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**Radical Ring Expansions of Benzocyclic
Carbonyl Compounds**

by

Paul Jeffrey Westlake

A Doctoral Thesis

**Submitted in partial fulfilment of the
requirements for the award of**

**Doctor of Philosophy of the
Loughborough University of Technology**

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Abstract

Radical Ring Expansions of Benzocyclic Carbonyl Compounds

Introduction

The thesis gives an account of the application of two methodologies, "Side Chain Incorporation" and "Cleavage of the Zero Bridge in Bicycles," to the ring expansion, by one, three, and four carbons, of five-, six-, and seven-membered ring benzocyclic carbonyl compounds.

Ring Expansion by Side Chain Incorporation

Suitable starting materials were prepared by *C*-alkylation, with straight-chain α,ω -dihalides, of β -keto esters. Treatment of the resultant halides with tributylstannane affords primary alkyl radicals, which can cyclise onto the ketone carbonyl. Regiospecific β -scission of the resultant tertiary alkoxy radical affords a stabilised tertiary alkyl radical, which is reduced to give a ring-expanded product. Reduction of the primary alkyl radical to afford a non-ring-expanded product is a competitive, and sometimes predominant, process.

One-carbon ring expansion of benzocarbocyclic five-, six-, and seven-membered ring β -keto esters was generally successful; multi-carbon ring expansion failed. Three-carbon ring expansion of the β -keto ester derived from 2,3-dihydro-3-oxobenzo[b]furan was successful; four-carbon ring expansion failed.

The one-carbon ring expansion of 3-methyl-1-phenyloxindole by bromomethylation and treatment of the resultant bromide with tributylstannane also succeeded. This ring expansion proceeded *via* cyclisation of the alkyl radical onto the fused benzene ring, rather than onto the lactam carbonyl.

Ring Expansion by Cleavage of the Zero Bridge in Bicycles

Samarium (II) iodide-mediated Barbier cyclisation of the above haloalkyl ketones afforded a bridgehead tertiary bicyclic alcohol. Treatment of the alcohol with iodobenzene diacetate afforded the hypoiodite. Photolysis of the hypoiodite afforded the alkoxy radical, which gave β -scission to a ring-expanded product as above.

Three-carbon ring expansion of 2-tetralone was successful; 1-tetralone afforded an intractable mixture of iodoketones, arising from the non-regiospecific β -scission of the intermediate alkoxy radical.

Nitrate esters were investigated as a precursor of alkoxy radicals. Attempts at forming the nitrate ester of tertiary bicyclic alcohols failed, owing to preferential dehydration.

Miscellaneous

Attempts at the ring-opening of 1-decalone and camphor by samarium (II) iodide-mediated ketyl formation failed; ring-opening of a more complex ketone succeeded. Various nitro compounds were reduced with tributylstannane.

Acknowledgements

I wish to thank Messrs. Alistair Daley, Paul Hartop and John Kershaw of the Technical Staff of the L.U.T. Chemistry Department for their constant assistance. I also wish to thank the inmates of Laboratories F0.01 and F0.09 for their comradeship.

Thanks are also due to The Boots Co. PLC for generously funding my research and for financial assistance. I am indebted to Drs. Ken Nichol and Bernard Armitage, and Ms. Carol Trelfa for their assistance during my three month period of industrial training with the company at Pennyfoot Street, Nottingham. I am also indebted to Dr. G. Haran and the staff of the Physical Chemistry section at Boots for performing elemental analyses and mass spectroscopy.

I wish to thank my supervisor, Dr. Russ Bowman, for his patient guidance and encouragement over three years, and for his proof-reading of the manuscript.

Finally, I should like to thank my parents and my wife, Liz Jones, for the massive forbearance they have shown in the course of my research.

List of abbreviations

AIBN	azoisobutyronitrile
b.p.	boiling point
C.I.	chemical ionisation
DMF	<i>N,N</i> -dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone
DMSO	dimethyl sufoxide
E.I.	electron-impact
EPR	electron paramagnetic resonance
GC-MS	gas chromatography-mass spectroscopy
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
IR	infra-red
LDA	lithium di- <i>iso</i> -propylamide
m.p.	melting point
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
r.t.	room temperature
SET	single electron transfer
THF	tetrahydrofuran
TLC	thin layer chromatography

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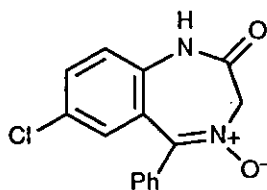
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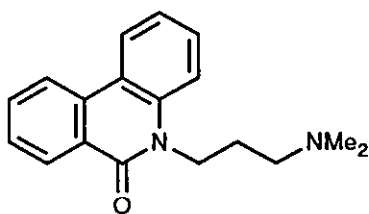
1. Introduction

1.1 Benzo-fused Compounds as Drugs

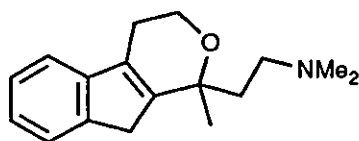
Many benzo-fused compounds have pharmacological activity¹⁻³ and are used clinically. Benzodiazepines have been extensively reviewed¹ and are well known as tranquillisers, *e.g.* demoxepam (1). Tricyclic antidepressants include fantridone (2) and pirandamine (3). Anti-inflammatory benzo-fused drugs include piroxicam (4), used in the oral treatment of osteo- and rheumatoid arthritis, and sulindac (5).



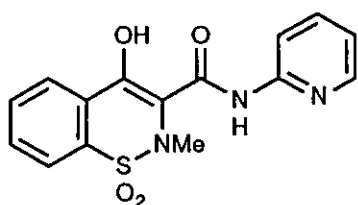
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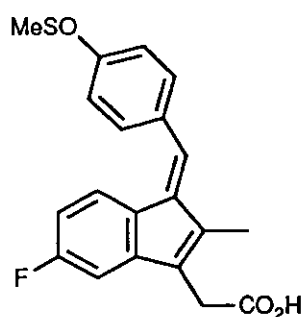
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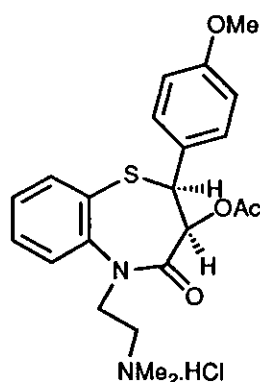
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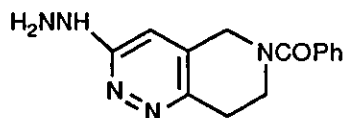
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Other known pharmacologically active compounds include examples of diuretics and analgaesics, but cardiovascular drugs make up the bulk of the rest. Diltiazem hydrochloride (6) is a calcium entry blocker used in the oral therapy of angina, endralazine (7) is a

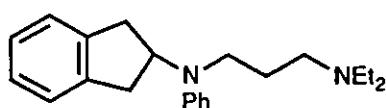
peripheral vasodilator, aprindine (8) is an anti-arythmic agent, and nadolol (9) is a β -adrenoceptor blocker used in the treatment of hypertension.



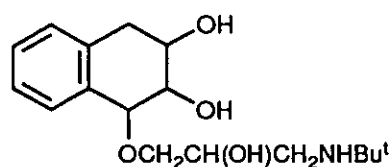
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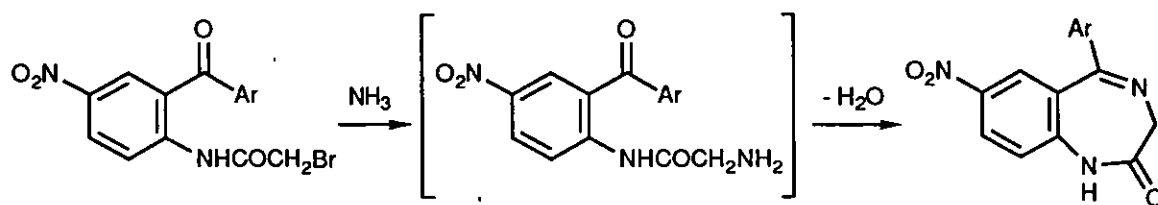


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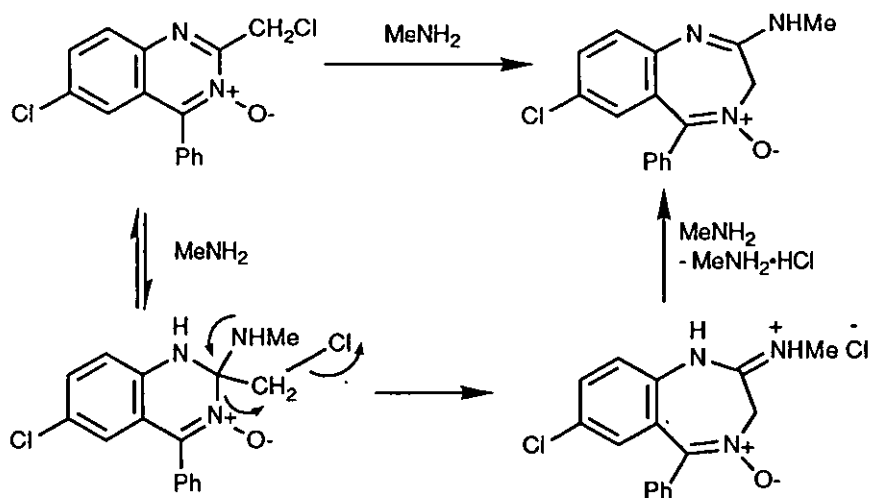


(9)

The synthetic routes to these benzoheterocycles tend to involve formation of the benzo-fused heterocyclic ring by intramolecular cyclisation of monosubstituted or *o*-disubstituted arenes, *e.g.* the synthesis of clonazepam (Scheme 1⁴). Thermodynamic considerations (*e.g.* entropy) become increasingly unfavourable as the size of the heterocyclic ring is increased from 6-membered rings upwards, so that reaction yields tend to decrease rapidly towards zero. Even in the case of 7-membered rings cyclisation can be problematic: in the formation of chlordiazepoxide (LIBRIUM) a one-atom ring expansion of a 6-membered ring (a quinazoline 3-oxide) to a 7-membered ring (a benzodiazepine) has been used to circumvent such problems (Scheme 2^{1b}).



Scheme 1 Ar = 2-Cl.C₆H₄



Scheme 2

Thus the synthetic concept of ring expansion appears to present a feasible route to novel medium-ring benzo-fused compounds. The Boots Company has an interest in screening such compounds for pharmacological activity. The aim of this research is to produce such compounds *via* novel ring expansion methodologies.

1.2 Strategies for Ring Expansion

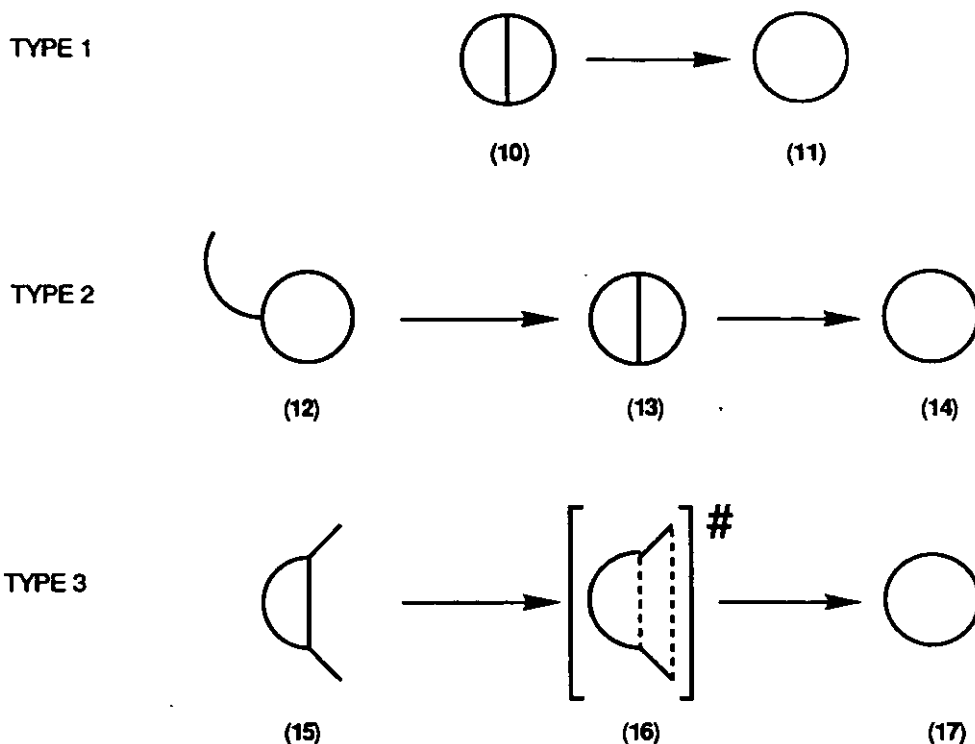
Ring expansions in organic chemistry have recently been extensively reviewed.⁵ They can be represented as belonging to three fundamental types: cleavage of the zero bridge in bicycles (Type 1); side chain incorporation (Type 2); and pericyclic reactions (Type 3). The three types are represented generally in Scheme 3.

In Type 1 ring expansion, the shortest bridge in a bicyclic starting material (**10**), *viz.* that between the two bridgehead atoms (the "zero bridge"), is broken to give a larger-ring monocycle (**11**).

In Type 2 ring expansion, the ring in a monocyclic starting material (**12**) is substituted by a side chain at a ring atom carrying a suitable group. During the expansion process the side chain is incorporated into the ring *via* an intermediate (**13**) similar to the bicyclic starting material of Type 1 ring expansions (**10**), which undergoes zero bridge cleavage to a ring-expanded product (**14**) in the same way.

In Type 3 ring expansion, two side chains are placed in the same monocyclic starting material (**15**) at an appropriate distance to each other. The starting material (**15**) undergoes an electrocyclic or sigmatropic rearrangement to a ring-expanded product (**17**). The transition state (**16**) for this one-step reaction is clearly similar to the starting material for Type 1 expansion (**10**).

Thus cleavage of the zero bridge in bicycles (Type 1) is the fundamental route to ring expansion.



Scheme 3: The Three Fundamental Types of Ring Expansion

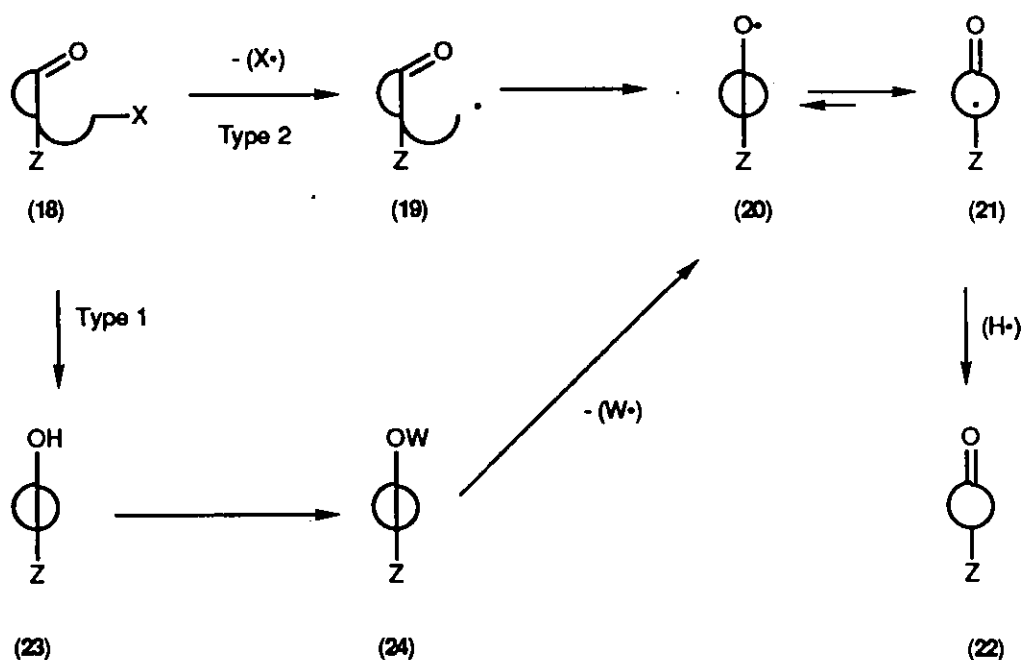
The use of free radicals (uncharged, often transient, species containing one or more unpaired electrons) as intermediates for ring expansion offers several advantages over the use of charged species, often combining favourable reactivity with chemo- and regio-specificity, thus tolerating a high level of functionality in starting materials.^{6,7}

Radicals are neutral species. Therefore protection of alcohol and amine functions is often unnecessary, epimerisation of sensitive centres (*e.g.* enolisable protons) tends not to occur and reactions do not need to be dry. Compared to ionic species, aggregation phenomena (*e.g.* solvation, co-ordination of counterions) are unimportant or non-existent. Thus reaction at hindered sites is possible and the polarity of other functions in the molecule may be unimportant.

Alkoxyl radicals ($R_3CO\cdot$) are common species, transient in nature and readily generated. Thus ring expansion of benzoheterocycles *via* transient alkoxyl radicals may offer a mild convenient route to novel compounds of pharmaceutical interest. The nature of the chemistry of alkoxyl radicals precludes ring expansions of Type 3, so only those of Types 1 and 2 will be considered.

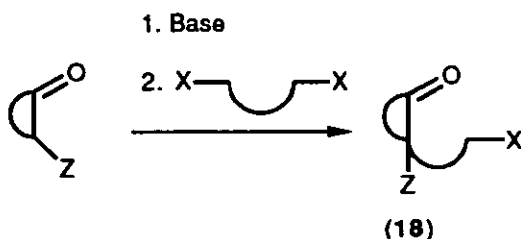
1.3 Strategies for Ring Expansion *via* Transient Alkoxy Radicals

The two fundamental types of ring expansion *via* transient alkoxy radicals are Cleavage of Zero Bridge in Bicycles (Type 1) and Side Chain Incorporation (Type 2) (Scheme 4). Common starting materials, *viz.* ketone (18), can be envisaged for both routes. The electron-withdrawing and radical-stabilising group, Z, facilitates synthesis of ketone (18) by alkylation, often (for synthetic convenience) with an α,ω -dihalide (Scheme 5), and should ensure that β -scission of the transient alkoxy radical (20) is regioselective, or even regiospecific. It also obviates dialkylation.



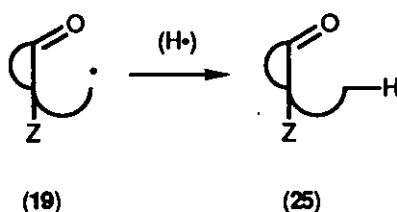
Scheme 4: Types 1 and 2 compared

X, W = radical leaving group
 Z = electron withdrawing/
 radical stabilising group



Scheme 5 X = Br, I

Type 2 has the obvious advantage of being one-step rather than three-step, like Type 1. However Type 2 allows the possibility of formation of a product (25) stemming from reduction without ring expansion (Scheme 6). The rate of cyclisation of alkyl radical (19) to afford alkoxy radical (20) relative to the rate at which alkyl radical (19) abstracts a hydrogen atom from a suitable hydride source to afford product (25) is of crucial importance, and will be discussed in detail (section 1.4).

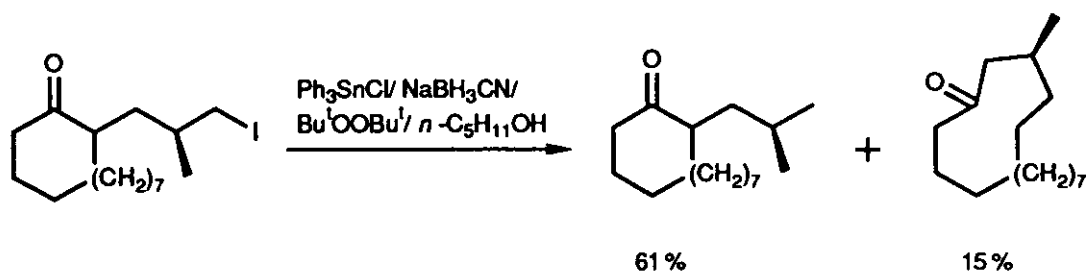


Scheme 6

Several examples of both types of ring expansion have appeared in the literature, mostly published after this study began. These examples, few of which involve benzo-fused compounds, are surveyed in the following two sections (1.4 and 1.5) and the practical and mechanistic aspects of each type are discussed. The specific aim of the research is to apply these two types of ring expansion to the synthesis of novel ring-expanded benzoheterocycles from readily available starting materials.

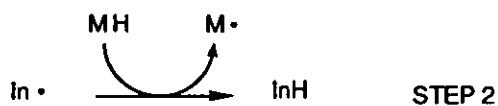
1.4 Ring Expansion by Side Chain Incorporation

The general mechanism for the radical chain reduction of ketone (18) by a group-14 organometallic hydride (MH) with initiator (In_2) is easily represented.⁶⁻⁸ (Scheme 7). The polymer-bound stannane⁹ and 1,1,1,2,3,3,3-heptamethyltrisilane¹⁰ $\{(\text{Me}_3\text{Si})_2\text{Si}(\text{Me})\text{H}\}$ obviate the tedious purification needed to remove organostannane residues from the crude product - a major practical advantage. Triphenylstannane may be generated slowly *in situ* by the action of sodium cyanoborohydride on triphenylchlorostannane (Scheme 8).¹¹

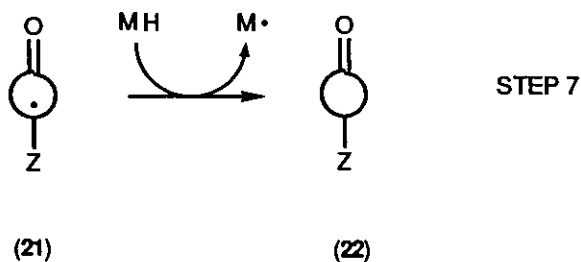
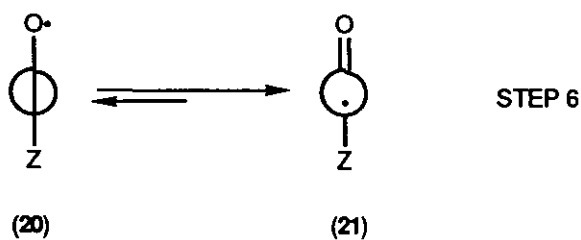
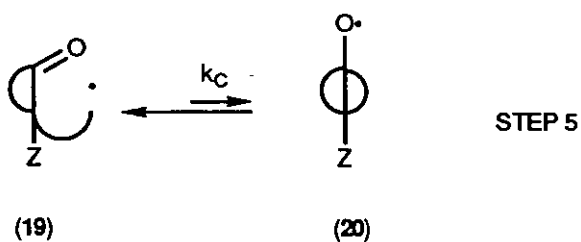
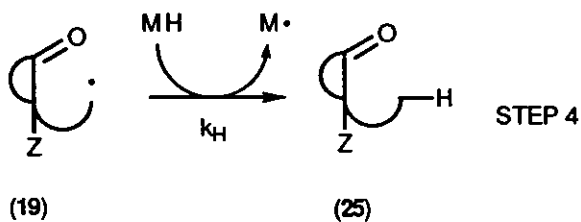
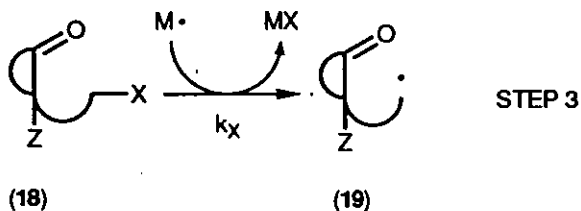


Scheme 8

INITIATION



PROPAGATION

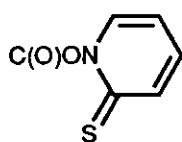


Scheme 7

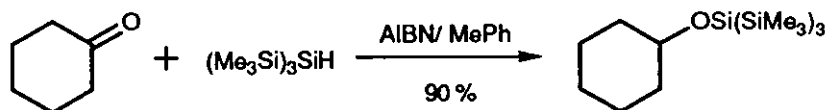
$\text{In}_2 = (\text{Bu}^t\text{O})_2, (\text{PhCO}_2)_2, (\text{CO}_3\text{Bu}^t)_2, \text{Me}_2\text{C}(\text{CN})\text{-N=N-CMe}_2(\text{CN})$

$\text{M} = (\text{Me}_3\text{Si})_2\text{SiMe}, \text{Bu}_3\text{Ge}, \text{Ph}_2\text{SnH}, \text{Ph}_3\text{Sn}, \text{Bu}_2\text{SnH}, \text{Bu}_3\text{Sn}, \text{POLYMER-SnBu}_2$

$\text{X} = \text{I}, \text{Br}, \text{Cl}, \text{OC}(\text{S})\text{Me}, \text{OC}(\text{S})\text{Ph}, \text{OC}(\text{S})\text{Im}, \text{OC}(\text{S})\text{OPh}, \text{OC}(\text{S})\text{SPh}, \text{OC}(\text{O})\text{CO}_2\text{Me}, \text{OC}(\text{O})\text{Cl}, \text{OC}(\text{O})\text{SePh}, \text{NC}, \text{NCS}, \text{NCSe}, \text{NO}_2, \text{SH}, \text{SePh},$

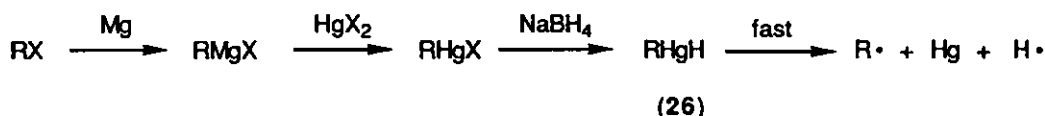


Radical-generating group-14 organometallic hydrides other than those shown are either incompatible with the substrate or are generated *in situ* by incompatible reagents. Tris(trimethylsilyl)silane, although toxicologically and ecologically more attractive than stannanes, hydrosilylates ketones (Scheme 9)¹² and is therefore unsuitable for radical reactions involving ketones.



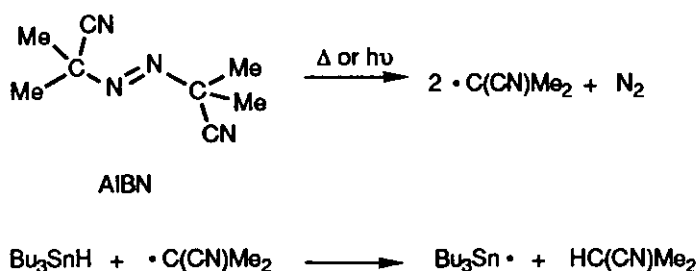
Scheme 9

In situ generation of organomercuric hydrides (26) is not only toxicologically and ecologically unattractive, but also involves use of Grignard reagents and sodium borohydride (Scheme 10).



Scheme 10 X = Cl, Br, I

Much is known about each step in the mechanism (Scheme 7). Initiators (In₂) are chosen to have the correct philicity for the group-14 organometallic hydride (MH, Step 2). Although radicals are neutral species, they may be electrophilic or nucleophilic. The nature of the philicity is determined by the nature of the radical centre (the atom bearing the unpaired electron) and by the nature of the groups attached to it. For example, the radical derived from thermolysis or photolysis of azobisisobutyronitrile (AIBN, Scheme 11), one of the most common initiators for radical chain reductions with group-14 organometallic hydrides, *viz.* •C(CN)Me₂, is electrophilic (by virtue of the electron-withdrawing cyano group) and



Scheme 11

e.g. the tributyltin radical ($\text{Bu}_3\text{Sn}\cdot$) is nucleophilic (by virtue of the electron-donating butyl groups). Consequently initiation Step 2 is thermodynamically favourable for AIBN and tributylstannane.

The correct choice of initiator is also determined by the operating temperature of the reaction (commonly, though not inevitably, the boiling point of the solvent). Thus the half-life for the decomposition of the initiator is an important consideration (For AIBN the half-life is *ca.* 1 h at 80°C and less than 6 min. at 110°C). Addition of the initiator as one portion (e.g. by pre-mixing of the initiator, hydride and substrate in the reaction vessel) can give rise to a flood of radicals which can combine and disproportionate counterproductively, so depressing the yield of reaction. Slow addition over a period of time is more effective.

The choice of solvent is limited, theoretically, by the capacity of alkyl radicals to react with halogenated and aromatic solvents.

The chosen operating temperature must be one at which the solvent is liquid and at which the initiator has an appropriate half-life.

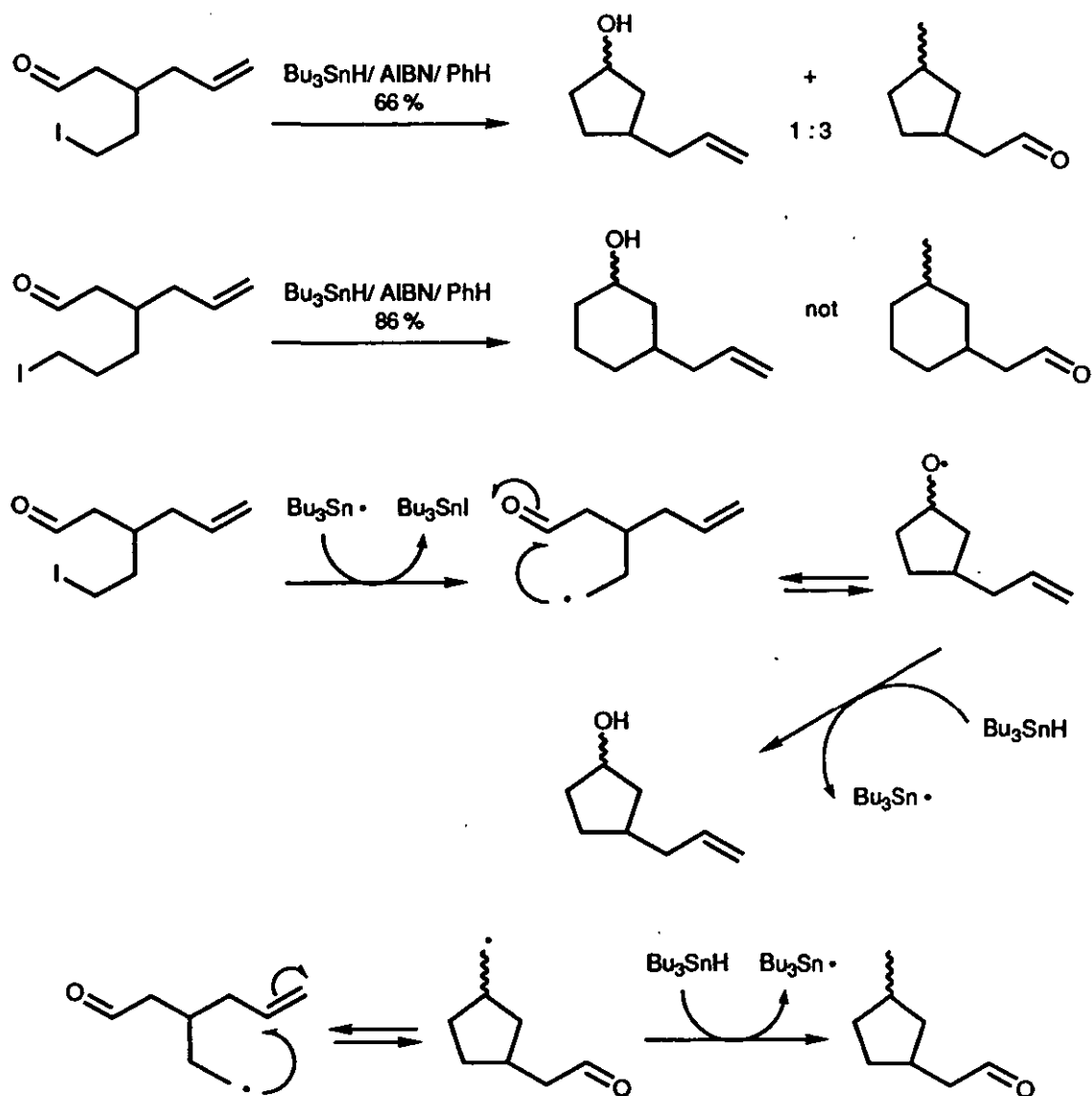
For chain reactions, the thermodynamics of the reaction are determined principally by the propagation steps (Scheme 7, Steps 3 to 7). One of the driving forces for the reduction is provided by the formation of strong carbon-hydrogen σ bonds (in products (22) and (25)) and strong metal-heteroatom σ bonds (in MX) at the expense of fission of weak carbon-heteroatom σ bonds [in starting material (18)] and weak metal-hydrogen σ bonds (in MH).

For radical chain reactions, the product of each propagation step is another radical. In the first propagation step (Scheme 7, Step 3), the metal-centred radical, $\text{M}\cdot$, a soft nucleophile, abstracts the soft heteroatom or heteroatom-bearing group, X, from the substrate (18) to give an alkyl radical (19), which is nucleophilic by virtue of the inductive effect of the alkyl group on the carbon radical centre. The alkyl radical (19) may suffer one of two fates: direct reduction (Scheme 7, Step 4) or rearrangement followed by reduction (Scheme 7, Steps 5, 6, 7). This capacity for rearrangement of radicals in the propagation step is a direct consequence of the chain nature of the mechanism.

For direct reduction (an $\text{S}_\text{H}2$ reaction) of the alkyl radical (19) (Scheme 7, Step 4) the alkyl radical abstracts the hydrogen atom from the group-14 organometallic hydride, MH, to perpetuate the chain. The step is formally reversible: the direction of the reaction is controlled by the relative bond strengths and the rate by its exothermicity. However, on the timescale of the reaction the step is not irreversible.

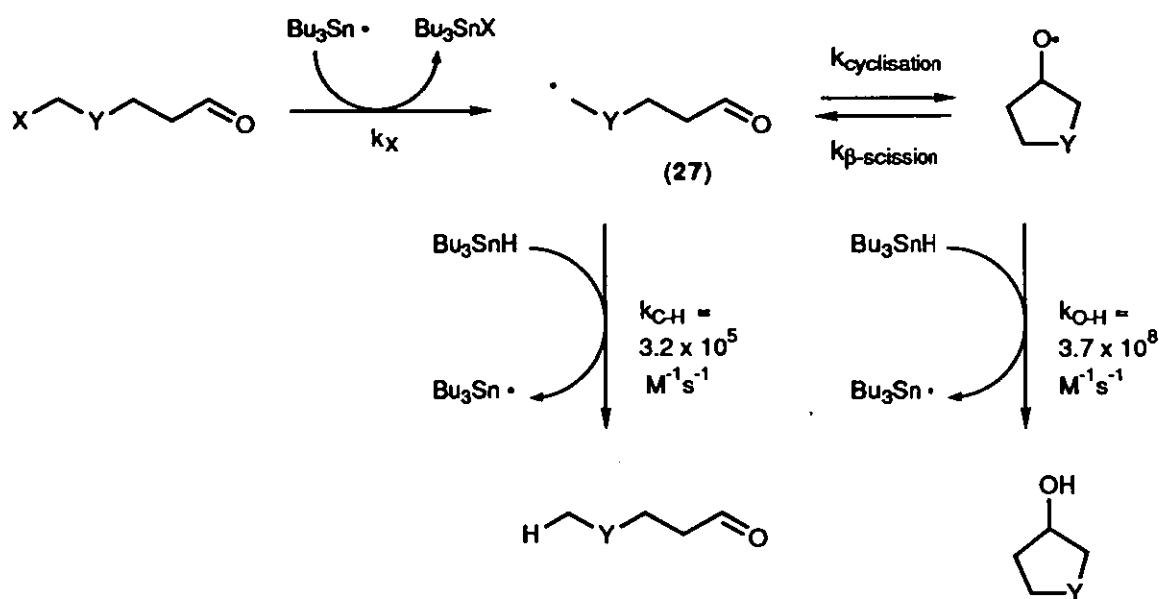
For rearrangement followed by reduction (Scheme 7, Steps 5, 6, 7), the nucleophilic alkyl radical (19) adds intramolecularly in an *exo* manner to the ketone carbonyl group to give an alkoxyl radical (20) (Scheme 7, Step 5). Addition of alkyl radicals onto carbonyl groups has been recognised only comparatively recently^{13,14}: for aldehydes, it is thermodynamically competitive with *exo* cyclisation of the 5-hexenyl and 6-heptenyl radicals (Scheme 12). The kinetics of the reaction have been investigated (Scheme 13).¹⁴ If

formation of the alkyl radical (27) is slow, *i.e.* when rate constant k_X is small (*e.g.* for $X = \text{Cl}$), addition of the metal-centred radical ($\text{M}\cdot$) to the carbonyl may occur preferentially (Scheme 14).



Scheme 12

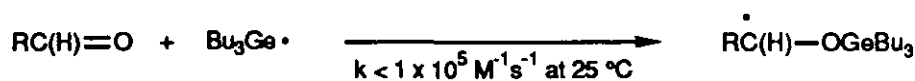
The addition of radicals to multiple bonds is reversible, the position of equilibrium being controlled by the relative bond strengths and radical stabilities. In the case of addition to a carbonyl group the process involves destruction of a carbon-oxygen π bond, which is almost as strong as a carbon-carbon σ bond. Consequently the process is not thermodynamically favoured and the equilibrium lies in favour of the alkyl radical (19). A corollary of this is that regioselective β -scission of alkoxy radical (20) to give a Z-stabilised tertiary alkyl radical (21) (Scheme 7, Step 6) is thermodynamically favoured.



Scheme 13

Y	$k_{\text{cyclisation}} / \text{s}^{-1}$	$k_{\beta\text{-scission}} / \text{s}^{-1}$
CH ₂	8.7×10^5	4.7×10^8
(CH ₂) ₂	1.0×10^6	1.1×10^7

X	$k_{\text{X}} / \text{M}^{-1} \text{s}^{-1}$
I	4.3×10^9
Cl	7.0×10^3

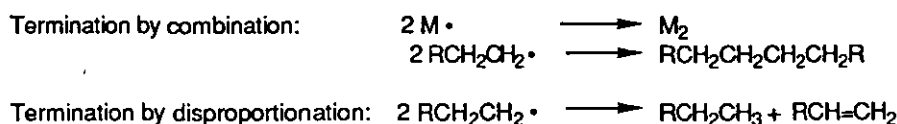


Scheme 14

The remarks pertaining to the chain transfer shown in Step 4 also apply to the chain transfer shown in Step 7 (Most carbon substituents attached to the radical centre have little effect on the rate constant for hydrogen abstraction).

The formation of the strong metal-heteroatom (M-X) bond and the destruction of the weak metal-hydrogen (M-H) bonds by rapid hydrogen abstraction by alkyl radicals (19) and (21) lead to constant exothermic regeneration of the chain-carrying radical, M•, and hence to long chain lengths in the propagation sequence. Propagation steps 3, 4 and 7 involve reaction of a radical with a neutral molecule. Consequently the concentration of alkyl and

chain-carrying radicals ($M\cdot$) is low, minimising the opportunity for chain termination by combination or disproportionation (Scheme 15).



Scheme 15

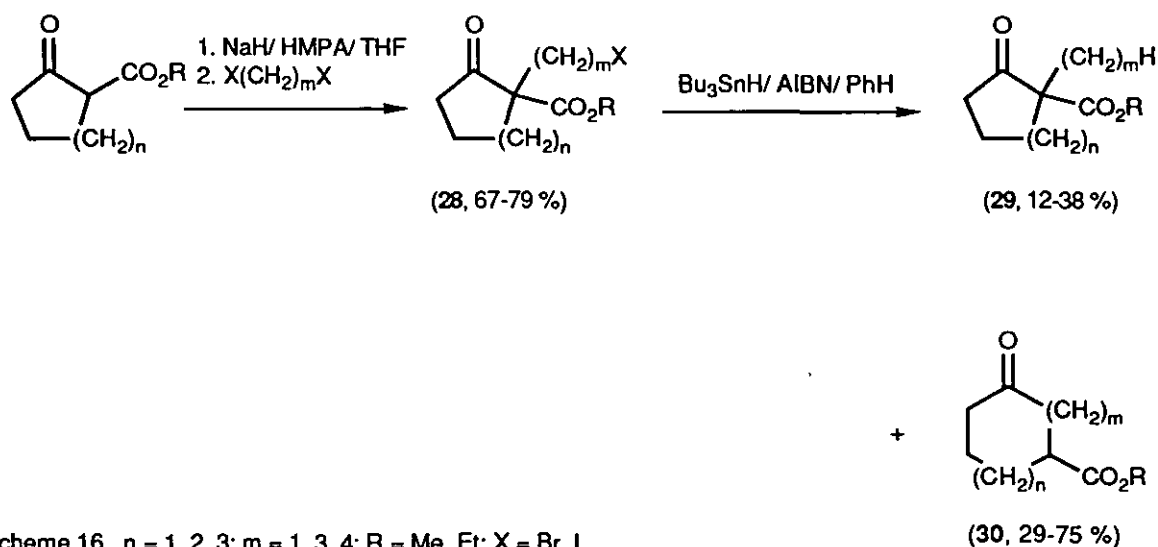
The product distribution, *i.e.* the relative yields of ketones (22) and (25), may be controlled in two ways, *viz.* variation of the group-14 organometallic hydride (MH) and of its concentration [MH]. The partition of alkyl radical (19) is determined by the relative rate of cyclisation (k_C) vs. the relative rate of hydrogen abstraction (k_H [MH]).

Minimising the concentration [MH], *e.g.* by use of high dilution, by use of polymer-bound hydrides, or by addition of hydride (MH) by syringe pump, favours the formation of products of ring-expansion (22) over products of direct reduction (25). However there is a lower limit to the hydride concentration [MH], below which the rates of propagation steps 3, 4 and 7 become so low that the chain collapses, *i.e.* termination occurs before propagation. Thus there exists a "window" in the concentration of group-14 organometallic hydride [MH], within which ring expansion is successful.

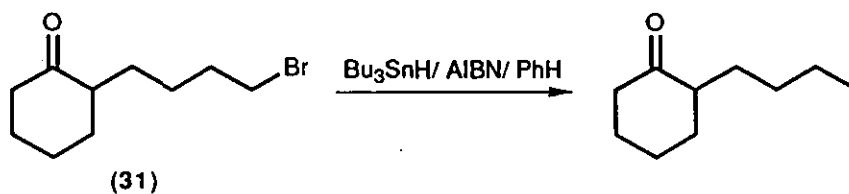
When syringe pumps are used and the rate constant for abstraction of the X-group from the substrate (18), k_X , is low, the group-14 organometallic hydride concentration [MH] may become higher than expected before chain propagation becomes viable. Often iodides (18, X = I) are the substrate of choice, since for them k_X approaches the diffusion-controlled limit.

The rate constant for direct reduction of the alkyl radical (19), k_H , decreases as the magnitude of the (M-H) bond strength, and thus the enthalpy of activation, increases. The magnitude of k_H decreases in the order: $Ph_2SnH_2 > Ph_3SnH > Bu_2SnH_2 > Bu_3SnH > Bu_3GeH > (Me_3Si)_2Si(Me)H$. Unfortunately using a group-14 organometallic hydride with a lower k_H value may bring no increase in the proportion of ring-expanded product (22) since a higher group-14 organometallic hydride concentration [MH] may be required, lest the propagation steps should become so slow that the chain fails.

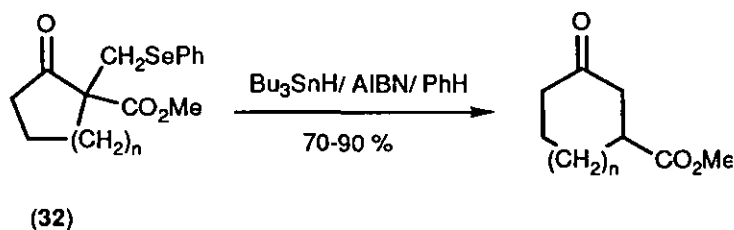
There are a growing number of examples of use of the Side Chain Incorporation approach (Scheme 4, Type 2) for ring expansions. The simplest such example is the ring expansion of the β -keto esters (28) (Scheme 16).¹⁵ In certain cases, non-ring-expanded reduction products (29) are obtained in addition to ring-expanded products (30). As expected yields of product (29) are suppressed by use of a syringe pump.



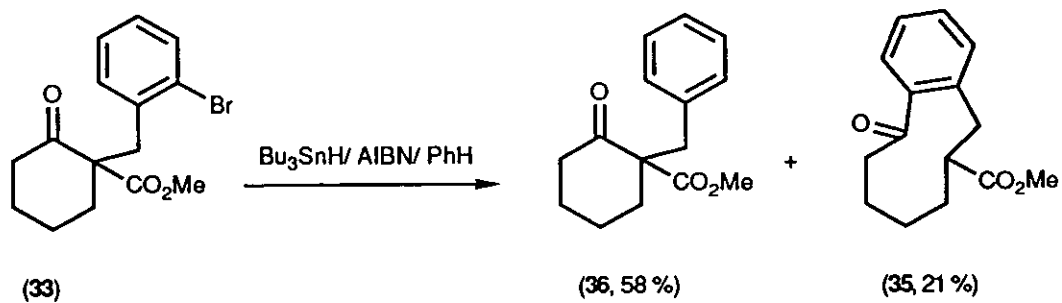
In the absence of a β -ester group, *e.g.* in ketone (31), ring expansion does not occur, indicating clearly that a radical-stabilising group (Z, Scheme 7) is necessary for the expansion of certain ring systems (Scheme 17).¹⁶



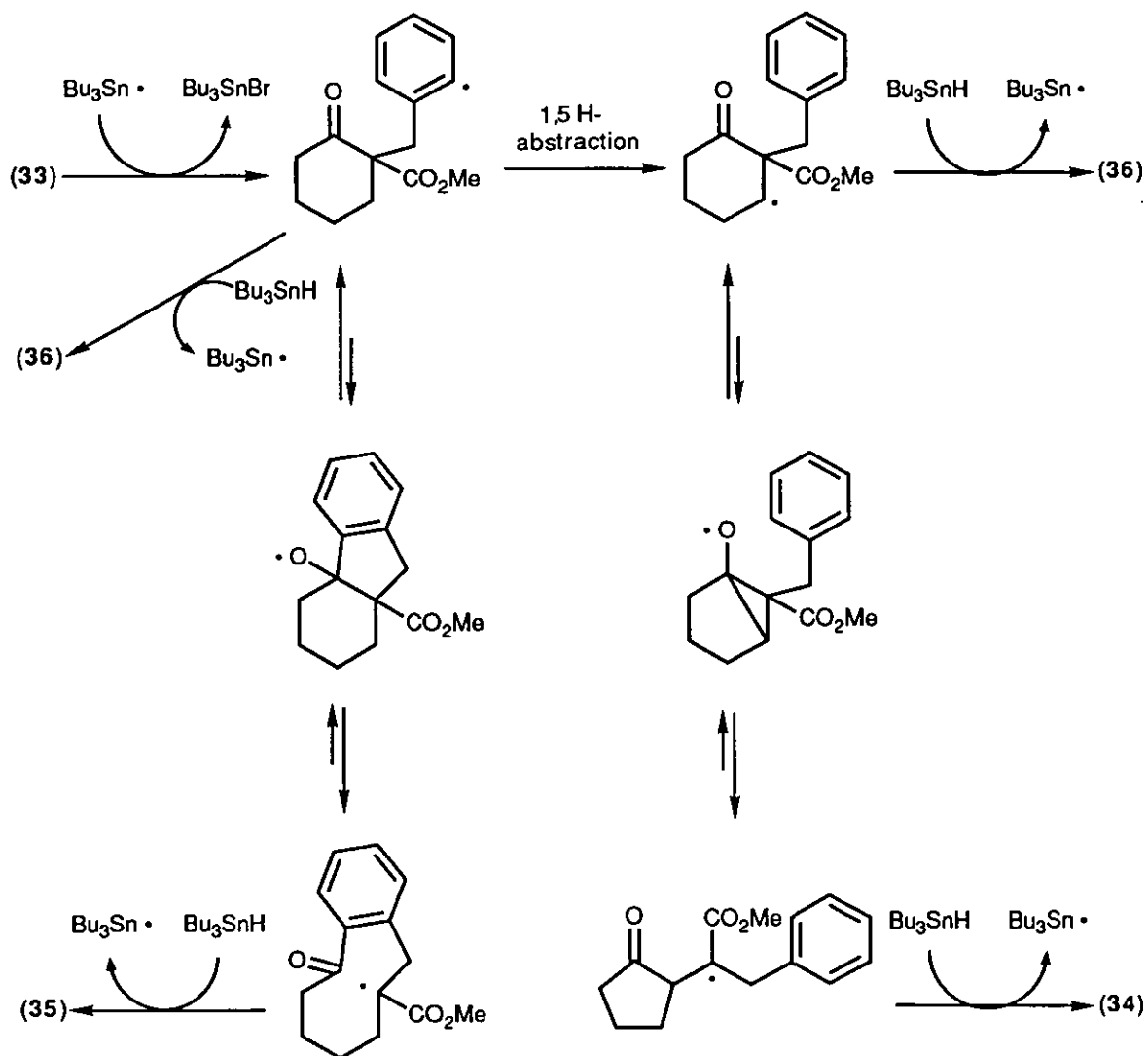
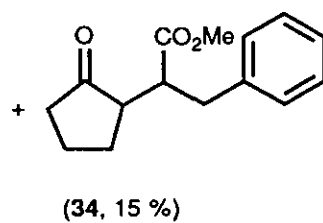
The pendant side chains may be selenides (32) (Scheme 18) or bromobenzenes (33) (Scheme 19).¹⁷ In the latter case a product of ring contraction (34) is isolated in addition to the expected products of ring-expansion (35) and of direct reduction (36).



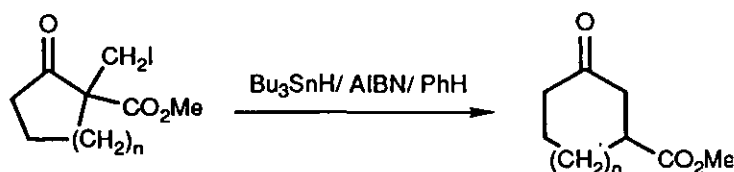
The method has been applied to the ring expansion of large ring carbocycles.¹¹ One-carbon ring expansions proceed in a straightforward manner (Scheme 20) but complications arise in the case of three-carbon ring expansions (Scheme 21). In the latter case, the presence



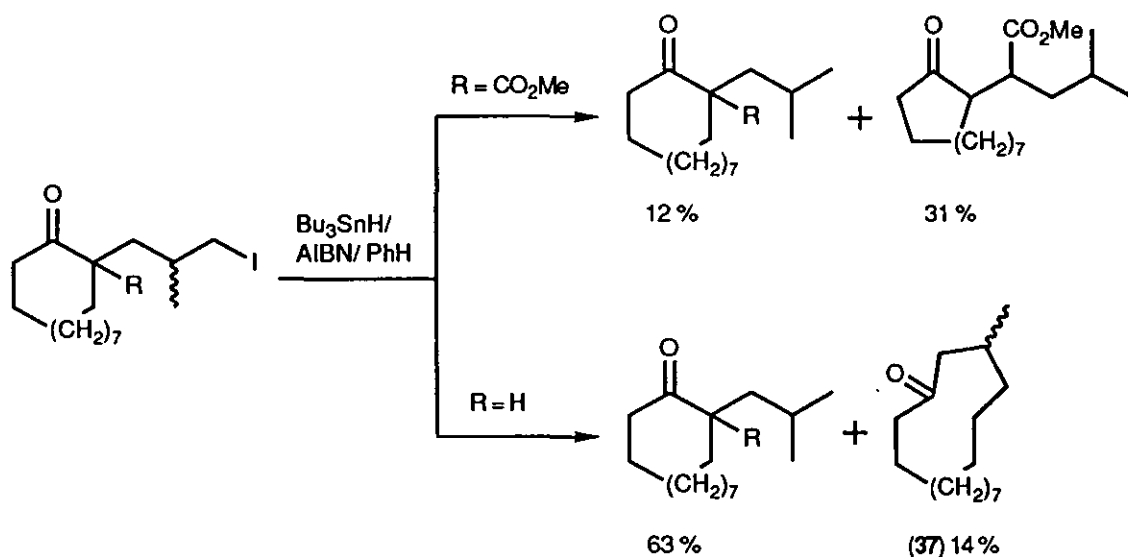
Scheme 19



of a β -ester group favours ring contraction over ring expansion. The likely mechanism is thought to involve a 1,5-hydrogen shift (*Cf.* the reduction of cyclohexanone (33) to cyclopentanone (34)). Removal of the ester group gives the expected ring expansion to muscone (37). Significantly, in this case, the product distribution indicates that $k_H[\text{Bu}_3\text{SnH}] > k_C$.



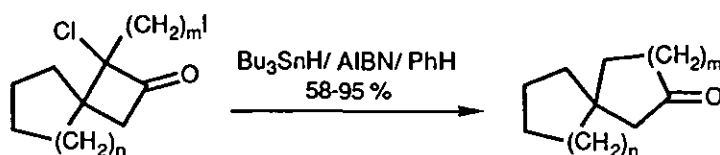
Scheme 20 $n = 8$ (79 %), 10 (50 %), 11 (67 %)



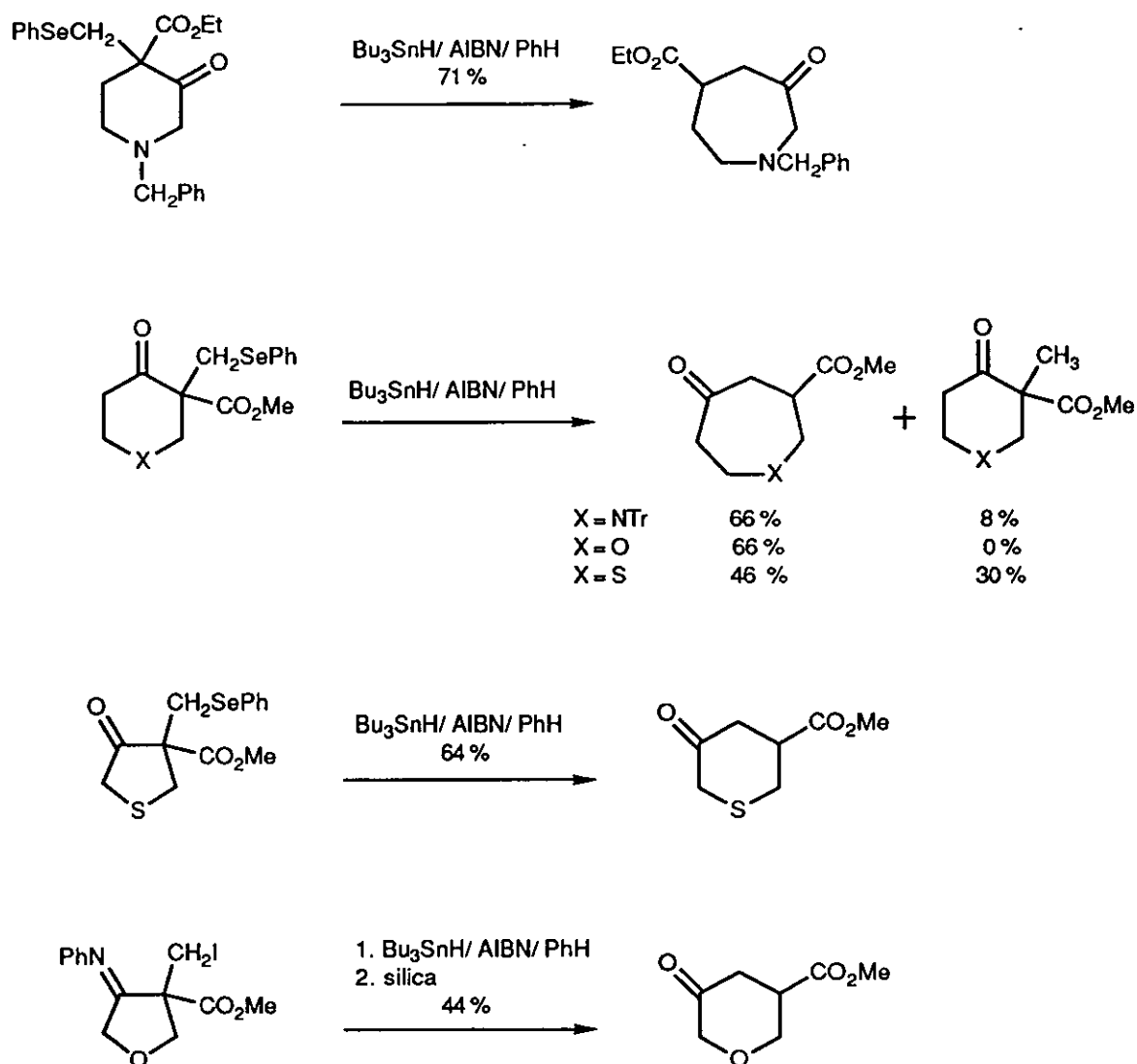
Scheme 21

The method has also been applied to the ring expansion of spiroannulated cyclobutanones (Scheme 22).¹⁸

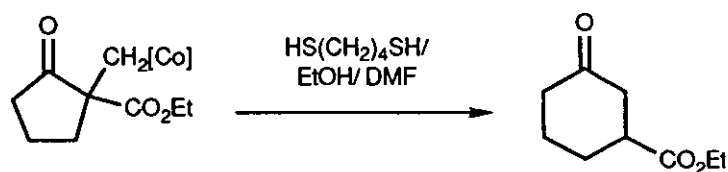
The method has been applied to the ring expansion of heterocycles (Scheme 23).¹⁹ Evidently the ketone may be successfully replaced with an imine group. It may also be replaced by an exocyclic methylene group (Scheme 24).²⁰



Scheme 22 $n = 1, 2, 4$; $m = 3, 4$



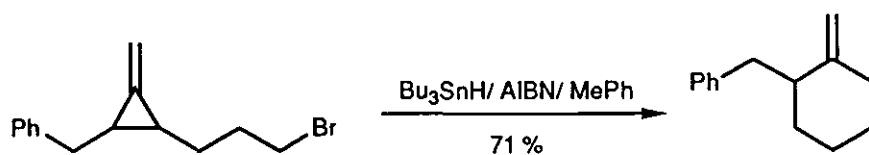
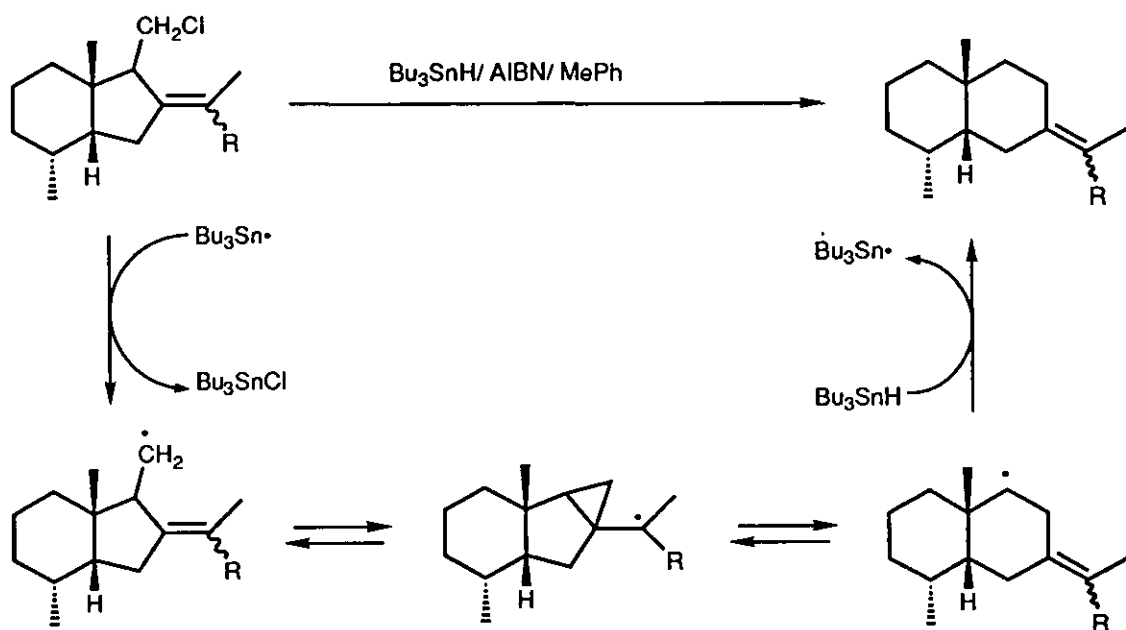
Scheme 23



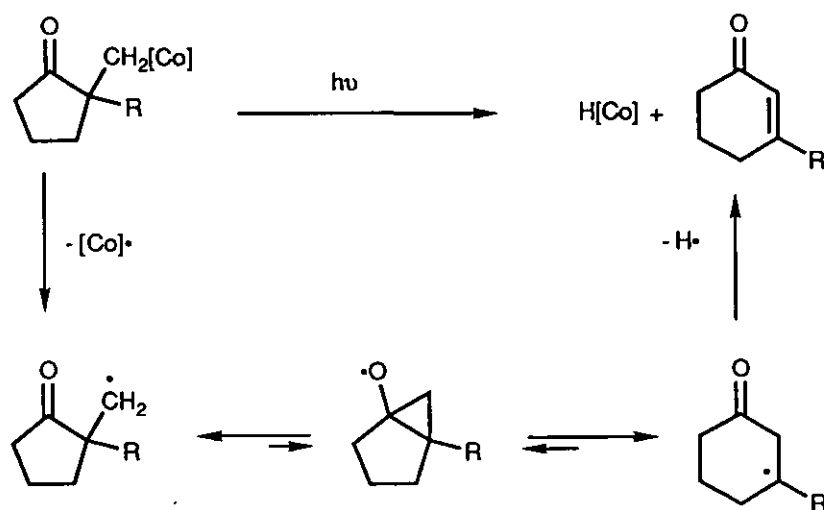
Scheme 25 [Co] = Co(Me₂glyme)py

The method has been applied as a model for the non-light-catalysed vitamin B₁₂ methylmalonyl isomerase reaction (Scheme 25)²¹ and as a model for the light-catalysed methylmalonyl coenzyme A mutase vitamin B₁₂ reaction (Scheme 26).²² In both cases the

leaving group is a cobaloxime species, but in the latter case the absence of a source of hydrogen causes the last mechanistic step to be one of oxidation rather than one of reduction.

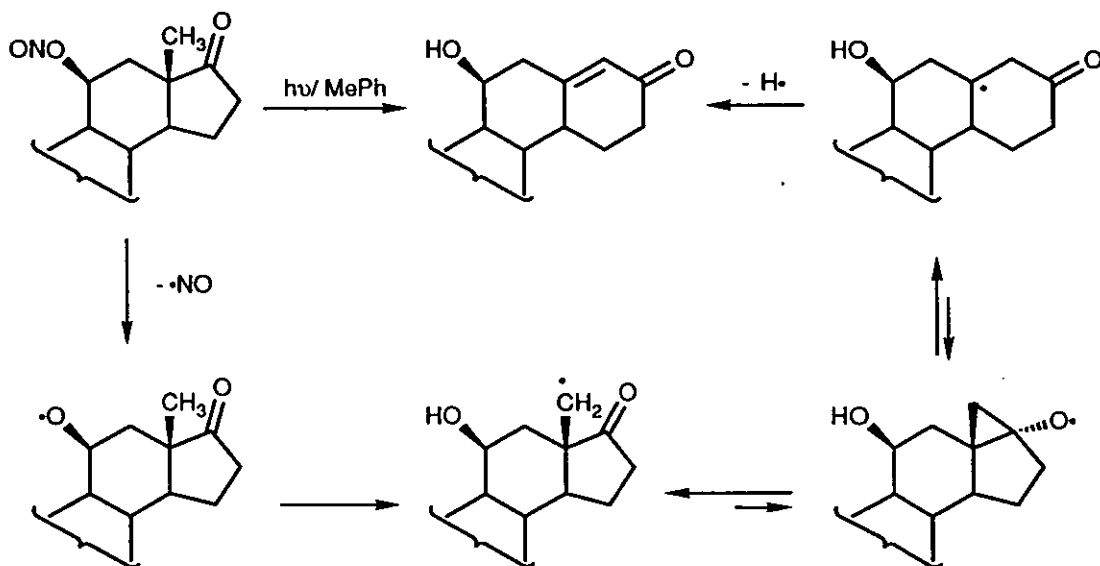


Scheme 24 $\text{R} = \text{H}, \text{Me}$



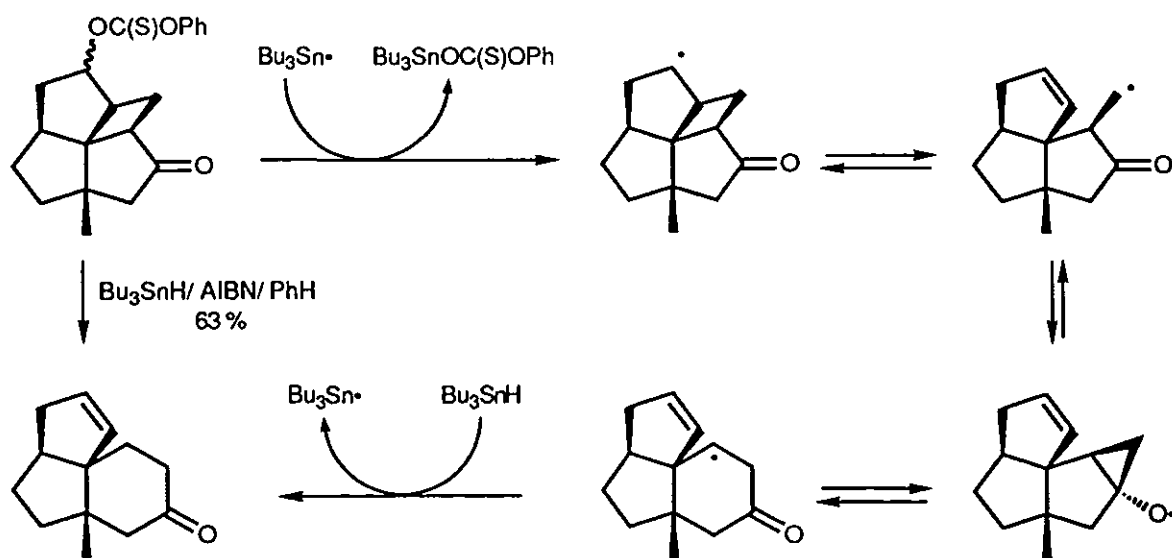
Scheme 26 $[\text{Co}] = \text{Co}(\text{Me}_2\text{glyme})\text{py}$; $\text{R} = \text{Ph}, \text{CO}_2\text{Et}$

The D-ring expansion of 4-androsten-11 β -ol-3,17-dione has been reported (Scheme 27).²³ The alkyl radical is formed by abstraction of a hydrogen atom from the bridgehead methyl group by an alkoxyl radical generated by photolysis of the 11 β -nitrite. Once again the absence of a suitable source of hydrogen causes the last mechanistic step to be oxidative.

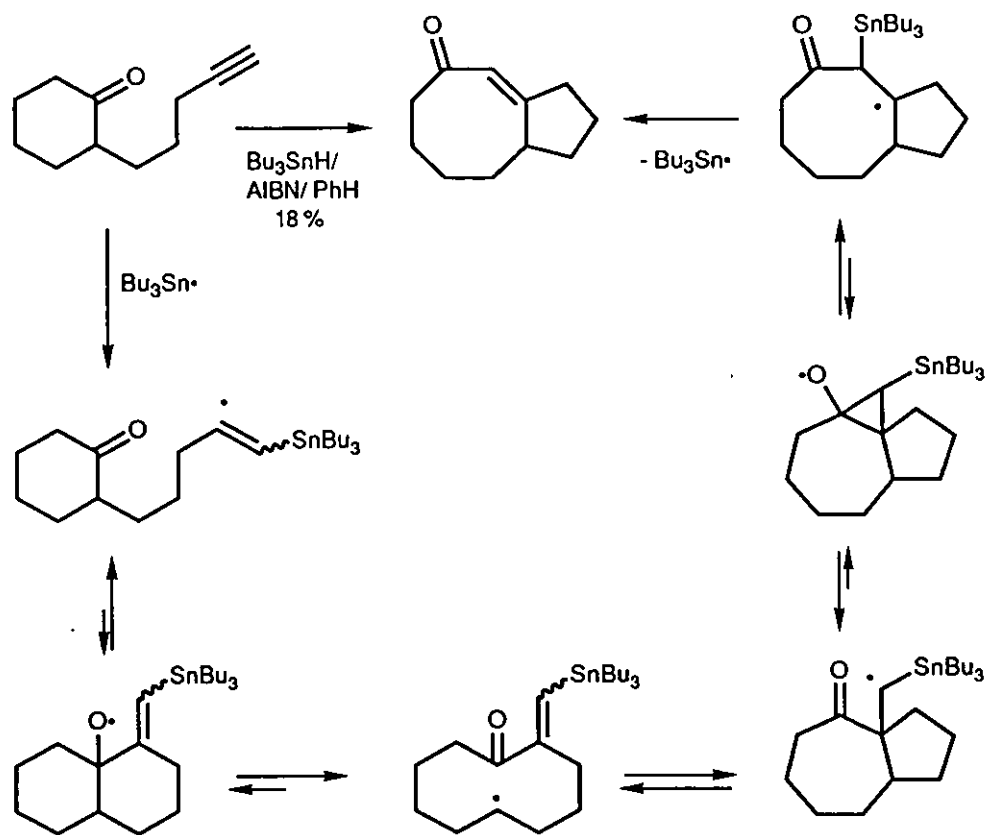


Scheme 27

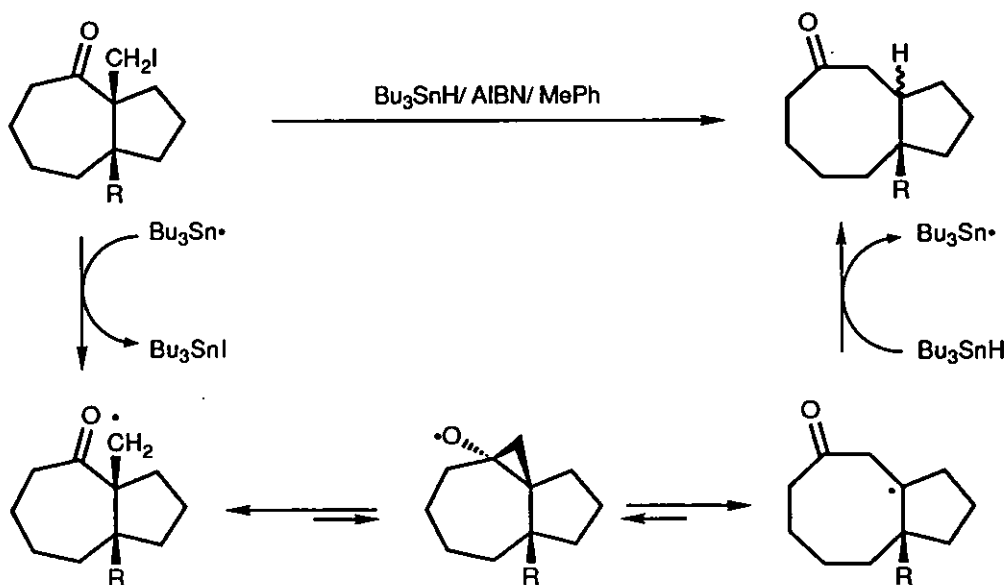
One-carbon ring expansions feature in more complex rearrangements (Schemes 28,²⁴ 29,²⁵ 30,²⁶ and 31²⁷): they outnumber examples of multi-carbon ring expansions due to (a) the favourable entropy for formation of cyclopropanoxyl radical (41) and (b) the loss of ring strain associated with its ring opening by β -scission (Scheme 32).



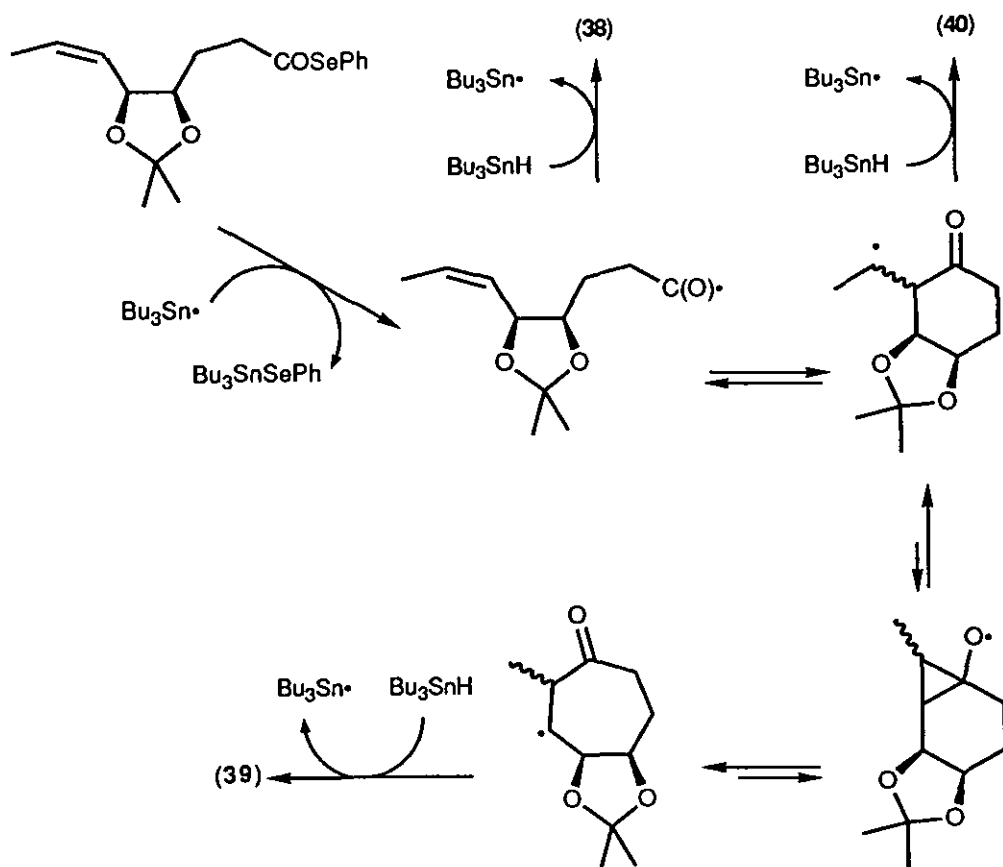
Scheme 28



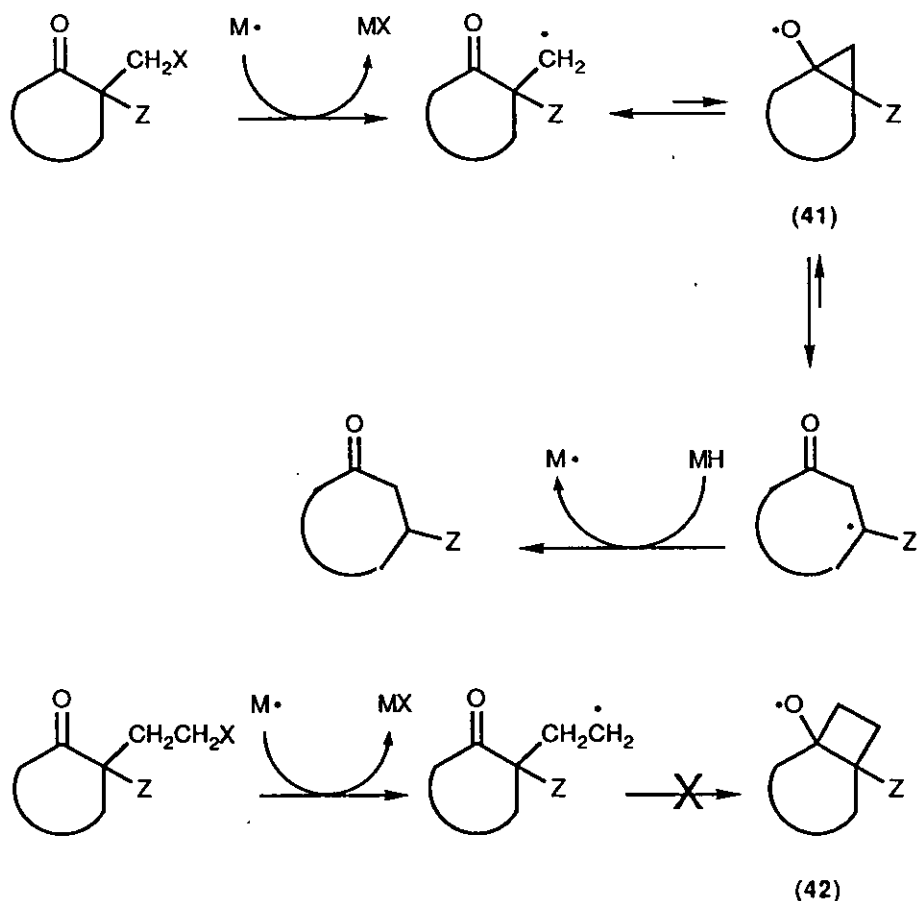
Scheme 29



Scheme 30 R = H (14 %), Me (20 %)

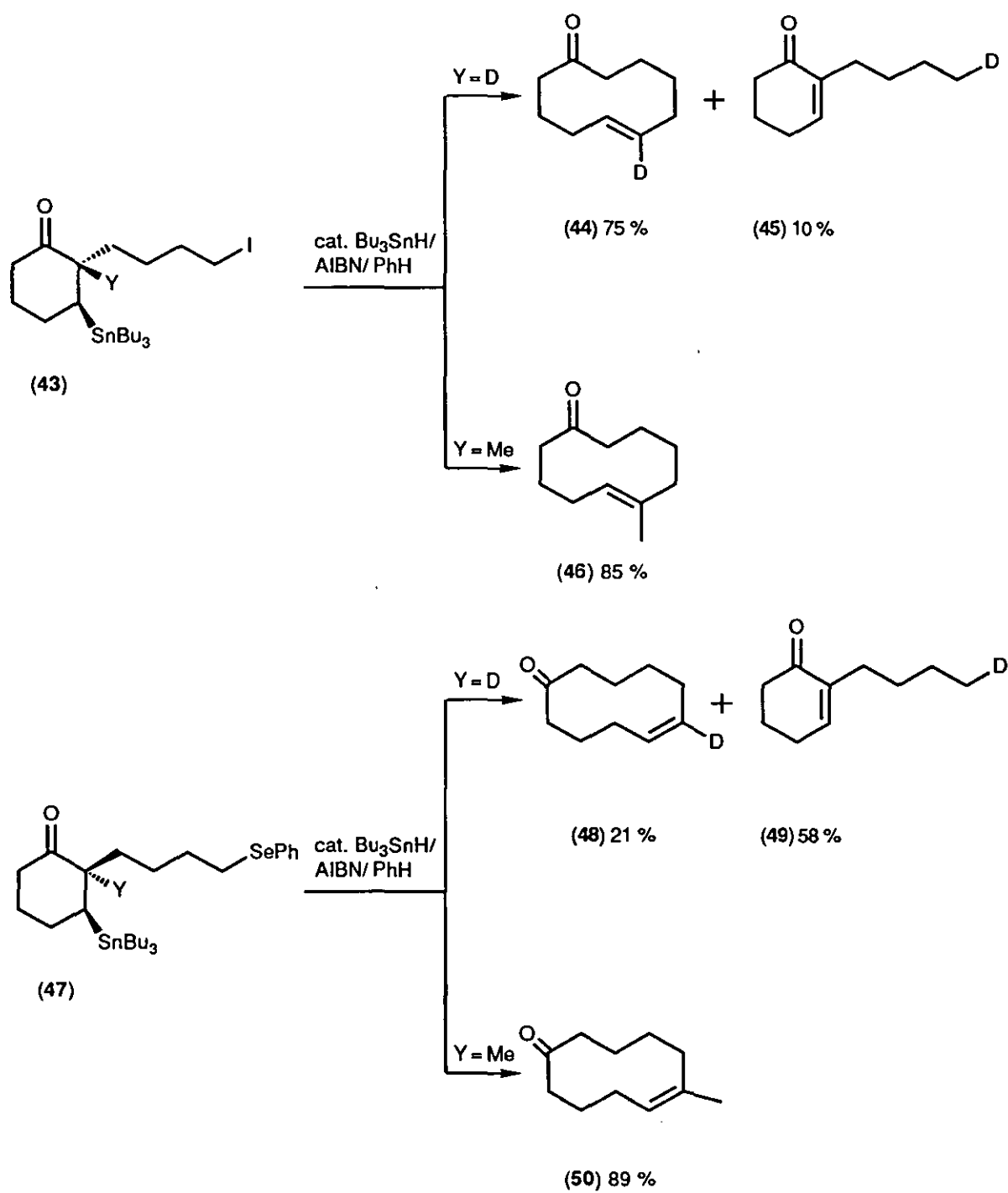


Two-carbon ring expansion by this route fails because 4-*exo* cyclisation to cyclobutanoxyl radical (42) is not competitive with hydrogen transfer.⁸

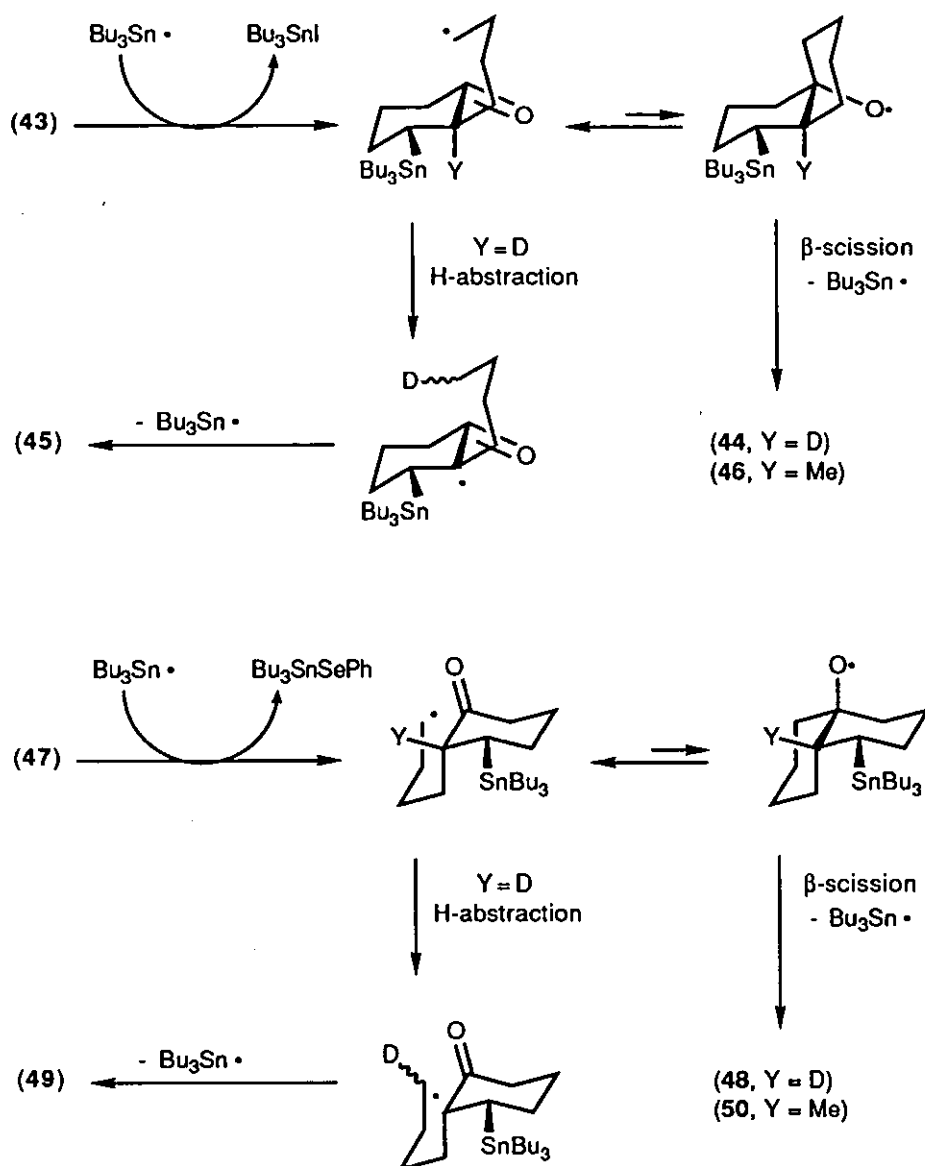


Scheme 32

Self-catalysed ring expansions requiring only catalytic tributylstannane and AIBN have been reported.^{28,29} The method has been applied to cyclohexanones (Schemes 33, 34²⁸). The low value of $[Bu_3SnH]$ completely suppresses formation of unwanted reduction products [*Cf.* reduction of ketone (31), Scheme 17], provided $Y \neq H$ (If $Y = H$, 1,6-H abstraction proceeds prior to reduction, radical geometry permitting). The *E/Z* relationship in the precursor [(43) or (47)] dictates the alkene geometry of the ring-expanded product [(44), (46), (48) or (50)].

