Stereoselective Tetrahydrofuran Synthesis

by

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Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

December 1993

DECLARATION

I hereby declare that the substance of this thesis has not been submitted nor is being concurrently presented for any other degree.

I also declare that the work embodied in this thesis is the result of my own investigations and where the work of other researchers has been used, this has been fully acknowledged in the text.

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D. E. SHAW

Director of Study

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D. W. KNIGHT

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I wish to take this opportunity to thank the many people who have assisted me during the preparation of this thesis.

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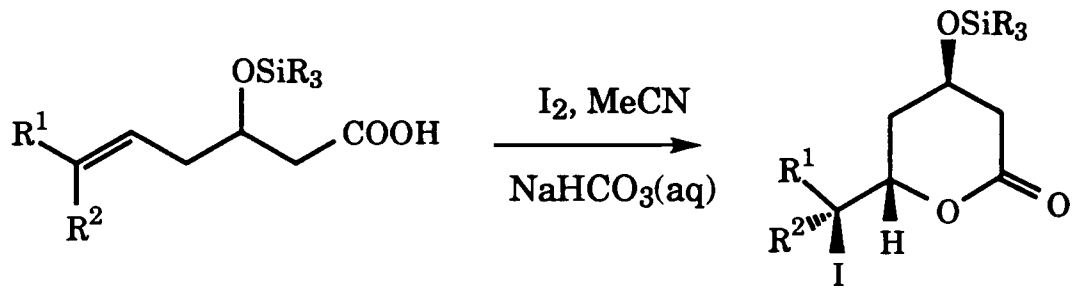
Finally, I would particularly like to thank Miss Michelle Burns for her constant support and encouragement during the course of this research.

ABSTRACT

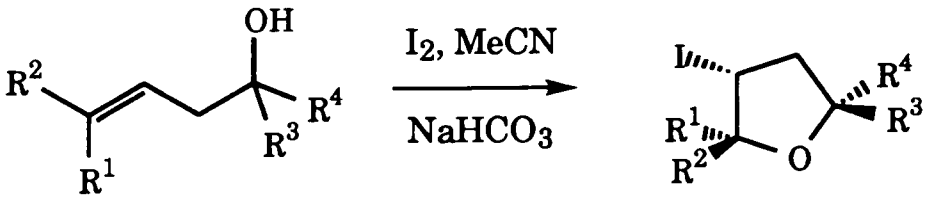
This thesis begins in Chapter One with a discussion of the role of electrophilic cyclisation in the synthesis of tetrahydrofurans. Chapter Two begins with a discussion of the synthesis of iodo-δ-lactones, by the iodolactonisation of β-silyloxy-δ-alkenoic acids (Scheme A). It will show how the potential of this chemistry has been expanded by proving the absolute stereochemistry at the iodine centre.

Scheme A



Chapter Two goes on to consider the stereospecific synthesis of 2,3,5-trisubstituted iodo-tetrahydrofurans by the related iodo-etherification of homoallylic alcohols (Scheme B). This is facilitated by the use of anhydrous conditions.

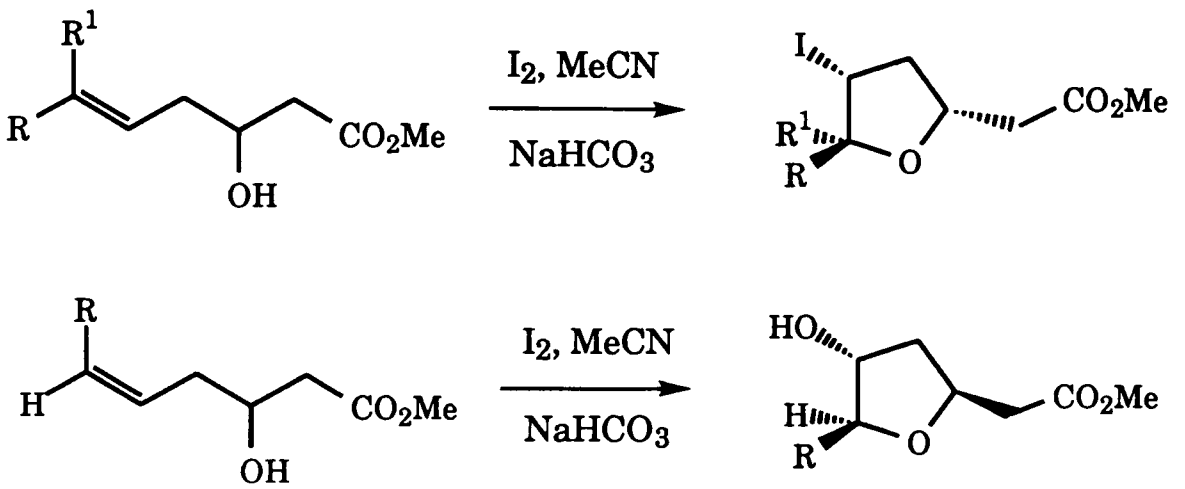
Scheme B



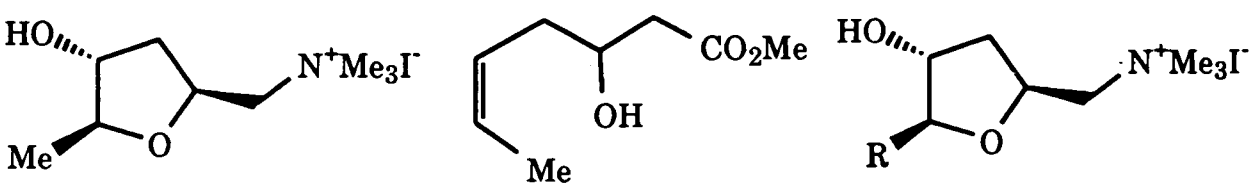
The synthesis of 2,3,5-trisubstituted iodo-tetrahydrofuranacetic

acid esters and 2,3,5-trisubstituted hydroxy-tetrahydrofuranacetic acid esters by the iodocyclisation of geometrically pure (E)- and (Z)-β-hydroxy-δ-alkenoates was then developed and the stereochemical outcome of the reactions was proven (Scheme C).

Scheme C



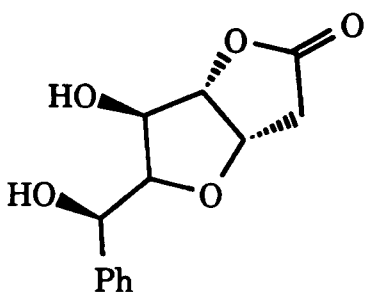
Targets were chosen which illustrated the utility of the key cyclisations of β-hydroxy-δ-alkenoates. Chapter Three discusses the synthesis of muscarine **93**. It was chosen to synthesise muscarine from the cyclisation of the (Z)-β-hydroxy-δ-alkenoate **146**. This synthesis is particularly versatile as it not only allows the preparation of muscarine itself, but also of various potentially highly biologically active analogues **146a**.



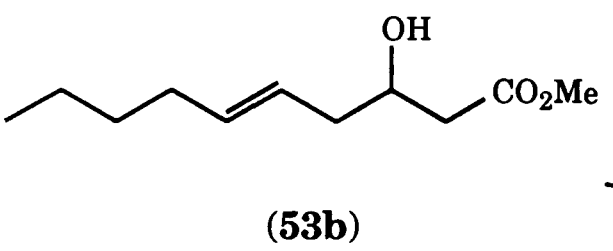
(93) **(146)** **(146a)**

The second target selected was Goniofufurone **170**.

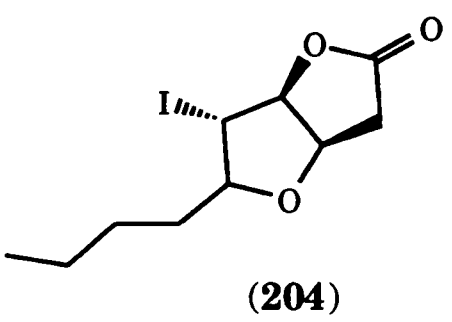
Approaches to this molecule will be discussed in Chapter Four. Model work in the synthesis of goniofufurone began with the cyclisation of the (E)-β-hydroxy-δ-alkenoate **53b**, which indeed, led to the facile synthesis of the iodolactone **204**. However, early attempts to incorporate the natural side chain met with limited success.



(170)



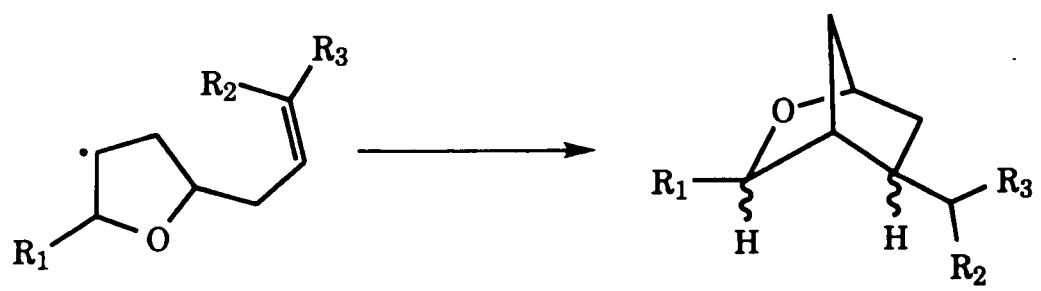
(53b)



(204)

Chapter Five discusses an approach to the 2-oxabicyclo-[2.2.1]-heptane ring system, which has been synthesised by the radical cyclisation of various β,γ-unsaturated tetrahydrofurans of the general form shown in Scheme D.

Scheme D



CONTENTS

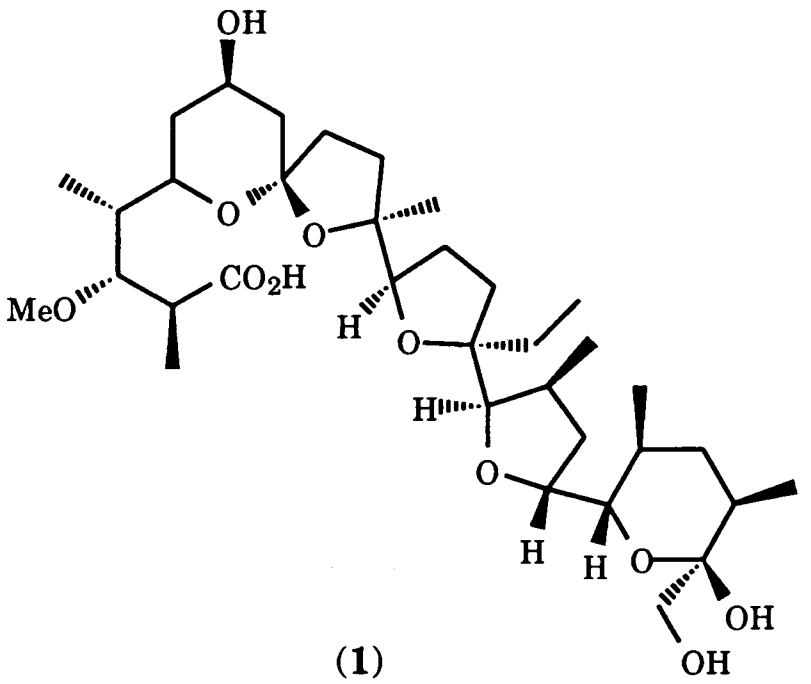
CHAPTER ONE

Electrophilic Cyclisation as a Route to Saturated Oxygen Heterocycles

Electrophilic Cyclisation as a Route to Saturated Oxygen Heterocycles

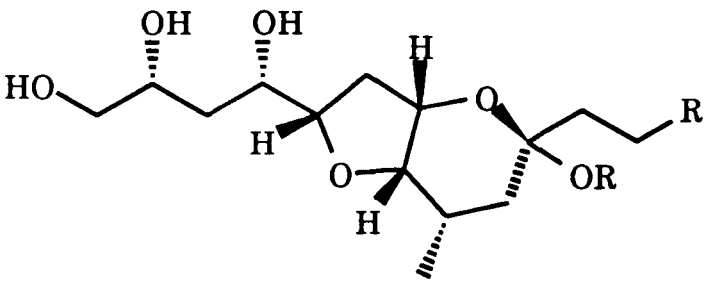
(I) Introduction

The stereocontrolled synthesis of saturated oxygen heterocycles is one of the key challenges of modern organic synthetic chemistry. The preparation of highly substituted tetrahydrofurans (THFs) and tetrahydropyrans (THPs), along with β-, γ- and δ- lactones, of defined stereochemistry, is of great importance, due to the vast array of biologically important natural products which contain this type of functionality.

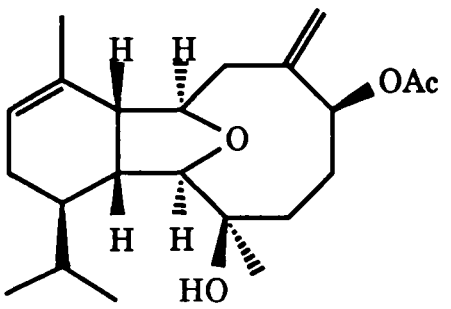


(1)

The polyether antibiotics (*eg* Monensin **1**) are extremely important because they have the ability to transport metal ions across biological membranes[1-2] and consequently, the range of their possible biological activity is extensive.[3] They are anti-microbial agents[4] and are known to provoke cardiovascular responses.[5] The key structural features of these molecules are THFs and THPs. Naturally there has been much synthetic interest in these natural products due to their biological and commercial importance and also due to the huge synthetic challenge which they present. Despite this, there have only been a few total syntheses reported.[6-11] There are also a wide range of other natural products which contain THFs as important sub-units, including steroids, C-nucleosides and marine natural products such as the Halichondrins **2** and Eunicellin diterpenoids **3**.

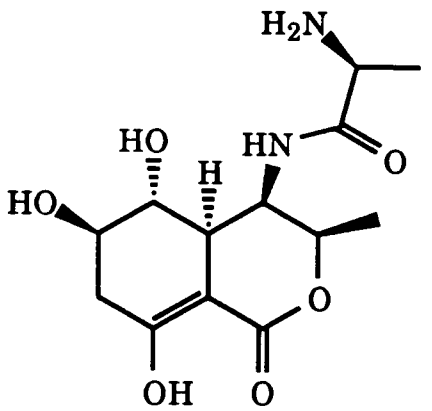


(**2**)



(**3**)

Lactones are also present in a wide range of natural products with various different roles in nature. Actinobolin **4** was isolated from Streptomyces cultures, whereas (+)-Nepetalactone **5** is a pheromone found in aphids.



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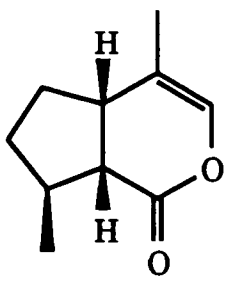


(5)

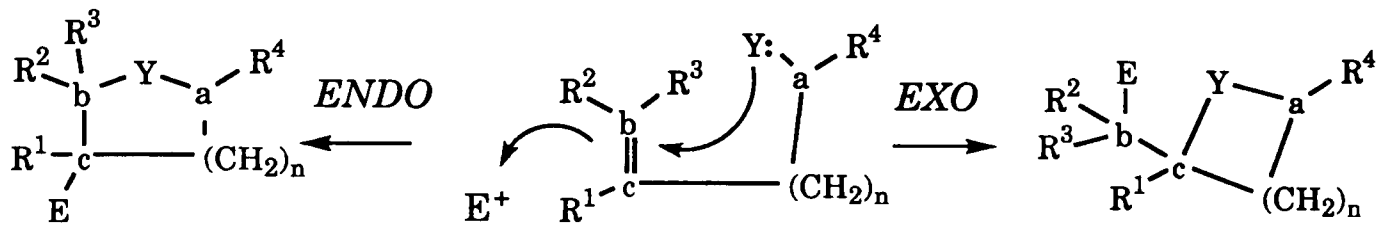
(II) Electrophilic Cyclisation

One of the most important routes to saturated oxygen heterocycles of known stereochemistry is the electrophilic cyclisation of unsaturated molecules containing internal nucleophiles. There are many electrophiles which allow this reaction to take place and there are a huge variety of examples of this process in synthesis. This section will outline the main types of electrophilic cyclisation and will give an idea of their scope in terms of organic synthesis.

The electrophilic cyclisation reaction follows the general equation shown in Scheme 1. As with most cyclisation processes the reaction can either take an *exo* or *endo* pathway. In most cases, these processes will broadly follow the empirical rules laid down by Baldwin[12] for the geometry of transition states and the balance of steric and electronic factors: *ie* 4-*exo*, 5-*exo* and 6-*exo* are favoured over 5-*endo*, 6-*endo* and 7-*endo*. In the cases of some of the reactions

which will be described, the transition state involved does not have even charge distribution and is therefore not equivalent to a normal double bond. This means that it will not be constrained by the stereoelectronic forces used by Baldwin when formulating his rules. In particular, in the cases of electrophiles which do not form standard "onium" complexes with the double bond, other factors can determine the mode of cyclisation.

Scheme 1



The cyclisation generally gives the opportunity to generate new stereocentres at sites **b** and **c** (Scheme 1). In most cases, the stereochemistry of centres **b** and **c** will be determined by the geometry of the double bond as there will normally be overall *anti* addition of nucleophile and electrophile to the double bond. The extent to which the stereochemistry of the new stereocentres is determined by the cyclisation process, and also the extent to which the stereochemistry is induced by other substituents, allows the usefulness of the individual cyclisations to be assessed.

(A) Electrophilic Lactonisation

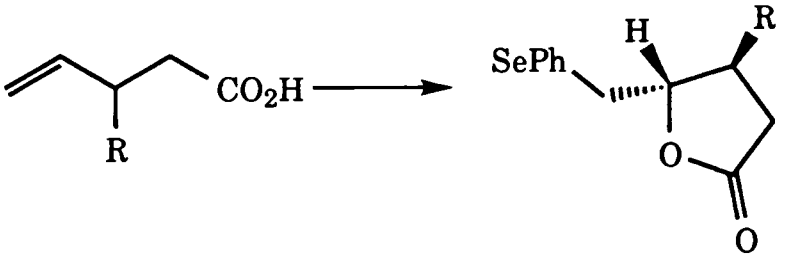
The electrophilic lactonisation of unsaturated acids to give functionalised lactones with generally excellant levels of stereocontrol

is, perhaps, the most important method of lactone synthesis available to organic chemists, beyond the simple intramolecular condensation of hydroxy-acids. This section will discuss some of the range of electrophiles available for such processes and the extent of their usefulness.

(i) Phenylselenolactonisation.[13]

Selenium mediated cyclisation has become popular due to the usefulness of the phenylselenenyl (PhSe) group which is incorporated into the resulting lactones. The PhSe group is versatile and can be easily manipulated. It can be oxidatively (H_2O_2) or reductively (Bu_3SnH) removed to give unsaturation and saturation respectively. The first reagent used in phenylselenolactonisation was phenylselenenyl chloride, and, in cyclic systems, this generally gives good stereocontrol. However, the rate of this reaction, even at -78°C, is usually so rapid that it probably does not allow thermodynamic control, so in the lactonisation of acyclic substrates, the stereocontrol is not high. The introduction of N-phenylselenophthalimide (NPSP)[14] brought much more reversibility into the lactonisation reaction and allows much better stereocontrol. (Scheme 2).

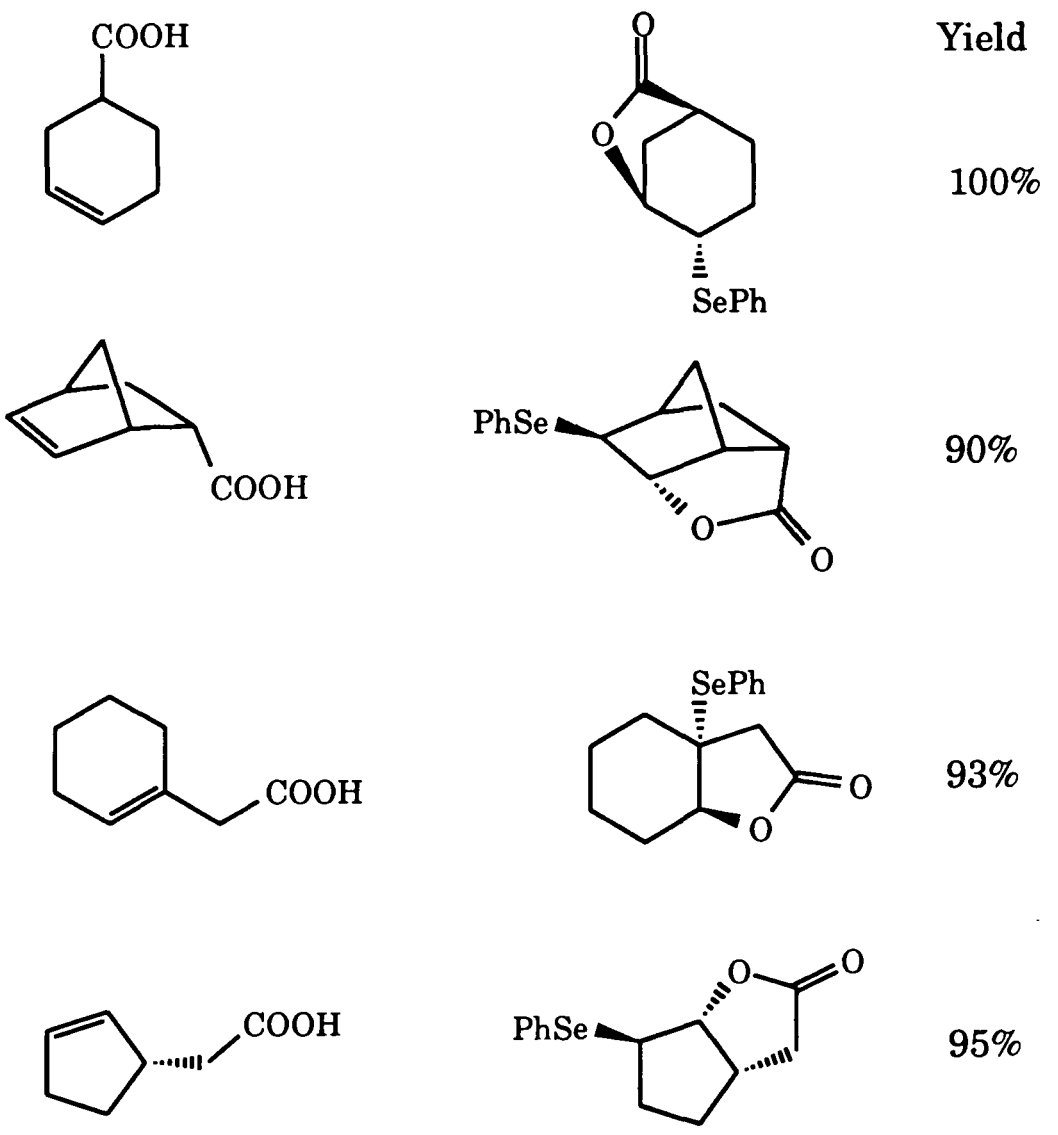
Scheme 2



R	Reagent	Conditions	Yield	*cis* :*trans*	Ref.
Me	PhSeCl	ether 25°C	69%	1 : 1	15
Ph	PhSeCl	dcm -78°C	54%	2.7:1	16
Ph	NPSP	ether 25°C	75%	15:1	16

The mode of cyclisation in the phenylselenolactonisation reaction is not so much controlled by Baldwin's rules as by the ability of the two possible sites to stabilise a carbonium ion.

