SEARCH FOR PRACTICAL ALTERNATIVES TO ORGANOTIN HYBRIDES

Paul A. Baguley

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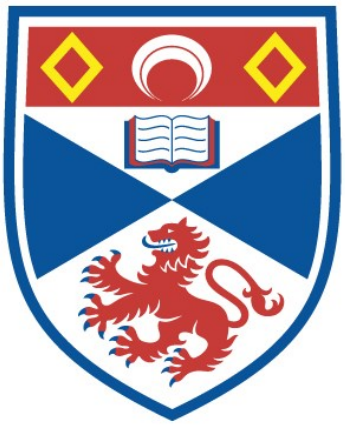
at the
University of St Andrews



1998

Search for Practical Alternatives to Organotin Hydrides

A thesis presented by Paul A. Baguley to the University of St. Andrews in application for the degree of Doctor of Philosophy

November 1997

Declarations

I, Paul Anthony Baguley hereby certify that this thesis has been composed by myself, that it is a record of my own work and that it has not been accepted in partial or complete fulfilment of any other degrees or professional qualification.

Signed _____ Date 13th Nov. 1997

I was admitted to the Faculty of Science of the University of St. Andrews under Ordinance General No. 12 on the 1st October 1994 and as a candidate for the degree of PhD. on the 1st October 1995.

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Abbreviations and Symbols

AIBN	Azobisisobutyronitrile
BOOB	Di-*tert*-butyl peroxide
bp	Boiling point
Bu_3SnH	Tributyltin hydride
$In^{\bullet}$	Initiator
DCC	Dicyclohexylcarbodiimide
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsuphoxide
EPR	Electron Paramagnetic Resonance
Ether	Diethyl ether
GC/MS	Gas Chromatography/Mass Spectrometry
hfs	Hyperfine splitting constants
Light Petroleum	40/60 Pet. ether
M^+	Molecular ion
mp	Melting point
m/z	Mass to charge ratio
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
r.t.	Room temperature
s, d, t, q, q^i	Singlet, doublet, triplet, quartet, quintet
TBS	*tert*-butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylene diamine
TMS	Trimethylsilyl

Abstract

A summary of the tin hydride method of generating radicals in organic synthesis is presented, followed by illustrative examples of other methods available for mediating radical reactions, with a particular emphasis on recent developments. This is followed by four chapters describing our efforts to introduce alternative methods for generating radicals. A range of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids have been prepared by Birch reduction-alkylation methodology and shown to generate the corresponding alkyl radical by thermal initiation with dibenzoyl peroxide. The 1-benzyl, cyclopentyl and *t*-butyl precursors (**17**, **15**, and **16** respectively), acted as sources of radicals which were trapped with cyclohexenone to give the corresponding 3-alkylcyclohexanone adducts in yields of 52%, 30% and 25% respectively. Addition products were also observed when acrylonitrile and vinyl benzoate were employed as the radical traps.

1-[2-(Cylohex-2-enyloxy)ethyl]cyclohexa-2,5-diene-1-carboxylic acid **32** and 1-[2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-ylmethoxy)ethyl]cyclohexa-2,5-diene-1-carboxylic acid **33** are new compounds which were prepared in four straightforward steps from cyclohexene and β-pinene respectively. The route leading to acid **32** involved the preparation of four new compounds and three new compounds were prepared during the synthesis of acid **33**. When refluxed in benzene in the presence of dibenzoyl peroxide, carboxylic acid **32** generated a primary alkyl radical which cyclised to yield 7-oxabicyclo[4.3.0]-nonane in 55% yield. The tin-mediated cyclisation of 3-(2'-iodoethoxy)cyclohexene **36** yielded the same compound in 60% yield, in addition to 3-ethoxycyclohexene (12%). Similarly, carboxylic acid **33** generated a primary alkyl radical which cyclised to yield the new compound oxacyclopentane-3-spiro-2-6,6-dimethylbicyclo[3.1.1]heptane in 10% yield. The tin-mediated cyclisation of 6,6-dimethyl-2-(2-iodoethoxymethyl)bicyclo[3.1.1]hept-2-ene **37** yielded the same spiro compound in 31% yield.

EPR spectroscopic studies provided direct evidence for the formation of the cyclohexadienyl radicals from all of the carboxylic acids investigated. Carboxylic acids **15-17** and 1-[2-(ethenyloxy)benzyl]cyclohexa-2,5-diene-1-carboxylic acid **34** also generated alkyl radicals which were clearly observed by EPR spectroscopy. The carboxylic acid radical precursors would have yielded products in higher yields if the competitive loss of a hydroxyformyl radical did not occur.

An account of our work directed towards the synthesis of 1-phenylcyclohexa-2,5-diene-1-carboxylic acid **8** is given. Thus, 1,4-dihydrobiphenyl was deprotonated with BuLi, added to CO_2 and the isomeric acid, 3-carboxylic acid-3,4-dihydrobiphenyl was removed by reacting with maleic anhydride to give the Diels-Alder adduct. 2-(Cyclohex-2-enyloxy)ethyl 1-phenylcyclohexa-2,5-diene-1-carboxylate **24** was treated with dibenzoyl peroxide to afford 7-oxabicyclo[4.3.0]nonane in yields of 32-36%.

A variety of *N*-carboalkoxy-1,2-dihydropyridines have been prepared from the reaction of pyridine and the appropriate chloroformate in the presence of $NaBH_4$. EPR studies have shown that these esters produce aza-cyclohexadienyl radicals on photolysis in the presence of di-*t*-butyl peroxide, but no decarboxylation was observed. These compounds do not generate alkyl radicals efficiently when reacted with dibenzoyl peroxide. In each case the major product identified was the corresponding benzoate ester, which resulted from the combination of an alkoxycarbonyl radical and a phenyl radical.

Chapter 1

Introduction

Methods for Generating Radicals in Organic Synthesis

Over the past twenty years the use of radical reactions in organic synthesis has increased rapidly. Perhaps the greatest asset of this type of reaction is the construction of polycyclic molecules *via* tandem radical cyclisations, since if successful, such reactions result in the conversion of comparatively simple starting materials into more complex and potentially useful molecules.[1] Other important radical reactions include intramolecular closure to produce monocyclic products, intermolecular addition of radicals to olefins and radical deoxygenations. Radical decarboxylation reactions have also found use in synthesis and some illustrative examples of all these types of reactions will be examined later.

The conventional method for generating radicals in organic synthesis involves treating an alkyl halide or selenide with a stoichiometric equivalent of tributyltin hydride. Because radical reactions are becoming more and more popular it therefore follows that the commercially available organotin hydrides are important reagents for organic synthesis. Although they have numerous advantages, the toxicity of organotin compounds is a major disadvantage and one that commonly rules against their use in the pharmaceutical industry. It is therefore highly desirable to have an alternative, non-toxic reagent which could replace tin in some, if not all applications. Furthermore, the hydrogen atom is easily abstracted from organotin hydrides by carbon-centred radicals and this can present a problem if the initial alkyl radical is required to react at a site of unsaturation before abstraction of hydrogen. The purpose of this introduction is to review the tin hydride method in more detail, and examine some of the alternative methods for generating radicals suitable for preparative purposes.

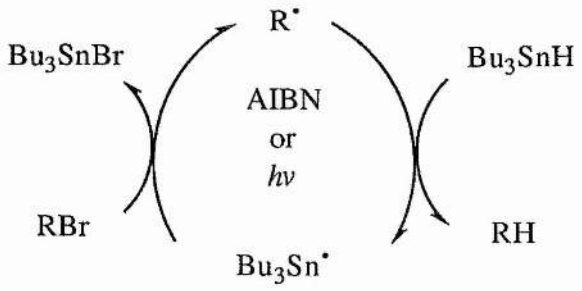
1. The Tin Hydride Method

The reduction of an alkyl halide, RX to RH (Scheme 1), was discovered in the 1960's.[2]

$$RX \xrightarrow[\text{AIBN or } h\nu]{Bu_3SnH} RH$$

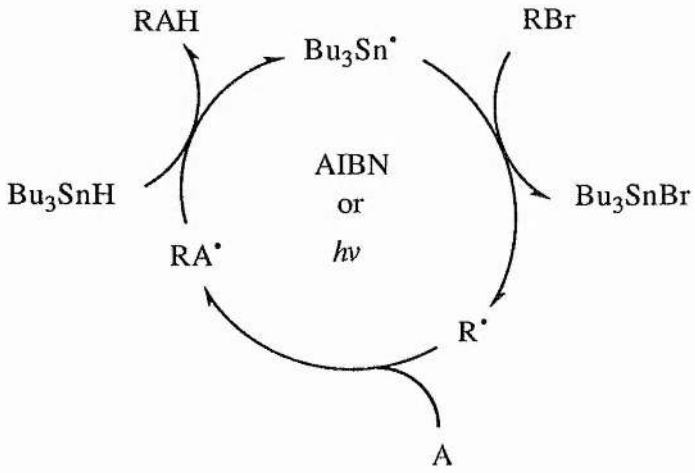
X=Br, I Scheme 1

The mechanism of this reduction, shown in Scheme 2, is straightforward. The Sn-H bond is relatively weak and can be broken homolytically when the organotin hydride is exposed either to radiation or to a catalytic amount of AIBN and heat. The resulting radical, $R_3Sn^{\bullet}$ has a high affinity for halogens and can readily abstract bromine (and particularly iodine) from the alkyl halide giving the desired carbon-centred radical and the tin byproduct containing the strong Sn-X bond. The resulting alkyl radical abstracts hydrogen from the tin hydride to give the desired product RH and regenerate a tin radical, (this last step is called the chain-transfer step). The success of this transformation is due to the maintenance of a low concentration of radicals during the reaction. Indeed, in the invention of new radical chain reactions, a method which balances the rate at which radicals are being formed and consumed has to be devised. This condition can often be fulfilled if the reaction mechanism employs an efficient chain-transfer step. This leads to the conversion of one radical into the desired product and the formation of a new radical which can continue the chain. Other precursors for generating alkyl radicals include phenylselenides (X=SePh), phenylsulphides (X=SPh) and xanthate esters, the latter are discussed in more detail later. The phenylselenides and phenylsulphides generate alkyl radicals in the analogous method for the alkyl halides, although by group rather than atom abstraction.



Scheme 2

From a synthetic point of view it is more common for an alkyl radical to be intercepted either inter- or intramolecularly with an alkene, A. Thus, the radical chain mechanism can be modified to the sequence of steps illustrated in Scheme 3. The alkyl radical R• therefore has two available options; either hydrogen abstraction from the tin hydride to give the undesired reduction product RH, or addition to A, to give the desired product RAH after hydrogen atom abstraction. There are various means by which the desired product RAH can be favoured and some of these are discussed in Stork's synthesis of prostaglandin $F_{2\alpha}$ (Scheme 5). Two other syntheses using tin hydride have been included to illustrate some of the important aspects of radical reactions.

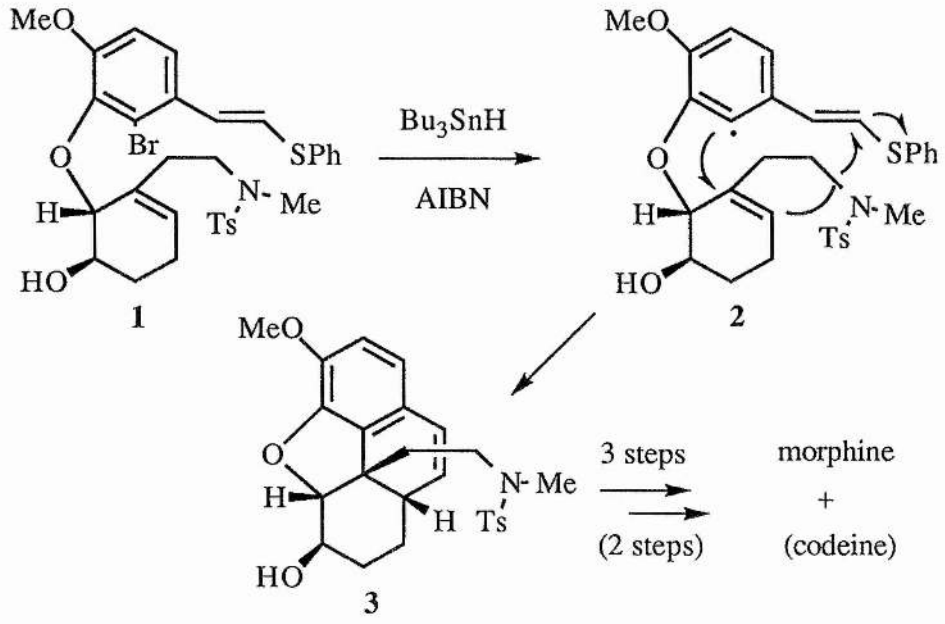


Scheme 3

Morphine

Parker's formal syntheses of (±)-morphine and (±)-codeine involved the preparation of aryl bromide **1** in 9 steps from commercially available *m*-methoxyphenethyl amine (Scheme 4).[3] This bromide was converted into tetracycle **3** in 35% yield when treated with tributyltin hydride and AIBN in a sealed tube. The aryl radical **2** cyclised via the 5-*exo* mode producing an intermediate secondary radical, which cyclised in a 6-*endo* fashion to give a benzyl radical. This was followed by elimination of •SPh and regeneration of the double bond. The 5-*exo* preference in the first cyclisation is the usual mode of ring closure for hexenyl-type radicals. Although this resulted in attack of the more hindered carbon, the geometrical possibilities in the transition state facilitated exclusive 5-*exo* closure. The

second cyclisation may have occurred by either *exo* or *endo* addition, but the latter mode was favoured. This was presumably due to the formation of the stabilised benzyl radical followed by the elimination of •SPh. This example illustrates some of the strengths of radical reactions conducted by organotin hydrides: (i) the selectivity of organotin radicals towards halides in the presence of other functionality, (ii) the formation of two rings in a stereoselective fashion and (iii) the ability to perform such reactions without the need to protect hydroxyl groups.

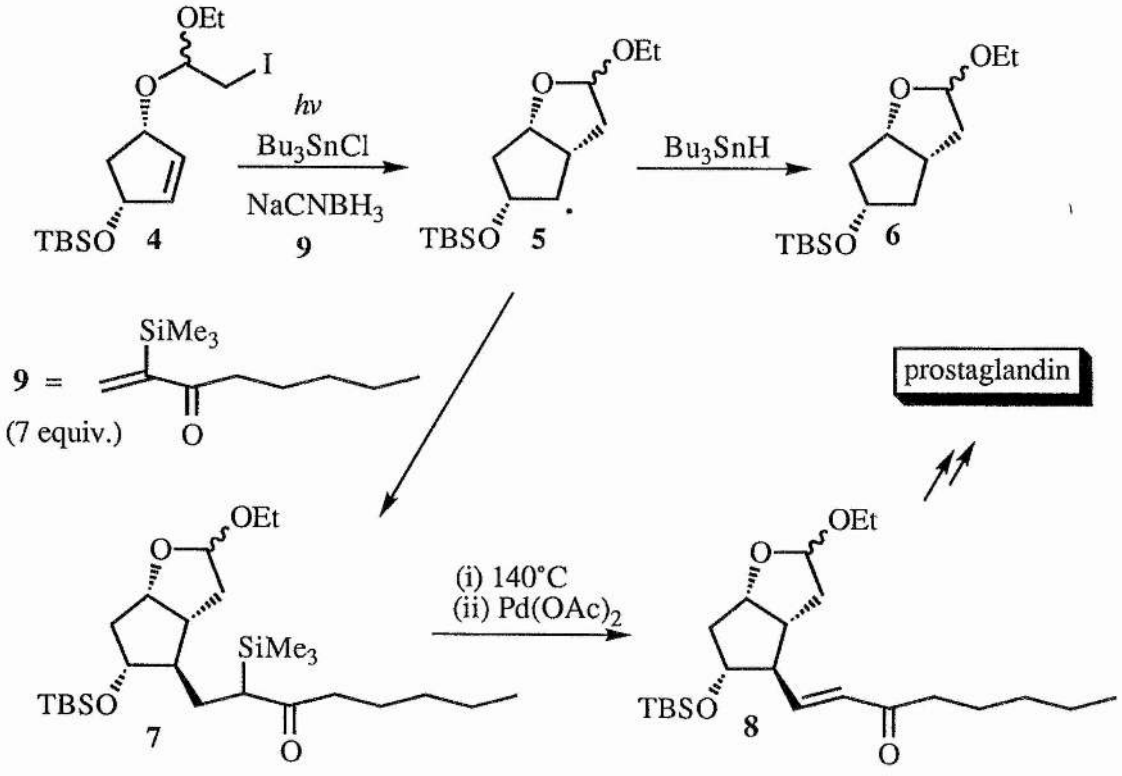


Scheme 4

Prostaglandin $F_{2\alpha}$

Stork was able to synthesise prostaglandin $F_{2\alpha}$ by the route shown in Scheme 5.[4] When iodide **4** was treated with tin hydride, generated *in situ*, under the given conditions the trimethylsilyl ketone **7** was obtained in crude form. This was isomerised to the corresponding trimethylsilyl enol ether (step i) and oxidised (step ii) to give unsaturated ketone **8** in 58% yield from iodide **4**. The primary alkyl radical resulting from iodine atom abstraction from **4** underwent 5-*exo* cyclisation to produce radical **5**, which added to alkene **9** yielding **7** after hydrogen atom abstraction. The initial cyclisation presented no problems though the following addition step was more troublesome. Since intermolecular reactions

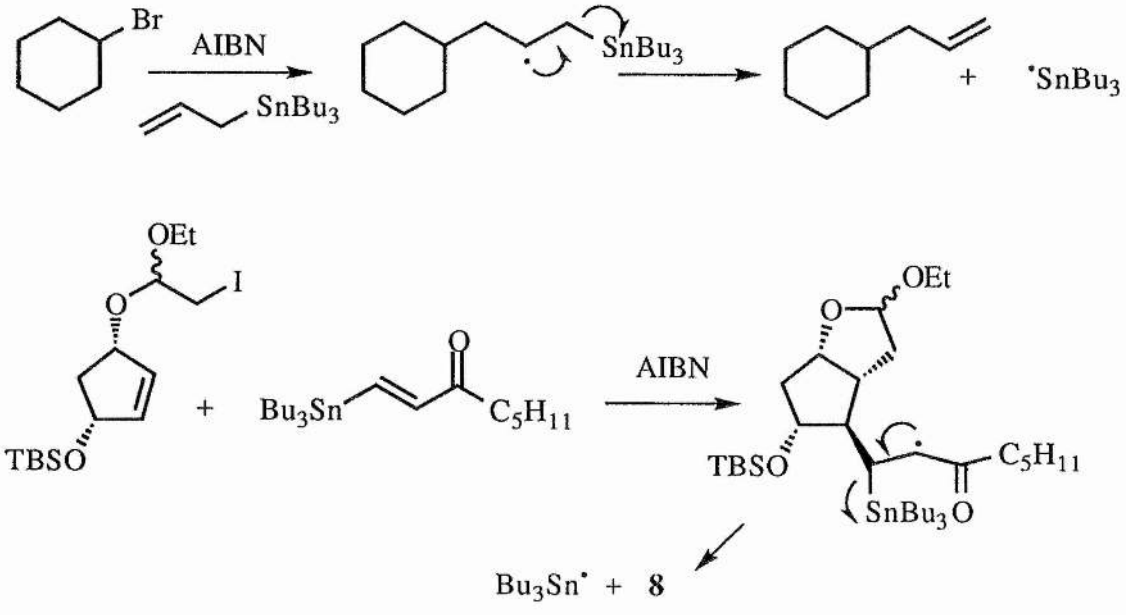
proceed more slowly than the analogous intramolecular reactions, there was the greater possibility that the intermediate radical **5** could abstract hydrogen from the tin hydride to produce the undesired product **6**. This can usually be controlled by various methods. One of the simplest ways to encourage radical addition is to use an excess of the alkene (*cf.* 7 equivalents of alkene **9** were used below). Another ploy is to use an activated alkene. Since alkyl radical **5** was nucleophilic and alkene **9** was electron-deficient, the rate of radical addition was enhanced. It is also possible to add tributyltin hydride portionwise to the reaction mixture to maintain a low concentration of the organotin hydride. Another way to achieve this is to use a catalytic amount of tributyltin chloride and a slight excess of a mild reducing agent, typically sodium borohydride[5] or sodium cyanoborohydride[6] as used in the Stork synthesis below. This method involves reduction of the tin chloride and the tin-halogen byproducts formed during the radical reaction, to the tin hydride, such that a catalytic cycle results.



Scheme 5

Another solution to the problems caused by the excellent hydrogen donating ability of tributyltin hydride is to use an organotin reagent which does not have a Sn-H bond. An example is hexamethylditin, Me_6Sn_2. Upon exposure to radiation, the tin-tin bond is cleaved, generating the organotin radical which reacts in the usual manner. For use in synthesis, a hydrogen source is required to avoid polymerisation. The decision amongst the range of hydrogen donors is usually based on the ease of hydrogen transfer.

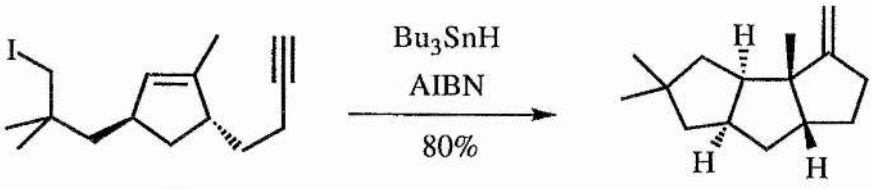
The use of allyl and vinyl stannanes in synthesis provides another alternative to the tin hydride chain-transfer step.[7] Alkyl halides can react with allyl or vinyl stannanes under certain conditions, to form unsaturated products. Two examples illustrating these reactions are given in Scheme 6. When cyclohexyl bromide and allylstannane were heated in the presence of AIBN, allylcyclohexane was formed in 88% yield. Keck and Burnett have used the vinyl stannane methodology in their synthesis of the prostaglandin precursor **8**.[8]



Scheme 6

Hirsutene

Curran's synthesis of (±)-hirsutene in 1985 represents one of the first examples illustrating the usefulness of tandem radical cyclisations.[9] Iodide **10**, prepared in approximately 14 steps from 2-methylcyclopentenone, was treated with tributyltin hydride and irradiated for 2h yielding approximately 80% of hirsutene, as determined by ^{1}H NMR and GC/MS (Scheme 7). The abstraction of iodine from **10** by a tin radical gave a primary radical which cyclised in the 5-*exo* mode to form a new, tertiary radical which attacked the triple bond and cyclised in a similar fashion. Hydrogen abstraction from tin hydride by the resulting vinyl radical completed the synthesis. The product was obtained in racemic form since iodide **10** was a 1:1 mixture of enantiomers (Scheme 7 illustrates only one of the enantiomers). Nevertheless, the radical cyclisation occurred with the usual stereoselectivity producing *cis* relationships at each of the two newly-formed ring junctions. (One enantiomeric form of hirsutene could in principle be obtained by initiating the synthesis with an asymmetric reduction of 2-bromocyclopentenone[10]). Purification of the product mixture by medium pressure liquid chromatography facilitated product isolation and four closely spaced compounds in a ratio of 6:100:2:2 were obtained, the major product being hirsutene. Two of the four compounds were unidentified whilst the last compound had a retention time identical to tributyltin hydride. This illustrates a further disadvantage associated with the tin hydride method: even after careful purification it is not possible to remove all the tin residues from the product mixture. Due to the toxicity of organotin compounds, this becomes a serious problem.



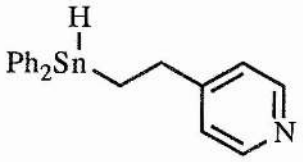
10 hirsutene

Scheme 7

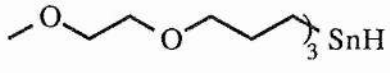
New Tin Reagents which aid product isolation

A common method to remove tin residues is the use of the potassium fluoride precipitation technique introduced by Jacobus in 1979.[11] Addition of a saturated solution of KF to the product mixture results in the cleavage of all Sn-Br, Sn-I and Sn-Sn bonds to produce, instead Sn-F bonds. The organotin fluorides are to known exist in hexameric arrays which precipitate out of the solution. Filtration therefore removes the majority of the tin residues. However, even after column chromatography there is usually 2 mol% of tin contamination.[12]

Clive has recently introduced stannane **11**, prepared from 4-vinyl pyridine, as an alternative to tributyltin hydride (Scheme 8).[13] The advantage with this reagent is that the tin-halogen byproducts have R_f values of approximately zero in ethyl acetate:hexane (1:3), and this allows the desired product to be easily isolated. This reagent can be used to form products in comparable yields to those obtained from the tributyltin hydride method.



11



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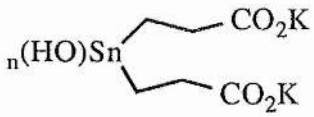


13

$(C_6F_{13}CH_2CH_2)_3SnH$

14

Scheme 8

The opposite approach to this is to produce tin residues that are extremely non-polar and can be eluted by column chromatography before the product. Crich has reported the relatively simple idea of treating the product mixture with an excess of sodium cyanoborohydride in *t*-butanol, (*cf* Corey's technique for *in-situ* regeneration of catalytic Bu_3SnH[4]), such that after completion, the reaction mixture simply contains the desired

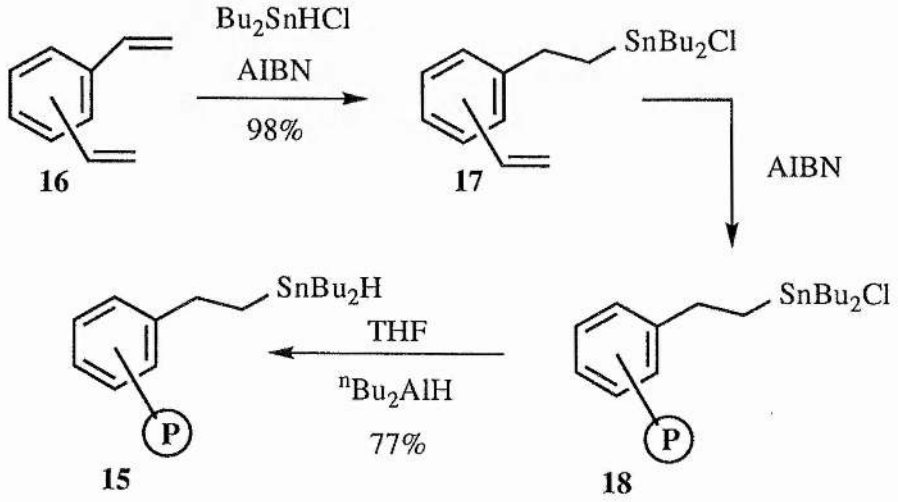
product and tributyltin hydride.[14] Column chromatography results in the isolation of the product and also the organtin hydride, which elutes from the column ahead of the product. This method can therefore result in the recovery of the tin hydride for further use and hence avoids the problem of disposal of tin compounds

Breslow has formed a water-soluble tin hydride **12** for radical reactions conducted in water (Scheme 8).[15] Thus, *m*-bromobenzoic acid can be photochemically reduced to benzoic acid in 88% yield in 5% $NaHCO_3$ at room temperature, 6-bromo-6-deoxy-α-methylglucopyranoside was reduced in 84% yield and 2-bromopentanoic acid in 37% yield. The polarity of the tin hydride **12** should facilitate product isolation, though its synthesis is rather lengthy. An alternative water-soluble tin reagent **13** has recently been described by Collum (Scheme 8).[16] When a mixture of an alkyl or aryl halide, $NaBH_4$, tin reagent **13** and the water soluble initiator 4,4'-azobis(4-cyanovaleric acid) (ACVA) are heated in degassed 1.5% KOH/H_2O at 86°C for several hours, reduced and cyclised products can form in yields comparable to the conventional Bu_3SnH/AIBN method. The $NaBH_4$ reduces organotin **13** to the corresponding tin hydride which is used *in situ* to generate the corresponding tin radical.

A convenient isolation technique of tin compounds, which relies on the mutual insolubility of hexane and acetonitrile, and the extraction of the tributyltin species into the hexane layer and the organic product into the acetonitrile layer, has been known for some time, though such a method may be limited by the relative solubilities of the organic product in both solvents.[17] A more recent example of this involves the use of fluorous reagent **14** which can be prepared in a three-step synthesis (Scheme 8).[18] When tin hydride **14** was used in the reduction of adamantyl bromide in benzene the results were not particularly encouraging. This was presumably due to the insolubility of **14** in benzene. However, in the presence of trifluoromethyl benzene, (a part hydrocarbon/fluorocarbon solvent), the bromide was cleanly reduced. The solvent was evaporated, dichloromethane and perfluorocyclohexane (a fluorocarbon solvent which extracted the fluorous tin byproducts)

were added to the residue to effect the clean isolation of adamantane in 90% yield. The method was also extended to the catalytic use of **14**, using the previously described reducing agent sodium cyanoborohydride.

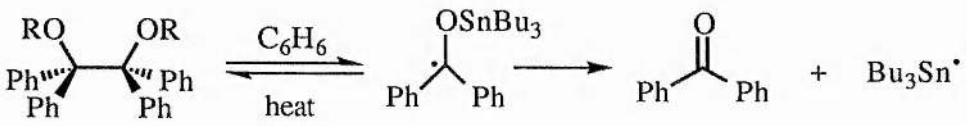
Polymer supported tin hydrides are without doubt the most effective alternatives for isolating a desired organic product free from the tin byproducts.[19,20,21] Since these polymers are insoluble in the reaction solvent the organic product can be isolated simply by filtration, followed by removal of the reaction solvent. The recovered polymeric tin halides can usually be recycled to the tin hydride for further use. Neumann has reported polymers of type **15** to be of general use in synthesis (Scheme 9).[19] However, since these reagents are not commercially available they have to be prepared prior to use and this is not a trivial task. Divinyl benzene **16** was selectively converted to the product of monohydrostannation (i.e. **17**) by treatment with dibutyltin hydride chloride. This styrene was polymerised with AIBN to give polymer **18** and reduction with di-*n*-butylaluminium hydride in THF was the most effective method for conversion to the tin hydride. Some of the reactions which can be performed successfully with these tin hydrides include the direct reduction of alkyl bromides, fragmentation of thiocarbonyl esters and cyclisation of 1-bromohex-5-ene. An improved synthesis of a polymer-supported distannane has also been published recently.[22]



Scheme 9

New Tin Reagents which minimise formation of direct reduction products

Some time ago, Neumann described the use of *bis*(trimethylstannyl)benzopinacolate **19** as a thermal source of trimethylstannyl radicals (Scheme 10).[23] More recently, Hart has demonstrated how this reagent can be used to generate alkyl radicals from halides and selenides, which can then add to the carbon-nitrogen double bond of O-benzylformaldoxime.[24] Due to the expense and toxicity of trimethylstannyl derivatives, the alternative reagent *bis*(tributylstannyl)benzopinacolate **20** has also been reported by Hart.[25] This tin compound can be prepared in almost quantitative yield by the reaction of benzopinacol and tributylstannyldimethylamine in benzene. When tin reagent **20** is warmed in benzene, homolysis of the central carbon-carbon bond produces carbon-centred radical **21**, which fragments to generate the tributyltin radical and benzophenone as a byproduct.



19 R=Me_3Sn
20 R=Bu_3Sn

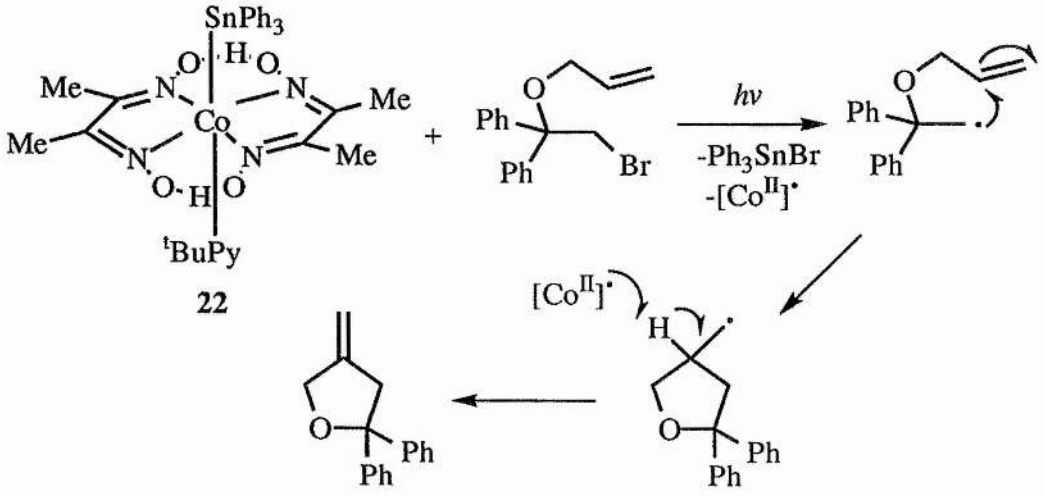
21

Scheme 10

The alkyl radicals generated from alkyl iodides by this method add intermolecularly to alkenes in moderate-good yields. Since direct reduction is not a problem it is not necessary to use a large excess of the alkene. A disadvantage with this method, however, is the difficult removal of both the tin residues and benzophenone.

More recently (triphenyltin)cobaloxime **22**, prepared from the reaction between chloro(4-^{t}Bu-pyridine)cobaloxime and triphenyltin chloride in 53% yield, has been reported to be an effective mediator of intramolecular radical cyclisations (Scheme 11).[26] Upon photolysis of this complex, the triphenyltin radical is generated and can abstract bromine from bromides producing alkyl radicals, which may undergo cyclisation if appropriately substituted. No direct reduction products are formed and the final radical abstracts hydrogen from the

solvent (e.g. THF). Hence a non-chain mechanism operates. Another advantage with this reagent is the possibility of the cobaloxime radical (also formed on photolysis of **22**), abstracting a hydrogen atom from the final radical, such that an alkene is produced. An example is given in Scheme 11 and other examples are illustrated in the section on cobalt-mediated radical reactions



Scheme 11

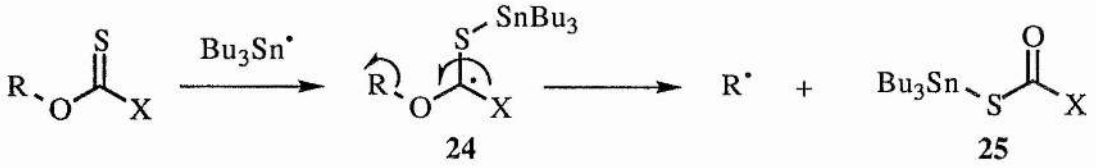
Deoxygenation reactions of thiocarbonyl esters

A useful transformation in organic synthesis is the replacement of a hydroxyl group by a hydrogen atom. The Barton-McCombie deoxygenation of primary and secondary alcohols is an effective method for achieving this and one that has found numerous applications in synthesis.[27] The method requires the conversion of the alcohol into a thiocarbonyl ester **23** as shown in Scheme 12.

X= SMe, Ph, Im, OPh, OC_6F_5, SPh. **23**

Scheme 12

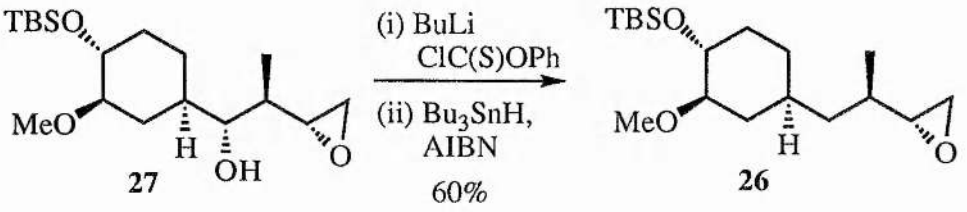
These esters can usually be prepared in good-excellent yield under mild conditions. When exposed to tributyltin hydride, usually in the presence of the initiator AIBN, a radical chain reaction results in the formation of the alkyl radical R• (Scheme 13). The mechanism involves the selective addition of the tin radical to the sulphur atom of the carbon-sulphur double bond (though Beckwith has proposed an alternative pathway[28,29]), to give carbon-centred radical **24** which fragments to generate the alkyl radical R• and the tin byproduct **25**.



24 **25**

Scheme 13

An example of this type of deoxygenation process is given in Scheme 14. Epoxide **26** was an important intermediate in Ley's synthetic approach to the biologically active natural product, rapamycin.[30] Having served its purpose in the asymmetric epoxidation step, the hydroxyl group present in epoxide **27** was converted into a thiocarbonyl ester group. Tin hydride mediated fragmentation then gave epoxide **26** in 60% overall yield.

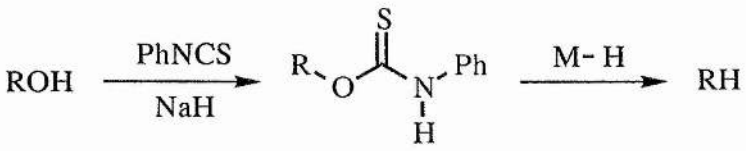


27 **26**

Scheme 14

Prompted by the low stability of the common derivatizing reagents (e.g. thiocarbonyldiimidazole) to moisture and also their expense, Nishiyama has recently described the deoxygenation of alcohols *via* N-phenylthioxocarbamates **28** (Scheme 15).[31] These alternative thiocarbonyl esters are prepared in good-excellent yields by the reaction of the appropriate alcohol with phenyl isothiocyanate in the presence of sodium hydride

(Scheme 15). The method can be used to convert primary, secondary and tertiary aliphatic alcohols and sugars and nucleosides containing hydroxyl groups, into the corresponding thiocarbamates. These esters undergo deoxygenation reactions using tributyltin hydride or a variety of silanes in the presence of an appropriate initiator. Using deuterated reducing agents, it was also possible to introduce deuterium stereoselectively into sugars and nucleosides.[31]



28

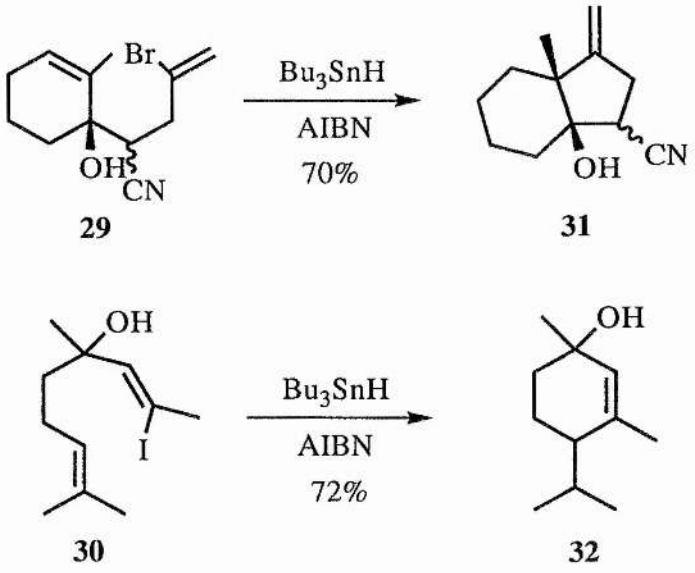
Scheme 15

Rather than search for alternatives to organotin hydrides, Fu has devised methods which involve the use of catalytic quantities of organotin compounds.[32,33] Most recently, he reports the first catalysed variant of the Barton-McCombie deoxygenation.[32] This procedure involves using a catalytic amount of $(Bu_3Sn)_2O$ and a stoichiometric amount of the reducing agent, polymethylhydrosiloxane (TMSO-$(SiHMeO)_n$-TMS). Thus, the tin reagent is reduced to tributyltin hydride and this facilitates the deoxygenation process in the presence of AIBN, and the tin byproducts are also reduced to the tin hydride. However, the reaction has to be performed in *n*-butanol to allow efficient reduction of the tin byproducts. The advantages with this method include the use of very cheap reagents (i.e. $(Bu_3Sn)_2O$ and polymethylhydrosiloxane are substantially cheaper than Bu_3SnH), negligible contamination problems and most importantly, the isolation of products in similar yields to the stoichiometric method.

Vinyl Radicals

The intramolecular cyclisation of a vinyl radical onto a double bond is a synthetically valuable transformation. Stork realised the potential of forming a cyclic product containing unsaturation, since this would serve as a site for further synthetic operations.[34] Thus, he

demonstrated how vinyl bromide **29** and vinyl iodide **30** could undergo their respective 5-*exo* and 6-*exo* radical cyclisations, when treated with tributyltin hydride, to produce in good yield, alcohols **31** and **32** respectively (Scheme 16).

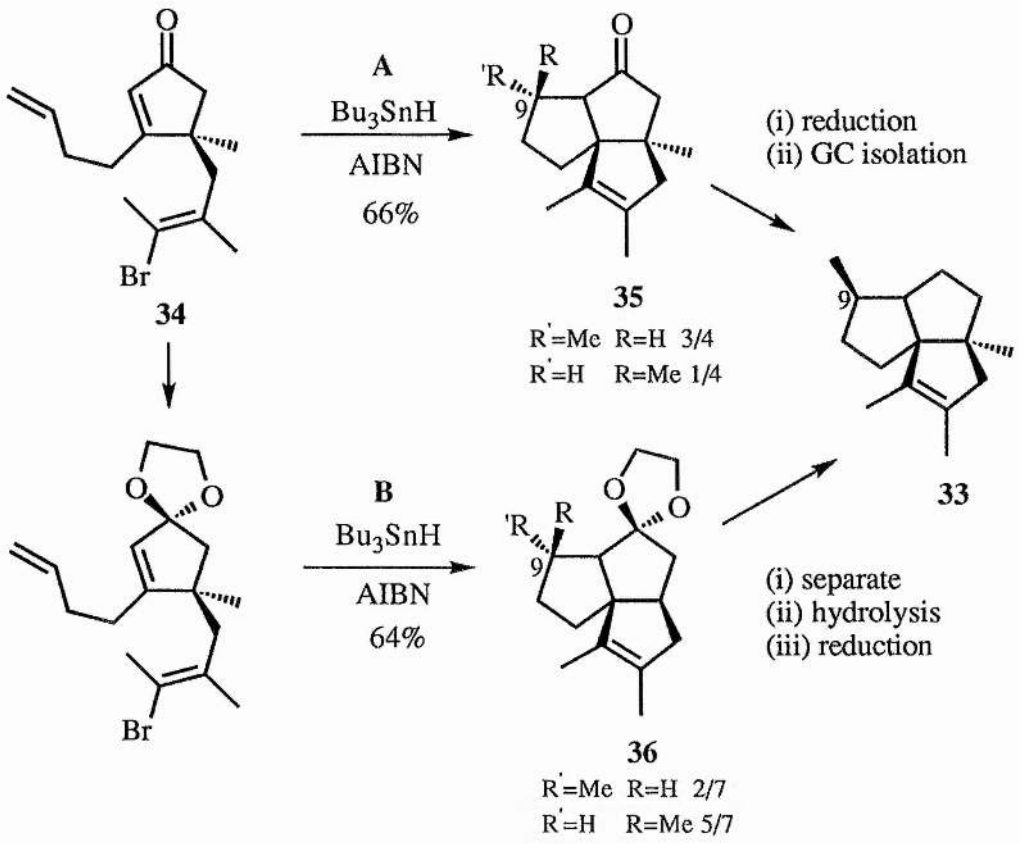


29 **31** **30** **32**

Scheme 16

Vinyl radicals are more reactive than their alkyl analogues and as a result, tend to undergo cyclisations more rapidly. Furthermore, they give better ratios of cyclic to direct-reduction products than for alkyl cyclisations. However, due to their relative instability, the formation of vinyl radicals is restricted to iodides and the most reactive bromides.

Earlier we saw an example of an intramolecular tandem cyclisation from the work of Curran, which resulted in the total synthesis of the linear triquinane, hirsutene. Curran, has also targeted the angular triquinanes, such as silphiperfolene **33** and has reported the total synthesis of this natural product in racemic form (Scheme 17).[35] The strategy involved the synthesis of vinyl bromide **34** followed by treatment with tin hydride, to give the corresponding vinyl radical which underwent two 5-*exo* cyclisations in tandem, forming the inseparable diastereoisomeric ketones **35**, epimeric at C_9 (route **A**). The natural product was obtained in racemic form after removal of the carbonyl group (Wolff-Kishner reduction), followed by isolation of the natural diastereoisomer by gas chromatography.



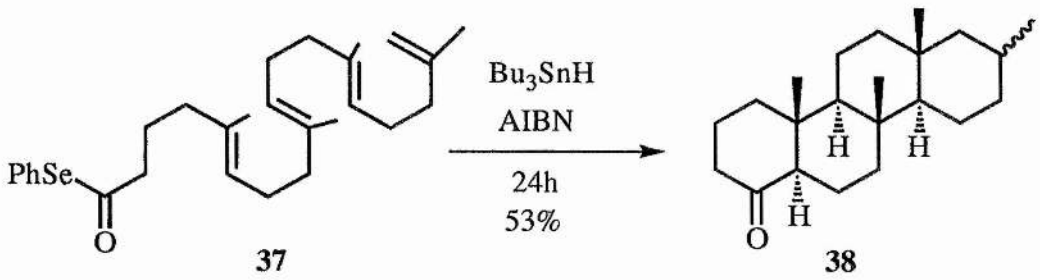
Scheme 17

Since the desired stereoisomer was the minor one, a slightly varied approach involving protection of the carbonyl as a ketal (route **B**) was predicted to impose steric interactions which would direct the second cyclisation in favour of the desired diastereoisomer. This turned out to be the case, affording a separable mixture of ketals **36**, which facilitated the isolation of the required product. This was converted to silphiperfolene **33** by hydrolysis of the ketal and reductive removal of the carbonyl group. The fact that the two sets of cyclisations performed, namely **A** and **B**, occured in almost identical overall yields, demonstrated that the rapid vinyl radical cyclisation of bromide **34** was not enhanced by the activating carbonyl group.

Acyl and other Radicals Generated with Tin Hydride

Phenyl selenyl esters are a convenient source of acyl radicals which can be prepared by the action of diphenylselenide[36] or N-phenylselenophthalimide[37] on the corresponding carboxylic acid in the presence of tri-*n*-butylphosphine. During Pattenden's investigations

directed towards the synthesis of steroids, phenylselenyl ester **37** underwent a series of 6-*endo* trig cyclisations forming compound **38** as a 1:1 mixture of methyl epimers in 53% yield (Scheme 18).[36] Interesting features of this transformation include the high stereoselectivity observed and the preferred 6-*endo* cyclisation of the acyl radical. The remaining three cyclisations are directed *endo* by the vinylic methyl substituents.



Scheme 18

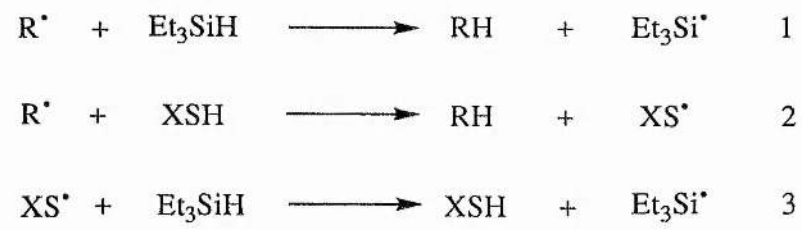
Recently, methods have emerged which describe the tin hydride mediated generation of α-sulfinyl, sulfonyl and sulfenyl radicals,[38,39] nitrogen-centred,[40] aminyl,[41] iminyl,[42,43] α–aminoalkyl,[44] 1-amidoalkyl,[45] aziridinyl,[46] propargyl,[47] oxiranyl[48] and alkyl[29] radicals. The fact that organotin hydrides can be used to generate a variety of different radical types, suitable for use in organic synthesis, contributes to the reagent's popularity. Combined with its availability and ease of use, it is not suprising that the toxicity and contamination problems associated with organotin hydrides are tolerated. The remaining pages of this introduction describe some of the alternative methods for generating radicals.

2. Silicon and Germanium Hydrides

Obvious alternatives to trialkyltin hydrides are the trialkylsilanes, R_3SiH. Silicon-centred radicals are extremely efficient in abstracting halogens from alkyl halides, hence generating the corresponding alkyl radicals. However, the silicon-hydrogen bond strength is usually too strong for efficient hydrogen abstraction and this disrupts the chain process.

Barton and Jaszberenyi have reported that diphenylsilane can be used to reduce bromides and isonitriles in excellent yields, although the only examples given were for 1-substituted adamantanes.[49] The corresponding iodides and chlorides however, were reduced in poor yields and the phenylselenyl and nitro-adamantane derivatives were completely unreactive. The method was extended to the deoxygenation of a variety of alcohols, including 1,2-diols which produced alkenes. The majority of these reactions involving diphenylsilane were initiated by either triethylborane-oxygen or AIBN in refluxing toluene, though the former method of initiation is not a particularly attractive one. Triethylsilane has also been reported to be a useful alternative to tributyltin hydride.[50,51,52] However, in such cases the reaction temperature is often undesirable and it is unlikely that either triethylsilane or diphenylsilane will be used in organic synthesis to mediate radical reactions.

An intelligent approach which allows trialkylsilanes to mediate free-radical reactions has been devised by Roberts.[53] Since alkyl radicals are nucleophilic and the hydrogen atom in triethylsilane is electron rich, reaction 1 illustrated in Scheme 19 is unfavourable, not only from a thermodynamic viewpoint, but also from a consideration of polar factors.

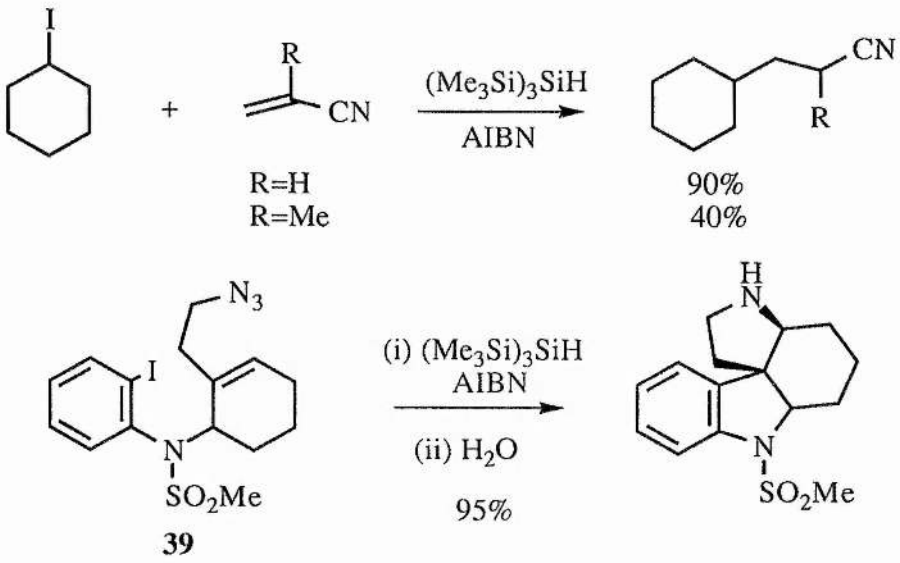


Scheme 19

However, this problem can be solved if a catalytic amount of a thiol is added to the reaction mixture. Alkyl radicals abstract hydrogen from thiols much more readily than from trialkylsilanes[54] and the resulting thiyl radical, which is electrophilic, abstracts hydrogen from the silane more readily than the alkyl radical. Thus, the thiol is regenerated along with the chain-carrying silyl radical (reactions 2 and 3, Scheme 19). This procedure, termed

polarity-reversal catalysis, has also been used to effect the efficient hydrosilylation of alkenes using triethylsilane as the silylating agent.[55]

In 1988 an alternative reagent for radical-chain reactions was introduced by Chatgilialoglu.[56,57] Tris(trimethylsilyl)silane, $(Me_3Si)_3SiH$ has found extensive use in synthesis because of its greater hydrogen donating ability compared to ordinary trialkylsilanes. This is due to stabilisation of the resulting silyl radical by back-bonding into the adjacent, vacant d orbitals on each of the three silicon atoms. In addition to its non-toxicity, tris(trimethylsilyl)silane has the additional advantage that fewer direct-reduction products are formed, since the Si-H bond strength is approximately 5 kcal/mol stronger than the Sn-H bond strength of tributyltin hydride. This often allows radical reactions to be performed with a stoichiometric amount of the silane in the initial reaction mixture, rather than portionwise addition. Some examples of intermolecular radical additions to activated alkenes[57] are given in Scheme 20, along with an example of an intramolecular double ring closure.[58]

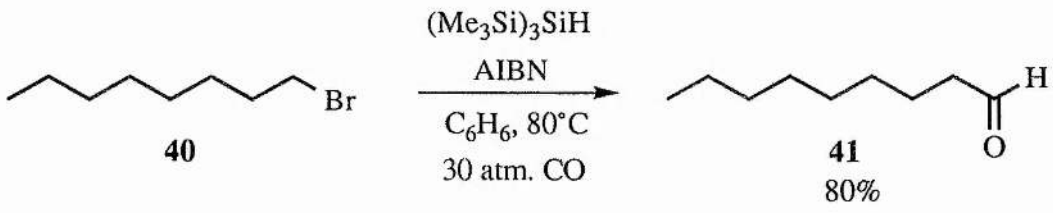


Scheme 20

When iodide **39** was treated with tris(trimethylsilyl)silane and AIBN, the aryl radical resulting from iodine atom abstraction, cyclised in a 5-*exo* fashion generating a new

carbon-centred radical which attacked the azide group, resulting in the formation of a heterocyclic ring and the elimination of nitrogen.[58]

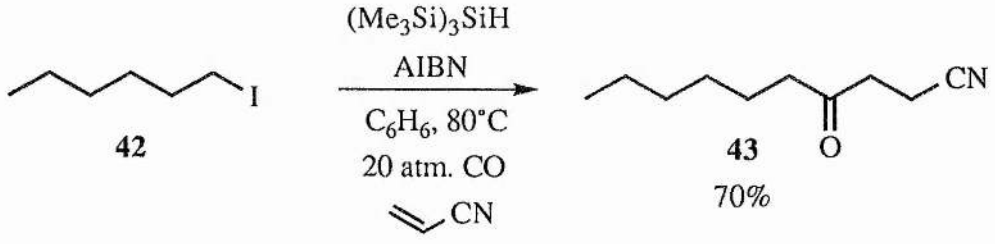
Free radical carbonylation reactions have recently gained distinction as a promising method for the introduction of a carbonyl group into a molecule. For example, octyl bromide **40** was converted into aldehyde **41** in 80% yield when refluxed in benzene in the presence of tris(trimethylsilyl)silane, AIBN and 30 atmospheres of CO (Scheme 21).[59]



40 **41** 80%

Scheme 21

Due to the stronger Si-H bond in tris(trimethysilyl)silane compared to tin hydride, direct reduction is less of a problem and this allows the pressure of CO to be reduced. When tributyltin hydride was used instead, the CO pressure had to be increased to 50 atmospheres and even then, the yield of aldehyde was only 63% with octane forming in 36% yield. Using tris(trimethylsilyl)silane it was also possible to carry out reactions which involved addition of an alkyl radical to CO, followed by addition of the resulting acyl radical to an alkene prior to hydrogen abstraction. Thus, iodide **42** was converted into ketone **43** in 70% yield as shown in Scheme 22.[59]



42 **43** 70%

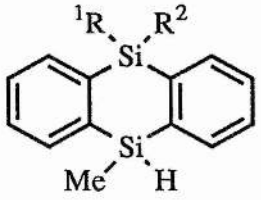
Scheme 22

Alkylated heteroaromatic bases are important fragments in organic synthesis and are often found in biologically active compounds. Hence, new methodology leading to such

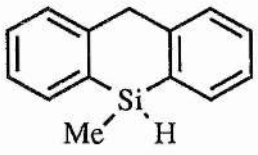
compounds is valuable. Togo and Yokoyama have recently described how alkyl bromides and iodides can be used to prepare alkylated heteroaromatic compounds using a variety of silanes, though the best results obtained were with tris(trimethylsilyl)silane and also tetrakis(trimethylsilyl)silane.[60]

In addition to its ability to deoxygenate alcohols *via* thiocarbonyl esters, it is clear that tris(trimethylsilyl)silane is a versatile reagent which can be used to mediate a number of useful radical reactions. However, few reagents in organic synthesis come complete with no disadvantages and tris(trimethylsilyl)silane is no exception. For example, the silyl radicals generated from this reagent can in some cases add to multiple bonds. In fact, Chatgilialoglu has shown that tris(trimethylsilyl)silane is an efficient reagent for hydrosilylating alkenes and alkynes.[61] Another disadvantage is that it is expensive, although it can be prepared by treating trichlorosilane and trimethylsilyl chloride with lithium.[62] This synthesis is however low yielding and the reagent is not particularly easy to handle. One solution to its high cost is to use the reagent in catalytic quantities. Chatgilialoglu and Griller have reported the catalytic use of tris(trimethylsilyl)silane using sodium borohydride to regenerate the reagent from the silicon-halogen byproducts.[63] Reduction of bromoadamantane (90%), cholesteryl iodide (55%) and 1-bromonaphthalene (88%) using this protocol, occurred in yields comparable to the stoichiometric method.

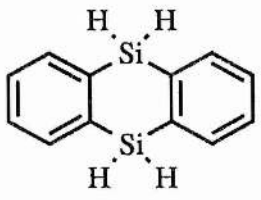
Nishiyama has recently introduced 9,10-dihydro-9,10-disilaanthracenes **44a-c** as new radical based reducing agents (Scheme 23).[64] Of the three silanes shown, **a-c**, the most effective reagent was silane **44a** and this was the reagent of choice for the reduction of alkyl halides and deoxygenation of alcohols. Silane **45** was a suprisingly poor reagent for mediating such reactions, usually giving trace amounts of product. The reason for this drastic difference between silanes **44** and **45** was thought to be due to transannular interaction between the silyl radical and the silicon atom, resulting in stabilisation of the silyl radical.



44a R^1=Me, R^2=H
b R^1=Ph, R^2=H
c R^1=Me, R^2=Me



45



46

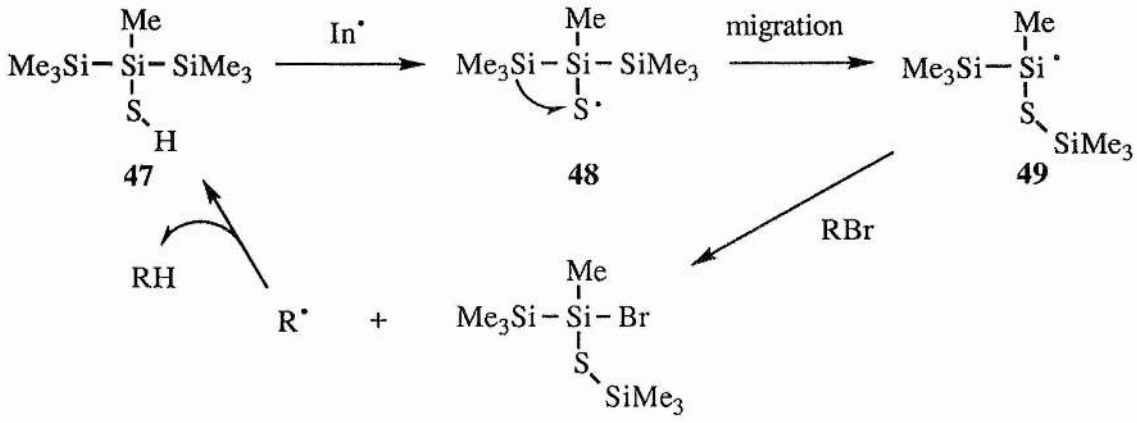
Scheme 23

Shortly after their introduction, Chatgilialoglu reported that the related silane **46** was also capable of deoxygenating alcohols under mild conditions.[65] Taking into consideration the ease of preparation of these silanes,[66] it is possible that they could succeed tris(trimethylsilyl)silane as new reducing agents.

Tri(alkylthio)silanes $(RS)_3SiH$ have also been shown to be useful reducing agents.[67] The silicon hydrogen bond strength in these compounds was predicted to be 82-83 kcal/mol, which is in between the values for the Sn-H and Si-H bond strengths of tributyltin hydride and triethylsilane. The invention of this reagent was based on the possibility that 3p-3p overlap between silicon and sulphur may have a stabilising effect on the silyl radical. The low electronegativity of sulphur was also a factor in designing a silane with adjacent sulphur atoms. In some simple experiments with bromides, iodides, isocyanides, xanthate esters and phenyl selenides the yields of reduced products were nearly quantitative with tri(methylthio)silane (as measured by GC analysis).[67]

Heptamethyltrisilane-2-thiol **47** is another alternative reagent (Scheme 24).[68] When treated with an appropriate initiator, hydrogen abstraction from the thiol generates the sulphur-centred radical **48**. This intermediate is short-lived and undergoes a trimethylsilyl group migration, such that the silyl radical **49** is formed. Since silicon radicals have good halogen atom abstracting properties, radical **49** can reduce a variety of alkyl bromides and iodides

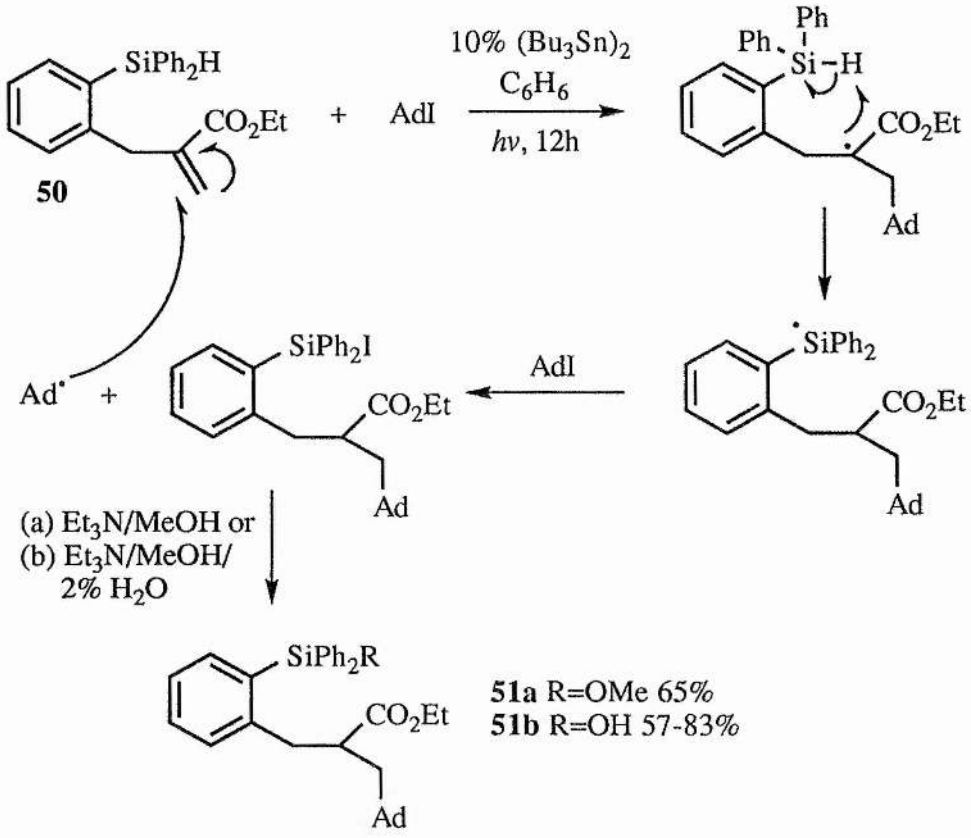
in virtually quantitative yields. Chain-transfer involves abstraction of hydrogen from the relatively weak S-H bond.



Scheme 24

The synthetic use of this reagent may however be limited due to its thermal instability towards rearrangement and also due to the fast rate of hydrogen atom abstraction from the thiol by a primary alkyl radical, which has been estimated to be approximately an order of magnitude greater than that of tributyltin hydride.[68] Chatgilialoglu introduced independently a related reagent to **47**, namely, tris(trimethylsilyl)silane-2-thiol, which works by the same principle to that illustrated in Scheme 24.[69]

The important chain-transfer step in the radical chain reactions described so far are bimolecular processes. Curran has suggested that unimolecular chain transfer reactions of silicon hydrides may provide an advantageous alternative to the normal bimolecular chain transfer step of organotin hydrides.[70] For example, aromatic silane **50** can react with adamantyl iodide in the presence of 10% hexamethylditin under photochemical conditions to produce either silyl ether **51a** or silanol **51b** depending on the exact experimental conditions (Scheme 25). Due to the instability of silicon iodides, the reaction was performed in the presence of triethylamine and methanol to produce *in situ* silyl ether **51a** or when 2% H_2O was added, silanol **51b**.[70]

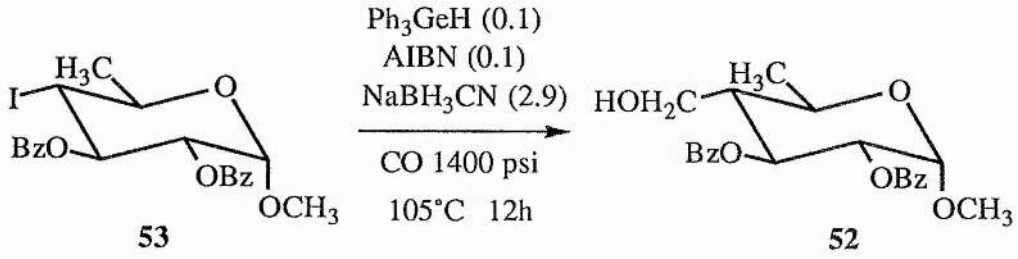


Scheme 25

Tributylgermanium hydride has been evaluated as a reagent for the alkylation of alkenes with alkyl halides.[71,72] Although this reagent has some advantages, it is not an ideal alternative to organotin hydrides, not least due to its cost. Tributylgermanium hydride has a relatively strong Ge-H bond and therefore direct reduction is usually not significant. In reactions with olefins, the intermolecular addition of the longer-lived alkyl radical can proceed with essentially equimolar amounts of the halide and the olefin. This would be an advantage in cases where the olefin was precious. However, the germanium hydride method is usually restricted to iodides as radical precursors, due to the lower reactivity of germanium radicals with halides. Furthermore, tributylgermanium hydride is more prone to react with olefins than its tin counterpart.

A recent example illustrating the use of triphenylgermanium hydride in synthesis is given in Scheme 26. Kahne required to synthesise monosaccharide **52** in an attempt to prove that

the hydroxylamine glycoside linkage present in the complex natural product calicheamicin, was critical for effective DNA binding, (using the hydroxymethyl linkage as a model).[73] Ionic-mediated attempts to substitute iodide **53** with hydroxymethyl substituents were thwarted by elimination reactions. Attention therefore turned towards generating the corresponding alkyl radical in an atmosphere of CO. Since the tin hydride method gave the direct-reduction product, it was apparent that the lifetime of the resulting radical had to be extended. Thus, the use of triphenylgermanium hydride under catalytic conditions, ($NaBH_3CN$), resulted in the isolation of the desired monosaccharide in a yield of 37%. An additional advantage with the catalytic method was the *in situ* reduction of the carbonyl functionality to the alcohol. Simpler iodides, such as adamantyl iodide, underwent the same reaction in yields exceeding 60%.[73]

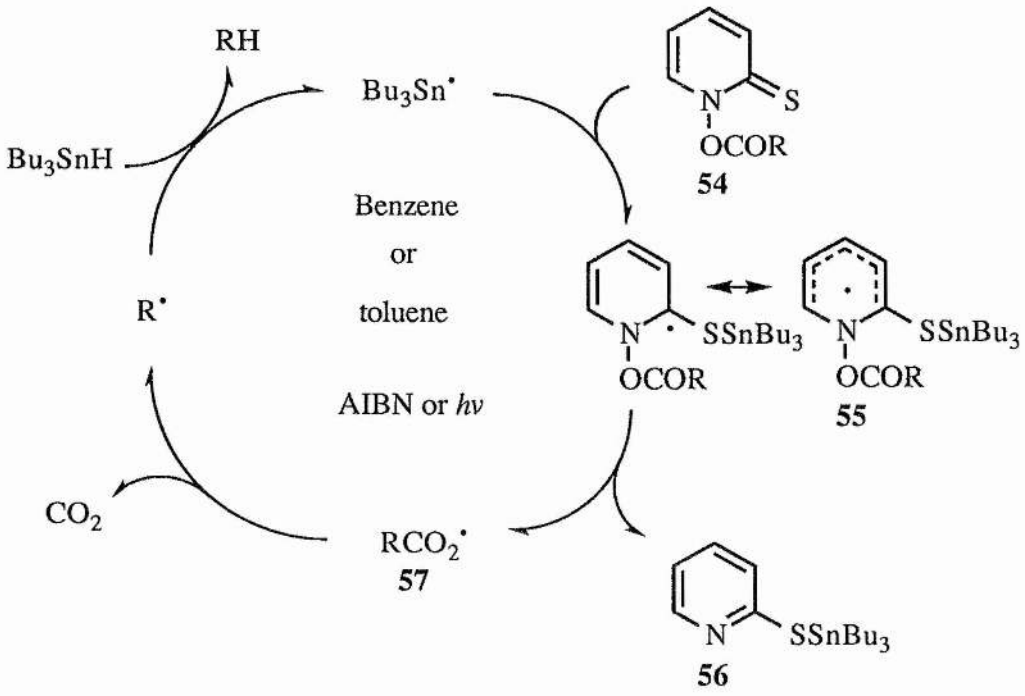


Scheme 26

Tris(trimethylsilyl)germane $(Me_3Si)_3GeH$ has also been introduced as a new radical-based reducing agent.[74] Similar to many of the other reducing agents described, this germane can reduce a variety of functional groups in high yield. The rate of hydrogen abstraction from tris(trimethylsilyl)germane by a primary alkyl radical, measured using the 5-hexenyl radical clock,[75] is even faster than for tributyltin hydride and this will limit the reagent's use in organic synthesis.[74]

3. Barton Esters

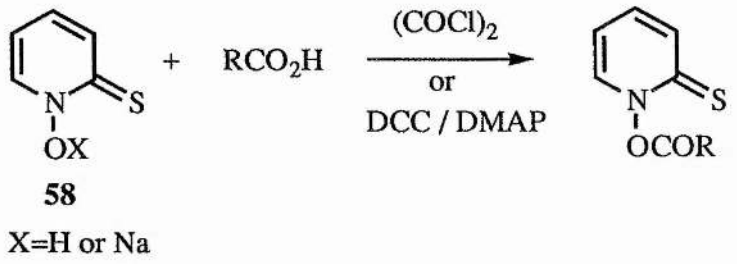
Thiohydroxamic esters **54** have been shown to generate carbon-centred radicals under mild conditions (Scheme 27).[76] When treated with tributyltin hydride in the presence of AIBN, or photochemically, the resulting tin radical adds to the sulphur atom of the thiocarbonyl group forming delocalised radical **55**. Radical **55** fragments to give the stannyl-2-pyridylsulphide **56** as a byproduct and alkoxycarbonyl radical **57**, which loses carbon dioxide, hence generating the carbon-centred radical R•. This radical abstracts hydrogen from the tin hydride giving the reduction product RH and the chain-carrying tin radical. The success of this methodology is due to the susceptibility of the thione function towards tin and sulphur-centred radicals,[77] the weakness of the N-O bond and the use of aromatisation as a favourable thermodynamic driving force.[76]



Scheme 27

The thiohydroxamic esters are prepared by esterifying mixtures of commercially available 2-mercaptopyridine N-oxide **58** and carboxylic acids activated by either oxalyl chloride or

DCC/DMAP (Scheme 28). The esters are not usually isolated but reacted immediately instead.



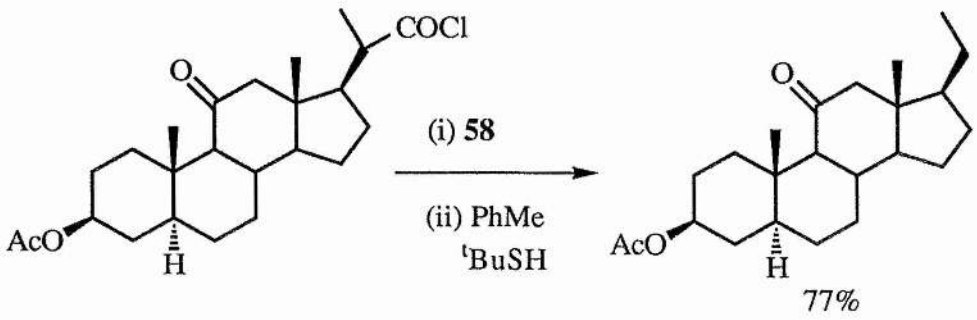
58

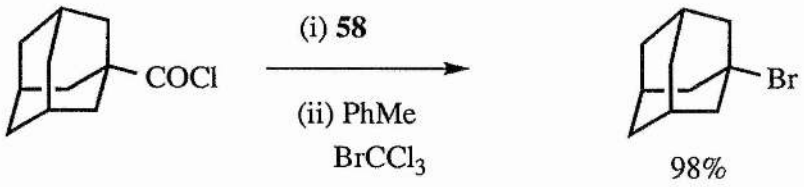
X=H or Na

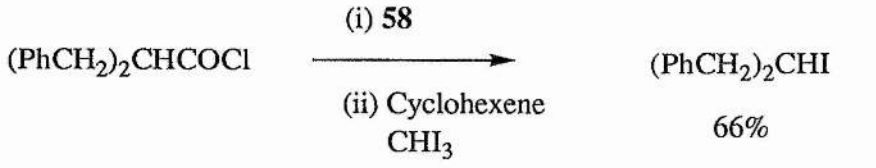
Scheme 28

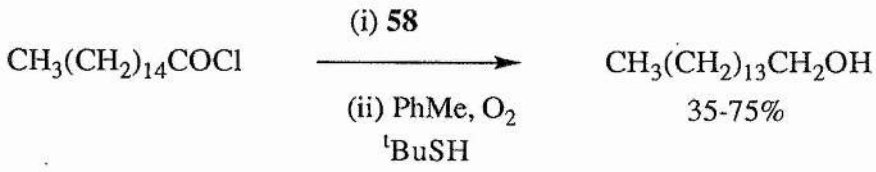
Since tributyltin hydride has several undesirable properties in radical reactions, alternative reagents have been used to initiate the chain reaction illustrated in Scheme 27. Thus, *t*-butylmercaptan was found to be a suitable replacement and is therefore the reagent of choice for the decarboxylation/reduction of carboxylic acids. Such chain reactions can also be initiated in the presence of carbon tetrachloride and bromotrichloromethane to yield alkyl chlorides and bromides respectively ($^{\bullet}CCl_3$ as the chain carrier) and with iodoform to give the alkyl iodides ($^{\bullet}CHI_2$ as the chain carrier). The latter reaction should be done in cyclohexene to trap any iodine formed during the reaction, which may attack the thiocarbonyl group of the ester **54**. Some examples of these types of reactions are illustrated in Scheme 29.[76]

Two examples illustrating the use of thiohydroxamic esters in organic synthesis are given in Schemes 30 and 31. Kocienski required (R)-3-cyclohexene carboxylic acid **59** in bulk quantities to begin synthetic studies towards the C_{24}-C_{34} segment of the natural product FK506.[78] Thus, selective enzyme catalysed hydrolysis of the commercially available meso-ester **60** furnished carboxylic acid **61**. This was converted *via* the acid chloride, into the corresponding Barton ester, which underwent smooth decarboxylation with *t*-butyl mercaptan in benzene, to give the required product after a further hydrolysis.

