 25 °C, 15 h.

Given that there was some precedent for the desired process, investigation of the potential rearrangement in the azabicyclic system was a matter of some urgency.

4.3 Radical Additions to 7-Boc-7-azabenzonorbornadiene

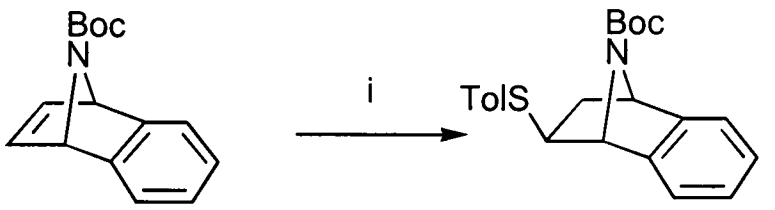
The 7-azabenzonorbornadienes e.g. **138**, are readily available[85] from benzyne cycloadditions using *N*-Boc pyrrole as the benzyne trap (Scheme 4.7, below):



138 (57%, lit. [86] 57%)

Scheme 4.7 Synthesis of 7-Boc-7-azabenzonorbornadiene. *Reagents and conditions*: Mg, THF, reflux, 2 h.

It was found that the procedure was readily reproducible and **138** was thus available in gram quantities. Since thiol radical additions had already produced some success, it was decided to use them once more to investigate rearrangement of the benzo-fused system. Treatment of adduct **138** with *p*-thiocresol gave only the *exo* product of simple addition **139** (Scheme 4.8).

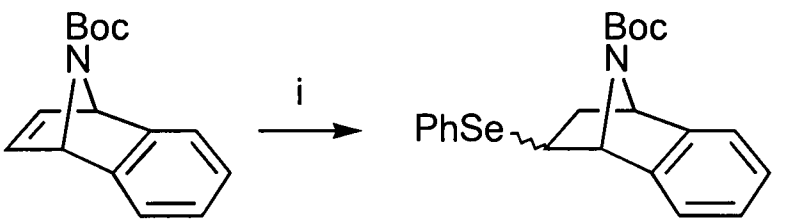


138 **139** (89%)

Scheme 4.8 Reagents and conditions: i, *p*-thiocresol (1.5 equiv.), toluene (0.1 mol dm^{-3}), 25 °C, 24 h.

This result suggested that any rearrangement was too slow to occur in the presence of a fast H-atom donor like an aromatic thiol.[6] Addition of Bu^nSH at 80 °C in a similar fashion gave a mixture of products, none of which was isolated. Given subsequent results it seems likely that some rearrangement had occurred, but purification proved to be a problem and another approach was sought.

Selenides are well known as free radical precursors.[1] Addition of benzeneselenol to adduct **138** first gave an excellent yield of epimeric selenides **140** (Scheme 4.9), but on subsequent occasions the reaction could not be driven to completion, even by using a large excess of benzeneselenol or heating the reaction to 80 °C. The product could not be separated from the starting material and it was decided to abandon the synthesis of a selenide precursor.



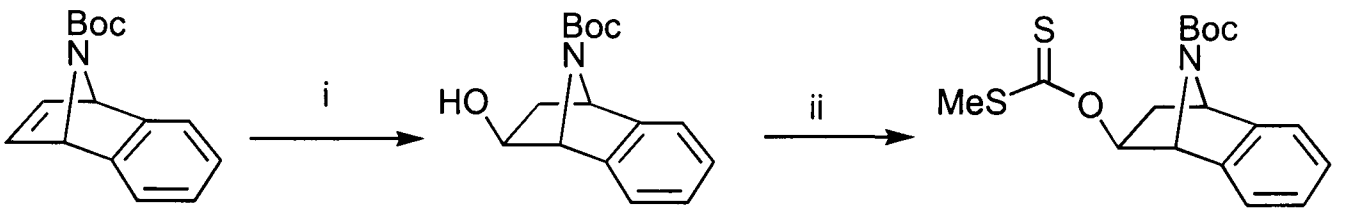
138 **140** (90%, *exo*: *endo*, 3 : 1, not reproducible)

Scheme 4.9 Attempted synthesis of a selenide radical precursor. *Reagents and conditions*: PhSeH, toluene or neat, 25-80 °C, 24-48 h.

4.4 The Barton Deoxygenation route - Optimisation

Barton deoxygenation of derivatised alcohols is a useful method for radical generation, [16] and conversion of an alkene to an alcohol is straightforward using hydroboration-oxidation.[87] 9-BBN is the hydroborating reagent most widely used

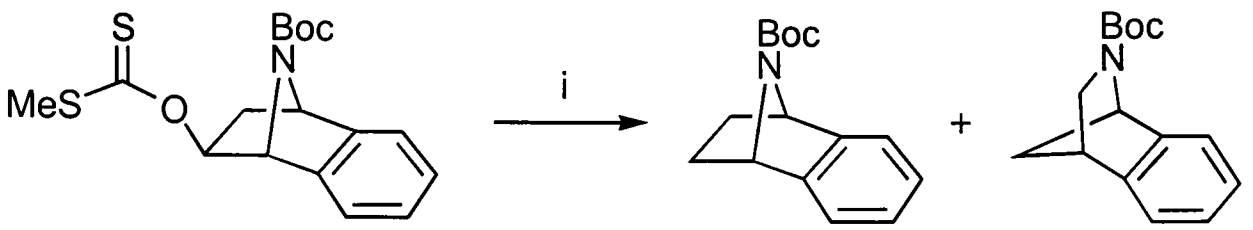
when both facial and regioselectivity is required, and it was found that treatment of **138** with 1.2-1.5 equivalents of a solution of 9-BBN in THF followed by oxidative work-up, gave the alcohol **141** (Scheme 4.10) as a single isomer in reproducible yields. The stereochemistry was assigned as *exo*, in accordance with previous hydroborations of 7-azabenzonorbornadienes.[88] Conversion to the xanthate **142** proceeded smoothly in good yield.



138 **141** (60-67%) **142** (up to 95%)

Scheme 4.10 Hydroboration-oxidation and xanthate preparation. *Reagents and conditions*: 9-BBN (1.5 equiv.), THF, 25 °C, 24 h, then 35 % aq. H_2O_2, 2 M NaOH, THF/H_2O, 25 °C, 5 h; ii, KH, THF, 0 °C → 25 °C, 20 min, then CS_2, 0 °C, 10 min, then MeI, 25 °C, 20 min.

A suitable radical precursor had been prepared successfully, and the potential radical rearrangement chemistry could now be examined. Directly-reduced product **143** (Scheme 4.11) was prepared by hydrogenation of **138** in 94 % yield to serve as a reference sample.[89] Treatment of the xanthate **142** with Bu_3SnH (0.04 M) and AIBN in toluene at reflux gave a 1 : 3 mixture (by ^{1}H NMR) of the directly-reduced compound **143** and rearranged product **126**, which was identified by the presence of only one bridgehead proton α to nitrogen at δ = 4.94 ppm in the ^{1}H NMR sprectrum. Problems in chromatographic removal of tin residues led to the use of tris(trimethylsilyl)silane (TTMSS) as the reducing agent instead. Ratios of **143** and **126** resulting from treatment of the xanthate with TTMSS/AIBN under various reaction conditions, and isolated yields of **126** are shown in table 4.1, overleaf.[90]



142 **143** **126**

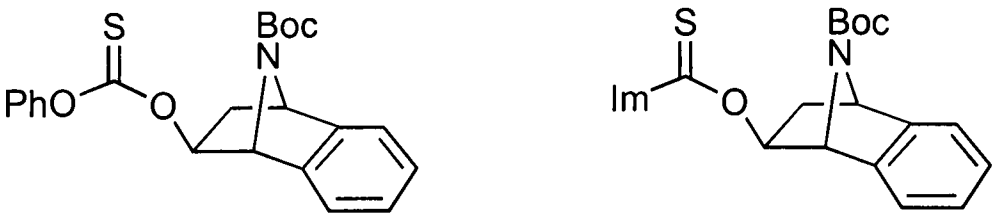
Scheme 4.11 Deoxygenation of **142**. Reagents and conditions: i, Bu_3SnH/TTMSS, AIBN, toluene, reflux.

RH	[RH]*/mol dm^{-3}	ratio **143** : **126** (^{1}H NMR)	yield **143**/%	yield **126**/%
Bu_3SnH	0.04	1 : 3	not purified	not purified
TTMSS	0.12	1 : 1	not purified	35
TTMSS	0.04	1 : 7	10	72
TTMSS	v. low**	1 : 20	trace	*90*

* initial H-atom donor concentration.
A mixture of the silane and AIBN was added by syringe pump to a preheated solution of **142 in toluene at reflux over 100 min. The reaction was left for a further 30 min before being allowed to cool.

Table 4.1 Optimisation of yield of 2-azabenzonorbornane **126**.

The use of other thiocarbonyl derivatives,[16] such as thiocarbonate **144** and thiocarbonyl imidazole **145**, gave similar product profiles, but led to lower yields of the desired products (Fig. 4.1, below).

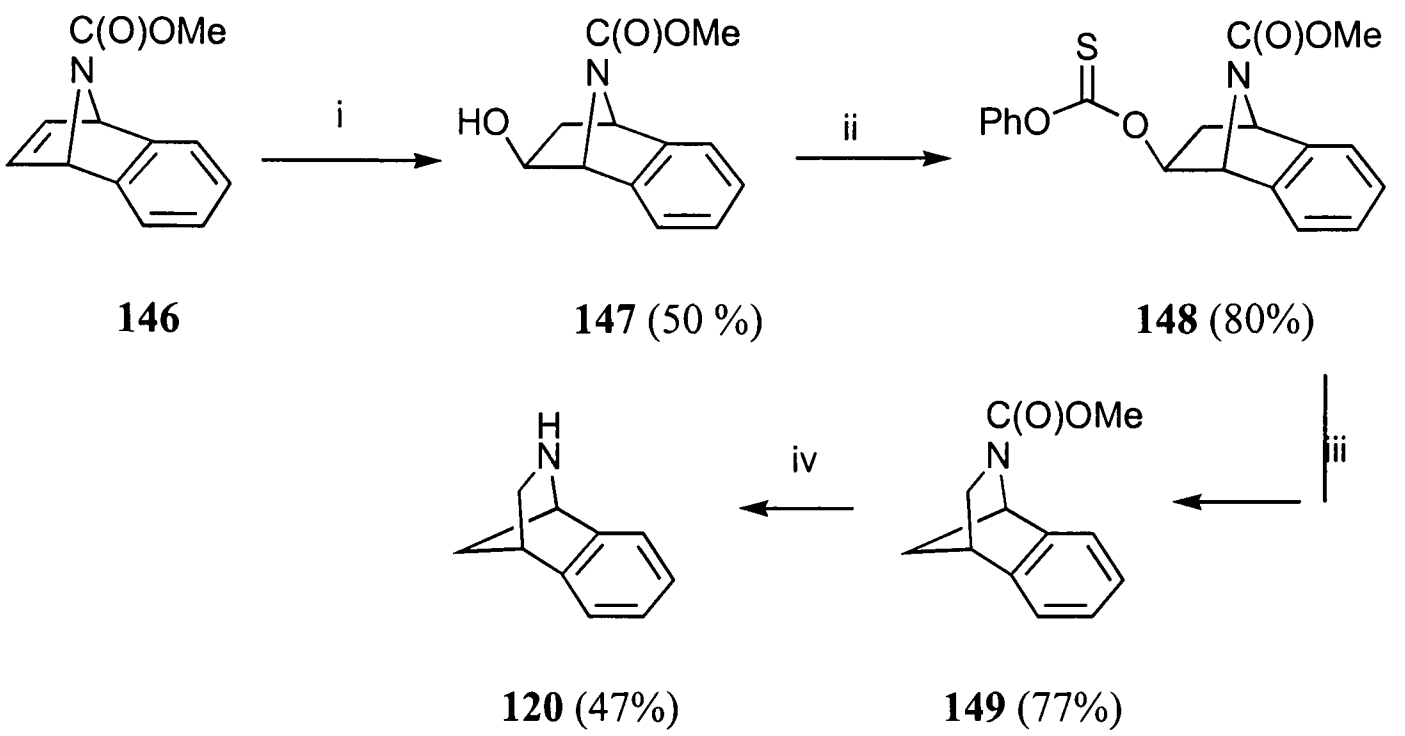


144 **145**

Fig. 4.1 Alternative radical deoxygenation precursors.

Encouraged by these results, methyl carbamate **146** was prepared by a literature method,[91] and analogous steps followed to those described previously for the Boc-protected substrate (Scheme 4.12) Deoxygenation of the thiobenzoate

derivative **148** gave rearranged product **149**, and subsequent treatment with KOH gave the known amine **120**,[80] identified by comparsion of its ^{1}H, ^{13}C and IR spectra with those previously reported. Thus the structure of the product had been confirmed.



146 **147** (50 %) **148** (80%)

120 (47%) **149** (77%)

Scheme 4.12 Confirmation of rearranged product structure. *Reagents and conditions*: i, 9-BBN, THF, 25 °C, 24 h, then aq. H_2O_2, 2M NaOH, 25 °C, 5 h; ii, PhOC(S)Cl, DMAP, CH_2Cl_2, 25 °C, 18 h; iii, TTMSS, AIBN, slow addition, toluene, reflux; iv, KOH, ethylene glycol/water 1 : 1, reflux, 16 h.

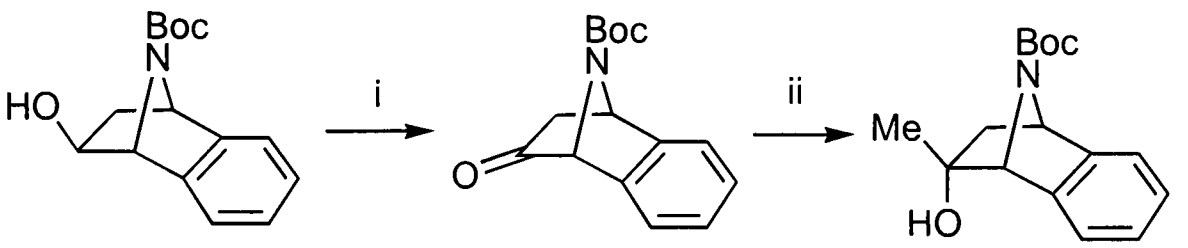
These results allow an estimation of the rate constant for this rearrangement. Entry 2 in table 4.1 suggests that under those conditions the rate of rearrangement **123** → **125** is similar to the rate of H-atom transfer. Using an approximate value of 1 x 10^6 dm^3 mol^{-1} s^{-1} for the second order H-atom transfer rate from TTMSS to a secondary alkyl radical[6] and an average silane concentration of ~0.1 M suggests that the rate constant for the rearrangement **123** → **125** is of the order of 10^5 s^{-1}. This means that the rearrangement is about 1000 times slower than that observed in the 7-azanorbornenyl system discussed in chapter three, reflecting the disruption of aromaticity involved in the neophyl-like rearrangement.

4.5 Effect of Substitution of the Bicyclic Core

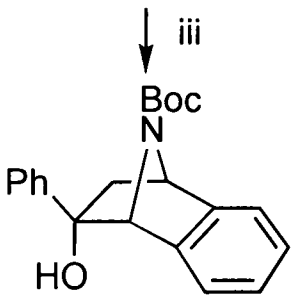
As the structure of the rearranged products **126** and **149** had been verified, it was felt appropriate to conduct a study of the effect of substitution on the rearrangement chemistry.

4.5.1 Attempted Deoxygenation of Tertiary Alcohols

A number of methods are now known for the radical deoxygenation of tertiary alcohols,[18,19] and an obvious way of making a substituted system from alcohol **141** was to oxidise it to the ketone **150** and react that with Grignard reagents, giving the alcohols **151** and **152** (Scheme 4.13).



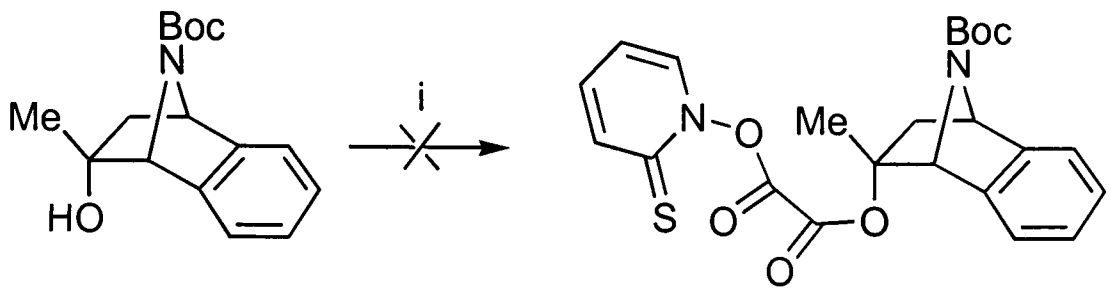
141 **150** (79%) **151** (93%)



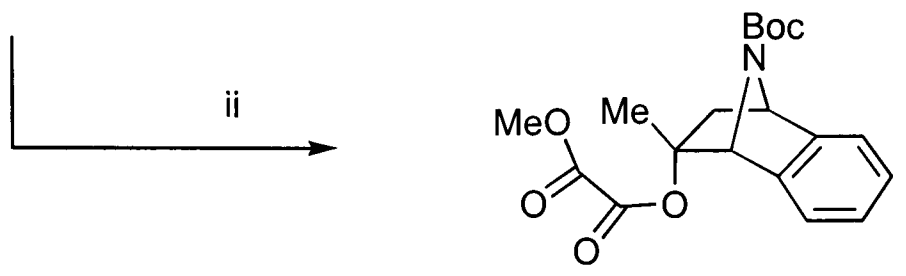
152 (69%)

Scheme 4.13 Synthesis of tertiary alcohols. *Reagents and conditions*: i, $(COCl)_2$, DMSO, Et_3N, THF, -78 °C → 25 °C, 1 h; ii, MeMgBr, Et_2O, 0 °C, 2 h; iii, PhMgCl, THF, 0 °C, 90 min.

Unfortunately, numerous efforts to deoxygenate the precursors failed. Alcohol **151** could not be transformed into the Barton ester **153**, possibly due to decomposition of the unstable PTOC salt, and no identifiable products were isolated after work-up. The reaction with methyl oxalyl chloride to give **154** was successful (Scheme 4.14, overleaf).



151 **153**



154 (90 % crude)

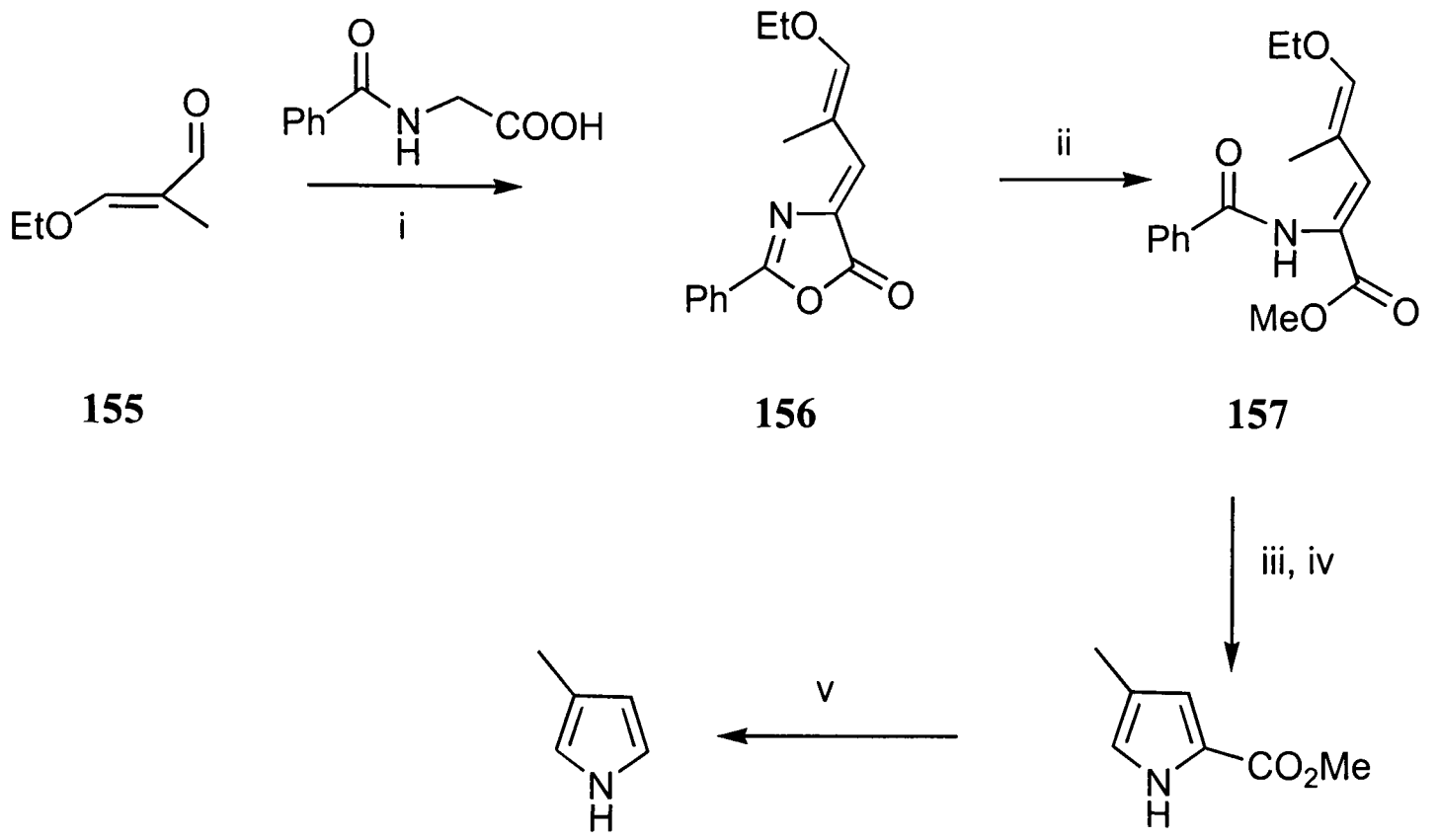
Scheme 4.14 Synthesis of deoxygenation precursors from tertiary alcohols. Reagents and conditions: i, $(COCl)_2$, benzene, DMF (cat.), 25 °C, 2 h, then sodium 2-thionopyridine-*N*-oxide, DMAP, reflux, 30 min; ii, MeOC(O)C(O)Cl, DMAP, MeCN, 25 °C,1 h.

Attempted deoxygenation of **154** failed with TTMSS, indicating that an electron transfer mechanism that is thought to occur with TBTH[19] does not occur with the silane. At the time it was decided to pursue other avenues of the project, as the use of highly toxic tin to effect this transformation was not considered an attractive option.

4.5.2 Preparation of 3-substituted pyrroles

Another obvious way to create substitution on the bicyclic core was to conduct cycloadditions with substituted pyrroles. In order to examine the regioselectivity of the hydroboration reaction, it was proposed that a benzyne cycloaddition with a 3-substituted Boc-protected pyrrole would be an important substrate.

An initial target was 3-methylpyrrole **159**, available most efficiently through the route of Cornforth,[92] presented overleaf.



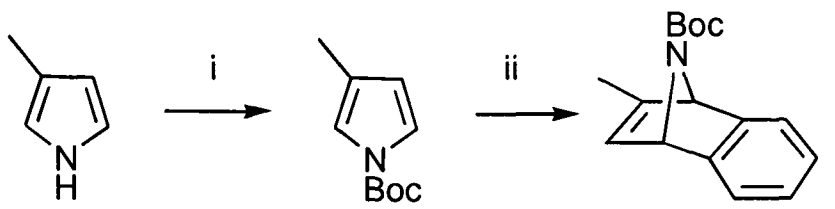
155 **156** **157**

159 (5-10%, lit. 90%) **158** (25% over 4 steps, lit. 45%)

Scheme 4.15 Cornforth's synthesis of 3-methylpyrrole. *Reagents and conditions*: i, Ac_2O, 70 °C, 2 h; ii, KOH, MeOH, 25 °C, 1 h; iii, HCl, AcOH, 25 °C, 2 h; iv, NaOMe, MeOH, 25 °C, 2 h; v, aq. NaOH, reflux, 1h, then HCl to pH 1, then sulfolane, 160 °C, 1 h.

Pyrrole ester **158** was accessed in gram quantities in this way, but the final decarboxylative distillation proved problematic. Attempts to distil the product from sulfolane failed at atmospheric pressure because the required flask temperature of 200 °C could not be achieved with the heating equipment used. Distillation at 100 mmHg pressure led to the recovery of small amounts of the desired pyrrole, but some material was lost due to volatility. Attempted column chromatography gave only a complex mixture of products, rather than the notoriously unstable 3-methylpyrrole.[92]

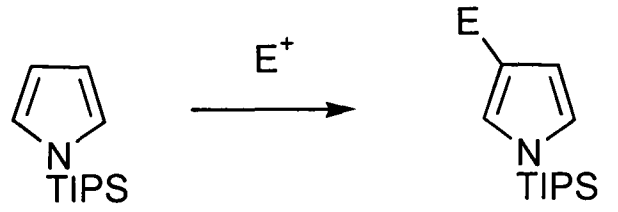
The small quantity of 3-methylpyrrole that had been synthesised was Boc-protected[93] and used in a small scale benzyne cycloaddition to give **161** (Scheme 4.16, overleaf) but a better method of making the pyrrole was clearly needed.



159 **160** (43%, lit.[94] 49%) **161** (23 %)

Scheme 4.16 *Reagents and conditions*: i, Boc_2O, DMAP, MeCN, 25 °C, 24 h; ii, *o*-bromofluorobenzene, Mg, THF, reflux, 2 h.

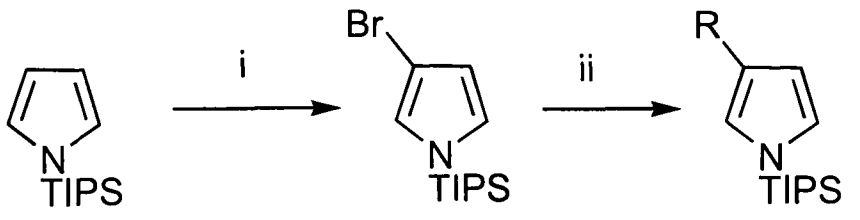
A direct method for the functionalisation of pyrroles is electrophilic aromatic substitution of pyrrole itself, but this leads predominantly to 2-substituted products.[95] However, methods have emerged using directing groups on nitrogen that allow direct substitution at the 3-position.[96] One such method is the use of the triisopropylsilyl (TIPS) protecting group. This very bulky group hinders approach to the more reactive 2-position, and allows electrophilic aromatic substitution at the 3-position.[97]



162 **163**

Scheme 4.17 Electrophilic aromatic substitution of N-TIPS pyrrole.

Bromination with NBS and then Li-halogen exchange, before trapping with alkyl halides was reported to be an effective route to 3-alkyl pyrroles (Scheme 4.18, below).

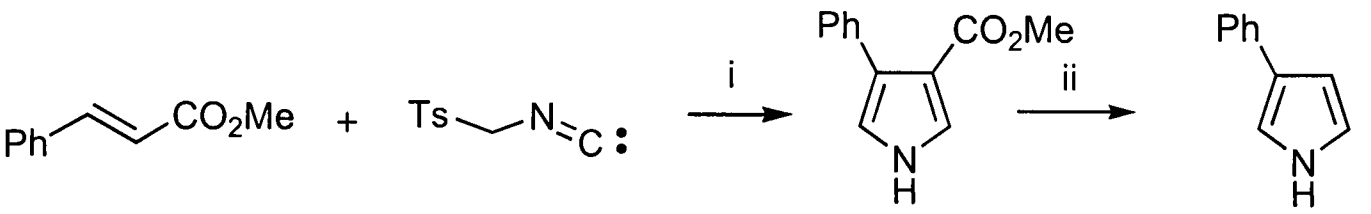


162 **164** **165**

Scheme 4.18 Reagents and conditions: i, NBS, THF, -78 °C, 2 h; ii, Bu^tLi, THF, −78 °C, 15 min, then RBr or RI, −78 °C → 25 °C.

However, on attempting to repeat these reactions, the bromination did not proceed with the reported selectivity. Treatment of *N*-TIPS-pyrrole with NBS at −78 °C gave a 7 : 1 mixture of 3-bromo- and 2-bromo-*N*-TIPS-pyrrole, rather than the reported 25 : 1. The mixture could not be separated chromatographically (both compounds had $R_f \sim 0.4$ in light petroleum). The 7 : 1 mixture was clearly not sufficient for further reaction and this potential method of synthesising 3-methylpyrrole was abandoned.

3-Phenylpyrrole **169** is available via a cyclisation reaction between TosMIC **167** and methyl *trans*-cinnamate **166**, followed by hydrolysis and decarboxylation of **168** (Scheme 4.19):[98]



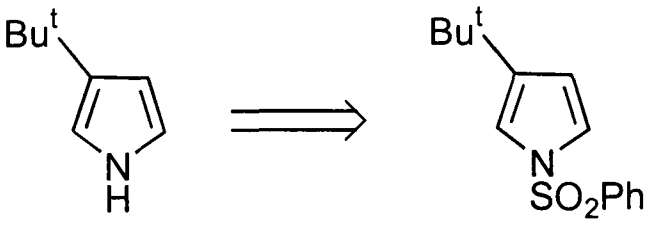
166 **167** **168** (33%, lit. 70%) **169** (56%, lit. 82%)

171 (36%) **170** (88%)

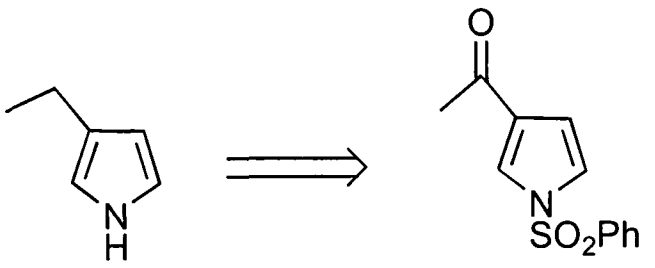
Scheme 4.19 *Reagents and conditions*: i, NaH, DMSO/Et_2O, 25 °C, 1 h; ii, KOH, MeOH/H_2O, reflux, 2 h; iii, Boc_2O, DMAP, MeCN, 25 °C, 24 h; *o*-bromofluorobenzene, Mg, THF, reflux, 2 h.

The desired pyrrole was successfully prepared in this way, then Boc-protected to give **170**. Cycloaddition to form **171**, however, proceeded only in low yield and the adduct was found to be unstable with a half life of a few hours at room temperature, and the compound had decomposed before hydroboration could be attempted.

N-benzenesulfonylpyrrole is also used to direct electrophilic aromatic substitution to the 3-position, which is achieved electronically rather than sterically in this case. The sulfonyl group decreases the electron density at the 2-position, thus deactivating it and allowing electrophilic attack at the 3-position.[96] Particularly selective are Friedel-Crafts acylation[99] and *t*-butylation[96] reactions, which occur with almost completely selective attack at the 3-position. With these results in mind, and a report suggesting that alkylpyrroles were readily available from the 3-acylpyrroles[100] led to the consideration of 3-*tert*-butylpyrrole and 3-ethylpyrrole as targets.



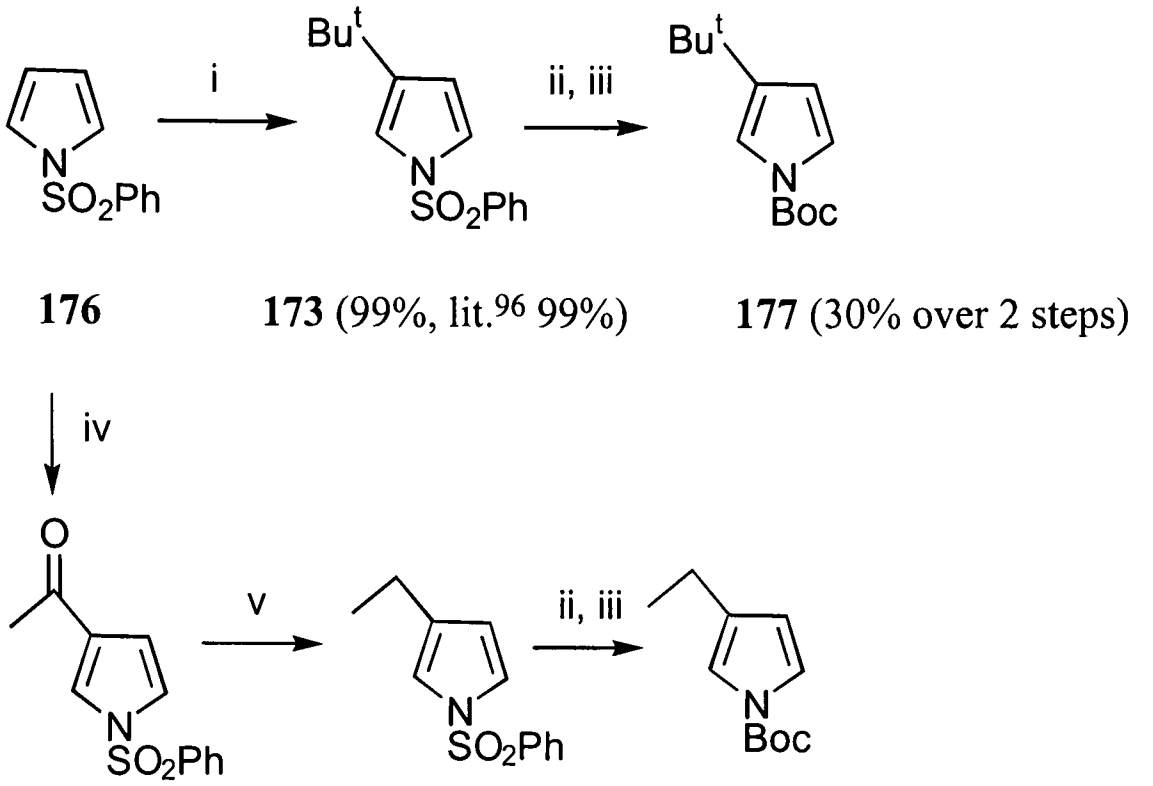
172 **173**



174 **175**

Fig. 4.2 Target pyrroles from *N*-benzenesulfonylpyrrole.

The pyrroles were prepared successfully in this way (Scheme 4.20, overleaf) and Boc- protected so that benzyne cycloadditions could be performed.



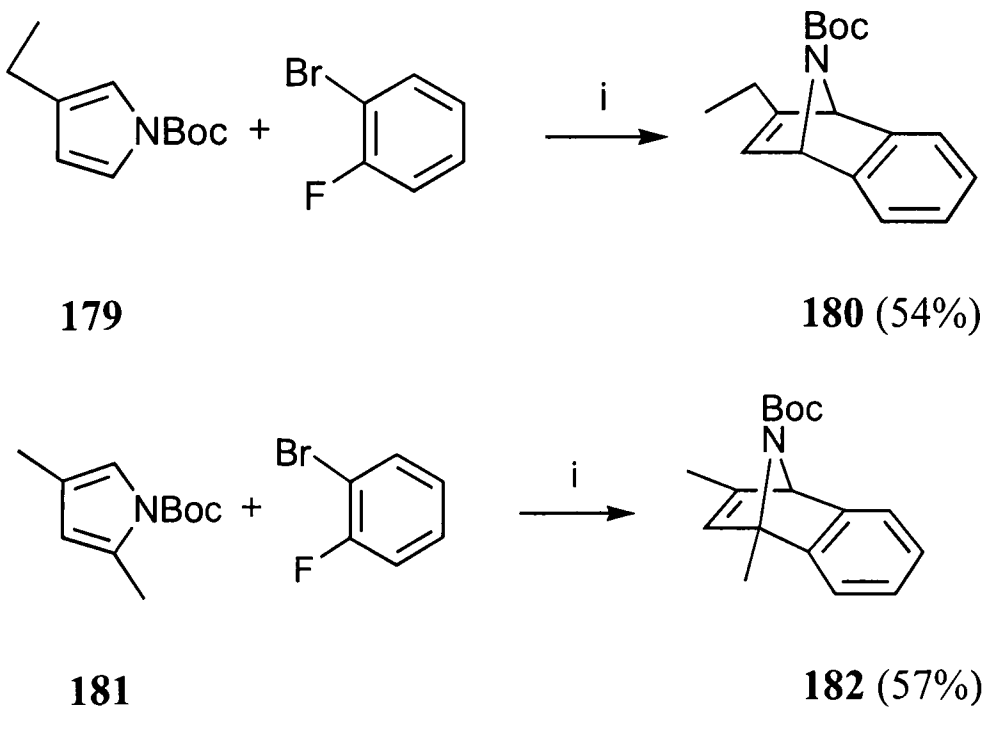
176 **173** (99%, lit.[96] 99%) **177** (30% over 2 steps)

175 (74%, lit.[99] 99%) **178** (88%, lit.[100] 88%) **179** (50% over 2 steps)

Scheme 4.20 *Reagents and conditions*: i, Bu^tCl, $AlCl_3$, CH_2Cl_2, 0 °C, 5 h; ii, NaOH, dioxane, 25 °C, 16 h; iii, Boc_2O, DMAP, MeCN, 25 °C, 24 h; iv, Ac_2O, $AlCl_3$, $(CH_2Cl)_2$, 25 °C, 2 h; v, $Bu^tNH_2.BH_3$, $AlCl_3$, CH_2Cl_2, 25 °C, 3 h.

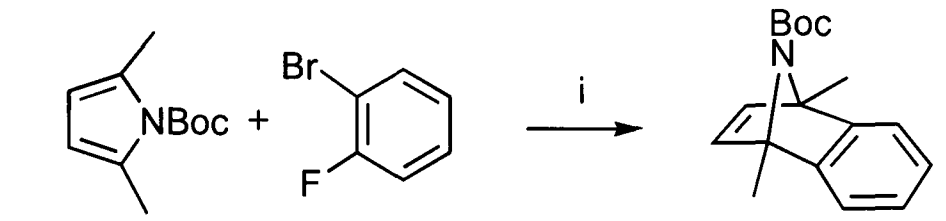
4.5.3 Benzyne cycloadditions

In addition to the 3-substituted pyrroles prepared above, commercially available 2,4- and 2,5-dimethylpyrrole were Boc-protected[93] in 85% and 63% yields respectively and used in the cycloadditions presented below and overleaf (Scheme 4.21). All occurred in satisfactory yield to give stable products, and so preparation of radical precursors was now possible.

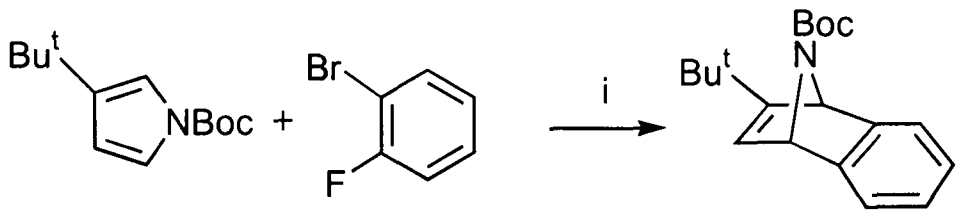


179 **180** (54%)

181 **182** (57%)



183 **184** (64%, lit. [101] 28%)

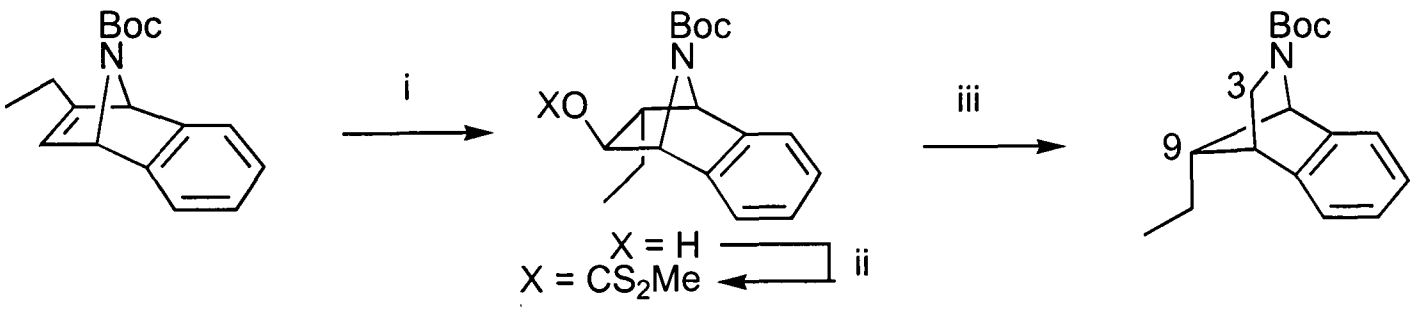


177 **185** (68%)

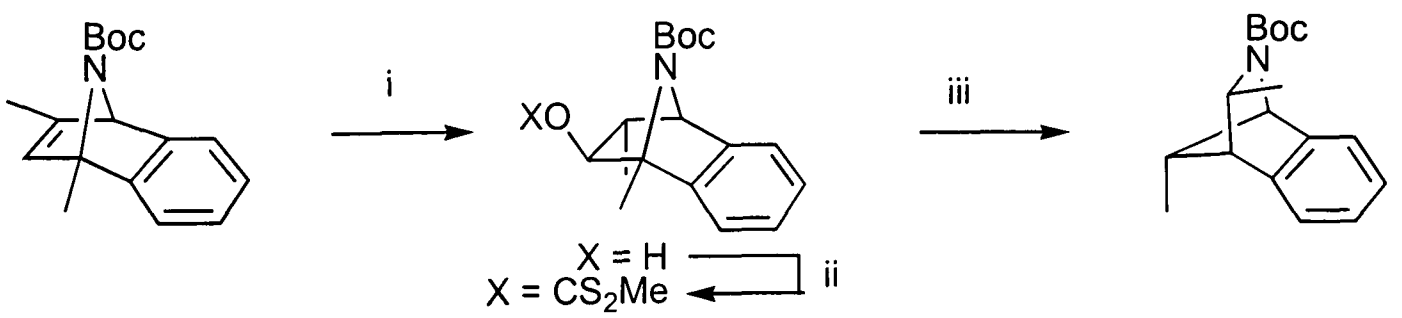
Scheme 4.21 Benzyne cycloadditions with Boc-protected pyrroles. *Reagents and conditions*: i, Mg, THF, reflux, 2 h.

4.5.4 Preparation of Radical Precursors and Rearrangements

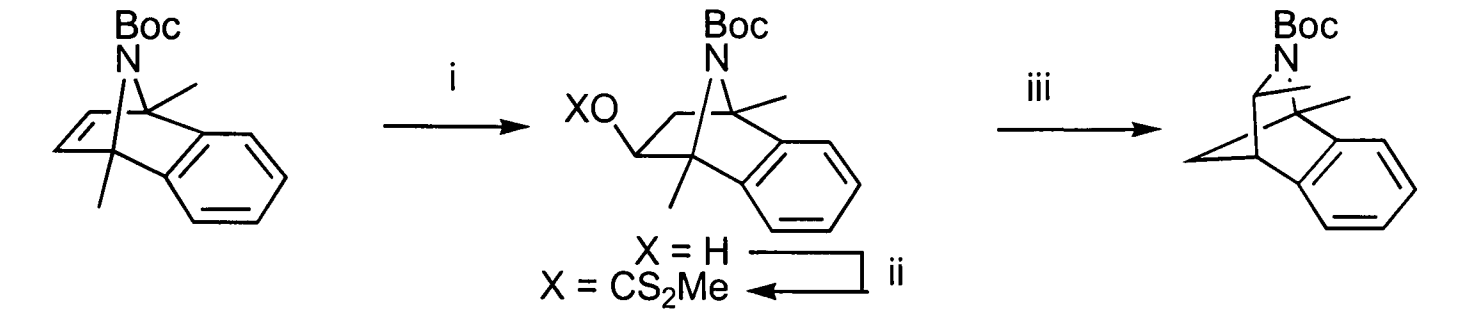
As the required substituted benzyne adducts had at last been prepared, their rearrangement chemistry could now be examined. Hydroboration-oxidation gave in each case a single isomer of the alcohol, assigned once more as having *exo* stereochemistry by analogy with **141** (Scheme 4.10, p.71). Xanthate formation was found to proceed without incident in these examples, then deoxygenation gave the rearranged products shown (Scheme 4.22).



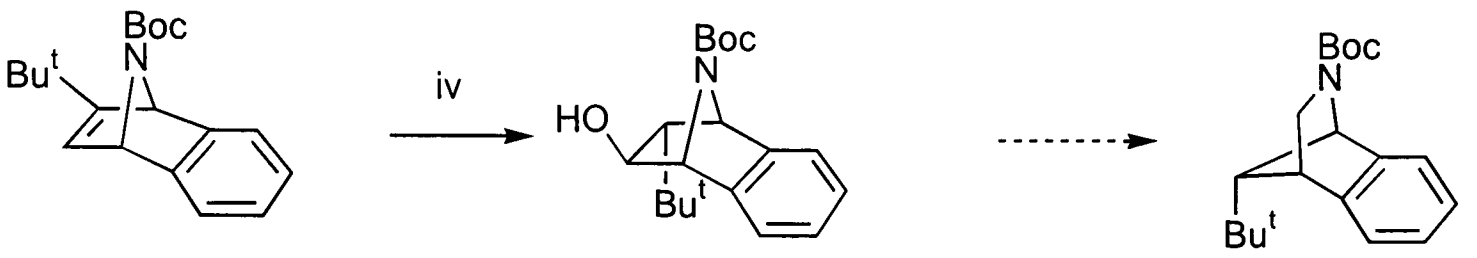
180 **186**, X = H (44%); **187**, X = CS_2Me (79%) **188** (73%)



182 **189**, X = H (64%); **190**, X = CS_2Me (78%) **191** (88%)



184 **192**, X = H (85%); **193**, X = CS_2Me (74%) **194** (25%)

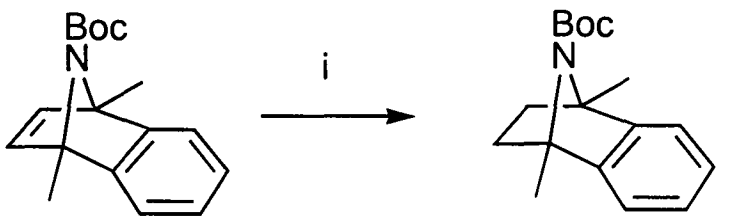


185 **195** (28%) **196**

Scheme 4.22 Rearrangement of substituted 7-azabenzonorbornanols. *Reagents and conditions*: i, 9-BBN, THF, 25 °C, 24 h, then NaOH, H_2O_2, 25 °C, 5 h; ii, KH, THF, 0 °C → 25 °C, 20-30 min, then CS_2, 0 °C, 10-20 min, then MeI, 25 °C, 20-30 min; iii, TTMSS, AIBN(slow addition), toluene, reflux, 2 h; iv, BH_3-THF complex, THF, 25 °C, 24 h, then NaOH, H_2O_2, 0 °C → 25 °C.

A 1D nOe experiment on **188** demonstrated that the ethyl group was *anti* to nitrogen, confirming that the hydroboration had been exclusively *exo* selective. Pleasingly only one isomer of **191** was seen, and the methyl groups were shown to be 9-*anti*, 3-*endo* by nOe experiments once again. This is consistent with *exo* selective hydroboration and then H-atom transfer exclusively from the expected *exo* face following rearrangement. This method therefore allows control of the relative stereochemistry at C-3 and C-9.

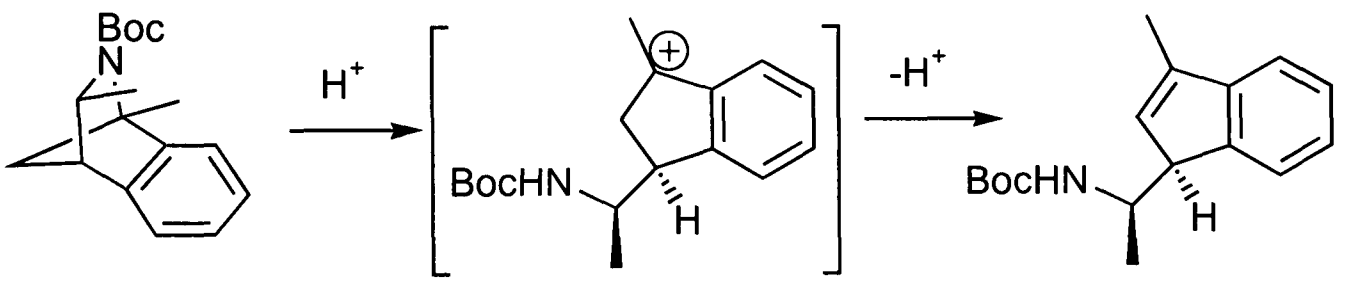
No trace of the directly-reduced product **197**[102] (obtained independently by hydrogenation of **184**, Scheme 4.23, overleaf) was found in this reaction, which is consistent with the formation of a more stable tertiary radical and therefore a stronger driving force for rearrangement than in the examples leading to secondary radicals, where traces of directly-reduced products could be seen.



184 **197** (24%, lit. 79%)

Scheme 4.23 Reduction of **184**. *Reagents and conditions*: H_2 (1 atm), Pd/C, MeOH, 25 °C, 5 min.

Product **194** was found to be unstable to ring-opening with a half-life of 2-3 hours, decomposing in the presence of moisture to give indene **199** quantitatively (Scheme 4.24).