Scheme 3



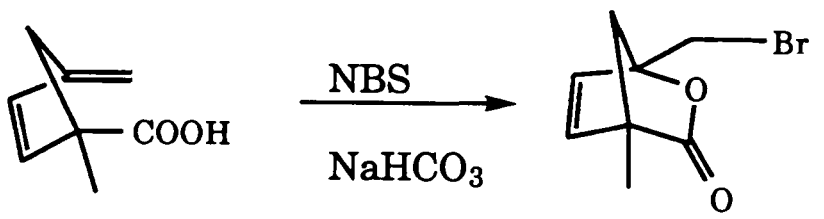
In general, the ring closure occurs at the carbon most able to stabilise a positive charge, although subsequent rearrangements are often possible. Empirical observations suggest that 5-membered lactones are prefered over the 4- and 6-membered alternatives. Some examples are shown in Scheme 3.

The oxidative removal of the PhSe group is particularly useful as the elimination proceeds selectively in a *syn* fashion and away from the oxygen atom. This directing effect is explained as the polar selenoxy function will tend to align *anti*-parallel to the oxygen lone pairs in order to minimise repulsion.[17] Interestingly, selenolactonisation can be reversed using sodium in liquid ammonia to reductively remove the selenium function. This enhances the power of this reaction as it can potentially be used as a protection step.

(ii) Halolactonisation

Halolactonisation is by no means a new process. As early as 1908, Bougault[18] investigated the process, but it is only recently that the full stereochemical and regiochemical subtleties have been studied. Early work suggested that only 5- and 6-membered lactones could be synthesised in this way, but this proved to be untrue. Indeed, according to Baldwin's rules and Markovnikov orientation, 4-*exo* lactonisation is the favoured process under kinetic conditions.[19] The cyclisation shown in Scheme 4 illustrates the type of strained systems which can be constructed in this way.

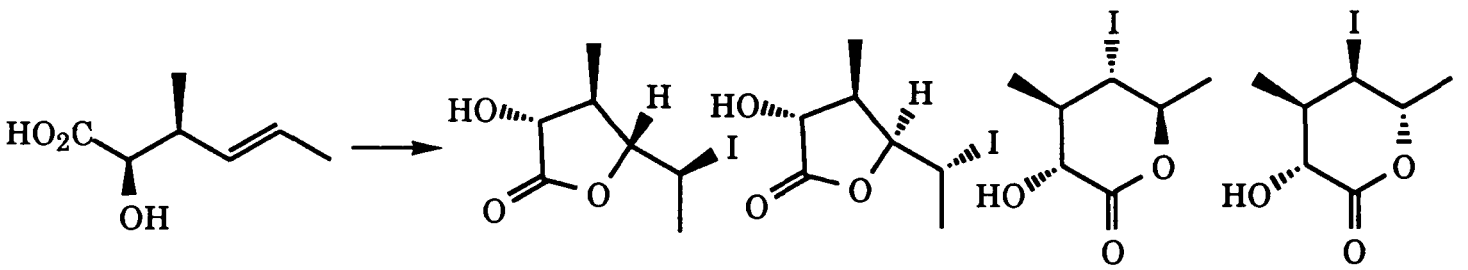
Scheme 4



Halolactonisation, unlike selenolactonisation, usually follows Baldwin's rules fairly closely.

Bartlett[20] brought a new dimension to the halolactonisation reaction when he advocated the use of thermodynamic conditions [I_2, non-basic solvent (usually acetonitrile)], instead of kinetic conditions [presence of base, $NaHCO_3$(aq)] or limiting the concentration of halonium ions (*i.e.* N-iodosuccinimide, $CHCl_3$) (Scheme 5).

Scheme 5

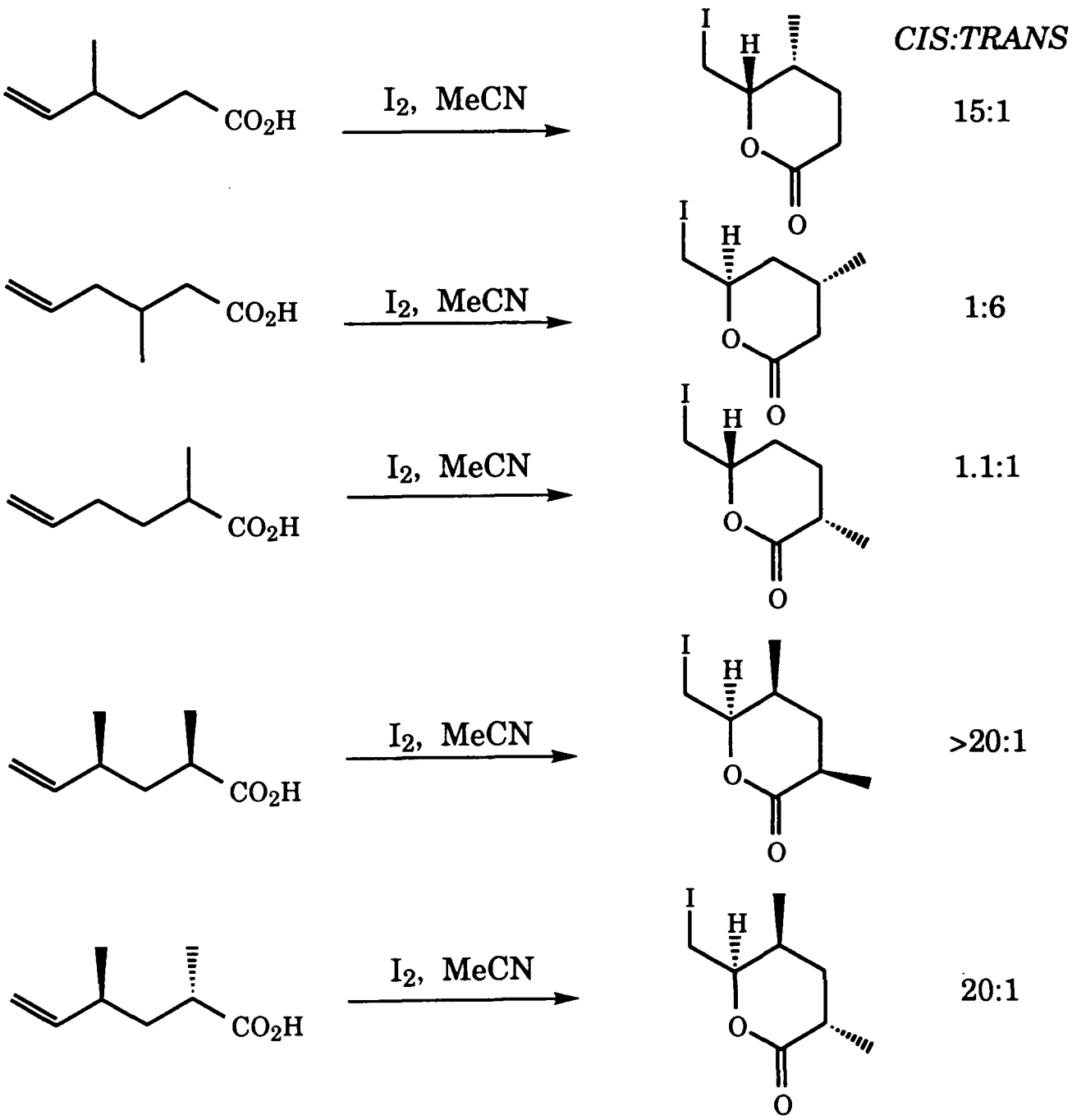


	yield	*trans*	*cis*	*trans*	*cis*
NIS, $CHCl_3$	75	2	2	3	1
I_2, Et_2O, $NaHCO_3$	73	3	1	0	0
I_2, CH_3CN	77	>20	1	0	0

The use of thermodynamic conditions allows the equilibration of the less thermodynamically stable *cis* lactone *via* protonation of the first lactone formed. This requires a certain amount of free

protons to be available. Iodine/ether/aqueous bicarbonate allows some equilibration (*i.e* no 6-*endo* cyclisation products are seen but there is no equilibration of *cis*-lactones to *trans*-lactones). In the formation of δ-lactones under thermodynamic conditions, 1,2- and 1,3- asymmetric induction can be achieved because of the well-defined "chair-like" transition state involved, but 1,4-induction is not generally very good (Scheme 6).[21]

Scheme 6

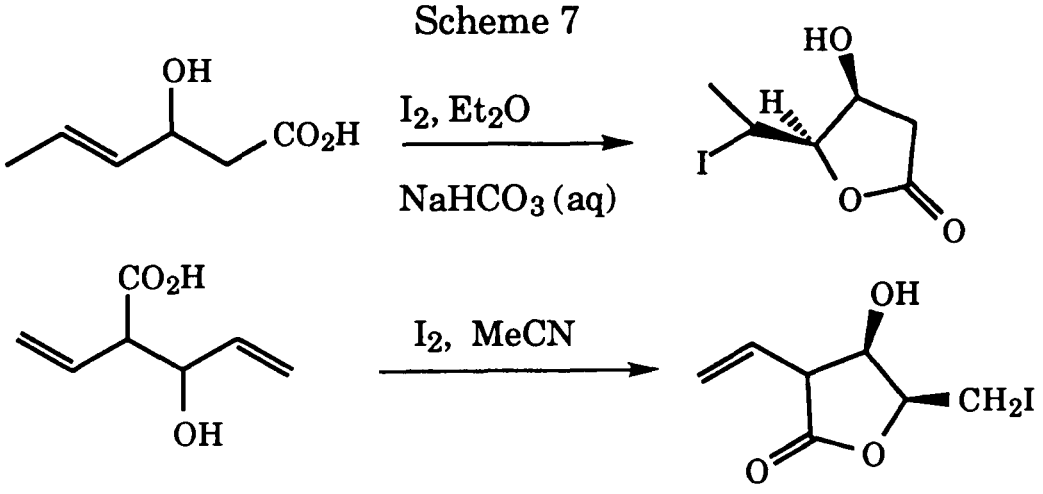


The use of 2,4-disubstituted substrates ensures good

asymmetric induction and this was used by Bartlett in his synthesis of Multistriatin[22] and Serricornin.[21]

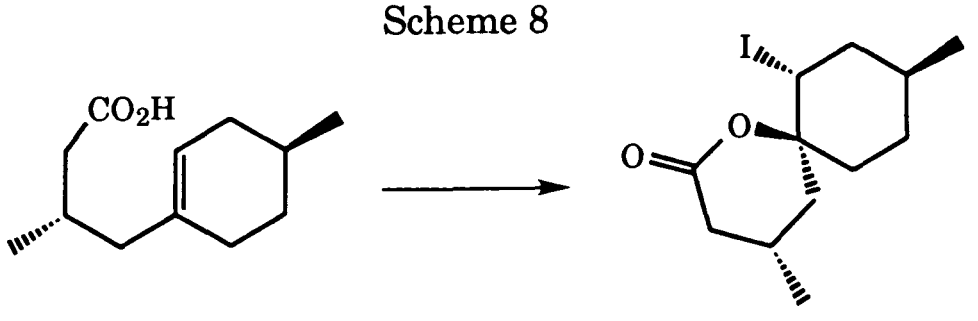
Chamberlain[23] and Katzenellenbogen[24] have also studied the effect of having a free hydroxyl function upon stereoselection in this reaction. In both cases, high selectivities for the *cis*-lactones were observed, this time in the case of γ-lactones (Scheme 7). In these examples, there is steric control over the cyclisation by the free hydroxyl group and only the isomers shown were isolated.

Scheme 7



Halolactonisation has been applied to a wide range of substrates. The spirolactonisation (Scheme 8) used by Wovkulich *et al*[25] in the approach work to a synthesis of Mevinolin illustrates this particularly well.

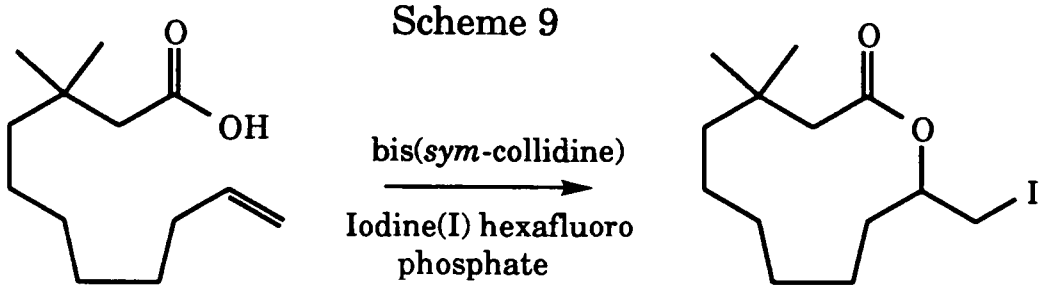
Scheme 8



Medium ring lactones can also be synthesised by

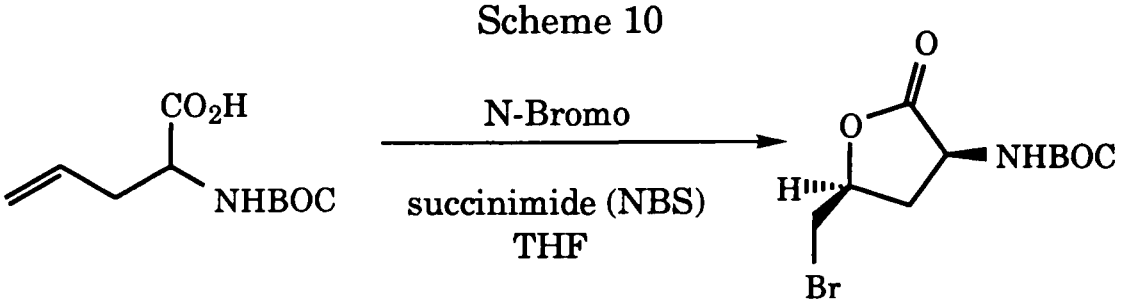
halolactonisation methods, as long as the substrate contains either hydroxyl or *gem*-dimethyl substituents.[26] Such substituents restrict the rotation of the substrate and give a much greater chance of cyclisation (Scheme 9).

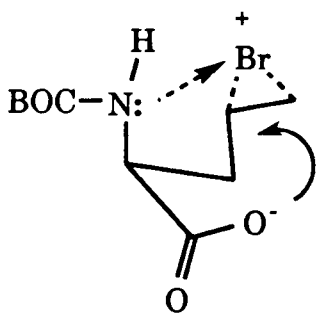
Scheme 9



Nitrogen substituted unsaturated acids can also be halolactonised with good asymmetric induction (Scheme 10). The high stereoselection is rationalised by the possibility of nitrogen stabilising the transition state creating the kinetically more favourable transition state **6**.[27]

Scheme 10



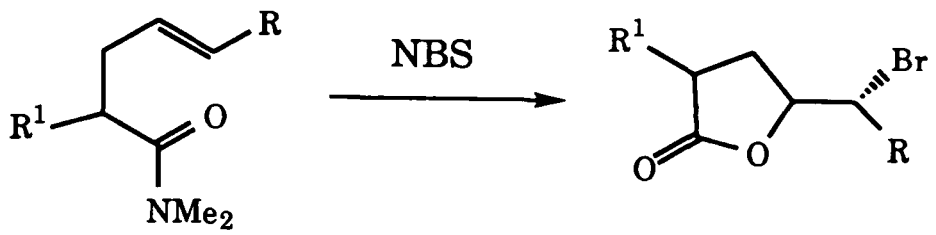


(**6**)

It is also possible to halolactonise unsaturated amides; indeed, this process is favoured over the alternative mode of cyclisation

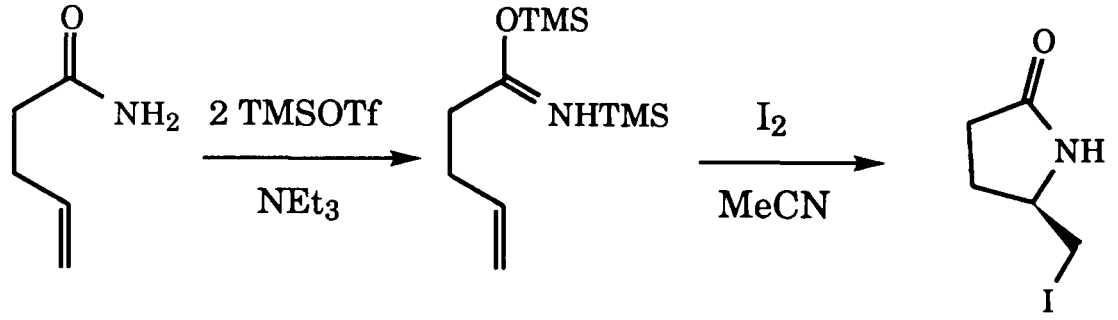
in which the nitrogen acts directly as the nucleophile (Scheme 11).[28]

Scheme 11



Knapp[29] has, however, demonstrated that upon protection of an amide with two equivalents of trimethylsilyl triflate, the N,O-bis-(trimethylsilyl)imidate can be induced to iodocyclise, *via* the nitrogen, to give the iodo-γ-lactam. (Scheme 12).

Scheme 12



(B) 5-*exo*-trig Electrophilic Cycloetherification.

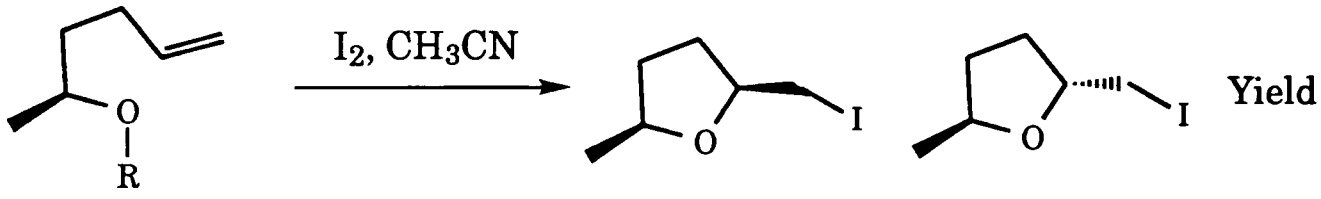
One of the key routes to the synthesis of THFs of controlled stereochemistry is the 5-*exo*-trig cycloetherification of γ,δ-unsaturated alcohols. This is by far the most common use of cycloetherification and it has therefore been studied extensively using a variety of different electrophiles. In this section the range of electrophiles and

the scope of the process will be discussed.

(i) Haloetherification

This approach was developed ten to fifteen years ago by Bartlett and his colleagues.[30] He found that γ,δ-unsaturated alcohols cyclised under thermodynamic conditions (iodine/acetonitrile) to give *trans* 2,5-disubstituted THFs with moderate selectivity (Scheme 13), whereas when the corresponding ethers were cyclised under the same conditions, *cis* 2,5-disubstituted THFs, the thermodynamically more stable isomers, were formed with moderate to good selectivity depending on the ether group used. The best stereoselectivity was obtained using sterically bulky ether groups, but some groups were found to be so bulky that they hindered cyclisation and led to much reduced yields.

Scheme 13

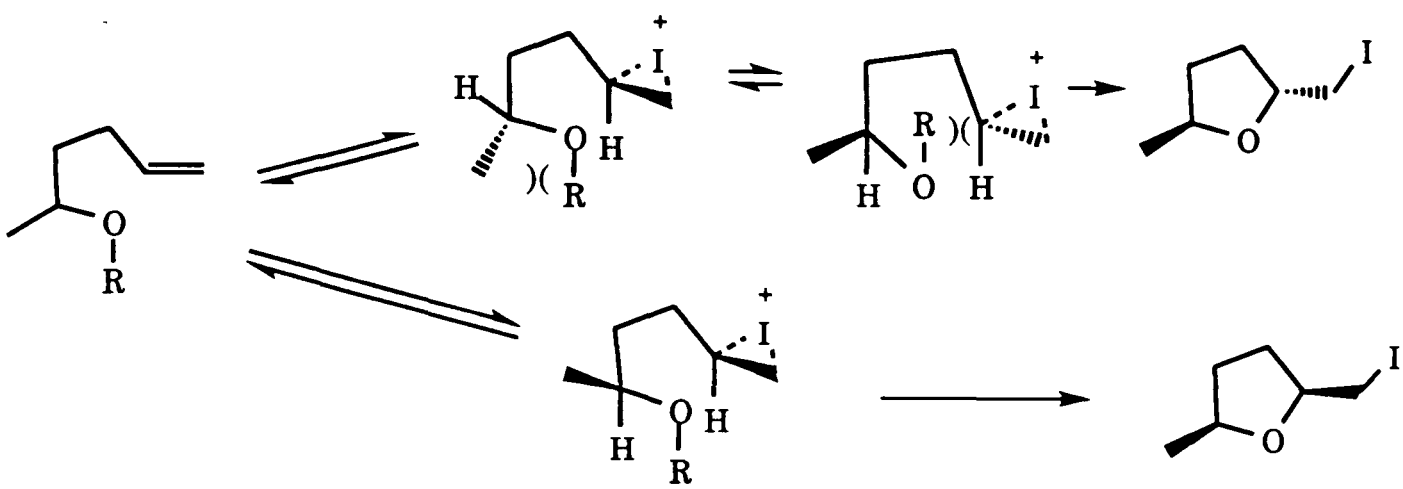


			Yield
R=H	1	2	66%
R=Bz	2	1	60%
R=DCB	21	1	63%

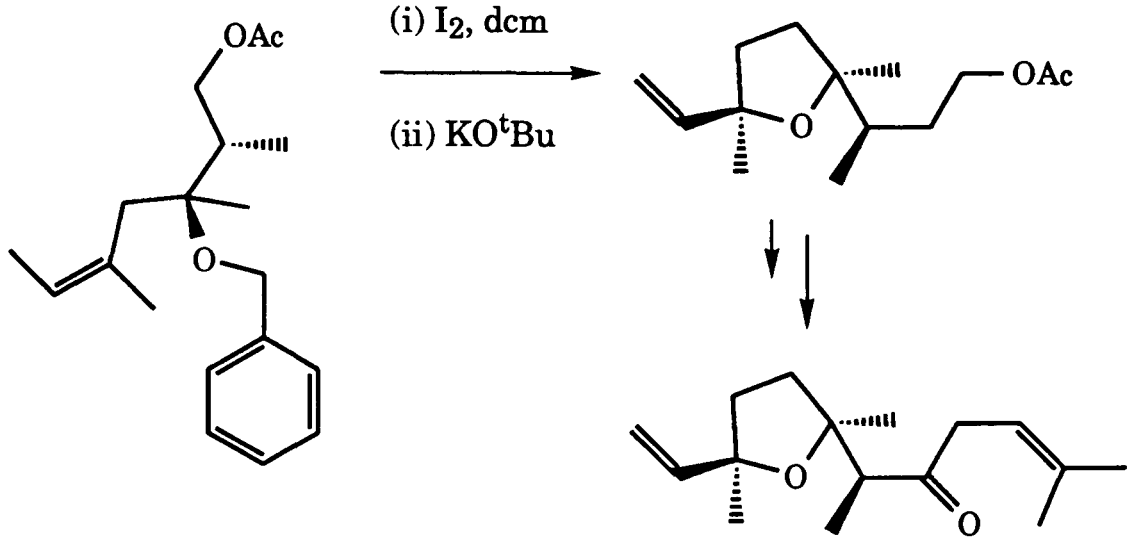
Bartlett found that the 2,6-dichlorobenzyl group (DCB) gave the best selectivities as it had the best balance of beneficial stereo- and electronic effects. More recently, Normant[31] found that the use of

^{t}butyl ethers gave an even better stereoselection (28:1 *cis*:*trans* ratio); these ethers are also easier to form than the corresponding DCB ethers. The rationale for these selectivities is shown in Scheme 14.