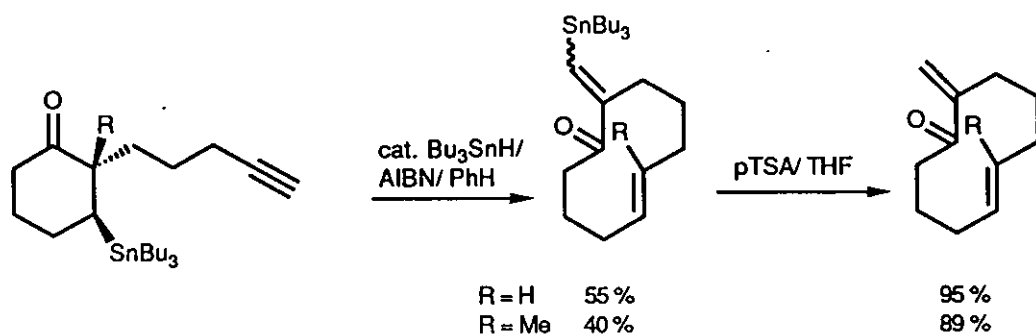
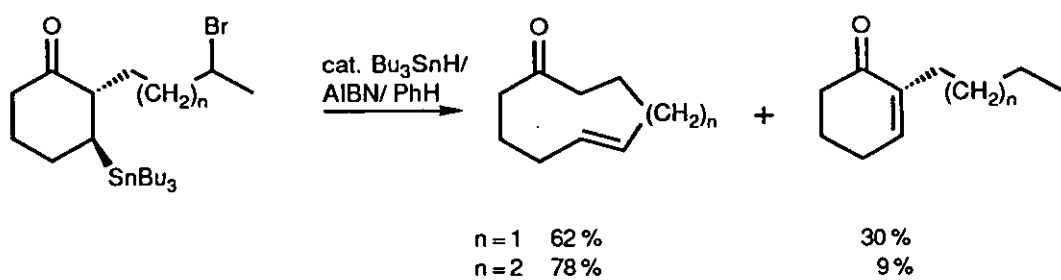


Scheme 33

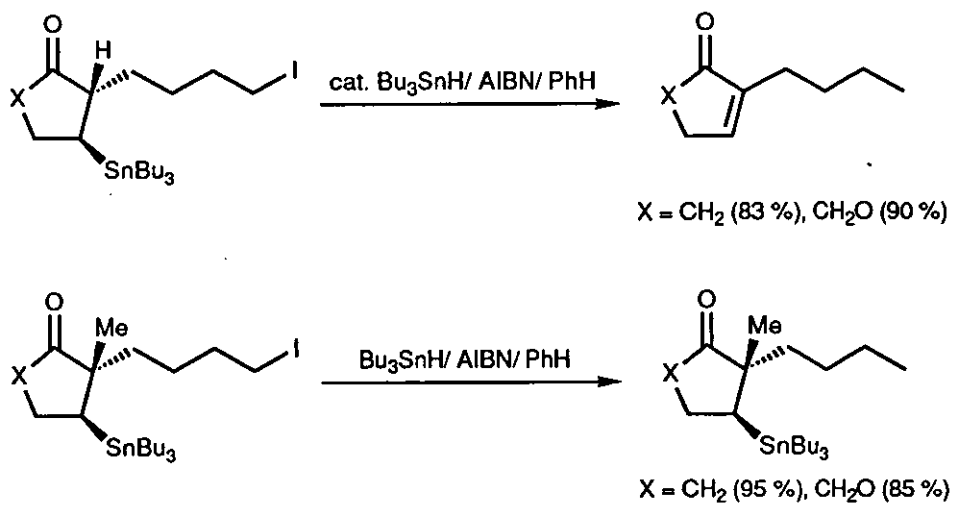


Scheme 34

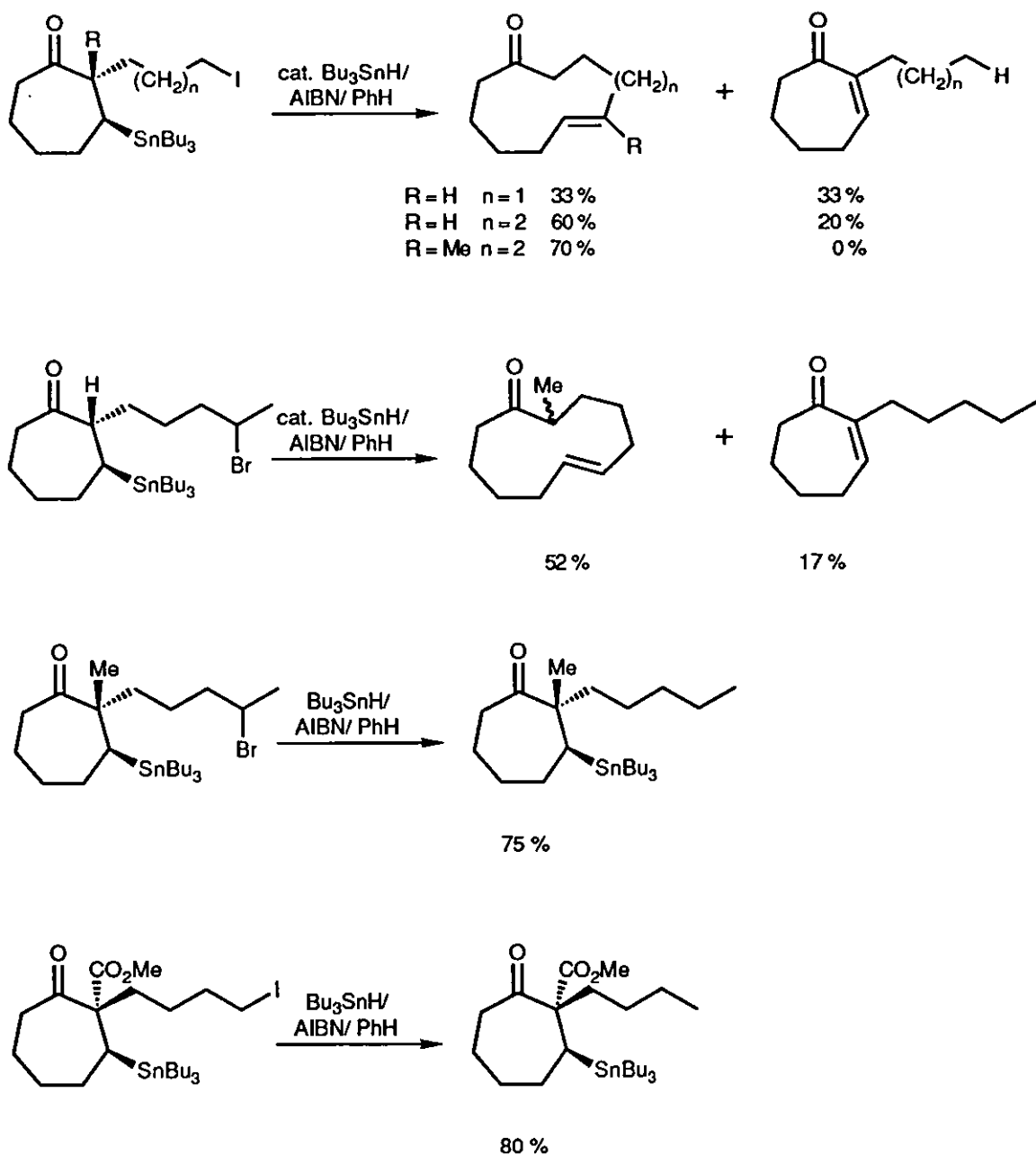
The scope of the method has been investigated further.²⁹ It is successful when the side chain is a terminal alkyne or secondary alkyl halide, rather than a primary alkyl halide or phenylselenide (Scheme 35). It fails when the side chain is a halo-alkene, giving products of reduction-without-expansion only. The method has been extended to cycloheptanones, where ring expansion is generally less successful than with the analogous cyclohexanones (Scheme 36). The method fails when applied to cyclopentanones, which are less reactive towards nucleophilic radical attack due to increased hindrance and the eclipsing interactions about the carbonyl group that occur on addition. The method also fails when applied to 6-membered ring lactones (Scheme 37).



Scheme 35



Scheme 37

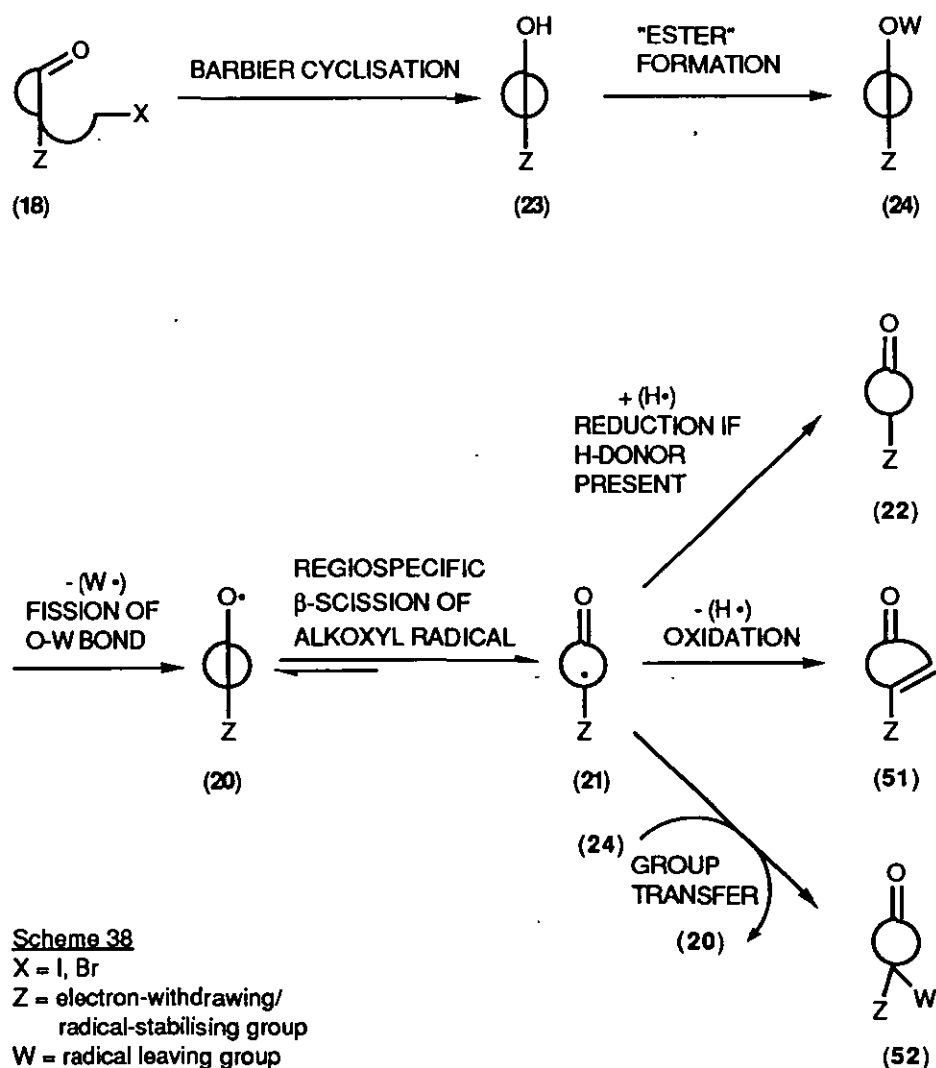


Scheme 36

Thus it may be seen that there are a growing number of examples of Ring Expansion *via* Side Chain Incorporation (Type 2). As will be shown in the next section the same cannot be said of Ring Expansion *via* Cleavage of the Zero Bridge in Bicycles (Type 1).

1.5 Ring Expansion by Cleavage of the Zero Bridge in Tertiary Bicyclic Alcohols

Ring expansion by cleavage of the zero bridge of a tertiary bicyclic alcohol (Type 1) is a process involving two fundamental steps, *viz.* formation of the tertiary bridgehead bicyclic alcohol (23) and ring opening of the derived alkoxyl radical (24) (Scheme 38).



The first step (exemplified in Section 1.5.1), formation of the tertiary bridgehead bicyclic alcohol (23), can be achieved by Barbier cyclisation of ketone (18). However [n.1.0] and [n.2.0]bicyclo-alkanols are accessible by carbenoid cyclopropanation and 2+2 photoinduced cycloaddition respectively.

The next step(s) (exemplified in Section 1.5.2) involve(s) ring opening of alcohol (23) *via* alkoxyl radical (20) to give the ring-expanded ketone [(22), (51) or (52)]. This process has been used to facilitate ring expansion by 2, 3 and 4 carbons. The alcohol (23) is

"esterified" to give a suitable precursor (24) to the alkoxyl radical (20): there are surprisingly few known methods for this process. The weakness of the oxygen-heteroatom (O-W) bond facilitates its homolysis to form alkoxyl radical (20), which can suffer one of three fates, depending on reaction conditions: reduction back to alcohol (23), if a suitable hydrogen-donor is present (For an example of hydrogen abstraction, see Scheme 27²³); addition to a nucleophilic alkene (alkoxyl radicals are strongly electrophilic); or β -scission in one of three different directions. For successful ring expansion, the alkoxyl radical (20) undergoes regioselective β -scission to the Z-stabilised radical (21): the stabilisation thermodynamically biases the direction of β -scission. Regioselectivity in the absence of a Z-group has been studied (See later).¹⁶ As discussed earlier, the driving force for the β -scission is the formation of the ketone double bond, and the reverse reaction is unfavourable. If a hydrogen-donor, *e.g.* tributylstannane (Bu₃SnH), is present, the radical (21) is reduced to ketone (22). Otherwise it is oxidised to enone (51), or intercepted by the "ester" (24) to give a product of group transfer (52).

As a whole, remarkably few examples of ring expansion by this method have been reported in the literature, although, as will be shown, examples of the application of each of the two fundamental steps are more common.

1.5.1 Formation of the Tertiary Bicyclic Alcohol

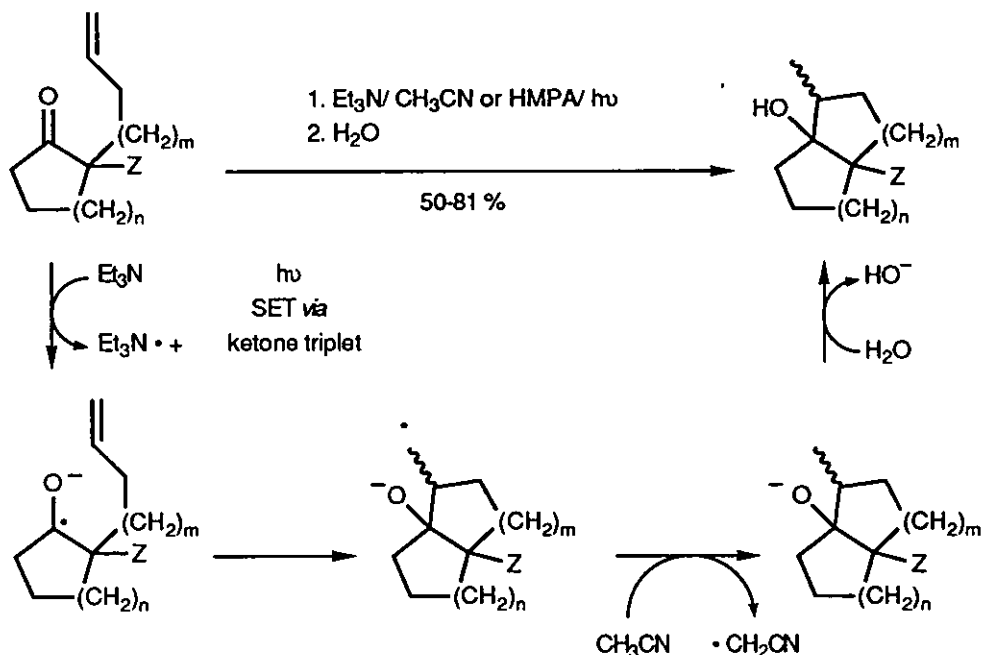
As has been implied, the formation of the tertiary bridgehead bicyclic alcohol (23) is generally *via* Barbier cyclisation of ketone (18).

(a) Grignard-Mediated Barbier Cyclisation

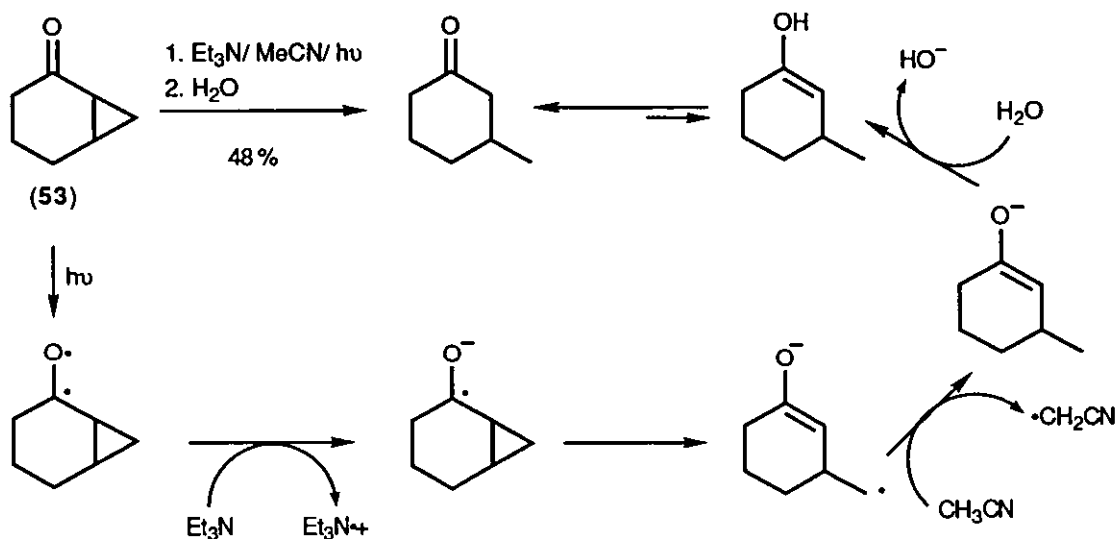
Use of standard reagents to mediate such reactions can be problematic. Formation of, and use of, the derived Grignard (18, X = MgBr or MgI) present several problems. Firstly the Z-group must be inert: this precludes the use of β -keto esters. Secondly formation of the Grignard may be sluggish, leading to low yields and/or incomplete conversion.³⁰ Reactive magnesium can be prepared by *in situ* reduction of magnesium halides by potassium (leading to a finely divided black powder), by sonication of magnesium turnings (which may disperse surface-bound water from the surface of the metal), by vigorous stirring under an inert atmosphere (the mechanically unstable magnesium turnings fragment to give microcrystalline particles with large oxide-free surface area), or by evaporative sublimation of high purity metal *in vacuo* with condensation into a solvent slurry at -196°C. Alternatively transmetalation with magnesium anthracene can be employed. In general, the use of Grignard reagents has been found to be notably unsuccessful, resulting in the formation of intractable mixtures or the recovery of the starting material.

(b) Photo-induced Barbier Cyclisation

An alternative approach involves cyclisation of ketyls, produced by photochemically induced single electron transfer (SET), onto a terminal alkene side-chain (Scheme 39).³¹ Conclusive proof of the intermediacy of the ketyl is afforded by the partial reduction of the cyclopropyl ketone (53) (Scheme 40). The ketyl is produced by SET from excited-state HMPA to ground-state ketone, or by SET from ground-state triethylamine to excited-state ketone.⁶



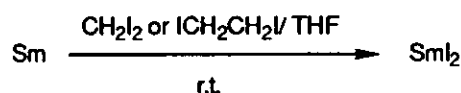
Scheme 39 $\text{Z} = \text{H}, \text{CO}_2\text{Me}; m, n = 1, 2$



Scheme 40

(c) Samarium (II) Iodide-Mediated Barbier Cyclisations

The most recent, and by far the most synthetically useful Barbier cyclisation method involves the use of samarium (II) iodide,³² which is quantitatively generated *in situ* from metallic samarium (Scheme 41)^{33,34} giving a characteristic blue-green solution in THF. Anhydrous conditions and an inert atmosphere are required.

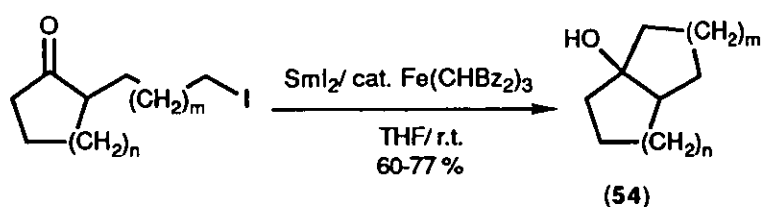


Scheme 41

Samarium is one of the most abundant of the lanthanides.³⁵ The metal and its salts are not known to be toxic. The salts have a pronounced ionic character and samarium has a large ionic radius.³⁶ Co-ordination numbers are high: the salts are oxophilic Lewis acids.

In spite of samarium (II) iodide being amongst the strongest reducing agents soluble in organic media ($E_{\text{Sm}^{3+}/\text{Sm}^{2+}} = -1.55 \text{ V}$),³⁷ its reactions are mild and selective³⁴ *e.g.* esters, amides, nitriles, alkenes and arenes are virtually inert under typical reaction conditions.³⁸ The order of halide reactivity is: iodide > bromide > chloride.³⁴

For Barbier cyclisations, 2 equivalents of samarium (II) iodide are required. Formation of cyclopentanol [e.g. (56)] from 1-(3-halogenopropyl)ketones [e.g. (55)] is generally successful but formation of cyclohexanol from 1-(4-halogenobutyl)ketones [e.g. (57)] is less predictably so (Schemes 42³⁸ and 43³⁹). Synthesis of cyclobutanol by this method has yet to be thoroughly investigated, but in one reported attempt³² the desired product could not be realised. In the formation of tertiary bicyclic alcohols (54), use of iron (III) catalysts, especially tris(dibenzoylmethanato)iron (III), favours formation of *cis* ring junctions.

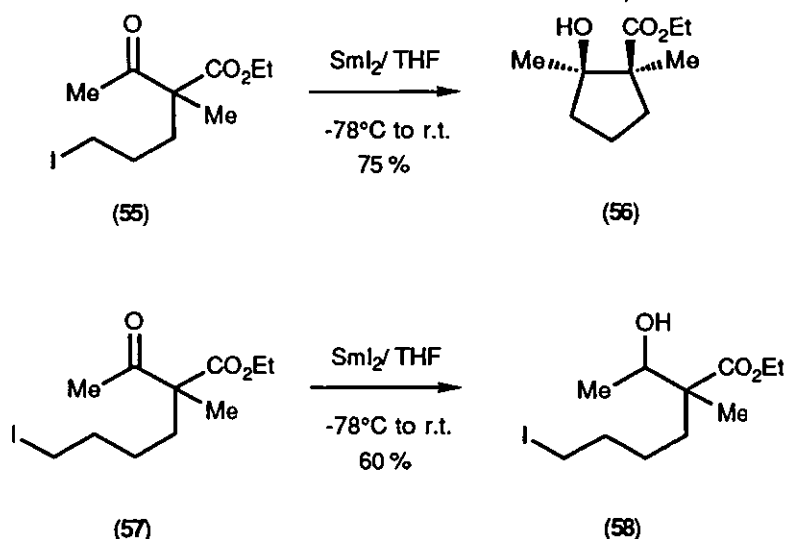


Scheme 42 $n = 1, 2, 3$; $m = 1, 2$

The catalytic activity of iron (III) salts, the ease with which samarium (II) is oxidised to samarium (III) and the fact that two equivalents of samarium (II) iodide are required for complete reaction in Barbier cyclisations tend to suggest a mechanism involving two single electron transfers [one from each of the two samarium (II) species] to the substrate. Scheme 44³⁷ shows tentative mechanistic pathways: the exact stoichiometry, solvation and degree of association are not known. Dissociative SET to the halogen, X, could lead to an alkyl radical

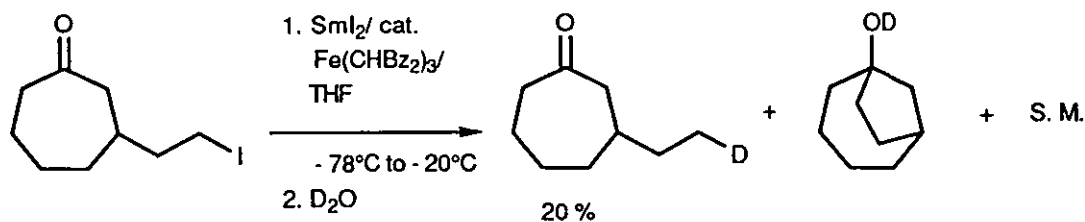
(19) which could undergo a second electron transfer to give an organosamarium species (59), which could undergo a pseudo-Grignard intramolecular cyclisation to give the alkoxide (60) (See Discussion). Alternatively SET to the ketone, giving rise to a ketyl (61), could be followed by dissociative SET to the halogen, X, giving rise to a diradical (62) capable of collapsing to alkoxide (60).

The Lewis acidity of samarium species and the apparent preference of the samarium (II) species for forming cyclopentanol over cyclohexanol suggests that it is co-ordinated to the oxygen of the carbonyl/ ketyl, and to the halogen atom, X.

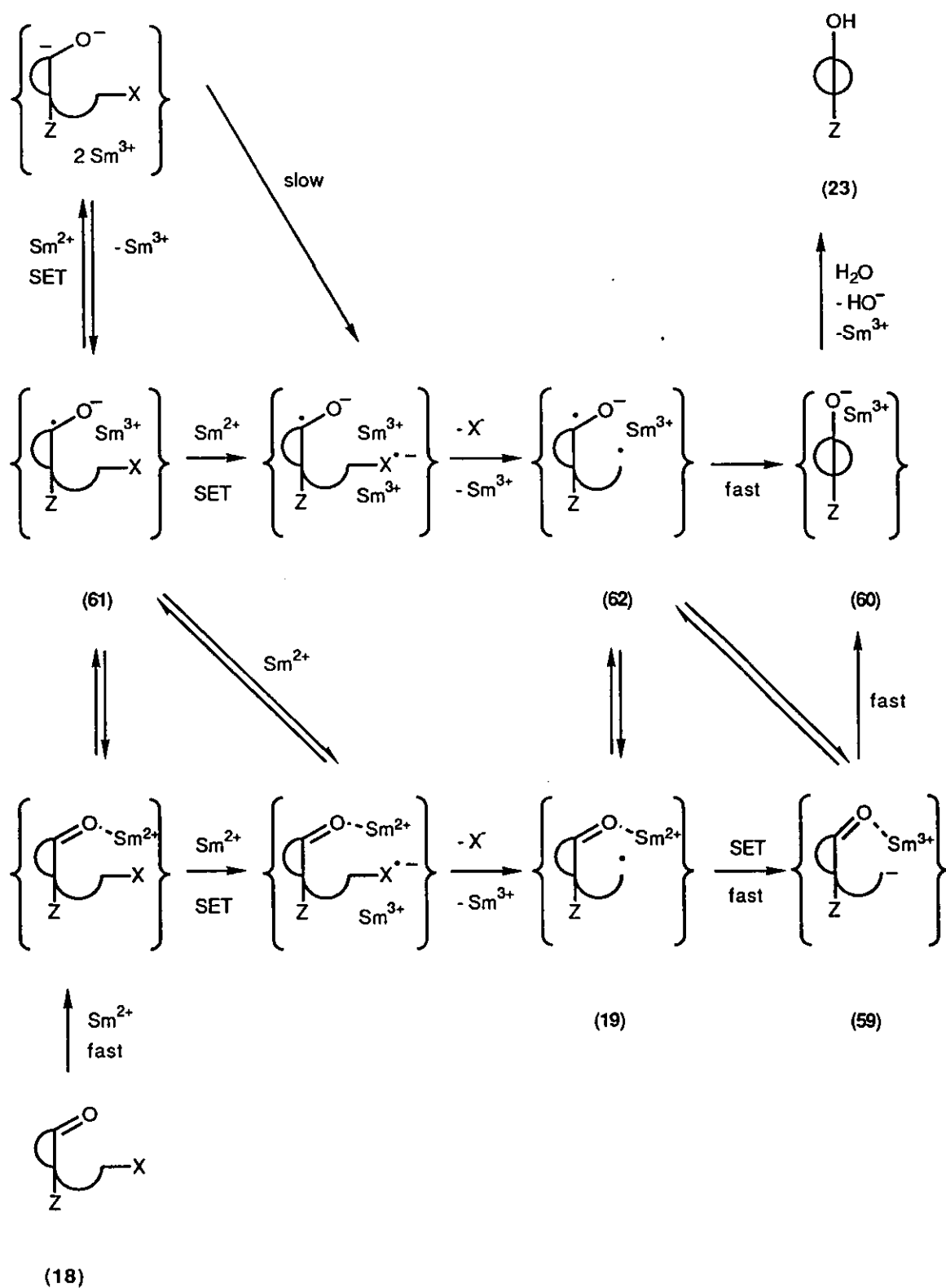


Scheme 43

Use of deuterium-labelling as a mechanistic probe leads to ambiguous results. Deuterium incorporation in the D_2O -quenched Barbier cyclisation of 2-(2-iodoethyl)cycloheptanone (Scheme 45³³) tends to confirm the intermediacy of organosamarium species, but this is contradicted by the absence of deuteration when simple halides are reduced (Scheme 46³⁷). In the latter case, solvent adducts are known to form (suggesting that alkyl radicals, $R\cdot$, are intermediates), but, surprisingly, Wurtz coupling dimers, RR , do not usually form (except in the reduction of benzylic or allylic halides where they are the predominant product).



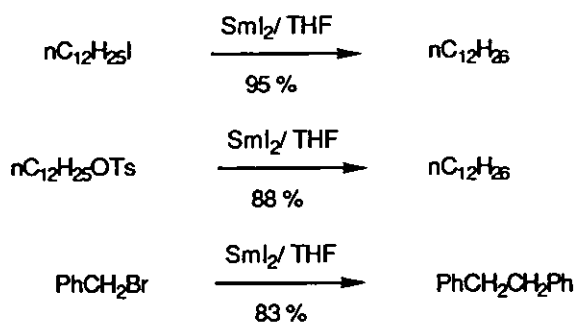
Scheme 45



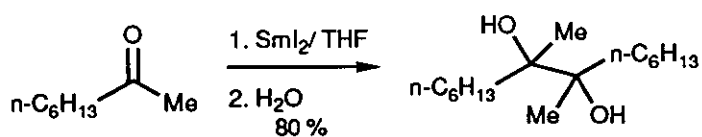
Scheme 44

Evidence for the intermediacy of ketyl radical anions is afforded by the formation of pinacol dimers by the action of samarium (II) iodide on ketones in the absence of a proton

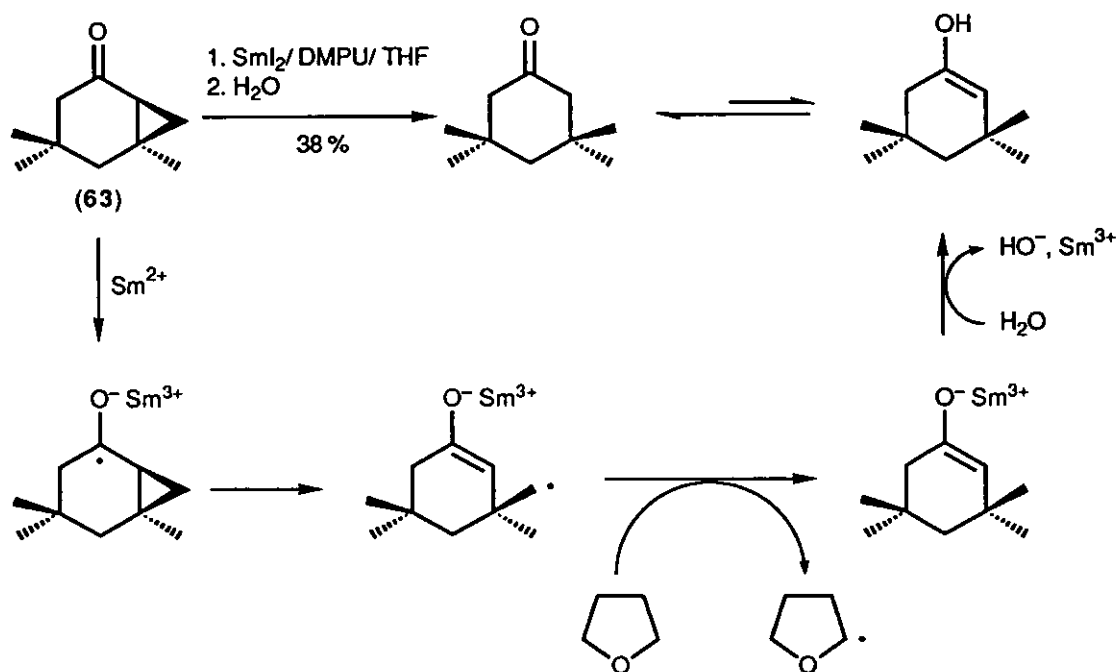
source (Scheme 47)³² and by the partial reduction of the cyclopropyl ketone (63) (Scheme 48).⁴⁰



Scheme 46



Scheme 47



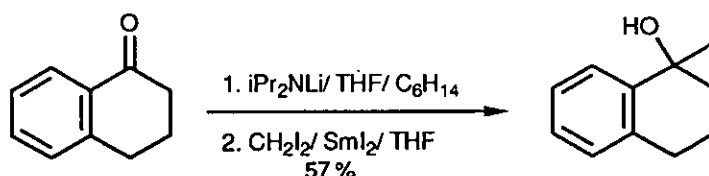
Scheme 48

Thus samarium (II) iodide reduces ketones, bromides and iodides as well as mediating Barbier cyclisations. Evidence suggests that the mechanism is substrate-dependent.³³ However it is clear that for the attempted cyclisation of iodide (58) organosamarium intermediates are not involved, and that the initial SET is onto the ketyl, *not* the iodide.

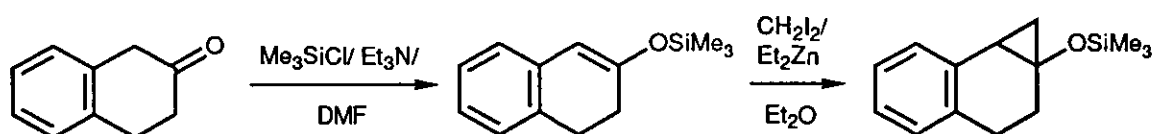
In summary, it may be said that the use of samarium (II) iodide is the method of choice for effecting Barbier cyclisations to cyclopentanol (and, less predictably, to cyclohexanol). Although the mechanism is poorly understood and substrate-dependent, the method is highly selective (often diastereoselective) and high-yielding.

(d) Miscellaneous Methods

[n.1.0]Bicyclo-alkanols (Scheme 49⁴¹) and their trimethylsilyl enol ethers (Scheme 50⁴²) are accessible by carbenoid cyclopropanation. In the former case alkylation and consequent *in situ* Barbier cyclisation is, of course, also a reasonable mechanism.

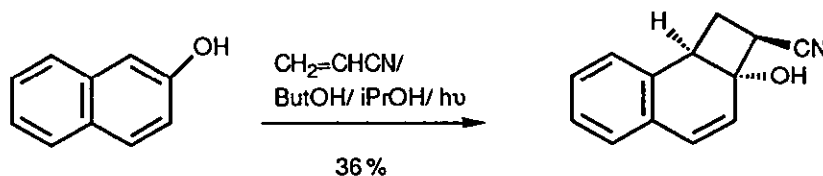


Scheme 49

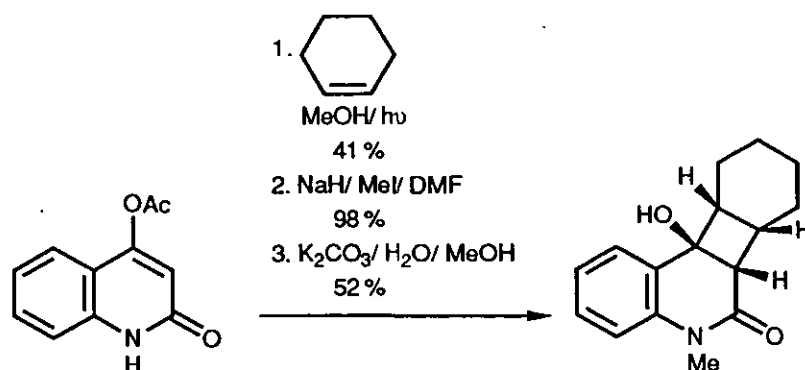


Scheme 50

[n.2.0]Bicyclo-alkanols can be obtained *via* (2+2) photoinduced cycloaddition (Schemes 51⁴³ and 52⁴⁴).



Scheme 51



Scheme 52

Thus there are efficient methods for the synthesis of bridgehead bicyclic cyclopropanols, cyclobutanols, cyclopentanols (and cyclohexanols). Ring opening of these alcohols via β -scission of the derived alkoxy radicals affords ring expansion by one, two, three (and four) carbons respectively.

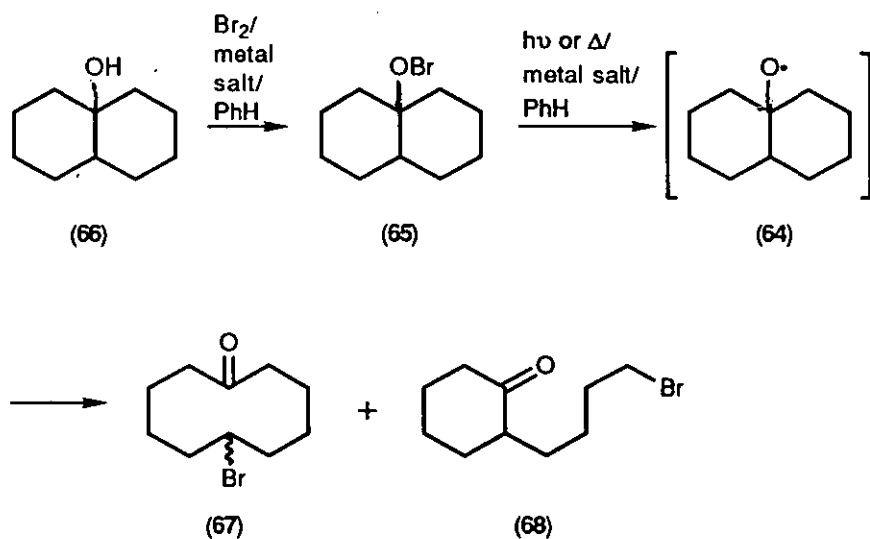
1.5.2 Ring Opening of the Tertiary Bicyclic Alcohol

(a) Proven Methods

The driving force for the β -scission of tertiary alkoxy radicals (**20**) is the formation of a strong ketone C=O bond. The direction of β -scission in simple tertiary bicyclic alcohols depends on the relative stability of the resultant alkyl radical.⁴⁵ Regioselectivity of β -scission of 9-decalinoxyl radicals (**64**) has been investigated.¹⁶ When the hypobromite (**65**), formed by exposure of 9-decalinol (**66**) to bromine, is heated or irradiated with a suitable light source, a mixture of bromoketones (**67**) and (**68**) is obtained (Scheme 53).

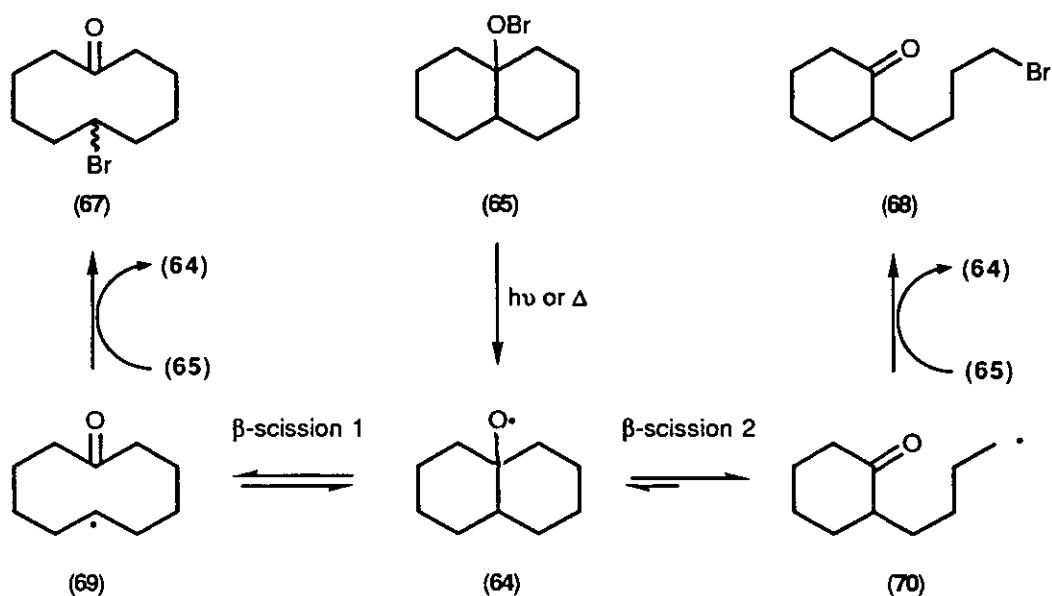
As demonstrated by the results shown below, within the limits of experimental error, the product distribution is independent of whether *cis*- or *trans*- 9-decalinol is used [implying that stereoelectronic effects are unimportant in determining regioselectivity of β -scission of 9-decalinoxyl radicals (**64**)], and of the nature of the metal salt.

The results also show that bromoketone (**67**) is the predominant product at low temperature, and that bromoketone (**68**) is the predominant product at high temperature. The temperature-dependence of the product distribution is readily rationalised (Scheme 54). The alkoxy radical (**64**) can undergo fast, reversible β -scission to afford secondary alkyl radical (**69**), which affords bromoketone (**67**) by group transfer. The alkoxy radical (**64**) can also undergo slow, irreversible (under the conditions of the reaction) β -scission to afford primary alkyl radical (**70**), which affords bromoketone (**68**) by bromine-transfer. The temperature-dependence of the product distribution is a consequence of competition between the trapping of radicals (**69**) and (**70**) and their interconversion *via* alkoxy radical (**64**).



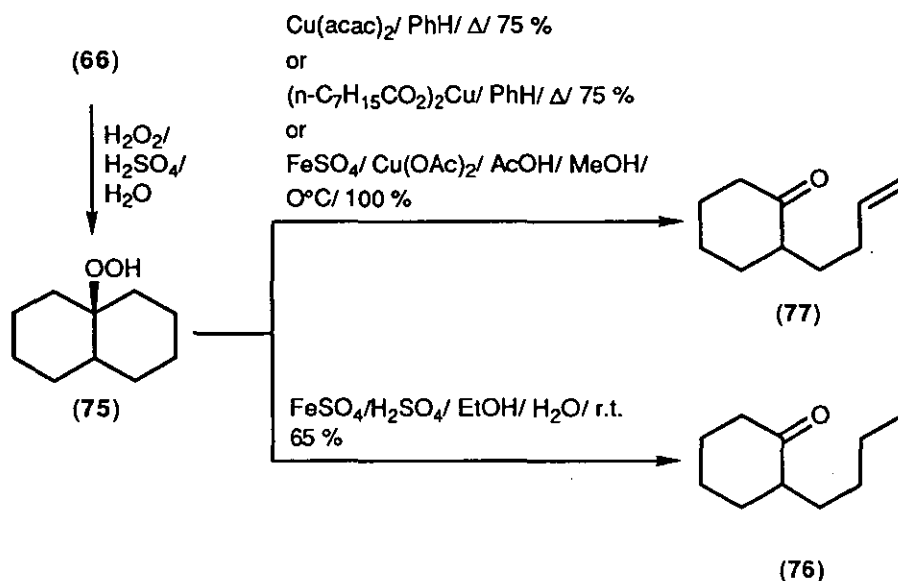
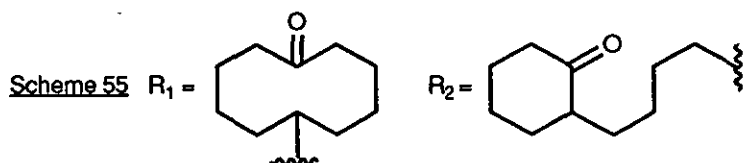
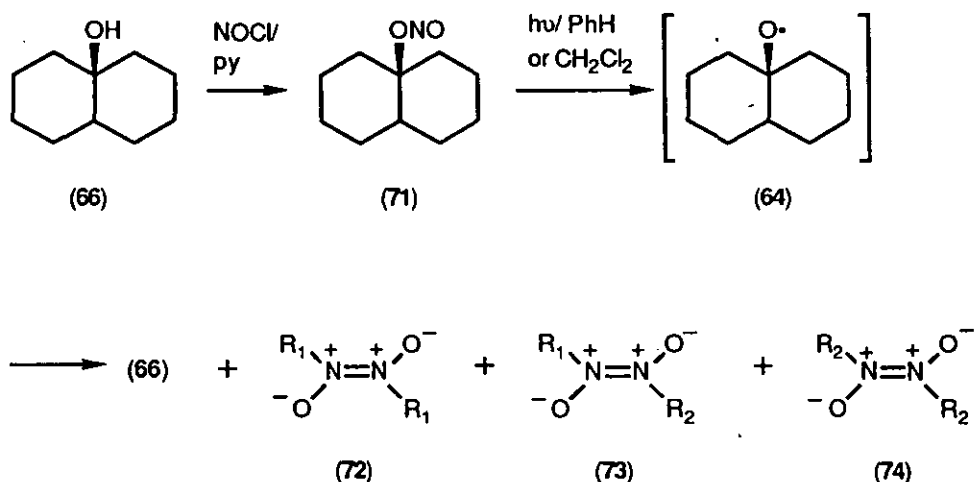
Scheme 53

<u>Isomer</u>	<u>Temperature/°C</u>	<u>Metal Salt</u>	<u>Relative Yield</u>	
			(67)/ %	(68)/ %
trans	0	AgOAc	100	0
cis	0	AgOAc	95	5
cis	50	AgOAc	80	20
cis	50	HgO	85	15
cis	0	HgO	100	0
cis	81	HgO	10	90



Scheme 54

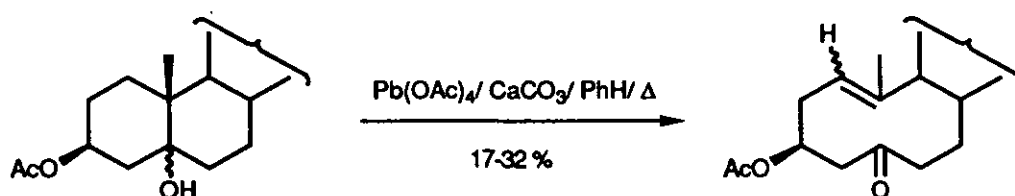
A similar temperature-dependence is observed in photolysis of the nitrite ester of 9-decalinol (**71**) (Scheme 55). The product distribution is more complex owing to dimerisation of the nitroso products. 9-Decalinol (**66**) is produced as a result of hydrogen-transfer from the solvent to the alkoxyl radical (**64**). As might be expected, nitroso compound (**72**) predominates at low temperature, whereas nitroso compound (**74**) predominates at higher temperatures.



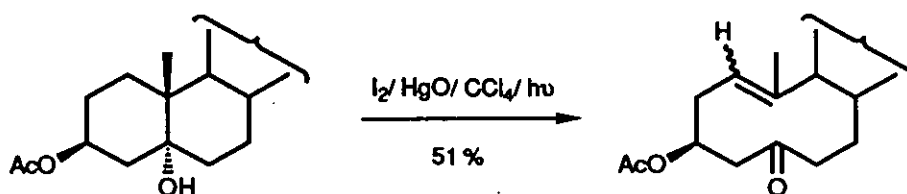
Scheme 56

No ring expansion is observed in the metal-catalysed homolysis of tertiary alkyl hydroperoxide (75) (Scheme 56). This implies that the trapping reactions of alkyl radical (70), viz. hydrogen-abstraction from the solvent to afford ketone (76), and copper (I) oxidation to afford enone (77), are faster than cyclisation to alkoxy radical (64). It is also implicit that the latter is faster than the former.

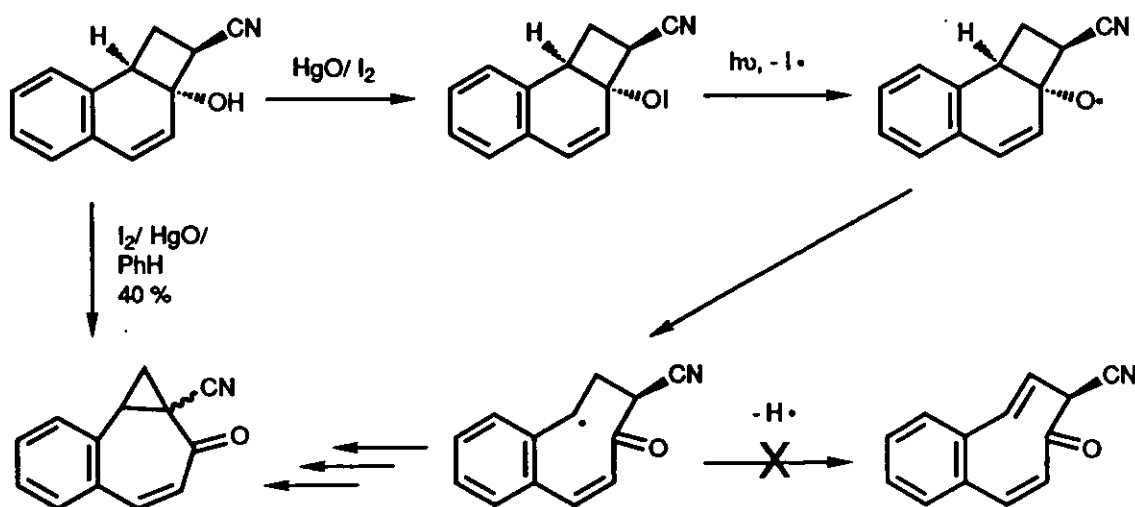
There are a number of examples in the literature of regiospecific ring opening of bridgehead tertiary bicyclic alcohols (23). The ring opening of 3 β -acetoxy-cholestan-5 β -ol and its 5 α -isomer (Scheme 57) proceeds *via* homolysis of a lead (IV) isomer [24, W = Pb(OAc)₃].⁴⁶ The reagent employed, lead (IV) acetate, has the obvious disadvantage of a lack of selectivity. A similar reaction occurs when hypoiodites (24, W = I) are photolysed (Scheme 58).⁴⁷



Scheme 57

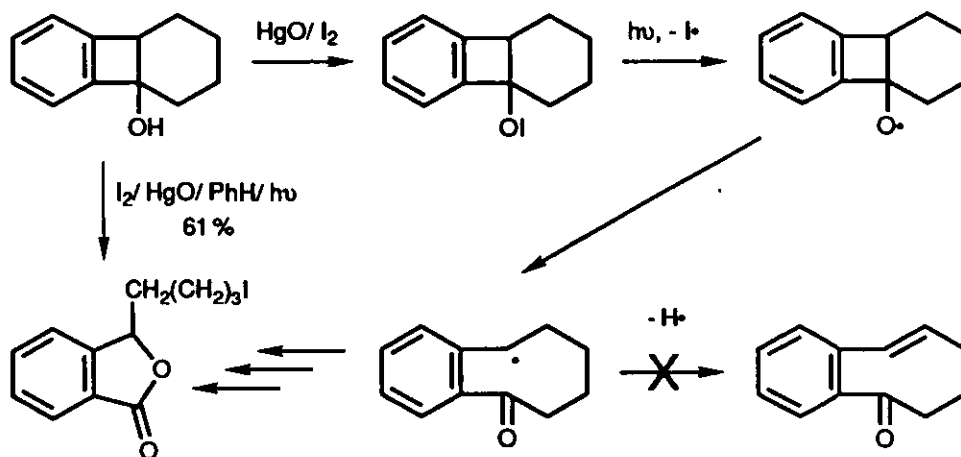


Scheme 58

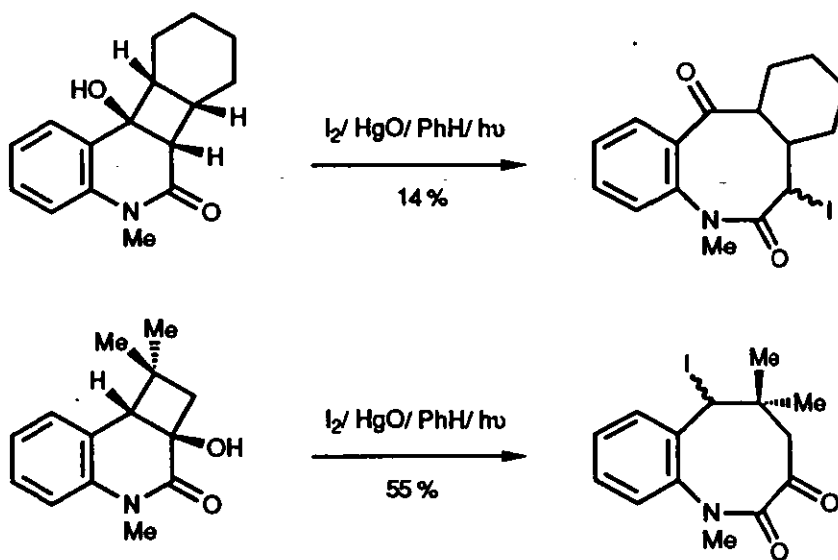


Scheme 59

Alkoxy radicals (20) can undergo β -scission to give a benzylic radical (Schemes 59⁴⁸ and 60⁴⁹), but the course of the reaction is not always simple. The hypiodite method has been applied to benzoheterocycles (Scheme 61^{44,50}).

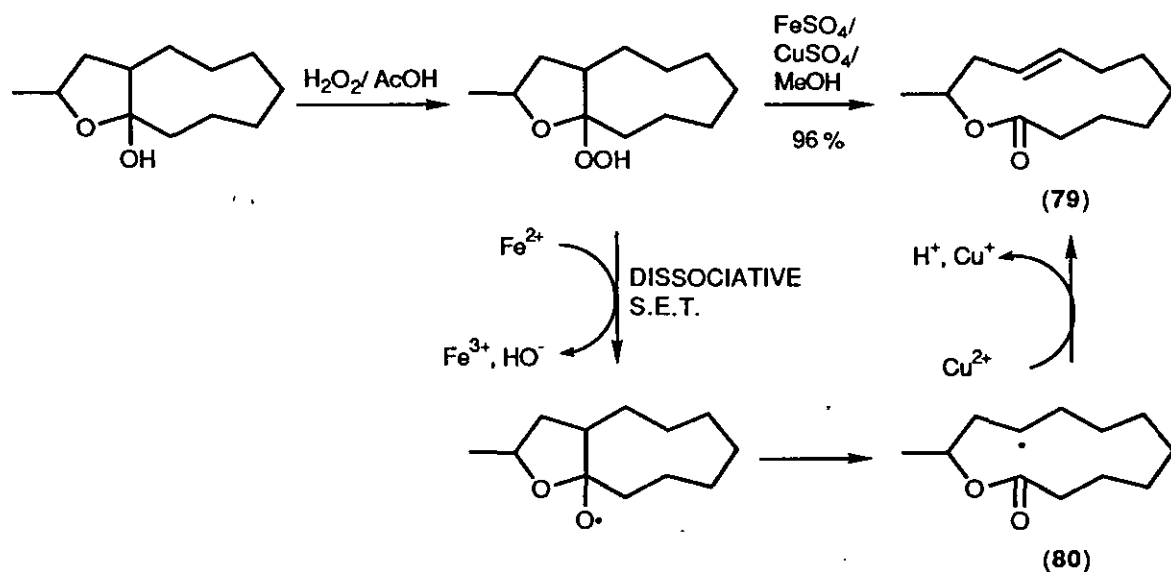


Scheme 60



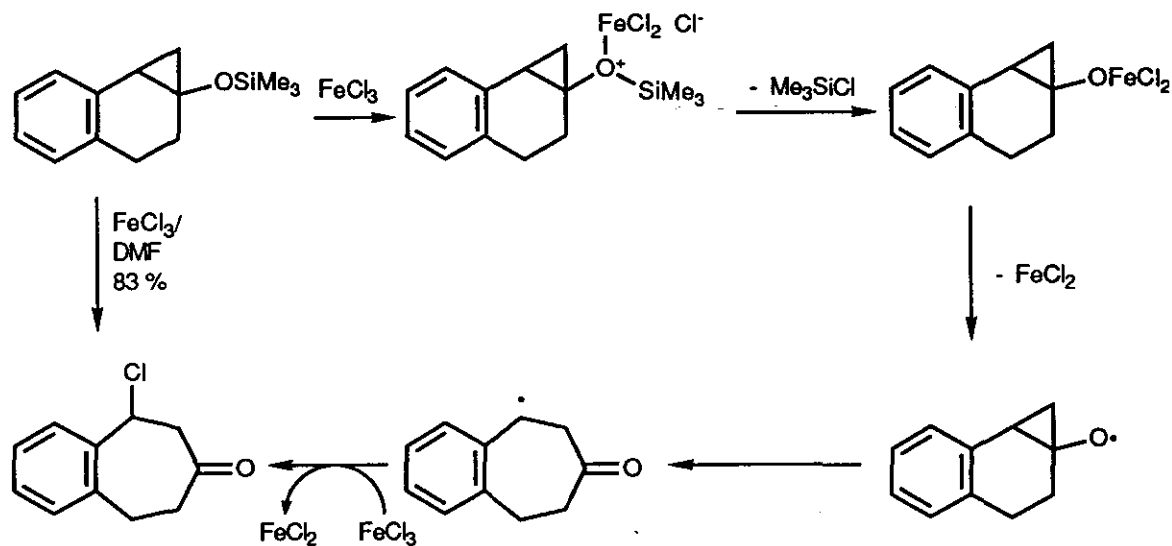
Scheme 61

The classical application of the use of hypiodites to ring opening, and indeed of Type 1 ring expansion *via* transient alkoxy radicals, is the synthesis of exaltone (78, $\text{R} = \text{H}$) and (\pm)-muscone (78, $\text{R} = \text{Me}$) from the commercially available cyclodecanone (Scheme 62⁵¹). If the hypiodite is generated with iodobenzene diacetate, rather than mercuric oxide, tungsten lamps may be used in place of high pressure mercury lamps (Scheme 63²⁶). This obviates the need for non-standard glassware.



Scheme 64

Trimethylsilyl ethers (24, $\text{W} = \text{SiMe}_3$) afford ring-expanded products when treated with iron (III) chloride or copper (II) chloride (Scheme 65⁴²). Neither hydroperoxides nor trimethylsilyl ethers give group transfer products (52): neither give chain reactions.

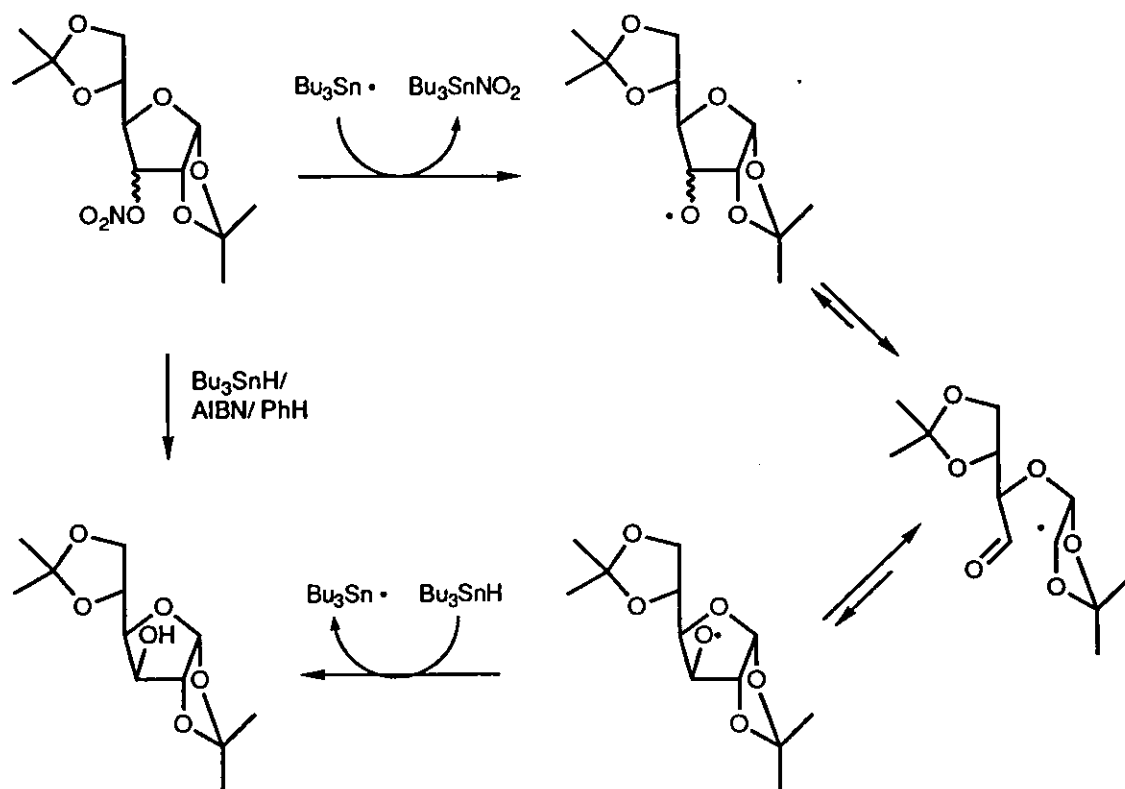


Scheme 65

As may be seen, hypiodites are the most common means of generating alkoxy radicals from bridgehead tertiary bicyclic alcohols (23). Other feasible, but untried methods are outlined below.

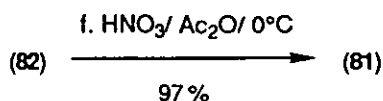
(b) Other Possible Methods

Nitrate esters (**24**, $W = \text{NO}_2$) are conceivable as precursors to alkoxyl radicals (**20**). Alkoxyl radicals may be generated from nitrate esters by tributylstannane (Schemes 66⁵³ and 67⁵³) or by photolysis.⁵³ The mechanisms of reactions between nitro groups and tributylstannane are discussed further in the Appendix at the end of the thesis.

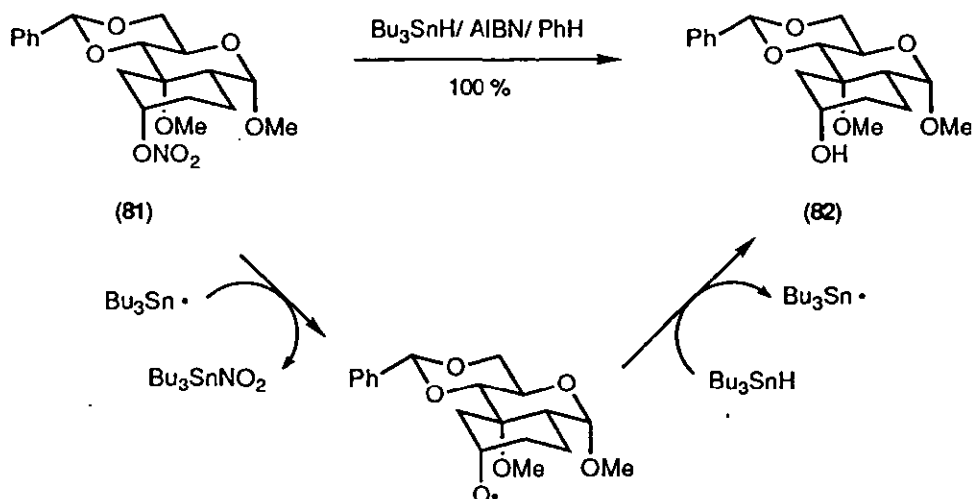


Scheme 66

There are remarkably few methods available for the preparation of nitrate esters.⁵⁴ Esters of primary and secondary alcohols can be prepared using mixtures of nitric acid and, *e.g.* acetic anhydride⁵⁵ (Scheme 68⁵³); esters of tertiary alcohols are not stable under the conditions.

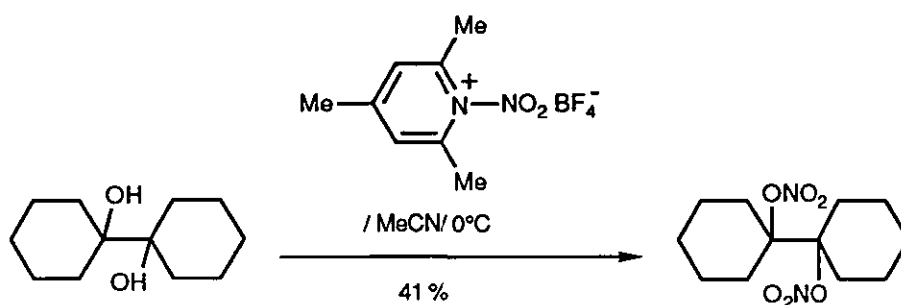


Scheme 68



Scheme 67

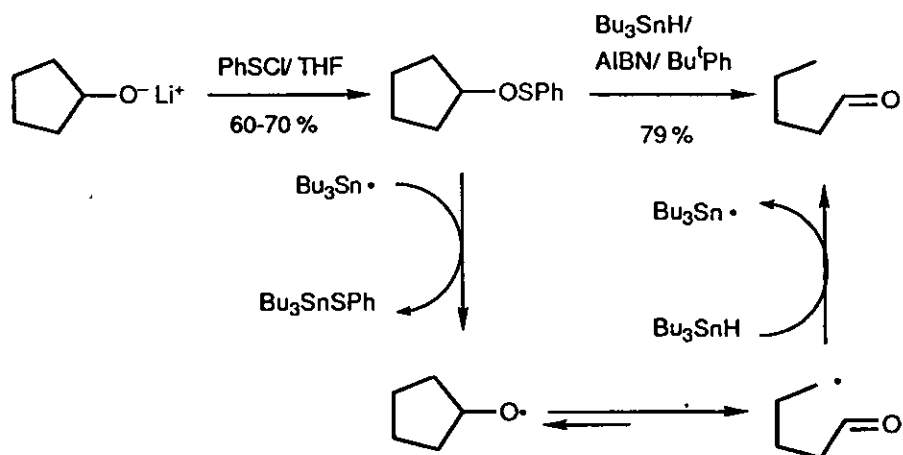
N-Nitrocollidinium tetrafluoroborate effects nitrations of primary, secondary and tertiary alcohols under essentially neutral conditions (Scheme 69⁵⁶). *N*-Nitropyridinium tetrafluoroborate and nitronium tetrafluoroborate itself also effect nitrations, but are less mild reagents.⁵⁴



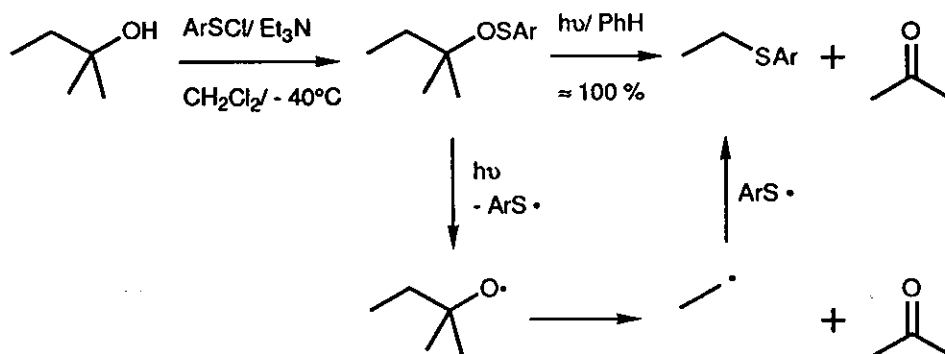
Scheme 69

O-Alkyl benzenesulphenates (**24**, W = SPh) are also conceivable as a precursor to alkoxyl radicals (**20**). *O*-Alkyl benzenesulphenates are readily prepared from the corresponding lithium alkoxide⁵⁷ or from the alcohol.⁵⁸ *O*-Alkyl *p*-nitrobenzenesulphenates are more thermally stable. Benzenesulphenates afford alkoxyl radicals upon treatment with tributylstannane (Scheme 70⁵⁷), or upon photolysis (Scheme 71⁵⁸).

Neither nitrate esters (**24**, W = NO₂), nor alkyl benzenesulphenates (**24**, W = SPh), of tertiary bridgehead bicyclic alcohols have been prepared. Consequently, neither "ester" has been used as a precursor to the derived alkoxyl radicals (**20**).



Scheme 70



Scheme 71 $\text{Ar} = \text{Ph}, p\text{-O}_2\text{NC}_6\text{H}_4$

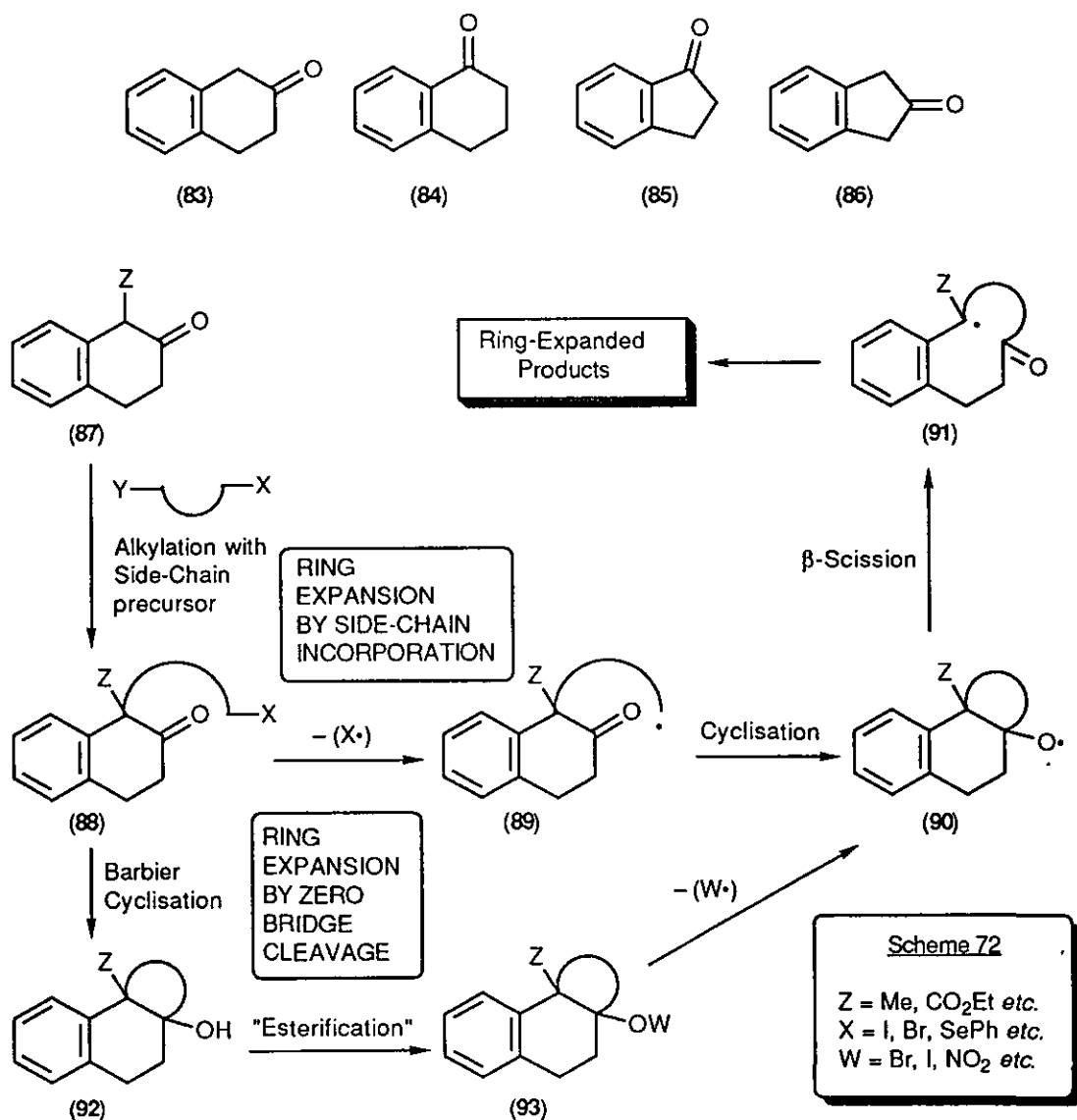
Conclusion

From the above literature survey, it is evident that there is excellent precedence for the research which is discussed in the next section.