194 **198** **199** (100%)

Scheme 4.24 Ring opening of 2-azabenzonorbornane **194**.

The ring-opening is presumably driven by the acid-catalysed formation of a stable tertiary benzylic carbocation **198**, which then loses a proton to give the final product. This demonstrates a possible route to stereodefined indenes, which are targets of considerable interest.[103]

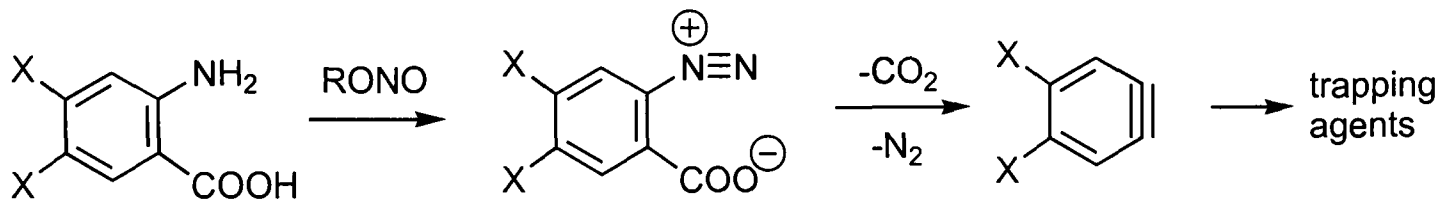
Benzyne adduct **185** (Scheme 4.22, p.82) was unreactive to 9-BBN, and the yield with the more reactive borane-THF complex was low. Conversion to the xanthate and rearrangement were ultimately not attempted due to lack of time and the fact that this clearly represented a limitation of the chemistry.

4.6 Electronic Effects in the Aromatic Ring

Having examined the effect of alkyl substitution on the bicyclic core, it was decided to alter the electronic character of the aromatic ring.

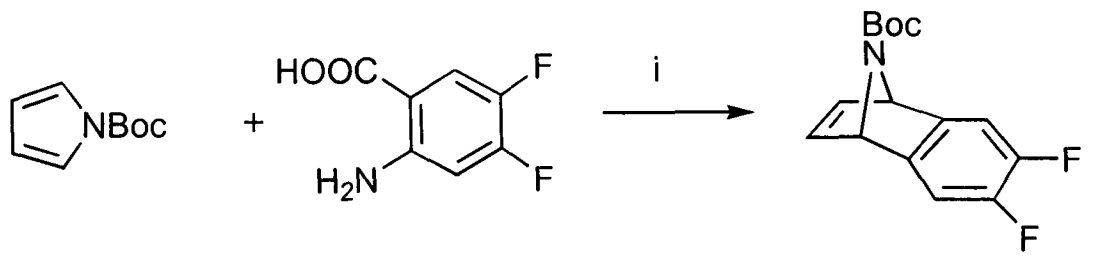
4.6.1 Synthesis of Benzyne and Naphthalyne Adducts

This was best achieved by reaction of substituted benzyne precursors with *N*-Boc pyrrole. Another class of benzyne precursors apart from *o*-bromofluorobenzenes is the anthranilic acids. In the presence of diazotising agents, such as organic nitrites, nitrogen and carbon dioxide are lost to produce benzynes (Scheme 4.25, below).

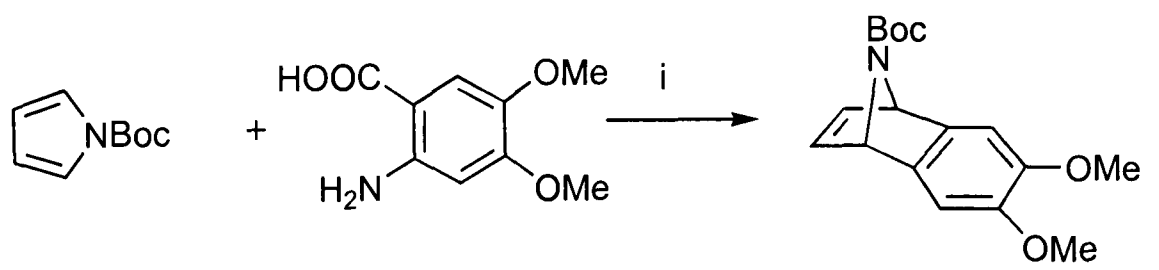


Scheme 4.25 Generation of benzynes from anthranilic acids.

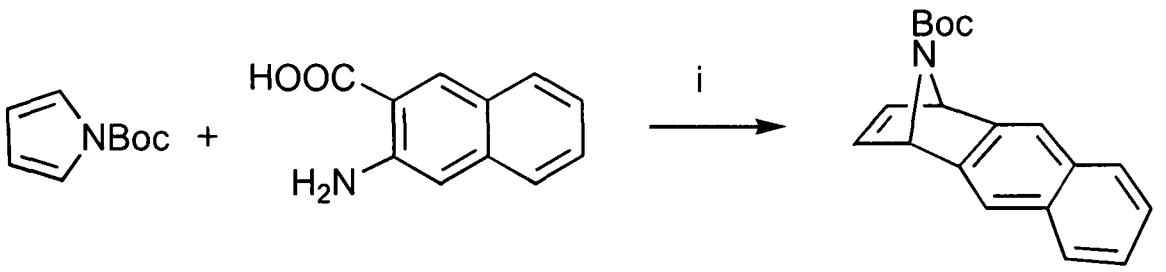
Both 3,4-difluoro- and 3,4-dimethoxyanthranilic acid are commercially available, and were found to react as expected with *N*-Boc pyrrole to give the adducts **200** and **201**. 2-amino-3-naphthoic acid was used in the preparation of the known naphthalyne adduct **202**[104] (Scheme 4.26, below and overleaf).



200 (14-20 %)



201 (41%)



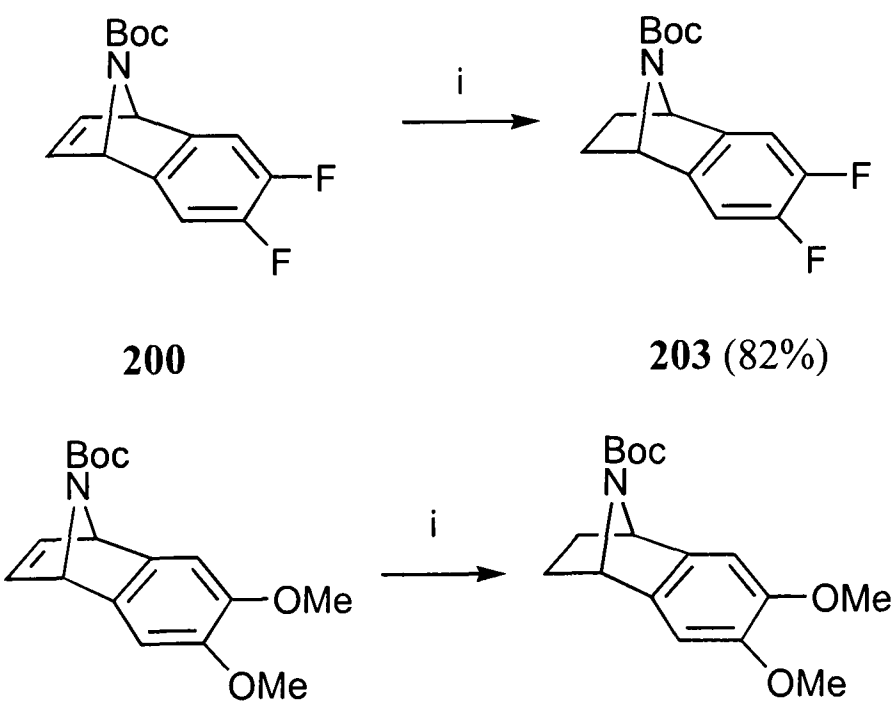
202 (39%, lit.[104] 49%)

Scheme 4.26 Benzyne cycloadditions with anthranilic acids. *Reagents and conditions*: isoamyl nitrite, THF or MeCN, reflux, 2-3 h.

Although the yield of **200** was low, the starting materials were available in large quantities and so this compound could be produced in gram batches.

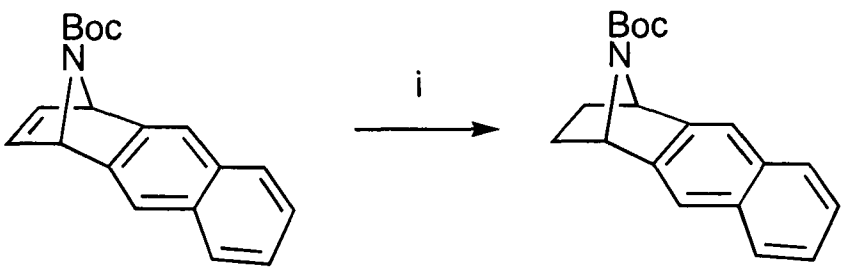
4.6.2 Hydrogenation of Benzyne Adducts

Hydrogenation of the benzyne adducts to give authentic samples of directly-reduced products was performed, so that detection of their presence in the crude reaction mixtures would be straightforward (Scheme 4.27, below and overleaf).



200 **203** (82%)

201 **204** (73%)

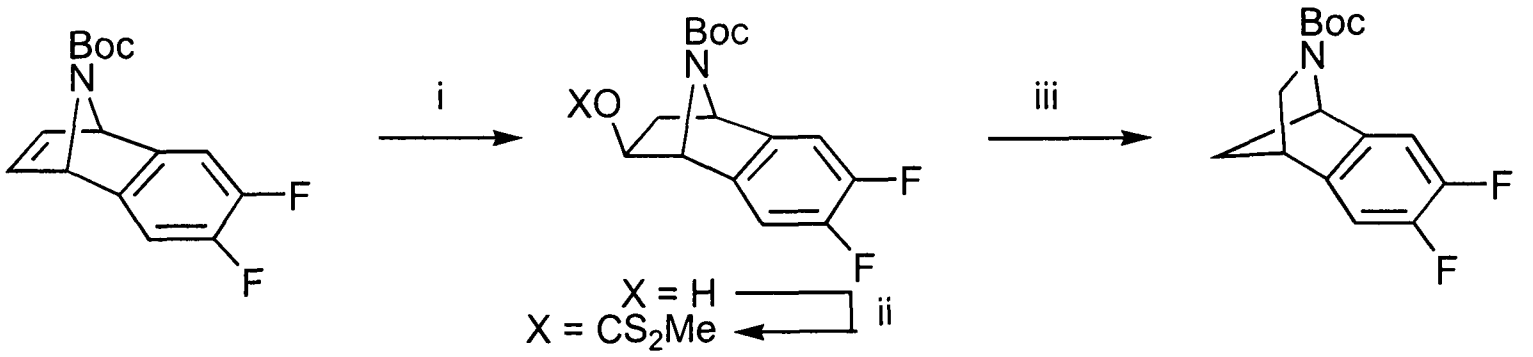


202 **205** (83%, lit.[104] 86%)

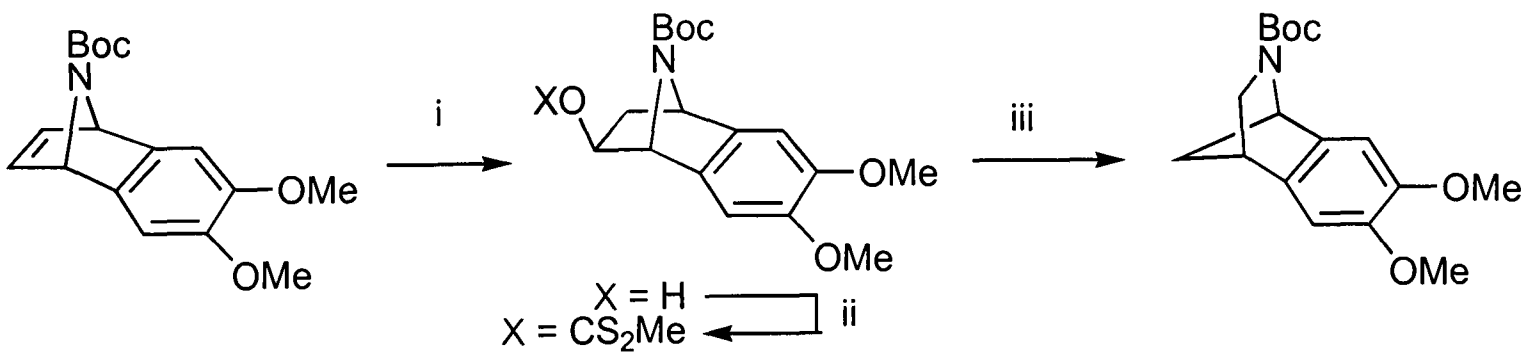
Scheme 4.27 Hydrogenation of benzyne adducts. *Reagents and conditions*: H_2 (1 atm), Pd/C, MeOH, 25 °C, 10 min.

4.6.3 Hydroboration and Rearrangements of Functionalised Benzyne Adducts

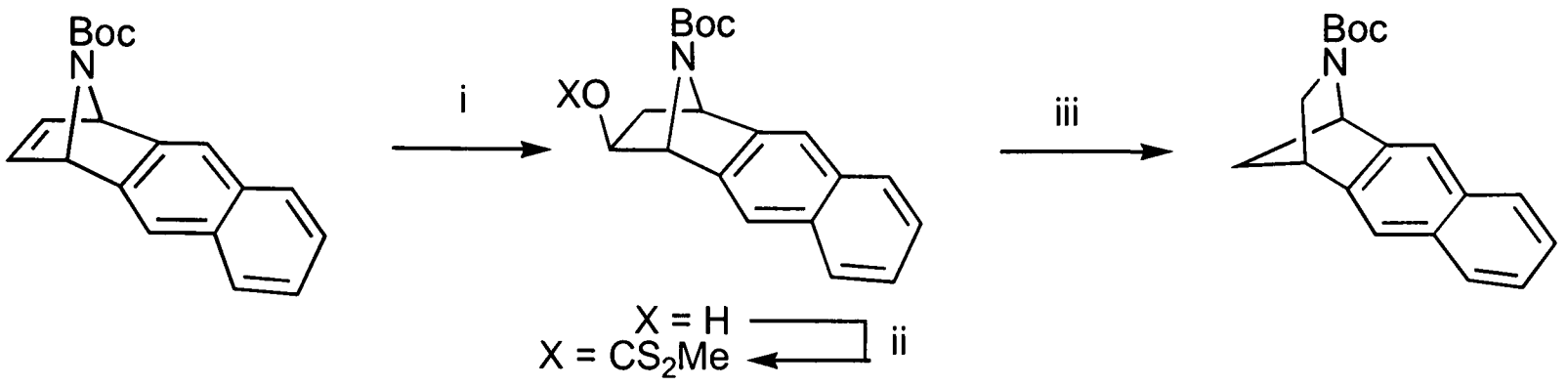
Hydroboration-oxidation was found to proceed smoothly once again to give only the *exo*-alcohols. Xanthate formation and deoxygenation gave the expected products in good yields (Scheme 4.28, below and overleaf).



200 **206**, X = H (49%); **207**, X = CS_2Me (79%) **208** (64%)



201 **209**, X = H (56%); **210**, X = CS_2Me (77%) **211** (77%) + **204** (13%)



202 **212**, X = H (59%); **213**, X = CS_2Me (63%) **214** (84%)

Scheme 4.28 Rearrangements to 2-azabenzonorbornanes with variation of the aromatic nucleus. *Reagents and conditions*: i, 9-BBN, THF, 25 °C, 24 h, then NaOH, H_2O_2, 25 °C, 5 h; ii, KH, THF, 0 °C → 25 °C, 20-30 min, then CS_2, 0 °C, 10-20 min, then MeI, 25 °C, 20-30 min; iii, TTMSS, AIBN, toluene, reflux, 2 h.

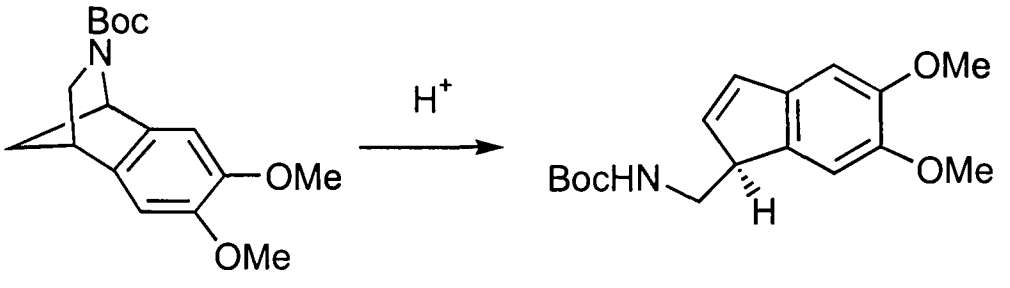
The first-formed radical from deoxygenation is nucleophilic in character, so it was expected that electron-withdrawing substituents on the aromatic ring would increase the rate of cyclisation relative to that for the unsubstituted system, thereby increasing the proportion of the rearranged product.

The difluorinated product **208** had to be separated from traces of the directly-reduced product **203** and by ^{1}H NMR spectroscopy the ratio **208** : **203** was no greater than the ratio **126** : **143** (Scheme 4.11, p. 72). This suggests that the fluorine substituents had little effect on the rate of rearrangement. Despite being very powerful σ-acceptors, fluorine atoms are also significant π-donors, so that they do not have a very powerful electron-withdrawing effect on an aromatic nucleus.[105] A similar product profile to the unsubstituted system is therefore not very surprising.

Conversely, electron-donating substituents were expected to decrease the rate of rearrangement. In addition to 77% of **211**, 13% of the directly-reduced **204** was isolated from deoxygenation of the dimethoxy-substituted xanthate. This represents a ratio of 6 : 1 compared to 20 : 1 in the unsubstituted system under the same conditions. It appears that the powerfully electron-donating methoxy groups

have had a slight retarding effect on the rate of rearrangement. From a synthetic point of view, it is useful that the rearrangement still occurs sufficiently rapidly to give good yields of products with an electron-rich aromatic ring.

In an analogous fashion to the ring-opening of **194** (Scheme 4.24, p. 83), **211** was also found to give the indene **215** on standing in moist air over a period of weeks (Scheme 4.29, below):



211 **215** (40%)

Scheme 4.29 Indene formation from the dimethoxy-substituted 2-azabenzonorbornane.

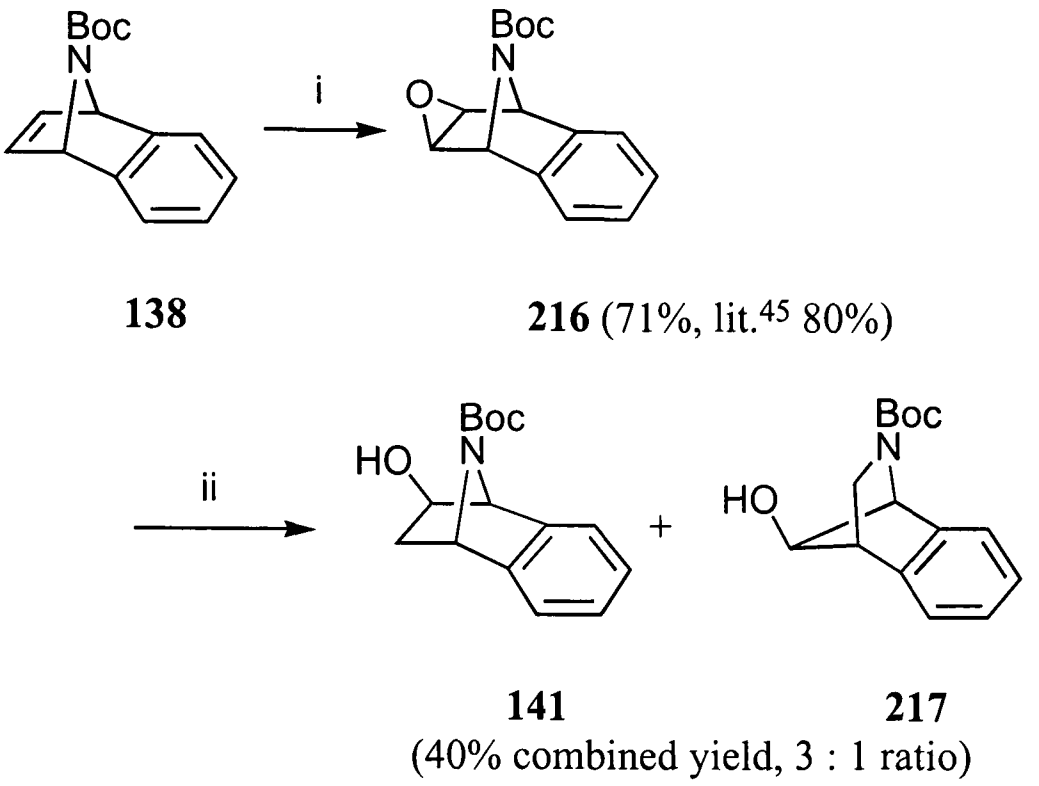
The proposed acid-catalysed ring-opening is presumably promoted by the presence of the methoxy-groups, which can stabilise the intermediate carbocation. This confirms that the rearrangement chemistry could be a viable route to substituted indenes, following suitable optimisation.

Reduction of the naphthalyne-derived xanthate did not appear to give any of the directly reduced product **205**, with **214** being the only detectable product. This is consistent with a rate enhancement for migration of the naphthyl group compared to phenyl, as has been previously documented.[43]

4.7 Radical Chemistry of 2,3-Epoxy-5,6-benzo-7-azanorbornene

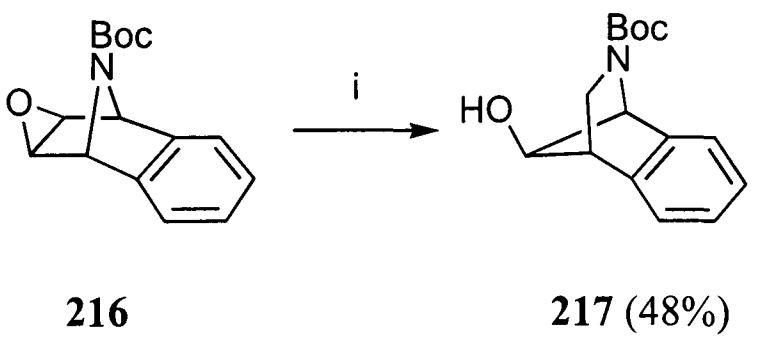
Once more the possibility of reductive ring opening of epoxides was investigated.[11] Alkene **138** was epoxidised with buffered dimethyldioxirane and then subjected to the catalytic ring-opening conditions of Gansauer.[29] This gave

rise to two products, identified as **141**, resulting from direct-reduction of the first formed radical and **217** from the expected rearrangement (Scheme 4.30, below).



Scheme 4.30 Reductive ring-opening of the benzo-fused epoxide **216**. Reagents and conditions: i, DMDO, Na_2EDTA, $NaHCO_3$, H_2O, Bu_4NHSO_4, CH_2Cl_2, 25 °C, 48 h; ii, 10 mol% Cp_2TiCl_2, Mn, collidine hydrochloride, 1,4-cyclohexadiene, THF, 25 °C, 24 h.

The alcohols appeared to be inseparable and in order to confirm the structure of the rearranged product, epoxide **216** was treated with boron trifluoride etherate and soidium cyanoborohydride, to give exclusively the alcohol **217** (Scheme 4.31, below).



Scheme 4.31 Lewis acid-mediated rearrangement to a functionalised 2-azabenzonorbornane. *Reagents and conditions*: $BF_3.Et_2O$, $NaBH_3CN$, THF, 25 °C, 16 h.

An analogous rearrangement of 7-azanorbornadiene oxide had been reported by Maxwell.[45]

Since only a small amount of the rearranged product had been formed in the Ti(III)-mediated ring opening, and the combined yield was low, it was decided that

the titanium chemistry would probably not be an effective way of conducting the rearrangement and further optimisation was not attempted.

4.8 Conclusions and Recommendations

A new nitrogen-directed neophyl-like rearrangement to give 2-azabenzonorbornanes has been discovered which is compatible with substitution on the bicyclic core and on the aromatic ring. In all cases only one diastereomer of the rearranged product is formed. The rearrangement chemistry shows only a slight dependence on the electronic nature of the aromatic ring, indicating that the reaction is of broad scope. The limitations appear to be mainly those of substrate synthesis, i.e. functionality must be compatible with the benzyne cycloaddition.

The problem of deoxygenation of tertiary alcohols could probably be surmounted by using TBTH instead of TTMSS as the reducing agent for the oxalyl ester. It would be interesting to discover if rearrangement of a tertiary radical could be effected with similar facility as for a secondary one.

The ring-opening to give indenes is an exciting development and should lead to interesting targets once the conditions have been optimised. Treatment of the rearranged products with mild acid is expected to give the indenes in useful yields. Further functionalisation of the 2-azanorbornanes should also be possible *via* standard aromatic chemistry, such as electrophilic aromatic substitution, Birch reduction or oxidative cleavage of the ring.

The failure of the titanium(III) chemistry to produce a large proportion of the rearranged product is disappointing, although it could possibly be used to make the alcohol **141** in an asymmetric fashion, and this will be discussed further in a later chapter.

Chapter 5: Asymmetric Hydroborations

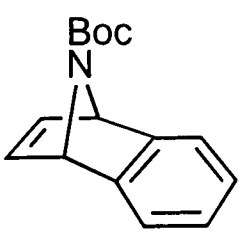
In the last chapter, the radical deoxygenation of 7-azabenzonorbornanols was shown to be an effective method for the synthesis of 2-azabenzonorbornanes *via* a nitrogen-directed neophyl-like rearrangement. Hydroboration was chosen as an aspect of this route partly because it is amenable to asymmetric synthesis. [106] Enantioenriched 7-azabenzonorbornanols would then lead to an asymmetric synthesis of 2-azabenzonorbornanes. This chapter details efforts to develop an asymmetric route to these compounds.

5.1 Methods of Asymmetric Hydroboration

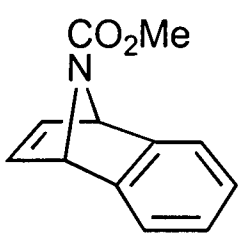
Amongst the first asymmetric hydroborations were those carried out by Brown and co-workers, using chiral boranes derived from natural products such as α-pinene and longifolene.[106] More recently, catalytic asymmetric methods have emerged. Usually these are mediated by a low oxidation state metal complex with attached chiral non-racemic ligands.[107] The catalytic method was particularly attractive, since it uses only a small amount of chiral material and had previously been used to desymmetrise *meso*-bicyclic compounds,[108] which is exactly what was required in this case.

5.2 Choice of Procedure

It was decided to use the procedure of Burgess[109] for the attempted desymmetrisation of *meso*-alkenes **138** and **146** by hydroboration (Fig. 5.1, below).



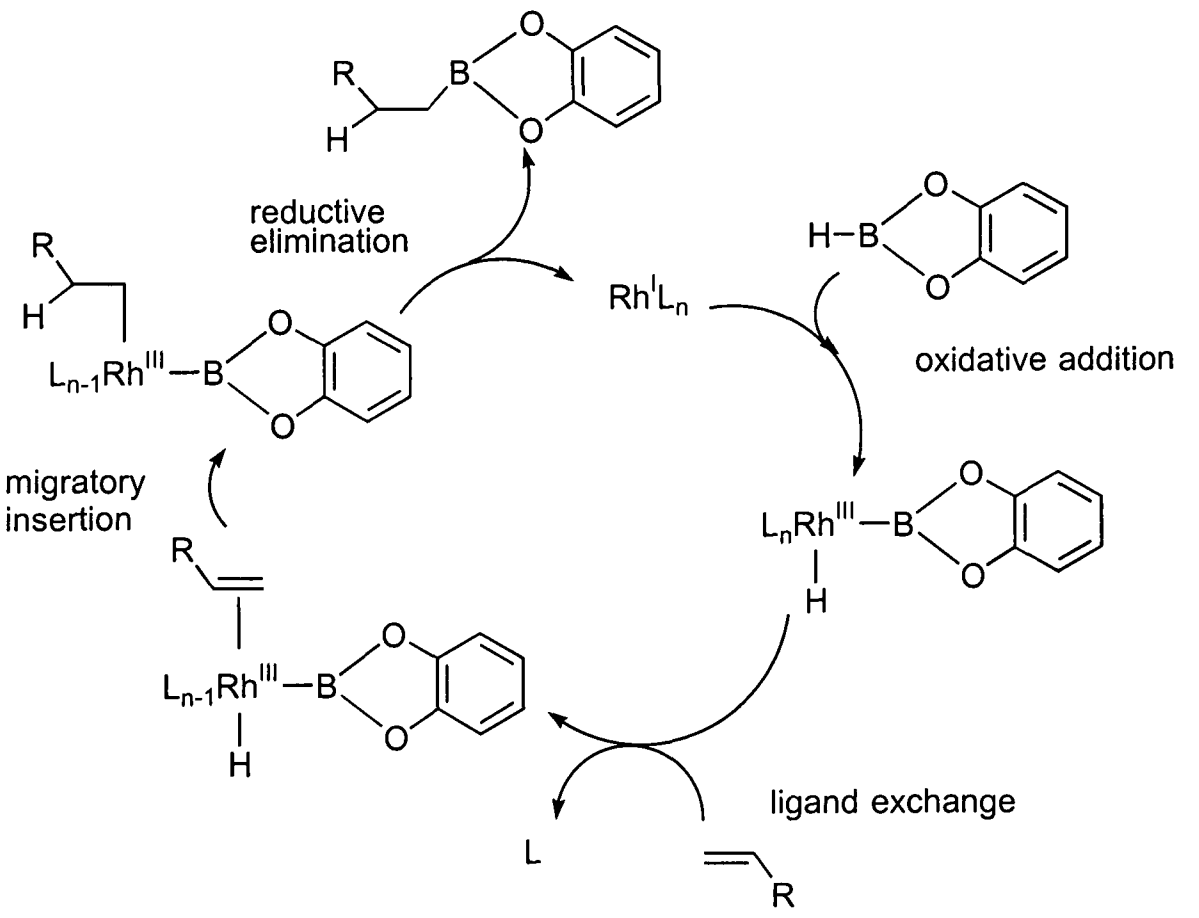
138



146

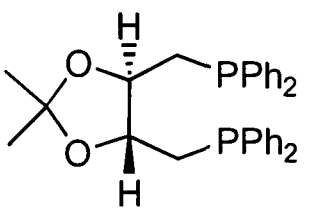
Fig. 5.1 Substrates for asymmetric hydroboration.

Treatment of norbornene in this way had occurred to give *exo*-norbornanol in up to 82% *ee* and this was seen as an appropriate starting point for our own studies. The method uses a dimeric rhodium(I) complex, $[Rh(COD)Cl]_2$. Chiral phosphine ligands are then bound to the metal *in situ* and oxidative addition of catecholborane then gives a Rh(III) species. Ligand exchange permits coordination of the alkene, and then migratory insertion of the alkene into the Rh-H bond produces a species that can reductively eliminate to give the enantioenriched organoborane and regenerates the catalyst (Scheme 5.1, below):[110]



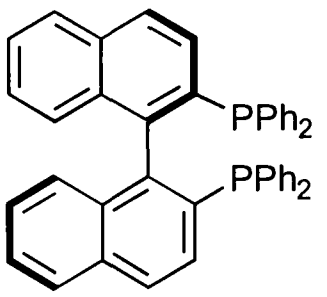
Scheme 5.1 Generalised Catalytic Cycle for Asymmetric Hydroboration.

Two of the chiral phosphine ligands used by Burgess[109] were adopted for use in these studies (Fig. 5.2, overleaf).



R,R-DIOP

218



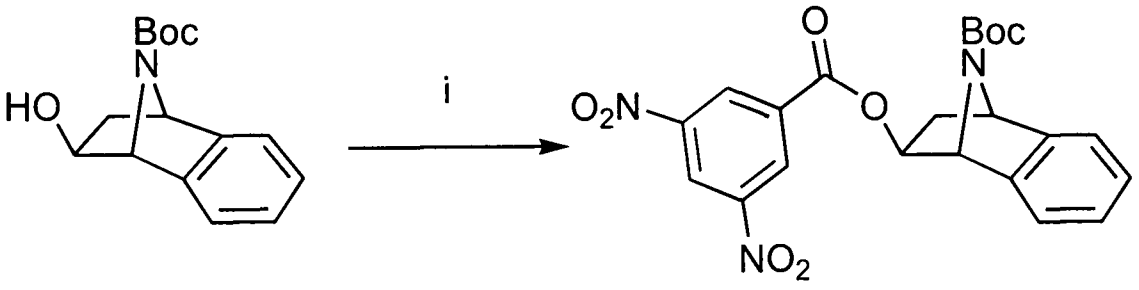
R-BINAP

219

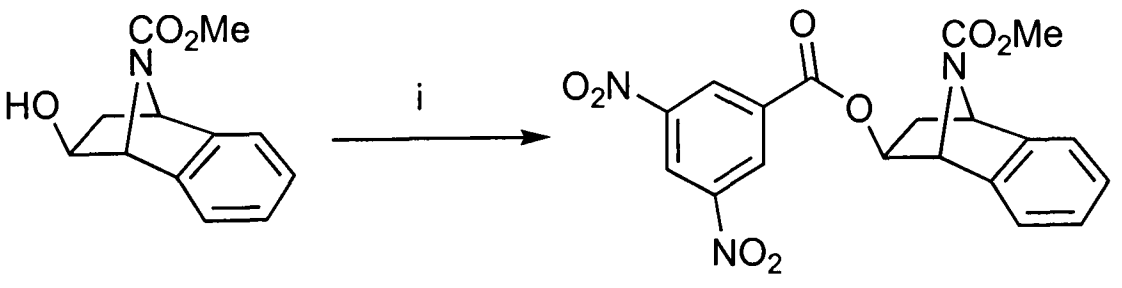
Fig. 5.2 Two ligands used in asymmetric hydroboration.

5.3 Separation of Enantiomers

Before attempts at asymmetric induction could be made, the enantiomers of racemic samples of alcohols **141** and **147** had to be separated in some way so that measurement of the *ee* was possible. Conversion of the alcohols to their 3,5-dinitrobenzoate esters gave compounds whose enantiomers could be readily separated by chiral HPLC (Scheme 5.2, below).



141 **220** (74%)

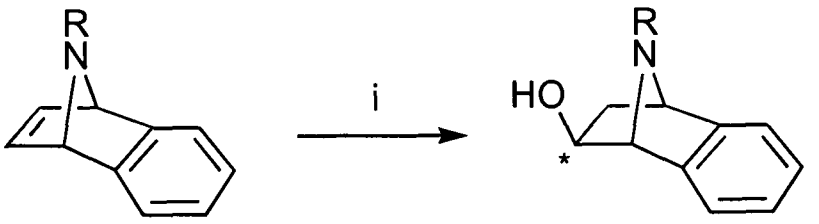


147 **221** (79%)

Scheme 5.2 Preparation of HPLC derivatives. *Reagents and conditions*: i, 3,5-dinitrobenzoylchloride, Et_3N, CH_2Cl_2, 25 °C, 16 h.

5.4 Asymmetric Hydroborations of 7-Azabenzonorbornadienes

Whilst in some cases, rhodium-catalysed hydroboration of bicyclic alkenes can proceed in 30 minutes at -50 °C,[108] the substrates examined here were found to be less reactive, requiring 5-6 h at 0 °C to go to completion. Results for the two substrates are presented below (Table 5.3, below):



Scheme 5.3 Asymmetric hydroboration. *Reagents and conditions*: i, $[Rh(COD)Cl]_2$ (1 mol%), ligand (2 mol%), catecholborane (2 equiv.), THF or toluene, -78 °C, 10 min, then 0 °C, 6 h, then MeOH, H_2O_2, NaOH, 0 °C → 25 °C, 16 h.

Entry	R	ligand	solvent	Yield alcohol/%	*ee*/%*	$[\alpha]_D^{25}$/degrees**
1	Boc	*R,R*-DIOP	THF	65	7	-1.2
2	Boc	*R,R*-DIOP	Toluene	82	6	-1.1
3	Boc	*R*-BINAP	THF	65	31	-4.6
4	MeOC(O)	*R,R*-DIOP	Toluene	49	2	-0.1
5	MeOC(O)	*R*-BINAP	Toluene	68	27	-2.7
6	MeOC(O)	*R*-BINAP	THF	55	23	-2.0

Table 5.1 Asymmetric hydroborations of *meso* alkenes. *As determined by chiral HPLC of the 3,5-dinitrobenzoyl esters. In all cases the first enantiomer to elute was in excess. **Recorded in chloroform at a concentration of 10 mg/cm^3.

These results represent only a preliminary screen of two chiral ligands and two solvents, but they are sufficient to verify that asymmetric induction is possible on these substrates. Use of lower temperatures and longer reaction times should improve the modest ee's observed to date. The better ligand for both substrates was *R*-BINAP (entries 1 and 3, and entries 4 and 5, Table 5.1). Marginally higher ee's were observed with the Boc-protected substrate when comparing equivalent run conditions (i.e. entries 2 and 4, and entries 3 and 6). Yields are similar to and in

some cases better than those of the stoichiometric hydroboration reactions discussed in chapter 4.

The marked dependence of *ee* on the ligand suggests that a more exhaustive screening of ligands could lead to much improved levels of induction. The nature of the possible diastereomeric transition states for the migratory insertion step is not known in sufficient detail to have become a predictive model for the sense and magnitude of induction,[110] so it is not yet possible to suggest which ligands or protecting groups on nitrogen could provide the best results. More data is required to confirm that *N*-Boc protection leads to greater levels of induction than *N*-CO_2Me, given the small differences in *ee* and low levels of induction found to date. Solvent-dependent differences in *ee* are not large enough to be considered significant on the basis of these results.

5.5 Conclusions and Recommendations

Asymmetric hydroboration has been shown to be a viable method of desymmetrising *meso* 7-azabenzonorbornadienes. A more detailed examination of catalysts, ligands and protecting groups should lead to 7-azabenzonorbornanols in high *ee*, which could be converted to enantioenriched 2-azabenzonorbornanes.

Stoichiometric asymmetric hydroboration of these alkenes should also be attempted as a comparison with the catalytic procedure. Typically the *ee*'s are high for bicyclic olefins,[111] so this could result in an instant improvement in ee.

Another possibility would be to use Ti(III) chemistry to access these alcohols. Given the results with the epoxide ring-opening chemistry presented in

the last chapter (Scheme 4.30, p.89) the use of chiral ligands on titanium should give enantioselective ring-opening and therefore enantioenriched 7-azabenzonorbornanols.[30]

Chapter Six: Variation of the protecting group on Nitrogen

The discovery of two new radical rearrangement processes was presented in Chapters 3 and 4. In the case of the nitrogen-directed neophyl rearrangement, the effect of substitution and electronics was investigated, and the feasibility of asymmetric hydroborations as a route to enantioenriched products was demonstrated (Chapter 5).

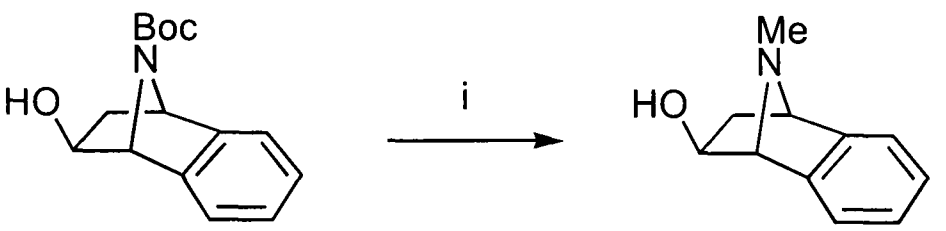
It seemed appropriate to return to an issue that had remained unresolved throughout much of the project, namely the investigation of the driving force for rearrangement. Two possibilities were thought likely: either (1) interaction of the radical centre with the adjacent *N*-lone pair conferred sufficient stability to induce its exclusive formation, or (2) increased amide-type resonance made the rearranged species more stable (Chapter 3, p.62). An appropriate choice of *N*-substituted substrates would allow clarification of this issue, and shed some light on why both homoallylic rearrangement and neophyl rearrangement occurred with the observed selectivity.

6.1 Choice of Protecting Groups

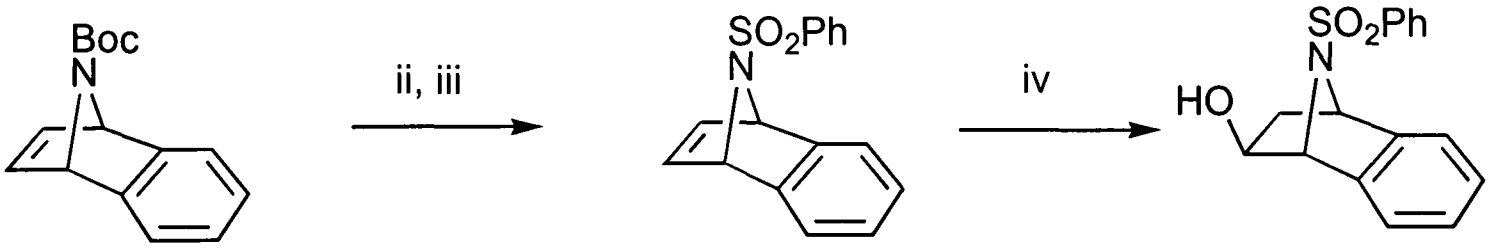
To distinguish between (1) and (2) above, it was decided to synthesise *N*-alkyl, *N*-sulfonyl and *N*-carbonyl protected 7-azabenzonorbornanols, and compare the product profile from radical deoxygenation under identical conditions to those used in the *N*-Boc system. The *N*-alkyl substrate would allow confirmation of whether amide-type resonance at nitrogen was essential for the process to occur, since it possesses a localised nitrogen lone pair. Similarly, reaction of the *N*-sulfonyl substrate would test the hypothesis that lone pair interaction with the radical centre was driving the rearrangement. In this case there is no amide-type resonance and the inductive effect of the sulfonyl group was expected to increase

the energy gap between the SOMO and the orbital containing the lone pair, thus decreasing any orbital overlap. The *N*-carbonyl substrate would allow direct comparison with the original *N*-Boc system, as for amides resonance is more significant than in carbamates, where the carbonyl group is stabilised by lone pairs from two adjacent atoms.

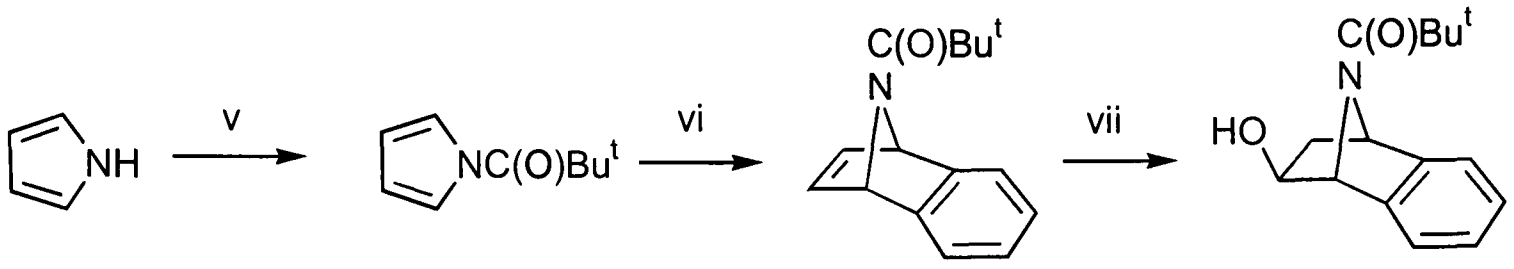
The three different *N*-protected systems were all synthesised in different ways. The *N*-methyl alcohol **222** was available directly from reduction of **141** in acceptable yield. The *N*-sulfonyl alcohol **224** came from Boc-deprotection and reprotection of **138** followed by hydroboration-oxidation. Finally, the *N*-*tert*-butylcarbonyl alcohol **227** was derived ultimately from a benzyne cycloaddition with pyrrole **225** (Scheme 6.1, below and overleaf). A rhodium-catalysed hydroboration was used for **227** because of the ease of purification associated with this method - the by-product catechol is easily washed from the crude reaction mixture with NaOH.



141 **222** (61%)



138 **223** (33%) **224** (74%)

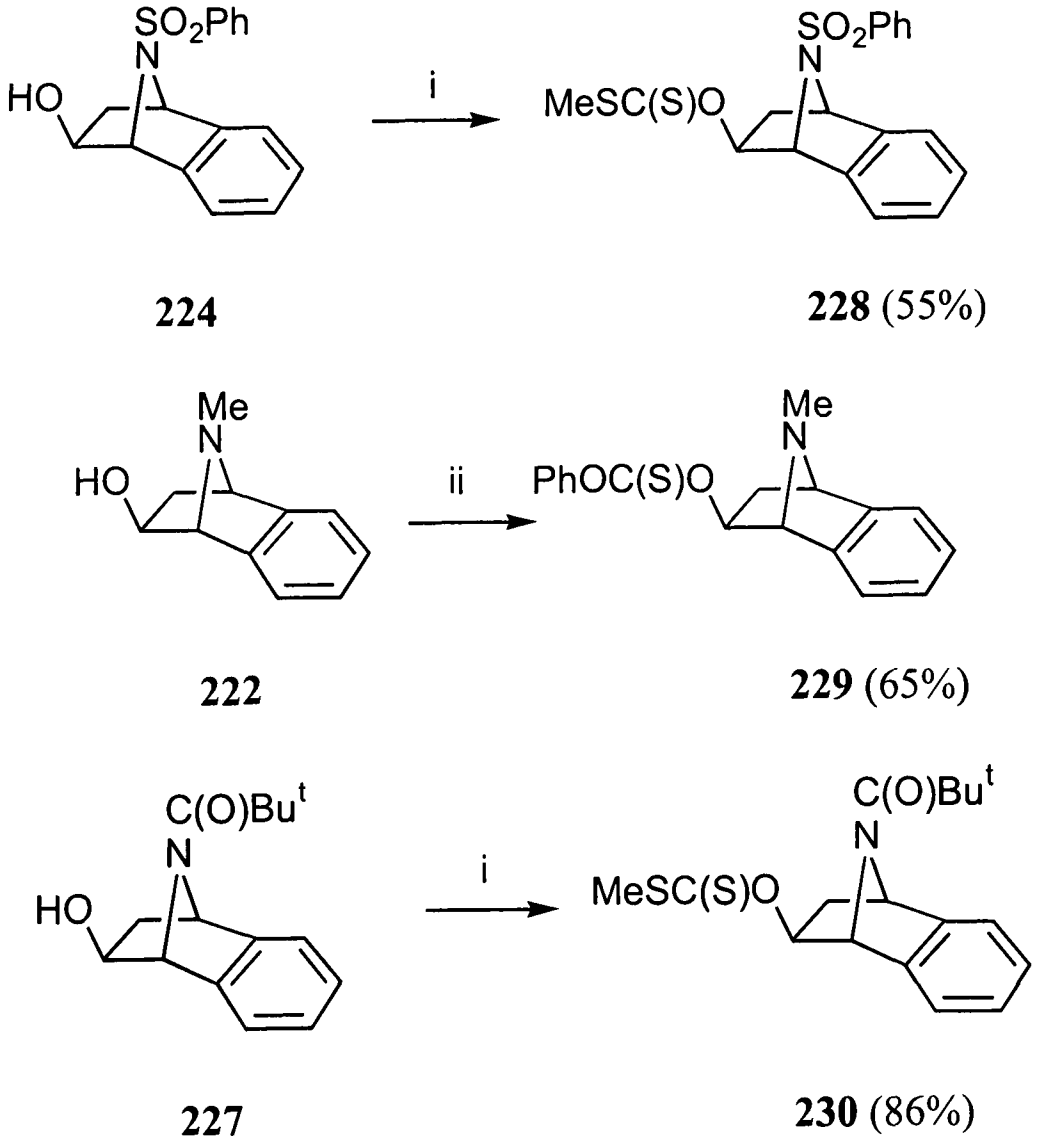


225 (58%) **226** (43%) **227** (57%)

Scheme 6.1 Synthesis of *N*-substituted 7-azabenzonorbornanols. *Reagents and conditions*: i, $LiAlH_4$, Et_2O, reflux, 16 h; ii, TFA, CH_2Cl_2, 25 °C, 2 h; iii, $PhSO_2Cl$, Et_3N, CH_2Cl_2, 25 °C, 72 h; iv, BH_3-THF complex, THF, 25 °C, 16 h then H_2O_2, NaOH, 20 min, 0 °C → 25 °C; v, Bu^{t}COCl, DMAP, Et_3N, CH_2Cl_2, 25 °C, 24 h; vi, anthranilic acid, isoamyl nitrite, THF, reflux, 3.5 h; vii, *rac*-BINAP, $[Rh(COD)Cl]_2$, catecholborane, THF, 25 °C, 3 h, then H_2O_2, NaOH, 0 °C → 25 °C, 16 h.

6.2 Effect of *N*-protecting group on product profile

Having successfully prepared the alcohols, the radical precursors were readily available (Scheme 6.2). In the case of the *N*-methyl substrate, the yield of the xanthate was low (49%), so the phenyl thionocarbonate **229** was used instead.