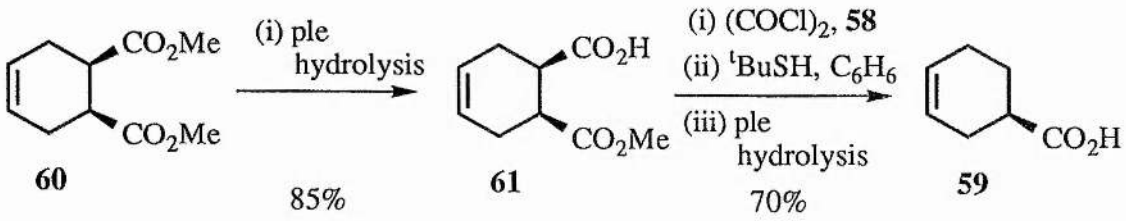








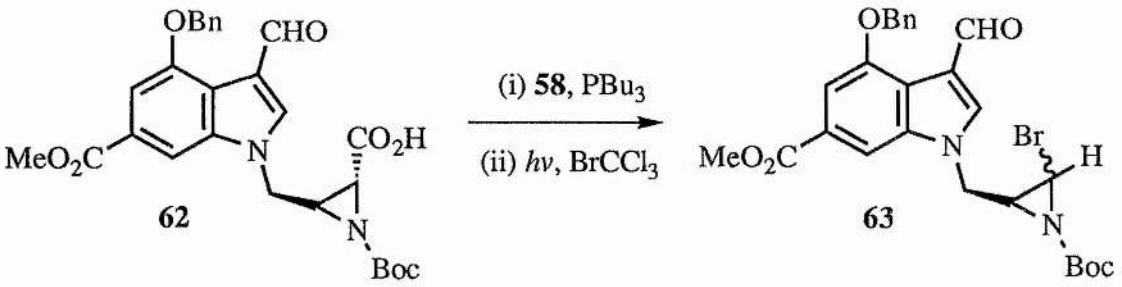
Scheme 29



Scheme 30

Ziegler has used the thiohydroxamic esters to generate oxiranyl[48] and aziridinyl radicals.[46] In studies towards the antitumour agent FR900482, carboxylic acid **62** was converted into the corresponding Barton ester which, when photolysed in bromotrichloromethane gave a

53% yield of bromide **63** (Scheme 31).[79] This bromide was itself treated with tributyltin hydride to regenerate the aziridinyl radical, which cyclised in a 5-*exo* fashion onto the proximate carbon atom of the alkene.



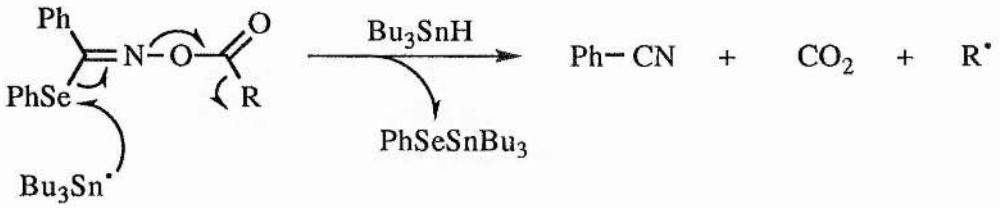
Scheme 31

Since their introduction there have been numerous reports by Barton and co-workers, concerning the use of this radical-based methodology. A few examples include (i) the conversion of carboxylic acids into thiols,[80] cyanides[81] and isothiocyanates[81] (ii) homologation of carboxylic acids either by 2 carbon atoms to yield amides[82] and α-keto acids[83] or by one carbon atom to give aldehydes[84] (iii) the generation of oxygen-centred radicals[85] and (iv) the use of alternative *N*-thiohydroxamic esters.[86]

An alternative Barton-type ester, 1-acyl-2(1H)-pyrimidine-2-thione, which can be stored for several days without decomposing, has recently been introduced by Liebscher.[87] Also, a new precursor for generating alkoxy radicals has been reported.[88] *N*-alkoxy-4-(*p*-chlorophenyl)thiazole-2(3H)-thione, derived from *p*-chloro acetophenone in 72% yield over 4 steps, can be converted into *O*-alkyl and *O*-acyl derivatives in moderate-good yields.[88] The *O*-alkyl derivatives have been shown to be sources of alkoxy radicals, based on the isolation of products derived from cyclisation.

A method for generating alkyl, aminyl and alkoxyl radicals derived from Se-phenyl benzoselenohydroximate derivatives **64** has appeared recently (Scheme 32).[89] Although

these radical precursors are different to Barton esters, they do bear some similarities since the generation of the appropriate radical occurs by homolytic cleavage of a N-O bond, followed by decarboxylation.

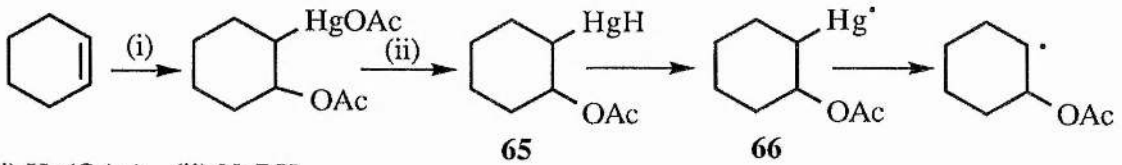


Scheme 32

This method has been used to convert (i) carboxylic acids, RCO_2H into the reduction products RH (*via* alkyl radicals), (ii) secondary amines, R_2NH into tosylates R_2NTs (*via* aminyl radicals) and (iii) alkyl halides, RBr into alcohols ROH (*via* alkoxyl radicals). The yields from reaction-types (i) and (iii) were virtually quantitative and those from reaction-type (ii) were at least 80%. However, the method involves the use of stoichiometric amounts of tributyltin hydride.

4. The Mercury Method

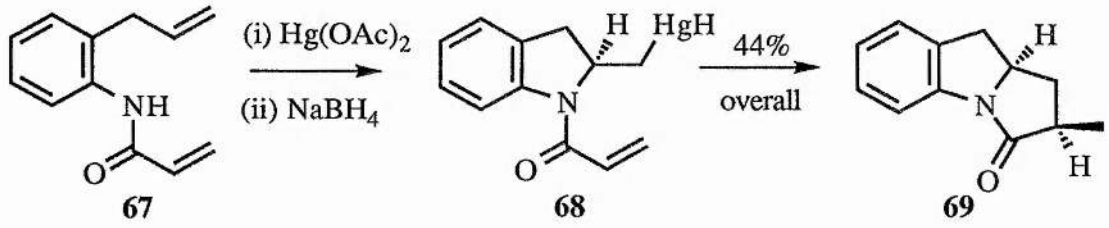
Organomercury hydrides can function as sources of radicals which can be used in synthesis.[90] The organomercury hydride is prepared *in situ* by the action of mercury (II) acetate on alkenes, (although precursors may also be prepared by reaction with certain cyclopropanes and ketones), followed by reduction using sodium borohydride to install the Hg-H bond (Scheme 33). Hydrides such as **65** undergo Hg-H bond dissociation producing the organomercury radical **66**, which rapidly loses mercury, forming the alkyl radical.



(i) $Hg(OAc)_2$ (ii) $NaBH_4$

Scheme 33

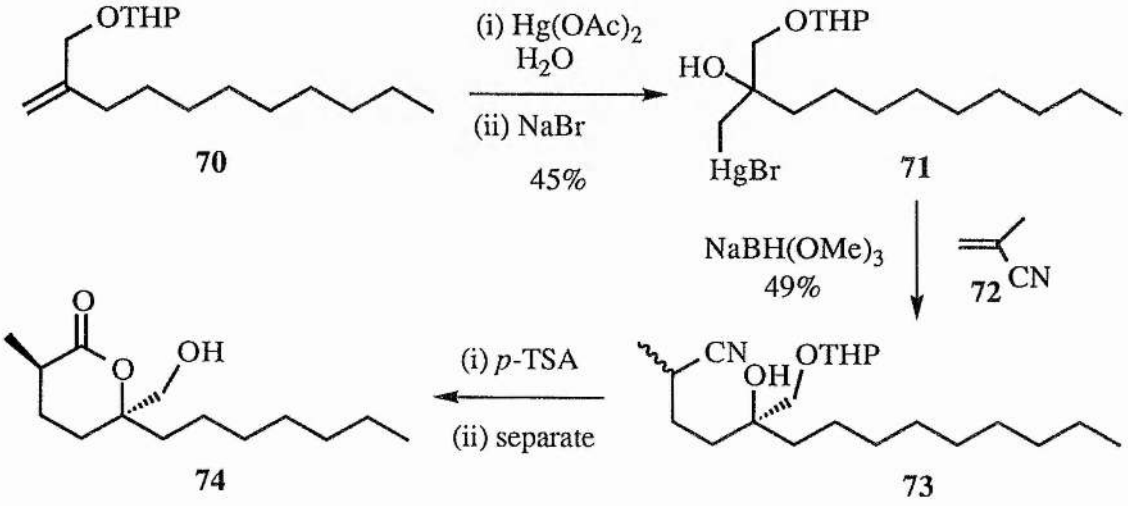
Two examples illustrating the preparation and reactivity of organomercury hydrides for use in synthesis are given in Schemes 34 and 35. Aryl amide **67** was converted to hydride **68** by treatment with mercury (II) acetate followed by sodium borohydride.[91] The formation of the first ring involved S_N2 attack of the amide nitrogen on the carbon bearing the acetyl group. The hydride **68** was not isolated, but instead fragmented to form a primary radical which cyclised in a 5-*exo* fashion to yield the tricyclic aromatic amide **69** in 44% yield from **67**.



67 **68** **69**

Scheme 34

Alkene **70** was treated with mercury (II) acetate followed by sodium bromide to give organomercury compound **71** (Scheme 35).[92] Reduction with sodium trimethoxyborohydride in the presence of an excess of radical trap methacrylonitrile **72**, resulted in the formation of nitrile **73** in 49% yield. This was treated with *p*-toluenesulphonic acid to effect the lactonisation and deprotection to give a 1:1 separable mixture containing the natural product malyngolide **74** and its methyl diastereoisomer.

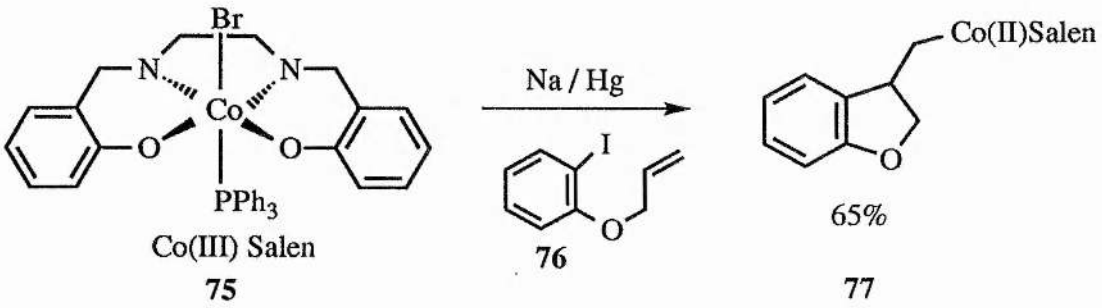


70 **71** **73** **74**

Scheme 35

5. Cobalt Reagents

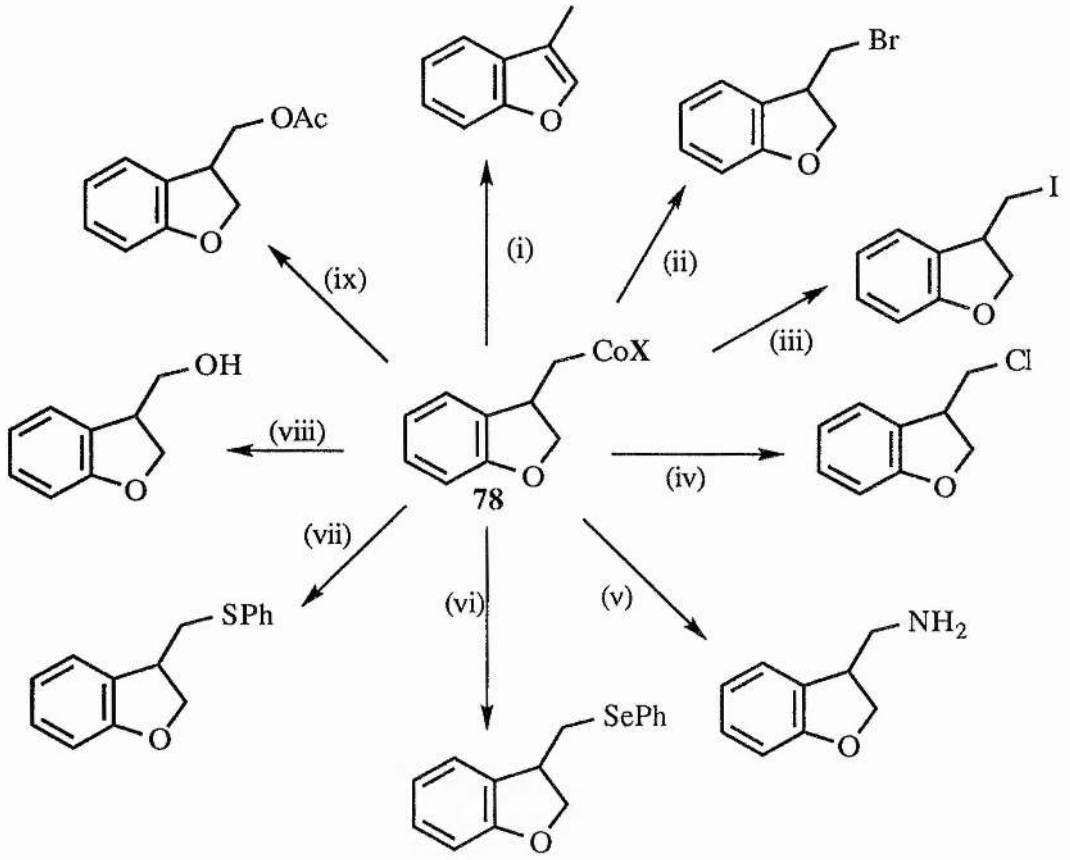
Organocobalt complexes such as cobalt (III) salen **75** can be used to generate alkyl, aryl and acyl radicals suitable for use in organic synthesis.[93] For example, when the cobalt complex **75** was treated with a small amount of sodium amalgam, followed by addition of aryl iodide **76**, benzofuran **77** was isolated in 65% yield (Scheme 36).[94] It is believed that the mechanism for this reaction, (and related reactions) involves reduction of the cobalt complex, followed by transfer of an electron to the aromatic compound **76**. This results in displacement of the iodide anion and formation of an aryl radical which cyclises onto the double bond, forming a primary radical, which is then trapped by the cobalt (II) complex to give **77**.



Scheme 36

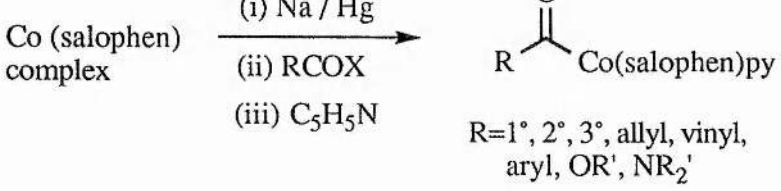
The attractive feature of this method is the fact that the cobalt compound **77** can undergo a series of reactions that allow the incorporation of new functionality into the molecule. Thus, the analogous cobalt (salophen) complex **78** has been converted into phenylselenides, phenylsulphides, oximes and amines, alcohols, esters, chlorides, bromides and iodides in good yields as shown in Scheme 37.[95]

Precursors for acyl radicals have been prepared by the reduction of the cobalt (salophen) complex, followed by treatment with the appropriate acid chloride and chromatographic purification in the presence of pyridine (Scheme 38).[96]



X=(salophen)py; (i) light, (ii) $BrCCl_3$, 79%, (iii) I_2, 42%, (iv) $MeSO_2Cl$, 78%, (v) NO, DMF, Et_3N, imine 78% then Na, ^iPrOH, (vi) Ph_2Se_2, 75%, (vii) Ph_2S_2, 85%, (viii) O_2 (ix) TEMPO (2,2,6,6-tetramethylpiperidinyloxyl), Zn, CH_3CO_2H

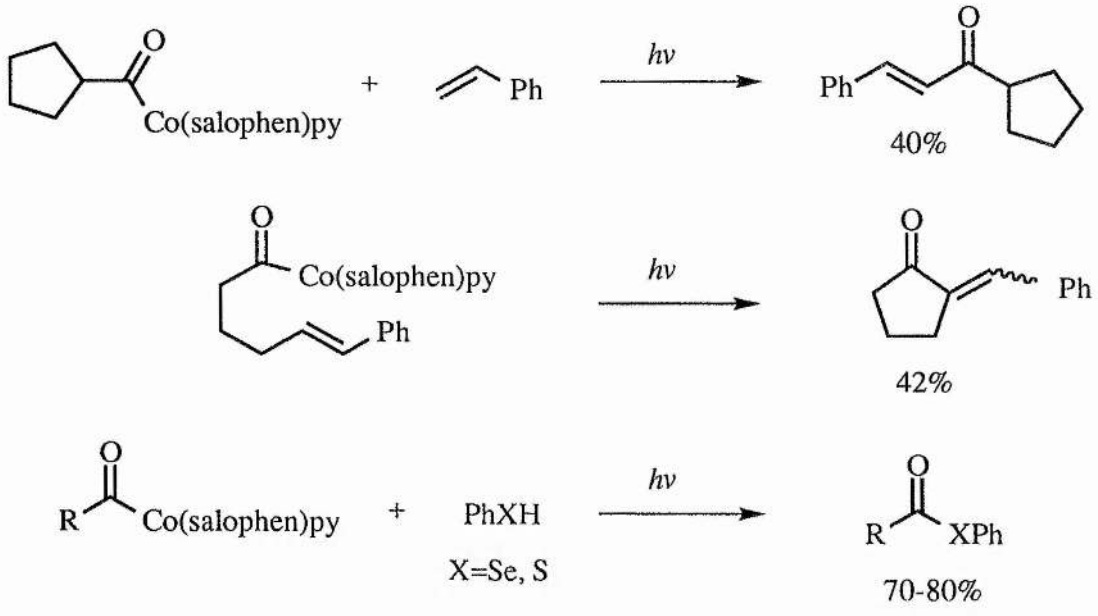
Scheme 37



Scheme 38

When heated, these complexes generate acyl radicals which can add to activated alkenes or react with phenylselenol or thiophenol(Scheme 39). In reactions with alkenes the resulting organocobalt species is short lived and suffers β-elimination to yield the conjugate enones.[96]

The cobalt-mediated radical reactions described above involved the isolation of the crystalline organocomplexes **77** or **78**, prior to their subsequent reactions. Giese has reported a series of cobalt-catalysed inter- and intramolecular radical reactions which can also be performed under mild reductive conditions.[97]

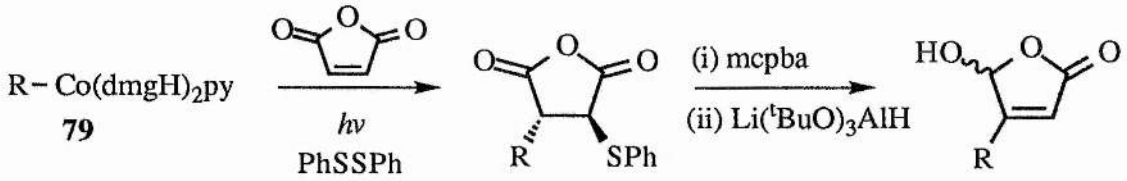


Scheme 39

Iqbal has also reported a cobalt-catalysed radical reaction.[98] He has shown that acyl radicals can be generated from enolizable aldehydes in the presence of [*bis*(salicylidene-N-phenethyl)]cobalt (II) chloride, (CoSAMP), and dioxygen. Subsequently, these radicals can be trapped with activated alkenes to produce, after incorporation of dioxygen, 2-hydroxyl-4-oxo esters. With unactivated alkenes, products arising from epoxidation of the alkenes are exclusively produced.

In studies towards butenolides, Branchaud has proposed a radical route involving intermolecular addition of an alkyl radical to maleic anhydride, and trapping of the adduct radical with diphenyl disulphide.[99] Incorporation of the phenyl sulphide functional group provided a means to regenerate the double bond, by oxidation to the sulphoxide followed by elimination. The radical precursor was cobaloxime **79** and the yields of the adducts

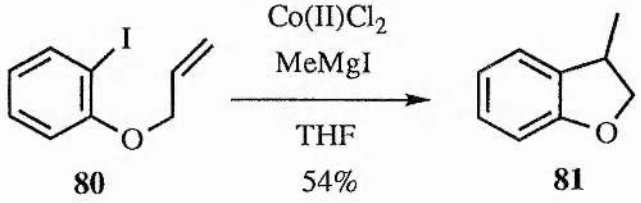
obtained were 78-85% as shown in Scheme 40, although for R=CH(CH$_3$)CN no addition was observed.



R=$(CH_2)_9CH_3$	80-88%
R=$CH(CH_3)(CH_2)_8CH_3$	78%
R=$CH(OAc)CH_2CH(CH_3)_2$	81%
R=$CH(CH_3)CN$	0%

Scheme 40

An alternative to tin hydride-mediated aryl radical cyclisations has been reported by Jones.[100] For example, iodide **80** was converted to dihydrobenzofuran **81** in 54% yield when added to anhydrous Co(II)Cl$_2$ in THF, followed by addition of the Grignard reagent, MeMgI, (or EtMgBr), and refluxing for the appropriate period of time (Scheme 41). The mechanism involves the formation of an organocobalt species, formed from the reaction of the Grignard reagent and Co(II) chloride, which reacts with the aryl iodide to generate the corresponding aryl radical. Other examples of such cyclisations were given.[100]

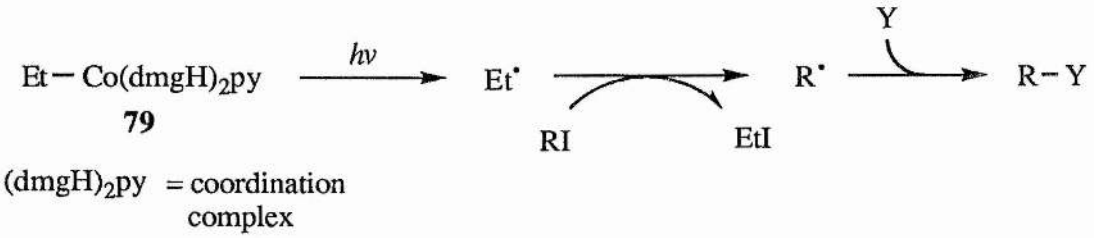


80 **81**

Scheme 41

Another method for generating radicals using cobalt chemistry has been published recently.[101] The idea outlined in Scheme 42, involves photolysing ethylcobaloxime **79** to generate the ethyl radical, which abstracts iodine from a suitable alkyl iodide to form the lower energy radical R$^{\bullet}$. This alkyl radical can undergo further reactions, such as radical

combination with 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) or addition to a protonated heteroaromatic.

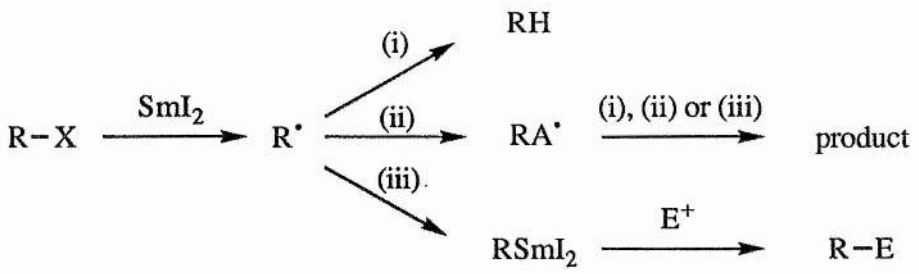


Scheme 42

The method reported only involved the use of substituted benzyl iodides and yields of the reactions with TEMPO varied from 33-72%, but were lower for radical additions to 4-methylquinoline. Although such a method has the advantage that the cobalt complex **79** can be used as a "shelf-reagent" source of ethyl radicals, it limits the choice of alkyl iodides for efficient iodine abstraction.

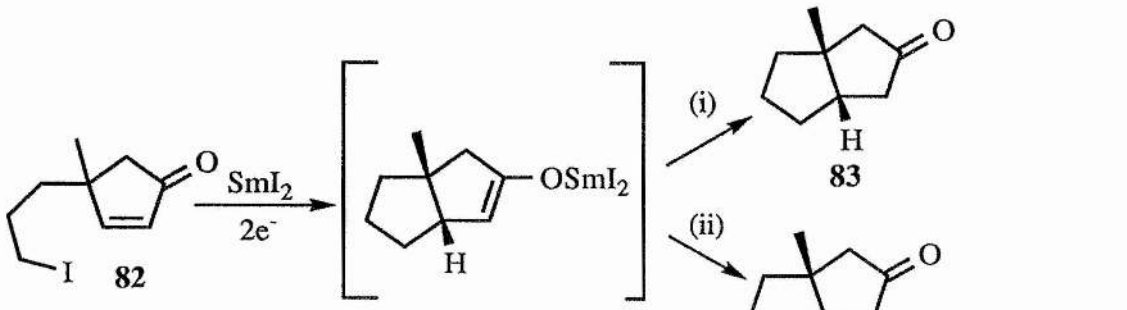
6. Samarium (II) Iodide promoted radical reactions

Samarium (II) iodide, SmI_2 has found numerous applications in organic synthesis since the introduction of the reagent to organic chemistry in the late 1970's, following the pioneering work of Kagan. Over the last few years this reagent has been used to mediate numerous radical reactions.[102] In common with the tin hydride method, a typical precursor for such a radical reaction is an alkyl halide (Scheme 43). Under certain reaction conditions, SmI_2 can transfer an electron to an alkyl halide, displacing the halide and forming an alkyl radical. Depending on the reaction conditions this alkyl radical has three options open to it; (i) abstraction of hydrogen from the solvent, (ii) conversion to a new radical typically *via* an intramolecular reaction and (iii) formation of an organosamarium Grignard-type reagent. The latter option makes SmI_2-mediated radical reactions attractive from a synthetic point of view, since further transformations can in principle be carried out.



Scheme 43

Curran demonstrated that when iodo compound **82** was treated with SmI_2 in THF, and in the presence of the additive DMPU (dimethylpropyleneurea), followed by acidic work-up, ketone **83** was isolated in 70% yield (Scheme 44).[103] The primary alkyl radical added to the alkene producing, after another electron transfer, an enolate trapped by the samarium reagent. On addition of a proton source, ketone **83** was obtained, although when aldehyde **84** was used in place of a proton source, aldol adduct **85** was obtained in moderate yield.

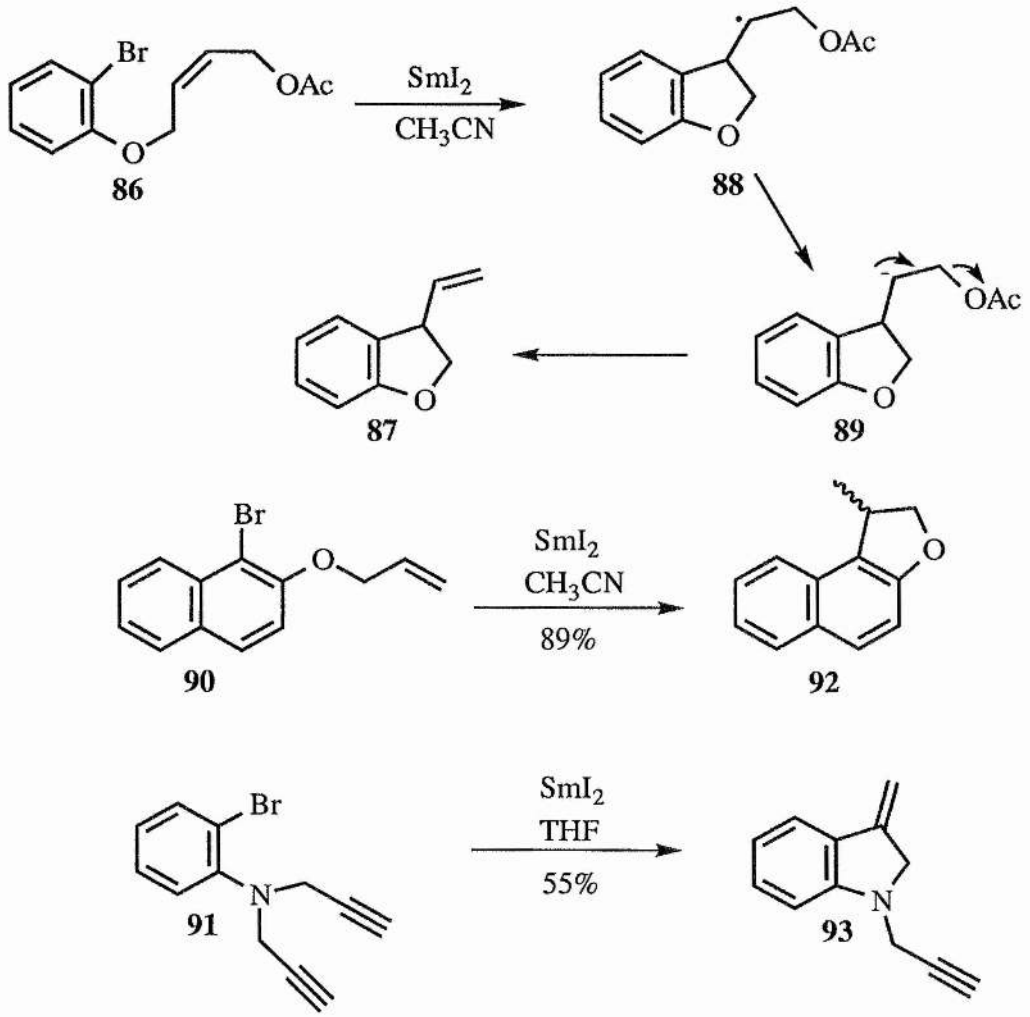


(i) H^+, 70%
(ii) $TBSO(CH_2)_3CHO$ **84**, 60%

Scheme 44

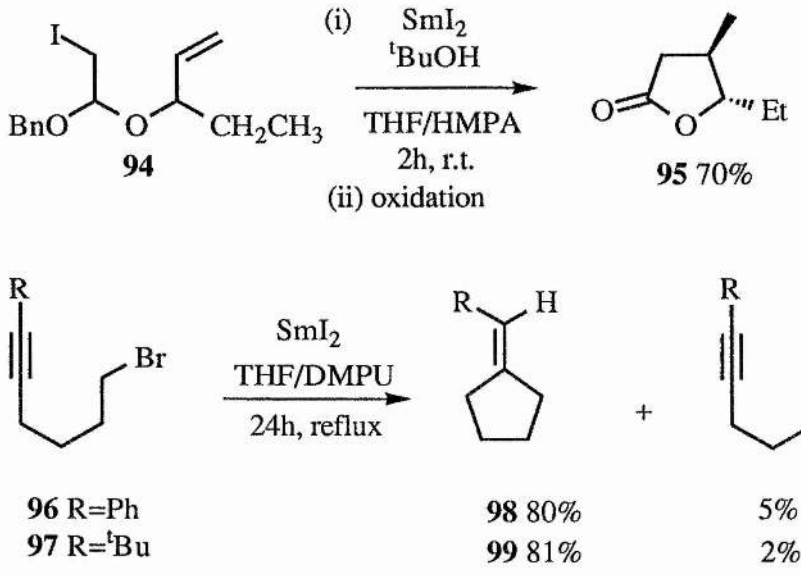
SmI_2 can also be used to generate aryl[104] and vinyl radicals.[105] For example, when bromide **86** was treated with the reducing agent, the substituted dihydrofuran **87** was isolated in 61% yield (Scheme 45). Cyclisation of the aryl radical yielded the secondary radical **88**. In the absence of a proton source, this radical accepted another electron from SmI_2, resulting in the formation of carbanion **89** which underwent β-elimination to furnish

87. Similar experiments on bromides **90** and **91** gave cyclic products **92** and **93** respectively.



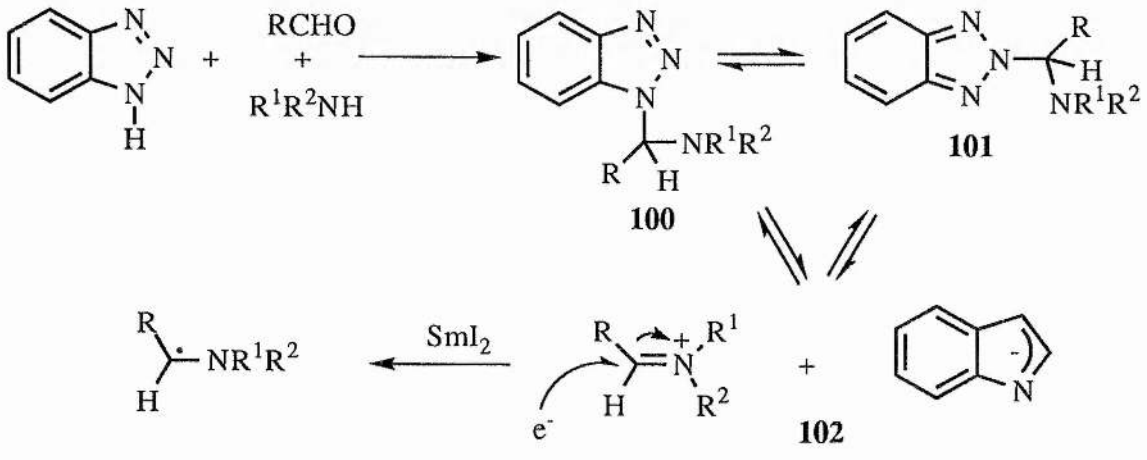
Scheme 45

Straightforward cyclisations of acyclic alkyl radicals onto alkenes[106] and alkynes[107] have also been reported. Iodide **94** was converted into lactone **95** by a two-step process involving treatment of the iodide with SmI_2 for 2h at room temperature, followed by Jones oxidation (Scheme 46).[106] Treatment of alkynyl bromides **96** and **97** with SmI_2 resulted in the formation of the corresponding cyclic products **98** and **99** respectively.[107] Small quantities of the direct reduction products were also observed and the yields were greatly improved by the addition of DMPU and to a lesser extent by refluxing.



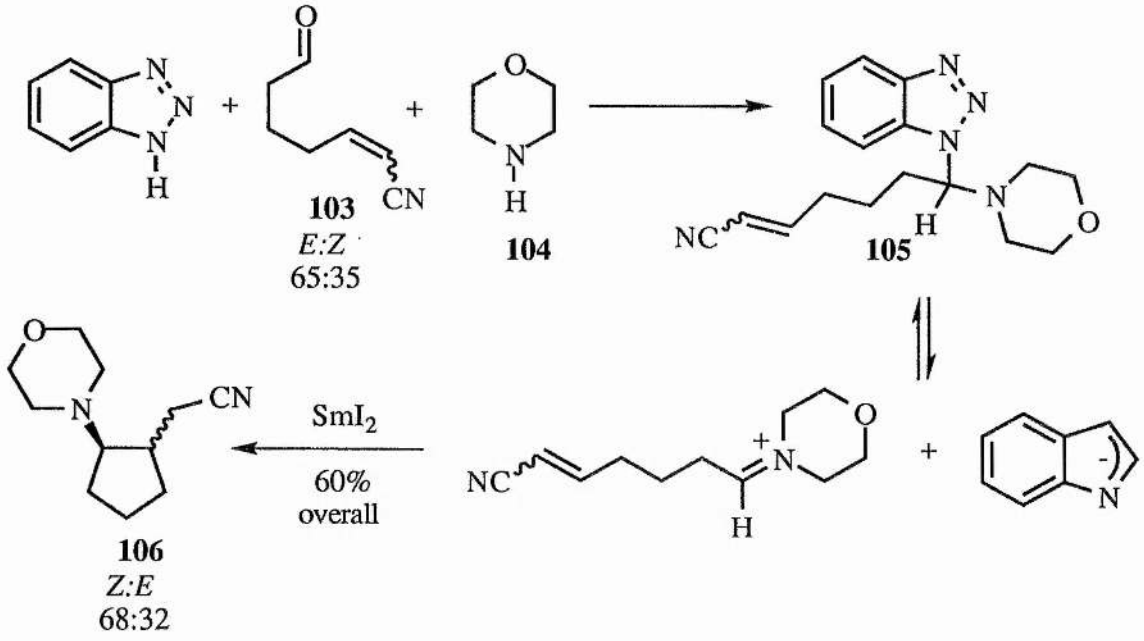
Scheme 46

N-(N',N'-dialkylaminoalkyl)benzotriazoles **100** behave as sources of α-amino radicals when treated with SmI_2.[108] Such precursors of α-amino radicals are easily prepared from an aldehyde, benzotriazole and a secondary amine by stirring overnight at room temperature, in the presence of 4Å molecular sieves (Scheme 47). The triazole product is in equilibrium with its regioisomer **101** and the iminium salt **102**. When treated with SmI_2 the iminium cation accepts an electron forming the α-amino radical, which may be incorporated into radical reactions when suitably functionalised.



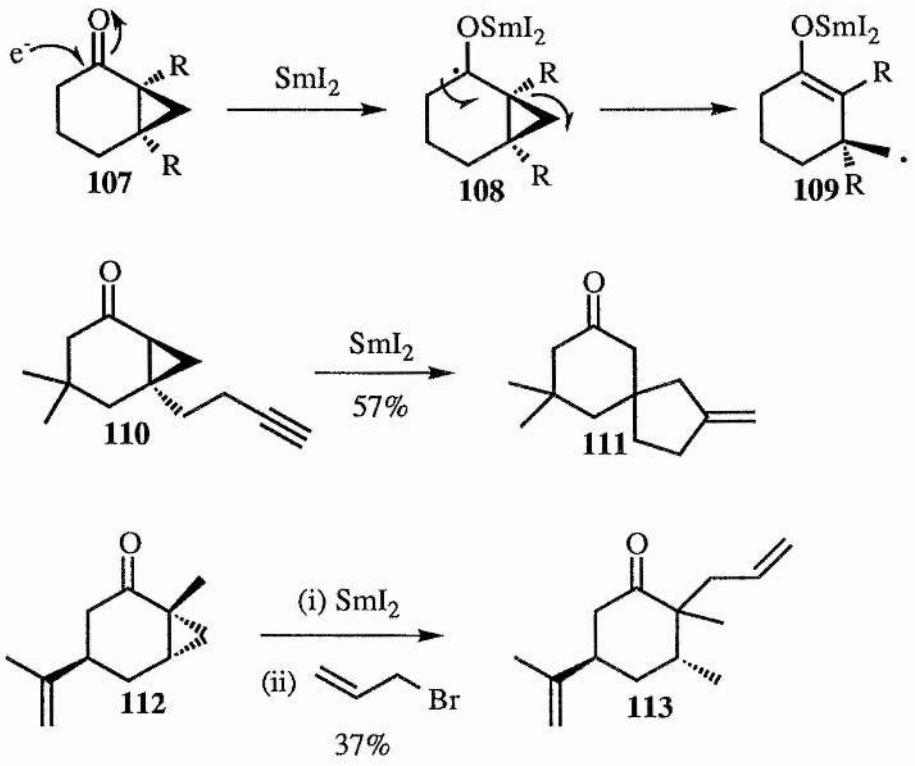
Scheme 47

An illustrative example of this methodology is given in Scheme 48. When aldehyde **103** was reacted with the secondary amine **104** and benzotriazole, the N-alkylated triazole **105** was not isolated, but was instead treated with SmI_2 resulting in the formation of the cyclic product **106** in 60% yield.[108] The cyclopentanes obtained in this manner predominantly exhibited a *trans* relationship between the vicinal substituted groups.



Scheme 48

The generation of alkyl radicals using SmI_2 is not restricted to alkyl halides. The reductive cleavage of cyclopropyl ketones can also lead to the formation of alkyl radicals as shown in Scheme 49.[109] When ketones of type **107** are treated with SmI_2, an electron transfer results in the formation of the organosamarium radical **108**, which undergoes ring opening to form the enolate-radical **109**. Thus, **109** has two potential sites for further elaboration; (i) the primary radical could undergo an intramolecular reaction with R, if appropriately functionalised (e.g **110** to **111**) and (ii) the samarium enolate could undergo a substitution reaction with a suitable electrophile (e.g. **112** to **113**). Examples illustrating both of these reaction types are given in Scheme 49.[109]

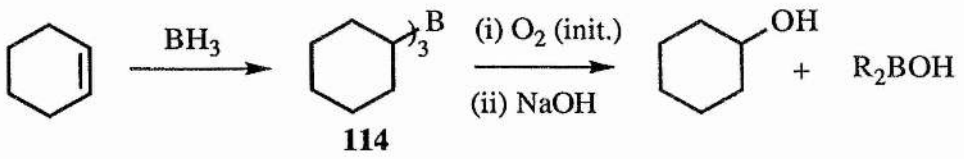


Scheme 49

The examples discussed in this section illustrate some of the uses of SmI_2 in synthesis. Although this section has not discussed the ketyl-alkene coupling reaction of SmI_2, a recent review covers such reactions in detail.[102] In some instances SmI_2 appears to be a viable alternative to tin hydride, especially when one takes into consideration the easier work-up procedure and the potential of the *in situ* formation of organosamarium intermediates. However, the studies so far have involved relatively simple molecules and it remains to be seen whether SmI_2 can be used with success in natural product synthesis.

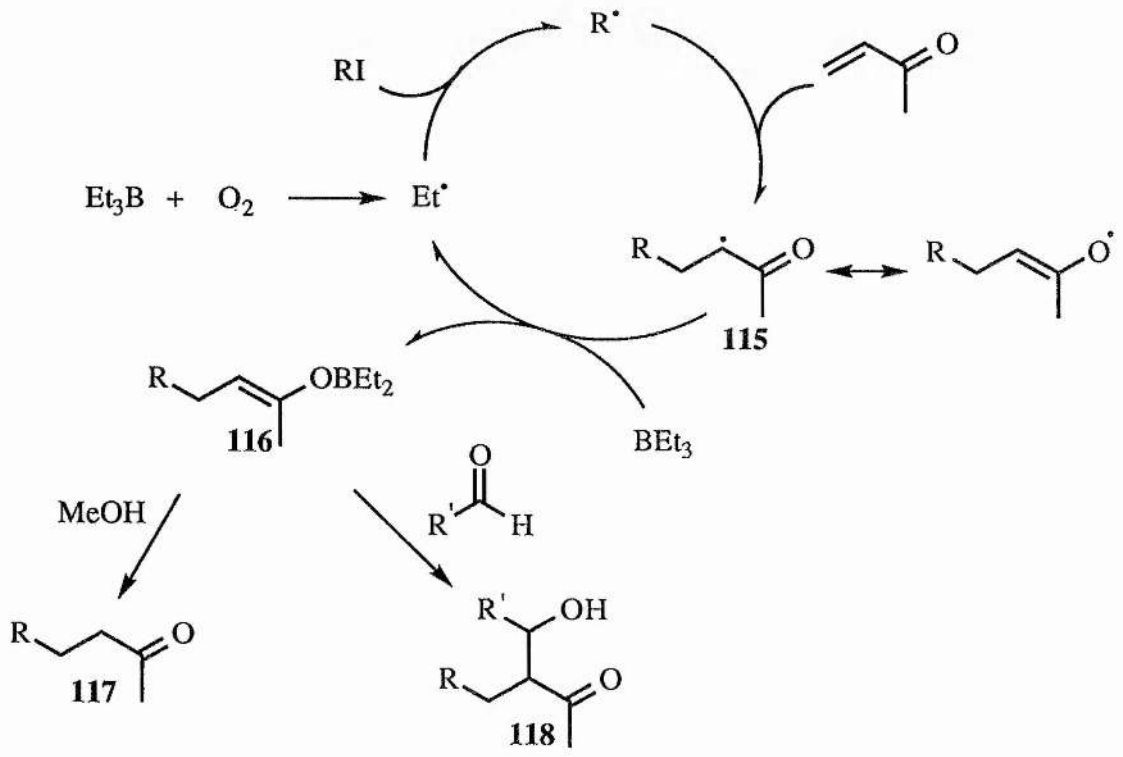
7. Boron radical chemistry.

It has been known for some time that trialkylboranes can generate alkyl radicals when exposed to enough oxygen to initiate a chain mechanism. Thus, hydroboration of cyclohexene yielded organoborane **114**, which when exposed to oxygen, followed by hydrolysis, gave cyclohexanol in quantitative yield (Scheme 50).[110]



Scheme 50

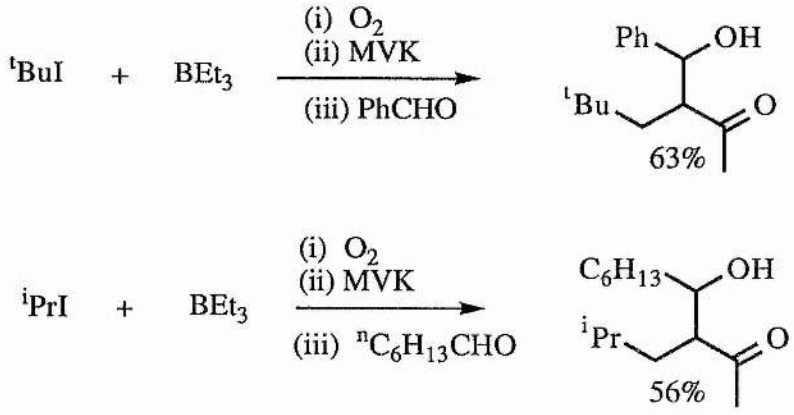
Furthermore, these alkyl boranes can undergo 1,4-addition reactions with conjugated enones to give alkylated aldehydes. Such methodology clearly has synthetic applications but is made less attractive, since only one of the alkyl groups from the organoborane can react. The problem however, can be avoided using triethylborane and an alkyl iodide; the ethyl radical formed on initiation, may abstract iodine from the alkyl iodide to form the lower energy alkyl radical.[111] An application of this is shown in Scheme 51.



Scheme 51

The resulting alkyl radical R•, adds to methyl vinyl ketone forming the resonance stabilised radical **115** which gives the boron enolate **116** by reaction with BEt_3. Enolate **116** can

react either with methanol, forming ketone **117** or react with an aldehyde, to give the aldol-type product **118**. Two examples of this latter reaction are given in Scheme 52.



MVK=methyl vinyl ketone

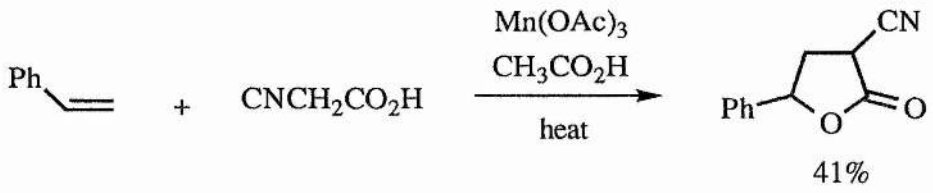
Scheme 52

Bacciochi has recently used this methodology to generate malonyl radicals which have been trapped by electron-rich aromatic compounds such as pyrroles.[112] Neckers has also shown that alkyl radicals generated from tetramethylammonium phenyltrialkylborides can add to activated alkenes in moderate yields by photoinduced one electron oxidation.[113]

8. Oxidative methods

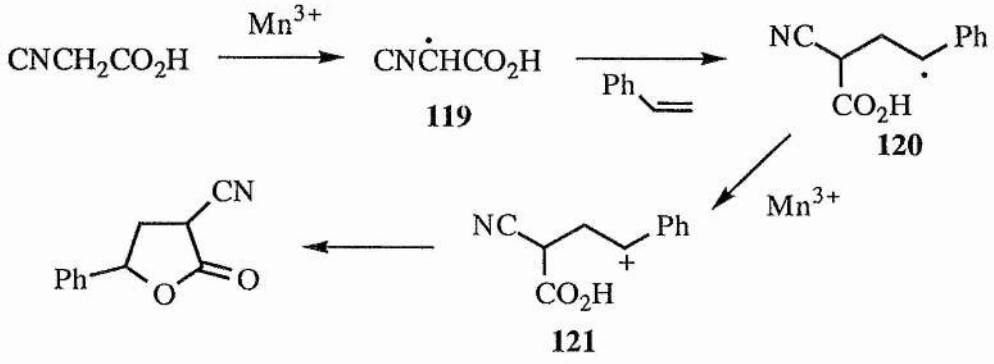
The formation of carbon-centred radicals by metal oxidants, particularly manganic acetate, $Mn(OAc)_3.2H_2O$, is another alternative to the methods discussed so far. However, this particular method is limited to the type of molecule which can act as a substrate for radical generation, and the majority of its applications are restricted to 1,3-dicarbonyl compounds. Nevertheless, the formation of carbon-centred radicals by metal oxidants has been used in natural product synthesis.

Heiba reported in 1974 the formation of lactones by the reaction between carboxylic acids having an α-hydrogen and alkenes, in the presence of metal carboxylates (Scheme 53).[114]



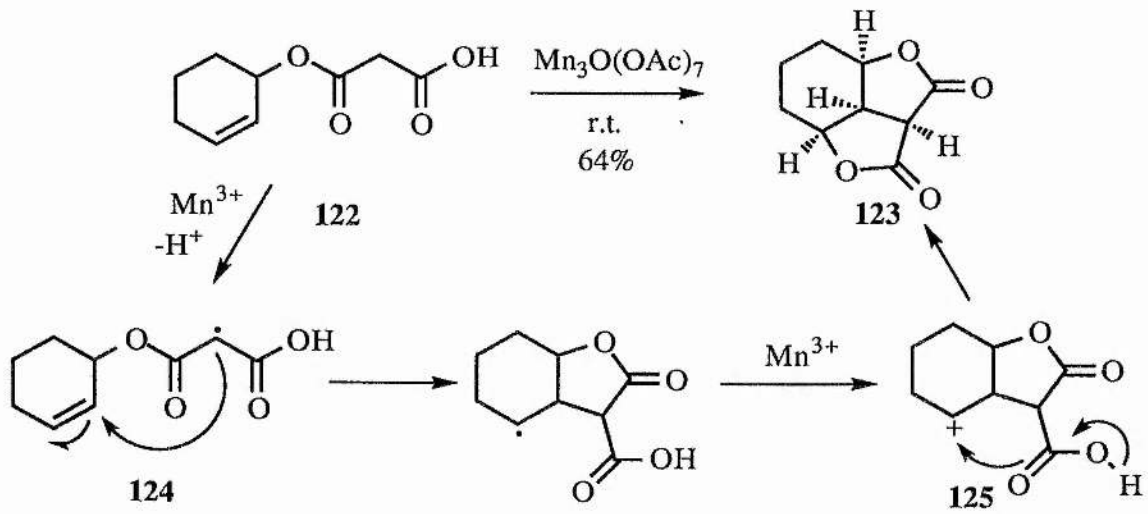
Scheme 53

The accepted mechanism for this reaction involves formation of the electrophilic radical **119** which attacks the electron-rich alkene, forming adduct radical **120** (Scheme 54). This radical is more prone to oxidation than **119**, and in the presence of Mn^{+3}, an electron transfer from the carbon-centred radical results in the formation of the corresponding cation **121**, which is attacked by the proximate carboxylic acid group. It is clear that this is not a chain reaction.



Scheme 54

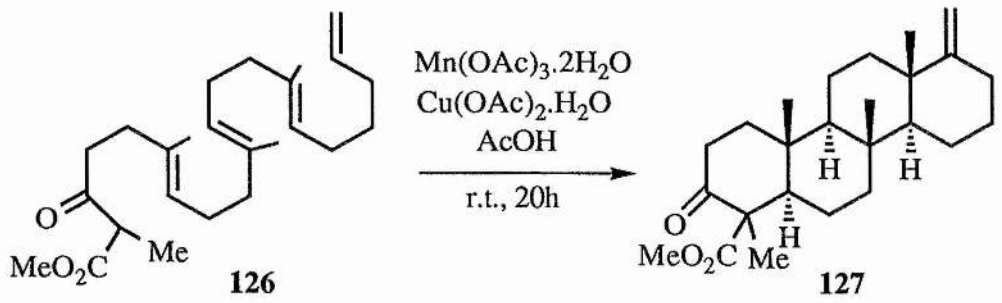
In studies towards the total synthesis of the natural product bilobalide, a member of the gingkolide family, Corey performed a series of experiments involving the lactonisation of unsaturated carboxylic acids using $Mn_3O(OAc)_7$ in the presence of acetic acid.[115] For example, under these conditions the half-malonate ester of 2-cyclohexen-1-ol, **122** yielded bis(δ-lactone) **123** in 64% isolated yield (Scheme 55).



Scheme 55

By analogy with the mechanism already provided, it seems reasonable to suggest that the half-malonate ester is initially oxidised to radical **124**, which undergoes intramolecular addition to the double bond (Scheme 55). This is followed by another oxidation, forming the desired lactone *via* cation **125**.

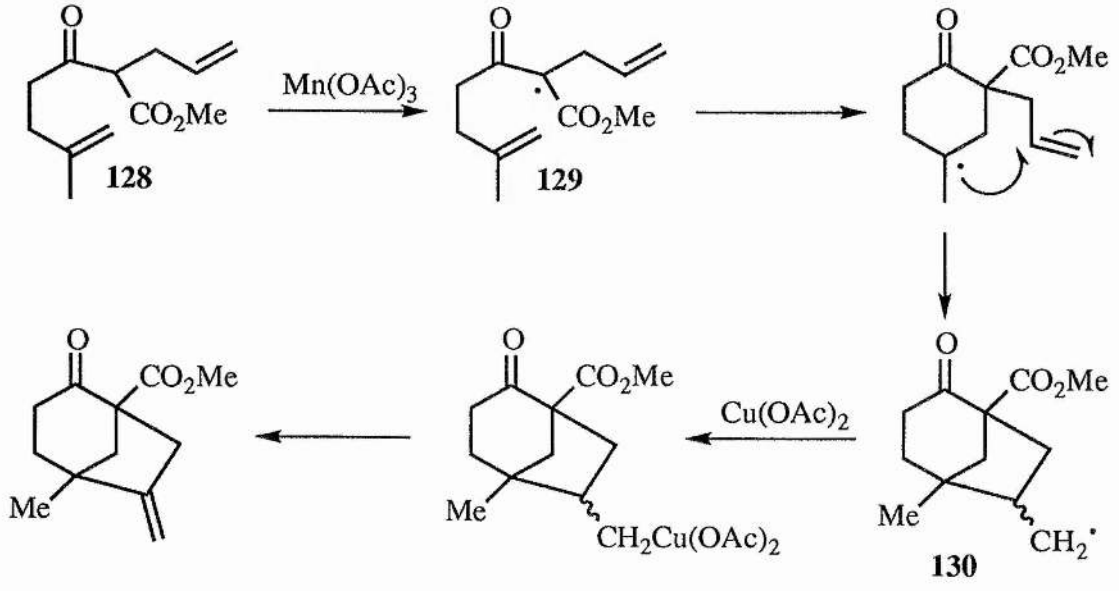
A series of tandem radical cyclisations similar to Pattenden's synthesis of compound **38** (Scheme 18) have been achieved by Zoretic using $Mn(OAc)_3$.[116] Thus, the β-keto ester **126** was converted into the tetracyclic system **127** in 31% yield (Scheme 56). As observed in Pattenden's synthesis, the tandem cyclisation process exhibited high stereoselectivity. The product was not obtained as a mixture of methyl epimers, (as in the Pattenden synthesis), since the final cyclisation to give a primary radical, was followed by β-hydride elimination to form an *exo*-positioned double bond. This was due to the presence of copper acetate, $Cu(OAc)_2$ in the reaction mixture, which has been shown by Heiba to result in oxidative termination. The advantage of terminating this tandem radical process with the formation of an alkene is obvious.



Scheme 56

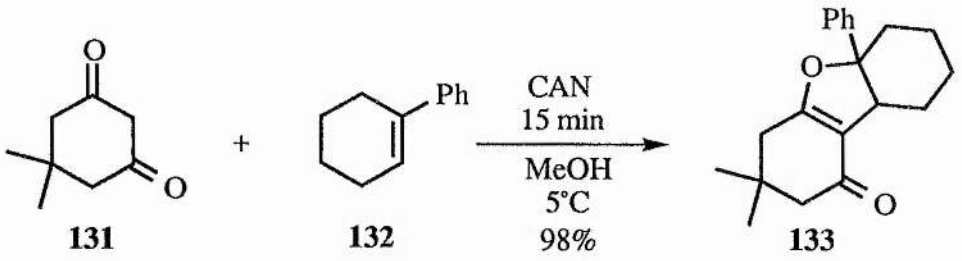
Snider has shown how β-keto ester **128** in the presence of $Mn(OAc)_3$ formed radical **129** which underwent selective 6-*endo* cyclisation, followed by 5-*exo* cyclisation to form primary radical **130** (Scheme 57).[117] This radical was oxidised by the co-oxidant $Cu(OAc)_2.H_2O$, resulting in β-hydride elimination to yield the unsaturated β-keto ester.

These examples serve to illustrate that such reactions can be performed in good yields to form complex natural products. Numerous references to other applications of this methodology are cited in Snider's paper.[117]



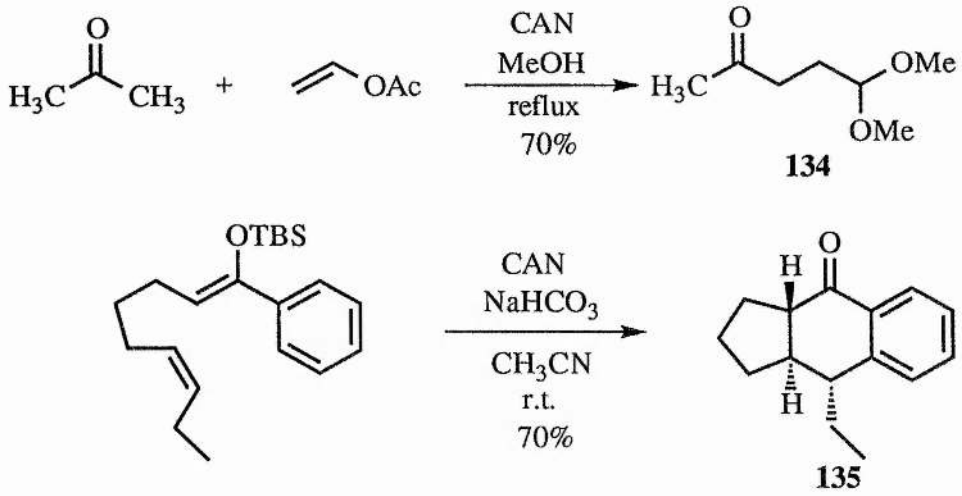
Scheme 57

In Heiba's original report, temperatures in the range 120-180°C were recommended.[114] However, the reactions illustrated in Schemes 55-57 were all performed at ambient temperature. Another metal oxidant, cerium(IV) ammonium nitrate (CAN), is also capable of generating electrophilic radicals suitable for use in organic synthesis. Furthermore, it can be used under milder reaction conditions than for manganic acetate. As an example, 1,3-dicarbonyl compound **131** can react with alkene **132** to give the tricyclic enone **133** in 98% yield, after only 15 min reaction at 5°C (Scheme 58).[118] This compared with a yield of only 41% when $Mn(OAc)_3$ was refluxed with the same starting materials in acetic acid.



Scheme 58

Two other examples illustrating the usefulness of CAN are given in Scheme 59. The formation of ketone **134** involved generation of the expected electrophilic radical, addition to the alkene, oxidation of the resulting adduct radical to the corresponding cation followed by trapping with the solvent.[118] In the second example, tricyclo-ketone **135** was formed by two radical cyclisations in tandem terminated by addition to the aromatic ring, giving a cyclohexadienyl radical which was oxidised to produce **135** in good yield.[118] The solubility of CAN in solvents such as methanol and acetonitrile, in addition to the mild reaction conditions, make this an attractive alternative reagent to manganic acetate.

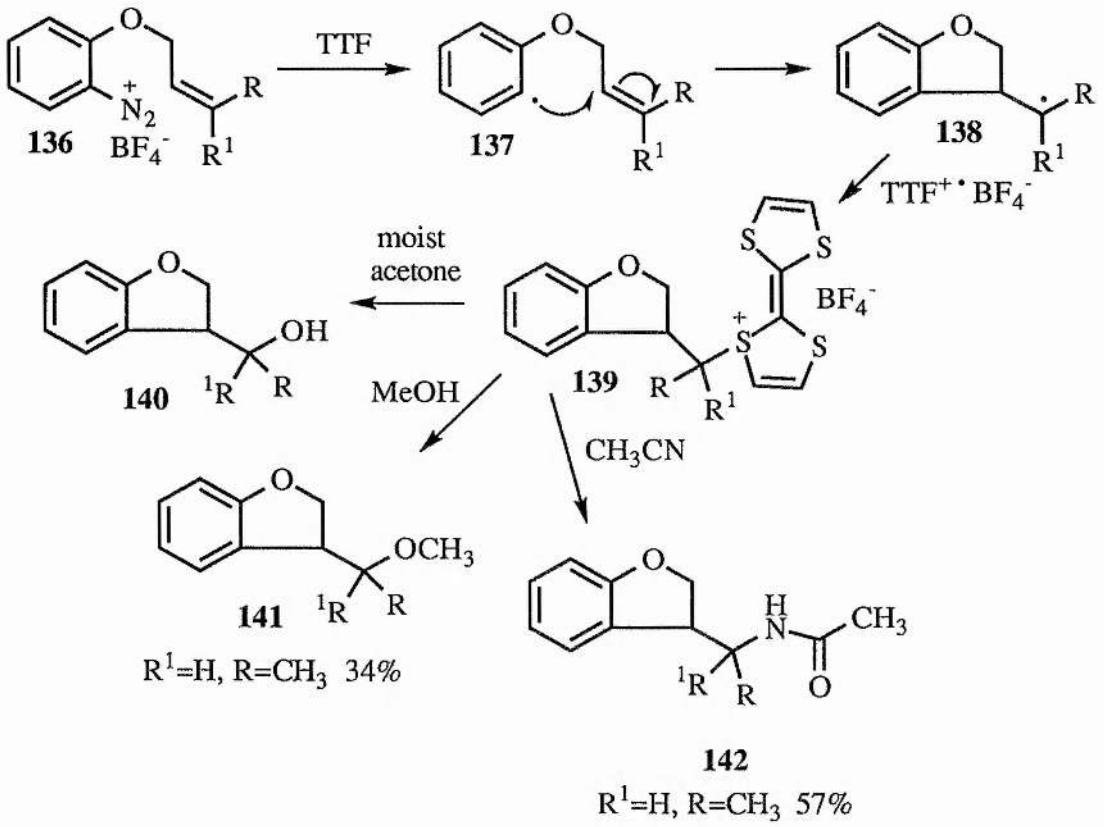


Scheme 59

9. Tetrathiafulvalene initiated radical reactions

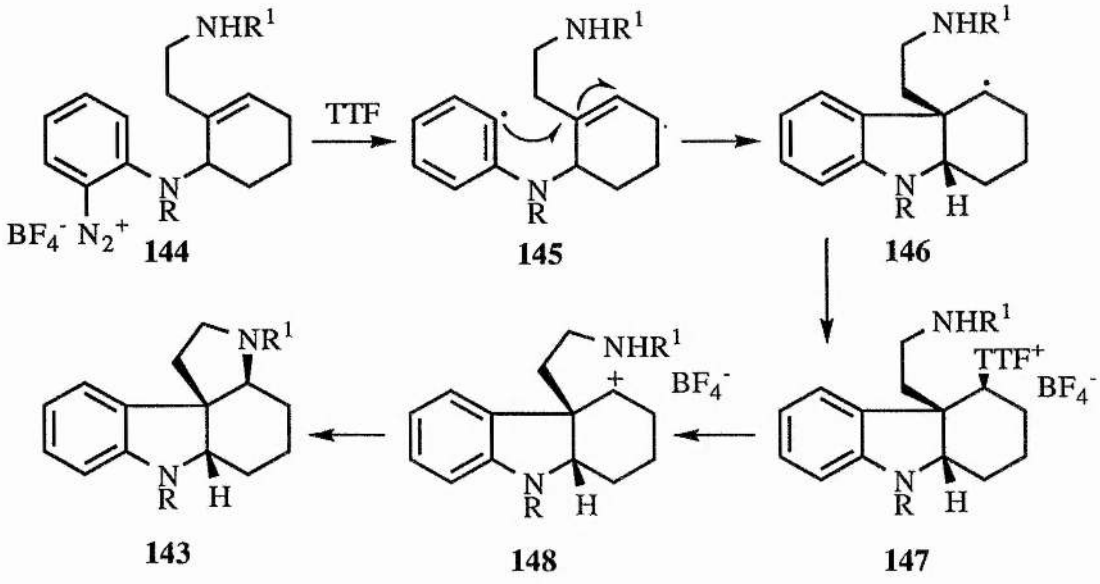
The uses of tetrathiafulvalene (TTF) in aryl radical reactions have recently been described by Murphy.[119-127] The precursor of the aryl radical is a diazonium salt which accepts an electron from TTF giving an aryl radical with loss of nitrogen. For example, treatment of diazonium salt **136** with TTF gave aryl radical **137**. Cyclisation of this radical yielded alkyl radical **138** and this was trapped by the TTF radical cation to give the crystalline compound **139** (Scheme 60).[119] In the presence of moist acetone the TTF salt **139** was converted into alcohol **140**, methyl ether **141** was formed when the solvent was methanol and, in acetonitrile, amide **142** was formed.

The attractive features of these reactions include the use of TTF in catalytic amounts and the ability to mediate radical cyclisations under mild conditions. Although tributyltin hydride can be used in catalytic amounts as described earlier, this involves the use of $NaBH_4$ or $NaCNBH_4$ which limits the scope of the reaction. Furthermore, the tin hydride method usually results in the destruction of two functional groups without creating any new ones, whereas the TTF-method provides the opportunity for the incorporation of new functionality.



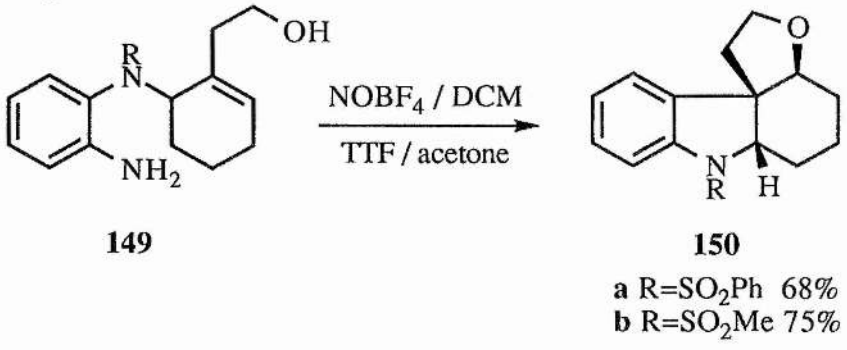
Scheme 60

The alkaloids aspidospermidine, strychnine and vinblastine all contain the tetracyclic substructure **143**, and it was proposed that such a fragment could be formed by a TTF-mediated sequence of reactions as shown in Scheme 61.[120,121] Thus, aryl radical **145**, generated by treating diazonium salt **144** with TTF, cyclises to give alkyl radical **146**. It was anticipated that this radical would be trapped by the TTF radical cation and then oxidised to give carbocation **148**, which is attacked by the proximate nitrogen lone pair to yield the tetracycle **143** with all *cis* stereochemistry. The stereoselective formation of the three contiguous centres would be expected, due to precedents concerning the *cis* preference of the initial radical cyclisation and the preference for the internal nucleophile to attack the less hindered face of carbocation **148**. In this respect it is also significant that the final step occurs *via* an S_N1 mechanism rather than S_N2, as the latter would result in the final cyclisation yielding the *cis-trans* product.

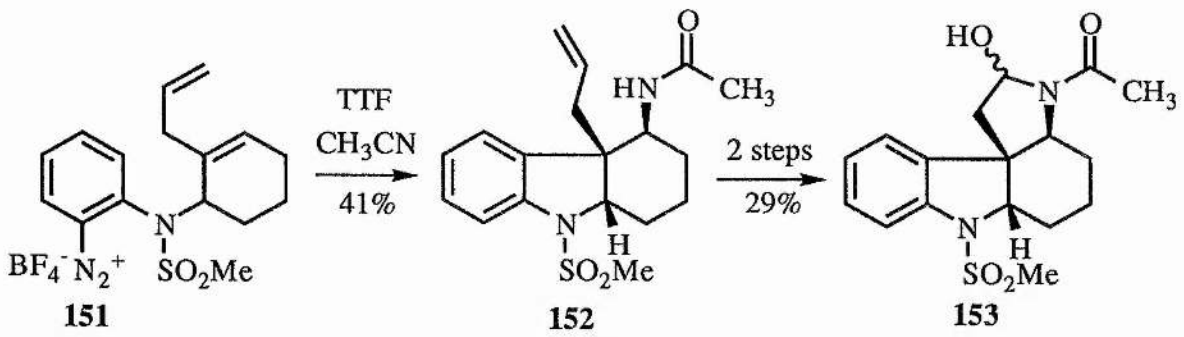


Scheme 61

This synthetic route was initially examined using the aniline derivative **149** (Scheme 62).[120] Diazotisation followed by treatment with TTF initiated the radical reaction and the all *cis* tetracycles **150a** and **150b** were formed in excellent overall yields. However, problems were encountered in applying this route towards the nitrogen analogue **143.** Instead, two alternative TTF-mediated routes were introduced and both yielded the key tetracyclic core present in the alkaloid natural products.[122] One of these routes is depicted in Scheme 63. In the presence of TTF, the diazonium salt **151** produced an aryl radical which cyclised to give a secondary alkyl radical trapped by the TTF radical cation. Amide **152** was then formed in 41% overall yield by displacement of TTF and nucleophilic attack of acetonitrile on the carbocation. This resulting tricycle was then converted into tetracycle **153** in two steps.

