THE REGIO- AND STEREO- CHEMISTRY OF
SOME ARYL RADICAL CYCLIZATIONS

by

SENDABA GERBA

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DECLARATION

The work described in this thesis is my own except where otherwise stated. It was carried out in the Research School of Chemistry, the Australian National University from 1985 to 1989 during the tenure of an Australian National Postgraduate Research Award.

Sendaba Gerba
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To Fekerete. Bethel. Tigest.

and in memory of

Shashitu and Woude
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ABSTRACT

Aryl radical cyclization have shown an increase in popularity with synthetic chemists over the last few years. This is mainly due to an increased knowledge of the rates and regiochemical outcome of these reactions, and in part, because the method offers an easy point of entry into the construction of bi- and polycyclic systems, many of which are related to important naturally occurring compounds.

In the introduction it will become apparent that previous work has been concerned with the ring closure of suitably constituted phenyl radicals and there have been no similar studies with polyaromatic systems.

This thesis presents the synthesis of a variety of fused carbocyclic compounds by naphthyl and phenyl radical cyclizations. The results are presented in four chapters.

Chapter 1 details the kinetic and mechanistic investigation of suitably constituted naphthyl radical cyclizations. Treatment of naphthyl radical precursors with tri-n-butyltin hydride give exclusively or predominatly exo cyclization products. In a few cases the initially formed exo cyclization radical intermediates were found to undergo neophyl rearrangement giving rise to significant amounts of endo cyclization products. The results obtained from these studies were compared with the observed rates and regiochemistry reported in similar phenyl radical cyclizations.

Chapter 2 deals with radical ring closure onto carbonyl or cyano groups. Treatment of suitably constituted aryl radical precursors affords rearranged products by a mechanism involving 1,4-acetyl or 1,4-cyano migration. Radicals derived from cyclic keto esters give macrocyclic products formed by 1,4-acyl migration, but also affords products formed by intramolecular 1,5-hydrogen atom transfer together with ring-contracted compounds arising by a novel 1,2-acyl migration.

Chapter 3 describes a short and efficient syntheses of tetrahydrofluorene, hydroindene and indolizidine derivatives by processes involving ring closure of aryl
Chapter 4 is devoted to the stereochemistry of the cyclization of C(3) and C(4) substituted alkenylaryl radicals. Treatment of C(3) and C(4) substituted (but-3-enyl)phenyl radicals are found to undergo exo ring closure exclusively or predominantly giving rise to a mixture of cis- and trans-dihydroindene derivatives. The results obtained from these studies compared with the observed stereochemical outcome reported in substituted hexenyl radical systems. Also presented is a molecular mechanics calculation study on the cis- and trans-exo transition structures.

A portion of the work described in this thesis has been published.


INTRODUCTION

The utility of intramolecular free radical addition reactions for the formation of carbon-carbon bonds has captured much attention in recent years. The common belief that prevailed for many years among many organic chemists was that free radical reactions are complicated with respect to reactivity and stereo-chemistry, unpredictable, unpredictable, and essentially mysterious. These reactions were thus frequently avoided for the more conventional polar principles in which nucleophiles and electrophiles interact to affect new bonds. The success in the application of free radical addition methods in various elegant synthetic systems, and more recently, in the synthesis of complex molecules, has led to the continuous efforts to exploit new synthetic strategies and methodologies. The pioneering fundamental studies provided both a large body of kinetic data, related mechanistic information, and detailed understanding of factors affecting the reactivity of organic free radicals. Largely through their work, it has been shown that (a) initial radical structure, (b) steric effects resulting from alpha substitution patterns, and (c) geometric constraints on the chain linking the arts and radicles are factors in governing cyclometalation stereochemistry.

INTRAMOLECULAR ADDITIONS OF ARYLP RADICALS

The systematic study of aryl radical cyclization was first reported by Brown and Glusker, who showed that arylyl, arylnitroxyl, and styrenyl radicals with alpha substituents containing double-bonds in the 3,4 or the 6,7 positions relative to their radical centers. The radical cyclization to benzoquinone clamped exclusively or predominantly in the 6,7 mode. When the medium was 1,4-dioxane or tetrahydrofuran, these reactions proceeded in the 6,7 mode. When the medium was 1,2-dichlorobenzene, the products observed were those derived from the primary radical. In the presence of aryl nitroxides, the spectrum observed was that of the primary radical, and in the presence of aryl nitroxides, the spectrum observed was that of the primary radical.
The utility of intramolecular free radical addition reactions for the formation of carbon-carbon bonds has received much attention in recent years. The common belief that prevailed for many years among many synthetic organic chemists was that free radical reactions are nonselective with regard to regio- and stereo-chemistry, unpredictable, unpromising and essentially mysterious. These reactions were thus frequently avoided for the more conventional polar processes in which nucleophiles and electrophiles interact to afford new bonds. The success in the application of free radical addition reactions in recent elegant syntheses owes much to the enormous effort directed towards their kinetics and mechanistic studies by Julia, Walling, Beckwith, and Ingold. Their pioneering fundamental studies provided both a large body of kinetic data, related mechanistic information and detailed understanding of factors affecting the reactivity of organic free radicals. Largely through their work it has been shown that (a) initial radical structure, (b) steric effects resulting from olefin substitution patterns, and (c) geometric constraints on the chain linking the olefin and radical are factors in governing cyclization regio-chemistry.

**INTRAMOLECULAR ADDITIONS OF ARYL RADICALS**

The systematic study of aryl radical cyclization was first reported by Beckwith and Gara, who showed that alkenylaryl, (alkenylamino)aryl or (alkenyl)aryl radicals with ortho substituents containing double bonds in the 5,6 or the 6,7 positions relative to their radical centres, like their alkenyl counterparts, undergo ring closure exclusively or predominantly in the exo mode. When the diazonium salt was reduced with titanium (III) or CO$_2^{-}$ at pH8 in the flow cell of an ESR spectrometer, the spectrum observed was that of the primary radical arising
from the exo cyclization of the aryl radical 2 (Scheme 1). Similar reduction of the homologous diazonium salt 4 gave the exo cyclization product 6 (Scheme 2). In neither case could a trace of the endo product be detected.

Scheme 1

\[
\begin{align*}
\text{Scheme 2}
\end{align*}
\]

The reduction of 1 with titanium (III) methoxide or isopropoxide ion, afforded 2,3-dihydro-3-methylbenzofuran, in poor yield. However, Beckwith and
Gara found that reduction of the aryl iodide 7 (Scheme 1) with tri-n-butyltin hydride afforded the exo cyclized product in quantitative yield. Similar reduction of 8 (Scheme 2) gave good yields of the bicyclic product. Beckwith and Gara also demonstrated the facility of exo cyclization of o-butenylphenyl radical 9 (Scheme 3). The cyclization of the radicals 10 (Scheme 4) and 11 (Scheme 5) also afforded the exo products.
Similarly radicals 12 (Scheme 6) and 13 (Scheme 7) gave exo cyclized products. It is particularly noteworthy that the radical 12 cyclizes exclusively in the exo mode, even though the endo cyclization would produce a radical which might be stabilized by the adjacent oxygen lone pairs. The comparatively slow rate of cyclization of radical 12 has been attributed to polar effects, or the loss of resonance energy by the disappearance of the vinyl ether bond.

![Scheme 6](image)

**Scheme 6**

The radical 13 like the (ethenyloxy)ethyl radical 14 afforded no cyclic product, whereas the radical 16 (Scheme 8) appeared to cyclize exclusively in the exo mode in contrast to the analogous 2-methylallyloxyethyl radical 17 which affords both exo and endo cyclization products (Scheme 8).

![Scheme 7](image)

**Scheme 7**
The greater regioselectivity of aryl radicals compared to alkyl radicals has been ascribed to stereoelectronic factors, including steric constraints associated with the rigid aromatic ring. Beckwith and Gara and more recently Beckwith and Abeywickrema studied the rates of some aryl radical cyclizations and found that aryl radicals have cyclization rate constants 2 to 3 orders of magnitude greater than those of analogous alkenyl radicals, and that the vinylic methyl group in radical decreases the rate of aryl ring closure by only a factor of 2 to 3, whereas in the corresponding alkyl radicals the rate decreases by a factor of 40. This is further evidence that the steric constraints in aryl radicals are relatively small.

The facile ring closure of aryl radicals suggested that such processes would be synthetically useful in the preparation of complex organic molecules. Semmelhack and co-workers reported the syntheses of cephalotaxine (Scheme 9) and a variety of cyclic ketones by aryl radical ring closure. This reaction is an example of a photolytic intramolecular $S_{RN}1$ reaction. The key step is the cyclization of aryl radical onto the enolate ion.
Although Semmelhack's reaction has been successfully applied to the haloketones 19 giving rise to six-, eight-, and ten-membered rings (Scheme 10). Yields were found to be poor for compounds 20 due to hydrogen atom transfer from the adjacent 2-carbon to the phenyl radical. The haloketones 20 yielded, inter alia, the two tricyclic compounds 21 and 22, indicating the existence of both internal and external enolates.

Scheme 9

Scheme 10
Beckwith and Meijis\textsuperscript{16} reported alternative methods for the generation of aryl radicals, and commented on mechanistic aspects. Treatment of o-alkenyloxy arenediazonium salts with a variety of reagents gave dihydrobenzofuran derivatives in moderate to good yields. The results show that tri-n-butyltin hydride in diethyl ether or tetrahydrofuran, or sodium iodide in acetone appear to be relatively efficient reagents for effecting radical cyclization of the diazonium salts \textsuperscript{1} or \textsuperscript{23} (Scheme 11).

![Scheme 11](image)

The diazonium salts \textsuperscript{1} and \textsuperscript{23} are also useful precursors for the synthesis of functionalized dihydrobenzofurans suitable for further elaboration. Beckwith and Meijis\textsuperscript{17} investigated the scope of the methods involving the use of thiolate ions, copper (II) halides (chloride or bromide), copper (I) cyanide/pyridine, or sodium iodide to effect cyclization in the \textit{exo} mode of aryl radicals derived from the diazonium salts \textsuperscript{1} and \textsuperscript{23}. The reactions afforded the dihydrobenzofuran derivatives which are functionalized at the site of cyclized radical in good yields (Scheme 11).
The radical chain mechanism proposed for bromo- or chlorodediazonation is outlined in Scheme 12, where \( \text{ArN}_2^+ \) represents the diazonium ion of 1 or 23 and \( R' \) represents a cyclized radical 24a or 24b. Beckwith and Meijs point out that the reaction is initiated by traces of Copper (I) in the Copper (II) bromide(chloride).

\[
\begin{align*}
\text{ArN}_2^+ + \text{Cu(I)} & \rightarrow \text{ArN}_2^- + \text{Cu(II)} \\
\text{ArN}_2^- & \rightarrow \text{Ar}' + \text{N}_2 \\
\text{Ar}' & \rightarrow R' \\
R' + \text{Cu(II)}X & \rightarrow RX + \text{Cu(I)}
\end{align*}
\]

Scheme 12

Beckwith and Abeywickrema\textsuperscript{18} demonstrated that treatment of the diazonium salt 4 with sodium benzenethiolate in dimethylsulfoxide gives mixtures of uncyclized 28 and cyclized 29 products (Scheme 13). The formation of 29 via the ring closure 26 \( \rightarrow \) 27 confirms the involvement of aryl radical intermediates.

Scheme 13
Beckwith and Abeywickrema proposed a radical chain mechanism (Scheme 14) for the thiodediazoniation reaction. Chain initiation possibly occurs by thermal or photochemical homolysis of diazosulfide. The rate constant for the reaction between aryl radicals and PhS⁻ was found to be $2 \cdot 4 \times 10^8 \text{ M}^{-1} \text{s}^{-1}$ (17 - 80 °C).

\[
\begin{align*}
\text{ArN}^+_{2} + \text{PhS}^- & \rightarrow \text{ArN} = \text{NSPh} \\
\text{ArN} = \text{NSPh} & \rightarrow \text{Ar}^- + \text{N}_2 + \text{PhS}^- \\
\text{Ar}^- + \text{PhS}^- & \rightarrow \text{ArSPh}^- \\
\text{ArN} = \text{NSPh} + \text{ArSPh}^- & \rightarrow \text{Ar}^- + \text{N}_2 + \text{PhS}^- + \text{ArSPh}
\end{align*}
\]

Scheme 14

Beckwith and Meijs investigated the scope and generality of iododediazoniation of a number of arene diazonium salts accompanied by aryl radical ring closure. Treatment of the alkynyl-substituted diazonium salt 30 with sodium iodide in acetone afforded two isomeric iodo olefins 31 and 32 in the ratio of 3:2 (Scheme 15). Similar treatment of the diazonium salt 33 gave the spirocyclic iodide 34 (Scheme 16).

Scheme 15

Scheme 16
Beckwith and Meijs have employed iododediazoniation of some arenediazonium salts in the syntheses of indoline derivatives. Treatment of the diazonium salt 35 with sodium iodide afforded the cyclized indoline 36 in good yield (Scheme 17). Similar treatment of the diazonium salt 37 gave the indoline derivative 38 in moderate yield (Scheme 18).

\[
\begin{align*}
35 & \quad \rightarrow \quad 36 \\
37 & \quad \rightarrow \quad 38
\end{align*}
\]

Scheme 17

Scheme 18

The results clearly show that the reaction between sodium iodide and suitably constituted arenediazonium salts affords cyclized products in good yield provided that the cyclization of the aryl radical is sufficiently fast compared with its direct iodination. Since the product contain a good nucleofuge in the iodo group, they are thus suitably functionalized for further elaboration.

Beckwith and Abeywickrema\textsuperscript{20} studied the kinetics and mechanism of iododediazoniation reaction and proposed a radical-chain mechanism to account for their observations (Scheme 19).
\[
\begin{align*}
\text{ArN}_2^+ + I^- & \rightarrow \text{Ar}^- + \text{N}_2 + I' \\
\text{ArN}_2^+ + I' I^- & \rightarrow \text{Ar}^- + \text{N}_2 + I_2 \\
\text{Ar}^- + I_2 & \rightarrow \text{Arl} + I' \\
\text{Ar}^- + I_3^- & \rightarrow \text{Arl} + I_2' - \\
I^- + I_2 & \rightarrow I_2' - \\
I^- + I' & \rightarrow I_2 \\
I_2 + I' & \rightarrow I_3^- \\
\end{align*}
\]

Scheme 19

They found that the rate constant for reaction between aryl radicals and \(I_2/I^-\) is \(5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}\) at 20 °C. The salient features of the above mechanism are (i) initiation occurs by single electron transfer from iodide ion to the diazonium ion; (ii) the aryl iodine bond is formed by iodine transfer to aryl radical from \(I_2\) and/or \(I_3^-\); and (iii) a chain transfer reagent, \(I_2' -\) is formed by coupling of \(I'\) with \(I^-\) and/or iodine atom transfer from \(I_3^-\).

Beckwith and Meijs treated the \(\alpha\)-alkenyloxy or \(\alpha\)-alkenylamino arenediazonium fluoroborates 39 with the nitrooxide 40 or 41 and obtained the bicyclic O,N,N-trisubstituted hydroxylamines 43 in good isolated yields (Scheme 20).

\[
\begin{align*}
\text{39} & \rightarrow \text{42} & \text{40 or 41} & \rightarrow \text{43}
\end{align*}
\]

Scheme 20
The interaction between the diazonium salt and the nitroxide is presumably a radical process involving initial electron transfer to form the aryl radical 42. Subsequent radical cyclization followed by coupling with the nitroxide 40 or 41 affords the hydroxylamine 43. Reduction of the hydroxylamines with zinc in acetic acid gave the corresponding alcohols.

Similar treatment of the o-alkynyloxy 44 or o-alkynylamino 45 arene diazonium salts with nitroxide 40 or 41 afforded aldehydes 46 in only moderate yields. The formation of the aldehydes has been attributed to acid catalysed elimination of amine from the intermediate o-vinylhydroxylamine 48. Beckwith and Meijs have also carried out ESR studies on a number of these diazonium salt in the presence of suitable spin traps. The detection of the adduct radicals confirmed the coupling process.
Uneo\textsuperscript{22} prepared a number of vinyl bicyclic systems from suitable aryl bromide precursors (Scheme 21). The aryl radical 48 generated from the bromide with tri-n-butyltin hydride, cyclized in the \textit{exo} mode to yield radical 49. This species then eliminates the thiophenoxyl radical, producing 50.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{scheme21}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 21}

Interest in synthetic applications of aryl radical mediated carbon-carbon bond formation has intensified enormously since the beginning of this work. Snieckus and co-workers\textsuperscript{23,24} have applied aryl radical cyclization towards the construction of substituted benzofurans, benzopyrans, furopyridines and furobenzofurans. An example is the cyclization of the aryl radical 51 in the synthesis of 52 (Scheme 22).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{scheme22}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 22}

Ditami and Ramanathan\textsuperscript{25} reported the synthesis of a variety of dihydroindole systems, while Jones\textsuperscript{26,27} and Bowman \textit{et al.}\textsuperscript{28} have employed aryl radical cyclization for the synthesis of oxindoles. Parker and co-workers\textsuperscript{29} have
incorporated an elegant tandem radical cyclization initiated by an aryl radical into the synthesis of the bridged hydrophenanthrenes 54 and 55 (Scheme 23).

Scheme 23

Boger and Coleman\textsuperscript{30} have employed aryl radical cyclization in the syntheses of the 3-methylideneindole 57 and the 3-vinylindoline 59 (Scheme 24).
Togo and Kikuchi\textsuperscript{31} have demonstrated that radicals arising from intramolecular aryl radical cyclization reactions can be trapped by intermolecular additions to electron deficient alkenes. This trapping technique increases the functionalization of the cyclized product, thereby making possible further chemical manipulation.

Pattenden et al.\textsuperscript{32-34} have employed intramolecular oxidative aryl radical cyclizations using cobalt complexes, in the syntheses of a range of ring-fused benzoheterocycles. Thus, treatment of aryl iodide 7 with cobalt (I)(salen) anion led to the formation of complex 60 (Scheme 25). In this case, an aryl radical is probably generated by single-electron transfer from cobalt (I) followed by loss of iodide. Irradiation of 60 in the absence of an added reagent induces elimination of cobalt hydride producing 64. However, when 60 is irradiated in the presence of added reagents, the cobalt moiety can be replaced by a number of functional groups including hydroxyl, halogen, oxime, and phenylthio or phenylseleno.

![Scheme 25](image-url)
Beckwith and Boat⁴⁵-⁴⁷ have reported the syntheses of fused heterocyclic systems containing either the azetidinone or pyrrolidinones nucleus by an intramolecular $S_H^2$ process. Beckwith³⁸,³⁹ also reported on the 1.2- or 1.4-acyl or cyano group migration during the addition of aryl radicals to ketones or nitriles.

It is apparent from this brief survey that much effort has been devoted to synthetic and mechanistic studies of aryl radical cyclizations, particularly those of phenyl radicals. In order to realize the full synthetic potential of radical cyclization, kinetic and mechanistic investigation of suitably constituted heteroaromatic and polynucleararomatic systems is desirable. Accordingly, the present study was undertaken with the aim of obtaining a good understanding of the rates, regio- and stereo-selectivity of naphthyl radical ring closures, and of exploiting the synthetic potential of such processes.

Chapters 1 and 2 of this work describe intramolecular homolytic additions of naphthyl radical to C=C, C=O, and C=N bonds. Suitably constituted phenyl radicals¹² have been recently found to undergo ring closure at very fast rates. Do analogous naphthyl radicals behave similarly? The addition of alkyl⁷ᵃ,⁴⁰ radicals to cyano and ketone groups is well known. Could these reactions be applied to naphthyl radicals? What is the scope of naphthyl radical cyclizations, and are the cyclizations regioselective?

Chapter 3 of this work is directed toward the study of the additions of naphthyl or phenyl radicals to silyl enol ethers and the N-terminus of an enamine or enamide double bond. The electronic effect of the substituents on the electronic properties of the double bonds, and the stereo-chemistry of the newly formed ring junction will be discussed in detail.
Chapter 4 describes the stereochemistry of C(3)- and C(4)-substituted α-
alkenylaryl radical cyclization. Both experimental observations and force-field
calculations will be discussed.
CHAPTER 1

There have been many recent examples \(^\text{11,16,17}\) of the syntheses of 
and polycyclic systems involving ring formation by intramolecular addition of 
carbon-carbon double bonds to suitably constituted alkynylaryl, alkynylarylidenaryl, 
or alkynylarynyl radicals. The success of such syntheses has been almost entirely 
based on the extensive studies by Frankel and co-workers \(^\text{15,17,18,21}\) directed towards the 
determination of the rates and regiochemistry of such reactions and the factors which 
affect them. Virtually all of the previous work has been concerned with 
intramolecular addition to suitably substituted phenyl radicals. There have been no 
studies concerning bicyclic and polycyclic aromatic systems. Investigation was 
therefore begun on the rates and regio-chemistry of similar reactions of naphthyl, 
radicals.

The radical precursors e.g. \(^\text{22,23}\) were prepared from readily 
available starting materials. Alcylation \(^\text{31}\) of 3-bromo-2-naphthol with either 3-
boranopropene or 3-bromocyclohexene \(^\text{5}\) in acetic acid provides dibromobenzene at a 
time afforded the bromo compound \(^\text{24}\) (43.5%) and \(^\text{25}\) (12.6%), respectively. Similar 
treatment of 2-bromo-1-naphthol \(^\text{32}\) with either 3-bromopropene or 3-
bromocyclohexene \(^\text{5}\) gave the bromo compounds \(^\text{26}\) (75.8%) and \(^\text{27}\) (40.0%) 
respectively. Similarly the keto ether \(^\text{24}\) was prepared in 51.9% yield upon treating 
1-keto-2-naphthol \(^\text{34}\) with 3-bromopropene and potassium carbonate in acetic acid.

Alkylation of 1-naphthol accomplished by the method of Beckwith and Starr \(^\text{10}\) 
with 4-bromon-1-benzene in water and sodium hydroxide at a base gave the bromo 
ether \(^\text{28}\) (62.6%). Similar treatment of 2-bromo-1-naphthol \(^\text{32}\) with 4-bromon-1-benzene 
did not afford the bromo ether \(^\text{29}\) in (1.5%) yield. A better yield (23%) of \(^\text{29}\) was 
obtained when potassium hydroxide was used as the base in ether.
1.1 KINETICS AND MECHANISM OF NAPHTHYL RADICAL CYCLIZATION

There have been many recent examples\(^{17,19,23-37}\) of the syntheses of bi- and poly-cyclic systems involving ring formation by intramolecular additions to carbon-carbon double bonds in suitably constituted alkenylaryl, (alkenylamino)aryl, or (alkenyloxy)aryl radicals. The success of such syntheses has been soundly based on the extensive studies by Beckwith and co-workers\(^{10,12,16,21}\) directed towards the determination of the rates and regio-chemistry of such reactions and the factors which affect them. Virtually all of the work in this area has been concerned with intramolecular addition in suitably substituted phenyl radicals. There have been no studies concerning bicyclic and polycyclic aromatic systems. Investigation was therefore begun on the rates and regio-chemistry of similar reactions of naphthyl radicals.

The radical precursors \(66, 69, 70-75\) were prepared from readily available starting materials. Alkylation\(^{41}\) of 1-bromo-2-naphthol with either 3-bromopropene or 3-bromocyclohexene\(^{42}\) in acetone and potassium carbonate as a base afforded the bromo compounds \(66 (85\%)\) and \(74 (82\%)\) respectively. Similar treatment of 2-bromo-1-naphthol\(^{43}\) with either 3-bromopropene or 3-bromocyclohexene\(^{42}\) gave the bromo compounds \(70 (79\%)\) and \(75 (60\%)\) respectively. Similarly the iodo ether \(71\) was prepared in \(81\%\) yield upon treating 1-iodo-2-naphthol\(^{44}\) with 3-bromopropyne and potassium carbonate in acetone.

Alkylation of 1-bromo-2-naphthol by the method of Beckwith and Gara\(^{10}\) with 4-bromobut-1-ene in water and sodium hydroxide as a base gave the bromo ether \(72 (42\%)\). Similar treatment of 2-bromo-1-naphthol\(^{43}\) with 4-bromobut-1-ene afforded the bromo ether \(73 (17\%)\) yield. A better yield \(55\%\) of \(73\) was obtained when potassium hydroxide was used as the base in ethanol.
The bromocompound 69 was prepared as depicted in Scheme 26. Treatment of 1-bromo-2-methylnaphthalene 67 with N-bromosuccinimide gave the required 1-bromo-2-(bromomethyl)naphthalene 68 (59%) which reacted with prop-2-en-1-ylmagnesium bromide to yield the bromo compound 69 (64%).

The radical precursors 66, 69, 70-75 displayed the expected $^1$H nmr, $^{13}$C nmr and infrared spectra. With these radical precursors in hand it was possible
to attempt ring closure by their treatment with tri-\textit{n}-butyltin hydride. For the sake of clarity, the behaviour of each radical precursor will be discussed individually.

Treatment of 1-bromo-2-\{prop-2-enyloxy\}naphthalene \textit{66} [0.05M] with a slight molar excess of tri-\textit{n}-butyltin hydride [0.06M] and azo-bisisobutyronitrile (AIBN) as initiator in boiling benzene afforded a mixture of two products detectable by gas chromatography (GC) in the ratio of \textit{10:1}. After separation by preparative GC they were identified by\textit{1}H and \textit{13}C nmr spectroscopy and by comparison with authentic samples as the \textit{exo 79} (65\%) and the \textit{endo 80} (6\%) cyclization products (Scheme 27).

![Scheme 27](image-url)
An authentic sample of endo cyclization product 80 was prepared by the method of Ringfusz et al. (Scheme 28). 2-Naphthol was alkylated with 3-bromopropan-1-ol to give the alcohol 82. Treatment of 82 with phosphorous pentoxide in toluene afforded the desired endo cyclization product 80.

[Image: Scheme 28]

The fact that the reaction of 66 with tri-n-butyltin hydride yielded no uncyclized product 81 indicates that intermolecular hydrogen atom transfer from stannane to 76 under these conditions ([Bu₃SnH = 0.06M]) cannot compete with the rapid cyclization of 76. There was, however, the possibility that it might be observed at high concentration of Bu₃SnH. The experiment was, therefore, repeated at relatively high concentration of tri-n-butyltin hydride [1M] under pseudo-first order conditions. Once again, only the exo cyclization product 79 was obtained.

Application of the usual steady state approximation to the reactions of Scheme 27 gives the integrated rate equation (Appendix A):

\[
k_c / k_H = ([C] / [U]) [Bu₃SnH]_m
\]
where \([C]\) is the final total concentration of cyclized products, \([U]\) is the final concentration of uncyclized product, \([\text{Bu}_3\text{SnH}]_m\) is the mean stannane concentration, \(k_c\) is the rate constant for cyclization, and \(k_H\) is the rate constant for hydrogen atom transfer from stannane to the naphthyl radical. If we assume that gas chromatography is capable of detecting 2% of the uncyclized product \(81\) if it were present, we can reliably take this value as an upper limit to the amount of uncyclized material present. On the assumption that the value of \(k_H\) for naphthyl radical is the same as that for phenyl radical\(^{46}\) (log \(k_H = 9.6 - 1.7/\theta\)), the lower limit for the cyclization rate constant for \(76\) must be, \(k_c > 1.7 \times 10^{10} \text{ s}^{-1}\) at 80 °C.

In the light of previous observations by Beckwith and Abeywickrema\(^{12}\) that cyclization of the analogous substituted phenyl radical \(2\) under similar experimental conditions gives only the exo product \(3\), the formation of \(80\) from \(66\) was unexpected. A possible explanation for the difference in behavior of the two radicals, \(76\) and \(2\), was that steric interaction between the hydrogen at C-8 in \(76\) and the terminal vinyl methylene in the side chain might destabilize the transition structure for 1,5-cyclization. However, when this hypothesis was tested by molecular mechanics calculations,\(^{47}\) it was found that these interactions are unimportant because of the relatively large nonbonded distances involved.

![Chemical Structures](image)

Further information about the route to the endo product was obtained by carrying out a series of experiments in which the concentration of stannane was varied tenfold from 0.01M to 0.1M. The usual steady state approach to kinetics of the steps in Scheme 27 shows that if the exo and endo products are generated solely...
by unimolecular 1.5 and 1.6 cyclizations respectively, then the ratio of these products, 79/80, at any fixed temperature should be independent of stannane concentration. The results are summarized in Table 1.

The data presented in Table 1 clearly show that the ratio of the products 79/80 at a fixed temperature is not independent of stannane concentration. We concluded that the endo product 80 does not arise solely via direct endo ring closure of 76. One possibility is that it arises mainly from rearrangement of the initially formed exo cyclized radical 77 (Scheme 27).

Table 1. Kinetic Data for Neophyl Rearrangement of 77a

<table>
<thead>
<tr>
<th>temp. °C</th>
<th>S₀ b, M</th>
<th>79/80 c</th>
<th>kᵣ/k_H, 10⁴ M</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>0.01</td>
<td>7.9</td>
<td>3.2</td>
</tr>
<tr>
<td>25</td>
<td>0.02</td>
<td>17.8</td>
<td>2.4</td>
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<tr>
<td>25</td>
<td>0.06</td>
<td>28.4</td>
<td>4.1</td>
</tr>
<tr>
<td>25</td>
<td>0.10</td>
<td>29.9</td>
<td>6.4</td>
</tr>
<tr>
<td>50</td>
<td>0.01</td>
<td>3.3</td>
<td>9.6</td>
</tr>
<tr>
<td>50</td>
<td>0.02</td>
<td>8.5</td>
<td>5.9</td>
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<tr>
<td>50</td>
<td>0.06</td>
<td>16.8</td>
<td>7.7</td>
</tr>
<tr>
<td>50</td>
<td>0.10</td>
<td>29.2</td>
<td>6.6</td>
</tr>
<tr>
<td>80</td>
<td>0.01</td>
<td>1.4</td>
<td>27.4</td>
</tr>
<tr>
<td>80</td>
<td>0.02</td>
<td>4.0</td>
<td>15.4</td>
</tr>
<tr>
<td>80</td>
<td>0.06</td>
<td>7.5</td>
<td>20.9</td>
</tr>
<tr>
<td>80</td>
<td>0.10</td>
<td>12.2</td>
<td>18.9</td>
</tr>
<tr>
<td>110</td>
<td>0.01</td>
<td>0.8</td>
<td>53.8</td>
</tr>
<tr>
<td>110</td>
<td>0.02</td>
<td>1.9</td>
<td>36.1</td>
</tr>
<tr>
<td>110</td>
<td>0.06</td>
<td>3.6</td>
<td>52.0</td>
</tr>
<tr>
<td>110</td>
<td>0.10</td>
<td>5.5</td>
<td>50.9</td>
</tr>
<tr>
<td>140</td>
<td>0.01</td>
<td>0.5</td>
<td>95.9</td>
</tr>
<tr>
<td>140</td>
<td>0.02</td>
<td>0.9</td>
<td>92.1</td>
</tr>
<tr>
<td>140</td>
<td>0.06</td>
<td>1.7</td>
<td>127.0</td>
</tr>
<tr>
<td>140</td>
<td>0.10</td>
<td>3.4</td>
<td>91.0</td>
</tr>
</tbody>
</table>

a All reactions in benzene solvent. b Initial concentration of Bu₃SnH; the final concentration of Bu₃SnH was zero in each case. c As determined by GC.
Application of steady state kinetics to the steps in Scheme 27 shows that if the endo product 80 comes exclusively from exo cyclized 77 via its ring expansion to 78 then the amount of endo product formed should conform to the integrated rate equation 2\textsuperscript{48} (Appendix A):

$$[C]_f = r \ln \left[ \frac{(S_0 + r)}{(S_f + r)} \right]$$  \hspace{1cm} (2)

where $[C]_f$ is the normalized final concentration of the rearranged products (in this case the endo product). $S_0$ and $S_f$ are the initial and final concentrations, respectively, of Bu\textsubscript{3}SnH, and $r$ is the ratio $(k_r/k_H)$ of $k_r$, the rate constant for rearrangement (in this case ring expansion), to $k_H$, the rate constant for transfer of a hydrogen atom from Bu\textsubscript{3}SnH (in this case to the primary radical 77). Fitting of the data to the rate equation (2) affords the apparent values of $k_r/k_H$ (Table 1). If all of the endo product 80 arises via the pathway 77 $\rightarrow$ 78 $\rightarrow$ 80, then $k_r/k_H$ should have a constant value at any fixed temperature. In fact the values of $k_r/k_H$ show considerable variation. One possible explanation is that 80 is partly formed via direct endo cyclization of 76 and partly via rearrangement of 77. If this were so, the apparent values of $k_r/k_H$ should show a consistent trend, varying from large to small with decreasing stannane concentration. In fact the variations of $k_r/k_H$ are erratic.
We conclude, therefore, that they arise from experimental errors, which are expected to be large under these circumstances when $S_0$ and 79/80 are respectively rather small and rather large.

In order to test further our conclusion that the endo product 80 arises mainly via rearrangement of the exo radical 77, we decided to examine the behaviour of 77 when it was directly generated by a different route. The required precursor 87 was prepared by the route shown in Scheme 29.
Scheme 29

Alkylation of 1-bromo-2-naphthol with ethyl 4-bromobut-2-enoate 83 (prepared from ethyl but-2-enoate by treatment with N-bromosuccinimide) afforded the bromo ester 84. Treatment of 84 with tri-n-butyltin hydride gave the cyclized product 85 in excellent yield (97%). Presumably the presence of the carboxylate substituent enhances the rate of cyclization. Hydrolysis of 85 with potassium hydroxide gave the corresponding acid 86 which was converted into the hydroxamic ester 87 by the method of Barton.

When 87 was treated (without purification) with 1 molar equivalent of tri-n-butyltin hydride [0.05M] in benzene, the only two products identified by GC of the crude mixture were 79 and 80 in the ratio of 11:1. Presumably their formation involves generation of the radical 77 from 87 by the mechanism described by...
Barton (Scheme 30) followed by its conversion into the final products according to the pathways given in Scheme 27 earlier.

In support of this view, the value of $k_r/k_H (1.1 \times 10^{-3} \text{M})$ at 80 °C calculated by fitting the data obtained from this result into equation 2 is in satisfactory agreement with values obtained when 66 was used as the radical precursor (Table 1).

Linear regression analysis of the data in Table 1 gives the Arrhenius expression for the temperature dependence of $k_r/k_H$ for neophysyl rearrangement of the radical 77: $$\log k_r/k_H(M) = (1.93 \pm 0.35) - (7.46 \pm 0.60)/\theta,$$ where $k_r$ is the rate constant for rearrangement, $k_H$ is the rate constant for hydrogen atom transfer from stannane, and $\theta = 2.3RT$. If we assume that $k_H$ in this reaction has Arrhenius
parameters similar to those for primary alkyl radicals \[ \log k_H = (9.1 \pm 0.2) - (3.7 \pm 0.3) / \theta \].\textsuperscript{46b} it follows that for \( 77 \rightarrow 78 \): \( \log k_r = (11.0 \pm 0.4) - (11.1 \pm 0.6) / \theta \), and \( k_r = 1.3 \times 10^4 \text{s}^{-1} \) (80 °C).

When the bromo compound 69 [0.05 M] was treated with a slight molar excess of tri-n-butyltin hydride [0.06 M] in benzene (AIBN as initiator) at 80 °C, three products were detected by GC in the ratio of 1:36.6:16.8. The minor component was identified as the direct reduction product 95 (2%) by gas chromatographic comparison with an authentic sample. The other two were identified as the exo cyclization product 91 (67%) and endo cyclization product 92 (31%) by \( ^1 \text{H} \) and \( ^{13} \text{C} \) nmr spectroscopy after separation by preparative GC (Scheme 31).

Scheme 31
An authentic sample of the reduction product $\text{95}$ was prepared by treatment of 2-(bromomethyl)naphthalene$^{52}$ with prop-2-en-1-ylmagnesium bromide as outlined in Scheme 32.

![Scheme 32](image)

Application of the usual steady state approximation to the reaction of Scheme 31 leads to the integrated rate equation 1 (Appendix A) when tri-$n$-butyltin hydride is in large excess. Table 2 gives data for reactions conducted with at least a ten-fold excess of stannane at a relatively high concentration. Application of the rate equation 1 gives values of $\frac{k_c}{k_H}$ where $k_c$ is the rate constant for ring closure of $\text{88}$ and $k_H$ is the rate constant for hydrogen atom transfer from stannane to $\text{88}$.

Linear regression analysis of the data in Table 2 gives the Arrhenius expression for the temperature dependence of $\frac{k_c}{k_H}$: $\log \frac{k_c}{k_H} = (0.73 \pm 0.11) - (0.54 \pm 0.18)/\theta$, where $\theta = 2.3RT$.

It is reasonable to assume that $k_H$ in this reaction has Arrhenius parameters very similar to phenyl radical ($\log k_H = 9.6 - 1.7/\theta$)$^{46}$ in which case the Arrhenius equation for the absolute rate constant for ring closure of $\text{88}$ is $\log k_c = (10.3) - (2.2)/\theta$ and $k_c = 9 \times 10^8 \text{ s}^{-1}$ at 80 $^\circ$C.
Table 2. Kinetic Data for Cyclization of 88

<table>
<thead>
<tr>
<th>temp. °C</th>
<th>[Bu₃SnH]b, M</th>
<th>(91 + 92)/95c</th>
<th>k_c/k_H, M</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.95</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>20</td>
<td>1.18</td>
<td>1.9</td>
<td>2.2</td>
</tr>
<tr>
<td>20</td>
<td>1.42</td>
<td>1.7</td>
<td>2.4</td>
</tr>
<tr>
<td>50</td>
<td>0.92</td>
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<td>2.2</td>
</tr>
<tr>
<td>50</td>
<td>1.16</td>
<td>2.0</td>
<td>2.3</td>
</tr>
<tr>
<td>80</td>
<td>0.89</td>
<td>2.5</td>
<td>2.2</td>
</tr>
<tr>
<td>80</td>
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<td>2.4</td>
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<td>80</td>
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</tr>
<tr>
<td>110</td>
<td>0.86</td>
<td>3.0</td>
<td>2.6</td>
</tr>
<tr>
<td>110</td>
<td>1.09</td>
<td>2.5</td>
<td>2.7</td>
</tr>
<tr>
<td>110</td>
<td>1.31</td>
<td>2.1</td>
<td>2.8</td>
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<tr>
<td>140</td>
<td>0.84</td>
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<td>2.9</td>
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<td>2.8</td>
<td>2.9</td>
</tr>
<tr>
<td>140</td>
<td>1.27</td>
<td>2.3</td>
<td>2.9</td>
</tr>
</tbody>
</table>

a) All reactions in benzene solvent. b) Average concentration of Bu₃SnH which is used in 10-fold excess. c) As determined by GC

The cyclization of the radical 88 with stannane gave a substantial amount of endo cyclization product 92 (31%) (Scheme 31). To elucidate the mechanism of its formation the dependence of 91/92 ratio with stannane concentration was studied (Table 3).

The data presented in Table 3 clearly show that the ratio of 91/92 is not independent of stannane concentration indicating that the endo product 92 does not arise solely via direct endo ring closure of the radical 88. When [Bu₃SnH] was <0.15M the yield of uncyclized product 95 was negligibly small. It was then possible to fit the data for the relative yields of cyclized to the rate equation 2. The
results summarized in Table 3 show that there is with one exception a fair agreement between the values of $k / k_H$ obtained at each temperature of the two concentrations of stannane employed. This indicates that the endo product 92 arises mainly via the pathway $89 \rightarrow 90 \rightarrow 92$.

Table 3. Kinetic Data for the Neophyl Rearrangement of 89

<table>
<thead>
<tr>
<th>temp. °C</th>
<th>$S_0$ M</th>
<th>$rvt$</th>
<th>$k_r / k_H \cdot 10^3$ M</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0.07</td>
<td>10.6</td>
<td>1.58</td>
</tr>
<tr>
<td>4</td>
<td>0.15</td>
<td>16.9</td>
<td>1.42</td>
</tr>
<tr>
<td>20</td>
<td>0.07</td>
<td>6.9</td>
<td>2.7</td>
</tr>
<tr>
<td>20</td>
<td>0.15</td>
<td>11.6</td>
<td>3.0</td>
</tr>
<tr>
<td>50</td>
<td>0.07</td>
<td>3.97</td>
<td>5.3</td>
</tr>
<tr>
<td>50</td>
<td>0.15</td>
<td>5.36</td>
<td>7.9</td>
</tr>
<tr>
<td>80</td>
<td>0.07</td>
<td>2.03</td>
<td>12.0</td>
</tr>
<tr>
<td>80</td>
<td>0.15</td>
<td>3.72</td>
<td>12.3</td>
</tr>
<tr>
<td>110</td>
<td>0.07</td>
<td>0.97</td>
<td>28.9</td>
</tr>
<tr>
<td>110</td>
<td>0.15</td>
<td>1.93</td>
<td>27.5</td>
</tr>
</tbody>
</table>

a All reaction in benzene solvent. b Initial concentration of Bu$_3$SnH; the final concentration of Bu$_3$SnH was zero in each case. c As determined by GC.