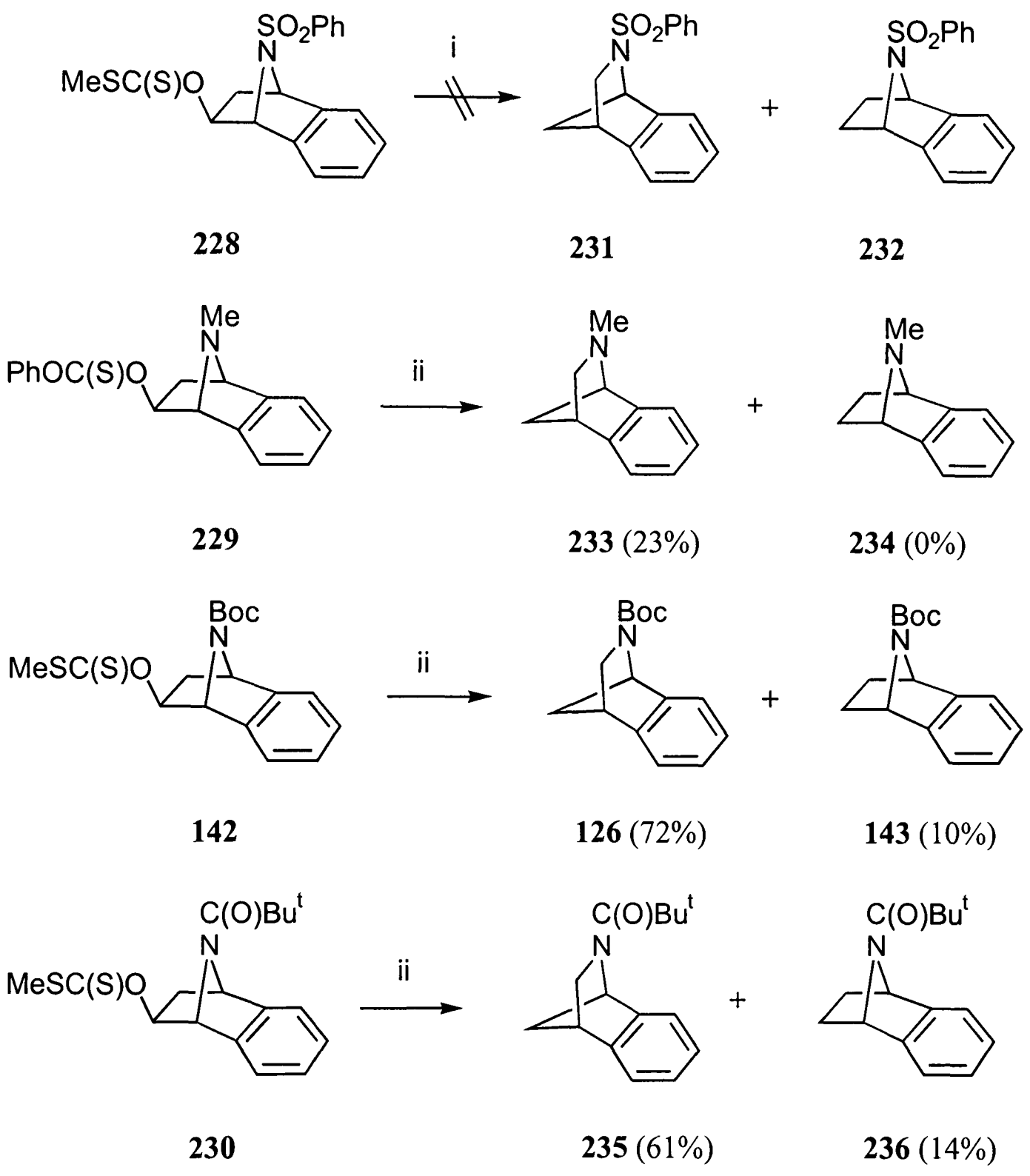
224 **228** (55%)

222 **229** (65%)

227 **230** (86%)

Scheme 6.2 Preparation of *N*-substituted precursors. *Reagents and conditions*: i, KH, CS_2, MeI, THF, 0 °C→ 25 °C, 60-90 min; ii, PhOC(S)Cl, DMAP, CH_2Cl_2, 25 °C, 16 h.

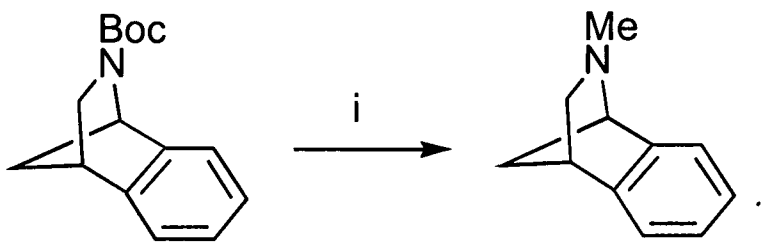
Deoxygenation with TTMSS/AIBN gave the product profiles shown below. The reducing agent was added as one portion in attempt to trap some of the directly reduced product in each case. The result of the *N*-Boc substrate from chapter 4 is also shown as a comparison.



Scheme 6.3 Deoxygenation of *N*-substituted radical precursors. *Reagents and conditions*: i, TBTH, AIBN, toluene, reflux, 2 h; ii, TTMSS, AIBN, toluene, reflux, 2 h.

The *N*-phenylsulfonyl xanthate was unreactive to TTMSS, so the reaction was performed with TBTH instead. No identifiable products were isolated from this reaction, and a tin-containing mixture was collected from chromatography.

The other results show an interesting trend. Only the rearranged product **233** was isolated from the reaction of **229**. The low yield is attributed partly to mechanical losses on chromatography on silica gel. A sample of known amine **234**[112] was prepared independently and was found to be stable to TTMSS and AIBN under the same conditions. The structure of **233** was verified by reduction of a sample of **126** (Scheme 6.4, below).



126 **233** (45 %)

Scheme 6.4 Reduction of **126**. *Reagents and conditions*: $LiAlH_4$, THF, reflux, 2 h.

Deoxygenation of the *N*-*tert*-butylcarbonyl xanthate **230** gave a smaller fraction of the rearranged product than did the *N*-Boc xanthate **142**. The results from the three different *N*-protected systems suggest that increased amide-type resonance is not the driving force for these rearrangements, as the process occurs where resonance does not (i.e. for *N*-Me). Indeed, use of the amide, where resonance is very significant, appears to decrease the propensity for rearrangement. Structural variations in the three systems are not thought to be significant, as modelling and database studies suggest very little variation in interatomic distances with nitrogen protecting group.[113]

6.3 A Model for Nitrogen-Directed Radical Rearrangements

Given these results, it seems likely that the interaction of the radical centre with the lone pair on nitrogen gives rise to a stabilising effect that leads to rearrangement. (Fig 6.1) The similar geometries of 7-azanorbornenes, 7-azabenzonorbornenes and the analogous rearranged products mean that it is

probably reasonable to assume that the driving force is the same for both nitrogen-directed homoallylic rearrangement and for neophyl rearrangement.

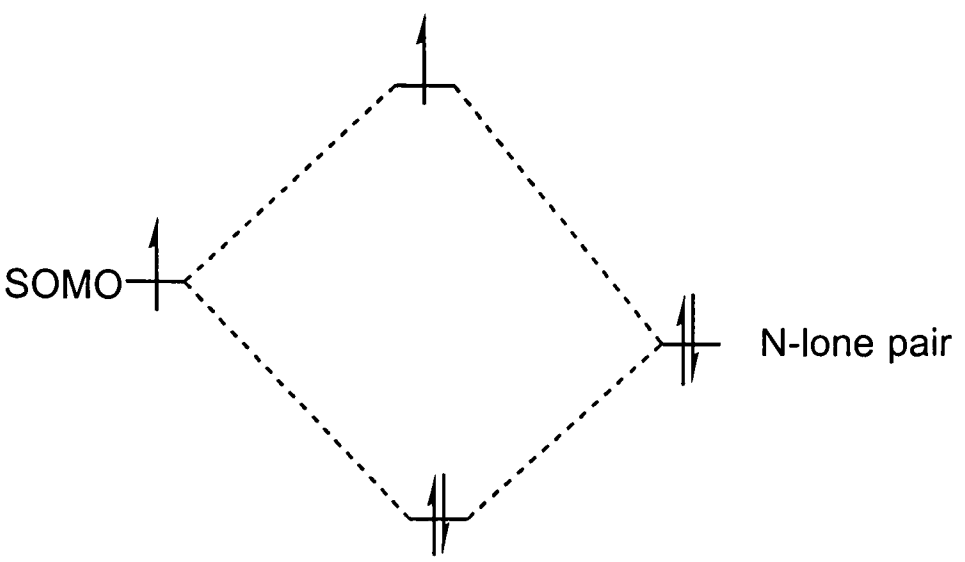


Fig 6.1 Proposed orbital interaction giving rise to nitrogen-directed rearrangement.

This would explain the product profiles observed. As the energy gap between the SOMO and the orbital containing the lone pair increases, the magnitude of the stabilisation decreases as the overlap becomes poorer. In the case of *N*-methyl, this energy gap will be minimised, leading to a stronger driving force for rearrangement and the complete selectivity for the rearranged product. Interactions of radical centres with adjacent lone pairs are well documented, and such an interaction is thought to be responsible for the low values obtained for dissocation energies of α-CH bonds of amines.[114, 115] Theoretical calculations suggest that the SOMO and the orbital containing the lone pair should be anticoplanar for maximum interaction, and this appears to be possible for the 2-azabenzonorbornanyl radical (Fig. 6.2, overleaf).

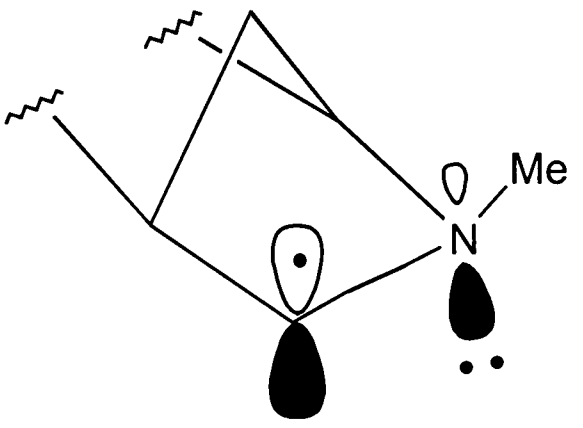


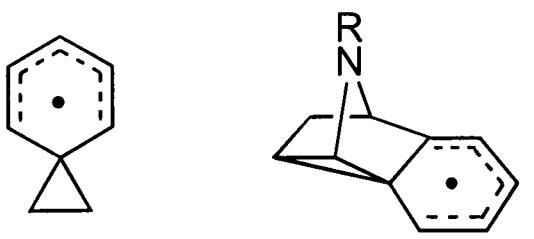
Fig. 6.2 Interaction of a radical centre with a nitrogen lone pair.

The conformation shown is likely, as it has the methyl group on the less hindered *exo* face.

The results of Maxwell,[45]those of the thiol additions (chapter 3) and that with the *N*-methyl substrate **229** above seem to indicate that the rearrangement is not reversible, so that there is not an equilibrium between rearranged and unrearranged radicals. It is certain that deoxygenation of **141** above gives a product profile that does not reflect equilibrium proportions of radicals, as the ratio of **126** to **143** is known to increase still further when the reducing agent is added slowly (Chapter 4, p.72).

6.4 Mechanism of Nitrogen-Directed Neophyl-like Rearrangement

As was explained in chapter one, there has been much debate on the mechanism of the neophyl rearrangement.[43] It is not known whether the radical **237** is an intermediate or a transition state (Fig. 6.3, below).



237 **238**

Fig. 6.3 Possible transition states for the neophyl rearrangement.

If the rate constant for the rearrangement could be shown to depend on the nature of the group attached to nitrogen, this would suggest that the radical **238** is a transition state rather than an intermediate. Decay of intermediates such as **237** is known to occur on the nanosecond timescale.[116] The intermediate **238** would probably have a longer lifetime on entropic grounds, by analogy with the ring opening of the nortricyclyl radical (Chapter 1, p.25). However, it seems unlikely that ring-opening of **238** would be sufficently slow to be the rate-determining step of the reaction, given that the rate of rearrangement is of the order of 10^5 s^{-1} (Chapter 4, p. 73). It seems more likely that cyclisation of the first formed radical to give **238** would be slower than its decay to the radical α to nitrogen (see Scheme 4.3, p. 66). Radical stabilisation could not then affect the rate-determining cyclisation. This does not explain the observed results because then the product profile would not be expected to vary with substitution on nitrogen, in the absence of significant differences in the geometry of the radicals involved.

Any rate-determining step must involve the developing radical α to nitrogen given the dependence of product profile on the *N*-protecting group. This condition is fulfilled if **238** is a transition state, which can therefore be lowered in energy by the stabilising effect of the nitrogen atom on the developing rearranged radical. The energy of the transition state would thus depend on the electronics at nitrogen, assuming a radical-lone pair interaction occurs as postulated. The issue of rate dependence on *N*-substitution is of considerable theoretical importance and worthy of further investigation, but from a synthetic point of view it is not of paramount importance.

6.5 Conclusions and Recommendations

The results suggest that lone pair-radical interactions are responsible for the rearrangement processes presented in this thesis. The nature of the transition state for the nitrogen-directed neophyl rearrangement has not been confirmed, but the model proposed explains concisely the results obtained. Mechanistic investigations, for example, independent generation of radical **238** by some H-atom abstraction method, could shed light on an issue of some importance to free radical chemistry.

Experimental - Chapter Two

General Procedure

All reactions requiring anhydrous conditions were conducted in flame dried apparatus under an atmosphere of argon. Syringes and needles for the transfer of reagents were oven dried and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from benzophenone ketyl, hydrocarbons from CaH_2, and alcohols from their magnesium alkoxides.

All reactions were monitored by TLC using commercially available (Merck or Camlab) plates, pre-coated with a 0.25 mm layer of silica containing a fluorescent indicator. Visualisation of reaction components was achieved with 254 nm light, and with vanillin or $KMnO_4$ dips. Organic layers were dried using $MgSO_4$, evaporated with a Buchi rotary evaporator, followed by drying on a high vacuum oil pump (~1 mm Hg). Column chromatography was carried out on Kieselgel 60 (40-63 μm).

Optical rotation was measured using a Perkin-Elmer 241 Polarimeter, with a path length of 10 cm, in chloroform. $[\alpha]_D$ values are given in 10^{-1} deg cm^{-2} g^{-1}. Enantiomeric enrichment was determined by HPLC using a chiralpak AD column (250 x 46 mm) operating at 254 nm eluting with EtOH/heptane.

IR spectra were recorded as either KBr discs or thin films, using a Perkin-Elmer 1750 FTIR spectrophotometer. Peak intensities are specified as strong (s), medium (m) or weak (w). Only selected absorbancies are reported. ^1H NMR spectra of compounds were recorded in $CDCl_3$ unless otherwise stated, using a Varian Gemini 200 (200 MHz), Bruker DPX400 (400 MHz) or AMX500 spectrometer (500 MHz). Chemical shifts (δ) are reported relative to $CHCl_3$ (δ 7.27). Coupling

constants (J) are given in Hz, multiplicities are given as multiplet (m), doublet (d), triplet (t) and quartet (q).

^{13}C NMR spectra were recorded on the Bruker DPX400 (100 MHz) or AMX500 (125 MHz). Chemical shifts are reported relative to $CDCl_3$ (central line of triplet δ 77.0) unless stated otherwise.

Mass spectra were obtained from the EPSRC Mass Spectrometry Service Centre, Swansea with a Micromass, ZAB-E instrument or 900 XLT high resolution double focusing mass spectrometer with tandem ion trap. Alternatively they were recorded in-house using a VG mass Lab. TRIO1 (GCMS) or Micromass platform APCI spectrometer.

All known compounds have at least ^1H NMR and IR for characterisation purposes. All novel compounds were characterised by R_f , accurate mass, microanalysis, ^1H NMR, ^{13}C NMR, GCMS and, where applicable, bp, mp, and $[\alpha]_D$.

All organolithiums were titrated against *N*-(2-methylphenyl)-1,1-dimethyl-ethyl amide before use. A known amount of the amide was dissolved in THF (2 cm^3) and the organolithium was then added to this stirring solution until a colour change is observed (clear colourless to bright orange).

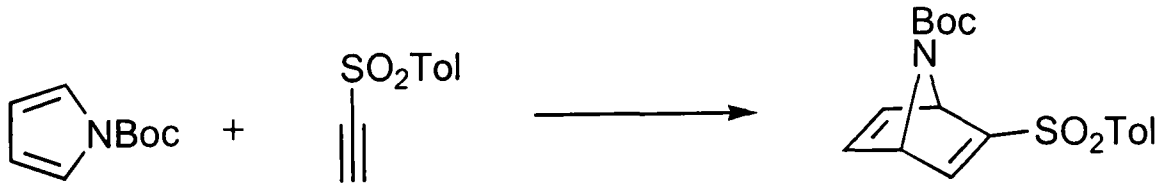
'Petroleum ether' refers to the fraction boiling in the range 30-40 °C.

Ethynyl *p*-tolyl sulfone 64 :[54]

64

p-Toluene sulfonyl chloride (24.6 g, 130.0 mmol) was added to powdered aluminium chloride (17.2 g, 130 mmol) in CH_2Cl_2 (100 cm^3). The solution was stirred at room temperature for 30 min and then added over 60 min by cannula to an ice-cold solution of bis(trimethylsilyl)acetylene (20.0 g, 116 mmol). The reaction was left to stir at room temperature for 24 h and then quenched with 1N HCl (200 cm^3) and poured onto crushed ice. The organic layer was separated, washed with water (100 cm^3) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to yield the crude 2-trimethylsilyl-1-*p*-toluenesulfonyl acetylene (24 g). Desilylation was effected without further purification: the crude silane (24 g, ~116 mmol) was dissolved in MeOH (240 cm^3) and a solution of KF (10.4 g, 180 mmol) in water (120 cm^3) was added dropwise using an addition funnel at 25 °C. The resulting suspension was stirred for a further 15 min and then the mixture was extracted with Et_2O (3 x 200 cm^3), washed with saturated $NaHSO_4$ (200 cm^3), brine (200 cm^3) and dried ($MgSO_4$). Removal of solvent at reduced pressure gave **64** (18 g, 78%, lit.[54] 84%) as a white solid; ν_{max}(KBr)/cm^{-1} 3250m, 2064s, 1333s, 1157s; δ_H (200 MHz) 7.90 (2 H, d, J 8.0, 2 x CH of aromatic), 7.34 (2 H, d, J 8.0, 2 x CH of aromatic), 3.45 (1 H, s, acetylenic H), 2.47 (3 H, s, Me); δ_C (100 MHz) 146.1, 137.8, 130.1, 127.7, 81.3, 80.1, 21.7.

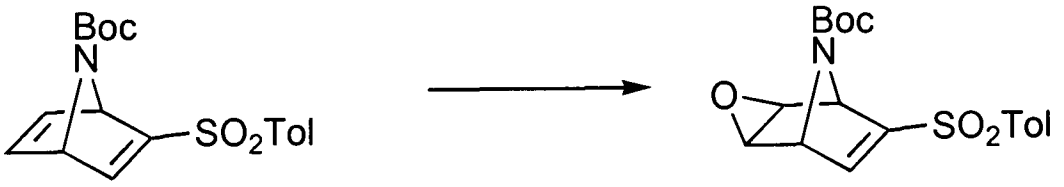
7-(*tert*-Butoxycarbonyl)-2-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]hepta-2,5-diene 65 :



65

A mixture of *N*-Boc pyrrole (11.3 g, 68 mmol) and ethynyl *p*-tolyl sulfone **64** (4.0 g, 22 mmol) was stirred under argon at 85 °C for 24 h. The resultant black mixture was dissolved in CH_2Cl_2 and loaded onto SiO_2. Chromatography (SiO_2, 30% Et_2O : petroleum ether to 60% Et_2O : petroleum ether, gradient elution) gave **65** (4.6 g, 60%, lit.[45] 81%) as a white solid; R_f (50% Et_2O : light petroleum) 0.21; ν_{max}(KBr)/cm^{-1} 2985m, 1710s, 1591s, 1370s, 1343s, 1316m, 1150s; δ_H (200 MHz) 7.75 (2 H, d, J 8.0, 2 x CH of aromatic), 7.60 (1 H, s, C(3)H), 7.35 (2 H, d, J 8.0, 2 x CH of aromatic), 7.00 (1 H, m, C(5)H or C(6)H), 6.90 (1 H, m, C(5)H or C(6)H), 5.40 (1 H, s, C(1)H or C(4)H), 5.17 (1 H, s, C(1)H or C(4)H), 2.45 (3 H, s, Me), 1.26 (9 H, s, Bu^t).

exo-2,3-(Epoxy)-6-(_p_-toluenesulfonyl)-7-(_tert_-butoxycarbonyl)-7-azabicyclo[2.2.1]hept-5-ene 66 :

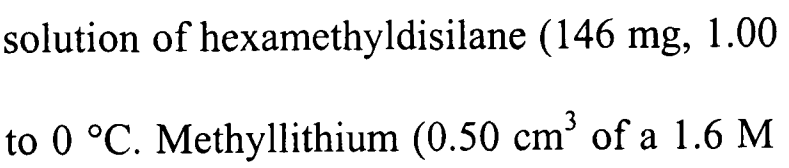


66

A mixture of *m*CPBA (2.36 g of 50% suspension in water, 6.9 mmol) was added slowly to a stirred solution of cycloadduct **65** (2.00 g, 5.76 mmol) in CH_2Cl_2 (30 cm^3). The mixture was heated at reflux for 36 h. After cooling, aqueous saturated Na_2SO_3 (20 cm^3) was added and the organic layer extracted with CH_2Cl_2 (2 x 20 cm^3). The organic layer was washed with $NaHCO_3$ (20 cm^3), water (20 cm^3) and brine (20 cm^3). It was dried with $MgSO_4$ and evaporated under reduced pressure to give a brown oil. Chromatography (50 % Et_2O : petroleum ether and then 100% EtOAc) gave epoxide **66** as a 1:1 mixture of rotamers (1.20 g, 58%, lit.[53] 70%); R_f (50% Et_2O : petroleum ether) 0.14; ν

$_{max}$(KBr)/cm^{-1} 2990m, 1720s, 1600s, 1365s, 1160s, 1110s; δ_H (200 MHz) 7.80 (2 H, m, 2 x CH of aromatic), 7.40 (1 H, d, J 8.0, CH of aromatic), 7.36 (1 H, d, J 8.0, CH of aromatic), 7.26 (0.5 H, d, J 2.0, HC=C), 7.14 (0.5 H, d, J 2.0, HC=C), 4.87 (0.5 H, d, J 2.5, C(1)H or C(4)H), 4.80 (0.5 H, s, C(1)H or C(4)H), 4.77 (0.5 H, s, C(1)H or C(4)H), 4.75 (0.5 H, s, C(1)H or C(4)H), 3.64 (0.5 H, d, J 3.5, CH-O), 3.59 (0.5 H, d, J 3.5,CH-O), 3.48 (0.5 H, d, J 3.5, CH-O), 3.48 (0.5 H, d, J 3.5, CH-O), 2.47 (3 H, s, Me), 1.43 (9 H, s, Bu^t).

3-(Trimethylsilyl)-cyclohexanone 76 :[56]

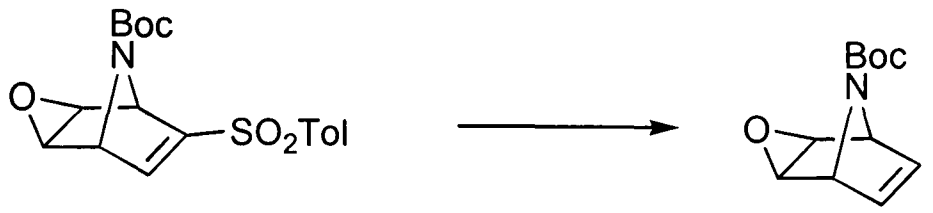


76

A solution of hexamethyldisilane (146 mg, 1.00 mmol) in HMPA (1 cm^3) was cooled to 0 °C. Methyllithium (0.50 cm^3 of a 1.6 M solution in hexanes, 0.8 mmol) was then added *via* syringe under argon and the mixture was stirred for 15 min to complete formation of trimethylsilyllithium. The resultant red solution was diluted with THF (5 cm^3) and cooled to −78 °C, whereupon it turned yellow. A solution of cyclohex-2-en-1-one **75** (56 mg, 0.58 mmol) in THF (2 cm^3) was added dropwise and the mixture allowed to stir for 5 min before it was allowed to warm to 0 °C, by which time the yellow colour had faded. The reaction was quenched with saturated aqueous NH_4Cl (5 cm^3) and the organic layer extracted with ether (2 x 10 cm^3) and washed with saturated aqueous $NaHCO_3$ (10 cm^3) and brine (10 cm^3). Column chromatography (30% Et_2O : petroleum ether) gave 3-(trimethylsilyl)-cyclohexanone (52 mg, 57%, lit.[57] 99%) as a colourless oil; δ_H (200 MHz) 2.30-

2.00 (4 H, m, 2 x CH_2-CO), 1.82-1.75 (2 H, m, CH_2), 1.42-1.38 (2 H, m, CH_2), 1.07-1.03 (1 H, m, CH-Si), –0.03 (9 H, s, Me_3Si).

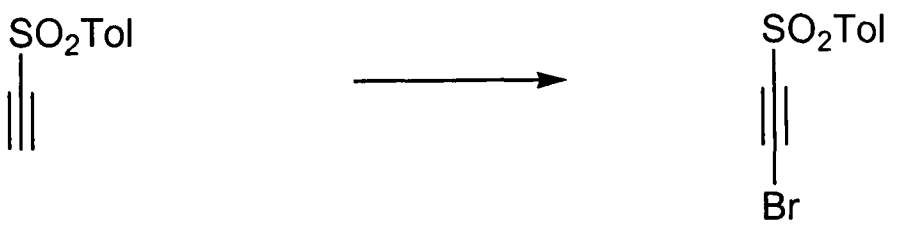
exo-2,3-(Epoxy)-7-(_tert_-butoxycarbonyl)-7-azabicyclo[2.2.1]hept-5-ene 61 :[45]



61

A stirred mixture of epoxide **66** (950 mg, 2.63 mmol), TBTH (1.03 cm^3, 3.9 mmol) and AIBN (120 mg) was heated to 90 °C in toluene (20 cm^3) for 2 h under argon. The vessel was allowed to cool and the solvent removed at reduced pressure. TBAF (20 cm^3 of 1 M solution in THF, 20 mmol) was added and the mixture was stirred for 4 h at room temperature. A solution of 1 M aq. NaOH (20 cm^3) was added and the mixture stirred for a further hour at room temperature. The organic layer was extracted with Et_2O (3 x 20 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (50% Et_2O : petroleum ether) gave **61** (170 mg, 30%, lit.[45] 17%) as a white solid: R_f (50% Et_2O : petroleum ether) 0.27; mp 102-103 °C, (lit.[45]102-103 °C); ν_{max}(KBr)/cm^{-1} 2980m, 1702s, 1381s, 1260s, 1170s, 1100s, 910s; δ_H (200 MHz) 6.51(2 H, s, C(5)H and C(6)H), 4.69 and 4.55 (2 H, 2 x s, C(1)H and C(4)H), 3.52-3.47 (2 H, m, C(2)H and C(3)H), 1.47 (9 H, s, Bu^t).

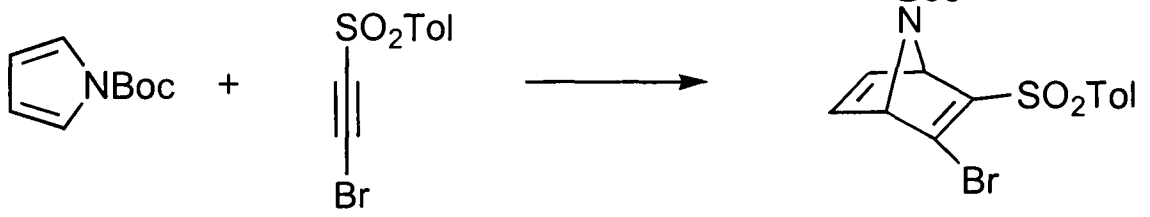
2-Bromoethynyl _p_-tolyl sulfone 77 :[58]



77

To a stirred solution of *p*-tolyl ethynyl sulfone **64** (2.0 g, 11 mmol) in acetone (60 cm^3) was added $AgNO_3$ (0.17 g, 1.1 mmol) and NBS (2.11 g, 12.2 mmol). The resultant solution was stirred at 25 °C for 30 minutes. The white precipitate was removed by filtration through celite and washed with a small amount of CCl_4. The solvent was removed at reduced pressure. Chromatography (50% Et_2O : petroleum ether) gave **77** (2.3 g, 84%, lit.[58] 95%) as a pale yellow solid: R_f (50 % Et_2O: petroleum ether) 0.18; δ_H (200 MHz) 7.80 (2 H, d, J 8.0, 2 x CH of aromatic), 7.40 (2 H, d, J 8.0, 2 x CH of aromatic), 2.49 (3 H, s, Me).

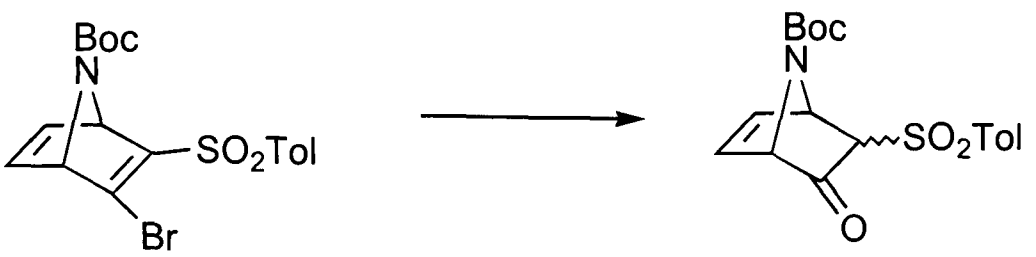
7-(*tert*-Butoxycarbonyl)-2-(*p*-toluenesulfonyl)-3-bromo-7-azabicyclo[2.2.1]hepta-2,5-diene 78 :[58]



78

A mixture of *N*-Boc pyrrole and sulfone **77** (2.1 g, 8.1 mmol) was heated to 90 °C in toluene (25 cm^3) for 24 h under argon. The vessel was allowed to cool and the solvent removed at reduced pressure. Chromatography (30% Et_2O : petroleum ether to 60% Et_2O : petroleum ether, gradient elution) gave **78** (1.9 g, 55%, lit.[58] 72%) as a pale yellow solid: R_f (50% Et_2O : petroleum ether) 0.25; δ_H (200 MHz) 7.82 (2 H, d, J 8.5, 2 x CH of aromatic), 7.36 (2 H, d, J 8.5, 2 x CH of aromatic), 7.00 (2 H, s, C(5)H and C(6)H), 5.51 (1 H, s, C(1)H or C(4)H), 5.20 (1 H, br s, C(1)H or C(4)H), 2.51 (3 H, s, Me), 1.38 (9 H, s, Bu^t).

***exo/endo*-6-(*p*-tolylsulfonyl)-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]hept-2-en-5-one 84 :**[58]

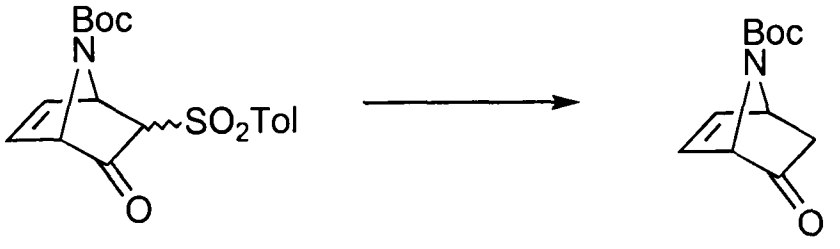


84

To a solution of cycloadduct **78** (3.06 g, 7.2 mmol) in MeCN (100 cm^3) was added Et_3N (3.1 cm^3, 22 mmol) and Et_2NH (820 µl, 7.9 mmol) and the mixture stirred for 30 min. 2N HCl (100 cm^3) was then added and the mixture stirred for a further 15 min.

The organic layer was extracted with ether (3 x 100 cm^3), washed with saturated $NaHCO_3$ (50 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, 50% Et_2O : petroleum ether) gave **84** (2.2 g, 85%) as an off-white solid: R_f (Et_2O) 0.55; δ_H (200 MHz) (*endo/exo,* 2.5 : 1) 7.83-7.77 (2 H, m, 2 x CH of aromatic), 7.40-7.28 (2 H, m, 2 x CH of aromatic), 6.95, 6.75, 6.55, 6.45 (2 H, 4 x dd, J 12.0 and 2.0, C(5)H and C(6)H), 5.45, 5.20, 4.70, 4.55 (2 H, 4 x s, C(1)H and C(4)H), 4.02 (0.3 H, d, J 4.0, CH-S *exo*) and 3.55 (0.7 H, s, CH-S *endo*), 2.45 (3 H, s, Me), 1.47 (9 H, s, Bu^t).

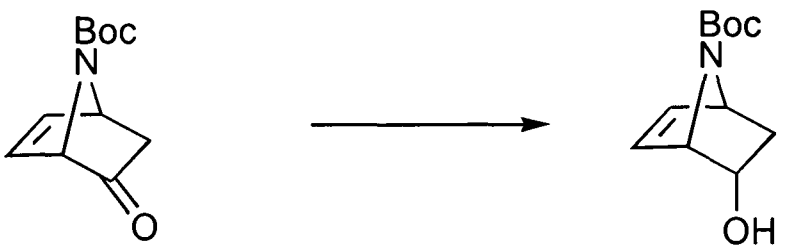
7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]hept-2-en-5-one 85 :[58]



85

Al-Hg (270 mg, 10 mmol Al) was prepared according to the procedure of Corey[117] and added to a preheated stirred solution of sulfone **84** (363 mg, 1.0 mmol) in a 9:1 mixture of THF and water (10 cm^3) at 80 °C buffered with Na_2HPO_4 (568 mg, 4.0 mmol). The mixture was stirred at 80 °C for 1 h, then cooled to room temperature and filtered through celite. Water (10 cm^3) was added and the organic layer extracted with diethyl ether (3 x 20 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Column chromatography (15% EtOAc : petroleum ether) gave the known ketone **85** (46 mg, 21%, lit.[58] 50-55%) as a colourless oil: R_f (15% EtOAc : petroleum ether) 0.35; δ_H (200 MHz) 6.72-6.68 (1 H, m, HC=C), 6.41-6.37 (1 H, m, HC=C), 5.05 (1 H, s, C(1)H), 4.52 (1 H, s, C(4)H), 2.20 (1 H, dd, J 10.0 and 2.0, C(6)H *exo*), 1.90 (1 H, d, J 10.0, C(6)H *endo*), 1.43 (9 H, s, Bu^t). This reaction was found not to be reproducible (yields varied from 0-21%) and as a result full characterisation of the subsequent novel compounds was not possible.

7-(*tert*-Butoxycarbonyl)-*endo*-7-azabicyclo[2.2.1]hept-2-en-5-ol 86 :

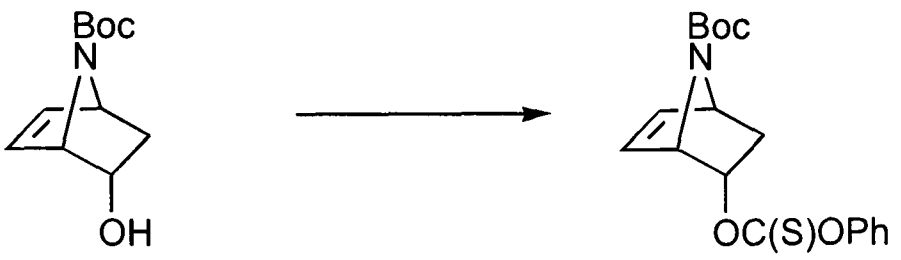


86

To a stirred solution of ketone **85** (100 mg, 0.47 mmol) in MeOH (5 cm^3) at -10°C was added $NaBH_4$ (16 mg, 0.42 mmol) and the mixture stirred for 2 h. The reaction was quenched with 1N HCl (5 cm^3), washed with brine and the aqueous layer extracted with CH_2Cl_2 and dried ($MgSO_4$). Chromatography (SiO_2, 60% Et_2O : petroleum ether) to give **86** as a white solid (60 mg, 60%): R_f (60% Et_2O : petroleum ether) 0.28; δ_H (200 MHz) 6.60 (1 H, m, HC=C), 6.33 (1 H, m, HC=C), 4.70 (1 H, s, C(1)H or C(4)H), 4.63 (1 H, s, C(1)H or C(4)H), 4.50 (1 H, s, C(H)-

O), 2.20 (1 H, m, H of CH_2), 1.85 (1 H, s, OH), 1.40 (9 H, s, Bu^t), 0.90 (1 H, dd, J 12.0 and 3.0, H of CH_2); m/z (CI^+, NH_3) 212 ($M+H^+$, 23%), 168 (73), 112 (100), 68 (72), 58 (61) (Found, $M+H^+$, 212.1285, $C_{11}H_{18}NO_3$ requires 212.1286).

***endo*-5-(Phenylthionocarbonate)-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]hept-2-ene 63 :**



63

To a solution of alcohol **86** (30 mg, 0.14 mmol) in dry acetonitrile (5 cm^3) was added DMAP (1.42 g, 1.15 mmol) and phenyl chlorothionocarbonate (134 µl, 0.73 mmol). The mixture was stirred under argon at room temperature for 20 h. The mixture was partitioned between ethyl acetate (10 cm^3) and water (10 cm^3) and the organic phase was washed with 1N HCl (10 cm^3), water (10 cm^3), saturated $NaHCO_3$ (10 cm^3), brine (10 cm^3) and then dried ($MgSO_4$). Column chromatography (40% Et_2O : petroleum ether) gave **63** as a colourless oil (19 mg, 40 %): R_f (40% Et_2O : petroleum ether) 0.33; δ_H (200 MHz) 7.45-7.25 (3 H, m, 3 x CH of Ph), 7.10-7.00 (2 H, m, 2 x CH of Ph), 6.68-6.60 (1 H, m, HC=C), 6.38-6.28 (1 H, m, HC=C), 5.73-5.67 (1 H, m, CH-O), 5.12 (1 H, s, C(1)H or C(4)H), 4.72 (1 H, s, C(1)H or C(4)H), 2.62-2.50 (1 H, m, H of CH_2), 1.45 (9 H, s, Bu^t), 1.30 (1 H, dd, J 12.0 and 3.0, H of CH_2).

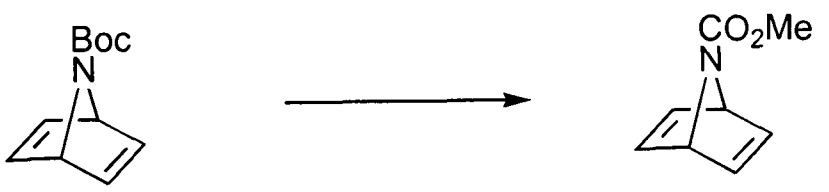
Experimental - Chapter 3

7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]hepta-2,5-diene 67 :[45]

67

Cycloadduct **65** (5.20 g, 14.9 mmol) was added to a 250 cm^3 beaker containing a stirrer bar, methanol (80 cm^3), Na_2HPO_4 (8.0 g, 55 mmol) and 6% Na-Hg (5.0 g) at −10 °C. The mixture was stirred at 0 °C for 6 h. Water (100 cm^3) was then added and the mixture filtered. The filtrate was extracted with CH_2Cl_2 (3 x 100 cm^3), washed with brine (100 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Column chromatography (25% Et_2O : petroleum ether) gave **67** (690 mg, 23%) as a colourless oil: R_f (25% Et_2O : petroleum ether) 0.24; ν_{max}(thin film)/cm^{-1} 2980s, 1710s, 1480s, 1460s, 1344s, 1170s; δ_H (200 MHz) 6.99 and 6.98 (4 H, 2 x s, 4 x HC=C), 5.20 (2 H, s, C(1)H and C(4)H), 1.41 (9 H, s, Bu^t).

7-(Methoxycarbonyl)-7-azabicyclo[2.2.1]hepta-2,5-diene 239 :

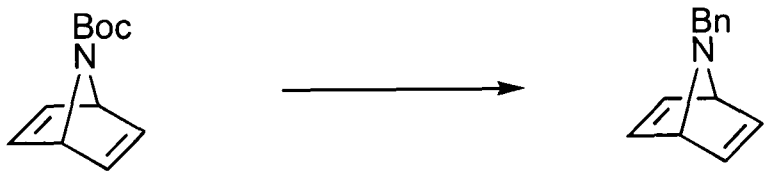


239

Trifluoroacetic acid (1.5 cm^3, 19.2 mmol) was added to a solution of diene **67** (186 mg, 0.96 mmol) in CH_2Cl_2 (15 cm^3) and stirred at room temperature for 1 h. The crude TFA salt was azeotroped with toluene (3 x 40 cm^3) and the resulting brown solid (310 mg) used without further purification. Methoxycarbonylation was achieved using the procedure of Corey[73] as follows: To a solution of the salt prepared in the previous step in acetone (5 cm^3) was added K_2CO_3 (830 mg, 6.0

mmol), and methyl chloroformate (310 μL, 4.0 mmol) and the mixture heated to reflux for 18 h. Water (10 cm^3) was added and the aqueous layer was extracted with Et_2O (3 x 5 cm^3) and the combined extracts washed with 1N NaOH (10 cm^3), brine (10 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, 50% Et_2O: petroleum ether) gave the carbamate **239** as a yellow oil (92 mg, 61% from **67**): R_f (50% Et_2O : petroleum ether) 0.35; δ_H (200 MHz) 7.02 and 7.01 (4 H, 2 x s, 4 x HC=C, split by carbamate rotamers), 5.25 (2 H, s, C(1)H and C(4)H), 3.62 (3 H, s, Me). In accordance with literature.[72]

7-Benzyl-7-azabicyclo[2.2.1] hepta-2,5-diene 116 :

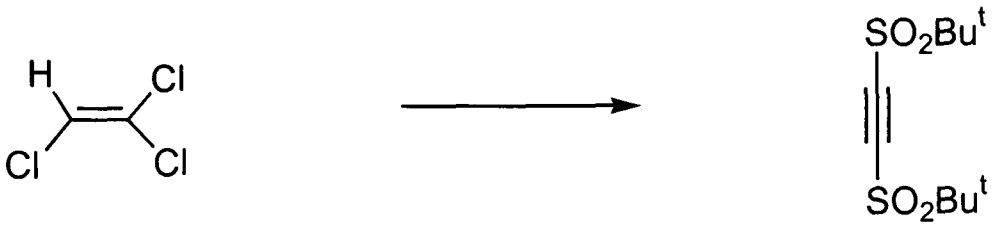


116

Trifluoroacetic acid (820 μL, 10.4 mmol) was added to a solution of diene **67** (100 mg, 0.52 mmol) in CH_2Cl_2 (8 cm^3) and stirred at room temperature for 1 h. The crude TFA salt was azeotroped with toluene (3 x 20 cm^3) and the resulting brown solid (150 mg) used without further purification. Benzylation was achieved as follows:[79] To a solution of the salt prepared in the previous step in CH_2Cl_2 (4 cm^3) was added water (2 cm^3), Na_2CO_3 (165 mg, 1.56 mmol), and benzyl bromide (71 μ L, 0.6 mmol) and the mixture heated to reflux for 5 h. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 cm^3) and the combined extracts dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, 30% Et_2O : petroleum ether, 1% Et_3N) gave the amine **116** as a yellow oil (36 mg, 38% from **67**): R_f (30% Et_2O : petroleum ether, 1% Et_3N) 0.23: ν_{max}(thin film)/cm^{-1} 3063m, 3026m, 2991s, 2838m, 1494s, 1454s, 1356s, 1290m, 1091m; δ_H (400 MHz), 7.15-

7.03 (5 H, m, 5 x H of Ph), 6.85 (2 H, s, 2 x HC=C), 6.60 (2 H, s, 2 x HC=C), 4.14 (2 H, s, C(1)H and C(4)H), 3.42 (2 H, s, CH_2); δ_C (100 MHz) 145.4, 140.2 (both C=C), 138.7 (C_{quat} of Ph), 128.9, (C of Ph), 128.1, (2 x C of Ph), 126.7 (2 x C of Ph), 70.3 (C1 and C4), 54.0 (CH_2); m/z (CI^+, NH_3) 184 ($M+H^+$, 31%), 158 (46), 125 (6), 108 (100), 94 (14), 78 (19) (Found $M+H^+$, 184.1124, $C_{13}H_{14}N$ requires 184.1126).

Bis(*tert*-butylsulfonyl)acetylene 240 :[118, 119]

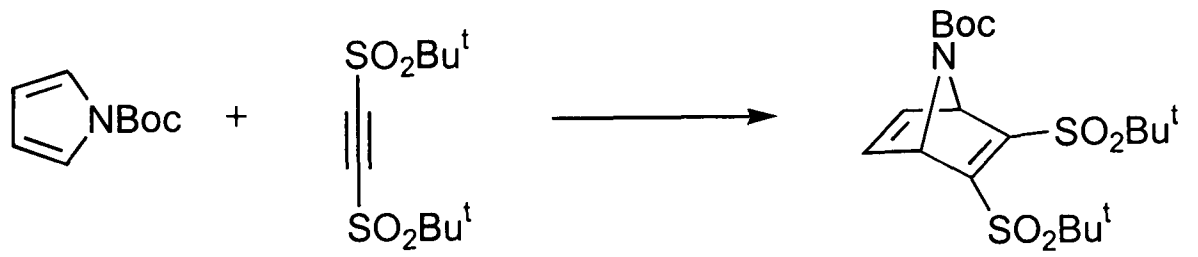


240

A solution of dichloroacetylene was prepared by the addition of trichloroethylene (0.9 cm^3, 10 mmol) to a suspension of KH (1.49 g of a 35% dispersion in mineral oil, 13 mmol) in THF (9.1 cm^3) under argon at 25 °C, followed by the addition of MeOH (10 μL, 0.25 mmol). The reaction was stirred for 1 h, when 2-methyl-2-propanethiol (1.82 g, 20 mmol) was added dropwise over 30 min at 0 °C. The reaction was then stirred at 25 °C for 3 h. The solution was then transferred by cannula to a flask containing KH (2.5g of a 35% dispersion, 22 mmol) and THF (2.5 cm^3) at 25 °C. The reaction was then stirred for 24 h. The mixture was diluted with light petroleum (20 cm^3) and water (5 cm^3), extracted with light petroleum (3 x 20 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure to give an oil. Column chromatography (SiO_2, petroleum ether) gave bis(*tert*-butylthio)acetylene as a white solid (760 mg, 38%, lit.[118] 98%) that was used immediately in the next step: *m*CPBA (6.00 g of 54% dispersion in H_2O, 18.8 mmol) was added to a solution of bis(*tert*-butylthio)acetylene (758 mg, 3.75 mmol) in CH_2Cl_2 (30 cm^3) at

0 °C. The mixture was allowed to warm to room temperature over 48 h and then filtered. A solution of Na_2SO_3 (10 cm^3 of a 10% aq. solution) was added to the filtrate, followed by saturated $NaHSO_4$ (10 cm^3). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 cm^3), dried ($MgSO_4$), and the solvent removed at reduced pressure. Chromatography (SiO_2, 50% Et_2O: petroleum ether) gave the bis-sulfone **240** as a white solid (610 mg, 62%): R_f (50% Et_2O : petroleum ether) 0.28; mp (from Et_2O) 140-142 °C, (lit.[119]145-146 °C, from Bu^tOH): R_f (50% Et_2O: petroleum ether) 0.20; δ_H (200 MHz) 1.47 (18 H, s, 2 x Bu^t); δ_C (50 MHz) 82.5 (C of acetylene), 62.3 (CMe_3), 22.6 (CMe_3).

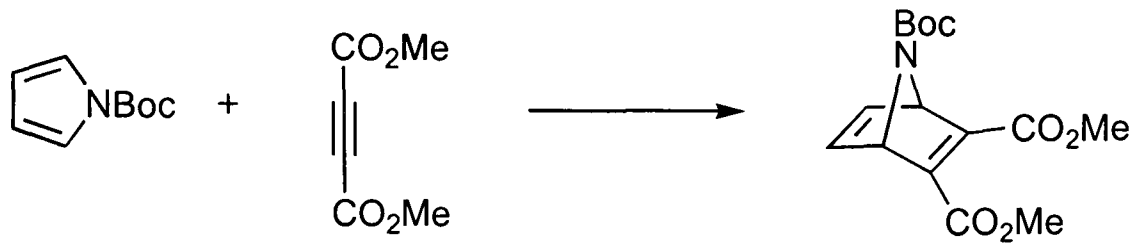
2,3-Bis-(*tert*-butylsulfonyl)-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]hepta-2,5-diene 114 :[55, 77]



114

A solution of *N*-Boc pyrrole (250 mg, 1.5 mmol) and acetylene **240** (200 mg, 0.75 mmol) in THF (2 cm^3) was stirred at room temperature for 24 h under argon. The solvent was removed at reduced pressure. Chromatography (SiO_2, 40% Et_2O : petroleum ether) gave the adduct **114** as a white solid (180 mg, 55%, lit.[77] 49%): R_f (50% Et_2O : petroleum ether) 0.33; δ_H (200 MHz) 7.24 (2 H, br s, 2 x HC=C), 5.63 (2 H, br s, C(1)H and C(4)H), 1.46 (27 H, s, 3 x Bu^t); δ_C (50 MHz) 163.4 (C=C quat.), 153.6 (C=O), 143.0 and 141.2 (C=C, split by rotamers), 82.7 (Me_3C-O), 73.2 (C1 and C4), 62.9 (S-CMe_3), 27.9 (OCMe_3), 23.7 (S-CMe_3).