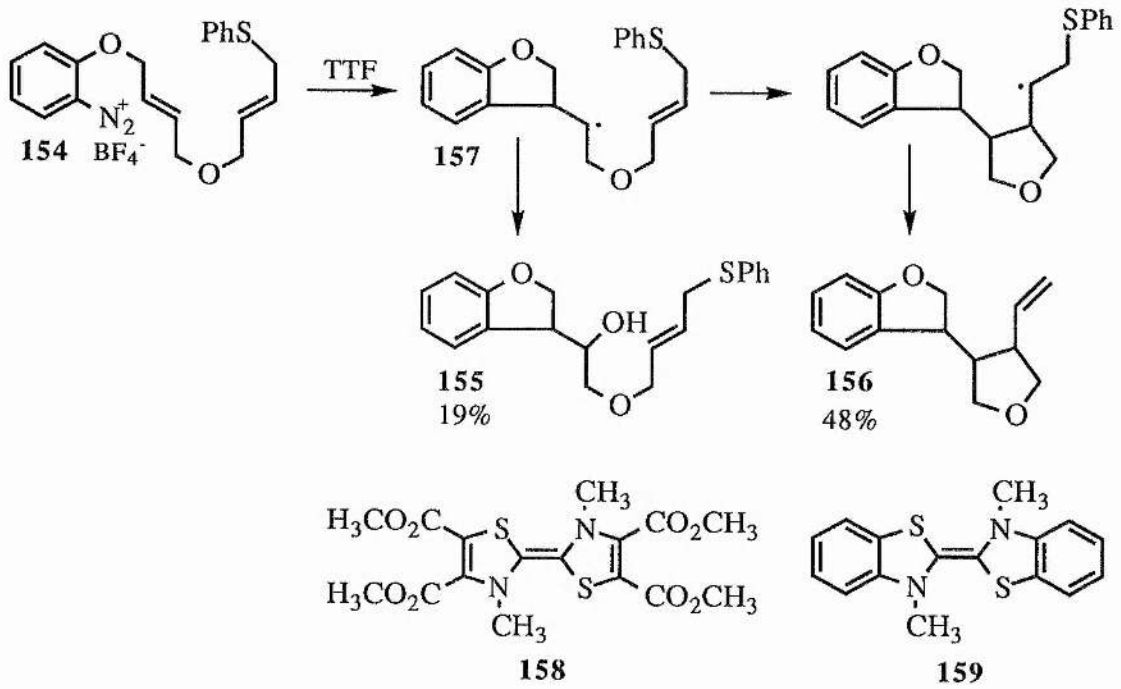


Scheme 62



Scheme 63

Two of the reasons for the success of TTF as a reagent to mediate aryl radical cyclisations lie in its ability to act as an effective electron donor and to trap the adduct radical with a sufficiently slow rate to allow the aryl radical to cyclise before being trapped itself. Recent studies have focused on understanding how these properties can be controlled by using alternative electron donors based on derivatives of TTF.[123,124] For example, when diazonium salt **154** was treated with TTF in acetone, alcohol **155** and alkene **156** were observed (Scheme 64).[123]



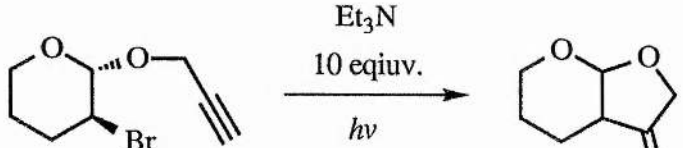
Scheme 64

The alkyl radical **157**, formed after cyclisation of the initially formed aryl radical, could either yield alcohol **155** or cyclise a second time to give alkene **156**. If on the other hand, diazadithiafulvalenes **158** and **159** were used instead of TTF, it was possible to obtain exclusively the alkene **156** in high yield. The reason for this selectivity was because of the slower rate of trapping of fulvalenes **158** and **159**, due to the greater steric crowding around the sulphur atoms of **158** and **159** compared to TTF.

Conclusively, these examples illustrate the use of tetrathiafulvalene and its derivatives for mediating aryl radical cyclisations which have the potential to find numerous applications in organic synthesis.

10. Miscellaneous

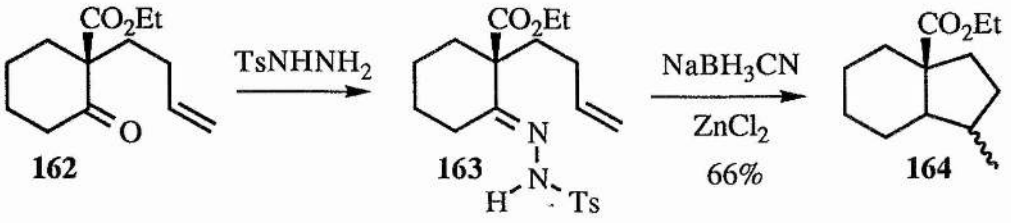
Cossy has reported that alkyl radicals can be generated from alkyl bromides and iodides by simply irradiating in the presence of an excess of triethylamine.[128] Thus, following this procedure for bromide **160** resulted in the formation of unsaturated bicycle **161** in almost quantitative yield (Scheme 65).



160 **161**

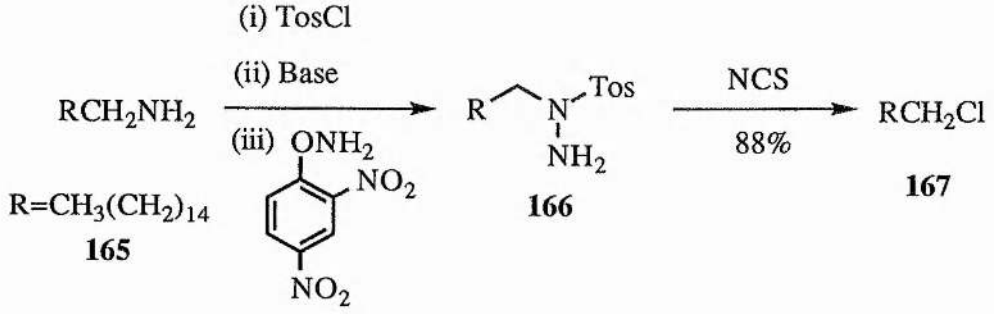
Scheme 65

When ketone **162** was treated with *p*-toluenesulphonyl hydrazine, to give hydrazone **163**, followed by reduction with $NaBH_3CN$ in the presence of $ZnCl_2$, ester **164** was obtained as a 3.5:1 mixtre of diasteroisomers, *via* a radical cyclisation (Scheme 66).[129] Thus, the ketone functional group in compound **162** could be regarded, in this reaction, as a synthetic equivalent to an alkyl radical.



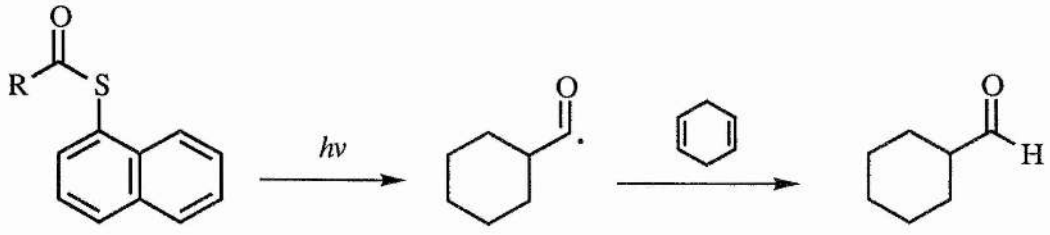
Scheme 66

Collazo has described a method for converting primary amines into the corresponding halides *via* a radical reaction.[130] For example, aliphatic amine **165** was converted into N-substituted-N-tosylhydrazine **166**, which yielded alkyl chloride **167** when dissolved in THF and stirred for 16h in the presence of N-chlorosuccinimide (Scheme 67). Bromides and alcohols could also be prepared by an analogous route.[130]



Scheme 67

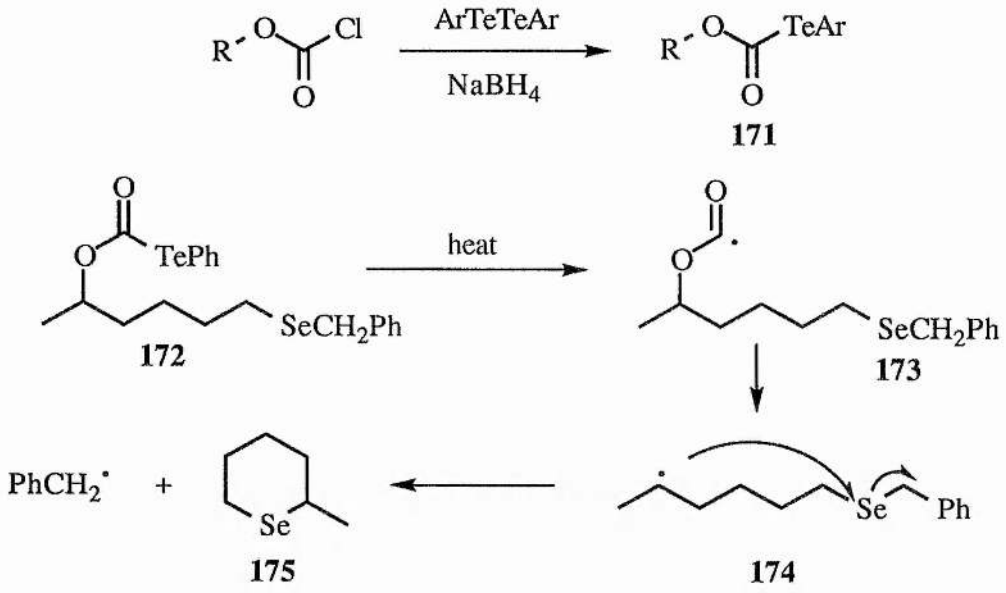
Penn has introduced 2-naphthyl thiolesters **168** as new sources of acyl radicals (Scheme 68).[131] Thus, when thioester **169** was dissolved in benzene and irradiated in the presence of the hydrogen donor cyclohexadiene, cyclohexylcarbaldehyde **170** was formed in essentially quantitiative yield. Crich has recently described acyl tellurides as acyl radical sources.[132]



169 R=$^{c}C_6H_{11}$

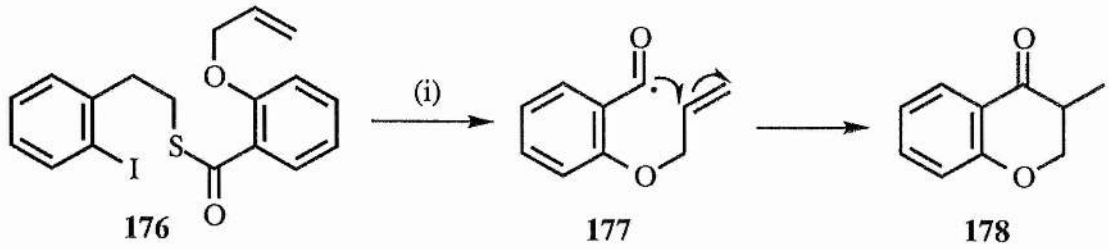
Scheme 68

(Aryltelluro)formates **171**, prepared from the corresponding chloroformates as shown in Scheme 69, generate alkyl radicals under thermal and photochemical conditions.[133] For example, when formate **172** was heated, alkoxycarbonyl radical **173** was formed and this decarboxylated to produce secondary radical **174**, which cyclised *via* a substitution reaction, yielding selenide **175** and the chain-carrying benzyl radical.



Scheme 69

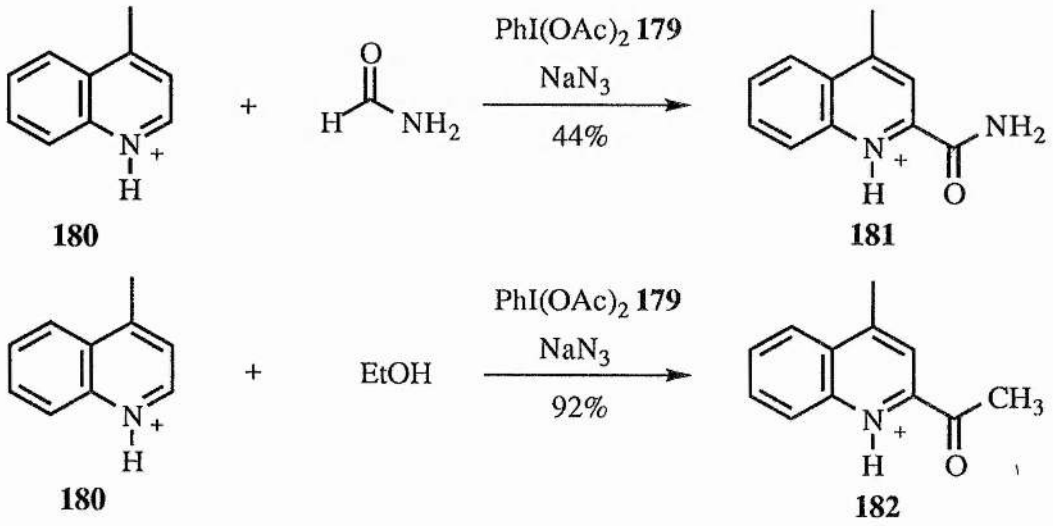
Crich has shown that thiolesters of type **176** can function as sources of acyl radicals *via* a fragmentation route (Scheme 70).[134] Thus, when thiolester **176** was treated with tris(trimethylsilyl)silane, the resulting aryl radical attacked the proximate sulphur atom and released acyl radical **177** which cyclised to give ketone **178**. Dihydrobenzothiophene was a byproduct in this reaction. Variants of this reaction were also reported.[134]



(i) $(Me_3Si)_3SiH$

Scheme 70

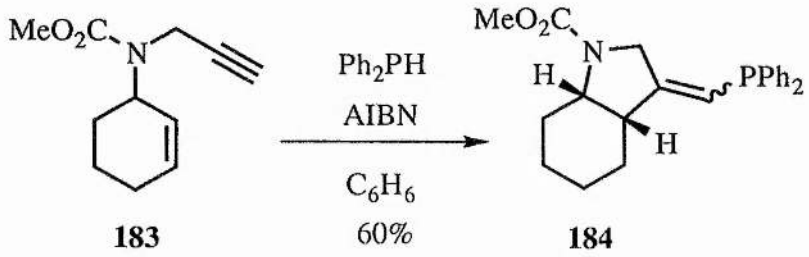
Minisci and Fontana have described a procedure for generating carbon-centred radicals from alcohols, ethers, aldehydes, amides and alkyl iodides (Scheme 71).[135] For example, using the protonated heteroaromatic **180** as a radical trap, it was possible to form aromatic amide **181** in 44% yield and aromatic ketone **182** in 92% yield. The latter product resulted from the oxidation of the initial alcohol adduct which could be compared to a Dess-Martin oxidation step.[136] This methodology is however limited from a synthetic point of view, since with the exception of alkyl iodides, the radical source is also the reaction solvent. Togo has recently reported, a method for the decarboxylative alkylation of heteroaromatic bases using trivalent iodine compounds.[137]



Scheme 71

Minisci has also reported that alkyl radicals can be generated by the silver-catalysed decarboxylation of oxalic acid monoesters using sodium thiosulphate.[138] As above, the radical trap was a protonated heteroaromatic and the yields of the resulting adducts usually exceeded 90%. In these reactions, the radical generated was tertiary, but for monoesters derived from secondary and particularly primary alcohols, the initial radical formed was an alkoxycarbonyl radical and this added to the radical trap before decarboxylation. Minisci described this as the simplest and cheapest method for the direct introduction of a carboxylic group in the heterocyclic ring.[138]

Simpkins has demonstrated how phosphorus can be incorporated into organic molecules using diphenyl phosphine and AIBN.[139] For example, unsaturated ester **183** was converted into bicycle **184** in 66% yield when refluxed in benzene in the presence of Ph_2PH and AIBN (Scheme 72). Due to stabilisation of the resulting phosphorus-centred radical, the P-H bond in Ph_2PH is weak enough to sustain a radical chain process. In fact, this reaction often suffers from the competitive formation of direct-reduction products.

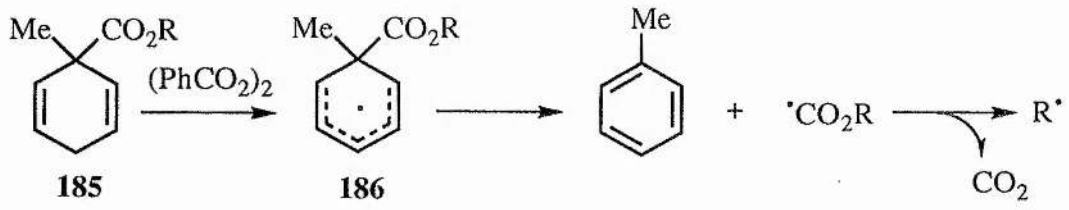


183 **184**

Scheme 72

11. Aims and Objectives of the research

It has been established that 1-methylcyclohexa-2,5-diene-1-carboxylate esters **185** can generate alkyl radicals which are able to participate in chain reactions.[140,141] These esters contain two *bis*-allylic hydrogen atoms which can be readily abstracted with an appropriate initiator, such as dibenzoyl peroxide, to produce the delocalised radical **186** (Scheme 73). This radical can then aromatise due to the favourable thermodynamic driving force, resulting in the formation of the alkoxycarbonyl radical $^{\bullet}CO_2R$, which decarboxylates to generate the alkyl radical $R^{\bullet}$. The byproduct of this reaction is toluene which is easily removed.

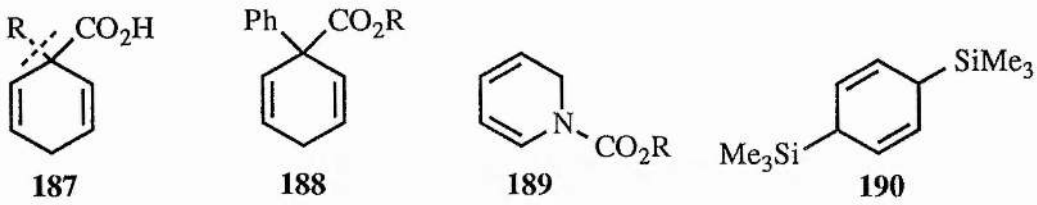


185 **186**

Scheme 73

The purpose of my research was to investigate alternative reagents for generating radicals based on the same principles illustrated in Scheme 73. This thesis describes our efforts to

develop four different reagents (**187-190**, Scheme 74) each of which is discussed separately in the following chapters.



187 **188** **189** **190**

Scheme 74

The bulk of the research has concentrated on 1-alkylcyclohexa-2,5-diene-1-carboxylic acids **187** (Chapter 2). In contrast to the esters **185** the alkyl radical would be generated by dissociation of the indicated carbon-carbon bond rather than decarboxylation (Scheme 74). The byproduct of this reaction would be benzoic acid which could easily be removed by an alkaline wash. 1-Phenylcyclohexa-2,5-diene-1-carboxylate esters **188** were expected to function more efficiently than the related esters **185** as sources of radicals and chapter 3 discusses the progress made in this area. Unfortunately, due to time limitations, it was not possible to complete full investigations on these compounds, but it is anticipated that research in this area will be continued. We also investigated *N*-carboalkoxy-1,2-dihydropyridines **189** (Chapter 4) as we were hopeful that such compounds would generate alkoxycarbonyl radicals capable of undergoing decarboxylation to give the corresponding alkyl radical R$^{\bullet}$. In this case the byproduct would be pyridine which could easily be removed by washing with acid. Finally, we have attempted to synthesise a variety of silyl compounds such as **190**. It was expected that such compounds could be used as sources of silyl radicals, which could react with alkyl halides to generate the corresponding alkyl radical. Hence, we were aiming to establish alternative reagents to the silicon hydrides, such as tris(trimethylsilyl)silane, which would be easier to prepare. Each chapter is composed of three sections, namely introduction, results and discussion and experimental. For convenience the numbers assigned to compounds and schemes begin from one in each chapter and hence, it is possible that a particular compound discussed in two chapters will have two different numbers.

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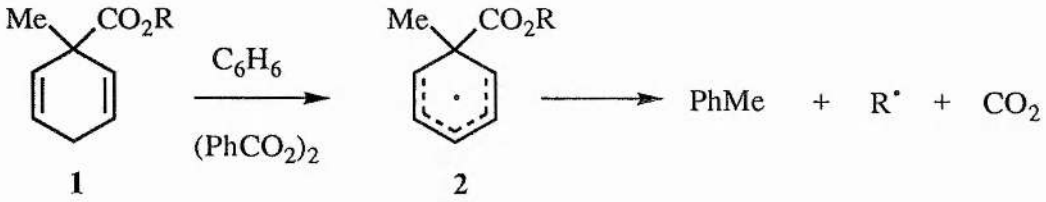
Chapter 2

1-Alkylcyclohexa-2,5-diene-1-carboxylic acids as reagents for generating radicals

1

Introduction

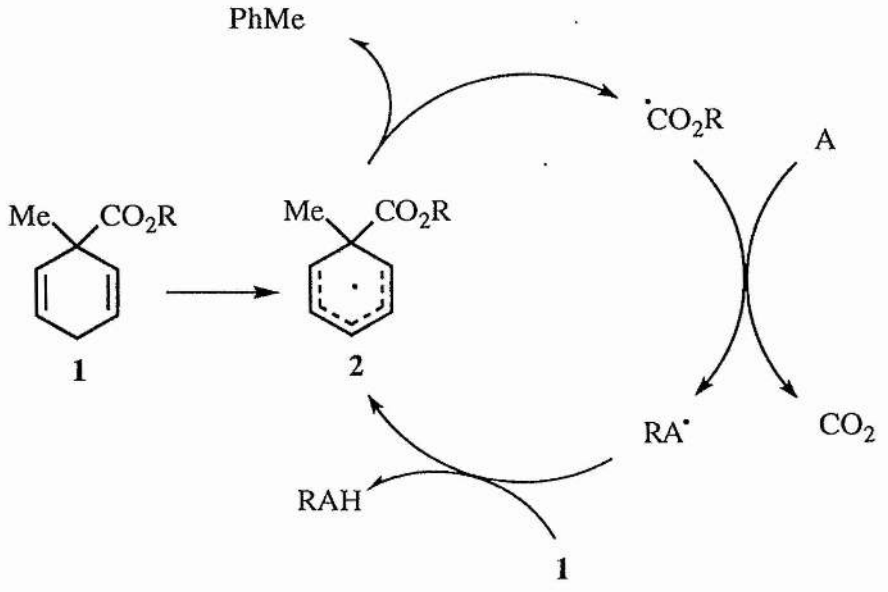
1-Methylcyclohexa-2,5-diene-1-carboxylates **1** have been shown to undergo radical induced fragmentation to give the alkyl radical R• and toluene, in the presence of the radical initiator dibenzoyl peroxide (Scheme 1).[1] One of the main reasons for believing that such compounds could generate radicals was the knowledge that the byproduct would be aromatic and hence that this would be a driving force for the formation of the radical.



1 **2**

Scheme 1

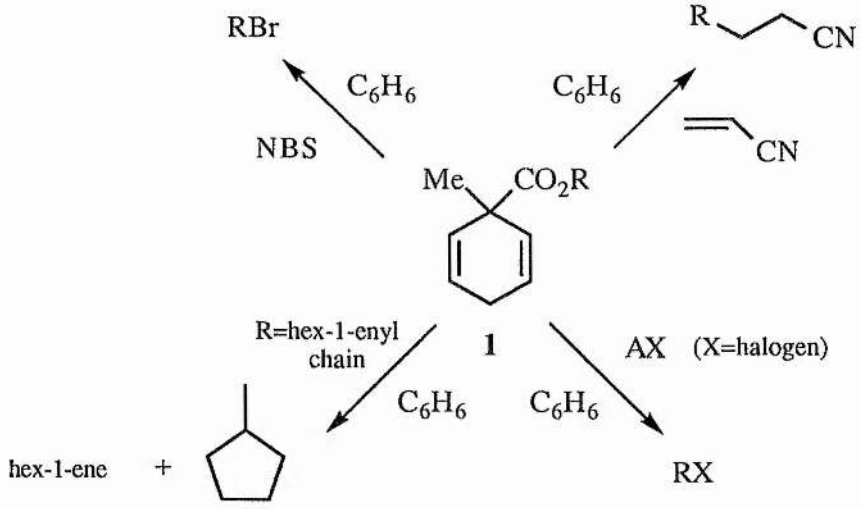
When treated with a hydrogen atom abstractor, such as dibenzoyl peroxide, it was found that allylic hydrogen atom abstraction took place to give the delocalised radical **2**, which could be observed by EPR spectroscopy. This was followed by aromatisation to give toluene and alkoxycarbonyl radical •CO_2R (Scheme 2) which underwent decarboxylation, thus generating the alkyl radical R•, (though for a variety of esters **1**, the alkyl R• was never observed by EPR spectroscopy). This alkyl radical then reacted to give RA• which abstracted hydrogen from **1** to give the product RAH and delocalised radical **2**, hence continuing the chain process. Radical R• gave bromides, RBr, in the presence of NBS, addition products when an appropriate alkene, such as acrylonitrile was added, cyclised products when the alkyl radical contained a double bond in close proximity to the radical centre and other products when suitable halogen donors were added (Scheme 3).



Scheme 2

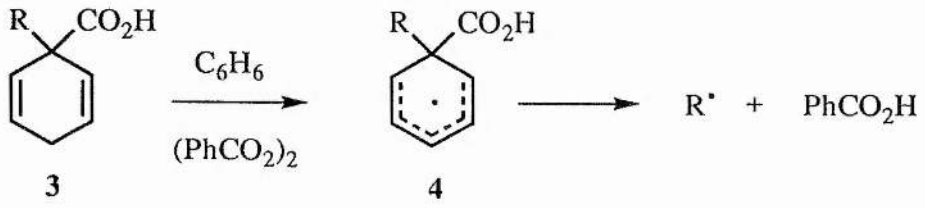
Using the known rate constant for cyclisation of the primary hex-5-enyl radical[2] the rate constant for hydrogen atom abstraction from **1** by a primary alkyl radical was determined by measuring the ratio of the directly-reduced product (hex-5-ene) and the cyclised product (methyl cyclopentane) when R in **1** was a hex-5-enyl unit. This radical clock method gave a rate constant of 0.82 x 10^5 $dm^3mol^{-1}s^{-1}$ at 140°C, which is approximately 150 times less than the rate constant for hydrogen atom abstraction from tributyltin hydride by a primary alkyl radical at the same temperature.[3] The yields of the products from these reactions were not particularly high and one of the reasons for this was due to the competitive loss of a methyl radical from the delocalised radical **2**, giving the corresponding benzoate esters in yields comparable to the desired products. On this basis we considered that the 1-alkylcyclohexa-2,5-diene-1-carboxylic acids **3** might function more efficiently as precursors for radical formation. Thus, treatment of carboxylic acids **3** with dibenzoyl peroxide generated delocalised radical **4** (Scheme 4) which could be observed by EPR spectroscopy, (the end of this chapter contains a section which discusses the results obtained from these EPR experiments). When the temperature of the EPR cavity was increased, the spectrum of **4** was replaced with a new spectrum consistent with the pattern expected for the alkyl radical R•. Furthermore, when the sample was cooled the original

spectrum re-appeared. We therefore had evidence that the carboxylic acid **3** could undergo hydrogen atom abstraction with an appropriate initiator and that these intermediate delocalised radicals could fragment to give the desired alkyl radical R. Hence, acids **3** could potentially mediate chain reactions by a route analogous to that of Scheme 2. An advantage of compounds **3** in synthetic applications would be that the aromatic byproduct, benzoic acid, could be easily removed from the desired product by an alkaline extraction.



Scheme 3

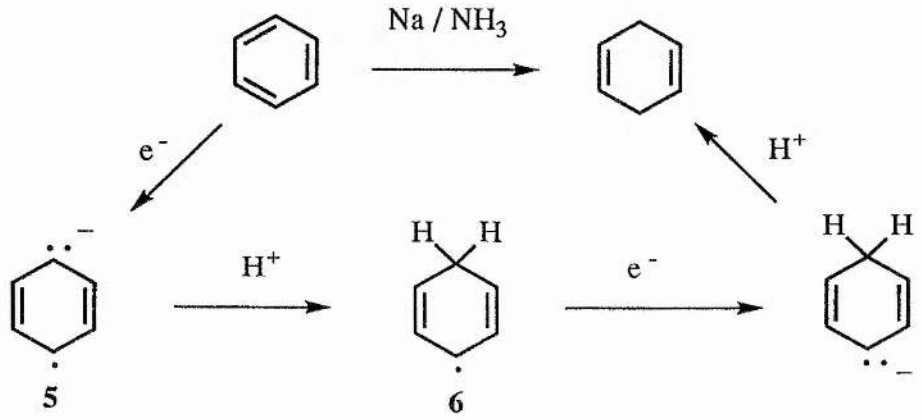
We were hopeful that the released alkyl radical would be able to add to the double bond of an alkene via an inter- or intramoleular reaction. A variety of carboxylic acids were prepared to investigate this and section 2 discusses the synthesis and radical reactions of such compounds. The carboxylic acids **3** were prepared by the Birch reduction-alkylation of benzoic acid and since this is an important reaction in the formation of these radical precursors it is necessary to briefly consider some aspects of this important reaction.



Scheme 4

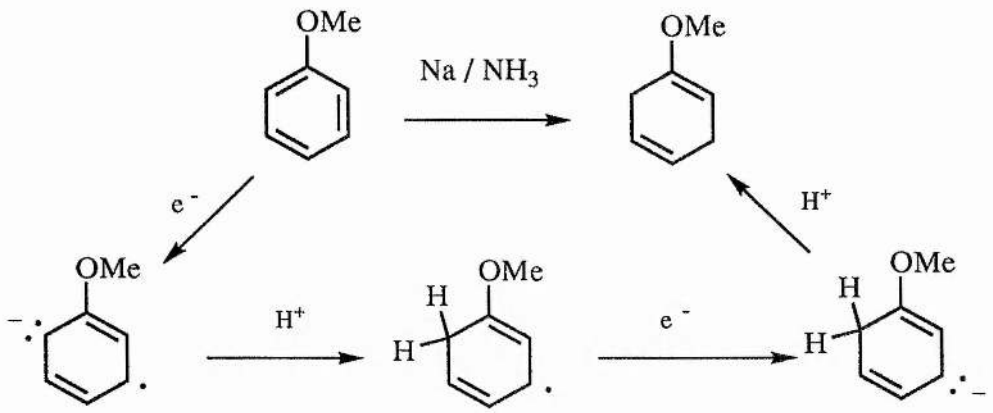
Birch Reductions

Aromatic compounds can be reduced to the corresponding non-conjugated cyclohexadienes by metal-ammonia reductions commonly referred to as Birch reductions,[4] named after the pioneering work of A. J. Birch in the 1940's and 50's. Thus, benzene can be reduced using Na and NH_3 to give cyclohexa-1,4-diene (Scheme 5). The mechanism of the reduction involves the transfer of an electron from the metal to the ammonia solution, forming a solution of solvated electrons. An electron is then able to add to the aromatic ring forming the radical anion **5** which abstracts a proton (usually from a proton source such as EtOH) to give radical **6**. The latter can accept another electron followed by a proton to give the product.



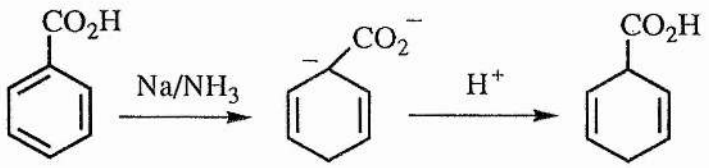
Scheme 5

When the aromatic ring is substituted a number of regioisomeric cyclohexadienes can in principle be formed, but one product usually predominates. It is well known that if the aromatic ring is monosubstituted with an electron-releasing substituent, the cyclohexadiene formed has the substituent bonded to an olefinic carbon. Thus, the Birch reduction of methoxybenzene results in the formation of 1-methoxycyclohexa-1,4-diene *via* the route given in scheme 6. It is also worth noting that the rate of reduction of methoxybenzene relative to benzene is lower since the aromatic ring has a higher electron density.



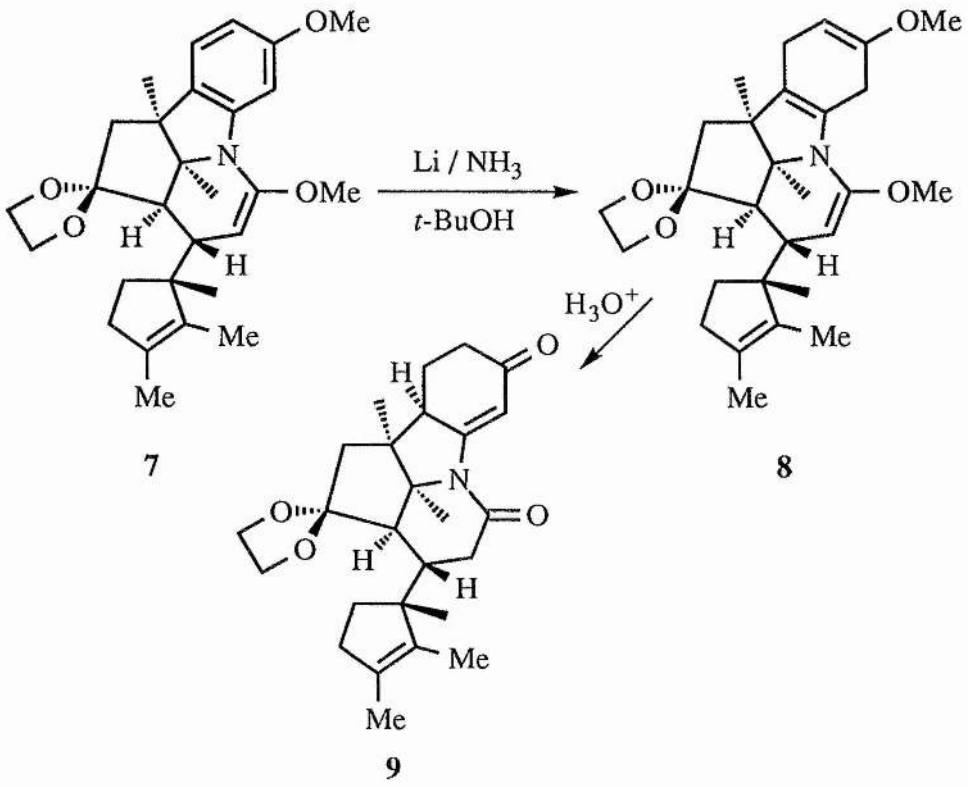
Scheme 6

For electron-withdrawing substituents the reduction occurs at an enhanced rate relative to benzene and the cyclohexadiene formed has the substituent bonded to a saturated carbon, and hence treatment of benzoic acid with Na and NH_3 gives cyclohexa-2,5-diene-1-carboxylic acid, (also called 1,4-dihydrobenzoic acid) (Scheme 7).



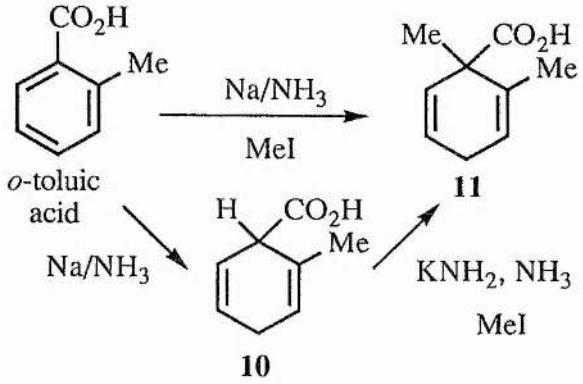
Scheme 7

An example of the importance of the Birch reduction in synthesis is illustrated in Scheme 8. In 1973 the collaborating groups of Woodward (Harvard) and Eschenmoser (Zurich) had succeeded in one of the greatest achievements of synthetic organic chemistry - the total synthesis of vitamin B_{12}.[5] One step involved the lithium-ammonia reduction of the aromatic ring in intermediate **7** to give the intermediate cyclohexadiene **8**, which was hydrolysed to the corresponding enone, pentacycenone **9**.



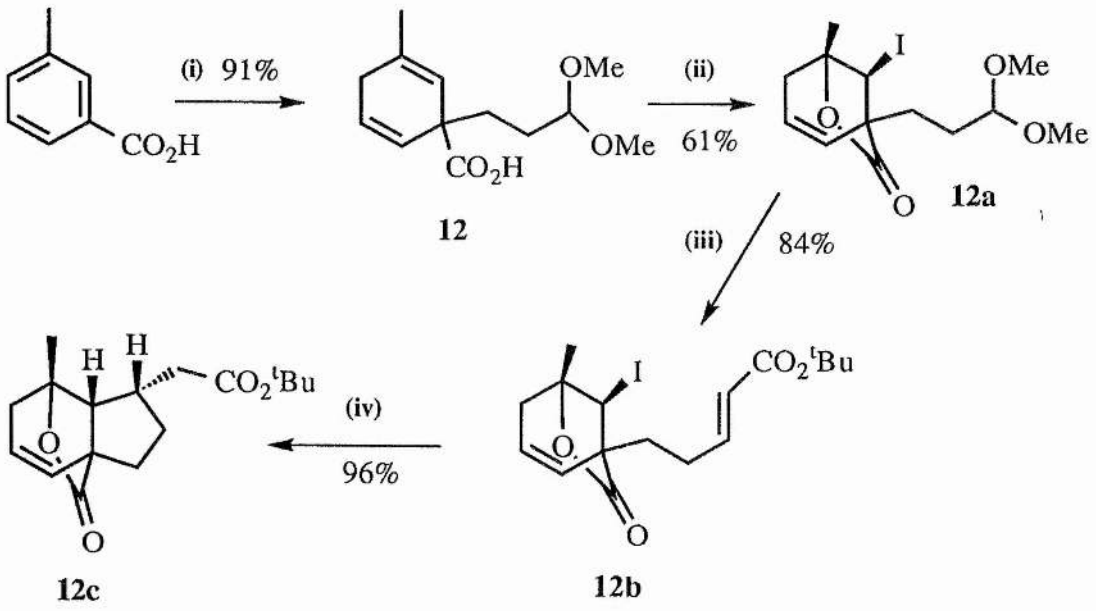
Scheme 8

In some of his earlier work, Birch found that *o*-toluic acid could be converted into the corresponding cyclohexadiene **10** (Scheme 9). When this was treated with potassium amide in NH_3 and quenched with methyl iodide, 1,2-dimethylcyclohexa-2,5-diene-1-carboxylic acid **11** was formed.[6] This reaction can in fact be accomplished in one step by treating *o*-toluic acid with Na in NH_3 followed by quenching with methyl iodide. This is referred to as a Birch reduction-alkylation reaction.



Scheme 9

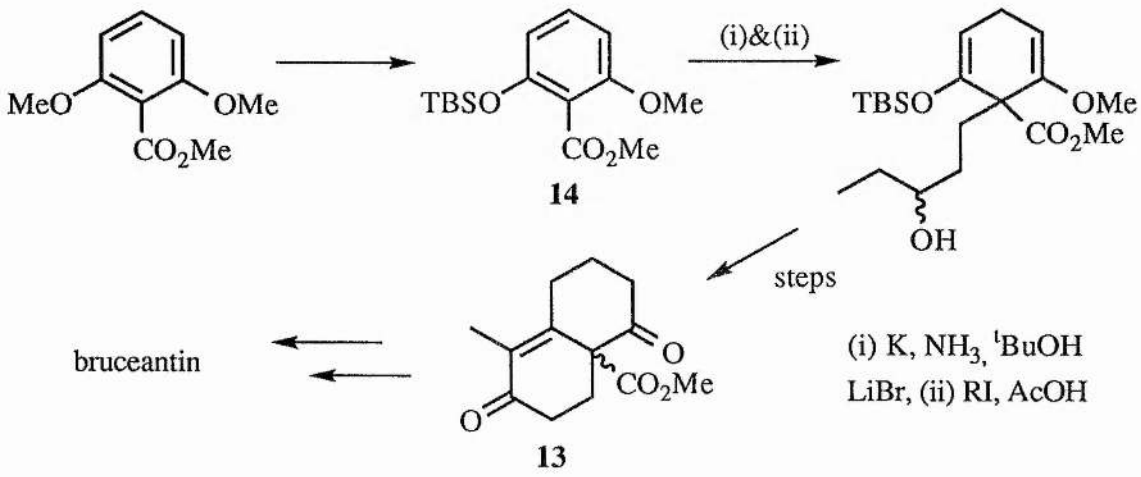
Birch reduction-alkylation reactions of benzoic acid and benzoate ester derivatives have also been applied in synthesis. An example given in scheme 10 illustrates Hart's synthesis of perhydroindane **12c**.[7] Since the short reaction sequence involves a Birch reduction-alkylation and a radical reaction, each of the 5 steps will be discussed briefly. The synthesis commenced with the Birch reduction-alkylation of *m*-toluic acid to give the 1-alkylcyclohexa-2,5-diene-1-carboxylic acid **12**. This was followed by iodolactonisation to give compound **12a**. It is noteworthy that iodine selectively attacks the more substituted double bond. Hydrolysis of the acetal functionality to the aldehyde, followed by olefination furnished iodo-alkene **12b**. Treatment of this with tributyltin hydride generated a secondary alkyl radical which was in close proximity to an electron-deficient double bond, hence allowing the efficient ring closure to give the desired product in excellent yield with good stereoselectivity.



Reagents: (i) Li / NH_3 , $Br(CH_2)_2CH(OMc)_2$; (ii) I_2 / $NaHCO_3$ / H_2O / Et_2O;
(iii) H_3O^+, $Ph_3P{=}CHCO_2{}^tBu$; (iv) Bu_3SnH, AIBN, PhH

Scheme 10

Other examples of Birch reduction-alkylation reactions of aromatic compounds can be found in some of the work by Mander and co-workers.[8] In synthetic studies towards the complex natural product bruceantin, bicyclic diketone **13** was considered to be a suitable precursor. Some of the steps in the synthesis of diketone **13** are outlined in scheme 11 and the reaction of interest here is the Birch reduction-alkylation of methyl benzoate derivative **14** with potassium, ammonia, *t*-butanol, LiBr and the alkyl iodide. The Birch reduction-alkylation reactions were also applied in Mander's synthesis of the complex natural product gibberellic acid.[9] Other examples of metal ammonia reductions of aromatic compounds can be found in reviews by Rabideau[10] and Kaiser.[11]



Scheme 11

We required an effective method for preparing 1-alkylcyclohexa-2,5-diene-1-carboxylic acids **3** and the Birch reduction-alkylation of benzoic acid seemed suitable for this purpose. The reduction of benzoic acid with Li metal in a solution of NH_3 is straightforward, and we anticipated that the addition of a range of alkyl halides would result in the formation of the desired carboxylic acid **3**. Furthermore, we realised that if our method for generating radicals was to be useful from a synthetic point of view, the Birch reduction-alkylation would need to proceed selectively in cases where the alkyl halide was multi-functional. Our initial investigations would, however, involve commercially available alkyl halides and on this basis we proceeded with our investigations.

2

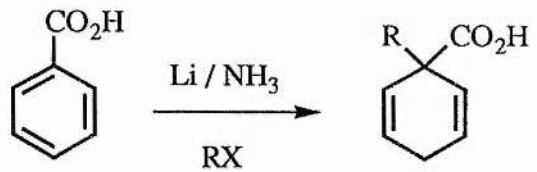
Results and Discussion

This section has been divided into two parts. Part A discusses the synthesis and reactions of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids designed for inter-molecular reactions. Part B is concerned with the analogous intra-molecular reactions and reports the chemistry involved in the formation of the more complex 1-alkylcyclohexa-2,5-diene-1-carboxylic acids and discusses the results of the radical reactions.

Part A

2.1 Preparation of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids

1-Alkylcyclohexa-2,5-diene-1-carboxylic acids **15**, **16** and **17** were all prepared in various yields using a modified procedure based on that due originally to Birch (Scheme 12).[12] Acids **15-17** have also been prepared by Zhurkovich *via* a similar procedure.[13]



15-17

15	R=$^{c}C_5H_9$, X=Br 71%
16	R=^{t}Bu , X=Br, I 18%, 29%
17	R=$PhCH_2$, X=Cl 100%

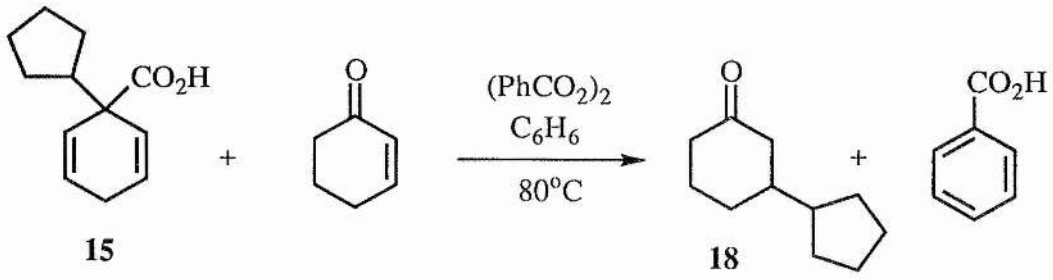
Scheme 12

The low yield of 1-*t*-butylcyclohexa-2,5-diene-1-carboxylic acid was understandable when taking into consideration that both carbon atoms of the newly formed carbon-carbon bond were quaternary. However, a slightly higher yield was achieved when *t*-butyl iodide was

used instead of the bromide. The crude yields were higher but the isolated yields were diminished because of the chromatographic separation required to obtain acid **16** free of benzoic acid and 1,4-dihydrobenzoic acid. This can often be a problem because unreacted benzoic acid, 1,4-dihydrobenzoic acid and the desired alkyl acid often show little or no separation by TLC. The formation of 1-benzylcyclohexa-2,5-diene-1-carboxylic acid **17** in quantitative yield was not unexpected since benzyl halides are more susceptible to nucleophilic substitution reactions than ordinary saturated alkyl halides.

2.2 Generation of the cyclopentyl radical in the presence of cyclohexenone

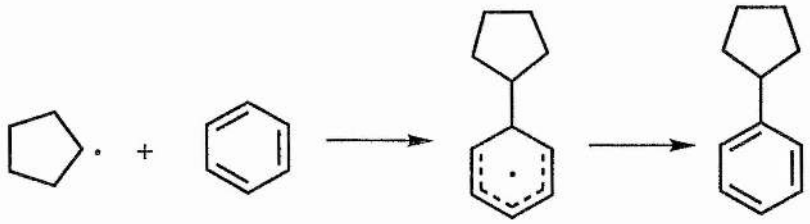
Treatment of 1-cyclopentylcyclohexa-2,5-diene-1-carboxylic acid **15** with dibenzoyl peroxide in the presence of cyclohexenone in a solution of benzene, resulted in the formation of 3-cyclopentylcyclohexanone in yields of 60%, (estimated from the ^{1}H NMR spectrum of the crude reaction mixture) (Scheme 13). The desired adduct was then isolated by column chromatography as a brown oil in 31% yield.



Scheme 13

The radical reactions were monitored by GC/MS and a typical series of results would detect the following compounds: unreacted cyclohexenone, unreacted carboxylic acid **15**, benzoic acid, 3-cyclopentylcyclohexanone **18**, 3-phenylcyclohexanone (formed after addition of a phenyl radical to cyclohexenone), biphenyl (formed by addition of a phenyl radical to benzene or the combination of two phenyl radicals) and phenylcyclopentane (formed as shown in Schemes 14 and 15).

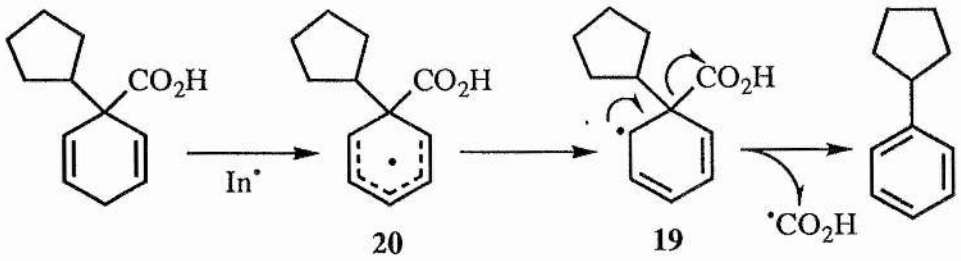
It was often found that after removal of benzoic acid with dilute NaOH, the acid fraction also contained unreacted starting acid **15**. This observation was not just restricted to this particular acid but was a typical result for most of the acids tested, suggesting that the rate of hydrogen atom abstraction from these carboxylic acids was slow. This was consistent with the appreciable quantities of initiator required. Therefore, to ensure that essentially all of the starting acid was consumed, portionwise addition of dibenzoyl peroxide was required, often amounting to 50-75% by wt. relative to the carboxylic acid. The use of large quantities of initiator accounted for the formation of the phenyl adduct and biphenyl, though their presence was relatively minor. The yield of phenylcyclopentane was calculated to be 9%, by comparing the ^{1}H NMR spectrum of the crude reaction mixture and a sample of pure phenylcyclopentane. The formation of phenylcyclopentane may have occurred by addition of the cyclopentyl radical to benzene to give radical **19** followed by oxidation (Scheme 14).



19

Scheme 14

Another route involved the formation of radical **20** by hydrogen atom abstraction, followed by loss of the hydroxyformyl radical, $^{\bullet}CO_2H$ (Scheme 15). When a related cyclohexadienyl acid was refluxed in amyl alcohol, the corresponding mono-substituted aromatic was also observed and this was evidence for loss of $^{\bullet}CO_2H$. The major product of the radical reaction, however, was the desired adduct, 3-cyclopentylcyclohexanone, which was isolated in modest yield. This was considered to be an encouraging result for an intermolecular reaction in which the alkene was only used in equimolar amounts.

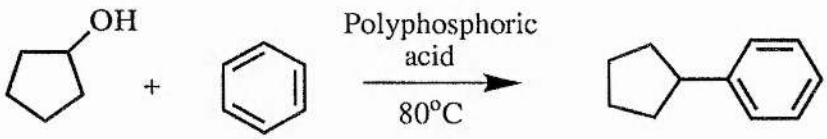


20 19

Scheme 15

2.3 Preparation of phenylcyclopentane[14]

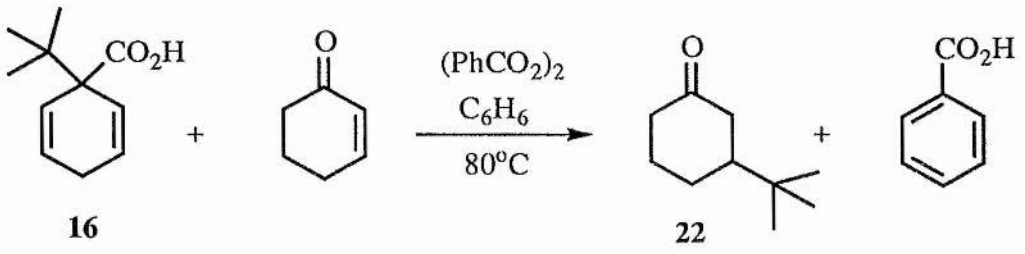
Phenylcyclopentane was prepared in order to compare it's ^{1}H NMR spectrum with that of the crude reaction mixture from the reaction discussed above. As shown in Scheme 16, the desired product was prepared in 24% yield by the reaction between benzene and cyclopentanol in the presence of polyphosphoric acid.[14]



Scheme 16

2.4 Generation of the *t*-butyl radical in the presence of cyclohexenone

When 1-*t*-butylcyclohexa-2,5-diene-1-carboxylic acid **16** was dissolved in benzene and refluxed for 1 day in the presence of cyclohexenone and 50% wt. of dibenzoyl peroxide, 3-*t*-butylcyclohexanone **22** formed in 25% (^{1}H NMR) yield (Scheme 17). This result was disappointing as we had observed by EPR spectroscopy that acid **16** generated the *t*-butyl radical more readily than carboxylic acids **15** and **17** generated their corresponding alkyl radicals. In order to observe the signal corresponding to this *cyclohexadienyl* radical, the temperature of the EPR cavity had to be 155K or lower. The radical reaction was followed by GC/MS and the main products detected were the starting acid, unreacted cyclohexenone and the desired product. A small amount of *t*-butylbenzene (3%), formed either by addition of the *t*-butyl radical to the solvent or loss of a hydroxyformyl radical from the intermediate cyclohexadienyl radical, was also observed by ^{1}H NMR spectroscopy.

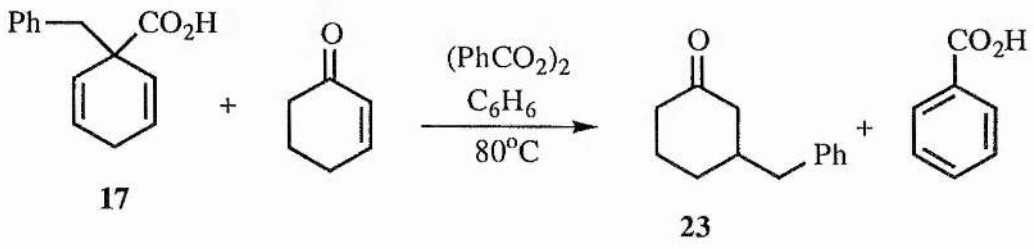


16 22

Scheme 17

2.5 Generation of the benzyl radical in the presence of cyclohexenone

When 1-benzylcyclohexa-2,5-diene-1-carboxylic acid and cyclohexenone were refluxed in benzene in the presence of dibenzoyl peroxide, the desired adduct 3-benzylcyclohexanone **23** was formed (Scheme 18). However, in addition to this adduct, other compounds detected by GC/MS included unreacted cyclohexenone, benzoic acid, biphenyl, diphenylmethane, toluene, benzaldehyde and benzyl alcohol. The latter two of these were considered to be oxidation products of the benzyl radical and hence the reaction was repeated under nitrogen. The other compounds listed are self-explanatory. The small amount of diphenylmethane was formed by competitive loss of the hydroxyformyl radical, (or addition of a benzyl radical to benzene), and toluene was formed after hydrogen atom abstraction by the benzyl radicals. When the reaction was repeated under nitrogen a cleaner reaction occurred and 3-benzylcyclohexanone was the only significant product, isolated by column chromatography in 52% yield, based on the amount of starting acid reacted.



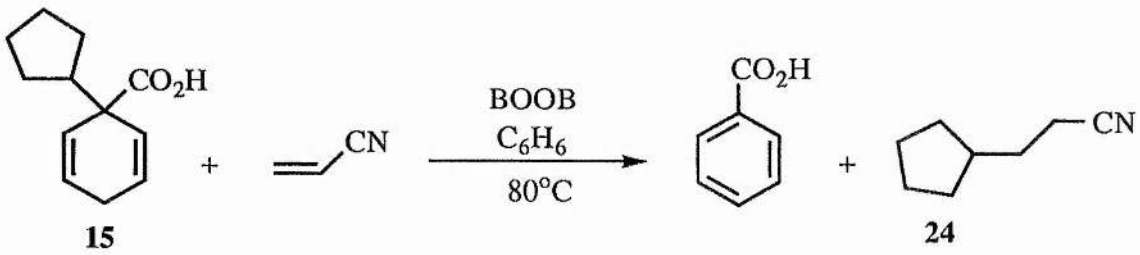
17 23

Scheme 18

2.6 Generation of the cyclopentyl radical in the presence of acrylonitrile

1-Cyclopentylcyclohexa-2,5-diene-1-carboxylic acid **15**, acrylonitrile, di-*t*-butyl peroxide and benzene were added to a glass tube which was degassed, sealed and heated for 24h in

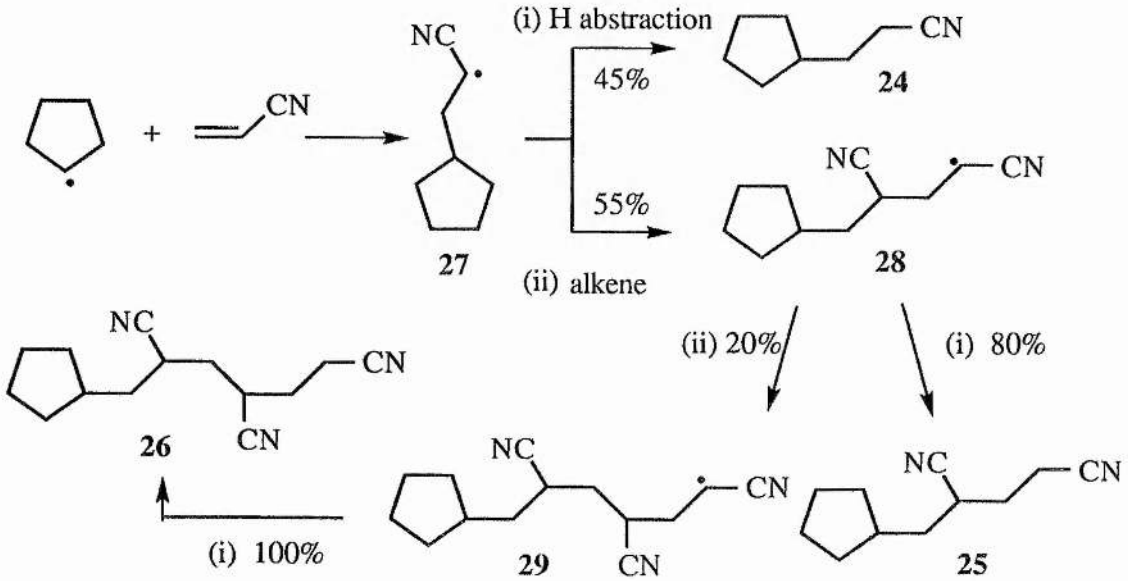
an oven at 140°C. The adduct, 3-cyclopentylpropionitrile **24** was not detected, but when the reaction was repeated at lower temperatures (80°C-120°C) the desired adduct was identified (Scheme 19), in addition to unreacted starting acid, benzoic acid, phenylcyclopentane, double addition product **25** and triple addition product **26**.



15 **24**

Scheme 19

The formation of nitriles **25** and **26** illustrated that the adduct radical **27** (Scheme 20) reacted with carboxylic acid **15** to give the desired adduct **24**, or reacted with another molecule of acrylonitrile, thus giving adduct radical **28**. Similarly, radical **28** could either abstract a hydrogen atom from **15** to give double addition product **25** or add to another molecule of acrylonitrile to give adduct radical **29** which gave triple addition product **26**.

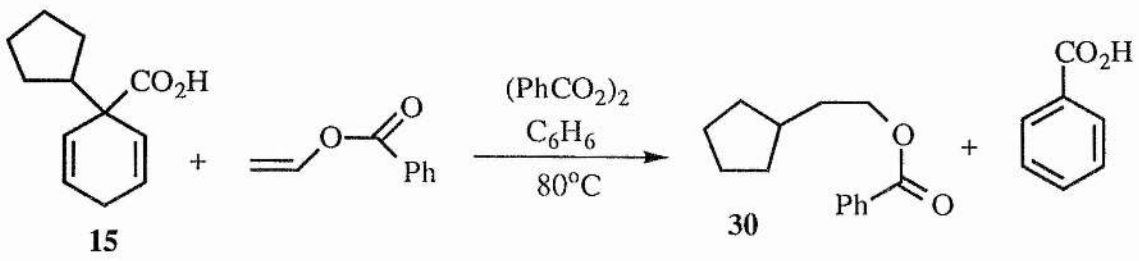


Scheme 20

Based on the assumption that nitriles **24**, **25** and **26** had similar GC detection efficiencies, then from their respective intensities (8:8:2) it was possible to calculate the proportions of the alternative routes for intermediate radicals **27** and **28** (see Scheme 20). It was not possible to estimate the yield of the adduct **24** from the ^{1}H NMR of the crude reaction mixture because this was complicated by the presence of double and triple addition products. The two protons adjacent to the cyano group give triplets at 2.25 ppm, but all three nitriles give such signals and therefore because of extensive overlap, it was not possible to calculate the yield of **24** accurately. Nevertheless, this experiment showed that 1-cyclopentylcyclohexa-2,5-diene-1-carboxylic acid generated a cyclopentyl radical, which in turn added to acrylonitrile to give the adduct **24** after hydrogen atom abstraction from acid **15**. The yield of **24** (and dimer **25** and trimer **26**) would have been higher if all the starting acid had reacted, but this was not the case.

2.7 Generation of the cyclopentyl radical in the presence of vinyl benzoate

When 1-cyclopentylcyclohexa-2,5-diene-1-carboxylic acid **15** was refluxed in benzene in the presence of vinyl benzoate and dibenzoyl peroxide the desired adduct, 2-cyclopentylethylbenzoate **30** was formed (Scheme 21). The yield of adduct **30** was determined to be 26% though this was not an isolated yield. From the ^{1}H NMR of the crude reaction mixture it was also possible to establish the formation of the double addition product (15%) and phenylcyclopentane (15%). Again the yields of these products would have been higher if the reaction had been allowed to run longer, since only 70% of the starting material had reacted.

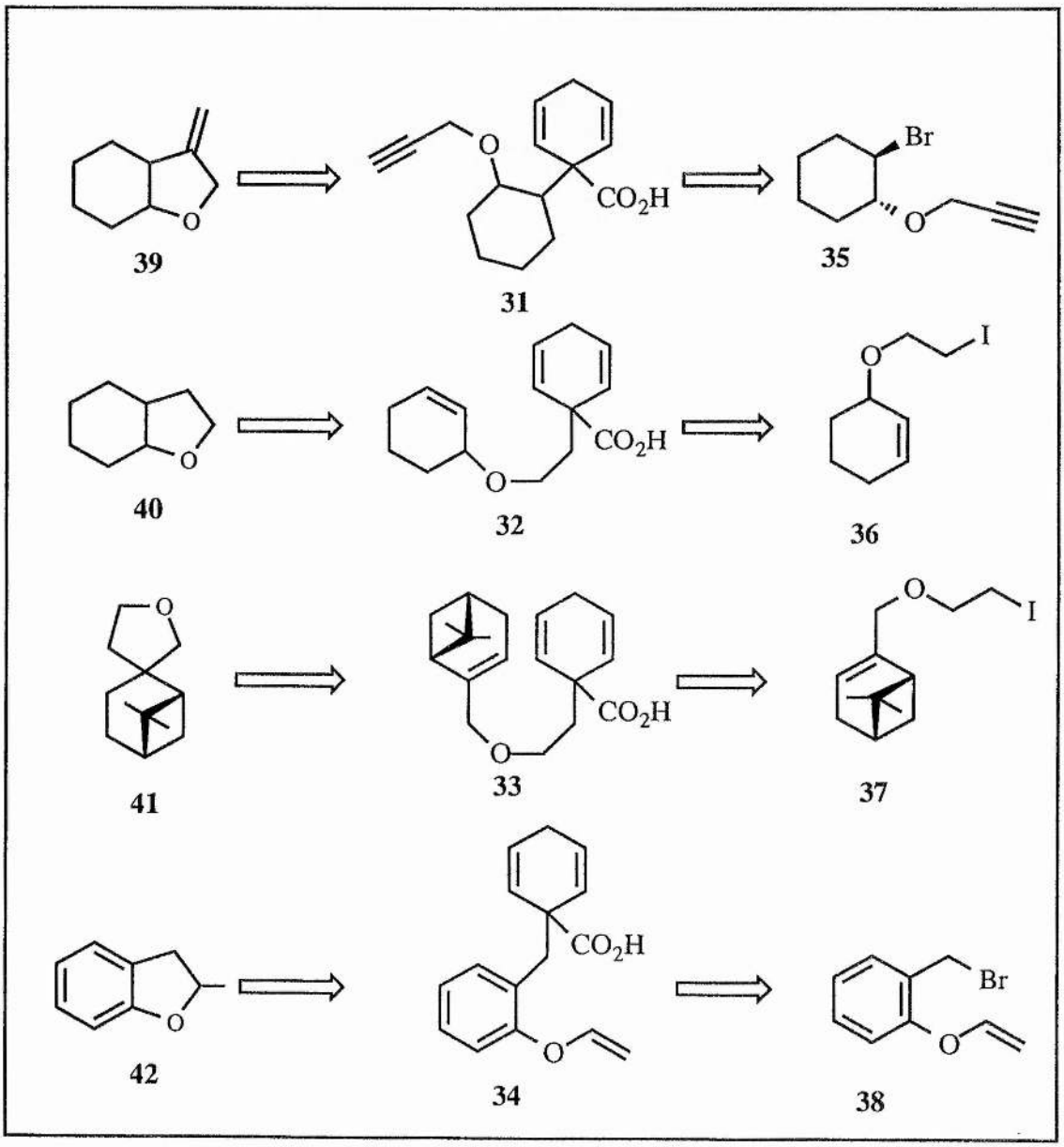


15 **30**

Scheme 21

Part B

Having illustrated that 1-alkylcyclohexa-2,5-diene-1-carboxylic acids **3** could react to give radicals capable of participating in chain reactions, we next turned our attention to preparing acids which would be capable of giving products of intramolecular addition. It was our hope that the yields of the intramolecular reactions would exceed those of the intermolecular reactions, since the radical generated would be in proximity to a double bond.

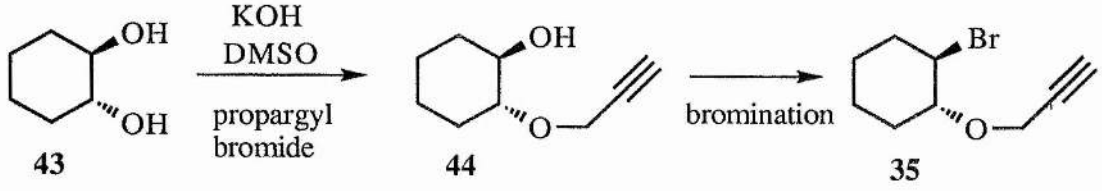


Scheme 22

Carboxylic acids **31-34** were targets which would allow us to determine the efficiency of these radical precursors in intramolecular reactions. The last step in the synthesis of these compounds would be a Birch reduction-alkylation and Scheme 22 illustrates the disconnections leading to the appropriate halides **35-38**. These halides could also be treated with tributyltin hydride to give the same ring closed products **39-42**, in yields which could be compared with those obtained from the radical fragmentations of acids **31-34**.

2.8 1-[2-(Propyn-3-yloxy)cyclohexyl]cyclohexa-2,5-diene-1-carboxylic acid (31)

Synthesis of carboxylic acid **31** required the preparation of bromide **35**. Our initial route to bromide **35** (Scheme 23) commenced with *trans*-1,2-cyclohexanediol **43**. Thus deprotonation of one of the hydroxyl groups with KOH in DMSO[15] and quenching with propargyl bromide resulted in the formation of the unsaturated alcohol **44** in 47% yield and the dialkylated product (7%).



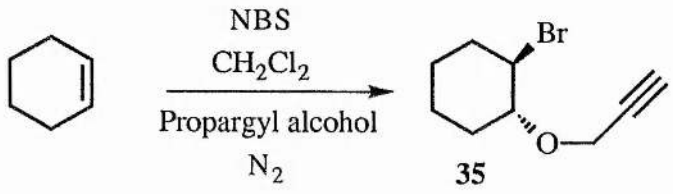
Scheme 23

The following step, bromination of the alcohol, proved troublesome and the desired bromide was not successfully prepared *via* this route. Our initial attempt using triphenylphosphine and bromine in DMF[16] resulted in the recovery of the starting alcohol and also triphenylphosphine-oxide as a byproduct. The more conventional method of using PBr_3 and pyridine in ether[17] was also unsuccessful. Analysis of the brown oil by ^1H NMR spectroscopy revealed the disappearance of the hydroxyl group, but attempts to distil any of the product from the reaction mixture failed. The bromination was also attempted in an NMR tube using thionyl bromide and deuterated chloroform.[18] The ^1H NMR spectrum

was encouraging as the OH signal had disappeared and there was some shifting of the signals, considered to be due to the presence of the bromide. The reaction was scaled up, but on work-up the alcohol was recovered. It was at this point that we found a one-step process for the successful conversion of cyclohexene into bromide **35**.[19]

2.8.1 *trans*-1-Bromo-2-(2-propyn-1-yloxy)cyclohexane (35)[19]

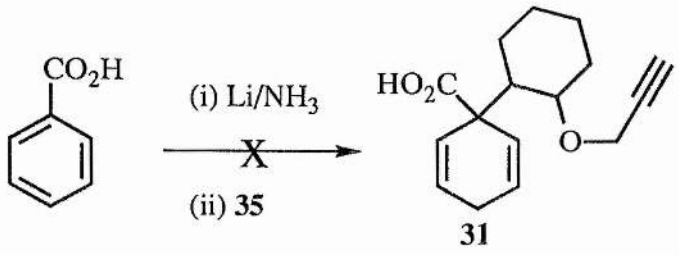
Bromide **35** can be prepared in moderate to good yield by adding *N*-bromosuccinimide over the course of 2h at -20°C to a mixture of cyclohexene, propargyl alcohol and dichloromethane under nitrogen and leaving the mixture stirring overnight at room temperature (Scheme 24).[19] This method yielded bromide **35** as a clear, colourless liquid in 68% yield after distillation.



Scheme 24

2.8.2 Attempted preparation of 1-[2-(propyn-3-yloxy)cyclohexyl]cyclohexa-2,5-diene-1-carboxylic acid (31)

Following the successful preparation of bromide **35**, the next step was to attempt the Birch reduction-alkylation of benzoic acid to give the cyclohexadienyl acid **31** (Scheme 25).

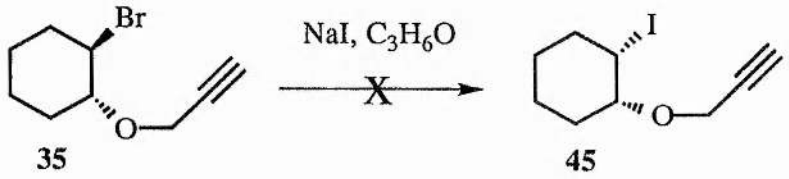


Scheme 25

We were disappointed to find that after work-up of the reaction mixture only unreacted benzoic acid and bromide **35** were obtained in addition to 1,4-dihydrobenzoic acid. A number of experiments were carried out, varying the ratio of benzoic acid to bromide, but none of the desired product was observed. It was evident that the propargyl arm present in the bromide was exerting an influence on the outcome of the reaction.

2.8.3 Attempted conversion of bromide 35 to iodide 45

Although the failure of the above reaction was likely to have been due to steric hindrance, we thought that it would be worthwhile to repeat the reaction with an iodide rather than a bromide. Unfortunately, under the usual conditions of a halogen-exchange reaction, the only product recovered from the reaction was the starting bromide (Scheme 26).[20]

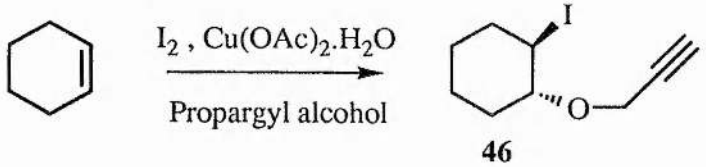


35 **45**

Scheme 26

2.8.4 *trans*-1-Iodo-2-(2-propyn-1-yloxy)cyclohexane (46)

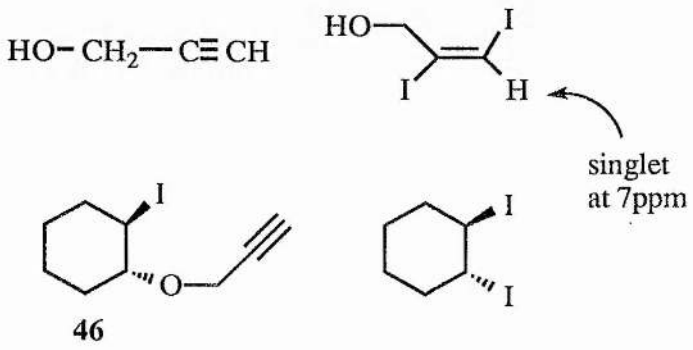
Vicinal alkoxyiodoalkanes can be prepared from alkenes by means of copper(II) acetate, iodine and the appropriate alcohol.[21] For example, the reaction between cyclohexene, iodine and methanol in the presence of copper(II) acetate monohydrate resulted in the formation of *trans*-1-iodo-2-methoxycyclohexane in excellent yield.[21] The mechanism involved an electrophilic attack of iodine on the double bond giving the iodonium ion intermediate which was opened up by the alcohol instead of the iodide anions, which were soaked up by the copper(II) salt. We prepared vicinal alkoxyiodoalkane **46** by this method (Scheme 27).



46

Scheme 27

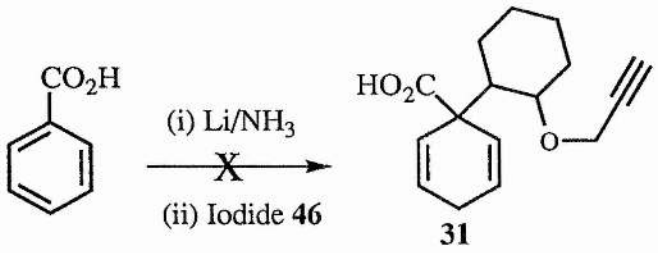
Although we expected the reaction to occur, we did not anticipate the yield of the product to be as high as that for the vicinal methoxyiodocyclohexane reaction because the original paper reported that when the alcohol was unsaturated, the reaction proceeded in lower yields.[21] The reactants were left stirring at room temperature for 15h, the reaction was worked-up and analysis by ^{1}H NMR and GC/MS indicated the presence of the compounds illustrated in Scheme 28, which included the desired product. Of the crude mixture, 7g was loaded onto a column of silica gel (i.e. 28% of the mixture), and the desired iodo ether **46** (1.92 g) was obtained after the appropriate fractions were combined and further purified by Kugelrohr distillation. Had the remainder of the mixture been purified in this manner, then one would have expected to obtain a further 5 g of the iodide giving an overall yield of 23%.



Scheme 28

2.8.5 Attempted preparation of 1-[2-(propyn-3-yloxy)cyclohexyl]cyclohexa-2,5-diene-1-carboxylic acid (31)

Having succeeded in preparing an adequate amount of the pure iodo compound **46** we could now investigate whether the iodide would behave more effectively than the bromide in the Birch reduction-alkylation reaction. Thus, the reaction illustrated in scheme 29 was attempted. Unfortunately, only benzoic acid and 1,4-dihydrobenzoic acid were obtained. At this early stage we realised that the Birch reduction-alkylation reaction was relatively sensitive to the alkyl halide used.

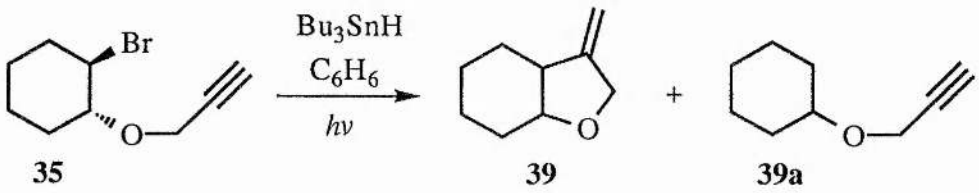


31

Scheme 29

2.8.6 Tin hydride mediated cyclisation of bromide 35

Although our attempts to prepare carboxylic acid **31** were fruitless it was nevertheless of interest to proceed with the tin hydride mediated cyclisation of bromide **35**. Thus bromide **35** was dissolved in benzene and irradiated with light, in the presence of tributyltin hydride, for 8h at room temperature (Scheme 29a).