Linear regression analysis of the data in Table 3 gives the Arrhenius relative rate expression for the temperature dependence of $k_r / k_H$ for neophyl rearrangement of the radical 89 as: $\log k_r / k_H (M) = (1.48 \pm 0.34) - (5.41 \pm 0.53) / \theta$.

If it is assumed that substituent effects on the rate of hydrogen atom transfer from stannane to the radical 89 are small, and that 89 has the same reactivity as a butyl radical$^{46}$ ($\log k_H = (9.1 \pm 0.2) - (3.7 \pm 0.3) / \theta$) then the Arrhenius equation for the absolute rate constant for the rearrangement of 89 $\rightarrow$ 90 can be calculated to be, $\log k_r = (10.6 \pm 0.4) - (9.1 \pm 0.6) / \theta$ and $k_r = 9.3 \times 10^4$ s$^{-1}$ at 80 °C.
Table 4. Rate Constants for Substituted Naphthyl and Phenyl Radical Rearrangements

<table>
<thead>
<tr>
<th>Reactions</th>
<th>( k, \text{s}^{-1} (80^\circ\text{C}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ \text{7.6} \rightarrow \text{7.7} ]</td>
<td>( &gt; 1.9 \times 10^{10} )</td>
</tr>
<tr>
<td>[ \text{7.7} \rightarrow \text{7.8} ]</td>
<td>( = 1.3 \times 10^{10} )</td>
</tr>
<tr>
<td>[ \text{8.8} \rightarrow \text{8.9} ]</td>
<td>( = 9 \times 10^{9} )</td>
</tr>
<tr>
<td>[ \text{8.9} \rightarrow \text{9.0} ]</td>
<td>( = 9.3 \times 10^{4} )</td>
</tr>
<tr>
<td>[ \text{2} \rightarrow \text{3}^{53} ]</td>
<td>( = 5.2 \times 10^{9} )</td>
</tr>
<tr>
<td>[ \text{9} \rightarrow \text{9a}^{53} ]</td>
<td>( = 3.7 \times 10^{9} )</td>
</tr>
<tr>
<td>[ \text{9a} \rightarrow \text{9b}^{54} ]</td>
<td>( = 3.2 \times 10^{2} )</td>
</tr>
<tr>
<td>[ \text{9a} \rightarrow \text{9b}^{53} ]</td>
<td>( = 2.9 \times 10^{3} )</td>
</tr>
</tbody>
</table>

The kinetic data summarized in Table 4 shows that neophyl rearrangement is considerably faster for the radicals 77 and 89 containing a naphthalene nucleus than it is for the analogous benzenoid radical 9a. Presumably this reflects the fact that naphthalene at the 1-position is more reactive than benzene.
toward homolytic attack.\textsuperscript{55} The high reactivity of 89 by comparison with 77 is consistent with the view that alkyl radicals are essentially nucleophilic in character.\textsuperscript{2,50} Thus the neophyl rearrangement will be facilitated by the presence of electron-attracting substituents and disfavoured by electron-donating substituents. Hence the rate retardation in 77 may be attributed to the electron-donating substituent (OR) which is not present in 89.

Comparison of the data in Table 4 shows that ring closure of 76 is at least 19 times faster than the ring closure of the all-carbon system 88. A similar enhancement of rates of cyclization of alkenyl\textsuperscript{56-58} and alkenylaryl\textsuperscript{10,12} upon substitution of a chain methylene by an oxygen atom has been previously noted and attributed to changes in the strain energies of the transition structures,\textsuperscript{47} arising from the facts that the C-O bond is shorter than the C-C bond and the bond angle C-O-C is smaller than C-C-C bond. This allows the two reactive centers to come into close juxtaposition without a large increase in strain energy. Beckwith\textsuperscript{15} has also suggested that conjugative interaction of the oxygen lone pairs with the aromatic ring, increases the population of conformers favourably disposed for cyclization.

The high reactivity of 76 by comparison with 2 and of 88 by comparison with 9 reflects the fact that 1-naphthyl radicals undergo ring closure more rapidly than equivalent phenyl radicals. Alternatively, the assumption that \( k_H (\text{naphthyl radicals}) = k_H (\text{phenyl radicals}) \) is incorrect and in fact, the former is less than the latter.

Treatment of the radical precursor 70 with tri-\( \eta \)-butyltin hydride \([0.06M]\) in benzene at 80 °C gave exclusively the exo cyclization product 97 in 81\% yield (Scheme 33). The product 97 was identified from its \( ^1H \) and \( ^{13}C \) nmr spectra. The reaction of 70 with stannane gave no uncyclized product, indicating that hydrogen atom transfer from stannane to 96 can not compete with the fast cyclization of 96. Even when the experiment was repeated with ten equivalents of stannane at relatively high concentration \([1M]\) no uncyclized product was detected.
Although an accurate rate constant for cyclization of 96 cannot be calculated from the present data, an approximate minimum value can be obtained. Based on a minimum detection level of 2% for the direct reduction product, it can be calculated that the rate constant for exo cyclization of radical 96 is > 1.7 x 10^{10} \text{s}^{-1} at 80 \degree C. The observed rate of cyclization for 96 is at least 5 times faster than that of the corresponding phenyl radical 2 (k_c = 3.4 \times 10^9 \text{ at } 80 \degree C).^{53} The cyclization of 96 unlike that of the 1-naphthyl radical 76 did not give rise to the endo cyclized product via neophyl rearrangement. Presumably this reflects the difference in reactivities of naphthalene at 1- and 2-position.

Reaction of compound 71 with tri-n-butyltin hydride at an initial concentration of 0.06 M in benzene at 80 \degree C afforded 100 in 82% yield (Scheme 34). The ^1H and ^13C nmr spectra of 100 are consistent with the assigned structure. Presumably, the rearrangement of the expected product 99 to 100 is acid catalysed and occurs during purification by chromatography on silica. Similar rearrangement has been noted by Beckwith and Meijs\textsuperscript{16} when the diazonium salt 44 was heated with tributylstannane (Scheme 35); the benzofuran 101 was the only product isolated. The formation of 101 was proposed to arise by the rearrangement of 64 to 101 catalysed by boron trifluoride, a by-product of the reduction reaction.
Clearly, the ring closure of the radical 98 is regiospecific and the process is so rapid that there is no effective competition by hydrogen atom transfer from tri-n-butyltin hydride to the radical 98. Although an accurate rate constant for cyclization of 98 cannot be calculated from the present data an approximation can be attempted. Assuming that the rate of hydrogen atom transfer from stannane to 98 is similar to that of the phenyl radical and a minimum detection level of 2% for the direct reduction product, a lower limit for the exo cyclization rate constant for 98 can be obtained. Application of the integrated rate equation 2 (Appendix A) to the data gives \( k_c > 5 \times 10^8 \text{ s}^{-1} \) at 80 °C.
When the bromide 72 was treated with tri-n-butyltin hydride [0.06M] and a catalytic amount of AIBN in boiling benzene, it afforded three products detected by GC in the ratio of 1:1:1:30. One of the minor products was identified as the reduction product 108a (3.5%) by GC comparison with an authentic sample. The other minor product was proved to be 106a (3%) on the basis of $^2$H nmr spectrum analysis of product mixtures obtained from reaction of 72 with tri-n-butyltin deuteride. The major product (93.5%) was identified as the exo cyclization product 105a by $^1$H and $^{13}$C nmr spectroscopy (Scheme 36a).

![Scheme 36 a / b](image-url)
The formation of 106a involves 1.5-intramolecular hydrogen atom transfer to 102 as depicted in Scheme 36a to give the allyl radical 104 which is then converted into a mixture of 108a and the steroisomers 106a. The contribution of the process 102 → 104 was evaluated by carrying out the reaction of 72 with tri-n-butyltin deuteride.

Repetition of the reaction of 72 with one equivalent of tri-n-butyltin deuteride [0.25M] at 20 °C gave 108b (5%), 107b (0.8%), 106b (3.8%), and 105b (90.3%) (Scheme 36b). The site of deuterium incorporation in the products from the above reaction was determined by measuring the chemical shifts in the deuterium nmr spectra and the product ratio were deduced from the integrated deuterium nmr spectrum.

The occurrence of 1.5-hydrogen atom migrations between carbon atoms is quite common and has been extensively reviewed.7a,59 These migrations are believed to proceed through a distorted six-membered cyclic transition structure, which allows the required collinear arrangement between the bond being broken and the bond being formed. Their occurrence is most likely to be observed when their formation through a six-membered transition state affords resonance stabilized species and they often exhibit relatively large rate constants.

When the bromo compound 73 was treated with tri-n-butyltin hydride [0.06M] in boiling benzene three products (Scheme 37a) were detected by GC in the ratio of 1.8:1:27. One of the minor products was identified as the reduction product 115a (6.2%) by GC comparison with an authentic sample. The other minor product was identified as 113a (3.5%) on the basis of 2H nmr spectrum analysis of product mixtures obtained from reaction of 73 with tri-n-butyltin deuteride. The major product (90.3%) was identified as the exo cyclization product 112a by 1H and 13C nmr spectroscopy.
When the above stannane promoted cyclization of 73 was repeated with tri-$n$-butyltin deuteride the contribution of the process $109 \rightarrow 111$ could be evaluated. Treatment of 73 with one equivalent of tri-$n$-butyltin deuteride [0.25M] at 20 °C gave four products identified as the exo cyclization product $112b$ (85 %), the directly reduced product $115b$ (9 %) and the indirectly reduced products $113b$ (5 %) and $114b$ (1 %) (Scheme 37b). The sites of deuterium incorporation were determined by $^2$H nmr and the product ratios were deduced from the integrated $^2$H nmr spectrum.
Application of the integrated rate equation 2 (Appendix A) to the results obtained from the reaction of 72 (Scheme 36b) and 73 (Scheme 36b) with tri-n-butyltin deuteride yielded values of $k_r/k_D$ and $k_r/k_H$, where $k_r$ is the rate constant for 1,5-hydrogen atom transfer. $k_D$ and $k_H$ are the respective rate constants for deuterium transfer from Bu$_3$SnD to naphthyl radicals, and for hydrogen atom transfer to naphthyl radicals from Bu$_3$SnH. The results are summarized in Table 5.

Table 5. Kinetic Data$^a$ for 1,5-hydrogen atom transfer

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reaction</th>
<th>Yield$^b$, %</th>
<th>Temp. °C</th>
<th>$k_r/k_D$</th>
<th>$k_r/k_H$</th>
<th>$k_r$, s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>102 → 104</td>
<td>4.6</td>
<td>20</td>
<td>2.5×10$^{-3}$</td>
<td>1.9×10$^{-3}$</td>
<td>6.6×10$^5$</td>
</tr>
<tr>
<td>102 → 104</td>
<td>12.7</td>
<td>3.0</td>
<td>110</td>
<td>9.7×10$^{-3}$</td>
<td>7.5×10$^{-3}$</td>
<td>2.6×10$^6$</td>
</tr>
<tr>
<td>73</td>
<td>109 → 111</td>
<td>5.6</td>
<td>20</td>
<td>3.2×10$^{-3}$</td>
<td>2.5×10$^{-3}$</td>
<td>8.7×10$^5$</td>
</tr>
<tr>
<td>109 → 111</td>
<td>10.6</td>
<td>5.0</td>
<td>110</td>
<td>7.5×10$^{-3}$</td>
<td>5.8×10$^{-3}$</td>
<td>2.0×10$^6$</td>
</tr>
</tbody>
</table>

$^a$[Bu$_3$SnD]$_0$ = 0.25M; [Bu$_3$SnD]$_f$ = 0. $^b$U$_R$ = Products formed by 1,5-hydrogen atom transfer; U = direct reduction product.

It should be noted that the following assumptions were made in obtaining these results: (i) the deuterium isotope effect ($k_H/k_D$) for hydrogen atom transfer from stannane to naphthyl radicals has the same value as $k_H/k_D$ for the phenyl radical$^{12}$ ($k_H/k_D = 1.3$). (ii) $k_H$ and $k_D$ will not vary in value between the various naphthyl radicals, and (iii) $k_H$ for naphthyl radicals has the same value as $k_H$ for phenyl radicals$^{46}$ ($\log k_H = 9.6 - 1.7/\theta$). The magnitude of these rate constants are similar to those for simple phenyl radicals.$^{10,37,39,60}$

It is also possible to determine rate constants for the cyclization of 102 and 109 from the above kinetic data. However, to obtain more accurate rate
constants, \( k_c \), and Arrhenius activation parameters the kinetics of the reactions in Schemes 36 and 37 were studied under pseudo first order conditions (ten-fold excess) in stannane.

Application of the usual steady-state theory to the reactions in Schemes 36 and 37 gives the integrated rate equation 3 (Appendix B):

\[
\frac{k_c}{k_H} = \frac{[(C/U_T - \alpha C)] [Sn]_m}{[U_T - \alpha C]} \tag{3}
\]

where [C] is the final concentration of the cyclized products, [U_T] is the final concentration of the total reduction products, [Sn]_m is the mean concentration of stannane, and \( \alpha \) is the ratio \( \frac{k_r}{k_c} \) of \( k_r \), the rate constant for 1,5-hydrogen atom transfer to \( k_c \), the rate constant for ring closure.

The values of \( \alpha \) were acquired from the reaction of the appropriate substrates with tri-n-butyltin deuteride at two different temperatures (20, 110 °C). Other values of \( \alpha \) were obtained from a plot of logarithms of \( \alpha \) against \( 1/T \). It was then possible to determine the values of \( k_c/k_H \) by fitting the appropriate data into the above rate equation (4). The results are summarized in Tables 6 and 7.
Table 6. Kinetic Data for Cyclization of 102\textsuperscript{a}

<table>
<thead>
<tr>
<th>Temp. °C</th>
<th>[Sn]\textsubscript{m}\textsuperscript{b}</th>
<th>C/U\textsubscript{T}\textsuperscript{c}</th>
<th>k\textsubscript{c}/k\textsubscript{H}\textsuperscript{d}</th>
<th>k\textsubscript{r}/k\textsubscript{c}\textsuperscript{e}</th>
<th>k\textsubscript{c}/k\textsubscript{H}\textsuperscript{f}</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>.475</td>
<td>2.986</td>
<td>1.418</td>
<td>0.0515</td>
<td>1.676</td>
</tr>
<tr>
<td>20</td>
<td>.712</td>
<td>2.184</td>
<td>1.556</td>
<td>1.753</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>.950</td>
<td>1.717</td>
<td>1.631</td>
<td>1.789</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>.475</td>
<td>3.346</td>
<td>1.589</td>
<td>0.0776</td>
<td>2.147</td>
</tr>
<tr>
<td>50</td>
<td>.712</td>
<td>2.317</td>
<td>1.651</td>
<td>2.013</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>.950</td>
<td>1.792</td>
<td>1.702</td>
<td>1.977</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>.475</td>
<td>3.496</td>
<td>1.661</td>
<td>0.1184</td>
<td>2.818</td>
</tr>
<tr>
<td>80</td>
<td>.712</td>
<td>2.760</td>
<td>1.966</td>
<td>2.921</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>.950</td>
<td>2.172</td>
<td>2.003</td>
<td>2.778</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>.475</td>
<td>3.507</td>
<td>1.666</td>
<td>0.1509</td>
<td>3.521</td>
</tr>
<tr>
<td>110</td>
<td>.712</td>
<td>3.067</td>
<td>2.186</td>
<td>4.069</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>.950</td>
<td>2.208</td>
<td>2.098</td>
<td>3.147</td>
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</tr>
</tbody>
</table>

\textsuperscript{a}All reactions in benzene solvent. \textsuperscript{b}Average concentration of Bu\textsubscript{3}SnH which is used in 10-fold excess. \textsuperscript{c}As determined by GC. \textsuperscript{d}Obtained from equation 1 (uncorrected for 1.5-H atom abstraction). \textsuperscript{e}Obtained from Bu\textsubscript{3}SnD experiment. \textsuperscript{f}Obtained from equation 3 (corrected for 1.5-H atom abstraction).
Table 7. Kinetic Data for Cyclization of 109\textsuperscript{a}

<table>
<thead>
<tr>
<th>Temp. °C</th>
<th>[Sn]_{m} \textsuperscript{b}</th>
<th>C/U_{T} \textsuperscript{c}</th>
<th>k_{c}/k_{H} \textsuperscript{d}</th>
<th>k_{r}/k_{c} \textsuperscript{e}</th>
<th>k_{c}/k_{H} \textsuperscript{f}</th>
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</thead>
<tbody>
<tr>
<td>3</td>
<td>.475</td>
<td>1.692</td>
<td>0.804</td>
<td>0.0550</td>
<td>0.866</td>
</tr>
<tr>
<td>3</td>
<td>.712</td>
<td>1.044</td>
<td>0.744</td>
<td>0.789</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>.950</td>
<td>0.829</td>
<td>0.787</td>
<td>0.825</td>
<td></td>
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<tr>
<td>23</td>
<td>.475</td>
<td>2.126</td>
<td>1.010</td>
<td>0.661</td>
<td>1.175</td>
</tr>
<tr>
<td>23</td>
<td>.712</td>
<td>1.352</td>
<td>0.964</td>
<td>1.058</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>.950</td>
<td>1.056</td>
<td>1.003</td>
<td>1.079</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>.475</td>
<td>2.359</td>
<td>1.121</td>
<td>0.0832</td>
<td>1.394</td>
</tr>
<tr>
<td>50</td>
<td>.712</td>
<td>1.708</td>
<td>1.217</td>
<td>1.418</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>.950</td>
<td>1.125</td>
<td>1.068</td>
<td>1.179</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>.475</td>
<td>2.790</td>
<td>1.325</td>
<td>0.1071</td>
<td>1.890</td>
</tr>
<tr>
<td>80</td>
<td>.712</td>
<td>1.981</td>
<td>1.412</td>
<td>1.792</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>.950</td>
<td>1.543</td>
<td>1.465</td>
<td>1.755</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>.475</td>
<td>3.517</td>
<td>1.671</td>
<td>0.1264</td>
<td>3.008</td>
</tr>
<tr>
<td>110</td>
<td>.712</td>
<td>2.235</td>
<td>1.592</td>
<td>2.219</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>.950</td>
<td>1.926</td>
<td>1.830</td>
<td>2.419</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>.475</td>
<td>3.915</td>
<td>1.860</td>
<td>0.1513</td>
<td>4.642</td>
</tr>
<tr>
<td>150</td>
<td>.712</td>
<td>2.543</td>
<td>1.812</td>
<td>2.967</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>.950</td>
<td>2.146</td>
<td>2.040</td>
<td>3.037</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}All reactions in benzene solvent. \textsuperscript{b}Average concentration of Bu\textsubscript{3}SnH which is used in 10-fold excess. \textsuperscript{c}As determined by GC. \textsuperscript{d}Obtained from equation 1 (uncorrected for 1.5-H atom abstraction). \textsuperscript{e}Obtained from Bu\textsubscript{3}SnD experiment. \textsuperscript{f}Obtained from equation 3 (corrected for 1.5-H atom abstraction).
Linear regression analysis of the data in Tables 6 and 7, and with the assumption that $k_H$ for naphthyl radical is the same as that for phenyl radical \(^4\) (log \(k_H = 9.6 - 1.7/2.3RT\)), gave the Arrhenius coefficients presented in Table 8.

### Table 8. Arrhenius Coefficients and Rate Constants\(^a\)

<table>
<thead>
<tr>
<th>Reactions</th>
<th>$\Delta \log A^{b}$</th>
<th>$\Delta E_{\text{act}}^{b}$</th>
<th>$\log A^{c}$</th>
<th>$E_{\text{act}}^{c}$</th>
<th>$k_c, 80^\circ C^{d}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>102 $\rightarrow$ 105</td>
<td>$1.6 \pm 0.1$</td>
<td>$1.9 \pm 0.2$</td>
<td>$11.2 \pm 0.1$</td>
<td>$3.6 \pm 0.2$</td>
<td>$1.1 \times 10^9$</td>
</tr>
<tr>
<td>109 $\rightarrow$ 112</td>
<td>$1.8 \pm 0.1$</td>
<td>$2.4 \pm 0.2$</td>
<td>$11.4 \pm 0.1$</td>
<td>$4.1 \pm 0.2$</td>
<td>$7.9 \times 10^8$</td>
</tr>
</tbody>
</table>

\(^a\)All reactions in benzene solvent. \(^b\)Reactions carried out below $50^\circ C$ were initiated by UV irradiation. \(^c\)Uncertainties at 95% confidence level. \(^d\)Calculated from Arrhenius coefficients.

The rates of cyclization of 102 and 109 (Table 8) are found to be much less than these exhibited by lower homologs. However, the observed rate constant indicates that the ring closure of 102 and 109 is faster than the corresponding 2-(but-3-enyloxy)phenyl\(^5\) radical ($k_c = 3.4 \times 10^8$ s\(^{-1}\) at $80^\circ C$).

Treatment of the bromide 74 with a slight molar excess of tri-butyltin hydride [0.05M] in boiling benzene gave exclusively the exo cyclization product 118 in 81% yield (Scheme 38).

Similar treatment of the bromide 75 gave the exo cyclization product 120 as the only isolated product in 76% yield (Scheme 39).
Examination of $^1$H nmr spectra of 118 and 120 afforded no clue to the stereochemistry of the newly formed ring junction. The assigned stereochemistries were by analogy with results obtained with related ring-fused systems. The failure of the reactions of 74 and 75 with stannane to afford the uncyclized products indicates that, under the reaction conditions, neither direct reduction product nor 1,5-hydrogen atom transfer is sufficiently fast to compete with ring closure. Accurate rate constants for cyclization of 117 and 119 can not be calculated from the present data. However, minimum values calculated on the basis of the known $k_H$ value for hydrogen atom transfer as described above, the rate constant for exo...
cyclization of radicals 117 and 119 can be estimated (equation 2) to be $> 4.1 \times 10^8$ s$^{-1}$ and $> 3.8 \times 10^8$ s$^{-1}$. respectively at 80 °C based on a minimum detection level of 2% for the direct reduction products if they were present.

Each of the radicals studied 76, 88, 96, 98, 102, 109, 117 and 119 underwent exo cyclization either predominantly or exclusively as expected on stereoelectronic grounds. Also, as expected, ring-closures of the radicals were found to be extremely rapid. Recent force-field calculations by Beckwith and Schiesser reveal that exo ring closure of alkenylaryl radicals is favoured over endo mainly because of more favorable bending and torsion energies of the transition structures for the former. The MM2 force-field calculations on the transition structures also reveal that the major factor facilitating the high rate of exo ring closure of alkenylaryl radicals is the low value of $\Delta E_s^{\text{exo}}$ for alkenylaryl systems as compared with $\Delta E_s^{\text{exo}}$ for their alkenyl counter parts. These, in turn, are associated with the absence of the protons on C(1) and C(2) which give rise to unfavourable interactions in the hexenyl system. Another factor favoring the cyclization of aryl system. may be the inherently high reactivity of aryl radicals.

In summary, the ring-closure of suitably substituted naphthyl radicals is a rapid processes. The high degree of regioselectivity observed, good isolated yields, and mild reaction conditions will find application in the synthesis of polycyclic aromatic rings.
1.2 INTERMOLECULAR TRAPPING OF RADICALS FROM CYCLIZATION REACTIONS

There have been a number of examples recently of intermolecular addition of radicals arising from cyclization reactions onto electron deficient alkenes. Such reactions are of great practical synthetic utility, since highly functionalized molecules can be assembled in one step. In the design of such a process, the selectivity requirements for each intermediate radical must be carefully assessed. The most straightforward approach involves the use of a very rapid intramolecular cyclization prior to an addition of the intermediate radical to an electron-deficient alkene. The aim of the present work was to study the applicability of cyclization-trapping methodology to the rapid naphthyl radical cyclizations. It was envisaged that trapping of radicals from cyclization of suitably substituted naphthyl radicals with activated alkenes would lead to functionalized polycyclic systems.

The required radical precursors, 1-bromo-2-(prop-2-enyloxy) naphthalene 66 and 1-iodo-2-(prop-2-enyloxy)naphthalene 121 were prepared from readily available starting materials. The synthesis of 66 is already described in the first section of this chapter. The iodo compound 121 was prepared by alkylation of 1-iodo-2-naphthol with 3-bromopropene and potassium carbonate in acetone in 76% yield. With the radical precursor 66 and 121 in hand it was possible to attempt radical cyclization-trapping.
When a mixture of the iodo compound 121, methyl acrylate (20 equivalent), and AIBN (0.1 equivalent), was heated with tri-\text{\textit{n}}-\text{butyl}tin hydride (1.5 equiv) at initial concentration of 0.025 M in boiling benzene, the major product isolated was the trapped product 123 in 35% yield (Scheme 40). The reaction also afforded (28%) of an inseparable mixture of 79 and 80 in the ratio of 20:1 by GC.

![Scheme 40](image)
The trapped product 123 was identified by its spectral data. The cyclized and then reduced products 79 and 80 were identified by GC comparison with authentic samples. As expected, no product arising from direct reduction of 76 with stannane nor addition of 76 to methyl acrylate could be detected, indicating that both processes could not compete with the fast cyclization of 76 \([k_c > 1.9 \times 10^{10} \text{ at } 80 \, ^\circ\text{C}]\). The formation of 80 presumably involves neophyl rearrangement of radical 77 as previously described in Scheme 27. The ratio of 79/80 (20:1) in this reaction (Scheme 40) compared to the previously observed ratio of 10:1 (Scheme 1) indicates that the neophyl rearrangement of 77 \(\rightarrow 80 \left[ k_r = 1.3 \times 10^4 \text{ (80 } ^\circ\text{C}) \right] \) is not efficiently competing with hydrogen atom transfer to 77 from stannane and addition of 77 to methyl acrylate. The comparable yields of 123 (35\%) and the 79 (26.7\%) presumably indicates that the addition of radical 77 to methyl acrylate and hydrogen atom transfer to radical 77 from stannane proceeds with similar rates under the conditions used. The yield of the trapped product 123 might be increased by further lowering the concentration of tri-n-butyltin hydride. This can be attained by slow addition of tri-n-butyltin hydride to the reaction mixture or by in situ generation of tri-n-butyltin hydride from tri-n-butyltin halides with sodium cyano-borohydride.\(^{62}\)

The bromo compound 66 gave, upon similar treatment with tri-n-butyltin hydride \([0.025\text{M}]\) and methyl acrylate, the trapped product 123 but in lower yield (16\%). Also isolated were unchanged starting material (29\%), and an inseparable mixture of 79 and 80 (31\%) in the ratio of 20:1. Unlike the reaction of the iodo compound 121, that of the bromide 66 with stannane did not go to completion. Presumably, this reflects their difference in rates of reaction with tri-n-butyltin radical. Unfortunately rate constants for the reaction of aryl iodides and bromides with tri-n-butyltin radicals are not available. However, by analogy with alkyl iodides which react with tri-n-butyltin radical about 100 times faster than alkylbromides,\(^{8a,64}\) it should be expected that aryl bromides react with tri-n-butyltin hydride much slower than do aryl iodides.
In conclusion, this short study was successful in demonstrating intermolecular trapping of radical arising from a cyclization reaction of naphthyl radical can lead to functionalized tricyclic products suitable for further elaboration. However, further work is required to optimize the yields, and to define appropriate conditions to make the method synthetically practical.
2.1 ARYL RADICAL RING CLOSURE ONTO THE CARBONYL GROUP

The ring closure of an aryl radical onto a carbon-oxygen double bond in
both aldehydes\(^{25-26}\) and ketones\(^{19,20,21-23}\) has received much attention recently.
However, only a few studies describing the additions of aryl radicals have been
reported\(^{19-21}\). The aim of the current study was to gain further insights into
acyclizations of phenyl radicals onto the carbon-oxygen double bond and the factors
which affect them, and to examine the behaviour of naphthyl radicals in similar
reactions.

CHAPTER 2

The radical precursors 124-126, 129-131 were prepared from readily
available starting materials. Thus, treatment of 1-bromo-2-naphthyl bromide with ethyl
acetacetate by the method of Back with \(^{19-21}\) followed by decarboxylation\(^{21-22}\) with
sodium chloride / DMF / water gave the bromide 126 (Scheme 41).

![Scheme 41](image)

Alkylation of 1-bromo-2-bromonaphthyl acetate with ethyl
acetacetate afforded the bromide 127 in 69% yield (Scheme 42). Similar treatment
of 1-bromo-2-bromonaphthyl acetate with either ethyl 2-oxo-cyclohexene-
acetate 125, methyl 2-oxo-cyclohexene-carboxylate 126, or methyl 3-oxo-

2.1 ARYL RADICAL RING CLOSURE ONTO THE CARBONYL GROUP

The ring closure of an alkyl radical onto a carbon-oxygen double bond in both aldehydes\(^{65-69}\) and ketones\(^{38,39,68,70-73}\) has received much attention recently. However, only a few studies describing the additions of aryl radical have been reported.\(^{38,39}\) The aim of the current study was to gain further insights into cyclizations of phenyl radicals onto the carbon-oxygen double bond and the factors which affect them, and to examine the behaviour of naphthyl radicals in similar reactions.

The radical precursors \(^{126},^{127},^{131-133}\) were prepared from readily available starting materials. Thus, treatment of o-bromobenzyl bromide with ethyl acetoacetate by the method of Beckwith et al.\(^{39}\) followed by decarboxylation\(^{74}\) with sodium chloride / DMSO / water gave the bromide \(^{126}\) (Scheme 41).

\[
\text{Br} \quad \text{Na} / \text{EtOH} \quad \text{Br} \quad \text{COMe} \quad \text{Br} \quad \text{COMe} \quad \text{NaCl} / \text{H}_2\text{O} \quad \text{DMSO}
\]

\[
124 \quad \text{CO}_2\text{Et} \quad 125 \quad \text{CO}_2\text{Et} \quad 126
\]

Scheme 41

Alkylation of 1-bromo-2-bromomethyl naphthalene \(^{68}\) with ethyl acetoacetate afforded the bromide \(^{127}\) in 61% yield (Scheme 42). Similar treatment of 1-bromo-2-bromomethyl naphthalene with either ethyl 2-oxo-cyclopentane-1-carboxylate \(^{128}\), methyl 2-oxo-cyclohexane-1-carboxylate \(^{129}\), or methyl 2-oxo-
The bromides 126, 127, 131-133 displayed the expected $^1$H nmr, $^{13}$C nmr and infrared spectra. With the radical precursors 126, 127, 131-133 in hand it was possible to attempt ring closure by their treatment with tri-$n$-butyltin hydride. The behaviour of each of the radical precursors will be discussed individually for the sake of clarity.
Treatment of the bromide 126 with a slight molar excess of tri-n-butyltin hydride \([0.05\text{M}]\) in boiling benzene gave three products identified as the aryl ketone 137 (5\%), the direct reduction product 138 (60\%) and the alcohol 139 (5\%) (Scheme 44).

The identification of the products 137, 138, and 139 was based upon their respective \(^1\text{H}\) nmr, \(^{13}\text{C}\) nmr and infrared spectra. To induce the intramolecular radical addition, the experiment was repeated under high-dilution conditions where tri-n-butyltin hydride in benzene solution was slowly added from a syringe pump to
the bromide 126 in boiling benzene. However, the major product isolated was still the open-chain product 138 (53%). The aryl ketone 137 and the alcohol 139 were isolated in 6% and 3% yields respectively.

The formation of 137 involves exo cyclization of the radical 134 followed by ring opening of the alkoxy radical 135. The net effect is 1,4-acetyl migration. It is well-known that alkoxy radicals, including those formed by alkyl38,39,67,68,71-73 and aryl38,39 radical ring closure onto a carbon-oxygen double bond readily undergo β-fission. Such β-scissions have been applied in various synthetically important transformations.3

In terms of the mechanism depicted in Scheme 44, the reaction 134 → 135 is too slow to compete effectively with hydrogen atom transfer from tri-n-butyltin hydride, even under high-dilution conditions. If it is assumed that steps 134 → 135 and 135 → 136 are irreversible, application of the known value of \( k_H \) (log \( k_H = 9.6 - 1.7/\theta \)), yields estimate of the rate constant \( k_c \) for cyclization of radical 134. Application of the integrated rate equation 2 (Appendix A) gives a \( k_c \) value of 1.4 x 10^6 s^{-1} (80 °C). The radical 134 undergoes exo ring closure approximately 2.5 times slower than radical 141 (scheme 45) for which \( k_c \) is estimated to be about 3.5 x 10^6 s^{-1} at 80 °C.39

By comparison, with the radical 14539 (Scheme 45) which under similar experimental conditions gives only the rearrangement product 148, the formation of 139 from radical 135 indicates that radical 135 undergoes β-fission more slowly than 145. The slow ring opening of radical 135 → 136 compared to 145 → 146 presumably reflects the difference in stability of the product radicals 136 and 146. The radical 146 is a secondary radical, stabilized by the ethoxycarbonyl group while 136 is a primary radical.
Treatment of the bromide 127 with tri-n-butyltin hydride [0.05M] in boiling benzene afforded two products of which the ester 153 (41%) was formed by a 1,4-carbonyl migration (Scheme 46). The ester 153 was identified by $^1$H nmr and infrared spectroscopy. The other product was identified as the direct reduction product 152 (58%) on the basis of its infrared and $^1$H nmr spectra.

The failure of the reaction to afford the alcohol 154 indicates that under the reaction conditions, $\beta$-fission of radical 150 is sufficiently fast to compete effectively with hydrogen atom transfer from tri-n-butyltin hydride. This presumably reflects the stabilizing effect of the ethoxycarbonyl group on the radical 151 and the relief of angle strain present in the five-membered ring. The strength of the C-O bond in the forming carbonyl group, the stability of the leaving alkyl radical, and the relief of steric strain are the major factors which influence the rates of $\beta$-fission of alkoxy radicals. 77-79
The lower yield of 153 compared to 152 indicates that the ring closure of radical 149 is slower than its hydrogen atom transfer from tri-n-butyltin hydride under the reaction conditions. On the reasonable assumption that radical addition onto the carbonyl group is irreversible and application of the known value of $k_H$ it is possible to estimate the rate constant $k_c$ for the cyclization of 149. Application of equation 2 (Appendix A) gives a $k_c$ value of $6.3 \times 10^6$ s$^{-1}$ at 80 °C. This result shows that the radical 149 undergoes rearrangement 1.9 times more rapidly than radical 141 ($k_c = 3.5 \times 10^6$ s$^{-1}$ at 80 °C)$^{39}$ and 4.5 times more rapidly than radical 134 ($k_c = 1.4 \times 10^6$ s$^{-1}$ at 80 °C).
The ring closure of the radicals 134 and 149 is regiospecific in agreement with stereoelectronic considerations.\textsuperscript{7b} Since the electronic interaction giving rise to the transition structure for the addition of an aryl radical onto a polar bond (C=O) might differ from that of the all-carbon analogue, it was expected that differences in regiochemistry might occur. However, the rearrangements of 134 and 149 showed a high degree of preference for exo ring closure. The specificity of the processes 134 → 135 (Scheme 44) and 149 → 150 (Scheme 46) is especially noteworthy, for in these cases, the alternative mode of ring closure would afford the tertiary radicals 140 and 155, respectively, which are stabilized by conjugation of the free-electron with the lone pair in the adjacent oxygen atom.

Following the 1,4-carbonyl migration of the bromides 126 and 127, it was decided to attempt aryl radical ring closure onto cyclic β-keto esters. Recent studies by Beckwith\textsuperscript{38,39} and Dowd\textsuperscript{71-73} show that rearrangements in radicals containing cyclic β-keto ester groups results in ring expanded products by addition to the carbonyl group followed by β-fission. It was envisaged that ring closure of an aryl radical onto the carbonyl group, for example radical 156 (Scheme 47), followed by β-fission of the newly formed alkoxy radical, could provide a synthetic pathway to macrocyclic ketones.

Thus, treatment of the bromide 131 with a slight molar excess of tri-n-butyltin hydride [0.05M] in boiling benzene afforded two products, of which the ester 160 was formed in 42% yield (Scheme 47). The minor product was identified as the macrocyclic ketone 161 (16%) on the basis of its \textsuperscript{1}H nmr and infrared spectra. The infrared spectrum of 161 contained an ester carbonyl band centered at 1730 cm\textsuperscript{-1} aryl ketone band at 1690 cm\textsuperscript{-1}.

The low yield of 161 indicates that under these reaction conditions the ring closure of 156 is too slow to compete efficiently with direct reduction and/or
1,5- hydrogen atom transfer. It is also known that addition of a stannyl radical onto an activated carbonyl group is a fast process.\textsuperscript{64,80-82} Thus, addition of the stannyl radical onto the macrocyclic ketone \textsuperscript{161} may indeed take place, but we expect it to be reversible under the reaction conditions. The low yield of macrocyclic ketone \textsuperscript{161} initiated further investigation. Inspection of models suggested that better overlap of the unpaired electron with the $\pi^+$ orbital of the carbonyl bond might be attained by an increase in the size of the $\beta$-ketoester ring. It was hoped that this might increase the rate of aryl radical ring closure compared with hydrogen atom transfer from tri-$n$-butyltin hydride, and lead to an improved yield of macrocyclic products.

\begin{align*}
\begin{array}{c}
\text{Scheme 47}
\end{array}
\end{align*}
However, treatment of the bromide 132 with a slight molar excess of trimethyltin hydride [0.05M] in benzene afforded four products, two of which were identified as the reduction product 169 (63%) and the macrocyclic ketone 170 (15%) (Scheme 48). The other two (total 17%) were identified as the two diastereoisomers of the cyclopentanone 171 in the ratio of 5:4.

Scheme 48
The infrared spectrum of 171 contained a broad absorption band at 1740 and 1730 cm\(^{-1}\) assigned to an ester carbonyl and a five membered ketone respectively. The \(^{13}\)C nmr resonances for the two diastereoisomers, although they could not be distinguished in the aromatic region, showed two distinct set of signals in the upfield region and for the ketone and the ester carbonyl. They occurred at \(\delta 20.6, 25.8, 36.1, 38.1, 49.0, 51.7\) (both \(\text{CH}_3\)). 174.6, 219.2 for the major isomer and at 20.7, 27.3, 35.8, 38.3, 47.7, 50.1, 173.6, 218.3 for the minor isomer.

The mechanism depicted in Scheme 48 shows that radical 163 undergoes three competitive reactions. Two of these comprise hydrogen atom transfer to form the reduction product 169 and addition onto the carbon atom of the carbonyl group to generate radical 164. The third pathway involves irreversible 1,5-hydrogen atom transfer to 163 to give radical 166. The radical 166 can then abstract a hydrogen atom from stannane to afford the reduction product 169 or undergo intramolecular addition onto the carbon atom of the carbonyl to form 167. Finally, \(\beta\)-fission of the radical 167 leads to the stabilized tertiary radical 168 which, on hydrogen atom transfer from stannane, gives the diastereoisomers 171.

Similar treatment of the bromide 133 with tri-\(n\)-butyltin hydride [0.05M] in boiling benzene afforded three products (Scheme 49). These were identified as the reduction product 176 (6\%) and the two diastereoisomers of the ring contracted product 177 (total 93\%) in the ratio of 1:1.3. Although the diastereoisomers were separated by chromatography, the spectroscopic data did not allow the two diastereoisomers to be distinguished.

The failure of the radical 172 to afford the ring expanded product 178 indicates that under the reaction conditions, direct reduction and 1,5-hydrogen atom transfer of radical 172 are sufficiently fast to compete with ring formation.
Previous studies indicate that 1,5-intramolecular hydrogen atom transfer from an unactivated saturated carbon-hydrogen position to an aryl radical center occurs readily with rate constants of the order of about $10^7$ s$^{-1}$. The reactions in Schemes 48 and 49 show that the final yield of ring-contracted products 171 and 177 depends on the ease with which both 1,5-hydrogen atom transfer and rearrangement of the resultant cyclic radicals 167 and 174 occurs. The ease with
which 1.5-hydrogen atom transfer takes place depends upon the strain energy
generated in the attainment of conformations containing the approximately colinear
disposition of the C-H-C centers required for efficient atom transfer.\textsuperscript{7b,59a}
Inspection of models suggests that such strain will decrease with increasing flexibility
of the $\beta$-keto ester ring. Accordingly, 1.5-hydrogen atom transfer is expected to
occur most readily in the radical 172 containing the cyclooctanone ring, and least
readily in 156, containing the cyclopentanone ring. If it is assumed that the addition
of radical 173 (Scheme 49) onto the carbonyl group is irreversible ($173 \rightarrow 174$) and
that it is more rapid than its hydrogen atom transfer from stannane ($173 \rightarrow 176$), then
the rate constant $k_{1,5}$ for 1.5-hydrogen atom transfer for radical 172 (Scheme 49) can
be estimated to be $1.6 \times 10^8 \text{s}^{-1}$ at 80 °C from the appropriate rate equation 2
(Appendix A). Similarly, the rate constant $k_{1,5}$ for 1.5-hydrogen atom transfer for
radical 163 (Scheme 48) was estimated to be $1.8 \times 10^6 \text{s}^{-1}$ at 80 °C. These results
clearly shows that the rate of 1.5-hydrogen atom transfer increases with increasing
size of the ketone ring.