2,3-(Dimethoxycarbonyl)-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]hepta-2,5-diene 115 :[78]



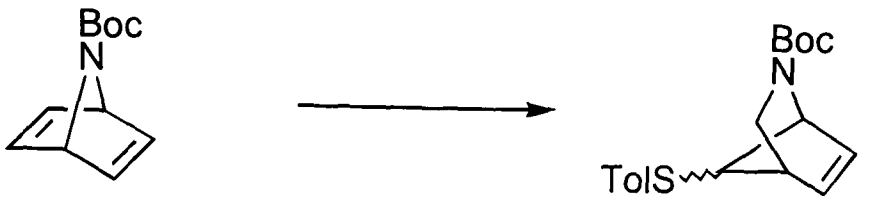
115

A mixture of *N*-Boc pyrrole (625 mg, 3.75 mmol) and DMAD (4.9 g, 34.6 mmol) was heated to 120 °C under argon for 4 h, after which time the reaction was allowed to cool. The resultant black oil was subjected to column chromatography (SiO_2, 20% Et_2O : petroleum ether to 50% Et_2O : petroleum ether, gradient elution) gave Diels-Alder adduct **115** as a colourless oil (920 mg, 79%, lit.[78] 84%): R_f (50% Et_2O : petroleum ether) 0.33; δ_H (200 MHz) 7.14 (2 H, s, 2 x HC=C), 5.50 (2 H, s, C(1)H and C(4)H), 3.80 (6 H, s, 2 x Me-O), 1.43 (9 H, s, Bu^t). In accordance with literature.

General procedure for thiol/selenol additions

The thiol or benzeneselenol (0.9 equiv.) was added as one portion to a solution of diene **67** or diene **239** (0.5 mol dm^{-3}) in benzene or toluene and stirred under argon for the specified time at the specified temperature. The solvent was then removed at reduced pressure. In all cases the products were obtained as an inseparable mixture of epimers. 1D nOe experiments established that the relative stereochemistry of the major epimer was with the thio- group *syn* to nitrogen for **105a**: irradiation of the proton at C7 showed enhancement of the olefinic protons. The stereochemistries of the other products were assigned by analogy.

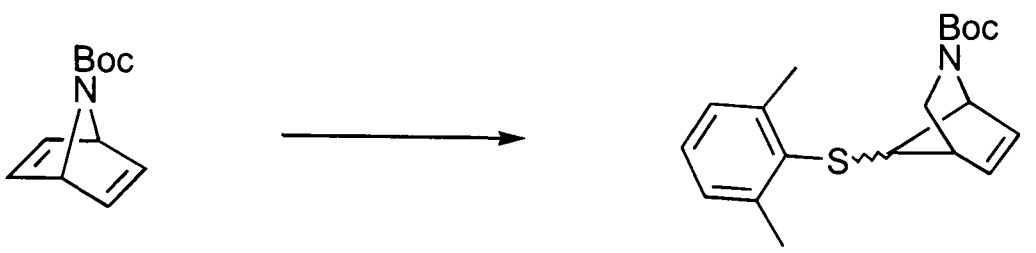
2-(*tert*-Butoxycarbonyl)-*syn/anti*-7-(*p*-tolylthio)-2-azabicyclo[2.2.1]hept-5-ene 105a :



105a

Reaction of diene **67** (100 mg, 0.52 mmol) and *p*-thiocresol (56 mg, 0.45 mmol) as described above for 24 h at 20 °C gave a yellow oil after removal of solvent. Column chromatography (SiO_2, 15% Et_2O : petroleum ether) gave **105a** as a colourless oil (132 mg, 92%): R_f (25% Et_2O : petroleum ether) 0.24; ν_{max}(thin film)/cm^{-1} 2975m, 2929s, 2889m, 1699s, 1493s, 1394s, 1363s, 1250s, 1177m, 1168s, 1100s; δ_H (500 MHz, 90 °C, DMSO-d_6, *syn* : *anti*, 3:1), (*syn*-epimer) 7.31 (2 H, d, J 8.0, 2 x CH of aromatic), 7.16 (2 H, d, J 8.0, 2 x CH of aromatic), 4.45 (1 H, s, C(1)H), 6.43 (2 H, m, HC=CH), 3.54 (1 H, dd, J 9.5 and 3.0, C(3)H *exo*), 3.25 (1 H, s, C(7)H), 3.06 (1 H, s, C(4)H), 2.59 (1 H, d, J 9.5, C(3)H *endo*), 2.30 (3 H, s, Me), 1.42 (9 H, s, Bu^t); (*anti*-epimer) 7.26 (2 H, d, J 8.0, 2 x CH of aromatic), 7.15 (2 H, d, J 8.0, 2 x CH of aromatic), 6.33 (2 H, m, HC=CH), 4.56 (1 H, s, C(1)H), 3.50 (1 H, s, C(7)H), 3.41 (1 H, dd, J 9.5 3.0, C(3)H *exo*), 3.25 (1 H, s, C(4)H), 2.57 (1 H, d, J 9.5, C(3)H *endo*), 2.30 (3 H, s, Me), 1.40 (9 H, s, Bu^t); δ_C (125 MHz, 90 °C, DMSO-d_6) (both epimers) 155.8, 155.4 (both C=O), 138.8, 137.4, 137.2, 136.0, 135.2, 132.9, 132.8, 131.9, 131.4, 130.6, 130.4 (all C=C or C-Ar), 79.7, 79.5 (both *C*Me_3), 65.9 (C7), 64.9, 63.8 (Both C1), 63.6 (C7), 49.2, 47.8 (Both C4), 47.2, 44.2 (Both C3), 29.0 (C*Me*$_3$), 21.3 (Me-Ar); m/z (CI^+, NH_3) 318 ($M+H^+$, 29%), 279 (33), 262 (100), 218 (48), 201 (23), 189 (23), 157 (14), 140 (13), 124 (14) 108 (6), 94 (78) (Found $M + H^+$, 318.1531, $C_{18}H_{24}NO_2S$ requires 318.1528).

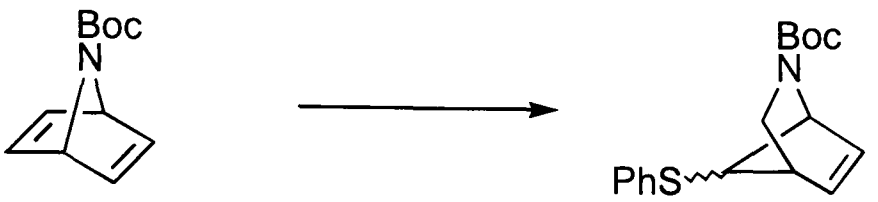
2-(*tert*-Butoxycarbonyl)-7-*syn/anti*-(2,6-dimethylphenylthio)-2-azabicyclo[2.2.1]hept-5-ene 105d :



105d

Reaction of diene **67** (97 mg, 0.50 mmol) and 2,6-dimethylbenzenethiol (62 mg, 0.45 mmol) according to the general procedure for 24 h at 20 °C gave a yellow oil after removal of solvent. Column chromatography (SiO_2, 15% Et_2O : petroleum ether) gave **105d** as a colourless oil (137 mg, 92%): R_f (25% Et_2O : petroleum ether) 0.25; ν_{max}(thin film)/cm^{-1} 2976m, 2927s, 2900m, 1694s, 1460s, 1392s, 1256s, 1172s, 1150s, 1103s; δ_H (500 MHz, 90 °C, DMSO-d_6, *syn* : *anti* 4 : 1) (*syn*-epimer) 7.15 (3 H, s, 3 x CH of aromatic), 6.33-6.41 (2 H, m, HC=CH), 4.32 (1 H, s, C(1)H), 3.61 (1 H, dd, J 9.5 3.0, C(3)H *exo*), 3.02(1 H, s, C(7)H) superposed on H_2O, 2.87 (1 H, s, C(4)H), 2.61 (1 H, d, J 9.5, C(3)H *endo*), 2.50 (6 H, s, 2 x Me-Ar), 1.43 (9 H, s, Bu^t), (*anti*-epimer) 7.15 (3 H, s, 3 x CH of aromatic), 6.33-6.41 (2 H, m, HC=CH), 4.42 (1 H, s, C(1)H), 3.33 (1 H, dd, 9.0 and 3.0, C(3) *exo*), 3.15 (1 H, br s, C(7)H), 3.12 (1 H, s, C(4)H), 2.54 (1 H, d, J 9.0, C(3)H *endo*), 2.48 (6 H, s, 2 x Me), 1.37 (9 H, s, Bu^t); δ_C (125 MHz, 90 °C, DMSO-d_6) (both epimers) 154.3, 154.0 (C=O), 142.1, 141.9, 137.4, 134.4, 133.8, 133.5, 132.8, 132.4, 131.7, 131.3, 127.8, 127.6, (all Ar or C=C), 78.3, 78.1 (both *C*Me_3), 65.0, 64.2 (both C7), 63.9, 63.3 (both C1), 48.1, 46.9 (both C4), 45.8, 43.0 (both C3), 27.8, 27.5 (both C*Me*$_3$), 21.3, 21.1 (both Me-Ar); m/z (CI^+, NH_3) 332 ($M+H^+$, 14%), 293 (16), 276 (48), 232 (18), 215 (12), 196 (13), 157 (33), 138 (50), 122 (19), 105(35), 96 (78), 80 (20) (Found $M + H^+$, 332.1684, $C_{19}H_{26}NO_2S$ requires 332.1684).

2-(*tert*-Butoxycarbonyl)-7-*syn/anti*-(phenylthio)-2-azabicyclo[2.2.1]hept-5-ene 105c :

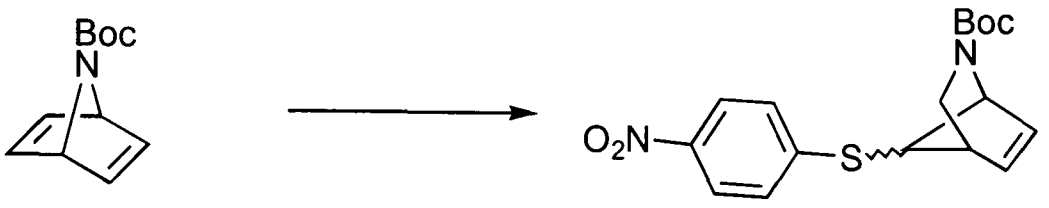


105c

Reaction of diene **67** (107 mg, 0.55 mmol) and thiophenol (55 mg, 0.50 mmol) according to the general procedure for 24 h at 20 °C gave a yellow oil after removal of solvent. Column chromatography (SiO_2, 15% Et_2O : petroleum ether) gave **105c** as a colourless oil which then crystallised on standing to a white solid (137 mg, 92%): R_f (25% Et_2O : petroleum ether) 0.24; mp (from petroleum ether) 50-52 °C (Found C, 66.8; H, 7.2; N, 4.6; $C_{17}H_{21}NO_2S$ requires C, 67.3; H, 7.0; N, 4.6 %); ν_{max}(KBr)/cm^{-1} 3068m, 2976s, 2883m, 1693s, 1583m, 1481s, 1391s, 1256s, 1155s, 1096s; δ_H (500 MHz, 90 °C, DMSO-d_6, *syn* : *anti*, 4 : 1) (*syn*-epimer) 7.41-7.25 (5 H, m, 5 x CH of Ph), 6.48-6.43 (2 H, m, HC=CH), 4.49 (1 H, br s, C(1)H), 3.54 (1 H, dd, J 9.0 and 3.0, C(3) *exo*), 3.32 (1 H, s, C(7)H), 3.10 (1 H, s, C(4)H), 2.61 (1 H, d, J 9.0, C(3) *endo*), 1.42 (9 H, s, Bu^t) (*anti*-epimer) 7.41-7.25 (5 H, m, 5 x CH of Ph), 6.37-6.33 (2 H, m, HC=CH), 4.61 (1 H, s, C(1)H), 3.57 (1 H, s, C(7)H), 3.44 (1 H, dd, J 9.0 and 3.0, C(3)H *exo*), 3.27 (1 H, s, C (4)H), 2.59 (1 H, d, J 9.0, C(3)H *endo*), 1.40 (9 H, s, Bu^t); δ_C (125 MHz, 90 °C, DMSO-d_6) (both epimers) 155.8, 155.5 (both C=O), 138.8, 136.6, 136.0, 135.6, 135.2, 133.0, 131.3, 130.7, 129.9, 127.5, 127.3 (all C of Ph or C=C), 79.7 and 79.6 (both CMe_3), 65.4 (C7), 64.8, 64.1 (both C1), 63.1 (C7), 49.2, 47.8 (both C4), 47.2, 44.3 (both C3), 29.1, 29.0 (both CMe_3); m/z (CI^+, NH_3) 321 ($M+NH_4^+$, 3%), 304 ($M+H^+$, 43%), 265 (70), 248 (27),

213 (10), 204 (38), 196 (17), 187 (4), 175 (19), 157 (68), 140 (12), 113 (34), 96 (100), 78 (24) (Found M + H^+, 304.1368, $C_{17}H_{22}NO_2S$ requires 304.1371).

2-(*tert*-Butoxycarbonyl)-7-*syn/anti*-(4-nitrophenylthio)-2-azabicyclo[2.2.1]hept-5-ene 105e :

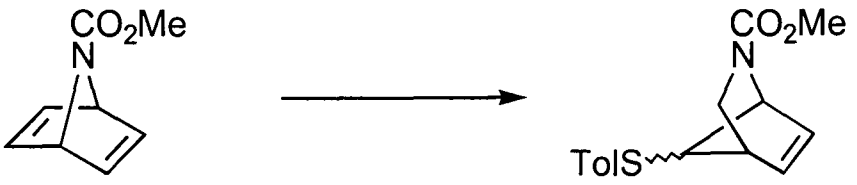


105e

Reaction of diene **67** (102 mg, 0.53 mmol) and *p*-nitrothiophenol[120] (78 mg, 0.50 mmol) according to the standard procedure for 72 h at 20 °C gave a yellow oil. Column chromatography (SiO_2, 30% Et_2O : petroleum ether) gave **105e** as a yellow solid (87 mg, 50%): R_f (40% Et_2O : petroleum ether) 0.29; mp (from Et_2O) 111-113 °C (Found C, 58.4; H, 5.9; N, 7.9; $C_{17}H_{20}N_2O_4S$ requires C, 58.6; H, 5.8; N, 8.0 %); ν_{max}(KBr)/cm^{-1} 2978m, 2942s, 2887m, 1686s, 1594s, 1576s, 1504m, 1477s, 1381s, 1336s, 1253s, 1178s, 1156s; δ_H (500 MHz, 90 °C, DMSO-d_6, *syn* : *anti,* 7:1) (*syn*-epimer) 8.13 (2 H, d, J 7.5, 2 x H of *p*-nitrophenyl), 7.59 (2 H, d, J 7.5, 2 x H of *p*-nitrophenyl), 6.53 (1 H, s, HC=CH), 6.50 (1 H, s, HC=CH), 4.59 (1 H, s, C(1)H), 3.59 (1 H, s, C(7)H), 3.51 (1 H, dd, J 9.5 and 3.0, C(3)H *exo*), 3.24 (1 H, s, C(4)H), 2.64 (1 H, d, J 9.5, C(3)H *endo*), 1.41 (9 H, s, Bu^t), (*anti*-epimer) 8.13 (2 H, d, J 7.5, 2 x CH of *p*-nitrophenyl), 7.54 (2 H, d, J 7.5, 2 x CH of *p*-nitrophenyl), 6.39 (1 H, s, HC=CH), 6.38 (1 H, s, HC=CH), 4.71 (1 H, s, C(1)H), 3.86 (1 H, s, C(7)H), 3.54 (1 H, dd, J 9.5 and 3.0, C(3)H *exo*), 3.39 (1 H, s, C(4)H), 2.64 (1 H, d, J 9.5, C(3)H *endo*), 1.43 (9 H, s, Bu^t); δ_C (125 MHz, 90 °C, DMSO-d_6) (both isomers) 155.8 (C=O), 147.4, 146.4, 146.3, 146.1, 138.8, 136.3, 135.0, 133.3, 129.7, 129.0, 128.4, 124.7 (all C of *p*-nitrophenyl or C=C), 79.9, 79.8 (both CMe_3),

64.7, 64.1 (both C1), 63.5, 60.7 (both C7), 49.0, 47.6 (both C4), 47.0, 44.4 (both C3), 29.0 (C*Me*$_3$); m/z (EI$^+$) 348 (M$^+$, 35%), 292 (50), 275 (45), 231 (61), 219 (100), 199 (26), 194 (38), 189 (35), 171 (89) (Found M$^+$, 348.1149, $C_{17}H_{20}N_2O_4S$ requires 348.1144).

2-(Methoxycarbonyl)-7-*syn/anti*-(*p*-tolylthio)-2-azabicyclo[2.2.1]hept-5-ene 105b :

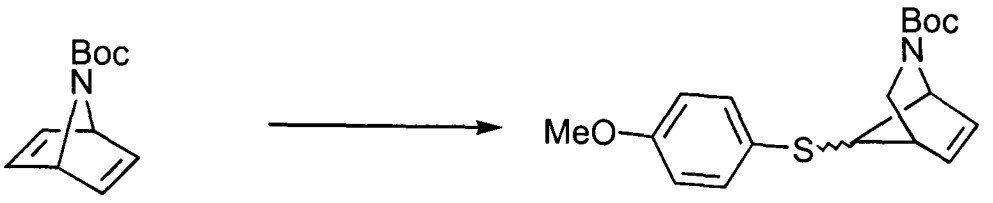


105b

Reaction of diene **239** (85 mg, 0.56 mmol) and *p*-thiocresol (66 mg, 0.53 mmol) according to the general procedure for 4 h at 20 °C gave a yellow oil. Column chromatography (SiO_2, 30% Et_2O : petroleum ether) gave **105b** as a colourless oil (96 mg, 66%): R_f (30% Et_2O : petroleum ether) 0.27; ν_{max}(thin film)/cm^{-1} 3068m, 2952m, 2887m, 1694s, 1492m, 1447s, 1386s, 1324m, 1305m, 1263m, 1190m, 1151m, 1106s; δ_H (500 MHz, 90 °C, DMSO-d$_6$, *syn* : *anti*, 4 : 1) (*syn* epimer) 7.30 (2 H, d, J 8.0, 2 x CH of aromatic), 7.16 (2 H, d, J 8.0, 2 x CH of aromatic), 6.48-6.45 (1 H, m, HC=CH), 6.43-6.40 (1 H, m, HC=CH), 4.52 (1 H, s, C(1)H), 3.62 (3 H, s, Me-O), 3.60 (1 H, dd, J 9.5 and 3.0, C(3)H *exo*), 3.28 (1 H, s, C(7)H), 3.10 (1 H, br s, C(4)H), 2.65 (1 H, d, J 9.5, C(3)H *endo*), 2.30 (3 H, s, Me-Ar), (*anti* epimer) 7.27 (2 H, d, J 8.0, 2 x CH of aromatic), 7.15 (2 H, d, J 8.0, 2 x CH of aromatic), 6.37-6.34 (1 H, m, HC=CH), 6.33-6.30 (1 H, m, HC=CH), 4.62 (1 H, s, C(1)H), 3.59 (3 H, s, Me-O), 3.53 (1 H, s, C(7)H), 3.48 (1 H, dd, J 9.0 and 3.0, C(3)H *exo*), 3.27 (1 H, s, C(4)H), 2.61 (1 H, d, J 9.0, C(3)H *endo*), 2.30 (3 H, s, Me-Ar); δ_C (125 MHz, 90 °C, DMSO-d$_6$) (both isomers) 156.7, 156.2 (both C=O),

139.0, 137.5, 137.3, 136.2, 135.3, 132.9, 132.7, 131.9, 131.7, 131.5, 130.6 (all C=C or C of aromatic), 66.1, 65.0 (both C7), 64.3, 63.7 (both C1), 52.8 (H_3C-O), 49.1, 47.8 (both C4), 47.1, 44.2 (both C3), 21.3 (H_3C-Ar); m/z (CI^+, NH_3) 276 ($M+H^+$, 3%), 154 (25), 132 (6), 108 (11), 91 (7), 52 (100) (Found M + H^+, 276.1053, $C_{15}H_{18}NO_2S$ requires 276.1058).

2-(*tert*-Butoxycarbonyl)-7-*syn/anti*-(4-methoxyphenylthio)-2-azabicyclo[2.2.1]hept-5-ene 105f :

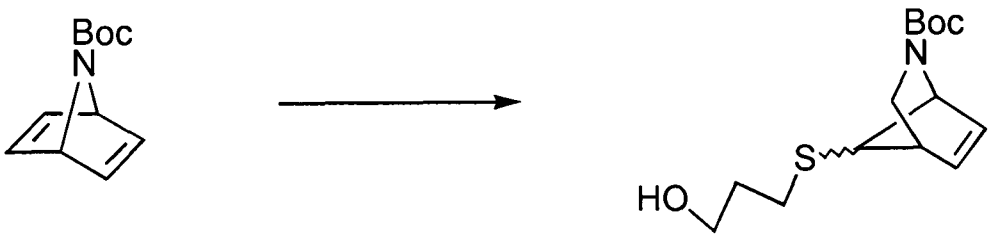


105f

Reaction of diene **67** (100 mg, 0.52 mmol) and *p*-methoxybenzenethiol (63 mg, 0.45 mmol) according to the general procedure for 24 h at 20 °C gave a yellow oil. Column chromatography (SiO_2, 10% Et_2O : petroleum ether to 20% Et_2O : petroleum ether, gradient elution) gave **105f** as a colourless oil (88 mg, 59%): R_f (20% Et_2O : petroleum ether) 0.18; ν_{max}(thin film)/cm^{-1} 3065w, 2973s, 2888m, 2835m, 1694s (C=O), 1592s, 1571m, 1495s, 1463m, 1393s, 1286s, 1246s, 1172s, 1150s, 1103s, 1031m, 886m, 867m, 844m, 829m; δ_H (500 MHz, 90 °C, DMSO-d_6, *syn* : *anti*, 2.5 : 1), (*syn* epimer) 7.37 (2 H, d, J 8.0, 2 x CH of aromatic), 6.83 (2 H, d, J 8.0, 2 x CH of aromatic), 6.45-6.38 (2 H, m, HC=CH), 4.52 (1 H, s, C(1)H), 3.78 (3 H, s, Me-O), 3.53 (1 H, dd, J 9.0 and 2.0, C(3)H *exo*), 3.17 (1 H, s, C(7)H), 3.03 (1 H, s, C(4)H), 2.59 (1 H, d, J 9.0, C(3)H *endo*), 1.43 (9 H, s, Bu^t), (*anti* epimer) 7.33 (2 H, d, J 8.5, 2 x CH of aromatic), 6.83 (2 H, d, J 8.0, 2 x CH of aromatic), 6.33-6.29 (2 H, m, HC=CH), 4.43 (1 H, s, C(1)H), 3.78 (3 H, s, Me-O), 3.41 (1 H, s, C(7)H), 3.38 (1 H, dd, J 9.5 and 2.0, C(3)H *exo*), 3.21 (1 H, s, C(4)H),

2.59 (1 H, d, J 9.5, C(3)H *endo*), 1.41 (9 H, s, Bu^t); δ_C (125 MHz, 90 °C, DMSO-d_6) (both epimers) 160.1, 160.0 (both aromatic C-O), 155.8, 155.4 (both C=O), 138.8, 135.8, 135.2, 134.6, 134.3, 132.8, 126.6, 125.6, 115.9 (all C=C or C of aromatic), 80.0, 79.5 (both *C*Me_3), 67.0 (C7), 64.9 (C1), 64.7 (C7), 63.9 (C1), 56.2 (H_3C-O), 49.2, 47.7 (Both C4), 47.3, 44.2 (Both C3), 29.0 (C*Me*$_3$); m/z (CI^+, NH_3) 334 ($M+H^+$, 12%), 295 (36), 278 (50), 234 (22), 217 (15), 162 (31), 147 (45), 124 (63), 110 (90), 96 (100) (Found M + H^+, 334.1474, $C_{18}H_{24}NO_3S$ requires 334.1477).

2-(*tert*-Butoxycarbonyl)-7-*syn/anti*-(3-hydroxypropylthio)-2-azabicyclo[2.2.1]hept-5-ene 105i :

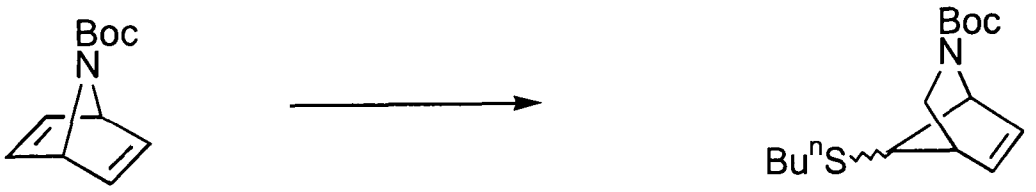


105i

Reaction of diene **67** (100 mg, 0.52 mmol) and 3-hydroxy-1-propanethiol (63 mg, 0.45 mmol) according to the general procedure for 24 h at 80 °C in benzene and removal of solvent gave a yellow oil. Column chromatography (SiO_2, Et_2O) gave **105i** as a colourless oil (72 mg, 56%): R_f (100% Et_2O) 0.23; ν_{max}(thin film)/cm^{-1} 3419br s, 3065w, 2970s, 2931s, 1694s, 1532m, 1490s, 1475s, 1420s, 1393s, 1367s, 1308m, 1258s, 1149s; δ_H (500 MHz, 90 °C, DMSO-d_6, *syn* : *anti,* 4 : 1) (*syn* epimer) 6.45-6.38 (2 H, m, HC=CH), 4.39 (1 H, s, C(1)H), 4.20-4.00 (1 H, br s, OH), 3.49 (2 H, t, J 7.0, CH_2-OH), 3.44 (1 H, dd, J 9.0 and 3.0, C(3)H *exo*), 3.01 (1 H, s, C(7)H), 2.92 (1 H, s, C(4)H), 2.62-2.58 (2 H, m, CH_2-S), 2.53 (1 H, d, J 8.0, C(3) *endo*), 1.73-1.68 (2 H, m, 2 x H of C*H*$_2$-CH_2OH), 1.42 (9 H, s, Bu^t), (*anti* epimer) 5.90-5.85 (2 H, s, HC=CH), 4.32 (1 H, s, C(1)H), 4.20-4.00 (1 H, br s,

OH), 3.55 (2 H, t, J 7.0, CH_2OH), 3.51 (1 H, dd, J 9.0 and 3.0, C(3)H *exo*), 2.96 (1 H, s, C(7)H), 2.85 (1 H, s, C(4)H), 2.68-2.65 (2 H, m, CH_2-S), 2.53 (1 H, d, J 8.0, C(3) *endo*), 1.81-1.73 (2 H, m, C*H*$_2$-CH_2-OH), 1.40 (9 H, s, Bu^t); δ_C (125 MHz, 90 °C, DMSO-d_6) (both epimers) 155.8 (C=O), 138.8, 136.2, 135.0, 131.5 (all C=C), 79.6, 78.8 (both *C*Me_3), 67.9 (CH_2-O), 64.9(C1), 62.0 (*C*H_2-O), 60.5, 60.3 (both C7), 51.0, 47.9 (both C4), 44.9, 44.2 (both C3), 34.1, 31.7 (both CH_2-S), 29.5 (C*Me*$_3$), 29.1 (*C*-CH_2-O), 28.8 (C*Me*$_3$), 28.0 (*C*-CH_2-O); m/z (CI^+, NH_3) 286 ($M+H^+$, 25%), 247 (18), 230 (90), 196 (17), 157 (87), 140 (46), 94 (100), 80 (18), 56 (32) (Found $M + H^+$, 286.1478, $C_{14}H_{24}NO_3S$ requires 286.1477).

2-(*tert*-Butoxycarbonyl)-7-*syn/anti*-(*n*-butylthio)-2-azabicyclo[2.2.1]hept-5-ene 105g :

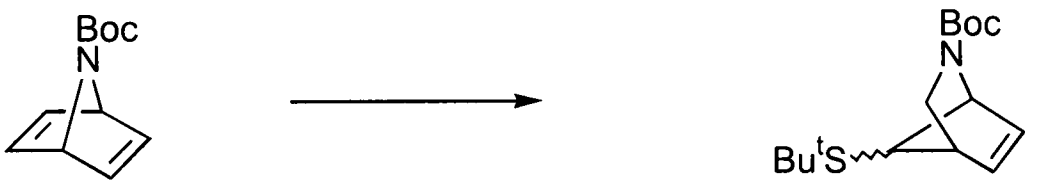


105g

Reaction of diene **67** (75 mg, 0.39 mmol) and *n*-butanethiol (27 mg, 0.3 mmol) according to the general procedure for 6 h at 80 °C in toluene and removal of solvent gave a yellow oil. Column chromatography (SiO_2, 15% Et_2O : petroleum ether) gave **105g** as a colourless oil (50 mg, 59%): R_f (20% Et_2O : petroleum ether) 0.21; ν_{max}(thin film)/cm^{-1} 3067w, 2961s, 2931s, 2888m, 1694s, 1478m, 1456m, 1391s, 1364s, 1308m, 1256s, 1177s, 1151s, 1101s, 886m, 864m, 848m; δ_H (500 MHz, 90 °C, DMSO-d_6, *syn* : *anti,* 4:1), (*syn* epimer) 6.45-6.39 (2 H, m, HC=CH), 4.39 (1 H, s, C(1)H), 3.43 (1 H, dd, J 9.0 and 3.0, C(3)H *exo*), 2.99 (1 H, s, C(4)H superposed on H_2O), 2.92 (1 H, s, C(7)H), 2.59-2.46 (3 H, m, CH_2-S and C(3)H

endo), 1.60-1.48 (2 H, m, C*H*$_2$-CH$_2$-S), 1.41 (9 H, s, Bu^t), 1.40-1.33 (2 H, m, C*H*$_2$-CH$_3$), 0.94-0.86 (3 H, m, Me); (*anti* epimer) 6.29-6.21 (2 H, m, HC=CH), 4.50 (1 H, s, C(1)H), 3.36 (1 H, dd, J 9.0 and 3.0, C(3)H *exo*), 3.14 (1 H, s, C(7)H), 3.12 (1 H, s, C(4)H), 2.59-2.46 (3 H, m, CH$_2$-S and C(3)H *endo*), 1.60-1.48 (2 H, m, C*H*$_2$-CH$_2$-S), 1.40 (9 H, s, Bu^t), 1.40-1.33 (2 H, m, C*H*$_2$-CH$_3$), 0.94-0.86 (3 H, m, Me); δ_C (125 MHz, 90 °C, DMSO-d$_6$) (both epimers) 155.9, 155.4 (C=O), 138.9, 135.7, 135.4, 132.8 (all C=C), 80.0, 79.3 (both *C*Me$_3$), 65.3, 64.4 (both C1), 63.7, 62.1 (both C7), 49.4, 48.0 (both C4), 47.3, 44.3 (both C3), 32.7, 32.3, 31.7 (*C*H$_2$-CH$_2$-S and CH$_2$-*C*H$_2$-S superposed), 29.0 (C*Me$_3$*), 22.0 (*C*H$_2$-CH$_3$), 14.1 (CH$_2$-*C*H$_3$); m/z (EI$^+$) 283 (M$^+$, 18%), 227 (24), 210 (39), 194 (16), 170 (100), (Found M$^+$, 283.1602, $C_{15}H_{25}NO_2S$ requires 283.1606).

2-(*tert*-Butoxycarbonyl)-7-*syn/anti*-(*t*-butylthio)-2-azabicyclo[2.2.1]hept-5-ene 105h :

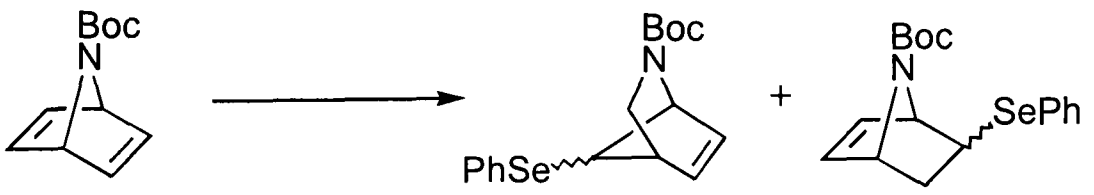


105h

Reaction of diene **67** (97 mg, 0.50 mmol) and 2-methyl-2-propanethiol (43 mg, 0.47 mmol) according to the general procedure for 24 h at 80 °C in toluene and removal of solvent gave a yellow oil. Column chromatography (SiO_2, 15% Et_2O : petroleum ether) gave **105h** as a colourless oil (64 mg, 48%): R_f(20% Et_2O : petroleum ether) 0.21; ν_{max}(thin film)/cm^{-1} 3046w, 2965s, 2890s, 2864m, 1693s, 1475s, 1459s, 1364s, 1364s, 1328m, 1306m, 1257s, 1179s, 1154s, 1091s, 1074m, 888m, 866s, 846m; δ_H (500 MHz, 90 °C, DMSO-d$_6$, *syn* : *anti*, 5 : 1) (*syn* epimer) 6.47-6.40 (2 H, m, HC=CH), 4.34 (1 H, s, C(1)H), 3.38 (1 H, dd, J 9.0 and 3.0, C(3)H *exo*), 2.95

(1 H, s, C(7)H), 2.93 (1 H, s, C(4)H), 2.50 (1 H, d, J 9.0, C(3)H *endo*),1.42 (9 H, s, O-Bu^t) 1.31 (9 H, s, S-Bu^t); (*anti* epimer) 6.29-6.22 (2 H, m, HC=CH), 4.48 (1 H, s, C(1)H), 3.42 (1 H, dd, J 9.0 and 3.0, C(3)H *exo*), 3.13 (1 H, s, C(7)H), 2.99 (1 H, s, C(4)H superposed on H_2O), 2.51 (1 H, d, J 9.0, C(3)H *endo*), 1.41 (9 H, s, O-Bu^t), 1.28 (9 H, s, S-Bu^t); δ_C (125 MHz, 90 °C, DMSO-d_6) (both epimers) 155.8 (C=O), 139.0, 136.2, 135.5, 133.1 (all C=C), 79.5, 79.3 (both C(O)*C*Me$_3$), 66.0, 65.7 (both C1), 60.3, 59.0 (both C7), 50.4, 49.2 (both C4), 47.3, 44.4 (both C3), 43.2, 42.9 (both S-*C*Me$_3$), 32.1 32.0, (both S-C*Me$_3$*), 29.0, 28.9 (O-C*Me$_3$*); m/z (EI$^+$) 283 (M$^+$, 3%), 170 (10), 137 (30), 126 (7), 97 (72), 84 (40), 57 (100) (Found M$^+$, 283.1603, $C_{15}H_{25}NO_2S$ requires 283.1606).

2-(*tert*-Butoxycarbonyl)-7-*syn/anti*-(phenylselenyl)-2-azabicyclo[2.2.1]hept-5-ene 111 and 7-(*tert*-butoxycarbonyl)-2-*exo/endo*-(phenylselenyl)-7-azabicyclo[2.2.1]hept-5-ene 110 :



111 **110**

Benzeneselenol (71 mg, 0.45 mmol) was added to a solution of diene **67** (99 mg, 0.51 mmol) in toluene under argon and the reaction was stirred at room temperature for 24 h. Removal of solvent at reduced pressure gave a yellow oil. Column chromatography (SiO_2, 15% Et_2O : 85% petroleum ether) first gave selenide **110** as a colourless oil which crystallised on standing to a white solid (19 mg, 12 %): R_f (30% Et_2O : 70% petroleum ether) 0.40; mp (from light petroleum) 70-72 °C; ν_{max}(thin film)/cm^{-1} 3045w, 2792s, 2926s, 1688s, 1578m, 1477m, 1436m, 1368s, 1285m, 1233w, 1169m, 1097m, 846m, 737m; δ_H (400 MHz, *exo* : *endo*, 1:6), (*endo*

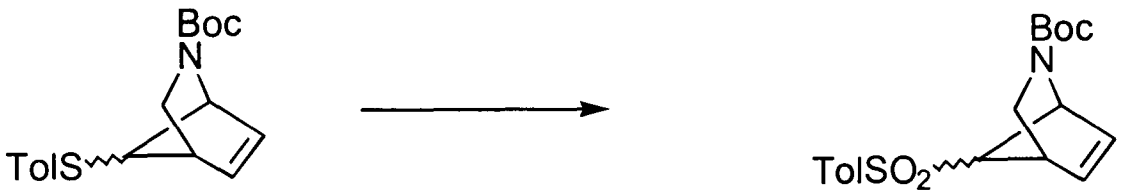
epimer) 7.55-7.51 (2 H, m, 2 x H of Ph), 7.31-7.23 (3 H, m, 3 x H of Ph), 6.40 (2 H, br s, 2 x HC=C), 4.81-4.60 (2 H, m, C(1)H and C(4)H), 3.64 (1 H, br s, C(2)H), 2.49 (1 H, br s, C(3)H *exo*), 1.44 (9 H, s, Bu^t), 1.10 (1 H, dd, J 12.0 and 4.0, C(3)H *endo*); (*exo* epimer) 7.55-7.51 (2 H, m, 2 x H of Ph), 7.31-7.23 (3 H, m, 3 x H of Ph), 6.22 (2 H, br s, 2 x HC=C), 4.81-4.60 (2 H, m, C(1)H and C(4)H), 3.48 and 3.40 (1 H, 2 x br s, C(2)H), 1.82 (1 H, br s, C(3)H *exo*), 1.44 (9 H, s, Bu^t), 1.10 (1 H, dd, J 12.0 and 4.0, C(3)H *endo*); δ_C (100 MHz) (*endo*-epimer observed only - *exo* too weak to appear in ^{13}C spectrum) 154.5 (C=O), 135.8, 133.9, 132.8, 130.1, 129.2, 127.1 (all C=C or C of Ph), 80.3 (CMe_3), 62.2, 60.5 (C1 and C4), 38.0 (C2), 34.5 (C3), 29.0 (Bu^t); m/z (FAB^+, NOBA Matrix) 374 ($M+Na^+$, 30%), 352 ($M+H^+$, 65%), 296 (100), 194 (62), 167 (68), 149 (77), 121 (56), 105 (75), (Found $M + H^+$, 352.0817, $C_{17}H_{22}NO_2Se$ requires 352.0815).

Second to elute was **111** as a colourless oil which crystallised on standing to a white solid (128 mg, 81%): R_f (30% Et_2O : petroleum ether) 0.27; mp (from petroleum ether) 58-59°C (Found, C, 57.9; H, 6.1; N, 4.0; $C_{17}H_{21}NO_3Se$ requires C, 58.3; H, 6.0; N 4.0); ν_{max}(thin film)/cm^{-1} 3064m, 2975m, 2937m, 1700s, 1578m, 1487s, 1392m, 1293s, 1253s, 1153s,1096m; δ_H (500 MHz, 90 °C, DMSO-d_6, *syn* : *anti,* 3:1) (*syn* epimer) 7.57-7.49 (2 H, m, 2 x CH of Ph), 7.35-7.28 (3 H, m, 3 x CH of Ph), 6.48-6.40 (2 H, m, HC=CH), 4.52 (1 H, s, C(1)H), 3.57 (1 H, dd, J 9.5 and 3.0, C(3) *exo*), 3.40 (1 H, s, C(7)H), 3.14 (1 H, s, C(4)H), 2.63 (1 H, d, J 9.5, C(3)H *endo*), 1.43 (9 H, s, Bu^t); (*anti* epimer) 7.57-7.49 (2 H, m, 2 x CH of Ph), 7.35-7.28 (3 H, m, 3 x CH of Ph), 6.40-6.33 (2 H, m, HC=CH), 4.68 (1 H, s, C(1)H), 3.43 (1 H, s, C(7)H), 3.40 (1 H, dd, J 9.5 and 3.0, C(3)H *exo*), 3.35 (1 H, s, C(4)H), 2.57 (1 H, d, J 9.0, C(3)H *endo*), 1.41 (9 H, s, Bu^t); δ_C (125 MHz, 90°C, DMSO-d_6) (both isomers) 155.8, 155.3 (C=O), 139.0, 137.4, 136.9, 135.5, 134.0, 133.9, 133.7,

133.6, 130.1, 129.9, 128.1, 127.9 (all C=C or C of Ph), 80.1, 79.6 (CMe_3), 65.6, 64.8 (C1), 61.2, 59.3 (C7), 50.2, 48.4 (C4), 47.2, 44.8 (C3), 29.0, 28.9 (CMe_3); m/z (EI^+) 351 (M^+, 2%), 222 (4), 220 (2), 194 (9), 184 (10), 171 (6), 157 (18), 138 (69), 120 (10), 94 (83), 84 (27), 77 (33) 65 (28), 57 (100), 49 (24), 41(41) (Found M^+, 351.0736 $C_{17}H_{21}NO_3Se$ requires 351.0737).

Other compounds synthesised by non-literature procedures:

2-(*tert*-Butoxycarbonyl)-7-*syn/anti*-(*p*-tolylsulfonyl)-2-azabicyclo[2.2.1]hept-5-ene 109 :

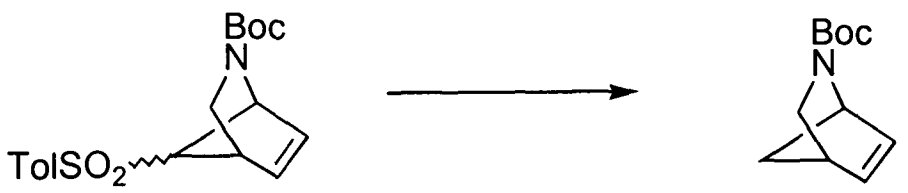


109

Peracetic acid (1.77 cm^3 of 36-40% solution in water, 9.5 mmol) was added to a mixture of sulfide **105a** (500 mg, 1.57 mmol), NaOAc (290 mg, 3.53 mmol) and Na_2HPO_4 (4.5 g, 31 mmol) in CH_2Cl_2 (50 cm^3) at 0 °C. The reaction was stirred at 0 °C for 6 h and then at 20 °C for 14 h. Water (50 cm^3) was added and the aqueous layer extracted with CH_2Cl_2 (3 x 50 cm^3). The combined organic extracts were washed with sodium bisulfite solution (50 cm^3), brine (50 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure to give a white solid. Column chromatography (SiO_2, Et_2O) gave **109** as a white solid (500 mg, 91%): R_f (50% Et_2O : petroleum ether) 0.28; mp (from Et_2O) 110-112 °C (Found, C, 61.7; H, 6.7; N, 4.0; $C_{18}H_{23}NO_4S$ requires C, 61.7; H, 6.6; N, 4.0 %); ν_{max}(KBr)/cm^{-1} 2963s, 2892m, 1688s, 1597s, 1408s, 1364s, 1260s, 1120s, 1068s; δ_H (500 MHz, 90 °C, DMSO-d_6, *syn* : *anti,* 3 : 1) (*syn* epimer) 7.77 (2 H, d, J 8.0, 2 x CH of aromatic),

7.47 (2 H, d, J 8.0, 2 x CH of aromatic), 6.50-6.47 (1 H, m, 1 x HC=C), 6.41-6.38 (1 H, m, 1 x HC=C), 4.66 (1 H, br s, C(1)H), 3.72 (1 H, dd, J 9.0 and 3.0, C(3)H *exo*), 3.39 (1 H, s, C(4)H), 3.31 (1 H, s, C(7)H), 2.52 (1 H, d, J 9.0, C(3)H *endo*), 2.45 (3 H, s, Me), 1.42 (9 H, s, Bu^t), (minor isomer) 7.69 (2 H, d, J 8.0, 2 x CH of aromatic), 7.46 (2 H, d, J 8.0, 2 x CH of aromatic), 6.20-6.17 (2 H, m, HC=CH), 4.67 (1 H, s, C(1)H), 3.79 (1 H, s, C(7)H), 3.39 (1 H, s, C(4)H), 3.37 (1 H, dd, J 9.5 and 3.0, C(3)H *exo*), 2.52 (1 H, d, J 9.0, C(3)H *endo*), 2.44 (3 H, s, Me), 1.38 (9 H, s, Bu^t); δ_C (125 MHz, 90 °C, DMSO-d_6) (both isomers) 155.8 (C=O), 145.4, 145.2, 139.2, 138.3, 137.3, 134.9, 134.4, 130.9, 130.7, 128.8, 128.7 (all C=C or C of aromatic), 80.6 (C7), 80.1, 79.7 (both CMe_3), 75.4 (C7), 62.2, 60.8 (both C1), 47.7 (C3), 45.9, 45.1 (both C4) , 44.1 (C3), 29.1, 29.0 (both CMe_3), 21.8 (Me-Ar); m/z (CI^+, NH_3) 367 ($M+NH_4^+$, 18%), 350 ($M+H^+$, 7), 311 (100), 250 (10), 238 (8), 201 (23), 189 (23), 157 (14), 140 (9), 113 (6), 96 (17) (Found $M+H^+$, 350.1429, $C_{18}H_{24}NO_4S$ requires 350.1426).

2-(*tert*-Butoxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene[71] 44 by desulfonylation :



44

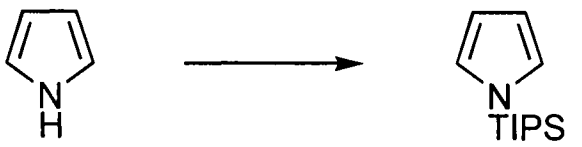
Freshly prepared 6% Na-Hg (3.76 g, 9.8 mmol Na), and Na_2HPO_4 (1.5 g, 10.5 mmol) were added to a stirred solution of sulfones **109** (376 mg, 1.07 mmol) in anhydrous methanol (10 cm^3) under argon at −10 °C. The reaction was warmed to 25 °C over 3 h and left for a further 9 h at 25 °C. Water (10 cm^3) was added and the mixture filtered. The filtrate was extracted with CH_2Cl_2 (3 x 20 cm^3), the combined extracts dried ($MgSO_4$) and the solvent removed at reduced pressure to give an oil.

Chromatography (SiO_2, 15% Et_2O : cyclohexane) gave the carbamate **44** as a clear colourless oil (73 mg, 33%): R_f (50% Et_2O: petroleum ether) 0.63; δ_H (400 MHz) (3 : 2 mixture of rotamers) 6.35 and 6.27 (2H, 2 x s, 2 x HC=C), 4.71 and 4.57 (1 H, 2 s, C(1)H), 3.30 (1 H, dd, J 9.0 and 3.0, C(3)H *exo*), 3.16 (1 H, s, C(4)H), 2.68-2.48 (1 H, m, C(3)H *endo*), 1.68-1.50 (2 H, m, CH_2), 1.44 (9 H, s, Bu^t); δ_C (125 MHz, mixture of rotamers) 155.8, 155.6 (C=O), 136.5 (C5), 134.4, 133.7 (C6), 78.9 (CMe_3), 61.1, 59.9 (C1), 48.0 (C7), 46.2, 45.8 (C7), 43.4, 42.9 (C4), 28.4 (CMe_3).

Experimental - Chapter Four

Pyrroles:

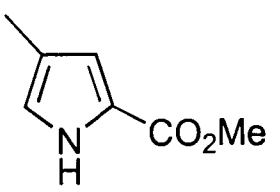
N-Triisopropylpyrrole 162 :[97]



162

A solution of pyrrole (2.58 cm^3, 37.2 mmol) in anhydrous DMF (50 cm^3) was added to a suspension of NaH (1.63 g of a 60% dispersion, 40.9 mmol) in DMF (20 cm^3) at 0 °C. When evolution of hydrogen had ceased, triisopropylsilyl chloride (7.95 cm^3, 37.2 mmol) was added dropwise and stirring continued for 45 min. The mixture was then partitioned between Et_2O (100 cm^3) and water (100 cm^3). The organic layer was then washed with water (100 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Column chromatography (SiO_2, petroleum ether to 10% Et_2O : 90% petroleum ether) gave the pyrrole **162** as a colourless oil (5.7g, 69% (lit.[97] 99%)). Data in accordance with the literature.

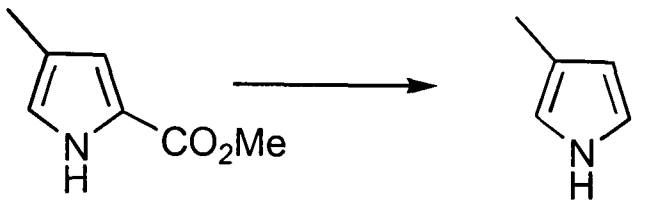
Methyl 4-methyl pyrrole-2-carboxylate 158 :[92]



158

Prepared according to the method of Cornforth starting from commercially available 3-ethoxymethacrolein (10 g, 88 mmol) and hippuric acid (16.6 g, 93 mmol) as a white solid (2.4 g, 20 %, lit.[92] 45%): δ_H (200 MHz) 9.10 (1 H, br s, NH), 6.80-6.70 (2 H, m, C(3)H and C(5)H), 3.84 (3 H, s, MeO), 2.10 (3 H, s, Me).