2. Discussion

2.1 Introduction

As stated in the conclusion to the Introduction to this thesis (section 1), there is excellent precedence for the ring expansion of benzocyclic ketones, *via* Side-Chain Incorporation and *via* Cleavage of the Zero Bridge in Bicycles. The commercially-available benzocyclic ketones 2-tetralone (83), 1-tetralone (84), 1-indanone (85) and 2-indanone (86) were chosen as substrates, upon which to develop the ring expansion methods. It is apparent that the ability to alkylate such ketones is a prerequisite to ring expansion by either method (See section 1.3, especially schemes 4 and 5).



Scheme 72 shows the synthetic strategy for the ring expansion of 2-tetralone (83). A derivative (87) is monoalkylated, with a side-chain precursor, to afford the tetralone (88), which is a suitable substrate for ring expansion by both methods (see section 1.3). For ring

expansion by Side-Chain Incorporation, the derived primary alkyl radical (89) cyclises onto the ketone moiety to afford the alkoxyl radical (90), which should undergo regiospecific β -scission to the benzylic radical (91). This radical should then afford ring-expanded products. For ring expansion by Cleavage of the Zero Bridge in Bicycles, Barbier cyclisation of derivative (88) should afford bridgehead bicyclic alcohol (92), whose derivative (93) should afford the alkoxyl radical (90), which should afford ring-expanded products *via* the radical (91). A similar strategy can be envisaged for benzocyclic ketones (84), (85) and (86).

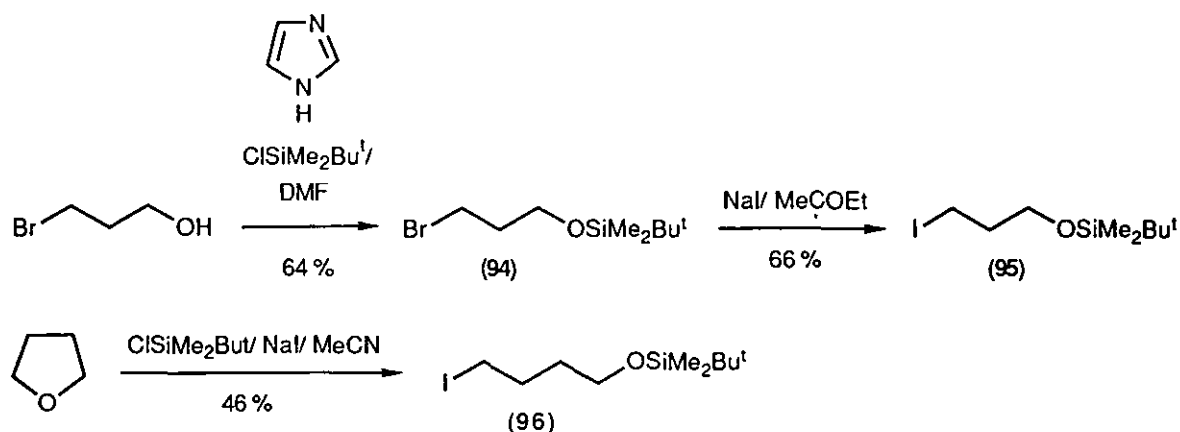
The synthesis of compounds analogous to structure (88) by alkylation of the benzocyclic ketones (83), (84), (85) and (86), or suitably functionalised derivatives thereof, was not a trivial task. Alkylation *via* the enamines, enolates and trimethylsilyl enol ethers of the ketones was generally unsuccessful (Section 2.2). Alkylation of 2-tetralone (83), *via* enamines and *via* enolates, with reactive electrophiles, is widely reported as being successful. However, the success of such methods of alkylation does not extrapolate to the use of less reactive electrophiles, contrary to suggestions in the literature.⁵⁹ Other workers have observed similar failures.⁶⁰ Fortunately, the alkylation of the derived β -keto esters (*e.g.* 87, Z = CO₂Et) was invariably successful and furnished compounds whose ring expansion was attempted, with varying degrees of success (Section 2.3 and 2.4).

Having established the methods, the ring expansion of benzoheterocycles was investigated. Ring expansion by Side-Chain Incorporation was applied to benzofurans (Section 2.5) with some success. The synthesis of six-membered-ring benzoheterocycles proved problematic (Section 2.6). The ring expansion of oxindoles was achieved, but not by the expected route (Section 2.7). Attempts to generate nitrate esters of tertiary alcohols as suitable precursors to alkoxyl radicals failed (Section 2.8).

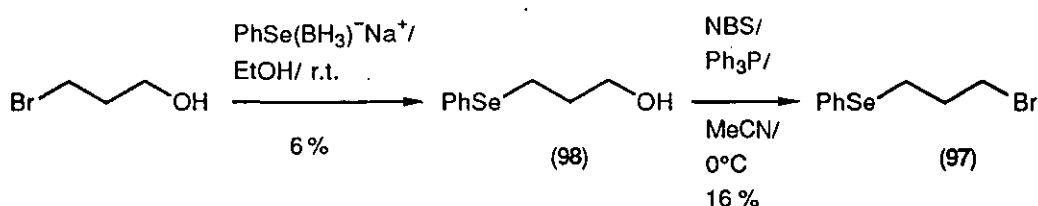
2.2 Attempted Alkylation of Benzocyclic Ketones

The attempted alkylations (and acylations) listed in the following subsection failed (unless otherwise stated), giving either recovery of starting materials or mixtures of intractable products. Had the alkylations been successful, some of the products would have been elaborated to substrates suitable for ring expansion [*e.g.* (88)]. Most of the alkylating agents used are commercially available [*e.g.* X(CH₂)_nX (X = Br, I; n = 1, 3, 4)], except 1-bromo-3-(*t*-butyldimethylsilyloxy)propane⁶¹ (94), 1-iodo-3-(*t*-butyldimethylsilyloxy)propane⁶¹ (95), 1-iodo-4-(*t*-butyldimethylsilyloxy)butane^{61,62} (96) (Scheme 73), and 1-bromo-3-benzeneselenylpropane⁶³ (97) (Scheme 74). The bromide (97) was synthesised by bromination of 1-benzeneselenylpropan-3-ol (98), which was obtained by treatment of the commercially-available 3-bromopropan-1-ol with sodium benzeneselenide, a potent S_N2 nucleophile.⁶⁴ This last species can be generated *in situ* by reduction of the commercially-available diphenyl diselenide (Scheme 75) with sodium (with sonication,⁶³ with photolysis

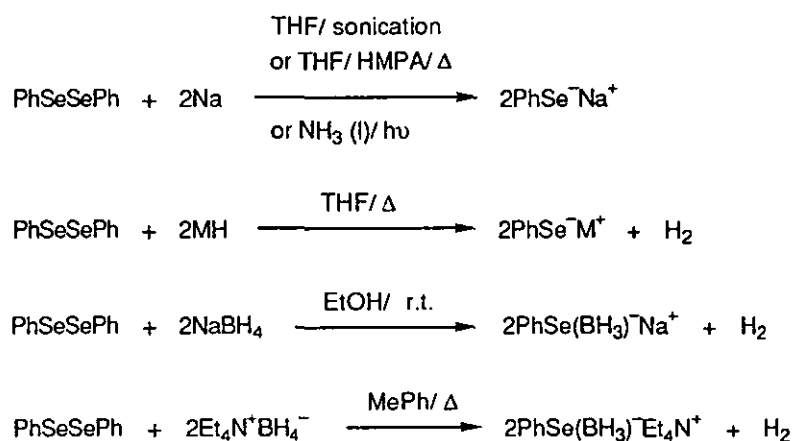
in liquid ammonia,⁶⁵ or at reflux⁶⁶), with hydride,⁶⁷ or with borohydride.⁶⁸ The last method was found to be the most convenient, even though the benzeneselenide is produced as the borane complex, which is reported to be less reactive.



Scheme 73



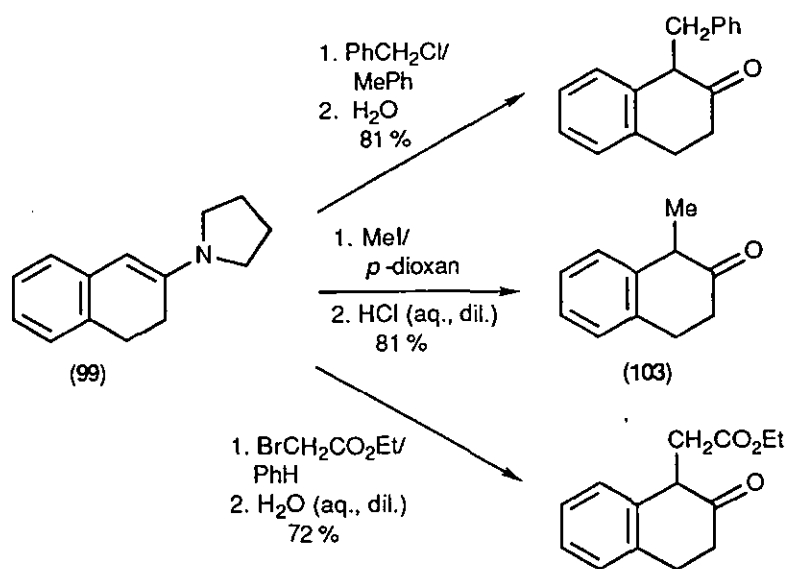
Scheme 74



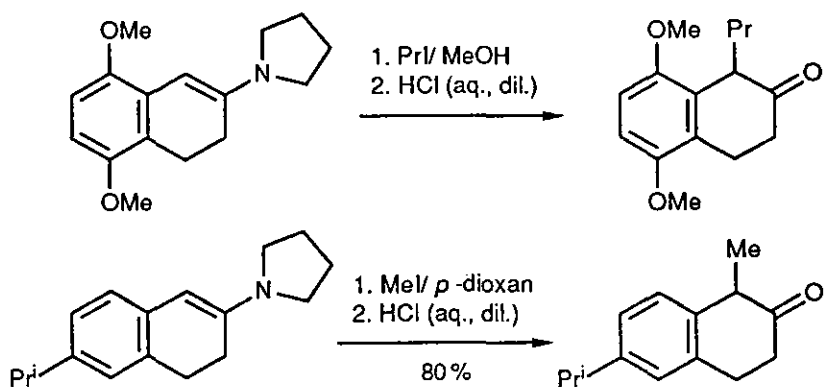
Scheme 75 M = Na, K

2.2.1 Alkylation *via* Enamines

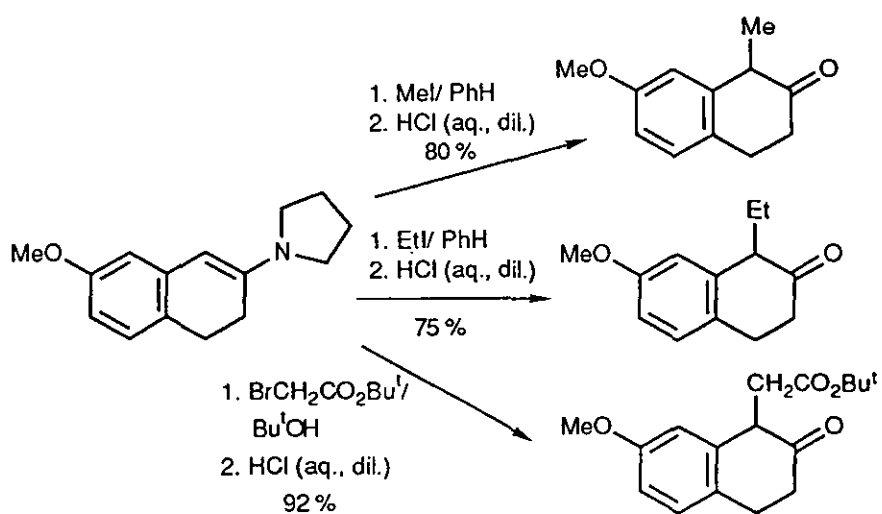
A number of alkylations of the pyrrolidine enamines of 2-tetralone⁵⁹ (83) and its derivatives are known (Schemes 76,^{59,69,70} 77,^{71,72} and 78^{73,74}).



Scheme 76



Scheme 77



Scheme 78

The enamines (99), (100), (101) and (102)* were prepared by the literature procedures^{59,75} (Scheme 79) and various alkylations were attempted with them. The methylation of 1,2-dihydro-3-pyrrolidinynaphthalene⁵⁹ (99) was successfully repeated, giving 1-methyl-2-tetralone (103) (34 %) on hydrolysis. However alkylations attempted under the following conditions failed:

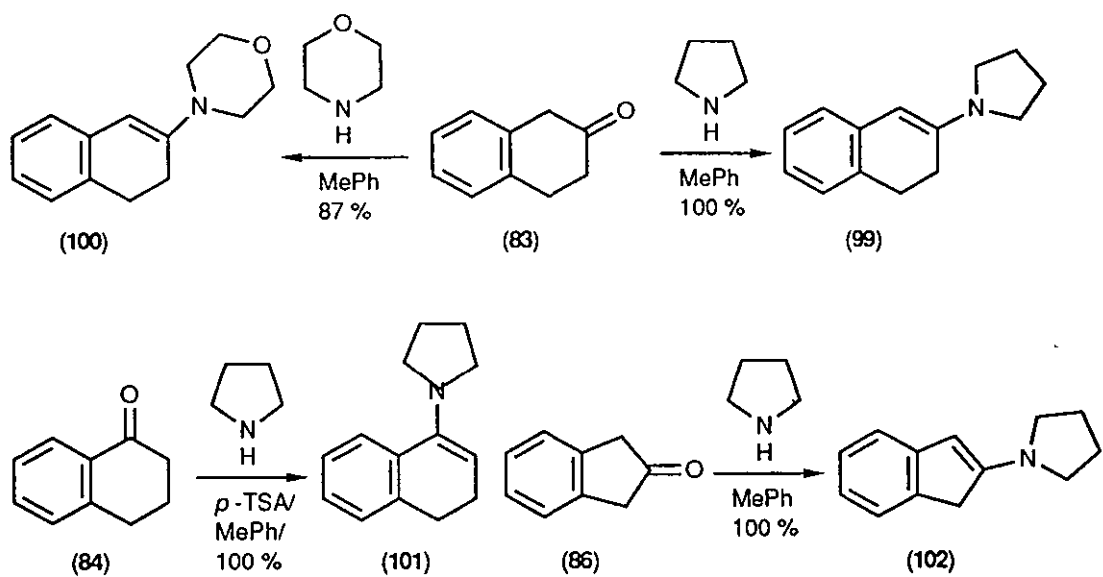
Enamine	Conditions
(99)	1. <i>o</i> -bromobenzyl bromide/ MePh/ Δ ; 2. HCl (aq., dil.)/ Δ . 1. PhSCH ₂ Cl/ <i>p</i> -dioxan/ Δ ; 2. HCl (aq., dil.)/ Δ . 1. I(CH ₂) ₄ OSiMe ₂ But/ <i>p</i> -dioxan/ Δ ; 2. HCl (aq., dil.)/ Δ . 1. BrCH ₂ CO ₂ Et/ MePh/ Δ ; 2. HCl (aq., dil.)/ Δ . <i>N</i> -methyloxazolidine/ Me ₃ SiCl/ MeCN/ r.t. (polymerises). <i>N</i> -methyloxazolidine/ Me ₃ SiCl/ CH ₂ Cl ₂ / -110°C (polymerises). 1. Ac ₂ O/ <i>p</i> -dioxan/ Δ ; 2. HCl (aq., dil.)/ Δ . 1. ClCO ₂ Et/ MePh/ Δ ; 2. HCl (aq., dil.)/ Δ .
(100)	1. AcCl/ Et ₃ N/ MePh/ Δ ; 2. HCl (aq., dil.)/ Δ . 1. AcCl/ <i>p</i> -dioxan/ Et ₃ N/ Δ ; 2. HCl (aq., dil.)/ Δ . 1. Cl(CH ₂) ₃ COCl/ Et ₃ N/ MePh/ Δ ; 2. HCl (aq., dil.)/ Δ .
(101)	1. ClCO ₂ Et/ MePh/ Δ ; 2. HCl (aq., dil.)/ Δ .
(102)	1. MeI/ <i>p</i> -dioxan/ Δ ; 2. HCl (aq., dil.)/ Δ . 1. Br(CH ₂) ₃ OSiMe ₂ Bu ⁴ / <i>p</i> -dioxan/ Δ ; 2. HCl (aq., dil.)/ Δ . 1. BrCH ₂ CO ₂ Et/ EtOH/ Δ ; 2. HCl (aq., dil.)/ Δ .

Following a general lack of success the method was abandoned in favour of alkylations *via* the enolate. In conclusion, it appears that alkylation *via* the enamine is successful, generally, only when the electrophile is small and/or particularly reactive. Hence it seems likely that approach of the electrophile to the enamine is sterically hindered. The stability of the enamines (due to conjugation with the arene moiety) may also be a problem.

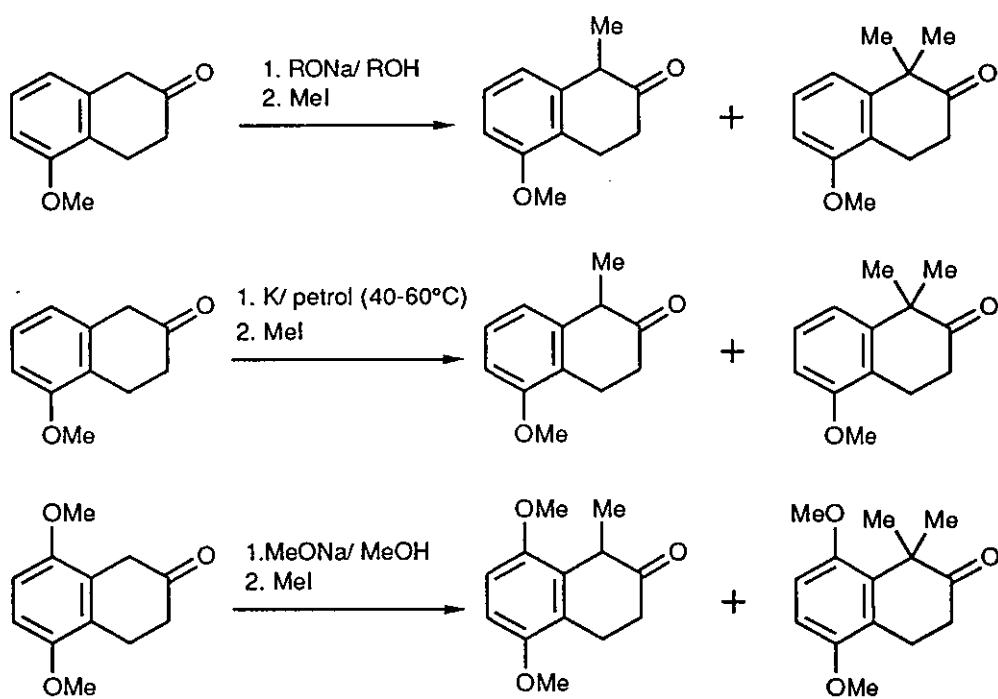
2.2.2 Alkylation *via* Enolates

A number of examples of alkylations of 2-tetralone (83), and its derivatives, *via* the enolate have been reported (Schemes 80⁷⁶ and 81⁷⁷), suggesting this route as a means of circumventing the difficulties presented by the enamine method of alkylation. Several of these alkylations afford 1,1-dialkylated products in addition to, or in preference to, the expected monoalkylated product: presumably this arises due to equilibration of the respective enolates *via* proton-transfer.^{76a}

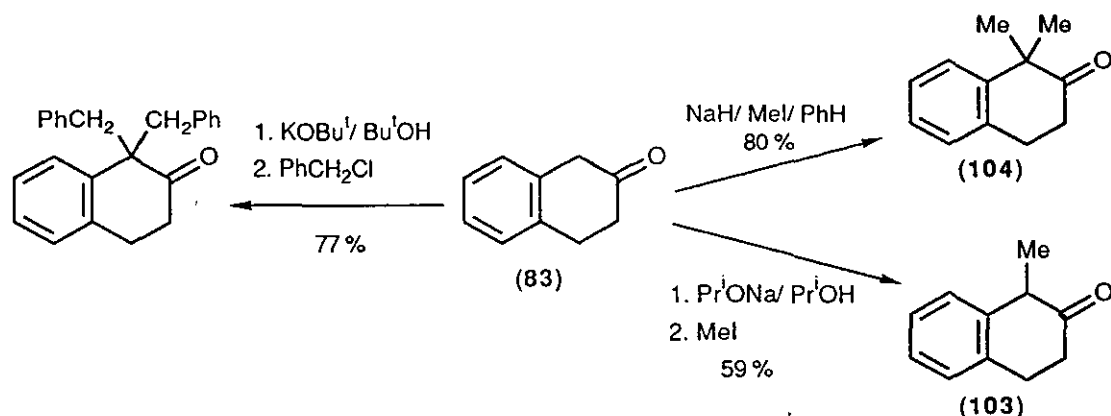
* See page 100: enamine (102) was not unambiguously characterised.



Scheme 79



Scheme 80 R = Me, Pr^j



Scheme 81

Alkylations of 2-tetralone (83) under the following conditions were attempted without success:

1. $\text{NaH} / \text{HMPA} / \text{THF}$; 2. $\text{Br}(\text{CH}_2)_3\text{Br} / \Delta$.
1. $\text{NaH} / \text{DMF} / \text{THF}$; 2. $\text{Br}(\text{CH}_2)_3\text{Br} / \Delta$.
1. NaH (2 equivalents) / THF ; 2. $\text{Br}(\text{CH}_2)_3\text{OH} / \Delta$.
1. NaH / THF ; 2. $\text{Br}(\text{CH}_2)_3\text{OSiMe}_2\text{But} / \Delta$.
1. $\text{LDA} / \text{C}_6\text{H}_{14} / \text{THF} / -78^\circ\text{C}$; 2. ICH_2Cl .
1. $\text{LDA} / \text{C}_6\text{H}_{14} / \text{THF} / -78^\circ\text{C}$; 2. BusI .
1. $\text{LDA} / \text{C}_6\text{H}_{14} / \text{THF} / -78^\circ\text{C}$; 2. MeI .

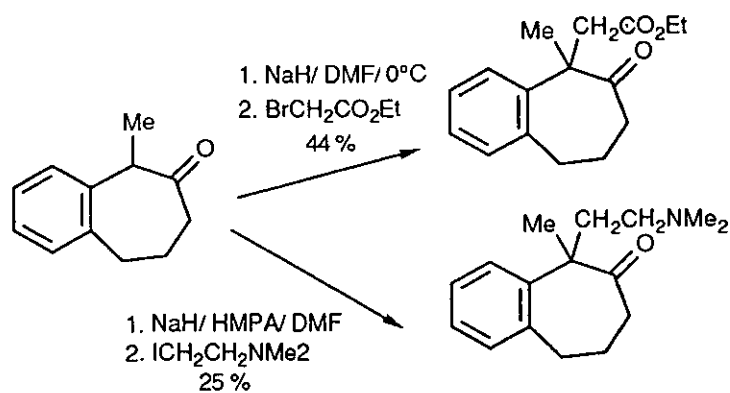
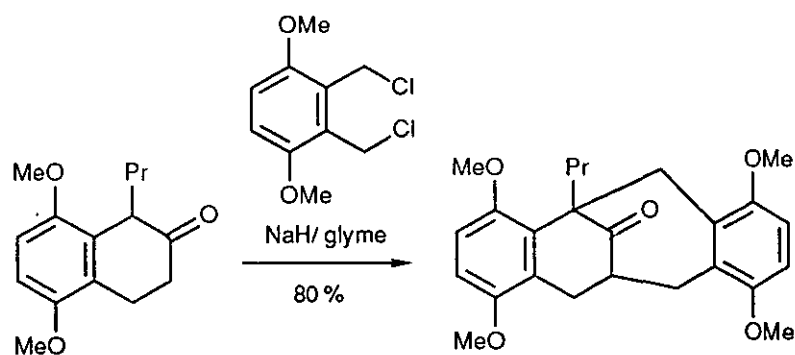
Alkylations of 1-tetralone (84) were attempted under the following conditions without success:

1. NaH / THF ; 2. $\text{ClCO}_2\text{Et} / \Delta$.
1. NaH / THF ; 2. $\text{Br}(\text{CH}_2)_3\text{Cl} / \Delta$.

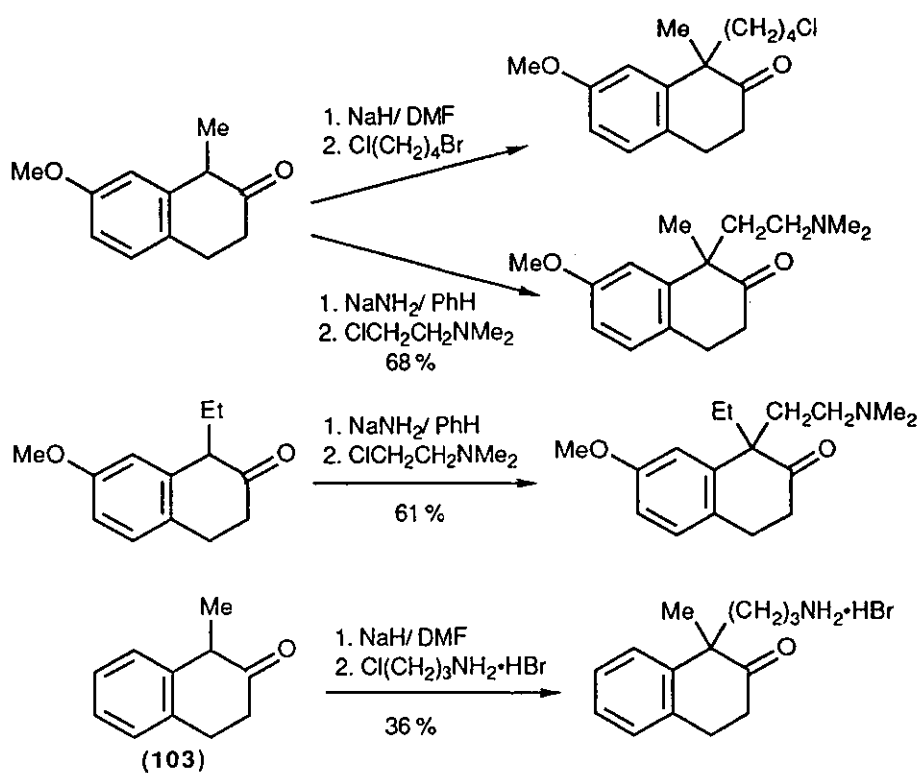
There are several examples of alkylation of 1-alkyl-2-tetralones and 1-alkyl-2-benzosuberones in the literature (Schemes 82^{71,78} and 83^{60,73,79}), suggesting such monoalkyl compounds are more readily alkylated than the parent 2-tetralones and 2-benzosuberones.

Alkylation of 1-methyl-2-tetralone⁵⁹ (103) under the following conditions was attempted without success:

1. NaH / DMF ; 2. $\text{Cl}(\text{CH}_2)_3\text{Br} / \text{r.t.}$.
1. $\text{LDA} / \text{C}_6\text{H}_{14} / \text{THF} / -78^\circ\text{C}$; 2. $\text{Cl}(\text{CH}_2)_3\text{Br}$.
1. $\text{LDA} / \text{C}_6\text{H}_{14} / \text{THF} / -78^\circ\text{C}$; 2. $\text{I}(\text{CH}_2)_4\text{OSiMe}_2\text{Bu}^t$.

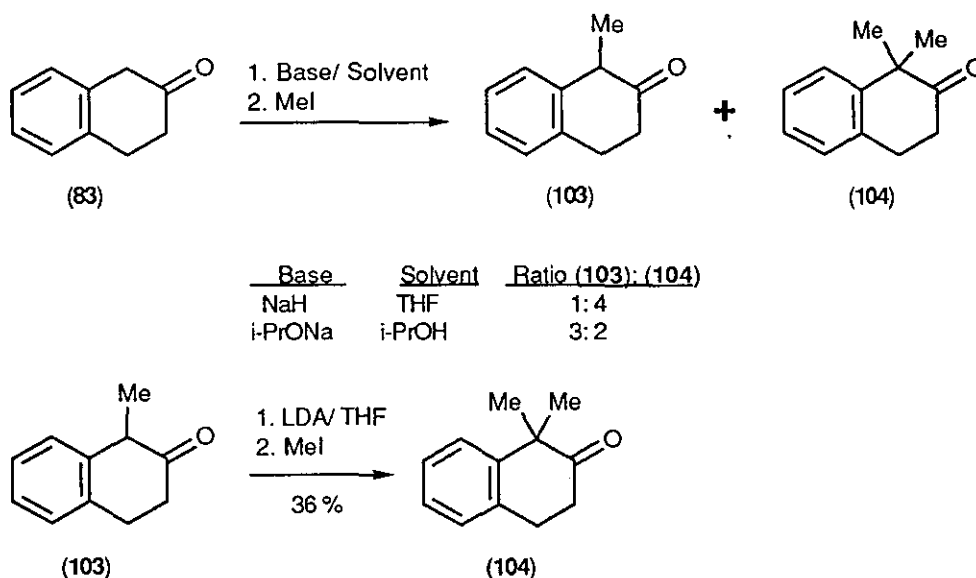


Scheme 82



Scheme 83

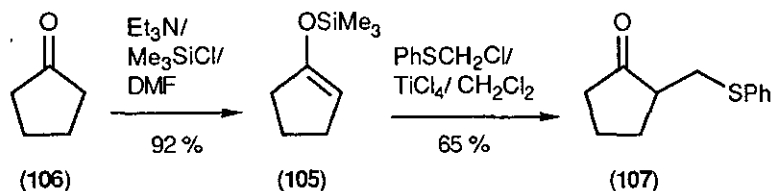
The only alkylations successfully achieved were methylation of 2-tetralone (**83**) and of 1-methyl-2-tetralone (**103**) (Scheme 84): the former afforded a mixture of 1-methyl-2-tetralone (**103**)⁵⁹ and 1,1-dimethyl-2-tetralone (**104**).^{77b} All other examples of attempted alkylations of these substrates failed. Following a general lack of success the method was abandoned, in favour of alkylations *via* the trimethylsilyl enol ether.



Scheme 84

2.2.3 Alkylation *via* the Trimethylsilyl Enol Ether

Trimethylsilyl enol ethers [*e.g.* (**105**)], which are readily accessible from ketones [*e.g.* (**106**)], have been used successfully for a variety of alkylations.⁸⁰ In particular, they can be alkylated with chloromethyl phenyl sulfide, with Lewis acid catalysis, to afford α -phenylthiomethyl ketones⁸¹ [*e.g.* (**107**)] (Scheme 85), which are potential substrates for one-carbon ring expansion (Scheme 86).



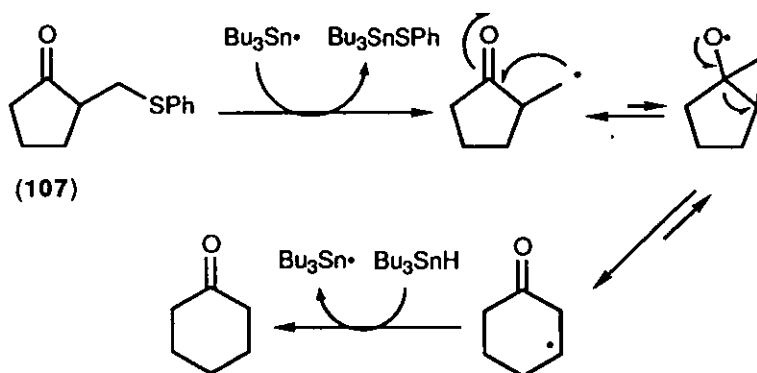
Scheme 85

1,2-Dihydro-3-trimethylsilyloxynaphthalene⁴² (**108**) was prepared from 2-tetralone (**83**) by the literature procedure⁸² (Scheme 87), which depends on the trapping of an enolate

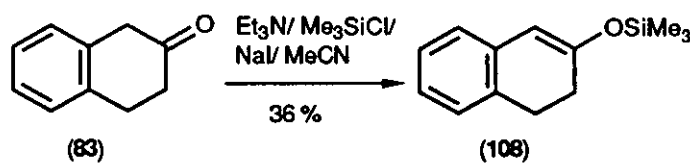
(the thermodynamic enolate in this case) with chlorotrimethylsilane. Alkylation of enol ether (108) under the following conditions failed, affording only the tetralone (83) on work-up:

PhSCH₂Cl/ ZnBr₂/ CH₂Cl₂/ r.t.

PhSCH₂Cl/ TiCl₄/ CH₂Cl₂/ -38°C.



Scheme 86



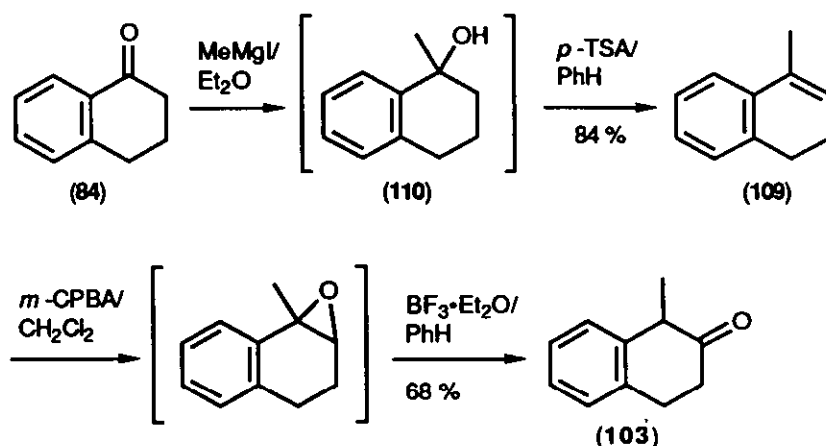
Scheme 87

Again, the method proved unsuccessful, and, following a general lack of success, the method was abandoned, in favour of an indirect method of alkylation. It seems likely that approach of the electrophile to the enol ether is sterically hindered. The stability of the enol ether (due to conjugation with the arene moiety) may also be a problem.

2.2.4 Alkylation *via* an Indirect Route

An indirect method for the preparation of 1-methyl-2-tetralone (103) from 1-tetralone (84), by the bimolecular Barbier (or Grignard) reaction, dehydration, epoxidation, and subsequent rearrangement, has been reported (Scheme 88).^{60,72} The sequence of reactions was partially repeated to afford alkene (109). Attempted epoxidation of the crude alkene (109) using urea-hydrogen peroxide⁸³ gave an intractable mixture of products.

With the success of the alkylation of β -keto esters (section 2.3), this method of alkylation, and the other methods of alkylation [*via* enamines (section 2.2.1), *via* enolates (section 2.2.2), and *via* silyl enol ethers (section 2.2.3)], were not investigated further. With considerable further investigation, it is probable that any or all of these methods of alkylation could be made to work.



Scheme 88

2.3 Ring Expansions of Benzocyclic β -Keto Esters by Side-Chain Incorporation

In general, β -keto esters are easier to alkylate than the parent ketones. The literature¹⁵ suggests that such alkylations are facile. When compared to the successful alkylations of the derived β -keto esters, the reasons for the failure of the alkylations of 2-tetralone (83), 1-tetralone (84), and 2-indanone (86) become even less clear, because the enolates of the derived β -keto esters are even more stable (due to a greater degree of conjugation) and even more sterically hindered (due to the bulk of the ester moiety).

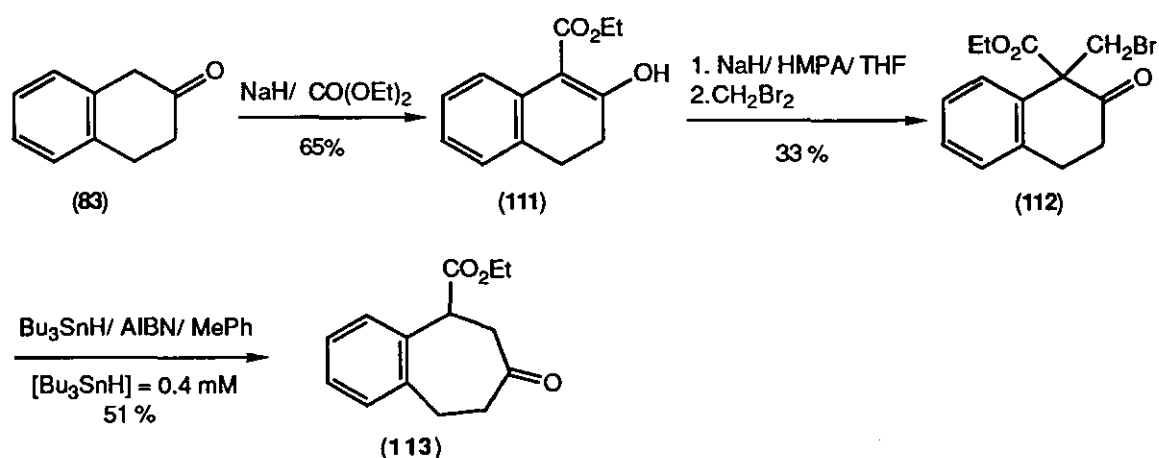
The β -keto esters were prepared from the parent ketones by treatment with sodium hydride or sodium ethoxide in diethyl carbonate. Treatment of the sodium hydride-generated enolates with ethyl chloroformate failed to afford the derived β -keto esters,⁸⁴ as did treatment of the enamines with ethyl chloroformate and subsequent acid hydrolysis.⁸⁵

The enolates of the β -keto esters were generated by sodium hydride in THF in the presence of HMPA or DMPU. The latter co-solvents are believed to enhance the basicity of the hydride ion by complexing with the sodium counterion, thus suppressing ion-pairing effects. Quenching of the resultant enolates with an excess (typically five-fold for α,ω -dibromides, and two-fold for the more reactive α,ω -di-iodides) of α,ω -dihalogenoalkanes afforded α -(ω -halogenoalkyl)- β -keto esters (Cf. 88, Z = CO₂Et). Products of dialkylation (at both ends of the α,ω -dihalide) were completely suppressed (on the basis of TLC and NMR spectroscopy) by the statistical effect. No evidence for the formation of *O*-alkylation products was obtained.

The alkylation products were treated with tributylstannane under various conditions and the results are discussed below.

(a) One-Carbon Ring Expansion of 2-Tetralones

Commercially available 2-tetralone (**83**) was transformed, by a literature procedure,^{85,86} into its fully enolised β -keto ester, ethyl 2-tetralone-1-carboxylate (**111**), which was alkylated with dibromomethane to afford ethyl 1-bromomethyl-2-tetralone-1-carboxylate (**112**). Treatment of the ketone (**112**) with tributylstannane, which was added slowly by syringe pump ([tributylstannane] = 0.4 mM), and AIBN in refluxing toluene afforded ethyl 5,6,8,9-tetrahydrobenzocyclohepten-7-one-5-carboxylate (**113**) as the only product (Scheme 89). The tributylstannane residues were removed by repetitive chromatography (typically three times). This purification procedure was adopted for all subsequent ring expansions (unless otherwise stated).

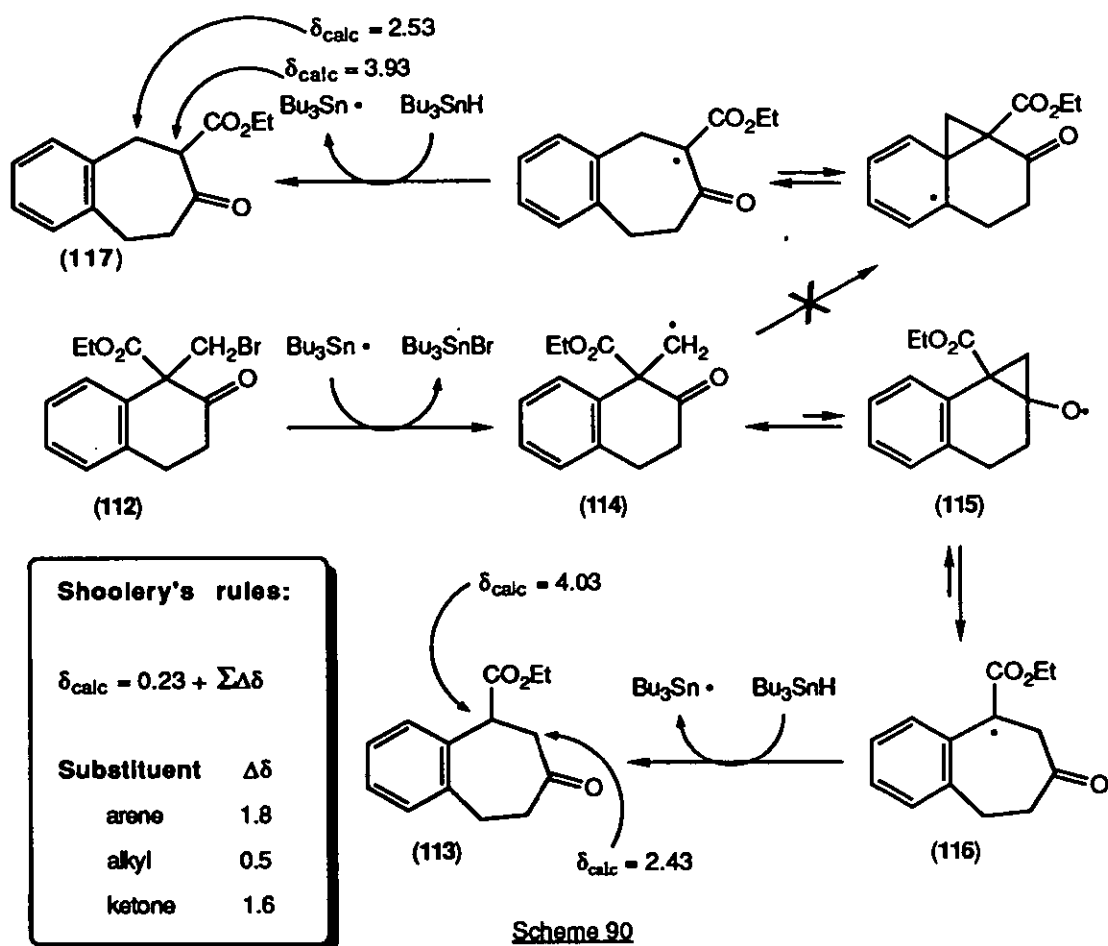


Scheme 89

The mechanism of the reaction is probably straightforward (Scheme 90). The tributylstannyl radical abstracts the bromine from ketone (**112**) to afford a nucleophilic primary alkyl radical (**114**), which cyclises onto the ketone carbonyl to form the alkoxy radical (**115**). This undergoes regioselective β -scission to the benzylic radical (**116**). This radical, which is also stabilised by the ester function, abstracts a hydrogen from tributylstannane, to form the benzosuberone (**113**), and so perpetuates the chain.

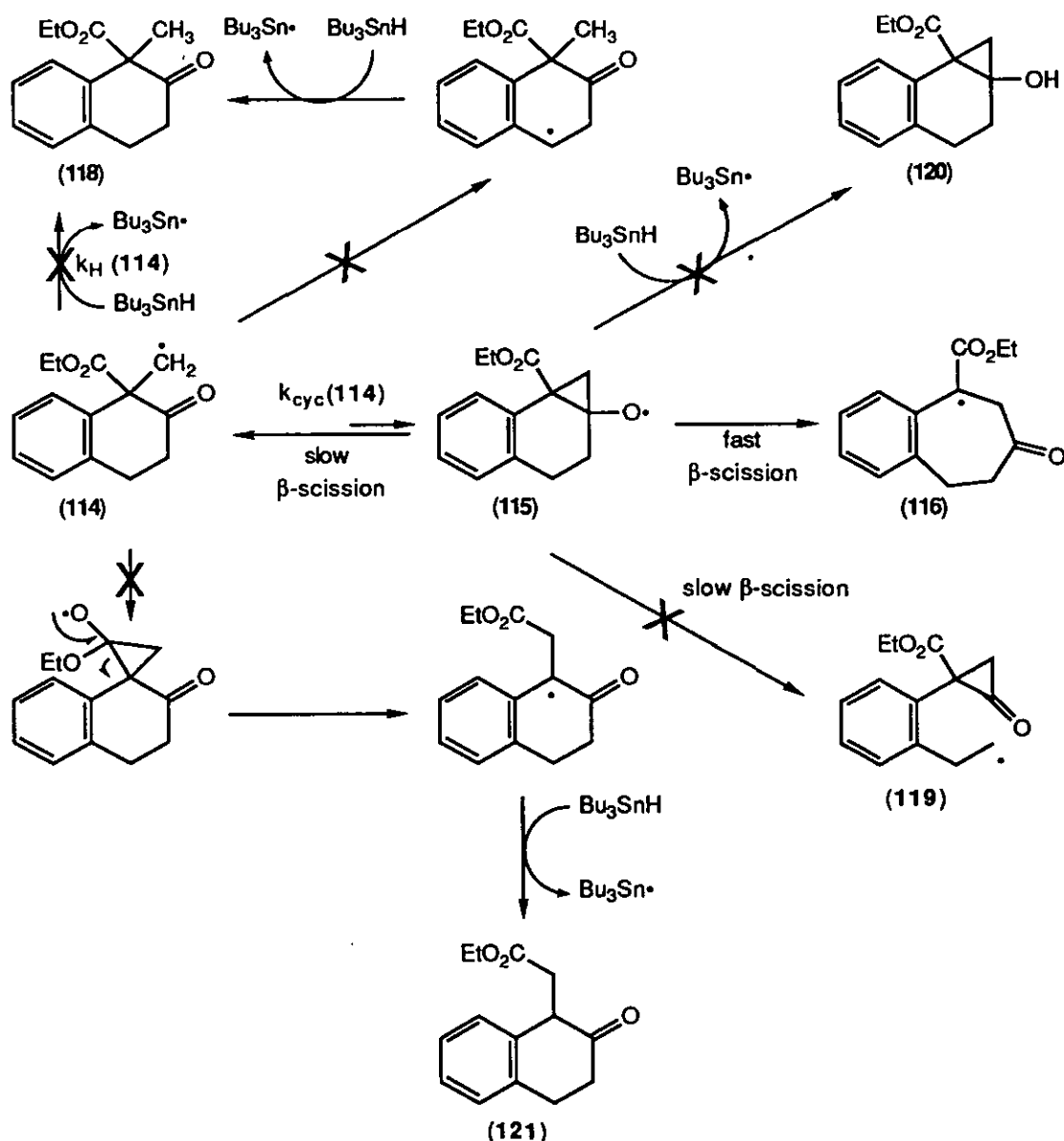
The ¹H and ¹³C NMR spectra of the ring-expanded product are also consistent with the structure of benzosuberone (**117**), which could arise by ring expansion *via* cyclisation of the alkyl radical (**114**) onto the fused arene moiety (See section 2.7 for a precedent). Estimated ¹H NMR spectroscopic shifts shown in Scheme 90 were calculated using Shoolery's rules.⁸⁷ 1-D nOe difference spectroscopy showed that structure (**113**) was correct, rather than structure (**117**). Irradiation at $\delta_H = 4.17$ (corresponding to the resonance of the methine hydrogen) caused nOe enhancement of the intensities of the resonances at $\delta_H = 7.43$ to $\delta_H = 7.19$ (corresponding to the arene hydrogens). Since nOe is active through space over a short range, it follows that the methine group and at least one of the aromatic

hydrogens must be close together in space. Of the two structures, (113) and (117), only structure (113) satisfies this condition. Thus the alkyl radical (114) does not cyclise onto the arene moiety.



Other feasible mechanistic pathways do not appear to occur (Scheme 91). The alkyl radical (114) does not dimerise, presumably due to steric hindrance. Since no direct reduction product (118) is formed, it follows that 1,5-hydrogen abstraction does not occur (also, presumably, on steric grounds). It also follows (a) that the relative rate of reduction of the alkyl radical (114), $k_{\text{H}}(114)[\text{Bu}_3\text{SnH}]$, is much slower than the relative rate of cyclisation, $k_{\text{cyc}}(114)$, [and hence that $k_{\text{H}}(114) \ll k_{\text{cyc}}(114)$], and (b) that the alkoxy radical (115) undergoes β -scission back to the alkyl radical (114) at a rate much slower than the rate at which it undergoes β -scission to the benzylic radical (116). β -Scission to the relatively unstable primary alkyl radicals (119), which is less stable than the benzylic radical (116), is also relatively slow, and, if it does occur, must be reversible. However, such thermodynamically unfavourable β -scissions are known to occur [See section 1.5.2(a)]. The absence of any product of reduction without ring expansion (118) bears testimony to

the power of the relatively stable benzylic radical, together with the ester moiety, to direct the β -scission: the unpaired electron is delocalised over an extended π system.



Scheme 91

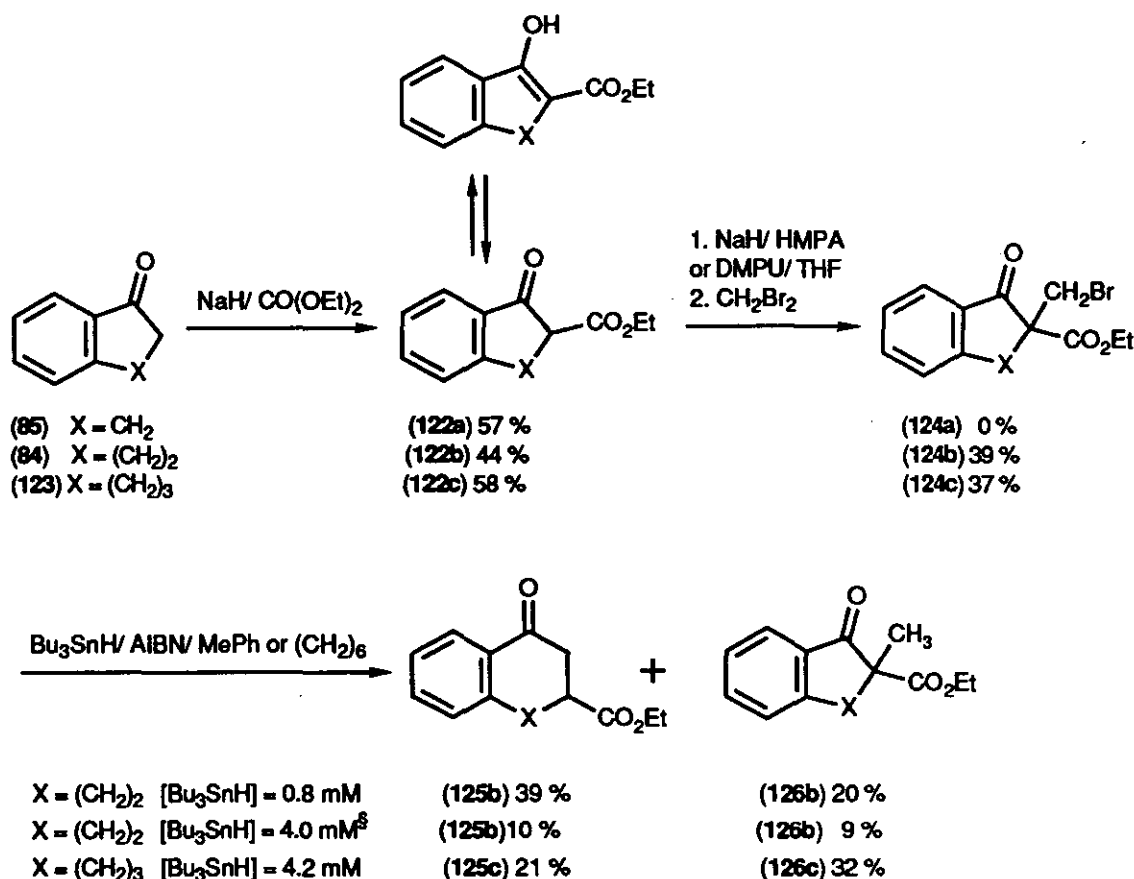
Alkoxyl radicals are strongly electrophilic and tributylstannane is strongly nucleophilic (See section 1.4), suggesting that the rate of formation of the cyclopropanol (120) by hydrogen-transfer should be fast. The absence of any cyclopropanol product (120) suggests that the rate of β -scission of the alkoxyl radical (115) to the benzylic radical (116) is an even faster process. The alkyl radical (114) does not appear to cyclise onto the ester carbonyl, since the product of subsequent β -scission and reduction (121) is not isolated. Presumably, the ester carbonyl is less susceptible to nucleophilic attack than the ketone

carbonyl because of overlap of one of the sp^3 orbitals of the EtO oxygen with the ester carbonyl π orbital, rendering the ester carbonyl less electropositive.

In subsequent ring expansions by Side Chain Incorporation, the only side reaction observed is reduction of the intermediate alkyl radicals prior to their cyclisation onto the ketone carbonyl group.

(b) One-Carbon Ring Expansion of 1-Tetralones and Homologues

The method of alkylation followed by treatment with tributylstannane using a syringe pump was applied to the benzocyclic β -keto esters (122) [ethyl 1-indanone-2-carboxylate⁸⁸ (122a), ethyl 1-tetralone-2-carboxylate^{88,89} (122b), and ethyl 6,7,8,9-benzocyclohepten-5-one-6-carboxylate⁹⁰ (122c)] which were synthesised from the corresponding α -aryl ketones (84), (85) and (123) by treatment with sodium hydride, or with sodium ethoxide, in diethyl carbonate (Scheme 92).



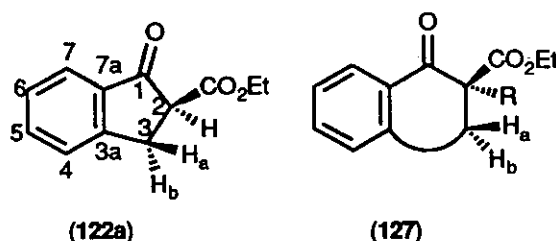
Scheme 92 \S = syringe pump not used

Interestingly, the extent of enolisation of the ketones (122) depends on the size of the benzo-fused ring. As determined by the ratios of the integrations of the ketone and enol

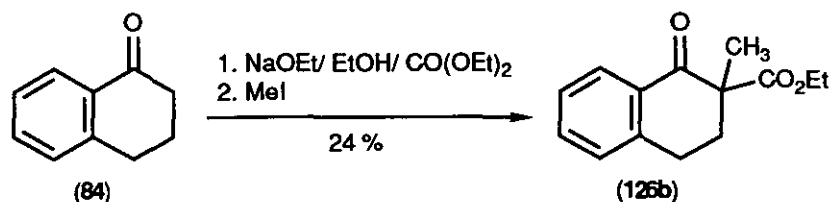
forms in the ^1H NMR spectra, ketones (**122b**) and (**122c**) are *ca.* 67 % enolised in chloroform-*d*, whereas the ketone (**122a**) exists almost entirely unenolised. It is also noteworthy that alkylation of the ketone (**122a**) with dibromomethane, and with di-iodomethane, failed. The ketone (**122a**) exhibited an interesting feature in its NMR spectrum. The ^{13}C - ^1H correlation, ^{13}C and ^1H spectra revealed the following information:

Ring	Position	δ_{C}	δ_{H}
	2	53.3	3.73-3.68 (m, 1 H)
	3	30.3	3.59-3.49 (m, 1 H) and 3.41-3.30 (m, 1 H)

Thus it is apparent that one of the diastereotopic hydrogens of the methylene group β to the ester group resonates at a higher range of values of δ_{H} than the other. The resonance at the higher range of δ_{H} values can be assigned to the hydrogen which is *cis* to the ester group, *viz.* H_{a} , since it lies within the deshielding cone of the ester carbonyl. Conversely, the resonance at the lower range of δ_{H} values can be assigned to the hydrogen which is *trans* to the ester group, *viz.* H_{b} , since it does not lie within the deshielding cone of the ester carbonyl group. As may be seen from the data quoted in section 3, this observation applies to β -keto esters of the same general form (**127**, $\text{R} = \text{H}$, alkyl).

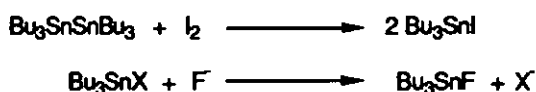


The effect of the concentration on the product distribution, and of varying the purification method, was investigated with regard to the ring expansion of ethyl 2-bromomethyl-1-tetralone-2-carboxylate (**124b**). Treatment with tributylstannane and a catalytic amount of AIBN in refluxing toluene gave two products: ethyl 6,7,8,9-tetrahydrobenzocyclohepten-5-one-7-carboxylate⁹¹ (**125b**) and ethyl 2-methyl-1-tetralone-2-carboxylate⁸⁹ (**126b**), which was also prepared by independent synthesis⁹² (Scheme 93).



Scheme 93

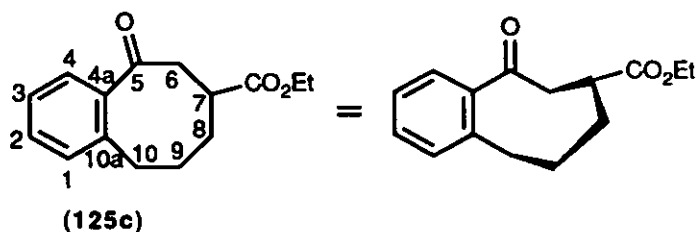
Under conventional conditions [immediate complete addition of the tributylstannane (4.0 mM) with pre-column purification⁷], the ring-expanded reduction product (**125b**) and the non-expanded reduction product (**126b**) were obtained in approximately equal yields (10 % and 9 % respectively). The purification (Scheme 94) consists of washing a dichloromethane solution of the crude product with aqueous potassium fluoride (to remove tributylbromostannane residues as the fluoride, which has some ionic character), drying and removal of solvent, washing of an acetonitrile solution of the crude with, *e. g.*, hexanes (this depends on the products being more polar than the stannane residues) and removal of solvent. As an optional first step, an ethereal solution of the crude may be titrated with an ethereal iodine solution (to convert hexabutyldistannane residues into tributyliodostannane).



Scheme 94 X = Br, I

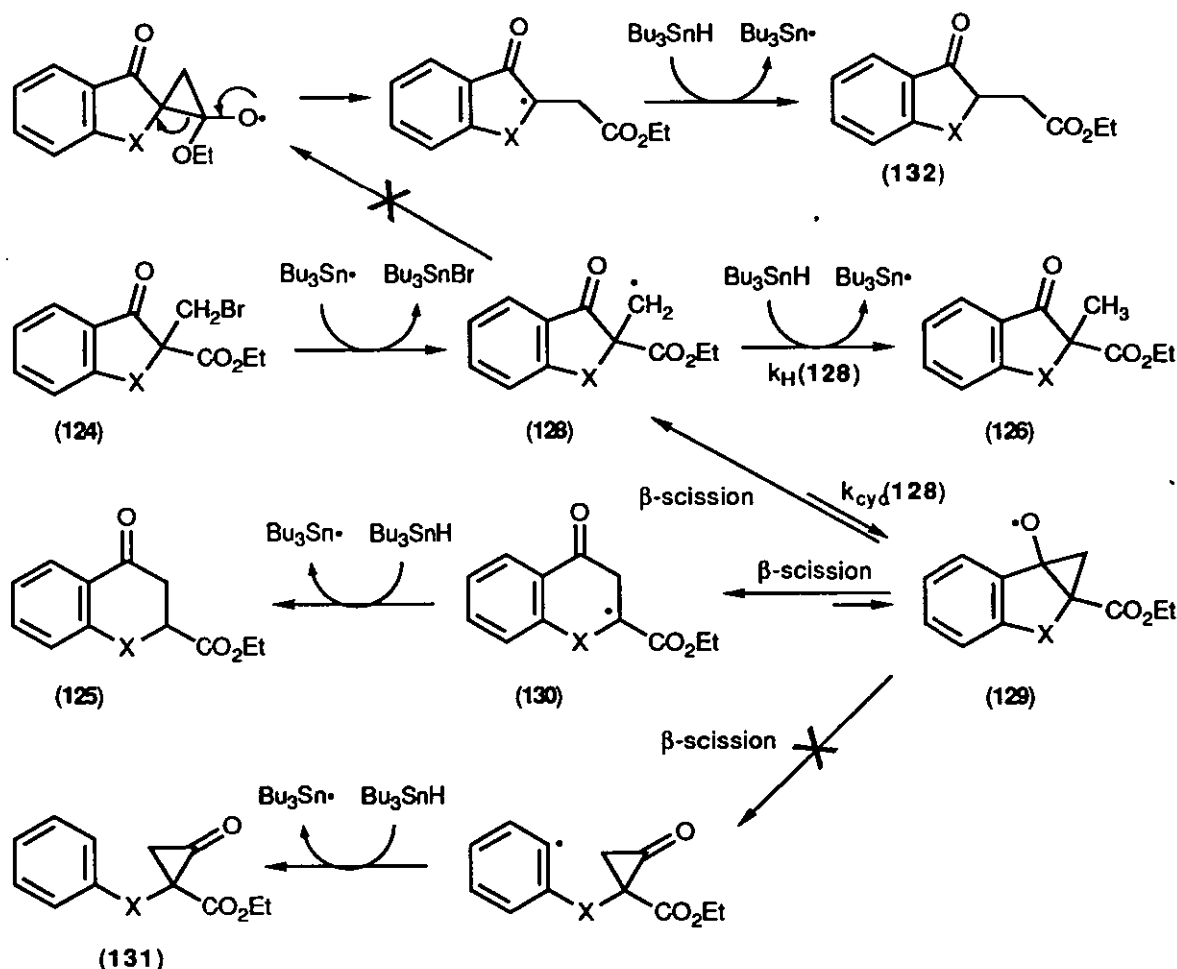
Slow addition of tributylstannane over a number of hours, lowering its concentration (0.8 mM), and omission of the pre-column work-up gave more ring-expanded product (**125b**) (39 %) than non-expanded product (**126b**) (20 %). Thus use of the syringe pump (which lowers [Bu₃SnH]) enhances the relative yield of the ring-expanded product (See section 1.4). It is also apparent that use of the purification procedure, to obviate repetitive chromatography, can be counterproductive in that it can severely depress reaction yields. Thus repetitive chromatography is the method of choice for the removal of stannane residues.

In the electroreductive ring expansion⁹¹ of the tetralone (**124b**) (which proceeds *via* two consecutive SET's to form an anion, rather than a radical), the ring-expanded product (**125b**) is produced to the exclusion of the non-expanded reduction product (**126b**): thus, for one-carbon ring expansion by Side-Chain Incorporation, electroreduction is a superior method to the use of tributylstannane.



The structure of the ketone (**125c**) was elucidated by ¹³C-¹H correlation spectroscopy, which showed that the ¹H resonance of each methylene group in the eight-membered ring is split into two one-hydrogen multiplets. Models show that the likely conformation of

the molecule (with the carbons of the α -aryl ketone group coplanar) is such that one hydrogen of each methylene group is likely to be deshielded, to some extent, by the conjugated π -system.



Scheme 95 a, $\text{X} = \text{CH}_2$; b, $\text{X} = (\text{CH}_2)_2$; c, $\text{X} = (\text{CH}_2)_3$

The mechanism of the ring expansion of the α -aryl ketones (124) (Scheme 95) is probably similar to that of the ring expansion of tetralone (112) (Scheme 90). The tributylstannyl radical abstracts a bromine from the ketone (124) to afford the alkyl radicals (128), which can cyclise onto the ketone carbonyl moiety to afford the alkoxy radicals (129). β -Scission to the tertiary alkyl radical (130) and subsequent reduction affords the ring-expanded ketones (125). However, the structural rigidity of, and the thermodynamic stability of, the α -aryl ketone system in the alkyl radical (128) contribute to a high activation energy for, and hence to a low relative rate [$k_{\text{cyc}}(128)$] of, cyclisation. The relative rate of cyclisation, $k_{\text{cyc}}(128)$, is comparable with $k_{\text{H}}(128)[\text{Bu}_3\text{SnH}]$, the relative rate of reduction. This probably accounts for the formation of the ketones (126). The effect of

adding the tributylstannane by syringe pump is to lower $[\text{Bu}_3\text{SnH}]$, and hence to lower the relative rate of reduction of the alkyl radical (128), so depressing the relative yield of the non-ring-expanded ketones (126). However, even at low $[\text{Bu}_3\text{SnH}]$, a proportion of the radicals (128) are still reduced rather than cyclised. Hence it follows that $k_{\text{H}}(128)$ is much greater than $k_{\text{cyc}}(128)$. Although the process by which the alkoxyl radicals (129) undergo β -scission to the tertiary alkyl radicals (130) does not involve formation of a benzylically-stabilised radical, it does involve re-formation of the carbonyl bond of an α -aryl ketone system. The cyclopropanones (131) were not isolated, suggesting that β -scission of the alkoxyl radicals (129) leading to the aryl radicals (which are particularly high energy species) doesn't occur. The ketones (132) were not isolated, suggesting that the alkyl radicals (128) do not cyclise onto the ester carbonyl moiety [Cf. the alkyl radicals (114)].

From the product distributions of the three successful one-carbon ring expansions, it is possible to make inferences about the relative magnitude of the associated rate constants. It is obvious that the parameters for the ring expansion of the ketones (124) are independent of ring size. Hence:

$$k_{\text{H}}(128\text{b}) \approx k_{\text{H}}(128\text{c}) \gg k_{\text{cyc}}(128\text{b}) \approx k_{\text{cyc}}(128\text{c})$$

It has already been argued that $k_{\text{cyc}}(114) \gg k_{\text{H}}(114)$. If it is assumed that, to a first approximation, the relative rates of reduction of the alkyl radicals are independent of the nature of the substrate, *i.e.* that $k_{\text{H}}(128\text{b}) \approx k_{\text{H}}(128\text{c}) \approx k_{\text{H}}(114)$, it follows that:

$$k_{\text{H}}(114) \gg k_{\text{cyc}}(128\text{b}) \approx k_{\text{cyc}}(128\text{c})$$

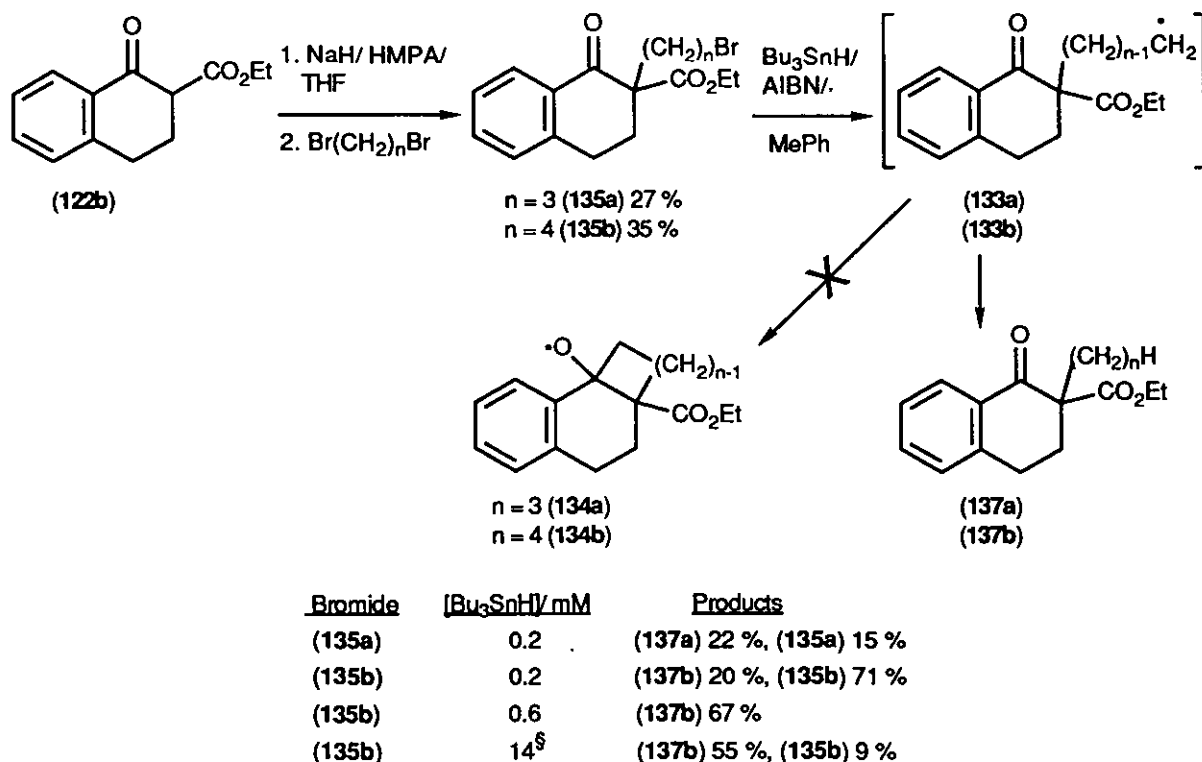
This is consistent with the reactivity of the respective ketone carbonyl groups.

As may be seen, one-carbon ring expansions by Side-Chain Incorporation proceed in a satisfactory manner. Accordingly analogous ring expansions by more than one carbon were investigated.

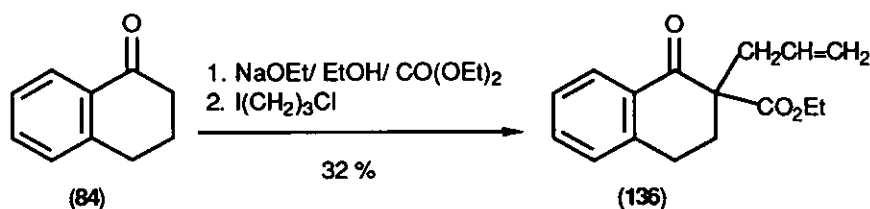
(c) Multi-Carbon Ring Expansions of 1-Tetralones

Since the one-carbon ring expansion of 1-tetralone was successful, three- and four-carbon ring expansions were investigated. The associated transition states for cyclisation of the alkyl radicals (133) to the alkoxyl radicals (134) are 5- and 6-membered respectively, and hence the reaction would appear to be favourable. Had both of these ring expansions been successful, five-carbon ring expansion (*via* a 7-membered transition state) and two-carbon ring expansion (*via* a 4-membered transition state) would have been investigated: on the basis of literature precedent,¹⁵ the latter ring expansion would not be expected to succeed (see section 1.4). Side-chains containing heteroatoms would also have been investigated.

Ethyl 2-(3-bromopropyl)-1-tetralone-2-carboxylate (**135a**) and ethyl 2-(4-bromobutyl)-1-tetralone-2-carboxylate (**135b**) were prepared from the β -keto ester (**122b**) by standard means (Scheme 96). In the synthesis of the tetralone (**135a**), ethyl 2-allyl-1-tetralone-2-carboxylate (**136**) was also obtained, as a result of dehydrobromination by excess base. Its identity was confirmed by independent synthesis, using a one-pot synthesis modified from the literature⁹² (Scheme 97).

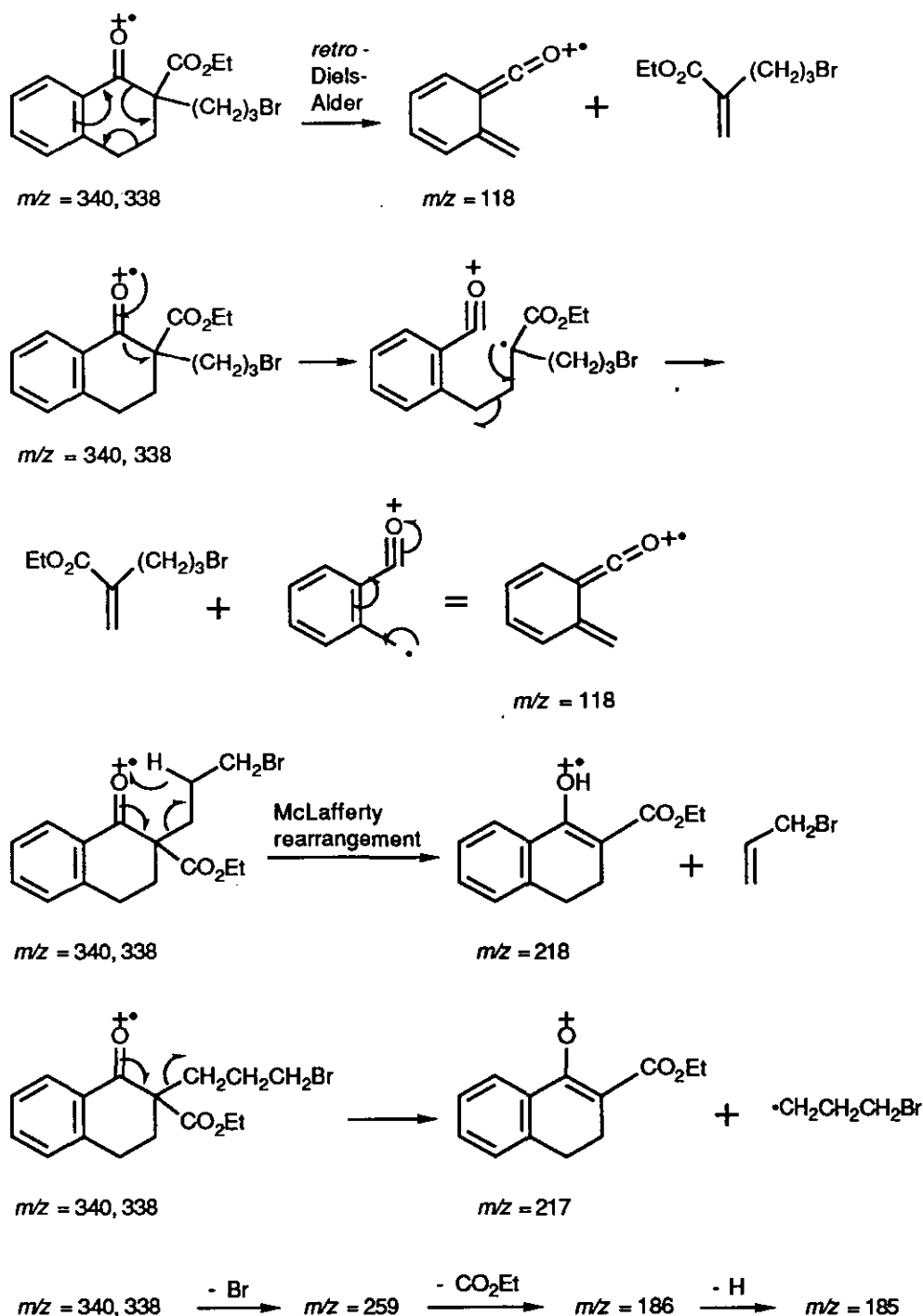


Scheme 96 § = syringe pump not used



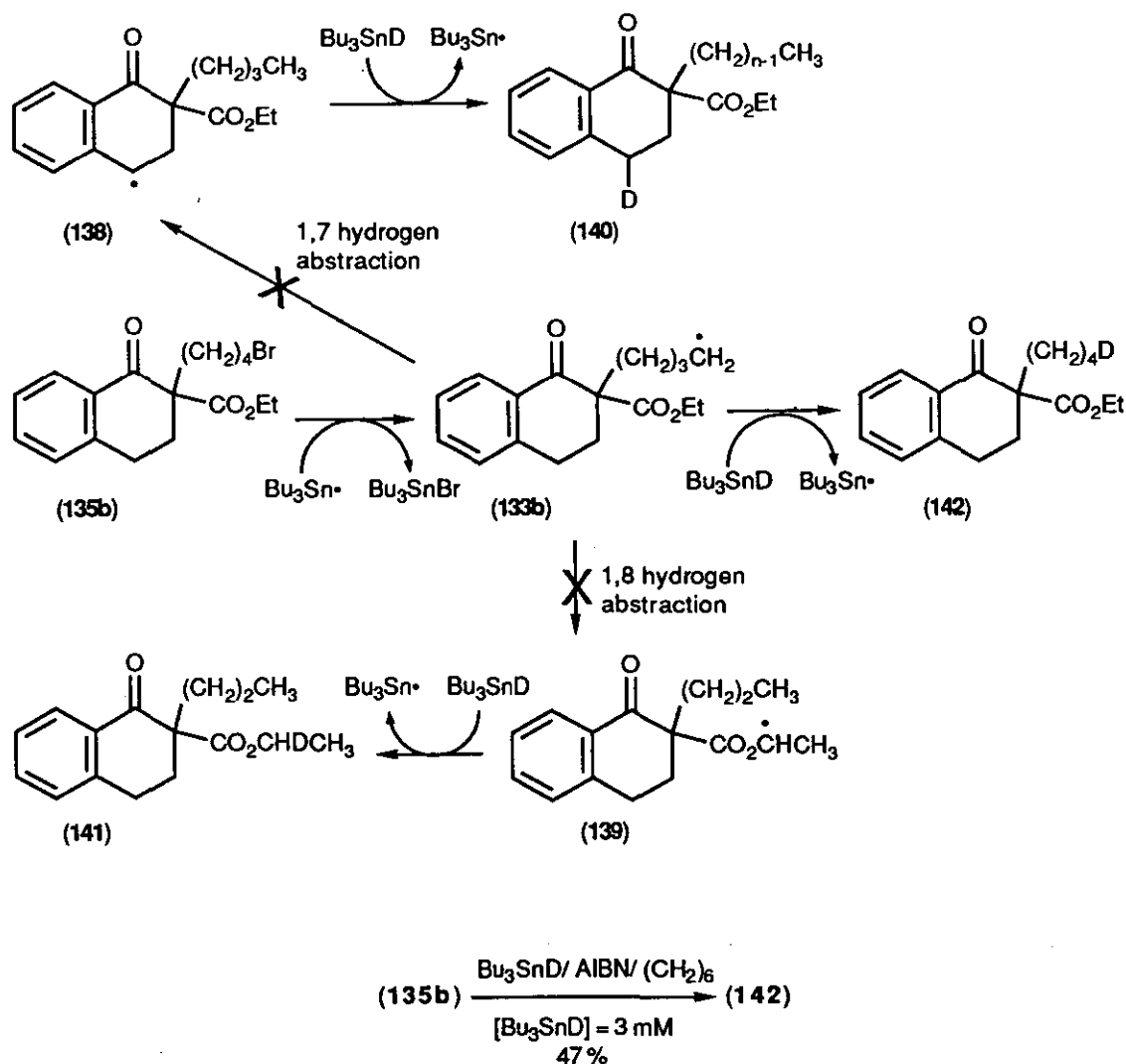
Scheme 97

The electron impact mass spectrum of the tetralone (**135a**) is illustrative of the fragmentation patterns typically observed in the mass spectra of ethyl 1-tetralone-2-carboxylate (**122b**) and its 2-alkyl derivatives (Scheme 98). The *retro*-Diels-Alder reaction is quite general. The same reaction could also occur by a stepwise mechanism. McLafferty rearrangement only occurs when the alkyl side-chain contains two or more carbon atoms. Loss of CO₂Et and EtO groups is also common.