The ease with which the radicals 166 (Scheme 48) and 173 (Scheme 49)
undergo transannular-addition reflects ring strain in the bicyclic alkoxy radicals 167
and 174, and in the product radicals 168 and 175. Clearly, such factors do not
present a substantial barrier to the ring contraction of the eight-membered cyclic
radical 173. However, they would be expected to disfavour rearrangement of the
cyclohexyl radical 166. Presumably the radical 157 (Scheme 47) also undergoes 1.5-
hydrogen atom transfer, but in this particular case ring contraction by acyl migration
is prevented by the strain engendered in formation of the [2.1.0]bicyclopentane
nucleus in the alkoxy radical intermediate 162. In support of this view the $^2$H nmr
spectrum of the reduction product 160 (Scheme 47) obtained after 131 was treated
with tri-$n$-butyltin deuteride showed the presence of deuterium on both the aryl and
cycloalkyl rings.
Hydrogen atom transfer from stannane to both of the radicals 163 and 166 affords the same reduction product 169 (Scheme 48). The reduction of both the radicals 172 and 173 also leads to same product 176 (Scheme 49). Since the relative contributions of the routes 163 → 169 and 166 → 169 to the formation of 169, and 172 → 176 and 173 → 176 to the formation of 176, cannot be accurately determined from the present data, it is not possible to obtain firm rate constants for the transannular-addition steps 166 → 167 (Scheme 48) and 173 → 174 (Scheme 49). However, if it is assumed that all of 169 arises from 166 and if the rate constant for the transfer of hydrogen atom from tri-n-butyltin hydride to 166 is similar to that for the cyclohexyl radical, then the rate constant $k_r$ for the rearrangement of 166 → 167 can be estimated to be $3.2 \times 10^4 \, \text{s}^{-1}$ at $80^\circ \text{C}$ from the integrated rate equation 2 (Appendix A). Similarly $k_r$ for the rearrangement of 173 → 174 was calculated to be $2.7 \times 10^6 \, \text{s}^{-1}$ at $80^\circ \text{C}$. The magnitude of these rate constants agrees with those reported for transannular-addition of similar aryl radicals.

The results presented above show that ring closure of aryl radical onto a carbonyl group results in rearranged products by a mechanism involving 1,4-acetyl migration. The results also show that the $\beta$-fission of alkoxy radicals is influenced by the stability of the leaving alkyl radical. For aryl radical ring closure onto cyclic keto esters, alkyl-to-aryl 1,5-hydrogen atom transfer is a serious competitive side reaction.
2.2 RING CLOSURE OF ARYL RADICAL ONTO THE CYANO GROUP

Although the ring closure of alkyl radicals onto the cyano group has been utilized for the synthesis of cyclic ketones, similar reactions of aryl radicals have not been widely studied. Therefore, a study was initiated to examine the synthetic feasibility of aryl radical ring closure onto the cyano group.

The radical precursors $180$ and $181$ were prepared from readily available starting materials. Alkylation of o-bromobenzyl bromide by the method of Beckwith and co-workers afforded the ester $179$ (Scheme 50). Decarboxylation of $179$ by heating with sodium chloride/water/DMSO gave the bromide $180$ in 85% yield. Alkylation of 1-bromo-2-bromomethylnaphthalene with ethyl cyanoacetate yielded the bromide $181$ in 38% (Scheme 51).

![Scheme 50](image)

![Scheme 51](image)
Treatment of the bromide 180 with tri-n-butyltin hydride under high-dilution conditions followed by acidic hydrolysis afforded two products. They were identified as the direct reduction product 185 (21%) and the ketone 186 in 7% yield (Scheme 52).

---

This result clearly shows that exo ring closure of radical 182 is taking place. The ketone 186 is formed by acidic hydrolysis of the initially formed imine 184. The poor isolated yield may be attributed to further reduction of the imine and/or nitrile bonds. Reductions of this kind have been previously described. 80,81
It is well-known that cyclic iminyl radicals formed by ring closure of alkyl\(^{87-90}\) and aryl radicals\(^{38,39}\) onto carbon-nitrogen triple bonds may undergo \(\beta\)-fission with a net migration of the nitrile group. By contrast with the related radical \(189^{39}\) (Scheme 53), the failure of \(183\) to afford \(188\) clearly shows that ring opening of radical \(183\) is too slow to compete with its hydrogen atom transfer from stannane.

![Scheme 53](image)

The difference in the behaviour of \(183\) and \(189\) presumably reflects the stabilities of the product radicals since the cleavage of the former gives a primary radical \(187\) while cleavage of the latter gives a secondary radical \(190\) stabilized by the ester group.

Reaction of the bromide \(181\) with a slight molar excess of tri-\(n\)-butyltin hydride \([0.05M]\) in boiling benzene afforded the nitrile \(195\) in 97\% yield (Scheme 54). The nitrile \(195\) was identified by its spectroscopic data. The infrared spectrum of \(195\) contained a strong absorption band at 2200 cm\(^{-1}\) which was assigned to an aromatic nitrile group.

An interesting mechanistic feature is the failure of radical \(193\) to afford any of the cyclic imine \(197\). This indicates that hydrogen atom transfer from stannane to \(193\) occurs too slowly to compete with its \(\beta\)-fission. The failure of the radical \(192\) to afford the reduction product \(196\) indicates that under the reaction conditions the ring closure competes efficiently with hydrogen atom abstraction.
If it is assumed that the rate of hydrogen atom transfer from stannane to radical 192 is the same as that of phenyl radical\(^{46}\), equation 2 (Appendix A) yields rate constant \(k_c\) for ring closure of radical 192 is \(\geq 4.9 \times 10^8\) s\(^{-1}\) (80 °C) based on a minimum detection level of 2% for the reduction product. The radical 192 undergoes ring closure 77 times more rapidly than its ketonic counterpart 149. For comparison, the radicals 198 and 199 undergo ring closure with a rate of \(5.3 \times 10^7\)
$s^{-1}$ ($80 \, ^\circ C$)$^{39}$ and $4 \times 10^4 \, s^{-1}$ ($80 \, ^\circ C$)$^{91,92}$ respectively. The relatively high $k_c$ of 192 compared with that of the equivalent phenyl radical 198 may either indicate that the 1-naphthyl radical is more reactive than the phenyl radical or that $k_H$ for 192 is not identical with $k_H$ for phenyl radical, but is indeed less.

\[ \begin{array}{c}
\text{198} \\
\begin{array}{c}
\text{CN} \\
\text{CO}_2\text{Et}
\end{array}
\end{array} \quad \begin{array}{c}
\text{199} \\
\begin{array}{c}
\cdot \\
\text{CN}
\end{array}
\end{array} \]

This brief study clearly shows that ring closure of aryl radical onto the cyano group is regiospecific. Comparison of the results of 181 and 127 indicates that cyano groups are transferred more readily than acyl groups. Furthermore, the rate of $\beta$-scission of iminyl radicals is influenced by the stability of the leaving alkyl radical.
CHAPTER 3

Several examples demonstrating the ring closure of aryl radicals and allyl ethers have been reported. However, there have been only a few reports in the literature describing the corresponding cyclization of aryl radicals. A study was therefore commenced to investigate the feasibility of cyclization of aryl radicals derived from suitably substituted allyl and ethers. The main thrust of the present work was twofold. Firstly it was directed towards the determination of the role, regio- and stereoselectivity of cyclizations on suitably substituted allyl and ethers, and to investigate the electronic effect of the allyl group on the cyclization. Secondly, the work was directed towards the synthetic utility of aryl radical cyclization for the construction of molecularized polycyclic systems. It was hoped that treatment of suitable radical precursors, such as 204 (Scheme 35), with a p-butylithi hydride would provide new synthetic pathways to the tetrahydrofluorene derivatives 227 with the hydroyl group located at the ring junction.

The desired radical precursors 202 and 203 were synthesized as outlined in Scheme 35.

\[
\begin{align*}
202 & : R_1 = H, R_2 = CH_3 \\
203 & : R_1 = CH_3, R_2 = H \\
204 & : R_1 = CO_2Me, R_2 = H
\end{align*}
\]
3.1 ARYL RADICAL RING CLOSURE ONTO SILYL ENOL ETHERS

Several examples demonstrating the ring closure of alkyl radicals onto enol ethers have been reported. However there have been only a few reports in the literature describing the corresponding cyclization of aryl radicals. A study was therefore commenced to investigate the feasibility of cyclization of aryl radicals derived from suitably substituted silyl enol ethers. The main thrust of the present work was twofold. Firstly it was directed towards the determination of the rates, regio- and stereo-chemistry of aryl radical cyclizations onto suitably constituted silyl enol ethers, and to investigate the electronic effect of the silyl ether group on the cyclization. Secondly, the work was directed towards the synthetic utility of aryl radical cyclization for the construction of functionalized polycyclic systems. It was hoped that treatment of suitable radical precursors, such as 205 (Scheme 58), with tri-n-butyltin hydride would provide new synthetic pathways to the tetrahydrofluorene derivatives 227 with the hydroxyl group located at the ring junction.

The desired radical precursors 202 and 205 were synthesized as outlined in Scheme 55.
Treatment$^{99}$ of $m$-hydroxybenzoate 200 with t-butyldimethylsilyl chloride in the presence of imidazole in dimethylformamide (DMF) gave the silyl ether 201 (90%). Similar treatment of o-hydroxybenzoate 203 gave the corresponding silyl ether 204 (99%). Reductive alkylation$^{100}$ of 201 with o-bromobenzyl bromide 124 gave the bromide 202 in 42% yield. Similarly, reductive alkylation of the silyl ether 204 with o-bromobenzyl bromide 124 afforded the bromide 205 in 85% yield.

The radical precursors 208, 209, 210, and 211 were prepared by the method of Mander and Sethi$^{101}$ (Scheme 56). Reaction of the ketone$^{39}$ 206 with t-butyldimethylsilyl triflate (t-BDMST) and triethylamine in dichloromethane gave the silyl ether 208 in 97% yield. Similar treatment of the ketone$^{39}$ 207 gave the corresponding silyl ether 209 in 70% yield. Similarly the ketones 128 and 129 were converted into their silyl enol ether derivatives 210 and 211 in 97% and 75% yield respectively.

![Scheme 56](https://example.com/scheme56.png)
With radical precursors 202, 205, 208, 209, 210, and 211 in hand, it was possible to attempt ring closure by their treatment with tri-n-butyltin hydride. The radical cyclizations were conducted by heating under reflux a degassed solution of the halide [0.04M] and tri-n-butyltin hydride [0.05M] in dry benzene containing 10% molar AIBN as initiator. The reactions were followed by GC or TLC and the structures of products assigned by means of nmr spectroscopy. The behaviour of each of the radical precursors will be discussed individually.

Treatment of the bromide 202 with tri-n-butyltin hydride gave three tricyclic products (94%) in the ratio of 1.2:2:1:1 by GC analysis. These were identified after the removal of the t-butyldimethylsilyl group with 50% aqueous hydrofluoric acid solution in acetonitrile as the ketone 218 (23%), formed by ring closure onto the less substituted double bond, while the others were identified as the epimeric alcohols 219 (42%) and alcohol 220 (19%) (Scheme 57). The infrared, $^1$H nmr and $^{13}$C nmr spectra were consistent with the three proposed structures 218-220.

The structures of the $\beta$-epimer 219 and the $\alpha$-epimer 220 were assigned on the assumption that approach of tri-n-butylstannane to the intermediate radicals 214 would occur most readily from the less hindered exo-face and that the major product 219 would consequently contain the hydroxyl substituent in the orientation trans to the carbomethyl group. In support of this view, inspection of models showed that the dihedral angle subtended between the bridgehead proton and the proton adjacent to the hydroxyl group is smaller for the $\beta$-epimer 219 if the hydroxyl group adopts the pseudo equatorial position. The $^1$H nmr spectrum of the $\alpha$-epimer 220 displayed a one proton doublet centered at 3.94 ppm with a coupling constant of $J = 5.4\text{Hz}$. This signal was attributed to the bridgehead proton. On the other hand the bridgehead proton of the $\beta$-isomer 219 displayed a doublet in its $^1$H nmr spectra at 4.01 ppm with a lower coupling constant of $J = 3.9\text{Hz}$. 
Scheme 57

2.0 2  \( R_2 = \text{OSi}^+\text{BuMe}_2 \)

2.1 2  \( R_2 = \text{OSi}^+\text{BuMe}_2 \)

2.1 3  \( R_2 = \text{OSi}^+\text{BuMe}_2 \)

2.1 4  \( R_2 = \text{OSi}^+\text{BuMe}_2 \)

2.1 5  \( R_2 = \text{OSi}^+\text{BuMe}_2 \)

2.1 6  \( R_2 = \text{OSi}^+\text{BuMe}_2 \)

2.1 7  \( R_2 = \text{OSi}^+\text{BuMe}_2 \)

2.1 8  \( R_2 = \text{OSi}^+\text{BuMe}_2 \)

2.1 9  \( R_2 = \text{OSi}^+\text{BuMe}_2 \)

2.2 0  \( R_2 = \text{OSi}^+\text{BuMe}_2 \)
Similar treatment of the bromide 205 with tri-n-butyltin hydride afforded two products (91%) in the ratio of 5:1 by GC analysis. After the removal of the tert-butyldimethylsilyl group, the products were identified as the ketone 226 (61%) formed by ring closure onto the less substituted double bond and the alcohol 227 (12%) arising from the ring closure onto the more substituted double bond (Scheme 58). The infrared, $^1$H nmr and $^{13}$C nmr spectra were consistent with the proposed structures 226 and 227.

![Scheme 58](image-url)
The stereochemistry of the newly formed ring junction in each of the products arising from the ring closure of radicals $212$ and $221$ is assigned cis on the assumption that the cyclizations take place via least strained transition states and by analogy with results obtained with related ring-fused system. Recent MM2 force-field calculations by Beckwith support these results. These calculations, based on stereoelectronic consideration, show the strain energy of the transition structure for the cis ring closure to be markedly less than those for their trans counterparts.

A noteworthy feature of ring closure of the radicals $212$ and $221$ is their high regioselectivity. Each of the radicals gave exclusively products of 1,5-cyclization and no trace of 1,6-cyclization products could be detected.

The radicals $221$ and $212$ are of special interest because they allow direct determination by internal competition of the effect of substituents on the rate of ring closure. In each of these species one double bond is unsubstituted while the other bears one substituent. Although accurate kinetic measurement have not been attempted, the effect of substituents on reaction rate can be estimated from the relative yields of the cyclic products. Since the cyclized radicals are converted quantitatively into products, the ratio of their relative yields, $(\text{substituted \%) / \text{(unsubstituted \%)})$, gives the ratio of the rate constants, $k(\text{substituted}) / k(\text{unsubstituted})$. For example, the radical $221$ cyclizes five times faster onto the less substituted of the two positions available for 1,5-ring closure. On the other hand, the substituent at the remote termini of the double bond in radical $212$ (Scheme 57) increases the rate of cyclization 2.6 times.

The regioselective cyclization of the radical $221$ ($226/227 = 5$) onto the less substituted double bond is presumably because of steric hindrance by the silyloxy
group. This observation is relevant to the view that homolytic addition is retarded by substitution at the seat of attack.\textsuperscript{7b,103,104} However, the formation of 227 from 221 indicates that steric constraints of aryl radicals are relatively small compared with related alkyl radicals. For example, the radical 228a fails to undergo exo ring closure at the more substituted of the two positions available for ring closures.\textsuperscript{49,94}

![Structures 228a and 228b](image)

The observed regioselectivity in the cyclization of 212 ((219 + 220)/218 = 2.6) indicates that the silyloxy group is weakly activating towards homolytic addition. Presumably the radical 214 formed by ring closure to the substituted double bond is stabilized by interaction of the unpaired electron with the adjacent oxygen lone pair. However, structurally related alkyl radical 228b undergoes 1,5-ring closure at the two available positions at approximately equal rates\textsuperscript{94} in accord with the view\textsuperscript{7b} that the transition state energy for intramolecular homolytic addition is only marginally affected by the stability of the product radical.

Treatment of the bromide 208 with tri-\textit{n}-butyltin hydride followed by removal\textsuperscript{102} of \textit{t}-butyldimethylsilyl group with aqueous hydrofluoric acid solution afforded three products in 58\% isolated yield (Scheme 59). These were identified as the direct reduction product 235 (7\%), the 1,5-cyclization product 236 (42\%), and the 1,6- cyclization product 237 (9\%). Compounds 235, 236, and 237 displayed the expected infrared, \textsuperscript{1}H nmr and \textsuperscript{13}C nmr spectra.
Scheme 59
Similar treatment of the bromide 210 with tri-n-butyltin hydride gave two products in 85% isolated yield. Desilylation\textsuperscript{105} of the major product (62\%) with a mixture of acetic acid / water / THF afforded the alcohol 244 (97\%) arising from the initial cyclization of 239 in the exo mode (Scheme 60). The minor product (23\%), after removal\textsuperscript{102} of tert-butyldimethylsilyl group with aqueous hydrofluoric acid gave the alcohol 245 (68\%) arising from the initial cyclization of 239 in the endo mode. None of the direct reduction product could be isolated.

\textbf{Scheme 60}
The formation of 237 from 229 (Scheme 59) and 245 from 239 (Scheme 60) proceeds by endo ring closure and involves the attack of the aryl radical at the less substituted carbon atom. The endo cyclized radicals 230 and 241 then undergo hydrogen atom abstraction from tri-\textit{n}-butyltin hydride. In spite of the expectation that hydrogen atom transfer from stannane would take place on either face of the radicals 230 and 241 and would lead to diastereomers, each of the radicals, 230 and 241 gave a single product, 234 and 243. This is probably due to steric reasons, the approach of stannane to transfer hydrogen takes place only at the less hindered face of the radicals 230 and 241. Although the $^1$H and $^{13}$C nmr spectrum of 237 and 245 were consistent with the main structures, they offered no clue to their stereochemistry, and consequently the stereochemistry of 237 and 245 remained undefined.

Although exo ring closure of the radicals 229 to give 236 and 239 to give 244 is still preferred, the formation of 237 from 229 and 245 from 239 is a significant process. This is presumably because of steric hindrance by silyloxy group the exo ring closure is slightly disfavoured. On the other hand, the endo cyclization radicals 230 and 241 are undoubtedly stabilized by interaction of the unpaired electron with the adjacent oxygen lone pair.

The failure of the radical 239 to give uncyclized product compared to 229 presumably reflects the fact that naphthalene at the 1-position is more reactive than benzene toward homolytic attack. The other possible explanation is that, the rate of hydrogen atom transfer from stannane to the naphthyl radical 239 may be slower than hydrogen atom transfer to the phenyl radical 229.

Solution of the integrated rate equation 2 (Appendix A) for the results obtained from the reactions of 208 with tri-\textit{n}-butyltin hydride gave a lower limit for
\( k_c \) to be \( > 5.1 \times 10^8 \text{ s}^{-1} \) for the ring closure of the radical 229 at 80 °C based on minimum detection level of 2% for the reduction product. Similarly the results obtained from the reaction of 210 with tri-n-butyltin hydride lead to a lower limit for \( k_c \) to be \( > 1.3 \times 10^8 \text{ s}^{-1} \) for the ring closure of 239 at 80 °C based on minimum detection level of 2% for the reduction product. These rate constants are subject to error since the calculations are based upon isolated yields. However, these results clearly indicates that silyl enol ethers undergo ring closure more readily than their ketone equivalents described in chapter 2 and elsewhere.\(^{39}\)

Treatment of the bromide 209 or 211 with tri-n-butyltin hydride [0.05M] in boiling benzene gave inseparable mixture of a number of products. Attempts to separate and identify the products failed as the mixtures isolated before or after attempted desilylation did not afford any discrete products. Presumably the problem encountered in separating and identifying the product mixtures from the reaction of 209 or 211 with stannane is due to the possible competing reaction pathways such as, 1,5-hydrogen atom abstraction, 1,5- and 1,6-ring closures, that the substrates (209, 211) are capable to undergo eventually leading to a number of products.
3.2 ARYL RADICAL RING CLOSURE ONTO THE N-TERMINUS OF AN ENAMINE AND ENAMIDE DOUBLE BOND

The utility of alkyl radical cyclization for the formation of nitrogen containing heterocyclic systems has been studied in recent years. However, relatively little attention has been given to the cyclization of aryl radicals. A brief study was therefore undertaken to examine the synthetic feasibility of aryl radical ring closure onto suitably constituted enamine or enamide double bonds. It was hoped that ring closure of species such as radical might provide further insights for the construction of nitrogen-containing polycyclic systems. Precedence for the viability of a cyclization of this type was provided by the work of Yamaguchi, who reported successful cyclization of radical (Scheme 61).

Apart from synthetic interest, the cyclization of radical such as is of interest from a mechanistic viewpoint. As the nitrogen is directly attached to the double bond in radical the electronic properties of the double bond might be markedly influenced by the heteroatom. The effect this alteration in the electronic character of the alkene has on the course of cyclization would provide further information on the factors controlling intramolecular radical additions.
The required radical precursors 250 and 252 were prepared as outlined in Scheme 62. Thus, reduction of methyl nicotinate 248 with hydrogen over 5% palladium/charcoal by the method of Wenkert et al.\textsuperscript{122} gave the tetrahydropyridine 249. Alkylation of 249 with 1-bromo-2-bromomethynaphthalene 68 yielded the bromide 250 (73%). Alkylation of 2-pyridone 251 with 1-bromo-2-bromomethynaphthalene 68 afforded the bromide 252 in 87% yield.

\[
\begin{align*}
\text{H}_3\text{CO}_2\text{C} & \quad \text{NaH/DMF} \\
\text{Br} & \quad \text{H}_2\text{CBr}
\end{align*}
\]

Scheme 62

Treatment of the bromide 250 with tri-\textit{n}-butyltin hydride [0.05M] in boiling benzene afforded three products in a total yield of 72%. These were identified as the reduction product 257 (9%) and the two diastereoisomers 258 (18%) and 259 (45%) as shown in Scheme 63.
The stereochemistry of the newly formed ring-junction of the cyclic products 258 and 259 appeared to be trans on the basis of their infrared spectra which exhibited Bohlmann bands\textsuperscript{123,124} at 2780 cm\textsuperscript{-1}. These bands are observed when two or more carbon-hydrogen bonds bear a trans-diaxial relationship to a nitrogen lone pair, and are diagnostic in this case for a trans-ring fusion.\textsuperscript{124,125}

Scheme 63
Previous reports indicate that alkyl, and aryl radical cyclizations leading to fused carbocyclic compounds usually afford cis-fused products. These arise because the transition structure leading to cis-fused products is significantly lower in energy than the transition structures for trans-fusion for steric and stereoelectronic reasons. However, the observed trans stereochemistry of the ring junction in each of the cyclic products 258 and 259 was not unexpected, due to the possibility of nitrogen inversion; the initially formed cis-fused radical rapidly isomerizes to the more stable trans-fused radical. For example, in simple fused indolizidines, the trans isomer is known to be some 2.4 kcal mol \(^{-1}\) more stable than the cis isomer. Hence the cyclization products 258 and 259 are epimeric only with respect to the orientation of the methoxycarbonyl group. The orientation of the carbomethoxy group in 258 and 259 was assigned on the assumption that approach of tri-n-butyltin hydride to the intermediate radical 255 would occur more readily from the less hindered, exo-face, and that the major product 259 would consequently contain the substituent on the six membered ring in the orientation syn to the fused ring.

Recent studies shows that intramolecular addition of alkyl, and aryl radical to cyclic vinylogous urethanes results in the formation of trans-fused ring junction. For example, cyclization of an aryl radical derived from the bromide 260 affords the benzo-fused 261 and 262 with a trans stereochemistry at the newly formed ring junction (Scheme 64). The orientation of the methoxycarbonyl substituent on the six membered ring in the major product 261 was found to be syn to the fused ring consistent with our observations.

Scheme 64
The reduction product 257 can be formed either by direct stannane reduction of the radical 253 or by 1.5-hydrogen atom transfer followed by reduction of the rearranged radical 254. In this case, 1.5-hydrogen atom transfer results in the formation of a secondary alkyl radical stabilized by an adjacent nitrogen atom. Since the relative proportions of 257 formed by direct reduction of 253 and via 1.5-hydrogen atom transfer cannot be determined accurately from the present data, it is not possible to obtain accurate rate constants for the ring closure step. However, if it is assumed that most of the reduction product arises from the direct reduction of radical 253 by stannane, then the rate constant for the ring closure of radical 253 can be estimated to be about $4.9 \times 10^7$ s$^{-1}$ at 80 °C from the rate equation 2 (Appendix A). Thus radical 253 undergoes exo ring closure 7.5 times slower than the 2-(3-butenyl)phenyl radical ($k_c = 3.7 \times 10^8$ s$^{-1}$ at 80 °C)$^{53}$ and 18.4 times slower than 2-(3-butenyl)naphthyl radical ($k_c = 9 \times 10^8$ s$^{-1}$ at 80 °C).$^{53}$ Thus it appears that the electron donating nitrogen atom in the radical 253 completely counteracts the usual activating effect of the ester group.$^{2,50}$

Reaction of the bromide 252 with tri-n-butyltin hydride [0.05M] in boiling benzene afforded two products, identified as the direct reduction product 266 (11%) and the exo cyclization product 267 in 79% yield (Scheme 65).

The infrared spectrum of the cyclic product 267 showed a Bohlmann bond at 2860 cm$^{-1}$ which indicates a trans-fused ring junction. The approximate rate constant for exo cyclization of radical 263 can be estimated to be $5 \times 10^7$ s$^{-1}$ at 80 °C, from the integrated rate equation 2 (Appendix A).
Although a limited number of examples have been examined, they are sufficiently representative to permit a few generalizations. Intramolecular addition of an aryl radical onto the N-terminus of an enamine or enamide double bond is regiospecific and affords a viable synthetic method. The regiospecificity of the processes 253 → 255 (Scheme 63) and 263 → 264 (Scheme 65) are especially noteworthy, for in these cases, the alternative mode of ring closure would afford the secondary radicals 256 and 264 which are stabilized by conjugation of the free electron with the lone pair in the adjacent nitrogen atom. However, the direct interaction of the nitrogen atom with the double bond changes the electronic character of the double bond such that the cyclization is not as efficient as the all carbon analogue.
CHAPTER 4

The stereochemical course of cyclization of substituted benzyl radicals has been widely studied\textsuperscript{70,120-123} and general guidelines with considerable predictive power have been put forth by Doak and coworkers.\textsuperscript{124} The guidelines state that 1- or 2-substituted benzyl radicals cyclize to give preferentially cis disubstituted products while the 3- or 4-substituted radicals give mainly the trans products (Scheme 66).

The behavior reflects the fact that the exo benzyl transition structure resembles the chair form of cyclohexane. Thus, the exo structure containing pseudo-equatorial substituents should be more stable than those with pseudo-axial substituents. An exo transition structure bearing a pseudo-equatorial substituent at position 1 or 2 yields a cis disubstituted product. Likewise, an exo transition structure with pseudo-equatorial substituent at positions 3 or 4 affords trans disubstituted product. Recently, Dearnley\textsuperscript{124,125} and Hanks\textsuperscript{126} used force field calculations to determine the steric energies of cyclohexane-like transition structures and observed a remarkable qualitative agreement between theory and experiment for ring closure of substituted benzyl radicals.
THE STEREOCHEMISTRY OF C(3)- AND C(4)-SUBSTITUTED ALKENYLARYL RADICAL CYCLIZATIONS

The stereochemical outcome of cyclization of substituted hexenyl radicals has been widely studied\textsuperscript{7b,129-131} and general guidelines with considerable predictive power have been put forth by Beckwith.\textsuperscript{132} The guidelines state that 1- or 3-substituted hexenyl radicals cyclize to give preferentially cis disubstituted products while the 2- or 4-substituted radicals give mainly the trans products (Scheme 66). Beckwith and co-workers\textsuperscript{7b,131} suggested that this behavior reflects the fact that the exo hexenyl transition structure resembles the chair form of cyclohexane. Thus, the exo structure containing pseudo-equatorial substituents should be more stable than those with pseudo axial substituents. An exo transition structure bearing a pseudo-equatorial substituent at position 1 or 3 yields a cis disubstituted product. Likewise, an exo transition structure with pseudo-equatorial substituent at positions 2 or 4 affords trans disubstituted product. Recently, Beckwith\textsuperscript{47,133} and Houk\textsuperscript{134} used force field calculations to determine the strain energies of cyclohexane-like transition structures and observed a remarkable qualitative agreement between theory and experiment for ring closure of substituted hexenyl radicals.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.4\textwidth]{scheme_66.png}};
\node at (3.5,0) {cis > trans};
\node at (0,-3) {\includegraphics[width=0.4\textwidth]{scheme_67.png}};
\node at (3.5,-3) {trans \textgreater} cis;
\end{tikzpicture}
\end{center}

Scheme 66
Unlike their alkenyl counterparts, there have been no studies involving the stereochemistry of cyclization of suitably substituted alkenylaryl radicals. It was envisaged that cyclization of an alkenylaryl radical bearing a substituent on the alkenyl side chain might also be stereoselective and conform to Beckwith’s guidelines. However, the presence of the aryl ring necessarily requires the transition structure to adopt a cyclohexenyl-like conformation and it seemed possible that this might cause a significant departure from the behaviour exhibited by simple substituted alkenyl radicals. It was decided, therefore, to examine the stereochemical outcome of the ring closure of various substituted alkenylaryl radicals.

The various free radical precursors 270, 272, 273, 274, 277, and 280 employed in this study were prepared from readily available starting materials. The bromo compounds 270, 272, and 273 were prepared as outlined in Scheme 67.

\[
\begin{align*}
\text{268} & \xrightarrow{\text{MeOH/H}^+} \text{269} & \text{LDA/THF} & \xrightarrow{\text{Br}} \text{270} \\
\text{273} & \xrightarrow{\text{NaBH(OCH₃)₃/HMPA}} \text{272} & \xrightarrow{\text{1.(CF₃CO)₂O/2.2Li}} \text{271} \\
\end{align*}
\]

Scheme 67

\(\sigma\)-Bromophenylacetic acid 268 was converted into its methyl ester 269 by treatment with sulphuric acid in methanol. Alkylation of the enolate ion generated
from 269 by lithium diisopropylamine (LDA) at -75 °C with 3-bromopropene afforded the bromoester 270 in virtually quantitative yield. Lithium aluminum hydride reduction of 270 yielded alcohol 271. Reaction of 271 with trifluoroacetic anhydride followed by lithium iodide according to the procedure of Camps135 gave iodide 272 in 44% yield. Reduction of 272 with sodium trimethoxyborohydride in HMPA/THF following the method of Hutchins et al136 afforded the desired radical precursor 273 (54%).

Treatment of 270 with a 2-fold excess of methylmagnesium iodide (derived from methyl iodide and magnesium metal) gave the bromo alcohol 274 in quantitative yield (Scheme 68).

![Scheme 68](image)

The bromo compounds 277 and 280 were prepared as outlined in Scheme 69. Vinylacetic acid was converted to the desired ester 276 by treatment with thionyl chloride followed by methanol according to the literature procedure.137 Alkylation of the enolate ion generated by treatment of ester 276 with LDA/THF/HMPA with benzyl bromide124 following the procedure of Cerfontain et al138 afforded the bromo ester 277 (81%). The same sequence of reactions described above gave 278, 279, and 280.
Treatment of the bromide 273 with a slight molar excess of tri-n-butyltin hydride [0.05M] and AIBN as initiator in boiling benzene afforded a mixture of two products identified as cis-1,3-dimethyl-2,3-dihydro-1H-indene 282 (68%) and its trans isomer 283 (32%) in 92% isolated yield (Scheme 70). Product ratios were determined by GC analysis.

The products were identified by $^1$H nmr and $^{13}$C nmr spectral analysis of the product mixtures. The $^1$H nmr of the minor product 283, showed that the
methylene protons were equivalent and absorbed at δ 1.89 (t, J = 6.7Hz, 2H), whereas the methylene protons in the major product 282 were non-equivalent and absorbed at δ 1.10 (m, 1H) and 2.48 (m, 1H) in agreement with literature data for cis- and trans-1,3-dimethylindan. The 13C nmr spectral analysis of the product mixture also revealed two distinct sets of signals. The major set with δ 19.36, 38.11, 45.06, 122.78, 126.17 and 148.48, is in excellent agreement with literature values reported for cis-1,3-dimethyl-2,3-dihydro-1H-indene.

When the reaction of 273 with tri-n-butyltin hydride [0.05M] was repeated at 5 °C with UV initiation a cis/trans ratio of 2.8 was observed by GC and 1H nmr analysis of the product mixtures. Since no uncyclized product could be detected by 1H nmr or GC, it is clear that the cyclization of 281 is so fast that hydrogen atom transfer from tri-n-butyltin hydride cannot effectively compete with it. Solution of the integrated rate equation 2 (Appendix A) for the results obtained from the reaction of 273 with tri-n-butyltin hydride gave, after multiplication by the appropriate value of kH, a lower limit for k (cis + trans) to be > 4.7 x 10^8 s^-1 for exo ring closure of 281 at 80 °C based on a minimum detection level of 2% for the unrearranged product.

Similar treatment of 272 with 2.4 equivalent of tri-n-butyltin hydride (AIBN initiator) in boiling benzene at an initial concentration of 0.05M also afforded cis- and trans- 1,3-dimethyl-2,3-dihydro-1H-indene (282 (67%), 283 (33%)) in 97% isolated yield (Scheme 71). The products were identified by 1H nmr and 13C nmr analysis and by comparison of gas chromatographic retention times with these of the product mixtures obtained from the cyclization of 273.

When the reaction of 272 was repeated at 5 °C, with 2.4 equivalents of tri-n-butyltin hydride [0.05M] and UV initiation a cis/trans ratio of 2.7 was obtained and again no direct reduction product could be detected.
These results clearly show that the cyclization of 281* (281* signifies the radical 281 which has been generated from precursor 272) is a fast process. Since there are two independent reaction sites in compound 272 which compete for stannyl radicals and the rate constants for the halide abstraction from aryl halides by stannyl radicals have not been determined, it is necessary to make the following assumptions to obtain the rate constant for ring closure of 281*. It is known that stannyl radicals abstract iodide from alkyl iodides approximately 100 times more rapidly than from corresponding bromides.\textsuperscript{8a,64} Also, it is known that alkyl bromides are more reactive with stannyl radical than aryl bromides.\textsuperscript{80,81} Hence, a vast difference in reactivity between aryl bromides and alkyl iodides is expected. Therefore, it is safe to assume that alkyl iodides react at a faster rate with tributyltin radicals than aryl bromides and in this case the reaction takes place first at the iodide site and it is possible to estimate the rate constant for cyclization of 281*. Thus lower limit for the cyclization rate constant for the radical cyclization of 281* is estimated to be >
$3.2 \times 10^8 \text{ s}^{-1}$ at $80^\circ \text{C}$ from the integrated rate equation 2 (Appendix A) based on a minimum detection level of 2% for the reduction product.

Treatment of the bromo ester 270 with a slight molar excess of tri-n-butyltin hydride [0.05M] in benzene at $80^\circ \text{C}$ yielded two products identified as cis-methyl 3-methyl-2,3-dihydro-1H-indene-1-carboxylate 285 (58%), and its trans isomer 286 (42%) in 98% isolated yield (Scheme 72).

![Scheme 72](image)

The stereochemistry of 285 and 286 was established by $^1\text{H}$ nmr spectra analysis of the product mixtures (Table 9).

**Table 9** $^1\text{H}$ nmr (CDCl$_3$) assignments for cis and trans-methyl 3-methyl-2,3-dihydro-1H-indene-1-carboxylate.

<table>
<thead>
<tr>
<th>Proton No.</th>
<th>285</th>
<th>286</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.35.d,J = 6.9Hz</td>
<td>1.28.d,J = 7.0Hz</td>
</tr>
<tr>
<td>2</td>
<td>1.96.dt,J = 12.7.9.6.9.6Hz</td>
<td>1.86.ddd,J = 12.7.8.4.7.3Hz</td>
</tr>
<tr>
<td>3</td>
<td>2.56.dt,J = 12.7.7.7.7.7Hz</td>
<td>2.67.ddd,J = 12.7.7.5.3.9Hz</td>
</tr>
<tr>
<td>4</td>
<td>3.20.sextet,J ~ 7.8Hz</td>
<td>3.45.sextet,J ~ 7.5Hz</td>
</tr>
<tr>
<td>5</td>
<td>3.76.s</td>
<td>3.68.s</td>
</tr>
<tr>
<td>6</td>
<td>4.00.dd,J = 9.6.7.7Hz</td>
<td>4.05.dd,J = 8.4.3.4Hz</td>
</tr>
<tr>
<td>ArH</td>
<td>7.1-7.4.m</td>
<td>7.1-7.4.m</td>
</tr>
</tbody>
</table>
In the major product **285** the methylene proton 2, centered at δ 1.96, is strongly coupled to the two vicinal protons 4 and 6 ($J_{2,4} = J_{2,6} = 9.6$ Hz). The other methylene proton 3 at δ 2.56 is coupled to the two vicinal protons 4 and 6 ($J_{3,4} = J_{3,6} = 7.7$ Hz) with a smaller coupling constant as compared with the observed vicinal couplings of 4 and 6 to proton 2. On the basis that $J_{\text{syn}} > J_{\text{anti}}$, proton 2, which demonstrated larger couplings to 4 and 6 than proton 3, is syn to 4 and 6. Conversely, proton 3 is anti to 4 and 6. Hence, the methyl and the ester substituent in **285** are cis to each other. In the minor product **286** a vicinal coupling constant of 8.4 Hz observed for protons 2 and 6 is greater than the vicinal coupling constant of 7.3 Hz observed for proton 2 and 4. This indicates that proton 2 is syn to proton 6 and anti to proton 4. Similarly $J_{3,6}$ (3.4 Hz) indicates that proton 3 is syn to proton 4 and anti to proton 6. Hence, it can be concluded that the methyl and ester substituents in **286** are trans to each other. A similar approach has been used by Tsybin et al.\textsuperscript{141} to establish the stereochemistry of 1,3-disubstituted indans.

When the reaction of **270** with tri-n-butyltin hydride [0.05M] was repeated at 5 °C with UV initiation three products were detected by gas chromatography. These were identified as cis-methyl 3-methyl-2,3-dihydro-1H-indene-1-carboxylate **285** (58%), its trans isomer **286** (29%) and the product of direct reduction **289** (13%).
An authentic sample of 289 was prepared by esterification of phenylacetic acid 287 to afford methyl 2-phenylacetate 288 which was then converted into 289 by treatment with LDA in THF followed by 3-bromopropene as outlined in Scheme 73.

![Scheme 73](image)

The small difference between the cis/trans ratio at 5 °C (2.0) and 80 °C (1.4) indicates that the activation parameters of the two cyclization routes are similar.

The results obtained from the reaction of 270 with stannane lead, by the application of the appropriate integrated rate equation 2 (Appendix A) and using the known value of \( k_8 \), to a lower limit for the cyclization rate constant for ring closure of 281 to be \( > 5 \times 10^8 \text{ s}^{-1} \) at 80 °C based on minimum detection level of 2% for the reduction product.

Treatment of the bromo alcohol 274 with a slight molar excess of tri-n-butyltin hydride [0.05M] in benzene at 80 °C yielded two products detected by gas chromatographic analysis in the ratio of 1:2.7. The products were identified as cis-2-(3-methyl-2,3-dihydro-1-indenyl)propan-2-ol 291 (27%), and its trans isomer 292 (73%) as outlined in Scheme 74.

Direct identification of the products 291 and 292 proved to be very difficult, since they could not be separated by fraction crystallization nor could signals of interest be resolved by \(^1\text{H} \text{nmr spectroscopy.} \)
The $^{13}$C nmr spectrum of the product mixture showed two distinct sets of lines. The major set showed resonance at $\delta$ 20.7, 26.3, 28.2, 37.7, 38.1, 55.0, 73.8, 123.3, 125.9, 126.2, 126.9, 143.2, and 149.2 ppm. The minor isomer absorbed at $\delta$ 19.4, 24.6, 30.0, 37.3, 38.4, 55.2, 73.4, 122.8, 125.8, 125.9, 126.3, 143.6, and 149.2 ppm, but these did not provide useful structural information.

Unlike cyclohexane derivatives, where shielding effects are readily recognizable due to the clearly defined axial and equatorial positioning of groups, cyclopentane derivatives do not allow clear spectral interpretation as the 5-membered ring is much flatter than the 6-membered ring. Unambiguous identification of the two products was readily achieved by the comparison of gas chromatographic retention times with those of an authentic mixture of 291 and 292 obtained by an alternative route as shown in Scheme 75.
Treatment of a 58:42 mixture of esters 285 and 286 with methylmagnesium iodide yielded a mixture of the alcohols 291 and 292. Gas chromatographic analysis of the mixture confirmed that the original isomer ratio of 58:42 had been retained. Thus, comparison of gas chromatographic retention times and $^{13}$C nmr of this known mixture with that obtained from the cyclization of 274 revealed that the major cyclization product was the trans isomer 292.

The failure of the reaction of 274 with tri-$n$-butyltin hydride to afford uncyclized product indicates that hydrogen atom transfer from stannane to 290 can not compete with its rapid cyclization. Although an accurate rate constant for the cyclization can not be obtained from the present data, lower limit for the cyclization rate constant for ring closure of radical 290 was found to be $> 4.6 \times 10^{8}$ s$^{-1}$ at 80 °C from the integrated rate equation 2 (Appendix A) based on minimum detection level of 2% for the reduction product.