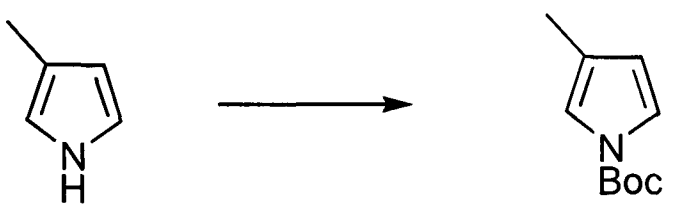
3-Methylpyrrole 159 :[92]



159

The ester **158** (2.4 g, 17 mmol) was heated at reflux in 2M aq. NaOH (25 cm^3) until completely dissolved, then allowed to cool and acidified to pH 1 by dropwise addition of 10 M HCl. The precipitate of the carboxylic acid (2.2 g, quantitative yield) was collected by filtration. The acid was then heated in sulfolane (2.2 cm^3) to 170 °C and the product **159** collected by atmospheric pressure distillation: (100 mg, 7 %, lit.[92] 90%): bp 131-132 °C; δ_H (200 MHz) 8.25-7.60 (1 H, br s, NH), 6.85-6.75 (1 H, m, C(5)H), 6.65 (1 H, s, C(2)H), 6.22 (1 H, s, C(4)H), 2.30 (3 H, s, Me). This unstable product was Boc-protected immediately.

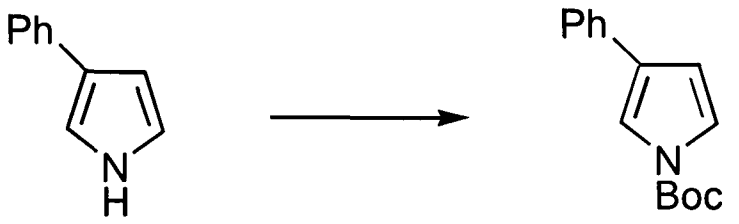
1-(*tert*-Butoxycarbonyl)-3-methylpyrrole 160 :[94]



160

DMAP (20 mg, 0.16 mmol) and Boc_2O (420 mg, 1.9 mmol) were added to a solution of **159** (130 mg, 1.60 mmol) in MeCN (1.5 cm^3) and the reaction stirred at 25 °C for 24 h under argon. The solvent was removed at reduced pressure to give an oil which was subjected to column chromatography (SiO_2, 10% Et_2O : 90% petroleum ether), giving the pyrrole **160** as a colourless oil (176 mg, 61%, lit.[94] 49%): δ_H (200 MHz, $CDCl_3$) 7.18-7.12 (1 H, m, C(5)H), 6.99 (1 H, s, C(2)H), 6.10-6.04 (1 H, m, C(4)H), 2.10 (3 H, s, Me), 1.60 (9 H, s, Bu^t).

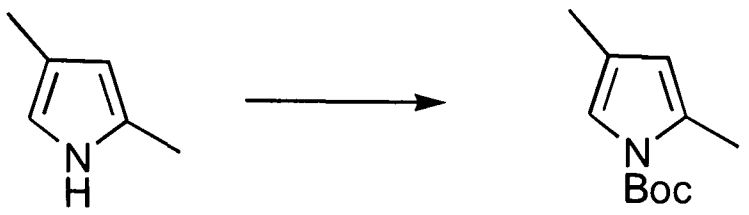
1-(*tert*-Butoxycarbonyl)-3-phenylpyrrole 170 :



170

DMAP (68 mg, 0.56 mmol) was added to a stirred solution of Boc_2O (1.47 g, 6.71 mmol) and 3-phenylpyrrole **169**[98] (800 mg, 5.60 mmol) in acetonitrile (5 cm^3) and CH_2Cl_2 (2 cm^3) and the reaction stirred under argon at 25 °C for 16 h. Imidazole (340 mg, 5 mmol) was added and the solution stirred for 15 min according to the procedure of Basel and Hassner[121] for removal of Boc_2O. CH_2Cl_2 (15 cm^3) was added and the solution was washed with 0.5 % aq. HCl (3 x 20 cm^3). The organic layer was separated, dried ($MgSO_4$) and the solvent was removed at reduced pressure. Column chromatography (SiO_2, petroleum ether to 5% Et_2O : petroleum ether, gradient elution) gave the pyrrole **170** as a yellow gum (1.20 g, 88%): R_f (10% Et_2O : 90% petroleum ether) 0.30; ν_{max}(thin film)/cm^{-1} 3061m, 2980s, 2934m, 1743s, 1502m, 1478m, 1450m, 1393s, 1369s, 1356s, 1285s, 1258s, 1151s, 974m, 849m, 757m; δ_H (400 MHz) 7.56 (3 H, m, 2 x CH of Ph and C(2)H), 7.40 (2 H, m, 2 x CH of Ph), 7.31 (1 H, s, C(5)H), 7.27 (1 H, m, CH of Ph), 6.57 (1 H, m, C(4)H), 1.64 (9 H, s, Bu^t); δ_C (100 MHz), 148.8 (C=O), 134.3, 128.7, 127.8, 126.5, 125.5, 120.9, 115.7, 110.4 (all Ar), 83.8 (CMe_3), 28.0 (CMe_3); m/z (EI^+) 243 (M^+,4%), 187 (32), 143 (M-Boc^+, 52), 115 (41), 89 (9), 63 (6), 57 (100), 41 (43) (Found: $M+H^+$, 244.1337, $C_{15}H_{17}NO_2$ requires 244.1337).

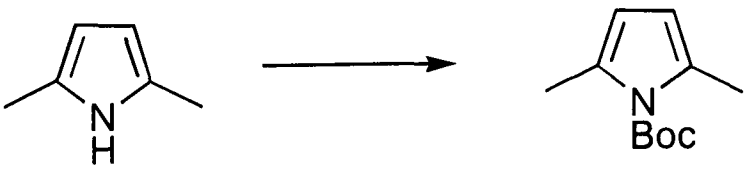
1-(*tert*-Butoxycarbonyl)-2,4-dimethylpyrrole 181 :



181

DMAP (180 mg, 1.5mmol) was added to a stirred solution of Boc_2O (650 mg, 3.00 mmol) and 2,4-dimethylpyrrole (500 mg, 5.25 mmol) in MeCN (5 cm^3) and the reaction stirred under argon at 25 °C for 16 h. The solvent was then removed at reduced pressure. Column chromatography (SiO_2, 3% Et_2O : petroleum ether) gave the pyrrole **181** as a colourless oil (325 mg, 55%): R_f (10% Et_2O : petroleum ether) 0.70; ν_{max}(thin film)/cm^{-1} 3153m, 3123m, 3089m, 2978s, 2929s, 2750m,1736s, 1607m, 1535s, 1479s, 1456s, 1432s, 1391s, 1340s, 1257s, 1169s, 1095s, 1039m, 1005m, 989m, 968m, 859s, 848s, 802s; δ_H (400 MHz) 6.93 (1 H, s, C(5)H), 5.79 (1 H, s, C(3)H), 2.40 (3 H, s, Me-C(2)), 2.01 (3 H, s, Me-C(4)), 1.59 (9 H, s, Bu^t); δ_C (100 MHz, $CDCl_3$), 149.6 (C=O), 131.6, 120.4, 117.5, 114.2 (all pyrrole C), 82.7 (CMe_3), 28.0 (CMe_3), 15.4 (H_3C-C(2)), 11.7 (H_3C-C(4)); m/z (CI^+, NH_3) 196 ($M+H^+$, 52%), 152 (7), 149 (17), 136 (4), 131(8), 96 ($M-Boc^+$, 52), 71 (5) (Found, $M+H^+$, 196.1328, $C_{11}H_{18}NO_2$ requires 196.1338).

1-(*tert*-Butoxycarbonyl)-2,5-dimethylpyrrole 183 :[101]

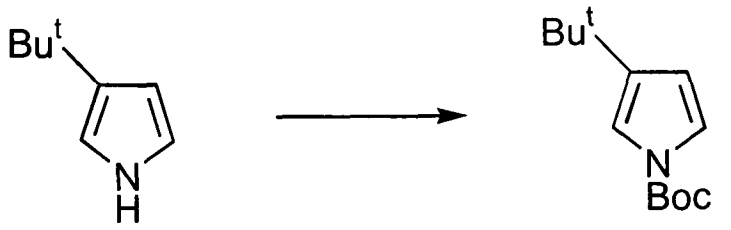


183

DMAP (321 mg, 2.6 mmol) was added to a stirred solution of Boc_2O (6.9 g, 32 mmol) and 2,5-dimethylpyrrole (2.5 g, 26 mmol) in MeCN (25 cm^3) and the

reaction stirred under argon at 25 °C for 16 h. The solvent was then removed at reduced pressure. Column chromatography (petroleum ether to 5% Et_2O : petroleum ether, gradient elution) gave the pyrrole **183** as a colourless oil (3.2 g, 63%): R_f (10% Et_2O : petroleum ether) 0.72; δ_H (200 MHz) 5.80 (2 H, s, C(3)H and C(4)H), 2.40 (6 H, s, 2 x Me), 1.60 (9 H, s, Bu^t).

1-(*tert*-Butoxycarbonyl)-3-*tert*-butylpyrrole 177 :

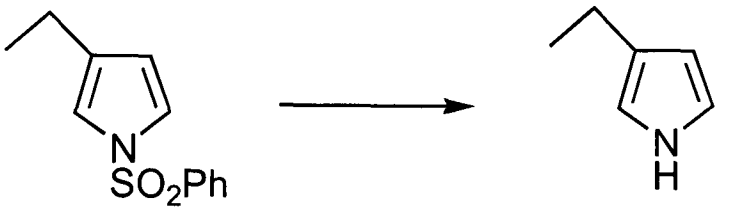


177

DMAP (160 mg, 1.3 mmol) was added to a stirred solution of Boc_2O (3.38 g, 15.7 mmol) and 3-*tert*-butylpyrrole[96] **172** (1.62 g, 13.1 mmol) in MeCN (12 cm^3) and the reaction stirred for 72 h under argon at 25 °C. Imidazole (1.06 g, 15.7 mmol) was added and the solution stirred for 15 min according to the procedure of Basel and Hassner[121] for removal of Boc_2O. CH_2Cl_2 (15 cm^3) was added and the solution washed with 0.5 % aq. HCl (3 x 30 cm^3). The organic layer was separated, dried ($MgSO_4$) and the solvent was removed at reduced pressure. Column chromatography (SiO_2, petroleum ether to 2.5% Et_2O : petroleum ether) gave the pyrrole **177** as a yellow oil (1.61 g, 54%): R_f (10% Et_2O : petroleum ether) 0.75; an analytical sample was prepared by Kugelrohr distillation (bp 100 °C at 10 mmHg): ν_{max}(thin film)/cm^{-1} 3151m, 3102m, 2961s, 2904s, 2869s, 1740s 1560m, 1488s, 1479s, 1462s, 1396s, 1348s, 1276s, 1239s, 1158s, 1102m, 1073s, 1024m, 974s, 949m, 856m, 829m; δ_H (400 MHz) 7.17 (1 H, s, C(5)H), 6.99 (1 H, s, C(2)H), 6.18 (1 H, s, C(4)H), 1.59 (9 H, s, Bu^t-O), 1.24 (9 H, s, Bu^t-C) ; δ_C (100 MHz), 149.0 (C=O), 138.7, 120.0, 114.2, 110.7 (all C of pyrrole), 83.1 (O-*C*Me_3), 31.0 (O-

C*Me*$_3$), 30.6 (C-*C*Me$_3$), 28.0 (C-C*Me*$_3$); m/z (CI$^+$, NH$_3$) 224 (M+H$^+$, 32%), 180 (3), 149 (14), 124 (M-Boc$^+$, 100), 108 (18) (Found, M+H$^+$, 224.1648, $C_{13}H_{22}NO_2$ requires 224.1651).

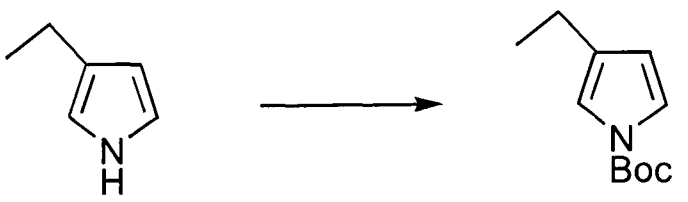
3-Ethylpyrrole 174 :[122]



174

A solution of 3-ethyl-1-phenylsulfonylpyrrole **178**[100] (1.60 g, 6.8 mmol) in methanol (26 cm^3) was added to a solution of 5 M NaOH (13 cm^3) and the mixture heated to reflux for 2.5 h under argon. The mixture was allowed to cool and extracted with EtOAc (3 x 50 cm^3). The combined organic extracts were washed with brine (100 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure to give spectroscopically pure **174** (520 mg, 80%): δ_H (200 MHz), 8.20-7.80 (1 H, br s, NH), 6.79-6.77 (1 H, m, C(5)H), 6.65 (1 H, s, C(2)H), 6.20 (1 H, s, C(4)H), 2.61 (2 H, q, J 8.0, CH_2), 1.31 (3 H, t, J 8.0, Me). The material was Boc-protected[93] immediately.

1-(*tert*-Butoxycarbonyl)-3-ethylpyrrole 179 :



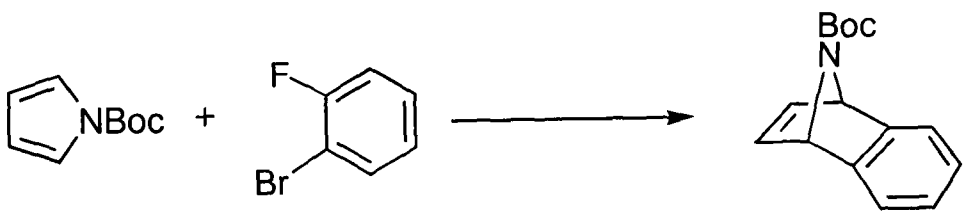
179

DMAP (256 mg, 2.1 mmol) was added to a stirred solution of Boc_2O (5.45 g, 25 mmol) and 3-ethylpyrrole **174**[122] (1.98 g, 21 mmol) in acetonitrile (20 cm^3) and the reaction left to stir for 24 h under argon at 25 °C. Imidazole (3.0 g, 44 mmol) was

added and the solution stirred for 15 min according to the procedure of Basel and Hassner[121] for removal of Boc_2O. CH_2Cl_2 (25 cm^3) was added and the solution washed with 0.5 % aq. HCl (3 x 50 cm^3). The organic layer was separated, dried ($MgSO_4$) and the solvent was removed at reduced pressure. Column chromatography (SiO_2, 3% Et_2O : petroleum ether) gave the pyrrole **179** as a yellow oil (2.58 g, 54%): R_f (10% Et_2O : petroleum ether) 0.67. An analytical sample was prepared by Kugelrohr distillation (bp 80°C at 10 mmHg). ν_{max}(thin film)/cm^{-1} 3148m, 3101m, 2969s, 2934s, 2874s, 1741s 1561m, 1489s, 1461s, 1404s, 1371s, 1313s, 1243s, 1162s, 1122s, 1071s, 1050m, 971s, 933m, 854s, 829m, 772s; δ_H (400 MHz) 7.17 (1 H, s, C(5)H), 7.00 (1 H, s, C(2)H), 6.18 (1 H, s, C(4)H), 2.47 (2 H, q, J 7.5, CH_2), 1.60 (9 H, s, Bu^t), 1.20 (3 H, t, J 7.5, Me); δ_C (100 MHz), 149.0 (C=O), 129.6, 120.0, 115.9, 112.6 (all pyrrole C), 83.1 (CMe_3), 28.0 (CMe_3), 20.0 (CH_2), 14.5 (Me); m/z (CI^+, NH_3) 196 ($M+H^+$, 100%), 152 (13), 149 (19), 140 (4), 96 ($M\text{-}Boc^+$, 100), 80 (9), 71 (3) (Found, $M+H^+$, 196.1329, $C_{11}H_{18}NO_2$ requires 196.1338).

Benzyne Cycloadducts:

***N*-(*tert*-Butoxycarbonyl)-1,4-dihydro-1,4-iminonaphthalene 138 :**[86]

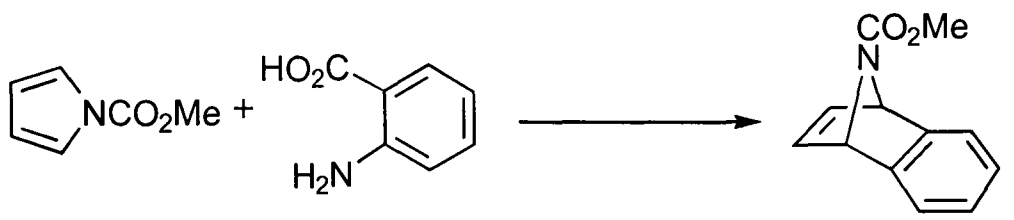


138

This compound was prepared according to the method of Carpino from *o*-bromofluorobenzene and *N*-Boc pyrrole in the presence of magnesium in 58% yield (lit.[86] 58%): mp 71-72 °C (lit. 72-73 °C); R_f 0.30 (30% Et_2O : petroleum ether); δ_H

(200 MHz) 7.30-7.21 (2 H, m, 2 x CH of aromatic), 7.02-6.92 (4 H, m, 2 x CH of aromatic and HC=CH), 5.50 (2 H, s, C(1)H and C(4)H), 1.40 (9 H, s, Bu^t).

_N_-Methoxycarbonyl-1,4-dihydro-1,4-iminonaphthalene 146 :[91]

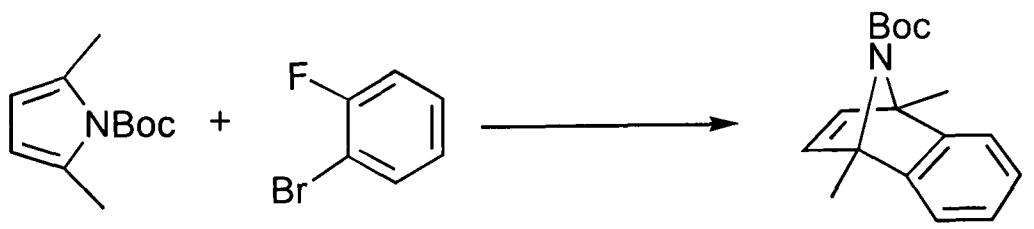


146

This compound was prepared according to the literature from anthranilic acid and commercially available *N*-methoxycarbonylpyrrole in 49% yield; R_f 0.23 (20% Et_2O : petroleum ether); δ_H (200 MHz) 7.33-7.20 (2 H, m, 2 x CH of aromatic), 7.05-6.90 (4 H, m, 2 x CH of aromatic and HC=CH), 5.58 (2 H, s, C(1)H and C(4)H), 3.62 (3 H, s, MeO).

_N_-(*tert*-Butoxycarbonyl)-1,4-dimethyl-1,4-dihydro-1,4-iminonaphthalene 184

:[101]

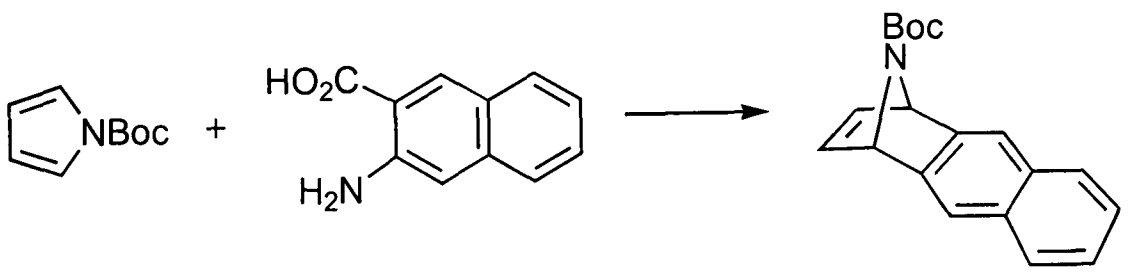


184

This compound was prepared in analogous fashion to **138**. Magnesium turnings (102 mg, 4.26 mmol) was activated with 30 μL of 1,2-dibromoethane in THF (1.2 cm^3). 1-(*tert*-butoxycarbonyl)-2,5-dimethylpyrrole **183** (770 mg, 3.94 mmol) in THF was added using a dropping funnel and the mixture heated to reflux. One quarter of a solution of *o*-bromofluorobenzene (433 μL, 3.94 mmol) in THF (12 cm^3) was added to initiate the reaction (darkening) and the remainder was added dropwise to maintain reflux. The mixture was left at reflux for 90 min after

completion of the addition and then allowed to cool to room temperature. A solution of ammonium chloride (1.75 g) in water (6 cm^3) was added with stirring and the mixture partitioned between Et_2O (50 cm^3) and water (50 cm^3). The aqueous layer was extracted with Et_2O (3 x 50 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Column chromatography (SiO_2, Biotage system™, 10% Et_2O : 90% petroleum ether) gave the product **184** as a pale yellow oil (674 mg, 63% yield lit.[101] 29%): R_f (20% Et_2O : petroleum ether) 0.45; δ_H (400 MHz) 7.17-7.14 (2 H, m, 2 x CH of aromatic), 6.99-6.96 (2 H, m, 2 x CH of aromatic), 6.65 (2 H, s, C(2)H and C(3)H), 2.09 (6 H, s, 2 x Me), 1.35 (9 H, s, Bu^t); δ_C (100 MHz) 155.5 (C=O), 152.3 (C quat.), 147.5, 124.6, 118.7 (all C of aromatic), 80.3 (CMe_3), 74.0 (C1 and C4), 28.3 (CMe_3) 15.7 (2 x Me); m/z (CI^+, NH_3) 272 ($M+H^+$, 4%), 233 (100), 216 (55), 172 (28), 156 (3), 130 (2) (Found, $M+H^+$, 272.1649, $C_{17}H_{22}NO_2$ requires 272.1650).

_N_-(*tert*-Butoxycarbonyl)-1,4-dihydro-1,4-iminoanthracene 202 :[104]

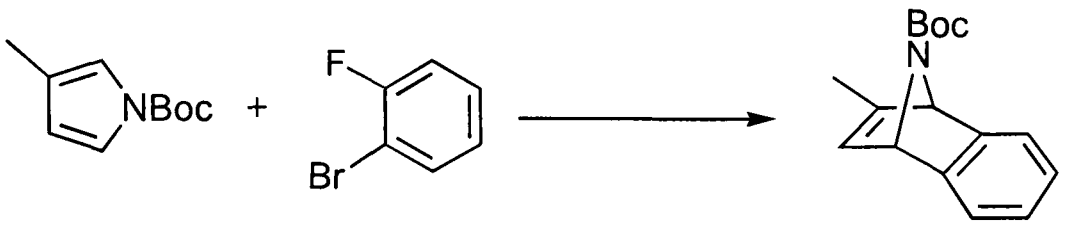


202

A solution of *N*-Boc pyrrole (2.45 cm^3, 14.7 mmol) in dioxan (12.5 cm^3) was brought to reflux and solutions of isoamyl nitrite (1.97 cm^3, 14.7 mmol) in dioxan (6.25 cm^3) and 3-amino-2-naphthoic acid (2.5 g of 80% tech. grade, 13.3 mmol) in dioxan (20 cm^3) were added using separate syringes over 2.5 h. The blood-red mixture was allowed to reflux for a further 90 minutes, then allowed to cool. The solvent was removed at reduced pressure to give a red oil. Column chromatography

(Biotage system™, 20% Et_2O : isohexane) gave the product **202** as a white solid (1.54 g, 39% yield, 49% assuming 80% pure acid, lit.[104] 49%): R_f (Et_2O) 0.80; δ_H (400 MHz, $CDCl_3$) 7.72-7.67 (2 H, m, 2 x CH of aromatic), 7.60 (2 H, s, Ar), 7.43-7.39 (2 H, m, 2 x CH of aromatic), 6.91 (2 H, br s, 2 x HC=C), 5.57 (2 H, br s, C(1)H and C(4)H), 1.37 (9 H, s, Bu^t); m/z (CI^+, NH_3) 294 ($M+H^+$, 19%), 255 (100), 238 (60), 194 (88), 179 (15) (Found, $M+H^+$, 294.1490, $C_{19}H_{20}NO_2$ requires 294.1494).

***N*-(*tert*-Butoxycarbonyl)-2-methyl-1,4-dihydro-1,4-iminonaphthalene 161 :**

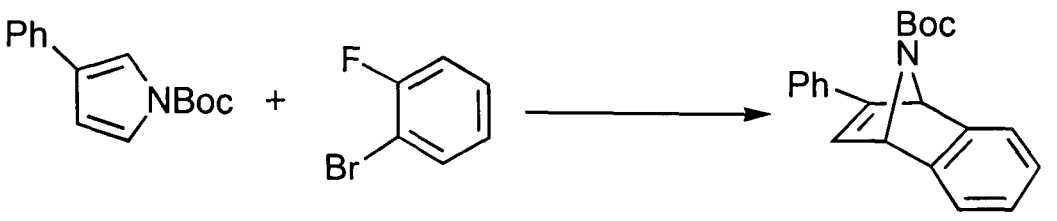


161

Boc-protected 3-methylpyrrole **160** (419 mg, 2.31 mmol) was subjected to the usual benzyne cycloaddition conditions with *o*-fluorobromobenzene (407 mg, 2.31 mmol) and magnesium turnings (61 mg, 2.5 mmol). The crude mixture was purified by chromatography (5% Et_2O : petroleum ether) to give the adduct **161** as a yellow oil (134 mg, 23%): R_f (5% Et_2O : petroleum ether) 0.28; ν_{max}(thin film)/cm^{-1} 3050w, 3004m, 2975s, 2931s, 2852w, 1695s, 1478m, 1456s, 1392s, 1368s, 1336s, 1253s, 1081s, 861s, 831s, 750s; δ_H (500 MHz, 90 °C, DMSO-d_6) 7.38-7.33 (2 H, m, 2 x CH of aromatic), 7.29-7.22 (2 H, m, 2 x CH of aromatic), 6.44 (1 H, s, HC=C), 5.35 (1 H, s, C(1)H), 5.10 (1 H, s, C(4)H), 1.86 (3 H, s, Me), 1.40 (9 H, s, Bu^t); δ_C (125 MHz, 90 °C, DMSO-d_6) 155.4 (C=O), 154.4, 150.2, 149.1 (3 x C quat.), 135.7 (C3), 125.6, 125.2, 121.3, 120.7 (4 x C of aromatic) 80.4 (CMe_3), 70.7 (C1), 67.4 (C4), 28.9 (CMe_3), 15.4 (Me); m/z (CI^+, NH_3) 258 ($M+H^+$, 46%), 219 (62), 202 (33),

196 (7), 182 (3), 158 (M-BOC$^+$, 100), 142 (10) 130 (4), 117 (16), 96 (5) (Found M + H$^+$, 258.1494, $C_{16}H_{20}NO_2$ requires 258.1494).

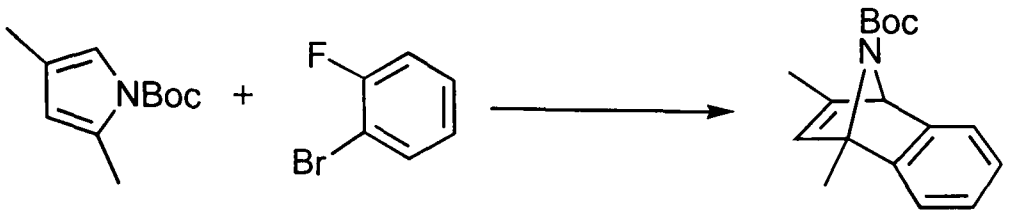
_N_-(*tert*-Butoxycarbonyl)-2-phenyl-1,4-dihydro-1,4-iminonaphthalene 171 :



171

Magnesium turnings (110 mg, 4.5 mmol) were added to dry THF (2 cm^3) under argon and stirred with 1,2-dibromoethane (25 μL) for 10 min. A solution of pyrrole **170** (1.0 g, 4.1 mmol) in THF (6 cm^3) was added and the mixture brought to reflux. One quarter of a solution of *o*-bromofluorobenzene (725 mg) in THF (2 cm^3) was added. When initiation occurred (darkening), the rest of the solution was added dropwise. After the addition was complete the mixture was allowed to reflux for a further 90 min. It was then allowed to cool, quenched with a solution of NH_4Cl (2.5 g) in water (8 cm^3) and the aqueous layer extracted with Et_2O (3 x 20 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, 10% Et_2O : petroleum ether to 20% Et_2O : petroleum ether, gradient elution) gave **171** as a yellow gum (470 mg, 36%): R_f (20% Et_2O : petroleum ether) 0.38; δ_H (200 MHz) 7.50-7.20 (7 H, m, 7 x CH of aromatic), 7.10-6.90 (3 H, m, 2 x CH, 1 x HC=C), 5.83 (1 H, br s, C(1)H), 5.61 (1 H, br s, C(4)H), 1.39 (9 H, s, Bu^t); Compound decomposed prior to full characterisation.

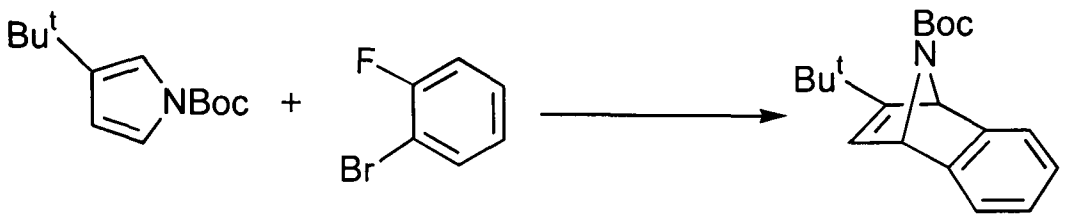
_N_-(*tert*-Butoxycarbonyl)-1,3-dimethyl-1,4-dihydro-1,4-iminonaphthalene 182 :



182

Magnesium turnings (406 mg, 16.7 mmol) were added to dry THF (7 cm^3) under argon and stirred with 1,2-dibromoethane (100 μL) for 10 min. A solution of pyrrole **181** (3.0 g, 15.3 mmol) in THF (25 cm^3) was added and the mixture brought to reflux. One quarter of a solution of *o*-bromofluorobenzene (2.68 g, 15.2 mmol) in THF (7 cm^3) was added. When initiation occurred (darkening), the rest of the solution was added dropwise. After the addition was complete the mixture was allowed to reflux for a further 90 min. It was then allowed to cool, quenched with a solution of NH_4Cl (9 g) in water (30 cm^3) and the aqueous layer extracted with Et_2O (3 x 50 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, 10% Et_2O : petroleum ether) gave **182** as a yellow oil (2.37 g, 57%): R_f (25% Et_2O : petroleum ether) 0.55; ν_{max}(thin film)/cm^{-1} 3067m, 3050m, 3006s, 2974s, 2931s, 2869s, 1713s, 1629m, 1478s, 1455s, 1366s, 1336s, 1292s, 1254s, 1169s, 1093s, 1073s, 1058s, 1030s, 1007m, 851s, 833s, 809s, 749s; δ_H (400 MHz) 7.29 (1 H, d, J 7.0, 1 x CH of aromatic), 7.15 (1 H, d, J 7.0, 1 x CH of aromatic), 7.05-6.90 (2 H, m, 2 x CH of aromatic), 6.12 (1 H, s, C(2)H), 5.12 (1 H, s, C(4)H), 2.10 (3 H, s, 3-Me), 1.89 (3 H, s, 1-Me), 1.38 (9 H, s, Bu^t); δ_C (100 MHz), 155.5 (C=O), 153.9, 152.3 (2 x C(quat) of aromatic), 148.7 (C3), 139.1 (C2), 125.0, 124.4, 120.2, 118.2 (4 x C of aromatic), 80.2 (*C*Me_3), 74.2, 70.7 (C1 and C4), 28.2 (C*Me*$_3$), 15.2 (Me), 14.9 (Me); m/z (CI^+, NH_3) 272 ($M+H^+$, 1%), 233 (100), 216 (17), 172 ($M-Boc^+$, 34), 156 (3), 131 (5) (Found, $M+H^+$, 272.1648, $C_{17}H_{22}NO_2$ requires 272.1650).

N-(*tert*-Butoxycarbonyl)-2-*tert*-butyl-1,4-dihydro-1,4-iminonaphthalene 185 :

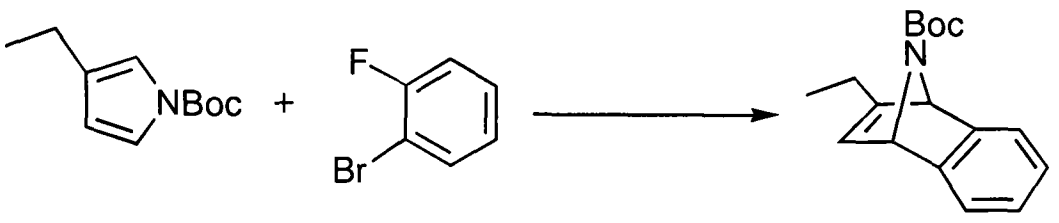


185

Magnesium turnings (154 mg, 6.33 mmol) were added to dry THF (3 cm^3) under argon and stirred with 1,2-dibromoethane (35 μL) for 10 min. A solution of pyrrole **177** (1.3 g, 5.8 mmol) in THF (10 cm^3) was added and the mixture brought to reflux. One quarter of a solution of *o*-bromofluorobenzene (1.02 g, 5.8 mmol) in THF (3 cm^3) was added. When initiation occurred (darkening), the rest of the solution was added dropwise. After the addition was complete the mixture was allowed to reflux for a further 90 min. It was then allowed to cool, quenched with a solution of NH_4Cl (3.5 g) in water (12 cm^3) and the aqueous layer extracted with Et_2O (3 x 20 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, 10% Et_2O : petroleum ether to 40% Et_2O : petroleum ether, gradient elution) gave **185** as a yellow solid (1.18 g, 68%): mp (from petroleum ether) 59-60 °C; R_f (10% Et_2O : petroleum ether) 0.25; ν_{max}(KBr)/cm^{-1} 3050m, 3027s, 2961s, 2868s, 1715s, 1607m, 1455s, 1368s, 1256s, 1166s, 1082s, 1048s, 1009m, 936m, 893m, 862s, 832s, 800s ; δ_H (500 MHz, 90 °C, DMSO-d_6), 7.38-7.32 (1 H, m, 1 x CH of aromatic), 7.30-7.23 (1 H, m, 1 x CH of aromatic), 6.99-6.91 (2 H, m, 2 x CH of aromatic), 6.39 (1 H, br s, C(3)H), 5.42 (1 H, s, C(1)H), 5.37 (1 H, s, C(4)H), 1.41 (9 H, s, O-Bu^t), 1.09 (9 H, s, C-Bu^t); δ_C (125 MHz, 90 °C, DMSO-d^6) 167.8 (C2), 155.2 (C=O), 149.9, 149.8 (2 x C quat. of aromatic), 132.2 (C3), 125.5, 125.2, 121.5, 120.7 (4 x C of aromatic), 80.4 (O*C*Me_3), 67.6, 67.3 (C1 and C4), 33.6 (*C*Me_3), 28.9 (OC*Me*$_3$), 28.8 (C-C*Me*$_3$) ; m/z (CI^+, NH_3) 300

(M+H$^+$, 42%), 261 (33), 244 (28), 217 (12), 200 (M-Boc$^+$, 100), 188 (16), 169 (12), 144 (35), 117 (83), 58 (10) (Found, M+H$^+$, 300.1968, $C_{19}H_{26}NO_2$ requires 300.1963).

_N_-(*tert*-Butoxycarbonyl)-2-ethyl-1,4-dihydro-1,4-iminonaphthalene 180 :



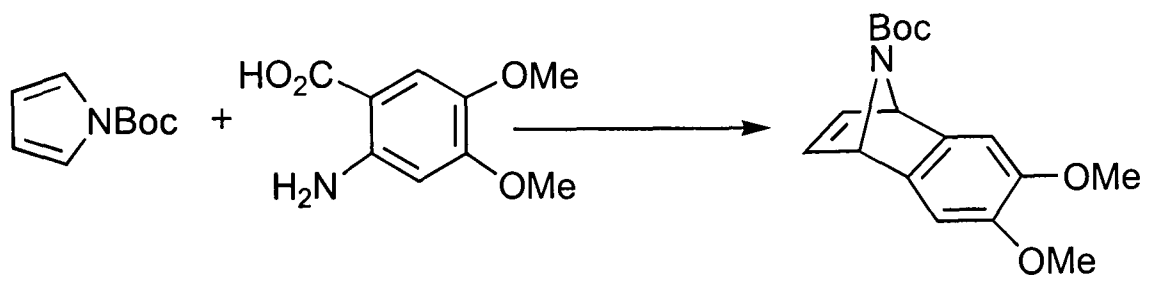
180

Magnesium turnings (272 mg, 11.2 mmol) were added to dry THF (5 cm^3) under argon and stirred with 1,2-dibromoethane (60 μL) for 10 min. A solution of pyrrole **179** (2.0 g, 10.3 mmol) in THF (15 cm^3) was added and the mixture brought to reflux. One quarter of a solution of *o*-bromofluorobenzene (1.79 g, 10.2 mmol) in THF (5 cm^3) was added. When initiation occurred (darkening), the rest of the solution was added dropwise. After the addition was complete the mixture was allowed to reflux for a further 90 min. It was then allowed to cool, quenched with a solution of NH_4Cl (6.0 g) in water (20 cm^3) and the aqueous layer extracted with Et_2O (3 x 50 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, 10% Et_2O : petroleum ether to 20% Et_2O : petroleum ether, gradient elution) gave **180** as a yellow oil (1.54 g, 54 %): R_f (30% Et_2O : petroleum ether) 0.63; ν_{max}(thin film)/cm^{-1} 3051m, 3025m, 2972s, 2934s, 2877s, 1713s, 1620w, 1478m, 1456s, 1392s, 1368s, 1332s, 1253s, 1169s, 1079s, 1036w, 1008w, 958w, 928m, 893m, 861s, 831s, 809s, 751s; δ_H (500 MHz, 90 °C, DMSO-d_6) 7.34-7.30 (1 H, m, CH of aromatic), 7.28-7.24 (1 H, m, CH of aromatic), 6.98-6.90 (2 H, m, 2 x CH of aromatic), 6.42 (1 H, s, C(3)H), 5.39 (1 H, s, C(1)H), 5.21 (1 H, s, C(4)H), 2.35 (2 H, m, 2 x H of CH_2), 1.35 (9 H, s, Bu^t), 1.00 (3 H, dd, J 7.0 and 7.0,

Me); δ_C (125 MHz, 90 °C, DMSO-d^6) 160.4 (C2), 155.4 (C=O), 150.2, 149.4 (C(quat.) of aromatic, 134.1 (C3), 125.5, 125.1, 121.2, 120.7 (4 x C of aromatic), 80.2 (CMe_3), 69.6, 67.5 (C1 and C4), 28.7 (CMe_3), 23.1 (CH_2), 12.2 (Me); m/z (TOF ES^+) 272 ($M+H^+$, 3%), 257 ($M+H^+-CH_3$, 100), 248 (10), 216 (33), 198 (42), 172 (8), 155 (28) (Found 272.1656, $C_{17}H_{22}NO_2$ requires 272.1651).

***N*-(*tert*-Butoxycarbonyl)-6,7-dimethoxy-1,4-dihydro-1,4-iminonaphthalene 201**

:

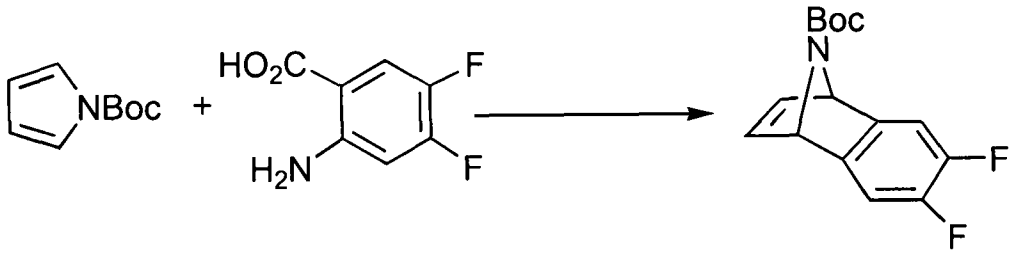


201

This procedure is adapted from that of Cragg et al.[123] who used 3,6-dimethoxyanthranilic acid. To a solution of *N*-Boc pyrrole (1.5 g, 9.0 mmol) in acetonitrile (60 cm^3) were simultaneously added solutions of 4,5-dimethoxyanthranilic acid (1.48 g, 7.5 mmol) in CH_2Cl_2 (35 cm^3) and isoamyl nitrite (1.76 g, 15 mmol) in acetonitrile (30 cm^3) over 30 min. The solution was brought to reflux and heated for 2 h, and after cooling the solvent was removed at reduced pressure. Chromatography (SiO_2, 30% Et_2O : petroleum ether to 50% Et_2O : petroleum ether, gradient elution) gave **201** as a yellow gum (924 mg, 41%): R_f (30% Et_2O : petroleum ether) 0.16; ν_{max}(thin film)/cm^{-1} 3079m, 2971s, 2932s, 2866s, 2833s, 1704s, 1604m, 1556w, 1480s, 1410s, 1392s, 1368s, 1318s, 1291s, 1258s, 1214s, 1162s, 1089s, 1062s, 1022s, 979m, 942w, 869m, 834m, 787m ; δ_H (400 MHz, mixture of rotamers observed) 7.01 and 6.96 (4 H, 2 x s, 2 x CH of aromatic, C(2)H and C(3)H), 5.46 and 5.42 (2 H, 2 x s, C(1)H and C(4)H), 3.84 (6

H, s, 2 x Me), 1.38 (9 H, s, ^{t}Bu); δ_C (125 MHz, 90 °C, DMSO) 154.9 (C=O), 147.0, 144.0, 142.5 (all C of aromatic), 110.2 (C2 and C3), 80.4 (*C*Me$_3$), 67.1(C1 and C4), 57.7 (2 x Me-O), 29.0 (C*Me*$_3$); m/z (CI$^+$, NH_3) 304 (M+H$^+$, 4%), 265 (55), 248 (100), 221 (3), 204 (91), 189 (69), 177 (19), 145 (6), 102 (8), 58 (10) (Found, M+H$^+$, 304.1546, $C_{17}H_{22}NO_4$ requires 304.1549).

***N*-(*tert*-Butoxycarbonyl)-6,7-difluoro-1,4-dihydro-1,4-iminonaphthalene 200 :**



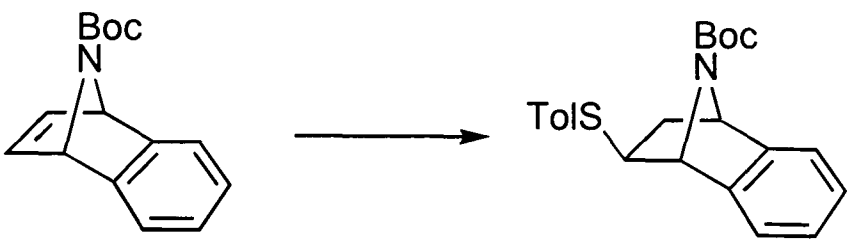
200

This procedure is adapted from that of Vernon et al.[91] who used anthranilic acid in a benzyne reaction with 1-Boc-2,5-dimethylpyrrole **183**. To a solution of *N*-Boc pyrrole (0.967 g, 5.8 mmol) in THF (20 cm^3) at reflux were simultaneously added solutions of 4,5-difluoroanthranilic acid (1.0 g, 5.8 mmol) in THF (10 cm^3) and isoamyl nitrite (0.75 g, 6.4 mmol) in THF (10 cm^3) over 30 min. The mixture was allowed to reflux for 1 h after the end of the addition, then allowed to cool. Water (40 cm^3) was added and the aqueous layer extracted with Et_2O (3 x 50 cm^3), the combined organic extracts dried ($MgSO_4$) and the solvent was removed at reduced pressure. Chromatography (SiO_2, 20% Et_2O : petroleum ether) gave **200** as a yellow solid (330 mg, 20%): R_f (25% Et_2O : petroleum ether) 0.31; mp (from Et_2O) 69-70 °C (Found, C, 64.3; H, 5.4; N, 5.0; $C_{15}H_{15}F_2NO_2$ requires C, 64.5; H, 5.4; N, 5.0%); ν_{max}(KBr)/cm^{-1} 3039m, 3006m, 2983s, 2934m, 1697s, 1466s, 1367s, 1345s, 1269sm 1249s, 1187s, 1168s, 1127s, 1102s, 1089s, 873s, 838s, 764s; δ_H (500 MHz, 90 °C, DMSO-d^6), 7.40-7.33 (2 H, m, 2 x CH of aromatic), 7.04 (2 H, s, C(2)H and C(3)H), 5.43 (2 H, s, C(1)H and C(4)H), 1.34 (9 H, s, Bu^t); δ_C (125

MHz, 90 °C, DMSO-d_6) 154.9 (C=O), 148.2 (2 x CF), 146.4 (2 x C of aromatic), 143.9 (2 x C of aromatic) 112.1 (C2 and C3), 81.0 (CMe_3), 66.8 (C1 and C4), 28.0 (CMe_3); δ_F (235 MHz, 25 °C) −142.9 and −142.8 (split by rotamers); m/z (CI^+, NH_3) 280 ($M+H^+$, 15%), 180 ($M+H-Boc^+$, 100), 164 (55), 153 (12), 125 (3), 88 (5) (Found, $M+H^+$, 280.1162, $C_{15}H_{16}F_2NO_2$ requires 280.1149).

Sulfide:

***N*-(*tert*-Butoxycarbonyl)-*exo*-2-(*p*-tolylthio)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 139 :**



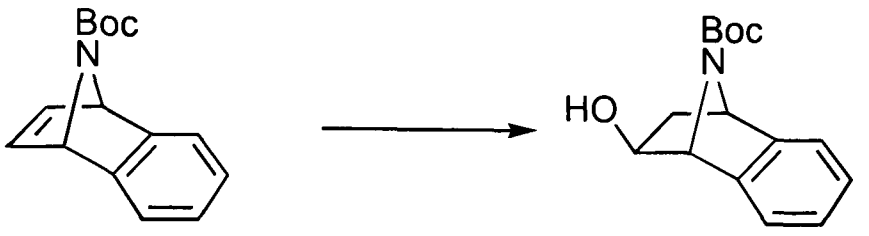
139

To a solution of **138** (100 mg, 0.41 mmol) in toluene (5 cm^3) was added *p*-thiocresol (77mg, 0.62 mmol). The mixture was stirred at 25 °C for 24 h under argon, after which time the solvent was removed at reduced pressure. Chromatography (10% Et_2O : petroleum ether) gave the sulfide **139** as a white solid (135 mg, 89%): R_f (10% Et_2O : 90% petroleum ether) 0.25; mp (from petroleum ether) 88-89 °C; ν_{max}(KBr)/cm^{-1} 3020s, 2977s, 2931s, 1698s, 1493s, 1460s, 1366s, 1279s, 1256s, 1169s, 1090s, 1017m, 973m, 908s, 812s, 753s; δ_H (400 MHz) 7.43-7.34 (2 H, m, 2 x CH of aromatic), 7.30-7.05 (6 H, 6 x CH of aromatic), 5.25 (1 H, br s, C(1)H) 5.05 (1 H, br s, C(4)H), 3.21 (1 H, s, C(2)H), 2.36 (3 H, s, Me), 2.02-1.95 (1 H, m, H of CH_2), 1.93-1.86 (1 H, m, H of CH_2), 1.44 (9 H, s, Bu^t); δ_C (100 MHz) 154.6 (C=O), 145.1 (C(quat) of aromatic), 143.6 (C(quat) of aromatic), 137.0 (C(quat) of aromatic), 132.2 (C(quat) of aromatic) 131.3, 129.8, 126.9, 126.6, 120.3, 119.8 (all C of aromatic), 80.2, (CMe_3), 65.2 (C4), 60.3 (C1), 48.4 (C2), 35.1

(C3), 28.3 (C*Me*$_3$), 21.1 (Me); m/z (EI$^+$) 367 (M$^+$, 1%), 267 (8), 217 (35), 161 (93), 117 (100), 91 (62), 84 (55), 57 (95) (Found, M+H$^+$, 368.1678, $C_{22}H_{26}NO_2S$ requires 368.1684).