35 **39** **39a**

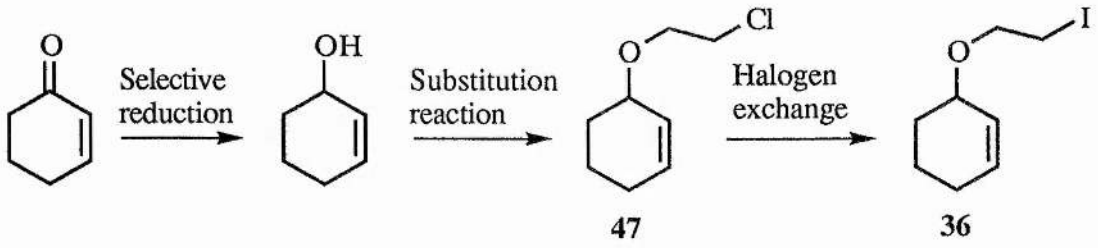
Scheme 29a

The reaction was monitored by GC/MS and revealed that after 8h photolysis the bromide **35** had been consumed and that two compounds, identified as 9-methylene-7-oxabicyclo[4.3.0]nonane **39** and the prop-2-ynyloxycyclohexane **39a** were formed. These two products were distilled using a Kugelrohr to give a combined yield of 61%.

2.9 1-[Ethyl-2-(cyclohex-2-enyloxyl)]cyclohexa-2,5-diene-1-carboxylic acid (32)

We anticipated that the successful synthesis of carboxylic acid **32** would require the preparation of iodide **36** (Scheme 30). Our initial route towards iodide **36** involved 3 steps and commenced with the Luche reduction of cyclohexenone to give 3-hydroxycyclohexene.[22] We predicted that removal of the hydroxyl hydrogen with a

suitable base would afford the corresponding alkoxide which would react with 1-bromo-2-chloroethane to yield chloride **47**. Iodide **36** would then be obtained by a standard halogen-exchange reaction.[20]

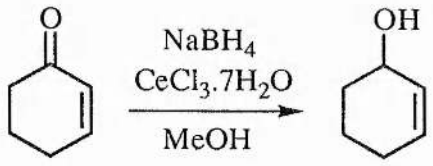


47 **36**

Scheme 30

2.9.1 3-Hydroxycyclohexene[22]

Treatment of cyclohexenone with $NaBH_4$ and $CeCl_3.7H_2O$ in methanol afforded the corresponding cyclohexenol as a clear, colourless liquid in 68% yield after distillation (Scheme 31). The Luche reduction of α,β-unsaturated carbonyl compounds is often an effective method for the selective reduction of the carbonyl group. Although $NaBH_4$ does not usually reduce alkenes, it will often partially reduce the double bond if in conjugation with a carbonyl group. This problem can, however, often be avoided by performing the reaction in the presence of $CeCl_3.7H_2O$. This reaction can also be performed stereoselectively to give just one enantiomer if desired.[23]

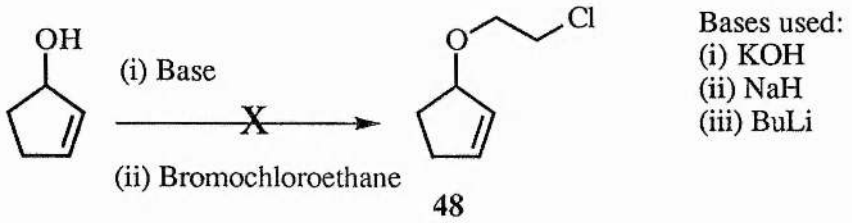


Scheme 31

2.9.2 Attempted preparation of 3-(2-chloroethoxy)cyclopentene (48)

Although we wanted to prepare chloride **47** we decided to prepare chloride **48** first, since we had 3-hydroxycyclopentene in stock. Our initial attempt was similar to the method which resulted in the successful preparation of alcohol **44** (Section 2.8). Thus 3-

hydroxycyclopentene was dissolved in DMSO and treated with KOH, followed by the addition of 1-bromo-2-chloroethane (Scheme 32). Unfortunately the desired product was not formed and after work-up only negligible quantities of material were obtained. The only viable explanation for this seemed to be loss of starting materials when evaporating the solvents under reduced pressure, though even this was not satisfactory.



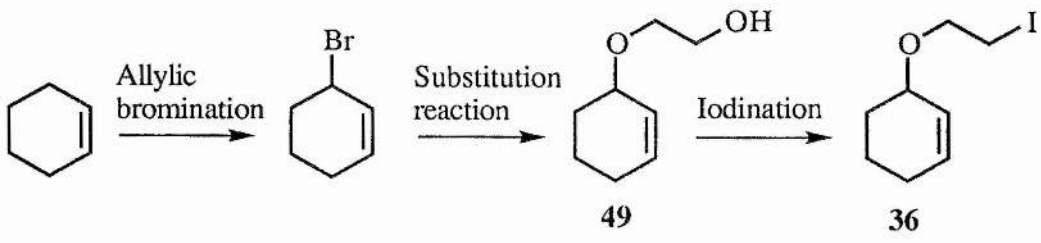
48

Scheme 32

Two further attempts to prepare **48** were made using the stronger bases NaH and BuLi, but still none of the desired product was formed. It was felt that the electrophile, 1-bromo-2-chloroethane, was simply not reactive enough since deprotonation of the hydroxyl group would surely have been achieved. In retrospect it may have been instructive to prove this by quenching with a more reactive halide such as methyl iodide.

2.9.3 Successful synthesis of iodide 36

Instead of pursuing the route above, we turned our attention to the steps illustrated in Scheme 33. Thus allylic bromination of cyclohexene would give 3-bromocyclohexene which was expected to undergo a nucleophilic substitution reaction with the alkoxide anion of ethylene glycol, hence forming alcohol **49**. A simple functional group transformation of a hydroxyl group to iodine would then complete the short synthesis.

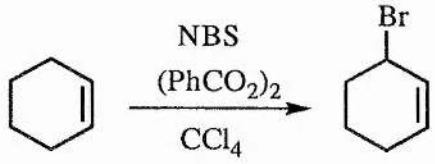


49 **36**

Scheme 33

2.9.4 3-Bromocyclohexene[24]

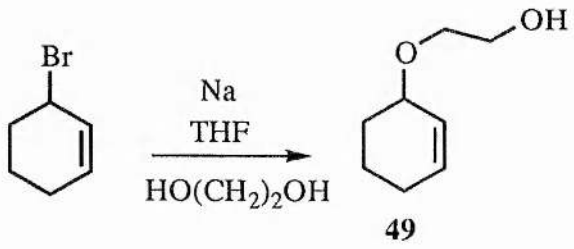
When a small amount of dibenzoyl peroxide was added to cyclohexene and *N*-bromosuccinimide dissolved in carbon tetrachloride an exothermic reaction was initiated (Scheme 34).[24] After refluxing for 4h, 3-bromocyclohexene was obtained as a slightly cloudy, colourless liquid in yields ranging from 47-68% after distillation. The bromination occurs *via* a free radical mechanism initiated by small amounts of Br•. The brominating agent is in fact molecular bromine, which reacts with carbon-centred radicals at the allylic site to give bromocyclohexene.



Scheme 34

2.9.5 3-(2'-Hydroxyethoxy)cyclohexene (49)

Alcohol **49** was readily prepared by adding sodium wire to an excess of ethylene glycol in dry THF, and refluxing the mixture overnight (Scheme 35). This was followed by the addition of 3-bromocyclohexene and after refluxing for the appropriate period of time, the alcohol was obtained as a clear, colourless liquid in yields exceeding 80%.

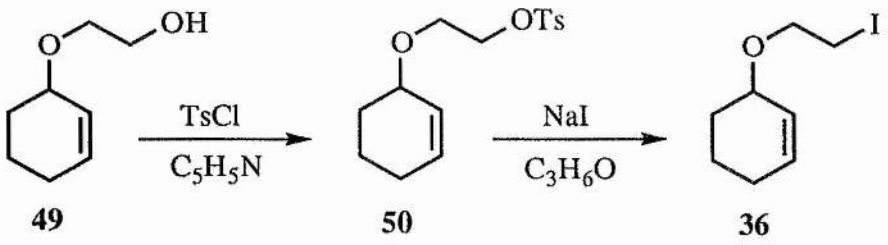


49

Scheme 35

2.9.6 3-(2'-Iodoethoxy)cyclohexene (36)

Alcohol **49** was converted into iodide **36** *via* formation of tosylate **50** (Scheme 36).[25] The iodide was obtained as a clear, colourless liquid in yields ranging from 40-65% after distillation.

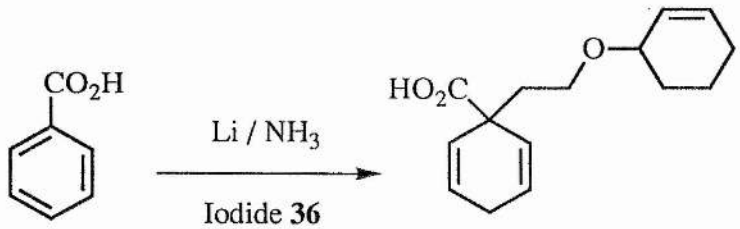


49 **50** **36**

Scheme 36

2.9.7 1-[2-(Cyclohex-2-enyloxy)ethyl]cyclohexa-2,5-diene-1-carboxylic acid (32)

Benzoic acid was dissolved in NH_3 and Li metal was added to the reaction mixture. After the solution had turned blue and reacted for approximately 10 min the mixture was quenched with the iodide, causing the solution to turn yellow (Scheme 37). Conventional work-up yielded the desired acid **32** together with some unreacted benzoic acid and 1,4-dihydrobenzoic acid.



32

Scheme 37

The reaction was repeated numerous times in order to improve the yield of the desired acid and reduce the amounts of benzoic acid and 1,4-dihydrobenzoic acid, which were difficult to remove by column chromatography. We found that varying the number of equivalents of iodide **36** had no significant effect on the outcome of the reaction and therefore the iodide was often used in a 1:1 ratio relative to benzoic acid (Table 1). Purification of the product mixture by column chromatography depleted the yield of acid **32** to 17%.

Table 1: Results obtained for the Birch reduction-alkylation experiments using iodide **36**

	Mass of benzoic acid used / g	Mole equivalents of iodide	Mass of material recovered / g	Yield % (Crude)
1	1	1	1.7	51
2	1	2	1.6	52
3	1	4	1.7	55
4	27	1	35.5	39
5*	1.3	2	2.1	67 (42%)[1]

*iodide added after 0.5h rather than 5-10 min as in case for entries 1-4; [1] isolated yield.

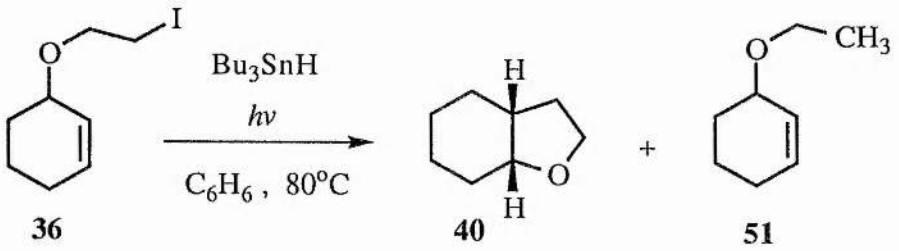
We followed an alternative experimental procedure which involved passing NH_3 through soda lime and condensing the gas with a cold finger into a flask containing benzoic acid.[8] When all the NH_3 required was added, the system was purged with nitrogen and the Birch reduction-alkylation was followed in the usual manner from this point onwards. However, this resulted in none of the desired acid being formed at all.

We noticed that in similar reactions described by Mander, the length of time between addition of all the Li and quenching with the appropriate halide was 30 min, compared to the 10 min period we had employed.[8] Thus, we repeated the Birch reduction-alkylation in the usual manner, but waited 30 min before quenching with the iodide. This resulted in a more efficient reaction and the product was isolated by column chromatography in an improved yield of 42% (entry 5, Table 1). There is no obvious explanation for this outcome.

2.9.8 Tin hydride-mediated cyclisation of iodide 36

Iodide **36** was dissolved in benzene and irradiated with light in the presence of tributyltin hydride for 6h at 70°C (Scheme 38). The reaction, monitored by GC/MS, resulted in the

total consumption of the iodide and the formation of two products identified as 7-oxabicylco[4.3.0]nonane **40** and the 3-ethoxycyclohexene **51**. The presence of compound **51** illustrates one of the common features observed in tin hydride radical chemistry, namely the formation of unwanted directly-reduced products, (unless of course the desired reaction is in fact substitution of iodine for hydrogen). It is likely, however, that the yield of the cyclic product **40** could have been increased at the expense of alkene **51** by simply adding the tin hydride portionwise. However, when we performed the reaction, we used 1.1 equivalents of tin hydride relative to the iodide. The unwanted tin compounds were removed by the addition of a saturated solution of potassium fluoride, and the products were distilled together using a Kugelrohr, yielding 60% of the cyclic ether **40** and 13% of alkene **51**.



36 **40** **51**

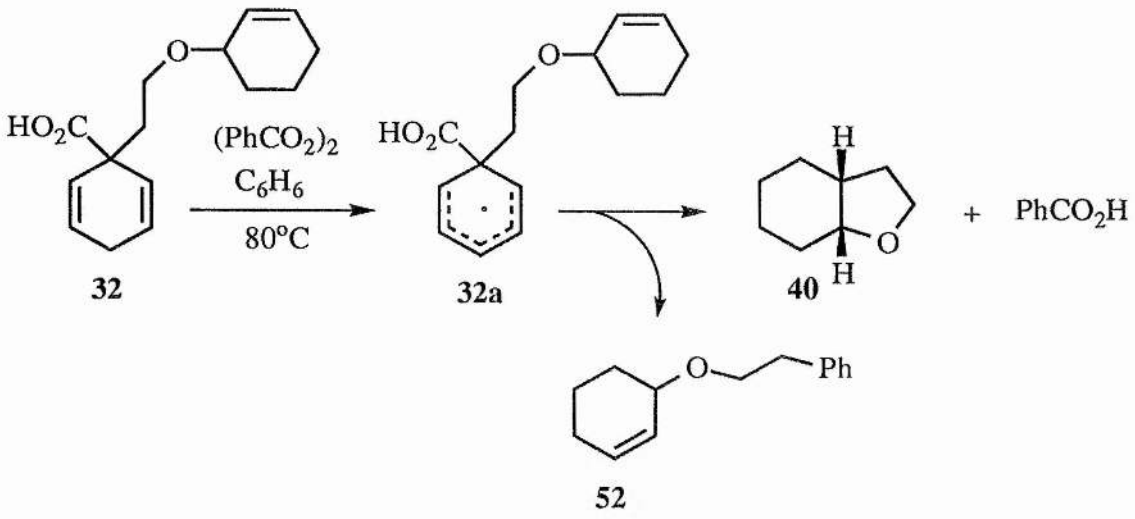
Scheme 38

2.9.9 Radical-induced fragmentation of carboxylic acid 32

Carboxylic acid **32** was dissolved in benzene, to which dibenzoyl peroxide was added. The mixture was refluxed for 1-5 days depending on the amount of initiator added at the beginning (Scheme 39). In each experiment performed, we observed by GC/MS the presence of two main products and also minor products. The two main products were the expected 7-oxabicylo[4.3.0]nonane **40** and also an aromatic compound identified as 3-(2-phenylethoxy)cyclohexene **52**. This indicated that under the reaction conditions described above, hydrogen atom abstraction from acid **32** resulted in the formation of delocalised radical **32a**. This radical fragmented in the usual manner to generate the primary alkyl radical which cyclised to give bicycle **40** after hydrogen atom abstraction (Scheme 39). The formation of the aromatic product **52** was mainly due to competitive loss of a

hydroxyformyl radical from cyclohexadienyl radical **32a**, as the same product was observed in appreciable quantities when the reaction was performed in amyl alcohol instead of benzene.

In the first three experiments performed, only 54-72% of the carboxylic acid **32** had reacted. This seemed to indicate that the delocalised radical **32a** was generated more slowly. When the reaction was performed over a three day period, with the portionwise addition of one equivalent of dibenzoyl peroxide, none of the starting acid was recovered. Instead, extraction of the acid products with dilute alkali simply resulted in the recovery of benzoic acid. The other fraction was shown by ^{1}H NMR and GC/MS to contain essentially two products, namely compounds **40** and **52**, together with a small amount of biphenyl. An attempt was made to isolate the cyclic product by Kugelrohr distillation at atmospheric pressure but this failed.



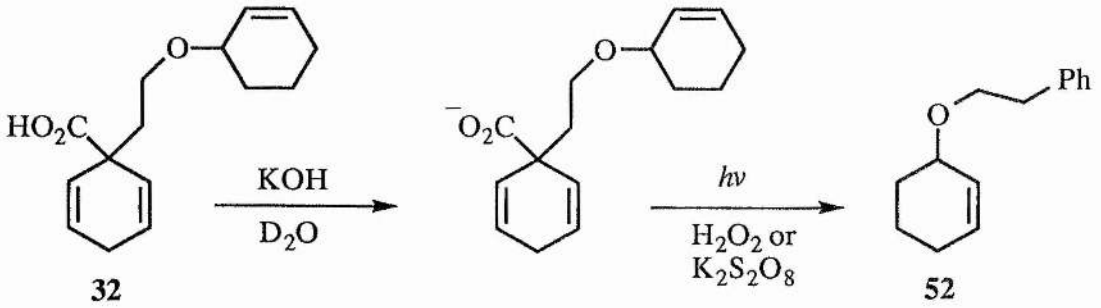
Scheme 39

We therefore tried to isolate bicyclic ether **40** using a specialised distillation kit that could be attached to a vacuum line. Using an oil pump, the product was distilled and condensed using a liquid nitrogen trap. Although the product was shown by ^{1}H and ^{13}C NMR spectroscopy to be the cyclic product **40** in pure form, the yield was depleted since much of the product remained in the distillation apparatus. This was a consequence of performing

the reaction on a small-scale, which was itself a result of the difficulty in isolating carboxylic acid **32** in appreciable quantities. From this pure sample it was possible to determine the coupling constants associated with the hydrogen atoms α to the oxygen atom. The *t*-H was split into a quartet with a coupling constant of 7.8Hz and the methylene group was a doublet of triplets. After searching the literature for 7-oxabicyclo[4.3.0]nonane, it was suprisingly not possible to obtain any information regarding the characterisation of this compound. Nevertheless, with a coupling constant of 7.8Hz associated with the hydrogen atoms of the ring junction we predicted that these were *cis* to each other.[26] This was also consistent with the known fact that hex-5-enyl cyclisations of this type give products with *cis* stereochemistry. The yields of cyclic ether **40** and aromatic ether **52** were calculated from the original ^{1}H NMR spectrum of the mixture and were determined to be 55% and 40% respectively. These results raise two main points: (i) the formation of bicycle **40** from carboxylic acid **32** was not a selective process and (ii) the yield of **40** was comparable to that obtained from the tin hydride mediated cyclisation of iodide **36**, although we did not have the problem of dealing with toxic tin residues that are difficult to remove.

2.9.10 Radical fragmentation of acid 32 in an aqueous medium

An experiment which involved dissolving carboxylic acid **32** in water by deprotonating with KOH, and investigating the effects of irradiating with light in the presence of either potassium persulphate or hydrogen peroxide was attempted (Scheme 40). Since only a small amount of acid **32** remained, the experiments were performed in NMR tubes.



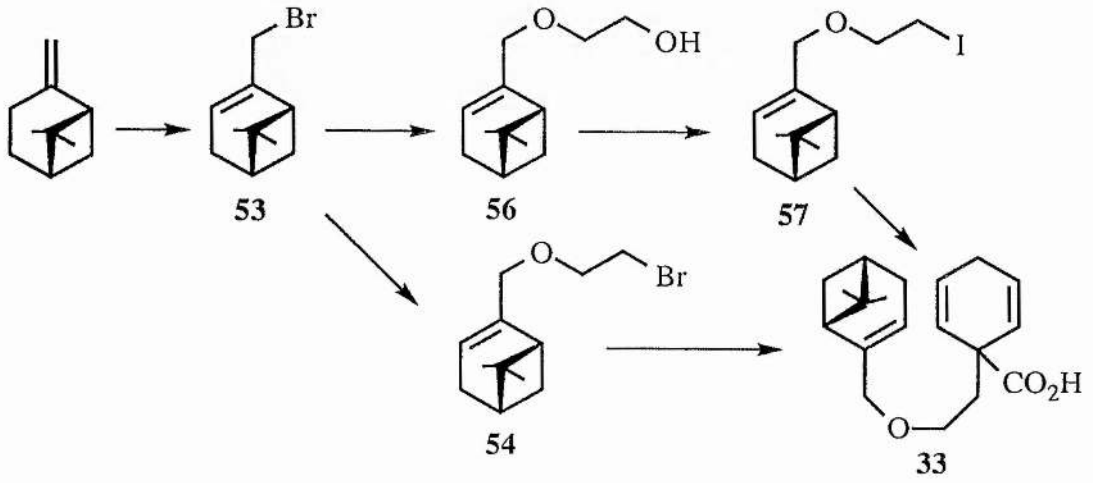
32 **52**

Scheme 40

We found that the reaction was completely selective in forming the undesired aromatic product **52**, which could be isolated in pure form after work-up. This result suggested that loss of the carbon dioxide radical anion occurred more readily than loss of the carbon dioxide radical. Minisci has also described the silver catalysed decarboxylation of oxalic monoesters by sodium persulphate.[27]

2.10 1-[2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-ylmethoxy)ethyl]cyclohexa-2,5-diene-1-carboxylic acid (33)

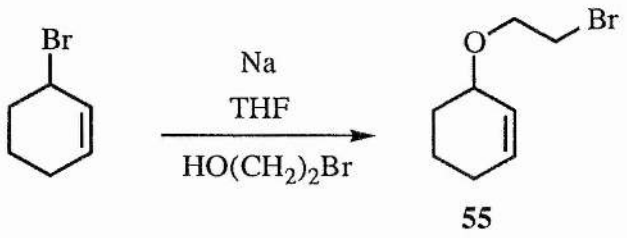
Having devised a convenient route to iodide **36** we decided to perform the same series of reactions using β-pinene as the starting material (Scheme 41). Pinene was considered to be suitable because it was readily available and also because the anticipated product of intramolecular radical cyclisation (spiro ether **41**, Scheme 22) would be less volatile than the lower molecular weight cyclic ether **40** prepared earlier. We considered that the synthesis of **33** might be achieved more rapidly by converting bromide **53** into bromide **54**, by treating the former with sodium and 2-bromoethanol in THF. Although primary iodides undergo Birch reduction-alkylations more readily than the corresponding bromides, we thought that it would be of interest to investigate whether bromide **54** could be used to synthesise **33**. Since we had some 3-bromocyclohexene remaining we decided to prepare bromide **55** first (Scheme 42).



Scheme 41

2.10.1 3-(2'-Bromoethoxy)cyclohexene (55)

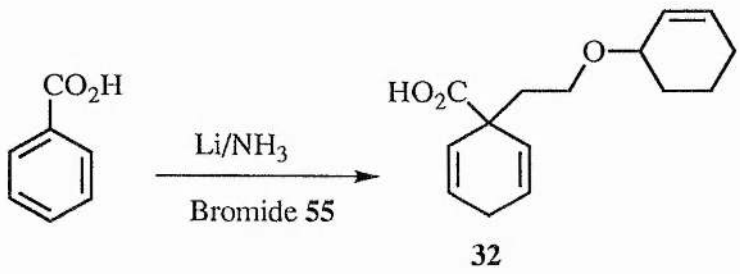
Bromide **55** could be prepared in one step from 3-bromocyclohexene, by adding the latter to 2-bromoethanol, dry THF and sodium wire and refluxing the mixture overnight (Scheme 42). The product was obtained as a clear, colourless liquid in 56% yield after distillation and no attempt was made to optimise the yield.



Scheme 42

2.10.2 Birch reduction-alkylation of benzoic acid with bromide 55: preparation of carboxylic acid (32)

Treating benzoic acid with Li/NH_3 followed by the addition of bromide **55** resulted in the formation of the desired carboxylic acid **32**, albeit in a low yield of 35%, together with 1,4-dihydrobenzoic acid (66%) (Scheme 43). Unreacted bromide **55** was also recovered from the reaction mixture.



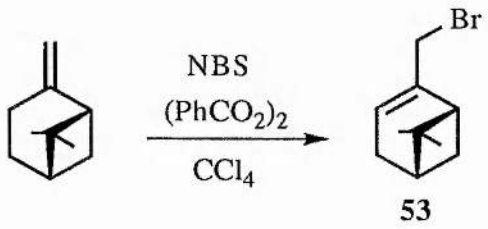
Scheme 43

The yield of **32** *via* this route may have been improved had the experiment been repeated, as had been the case with the reactions involving iodide **36**. Since bromide **55** could be prepared in one step from 3-bromocyclohexene and could undergo the reaction shown in

scheme 43, we thought it would be worthwhile to investigate whether carboxylic acid **33** could be prepared more efficiently from bromide **54** rather than the iodide **57**.

2.10.3 Myrtenyl Bromide (53)

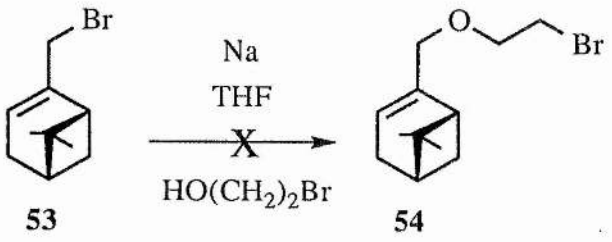
The same experimental procedure for bromination of cyclohexene, which involved using three mole equivalents of the alkene, was followed (section 2.9.4). Thus, pinene was dissolved in CCl_4 and added to NBS containing a small amount of dibenzoyl peroxide (Scheme 44). The mixture was refluxed for approximately 4h after which all the NBS had reacted. The excess pinene was recovered using a rotary evaporator and the resulting residue was distilled to give the product as a clear colourless liquid in moderate yields.



Scheme 44

2.10.4 Attempted preparation of 6,6-dimethyl-2-(2-bromoethoxymethyl) bicyclo[3.1.1]hept-2-ene

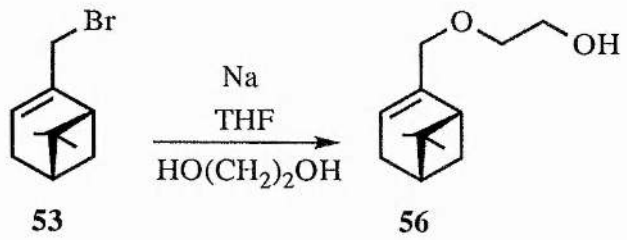
Bromide **53** was dissolved in dry THF to which 2-bromoethanol and sodium wire were added (Scheme 45). The mixture was refluxed overnight but unfortunately no reaction was observed and we returned to the original route.



Scheme 45

2.10.5 6,6-dimethyl-2-(2-hydroxyethoxymethyl)bicyclo[3.1.1]hept-2-ene

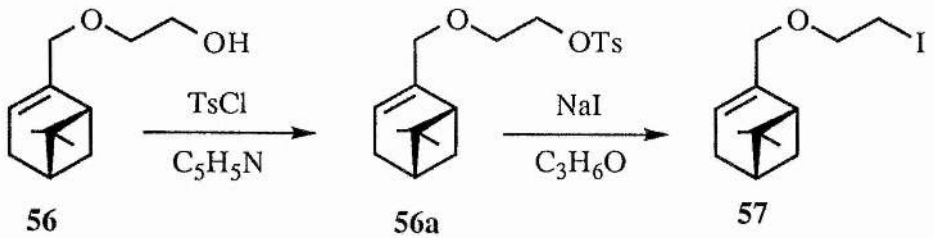
An excess of ethylene glycol dissolved in dry THF containing sodium wire was refluxed overnight and to this mixture was added bromide **53** (Scheme 46). After refluxing this mixture for the appropriate period of time the reaction was worked-up and this resulted in the formation of alcohol **56** as a pale yellow liquid in yields ranging from 85-100%. An attempt was made to distil alcohol **56** in order to improve its purity and obtain its boiling point. However, the boiling point of the alcohol was too high (›100°C) even at low pressure (0.1 mmHg) and hence this was abandoned to avoid decomposition.



Scheme 46

2.10.6 6,6-dimethyl-2-(2-iodoethoxymethyl)bicyclo[3.1.1]hept-2-ene

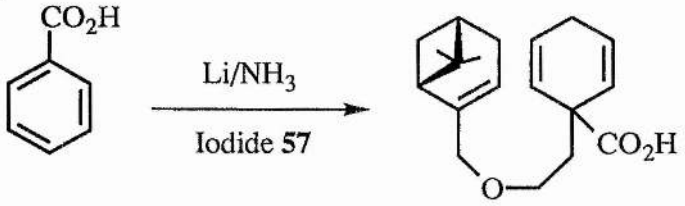
Alcohol **56** was converted into the corresponding tosylate, which when heated with NaI in acetone resulted in formation of the iodide **57** as a dark-red liquid in an excellent overall yield of 96% yield (Scheme 47). The iodide, unlike the alcohol, could be purified by Kugelrohr distillation to give an almost clear and colourless liquid, though we usually used the iodide for the next reaction in the crude form, since this also had a clean ^{1}H NMR spectrum.



Scheme 47

2.10.7 1-[2-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-ylmethoxy)ethyl]-cyclohexa-2,5-diene-1-carboxylic acid (33)

Benzoic acid was dissolved in NH_3 to which Li was added and the resulting mixture was quenched with iodide **57** after the appropriate period of time (Scheme 48). As observed in the synthesis of carboxylic acid **32** the yield of **33** was maximised when benzoic acid was reacted for 0.5h before quenching with the iodide. Thus, the crude yields of **33** were initially in the range 40-50% but were optimised to 70-80%. The product was obtained as a brown, viscous oil which also contained a small amount of benzoic acid and 1,4-dihydrobenzoic acid. Although carboxylic acid **33** could be purified by dry-flash chromatography, the majority of the product co-eluted with the small amount of benzoic acid. The acid was therefore used in the radical fragmentation reaction in the form obtained after the normal work-up procedure. This was considered to be acceptable because the amount of benzoic acid present was not significant and the radical reaction would itself yield benzoic acid.



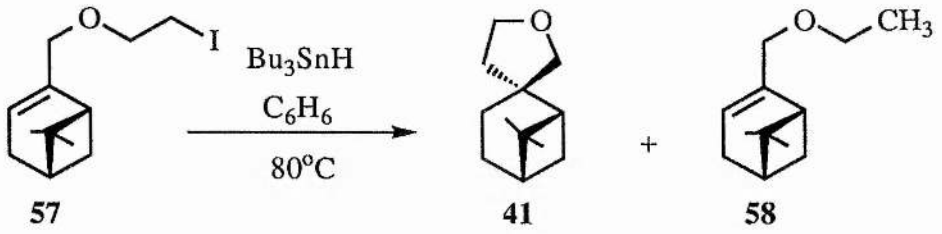
33

Scheme 48

2.10.8 Tin hydride mediated cyclisation of iodide 57

Iodide **57** was dissolved in benzene and treated with tributyltin hydride at 80°C for 3.5h and analysis by GC/MS indicated all of the iodide **57** had disappeared and in its place two compounds were formed. These were identified as cyclic ether **41** and the direct reduction product **58**. Their identity was confirmed as follows: (i) the product of 5-*exo* cyclisation, cyclic ether **41**, was established by careful analysis of the ^{13}C NMR spectrum obtained and also by the fact that compound **41** gave a molecular ion in the GC/MS analysis and (ii) the

direct-reduction product **58** gave identical GC/MS and ^{13}C NMR data to that of a pure sample prepared as described in the next section.



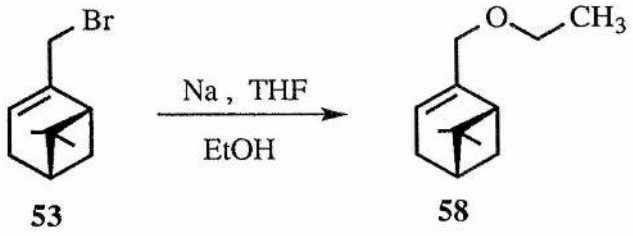
57 **41** **58**

Scheme 49

The tin residues were partly removed using potassium fluoride and the cyclised product **41** and the directly-reduced product **58** were obtained by distillation using a Kugelrohr, giving yields of 31% and 8% respectively. Analysis of the distillation residue by ^{1}H NMR indicated the presence of only tin residues and therefore the remaining 61% of product was unaccounted for. Since the distillation was carried out under low pressure, some of the product may have been lost, although every effort was made to keep the receiver flask at low temperature. The low yield may also have been due to difficulties encountered in the cyclisation step, or perhaps the substrate was susceptible to decomposition under the reaction conditions. Obviously, the yield may have been improved had the reaction been repeated. Although we did not have any available evidence concerning the stereoselectivity of the ring closure, it was expected that the primary alkyl radical would attack the less hindered face of the olefin i.e. *anti* to the methyl groups.

2.10.9 6,6-dimethyl-2-(ethoxymethyl)bicyclo[3.1.1]hept-2-ene (58)

Bromide **53** was added to a mixture of THF, EtOH and sodium wire and stirred for 0.5h. Conventional work-up resulted in the quantitative isolation of compound **58** which was purified by Kugelrohr distillation giving a yield of 81% (Scheme 50).



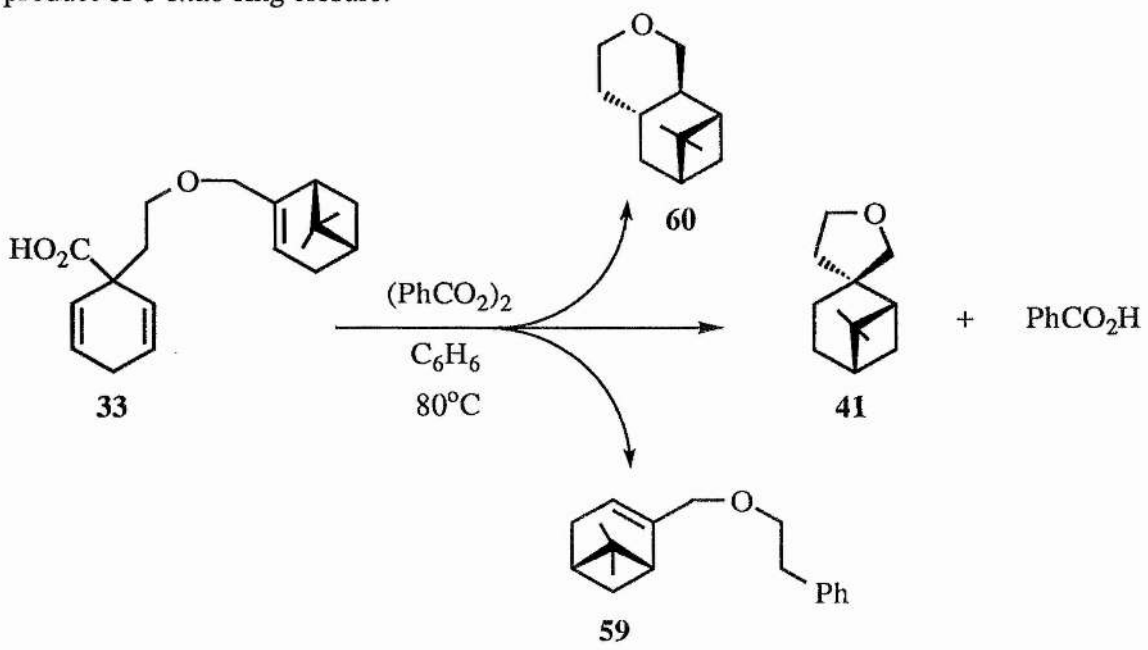
53 **58**

Scheme 50

2.10.10 Radical induced fragmentation of carboxylic acid 33

Since carboxylic acid **33** was difficult to obtain in pure form, it was used for the radical fragmentation reaction in the presence of minor quantities of benzoic acid and 1,4-dihydrobenzoic acid. Thus, carboxylic acid **33** was dissolved in benzene and refluxed in the presence of dibenzoyl peroxide (Scheme 51). Analysis of the reaction mixture by GC/MS indicated the presence of three compounds in addition to benzoic acid. These three products were identified as the desired cyclic ether **41**, the undesired aromatic ether **59** and the cyclic ether **60**. The cyclic ether **41** was confirmed by giving identical GC/MS and ^{1}H NMR data to that observed from the tin hydride mediated cyclisation of iodide **57**. The aromatic product was assigned on the basis that it had a similar retention time to the analogous aromatic product formed from carboxylic acid **32**. The presence of compound **60**, the product of a 6-*endo* cyclisation, is however not certain. Although it has a similar GC retention time to the direct-reduction product **58**, formed from iodide **57** (Scheme 49), they are not identical and they gave significantly different ^{1}H NMR chemical shifts corresponding to the methyl singlets. We also considered the formation of the rearranged product **60a** (Scheme 52). However, there was no evidence for the formation of this product by ^{1}H NMR. No olefinic signal was observed and although the methyl groups in **60a** are diastereotopic, it is unlikely that the difference in chemical shift for such groups would be as large as 0.6 ppm as determined from ^{1}H NMR. The product resulting from ring closure on the opposite face of the olefin was also discounted, since we felt this would have also been observed in the tin hydride method, had such a cyclisation taken place. We

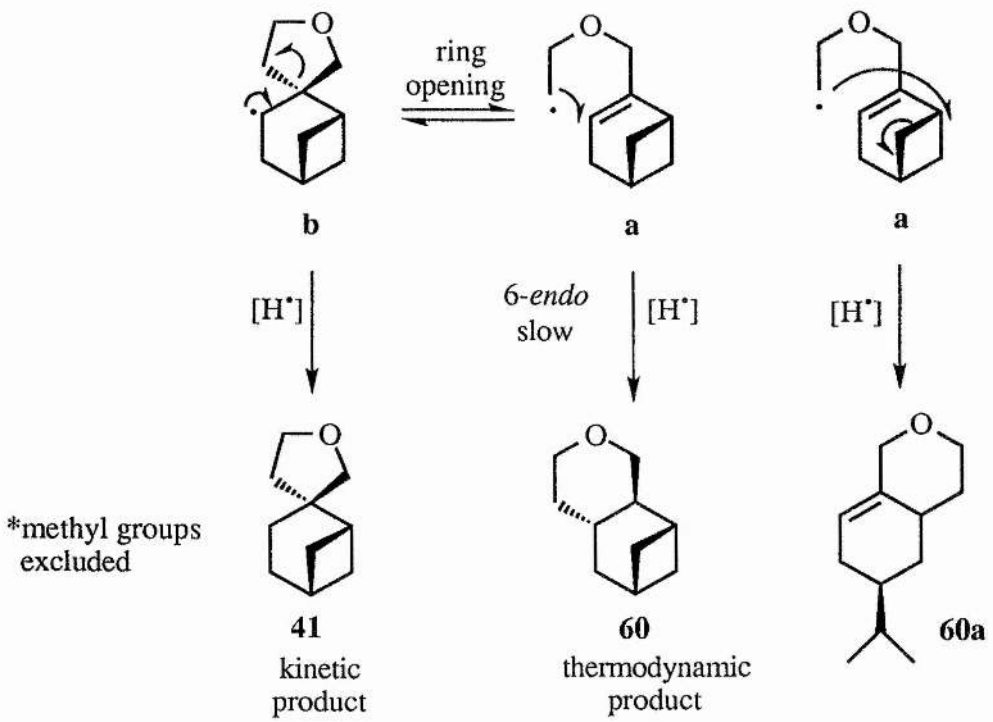
have therefore assigned the third compound from this radical cyclisation reaction to be the product of 6-*endo* ring closure.



Scheme 51

The formation of cyclic ether **60** implied that the initial radical **a** underwent rapid 5-*exo* cyclisation giving the more stable secondary radical **b** (Scheme 52). This radical could then either abstract a hydrogen atom from carboxylic acid **33** (or the solvent) to give the kinetic product **41** or undergo ring opening back to radical **a**. In addition to 5-*exo* cyclisation, radical **a** may have had a long enough lifetime to ring close 6-*endo*, forming the more thermodynamically stable compound **60** after hydrogen atom abstraction. Such a process relieves the steric hindrance at the newly formed quaternary centre present in radical **b**.

The 6-*endo* product was not observed when iodide **57** was treated with tin hydride since radical **a** abstracted hydrogen from tin hydride more rapidly than it could cyclise *via* the 6-*endo* mode. This was also consistent with our kinetic studies which illustrate that hydrogen atom abstraction from carboxylic acids of structure **3** are 1-2 orders of magnitude slower than for tin hydride at the same temperature.[28]



Scheme 52

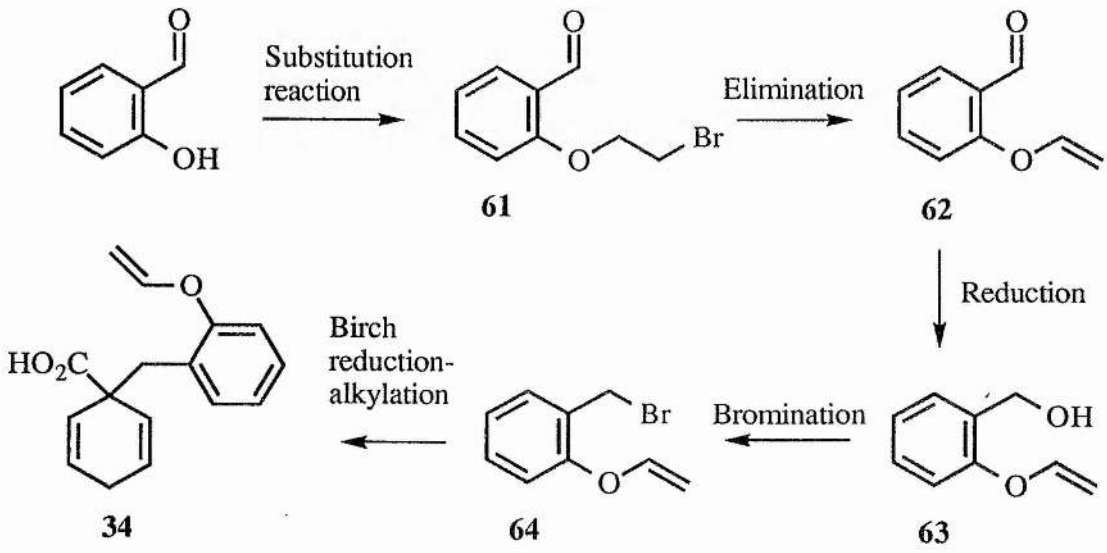
The product mixture was simplified by column chromatography and two main fractions were obtained. The first compound to be eluted was aromatic ether **59** followed by co-elution of compounds **41** and **60**. From this it was possible to calculate the yields of these products which were found to be 7%, 10% and 5% respectively. As in the case for the radical cyclisation of iodide **57** the yield of the desired cyclic ether **41** was poor (10%). Although we could have argued that the radical generated was a primary radical, and hence not particularly stable, we observed that the alternative route leading to the aromatic product **59** was also poor yielding (7%). The remainder of the material which was eluted from the column was not identified, but since the ^{1}H NMR spectra of these later fractions gave poorly resolved signals, it was considered that this might have been polymeric material.

An attempt was also made to isolate the product by distillation but this was unsuccessful and hence the only method remaining was column chromatography, (incidentally, the same technique was attempted to isolate cyclic ether **40** from the radical fragmentation of carboxylic acid **32**, but this did not result in the isolation of compound **40**. It was thought that the compound was simply too volatile for a successful column to work). The results of this particular experiment were therefore disappointing when compared to the analogous

reaction of carboxylic acid **32**, though poor yields were also obtained for the tin hydride mediated radical cyclisation of iodide **57**. It was apparent that carboxylic acid **33** was relatively sensitive to the conditions of a radical reaction, leading to an unselective reaction, ultimately resulting in the formation of unwanted products in addition to the desired cyclic compounds **41** and **60**.

2.11 1-[2-(Ethenyloxy)benzyl]cyclohexa-2,5-diene-1-carboxylic acid (34)

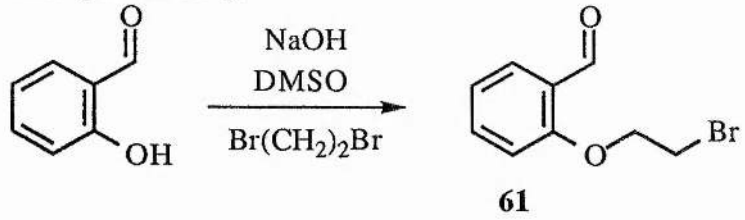
We considered **34** to be an attractive target based largely on the results obtained from the synthesis and radical reactions of 1-benzylcyclohexa-2,5-diene-1-carboxylic acid **17**, i.e. we expected the Birch reduction-alkylation reaction to proceed efficiently, since bromide **64** was benzylic. Furthermore, we expected acid **34** to selectively produce a substituted benzyl radical when treated with dibenzoyl peroxide in refluxing benzene. We realised that due to the stability of benzyl radicals, the rate of cyclisation to give dihydrobenzofuran **42**, would be relatively slow. With the tin hydride-mediated radical reaction, we expected direct reduction to predominate, but thought that if the same radical was generated from carboxylic acid **34**, the cyclisation product would be formed in higher yield due to the poorer hydrogen donating ability of 1-alkylcyclohexa-2,5-diene-1 carboxylic acids. We followed a literature procedure to prepare bromide **64** (Scheme 53).[29]



Scheme 53

2.11.1 2-(2-Bromoethoxy)benzaldehyde (61)

Salicylaldehyde was treated with NaOH in H_2O and refluxed for 2 days in the presence of an excess of 1,2-dibromoethane, yielding 2-(2-bromoethoxy)benzaldehyde **61** as a solid in a crude yield of 60% (Scheme 54).

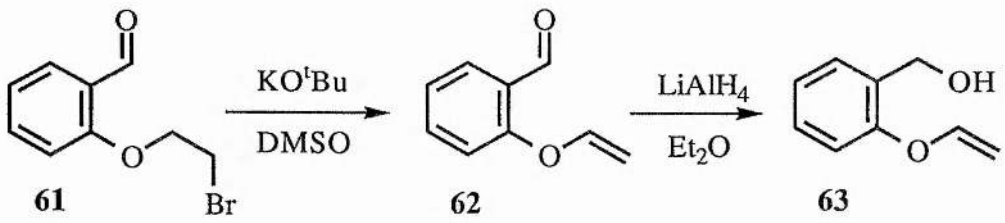


61

Scheme 54

2.11.2 2-(Ethenyloxy)benzyl alcohol (63)

The crude bromide **61** was dissolved in DMSO and treated with potassium-*t*-butoxide, yielding alkene **62** in the range 27-32% (Scheme 55). Although the yield of this reaction was some 20% less than the reported yield,[29] the fact that we did not purify bromide **61** prior to this particular reaction was one reason for the lower yield. Aldehyde **62** was reduced in essentially quantitative yield to give the corresponding alcohol **63** in pure form.

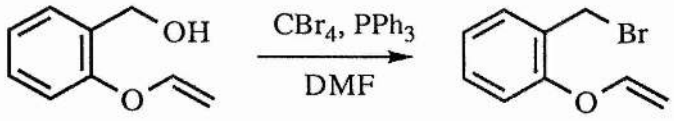


61 **62** **63**

Scheme 55

2.11.3 1-(Bromomethyl)-2-(ethenyloxy)benzene (64)

The alcohol **63** was added to a solution of triphenylphosphine in DMF containing carbon tetrabromide at 0°C and stirred for 90 min at room temperature (Scheme 56). Conventional work-up yielded a mixture of the bromide, carbon tetrabromide and some phosphorous containing impurities. A simple column afforded the bromide as a clear, colourless liquid in 44% yield. This yield could have been increased had other mixed fractions been purified.

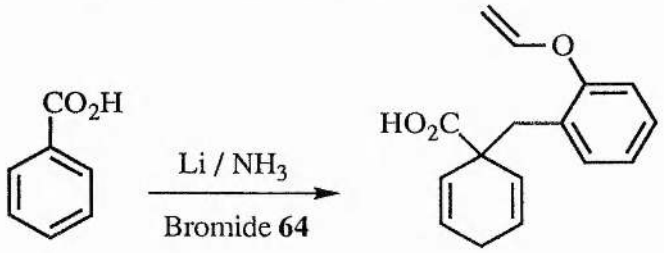


63 64

Scheme 56

2.11.4 1-[2-(ethenyloxy)benzyl]cyclohexa-2,5-diene-1-carboxylic acid (34)

Benzoic acid was dissolved in NH_3 to which Li was added causing the solution to turn blue. After 20 min the mixture was quenched with bromide **64** yielding the product in 25% yield, worsened by the presence of substantial amounts of benzoic acid (Scheme 57). Attempts to isolate carboxylic acid **34** by column chromatography failed as it co-eluted with benzoic acid under a variety of solvent conditions.



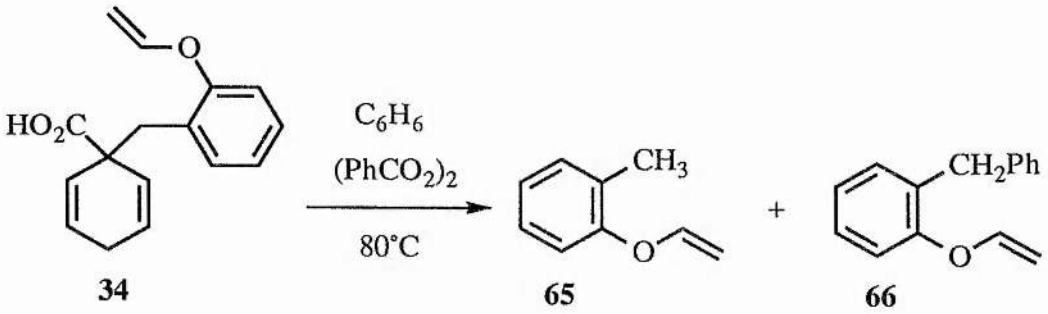
34

Scheme 57

The reaction was repeated a further three times. On one occasion the results were comparable to those given above, on another, a viscous oil, which was a product of decomposition was obtained and in a final experiment the desired product was formed in 50% yield. Pure acid **34** was obtained from this last reaction by recrystallisation, and although the isolated yield was only 25% no attempt was made to isolate the remainder of the product from the mother liquors. It was not possible to rationalise the reasons for the differences in these results, although it was suggested that the bromide should only be added to the mixture 30 min after the last portion of lithium was added. Also, it seemed advantageous if the NH_3 was allowed to evaporate over a 2h period with the aid of a water bath, rather than overnight. The carboxylic acid **34** was reasonably unstable and it was plausible that if it was left in contact with NH_3 for too long then decomposition took place.

2.11.5 Radical fragmentation of carboxylic acid 34

After obtaining acid **34** in pure form, the radical fragmentation of this compound was investigated. We were hopeful that the benzyl radical would be generated smoothly, and that the slow rate of hydrogen abstraction from the cyclohexadienyl carboxylic acid, would encourage such a radical to cyclise onto the proximate olefin, but unfortunately there was no evidence for the cyclised product. Analysis by GC/MS identified 1-(ethenyloxy)-2-methylbenzene **65** and 1-(ethenyloxy)-2-benzylbenzene **66** as the main products in addition to minor amounts of 1-(ethoxy)-2-methylbenzene and 1-(ethoxy)-2-benzylbenzene (Scheme 58).



34 **65** **66**

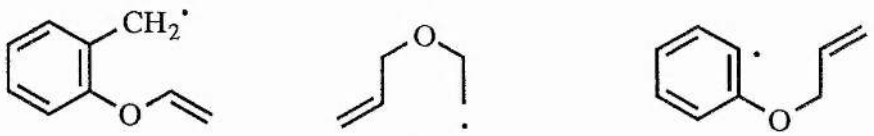
Scheme 58

Attempts were made to isolate these compounds by column chromatography, although analysis by TLC revealed a complex mixture, which was consistent with the ^{1}H NMR spectrum of the crude reaction mixture. As expected it was not possible to isolate any of the products. The first fraction which eluted contained the least amount of material, but this was the only one which gave a considerably simplified ^{1}H NMR spectrum. From this, the yields of 1-(ethenyloxy)-2-methylbenzene **65** and 1-(ethenyloxy)-2-benzylbenzene **66** were only 3% and 4% respectively! Although other fractions gave evidence for these compounds, it was not possible to determine their yields due to the presence of other material which was not identified.

Evidently, this reaction did not follow the intended course. The complex ^{1}H NMR spectrum suggested that carboxylic acid **34** was unstable and produced polymeric material. Indeed, when compound **34** was dissolved in chloroform and left in an NMR tube for 5

days at room temperature, significant decomposition had occurred and a complex ^{1}H NMR spectrum was obtained. We were surprised to find that the aromatic product **66** and the reduction product **65** were formed in comparable yields. This compound was likely to have formed by loss of the hydroxyformyl radical, $^{\bullet}CO_2H$ from the corresponding cyclohexadienyl radical, and not by addition of the benzyl radical to benzene. This was easily proven, since the same product was obtained when the reaction was repeated in deuterated benzene. This was an unexpected result as we anticipated that the benzyl radical would be produced more easily than the hydroxyformyl radical due to its greater stability.

Finally, we should comment on the absence of the cyclised product. After building a simple model of benzyl radical **67**, we saw no reason why such a radical would not cyclise, although we did realise that such a process would be less feasible than for the similar cyclisations of radicals **68** and **69** (Scheme 59). For example, alkyl radical **68** is a primary radical which has more freedom to orientate itself into a reactive conformation. Aryl radical **69** also has more freedom than radical **67** and furthermore, it is a sigma radical and will therefore cyclise rapidly. Although benzyl radical **67** would have a slower rate of cyclisation, this was one of the features we were interested in, since we wanted to find out if the cyclohexadienyl acids would permit relatively slow cyclisations to occur. The fact that none of the cyclised product was observed but the reduction product was, indicated that the benzyl radical generated did not cyclise.



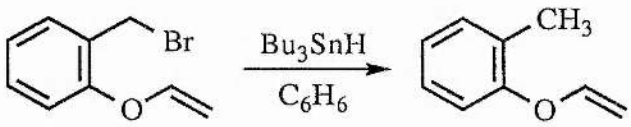
67 **68** **69**

Scheme 59

2.11.6 Tin hydride mediated reduction of bromide 64

Bromide **64** and 1.1 equivalents of tributyltin hydride were dissolved in benzene and irradiated with light for 6h at room temperature (Scheme 60). The reaction was monitored

by TLC and worked up when the reaction was complete. The major product was 1-(ethenyloxy)-2-methylbenzene **65**, although analysis by GC/MS identified a minor amount of 1-(ethoxy)-2-methylbenzene and another product which was not identified. The crude yield of the aromatic product **65** was *ca.* 90% and no attempt was made to purify the product, because the ^{1}H NMR spectrum revealed that the product was essentially pure. As expected, the tributyltin radical attacked the bromine atom of bromide **64** to give the corresponding benzyl radical, which abstracted hydrogen from the tin hydride to give the aromatic product **65**.



64 **65**

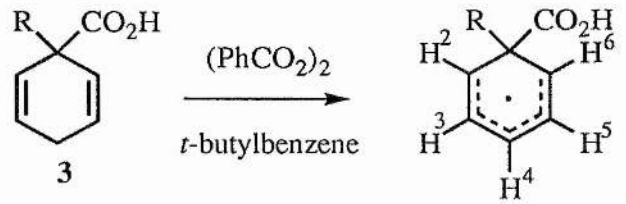
Scheme 60

2.12 EPR spectroscopic studies on 1-alkylcyclohexa-2,5-diene-1-carboxylic acids.

Introduction

Electron Paramagnetic Resonance (EPR) spectroscopy is a technique used to investigate molecules containing one or more unpaired electrons, such as free radicals and transition metal complexes. The method is similar to NMR spectroscopy except that EPR is concerned with electrons, whereas NMR is associated with atomic nuclei. A recent review covers some important aspects of EPR spectroscopy of organic radicals including the generation of transient radicals for EPR spectroscopy, characterisation of organic radicals, determination of radical conformations and the kinetics of free radical reactions.[30]

We have used EPR spectroscopy to prove that carboxylic acids of structure **3**, can produce cyclohexadienyl radicals **4** when treated with dibenzoyl peroxide, since the resulting radical produces a characteristic spectrum.



3 **4**

The EPR spectrum obtained for a particular radical, allows one to predict the type of radical present. It is, for example, relatively straightforward to establish whether a particular radical is primary, secondary or tertiary in nature. Unpaired electrons which are delocalised can also be identified. In such cases, the electron can interact with various atomic nuclei and a more complex spectrum usually results. An example of this is the cyclohexadienyl radical **4** which we have studied. The delocalised electron interacts with five hydrogen atoms and the resulting spectrum is a doublet of triplets of triplets. This characteristic signal allows one to easily identify when the cyclohexadienyl radical is present. Furthermore, β-

scission of a cyclohexadienyl radical yields the corresponding alkyl radical R•. Hence, we planned to use EPR spectroscopy to check for the ease of this process and possibly determine the rate constant for fragmentation. It follows that EPR spectroscopy is a convenient method for detecting radicals and also for providing information regarding the structure of the radical.

Results and discussion

We have investigated 8 different cyclohexadienyl acids **3** where R has been methyl, ethyl, *i*-propyl, cyclopentyl, *t*-butyl, benzyl, phenyl and cyclohex-2-enyloxyethyl.

Preparation of EPR Samples

1-*tert*-Butylcyclohexa-2,5-diene-1-carboxylic acid (20-30 mg) was added to a quartz EPR tube, 2-3 drops of di-*t*-butyl peroxide were added and the EPR tube was attached to a vacuum line connected to a cyclopropane storage bulb. The sample was cooled using a flask containing liquid nitrogen and the taps connecting both the EPR tube and the bulb of cyclopropane were opened, until sufficient cyclopropane had condensed into the EPR tube. The sample was degassed using the "freeze, pump and thaw" technique, flame sealed and immediately used in the EPR experiment. The lower freezing point of cyclopropane compared to *t*-butylbenzene allowed low temperature studies to be carried out. 1-Benzylcyclohexa-2,5-diene-1-carboxylic acid was also dissolved in cyclopropane. For the remaining acids, the carboxylic acid (20-30 mg) was added to a sample vial and dissolved in *t*-butylbenzene and 2-3 drops of BOOB were added. The contents were transferred to an EPR tube, the sample was degassed with nitrogen for 15-20 min, capped and the EPR experiment was carried out immediately after degassing.

The EPR experiments

The EPR tube was placed in the cavity of the EPR spectrometer, the experimental parameters were adjusted, the sample was exposed to radiation and the spectrum was recorded. The settings of the EPR spectrometer were optimised during the course of the

experiment and the temperature in the EPR cavity was varied until we obtained the best spectrum for the cyclohexadienyl radical. In order to observe the alkyl radical, generated by fragmentation of the cyclohexadienyl radical, the temperature was increased at intervals. The cavity was never heated to temperatures exceeding 373K.

Table 1 provides information regarding these experiments: (i) the temperature required to observe the cyclohexadienyl radical (T), (ii) the hyperfine coupling constants (hfs) resulting from the 5 hydrogen nuclei and (iii) the temperature required to obtain a spectrum consisting of both the cyclohexadienyl and alkyl radical at approximately equal concentrations ($T_{1/2}$).

Table 1. EPR data for radicals obtained from some cyclohexadienyl carboxylic acids[a]

R	T. (K)	a (H^4) (G)	a ($H^{2,6}$) (G)	a ($H^{3,5}$) (G)	a (H^{other}) (G)	$T_{1/2}$ (K)
Me[b]	220	13.20	9.2	2.65		> 400
Et[b]	240	13.1	8.90	2.8		> 365
^{i}Pr[b]	220	13.30	9.2	2.8		265
^{t}Bu	145	13.3	9.2	2.8		155
$^{c}C_5H_9$	215	13.65	9.2	2.8		290
$PhCH_2$	150	13.2	9.2	2.7	1.2 (1H)	195
Ph	220	13.4	9.25	2.7		
R in acid **32**	225	13.2	9.2	2.7		>380

[a] All g-factors were 2.003±0.001. [b]Data which had been determined previously.[31]

Some general observations

(i) For the majority of the carboxylic acids investigated, the temperature at which the cyclohexadienyl radical was most clearly observed, was in the range 215-240K.

(ii) For the *t*-butyl and benzyl substituted carboxylic acids, (**16** and **17** respectively), the temperature of the EPR cavity had to be lowered to 145-150K in order to see the cyclohexadienyl radical instead of the corresponding alkyl radical.

(iii) The methyl, ethyl and cyclohex-2-enyloxylethyl (generated from acid **32**) radicals were not observed when the respective carboxylic acids were heated in the cavity.

(iv) The *i*-propyl, *t*-butyl, cyclopentyl and benzyl radicals were all clearly identified when the corresponding carboxylic acids were heated in the cavity. The temperature required to observe these radicals followed roughly the expected trend in terms of the stability of these radicals i.e.,

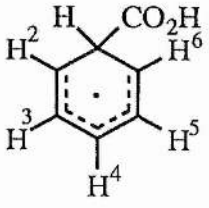
t-butyl > benzyl > cyclopentyl ~isopropyl> primary> methyl

increasing stability ←——— ———→ increasing temperature required to observe the alkyl radical

although the *t*-butyl radical was generated more readily than expected.

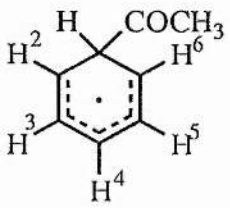
(v) As mentioned in (iv), the *i*-propyl, *t*-butyl, cyclopentyl and benzyl carboxylic acids generated the corresponding alkyl radicals which were observed by EPR. Furthermore, when the temperature of the cavity was lowered the signal corresponding to the alkyl radical was replaced with the original signal corresponding to the cyclohexadienyl radical.

(vi) All of the cyclohexadienyl radicals detected gave very similar hyperfine coupling constants. They were also comparable to hfs reported for the related cyclohexadienyl radicals **66**, **67** and **68**.[32]



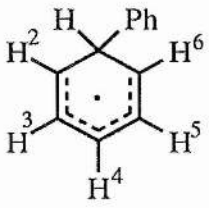
66

a (2H) (2,6) = 9.39
a (2H) (3,5) = 2.65
a (1H) (4) = 13.65



67

a (2H) (2,6) = 9.0
a (2H) (3,5) = 2.80
a (1H) (4) = 13.0



68

a (2H) (2,6) = 8.92
a (2H) (3,5) = 2.75
a (1H) (4) = 13.18

(vii) We intended to measure the rate of fragmentation of the cyclohexadienyl radicals, but unfortunately the quality of the spectra obtained were not sufficient for accurate measurements to be made.

Figures 1-3 illustrate some of the EPR spectra obtained during our investigations. Figure 1 provides three spectra. The top spectrum corresponds to the cyclohexadienyl radical formed from carboxylic acid **15**. The middle spectrum corresponds to the cyclopentyl radical generated on heating the cyclohexadienyl radical and the lower spectrum is a simulation of the cyclopentyl radical using the hyperfine coupling constants measured from spectrum 2 (a(1H)= 22.1 and a(4H)= 35.2G). The top spectrum of figure 2 corresponds to the cyclohexadienyl radical formed from benzyl carboxylic acid **17**. The lower spectrum shows the benzyl radical generated on heating this cyclohexadienyl radical. Figure 3 provides one spectrum corresponding to the cyclohexadienyl radical of 1-phenylcyclohexa-2,5-diene-1-carboxylic acid. The preparation of this acid is described in Chapter 3.

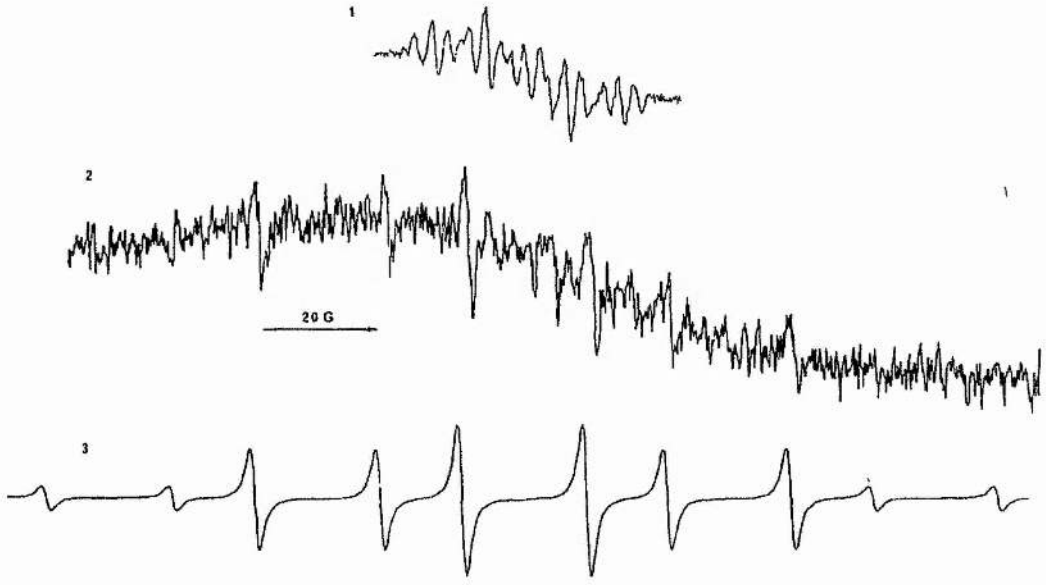


Figure 1. EPR spectra of (**1**) the cyclohexadienyl radical generated from carboxylic acid **15** at 215K, (**2**) the cyclopentyl radical at 320K and (**3**) the simulated spectrum of the cyclopentyl radical.

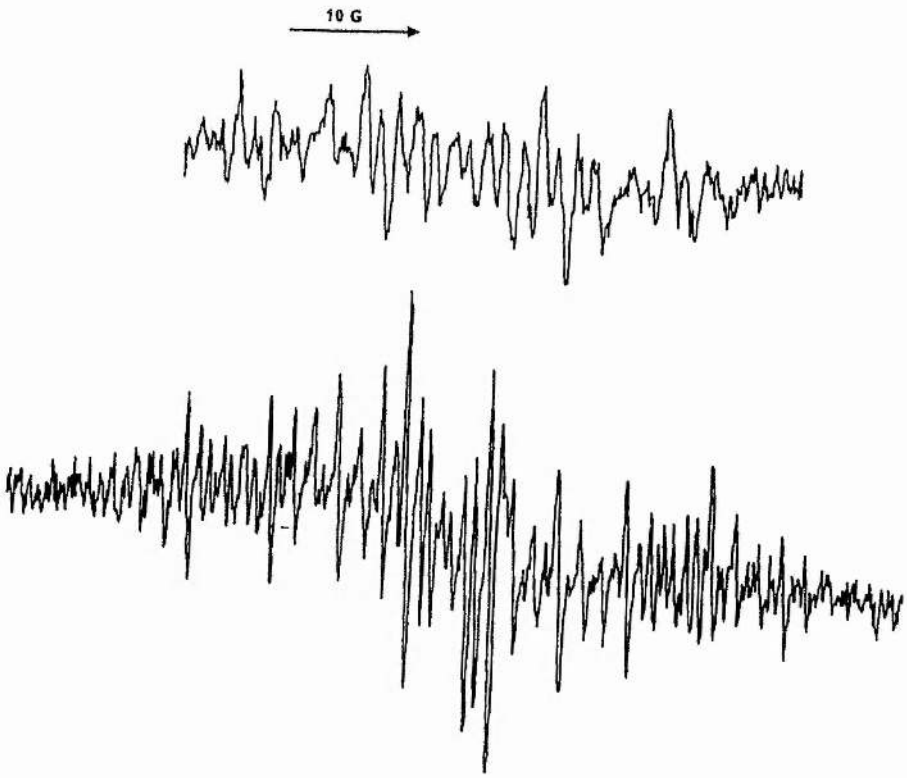


Figure 2. EPR spectrum of the cyclohexadienyl radical generated from carboxylic acid **17** at 175K (top) and the benzyl radical at 210K.

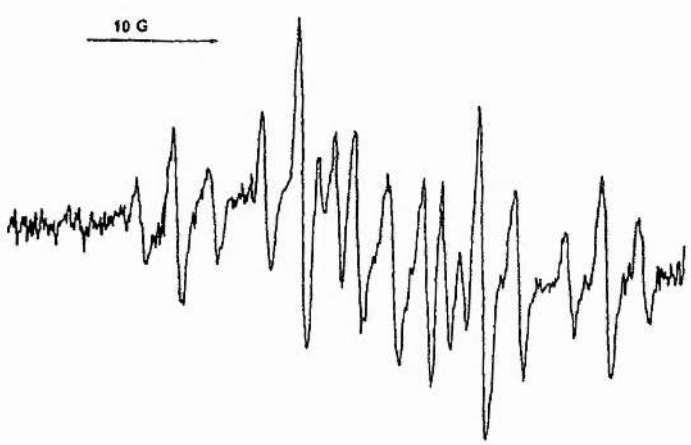


Figure 3. EPR spectrum of the cyclohexadienyl radical generated from 1-phenylcyclohexa-2,5-diene-1-carboxylic acid.

Conclusions and future work

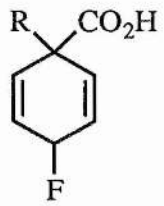
This chapter presents a discussion of our investigations into the possible use of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids as sources of alkyl radicals, and Table 2 provides a summary of the main results.

For our method to be an attractive alternative to the tin hydride route, it was necessary that the 1-alkylcyclohexa-2,5-diene-1-carboxylic acids could be prepared in high yield, because it already incorporates one extra step in the synthesis. Unfortunately, the Birch reduction-alkylation reaction does not always give high yields of functionalised cyclohexadienyl acids (Table 2, entries 2 and 6). The carboxylic acids investigated can participate in radical chain reactions to generate alkyl radicals, although the chains are relatively short. Therefore, portionwise addition of dibenzoyl peroxide during the course of the reaction is required to ensure complete reaction of the carboxylic acid. We have shown that acids **15, 16** and **17** act as sources of secondary, tertiary and benzyl radicals respectively, and have directly observed these radicals by EPR spectroscopy. Moreover, we have succeeded in producing adducts derived from addition of such radicals to olefins. Although cyclohexenone is apparently a rather poor radical acceptor,[33] we observed the 3-alkylcyclohexanone adducts in experiments involving acids **15-17** and in experiments involving acids **15** and **17**, these adducts were isolated and characterised. The yields from these reactions were also encouraging, especially since cyclohexenone was not used in excess, as is commonly the case. The byproducts from these reactions are thought to be due to loss of a hydroxyformyl radical from the intermediate cyclohexadienyl radical. Acid **15** was also reacted in the presence of acrylonitrile and vinyl benzoate. In the latter case, no attempt was made to isolate the product by column chromatography. Problems were initially encountered with acrylonitrile due to its tendency to polymerise, although when the reaction temperature was reduced, the desired adduct was observed. However, due to the presence of the double addition product in comparable amounts and also the triple addition product, it was not possible to determine an NMR yield with any reasonable accuracy.

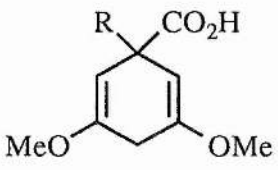
Cyclohexadienyl radicals were also observed when the acids **32-34** were examined by EPR spectroscopy, which was further evidence for the ease of allylic hydrogen atom abstraction. The benzyl radical produced from the carboxylic acid **34** was also detected. When acids **32** and **33** were reacted, cyclised products were formed. Acid **32** yielded 7-oxabicyclo[4.3.0]nonane **40** in comparable yield to the tin hydride method. Acid **33** afforded the spiro product **41** in 10% yield compared to the 31% yield obtained by the tin hydride mediated cyclisation of the corresponding iodide. The low yields obtained were not unexpected since the radical generated attacked a hindered olefinic carbon atom and resulted in the formation of a spiro junction, which presumably impaired further steric hindrance. Acid **34** was an unstable compound which decomposed readily at room temperature, although EPR studies gave clear evidence for the formation of the benzyl radical when photolysed in the presence of BOOB. The absence of the cyclic product was due to the very slow cyclisation step. Another reason for lower yields obtained, was due to the competitive loss of a hydroxyformyl radical from the corresponding cyclohexadienyl radical, which became more pronounced as the 1-alkyl substituent increased in size. For example, acid **32** produced a comparable proportion of the aromatic byproduct relative to the cyclised product (entry 4).

There is the opportunity for more research to be directed towards the 1-alkylcyclohexa-2,5-diene-1-carboxylic acids. It is feasible that the chain process might occur more efficiently if the rate of allylic hydrogen abstraction from the cyclohexadienyl acid could be increased. For example, carboxylic acid **69** may provide a more labile hydrogen due to the electron-withdrawing fluorine atom (Scheme 61). However, when we attempted the Birch reduction-alkylation of 4-fluorobenzoic acid, quenching with cyclopentyl bromide, the isolated product was 1-cyclopentylcyclohexa-2,5-diene-1-carboxylic acid **15**. Thus, the C-F bond was replaced with a C-H bond. Perhaps a more realistic alternative would be carboxylic acids of type **70**. Birch reduction of 3,5-dimethoxybenzoic acid yields 3,5-dimethoxycyclohexa-2,5-diene-1-carboxylic acid and it is plausible that the Birch

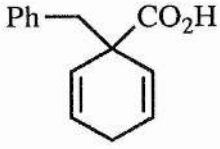
reduction-alkylation reaction would provide a range of acids.[34] Mander has already demonstrated that such compounds can be prepared by the Birch reduction-alkylation technique and also commented on their tendency to decompose, presumably *via* a radical process.