Scheme 14



Scheme 15

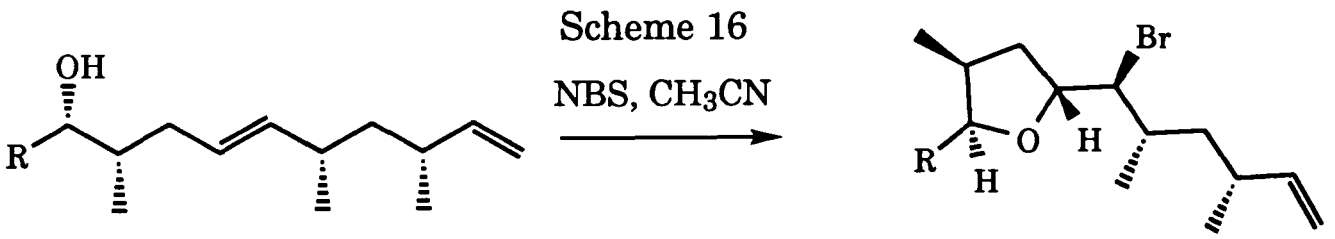


cis-2,5-Disubstituted THFs are the major products when the ether group is bulky because there is a transition state available where the steric interactions are minimised, whereas both possible transition states that would result in the corresponding *trans*-2,5-disubstituted THFs being formed have an unfavourable interaction between one of the substituents and the ether group. There are vast

numbers of examples of these reaction in synthesis; Bartlett[32] has exemplified the process in the synthesis of Davanone **7** (Scheme 15)

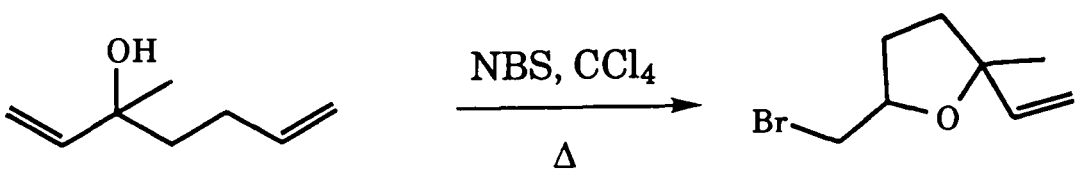
Many other halogen sources have been used in this process. Kishi[33] used an NBS mediated cyclisation as part of an approach to the right-hand half of Monensin **1** and obtained a stereochemically pure 2,5-*trans* disubstituted THF (Scheme 16). This stereoselectivity is surprising in the context of Bartlett's work, but the effect of the 3-methyl substituent must be large.

Scheme 16



As early as 1970, Rhoads[34] used NBS in refluxing carbon tetrachloride to effect the cyclisation of an unsaturated alcohol (Scheme 17) under thermodynamic conditions, although the stereochemical purity was low.

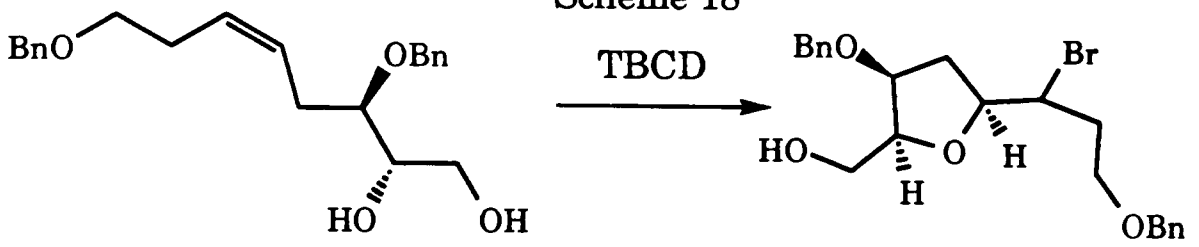
Scheme 17



Torr[35] used 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCD) as a source of bromonium ions in the 5-*exo* cycloetherification of a polyhydroxylated substrate with reasonable *cis*-selectivity

(Scheme 18).

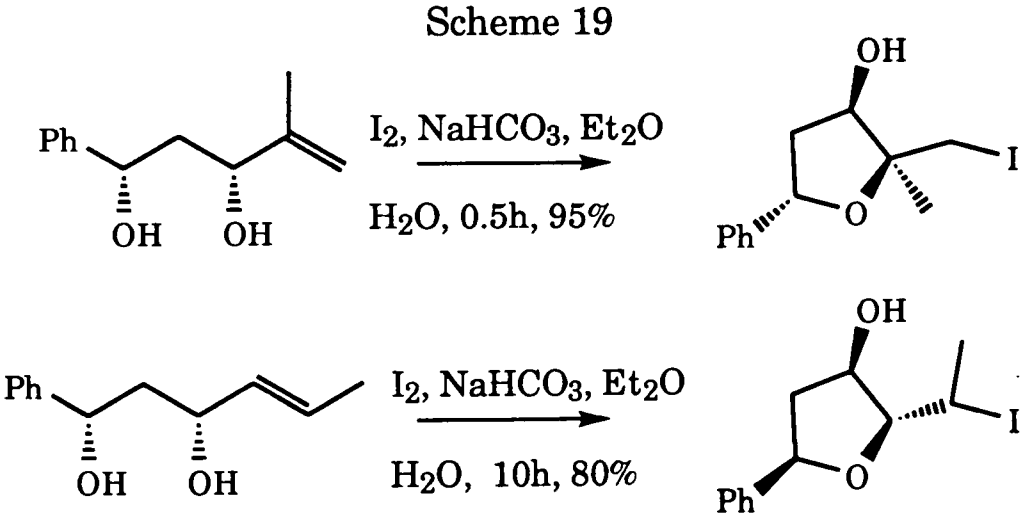
Scheme 18



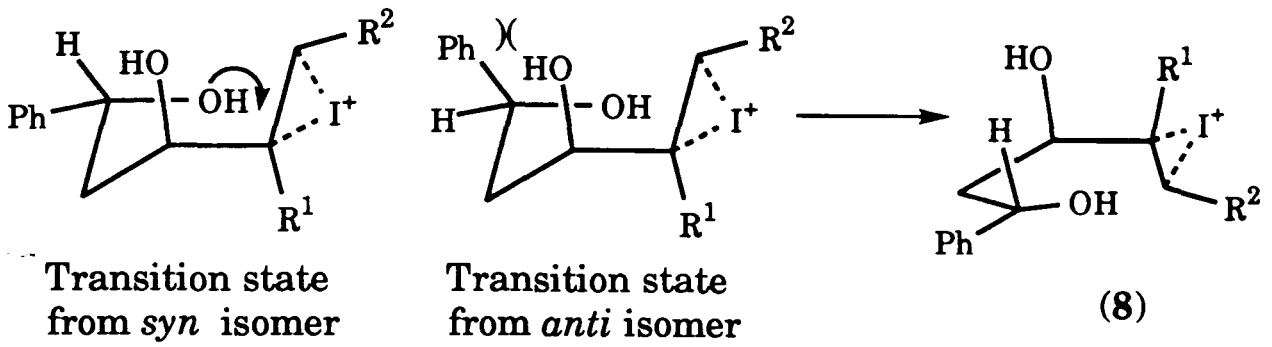
The use of bis-(*sym*-collidine)iodine(I) perchlorate, as devised by Schauble,[36] allows the formation of cyclic ethers of ring size 3-7 with high regioselectivity (generally consistant with Baldwin's rules), and is consequently of great interest in the synthesis of epoxides and oxetanes of controlled stereochemistry.

Incorporation of an extra free hydroxyl function into the substrate, other than that which cyclises, was pioneered by Yoshida.[37] It was found that 1,3-*syn* diols gave high stereoselectivity for 2,5-*trans*-THFs (95%), whereas 1,3-*anti* diols gave a poorer selectivity of 2:1 *trans*:*cis* (Scheme 19). This was rationalised by proposing the transition states shown (Scheme 20).

Scheme 19



Scheme 20



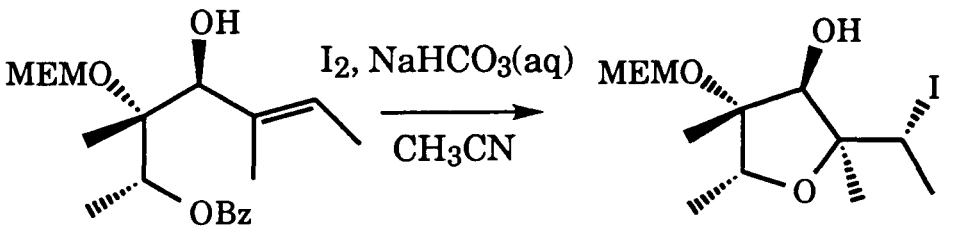
Transition state from *syn* isomer

Transition state from *anti* isomer

(**8**)

The transition state that gives the *trans*-THF from the *syn*-diol is favoured due to the lower steric hindrance, so the cyclisation is fast and selective, whereas the corresponding transition state from the *anti*-diol has serious steric hindrance preventing one-step cyclisation to the *cis*-THF. It therefore rotates to give the transition state **8** which cyclises to give the *trans*-THF preferentially. This stereochemical outcome is also seen in the work of Williams[38] where the benzyl ether **9** was cyclised with a similar stereochemical outcome (Scheme 21).

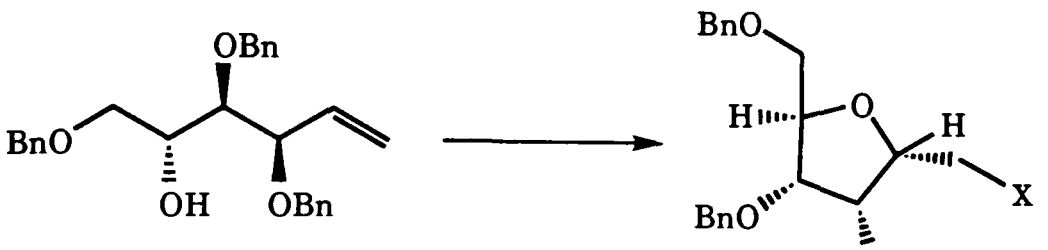
Scheme 21



(**9**)

Another example of note in this field is the work of Reitz[39] in which the glycoside derivative **10** was cyclised. It was shown that NBS in dimethylformamide (DMF) gave a slightly better selectivity for the *trans*-THF than iodine/THF/sodium carbonate (Scheme 22).

Scheme 22

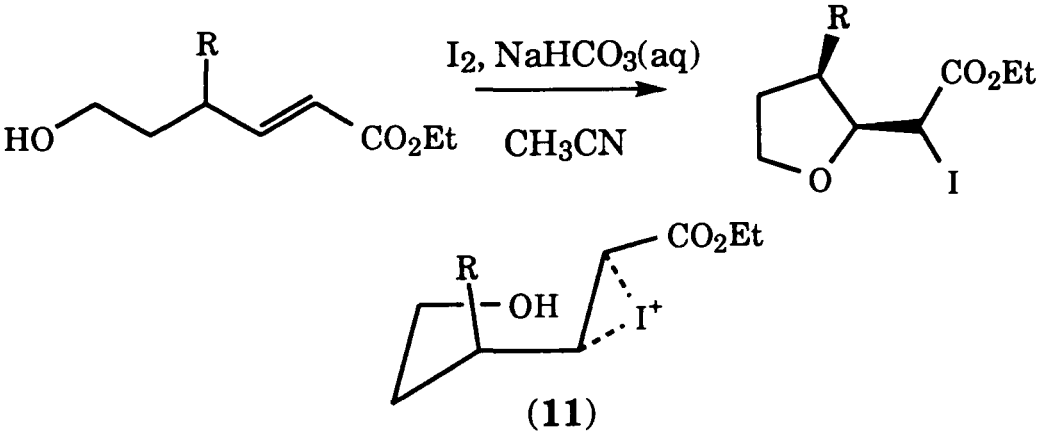


(10)

NBS, DMF (X = Br)	89:11
I_2, $NaHCO_3$(aq) THF (X = I)	82:18

Labelle[40] investigated the mechanism of allylic control in stereoselection and found that the effect varied with the nature of the substituent (Scheme 23). It was shown that the effect was in the order F > OH > Me. The transition state **11** was postulated to be the most favourable and leads to a 2,3-*cis* relationship between the substituents. It should be noted that in all the favoured transition states, the allylic substituent is positioned pseudoaxially.

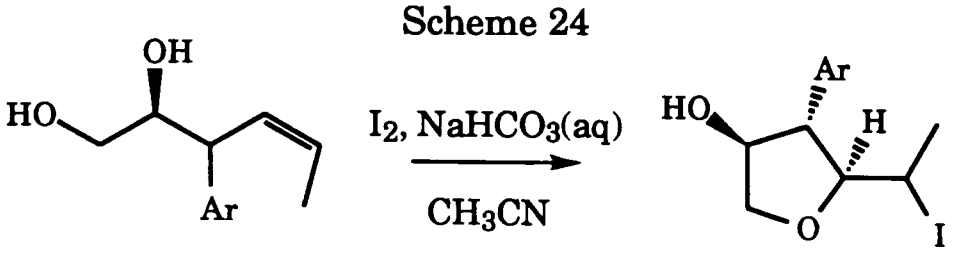
Scheme 23



(11)

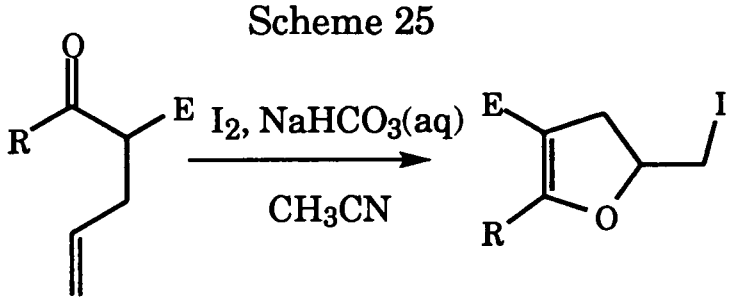
Where it is possible for both 5-*exo* and 5-*endo* iodo-etherification to occur, the faster 5-*exo* process occurs exclusively (Scheme 24).[41]

Scheme 24



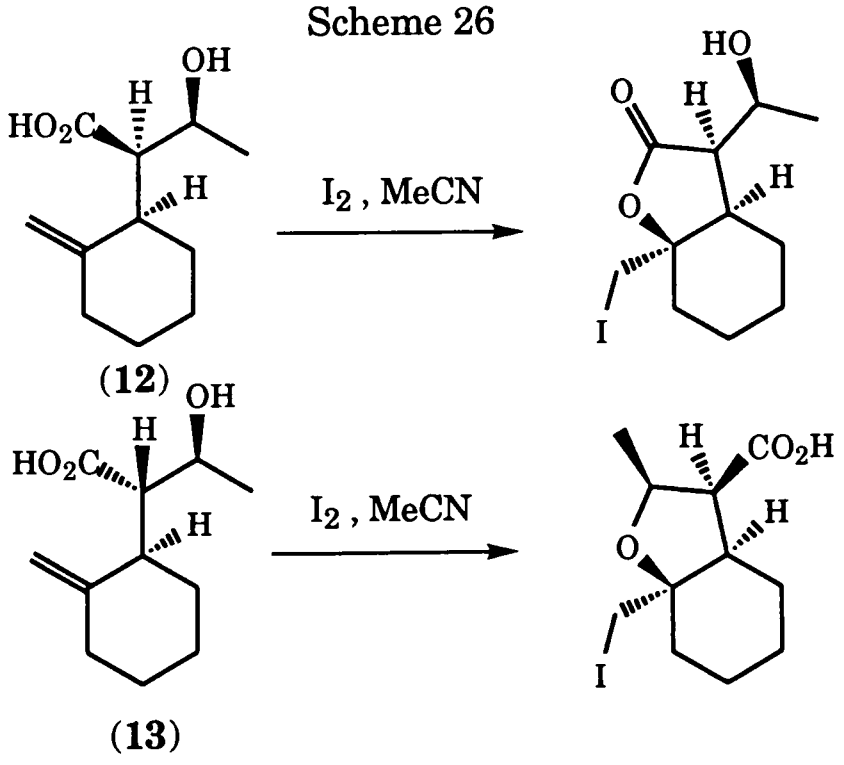
5-*exo*-Trig iodoetherification has also been used by several groups to synthesise 2,3-dihydrofurans (Scheme 25).[42-44] The electron withdrawing group E is necessary, as these reactions involve the iodocyclisation of the corresponding enol. It is therefore important that a high proportion of the enol form is present in the reaction conditions.

Scheme 25



E = CO_2Me
SO_2Ph
C(O)Me

Scheme 26



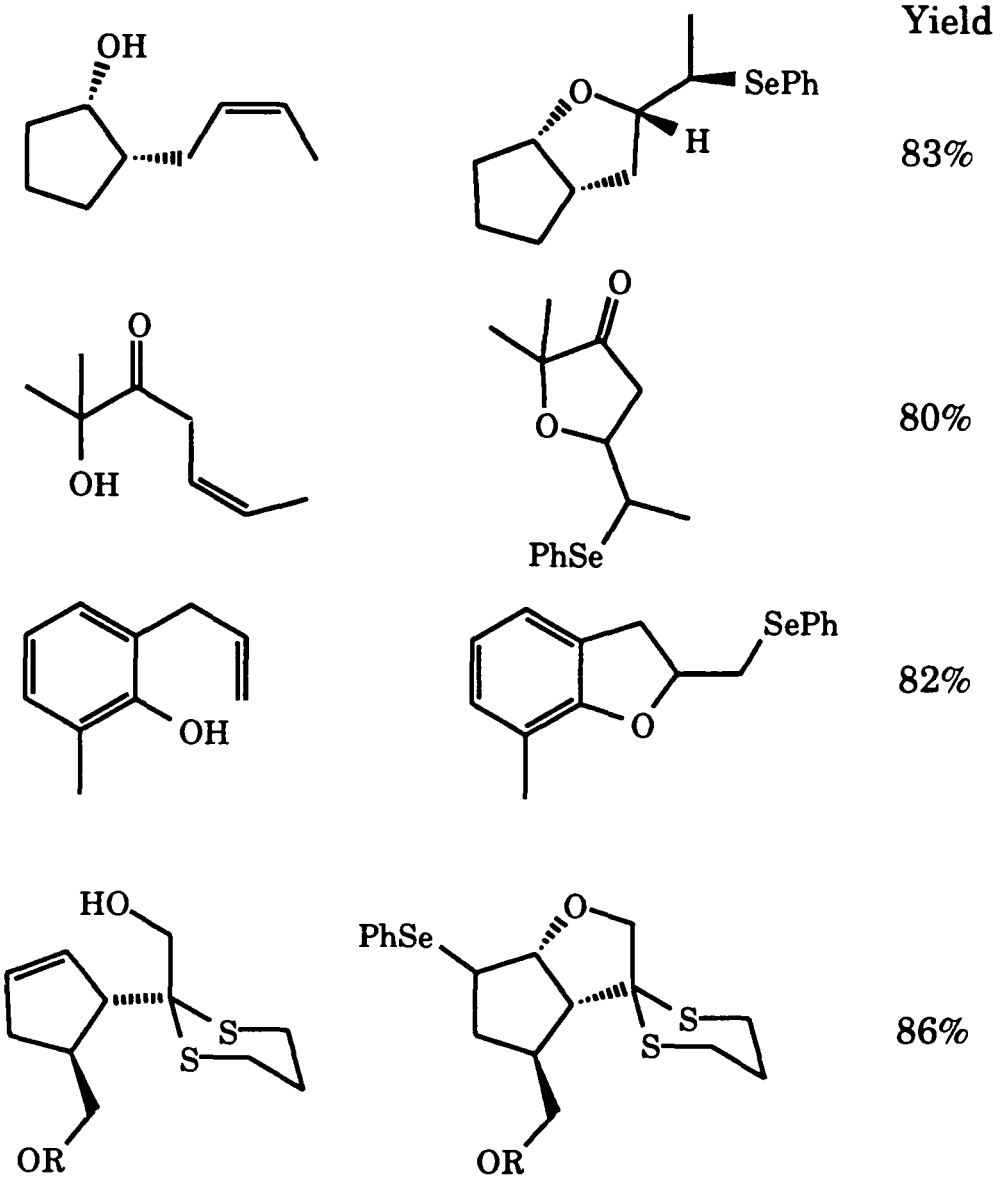
Kurth[45] showed that the difference in energy between halolactonisation and haloetherification is exceptionally small, by cyclising the stereoisomers **12** and **13**; this illustrated that either process can occur exclusively at the expense of the other, on purely stereochemical grounds (Scheme 26).