When the bromo compound 280 was treated with tri-$n$-butyltin hydride [0.05M] in benzene (AIBN initiator) at 80 °C, three products were detected by GC. These were identified as cis-1,2-dimethyl-2,3-dihydro-1H-indene 294 (20%), its trans isomer 295 (73%), and the endo product 2-methyl-1,2,3,4-tetrahydronaphthalene 296 (7%), as illustrated in Scheme 76. The products were identified by $^1$H nmr and gas chromatographic retention times comparison with authentic samples of 294 and 296 prepared by an alternative route.

Since no direct reduction product was detected, the cyclization of 293 is clearly a very fast process. Application of the appropriate integrated rate equation 2 (Appendix A) in conjunction with a known$^{46}$ value of $k_H$ gives a lower limit for a cyclization rate constant for ring closure of 293 to be $> 4.5 \times 10^8$ s$^{-1}$ at 80 °C.
An authentic sample of 294 was prepared as depicted in Scheme 77. Conversion of 3-methyl-1H-indene-2-carboxylic acid 297 into its methyl ester derivative by treating with sulphuric acid in methanol, followed by hydrogenation with hydrogen over a palladium catalyst, afforded ester 299 (83%). Analytical GC showed ester 299 to be homogenous. Ester 299 was reduced to alcohol 300 (87%) with lithium aluminum hydride. Treatment of 300 with trifluoroacetic anhydride and lithium bromide following the procedure of Camps gave the bromide 301. Reduction of 301 with tri-n-butyltin hydride yielded cis-1,2-dimethyl-2,3-dihydro-1H-indene 294, which was shown to be homogenous by GC analysis.

The preparation of authentic sample of the endo cyclization product 296 is outlined in Scheme 78. Reaction of 1,2,3,4-tetrahydro-2-naphthoic acid 302 with sulphuric acid in methanol afforded ester 303, which was then converted to 2-methyl-1,2,3,4-tetrahydronaphthalene 296 in three steps following the procedure described above for the preparation of 294.
Scheme 77

Since the reaction of 280 with tri-n-butyltin hydride gave a significant amount of the endo product 296 (7%), further information was required to elucidate the mechanism for its formation. Examples have been reported for the formation of endo cyclopropanes 302 (4.29%) and the direct reaction product 303 (9.3%) as depicted in Scheme 78.
endo products both by direct\textsuperscript{12} endo ring closure and by neophyl rearrangement of the initially formed exo radical.\textsuperscript{53} Information about the route to the endo product 296 was obtained by carrying out a series of experiments in which the concentration of tri-n-butyltin hydride was varied (Table 1). The usual steady state approach to the kinetics of the steps in Scheme 76 shows that if the exo and endo products are generated solely by direct 1,5- and 1,6-cyclizations, respectively, then the ratio of those products \((294 + 295) / 296\) should be independent of stannane concentration. The data presented in Table 10 for the reaction of 280 with tri-n-butyltin hydride clearly show that the ratio of the products \((294 + 295) / 296\) at a fixed temperature is independent of stannane concentration, thus indicating that the product 296 is formed by direct \textit{endo} cyclization of radical 293.

Table 10 Reaction of 280 with tri-n-butyltin hydride\textsuperscript{a}

<table>
<thead>
<tr>
<th>temp, °C</th>
<th>(S_0) b,M</th>
<th>((294 + 295)/296)</th>
<th>trans/cis\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>.05</td>
<td>18.10</td>
<td>4.10</td>
</tr>
<tr>
<td>40</td>
<td>.1</td>
<td>17.96</td>
<td>4.20</td>
</tr>
<tr>
<td>80</td>
<td>.05</td>
<td>12.90</td>
<td>3.60</td>
</tr>
<tr>
<td>80</td>
<td>.1</td>
<td>13.20</td>
<td>3.60</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All reactions in benzene solution. \textsuperscript{b}Initial concentration of Bu\textsubscript{3}SnH: the final concentration of Bu\textsubscript{3}SnH was zero in each case. \textsuperscript{c}As determined by GC.

When the bromoester 277 was treated with a slight molar excess of tri-n-butyltin hydride [0.05M] in benzene in the presence of AIBN at 80 °C, four products were detected by GC. These were identified as \textit{cis}-methyl 3-methyl-2,3-dihydro-1H-indene-2-carboxylate 299 (11%) and its trans isomer 307 (78%), the endo cyclization product 303 (9%), and the direct reduction product 308 (2%) as depicted in Scheme 79.
The products were identified by $^1$H nmr and by comparison of their GC retention times with those of authentic samples prepared by different routes. Preparation of the cis isomer 299 and the endo product 303 has been described above (Scheme 77 and 78). The directly reduced product 309 was prepared by the alkylation of the enolate ion of ester 276 with benzyl bromide as depicted in Scheme 80.
When the reaction of 277 was repeated at 5 °C using tri-n-butyltin hydride [0.05M] and UV initiation the product distribution was found by GC to be 299 (8%), 307 (83%), 303 (5%), and 308 (4%).

The results obtained for the reaction of 277 with tri-n-butyltin hydride at 80 °C lead to the application of the appropriate integrated rate equation 2 (Appendix A) in conjunction with the known value of $k_H$ to a total (exo + endo) cyclization rate constant of $4.8 \times 10^8$ s$^{-1}$ for the ring closure of radical 306. The exo and endo cyclization rate constants are found to be $4.3 \times 10^8$ s$^{-1}$ and $4.4 \times 10^7$ s$^{-1}$ at 80 °C, respectively.

The cyclization of 277 like 280 also gave a significant amount of endo cyclized product 303 (9% at 80 °C and 5% at 5 °C). However, the experimental results at hand do not allow us to conclude whether 303 is formed by direct 1,6-cyclization or by neophyl rearrangement of the initially formed exo cyclized radical. Hence, the detailed mechanism for its formation requires further investigation.

The results of the cyclization of substituted alkenylaryl radicals studied 281, 281*, 284, 290, 293, and 306 are summarized in Table 11. Inspection of Table 11 reveals several notable features of the radicals studied.

The radicals with substituents at C(3) (for all substituted radicals here the carbon are numbered on the basis of hexenyl radical system i.e., from the radical center C(1)) 281, 281*, 284 conform to the guideline put forth by Beckwith for ring closure of substituted hexenyl radicals. However, the stereoselectivity observed is slightly less than that observed for the simple substituted alkenyl radical($^{130}$) 309 (cis/trans = 2.6 at 80 °C). This is not unexpected, as the transition state structure of alkenyl radical cyclization is cyclohexane-like with a marked difference between the pseudo-axial and pseudo-equatorial bonds. In alkenylaryl radicals the transition
Table 11. Cyclization of substituted alkenylaryl radicals in tri-n-butyltin hydride\textsuperscript{a} and product distribution.\textsuperscript{b}

<table>
<thead>
<tr>
<th>radicals</th>
<th>temp. °C</th>
<th>( ^{b})relative yield</th>
<th>cis/trans ratio</th>
<th>( ^{c})total yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>reduced</td>
<td>cis</td>
<td>trans</td>
</tr>
<tr>
<td>( ^{281} )</td>
<td>80</td>
<td>68</td>
<td>32</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>74</td>
<td>26</td>
<td>2.8</td>
</tr>
<tr>
<td>( ^{281} \ast )</td>
<td>80</td>
<td>67</td>
<td>33</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>73</td>
<td>27</td>
<td>2.7</td>
</tr>
<tr>
<td>( ^{284} )</td>
<td>80</td>
<td>58</td>
<td>42</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>13</td>
<td>58</td>
<td>2.0</td>
</tr>
<tr>
<td>( ^{290} )</td>
<td>80</td>
<td>27</td>
<td>73</td>
<td>1/2.7</td>
</tr>
<tr>
<td>( ^{293} )</td>
<td>80</td>
<td>20</td>
<td>73</td>
<td>1/3.7</td>
</tr>
<tr>
<td>( ^{306} )</td>
<td>80</td>
<td>2</td>
<td>11</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4</td>
<td>8</td>
<td>83</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Stannane reactions were carried out in benzene. substrate = 0.04M. \textsuperscript{b}Bu\textsubscript{3}SnH = 0.05M. AIBN = 5% molar equivalent. \textsuperscript{b}Cis/trans ratios and relative product distribution determined by GC. \textsuperscript{c}Isolated yield. \( ^{281} \ast \) signifies the radical \( ^{281} \) which has been generated from precursor \( ^{272} \).
state structure is cyclohexene-like with little difference between the pseudo-axial and pseudo-equatorial bonds. As a result lower stereoselectivity is expected for alkenylaryl radical cyclizations. The observed stereoselectivity clearly supports this assumption.

Radical 290 does not conform to the guideline.\textsuperscript{132} Thus, while preferential formation of the cis isomer was predicted according to the guideline, the experiment showed the trans isomer to be the major product. Inspection of models for the conformer leading to the cis isomer reveal an unfavourable interaction between the bulky substituent and the hydrogen on the aromatic ring at C(3). The conformer leading to the trans isomer suffers from no such interaction. There is a monotonic decrease in the cis/trans ratio observed for the radicals 281, 284, and 290 at 80 °C. These results presumably indicate that the interaction between the substituent and the proton at C(3) of the ring, which disfavours the conformer leading to the cis isomer, becomes more severe as the steric bulk of the substituents increases.

Radicals 293 and 306 bearing a substituent at C(4) on the alkyl side chain cyclized preferentially in the trans mode as predicted.\textsuperscript{132} However, the observed stereoselectivity for radical 293 is less than that observed for the analogous methyl substituted alkyl radical 310\textsuperscript{130} (trans/cis = 4.9) at 80 °C in accord with the explanation given above. The observed stereoselectivity is more pronounced for the ester substituted radical 306 which showed a trans/cis ratio of 7.1 at 80 °C and 10.4 at 5 °C. This enhanced stereoselectivity is presumably due to the difference in the steric bulk of the substituents. Since the degree of stereoselectivity reflects the conformational preference of the substituents in the transition structure, it is likely to be more pronounced for systems containing bulky substituents. For example, the substituted peroxy radical 311\textsuperscript{143} undergoes ring closure to afford exclusively the cis product (Scheme 81). Recent studies by Beckwith\textsuperscript{144} also show that the
stereoselectivity (cis/trans) increases from 2.6 for the methyl substituted radical 309 to 4 for the t-butyl substituted radical 312 at 80 °C. The difference in stereoselectivity of 309 and 312 is attributed to the difference in the bulk of the substituents.

![Diagram](attachment:diagram.png)

Scheme 81

Unlike the C(3) substituted radicals, the C(4) substituted radicals 293 and 306 gave products arising from both exo and endo modes of cyclization. The observed exo/endo ratios for radicals 293 and 306 are 13.3 and 9.9 at 80 °C, respectively. Previous studies show that the analogous unsubstituted 2-(but-3-enyl)phenyl radical12 undergoes ring closure giving rise to both exo and endo cyclization products in the ratio of 20:1 with a cyclization rate constants of $k_{\text{exo}} = 3.7 \times 10^8 \text{ s}^{-1}$ and $k_{\text{endo}} = 1.8 \times 10^7 \text{ s}^{-1}$ at 80 °C.53 Examination of the individual rate constants for radical 306 is enhanced by a factor of 1.2 whereas the rate of endo ring closure is enhanced by a factor of 2.4. The rate enhancement observed for radical 306 may reasonably attributed to the "gem-dialkyl" effect of the substituents.
first proposed by Allinger and Zalkow. In terms of the explanation advanced by Allinger and Zalkow, substituents causes extra gauche interactions in the ground state which are partly relieved when the cyclic transition state is attained. The net result is that the ground state energy of the reactant is raised relative to that of the cyclic transition state and the rate of ring closure is enhanced accordingly.

Except radical 306 only lower limits could be estimated for the rates of the ring closure because the yields of the unrearranged products were below detection limits (< 2%). However, it is clear that these reactions are relatively fast and perhaps similar in magnitude to those of unsubstituted alkenylaryl radicals.

In light of the recent application of the MM2 force field calculations to rationalize the stereo- and regio-chemical outcome of free radical cyclizations by Beckwith and Schiesser, it was of interest to see if the method could also be used to predict the stereochemical outcome of the ring closure of substituted alkenylaryl radicals. Thus, MM2 calculations were carried out on the reactions in Table 1. In this study, for each of the radicals studied the geometry of the intimate array of reactive centres, for both the cis and trans exo-transition states, were held as described by Beckwith and Schiesser. It was also assumed that the intimate array of the reactive centres for both the cis and trans transition structures were the same in each system. The dimensions employed in this study were: C(1) - C(5), 2.25 Å; C(5) - C(6), 1.38 Å; < C(1) C(5) C(6), 98°.

Typical transition structures are shown in Figure 1. The figure clearly display the pseudo-equatorial and pseudo-axial positioning of the methyl group in the two conformationally distinct exo transition structures for the cyclization of radicals 281.
The data in Table 12 compares the calculated transition state strain energies for the cis and trans modes of cyclization of the radicals with the experimental data.

Table 12  Comparison between transition structure strain energies,\(^a\) and experimental cis/trans ratio\(^b\) for ring closure of substituted alkenylaryl radicals.

<table>
<thead>
<tr>
<th>Radicals</th>
<th>Transition state strain energy</th>
<th>cis/trans ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cis</td>
<td>trans</td>
</tr>
<tr>
<td>281</td>
<td>14.089</td>
<td>14.157</td>
</tr>
<tr>
<td>284</td>
<td>18.216</td>
<td>18.223</td>
</tr>
<tr>
<td>313</td>
<td>21.099</td>
<td>20.675</td>
</tr>
<tr>
<td>293</td>
<td>15.776</td>
<td>13.399</td>
</tr>
<tr>
<td>306</td>
<td>19.16</td>
<td>17.853</td>
</tr>
<tr>
<td>314</td>
<td>24.308</td>
<td>18.222</td>
</tr>
</tbody>
</table>

\(^a\)Energies in kcal mol\(^{-1}\). \(^b\)Cis/trans ratio at 80 °C as determined by GC. \(^c\)Experimental value not available.
Inspection of the data in Table 12 indicates that there is qualitative agreement between theory and experiment in that the calculations correctly predict the preferred mode of cyclization for the C(4) substituted radicals 293 and 306. Conformers of transition state structures leading to trans isomers are found to be of lower energy than conformers leading to cis isomers. However, for the C(3) substituted radicals 281 and 284 the calculations were not accurate enough to predict the preferred stereochemistry of the cyclizations. The transition state strain energies of the conformers leading to cis and trans were found to be too close to reflect the cis-trans preference observed experimentally.

In summary, from this brief study it appears that the stereochemical outcome of the cyclization of C(3) and C(4) substituted alkenylaryl radicals like its alkenyl counterparts is controlled by steric factors.
EXPERIMENTAL

GENERAL NOTES

1. Melting points were determined on a Reichert hot stage microscope. Melting points are uncorrected.

2. Elemental analyses were performed by the AHU Analytical Service Unit.

3. Infrared spectra were measured on a Perkin Elmer 583 infrared Spectrophotometer. Samples were run as liquid films (neat), peaks were reported (cm$^{-1}$) followed by assignments, if appropriate.

4. Proton (1H) nmr were measured on either:
   (a) JOEL-PN 240 operating at 200 MHz
   (b) VARIAN XL-300 (300 MHz)
   (c) VARIAN XL-500 (500 MHz)

Samples were run in deuteriochloroform (99.8% from BDH) unless otherwise stated.

Chemical shifts (δ) of proton signals were reported in parts per million (ppm) downfield from an internal tetramethylsilane standard (TMS, δ 0.00 ppm) followed by their multiplicities, coupling constants (J Hz), if appropriate, and assignments.

Abbreviations used are σ (triplet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dd (doublet of doublets), or multiplet), etc. Exchangeable protons were identified by their disappearance upon addition of deuterium oxide.

5. Carbon-13 (13C) nmr were measured on either:
   (a) JOEL-PS 240 operating at 50.1 MHz
   (b) VARIAN XL-300 operating at 30.3 MHz

Assignment of hydrogen substitution of each carbon (CH$_3$, CH$_2$, CH, C$_2$ quaternary carbon) in complex spectra was made from the broad band decoupled refocused INEPT (2H) spectra.

6. Deuterium (1H) nmr were measured using:
   (a) BRUCKER CFX-200 operating at 30.2 MHz
   (b) VARIAN XL-200 operating at 30.2 MHz
EXPERIMENTAL

GENERAL NOTES

i) Melting points were determined on a Reichert hot stage microscope. Melting points and boiling points are uncorrected.

ii) Elemental analyses were performed by the ANU Analytical Service Unit.

iii) Infrared spectra were measured on a Perkin Elmer 683 Infrared Spectrophotometer. Samples were run as liquid films (neat), peaks were reported (cm⁻¹) followed by assignments, if appropriate.

iv) Proton (¹H) nmr were measured on either:
(a) JOEL PNM FX-200 (200 MHz)
(b) VARIAN XL-200 (200 MHz)
(c) VARIAN XL-500 (500 MHz)

Samples were run in deuterochloroform (99.8% atom %D) unless otherwise stated. Chemical shifts (δ) of proton signals were reported in parts per million (ppm) downfield from an internal tetramethysilane standard (TMS, δ 0.00 ppm) followed by their multiplicities, coupling constants (J Hz), if appropriate, and assignments. Abbreviations used are s (singlet), d (doublet), t (triplet), q (quarter), dd (doublet of doublets), ddd (doublet of doublet of doublets), m (multiplet), etc. Exchangeable protons were identified by their disappearance upon addition of deuterium oxide.

v) Carbon-13 (¹³C) nmr were measured on either
(a) JOEL PNM FX-200 operating at 50.1 MHz
(b) VARIAN XL-200 operating at 50.3 MHz

Assignment of hydrogen substitution of each carbon (CH₃, CH₂, CH, C₉ - quaternary carbon) in complex spectra was made from the broad band decoupled refocussed INEPT¹⁵⁷ spectra.

(vi) Deutrium (²H) nmr were measured on either:
(a) BRUCKER CPX-200 operating at 30.7 MHz
(b) VARIAN XL-200 operating at 30.7 MHz
Samples were run in dichloromethane (unless otherwise stated), and chemical shifts are measured relative to $\text{d}_2$-dichloromethane as the internal standard.

vii) Mass spectra were measured at 70 eV on a VG-Micromass 7070F medium resolution mass spectrometer. The molecular ions ($M^+$) are reported as the mass/charge ratios (m/e), followed by their relative ion intensities as ratios of the base peak (100%). High resolution resolution mass spectrometry (Exact mass) was carried out on a MS-902 high resolution mass spectrometer.

ix) Thin layer chromatography (TLC) was conducted on Whatman silica precoated microscope slides (75 x 25 mm). Chromatograms were visualised under ultraviolet light or upon exposure to iodine vapour or spraying with a colour reagent (5% phosphomolybdic acid in ethanol or 5% vanillin in sulphuric acid), followed by heating at 200 °C.

x) Column chromatography was usually carried out by one of the following:

(a) flash chromatography over silica as described by Clark-Still et al.\textsuperscript{158}

(b) medium pressure liquid chromatography (MPLC) using Merck prepacked LiChroprep Si 60 (40-63μm) columns (size A or B). Compounds were detected in the eluates using a Waters R403 differential refractometer or by TLC.

xi) Gas liquid chromatography (GC) was carried out with the following columns with helium as the carrier gas:

A 2m x 1.5mm. 2% OV-17 on Gaschrom Q (60-80 mesh)
B 2m x 4mm. 2% OV-17 on Gaschrom Q (80-100 mesh)
C 25m x 0.2mm. Vitreous Silica Capillary Column (SGE25QC2/BP5 1.0)
D 25m x 0.2mm. Vitreous Silica Capillary Column (SGE25QC2/BP1 1.0)

Columns A and B were constructed from pyrex glass. GC analyses were performed on Varian 3400 and 6000 gas chromatograph equipped with a Flame Ionisation Detector, and coupled to a Hewlett-Packard 3390A Reporting Integrator.
Kugelrohr distillations were carried out on a Büchi GKR-50 glass oven and the boiling points are the temperatures needed for distillation.

Anhydrous tetrahydrofuran (THF) and diethyl ether (ether) were freshly distilled from the ketyl formed by reaction between sodium and freshly distilled from the ketyl formed by reaction between sodium and benzophenone. tert-Butyl alcohol was dried over anhydrous sodium carbonate. Tributyltin hydride (Aldrich) was stored under nitrogen in the freezer. Other solvents and reagents were purified according to published procedures.

Organic extracts were dried using anhydrous sodium sulphate or magnesium sulphate and the bulk of the solvent removed under reduced pressure using a Büchi Rotavapor. The last traces of solvent were removed under high vacuum.
CHAPTER 1

1-Bromo-2-(prop-2-enyloxy)naphthalene 66

Following the general procedure of Ford and Waters, a mixture of 1-bromo-2-naphthol (6.0 g, 2.7 mmol), 3-bromopropene (4.56 g, 38 mmol), and potassium carbonate (5.94 g, 43 mmol) in dry acetone (50 ml) was refluxed under nitrogen for 16 hours. After removal of the solvent under reduced pressure, the residue was diluted with water (50 ml) and extracted with ether (3 x 25 ml). The extracts were washed with 5% aqueous sodium hydroxide solution (2 x 25 ml), water (30 ml), and dried (MgSO₄). The crude product obtained after removal of the solvent under reduced pressure was purified by recrystallization from pentane giving 1-bromo-2-(prop-2-enyloxy)naphthalene 66 (6.0 g, 84.5%) as white crystals. m.p. 41 - 42 °C. (Found: C, 58.97; H, 4.23. \text{C}_{13}\text{H}_{11}\text{BrO} \text{requires} \ C, 59.34; \ H, 4.21). ¹H nmr (CDCl₃) δ 4.75 (d, J = 4.9Hz, 2H, OCH₂); 5.23 - 5.56 (m, 2H, CH=CH₂); 6.05 - 6.13 (m, 1H, CH=CH₂); 7.21 - 7.79 (m, 5H, ArH); 8.23 (d, J = 8.6Hz, ArH). ¹³C nmr (CDCl₃) δ 70.43 (t), 109.58 (s), 115.25 (t), 117.67 (d), 124.39 (d), 126.08 (d), 127.51 (d), 127.95 (d), 128.62 (d), 129.88 (s), 132.79 (d), 132.89 (s), 152.48 (s).

1-Bromo-2-(bromomethyl)naphthalene 68

A stirred mixture of 1-bromo-2-methylnaphthalene 67 (10 g, 45 mmol), dry N-bromosuccinimide52 (8 g, 45 mmol), benzyol peroxide (200 mg) and dry carbon tetrachloride (50 ml) was refluxed under nitrogen for 3 hours while being irradiated by a 250W Mercury lamp. Further portions (100 mg) of peroxide were added to the reaction mixture at 1 hour intervals until no further change was noticed in the ¹H nmr spectrum. The mixture was cooled and filtered. The residue of succinimide was washed with carbon tetrachloride and the filtrate evaporated under reduced pressure. The residue was recrystallized from ether to yield 1-bromo-2-(bromomethyl)naphthalene 68 (8 g, 59%) as light yellow crystals. m.p. 107 - 108
116.

1-Bromo-2-(but-3-enyl)naphthalene 69

A solution of 1-bromo-2-(bromomethyl)naphthalene 68 (3.0 g, 10 mmol) in dry ether (10 ml) was added dropwise to an ice-cold solution of prop-2-en-1-ylmagnesium bromide prepared from 3-bromopropene (2.42 g, 20 mmol), magnesium (1.44 gm, 60 mmol) and a crystal of iodine in dry ether (100 ml). When the addition was complete the mixture was stirred at room temperature. After 2 days it was poured into 2N hydrochloric acid (100 ml) and stirred until it became clear. The organic layer was then separated and the aqueous layer extracted with ether (2 x 25 ml). The ether extracts were washed with saturated aqueous sodium bicarbonate solution (2 x 30 ml), water (50 ml), dried (MgSO₄) and filtered. The residue obtained after removal of the solvent under reduced pressure was purified by flash chromatography (3% ethyl acetate/hexane) to afford 1-bromo-2-(but-3-enyl)naphthalene 69 (1.67 g, 64%) as a clear oil. (Found: C, 64.29; H, 4.98. C₁₄H₁₃Br requires C, 64.39; H, 5.02). ¹H nmr (CDCl₃) δ 2.39 - 2.55 (m, 2H, CH₂CH); 3.1 (t, J = 7.5Hz, 2H, ArCH₂); 4.98 - 5.18 (m, 2H, CH=CH₂); 5.84 - 6.08 (m, 1H, CH=CH₂); 7.31 - 7.84 (m, 5H, ArH); 8.35 (d, J = 8.3Hz, 1H, ArH). ¹³C nmr (CDCl₃) δ 34.01 (t), 36.85 (t), 115.22 (t), 123.66 (s), 125.79 (d), 127.22 (d, 2C), 127.43 (d), 127.95 (d), 128.10 (d), 133.21 (s), 137.57 (d), 139.25 (s); one quaternary carbon was not detected.

2-Bromo-1-(prop-2-enyloxy)naphthalene 70

The title compound was prepared from 2-bromo-1-naphthol ⁴³ (2.5 g, 11.2 mmol) and 3-bromopropene (1.9 g, 15.7 mmol) as described above for 1-bromo-2-(prop-2-enyloxy)naphthalene 66. The residue after workup was purified by flash chromatography (10% ethyl acetate/hexane) to afford 2-bromo-1-(prop-2-enyloxy)naphthalene 70 (2.3 g, 79%) as a clear oil. ¹H nmr (CDCl₃) δ 4.60 (d, J =
5.62Hz. 2H. OCH\textsubscript{2}); 5.24 - 5.57 (m. 2H. CH = CH\textsubscript{2}); 6.10 - 6.33 (m. 1H. CH = CH\textsubscript{2}); 7.40 - 8.18 (m. 6H. ArH). \textsuperscript{13}C nmr (CDCl\textsubscript{3}) \( \delta \) 74.65 (t), 112.66 (s), 116.62 (d), 122.17 (d), 125.18 (d), 126.63 (d), 126.66 (d), 127.69 (d), 129.36 (s), 130.62 (d), 133.42 (d), 133.67 (s), 152.07 (s). Mass spectrum: m/e = 264 (31%), 262 (30%, M\textsuperscript{+}), 223 (94%), 221 (100%), 195 (89%), 193 (87%), 183 (78%), 114 (90%), 115 (46%). Exact mass: (C\textsubscript{13}H\textsubscript{11}OBr\textsubscript{79} requires: M\textsuperscript{+} = 261.9993. Found: M\textsuperscript{+} = 261.9992).

1-Iodo-2-(prop-2-ynyloxy)naphthalene 71

The title compound was prepared from 1-iodo-2-naphthol\textsuperscript{44} (4 g, 14.8 mmol) and 3-bromopropyne (2.5 g, 20.7 mmol) following the procedure described fro 1-bromo-2-(prop-2-enyloxy)naphthalene 66. The crude product obtained after workup was purified by recrystallization from petroleum ether 40 - 60 °C to afford 1-iodo-2-(prop-2-ynyloxy)naphthalene 71 (3.7 g, 81%) as light yellow crystals. m.p. 59 - 60 °C. (Found: C, 50.64; H, 2.92. C\textsubscript{13}H\textsubscript{9}OI requires C, 50.68; H, 2.94). \( \nu_{\text{max}} \) (Nujol) 3290, 1590, 1500 cm\textsuperscript{-1}. \textsuperscript{1}H nmr (CDCl\textsubscript{3}) \( \delta \) 2.52 (t, J = 2.32Hz. 1H, C=CH); 4.85 (d, J = 2.44Hz. OCH\textsubscript{2}); 7.20 - 7.80 (m, 5H, ArH); 8.14 (d, J = 8.54Hz. 1H, ArH). \textsuperscript{13}C nmr (CDCl\textsubscript{3}) \( \delta \) 57.88 (d), 76.15 (t), 78.22 (s), 89.41 (s), 114.84 (d), 124.77 (d), 128.10 (d, 2C), 130.08 (d), 130.32 (s), 131.40 (d), 135.54 (s), 154.99 (s).

1-Bromo-2-(but-3-enyloxy)naphthalene 72

Following the general procedure of Beckwith\textsuperscript{10} a mixture of 1-bromo-2-naphthol (6 g, 26.9 mmol), 4-bromobut-1-ene (5.1 g, 37.8 mmol), sodium hydroxide (1.51 g, 37.8 mmol), and water (20 ml) was heated under reflux for 5 hours. The mixture was cooled, diluted with water (75 ml), and extracted with ether (3 x 50 ml). The ether layer was washed successively with 5% sodium hydroxide solution (3 x 25 ml), water (2 x 25 ml), brine (50 ml), and dried (MgSO\textsubscript{4}). The crude product after removal of solvent was purified by recrystallization from pentane to afford 1-bromo-
2-(but-3-enyloxy)naphthalene 72 (3.2 g, 42%) as white crystals. m.p. 31 °C. 
(Found: C, 60.96; H, 4.60; Br, 28.84. C_{14}H_{13}OBr requires C, 60.67; H, 4.73; Br, 28.83). \( \nu_{\text{max}} \) (Nujol) 1630. 1600 cm\(^{-1}\). \( ^1H \text{nmr} \) (CDCl\(_3\)) \( \delta \) 2.57 - 2.67 (m, 2H, CH\(_2\)); 4.20 (t, J = 6.83Hz, 2H, OCH\(_2\)); 5.08 - 5.28 (m, 2H, CH=CH\(_2\)) 5.88 - 6.10 (m, 1H, CH=CH\(_2\)); 7.16 - 7.80 (m, 6H, ArH); 8.2 (d, J = 8.54Hz, 1H, ArH). \( ^{13}C \text{nmr} \) (CDCl\(_3\)) \( \delta \) 33.90 (t), 69.70 (t), 109.82 (t), 115.40 (d), 117.26 (d), 124.36 (d), 126.29 (d), 127.54 (d), 127.92 (d) 128.74 (d), 129.97 (s), 133.21 (s), 134.17 (d), 153.24 (s).

2-Bromo-1-(but-3-enyloxy)naphthalene 73

The title compound was prepared from 2-bromo-1-naphthol\(^43\) (1.6 g, 7.2 mmol) and 4-bromobut-1-ene (1.1 g, 8.1 mmol) as described above for 1-bromo-2-(but-3-enyloxy)naphthalene 72 with the exception that potassium hydroxide (7.2 mmol) was used as a base and ethanol as a solvent. The residue obtained after workup was purified by flash chromatography (5% ethyl acetate/hexane) to afford 2-bromo-1-(but-3-enyloxy)naphthalene 73 (1.1 g, 55%) as a clear oil which darkened on storage. \( \nu_{\text{max}} \) (Neat) 1645. 1590. 1580. cm\(^{-1}\). \( ^1H \text{nmr} \) (CDCl\(_3\)) \( \delta \) 2.65 - 2.77 (m, 2H, OCH\(_2\)CH\(_2\)); 4.13 (t, J = 6.86Hz, 2H, OCH\(_2\)); 5.10 - 5.30 (m, 2H, CH=CH\(_2\)); 5.81 - 6.14 (m, 1H, CH=CH\(_2\)); 7.40 - 8.17 (m, 6H, ArH). \( ^{13}C \text{nmr} \) (CDCl\(_3\)) \( \delta \) 34.66 (t), 73.26 (t), 112.77 (s), 117.14 (d), 122.11 (d), 125.06 (d), 126.43 (d), 126.55 (d), 127.89 (d), 129.30 (s), 130.00 (d), 133.91 (s), 134.46 (d), 152.24 (s). Mass spectrum: m/e = 278 (11%); 276 (11%, \( M^+ \)); 224 (63%); 222 (67%); 115 (35%); 114 (38%); 55 (100%). Exact mass (C\(_{13}H_{11}OBr\)\(^79\)) requires: \( M^+ = 276.0150 \). Found: \( M^+ = 276.0150 \)

1-Bromo-2-(cyclohex-2-enyloxy)naphthalene 74

The title compound was prepared from 1-bromo-2-naphthol (2.5 g, 11.2 mmol) and 3-bromocyclohexene (2.5 g, 15.7 mmol) following the procedure described for 1-bromo-2-(prop-2-enyloxy)naphthalene 66. The residue isolated after
workup was purified by flash chromatography (5% ethyl acetate/hexane) to afford 1-bromo-2-(cyclohex-2-enyloxy)naphthalene 74 (3.4 g, 82%) as a clear oil. (Found: C. 63.17; H. 4.91. C_{16}H_{15}BrO requires C. 63.38; H. 4.99). ν_{max} (Neat) 3030, 2940, 1630, 1560, 1500 cm\(^{-1}\). ¹H nmr (CDCl\(_3\))  δ 1.4 - 2.23 (m, 6H, 3 x CH\(_2\)); 4.82 (s. broad. 1H, CH); 5.82 - 6.03 (m, 2H, CH=CH); 7.25 - 7.76 (m, 5H, ArH); 8.2 (d, J = 8.5Hz, 1H, ArH). ¹³C nmr (CDCl\(_3\)) δ 18.78 (t), 25.02 (t), 28.62 (t), 73.93 (d), 114.46 (s), 117.67 (d), 124.36 (d), 126.1 (d), 126.3 (d), 127.4 (d), 127.8 (d), 128.5 (d), 130.1 (s), 132.4 (d), 133.2 (s), 152.6 (s).

2-Bromo-1-(cyclohex-2-enyloxy)naphthalene 75

The title compound was prepared from 2-bromo-1-naphthol (1.5 g, 6.7 mmol) and 3-bromocyclohexene\(^{42}\) (1.5 g, 9.4 mmol) following the procedure described for 1-bromo-2-(prop-2-enyloxy)naphthalene 66. The residue obtained after workup was purified by flash chromatography (3% ethyl acetate/hexane) to afford 2-bromo-1-(cyclohex-2-enyloxy)naphthalene 75 as a clear oil (1.2 g, 60%). (Found: C. 63.71; H. 4.99. C_{16}H_{15}BrO requires C. 63.38; H. 4.99). ν_{max} (Neat) 2940, 2840, 1600 1535, 1520 cm\(^{-1}\). ¹H nmr (CDCl\(_3\))  δ 1.5 - 2.3 (m, 6H, 3 x CH\(_2\)); 4.88 (s broad, 1H, CH); 5.95 (m, 2H, CH = CH); 7.35 - 8.30 (m, 6H, ArH).

1-Methyl-1.2-dihydronaphto[2.1-b]furan 79 and 2,3-Dihydro-1H-naphto[2,1-b]pyran 80

A solution of 1-bromo-2-(prop-2-enyloxy)naphthalene 66 (500 mg, 1.9 mmol), AIBN (34 mg, 0.2 mmol), and tri-n-butyltin hydride (664 mg, 2.25 mmol, 0.06M) in dry benzene (38 ml) was degassed and refluxed under nitrogen for 16 hours. The solvent was removed under reduced pressure and the residue was taken up in ether (20 ml) and was stirred with 10% aqueous solution of potassium flouride (10 ml) for 4 hours. The precipitate was then removed by filtration and the two layers were separated. The aqueous layer was extracted with ether (2 x 20 ml) and the combined extracts washed with brine (2 x 15 ml), dried (MgSO\(_4\)), and
concentrated under reduced pressure. The crude product was purified by MPLC (10% ethyl acetate/hexane) to afford the title products (184 mg, 71%) in the ratio of 10:1 by GC. The minor product (6%) corresponded with an authentic sample of the endo cyclization product. 2,3-dihydro-1H-naphto[2,1-b]pyran 80.

Preparative GC of the mixture gave 1-methyl-1,2-dihydronaphtho[2,1-
b]furan 79 (65%) as a clear oil. (Found: C. 84.75; H. 6.24. C_{13}H_{12}O requires C. 84.75; H. 6.56). \( ^1H \) nmr (CDCl\textsubscript{3}) \( \delta \) 1.45 (d, J = 6.8Hz, 3H, CHCH\textsubscript{3}); 3.92 (m, 1H, ArCH); 4.35 (m, 1H, OCH\textsubscript{2}(H)); 4.78 (m, 1H, OCH(H)); 7.10 - 7.85 (m, 6H, ArH). \( ^{13}C \) nmr (CDCl\textsubscript{3}) \( \delta \) 20.35 (q), 36.18 (d), 79.3 (t), 112.27 (d), 122.23 (d), 122.64 (d), 123.51 (s), 126.52 (d), 128.97 (d), 129.18 (d), 129.51 (s), 130.52 (s), 156.97 (s).

Followed by 2,3-dihydro-1H-naphto[2,1-b]pyran 80 (6%) as white crystals. m.p. 40 - 42 °C / ethanol (lit.\textsuperscript{45} m.p. 41 - 42 °C). \( ^1H \) nmr (CDCl\textsubscript{3}) \( \delta \) 2.15 - 2.30 (m, 2H, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}); 3.1 (t, J = 6.1Hz, 2H, ArCH\textsubscript{2}CH\textsubscript{2}); 4.3 (t, J = 5.1Hz, 2H, OCH\textsubscript{2}CH\textsubscript{2}); 7.05 - 7.90 (m, 6H, ArH). \( ^{13}C \) nmr (CDCl\textsubscript{3}) \( \delta \) 21.32 (t), 22.31 (t), 66.14 (t), 113.79 (s), 119.07 (d), 121.76 (d), 123.16 (d), 126.26 (d), 127.57 (d), 128.39 (d), 128.91 (s), 133.27 (s), 152.57 (s).

2,3-Dihydro-1H-naphto[2,1-b]pyran 80

The title compound was prepared according to Rindifusz et al.\textsuperscript{45} m.p. 40 - 42 °C (lit.\textsuperscript{45} m.p. 41 - 42 °C).

**Ethyl 4-bromobut-2-enoate 83**

The title compound was prepared from ethyl but-2-enoate (10.9 g, 95.6 mmol) and N-bromosuccinimide (17 g, 95.6 mmol) as described for 1-bromo-2-(bromomethyl)naphthalene 68. The residue obtained after workup was purified by distillation to afford ethyl 4-bromobut-2-enoate 83 (12.77 g, 69%) as a clear oil. b.p. 72 - 76 °C/2 mmHg (lit.\textsuperscript{148} b.p. 78 - 82 °C/2 mmHg).
Ethyl 4-(1-bromo-2-naphthoxy)but-2-enoate 84

The title compound was prepared from 1-bromo-2-naphthol (6 g, 26.9 mmol) and ethyl 4-bromobut-2-enoate (6.23 g, 32.28 mmol) as described for 1-bromo-2-(prop-2-enyloxy)naphthalene 66. The residue obtained after workup was purified by flash chromatography (15% ethyl acetate/hexane) to afford ethyl 4-(1-bromo-2-naphthoxy)but-2-enoate 84 (3.3 g, 37%) as a light yellow oil. (Found: C, 57.20; H, 4.41. C₁₆H₁₅BrO₃ requires C, 57.33; H, 4.51. νₘₐₓ(Neat) 1720, 1660, 1625, 1600 cm⁻¹. ¹H nmr (CDCl₃) δ 1.28 (t, J = 6.9 Hz, CH₂CH₃); 4.20 (q, J = 6.7 Hz, 2H, CH₂CH₃); 4.75 (m, 2H, OCH₂); 6.34 (m, 1H, CH); 7.00-7.75 (m, 6H, CH + ArH); 8.18 (d, J = 7.8 Hz, 1H, ArH). ¹³C nmr (CDCl₃) δ 14.19 (q), 60.50 (t), 68.21 (t), 109.67 (s), 114.69 (d), 122.34 (d), 124.62 (d), 126.17 (d), 127.78 (d), 127.98 (d), 128.91 (d), 130.05 (s), 133.06 (s), 141.73 (d), 152.27 (s), 165.94 (s).