Alcohols/ketones:

***N*-(*tert*-Butoxycarbonyl)-*exo*-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 141 :**

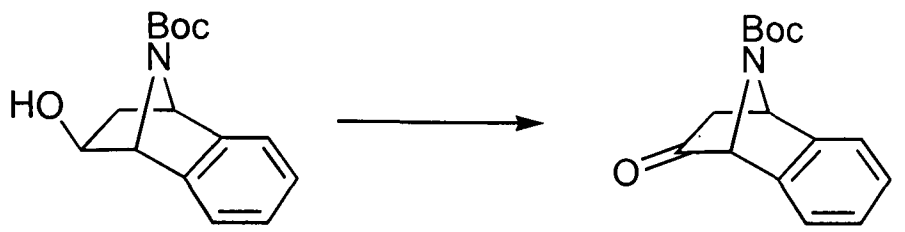


141

9-BBN (0.5 M in THF, 2.40 cm^3, 1.20 mmol) was added dropwise to a stirred solution of **138** (250 mg, 1.02 mmol) in THF (3 cm^3) under argon at 25 °C. The reaction was left to stir for 24 h. The flask was then cooled to 0 °C and H_2O_2 (1.25 cm^3 of a 30% aq. solution) was added, followed by aqueous NaOH (1.7 cm^3 of a 2 M solution). The reaction was removed from the ice bath and then stirred at 25 °C for 5 h. The mixture was washed with saturated K_2CO_3 (10 cm^3) and extracted with Et_2O (3 x 20 cm^3). The combined extracts were dried ($MgSO_4$) and the solvent removed at reduced pressure to give an oil. Column chromatography (50% Et_2O : petroleum ether) gave the alcohol **141** as an oil which crystallised on standing to a white solid (180 mg, 67%): R_f (50% Et_2O : petroleum ether) 0.23; mp (from Et_2O) 90-91 °C; ν_{max}(thin film)/cm^{-1} 3254br s, 3024m, 2978s, 2928m, 2893s, 1704s, 1690s, 1456s, 1366s, 1348s, 1294m, 1251s, 1158s, 1141m, 1102s, 1088s, 1057s, 903m, 746s; δ_H (400 MHz) 7.27-7.23 (1 H, m, CH of aromatic), 7.19-7.17 (1 H, m, CH of aromatic), 7.14-7.06 (2 H, m, 2 x H of aromatic), 5.11 (1 H, br s, C(1)H), 5.01 (1 H, br s, C(4)H), 4.04-4.00 (1 H, m, C*H*-OH), 3.20 (1 H, br. s, OH), 1.87-

1.84 (2 H, m, CH_2), 1.38 (9 H, s, Bu^t); δ_C (100 MHz) 156.5 (C=O), 146.2, 141.5, 127.0, 126.4, 121.3, 119.6 (all C of aromatic), 80.4 (CMe_3), 72.0 (CH-O), 68.4 (C1), 60.8 (C4), 39.4 (C3), 28.2 (Bu^t); m/z (CI^+, NH_3), 279 ($M+NH_4^+$, 5%), 262 ($M+H^+$, 70), 162 (100), 118 (25) (Found $M+H^+$, 262.1440, $C_{15}H_{20}NO_3$ requires 262.1443).

_N_-(*tert*-Butoxycarbonyl)-1,2,3,4-dihydro-1,4-iminonaphthalen-2-one 150 :

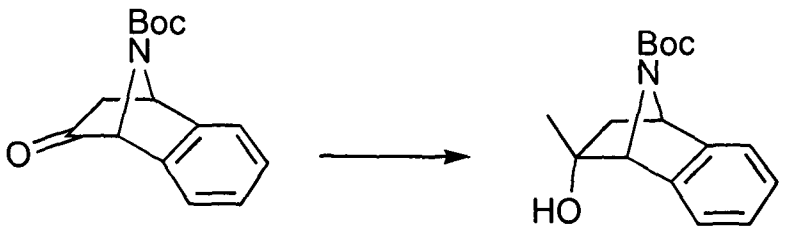


150

DMSO (62 μL, 0.88 mmol) was added to a stirred solution of oxalyl chloride (40 μ L, 0.46 mmol) in CH_2Cl_2 (3 cm^3) at –78 °C under argon. After 30 min, a solution of alcohol **141** (100 mg, 0.38 mmol) was added dropwise to the mixture. After a further 30 min at -78 °C, Et_3N (0.32 cm^3, 2.3 mmol) was added and the reaction allowed to warm to 25°C. Water (5 cm^3) was added and the aqueous layer extracted with CH_2Cl_2 (3 x 5 cm^3), washed with brine (10 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, 40% Et_2O : petroleum ether) gave the ketone **150** as a white solid (78 mg, 79%): R_f (50% Et_2O : petroleum ether) 0.45; mp (from Et_2O/ petroleum ether) 67-68 °C; ν_{max}(thin film)/cm^{-1} 3050m, 2976s, 2931s, 2871m, 1765s, 1710s, 1477s, 1460s, 1369s, 1277s, 1254s, 1166s, 1125s, 1080s, 969m, 858s, 757s; δ_H (400 MHz) 7.45 (1 H, d, J 8.0, CH of aromatic), 7.35 (1 H, d J 8.0, CH of aromatic), 7.31-7.20 (2 H, m, 2 x CH of aromatic), 5.45 (1 H, d, J 4.0, C(4)H), 5.00 (1 H, s, C(1)H), 2.60 (1 H, dd, J 16.0 and 4.0, C(3)H *exo*), 2.02 (1 H, d, J 16.0, C(3)H *endo*), 1.40 (9 H, s, Bu^t); δ_C (100 MHz) 204.9 (C=O) 154.9 (C=O of Boc), 146.0, 137.4 (2 x C(quat)), 128.5, 127.6,

123.0, 120.7 (all C of aromatic), 81.5 (CMe_3), 69.4 (C1), 60.9 (C4), 39.3 (CH_2), 28.1 (Bu^t); m/z (CI^+) 277 ($M+NH_4^+$, 34 %), 260 ($M+H^+$, 12), 221 (6), 177 (28), 160 (100) 144 (4), 130 (8), 118 (12) (Found $M+NH_4^+$, 277.1556, $C_{15}H_{21}N_2O_3$ requires 277.1552).

_N_-(*tert*-Butoxycarbonyl)-2-methyl-*endo*-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 151 :

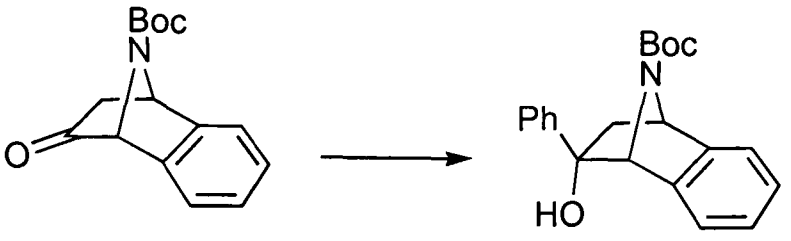


151

Methylmagnesium bromide (256 μL of a 3 M solution in Et_2O, 0.77 mmol) was added dropwise to a stirred solution of ketone **150** (100 mg, 0.38 mmol) in Et_2O (5 cm^3) under argon at 0 °C. The mixture was stirred for 1 h at 0 °C, at which point 1 N HCl (2 cm^3) was added dropwise. Water (5 cm^3) was then added and the aqueous layer extracted with Et_2O (3 x 5 cm^3), dried ($MgSO_4$), and the solvent removed at reduced pressure. Chromatography (SiO_2, 50% Et_2O : petroleum ether) gave the alcohol **151** as a white solid (99 mg, 93%): R_f (50% Et_2O : petroleum ether) 0.18; mp (from Et_2O) 123-124 °C; ν_{max}(KBr)/cm^{-1} 3410s, 3027m, 2972s, 2937s, 2866w, 1660s, 1416s, 1370s, 1282s, 1169s, 1105s, 1055s, 858m; δ_H (400 MHz) 7.40 (1 H, d, J 6.0, CH of aromatic), 7.30 (1 H, m, CH of aromatic), 7.14-7.06 (2 H, m, 2 x CH of aromatic), 5.11 (1 H, br s, C(1)H), 4.68 (1 H, br s, C(4)H), 4.00 (1 H, m, C*H*-OH), 2.27 (1 H, dd, J 12.0 and 5.0 C(3)H *exo*), 1.61 (3 H, s, Me), 1.38 (9 H, s, Bu^t) 1.23 (1 H, d, J 12.0, C(3)H *endo*); δ_C (100 MHz) (broadened due to *N*-Boc rotamers, C=O, bridgeheads and quaternary aromatics not observed) 127.5, 126.5, 124.1, 120.0 (all C of aromatic), 80.3 (CMe_3), 70.1 (C2), 46.5 (CH_2), 28.2 (CMe_3),

27.3 (Me); m/z (CI^+, NH_3) 276 ($M+H^+$, 43%), 237 (6), 220 (7), 193 (9) 176 (M+H-BOC^+, 100), 158 (5) 132 (3) 117 (26) (Found, $M+H^+$, 276.1596, $C_{16}H_{22}NO_3$ requires 276.1599).

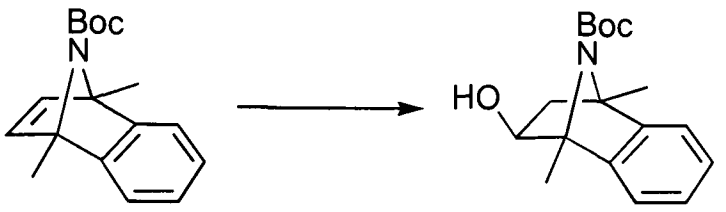
_N_-(*tert*-Butoxycarbonyl)-2-phenyl-*endo*-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 152 :



Phenylmagnesium chloride (0.55 cm^3 of a 2 M solution in THF, 1.1 mmol) was added dropwise to a stirred solution of ketone **150** (144 mg, 0.3 mmol) in THF (5 cm^3) under argon at 0 °C. The mixture was stirred for 1 h at 0 °C, at which point 1 N HCl (2 cm^3) was added dropwise. Water (5 cm^3) was then added and the aqueous layer extracted with Et_2O (3 x 5 cm^3), the combined organic extracts dried ($MgSO_4$), and the solvent removed at reduced pressure. Chromatography (SiO_2, 40% Et_2O : petroleum ether) gave the alcohol **152** as a white solid (130 mg, 69%): R_f (50% Et_2O : petroleum ether) 0.21; mp (from Et_2O) 121-122 °C; ν_{max}(thin film)/cm^{-1} 3432s, 3021m, 2989m, 2950m, 1674s, 1460m, 1370s, 1272s, 1166s, 1096s, 1053m, 902m, 754s; δ_H (400 MHz) 7.71 (2 H, d, J 8.0, 2 x CH of aromatic), 7.47-7.17 (7H, m, 7 x CH of aromatic), 5.26 (1 H, br s, C(1)H), 5.11 (1 H, br. s, C(4)H), 2.85 (1 H, dd, J 12.0 and 5.0, C(3)H *exo*), 1.58 (1 H, d, J 12.0, C(3)H *endo*), 1.50 (1 H, br s, OH), 1.31 (9 H, s, Bu^t); δ_C (100 MHz, broadened due to Boc rotamers, C4 and benzo carbons not observed) 145.6 (C(quat) of Ph), 128.3, 127.7, 127.3, 126.6, 125.7 (5 x C of aromatic), 80.5 (CMe_3), 70.4 (C1), 48.6 (C3), 28.1

(C*Me*$_3$); m/z (CI$^+$, NH_3) 338 (M+H$^+$, 39%), 299 (6), 282 (4), 238 (M-Boc$^+$, 74), 218 (20), 138 (30), 118 (100) (Found, M+H$^+$, 338.1761, $C_{21}H_{24}NO_3$ requires 338.1756).

_N_-(*tert*-Butoxycarbonyl)-1,4-dimethyl-*exo*-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 192 :

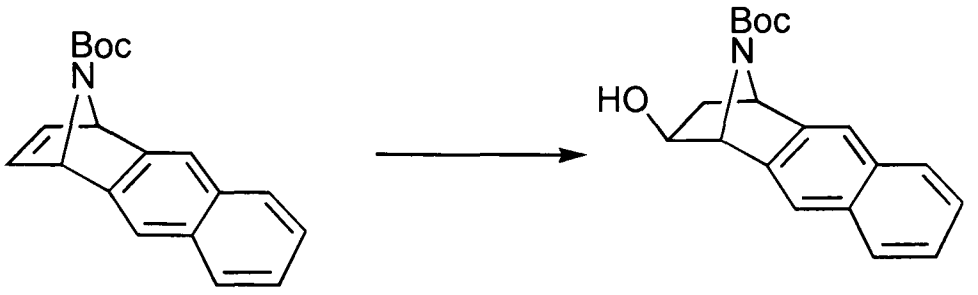


192

9-BBN (2.81 cm^3 of 0.5 M solution in THF, 1.4 mmol) was added dropwise to a stirred solution of alkene **184** (254 mg, 0.94 mmol) in THF (2 cm^3) at 25 °C. The solution was stirred for 24 h. Water (1.5 cm^3), hydrogen peroxide (1.5 cm^3 of a 35% solution in water) and NaOH (2.0 cm^3 of 2 M aq. solution) were added at 0 °C. The reaction was allowed to warm to room temperature and stirred for 5 h. The mixture was then washed with saturated K_2CO_3 (2 x 10 cm^3) and the organic layer extracted with Et_2O (2 x 20 cm^3), and the solvent removed at reduced pressure. Chromatography (SiO_2, 30% Et_2O : petroleum ether to 50% Et_2O : petroleum ether, gradient elution) gave the alcohol **192** as a colourless oil (210 mg, 77%): R_f (50% Et_2O : petroleum ether) 0.28; ν_{max}(Nujol)/cm^{-1} 3448m, 2924s, 2880s, 1704s, 1678m, 1456s, 1377m, 1301m, 1252m, 1154m, 1097m, 1071m, 1054m, 1042m, 748m; δ_H (400 MHz) 7.18-7.15 (3 H, m, 3 x CH of aromatic), 7.10-7.08 (1 H, m, 1 x CH of aromatic), 3.68 (1 H, d, J 5.0, C*H*-OH), 2.46 (1 H, br s, OH), 2.00 (3 H, s, Me), 1.99 (3 H, s, Me), 1.96 (1 H, d, J 12.0, H of CH_2), 1.72 (1 H, dd, J 12.0 and 2.0, H of CH_2), 1.41 (9 H, s, Bu^t); δ_C (100 MHz) 156.7 (C=O), 149.0, 145.2 (both C(quat)), 127.1, 126.5, 119.3, 117.5 (4 x CH of aromatic), 80.2 (*C*Me$_3$), 76.6 (C2), 73.2 (C1), 68.0 (C4), 47.2 (C3), 28.3 (C*Me*$_3$), 17.5 (Me), 13.9 (Me); m/z (CI$^+$, NH_3)

290 ($M+H^+$, 50%), 272 (8), 246 (5), 233 (100), 216 (34), 190 (77), 172 (13), 156 (18), 146 (55), 135 (10) (Found, $M+H^+$, 290.1756, $C_{17}H_{24}NO_3$ requires 290.1756).

_N_-(_tert_-Butoxycarbonyl)-_exo_-1,2,3,4-tetrahydro-1,4-iminoanthracen-2-ol 212 :

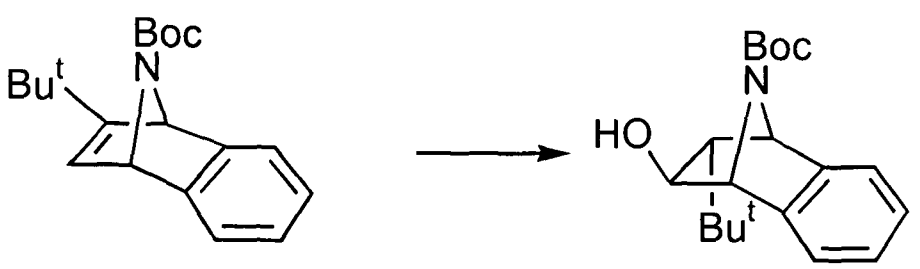


212

9-BBN (6.8 cm^3 of 0.5 M solution in THF, 3.4 mmol) was added dropwise to a stirred solution of alkene **202** (500 mg, 1.70 mmol) in THF (5 cm^3) at 0 °C. The solution was allowed to warm to room temperature and stirred for 16 h. The flask was then cooled to 0 °C and H_2O_2 (2.0 cm^3 of a 30% aq. solution) was added, followed by aqueous NaOH (3.0 cm^3 of a 2 M solution). The reaction was then stirred at 25 °C for 5 h. The aqueous layer was saturated with K_2CO_3, and extracted with Et_2O (3 x 30 cm^3). The combined extracts were dried ($MgSO_4$) and the solvent removed at reduced pressure to give an oil. Chromatography (SiO_2, 40% Et_2O : petroleum ether to 60% Et_2O : petroleum ether, gradient elution) gave the alcohol **212** as a white solid (311 mg, 59%): R_f (50% Et_2O : petroleum ether) 0.21; mp (from Et_2O) 177-178 °C; ν_{max}(KBr)/cm^{-1} 3512 br s, 2985m, 2919m, 1670s, 1391s, 1370m, 1165m, 1097m, 1046m, 888m, 749m ; δ_H (500 MHz) 7.81-7.77 (2 H, m, 2 x CH of aromatic), 7.70 (1 H, s, CH of aromatic), 7.60 (1 H, s, CH of aromatic), 7.50-7.44 (2 H, m, 2 x CH of aromatic), 5.25 (1 H, br s, C(1)H), 5.15 (1 H, br s, C(4)H), 4.10 (1 H, br s, C*H*-OH), 2.9-2.6 (1 H, br s, OH), 2.00 (2 H, m, CH_2), 1.39 (9 H, s, Bu^t); δ_C (125 MHz), 156.5 (C=O), 143.6, 139.1, 132.5, 132.8, 128.1, 128.0, 125.9, 125.7, 120.0, 117.6 (10 x C of aromatic), 80.6 (*C*Me_3), 73.2 (C-OH), 68.7

(C1), 60.2 (C4), 40.5 (C3), 28.1 (C*Me*$_3$); m/z (CI$^+$, NH_3) 312 (M+H$^+$, 52%), 273 (4), 256 (8), 238 (6) 212 (M-Boc$^+$, 100), 194 (11) 167 (21) 90 (4) (Found, M+H$^+$, 312.1597, $C_{19}H_{22}NO_3$ requires 312.1599).

_N_-(_tert_-Butoxycarbonyl)-_endo_-(3-_tert_-butyl)-_exo_-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 195 :

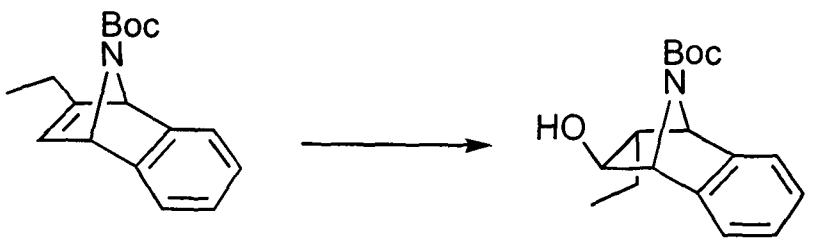


195

BH_3-THF complex (0.80 cm^3 of 1.0 M solution in THF, 0.8 mmol) was added to alkene **185** (200 mg, 0.67 mmol) in THF (2 cm^3) under argon at 0 °C. The reaction was stirred at 25 °C for 24 h. It was then cooled to 0 °C and water 1.0 cm^3 was added, followed by H_2O_2 (1.0 cm^3 of a 35% aqueous solution) and aq. NaOH (0.25 cm^3 of a 2 M solution), over 15 min. The mixture was allowed to warm to 25 °C and stirred for 10 min. The aqueous layer was saturated with K_2CO_3 and extracted with Et_2O (3 x 25 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, 30% Et_2O : petroleum ether to 50% Et_2O : petroleum ether, gradient elution) gave starting material (70 mg, 35%) and then **195** as a colourless gum (60 mg, 28%, 43% based on rsm): R_f (30% Et_2O : petroleum ether) 0.12; ν_{max}(thin film)/cm^{-1} 3447 br s, 2956s, 2910m, 2870s, 1663s, 1481s, 1462s, 1397s, 1366s, 1322s, 1256m, 1171s, 1154m, 1102s, 1060m, 746m; δ_H (400 MHz) 7.30-7.22 (2 H, m, 2 x CH of aromatic), 7.12-7.05 (2 H, m, 2 x CH of aromatic), 5.00 and 4.90 (2 H, 2 x br s, C(1)H and C(4)H), 3.77 (1 H, d, J 3.0, CH-O), 2.80-2.20 (1 H, br s, OH), 2.01 (1 H, t, J 4.0, C(3)H), 1.35 (9 H, s, O-Bu^t), 0.65 (9 H, s, C-Bu^t); δ_C (100 MHz) 156.4 (C=O), 143.9, 142.5 (both C(quat)) 126.7,

126.3, 122.3, 121.0 (4 x C of aromatic), 80.4 (O-*C*Me$_3$), 75.0 (C2), 70.3, 63.9 (C1 and C4), 62.3 (C3), 31.1 (C-*C*Me$_3$), 28.3 (C*Me*$_3$), 28.1 (*C*Me$_3$); m/z (CI$^+$, NH_3) 318 (M+H$^+$, 20%), 218 (M-Boc$^+$, 24), 117 (100), 98 (17), 52 (39) (Found, M+H$^+$, 318.2073, $C_{19}H_{28}NO_3$ requires 318.2069).

***N*-(*tert*-Butoxycarbonyl)-*endo*-(3-ethyl)-*exo*-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 186 :**

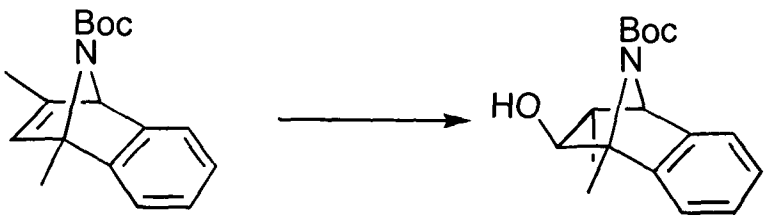


186

9-BBN (4.5 cm^3 of 0.5 M solution in THF, 2.25 mmol) was added to alkene **180** (308 mg, 1.13 mmol) under argon. The reaction was stirred at 25 °C for 24 h. It was then cooled to 0 °C and H_2O_2 (2.5 cm^3 of a 35% aqueous solution) was added, followed by NaOH (3.3 cm^3 of a 2 M solution). The mixture was allowed to warm to 25 °C and stirred for 5 h. The aqueous layer was saturated with K_2CO_3 and extracted with Et_2O (3 x 25 cm^3), the combined organic extracts dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (30% Et_2O : petroleum ether to 40% Et_2O : petroleum ether) gave **186** as a colourless gum (145 mg , 44%): R_f (50% Et_2O : petroleum ether) 0.23; ν_{max}(thin film)/cm^{-1} 3418 br s, 2970s, 2930s, 2890s, 1682s, 1470s, 1392s, 1249s, 1165s, 1110s, 1055s, 1012s, 903s, 753s; δ_H (400 MHz) 7.27-7.17 (2 H, m, 2 x CH of aromatic), 7.14-7.08 (2 H, m, 2 x CH of aromatic), 4.95 and 4.93 (2 H, 2 x s, C(1)H and C(4)H), 3.38 (1 H, d, J 2.0, CH-O), 3.05-2.75 (1 H, br s, OH), 2.06-2.00 (1 H, m, C(3)H), 1.36 (9 H, s, Bu^t), 1.02-0.91 (1 H, m, H of CH_2), 0.90 (3 H, t, J 7.0, Me), 0.78-0.68 (1 H, m, H of CH_2); δ_C (100 MHz) 156.6 (C=O), 143.3, 141.6 (both C(quat)) 126.7, 126.5, 121.0, 120.4 (4 x C

of aromatic), 80.4 (*C*Me$_3$), 79.2 (C2), 69.4, 64.1 (C1 and C4), 52.7 (C3), 29.2 (C*Me*$_3$), 24.0 (CH_2), 12.2 (Me); m/z (TOF ES$^+$) 290 (M+H$^+$, 20%), 275, (M+H-CH_3^+, 15), 234 (21), 216 (100), 198 (16), 190 (M+H-Boc$^+$, 25), 173 (39) (Found, M+H$^+$, 290.1756, $C_{17}H_{24}NO_3$ requires 290.1756).

_N_-(*tert*-Butoxycarbonyl)-*endo*-(1,3-dimethyl)-*exo*-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 189 :

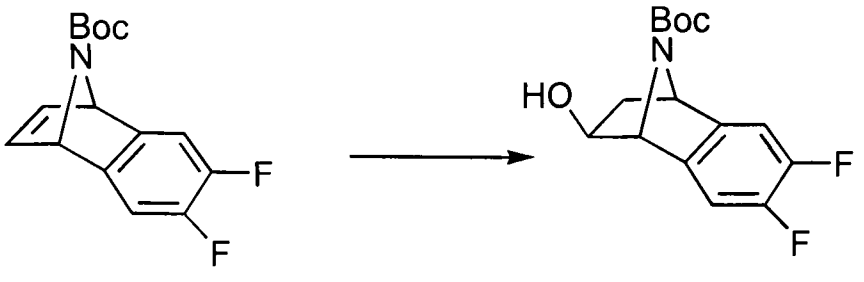


189

9-BBN (7.4 cm^3 of a 0.5 M solution in THF, 3.7 mmol) was added to neat alkene **182** (500 mg, 1.84 mmol) under argon at 25 °C. The mixture was stirred for 24 h, then cooled to 0 °C. H_2O_2 (3.9 cm^3 of a 35% aq. solution) was added dropwise, followed by NaOH (5.25 cm^3 of a 2 M aq. solution). The mixture was allowed to stir at 25 °C for 5 h. The aqueous layer was saturated with K_2CO_3, and extracted with Et_2O (3 x 20 cm^3), the combined organic extracts dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, 30% Et_2O : petroleum ether to 50% Et_2O : petroleum ether, gradient elution) gave **189** as a white solid (340 mg, 64 %): R_f (50% Et_2O : petroleum ether) 0.19; mp (from Et_2O) 86-88 °C; ν_{max}(thin film)/cm^{-1} 3414s, 2977s, 2963s, 2930m, 2884m, 1659s, 1458s, 1381s, 1253m, 1175s, 1116m, 1056m, 863s, 751s; δ_H (400 MHz) 7.20-7.07 (4 H, m, 4 x CH of aromatic), 4.85 (1 H, d, J 4.0, C(4)H), 3.07 (1 H, d, J 4.0, CH-O), 2.41 (1 H, d, J 7.0, OH), 2.15-2.07 (1 H, m, C(3)H), 1.94 (3 H, s, 1-Me), 1.38 (9 H, s, Bu^t), 0.67 (3 H, d, J 7.0, 3-Me); δ_C (100 MHz) 156.4 (C=O), 145.3, 143.1 (2 x C(quat) of aromatic), 126.7, 126.4, 121.7, 119.2 (4 x C of aromatic), 83.8 (*C*H-O),

80.1 (CMe_3), 73.1 (C1), 65.3 (C4), 44.6 (C2), 28.3 (CMe_3), 15.5 (3-Me), 13.1 (1-Me); m/z (TOF ES^-) 288 ($M\text{-}H^+$, 42%), 283 (15), 269 (12), 265 (12), 239 (23), 232 (100), 214 (48), 212 (35), 202 (20), 199 (13), 157 (21) (Found, $M\text{-}H^+$, 288.1598, $C_{17}H_{22}NO_3$ requires 288.1600).

***N*-(*tert*-Butoxycarbonyl)-6,7-difluoro-*exo*-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 206 :**

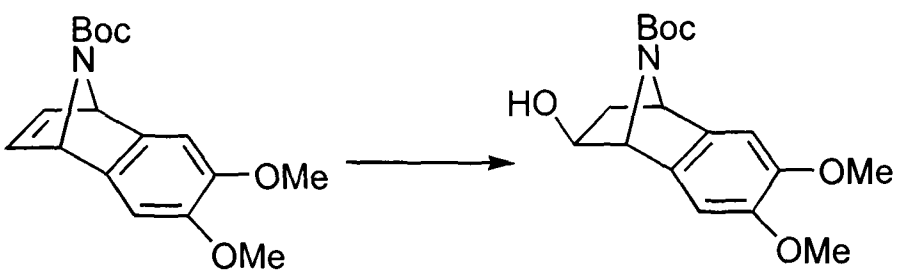


206

9-BBN (6.4 cm^3 of a 0.5 M solution in THF, 3.2 mmol) was added to neat alkene **200** (450 mg, 1.6 mmol) under argon at 25 °C. The mixture was stirred for 24 h, then cooled to 0 °C. H_2O_2 (3.4 cm^3 of a 35% aq. solution) was added dropwise, followed by NaOH (4.6 cm^3 of a 2 M aq. solution). The reaction was allowed to warm to 25 °C and stirred for 5 h. The aqueous layer was saturated with K_2CO_3, extracted with Et_2O (3 x 20 cm^3), the combined organic extracts dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, 50% Et_2O : petroleum ether to 100% Et_2O, gradient elution) gave **206** as a white solid (235 mg, 49%): R_f (Et_2O) 0.59; mp (from Et_2O) 115-116 °C; ν_{max}(KBr)/cm^{-1} 3259s, 3028m, 2985s, 2963s, 1694s, 1615m, 1482s, 1350s, 1301m, 1271m, 1254m, 1170s, 1089m, 1071m, 1041m, 803m ; δ_H (400 MHz) 7.11 (1 H, dd, J 9.0 and 7.0, CH of aromatic), 7.03 (1 H, dd, J 9.0 and 7.0, CH of aromatic), 5.06 (1 H, s, C(1)H), 4.96 (1 H, s, C(4)H), 3.96-3.92 (1 H, m, CH-O), 3.00-2.65 (1 H, br s, OH), 1.87-1.84 (2 H, m, CH_2), 1.37 (9 H, s, Bu^t); δ_C (100 MHz) 156.2 (C=O), 149.3 (dd, J 246 and 13,

C-F), 148.9 (dd, 245 and 13, C-F), 142.3 (C(quat) of aromatic), 137.5 (C(quat) of aromatic), 111.3 (d, J 19, C of aromatic), 109.8 (d, J 19, C of aromatic), 81.0 (*C*Me$_3$), 72.6 (*C*H-O), 68.5 (C1), 60.6 (C4), 39.3 (C3), 28.3 (C*Me$_3$*); ^{19}F (235 MHz) −139.3 (1 F, d, J 19, CF), −140.2 (1 F, d, J 19, CF); m/z (TOF CI$^+$) 298 (M+H$^+$, 52%), 242 (10), 198 (100), 153 (30) (Found, M+H$^+$, 298.1246, $C_{15}H_{18}F_2NO_3$ requires 298.1255).

_N_-(*tert*-Butoxycarbonyl)-6,7-dimethoxy-*exo*-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 209 :

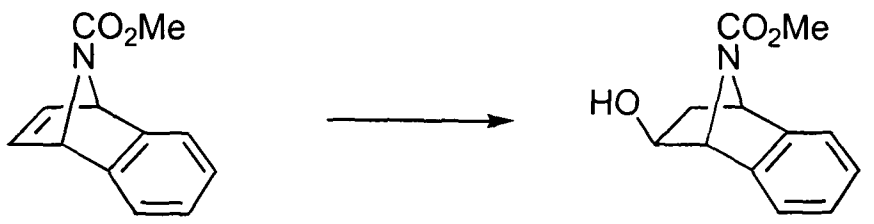


209

9-BBN (10.9 cm^3 of a 0.5 M solution in THF, 5.45 mmol) was added to alkene **201** (830 mg, 2.73 mmol) under argon at 25 °C. The mixture was stirred for 24 h, then cooled to 0 °C. H_2O_2 (5.8 cm^3 of a 35% aq. solution) was added dropwise, followed by NaOH (7.8 cm^3 of a 2 M aq. solution). The mixture was allowed to warm to 25 °C and stirred for 5 h. The aqueous layer was saturated with K_2CO_3, and extracted with Et_2O (3 x 30 cm^3), the combined organic extracts were dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, Et_2O) gave **209** as a colourless gum (490 mg, 56%): R_f (50% EtOAc : petroleum ether) 0.44; ν_{max}(thin film)/cm^{-1} 3428s, 2978s, 2939s, 1690s, 1492s, 1466s, 1367s, 1307s, 1251s, 1214s, 1159s, 1095s, 1055s, 912s, 733s ; δ_H (400 MHz) 6.87 (1 H, s, CH of aromatic), 6.80 (1 H, s, CH of aromatic), 5.01 (1 H, s, C(1)H), 4.91 (1 H, s, C(4)H), 3.92 (1 H, s, CH-O), 3.83 and 3.82 (6 H, 2 x s, 2 x MeO), 2.90 (1 H, br s, OH), 1.84-1.79 (2 H, m, C(3)H), 1.36 (9 H, s, Bu^t); δ_C (100 MHz) 156.5 (C=O), 148.1, 147.5, 138.7,

133.5 (4 x C(quat) of aromatic), 105.9, 104.5 (2 x CH of aromatic), 80.4 (*C*Me_3), 73.2 (*C*H-O), 69.0 (C1), 61.0 (C4), 56.2 and 56.1 (2 x MeO), 40.1 (C2), 28.3 (C*Me*$_3$); m/z (TOF ES^+) 344 ($M+Na^+$, 6%), 329 ($M-Me+H^+$, 12), 322 ($M+H^+$, 13%), 289(17), 266 (14), 248 (64), 205 (100), 177 (4) (Found, $M+Na^+$, 344.1474, $C_{17}H_{23}NNaO_5$ requires 344.1485).

_N_-(Methoxycarbonyl)-*exo*-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 147 :

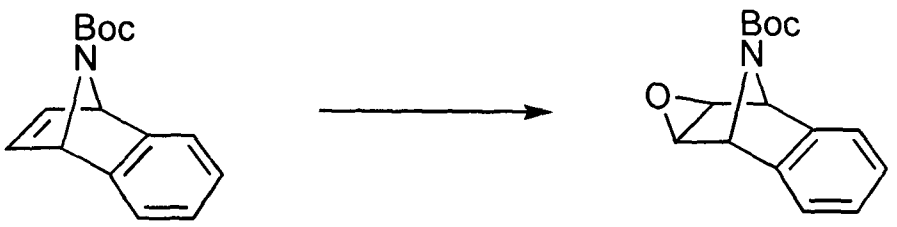


147

Racemic BINAP (31.0 mg, 50 μmol) and $[Rh(COD)Cl]_2$ (12.3 mg, 25 μmol), were placed in a flame-dried flask under argon. Toluene (5 cm^3) was added and the solution was stirred for 10 min. A solution of alkene **146** (500 mg, 2.5 mmol) in toluene (5 cm^3) was added and the solution cooled to −78 °C and stirred 10 min. Catecholborane (595 mg, 5.0 mmol) was added and the mixture stirred for a further 30 min, then allowed to warm to 25 °C and stirred for 3 h. The flask was then cooled to 0 °C and EtOH (2.5 cm^3) was added followed by H_2O_2 (2.0 cm^3 of a 35% aq. solution) and aqueous NaOH (5.0 cm^3 of a 2 M solution) dropwise over 5 min. The reaction was removed from the ice bath and then stirred at 25 °C for 16 h. The mixture was diluted with 1 M NaOH (30 cm^3) and extracted with Et_2O (3 x 50 cm^3). The combined extracts were washed with 1 M NaOH (60 cm^3) and water (60 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure to give an oil. Column chromatography (SiO_2, 80% Et_2O : petroleum ether to 100% Et_2O, gradient elution) gave the alcohol **147** as a colourless oil that crystallised on standing to a

white solid (305 mg, 56%): mp (from Et_2O) 82-83 °C; R_f (Et_2O) 0.31; ν_{max}(thin film)/cm^{-1} 3424 br s, 3025m, 2982m, 2953s, 1694s, 1447s, 1367s, 1290s, 1252s 1195s, 1167s, 1102s, 1055s, 967m, 921m, 756s, 733s; δ_H (400 MHz) 7.29-7.23 (1 H, m, CH of aromatic), 7.20-7.15 (1 H, m, CH of aromatic), 7.14-7.08 (2 H, m, 2 x CH of aromatic), 5.19 (1 H, s, C(1)H), 5.07 (1 H, s, C(4)H), 4.03-3.99 (1 H, m, C*H*-OH), 3.63 (3 H, s, Me-O), 3.26 (1 H, br s, OH), 1.90-1.82 (2 H, m, CH_2); δ_C (100 MHz) 157.0 (C=O), 146.1, 141.3 (both C(quat)), 127.2, 126.6, 121.3, 119.7 (4 x C of aromatic), 72.8 (CH-O), 68.9 (C1), 60.6 (C4), 52.7 (MeO), 39.5 (C3); m/z (CI^+, NH_3), 237 ($M+NH_4^+$, 40%), 220 ($M+H^+$, 100), 202 (8), 188 (3), 175 (12), 160 (2), 118 (2), 52 (8) (Found $M+H^+$, 220.0970, $C_{12}H_{14}NO_3$ requires 220.0973).

***N*-(*tert*-Butoxycarbonyl)-*exo*-2,3-epoxy-1,2,3,4-tetrahydro-1,4-iminonaphthalene 216 :**[45]



216

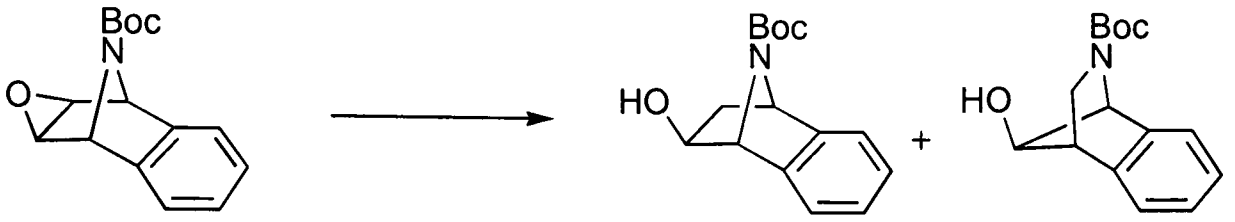
Alkene **138** was epoxidised according to the procedure of Maxwell using buffered dimethyldioxirane in 71% yield, lit.[45] 80%. δ_H (200 MHz) 7.40-7.28 (2 H, m, 2 x CH of aromatic), 7.22-7.14 (2 H, m, 2 x CH of aromatic), 5.19 and 5.05 (2 H, 2 x s, C(1)H and C(4)H), 3.52-3.48 (2 H, m, 2 x CH-O), 1.51 (9 H, s, Bu^t).

***N*-(*tert*-Butoxycarbonyl)-*syn*-1,4-methano-1,2,3,4-tetrahydroisoquinolin-9-ol 217 :**

217

$NaCNBH_3$ (72 mg, 1.14 mmol) and then $BF_3.Et_2O$ (93 μL, 0.76 mmol) were added to a solution of epoxide **216** (100 mg, 0.38 mmol) in THF (5 cm^3) under argon at 25 °C and the mixture stirred for a total of 30 h with more $NaCNBH_3$ (72 mg) and $BF_3.Et_2O$ (93 μL) added after 24 h. Brine (5 cm^3) was then added and the mixture extracted with Et_2O (3 x 5 cm^3), the combined extracts dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, 60 % Et_2O : petroleum ether) gave starting material (27 mg) and the alcohol **217** as a white solid (48 mg, 48%, 65% wrt recovered starting material): R_f (Et_2O) 0.40; mp 111-112 °C; ν_{max}(thin film)/cm^{-1} 3386 br s, 3025w, 2976s, 2931m, 2893m, 1674s, 1456s, 1418s, 1367s, 1313m, 1253m, 1179s, 1155, 1140, 1102s, 911m, 732s; δ_H (400 MHz, 2:3 mixture of rotamers) 7.42-7.11 (4 H, m, 4 x CH of aromatic), 4.91 and 4.72 (1 H, 2 x br s, C(1)H), 4.10-3.70 (1 H, br s, OH), 3.86 (1 H, s, C*H*OH), 3.76 (1 H, d, J 9.0, C(3) *exo*), 3.39 (1 H, s, C(4)H), 2.85 and 2.79 (1 H, 2 x d, J 9.0, C(3) *endo*), 1.43 and 1.38 (9 H, s, Bu^t); δ_C (100 MHz) 156.4, 155.9 (C=O), 143.0, 142.7, 141.3, 141.1 (2 x C(quat.) of aromatic), 127.8, 126.7, 122.5, 122.1, 121.3 (4 x C of aromatic), 80.9 (C9), 80.2 (*C*Me_3), 79.9 (C9), 65.1, 64.1 (C1), 48.6, 48.1 (C4), 45.6, 44.9 (C3), 28.5 (C*Me*$_3$); m/z (CI^+) 262 ($M+H^+$, 54%), 206 (6), 179 (4), 162 (M-Boc^+, 100), 130 (4) 102 (3) (Found $M+H^+$, 262.1435, $C_{15}H_{20}NO_3$ requires 262.1443).

***N*-(*tert*-Butoxycarbonyl)-*exo*-1,2,3,4-tetrahydro-1,4-iminonapthalen-2-ol 141** and ***N*-(*tert*-butoxycarbonyl)-*syn*-1,4-methano-1,2,3,4-tetrahydroisoquinolin-9-ol 217** from titanium chemistry:

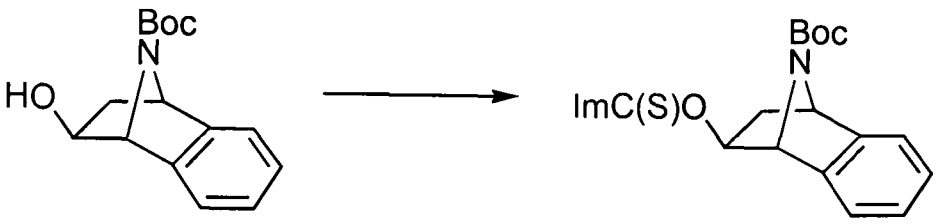


141 **217**

Collidine hydrochloride (91 mg, 0.58 mmol) was added to THF (5 cm^3) under argon, followed by epoxide **216** (100 mg, 0.38 mmol), 1,4-cyclohexadiene (132 mg, 1.65 mmol), titanocene dichloride (10 mg, 0.039 mmol, 0.1 equiv), and manganese powder (32 mg, 0.58 mmol). The reaction was stirred at 25 °C under argon for 24 h, during which time the mixture changed colour from red to yellow then green and finally blue. The stirrer bar was removed and the mixture decanted to remove the remaining manganese. Et_2O (5 cm^3) was added and the mixture washed with 1 M HCl (5 cm^3) and then water (10 cm^3) and finally saturated $NaHCO_3$ (10 cm^3). The mixture was extracted with Et_2O (3 x 10 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, 50 % Et_2O : petroleum ether to 100% Et_2O, gradient elution) gave starting material (6 mg) and a 3:1 mixture of alcohols **141** (major) and **217** (minor) as an oil (40 mg, 40%, 42% by rsm), as judged by the ^1H NMR spectrum.

Radical precursors:

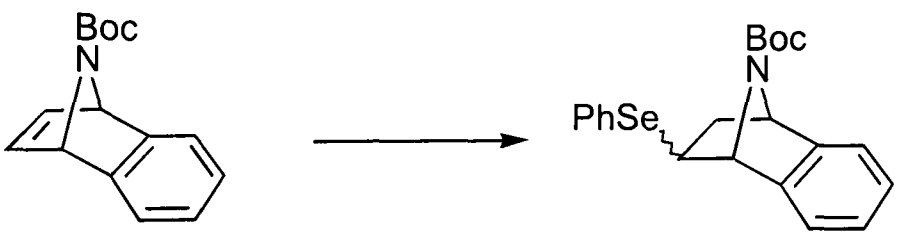
N-(*tert*-Butoxycarbonyl)-*exo*-2-(3*H*-imidazole-1-carbothioyloxy)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 145 :



145

Thiocarbonyldiimidazole (304 mg, 1.7 mmol) was added to a solution of alcohol **141** (100 mg, 0.38 mmol) in CH_2Cl_2 (3 cm^3) and the mixture was stirred under nitrogen for 16 h at 25 °C. The solvent was removed at reduced pressure and chromatography (SiO_2, Et_2O as eluant) gave the product **145** (140 mg, 100% yield) which was not fully characterised but identified by the appearance of signals at 5.3, 7.0, 7.65 and 8.35 ppm corresponding to the C(H)O proton and the 3 imidazole protons.

***N*-(*tert*-Butoxycarbonyl)-*endo/exo*-2-phenylseleno-1,2,3,4-tetrahydro-1,4-iminonapthalene 140 :**



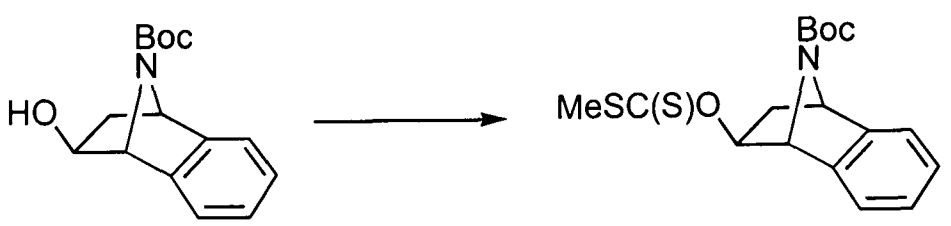
140

Benzeneselenol (175 μL, 164 mmol) was added to a solution of alkene **138** (200 mg, 0.82 mmol) in toluene (1 cm^3) under nitrogen and the mixture stirred at 25 °C for 24 h, then allowed to cool. The solvent was removed at reduced pressure and chromatography (SiO_2, Biotage system™, 10% Et_2O : isohexane) gave the

selenides **140** as a pale yellow oil (3 : 1 mixture of *exo* and *endo* isomers) (298 mg, 90%): R_f (50 % Et_2O : 50% petroleum ether) 0.50; δ_H (400 MHz) (*exo* isomer) 7.58 (2 H, m, 2 x CH of aromatic), 7.30-7.08 (7H, m, 7 x CH of aromatic), 5.19 (1 H, br s, C(1)H), 5.10 (1 H, br s, C(4)H), 3.22 (1 H, br s , CH-Se), 2.15-2.08 (2 H, m, C(3)H *exo* and *endo*), 1.41 (9 H, s, Bu^t), (*endo* isomer) 7.49 (2 H, m, 2 x CH of aromatic), 7.32-7.08 (7H, m, 7 x CH of aromatic), 5.14 (2 H, br s, C(1)H and C(4)H), 3.91(1 H, m, CH-Se), 2.77-2.72 (1 H, m, C(3)H *exo*), 1.40 (9 H, s, Bu^t), 1.27 (1 H, dd, J 10.0 and 4.0, C(3)H *endo*).

General procedure for xanthate preparation:

***N*-(*tert*-Butoxycarbonyl)-*exo*-2-(methylsulfanylthiocarboxyoxy)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 142 :**



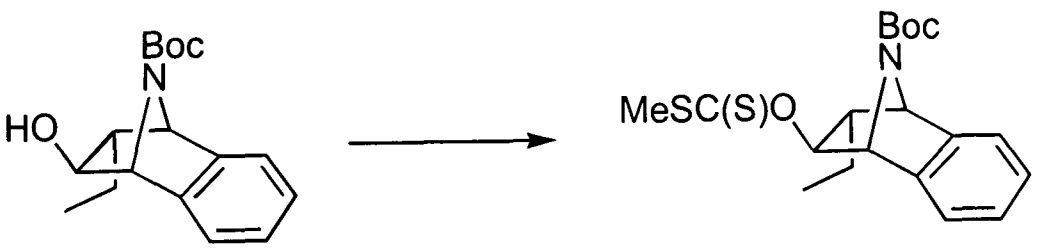
142

Alcohol **141** (200 mg, 0.76 mmol) was added to KH (400 mg of 30% suspension, 3 mmol) in THF (10 cm^3) at 0 °C and the mixture was then stirred at room temperature for 20 min. The mixture was cooled to 0 °C and CS_2 (228 mg, 3 mmol) was added and the mixture stirred for 10 min at 0 °C. Finally MeI (425 mg, 3 mmol) was added and the solution was stirred at room temperature for 20 min. The reaction was quenched with dropwise addition of water until effervescence had ceased and the aqueous layer extracted with Et_2O (2 x 10 cm^3), the combined extracts dried ($MgSO_4$), and the solvent removed at reduced pressure. Column chromatography (SiO_2, 20% Et_2O : petroleum ether) gave **142** as a yellow solid which was not fully characterised (220 mg, 83%): R_f (50% Et_2O : petroleum ether)

0.59; ν_{max}(KBr)/cm^{-1} 3019m, 2975s, 2924s, 1696s, 1372s, 1294s, 1269s, 1222s, 1160s, 1092s, 1060s, 1002m, 771s; δ_H (400 MHz) 7.37 (1 H, s, CH of aromatic), 7.30-7.15 (3 H, m, 3 x CH of aromatic), 5.42 (2 H, s, C(1)H and C(4)H), 5.21 (1 H, s, CH-O), 2.59 (3 H, s, SMe), 2.23-2.15 (1 H, m, H of CH_2), 2.09-1.99 (1 H, m, H of CH_2), 1.43 (9 H, s, Bu^t); m/z (CI$^+$, NH_3) 369 (M+NH_4^+, 2%), 352 (M+H$^+$, 15), 262 (43), 252 (50), 218 (16), 207 (38), 189 (10), 162 (69), 146 (100), 118 (62), 90 (19) (Found, M+H$^+$, 352.1041, $C_{17}H_{21}NO_3S_2$ requires 352.1041).

The other xanthates were not fully characterised, but were identified by the appearance of a 3 H singlet at ~2.6 ppm and a shift of the CH-O proton from ~4.0 ppm to ~5.3 ppm.

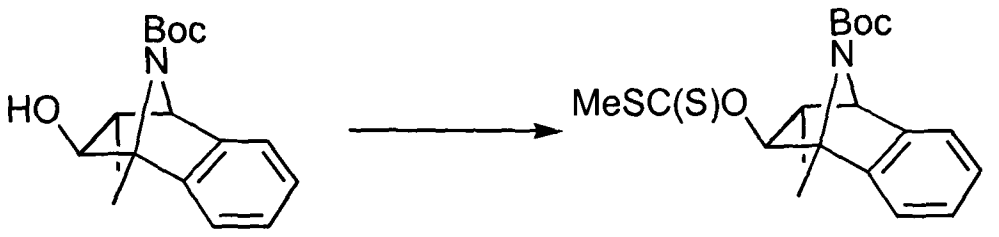
_N_-(*tert*-Butoxycarbonyl)-*exo*-2-(methylsulfanylthiocarboxyoxy)-*endo*-3-ethyl-1,2,3,4-tetrahydro-1,4-iminonaphthalene 187 :



187

Reaction of alcohol **186** (200 mg, 0.69 mmol) according to the standard procedure above gave an oil. Chromatography (SiO_2, 10% Et_2O : petroleum ether to 30 % Et_2O : petroleum ether) gave xanthate **187** (208 mg, 79%) as an oil : R_f (25% Et_2O : petroleum ether) 0.53.