(ii) Selenoetherification[13]

Selenium mediated electrophilic etherification has been widely used in synthesis, and as mentioned earlier, the incorporation of the PhSe group is a great advantage in synthetic terms. It is, in many ways, complementary to the haloetherification reaction and the controlled elimination away from oxygen provides an excellent route to allylic ethers.

5-*exo*-Selenoetherification was first introduced by Clive[46] in 1977, initially for the cyclisation of phenols and subsequently for more general cyclisations. Phenylselenenyl chloride induces phenylselenoetherification rapidly at -78°C. The methodology is therefore tolerant of a wide range of functionality (Scheme 27). Although in cyclic systems selenoetherification gives good stereocontrol, in the etherification of acyclic substrates, there is little stereoselectivity, although the addition of a mild base such as potassium carbonate can increase this in some cases.[47]

Scheme 27



Yield

83%

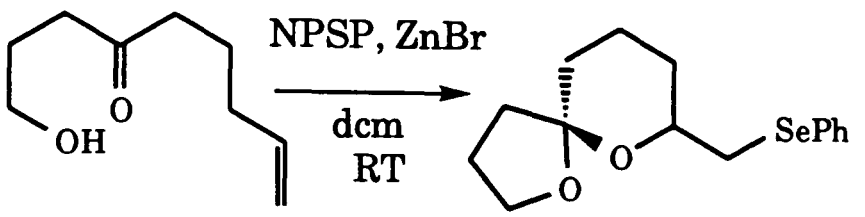
80%

82%

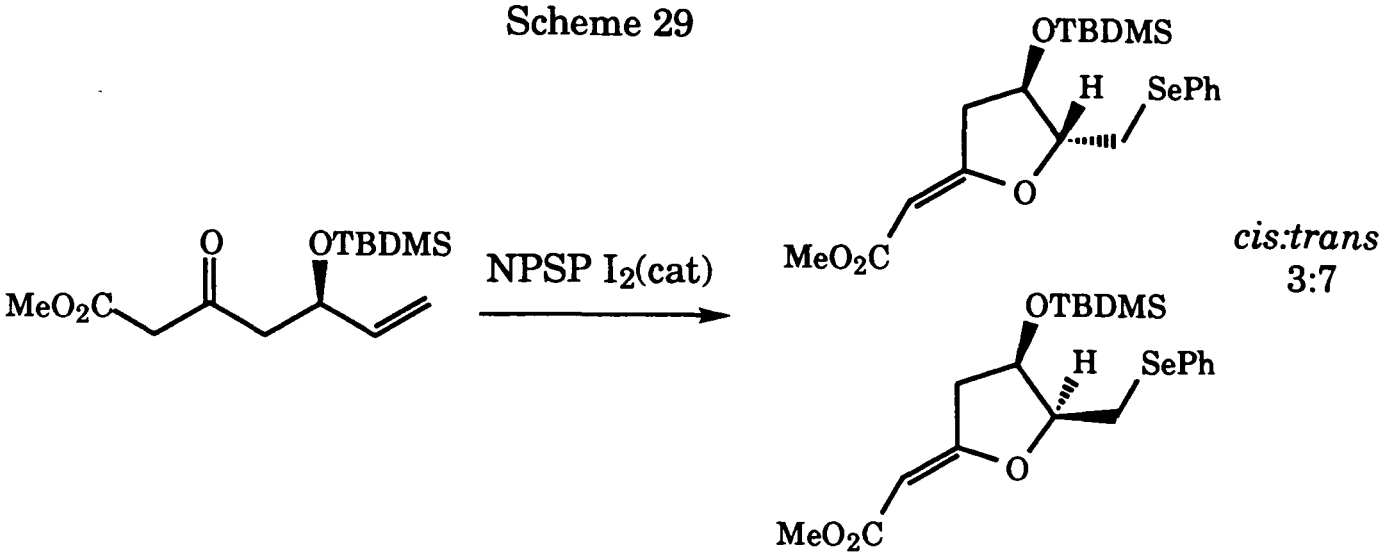
86%

The work of Ley in this area is also worth noting. His group has shown that hydroxy-ketones can be cyclised to give the spiroacetals shown, with moderate stereocontrol, using NPSP as the selenium ion source (Scheme 28).[48] More recently, Ley[49] has extended this idea to include a THF synthesis in which the enolic hydroxy group of a β-keto ester acts as a nucleophile in selenoetherifications leading to an ylidene THF (Scheme 29). Asymmetric induction from the allylic substituent was observed and a facile reduction furnished the corresponding 2,5-*cis*-THF exclusively.

Scheme 28



Scheme 29

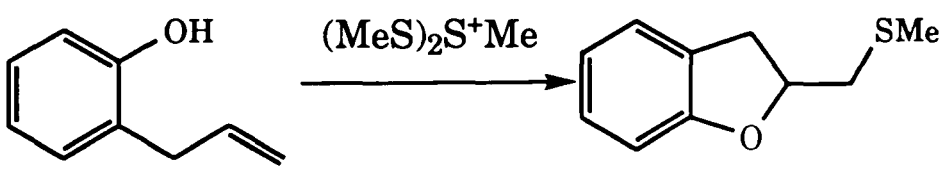


(iii) Sulphenyl Etherification

Sulphur is not as commonly used in electrophilic cyclisations because it is less able to stabilise a positive charge and so the necessary sulphonium ion sources are less easily obtained. There are, however, a large number of sulphur reagents for 5-*exo*-trig electrophilic cyclisation now available.

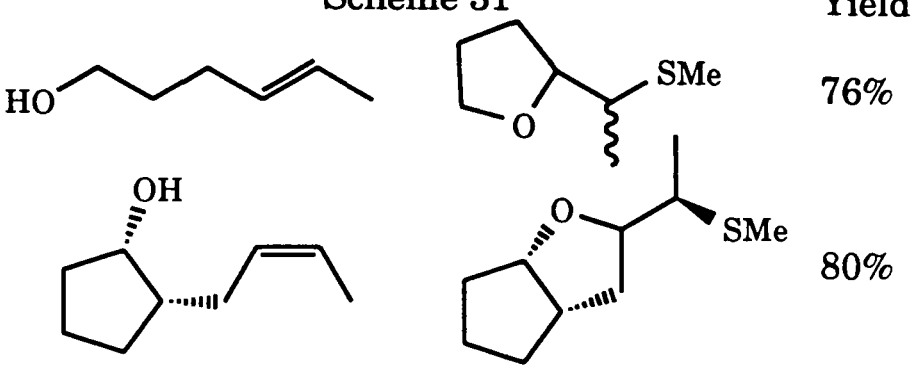
In 1981, Capozzi[50] used methyl *bis*(methylthio)sulphonium (MBMT) salts to cyclise *ortho*-allylic phenols, with some success, in the synthesis of α-thiomethylbenzofurans (Scheme 30).

Scheme 30



Cava[51] used dimethyl(methylthio)sulphonium tetrafluoroborate and base in acetonitrile to effect 5-*exo*-trig cyclisations of various γ,δ-unsaturated alcohols. Although the stereochemistry of the products from acyclic substrates was not addressed, the stereocontrol in cyclic systems was good (Scheme 31).

Scheme 31



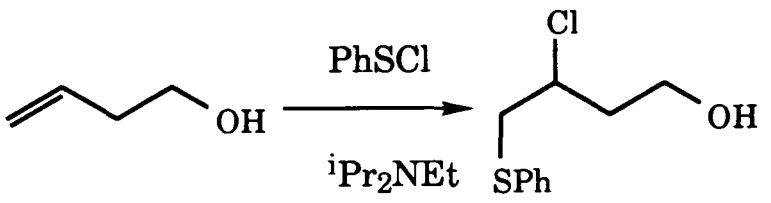
Yield

76%

80%

Brownbridge[52] used N-(phenylthio)morpholine as a source of phenylsulphonium ions and carried out various 5-, 6- and 7-*exo* cyclisations. This reagent was also used to repeat the work of Capozzi in significantly improved yields. Again there was no attempt to effect stereocontrol or define stereochemistry.

Scheme 32



Fallis[53] used phenylsulphenyl chloride and base to perform a number of sulphenyletherifications. It is interesting to note that when a homoallylic alcohol was subjected to the cyclisation conditions, an overall addition of phenylsulphenyl chloride was observed (Scheme 32). This illustrates the favourability of the 5-*exo* process over the 5-

endo process because the attack of chloride occurs preferentially to cyclisation.

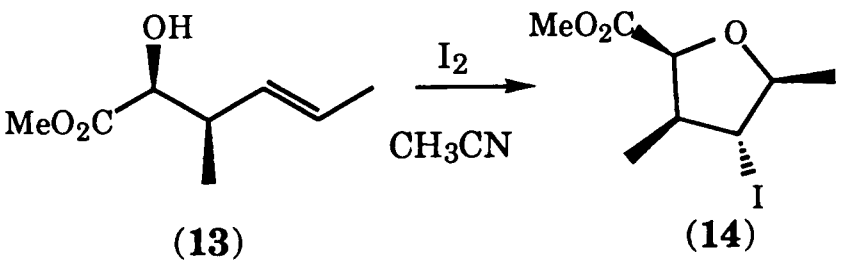
Recently, Capozzi[54] demonstrated that the cyclisation of acyclic γ,δ-unsaturated alcohols using MBMT salts proceeds with very little stereoselectivity, illustrating how much more development is needed before this process becomes viable in stereoselective synthesis.

(C) "5-*endo*-trig" Electrophilic Cycloetherification

The electrophilic cyclisation of homoallylic alcohols is a potentially attractive route to 2,3,5-trisubstituted THFs and higher homologues of defined stereochemistry, as a single stereocentre can be used to generate two more, and is therefore of potentially significant synthetic importance. In recent years, there have been a number of examples using a range of electrophiles. This section will deal with the various types of reaction known so far, and their scope. It will also tackle the stereochemical aspects of the cyclisation.

(i) Halocyclisation

Scheme 33



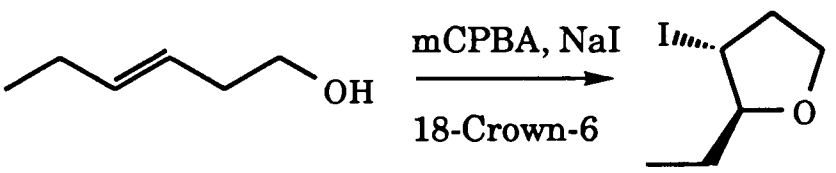
(13) **(14)**

In 1978, Bartlett[20] made what was then an isolated

observation, that the α-hydroxy ester **13** cyclised in a 5-*endo*-trig fashion to give the iodo-THF **14** as the only product (Scheme 33). The stereochemistry of the product was not proven, but since only one product was isolated, it was assumed to be the most thermodynamically stable isomer. The iodocyclisation of the corresponding methyl ether gives 33% of the iodo-THF **14**.

In 1984, Mechoulam[55] introduced a novel source of presumably iodine(I) for electrophilic cyclisation, by reacting sodium iodide with *m*-chloroperbenzoic acid, although most of the regiochemical outcomes were similar to those in established iodoetherification reactions. (E)-3-Hexen-1-ol however was also succesfully cyclised, effectively *via* a 5-*endo*-trig process (Scheme 34).

Scheme 34

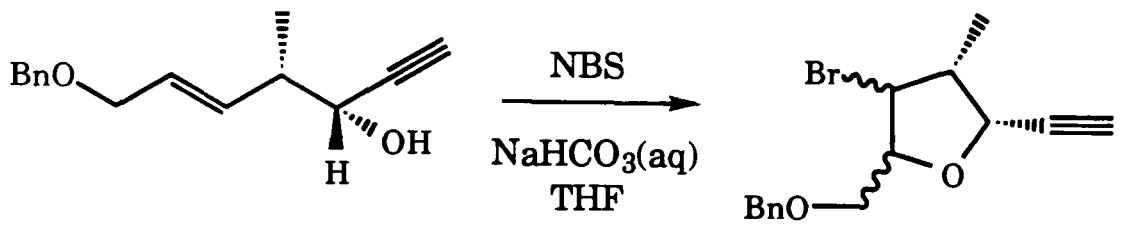


Schauble[36] also observed the same reaction when he treated (E)-3-hexen-1-ol with bis(*sym*-collidine)iodine(I) perchlorate, another source of anhydrous iodonium ions. He noted, however, that other homoallylic alcohols cyclised *via* the "4-*exo*-trig" pathway under these conditions to give iodomethyl-oxetanes.

Takano[56] used a 5-*endo*-trig bromoetherification in his synthesis of intermediates from Mycinamycin (Scheme 35). This example is unique as it occurs in the presence of water where one might expect the intermediate bromonium ion to be opened

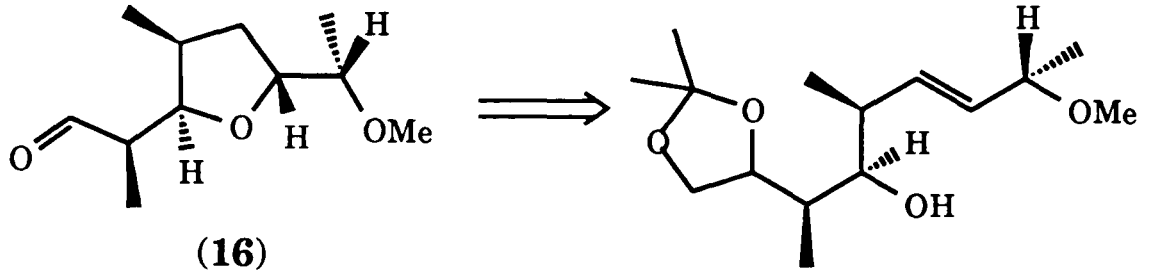
intermolecularly by water. The authors make no comment as to the unusual nature of this cyclisation.

Scheme 35



In 1992, Lipshutz and Barton[57] were the first to report detailed work on the stereochemical nature of the iodoetherification of homoallylic alcohols. As part of their investigations of an approach to the THF portion of Tetronasin **16**, it was envisaged that such a cyclisation could be useful (Scheme 36).

Scheme 36

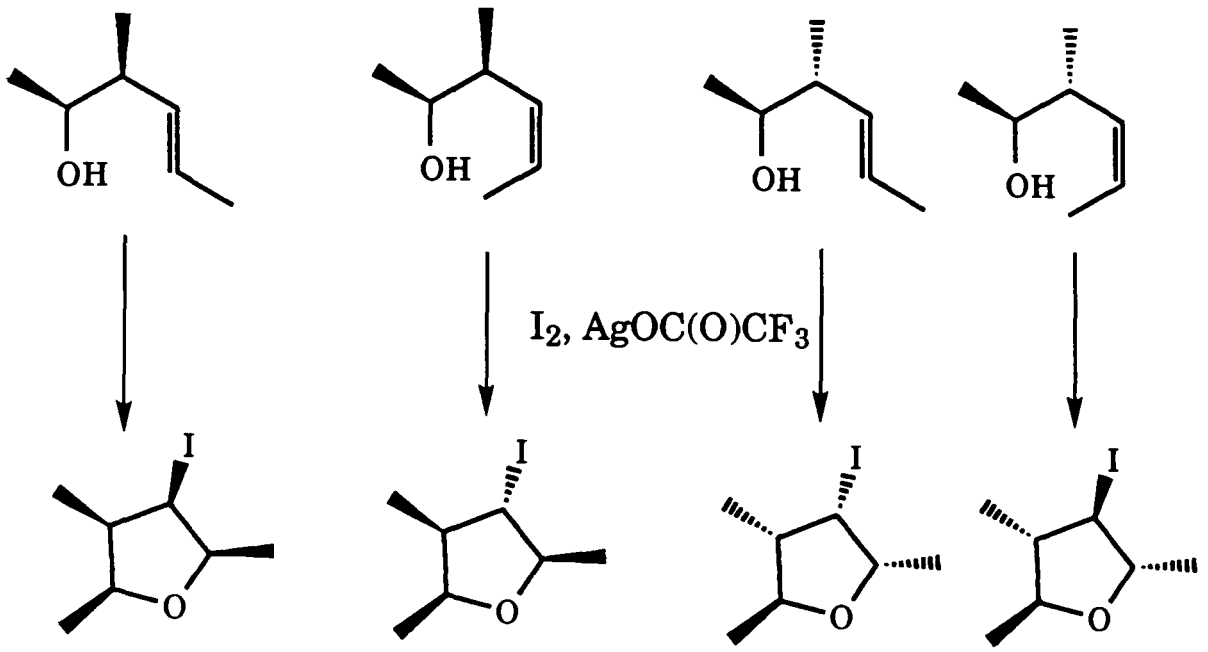


(16)

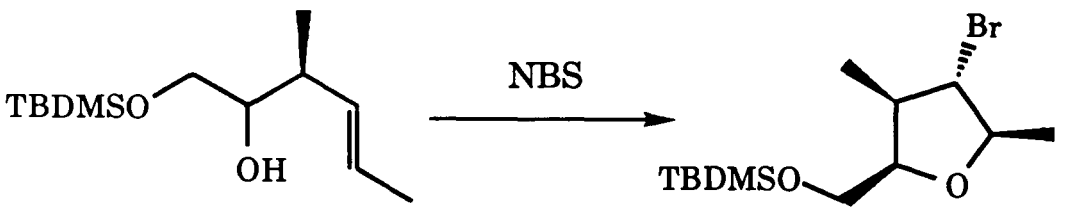
It was found that the stereochemistry of the products varied with the choice of electrophile. The results were also unusual in that there appears to be an overall *syn* addition of the electrophile and the hydroxyl oxygen to the double bond (Scheme 37). This suggests that a complex mechanism may be involved. These results are difficult to explain in terms of a simple transition state and, as yet, the authors have offered no explanation. The results differ from others in the area in terms of the stereochemical outcome.[58] One possible explanation is the presence of the β-methyl substituent. Interestingly, when NBS

was used for these cyclisations, the expected stereochemistry resulting from *anti* addition to the double bond was obtained (Scheme 38).

Scheme 37

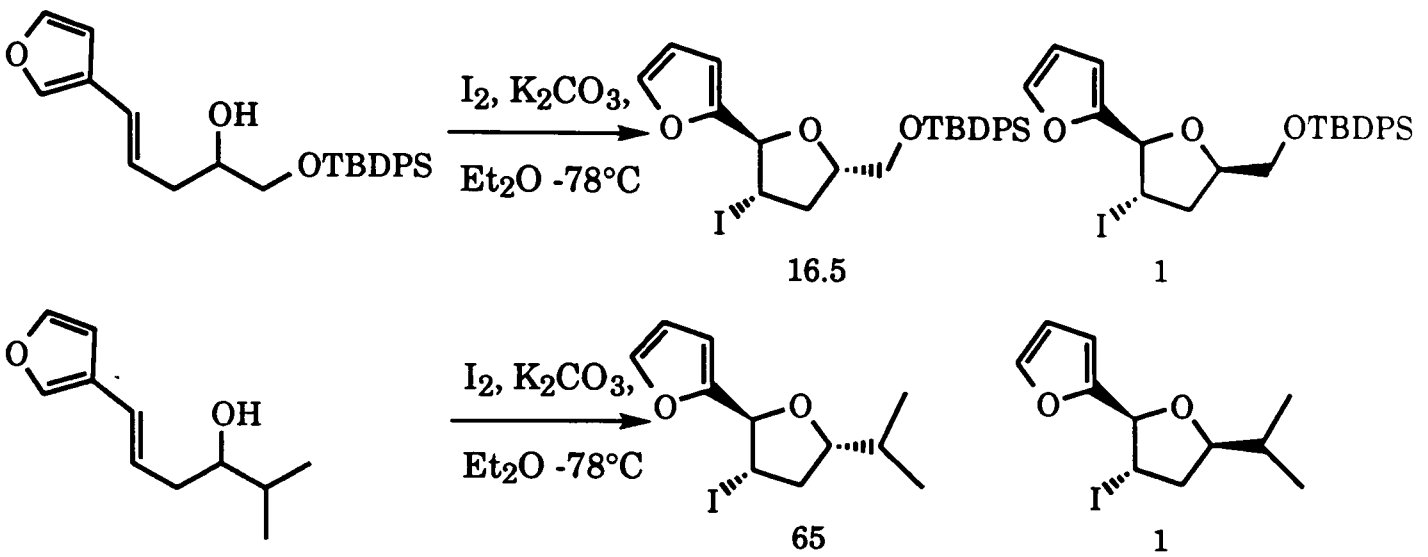


Scheme 38



Recently Kang[59] has also examined the 5-*endo*-trig iodoetherification of homoallylic alcohols. The investigation was, however, restricted to substrates wherein the olefin is in conjugation with an aromatic system (*ie.* where a 5-*endo*-trig cyclisation is favoured by the possibility of an allylic carbocation existing). It was found that treatment of the substrates in the presence of potassium carbonate at -78°C in diethyl ether with iodine led to up to a 65:1 ratio of 2,5-*trans*: 2,5-*cis* THFs under slow addition conditions (Scheme 39).

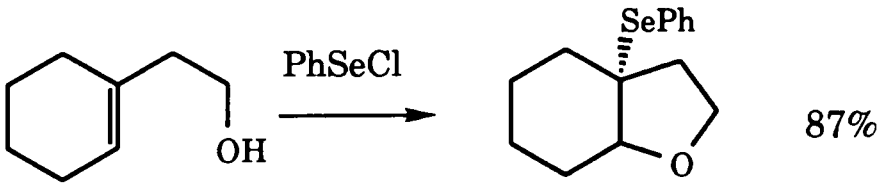
Scheme 39



(ii) Selenoetherification

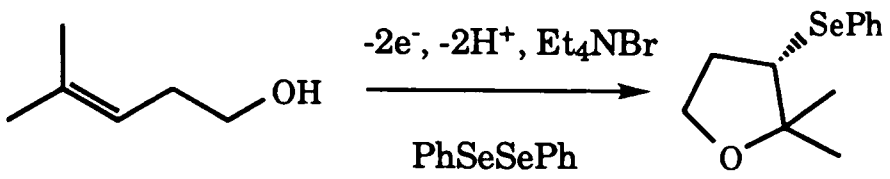
Nicolaou[13] noted some time ago that selenium mediated cyclisations can be used to form five membered rings preferentially over four membered rings and also that the selenoetherification of homoallylic alcohols led to the formation of 2,3,5-substituted THFs by a "5-*endo*-trig" cyclisation (Scheme 40).