Ethyl 1,2-dihydronaphthal[2,1-b]furan-1-acetate 85

A solution of tri-n-butyltin hydride (1.91 g, 6.57 mmol) in dry benzene (20 ml) was added dropwise over a period of 1 hour to a mixture of ethyl 4-(1-bromo-2-naphthoxy)but-2-enoate 84 (2.0 g, 5.97 mmol) and AIBN (20 mg) in refluxing benzene (60 ml) under nitrogen. The mixture was refluxed for an additional 30 min, then cooled, and concentrated under reduced pressure. The residue was taken up in ether (24 ml) and stirred with 10% aqueous potassium fluoride solution (10 ml) for 4 hours. The precipitate was removed by filtration and the two layers of the filtrate were separated. The aqueous layer was extracted with ether (2 x 20 ml) and the combined extracts were washed with brine (30 ml) and dried (MgSO₄). The residue obtained after the removal of the solvent under reduced pressure was subjected to flash chromatography (15% ethyl acetate/hexane) to afford ethyl 1,2-dihydronaphthal[2,1-b]furan-1-acetate 85 (1.49 g, 97%) as a thick yellow oil which solidified on standing at room temperature. Pure 85 formed white crystals from hexane. m.p. 55-57 °C. (Found: C, 74.67; H, 6.25. C₁₆H₁₆O₃
1.2-Dihyronaphtho[2,1-b]furan-1-acetic acid 86

A solution of ethyl 1.2-dihyronaphtho[2,1-b]furan-1-acetate 85 (1.0 g, 3.9 mmol) and potassium hydroxide (0.26 g, 4.6 mmol) in a 1:1 mixture of water-ethanol (10 ml) was stirred at room temperature for 2 hours. Ethanol was then removed under reduced pressure, and the residue was acidified with 1N sulphuric acid and extracted with ether and dichloromethane. The extracts were washed with water, dried (MgSO\(_4\)), and concentrated under reduced pressure to afford the crude product. Recrystallization from dichloromethane - hexane afforded 1.2-dihyronaphtho[2,1-b]furan-1-acetic acid 86 (0.88 g, 99%) as white crystals. m.p. 143 - 145 °C. (Found: C, 73.99; H, 5.29. \(\text{C}_{14}\text{H}_{12}\text{O}_{3}\) requires C, 73.67; H, 5.30). \(\nu\)\(_{\text{max}}\) (Nujol) 1685 cm\(^{-1}\) (C=O). \(^1\)H nmr (CDCl\(_3\)) \(\delta\) 1.27 (t, \(J = 6.90\) Hz, 3H, CH\(_2\)CH\(_3\)); 2.78 (m, 2H, CHCH\(_2\)); 4.1 - 4.30 (m, 3H, CH\(_2\)CH\(_3\) + ArCH); 4.5 - 4.8 (m, 2H, OCH\(_2\)); 7.2 - 7.8 (m, 6H, ArH). \(^1^3\)C nmr (CDCl\(_3\)) \(\delta\) 14.13 (q), 38.10 (d), 38.51 (t), 60.62 (t), 77.31 (t), 112.18 (d), 120.18 (s), 121.82 (d), 122.78 (d), 126.81 (d), 128.97 (d), 129.43 (s), 129.79 (d), 130.11 (s), 157.23 (s), 171.66 (s).

Preparation of the Thiohydroxamate 87 and its treatment with tri-n-butyltin hydride

A mixture of the foregoing acid 86 (100 mg, 0.44 mmol) and oxalyl chloride (133 mg, 1.0 mmol) in benzene (5 ml) was refluxed for 2 hours and then concentrated under reduced pressure. The residue was taken up in dry ether (5 ml) and was stirred with 3-hydroxy-4-methylthiazole-2(3H)-thione\(^{57}\) (68 mg, 0.46 mmol), pyridine (80 ml), and DMAP (4 mg, 0.03 mmol) at room temperature for 20 min. The precipitated pyridinium hydrochloride was removed by filtration and the ether
layer was washed with dilute sulphuric acid (1N), water, dried (MgSO₄), and evaporated under reduced pressure. Without purification the residual thiohydroxamate 87 was mixed with tri-n-butyltin hydride (153 mg, 0.56 mmol) and AIBN (2 mg) in dry degassed benzene (10.5 ml) and refluxed for 40 min. The mixture was cooled to room temperature and analyzed by GC. The GC analysis revealed the presence of 79 and 80 in the ratio 11:1. The residue isolated, after the removal of solvent was purified by flash chromatography (10% ethyl acetate/hexane) to afforded a mixture of 79 and 80 (23 mg, 29%).

2-(But-3-enyl)naphthalene 95, 1-Methyl-2,3-dihydro-1H-benzo[g]indine 91, and 1,2,3,4-Tetrahydrophenthrene 92

A solution of 1-bromo-2-(but-3-enyl)naphthalene 10 (300 mg, 1.15 mmol), AIBN (19 mg, 0.11 mmol), and tri-n-butyltin hydride (368 mg, 1.25 mmol, 0.06M) in dry benzene (21 ml) was degassed and refluxed under nitrogen for 16 hours. The solvent was removed under reduced pressure and the residue purified by flash chromatography (hexane) to afford a mixture of three products (200 mg, 96%) in the ratio of 1:36:16.8 by GC. The minor component (2%) corresponded with an authentic sample of the direct reduction product 2-(but-3-enyl)naphthalene 95. Preparative GC of the mixture afforded 1-methyl-2,3-dihydro-1H-benzo[g]indine 91 (65%) as a clear oil. (Found: C, 92.14; H, 7.61. C₁₄H₁₄ requires C, 92.26; H, 7.74). ¹H nmr (CDCl₃) δ 1.3 (d, J = 6.1 Hz, 3H, CHCH₃); 1.9 (m, 1H, CH₂CH(H)CH); 2.4 (m, 1H, CH₂CH(H)CH); 2.9 - 3.3 (m, 2H, ArCH₂); 3.78 (m, 1H, ArCH); 7.3 -7.9 (m, 6H, ArH). ¹³C nmr (CDCl₃) δ 20.44 (q), 31.62 (t), 33.64 (t), 38.22 (d), 123.45 (d), 124.04 (d), 124.48 (d), 125.76 (d), 126.96 (d), 128.65 (d), 129.94 (s), 132.94 (s), 139.92 (s), 144.10 (s).

Followed by 1,2,3,4-tetrahydrophenthrene 92 (29%) as a clear oil. (Found: C, 92.06; H, 7.88. C₁₄H₁₄ requires C, 92.26; H, 7.74). ¹H nmr (CDCl₃) δ 1.9 (m, 4H, 2 x CH₂); 2.88 (t, J = 5.3 Hz, 2H, ArCH₂); 3.1 (t, J = 5.3 Hz, 2H,
2-(Bromomethyl)naphthalene 94

The title compound was prepared according to Chapman and Williams.\textsuperscript{52} m.p. 52 - 53 °C. (lit.\textsuperscript{52} m.p. 54 °C). \textsuperscript{1}H nmr (CDCl\textsubscript{3}) δ 4.68 (s, 2H, CH\textsubscript{2}); 7.45 - 7.90 (m, 7H, ArH).

2-(But-3-enyl)naphthalene 95

The title compound was prepared from 2-(bromomethyl)naphthalene 94 (1.0 g, 4.5 mmol) and prop-2-en-1-ylmagnesium bromide (prepared from 3-bromopropene (1.1 g, 9.0 mmol) and magnesium (0.66 g, 27.5 mmol) following the procedure described for 1-bromo-2-(but-3-enyl)naphthalene 69. The residue obtained after workup was purified by flash chromatography (hexane) to yield 2-(but-3-enyl)naphthalene 95 (300 mg, 38%) as a clear oil. (Found: C, 92.25; H, 7.67. C\textsubscript{14}H\textsubscript{14} requires C, 92.26; H, 7.74). \(\nu_{max}\) (Neat) 1640, 1600, 1510 cm\(^{-1}\). \textsuperscript{1}H nmr (CDCl\textsubscript{3}) δ 2.35 - 2.50 (m, 2H, ArCH\textsubscript{2}CH\textsubscript{2}); 2.82 (t, J = 7.5Hz, 2H, ArCH\textsubscript{2}); 4.9 - 5.10 (m, 2H, CH = CH\textsubscript{2}); 5.77 - 5.98 (m, 1H, CH = CH\textsubscript{2}); 7.24 - 7.80 (m, 7H, ArH). \textsuperscript{13}C nmr (CDCl\textsubscript{3}) δ 35.33 (t), 35.48 (t), 114.96 (t), 125.03 (d), 125.76 (d), 126.34 (d), 127.37 (d), 127.51 (d), 127.75 (d), 131.95 (s), 133.56 (s), 137.9 (d), 139.28 (s).

3-Methyl-2,3-dihydronaphpto[1,2-b]furan 97

A solution of 2-bromo-1-(prop-2-enyloxy)-naphthalene 70 (300 mg, 1.14 mmol), AIBN (25 mg, 0.15 mmol) and tri-n-butyltin hydride (398 mg, 1.37 mmol, 0.06M) in benzene (22.8 ml) was refluxed for 16 hours. The solvent was removed under reduced pressure and the residue purified by flash chromatography (15% ethyl acetate/hexane) to afford 3-methyl-2,3-dihydronaphpto[1,2-b]furan 97 (169 mg, 81%).
as a clear oil which darkened on storage. (Found: C. 84.58; H. 6.49. $\text{C}_{13}\text{H}_{12}\text{O}$ requires C. 84.75; H. 6.56). $^1\text{H nmr (CDCl}_3) \delta 1.33$ (d. J = 6.8Hz. 3H. CH$_3$); 3.65 (m. 1H, ArCH); 4.24 (t. J = 7.9Hz. 1H, OCH(=H)); 4.83 (t. J = 8.9, 1H, OCH(=H)); 7.2 - 8.0 (m. 6H, ArH). $^{13}\text{C nmr (CDCl}_3) \delta 19.8$ (q). 37.32 (d). 79.13 (t). 120.21 (d). 120.65 (s). 121.41 (d). 121.70 (d). 125.21 (d). 125.56 (d). 127.84 (d). 134.03 (s. 2C). 154.96 (s).

1-Methylnapht[2.1-b]furan 100

A solution of 1-iodo-2-(prop-2-ynyloxy)naphthalene 71 (308 mg, 1 mmol), AIBN (16 mg, 0.1 mmol), and tri-n-butyltin hydride (350 mg, 1.2 mmol, 0.06M) in benzene (20 ml) was refluxed for 1 hour. The solvent was removed under reduced pressure and the residue subjected to flash chromatography (10% ethyl acetate/hexane) to afford 1-methylnapht[2.1-b]furan 45 (150 mg, 82%) as white crystals. m.p. 56 °C. $^1\text{H nmr (CDCl}_3) \delta 2.5$ (s. 3H. CH$_3$); 7.4 - 8.4 (m. 7H, CH+ArH). $^{13}\text{C nmr (CDCl}_3) 11.18$ (q). 112.59 (d). 117.44 (s). 121.93 (s). 122.98 (d). 123.9 (d). 125.15 (d). 126 (d). 128.83 (d). 128.97 (s). 130.49 (s). 141 (d). 153.1 (s). Mass spectrum: m/e = 182 (100%, M$^+\text{).}$ 181 (33%). 153 (45%). 152 (31%). 91 (22%). 90 (21%). 76 (41%). Exact mass (C$_{13}$H$_{10}$O requires: M$^+ = 182.0732).$ Found: M$^+ = 182.0731$.

1-Methyl-2,3-dihydro-1H-naphto[2.1-b]pyran 105a, 2-(E- and Z-but-2-enyloxy)naphthalene 106a, and 2-(But-3-enyloxy)naphthalene 108a

A solution of 1-bromo-2-(but-3-enyloxy)naphthalene 72 (300 mg, 1.1 mmol), AIBN (25 mg, 0.15 mmol) and tri-n-butyltin hydride (378 mg, 1.3 mmol, 0.06M) in benzene (21.6 ml) was refluxed for 16 hours. The solvent was removed under reduced pressure and the residue taken up in ether (10 ml) and stirred with 10% aqueous solution of potassium fluoride (5 ml) for 12 hours. The precipitate was removed by filtration and the two layers separated. The ether layer was dried (MgSO$_4$) and concentrated under reduced pressure. The crude product was purified
by MPLC (10% ethyl acetate/hexane) to afford a mixture of three products (160 mg, 75%) in the ratio of 1:1:1:30 by GC. One of the minor product was identified as the 1.5-hydrogen atom transfer product. 2-(E-and-2-enyloxy)naphthalene 106a (2.3%) by \(^2\)H nmr spectrum analysis of product mixture obtained from reaction of 72 with tri-n-butyl deuteride described below. The other minor product was identified as the direct reduction product. 2-(but-3-enyloxy)naphthalene 108a (2.6%) by GC retention times comparison with authentic sample. Recrystallization of the product mixture from pentane gave the major product. 1-methyl-2,3-dihydro-1H-naphto[2,1-b]pyran 105a (149 mg, 70%) as white crystals. m.p. 62 - 63 °C. (Found: C, 84.47; H, 7.27. C\(_{14}\)H\(_{14}\)O requires C, 84.81; H, 7.12). \(^1\)H nmr (CDCl\(_3\)) \(\delta\) 1.45 (d, \(J = 6.8\) Hz, 3H, CHCH\(_3\)); 1.7 - 2.35 (m, 2H, CHCH\(_2\)); 3.53 (m, 1H, ArCH); 4.32 (m, OCH\(_2\)); 6.93 - 7.9 (m, 6H, ArH). \(^{13}\)C nmr (CDCl\(_3\)) \(\delta\) 22 (q), 24.4 (t), 28.8 (d), 61.6 (t), 118.7 (s), 119.1 (d), 128.8 (d), 126.2 (d), 127.9 (d), 128.7 (d), 129.2 (s), 132.6 (s), 151.4 (s).

2-(But-3-enyloxy)naphthalene 108a

The title compound was prepared from 2-naphthol (2 g, 13.9 mmol) and 4-bromobut-1-ene (2.1 g, 15.6 mmol) following the procedure described for 1-bromo-2-(but-3-enyloxy)naphthalene 72. The residue isolated after workup was purified by distillation to yield 2-(but-3-enyloxy)naphthalene 108a (1.3 g, 48%) as a clear oil. b.p. 120 - 122 °C/1.5 mmHg. (Found: C, 84.94; H, 7.30. C\(_{14}\)H\(_{14}\)O requires C, 84.81; H, 7.12). \(\nu_{\text{max}}\) (Neat) 1630. 1600 cm\(^{-1}\). \(^1\)H nmr (CDCl\(_3\)) \(\delta\) 2.53 - 2.63 (m, 2H, OCH\(_2\)CH\(_2\)); 4.10 (t, \(J = 6.7\) Hz, 2H, OCH\(_2\)); 5.06 - 5.26 (m, 2H, CH=CH\(_2\)); 5.83 - 6.04 (m, 1H, CH=CH\(_2\)); 7.08 - 7.79 (m, 7H, ArH). \(^{13}\)C nmr (CDCl\(_3\)) \(\delta\) 33.61 (t), 67.25 (t), 106.84 (d), 116.97 (d), 118.96 (d), 123.54 (d), 126.28 (d), 127.60 (d), 129.06 (s), 129.32 (d), 134.46 (d), 134.61 (s), 156.0 (s).
1-(Monodeuteriomethyl)-2,3-dihydro-1H-naphto[2,1-b]pyrm 105b. 2-(E- and Z-4-monodeuteriobut-2-enyloxy)naphthalene 106b. 2-(2-Monodeuteriobut-3-enyloxy)naphthalene 107b. and 1-Deuterio-2-(but-3-enyloxy)naphthalene 108b

A solution of 1-bromo-2-(but-3-enyloxy)naphthalene 72 (75 mg, 0.27 mmol), AIBN (5 mg, 0.027 mmol), tri-n-butyltin deuteride (73 mg, 0.25 mmol, 0.25M), in benzene (1 ml) was transferred to a 5 ml pyrex tube, freeze-thawed and sealed under vacuum. The tube was then immersed in a constant temperature water bath at 20 °C and irradiated with a 250W Mercury lamp for 16 hours. The tube was opened and the solvent evaporated under reduced pressure. $^2$H nmr of the product mixture showed the formation of 105b (90.3 %), 106b (3.8 %), 107b (0.8 %), and 108b (5 %). Product distribution was determined from the integrated $^2$H nmr spectrum. $^2$H nmr (CH$_2$Cl$_2$) δ 1.1, 1.85, 2.6, 7.2.

The reaction was repeated on the same scale by heating at 110 °C for 16 hours using di-t-butyl peroxide (BOOB) instead of AIBN. $^2$H nmr spectrum of the reaction mixture showed the formation of 105b (84.2 %), 106b (9.4 %), 107b (3.3 %), 108b (3 %).

4-Methyl-3-4-dihydro-2H-naphto[1.2-b]pyran 112a. 1-(E- and Z-but-2-enyloxy)naphthalene 113a. and 1-(But-3-enyloxy)naphthalene 115a

A solution of 2-bromo-1-(but-3-enyloxy)naphthalene 73 (300 mg, 1.1 mmol), AIBN (25 mg, 0.15 mmol). and tri-n-butyltin hydride (378 mg, 1.3 mmol, 0.06M) in benzene (21.7 ml) was refluxed for 16 hours. The residue obtained after the removal of solvent under reduced pressure was purified by flash chromatography (5% ethyl acetate/hexane) to give a mixture of three products (153 mg, 72 %) in the ratio of 1.8:1:27 by GC. One of the minor product was identified as the 1,5-hydrogen atom transfer product, 1-(E-and Z-but-2-enyloxy)naphthalene 113a (2.5 %) by $^2$H nmr spectrum analysis of product mixtures obtained from reaction of 73 with tri-n-butyltin deuteride described below. The other minor product was identified as
the direct reduction product. 1-(but-3-enyloxy)naphthalene 115a by GC comparison with authentic sample. The product mixture was subjected to MPLC (5% ethyl acetate/hexane) twice to give the major product 4-methyl-3,4-dihydro-2H-naphto[1,2-b]pyran 112a (65%) as a clear oil which darkened on storage. (Found: C, 84.60; H, 7.09. C\textsubscript{14}H\textsubscript{14}O requires C, 84.81; H, 7.12). \textsuperscript{1}H nmr (CDCl\textsubscript{3}) δ 1.34 (d, J = 7.1Hz, 3H, CHCH\textsubscript{3}); 1.7 - 2.26 (m, 2H, CHCH\textsubscript{2}); 3.0 (m, 1H, ArCH); 3.32 (m, 2H, OCH\textsubscript{2}); 7.2 - 8.2 (m, 6H, ArH). \textsuperscript{13}C nmr (CDCl\textsubscript{3}) δ 22.5 (q), 28.5 (t) 30.2 (d), 63.8 (t), 119.5 (d), 121 (s), 121.6 (d), 125.1 (d), 125.6 (d), 126.8 (d), 127.3 (d), 133.1 (s), 149.2 (s); one quaternary carbon not observed.

1-(But-3-enyloxy)naphthalene 115a

The title compound was prepared from 1-naphthol (2g, 13.9 mmol) and 4-bromobut-1-ene (2.1 g, 15.6 mmol) following the procedure described for 1-bromo-2-(but-3-enyloxy)naphthalene 72, with the exception that potassium hydroxide (13.9 mmol) was used instead of sodium hydroxide and ethanol as a solvent. The residue obtained after workup was purified by flash chromatography (5% ethylacetate/hexane to afford 1-(but-3-enyloxy)naphthalene 115a (1.4 g, 51%) as a clear oil. (Found: C, 85.12; H, 7.26. C\textsubscript{14}H\textsubscript{14}O requires C, 84.85; H, 7.12). \nu\textsubscript{max} (Neat) 1645, 1630, 1600, 1580 cm\textsuperscript{-1}. \textsuperscript{1}H nmr (CDCl\textsubscript{3}) δ 2.58 - 2.68 (m, 2H, OCH\textsubscript{2}CH\textsubscript{2}); 4.11 (t, J = 6.47Hz, 2H, OCH\textsubscript{2}); 5.06 - 5.28 (m, 2H, CH=CH\textsubscript{2}); 5.82 - 6.08 (m, 1H, CH=CH\textsubscript{2}); 6.68 - 8.3 (m, 7H, ArH).

4-(Monodeuteriomiethyl)-3,4-dihydro-2H-naphto[1,2-b]pyran 112b, 1-(E- and Z-4-monodeuteriobut-2-enyloxy)naphthalene 113b, 1-(2-Monodeuteriobut-3-enyloxy)naphthalene 114b, and 2-Deuterio-2-(but-3-enyloxy)naphthalene 115b

2-Bromo-1-(but-3-enyloxy)naphthalene 73 (75 mg, 0.27 mmol) was reacted with tri-n-butyltin deuteride (73 mg, 0.25 mmol, 0.25M) at 20°C as described above for 1-bromo-2-(but-3-enyloxy)naphthalene 72. \textsuperscript{2}H nmr spectrum of the product mixture showed the formation of 112b (85.5%), 113b (4.9%), 114b
(0.7%). 115B (8.9%). The product distribution was determined from the integrated
\(^2\text{H} \text{nmr spectrum}. \ \ ^2\text{H} \text{nmr (CH}_2\text{Cl}_2 \ \delta 1.21, 1.59, 2.57, 7.11.

The reaction was repeated on the same scale at 110°C as described for
1-bromo-2-(but-3-enyloxy)naphthalene 72. \(^2\text{H} \text{nmr spectrum of the reaction mixture
showed the formation of } 112\text{b (84.3%), 113b (8.3%), 114b (2.3%), 115b (5.1%).

7a,11a-Dihydrocyclohexano[b]naphto[1.2-d]furan 118

A solution of 1-bromo-2-(cyclohex-2-enyloxy)naphthalene 74 (303 mg, 1
mmol), AIBN (16 mg, 0.1 mmol) and tri-n-butyltin hydride (350 mg, 1.2 mmol,
0.05M) in benzene (24 ml) was refluxed for 16 hours. The solvent was removed
under reduced pressure and the residue subjected to flash chromatography (hexane)
to afford 7a,11a-dihydrocyclohexano[b]naphto[1.2-d]furan 118 (182 mg, 81%) as a
clear oil which darkened on storage. (Found: C, 85.84; H, 7.18. C\textsubscript{16}H\textsubscript{16}O
requires C, 85.68; H, 7.19). \(^1\text{H} \text{nmr (CDCl}_3 \ \delta 1.07 - 2.4 \text{ (m, 8H, 4 x CH}_2\text{);} 3.4
(m, 1H, ArCH); 4.75 (m, 1H, OCH); 7.1 - 7.8 (m, 6H, ArH). \(^13\text{C} \text{nmr (CDCl}_3 \ \delta 20.3 \text{ (t), 22.5 (t), 27.3 (t), 29.0 (t), 39.7 (d), 83.4 (d), 112.5 (d), 122.6 (d, 2C),
126.3 (d), 126.7 (s), 128.4 (d), 128.8 (d), 129.4 (s), 130.2 (s), 156.6 (s).

6b,10a-Dihydrocyclohexano[b]naphto[2.1-d]furan 120

A solution of 2-bromo-1-(cyclohex-2-enyloxy)naphthalene 75 (303 mg, 1
mmol), AIBN (16 mg, 0.1 mmol) and tri-n-butyltin hydride (350 mg, 1.2 mmol,
0.05M) in benzene (24 ml) was refluxed for 16 hours. The solvent was removed
under reduced pressure and the residue was purified by flash chromatography
(hexane) to give 6b,10a-dihydrocyclohexano[b]naphto[2.1-d]furan 120 (171 mg,
76%) as a light brown oil which darkened on storage. (Found: C, 85.57; H, 7.59.
C\textsubscript{16}H\textsubscript{16}O requires C, 85.68; H, 7.19). \(^1\text{H} \text{nmr (CDCl}_3 \ \delta 1.1 - 2.2 \text{ (m, 8H, 4 x
CH}_2\text{);} 3.3 \text{ (m, 1H, ArCH); 4.85 (m, 1H, OCH); 7.2 - 8.1 \text{ (m, 6H, ArH}).}
1-Iodo-2-(prop-2-enyloxy)naphthalene 121

The title compound was prepared from 1-iodo-2-naphthol (7.5 g, 27.8 mmol) 3-bromopropene (4.7 g, 38.9 mmol) following the procedure described for 1-bromo-2-(prop-2-enyloxy)naphthalene 66. The residue obtained after workup was purified by recrystallization from pentane to yield 1-iodo-2-(prop-enityloxy)naphthalene 121 (6.5 g, 75.6%) as light yellow crystals, m.p. 58 °C. (Found: C. 50.39; H, 3.32. C_{13}H_{11}O_{1} requires C. 50.35; H, 3.57). \(^1H\) nmr (CDCl\(_3\)) \(\delta\) 4.70 (d, \(J = 4.90Hz, 2H, OCH_{2}\)): 5.28 - 5.6 (m, 2H, CH=CH\(_2\)): 6.0 - 6.20 (m, 1H, CH=CH\(_2\)): 7.10 - 7.80 (m, 5H, ArH): 8.15 (d, \(J = 8.5Hz, 1H, ArH\)).

Methyl 1,2-Dihydrornaphpto[2,1-b]furan-1-butanoate 123

A solution of 1-iodo-2-(prop-2-enyloxy)naphthalene 121 (155 mg, 0.5 mmol), AIBN (8 mg, 0.05 mmol), methyl acrylate (860 mg, 10 mmol), tri-n-butyltin hydride (218 mg, 0.75 mmol, 0.025M) in benzene (30 ml) was refluxed for 16 hours. The solvent was removed under reduced pressure and the residue subjected to flash chromatography (5% ethyl acetate/hexane) to give (26 mg, 28%) an inseparable mixture of 79 and 80 in the ratio of 20:1 by GC.

Further elution (10% ethyl acetate/hexane) afforded methyl 1,2-dihydrornaphpto[2,1-b]furan-1-butanoate 123 (45 mg, 35%) as a clear oil. \(\nu_{\text{max}}\) (Neat) 1730, 1630, 1600 cm\(^{-1}\). \(^1H\) nmr (CDCl\(_3\)) \(\delta\) 1.5 - 2.0 (m, 4H, 2 x CH\(_2\)): 2.34 (t, J = 7.1Hz, 2H, CH\(_2\)CO\(_2\)): 3.62 (s, 3H, CO\(_2\)CH\(_3\)): 3.78 (m, 1H, ArCH\(_2\)): 4.52 (dd, J = 9.2 and 3.3Hz, 1H, OCH(H)): 4.67 (t, \(J = 8.8Hz, 1H, OCH(H)\)): 7.0 - 7.85 (m, 6H, ArH). \(^13C\) nmr (CDCl\(_3\)) \(\delta\) 22.2 (t), 33.5 (t), 33.9 (t), 41.3 (d), 51.4 (q), 76.8 (t), 112.2 (d), 122.2 (d), 122.7 (d), 123.3 (s), 126.6 (d), 129 (d), 129.4 (d), 129.6 (s), 130.5 (s), 157.3 (s), 173.6 (s). Mass spectrum: m/e = 270 (11%, M\(^+\)). 170 (13%), 169 (100%), 141 (26%), 115 (7%). Exact mass (C\(_{17}\)H\(_{18}\)O\(_3\) requires: M\(^+\) = 270.1256. Found: M\(^+\) = 270.1257).
In a separate reaction a solution of 1-bromo-2-(prop-2-enyloxy)-
naphthalene 66 (131.5 mg, 0.5 mmol), AIBN (8 mg, 0.05 mmol), methyl acrylate
(860 mg, 10 mmol) and tri-n-butyltin hydride (218 mg, 0.75 mmol, 0.025M) in
benzene (30 ml) was refluxed for 26 hours with further addition of AIBN (8 mg)
after 16 hours. The reaction was worked up, as described above, to afford, after
chromatography (5% ethyl acetate/hexane) a mixture (20 mg, 31%) of 79 and 80 (in
the ratio of 20:1 by GC) followed by bromide 77 (38 mg, 29%). Further elution
(10% ethyl acetate/hexane) afforded 123 (14 mg, 16%) as a clear oil.

KINETIC METHODS

(a) Kinetic studies

Solutions in benzene containing accurately weighed amounts of the
radical precursors and tri-n-butyltin hydride so as to yield the desired concentrations
were prepared in volumetric flasks and kept frozen under a nitrogen atmosphere until
needed. For kinetic experiments, 200µL of each solution was carefully syringed into
a glass ampoule and 1-2µL of 0.2M solution of azo-bisisobutyronitrile (AIBN) or di-
tert-butyl peroxide (BOOB) in benzene was added as initiator such that its
concentration was 1-2% of the halide. After being degassed by the freeze-thaw
technique, the ampoules were sealed under vacuum and immediately transferred to a
constant temperature bath until the reaction was complete. The ampoules were then
removed, frozen, cracked open and the contents analysed by gas chromatography.
The products of the free-radical reactions were identified by the comparison of
retention times with those of authentic samples, and product ratios were calculated
from peak areas. The results obtained have been compiled in Tables 1, 2, 3, 6, 7.
Each item of data is the result of one or more triplicate determinations.
(b) Temperature control, initiation, and reaction times

Thermolyses were carried out in thermostatted oil baths accurate to ± 0.3 °C in the temperature range 50 - 150 °C. A thermostatted water bath was used in temperature range 1 - 40 °C with UV initiation. The reaction times were dependent on the temperature used. High temperatures were generally carried out for 30 min to 1 hour, while low temperatures were approximately 3 hours. Longer reaction times were required in experiments conducted under second order conditions. Gas chromatography was carried out with Column C or D.
CHAPTER 2

Ethyl 2-acetyl-3-(2-bromophenyl)propionate 125

The title compound was prepared by the method of Beckwith et al.\textsuperscript{39} b.p. 118 - 120 °C/1 mmHg (lit.\textsuperscript{39} b.p. 118 °C/0.9 mmHg).

4-(2-Bromophenyl)-2-butanone 126

Following the procedure of Krapcho,\textsuperscript{74} a mixture of ethyl -(2-acetyl-3-(2-bromophenyl)propionate 125 (5.8 g, 19.70 mmol), sodium chloride (1.3 g, 22.2 mmol), and water (0.72 g, 40 mmol) in DMSO (10 ml) was heated at 170 - 180 °C for 5 hours. The reaction mixture was cooled and diluted with water (25 ml) and extracted with ether (3 x 25 ml). The combined ether extracts were washed with water (2 x 20 ml) and dried (MgSO\textsubscript{4}). The residue obtained after removal of the solvent under reduced pressure was purified by flash chromatography (10% ethyl acetate/hexane) to afford 4-(2-bromophenyl)-2-butanone 126 (3.7 g, 83%) as a clear oil. (Found: C, 53.04; H, 5.08. C\textsubscript{10}H\textsubscript{11}BrO requires C, 52.89; H, 4.88). \(\nu_{\text{max}}\) (Neat) 1720 (CO) cm\(^{-1}\). \(^1\)H nmr (CDCl\(_3\)) \& 2.15 (s, 3H, CH\(_3\)); 2.76 (t, J = 7.3Hz, 2H, ArCH\(_2\)CH\(_2\)); 3.00 (t, J = 7.0Hz, 2H, ArCH\(_2\)CH\(_2\)); 7.0 - 7.25 (m, 3H, ArH); 7.52 (d, J = 8Hz, 1H, ArH).

Ethyl 2-acetyl-3-(1-bromonaphth-2-yl)propionate 127

Standard Alkylation Procedure A

Ethyl acetoacetate (3.47 g, 26.7 mmol) was added to an ethanolic solution of sodium ethoxide prepared by the addition of sodium (0.18 g, 7.8 mmol) to dry ethanol (20 ml) and the mixture was stirred for 10 min at room temperature. 1-Bromo-2-bromomethyl naphthalene 68 (2 g, 6.7 mmol) was added, and the reaction mixture was heated under reflux for 16 hours. The mixture was concentrated under reduced pressure and the residue was diluted with water (50 ml) and extracted with ether (2 x 50 ml). The combined extracts were washed with brine (2 x 25 ml) and
dried (MgSO₄). The residue obtained after removal of the solvent under reduced pressure was purified by recrystallization from hexane to afford ethyl 2-acetyl-3-((1-bromo-2-naphthyl)propionate 127 (1.4 g, 61%) as white crystals. m.p. 48 °C. (Found: C, 58.50; H, 4.82. C₁₇H₁₇BrO₃ requires C, 58.47; H, 4.91). νmax (Nujol) 1740 - 1710 (ester + ketone) cm⁻¹. \(^1\)H nmr (CDCl₃) δ 1.17 (t, J = 7Hz. 3H, (CH₂CH₃); 2.22 (s, 3H, COCH₃); 3.35 - 3.65 (m, 2H, ArCH₂); 4.0 - 4.27 (m, 3H, CH + CH₂CH₃); 7.30 - 8.32 (m, 6H, ArH).

Methyl 2-oxo-cyclohexane-1-carboxylate 129

The title compound was prepared according to Frew and Procter. b.p. 88 °C/4 mmHg (lit. 94 - 95 °C/10 mmHg).

Methyl 2-oxo-cyclooctane-1-carboxylate 130

The title compound was prepared according to Krapcho et al. b.p. 58 - 63 °C/0.15 mmHg (lit. 128 - 132 °C/16 mmHg).

Ethyl 1-[(1-bromonaphth-2-yl)methyl]-2-oxo-cyclopentane-1-carboxylate 131

Following standard procedure A, ethyl 2-oxo-cyclopentane-1-carboxylate 128 (1.87 g, 12 mmol) was alkylated with 1-bromo-2-bromomethyl-naphthalene 68 (3 g, 10 mmol). The residue obtained after workup was purified by flash chromatography (20% ethyl acetate/hexane) to give ethyl 1-[(1-bromonaphth-2-yl)methyl]-2-oxo-cyclopentane-1-carboxylate 131 (3.2 g, 85%) as a pale yellow oil. (Found: C, 60.97; H, 5.08. C₁₉H₁₉BrO₃ requires C, 60.81; H, 5.10). νmax (Neat) 1750 - 1725 (ester + ketone) cm⁻¹. \(^1\)H nmr (CDCl₃) δ 1.26 (t, J = 7.2Hz. 3H, CH₂CH₃); 1.6 - 2.5 (m, 6H, 3 x CH₂); 3.58 (d, J = 14.2Hz 1H, ArCH(H)); 3.85 (d, J = 14.2Hz, 1H, ArCH(H)); 4.7 (q, J = 7.2Hz, 2H, CH₂CH₃); 7.2 - 8.36 (m, 6H, ArH).
Methyl 1-[(1-bromonaphth-2-yl)methyl]-2-oxo-cyclohexane-1-carboxylate 132

Following standard procedure A. methyl 2-oxo-cyclohexane-1-carboxylate 129 (1.1 g, 7.3 mmol) was alkylated with 1-bromo-2-bromomethylnaphthalene 68 (2 g, 6.7 mmol) with the exception that the mixture was refluxed for 5 hours. The residue obtained after workup was purified by recrystallization from ether/hexane to afford methyl 1-[(1-bromonaphth-2-yl)methyl]-2-oxo-cyclohexane-1-carboxylate 132 (2.2 g, 88%) as white crystals. (Found: C. 61.12; H, 5.19. C_{19}H_{19}O_{3}Br requires C. 60.81; H, 5.10). m.p. 110 °C. \( \nu_{\text{max}} \) (Nujol) 1745 (ester), 1710 (ketone) cm\(^{-1}\). \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 1.5 - 2.6 (m, 8H, 4 x CH\(_2\)); 3.55 (d, \( J = 14.3 \text{Hz} \), 1H, ArCH(H)); 3.68 (s, 3H, OCH\(_3\)); 3.73 (d, \( J = 14.3 \text{Hz} \), 1H, ArCH(H)); 7.2 - 8.35 (m, 6H, ArH).

Methyl 1-[(1-bromonaphth-2-yl)methyl]-2-oxo-cyclooctane-1-carboxylate 133

Following standard procedure A. methyl 2-oxo-cyclooctane-1-carboxylate 130 (2.21 g, 12 mmol) was alkylated with 1-bromo-2-bromomethylnaphthalene (3 g, 10 mmol). After workup the residue crystals were recrystallized from ether/hexane to afford methyl 1-[(1-bromonaphth-2-yl)methyl]-2-oxo-cyclooctane-1-carboxylate 133 (3.2 g, 80%) as white crystals. m.p. 90 - 93 °C. (Found: C. 62.35; H, 5.85. C\(_{21}\)H\(_{23}\)BrO\(_3\) requires C. 62.54; H, 5.75). \( \nu_{\text{max}} \) (Nujol) 1715 (ester), 1690 (ketone) cm\(^{-1}\). \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 1.1 - 2.73 (m, 12H, 6 x CH\(_2\)); 3.55 (d, \( J = 14.6 \text{Hz} \), 1H, ArCH(H)); 3.6 (s, 3H, COCH\(_3\)); 3.8 (d, \( J = 14.6 \text{Hz} \), 1H, ArCH(H)); 7.2 - 8.34 (m, 6H, ArH).
**1-Acetyl-2-ethylbenzene 137. 4-Phenyl-2-butanone 138. and 1-Methyl-2.3- dihydroindene-1-ol 139**

A solution of 4-(2-bromophenyl)-2-butanone 126 (227 mg, 1 mmol), AIBN (17 mg, 0.1 mmol), and tri-n-butyltin hydride (350 mg, 1.2 mmol, 0.05 M) in deaerated benzene (24 ml) was refluxed for 2 hours. The solvent was removed under reduced pressure and the residue subjected to flash chromatography (10% ethyl acetate/hexane) to afford 1-acetyl-2-ethylbenzene 137 as a clear liquid (7 mg, 4.7%).

(Found: C, 81.62; H, 8.19. C_{10}H_{12}O requires C, 81.08; H, 8.16). \( \nu_{\text{max}} \) (Neat) 1690 (CO) cm\(^{-1}\). \(^1\)H nmr (CDCl\(_3\)) \( \delta \) 1.2 (t, \( J = 7.6 \)Hz, 3H, CH\(_2\)CH\(_3\)); 2.6 (s, 3H, COCH\(_3\)); 2.9 (q, \( J = 7.6 \)Hz, 2H, CH\(_2\)CH\(_3\)); 7.2 - 7.7 (m, 4H, ArH).

\(^{13}\)C nmr (CDCl\(_3\)) \( \delta \) 18.8 (q), 26.9 (q), 29.8 (t), 125.5 (d), 128.8 (d), 130.3 (d), 131.3 (d), 138 (s), 144.1 (s), 202.1 (s).

Further elution yielded 4-phenyl-2-butanone 138 (89 mg, 60%) as a clear liquid. (Found: C, 80.95; H, 8.08. C\(_{10}\)H\(_{12}\)O requires C, 81.08; H, 8.16). \( \nu_{\text{max}} \) (Neat) 1720 (CO) cm\(^{-1}\). \(^1\)H nmr (CDCl\(_3\)) \( \delta \) 2.1 (s, 3H, COCH\(_3\)), 2.7 - 2.9 (m, 4H, 2 x CH\(_2\)); 7.1 - 7.3 (m, 5H, ArH). \(^{13}\)C nmr (CDCl\(_3\)) \( \delta \) 29.7 (t), 29.9 (q), 45.1 (t), 126 (d), 128.2 (d, 2C), 128.4 (d, 2C), 140.9 (s), 207.7 (s).

Further elution with 20% ethyl acetate/hexane gave 1-methyl-2.3-dihydroindene-1-ol 139 (7.0 mg, 4.7%) as white crystals. m.p. 55 - 56 °C (pentane) (lit. m.p. 56 - 57 °C). (Found: C, 80.94; H, 8.34. C\(_{10}\)H\(_{12}\)O requires C, 81.08; H, 8.16). \( \nu_{\text{max}} \) (Nujol) 3520 (broad, OH) cm\(^{-1}\). \(^1\)H nmr (CDCl\(_3\)) \( \delta \) 1.97 (s, broad, 1H, OH); 2.1 - 2.2 (m, 2H, ArCH\(_2\)CH\(_2\)); 2.7 - 3.16 (m, 2H, ArCH\(_2\)CH\(_2\)); 7.1 - 7.4 (m, 4H, ArH). \(^{13}\)C nmr (CDCl\(_3\)) \( \delta \) 27.3 (q), 29.3 (t), 42.2 (t), 81.1 (s), 122.2 (d), 124.8 (d), 126.7 (d), 128.1 (d), 142.6 (s), 148.4 (s).

The spectra are consistent with literature sources.\(^{153}\)
The experiment was repeated by adding a solution of tri-$n$-butyltin hydride (350 mg, 1.2 mmol) and AIBN (17 mg, 0.1 mmol) in benzene (15 ml) by syringe pump to a refluxing solution of the bromide \(126\) (227 mg, 1 mmol) in benzene (10 ml) over a period of 2 hours. The reaction mixture was heated at reflux for a further 1 hour. After purification the reaction afforded the aryl ketone \(137\) (9 mg, 6%), the open chain product \(138\) (78 mg, 53%) and the alcohol \(139\) (4 mg, 3%).

**Ethyl 2-acetyl-3-(naphth-2-yl)propionate 152 and Ethyl 3-(1-acetylnaphth-2-yl)propionate 153**

A solution of ethyl 2-acetyl-3-(1-bromonaphth-2-yl)propionate \(127\) (349 mg, 1 mmol), AIBN (17 mg, 0.1 mmol), and tri-$n$-butyltin hydride (350 mg, 1.2 mmol, 0.05M) in degassed benzene (24 ml) was refluxed for 2 hours. The solvent was removed under reduced pressure and the residue subjected to MPLC (15% ethyl acetate/hexane) to afford ethyl 2-acetyl-3-(naphth-2-yl)propionate \(152\) (156 mg, 58%) as a clear oil. (Found: C. 75.30; H. 6.80. \(C_{17}H_{18}O_3\) requires C. 75.53; H, 6.71). \(\nu\) \(_{\text{max}}\) (Neat) 1740-1710 (ketone + ester) cm\(^{-1}\). \(^1\)H nmr (CDCl\(_3\)) \(\delta\) 1.14 (t, \(J = 7.1\)Hz, 3H, CH\(_2\)CH\(_3\)); 2.18 (s, 3H, COCH\(_3\)); 3.3 (d, \(J = 7.6\)Hz, 2H, ArCH\(_2\)); 3.87 (t, \(J = 7.6\)Hz, 1H, CH); 4.14 (q, \(J = 7.1\)Hz, 2H, CH\(_2\)CH\(_3\)); 7.2 - 7.80 (m, 7H, ArH).