69



70

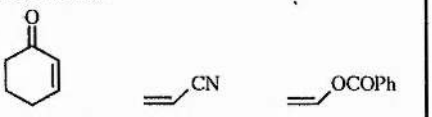
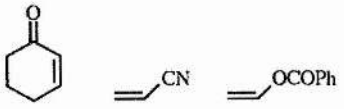
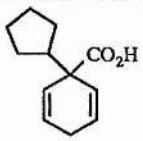
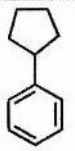
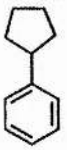
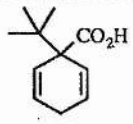
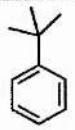
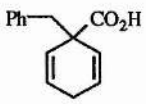
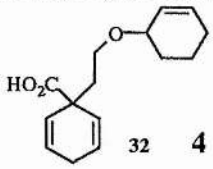
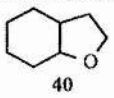
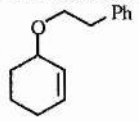
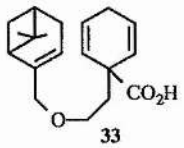
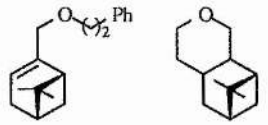
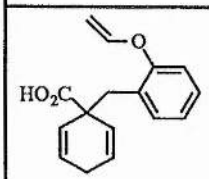
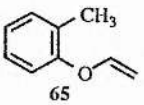
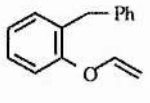


17

Scheme 61

Finally, although it has not been mentioned in this section, 1-benzylcyclohexa-2,5-diene-1-carboxylic acid **17** has been investigated as a possible chain-transfer agent in the polymerisation of styrene.[35] The conventional reagents for controlling this process are thiols which are not ideal. The attractive feature of cyclohexadienyl acid **17** is its ability to generate a benzyl radical which could add to a molecule of styrene, maintaining the aromatic backbone, and initiate polymerisation. In an ideal situation, the length of the polymer chain would be controlled by the concentration of the chain-transfer agent. We found that as the concentration of carboxylic acid **17** in styrene, containing a catalytic amount of AIBN, was increased, the average molecular weight of the styrene polymer decreased. The advantage with this method is the fact that the byproduct is benzoic acid which is relatively benign. Unfortunately, however, the amount of time devoted to this area of research was not sufficient to provide conclusive results.

Table 2: Summary of the main results from this chapter

Acid Entry N°	Yield	Inter / Intramolecular radical reactions 	Byproducts 
 15 **1**	71%	30% nd (36%)[b] (59%)[a]	 Dimer and trimer nd  (9%) (21%)
 16 **2**	18% 29%	(25%)	 (3%)
 17 **3**	100%	52%[b]	$PhCH_2Ph$ 3%
 32 **4**	42% 75%[c]	 40 (55%) [60%][d]	 (40%)
 33 **5**	67%[c]	 41 10% [31%]	 8% 5%
 34 **6**	25% (50%)	 65 3% [ca.90%]	 4%

[a]Yields in round brackets are crude yields; [b]Yield based on the amount of acid reacted; [c]Some benzoic acid present; [d]Yields in square brackets refer to the yield of product obtained from the tin hydride method; nd=not determined.

3 Experimental

^{1}H NMR spectra were obtained using a Varian Gemini 200 MHz spectrometer unless otherwise stated, in which case the spectrum was obtained using a Bruker AM 300 spectrometer. The majority of the ^{13}C NMR spectra were run at 75 MHz using the Bruker mentioned above unless otherwise stated, in which case the spectrum was run at 50 MHz on the Gemini mentioned above. All samples were dissolved in deuterated chloroform unless otherwise stated, using Me_4Si as an internal standard. GC/MS work was carried out using a Finnigan Incos 50 quadrupole mass spectrometer interfaced with a Hewlett-Packard HP5890 capillary gas chromatograph fitted with a column coated with methylsilicone as the stationary phase. Mass spectra were obtained with 70 eV electron impact ionisation on a Kratos M25RF spectrometer. Solvents which have been removed using a rotatory evaporator are referred to as being evaporated. All NaOH and HCl solutions were approximately 2M. Chromatographic purification was carried out using silica gel (either Sorbsil C60 40/60A or BDH 40-63 μm) eluting with the given solvent mixture. Each experimental procedure is referred to the corresponding scheme in the results and discussion section to allow a quick reminder of the actual reaction discussed. Some molecular structures have also been included in this section to aid assignment of carbon and hydrogen spectra.

1-Cyclopentylcyclohexa-2,5-diene-1-carboxylic acid (15) (Scheme 12)

Ammonia (600 cm^3) was added to benzoic acid (10 g, 82 mmol) with careful stirring. To this, Li (1.6 g, 0.231 mol) was added portionwise until a permanent blue colour persisted, followed by dropwise addition of bromocyclopentane (25 cm^3, 0.233 mol). The reaction mixture was left for 1h whilst the NH_3 evaporated and ice was added to the remaining solid followed by dilute H_2SO_4. The product was extracted with ether (3 x 150 cm^3) and the combined ethereal extracts were dried ($MgSO_4$) and the solvent was evaporated leaving a solid which was recrystallised in light petroleum, yielding the title compound as fine white crystals (7.5 g, 48%†), mp 115°C (lit.,[13] mp 96°C) (Found: C, 75.28; H, 8.58. Calc. for $C_{12}H_{16}O_2$: C, 74.95; H, 8.40%); δ_H 1.2-1.4 (2 H, m, methylene-H, cyclopentyl ring) 1.4-1.7 (6 H, m, methylene-H, cyclopentyl ring), 2.3-2.5 (1 H, q^i, *J* 8, *t*-H, cyclopentyl ring), 2.6-2.7 (2 H, s, allylic-H), 5.7-6.0 (4 H, m, olefinic-H); δ_C 25.7, 26.5, 27.2 (5 x methylene-C), 47.8 (*t*-C), 49.8 (quaternary-C), 125.9, 126.4 (4 x olefinic-C), 180.2 (carbonyl-C).† Concentration of the mother liquors gave a further 3.95 g of product (crude yield 71%).

1-*t*-Butylcyclohexa-2,5-diene-1-carboxylic acid (16) (Scheme 12)

Prepared by essentially the same procedure as described above, except that the reaction mixture was quenched with *t*-butyl bromide. Purification by dry flash chromatography, eluting with 20% ethyl acetate in light petroleum yielded the title compound as white crystals (2.6 g, 18%), mp 101°C (lit.,[13] mp 105°C) (Found: C, 73.47; H, 9.35. Calc. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95%); δ_H 1.00 (9 H, s, *t*-butyl-H), 2.57-2.63 (2 H, s, allylic-H), 5.88-6.10 (4 H, m, olefinic-H); δ_C 26.0 (3 x methyl-C), 26.2 (allylic-C), 38.6 (quaternary-C), 52.9 (quaternary-C), 125.5, 126.2 (4 x olefinic-C), 180.4 (carbonyl-C).

1-Benzylcyclohexa-2,5-diene-1-carboxylic acid (17) (Scheme 12)

Prepared by essentially the same procedure as described above, except that the reaction was quenched with benzyl chloride. The title compound was obtained in pure form after recrystallisation from cyclohexane (7.24 g, 41%†), mp 76-77°C (lit.,[13] mp 76°C) (Found:

C, 78.17; H, 6.67. Calc. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59%); δ_H 2.27-2.63 (2 H, m, allylic-H), 3.03 (2 H, s, benzylic-H), 5.80-5.90 (4 H, m, olefinic-H), 7.11-7.29 (5 H, m, arom-H); δ_C 25.0 (allylic-C), 46.1 (benzylic-C), 48.8 (quaternary-C), 126.5, 126.7, 127.9, 130.7, 136.1 (10 x olefinic, arom-C), 179.7 (carbonyl-C). †Concentration of the mother liquors provided a further 7.68 g of product (crude yield 85% and quantitative on a 1 g scale).

1-*t*-Butylcyclohexa-2,5-diene-1-carboxylic acid (16) (Scheme 12)

Ammonia (300 cm^3) was added to benzoic acid (3 g, 24.6 mmol) and to this was added Li (0.48 g, 69.2 mmol) causing the solution to turn blue. The mixture was stirred for 0.5h and quenched with *t*-butyl iodide (13.2 g, 72 mmol) causing immediate decolourisation. The reaction was worked up in a manner identical to previously described, yielding a pale yellow solid (4.0 g) containing the title compound (2 g, 45%), benzoic acid and 1,4-dihydrobenzoic acid. The title compound (1.3 g, 29%) was obtained as a pale brown crystalline solid by dry flash chromatography, eluting with 25% ethyl acetate in light petroleum. The product gave identical ^1H and ^{13}C NMR spectra identical to those given previously.

3-Cyclopentylcyclohexanone (18)

Radical reaction involving carboxylic acid 15 and cyclohexenone (Scheme 13)

1-Cyclopentylcyclohexa-2,5-diene-1-carboxylic acid (1g, 5.2 mmol), cyclohexenone (0.5g, 5.2 mmol) and *t*-butyl peroxybenzoate† (0.1g, 10%wt) were dissolved in benzene (5 cm^3) and refluxed for 1 week, during which a further 4 portions of initiator were added (0.55 g, 55% wt. overall). Analysis of the reaction mixture by GC/MS indicated the presence of unreacted cyclohexenone, 3-cyclopentylcyclohexanone and phenylcyclopentane‡. The reaction contents were diluted with ether (50 cm^3) and washed with NaOH (3 x 25 cm^3). The alkaline extracts were combined, washed with light petroleum and the organic fractions were combined, dried ($MgSO_4$) and the solvent was evaporated yielding an oil (0.91 g; 0.51 g, 59%, 3-cyclopentylcyclohexenone and 0.07 g,

9%, phenylcyclopentane). The mixture was purified by column chromatography using 5% ethyl acetate in light petroleum, yielding the title compound as a colourless oil (0.27 g, 31%), (lit.,[36] bp 82°C at 1 mmHg); δ_H (300 MHz) 1.02-1.22 (2 H, m, methylene-H, δ to carbonyl), 1.34-1.44 (1 H, m, methylene-H, β to carbonyl), 1.45-1.80 (9 H, m; 8 H, methylene-H, cyclopentyl ring and 1 H, β to carbonyl), 1.87-2.00 (1 H, m, *t*-H, cyclohexyl ring), 2.00-2.13 (2 H, m, methylene-H, α to carbonyl), 2.20-2.42 (2 H, m, methylene-H, α to carbonyl), 2.43-2.54 (1 H, *t*-H, cyclopentyl ring); δ_C 25.2, 25.4 (2 x C, methylene-C, cyclopentyl ring), 30.3, 30.4, 30.7 (4 x methylene-C), 41.5 (methylene-C, α to carbonyl), 45.0 (*t*-C), 46.2 (*t*-C), 47.5 (methylene-C, α to carbonyl), 212.4 (carbonyl-C);*m/z* 166 (M^+, 27%), 148 (10), 123 (38), 108 (53), 97 (100), 81 (18), 69 (40), 67 (42), 55 (48) (Found: M^+, 166.1365. $C_{11}H_{18}O$ requires 166.1358). The acid compounds were regenerated using excess H_2SO_4, extracted with ether, dried ($MgSO_4$) and the solvent was evaporated yielding benzoic acid (1.12 g) as the only product. †Dibenzoyl peroxide and *t*-butyl peroxybenzoate were both found to be appropriate initiators. ‡Identified by comparison with a sample prepared by the procedure below.

Phenylcyclopentane (Scheme 16)[14]

Polyphosphoric acid (184 g) was heated on an oil bath at 80-85°C followed by the addition of cyclopentanol (18.4 g, 0.21 mol) and benzene (49.7 g, 1.56 mol). The mixture was refluxed for 1.5h, the reaction contents were diluted with H_2O (900 cm^3) and the aqueous layer was extracted with benzene (100 cm^3). The combined organic extracts were dried ($MgSO_4$), the majority of the benzene was evaporated and the title compound was obtained as a clear, colourless liquid after distillation (7.5 g, 24%), bp 92°C at 12 mmHg (lit.,[14] bp 215-217°C at atmospheric pressure); δ_H 1.6-2.0 (6 H, m, methylene-H, cyclopentyl ring), 2.1-2.3 (2 H, m, methylene-H, cyclopentyl ring), 3.0-3.2 (1 H, q^i, *J* 10, *t*-H, cyclopentyl ring), 7.2-7.5 (5 H, m, aromatic-H); δ_C 25.4, 34.5, 45.8, 125.5, 127.0, 128.1, 146.4.

3-*t*-Butylcyclohexanone (22)

Radical reaction involving carboxylic acid 16 and cyclohexenone (Scheme 17) 1-*t*-Butylcyclohexa-2,5-diene-1-carboxylic acid **16** (1.0 g, 6 mmol) cyclohexenone (0.54 g, 6 mmol) and dibenzoyl peroxide (0.5 g, 50% wt.) were refluxed in benzene (5 cm^3) for 24 h. Analysis of the reaction mixture by GC/MS indicated the presence of 3-*t*-butylcyclohexanone, the phenyl adduct, *t*-butyl benzene, benzoic acid, unreacted cyclohexenone and two other compounds, one of which was a small amount of the unreacted starting acid **16**. The product mixture was extracted with NaOH (5 cm^3) and the alkaline fraction was extracted with benzene (2 x 10 cm^3). The aqueous fraction was acidified with excess acid and extracted with ether (3 x 25 cm^3), the ethereal extracts were combined, dried ($MgSO_4$) and the solvent was evaporated yielding a solid (0.54 g) which was a mixture of benzoic acid and also some unreacted acid **16**. The original benzene fractions were combined, dried ($MgSO_4$) and the solvent was evaporated to yield an orange oil (0.55 g). An attempt to isolate the adduct by flash chromatography resulted in poor recovery of material. The yields were estimated from the ^1H NMR of the mixture which indicated 25% of the title compound and 3% of *t*-butylbenzene.

3-Benzylcyclohexanone (23)

Radical reaction involving carboxylic acid 17 and cyclohexenone (Scheme 18) 1-Benzylcyclohexa-2,5-diene-1-carboxylic acid (2.5 g, 12 mmol), cyclohexenone (1.13 g, 12 mmol) and dibenzoyl peroxide (0.25 g, 10% wt) were refluxed in benzene (20 cm^3) under an atmosphere of N_2 for 5 days, during which a further 0.75 g (40% wt. overall) of initiator was added. Analysis of the reaction mixture by GC/MS indicated the presence of cyclohexenone, diphenylmethane, 3-benzylcyclohexanone and benzoic acid. The reaction contents were diluted with ether (50 cm^3) and extracted with NaOH (3 x 10 cm^3). The combined alkaline extracts were washed with light petroleum (20 cm^3), neutralised with excess HCl and extracted with ether (3 x 50 cm^3). The combined ethereal extracts were dried ($MgSO_4$) and the solvent was evaporated yielding a brown solid (2.08 g; 1.11 g unreacted starting acid **28**; 0.96 g benzoic acid). The original ether fraction was combined

with the petroleum washing, dried ($MgSO_4$) and the solvent was evaporated yielding an oil (1.42 g). This was purified by column chromatography yielding the title compound as a pale yellow oil (0.64 g 52%†); δ_H‡ 1.35-2.50 (9 H, m, methylene, methine-H), 2.60-2.67 (2 H, d, *J* 6.2, benzylic-H), 7.10-7.40 (5 H, m, arom-H); δ_C (50MHz), 25.3, 31.0 (2 x methylene-C), 41.0, 41.6, 43.1, 48.0 (4 x C; 3 x methylene-C and 1 x *t*-C), 126.3 (*p*-arom-C), 128.5, 129.2 (4 x arom-C), 139.5 (*ipso*-arom-C), 211.8 (carbonyl-C). †Based on the amount of acid reacted. ‡Identical ^{1}H NMR spectrum to that given by Yamamoto.[37]

3-Cyclopentylpropionitrile (24)

Radical reaction involving carboxylic acid 15 and acrylonitrile (Scheme 20)

1-Cyclopentylcyclohexa-2,5-diene carboxylic-1-acid **15** (0.5 g, 2.6 mmol), acrylonitrile (0.138 g, 2.6 mmol), di-*t*-butyl peroxide (0.1 g, 20% wt.) and benzene (5 cm^3) were added to a test tube which was degassed using the "freeze, pump and thaw" method, sealed and heated in an oven at 100°C for 7h. The tube was cooled in liquid nitrogen, opened and a sample was submitted for GC/MS; peak no. 151, 3-cyclopentylpropionitrile **24**, *m/z* (relative intensity), 122 (9), 108 (7), 95 (54), 82 (35), 69 (38), 55 (100), 41 (66), 27 (21); peak no. 200, phenylcyclopentane, 146 (M^+), 117 (100), 104 (83), 91 (58), 77 (21), 39 (29); peak no. 238, benzoic acid; peak no. 325, double addition product **25**, 135 (54), 122 (18), 108 (22), 95 (35), 82 (40), 68 (48), 55 (84), 41 (100), 27 (22); peak no. 479, triple addition product **26**, 221 (16), 188 (7), 147 (51), 23 (44), 105 (50), 95 (30), 83 (48), 77 (53), 73 (94), 41 (100), 54 (64), 28 (59), 36 (41). NaOH (30 cm^3) was added and the layers were separated. The alkaline fraction was extracted with benzene (10 cm^3) and the combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated leaving a yellow oil; δ_H 1.5 (m, methylene-H, cyclopentyl ring, **24**, **25**, **26**), 1.6-2.0 (m, methylene-H, aliphatic chain, **24**, **25**, **26**), 2.25 (t, *J* 8.5, *t*-H, **24**, **25**, **26**), 2.5 (m, adduct, **24**, **25**, **26**). Unfortunately it was not possible to determine the yield of the adduct from this spectrum. The acid compounds were regenerated using H_2SO_4, extracted with ether, the combined extracts were dried ($MgSO_4$) and evaporated to give a white solid, shown by ^{1}H NMR to contain benzoic acid and unreacted starting acid.

2-Cyclopentylethyl benzoate (30)

Radical reaction involving carboxylic acid 15 and vinyl benzoate (Scheme 21) 1-Cyclopentylcyclohexa-2,5-diene-1-carboxylic acid **15** (0.5 g, 2.6 mmol), vinyl benzoate (0.385 g, 2.6 mmol), dibenzoyl peroxide (50 mg, 10% wt.) and benzene (5 cm^3) were refluxed at 80°C, with magnetic stirring, for 5 days, during which a further 100 mg of dibenzoyl peroxide was added portionwise (4 x 25 mg). Analysis of the reaction mixture by GC/MS indicated the presence of unreacted vinyl benzoate, phenylcyclopentane, benzoic acid, biphenyl, 2-cyclopentylethyl benzoate and another compound which was not identified from it's mass spectrum. NaOH (30 cm^3) was added to the mixture, the layers were separated and the aqueous fraction was extracted with benzene (10 cm^3). The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated to yield a brown oil (0.39 g†; 2-cyclopentylethyl benzoate 36%, double addition product 21%, phenylcyclopentane 21%); δ_H 1.0-1.25 (m, aliphatic-H, adduct, double addition product, phenylcyclopentane), 3.1 (1 H, q^i, *J* 10, phenylcyclopentane), 4.3-4.6 (3 H, m; 2 H, methylene-H, α to O, adduct and 1 H, methine-H, α to O, double addition product), 4.7-4.8 (1 H, dd *J* 6.2, 1.8, olefinic-H, vinyl benzoate), 5.0-5.2 (1 H, dd *J* 14.0, 1.8, olefinic-H, vinyl benzoate), 5.3-5.6 (broad multiplet, unidentified), 7-7.7 (m, arom-H, vinyl benzoate, adduct, double addition product and 1 H, olefinic-H, vinyl benzoate), 7.8-8.2 (m, arom-H, vinyl benzoate, adduct, double addition product). The acid compounds were regenerated using excess H_2SO_4, extracted with ether (2 x 50 cm^3), the ethereal fractions were combined, dried ($MgSO_4$) and the solvent was evaporated leaving a white solid (0.52 g) which was shown by ^1H NMR to be a mixture of benzoic acid (0.38 g) and unreacted starting acid (0.12 g). †Yield based on mass of starting acid reacted.

***trans*-2-(Prop-2-ynyloxy)cyclohexanol (44)** (Scheme 23)[15]

trans-Cyclohexane-1,2-diol **43** (15 g, 0.129 mol) was added to a stirred mixture of DMSO (150 cm^3) containing KOH (9 g, 0.161 mol), followed immediately by addition of propargyl bromide (19.2 g, 0.129 mol), and the mixture was left stirring for 2.5h. This was poured into H_2O (800 cm^3) and the product was extracted with dichloromethane (3 x

300 cm^3). The dichloromethane extracts were washed with H_2O (5 x 100 cm^3), dried ($MgSO_4$) and the solvent evaporated, yielding an orange coloured liquid, (11.2 g; 9.4 g, 47%, **44** and 1.8 g, 7%, **44a**). Of this mixture 5 g was purified by column chromatography eluting with 35% ethyl acetate in light petroleum, and the title compound (3.0 g) was obtained as a clear, colourless liquid; δ_H 1.12-1.35 (4 H, m, methylene-H), 1.53-1.80 (2 H, m, methylene-H), 1.98-2.17 (2 H, m, methylene-H), 2.42-2.50 (1 H, m, alkyne-H), 2.60-2.74 (1 H, m, OH), 3.20-3.52 (2 H, m, methine-H), 4.20-4.30 (2 H, m, propargylic-H); δ_C (50 MHz) 24.3, 24.6, 29.5, 32.6, 56.6, 73.0, 74.0, 80.7, 83.5. The dialkylated product was also obtained in pure form (1.2 g); δ_H 1.15-1.30 (4 H, m, methylene-H), 1.58-1.71 (2 H, m, methylene-H), 1.95-2.08 (2 H, m, methylene-H), 1.95-2.03 (2 H, m, alkyne-H), 3.33-3.48 (2 H, m, methine-H), 4.25-4.37 (4 H, m, propargylic-H); δ_C (50 MHz) 23.9, 30.8, 57.7, 74.2, 81.1, 81.2.

Attempted bromination of alcohol 44 (Scheme 23)

(i) Triphenylphosphine and bromine[16]

Triphenylphosphine (1.58 g, 6.0 mmol) was added to alcohol **44** (0.86 g, 5.6 mmol) dissolved in DMF (7 cm^3) and the stirred mixture was cooled in an ice bath. To this mixture, bromine (0.91 g, 5.7 mmol) dissolved in DMF (2 cm^3) was added dropwise and the resulting mixture was left stirring for 2h. The reaction contents were added to H_2O (150 cm^3), the organic material was extracted with ether (3 x 50 cm^3), washed with H_2O, (3 x 25 cm^3), dried ($MgSO_4$) and the solvent was evaporated yielding a solid (1.48 g).which was found to be triphenylphosphine oxide. The aqueous fraction was extracted with dichloromethane (3 x 50 cm^3), washed with H_2O, (2 x 25 cm^3) and dried ($MgSO_4$) to give an orange liquid (0.27 g), which was shown by ^1H NMR to be unreacted starting material.

(ii) Phosphorus tribromide[17]

PBr_3 (6.62 g, 24.5 mmol) dissolved in dry ether (10 cm^3) was added dropwise to a stirred solution of the alcohol **44** (9.4 g, 61 mmol) and pyridine (1.35 g, 17 mmol) dissolved in dry ether (15 cm^3) and cooled to -5°C. The mixture was left stirring at 0°C for 1.5h and the

temperature was allowed to rise for 0.5h. The reaction contents were added to ether (150 cm^3), washed with H_2O (100 cm^3), the ether layer was dried ($MgSO_4$) and the ether evaporated yielding a brown oil which was shown by ^{31}P NMR to be a mixture of phosphorus compounds which were not identified.

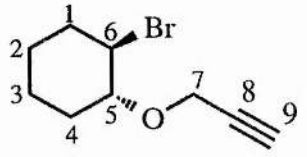
(iii) Thionyl Bromide[18]

Thionyl bromide (1.03 g, 5.9 mmol) was added to a mixture of the alcohol, **44** (0.51 g, 3.3 mmol) dissolved in deuterated chloroform (5 cm^3) and pyridine (0.074 g, 9.3 mmol) stirred at 0°C. After 10 min a sample was submitted for ^1H NMR which indicated that the OH signal had disappeared. The work-up involved was analogous to the method used in (ii), and this yielded a brown liquid (0.45 g) which was shown by ^1H NMR to be the starting material.

***trans*-1-Bromo-2-(2-propyn-1-yloxy)cyclohexane (35)** (scheme 24)[19]

Cyclohexene (19 g, 0.23 mol), propargyl alcohol (38.9 g, 0.69 mol) and dichloromethane (20 cm^3) were stirred at -20°C under an atmosphere of N_2. *N*-Bromosuccinimide (50 g, 0.28 mol) was added over the course of 40 min and the resulting mixture was stirred at the same temperature for 2h and then at room temperature for a further 15h. To the resulting mixture H_2O (75 cm^3) was added and the product was extracted with dichloromethane (3 x 25 cm^3). The combined organic extracts were washed with $NaHSO_3$ (1M, 75 cm^3), K_2CO_3 (1M, 75 cm^3) and H_2O (75 cm^3), dried ($MgSO_4$) and the solvent removed. The title compound was obtained as a clear, colourless liquid by distillation (31.9 g, 64%), bp 70-75°C at 10-12 mmHg; δ_H† (300 MHz) 1.25-1.45 (3 H, m, methylene-H), 1.65-1.95 (3 H, m, methylene-H), 2.15-2.25 (1 H, m, methylene-H, cyclohexyl ring), 2.25-2.40 (1 H, m, methylene-H, cyclohexyl ring), 2.42-2.45 (1 H, t, *J* 2.3, 9-H), 3.52-3.60 (1 H, td, *J* 8.4, 4.4, 6-H), 3.95-4.04 (1 H, ddd, *J* 10, 8.2, 4.3, 5-H), 4.29-4.32 (2 H, dd, *J* 2.3, 1.3, 7-H); δ_C 23.0, 25.0 (2 x 2,3-C), 30.6, 35.3, (2 x 1,4-C) 54.9 (6-C), 57.0 (7-C), 74.0 (9-C), 79.9 (8-C), 80.8 (5-C); GC/MS peak no. 349, *m/z* (relative intensity), 218

(M^+), (1), 216 (1), 162 (1), 119 (5), 107 (9), 95 (32), 82 (100), 81 (72), 79 (31), 67 (43), 55 (19), 39(29). †Identical to the published ^1H NMR spectrum.[19]



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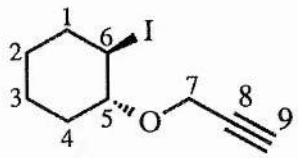

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Attempted preparation of 1-[2-(propyn-3-yloxy)cyclohexyl]cyclohexa-2,5-diene-1-carboxylic acid (31) (Scheme 25)

Benzoic acid (5 g, 41 mmol) was dissolved in ammonia (300 cm^3) to which Li (0.8 g, 0.12 mol) was added portionwise, causing the solution to turn deep blue. *trans*-1-Bromo-2-(2-propyn-1-yloxy)cyclohexane, **64** (5 g, 23 mmol) dissolved in dry ether (50 cm^3) was added dropwise, causing the solution to turn yellow. After the NH_3 had evaporated, NaOH (150 cm^3) was added. This was washed with dichloromethane (2 x 100cm^3), the carboxylic acids were regenerated by adding excess HCl, extracted with ether (2 x 200 cm^3), dried ($MgSO_4$) and the solvent was evaporated, yielding a solid (5.93 g) shown by ^1H NMR to be a mixture of benzoic acid and 1,4-dihydrobenzoic acid. The combined dichloromethane extracts were dried ($MgSO_4$) and the solvent removed to give a liquid (2.91 g) which was shown by ^1H NMR to contain mainly the bromide **35** and the alcohol **44**.

Attempted preparation of *trans*-1-iodo-2-(2-propyn-1-yloxy)cyclohexane (46) (Scheme 26)[20]

Dry NaI (16.3 g, 0.109 mol) was added to a mixture of *trans*-1-bromo-2-(2-propyn-1-yloxy)cyclohexane **35** (18.85 g, 87 mmol), dissolved in acetone (110 cm^3). This mixture was refluxed for 3.5 days. The acetone was evaporated leaving the sodium salts and the organic compounds. These were dissolved in dichloromethane (150 cm^3) which was washed with H_2O (3 x 150 cm^3). The combined aqueous washings were washed with dichloromethane (100 cm^3) and the organic fractions were combined, dried ($MgSO_4$) and

the solvent was evaporated yielding a dark brown liquid (≈30g). This was taken up in dichloromethane (150 cm^3) and washed with an excess of $Na_2S_2O_3$ until the colour of the organic layer became lighter. The layers were separated, the organic layer dried ($MgSO_4$) and the solvent was evaporated to give a brown liquid which was purified by Kugelrohr distillation to give a faintly coloured liquid (14.6g). ^1H NMR and ^{13}C NMR corresponded exactly to the starting material.

***trans*-1-Iodo-2-(2-propyn-1-yloxy)cyclohexane (46)** (Scheme 27)[21]

Iodine (21.6 g, 85 mmol) was added over the course of 0.5h to a mixture of cyclohexene (9.35 g, 0.114 mol), $Cu(OAc)_2.H_2O$ (11.4 g, 57 mmol) and propargyl alcohol (100 cm^3) under N_2. This mixture was stirred mechanically for 15h. The reaction contents were filtered, the filtrate was washed with H_2O (2 x 200 cm^3), dried ($MgSO_4$) and the solvent was evaporated to yield an orange liquid (24.64 g); GC/MS; peak no. 362, diiodo olefin (see scheme 28), *m/z* (relative intensity), 310 (M^+) (11), 183 (88), 153 (28), 55 (52); peak no. 388, 1,2-diiodocyclohexane‡, 127 (15), 99 (16), 81 (88), 43 (100), 39 (14); peak no. 399, *trans*-1-iodo-2-(2-propyn-1-yloxy)cyclohexane **46**, 137 (26), 127 (8), 109 (5), 91 (8), 81 (100), 69 (48), 55 (16), 39 (46). 7 g of the mixture was purified by chromatography, eluting with 10% ethyl acetate in light petroleum, yielding a yellow liquid. The title compound was then obtained as a clear colourless liquid after Kugelrohr distillation (1.92 g, 23%†), bp 80°C at 0.15 mmHg (Found: C, 40.77; H, 5.09. Calc. for $C_9H_{13}OI$: C, 40.93; H, 4.96%); δ_H (300 MHz) 1.20-1.50 (3 H, m, methylene-H) 1.50-1.70 (1 H, m, methylene-H), 1.75-1.90 (1 H, m, methylene-H), 1.92-2.05 (1 H, m, methylene-H), 2.16-2.3 (1 H, m, methylene-H), 2.34-2.40 (1 H, m, methylene-H), 2.42-2.46 (1 H, t, *J* 2.4, 9-H), 3.53-3.62 (1 H, td, *J* 8.6, 4.3, 6-H), 4.04-4.14 (1 H, ddd, *J* 10.4, 8.6, 4.2, 5-H), 4.27-4.30 (2 H, t, *J* 2.3, 7-H); δ_C 23.6, 27.0 (2 x 2,3-C), 31.2 (1 or 4-C), 34.8 (6-C), 37.7 (4 or 1-C), 56.9 (7-C), 74.4 (9-C), 80.1 (8-C), 81.9 (5-C); GC/MS peak no. 399, *m/z* (relative intensity) 137 (26), 127 (8), 109 (5), 91 (8), 69 (48), 55 (16), 39 (46). ‡Identification based on the tendency of diiodo compounds to lose I and then HI in the GC (i.e. *m/z* =81).†Yield based on the proportion of product purified.

Attempted preparation of 1-[2-(propyn-3-yloxy)cyclohexyl]cyclohexa-2,5-diene-1-carboxylic acid (31) (Scheme 29)

Benzoic acid (1 g, 82 mmol) was dissolved in ammonia (60 cm^3) with magnetic stirring and to this Li (0.16 g, 23 mmol) was added portionwise causing the solution to turn deep blue. *trans*-1-Iodo-2-(2-propyn-1-yloxy) cyclohexane, **46** (1.50 g, 5.7 mmol) dissolved in dry ether (5 cm^3) was added dropwise. After the NH_3 had evaporated, HCl (25 cm^3) was added and the organic compounds were extracted into ether (2 x 100 cm^3), the ethereal extracts were combined, dried ($MgSO_4$) and the solvent was evaporated yielding a brown solid which was shown by ^1H NMR to be a mixture of 1,4-dihydrobenzoic acid and benzoic acid. Neither the title compound or unreacted iodide were obtained.

9-methylene-7-oxabicyclo[4.3.0]heptane (39)

Tin hydride mediated cyclisation of bromide 35 (Scheme 29a)

trans-1-Bromo-2-(2-propyn-1-yloxy)cyclohexane **35** (2 g, 9.2 mmol), tributyltin hydride (2.91 g, 10 mmol) and benzene (5 cm^3) were added to a 1 cm diameter ^{13}C NMR tube and irradiated using a medium pressure 125 W Hg lamp for 8h at room temperature. A sample of the reaction mixture was analysed by GC/MS; peak no. 253, propyn-3-yloxycyclohexane, *m/z* (relative intensity), 138 (M^+) (4), 109 (9), 95 (54), 82 (95), 81 (100), 79 (18), 67 (72), 55 (75), 41 (49), 39 (74); peak no. 264, 9-methylene-7-oxabicyclo[4.3.0]heptane **39**, 138 (M^+) (27), 120 (26), 109 (61), 95 (86), 81 (95), 79 (68), 68 (56), 67 (100), 41 (47), 39 (45). The benzene was removed by distillation at room temperature and the product was distilled using a Kugelrohr (0.2 mmHg) and collected in a liquid nitrogen trap (0.78 g, 61%); δ_H (300 MHz) 1.10-1.20 (8 H, m, methylene-H), 2.50-2.60 (1 H, m, *t*-allylic-H), 3.95-4.00 (1 H, qd, *J* 7.8, 1.4, *t*-H), 4.25-4.32 (1 H, dq^i,*J* 12.5, 1.4, methylene allylic-H), 4.42-4.50 (1 H, dq, *J* 12.3, 1.9, methylene allylic-H), 4.82-4.85 (1 H, q, *J* 2.0, olefinic-H), 4.88-4.91 (1 H, q, *J* 2.0, olefinic-H); δ_C 21.2, 23.0, 27.0, 27.6, 43.3, 69.6, 77.8, 102.4, 152.6; *m/z* 138 (M^+, 27%), 137 (55), 124 (10), 119 (13), 109 (30), 95 (40), 91 (29), 82 (63), 79 (50), 67 (100), 55 (57) (Found: M^+ 138.1049. $C_9H_{14}O$ requires 138.1045).

3-Hydroxycyclohexene (Scheme 31)[22]

Cyclohexenone (2 g, 21 mmol) was dissolved in a 0.4 M solution of $CeCl_3.7H_2O$ (7.82 g) in Analar methanol (50 cm^3). To this $NaBH_4$ (0.79 g, 21 mmol) was added over a 2 min period and the resulting mixture was left stirring for a further 4 min followed by the addition of H_2O (100 cm^3). The product was extracted into ether (2 x 75 cm^3), the ethereal extracts were combined and dried ($MgSO_4$). The solvent was evaporated and the title compound was obtained as a clear, colourless liquid by distillation (1.4 g, 68%); δ_H 1.50-2.10 (7 H, m; 6 H, methylene-H and 1 H, hydroxyl-H), 4.10-4.25 (1 H, m, *t*-H), 5.65-5.90 (2 H, m, olefinic-H); δ_C (50 MHz) 19.5, 22.5, 32.4 (3 x methylene-C), 69.9 (*t*-C), 130.5, 130.8 (2 x olefinic-C).

Attempted preparation of 3-(2'-chloroethoxy)cyclopentene (48) (Scheme 32)

(i) Using KOH as base

Finely powdered KOH (8.1 g, 0.144 mol) was added to DMSO (70 cm^3). After allowing the mixture to stir for 5 min, 2-cyclopenten-1-ol (3 g, 36 mmol) was added, followed by 1-bromo-2-chloroethane (6.2 g, 43.2 mmol) and this mixture was left stirring for 5h. To the mixture H_2O (300 cm^3) was added and the mixture was extracted with dichloromethane (3 x 75 cm^3), the combined organic extracts were washed with H_2O (6 x 100 cm^3), dried ($MgSO_4$) and the solvent was evaporated yielding a very small quantity of a brown oil (0.1 g), which did not contain the desired product.

(ii) Using NaH as base

NaH (1.44 g, 36 mmol) was stirred in dry THF (70 cm^3) for 5 min, the solvent was removed using a cannula and fresh, dry THF (70 cm^3) was added. 2-Cyclopenten-1-ol (3 g, 36 mmol) dissolved in dry THF (20 cm^3) was added to the reaction mixture over a 2 min period at -20°C. The reaction was left stirring for 0.5h before 1-bromo-2-chloroethane (6.2 g, 43.2 mmol) dissolved in dry THF (10 cm^3) was added over a 20 min period. The reaction mixture was filtered, washed with H_2O (100 cm^3) and the solvent was evaporated to give a liquid (1.78 g) which was shown by ^1H NMR not to be the desired product.

(iii) Using BuLi as base

The alcohol (1.5 g, 18 mmol) was dissolved in dry THF (75 cm^3) under N_2. To the mixture BuLi (1.3 g, 20 mmol) was added at -40°C and after a 40 min period 1-bromo-2-chloroethane (3.2 g, 22 mmol) was added and the mixture was left stirring overnight. The solvent was evaporated to yield a yellow liquid (1.41 g) which was shown by ^1H NMR to be 2-cyclopenten-1-ol and 1-bromo-2-chloroethane. Another reaction was attempted which was left stirring for 3 days under N_2 before work-up. The reaction was monitored by TLC but no significant change was observed and the starting materials were again recovered after work-up.

3-Bromocyclohexene (Scheme 34)[24]

Cyclohexene (238 g, 2.89 mol) and *N*-bromosuccinimide (188 g, 1.06 mol) were added to carbon tetrachloride (725 cm^3) and to this dibenzoyl peroxide (1.5 g) was added as initiator. The mixture was stirred at room temperature for 2h and refluxed for 2h. The succinimide was filtered off and the majority of the carbon tetrachloride was evaporated. The title compound was obtained as a clear, colourless liquid by distillation (108 g, 64%), bp 60°C at 10-12 mmHg (lit.,[24] bp 57-58°C at 12 mmHg); δ_H 1.60-2.35 (6 H, m, methylene-H), 4.8-4.9 (1 H, m, *t*-H), 5.75-6.0 (2 H, m, olefinic-H).

Attempted preparation of 3-(2'-hydroxyethoxy)cyclohexene (49)

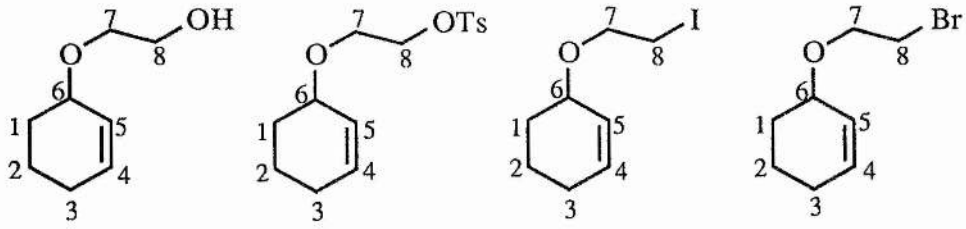
Powdered KOH (0.77 g, 13.7 mmol) was added to DMSO (50 cm^3) followed by ethylene glycol (0.85 g, 13.7 mmol). After allowing this mixture to react for 15 min bromocyclohexene (2 g, 12.4 mmol) was added and the mixture was left stirring at room temperature for 16h. The reaction contents were added to H_2O (400 cm^3) and extracted with ether (3 x 100 cm^3). The ethereal extracts were combined, washed with H_2O (5 x 75 cm^3), dried ($MgSO_4$) and the solvent was evaporated to yield an orange liquid (1.02 g) which was found to be mainly ethylene glycol.

3-(2'-Hydroxyethoxy)cyclohexene (49) (Scheme 35)

Ethylene glycol (6.16 g, 99 mmol) was added to dry THF (50 cm^3) and to this sodium wire (0.3 g, 12.4 mmol) was added and this mixture was refluxed overnight. 3-Bromocyclohexene (2 g, 12.4 mmol) was added to the reaction mixture and this was left refluxing for a further 12h. The THF was evaporated and ether (100 cm^3) and H_2O (100 cm^3) were added to the residue. The layers were separated and the aqueous layer was extracted with ether (100 cm^3). The ethereal extracts were combined, dried ($MgSO_4$) and the solvent was evaporated. The title compound was obtained as a clear, colourless liquid after distillation (1.56 g, 88%), bp 68°C at 0.7 mmHg; δ_H 1.40-2.10 (6 H, m, 1,2,3-H), 2.50 (1 H, m, hydroxyl-H), 3.50-3.75 (4 H, m, methylene 7,8-H), 3.85-3.95 (1 H, m, *t* 6-H), 5.70-5.90 (2 H, m, olefinic 4,5-H); δ_C (50 MHz) 19.6, 25.7, 28.7 (3 x 1,2,3-C), 62.5 (8-C), 69.7 (7-C), 73.7 (6-C), 128.0, 131.6 (2 x 4,5-C); *m/z* 143 (MH^+, 6%), 119 (3), 81 (100), 55 (44), 44 (43), 42 (24), 41 (58) (Found: MH^+, 143.1065. $C_8H_{15}O_2$ requires 143.1072).

3-(2'-Tosylethoxy)cyclohexene (50) (Scheme 36)

3-(2'-Hydroxyethoxy)cyclohexene **49** (10 g, 70 mmol) was dissolved in pyridine (80 cm^3) and to this *p*-toluenesulphonyl chloride (20 g, 0.105 mol) was added at -10°C. The resulting mixture was left stirring for 24h at 0°C. The reaction contents were added to H_2O (200 cm^3) and the product was extracted with ethyl acetate (2 x 100 cm^3). The organic extracts were combined, dried ($MgSO_4$) and the solvent was evaporated to yield the title compound as an orange liquid (16 g, 77%); δ_H 1.40-2.10 (6 H, m, methylene 1,2,3-H) 2.40 (3 H, s, methyl-H, tosyl group), 3.55-3.77 (2 H, m, methylene 7-H), 3.80 (1 H, m, *t* 6-H), 4.10-4.20 (2 H, t, *J*, 5.6, methylene 8-H), 5.60-5.90 (2 H, m, olefinic 4,5-H), 7.25-7.40 (2 H, d, *J* 8.1, arom-H), 7.75-7.85 (2 H, d, *J* 8.2, arom-H); δ_C (50 MHz) 22.2 (C, methyl of tosyl group), 19.5, 25.6, 28.6 (3 x 1,2,3-C), 65.9 (8-C), 70.2 (7-C), 73.8 (6-C), 127.6, 128.5, 130.3, 131.8, 133.4, 145.3 (8 x olefinic, arom-C).



49 **50** **36** **55**

3-(2'-Iodoethoxy)cyclohexene (36) (Scheme 36)

The tosylate **50** (5 g, 17 mmol) was dissolved in Analar acetone (70 cm^3) to which sodium iodide (15 g, 0.1 mol) was added and the resulting mixture was refluxed for 20h. The acetone was evaporated and ethyl acetate (100 cm^3) was added to the residue. This was washed with sodium thiosulphate (100 cm^3), brine (100 cm^3), dried ($MgSO_4$) and the solvent was evaporated. The title compound was obtained as a clear, colourless liquid by distillation (3.6 g, 84%), bp 68-71°C at 0.2-0.3 mmHg (Found: C, 38.20; H, 5.18. Calc. for $C_8H_{13}OI$: C, 38.11; H, 5.20%); δ_H 1.50-2.15 (6 H, m, methylene 1,2,3-H), 3.15-3.30 (2 H, t, *J* 7.0, methylene 8-H), 3.65-3.80 (2 H, m, methylene 7-H), 3.85-4.00 (1H, m, *t* 6-H), 5.70-6.00 (2 H, m, olefinic 4,5-H); δ_C (50 MHz) 4.4 (8-C), 19.6, 25.7, 28.8 (3 x 1,2,3-C), 69.6 (7-C), 73.6 (6-C), 127.8, 132.0 (2 x 4,5-C).

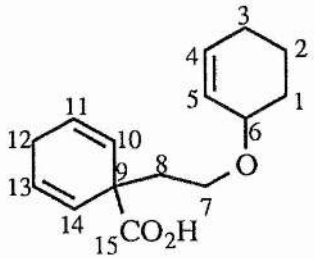
3-(2'-Bromoethoxy)cyclohexene (55) (Scheme 42)

Bromocyclohexene (2.6 g, 16 mmol), 2-bromoethanol (25 g, 0.2 mol) and dry THF (40 cm^3) were stirred at r.t. and to this mixture was added sodium wire (0.92 g, 0.04 mol). The resulting mixture was refluxed for 24h, the NaBr precipitate was filtered off and the THF was evaporated. To the residue H_2O (100 cm^3) and cyclohexane (50 cm^3) were added. The layers were separated and the aqueous layer was extracted with more cyclohexane (2 x 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent was evaporated to yield a brown liquid. The title compound was obtained as a clear, colourless liquid by distillation (1.84 g, 56%†), bp 44-46°C at 0.1-0.2 mmHg (Found: C, 47.14; H, 6.40. Calc. for $C_8H_{13}OBr$: C, 46.85; H, 6.39%); δ_H 1.44-2.12 (6 H, m, methylene 1,2,3-H), 3.42-3.47 (2 H, t, *J* 6.5, methylene 8-H), 3.75-3.86 (2 H, m,

methylene 7-H), 3.87-3.95 (1 H, m, *t* 6-H), 5.72-5.93 (2 H, m, olefinic 4,5-H); δ_C 19.5, 25.6, 28.7 (3 x 1,2,3-C), 31.3 (8-C), 68.7 (7-C), 73.9 (6-C), 127.9, 132.1 (2 x 4,5-C). †Unoptimised yield.

1-[2-(Cyclohex-2-enyloxy)ethyl]cyclohexa-2,5-diene-1-carboxylic acid (32) (Scheme 37)

Ammonia (250 cm^3) was added to benzoic acid (1.3 g, 10.7 mmol) followed by the portionwise addition of Li (0.24 g, 34 mmol) causing the solution to turn blue. This mixture was allowed to stir for 25 min before the addition of 3-(2'-iodoethoxy)cyclohexene **36** (3.23 g, 12.8 mmol) dissolved in dry THF (5 cm^3), causing an exothermic reaction and a colour change to yellow. The NH_3 was left to evaporate and NaOH (70 cm^3) and ether (100 cm^3) were added to the resulting residue. The layers were separated and the organic fraction was extracted with NaOH (70 cm^3). The alkaline fractions were combined, washed with light petroleum and neutralised with excess HCl. The product was extracted with ether (3 x 100 cm^3), the ethereal extracts were combined, dried ($MgSO_4$) and the solvent was evaporated yielding an oil (2.07 g; 1.76 g, 67% title compound and 0.31 g, 24% unreacted benzoic acid). The mixture was purified by column chromatography using 10% ethyl acetate in light petroleum yielding the title compound as a viscous oil (1.12 g, 42%); δ_H (300MHz) 1.40-1.80 (4 H, m, methylene 1,2-H), 1.85-2.10 (4 H, m; 2 H, allylic 3-H and 2 H, t, *J* 7.1, methylene-H 8-H), 2.60-2.70 (2 H, m, allylic 12-H), 3.40-3.55 (2 H, dt, *J* 9.7, 7.2, methylene 7-H), 3.75-3.85 (1 H, m, *t* 6-H), 5.70-5.95 (6 H, m, olefinic 4,5,10,11,13,14-H); δ_C 19.6 (2-C), 25.7, 26.5, 28.7 (3 x 1,3,12-C), 39.6 (8-C), 46.5 (9-C), 64.7 (7-C), 73.6 (6-C), 126.5, 127.0 (4 x 10,11,13,14-C), 128.0, 131.4 (2 x 4,5-C), 180.6 (15-C); *m/z* 248 (M^+, 2%), 204 (5), 168 (6), 151 (17), 149 (20), 123 (25), 121 (13), 117 (2), 105 (55), 97 (20), 91 (26), 81 (100), 79 (15) (Found: M^+, 248.1412. $C_{15}H_{20}O_3$ requires 248.1421). The title compound was also obtained in an unoptimised yield of 35% when the blue ammonia solution was quenched with 3-(2'-bromoethoxy)cyclohexane.



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7-Oxabicyclo[4.3.0]nonane (40)

Tin hydride mediated cyclisation of 3-(2'-iodoethoxy)cyclohexene 36 (Scheme 38)

Iodide **36** (1 g, 4 mmol), tributyltin hydride (1.3 g, 4 mmol) and benzene (5 cm^3) were irradiated using a medium pressure 125 W Hg lamp for 6h at 70°C. A sample of the reaction mixture was submitted for GC/MS analysis; peak no. 244, 3-ethoxycyclohexene, *m/z* (relative intensity), 126 (M^+) (14), 83 (100), 67 (12), 55 (30), 41 (28), 39 (24), 29 (17), 27 (24); peak no. 213, 7-oxabicyclo[4.3.0]nonane, 126 (M^+) (9), 98 (37) 78 (47), 70 (42), 41 (35), 39 (27), 31 (37), 28 (66), 18 (100). To the reaction mixture ether (10 cm^3) and a saturated solution of KF were added. The resulting mixture was left stirring for 24h and polymeric tin fluoride was filtered off. The layers were separated, the ether layer was washed with H_2O (2 x 10 cm^3), dried ($MgSO_4$) and the solvent was removed by atmospheric distillation. The resulting residue was distilled to yield the two products identified above (0.36 g; 60% **40** and 13% **51**); δ_H 1.15-2.10 (20 H, m; 11 H, methylene, methine-H, **40** and 9 H, methylene, methyl-H, **51**), 3.45-3.62 (2 H, m, methylene-H, **51**), 3.76-3.88 (3 H, m; 2 H, methylene-H, **40** and 1 H, *t*-H, **51**), 3.89-4.06 (1 H, q, *J* 8, *t*-H, **40**), 5.75-5.88 (2 H, m, olefinic-H, **51**).

7-Oxabicyclo[4.3.0]nonane (40)

Radical fragmentation of carboxylic acid 32 (Scheme 39)-*First Reaction*

Carboxylic acid **32** (1.21 g, 4.9 mmol) was dissolved in benzene (5 cm^3) to which dibenzoyl peroxide (0.6 g, 50% wt.) was added and this mixture was refluxed for 30h. A sample of the reaction mixture was submitted for analysis by GC/MS; peak no. 239, 7-

oxabicyclo[4.3.0]nonane, *m/z* (relative intensity), 126 (M^+) (13), 83 (100), 67 (17), 55 (50), 41 (51), 39 (54), 29 (41), 27(49); peak no. 362, benzoic acid, 122 (M^+) (49), 105 (85), 77 (100), 51 (79); peak no. 396, biphenyl, 154 (M^+) (6), 122 (8), 105 (14), 91 (100), 78 (75) 65 (17), 51 (30), 39 (31); peak no. 474, 3-(2-phenylethoxy)cyclohexene, 202 (M^+) (1), 105 (36), 97 (15), 91 (25) 81 (100) 65 (18), 53 (22), 41 (37), 27 (28). Ether (20 cm^3) was added to the reaction mixture and this was washed with NaOH (2 x 20 cm^3). The alkaline fractions were neutralised with excess acid, extracted with ether (2 x 50 cm^3), dried ($MgSO_4$) and the solvent was evaporated to yield benzoic acid (0.8 g) and unreacted acid **32** (0.61 g). The original organic fraction was dried ($MgSO_4$) and the solvent was removed by distillation at atmospheric pressure yielding an orange liquid (0.44 g) containing three compounds (0.17 g, 47%, 7-oxabicyclo[4.3.0.]nonane†; 0.21 g, 36%, 3-(2-phenylethoxy)cyclohexene; 0.1 g, biphenyl); δ_H‡ 1.20-2.10 (17 H, m, 11 H, methylene, methine-H, **40** and 6 H, methylene-H, **52**), 2.85-3.00 (2 H, t, *J* 7.5, methylene-H, **52**), 3.65-3.78 (2 H, m, methylene-H, **52**), 3.78-3.92 (3 H, m; 2H, methylene-H, **40** and 1 H, *t*-H, **52**), 3.92-4.05 (1 H, q, *J* 7.8, *t*-H, **40**), 5.75-5.92 (2 H, m, olefinic-H, **52**), 7.20-7.68 (5 H, m, arom-H, **52**). A small amount of the title compound (0.2 g, 34%†) was isolated in pure form using a micro-distillation kit; δ_H 1.15-1.30 (2 H, m, methylene-H), 1.35-1.75 (6 H, m, methylene-H), 1.84-2.10 (3 H, m, methylene-H), 3.75-3.90 (2 H, dt, *J* 4.5, 8.6, methylene-H), 3.90-4.05 (1 H, q, *J* 7.8, *t*-H); δ_C (50 MHz) 21.0, 24.1, 27.5, 28.1, 32.0 (5 x methylene-C), 37.6 (*t*-C), 66.0 (methylene-C), 77.1 (*t*-C). †Yield based on amount of acid reacted. ‡Does not include the signals for biphenyl.

7-Oxabicyclo[4.3.0]nonane (40)

Radical fragmentation of carboxylic acid 32 (Scheme 39)

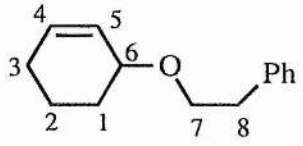
Carboxylic acid **32** (1.60 g, 6.4 mmol) was dissolved in benzene (6 cm^3) to which dibenzoyl peroxide (0.8 g, 50% wt.) was added. This mixture was refluxed for 3 days during which a further 0.8 g of initiator was added. A sample of the reaction mixture was submitted for analysis by GC/MS, the result of which was essentially the same as reported

above. Ether (20 cm^3) was added to the reaction mixture and benzoic acid was removed with NaOH (2 x 20 cm^3). Work-up of the alkaline fraction gave benzoic acid only. The ether and benzene were removed by atmospheric distillation yielding a liquid (1.30 g) containing four compounds (0.44 g, 55%, 7-oxabicyclo[4.3.0]nonane; 0.52 g, 40%, 3-(2-phenylethoxy)cyclohexene; 0.34 g, biphenyl and unreacted dibenzoyl peroxide). The ^1H NMR spectrum was in agreement with this assignment and was very similar to the spectrum reported above.

3-(2-Phenylethoxy)cyclohexene (52)

Radical fragmentation of carboxylic acid 32 in D_2O (Scheme 40)

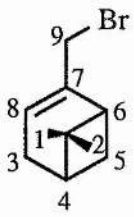
Carboxylic acid **32** (0.18 g, 0.7 mmol) was dissolved in a solution of D_2O (800 μl) containing KOH (0.045 g, 0.8 mmol). This mixture was added to an NMR tube containing potassium persulphate (98 mg, 0.36 mmol). The contents of the tube were irradiated using a medium pressure 125 W Hg lamp for 7h at 70°C. Analysis by ^1H NMR seemed to indicate total consumption of the starting acid **32**. Deuterated chloroform was added to the NMR tube and the layers were separated. The aqueous fraction was washed with a further portion of chloroform and then neutralised with excess HCl. The aqueous layer was extracted with ether, the ethereal extracts were combined, dried ($MgSO_4$) and the solvent removed giving an oil (0.044 g, 25%) which was shown by ^1H NMR spectroscopy to be unreacted acid **32**. The chloroform extracts were combined, dried using molecular sieves and the mixture was filtered, yielding the title compound in $CDCl_3$ (63%†); δ_H 1.50-2.10 (6 H, m, methylene-H), 2.85-3.00 (2 H, t, *J* 7.5, methylene-H), 3.60-3.80 (2 H, m, methylene-H), 3.80-3.95 (1 H, m, *t*-H) , 5.75-5.91 (2 H, m, olefinic-H), 7.2-7.4 (5 H, m, arom-H); δ_C 19.2 (2-C), 25.2, 28.3 (2 x 1,3-C), 36.9 (8-C), 69.3 (7-C), 73.0 (6-C), 126.2, 128.0, 128.4, 129.1, 130.9 (2 x 4,5-C and 5 x arom-C), 139.3 (*ipso*-arom-C); GC/MS peak no. 472, *m/z* (relative intensity), 202 (M^+) (1), 173 (1), 105 (29), 97 (15), 91 (14), 81 (100), 65 (10), 53 (15), 41 (26), 27 (23), 18 (12).(Found: M^+, 202.1349. $C_{14}H_{18}O$ requires 202.1358). †Yield based on the amount of cyclohexadiene acid reacted using benzyl alcohol as a standard.



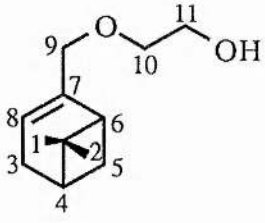
52

2-Bromomethyl-6,6-dimethylbicyclo[3.1.1]hept-2-ene (53) (Scheme 44)

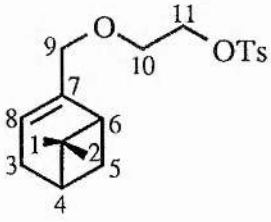
α-Pinene (60 g, 0.44 mol) and NBS (30 g, 0.167 mol) were refluxed in CCl_4 (250 cm^3) containing dibenzoyl peroxide (0.3 g) for 4h. The succinimide was filtered off and the solvent and unreacted pinene were removed on the Buchi yielding a brown liquid. The title compound was obtained as a clear, colourless liquid by distillation, using a Vigreux column and a pig to collect individual fractions (21 g, 59%), bp 64-68°C at 0.5 mmHg (lit.,[39] bp 52-58°C at 0.6 mmHg); δ_H (300 MHz) 0.83 (3 H, s, methyl-H), 1.09-1.12 (1 H, d, *J* 8.7, methylene 5-H), 1.31 (3 H, s, methyl-H), 2.06-2.13 (1H, m, methylene or methine-H), 2.21-2.32 (3 H, m, methylene, methine-H), 2.32-2.40 (1 H, dt, *J* 9, 5.4, methylene 5-H), 3.96 (2 H, s, allylic 9-H), 5.69 (1 H, s, olefinic 8-H); δ_C 21.0, 25.9 (2 x 1,2-C), 31.2, 31.4 (2 x 3,5-C), 37.6 (quaternary-C), 37.8 (9-C), 40.2, 44.7 (2 x 4,6-C), 123.0 (8-C), 144.0 (7-C).



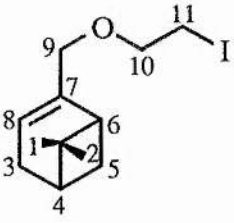
53



56



56a



57

Attempted preparation 6,6-dimethyl-2-(2-bromoethoxymethyl)bicyclo-[3.1.1]hept-2-ene (54) (Scheme 45)

Myrtenyl bromide **53** (1.5 g, 7 mmol) and 2-bromoethanol (7 g, 56 mmol) were dissolved in dry THF (20 cm^3) and to this sodium wire (0.4 g, 17.5 mmol) was added. The mixture was refluxed for 15h, the NaBr was filtered off, the solvent was evaporated and to the residue H_2O (100 cm^3) and cyclohexane (50 cm^3) were added. The layers were separated

and the aqueous layer was extracted with more cyclohexane (3 x 50 cm^3). The organic fractions were combined, dried ($MgSO_4$) and the solvent was evaporated yielding a pale yellow liquid (1.47 g) which was shown by ^1H NMR to be unreacted starting material.

6,6-Dimethyl-2-(2-hydroxyethoxymethyl)bicyclo[3.1.1]hept-2-ene (56)

(Scheme 46)

Ethylene glycol (39.3 g, 0.663 mol) was added to dry THF (250 cm^3) and to this mixture sodium wire (2.2 g, 0.095 mol) was added. The mixture was refluxed overnight followed by the addition of myrtenyl bromide **53** (15 g, 79 mmol) dissolved in dry THF (20 cm^3) and the resulting mixture was refluxed for 10h. The NaBr was filtered off and the THF was evaporated. To the residue H_2O (100 cm^3) and ether (100 cm^3) were added and the layers were separated. The aqueous fraction was extracted with ether (2 x 100 cm^3), the organic extracts were combined and washed with H_2O (100 cm^3). The resulting organic fraction was dried ($MgSO_4$) and the solvent was evaporated to yield the title compound as a pale yellow liquid (13.7 g, 100%), (Found: C, 72.60; H, 10.75. Calc. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27%); δ_H 0.85 (3 H, s, methyl-H), 1.19-1.21 (1 H, d, *J* 9, methylene 5-H), 1.32 (3 H, s, methyl-H), 2.09-2.43 (5 H, m, methylene-H, methine-H), 3.50-3.57 (2 H, m, methylene 10-H), 3.70-3.73 (2 H, t, *J* 4.5, methylene 11-H), 3.94 (2 H, s, allylic 9-H), 5.51 (1 H, s, olefinic 8-H); δ_C 21.5, 26.6 (2 x 1,2-C), 31.6, 31.9 (2 x 3,5-C), 38.4 (quaternary-C), 41.3, 43.7 (2 x 4,6-C), 62.3 (11-C), 71.2, 74.4 (2 x 9,10-C), 120.7 (8-C), 145.7 (7-C).

6,6-Dimethyl-2-(2-tosylethoxymethyl)bicyclo[3.1.1]hept-2-ene (56a)

(Scheme 47)

The alcohol **56** (14 g, 71 mmol) was dissolved in pyridine (100 cm^3) and *p*-toluenesulphonyl chloride (19 g, 100 mmol) was added at -10°C and this mixture was stirred for 16-20h at -10°C to 5°C. The reaction contents were poured into ice water (200 cm^3) and the product was extracted with ethyl acetate (3 x 200 cm^3) and the combined organic extracts were washed with H_2O (100 cm^3), dried ($MgSO_4$), and the solvent was

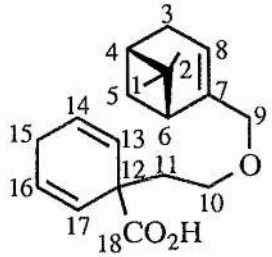
evaporated to yield the title compound (24.5 g, 96%); δ_H 0.78 (3 H, s, methyl-H), 1.07-1.11 (1 H, d, *J* 8.4, methylene 5-H), 1.25 (3 H, s, methyl-H), 2.00-2.48 (8 H, m, methyl, methylene, methine-H), 3.52-3.57 (2 H, t, *J* 4.8, methylene 10-H), 3.78 (2 H, s, allylic 9-H), 4.10-4.15 (2 H, t, *J* 4.8, methylene 11-H), 5.38-5.45 (1 H, m, olefinic 8-H), 7.26-7.30 (2 H, m, arom-H), 7.76-7.80 (2 H, d, *J* 8.2, arom-H); δ_C 21.1, 21.8, 26.3 (2 x 1,2-C and 1 x methyl of tosyl group), 31.4, 31.6 (2 x 3,5-C) 38.1 (quaternary-C), 40.9, 43.2 (2 x 4,6-C), 67.0 (11-C), 69.5, 74.1 (2 x 9,10-C), 120.6 (8-C), 128.1, 130.0, 130.0, 133.1 (6 x arom-C), 144.9 (7-C).

6,6-Dimethyl-2-(2-iodoethoxymethyl)bicyclo[3.1.1]hept-2-ene (57) (Scheme 47)

The tosylate **56a** (24.5 g, 70 mmol) was dissolved in Analar acetone (250 cm^3) and to the mixture NaI (64.5 g, 0.43 mol) was added. The mixture was stirred at room temperature for 5h and refluxed overnight. The precipitate was filtered off and the acetone was removed under reduced pressure. Dichloromethane (200 cm^3) and H_2O (200 cm^3) were added to the residue, the layers were separated and the aqueous layer was extracted with dichloromethane (2 x 100 cm^3). The organic fractions were combined, washed with a saturated solution of sodium thiosulphate (2 x 150 cm^3), dried ($MgSO_4$) and the solvent was evaporated to give the title compound (21.8 g, 100%) as a dark-red liquid which was distilled using the Kugelrohr to yield a clear colourless liquid, bp 80-100°C at 0.1 mmHg; δ_H 0.83 (3 H, s, methyl-H), 1.14-1.19 (1 H, d, *J* 8.9, methylene 5-H), 1.28 (3 H, s, methyl-H), 2.03-2.49 (5 H, m, methylene, methine-H), 3.22-3.29 (2 H, t, *J* 6.8, methylene 11-H), 3.62-3.69 (2 H, t, *J* 6.8, methylene 10-H), 3.89 (2 H, s, allylic 9-H), 5.46-5.52 (1 H, m, olefinic 8-H); δ_C 3.1 (11-C), 20.9, 26.1 (2 x 1,2-C), 31.2, 31.4 (2 x 3,5-C), 37.9 (quaternary-C), 40.7, 43.1 (2 x 4,6-C), 70.1, 73.5 (2 x 9,10-C), 120.3 (8-C), 150.0 (7-C); *m/z* 306 (M^+, 12%), 191 (14), 185 (13), 155 (14), 151 (15), 136 (37), 135 (100), 121 (10), 107 (22), 93 (55), 91 (27), 79 (61), 57 (10) (Found: M^+, 306.0467. $C_{12}H_{19}OI$ requires 306.0481).

1-[2-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-ylmethoxy)ethyl]cyclohexa-2,5-diene-1-carboxylic acid (33) (Scheme 48)

Ammonia (500 cm^3) was added to benzoic acid (2.5 g, 20.4 mmol) to which Li (0.45 g, 65.2 mmol) was added portionwise causing the solution to turn blue. This mixture was left stirring for 30 min followed by the addition of 6,6-dimethyl-2-(2-iodo-ethoxymethyl)-bicyclo[3.1.1]hept-2-ene **57** (7.5 g , 24.5 mmol) dissolved in dry THF (5 cm^3), causing the solution to turn brown. The NH_3 was allowed to evaporate, ice was added to the residue followed by NaOH (100 cm^3) and dichloromethane (100 cm^3). The layers were separated and the dichloromethane fraction was extracted with NaOH (100 cm^3), the alkaline fractions were combined and neutralised with excess HCl. The product was extracted with ether (3 x 100 cm^3), the ethereal extracts were combined, dried ($MgSO_4$) and the solvent was evaporated yielding a dark oil (5.18 g; 4.56 g, 74%, title compound and 0.28 g, 11% dihydrobenzoic acid and 0.34 g, 14% unreacted benzoic acid); δ_H 0.81 (3 H, s, methyl-H), 1.10-1.16 (1 H, d, *J* 8.4, methylene 5-H), 1.24 (3 H, s, methyl-H), 1.90-2.05 (2 H, t, *J* 7.2, methylene 11-H), 1.95-2.43 (5 H, m, methylene, methine-H), 2.59-2.75 (4 H, m; 2 H, allylic 15-H and 2 H, allylic-H, dihydrobenzoic acid), 3.34-3.44 (2 H, t, *J* 7.3, methylene 10-H), 3.75-3.83 (2 H, m, allylic 9-H), 5.40-5.50 (1 H, m, olefinic 8-H), 5.80-5.98 (8 H, m; 4 H, olefinic 13,14,16,17-H and 4 H, olefinic-H, dihydrobenzoic acid), 7.20-7.50 (3 H, m, arom-H, benzoic acid), 8.05-8.22 (2 H, m, arom-H, benzoic acid). A small amount of the title compound was isolated after two successive purification steps by column chromatography, to give essentially pure material as a viscous oil; δ_C 21.0, 26.0, 26.2 (3 x 1,2,15-C), 31.3, 31.5 (2 x 3,5-C), 38.0 (quaternary-C), 38.7 (11-C), 41.0, 41.3 (2 x 4,6-C), 46.1 (12-C), 66.0 (10-C), 73.8 (9-C), 119.7 (8-C), 126.0, 126.6 (4 x 13,14,16,17-C), 145.4 (7-C), 180.2 (18-C); *m/z* 302 (M^+, 2%), 195 (4), 151 (28), 134 (58), 119 (36), 107 (39), 105 (68), 93 (51), 92 (52), 91 (100), 79 (64), 77 (46) (Found: M^+: 302.1884. $C_{19}H_{26}O_3$ requires 302.1882).



33

Oxacyclopentane-3-spiro-2'-6',6'-dimethylbicyclo[3.1.1]heptane (41)

Tin hydride mediated cyclisation of iodide 57 (Scheme 49)

6,6-Dimethyl-2-(2-iodoethoxymethyl)bicyclo[3.1.1]heptane **57** (0.5 g, 1.63 mmol) and tributyltin hydride (0.52 g, 1.8 mmol) were dissolved in benzene (5 cm^3) and added to a 1 cm diameter ^{13}C NMR tube. The tube was capped and irradiated with light from a 125 W medium pressure Hg lamp for 2.5h at room temperature and 3.5h at 70-90°C. Analysis of the reaction mixture by GC/MS indicated that all the iodide had been consumed; peak no. 306, 2-(ethoxymethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene **58**, *m/z* (relative intensity), 136 (12), 119 (29), 105 (16), 93 (33), 92 (46), 91 (100), 79 (31), 77 (52), 59 (82), 41 (69), 31 (49), 29 (46), 27 (43), 18 (19); peak no. 373, oxacyclopentane-3-spiro-2'-6',6'-dimethylbicyclo[3.1.1]heptane **41**, 180 (M^+) (1), 165 (1), 137 (8), 107 (16), 95 (24), 82 (25), 79 (42), 67 (41), 55 (38), 41 (100), 29 (32), 27 (40). The reaction contents were transferred to a round-bottomed flask and a saturated solution of KF (10 cm^3) was added and the mixture was stirred for 3 days. The polymeric tin fluoride was filtered off and the layers were separated. The aqueous layer was extracted with ether and the ethereal extracts were combined, dried ($MgSO_4$) and the solvent was evaporated yielding an orange liquid, which when analysed by ^1H NMR, still contained some tin residues. The liquid was distilled using a Kugelrohr (80-100°C, 1 mmHg) giving a clear colourless liquid (0.114 g, 8% **58**, 31% **41**); δ_H 0.83 (3 H, s, methyl-H, **58**), 0.86 (3 H, s, methyl-H, **41**), 1.12-1.30 (11 H, m; 4 H, **41** and 7 H, **58**), 1.70-1.94 (8 H, m, methylene, methine-H, **41**), 2.02-2.45 (6 H, m; 1 H, **41** and 5 H, methylene, methine-H, **58**), 3.38-3.75 (6 H, m; 4 H, methylene-H, **41** and 2 H, methylene-H, **58**), 3.78-3.82 (2 H, m, allylic-H, **58**),

5.40-5.50 (m, 1 H, olefinic-H, **58**); δ_C† 23.5 (1 or 2-C), 25.1 (8-C), 27.2 (1 or 2-C), 28.7, 28.9 (2 x 3,5-C), 38.8 (quaternary-C), 40.4, 43.4 (2 x 4,6-C), 47.9 (7-C), 51.2 (9-C), 66.2 (11-C), 80.4 (10-C). †Only the major signals corresponding to the cyclised product are given, although the minor signals due to the direct reduction product were present and corresponded almost exactly with the pure sample prepared as described below.

2-(Ethoxymethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene (58) (Scheme 50)

Myrtenyl bromide **53** (1 g, 4.65 mmol) was added to a mixture of sodium (0.13 g, 5.6 mmol) and ethanol (1.72 g, 37 mmol) in dry THF (20 cm^3) which had been stirring for 15 min. The resulting mixture was stirred for 0.5h. The solution was filtered, the solvent was evaporated leaving a residue to which H_2O (30 cm^3) and ether (50 cm^3) were added. The layers were separated and the aqueous fraction was washed with ether (2 x 20 cm^3). The ethereal extracts were combined, dried ($MgSO_4$) and the solvent was evaporated yielding a yellow oil. The title compound was obtained as a clear, colourless liquid after Kugelrohr distillation (0.68 g, 81%), bp 50-60°C at 0.5 mmHg (lit.,[38] bp 30°C at 0.2 mmHg); δ_H 0.85 (3 H, s, methyl-H), 1.17-1.20 (4 H; 3 H, t, *J* 7.1, methyl 11-H and 1 H, methylene 5-H), 1.28 (3 H, s, methyl-H), 2.06-2.44 (5 H, m, methylene, methine-H), 3.41-3.48 (2 H, q, *J* 7.0, methylene 10-H), 3.82 (2 H, m, allyic 9-H), 5.40-5.50 (1 H, s, olefinic 8-H); δ_C 15.2 (11-C), 21.0, 26.2 (2 x 1,2-C), 31.3, 31.6 (2 x 3,5-C), 38.0 (quaternary-C), 41.0, 43.4 (2 x 4,6-C), 65.2 (10-C), 73.4 (9-C), 119.2 (8-C), 145.7 (7-C).