Scheme 40

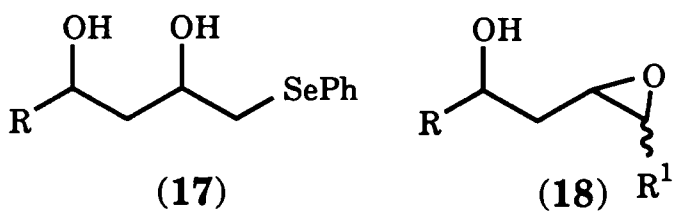


Mihailoviç[60] also noted an isolated example of this reaction in acyclic homoallylic alcohols (Scheme 41) during studies of electrochemical selenoetherification.

Scheme 41

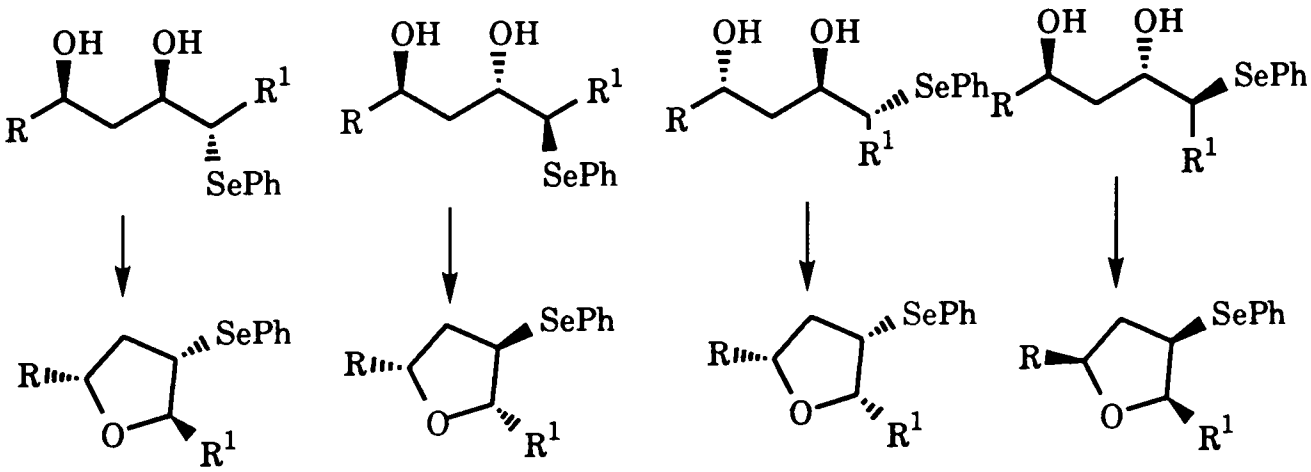


Mihelich[61] showed that 5-*endo*-trig selenoetherification of acyclic substrates was an extremely viable process when he generated the selenodiols **17** by treating the epoxy alcohols **18** with sodium phenyl selenide.



The selenodiols were then induced to form selenonium ions by treatment with acid ($HClO_4$, THF) and these intermediates underwent facile 5-*endo*-trig cyclisation to give THFs (Scheme 42).

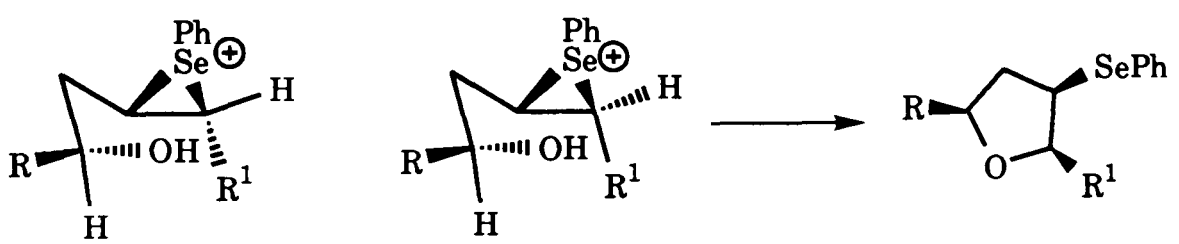
Scheme 42



In the first three cases, the selectivity results from the formation of a single selenonium ion. The final result has been rationalised by suggesting that the intermediate generates an olefin by

elimination and then reforms the alternative selenonium ion intermediate. This suggests that the cyclisation must be highly stereoselective and that the cyclisation of the transition state which eliminates the selenium moiety must be highly disfavoured (Scheme 43).

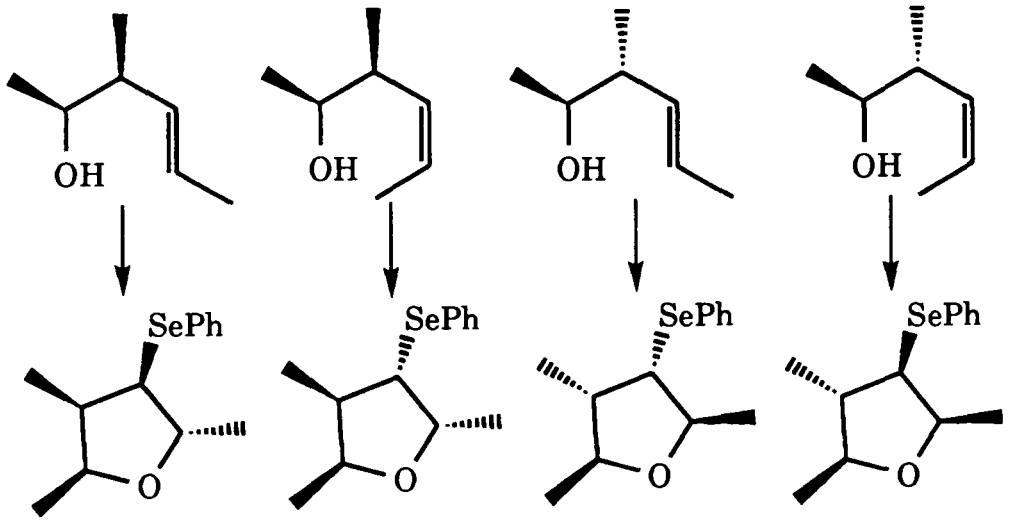
Scheme 43



Hindered transition state

Favoured transition state

Scheme 44

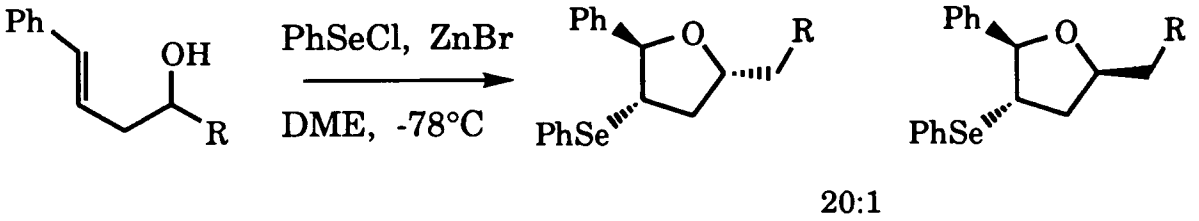


Lipshutz and Barton[57] found that phenylselenenyl chloride can be used to induce stereoselective 5-*endo*-trig cyclisations of homoallylic alcohols (Scheme 44). The stereochemistry obtained from these was different from that obtained by iodocyclisation (*vide supra*). It is interesting to note that when Lipshutz generated the transition state analogous to that found to be disfavoured by Mihelich (with the extra methyl group in the 2-position) smooth cyclisation was observed.

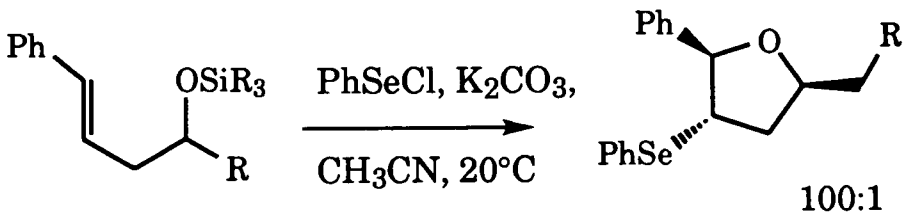
One possible explanation is the fact that Mihelich used acidic conditions for the cyclisations and therefore the rearrangements may have been acid catalysed.

Kang[62] has also investigated 5-*endo*-trig selenoetherification although his studies were limited to cases in which the olefin was in conjugation with an aromatic system. High stereoselection was obtained at -78°C under Lewis acid catalysis (Scheme 45). The cyclisation of the corresponding silyl ethers was also investigated[63] (Scheme 46), and these were found to cyclise at 20°C in the absence of catalysis and in the presence of potassium carbonate to give even better stereoselection.

Scheme 45



Scheme 46

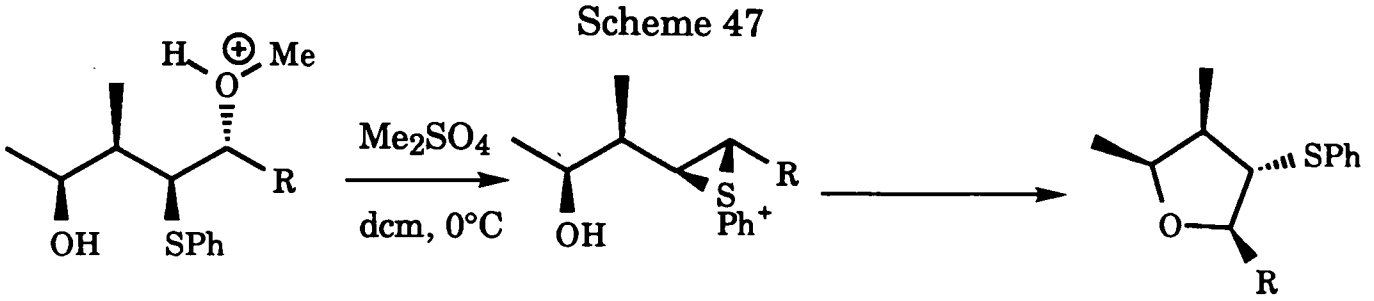


(iii) Sulphenyl etherification

Williams[64] developed a route to 2,3,4,5-tetrasubstituted THFs *via* the sulphur-mediated 5-*endo*-trig cyclisation of 2-methyl-3-thiophenyl-1,4-diols. The process probably involves the formation of an

intermediate episulphonium ion, by the elimination of methanol, upon treatment with dimethyl sulphate in dichloromethane at 0°C (Scheme 47).

Scheme 47



This was carried out on both stabilised (α-phenyl) and unstabilised sulphonium ions without any trace of 4-*exo*-trig products. Good stereochemical purity was maintained throughout and there were no anomalous results similar to those found by Mihelich in the selenium-based work.

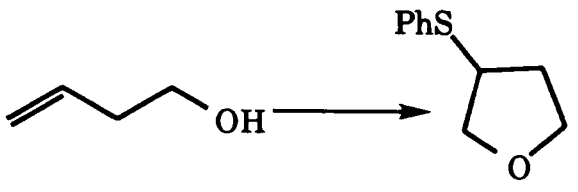
Warren[65] found that this reaction could be extended to tertiary thioethers, as long as the stereochemistry of the molecules was favourable, and thus was able to construct spiro-THFs (Scheme 48).

Scheme 48

Brownbridge[52] observed an example of a 5-*endo*-trig sulphenyletherification using N-(phenylthio)morpholine (Scheme 49);

Fallis[53] did not observe a similar reaction, although the presence of chloride ions in the latter reaction may explain this.

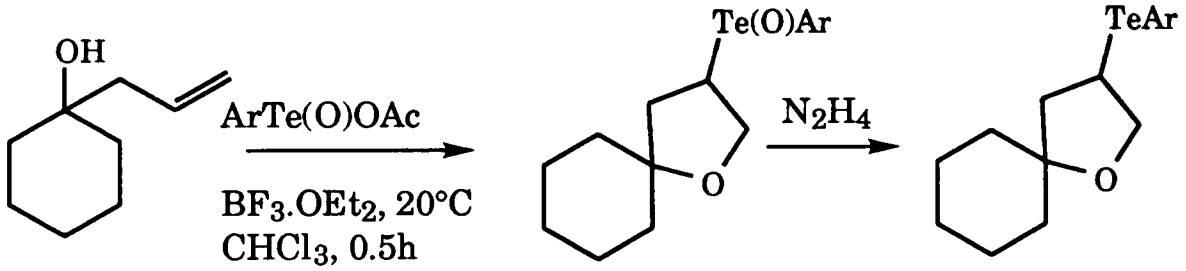
Scheme 49



(iv) Other Electrophiles

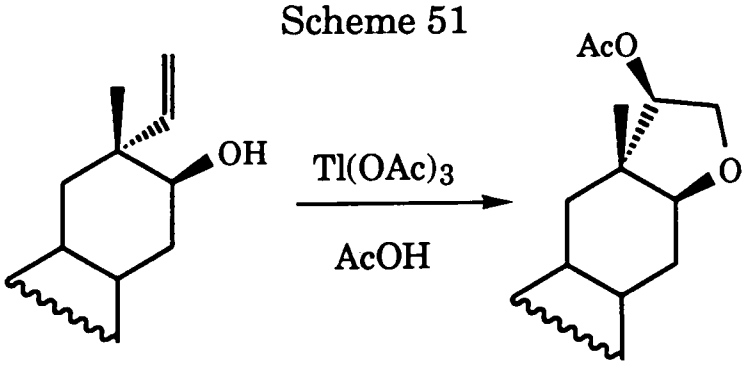
Hu[66] used aryltellurinyl acetates to effect 5-*endo*-trig cyclisations of 3-alkenols (Scheme 50). Interestingly, iodoetherification of this molecule resulted in 4-*exo*-trig cyclisation.[36]

Scheme 50



Thallium triacetate has also been used to mediate 5-*endo*-trig cyclisations of alkenols by Ferraz[67] with good stereochemical purity (Scheme 51).

Scheme 51



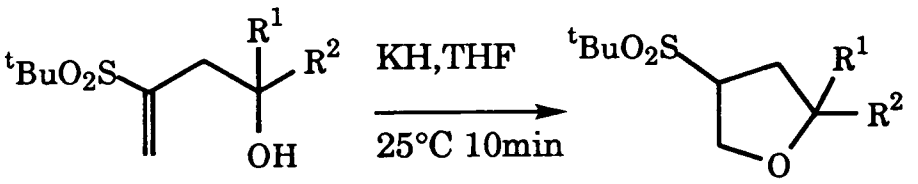
(III) Other Routes to 2,3,5-Trisubstituted Tetrahydrofurans

Although electrophilic etherification is an important route to substituted THFs, there are many other routes available; in this section, some of the major approaches will be briefly outlined. Comprehensive reviews of this topic have been published.[68]

(A) Michael Addition Processes

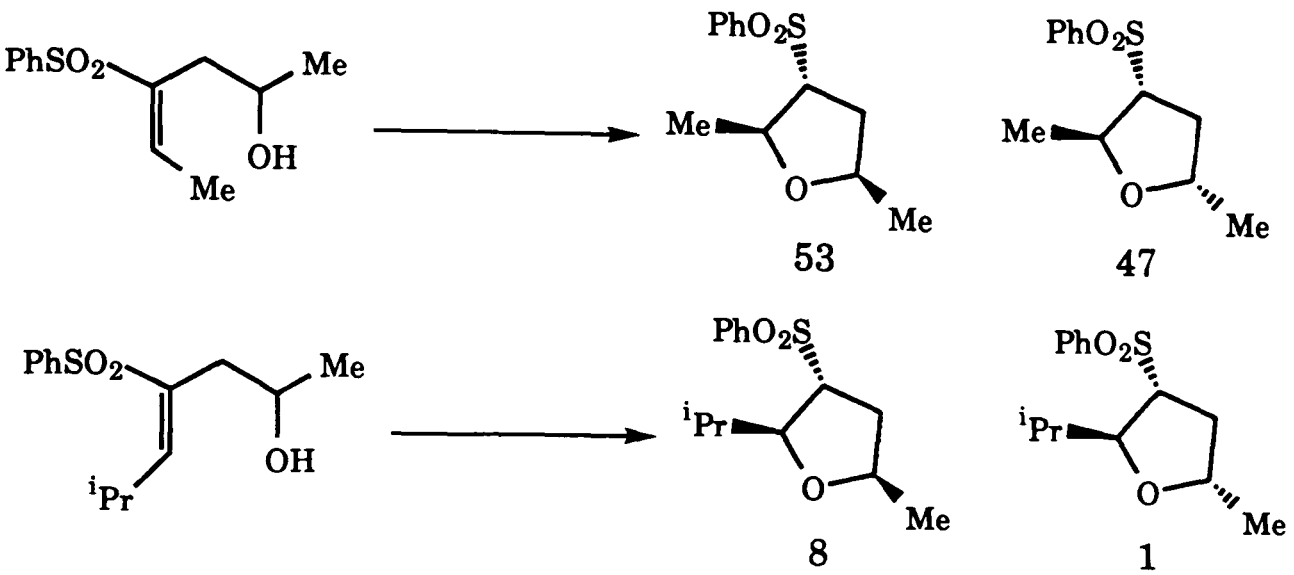
Homoallylic alcohols possessing a sulphone group at the 3-position undergo cyclisation when treated with potassium hydride in THF at RT to afford a 2,2,4-trisubstituted THF, as shown by Normant[69] (Scheme 52).

Scheme 52



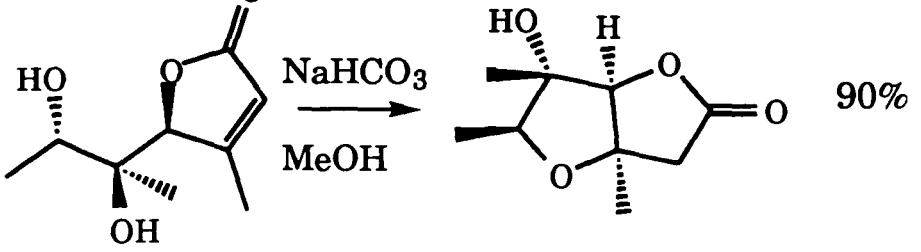
More recently, Craig[70] has prepared 2,3,5-trisubstituted THFs by the same strategy, using potassium ^{t}butoxide in ^{t}butanol; the products have a 2,3-*anti* configuration. The cyclisation leads to a moderate selectivity for 2,5-*trans*-THFs over 2,5-*cis*-THFs. The selectivity is much greater in the case of the (E)-isomers than in the case of the (Z)-isomers (Scheme 53).

Scheme 53



Cha[71] used a similar idea in the approach to Verrucosidin (Scheme 54).

Scheme 54

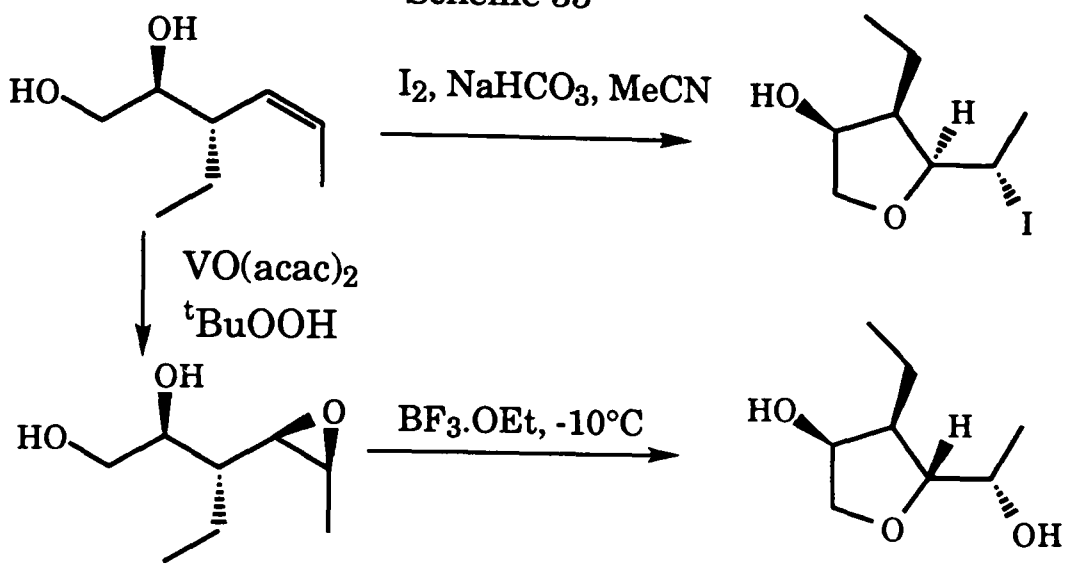


(B) Epoxide Opening Methods

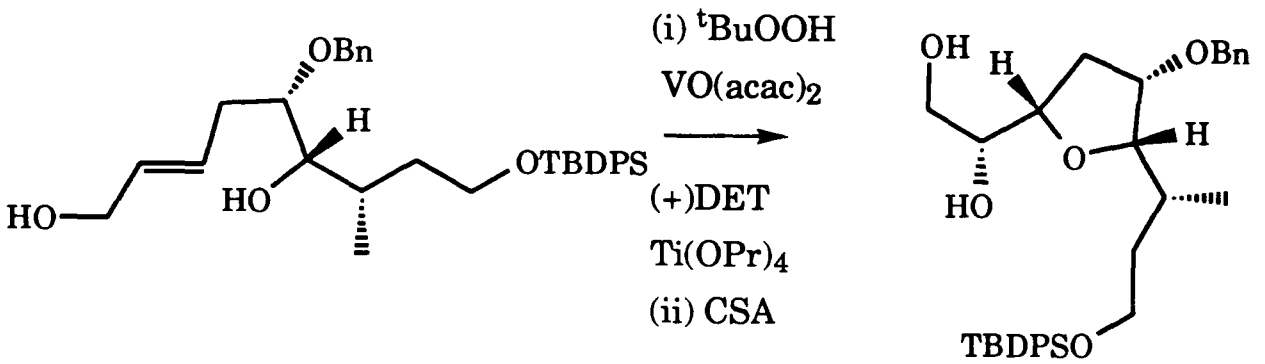
This route involves the acid catalysed 5-*exo*-tet opening of a γ,δ-epoxide by an alcohol and it has increased in popularity due to the obvious compatability with Sharpless[72] epoxidation methodology. This approach is, in many ways, complementary to the use of electrophiles such as halogens because the stepwise cyclisation will lead to a different stereochemistry (Scheme 55). Kishi[73] used this approach as

part of his work towards the Halichondrins (Scheme 56).