Further elution gave ethyl 3-(1-acetylnaphth-2-yl)propionate \(153\) (112 mg, 41%) as a clear oil. (Found: C. 75.46; H. 6.81. \(C_{17}H_{18}O_3\) requires C. 75.53; H, 6.71). \(\nu\) \(_{\text{max}}\) (Neat) 1730 (ester), 1700 (arylketone) cm\(^{-1}\). \(^1\)H nmr (CDCl\(_3\)) \(\delta\) 1.22 (t, \(J = 7.1\)Hz, 3H, CH\(_2\)CH\(_3\)); 2.64 (s, 3H, COCH\(_3\)); 2.68 (t, \(J = 7.8\)Hz, 2H, ArCH\(_2\)CH\(_2\)); 3.0 (t, \(J = 7.8\)Hz, 2H, ArCH\(_2\)); 4.12 (q, \(J = 7.1\)Hz, 2H, CH\(_2\)CH\(_3\)); 7.3 - 7.88 (m, 6H, ArH).
Ethyl 1-[(naphth-2-yl)methyl]-2-oxo-cyclopentane-1-carboxylate 160 and
Ethyl 12-oxo-7,8,9,10,11,12-hexahydronaphto[1,2-b]cyclooctene-8-carboxylate 161

A solution of ethyl 1-(1-bromonaphth-2-yl)methyl-2-oxo-cyclopentane-1-carboxylate 131 (300 mg, 0.8 mmol), AIBN (14 mg, 0.08 mmol) and tri-n-butyltin hydride (279 mg, 0.96 mmol, 0.05M) in benzene (19.2 ml) was refluxed for 7 hours. The solvent was removed under reduced pressure and the residue subjected to MPLC (20% ethyl acetate/hexane) to afford ethyl 1-[(naphth-2-yl)methyl]-2-oxo-cyclopentane-1-carboxylate 160 (100 mg, 42%) as a clear oil. (Found: C, 76.87; H, 6.76. C₁₉H₂₀O₃ requires C, 77.0; H, 6.80). ν̇max (Neat) 1750-1725 (ester + ketone) cm⁻¹. ¹H nmr (CDCl₃) δ 1.26 (t, J = 7.2 Hz, 3H, CH₂CH₃); 1.5 - 2.5 (m, 6H, 3 x CH₂); 3.33 (d, J = 4.2 Hz, 2H, ArCH₂); 4.77 (q, J = 7.2 Hz, 2H, CH₂CH₃); 7.8 (m, 7H, ArH).

Further elution afforded ethyl 12-oxo-7,8,9,10,11,12-hexahydronaphtho[1,2-b]cyclooctene-8-carboxylate 161 as a clear oil (35 mg, 16%). (Found: C, 76.82; H, 6.48. C₁₉H₂₀O₃ requires C, 77.0; H, 6.80). ν̇max (CHCl₃) 1730 (ester). 1690 (ketone) cm⁻¹. ¹H nmr (CDCl₃) δ 1.28 (t, J = 7.1 Hz, 3H, CH₂CH₃); 1.6 - 2.0 (m, 4H, 2 x CH₂); 2.4 - 3.5 (m, 5H, ArCH₂ + CH + COCH₂); 4.17 (q, J = 7.1 Hz, 2H, CH₂CH₃); 6.92 - 7.9 (m, 6H, ArH).

Methyl 1-[(naphth-2-yl)methyl]-2-oxo-cyclohexane-1-carboxylate 169

Methyl 13-oxo-8,9,10,11,12,13-hexahydro-7H-naphto[1,2-b]cyclononene-8-carboxylate 170 and 2-[(1-carbomethoxy-2-naphth-2-yl)ethyl]cyclopentane-1-one 171

A solution of methyl 1-(1-bromonaphth-2-yl)methyl-2-oxo-cyclohexane-1-carboxylate 132 (375 mg, 1 mmol), AIBN (17 mg, 0.1 mmol), and tri-n-butyltin hydride (350 mg, 1.2 mmol, 0.05M) in deaerated benzene (24 ml) was refluxed for 6 hours. The solvent was removed under reduced pressure and the residue subjected to flash chromatography (15% ethyl acetate/petroleum ether (60 - 80 °C)) to afford methyl [1-(naphth-2-yl)methyl]-2-oxo-cyclohexane-1-carboxylate 169 as a colourless
Further elution afforded methyl 13-oxo-8.9.10.11.12,13-hexahydro-7H-naphto[1,2-b]cyclocononene-8-carboxylate 170 (45 mg, 15%) as a colourless oil. $v_{\text{max}}$ (CHCl$_3$) 1740 (ester), 1700 (ketone) cm$^{-1}$. $^1$H nmr (CDCl$_3$) $\delta$ 1.45 - 2.1 (m. 6H, 3 x CH$_2$); 2.78 (m, 1H, CH); 3.0 (m, 2H, ArCOCH$_2$); 3.17 (d, $J = 5.4$ Hz, 2H, ArCH$_2$); 3.75 (s, 3H, CO$_2$CH$_3$); 7.2 - 7.9 (m, 6H, ArH). $^{13}$C nmr (CDCl$_3$) $\delta$ 23.1 (t), 24.4 (t), 24.6 (t), 32.6 (t), 43.2 (t), 44.6 (d), 51.8 (q), 124.3 (d), 125.9 (d), 126.9 (d), 127.4 (d), 129.1 (d), 131.6 (s), 132.1 (s), 141.1 (s, 2C), 175.2 (s), 213.3 (s). Mass spectrum: m/e = 296 (54%, $M^+$) 237 (59%), 208 (60%), 181 (65%), 180 (84%), 165 (66%), 152 (57%), 141 (100%), 139 (42%). Exact mass (Found: $M^+ = 296.1411$. C$_{19}$H$_{20}$O$_3$ requires $M^+ = 296.1412$).

Further elution afforded the two inseparable epimers of 2-[(1-carbomethoxy-2-naphth-2-yl)ethyl]cyclopentane-1-one 171 as a clear oil (51 mg, 17%). (Found: C. 76.92. H. 6.53. C$_{19}$H$_{20}$O$_3$ requires C. 77.0; H. 6.80). $v_{\text{max}}$ (CHCl$_3$) 1740 (ester), 1730 (ketone) cm$^{-1}$. $^1$H nmr (CDCl$_3$) $\delta$ 1.5 - 2.5 (m. 8H, 3 x CH$_2$ + 2 x CH); 2.9 - 3.5 (m, 2H, ArCH$_2$); 3.59 and 3.64 (both s, 3H, CO$_2$CH$_3$); 7.23 - 7.87 (m, 7H, ArH). The $\alpha$- and $\beta$-methyl esters have an integration intensity ratio of 5:4.
Methyl 1-[(naphth-2-yl)methyl]-2-oxo-cyclooctane-1-carboxylate 176 and the two epimers of 2-[(1-carbomethoxy-2-naphth-2-yl)ethyl]cycloheptan-1-one 177

A solution of methyl 1-(1-bromonaphth-2-yl)methyl-2-oxo-cyclooctanone-1-carboxylate 133 (403 mg, 1 mmol), AIBN (17 mg, 0.1 mmol) and tri-n-butyltin hydride (350 mg, 1.2 mmol, 0.05M) in benzene (24 ml) was refluxed for 4 hours. The solvent was removed under reduced pressure and the residue subjected to MPLC (20% ethyl acetate/hexane) to yield methyl 1-[(naphth-2-yl)methyl]-2-oxo-cyclooctane-1-carboxylate 176 (20 mg, 6%) as white crystals. m.p. 68 °C. (Found: C, 77.40; H, 7.80. C₂₁H₂₄O₃ requires C, 77.75; H, 7.46). ν_max (Nujol) 1715 (ester). 1690 (ketone) cm⁻¹. ¹H nmr (CDCl₃) δ 1.0 - 2.7 (m, 12H, 6 x CH₂); 3.16 (d, J = 14.6Hz; 1H, ArCH(H)); 3.6 (s, 3H, CO₂CH₃); 3.63 (d, J = 14.6Hz. 1H, ArCH(H)); 7.1 - 7.8 (m, 7H, ArH). ¹³C nmr (CDCl₃) δ 23.1 (t), 24.5 (t), 25.7 (t), 28.46 (t), 28.58 (t), 27.1 (t), 52.1 (q), 64.3 (s), 125.5 (d), 125.9 (d), 127.5 (d, 2C), 127.6 (d), 128.1 (d), 128.6 (d), 132.3 (s), 133.3 (s), 134.7 (s), 171.6 (s), 211.4 (s).

Further elution afforded 130 mg (40%) of one diastereoisomer of 2-[(1-carbomethoxy-2-naphth-2-yl)ethyl]cycloheptan-1-one 177 as a light brown oil. (Found: C, 77.48; H, 7.46. C₂₁H₂₄O₃ requires C, 77.75; H, 7.46). ν_max (Neat) 1740 (ester). 1700 (ketone) cm⁻¹. ¹H nmr (CDCl₃) δ 1.2 - 2.0 (m, 8H, 4 x CH₂); 2.5 (m, 2H, COCH₂); 2.7 - 3.35 (m, 4H, ArCH₂ + 2 x CH); 3.5 (s, 3H, CO₂CH₃); 7.2 - 7.8 (m, 7H, ArH). ¹³C nmr (CDCl₃) δ 23.9 (t), 28.7 (t) 29.1 (t), 29.2 (t), 36.7 (t), 43.9 (t), 49.5 (d), 51.6 (q), 53.3 (d), 125.5 (d), 126.1 (d), 127.4 (d, 2C), 127.7 (d), 127.8 (d), 128.2 (d), 132.4 (d), 132.4 (s), 133.6 (s), 136.6 (s). 174.7 (s), 214.1 (s).

Further elution afforded 172 mg (53%) of the other diastereoisomer of 177 as a light brown oil. (Found: C, 77.32; H, 7.56. C₂₁H₂₄O₃ requires C, 77.75; H, 7.46). ν_max (Neat) 1740 (ester). 1700 (ketone) cm⁻¹. ¹H nmr (CDCl₃) δ
1.2 - 2.1 (m, 8H, 4xCH₂); 2.3 - 2.6 (m, 1H, COCH₂); 2.8 - 3.18 (m, 4H, ArCH₂ + 2xCH); 3.5 (s, 3H, CO₂CH₃); 7.2 - 7.8 (m, 7H, ArH). ¹³C nmr (CDCl₃) δ 23.7 (t), 28.3 (t), 29.1 (t), 29.2 (t), 35.5 (t), 43.5 (t), 48.8 (d), 51.4 (q), 52.6 (d), 125.3 (d), 125.9 (d), 127.4 (d, 2C), 127.5 (d), 127.6 (d), 127.9 (d), 132.2 (s), 133.4 (s), 136.4 (s), 175 (s), 214.3 (s).

Ethyl 2-Cyano-3-(2-bromophenyl)propionate 179

The title compound was prepared by the method of Beckwith et al.³⁹ m.p 38 - 40 °C (lit.³⁹ m.p. 38 - 40 °C).

3-(2-bromophenyl)propanenitrile 180

The title compound was prepared by the method of Krapcho⁷⁴ from ethyl 2-cyano-3-(2-bromophenyl)propionate 179 (4 g, 14 mmol), sodium chloride (0.9 gm, 15.4 mmol), water (0.5 g, 28 mmol) and DMSO (10 ml) as described for 4-(2-bromophenyl)-2-butanone 126. After workup, purification was achieved by flash chromatography (10% ethyl acetate/hexane) to give 3-(2-bromophenyl)propanenitrile 180 (2.5 g, 85%) as a clear oil. (Found: C, 51.41; H, 3.80. C₉H₈NBr requires C, 51.46; H, 3.84). νmax (Neat) 2250 (nitrile) cm⁻¹. ¹H nmr (CDCl₃) δ 2.68 (t, J = 7.3Hz, 2H, CH₂CN): 3.1 (t, J = 7.3Hz, 2H, ArCH₂) 7.1 - 7.6 (m, 4H, ArH). ¹³C nmr (CDCl₃) δ 17.6 (t), 32.1 (t), 118.7 (s), 124 (s), 128 (d), 129.1 (d), 130.8 (d), 133.2 (d), 137.2 (s).

Ethyl 2-cyano-3-(1-bromonaphth-2-yl)propionate 181

Ethyl cyanoacetate (4.5 g, 40 mmol) was alkylated with 1-bromo-2-bromomethylnaphthalene 68 (3 g, 10 mmol) following standard procedure A. After workup, the residue crystals were recrystallized from ether/hexane to afford ethyl 2-cyano-3-(1-bromonaphth-2-yl)propionate 181 as white crystals (1.2 g, 38%). m.p. 85 - 86 °C. (Found: C, 57.85; H, 4.25; N, 4.22). νmax (Nujol) 2250 and 220 (nitrile), 1725 (CO₂C₂H₅) cm⁻¹. ¹H nmr (CDCl₃) δ 1.3 (t, J = 7.1Hz, 3H,
3-Phenylpropanenitrile 185 and 2,3-dihydro-1H-indene-1-one 186

To a refluxing solution of 3-(2-bromophenyl)-propanenitrile 180 (210 mg, 1 mmol) in benzene (10 ml) a solution of AIBN (17 mg, 0.1 mmol) and tri-n-butyltin hydride (350 mg, 1.2 mmol) in benzene (15 ml) was added by a syringe pump over 5 hours. The reaction mixture was heated at reflux for a further 15 hours. The benzene was removed under reduced pressure. The residue was diluted with ether (10 ml) and stirred with 80% v/v acetic acid/water (5 ml) for 1 hour. The layers were separated and the aqueous phase extracted with ether (2 x 20 ml). The combined ether layers were washed with water (2 x 10 ml) and dried (MgSO₄).

After removal of solvent the residue was subjected to flash chromatography (10% ethyl acetate/hexane) to afford 3-phenylpropanenitrile 185 (27 mg, 21%) as a colourless liquid. (Found: C, 82.52; H, 7.06. C₉H₉N requires C, 82.41; H, 6.92). ν_max (Neat) 2250 (nitrite) cm⁻¹. ¹H nmr (CDCl₃) δ 2.6 (t, J = 7.2 Hz, 2H, CH₂CN); 2.9 (t, J = 7.2 Hz, 2H, ArCH₂); 7.3 (m, 5H, ArH).

Further elution afforded 9 mg (7%) of 2,3-dihydro-1H-indene-1-one 186 as white crystals. m.p. 42 °C (petroleum ether). GC retention times of 186 was found to be identical with commercially available authentic sample.

Ethyl 3-(1-cyanonaphth-2-yl)propionate 195

A solution of ethyl 2-cyano-3-(1-bromonaphth-2-yl)propionate 181 (332 mg, 1 mmol), AIBN (17 mg, 0.1 mmol), and tri-n-butyltin hydride (350 mg, 1.2 mmol, 0.05M) in benzene (24 ml) was refluxed for 2 hours. The solvent was removed under reduced pressure and the residue subjected to MPLC (20% ethyl
acetate/hexane) to afford ethyl 3-(1-cyanonaphth-2-yl)propionate 195 as white crystals (235 mg, 97%). m.p. 47 °C (ether/hexane). (Found: C, 75.68; H, 6.11; N, 5.67. C₁₆H₁₅NO₂ requires C, 75.87; H, 5.97; N, 5.53). νₘₐₓ (CHCl₃) 2220 (nitrile). 1730 (ester) cm⁻¹. ¹H nmr (CDCl₃) δ 1.2 (t, J = 7.1Hz, 3H, CH₂CH₃); 2.7 (t, J = 7.6Hz, 2H, CH₂CO); 3.36 (t, J = 7.6Hz, 2H, ArCH₂); 4.14 (q, J = 7.6Hz, 2H, CH₂CH₃); 7.2 - 8.2 (m, 6H, ArH). ¹³C nmr (CDCl₃) δ 14.3 (q). 30.4 (t), 35.0 (t), 60.8 (t), 109.3 (s), 116.7 (s), 125.1 (d), 126.8 (d), 127.0 (d), 128.5 (d), 128.7 (d), 131.6 (s), 132.8 (s), 133.1 (d), 145.4 (s), 172.1 (s).
CHAPTER 3

Methyl 3-hydroxybenzoate 200

A stirred mixture of 3-hydroxybenzenecarboxylic acid 1 (7 g, 50 mmol), methanol (16 g, 500 mmol) and concentrated sulphuric acid (2 ml) was refluxed for 5 hours. The excess methanol was removed under reduced pressure and the residue was diluted with water and extracted with ether (3 x 50 ml). The combined extracts were washed with saturated sodium bicarbonate solution (2 x 50 ml), water (75 ml) and were (MgSO\(_4\)). The solvent was removed under reduced pressure and the residue was recrystallized from benzene/petroleum ether to afford methyl 3-hydroxybenzoate 200 (6.5 g, 84%). m.p. 72 °C (lit.\(^{154}\) m.p. 72 °C).

Methyl 3-(t-butyldimethylsilyloxy)benzoate 201

Following the general procedure of Corey,\(^99\) a solution of methyl 3-hydroxybenzoate 200 (4 g, 26.3 mmol), imidazole (4.46 g, 65.8 mmol), and t-butyldimethylsilyl chloride (4.78 g, 31.6 mmol) in dimethylformamide (DMF) (20 ml) was stirred at room temperature for 18 hours. The solution was diluted with water, and extracted with ethyl acetate (3 x 50 ml). The combined extracts were washed with brine (50 ml) and dried (MgSO\(_4\)). The residue obtained after removal of solvent under reduced pressure was purified by flash chromatography (2% ethyl acetate/hexane) to give methyl 3-(t-butyldimethylsilyloxy)benzoate 201 (6.3 g, 90%) as a clear oil. (Found: C. 63.30; H. 8.16. C\(_{14}\)H\(_{22}\)O\(_3\)Si requires C. 63.13; H. 8.27). \(^1\)H nmr (CDCl\(_3\)) \(\delta\) 0.22 (s, 6H, Si(CH\(_3\))\(_2\)); 1.00 (s, 9H, SiC(CH\(_3\))\(_3\)); 3.90 (s, 3H, CO\(_2\)CH\(_3\)); 7.0 - 7.70 (m, 4H, ArH). \(^13\)C nmr (CDCl\(_3\)) \(\delta\) - 4.41 (q, 2C), 18.22 (s), 25.72 (q, 3C), 52.08 (q), 121.05 (d), 122.60 (d), 124.79 (d), 129.37 (d), 131.59 (s), 155.74 (s), 166.90 (s).
Methyl 1-(o-bromobenzyl)-3-(t-butyldimethylsilyloxy)-2,5-cyclohexadiene-1-carboxylate 202

Following the general procedure of Mander,100 a solution of methyl 3-(t-butyldimethylsilyloxy)benzoate 201 (2 g, 7.5 mmol), and dry t-butyl alcohol (0.56 g, 7.5 mmol), in dry ammonia (~100 ml) and dry THF (3.0 ml) was cooled with stirring to -78 °C under nitrogen. Lithium metal (~104 mg, 15.0 mmol) was added in small pieces until a deep blue colour persisted for 45 min. o-Bromobenzyl bromide 124 (1.76 g, 7.2 mmol) in dry THF (2.0 ml) was added and the solution stirred at -78 °C for further 3 hours. The ammonia was then allowed to evaporate, the residue was diluted with pH 5.5 buffer and extracted with ether (2 x 50 ml). The ether extracts were washed with brine (40 ml), dried, and evaporated to yield a yellow oil. The residue was subjected to flash chromatography (5% ethylacetate/hexane) to afford methyl 1-(o-bromobenzyl)-3-(t-butyldimethylsilyloxy)-2,5-cyclohexadiene-1-carboxylate 202 (1.38 g, 42%) as a light yellow oil. (Found: C, 57.65; H, 6.78. C_{21}H_{29}BrO_3Si requires C, 57.66; H, 6.68). ν_{max} (Neat) 1730, 1690, 1650 cm\(^{-1}\). H nmr (CDCl\(_3\)) δ 0.08 (s, 3H, SiCH\(_3\)); 0.12 (s, 3H, SiCH\(_3\)); 0.90 (s, 9H, SiC(CH\(_3\))\(_3\)); 2.25 - 2.60 (m, 2H, CH\(_2\)); 3.25 (d, J = 2Hz, 2H, ArCH\(_2\)); 3.72 (s, 3H, CO\(_2\)CH\(_3\)); 5.03 (s, 1H, CH=COSi); 5.70 - 5.90 (m, 2H, CH=CHCH\(_2\)); 7.0 - 7.30 (m, 3H, ArH); 7.50 (d, J = 7.7Hz, 1H, ArH). C\(_{13}\) nmr (CDCl\(_3\)) δ - 4.41 (q), - 4.32 (q), 17.98 (s), 25.63 (q, 3C), 30.47 (t), 44.45 (t), 52.06 (s), 52.33 (q), 104.36 (d), 125.03 (d), 126.28 (s), 126.63 (d, 2C), 128.0 (d), 131.91 (d), 132.78 (d), 136.73 (s), 149.92 (s), 175.08 (s).

Methyl 2-(t-butyldimethylsilyloxy)benzoate 204

The title compound was prepared from methyl 2-hydroxybenzoate 203 (4 g, 26.3 mmol) and t-butyldimethylsilyl chloride (4.78 g, 31.6 mmol) as described above for methyl 3-(t-butyldimethylsilyloxy)benzoate 201. The residue obtained after workup was purified by flash chromatography (3% ethyl acetate/hexane) to afford methyl 2-(t-butyldimethylsilyloxy)benzoate 204 (6.93 g, 99%) as a clear oil.
Methyl 1-(o-bromobenzyl)-2-(t-butyldimethylsilyloxy)-2,5-cyclohexadiene-1-carboxylate 205

The title compound was prepared from methyl 2-(t-butyldimethylsilyloxy)benzoate 204 (2 g, 7.5 mmol) and o-bromobenzyl bromide 124 (1.76 g, 7.2 mmol) as described above for methyl 1-(o-bromobenzyl)-3-(t-butyldimethylsilyloxy)-2,5-cyclohexadiene-1-carboxylate 202. The crude residue isolated after workup was purified by flash chromatography (5% ethyl acetate/hexane) to afford methyl 1-(o-bromobenzyl)-2-(t-butyldimethylsilyloxy)-2,5-cyclohexadiene-1-carboxylate 205 (2.79 g, 85%) as a clear oil which solidified on standing. m.p. 58 °C. νmax (Nujol) 1740, 1690, 1650 cm⁻¹. ¹H nmr (CDCl₃) δ 0.20 (s, 3H, SiCH₃); 0.30 (s, 3H, SiCH₃); 0.96 (s, 9H, SiC(CH₃)₃); 2.00 - 2.64 (m, 2H, CH₂); 3.3 (d, J = 13.67Hz, 1H, ArCH(H)); 3.61 (d, J = 13.63Hz, 1H, ArCH(H)); 3.74 (s, 3H, CO₂CH₃); 4.88 (m, 1H, C=CHCH₂); 5.58 - 5.73 (m, 2H, CH = CHCH₂); 6.98 - 7.27 (m, 3H, ArH); 7.47 (d, J = 7.8Hz, 1H, ArH). ¹³C nmr (CDCl₃) δ 5.68 (q), -4.01 (q), 17.95 (s), 25.51 (q, 3C), 26.27 (t), 38.18 (t), 52.35 (q), 54.62 (s), 102.4 (d), 125.4 (d), 126.20 (d, 2C), 126.40 (s), 127.6 (d), 132.20 (d, 2C), 137.10 (s), 146.50 (s), 173.60 (s). Mass spectrum: m/e = 439 (3%), 437 (4%, M + 1), 381 (12%), 379 (17%), 267 (45%), 210 (42%), 209 (100%), 171 (41%), 169 (43%). Exact mass (C₂₁H₃₀O₃Br₇₉Si requires: (M + 1) = 437.1148. Found: (M + 1) = 437.1013).

Ethyl 1-(o-bromobenzyl)-2-oxo-cyclopentane-1-carboxylate 206

The title compound was prepared according to the method of Beckwith.³⁹ b.p. 190 - 191 °C/4.5 mmHg (lit.³⁹ b.p. 190 °C/4.5 mmHg).
Methyl 1-(o-bromobenzyl)-2-oxo-cyclohexane-1-carboxylate 207

The title compound was prepared according to the method of Beckwith.\(^39\) m.p. 50 - 51 °C (lit.\(^39\) m.p. 50 - 51 °C).

Ethyl 1-(o-bromobenzyl)-2-(t-butyldimethylsilyloxy)-2-cyclopentene-1-carboxylate 208

Following the procedure of Mander and Sethi.\(^101\) a solution of ethyl 1-(o-bromobenzyl)-2-oxo-cyclopentane-1-carboxylate 206 (1 g, 3.07 mmol), triethylamine (465 mg, 4.61 mmol), and t-butyldimethylsilyl triflate (974 mg, 3.68 mmol) in dichloromethane (10 ml) was stirred at room temperature for 30 min. The reaction mixture was diluted with dichloromethane (50 ml), washed with cold sodium bicarbonate solution (2 x 25 ml), and dried (Na\(_2\)SO\(_4\)). The residue obtained after the removal of solvent under reduced pressure was taken up in dry ether and filtered. The ether solution was concentrated and the residue purified by flash chromatography (5% ethyl acetate/hexane) to afford ethyl 1-(o-bromobenzyl)-2-(t-butyldimethylsilyloxy)-2-cyclopentene-1-carboxylate 208 (1.31 g, 97%) as a clear oil. 

\(\nu_{\text{max}}\) (Neat) 1730, 1650 cm\(^{-1}\). \(\text{H nmr} (\text{CDCl}_3) \delta 0.18 (s, 3H, SiCH}_3\); 0.25 (s, 3H, SiCH\(_3\)); 0.96 (s, 9H, SiC(CH\(_3\))\(_3\)); 1.25 (t, J = 7.1Hz, 3H, CO\(_2\)CH\(_2\)CH\(_3\)); 1.70 - 2.30 (m, 4H, 2 x CH\(_2\)); 3.12 (d, J = 14.2Hz, 1H, ArCH(H)); 3.55 (d, J = 14.2Hz, 1H, ArCH(H)); 4.15 (q, J = 7.1Hz, 2H, CO\(_2\)CH\(_2\)CH\(_3\)); 4.65 (t, J = 2.3Hz, 1H, C=CHCH\(_2\)); 7.0 - 7.50 (m, 4H, ArH). Mass spectrum: m/e = 383 (17%), 381 (16%, M\(^+\) - C(CH\(_3\))\(_3\)), 212 (53%), 184 (21%), 109 (18%), 75 (44%), 73 (100%).

Exact mass (C\(_{21}\)H\(_{31}\)O\(_3\)Br\(_79\)Si requires: M\(^+\) - C(CH\(_3\))\(_3\) = 381.0522. Found: M\(^+\) - C(CH\(_3\))\(_3\) = 381.0523).

Methyl 1-(o-bromobenzyl)-2-(t-butyldimethylsilyloxy)-2-cyclohexene-1-carboxylate 209

The title compound was prepared from methyl 1-(o-bromobenzyl)-2-oxo-cyclohexane-1-carboxylate 207 (1 g, 3.07 mmol) and t-butyldimethylsilyl triflate (1.2
g, 4.54 mmol) as described above for 208. The residue obtained after workup was purified by flash chromatography (5% ethyl acetate/hexane) to afford methyl 1-(o-bromobenzyl)-2-(t-butyldimethylsilyloxy)-2-cyclohexene-1-carboxylate 209 (940 mg, 70%) as a clear oil. ν<sub>max</sub> (Neat) 1730, 1660 cm<sup>-1</sup>. <sup>1</sup>H nmr (CDCl<sub>3</sub>) δ 0.18 (s, 3H, SiCH<sub>3</sub>); 0.26 (s, 3H, SiCH<sub>3</sub>); 0.93 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>); 1.20 - 2.10 (m, 6H, 3 x CH<sub>2</sub>); 3.30 (d, J = 14.6 Hz, 1H, ArCH(H)); 3.58 (d, J = 13.9 Hz, 1H, ArCH(H)); 3.71 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>); 4.93 (t, J = 4.0 Hz, 1H, C=CHCH<sub>2</sub>); 7.0 - 7.60 (m, 4H, ArH). 13C nmr (CDCl<sub>3</sub>) δ 5.54 (q), - 3.94 (q), 18.14 (s), 19.13 (t), 23.83 (t), 25.67 (q, 3C), 31.33 (t), 38.02 (t), 51.89 (q), 52.94 (s), 106.55 (d), 126.87 (d), 127.69 (d), 132.07 (d), 132.57 (d), 137.88 (s), 148.13 (s), 175.84 (s). Mass spectrum: m/e = 383 (26%), 381 (25%, M<sup>+</sup> - C(CH<sub>3</sub>)<sub>3</sub>). 212 (100%), 89 (27%), 73 (48%). Exact mass (C<sub>21</sub>H<sub>31</sub>0<sub>3</sub>Br<sup>79</sup>Si requires: M<sup>+</sup> - C(CH<sub>3</sub>)<sub>4</sub> = 381.0523).

Ethyl 1-[(1-bromonaphth-2-yl)methyl]-2-(t-butyldimethylsilyloxy)-2-cyclopentene-1-carboxylate 210

The title compound was prepared from ethyl 1-[(1-bromonaphth-2-yl)methyl]-2-oxo-cyclopentane-1-carboxylate 128 (1.5 g, 4 mmol) as described above for 208. The residue obtained after workup was purified by flash chromatography (5% ethyl acetate/hexane) to give ethyl 1-[(1-bromonaphth-2-yl)methyl]-2-(t-butyldimethylsilyloxy)-2-cyclopentene-1-carboxylate 210 (1.9 g, 97%) as a clear oil which solidified on standing. m.p 62-64 °C. ν<sub>max</sub> (Neat) 1740, 1650 cm<sup>-1</sup>. <sup>1</sup>H nmr (CDCl<sub>3</sub>) δ 0.19 (s, 3H, SiCH<sub>3</sub>); 0.28 (s, 3H, SiCH<sub>3</sub>); 0.98 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>); 1.27 (t, J = 7.3 Hz, 3H, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 1.50 - 2.32 (m, 4H, 2 x CH<sub>2</sub>); 3.37 (d, J = 7.1 Hz, 1H, ArCH(H)); 3.84 (d, J = 7.1 Hz, 1H, ArCH(H)); 4.18 (q, J = 7.1 Hz, 2H, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); 4.65 (s, 1H, C=CH), 7.40 - 7.80 (m, 5H, ArH); 8.33 (d, J = 7.8 Hz, 1H, ArH). 13C nmr (CDCl<sub>3</sub>) δ 5.48 (q), - 4.62 (q), 14.30 (q); 18.13 (s), 25.66 (q, 3C), 26.71 (t), 30.42 (t), 38.65 (t), 59.68 (s), 60.87 (t), 104.41 (d), 125.96 (d), 126.75 (d), 127.10 (d), 127.89 (d, 2C), 128.97 (d), 132.56 (s), 133.40 (s), 136.57 (s, 2C) 153.06 (s), 175.25 (s). Mass spectrum: m/e = 433 (28%), 431
Methyl 1-[(1-bromonaphth-2-yl)methyl]-2-(t-butyldimethylsilyloxy)-2-cyclohexene-1-carboxylate 211

The title compound was prepared from methyl 1-[(1-bromonaphth-2-yl)methyl]-2-oxo-cyclohexane-1-carboxylate 129 (900 mg, 2.40 mmol) and t-butyldimethylsilyl triflate (698 mg, 2.64 mmol) as described above for 208. The residue obtained after workup was purified by flash chromatography (5% ethyl acetate/hexane) to afford methyl 1-[(1-bromonaphth-2-yl)methyl]-2-(t-butyldimethylsilyloxy)-2-cyclohexene-1-carboxylate 211 (880 mg, 75%) as a clear oil.

v\text{max} (Neat) 1730, 1665 cm\(^{-1}\). \(^1\)H nmr (CDCl\(_3\)) \(\delta\) 0.20 (s, 3H, SiCH\(_3\)); 0.29 (s, 3H, SiCH\(_3\)); 0.95 (s, 9H, SiC(CH\(_3\))\(_3\)); 1.10 - 2.10 (m, 6H, 3 x CH\(_2\)); 3.53 (d, J = 13.92Hz, 1H, ArCH(H)); 3.73 (s, 3H, CO\(_2\)CH\(_3\)); 3.92 (d, J = 13.43Hz, 1H, ArCH(H)); 4.95 (t, J = 4.02Hz, 1H, C=CHCH\(_2\)); 7.40 - 7.82 (m, 5H, ArH); 8.34 (d, J = 8.54Hz, 1H, ArH). \(^13\)C nmr (CDCl\(_3\)) \(\delta\) 5.60 (q), -3.99 (q), 18.13 (s), 19.12 (t), 23.74 (t), 25.64 (q, 3C), 31.39 (t), 39.30 (t), 51.92 (q), 52.97 (s), 106.63 (d), 125.88 (d), 126.44 (s), 126.75 (d), 126.99 (d), 127.80 (d), 127.98 (d), 129.12 (d), 132.51 (s), 133.41 (s), 136.48 (s), 148.13 (s), 175.87 (s). Mass spectrum: m/e = 433 (31%), 431 (28%, M\(^+\) - C(CH\(_3\))\(_3\)), 219 (21%), 212 (100%), 211 (34%), 140 (21%), 89 (33%), 73 (86%). Exact mass (C\(_{25}\)H\(_{33}\)O\(_3\)Br\(^{79}\)Si requires M\(^+\) - C(CH\(_3\))\(_3\) = 431.0678). Found: M\(^+\) - C(CH\(_3\))\(_3\) = 431.0677.

Methyl 2-oxo-2,3,4,4a,9,9a-hexahydro-1H-fluorene-9a-carboxylate 218.

Methyl 4β-hydroxy-4a,9,9a-tetrahydro-3H-fluorene-9a-carboxylate 219, and
Methyl 4α-hydroxy-4a,9,9a-tetrahydro-3H-fluorene-9a-carboxylate 220

A solution of methyl 1-[(α-bromobenzyl)-3-(t-butyldimethylsilyloxy)-2,5-cyclohexadiene-1-carboxylate 202 (437 mg, 1 mmol), AIBN (20 mg, 0.12 mmol)
and tri-n-butyltin hydride (350 mg, 1.2 mmol, 0.05M) in dry deaerated benzene (24 ml) was refluxed for 3 hours. GC analysis of the reaction mixture showed the formation of three products in the ratio of 1:2:2:1. The solvent was removed under reduced pressure and the residue subjected to flash chromatography (hexane) to afford an inseparable mixture (338 mg, 94%) of the products.

A solution of the product mixture (338 mg, 0.94 mmol) in acetonitrile (10 ml) was stirred with 50% aqueous solution of hydrofluoric acid (1 ml) at room temperature for 24 hours. The mixture was diluted with water (25 ml) and extracted with chloroform (3 x 25 ml). The combined extracts were washed with brine (2 x 25 ml) and dried (Na₂SO₄). The solvent was removed under reduced pressure and the residue was purified by flash chromatography. Initial elution with 20% ethyl acetate/hexane gave methyl 2-oxo-2,3,4,4a,9,9a-hexahydro-1H-fluorene-9a-carboxylate 218 (53 mg, 23%) as a clear oil. v_max (Neat) 1725 (broad, ester + ketone) cm⁻¹. ¹H nmr (CDCl₃) δ 2.0 - 2.50 (m, 6H, 3 x CH₂), 2.74 (d, J = 16.1 Hz, 1H, ArCH); 3.61 (d, J = 16.1 Hz, 1H, ArCH); 3.75 (s, 3H, CO₂CH₃); 3.79 (s, 1H, CH); 7.24 (s, 4H, ArH). ¹³C nmr (CDCl₃) δ 25.29 (t), 36.09 (t), 45.52 (d), 46.72 (t), 52.47 (q), 55.28 (s), 123.31 (d), 125.09 (d), 127.19 (d), 127.40 (d), 140.48 (s), 142.73 (s), 175.99 (s), 209.42 (s). Mass spectrum: m/e = 244 (27%, M⁺), 216 (84%), 184 (98%), 142 (100%), 128 (98%). Exact mass (C₁₅H₁₆O₃ requires M⁺ = 244.1099). Found: M⁺ = 244.1099).

Further elution with 30% ethyl acetate/hexane afforded methyl 4β-hydroxy-4,4a,9,9a-tetrahydro-3H-fluorene-9a-carboxylate 219 (97 mg, 42%) as white crystals. m.p. 115-116 °C (dichloromethane/hexane). v_max (Nujol) 3500 (broad, 0H). 1720 (ester) cm⁻¹. ¹H nmr (CDCl₃) δ 2.0 - 2.40 (m, 3H, CH₂ + OH); 2.99 (d, J = 15.6 Hz, 1H, ArCH(H)); 3.39 (d, J = 15.9 Hz, ArCH(H)); 3.74 (s, 3H, CO₂CH₃); 4.01 (d, J = 3.90 Hz, 1H, ArCHCH); 4.42 (m, 1H, CHOH); 5.61 (m, 2H, CH=CHCH₂); 7.1 - 7.70 (m, 4H, ArH). ¹³C nmr (CDCl₃) 29.54 (t), 43.45 (t),
Further elution afforded methyl 4α-hydroxy-4,4a,9,9a-tetrahydro-3H-fluorene-9a-carboxylate 219 (44 mg, 19%) as white crystals. m.p. 69 °C (hexane). 

ν_{max} (Nujol) 3340 (broad, OH), 1730 (ester) cm^{-1}. ^1H nmr (CDCl₃) δ 2.15 (m, 2H, CH₂); 3.0 (d, J = 15.6Hz, 1H, ArCH(H)); 3.42 (d, J = 5.4Hz, 1H, OH); 3.52 (d, J = 15.6Hz, 1H, ArCH(H)); 3.77 (s, 3H, CO₂CH₃); 3.94 (d, J = 5.4Hz, 1H, ArCH(H)); 4.44 (m, 1H, CHCH₂); 5.70 (m, 2H, CH=CH); 7.2 (s, 4H, ArH).

^{13}C nmr δ 29.48 (t), 43.56 (t), 51.56 (d), 52.84 (q), 53.95 (s), 65.98 (d), 123.77 (d), 125.02 (d), 125.99 (d), 126.83 (d), 127.33 (d), 128.03 (d), 140.47 (s), 141.99 (s), 176.85 (d). Mass spectrum: m/e = 244 (2%, M^+), 226 (80%), 168 (65%), 167 (100%), 166 (72%), 165 (54%), 155 (53%), 115 (60%). Exact mass (C₁₅H₁₆O₃ requires: M^+ = 244.1099. Found: M^+ = 244.1099).

Methyl 1-oxo-1,3,4,4a,9,9a-hexahydro-2H-fluorene-9a-carboxylate 226

Methyl 4a-hydroxy-4,4a,9,9a-tetrahydro-3H-fluorene-9a-carboxylate 227

A solution of methyl 1-(o-bromobenzyl)-2-(t-butyldimethylsilyloxy)-2,5-cyclohexadiene-1-carboxylate 205 (437 mg, 1 mmol), AIBN (20 mg, 0.12 mmol) and tri-n-butyltin hydride (350 mg, 1.2 mmol, 0.05M) in dry deaerated benzene (24 ml) was refluxed for 2 hours. GC analysis of the reaction mixture showed the formation of two new products in the ratio 5:1. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (hexane) to afford an inseparable mixture (326 mg, 91%) of the products.

A solution of the product mixture (326 mg, 0.91 mmol) in acetonitrile (10 ml) was stirred with 50% aqueous solution of hydrofluoric acid (1 ml) at room
temperature for 24 hours. The reaction mixture was diluted with water (25 ml) and extracted with chloroform (3 x 25 ml). The combined extracts were washed with brine (2 x 25 ml), and dried (Na₂SO₄). The residue obtained after removal of the solvent was purified by flash chromatography. Initial elution with 20% ethyl acetate/hexane gave methyl 1-oxo-1,3,4-4a,9,9a-hexahydro-2H-fluorene-9a-carboxylate 226 (151 mg, 61%) as a clear oil. v_max (Neat) 1725 (broad, ketone + ester) cm⁻¹. ¹H nmr (CDCl₃) δ 1.50 - 2.65 (m, 6H. 3 x CH₂); 3.20 (d, J = 16Hz. 1H ArCH(H)); 3.77 (s, 3H. CO₂CH₃); 3.80 (d, J = 16Hz, 1H. ArCH(H)); 4.1 (m, 1H. CHCH₃); 7.0 - 7.30 (m, 4H. ArH). ¹³C nmr (CDCl₃) δ 22.25 (t), 24.97 (t), 37.87 (t), 40.29 (t), 51.04 (d), 52.73 (q), 67.30 (s), 122.46 (d), 124.65 (d), 126.89 (d), 127.25 (d), 141.29 (s), 141.59 (s), 171.87 (s). Mass spectrum: m/e = 244 (2%, M⁺) 185 (100%), 156 (26%), 129 (24%), 128 (20%), 115 (23%). Exact mass (C₁₅H₁₆O₃ requires: M⁺ = 244.1099. Found: M⁺ = 244.1099).