Scheme 98

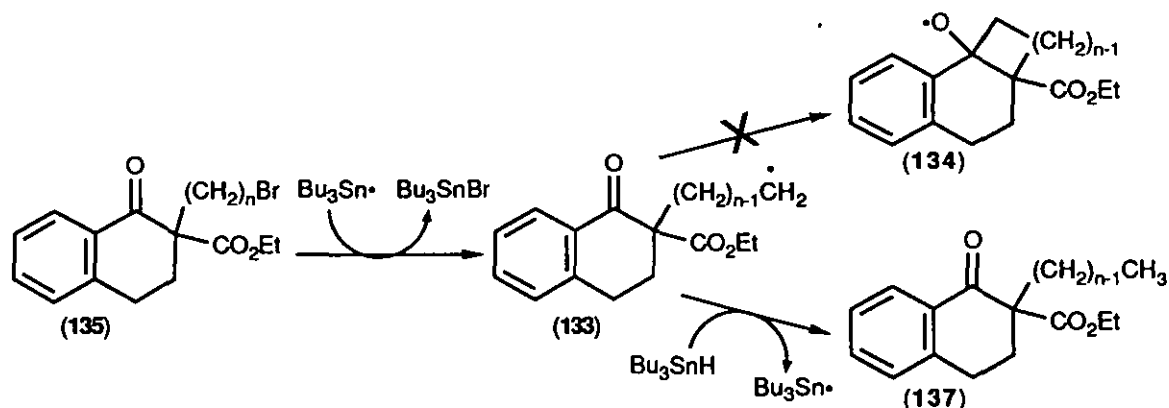
Attempted ring expansions with multi-carbon side-chains failed, under a variety of conditions, affording only products of reduction without ring expansion.⁸⁹ It was postulated that intramolecular hydrogen abstraction⁹³ may account for the failure of multi-carbon ring expansion and this was investigated with a deuterium-labelling experiment (Scheme 99).



Scheme 99

Conceivable rearrangements of the alkyl radical (133b) include 1,7-hydrogen abstraction to afford the benzylic radical (138), and, less probably, 1,8-hydrogen abstraction to afford the radical (139). Subsequent deuterium-transfer would afford the tetralones (140) and (141) respectively. Reduction of the tetralone (135b), using the syringe pump to add *d*-tributylstannane ([*d*-tributylstannane] *ca.* 3 mM), gave only one product, ethyl 2-(4-*d*-butyl)-1-tetralone-2-carboxylate (142), which was conclusively identified by comparison of its ^{13}C and ^1H NMR spectra with those of the non-deuterated product (137b). The ^1H NMR spectrum of the non-deuterated product (137b) exhibited a three-proton triplet ($J = 6.9 \text{ Hz}$) at $\delta_{\text{H}} = 0.91$, corresponding to the methyl group in the butyl side-chain; the ^1H NMR spectrum of the deuterated product (142) exhibited a two-proton multiplet at $\delta_{\text{H}} = 0.93$ to $\delta_{\text{H}} = 0.89$. The off-resonance ^{13}C NMR spectrum of the non-deuterated product (137b) exhibited a methyl resonance at $\delta_{\text{C}} = 13.9$, corresponding to the

methyl group in the butyl side-chain; the off-resonance ^{13}C NMR spectrum of the deuterated product (**142**) exhibited a triplet at $\delta_{\text{C}} = 13.9$ ($J_{\text{C-D}} = 45$ Hz). All other resonances in the NMR spectra were identical. The IR spectrum of the deuterated product (**142**) exhibits a C-D stretch ($\nu_{\text{max}} 2160\text{ cm}^{-1}$) and its E.I. mass spectrum confirms monodeuteration: M^+ 275.1589 ($\text{C}_{17}\text{H}_{21}\text{DO}_3$ requires 275.1632). It is clear that no intramolecular hydrogen-abstraction occurs, since the tetralone (**142**) arises from deuterium-transfer to the alkyl radical (**133b**).



Scheme 100 a, $n = 3$; b, $n = 4$

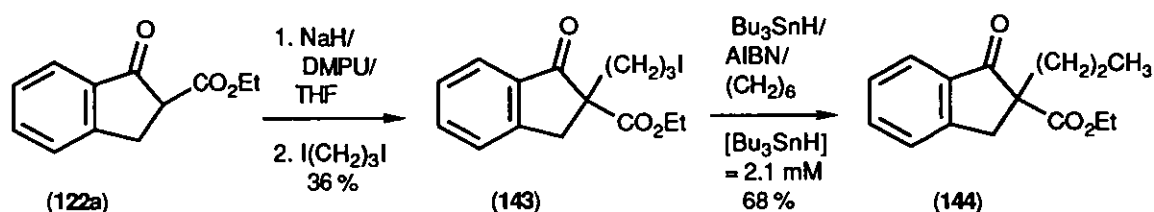
The results can be rationalised simply as before (Scheme 100). The relative rate of reduction of the alkyl radical (**133**), $k_{\text{H}}(\textbf{133})[\text{Bu}_3\text{SnH}]$, is obviously much faster than the relative rate of cyclisation to the alkoxyl radical (**134**), $k_{\text{cyc}}(\textbf{133})$, regardless of the value of $[\text{Bu}_3\text{SnH}]$, *i.e.* $k_{\text{H}}(\textbf{133}) \gg k_{\text{cyc}}(\textbf{133})$.

It is instructive to compare the fate, as inferred from the respective product distributions, of the tetralone-derived alkyl radicals (**128b**), (**133a**) and (**133b**). All three alkyl radicals are reduced to non-expanded products [(**126b**), (**137a**) and (**137b**) respectively]; only the radical (**128b**) rearranges to a ring-expanded radical, *viz.* (**130b**). Once again, assuming that the rate of reduction of alkyl radicals is substrate-independent, *i.e.* that $k_{\text{H}}(\textbf{128b}) \approx k_{\text{H}}(\textbf{133})$, it follows that $k_{\text{cyc}}(\textbf{128b}) \gg k_{\text{cyc}}(\textbf{133})$. Thus, it seems likely that $k_{\text{cyc}}(\textbf{133})$ is so low that the alkoxyl radicals (**134**) are not formed. It seems likely that cyclisation of the alkyl radicals (**133**) to form the alkoxyl radicals (**134**) is less entropically favourable than cyclisation of the alkyl radicals (**128b**) to form the alkoxyl radicals (**129b**), owing to the greater flexibility of the longer pendant side-chain.

The recovered starting material (**135**) probably resulted from chain failure owing to lack of hydride and/or lack of initiator.

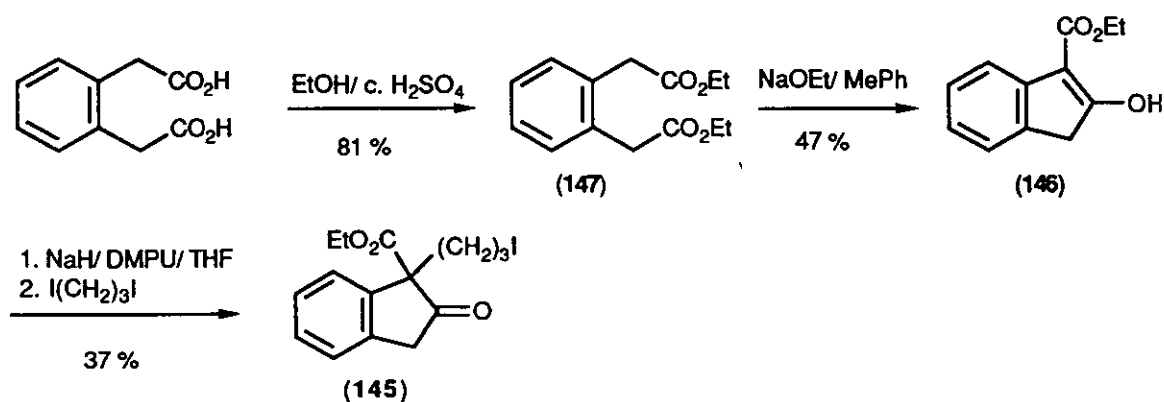
(d) Multi-Carbon Ring Expansions of 1- and 2-Indanones

It seems unlikely that the failure of the ring expansion is a function of size of the ketone ring, since treatment of ethyl 2-(3-iodopropyl)-1-indanone-2-carboxylate (**143**) with tributylstannane ($[\text{Bu}_3\text{SnH}]$ ca. 2.1 mM) using a syringe pump afforded the non-ring-expanded ethyl 2-propyl-1-indanone-2-carboxylate (**144**) as the only product (Scheme 101). Presumably the ring expansion failed because of the unfavourable entropy associated with formation of the intermediate alkoxyl radical. The ketone (**143**) was synthesised from the β -keto ester (**122a**) by alkylation with 1,3-di-iodopropane.



Scheme 101

When the same procedure was applied to ethyl 1-(3-iodopropyl)-2-indanone-1-carboxylate (**145**), decomposition to an intractable mixture resulted. The indanone (**145**) was obtained by alkylation of ethyl 2-indanone-1-carboxylate⁹⁴ (**146**) with 1,3-di-iodopropane. The indanone (**146**), which is fully enolised, was obtained by Dieckmann condensation of diethyl phenylenediacetate⁹⁴ (**147**), which was obtained by diesterification of the commercially available phenylenediacetic acid (Scheme 102).

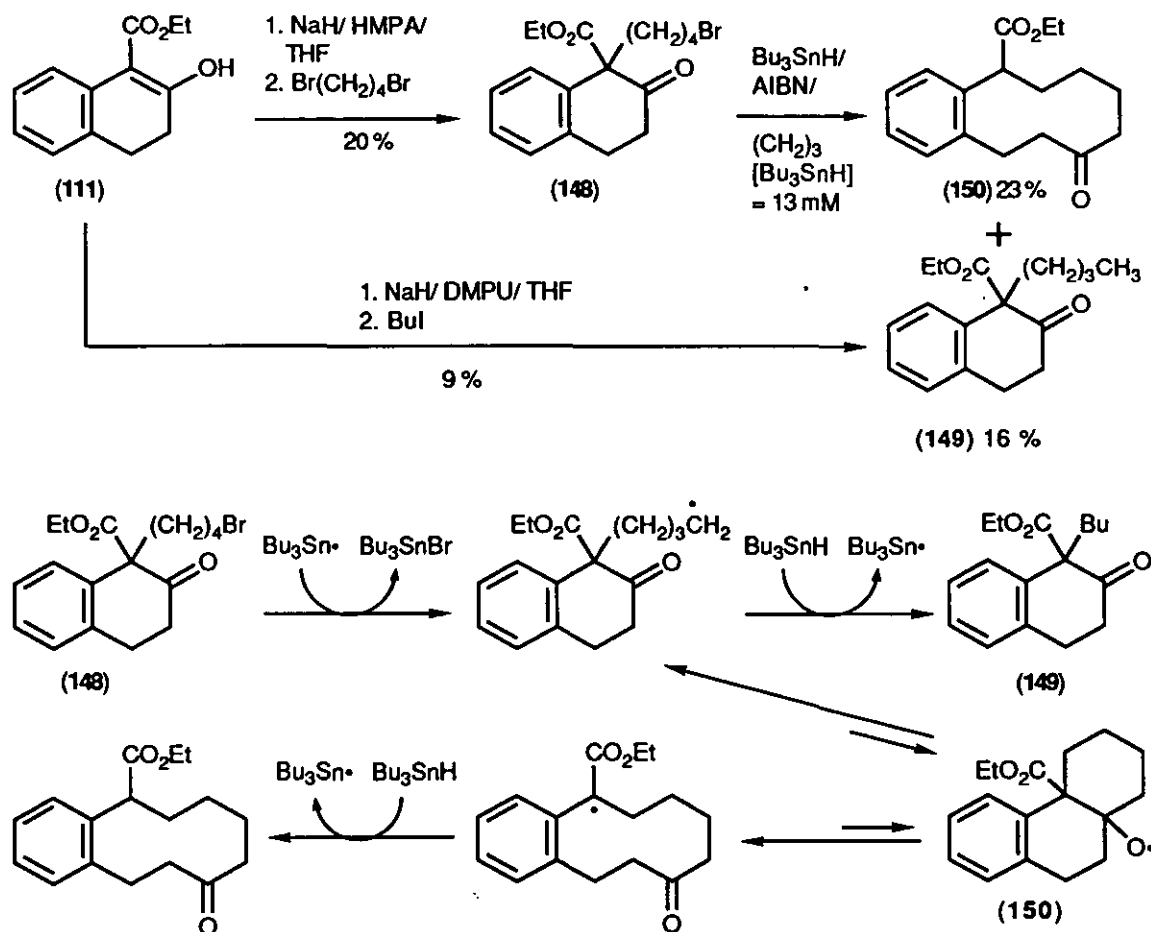


Scheme 102

(e) Multi-Carbon Ring Expansion of 2-Tetralones

Ring expansion of ethyl 1-(4-bromobutyl)-2-tetralone-1-carboxylate (**148**), which was prepared from ethyl 2-tetralone-1-carboxylate (**111**) by alkylation with 1,4-dibromobutane,

using a syringe pump ($[\text{Bu}_3\text{SnH}]$ *ca.* 13 mM), gave an intractable mixture of products (Scheme 103).



Scheme 103

TLC showed the absence of starting material. The tributylstannane residues were removed, by means of dry flash chromatography (twice) and preparative TLC, to give a product, which exhibited one spot only by TLC (when eluted with a variety of solvent systems). The IR spectrum indicated the presence of a ketone, and possibly, ester groups [$\nu_{\text{max}}(\text{neat})$ 1731 cm^{-1}]. The NMR spectra indicated the presence of ethyl 1-butyl-2-tetralone-1-carboxylate (**149**), which was also prepared independently by alkylation of the tetralone (**111**), and of a further compound bearing the $-\text{CO}_2\text{Et}$ group and a methine group (δ_{H} *ca.* 3.65, and $\delta_{\text{C}} = 54.2$). GC and GC-MS analysis confirmed that one of the mixture's components was the tetralone (**149**) ($m/z = 218$, 60 %, $M - \text{CH}_2=\text{CHCH}_2\text{CH}_3$). The other, more polar, major product had the same molecular mass ($m/z = 274$, M^+ , 20 %) and was assumed to be ethyl 5,6,7,8,9,10,11,12-octahydro-7-oxobenzocyclodecene-12-carboxylate (**150**). The GC yields were determined by assuming that both products gave equal responses to the flame ionisation detector.

Clearly the ring expansion is successful, but the products do not differ sufficiently in polarity to be separated using normal chromatographic methods (Preparative HPLC would probably be suitable). Presumably the mechanism of the ring expansion is analogous to that of the ring expansion of the tetralone (**112**): presumably the non-ring-expanded reduction product (**149**) arises because the unfavourable entropy associated with formation of the intermediate alkoxyl radical depresses k_{cyc} [Cf. the ring expansion of the tetralone (**112**)].

(f) Conclusions

Obviously, for the Side-Chain Incorporation methodology (using tributylstannane) to be successful, it is critically important that the starting ketone [*e.g.* (**18**), Scheme 5] is thermally stable. Ring expansions of benzocyclic ketones are less successful than ring expansions of the analogous monocyclic ketones.¹⁵

It is manifest that multi-carbon ring expansion by the Side-Chain Incorporation methodology is often less successful than one-carbon ring expansion by the same route. This observation has a precedent in the literature^{11,29} and can be rationalised in terms of the ring size of the transition state leading from the associated primary alkyl radical to the associated alkoxyl radical, and the rate of this process (which leads to ring expansion). The latter parameter is a function of activation energy (and hence is also a function of activation entropy). The activation entropy for the formation of alkoxyl radicals associated with multi-carbon ring expansions is less favourable than the activation entropy for the formation of alkoxyl radicals associated with one-carbon ring expansions. Consequently the rate of the former reaction becomes similar to, or less than, the rate of reduction of the associated primary alkyl radical.

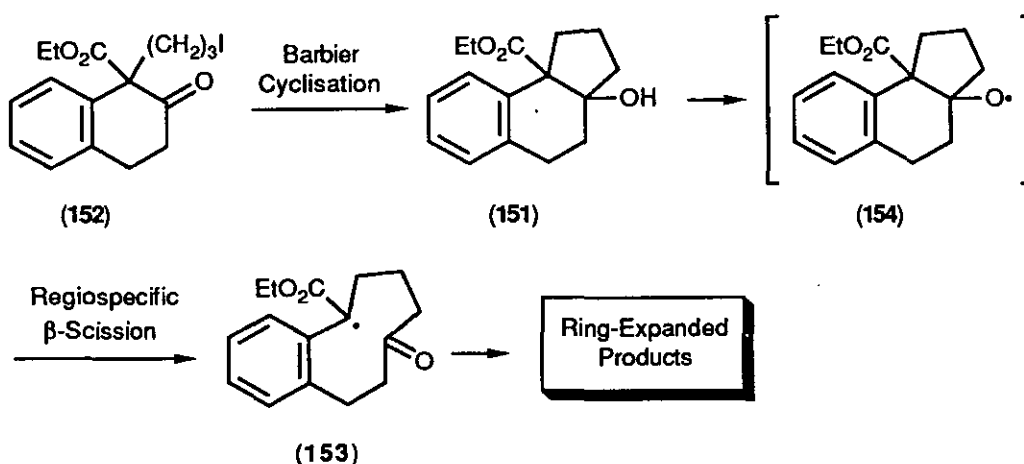
It is also manifest that ring expansions of 2-tetralones tend to be more successful than ring expansions of 1-tetralones (and homologues). Once again, the explanation lies in the rate of, and hence the activation energy for, the cyclisation of the associated primary alkyl radicals [(**114**) and (**128b**) respectively, for one-carbon ring expansions] to the associated alkoxyl radicals [(**115**) and (**129b**) respectively]. For 1-tetralones (and homologues) this process involves the destruction of a conjugated α -aryl ketone system, leading to a high activation energy relative to that of 2-tetralones, and hence to a relatively slow rate (which is of a similar order of magnitude to the rate of reduction of the associated primary alkyl radicals).

Multi-carbon ring expansion of 1-tetralones (and homologues) fails completely. Multi-carbon ring expansion of 2-tetralones (and homologues) affords an intractable mixture of products: because of this severe practical disadvantage the methodology was not further investigated. The Cleavage of the Zero Bridge in Bicycles methodology was investigated as a means of circumventing this last limitation.

2.4 Ring Expansion of Benzocyclic β -Keto Esters by Cleavage of the Zero Bridge in Bicycles

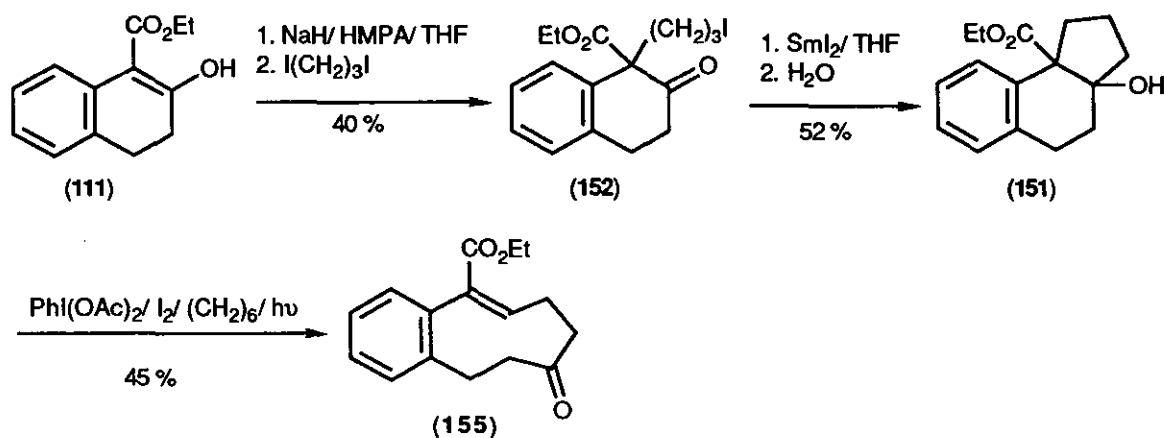
(a) Ring Expansion of 2-Tetralone

The method requires a bridgehead bicyclic alcohol: it was developed on ethyl 2,3,3a,4,5,9b-hexahydro-3a-hydroxy-(1*H*)-benz[*e*]indene-9b-carboxylate (**151**), which should be available from Barbier cyclisation of ethyl 1-(3-iodopropyl)-2-tetralone-1-carboxylate (**152**) (Scheme 104). The stability of the benzylic radical (**153**) should direct β -scission of the alkoxyl radical (**154**), derived from the alcohol (**151**), to give ring-expanded products.



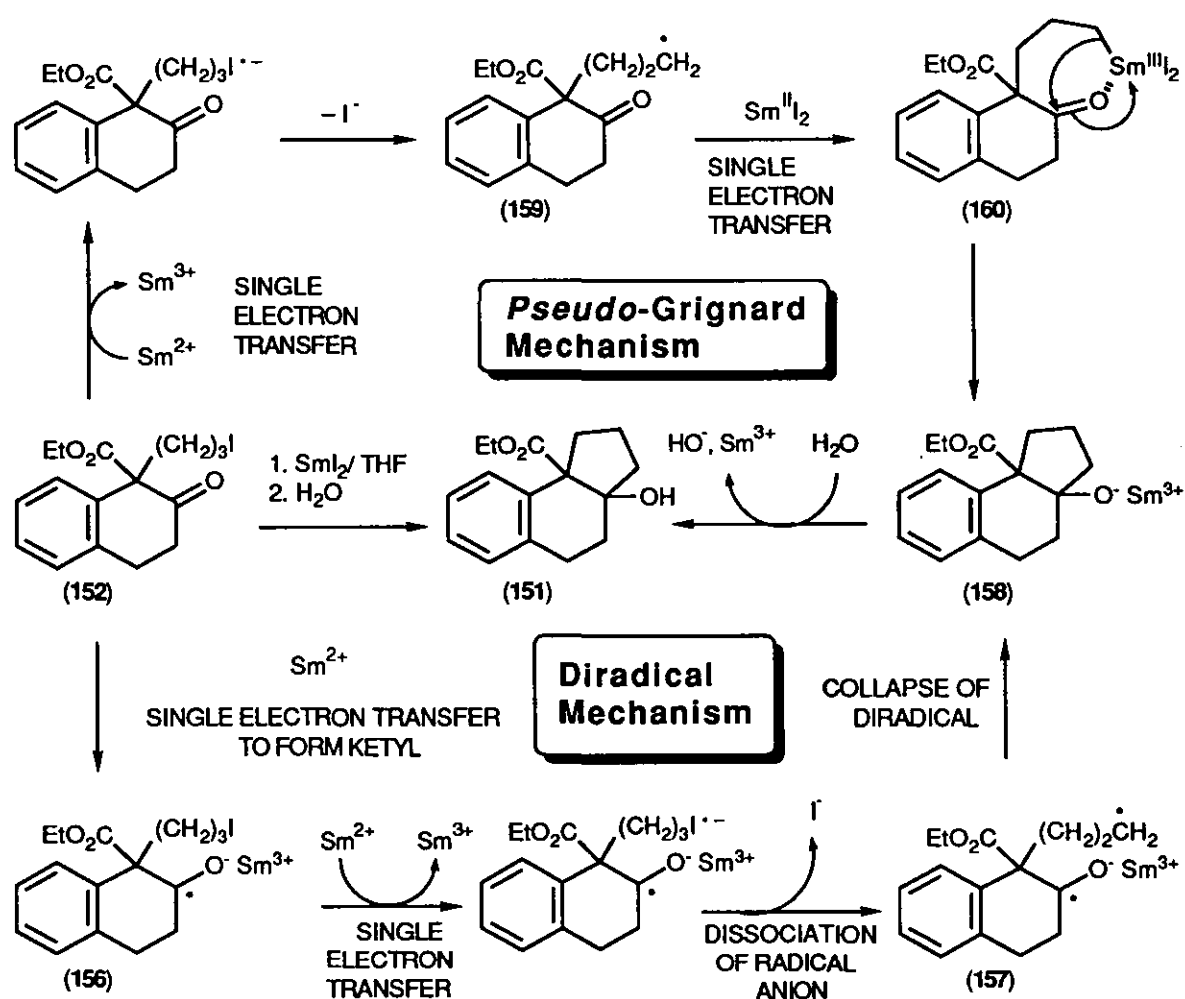
Scheme 104

Alkylation of the β -keto ester (**111**) with 1,3-di-iodopropane gave the iodide (**152**), which, on treatment with a dilute THF solution (0.1 M) of samarium (II) iodide at -78°C ,³⁹ gave the alcohol (**151**), as a 1:1 mixture of *E* and *Z* isomers (Scheme 105).



Scheme 105

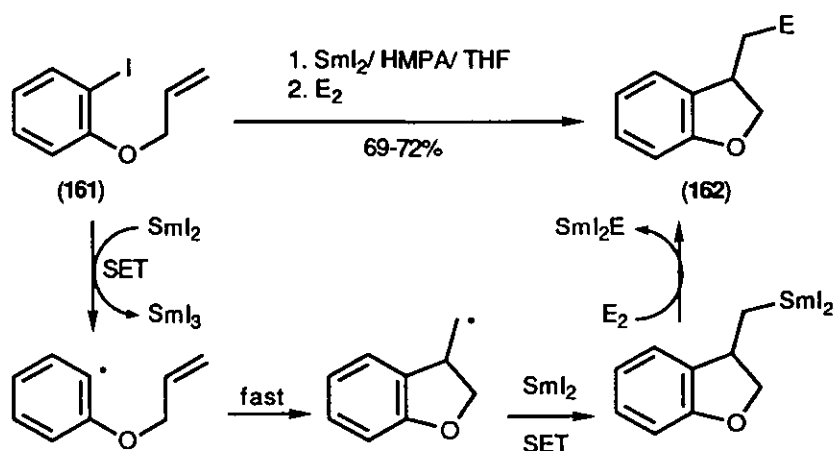
The compound's IR spectrum exhibited a broad, intense band at 3542 cm^{-1} corresponding to the alcohol O-H stretch, and a narrow, intense band at 1723 cm^{-1} corresponding to the ester carbonyl stretch (a lower value than would be expected). The ^1H NMR spectrum exhibited an exchangeable one-hydrogen broadened singlet at $\delta_{\text{H}} = 2.80$ to $\delta_{\text{H}} = 2.40$, corresponding to the alcohol -OH group, together with two overlapping quartets, of equal intensity, with equal coupling constants ($J = 7.1\text{ Hz}$), at $\delta_{\text{H}} = 4.14$, corresponding to the ester $-\text{CO}_2\text{CH}_2\text{CH}_3$ groups of the *E* and *Z* isomers. The ^{13}C NMR spectrum exhibited a quaternary carbon at $\delta_{\text{C}} = 81.1$, corresponding to R_3COH , and no ketonic carbonyl group. The electron-impact mass spectrum showed a molecular ion at $m/z = 260$, and peaks consistent with the loss of water and the CO_2Et moiety.



Scheme 106

The mechanism of the formation of the alcohol (151) is believed to involve two consecutive SET's [Scheme 106, see also section 1.5.1(c)]. As already stated, there is evidence (*e.g.* deuterium incorporation on quenching of reaction mixtures with D_2O)³³ to

suggest that samarium (II) iodide-mediated Barbier reactions proceed *via* organosamarium (III) species. Recent research⁹⁵ has optimised reaction conditions and suggests that such "*pseudo*-Grignard" mechanistic pathways occur in preference to "Diradical" mechanistic pathways. Both can be rationalised in terms of the requirement for two equivalents of samarium (II) iodide: the principal difference between the two pathways lies in the sites at which the two consecutive SET's from samarium (II) iodide to the substrate [*e.g.* (152)] occur. In the "Diradical" mechanism SET to the ketone moiety forms a ketyl (156). Sequential dissociative SET to the halogen moiety forms an alkyl radical-ketyl system (157), which collapses *via* a five-membered transition state to form the alkoxide (158). In the "*pseudo*-Grignard" mechanism, dissociative SET to the halogen moiety forms a primary alkyl radical (159), which is rapidly reduced, by a second equivalent of samarium (II) iodide, to form an organosamarium (III) species (160). This species attacks the ketone moiety in a Grignard-like manner, *via* a seven-membered transition state, to form the alkoxide (158). In both cases, aqueous work-up affords the cyclised alcohol (151).



Scheme 107 E = I, PhS, PhSe

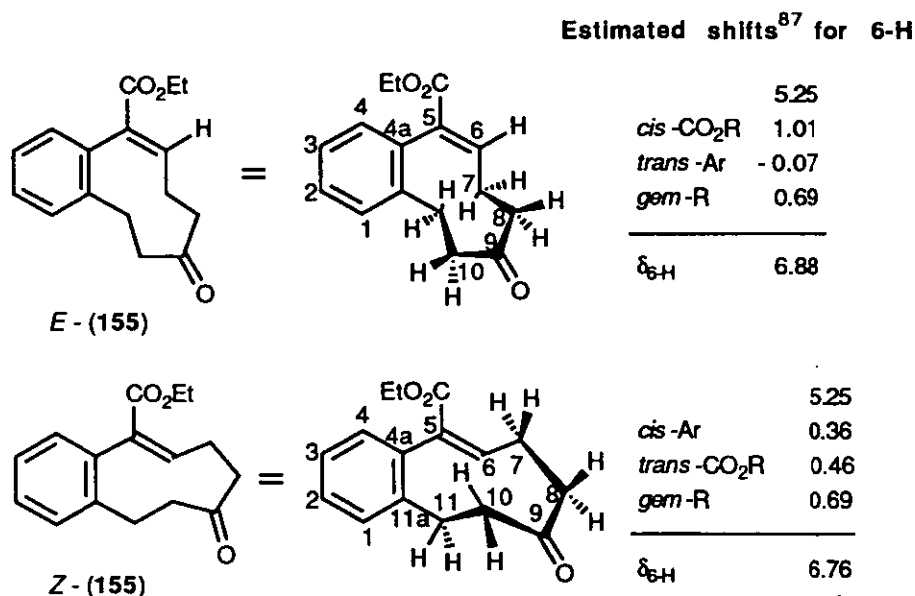
Evidence for the operation of the "*pseudo*-Grignard" mechanism in the case of the bimolecular Barbier reaction is afforded by the capacity of the iodide (161) to form a solution-stable cyclised reagent, when treated with two equivalents of samarium (II) iodide. The cyclised organosamarium (III) reagent reacts with a series of electrophiles, E_2 , which are not stable to samarium (II) iodide (Scheme 107),⁹⁵ to afford the species (162).

Irradiation of the alcohol (151) in the presence of iodine and iodobenzene diacetate in cyclohexane,²⁶ followed by irradiation of the crude product in the presence of tributylstannane in cyclohexane, gave ethyl 7,8,9,10-tetrahydro-9-oxo-(1*H*)-benzocyclononene-5-carboxylate (155) (50 %). The purpose of the latter step was to reduce any iodine moiety in the product. However, inspection of the ^{13}C and ^1H NMR spectra of the crude product showed that the styrene (155) was obtained directly, and hence that the second step was

unnecessary. Irradiation of the alcohol (**151**) in the presence of iodine and iodobenzene diacetate in cyclohexane gave the styrene (**155**) (45 %).

The characterisation of the styrene (**155**) is worthy of comment. The E.I. mass spectrum showed fragmentation peaks consistent with both of the diastereoisomers *E*- and *Z*- (**155**), viz. $m/z = 213$ (18 %, *M* - EtO), 212 (100, *M* - EtOH), 185 (31, *M* - CO₂Et). The IR spectrum exhibited stretches at 1711 cm⁻¹ ($\alpha\beta$ -unsaturated ester C=O), 1705 cm⁻¹ (shoulder, ketone C=O), and 1640 cm⁻¹ (styrene C=C). Evidently carbons 1, 2, 3, 4, 4a, 5, 6, 7, 12, 12a and 5-CO₂Et must be coplanar, suggesting, on the basis of models, that the molecule exists in one of the two conformations shown below. .

The fully coupled resonance of the ester carbonyl (5-CO₂Et) in the 100 MHz ¹³C NMR spectrum ($\delta_C = 166.3$) does not show any large couplings (All apparent coupling constants for this resonance are *ca.* 3 Hz). This suggests that the ³J_{H-C} coupling constant across the C=C double bond between 5-CO₂Et and 6-H is small, which, in turn, suggests that 5-CO₂Et and the styrene hydrogen (6-H) are *cis* with respect to each other, *i.e.* that *E*- (**155**) was obtained experimentally.



The value of δ_H at which olefinic hydrogens resonate can be estimated, by the application of a set of rules,⁸⁷ from the nature of the substituents attached to the C=C bond. This value can be dependent on the geometry of the double bond. As shown above, the values calculated for the resonance of the olefinic hydrogen (6-H) of the styrene (**155**) are not markedly different for the *E*- and *Z*-isomers. The olefinic hydrogen actually resonates at $\delta_H = 7.13$ to $\delta_H = 7.08$, a markedly higher value than that calculated (The assignment of the olefinic hydrogen, 6-H, is discussed below). ¹H-¹H Correlation spectroscopy (at 250 MHz) showed strong coupling between the one-hydrogen multiplet at $\delta_H = 2.38$ to $\delta_H = 2.28$ and

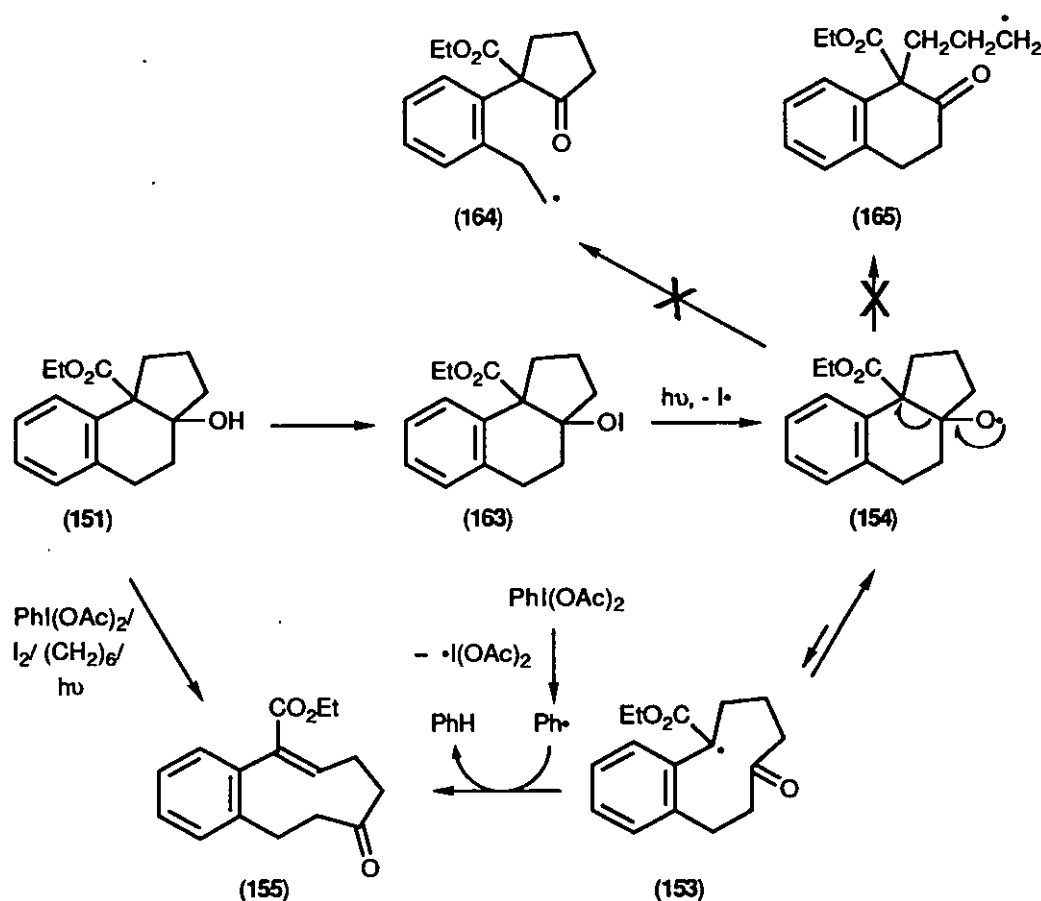
at least one of the two hydrogens resonating between $\delta_{\text{H}} = 7.13$ to $\delta_{\text{H}} = 7.02$. Hence the one-hydrogen multiplet resonating between $\delta_{\text{H}} = 2.38$ and $\delta_{\text{H}} = 2.28$ probably corresponds to one of the allylic methylene hydrogens (7-H), and one of the hydrogens resonating between $\delta_{\text{H}} = 7.13$ and $\delta_{\text{H}} = 7.02$ is probably olefinic, *i.e.* one of the latter hydrogens is probably the styrene hydrogen (6-H). Clearly the other hydrogen in this two-hydrogen multiplet is one of the arene hydrogens (1-H, 2-H, 3-H, or 4-H). In the 400 MHz ^1H NMR spectrum, this signal is split into two one-hydrogen multiplets: one at $\delta_{\text{H}} = 7.13$ to $\delta_{\text{H}} = 7.06$; the other at $\delta_{\text{H}} = 7.04$ to $\delta_{\text{H}} = 7.02$.

nOe Difference spectroscopy was used to assign the geometry of the C=C bond, and hence to determine which of the two diastereoisomers, *E*- and *Z*-(**155**), was obtained experimentally. Irradiation at $\delta_{\text{H}} = 7.03$ caused enhancement of the intensity of the three-hydrogen arene multiplet at $\delta_{\text{H}} = 7.31$ to $\delta_{\text{H}} = 7.19$, and enhancement of the intensities of the two-hydrogen quartet at $\delta_{\text{H}} = 4.14$ and of the three-hydrogen triplet at $\delta_{\text{H}} = 1.21$ (the resonances associated with the 5-CO₂Et moiety). Consequently the resonance at $\delta_{\text{H}} = 7.04$ to $\delta_{\text{H}} = 7.02$ probably corresponds to an arene hydrogen (4-H). Irradiation at $\delta_{\text{H}} = 7.06$ (corresponding to the styrene hydrogen, 6-H) caused enhancement of the intensities of all of the resonances between $\delta_{\text{H}} = 5$ and $\delta_{\text{H}} = 0$. Since nOe is a short-range through-space effect,⁸⁷ it follows that the styrene hydrogen (6-H) is close to the 5-CO₂Et moiety and all of the ring methylene groups. Of the two diastereoisomers, *E*- and *Z*-(**155**), only *Z*-(**155**) meets this condition.

The model of the styrene *E*-(**155**) shows that one of the hydrogens of the benzylic methylene group (11-H) would buttress one of the hydrogens of the allylic methylene group (7-H). However, irradiation at $\delta_{\text{H}} = 2.95$ (corresponding to the resonance of one of the benzylic methylene hydrogens, 11-H) shows no nOe enhancement of the intensity of either of the one-hydrogen resonances at $\delta_{\text{H}} = 2.38$ to $\delta_{\text{H}} = 2.28$, and at $\delta_{\text{H}} = 2.16$ to $\delta_{\text{H}} = 2.02$ (corresponding to the resonances of the allylic methylene hydrogens, 7-H). Similarly, irradiation at $\delta_{\text{H}} = 2.11$ and at $\delta_{\text{H}} = 2.32$ (corresponding to the resonances of each of the allylic methylene hydrogens, 7-H) shows no enhancement of the one-hydrogen resonance at $\delta_{\text{H}} = 2.98$ to $\delta_{\text{H}} = 2.92$ (corresponding to the resonance of one of the benzylic methylene hydrogens). Since nOe is a short-range through-space effect,⁸⁷ it follows that 11-H and 7-H are not very close together in space. This is consistent with a *Z* C=C double bond and inconsistent with an *E* C=C double bond.

The mechanism of the ring opening of the alcohol (**151**) is not entirely clear (Scheme 108). It seems likely that the iodobenzene diacetate, a hypervalent iodine species, mediates the formation of the alkoxyl radical (**154**): the literature gives no indication of the mechanistic pathway for this process.²⁶ The alkoxyl radical (**154**) species may be generated by photolysis of the hypoiodite (**163**), which would be expected to cause homolytic cleavage of the weak oxygen-iodine bond. Alternatively, photolysis of iodobenzene diacetate may afford

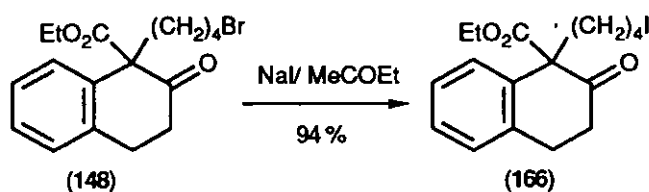
phenyl radicals by homolytic cleavage of the carbon-iodine bond: this radical could then afford the alkoxyl radical (154) by abstracting the alcoholic hydrogen from the alcohol (151). β -Scission of the alkoxyl radical (154) gives the benzylic radical (153), which is also stabilised by the inductive effect of a primary alkyl group, and by delocalisation of the unpaired electron over the ester group and over the arene π electron system. The benzylic radical (153) is oxidised to the styrene (155) by loss of a hydrogen atom, the driving force for this last step probably being the extended conjugation of the phenacrylate system. The alternative β -scissions lead to the less stable primary alkyl radicals (164) and (165), which are stabilised solely by the inductive effect of a primary alkyl group. The absence of any derived products suggests that these β -scissions do not occur.



Scheme 108

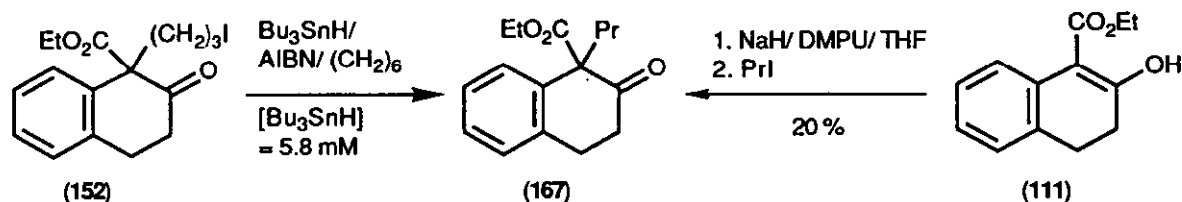
When ethyl 1-(4-iodobutyl)-2-tetralone-1-carboxylate (166), which was prepared from the bromide (148) by the Finkelstein reaction, was treated with samarium (II) iodide under the same conditions as the iodide (152), the result was an intractable mixture of decomposition products (Scheme 109). This suggests that Lewis acid bonding of the samarium (III) "Grignard" requires a seven-membered ring transition state rather than an

eight-membered ring transition state: models of the seven- and eight-membered ring transition states show no obvious reason for these contrasting results. In general, the literature suggests that the samarium (II) iodide-mediated cyclisation of 2-(3-halogenopropyl) ketones to cyclopentanols and the analogous cyclisation of 2-(4-halogenobutyl) ketones to cyclohexanols should be equally successful.^{32,38} However there are reports of the failure of the latter class of reaction, where the former class succeeds³⁹ [See section 1.5.1 (c), especially Scheme 43].



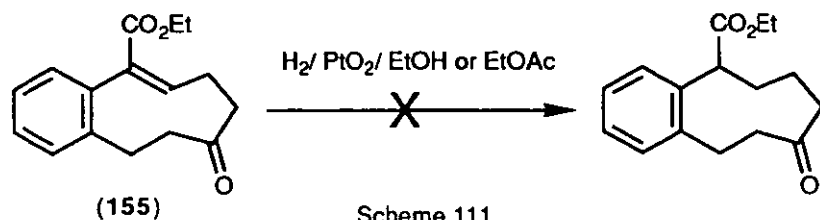
Scheme 109

Attempts to form the Grignard reagent^{30,96} of the bromide (148) also gave an intractable mixture of products. The same result occurred when the iodide (145) was treated with samarium (II) iodide: this result is less readily rationalised.



Scheme 110

To compare the two routes to ring expansion *via* transient alkoxyl radicals, the iodide (152) was treated with tributylstannane, using a syringe pump ([Bu₃SnH] = 5.8 mM), to afford, in low yield, an impure sample of ethyl 1-propyl-2-tetralone-1-carboxylate (167), which was also prepared independently by alkylation of the β -keto ester (111) (Scheme 110). In a replicate ring expansion experiment, NMR spectroscopic, GC-MS and HPLC analysis of the crude product showed the presence of the tetralone (167) (21 %) as the only product. Clearly pyrolysis is a major problem. The reason for this lack of thermal stability is unclear.

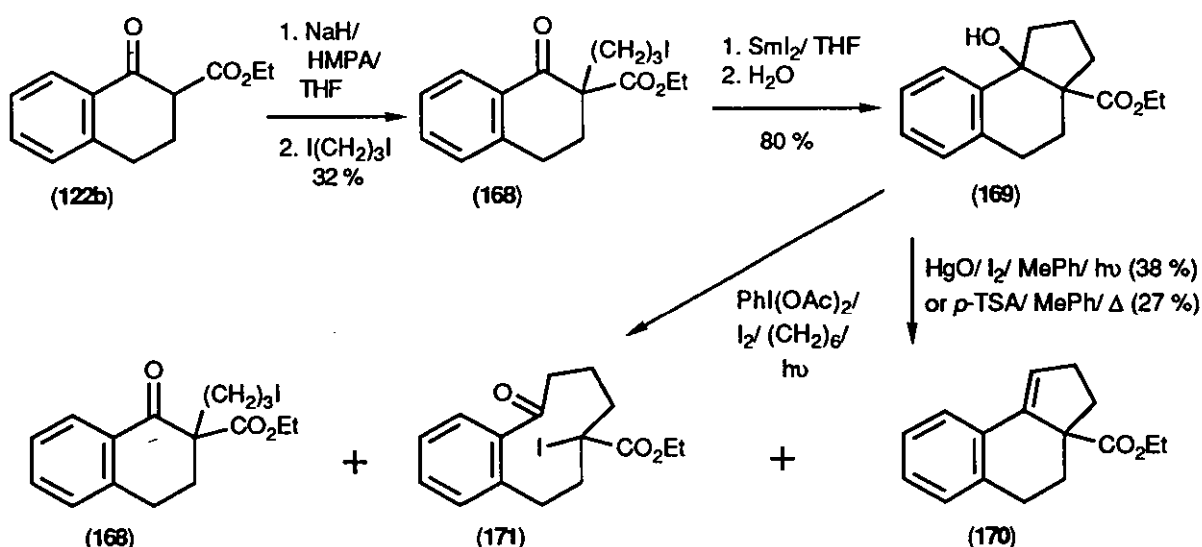


Scheme 111

The hydrogenation of the styrene (**155**) failed using 10 % palladium on charcoal in ethyl acetate (H_2 at 1 atm or 45 p.s.i.) or in ethanol (H_2 at 1 atm) (Scheme 111).

(b) Ring Expansion of 1-Tetralones

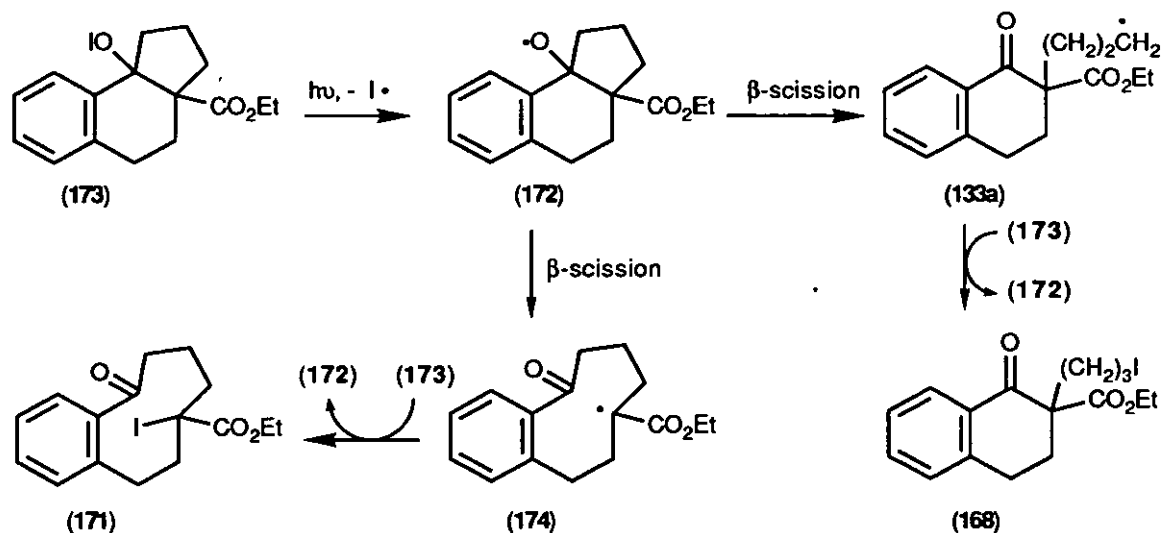
When the alcohol's structure is such that it lacks the potential to afford benzylically stabilised radicals after β -scission of the derived alkoxy radical, the reaction takes a different course. The nature of this course is dependent on the conditions under which the hypoiodite is generated (Scheme 112). Samarium (II) iodide mediated cyclisation of ethyl 2-(3-iodopropyl)-1-tetralone-2-carboxylate (**168**), which was obtained by alkylation of the β -keto ester (**122b**)^{88,89} with 1,3-di-iodopropane, afforded ethyl 2,3,3a,4,5,9b-hexahydro-9b-hydroxy-(3*H*)-benz[e]indene-3a-carboxylate (**169**) as a 1:1 mixture of *E* and *Z* isomers, with spectra similar to that of its isomer (**151**).



Scheme 112

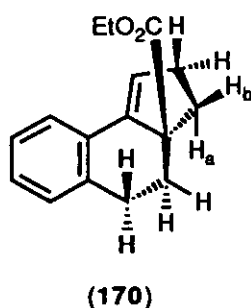
Irradiation of the alcohol (**169**) in the presence of iodine and mercuric oxide⁴⁷⁻⁵¹ afforded ethyl 2,3a,4,5-tetrahydro-(3*H*)-benz[e]indene-3a-carboxylate (**170**), which was also obtained when the alcohol (**169**) was dehydrated by *p*-toluenesulfonic acid in refluxing toluene. Clearly mercury oxide-mediated hypoiodite formation is not competitive with thermal dehydration. Irradiation of the alcohol (**169**) in the presence of iodobenzene diacetate and iodine²⁶ afforded an intractable mixture, which was analysed qualitatively by GC-MS. The mixture was found to contain the iodide (**168**) [$m/z = 217$ (60 %, *M* - CH₂CH₂CH₂I)], 118 [100, *M* - CH₂=C(CO₂Et)CH₂CH₂CH₂I], 185 (35, *M* - CO₂Et), the styrene (**170**) [$m/z = 242$ (35 %, *M*⁺), 169 (100, *M* - CO₂Et)], and a second, more polar iodide [$m/z = 386$ (10 %, *M*⁺), $m/z = 185$ (70, *M* - I - CO₂Et)], to which was assigned the

structure (171), that of ethyl 7-iodo-5,6,7,8,9,10-hexahydro-11-oxo-(11*H*)-benzocyclo-nonene-7-carboxylate.



Scheme 113

The formation of the two iodides (171) and (168) can be rationalised by assuming that β -scission of alkoxyl radical (172), which arises from photolysis of hypiodite (173), is not regiospecific (Scheme 113). This is not especially surprising, since neither of the resultant alkyl radicals, (174) and (133a), have the degree of stabilisation associated with benzylic radicals [although the radical (174) is stabilised by two alkyl moieties and an ester group compared to the single alkyl group stabilising radical (133a)]. The iodides (168) and (171) are produced by iodine-transfer from the hypiodite (173) to the alkyl radicals (174) and (133a).



The styrene (170) showed a molecular ion at $m/z = 242$ in its E.I. mass spectrum, and a peak at 1688 cm^{-1} in its IR spectrum corresponding to a styrene $\text{C}=\text{C}$ bond within a five-membered ring. An olefinic $-\text{CH}-$ group was apparent from the compound's NMR spectra ($\delta_{\text{H}} = 6.25$, $\delta_{\text{C}} = 124.7$). The ^1H NMR spectrum exhibited two distinct one-hydrogen resonances: one at $\delta_{\text{H}} = 1.96$ to $\delta_{\text{H}} = 1.88$, and one at $\delta_{\text{H}} = 1.74$ to $\delta_{\text{H}} = 1.63$. By

building models, it is apparent that H_a is significantly closer to the centre of the deshielding cone of the styrene $C=C$ bond than H_b is. Thus H_a is likely to resonate at a higher range of values of δ_H than H_b .

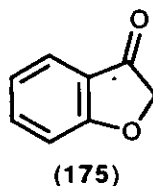
(c) Conclusions

Three-carbon ring expansion of benzocarbocycles by Cleavage of the Zero Bridge in Bicycles is moderately successful. The success of the method hinges on the ability to form a bridgehead bicyclic alcohol (23) by Barbier cyclisation (See section 1.3). This appears to be less favourable for four-carbon ring expansions than for three-carbon ring expansions. The process appears to be affected severely by the ring-size of the starting ketone (18). If the structure of the alkoxyl radical (20) derived from the bridgehead bicyclic alcohol is not such that β -scission is likely to be regiospecific, an intractable mixture of products may result.

The potential for the use of this radical ring expansion methodology has been demonstrated. Further studies are required to determine fully the scope of the method.

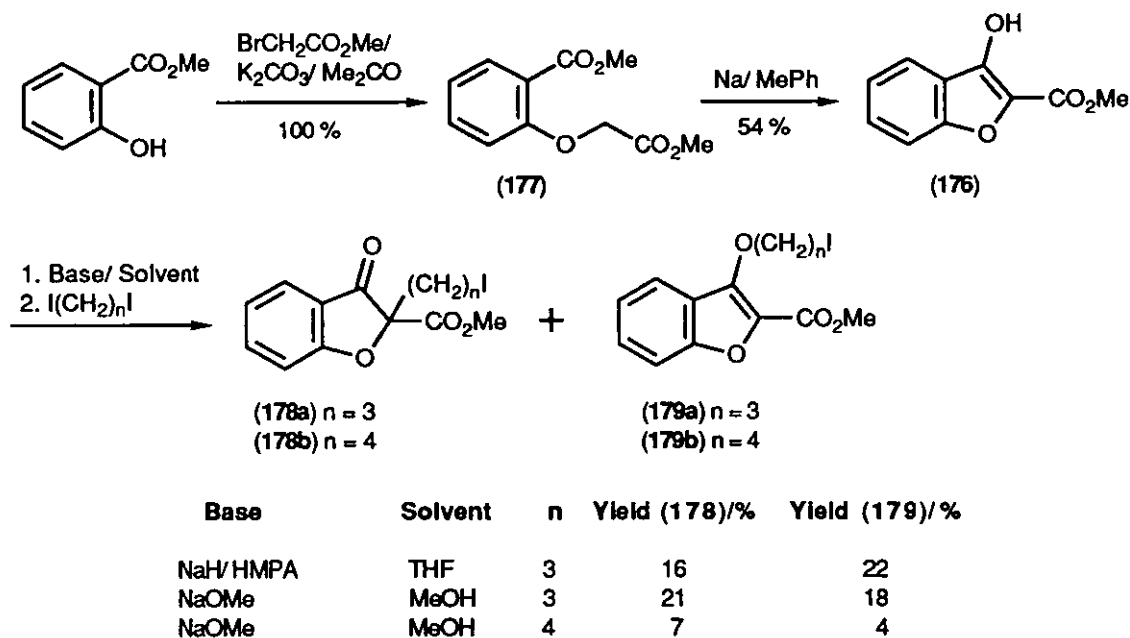
2.5 Ring Expansion of 2,3-Dihydro-3-oxobenzo[b]furans

The Boots Company is particularly interested in benzoheterocycles with a heterocyclic ring containing six atoms or more. The feasibility of applying the ring expansion methodologies, which were developed on carbocyclic ketones, to the 2,3-dihydro-3-oxobenzo[b]furan (175) system was investigated as a representative example of a class of benzoheterocycles.



Methyl 3-hydroxybenzo[b]furan-2-carboxylate⁹⁷ (176) was prepared by a Dieckmann-type cyclisation of methyl 2-methoxycarbonylphenoxyacetate (177), which was prepared from the commercially available methyl salicylate. Methyl 3-hydroxybenzo[b]furan-2-carboxylate (176), which can be regarded as a completely enolised β -keto ester, was alkylated with 1,3-di-iodopropane and with 1,4-di-iodobutane (Scheme 114). In addition to the desired products of *C*-alkylation, viz. methyl 2-(3-iodopropyl)-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (178a) and methyl 2-(4-iodobutyl)-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (178b) respectively, products of *O*-alkylation, viz. methyl 3-(3-iodopropoxy)benzo[b]furan-2-carboxylate (179a) and methyl 3-(4-iodobutyloxy)benzo[b]furan-2-carboxylate (179b) respectively, were obtained. Surprisingly, when a protic solvent, viz. methanol, is used, *O*-alkylation products are still obtained, albeit with depressed relative

yield. Presumably this results from the competing effects of the aromatic stabilisation of the benzo[b]furan system (highly enolised β -keto esters favour *O*-alkylation⁹⁸) and the co-ordination by hydrogen-bonding of the protic solvent to the enolate oxygen together with the use of soft alkylating agents, *viz.* iodides (both of which favour *C*-alkylation⁹⁸). Fortunately the products are separable by chromatography [albeit with poor recovery in the case of the products (178b) and (179b) because of similar polarity, and hence similar R_f values].

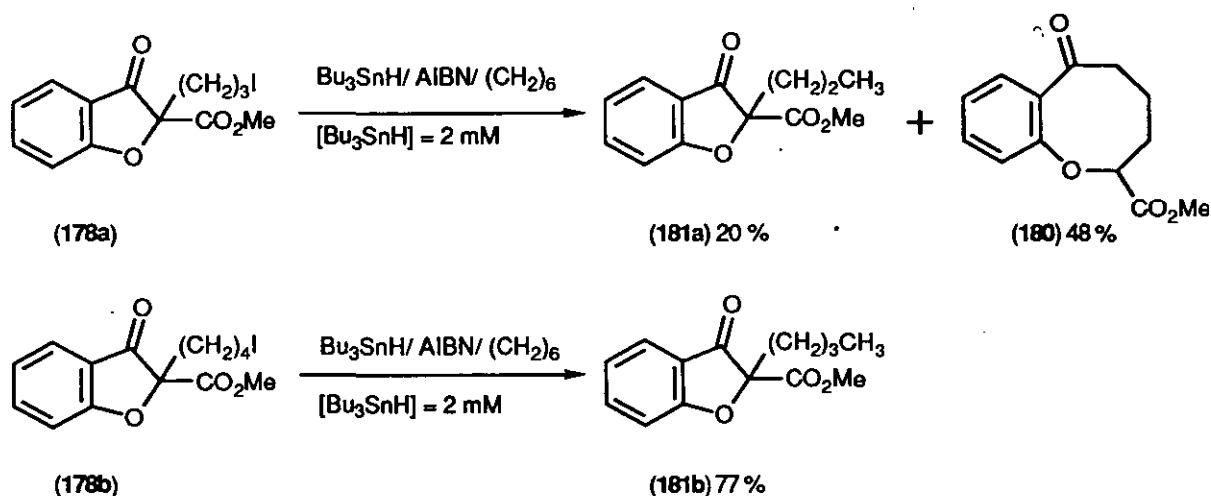


Scheme 114

Attempts at producing suitable starting materials for the one-carbon ring expansion of the benzo[b]furan (176) were unsuccessful. Alkylation of the benzo[b]furan (176) with the following reagents all failed, resulting in the formation of intractable mixtures: (i) sodium hydride and dibromomethane in THF; (ii) sodium hydride and di-iodomethane in THF and HMPA; (iii) LDA and di-iodomethane in THF; (iv) sodium methoxide, chloromethyl phenyl sulfide and sodium iodide in methanol.

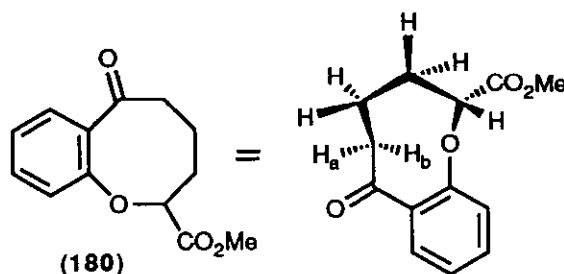
The Side Chain Incorporation methodology was applied to the ketones (178) with a degree of success (Scheme 115). When the ketones (178a) and (178b) were treated with tributylstannane (1.3 equivalents) and AIBN (0.1 equivalents) in refluxing cyclohexane under identical conditions, *viz.* addition of the reagents by syringe pump ([tributylstannane] *ca.* 2 mM), the outcome of the reactions was markedly different. The ketone (178a) gave two reduction products: one product ring-expanded by three carbons, methyl 3,4,5,6-tetrahydro-6-oxo-(2*H*)-benzoxocin-2-carboxylate (180), and one non-ring-expanded product, methyl 2-propyl-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (181a). The ketone

(178b) gave only one, non-ring-expanded product, methyl 2-butyl-2,3-dihydro-3-oxo-benzo[b]furan-2-carboxylate (181b). Thus extension of the side chain by one carbon, from three carbons to four, apparently prevents ring expansion.



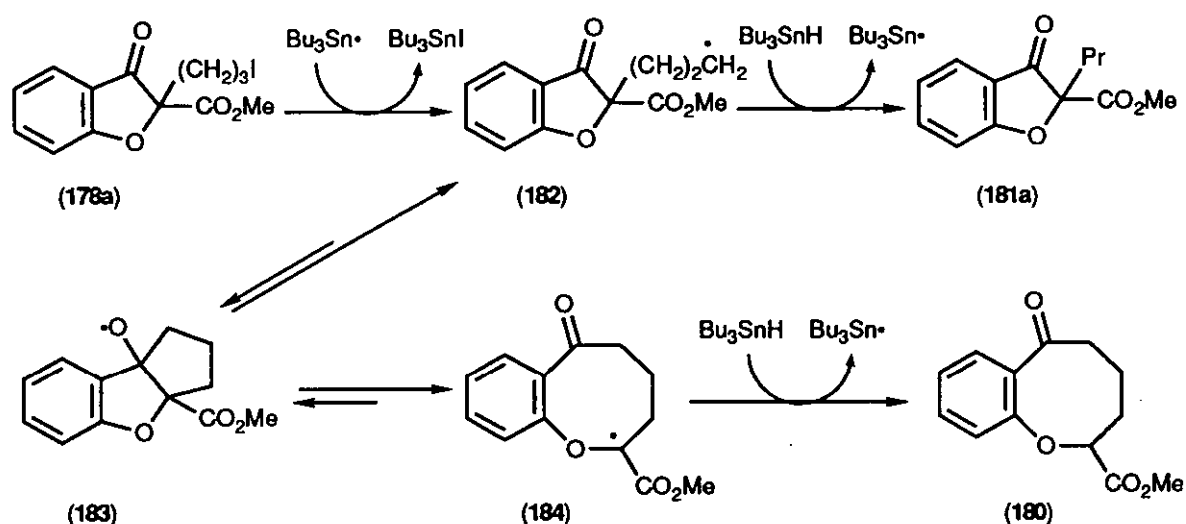
Scheme 115

The ^1H NMR spectrum of the ring-expanded ketone (180) showed a remarkable splitting of the resonance of the methylene group α to the ketone carbonyl (*i.e.* 5-H) into two one-hydrogen resonances. This was revealed by ^{13}C - ^1H correlation spectroscopy, which showed that the carbon resonating at $\delta_{\text{C}} = 41.4$ bears two hydrogens, one of which resonates at $\delta_{\text{H}} = 3.58$ to $\delta_{\text{H}} = 3.47$, and the other of which resonates at $\delta_{\text{H}} = 2.85$ to $\delta_{\text{H}} = 2.76$. This splitting can be rationalised in terms of the conformation of the oxecane ring in solution. From the IR spectrum, it is evident that the arene moiety and the ketone carbonyl are coplanar as expected [$\nu_{\text{max}}(\text{C}=\text{O}) = 1669 \text{ cm}^{-1}$]. Models suggest that the remainder of the ring assumes a chair-like conformation. In that event, H_{a} lies within the deshielding cone of the ketone carbonyl, and hence resonates at a higher value of δ_{H} than that of H_{b} (which does not lie within the cone).



The probable mechanism of the successful three-carbon ring expansion is shown below (Scheme 116). The primary alkyl radical (182) cyclises onto the α -aryl ketone

carbonyl group to afford the alkoxyl radical (183) which undergoes β -scission to give the tertiary alkyl radical (184). The alkyl radical (184) is stabilised by a heteroatom and an ester group, both of which are α to the radical centre. It undergoes a hydrogen-transfer reaction with tributylstannane to perpetuate the chain, forming the ketone (180). The primary alkyl radical (182) can also undergo a hydrogen-transfer reaction with tributylstannane to afford the ketone (181a). It is noteworthy that the ring expansion of the carbocyclic analogue, the ketone (143), failed (Scheme 101, see section 2.3). Thus it seems that the presence of the α -heteroatom in the radical (184) is critical to the success of this type of ring expansion, either to help stabilise the final radical in the mechanistic sequence, or to change the conformation of the ring. The reasons for the failure of the attempted ring expansion of ketone (178b) are unclear, even when models are used.

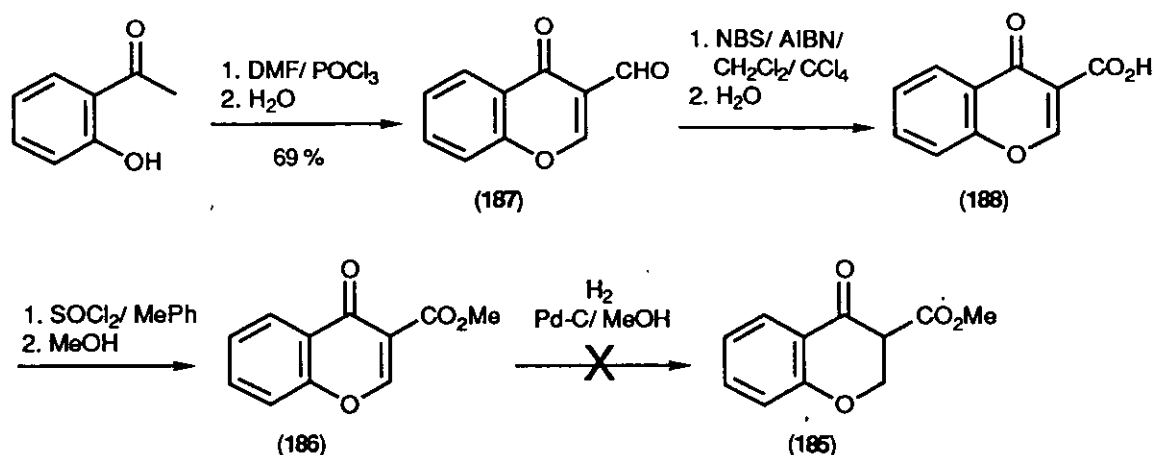


Scheme 116

Application of the Zero Bridge Cleavage Methodology to the ketones (178) failed. Treatment of the ketone (178a) with a THF solution of samarium (II) iodide at -78°C produced, surprisingly, an intractable mixture of decomposition products.

2.6 Preparation of Other Benzoheterocycles Suitable for Ring Expansion

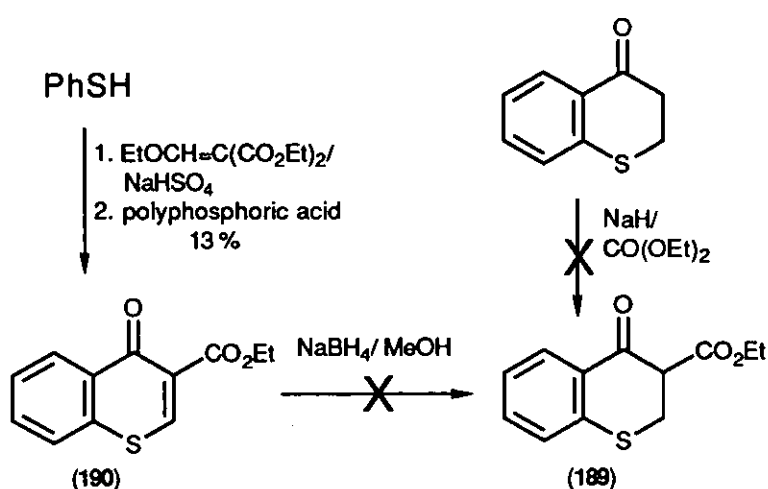
Plans for the expansion of a range of other benzoheterocyclic ketones were unsuccessful, due to difficulties associated with synthesis of suitable starting materials. The synthesis of heterocyclic analogues of the β -keto ester (122b) for further elaboration was investigated, without any success.



Scheme 117

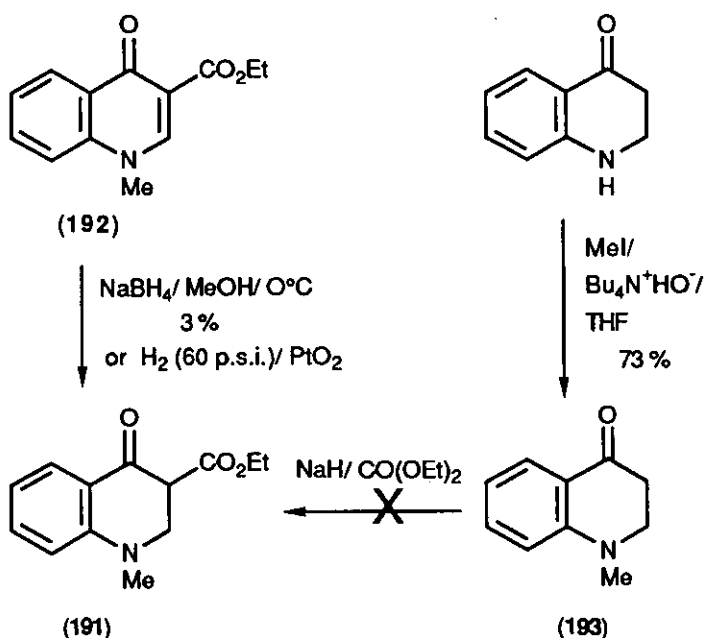
An attempt to prepare the chromanone (**185**) *via* the chromenone (**186**) was unsuccessful (Scheme 117). The first step of a literature synthesis⁹⁹ of the latter, the preparation of 4-oxo-4*H*-chromene-3-carbaldehyde (**187**) from 2-hydroxyacetophenone, was successfully repeated. Oxidation of the aldehyde (**187**) to the carboxylic acid (**188**) failed, yielding an intractable mixture. Attempted catalytic hydrogenation of an authentic sample (kindly supplied by the Boots Co. PLC) of the chromenone (**186**) gave an intractable mixture of products. There are few examples of such hydrogenations in the literature.¹⁰⁰

Similarly, preparation of ethyl 4-oxothiochroman-3-carboxylate (**189**) was unsuccessful (Scheme 118). Ethyl 4-oxo-4*H*-thiochromene-3-carboxylate (**190**) was prepared from thiophenol,¹⁰¹ and afforded an intractable mixture of products when reduction with sodium borohydride was attempted. Preparation of the thiochromanone (**189**) by ethoxycarbonylation of thiochromanone itself also failed.

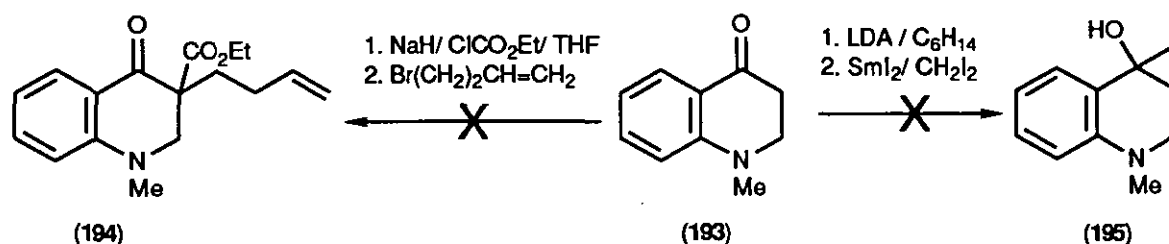


Scheme 118

Ethyl 1,2,3,4-tetrahydro-1-methyl-4-oxoquinoline-3-carboxylate (**191**) was prepared by borohydride reduction of its 1,4-dihydro analogue (**192**), albeit in poor yield (Scheme 119). High pressure hydrogenation [60 p.s.i.; platinum (IV) oxide] of the quinolone (**191**) afforded a crude product with a similar TLC and fluoresceine-like colouration to the crude product of the borohydride reduction. The crude product was not purified. The quinoline (**191**) is probably re-oxidised to the quinoline (**192**), presumably by triplet oxygen (This would rationalise the low yield). Attempted ethoxycarbonylation of ethyl 1,2,3,4-tetrahydro-1-methyl-4-oxoquinoline (**193**), which was prepared from ethyl 1,2,3,4-tetrahydro-4-oxoquinoline by *N*-methylation, failed.



Scheme 119



Scheme 120

The attempted one-pot synthesis of the quinolinone (**194**) (a suitable precursor for photochemical cyclisation to a bridgehead bicyclic alcohol³¹) by ethoxycarbonylation and subsequent *in situ* alkylation of the quinolone (**193**) resulted in recovery of the starting material. The attempted preparation of cyclopropanol (**195**) by carbenoid-mediated cyclo-

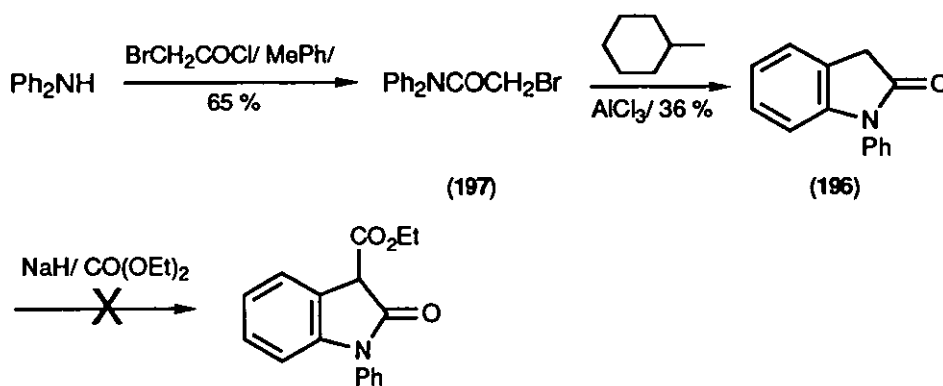
propanation of the enolate⁴¹ of the quinolinone (**193**) also afforded recovered starting material as the only product (Scheme 120).

Evidently the heteroatom modifies the chemistry of the benzo-fused ring, so that reactions which are standard for carbocyclic analogues fail. This area of investigation was abandoned although further effort would probably have permitted successful synthesis of the required precursors.

2.7 Ring Expansion of Oxindoles by Side Chain Incorporation

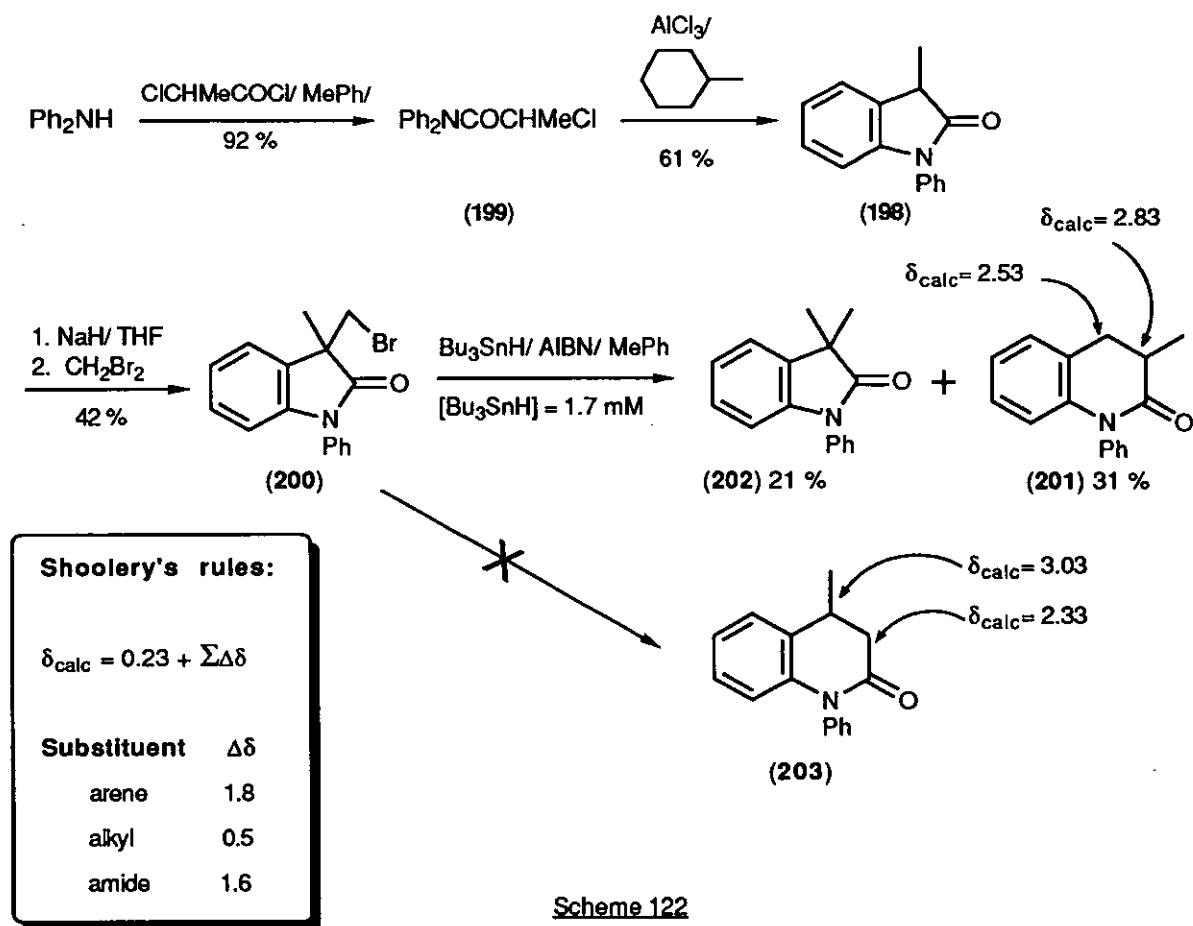
The feasibility of ring expansions of benzo-fused lactams by side chain incorporation was investigated. The general method would not be predicted to work because of the energy barrier to cyclisation onto the stable lactam carbonyl group: this arises due to the delocalisation of the lactam nitrogen atom's lone pair of electrons onto the carbonyl. However, in the case of 1-phenyloxindole (**196**), the lactam nitrogen atom's lone pair of electrons is delocalised onto the aromatic moieties as well as onto the lactam carbonyl, possibly affording the latter some ketonic character.