Scheme 55



Scheme 56



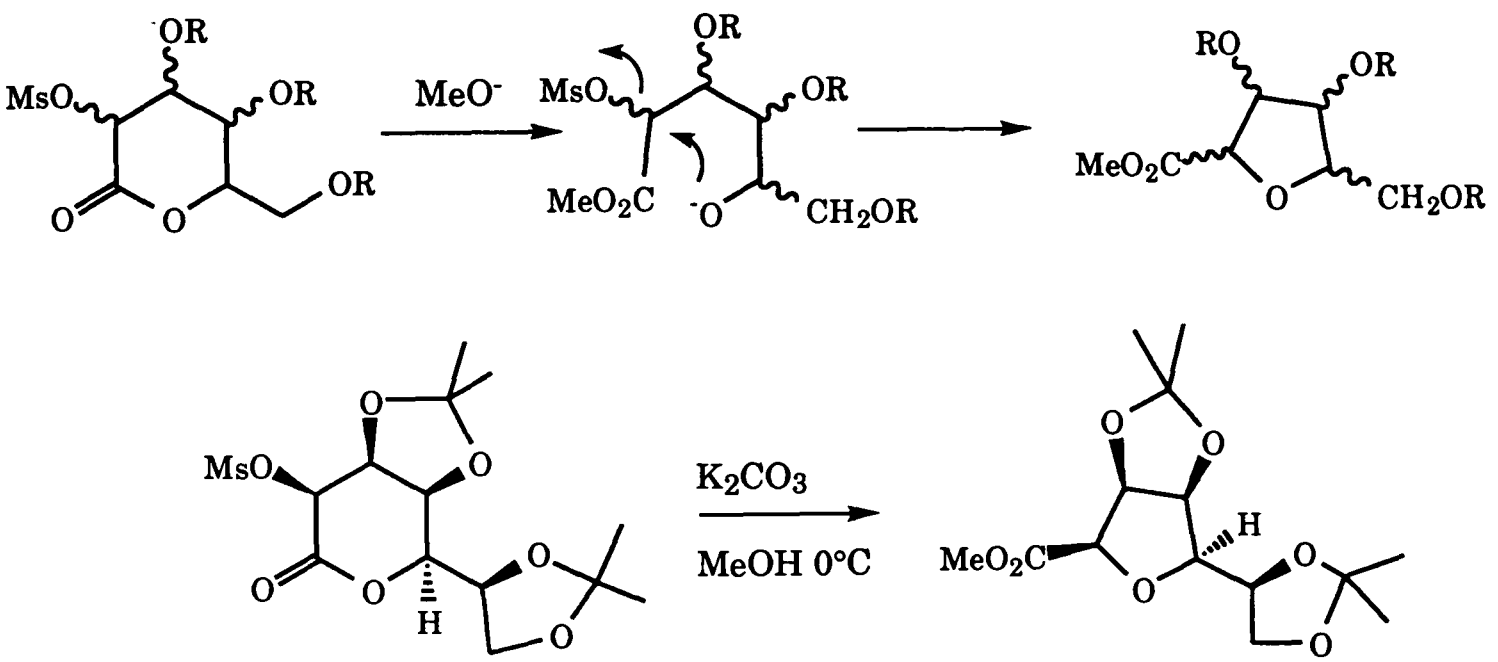
(C) Condensation of Diols

Scheme 57

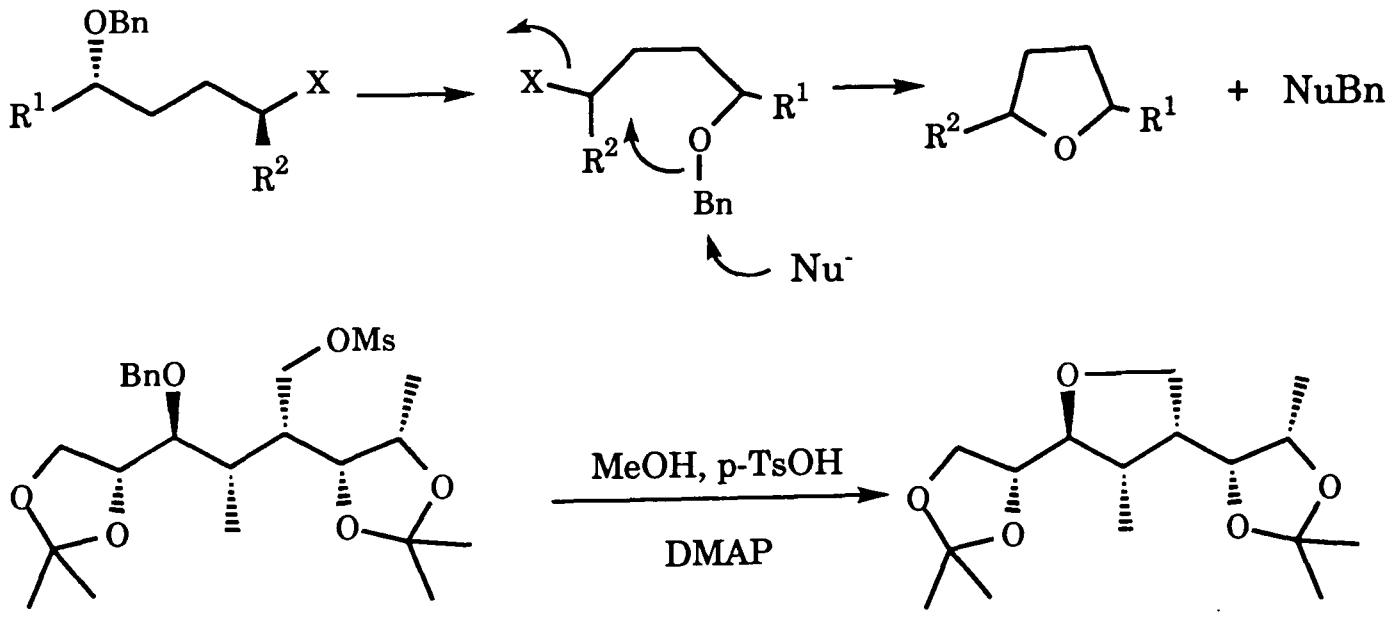
Condensation of 1,4-diols under acidic conditions has been used extensively in the synthesis of substituted THFs (Scheme 57). Fleet[74] has used the ring contraction of δ-lactones with leaving groups as α-substituents (*ie* 1,4-diols) extensively in carbohydrate chemistry, to generate highly substituted THFs (Scheme 58). Mulzer[75] used a

similar approach when he cyclised benzyl ethers with γ-leaving groups to give 2,5-substituted THFs of defined stereochemistry (Scheme 59).

Scheme 58



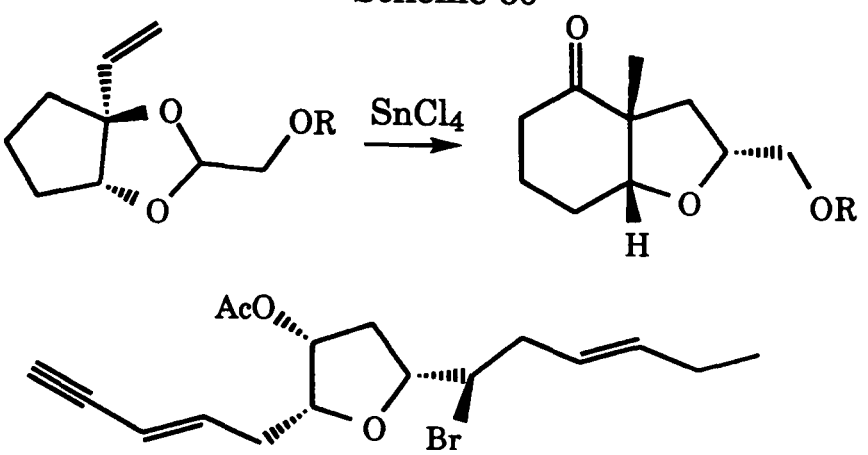
Scheme 59



(D) Lewis Acid Catalysed Rearrangement

Overman[76] has developed a concise route to 2,3,5-substituted THFs by the rearrangement of *trans*-vinylic-1,2-diol acetals (Scheme 60). He has used this approach in the synthesis of the Kumausallenes (*eg trans*-Kumausallene).

Scheme 60

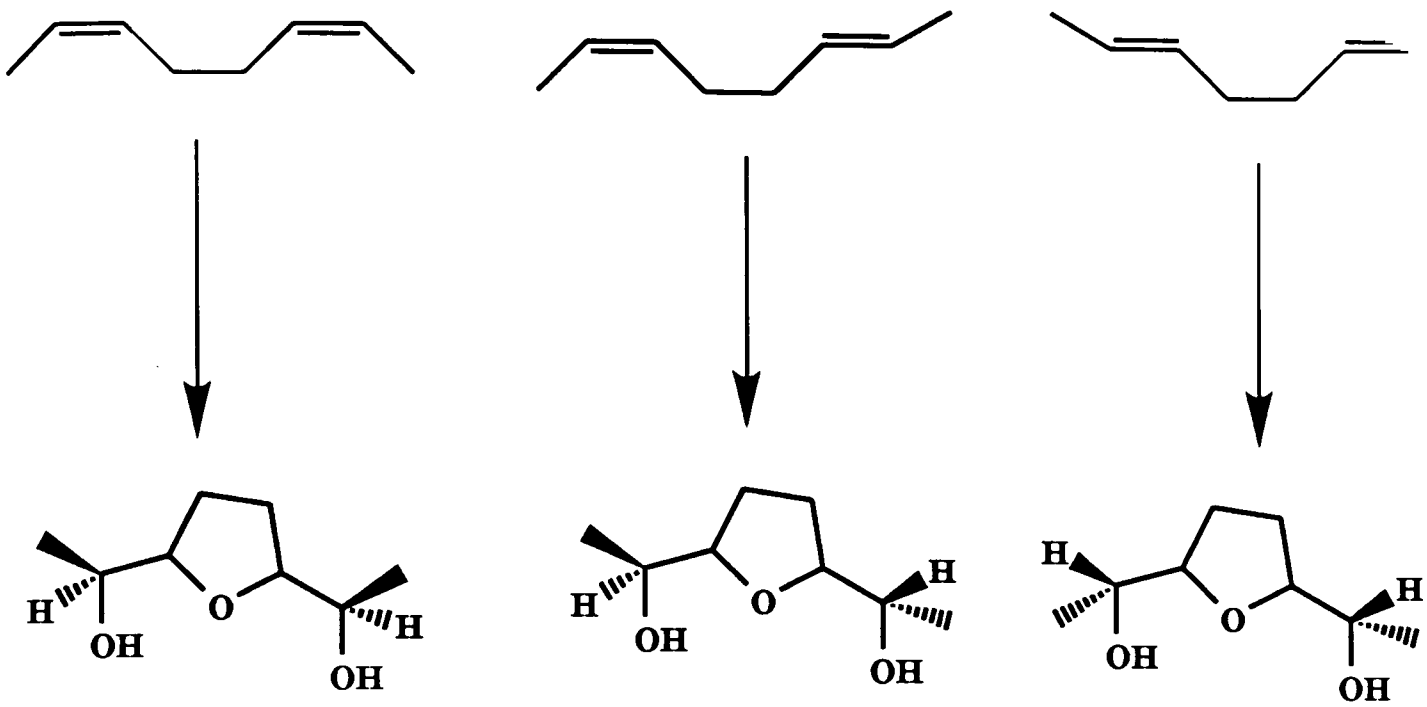


trans -Kumausallene

(E) Oxidative Cyclisation of 1,5 Dienes[77]

Potassium permanganate can be used under mildly alkaline conditions to generate 2,5-*cis*-disubstituted THFs in which the stereochemistry at the positions α to the THF ring is defined by the geometry of the starting diene (Scheme 61). These highly oxidative conditions can be a little too harsh to use in the course of synthesising complex multi-functional molecules, but they do give THFs of predictable stereochemistry. This was among the first routes to allow such stereocontrol.

Scheme 61



CHAPTER TWO

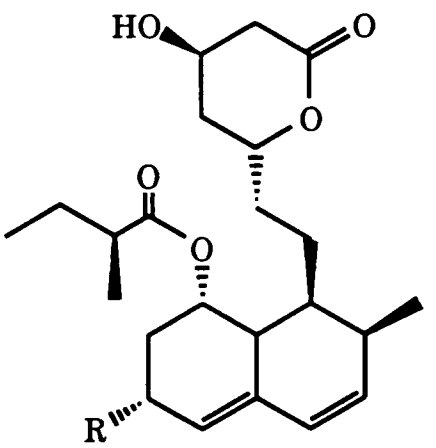
New Stereoselective Routes to Tetrahydrofurans

New Stereoselective Routes to Tetrahydrofurans

(I) Valerolactone Chemistry

Work concerning electrophilic cyclisations began within our group as a part of the approach to analogues of the mevinic acids, Compactin **19** and Mevinolin **20** (Scheme 62), which are among the worlds best selling pharmaceuticals in their role as inhibitors of cholesterol biosynthesis in man.

Scheme 62

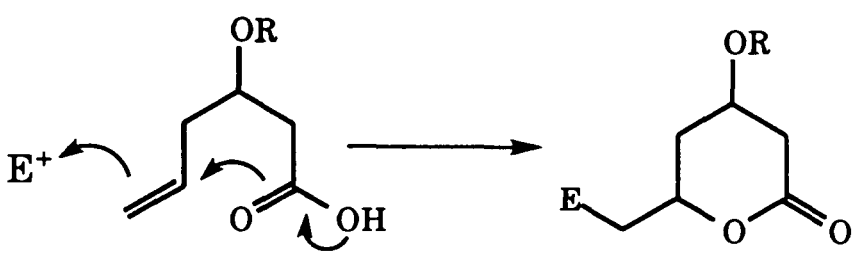


(+)-Compactin R=H (**19**)
(+)-Mevinolin R=Me (**20**)

The active δ-lactone portion in its open chain form acts as a mimic of mevalonic acid, a crucial intermediate in the terpenoid biosynthetic pathway leading to cholesterol. The mevinic acids act as

potent inhibitors of the pathway by blocking a major rate limiting step, the conversion of HMGCoA [3-hydroxy-3-methylglutaric acid co-enzyme A] into mevalonic acid. The mevinic acids block the action of HMGCoA reductase presumably by occuping the active site of the enzyme. One possible synthetic approach to the mevinic acids which has been studied at Nottingham is the electrophilic lactonisation of a β-hydroxy- or silyloxy-δ-alkenoic acid (Scheme 63).

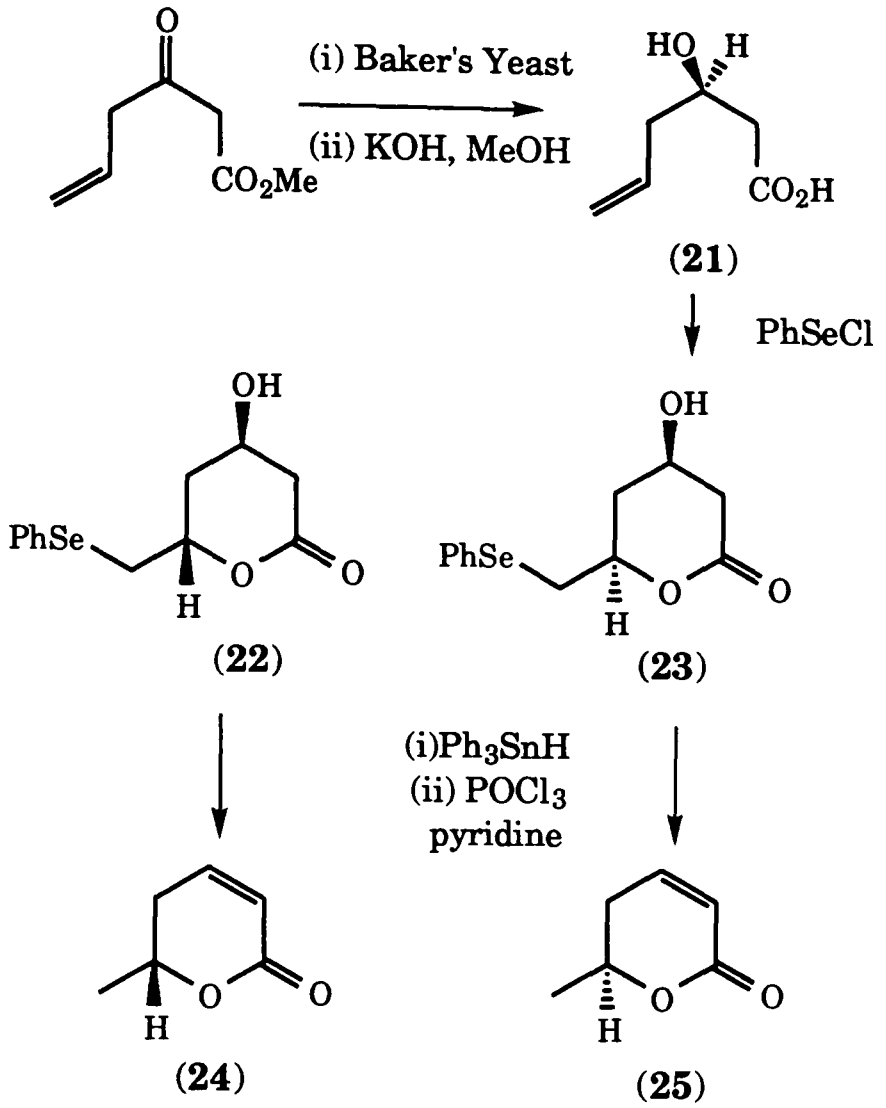
Scheme 63



This led to the requirement of a chiral route to such molecules. Bennett[78] used baker's yeast reduction of the corresponding β-keto esters as a route to the hydroxy-acids **21**. Bennett[78] then used selenolactonisation of the hydroxy-acid **21** to prove the absolute stereochemistry produced by the enzymes in baker's yeast (Scheme 64).

The non-stereoselective selenolactonisation gave the lactones **22** and **23**. The selenium group was reductively removed to give a mixture of hydroxy-lactones which were then chromatographically separated and individually converted into the R- and S-enantiomers of natural parasorbic acid **24** and **25**. From the optical purity of these isomers the optical purity and the absolute stereochemistry of the yeast reduction product was deduced.

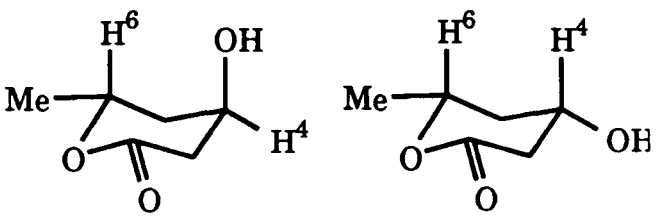
Scheme 64



Detailed analysis of the coupling constants in the lactones after the removal of the selenium function showed that the less polar isomer derived from **22** exhibited resonances at δ_H 4.38 (br quin, J = 3.7) and at 4.87 (ddq, J = 11.3, 6.4 and 3.1). Assigning these resonances by COSY experiments as the 4-H and 6-H respectively and assuming that the methyl group is likely to adopt the equatorial position, led to the conclusion that this was the *trans* isomer which exists in conformation **26** (Scheme 65). The more polar isomer derived from **23** exhibited the corresponding

resonances at δ_H 4.25 (dddd, J = 9.1, 7.6, 5.8 and 5.6, 4-H) and 4.37 (dqd, J = 11.7, 6.2 and 3.0, 6-H). These data are consistent with the corresponding *cis* isomer which adopts conformation **27** in which both 4- and 6-protons are in axial positions.

Scheme 65

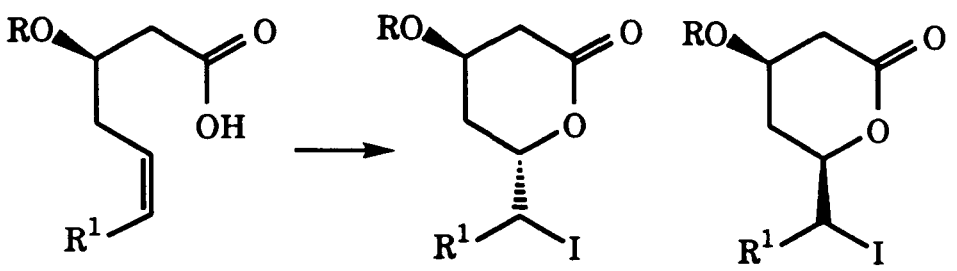


(26) **(27)**

As the absolute stereochemistry and optical purity of the 4-centre in the lactones is transfered to the 6-centre, the stereochemistry of the yeast product can be deduced. The *trans* lactone gave unnatural (R)-parasorbic acid **24**. This implies that the yeast product must have had the S-configuration as shown above. From measurements of optical rotation an optical purity of lactones **24** and **25** 78% was deduced for the initial product **21**.

By contrast the corresponding silyl ethers of the hydroxy-acid **21** could be iodolactonised, with good stereoselectivities, to give predominantly *trans*-iodolactones. The stereoselectivity increased with increasing bulk of the silicon protecting group; indeed, a selectivity of 5.5:1 was achieved using the triisopropylsilyl group. In the case of the homologous acids with a *cis* stereochemistry at the double bond, even higher selectivities of up to 10.5:1 were observed (Scheme 66).[79]

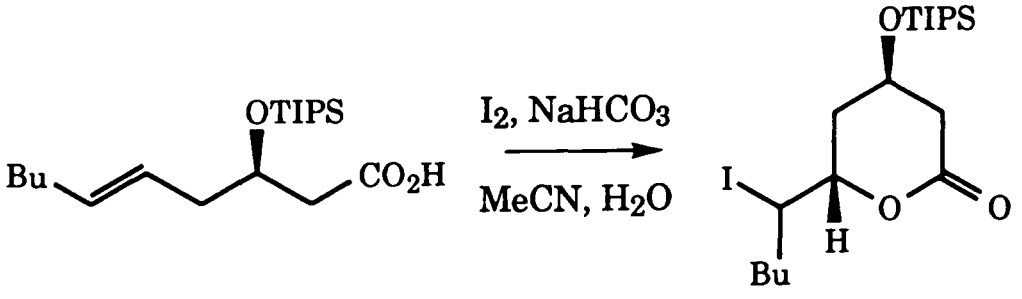
Scheme 66



R	R^1	*trans*	*cis*	Yield (%)
H	H	2.4	1	23
TBDMS	H	3	1	84
TBDPS	H	4	1	87
TIPS	H	5.5	1	81
TIPS	Bu	10.5	1	93

The selectivity of 10.5:1 observed in the cyclisation of (Z)-3-triisopropylsilyloxy-dec-5-enoic acid was seen to improve even further in the cyclisation of the corresponding (E)-isomer **28** in an isolated observation by a previous researcher.[80] Cyclisation gave a single isomer of the valerolactone **29** which differed from the major product of the cyclisation of the corresponding (Z)-isomer only in the configuration at the iodine centre. However, when this reaction was repeated as part of this present project, selectivities of around 8:1 were observed (*vide infra*) (Scheme 67)

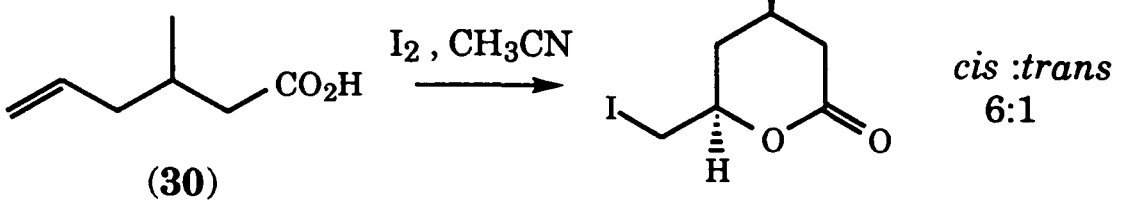
Scheme 67



(**28**) (**29**)

Elaboration of these *trans* iodo-lactones provides an efficient route to mevinic acid analogues. The *trans* selectivity, although important in the synthesis of such compounds, was not the expected result from these iodolactonisations.