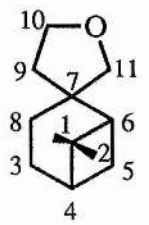
Oxacyclopentane-3-spiro-2'-6',6'-dimethylbicyclo[3.1.1]heptane (41)

Radical fragmentation of carboxylic acid 33 (Scheme 51)

Carboxylic acid **33** (2.12 g, 7.0 mmol‡) was refluxed in benzene for 5 days with portion-wise addition of dibenzoyl peroxide (3 x 0.2 g, 30% wt. overall). A sample of the reaction mixture was submitted for GC/MS; peak no. 297, 6-*endo* product **60**†, *m/z* (relative intensity), 150 (1), 135 (6), 117 (4), 107 (43), 91 (37), 79 (100), 77 (46), 65 (18), 53 (18), 51 (70), 45 (22), 39 (55), 29 (350, 27 (44); peak no. 338, benzoic acid, 122 (M^+)

(49), 105 (85), 77 (100), 51 (79); peak no. 375, oxacyclopentane-3-spiro-2'-6',6'-dimethylbicyclo[3.1.1]heptane **41**, 180 (M^+) (1), 165 (3), 154 (5), 137 (9), 107 (21), 95 (25), 91 (28), 82 (28), 79 (37), 77 (29), 67 (43), 55 (39), 41 (100), 39 (53), 29 (28), 27 (44); peak no. 428, unidentified product; peak no. 540, 6,6-dimethyl-2-(2-phenyl-ethoxymethyl)bicyclo[3.1.1]hept-2-ene **59**, 195 (3), 136 (11), 119 (16), 105 (79), 91 (100), 79 (35), 77 (36), 65 (17), 55 (12), 41 (46), 27 (23). The benzene was evaporated and the resulting solid was dissolved in ether (50 cm^3) and extracted with NaOH (2 x 20 cm^3). The ether was evaporated to yield a liquid (1.03 g) shown by ^1H NMR to be a complex mixture of products. The cyclised and aromatic products were isolated by column chromatography eluting with 5% ethyl acetate in light petroleum, to yield two main fractions, (0.19 g, 10% **41**; 5% **60** and 0.14 g, 7.4% **59**). No other identifiable products were collected. Oxacyclopentane-3-spiro-2'-6',6'-dimethylbicyclo[3.1.1]heptane **41**;¶ δ_H 0.88 (3 H, s, methyl-H), 1.14-1.25 (4 H; 3 H, methyl-H and 1 H, methylene 5-H), 1.65-1.93 (8 H, m, methylene, methine-H), 2.15-2.25 (1 H, methylene or methine-H), 3.45-3.80 (4 H, m, methylene-H); *m/z* 181 (MH^+, 100%), 167 (45), 103 (18), 151 (13), 139 (11), 123 (16), 105 (6), 95 (5), 57 (45) (Found: MH^+ 181.1586. $C_{12}H_{21}O$ requires 181.1592); GC/MS peak no. 301, 6-*endo* product; peak no. 378, 5-*exo* product. 6,6-Dimethyl-2-(2-phenylethoxymethyl)bicyclo[3.1.1]hept-2-ene **59**; δ_H 0.85 (3 H, s, methyl-H), 1.15-1.20 (1 H, d, *J* 8.6, methylene 5-H), 1.30 (3 H, s, methyl-H), 2.10-2.48 (5 H, m, methylene and methine-H), 2.86-2.98 (2 H, t, *J* 7.2, 11-H), 3.57-3.67 (2 H, t, *J* 7.3, 10-H), 3.89 (2 H, s, allylic 9-H), 5.45-5.52 (1 H, s, olefinic 8-H), 7.20-7.40 (5 H, m, arom-H); δ_C 21.0, 26.2 (2 x 1,2-C), 31.5, 31.2 (2 x 3,5-C), 36.4 (11-C), 38.0 (quaternary-C), 40.9, 43.3 (2 x 4,6-C), 70.8, 73.7 (2 x 9,10-C), 119.6 (8-C), 126.1, 127.2, 128.3, 128.9 (6 x arom-C), 145.5 (7-C); *m/z* 257 (MH^+, 10%), 239 (12), 213 (5), 195 (14), 181 (27), 167 (24), 155 (9), 135 (100), 123 (10), 105 (23), 93 (40), 79 (10), 58 (54), 56 (38) (Found: MH^+ 257.1913. $C_{18}H_{25}O$ requires 257.1905). The alkaline fractions were neutralised with excess acid and the mixture was extracted with ether to give benzoic acid (1.21 g). ‡A mixture of carboxylic acid **33** (2.12 g) and benzoic/1,4-dihydrobenzoic acid (0.15 g). †Considered to be the 6-*endo* product when analysed by ^1H

NMR. ¶ This spectrum also contained two extra singlets corresponding to methyl groups and this was evidence for another product, tentatively assigned as the 6-*endo* product **60**.



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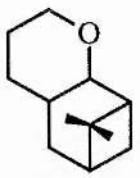

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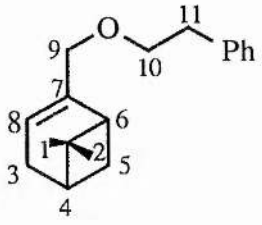

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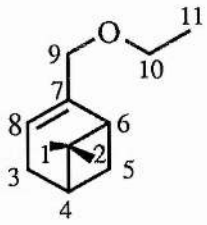


58

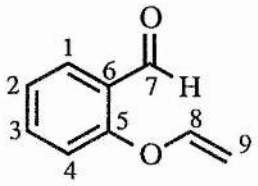
2-(2-Bromoethoxy)benzaldehyde (61) (Scheme 54)[29]

Salicylaldehyde (50 g, 0.41 mol), 1,2-dibromoethane (152.6 g, 0.812 mol) and NaOH (20 g, 0.5 mol) were refluxed in H_2O (300 cm^3) for 3 days. The layers were separated, the aqueous layer was extracted with chloroform (3 x 100 cm^3) and these extracts were combined with the dibromoethane layer. This mixture was washed with NaOH (10%, 3 x 100 cm^3), HCl (10%, 300 cm^3) and H_2O (300 cm^3), dried ($MgSO_4$) and the solvent was evaporated. Residual 1,2-dibromoethane was removed under low pressure (0.1 mmHg) yielding a solid (58 g, 62% crude yield) which was not fully pure but was mainly the desired product; δ_H 3.62-3.76 (2 H, m, methylene-H, α to O), 4.00-4.10 (minor impurity), 4.19-4.26 (minor impurity), 4.37-4.48 (2 H, m, methylene-H, α to Br), 4.54 (4 H, s, methylene-H, residual 1,2-dibromoethane), 6.93-7.13 (2 H, m, arom-H), 7.50-7.62 (1 H, m, arom-H), 7.81-7.90 (1 H, m, arom-H), 10.55 (1 H, s, aldehyde-H).

2-(Ethenyloxyl)benzaldehyde (62) (Scheme 55)[29]

2-(2-Bromoethoxy)benzaldehyde **61** (58 g, 0.253 mol) was dissolved in DMSO (200 cm^3) and cooled to below room temperature (*ca.* 10°C). To this potassium-*t*-butoxide (28.4 g, 0.253 mol) dissolved in DMSO (200 cm^3) was added dropwise. The resulting mixture was stirred for 20 min at room temperature, poured into ice-water (400 cm^3) and a few drops of H_2SO_4 were added. The product was extracted with ether (3 x 150 cm^3), the combined ether layers were washed $NaHCO_3$ (200 cm^3), H_2O (200 cm^3) and dried ($MgSO_4$). The

solvent was evaporated to give an orange liquid (34.7 g) and the title compound was obtained as a clear, colourless liquid after distillation (10 g, 27%), bp 64°C at 0.2 mmHg (lit.,[40] bp 59°C at 0.3 mmHg); δ_H (300 MHz) 4.57-4.65 (1 H, d, *J* 6.0, olefinic 9-H), 4.83-4.90 (1 H, d, *J* 13.6, olefinic 9-H), 6.66-6.76 (1 H, dd, *J* 13.8, 5.8, olefinic 8-H), 7.05-7.25 (2 H, m, arom-H), 7.54-7.62 (1 H, t, *J* 7.7, arom 3-H), 7.86-7.90 (1 H, d, *J* 7.8, arom 1-H), 10.45 (1 H, s, aldehyde-H); δ_C (50 MHz) 97.8 (9-C), 117.4 (4-C), 123.9 (2-C), 126.5 (6-C), 128.9, 136.8 (2 x 1,3-C), 148.0 (8-C), 159.3 (5-C), 189.5 (7-C).



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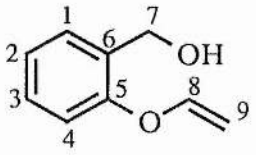

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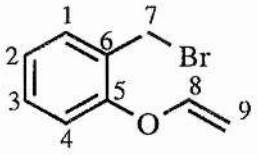


64

2-(Ethenyloxy)benzyl alcohol (63) (Scheme 55)[29]

To a solution of $LiAlH_4$ (2.3 g, 61 mmol) in dry ether (200 cm^3) was added with stirring a solution of 2-(ethenyloxyl)benzaldehyde **62** (15 g, 0.103 mol) in ether (100 cm^3) at room temperature. The mixture was refluxed for 1h, wet ether (50 cm^3) followed by H_2O (100 cm^3) were added to the reaction mixture and the resulting lithium salts were filtered. The solvent was evaporated to yield the title compound as an almost clear and colourless liquid (14.8 g, 97%); δ_H 4.43-4.48 (1 H, dd, *J* 1.8, 6.2, olefinic 9-H), 4.69-4.76 (1 H, dd, *J* 1.8, 13.8, olefinic 9-H), 4.71 (2 H, s, benzylic 7-H), 6.60-6.70 (1 H, dd, *J* 6, 13.6, olefinic 8-H), 6.96-7.00 (1 H, d, *J* 7.6, arom 4-H), 7.06-7.14 (1 H, t, *J* 7.6, arom 2-H), 7.24-7.32 (1 H, t, *J* 7.6, arom 3-H), 7.38-7.41 (1 H, d, *J* 7.6, arom 1-H); δ_C (50 MHz) 61.4 (7-C), 95.7 (9-C), 116.9 (4-C), 124.1 (2-C), 129.4, 129.5 (2 x 1,3-C), 131.2 (6-C), 148.8 (8-C), 154.7 (5-C).

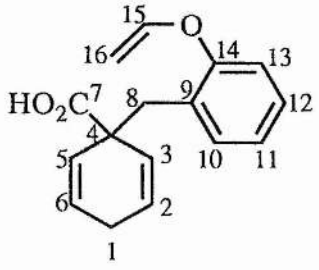
1-(Bromomethyl)-2-(ethenyloxy)benzene (64) (Scheme 56)[28]

To a solution of triphenylphosphine (22 g, 84 mmol) in DMF (300 cm^3) was added at 0°C carbon tetrabromide (27.8 g, 84 mmol). To this mixture 2-(ethenyloxyl)benzyl alcohol **63** (9 g, 60 mmol) was added and stirred at 0°C for 15 min followed by 90 min at room temperature. The mixture was diluted with ice and water (500 cm^3), extracted with pentane (4 x 75 cm^3), these fractions were combined, dried ($CaCl_2$) and the solvent was evaporated to give an orange liquid (24.16 g). This was purified by column chromatography eluting with 2% ethyl acetate in light petroleum yielding the clear, colourless bromide (5.7 g, 44%); δ_H 4.48-4.52 (1 H, dd, *J* 6.0, 1.7, olefinic 9-H), 4.56 (2 H, s, benzylic 7-H), 4.70-4.85 (1 H, dd, *J* 13.4, 1.8, olefinic 9-H), 6.60-6.70 (1 H, dd, *J* 13.6, 6.4, olefinic 8-H), 6.95-7.03 (1 H, dt, *J* 1.4, 7.1, arom 2-H), 7.07-7.11 (1 H, dd, *J* 7.6, 1.2, arom 4-H), 7.26-7.34 (1 H, dt, 2.0, 7.8, arom 3-H), 7.35-7.43 (1 H, dd, *J* 1.8, 7.4, arom 1-H); δ_C (50 MHz) 28.1 (7-C), 95.5 (9-C), 116.9, 123.7 (2 x 2,4-C) 127.9 (6-C), 130.3, 131.3 (2 x 1,3-C), 148.2 (8-C), 154.7 (5-C).

1-[2-(Ethenyloxy)benzyl]cyclohexa-2,5-diene-1-carboxylic acid (34) (Scheme 57)

Ammonia (250 cm^3) was added to benzoic acid (2.6 g, 21.4 mmol) to which Li (0.47 g, 68.2 mmol) was added portionwise causing the solution to turn blue. After 30 min the solution was quenched with 1-(bromomethyl)-2-(ethenyloxy)benzene **64** (5 g, 23.5 mmol) causing the solution to turn red. The NH_3 was evaporated using a water bath, ice was added to the residue followed by NaOH (50 cm^3) and ether (100 cm^3). The ether layer was extracted with NaOH (30 cm^3), the alkaline fractions were combined, washed with ether (100 cm^3) and neutralised with excess HCl. The product was extracted with ether (3 x 100 cm^3), the ethereal extracts were combined, dried ($MgSO_4$) and the solvent was evaporated yielding a yellow oil (3.25 g; 2.75 g, 50%, title compound and 0.5 g, unreacted benzoic acid). The title compound was recrystallised from cyclohexane yielding white crystals (1.37 g, 25%), mp 99-101°C (Found: C, 74.76; H, 6.34. Calc. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29%); δ_H 2.15-2.60 (2 H, m, allylic-H), 3.13 (2 H, s, benzylic-H), 4.37-4.40 (1 H,

dd, *J* 6.1, 1.6, olefinic 16-H), 4.67-4.72 (1 H, dd, *J* 13.8, 1.6, olefinic 16-H), 5.73-5.98 (4 H, m, olefinic 2,3,5,6-H), 6.50-6.56 (1 H, dd, *J* 13.7, 6.1, olefinic 15-H), 6.88-7.22 (4 H, m, arom-H); δ_C 25.8 (1-C), 39.0 (8-C), 48.8 (4-C), 94.7 (16-C), 116.1, 122.5 (2 x 11,13-C), 126.1, 126.4 (4 x 2,3,5,6-C), 126.4 (9-C), 127.9, 132.6 (2 x 10,12-C), 148.5 (15-C), 155.4 (14-C), 180.1 (7-C).



34

Radical fragmentation of carboxylic acid 34 (Scheme 58)

1-[2-(Ethenyloxyl)benzyl]cyclohexa-2,5-diene-1-carboxylic acid (1 g, 3.91 mmol) and dibenzoyl peroxide (0.25 g, 25% wt.) were dissolved in benzene (10 cm^3) and refluxed for 2 days under nitrogen, during which a further portion of initiator (0.20 g) was added. A sample of the reaction mixture was submitted for GC/MS analysis; peak no. 231, 1-(ethenyloxy)-2-methylbenzene, *m/z* (relative intensity), 134 (M^+) (60), 119 (27), 105 (37), 91 (100), 77 (59), 65 (57), 51 (43), 39 (78), 27 (61), 18 (47); peak no. 264, 1-(ethoxy)-2-methylbenzene, 136 (M^+) (28), 108 (62), 107 (50), 91 (17), 84 (27), 79 (26), 77 (31), 65 (14), 52 (15), 51 (19), 18 (100); peak no. 356, benzoic acid; peak no. 474, 1-(ethenyloxy)-2-methylphenyl benzene, 210 (M^+) (34), 195 (32), 181 (29), 165 (68), 152 (26), 115 (40), 105 (29), 91 (79), 77 (81), 63 (38), 51 (67), 39 (61), 27 (100), 18 (96); peak no. 564, 1-(ethoxy)-2-methylphenyl benzene, 212 (M^+) (5), 184 (7), 163 (8), 106 (7), 105 (100), 91 (9), 78 (65), 77 (56), 51 (33), 39 (31), 27 (16), 18 (24). The mixture was passed down a column of silica gel which only resulted in one fraction which gave a well-resolved ^1H NMR spectrum (60 mg; 11 mg, 3%, **65**; 36 mg, 4%, **66**; 13 mg, biphenyl) δ_H 2.36 (3 H, s, methyl-H, **65**), 3.98 (2 H, s, benzylic-H, **66**), 4.37-4.40 (2

H, m, olefinic-H, **65**, **66**), 4.58-4.70 (2 H, m, olefinic-H, **65**, **66**), 6.57-6.671 (2 H, m, olefinic-H, **65**, **66**), 6.95-7.70 (23 H, m, arom-H, **65**, **66**, biphenyl).

Tin hydride mediated reduction of bromide 64 (Scheme 60)

1-(Bromomethyl)-2-(ethenyloxy)benzene **64** (1 g, 4.7 mmol) and tributyltin hydride (1.5 g, 5.2 mmol) were dissolved in benzene (10 cm^3) and irradiated using a medium pressure 125 W Hg lamp for 6h. The reaction was monitored by TLC until all the bromide had been consumed. Analysis by GC/MS identified the main product as 1-(ethenyloxy)-2-methylbenzene, although two other products were detected; GC/MS peak no. 231, 1-(ethenyloxy)-2-methylbenzene, *m/z* (relative intensity), 134 (M^+) (36), 119 (25), 105 (23), 91 (65), 77 (53), 65 (63), 51 (47), 39 (100), 27 (78); peak no. 260, 1-(ethoxy)-2-methylbenzene, 136 (M^+) (46), 108 (100), 107 (83), 90 (37), 79 (48), 77 (53), 65 (18), 51 (26), 39 (29), 27 (46), 18 (35); peak no. 513, unidentified, 242 (1), 135 (42), 107 (30), 91 (100), 27(32), 65 (72), 39 (14). A saturated solution of KF (10 cm^3) was added, the resulting mixture was stirred for 24h and the tin residues were filtered off. The solvent was evaporated to yield an orange liquid (0.57 g, *ca.* 92%†); δ_H 2.16 (3 H, s, methyl-H), 4.31-4.39 (1 H, dd, *J* 6.2, 2.0, olefinic-H), 4.57-4.64 (1 H, dd, *J* 13.6, 2.0, olefinic-H), 6.56-6.66 (1 H, dd, *J* 13.5, 6.4, olefinic-H), 6.90-7.32 (4 H, m, arom-H). †This was a crude yield since the GC/MS analysis detected two other compounds, although ^1H NMR revealed that 1-(ethenyloxy)-2-methylbenzene was the only significant product.

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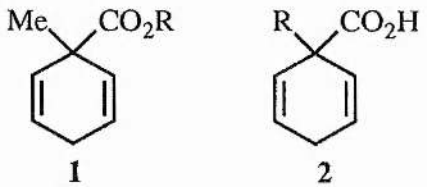
Chapter 3

1-Phenylcyclohexa-2,5-diene-1-carboxylate esters as reagents for generating radicals

1 Introduction

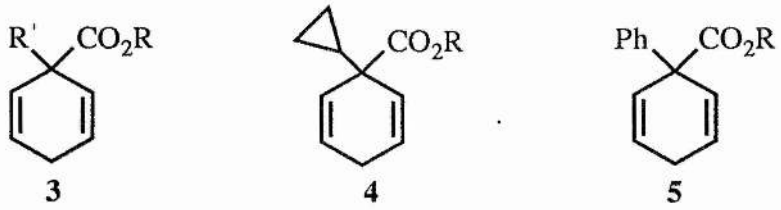
The work presented in the previous chapter, in addition to the investigations carried out on 1-methylcyclohexa-2,5-diene-1-carboxylate esters **1**,[1] has shown that cyclohexadienyl compounds **1** and **2** can function as sources of alkyl radicals R• (Scheme 1). However, as discussed previously, it was clear to us that this methodology had its limitations. In the case of the carboxylate esters **1** the yields of the products obtained by generation of the alkyl radical R• and addition to a double bond, were not as high as we would have liked. The carboxylic acids **2**, generated radicals more efficiently, but these compounds were not always straightforward to prepare. We realised, that in order to succeed in establishing a synthetically useful method for generating radicals, both of these limitations had to be overcome.



1 **2**

Scheme 1

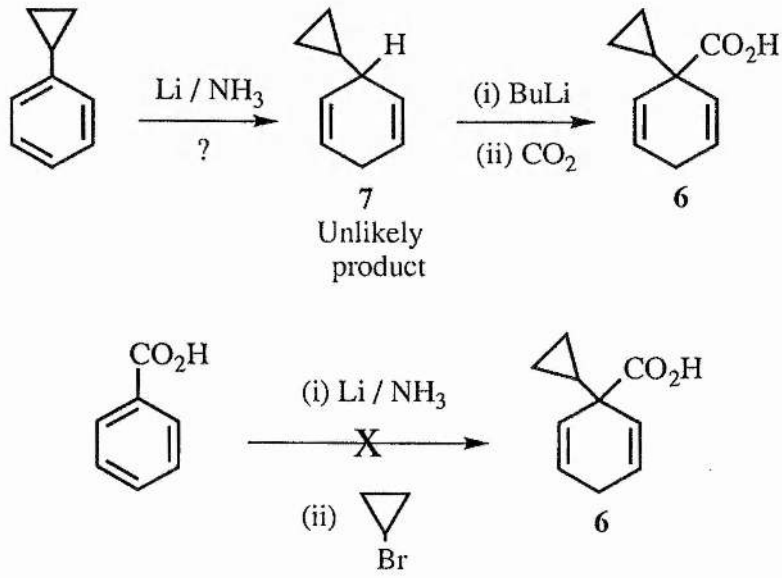
We decided to direct our efforts towards cyclohexadienyl esters of structure **3**, where R is the alkyl group we intend to generate as an alkyl radical and R' is an alternative to a methyl group (Scheme 2). Our reasons for choosing a compound of this type were based on our attempts to overcome the two limitations mentioned above: (i) the esterification of a carboxylic acid is a general reaction and one that was successful in forming carboxylate esters **1** i.e. the synthesis of the precursor carboxylates should be relatively straightforward and (ii) the radical fragmentation of the ester should occur in a selective manner *via* decarboxylation by careful choice of R'. We realised, therefore, that the group R' had to be an entity which would not form the corresponding radical R'• as easily as the methyl radical was produced from esters **1**. Since cyclopropyl and phenyl radicals are relatively unstable, we proposed that the corresponding esters **4** and **5** might be suitable for our purpose.



3 4 5

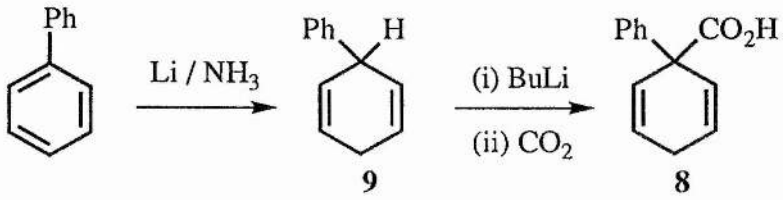
Scheme 2

In order to synthesise a range of cyclopropyl esters **4** we required the corresponding carboxylic acid **6** (Scheme 3). Since the Birch reduction of an aromatic compound is an effective method to produce a cyclohexadienyl ring, we considered the two routes shown in Scheme 3. The reduction of cyclopropylbenzene would, however, be unlikely to give the dihydro compound **7**. It would be more likely to result in the formation of the undesired regioisomer and as a result this reaction was not attempted. The conversion of benzoic acid into cyclopropyl acid **6**, by quenching the anion resulting from the Birch reduction with cyclopropyl bromide, was considered to be a more likely route. However, this latter reaction failed to yield any of the desired product. This was perhaps not too suprising; the carbon-carbon single bonds in the cyclopropane ring are not particularly strong, whereas the bonds between carbon and its substituents (e.g. bromine in cyclopropyl bromide) are much stronger, hence not easy to break.



Scheme 3

Owing to the difficulties in forming the cyclopropyl acid **6** we decided to concentrate our efforts on the phenyl esters **5** which would be prepared from carboxylic acid **8** (Scheme 4). A brief literature note indicated that carboxylic acid **8** could be prepared by treating 1,4-dihydrobiphenyl **9** with base followed by carbon dioxide.[2] Dihydrobiphenyl is itself readily available from biphenyl and the intended two-step sequence to carboxylic acid **8** is shown in Scheme 4. The majority of this chapter discusses the work done in this area.

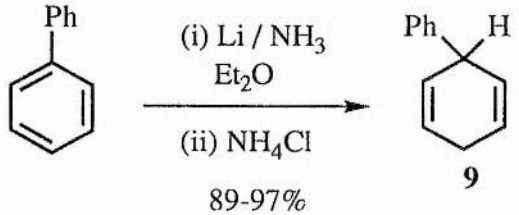


Scheme 4

2 Results and discussion

2.1 1,4-Dihydrobiphenyl (9)[3]

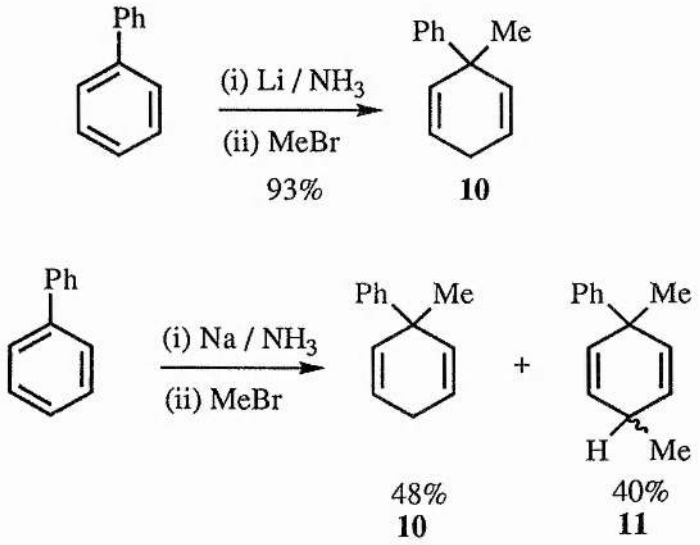
Biphenyl was converted into 1,4-dihydrobiphenyl in high yield according to the procedure of Harvey (Scheme 5).[3] This experiment was carried out numerous times, each time the amount of biphenyl in 1 litre of ammonia was increased until the optimum amount of 17-20g was reacted. Exceeding this value resulted in some unreacted biphenyl. The product was obtained as a clear, colourless liquid by distillation in almost quantitative yields. The ^{1}H NMR spectrum of 1,4-dihydrobiphenyl is given in figure 1, immediately before the experimental section, in order to compare with some of the other compounds prepared.



Scheme 5

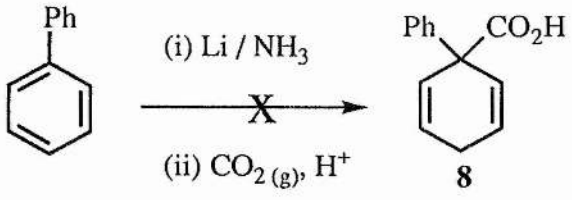
2.2 Attempted preparation of 1-phenylcyclohexa-2,5-diene-1-carboxylic acid (8)

Harvey has also described the preparation of 1-methyl-1,4-dihydrobiphenyl **10** by reducing biphenyl under the usual Birch conditions and then bubbling methyl bromide into the reaction mixture (Scheme 6).[3] Interestingly, the use of Na instead of Li yielded the dimethylated product **11** in comparable yield to **10**.



Scheme 6

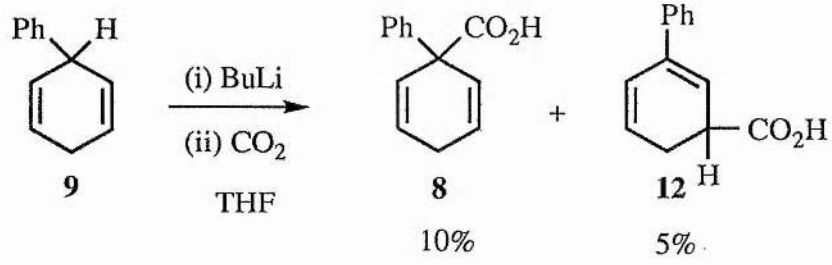
We therefore considered repeating the same reaction but bubbling carbon dioxide into the reaction mixture instead of methyl bromide (Scheme 7), but were disappointed to find that after work-up, the main compounds present were biphenyl and 1,4-dihydrobiphenyl. None of the carboxylic acid **8** had formed in this reaction.



Scheme 7

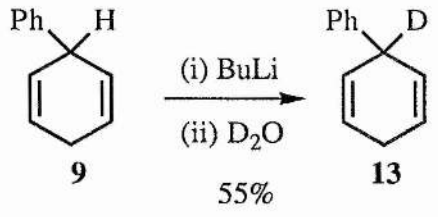
2.3 1-Phenylcyclohexa-2,5-diene-1-carboxylic acid (8)

Our following attempts to prepare carboxylic acid **8** involved treating dihydrobiphenyl with BuLi for an appropriate period of time, followed by quenching the reaction mixture with carbon dioxide. Table 1, (immediately before the experimental section), provides some information regarding these reactions. The initial attempt involved bubbling carbon dioxide into the mixture as described by Birch (entry 1, Table 1).[2] However, we found this method failed to yield any of the required product. When pellets of dry ice were added to the reaction mixture instead, the results were still poor, yielding acid **8** in typical yields of ≈10%, which was accompanied by the presence of the isomeric acid **12**, (see entries 2-4, Table 1 and Scheme 8). It was clear these methods were not going to produce appreciable quantities of acid **8**.



Scheme 8

We attempted to prepare acid **8** by varying the base, but methyl lithium (entries 5-6) and sodium hydride (entry 7) were found to be no better than BuLi. In order to establish whether the *t*-C was being deprotonated, dihydrobiphenyl **9** was treated with BuLi and quenched with D_2O after 2h (Scheme 9 and entries 8-9). Analysis by ^1H NMR spectroscopy indicated the disappearance of the *t*-H signal and ^2D NMR indicated the formation of a singlet corresponding to the *t*-deuterium atom present in compound **13**. The yield of dihydrobiphenyl **13** was 55% and this was accompanied by some biphenyl (16%). It was evident from this simple experiment that the *t*-hydrogen present in **9** could be removed with BuLi to give the corresponding anion, which could be quenched regioselectively with D_2O.



9 **13**

Scheme 9

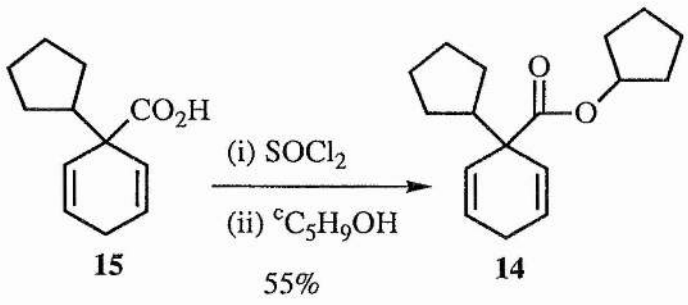
Having demonstrated that 1,4-dihydrobiphenyl could be deprotonated and then quenched with D_2O, we thought that the difficulties in obtaining carboxylic acid **8** were due to the limited reactivity between the anion and carbon dioxide. It was at this point when we decided that it may be more successful if the reaction mixture was poured *onto* dry ice, rather than addition of solid or gaseous carbon dioxide to the reaction mixture. The results of this experiment were encouraging since the desired acid could be obtained as the major isomer in a mixture of acids **8** and **12** (entries 10-15). In this way it was possible to convert dihydrobiphenyl into the acids, to give an overall yield of typically 80% for the conversion. The ^1H NMR spectrum of the mixture of acids **8** and **12** is given in figure 1. From this spectrum it is clear that the signal corresponding to the *t*-H in **9**, has been removed. The two allylic signals between 2.5 and 3 ppm correspond to the two sets of allylic signals present in the two acids **8** and **12** and the doublet at 6.35 ppm corresponds to one of the olefin hydrogens in **12**.

Unfortunately, it was not possible to separate the two regioisomers either by chromatography or recrystallisation, but this was not too suprising. Analysis by TLC revealed streaking over a range of solvent mixtures, and although column chromatography was attempted a few times, the two acids eluted together. Selective recrystallisation of one of the isomers was considered to be even more unlikely and unsurprisingly this method failed to yield any of carboxylic acid **8** in pure form. We decided to esterify the mixture of carboxylic acids with the appropriate alcohol, separate the esters by column chromatography and use the isolated ester **5** in the radical reactions we were investigating.

A recent paper by Birch gave experimental information concerning the preparation of the methyl ester of carboxylic acid **8**.[4] This procedure involved treating dihydrobiphenyl with BuLi at -70°C for 15 min in THF and a small amount of HMPA, and quenching with gaseous CO_2. We followed this procedure (entry 16, Table 1), and although the yields were improved compared to our previous reaction involving gaseous CO_2 (entry 1), we identified the presence of both acids **8** and **12** in yields of 24% and 14% respectively. This was not consistent with the data given by Birch, which described the formation of only the 1,4-diene methyl ester in 48% yield after methylation.[4]

2.4 Cyclopentyl 1-cyclopentylcyclohexa-2,5-diene-1-carboxylate (14)

Cyclopentyl acid **15** was converted into the cyclopentyl ester **14** in 55% yield (Scheme 10). Although we did not require **14** for experimental reasons, this transformation was simply used as a model for the esterification of acid **8**, since plenty of acid **15** was available.

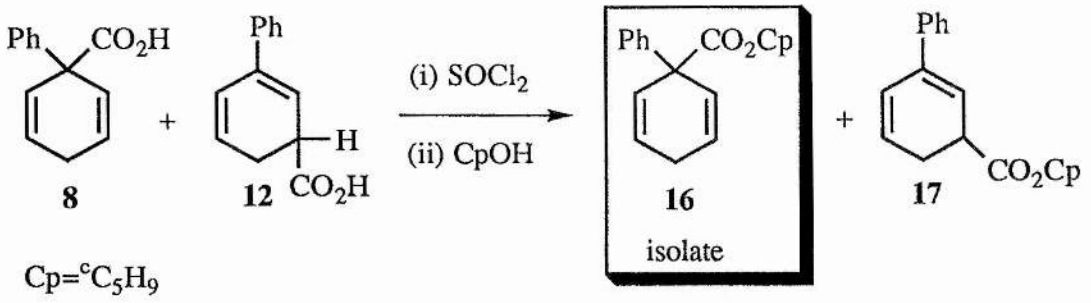


15 **14**

Scheme 10

2.5 Cyclopentyl 1-phenylcyclohexa-2,5-diene-1-carboxylate (16)

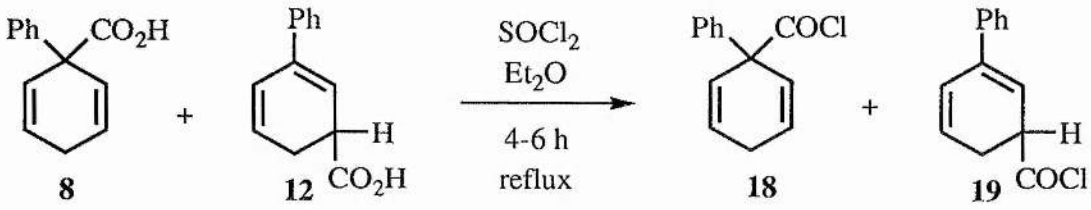
Our intention was to esterify the mixture of carboxylic acids **8** and **12** by the same procedure as shown above. We anticipated that the two resulting esters **16** and **17** would be easier to separate than acids **8** and **12** by column chromatography. Thus, the intended sequence of events are summarised in Scheme 11. It turned out, however, that this was more difficult to do than originally thought.



Scheme 11

Formation of the acid chloride

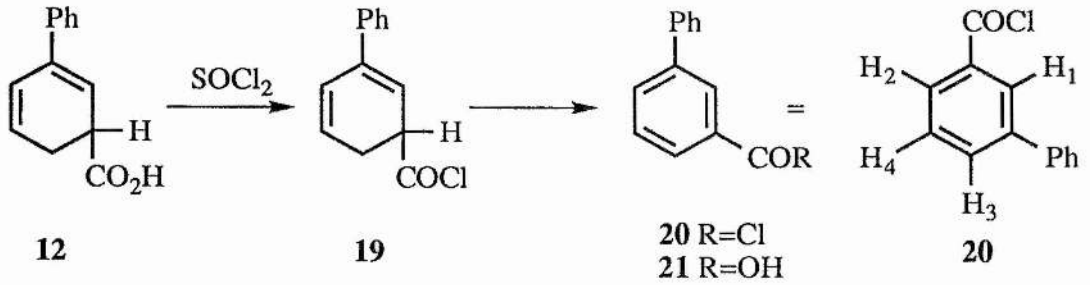
The conversion of carboxylic acids **8** and **12** into the corresponding acid chlorides **18** and **19** was assessed by ^{1}H NMR spectroscopy instead of IR, since on completion, the multiplet corresponding to the olefinic hydrogens was replaced by a singlet (see figure 2, spectrum 2).



Scheme 12

Inspection of the spectra given in figure 2, reveals some interesting features. As already mentioned, when the mixture of acids **8** and **12** (spectrum 1), were treated with thionyl chloride, a singlet at 6.1 ppm denoted complete reaction (spectrum 2). This was accompanied by the disappearance of the allylic group at 2.55 ppm and the olefinic signal at 6.35 ppm, both associated with carboxylic acid **12**. Taking into consideration the appearance of the new aromatic signals between 7.9 and 8.4 ppm, it seemed reasonable to suggest that carboxylic acid **12** was converted into the corresponding acid chloride **19**, which was unstable and immediately aromatised to give acid chloride **20**, (Scheme 13). It was not too surprising that acid chloride **20** was unstable, as it has been reported that 3,4-dihydrobiphenyl is an unstable compound which cannot be isolated.[5] The signal at 8.35

ppm corresponded to hydrogen H_1 of compound **20** and the two doublets at 8.12 ppm and 7.92 ppm corresponded to hydrogens H_2 and H_3 respectively. Hydrogen H_4, being *meta* to both the acid and the phenyl groups, was not as electron-deficient as the other hydrogen atoms and its signal was hidden underneath the other aromatic signals. Additionally, the signal at 7.62 ppm in spectrum 2 corresponded to a small amount of biphenyl, formed mainly from acid chloride **20**.



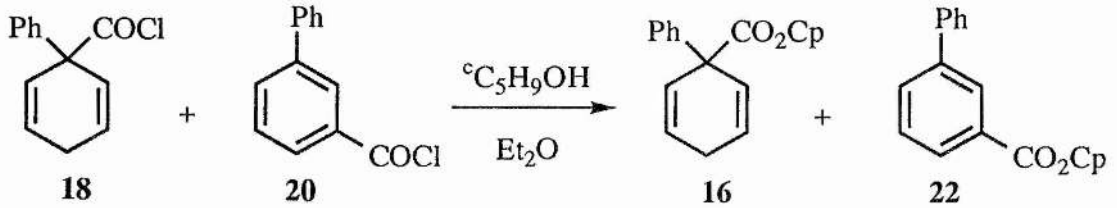
12 **19** **20** R=Cl **21** R=OH **20**

Scheme 13

We also noted that if the mixture of acids **8** and **12** only were simply refluxed in ether for 24-48h, carboxylic acid **12** eventually disappeared and the corresponding aromatic acid **21** appeared in its place. Spectrum 3, in figure 2, indicates the gradual disappearance and appearance of carboxylic acids **12** and **21** respectively, in addition to carboxylic acid **8** and some residual ether.

Conversion of the acid chlorides into the esters

The acid chlorides **18** and **20** were added to a slight excess of cyclopentanol dissolved in dry ether, and this mixture was refluxed until we considered the reaction to be complete (Scheme 14).



18 **20** **16** **22**

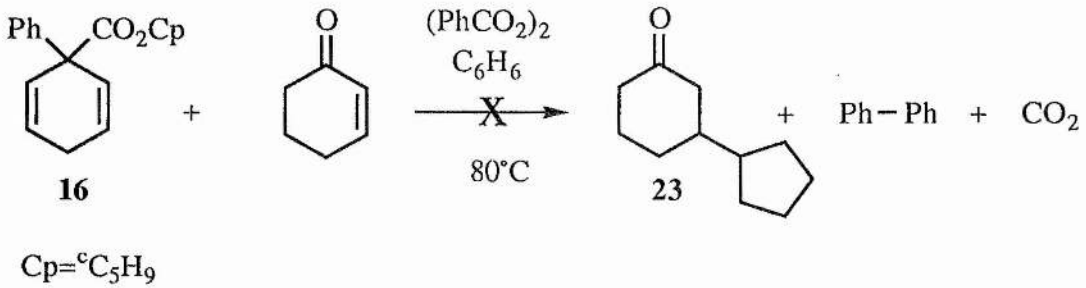
Cp=$^{c}C_5H_9$

Scheme 14

This reaction was carried out a number of times, but on each occasion the yield of the ester was poor and significant purification was needed. During the work-up, appreciable quantities of the unreacted acids **8** and **21** were regenerated, and this was one of the reasons for the low yield of product. The esters which were obtained from this reaction were a mixture of **16** and **22** and it was very difficult to separate them. However, a small amount of **16** was isolated in sufficiently pure form to be used in the radical reaction described below.

2.6 Radical initiated reaction of cyclopentyl ester 16 with cyclohexenone

A small amount of cyclopentyl ester **16** obtained in almost pure form by chromatography, was refluxed in benzene in the presence of cyclohexenone and dibenzoyl peroxide (Scheme 15). This mixture was refluxed for 24h and monitored by GC/MS, but unfortunately none of the desired adduct **23** was observed. Over this period of time the ester had remained largely unreacted and was recovered almost unchanged.



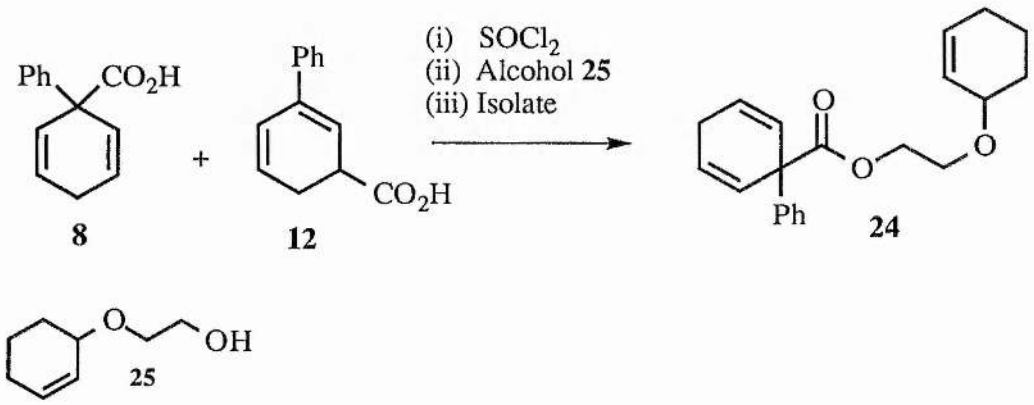
Scheme 15

The results from this experiment were disappointing as we had hoped for a more encouraging outcome, which would have merited further investigation into the esters **5**. Although difficulties were met in forming esters such as **16**, in addition to the absence of any addition product **23** in the above experiment, we thought that further studies were required. If an ester **5** containing an R group suitable for an intramolecular radical reaction to take place, could be prepared in pure form, then we would be in a better position to

judge their potential as efficient sources of alkyl radicals. The preparation of ester **24** was therefore attempted.

2.7 2-(Cyclohex-2-enyloxy)ethyl 1-phenylcyclohexa-2,5-diene-1-carboxylate (24)

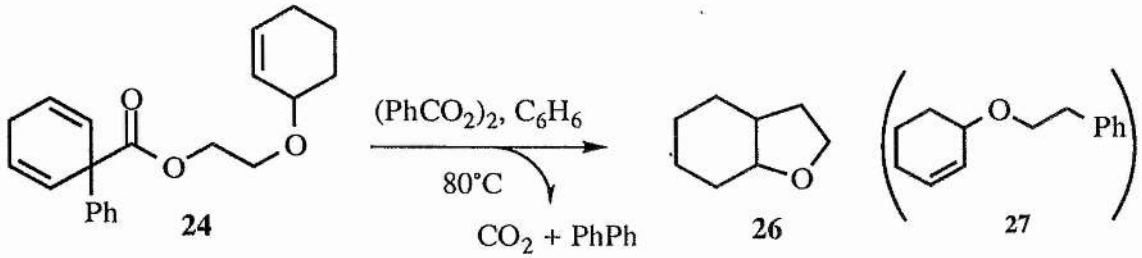
The two carboxylic acids **8** and **12** were treated with thionyl chloride yielding acid chlorides **18** and **20**. This mixture was added to some dry ether containing alcohol **25**, and the desired ester **24** was isolated in relatively pure form, for use in the radical fragmentation reaction (Scheme 16). In this manner, ester **24** was obtained as an almost clear, colourless oil in 30% yield from the corresponding acid **8**.



Scheme 16

2.8 Radical-induced fragmentation of ester 24

The ester obtained from the reaction mixture above was dissolved in benzene and treated with dibenzoyl peroxide (Scheme 17). The mixture was refluxed for 24h and analysis by GC/MS indicated that only a trace amount of the ester remained, and the two major products from the reaction were biphenyl and 7-oxabicyclo[4.3.0]nonane **26**. Two other minor products were observed by GC/MS, one of which was unidentified, whilst the other was identified as 3-(2-phenylethoxy)cyclohexene **27**. The only viable explanation for the formation of the latter compound was considered to be generation of the expected radical followed by addition to the solvent before cyclisation.



Scheme 17

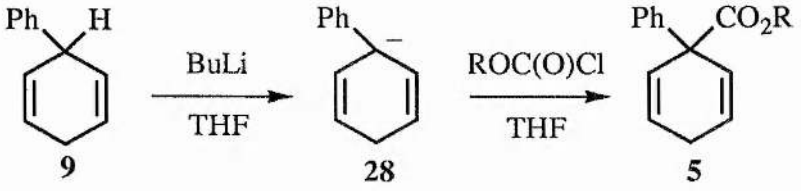
Since only a small amount of ester **24** was used in this experiment, it was difficult to determine the yield of cyclic product **26** accurately. The benzene was removed by atmospheric distillation but analysis of the residue by ^{1}H NMR revealed some residual benzene. An attempt to establish the yield of **26** by GC using a standard, gave a disappointing result of only 31%. We believed, however, that the true yield of **26** was higher than this. Nevertheless, this experiment had provided clear evidence that ester **24** could undergo decarboxylative fragmentation to generate a primary radical capable of cyclising to give bicyclononane **26**. Furthermore, none of the benzoate ester resulting from loss of a phenyl radical was identified. This was consistent with our prediction that such cyclohexadienes would fragment in a selective manner.

At this stage a lot of work had been put into this area of the project and it was realised that a method was required to enable easy isolation of carboxylic acid **8**. We did not believe that it would be worthwhile varying the reaction conditions, (e.g. solvent, base), for the conversion of dihydrobiphenyl **9** into acid **8**, as it was anticipated that this would still result in the formation of a mixture of acids. Either an effective, reproducible technique for separating acids **8** and **12** had to be introduced or a new route to the esters had to be proposed.

2.9 An alternative approach to prepare esters 5

We thought that it might be feasible to go direct from 1,4-dihydrobiphenyl to the corresponding esters **5**, by deprotonating with base and quenching the resulting anion **28** with the appropriate chloroformate (Scheme 18). Such a route was worthy of investigation

since chloroformates can, in general, be prepared in good yield by reacting the corresponding alcohol with phosgene.[6] Furthermore, the experiments involving deprotonation of dihydrobiphenyl **9** and quenching with an electrophile are straightforward to perform.



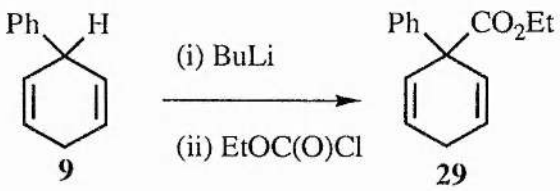
9 **28** **5**

Scheme 18

On the other hand we realised that this method posed two potential problems. Firstly, when the anion **28** was quenched with D_2O (Scheme 9), only one deuterated product was formed. With carbon dioxide, two regioisomers were produced and it was thought that this was due to the greater steric hindrance encountered in attacking a relatively congested centre. Since chloroformates are even bulkier, we realised that a mixture of isomeric esters might result and therefore re-introduce the original problems. Secondly, the successful preparation of acid **8** required the addition of anion **28** to a large excess of dry ice. This procedure would not be attractive from a preparative point of view, if the chloroformate and the precursor alcohol had to be prepared.

2.9.1 Ethyl 1-phenylcyclohexa-2,5-diene-1-carboxylate (29)

Dihydrobiphenyl was deprotonated with BuLi and after an appropriate period of time the resulting anion was quenched with a slight excess of ethyl chloroformate (Scheme 19).



9 **29**

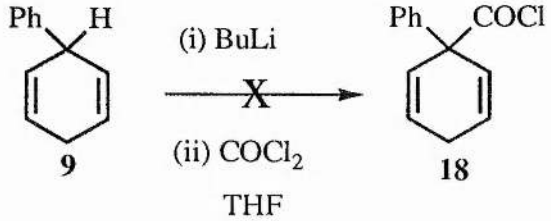
Scheme 19

Analysis of the product mixture by ^1H NMR indicated that the reaction did not proceed in a clean and selective manner. The mixture was purified by column chromatography enabling isolation of ester **29** in a disappointing yield of 27%. Further experiments were carried out

to try and improve the yield, including the addition of a large excess of the chloroformate to the reaction mixture or adding the reaction mixture to a large excess of the chloroformate. However, neither of these alternative procedures significantly improved the yield of **29**. An experiment was also performed, whereby the anion was quenched with cyclopentyl chloroformate, but a complex ^{1}H NMR spectrum was obtained, illustrating a poor yield of the cyclopentyl ester **16**. The major byproducts in these experiments were biphenyl and unreacted starting material, which suggested that the anion **28** was not particularly reactive towards the chloroformates. There was no evidence for the formation of the regioisomeric ester when anion **28** was quenched with ethyl chloroformate, though with cyclopentyl chloroformate the aromatic ester **22** was observed to a small extent by ^{1}H NMR. Although these reactions had shown that it was possible to form esters **5** direct from 1,4-dihydrobiphenyl, this method was less effective than the esterification procedure discussed in the previous section.

2.10 Attempted preparation of 1-phenylcyclohexa-2,5-diene-1-carbonyl chloride (18)

The preparation of acid chloride **18** was attempted, by treating 1,4-dihydrobiphenyl with BuLi and then adding this mixture to phosgene (Scheme 20). However, a significant amount of the starting material was regenerated on work-up and there was no evidence for acid chloride **18**. Since these routes to esters **5** were either low-yielding or simply did not work, they were not pursued any further. Following this, a successful method which allowed carboxylic acid **8** to be obtained in pure form was established. We were therefore in a position to prepare esters **5** without having to encounter the purification difficulties discussed so far.

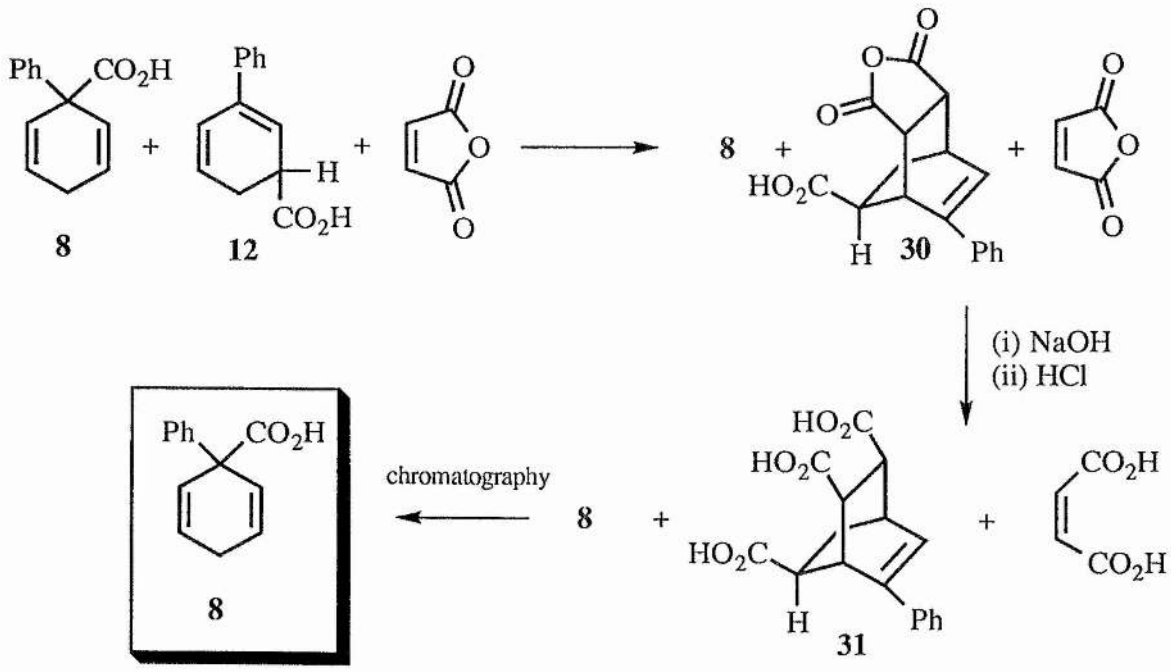


9 **18**

Scheme 20

2.11 Purification of 1-phenylcyclohexa-2,5-diene-1-carboxylic acid (8)

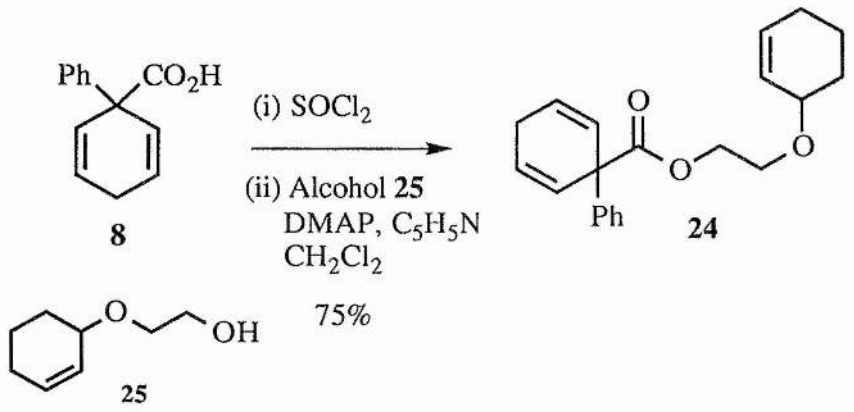
Carboxylic acid **8** was isolated by dissolving the two acids in dichloromethane and adding maleic anhydride. The resulting mixture was refluxed for an appropriate period of time, treated with NaOH, reacidified with HCl, then worked up in a conventional manner and eluted through silica gel, resulting in good recovery of **8** from the product mixture. Since the regioisomeric acid **12** is a 1,3-conjugated diene it reacts with maleic anhydride to give the Diels-Alder adduct **30** (Scheme 21). Treating the resulting mixture with NaOH opens the anhydride present in both the adduct and excess maleic anhydride. Addition of HCl regenerates acid **8** and yields triacid **31** and maleic acid. The latter two compounds are not particularly mobile on silica gel and this allows acid **8** to be eluted from the column in pure form with 30% ethyl acetate in light petroleum. In this manner, carboxylic acid **8** was obtained as a very pale, yellow solid in 35-40% yield from 1,4-dihydrobiphenyl. The ^{1}H NMR spectrum of the purified acid **8** is given in figure 1.



Scheme 21

2.12 2-(Cyclohex-2-enyloxy)ethyl 1-phenylcyclohexa-2,5-diene-1-carboxylate (24)

The purified carboxylic acid **8** was converted to the corresponding acid chloride **18** which was added to a mixture of dichloromethane containing pyridine, DMAP and alcohol **25** (Scheme 22). The ester was purified by column chromatography affording an almost colourless, clear liquid in 75% yield.

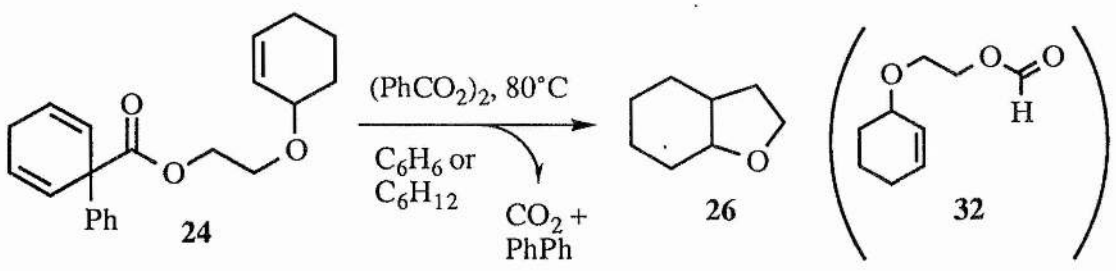


Scheme 22

2.13 Radical-induced fragmentations of ester 24

Small-Scale Reactions

It was previously observed (Scheme 17) that when ester **24** was treated with dibenzoyl peroxide in benzene, the aromatic product **27** formed. Our explanation for this observation was addition of the initially formed primary radical to benzene. We therefore performed two experiments, one using benzene as the solvent and the other using cyclohexane and compared the results (Scheme 23). Both experiments produced near identical results, as determined by GC/MS analysis. Four products were formed in both reactions. The expected products, biphenyl and bicyclic product **26** were the major components. Benzoic acid, presumably resulting from reaction of the initiator, was also observed. The fourth compound was formate **32** which may have resulted from formation of the alkoxy carbonyl radical followed by hydrogen abstraction before decarboxylation. Neither reaction gave 3-(2-phenylethoxy)cyclohexene **27**.



Scheme 23

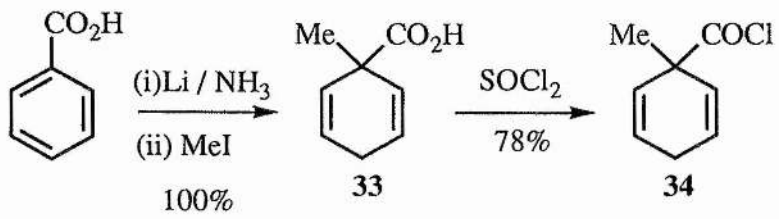
Another experiment with ester **24** was also done on a small-scale using amyl alcohol (2-methylbutan-2-ol) as the solvent[7] and *t*-butyl peroxybenzoate as the initiator. The mixture was refluxed at 100°C for 14h, after which all of the ester had reacted. Analysis of the reaction mixture by GC/MS indicated the formation of both biphenyl and the cyclic product **26**. There was also a minor amount of the formate **32**, but no other products were detected. It was obvious that the reaction proceeded more cleanly when amyl alcohol was used as the solvent in place of either benzene or cyclohexane. Since the reaction temperature was 100°C rather than 80°C, the reaction was finished in a shorter period of time, without the need to add further portions of initiator. Although formate **32** was still detected, the proportion was significantly less, indicating that the higher reaction temperature increased the rate of decarboxylation. The practical problem with this experiment, however, was the need to remove the higher boiling solvent without losing the volatile product.

We decided to bypass this problem by determining the GC yield of 7-oxabicyclo[4.3.0]nonane **26** using hexadecane as a standard. Using this technique the estimated yield of the cyclic product **26** was only 36%. Since this value was lower than we had expected the reaction was repeated and this time the yield was 32%. Although these yields were low, they were consistent and hence the majority of the starting material was unaccounted for. Since only two main products were observed by GC/MS analysis, the amyl alcohol was evaporated to evaluate whether polymeric material had been formed. Analysis of the residue by ^{1}H NMR revealed the presence of residual hexadecane and

biphenyl, with no evidence for polymer. Further work with related esters is currently being pursued to determine the potential of esters **5** as sources of alkyl radicals.

2.14 1-Methylcyclohexa-2,5-diene-1-carbonyl chloride (34)

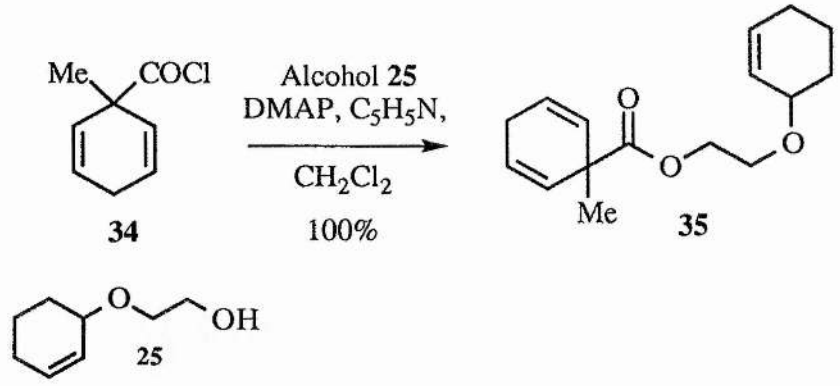
We decided to prepare the analogous ester of carboxylic acid **33** and determine how it behaved under similar conditions to the radical reactions explained above. This would allow us to directly compare the effect of substituting a methyl group with a phenyl group. It was already known that the ester **24** underwent radical fragmentation without generating the phenyl radical, and it was sensible to determine whether ester **35** would generate methyl radicals in competition with decarboxylation. 1-Methylcyclohexa-2,5-diene-1-carboxylic acid was formed in quantitative yield *via* the Birch reduction-methylation of benzoic acid (Scheme 24).[1] The acid **33** was treated with thionyl chloride yielding the acid chloride **34** as a clear, colourless liquid in 78% yield after distillation.



Scheme 24

2.15 2-(Cyclohex-2-enyloxy)ethyl 1-methylcyclohexa-2,5-diene-1-carboxylate (35)

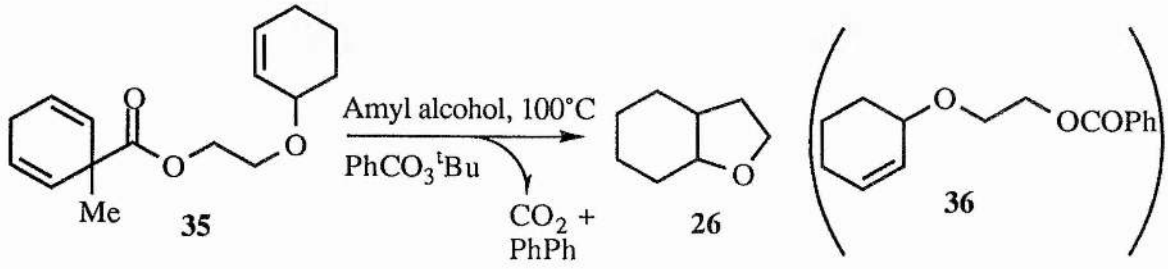
Acid chloride **34** was added to a mixture of dichloromethane, DMAP, pyridine and alcohol **25**. This yielded ester **35** isolated as a pale yellow liquid in quantitative yield (Scheme 25). It was convenient to purify the acid chloride by distillation, since the esterification step yielded the ester which was pure enough to be used directly in the following radical reaction. For these reasons, it would have been convenient if acid chloride **18** was also purified by distillation, but the higher temperature required resulted in decomposition.



Scheme 25

2.16 Radical reaction of ester 35 *Small-scale reaction*

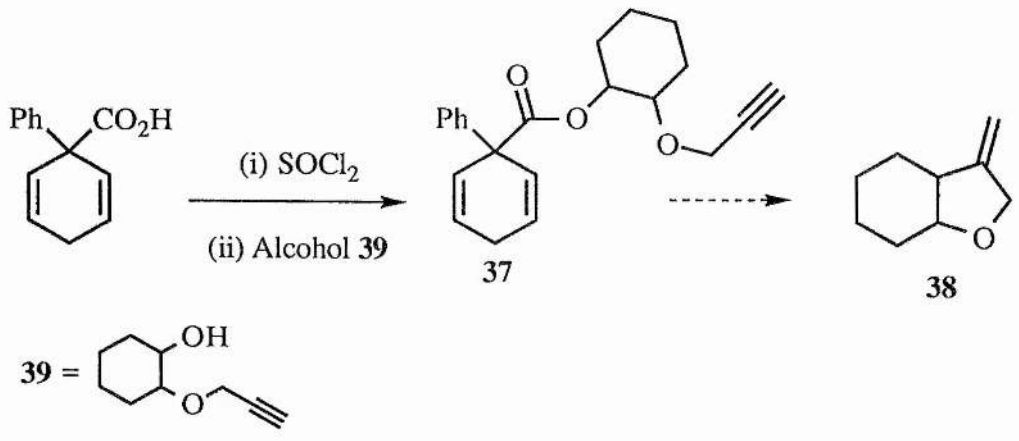
Ester **35** was dissolved in amyl alcohol and refluxed for 24h in the presence of *t*-butyl peroxybenzoate (Scheme 26). Analysis of the reaction mixture by GC/MS detected 7-oxabicyclo[4.3.0]nonane **26**, some unreacted ester **35** and 2-(cyclohex-2-enyloxy)ethyl benzoate **36**. The presence of the aromatic ester was confirmed by comparison with a pure sample prepared from benzoic acid. A control experiment, which involved refluxing ester **35** in amyl alcohol in the absence of any other chemicals, for 24h revealed no decomposition had taken place. Therefore, this proved that the ester **36** had formed by loss of a methyl radical from the intermediate cyclohexadienyl radical. It was also apparent that ester **35** reacted more slowly than the analogous ester **24**, because the latter was usually consumed within 12-14h, whereas the former could still be detected after refluxing for 24h.



Scheme 26

2.17 2-(Prop-2-ynyloxy)cyclohexyl 1-phenylcyclohexa-2,5-diene-1-carboxylate (37)

Recently, attempts have been made to prepare ester **37** using alcohol **39** which had been prepared previously (Chapter 2 and Scheme 27 below). The radical initiated fragmentation of ester **37** would produce unsaturated 9-methylene-7-oxa-bicyclo[4.3.0]nonane **38** which would be compared with the results obtained from a similar area of study in the previous chapter. Although the desired ester has not been isolated, the reaction has only been performed on a small-scale. ^{1}H NMR evidence indicated that the product and unreacted alcohol (1 equivalent) existed in approximate ratios of 1:1. The reaction was not performed on a larger scale until optimum conditions could be found, and since this work was carried out late in the PhD there was no time to isolate and react this ester. Nevertheless, the fact that the compound was present indicated the advantage of the esterification method over the Birch reduction-alkylation method for preparing the radical precursors (*cf.* attempts to prepare carboxylic acid **31** in the previous chapter were unsuccessful).

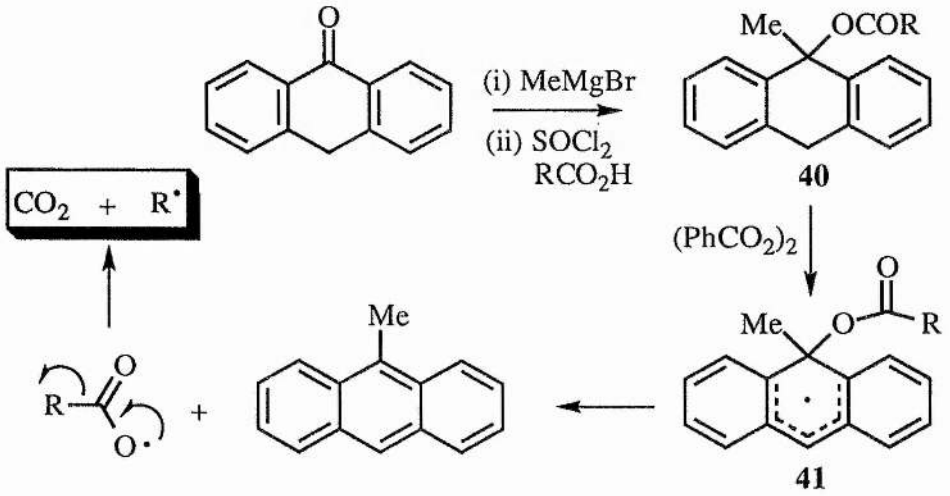


Scheme 27

2.18 Ester derivatives of 9-methylanthrol as potential sources of radicals.

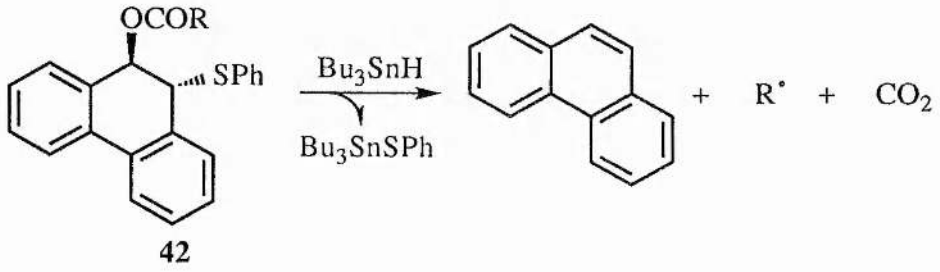
Preliminary investigations have also focused on esters **40** as potential sources of alkyl radicals (Scheme 28). We expected *bis*-allylic hydrogen atom abstraction to take place when such esters were treated with dibenzoyl peroxide, to give delocalised radical **41**

which could in principle, aromatise *via* C-O bond cleavage. Decarboxylation of the resulting carbonyloxyl radical would then afford the corresponding alkyl radical, R•.



Scheme 28

Barton has shown that esters **42**, prepared by ring opening of phenanthrene epoxide with thiophenoxide and esterification of the resulting alcohol, can participate in radical chain reactions resulting in the decarboxylation of a range of carboxylic acids (Scheme 29).[8] When treated with tributyltin hydride and AIBN, the thiophenyl group was displaced by the tin radical, $Bu_3Sn^•$ and the resulting benzylic radical underwent aromatisation to generate the carbonyloxyl radical which decarboxylated to generate the alkyl radical R•.

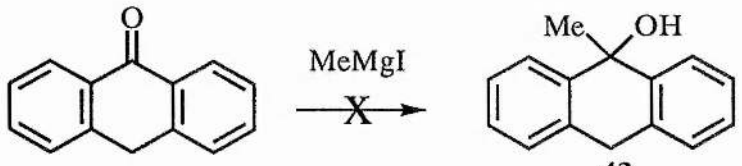


Scheme 29

The similarity between this method and the one illustrated in Scheme 28 is the formation of an aromatic ring flanked by two pre-existing aromatic rings. The thermodynamic driving force for aromatisation in esters **40** and **42** compared to esters **1** and **5**, would however, be less due to the smaller delocalisation energy of the central ring of a three ring system relative to a single aromatic ring.

2.18.1 Attempted preparation of 9-methylanthr-9-ol.

We attempted to prepare alcohol **43** by treating anthrone with MeMgI (Scheme 30). This immediately presented a problem due to the limited solubility of anthrone in organic solvents. The Grignard reagent MeMgI is prepared by treating Mg with methyl iodide in *ether*, but anthrone is insoluble in ether. We found anthrone to be sufficiently soluble in THF to mediate a reaction, but MeMgI cannot be successfully prepared in THF.



43

Scheme 30

Thus, when anthrone was dissolved in THF and added dropwise to MeMgI in ether, a precipitate immediately formed. Nevertheless, the reaction was continued and analysis by TLC indicated that a new product was forming. However, this product was less polar than anthrone and this was evidence for methyl addition to the carbonyl group, followed by dehydration of the resulting alcohol. Column chromatography of the reaction mixture did indeed result in the isolation of 9-methylanthracene (30%) and also unreacted anthrone (15%). These were the only two products isolated as the remaining fractions were mixtures of compounds. However, the presence of a broad peak at 1.5 ppm was evidence for the formation of alcohol **43**, but this was not isolated in pure form. In an attempt to reduce the amount of 9-methyanthracene formed and encourage formation of the alcohol, the reaction was performed at lower temperature (-25°C instead of r.t.), but the major products observed by ^{1}H NMR were again unreacted anthrone and 9-methylanthracene. As this route was presenting problems, our efforts concentrated on the phenyl esters **5**. We realised alcohol **43** could be prepared at a later date, since its preparation should only be a matter of experimentation.

Conclusions

After devoting much effort into preparing and isolating 1-phenylcyclohexa-2,5-diene-1-carboxylic acid **8** we eventually succeeded in this respect. Although Birch has commented on how to prepare this compound, to our knowledge there exists no characterisation of this compound in the literature.[2] The methyl ester of acid **8** has been reported and characterised, but the isomeric ester originating from acid **12** has probably been overlooked.[4] As mentioned already, we thought that appropriate esters of carboxylic acid **8** would function as efficient sources of alkyl radicals. We saw no reason why such compounds would not at least be as useful as the corresponding methyl esters, which have also been used by Clark to generate amidyl radicals.[9] The radical-induced fragmentation of ester **24** however, yielded 7-oxabicyclo[4.3.0]nonane **26** in lower than expected yields, which varied between 30-40%. This was significantly lower than what had been achieved with the corresponding 1-alkylcyclohexa-2,5-diene-1-carboxylic acid **32** discussed in the previous chapter. We do not understand why the yields are as low as this, since removal of the solvent under reduced pressure gave mainly biphenyl (most of the cyclic product evaporated), with no evidence for polymeric build-up. Furthermore, there was no competitive loss of a phenyl radical to give the corresponding benzoate esters - such problems with selectivity had reduced the yields of desired products from the 1-alkylcyclohexadienyl acids and the 1-methyl carboxylate esters. Carboxylic acid **8** was isolated in the latter course of the PhD project and only a small amount of time was devoted to preparing esters and examining them as sources of alkyl radicals. However, continuation of this work should provide a clearer picture of the usefulness of these compounds.

Table 1. Attempts to convert 1,4-dihydrobiphenyl **9** into carboxylic acid **8**.

Rxn No.	Mass of 24 used	Base used	Temp	Rxn. time	Products and yields	Comments
1	1 g	BuLi	-70°C	2h	No product	Gaseous CO_2 was bubbled through[2]
2†	1.5 g	BuLi	-70°C	1h	Acid **8** 21% Acid **12** 10% Biphenyl 7% **9** 16%	
3†	5 g	BuLi	-7O°C	1h	Acid **8** 8% Acid **12** 5% **9** 73%	Essentially unreacted starting material
4†	5 g	BuLi	-70 to -20°C	3h	Acid **8** 13% Acid **12** 7%	
5†	2.4 g	MeLi	-70 to -20°C	4.5h	Acid **8** 3% Acid **12** 1.3%	Even worse results obtained with MeLi
6†	5 g	MeLi	-70°C to r.t.	6h	Acid **8** 15%	
7	3.8 g	NaH	-20°C to r.t.	15h	Reaction was terminated	NaH was unreactive
8	2 g	BuLi	-10 to 10°C	5h	Deuterated product 55% Biphenyl 37%	Contents successfully quenched with D_2O

†Pellets of dry ice were added to the reaction mixture after the given time.