1-Phenyloxindole (**196**) was synthesised by acylation of diphenylamine with bromoacetyl chloride, to afford *N,N*-diphenylbromoacetamide (**197**), and subsequent Friedel-Crafts cyclisation mediated by aluminium (III) chloride.¹⁰² Attempted ethoxycarbonylation, by standard means, failed (Scheme 121).



Scheme 121 .

To circumvent this obstacle, 3-methyl-1-phenyloxindole (**198**) was synthesised by an analogous literature procedure,¹⁰² via *N,N*-diphenyl-2-chloropropionamide (**199**), and bromomethylated.^{102,103} Treatment of 3-bromomethyl-3-methyl-1-phenyloxindole (**200**) in refluxing toluene with tributylstannane (2.2 equiv in two portions), using a syringe pump ([tributylstannane] = 1.7 mM), gave a ring-expanded product, 3,4-dihydro-3-methyl-1-phenylquinolin-2(1*H*)-one (**201**), and a product of direct reduction, 3,3-dimethyl-1-phenyloxindole (**202**) (Scheme 122).



The quinolinone (201) has the assigned structure rather than that of its isomer (203), although the ^1H (according to Shoolery's rules⁸⁷) and ^{13}C spectra are consistent with both structures, *i.e.* there are resonances consistent with a lactam carbonyl, two benzene moieties and the $-\text{CH}_2\text{CHMe}-$ moiety. The absence of any nOe interaction between the methyl group and the aromatic hydrogens in the compound's ^1H NMR spectrum precludes structure (203), since nOe is operative through space over a short range. This was confirmed by 1-D nOe difference spectroscopy. Irradiation at $\delta_{\text{H}} = 1.33$ [corresponding to the three-hydrogen resonance of the methyl group ($-\text{CH}_2\text{CHMe}-$)] showed no nOe enhancement of the intensity of the one-hydrogen resonance at $\delta_{\text{H}} = 3.02$ to $\delta_{\text{H}} = 3.09$. Consequently this latter signal must correspond to the methylene group hydrogen which is *trans* to the methyl group ($-\text{CH}_2\text{CHMe}-$), rather than the methine hydrogen ($-\text{CH}_2\text{CHMe}-$). Irradiation at $\delta_{\text{H}} = 3.06$ caused nOe enhancement of the intensity of the one-hydrogen resonance in the aromatic region at $\delta_{\text{H}} = 7.19$ to $\delta_{\text{H}} = 7.26$. Therefore, the methylene group and one of the aromatic hydrogens must be close together in space. Of the two structures, (201) and (203), only (201) meets this condition.

The formation of the two products (201) and (202) is readily rationalised (Scheme 123). The initially-formed methyl radical (204) leads directly to the direct reduction product

The reaction scheme illustrates the interconversion of indole derivatives (203) through (206) via radical intermediates (204) and (205) using trialkyltin reagents.

Key reactions shown:

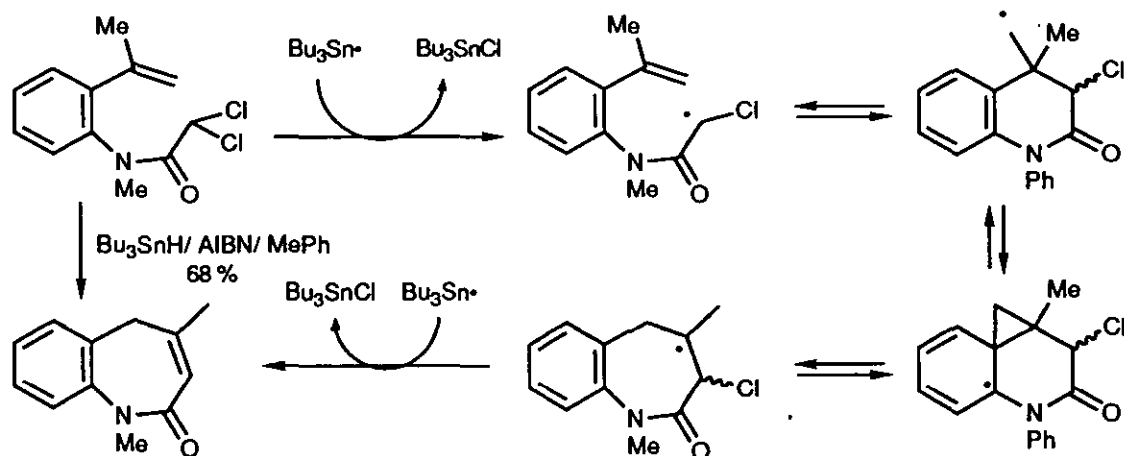
- (203) to (204):** Reaction with $\text{Bu}_3\text{Sn}^\bullet$ and Bu_3SnH to form radical (204).
- (204) to (205):** Radical (204) is in equilibrium with radical (205).
- (205) to (206):** Radical (205) is in equilibrium with radical (206).
- (206) to (201):** Reaction with $\text{Bu}_3\text{Sn}^\bullet$ and Bu_3SnH to form radical (201).
- (201) to (202):** Reaction with Bu_3SnH to form radical (202).
- (202) to (200):** Reaction with $\text{Bu}_3\text{Sn}^\bullet$ and Bu_3SnBr to form radical (200).
- (200) to (203):** Reaction with $\text{Bu}_3\text{Sn}^\bullet$ and Bu_3SnH to form radical (203).

Radical intermediates (204) and (205) are shown in equilibrium with their corresponding indole derivatives (203) and (206) respectively, as indicated by the double-headed arrows.

Scheme 123

As may be expected, ring-strain causes the wavenumber associated with the carbonyl stretch of the 5-membered-ring lactams (**200**) and (**202**) to be higher than the wavenumber associated with the carbonyl stretch of the 6-membered-ring lactam (**201**):

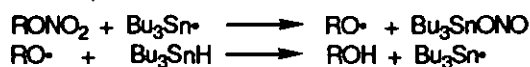
Lactam	$\nu(\text{C=O})/\text{cm}^{-1}$
(200)	1720
(202)	1722
(201)	1676



Scheme 124

2.8 Formation of the Nitrate Ester of Fused Tertiary Bicyclic Alcohols

As shown in the Introduction to this thesis [Section 1.5.2 (b)], alkoxyl radicals are readily generated from nitrate esters using tributylstannane (Scheme 125).⁵³ Accordingly the nitrate esters of tertiary alcohols (**24**, W = NO₂) would be useful intermediates for ring expansion by Cleavage of the Zero Bridge in Bicycles. There are no examples of this process in the literature and few methods for generating the esters.^{53-56,105} Therefore the formation of nitrate esters of fused tertiary bicyclic alcohols (**24**, W = NO₂) was attempted.

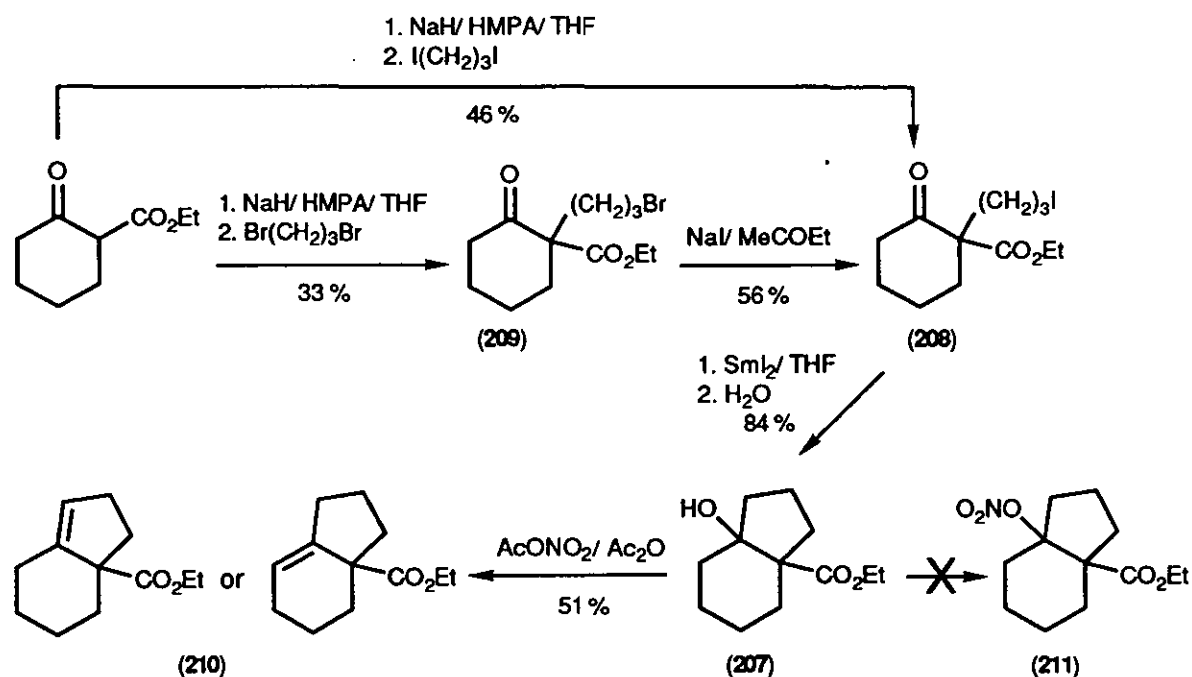


Scheme 125

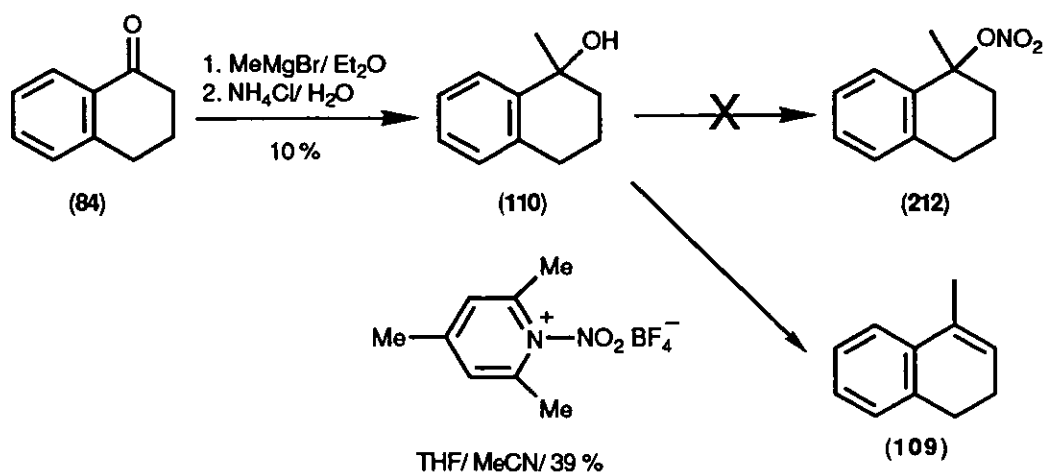
Ethyl 1-hydroxy[4.3.0]bicyclononane-5-carboxylate¹⁰⁶ (**207**) was synthesised from ethyl 1-(3-iodopropyl)-2-oxocyclohexanecarboxylate¹⁵ (**208**) by samarium (II) iodide-mediated Barbier cyclisation. When the samarium (II) iodide was added to the iodide (**208**) using a syringe pump, no alcohol (**207**) was formed and the starting material was recovered. This suggests that alkoxyl radicals are not intermediates in the cyclisation. The iodide (**208**) was synthesised from ethyl 1-(3-bromopropyl)-2-oxocyclohexanecarboxylate¹⁵ (**209**) by a Finkelstein reaction, or from the commercially available ethyl 2-oxocyclohexanecarboxylate by alkylation with 1,3-di-iodopropane (Scheme 126). Treatment of the alcohol (**207**) with a potentially explosive nitrating mixture of fuming nitric acid and acetic anhydride⁵⁵ [which affords nitronium acetate (AcONO₂) as the nitrating species] gave a product of dehydration, viz. the alkene (**210**), in preference to the nitrate ester (**211**).

As a model for the tetralone-derived alcohol (**169**), 1-methyl-1-tetralol (**110**) was prepared by treatment of 1-tetralone (**84**) with methylmagnesium bromide⁶⁰ (Scheme 127). Treatment of the tetralol (**110**) with *N*-nitrocollidinium tetrafluoroborate afforded a product

of dehydration, viz. 1,2-dihydro-4-methylnaphthalene (**109**),⁶⁰ rather than the expected nitrate ester (**212**). This is surprising, since the reagent, which is conveniently prepared *in situ* from nitronium tetrafluoroborate and collidine, is used for the preparation of nitrate esters from various tertiary alcohols [See Section 1.5.2 (b)].⁵⁶ The results suggest that dehydration of a tertiary alcohol is often faster than its nitration.



Scheme 126



Scheme 127

Attempts to use *N*-nitrosaccharin⁵⁴ (**213**) as a nitrating agent failed (Scheme 128). 1-Adamantanol (**214**) was chosen as the substrate, on which to develop the method: this tertiary alcohol is incapable of dehydrating, since the structure cannot sustain the require-

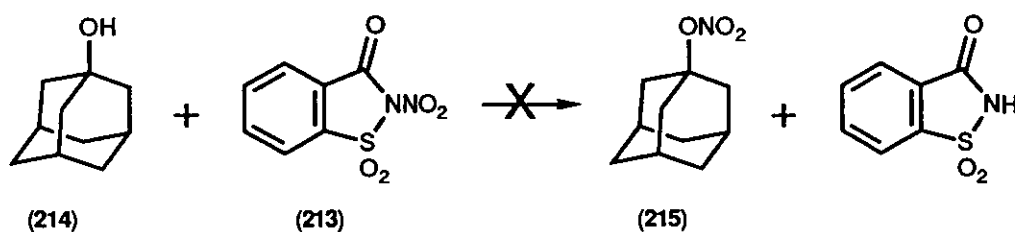
ment for coplanarity imposed by the sp^2 hybridisation of olefinic carbons. Reaction under the following conditions gave the starting material (214) as the only product (as shown by TLC, and NMR and IR spectra):

N-nitrosaccharin (213)/ NaH/ MeCN/ THF/ 0°C to r.t.;

N-nitrosaccharin (213)/ NaH/ DMF/ r.t.;

N-nitrosaccharin (213)/ NaH/ THF/ Δ .

In no case was the nitrate ester (215)⁵⁶ [$\nu(\text{RONO}_2)$ 1621 cm^{-1}] obtained.



Scheme 128

Nitronium tetrafluoroborate and *N*-nitrocollidinium tetrafluoroborate are too reactive for the formation of the nitrate esters of tetralols; *N*-nitrosaccharin is not reactive enough. After a general lack of success, this line of work was abandoned.

There are two conceivable mechanisms for the reduction of nitrate esters, and of nitro compounds, by tributylstannane. Investigations into the mechanism of this process are reported in Appendix 2.

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General

All solvents were dried and distilled before use: ethanol from magnesium; dibromomethane, dichloromethane, cyclohexane and acetonitrile from phosphorus pentoxide; DMF, acetonitrile and diethyl carbonate from calcium hydride; toluene and di-*iso*-propylamine from sodium hydride; *p*-dioxan from sodium; THF from lithium aluminium hydride, sodium amalgam or sodium/ benzophenone ketyl; petrol, diethyl ether, and ethyl acetate from calcium chloride.

Starting materials were obtained predominantly from Aldrich Chemical Co. Ltd. or from Lancaster Synthesis Ltd., and recrystallised or distilled, if appropriate. 1,2,3,4-Tetrahydro-4-oxoquinoline, 1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate and 4b,5,6,7,8,8a,9,10-octahydro-2,4-dimethoxy-9-oxophenanthrene (**216**) were obtained from The Boots Co. PLC. Pyrrolidine, morpholine and triethylamine were distilled from potassium hydroxide. Di-iodomethane was distilled from copper wire. Di-iodoethane was taken up in diethyl ether, washed with saturated aqueous sodium thiosulfate, dried over magnesium sulfate and evaporated to dryness. Sodium iodide was dried at 150°C overnight. Other reagents were used as obtained commercially.

Tungsten 'white light' fluorescence lamps (2 x 150 W) (mercury blended) were used for irradiation studies, unless otherwise stated.

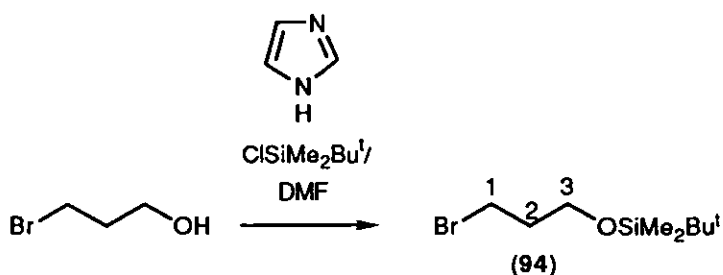
HPLC analyses (reverse phase) were carried out on a 25 cm Shandon column packed with 5 μ Hypersil ODS, with a Pye Unicam 4015 pump set at 1.0 cm³ min⁻¹ and a Pye Unicam 4020 UV detector set at 230 nm or 254 nm (as appropriate). Unless otherwise stated, the eluent was water-acetonitrile (50:50 v/v). TLC was performed on aluminium plates coated with Merck silica gel 60F254 (unless otherwise stated). Compounds were visualised by UV light.

Temperatures quoted for Kugelrohr distillations are those of the heating bath.

IR spectra were obtained using a Pye Unicam PU9516 spectrometer and a Nicolet 205 FT-IR spectrometer. Elemental analyses, 360 MHz NMR spectra, and mass spectra were provided by the Boots Company PLC. 400 MHz and nOe difference spectra were provided by the SERC High Field NMR Service at the University of Warwick. 250 MHz NMR spectra were obtained using a Bruker AC250 spectrometer. *d*-Chloroform was used as the NMR solvent (unless otherwise stated) with tetramethylsilane as internal standard. 60 MHz NMR spectra were obtained using a Varian EM360A spectrometer. GC-MS spectra were provided by the SERC Mass Spectrometry Service at University College, Swansea.

For a number of compounds, especially those which are oils and/ or alkyl halides, the data for elemental analyses were unsatisfactory. These unsatisfactory data are not quoted. However, the spectroscopic data obtained from other techniques permitted unambiguous characterisation of the compounds in question.

Preparation of 1-bromo-3-(*t*-butyldimethylsilyloxy)propane (94)⁶¹



3-Bromo-1-propanol (6.0 g, 43 mmol) was added under an atmosphere of nitrogen to a stirred solution of *t*-butyldimethylchlorosilane (7.9 g, 52 mmol) and imidazole (7.9 g, 116 mmol) in DMF (40 cm³). After 63 h the solution was poured into water (100 cm³) and extracted with petrol (b.p. 40–60 °C) (8 x 100 cm³). The combined extract was washed with saturated ammonium chloride solution (120 cm³), saturated sodium bicarbonate solution (100 cm³), water (2 x 100 cm³) and brine (100 cm³). The solution was dried over magnesium sulfate and the solvent was removed *in vacuo* to give a colourless liquid. Distillation gave 1-bromo-3-(*t*-butyldimethylsilyloxy)propane (94) as a colourless liquid (5.9 g, 23 mmol, 54 %), b.p. 35–44 °C (0.8 mm Hg), *R*_f [silica, petrol (b.p. 40–60 °C): ethyl acetate (3:1)] 0.67.

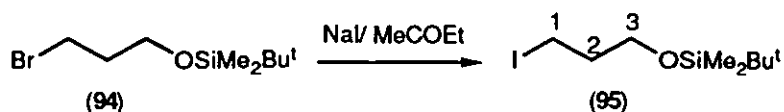
ν_{\max} (neat) 2956, 2856 (C–H), and 1470 cm^{–1}

δ_{H} (250 MHz) 3.74 (2 H, t, *J* = 5.7 Hz, 3-H), 3.51 (2 H, t, *J* = 6.4 Hz, 1-H), 2.03 (2 H, qu, *J* = 6.1 Hz, 2-H), 0.90 (9 H, s, 3-OSiBu^t), and 0.03 (6 H, s, 3-OSiMe₂).

δ_{C} (62.5 MHz) 60.3 (3-C), 35.5 (2-C), 30.5 (1-C), 25.8 (3-OSiC(CH₃)₃), –3.1 (3-OSiMe₂), and –5.5 (SiC(CH₃)₃).

The spectroscopic data correspond to those reported.⁶¹ Repetition on a smaller scale, using 3-bromo-1-propanol (5.0 g, 36 mmol) gave 1-bromo-3-(*t*-butyldimethylsilyloxy)propane (94) (2.1 g, 8.4 mmol, 23 %). Repetition on a larger scale using 3-bromo-1-propanol (18.8 g, 135 mmol), and omitting to wash the petroleum extract, gave 1-bromo-3-(*t*-butyldimethylsilyloxy)propane (94) (21.8 g, 86 mmol, 64 %).

Preparation of 3-(*t*-butyldimethylsilyloxy)-1-iodopropane (95)⁶¹



1-Bromo-3-(*t*-butyldimethylsilyloxy)propane (**94**) (2.8 g, 11 mmol) and sodium iodide (1.8 g, 12 mmol) in butanone were heated at reflux for 5 h and allowed to cool. The solution was filtered and washed with aqueous sodium sulfite and brine. The solution was dried over magnesium sulfate and the solvent was removed *in vacuo* to give 3-(*t*-butyldimethylsilyloxy)-1-iodopropane (**95**) as a yellow liquid (2.2 g, 7.2 mmol, 66 %), R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (3:1)] 0.69.

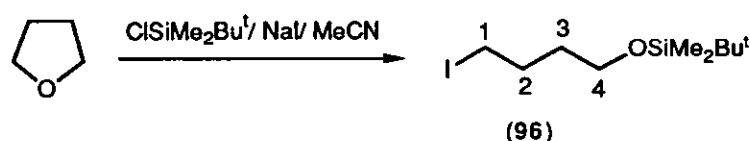
ν_{\max} (neat) 2948 (C-H) and 1468 cm^{-1}

δ_H (250 MHz) 3.67 (2 H, t, $J = 5.7$ Hz, 3-H), 3.28 (2 H, $J = 6.7$ Hz, 1-H), 1.99 (2 H, qu, $J = 6.2$ Hz, 2-H), 0.90 (9 H, s, 3-OSiBu^{*t*}), and 0.02 (6 H, s, 3-OSiMe₂).

δ_C (62.5 MHz) 62.3 (3-C), 36.2 (2-C), 25.9 (3-OSiC(CH₃)₃), 3.6 (1-C), -2.9 (3-OSiMe₂), and -5.3 (3-OSiC(CH₃)₃).

The spectroscopic data correspond to those reported.⁶¹

Preparation of 1-iodo-4-(*t*-butyldimethylsilyloxy)butane (**96**)^{61,62}



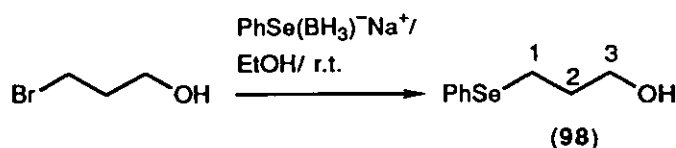
THF (4.0 cm³, 3.5 g, 49 mmol) was added under an atmosphere of nitrogen to a stirred solution of *t*-butyldimethylchlorosilane (3.0 g, 20 mmol) and sodium iodide (5.8 g, 39 mmol) in acetonitrile (55 cm³). After 23 h, the solution was poured into water (60 cm³) and extracted with petrol (b.p. 40-60°C) (4 x 100 cm³). The combined extracts were washed with saturated sodium bicarbonate (50 cm³) and brine (50 cm³). The solution was dried over magnesium sulfate and the solvent was removed *in vacuo* to give 1-iodo-4-(*t*-butyldimethylsilyloxy)butane (**96**) as an orange oil (2.9 g, 9.2 mmol, 46 %).

ν_{\max} (neat) 3342, 2952, 2856 (C-H), and 1471 cm^{-1}

δ_H (60 MHz) 3.60 (2 H, t, $J = 5.7$ Hz, 4-H), 3.20 (2 H, $J = 7$ Hz, 1-H), 3.20-1.50 (4 H, m, 2-H and 3-H), 0.9 (9 H, s, 4-OSiBu^{*t*}), and 0.05 (6 H, s, 4-OSiMe₂).

The spectroscopic data correspond to those reported.^{61,62}

Preparation of 1-benzeneselenenyl-3-propanol (**98**)^{63,68}



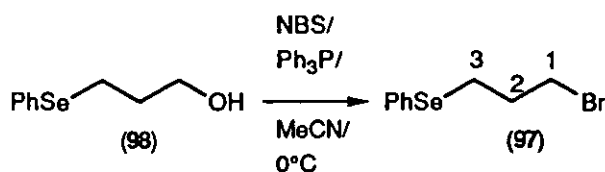
Sodium borohydride (2.7 g, 72 mmol) was added under an atmosphere of nitrogen to a stirred solution of diphenyl diselenide (9.9 g, 32 mmol) in absolute ethanol (500 cm³). After 20 min, 3-bromo-1-propanol (5.8 cm³, 8.9 g, 64 mmol) was added. After 16 h the solution was concentrated to half its original volume and hydrochloric acid (2 M, 80 cm³) was added. The solution was extracted with petrol (b.p. 40-60°C) (8 x 100 cm³). The combined extracts were washed with hydrochloric acid (2 M, 80 cm³), saturated sodium bicarbonate solution (200 cm³), water (200 cm³), and brine (200 cm³). The solution was dried over magnesium sulfate and the solvent was removed *in vacuo* to give a yellow oil. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate (4:1) as eluent gave 1-benzeneselenenyl-3-propanol (**98**) (1.1 g, 4.9 mmol, 8 %), *R*_f 0.20.

ν_{max} (neat) 3362, 2936 (C-H), 1577, and 1475 (arene C-C) cm⁻¹

δ_{H} (60 MHz) 7.30-7.15 (5 H, m, 1-SePh), 3.90-3.30 (1 H, br s, D₂O ex., 3-OH), 3.25 (2 H, t, *J* = 8 Hz, 3-H), 2.80 (2 H, t, *J* = 8 Hz, 1-H), and 1.95 (2 H, qu, *J* = 8 Hz, 2-H).

The spectroscopic data correspond to those reported.⁶³

Preparation of 1-bromo-3-benzeneselenenylpropane (**97**)⁶³



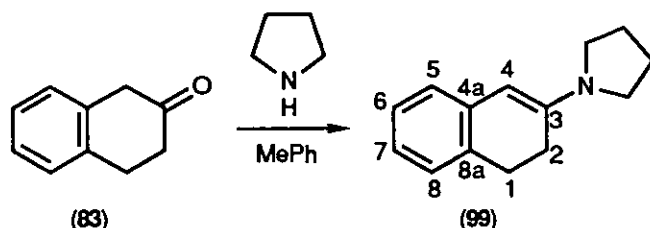
Triphenylphosphine (1.0 g, 3.8 mmol) and *N*-bromosuccinimide (0.7 g, 3.9 mmol) were added to 1-benzeneselenenyl-3-propanol (**98**) (0.8 g, 3.8 mmol) in acetonitrile (5 cm³) and the mixture was stirred for 13 h, then stored in a freezer for 64 h. Flash chromatography (silica, dichloromethane) gave 1-bromo-3-benzeneselenenylpropane (**97**) (0.2 g, 0.6 mmol, 16 %) as an orange oil, *R*_f 0.71.

ν_{max} (neat) 3070, 2920 (C-H), 1575, and 1475 cm⁻¹

δ_{H} (60 MHz) 7.30-7.15 (5 H, m, 3-SePh), 3.25 (2 H, t, $J = 8$ Hz, 1-H), 2.80 (2 H, t, $J = 8$ Hz, 3-H), and 1.95 (2 H, qu, $J = 8$ Hz, 2-H).

The spectroscopic data correspond to those reported.⁶³

Preparation of 1,2-dihydro-3-pyrrolidinynaphthalene (99)⁵⁹



2-Tetralone (83) (5.0 g, 34 mmol) and pyrrolidine (5 cm³, 4 g, 60 mmol) in toluene (100 cm³) were heated at reflux with a Dean-Stark water separator under an atmosphere of nitrogen for 3.5 h. The solution was evaporated to dryness to give 1,2-dihydro-3-pyrrolidinynaphthalene (99) practically pure as black-brown crystals (7.2 g, 35 mmol, 100 %).

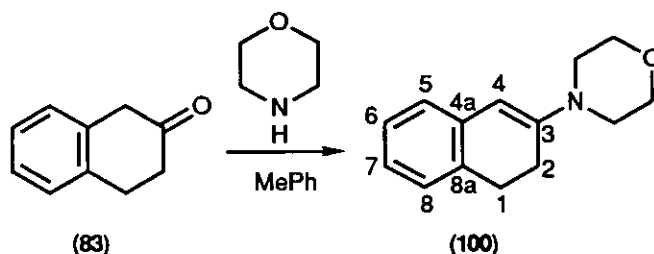
ν_{max} (Nujol) 1730, 1610 (enamine C=C), and 1564 (arene C-C) cm⁻¹

δ_{H} (250 MHz) 7.03-6.97 (2 H, m, 8-H and 5-H), 6.85-6.78 (2 H, m, 6-H and 7-H), 5.12 (1 H, s, 4-H), 3.23 (4 H, t, $J = 7.5$ Hz, 3-CH₂CH₂N), 2.82 (2 H, t, $J = 7.9$ Hz, 1-H), 2.46 (2 H, t, $J = 7.9$ Hz, 2-H), and 1.94-1.88 (4 H, m, 3-CH₂CH₂N).

δ_{C} (62.5 MHz) 147.5 (3-C), 138.2 and 130.1 (8a-C and 4a-C), 126.5 (2 signals), 122.8, and 121.6 (8-C, 7-C, 6-C and 5-C), 93.2 (4-C), 47.3 (3-NCH₂CH₂), 28.6 and 26.3 (1-C and 2-C), and 25.1 (3-NCH₂CH₂).

Recrystallisation was judged unnecessary. On a replicate run, the crude product was recrystallised from petrol (b.p. 40-60°C) to give 1,2-dihydro-3-pyrrolidinynaphthalene (99) (49 %) as brown needles, m.p. 82-83°C (lit.⁷⁵ 80-82°C), R_{f} [silica, petrol (b.p. 40-60°C): ethyl acetate (2:1)] 0.46, with identical ¹H NMR spectrum.

Preparation of 1,2-dihydro-3-morpholinonaphthalene (100)⁷⁵

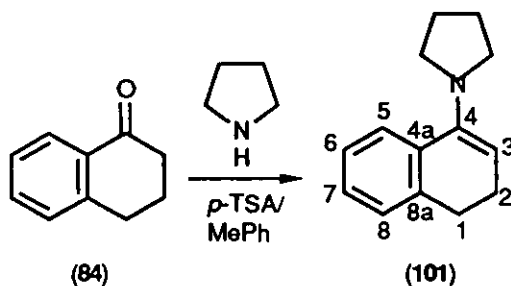


2-Tetralone (83) (5.5 g, 38 mmol) and morpholine (6.5 cm³, 6.5 g, 75 mmol) in toluene (50 cm³) were heated at reflux with a Dean-Stark water separator under an atmosphere of nitrogen for 20 h. The solvent was removed *in vacuo* to give a brown oil. Recrystallisation from petrol (b.p. 40-60°C) gave 1,2-dihydro-3-morpholinonaphthalene (100) (7.0 g, 33 mmol, 87 %) as brown needles, m.p. 51-56°C (lit.⁷⁵ 56-57°C), *R*_f [silica, petrol (b.p. 40-60°C): ethyl acetate (2:1)] 0.52.

δ_{H} (60 MHz) 7.00 (4 H, s, 5-H, 6-H, 7-H, and 8-H), 5.45 (1 H, s, 4-H), 3.70 (4 H, t, *J* = 5 Hz, 3-NCH₂CH₂O), 2.95 (4 H, t, *J* = 5 Hz, 3-NCH₂CH₂O), 2.70 (2 H, t, *J* = 8 Hz, 1-H), and 2.30 (2 H, t, *J* = 8 Hz, 2-H).

Repetition on a smaller scale, using 2-tetralone (83) (1.9 g, 13 mmol), gave 1,2-dihydro-3-morpholinonaphthalene (100) (1.3 g, 6.2 mmol, 49 %).

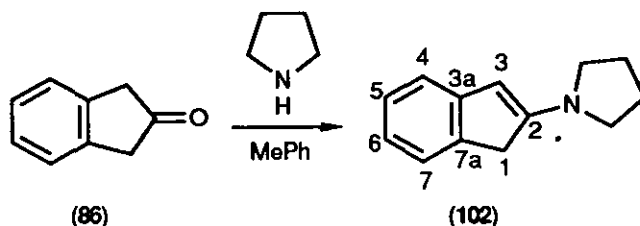
Preparation of 1,2-dihydro-4-pyrrolidinynaphthalene (101)⁷⁵



1-Tetralone (84) (3.0 g, 21 mmol), pyrrolidine (3 cm³, 3 g, 0.03 mol) and *p*-toluenesulfonic acid monohydrate (0.1 g, 0.7 mmol) in toluene (30 cm³) were heated at reflux with a Dean-Stark water separator under an atmosphere of nitrogen for 19 h. The solvent was removed *in vacuo* to give 1,2-dihydro-4-pyrrolidinynaphthalene (101) (4.1 g, 21 mmol, 100 %) as a brown oil.

δ_H (60 MHz) 7.50-7.00 (4 H, m, 5-H, 6-H, 7-H, and 8-H), 5.10 (1 H, t, $J = 5$ Hz, 3-H), 3.25-2.45 (6 H, m, 4-NCH₂CH₂ and 1-H), and 2.45-1.75 (6 H, m, 4-NCH₂CH₂ and 2-H).

Preparation of 2-pyrrolidinyl-(1*H*)-indene (102)



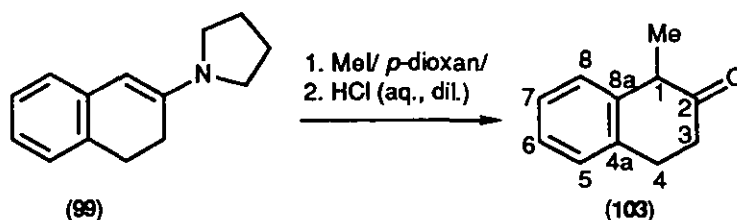
2-Indanone (86) (2.2 g, 16 mmol) and pyrrolidine (2.0 cm³, 1.7 g, 24 mmol) in toluene (40 cm³) were heated at reflux with a Dean-Stark water separator under an atmosphere of nitrogen for 3 h. The solution was evaporated to dryness to give 2-pyrrolidinyl-(1*H*)-indene (102) practically pure as black crystals (3.0 g, 16 mmol, 100 %).

ν_{\max} (Nujol mull) 2920 (C-H), 1745 (enamine C=C), and 1305 cm⁻¹

δ_H (60 MHz) 7.25 (4 H, m, 4-H, 5-H, 6-H, 7-H), 5.25 (1 H, s, 3-H), 3.25 (6 H, t and s, $J = 6$ Hz, 1-H and 2-NCH₂CH₂), and 2.00 (4 H, qu, $J =$ Hz, 2-NCH₂CH₂).

Recrystallisation was judged unnecessary.

Preparation of 1-methyl-2-tetralone (103)⁵⁹



1,2-Dihydro-3-pyrrolidinynaphthalene (99) (4.1 g, 20 mmol) and iodomethane (6 cm³, 14 g, 96 mmol) in *p*-dioxan (10 cm³) were heated at reflux for 14.5 h. Hydrochloric acid (6 M; 8 cm³) was added and reflux was continued for 5 h. Sulphuric acid (2 M; 20 cm³) was added and the solution was extracted with petrol (b.p. 40-60°C) (4 x 50 cm³). The combined extracts were washed with saturated sodium thiosulfate solution (2 x 50 cm³) and water (5 x 100 cm³). The solution was dried over magnesium sulfate and the solvent was removed *in*

* This value appears to be rather high, possibly suggesting that the ketone is present

vacuo to give a red-brown oil. Kugelrohr distillation gave 1-methyl-2-tetralone (**103**) (1.1 g, 6.8 mmol, 34 %) as a pale yellow liquid, b.p. 110°C (3.5 mm Hg) [lit.⁵⁹ 138-142°C (20 mm Hg)], *R*_f [silica, petrol (b.p. 40-60°C): ethyl acetate (3:1)] 0.43.

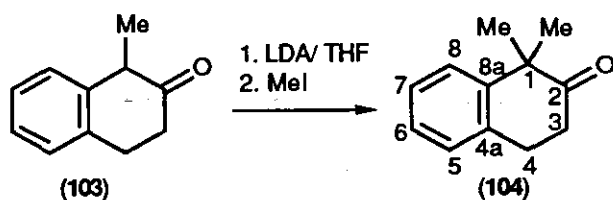
ν_{max} (neat) 3064 (C-H), 1712 (C=O), 1486 (arene C-C), and 1452 cm⁻¹

δ_{H} (250 MHz) 7.38-6.88 (4 H, m, 5-H, 6-H, 7-H, and 8-H), 3.50 (1 H, q, *J* = 7.0 Hz, 1-H), 3.13-2.96 (2 H, m, 4-H), 2.66-2.37 (2 H, m, 3-H), and 1.49 (3 H, d, *J* = 7.0 Hz, 1-Me).

δ_{C} (62.5 MHz) 212.2 (2-C), 138.0 and 136.9 (4a-C and 8a-C), 127.5, 127.1, 126.7, and 126.1 (8-C, 7-C, 6-C, and 5-C), 47.5 (1-C), 37.2 (4-C), 28.1 (3-C), and 14.2 (1-Me).

m/z (E.I.) 160.0960 (*M*⁺, 8 %, C₁₁H₁₂O requires 160.0888), and 118 (12, *M* - CH₂=C=O).

Preparation of 1,1-dimethyl-2-tetralone (**104**)



A hexane solution of *n*-butyllithium (1.7 M; 2.3 cm³, 3.9 mmol) was added to a solution of di-*iso*-propylamine (0.6 cm³, 0.4 g, 4 mmol) in THF (15 cm³) in an ice-bath under an atmosphere of nitrogen. After stirring for 15 min, the solution was cooled with a toluene-liquid nitrogen bath. 1-Methyl-2-tetralone (**103**) (0.5 g, 3 mmol) was added and the solution was stirred with cooling for 25 min. Iodomethane (2.3 cm³, 5.2 g, 37 mmol) was added and the solution was allowed to warm to room temperature. Saturated sodium bicarbonate solution (10 cm³) was added and the solution was extracted with petrol (b.p. 40-60°C) (4 x 20 cm³). The combined extracts were washed with water (2 x 20 cm³), dried and the solvent was removed *in vacuo* to a brown oil. Kugelrohr distillation gave 1,1-dimethyl-2-tetralone (**104**) (0.2 g, 1.1 mmol, 36 %) as a colourless oil, b.p. 60-70°C (0.1 mm Hg) [lit.^{76b} 73-77°C (0.1 mm Hg)], *R*_f [silica, petrol (b.p. 40-60°C): ethyl acetate (3:1)] 0.49.

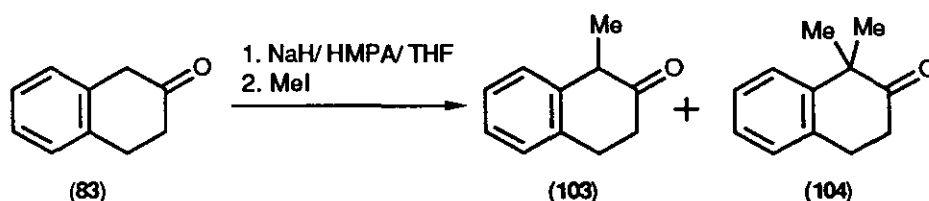
ν_{max} (neat) 3030, 2970 (C-H), 1710 (C=O), 1605, 1580, and 1485 (arene C-C) cm⁻¹

δ_{H} (250 MHz) 7.36-7.15 (4 H, m, 5-H, 6-H, 7-H, and 8-H), 3.10 (2 H, t, $J = 6.9$ Hz, 4-H), 2.68 (2 H, t, $J = 6.9$ Hz, 3-H), and 1.44 (6 H, s, 1-Me).

δ_{C} (62.5 MHz) 214.7 (2-C), 143.5 and 135.1 (8a-C and 4a-C), 128.1, 127.1, 126.4, and 126.1 (8-C, 7-C, 6-C, and 5-C), 47.7 (1-C), 37.2 (4-C), 28.6 (3-C), and 26.9 (1-Me).

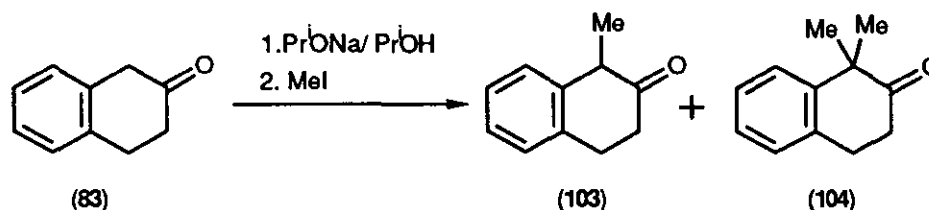
m/z (E.I.) 174.105 (M^+ , 91 %, $\text{C}_{12}\text{H}_{14}\text{O}$ requires 174.104), 132 (84, $M - \text{CH}_2=\text{C}=\text{O}$).

Attempted preparation of 1-methyl-2-tetralone (103) [1]



2-Tetralone (83) (1.0 g, 6.9 mmol) was added under an atmosphere of nitrogen to a stirred suspension of sodium hydride (80 %; 0.2 g, 7 mmol) in HMPA (1.2 cm³, 1.2 g, 6.9 mmol) and THF (20 cm³). After 1 h, iodomethane (1.0 cm³, 2.3 g, 16 mmol) was added and the solution was heated at reflux for 18 h. The solution was poured into diethyl ether and washed with water, and saturated aqueous sodium thiosulfate. The solution was dried over magnesium sulfate and the solvent was removed *in vacuo* to give a brown oil (0.9 g). The ¹H NMR spectrum showed a 4:1 mixture of 1,1-dimethyl-2-tetralone (104) and 1-methyl-2-tetralone (103).

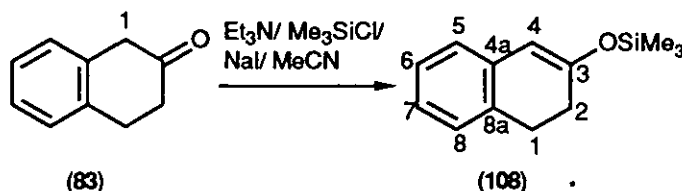
Attempted preparation of 1-methyl-2-tetralone (103) [2]



Iso-propanol (50 cm³) was added to sodium hydride (80 %; 0.5 g, 21 mmol) and allowed to dissolve. 2-Tetralone (83) (2.3 g, 16 mmol) was added and the solution was allowed to stir for 0.5 h. Iodomethane (7 cm³, 16 g, 112 mmol) was added and the solution was heated at reflux for 2 h and allowed to stir overnight. The solution was diluted with water and extracted with diethyl ether (4 x). The combined extracts were washed with sodium thiosulfate (3 x) and dried over magnesium sulfate. Removal of solvent *in vacuo* gave a

brown oil (2.5 g). The ^1H NMR spectrum showed a 2:3 mixture of 1,1-dimethyl-2-tetralone (**104**) and 1-methyl-2-tetralone (**103**).

Preparation of 1,2-dihydro-3-(trimethylsilyloxy)naphthalene (**108**)⁸²

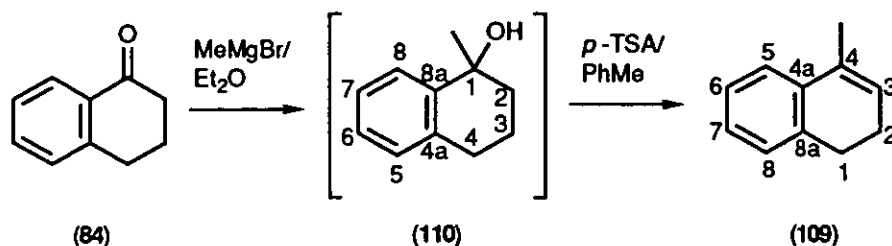


Trimethylchlorosilane (11.5 cm³, 9.8 g, 91 mmol) was added dropwise at 0°C under an atmosphere of nitrogen to a stirred solution of 2-tetralone (**83**) (8.6 g, 59 mmol) in triethylamine (12 cm³, 8.7 g, 86 mmol). After stirring in a warm water bath for 30 min, sodium iodide (7.6 g, 51 mmol) in acetonitrile (70 cm³) was added. After stirring for 8 h, the solution was poured into iced water (100 cm³) and extracted with petrol (40–60°C) (6 x 20 cm³). The combined extracts were dried over magnesium sulfate and the solvent was removed *in vacuo* to give a brown oil [6.8 g, *ca.* 31 mmol, 35 %: 1,2-dihydro-3-(trimethylsilyloxy)naphthalene⁴² (**108**); *ca.* 15 % 2-tetralone (**83**) by ^1H NMR analysis], R_f (silica, dichloromethane) 0.71 [1,2-dihydro-3-(trimethylsilyloxy)naphthalene (**108**)] and 0.33 [2-tetralone (**83**)].

δ_{H} (60 MHz) 7.00 (4 H, s, 5-H, 6-H, 7-H, 8-H), 5.70 (1 H, s, 4-H) 3.50 [s, 1-H: 2-tetralone (**83**)], 2.90 (2 H, t, $J = \text{Hz}$, 1-H), 2.25 (2 H, t, $J = 7 \text{ Hz}$, 2-H), and 0.25 (9 H, s, 3-OSiMe₃).

Repetition on a smaller scale using 2-tetralone (**83**) (3.7 g) gave a yellow liquid [2.7 g: *ca.* 40 % 1,2-dihydro-3-(trimethylsilyloxy)naphthalene (**108**); *ca.* 20 % 2-tetralone (**83**) by ^1H NMR spectroscopic analysis].

Preparation of 1,2-dihydro-4-methylnaphthalene (**109**)⁶⁰



1-Tetralone (**84**) was slowly added, under an atmosphere of nitrogen, to methylmagnesium bromide (3.0 M; 30 cm³) in diethyl ether. After heating at reflux for 3 h, the solution was washed with saturated aqueous ammonium chloride (3 x 15 cm³). The aqueous extracts were washed with diethyl ether (3 x 15 cm³) and the combined organic solutions were dried over magnesium sulfate. Removal of solvent *in vacuo* gave 1-methyl-1-tetralol (**110**) as a yellow solid. The crude alcohol (**110**) (2.7 g) and *p*-toluenesulfonic acid (0.1 g) in toluene (50 cm³) were heated at reflux in a Dean-Stark water separator under an atmosphere of nitrogen for 3 h. The solution was washed with saturated sodium bicarbonate solution (2 x 40 cm³) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give crude 1,2-dihydro-4-methylnaphthalene (**109**) as a black oil (1.7 g, 12 mmol, 44 %).

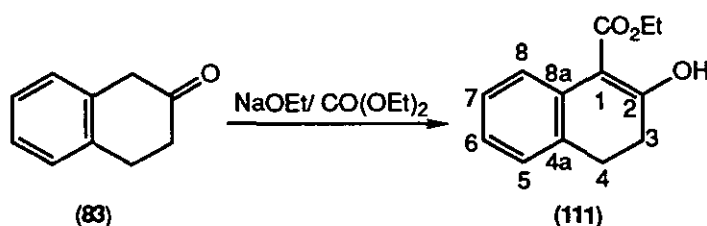
1-Methyl-1-tetralol (**110**)

δ_{H} (60 MHz) 7.80-7.00 (4 H, 5-H, 6-H, 7-H, and 8-H), 3.00-2.55 (2 H, m, 2-H), 2.10-1.75 (5 H, m, 3-H, 4-H, and 1-OH), and 1.55 (3 H, s, 1-Me).

1,2-Dihydro-4-methylnaphthalene (**109**)

δ_{H} (60 MHz) 7.25-7.00 (4 H, m, 5-H, 6-H, 7-H, and 8-H), 5.95-5.65 (1 H, m, 3-H), 2.95-2.00 (4 H, m, 1-H and 2-H), and 2.00 (3 H, s, 4-Me).

Preparation of ethyl 2-tetralone-1-carboxylate (**111**) [1]



Sodium (2.0 g, 87 mmol) was added to absolute ethanol (50 cm³) under an atmosphere of nitrogen and allowed to dissolve. The solution was evaporated to dryness, and the resultant solid was taken up in diethyl carbonate (60 cm³). 2-Tetralone (**83**) (6.6 g, 45 mmol) was added under an atmosphere of nitrogen and the solution was heated at reflux 24 h. The solution was allowed to cool and neutralised with hydrochloric acid (2 M). The solution was filtered, to remove a white solid and the phases were separated. The aqueous phase was repeatedly extracted with ethyl acetate and the combined extracts were dried over magnesium sulfate. Removal of solvent *in vacuo* gave a brown liquid. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C) as eluent gave *ethyl 2-tetralone-1-carboxylate* (**111**) (4.6 g, 21 mmol, 46 %) as a yellow liquid, R_{f} [petrol (b.p. 40-60°C): ethyl acetate (10:1)] 0.50.

Found: C, 71.4; H, 6.55 %. $C_{13}H_{14}O_3$ requires C, 71.5; H, 6.55 %.

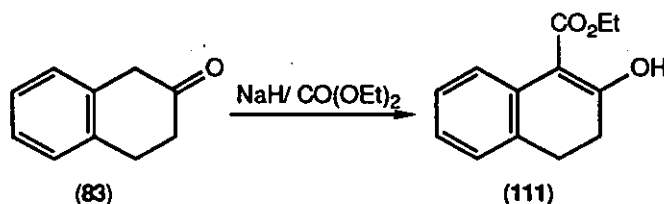
ν_{\max} (neat) 3256 (C-H), 1740 (ester C=O), 1712 (ketone C=O), 1638, 1566, 1486, and 1452 (arene C-C) cm^{-1}

δ_H (250 MHz) 13.43 (1 H, s, D_2O ex., 2-OH), 7.72 (1 H, d, $J = 7.8$ Hz, 8-H), 7.23-7.00 (3 H, m, 5-H, 6-H, and 7-H), 4.37 (2 H, q, $J = 7.1$ Hz, 1- $CO_2CH_2CH_3$), 2.79 (2 H, t, $J = 7.0$ Hz, 4-H), 2.50 (2 H, t, $J = 7.1$ Hz, 3-H), and 1.34 (3 H, t, $J = 7.1$ Hz, 1- $CO_2CH_2CH_3$).

δ_C (62.5 MHz) 178.4 (1-C), 172.1 (1- CO_2Et), 133.2 and 131.5 (8a-C and 4a-C), 127.2, 126.4, 125.9, and 124.9 (8-C, 7-C, 6-C, and 5-C), 99.9 (2-C), 61.0 (1- $CO_2CH_2CH_3$), 29.6 (4-C), 27.8 (3-C), and 14.3 (1- $CO_2CH_2CH_3$).

m/z (E.I.) 218.0927 (M^+ , 29 %, $C_{13}H_{14}O_3$ requires 218.0943), 173 (16, $M - EtO$), 173 (16, $M - EtO$), and 172 (100, $M - EtOH$).

Preparation of ethyl 2-tetralone-1-carboxylate (**111**) [2]

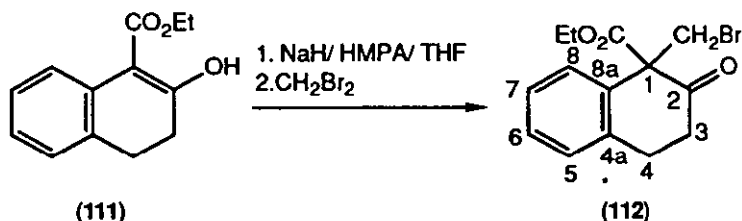


2-Tetralone (**83**) (5.0 g, 34 mmol) was added to a stirred suspension of sodium hydride (60 %; 1.5 g, 38 mmol) in diethyl carbonate (75 cm^3) under an atmosphere of nitrogen. After effervescence had ceased, the solution was heated at reflux for 2 h. The resultant solid was dissolved in hydrochloric acid (2 M, 20 cm^3) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 20 cm^3). The combined organic solutions were dried over magnesium sulfate and the solvent was removed *in vacuo* to give a brown liquid. Kugelrohr distillation gave ethyl 2-tetralone-1-carboxylate (**111**) (4.8 g, 22 mmol, 65 %) as a yellow liquid, b.p. 140°C (2 mm Hg), R_f [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.40, with NMR spectra identical to the above.

Repetition using 2-tetralone (**83**) (25.0 g, 171 mmol) gave ethyl 2-tetralone-1-carboxylate (**111**) (21.5 g, 98.5 mmol, 58 %). Repetition using 2-tetralone (**83**) (5.0 g, 30 mmol) gave ethyl 2-tetralone-1-carboxylate (**111**) (6.2 g, 29 mmol, 83 %). Repetition using

2-tetralone (**83**) (10 g, 60 mmol) gave ethyl 2-tetralone-1-carboxylate (**111**) (8.2 g, 38 mmol, 55 %).

Preparation of ethyl 1-bromomethyl-2-tetralone-1-carboxylate (**112**)



Ethyl 2-tetralone-1-carboxylate (**111**) (0.8 g, 3.7 mmol) was added to a stirred suspension of sodium hydride (80 %; 0.1 g, 4 mmol) and HMPA (0.8 cm³, 0.8 g, 5 mmol) in THF (7 cm³) under an atmosphere of nitrogen. After stirring for 1.0 h, dibromomethane (1.4 cm³, 3.5 g, 20 mmol) was added and the solution was heated at reflux for 72 h. The mixture was taken up in diethyl ether (100 cm³) and washed with water (3 x 5 cm³), dried over potassium carbonate, and the solvent was removed *in vacuo* to give a yellow oil. Flash chromatography on silica gel, with petrol (b.p. 40-60°C): ethyl acetate (10:1) as eluent, gave *ethyl 1-bromomethyl-2-tetralone-1-carboxylate* (**112**) (0.4 g, 1 mmol, 33 %) as a yellow oil, *R_f* 0.27.

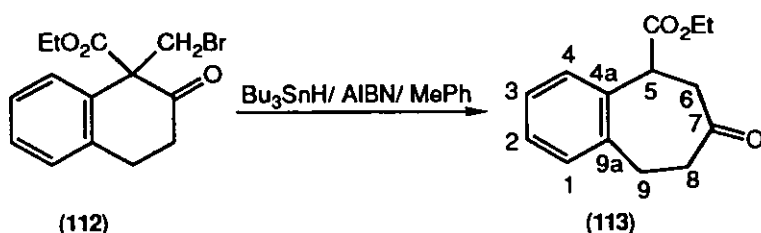
ν_{max} (neat) 3060, 2976 (C-H), 1740 (ester C=O), 1718 (ketone C=O), 1600, and 1492 (arene C-C) cm⁻¹

δ_{H} (250 MHz) 7.45-7.23 (4 H, m, 8-H, 7-H, 6-H and 5-H), 4.33 and 3.95 (2 H, 2 d, *J_{AB}* = 10.2 Hz, 1-CH₂Br), 4.09 (2 H, q, *J* = 7.2 Hz, 1-CO₂CH₂CH₃), 3.22-3.16 (2 H, m, 4-H), 3.03-2.91 and 2.79-2.68 (2 H, 2 m, 3-H), and 1.13 (3 H, t, *J* = 7.2 Hz, 1-CO₂CH₂CH₃).

δ_{C} (62.5 MHz) 205.8 (2-C), 168.9 (1-CO₂Et), 137.2 and 134.5 (8a-C and 4a-C), 128.7, 128.1, 127.4, and 126.3 (8-C, 7-C, 6-C, and 5-C), 62.9 (1-C), 62.4 (1-CO₂CH₂CH₃), 39.0 (1-CH₂Br), 35.8 (4-C), 27.7 (3-C), and 13.7 (1-CO₂CH₂CH₃).

m/z (E.I.) 312.0193 (*M*⁺, 2 %, C₁₄H₁₅O₃Br requires 312.0185 and 310.0205), 231 (83, *M* - Br), 217 (35, *M* - CH₂Br), 158 (12, *M* - Br - CO₂Et), and 157 (33, *M* - Br - HCO₂Et).

Ring expansion of ethyl 1-bromomethyl-2-tetralone-1-carboxylate (**112**)



Tributylstannane (0.1 g, 0.4 mmol) in toluene (24 cm³) was added by syringe pump, under an atmosphere of nitrogen, to a refluxing solution of ethyl 1-bromomethyl-2-tetralone-1-carboxylate (**112**) (0.1 g, 0.3 mmol) in toluene (37 cm³) ([tributylstannane] *ca.* 0.4 mM). AIBN (*ca.* 2 mg) in toluene (1 cm³) was added at 0, 10, and 28 h. The solution was heated at reflux for a further 9 h and stirred for 53 h. The solvent was removed *in vacuo* to give an orange oil. Dry flash chromatography, on silica gel with petrol (b.p. 40–60°C): ethyl acetate as eluent, and preparative TLC, on silica gel with petrol (b.p. 40–60°C): ethyl acetate (10:1) as eluent, gave *ethyl 5,6,8,9-tetrahydrobenzocyclohepten-7-one-5-carboxylate* (**113**) (0.031 g, 0.13 mmol, 51 %) as a yellow oil, R_f 0.17.

Found: C, 71.6; H, 7.3 %. C₁₄H₁₆O₃ requires C, 72.4; H, 6.9 %.

ν_{max} (neat) 2956 (C-H), 1726 (ester and ketone C=O), 1696 (shoulder), and 1492 (arene C-C) cm⁻¹

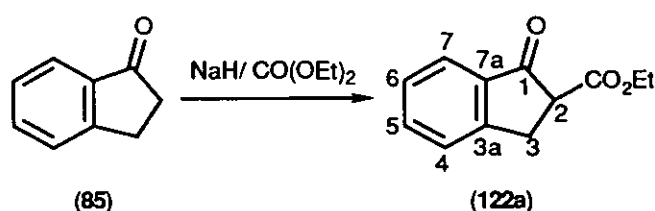
δ_{H} (400 MHz) 7.26–7.19 (4 H, m, 4-H, 3-H, 2-H, and 1-H), 4.15 (2 H, q, *J* = 7.1 Hz, 5-CO₂CH₂CH₃), 4.01 (1 H, dd, *J* = 4.1 Hz, *J* = 7.4 Hz, 5-H), 3.13–3.02 (2 H, m, 6-H and 8-H), 2.88–2.82 (1 H, m, 8-H), 2.76–2.69 (2 H, m, 6-H and 9-H), 2.58–2.51 (1 H, m, 9-H), and 1.21 (3 H, t, *J* = 7.1 Hz, 5-CO₂CH₂CH₃).

The assigned structure was confirmed by nOe difference spectroscopy.

δ_{C} (62.5 MHz) 208.9 (7-C), 172.73 (5-CO₂Et), 140.2 and 137.2 (4a-C and 9a-C), 130.1, 129.8, 128.2, and 127.4 (4-C, 3-C, 2-C, and 1-C), 61.5 (5-CO₂CH₂CH₃), 47.3 (5-C), 45.3 (9-C), 44.3 (8-C), 29.8 (6-C), and 14.1 (5-CO₂CH₂CH₃).

m/z (E.I.) 232.1137 (*M*⁺, 39 %, C₁₄H₁₆O₃ requires 232.1099), 187 (24, *M* - EtO), 159 (100, *M* - CO₂Et), 158 (29, *M* - HCO₂Et), and 131 (35, *M* - CO₂Et - CO).

Preparation of ethyl 1-indanone-2-carboxylate (122a)



1-Indanone (85) (11 g, 83 mmol) was added to a stirred suspension of sodium hydride (60 %; 3.7 g, 92 mmol) in diethyl carbonate (250 cm³) under an atmosphere of nitrogen. After effervescence had ceased, the solution was heated at reflux for 6 h. The solution was neutralised with dilute hydrochloric acid and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 50 cm³). The combined organic solutions were dried over magnesium sulfate and the solvent was removed *in vacuo*. Kugelrohr distillation gave ethyl 1-indanone-2-carboxylate⁸⁸ (122a) (9.8 g, 48 mmol, 57 %) as a yellow liquid, b.p. 170°C (0.8 mm Hg) [lit.⁸⁸ 179-180°C (15 mm Hg)], *R_f* [petrol (b.p. 40-60°C): ethyl acetate (2:1)] 0.40.

Found: C, 71.3; H, 6.5 %. C₁₂H₁₂O₃ requires C, 70.6; H, 5.9 %.

ν_{max} (neat) 2961 (C-H), 1741 (ester C=O), 1717 (5-membered ring α -aryl ketone C=O), 1681, 1654, 1626, 1592, 1573, 1465, and 1475 (arene C-C) cm⁻¹

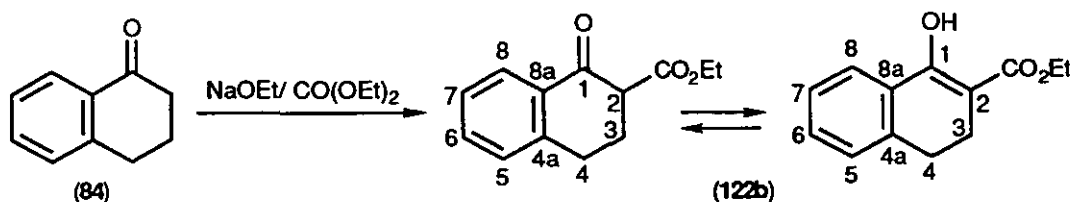
δ_{H} (250 MHz) 7.68 (1 H, d, *J* = 7.2 Hz, 7-H), 7.63-7.30 (3 H, m, 6-H, 5-H and 4-H), 4.24 (2 H, q, *J* = 6.3 Hz, 2-CO₂CH₂CH₃), 3.73-3.68 (1 H, m, 2-H), 3.59-3.49 and 3.41-3.30 (2 H, 2 m, 3-H), and 1.30 (3 H, t, *J* = 7.1 Hz, 2-CO₂CH₂CH₃).

δ_{C} (62.5 MHz) 199.5 (1-C), 169.9 (2-CO₂Et), 153.6 and 124.7 (7a-C and 3a-C), 135.4, 127.8, 126.6, and 124.6 (7-C, 6-C, 5-C, and 4-C), 61.7 (2-CO₂CH₂CH₃), 53.3 (2-C), 30.3 (3-C), 14.2 (2-CO₂C H₂CH₃).

The β -keto ester (122a) exists almost entirely in the ketonic form. The assigned structure was confirmed by ¹³C-¹H spectroscopy.

m/z (E.I.) 204.0784 (38 %, *M*⁺, C₁₂H₁₂O₃ requires 204.0786), 131 (59, *M* - CO₂Et).

Preparation of ethyl 1-tetralone-2-carboxylate (122b) [1]



Sodium (5.5 g, 0.24 mol) was added to absolute ethanol (50 cm³) under an atmosphere of nitrogen and allowed to dissolve. Diethyl carbonate (125 cm³) and 1-tetralone (84) (17.3 g, 0.12 mol) were added under an atmosphere of nitrogen and the solution was heated at reflux for 46 h. The solution was allowed to cool and neutralised with hydrochloric acid (2 M). The phases were separated and the aqueous phase was repeatedly extracted with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, and the solvent was removed *in vacuo* to give a brown liquid. Flash chromatography on silica gel, with petrol (b.p. 40-60°C): ethyl acetate (10:1) as eluent, gave ethyl 1-tetralone-2-carboxylate^{88,89} (122b) (4.2 g, 0.019 mol, 16 %) as an orange liquid, *R*_f 0.42.

ν_{max} (neat) 3068, 2976 (C-H), 1738 (ester C=O), 1686 (α -aryl ketone C=O), 1634, 1568, and 1482 (arene C-C) cm⁻¹

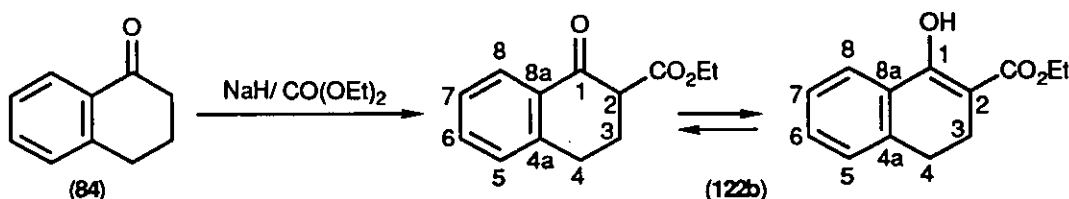
δ_{H} (250 MHz) 12.49 (1 H, s, D₂O ex., enol 1-OH), 7.80 (1 H, d, *J* = 9.0 Hz, 8-H, ketone), 7.49 (1 H, d, *J* = 1.4 Hz, 8-H, enol), 7.35-7.15 (3 H, m, 7-H, 6-H, and 5-H, ketone and enol), 4.28 (2 H, q, *J* = 7.1 Hz, 2-CO₂CH₂CH₃, ketone), 4.25 (2 H, q, *J* = 5.5 Hz, 2-CO₂CH₂CH₃, enol), 3.04-2.53 (4 H, m, 4-H and 3-H, ketone and enol), 1.34 (3 H, t, *J* = 5.5 Hz, 2-CO₂CH₂CH₃, enol), and 1.29 (3 H, t, *J* = 7.1 Hz, 2-CO₂CH₂CH₃, ketone). The ketone: enol ratio is 1:2.

δ_{C} (62.5 MHz) 193.2 (1-C, ketone), 172.7 and 170.2 (2-CO₂Et, ketone and enol), 165.0 (1-C, enol), 143.7 and 139.4 (8a-C, ketone and enol), 133.8 and 130.5 (8-C, ketone and enol), 131.8 and 130.0 (4a-C, ketone and enol), 128.8 and 127.6 (7-C, ketone and enol), 127.4 and 126.8 (6-C, ketone and enol), 126.5 and 124.3 (5-C, ketone and enol), 97.0 (2-C, enol), 61.2 and 60.5 (2-CO₂CH₂CH₃, ketone and enol), 54.6 (2-C, ketone), 27.7 and 27.6 (4-C, ketone and enol), 26.4 and 20.5 (3-C, ketone and enol), and 14.3 and 14.2 (2-CO₂CH₂CH₃, ketone and enol).

m/z (E.I.) 218.0945 (M^+ , 91 %, $C_{13}H_{14}O_3$ requires 218.0943), 173 (30, $M - EtO$), 172 (89, $M - EtOH$), 145 (42, $M - CO_2Et$), 144 (100, $M - HCO_2Et$), 118 [67, $M - CH_2=CH(CO_2Et)$], and 90 [38, $M - CH_2=C(CO_2Et)H - CO$].

Repetition, using 1-tetralone (**84**) (19.0 g, 0.13 mol) gave ethyl 1-tetralone-2-carboxylate (**122b**) (7.7 g, 0.035 mol, 27 %).

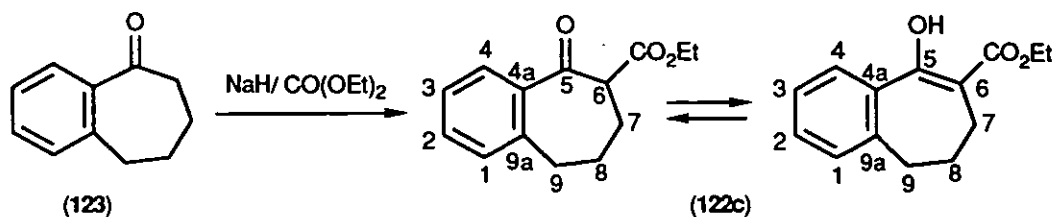
Preparation of ethyl 1-tetralone-2-carboxylate (**122b**) [2]



1-Tetralone (**84**) (9.4 g, 64 mmol) was added to a stirred suspension of sodium hydride (80 %; 2.2 g, 75 mmol) in diethyl carbonate (50 cm³) under an atmosphere of nitrogen. After effervescence had ceased, the solution was heated at reflux for 2 h. The resultant solid was dissolved in hydrochloric acid (2 M) and the phases were separated. The aqueous phase was extracted with ethyl acetate (4 x). The combined organic solutions were dried over potassium carbonate and the solvent was removed *in vacuo* to give a brown liquid. Kugelrohr distillation gave ethyl 1-tetralone-2-carboxylate^{88,89} (**122b**) (7.7 g, 35 mmol, 55 %) as a yellow liquid, b.p. 140°C (0.4 mm Hg) [lit.⁸⁸ 183°C (15 mm Hg)], R_f [petrol (b.p. 40–60°C): ethyl acetate (9:1)] 0.41, with NMR spectra identical to those reported above.

Repetition using 1-tetralone (**84**) (10 g, 0.07 mol) gave ethyl 1-tetralone-2-carboxylate (**122b**) (11.8 g, 54 mmol, 79 %).

Preparation of ethyl 6,7,8,9-tetrahydrobenzocyclohepten-5-one-6-carboxylate (**122c**)⁹⁰



1-Benzosuberone (**123**) (9.4 g, 59 mol) was added to a stirred suspension of sodium hydride (60 %; 2.6 g, 65 mmol) in diethyl carbonate (50 cm³) under an atmosphere of nitrogen. After effervescence had ceased, the solution was heated at reflux for 2.5 h and

allowed to stir overnight. The solution was washed with hydrochloric acid (2 M; 2 x) and the aqueous phase was extracted with ethyl acetate (3 x). The combined organic solutions were dried over magnesium sulfate and the solvent was removed *in vacuo* to give a pale yellow liquid. Distillation gave ethyl 6,7,8,9-tetrahydrobenzocyclohepten-5-one-6-carboxylate⁹⁰ (**122c**) (7.9 g, 34 mmol, 58 %) as a yellow liquid, b.p. 125-130°C (0.8 mm Hg) [lit.⁹⁰ 125-134°C (1 mm Hg)], *R_f* [silica, petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.54.

Found: C, 72.7, H, 7.5 %. $C_{14}H_{16}O_3$ requires C, 72.4; H, 6.9 %.

ν_{\max} (neat) 2940, 2860 (C-H), 1740 (ester C=O), 1680 (α -aryl ketone C=O), 1590, and 1450 (arene C-C) cm^{-1}

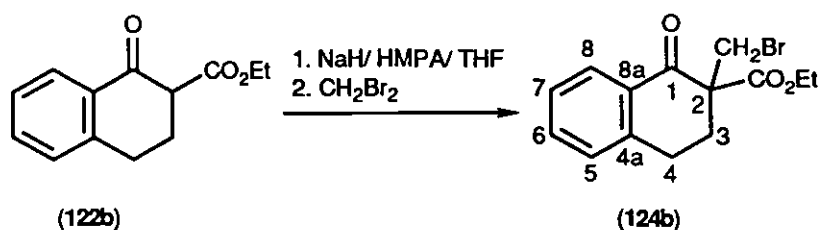
δ_H (250 MHz) 12.70 (1 H, s, D_2O ex., enol 5-OH), 7.75 (1 H, d, $J = 7.6$ Hz, 4-H, ketone), 7.63-7.60 (1 H, m, 4-H, enol), 7.42-7.14 (3 H, m, 1-H, 2-H, and 3-H, ketone and enol), 4.28 (2 H, q, $J = 7.1$ Hz, 6- $CO_2CH_2CH_3$, ketone and enol), 2.96-2.92 (1 H, m, 6-H, ketone), 2.66-2.60 (2 H, m, 9-H, ketone and enol), 2.17-2.00 (4 H, m, 8-H and 7-H, ketone and enol), 1.34 (3 H, t, $J = 7.2$ Hz, 6- $CO_2CH_2CH_3$, enol), and 1.26 (3 H, t, $J = 7.2$ Hz, 6- $CO_2CH_2CH_3$, ketone). The ketone: enol ratio is 1:2.

δ_C (62.5 MHz) 200.6 (5-C, ketone), 173.0 and 170.3 (6- CO_2Et , ketone and enol), 141.2 and 138.1 (9a-C and 4a-C, enol), 141.1 and 132.4 (9a-C and 4a-C, ketone), 130.0, 128.9, 127.1, and 126.3 (1-C, 2-C, 3-C, and 4-C, enol), 129.9, 129.1, 127.8, and 126.7 (1-C, 2-C, 3-C, and 4-C, ketone), 100.4 (6-C, enol), 61.2 and 60.6 (6- $CO_2CH_2CH_3$, ketone and enol), 56.7 (6-C, ketone), 33.5 and 32.9 (9-C, enol and ketone), 31.8 and 25.4 (8-C, ketone and enol), 24.4 and 21.8 (7-C, ketone and enol), and 14.3 and 14.1 (6- $CO_2CH_2CH_3$, ketone and enol).

m/z (E.I.) 232.101 (M^+ , 81%, $C_{14}H_{16}O_3$ requires 232.110), 187 (22, $M - EtO$), 186 (100, $M - EtOH$), 158 (45, $M - CO_2Et$), 157 (20, $M - HCO_2Et$), and 129 (54, $M - HCO_2Et - CO$).

Repetition on a smaller scale, using 1-benzosuberone (**123**) (3.0 g, 19 mmol), gave ethyl 6,7,8,9-tetrahydrobenzocyclohepten-5-one-6-carboxylate (**122c**) (2.9 g, 13 mmol, 67 %).

Preparation of ethyl 2-bromomethyl-1-tetralone-2-carboxylate (**124b**)



Ethyl 1-tetralone-2-carboxylate (**122b**) (3.4 g, 16 mmol) was added to a stirred suspension of sodium hydride (80 %; 0.6 g, 19 mmol) and HMPA (3.5 cm³, 3.6 g, 20 mmol) in THF (40 cm³) under an atmosphere of nitrogen. After stirring for 1.0 h, dibromomethane (5.5 cm³, 14 g, 78 mmol) was added and the solution was heated at reflux for 22 h. The mixture was taken up in diethyl ether (150 cm³) and washed with water (5 x 10 cm³), dried over potassium carbonate, and the solvent was removed *in vacuo* to give an orange oil. Flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate (15:1) as eluent gave ethyl 2-bromomethyl-1-tetralone-2-carboxylate⁹¹ (**124b**) (2.1 g, 6.9 mmol, 44 %) as a yellow oil, *R*_f 0.23.

ν_{max} (neat) 3064, 2980 (C-H), 1730 (ester C=O), 1688 (α -aryl ketone C=O), 1600, and 1450 (arene C-C) cm⁻¹

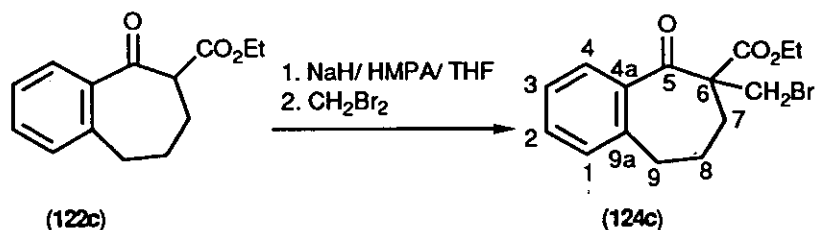
δ_{H} (250 MHz) 8.04 (1 H, d, *J* = 7.8 Hz, 8-H), 7.49 (1 H, t, *J* = 7.4 Hz, 6-H), 7.44-7.20 (2 H, m, 7-H and 5-H), 4.19 (2 H, q, *J* = 7.3 Hz, 2-CO₂CH₂CH₃), 3.93 and 3.88 (2 H, 2 d, *J*_{AB} = 10.4 Hz, 2-CH₂Br), 3.18-2.92 (2 H, m, 4-H), 2.70-2.42 (2 H, m, 3-H), and 1.22 (3 H, t, *J* = 8.6 Hz, 2-CO₂CH₂CH₃).

δ_{C} (62.5 MHz) 192.4 (1-C), 169.0 (2-CO₂Et), 143.2 and 131.3 (8a-C and 4a-C), 134.0, 128.9, 128.0, and 126.9 (8-C, 7-C, 6-C, and 5-C), 62.0 (2-CO₂CH₂CH₃), 58.3 (2-C), 34.5 (2-CH₂Br), 30.2 (4-C), 25.4 (3-C), and 14.0 (2-CO₂CH₂CH₃).

m/z (E.I.) 312.0315 and 310.0186 (*M*⁺, 31 and 29 % respectively, C₁₄H₁₅O₃Br requires 312.0185 and 310.0205 respectively), 231 (76, *M* - Br), 217 (100, *M* - CH₂Br), 158 (99, *M* - Br - CO₂Et), 157 (78, *M* - Br - HCO₂Et), 130 (29, *M* - Br - CO₂Et - CO), and 118 [61, *M* - CH₂=C(CO₂Et)CH₂Br].

Repetition on a smaller scale using ethyl 1-tetralone-2-carboxylate (**122b**) (0.7 g, 3 mmol) gave ethyl 2-bromomethyl-1-tetralone-2-carboxylate (**124b**) (0.4 g, 1 mmol, 39 %).

Preparation of ethyl 6-bromomethyl-6,7,8,9-tetrahydrobenzocyclo-hepten-5-one-6-carboxylate (124c)



Ethyl 6,7,8,9-tetrahydrobenzocyclohepten-5-one-6-carboxylate (**122c**) (5.7 g, 25 mmol) was added to a stirred suspension of sodium hydride (60 %; 1.3 g, 34 mmol) and HMPA (6.0 cm³, 6.2 g, 34 mmol) in THF (20 cm³) under an atmosphere of nitrogen. After stirring for 1.0 h, dibromomethane (8.0 cm³, 20 g, 114 mmol) was added and the solution was heated at reflux for 4 h and allowed to stir overnight. The mixture was taken up in diethyl ether (100 cm³), washed with water (5 x 5 cm³), dried over potassium carbonate, and the solvent was removed *in vacuo* to give a yellow oil. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave *ethyl 6-bromomethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one-6-carboxylate* (**124c**) (2.9 g, 9.0 mmol, 37 %) as a colourless liquid, *R_f* [silica, petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.21.