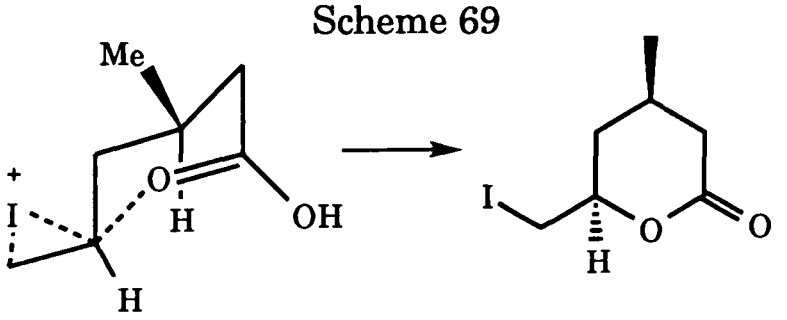
Scheme 68



(30)

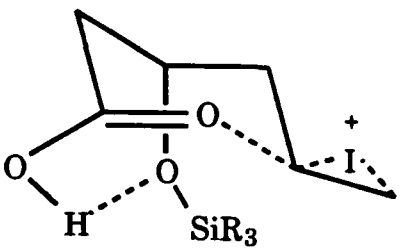
The stereoselectivity obtained is higher than that found by Bartlett[21] in the iodocyclisation of acid **30** (Scheme 68) and, more remarkably, it gives predominantly the *trans*- and not the *cis*-iodolactone (*ie.* it is overriding the "normal" selectivity). The selectivity which Bartlett observed is consistent with the adoption of a 'chair-like' transition state in which the methyl group will be predominantly in an 'equatorial' position (Scheme 69).

Scheme 69



This implies that the stereoselectivity in the cyclisation of β-hydroxy-δ-alkenoic acids is the result of iodolactonisation *via* a transition state **31** in which the silyloxy function is predominantly in the axial

position.



(31)

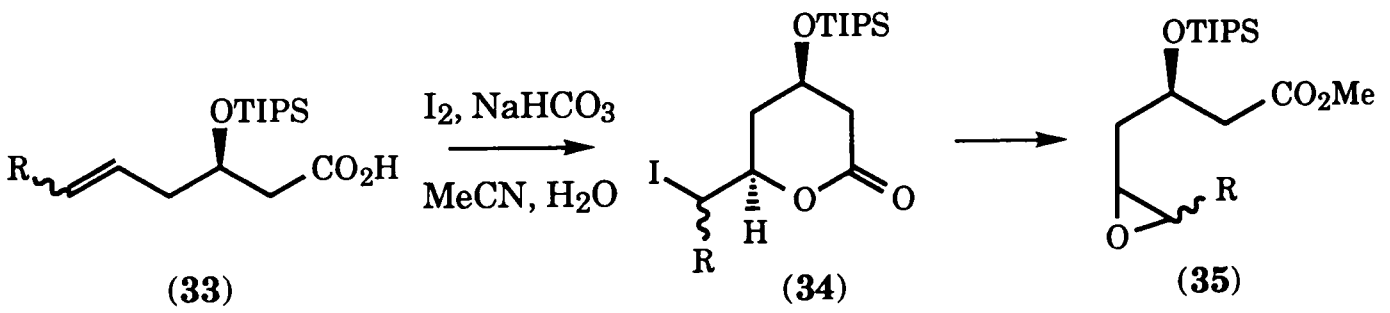
The suggested reason[79] for the predominance of transition state **31** is hydrogen bonding between the acid group and the oxygen of the silyloxy function. This provides stabilisation for the transition state **31** to such an extent that it becomes favourable to have the silicon group in the axial position.

This explanation is deficient in that it does not explain the increasing selectivity associated with the increasing bulk of the silicon protecting group, unless increasing electron density at silicon causes an increase in electron donation to the oxygen atom enabling it to hydrogen bond more efficiently. There are also only a few examples of the involvement of silyl ethers in hydrogen bonding of this sort.[81] There have, however, been no alternative explanations proposed so far.

This project began with these results in hand. In order to enhance the utility of the iodolactones, it was necessary to determine the stereochemistry of the iodine centre in these lactones. Previous workers had generally removed the iodine reductively as a first step after iodocyclisation. However, it was envisaged that the iodine could be used to enable the introduction of additional functional groups with known stereochemistry into the side chain, as well as provide other synthetic opportunities.

The approach used in this project to determine the stereochemistry at the iodine centre was the synthesis of the (Z)- and (E)-β-hydroxy-δ-alkenoic acids **32** and **28** in such a way that pure geometrical isomers were obtained. The geometrical purity was required to ensure that the stereoselectivity with which the iodine centre was formed was a true reflection of the stereoselectivity of the reaction. These acids were investigated separately as it was anticipated that the geometry of the olefin would be important. It was envisaged that the stereochemistry at the iodine centre could be determined as follows: iodolactonisation[78] of the acids **33** and treatment of the resulting lactones **34** with sodium carbonate in methanol was expected to give just, the epoxy methyl esters **35**;[20] by methanolysis of the lactone ring; base induced cyclisation of the resulting iodohydrin completes the sequence. It was anticipated that the stereochemistry of these epoxides could then be determined by NMR studies allowing the original stereochemistry at iodine to be deduced (Scheme 70).

Scheme 70

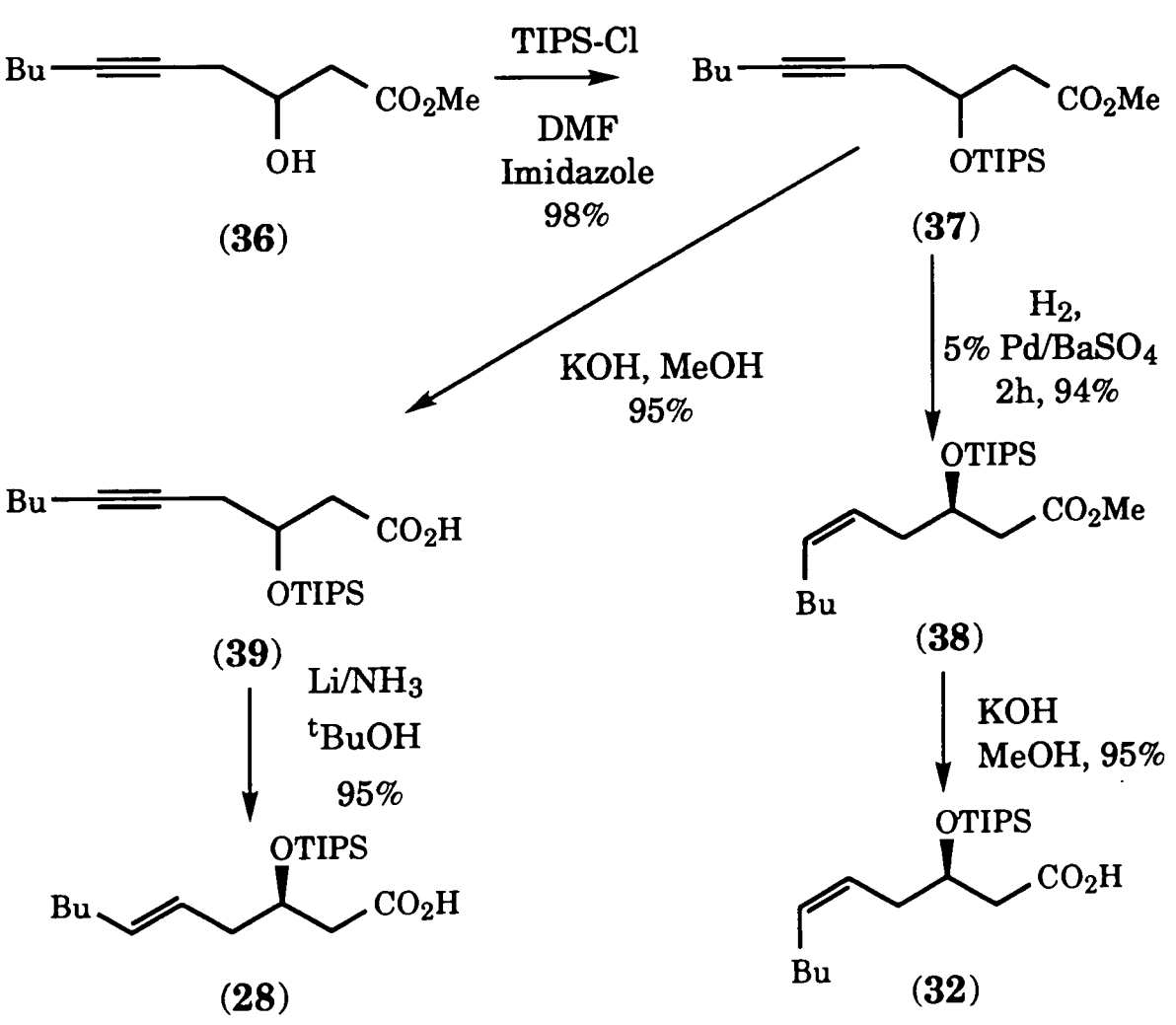


(33) **(34)** **(35)**

The alkyne **36** was prepared by a method to be described later (p. 73) and silylated in good yield using triisopropylsilyl chloride and imidazole in dimethylformamide. The resulting silyl ether **37** was Lindlar reduced, using 5% palladium on barium sulphate, poisoned with

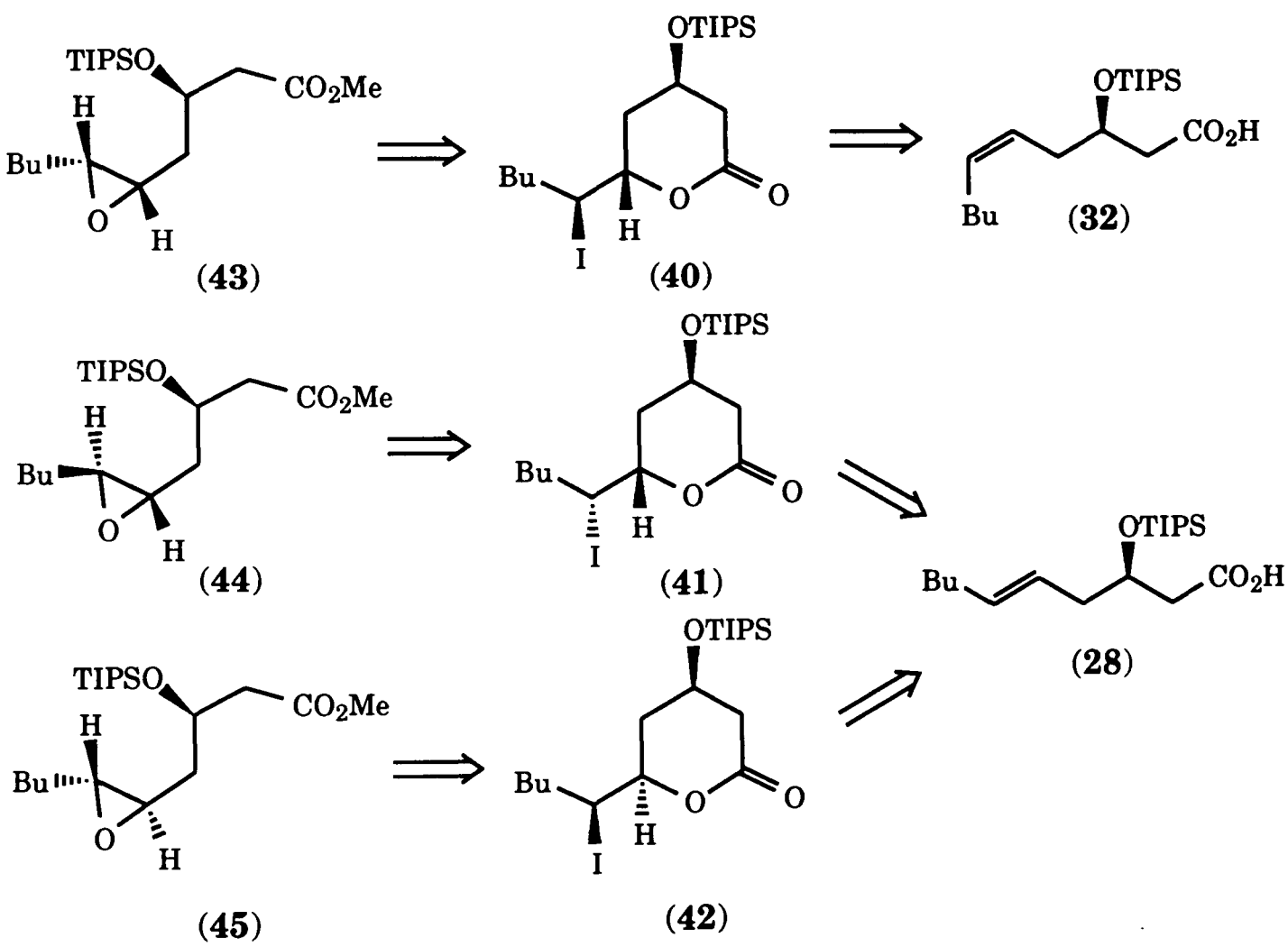
quinoline in ethyl acetate,[82] to furnish the (Z)-ester **38**, which was saponified to give the desired (Z)-acid **32**, in high yield, as a single geometrical isomer (according to ^{13}C NMR). The silyl ether **37** was itself saponified to give the acid **39** in good yield. Reduction of the acetylene function in the acid **39** using lithium in ammonia[83] gave the desired (E)-acid **28** as a single geometrical isomer (by ^{13}C NMR), in high yield (Scheme 71). Cyclisation of the (Z)-β-hydroxy-δ-alkenoic acid **32** (in aqueous acetonitrile, at 0°C, using 3 equivalents of iodine and 3 equivalents of sodium bicarbonate, for 3 hours) led to the iodolactone **40**, whereas cyclisation of the corresponding (E)-β-hydroxy-δ-alkenoic acid **28** in the same way led to the iodolactones **41** and **42** in a ratio of 8:1.

Scheme 71



The relative stereochemistries of these lactones were determined primarily by consideration of coupling constants; the major lactone **41** exhibited a narrow resonance for the 4-H with couplings to the adjacent 3-H_{ax} and 5-H_{ax} which indicated it was in an equatorial position and therefore *trans* to the clearly axially positioned 6-H. The minor lactone **42** showed data indicating that both 4-H and 6-H were axially positioned. All three iodolactones were converted into the corresponding epoxides **43**, **44** and **45** as described above.

Scheme 72

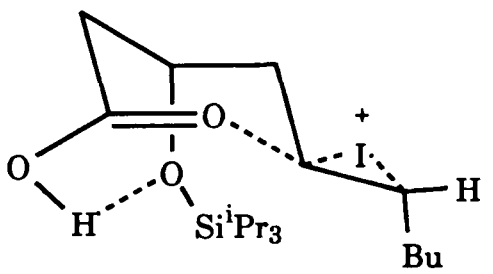


Analysis of the 400 MHz ^{1}H NMR spectra of the three epoxides allowed the 5-H to 6-H (cross epoxide) coupling constant [$J_{5,6}$] to be found

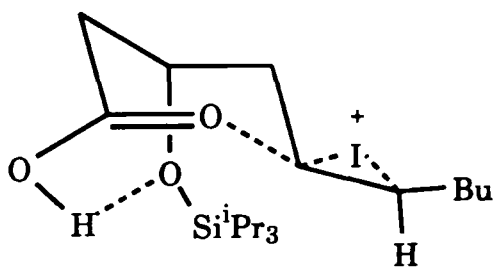
in each case, by determining which coupling was present in both the 5-H and 6-H resonances. In epoxide **43** derived from the (Z)-acid **32**, $J_{5,6}$ was 4.6 Hz, whereas in the epoxides **44** and **45**, derived from the (E)-acid **28**, $J_{5,6}$ was 2.3 and 2.7 Hz respectively. These values correspond to literature values for such epoxide coupling constants; *cis* epoxides show cross epoxide coupling constants of 4-6 Hz whereas *trans* epoxides have corresponding values of 2-3 Hz.[84] This demonstrates that the (E)-acids lead to *trans* epoxides and (Z)-acids lead to *cis* epoxides. This enables the assignment of the stereochemistry at the iodine centres to be deduced as shown (Scheme 72).

The stereochemistry proven to exist at the iodine centre is consistent with the transition state **31** and also shows that the expected overall *anti* addition of iodine to the olefin has occurred. This provides evidence for the transition states shown in Scheme 73 (*vide supra*).

Scheme 73



Transition state for cyclisation of the (E)-isomer



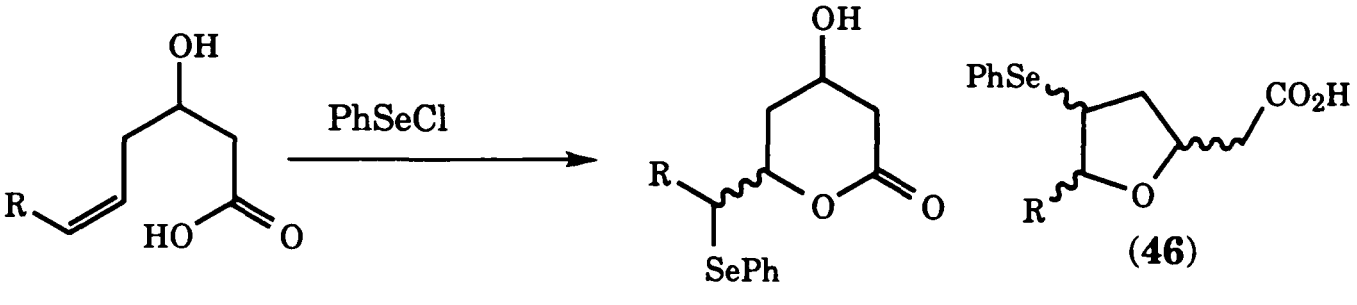
Transition state for cyclisation of the (Z)-isomer

(II) Tetrahydrofurans By Overall 5-*endo*-trig Cyclisations

During the course of his work on selenolactonisation, Bennett

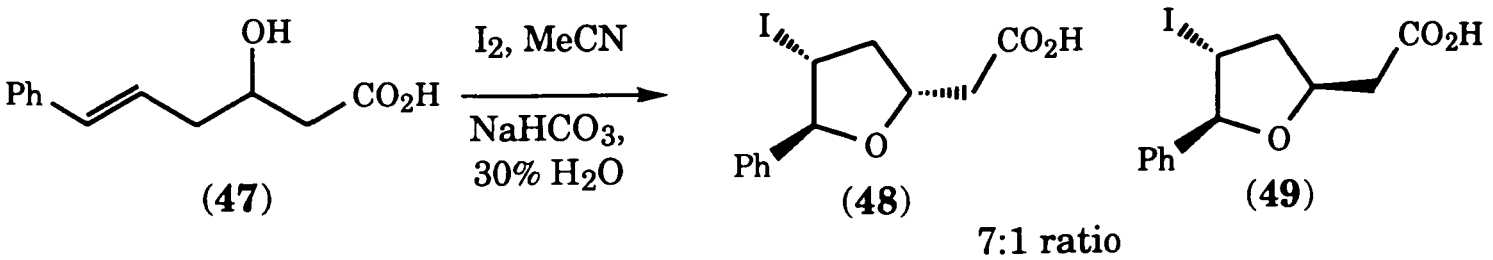
used hydroxy-acids because the silicon protecting groups used in the iodolactonisations were incompatible with the use of selenium. In these reactions, he noted the occurrence of side products which were identified as the seleno-THFs **46**. There was little stereoselection observed under the conditions used (Scheme 74).

Scheme 74

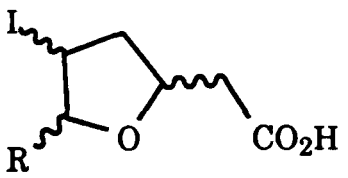


Bennett also iodocyclised the hydroxy acid **47** and obtained the THF acids **48** and **49** exclusively. This can be explained by the fact that lactonisation would require a positive charge to be effectively generated β to the aryl system and is therefore disfavoured relative to overall "5-endo-trig" cyclisation *via* a stabilised positive charge in a benzylic position (Scheme 75).

Scheme75



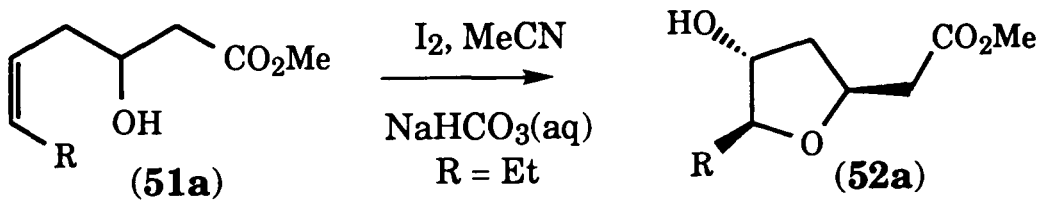
Also, whilst working on the foregoing iodolactonisation reactions, Bennett[78] noted the occurrence of the THF acids **50** as trace by-products (less than 5%).