9	2 g	BuLi, TMEDA	-10°C	2h	Deuterated product 56% Biphenyl 16%	Contents successfully quenched with D_2O
10‡	5 g	BuLi, TMEDA	-30 to 0°C	75 min	Acid **8** 57% Acid **12** 22%	Product formed at last
11‡	5 g	BuLi, TMEDA	-40 to 0°C	50 to 55 min	Acid **8** 35% Acid **12** 14%	Lower yield after shorter reaction time
12‡	5 g	BuLi, TMEDA	-40 to 4°C	80 min	Acid **8** 70%	No significant amount of isomer detected
13‡	10 g	BuLi, TMEDA	-40 to 0°C	80 min	Acid **8** 40% Acid **12** 29%	Lower yield when reaction was scaled up
14‡	5 g	BuLi, TMEDA	-40 to 0°C	85 min	Acid **8** 55% Acid **12** 29%	
15‡	5 g	BuLi	-40 to 0°C	95 min	Acid **8** 53% Acid **12** 27%	Similar yield without TMEDA, viscous oil
16	1.45 g	BuLi	-70°C	15-20 min	Acid **8** 28% Acid **12** 14%	Following the procedure of Birch[4]

‡Reaction contents added to dry ice.

Figure 1

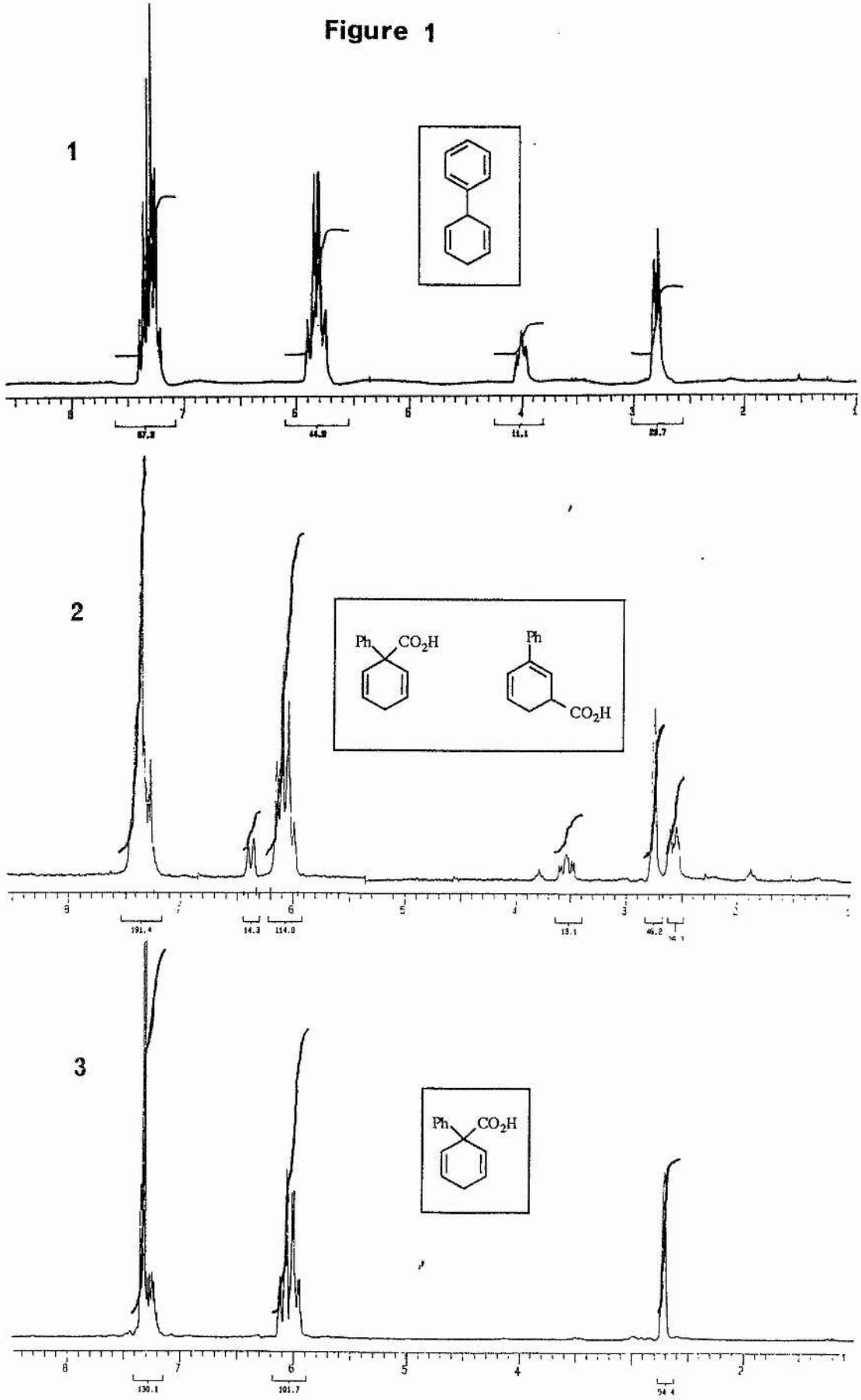
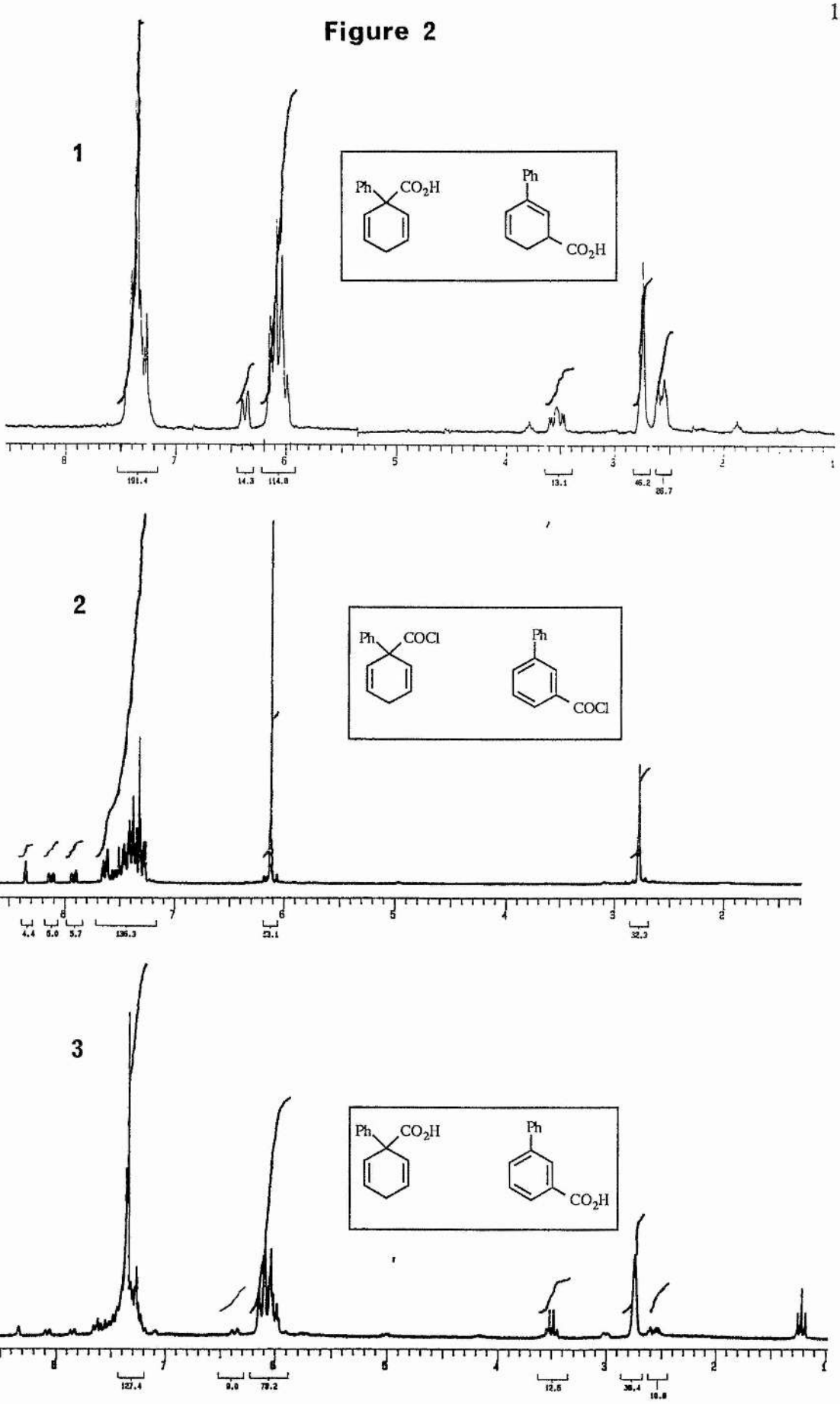


Figure 2



Experimental

Refer to the experimental section from Chapter 2 for information regarding the collection of experimental data etc. GC analyses were carried out using a Pye Unicam PU 4500 instrument fitted with a 3m glass column (id 5mm) packed with methyl silicone on Chromasorb operated isothermally. Detector response was calibrated using model compounds of similar structure. The order of this section is essentially the same as given in the results and discussion section.

Attempted preparation of 1-cyclopropylcyclohexa-2,5-diene-1-carboxylic acid (6) (Scheme 3)

Ammonia (300 cm^3) was added to benzoic acid (5 g, 41 mmol) with careful stirring. To this Li (0.8 g, 0.116 mmol) was added portionwise causing the solution to turn deep blue. After 10 min, cyclopropyl bromide (14.2 g, 0.17 mol) was added dropwise, causing the solution to turn yellow, and the NH_3 was allowed to evaporate overnight. Ice was added to the residue followed by HCl (200 cm^3) and the mixture was extracted with ether (3 x 100 cm^3). The ethereal extracts were combined, dried ($MgSO_4$) and the solvent was evaporated to give a pale yellow liquid (6.68 g). Analysis of this liquid by ^1H NMR revealed a mixture of 1,4-dihydrobenzoic acid, benzoic acid and residual ether. There was no evidence for the presence of acid **6**.

1,4-Dihydrobiphenyl (9) (Scheme 5)[3]

Biphenyl (17 g, 0.11 mol) was dissolved in dry ether (500 cm^3) and added to a solution of ammonia (1 litre). To this, Li (1.7 g, 0.245 mol) was added portionwise and the resulting deep blue solution was stirred for 25 min. The colour was discharged by careful addition of NH_4Cl (~ 80 g) followed by H_2O (250 cm^3) and ether (200 cm^3). The ether layer was separated, washed with H_2O (2 x 100 cm^3), dried ($MgSO_4$) and evaporated. The title compound was obtained as a clear, colourless liquid after distillation (15.8 g, 92%), bp 70°C at 0.1 mmHg; δ_H 2.72-2.82 (2 H, m, allylic-H), 3.92-4.07 (1 H, t, *J* 8.0, *t*-H),

5.70-5.90 (4 H, m, olefinic-H), 7.20-7.40 (5 H, m, arom-H); δ_C (50 MHz) 26.4 (allylic-C), 42.6 (*t*-C), 124.3 (2 x arom-C), 126.9 (2 x olefinic-C), 128.6 (2 x olefinic-C), 129.1 (3 x arom-C), 145.7 (quaternary, arom-C).

1-Deuterio-1,4-dihydrobiphenyl (13) (Scheme 9)

1,4-Dihydrobiphenyl (2 g, 13 mmol) was dissolved in dry THF (60 cm^3) under an atmosphere of N_2. To this was added BuLi (0.90 g, 14 mmol) at -10°C and the deep red solution was stirred for 5h at approximately -10°C. The mixture was quenched with D_2O (0.31 g, 15 mmol) dissolved in dry THF (1 cm^3). After 15 min the solvent was evaporated and ether (50 cm^3) and H_2O (50 cm^3) were added to the residue. The aqueous layer was extracted with ether (50 cm^3), the ethereal extracts were combined, dried ($MgSO_4$) and the solvent was evaporated to give a yellow liquid (1.78 g) consisting of the title compound (1.1 g, 55%) and biphenyl (0.61 g, 31%); δ_H 2.76-2.84 (2 H, m, allylic-H), 5.74-5.92 (4 H, m, olefinic-H), 7.25-7.70 (15 H, m, arom-H, **13**, biphenyl); δ_D (46 MHz) 4.05 (1 D, s, *t*-D); GC/MS peak no. 329, 1-deuterio-1,4-dihydrobiphenyl, *m/z* (rel. intensity), 157 (M^+) (100), 142 (36), 129 (66), 116 (44), 104 (31), 91 (52), 78 (60), 51 (39).

1-Phenylcyclohexa-2,5-diene-1-carboxylic acid and 3-carboxylic acid-3,4-dihydrobiphenyl (8 and 12) (Scheme 8)

1,4-Dihydrobiphenyl (5 g, 32 mmol) was dissolved in dry THF (150 cm^3), the flask was furnished with N_2 and to this was added BuLi (2.26 g, 35 mmol) at -40°C. The mixture was left stirring for 80 min as the temperature was allowed to rise to 0°C, then cooled to -70°C and poured into a conical flask containing solid carbon dioxide. The contents were left overnight and the product was extracted using NaOH (2 x 100 cm^3) and washed with light petroleum (75 cm^3). The carboxylic acids were regenerated using excess HCl, extracted with ether (3 x 100 cm^3), the combined ethereal extracts were dried ($MgSO_4$) and the solvent was evaporated to yield a white solid (5.0 g) which was a mixture of acids **8** (3.5 g, 55%) and **12** (1.5 g, 24%); δ_H 2.55-2.61 (2 H, m, allylic-H, **12**), 2.70-2.75 (2

H, m, allylic-H, **8**) 3.43-3.56 (1 H, m, *t*-H, **12**), 5.95-6.20 (6 H, m, olefinic-H, **8**, **12**), 6.31-6.40 (1 H, d, *J* 10, olefinic-H, **12**), 7.23-7.50 (10 H, m, arom-H, **50**, **53**).

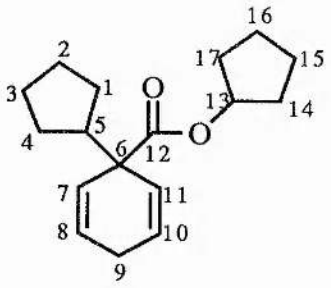
Cyclopentyl 1-cyclopentylcyclohexa-2,5-diene-1-carboxylate (14) (Scheme 10)

Thionyl chloride (1.5 g, 12.5 mmol) dissolved in dry ether (10 cm^3) was added to 1-cyclopentylcyclohexa-2,5-diene-1-carboxylic acid **15** (2 g, 14 mmol) dissolved in dry ether (10 cm^3). This mixture was refluxed for 6h and the solvent was evaporated to give the corresponding acid chloride; δ_H 1.20-1.74 (8 H, m, methylene-H), 2.41-2.60 (1 H, q *J* 8.3, *t*-H), 2.61-2.73 (2 H, m, allylic-H), 5.70-6.09 (4 H, m, olefinic-H). The acid chloride was dissolved in cyclopentanol (10 cm^3) and heated at 70°C for 4h. The cyclopentanol was removed by Kugelrohr distillation, the residue was dissolved in ether (30 cm^3) and washed with NaOH (2 x 15 cm^3). The organic layer was dried ($MgSO_4$) and the solvent was evaporated to give the title compound as a pale brown liquid (1.5 g, 55%); δ_H 1.20-1.90 (16 H, m, methylene-H), 2.20-2.37 (1 H, q^i, *J* 8.0, *t*-H), 2.53-2.62 (2 H, m, allylic-H), 5.07-5.20 (1 H, m, *t*-H), 5.70-5.90 (4 H, m, olefinic-H); δ_C 23.6 (2 x 15,16-C), 25.8 (2 x 2,3 or 1,4-C) 26.5 (9-C), 27.2 (2 x 1,4-C or 2,3-C), 31.5 (2 x 14,17-C), 47.9 (5-C), 49.9 (6-C), 77.2 (13-C), 125.7, 126.6 (4 x 7,8,10,11-C), 174.5 (12-C); *m/z* 261 (MH^+, 25%), 207 (14), 193 (100), 191 (21), 147 (17), 123 (95), 105 (11), 69 (5), 50 (17) (Found: MH^+, 261.1851. $C_{18}H_{25}O_2$ requires 261.1855).

Cyclopentyl 1-phenylcyclohexa-2,5-diene-1-carboxylate (16) (Scheme 11)

Thionyl choride (11.9 g, 0.1 mol) was added to a mixture of carboxylic acids **8** and **12** (4.2 g, 21 mmol; 2.70 g, 16 mmol, **8**) dissolved in dry ether (30 cm^3). This mixture was refluxed for 6h and the solvent was evaporated to give acid chlorides **18** and **20** (some biphenyl had also formed). The acid chlorides were dissolved in dry ether (35 cm^3), added to cyclopentanol (3.23 g, 37.5 mmol) dissolved in dry ether (10 cm^3), and refluxed for an appropriate period of time. NaOH (2 x 20 cm^3) was added, the layers were separated, the organic layer was dried ($MgSO_4$) and the solvent was evaporated to yield an orange liquid

(4.0 g). The title compound was obtained as a slightly yellow oil by column chromatography eluting with 2% ethyl acetate in light petroleum (0.89 g, 25%‡); δ_H 1.52-1.95 (8 H, m, methylene-H), 2.70-2.77 (2 H, m, allylic-H), 5.21-5.28 (1 H, m, *t*-H), 5.91-6.15 (4 H, m, olefinic-H), 7.20-7.40 (5 H, m, arom-H); δ_C 23.6 (2 x 16,17-C), 25.8 (10-C), 32.4 (2 x 15,18-C), 52.4 (7-C), 78.0 (14-C), 124.8, 126.4, 126.8, 127.9, 128.7 (9 x 1,2,3,4,5,8,9,11,12-C), 144.2 (6-C), 173.4 (13-C); GC/MS peak no. 654,*m/z* (rel. intensity), 201 (2), 156 (100), 155 (25), 128 (6), 115 (8), 77 (44), 69 (42), 51 (19), 41 (68), 39 (19). ‡Analysis by GC/MS indicated ~5-10% of cyclopentyl ester **22**.



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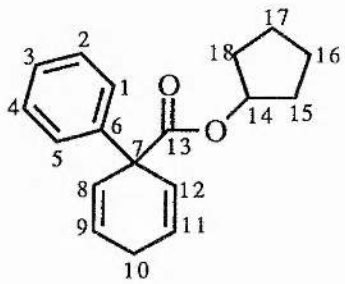


16

Radical-initiated reaction of ester 16 with cyclohexenone (Scheme 15)

Cyclopentyl 1-phenylcyclohexa-2,5-diene-1-carboxylate **16** (0.05 g, 0.19 mmol), cyclohexenone (0.018 g, 0.19 mmol) and dibenzoyl peroxide (0.025 g, 50% wt.) were dissolved in benzene (5 cm^3). The mixture was refluxed for 48h and analysed during the course of the reaction by GC/MS, which indicated the presence of unreacted ester **16** and cyclohexenone and some biphenyl. There was no evidence for any of the desired adduct.

2-(Cyclohex-2-enyloxy)ethyl 1-phenylcyclohexa-2,5-diene-1-carboxylate (24) (Scheme 16)

Thionyl chloride (1.07 g, 9.0 mmol) was dissolved in dry ether (2 cm^3) and added to a mixture of carboxylic acids **8** and **12** (1.64 g, 8.2 mmol; 1.04 g, 5.2 mmol, **8**) dissolved in dry ether (10 cm^3). This mixture was refluxed for 6.5h and the solvent was evaporated to yield acid chlorides **18** and **20**, (some biphenyl had also formed). The acid chlorides were dissolved in dry ether (10 cm^3), added to 3-(2-hydroxyethoxy)cyclohexene **25** (1.56

g, 11 mmol) dissolved in dry ether (5 cm^3) and refluxed for 18h.‡ The mixture was washed with NaOH (15 cm^3) and the ether fraction was dried ($MgSO_4$) and the solvent was evaporated to give a yellow oil (2.12 g). The title compound was obtained as a pale yellow oil by column chromatography eluting with 10% ethyl acetate in light petroleum (0.5 g, 30%†); δ_H 1.45-2.10 (6 H, m, methylene-H), 2.69-2.77 (2 H, m, allylic-H), 3.64-3.74 (2 H, m, methylene-H), 3.80-3.90 (1 H, m, *t*-H), 4.29-4.36 (2 H, t, *J* 5.1, methylene-H), 5.69-6.19 (6 H, m, olefinic-H), 7.20-7.39 (5 H, m, arom-H). ‡Prolonged refluxing was required; †^{1}H NMR indicated 9% of aromatic ester.

Radical-induced fragmentation of ester 24 (Scheme 17) *First Attempt*

Ester **24** (0.43 g, 1.3 mmol) and dibenzoyl peroxide (0.24 g, 56% wt.) were dissolved in benzene (2.5 cm^3) and refluxed for 24h. A sample of the reaction mixture was submitted for GC/MS; peak no. 248, 7-oxabicyclo[4.3.0]nonane **26**, *m/z* (rel. intensity), 126 (M^+) (11), 83 (100), 55 (35), 41 (28), 39 (31), 29 (22), 27 (32); peak no. 404, biphenyl; peak no. 491, 3-(2-phenylethoxy)cyclohexene **27**, 202 (M^+) (4), 105 (100), 97 (15), 81 (36), 79 (60), 77 (64), 51 (37), 41 (24), 27 (20), 18 (11). Ether (10 cm^3) was added to the reaction flask and the contents were washed with NaOH (2 x 10 cm^3). The alkaline fractions were combined and washed with light petroleum (10 cm^3). The organic fractions were combined, dried ($MgSO_4$) and the solvents were removed by atmospheric distillation using a Vigreux column. Residual benzene was still present and the yield of the reaction was estimated by adding 9-methylene-7-oxabicyclo[4.3.0]-nonane (compound **39** in chapter 2) as a standard. The mixture was analysed by GC/MS and the peaks corresponding to 7-oxabicyclo[4.3.0]nonane **26** and 9-methylene-7-oxabicyclo[4.3.0]-nonane were compared and using an approximate value of 0.86 g/ml for the density of **26**, the yield of product **26** was calculated to be 31%.

Ethyl 1-phenylcyclohexa-2,5-diene-1-carboxylate (29) (Scheme 19)

1,4-Dihydrobiphenyl (2 g, 12.8 mmol) was dissolved in dry THF (75 cm^3) under an atmosphere of N_2. To this was added BuLi (0.95 g, 14 mmol) at -40°C and the resulting dark red solution was left stirring for 80 min as the temperature was allowed to rise to 0°C. The mixture was quenched with ethyl chloroformate (1.53 g, 14 mmol) dissolved in dry THF (5 cm^3) causing the solution to turn pale red. Another addition of ethyl chloroformate (1.53 g, 14 mmol) caused the solution to turn yellow and this mixture decolourised overnight. The solvent was evaporated, ether (150 cm^3) was added to the residue and this was washed with H_2O (2 x 100 cm^3). The ether layer was dried ($MgSO_4$) and the solvent was evaporated to give an orange oil (3.47 g). The title compound was obtained as a slightly discoloured liquid by column chromatography eluting with 15% ethyl acetate in light petroleum (0.78 g, 27%); δ_H† 1.23-1.31 (3 H, t, *J* 7.2, methyl-H), 2.93-3.00 (2 H, m, allylic-H), 4.18-4.30 (2 H, q, *J* 7.2, methylene-H), 5.98-6.38 (4 H, m, olefinic-H), 7.29-7.50 (5 H, m, arom-H). †This spectrum was in agreement with ester **29**, although the integrals corresponding to the ethyl group fragment were proportionally greater than the other signals.

Attempted preparation of 1-phenylcyclohexa-2,5-diene-1-carbonyl chloride (18) (Scheme 20)

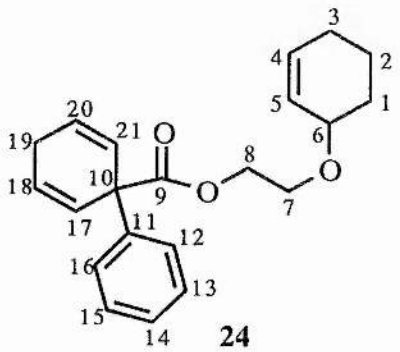
1,4-Dihydrobiphenyl (1 g, 6.41 mmol) was dissolved in dry THF (50 cm^3) under an atmosphere of N_2. To this was added BuLi (0.45 g, 7.04 mmol) at -78°C and the resulting dark, red solution was left stirring for 80 min at -60°C to -78°C. Using a cannula, the mixture was added to phosgene (0.76 g, 7.7 mmol) in toluene cooled to -78°C, and the resulting mixture was left stirring overnight. The solvent was evaporated and ether (50 cm^3) was added to the residue and this was washed with H_2O (50 cm^3). The ether layer was dried ($MgSO_4$) and the solvent was evaporated to give a liquid which was shown by ^1H NMR to be a mixture of unreacted 1,4-dihydrobiphenyl and biphenyl.

1-Phenylcyclohexa-2,5-diene-1-carboxylic acid (8) (Scheme 21)

1,4-Dihydrobiphenyl (13.3 g, 83.3 mmol) was dissolved in dry THF (350 cm^3) containing TMEDA (10.7 g, 83.3 mmol) and the flask was flushed with N_2. To this was added BuLi (5.9 g, 92.2 mmol) at -40°C and the resulting deep red solution was stirred for 80 min as the temperature was allowed to rise to 0°C. The mixture was cooled to -70°C and poured into a conical flask containing crushed dry ice, causing immediate decolourisation. The THF was evaporated to yield a solid, to which ether (100 cm^3) and NaOH (70 cm^3) were added. The layers were separated and the ether layer was extracted with NaOH (2 x 70 cm^3). The alkaline fractions were combined and neutralised with excess HCl. The product was extracted with ether (3 x 150 cm^3), the ethereal extracts were combined, dried ($MgSO_4$) and the solvent was evaporated to yield a white solid (12 g) consisting of the title compound (7.8 g, 45%) and carboxylic acid **12** (4.2 g, 24%); δ_H 2.50-2.62 (2 H, m, allylic-H, **12**), 2.68-2.78 (2 H, m, allylic-H, **8**), 3.43-3.59 (1 H, m, *t*-H, **12**), 5.95-6.17 (6 H, m, olefinic-H, **8**, **12**), 6.31-6.40 (1 H, d, *J* 10, olefinic-H, **12**), 7.23-7.46 (10 H, m, arom-H, **8**, **12**). This mixture containing diene **12** (4.2 g, 21 mmol) was dissolved in dichloromethane (100 cm^3) to which maleic anhydride (5.56 g, 56.7 mmol) was added, and refluxed for 5h. The mixture was extracted with NaOH (4 x 40 cm^3), the alkaline fractions were combined and neutralised with excess HCl. The product was extracted with ether (3 x 100 cm^3), the ethereal extracts were combined, dried ($MgSO_4$) and the solvent was evaporated to yield an orange liquid (15.41 g). Dichloromethane (50 cm^3) and silica gel were added to the product and the solvent was removed. The product adsorbed onto silica gel, was added to a sinter funnel packed with silica gel and the column was eluted with 30% ethyl acetate in light petroleum. The title compound was obtained as a white solid (6.2 g, 35%), mp 122-124°C (Found: C, 78.27; H, 6.26. Calc. for $C_{13}H_{12}O_2$: C, 77.98, H, 6.04%); δ_H 2.68-2.78 (2 H, m, allylic-H), 5.94-6.14 (4 H, m, olefinic-H) 7.21-7.40 (5 H, m, arom-H); δ_C (50 MHz) 25.9 (allylic-C), 52.4 (quaternary-C), 125.0, 126.6, 127.2, 129.0 (9 x olefinic, arom-C), 143.3 (quaternary, arom-C), 180.0 (carbonyl-C).

2-(Cyclohex-2-enyloxy)ethyl 1-phenylcyclohexa-2,5-diene-1-carboxylate (24) (Scheme 22)

Thionyl chloride (7.14 g, 60 mmol) was added to 1-phenylcyclohexa-2,5-diene-1-carboxylic acid **8** (3 g, 15 mmol) dissolved in dry dichloromethane (30 cm^3). This was refluxed for 6h and the solvent was evaporated to yield acid chloride **18** (3.3 g); δ_H 2.74-2.80 (2 H, m, allylic-H), 6.07-6.14 (4 H, s, olefinic-H), 7.24-7.47 (5 H, m, arom-H). The acid chloride was dissolved in dichloromethane (15 cm^3) and added dropwise to a mixture of 3-(2-hydroxyethoxy)cyclohexene **25** (1.92 g, 13.5 mmol), pyridine (1.2 g, 15 mmol) and a catalytic amount of DMAP, in dry dichloromethane (30 cm^3) and the mixture was refluxed for 2.5h. The contents were washed with NaOH (2 x 20 cm^3) followed by HCl (2 x 20 cm^3). The organic layer was dried ($MgSO_4$) and the solvent was evaporated to yield an orange oil (4.8 g). The title compound was obtained as a pale yellow liquid by column chromatography eluting with 20% ethyl acetate in light petroleum (3.48 g, 75%); δ_H 1.51-2.05 (6 H, m, methylene-H), 2.65-2.75 (2 H, m, allylic-H), 3.55-3.95 (3 H, m, methylene-H, *t*-H), 4.28-4.32 (2 H, t, *J* 4.9, methylene-H), 5.61-6.15 (6 H, m, olefinic-H), 7.18-7.25 (5 H, m, arom-H); δ_C 19.1 (2-C), 25.2, 25.8, 28.1, (3 x 1,3,19-C), 52.4 (10-C), 64.7, 65.7 (2 x 7,8-C), 73.1 (6-C), 124.8, 126.3, 127.6, 128.6 (8 x 12,13,15,16,17,18,20,21-C), 126.8, 125.5, 131.0 (3 x 4,5,14-C), 143.8 (11-C), 173.5 (9-C); *m/z* 324 (M^+, 1%), 242 (6), 228 (6), 225 (7), 181 (5), 155 (100), 128 (10), 115 (10), 81 (36), 77 (27) (Found: M^+, 324.1737. $C_{21}H_{24}O_3$ requires 324.1725).



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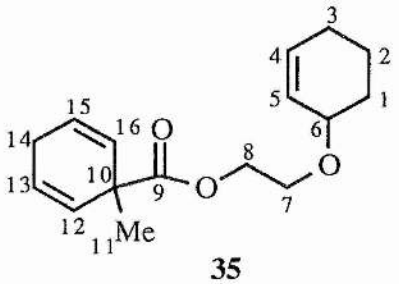

35

Radical-induced fragmentation of ester 24 (Scheme 23) *Second attempt*

Ester **24** (0.49 g, 1.4 mmol) and hexadecane (0.105 g, 0.46 mmol) were dissolved in amyl alcohol (5 cm^3) to which *t*-butyl peroxybenzoate (0.24 g, 50% wt.) was added. This mixture was refluxed for 15h and a sample was analysed by GC/MS; peak no. 236, 7-oxabicyclo[4.3.0]nonane **26**, *m/z* (rel. intensity), 126 (M^+) (12), 83 (100), 55 (49), 41 (47), 39 (47), 29 (77), 27 (38), 18 (13); peak no. 346, 2-(cyclohex-2-enyloxy)ethyl formate **32**, 125 (1), 97 (12), 81 (28), 79 (21), 74 (41), 73 (68), 45 (35), 41 (26), 39 (21), 28 (27); peak no. 387, biphenyl. None of the starting ester remained according to the GC/MS analysis and the reaction was terminated. Using hexadecane and 2-methyltetrahydrofuran as standards the GC yield of cyclic product **26** was calculated to be 33% and the yield of biphenyl was 66%. The solvent was evaporated to give predominantly biphenyl and hexadecane. From the ^1H NMR spectrum of this product mixture the yield of biphenyl was calculated to be 62%, which was in agreement with the GC yield. A repeat experiment yielded similar results.

1-Methylcyclohexa-2,5-diene-1-carboxylic acid (33) (Scheme 24)[1]

Ammonia (400 cm^3) was added to benzoic acid (5 g, 41 mmol) and Li (0.85 g, 0.123 mol) was added portionwise causing the solution to turn deep blue. After 15 min the mixture was quenched with methyl iodide (18.9 g, 0.133 mol) causing the solution to turn yellow, and the NH_3 was allowed to evaporate overnight. HCl (150 cm^3) was added to the residue, the product was extracted with ether (3 x 120 cm^3), the ethereal extracts were combined, washed with a saturated solution of sodium thiosulphate and dried ($MgSO_4$). The solvent was evaporated to yield the title compound as an orange liquid (5.72 g, 100%); δ_H 1.40 (3 H, s, methyl-H), 2.62-2.75 (2 H, m, allylic-H), 5.78-5.94 (4 H, m, olefinic-H).

1-Methylcyclohexa-2,5-diene-1-carbonyl chloride (34) (Scheme 24)[1]

Thionyl chloride (15.7 g, 0.132 mol) was added to carboxylic acid **33** (4 g, 29 mmol) dissolved in dry ether (50 cm^3). This mixture was refluxed for 7h and the solvent was evaporated to yield a yellow liquid which was distilled to give the title compound as a clear,

colourless liquid (3.53 g, 78%), bp 70-80°C at 0.15 mmHg (lit.,[1] bp 62°C at 0.2 mmHg); δ_H 1.45 (3 H, s, methyl-H), 2.68-2.81 (2 H, m, allylic-H), 5.68-6.08 (4 H, m, olefinic-H).

2-(Cyclohex-2-enyloxy)ethyl 1-methylcyclohexa-2,5-diene-1-carboxylate (35) (Scheme 25)

Acid chloride **34** (1.5 g, 9.6 mmol) was dissolved in dry dichloromethane (10 cm^3) and added dropwise to a mixture of 3-(2-hydroxyethoxy)cyclohexene **25** (1.36 g, 9.6 mmol), pyridine (0.76 g, 9.6 mmol) and a catalytic amount of DMAP, dissolved in dry dichloromethane (10 cm^3). The mixture was refluxed for 5h, washed with HCl (2 x 15 cm^3), dried ($MgSO_4$) and the solvent was evaporated to give the title compound as a pale yellow liquid (2.51 g, 100%); δ_H 1.48 (3 H, s, methyl-H), 1.60-2.10 (6 H, m, methylene-H), 2.62-2.70 (2 H, m, allylic-H), 3.65-3.78 (2 H, m, methylene-H), 3.84-3.97 (1 H, m, *t*-H), 4.21-4.28 (2 H, t, *J* 7.0, methylene-H), 5.70-5.93 (6 H, m, olefinic-H); GC/MS peak no. 562, *m/z* (rel. intensity), 119 (6), 93 (100), 92 (33), 91 (40), 81 (91), 80 (17), 79 (25), 77 (67), 65 (19), 53 (30), 45 (47), 41 (100), 39 (59), 27 (41). A small amount of the product was purified by column chromatography (Found: C, 73.26; H, 8.90. Calc. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45%); δ_C 19.1 (2-C), 25.2, 25.9, 28.2 (3 x 1,3,14-C), 27.4 (11-C), 43.9 (10-C), 64.4, 65.9 (2 x 7,8-C), 73.2 (6-C), 124.4, 127.5, 128.7, 131.1 (6 x 4,5,12,13,15,16-C), 175.1 (9-C).

Attempted preparation of 9-methylanthr-9-ol (40) (Scheme 30)

Two drops of 1,2-dibromoethane were added to Mg turnings (0.32 g, 13 mmol) followed by the addition of dry ether (8 cm^3). To this mixture, methyl iodide (1.85 g, 13 mmol) dissolved in dry ether (3 cm^3) was added dropwise and the resulting mixture was stirred for 1.5h. Anthrone (2 g, 10.3 mmol) dissolved in dry THF (20 cm^3) was added dropwise to the mixture and an exothermic reaction was observed. The resulting mixture was stirred at r.t. for 0.5h, refluxed for 2h and left stirring overnight at r.t. To the mixture H_2O (10 cm^3) and HCl (100 cm^3) were added and the product was extracted with dichloromethane

(3 x 75 cm^3). The combined organic extracts were washed with a saturated solution of sodium thiosulphate (100 cm^3), dried ($MgSO_4$) and the solvent was evaporated to give an orange liquid (2.35 g). Analysis of this mixture by ^1H NMR revealed a mixture of products. The mixture was purified by column chromatography eluting with 10% ethyl acetate in light petroleum yielding pure starting material (0.31 g, 15%) and 9-methylanthracene as a yellow solid (0.60 g, 30%); δ_H 3.1 (3 H, s, methyl-H), 7.45-7.60 (4 H, m, arom-H), 7.98-8.07 (2 H, m, arom-H), 8.28-8.39 (3 H, m, arom-H).

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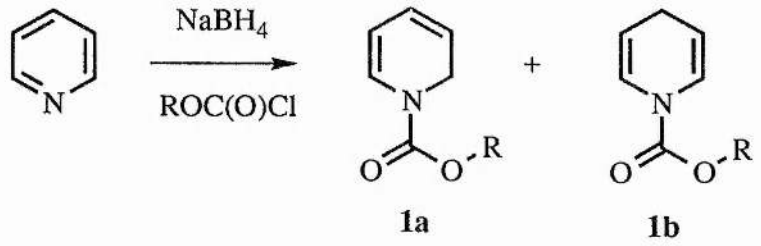
Chapter 4

N-Carboalkoxy-1,2-dihydropyridines as reagents for generating radicals

1 Introduction

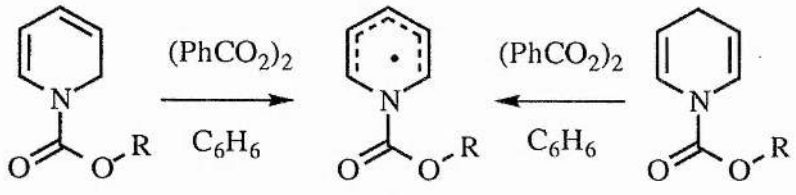
N-Carboalkoxy-1,2-dihydropyridines **1a** can be prepared by treating pyridine with sodium borohydride in methanol and the appropriate chloroformate (Scheme 1).[1] The isomeric 1,4-dihydropyridine **1b** can also be prepared by modification of the reaction conditions.



1a **1b**

Scheme 1

Streith has used *N*-carbomethoxy and *N*-carbobenzyloxy-1,2-dihydropyridines in the synthesis of (±)-aminoarabinose and (±)-aminoaltrose derivatives *via* a double dihydroxylation reaction[2] and Wender has used the methoxy compound in a synthesis of *cis*-hydroisoquinoline.[3] We were interested in these dihydropyridines as potential reagents for generating alkyl radicals in organic synthesis as they can be prepared in good to excellent yields for a range of chloroformates. It was anticipated that allylic hydrogen atom abstraction would give the corresponding delocalised radical **2** (Scheme 2) which would generate an alkyl radical by N-C bond scission followed by decarboxylation of the resulting alkoxycarbonyl radical. The byproduct, pyridine, would then be removed by an acid wash. The main reason for investigating this method was based on the expectancy that the driving force for aromatisation of the aza-cyclohexadienyl radical **2** would occur in a selective manner.

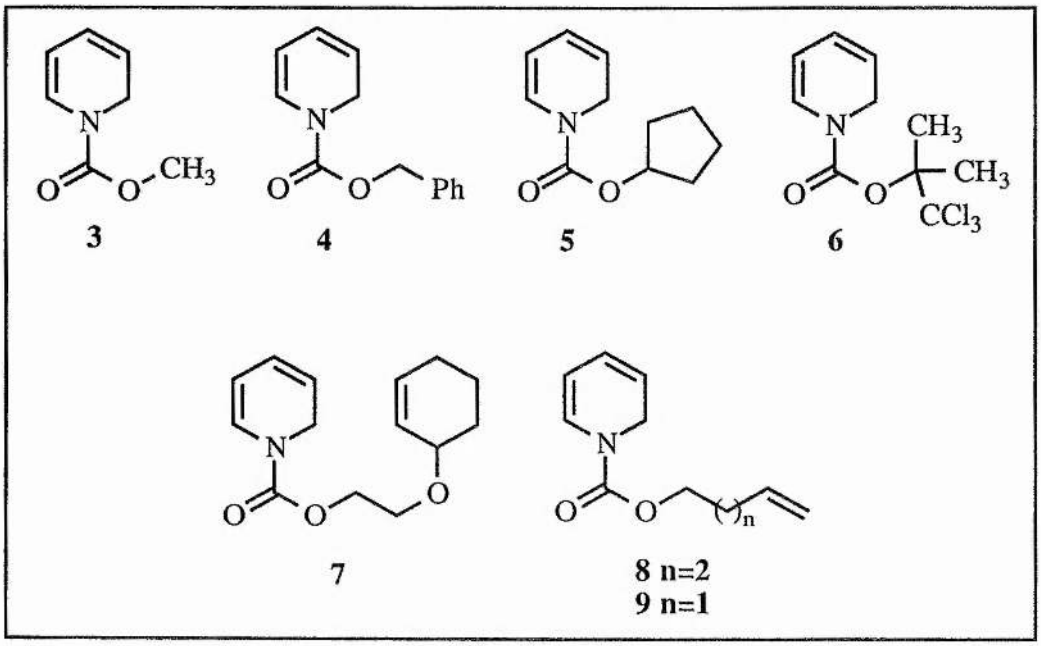


1a **2** **1b**

Scheme 2

2 Results and Discussion

The dihydropyridines **3-9** (Scheme 3) have all been prepared in good yields by the above method. The chloroformates (except methyl chloroformate, benzylchloroformate and 2,2,2-trichloro-1,1-dimethylethyl chloroformate which were commercially available) were prepared by treating the corresponding alcohol with phosgene in toluene.[4]



Scheme 3

The ^{1}H NMR spectra of these dihydropyridines were in good agreement with structure **1a**, though analysis by ^{13}C NMR gave evidence for the presence of **1b** in small quantities. However, this was not considered to be a problem since both would give the same delocalised radical **2** when treated with an initiator. An attempt was made to purify the methyl dihydropyridine **3** by column chromatography to a condition suitable for microanalysis, but this was unsuccessful as the compound rapidly decolourised. Thus, the dihydropyridines were worked up in a conventional manner and stored in the freezer under nitrogen prior to use. We investigated whether these dihydropyridines would be more suitable for use as radical precursors than the cyclohexadienyl acids and esters discussed in

the previous chapters. The dihydropyridines **3-6** were dissolved in benzene and refluxed for an appropriate period of time in the presence of an initiator, usually dibenzoyl peroxide, and a suitable electron-deficient alkene i.e. cyclohexenone. Dihydropyridines **7-9** were tested in the same manner as above, except that it was anticipated that the unsaturated alkyl radical generated would cyclise by intramolecular addition to the double bond.

2.1 EPR spectroscopic studies on *N*-carboalkoxy-1,2-dihydropyridines

Dihydropyridines **3-9** have all been investigated by EPR spectroscopy. We were interested in determining whether allylic hydrogen atom abstraction, to give aza-cyclohexadienyl radical **2**, would be a feasible process. Also, it was important to establish whether the decarboxylation process to generate the corresponding alkyl radical could be observed at accessible temperatures.

The quality of the EPR spectra were improved when the samples were dissolved in neat *t*-butyl peroxide, rather than *t*-butylbenzene. The samples were degassed with nitrogen for approximately 15-20 min, the EPR tube was placed in the cavity of the spectrometer and irradiated. It soon became clear that under these conditions all of the dihydropyridines produced intense, well-resolved EPR spectra, which were straightforward to characterise. For example, figure 1 provides two of the spectra recorded during these studies. The top one illustrates the aza-cyclohexadienyl radical derived from the cyclopentyl-dihydropyridine **5** and the lower spectrum resulted from the *t*-butyl-dihydropyridine **6**. Figure 2 provides two spectra corresponding to the aza-cyclohexadienyl radical formed from dihdropyridine **4** (top spectrum) and the simulated spectrum for this radical (lower spectrum). Since this particular delocalised radical has additional hfs from the benzylic methylene group, the spectrum is relatively complex. The radical derived from cyclopentyl-dihydropyridine **5** however, only has one extra hfs from the *t*-H, giving a less complex spectrum and the simplest spectrum was obtained from dihydropyridine **6**, since no additional proximate hydrogens were present.

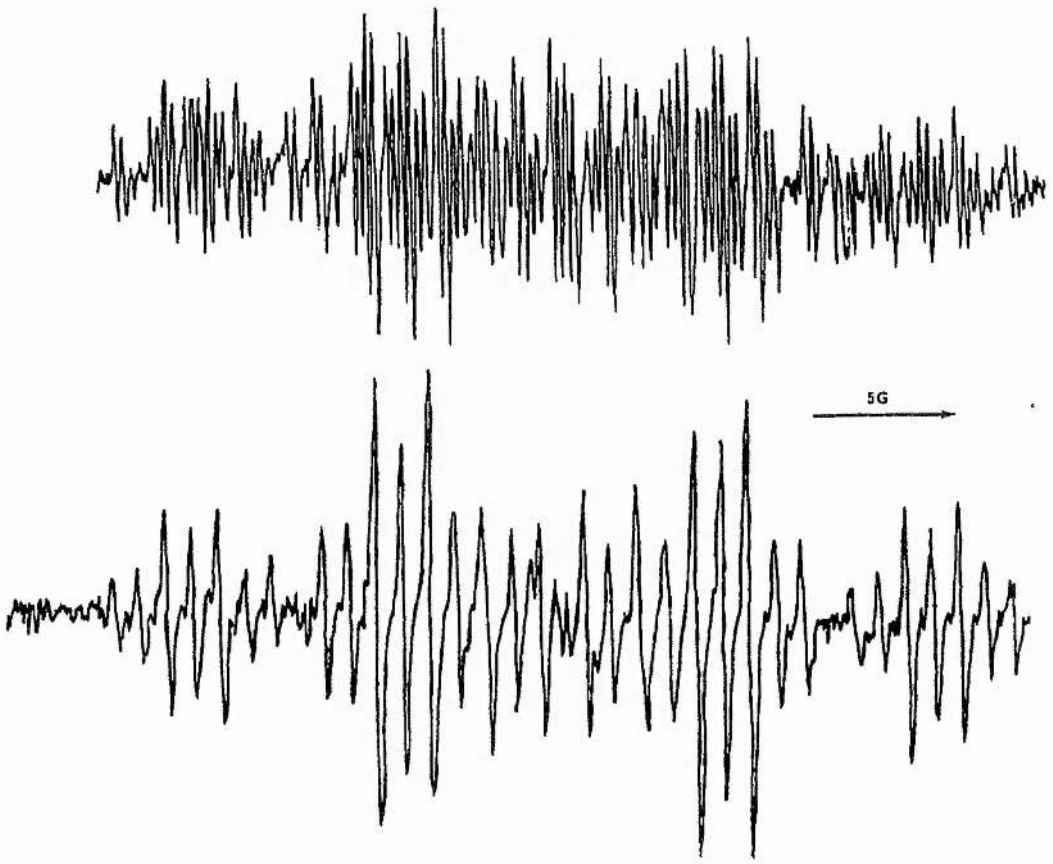


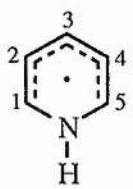
Figure 1. EPR spectra of the azacyclohexadienyl radicals derived from dihydropyridines **5** (top spectrum) and **6** (lower spectrum) recorded at 250-260K.

Table 1 summarises the temperatures at which the best spectra were observed together with the hfs. Each of these dihydropyridines investigated gave hfs from the nitrogen and the three sets of hydrogens H_1-H_5. As already mentioned, additional hfs were also observed from the proximate hydrogens of the alkyl group. All of these dihydropyridines gave similar values and except for the nitrogen hfs, these values were comparable to those reported for the aza-cyclohexadienyl radicals I and II.[5] Since dihydropyridines **3-9** have an electron-withdrawing substituent bonded to the nitrogen atom, spin density is withdrawn from the nitrogen atom, with the result that the hfs associated with the nitrogen atoms are lower than for cases where the substituent on nitrogen is not electron-withdrawing, as in the case for radicals I and II. Furthermore, an additional splitting (H^{other}) observed for the

aza-cyclohexadienyl radicals resulted from the α-alkoxy hydrogen atoms and this was further evidence for the electron-withdrawing effect of the substituent.

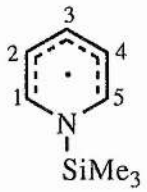
Table 1. EPR data for aza-cyclohexadienyl radicals derived from dihydropyridines 3-9

R / cpd no.	T. (K)	a (N) (G)	a (H^3) (G)	a ($H^{1,5}$) (G)	a ($H^{2,4}$) (G)	a (H^{other}) (G)
CH_3 / **3**	260	1.30	12.00	7.65	1.95	0.45 (3 H)
$PhCH_2$ / **4**	260	1.18	11.70	7.60	1.93	0.37 (2 H)
C_5H_9 / **8**	250	1.26	11.74	7.52	1.90	0.38 (2 H)
C_4H_7 / **9**	260	1.25	11.77	7.65	1.90	0.38 (2 H)
$C_8H_{13}O$ / **7**	250	1.20	11.93	7.73	1.90	0.37 (2 H)
$^cC_5H_9$ / **5**	260	1.37	11.80	7.52	1.97	0.27 (1H)
cpd **6**	250	0.95	11.85	7.75	2.00	-



I

<u>a</u> (N) 5.85
<u>a</u> (2H) (1,5) 5.91
<u>a</u> (2H) (2,4) 0.97
<u>a</u> (1H) (3) 11.62
<u>a</u> (1H) (NH) 3.47



II

<u>a</u> (N) 4.20
<u>a</u> (2H) (1,5) 6.26
<u>a</u> (2H) (2,4) 1.38
<u>a</u> (1H) (3) 11.55

Scheme 4

When the temperature of the EPR cavity was increased, there was no evidence for decarboxylation of any of the aza-cyclohexadienyl radicals as no signals corresponding to alkyl radicals were observed, even for the benzyl and *t*-alkyl cases **4** and **6** respectively.

This result was consistent with the 1-methylcyclohexa-2,5-dienyl-1-carboxylate esters which did not give EPR evidence for decarboxylation either.[6]

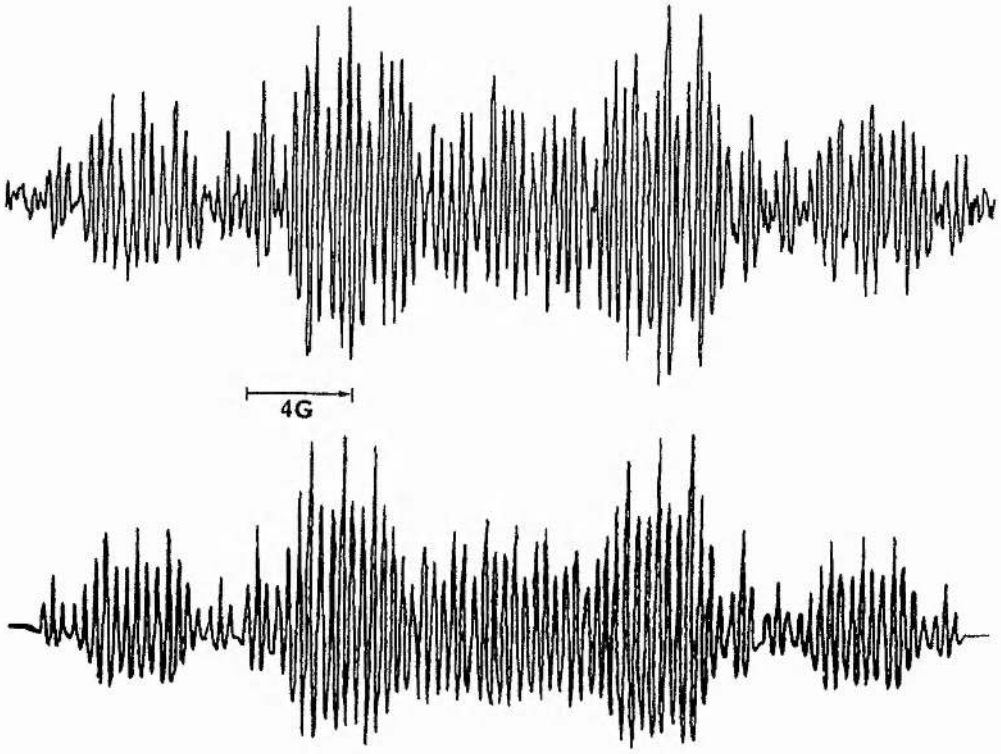
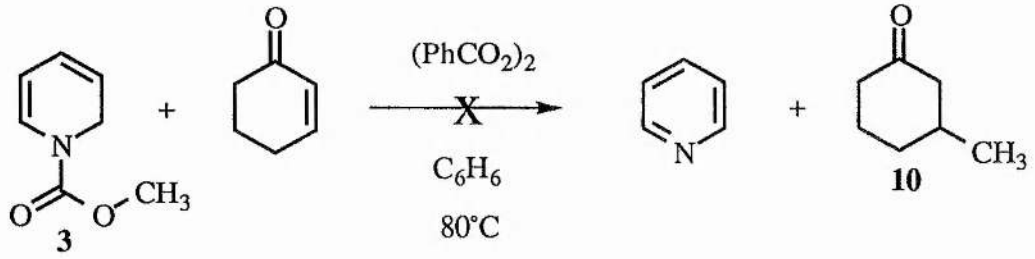


Figure 2. EPR spectra of the aza-cyclohexadienyl radical derived from dihydropyridine **4** (top spectrum) and its simulated spectrum (lower spectrum) using the hfs values in table 1.

2.2 Radical initiated reaction of dihydropyridine 3 with cyclohexenone

N-Carbomethoxy-1,2-dihydropyridine **3** was prepared in 63% yield according to the reported procedure[1] and was refluxed under nitrogen, in benzene in the presence of dibenzoyl peroxide and cyclohexenone (Scheme 5).

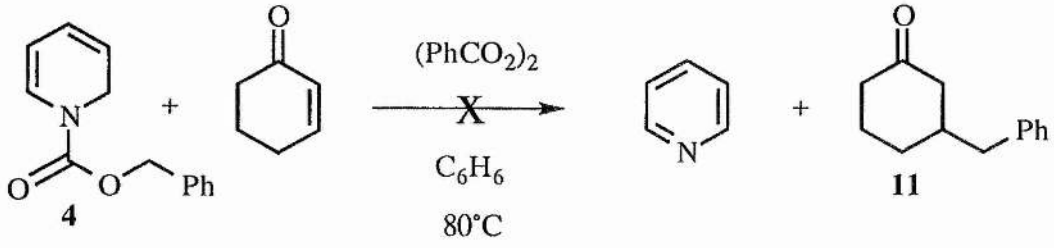


Scheme 5

The mixture was refluxed for 3 days and monitored by GC/MS which detected pyridine and unreacted cyclohexenone but gave no evidence for 3-methylcyclohexanone **10**. Analysis by ^{1}H NMR confirmed the presence of pyridine and cyclohexenone and the consumption of dihydropyridine **3**. An attempt to clean the residue by column chromatography resulted in removal of cyclohexenone and benzoic acid. Other fractions collected gave neither clean nor particularly well resolved spectra. The majority of dihydropyridine **3** decomposed under these conditions giving unidentifiable products which were mainly the result of polymerisation.

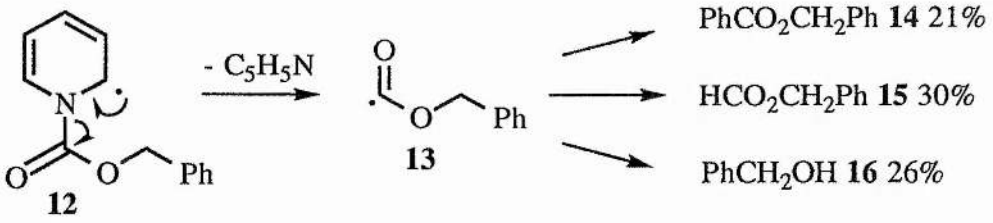
2.3 Radical initiated reaction of dihydropyridine 4 with cyclohexenone

N-Carbobenzyloxy-1,2-dihydropyridine **4** was refluxed in benzene for 2 days in the presence of dibenzoyl peroxide and cyclohexenone, but none of the adduct **11** was detected (Scheme 6).



Scheme 6

After purifying the reaction mixture by column chromatography it was possible to identify the main products as being benzyl benzoate **14**, benzyl formate **15** and benzyl alcohol **16** (Scheme 7). Such compounds may have been formed *via* alkoxycarbonyl radical **13**, which would itself have been generated by hydrogen abstraction from dihydropyridine **4** to give aza-cyclohexadienyl radical **12**, followed by homolytic cleavage of the N-C bond. The resulting radical **13** could therefore combine with a phenyl radical to give benzyl benzoate, abstract a hydrogen atom to give the formate or decarbonylate to give benzyl alcohol after hydrogen abstraction.

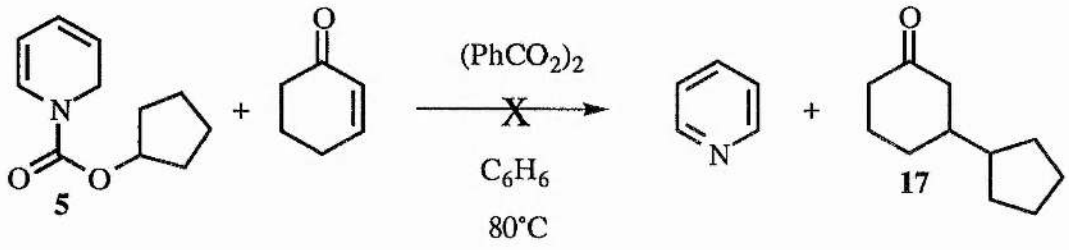


Scheme 7

Benzyl benzoate and benzyl alcohol were straightforward to identify by ^1H NMR spectroscopy and GC/MS. Although the peak corresponding to the formate gave a clear molecular ion (M^+=136), we were not totally convinced with this identification. When the reaction mixture was purified by column chromatography, this compound co-eluted with benzyl benzoate and we expected the ^1H NMR spectrum of the mixture to contain a singlet at approximately 8.1 ppm, corresponding to the formyl hydrogen in the formate. However, due to the aromatic signals from benzyl benzoate this singlet was not easy to observe. When we repeated the reaction using a smaller amount of initiator (i.e. 3% by wt. instead of 50%), the amount of benzyl benzoate decreased as expected and the main product identified by GC/MS was benzyl formate. A sample of this mixture was submitted for MS and the resulting spectrum was identical to a library fit, and on this basis we were assured that the main product from this reaction was benzyl formate.

2.4 Radical initiated reaction of dihydropyridine 5 with cyclohexenone.

N-Carbocyclopentyloxy-1,2-dihydropyridine **5** was refluxed in benzene in the presence of dibenzoyl peroxide and cyclohexenone, but none of the desired adduct **17** was detected (Scheme 8).

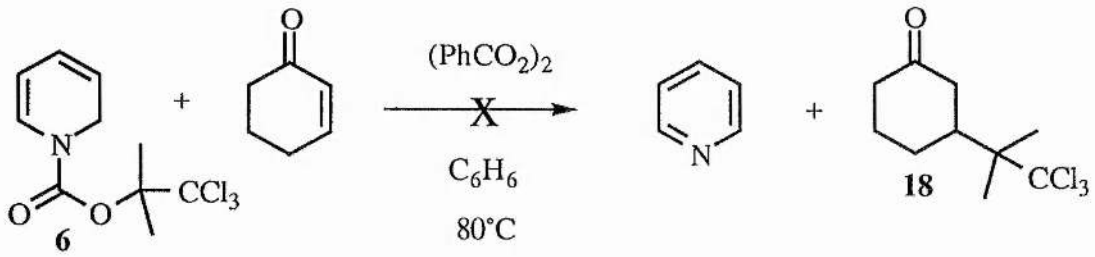


Scheme 8

Analysis of the reaction mixture by GC/MS detected mainly unreacted cyclohexenone, pyridine, cyclopentyl benzoate and a fourth compound which was not easy to identify due to limited data from the mass spectrum. A few other minor compounds were also observed but these were not identified. The mixture was purified by column chromatography and as in the previous experiment, the majority of the benzoate ester (formed in 41% yield) co-eluted with another compound. This other compound was also thought to be a formate (i.e. cyclopentyl formate), although it did not show a molecular ion in the mass spectrum. The ^{1}H NMR spectrum of the mixture of these two compounds did not help to confirm the presence of cyclopentyl formate, because there was no obvious peak corresponding to the formyl hydrogen, although such a signal may have been hidden by some of the aromatic signals from the benzoate ester. We also contemplated the possibility that this product may have been the dimer resulting from the combination of two alkoxycarbonyl radicals. However, the dimer dicyclopentyl oxalate was a compound which had been prepared earlier as a byproduct in an esterification reaction involving oxalyl chloride, and by comparisons of the two ^{1}H NMR spectra, it was concluded that the fourth product from the reaction above was the formate and not the dimer.

2.5 Radical initiated reaction of dihydropyridine 6 with cyclohexenone

Although dihydropyridines **3-5** had all failed to give evidence for the formation of the corresponding cyclohexanone adduct, we made one further attempt to achieve this. Since tertiary radicals are more stable than primary and secondary radicals we decided to prepare a dihydropyridine ester which would generate such a radical if decarboxylation took place. Since *t*-butyl chloroformate cannot be prepared by the reaction between phosgene and *t*-butanol (nor is it commercially available) we prepared the trichloromethyl analogue **6**, using commercially available 2,2,2-trichloro-1,1-dimethylethyl chloroformate. *N*-Carbo(1-methyl-1-trichloromethylethoxy)-1,2-dihydropyridine **6** was dissolved in benzene in the presence of cyclohexenone and dibenzoyl peroxide, and refluxed for 2.5 days (Scheme 9). As with the previous experiments the reaction was monitored by GC/MS, but again, there was no evidence for the formation of the desired adduct. A major product was the *t*-alcohol resulting from decarbonylation of the aza-cyclohexadienyl radical followed by hydrogen abstraction. In addition to the alcohol there were three other major products but these were not identified. The GC/MS data regarding these compounds was limited, although it was suspected that two of the products were the benzoate ester and the formate.



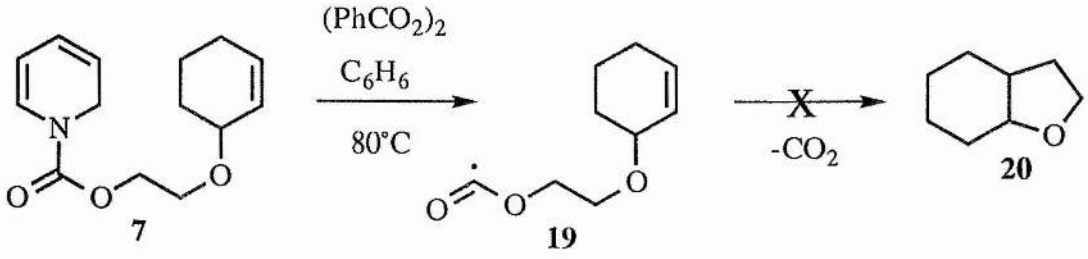
Scheme 9

The reactions discussed in the previous four sections involved using cyclohexenone as the radical trap. Since cyclohexenone is an electron deficient alkene it was feasible that it could have reacted with the 1,3-diene moiety of the dihydropyridine to give the corresponding Diels-Alder adduct. However, this was ruled out since the corresponding adducts were not observed in any of the GC/MS experiments, and also because the cyclohexenone remained unreacted and could be recovered by column chromatography. Furthermore, these dihydropyridines were not particularly reactive dienes due to the electron-withdrawing

substituent bonded to the nitrogen atom, although such reactions could proceed to give the Diels-Alder adduct if the dieneophile was maleic anhydride and the reaction contents were refluxed for a long enough period of time (Section 2.10).

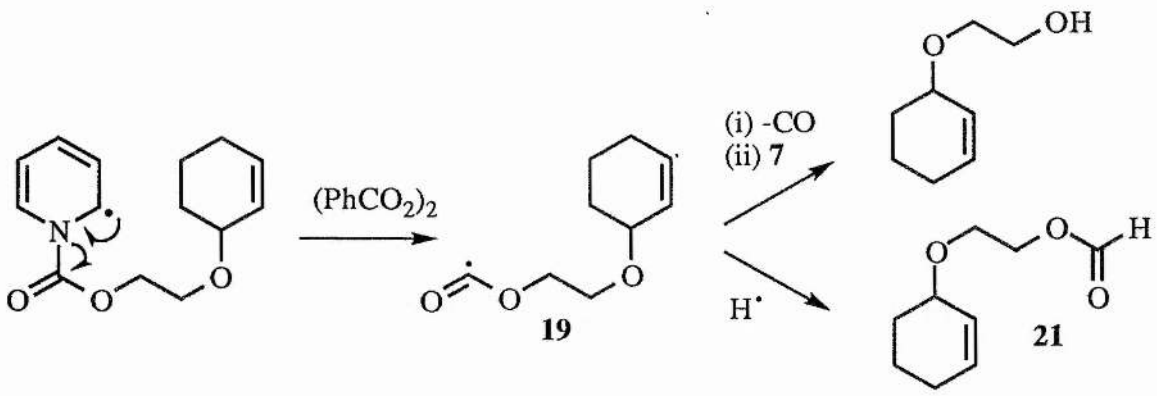
2.6 Radical initiated reaction of dihydropyridine 7 in benzene.

We investigated whether *N*-carbo[2-(cyclohex-2-enyloxy)ethoxy]-1,2-dihydropyridine **7** would generate an alkyl radical *via* decarboxylation and yield 7-oxabicyclo[4.3.0]nonane **20**, which would be easy to identify by comparisons with previous experiments (Scheme 10). We were not particularly optimistic about the success of this reaction, since we had not observed any decarboxylation with previous experiments, even in the cases where more stable radicals would have been produced. On the other hand, we did not have any evidence to prove that decarboxylation was not occurring and it was believed that dihydropyridine **7** would generate alkoxycarbonyl radicals of type **19**, which have been shown to decarboxylate under similar reaction conditions to give bicyclononane **20** (Chapter 3).



Scheme 10

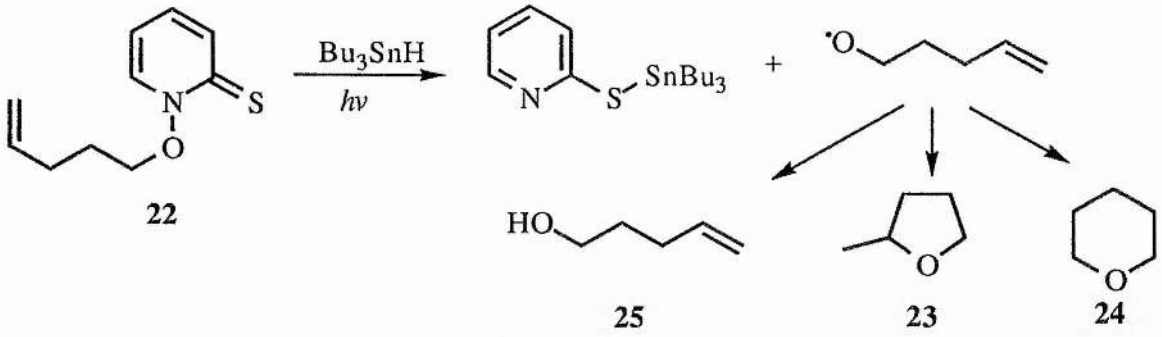
However, when the reaction was performed, there was no evidence for the ring cyclised product and the only compounds isolated were 3-(2-hydroxyethoxy)cyclohexene and 2-(cyclohex-2-enyloxy)ethyl formate **21** formed in yields of 19% and 15% receptively (Scheme 11). Also, the benzoate ester formed by combination of a phenyl radical with alkoxycarbonyl radical **19** was identified by GC/MS but not isolated in pure form.



Scheme 11

2.7 Radical initiated reaction of dihydropyridine 8 in benzene.

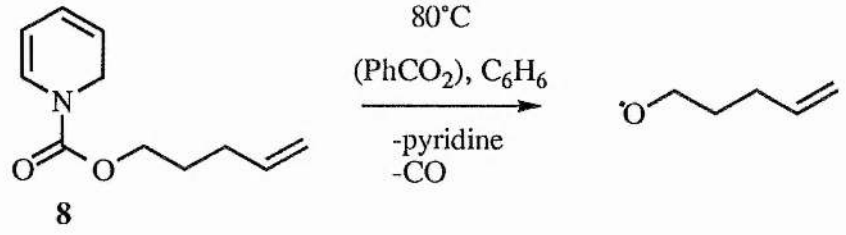
The radical reactions carried out on dihydropyridines **3-7** did not give any evidence for the production of an alkyl radical by decarboxylation. However, based on the formation of benzyl alcohol (section 2.3) and 3-(2-hydroxyethoxy)cyclohexene (section 2.6) there was evidence for the formation of the oxygen-centred radical R-O•. Therefore, we thought that if a pentenyloxy radical could be generated from *N*-carbo(pent-4-enyloxy)-1,2-dihydropyridine **8**, then it should be possible for this radical to cyclise *via* the conventional 5-*exo* manner to give 2-methyltetrahydrofuran. Hartung has investigated the stereoselective ring closure of 4-pentenyl-1-oxy radicals generated by the tin hydride induced fragmentation of *N*-(pentenyloxy)pyridine-2(1H)-thione **22** (Scheme 12).[7] The ratio of products, not surprisingly, depended on the amount of tin hydride used and in one experiment 2-methyltetrahydrofuran **23** and tetrahydropyran **24** were obtained in yields of 52% and 1% respectively. 4-Penten-1-ol **25**, a product of hydrogen abstraction from tin hydride by the corresponding alkoxy radical, was formed in 31% yield. The rate constant for cyclisation of the pentenyloxyl radical was estimated to be 4±2 x $10^8 s^{-1}$ at 30°C, which is more rapid than the hex-5-enyl radical cyclisation. It followed that such a fast cyclisation should result in the formation of 2-methyltetrahydrofuran **23** from dihydropyridine **8** if the corresponding pentenyloxyl radical were to be produced.



22 25 23 24

Scheme 12

Therefore, dihydropyridine **8** was dissolved in benzene containing dibenzoyl peroxide and refluxed for 24h, but analysis by GC/MS indicated that there was no evidence for either of the ring closed products (Scheme 13). We thought that the cyclic products may have been hidden underneath the solvent peaks, but when the GC/MS conditions were altered, and authentic samples of 2-methyltetrahydrofuran and tetrahydropyran were injected, there was no correlation between the peaks corresponding to the pure samples and the crude reaction mixture.



8

Scheme 13

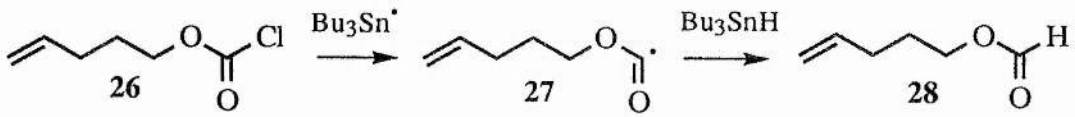
Therefore, the fact that neither 2-methyltetrahydrofuran or tetrahydropyran were detected, but a small amount of pent-4-en-1-ol was, suggested that the pentenyloxyl radical abstracted hydrogen from dihydropyridine **8** prior to cyclisation. However, this was unexpected since the rate of cyclisation of the pentenyloxyl radical is faster than the rate of hydrogen abstraction from the dihydropyridine.[7,8]

Analysis of the reaction mixture identified the presence of two main products, which were pent-4-enyl benzoate and the corresponding formate. A small amount of pent-4-en-1-ol was also detected. The residue was purified by column chromatography and this resulted in the co-elution of two products. One of these was the benzoate ester, though the major

component was the formate. As previously observed, the ^{1}H NMR signal corresponding to the formyl hydrogen was not as prominent as the other signals corresponding to the alkyl fragment of the formate. However, all the other data was in agreement with this assignment and the most convincing evidence came from the experiment described in the following section. Pent-4-enyl chloroformate was reduced with Bu_3SnH and the main product from this reaction had an identical retention time and mass spectrum to the product above, which we believed was the formate.

2.8 Radical initiated reaction of pent-4-enyl chloroformate with Bu_3SnH

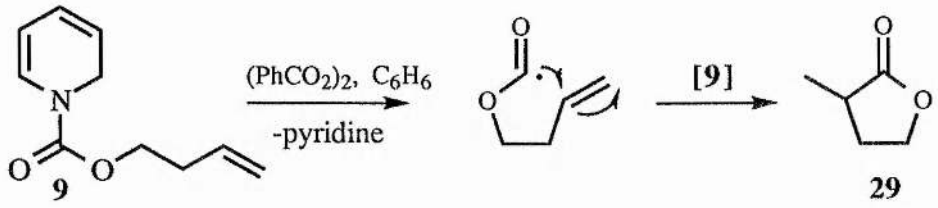
We anticipated that if pent-4-enyl chloroformate **26** was photolysed in the presence of Bu_3SnH in benzene, the main product would be the corresponding formate **28** (Scheme 14). On completion of this experiment it was evident that this was indeed the main product. This compound was formed presumably by chlorine abstraction from the chloroformate **26** to give alkoxycarbonyl radical **27** which abstracted hydrogen from the tin hydride to give the product. A positive correlation between this compound and one of the products detected from the previous experiment, was confirmation that dihydropyridine **8** also resulted in formation of formate **28**. Since the ^{1}H NMR analysis of the formate obtained in the previous experiment did not produce conclusive evidence for the signal corresponding to the formyl hydrogen, we thought that this product may have actually been a dimer, resulting from alkoxycarbonyl radical combination. However, such a product would be very unlikely to form in the tin hydride reduction of chloroformate **26**, because the alkoxycarbonyl radical **27** would abstract hydrogen from the tin hydride more readily than combine with another such radical. We concluded that pent-4-en formate was formed in this reaction and the one described in section 2.7.