ν_{max} (neat) 2940 (C-H), 1740 (ester C=O), 1680 (α -aryl ketone C=O), 1600, and 1450 (arene C-C) cm⁻¹

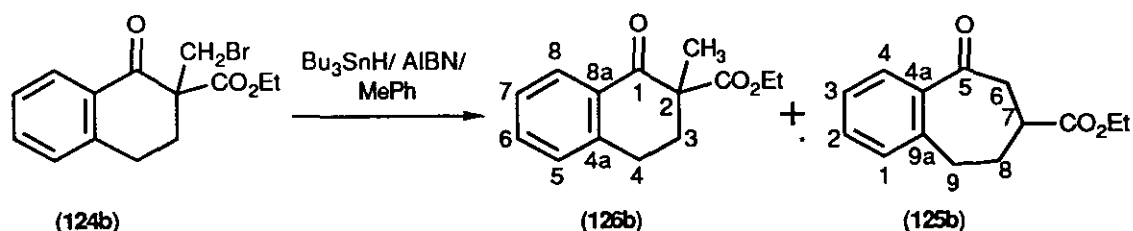
δ_{H} (250 MHz) 7.35 (1 H, d, *J* = 7.4 Hz, 4-H), 7.31 (1 H, t, *J* = 13.4 Hz, 2-H), 7.22 (1 H, t, *J* = 10.3 Hz, 1-H), 7.14 (1 H, d, *J* = 7.4 Hz, 3-H), 4.07 (2 H, q, *J* = 7.1 Hz, 6-CO₂CH₂CH₃), 3.89 and 3.81 (2 H, 2 d, *J_{AB}* = 10.2 Hz, 6-CH₂Br), 3.09-3.01 and 2.88-2.80 (2 H, 2 m, 9-H), 2.62-2.53 (1 H, m, 7-H), 2.04-1.85 (3 H, m, 7-H and 8-H), and 1.07 (3 H, t, *J* = 7.1 Hz, 6-CO₂CH₂CH₃).

δ_{C} (62.5 MHz) 202.6 (5-C), 169.5 (6-CO₂Et), 139.3 and 139.1 (4a-C and 9a-C), 131.5, 129.3, 129.0, and 128.4 (4-C, 3-C, 2-C, and 1-C), 63.0 (6-C), 61.8 (6-CO₂CH₂CH₃), 37.2 (6-CH₂Br), 33.2 (9-C), 32.3 (7-C), 23.8 (8-C), and 13.8 (6-CO₂CH₂CH₃).

m/z (E.I.) 326.034 and 324.0321 (*M*⁺, 8 and 10 % respectively, C₁₅H₁₇O₃Br requires 326.0341 and 324.0361 respectively), 245 (100, *M* - Br), 200 (17, *M* - Br - EtO), 199 (65, *M* - Br - EtOH), 172 (31, *M* - Br - CO₂Et), 171 (58, *M* - Br - HCO₂Et), and 144 (70, *M* - Br - CO₂Et - CO).

Repetition on a smaller scale, using ethyl 6,7,8,9-tetrahydrobenzocyclohepten-5-one-6-carboxylate (**122c**) (2.8 g, 12 mmol) gave ethyl 6-bromomethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one-6-carboxylate (**124c**) (3.0 g, 9.3 mmol, 77 %).

Ring expansion of ethyl 2-bromomethyl-1-tetralone-2-carboxylate (**124b**)



(a) Syringe Pump Method

Tributylstannane (0.2 g, 0.7 mmol) in toluene (10 cm³) was added by syringe pump over 50 h ([tributylstannane] *ca.* 0.8 mM) under an atmosphere of nitrogen, to a refluxing solution of ethyl 2-bromomethyl-1-tetralone-2-carboxylate (**124b**) (0.1 g, 0.3 mmol) in toluene (15 cm³). AIBN (*ca.* 2 mg) in toluene (1 cm³) was added at 0, 18, 30, and 40 h. The solution was heated at reflux for a further 12 h, and then the solvent was removed *in vacuo* to give a yellow liquid. Flash chromatography and preparative TLC on silica gel, with petrol (b.p. 40–60°C): ethyl acetate (10:1) as eluent, gave ethyl 6,7,8,9-tetrahydrobenzocyclohepten-5-one-7-carboxylate⁹¹ (**125b**) (0.031 g, 0.13 mmol, 39 %) as an orange oil, *R*_f 0.19.

Found: C, 72.7; H, 7.1 %. $\text{C}_{14}\text{H}_{16}\text{O}_3$ requires C, 72.4; H, 6.9 %.

ν_{max} (neat) 3056, 2980 (C-H), 1726 (ester C=O), 1676 (α -aryl ketone C=O), 1598, and 1478 (arene C-C) cm⁻¹

δ_{H} (250 MHz) 7.71 (1 H, d, *J* = 6.3 Hz, 4-H), 7.42 (1 H, t, *J* = 3.7 Hz, 2-H), 7.30 (1 H, t, *J* = 7.6 Hz, 1-H), 7.21 (1 H, d, *J* = 7.5 Hz, 3-H), 4.08 (2 H, q, *J* = 7.1 Hz, 7-CO₂CH₂CH₃), 3.11–2.82 (5 H, m, 6-H, 7-H, and 9-H), 2.28–2.10 (2 H, m, 8-H), and 1.21 (3 H, t, *J* = 7.1 Hz, 7-CO₂CH₂CH₃).

δ_{C} (62.5 MHz) 202.7 (5-C), 174.72 (7-CO₂Et), 140.7 and 138.1 (4a-C and 9a-C), 132.5, 129.7, 128.7, and 126.9 (4-C, 3-C, 2-C, and 1-C), 60.9 (7-CO₂CH₂CH₃), 42.8 (6-C), 38.2 (7-C), 31.1 (9-C), 28.5 (8-C), and 14.1 (7-CO₂CH₂CH₃).

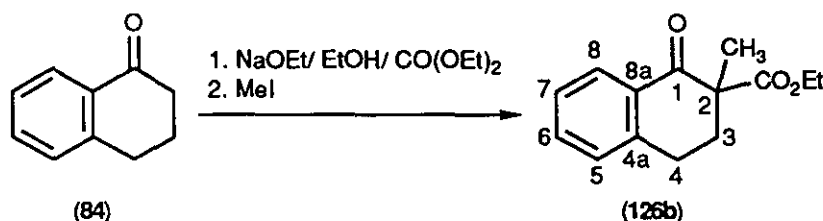
m/z (E.I.) 232.1075 (*M*⁺, 76 %, $\text{C}_{14}\text{H}_{16}\text{O}_3$ requires 232.1099). 187 (24, *M* - EtO), 159 (100, *M* - CO₂Et), 158 (29, *M* - HCO₂Et), and 131 (16, *M* - CO₂Et - CO).

The spectra corresponded to those reported.⁹¹ An additional product, ethyl 2-methyl-1-tetralone-2-carboxylate⁸⁹ (**126b**), (0.016 g, 0.069 mmol, 20 %) was obtained as an orange liquid, R_f 0.39, with identical NMR spectra to those reported below.

(b) High Dilution Method

Tributylstannane (0.3 g, 1.0 mmol) was added under an atmosphere of nitrogen to a solution of 2-bromomethyl-1-tetralone-2-carboxylate (**124b**) (0.2 g, 0.8 mmol) and AIBN (48 mg) in toluene (250 cm³) ([tributylstannane] *ca.* 4.0 mM). After refluxing for 20 h, the solution was allowed to cool and the solvent was removed *in vacuo* to give an orange liquid. The liquid was taken up in dichloromethane (50 cm³), washed with saturated aqueous potassium fluoride solution (10 x 3 cm³), dried over potassium carbonate, and the solvent was removed *in vacuo* to give a yellow liquid. The liquid was taken up in acetonitrile (40 cm³), washed with hexane (4 x 7 cm³) and the solvent was removed *in vacuo* to give an orange oil. Flash chromatography and preparative TLC, on silica gel with petrol (b.p. 40-60°C): ethyl acetate (10:1) as eluent, gave ethyl 6,7,8,9-tetrahydrobenzocyclohepten-5-one-7-carboxylate⁹¹ (**125b**) (0.017 g, 0.073 mmol, 10 %) as an orange oil, R_f 0.38, and ethyl 2-methyl-1-tetralone-2-carboxylate⁸⁹ (**126b**) (0.016 g, 0.069 mmol, 9 %) was obtained as an orange oil, R_f 0.52. For both compounds, NMR spectra were identical to those reported above.

Preparation of ethyl 2-methyl-1-tetralone-2-carboxylate (126b**)**



Sodium (0.7 g, 0.03 mol) was added to absolute ethanol (20 cm³) under an atmosphere of nitrogen and allowed to dissolve. The solvent was removed *in vacuo* to give a white solid, which was taken up in diethyl carbonate (20 cm³). 1-Tetralone (**84**) (0.9 g, 6 mmol) was added and the solution was heated at reflux for 2 h. Iodomethane (1.8 cm³, 4.1 g, 29 mmol) was added and the solution was stirred for 66 h. The solution was heated at reflux for 0.5 h, cooled and neutralised with acetic acid (2 M). The solvent was removed *in vacuo*, taken up in toluene (50 cm³) and filtered. The solvent was removed *in vacuo* to give a brown oil. Flash chromatography, on silica gel with petrol (b.p. 40-60°C): ethyl acetate (9:1) as eluent, gave ethyl 2-methyl-1-tetralone-2-carboxylate⁸⁹ (**126b**) (0.4 g, 2 mmol, 24 %) as a yellow oil, R_f 0.25.

Found: C, 72.0; H, 6.9 %. $C_{14}H_{16}O_3$ requires C, 72.4; H, 6.9 %.

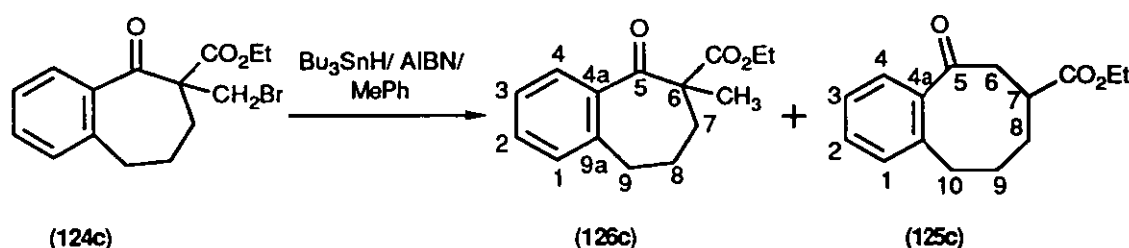
ν_{\max} (neat) 3064, 2984 (C-H), 1732 (ester C=O), 1600, and 1456 (arene C-C) cm^{-1}

δ_H (250 MHz) 8.04 (1 H, d, $J = 7.8$ Hz, 8-H), 7.25-7.20 (3 H, m, 5-H, 6-H, and 7-H), 4.14 (2 H, q, $J = 7.1$ Hz, 2-CO₂CH₂CH₃), 3.05-2.89 (2 H, m, 4-H), 2.66-2.56 and 2.11-1.99 (2 H, 2 m, 3-H), 1.50 (3 H, s, 2-CH₃), and 1.16 (3 H, t, $J = 7.1$ Hz, 2-CO₂CH₂CH₃).

δ_C (62.5 MHz) 196.1 (1-C), 172.8 (2-CO₂Et), 143.1 and 131.8 (8a-C and 4a-C), 133.4, 128.7, 127.9, 126.7 (8-C, 7-C, 6-C, and 5-C), 61.2 (2-CO₂CH₂CH₃), 53.8 (2-C), 33.9 (4-C), 26.0 (3-C), 20.5 (2-C H₃), and 14.0 (2-CO₂CH₂CH₃).

m/z (E.I.) 232.1143 (M^+ , 41 %, $C_{14}H_{16}O_3$ requires 232.1099), 217 (7, $M - Me$), 187 (4, $M - EtO$), 159 (40, $M - CO_2Et$), 158 (100, $M - HCO_2Et$), 131 (24, $M - CO_2Et - CO$), 118 [58, $M - CH_2=C(CO_2Et)Me$], and 90 [41, $M - CH_2=C(CO_2Et)Me - CO$].

Ring expansion of ethyl 6-bromomethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one-6-carboxylate (124c)



Tributylstannane (0.8 g, 2.6 mmol) in toluene (25 cm^3) was added by syringe pump over 5 h ([tributylstannane] *ca.* 4.2 mM) under an atmosphere of nitrogen, to a refluxing solution of ethyl 6-bromomethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one-6-carboxylate (124c) (0.5 g, 1.6 mmol) and AIBN (*ca.* 2 mg) in toluene (120 cm^3). Reflux was continued for a further 1.5 h. The solution was allowed to cool and the solvent was removed *in vacuo*. Dry flash chromatography (twice) on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave ethyl 6-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one-6-carboxylate (126c) (0.1 g, 0.5 mmol, 32 %) as an orange oil, R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.36, and ethyl 7,8,9,10-tetrahydro-5(6H)-benzocyclo-octenone-7-carboxylate (125c) (0.1 g, 0.4 mmol, 21 %) as an orange oil, R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.18.

Ethyl 6-methyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one-6-carboxylate (126c)

ν_{\max} (neat) 3064, 2976, 2932, 2864 (C-H), 1736 (ester C=O), 1684 (α -aryl ketone C=O), 1598, and 1448 (arene C-C) cm^{-1}

δ_{H} (250 MHz) 7.44 (1 H, dd, $J = 7.4$ Hz, $J = 1.5$ Hz, 4-H), 7.33 (1 H, dd, $J = 7.4$ Hz, $J = 1.6$ Hz, 2-H), 7.25 (1 H, dt, $J_{\text{d}} = 1.3$ Hz, $J_{\text{t}} = 7.4$ Hz, 1-H), 7.12 (1 H, dd, $J = 7.4$ Hz, $J = 0.8$ Hz, 3-H), 4.05 (2 H, q, $J = 7.1$ Hz, 6-CO₂CH₂CH₃), 2.94-2.89 and 2.84-2.78 (2 H, 2 m, 9-H), 2.37-2.30 (1 H, m, 7-H), 2.03-1.70 (3 H, m, 7-H and 8-H), 1.48 (3 H, s, 6-CH₃), and 1.07 (3 H, t, $J = 7.1$ Hz, 6-CO₂CH₂CH₃).

δ_{C} (62.5 MHz) 206.7 (5-C), 173.3 (6-CO₂Et), 140.2 and 138.4 (4a-C and 9a-C), 131.1, 129.0, 128.8, and 126.4 (4-C, 3-C, 2-C, and 1-C), 61.1 (6-CO₂CH₂CH₃), 57.9 (6-C), 34.3 (9-C), 32.8 (8-C), 23.6 (7-C), 22.1 (6-CH₃), and 13.8 (6-CO₂CH₂CH₃).

m/z (E.I.) 246.1218 (M^+ , 83 %, C₁₅H₁₈O₃ requires 246.1256), 218 (21, $M - \text{CO}$), 201 (22, $M - \text{EtO}$), 200 (66, $M - \text{EtOH}$), 173 (25, $M - \text{CO}_2\text{Et}$), 172 (36, $M - \text{HCO}_2\text{Et}$), and 145 (100, $M - \text{CO}_2\text{Et} - \text{CO}$).

Ethyl 7,8,9,10-tetrahydro-5 (6H)-benzocyclo-octenone-7-carboxylate (125c)

Found: C, 73.1; H, 7.2 %. C₁₅H₁₈O₃ requires C, 73.15; H, 7.4 %.

ν_{\max} (neat) 3056, 2976, 2932 (C-H), 1722 (ester C=O), 1664 (α -aryl ketone C=O), 1596, 1476, and 1462 (arene C-C) cm^{-1}

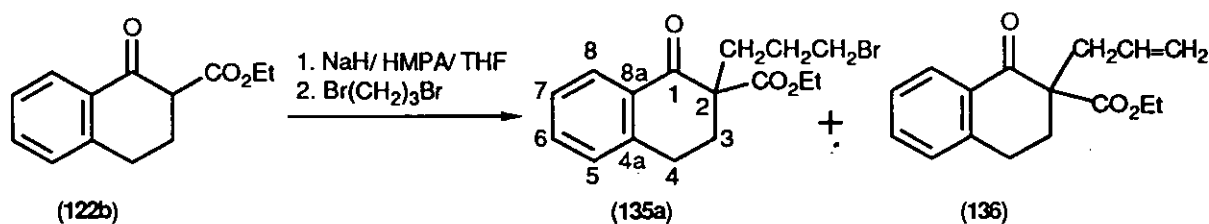
δ_{H} (250 MHz) 7.79 (1 H, dd, $J = 7.7$ Hz, $J = 1.5$ Hz, 4-H), 7.41 (1 H, dd, $J = 7.4$ Hz, $J = 6.1$ Hz, 2-H), 7.30 (1 H, dd, $J = 6.1$ Hz, $J = 7.4$ Hz, 1-H), 7.18 (1 H, dd, $J = 7.6$ Hz, $J = 0.8$ Hz, 3-H), 4.17 (2 H, q, $J = 7.2$ Hz, 7-CO₂CH₂CH₃), 3.48-3.37 (2 H, m, 10-H and 6-H), 3.07-2.91 (3 H, m, 10-H, 7-H, and 6-H), 2.05-1.90 (1 H, m, 8-H), 1.83-1.76 (3 H, m, 9-H and 8-H), and 1.24 (3 H, t, $J = 7.2$ Hz, 7-CO₂CH₂CH₃).

δ_{C} (62.5 MHz) 203.6 (5-C), 174.1 (7-CO₂Et), 139.9 and 139.1 (4a-C and 10a-C), 132.3, 131.3, 128.6, and 126.6 (4-C, 3-C, 2-C, and 1-C), 60.9 (7-CO₂CH₂CH₃), 44.8 (6-C), 40.8 (7-C), 34.3 (10-C), 27.0 (9-C), 25.1 (8-C), and 14.2 (7-CO₂CH₂CH₃).

The assignments were confirmed by ¹³C-¹H correlation spectroscopy.

m/z (E.I.) 246.1247 (M^+ , 46 %, $C_{15}H_{18}O_3$ requires 246.1256), 201 (15, $M - EtO$), 200 (22, $M - EtOH$), 173 (100, $M - CO_2Et$), 172 (13, $M - HCO_2Et$), and 145 (18, $M - CO_2Et - CO$).

Preparation of ethyl 2-(3-bromopropyl)-1-tetralone-2-carboxylate (135a)



Ethyl 1-tetralone-2-carboxylate (**122b**) (0.9 g, 4 mmol) was added to a stirred suspension of sodium hydride (80 %; 0.1 g, 5 mmol) and HMPA (1 cm³, 1 g, 6 mmol) in THF (40 cm³) under an atmosphere of nitrogen. After stirring for 1.0 h, 1,3-dibromopropane (2.0 cm³, 4.0 g, 20 mmol) was added and the solution was heated at reflux for 22 h. The mixture was allowed to cool and taken up in diethyl ether (150 cm³) and washed with water (5 x 50 cm³), dried over potassium carbonate, and the solvent was removed *in vacuo* [at r.t. (20 mm Hg) and at 60°C (1 mm Hg)] to give a yellow liquid. Flash chromatography, on silica gel with petrol (b.p. 40-60°C): ethyl acetate (15:1) as eluent, gave *ethyl 2-(3-bromopropyl)-1-tetralone-2-carboxylate* (**135a**) (0.3 g, 0.8 mmol, 21%) as an orange oil, R_f 0.30.

Found: C, 56.6; H, 5.7 %. $C_{16}H_{19}O_3Br$ requires C, 56.65; H, 5.65 %.

ν_{max} (neat) 3064, 2960 (C-H), 1730 (ester C=O), 1682 (α -aryl ketone C=O), and 1450 (arene C-C) cm⁻¹

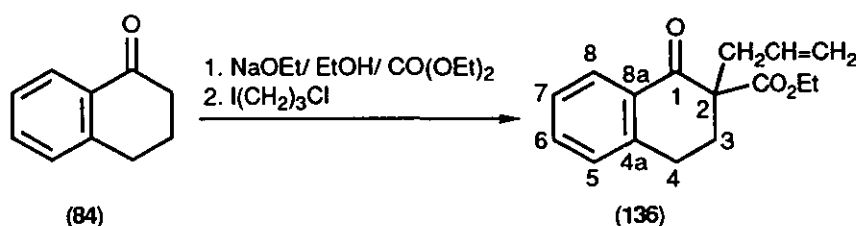
δ_H (250 MHz) 8.04 (1 H, d, $J = 7.8$ Hz, 8-H), 7.49 (1 H, t, $J = 7.4$ Hz, 6-H), 7.44-7.20 (2 H, m, 7-H and 5-H), 4.15 (2 H, q, $J = 7.1$ Hz, 2- $CO_2CH_2CH_3$), 3.44 and 3.42 (2 H, d, $J_{AB} = 4.6$ Hz, 2- $CH_2CH_2CH_2Br$), 3.07-2.90 (2 H, m, 4-H), 2.62-2.53 (1 H, m, 3-H), 2.19-1.89 (5 H, m, 3-H and 2- $CH_2CH_2CH_2Br$), and 1.17 (3 H, t, $J = 8.6$ Hz, 2- $CO_2CH_2CH_3$).

δ_C (62.5 MHz) 195.2 (1-C), 171.6 (2- CO_2Et), 142.8 and 131.9 (8a-C and 4a-C), 133.5, 128.7, 127.9, and 126.8 (8-C, 7-C, 6-C, and 5-C), 61.4 (2- $CO_2CH_2CH_3$), 57.0 (2-C), 33.7 (2- $CH_2CH_2CH_2Br$), 32.7 (2- $CH_2CH_2CH_2Br$), 30.8 (4-C), 28.2 (2- $CH_2CH_2CH_2Br$), 25.8 (3-C), and 14.0 (2- $CO_2CH_2CH_3$).

m/z (E.I.) 340.0555 and 338.0503 (M^+ , 12 %, and 13 %, $C_{16}H_{19}O_3Br$ requires 340.0498 and 338.0518 respectively), 259 (70, $M - Br$), 218 (14, $M - CH_2=CHCH_2Br$), 217 (48, $M - CH_2CH_2CH_2Br$), 186 (14, $M - Br - CO_2Et$), 185 (79, $M - Br - CO_2Et$), and 118 [100, $M - CH_2=C(CO_2Et)CH_2CH_2CH_2Br$].

As a by-product, ethyl 2-allyl-1-tetralone-2-carboxylate (**136**) (0.1 g, 0.5 mmol, 14 %) was obtained as an orange oil, R_f 0.40, with identical 1H NMR spectroscopic data to those reported below. Repetition on a larger scale using ethyl 1-tetralone-2-carboxylate (**122b**) (2.0 g, 9.2 mmol) gave ethyl 2-(3-bromopropyl)-1-tetralone-2-carboxylate (**135a**) (0.8 g, 2 mmol, 27 %) and ethyl 2-allyl-1-tetralone-2-carboxylate (**136**) (0.5 g, 2 mmol, 22 %).

Preparation of ethyl 2-allyl-1-tetralone-2-carboxylate (**136**)



Sodium (1.0 g, 45 mmol) was added to absolute ethanol (30 cm³) under an atmosphere of nitrogen and allowed to dissolve. The solvent was removed *in vacuo* to give a white solid, which was taken up in diethyl carbonate (40 cm³). 1-Tetralone (**84**) (1.6 g, 11 mmol) was added under an atmosphere of nitrogen and the solution was heated at reflux for 2 h. 3-Chloro-1-iodopropane (1.8 cm³, 3.4 g, 17 mmol) was added and the solution was heated at reflux for 2 h. The solution was stirred overnight and evaporated to dryness. The resultant solid was taken up in toluene, filtered and the solvent was removed *in vacuo* to give an orange liquid. Flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate (10:1) as eluent, followed by Kugelrohr distillation, gave ethyl 2-allyl-1-tetralone-2-carboxylate (**136**) (0.9 g, 4 mmol, 32 %) as a colourless liquid, R_f 0.27, b.p. 165°C (1.5 mm Hg).

ν_{max} (neat) 3027, 2980 (C-H), 1722 (ester and α -aryl ketone C=O), 1636 (allyl C=C), 1600, and 1476 (arene C-C) cm⁻¹

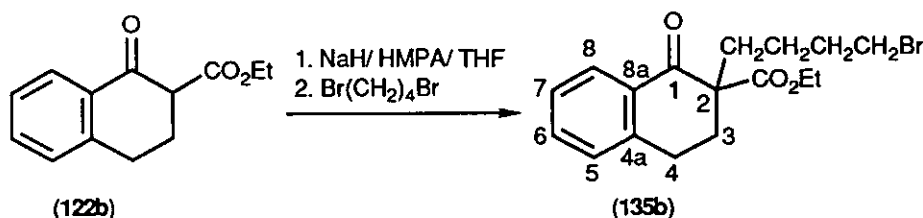
δ_H (250 MHz) 8.04 (1 H, d, $J = 8.1$ Hz, 8-H), 7.44-7.19 (3 H, m, 5-H, 6-H, and 7-H), 5.92-5.76 (1 H, m, 2-CH₂CH=CH₂), 5.17-5.02 (2 H, m, 2-CH₂CH=CH₂), 4.14 (2 H, q, $J = 7.1$ Hz, 2-CO₂CH₂CH₃), 3.08-2.88 (2 H, m, 4-H), 2.74-2.69 (2 H, m, 2-

$\text{CH}_2\text{CH}=\text{CH}_2$), 2.58-2.48 and 2.19-2.08 (2 H, 2 m, 3-H), and 1.16 (3 H, t, $J = 7.1$ Hz, $2\text{-CO}_2\text{CH}_2\text{CH}_3$).

δ_{C} (62.5 MHz) 194.8 (1-C), 171.3 (2-CO₂Et), 143.1 and 132.0 (8a-C and 4a-C), 133.5, 128.8, 127.9, and 126.7 (8-C, 7-C, 6-C, and 5-C), 126.0 (2-CH₂CH=CH₂), 118.8 (2-CH₂CH=CH₂), 61.2 (2-CO₂CH₂CH₃), 57.2 (2-C), 38.5 (2-CH₂CH=CH₂), 30.5 (4-C), 25.8 (3-C), and 14.0 (2-CO₂CH₂CH₃).

m/z (E.I.) 258.1331 (M^+ , 41 %, $\text{C}_{16}\text{H}_{18}\text{O}_3$ requires 258.1256), 217 (10, $M - \text{CH}_2\text{CH}=\text{CH}_2$), 213 (3, $M - \text{EtO}$), 185 (7, $M - \text{CO}_2\text{Et}$), 184 (4, $M - \text{HCO}_2\text{Et}$), 118 (12, $M - \text{CH}_2=\text{C}(\text{CO}_2\text{Et})\text{CH}_2\text{CH}=\text{CH}_2$), and 90 (9, $M - \text{CH}_2=\text{C}(\text{CO}_2\text{Et})\text{CH}_2\text{CH}=\text{CH}_2 - \text{CO}$).

Preparation of ethyl 2-(4-bromobutyl)-1-tetralone-2-carboxylate (135b)



Ethyl 1-tetralone-2-carboxylate (122b) (0.8 g, 3.7 mmol) was added to a stirred suspension of sodium hydride (80 %; 0.1 g, 5 mmol) and HMPA (1.0 cm³, 1.0 g, 6 mmol) in THF (25 cm³) under an atmosphere of nitrogen. After stirring for 1.0 h, 1,4-dibromobutane (3.0 cm³, 5.4 g, 25 mmol) was added and the solution was heated at reflux for 16 h. The mixture was allowed to cool and taken up in diethyl ether (150 cm³) and washed with water (20 cm³), dried over potassium carbonate, and the solvent was removed *in vacuo* [at r.t. (20 mm Hg) and at 70°C (5 mm Hg)] to give an orange oil. Flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate (10:1) as eluent gave *ethyl 2-(4-bromobutyl)-1-tetralone-2-carboxylate* (135b) (0.5 g, 1.4 mmol, 35 %) as an orange oil, R_f 0.26.

Found: C, 57.5; H, 5.7 %. $\text{C}_{17}\text{H}_{21}\text{O}_3\text{Br}$ requires C, 57.8; H, 6.0 %.

ν_{max} (neat) 3060, 2936 (C-H), 1728 (ester C=O), 1686 (α -aryl ketone C=O), 1600, and 1452 (arene C-C) cm⁻¹

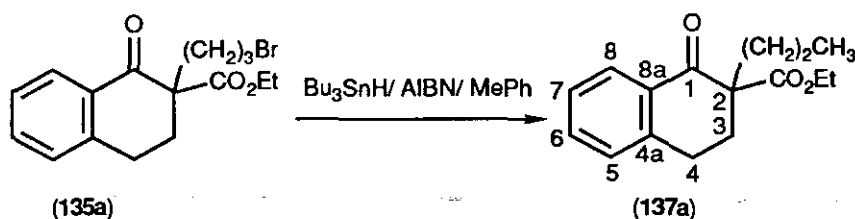
δ_{H} (250 MHz) 8.04 (1H, d, $J = 7.8$ Hz, 8-H), 7.47 (1H, t, $J = 1.3$ Hz, 6-H), 7.31-7.20 (2 H, m, 7-H and 5-H), 4.15 (2 H, q, $J = 7.1$ Hz, 2-CO₂CH₂CH₃), 3.42 (2 H, t, $J = 6.7$ Hz, 2-CH₂CH₂CH₂CH₂Br), 3.09-2.94 (2 H, m, 4-H), 2.62-2.53 and 2.21-2.11 (2 H, 2 m, 3-

H), 2.01-1.85 (4 H, m, 2-CH₂CH₂CH₂CH₂Br), 1.65-1.48 (2 H, m, 2-CH₂CH₂CH₂CH₂Br), and 1.17 (3 H, t, J = 7.1 Hz, 2-CO₂CH₂CH₃).

δ_C (62.5 MHz) 195.4 (1-C), 171.7 (2-CO₂Et), 143.0 and 132.0 (8a-C and 4a-C), 133.4, 128.7, 128.0, and 126.8 (8-C, 7-C, 6-C, and 5-C), 61.3 (2-CO₂CH₂CH₃), 57.4 (2-C), 33.3, 33.0, and 32.9 (2-CH₂CH₂CH₂CH₂Br), 30.5 (4-C), 25.9 (3-C), 23.4 (2-CH₂CH₂CH₂CH₂Br), and 14.1 (2-CO₂CH₂CH₃).

m/z (E.I.) 354.0759 and 352.0658 (M^+ , 4 %, and 6 %, C₁₇H₂₁O₃Br requires 354.0654 and 352.0674 respectively), 273 (10, M - Br), 218 (100, M - CH₂=CHCH₂CH₂Br), 217 (24, M - CH₂CH₂CH₂CH₂Br), 172 (14, M - Br - CO₂Et - CO), and 118 [67, M - CH₂=C(CO₂Et)CH₂CH₂CH₂CH₂Br].

Attempted ring expansion of ethyl 2-(3-bromopropyl)-1-tetralone-2-carboxylate (135a)



Tributylstannane (0.6 g, 2.1 mmol) in toluene (50 cm³) was added by syringe pump, under an atmosphere of nitrogen, to a refluxing solution of ethyl 2-(3-bromopropyl)-1-tetralone-2-carboxylate (135a) (0.5 g, 0.3 mmol) in toluene (250 cm³) over 50 h ([tributylstannane] *ca.* 0.2 mM). AIBN (*ca.* 2 mg) in toluene (1 cm³) was added at 0, 18, 26, and 42 h. The solution was heated at reflux for a further 18 h, and then the solvent was removed *in vacuo* to give an orange liquid. Flash chromatography and preparative TLC, on silica gel with petrol (b.p. 40-60°C): ethyl acetate (8:1) as eluent, gave ethyl 2-propyl-1-tetralone-2-carboxylate⁸⁹ (137a) (0.084 g, 0.32 mmol, 22 %) a yellow oil, R_f 0.36.

ν_{\max} (neat) 3060, 2956, 2872 (C-H), 1730 (ester C=O), 1682 (α -aryl ketone C=O), 1600, and 1452 (arene C-C) cm⁻¹

δ_H (250 MHz) 8.04 (1H, d, J = 7.8 Hz, 8-H), 7.45-7.42 (1H, m, 6-H), 7.32-7.19 (2 H, m, 7-H and 5-H), 4.14 (2 H, q, J = 7.1 Hz, 2-CO₂CH₂CH₃), 3.05-2.92 (2 H, m, 4-H), 2.59-2.54 and 2.19-2.09 (2 H, 2 m, 3-H), 1.97-1.84 (2 H, m, 2-CH₂CH₂CH₃), 1.42-1.26

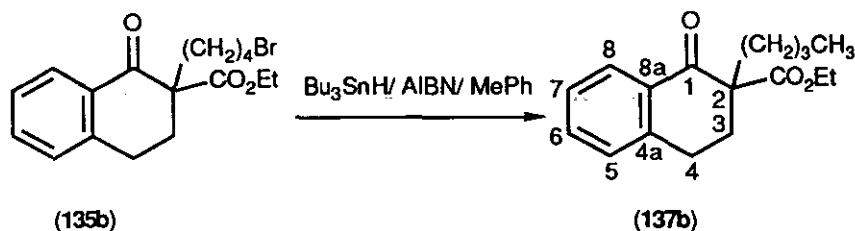
(2 H, m, 2-CH₂CH₂CH₃), 1.16 (3 H, t, J = 7.1 Hz, 2-CO₂CH₂CH₃), and 0.95 (3 H, t, J = 7.1 Hz, 2-CH₂CH₂CH₃).

δ_C (62.5 MHz) 195.6 (1-C), 171.9 (2-CO₂Et), 143.1 and 132.1 (8a-C and 4a-C), 133.3, 128.7, 128.0, and 126.7 (8-C, 7-C, 6-C, and 5-C), 61.1 (2-CO₂CH₂CH₃), 57.6 (2-C), 36.0 (2-CH₂CH₂CH₃), 30.4 (4-C), 25.9 (3-C), 18.1 (2-CH₂CH₂CH₃), 14.6 (2-CH₂CH₂CH₃), and 14.1 (2-CO₂CH₂CH₃).

m/z (E.I.) 260.1442 (M^+ , 29 %, C₁₆H₂₀O₃ requires 260.1412), 218 (14, M - CH₂=CHCH₃), 217 (48, M - CH₂CH₂CH₃), 215 (27, M - EtO), 187 (M - CO₂Et), and 118 [100, M - CH₂=C(CO₂Et)CH₂CH₂CH₃].

Ethyl 2-(3-bromopropyl)-1-tetralone-2-carboxylate (**135a**) (0.077 g, 0.23 mmol, 15 %), R_f 0.27, was also recovered.

Attempted ring expansion of ethyl 2-(4-bromobutyl)-1-tetralone-2-carboxylate (**135b**)



(a) Syringe Pump Method

Tributylstannane (0.3 g, 1 mmol) in toluene (50 cm³) was added by syringe pump, under an atmosphere of nitrogen, to a refluxing solution of ethyl 2-(4-bromobutyl)-1-tetralone-2-carboxylate (**135b**) (0.2 g, 0.7 mmol) in toluene (140 cm³) over 50 h ([tributylstannane] *ca.* 0.2 mM). AIBN (*ca.* 2 mg) in toluene (1 cm³) was added at 0, 10, 22, 32 and 45 h. The solution was heated at reflux for a further 50 h, and then the solvent was removed *in vacuo* to give an orange liquid. Dry flash chromatography, on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent, and preparative TLC, on silica gel with petrol (b.p. 40-60°C): ethyl acetate (10:1) as eluent, gave ethyl 2-butyl-1-tetralone-2-carboxylate⁸⁹ (**137b**) (0.037 g, 0.13 mmol, 20 %) a yellow oil, R_f 0.35.

Found: C, 74.1; H, 8.0 %. C₁₇H₂₂O₃ requires C, 74.4; H, 8.1 %.

ν_{max} (neat) 2956, 2872 (C-H), 1726 (ester C=O), 1686 (α -aryl ketone C=O), 1600, and 1452 (arene C-C) cm^{-1}

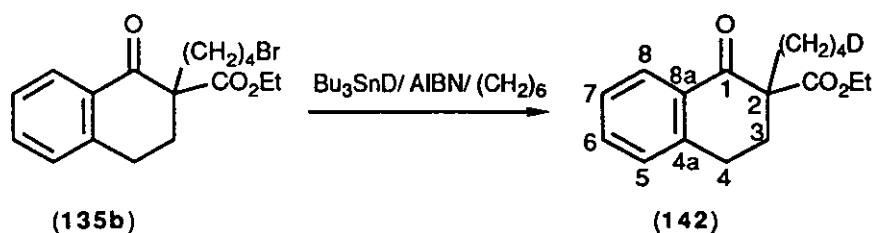
δ_{H} (250 MHz) 8.04 (1H, d, $J = 7.9$ Hz, 8-H), 7.48-7.42 (1H, m, 6-H), 7.33-7.06 (2 H, m, 7-H and 5-H), 4.14 (2 H, q, $J = 7.1$ Hz, 2-CO₂CH₂CH₃), 3.51-2.81 (2 H, m, 4-H), 2.61-2.54 and 2.20-2.12 (2 H, 2 m, 3-H), 1.99-1.88 (2 H, 2-CH₂CH₂CH₂CH₃), 1.41-1.26 (4 H, m, 2-CH₂CH₂CH₂CH₃), 1.16 (3 H, t, $J = 7.1$ Hz, 2-CO₂CH₂CH₃), and 0.91 (3 H, t, $J = 6.9$ Hz, 2-CH₂CH₂CH₂CH₃).

δ_{C} (62.5 MHz) 195.7 (1-C), 171.9 (2-CO₂Et), 143.0 and 132.1 (8a-C and 4a-C), 133.3, 128.6, 128.0, and 126.6 (8-C, 7-C, 6-C, and 5-C), 61.1 (2-CO₂CH₂CH₃), 57.5 (2-C), 33.5 (2-CH₂CH₂CH₂CH₃), 30.3 (4-C), 26.8 and 23.1 (2-CH₂CH₂CH₂CH₃), 25.9 (3-C), 14.0 (2-CO₂CH₂CH₃), and 13.9 (2-CH₂CH₂CH₂CH₃).

m/z (E.I.) 274.1489 (M^+ , 9 %, C₁₇H₂₂O₃ requires 274.1569), 218 (100, M - CH₂=CHCH₂CH₃), 217 (14, M - CH₂CH₂CH₂CH₃), 229 (4, M - EtO), 201 (22, M - CO₂Et), 118 [57, M - CH₂=C(CO₂Et)CH₂CH₂CH₂CH₃], and 90 [24, M - CH₂=C(CO₂Et)CH₂CH₂CH₂CH₃ - CO].

Ethyl 2-(4-bromobutyl)-1-tetralone-2-carboxylate (**135b**) (0.2 g, 0.5 mmol, 71 %), R_f 0.24, was also recovered. Repetition at [tributylstannane] *ca.* 0.6 mM gave ethyl 2-butyl-1-tetralone-2-carboxylate (**137b**) (0.13 g, 0.47 mmol, 67 %).

(b) Syringe Pump Method using *d*-Tributylstannane



d-Tributylstannane (1.0 g, 3.4 mmol) in cyclohexane (24 cm³) was added by syringe pump, under an atmosphere of nitrogen, to a refluxing solution of ethyl 2-(4-bromobutyl)-1-tetralone-2-carboxylate (**135b**) (0.8 g, 2.4 mmol) in cyclohexane (45 cm³) over 24 h ([*d*-tributylstannane] *ca.* 3 mM). AIBN (*ca.* 2 mg) in toluene (1 cm³) was added at 0, 6 and 21 h. The solution was heated at reflux for a further 8 h, and the solvent was removed *in vacuo* to give a yellow liquid (1.6 g). A portion (1.2 g) was subjected to dry flash chromatography (twice), on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent, to give *ethyl 2-(4-*d**

butyl)-1-tetralone-2-carboxylate (142) (0.2 g, 0.9 mmol, 36 %, 47 % corrected) as a yellow liquid, R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (10:1)] 0.44.

Found: C, 73.6; H, 7.9 %. $C_{17}H_{21}DO_3$ requires C, 74.2; H, 8.4 %.

ν_{\max} (neat) 2920, 2860 (C-H), 2160 (C-D), 1730 (ester C=O), 1690 (α -aryl ketone C=O), 1600, and 1450 (arene C-C) cm^{-1}

δ_H (360 MHz) 8.04 (1H, dd, $J = 7.9$, $J = 1.1$ Hz, 8-H), 7.46 (1 H, dt, $J_d = 3.0$ Hz, $J_t = 7.4$ Hz, 6-H), 7.30 (1 H, t, $J = 9.2$ Hz, 5-H), 7.21 (1H, d, $J = 7.6$ Hz, 7-H), 4.14 (2 H, q, $J = 7.1$ Hz, 2-CO₂CH₂CH₃), 3.06-3.03 and 2.94-2.89 (2 H, 2 m, 4-H), 2.59-2.53 and 2.18-2.12 (2 H, 2 m, 3-H), 1.99-1.87 (2 H, m, 2-CH₂CH₂CH₂CH₂D), 1.39-1.29 (4 H, 2-CH₂CH₂CH₂CH₂D), 1.17 (3 H, t, $J = 7.1$ Hz, 2-CO₂CH₂CH₃), and 0.93-0.89 (2 H, m, 2-CH₂CH₂CH₂CH₂D).

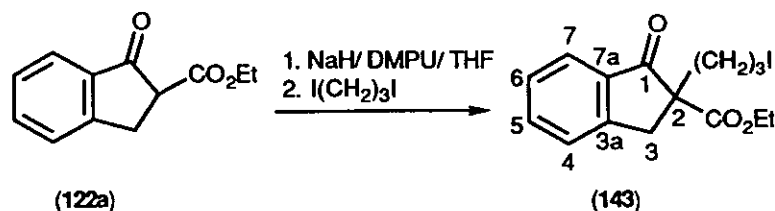
δ_C (90 MHz) 195.6 (1-C), 171.9 (2-CO₂Et), 143.0 and 132.1 (8a-C and 4a-C), 133.3, 128.6, 128.0, and 126.6 (8-C, 7-C, 6-C, 5-C), 61.1 (2-CO₂CH₂CH₃), 57.5 (2-C), 33.5 (2-CH₂CH₂CH₂CH₂D), 30.3 (4-C), 26.8 and 23.1 (2-CH₂CH₂CH₂CH₂D), 25.9 (3-C), 14.0 (2-CO₂CH₂CH₃), and 13.9 (t, $J_{C-D} \approx 45$ MHz, 2-CH₂CH₂CH₂CH₂D).

m/z (E.I.) 275.1589 (M^+ , 15 %, $C_{17}H_{21}DO_3$ requires 275.1632), 230 (3, M - EtO), 218 (100, M - CH₂=CHCH₂CH₂D), 217 (19, M - CH₂CH₂CH₂CH₂D), 202 (12, M - CO₂Et), and 118 [40, M - CH₂=C(CO₂Et)CH₂CH₂CH₂CH₂D].

(c) High Dilution Method

Tributylstannane (0.3 g, 1.0 mmol) was added, under an atmosphere of nitrogen, to a solution of ethyl 2-(4-bromobutyl)-1-tetralone-2-carboxylate (135b) (0.2 g, 0.5 mmol) and AIBN (few mg) in toluene (60 cm³) ([tributylstannane] *ca.* 14 mM). After refluxing for 24 h, the solution was allowed to cool and the solvent was removed *in vacuo* to give an orange oil. Dry flash chromatography, on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent, and preparative TLC, on silica gel with petrol (b.p. 40-60 °C): ethyl acetate (10:1) as eluent, gave ethyl 2-butyl-1-tetralone-2-carboxylate⁸⁹ (137b) (0.1 g, 0.3 mmol, 55 %), R_f 0.35, with spectra as reported above, and recovered ethyl 2-(4-bromobutyl)-1-tetralone-2-carboxylate (135b) (9 %), R_f 0.24.

Preparation of ethyl 2-(3-iodopropyl)-1-indanone-2-carboxylate (122a)



Ethyl 1-indanone-2-carboxylate (**122a**) (1.7 g, 8.3 mmol) was added to a stirred suspension of sodium hydride (60 %; 0.4 g, 9.1 mmol) and DMPU (2.0 cm³, 2.1 g, 17 mmol) in THF (10 cm³) under an atmosphere of nitrogen. After stirring for 1.0 h, 1,3-di-iodopropane (2.0 cm³, 5.2 g, 17 mmol) was added and the solution was heated at reflux for 8 h. The mixture was allowed to cool and taken up in diethyl ether (100 cm³). The solution was washed with water (6 x 5 cm³) and dried over magnesium sulphate. The solvent was removed *in vacuo* [at r.t. (20 mm Hg) and at 100°C (4 mm Hg)]. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave *ethyl 2-(3-iodopropyl)-1-indanone-2-carboxylate* (**143**) (1.1 g, 3.0 mmol, 36 %) as an orange oil, *R_f* [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.13.

Found: C, 48.9; H, 4.7 %. C₁₅H₁₇IO₃ requires C, 48.4; H, 4.6 %.

ν_{max} (neat) 2934 (C-H), 1747 (ester C=O), 1702 (5-membered ring α -aryl ketone C=O), 1608, 1590, 1476, 1465, and 1445 (arene C-C) cm⁻¹

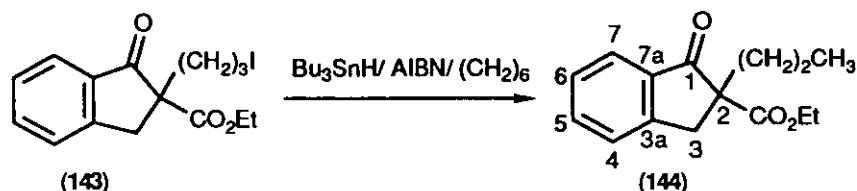
δ_{H} (250 MHz) 7.79 (1 H, d, *J* = 5.7 Hz, 7-H), 7.64 (1 H, dt, *J_d* = 1.2 Hz, *J_t* = 7.4 Hz, 5-H), 7.52-7.49 (1 H, m, 4-H), 7.40 (1 H, dd, *J* = 0.8 Hz, *J* = 14.8 Hz, 6-H), 4.15 (2 H, q, *J* = 7.1 Hz, 2-CO₂CH₂CH₃), 3.72 and 3.08 (2 H, 2 d, *J_{AB}* = 17.4 Hz, 3-H), 3.15 (2 H, t, *J* = 6.6 Hz, 2-CH₂CH₂CH₂I), 2.22-2.16 (1 H, m, 2-CH₂CH₂CH₂I), 2.03-1.76 (3 H, m, 2-CH₂CH₂CH₂I), and 1.20 (3 H, t, *J* = 7.1 Hz, 2-CO₂CH₂CH₃).

δ_{C} (62.5 MHz) 202.1 (1-C), 170.7 (2-CO₂Et), 152.8 and 135.0 (7a-C and 3a-C), 135.5, 127.8, 126.4, and 124.7 (7-C, 6-C, 5-C, 4-C), 61.7 (2-CO₂CH₂CH₃), 59.8 (2-C), 36.9 (3-C), 35.6 (2-CH₂CH₂CH₂I), 28.8 (2-CH₂CH₂CH₂I), 14.0 (2-CO₂CH₂CH₃), and 5.9 (2-CH₂CH₂CH₂I).

m/z (E.I.) 245.1161 (1 %, *M* - I, C₁₅H₁₇O₃ requires 245.1178).

m/z (C.I.) 373 (20 %, *M*+ H), and 245 (10, *M* - I).

Attempted ring expansion of ethyl 2-(3-iodopropyl)-1-indanone-2-carboxylate (143)



Tributylstannane (0.4 g, 1.3 mmol) and AIBN (29 mg, 0.18 mmol) in cyclohexane (20 cm^3) was added by syringe pump, under an atmosphere of nitrogen, to a refluxing solution of ethyl 2-(3-iodopropyl)-1-indanone-2-carboxylate (143) (0.4 g, 1.0 mmol) in cyclohexane (150 cm^3) ([tributylstannane] *ca.* 2.1 mM). The solution was heated at reflux for a further 1 h and the solvent was removed *in vacuo*. Dry flash chromatography, on silica gel with petrol (b.p. 40-60°C): ethyl acetate, and preparative TLC, on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent, gave *ethyl 2-propyl-1-indanone-2-carboxylate* (144) (0.2 g, 0.7 mmol, 68 %) as a yellow oil, R_f [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.22.

Found: C, 72.5; H, 7.3 %. $\text{C}_{15}\text{H}_{18}\text{O}_3$ requires C, 73.15; H, 7.4 %.

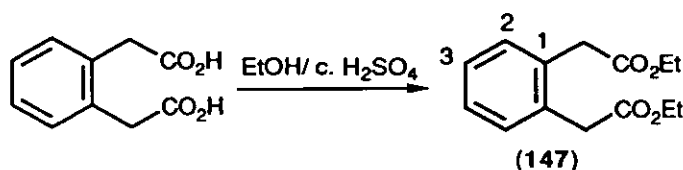
ν_{max} (neat) 2962, 2934 (C-H), 1741 (ester C=O), 1716 (5-membered ring α -aryl ketone C=O), 1608, and 1465 (arene C-C) cm^{-1}

δ_{H} (250 MHz) 7.76 (1 H, d, $J = 7.6$ Hz, 7-H), 7.62 (1 H, dt, $J_{\text{d}} = 1.1$ Hz, $J_{\text{t}} = 7.4$ Hz, 5-H), 7.49 (1 H, dt, $J_{\text{t}} = 0.8$ Hz, $J_{\text{d}} = 7.6$ Hz, 4-H), 7.38 (1 H, dd, $J = 0.7$ Hz, $J = 14.8$ Hz, 6-H), 4.16 (2 H, q, $J = 7.2$ Hz, 2- $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.73 and 3.07 (2 H, 2 d, $J_{\text{AB}} = 17.4$ Hz, 3-H), 2.14-2.04 and 1.92-1.80 (2 H, 2 m, 2- $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.28-1.18 (2 H, m, 2- $\text{CH}_2\text{CH}_2\text{CH}_3$), 1.25 (3 H, t, $J = 7.2$ Hz, 2- $\text{CO}_2\text{CH}_2\text{CH}_3$), and 0.91 (3 H, t, $J = 7.2$ Hz, 2- $\text{CH}_2\text{CH}_2\text{CH}_3$).

δ_{C} (62.5 MHz) 203.0 (1-C), 171.0 (2- CO_2Et), 153.0 (7a-C), 135.2 (3a-C), 135.1 (7-C), 127.5 (6-C), 126.2 (5-C), 124.5 (4-C), 61.3 (2- $\text{CO}_2\text{CH}_2\text{CH}_3$), 60.7 (2-C), 36.9 (3-C), 36.5 (2- $\text{CH}_2\text{CH}_2\text{CH}_3$), 17.9 (2- $\text{CH}_2\text{CH}_2\text{CH}_3$), 14.2 (2- $\text{CO}_2\text{CH}_2\text{CH}_3$), and 13.9 (2- $\text{CH}_2\text{CH}_2\text{CH}_3$).

m/z (E.I.) 246.1215 (12 %, M^+ , $\text{C}_{15}\text{H}_{18}\text{O}_3$ requires 246.1256), 217 (11, $M - \text{Et}$), 204 (100, $M - \text{CH}=\text{CH}_2\text{CH}_3$), 203 (6, $M - \text{CH}_2\text{CH}_2\text{CH}_3$), 201 (10, $M - \text{EtO}$), 173 (33, $M - \text{CO}_2\text{Et}$), and 172 (34, $M - \text{HCO}_2\text{Et}$).

Preparation of diethyl phenylenediacetate (147)⁹⁴



Phenylenediacetic acid (6.0 g, 31 mmol) and concentrated sulphuric acid (5 drops) in ethanol (125 ml) were heated at reflux for 5 h. The solution was allowed to cool, poured into water (100 ml), neutralised with dilute aqueous sodium hydroxide, and extracted with dichloromethane (5 x 50 ml). The combined extracts were dried over magnesium sulphate and the solvent was removed *in vacuo*. Kugelrohr distillation gave diethyl phenylenediacetate (147) (5.4 g, 21.6 mmol, 70 %) as a colourless liquid, b.p. 130°C (0.3 mm Hg) [lit.⁹⁴ 173-174°C (10 mm Hg)], R_f [petrol (b.p. 40-60°C): ethyl acetate (9:2)] 0.38.

Found: C, 67.35; H, 7.1 %. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.2 %.

ν_{\max} (neat) 2983 (C-H), 1743 (ester C=O), 1463, and 1455 (arene C-C) cm^{-1}

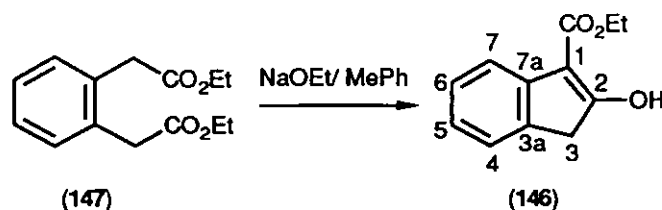
δ_H (250 MHz) 7.24 (4 H, s, 2-H and 3-H), 4.13 (4 H, q, $J = 7.1$ Hz, 1- $CH_2CO_2CH_2CH_3$), 3.70 (4 H, s, 1- $CH_2CO_2CH_2CH_3$), and 1.24 (6 H, t, $J = 7.1$ Hz, 1- $CH_2CO_2CH_2CH_3$).

δ_C (62.5 MHz) 171.3 (1- $CH_2CO_2CH_2CH_3$), 133.3 (1-C), 130.8 (2-C), 127.6 (3-C), 60.9 (1- $CH_2CO_2CH_2CH_3$), 30.9 (1- $CH_2CO_2CH_2CH_3$), and 14.2 (1- $CH_2CO_2CH_2CH_3$).

m/z (E.I.) 250.1208 (30 %, M^+ , $C_{14}H_{18}O_4$ requires 250.1205), 205 (44, $M - EtO$), 204 (100, $M - EtOH$), 177 (41, $M - CO_2Et$), 176 (42, $M - HCO_2Et$), 158 (62, $M - 2 EtOH$), 132 (12, $M - EtO - CO_2Et$), 131 (43, $M - HCO_2Et - EtO$), 130 (80, $M - HCO_2Et - EtOH$).

Repetition using phenylenediacetic acid (5.0 g, 25.7 mmol) gave diethyl phenylenediacetate (147) (5.2 g, 20.9 mmol, 81 %).

Preparation of ethyl 2-indanone-1-carboxylate (146)⁹⁴



Diethyl phenylenediacetate (147) (5.4 g, 21.6 mmol) in toluene (100 ml) was added to a stirred suspension of sodium hydride (60 %; 1.0 g, 25.9 mmol) in ethanol (20 ml) and toluene (50 ml). The resultant white mass was heated at reflux for 5 h and allowed to stand over-night. The solution was neutralised with dilute aqueous hydrochloric acid and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x). The combined extracts were dried over magnesium sulphate and the solution was evaporated to dryness. Recrystallisation from ethanol gave ethyl 2-indanone-1-carboxylate (146) (1.8 g, 8.7 mmol, 40 %), as a brown solid, m.p. 65-66°C, (lit.⁹⁴ 65°C), R_f [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.32.

Found: C, 70.75; H, 6.0 %. $C_{12}H_{12}O_3$ requires C, 70.6; H, 5.9 %.

ν_{\max} (neat) 2655 (C-H), 1656 (acrylate C=O), and 1595 (acrylate and arene C-C) cm^{-1}

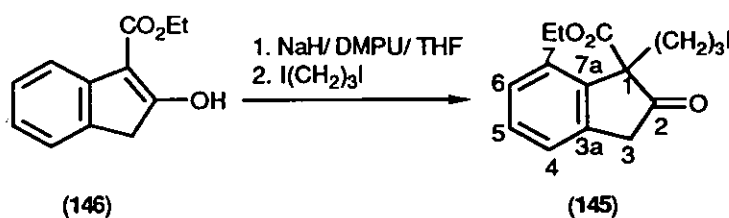
δ_H (250 MHz) 11.20-10.90 (1 H, br s, D_2O ex., 2-OH), 7.57 (1 H, dd, $J = 1.8$ Hz, $J = 6.7$ Hz, 7-H) 7.35-7.21 (2 H, m, 4-H and 5-H), 7.07 (1 H, t, $J = 7.3$ Hz, 6-H), 4.39 (2 H, q, $J = 7.3$ Hz, 1-CO₂CH₂CH₃), 3.51 (2 H, s, 3-H), and 1.13 (3 H, t, $J = 7.1$ Hz, 1-CO₂CH₂CH₃).

δ_C (62.5 MHz) 181.0 (1-CO₂Et), 169.0 (1-C), 139.5 and 133.1 (7a-C and 3a-C), 126.9, 123.6, 123.5, and 120.1 (7-C, 6-C, 5-C, and 4-C), 105.1 (2-C), 60.5 (1-CO₂CH₂CH₃), 37.5 (3-C), and 14.3 (1-CO₂CH₂CH₃).

m/z (E.I.) 204.0783 (31 %, M^+ , $C_{12}H_{12}O_3$ requires 204.0786), 159 (13, $M - EtO$), 158 (100, $M - EtOH$), 131 (12, $M - CO_2Et$), and 130 (38, $M - HCO_2Et$).

Repetition using diethyl phenylenediacetate (147) (5.2 g, 20.9 mmol) gave ethyl 2-indanone-1-carboxylate (146) (2.0 g, 9.7 mmol, 40 %) (5.2 g, 20.9 mmol, 47 %).

Preparation of ethyl 1-(3-iodopropyl)-2-indanone-1-carboxylate (**145**)



Ethyl 2-indanone-1-carboxylate (**146**) (1.7 g, 8.3 mmol) in THF (10 ml) was added to a stirred suspension of sodium hydride (60 %; 0.4 g, 9.1 mmol) and DMPU (1.5 cm³, 1.6 g, 12 mmol) in THF (20 cm³) under an atmosphere of nitrogen. After stirring for 1.0 h, 1,3-diiodopropane (2.0 cm³, 5.2 g, 17 mmol) was added and the solution was heated at reflux for 5 h. The mixture was allowed to cool, taken up in diethyl ether (100 cm³) and washed with water (5 x 6 cm³). The solution was dried over magnesium sulphate, and the solvent was removed *in vacuo* [at r.t. (20 mm Hg) and at 100°C (4 mm Hg)]. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave *ethyl 1-(3-iodopropyl)-2-indanone-1-carboxylate* (**145**) (1.1 g, 3.1 mmol, 37 %) as an orange oil, *R_f* [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.23.

ν_{max} (neat) 2979, 2906 (C-H), 1735 (ester C=O), 1725 (ketone C=O), 1477, 1461, and 1446 (arene C-C) cm⁻¹

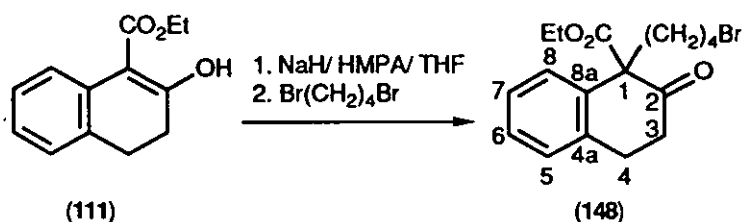
δ_{H} (250 MHz) 7.37-7.17 (4 H, m, 7-H, 6-H, 5-H and 4-H), 4.07 (2 H, q, *J* = 7.1 Hz, 1-CO₂CH₂CH₃), 3.81 and 3.50 (2 H, 2 d, *J_{AB}* = 22.7 Hz, 3-H), 3.10-3.02 (2 H, t, *J* = 6.6 Hz, 1-CH₂CH₂CH₂I), 2.34-2.24 (2 H, m, 1-CH₂CH₂CH₂I), 1.57-1.49 (2 H, m, 1-CH₂CH₂CH₂I), and 1.13 (3 H, t, *J* = 7.1 Hz, 1-CO₂CH₂CH₃).

δ_{C} (62.5 MHz) 211.9 (2-C), 169.8 (1-CO₂Et), 140.1 and 137.1 (7a-C and 3a-C), 128.6, 128.0, 125.0, and 123.9 (7-C, 6-C, 5-C, and 4-C), 64.4 (1-C), 61.7 (1-CO₂CH₂CH₃), 43.3 (1-CH₂CH₂CH₂I), 34.7 (3-C), 28.2 (1-CH₂CH₂CH₂I), 14.1 (1-CO₂CH₂CH₃), and 5.4 (1-CH₂CH₂CH₂I).

m/z (E.I.) 372.0239 (10 %, *M*⁺, C₁₅H₁₇IO₃ requires 372.0224), 245 (25, *M* - I), and 244 (45, *M* - HI).

Repetition using ethyl 2-indanone-1-carboxylate (**146**) (2.0 g, 9.7 mmol) gave *ethyl 1-(3-iodopropyl)-2-indanone-1-carboxylate* (**145**) (1.8 g, 4.9 mmol, 50 %).

Preparation of ethyl 1-(4-bromobutyl)-2-tetralone-1-carboxylate (148)



Ethyl 2-tetralone-1-carboxylate (**111**) (1.0 g, 4.6 mmol) was added to a stirred suspension of sodium hydride (80%; 0.1 g, 5 mmol) and HMPA (0.8 cm³, 0.8 g, 5.0 mmol) in THF (12 cm³) under an atmosphere of nitrogen. After stirring for 1.0 h, 1,4-dibromobutane (2.8 cm³, 5.1 g, 23 mol) was added and the solution was heated at reflux for 20 h. After standing for 70 h, the mixture was taken up in diethyl ether (100 cm³), washed with water (3 x 5 cm³), dried over potassium carbonate, and the solvent was removed *in vacuo* [at r.t. (20 mm Hg) and at 90°C (6 mm Hg)] to give an orange oil. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave *ethyl 1-(4-bromobutyl)-2-tetralone-1-carboxylate* (**148**) (0.4 g, 1 mmol, 22 %) as an orange oil, *R_f* [silica, petrol (b.p. 40-60°C): ethyl acetate (10:1)] 0.20.

ν_{\max} (neat) 3060, 2956 (C-H), 1728 (br, ester and ketone C=O), 1600, and 1492 (arene C-C) cm⁻¹

δ_{H} (250 MHz) 7.26-7.23 (1 H, m, 8-H), 7.15-7.05 (3 H, m, 7-H, 6-H and 5-H), 4.35 (2 H, q, *J* = 7.1 Hz, 1-CO₂CH₂CH₃), 3.96 and 3.46 (2 H, 2 d, *J* = 6.3 Hz, 1-CH₂CH₂CH₂CH₂Br), 2.92 (2 H, t, *J* = 8.0 Hz, 4-H), 2.52 (2 H, t, *J* = 8.0 Hz, 3-H), 2.05-1.96 (2 H, m, 1-CH₂CH₂CH₂CH₂Br), 1.89-1.81 (2 H, m, 1-CH₂CH₂CH₂CH₂Br), 1.37 (3 H, t, *J* = 7.1 Hz, 1-CO₂CH₂CH₃), and 1.12 (2 H, t, *J* = 7.1 Hz, 1-CH₂CH₂CH₂CH₂Br).

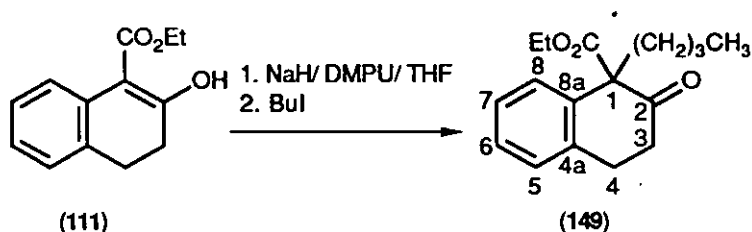
δ_{C} (62.5 MHz) 208.0 (2-C), 167.8 (1-CO₂Et), 135.9 and 131.6 (8a-C and 4a-C), 127.1, 126.7, 125.6, and 123.3 (8-C, 7-C, 6-C, and 5-C), 62.7 (1-C), 60.7 (1-CO₂C H₂CH₃), 35.4 (4-C), 33.4, 33.0, 32.8, and 23.7 (1-CH₂CH₂CH₂CH₂Br), 29.1 (3-C), and 14.4 (1-CO₂CH₂CH₃).

m/z (C.I.) 355 and 353 (22 and 25 % respectively, *M* + H), 273 (10, *M* - Br), 219 (100, *M* + H - CH₂=C=O), and 218 (22, *M* - CH₂=C=O).

m/z (E.I.) 218.0953 (45 %, $M - \text{CH}_2=\text{CHCH}_2\text{CH}_2\text{Br}$, $\text{C}_{13}\text{H}_{14}\text{O}_3$ requires 218.0943), 217 (5, $M - \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br}$), and 172 (100, $M - \text{Br} - \text{CO}_2\text{Et} - \text{CO}$).

Repetition on a larger scale, using ethyl 2-tetralone-1-carboxylate (**111**) (3.0 g, 13.8 mmol) gave ethyl 1-(4-bromobutyl)-2-tetralone-1-carboxylate (**148**) (1.0 g, 2.8 mmol, 20 %).

Preparation of ethyl 1-butyl-2-tetralone-1-carboxylate (**149**)



Ethyl 2-tetralone-1-carboxylate (**111**) (2.0 g, 9.2 mmol) in THF (10 cm³) was added to a stirred suspension of sodium hydride (60 %; 0.4 g, 11 mmol) and DMPU (1.2 cm³, 2.1 g, 11 mmol) in THF (20 cm³) under an atmosphere of argon. After stirring for 1.0 h, 1-iodobutane (1.2 cm³, 1.9 g, 11 mmol) was added and the solution was heated at reflux for 3 h. After stirring at room temperature overnight, the mixture was poured into diethyl ether (100 cm³), washed with water (10 x 4 cm³), washed with saturated aqueous sodium thiosulfate (2 x 5 cm³) and dried over magnesium sulfate. The solvent was removed *in vacuo* [at r.t. (20 mm Hg) and at 90°C (6 mm Hg)] to give an orange oil. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave *ethyl 1-butyl-2-tetralone-1-carboxylate* (**149**) (0.2 g, 0.9 mmol, 9 %) as a yellow oil, R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (4:1)] 0.38.

ν_{max} (neat) 2959, 2929, 2873 (C-H), 1728 (ester and ketone C=O), and 1464 (arene C-C) cm⁻¹

δ_{H} (250 MHz) 7.26-7.19 (4 H, m, 8-H, 7-H, 6-H and 5-H), 4.08 (2 H, q, $J = 7.1$ Hz, 1-CO₂CH₂CH₃), 3.13-2.87 (4 H, m, 4-H and 1-CH₂CH₂CH₂CH₃), 2.65-2.25 (2 H, m, 3-H), 2.20-2.10 (1 H, m, 1-CH₂CH₂CH₂CH₃), 1.39-0.76 (3 H, m, 1-CH₂CH₂CH₂CH₃), 1.11 (3 H, t, $J = 7.1$ Hz, 1-CO₂CH₂CH₃), and 0.79 (3 H, t, $J = 7.3$ Hz, 1-CH₂CH₂CH₂CH₃).

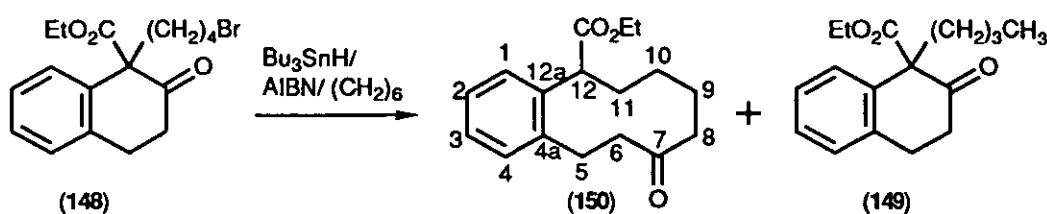
δ_{C} (62.5 MHz) 208.0 (2-C), 171.2 (1-CO₂Et), 136.5, 136.4 (8a-C and 4a-C), 128.4, 127.3, 126.7, and 125.5 (8-C, 7-C, 6-C, and 5-C), 62.9 (1-C), 61.6 (1-CO₂CH₂CH₃),

39.4 (1-CH₂CH₂CH₂CH₃), 36.4 (4-C), 28.0 (3-C), 26.3 and 23.0 (1-CH₂CH₂CH₂CH₃), and 13.8 (2 signals, 1-CO₂CH₂CH₃ and 2-CH₂CH₂CH₂CH₃).

The NMR assignments were confirmed by ¹H-¹³C correlation spectroscopy.

m/z (E.I.) 274.1565 (*M*⁺, 13 %, C₁₇H₂₂O₃ requires 274.1569), 218 (64, *M* - CH₂=CHCH₂CH₃), 217 (54, *M* - CH₂CH₂CH₂CH₃), 201 (35, *M* - CO₂Et), and 200 (13, *M* - HCO₂Et).

Attempted ring expansion of ethyl 1-(4-bromobutyl)-2-tetralone-1-carboxylate (148)



Tributylstannane (0.7 g, 2.3 mmol) and AIBN (0.02 g, 0.1 mmol) in cyclohexane (20 cm³) was added by syringe pump, under an atmosphere of nitrogen, to a refluxing solution of ethyl 1-(4-bromobutyl)-2-tetralone-1-carboxylate (148) (0.4 g, 1.1 mmol) in cyclohexane (30 cm³) over 5 h ([tributylstannane] *ca.* 13 mM). The solution was heated at reflux for a further 1 h, and then the solvent was removed *in vacuo* to give an orange liquid. Dry flash chromatography, on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent, and preparative TLC, on silica gel with petrol (b.p. 40-60°C): ethyl acetate (10:1) as eluent, gave a yellow oil, *R*_f 0.43. TLC using a variety of solvent systems showed one spot only, corresponding to ethyl 1-butyl-2-tetralone-1-carboxylate (149). High field NMR indicated the absence of starting material and the presence of two or more products, one of which appeared to be ethyl 1-butyl-2-tetralone-1-carboxylate (149), and the other of which was assumed to be ethyl 5,6,7,8,9,10,11,12-octahydro-7-oxobenzocyclodecene-12-carboxylate (150). The available NMR data for the latter product are shown below.

ν_{max} (neat) 2957, 2935, 2873 (C-H), 1731 (ester and C=O), and 1451 (arene C-C) cm⁻¹

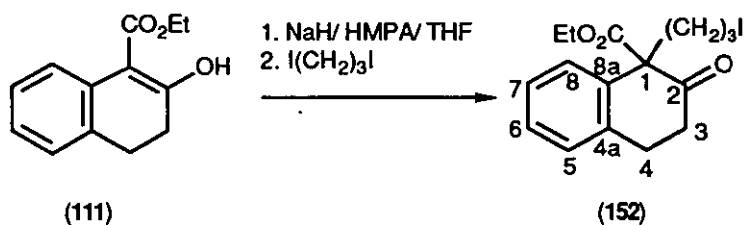
δ_{H} (250 MHz) 3.65 (1 H, m, 12-H).

δ_{C} (62.5 MHz) 208.0 (7-C), 172.4 (12-CO₂Et), 61.2 (12-CO₂CH₂CH₃), 54.2 (12-C), 39.4, 36.4, and 31.8 (5-C, 6-C and 8-C), and 14.3 (12-CO₂CH₂CH₃).

Gas chromatography on a Pye Unicam Series 104 Chromatograph at 258°C on a 3 % Apiezon L column, with nitrogen as the carrier gas (40 cm³ min⁻¹) and flame ionisation detection, indicated two major components: ethyl 1-butyl-2-tetralone-1-carboxylate (**149**) (0.2 mmol, 16 %), *t_R* 1.8 min; and a second, more polar component likely to be ethyl 5,6,7,8,9,10,11,12-octahydro-7-oxobenzocyclodecene-12-carboxylate (**150**) (0.3 mmol, 23 %), *t_R* 2.9 min. GC-MS analysis suggested the presence of the following compounds:

Compound	<i>t_R</i> / min	Interpreted spectroscopic peaks
Tetralone (149)	17.1	218 (60 %, <i>M</i> - CH ₂ =CHCH ₂ CH ₃), 172 (100, <i>M</i> - EtOH - CH ₂ =CHCH ₂ CH ₃).
Ketone (150)	19.0	274 (20 %, <i>M</i> ⁺), 228 (<i>M</i> - EtOH), 201 (50, <i>M</i> - CO ₂ Et), 200 (60, <i>M</i> - HCO ₂ Et).

Preparation of ethyl 1-(3-iodopropyl)-2-tetralone-1-carboxylate (**152**)



Ethyl 2-tetralone-1-carboxylate (**111**) (2.0 g, 9.1 mmol) in THF (10 cm³) was added to a stirred suspension of sodium hydride (60 %; 0.4 g, 10 mmol) and HMPA (2 cm³, 2 g, 11 mmol) in THF (10 cm³) under an atmosphere of nitrogen. After stirring for 1.0 h, 1,3-di-iodopropane (2.0 cm³, 5.2 g, 17 mmol) was added. The solution was heated at reflux for 2 h and allowed to stir overnight. The mixture was taken up in diethyl ether (100 cm³) and washed with water (10 x 5 cm³), dried over potassium carbonate, and the solvent was removed *in vacuo* to give a brown oil. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave *ethyl 1-(3-iodopropyl)-2-tetralone-1-carboxylate* (**152**) (1.2 g, 3.2 mmol, 35 %) as a yellow oil, *R_f* [silica, petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.40.

ν_{\max} (neat) 3060, 2960 (C-H), 1738 (ester and ketone C=O), 1634, and 1488 (arene C-C) cm⁻¹

δ_{H} (250 MHz) 7.30-7.06 (4 H, m, 5-H, 6-H, 7-H, and 8-H), 4.10 (2 H, q, *J* = 7.1 Hz, 1-CO₂CH₂CH₃), 3.14-2.91 (4 H, m, 4-H and 1-CH₂CH₂CH₂I), 2.66-2.04 (2 H, m, 3-H),

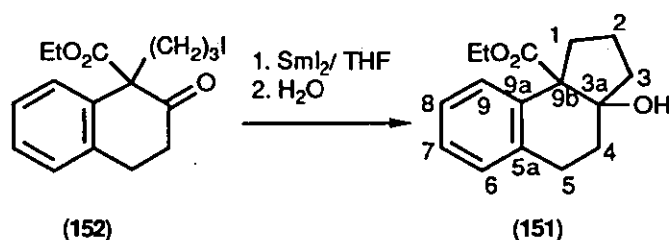
2.31-2.04 (2 H, m, 1-CH₂CH₂CH₂I), 1.52-1.29 (2 H, m, 1-CH₂CH₂CH₂I), and 1.13 (3 H, t, J = 7.1 Hz, 1-CO₂CH₂CH₃).

δ_C (62.5 MHz) 208.2 (2-C), 170.6 (1-CO₂Et), 136.2 and 135.5 (8a-C and 4a-C), 128.4, 127.5, 127.3 and 126.6 (5-C, 6-C, 7-C and 8-C), 62.1 (1-C), 61.7 (1-CO₂CH₂CH₃), 39.0 (1-CH₂CH₂CH₂I), 37.0 (4-C), 28.4 (1-CH₂CH₂CH₂I), 27.8 (3-C), 13.7 (1-CO₂CH₂CH₃), and 5.5 (1-CH₂CH₂CH₂I).

m/z (E.I.) 386.0328 (M^+ , 3 %, C₁₆H₁₉O₃I requires 386.0381), 259 (20, $M - I$), 217 (28, $M - CH_2CH_2CH_2I$), and 185 ($M - I - HCO_2Et$).

Repetition on the same scale gave ethyl 1-(3-iodopropyl)-2-tetralone-1-carboxylate (**152**) (1.2 g, 3.2 mmol, 35 %). Repetition on a larger scale using ethyl 2-tetralone-1-carboxylate (**111**) (6.2 g, 29 mmol) gave ethyl 1-(3-iodopropyl)-2-tetralone-1-carboxylate (**152**) (4.4 g, 11 mmol, 40 %).

Preparation of ethyl 2,3,3a,4,5,9b-hexahydro-3a-hydroxy-(1H)-benz[e]-indene-9b-carboxylate (**151**)



Ethyl 1-(3-iodopropyl)-2-tetralone-1-carboxylate (**152**) (2.6 g, 6.8 mmol) in THF (10 cm³) was added slowly to a stirred solution of samarium (II) iodide in THF (0.1 M; 150 cm³, 15 mmol) under an atmosphere of argon at -60°C and the solution was allowed to warm to room temperature overnight. The solution was poured into saturated aqueous potassium carbonate (50 cm³). The phases were separated and the aqueous phase was extracted with diethyl ether (2 x 15 cm³). The combined organic phases were washed with saturated aqueous sodium thiosulfate (10 cm³) and water (10 cm³). The solution was dried (magnesium sulfate) and the solvent was removed *in vacuo* to give an orange liquid. The procedure was repeated using ethyl 1-(3-iodopropyl)-2-tetralone-1-carboxylate (**152**) (1.7 g, 4.4 mmol) in THF (10 cm³) and samarium (II) iodide in THF (0.1 M; 98 cm³, 9.8 mmol), and the crude products were combined. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave ethyl 2,3,3a,4,5,9b-hexahydro-3a-hydroxy-(1H)-benz[e]indene-9b-carboxylate (**151**) (1.5 g, 5.8 mmol, 52 %) as a brown oil, R_f [silica, petrol (b.p. 40-

60°C): ethyl acetate (1:1)] 0.16. On cooling in a refrigerator for several weeks, the oil solidified to give light brown crystals, m.p. 42-47°C.

Found C, 73.2 ; H, 7.8 %. $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.7 %.

ν_{\max} (neat) 3542 (br, O-H), 2959 (C-H), 1723 (ester C=O), and 1451 (arene C-C) cm^{-1}

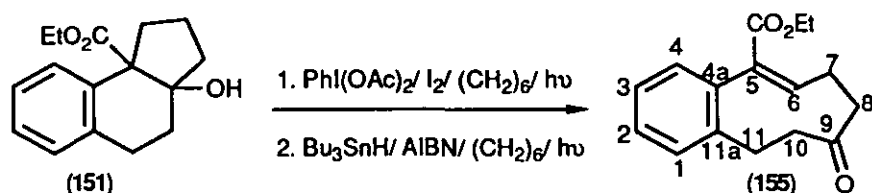
δ_H (250 MHz) 7.36-7.25 (1 H, m, 9-H), 7.19-7.06 (3 H, m, 6-H, 7-H, and 8-H), 4.14 (2 H, 2 q, $J = 7.1$ Hz, 9b- $CO_2CH_2CH_3$, *E* and *Z*), 2.98-2.77 (2 H, m, 5-H), 2.80-2.40 (1 H, br s, D_2O ex., 3a-OH), 2.33-2.28 (1 H, m, 1-H), 2.11-1.76 (7 H, m, 1-H, 2-H, 3-H and 4-H), and 1.20 (3 H, t, $J = 7.1$ Hz, 9b- $CO_2CH_2CH_3$).

δ_C (62.5 MHz) 174.6 (9b- CO_2Et), 138.1 and 135.6 (5a-C and 9a-C), 128.7, 128.0, 126.6 and 126.4 (6-C, 7-C, 8-C and 9-C), 81.1 (3a-C), 77.1 (9b-C), 61.0 (9b- $CO_2CH_2CH_3$), 37.0 (2 signals), 31.7, and 27.6 (1-C, 3-C, 4-C and 5-C), 20.9 (2-C), and 14.1 (9b- $CO_2CH_2CH_3$).

m/z (E.I.) 260.1501 (2 %, M^+ , $C_{16}H_{20}O_3$ requires 260.1412), 243 (3, $M - OH$), 242 (15, $M - H_2O$), 170 (23, $M - OH - CO_2Et$), 169 (100, $M - H_2O - CO_2Et$), and 168 (25, $M - H_2O - HCO_2Et$).