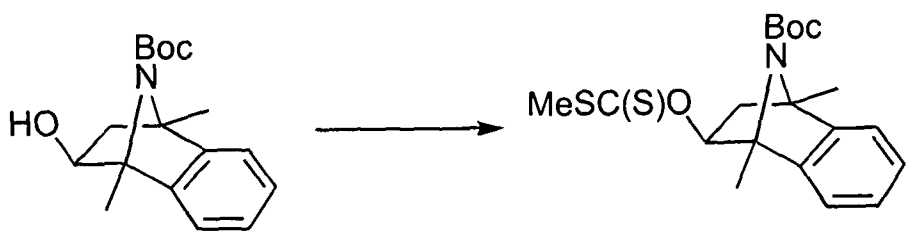
_N_-(*tert*-Butoxycarbonyl)-*endo*-1,3-dimethyl-*exo*-2-(methylsulfanylthiocarboxyoxy)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 190 :



190

Reaction of alcohol **189** (238 mg, 0.82 mmol) according to the standard procedure above gave an oil. Chromatography (SiO_2, 10% Et_2O : petroleum ether) gave xanthate **190** (244 mg, 78%) as an oil : R_f (30% Et_2O : petroleum ether) 0.53.

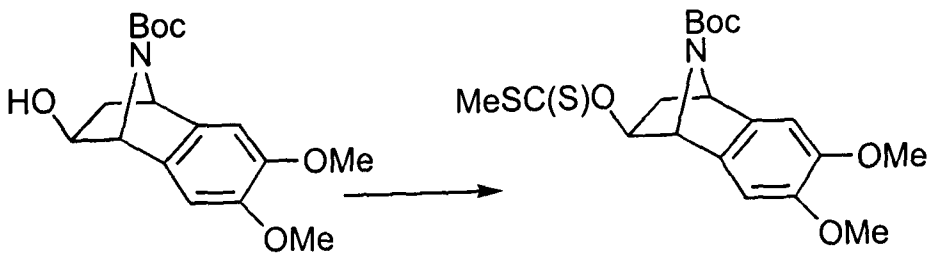
_N_-(_tert_-Butoxycarbonyl)-1,4-dimethyl-_exo_-2-(methylsulfanylthiocarboxyoxy)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 193 :



193

Reaction of alcohol **192** (450 mg, 1.56 mmol) according to the standard procedure above gave an oil. Chromatography (SiO_2, 5% Et_2O : petroleum ether to 20% Et_2O : petroleum ether) gave xanthate **193** (437 mg, 74%) as an oil: R_f (20% Et_2O : petroleum ether) 0.45.

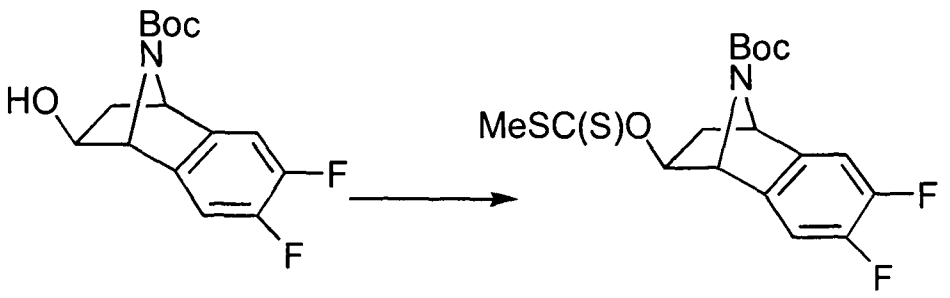
_N_-(_tert_-Butoxycarbonyl)-_exo_-2-(methylsulfanylthiocarboxyoxy)-6,7-dimethoxy-1,2,3,4-tetrahydro-1,4-iminonaphthalene 210 :



210

Reaction of alcohol **209** (140 mg, 0.43 mmol) according to the general procedure above gave an oil. Chromatography (SiO_2, 50% Et_2O : petroleum ether) gave xanthate **210** (137 mg, 77%) as an oil : R_f (50% Et_2O : petroleum ether) 0.24.

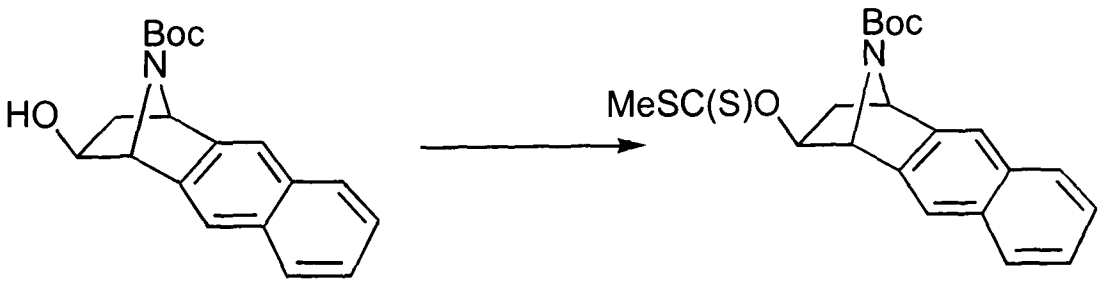
_N_-(_tert_-Butoxycarbonyl)-_exo_-2-(methylsulfanylthiocarboxyoxy)-6,7-difluoro-1,2,3,4-tetrahydro-1,4-iminonaphthalene 207 :



207

Reaction of alcohol **206** (144 mg, 0.48 mmol) according to the general procedure above gave an oil. Chromatography (SiO_2, 10% Et_2O : petroleum ether to 15 % Et_2O : petroleum ether, gradient elution) gave xanthate **207** (150 mg, 79%) as an oil : R_f (25% Et_2O : petroleum ether) 0.33.

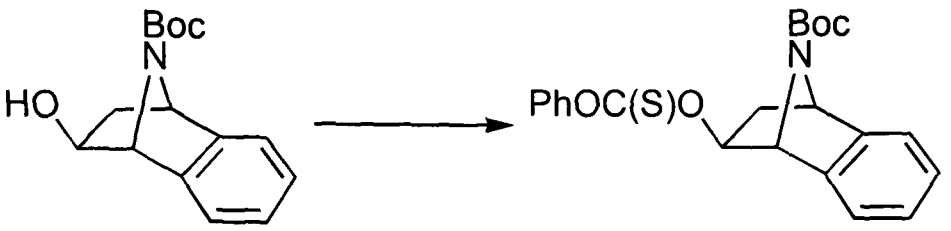
_N_-(_tert_-Butoxycarbonyl)-_exo_-2-(methylsulfanylthiocarboxyoxy)-1,2,3,4-tetrahydro-1,4-iminoanthracene 213 :



213

Reaction of alcohol **212** (227 mg, 0.73 mmol) according to the general procedure above gave an oil. Chromatography (SiO_2, 5% Et_2O : petroleum ether to 10% Et_2O : petroleum ether) gave xanthate **213** (185 mg, 63%) as an oil: R_f (20% Et_2O : petroleum ether) 0.40.

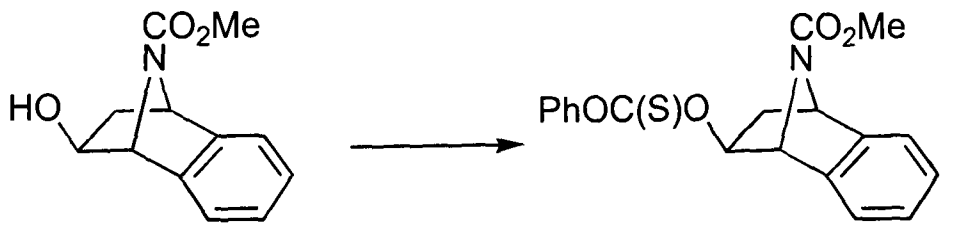
_N_-(*tert*-Butoxycarbonyl)-*exo*-2-(phenoxythiocarbonyloxy)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 144 :



144

Alcohol **141** (145 mg, 0.55 mmol), phenyl chlorothionocarbonate (143 mg, 0.83 mmol) and DMAP (267 mg, 2.2 mmol) were stirred in CH_2Cl_2 (5 cm^3) at 25 °C for 18 h. MeOH (1 cm^3) was added and the organic layer washed with 1 M HCl (2 x 5 cm^3), extracted with CH_2Cl_2 (2 x 10 cm^3), dried ($MgSO_4$), and the solvent removed at reduced pressure. Column chromatography (SiO_2, 15% Et_2O : petroleum ether) gave **144** as a yellow solid (200 mg, 90 %): R_f (20% Et_2O : petroleum ether) 0.21. This precursor was not fully characterised, but was identified by a shift in the CH–O proton signal in the ^1H NMR spectrum from 4.00 to 5.2 ppm and an increase in the aromatic proton integral from 4 H to 9 H.

_N_-(Methoxycarbonyl)-*exo*-2-(phenoxythiocarbonyloxy)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 148 :



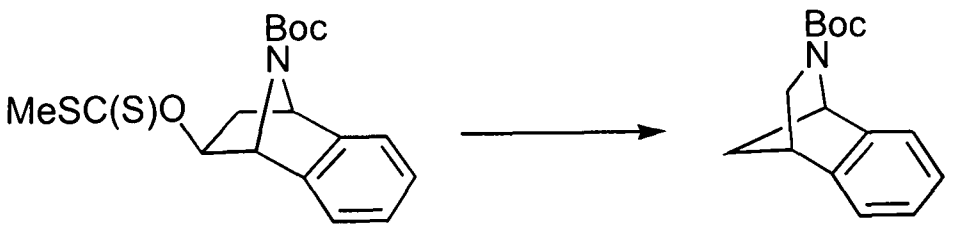
148

To a solution of alcohol **147** (200 mg, 0.91 mmol) in CH_2Cl_2 (5 cm^3) was added DMAP (333 mg, 2.7 mmol) and phenyl chlorothionocarbonate (314 mg, 1.8 mmol). The reaction was stirred overnight under argon. MeOH (1 cm^3) was added and the organic layer washed with 2 M HCl (2 x 5 cm^3), the mixture extracted with CH_2Cl_2

(3 x 10 cm^3), the combined organic extracts dried ($MgSO_4$), and the solvent removed at reduced pressure. Column chromatography (SiO_2, 30% Et_2O : petroleum ether) gave thiobenzoate **148** as a yellow oil (258 mg, 80%): R_f (50% Et_2O : petroleum ether) 0.41. The product was not fully characterised but instead was identified by a change in chemical shift of the CH-O proton from 4.0 in the starting alcohol to 5.1 ppm in the ^1H NMR spectrum and an increase in the aromatic proton integral from 4 H to 9 H.

Rearranged products:

***N*-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydro-1,4-methanoisoquinoline 126 :**

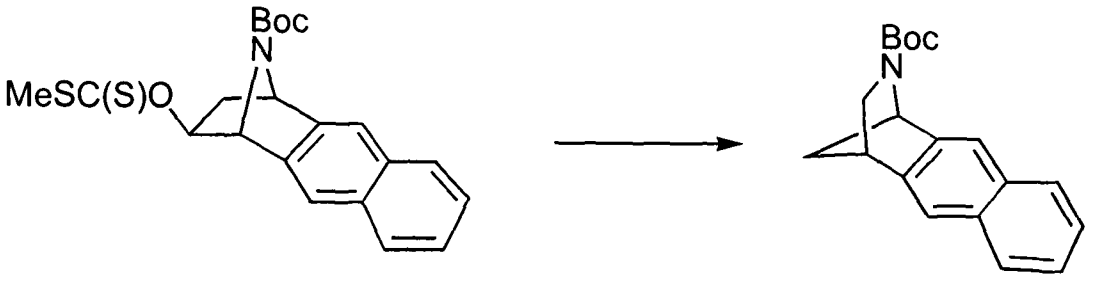


126

A mixture of AIBN (60 mg, 0.36 mmol) and TTMSS (266 mg, 1.07 mmol), in toluene (2 cm^3), was added over 100 min to a preheated solution of xanthate **142** (250 mg, 0.71 mmol) in toluene (21 cm^3). The reaction was left at reflux for a further 30 min after completion of the addition, allowed to cool, and the solvent removed at reduced pressure. Column chromatography (SiO_2, 10% Et_2O : petroleum ether) gave **126** as a colourless oil that crystallised on standing to a white solid (158 mg, 90%); R_f (50% Et_2O : petroleum ether) 0.54; mp (from petroleum ether) 65-66°C; ν_{max}(thin film)/cm^{-1} 2977s, 2889m, 1698s, 1462m, 1392s, 1251m, 1181m, 1152s, 1093s, 838m, 755m ; δ_H (500 MHz, DMSO–d_6, 90 °C) 7.34 (1 H, d, J 7.0, CH of aromatic), 7.24 (1 H, d, J 7.0, CH of aromatic), 7.21-7.11 (2 H, m, 2 x CH of aromatic), 4.94 (1 H, br s, C(1)H), 3.66 (1 H, s, C(4)H), 3.48 (1 H, dd, J 9.0

and 3.0, C(3)H *exo*), 2.64 (1 H, dd, J 9.0 and 2.0, C(3)H *endo*), 1.96 (1 H, d, J 9.0, C(9)H), 1.79 (1 H, d, J 9.0, C(9)H), 1.37 (9 H, s, Bu^t); δ_C (125 MHz, DMSO–d_6, 90 °C) 155.4 (C=O), 146.4, 145.1 (2 x C(quat) of aromatic), 127.8, 126.7, 122.2, 121.0 (4 x CH of aromatic), 79.4 (*C*Me_3), 62.2 (C1), 49.5 (C3), 49.1 (C9), 44.5 (C4), 28.2 (Bu^t); m/z (CI^+, NH_3) 263 ($M+NH_4^+$, 21%), 246 ($M+H^+$, 25), 207 (100), 190 (4), 163 (8), 146 ($M+H\text{-}Boc^+$, 96) 116 (5) (Found $M+H^+$, 246.1494, $C_{15}H_{20}NO_2$ requires 246.1494).

_N_-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydro-1,4-methano-2-azaanthracene 214 :

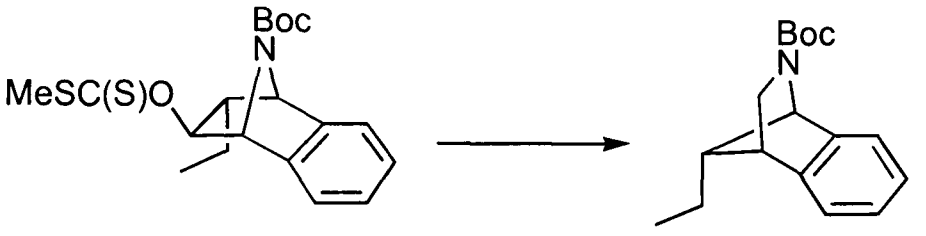


214

AIBN (40 mg, 0.24 mmol) and TTMSS (172 mg, 0.69 mmol) in toluene (2 cm^3) were added to a pre-heated solution of xanthate **213** (185 mg, 0.46 mmol) in toluene at reflux (14 cm^3) over 100 min. The reaction was left for a further 30 min at reflux, allowed to cool and then the solvent removed at reduced pressure. Chromatography (SiO_2, 10% Et_2O : 90% petroleum ether) gave the product **214** as a white solid (115 mg, 84%): R_f (10% Et_2O : 90% petroleum ether) 0.21; mp (from petroleum ether) 130-132 °C (Found, C, 77.3; H, 7.3; N, 4.8; $C_{19}H_{21}NO_2$ requires C, 77.3; H, 7.2; N, 4.7%); ν_{max}(KBr)/cm^{-1} 2987s, 2960m, 2930m, 1681s, 1367s, 1284m, 1150s, 1090s, 865m; δ_H (500 MHz, DMSO-d_6, 90 °C), 7.89-7.84 (2 H, m, 2 x CH of aromatic), 7.78 (1 H, s, CH of aromatic), 7.68 (1 H, s, CH of aromatic), 7.47-7.44 (2 H, m, 2 x CH of aromatic), 5.08 (1 H, s, C(1)H), 3.78 (1 H, s, C(4)H), 3.58 (1 H, dd, J 9.0 and 3.0, C(3)H *exo*), 2.81 (1 H, dd, J 9.0 and 3.0, C(3)H *endo*),

2.10 (1 H, d, J 9.0, C(11)H), 1.88 (1 H, d, J 9.0, C(11)H), 1.37 (9 H, s, Bu^t); δ_C (125 MHz, DMSO-d_6, 90 °C) 155.2 (C=O), 144.8, 143.4, 133.8, 133.2 (4 x C(quat) of aromatic) 128.9, 128.6, 126.3, 126.1, 120.3, 118.8 (6 x C of aromatic), 79.5 (CMe_3), 61.6 (C1), 50.4, 48.1 (C3 and C11), 44.2 (C4), 29.1 (CMe_3) ; m/z (CI^+, NH_3) 313 ($M+NH_4^+$, 10%), 296 ($M+H^+$, 8), 257 (100), 240 (8), 196 ($M+H\text{-}Boc^+$, 63), 166 (12) 154 (3) (Found, $M+H^+$, 296.1648, $C_{19}H_{22}NO_2$ requires 296.1650).

_N_-(*tert*-Butoxycarbonyl)-*anti*-9-ethyl-1,2,3,4-tetrahydro-1,4-methanoisoquinoline 188 :

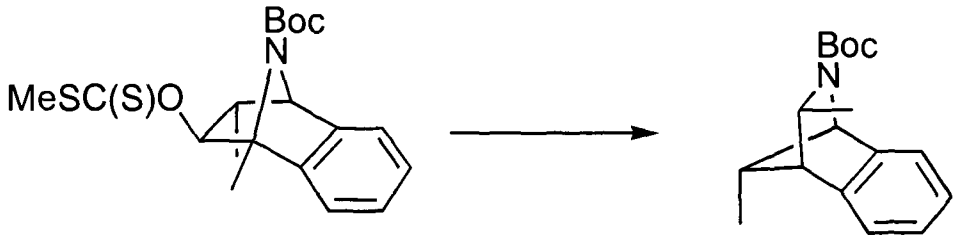


188

A mixture of AIBN (46 mg, 0.28 mmol) and TTMSS (205 mg, 0.83 mmol), in toluene (2 cm^3), was added over 100 min to a preheated solution of xanthate **187** (208 mg, 0.55 mmol) in toluene (16 cm^3) at reflux. The reaction was left at reflux for a further 30 min after completion of the addition, allowed to cool, and the solvent removed at reduced pressure. Column chromatography (SiO_2, 50% CH_2Cl_2 : petroleum ether) gave **188** as a colourless oil (110 mg, 73%); R_f (20% Et_2O : petroleum ether) 0.33; ν_{max}(thin film)/cm^{-1} 2963s, 2929s, 2889s, 1694s, 1477s, 1455s, 1391s, 1363s, 1247m, 1174s, 1144s, 1103s, 864m; δ_H (500 MHz, DMSO–d_6, 90 °C) 7.33 (1 H, d, J 6.5, CH of aromatic), 7.25 (1 H, d, J 7.0, CH of aromatic), 7.23-7.13 (2 H, m, 2 x CH of aromatic), 4.73 (1 H, s, C(1)H), 3.48 (1 H, d, J 7.0, C(3)H *exo*), 3.42 (1 H, s, C(4)H), 2.64 (1 H, d, J 7.0, C(3)H *endo*), 2.34-2.28 (1 H, m, C(9)H), 1.37 (9 H, s, Bu^t), 0.97-0.86 (2 H, m, 2 x H of CH_2), 0.85-0.78 (3 H, m, Me); δ_C (100 MHz, 3:1 mixture of rotamers) 154.7 and 153.8 (C=O), 143.8 and

143.5 (C(quat) of aromatic), 142.3 (C(quat) of aromatic), 127.2 and 127.1, 126.0, 122.8 and 122.7, 121.6 and 121.2 (4 x CH of aromatic), 78.5 and 78.4 (*C*Me_3), 64.0 and 62.6 (C1), 60.5 and 60.4 (C9), 49.4 and 49.3 (C4), 47.0 and 46.3 (C3), 28.1 and 28.0 (Bu^t), 19.3 (Me-*C*H_2), 12.2 and 12.1(Me); m/z (CI^+, NH_3) 274 ($M+H^+$, 24%), 235 (97), 218 (67), 174 (100), 144 (25) (Found $M+H^+$, 274.1813, $C_{17}H_{24}NO_2$ requires 274.1813). 1D nOe experiment: irradiation of C(9)H at 2.30 ppm showed enhancement of the signal at 3.48 ppm, assigned as C(3)H *exo*, demonstrating that the proton attached to C9 is *syn*- to nitrogen.

_N_-(*tert*-Butoxycarbonyl)-*endo,anti*-3,9-dimethyl-1,2,3,4-tetrahydro-1,4-methano isoquinoline 191 :

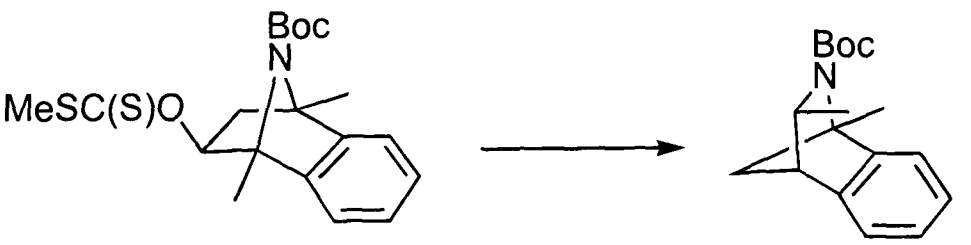


191

A mixture of AIBN (77 mg, 0.47 mmol) and TTMSS (316 mg, 1.28 mmol), in toluene (4 cm^3), was added over 70 min to a preheated solution of xanthate **190** (244 mg, 0.64 mmol) in toluene (14 cm^3) at reflux. The reaction was left at reflux for a further 30 min after completion of the addition, allowed to cool, and the solvent removed at reduced pressure. Column chromatography (SiO_2, 50% CH_2Cl_2 : petroleum ether to 100% CH_2Cl_2) gave **191** as a colourless oil (155 mg, 88%) ; R_f (20% Et_2O : petroleum ether) 0.40; ν_{max}(thin film)/cm^{-1} 2972s, 2929s, 2876s, 1694s, 1478s, 1459s, 1394s, 1343s, 1289s, 1246s, 1178s, 1142s, 1095s, 871m ; δ_H (400 MHz, 2:1 mixture of rotamers) 7.36-7.30 (1 H, m, CH of aromatic), 7.28-7.21 (1 H, m, CH of aromatic), 7.20-7.13 (2 H, m, 2 x CH of aromatic), 4.90 and 4.72 (1 H, 2 x s, C(1)H), 4.03 and 3.96 (1 H, 2 x br s, C(3)H), 3.11 (1 H, s, C(4)H), 2.55-

2.49 (1 H, m, C(9)H), 1.46 and 1.42 (9 H, 2 x s, Bu^t), 0.82 and 0.76 (3 H, 2 x d, J 6.0, 3-Me), 0.66 (3 H, d, J 6.0, 9-Me) ; δ_C (100 MHz, $CDCl_3$) 154.7 and 153.8 (C=O), 143.2 and 143.1 (C(quat) of aromatic), 142.0 (superposed signals, C(quat) of aromatic), 126.7 and 126.4 (both superposed signals), 125.1 and 124.9, 122.4 and 121.8, (4 x CH of aromatic), 79.1 and 78.9 (CMe_3), 66.9 and 65.8 (C1), 56.0 and 55.5 (C4), 54.8 (C9), 54.6 and 54.0 (C3), 28.4 and 28.3 (Bu^t), 18.0 and 16.9 (3-Me), 11.9 (9-Me); m/z (CI^+, NH_3) 274 ($M+H^+$, 28%), 235 (90), 218 (73), 174 (100), 130 (32) (Found $M+H^+$, 274.1795, $C_{17}H_{24}NO_2$ requires 274.1807). 1D nOe experiment: irradiation of C(9)H at 2.52 ppm showed enhancement of both signals at 4.03 and 3.96 ppm, assigned as C(3)H, demonstrating that the protons attached to C9 and C3 are syn to one another. Irradiation of C(3)H also gave enhancement of the C(9)H signal.

_N_-(*tert*-Butoxycarbonyl)-*endo*-1,3-dimethyl-1,2,3,4-tetrahydro-1,4-methanoisoquinoline 194 :

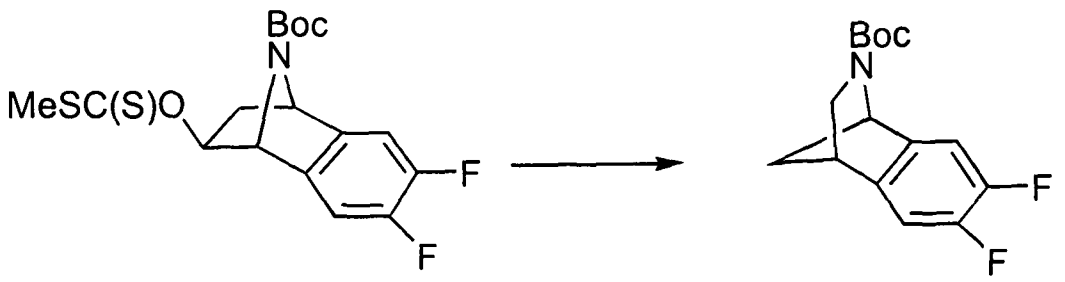


194

A mixture of AIBN (95 mg, 0.57 mmol) and TTMSS (391 mg, 1.58 mmol), in toluene (5 cm^3), was added over 70 min to a preheated solution of xanthate **193** (300 mg, 0.79 mmol) in toluene (17 cm^3) at reflux. The reaction was left at reflux for a further 30 min after completion of the addition, allowed to cool, and the solvent removed at reduced pressure. Column chromatography (SiO_2, 50% CH_2Cl_2 : petroleum ether to 100% CH_2Cl_2) gave **194** as a white solid (55 mg, 25%); R_f (10% Et_2O : petroleum ether) 0.33; δ_H (200 MHz) 7.30-7.05 (4 H, m, 4 x CH of

aromatic), 4.15-4.01 (1 H, m, C(3)H), 3.28 (1 H, s, C(4)H), 2.05 (1 H, d, J 12.0, C(9)H), 1.97 (3 H, s, 3-Me), 1.86 (1 H, d, J 12.0, C(9)H), 1.43 (9 H, s, Bu^t), 0.81 (3 H, d, J 8.0, 3-Me); Compound was found to be unstable to ring opening to give **199** (see later).

_N_-(*tert*-Butoxycarbonyl)-6,7-difluoro-1,2,3,4-tetrahydro-1,4-methanoisoquinoline 208 :

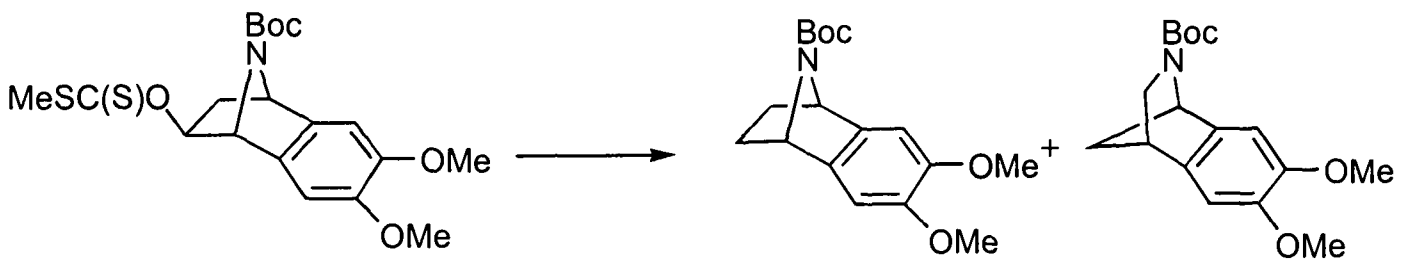


208

A mixture of AIBN (33 mg, 0.20 mmol) and TTMSS (143 mg, 0.58 mmol), in toluene (2 cm^3), was added over 100 min to a preheated solution of xanthate **207** (150 mg, 0.39 mmol) in toluene (9 cm^3) at reflux. The reaction was left at reflux for a further 30 min after completion of the addition, allowed to cool, and the solvent removed at reduced pressure. Column chromatography (SiO_2, 15% Et_2O : petroleum ether) gave **208** as a colourless oil (70 mg, 64%) ; R_f (20% Et_2O : petroleum ether) 0.22; ν_{max}(thin film)/cm^{-1} 2977s, 2890s, 1694s, 1614s, 1478s, 1392s, 1363s, 1276s, 1249s, 1149s, 1046s, 1008m, 867s; δ_H (400 MHz, 2 : 1 mixture of rotamers) 7.19-6.95 (2 H, m, 2 x CH of aromatic), 5.04 and 4.90 (1 H, 2 x br s, C(1)H), 3.59 (1 H, s, C(4)H), 3.51 (1 H, dd, J 9.0 and 3.0, C(3)H *exo*), 2.79 and 2.70 (1 H, 2 x d, J 9.0, C(3)H *endo*), 2.07-1.93 (1 H, m, C(9)H), 1.87 (1 H, d, J 9.0, C(9)H), 1.43 and 1.35 (9 H, 2 x s, Bu^t); δ_C (100 MHz) 155.2 and 154.8 (C=O), 149.4 (dd, J 245 and 12, C-F), 148.8 (dd, J 245 and 13, C-F), 141.2, 140.2 (2 x C(quat) of aromatic), 111.4 and 111.0 (2 x d, J 20, CH of aromatic), 110.7 and

109.8 (2 x d, J 20, CH of aromatic), 79.7 (*C*Me$_3$), 61.4 and 60.3 (C1), 48.8 and 48.6 (C3), 48.2 (C9), 44.3 and 44.0 (C4), 28.5 and 28.3 (Bu^t); ^{19}F (235 MHz) −140.2 (d, J 19, CF), −140.5 (d, J 20, CF), −141.3 (d, J 20, CF), −141.5 (d, J 19, CF); m/z (CI$^+$, NH_3) 299, (M+NH_4^+, 5%), 282 (M+H^+, 15), 243 (62), 226 (22), 182 (100), 152 (24) (Found M+H^+, 282.1305, $C_{15}H_{18}F_2NO_2$ requires 282.1306).

_N_-(*tert*-Butoxycarbonyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-1,4-iminonaphthalene 204 and **_N_-(*tert*-butoxycarbonyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-1,4-methanoisoquinoline 211 :**



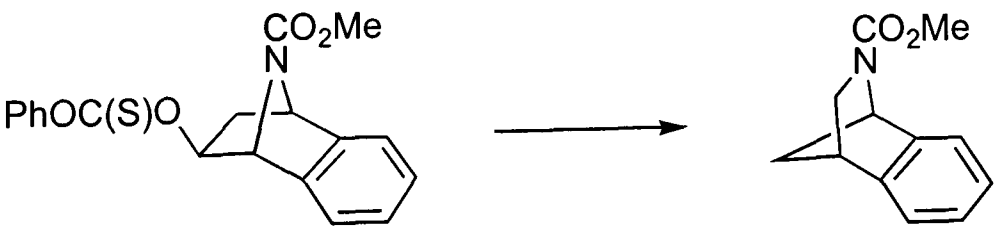
204 **211**

A mixture of AIBN (28 mg, 0.16 mmol) and TTMSS (124 mg, 0.50 mmol) in toluene (2 cm^3) was added over 100 min to a preheated solution of xanthate **210** (137 mg, 0.33 mmol) in toluene (8 cm^3) at reflux. The reaction was left at reflux for a further 30 min after completion of the addition, allowed to cool, and the solvent removed at reduced pressure. Column chromatography (SiO_2, 40% Et_2O : petroleum ether) first gave **204** as a colourless oil (13 mg, 13%): R_f (40% Et_2O : petroleum ether) 0.24; ν_{max}(thin film)/cm^{-1} 2976s, 2872s, 2833s, 1694s, 1614s, 1502s, 1454s, 1392s, 1256s, 1220s, 1168s, 1099s, 969s, 910s; δ_H (400 MHz) 6.83 (2 H, s, 2 x CH of aromatic), 5.03 (2 H, s, C(1)H and C(4)H), 3.83 (6 H, s, 2 x Me-O), 2.05 (2 H, d, J 7.0, 2 x CH *exo*), 1.37 (9 H, s, Bu^t), 1.21 (2 H, d, J 7.0, 2 x CH *endo*); δ_C (100 MHz) 155.2 (C=O), 147.5 (2 x C(quat)), 137.1 (2 x C of aromatic), 104.3 (2 x C of aromatic), 79.9 (*C*Me$_3$), 61.4 (C1 and C4), 56.1 (2 x Me-O), 28.2

(C*Me*$_3$), 27.1 (C2 and C3); m/z (CI$^+$, NH_3) 306 (M+H$^+$, 5%), 277 (7), 250 (35), 221 (12), 206 (39), 189 (100), 177 (38) (Found M+H$^+$, 306.1697, $C_{17}H_{24}NO_4$ requires 306.1705).

Second to elute was **211** as a colourless oil (79 mg, 77%) ; R_f (40% Et_2O : petroleum ether) 0.15; ν_{max}(thin film)/cm^{-1} 2976s, 2886s, 1694s, 1613s, 1492s, 1392s, 1328s, 1298s, 1251s, 1217s, 1183s, 1145s, 1119s, 1092s, 1070s, 1020m, 916m, 855s; δ_H (400 MHz, 3 : 2 mixture of rotamers) 6.96 and 6.83 (1 H, 2 x s, CH of aromatic), 6.89 (1 H, s CH of aromatic), 5.06 and 4.88 (1 H, 2 x s, C(1)H), 3.85 (6 H, s, 2 x Me), 3.55 (1 H, s, C(4)H), 3.50-3.43 (1 H, m, C(3)H *exo*), 2.75 and 2.67 (1 H, 2 x d, J 9.0, C(3)H *endo*), 1.97 and 1.92 (1 H, 2 x d, J 9.0, C(9)H), 1.84 (1 H, d, J 9.0, C(9)H), 1.41 and 1.35 (9 H, 2 x s, Bu^t); δ_C (100 MHz) 155.6 and 154.8 (C=O), 148.2 and 147.9, 147.8 and 147.2, 137.6 and 137.5, 136.7 and 136.5 (4 x C(quat) of aromatic), 106.3 and 105.9 (CH of aromatic), 105.6 and 105.4 (CH of aromatic), 80.4 (*C*Me$_3$), 62.2 and 61.0 (C1), 56.2 and 56.1 (2 x Me-O), 48.9 and 48.6 (C3), 48.8 (C9), 44.6 and 44.0 (C4), 28.7 and 28.5 (Bu^t); m/z (CI$^+$, NH_3) 323 (M+NH_4^+, 3%), 306 (M+H$^+$, 23), 250 (100), 232 (53), 206 (35), 191 (17) (Found M+H$^+$, 306.1710, $C_{17}H_{24}NO_4$ requires 306.1705).

_N_-(Methoxycarbonyl)-1,2,3,4-tetrahydro-1,4-methanoisoquinoline 149 :

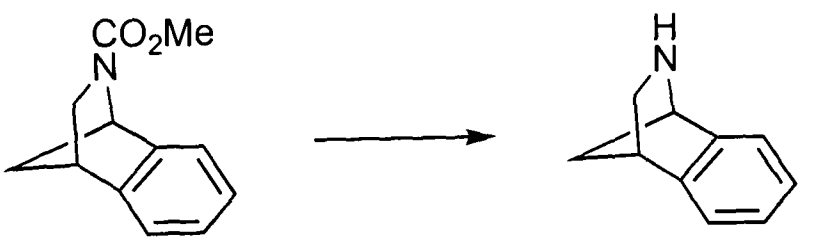


149

A mixture of AIBN (59 mg, 0.36 mmol) and TTMSS (269 mg, 1.09 mmol) in toluene (2 cm^3) was added over 100 min to a preheated solution of thiobenzoate **148** (258 mg, 0.73 mmol) in toluene (18 cm^3). The reaction was left at reflux for a

further 30 min after completion of the addition, allowed to cool, and the solvent removed at reduced pressure. Column chromatography (10% Et_2O : petroleum ether) gave **149** as a colourless oil (115 mg, 78%); R_f (50% Et_2O : petroleum ether) 0.26; ν_{max}(thin film)/cm^{-1} 2988s, 2954s, 2887m, 1698s, 1449s, 1387s, 1310m, 1275m, 1252m, 1191m, 1154s, 1120m, 1101s, 759s; δ_H (500 MHz, 1:1 mixture of rotamers) 7.38-7.08 (4 H, m, 4 x CH of aromatic), 5.17 and 5.04 (1 H, 2 x s, C(1)H), 3.69 and 3.59 (3 H, 2 x s, Me-O), 3.66 (1 H, s, C(4)H), 3.61-3.55 (1 H, m, C(3)H *exo*), 2.87 and 2.80 (1 H, 2 x d, J 9.0, C(3)H *endo*), 2.02 and 1.99 (1 H, 2 x d, J 9.0, C(9)H), 1.91 (1 H, d, J 9.0, C(9)H); δ_C (125 MHz) 156.1 and 155.7 (C=O), 145.3 and 145.2, 144.0 and 143.9 (2 x C(quat) of aromatic), 127.1 and 127.0, 126.3 and 126.1, 121.5 and 121.2, 120.8 and 120.3 (4 x CH of aromatic), 61.5 and 61.1 (C1), 52.1 and 52.0 (Me-O), 48.8 and 48.7, 48.5 and 48.4 (C3 and C9), 44.4 and 43.8 (C3); m/z (EI^+) 203 (M^+, 20%), 188 (8), 175 (4), 158 (2), 144 (7), 128 (17), 116 (100), 105 (6), 84 (14), 77 (6), 59 (29), 49 (25) (Found, $M+H^+$, 204.1026, $C_{12}H_{14}NO_2$ requires 204.1024).

1,2,3,4-tetrahydro-1,4-methanoisoquinoline 120 :[80]



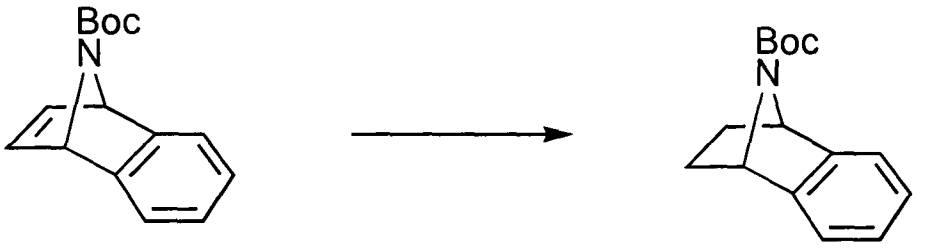
120

To a solution of carbamate **149** (150 mg, 0.76 mmol) in ethylene glycol (8 cm^3) was added 10% aq. KOH (8 cm^3). The mixture was brought to reflux and left for 14 h. The mixture was allowed to cool, extracted with Et_2O (5 x 100 cm^3), the organic extracts washed with water (2 x 100 cm^3), dried (K_2CO_3) and the solvent removed at reduced pressure. Chromatography (Et_2O, 1% MeOH, 2% Et_3N) gave the known

amine **120** (50 mg, 47%): R_f (Et_2O, 2% Et_3N) 0.12; ν_{max}(thin film)/cm^{-1} 3327 br m, 3239 br m, 3044m, 2977s, 2871m, 1698s, 1460s, 1374w, 1256w, 1167w, 1049w, 966w, 754s; δ_H (400 MHz) 7.30-7.05 (4 H, m, 4 x CH of aromatic), 4.38 (1 H, s, C(1)H), 3.56 (1 H, s, C(4)H), 3.18 (1 H, dd, J 9.0 and 3.0, C(3)H *exo*), 2.27 (1 H, dd, J 9.0 and 1.0, C(3)H *endo*), 1.95-1.65 (1 H, br s, NH), 1.86 (1 H, d, J 7.0, C(9)H), 1.76 (1 H, d, J 7.0, C(9)H); δ_C (100 MHz) 146.5, 145.2 (both C(quat) of aromatic), 144.0 and 143.9 (2 x C(quat) of aromatic), 126.4, 125.9, 121.0, 119.1 (4 x CH of aromatic), 60.8 (C1), 48.3 (C9), 46.6 (C3), 44.4(C1).

Reduced Benzyne adducts:

***N*-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 143 :**[124]

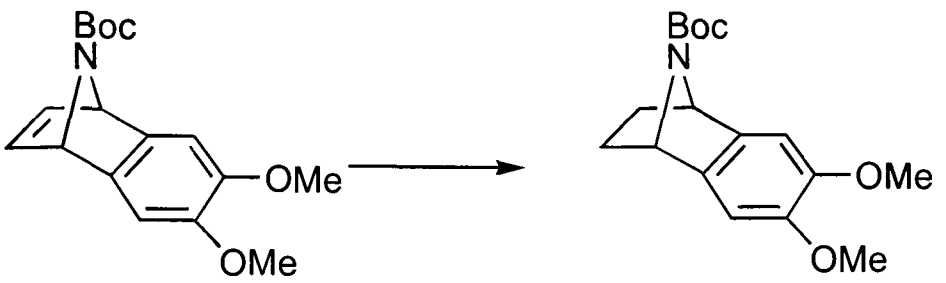


143

Alkene **138** (100 mg, 0.41 mmol) was dissolved in MeOH (3 cm^3), and 10% Pd/C (42 mg, 0.04 mmol Pd) was added. The mixture was placed under 1 atm of hydrogen for 10 min at 25 °C using a balloon. The flask was then opened to the atmosphere and the mixture filtered through a celite pad. The solvent was removed at reduced pressure to give an oil. Chromatography (SiO_2, 15% Et_2O : petroleum ether) gave the compound **143** as a white solid (95 mg, 94%, lit.[124] 86%); mp 40-41 °C (lit. 41-42 °C); δ_H (400 MHz) 7.26-7.18 (2 H, m, 2 x CH of aromatic), 7.14-7.09 (2 H, m, 2 x CH of aromatic), 5.12 (2 H, s, C(1)H and C(4)H), 2.11 (2 H, d, J 8.0, 2 x CH *exo*), 1.41 (9 H, s, Bu^t), 1.29 (2 H, d, J 8.0, 2 x CH *endo*); δ_C (100 MHz, $CDCl_3$), 155.2 (C=O), 144.8 (2 x C (quat) of aromatic), 126.3 (2 x C of aromatic),

119.4 (2 x C of aromatic), 79.9 (CMe$_3$), 61.0 (C1 and C4), 26.7 (C2 and C3), 28.2 (CMe_3).

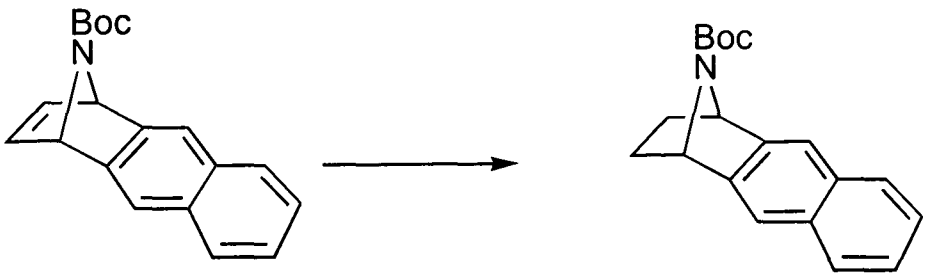
N-(*tert*-Butoxycarbonyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-1,4-iminonaphthalene 204 :



204

Alkene **201** (100 mg, 0.33 mmol) was dissolved in MeOH (5 cm^3), and 10% Pd/C (35 mg, 0.033 mmol Pd) was added. The mixture was placed under 1 atm of hydrogen for 10 min at 25 °C using a balloon. The flask was then opened to the atmosphere and the mixture filtered through a celite pad. The solvent was removed at reduced pressure to give an spectroscopically pure **204** as an oil (74 mg, 73%) without the need for chromatography: data as above.

N-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydro-1,4-iminoanthracene 205 :[104]

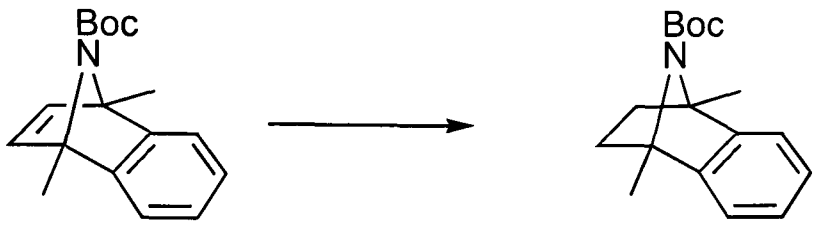


205

10% Pd/C (36 mg, 0.034 mmol Pd) was added to a stirred solution of alkene **202** (100 mg, 0.34 mmol) in MeOH (3 cm^3). The mixture was hydrogenated at 1 atm H_2 using a balloon for 10 min, after which time the flask was opened to the atmosphere and the mixture filtered through a pad of celite. Removal of the solvent at reduced pressure gave the spectroscopically pure **205** as a pale yellow oil (84 mg, 83%,

lit.[104] 84%): δ_H (200 MHz) 7.82 (2 H, m, Ar-H), 7.66 (2 H, s, Ar), 7.46 (2 H, m, Ar), 5.26 (2 H, s, C(1)H and C(4)H), 2.22 (2 H, d, J 8, 2 x CH *exo*), 1.44 (2 H, m, 2 x CH *endo*),1.39 (9 H, s, Bu^t); in accordance with the literature.

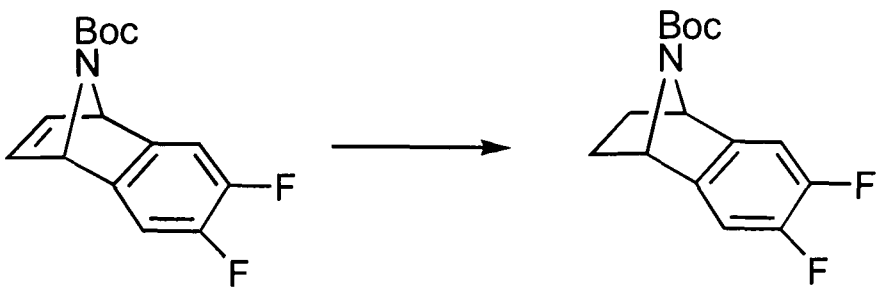
_N_-(*tert*-Butoxycarbonyl)-1,4-dimethyl-1,2,3,4-tetrahydro-1,4-iminonaphthalene 197 :[102]



197

Hydrogenation of alkene **184** (100 mg, 0.37 mmol) on 10% Pd/C in the same manner as described above for 5 min gave a crude mixture that was purified by chromatography (SiO_2, 10% Et_2O : petroleum ether) to give **197** as a colourless oil (24 mg, 24%, lit.[102] 79%): R_f (20% Et_2O : petroleum ether) 0.55; δ_H (400 MHz) 7.20-7.09 (4 H, m, 4 x CH of aromatic), 2.05 (6 H, s, 2 x Me), 2.02 (2 H, d, J 12.0, 2 x CH *exo*), 1.43 (9 H, s, Bu^t), 1.37 (2 H, dd, J 12.0 and 1.5, 2 x CH *endo*); δ_C (100 MHz), 155.5 (C=O), 147.7 (2 x C (quat) of aromatic), 126.4 (2 x C of aromatic), 117.4 (2 x C of aromatic), 79.7 (*C*Me_3), 68.9 (C1 and C4), 35.4 (C2 and C3), 28.4 (C*Me*$_3$), 17.9 (2 x *Me*C-N); m/z (CI^+, NH_3) 291 ($M+NH_4^+$, 2%), 274 ($M+H^+$, 54), 245 (8), 235 (48), 218 (54), 174 ($M-Boc^+$, 100), 159 (17), 145 (42), 135 (7), 79 (3) (Found 274.1810, $C_{17}H_{24}NO_2$ requires 274.1807).