Scheme 14

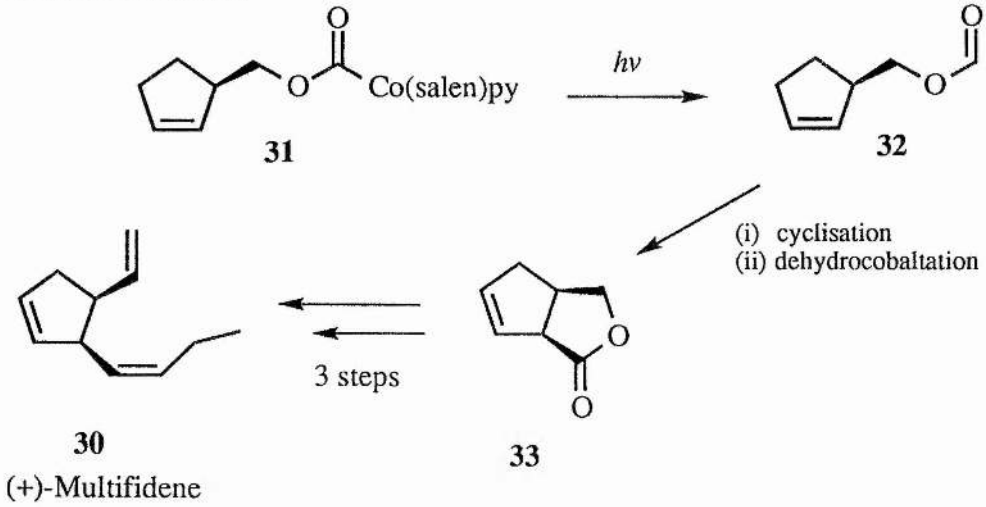
2.9 Radical initiated reaction of dihydropyridine 9 in benzene.

We decided to investigate whether *N*-carbo(but-3-enyloxy)-1,2-dihydropyridine **9** would generate an alkoxycarbonyl radical, which would cyclise to yield the cyclic lactone **29** (Scheme 15).



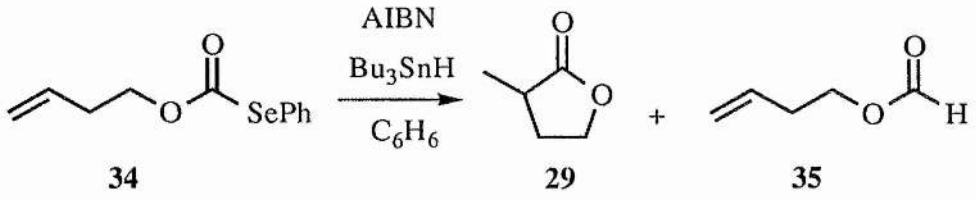
Scheme 15

There are examples where alkoxycarbonyl radicals have been formed and reacted intramolecularly for synthetic purposes, such as in the synthesis of (+)-multifidene **30** (Scheme 16).[9] When cobalt complex **31** was photolysed, the alkoxycarbonyl radical **32** was produced and this cyclised to give the unsaturated bicyclic lactone **33** in 65% yield after dehydrocobaltation.



Scheme 16

In an investigation into the free-radical annelation of phenylselenoalkoxy carbonyl compounds by Bachi, a variety of O-alkenyl and O-alkynyl seleno carbonates were treated with Bu_3SnH and AIBN (Scheme 17).[10] For example but-3-enyl-selenocarbonate **34** yielded the lactone **29** in 92% yield and at higher tin hydride concentrations, formate **35** formed in high yield. This particular reaction is analogous to the one given in Scheme 15.



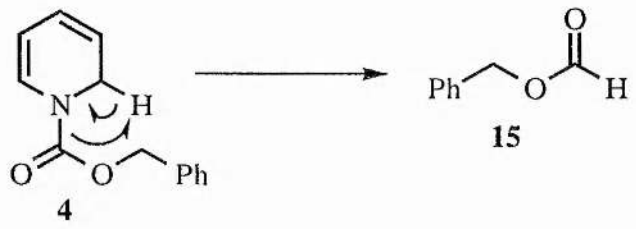
34 **29** **35**

Scheme 17

When *N*-carbo(but-3-enyloxy)-1,2-dihydropyridine was refluxed in benzene in the presence of dibenzoyl peroxide, two main products were detected by GC/MS. As in all the previous reactions these two compounds were identified as the corresponding benzoate ester and formate. However, the combined yield of these two products was only 14% and the remaining material which was eluted by column chromatography was not identified.

2.10 Preparation and reactions of *N*-benzyloxy-1,4-dihydropyridine (36)

The formates which were identified as products from the radical reactions of the dihydropyridines **4-9** may have formed by a non-radical process. The main evidence for this was the fact that when the 1,2-dihydropyridine **4** was refluxed in benzene with no other compounds present, a small amount of benzyl formate **15** was identified and this may have occurred by an elimination process involving the allylic hydrogen atoms (Scheme 18).

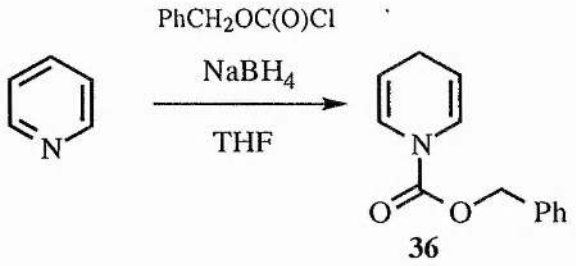


4 **15**

Scheme 18

Thus, the 1,4-dihydropyridine **36** was prepared to try and shed some light on this. If the mechanism given in Scheme 18 was responsible for the formation of benzyl formate, then this compound should not be formed from the 1,4-dihydropyridine since the allylic group would be further away from the nitrogen substituent. Thus, the 1,4-dihydropyridine **36** was prepared by lowering the reaction temperature, using THF instead of methanol and trapping out the 1,2-dihydropyridine as a Diels-Alder adduct using maleic anhydride

(Scheme 22).[1] In this way it was possible to obtain the 1,4-dihydropyridine **36** in *ca.* 16% yield and although the yield was low this was not the main concern.



36

Scheme 22

When dihydropyridine **36** was refluxed in benzene in the absence of any other chemicals, analysis by GC/MS indicated that the compound had been consumed, but benzyl formate was not observed. This supported the theory that the formates which had been identified in previous experiments were forming by a process involving the proximate allylic hydrogen atoms. When the 1,4-dihydropyridine was refluxed in the presence of dibenzoyl peroxide and cyclohexenone there was no evidence for the formation of the benzyl radical and this was consistent with the previous results. The major product was benzyl benzoate formed in an approximate yield of 32%. The reactions were repeated in amyl alcohol to encourage decarboxylation of the alkoxycarbonyl radical, but again, there was no evidence for formation of the benzyl radical at this elevated temperature.

Conclusions

The 1,2-dihydropyridines **3-9** were readily prepared from pyridine and the appropriate chloroformate in the presence of $NaBH_4$. These were investigated by EPR spectroscopy and it was evident that in the presence of a hydrogen atom abstractor, such as dibenzoyl peroxide, the corresponding aza-cyclohexadienyl radicals were formed and produced well-resolved and intense spectra. However, these compounds did not give any evidence for the generation of the alkyl radicals, either in the EPR experiments or in the radical reactions. When the dihydropyridines **3-6** were refluxed under the usual radical-initiating conditions and in the presence of cyclohexenone, no adduct was detected and the dihydropyridines **7-9** did not provide any evidence which suggested that the products of cyclisation had been formed. The radical reactions involving the 1,2-dihydropyridines usually resulted in the formation of two main products which could be isolated by column chromatography. These two compounds were the benzoate esters and the formates. We believed that the benzoate esters were formed by the generation of an alkoxycarbonyl radical, followed by combination with a phenyl radical from the initiator. The formate formed either by hydrogen abstraction by the alkoxycarbonyl radical or an elimination process involving the C-2 allylic hydrogen atoms of the 1,2-dihydropyridine or perhaps both. In addition to these products, alcohols were usually detected and these presumably formed by decarbonylation of the alkoxycarbonyl radical, followed by hydrogen abstraction. We also considered investigating *N*-acyloxy-1,2-dihydropyridines as reagents for generating radicals, since we thought that a carbonyloxy radical would decarboxylate more readily than an alkoxycarbonyl radical. However, these precursors appear to be more difficult to prepare than the 1,2-dihydropyridines discussed in this Chapter.

3 Experimental

Refer to the experimental section from Chapter 2 for information regarding the collection of experimental data etc.

Preparation of chloroformates[4]

Methyl chloroformate, benzyl chloroformate and 2,2,2-trichloro-1,1-dimethylethyl chloroformate were purchased from Aldrich. Cyclopentyl chloroformate **37** was prepared by the following method and chloroformates **26**, **38** and **39** were made in a similar manner with the appropriate alcohol:

Cyclopentanol (15 g, 0.174 mol) and quinoline (22.5 g, 0.174 mol) dissolved in dry ether (50 cm^3) were added dropwise to a stirred mixture of phosgene (19 g, 0.192 mol) in toluene at 0°C and the mixture was left stirring for 16-24h. To the reaction mixture HCl (100 cm^3) was added and the resulting layers were separated. The aqueous layer was extracted with ether (100 cm^3), the organic fractions were combined, dried ($MgSO_4$) and the solvents were evaporated and the chloroformate was purified by distillation.

Cyclopentyl chlorofomate (37)

The title compound was obtained as a clear, colourless liquid (82%), bp 56-58°C at 10-12 mmHg (lit.,[11] bp 69-71°C at 25 mmHg); δ_H 1.50-2.00 (8 H, m, methylene-H), 5.25-5.35 (1 H, m, *t*-H); δ_C (50 MHz) 23.4 (2 x 2,3-C), 32.4 (2 x 1,4-C), 86.4 (5-C), 150.0 (6-C).

2-(Cyclohex-2-enyloxy)ethyl chloroformate (38)

The title compound was obtained as a clear, colourless liquid (90%), bp 70-75°C at 0.1 mmHg (Found: C, 53.34; H, 6.64. Calc. for $C_9H_{13}O_3Cl$: C, 52.82; H, 6.40%); δ_H 1.45-2.15 (6 H, m, methylene-H), 3.72-3.80 (2 H, q, *J* 4.4, methylene 7-H), 3.85-4.00 (1 H, m, *t* 6-H), 4.41-4.49 (2 H, t, *J* 4.8, methylene 8-H), 5.70-5.97 (2 H, m, olefinic 4,5-H);

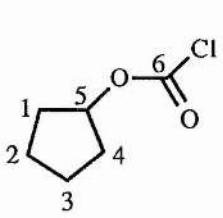
δ_C 18.8 (2-C), 25.0, 27.9 (2 x 1,3-C), 64.8 (7-C), 71.0 (8-C), 73.3 (6-C), 126.9, 131.4 (2 x 4,5-C), 151.2 (9-C).

Pent-4-enyl chloroformate (26)

The title compound was obtained as a clear, colourless liquid (61%), bp 56-58°C at 0.1 mmHg (Found: C, 48.48; H, 6.26. Calc. for $C_6H_9O_2Cl$: C, 48.50; H, 6.10%); δ_H 1.80-1.92 (2 H, q^i, *J* 6.9, methylene 4-H), 2.11-2.24 (2 H, q, *J* 7.1, allylic 3-H) 4.30-4.39 (2 H, t, *J* 6.6, methylene 5-H), 5.00-5.10 (2 H, m, olefinic 1-H), 5.70-5.85 (1 H, m, olefinic 2-H); δ_C 27.9, 30.0 (2 x 3,4-C), 72.0 (5-C), 116.5 (1-C), 137.0 (2-C), 151.1 (6-C).

But-3-enyl chloroformate (39)

The title compound was obtained as a clear, colourless liquid (33%†), bp 40-50°C at 10 mmHg; δ_H 2.41-2.56 (2 H, m, allylic 3-H), 4.33-4.42 (2 H, t, *J* 8.5, methylene 4-H), 5.10-5.26 (2 H, m, olefinic 1-H), 5.70-5.90 (1 H, m, olefinic 2-H); δ_C 32.8 (3-C), 71.0 (4-C), 118.6 (1-C), 132.5 (2-C), 151.2 (5-C). †Unoptimised yield.



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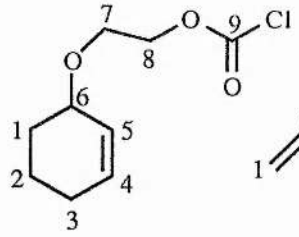

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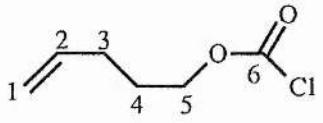

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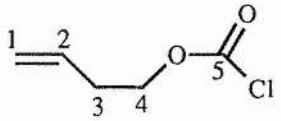

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Preparation of *N*-carboalkoxy-1,2-dihydropyridines 3-9 (Scheme 1)

N-Carbomethoxy-1,2-dihydropyridine **3** was prepared by the following method and dihydropyridines **4-9** were made in a similar manner with the appropriate chloroformate. The yields given are based on the mass of dihydropyridine obtained, although analysis by ^{1}H NMR usually revealed traces of impurities.

Methyl chloroformate (5.95 g, 0.063 mol) in dry ether (10 cm^3) was added slowly to sodium borohydride (2.5 g, 0.066 mol) and pyridine (5 g, 0.063 mol) in Analar methanol (25 cm^3) at -78°C under nitrogen. The reaction mixture was left stirring for 1.5-2h and the reaction contents were poured into ice water (200 cm^3) and the product was extracted with ether (3 x 100 cm^3). The combined ethereal extracts were washed with H_2O (5 x 50 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure to give the desired compound which was stored in the freezer.

_N_-Carbomethoxy-1,2-dihydropyridine (3)

The title compound was obtained as a light yellow liquid (63%); δ_H 2.75-2.85 (minor impurity), 3.70-3.80 (3 H, m, methyl-H), 4.25-4.40 (2 H, m, allylic-H), 4.75-4.90 (minor impurity), 5.00-5.20 (1 H, m, olefinic-H), 5.35-5.60 (1 H, m, olefinic-H), 5.70-5.90 (1 H, m, olefinic-H), 6.55-6.80 (1 H, m, olefinic-H).

_N_-Carbobenzyloxy-1,2-dihydropyridine (4)

The title compound was obtained as a grey liquid (92%); δ_H 4.40 (2 H, s, benzyl 1-H), 5.15-5.30 (m, 3 H; 2 H, allylic 7-H and 1 H olefinic-H), 5.40-5.60 (1 H, m, olefinic-H), 5.80-5.90 (1 H, m, olefinic-H), 6.70-6.87 (1 H, m, olefinic-H), 7.25-7.45 (5 H, m, arom-H); δ_C 43.6 (7-C), 44.1 (u), 66.2 (u), 67.8 (1-C), 104.9 (4-C), 119.2, 121.9, 125.5 (3 x 3,5,6-C), 128.1, 128.3, 128.5, 128.6 (6 x arom-C), 150.2 (u), 161.6 (2-C); *m/z* 215 (M^+, 10%), 170 (15), 136 (8), 108 (13), 91 (100), 79 (21), 65 (11) (Found: M^+, 215.0956. $C_{13}H_{13}NO_2$ requires 215.0946). u=unidentified.

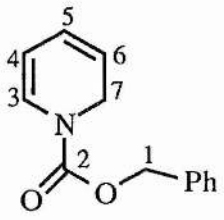
_N_-Carbocyclopentoxy-1,2-dihydropyridine (5)

The title compound was obtained as a light yellow liquid (74%); δ_H 1.50-2.00 (8 H, m, methylene-H), 4.25-4.40 (2 H, m, allylic 11-H), 5.00-5.20 (2 H, m; 1 H, *t* 5-H and 1 H, olefinic-H), 5.35-5.55 (1 H, m, olefinic-H), 5.75-5.85 (1 H, m, olefinic-H), 6.55-6.80 (1 H, m, olefinic-H); δ_C 23.6 (2 x 2,3-C), 32.4 (2 x 1,4-C), 43.4 (11-C), 79.0 (5-C), 104.4 (8-C), 119.1, 122.0, 125.9 (3 x 7,9,10-C), 150.0 (6-C); *m/z* 193 (M^+, 43%), 192 (15),

151 (16), 124 (50), 108 (10), 80 (91), 79 (26), 70 (53), 68 (56), 53 (34). (Found: M^+, 193.1100. $C_{11}H_{15}NO_2$ requires 193.1103).

***N*-Carbo[(1-methyl-1-trichloromethyl)-ethoxy]-1,2-dihydropyridine (6)**

The title compound was obtained as a light yellow solid (91%); δ_H 1.65 (unidentified signal), 1.90-2.00 (6 H, m, methyl-H), 2.80-2.90 and 3.80 (unidentified signal), 4.30-4.45 (2 H, m, allylic 10-H) 5.10-5.20 (1 H, m, olefinic-H), 5.45-5.60 (1 H, m, olefinic-H), 6.65-6.75 (1 H, m, olefinic-H), 5.75-5.95 (1 H, m, olefinic-H), >7 trace amounts of pyridine; δ_C 21.6 (2 x 1,2-C), 24.9, 43.4 (minor impurities), 89.5 (3-C), 105.4 (7-C), 119.2, 122.1, 125.8 (3 x 6,8,9-C) 149.3 (5-C); *m/z* 285/283 (M^+, $^{37}Cl/^{35}Cl$, 10/10%), 163 (10), 161 (20), 159 (15), 125 (61), 124 (43), 123 (30), 108 (18), 80 (63), 79 (44), 59 (100) (Found: M^+, 282.9940. $C_{10}H_{12}Cl_3NO_2$ requires 282.9934).



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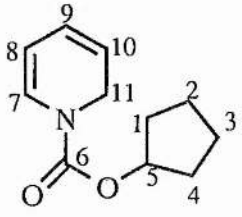

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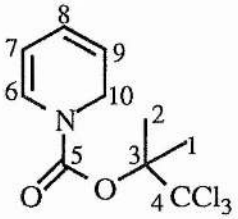

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***N*-Carbo[2-(cyclohex-2-enyloxy)ethoxy]-1,2-dihydropyridine (7)**

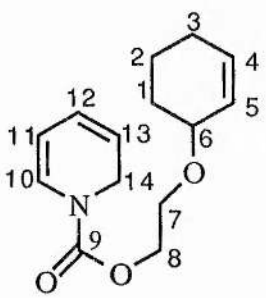
The title compound was obtained as a grey liquid (77%); δ_H 1.50-2.20 (6 H, m, methylene 1,2,3-H), 3.60-3.80 (2 H, m, methylene 7-H), 3.80-3.95 (1 H, m, *t* 6-H), 4.25-4.45 (4 H, m, methylene 8 and 14-H), 5.05-5.20 (1 H, m, olefinic-H), 5.40-5.60 (1 H, m, olefinic-H), 5.70-5.95 (3 H, m; 2 H, olefinic 4,5-H and 1 H, olefinic-H), 6.65-6.85 (1 H, m, olefinic-H); δ_C 19.5 (2-C), 25.5, 28.2 (2 x 1,3-C), 44.0 (14-C), 66.1, 66.3 (2 x 7,8-C), 73.5 (6-C), 105.0 (11-C), 119.1, 122.2, 126.0 (3 x 10,12,13-C), 127.9, 131.6 (2 x 4,5-C), 160.9 (9-C); *m/z* 249 (M^+, 5%), 168 (14), 124 (6), 99 (18), 97 (21), 81 (100), 80 (31), 79 (38), 73 (61) (Found: M^+, 249.1374. $C_{14}H_{19}NO_3$ requires 249.1365).

N-Carbo(pent-4-enyloxy)-1,2-dihydropyridine (8)

The title compound was obtained as a grey liquid (76%); δ_H 1.68-1.84 (2 H, q^i, *J* 6.8, methylene 4-H), 2.05-2.20 (2 H, q, *J* 7.1, allylic 3-H), 4.12-4.20 (2 H, t, *J* 6.5, methylene 5-H), 4.30-4.40 (2 H, m, allylic 11-H), 4.95-5.20 (3 H, m; 2 H, olefinic 1-H and 1 H, olefinic-H), 5.40-5.60 (1 H, m, olefinic-H), 5.70-5.95 (2 H, m; 1 H, olefinic 2-H and 1 H, olefinic-H), 6.50-6.85 (1 H, m, olefinic-H); δ_C 28.3, 30.0 (2 x 3,4-C), 44.0 (11-C), 65.9 (5-C), 105.0 (8-C), 115.9, 119.5, 122.1 (3 x 7,9,10-C), 126.0 (1-C), 138.2 (2-C), 161.3 (6-C); *m/z* 193 (M^+, 48%), 148 (7), 125 (62), 124 (68), 108 (10), 86 (21), 86 (21), 80 (100), 79 (49), 69 (71), 57 (56).

N-Carbo(but-3-enyloxy)-1,2-dihydropyridine (9)

The title compound was obtained as a grey liquid (75%); δ_H 2.37-2.50 (2 H, m, allylic 3-H), 4.19-4.27 (2 H, t, *J* 6.6, methylene 4-H), 4.35-4.42 (2 H, m, allylic 10-H), 5.12-5.23 (3 H, m; 2 H, olefinic 1-H and 1 H, olefinic-H), 5.44-5.60 (1 H, m, olefinic-H), 5.74-5.93 (2 H, m; 1 H, olefinic 2-H and 1 H olefinic-H), 5.63-5.83 (1 H, broad doublet, olefinic-H); δ_C 33.3 (3-C), 43.5 (10-C), 65.1 (4-C), 104.8 (7-C), 117.4 (1-C), 119.2, 122.0, 125.7 (3 x 6,8,9-C), 134.0 (2-C), 150.0 (5-C); *m/z* 179 (M^+, 42%), 134 (18), 124 (23), 108 (7), 80 (69), 55 (100) (Found: M^+, 179.0941. $C_{10}H_{13}NO_2$ requires 179.0946).



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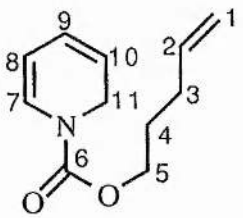

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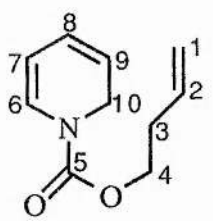

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Radical initiated reaction of dihydropyridine 3 with cyclohexenone (Scheme 5). *N*-Carbomethoxy-1,2-dihydropyridine **3** (0.4 g, 3 mmol) was dissolved in benzene (3 cm^3) and added to a refluxing mixture of benzene (7 cm^3), dibenzoyl peroxide (0.2 g, 50% wt.) and cyclohexenone (0.28 g, 3 mmol) under nitrogen. The mixture was refluxed under

nitrogen for 3 days and analysis by GC/MS indicated that the main component was unreacted cyclohexenone with no evidence for 3-methylcyclohexanone. The benzene was evaporated yielding a liquid (0.85 g) which was eluted through a column of silica gel using 30% ethyl acetate in 70% redistilled light petroleum, but no products were isolated in pure form. The reaction yielded mainly unidentifiable polymeric material.

Radical initiated reaction of dihydropyridine 4 with cyclohexenone (Scheme 6). *N*-Carbobenzyloxy-1,2-dihydropyridine (1 g, 4.6 mmol), cyclohexenone (0.89 g, 9.3 mmol) and dibenzoyl peroxide (0.5 g, 50% wt.) were refluxed in benzene for 2 days under nitrogen. The benzene was evaporated yielding an oil (2.17 g) which was purified by column chromatography eluting with ethyl acetate (30%) and light petroleum (70%) resulting in the isolation of benzyl benzoate (0.21 g, 21%), benzyl formate (0.19 g, 30%) and benzyl alcohol (0.13 g, 26%). Benzyl benzoate; δ_H 5.4 (2 H, s, benzyl-H), 7.4-7.7 (8 H, m, arom-H), 8.0-8.2 (2 H, m, arom-H); GC/MS peak no. 527, *m/z* (relative intensity), 212 (M^+) (3), 195 (1), 168 (1), 105 (100), 91 (68), 77 (63), 65 (29), 51 (50), 39 (24), 18 (9). Benzyl formate; *m/z*†(relative intensity), 136 (M^+) (24), 108 (22), 107 (25), 91 (100), 79 (54), 77 (62), 65 (58), 51 (74), 39 (81), 29 (70), 18 (9); δ_H‡ 5.22 (2 H, s, benzyl-H), 7.32-7.50 (5 H, m, arom-H). Benzyl alcohol; δ_H 4.65 (2 H, s, benzyl-H), 7.28-7.32 (5 H, m, arom-H). †Identical to the library fit. ‡Formyl hydrogen hidden under aromatic signals of benzyl benzoate.

Radical initiated reaction of dihydropyridine 5 with cyclohexenone (Scheme 11). *N*-Carbocyclopentoxy-1,2-dihydropyridine **5** (0.68 g, 3.5 mmol) was added to a refluxing mixture of cyclohexenone (0.34 g, 3.5 mmol), *t*-butyl peroxybenzoate (0.34 g, 50% wt.) and benzene (6 cm^3) under nitrogen. This mixture was refluxed for 3 days during which a further 0.34 g of initiator was added. A sample of the reaction mixture was submitted for GC/MS analysis which gave no evidence for the desired adduct, but detected cylohexenone, cyclopentyl benzoate, cyclopentyl formate and three minor components which were not identified. The benzene was evaporated giving a liquid (1.33 g) which was

shown by ^{1}H NMR spectroscopy to contain unreacted cyclohexenone, pyridine and compounds bearing cyclopentyl fragments. The mixture was purified by column chromatography eluting with 30% ethyl acetate and 70% redistilled light petroleum yielding a mixture (0.4 g) of cyclopentyl benzoate (0.31 g, 41 %) and cyclopentyl formate (0.09 g, 23%); δ_H 1.50-2.10 (16 H, m; 8 H, methylene-H, cyclopentyl benzoate and 8 H, methylene-H, cyclopentyl formate), 5.00-5.10 (1 H, m, *t*-H, formate), 5.35-5.50 (1 H, m, *t*-H, benzoate), 7.35-7.60 (3 H, m, arom-H, benzoate), 8.00-8.10 (3 H, m; 2 H, arom-H, benzoate and 1 H, formyl-H, formate); δ_C (50 MHz) 22.9 (2 x methylene-C, formate), 23.1 (2 x methylene-C, benzoate), 31.9 (2 x methylene-C, formate), 32.0 (2 x methylene-C, benzoate), 77.0 (1 x *t*-C, benzoate), 79.9 (1 x *t*-C, formate), 127.5, 128.7, 130.2, 132.0 (6 x arom-C, benzoate), 153.8 (carbonyl-C, formate), 165.6 (carbonyl-C, benzoate); GC/MS peak no. 413, cyclopentyl formate, *m/z* (relative intensity), 85 (4), 69 (88), 57 (34), 41 (100), 27 (30), 18 (6); peak no. 440, cyclopentyl benzoate, 190 (M^+) (1), 173 (1), 140 (1), 134 (1), 123 (31), 105 (100), 77 (70), 68 (17), 51 (32), 41 (37), 27 (20), 18 (8).

Radical initiated reaction of dihydropyridine 6 with cyclohexenone (Scheme 10). *N*-Carbo-(1-methyl-1-trichloromethylethoxy)-1,2-dihydropyridine (1.0 g, 3.5 mmol), cyclohexenone (0.34 g, 3.5 mmol) and dibenzoyl peroxide (0.1 g, 10% wt.), were refluxed in benzene and under nitrogen for 2 days during which a further 0.2 g of initiator was added. A sample of the reaction mixture was submitted for GC/MS analysis; *m/z* (rel. intensity), peak no. 195, cyclohexenone; peak no. 220, 2,2,2-trichloro-1,1-dimethyl ethanol, 163 (2), 161 (2), 127 (6), 125 (5), 77 (13), 59 (100), 43 (65), 31 (60); peak no. 324, identity was not confirmed, but presumably the formate, 177 (2), 161 (4), 159 (4), 125 (8), 123 (11), 77 (27), 73 (100), 59 (41), 43 (79), 41 (25); peak no. 505, unidentified product, 199 (1), 189 (1), 161 (2), 124 (25), 105 (100), 89 (15), 80 (64), 77 (73), 53 (45), 51 (47), 39 (38); peak no. 566, identity was not confimed but presumably the benzoate ester, 226 (1), 198 (3), 105 (100), 77 (76), 51 (47).

Radical initiated reaction of dihydropyridine 7 in benzene (Scheme 12)

N-Carbo[2-(cyclohex-2-enyloxy)ethoxy]-1,2-dihydropyridine **7** (2 g, 8.0 mol) and dibenzoyl peroxide (0.2 g, 10% wt.) were refluxed in benzene for 3 days under nitrogen. The benzene was evaporated and the resulting oil (2.42 g) was purified by column chromatography eluting with 40% light petroleum in ether. This resulted in the isolation of 3-(2-hydroxyethoxy)cyclohexene (0.22 g, 19%) and 2-(cyclohex-2-enyloxy)ethyl formate **19** (0.2 g, 15%).3-(2-Hydroxy)cyclohexene: identical ^{1}H NMR and ^{13}C NMR to those previously given in Chapter 2. 2-(Cyclohex-2-enyloxy)ethyl formate: δ_H (300 MHz) 1.42-2.10 (6 H, m, methylene-H), 3.62-3.80 (2 H, m, methylene-H), 3.84-3.94 (1 H, m, *t*-H), 4.21-4.35 (2 H, m, methylene-H), 5.65-5.92 (2 H, m, olefinic-H), 8.08 (1 H, s, acyl-H); δ_C 19.1, 25.1, 28.2 (3 x methylene C, cyclohexenyl ring), 63.6, 65.6 (2 x methylene C, ethyl chain), 73.4 (*t*-C), 127.4, 131.5 (2 x olefinic C), 161.3 (carbonyl-C); *m/z* 171 (MH^+, 5%), 137 (10), 123 (9), 97 (10), 81 (88), 72 (24) (Found: 171.1026. $C_9H_{15}O_3$ requires 171.1021).

Radical initiated reaction of dihydropyridine 8 in benzene (Scheme 14)

N-Carbo(pent-4-enyloxy)-1,2-dihydropyridine **8** (2 g, 10.4 mmol) and dibenoyl peroxide (0.05 g, 2.5% wt.) were refluxed in benzene and under nitrogen for 3.5 days during which a further 0.2 g of initiator was added. The benzene was evaporated yielding a brown oil (1.89 g). This mixture was purified by column chromatography with 10% ethyl acetate and 90% light petroleum yielding a mixture (0.32 g) of pent-4-enyl benzoate **24** (0.07 g, 4%) and pent-4-enyl formate **35** (0.25 g, 22%); δ_H 1.68-1.96 (4 H, m, methylene-H, pent-4-enyl benzoate and pent-4-enyl formate), 2.01-2.30 (4 H, m, methylene-H, benzoate and formate), 4.15-4.18 (2 H, t, *J* 6.5, methylene-H, formate), 4.30-4.37 (2 H, t *J* 7, methylene-H, benzoate), 4.95-5.18 (4 H, m, olefinic-H, benzoate and formate), 5.70-5.93 (2 H, m, olefinic-H, benzoate and formate), 7.38-7.60 (3 H, m, arom-H, benzoate), 8.00-8.10 (3 H, m; 2 H, arom-H, benzoate and 1 H, formyl-H, formate); δ_C (50 MHz) 28.3 (methylene-C, formate), 28.4 (methylene-C, benzoate), 30.3 (methylene-C, formate), 30.7 (methylene-C, benzoate), 64.8 (methylene-C, benzoate), 67.7 (methylene-C, formate),

115.9 (olefinic-C, formate), 116.1 (olefinic-C, benzoate), 137.7 (olefinic-C, formate), 137.9 (olefinic-C, benzoate), 155.8 (carbonyl-C, formate); GC/MS peak no. 363, pent-4-enyl formate, *m/z* (relative intensity), 68 (62), 67(51), 41 (100), 39 (30), 29 (15), 18 (10); peak no. 411, pent-4-enyl benzoate, *m/z* 123 (3), 105 (100), 77 (65), 68 (93), 51 (26), 41 (22), 39 (19), 28 (20), 18 (55). All other fractions appeared be the products of polymerisation.

Treatment of pent-4-enyl chloroformate with Bu_3SnH (Scheme 16)

Pent-4-enyl chloroformate (0.2 g, 1.4 mmol) was dissolved in deuterated benzene (0.75 cm^3) and added to an NMR tube. To this, tributyltin hydride (0.2 g, 0.7 mmol) was added and the mixture was photolysed with a 125 W Hg lamp for 15 min at r.t. and at 40°C for 2.5h. A sample of the reaction mixture was analysed by GC/MS: peak no. 159, 5-chloropent-1-ene, *m/z* (relative intensity) 106 (M^+) (2), 104 (M^+) (6), 84 (16), 68 (38), 67 (55), 55 (98), 41 (100), 53 (26), 40 (63), 39 (84), 29 (30), 27 (76); peak no. 202, 4-penten-1-ol, 68 (54), 67 (100), 53 (73), 41 (48), 39 (85), 31 (65), 29 (81), 27 (27); peak no. 291, pent-4-enyl chloroformate, 69 (13), 68 (48), 67 (95), 63 (30), 55 (22), 53 (36), 41 (100), 40 (31), 39 (84), 29 (30), 28 (25), 27 (55); peak no. 619‡, pent-4-enyl formate, 69 (17), 68 (48), 67 (42), 53 (11), 41 (100), 39 (28), 29 (15), 27 (11); peak no. 843, tributyltin chloride, 269 (14), 213 (11), 177 (15), 155 (26), 121 (18), 57 (58), 41 (67), 29 (100). †Different retention time to the previous experiment since the GC/MS experiment was performed under different conditions.

Radical initiated reaction of dihydropyridine 9 (Scheme 17)

N-Carbo(but-3-enyloxy)-1,2-dihydropyridine **9** (1 g, 5.6 mmol) and dibenzoyl peroxide (0.3 g, 30% wt.) were refluxed in benzene for 2 days under nitrogen. Analysis of the reaction mixture showed the formation of two main products; GC/MS peak no. 352, but-3-enyloxy formate, *m/z* (relative intensity), 55 (100), 54 (93), 39 (45), 29 (44), 27 (33), 18 (12); peak no. 460, 3-butenyl benzoate, 176 (M^+) (1), 105 (100), 77 (77), 54 (64), 51 (40), 39 (28), 17 (28). The benzene was evaporated yielding an oil which was purified by

column chromatography eluting with 20% ethyl acetate in light petroleum yielding a mixture (0.14 g) of but-3-enyl benzoate (0.11 g, 11%) and but-3-enyl formate (0.03 g, 6%); δ_H 2.40-2.65 (4 H, m, allylic-H, but-3-enyl benzoate and but-3-enyl formate), 4.13-4.27 (2 H, t, *J* 7.2, methylene-H, formate), 4.35-4.43 (2 H, t, *J* 6.8, methylene-H, benzoate), 5.08-5.28 (4 H, m, olefinic-H, benzoate and formate), 5.80-6.00 (2 H, m, olefinic-H, benzoate and formate), 7.40-7.60 (3 H, m, arom-H, benzoate), 8.00-8.10 (3 H, m; 2 H, arom-H, benzoate and 1 H, formyl-H, formate). The remainder of the fractions gave poorly resolved ^{1}H NMR spectra and were considered to contain the products of polymerisation.

***N*-Carbobenzyloxy-1,4-dihydropyridine (36)** (Scheme 22)

Benzyl chloroformate (21.5 g, 0.126 mol) was added dropwise at -10°C to a mixture of pyridine (10 g, 0.126 mol) and $NaBH_4$ (5 g, 0.133 mol) in dry THF (100 cm^3) under nitrogen. The mixture was stirred at this temperature for 2h and poured onto ice water (200 cm^3). The product was extracted with ether (3 x 100 cm^3), these extracts were combined, washed with H_2O (100 cm^3) and dried ($MgSO_4$). The solvent was evaporated to yield a mixture of the 1,4- and 1,2-dihydropyridines in the respective ratios of 1:0.65. The products were dissolved in dichloromethane (150 cm^3) to which maleic anhydride (10 g, 0.1 mol) was added and the mixture was stirred at r.t. for 24h and then refluxed for 10h. A further 10 g of maleic anhydride was added and the mixture was refluxed for an additional 27h to consume all of the 1,2-dihydropyridine. The adduct was removed with NaOH (3 x 50 cm^3), the organic layer was dried ($MgSO_4$) and the solvent was evaporated to yield an orange liquid. This contained some benzyl chloride which was removed by stirring under low pressure (0.15 mmHg) for 10h, yielding the title compound (7.1 g†); δ_H 2.80-2.88 (2 H, m, allylic-H), 4.79-5.02 (2 H, m, olefinic-H), 5.20 (2 H, s, benylic-H), 6.66-6.87 (2 H, m, olefinic-H), 7.28-7.42 (5 H, m, arom-H); GC/MS *m/z* (rel. intensity), 215 (M^+) (3), 170 (8), 91 (100), 80 (6), 65 (18), 51 (8), 39 (12). †This also contained an impurity which was not removed and the yield of the title compound was estimated to be *ca.* 16%.

Radical initiated reaction of 1,4-dihydropyridine 36

N-Carbobenzyloxy-1,4-dihydropyridine (1 g, 4.65 mmol), cyclohexenone (0.45 g, 4.7 mmol) and dibenzoyl peroxide (0.4 g, 40% wt.) were refluxed in benzene (5 cm^3) for 24h under nitrogen. The benzene was evaporated yielding an oil which was shown by ^1H NMR to contain unreacted cyclohexenone, pyridine, benzoic acid, benzyl benzoate and the impurity from the starting material. The mixture was purified by column chromatography eluting with 30% ethyl acetate in light petroleum, yielding two compounds (0.32 g) one of which was identified as benzyl benzoate†; δ_H 5.40 (2 H, s, benzyl-H, benzyl benzoate), 7.35-7.57 (8 H, arom-H, benzyl benzoate), 8.06-8.13 (2 H, m, arom-H, benzyl benzoate). †The other compound was the impurity present in the original 1,4-dihydropyridine **36**. The approximate yield of benzyl benzoate was 32%.

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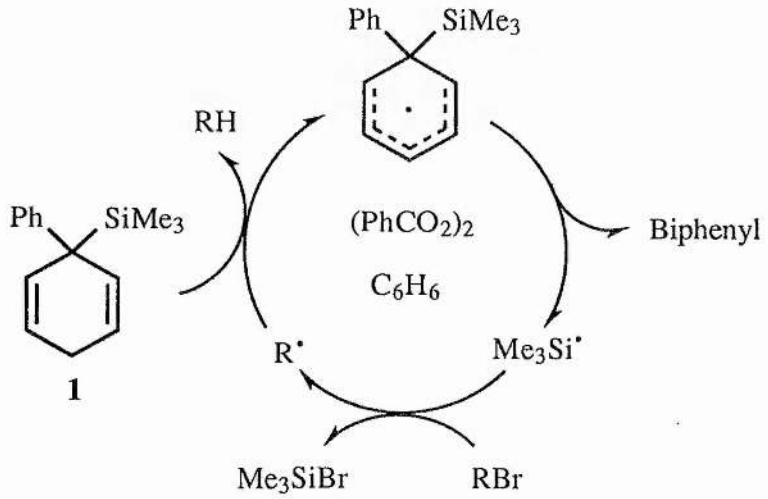
Chapter 5

Silicon Derivatives of Cyclohexadienes as Reagents for Generating Radicals

1 Introduction

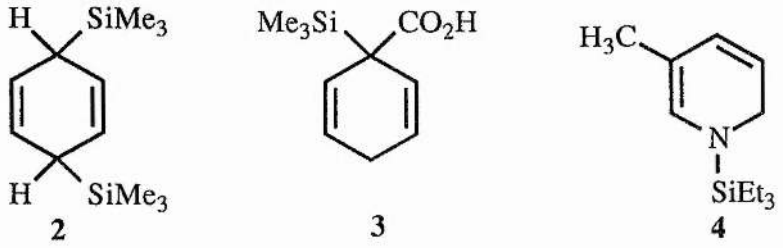
In chapter 1 we mentioned some of the compounds which can be used to generate silyl radicals capable of participating in radical chain reactions. The purpose of these reagents was to effect the reduction of alkyl halides and hence to act as replacements for the undesirable organotin hydrides. Of these, *tris*-(trimethylsilyl)silane, $(Me_3Si)_3SiH$ is a useful reagent which is commercially available, although it is relatively expensive and has some disadvantages. We have also been interested in preparing reagents which can release trialkylsilyl radicals under appropriate conditions. In many cases, silicon-centred radicals will readily abstract bromine and iodine from the corresponding alkyl halide, RX to produce the alkyl radical R•. This carbon-centred radical will then abstract hydrogen from the silicon reagent to give the reduction product and the chain-carrying silyl radical.

Following the theme of cyclohexadienyl radicals and the use of aromatisation as a favourable thermodynamic driving force for generating radicals, in addition to the knowledge gained from work done thus far, a compound which may serve as a source of the trimethylsilyl radical is 1-trimethylsilyl-1,4-dihydrobiphenyl **1**. It was believed that such a compound could participate in a radical chain process as shown in Scheme 1.



Scheme 1

In addition to silyl compound **1** we have been interested in the silyl cyclohexadienes **2** and **3** and the silyl dihydropicoline **4** (Scheme 2). It was thought that these compounds could function as sources of silyl radicals by a chain process similar to the one illustrated above.



2 **3** **4**

Scheme 2

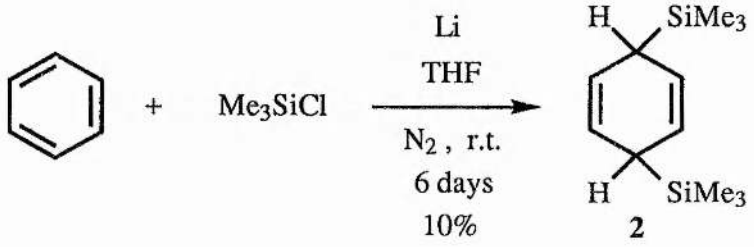
1,4-Bis(trimethylsilyl)cyclohexa-2,5-diene **2** is a known compound and can be prepared, albeit in low yield, from benzene and trimethylsilyl chloride in the presence of lithium.[1] This compound has already been shown to generate silyl radicals which can be trapped by addition to carbon-carbon double bonds.[2] 1-Trimethylsilylcyclohexa-2,5-diene-1-carboxylic acid **3** may also function as a source of silyl radicals. As with the cyclohexadienyl acids discussed in chapter 2, it was anticipated that allylic hydrogen atom abstraction would give a cyclohexadienyl radical which would fragment to give the corresponding silyl radical and benzoic acid. 1-Trimethylsilyl-3-methyl-1,4-dihydropyridine is a known compound prepared from 3-methylpyridine (3-picoline) and trimethylsilane in the presence of 10% Pd over carbon.[3] We wanted to avoid the use of gaseous trimethylsilane and use triethylsilane instead to prepare the related silyl compound **4**, under otherwise identical conditions. Treating this compound with an initiator would give a cyclohexadienyl radical which would be expected to aromatise *via* N-Si bond dissociation, to generate the triethylsilyl radical.

There is little doubt that this area of the project has been the most difficult and as such, has not produced as many positive results as we would have liked. The remainder of this chapter describes what has been achieved to date and the problems encountered.

2 Results and Discussion

2.1 1,4-Bis(trimethylsilyl)cyclohexa-2,5-diene (2)[1]

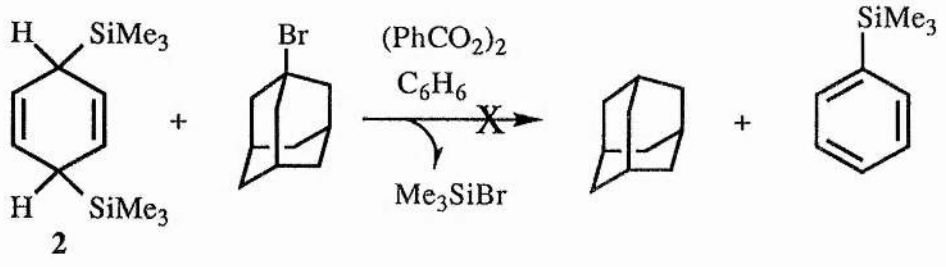
The disilyl cyclohexadiene **2** can be prepared by treating benzene and trimethylsilyl chloride with finely ground Li for 6 days (Scheme 3).[1] After work-up, the product was recrystallised from methanol to yield the desired product as white plates. This compound was unstable and readily aromatised to 1,4-bis(trimethylsilyl)benzene, which formed as white needles. This oxidative process can be controlled by storing the product under N_2 and in the freezer, although it is best to use the compound soon after it has been prepared.



Scheme 3

2.2 Radical initiated reaction of 1,4-bis(trimethylsilyl)cyclohexa-2,5-diene with 1-bromoadamantane

1,4-Bis(trimethylsilyl)cyclohexa-2,5-diene **2**, 1-bromoadamantane, dibenzoyl peroxide and benzene were exposed to radiation using a medium pressure 125 W Hg lamp (Scheme 4).



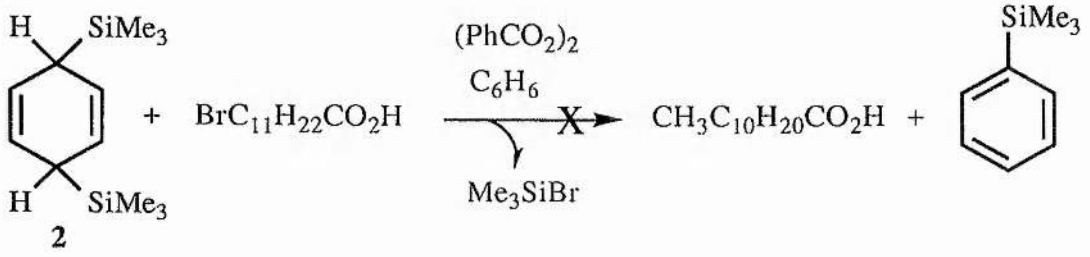
Scheme 4

It was expected that the initiator would abstract hydrogen from silyl compound **2** and that the resulting cyclohexadienyl radical would fragment to form the trimethylsilyl radical. This

radical would then abstract bromine from bromoadamantane to produce the corresponding adamantyl radical, which would undergo chain-transfer by abstracting hydrogen from **2**. Unfortunately, the only significant reaction observed was conversion of the silyl cyclohexadiene into 1,4-bis(trimethylsilyl)benzene. A similar result was obtained when the reaction was attempted by thermal initiation in refluxing benzene. Analysis of the reaction mixture by GC/MS indicated the presence of the disilyl aromatic product, unreacted 1-bromoadamantane, small amounts of trimethylsilylbenzene and the starting material **2**. Trimethylsilyl benzene resulted from decomposition of the disilyl compound **2** in the injector port of the GC/MS, as the same compound was observed when a pure sample of compound **2** was injected. The results from this experiment were not encouraging, and another experiment was attempted using a less hindered alkyl bromide.

2.3 Radical initiated reaction of 1,4-bis(trimethylsilyl)cyclohexa-2,5-diene with 12-bromododecanoic acid

When 1,4-bis(trimethylsilyl)cyclohexa-2,5-diene and 12-bromododecanoic acid were refluxed in benzene, in the presence of dibenzoyl peroxide, the main product formed was 1,4-bis(trimethylsilyl)benzene (Scheme 5). No dodecanoic acid was detected by GC/MS.

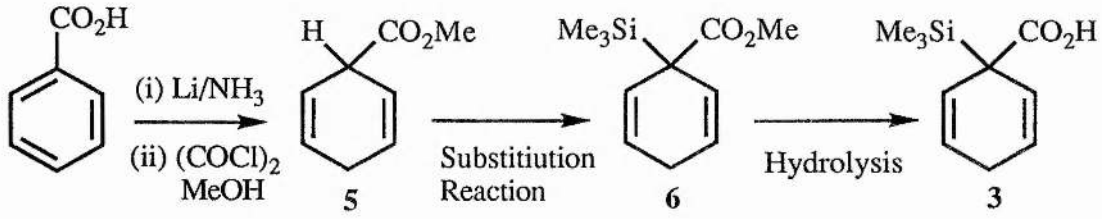


Scheme 5

It was obvious that silyl compound **2** was an unsuitable reagent for generating silyl radicals, since it rapidly oxidised to the corresponding disilyl compound. We therefore decided to direct our efforts towards investigating alternative reagents.

2.4 Attempted preparation of 1-trimethylsilylcyclohexa-2,5-diene-1-carboxylic acid (3)

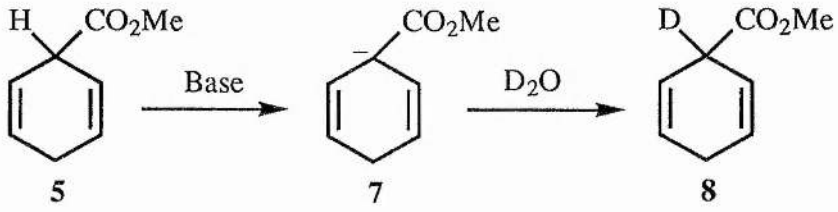
We attempted to prepare silyl compound **3** by converting benzoic acid into the known methyl ester **5**,[4] deprotonating ester **5** and quenching with a suitable silyl reagent to yield silyl compound **6**, followed by a hydrolysis step to give the desired acid **3** (Scheme 6). Although we realised that the last step may be a problem, we were aware that silyl compound **6** may be an equally useful source of silyl radicals.



Scheme 6

2.4.1 Studies towards methyl 1-trimethylsilylcyclohexa-2,5-diene-1-carboxylate ester (6)

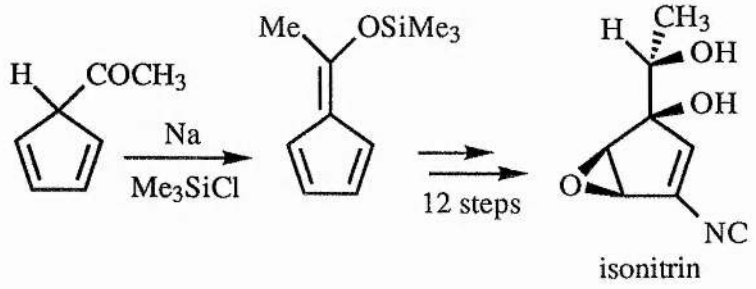
Our initial efforts concentrated on deprotonating the *t*-C in compound **5** to give the anion **7**, followed by quenching with D_2O to produce the deuterated compound **8** (Scheme 7).



Scheme 7

However, when we treated ester **5** with either BuLi or MeLi and quenched with D_2O, the ^1H NMR spectra of the residue revealed that the desired product had not been formed. In fact, it was not obvious what had happened since many signals had appeared. This was suprising considering the work carried out by Shibasaki[5] and Swartz[6] involving the deprotonation of ester **5** with BuLi and LDA to give anion **7**, followed by quenching with

primary alkyl halides. Unfortunately, we did not follow the experimental procedure given in these papers since the work was only found at a later date, but this experiment is now unnecessary. We also realised that conversion of ester **5** into silyl derivative **6** may be more difficult than originally thought, due to the preference of trialklylsilyl halides to react with enolates at oxygen rather than carbon. A relevant example can be found in Baldwin's synthesis of the complex natural product isonitrin (Scheme 8).[7] Although it is possible to help direct the reaction at carbon using trimethylsilyl triflate, this may be more difficult with a more sterically crowded carbon as in anion **7**.



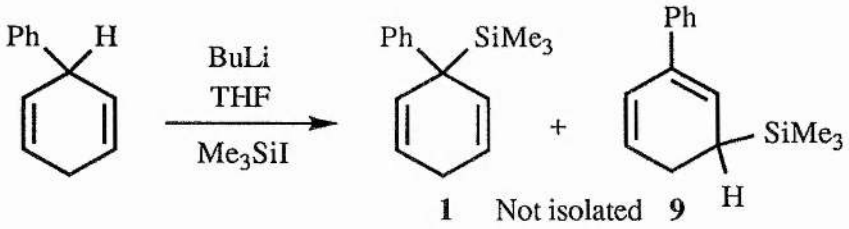
Scheme 8

Neither 1-trimethylsilylcyclohexa-2,5-diene-1-carboxylic acid or its methyl ester have been prepared. Instead we turned our attention to 1-trimethylsilyl-1,4-dihydrobiphenyl **1**.

2.5 Attempted preparation of 1-trimethylsilyl-1,4-dihydrobiphenyl (1)

We had already demonstrated that 1,4-dihydrobiphenyl could be deprotonated with base and quenched successfully with D_2O, CO_2 and ethyl chloroformate to give the corresponding 1-substituted-1,4-dihydrobiphenyl product. When a similar reaction was attempted, quenching with trimethylsilyl iodide instead, a complex mixture was indicated by ^1H NMR spectroscopy. Analysis by GC/MS detected 4 main components in addition to 3 other minor components, which were not identified. Two of the major components gave peaks corresponding to the molecular weight of the desired compound **1**. This suggested that the silyl compound **1** had been formed in addition to the isomer, 3-trimethylsilyl-3,4-dihydrobiphenyl **9** (Scheme 9). The formation of the latter compound was also supported

by ^{1}H NMR due to the presence of a doublet at 6.30 ppm (*cf.* a similar signal at 6.35 ppm observed in the ^{1}H NMR spectrum of 3,4-dihydrobiphenyl-3-carboxylic acid **10** Chapter 3). Of the remaining two major compounds detected, one was biphenyl and the other was not identified.



1 Not isolated **9**

Scheme 9

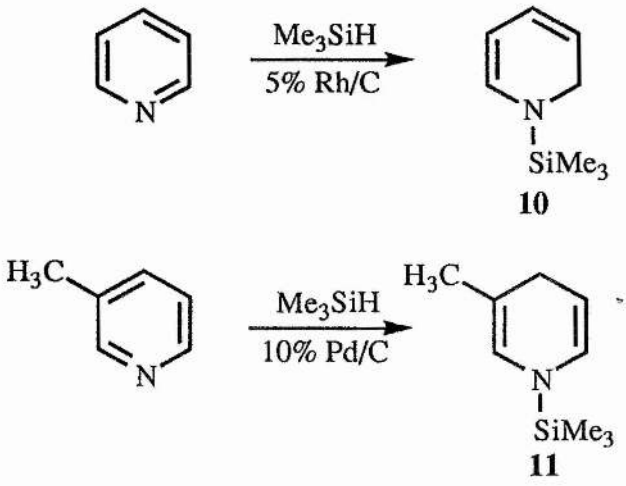
An attempt was made to purify the mixture by column chromatography, but this failed to yield any of the silyl compound **1** in pure form. Furthermore, the fractions collected were shown to be equally complex and this was consistent with the streaking which occurred on TLC plates. When 1,4-dihydrobiphenyl was treated with BuLi for the appropriate period of time in THF and then added under nitrogen, to 2 equivalents of trimethylsilyl iodide and worked-up, the product obtained was difficult to characterise.

These two procedures were therefore not satisfactory for the synthesis of 1-trimethylsilyl-1,4-dihydrobiphenyl and this may have been due to steric and ionic reasons. Also, trimethylsilyl iodide is perhaps too reactive, contributing to the formation of a complex mixture of products. An obvious possibility is the formation and reaction of iodine with the sites of unsaturation. It may have been worthwhile to perform the same reaction, but to quench with trimethylsilyl chloride instead.

2.6 Attempted preparation of 1-triethylsilyl-3-methyl-1,4-dihydropyridine

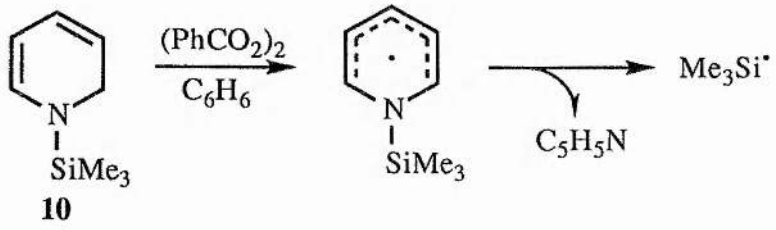
1-Trimethylsilyl-1,2-dihydropyridine **10** can be prepared from the reaction between pyridine and trimethylsilane in the presence of a catalytic amount of Rh (Scheme 10).[3] In a similar manner, 1-trimethylsilyl-3-methyl-1,4-dihydropyridine **11** can be prepared from the

reaction between picoline and trimethylsilane in the presence of a catalytic amount of Pd. We thought that both of these products might be attractive reagents for generating silyl radicals.



Scheme 10

Abstraction of one of the two allylic hydrogen atoms from either dihydropyridine **10** or dihydropicoline **11** would give the corresponding delocalised radical (Scheme 11). It would then be feasible that this radical would aromatise to give pyridine or picoline and the trimethysilyl radical, which may be incorporated into a radical chain mechanism for the reduction of alkyl halides.

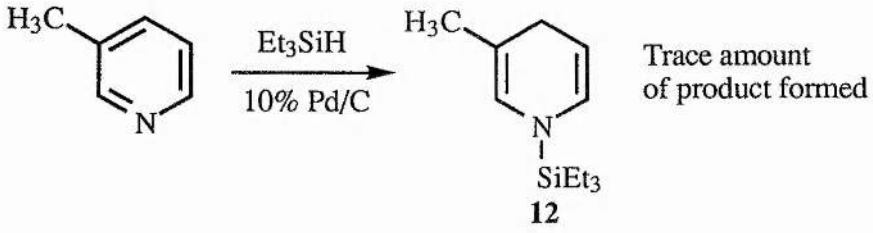


Scheme 11

The synthesis of compounds **10** and **11** is however not trivial. Unless the reaction conditions are carefully controlled, a range of silylated products result, which are very difficult to separate. Furthermore, these dihydro-compounds are sensitive to air and moisture and will decompose rapidly if not handled properly. Nevertheless, the authors

reported that compounds **10** and **11** could be prepared in yields exceeding 90% if the appropriate experimental conditions were fulfilled.[3]

Trimethylsilane is a gas which is expensive to buy and is inconvenient since it is delivered in glass ampoules. Since triethysilane is a liquid and readily available, we thought that it might be possible to prepare the corresponding triethylsilyl products of **10** and **11**. Thus, triethylsilane was added to a mixture of picoline and 10% Pd over carbon and the resulting mixture was stirred at 40°C under an atmosphere of Ar (Scheme 12).



12

Scheme 12

The reaction was analysed by GC and the mixture was left stirring at this temperature until all the triethylsilane had disappeared. As the silane reacted, a new peak appeared in the GC trace and it was anticipated that this was the desired product **12**. The mixture was worked-up, maintaining the product under an atmosphere of Ar whenever convenient and the excess picoline was removed by distillation. Analysis by ^{1}H NMR indicated only a very small amount of what we believed to be the desired product **12**. The major product was hexaethyldisiloxane $Et_3SiOSiEt_3$ which suggested that oxygen was entering the reaction system. The fact that only a trace amount of the desired product was formed was possibly due to two main reasons: (i) the reported experimental conditions were not followed exactly since triethylsilane was used instead of trimethylsilane and (ii) performing the reaction under an atmosphere of Ar using a balloon, was not ideal an set-up. Furthermore, we did not have access to a dry N_2 box as advised in the original paper.[3] Nevertheless, since this work was being carried out in Belgium over a one month period, we continued with our efforts. When triethylsilane was dissolved in dry ether and added to 10% Pd/C and stirred under Ar for 4h, analysis by GC indicated that hexaethyldisiloxane was again being

formed. It was evident that the silane became adsorbed onto the catalyst surface, whereupon it was oxidised to the siloxane with loss of hydrogen.

In a modified procedure, picoline was added to the Pd/C catalyst and stirred for 10h before triethylsilane was introduced. The reasoning here was to adsorb picoline onto the catalyst surface before the silane, but as observed in the previous 2 experiments, hexaethyldisiloxane was the only product. A final attempt to prepare silyl compound **12** was made and this involved pre-treating the catalyst with hydrogen followed by the addition of the reactants. We thought that by doing this, most of the catalyst active sites would be occupied by hydrogen and also, the oxidation of triethylsilane to the siloxane with loss of hydrogen, would be suppressed. The catalyst surface was treated with hydrogen until it was believed to be saturated and then the reactants were added. Unfortunately, hexaethyldisiloxane was the only product formed. No further attempts were made to prepare silyl **12** since the experiments above did not produce any promising results.

Conclusions

1,4-Bis(trimethylsilyl)cyclohexa-2,5-diene **2** was prepared according to the published procedure. This compound did not reduce 1-bromoadamantane or 12-bromododecanoic acid and did not participate in any radical chain-reaction. One of the reasons for this was the rapid oxidation of the silyl derivative to the corresponding aromatic compound.

The alternative silyl reagents **1**, **3**, and **4** have not been prepared. We anticipated that 1-trimethylsilyl-1,4-dihydrobiphenyl **1** would be a useful reagent for reducing alkyl halides, although we were aware that this compound might be difficult to prepare from 1,4-dihydrobiphenyl. In fact, GC/MS evidence indicated that this compound was present in the reaction mixture, although the ^{1}H NMR spectrum of the residue was not simple and column chromatography did not succeed in isolating this compound. The conversion of methyl ester **5** into silyl **6** has not been attempted due to time restrictions. Dihydropicoline **4** could not be prepared from picoline and triethylsilane under a variety of conditions.

3 Experimental

Refer to the experimental section from Chapter 2 for information regarding the collection of experimental data etc. The order of this section is essentially the same as given in the results and discussion section.

1,4-Bis(trimethylsilyl)cyclohexa-2,5-diene (2) (Scheme 3)[1]

Finely ground Li (2.25 g, 0.75 mol) in mineral oil was added to a flask which was attached to a nitrogen line. Dry ether (50 cm^3) was added to the flask and then removed using a cannula, leaving dry Li. To this, benzene (10 g, 0.125 mol), trimethylsilyl chloride (109 g, 1 mol) and dry THF (70 cm^3) were added and the contents were left stirring for 6 days under N_2. The mixture was filtered, washed with isopropanol and then water. The solvent was evaporated to give a white solid which was recrystallised from methanol to yield the title compound as white plates (2.85 g, 10%); δ_H 0.05 (18 H, s, methyl-H), 2.1 (2 H, s, allylic-H), 5.4 (4 H, s, olefinic-H).

Radical-initiated reaction of 1,4-bis(trimethylsilyl)cyclohexa-2,5-diene with 1-bromoadamantane (Scheme 4)

(i) 1-Bromoadamantane (20 mg, 0.093 mmol), 1,4-bis(trimethylsilyl)cyclohexa-2,5-diene (20.8 mg, 0.093 mmol), dibenzoyl peroxide (5 mg, 25% wt.) and deuterated benzene were added to an NMR tube. The NMR tube was placed in an oil bath at 50°C and exposed to radiation from a 125 W medium pressure Hg lamp for 5h. The ^1H NMR spectrum indicated that the silyl compound aromatised and there was very little evidence for reduction.

(ii) 1-Bromoadamantane (0.447 g, 2.2 mmol), 1,4-bis(trimethylsilyl)cyclohexa-2,5-diene (0.5 g, 2.2 mmol), dibenzoyl peroxide (0.05 g, 10% wt.) and benzene (5 cm^3) were refluxed for 5 days, with stirring at 80°C under N_2. During the course of the reaction another 25 mg of initiator was added. Analysis of the reaction mixture by GC/MS gave no

evidence for the formation of adamantane. The benzene was evaporated to yield an orange solid containing white needles, which was shown by ^1H NMR to be a mixture of unreacted silyl compound **2** and 1,4-bis(trimethylsilyl)benzene.

Radical-initiated reaction of 1,4-bis(trimethylsilyl)cyclohexa-2,5-diene with 12-bromododecanoic acid (Scheme 5)

12-Bromododecanoic acid (0.56 g, 2 mmol), 1,4-bis(trimethylsilyl)cyclohexa-2,5-diene **2** (0.45 g, 2 mmol), dibenzoyl peroxide (45 mg, 10% wt.), and benzene (5 cm^3) were refluxed for 24h, with stirring at 80°C under N_2. NaOH (50 cm^3) was added and the aqueous fraction was washed with benzene (10 cm^3). The organic fractions were combined, dried ($MgSO_4$) and the solvent evaporated to give an orange oil; δ_H 0.1 (18 H, s, methyl-H, silyl **2**), 0.35 (18 H, s, methyl-H, aromatic silyl), 0.9 (m, unidentified), 1.3 (m, unidentified), 2.2 (2 H, s, allylic-H, silyl **2**), 2.35 (s, unidentified), 5.5 (4 H, s, olefinic-H, silyl **2**), 7-7.4 (m, mainly biphenyl), 7.6 (4 H, s, arom-H, aromatic silyl). The carboxylic acids were regenerated with excess H_2SO_4, extracted with ether (2 x 50 cm^3), dried ($MgSO_4$) and the solvent evaporated to yield 12-bromododecanoic acid and benzoic acid

Cyclohexa-2,5-diene-1-carboxylic acid (Scheme 6)

Ammonia (900 cm^3) was added to benzoic acid (10 g, 82 mmol) to which Li (1.9 g, 0.27 mol) was added portionwise causing the solution to turn blue. After reacting for 10 min the mixture was quenched with NH_4Cl (20 g) and the NH_3 was allowed to evaporate overnight. To the residue, ice was added followed by HCl until the pH of the reaction mixture was 1. The product was extracted with ether (2 x 200 cm^3), the combined ethereal extracts were dried ($MgSO_4$) and the solvent was evaporated to give the title compound as a yellow liquid (9.33 g, 92%); δ_H 2.6-2.8 (2 H, m, allylic-H), 3.7-3.9 (1 H, m, *t*-H), 5.8-6.1 (4 H, m, olefinic-H).

Methyl cyclohexa-2,5-diene-1-carboxylate (6) (Scheme 6)[5]

Cyclohexa-2,5-diene-1-carboxylic acid (9.3 g, 75 mmol) was dissolved in dry ether (60 cm^3) to which oxalyl chloride (12 g, 94.8 mmol) was added at 0°C. The mixture was left stirring overnight at room temperature. The ether was evaporated to give a yellow liquid identified as the acid chloride; δ_H 2.70-2.80 (2 H, m, allylic-H), 4.10-4.22 (1 H, m, *t*-H), 5.80-6.10 (4 H, m, olefinic-H). The acid chloride was redissolved in dry ether (50 cm^3) and cooled to 0°C followed by the addition of Analar methanol (6.25 g, 79 mmol) and the resulting mixture was refluxed overnight. The solution was diluted with ether (75 cm^3) and washed with H_2O (3 x 50 cm^3). The ether solution was dried ($MgSO_4$) and the solvent was evaporated to give a yellow liquid (8.57 g). The title compound was obtained as a clear, colourless liquid by distillation (6.65 g, 61%), bp 80°C at 0.02 mmHg; δ_H 2.62-2.71 (2 H, m, allylic-H), 3.69-3.80 (4 H, m, methyl-H & *t*-H), 5.76-5.92 (4 H, m, olefinic-H).

Attempted preparation of methyl 1-deuteriocyclohexa-2,5-diene-1-carboxylate (8) (Scheme 7)

(i) Methyl cyclohexa-2,5-diene-1-carboxylate (0.9 g, 6.5 mmol) was dissolved in dry THF (40 cm^3) under an atmosphere of nitrogen and the mixture was cooled to -50°C. To this BuLi (0.46 g, 7.2 mmol) was added causing the solution to turn brown. After stirring for 1h, the temperature being allowed to rise to 0°C, the contents were quenched with D_2O (0.2 g, 9.8 mmol) causing the solution to turn yellow and then red. The solvent was evaporated, H_2O (50 cm^3) and ether (50 cm^3) were added to the residue and the layers were separated. The aqueous layer was further extracted with ether (50 cm^3), the ethereal extracts were combined, dried ($MgSO_4$) and the solvent was evaporated to yield a yellow oil (0.8 g) which was shown by ^1H NMR to be a complex mixture of compounds.

(ii) Methyl cyclohexa-2,5-diene-1-carboxylate (1 g, 7.24 mmol) was dissolved in dry THF (40 cm^3) under an atmosphere of nitrogen and the mixture was cooled to -78°C. To this mixture, MeLi (0.175 g, 7.96 mmol) was added and the mixture was left stirring at this temperature for 25 min before the addition of D_2O (0.22 g, 11 mmol). The mixture was stirred for 3h and worked up in an identical manner to that given in the previous

experiment, yielding a yellow oil (0.47 g) which was again shown by ^{1}H NMR to be a complex mixture of products.

Attempted preparation of 1-trimethylsilyl-1,4-dihydrobiphenyl (1) (Scheme 9 (i) 1,4-Dihydrobiphenyl (2 g, 12.8 mmol) was dissolved in dry THF (75 cm^3) and this mixture was cooled to -40°C. To this BuLi (0.9 g, 14.1 mmol) was added and the mixture was left stirring for 80 min as the temperature was allowed to rise to 5°C. The anion was quenched with trimethysilyl iodide (2.6 g, 12.8 mmol) causing the solution to turn deep red through to light yellow. The solvent was evaporated and ether (100 cm^3) and H_2O (100 cm^3) were added to the residue. The layers were separated and the aqueous layer was extracted with ether (100 cm^3). The combined ethereal extracts were dried ($MgSO_4$) and the solvent was evaporated to give a yellow liquid (3.43 g) which was shown by ^{1}H NMR and GC/MS to be a complex mixture of products; GC/MS peak no. 322, trimethysilyl bearing compound, *m/z* (relative intensity) 257 (4), 215 (23), 185 (35), 145 (54), 129 (11), 103 (32), 73 (100); peak no. 392, biphenyl; peak no. 479, molecular weight of silyl compound **1** is 228, 228 (M^+) (1), 211 (1), 195 (1), 154 (59), 73 (100), 77 (14), 59 (19), 45 (46); peak no. 499, essentially identical with previous spectrum. Analysis of the reaction mixture by TLC revealed streaking under a variety of solvent mixtures. Light petroleum (100%) gave some separation on TLC but the title compound was not isolated.

(ii) 1,4-Dihydrobiphenyl (2 g, 12.8 mmol) was dissolved in dry THF (75 cm^3) and the mixture was cooled to -40°C. To this BuLi (0.9 g, 14 mmol) was added and the mixture was left stirring for 80 min as the temperature was allowed to rise to 0°C. The reaction flask was cooled to -20°C and the contents were added, *via* a cannula, to trimethylsilyl iodide (5.82 g, 28 mmol) cooled to -20°C and the resulting mixture was stirred overnight. The THF was evaporated, ether (100 cm^3) and a solution of $Na_2S_2O_3$ (100 cm^3) were added to the residue. The layers were separated and the ethereal layer was dried ($MgSO_4$) and the solvent was evaporated to give a yellow oil (6.60 g). Unfortunately, analysis by ^{1}H NMR gave little evidence for the desired product.

Attempted preparation of 1-triethylsilyl-3-methyl-1,4-dihydropyridine (12) (Scheme 12)

(i) 10% Pd (0.01 g) on activated carbon was added to a 50 ml two-necked flask and to this 3-picoline (7.54 g, 81 mmol) was added. A rubber septum was attached to one of the outlets and a balloon containing argon was attached to the other. A needle was used to pierce the septum and flush the vessel with Argon. Triethylsilane (3.14 g, 27 mmol) was added over a 40 min period and the resulting mixture was warmed for 24 h at 40°C. Analysis of this mixture by GC revealed consumption of triethylsilane. The mixture was filtered inside a large plastic bag filled with argon and the excess picoline was removed by distillation under an atmosphere of argon, yielding a yellow residue (1.91 g); δ_H (C_6D_6, 300 MHz), 0.64-0.75 (12 H, q, *J* 8.1, methylene-H, hexaethyldisiloxane), 1.06-1.17 (18 H, t, *J* 8.2, methyl-H, hexaethyldisiloxane); GC/MS peak no. 184, unidentified silyl compound, *m/z* (relative intensity), 103 (57), 75 (100), 47 (46), 45 (44); peak no. 357, hexaethyldisiloxane, 217 (81), 188 (95), 161 (77), 133 (44), 105 (68), 103 (54), 80 (61), 66 (95), 59 (100). Minor signals which were evidence for the formation of a trace amount of the desired product were observed by ^{1}H NMR i.e. δ_H 1.39 (3 H, s, methyl-H), 2.71-2.79 (2 H, m, allylic-H), 4.40-4.45 (1 H, m, olefinic-H), 5.62-5.70 (1 H, m, olefinic-H), 5.77-5.85 (1 H, m, olefinic-H).

(ii) 3-Picoline (3.77 g, 41 mmol) was added to 10% Pd (0.05 g) on activated carbon and left stirring under Ar for 10h. Triethylsilane (1.57 g, 13.5 mmol) was added over 2h and the resulting mixture was left stirring for 5h. Analysis of the reaction mixture by GC showed that the new product formed was hexaethyldisiloxane.

(iii) 10% Pd (0.05 g) on activated carbon was treated with H_2 followed by the addition of 3-picoline (3.77 g, 41 mmol).‡ The system was purged with Ar and over a 20 min period triethylsilane (1.57 g, 13.5 mmol) was added. The mixture was left stirring at r.t. for 3h and analysis by GC indicated the formation of hexaethyldisiloxane.

‡Adsorption of H_2 onto the catalyst surface was monitored using a pressure guage.

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