Repetition on a larger scale using ethyl 1-(3-iodopropyl)-2-tetralone-1-carboxylate (**152**) (4.4 g, 11 mmol) and generating the samarium (II) iodide from samarium (2.0 g, 14 mmol) and di-iodomethane (3.3 g, 13 mmol) gave ethyl 2,3,3a,4,5,9b-hexahydro-3a-hydroxy-(1*H*)-benz[*e*]indene-9b-carboxylate (**151**) (51 %).

Ring opening of ethyl 2,3,3a,4,5,9b-hexahydro-3a-hydroxy-(1*H*)-benz[*e*]indene-9b-carboxylate (**151**) [1]



Ethyl 2,3,3a,4,5,9b-hexahydro-3a-hydroxy-(1*H*)-benz[*e*]indene-9b-carboxylate (**151**) (0.3 g, 1.0 mmol), iodobenzene diacetate (0.4 g, 1.1 mmol) and iodine (0.3 g, 1.0 mmol) in cyclohexane (100 cm^3) were irradiated, under an atmosphere of argon for 2.5 h (until the IR spectrum of the crude product showed consumption of the alcohol). The solution was poured

into water (20 cm³) and the phases were separated. The aqueous phase was extracted with dichloromethane (3 x 30 cm³). The combined organic phases were washed with saturated aqueous sodium thiosulfate (20 cm³) and water, then dried over magnesium sulfate. Removal of solvent *in vacuo* gave an oil, which was taken up in cyclohexane (25 cm³). Tributylstannane (0.4 g, 1.5 mmol) and AIBN (16 mg) were added and the solution was irradiated, under an atmosphere of argon for 1.5 h. Removal of solvent *in vacuo* gave an oil. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent and preparative TLC on silica gel with petrol (b.p. 40-60°C): ethyl acetate (2:1) as eluent gave *ethyl 7,8,9,10-tetrahydro-9-oxo-(1H)-benzocyclononene-5-carboxylate (155)* (0.1 g, 0.5 mmol, 50 %) as an orange oil, *R*_f 0.20.

ν_{max} (neat) 2978, 2958, 2936, 2873 (C-H), 1711 ($\alpha\beta$ -unsaturated ester C=O), 1706 (shoulder, ketone C=O), 1640 (styrene C=C), and 1453 (arene C-C) cm⁻¹

δ_{H} (400 MHz) 7.31-7.19 (3 H, m, 1-H, 2-H, and 3-H), 7.13-7.06 (1 H, m, 6-H), 7.04-7.02 (1 H, m, 4-H), 4.14 (2 H, q, *J* = 7.1 Hz, 5-CO₂CH₂CH₃), 2.98-2.92 (1 H, m, 11-H), 2.71-2.42 (5 H, m, 11-H, 10-H and 8-H), 2.38-2.28 and 2.16-2.02 (2 H, 2 m, 7-H), and 1.21 (3 H, t, *J* = 7.1 Hz, 5-CO₂CH₂CH₃).

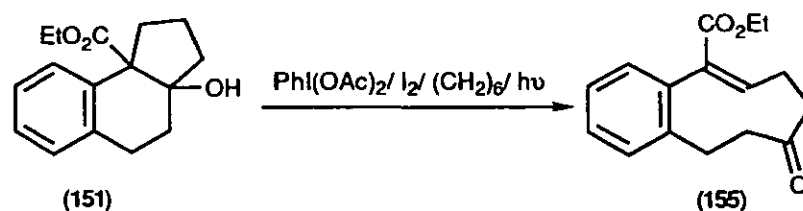
The assigned structure was confirmed by ¹H-¹H and nOe difference spectroscopy.

δ_{C} (62.5 MHz) 211.9 (9-C), 166.4 (5-CO₂Et), 142.4 (6-C), 140.2 (5-C), 134.6 and 134.0 (4a-C and 11a-C), 129.5 (2 signals), 128.4 and 126.5 (1-C, 2-C, 3-C and 4-C), 60.9 (5-CO₂CH₂CH₃), 43.7 and 42.6 (7-C and 11-C), 29.4 and 23.9 (8-C and 10-C), and 14.2 (5-CO₂CH₂CH₃).

m/z (E.I.) 213.0892 (*M* - EtO, 18 %, C₁₄H₁₃O₂ requires 213.0915), 212 (100, *M* - EtOH), 185 (31, *M* - CO₂Et), and 184 (14, *M* - HCO₂Et).

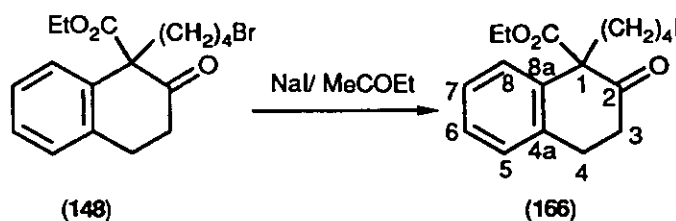
Repetition on a larger scale using ethyl 2,3,3a,4,5,9b-hexahydro-3a-hydroxy-(1*H*)-benz[e]indene-9b-carboxylate (**151**) (0.6 g, 2.3 mmol) at twice the concentration gave ethyl 7,8,9,10-tetrahydro-9-oxo-(1*H*)-benzocyclononene-5-carboxylate (**155**) (0.1 g, 0.4 mmol, 19 %).

Ring opening of ethyl 2,3,3a,4,5,9b-hexahydro-3a-hydroxy-(1*H*)-benz[e]indene-9b-carboxylate (151**) [2]**



Ethyl 2,3,3a,4,5,9b-hexahydro-3a-hydroxy-(1*H*)-benz[e]indene-9b-carboxylate (**151**) (0.3 g, 1.0 mmol), iodobenzene diacetate (0.4 g, 1.1 mmol) and iodine (0.3 g, 1.0 mmol) in cyclohexane (100 cm³) were irradiated, under an atmosphere of argon, for 4 h. The solution was poured into saturated aqueous sodium thiosulfate (20 cm³) and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 30 cm³). The combined organic phases were dried over magnesium sulfate and the solvent was removed *in vacuo* gave an oil. The procedure was repeated twice using ethyl 2,3,3a,4,5,9b-hexahydro-3a-hydroxy-(1*H*)-benz[e]indene-9b-carboxylate (**151**) (0.3 g, 1.0 mmol and 0.2 g, 0.9 mmol respectively) and the crude products were combined. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave ethyl 7,8,9,10-tetrahydro-9-oxo-(1*H*)-benzocyclononene-5-carboxylate (**155**) (0.3 g, 1.3 mmol, 45 %) as an orange oil, *R_f* [petrol (b.p. 40-60°C): ethyl acetate (2:1)] 0.20 with NMR spectroscopic data as reported above.

Preparation of ethyl 1-(4-iodobutyl)-2-tetralone-1-carboxylate (166**)**



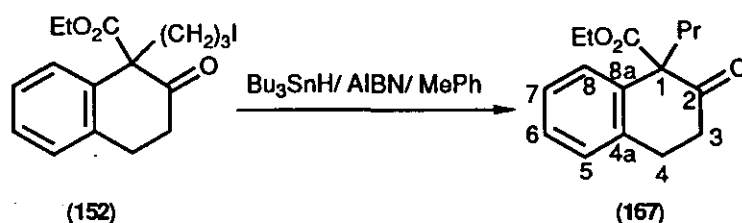
Ethyl 1-(4-bromobutyl)-2-tetralone-1-carboxylate (**148**) (0.9 g, 2.7 mmol) and sodium iodide (0.4 g, 2.7 mmol) in butanone (50 cm³) were heated at reflux for 5 h and allowed to cool. The solution was filtered and washed with aqueous sodium sulphite and brine. The solution was dried over magnesium sulfate and the solvent was removed *in vacuo* to give ethyl 1-(4-iodobutyl)-2-tetralone-1-carboxylate (**166**) as a red liquid (1.0 g, 2.5 mmol, 94 %), *R_f* [silica, petrol (b.p. 40-60 °C): ethyl acetate (3:1)] 0.61.

ν_{max} (neat) 2988, 2977, 2938 (C-H), 1737 (ester C=O), 1728 (ketone C=O), 1646, and 1600 (arene C-C) cm^{-1}

δ_{H} (250 MHz) 7.25-7.18 (4 H, m, 5-H, 6-H, 7-H, and 8-H), 4.39 (2 H, q, $J = 7.1$ Hz, 1-CO₂CH₂CH₃), 3.26-3.17 (2 H, m, 1-CH₂CH₂CH₂CH₂I), 2.82 (2 H, t, $J = 7.5$ Hz, 4-H), 2.53 (2 H, t, $J = 7.5$ Hz, 3-H), 1.97-1.91 (4 H, m, 1-CH₂CH₂CH₂CH₂I), 1.45 (3 H, t, $J = 7.1$ Hz, 1-CO₂CH₂CH₃), and 1.23-1.09 (2 H, m, 1-CH₂CH₂CH₂CH₂I).

δ_{C} (62.5 MHz) 208.2 (2-C), 178.4 (1-CO₂Et), 133.2 and 128.5 (4a-C and 8a-C), 126.8, 127.9, 125.8 and 124.9 (5-C, 6-C, 7-C and 8-C), 63.8 (1-C), 61.0 (1-CO₂CH₂CH₃), 39.3 (1-CH₂CH₂CH₂CH₂I), 33.8 (4-C), 29.5 and 25.2 (1-CH₂CH₂CH₂CH₂I), 27.8 (3-C), 14.3 (1-CO₂CH₂CH₃), and 4.9 (1-CH₂CH₂CH₂CH₂I).

Attempted ring expansion of ethyl 1-(3-iodopropyl)-2-tetralone-1-carboxylate (**152**)

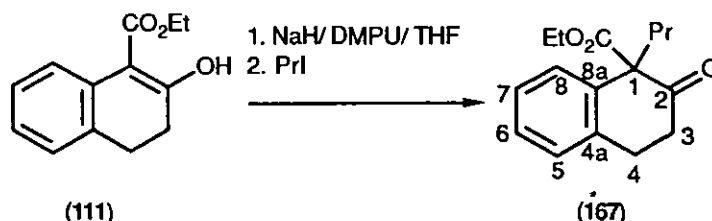


Tributylstannane (1.1 g, 3.6 mmol) in toluene (20 cm³) was added by syringe pump, under an atmosphere of nitrogen, to a refluxing solution of ethyl 1-(3-iodopropyl)-2-tetralone-1-carboxylate (**152**) (0.7 g, 1.8 mmol) and AIBN (*ca.* 2 mg) in toluene (120 cm³) over 5 h ([tributylstannane] *ca.* 5.8 mM). A further portion of AIBN (50 mg) was added, followed by syringe pump addition of a further portion of tributylstannane (1.1 g, 3.6 mmol) in toluene (20 cm³) over 5 h. The solution was allowed to reflux for a further 1 h, and then the solvent was removed *in vacuo* to give an orange liquid. Repetitive dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave an impure sample of *ethyl 1-propyl-2-tetralone-1-carboxylate* (**167**) (0.041 g, 0.15 mmol, 8 %) as a yellow oil, R_{f} [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.36, with spectra as reported below.

The procedure was repeated under the same conditions. Analysis of the ¹³C and ¹H NMR spectra of the crude product indicated the presence of one ester only. HPLC analysis with methanol: water (70:30) as eluent, against a standard prepared as described below, indicated the presence of *ethyl 1-propyl-2-tetralone-1-carboxylate* (**167**) (21 %). The identity of the product was confirmed by gas chromatography [on a Pye Unicam Series 104

Chromatograph at 218°C on a 3 % Apiezon L column, with nitrogen as the carrier gas (40 cm³ min⁻¹) and flame ionisation detection] (tr 3.9 min.) and GC-MS analysis.

Preparation of ethyl 1-propyl-2-tetralone-1-carboxylate (167)



Ethyl 2-tetralone-1-carboxylate (111) (3.0 g, 14 mmol) in THF (25 cm³) was added to a stirred suspension of sodium hydride (60 %; 0.6 g, 15 mmol) and DMPU (2.0 cm³, 2.1 g, 17 mmol) in THF (8 cm³) under an atmosphere of nitrogen. After stirring for 1.0 h, 1-iodopropane (2.5 cm³, 4.4 g, 26 mmol) was added and the solution was heated at reflux for 7 h. After stirring at room temperature overnight, the mixture was poured into diethyl ether (100 cm³), washed with water (5 x 6 cm³), and dried over magnesium sulfate. The solvent was removed *in vacuo* to give an orange oil. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave ethyl 1-propyl-2-tetralone-1-carboxylate (167) (0.7 g, 2.8 mmol, 20 %) as a yellow oil, *R_f* [silica, petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.23.

Found: C, 73.2; H, 7.75 %. C₁₆H₂₀O₃ requires C, 73.8; H, 7.7 %.

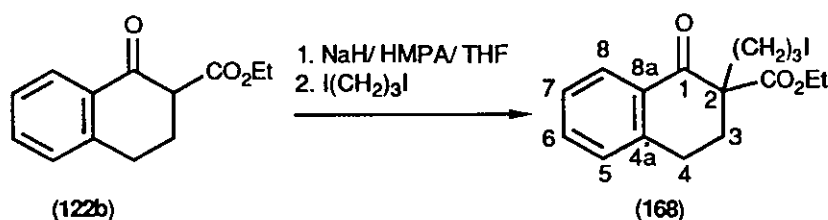
ν_{max} (neat) 3063, 2970, 2871 (C-H), 1735 (ester C=O), 1715 (ketone C=O), 1636, 1576, 1490, 1457, and 1442 (arene C-C) cm⁻¹

δ_{H} (250 MHz) 7.36-7.20 (4 H, m, 8-H, 7-H, 6-H and 5-H), 4.06 (2 H, q, *J* = 7.1 Hz, 1-CO₂CH₂CH₃), 3.12-2.87 (4 H, m, 4-H and 1-CH₂CH₂CH₃), 2.67-2.52 (4 H, m, 3-H and 1-CH₂CH₂CH₃), 1.11 (3 H, t, *J* = 7.1 Hz, 1-CO₂CH₂CH₃), and 0.82 (3 H, t, *J* = 7.3 Hz, 1-CH₂CH₂CH₃).

δ_{C} (62.5 MHz) 209.0 (2-C), 171.2 (1-CO₂Et), 136.4 (8a-C), 128.4, 127.3, 127.2 and 127.0 (5-C, 6-C, 7-C and 8-C), 119.3 (4a-C), 62.9 (1-C), 61.6 (1-CO₂CH₂CH₃), 39.3 (2 signals, 1-CH₂CH₂CH₃ and 4-C), 28.0 (3-C), 17.6 (1-CH₂CH₂CH₃), 14.4 and 14.1 (1-CO₂CH₂CH₃ and 1-CH₂CH₂CH₃).

m/z (E.I.) 260.1455 (M^+ , 37 %, $C_{16}H_{20}O_3$ requires 260.1412), 218 (66, M - $CH_2=CHCH_3$), 217 (90, M - $CH_2CH_2CH_3$), 187 (90, M - CO_2Et), 143 (29, M - HCO_2Et - $CH_2CH_2CH_3$).

Preparation of ethyl 2-(3-iodopropyl)-1-tetralone-2-carboxylate (168)



Ethyl 1-tetralone-2-carboxylate (**122b**) (2.1 g, 9.4 mmol) in THF (7 cm³) was added to a stirred suspension of sodium hydride (60 %; 0.4 g, 11 mmol) and HMPA (2 cm³, 2 g, 11 mmol) in THF (12 cm³) under an atmosphere of nitrogen. After stirring for 1.0 h, 1,3-diiodopropane (2.0 cm³, 5.2 g, 17 mmol) was added and the solution was heated at reflux for 2 h and allowed to stir overnight. The mixture was taken up in diethyl ether (100 cm³), washed with water (5 x 5 cm³), and dried over potassium carbonate. The solvent was removed *in vacuo* to give a yellow oil. Dry flash chromatography on silica gel with petrol (b.p. 40–60°C): ethyl acetate as eluent gave *ethyl 2-(3-iodopropyl)-1-tetralone-2-carboxylate* (**168**) (1.2 g, 3.0 mmol, 32 %) as a yellow oil, R_f [silica, petrol (b.p. 40–60°C): ethyl acetate (9:1)] 0.22.

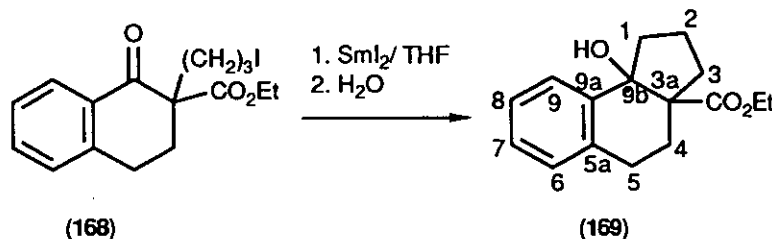
ν_{\max} (neat) 3064, 2976 (C-H), 1724 (ester C=O), 1682 (α -aryl ketone C=O), 1600 (arene C-C), and 1450 cm⁻¹

δ_H (250 MHz) 8.04 (1 H, dd, $J = 1.4$ Hz, $J = 7.8$ Hz, 8-H), 7.46 (1 H, dt, $J_d = 6.0$ Hz, $J_t = 7.5$ Hz, 6-H), 7.34–7.20 (2 H, m, 7-H and 5-H), 4.15 (2 H, q, $J = 7.1$ Hz, 2- $CO_2CH_2CH_3$), 3.21 and 3.18 (2 H, 2 q, $J_{AB} = 4.3$ Hz, 2- $CH_2CH_2CH_2I$), 3.03–2.95 (2 H, m, 4-H), 2.60–2.52 (1 H, m, 3-H), 2.18–1.96 (5 H, m, 3-H and 2- $CH_2CH_2CH_2I$), and 1.17 (3 H, t, $J = 7.1$ Hz, 2- $CO_2CH_2CH_3$).

δ_C (62.5 MHz) 195.3 (1-C), 172.0 (2- CO_2Et), 142.9 and 132.0 (8a-C and 4a-C), 133.5, 128.7, 128.0, 126.8 (5-C, 6-C, 7-C and 8-C), 61.4 (2- $CO_2CH_2CH_3$), 57.0 (2-C), 35.0 (2- $CH_2CH_2CH_2I$), 30.9 (4-C), 29.0 (2- $CH_2CH_2CH_2I$), 25.9 (3-C), 14.1 (2- $CO_2CH_2CH_3$), and 6.3 (2- $CH_2CH_2CH_2I$).

m/z (E.I.) 386.0366 (M^+ , 3 %, $C_{16}H_{19}O_3I$ requires 386.0381), 259 (9, $M - I$), 218 (28, $M - CH_2=CHCH_2I$), 217 (41, $M - CH_2CH_2CH_2I$), 186 (16, $M - I - CO_2Et$), 185 (10, $M - HCO_2Et$), and 118 [100, $M - CH_2=C(CO_2Et)CH_2CH_2CH_2I$].

Preparation of ethyl 2,3,3a,4,5,9b-hexahydro-9b-hydroxy-(3*H*)-benz[*e*]indene-3a-carboxylate (169)



To samarium powder (40 mesh; 1.2 g, 8.1 mmol), flame-dried and cooled under an atmosphere of argon, in THF (3 cm³) was added di-iodoethane (1.7 g, 6.0 mmol) in THF (3 cm³). The solution was stirred at room temperature for 1 h and then cooled to -78°C. Ethyl 2-(3-iodopropyl)-1-tetralone-2-carboxylate (168) (1.2 g, 3.0 mmol) in THF (5 cm³) was added slowly and the solution was allowed to warm to room temperature, with stirring, overnight. The solution was poured into aqueous potassium carbonate (1 M; 100 cm³) and extracted with diethyl ether (5 x 50 cm³). The combined extracts were dried over potassium carbonate and the solvent was removed *in vacuo* to give an orange liquid. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave *ethyl 2,3,3a,4,5,9b-hexahydro-9b-hydroxy-(3H)-benz[*e*]indene-3a-carboxylate* (169) (0.2 g, 0.8 mmol, 28 %) as a yellow oil, R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (1:1)] 0.70.

ν_{\max} (neat) 3500 (br, O-H), 2948 (C-H), 1720 (ester C=O), and 1450 (arene C-C) cm⁻¹

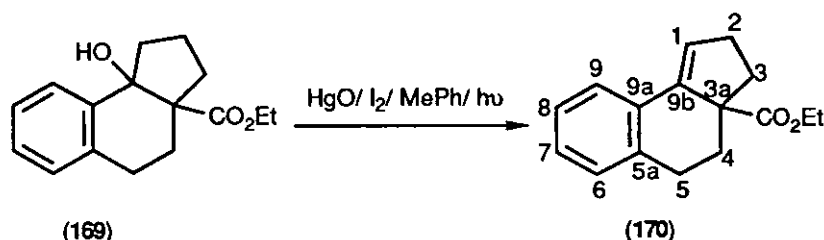
δ_H (250 MHz) 7.66 (1 H, dd, $J = 1.4$ Hz, $J = 7.7$ Hz, 9-H), 7.22-7.03 (2 H, m, 7-H and 8-H), 7.02 (1 H, d, $J = 5.8$ Hz, 6-H), 4.18 and 4.17 (2 H, 2 q, $J = 7.1$ Hz, 3a- $CO_2CH_2CH_3$, *E* and *Z*), 4.31-4.13 (1 H, br s, D₂O ex., 9b-OH), 2.78-2.72 (2 H, m, 5-H), 2.46-1.85 (8 H, m, 1-H, 2-H, 3-H and 4-H), and 1.26 (3 H, t, $J = 7.1$ Hz, 3a- $CO_2CH_2CH_3$).

δ_C (62.5 MHz) 176.7 (3a- CO_2Et), 142.0 and 133.9 (5a-C and 9a-C), 127.9, 126.9, 126.8 and 126.7 (6-C, 7-C, 8-C and 9-C), 82.0 (9b-C), 60.7 (3a- $CO_2CH_2CH_3$), 56.0 (3a-C), 41.9, 34.9, 31.9 and 27.0 (1-C, 3-C, 4-C and 5-C), 20.5 (2-C), and 14.2 (3a- $CO_2CH_2CH_3$).

m/z (E.I.) 243.1321 (6 %, M - OH, $C_{16}H_{19}O_2$ requires 243.1385), 242 (31, M - H_2O), 218 [4, M - $(CH_2)_3$], and 169 (100, M - H_2O - CO_2Et).

Repetition on a similar scale using ethyl 2-(3-iodopropyl)-1-tetralone-2-carboxylate (**168**) (1.3 g, 3.4 mmol) gave ethyl 2,3,3a,4,5,9b-hexahydro-9b-hydroxy-(3*H*)-benz[e]-indene-3a-carboxylate (**169**) (0.7 g, 2.8 mmol, 80 %).

Attempted formation of, and photolysis of, the hypiodite of ethyl 2,3,3a,4,5,9b-hexahydro-9b-hydroxy-(3*H*)-benz[e]indene-3a-carboxylate (**169**)



Ethyl 2,3,3a,4,5,9b-hexahydro-9b-hydroxy-(3*H*)-benz[e]indene-3a-carboxylate (**169**) (0.1 g, 0.4 mmol), mercury (II) oxide (0.3 g, 1 mmol) and iodine (0.3 g, 1 mmol) in toluene (70 cm³) were irradiated, under an atmosphere of nitrogen, in a Hanovia UVS 100 medium pressure lamp for 2 h. The solution was filtered through Fluka Hyflo Super Cel, which was washed with petrol (b.p. 40-60°C) (130 cm³). The combined filtrate and washings were washed with saturated aqueous sodium thiosulfate (4 x 25 cm³) and dried over magnesium sulfate. Removal of solvent *in vacuo* gave an oil. Preparative TLC on silica gel with petrol (b.p. 40-60°C): ethyl acetate (9:1) as eluent gave ethyl 2,3a,4,5-tetrahydro-(3*H*)-benz[e]indene-3a-carboxylate (**170**) (0.035 g, 0.14 mmol, 38 %) as an orange oil, R_f 0.50.

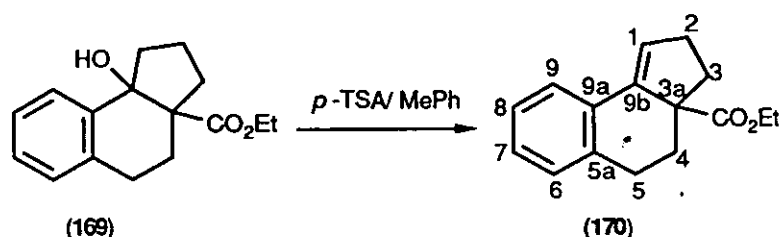
ν_{\max} (neat) 3052, 2948 (C-H), 1722 (ester C=O), 1688 (shoulder, 5-membered ring styrene C=C), and 1482 (arene C-C) cm⁻¹

δ_H (250 MHz) 7.59 (1 H, dt, $J_d = 6.5$ Hz, $J_t = 2.6$ Hz, 9-H), 7.16-7.05 (3 H, m, 6-H, 7-H and 8-H), 6.25 (1 H, t, $J = 2.6$ Hz, 1-H), 4.07 (2 H, q, $J = 7.1$ Hz, 3a- $CO_2CH_2CH_3$), 2.82-2.80 (2 H, m, 5-H), 2.60-2.40 (4 H, m, 2-H and 4-H), 1.96-1.88 and 1.74-1.63 (2 H, 2 m, 3-H), and 1.15 (3 H, t, $J = 7.1$ Hz, 3a- $CO_2CH_2CH_3$).

δ_C (62.5 MHz) 176.0 (3a- CO_2Et), 141.1, 135.5 and 132.0 (5a-C, 9a-C and 9b-C), 128.9, 127.1, 125.9 and 125.1 (9-C, 8-C, 7-C and 6-C), 124.7 (1-C), 60.5 (3a- $CO_2CH_2CH_3$), 56.5 (3a-C), 38.3 and 33.4 (2-C and 5-C), 31.1 and 28.0 (3-C and 4-C), and 14.2 (3a- $CO_2CH_2CH_3$).

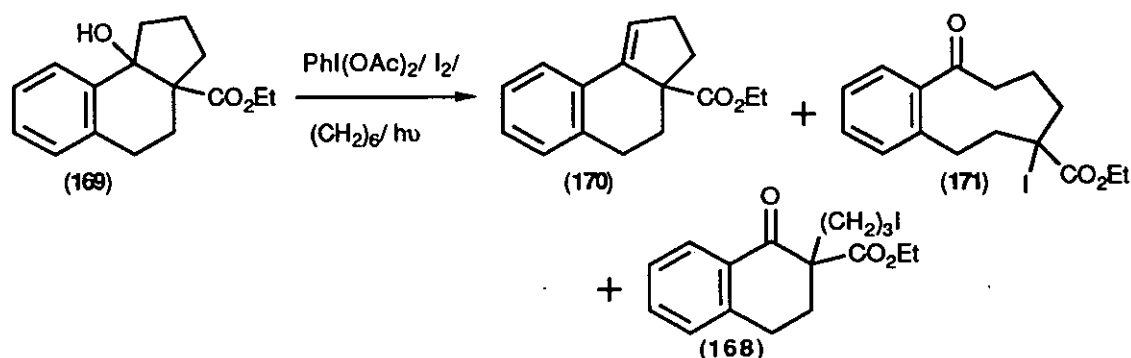
m/z (E.I.) 242.1290 (16 %, M^+ , $C_{16}H_{18}O_2$ requires 242.1307), 170 (50, $M - CH_2=CH_2 - CO_2$), 169 (100, $M - CO_2Et$), and 168 (36, $M - HCO_2Et$).

Dehydration of ethyl 2,3,3a,4,5,9b-hexahydro-9b-hydroxy-(3*H*)-benz[e]indene-3a-carboxylate (169)



Ethyl 2,3,3a,4,5,9b-hexahydro-9b-hydroxy-(3*H*)-benz[e]indene-3a-carboxylate (169) (0.2 g, 0.8 mmol) and *p*-toluenesulfonic acid (0.2 g) in toluene (40 ml) were heated at reflux using a Dean-Stark water separator for 6 h and allowed to cool. The solution was washed with saturated aqueous sodium bicarbonate and dried over magnesium sulfate. Removal of solvent gave a brown oil. Preparative TLC on silica gel with petrol (b.p. 40-60°C): ethyl acetate (9:1) as eluent gave ethyl 2,3a,4,5-tetrahydro-(3*H*)-benz[e]indene-3a-carboxylate (170) (0.05 g, 0.2 mmol, 27 %) as an orange oil, R_f 0.50, with spectroscopic data identical to those quoted above.

Formation of, and photolysis of, the hypiodite of ethyl 2,3,3a,4,5,9b-hexahydro-9b-hydroxy-(3*H*)-benz[e]indene-3a-carboxylate (169)

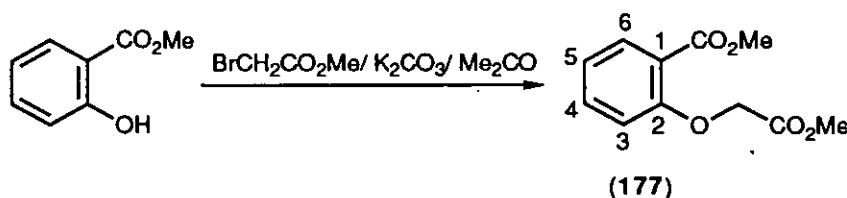


Ethyl 2,3,3a,4,5,9b-hexahydro-9b-hydroxy-(1*H*)-benz[e]indene-3a-carboxylate (169) (0.3 g, 1.0 mmol), iodobenzene diacetate (0.4 g, 1.1 mmol) and iodine (0.3 g, 1.0 mmol) in cyclohexane (100 cm³) were irradiated, under an atmosphere of argon, for 4 h, when the IR spectrum of the crude product showed consumption of starting material. The solution was poured into saturated aqueous sodium thiosulfate (20 cm³) and the phases were separated.

The aqueous phase was extracted with diethyl ether (3 x 20 cm³). The combined organic phases were dried over magnesium sulfate and the solvent was removed *in vacuo* gave an oil. Dry flash chromatography (twice) on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent, and preparative TLC on silica gel with petrol (b.p. 40-60°C): ethyl acetate (4:1) as eluent, gave a yellow oil (45 mg), *R*_f 0.72. The NMR spectra of the product showed the presence of more than one compound. GC-MS analysis suggested the presence of the following compounds:

Compound	<i>t</i> _R / min	Interpreted spectroscopic peaks
Iodide (168)	10.4	258 (5 %, <i>M</i> - HI), 217 (60, <i>M</i> - CH ₂ CH ₂ CH ₂ I), 185 (35, <i>M</i> - CO ₂ Et), 118 [100, <i>M</i> - CH ₂ =C(CO ₂ Et)CH ₂ CH ₂ CH ₂ I].
Styrene (170)	10.9	242 (35 %, <i>M</i> ⁺), 169 (100, <i>M</i> - CO ₂ Et).
Iodide (171) ?	15.1	386 (10 %, <i>M</i> ⁺), 185 (70, <i>M</i> - I - CO ₂ Et).

Preparation of methyl 2-methoxycarbonylphenoxyacetate (177)⁹⁷



Methyl salicylate (16.8 g, 110 mmol), methyl bromoacetate (12.5 cm³, 20.2 g, 132 mmol), and potassium carbonate (50.4 g, 364 mmol) in acetone (200 cm³) were heated at reflux for 5 h. The solution was filtered. The solvent was removed *in vacuo* and poured into water (100 cm³). The aqueous solution was extracted with diethyl ether (4 x 100 cm³). The combined extracts were dried over magnesium sulfate and the solvent was removed *in vacuo* to give methyl 2-methoxycarbonylphenoxyacetate (177) (25.1 g, 110 mmol, 100 %) practically pure as a pale yellow oil, *R*_f [silica, toluene: glacial acetic acid (9:1)] 0.27. The compound was used without further purification.

Found C, 58.55; H, 5.4 %. C₁₁H₁₂O₅ requires C, 58.9; H, 5.4 %.

*ν*_{max} (neat) 3000, 2960 (C-H), 1770, 1730 (ester C=O), 1600, 1580, 1500, and 1450 (arene C-C) cm⁻¹

*δ*_H (250 MHz) 7.83 (1 H, dd, *J* = 1.8 Hz, *J* = 7.7 Hz, 6-H), 7.44 (1 H, dt, *J*_d = 1.8 Hz, *J*_t = 4.6 Hz, 4-H), 7.04 (1 H, dt, *J*_d = 0.8 Hz, *J*_t = 7.6 Hz, 5-H), 6.88 (1H, d, *J* = 8.4 Hz, 3-

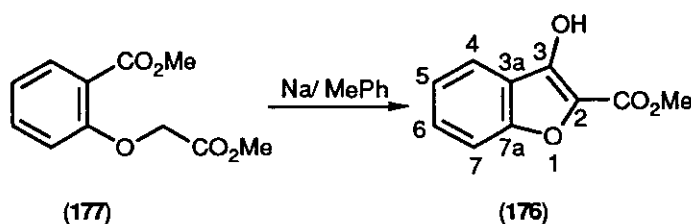
H), 4.73 (2 H, s, 2-OCH₂CO₂Me), 3.89 (3 H, s, 1-CO₂Me), and 3.78 (3 H, s, 2-OCH₂CO₂Me).

δ_C (62.5 MHz) 169.1 (1-CO₂Me), 166.3 (2-OCH₂CO₂Me), 157.4 (1-C), 133.5, 131.9, 121.7, and 114.2 (6-C, 5-C, 4-C, and 3-C), 121.2 (2-C), 66.5 (2-OCH₂CO₂Me), 52.3 (1-CO₂Me), and 52.1 (2-OCH₂CO₂Me).

m/z (E.I.) 224.0692 (26 %, M^+ , C₁₁H₁₂O₅ requires 224.0685), 193 (17, M - MeO), 192 (34, M - MeOH), and 165 (100, M - CO₂Me).

Repetition on a larger scale using methyl salicylate (25.0 g, 164 mmol) gave methyl 2-methoxycarbonylphenoxyacetate (**177**) (26.2 g, 117 mmol, 71 %).

Preparation of methyl 3-hydroxybenzo[b]furan-2-carboxylate (**176**)⁹⁷



Methyl 2-methoxycarbonylphenoxyacetate (**177**) (24.4 g, 109 mmol) was added, under an atmosphere of nitrogen, to a stirred suspension of sodium (2.5 g, 109 mmol) in toluene (120 cm³). The solution was allowed to reflux for 3 h and allowed to stand overnight. The resultant semi-solid was evaporated to dryness and taken up in dilute hydrochloric acid (500 cm³). The aqueous solution was extracted with toluene (5 x 100 cm³). The combined extracts were dried over magnesium sulfate and evaporated to dryness. Recrystallisation of the resultant solid from petrol (b.p. 60-80°C): ethyl acetate gave methyl 3-hydroxybenzo[b]furan-2-carboxylate (**176**) (7.7 g, 40 mmol, 37 %), as a yellow solid, m.p. 97-100°C (lit.⁹⁷ 95-97°C), R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (1:1)] 0.51.

Found C, 62.4; H, 4.2 %. C₁₀H₈O₄ requires C, 62.5; H, 4.2 %.

ν_{\max} (KBr disc) 3360 (br, O-H), 3080, 3040, 2960 (C-H), 1680 (arene ester C=O), 1610, 1580, 1500, and 1450 (arene C-C) cm⁻¹

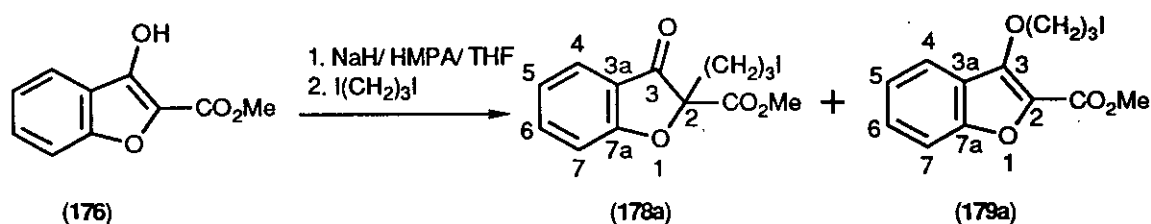
δ_H (250 MHz) 8.20-8.00 (1 H, br s, D₂O ex., 3-OH), 7.76-7.68 (1 H, m, 4-H), 7.50-7.47 (1 H, m, 6-H), 7.33-7.27 (2 H, m, 7-H and 5-H), and 4.01 (3 H, s, 2-CO₂Me).

δ_C (62.5 MHz) 153.7 (2-CO₂Me), 139.2, 135.1, 132.8, and 113.5 (2-C, 3-C, 3a-C and 7a-C), 129.4, 123.2, 120.6, and 112.6 (7-C, 6-C, 5-C, and 4-C), and 52.1 (2-CO₂Me).

m/z (E.I.) 192.0405 (77 %, M^+ , C₁₀H₈O₄ requires 192.0423), 161 (17, M - MeO), and 160 (100, M - MeOH).

Repetition on a similar scale using methyl 2-methoxycarbonylphenoxyacetate (177) (26.2 g, 117 mmol) gave methyl 3-hydroxybenzo[b]furan-2-carboxylate (176) (12.0 g, 62.5 mmol, 54 %).

Preparation of methyl 2-(3-iodopropyl)-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (178a) [1]



Methyl 2-hydroxybenzo[b]furan-2-carboxylate (176) (1.0 g, 5.2 mmol) was added to a stirred suspension of sodium hydride (60 %; 0.2 g, 6 mmol) and HMPA (1 cm³, 1 g, 6 mmol) in THF (5 cm³) under an atmosphere of argon. After stirring for 1.0 h, 1,3-di-iodopropane (2 cm³, 5 g, 17 mmol) was added and the solution was heated at reflux for 5 h, then allowed to stir overnight. The mixture was allowed to cool and taken up in diethyl ether (100 cm³), washed with saturated sodium thiosulfate solution (3 x 10 cm³), washed with water (2 x 10 cm³) and dried over potassium carbonate. The solvent was removed *in vacuo* [at r.t. (20 mm Hg) and at 80°C (3 mm Hg)] to give an orange liquid. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave methyl 2-(3-iodopropyl)-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (178a) (0.3 g, 1 mmol, 16 %) as a yellow liquid, R_f [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.17, and methyl 3-(3-iodopropoxy)benzofuran-2-carboxylate (179a) (0.4 g, 1 mmol, 22 %) as a yellow solid, R_f [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.25. Recrystallisation of the latter compound from petrol: diethyl ether gave flaky yellow prisms, m.p. 57-59°C.

Methyl 2-(3-iodopropyl)-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (178a)

ν_{\max} (neat) 2952 (C-H), 1754 (5-ring α -aryl ketone C=O and ester C=O), 1606, and 1474 (arene C-C) cm⁻¹

δ_H (250 MHz) 7.75-7.60 (2 H, m, 4-H and 6-H), 7.25-7.12 (2 H, m, 5-H and 7-H), 3.77 (3 H, s, 2-CO₂Me), 3.16 (2 H, t, $J = 6.9$ Hz, 2-CH₂CH₂CH₂I), 2.50-2.38 and 2.23-2.11 (2 H, 2 m, 2-CH₂CH₂CH₂I), and 1.90 (2 H, qu, $J = 6.9$ Hz, 2-CH₂CH₂CH₂I).

δ_C (62.5 MHz) 195.5 (3-C), 172.2 (2-CO₂Me), 166.0 and 119.3 (3a-C and 7a-C), 138.8, 125.0, 122.9 and 113.6 (4-C, 5-C, 6-C and 7-C), 90.6 (2-C), 53.4 (2-CO₂Me), 34.9 (2-CH₂CH₂CH₂I), 27.3 (2-CH₂CH₂CH₂I), and 4.7 (2-CH₂CH₂CH₂I).

m/z (E.I.) 359.9932 (100 %, M^+ , C₁₃H₁₃IO₄ requires 359.9860), and 233 (100, $M - I$).

Methyl 3-(3-iodopropoxy)benzo[*b*]furan-2-carboxylate (179a)

Found C, 43.9; H, 3.6 %. C₁₃H₁₃IO₄ requires C, 43.4; H, 3.6 %.

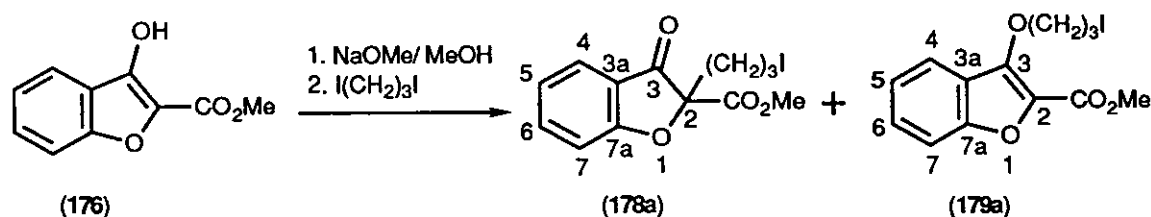
ν_{max} (neat) 3060, 2948 (C-H), 1724 (ester C=O), 1594, and 1480 (arene C-C) cm⁻¹

δ_H (250 MHz) 7.80-7.73 (1 H, m, 4-H), 7.49-7.45 (2 H, m, 6-H and 5-H), 7.31-7.28 (1 H, m, 7-H), 4.51 (2 H, t, $J = 7.0$ Hz, 3-OCH₂CH₂CH₂I), 3.97 (3 H, s, 2-CO₂Me), 3.30 (2 H, t, $J = 7.0$ Hz, 3-OCH₂CH₂CH₂I), and 2.28 (2 H, qu, $J = 7.0$ Hz, 3-OCH₂CH₂CH₂I).

δ_C (62.5 MHz) 159.6 (2-CO₂Me), 153.2, 148.3, 131.5 and 122.3 (2-C, 3-C, 3a-C and 7a-C), 128.5, 123.3, 120.9 and 112.8 (4-C, 5-C, 6-C and 7-C), 73.6 (3-OCH₂CH₂CH₂I), 52.0 (2-CO₂Me), 33.5 (3-OCH₂CH₂CH₂I), and 2.2 (3-OCH₂CH₂CH₂I).

m/z (E.I.) 359.9901 (68 %, M^+ , C₁₃H₁₃IO₄ requires 359.9860), and 233 (14, $M - I$).

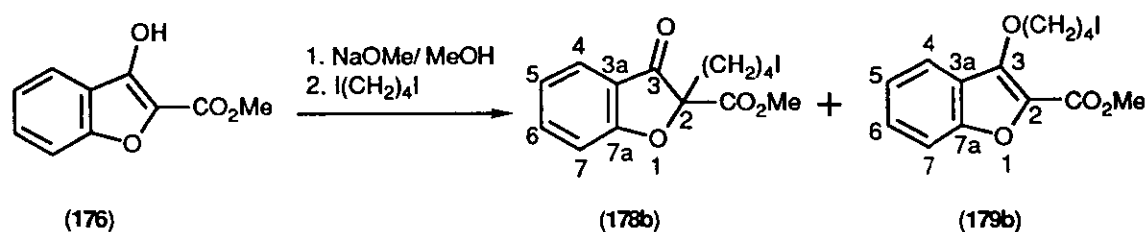
Preparation of methyl 2-(3-iodopropyl)-2,3-dihydro-3-oxobenzo[*b*]furan-2-carboxylate (178a) [2]



Methyl 2-hydroxybenzo[*b*]furan-2-carboxylate (176) (4.0 g, 21 mmol) was added to a stirred suspension of sodium hydride (60 %; 0.8 g, 22 mmol) in methanol (200 cm³) under an atmosphere of argon. After stirring at reflux for 1.0 h, 1,3-di-iodopropane (8 cm³, 21 g,

68 mmol) was added and the solution was heated at reflux for 5 h and allowed to stir overnight. The solvent was removed *in vacuo* [at r.t. (20 mm Hg) and at 70°C (2 mm Hg)] and the residue was taken up in diethyl ether (100 cm³), washed with saturated sodium thiosulfate solution (3 x 10 cm³), washed with water (2 x 10 cm³) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give an orange liquid. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave methyl 2-(3-iodopropyl)-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (**178a**) (1.5 g, 4.3 mmol, 21 %) as a yellow liquid, *R*_f [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.17, with NMR spectra as above, and methyl 3-(3-iodopropoxy)benzo[b]furan-2-carboxylate (**179a**) (1.3 g, 3.7 mmol, 18 %) as a yellow solid, *R*_f [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.25, with NMR spectra as above.

Preparation of methyl 2-(4-iodobutyl)-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (**178b**)



Methyl 2-hydroxybenzo[b]furan-2-carboxylate (**176**) (4.0 g, 21 mmol) in methanol (20 cm³) was added to a stirred suspension of sodium hydride (60 %; 0.9 g, 23 mmol) in methanol (20 cm³) under an atmosphere of nitrogen. After stirring at reflux for 1.0 h, 1,4-di-iodobutane (6 cm³, 14 g, 45 mmol) was added and the solution was heated at reflux for 6 h, then allowed to stir overnight. The solution was concentrated *in vacuo* [at r.t. (20 mm Hg) and at 150°C (2 mm Hg)] and taken up in diethyl ether (100 cm³), washed with saturated sodium thiosulfate solution (3 x 10 cm³), washed with water (6 x 5 cm³) and dried over magnesium sulfate. The solvent was removed *in vacuo* to give a red oil. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave methyl 2-(4-iodobutyl)-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (**178b**) (0.5 g, 1.4 mmol, 7 %) as a yellow liquid, *R*_f [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.15, and methyl 3-(4-iodobutyloxy)-benzo[b]furan-2-carboxylate (**179b**) (0.2 g, 0.8 mmol, 4 %) as a yellow solid, *R*_f [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.23.

Methyl 2-(4-iodobutyl)-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (**178b**)

ν_{max} (neat) 2955 (C-H), 1748 (ester C=O), 1724 (5-ring ketone C=O), 1621, 1477, and 1442 (arene C-C) cm⁻¹

δ_H (250 MHz) 7.68 (2 H, dt, $J_d = 1.5$ Hz, $J_t = 7.3$ Hz, 4-H and 6-H), 7.22 (1 H, d, $J = 0.9$ Hz, 5-H), 7.15 (1 H, dt, $J_d = 0.8$ Hz, $J_t = 7.5$ Hz, 7-H), 3.77 (3 H, s, 2-CO₂Me), 3.14 (2 H, t, $J = 7.0$ Hz, 2-CH₂CH₂CH₂CH₂I), 2.38-2.29 and 2.14-2.02 (2 H, 2 m, 2-CH₂CH₂CH₂CH₂I), 1.85 (2 H, qu, $J = 7.2$ Hz, 2-CH₂CH₂CH₂CH₂I), and 1.47 (2 H, qu, $J = 6.1$ Hz, 2-CH₂CH₂CH₂CH₂I).

δ_C (62.5 MHz) 195.7 (3-C), 172.2 (2-CO₂Me), 166.1 and 119.4 (3a-C and 7a-C), 138.7, 124.9, 122.7 and 113.5 (4-C, 5-C, 6-C and 7-C), 91.2 (2-C), 53.4 (2-CO₂Me), 33.0, 32.9 and 24.2 (2-CH₂CH₂CH₂CH₂I), and 5.6 (2-CH₂CH₂CH₂CH₂I).

m/z (E.I.) 247.0952 (25 %, $M - I$, C₁₄H₁₅O₄ requires 247.0970), and 188 (12, $M - I - CO_2Et$).

m/z (C.I.) 375 (70 %, $M + H$), and 247 (78 %, $M - I$).

Methyl 3-(4-iodobutyloxy)benzo[b]furan-2-carboxylate (179b)

Found C, 45.6; H, 4.2 %. C₁₄H₁₅IO₄ requires C, 44.9; H, 4.0 %.

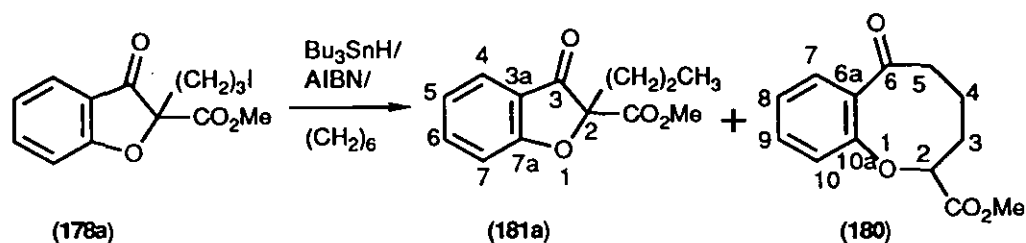
ν_{max} (neat) 2951 (C-H), 1716 (ester C=O), 1614, 1598, 1575, and 1480 (arene C-C) cm⁻¹

δ_H (250 MHz) 7.71 (1 H, t, $J = 8.3$, 4-H), 7.52-7.37 (2 H, m, 5-H and 6-H), 7.31-7.25 (1 H, m, 7-H), 4.48 (2 H, t, $J = 5.9$ Hz, 3-OCH₂CH₂CH₂CH₂I), 3.97 (3 H, s, 2-CO₂Me), 3.30 (2 H, t, $J = 6.7$ Hz, 3-OCH₂CH₂CH₂CH₂I), and 2.01-1.86 (4 H, m, 3-OCH₂CH₂CH₂CH₂I).

δ_C (62.5 MHz) 159.6 (2-CO₂Me), 153.1, 148.3, 131.9 and 122.3 (2-C, 3-C, 3a-C and 7a-C), 128.4, 123.1, 120.8, and 112.7 (4-C, 5-C, 6-C and 7-C), 73.1 (3-OCH₂CH₂CH₂CH₂I), 51.9 (2-CO₂Me), 30.7 and 29.7 (3-OCH₂CH₂CH₂CH₂I), and 6.2 (3-OCH₂CH₂CH₂CH₂I).

m/z (C.I.) 375 (19 %, $M + H$), and 247 (35 %, $M - I$).

Ring Expansion of methyl 2-(3-iodopropyl)-2,3-dihydro-3-oxobenzo[b]-furan-2-carboxylate (178a)



Tributylstannane (0.5 g, 1.6 mmol) and AIBN (0.030 g, 0.2 mmol) in cyclohexane (20 cm³) was added by syringe pump, over 5 h, under an atmosphere of nitrogen, to a refluxing solution of methyl 2-(3-iodopropyl)-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (178a) (0.4 g, 1.2 mmol) in cyclohexane (150 cm³) ([tributylstannane] *ca.* 2.0 mM). The solution was allowed to reflux for a further 1 h, and then the solvent was removed *in vacuo* to give a yellow oil. Dry flash chromatography on silica gel with petrol (b.p. 40–60°C): ethyl acetate as eluent gave *methyl 2-propyl-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate* (181a) (0.06 g, 0.2 mmol, 20 %) as a colourless liquid, R_f [petrol (b.p. 40–60°C): ethyl acetate (9:1)] 0.28, and *methyl 3,4,5,6-tetrahydro-6-oxo-(2H)-1-benzoxocin-2-carboxylate* (180) (0.1 g, 0.6 mmol, 48 %) as a yellow liquid, R_f [petrol (b.p. 40–60°C): ethyl acetate (9:1)] 0.13.

***Methyl 3,4,5,6-tetrahydro-6-oxo-(2H)-1-benzoxocin-2-carboxylate* (180)**

Found C, 66.4; H, 6.1 %. $\text{C}_{13}\text{H}_{14}\text{O}_4$ requires C, 66.7; H, 6.0 %.

ν_{max} (neat) 3072, 2953, 2874 (C–H), 1739 (ester C=O), 1669 (α -aryl ketone C=O), 1598, 1566, 1475, and 1453 (arene C–C) cm^{–1}

δ_{H} (250 MHz) 7.94 (1 H, dt, $J_{\text{d}} = 7.4$ Hz, $J_{\text{t}} = 1.0$ Hz, 7-H), 7.52 (1 H, dt, $J_{\text{t}} = 7.6$ Hz, $J_{\text{d}} = 1.7$ Hz, 9-H), 7.23 (2 H, t, $J = 7.5$ Hz, 8-H and 10-H), 4.51 (1 H, dd, $J = 3.6$ Hz, $J = 5.8$ Hz, 2-H), 3.84 (3 H, s, 2-CO₂Me), 3.58–3.47 and 2.85–2.76 (2 H, 2 m, 5-H), and 2.18–1.89 (4 H, m, 3-H and 4-H).

δ_{C} (62.5 MHz) 202.0 (6-C), 170.7 (2-CO₂Me), 157.6 and 132.1 (10a-C and 6a-C), 134.9, 129.9, 125.0 and 124.1 (10-C, 9-C, 8-C, and 7-C) 82.2 (2-C), 52.4 (2-CO₂Me), 41.4 (5-C), and 27.6, 22.2 (3-C and 4-C).

The assigned structure was confirmed by ¹H-¹³C correlation spectroscopy.

m/z (E.I.) 234.0873 (68 %, M^+ , $C_{13}H_{14}O_4$ requires 234.0892), 175 (38, $M - CO_2Me$), and 147 (44, $M - CO_2Me - CO$).

Methyl 2-propyl-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (181a)

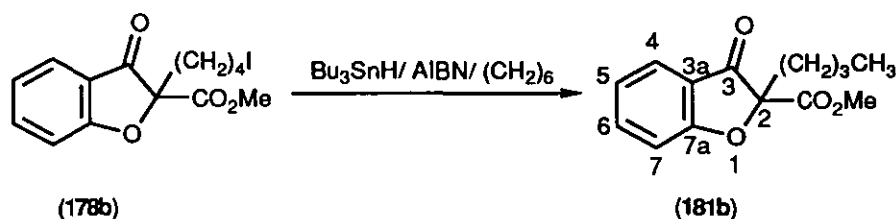
ν_{max} (neat) 2964 (C-H), 1741 (ester C=O), 1714 (5-ring α -aryl ketone C=O), 1612, 1476 and 1463 (arene C-C) cm^{-1}

δ_H (250 MHz) 7.69-7.63 (2 H, m, 4-H and 6-H), 7.24 (1 H, t, $J = 9.1$ Hz, 5-H), 7.13 (1 H, dt, $J_d = 0.7$ Hz, $J_t = 7.4$ Hz, 7-H), 3.77 (3 H, s, 2- CO_2Me), 2.36-2.23 and 2.13-2.00 (2 H, 2 m, 2- $CH_2CH_2CH_3$), 1.32 (2 H, qu, $J = 7.8$ Hz, 2- $CH_2CH_2CH_3$), and 0.92 (2 H, t, $J = 7.3$ Hz, 2- $CH_2CH_2CH_3$).

δ_C (62.5 MHz) 195.0 (3-C), 173.0 (2- CO_2Me), 167.0 and 119.5 (3a-C and 7a-C), 138.4, 124.8, 122.4 and 113.4 (4-C, 5-C, 6-C and 7-C), 91.7 (2-C), 53.2 (2- CO_2Me), 36.2 (2- $CH_2CH_2CH_3$), 16.6 (2- $CH_2CH_2CH_3$), and 13.8 (2- $CH_2CH_2CH_3$).

m/z (E.I.) 234.0853 (12 %, M^+ , $C_{13}H_{14}O_4$ requires 234.0892), 192 (100, $M - CH_2=CHCH_3$), 175 (12, $M - CO_2Me$), and 147 (8, $M - CO_2Me - CO$).

Attempted ring expansion of methyl 2-(4-iodobutyl)-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (178b)



Tributylstannane (0.4 g, 1.2 mmol) and AIBN (0.023 g, 0.1 mmol) in cyclohexane (20 cm^3) was added by syringe pump, over 4 h, under an atmosphere of nitrogen, to a refluxing solution of methyl 2-(4-iodobutyl)-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (178b) (0.4 g, 0.9 mmol) in cyclohexane (150 cm^3) ([tributylstannane] *ca.* 2.0 mM). The solution was allowed to reflux for a further 1 h, and then the solvent was removed *in vacuo* to give a yellow oil. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave methyl 2-butyl-2,3-dihydro-3-oxobenzo[b]furan-2-carboxylate (181b) (0.2 g, 0.7 mmol, 77 %) as an orange liquid, R_f [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.17.

Found C, 66.9; H, 6.7 %. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5 %.

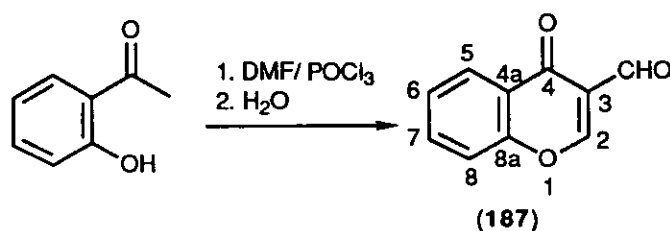
ν_{\max} (neat) 2959, 2931 (C-H), 1734 (ester C=O and 5-ring α -aryl ketone C=O), 1617, 1477, 1460, and 1438 (arene C-C) cm^{-1}

δ_{H} (250 MHz) 7.71-7.64 (2 H, m, 4-H and 6-H), 7.23 (1 H, dt, $J_{\text{d}} = 0.8 \text{ Hz}$, $J_{\text{t}} = 4.5 \text{ Hz}$, 5-H), 7.13 (1 H, dt, $J_{\text{d}} = 0.8 \text{ Hz}$, $J_{\text{t}} = 7.5 \text{ Hz}$, 7-H), 3.77 (3 H, s, 2-CO₂Me), 2.35-2.26 and 2.15-2.04 (2 H, 2 m, 2-CH₂CH₂CH₂CH₃), 1.37-1.23 (4 H, m, 2-CH₂CH₂CH₂CH₃), and 0.88 (2 H, t, $J = 6.7 \text{ Hz}$, 2-CH₂CH₂CH₂CH₃).

δ_{C} (62.5 MHz) 196.1 (3-C), 172.4 (2-CO₂Me), 166.5 and 119.7 (3a-C and 7a-C), 138.6, 124.9, 122.6 and 113.6 (4-C, 5-C, 6-C and 7-C), 91.8 (2-C), 53.3 (2-CO₂Me), 34.0, 25.2 and 22.6 (2-CH₂CH₂CH₂CH₃), and 13.7 (2-CH₂CH₂CH₂CH₃).

m/z (E.I.) 248.1048 (17 %, M^+ , C₁₄H₁₆O₄ requires 248.1049), 216 (M - MeOH), 192 (100, M - CH₂=CHCH₂CH₃), 189 (12, M - CO₂Me), and 161 (19, M - CO₂Me - CO).

Preparation of 4-oxo-4H-chromene-3-carbaldehyde (187)⁹⁹



Phosphoryl chloride (19 cm^3 , 31 g, 204 mmol) was added dropwise with stirring to DMF (77 cm^3 , 73 g, 994 mmol) and the resultant mixture was stirred for 20 min. 2-Hydroxyacetophenone (13.6 g, 100 mmol) was added dropwise (Temperature was maintained at below 5°C using an ice-bath throughout). The solution was allowed to warm to room temperature overnight. The resultant semi-solid was poured into ice-water (400 g) and stirred for 2 h. The precipitated solid was collected by filtration, washed with water (2 x 50 cm^3) and dried *in vacuo* to give a brown solid. Recrystallisation from ethyl acetate gave 4-oxo-4H-chromene-3-carbaldehyde (187) (9.3 g, 53 mmol, 53 %) as brown needles, m.p. 146-148°C (lit.⁹⁹ 149-151°C), R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.07.

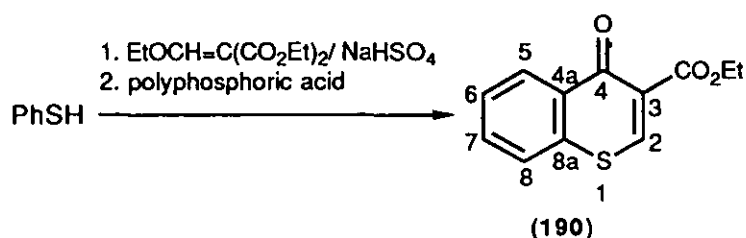
Found C, 68.9; H, 3.4 %. C₁₀H₆O₃ requires C, 69.0; H, 3.5 %.

ν_{\max} (KBr disc) 3440, 3080, 3060 (C-H), 2880 (aldehyde C-H), 1700 (aryl ketone C=O), 1650 ($\alpha\beta$ -unsaturated aldehyde/ketone C=C), 1610, 1560 (arene C-C), and 1460 cm^{-1}

δ_{H} (90 MHz) 10.42 (1 H, s, 3-CHO), 8.55 (1 H, s, 2-H), 8.37-8.25 (1 H, m, 5-H), 7.88-7.70 (1 H, m, 7-H), 7.68-7.51 (1 H, m, 6-H), and 7.50-7.41 (1 H, m, 8-H).

Repetition on a larger scale using 2-hydroxyacetophenone (27.3 g, 200 mmol) gave 4-oxo-4*H*-chromene-3-carbaldehyde (**187**) (24.1 g, 139 mmol, 69 %).

Preparation of ethyl 4-oxo-4*H*-thiochromene-3-carboxylate (**191**)¹⁰¹



Thiophenol (30.0 g, 272 mmol), diethyl ethoxymethylenemalonate (62.0 g, 287 mmol) and sodium hydrogensulfate (0.6 g, 16 mmol) were heated and stirred until no volatile products were observed to distil out of the mixture. Polyphosphoric acid (100 cm³) was added and the mixture was heated at 80°C for 13 h. The viscous solution was poured into ice (500 cm³) and stirred until the tar dissolved. The solution was extracted with diethyl ether (6 x 100 cm³). The combined extracts were washed with saturated sodium bicarbonate solution (2 x 100 cm³), dried over magnesium sulfate and the solvent was removed *in vacuo* to give a brown viscous liquid. Trituration with petrol (b.p. 60-80°C) gave ethyl 4-oxo-4*H*-thiochromene-3-carboxylate (**190**) (8.4 g, 36 mmol, 13 %) as a grey solid, m.p. 65-67°C (lit.¹⁰¹ 65-70°C), R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (1:1)] 0.33.

Found C, 61.5; H, 4.3; S, 13.8 %. C₁₂H₁₀O₃S requires C, 61.5; H, 4.2; S, 13.7 %.

ν_{max} (KBr disc) 3080, 3040, 2960 (C-H), 1725 (ester C=O and aryl ketone C=O), 1620, 1590, and 1520 (arene C-C) cm⁻¹

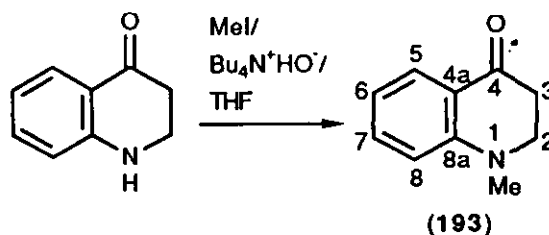
δ_{H} (360 MHz) 8.70 (1 H, s, 2-H), 8.59 (1 H, dt, $J_d = 7.3$ Hz, $J_t = 1.0$ Hz, 5-H), 7.65-7.56 (3 H, m, 6-H, 7-H and 8-H), 4.41 (2 H, q, $J = 7.1$ Hz, 3-CO₂CH₂CH₃), and 1.40 (3 H, t, $J = 7.1$ Hz, 3-CO₂CH₂CH₃).

δ_{C} (90 MHz) 176.0 (4-C), 164.1 (3-CO₂Et), 145.2 (2-C), 135.1 (3-C), 133.2 and 127.1 (8a-C and 4a-C), 131.7, 129.4, 128.5, and 126.6 (5-C, 6-C, 7-C, and 8-C), 61.6 (3-CO₂CH₂CH₃), and 14.2 (3-CO₂CH₂CH₃).

m/z (E.I.) 234.030 (20 %, M^+ , $C_{12}H_{10}O_3S$ requires 234.035), 189 (39, $M - EtO$), and 161 (5, $M - CO_2Et$).

The preparation was repeated, but purification, by trituration or chromatography, proved to be impossible.

Preparation of 1,2,3,4-tetrahydro-1-methyl-4-oxoquinoline (193)



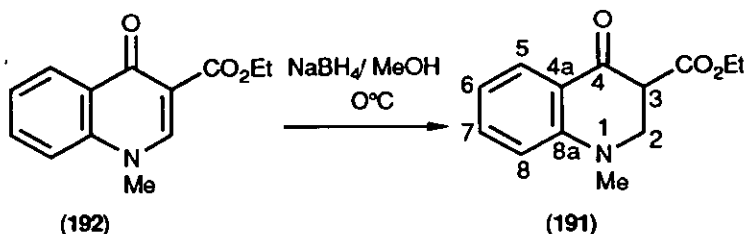
1,2,3,4-Tetrahydro-4-oxoquinoline (31.1 g, 0.211 mol), iodomethane (50 cm³, 114 g, 0.80 mol) and aqueous tetrabutylammonium hydroxide (40 %; 15 cm³) in THF (300 cm³) were heated at reflux for 44 h. Dilute aqueous potassium hydroxide (100 cm³) was added and the solution was extracted with dichloromethane (5 x 150 cm³). The combined extracts were washed with water (3 x 60 cm³) and brine (60 cm³). The solution was dried over magnesium sulfate and the solvent was removed *in vacuo* to give a red sticky semi-solid. Distillation gave 1,2,3,4-tetrahydro-1-methyl-4-oxoquinoline (193) (24.7 g, 0.153 mol, 73 %) as a yellow liquid, b.p. 82-120°C (0.2 mm Hg), R_f [alumina, petrol (b.p. 40-60°C): ethyl acetate (3:1)] 0.51.

ν_{\max} (neat) 3548, 3064, 2956 (C-H), 1666 (aryl C=O), 1598, 1560, and 1494 (arene C-C) cm⁻¹

δ_H (250 MHz) 7.89 (1 H, dd, $J = 1.7$ Hz, $J = 7.8$ Hz, 5-H), 7.37 (1 H, dt, $J_d = 1.7$ Hz, $J_t = 7.8$ Hz, 7-H), 6.75-6.55 (2 H, m, 8-H and 6-H), 3.42 (2 H, t, $J = 7.0$ Hz, 2-H), 2.94 (3 H, s, 1-Me), and 2.65 (2 H, t, $J = 7.0$ Hz, 3-H).

δ_C (62.5 MHz) 193.0 (4-C), 152.5 and 120.9 (4a-C and 8a-C), 135.4, 127.9, 117.0, 113.2 (5-C, 6-C, 7-C, and 8-C), 51.3 (2-C), 39.3 (1-Me), and 38.2 (3-C).

Preparation of ethyl 1,2,3,4-tetrahydro-1-methyl-4-oxoquinoline-3-carboxylate (**191**)



Sodium borohydride (2.0 g, 54 mmol) was added in one portion to a stirred solution of 1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (**192**) (11.0 g, 47.4 mmol) in methanol (250 cm³) at 0°C. The solution was allowed to warm to room temperature with stirring overnight, and concentrated *in vacuo*. The residue was taken up in water (40 cm³) and extracted with diethyl ether (3 x 80 cm³) and ethyl acetate (5 x 80 cm³). The combined extracts were dried over magnesium sulfate and the solvent was removed *in vacuo* to give an orange oil. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent, and recrystallisation from ethanol gave 1,2,3,4-tetrahydro-1-methyl-4-oxoquinoline-3-carboxylate (**191**) (0.3 g, 1.3 mmol, 3 %) as a yellow solid, m.p. 89-94°C, R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (3:1)] 0.44.

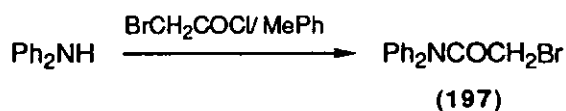
Found C, 66.6; H, 6.45; N, 6.0 %. C₁₃H₁₅NO₃ requires C, 66.9; H, 6.5; N, 6.0 %.

ν_{\max} (KBr disc) 3080, 3040, 2980, 2920, 2860, 2820 (C-H), 1730 (ester C=O), 1660 (aryl ketone C=O), 1620, 1560, 1520, and 1460 (arene C-C) cm⁻¹

The compound re-oxidised back to 1,4-dihydro-1-methyl-4-oxoquinoline-3-carboxylate (**192**) before NMR spectra could be obtained.

m/z (E.I.) 233.102 (29 %, M^+ , C₁₃H₁₅NO₃ requires 233.105), 204 (3, M - Et), 188 (6, M - EtO), and 160 (47, M - CO₂Et).

Preparation of *N,N*-diphenylbromoacetamide (**197**)¹⁰²



Bromoacetyl chloride (12 cm³, 23 g, 145 mmol) was added dropwise over 0.5 h to a stirred solution of diphenylamine (15.5 g, 91.8 mmol) in toluene (50 cm³). The resultant solution

was allowed to reflux for 18 h and evaporated to dryness to give a brown solid. Recrystallisation from acetone gave *N,N*-diphenylbromoacetamide (**197**) (17.4 g, 60.0 mmol, 65 %) as brown-tinted crystals, m.p. 109-112°C, *R*_f [silica, toluene:acetic acid (9:1)] 0.38.

Found C, 58.2; H, 4.4; N, 5.0 %. C₁₄H₁₂NOBr requires C, 57.95; H, 4.2; N, 4.8 %.

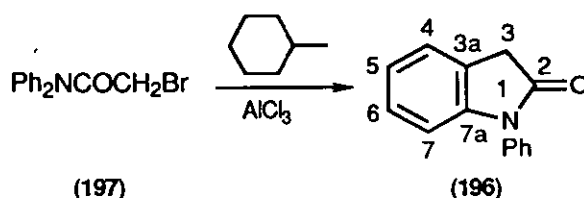
ν_{\max} (KBr disc) 3060, 3000, 2840 (C-H), 1670 (amide C=O), 1600, 1490, 1450, and 1430 (arene C-C) cm⁻¹

δ_{H} (250 MHz) 7.32 (10 H, br s, Ph₂NCOCH₂Br) and 3.85 (2 H, Ph₂NCOCH₂Br).

δ_{C} (62.5 MHz, CDCl₃) 166.5 (Ph₂NCOCH₂Br), 142.1, 129.9, 128.6 and 126.7 (Ph₂NCOCH₂Br), and 28.0 (Ph₂NCOCH₂Br).

m/z (E.I.) 291.0035 and 289.0094 (21 and 26 % respectively, *M*⁺, C₁₄H₁₂NOBr requires 291.0082 and 289.0102 respectively), 210 (2, *M* - Br), 196 (1, *M* - CH₂Br), 168 (52, *M* - COCH₂Br), and 77 (22, *M* - PhNCOCH₂Br).

Preparation of 1-phenylindoxindole (**196**)¹⁰²



N,N-Diphenylbromoacetamide (**197**) (16.5 g, 56.8 mmol) and anhydrous aluminium chloride (16.4 g, 123 mmol) in methylcyclohexane (100 cm³) were heated at reflux for 50 h and allowed to cool. The suspension was poured into crushed ice (500 cm³) and hydrochloric acid (5 M; 50 cm³). Stirring, filtration and drying *in vacuo* gave a solid which was recrystallised from petrol (b.p. 60-80°C) to give 1-phenylindoxindole (**196**) (4.3 g, 20 mmol, 36 %) as pink-tinted crystals, m.p. 115-117°C (lit.¹⁰² 120-121°C), *R*_f [silica, petrol (b.p. 40-60°C): ethyl acetate (3:1)] 0.25.

Found C, 79.7; H, 5.5; N, 6.7 %. C₁₄H₁₁NO requires C, 80.4 ; H, 5.3; N, 6.7 %.

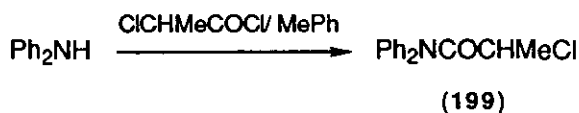
ν_{\max} (KBr disc) 3060, 2960 (C-H), 1710 (5-ring lactam C=O), 1610, 1600, 1500, 1480, and 1460 (arene C-C) cm⁻¹

δ_H (360 MHz, d_6 -DMSO) 7.59-7.41 (5 H, m, 1-*Ph*), 7.35 (1 H, d, $J = 7.1$ Hz, 4-H), 7.21 (1 H, t, $J = 7.5$ Hz, 6-H), 7.06 (1 H, t, $J = 7.2$ Hz, 5-H), 6.70 (1 H, d, $J = 7.8$ Hz, 7-H), and 3.76 (2 H, s, 3-H).

δ_C (90 MHz, d_6 -DMSO) 173.8 (2-C), 144.8, 134.5, 129.5, 127.9, 127.5, 126.7, 124.8, 124.7, 122.4, and 108.6 (1-*Ph*, 3a-C, 4-C, 5-C, 6-C, 7-C, and 7a-C), and 35.4 (3-C).

m/z (E.I.) 209.088 (50 %, M^+ , $C_{14}H_{11}NO$ requires 209.084), and 181 (17, $M - CO$).

Preparation of *N,N*-diphenyl-2-chloropropionamide (199)¹⁰²



2-Chloropropionyl chloride (25 g, 197 mmol) was added dropwise over 0.5 h to a stirred solution of diphenylamine (25 g, 148 mmol) in toluene (140 cm³). The resultant solution was allowed to reflux for 24 h and evaporated to dryness to give a purple solid. Trituration with petrol (b.p. 60-80°C) gave *N,N*-diphenyl-2-chloropropionamide (199) (35.3 g, 136 mmol, 92 %) as pink crystals, m.p. 83-84°C (lit.¹⁰² 90-93°C), R_f [silica, toluene: acetic acid (9:1)] 0.39.

Found C, 69.6; H, 5.5; N, 5.3; Cl, 13.5 %. $C_{15}H_{14}NOCl$ requires C, 69.4; H, 5.4; N, 5.4; Cl, 13.65 %.

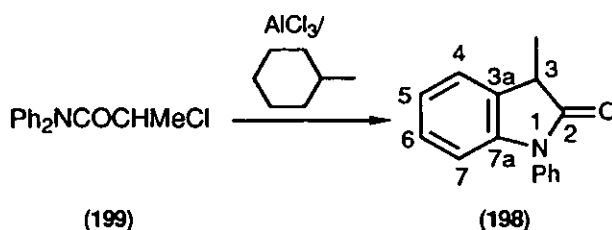
ν_{\max} (KBr disc) 3080, 3040, 2960 (C-H), 1680 (amide C=O), 1600, 1490 (arene C-C), and 1440 cm⁻¹

δ_H (250 MHz) 7.32 (10 H, br s, $\text{Ph}_2\text{NCOCHClMe}$), 4.47 (1 H, q, $J = 6.6$ Hz, $\text{Ph}_2\text{NCOCHClMe}$), and 1.67 (3 H, d, $J = 6.6$ Hz, $\text{Ph}_2\text{NCOCHClMe}$).

δ_C (62.5 MHz, CDCl_3) 169.5 ($\text{Ph}_2\text{NC OCHClMe}$), 129.9, 129.1, 128.5 and 126.3 ($\text{Ph}_2\text{NCOCHClMe}$), 50.8 ($\text{Ph}_2\text{NCOCHClMe}$), and 21.1 ($\text{Ph}_2\text{NCOCHClMe}$).

m/z (E.I.) 261.0814 and 259.0812 (10 and 34 % respectively, M^+ , $C_{15}H_{14}NOCl$ requires 261.0734 and 259.0764 respectively), 224 (2, $M - Cl$), 196 (21, $M - \text{CHClMe}$), 168 (48, $M - \text{COCHClMe}$), and 77 (27, $M - \text{PhNCOCHClMe}$).

Preparation of 3-methyl-1-phenylindoxindole (198)¹⁰²



Anhydrous aluminium chloride (38.3 g, 287 mmol) was added portion-wise to a stirred solution of *N,N*-diphenyl-2-chloropropionamide (199) (35.0 g, 135 mmol) in methylcyclohexane (100 cm³) and heated at reflux for 2 h. The cooled solution was poured into crushed ice (500 cm³) and hydrochloric acid (5 M; 50 cm³). Stirring, filtration and drying *in vacuo* gave a brown solid which was recrystallised from ethanol to give 3-methyl-1-phenylindoxindole (198) (18.2 g, 82 mmol, 61 %) as a brown solid, m.p. 76-78°C (lit.¹⁰² 80-81°C), *R*_f [petrol (b.p. 40-60°C): ethyl acetate (3:1)] 0.30.

Found C, 80.3; H, 5.9; N, 6.15 %. C₁₅H₁₃NO requires C, 80.7 ; H, 5.9; N, 6.3 %.

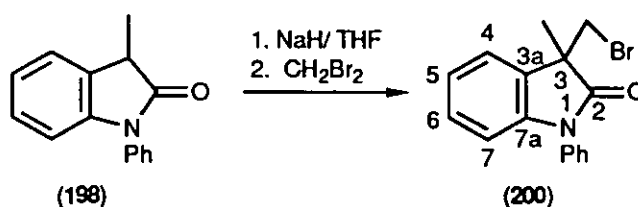
ν_{max} (KBr disc) 3340, 3060, 3000, 2940, 2920, 2840 (C-H), 1710 (5-ring lactam C=O), 1620, 1600, 1500, and 1460 (arene C-C) cm⁻¹

δ_{H} (360 MHz, *d*₆-DMSO) 7.52 (2 H, t, *J* = 5.4 Hz, 1-*Ph*: *meta*-H), 7.41 (3 H, d, *J* = 7.7 Hz, 1-*Ph*: *ortho*-H and *para*-H), 7.28 (1 H, t, *J* = 8.5 Hz, 4-H), 7.19 (1 H, t, *J* = 7.6 Hz, 6-H), 7.08 (1 H, t, *J* = 7.0 Hz, 5-H), 6.81 (1 H, d, *J* = 7.6 Hz, 7-H), 3.62 (1 H, q, *J* = 7.6 Hz, 3-H), and 1.59 (3 H, d, *J* = 7.6 Hz, 3-*Me*).

δ_{C} (90 MHz, *d*₆-DMSO) 178.0 (2-C), 143.9 and 134.6 (3a-C and 7a-C), 130.5, 129.6, 128.0, 127.8, 126.6, 123.8, 122.9, and 109.3 (1-*Ph*, 7-C, 6-C, 5-C, and 4-C), 40.8 (3-C), and 15.7 (3-*Me*).

m/z (E.I.) 223.1016 (100 %, *M*⁺, C₁₅H₁₃NO requires 223.0997), and 195 (27, *M* - CO).