Further elution with 30% ethyl acetate/hexane afforded methyl 4a-hydroxy-4,4a,9,9a-tetrahydro-3H-fluorene-9a-carboxylate 227 (29 mg, 12%) as white crystals. m.p. 100-102°C (dichloromethane/hexane). v_max (Nujol) 3420 (broad, OH). 1715 (ester) 1460 cm⁻¹. ¹H nmr (CDCl₃) δ 1.8 - 2.4 (m, 4H. 2 x CH₂); 2.88 (d, J = 16.0Hz, 1H, ArCH(H)); 3.2 (s. broad. 1H. OH); 3.75 (d, J = 16.0Hz, 1H. ArCH(H)); 3.77 (s, 3H. CO₂CH₃); 5.5 - 5.8 (m, 2H. CH=CH); 7.1 - 7.4 (m, 4H. ArH). ¹³C nmr (CDCl₃) δ 23.62 (t), 29.41 (t), 40.77 (t), 52.27 (q), 58.52 (s), 81.58 (s), 122.64 (d), 125.50 (d), 126.96 (d), 128.86 (d, 2C), 129.50 (d), 140.92 (s), 143.60 (s), 174.55 (s). Mass spectrum: m/e = 227 (12%), 226 (77%), 168 (18%), 167 (100%), 166 (32%), 141 (11%), 128 (10%), 115 (12%). Exact mass (C₁₅H₁₆O₃ requires: M⁺ - H₂O = 226.0994. Found: M⁺ - H₂O = 226.0993).
Ethyl 1-benzyl-2-oxo-cyclopentane-1-carboxylate 235

Ethyl 3a-hydroxy-1.2.3.3a,8.8a-hexahydrocyclopenta[a]indene-8a-carboxylate 236

and

Ethyl 10-hydroxy-5.6.7.8.9-pentahydro-6.9-methanobenzocycloheptene-6-carboxylate 237

A solution of ethyl 1-(o-bromobenzyl)-2-(t-butyldimethylsilyloxy)-2-cyclopentene-1-carboxylate 208 (439 mg. 1 mmol). AIBN (16 mg, 0.1 mmol), and tri-n-butyltin hydride (350 mg, 1.2 mmol, (0.05M) in deoxygenated benzene (24 ml) was refluxed for 16 hours. The solvent was removed under reduced pressure. The residue was taken up in acetonitrile (10 ml) and stirred with 50% aqueous solution of hydrofluoric acid (1 ml) for 24 hours. The reaction mixture was diluted with water (25 ml) and extracted with chloroform (3 x 25 ml). The combined extracts were washed with brine (2 x 25 ml), dried (Na₂SO₄), and concentrated. The residual oil was purified by flash chromatography (20% ethyl acetate/hexane) to give initially ethyl 1-benzyl-2-oxo-cyclopentane-1-carboxylate 235 (22 mg, 6.85) as a clear oil. ¹H nmr (CDCl₃) δ 1.28 (t. J = 7.1Hz; 3H, CH₂CH₃); 1.5 - 2.5 (m. 6H, 3 x CH₂); 3.16 (d. J = 6.1Hz; ArCH₂); 4.17 (q. J = 7.1Hz; 2H, CH₂CH₃); 7.22 (m. 5H, ArH). The ¹H nmr spectrum of 235 was identical with that reported in the literature. 39

Further elution afforded ethyl 3a-hydroxy-1.2.3.3a,8.8a-hexahydrocyclopenta[a]indene-8a-carboxylate 236 (137 mg, 42.2%) as a clear oil. νmax (Neat) 3480 (broad, OH). 1720 (broad, ester) cm⁻¹. ¹H nmr (CDCl₃) δ 1.28 (t. J = 7.1Hz; 3H, CH₂CH₃); 1.65 - 2.62 (m. 6H, 3 x CH₂); 2.85 (d. J = 15.6Hz. 1H, ArCH(H)); 3.16 (s, 1H, OH); 3.72 (d. J = 15.6Hz. 1H, ArCH(H)); 4.20 (q, J = 7.1Hz, 2H, CH₂CH₃); 7.1 - 7.4 (m. 4H, ArH). ¹³C nmr (CDCl₃) δ 14.20 (q). 23.13 (t), 37.79 (t), 41.12 (t), 42.46 (t), 60.85 (t). 61.47 (s), 94.61 (s), 123.78 (d), 124.42 (d), 127.42 (d), 128.65 (d), 141.44 (s), 145.76 (s), 175.66 (s). Mass spectrum: m/e = 246 (0.8%, M⁺). 228 (75%). 199 (26%). 173 (30%). 172 (49%). 157 (34%), 155 (100%), 154 (33%). Exact mass (C₁₅H₁₈O₃ requires: M⁺ = 246.1256. Found: M⁺ = 246.1257).
Further elution afforded ethyl 10-hydroxy-5,6,7,8,9-pentahydro-6,9-methanobenzocycloheptene-6-carboxylate 237 (28 mg, 8.6%) as a clear oil. \( \nu_{\text{max}} \) (Neat) 3450 (broad, OH), 1720 (ester) cm\(^{-1}\). \(^1\)H nmr (CDCl\(_3\)) \( \delta \) 1.31 (t, \( J = 7.1\) Hz, 3H, CH\(_2\)CH\(_3\)); 1.60 - 2.25 (m, 4H, 2 x CH\(_2\)); 2.32 (d, \( J = 4.9\) Hz, 1H, CHOH); 2.86 (d, \( J = 16.8\) Hz, 1H, ArCH(H)); 3.13 (dd, \( J = 9.3\) Hz and 4.6 Hz, 1H, ArCH(H)); 4.34 (d, \( J = 9.5\) Hz and 4.8 Hz, 1H, CHCHOH); 7.0 - 7.30 (m, 4H, ArH). \(^{13}\)C nmr (CDCl\(_3\)) \( \delta \) 14.23 (q), 30.46 (t), 31.45 (t), 36.47 (t), 45.99 (d), 49.99 (s), 60.82 (t), 75.13 (d), 126.55 (d, 2C), 128.57 (d), 128.77 (d), 133.12 (s), 139.05 (s), 176.42 (s). Mass spectrum: m/e = 246 (2%, M\(^+\)), 155 (44%), 128 (18%), 115 (13%), 83 (100%). Exact mass: (C\(_{15}\)H\(_{18}\)O\(_3\) requires: M\(^+\) = 246.1256. Found: M\(^+\) = 246.1257).

**Ethyl 7.7a,8.9,10.10a-hexahydro-10a-hydroxypentaleno[1.2-a]naphthalene-7a-carboxylate 244**

**Ethyl 12-hydroxy-7,8,9,10,11-pentahydro-8,10-methanonaphto[1.2-a]cycloheptene-8-carboxylate 245**

A solution of ethyl 1-(1-bromonaphth-2-yl)methyl-2-(t-butyl(dimethyl)silyloxy)-2-cyclopentene-1-carboxylate 210 (489 mg, 1 mmol), AIBN (16 mg, 0.1 mmol) and tri-n-butyltin hydride (350 mg, 1.2 mmol, 0.05M) in deoxygenated benzene (24 ml) was refluxed for 16 hours. The solvent was removed and the residual oil subjected to flash chromatography (2% ethyl acetate/hexane) to afford two products (85%) in the ratio of 2.7:1.

A solution of the major product (62%) (254 mg, 0.62 mmol) in 22 ml of a acetic acid/water/THF mixture (3:1:1.5) was stirred at 50 °C for 24 hours. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with 5% aqueous sodium bicarbonate solution (3 x 30 ml), water (3 x 30 ml) and dried (Na\(_2\)SO\(_4\)). The solvent was removed under reduced pressure and the residue was purified by
flash chromatography (30% ethyl acetate/hexane) to afford ethyl 7.7a,8,9,10,10a-
hexahydro-10a-hydroxypentaleno[1.2-a]naphthalene-7a-carboxylate 244 (177 mg.
97%) as white crystals. m.p. 67 °C. $\nu_{\text{max}}$ (Nujol) 3470 (broad, OH), 1705 (ester)
cm$^{-1}$. $^1$H nmr (CDCl$_3$) $\delta$ 1.26 (t, $J$ = 7.1Hz, 3H, CH$_2$CH$_3$); 1.70 - 2.70 (m, 6H.
3 x CH$_2$); 2.93 (d, $J$ = 17.6Hz, 1H, ArCH(H)); 3.20 (s, 1H, OH); 3.84 (d, $J$
= 16.8Hz, 1H, ArCH(H)); 4.20 (q, $J$ = 7.1Hz, 2H, CH$_2$CH$_3$); 7.24 - 8.38 (m, 6H.
ArH). $^{13}$C nmr (CDCl$_3$) $\delta$ 14.28 (q). 24.24 (t). 27.67 (t). 41.32 (t). 43.83 (t).
60.97 (t). 62.66 (s). 96.65 (s). 127.70 (d). 124.27 (d). 125.15 (d). 126.35 (d).
128.68 (d). 129.56 (s). 129.73 (d). 133.91 (s). 138.72 (s). 139.22 (s). 175.55 (s).
Mass spectrum: m/e = 296 (4%, M$^+$). 279 (21%), 278 (100%). 222 (34%), 205
(74%). 165 (39%). Exact mass (C$_{19}$H$_{20}$O$_3$ requires: M$^+$ = 296.1412. Found:
M$^+$ = 296.1411).

A solution of the minor product (23%) (95 mg, 0.23 mmol) in
acetonitrile (5 ml) was stirred with 50% aqueous solution of hydrofluoric acid (500
ml) for 24 hours at room temperature. The mixture was diluted with water (10 ml)
and extracted with chloroform (3 x 15 ml). The combined extracts were washed with
brine (10 ml) and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure
and the residue was subjected to flash chromatography (30% ethyl acetate/hexane) to
afford ethyl 12-hydroxy-7.8,9,10,11-pentahydro-8,10-methanonaphto[1.2-
a]cycloheptene-8-carboxylate 245 (45 mg, 68%) as white crystals. m.p 98 - 100 °C.
$\nu_{\text{max}}$ (Nujol) 3470 (broad, OH). 1720 (ester) cm$^{-1}$. $^1$H nmr (CDCl$_3$) $\delta$ 1.33 (t, $J$
= 7.1Hz, 3H, CH$_2$CH$_3$); 1.70 - 2.10 (m, 4H, 2 x CH$_2$); 2.26 (d, $J$ = 5.8Hz, 1H.
OH); 2.98 (d, $J$ = 16.8Hz, 1H, ArCH(H)); 3.64 (d, $J$ = 17.1Hz. 1H, ArC(H)H);
3.97 (dd, $J$ = 9.8Hz and 4.88Hz, 1H, ArCHCH$_2$); 4.25 (q, $J$ = 7.1Hz. 2H.
CH$_2$CH$_3$); 4.73 (dd, $J$ = 10.5Hz and 10.2Hz, 1H, CHCHOH); 7.20 - 8.10 (m, 6H.
ArH). $^{13}$C nmr (CDCl$_3$) $\delta$ 14.25 (q). 29.87 (t). 32.27 (t). 37.41 (t). 40.38 (d).
49.79 (s). 60.88 (t). 75.19 (d). 122.23 (d). 125.05 (d). 126.11 (d). 126.76 (d).
127.16 (d). 128.71 (d). 130.46 (s). 131.66 (s). 132.89 (s). 133.33 (s). 176.39 (s).
Mass spectrum: m/e = 296 (78%, M⁺), 250 (32%), 222 (89%), 205 (100%) 194 (36%), 178 (39%), 165 (36%). Exact mass (C₁₉H₂₀O₃ requires: M⁺ = 296.1412. Found: M⁺ = 296.1411).

1-[(1-Bromonaphth-2-yl)methyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine 250

Hexane-washed sodium hydride (204 mg, 4.2 mmol) was suspended in dimethylformamide (DMF) (15 ml). A solution of 3-methoxycarbonyl-1,4,5,6-tetrahydropyridine 249/252 (500 mg, 3.5 mmol) in DMF (5 ml) was added dropwise and the reaction mixture was stirred at room temperature for 30 min. A solution of 1-bromo-2-bromomethylnaphthalene 68 (1.2 g, 3.9 mmol) in DMF (5 ml) was added and the reaction mixture was stirred for 3 hours at room temperature. The mixture was diluted with water (50 ml) and extracted with ether (2 x 50 ml). The combined extracts were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography (30% ethyl acetate/hexane) to give 250 (950 mg, 73%) as a yellow oil. v max (Neat) 3060, 1730, 1680, 1620 cm⁻¹. ¹H nmr (CDCl₃) δ 1.82 (m, 2H, CH₂CH₂CH₂); 2.32 (t, J = 6.2Hz, 2H, C=CH₂CH₂); 3.05 (t, J = 5.7Hz, 2H, NCH₂); 3.69 (s, 3H, CO₂CH₃); 4.63 (s, 2H, ArCH₂N); 7.23 - 7.85 (m, 6H, ArH + NCH=C); 8.30 (d, J = 8.5Hz, 1H, ArH). ¹³C nmr (CDCl₃) δ 19.98 (t), 21.21 (t), 45.71 (t), 50.46 (q), 60.04 (t), 95.16 (s), 123.54 (s), 125.6 (d), 126.67 (d), 127.14 (d), 127.63 (d), 128.01 (d), 128.22 (d), 132.36 (s), 133.94 (s), 134.06 (s), 146.20 (d), 168.86 (s). Mass spectrum: m/e = 361 (25%), 359 (28%, M⁺), 221 (97%), 219 (100%), 140 (58%), 136 (43%), 129 (37%), 128 (30%). Exact mass (C₁₈H₁₈O₂NBr requires: M⁺ 359.0521. Found: M⁺ = 359.0520).
Attempted reactions of Methyl 1-(0-bromobenzyl)-2-(t-butyl-dimethylsilyloxy)-2-cyclopentene-1-carboxylate 209 and Methyl 1-[(1-bromonaphth-2-yl)methyl]-2-(t-butyl(dimethyl-silyloxy))-2-cyclohexene-1-carboxylate 211

A solution of 209 (439 mg, 1 mmol) or 211 (489, 1 mmol), tri-n-butyltin hydride (350 mg, 1.2 mmol, 0.05M), AIBN (17 mg, 0.1 mmol) in benzene (24 ml) was refluxed for 16 hours. The solvent was removed under reduced pressure and the residue subjected to flash chromatography (2% ethyl acetate/hexane) to afford inseparable mixture of products. Attempts to separate the mixtures were unsuccessful.

The mixtures were dissolved in acetonitrile (10 ml) and stirred with 50% aqueous solution of hydrofluoric acid (1 ml) at room temperature for 24 hours. The mixture was diluted with water (25 ml) and extracted with chloroform (3 x 25 ml). The combined extracts were washed with brine (2 x 25 ml) and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure to afford a mixture of products. Attempts to separate and identify the mixtures failed as no discrete products were isolated.

1-[(1-Bromonaphth-2-yl)methyl]-2-pyridone 252

A mixture of 2-pyridone 251 (0.6 g, 6.3 mmol) 1-bromo-2-bromomethyl-naphthalene (1.6 g, 5.3 mmol), and potassium carbonate (0.73 g, 5.3 mmol) in DMF (20 ml) was refluxed for 16 hours. The solvent was removed under reduced pressure and the residue taken up in water (10 ml) and extracted with ethyl acetate (3 x 50 ml). The combined extracts were dried (MgSO$_4$), and concentrated. The residue crystal was recrystallized from methanol/ethyl acetate to afford 1-[(1-bromonaphth-2-yl)methyl]-2-pyridone 252 (1.2 g, 71%) as brown crystals m.p. 155°C. $\nu_{max}$ (Nujol) 1660, 1590 cm$^{-1}$. $^1$H nmr (DMSO) $\delta$ 5.5 (s, 2H); 6.4 (t, $J = 6.6$Hz, 1H); 6.65 (d, $J = 9.5$Hz, 1H); 7.26 (d, $J = 6.8$Hz, 1H); 7.52 - 8.38 (m, 7H). Mass spectrum: m/e = 235 (18%), 234 (100%), 140 (26%), 139 (24%), 117
Methyl 1,4,5,6-tetrahydro-1-[(naphth-2-yl)methyl]pyridine-3-carboxylate 257. 

(12S, 12aS)Methyl 7,8,9,10,11,12,12a-pentahydrobenzo[g]pyrido[2,1-a]isoindole-3-carboxylate 258. and 

(12R, 12aS)Methyl 7,8,9,10,11,12,12a-pentahydrobenzo[g]pyrido[2,1-a]isoindole-3-carboxylate 259

A solution of 1-(1-bromonaphth-2-yl)methyl-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine 250 (346 mg, 1 mmol). AIBN (16 mg, 0.1 mmol), and tri-n-butyltin hydride (350 mg, 1.2 mmol, 0.05M) in deoxygenated benzene (24 ml) was refluxed 16 hours. The solvent was removed under reduced pressure and the residue subjected to flash chromatography (30% ethyl acetate/hexane) to afford methyl 1,4,5,6-tetrahydro-1-[(naphth-2-yl)methyl]pyridine-3-carboxylate 257 (25 mg, 9%) as a yellow oil. νmax (Neat) 3060, 1730, 1680, 1620 cm⁻¹. ¹H nmr (CDCl₃) δ 1.82 (m, 2H, CH₂CH₂CH₂); 2.3 (t, J = 6.3Hz, 2H, CCH₂CH₂); 3.02 (t, J = 5.7Hz, NCH₂CH₂); 3.7 (s, 3H, CO₂CH₃); 4.4 (s, 2H, ArCH₂); 7.23 - 7.9 (m, 8H, ArH + NCH=C). ¹³C nmr (CDCl₃) δ 20.2 (t), 21.3 (t), 45.6 (t), 50.5 (q), 59.9 (t), 94.6 (s), 125.3 (d), 126.1 (d), 126.3 (d, 2C), 127.8 (d, 2C), 128.6 (d), 133 (s), 133.4 (s), 134.5 (s), 146.2 (d), 169 (s). Mass spectrum: m/e = 281 (19%, M⁺), 142 (17%), 141 (100%), 115 (115). Exact mass (C₁₈H₁₉O₂N requires: M⁺ = 281.1416. Found: M⁺ = 281.1415).

Further elution (60% ethyl acetate/hexane) afforded (12S, 12aS)methyl 7,8,9,10,11,12,12a-pentahydrobenzo[g]pyrido[2,1-a]isoindole-3-carboxylate 258 (48 mg, 18%) as a yellow oil which darkened on storage. νmax (CDCl₃) 2780, 1730 cm⁻¹. ¹H nmr (CDCl₃) δ 1.5 - 1.9 (m, 2H, CH₂CH₂CH₂); 2.1 - 2.4 (m, 2H, CHCH₂CH₂); 2.76 (m, 1H, CHCH₂); 3.1 (s, 3H, CO₂CH₃); 3.3 (m, 1H, NCH(H)CH₂); 3.66 (m, 1H, NCH(H)CH₂); 3.77 (dd, J = 12.3 and 3.4Hz, 1H, NCH(H)CH₂).
ArCH(H)N): 4.3 (m, 1H, ArCHCH): 4.4 (dd, J = 12.3 and 2.4Hz, ArCH(H)N): 7.3 - 7.97 (m, 6H, ArH). $^{13}$C nmr (CDCl$_3$) δ 20.8 (t), 26.4 (t), 43 (d), 50.7 (t and q, 2C), 57.9 (t), 68.1 (d), 120.6 (d), 123.5 (d), 124.5 (d), 125.7 (d), 127.5 (d), 128.4 (d), 132.8 (s), 137 (s), 137.2 (s), 173.2 (s), and one quaternary carbon not observed. Mass spectrum: m/e = 281 (53%, M$^+$), 220 (15%), 195 (20%), 194 (24%), 181 (100%). 167 (63%). Exact mass (C$_{18}$H$_{19}$O$_2$N requires: M$^+$ = 281.1416). Found: M$^+$ = 281.1415).

Further elution gave (12R, 12aS)methyl 7.8.9.10.12.12a-pentahydrobenzo[g]pyridol[2,1-alisoindole-3-carboxylate 259 (120 mg, 45%) as a clear oil which darkened on storage. $\nu$$_{max}$ (Neat) 2780, 1730 cm$^{-1}$. $^1$H nmr (CDCl$_3$) δ 1.4 - 2.35 (m, 5H); 3.15 - 3.27 (m, 2H, NCH$_2$CH$_2$); 3.34 (s, 3H, CO$_2$CH$_3$); 4.0 (d, J = 12.93Hz, 1H, ArCH(H)N); 4.3 (d, J = 12.93Hz, 1H, ArC(H)HN); 4.8 (d, J = 11.2Hz, ArCHCH) 7.3 - 7.9 (m, 6H, ArH). $^{13}$C nmr (CDCl$_3$) δ 18.02 (t), 27.09 (t), 44.5 (d), 46.8 (t), 51.5 (q), 54.02 (t), 63.77 (d), 120.91 (d), 123.95 (d), 124.74 (d), 125.76 (d), 127.81 (d), 128.36 (d), 132.48 (s), 137.03 (s, 2C), 139.63 (s), 173.72 (s). Mass spectrum: m/e = 281 (45%, M$^+$), 195 (23%), 194 (27%), 181 (100%). 180 (23%). 167 (735). Exact mass (C$_{18}$H$_{19}$O$_2$N requires: M$^+$ = 281.1416). Found: M$^+$ = 281.1415).

1-[(naphth-2-yl)methyl]-2-pyridone 266 and.

7.8.12.12a-Tetrahydrobenzo[g]pyrido[6,1-alisoindole-9-one 267

A solution of 1-(1-bromonaphth-2-yl)methyl-2-pyridone 252 (314 mg, 1 mmol), AIBN (16 mg, 0.1 mmol), tri-n-butyltin hydride (350 mg, 1.2 mmol, 0.05M) in deoxygenated benzene (24 ml) was refluxed 16 hours. The solvent was removed under reduced pressure and the residue subjected to flash chromatography (2% methanol/dichloromethane) to yield 1-[(naphth-2-yl)methyl]-2-pyridone 266 (25 mg, 11%) as white crystals. m.p. 85 °C. $\nu$$_{max}$ (CHCl$_3$) 1660, 1590 cm$^{-1}$. $^1$H nmr (CDCl$_3$) δ 5.3 (s, 2H, ArCH$_2$); 6.1 (t, J = 6.6Hz, 1H); 6.6 (d, J = 9.5Hz, 1H);
7.26 (d, J = 6.8Hz. 1H): 7.3 - 7.87 (m. 8H). ¹³C nmr (CDCl₃) δ 51.8 (t). 106.1 (d), 124.1 (d). 125.8 (d). 126.1 (d). 126.3 (d). 127.1 (d). 127.6 (d). 127.8 (d). 128.7 (d). 132.9 (s). 133.2 (s). 133.8 (s). 137.1 (d). 139.3 (d). 162.6 (s) Mass spectrum: m/e = 235 (25%. M⁺), 142 (12%). 141 (100%). 115 (14%). Exact mass (C₁₆H₁₃NO requires: M⁺ = 234.0997. Found: M⁺ = 235.0997).

Further elution afforded 7.8.12.12a-
tetrahydrobenzo[g]pyrido[6.1-a]isoindole-9-one 267 (185 mg. 79%) as white crystals. m.p. 140 - 142 °C. νmax (CHCl₃) 2860. 1660. 1610. 1590 cm⁻¹. ¹H nmr (CDCl₃) δ 2.5 (m. 1H): 3.3 (m. 1H). 4.8 (dd. J = 15.9 and 2.1Hz. 1H): 5.15 (dd. J = 15.9 and 2.7Hz. 1H): 5.6 (m. 1H). 6.15 (m. 1H). 6.7 (m. 1H). 7.3 - 8 (m. 6H. ArH). ¹³C nmr (CDCl₃) δ 30.7 (t). 51.1 (t). 61.8 (d). 120.9 (d). 122.9 (d). 125.6 (d). 126.1 (d). 126.8 (d). 129.1 (d). 129.2 (d). 133.3 (s). 134.4 (s). 134.4 (s). 134.5 (s. 2C). 138.4 (d). 162.8 (s). Mass spectrum: m/e = 235 (38%. M⁺). 234 (11%). 168 (36%). 167 (100%). 141 (27%). 139 (27%) 82 (15%). Exact mass (C₁₆H₁₃NO requires: M⁺ 235.0997. Found: M⁺ = 235.0997).
CHAPTER 4

Methyl (o-bromophenyl)acetate 269

A stirred mixture of (o-bromophenyl)acetic acid 268 (10 g, 0.05 mol), methanol (3 g, 0.09 mol), and concentrated sulphuric acid (2 ml) was refluxed for 5 hours. The excess methanol was removed under reduced pressure and the residue was diluted with water and extracted with ether (3 x 50 ml). The combined extracts were washed with saturated aqueous sodium bicarbonate solution (75 ml), water (50 ml), and dried (MgSO₄). The solvent was removed under reduced pressure and the residue was distilled to afford methyl (o-bromophenyl)acetate 269 as a colourless oil (9 g, 85%). b.p. 123 °C / 0.1 mmHg. (Found: C, 47.27; H, 3.94. C₉H₉BrO₂ requires C, 47.19; H, 3.96). νmax (Neat) 1740 (CO₂CH₃), 1165 cm⁻¹ ¹H nmr (CDCl₃) δ 3.70 (s, 3H, CO₂CH₃); 3.79 (s, 2H, ArCH₂); 7.04 - 7.30 (m, 3H, ArH); 7.56 (d, J = 7.57 Hz, 1H, ArH). ¹³C nmr (CDCl₃) δ 41.35 (t), 51.95 (q), 124.89 (s), 127.40 (d), 128.71 (d), 131.31 (d), 132.68 (d), 134.11 (s), 170.70 (s).

Methyl (o-bromophenyl)pent-4-enoate 270

n-Butyl lithium (11.64 ml, 1.5M in hexane, 17.5 mmol) was added to a stirred solution of diisopropylamine (1.78 g, 17.6 mmol) in THF (10 ml) cooled in an ice-salt bath under nitrogen. The addition was at a rate such that the reaction temperature was maintained below 0 °C. After 15 min at 0 °C, the solution was cooled in an acetone-dry ice bath to -75 °C and methyl (o-bromophenyl)acetate 269 (4 g, 17.5 mmol) in THF (5 ml) was added over a period of 30 min. The mixture was stirred at this temperature for a further 30 min and a solution of allyl bromide (2.83 g, 23 mmol) in dry THF (5 ml) was added over a period of 30 min. After the addition of the alkylating agent the reaction mixture was kept at -75 °C for 90 min and was allowed to warm to room temperature and was stirred for a further 90 min. The solution was concentrated and the residue treated with aqueous hydrochloric acid
(3M, 75 ml) and then extracted with ether (3 x 25 ml). The ether extracts were washed with aqueous hydrochloric acid (3M, 50 ml), brine (50 ml), and dried (MgSO₄). The residue obtained after evaporation of the solvent was purified by flash chromatography (5% ethyl acetate/hexane) to afford methyl (o-bromophenyl)pent-4-enoate 270 as a clear oil (4.7 g, 100%). (Found: C, 53.63; H, 4.77. C₁₂H₁₁BrO₂ requires C, 53.55; H, 4.87). ν_max (Neat) 1740 (CO₂CH₃), 1645 (C=CH) cm⁻¹. ¹H nmr (CDCl₃) δ 2.20 - 2.88 (m, 2H, CH₂CH₂CH₃); 3.68 (s, 3H, CO₂CH₃); 4.26 (t, J = 7.8Hz, 1H, ArCHCH₂); 4.95 - 5.14 (m, 2H, CH=CH₂) 5.65 - 5.88 (m, 1H, CH₂CH=CH₂); 7.06 - 7.42 (m, 3H, ArH); 7.57 (d, J = 8.30Hz, 1H, ArH). ¹³C nmr (CDCl₃) δ 37.08 (t), 49.82 (d), 52.00 (q), 117.18 (t), 124.77 (s), 127.69 (d), 128.65 (d), 128.80 (d), 133.03 (d), 134.81 (d), 138.14 (s), 173.24 (s).

2-(o-Bromophenyl)pent-4-en-1-ol 271

A solution of methyl (o-bromophenyl)pent-4-enoate 270 (1.5 g, 5.6 mmol) in dry ether (10 ml) was added dropwise to a suspension of lithium aluminum hydride (0.42 g, 11.2 mmol) in dry ether (20 ml) and stirred at room temperature for 2 hours. The mixture was cooled in an ice-bath, and was quenched by the sequential slow addition of water (50 ml) and 20% aqueous sulphuric acid (50 ml). The mixture was extracted with ether (3 x 50 ml) and the combined extracts were washed with water and dried (Na₂SO₄). The residue obtained after evaporation of the solvent was purified by flash chromatography (20% ethyl acetate/hexane) to afford 2-(o-bromophenyl)pent-4-en-1-ol 271 (1.1 g, 85%) as a clear oil. (Found: C, 54.58; H, 5.43. C₁₁H₁₃BrO requires C, 54.79; H, 5.43). ν_max (Neat) 3350 (broad. OH). 1640 (C=C) cm⁻¹. ¹H nmr (CDCl₃) δ 1.60 (s, 1H, OH); 2.30 - 2.60 (m, 2H, CH₂CH); 3.40 - 3.58 (m, 1H, ArCH); 3.80 (d, J = 7.19Hz, 2H, CH₂OH); 4.90 - 5.10 (m, 2H, CH=CH₂); 5.63 - 5.85 (m, 1H, CH=CH₂); 7.02 - 7.34 (m, 3H, ArH); 7.58 (d, J = 8.3Hz, 1H, ArH). ¹³C nmr (CDCl₃) δ 35.89 (t), 45.85 (d), 65.47 (t), 116.68 (t), 125.68 (s), 127.51 (d), 128.01 (d), 128.24 (d), 133.12 (d), 134.84 (d), 140.92 (s).
1-Bromo-2-(l-iodomethylbut-3-enyl)benzene 272

Following the general procedure of Camps\textsuperscript{135}, trifluoroacetic anhydride (1.1 g, 5.2 mmol) was added to a solution of 2-(o-bromophenyl)pent-4-en-1-ol 271 (1 g, 4.3 mmol) and the resulting mixture was stirred for 15 min at room temperature. The trifluoroacetic acid formed in the reaction was removed under reduced pressure, and the residue was diluted with dry THF (25 ml) and HMPA (25 ml) followed by the addition of lithium iodide (1.87 g, 21.5 mmol). The resulting suspension was heated under reflux for 6 hours. The reaction mixture was diluted with water (150 ml) and extracted with ether (3 x 50 ml). The combined extracts were washed with water (4 x 30 ml), dried (MgSO\textsubscript{4}) and concentrated. The crude product was subjected to flash chromatography (hexane) to afford 1-bromo-2-(1-iodomethylbut-3-enyl)benzene 272 (670 mg, 45%) as a clear oil. (Found: C, 37.86; H, 3.36. C\textsubscript{11}H\textsubscript{12}Brl requires C, 37.64; H, 3.45). $\nu_{max}$ (Neat) 1640 (C=C) cm\textsuperscript{-1}.

$^1$H nmr (CDCl\textsubscript{3}) $\delta$ 2.40 - 2.68 (m, 2H, CH\textsubscript{2}CH=CH\textsubscript{2}); 3.35 - 3.55 (m, 3H, ArCH and CH\textsubscript{2}I); 5.00 - 5.15 (m, 2H, CH=CH\textsubscript{2}); 5.50 - 5.80 (m, 1H, CH=CH\textsubscript{2}) 7.05 - 7.62 (m, 4H, ArH). $^{13}$C nmr (CDCl\textsubscript{3}) $\delta$ 11.36 (t), 38.86 (t), 44.76 (d), 117.57 (d), 125.149 (s), 127.43 (d), 127.89 (d), 128.35 (d), 133.05 (d), 134.31 (d), 141.23 (s).

1-Bromo-2-(1-methylbut-3-enyl)benzene 273

Following the general procedure of Hutchins et al.\textsuperscript{136} a solution of 1-bromo-2-(1-iodomethylbut-3-enyl)benzene 272 (600 mg, 1.71 mmol) in HMPA (5 ml) was added slowly to an ice cold solution of sodium trimethoxyborohydride (875 mg, 6.8 mmol) in HMPA (10 ml). The reaction mixture was stirred for 3 hours at room temperature, diluted with water (50 ml) and extracted with ether (3 x 30 ml). The combined extracts were washed with water (2 x 25 ml), dried (MgSO\textsubscript{4}), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane) to yield 1-bromo-2-(1-methylbut-3-enyl)benzene 273 (206 mg, 54%) as a clear oil. $\nu_{max}$ (Neat) 1640 (C=C) cm\textsuperscript{-1}. $^1$H nmr (CDCl\textsubscript{3}) $\delta$ 1.22 (d, J = 6.83Hz, 3H, CH\textsubscript{3}); 2.20 - 2.48 (m, 2H, CH\textsubscript{2}); 3.28 - 3.40 (m, 1H, ArCH);
4.93 5.07 (m, 2H, CH=CH₂); 5.67 - 4.81 (m, 1H, CH=CH₂); 7.00 - 7.30 (m, 3H, ArH); 7.53 (d, J = 8.06 Hz, 1H, ArH). ¹³C nmr (CDCl₃) δ 20.21 (q), 37.79 (t), 41.29 (d), 116.24 (t), 124.65 (s), 127.34 (d), 127.48 (d), 132.80 (d), 136.51 (d), 145.62 (s). Mass Spectrum: m/e = 224 (7%, M⁺); 183 (95%); 145 (15%); 104 (100%); 103 (52%); 77 (36%). Exact mass (C₁₁H₁₃Br₇₉ requires: M⁺ = 224.0200. Found: M⁺ = 224.0201).

3-(o-Bromophenyl)-2-methylhex-5-en-2-ol 274

A solution of methyl (o-bromophenyl)pent-4-enoate 270 (1.5 g, 5.6 mmol) in dry ether (5 ml) was added dropwise to an ice cold solution of methylmagnesium iodide (prepared from methyl iodide (2.0 g, 14 mmol), magnesium metal (377 mg, 15.7 mmol) and crystal of iodine in dry ether (20 ml)). The mixture was heated under reflux for 2 hours, cooled and poured into ice-cold 10% aqueous hydrochloric acid (100 ml). The organic layer was separated and the aqueous layer extracted with ether (3 x 50 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution, dried (MgSO₄), and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (20% ethylacetate/hexane) to afford 3-(o-bromophenyl)-2-methylhex-5-en-2-ol 274 (1.5 g, 100%) as a colourless oil. (Found: C, 58.02; H, 6.8. C₁₃H₁₇BrO requires C, 58.01; H, 6.37). νmax (Neat) 3450 (broad, OH), 1645 (C=C) cm⁻¹. ¹H nmr (CDCl₃) δ 1.17 (s, 3H, CH₃); 1.33 (s, 3H, CH₃); 1.51 (s (broad), 1H, OH); 2.40 - 2.80 (m, 2H, CHCH₂CH); 3.47 (dd, J = 11.72, 4.15 Hz 1H, ArCH); 4.75 - 4.96 (m, 2H, CH=CH₂); 5.40 - 5.65 (m, 1H, CH=CH₂); 7.00 - 7.58 (m, 4H, ArH). ¹³C nmr (CDCl₃) δ 28.29 (q), 28.64 (q), 34.72 (t), 53.00 (d), 73.35 (s), 115.55 (t), 127.22 (d), 127.30 (s), 127.40 (d), 127.78 (d), 129.35 (d), 132.53 (d), 136.74 (s).
Methyl but-3-enoate 276

The title compound was prepared from but-3-enoic acid (7 g, 67 mmol) (prepared from but-3-enoic acid and thionyl chloride) and methanol (2.15 g, 67.2 mmol) according to a general literature procedure. The product was obtained as a colourless liquid (9 g, 60%). b.p. 104 - 106 °C / 760 mmHg. v_max (Neat) 1740 (C=O), 1645 (C=C) cm⁻¹. ¹H nmr (CDCl₃) δ 3.08 - 3.12 (m, 2H, CHCH₂); 3.70 (s, 3H, CO₂CH₃); 5.10 - 5.25 (m, 2H, CH=CH₂); 5.82 - 6.05 (m, 1H, CH=CH₂). ¹³C nmr (CDCl₃) δ 38.93 (t), 51.77 (q), 118.52 (t), 130.20 (d), 171.87 (s).

Methyl 2-(o-Bromophenylmethyl)but-3-enoate 277

Following the procedure of Cerfontain to a stirred solution of diisopropylamine (2.02 g, 20 mmol) in dry THF (15 ml) cooled in an ice-salt bath a solution of n-butyl lithium (13.3 ml, 1.5 M in hexane, 20 mmol) was added dropwise. After 15 min the mixture was cooled to −78 °C and HMPA (4.3 g, 24 mmol) was added dropwise and the mixture was stirred for 1 hour. A solution of methyl but-3-enoate 276 (2.2 g, 22 mmol) in THF (5 ml) was added over a period of 30 min and the mixture was stirred for 1 hour. o-Bromobenzyl bromide 124 (5 g, 20 mmol) in THF (6 ml) was added in one portion to the reaction mixture and the mixture was stirred for further 1 hour. The mixture was quenched with wet THF (50 ml) and acidified with 5% aqueous hydrochloric acid (100 ml). The mixture was warmed to 10 °C and was extracted with ether (3 x 50 ml). The combined extracts were washed successively with 5% aqueous hydrochloric acid (3 x 50 ml), water (50 ml), brine (50 ml), and dried (MgSO₄). The solvents were removed under reduced pressure, and the yellow oily residue was purified by flash chromatography (5% ethylacetate/hexane) to afford methyl 2-(o-bromophenylmethyl)but-3-enoate 277 as a colourless oil (4.4 g, 81%). (Found: C, 53.83; H, 4.96. C₁₂H₁₃BrO₂ requires C, 53.55; H, 4.87). v_max (Neat) 1740, 1640 cm⁻¹. ¹H nmr (CDCl₃) δ 2.97 (dd, J = 13.7, 7.3Hz, 1H, ArCH(H)CH); 3.2 (dd, J = 13.8, 7.9Hz, 1H, ArCH(H)CH); 3.47
2-(o-Bromophenylmethyl)but-3-en-1-ol 278

The title compound was prepared from methyl 2-(o-bromophenylmethyl)but-3-en-1-oenoate 277 (3 g, 11.5 mmol) and lithium aluminum hydride (848 mg, 22.30 mmol) as described above for 2-(o-bromophenyl)pent-4-en-1-ol 271. The residue isolated from workup of the reaction mixture was purified by flash chromatography (20% ethyl acetate/hexane) to afford 2-(o-bromophenylmethyl)but-3-en-1-ol 278 (2.1 g, 78%) as a clear oil. (Found: C, 54.65; H, 5.49. C_{11}H_{13}BrO requires C, 54.79; H, 5.43). $\nu_{\text{max}}$ (Neat) 3350 (broad, OH). 1640 (C=C) cm$^{-1}$.

$^1$H nmr (CDCl$_3$) $\delta$ 1.70 (s, broad, 1H, OH); 2.55 - 3.00 (m, 3H, ArCH$_2$CH); 3.45 - 3.60 (m, 2H, CH$_2$OH); 5.00 - 5.17 (m, 2H, CH=CH$_2$); 5.64 - 5.83 (m, 1H, CH=CH$_2$); 7.00 - 7.24 (m, 3H, ArH); 7.52 (d, J = 7.8Hz, 1H, ArH). $^{13}$C nmr (CDCl$_3$) $\delta$ 37.23 (t), 46.52 (d), 64.68 (t), 117.47 (t), 124.68 (s), 127.67 (d), 127.74 (d), 131.36 (d), 132.77 (d), 138.64 (d), 139.11 (s).

1-Bromo-2-(2-iodomethylbut-3-enyl)benzene 279

The title compound was prepared from 2-(o-bromophenylmethyl)but-3-en-1-ol 278 (1.25 g, 5.2 mmol), trifluoroacetic anhydride (1.4 g, 5.3 mmol) and lithium iodide (3.5 g, 21.6 mmol) as described above for 1-bromo-2-(1-iodomethylbut-3-enyl)benzene 272. The residue isolated after workup was purified by flash chromatography (hexane) to afford 1-bromo-2-(2-iodomethylbut-3-enyl)benzene 279 (860 mg, 48%) as a pale oil. $\nu_{\text{max}}$ (Neat) 1640 (C=C) cm$^{-1}$.