_N_-(*tert*-Butoxycarbonyl)-6,7-difluoro-1,2,3,4-tetrahydro-1,4-iminonaphthalene 203 :

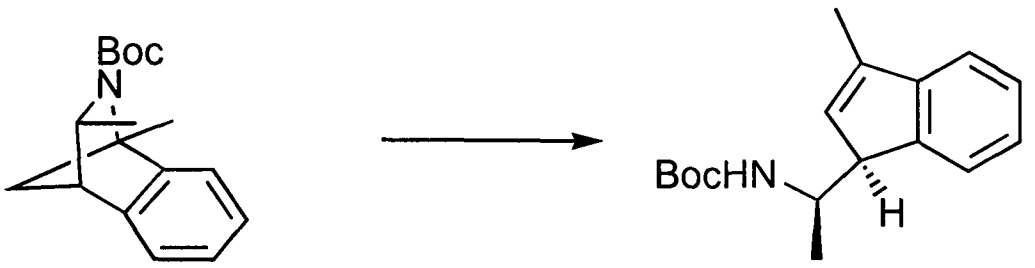


203

Hydrogenation of alkene **200** (100 mg, 0.36 mmol) on 10% Pd/C in MeOH in the manner as described above for 10 min gave spectroscopically pure **203** without the need for chromatography as a colourless oil that crystallised on standing to a white solid (83 mg, 82%): mp (from Et_2O) 78-80 °C; ν_{max}(KBr)/cm^{-1} 3061m, 3028m, 2986s, 2955m, 1691s, 1478s, 1456m, 1373s, 1350m, 1279s, 1258m, 1166s, 1108s, 1086m, 1066m, 912m, 788s; δ_H (400 MHz) 7.05 (2 H, t, J 8.0, 2 x CH of aromatic), 5.07 (2 H, s, C1 and C4), 2.10 (2 H, d, J 8.0, 2 x CH *exo*), 1.38 (9 H, s, Bu^t), 1.25 (2 H, d, J 8.0, 2 x CH *endo*); δ_C (100 MHz) 155.1 (C=O), 148.9 (dd, J 247 and 15, 2 x CF), 140.9 (2 x C of aromatic), 109.4 (2 x C of aromatic), 80.4 (*C*Me$_3$), 60.8 (C1 and C4), 28.1 (C*Me$_3$*), 26.6 (C2 and C3); δ_F (235 MHz) –141.0; m/z (CI$^+$, NH_3) 282 (M+H$^+$, 26%), 253 (4), 226 (4), 182 (100), 153 (40) (Found, M + H$^+$, 282.1298, $C_{15}H_{18}F_2NO_2$ requires 282.1306).

Indenes from acid-catalysed ring opening:

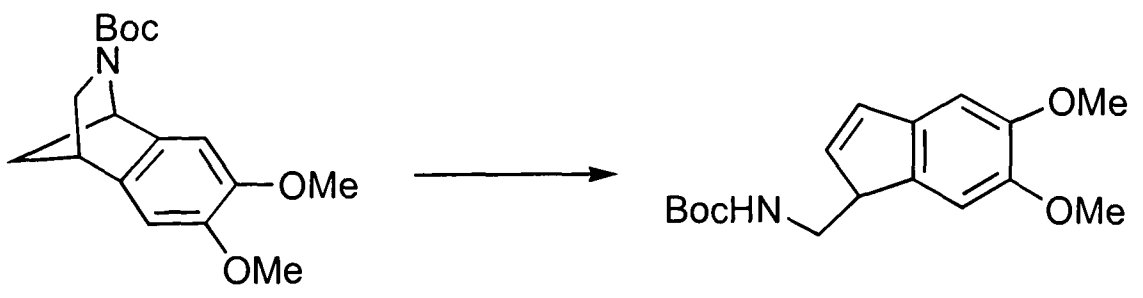
(1*RS*,1'*SR*)-[1-(3'-Methyl-1'*H*-inden-1'-yl)-ethyl]-carbamic acid *tert*-butyl ester 199 :



199

Upon standing in $CDCl_3$ (0.5 cm^3), **194** (50 mg, 0.18 mmol) was converted quantitatively to **199** with half-life of a few hours. Removal of solvent gave a white solid: mp (from Et_2O) 94-96 °C; ν_{max}(KBr)/cm^{-1} 3370s, 2981s, 2938m, 1638s, 1523s, 1455m, 1381m, 1366m, 1339m, 1250m, 1170s, 1081m, 1050m; δ_H (400 MHz) 7.50-7.38 (1 H, m, CH of aromatic), 7.30-7.21 (2 H, m, 2 x CH of aromatic), 7.20-7.15 (1 H, m, CH of aromatic), 6.12 (1 H, s, HC=C), 4.56 (1 H, d, J 7.5, NH), 4.29 (1 H, br s, C*H*-Me), 3.71 (1 H, s, C(1)H of indene), 2.15 (3 H, s, Me-C=C), 1.48 (9 H, s, Bu^t), 0.88 (3 H, d, J 7.0, *Me*-CH); δ_C (100 MHz), 155.2 (C=O), 146.1, 144.3, 140.9 (3 x C(quat)), 129.9 (C2 of indene), 126.7, 124.8, 123.1, 118.9 (4 x C of aromatic), 79.1 (*C*Me_3), 53.8 (C1 of indene), 47.7 (C-NH), 28.3 (C*Me*$_3$), 16.6 (*Me*-C=C), 12.9 (Me); m/z (ES^+) 274 ($M+H^+$, 9%), 259 (27), 229 (4), 218 (100), 172 (9), 157 (67) (Found 274.1802, $C_{17}H_{24}NO_2$ requires 274.1807).

5,6-Dimethoxy-(1*H*-inden-1-yl-methyl)-carbamic acid *tert*-butyl ester 215 :



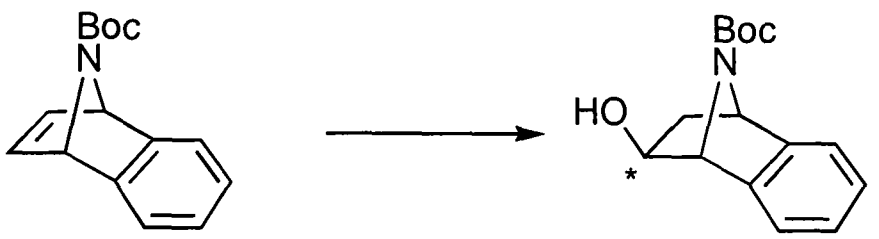
215

Upon standing in air, **211** (95 mg) was converted to **215** with over a period of 5-6 weeks. Chromatography (SiO_2, CH_2Cl_2 then Et_2O) gave a colourless oil (38 mg, 40%): ν_{max}(KBr)/cm^{-1} 3370s, 2973s, 2833s, 1694s, 1549s, 1532s, 1504s, 1467s, 1409s, 1388s, 1363s, 1293s, 1214s, 1166s, 1071s, 969m, 947m, 852s, 793s, 757s; δ_H (400 MHz) 7.04 (1 H, s, CH of aromatic), 6.93 (1 H, s, CH of aromatic), 6.77 (1 H, d, J 5.5, C(3)H of indene), 6.39 (1 H, s, C(2)H), 4.47 (1 H, s, NH), 3.90 (6 H, s, 2 x MeO), 3.75-3.60 (2 H, m, C(1)H of indene and H of CH_2), 3.30-3.20 (1 H, m, H of CH_2), 1.40 (9 H, s, Bu^t); δ_C (100 MHz), 156.0 (C=O), 148.6, 147.3, 137.3, 137.0 (4 x C(quat)), 135.4 and 132.3 (C2 and C3 of indene), 107.3, 104.8 (2 x C of aromatic), 79.2 (CMe_3), 56.2 and 56.1 (2 x MeO), 50.6 (C1 of indene), 41.8 (CH_2), 28.3 (CMe_3); m/z (ES^+) 306 ($M+H^+$, 9%), 250 (100), 230 (2), 189 (3), 160 (6) (Found 306.1700, $C_{17}H_{24}NO_4$ requires 306.1705).

Experimental - Chapter Five

Characterisation data for the two alcohols **141** and **147** included here has been reported in the experimental for chapter four.

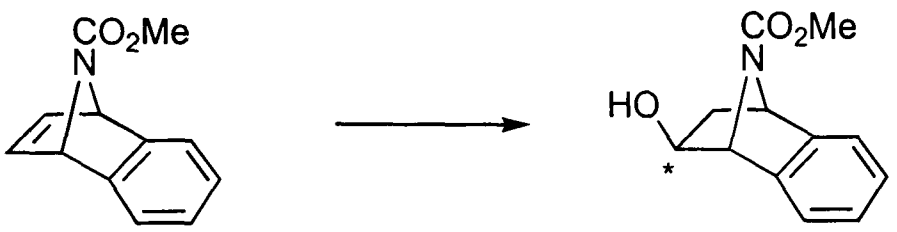
Asymmetric hydroboration - best result with 138 :



141

R-BINAP (10.2 mg, 16 μmol, 2 mol%) and $[Rh(COD)Cl]_2$ (4.0 mg, 8 μmol, 1 mol%) were placed in a flame-dried flask under argon. THF (2.0 cm^3) was added and the solution was stirred for 10 min. A solution of alkene **138** (200 mg, 0.82 mmol) in THF (2.0 cm^3) was added and the solution cooled to −78 °C and stirred 10 min. Catecholborane (171 μL, 1.6 mmol, 2 equiv.) was added as one portion and the mixture stirred for a further 30 min, then allowed to warm to 0 °C and stirred for 6 h. EtOH (1.0 cm^3) was added followed by H_2O_2 (1.0 cm^3 of a 35% aq. solution) and then aqueous NaOH (2.5 cm^3 of a 2 M solution) dropwise over 5 min. The reaction was removed from the ice bath and then stirred at 25 °C for 16 h. The mixture was diluted with 1 M NaOH (15 cm^3) and extracted with Et_2O (3 x 25 cm^3). The combined extracts were washed with 1 M NaOH (30 cm^3) and water (30 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure to give an oil. Column chromatography as previously described for **141** gave the alcohol (140 mg, 65%), *ee* = 31%, $[\alpha]_D^{25} = -4.6°$ (*c* = 1.0 in $CDCl_3$).

Asymmetric hydroboration - best result with 146 :



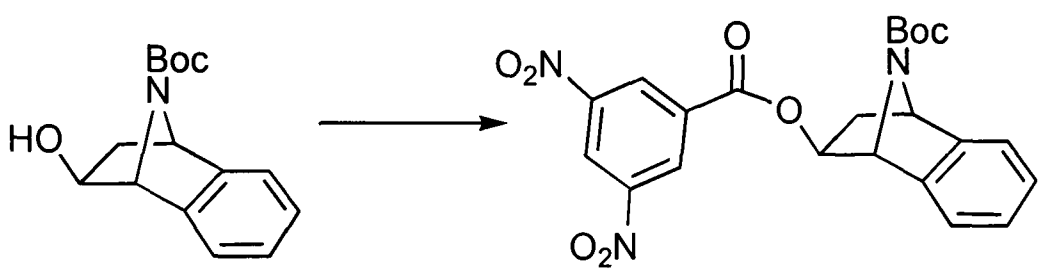
147

R-BINAP (12.3 mg, 20 μmol, 2 mol%) and $[Rh(COD)Cl]_2$ (4.9 mg, 10 μmol, 1 mol%) were placed in a flame-dried flask under argon. Toluene (2.0 cm^3) was added and the solution was stirred for 10 min. A solution of alkene **146** (200 mg, 0.99 mmol) in toluene (2.0 cm^3) was added and the solution cooled to −78 °C and stirred 10 min. Catecholborane (211 μL, 2.0 mmol, 2 equiv.) was added as one portion and the mixture stirred for a further 30 min, then allowed to warm to 0 °C and stirred for 6 h. MeOH (1.0 cm^3) was added followed by H_2O_2 (1.0 cm^3 of a 35% aq. solution) and then aqueous NaOH (2.5 cm^3 of a 2 M solution) dropwise over 5 min. The reaction was removed from the ice bath and then stirred at 25 °C for 16 h. The mixture was diluted with 1M NaOH (15 cm^3) and extracted with Et_2O (3 x 25 cm^3). The combined extracts were washed with 1 M NaOH (30 cm^3) and water (30 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure to give an oil. Column chromatography as previously described for **147** gave the alcohol (150 mg, 65%), *ee* = 31%, $[\alpha]_D^{25} = -2.7°$ (*c* = 1.0 in $CDCl_3$).

Determination of Enantiomeric Excess (*ee*)

The alcohols were converted into their 3,5-dinitrobenzoate esters for separation of the enantiomers by chiral HPLC:

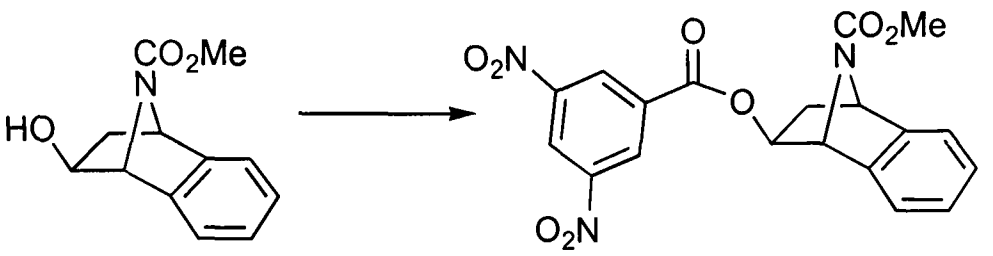
_N_-(*tert*-Butoxycarbonyl)-*exo*-2-(3,5-dinitrobenzoyloxy)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 220 :



220

Alcohol **141** (20 mg, 0.08 mmol) was added to CH_2Cl_2 (4 cm^3) followed by 3,5-dinitrobenzoylchloride (88 mg, 0.38 mmol) and then Et_3N (80 mg, 0.8 mmol). The mixture was stirred at 25 °C for 16 h and the solvent was removed at reduced pressure. Chromatography (50% Et_2O : petroleum ether) gave the ester **220** (28 mg, 74%) as a solid: R_f (50% Et_2O : petroleum ether) 0.75; δ_H (400 MHz) 9.25 (1 H, s, CH of DNB), 9.20 (2 H, s, 2 x CH of DNB), 7.44-7.40 (1 H, m, CH of aromatic), 7.30-7.15 (3 H, m, 3 x CH of aromatic), 5.40 (1 H, s, CH-O), 5.29 and 5.10 (2 H, 2 x s, C(1)H and C(4)H), 2.30-2.20 (1 H, m, H of CH_2), 2.16-2.09 (1 H, m, H of CH_2), 1.40 (9 H, s, Bu^t). The enantiomers were separated by chiral HPLC using a Chiralpak AD column eluted at 1 cm^3/min with degassed 30% EtOH : 70% heptane, t_r = 19 min and 30 min.

_N_-(Methoxycarbonyl)-*exo*-2-(3,5-dinitrobenzoyloxy)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 221 :

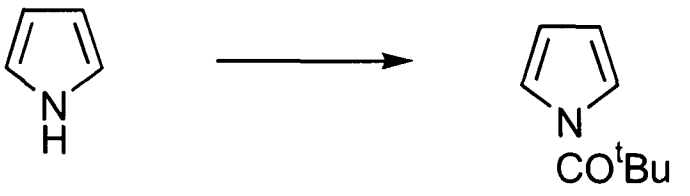


221

Alcohol **147** (10 mg, 0.045 mmol) was added to CH_2Cl_2 (2 cm^3) followed by 3,5-dinitrobenzoylchloride (52 mg, 0.23 mmol) and then Et_3N (46 mg, 0.45 mmol). The mixture was stirred at 25 °C for 16 h and the solvent was removed at reduced pressure. Chromatography (Et_2O) gave the ester **221** (15 mg, 79%) as a solid: R_f (Et_2O) 0.80; δ_H (400 MHz) 9.24 (1 H, s, CH of DNB), 9.19 (2 H, s, 2 x CH of DNB), 7.49-7.42 (1 H, m, CH of aromatic), 7.35-7.20 (3 H, m, 3 x CH of aromatic), 5.43 (1 H, s, CH-O), 5.36 and 5.20 (2 H, 2 x s, C(1)H and C(4)H), 3.71 (3 H, s, MeO), 2.29-2.21 (1 H, m, H of CH_2), 2.18-2.08 (1 H, m, H of CH_2). The enantiomers were separated by chiral HPLC using a Chiralpak AD column eluted at 1 cm^3/min with degassed 80% EtOH : 20% heptane, t_r = 24.5 min and 37 min.

Experimental - Chapter Six

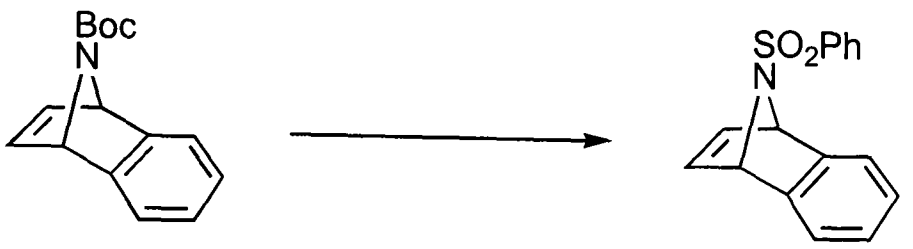
1-(*tert*-Butylcarbonyl)pyrrole 225 :[125]



225

Et_3N (5.66 g, 56 mmol) was added dropwise to a solution of trimethylacetyl chloride (6.75 g, 56 mmol) and pyrrole (5.0 g, 76 mmol) in dry CH_2Cl_2 (30 cm^3) under argon at 25 °C. DMAP (0.68 g, 5.6 mmol) was then added as one portion and the mixture stirred overnight at 25 °C. The solution was then diluted with Et_2O (30 cm^3), washed with saturated $KHSO_4$ (20 cm^3), saturated $NaHCO_3$ (20 cm^3) and water (40 cm^3). The organic layer was dried ($MgSO_4$) and the solvent removed at reduced pressure to give an oil. Column chromatography (SiO_2, 3% Et_2O : petroleum ether) gave **225** as a colourless oil (4.9 g, 58%): R_f (10% Et_2O : petroleum ether) 0.80; ν_{max}(thin film)/cm^{-1} 2978s, 2935m, 2908w, 2877w, 1705s, 1460s, 1406m, 1371m, 1296s, 1223s, 1101s, 1078m, 1052m, 903s, 714s; δ_H (200 MHz), 7.48-7.40 (2 H, m, C(2)H and C(5)H), 6.28-6.22 (2 H, m, C(3)H and C(4)H), 1.45 (9 H, s, Bu^t) ; δ_C (100 MHz) 175.8 (C=O), 120.5 (C2 and C5), 111.9 (C3 and C4), 40.6 (CMe_3), 28.5 (CMe_3); m/z (TOF CI^+, NH_3) 152 ($M+H^+$, 100%), 131 (63), 87 (24), 70 (29) (Found $M + H^+$, 152.078, $C_9H_{13}NO$ requires 152.075).

_N_-(Phenylsulfonyl)-1,4-dihydro-1,4-iminonaphthalene 223 :



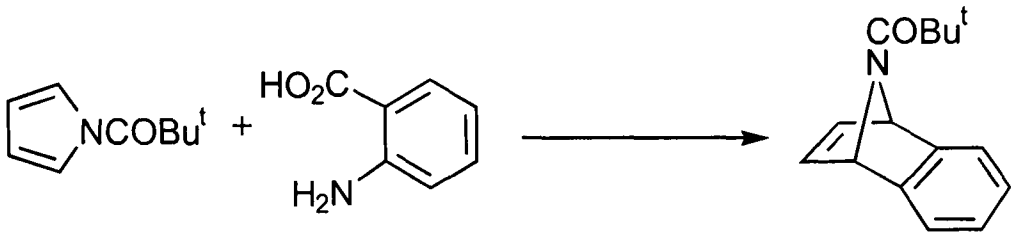
223

Trifluoroacetic acid (770 μL, 10.0 mmol) was added to a solution of alkene **138** (500 mg, 2.04 mmol) in CH_2Cl_2 (8 cm^3) dropwise at room temperature and mixture was stirred for 2 h. The solvent was then removed at reduced pressure and water (10 cm^3) was added to the crude product, followed by Et_2O (10cm^3). The aqueous layer was basified with Na_2CO_3 and then extracted with Et_2O (3 x 10 cm^3). The solvent was removed at reduced pressure to give the crude amine, which was not purified further at this stage but taken directly to the next step:

Benzenesulfonyl chloride (319 μL, 2.5 mmol) was added to a stirred solution of the amine prepared above (~2 mmol) and Et_3N (348 μL, 2.5 mmol) in CH_2Cl_2 (5 cm^3) under nitrogen. The mixture was stirred at 25 °C for 72 h and then 1N HCl (5 cm^3) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 cm^3), the combined organic layers dried ($MgSO_4$) and the solvent removed at reduced pressure. Chromatography (SiO_2, Biotage™ system, 50% CH_2Cl_2 : isohexane to 100% CH_2Cl_2, gradient elution), gave the sulfonamide **223** as a white solid (189 mg, 33% from **138**): R_f (50% CH_2Cl_2 : isohexane) 0.15; mp (from Et_2O) 177-178°C (Found C, 68.0; H, 4.6; N, 4.9; $C_{16}H_{13}NO_2S$ requires C, 67.8; H, 4.6; N, 5.1); ν_{max}(KBr)/cm^{-1} 3086m, 3053s, 3008m, 1454m, 1446s, 1335s, 1169s, 1155s, 1091s, 1075m, 1014s, 724s; δ_H (400 MHz) 7.57 (2 H, d , J 7.0, 2 x CH of aromatic), 7.40-7.38 (1 H, m, CH of aromatic), 7.28-7.31 (2 H, m, 2 x CH of aromatic), 7.04-7.01 (2 H, m, 2 x CH of aromatic), 6.80 (2 H, s , 2 x HC=CH), 6.78-6.74 (2 H, m, 2

x CH of aromatic), 5.46 (2 H, s, C(1)H and C(4)H); δ_C (100 MHz) 147.1, 142.4, 138.1, 132.4, 128.7, 128.2, 125.1, 121.1 (All olefinic or aromatic) 67.7 (C1 and C4); m/z (CI^+, NH_3) 301 ($M+NH_4^+$, 45%), 284 ($M+H^+$, 100), 175 (7), 159 (4), 143 (40), 126 (4), 94 (5) (Found, $M+H^+$, 284.0739, $C_{16}H_{14}NO_2S$ requires 284.0745).

***N*-(*tert*-Butylcarbonyl)-1,4-dihydro-1,4-iminonaphthalene 226 :**

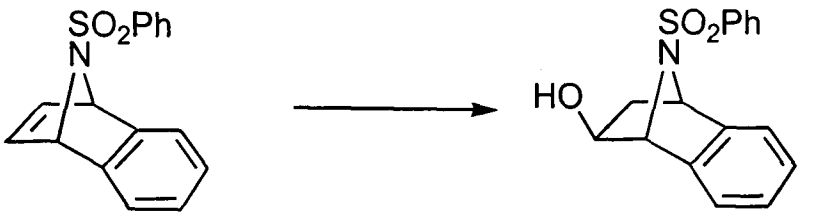


226

Isoamyl nitrite (3.10 g, 26.5 mmol) in THF (10 cm^3) and anthranilic acid (3.63 g, 26.5 mmol) in THF (10 cm^3) were added simultaneously to a solution of pyrrole **225** (4.0 g, 26.5 mmol) in THF (40 cm^3) at reflux over 2 h. The reaction was left at reflux for a further 1.5 h, then allowed to cool. Water (50 cm^3) was added and the mixture extracted with Et_2O (3 x 100 cm^3). The combined organic extracts were washed with saturated $NaHCO_3$ (100 cm^3), water (100 cm^3) and dried ($MgSO_4$). The solvent was then removed at reduced pressure to give an oil. Chromatography (SiO_2, 20% Et_2O : petroleum ether) gave the amide **226** as a white solid (2.6 g, 43%): R_f (30% Et_2O : petroleum ether) 0.36; mp (from EtOAc/petroleum ether) 133-134 °C (Found C, 79.3; H, 7.6; N, 6.2; $C_{15}H_{17}NO$ requires C, 79.3; H, 7.5; N, 6.2); ν_{max}(KBr)/cm^{-1} 3042m, 2985s, 2970m, 1622s, 1474m, 1447m, 1403m, 1366s, 1292m, 1196m, 759s ; δ_H (400 MHz) 7.26 (2 H, s, 2 x CH of aromatic), 7.02 (2 H, br s, HC=CH), 6.96-6.92 (2 H, m, 2 x CH of aromatic), 5.89 (2 H, s, C(1)H and C(4)H), 1.18 (9 H, s , Bu^t) ; δ_C (100 MHz) 173.7 (C=O), 148.2 (2 x C(quat) of aromatic), 144.8 and 142.0 (2 x C=C), 125.0 (2 x C of aromatic), 121.4 and 120.2 (2 x C of aromatic), 66.3 and 64.8 (C1 and C4), 38.4 (CMe_3), 27.3 (CMe_3) ; m/z (EI^+)

227 (M^+, 5%), 170 (14), 142 (41), 128 (38), 115 (52), 102 (5), 89 (16), 57 (100), 41 (52) (Found, $M+H^+$, 228.1381, $C_{15}H_{18}NO$ requires 228.1388).

_N_-(Phenylsulfonyl)-_exo_-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 224 :

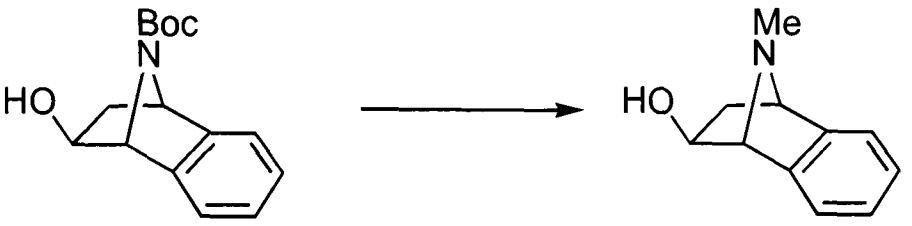


224

BH_3-THF complex (0.59 cm^3 of 1.5 M solution in THF, 0.88 mmol) was added to a solution of alkene **223** (342 mg, 1.21 mmol) in THF (8 cm^3) at 0 °C. The reaction was allowed to warm to room temperature and then stirred for 16 h. Water (3 cm^3), H_2O_2 (3 cm^3 of 35% solution in H_2O) and NaOH (0.5 cm^3 of 1 M solution in water) were sequentially added over 15 min. The aqueous layer was extracted with Et_2O (3 x 10 cm^3), the combined organic extracts dried ($MgSO_4$) and the solvent removed at reduced pressure. Column chromatography (SiO_2, 50% Et_2O : isohexane to 75% Et_2O : isohexane, gradient elution) gave the alcohol **224** as a white solid (271 mg, 74%): R_f (Et_2O) 0.35; mp (from Et_2O) 160-161 °C; ν_{max}(thin film)/cm^{-1} 3507s, 3056m, 2980m, 2945m, 1459m, 1447s, 1331s, 1150s, 1087s, 1065s, 1027m, 1013m; δ_H (400 MHz) 7.49-7.43 (2 H, m, 2 x CH of aromatic), 7.29-7.25 (1 H, m, CH of aromatic), 7.14 (2 H, t, J 6.0, 2 x CH of aromatic), 6.94-6.91 (1 H, m, CH of aromatic), 6.87-6.81 (3 H, m, 3 x CH of aromatic), 5.07-5.04 (1 H, m, C(1)H), 4.91 (1 H, s, C(4)H), 3.94 (1 H, m, C*H*OH), 2.30 (1 H, br s, OH), 2.03-1.96 (1 H, m, H of CH_2), 1.95-1.90 (1 H, m, H of CH_2); δ_C (100 MHz) 143.9 (C(quat)-SO_2), 138.9 (C(quat)), 137.6 (C(quat)), 132.3 (2 x CH of Ph), 128.4, 127.9, 127.4, 126.8 (4 x CH of aromatic), 121.6 (2 x CH of Ph), 120.0 (CH of Ph), 72.5, 71.3 (C1 and C4), 63.2 (C2), 41.1 (C3); m/z (CI^+, NH_3) 319 ($M+NH_4^+$, 53%), 302 ($M+H^+$, 60), 284

(6), 257 (8), 238 (4), 220 (5), 175 (5), 162 (39), 144 (15), 132 (5), 118 (100) (Found, $M+H^+$, 302.0848, $C_{16}H_{16}NO_3S$ requires 302.0851).

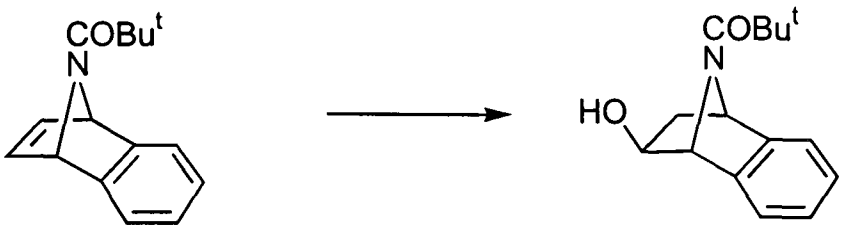
_N_-(Methyl)-_exo_-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 222 :



222

A solution of $LiAlH_4$ (1.0 M in Et_2O, 1.5 cm^3, 1.5 mmol) was added to a stirred solution of alcohol **141** (100 mg, 0.38 mmol) in Et_2O (3.5 cm^3) at 25 °C and the mixture heated to reflux overnight. The mixture was then allowed to cool and aqueous NaOH (2 M, 2.5 cm^3) was added, followed by water (10 cm^3) and the aqueous layer was extracted with Et_2O (3 x 20 cm^3). The solvent was removed at reduced pressure. Column chromatography (EtOAc containing 2% Et_3N) gave alcohol **222** as a white solid (43 mg, 61%): R_f (EtOAc containing 2% Et_3N) 0.13; mp 123-124 °C; ν_{max}(thin film)/cm^{-1} 3352s, 3249s, 2974s, 2946s, 2860m, 1446s, 1415s, 1337m, 1294m, 1167s, 1105s, 1066s, 1003m, 748s; δ_H (400 MHz) 7.30-7.27 (1 H, m, CH of aromatic), 7.21-7.12 (3 H, m, 3 x CH of aromatic), 4.06 (1 H, s, C(1)H), 3.98 (1 H, s, C(4)H), 3.86-3.83 (1 H, m, C*H*-O), 3.47 (1 H, br s, OH), 2.13 (3 H, s, Me), 1.89-1.84 (2 H, m, CH_2); δ_C (100 MHz), 145.8, 140.6 (both C(quat)), 127.0, 126.5, 123.5, 122.0 (4 x CH of aromatic), 75.4, 72.6 (C1 and C4), 66.7 (C2), 40.6 (C3) 35.2 (Me); m/z (CI^+, NH_3) 176 ($M+H^+$,100%), 160 (5), 143 (29), 98 (5), 84 (8), 72 (5) (Found, $M+H^+$, 176.1072, $C_{11}H_{14}NO$ requires 176.1075).

N-(*tert*-Butylcarbonyl)-*exo*-1,2,3,4-tetrahydro-1,4-iminonaphthalen-2-ol 227 :

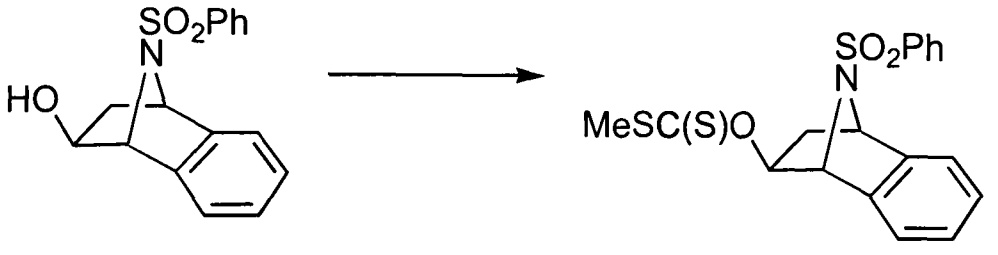


227

Racemic BINAP (19.6 mg, 32 μmol) and $[Rh(COD)Cl]_2$ (7.8 mg, 16 μmol), were placed in a flame-dried flask under argon. THF (3.5 cm^3) was added and the solution was stirred for 10 min. A solution of alkene **226** (360 mg, 1.6 mmol) in THF (3.5 cm^3) was added and the solution cooled to −78 °C and stirred 10 min. Catecholborane (383 mg, 3.2 mmol) was added and the mixture stirred for a further 30 min, then allowed to warm to 25 °C and stirred for 3 h. The mixture was then cooled to 0 °C and EtOH (1.5 cm^3) was added followed by H_2O_2 (1.5 cm^3 of a 35% aq. solution) and then aqueous NaOH (1.7 cm^3 of a 2 M solution) dropwise over 5 min. The reaction was then stirred at 25 °C for 16 h. The mixture was diluted with 1 M NaOH (10 cm^3) and extracted with Et_2O (3 x 20 cm^3). The combined extracts were washed with 1 M NaOH (30 cm^3) and water (30 cm^3), dried ($MgSO_4$) and the solvent removed at reduced pressure to give an oil. Column chromatography (80% Et_2O : petroleum ether to 100% Et_2O, gradient elution) gave the alcohol **227** as a white solid (220 mg, 57%): R_f (Et_2O) 0.33; mp (from Et_2O) 138-139 °C; ν_{max}(thin film)/cm^{-1} 3340 br s, 2968s, 2907s, 1622s, 1574s, 1476m, 1451m, 1417s, 1363m, 1325m, 1209w, 1159m, 1088m, 1050m, 753m; δ_H (400 MHz) 7.33-7.28 (1 H, m, CH of aromatic), 7.22-7.18 (1 H, m, CH of aromatic), 7.16-7.10 (2 H, m, 2 x CH of aromatic), 5.53 (1 H, br s, C(1)H), 5.47 (1 H, br s, C(4)H), 4.07 (1 H, s, C*H*-OH), 3.45 (1 H, br s, OH), 1.96-1.82 (2 H, m, CH_2), 1.24 (9 H, s, Bu^t); δ_C (100 MHz) 176.3 (C=O), 146.0, 141.3 (both C(quat)), 127.2, 126.6, 121.0, 119.4 (4 x C of

aromatic), 72.8 (CH-O), 68.1 (C1), 60.3 (C4), 39.4 (C3), 38.8 (*C*Me$_3$), 27.8 (C*Me$_3$*); m/z (CI$^+$, NH$_3$), 246 (M+H$^+$, 100%), 230 (7), 212 (5), 201 (7), 118 (12), 102 (14) (Found M+H$^+$, 246.1492, $C_{15}H_{20}NO_2$ requires 246.1494).

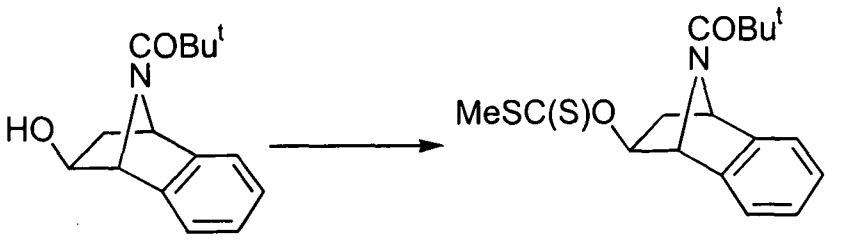
_N_-(Phenylsulfonyl)-_exo_-2-(methylsulfanylthiocarboxyoxy)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 228 :



228

Reaction of alcohol **224** (146 mg, 0.49 mmol) according to the general procedure (Experimental - Chapter Four) gave an oil. Chromatography (Biotage™ system, 30% Et_2O : isohexane) gave xanthate **228** (105 mg, 55%) as an oil : R_f (Et_2O) 0.75.

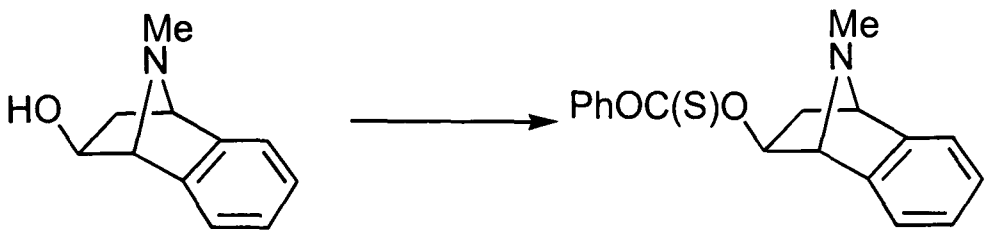
_N_-(_tert_-Butylcarbonyl)-_exo_-2-(methylsulfanylthiocarboxyoxy)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 230 :



230

Reaction of alcohol **227** (150 mg, 0.61 mmol) according to the general procedure (Experimental - Chapter Four) gave an oil. Chromatography (SiO_2, 10% Et_2O : petroleum ether to 30% Et_2O : petroleum ether, gradient elution) gave xanthate **230** (176 mg, 86%) as an oil: R_f (15% Et_2O : petroleum ether) 0.14.

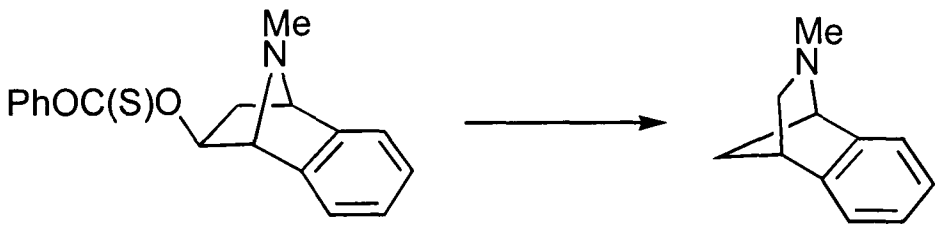
_N_-Methyl-_exo_-2-(phenyoxythiocarbonyloxy)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 229 :



229

To a solution of alcohol **222** (122 mg, 0.70 mmol) in CH_2Cl_2 (5 cm^3) was added DMAP (342 mg, 2.8 mmol) and phenyl chlorothionocarbonate (144 mg, 0.83 mmol). The reaction was stirred for 16 h under argon and the solvent was then removed at reduced pressure. Column chromatography (SiO_2, 20 % Et_2O : petroleum ether containing 2% Et_3N) gave thiobenzoate **229** as a yellow oil (140 mg, 65%): R_f (EtOAc containing 2% Et_3N) 0.55. The product was not fully characterised but instead was identified by a change in chemical shift of the CH-O proton from 3.8 in the starting alcohol to 5.1 ppm in the product and an increase in the aromatic proton integral from 4 H to 9 H.

***N*-Methyl-1,2,3,4-tetrahydro-1,4-methanoisoquinoline 233 :**



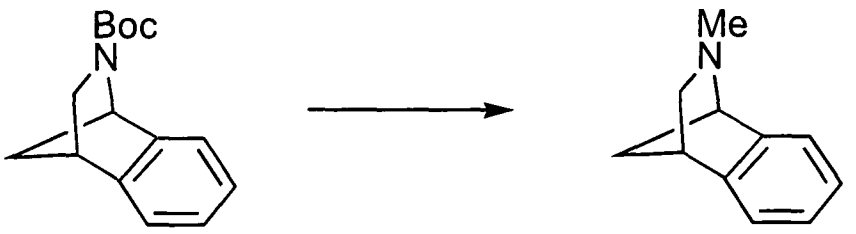
233

a) from radical deoxygenation

AIBN (18 mg, 0.10 mmol) and TTMSS (166 mg, 0.67 mmol) were added to a solution of thiobenzoate **229** (140 mg, 0.44 mmol) in toluene (17.5 cm^3) and the flask was then lowered into an oil bath preheated to 125 °C. The mixture was stirred at reflux for 2 h and then allowed to cool. The solvent was removed at reduced pressure. Column chromatography (SiO_2, EtOAc containing 2% Et_3N) gave amine **233** as a yellow oil (16 mg, 23%): R_f (EtOAc containing 2% Et_3N) 0.17; ν_{max}(thin

film)/cm^{-1} 3045m, 2974s, 2855s, 2780s, 1459m, 1275m, 1194m, 1174m, 1151m, 1128m, 1091m, 1032m, 1013m, 954w, 909w, 754m ; δ_H (400 MHz) 7.29-7.23 (1 H, m, CH of aromatic), 7.21-7.13 (3 H, m, 3 x CH of aromatic), 4.08 (1 H, s, C(1)H), 3.45 (1 H, dd, J 8.0 and 2.0, C(3)H *exo*), 3.41 (1 H, s, C(4)H), 2.04 (1 H, dd, J 9.5 and 3.0, C(9)H), 1.95 (3 H, s, Me), 1.82 (1 H, dd, J 9.5 and 3.0, C(9)H) 1.44 (1 H, dd, J 8.0 and 2.0, C(3)H *endo*); δ_C (100 MHz), 146.5, 140.8 (both C(quat)), 126.7, 125.2, 122.7, 120.5 (4 x CH of aromatic), 67.3 (C1), 56.0 (C3), 49.1 (C9), 45.0 (C4), 40.8 (Me); m/z (TOF ES^+) 160 ($M+H^+$, 100%); (Found, $M+H^+$, 160.1129, $C_{11}H_{14}N$ requires 160.1126).

b) from hydride reduction

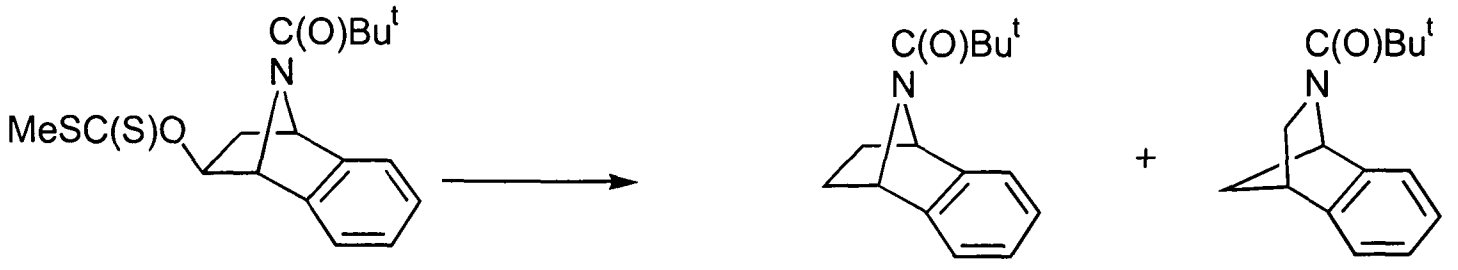


233

$LiAlH_4$ (1.0 M in THF, 0.92 cm^3, 0.92 mmol) was added to a solution of amine **126** (150 mg, 0.61 mmol) in THF (4 cm^3) and the mixture heated at reflux for 2 h. The mixture was then allowed to cool and aqueous NaOH (2 M, 1.5 cm^3) was added, followed by water (6 cm^3). The aqueous layer was extracted with Et_2O (3 x 5 cm^3), the combined organic extracts dried ($MgSO_4$), and the solvent removed at reduced pressure. Column chromatography (SiO_2, EtOAc containing 2% Et_3N) gave amine **233** as a yellow oil (44 mg, 45%): R_f (EtOAc containing 2% Et_3N) 0.17. Other data as above.

_N_-(*tert*-Butylcarbonyl)-1,2,3,4-tetrahydro-1,4-iminonaphthalene 236 and

_N_-(*tert*-butylcarbonyl)-1,2,3,4-tetrahydro-1,4-methanoisoquinoline 235 :



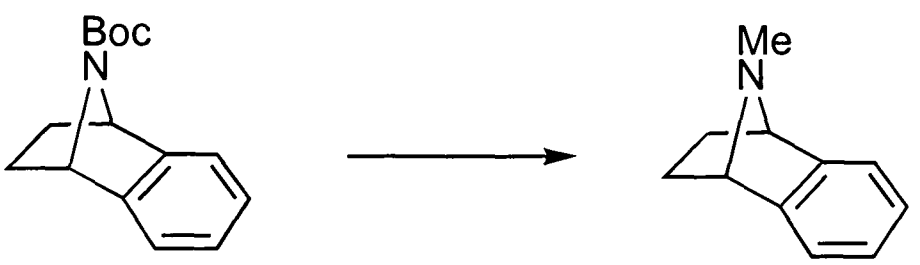
236 **235**

AIBN (21 mg, 0.13 mmol) and TTMSS (197 mg, 0.79 mmol) were added to a solution of xanthate **230** (176 mg, 0.52 mmol) in toluene (21 cm^3). The mixture was brought to reflux and left for 2 h. The mixture was then allowed to cool, and the solvent removed at reduced pressure. Column chromatography (SiO_2, 30% Et_2O : petroleum ether) first gave **236** as a colourless oil that crystallised on standing to a white solid (17 mg, 14%); R_f (30% Et_2O : 70 % petroleum ether) 0.30; mp (from Et_2O/petroleum ether) 128-129 °C; ν_{max}(KBr)/cm^{-1} 3021w, 2985m, 2947m, 2873w, 1619s, 1477m, 1451m, 1415m, 1362m, 1216m, 1164m, 1104m, 883m, 844m, 765m; δ_H (500 MHz) 7.28-7.21 (2 H, m, 2 x CH of aromatic), 7.16-7.11 (2 H, m, 2 x CH of aromatic), 5.53 (2 H, s, C(1)H and C(4)H), 2.18-2.07 (2 H, m, 2 x CH *exo*), 1.34 (2 H, d, J 7.0, 2 x CH *endo*), 1.20 (9 H, s, Bu^t); δ_C (100 MHz) 174.2 (C=O), 144.7 (2 x C(quat) of aromatic), 136.5 (2 x CH of aromatic), 119.2, (2 x CH of aromatic), 60.3 (C1 and C4), 38.9 (CMe_3), 27.6 (CMe_3), 27.3 (br, C2 and C3); m/z (EI^+) 229 (M^+, 1%), 215 (3), 201 (9), 188 (4), 129 (6), 117 (18), 84 (35), 57 (82), 49 (100) (Found, $M+H^+$, 230.1544, $C_{15}H_{20}NO$ requires 230.1545).

Second to elute was **235** as a white solid (73 mg, 61%): R_f (30% Et_2O : petroleum ether) 0.19; mp (from petroleum ether) 102-103 °C; ν_{max}(KBr)/cm^{-1} 2974s, 2882m, 1602s, 1475m, 1416s, 1386m, 1364m, 1309m, 1262m, 1212m, 1113m, 1003s, 764s;

δ_H (500 MHz, toluene–d_8, 90 °C) 7.15 (1 H, d, J 6.5, CH of aromatic), 7.02-6.85 (3 H, m, 3 x CH of aromatic), 5.33 (1 H, br s, C(1)H), 3.45 (1 H, dd, J 9.5 and 4.0, C(3)H *exo*), 3.14 (1 H, s, C(4)H), 2.77 (1 H, d, J 9.5, C(3)H *endo*), 1.57-1.49 (2 H, m, 2 x C(9)H), 1.07 (9 H, s, Bu^t); δ_C (125 MHz, Toluene–d_8, 90 °C) 175.4 (C=O), 146.0, 144.8 (2 x C(quat) of aromatic), 127.1, 126.4, 121.2, 121.0 (4 x CH of aromatic), 62.4 (C1), 50.5 (C3), 47.8 (C9), 44.7 (C4), 38.9 (*C*Me_3), 27.8 (C*Me*$_3$); m/z (EI^+) 229 (M^+, 21%), 214 (5), 172 (6), 144 (11), 129 (82), 116 (63), 84 (15), 57 (100) (Found M+H^+, 230.1547, $C_{15}H_{20}NO$ requires 230.1545).

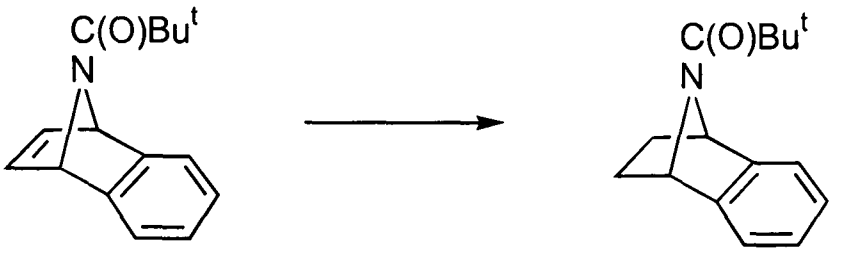
***N*-Methyl-1,2,3,4-tetrahydro-1,4-iminonaphthalene 234 :**[112]



234

A solution of $LiAlH_4$ (1.0 M in Et_2O, 1.0 cm^3, 1.0 mmol) was added to a stirred solution of carbamate **143** (100 mg, 0.41 mmol) in Et_2O (4 cm^3) at 25 °C and the mixture heated to reflux overnight. The mixture was then allowed to cool and aqueous NaOH (2 M, 2.5 cm^3) was added, followed by water (10 cm^3) and the aqueous layer was extracted with Et_2O (3 x 20 cm^3). The solvent was removed at reduced pressure. Column chromatography (EtOAc containing 2% Et_3N) gave amine **234** as a yellow oil (35 mg, 54%): R_f (EtOAc containing 2% Et_3N) 0.20; δ_H (400 MHz) 7.22-7.17 (2 H, m, 2 x CH of aromatic), 7.13-7.07 (2 H, m, 2 x CH of aromatic), 4.06 (2 H, s, C(1)H and C(4)H), 2.11 (2 H, d, J 8.0, 2 x CH *exo*), 2.03 (3 H, s, Me), 1.20 (2 H, dd, J 8.0 2.0, 2 x CH *endo*); δ_C (100 MHz) 144.3 (2 x C (quat) of aromatic), 126.2 (2 x C of aromatic), 121.7 (2 x C of aromatic), 67.3 (C1 and C4), 35.4 (Me), 27.1 (C2 and C3).

_N_-(*tert*-Butylcarbonyl)-1,2,3,4-tetrahydro-1,4-iminonapthalene 236 by hydrogenation :



236

Alkene **227** (100 mg, 0.44 mmol) was dissolved in MeOH (4 cm^3) and 10% Pd/C (47 mg, 0.044 mmol Pd) was added. The mixture was placed under 1 atm of hydrogen for 10 min at 25 °C using a balloon. The flask was then opened to the atmosphere and the mixture filtered through a celite pad. The solvent was removed at reduced pressure to give a solid. Chromatography (30% Et_2O : petroleum ether) gave the compound **236** as a white solid (97 mg, 97%); data as above.

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