Preparation of 3-bromomethyl-3-methyl-1-phenylindoxindole (200)



3-Methyl-1-phenylindolinone (**198**) (8.1 g, 36 mmol) was added portion-wise under an atmosphere of nitrogen to a stirred suspension of sodium hydride (60 %; 1.8 g, 45 mmol) in THF (60 cm³). After 0.5 h, the suspension was heated at reflux for 1 h and allowed to cool. Dibromomethane (13 cm³, 32 g, 185 mmol) was added and reflux was continued for 1.5 h. The solution was allowed to stir overnight and poured into water (25 cm³). The phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 25 cm³). The combined organic phases were dried over magnesium sulfate and the solvent was removed *in vacuo* to give a brown solid. Recrystallisation from ethanol gave 3-bromomethyl-3-methyl-1-phenyloxindole (**200**) (4.9 g, 15 mmol, 42 %) as a brown solid, m.p. 112-113°C, *R*_f [petrol (b.p. 40-60°C): ethyl acetate (3:1)] 0.40.

Found C, 60.9; H, 4.55; N, 4.4; Br, 25.2 %. C₁₆H₁₄NOBr requires C, 60.8 ; H, 4.5; N, 4.4; Br, 25.3 %.

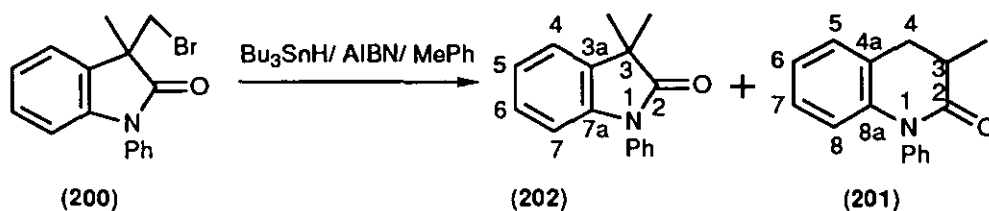
ν_{\max} (KBr disc) 3080, 3040, 2960, 2920, 2860 (C-H), 1720 (5-ring lactam C=O), 1610, 1600, 1490, 1480, 1460, and 1440 (arene C-C) cm⁻¹

δ_{H} (250 MHz) 7.49 (2 H, t, *J* = 14.2 Hz, 1-*Ph*: meta-H), 7.38 (3 H, t, *J* = 11.8 Hz, 1-*Ph*: ortho-H and para-H), 7.34 (1 H, d, *J* = 7.3 Hz, 4-H), 7.22 (1 H, t, *J* = 7.6 Hz, 6-H), 7.13 (1 H, t, *J* = 7.4 Hz, 5-H), 6.84 (1 H, d, *J* = 7.9 Hz, 7-H), 3.83 and 3.68 (2 H, 2 d, *J* = 9.9 Hz, 3-CH₂Br), and 1.60 (3 H, s, 3-Me).

δ_{C} (62.5 MHz) 177.0 (2-C), 144.0 and 135.0 (3a-C and 7a-C), 132.0, 129.6, 128.5, 128.2, 126.7, 123.2, 123.0, and 109.5, (1-*Ph*, 7-C, 6-C, 5-C and 4-C), 49.2 (3-C), 37.4 (3-CH₂Br), and 22.4 (3-Me).

m/z (E.I.) 317.0170 and 315.0212 (40 and 38 % respectively, *M*⁺, C₁₆H₁₄NOBr requires 317.0239 and 315.0259), 236 (8, *M* - Br), and 222 (100, *M* - CH₂Br).

Ring expansion of 3-bromomethyl-3-methyl-1-phenyloxindole (**200**)



Tributylstannane (0.5 g, 1.8 mmol) in toluene (20 cm³) was added by syringe pump, over 5 h, under an atmosphere of nitrogen, to a refluxing solution of 3-bromomethyl-3-methyl-1-phenyloxindole (**200**) (0.5 g, 1.6 mmol) and AIBN (few mg) in toluene (200 cm³) ([tributylstannane] *ca.* 1.7 mM). The solution was allowed to reflux for a further 1 h, and then stood overnight. A further portion of tributylstannane (0.5 g, 1.8 mmol) and AIBN (few mg) in toluene (20 cm³) was added by syringe pump over 5 h. The solvent was removed *in vacuo* to give a yellow oil. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave two oils. Trituration of one of the oils with chloroform gave 3,3-dimethyl-1-phenyloxindole (**202**) (0.08 g, 0.33 mmol, 21 %) as a colourless solid, m.p. 70-75°C, *R*_f [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.21, and trituration of the other oil with petrol (b.p. 40-60°C) gave 3,4-dihydro-3-methyl-1-phenylquinolin-2(1*H*)-one (**201**) (0.12 g, 0.50 mmol, 31 %) as a colourless solid, m.p. 89-93°C, *R*_f [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.12.

3,3-Dimethyl-1-phenyloxindole (**202**)

ν_{\max} (CDCl₃) 3056, 2968, 2928 (C-H), 1722 (5-ring lactam C=O), 1610, and 1494 (arene C-C) cm⁻¹

δ_{H} (250 MHz) 7.51-7.48 (2 H, m, 1-*Ph*: *meta*-H), 7.44-7.38 (3 H, m, 1-*Ph*: *ortho*-H and *para*-H), 7.26-7.09 (3 H, m, 4-H, 5-H, and 6-H), 6.86 (1 H, d, *J* = 0.9 Hz, 7-H), and 1.49 (6 H, s, 3-*Me*).

δ_{C} (62.5 MHz) 181.0 (2-C), 142.5 and 135.6 (3a-C and 7a-C), 135.0, 129.6, 127.9, 127.6, 126.6, 123.0, 122.6, and 109.4 (7-C, 6-C, 5-C, 4-C and 1-*Ph*), 44.3 (3-C), and 24.8 (3-*Me*).

m/z (E.I.) 237.1163 (100 %, *M*⁺, C₁₆H₁₅NO requires 237.1154), 222 (51, *M* - Me), and 194 (37, *M* - Me - CO).

3,4-Dihydro-3-methyl-1-phenylquinolin-2(1*H*)-one (**201**)

Found C, 80.3; H, 6.9; N, 5.3 %. C₁₆H₁₅NO requires C, 81.0; H, 6.4; N, 5.9 %.

ν_{\max} (CDCl₃) 3060 (C-H), 1676 (6-ring lactam C=O), 1602, 1492, and 1458 (arene C-C) cm⁻¹

δ_{H} (250 MHz) 7.52-7.39 (3 H, m, 1-*Ph*: *meta*- and *para*-H), 7.24-7.17 (3 H, 5-H and 1-*Ph*: *ortho*-H), 7.03-6.96 (2 H, 7-H and 6-H), 6.35-6.32 (1 H, 8-H), 3.13-2.99 (1 H, m, 4-H

trans to 3-*Me*), 2.93-2.75 (2 H, m, 3-H and 4-H *cis* to 3-*Me*), and 1.33 (3 H, d, $J = 6.4$ Hz, no nOe with ArH, 3-*Me*).

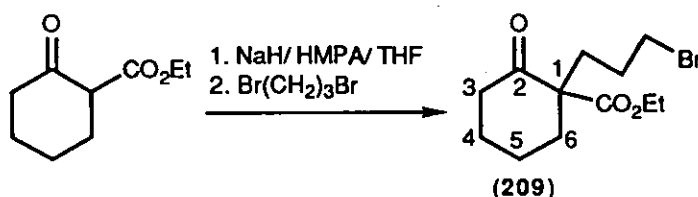
δ_H (400 MHz) 7.49 (2 H, t, $J = 7.6$ Hz, 1-*Ph*: *meta*-H), 7.40 (1 H, t, $J = 7.6$ Hz, 1-*Ph*: *para*-H), 7.26-7.19 (3 H, 5-H and 1-*Ph*: *ortho*-H), 7.03 (1 H, dt, $J_d = 1.5$ Hz, $J_t = 7.7$ Hz, 7-H), 6.97 (1 H, dd, $J = 6.3$ Hz, $J = 7.3$ Hz, 6-H), 6.33 (1 H, d, $J = 7.9$ Hz, 8-H), 3.09-3.03 (1 H, m, 4-H *trans* to 3-*Me*), 2.91-2.79 (2 H, m, 3-H and 4-H *cis* to 3-*Me*), and 1.33 (3 H, d, $J = 6.5$ Hz, 3-*Me*).

The assigned structure was confirmed by nOe difference spectroscopy.

δ_C (62.5 MHz) 173.0 (2-C), 142.0 and 138.8 (8a-C and 4a-C), 129.9, 129.8, 129.0, 128.0, 127.0, 125.2, 122.8, and 116.8 (8-C, 7-C, 6-C, 5-C and 1-*Ph*), 35.9 and 33.5 (3-C and 4-C), and 15.5 (4-*Me*).

m/z (E.I.) 237.1164 (100 %, M^+ , $C_{16}H_{15}NO$ requires 237.1154), 222 (6, $M - Me$), and 209 (8, $M - CO$).

Preparation of ethyl 1-(3-bromopropyl)-2-oxocyclohexanecarboxylate (209)¹⁵



Ethyl 2-oxocyclohexanecarboxylate (10.0 g, 58.8 mmol) was added to a stirred suspension of sodium hydride (60 % dispersion; 2.5 g, 63 mmol) and HMPA (11 cm³, 11 g, 63 mmol) in THF (30 cm³) under an atmosphere of nitrogen. After stirring for 1.0 h, 1,3-dibromopropane (30 cm³, 60 g, 296 mmol) was added and the solution was heated at reflux for 2 h and allowed to stir overnight. The mixture was allowed to cool and taken up in diethyl ether (100 cm³), washed with water (5 x 5 cm³), dried over potassium carbonate, and the solvent was removed *in vacuo* [at r.t. (20 mm Hg) and at 70°C (1 mm Hg)] to give a yellow liquid. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave ethyl 1-(3-bromopropyl)-2-oxocyclohexanecarboxylate (209) (5.6 g, 19 mmol, 33 %) as a yellow liquid, R_f [petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.16.

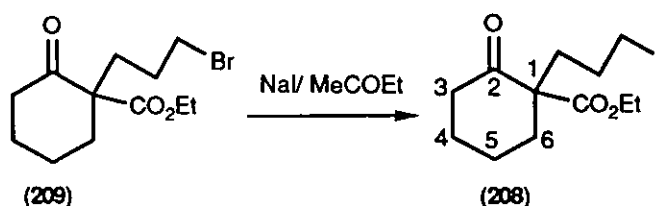
ν_{max} (neat) 2940, 2864 (C-H), 1738 (ester C=O and ketone C=O), and 1442 cm⁻¹

δ_{H} (250 MHz) 4.22 (2 H, q, $J = 7.1$ Hz, 1-CO₂CH₂CH₃), 3.39 (2 H, t, $J = 5.9$ Hz, 1-CH₂CH₂CH₂Br), 2.51-2.43 (2 H, m, 3-H), 2.04-1.63 (10 H, m, 4-H, 5-H, 6-H and 1-CH₂CH₂CH₂Br), and 1.28 (3 H, t, $J = 7.1$ Hz, 1-CO₂CH₂CH₃).

δ_{C} (62.5 MHz) 207.6 (2-C), 171.8 (1-CO₂Et), 61.4 (1-CO₂CH₂CH₃), 60.4 (1-C), 41.0 (1-CH₂CH₂CH₂Br), 36.3, 33.7, 33.5, 27.9, 27.6, and 22.6 (3-C, 4-C, 5-C, 6-C and 1-C H₂CH₂CH₂Br), and 14.2 (1-CO₂CH₂CH₃).

The spectroscopic data correspond to those published.¹⁵

Preparation of ethyl 1-(3-iodopropyl)-2-oxocyclohexanecarboxylate (208) [1]



Ethyl 1-(3-bromopropyl)-2-oxocyclohexanecarboxylate (209) (5.6 g, 19 mmol) and sodium iodide (2.9 g, 19 mmol) in butanone (100 cm³) were heated at reflux for 6 h and allowed to cool. The solution was filtered and washed with aqueous sodium sulphite and brine. The solution was dried over magnesium sulfate and the solvent was removed *in vacuo* to give ethyl 1-(3-iodopropyl)-2-oxocyclohexanecarboxylate¹⁵ (208) as a yellow liquid (3.7 g, 11 mmol, 56 %), R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (3:1)] 0.50.

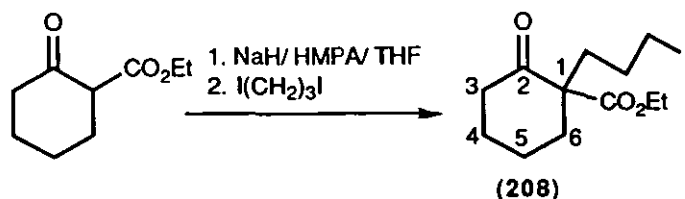
ν_{max} (neat) 2940, 2864 (C-H), 1718 (ester C=O and ketone C=O), and 1446 cm⁻¹

δ_{H} (250 MHz) 4.22 (2 H, q, $J = 7.1$ Hz, 1-CO₂CH₂CH₃), 3.16 (2 H, 2 d, $J_{\text{AB}} = 5.9$ Hz, 1-CH₂CH₂CH₂I), 2.51-2.43 (2 H, m, 3-H), 2.04-1.63 (10 H, m, 1-CH₂CH₂CH₂I, 4-H, 5-H, and 6-H), and 1.28 (3 H, t, $J = 7.1$ Hz, 1-CO₂CH₂CH₃).

δ_{C} (62.5 MHz) 207.7 (2-C), 171.7 (1-CO₂Et), 61.3 (1-CO₂CH₂CH₃), 60.3 (1-C), 41.0, 36.3, 35.7, 28.5, 27.5, and 27.5 (1-CH₂CH₂CH₂I, 3-C, 4-C, 5-C, and 6-C), 14.2 (1-CO₂CH₂CH₃), and 6.4 (1-CH₂CH₂CH₂I).

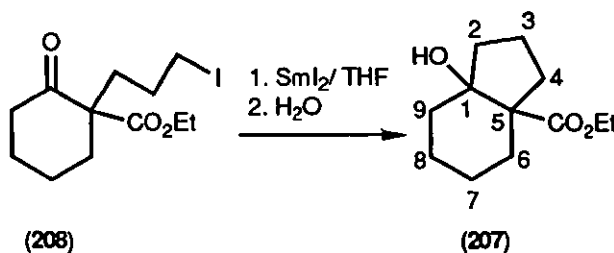
The spectroscopic data correspond to those published.¹⁵

Preparation of ethyl 1-(3-iodopropyl)-2-oxocyclohexanecarboxylate (208)
[2]¹⁵



Ethyl 2-oxocyclohexanecarboxylate (6.5 g, 38 mmol) was added to a stirred suspension of sodium hydride (60 % dispersion; 1.7 g, 43 mmol) and HMPA (7 cm³, 7 g, 40 mmol) in THF (40 cm³) under an atmosphere of nitrogen. After stirring for 1.0 h, 1,3-di-iodopropane (7 cm³, 18 g, 61 mmol) was added and the solution was heated at reflux for 5 h and allowed to stir overnight. The mixture was allowed to cool and taken up in diethyl ether (100 cm³), washed with water (6 x 5 cm³), dried over potassium carbonate, and the solvent was removed *in vacuo* [at r.t. (20 mm Hg) and at 70°C (1 mm Hg)] to give a yellow liquid. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave ethyl 1-(3-iodopropyl)-2-oxocyclohexanecarboxylate (208) (6.0 g, 18 mmol, 46 %) as a yellow liquid, *R_f* [petrol (b.p. 40-60°C): ethyl acetate (3:1)] 0.50. The spectroscopic data correspond to those published.¹⁵

Preparation of ethyl 1-hydroxy[4.3.0]bicyclononane-5-carboxylate (207)



To samarium powder (40 mesh; 3.0 g, 20 mmol), flamed and cooled under an atmosphere of argon, in THF (10 cm³) was added di-iodoethane (4.2 g, 15 mmol) in THF (20 cm³). The solution was stirred at room temperature for 1 h and then cooled to -78°C. Ethyl 1-(3-iodopropyl)-2-oxocyclohexanecarboxylate (208) (2.5 g, 7.4 mmol) in THF (2 cm³) was added slowly and the solution was allowed to warm to room temperature, with stirring, overnight. The solution was poured into aqueous potassium carbonate (1 M; 100 cm³) and extracted with diethyl ether (5 x 30 cm³). The combined extracts were dried (potassium carbonate) and the solvent was removed *in vacuo* to give an orange liquid. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave ethyl 1-hydroxy[4.3.0]bi-

cyclononane-5-carboxylate¹⁰⁶ (**207**) (0.6 g, 3 mmol, 40 %) as a yellow liquid, R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (1:1)] 0.60.

Found: C, 67.0; H, 9.0 %. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.5 %.

ν_{\max} (neat) 3496 (O-H), 2936 (C-H), 1702 (ester C=O), and 1464 cm^{-1}

δ_H (250 MHz) 4.19 and 4.18 (2 H, 2 q, $J = 7.1$ Hz, 5-CO₂CH₂CH₃, *E* and *Z*), 4.40-2.90 (2 H, br s, D₂O ex., 1-OH), 2.34-2.19 (1 H, m, 2-H, 3-H, 4-H, 6-H, 7-H, 8-H, or 9-H), 2.03-1.23 (13 H, m, 2-H, 3-H, 4-H, 6-H, 7-H, 8-H, and 9-H), 1.27 (3 H, t, $J = 7.1$ Hz, 5-CO₂CH₂CH₃).

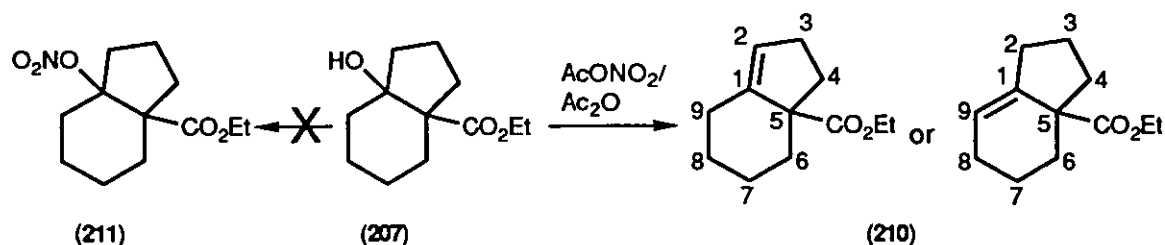
δ_C (62.5 MHz) 177.6 (5-CO₂Et), 81.4 (5-C), 60.5 (5-CO₂CH₂CH₃), 56.0 (1-C), 34.6, 34.2, 33.2, 23.9, 22.8, and 19.0 (2-C, 3-C, 4-C, 6-C, 7-C, 8-C, and 9-C), and 14.0 (5-CO₂CH₂CH₃).

m/z (E.I.) 212.1467 (M^+ , 20 %, $C_{12}H_{20}O_3$ requires 212.1412), 170 [100, $M - (CH_2)_3$], 167 (26, $M - EtO$), 166 (30, $M - EtOH$), 139 ($M - CO_2Et$), and 138 (37, $M - HCO_2Et$).

The spectroscopic data correspond to those published.¹⁰⁶ Repetition on a smaller scale using ethyl 1-(3-iodopropyl)-2-oxocyclohexanecarboxylate (**208**) (1.0 g, 3.0 mmol) gave ethyl 1-hydroxy[4.3.0]bicyclononane-6-carboxylate (**207**) (0.4 g, 2 mmol, 64 %).

Repetition on a larger scale using ethyl 1-(3-iodopropyl)-2-oxocyclohexanecarboxylate (**208**) (4.9 g, 14 mmol) gave ethyl 1-hydroxy[4.3.0]bicyclononane-6-carboxylate (**207**) (1.4 g, 6.8 mmol, 47 %).

Attempted preparation of the nitrate ester of ethyl 1-hydroxy[4.3.0]bicyclononane-5-carboxylate (**207**) [1]



Fuming nitric acid (decolourised by urea; 0.2 cm³, 4.7 mmol) was added dropwise to stirred, cooled (ice-bath) acetic anhydride (1.0 cm³, 11 mmol). A portion of the solution (1.0 cm³, 3.5 mmol based on nitric acid) was added to a stirred, cooled (ice-bath) solution of

ethyl 1-hydroxy[4.3.0]bicyclononane-5-carboxylate (**207**) (0.2 g, 1.0 mmol) in acetic anhydride (2 cm³). The resulting mixture was stirred for 10 min, then poured into saturated aqueous sodium bicarbonate. The solution was stirred for 0.5 h, then extracted with diethyl ether (5 x 20 cm³). The combined extracts were dried (sodium sulfate) and the solvent was removed *in vacuo* to give a yellow oil. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave the alkene (**210**) (0.1 g, 0.5 mmol, 51 %) as a yellow oil, *R_f* [silica, petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.53.

ν_{max} (neat) 3044, 2932 (C-H), 1724 (ester C=O), 1628 (C=C), and 1446 cm⁻¹

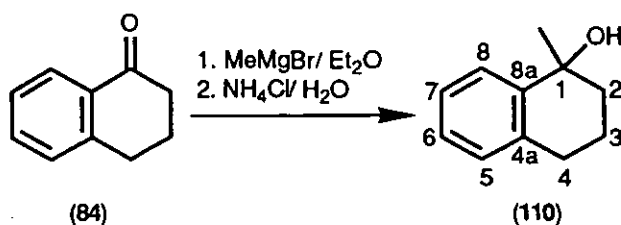
δ_{H} (250 MHz) 5.45 (1 H, s, 2/9-H), 4.17 (2 H, 2 q, *J* = 7.4 Hz, 5-CO₂CH₂CH₃), 2.43-2.24 (2 H, m), 1.82-1.18 (10 H, m), 1.22 (3 H, t, *J* = 7.4 Hz, 5-CO₂CH₂CH₃), and 0.88 (2 H, t, *J* = 7.4 Hz).

δ_{C} (62.5 MHz) 176.6 (5-CO₂Et), 144.3 (1-C), 124.0 (2/9-C), 60.3 (5-CO₂CH₂CH₃), 57.6 (5-C), 38.2, 37.7, 30.4, 27.8, 27.2, and 24.1 (9/2-C, 8-C, 7-C, 6-C, 4-C, and 3-C), and 14.0 (5-CO₂CH₂CH₃).

Attempted preparation of the nitrate ester of ethyl 1-hydroxy[4.3.0]bicyclononane-5-carboxylate (**207**) [2]

Fuming nitric acid (decolourised by urea; 0.2 cm³, 4.7 mmol) was added dropwise to stirred, cooled (ice-bath) acetic anhydride (1.0 cm³, 11 mmol). A portion of the solution (0.8 cm³, 2.8 mmol based on nitric acid) was added to a stirred, cooled (sodium chloride ice-bath) solution of ethyl 1-hydroxy[4.3.0]bicyclononane-5-carboxylate (**207**) (0.2 g, 1.0 mmol) in acetic anhydride (1 cm³). The resulting mixture was stirred for 6 min, then poured into saturated aqueous sodium bicarbonate. The solution was extracted with diethyl ether (5 x 20 cm³). The combined extracts were dried (sodium sulfate) and the solvent was removed *in vacuo* to give a yellow oil. Dry flash chromatography on alumina gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave recovered starting material (**207**) (0.1 g, 0.6 mmol, 31 %) as a yellow oil, *R_f* [alumina, petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.40.

Preparation of 1-methyl-1-tetralol (**110**)⁶⁰



1-Tetralone (**84**) (8.5 g, 58 mmol) in THF (20 cm³) was added slowly at 0°C under an atmosphere of nitrogen to a stirred solution of methylmagnesium bromide (3.0 M; 22 cm³, 66 mmol) in diethyl ether. The solution was allowed to reflux for 3 h, then allowed to stir over the weekend. The solution was poured into saturated aqueous ammonium chloride and the phases were separated. The aqueous phase was extracted with diethyl ether (4 x 20 cm³) and the combined organic phases were dried over magnesium sulfate. Removal of solvent *in vacuo* gave a black solid which was recrystallised twice from petrol: ethyl acetate to give 1-methyl-1-tetralol⁶⁰ (**110**) (1.0 g, 6.0 mmol, 10 %) as a grey-brown powder, m.p. 88-89°C, *R*_f [silica, petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.12.

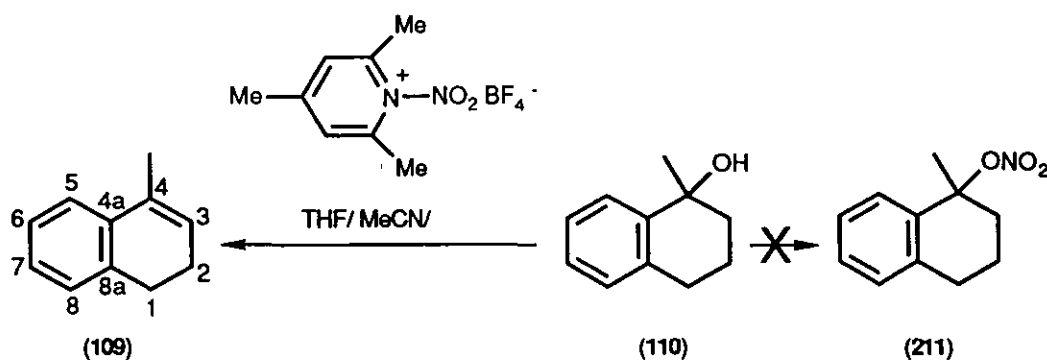
ν_{max} (CCl₄) 3615 (br, O-H), 2976, 2871 (C-H), 1489, 1442 and 1458 (arene C-C) cm⁻¹

δ_{H} (250 MHz) 12.02 (1 H, s, D₂O ex., 1-OH), 7.54 (1 H, d, *J* = 7.2 Hz, 8-H), 7.21-7.10 (2 H, m, 7-H and 6-H), 7.03 (1 H, d, *J* = 6.8 Hz, 5-H), 2.85-2.68 (2 H, m, 4-H), 1.98-1.62 (4 H, m, 2-H and 3-H) and 1.52 (3 H, s, 1-Me).

δ_{C} (62.5 MHz) 142.9 and 136.2 (8a-C and 4a-C), 128.8, 127.0, and 126.3 (2 signals) (5-C, 6-C, 7-C, and 8-C), 70.5 (1-C), 39.7 (4-C), 30.7 (1-Me), 29.7 (2-C), and 20.4 (3-C).

m/z (E.I.) 162.1044 (*M*⁺, 8 %, C₁₁H₁₄O requires 162.1045), 147 (100, *M* - Me), 144 (19, *M* - H₂O).

Attempted preparation of the nitrate ester of 1-methyl-1-tetralol (**211**)



2,4,6-collidine (1.0 g, 8.0 mmol) in acetonitrile (5 ml) was slowly added under an atmosphere of nitrogen at 0°C to nitronium fluoroborate (1.0 g, 7.7 mmol) in acetonitrile (3 ml). The resultant cloudy yellow solution was stirred at 0°C for 0.5 h and 1-methyl-1-tetralol (**110**) (0.3 g, 1.8 mmol) in THF (8 ml) was slowly added. The resultant orange solution was allowed to warm to room temperature over 3 h, then poured into ice-water (50 ml) and

extracted with diethyl ether (4 x 50 ml). The combined extracts were dried over magnesium sulphate and the solvent was removed *in vacuo* to give an orange oil. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave 1,2-dihydro-4-methylnaphthalene⁶⁰ (**109**) (0.1 g, 0.7 mmol, 39 %) as an orange oil, R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (9:1)] 0.62.

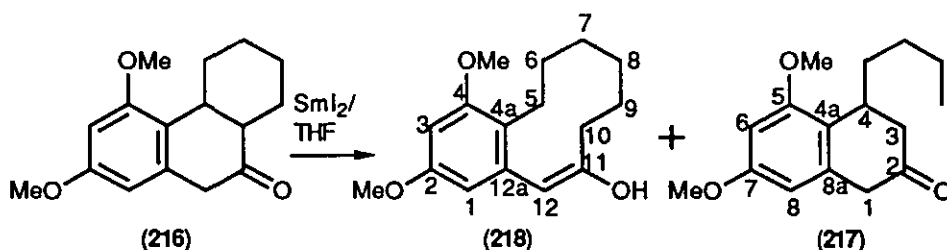
ν_{\max} (neat) 3027, 2965, 2932, 2884, 2859, 2831 (C-H), 1675 (alkene C=C), 1589, 1488, 1451, and 1439 (arene C-C) cm^{-1}

δ_H (250 MHz) 7.35-7.22 (4 H, m, 5-H, 6-H, 7-H and 8-H), 5.97-5.93 (1 H, m, 3-H), 2.86 (2 H, t, $J = 8.0$ Hz, 1-H), 2.39-2.30 (2 H, m, 2-H), and 2.17 (3 H, s, 4-Me).

δ_C (62.5 MHz) 136.3 and 132.2 (8a-C and 4a-C), 127.3, 126.7, 126.3 and 125.4 (5-C, 6-C, 7-C and 8-C), 107.8 (4-C), 28.3 (1-C), 23.2 (2-C), and 19.3 (4-Me).

m/z (E.I.) 144.0911 (M^+ , 54 %, $C_{11}H_{12}$ requires 144.0939).

Samarium (II) iodide-mediated ring opening of 4b,5,6,7,8,8a,9,10-octahydro-2,4-dimethoxy-9-oxophenanthrene (**216**)



Di-iodomethane (0.3 g, 1.3 mmol) in THF (5 cm^3) was added, at room temperature under an atmosphere of nitrogen, to a stirred suspension of samarium (0.2 g, 1.4 mmol) in THF (5 cm^3). After stirring for 1 h, the solution was cooled to -78°C and 4b,5,6,7,8,8a,9,10-octahydro-2,4-dimethoxy-9-oxophenanthrene (**216**) (0.3 g, 1.2 mmol) in THF (20 cm^3) was slowly added. The solution was allowed to warm to room temperature overnight, then poured into saturated aqueous potassium carbonate (30 cm^3) and extracted with diethyl ether (6 x 30 cm^3). The combined extracts were dried over magnesium sulfate and the solvent was removed *in vacuo* to give a brown semi-solid. Dry flash chromatography on silica gel with petrol (b.p. 40-60°C): ethyl acetate as eluent gave 4-butyl-5,7-dimethoxy-2-tetralone (**217**) (0.068 g, 0.26 mmol, 22 %) as a black solid, R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (4:1)] 0.49, and 5,6,7,8,9,10-hexahydro-2,4-dimethoxybenzocyclodecen-11-ol (**218**)

(0.037 g, 0.14 mmol, 12 %) as a purple solid, R_f [silica, petrol (b.p. 40-60°C): ethyl acetate (4:1)] 0.22. NMR spectra of both products were obtained, but both compounds decomposed on attempted recrystallisation from petrol (b.p. 40-60°C): ethyl acetate.

4-butyl-5,7-dimethoxy-2-tetralone (217)

δ_H (250 MHz) 6.90 (1 H, d, $J = 1.9$ Hz, 8-H), 6.39 (1 H, d, $J = 1.9$ Hz, 6-H), 3.89 and 3.82 (5-OMe and 7-OMe), 3.95-3.76 (1 H, m, 4-H), 3.56-3.36 (2 H, m, 1-H), 2.82-2.75 (2 H, 3-H), 1.77 (2 H, t, $J = 3.1$ Hz, 4-CH₂CH₂CH₂CH₃), 2.04-0.88 (4 H, m, 4-CH₂CH₂CH₂CH₃), and 0.84 (3 H, t, $J = 2.7$ Hz, 4-CH₂CH₂CH₂CH₃).

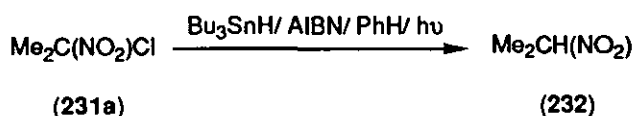
δ_C (62.5 MHz) 210.2 (2-C), 159.4, 158.3, 152.8, and 122.8 (8a-C, 7-C, 5-C, and 4a-C), 137.3 and 135.5 (6-C and 8-C), 55.4, 55.3, and 55.1 (7-OMe, 5-OMe, and 4-C), 31.8 and 30.3 (1-C and 3-C), 25.9, 23.5, and 21.9 (4-CH₂CH₂CH₂CH₃), and 14.0 (4-CH₂CH₂CH₂CH₃).

5,6,7,8,9,10-hexahydro-2,4-dimethoxybenzocyclodecen-11-ol (218)

δ_H (400 MHz) 6.81 (1 H, s, 11-H), 6.51 (1 H, d, $J = 2.4$ Hz, 1-H), 6.32 (1 H, d, $J = 2.4$ Hz, 3-H), 4.85-4.77 (1 H, br s, 11-OH), 3.86 and 3.84 (2-OMe and 4-OMe), 3.40 (2 H, t, $J = 6.0$ Hz, 5-H), 2.72 (2 H, t, $J = 6.0$ Hz, 10-H), and 1.84-1.75 (8 H, m, 6-H, 7-H, 8-H, and 9-H).

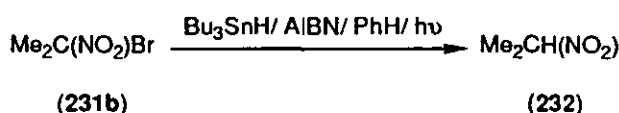
δ_C (62.5 MHz) 159.3, 157.2, 136.4, 136.0, and 122.6 (2-C, 4-C, 4a-C, 11-C, and 12a-C), 106.5, 97.8, and 96.4 (1-C, 3-C, and 12-C), 55.1 and 55.0 (2-OMe and 4-OMe), 30.2 and 29.6 (5-C and 10-C), 24.2, 23.6, 21.7, and 20.9 (6-C, 7-C, 8-C, and 9-C).

Reduction of 2-chloro-2-nitropropane (231a) with tributylstannane



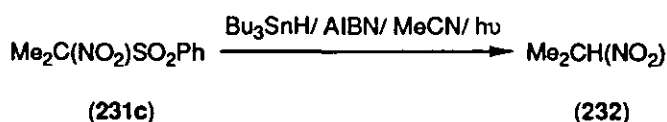
2-Chloro-2-nitropropane (231a) (0.3 g, 2.5 mmol), tributylstannane (0.9 g, 3.0 mmol) and AIBN (0.07 g, 0.4 mmol) in benzene (15 cm³) in a Carius tube were deoxygenated with nitrogen and frozen. The tube was irradiated for 19 h, opened and the solution was made up to 25 cm³ in methanol. HPLC analysis against internal standards (prepared by previous researchers) showed the solution to contain 2-nitropropane (232) (47 %) and 2-chloro-2-nitropropane (231a) (3 %).

Reduction of 2-bromo-2-nitropropane (231b) with tributylstannane



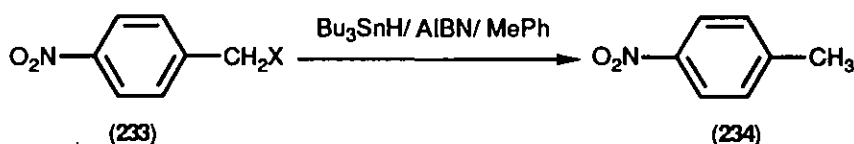
2-Bromo-2-nitropropane (231b) (0.4 g, 2.5 mmol), tributylstannane (0.9 g, 3.0 mmol) and AIBN (0.07 g, 0.4 mmol) in benzene (15 cm³) in a Carius tube were deoxygenated with nitrogen and frozen. The tube was irradiated for 9 h, opened and the solution was made up to 25 cm³ in methanol. HPLC analysis against internal standards (prepared by previous researchers) showed the solution to contain 2-nitropropane (232) (66 %).

Reduction of 1-methyl-1-nitroethyl phenyl sulfone (231c) with tributylstannane



1-Methyl-1-nitroethyl phenyl sulfone (231c) (0.6 g, 2.5 mmol), tributylstannane (2.2 g, 7.5 mmol) and AIBN (0.07 g, 0.4 mmol) in acetonitrile (25 cm³) in a Carius tube were deoxygenated with nitrogen and frozen. The tube was irradiated for 70 h, opened and the solution was made up to 25 cm³ in methanol. HPLC analysis against internal standards (prepared by previous researchers) showed the solution to contain 2-nitropropane (232) (32 %) and 1-methyl-1-nitroethyl phenyl sulfone (231c) (15 %).

Reduction of *p*-nitrobenzyl halides (233) with tributylstannane



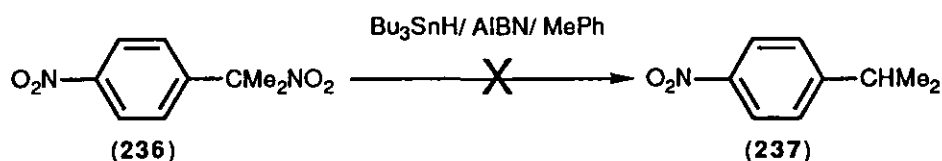
A solution of the *p*-nitrobenzyl halide (233) (2.4 mmol) and tributylstannane (1.5 g, 5.2 mmol) in toluene (5 cm³) was stirred under a stream of nitrogen for 40 min. AIBN (0.1 g, 0.6 mmol) in toluene (5 cm³) was added and the solution was irradiated or refluxed for the specified period of time. The solvent was removed *in vacuo* to give an oil, which was analysed directly either by ¹H NMR spectroscopy using *p*-dimethoxybenzene as an internal standard to measure yields of products, or by making up the solution to 25 cm³ with methanol and analysing by HPLC. The eluent for the HPLC analysis of the crude product of

the reduction of *p*-nitrobenzyl chloride (233a) was methanol-water (70:30 v/v). The results are tabulated below:

Substrate (233)	Conditions	Bu ₃ SnH/ equiv.	Yield of (234)/ %	Substrate (233) recovered/ %
(233a)	hν, 3 h	2.17	24	77
(233d)	hν, 3 h		32	55
(233c)	hν, 3.5 h		71	0
(233b)	hν, 1 h		30	51
	hν, 3 h		60	10
	hν, 4 h		75	0
	Δ, 1 h		47	0
	Δ, 2 h		60	0
	hν, 1.5 h	2.09	45	52
	hν, 1.5 h, Bu ^t ₂ NO• (0.6 equiv)		0	33
	dark, 1.5 h		0	88
	dark, 1.5 h, Δ		100	0
	hν, 1.5 h, <i>p</i> -(NO ₂) ₂ C ₆ H ₄ (0.25 equiv)		0	100
	hν, 1.5 h, no AIBN		9	15
	hν, 1.5 h, no N ₂		0 [§]	0

§ Yield of *p*-NO₂-C₆H₄CH₂OH (235) 31 %.

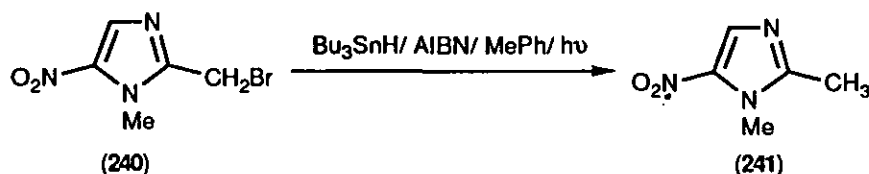
Attempted reduction of 2-nitro-2-(4-nitrophenyl)propane (236) with tributylstannane



A solution of 2-nitro-2-(*p*-nitrophenyl)propane (**236**) (0.5 g, 2.5 mmol) and tributylstannane (1.5 g, 5.2 mmol) in toluene (50 cm³) was stirred under a stream of nitrogen for 40 min. AIBN (0.1 g, 0.6 mmol) in toluene (5 cm³) was added and the solution was refluxed for 47 h. The solvent was removed *in vacuo* to give an orange oil, which was made up to 25

cm³ with methanol. HPLC analysis against internal standards (prepared by previous researchers) against standards showed 2-nitro-2-(4-nitrophenyl)propane (236) (80 %). No *p*-nitrocumene (237) was detected.

Reduction of 2-bromomethyl-1-methyl-5-nitroimidazole (240) with tributylstannane



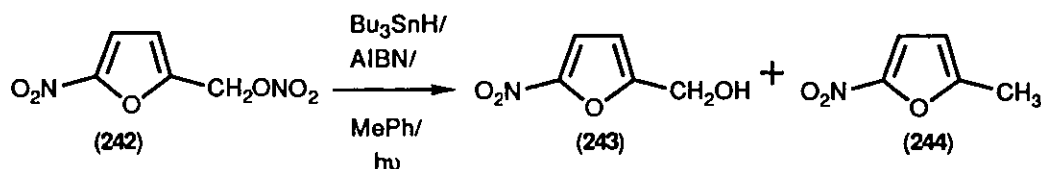
2-Bromomethyl-1-methyl-5-nitroimidazole (240) (1.4 g, 6.4 mmol), tributylstannane (3.0 g, 13 mmol) and AIBN (0.1 g, 0.6 mmol) in toluene (60 cm³) were irradiated under an atmosphere of nitrogen for 5 h. The solution was evaporated to dryness and the resultant solid was taken up in dichloromethane. The solution was extracted with hydrochloric acid (2 M) and the acid extract was washed with diethyl ether. The acidic extract was basified with sodium carbonate and extracted with dichloromethane. The extract was dried over magnesium sulfate and evaporated to dryness. Recrystallisation from aqueous methanol gave 1,2-dimethyl-5-nitroimidazole (241) (0.6 g, 4.3 mmol, 63 %) as colourless crystals, m.p. 134-135°C (lit.¹⁰⁷ 135-136°C).

ν_{max} 3121 (C-H), 1762, 1525, and 1463 (C=C and C=N) cm⁻¹

δ_{H} (60 MHz) 7.55 (1 H, s, 4-H), 3.7 (3 H, s, 1-Me), and 2.35 (3 H, s, 2-Me).

The spectroscopic data were identical to those of the authentic material.

Reduction of (5-nitro-2-furyl)methyl nitrate (242) with tributylstannane



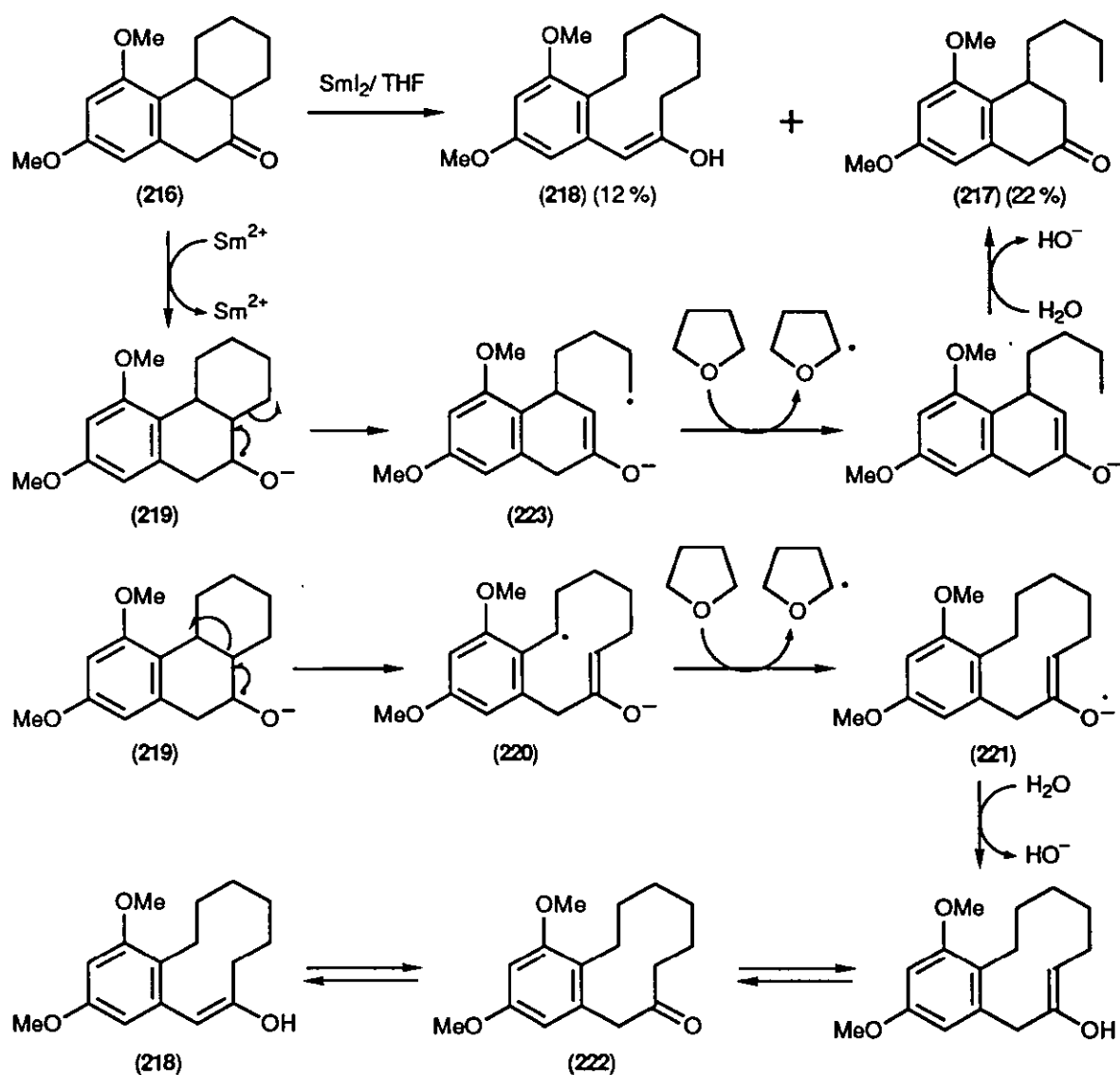
(5-Nitro-2-furyl)methyl nitrate (242) (0.5 g, 2.5 mmol), tributylstannane (1.5 g, 5.2 mmol) and AIBN (0.1 g, 0.6 mmol) in toluene (30 cm³) were irradiated under an atmosphere of nitrogen for 3 h. *p*-Dimethoxybenzene (0.09 g, 0.6 mmol) was added and the solution was removed *in vacuo* to give a brown oil. NMR spectroscopic analysis of the crude product

against the internal standard by comparison of integrals, as shown, gave the following estimated yields:

Compound	NMR resonance	$\delta_{\text{H}}/$ ppm	Estimated yield/ %
<i>p</i> -dimethoxybenzene	<i>p</i> -OCH ₃	3.6	-
2-methyl-5-nitrofuran (244)	2-CH ₃	2.45	43
2-hydroxymethyl-5-nitrofuran (243)	2-CH ₂ OH	4.6	54

4. Appendix 1: Samarium (II) Iodide-Mediated Ring Expansion

As discussed in the Introduction to this Thesis [See section 1.5.1(c), especially Schemes 47³² and 48⁴⁰], there is evidence, in particular the ring opening of α -cyclopropyl ketones, to suggest that samarium (II) iodide mediates the formation of ketyl radical-anions from ketones by SET and that such ketyls are capable of mediating the ring opening of bicyclic compounds. Thus samarium (II) iodide should be capable of mediating the ring expansion of suitably functionalised ketones, *e.g.* 4b,5,6,7,8,9,10-octahydro-2,4-dimethoxy-9-oxophenanthrene (**216**) (Scheme 129), by Cleavage of the Zero Bridge in Bicycles.



Scheme 129

The ketone (216), a small amount of which was purchased from the Aldrich ABC Collection of Rare Chemicals by the Boots Co. PLC, was treated with samarium (II) iodide in THF to afford two unstable products, which were tentatively characterised, on the basis of high field ^{13}C and ^1H NMR spectra, as 4-butyl-5,7-dimethoxy-2-tetralone (217) and 5,6,7,8,9,10-hexahydro-2,4-dimethoxybenzocyclodecen-11-ol (218).

The products (217) and (218) could arise by a sequence of SET, β -scission, hydrogen-abstraction and protonation (Scheme 129). The ketyl (219), which is formed from the ketone (216) by SET, is aligned for ring-opening (and ring expansion), *via* β -scission, to the enolate (220), which is also a benzylic radical. Hydrogen-transfer from the solvent should give the enolate (221), which would afford the cyclodecanone (222) on aqueous work-up. However the compound's high field NMR spectra appears to indicate that the ketone exists as the enol (218). This enolisation can be rationalised in terms of the resultant extension of conjugation. This is in stark contrast to the lack of enolisation exhibited by the ketones (83), (216), and (217). The alternative β -scission of the ketyl (219), which would give ring-opening without ring expansion, would afford the enolate (223), which is also a primary alkyl radical. This species is far less thermodynamically stable than the benzylic radical (220). However, the reverse reaction, *viz.* the 6-*exo* cyclisation of the radical (223) to give the ketyl (219), would involve the attack of a nucleophilic alkyl moiety on the β -position of an enolate moiety, which is also nucleophilic. Hence the process is kinetically disfavoured. Subsequent hydrogen-abstraction and protonation would afford the tetralone (217). Thus the β -scission of the ketyl (219) would appear to be non-regiospecific: evidently the transition energies for β -scission to radicals (223) and (220) are of a similar order of magnitude. Such transition energies are determined, at least in part, by relief of steric strain, an imponderable effect. This is analogous to the non-regiospecific β -scission of the alkoxyl radicals (64)¹⁶ [See section 1.5.2(b)] and (172) [See section 2.4(b)].

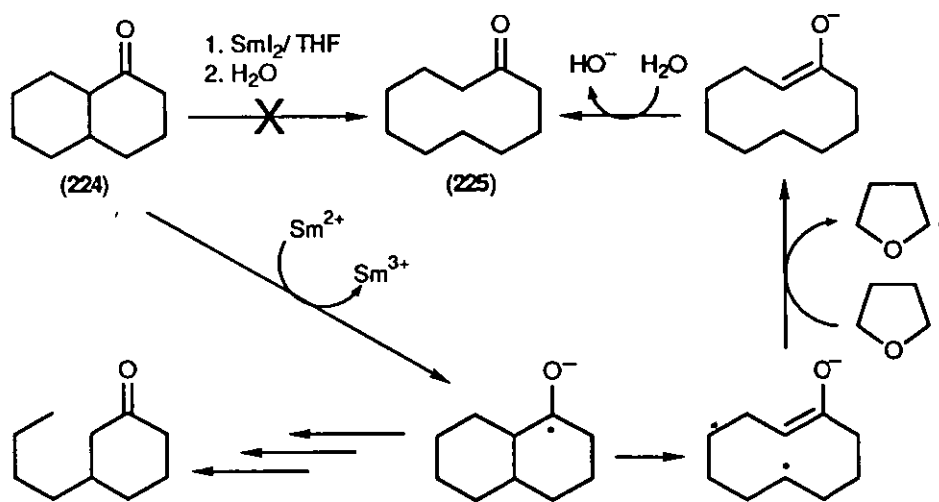
The products decomposed prior to further characterisation and insufficient starting material was available to repeat the experiment. Given time, further elaborate starting materials would have been prepared.

In an effort to find a substrate with more stable products, the ring expansion of 1-decalone (224) to cyclodecanone (225) *via* β -scission of the ketyl was investigated (Scheme 130). The alternative β -scission, that which leads to a primary alkyl radical, would give 3-butylcyclohexanone. The reaction failed under the following conditions, giving recovered starting material (224) as the only product on aqueous work-up:

SmI_2 (1.1 equivalents)/ THF/ -78°C to r.t.;³⁹

SmI_2 (1.1 equivalents)/ THF/ r.t.;

SmI_2 (1.5 equivalents *via* syringe pump)/ THF/ DMPU/ r.t.⁴⁰

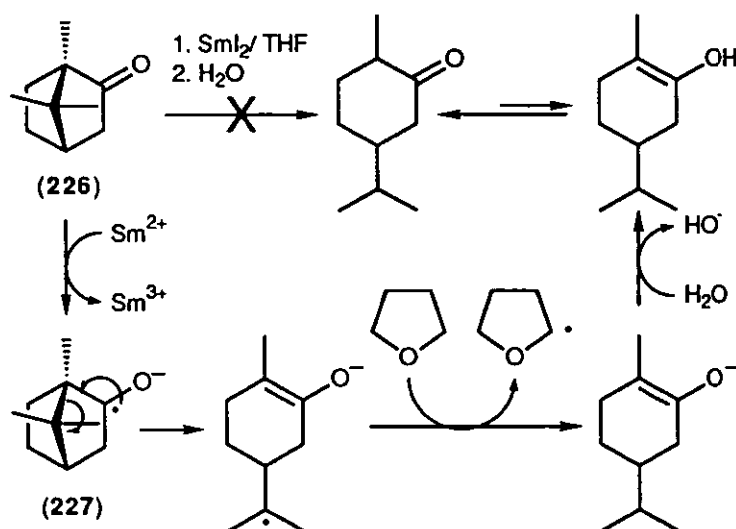


Scheme 130

The ring-opening of camphor (226) *via* the ketyl (227) was also envisaged (Scheme 131). Ring opening of the ketyl (227) should give a stable tertiary alkyl radical, thereby relieving strain in the [2.2.1]bicycloheptane ring system, and therefore should be a favourable process. The samarium (II) iodide-mediated formation of the ketyl of a similar species (228) offers a literature precedent¹⁰⁸ (Scheme 132). The reaction failed under the following conditions, giving recovered starting material as the only product on aqueous work-up:

SmI₂ (1.1 equivalents)/ THF/ 0°C to r.t.;³⁹

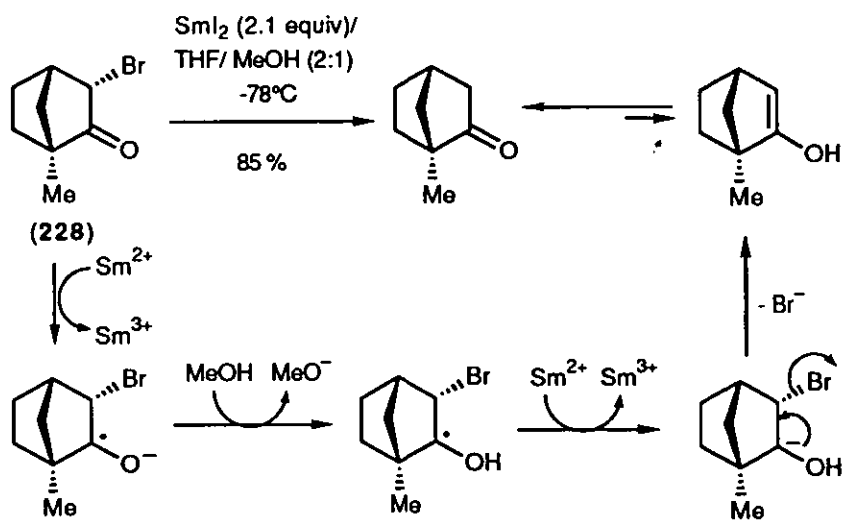
SmI₂ (1.1 equivalents)/ THF/ MeOH/ 0°C to r.t.¹⁰⁸



Scheme 131

The recovery of starting material was not expected because, even if ring-opening failed, reduction to an alcohol was expected. A possibility exists that the samarium (II) iodide was not fully formed and hence that the reaction was feasible, but did not take place.

However reactions were carried out under the normal conditions and the expected colour change, viz. from blue to green or yellow, were observed. With shortage of time, and following a general lack of success, this line of work was abandoned. However, given further work, it promises a novel route to ring expansion that avoids the tedious purification procedures associated with tributylstannane-mediated reactions.

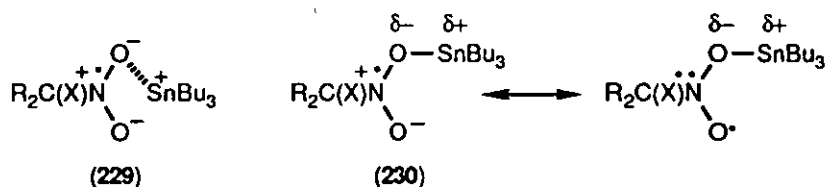


Scheme 132

5. Appendix 2: Reduction of Substituted Nitro Compounds with Tributylstannane

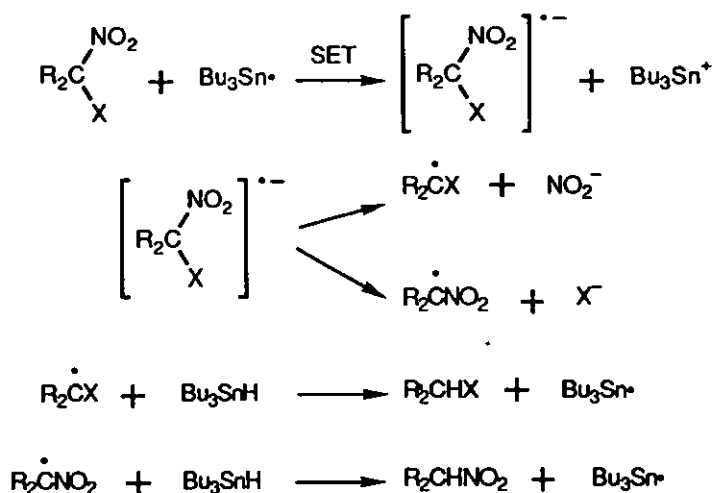
As stated in the Introduction [section 1.5.1(b)] and in the Discussion (section 2.8), there are at least two conceivable mechanisms for the radical reduction of nitro compounds. Both the Radical-Anion and the Nitroxide mechanisms (the two most likely mechanisms¹⁰⁹) are supported by experimental evidence which indicates a chain mechanism. Tributylstannane-mediated reduction of secondary and tertiary nitroalkanes yields the corresponding alkanes without providing any means of deciding which mechanism is operating. It was considered that the tributylstannane-mediated reduction of α -substituted nitro compounds, where the α -substituent is a good leaving group, might provide this mechanistic information. The Radical-Anion mechanism and the Nitroxide mechanism for the reduction of such compounds are shown below (Scheme 133). If the Radical-Anion mechanism operates, then dissociation of the radical-anion with loss of the α -substituent could occur. If the Nitroxide mechanism operates exclusively, then only loss of nitrite would be expected.

The apparent dichotomy between the two mechanisms is possibly false. If the radical-anion exists as a close ion-pair¹¹⁰ (229) with the tributyltin cation, its structure is similar to that of one of the canonical forms (230) of the nitroxide. The structures (229) and (230) may be in equilibrium. In any event, they are so similar that they are probably indistinguishable by EPR spectroscopy.¹⁰⁹⁻¹¹¹

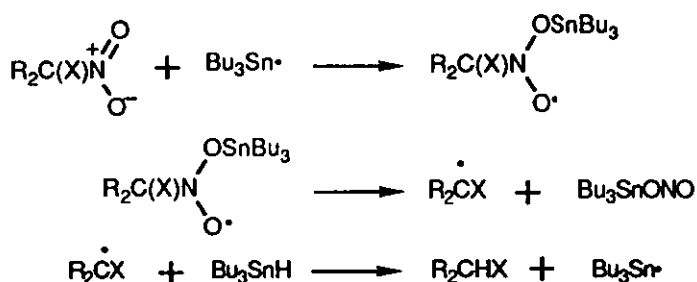


In an effort to investigate which of the putative mechanisms is operative, benzene solutions of a number of 2-substituted 2-nitropropanes (231) were irradiated in the presence of AIBN and tributylstannane (1.2 equivalents) and the crude products were analysed by HPLC against standards made up from authentic materials prepared by previous researchers (Scheme 134). In all cases the only product obtained, other than starting material, was 2-nitropropane (232). Thus the α -substituent is lost in preference to the nitro group, indicating that the Radical-Anion mechanism probably operates in at least some circumstances. The slowness of the reduction of the α -nitro sulfone (231c) compared to the halides (231a) and (231b) is indicative of the relative stabilities of the associated radical-anions.¹¹¹ $S_{\text{RN}}1$ studies have shown that the dissociation of the radical-anion of α -nitro sulfone (231c) is slow.¹¹² Therefore, if the nitroxide is a possible intermediate, loss of nitrite would be expected (Scheme 135): the resultant α -sulfonyl radical is stabilised.

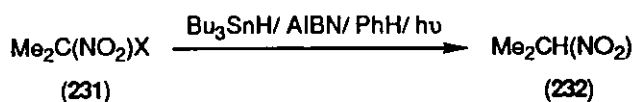
Radical-Anion Mechanism



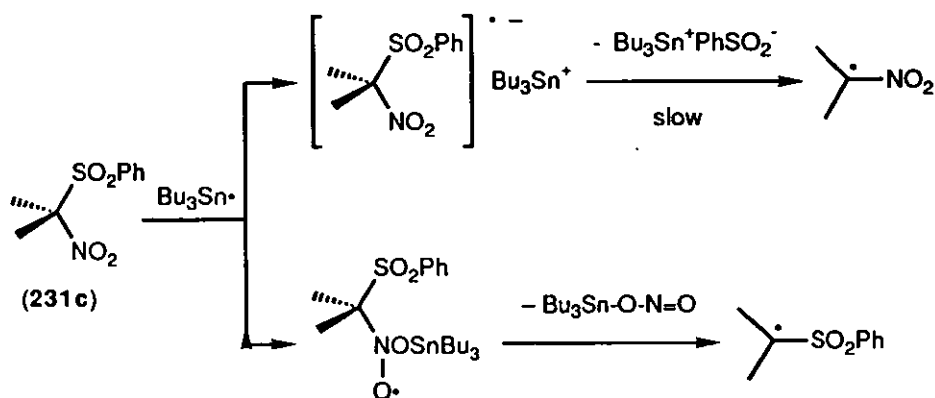
Nitroxide Mechanism



Scheme 133



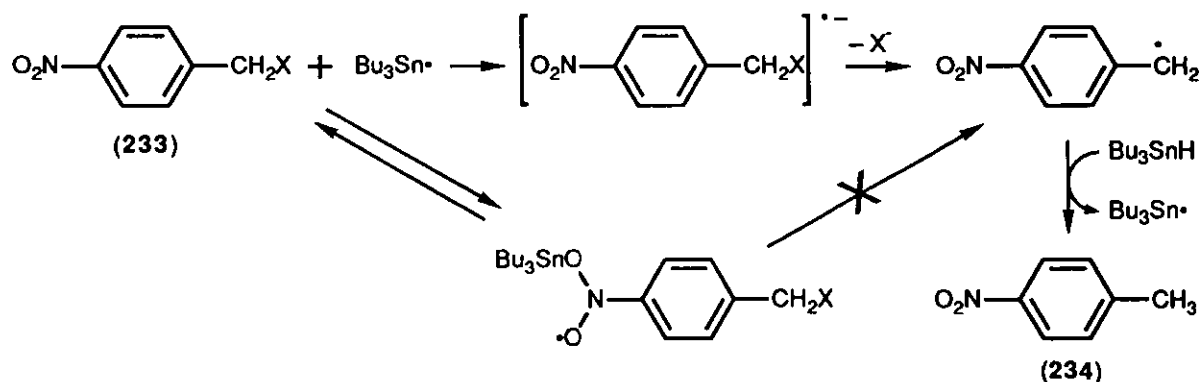
Scheme 134 a, X = Cl (47 %); b, X = Br (66 %); c, X = SO₂Ph (32 %)



Scheme 135

The relative rates of reaction, as inferred from the product yields, are in accordance with the rates of dissociation of the radical-anions derived from the nitropropanes (231). These rates increase with the nucleofugacity (leaving group ability) of the α -substituent, X, *i.e.* with the stability of the derived anion, X^- . Hence the rates increase in the order: $\text{PhSO}_2 < \text{Cl} < \text{Br}$. The relative rates of reduction of the nitroxides would be expected to be approximately equal, and hence independent of the nature of the α -substituent, X, provided the stability it afforded to the 2-propyl radical was similar.

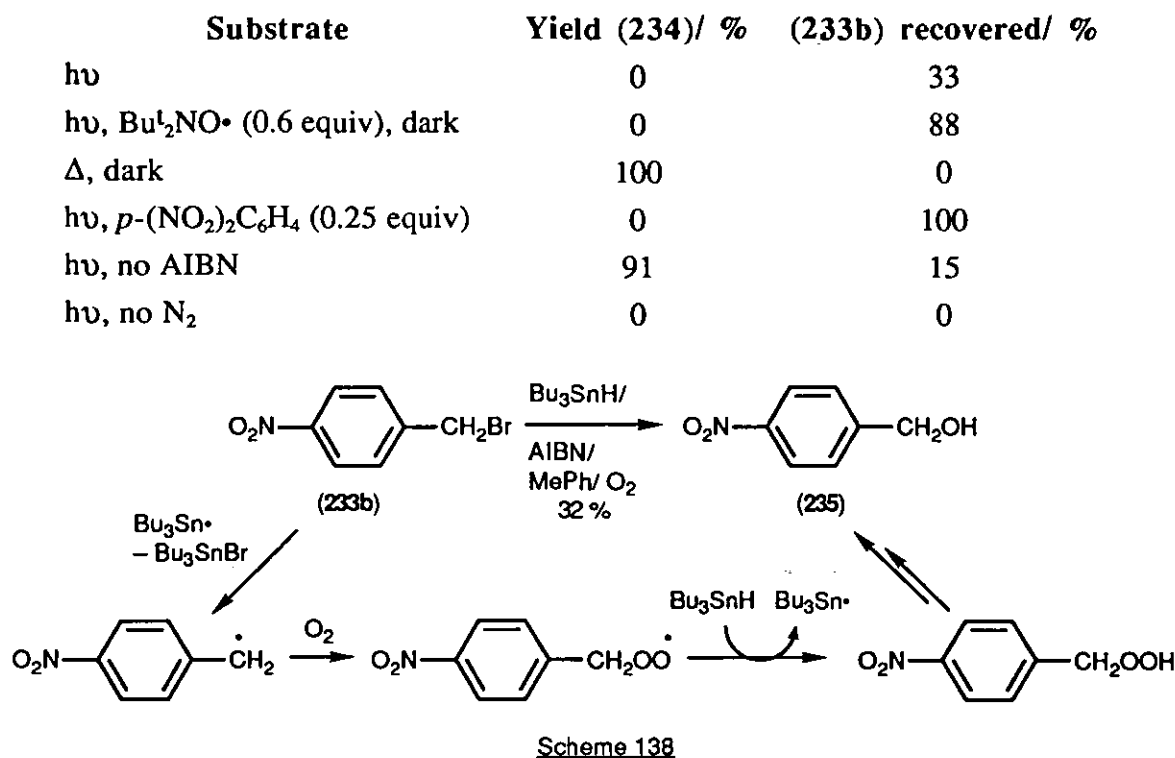
In order to further test the nature of the mechanism, a group of substituted nitro compounds in which the nitro group and the other potential nucleofuge are conjugatively separated, was investigated. The tributylstannane-mediated reduction of *p*-nitrobenzyl halides (233) was investigated (Scheme 136). Addition of the tributylstannyl radical to the nitro group should not lead to cleavage of the arene carbon-nitrogen bond, since a highly unstable arene σ radical would result. Therefore the nitroxide formation, if feasible, should be reversible and the Nitroxide mechanism is unlikely to be operative. However the radical-anions derived from *p*-nitrobenzyl halides (233) are known to undergo dissociation to *p*-nitrobenzyl radicals. Thus the Radical-Anion mechanism is likely to be operative. The crude products of the reactions were analysed by HPLC against standards made up from authentic materials prepared by previous researchers, or by ^1H NMR spectroscopy with *p*-dimethoxybenzene as the internal standard. In all cases the only product obtained was *p*-nitrotoluene (234) (Scheme 137). In some cases, some starting material (233) was also detected.



Scheme 137 a, X = Cl (24 %); b, X = Br (75 %); c, X = I (71 %); d, X = SCN (32 %)

The mechanism of the reduction of *p*-nitrobenzyl bromide (233b) was investigated. The reduction was carried out several times under a standard set of conditions modified as shown in the table below. The reduction was inhibited using radical traps [di-*t*-butyl]

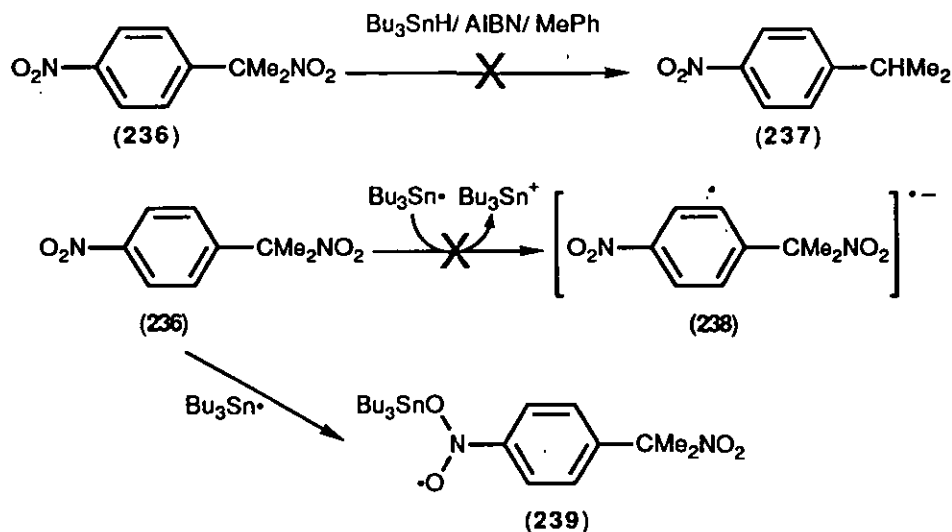
nitroxide ($\text{Bu}_3\text{SnO}^\bullet$) and oxygen]. In the oxygen inhibition reaction, *p*-nitrobenzyl alcohol (235) was formed (Scheme 138), indicating trapping of the *p*-nitrobenzyl radical by triplet oxygen.¹¹³ The reaction was shown to be light-catalysed or thermally initiated. AIBN catalysed the reaction but was not essential. Strong electron acceptors (oxygen and *p*-dinitrobenzene) also inhibited the reaction suggesting that radical-anions are intermediates. However *p*-dinitrobenzene is also a good trap for tributylstannyl radicals,^{109a} so that use of this inhibitor is not conclusive evidence for the intermediacy of radical-anions.



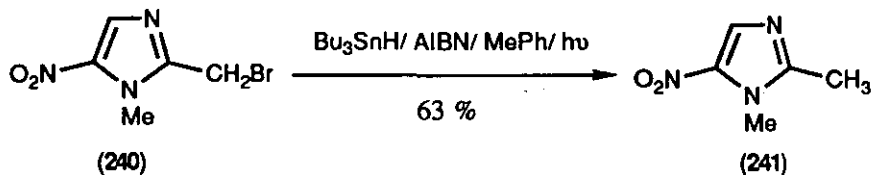
2-Nitro-2-(4-nitrophenyl)propane (236) was completely inert towards tributylstannane, even after prolonged heating, and no sign of *p*-nitrocumene (237) was observed (Scheme 139). This result supports the reported inertness to tributylstannane.^{109b-c} In contrast, the analogous *p*-cyano- and *p*-methoxycumenes are readily reduced.^{109a-c} 2-Nitro-2-(4-nitrophenyl)propane (236) does slowly undergo $\text{S}_{\text{RN}}1$ reactions^{112,113} and the radical-anion (238) does dissociate to the *p*-nitrocumyl radicals.¹¹⁴ This suggests that the tributylstannyl radicals attack the aromatic nitro group to yield a nitroxide (239) in which the C-N bond is unlikely to break,^{109c} and that the radical-anion (238) is not formed. It is difficult to explain why similar auto-inhibitory behaviour is not observed in the tributylstannane-mediated reduction of the *p*-nitrobenzyl halides (233).

The tributylstannane-mediated reduction of two aromatic heterocyclic analogues was also investigated. Such compounds are known to undergo $\text{S}_{\text{RN}}1$ reactions,¹¹⁵ *i.e.* they are able to undergo SET reduction to yield radical-anions which dissociate to yield stabilised

"benzylic" radicals. These radical-anions have also been identified by EPR spectroscopy and their dissociation has been observed at low temperature.¹¹⁶ 2-Bromomethyl-1-methyl-5-nitroimidazole (**240**) was reduced to the 2-methyl derivative (**241**) (Scheme 140). The result provides further evidence for the operation of the Radical-Anion mechanism.

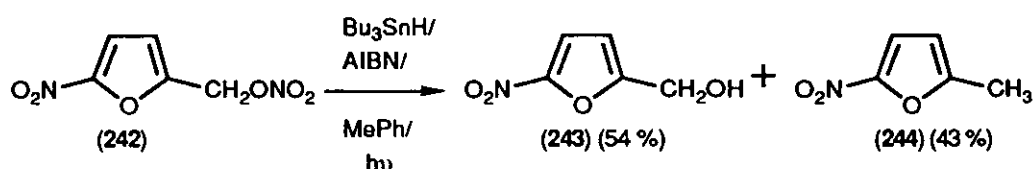


Scheme 139



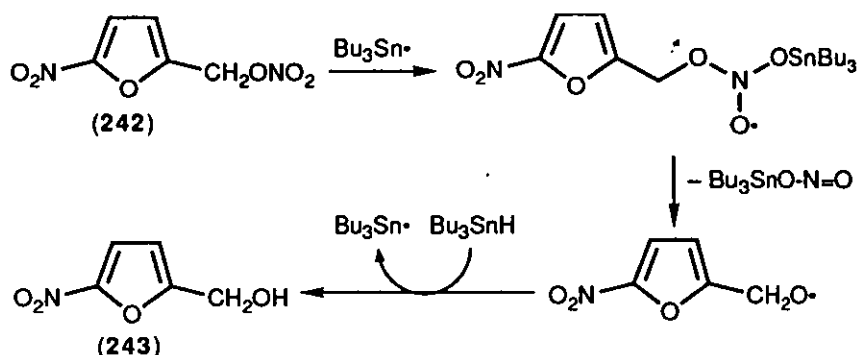
Scheme 140

The tributylstannane-mediated reduction of (5-nitro-2-furyl)methyl nitrate (**242**) yielded two products in approximately equal yield: 2-hydroxymethyl-5-nitrofuran (**243**) and 2-methyl-5-nitrofuran (**244**) (Scheme 141). The two products (**243**) and (**244**) probably arise by the operation of the Nitroxide and Radical-Anion mechanisms respectively (Scheme 142). EPR spectroscopic¹¹⁶ and $S_{\text{RN}}1$ ¹¹⁵ studies have shown that dissociation of the radical-anion proceeds rapidly and yields the 5-nitrofurfuryl radical. Hence if only the Radical-Anion mechanism is operative, the furan (**244**) would be expected as the only product. If only the nitroxide is operative (See section 1.5.2(b), Schemes 66⁵³ and 67⁵³) the furan (**243**) would be expected as the only product. Therefore the observation that both products are formed suggests that mechanisms are operating. The operation of the Radical-Anion mechanism could, if widespread, be a serious side-reaction in the use of nitrate esters (**24**, $\text{W} = \text{NO}_2$) as precursors to alkoxyl radicals (**25**).

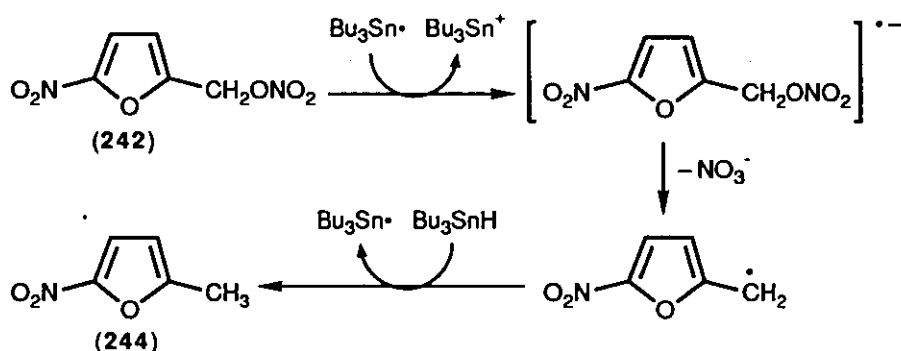


Scheme 141

Nitroxide Mechanism



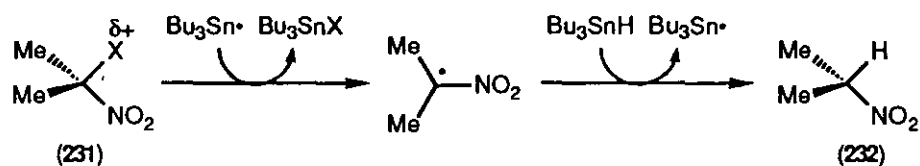
Radical-Anion Mechanism



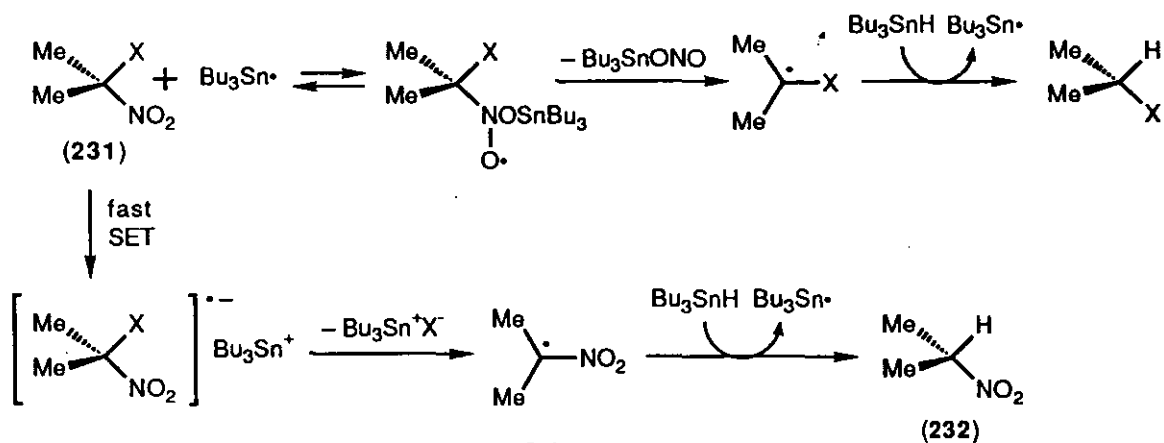
Scheme 142

The results, in particular the loss of the α -substituent from the α -substituted nitro compounds (231), favour the operation of the Radical-Anion mechanism over the Nitroxide mechanism for the reduction of such compounds. However the results can also be rationalised by an S_H2 mechanism (Scheme 143), where nucleophilic tributylstannyl radical⁹³ abstracts the α -substituent, which is rendered electropositive by the inductively electron-withdrawing effect of the nitro group. The results can also be explained by competition between the Radical-Anion mechanism and the Nitroxide mechanism (Scheme 144), provided the following conditions are met: (i) addition of the tributylstannyl radical to the nitro group is reversible; (ii) scission of the resultant nitroxide radical is slow; (iii) SET from the tributylstannyl radical to the α -substituted nitro compound is faster than formation

of the nitroxide. Presumably these conclusions can be extrapolated to the reduction of unsubstituted nitro compounds.



Scheme 143



Scheme 144

6. References

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