$^1$H nmr (CDCl$_3$) $\delta$ 2.45 - 2.64 (m, 1H, CHCH$_2$I); 2.75 - 3.00 (m, 2H, ArCH$_2$); 3.10 - 3.32 (m, 2H, CH$_2$I); 4.93 - 5.12 (m, 2H, CH=CH$_2$); 5.60 - 5.80 (m, 1H, CH=CH$_2$); 7.00 - 7.25 (m, 3H, ArH); 7.52 (d, J = 7.8Hz, 1H, ArH). $^{13}$C nmr
1-Bromo-2-(2-methylbut-3-enyl)benzene 280

The title compound was prepared from 1-bromo-2-(2-iodomethylbut-3-enyl)benzene 279 (700 mg, 2 mmol) as described above for 1-bromo-2-(1-methylbut-3-enyl)benzene 273. The residue isolated after workup was purified by flash chromatography (hexane) to give 1-bromo-2-(2-methylbut-3-enyl)benzene 280 (250 mg, 57%) as a clear oil. \( \nu_{\text{max}} \) (Neat) 1640 (C=C) cm\(^{-1}\). \(^1\text{H nmr} (\text{CDCl}_3) \delta 1.02 (\text{d}, J = 6.35\text{Hz}, 3\text{H}, \text{CHCH}_3); 2.50 - 2.85 (\text{m}, 3\text{H}, \text{ArCH}_2\text{CH} -); 4.83 - 5.00 (\text{m}, 2\text{H}, \text{CH}=\text{CH}_2); 5.70 - 5.90 (\text{m}, 1\text{H}, \text{CH}=\text{CH}_2); 7.00 - 7.25 (\text{m}, 3\text{H}, \text{ArH}); 7.25 (\text{d}, J = 7.80\text{Hz}, 1\text{H}, \text{ArH}). \(^{13}\text{C nmr} (\text{CDCl}_3) \delta 19.36 (\text{q}), 37.79 (\text{t}), 43.07 (\text{d}), 113.03 (\text{t}), 124.86 (\text{s}), 126.93 (\text{d}), 127.54 (\text{d}), 131.49 (\text{d}), 132.74 (\text{d}), 140.01 (\text{s}), 143.40 (\text{d}). \) Mass spectrum: m/e = 224 (22%, M\(^+\)); 182 (29%); 169 (25%); 145 (100%). Exact mass (C\(_{11}\)H\(_{13}\)Br\(_7\)) requires: M\(^+\) = 224.0200. Found: M\(^+\) = 224.0201.

Cis-and trans-1,3-dimethyl-2,3-dihydro-1H-indene (282, 283)

A solution of 1-bromo-2-(1-methylbut-3-enyl)benzene 273 (90 mg, 0.4 mmol), AIBN (7 mg, 0.04 mmol), and tri-n-butyltin hydride (141 mg, 0.48 mmol, 0.05M) in degassed benzene (9.6 ml) was refluxed for 16 hours. GC analysis of the reaction mixture showed the formation of two products in the ratio of 2.1:1. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexane) to yield the title compounds as a clear oil (54 mg, 92%).

The major isomer proved to be cis-1,3-dimethyl-2,3-dihydro-1H-indene 282. \(^1\text{H nmr} (\text{CDCl}_3) \delta 1.1 (\text{m}, 1\text{H}, \text{CH(H)}); 1.3 (\text{d}, J = 6.8\text{Hz}, 2 \times \text{CH}_3); 2.4 -
2.5 (m, 1H, CH(H)); 2.9 - 3.17 (m, 2H x ArCH); 7.22 (s, 4H, ArH). $^{13}$C nmr (CDCl$_3$) δ 19.36 (q), 38.11 (d), 45.06 (t), 122.78 (d), 126.17 (d), 148.48 (s). The $^1$H nmr and $^{13}$C nmr spectra are consistent with literature sources.$^{139,140}$

The minor isomer proved to be trans-1,3-dimethyl-2,3-dihydro-1H-indene 283. $^1$H nmr (CDCl$_3$) δ 1.23 (d, J = 7.1 Hz, 6H, 2 x CH$_3$); 1.89 (t, J = 6.7 Hz, 2H, CH$_2$); 3.22 - 3.35 (m, 2H, 2 x ArCH); 7.22 (s, 4H, ArH). The $^1$H nmr spectrum is consistent with literature sources.$^{139}$ $^{13}$C nmr (CDCl$_3$) δ 20.56 (q), 37.6 (d), 43 (t), 123.36 (d), 126.32 (d), 148.48 (s).

Cis- and trans-1,3-dimethyl-2,3-dihydro-1H-indene (282, 283) from 1-bromo-2-(1-iodomethylbut-3-enyl)benzene 272 as a radical precursor

A solution of 1-bromo-2-(1-iodomethylbut-3-enyl)benzene 272 (420 mg, 1.2 mmol), AIBN (12 mg, 0.07 mmol), and tri-n-butyltin hydride (836 mg, 2.8 mmol, 0.05M) in degassed benzene (56 ml) was heated under reflux for 16 hours. GC analysis of the reaction mixture showed the presence of two compounds in the ratio of 2:1. The solvent was removed under reduced pressure and the residue was purified by flash chromatography to afford 174 mg (97%) of a mixture of the two reaction products. $^1$H nmr, $^{13}$C nmr and GC analysis of the mixture indicated that the major component correspond with cis-1,3-dimethyl-2,3-dihydro-1H-indene 282 and the minor component with trans-1,3-dimethyl-2,3-dihydro-1H-indene 283.

Cis- and trans-methyl 3-methyl-2,3-dihydro-1H-indene-1-carboxylate (285, 286)

A solution of methyl (o-bromophenyl)pent-4-enoate 270 (269 mg, 1 mmol). AIBN (17 mg, 0.1 mmol) and tri-n-butyltin hydride (350 mg, 1.2 mmol, 0.05M) in degassed benzene (24 ml) was refluxed for 6 hours. GC analysis of the reaction mixture showed the presence of two compounds in the ratio of 1.4:1. The solvent was removed under reduced pressure. The residue was subjected to flash chromatography to afford an inseparable mixture of the title compounds as a clear oil
The major component proved to be cis-methyl 3-methyl-2,3-dihydro-1H-indene-1-carboxylate 285. $^1$H nmr as described in the text. $^{13}$C nmr (CDCl$_3$) δ 19.63 (q), 37.90 (d), 38.25 (d), 48.97 (t), 51 (q), 123.34 (d), 124.42 (d), 126.52 (d), 127.49 (d), 140.42 (s), 148.28 (s), 174.32 (s).

The minor isomer proved to be trans-methyl 3-methyl-2,3-dihydro-1H-indene-1-carboxylate 286. $^1$H nmr as described in the text. $^{13}$C nmr (CDCl$_3$) δ 20.12 (q), 37.90 (d), 38.34 (d), 48.85 (t), 51 (q), 123.37 (d), 124.95 (d), 126.52 (d), 127.75 (d), 140.24 (s), 148.83 (s), 174.20 (s).

In another experiment, a solution of bromide 270 (10 mg, 0.037 mmol), AIBN (~ 2 mg), and tri-η-butylltin hydride (1.3 mg, 0.045 mmol, 0.05M) in benzene (892 µL) was irradiated with UV lamp at 5 °C for 42 hours. GC analysis of the reaction mixture showed the formation of three products in the ratio 13:58:29. The minor product (13%) corresponded with an authentic sample of the direct reduction product, methyl 2-phenylpent-4-enoate 289. The other products were identified as the cyclization products 285 (58%) and 286 (29%). An authentic sample of the reduction product 289 was prepared in two steps as described below.

**Methyl phenylacetate 288**

The title compound was prepared from phenylacetic acid (3 g, 0.02 mmol) as described above for methyl (o-bromophenyl)acetate 269. The residue obtained after workup was purified by flash chromatography (5% ethylacetate/hexane) to afford methyl phenylacetate 288 as a clear oil (3 g, 90%). (Found: C, 71.81; H, 6.49. C$_9$H$_{10}$O$_2$ requires C, 71.98; H, 6.71). $v_{\text{max}}$ (Neat) 1740 (CO$_2$CH$_3$), 1605, 1590, 1165 cm$^{-1}$. $^1$H nmr (CDCl$_3$) δ 3.62 (s, 2H, CH$_2$):
3.68 (s, 3H, CO₂CH₃); 7.20 - 7.40 (m, 5H, ArH). ¹³C nmr (CDCl₃) δ 41.12 (t), 51.89 (q), 127.02 (d), 128.48 (d, 2C), 129.18 (d, 2C), 133.94 (s), 171.87 (s).

Methyl 2-phenylpent-4-enoate 289

The title compound was prepared from methyl phenylacetate 288 (2.5 g, 16.7 mmol) and allyl bromide (2.83 g, 23 mmol) as described above for methyl (o-bromophenyl)pent-4-enoate 270. The residue isolated from workup of the reaction mixture was purified by flash chromatography (5% ethyl acetate/hexane) to afford methyl 2-phenylpent-4-enoate 289 (2.8 g, 88%) as a clear oil. (Found: C, 75.89; H, 7.51. C₁₂H₁₄O₂ requires C, 75.76; H, 7.42). ν max (Neat) 1740 (CO₂CH₃), 1640 (C=C) cm⁻¹. ¹H nmr (CDCl₃) δ 2.40 - 2.91 (m, 2H, CH₂CH=CH₂); 3.60 - 3.68 (t, J = 7.81Hz, 1H ArCHCH₂); 3.64 (s, 3H, CO₂CH₃); 4.94 - 5.12 (m, 2H, CH=CH₂); 5.60 - 5.83 (m, 1H, CH=CH₂); 7.20 - 7.40 (m, 5H, ArH). ¹³C nmr (CDCl₃) δ 37.56 (t), 51.42 (d), 51.86 (q), 118.89 (t), 127.28 (d), 127.89 (d, 2C), 128.59 (d, 2C), 133.22 (d), 138.55 (s), 173.80 (s).

Cis and trans-2-(3-methyl-2,3-dihydro-1-indenyl)propan-2-ol (291, 292)

A solution of 3-(o-bromophenyl)2-methylhex-5-en-2-ol 274 (269 mg, 1 mmol), AIBN (17 mg, 0.1 mmol), and tri-n-butyltin hydride (350 mg, 1.2 mmol, 0.05M) in degassed benzene (24 ml) was refluxed for 5 hours. GC analysis of the reaction mixture showed the formation of two products in the ratio 1:2.7. The residue obtained after the removal of the solvent was purified by flash chromatography (20% ethyl acetate/hexane) to afford an inseparable mixture of title products (172 mg, 91%) as a clear oil which solidified on standing. m.p. 53 - 55°C. (Found: C, 82.01; H, 9.81. C₁₃H₁₈O requires C, 82.06; H, 9.53).

The minor product (27%) proved to be cis-2-(3-methyl-2,3-dihydro-1-indenyl)propan-2-ol 291 by GC and ¹³C nmr comparison with an authentic sample. ¹³C nmr (CDCl₃) δ 19.4 (q), 24.6 (q), 30 (q), 37.3 (d), 38.4 (t), 55.2 (d), 73.4 (s), 122.8 (d), 125.8 (d), 125.9 (d), 126.3 (d), 143.6 (s), 149.2 (s).
Similarly the major product (73%) was identified as trans-2-(3-methyl-2,3-dihydro-1-indenyl)propan-2-ol 292. $^{13}$C nmr (CDCl$_3$) $\delta$ 20.7 (q), 26.3 (q), 28.2 (q), 37.7 (t), 38.1 (d), 73.8 (s), 123.3 (d), 125.9 (d), 126.2 (d), 126.9 (d), 143.2 (s), 149.2 (s).

Authentic samples of 291 and 292.

A 58:42 mixture (100 mg, 0.54 mmol) of cis- and trans-methyl-2,3-dihydro-1H-indene-1-carboxylate (285 and 286) (obtained from reaction of bromide 270 with tri-n-butyltin hydride [0.05M] at 80 °C) was treated with methylmagnesium iodide (prepared from methyl iodide (193 mg, 1.35 mmol) and magnesium metal (36 mg, 1.5 mmol) as described above for 3-(o-bromophenyl)-2-methylhex-5-en-2-ol 274. The residue obtained after workup was purified by flash chromatography (20% ethyl acetate/hexane) to afford 89 mg (89%) of a mixture of 291 and 292 as a clear oil which solidified on standing. GC analysis showed the mixture to have retained the original cis:trans ratio (58:42). Physical data are consistent with product mixture (291 and 292) obtained from reaction of 274 with tri-n-butyltin hydride.

Cis- and trans-1,2-dimethyl-2,3-dihydro-1H-indene (294, 295) and 2-Methyl-1,2,3,4-tetrahydronaphthalene 296

A solution of 1-bromo-2-(2-methylbut-3-enyl)benzene 280 (80 mg, 0.35 mmol), AIBN (5 mg, 0.03 mmol), and tri-n-butyltin hydride (126 mg, 0.43 mmol, 0.05M) in benzene (8.5 ml) was refluxed for 16 hours. GC analysis of the reaction mixture showed the formation of three products in the ratio 1:2.8:10.4. The solvent was removed under reduced pressure and the residue subjected to flash chromatography (hexane) to afford the title products (47 mg, 90%) as a clear oil. (Found: C. 90.06; H. 9.65. C$_{11}$H$_{14}$ requires C. 90.35; H. 9.65).

The minor product (7%) corresponded with an authentic sample of the endo cyclization product, 2-methyl-1,2,3,4-tetrahydronaphthalene 296. Similarly the
other product (20%) was identified as cis-1,2-dimethyl-2,3-dihydro-1H-indene 294 by GC comparison with an authentic sample. Authentic samples of the cis-isomer 294 and the endo-cyclization product 296 were prepared as described below.

The major product (73%) proved to be trans-1,2-dimethyl-2,3-dihydro-1H-indene 295. $^1$H nmr (CDCl$_3$) $\delta$ 1.18 (d, J = 6.6 Hz, 3H, CH$_3$); 1.28 (d, J = 5.9 Hz, 3H, CH$_3$); 1.92 - 2.02 (m, 1H, CHCH$_2$); 2.5 (dd, J = 15.7, 9.8 Hz, 1H, ArCH(H)); 2.65 - 2.68 (m, 1H, ArCHCH); 3.0 (dd, J = 15.4, 7.6 Hz, 1H, ArCH(H)); 7.14 (m, 4H, ArH). $^{13}$C nmr (CDCl$_3$) $\delta$ 17.6 (q), 18.5 (q), 40.2 (t), 44 (d), 46.8 (d), 123 (d), 124.1 (d), 126 (d, 2C), 143.1 (s), 148.6 (s).

Methyl 3-methyl-1H-indene-2-carboxylate 298

The title ester was prepared from 3-methyl-1H-indene-2-carboxylic acid 297 (1.5 g, 8.6 mmol) by the procedure described above for methyl (o-bromophenyl)acetate 269. The residue obtained after workup was purified by recrystallization from hexane to give methyl 3-methyl-1H-indene-2-carboxylate 298 (1.32 g, 82%) as white needles. m.p. 65 °C. $\nu_{\text{max}}$ (Nujol) 1715, 1610, 1465, 1380 cm$^{-1}$. $^1$H nmr (CDCl$_3$) $\delta$ 2.55 (t, J = 2.20 Hz, 3H, CH$_3$); 3.64 (q, J = 2.44 Hz, 2H, ArCH$_2$); 3.84 (s, 3H, CO$_2$CH$_3$); 7.23 - 7.55 (m, 4H, ArH). Mass spectrum: m/e = 188 (74%, M$^+$); 157 (25%); 129 (100%); 128 (53%); 127 (23%). Exact mass (C$_{12}$H$_{12}$O$_2$ requires: M$^+$ = 188.0837. Found: M$^+$ = 188.0837).

Cis-Methyl 1-methyl-2,3-dihydro-1H-indene-2-carboxylate 299

To a solution of methyl 3-methyl-1H-indene-2-carboxylate 298 (500 mg, 2.66 mmol) in methanol (10 ml) 10% palladium on carbon (200 mg) was added and the mixture was stirred under an atmosphere of hydrogen for 16 hours. The reaction mixture was diluted with ether (100 ml) and was filtered through a celite pad. The solvents were removed under reduced pressure and the residue was subjected to flash chromatography (hexane) to yield cis-methyl 1-methyl-2,3-dihydro-1H-indene-2-
carboxylate 299 (440 mg, 83%) as a clear oil. The ester 299 was homogenous by GC. \( \nu_{\text{max}} \) (Neat) 3065, 3020, 2950, 2870, 1740 (CO\(_2\)CH\(_3\)) cm\(^{-1}\). \(^1\)H nmr (CDCl\(_3\)) \( \delta 1.12 \) (d, J = 6.83 Hz, 3H, CH\(_3\)); 2.9 - 3.1 (m, 1H); 3.3 - 3.6 (m, 3H) 3.72 (s, 3H, CO\(_2\)CH\(_3\)); 7.71 (s, 4H, ArH). \(^13\)C nmr (CDCl\(_3\)) \( \delta 16.97 \) (q). 33.06 (t). 41.82 (d). 48.39 (d). 51.36 (q). 123.46 (d). 124.42 (d). 126.61 (d). 126.78 (d). 140.86 (s). 146.70 (s). 174.06 (s). Mass spectrum: m/e = 190 (37%, M\(^+\)); 131 (67%); 130 (100%); 115 (39%). Exact mass (C\(_{12}\)H\(_{14}\)O\(_2\) requires: M\(^+\) = 190.0994. Found: M\(^+\) = 190.0994).

Cis-1-methyl-2,3-dihydro-1H-indene-2-methanol 300

The title compound was prepared from cis-methyl 1-methyl-2,3-dihydro-1H-indene-2-carboxylate 299 (440 mg, 2.32 mmol) and lithium aluminum hydride (440 mg, 11.58 mmol) as described above for 2-(o-bromophenyl)pent-4-en-1-ol 271. The residue obtained after workup was purified by flash chromatography (20% ethyl acetate/hexane) to afford cis-1-methyl-2,3-dihydro-1H-indene-2-methanol 300 (324 mg, 87%) as a clear oil. (Found: C, 81.50; H, 8.61. C\(_{11}\)H\(_{14}\)O requires C, 81.48; H, 8.64). \( \nu_{\text{max}} \) (Neat) 3345 (broad, OH) cm\(^{-1}\). \(^1\)H nmr (CDCl\(_3\)) \( \delta 1.16 \) (d, J = 7.08 Hz, 3H, CH\(_3\)); 1.74 (s (broad). 1H, OH) 2.60 - 3.00 (m, 3H); 3.24 - 3.40 m (1H); 3.56 - 3.65 (m, 1H); 3.76 - 3.81 (m, 1H); 7.15 (s, 4H, ArH). \(^13\)C nmr (CDCl\(_3\)) \( \delta 14.93 \) (q). 34.17 (t). 40.50 (d). 45.44 (d). 63.21 (t). 123.34 (d). 124.51 (d). 126.35 (d, 2C). 141.79 (s). 148.54 (s).

Cis-1-methyl-2-(bromomethyl)-2,3-dihydro-1H-indene 301

The title compound was prepared from cis-1-methyl-2,3-dihydro-1H-indene-2-methanol 300 (234 mg, 1.45 mmol) in identical manner to that of 1-bromo-2-(1-iodomethylbut-3-enyl)benzene 272 with the exception that lithium bromide (700 mg, 8 mmol) was used instead of lithium iodide. The residue isolated from workup of the reaction mixture was purified by flash chromatography (hexane) to afford cis-1-methyl-2-(bromomethyl)2,3-dihydro-1H-indene 301 (200 mg, 72%) as a clear oil.
\[ \nu_{\text{max}} \text{(Neat) } 1590, 1480, 1460, 1440 \text{ cm}^{-1}. \]

\[ ^1H \text{ nmr (CDCl}_3\text{) } \delta 1.1 \text{ (d, } J = 7.00, 3H, \text{ CH}_3); 2.72 - 3.08 \text{ (m, } 3H); 3.25 - 3.60 \text{ (m, } 3H); 7.15 \text{ (s, } 4H, \text{ ArH).} \]

\[ ^{13}C \text{ nmr (CDCl}_3\text{) } \delta 14.63 \text{ (q), 34.40 (t), 36.33 (t), 41.58 (d), 46.05 (d), 123.54 (d), 124.57 (d), 126.52 (d, } 2C), 141.09 \text{ (s), 147.95 (s).} \]

Mass spectrum: m/e = 224 (40\%\), \(M^+\): 145 (100\%\); 129 (62\%\); 128 (34\%). \(\text{Exact mass (C}_{11}H_{13}Br\text{ requires: } M^+ = 224.0200. \text{ Found: } M^+ = 224.0201).\]

**Authentic sample of cis-1,2-dimethyl-2,3-dihydro-1H-indene 294**

A solution of cis-1-methyl-2-(bromomethyl)-2,3-dihydro-1H-indene 301 (100 mg, 0.44 mmol), tri-\(\text{-}\)butyltin hydride (155 mg, 0.533 mmol), and AIBN (4 mg, 0.024 mmol) in degassed benzene (10.7 ml) was heated under reflux for 5 hours. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexane) to afford cis-1,2-dimethyl-2,3-dihydro-1H-indene 294 (46 mg, 71\%) as a clear oil (Found: C, 90.62; H, 9.35. \(\text{C}_{11}H_{14}\) requires C, 90.41; H, 9.59). \(^1H \text{ nmr (CDCl}_3\text{) } \delta 0.96 \text{ (d, } J = 6.72\text{Hz, } 3H, \text{ CH}_3); 1.12 \text{ (d, } J = 7.32\text{Hz, } 3H, \text{ CH}_3); 2.49 - 2.63 \text{ (m, } 1H, \text{ ArCH}_2\text{CH}); 2.90 - 3.00 \text{ (m, } 2H, \text{ ArCH}_2); 3.07 - 3.21 \text{ (m, } 1H, \text{ ArCH}); 7.14 \text{ (s, } 4H, \text{ ArH).} \]

\[ ^{13}C \text{ nmr (CDCl}_3\text{) } \delta 14.5 \text{ (q), 15.8 (q), 38.0 (d), 39.3 (t), 42.3 (d), 123.66 (d), 124.48 (d), 126.23 (d, } 2C), 142.87 \text{ (s), 148.80 (s).} \]

Methyl 1,2,3,4-tetrahydro-2-naphthalene-2-carboxylate 303

The title ester was prepared from 1,2,3,4-tetrahydro-2-naphthoic acid 302 (528 mg, 3 mmol) in identical manner to that of methyl (o-bromophenyl)acetate 269. The residue obtained after workup was purified by flask chromatography (5\% ethyl acetate/hexane) to afford methyl 1,2,3,4-tetrahydro-2-naphthalene-2-carboxylate 303 (166 mg, 93\%) as a clear oil. \(\nu_{\text{max}} \text{(Neat) } 1735 \text{ (broad, CO}_2\text{CH}_3\text{) cm}^{-1}. \]

\[ ^1H \text{ nmr (CDCl}_3\text{) } \delta 1.75 - 2.30 \text{ (m, } 2H, \text{ ArCH}_2\text{CH}_2); 2.63 - 3.02 \text{ (m, } 3H, \text{ ArCH}_2\text{CH}_2\text{CH}); 3.00 \text{ (d, } J = 3.0\text{Hz, } 2H, \text{ ArCH}_2\text{CH}); 3.71 \text{ (s, } 3H, \text{ CO}_2\text{CH}_3\text{); 7.09 \text{ (s, } 4H, \text{ ArH).} \]

\[ ^{13}C \text{ nmr (CDCl}_3\text{) } \delta 25.87 \text{ (t), 28.50 (d), 31.63 (t), 39.92 (t), 51.68} \]
(q), 125.76 (d), 125.88 (d), 128.80 (d), 129.00 (d), 134.84 (s), 135.66 (s),
175.7808 (s). Mass spectrum: m/e: 190 (35%, M⁺); 158 (11%); 131 (46%); 130
(100%); 129 (31%); 115 (14%). Exact mass (C₁₂H₁₄O₂ requires: M⁺ =
190.0994. Found: M⁺ = 190.0994).

1.2.3.4-Tetrahydro-2-naphthalene methanol 304

The title compound was prepared from methyl 1.2.3.4-
tetrahydronaphthalene-2-carboxylate 303 (400 mg, 2.10 mmol) as described above
for 2-(o-bromophenyl)pent-4-en-1-ol 271. The residue obtained after workup was
purified by flash chromatography (20% ethyl acetate/hexane) to afford 1.2.3.4-
tetrahydro-2-naphthalenemethanol 304 (266 mg, 78%) as a colourless oil. νmax
(Neat) 3330 (broad, OH), 1065, 1025 cm⁻¹. ¹H nmr (CDCl₃) δ 1.26 - 1.54 (m, 1H,
CH₂CH₂CH); 1.70 (s (broad) 1H, OH): 1.80 - 2.1 (m, 2H, CH₂CH₂CH); 2.40 -
2.94 (m, 4H, 2 x ArCH₂); 3.6 (d, J = 6.59Hz, CHCH₂OH); 7.05 (s, 4H, ArH).
¹³C nmr (CDCl₃) δ 25.87 (t), 28.68 (d), 32.39 (t), 37.06 (t), 67.66 (t), 125.62 (d,
2C), 128.80 (d), 129.18 (d), 135.89 (s), 136.71 (s). Mass spectrum: m/e = 162
(29%, M⁺); 144 (22%); 131 (15%) 129 (100%), 116 (15%). Exact mass (C₁₁H₁₄O
requires: M⁺ = 162.1045. Found: M⁺ = 162.1045).

2-(Bromomethyl)-1.2.3.4-tetrahydronaphthalene 305

The title compound was prepared from 1.2.3.4-tetrahydro-2-
naphthalenemethanol 303 (250 mg, 1.54 mmol) and trifluoroacetic anhydride (410
mg, 2 mmol) as described above for 1-bromo-2-(1-iodomethylbut-3-enyl)benzene 272
with the exception that lithium bromide (700 mg, 8.1 mmol) was used instead of
lithium iodide. The residue obtained after workup was purified by flash
chromatography (hexane) to afford 2-(bromomethyl)-1.2.3.4-tetrahydronaphthalene
305 (236 mg, 68%) as a clear oil. ¹H nmr (CDCl₃) δ 1.43 - 2.22 (m, 3H, -CH₂CH-
); 2.5 - 3.07 (m, 4H, 2 x ArCH₂): 3.46 (d, J = 6.3Hz, 2H, CHCH₂Br); 7.08 (s,
4H, ArH). ¹³C nmr (CDCl₃) δ 28.15 (t), 28.65 (d), 36.74 (t), 39.28 (t) 125.76 (d).
125.82 (d), 128.77 (d), 129.12 (d), 135.28 (s), 136.07 (s). Mass spectrum: m/e = 224 (55%, M⁺): 145 (100%); 129 (34%); 104 (37%). Exact mass (C₁₁H₁₃Br) requires: M⁺ = 224.0200. Found: M⁺ = 224.0201.

Authentic sample of 2-Methyl-1,2,3,4-tetrahydronaphthalene 296

A solution of 2-(bromomethyl)-1,2,3,4-tetrahydronaphthalene (150 mg, 0.67 mmol, 0.04M). AIBN (10 mg, 0.07 mmol) and tri-n-butyltin hydride (234 mg, 0.80 mmol, 0.05M) in dry degassed benzene (16 ml) was heated under reflux for 16 hours. The reaction mixture was concentrated and the residue was subjected to flash chromatography (hexane) to afford 2-methyl-1,2,3,4-tetrahydronaphthalene (55 mg, 57%) as a colourless oil. υ max (Neat) 3060, 3010, 2950, 2875, 2850, 1495, 1455, 1435 cm⁻¹. ¹H nmr (CDCl₃): δ 1.05 (d, J = 6.35, 3H, CH₃); 1.3 - 1.5 (m, 1H, 1 x H-3); 1.7 - 1.95 (m, 2H, 1 x H-3 + H-2); 2.3 - 2.4 (m, 1H, 1 x H-4); 2.6 - 2.9 (m, 3H, 1 x H-4 + 2 x H-1); 7.05 (s, 4H, ArH). ¹³C nmr (CDCl₃): δ 21.90 (q), 29.20 (t, d, 2C), 31.45 (t), 38.08 (t), 125.32 (d, 2C), 128.74 (d), 128.97 (d), 136.57 (s), 136.86 (s). Mass spectra: m/e = 146 (78%, M⁺); 131 (25%); 104 (100%); 91 (36%). Exact mass (C₁₁H₁₄O₂) requires M⁺ = 146.1096. Found: M⁺ = 146.1096. The spectra are consistent with literature sources.¹⁵⁵.¹⁵⁶

Methyl 2-(phenylmethyl)but-3-enoate 308. Cis- and trans-Methyl 1-methyl-2,3-dihydro-1H-indene-2-carboxylate (299, 307), and Methyl 1,2,3,4-tetrahydro-2-carboxylate 303

A solution of methyl 2-((o-bromophenylmethyl)but-3-enoate (269 mg, 1 mmol), AIBN (17 mg, 0.1 mmol), and tri-n-butyltin hydride (350 mg, 1.2 mmol, 0.05M) in benzene (24 ml) was refluxed for 3 hours. GC analysis of the reaction mixture showed the formation of four products in the ratio 2:11:78:9. The solvent was removed under reduced pressure and the residue subjected to flash chromatography (5% ethyl acetate/hexane) to afford the title products (184 mg, 96%) as a clear oil. (Found: C, 76.02; H, 7.47. C₁₂H₁₄O₂ requires C, 75.76; H, 7.42).
Three of the products were identified as the direct reduction product methyl 2-(phenylmethyl)but-3-enoate 308 (2%), cis-methyl 1-methyl-2,3-dihydro-1H-indene-2-carboxylate 299 (11%) and the endo cyclization product, methyl 1,2,3,4-tetrahydronaphthalene-2-carboxylate 303 (9%) by GC retention times comparison with authentic samples.

The major component was identified as trans-methyl 1-methyl-2,3-dihydro-1H-indene-2-carboxylate 307 (78%). \( ^1 \text{H nmr (CDCl}_3 \): \( \delta \) 1.4 (d, \( J = 6 \text{Hz}, 3 \text{H}, \text{CH}_3 \); 2.78 - 2.92 (m, 1H); 3.16 - 3.21 (m, 2H); 3.43 - 3.54 (m, 1H); 3.75 (s, 3H, \text{CO}_2\text{CH}_3 \); 7.2 (s, 4H, \text{ArH}). \( ^{13} \text{C nmr (CDCl}_3 \): \( \delta \) 18.98 (q), 35.25 (t), 43.16 (d), 51.68 (q), 52.62 (d), 123.05 (d), 124.13 (d), 126.69 (d, 2C), 140.92 (s), 146.14 (s), 175.31 (s).

In another experiment, a solution of bromide 277 (10 mg, 0.037 mmol), AIBN (2 mg), and tri-n-butyltin hydride (13 mg, 0.045 mmol, 0.05M) in benzene (892 µL) was irradiated with UV lamp of at 5°C for 48 hours. GC analysis of the reaction mixture showed the ratio of the products 308:299:307:303 to be 4:8:83:5. and cis/trans ratio 1:10.4.

**Methyl 2-(phenylmethyl)but-3-enoate 308**

The title compound was prepared from methyl but-3-enoate 276 (500 mg, 5 mmol) and benzyl bromide (355 mg, 5 mmol) in identical manner with that of methyl 2-(o-bromophenylmethyl)but-3-enoate 277. The residue obtained after workup was purified by flash chromatography (5% ethyl acetate/hexane), to yield methyl 2-(phenylmethyl)but-3-enoate 308 (574 mg, 60%) as a colourless oil.

(Found: C, 75.76; H, 7.42. \( \text{C}_{12}\text{H}_{14}\text{O}_2 \) requires C, 75.47; H, 7.33). \( \nu \text{max (Neat) } \) 1740 (\text{CO}_2\text{CH}_3 \), 1640 (\text{C=Cr}), 1165 cm\(^{-1} \). \( ^1 \text{H nmr (CDCl}_3 \): \( \delta \) 2.84 (dd, \( J = 7.33, 13.4 \text{Hz}, 1\text{H, ArCH(H)} \); 3.08 (dd, \( J = 7.57, 13.67 \text{Hz}, 1\text{H, ArCH(H)} \); 3.25 - 3.40 (m, 1H, \text{CH} \); 3.62 (s, 3H, \text{CO}_2\text{CH}_3 \); 7.10 - 7.34 (m, 5H, \text{ArH}). \( ^{13} \text{C nmr (CDCl}_3 \)
δ 38.37 (t), 51.71 (d), 51.88 (q), 117.52 (t), 126.35 (d), 128.24 (d), 128.91 (d), 135.28 (d), 138.55 (s), 173.65 (s).
APPENDIX

Consider the rearrangement reaction depicted in Scheme A1. The rearrangement of $R^*$ to give $R^1$ is a first order process. $R^1$ once formed will react exclusively with an $a$-butylthio hydride (Bu$_2$SnH) in a second order manner to give the rearranged product $C$. In competition with this process is the direct hydrogen abstraction by $R^*$ from Bu$_2$SnH in a second order manner to give the reduced product $U$.

Thus:

$$\frac{d[R^1]}{dt} = k_{1}[R^*][Bu_2SnH]$$

$$\frac{d[U]}{dt} = k_{2}[R^*][Bu_2SnH]$$

Combining we obtain:

$$\frac{d[R^1]}{d[U]} = k_{1}/k_{2}[Bu_2SnH]$$

Under pseudo first order conditions where $[Bu_2SnH] >> [R^*]$, this is a good approximation $[Bu_2SnH] = constant$, thus we integrate for:
Consider the rearrangement reaction depicted in Scheme A1. The rearrangement of \( R^* \) to give \( R^1 \) is a first order process. \( R^1 \) once formed will react exclusively with tri-\( n \)-butyltin hydride (\( Bu_3SnH \)) in a second order manner to give the rearranged product \( C \). In competition with this process is the direct hydrogen abstraction by \( R^* \) from \( Bu_3SnH \) in a second order manner to give the reduced product \( U \).

Thus:

\[
\frac{d[R^1]}{dt} = k_r [R^*] \quad (a)
\]

\[
\frac{d[U]}{dt} = k_H [R^*][Bu_3SnH] \quad (b)
\]

combining we obtain:

\[
\frac{d[R^1]}{d[U]} = \frac{k_r}{k_H[Bu_3SnH]^{-1}} \quad (c)
\]

Under pseudo first-order conditions where \( [Bu_3SnH] \gg [R^*] \), then to a good approximation \( [Bu_3SnH] \) constant, thus (c) integrates to:
where

\[
[C] / [U] = \frac{k_r}{k_H [Bu_3SnH]_m} \quad (d)
\]

When the unimolecular rearrangement \( R^* \rightarrow R^1 \) represents a cyclization, then expression \( (d) \) becomes:

\[
k_c / k_H = ([C] / [U]) (Bu_3SnH)
\]

which is equation 1 used throughout the text of this thesis.

If the pseudo first-order conditions are not met, then integration of expression \( (e) \) leads to:

\[
[C] = r \ln \left( \frac{(S_o + r)}{(S_f + r)} \right)
\]

where the subscripts "f" and "o" denote "final" and "initial" respectively, and \( r = k_r / k_H \).

Equation 2 cannot be solved by simple graphical or arithmetic means. In all of work discussed in this thesis a computer based iterative method\(^{160} \) (ITRATF) was employed.
Consider the reaction depicted in Scheme A2 in which the cyclization reaction (U' → C') and 1,5-hydrogen atom transfer (U' → UR') competes with bimolecular hydrogen atom transfer from Bu₃SnH.

Thus:

\[
\frac{d[U'R']}{dt} = k_r[U'] \\
\frac{d[C']}{dt} = k_c[U'] \\
\frac{d[UH]}{dt} = k_H[U'][Bu_3SnH]
\]

Combining (i) and (ii) we obtain:

\[
\frac{d[U'R']}{d[C']} = \frac{k_r}{k_c}
\] (iv)

Under pseudo first-order conditions expression (iv) integrates to:

\[
\frac{[UR]}{[C]} = \frac{k_r}{k_c} = \alpha
\] (v)
where

\[ [\text{UR}] = \text{the final concentration of 1,5-hydrogen atom abstraction product} \]

\[ [\text{C}] = \text{the final concentration of cyclization product} \]

and

\[ \alpha = \text{the ratio (} k_r / k_c \text{) of } k_r \text{, the rate constant for 1,5-hydrogen abstraction to } k_c \text{ the rate constant for ring closure.} \]

Combining (ii) and (iii) we obtain:

\[
\frac{d[C^*]}{d[UH]} = \frac{k_c}{k_H[Bu_3Sn^{-1}]}
\]

Under pseudo-first order conditions expression (v) integrates to:

\[
\frac{[\text{C}]}{[\text{UH}]} = \frac{k_c}{k_H[Bu_3SnH]_m^{-1}}
\]

where \([\text{UH}]=\text{the final concentration of the direct reduction product}\)

\[
[\text{UH}] = [U_T] - [\text{UR}]
\]

where \([U_T]=\text{is the final concentration of the total reduction products}\)

Substituting expression (v) for \([\text{UR}]\) we obtain:

\[
[\text{UH}] = [U_T] - \alpha [\text{C}]
\]
Substituting (ix) to expression (vii) and rearranging we obtain:

\[ \frac{k_c}{k_H} = [(C / U_T) - \alpha C][Bu_3SnH]_m \]  

(3)

which is Equation 3 used in the text of this thesis.
REFERENCES


REFERENCES


46. (a) Professor K.U. Ingold in a private Communication has indicated that the values of $k_H$, the rate constant for the reaction of aryl radicals with tri-$n$-butyltin hydride given in reference 46b are probably in error. However, an independent determination by Beckwith and Bowry\textsuperscript{46c} give the following Arrhenius equation for the reaction of tri-$n$-butyltin hydride and aryl radicals: $\log k_H = 9.6 - 1.7/\theta$. Hence this value was used to obtain $k_c$ in this work. (b) L.J. Johnston, J. Lusztyk, D.D.M. Wayner, A.N. Abeywickrema, A.L.J. Beckwith, J.C. Scaiano, and K.U. Ingold. J. Am. Chem. Soc., 107, 4595 (1985); (c) A.L.J. Beckwith, and V.W. Bowry, unpublished observations.
53. Reference 12, but corrected in the light of the new data for the reaction of aryl radicals with tri-n-butyltin hydride (see reference 46).
70. A. Nikon, R. Ferguson, A. Bosch, and T. Iwadare. J. Am. Chem. Soc., 99,
4518 (1977)
references cited therein.
83. C. Chatgilialogly, K.U. Ingold, and J.C. Scaiano. J. Am. Chem. Soc., 103,
7739 (1981)
and references cited therein.
119. T. Ueda, and S. Shuto, Heterocycles, 17, 95 (1982)
144. A.L.J. Beckwith, and J. Zimmermann, unpublished observation
146. F. Mayer, and A. Sieglitz, Chem. Ber., 55, 1835 (1922)


Addendum

The rearrangements of the radicals 77→78 and 89→90 are not made clear in the text of this thesis in that the experiments in itself do not unambiguously define the mechanisms of the rearrangements.

In principle this could occur either by a neophyl rearrangement or by a 1,2-alkyl shift. A distinction between these two mechanisms could be made by conducting experiments with tributyltin deuteride. The formation of the endo product with deuterium in the benzylic position would indicate the occurrence of a 1,2-alkyl shift while the formation of the product with deuterium in the position α- to the aromatic ring would indicate the occurrence of the neophyl rearrangement. However, in view of the fact that there are no known authentic examples of a 1,2-alkyl shift in alkyl radicals, whereas neophyl rearrangements have been extensively studied\textsuperscript{7a} and known to show the same features as those observed in the present work it was not considered necessary to conduct further experiments.

Sendaba Gerba

August 1989
Errata

P. 2 1st line of 2nd paragraph, cyclization should be cyclization

P. 7 Scheme 10, the structure of product of reaction of 19 should be

\[
\begin{align*}
\text{(CH}_2\text{)}_{n+1} \\
\text{(CH}_2\text{)}_n
\end{align*}
\]

P. 7 Scheme 10, the structure of compound 22 should be

\[
\begin{align*}
\text{(CH}_2\text{)}_{n+1} \\
\text{(CH}_2\text{)}_n
\end{align*}
\]

22

P. 13 4th line of 2nd paragraph, 48 should be 47

P. 14 4th line, eliminates should be eliminates

P. 17 1st line of 1st paragraph, Boat should be Boate

P. 17 2nd line of 3rd paragraph, readical should be radicals

P. 26 2nd line, exo should be exo

P. 26 10th line, valves should be values
P. 26 17th line, form should be from

P. 33 the rate constant for 77-78 should be $1.3 \times 10^4 \text{ s}^{-1}$

P. 34 8th line of 2nd paragraph, reference 15 should be 10

P. 37 Scheme 36 a/b, the structure of compound 108 should be

```
\begin{align*}
\text{108} & \quad X = H \\
& \quad X = D
\end{align*}
```

P. 45 2nd line, stereochemistries should be stereochemistries

P. 45 3rd line, related should be related

P. 47 6th line of 2nd paragraph, precursor should be precursors

P. 69 3rd line, 1-naphthyl should be 1-naphthyl

P. 80 1st line of 4th paragraph should be, "Solution of the integrated rate equation 2 (Appendix A) for the results obtained from the reaction of 208 with tri-n-butyltin hydride gave $k_c$ to be $> 5.1 \times 10^7 \text{ s}^{-1}$ for the ring closure of the radical 229 at 80 °C."

P. 87 7th line, 264 should be 265
P. 98 2nd line, resonance should be resonances

P. 103 4th line, 309 should be 308

P. 151 6th line, 219 should be 220

P. 187 reference 21, 136 should be 595

P. 187 reference 30, Borger should be Boger

P. 187 reference 32, PPtel should be Patel

P. 188 reference 38, Wood should be Westwood

P. 189 reference 56, Phillipon should be Phillipou

P. 189 reference 59, Witt should be Wilt

P. 190 reference 77, Padawa should be Padwa

P. 190 reference 78, Wallig should be Walling

P. 190 reference 83, Chatgilialogly should be Chatgilialoglu

P. 192 reference 115, Padaw should be Padwa

P. 192 reference 129, Phillipon should be Phillipou