(50)

It was assumed that these compounds arose from loss of the silicon group and subsequent cyclisation of the hydroxyl function in a 5-*endo* trig fashion. It became obvious that to further investigate these reactions, β-hydroxy-δ-alkenoate esters needed to be synthesised. By blocking the lactonisation process and favouring the etherification process, it was thought that the "5-*endo*-trig" cyclisation process could be induced to occur to a greater or even exclusive extent. Unexpectedly, when the methyl (Z)-β-hydroxy-δ-alkenoate **51a** was cyclised under the standard kinetic conditions developed by Bartlett, the hydroxy-THF **52a** was obtained as a single diastereoisomer (Scheme 76). Bedford[80] had carried out a small number of these reactions in aqueous acetonitrile and had obtained somewhat lower yields of the hydroxy-THFs. He also cyclised (Z)-β-hydroxy-δ-alkenoates under anhydrous conditions but obtained a mixture of hydroxy- and iodo-THFs.

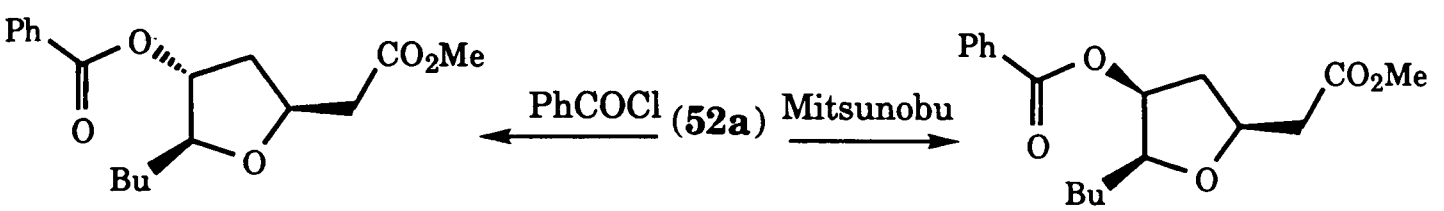
Scheme 76



Bennett[85] synthesised the benzoate ester of the hydroxy-THF product **52a** and also of its epimer (synthesised by Mitsunobu inversion).[86] The spectral data from these compounds were compared to the examples

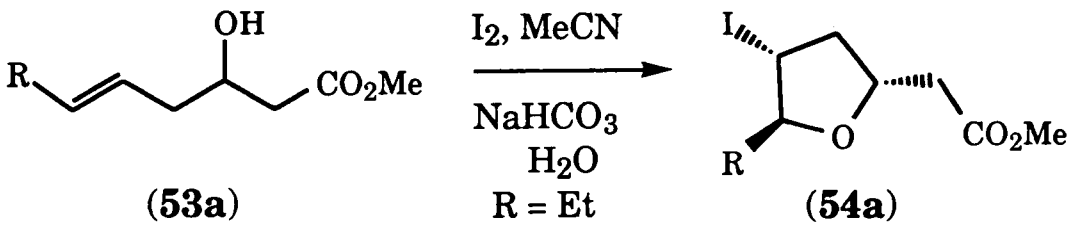
given by Williams[87] for similar systems and the stereochemical assignments thus derived were consistent with those derived from NOE irradiation data (Scheme 77).

Scheme77



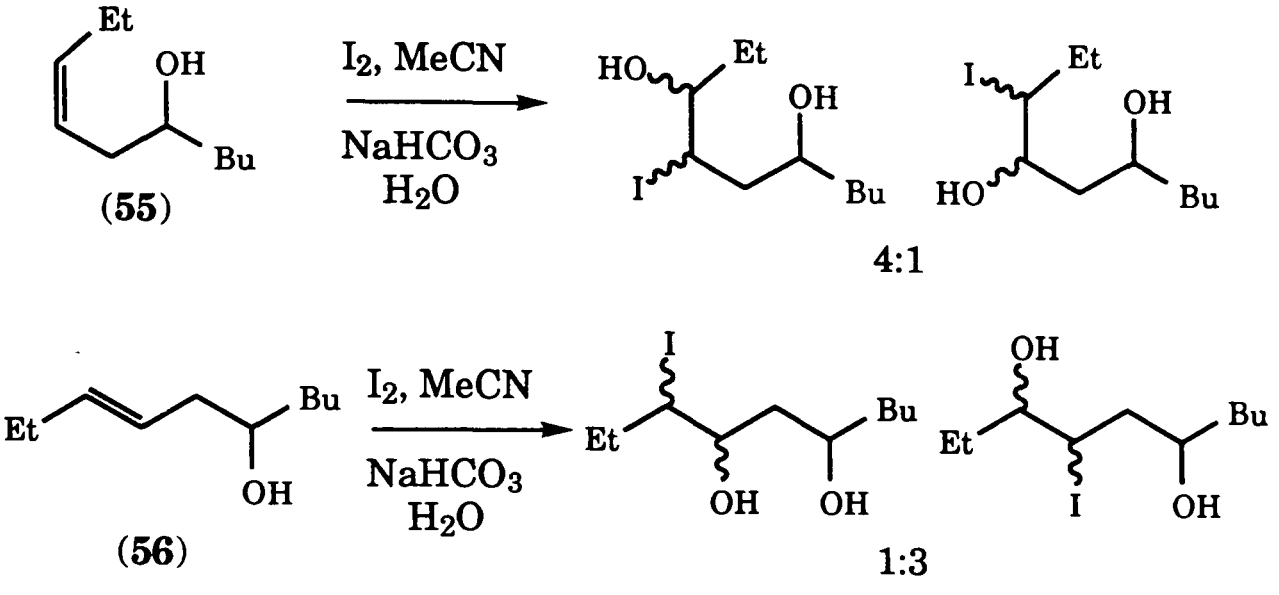
The situation was further complicated by the fact that upon treatment of the (E)-β-hydroxy-δ-alkenoate **53a** in aqueous acetonitrile with 3 equivalents of iodine and 3 equivalents of sodium bicarbonate at 0°C, good yields of the iodo-THF ester **54a** were obtained with very high stereoselectivity (Scheme 78).[80]

Scheme 78



With these results in hand, it was decided to investigate the generality of this process. Bedford[80] had attempted to cyclise the homoallylic alcohols **55** and **56** under aqueous conditions and recovered regio- and stereoisomers of the iodohydrins resulting from the addition of water to the iodonium ion; significant regioselectivity was observed (Scheme 79).

Scheme 79



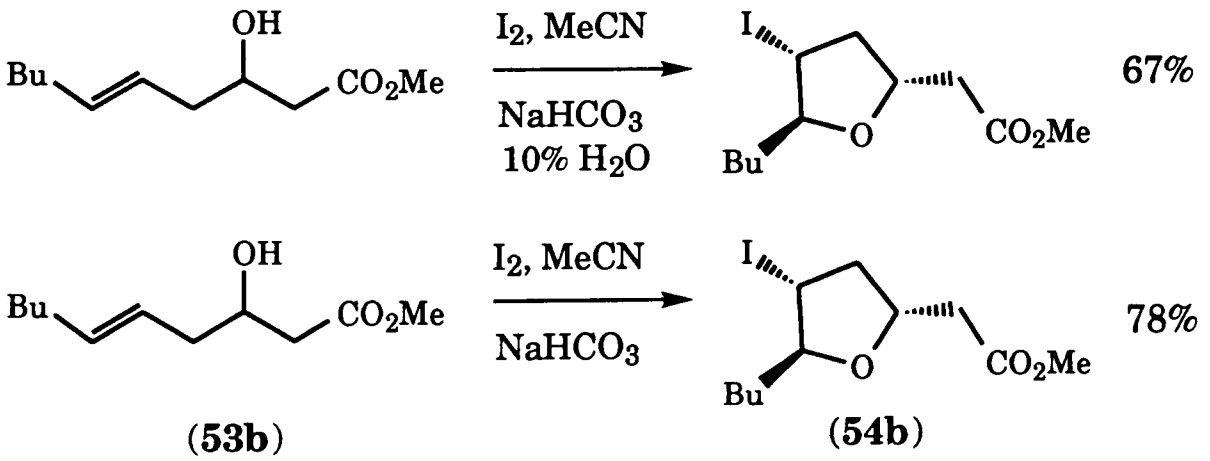
It was against the background of these somewhat confusing results that the present project began. There were three primary objectives: (i) To establish a consistent pattern for the iodocyclisation of β-hydroxy-δ-alkenoates and a mechanistic rationalisation, (ii) To attempt to extend this to give a pattern for homoallylic alcohols in general, and (iii) To devise efficient routes to the cyclisation precursors.

The observation of iodohydrin formation in the attempted cyclisation of homoallylic alcohols **55** and **56**, presumably by the attack of water upon the iodonium ions, suggested that the removal of all the water from the reaction mixture would lead to interesting results. This was achieved using Aldrich HPLC grade acetonitrile, distilled under an atmosphere of nitrogen from P_2O_5 (Super dry acetonitrile), as the solvent. The use of molecular sieves or the addition of dried magnesium sulphate was considered, but it was decided to postpone these investigations, as it was felt that the use of such additives could complicate the results still further. It has been discovered that the cyclisation of (Z)-β-hydroxy-δ-alkenoates to give a hydroxy-THF is an unusual and so far unique result

which was in some ways misleading during the early stages of this work.

As the first part of this present project, it was established that the 5-*endo*-trig cyclisation of (E)-β-hydroxy-δ-alkenoates **53b** is relatively insensitive to the presence of water. The ester **53b** was obtained as a single geometrical isomer by a route to be described later (p. 76). A single sample of the ester **53b** was divided into two equal portions and one was iodocyclised using anhydrous conditions as described above and the other was iodocyclised using acetonitrile containing 10% water. The iodo-THF **54b** was obtained as a single diastereoisomer in high yield in both cases, although a slightly higher yield was obtained in the former case under anhydrous conditions (Scheme 80). This finding proved to be extremely significant.

Scheme 80



(53b) **(54b)**

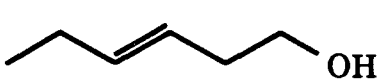
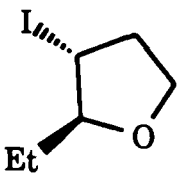
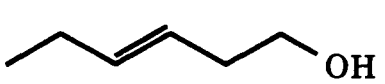
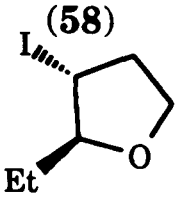
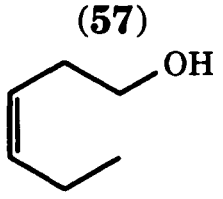
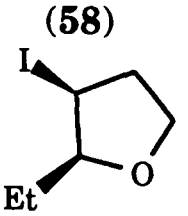
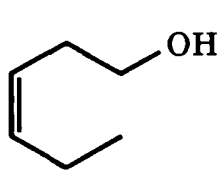
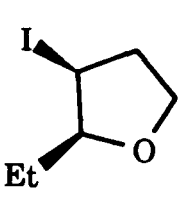
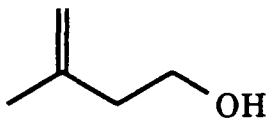
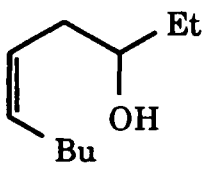
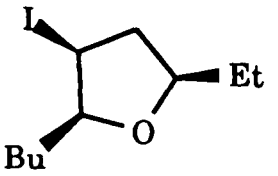
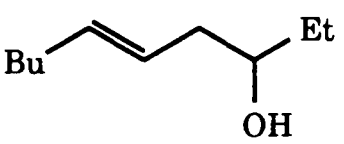
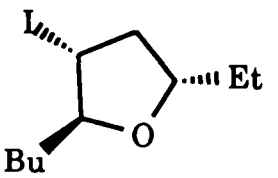
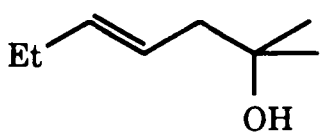
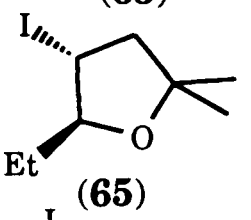
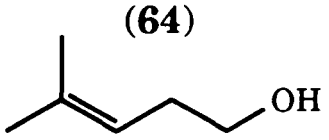
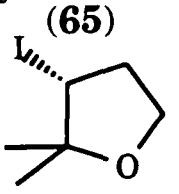
The cyclisations of a variety of homoallylic alcohols in super dry acetonitrile have been investigated, and it was pleasing to find that generally good yields of a variety of iodo-THFs have been obtained. (E)-Hex-3-en-1-ol **57** underwent a facile cyclisation in less than 5 min at 0°C or in under 2 hours at -25°C to give the iodo-THF **58** in equally high yield in either case (Scheme 81). There was absolutely no trace of any other

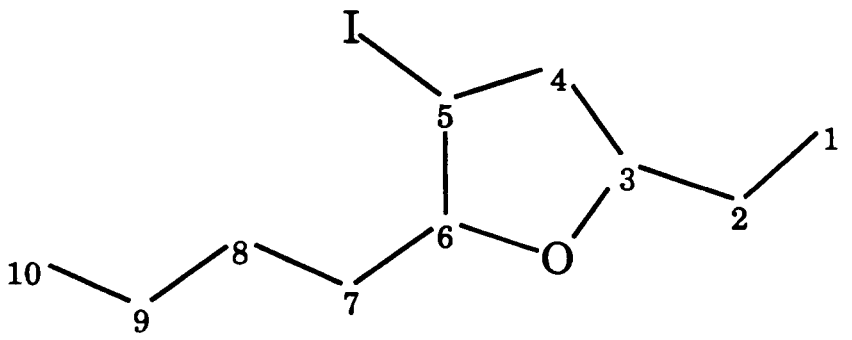
products upon work up and a crude ^{13}C NMR showed only resonances assignable to the iodo-THF **58** (Figure 1). The data obtained for this compound corresponded to those quoted by Schauble *et al.*[36] Further investigation by NOE experiments proved the *trans* stereochemistry of the product obtained. (Z)-Hex-3-en-1-ol **59** cyclised only slowly at 0°C, but under the anhydrous conditions, and with periodic addition of iodine, reasonable yields of the iodo-THF **60** were eventually obtained, using either nucleophilic ($NaHCO_3$) or non-nucleophilic (MgO) bases. Detailed NMR studies of the product revealed that it was definitely a THF and not the corresponding iodomethyloxetane which would result from an overall "4-*exo*-trig" cyclisation. This was proven by the use of ^{13}C-^{1}H correlation experiments which identified the proton resonance which was related to the easily identifiable carbon bonded to iodine (*ie* the resonance is shifted significantly upfield in the ^{13}C spectrum); this was a methine C<u>H</u>I and comparison of its couplings in the ^{1}H-^{1}H COSY spectrum showed that it was coupled to the resonances of the CH_2 protons in the ring and to the 2-C<u>H</u>O resonance. There was no coupling to the side chain proton resonances as would be observed in the case of an iodomethyloxetane. In compound **60**, there is also a significant upfield shift of the resonance resulting from the 2-C<u>H</u>O, which is observed at δ_H = 2.80. This phenomenon has yet to be fully explained but it could result from the strained configuration of the molecule. Cyclisation of 4-methylpent-4-en-1-ol **61** gave no THF products, probably because the expected educt, being a tertiary iodide, underwent rapid decomposition. The black oily nature of the crude reaction product and its ^{1}H NMR spectrum suggested this had

occurred. The secondary alcohols **55** and **56**, which Bedford used to produce iodohydrins, were cyclised under the present anhydrous conditions to give the iodo-THFs **62** and **63** respectively; the stereochemistries of which were proven by NOE experiments. The (E)-isomer again underwent a much smoother cyclisation, which was complete after 16 hours. In reality, the cyclisation was probably over in about 2 hours (*cf* cyclisation of primary homoallylic alcohols); crude ^{1}H NMR showed a single product which was isolated in 80% yield after chromatography. In the case of the (Z)-isomer, cyclisation required a longer period of time but proceeded in a reasonable yield, after chromatography, of 70%.

The tertiary alcohol, (E)-2-methyl-hept-4-en-2-ol **64**, was found to cyclise in equally high yield in less than 1 hour to give the 5,5-dimethyliodo-THF **65** which showed data appropriate to the structure shown. Comparison with the data for iodo-THFs **58** and **60** showed that the 2,3-*trans* relationship was obtained. Disubstituted double bonds could also be incorporated. For example, 4-methylpent-3-en-1-ol **66** was found to cyclise in less than 1 hour, and in high yield, to give the 2,2-dimethyliodo-THF **67** (Scheme 81). The determination of structure and stereochemistry for the iodo-THF systems involved analysis of 400 MHz ^{1}H, ^{13}C, ^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY and NOE spectra. As an example, the structural and stereochemical information for the iodo-THF **62** is analysed (Figure 2 a-j) [the ^{1}H spectrum of the iodo-THF **63** is included for comparison (Figure 3)] to illustrate how the structures of all the THFs synthesised during the course of this project were deduced.

Scheme 81

	Conditions		Yield
 **(57)**	I_2, MeCN, $NaHCO_3$ 5 min, 0°C	 **(58)**	90%
 **(57)**	I_2, MeCN, $NaHCO_3$ 2h , -25°C	 **(58)**	90%
 **(59)**	I_2, MeCN, $NaHCO_3$ 72h, 0°C	 **(60)**	60%
 **(59)**	I_2, MeCN, MgO 72h, 0°C	 **(60)**	63%
 **(61)**	I_2, MeCN, $NaHCO_3$ 16h, 0°C		0%
 **(55)**	I_2, MeCN, $NaHCO_3$ 72h, 0°C	 **(62)**	70%
 **(56)**	I_2, MeCN, $NaHCO_3$ 16h, 0°C	 **(63)**	80%
 **(64)**	I_2, MeCN, $NaHCO_3$ 1h, 0°C	 **(65)**	90%
 **(66)**	I_2, MeCN, $NaHCO_3$ 1h, 0°C	 **(67)**	80%



(62)

Analysis of the ^{13}C-^{1}H COSY spectrum (Figure 2e) allowed the resonances at δ_C = 32.35 and δ_H = 4.40 to be assigned as those corresponding to the 5-C and 5-H respectively; the large upfield shift in the resonance due to the carbon bonded to iodine means that it can easily be identified. Comparison with the ^{1}H-^{1}H COSY spectrum (Figure 2d) showed that the 5-H resonance exhibited coupling to the resonances at δ_H = 2.76 and 2.92. The fact that there is no coupling apparent to the side chain allows the isomeric oxetane product of the cyclisation to be discounted. The resonance at δ_H = 2.76 was assigned as the 6-H because it was related to the ^{13}C signal in the ^{13}C-^{1}H COSY at δ_C = 81.60, and therefore it was known to be a methine $\underline{C}$HOR; the coupling to the 5-H resonance proved that it was not the 3-H. The resonance at δ_H = 2.92 was related to the ^{13}C signal in the ^{13}C-^{1}H COSY at δ_C = 43.90, and therefore it was known to be part of a methylene $\underline{C}H_2$; the coupling to the 5-H resonance suggesed that it was the 4-H_A (*ie* the proton on the same face of the molecule as the 5-H). The 6-H resonance showed couplings to the side chain resonances at δ_H = 1.69 and 1.83, as well as to the 5-H in the ^{1}H-^{1}H COSY. Both of these side chain resonances were related to the ^{13}C peak at δ_C = 36.99 and these signals were therefore

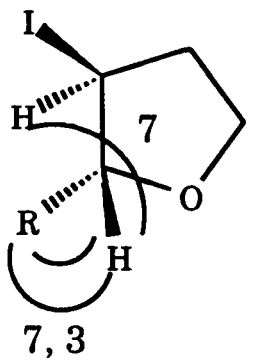
assigned as the 7-CH_2. The 4-H_A showed a strong geminal coupling to the resonance at δ_H = 2.31 in the ^1H-^1H COSY, suggesting that the latter was the 4-H_B. This was confirmed by the fact that both of these resonances were related to a single ^{13}C signal at δ_C = 43.90. The remaining CH signal in the ^{13}C spectrum was thought to be the 3-H and this was confirmed by the fact that the corresponding ^1H resonance at δ_H = 3.87 showed coupling to the 4-H_A and 4-H_B in the ^1H-^1H COSY. Having assigned the relevant ^{13}C and ^1H resonances, the coupling constants (determined from the 400 MHz ^1H NMR), and subsequently the NOE data, were analysed.

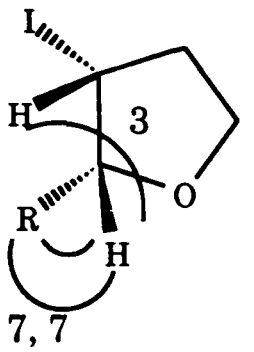
Resonance	δ_H	multiplicity	*J* values
4-H_B	2.31	ddd	14.6, 6.4 and 3.0
6-H	2.76	ddd	6.4, 6.4 and 4.0
4-H_A	2.92	ddd	14.6, 8.0 and 7.0
3-H	3.86	dddd	8.0, 6.4, 6.4 and 6.4
5-H	4.40	ddd	7.0, 4.0 and 3.0

These coupling constants give a great deal of information about the stereochemistry of the product. During these studies, it has been found that those systems in which the iodine has a *cis* relationship to the adjacent CHOR, the coupling constants observed for the adjacent CHOR are of the pattern *J*= ~7, 4-7 and ~3. Those systems in which the iodine has a *trans* relationship to the adjacent CHOR, the coupling constants for the adjacent CHOR are again of the pattern *J*= ~7, 4-7 and ~3. However, in the case of the *cis* example, the smallest coupling is between the CHI and the CHOR, whereas, in the case of the *trans* examples, the smallest

coupling is between the C<u>H</u>OR and one of the side chain protons closest to the iodine atom (Figure 4).

Figure 4





These coupling constants therefore suggested a *cis* relationship between the 6-H and 5-H, as the coupling constant was 4.0 Hz, whereas the couplings to the side chain were both 6.4 Hz. The 4-H_A appears to be on the same face as both the 5-H and the 3-H, as it has large couplings to both of these resonances. NOE data (Figure 2f-j) confirmed this as shown, suggesting an all-*cis* stereochemistry for the iodo-THF **62**. The strong enhancement of both the 3-H and the 5-H, by irradiation of the 4-H_A, shows that these three protons share the same face of the molecule. The enhancement of 6-H, by irradiation of the 5-H, confirms an all-*cis*-stereochemistry.

	3	**4_A**	**4_B**	**5**	**6**
3	X	Strong	Weak	0	Strong
4_A	Strong	X	Strong	Strong	0
4_B	0	Strong	X	Weak	0
5	0	Strong	0	X	Strong
6	Weak	0	0	Strong	X

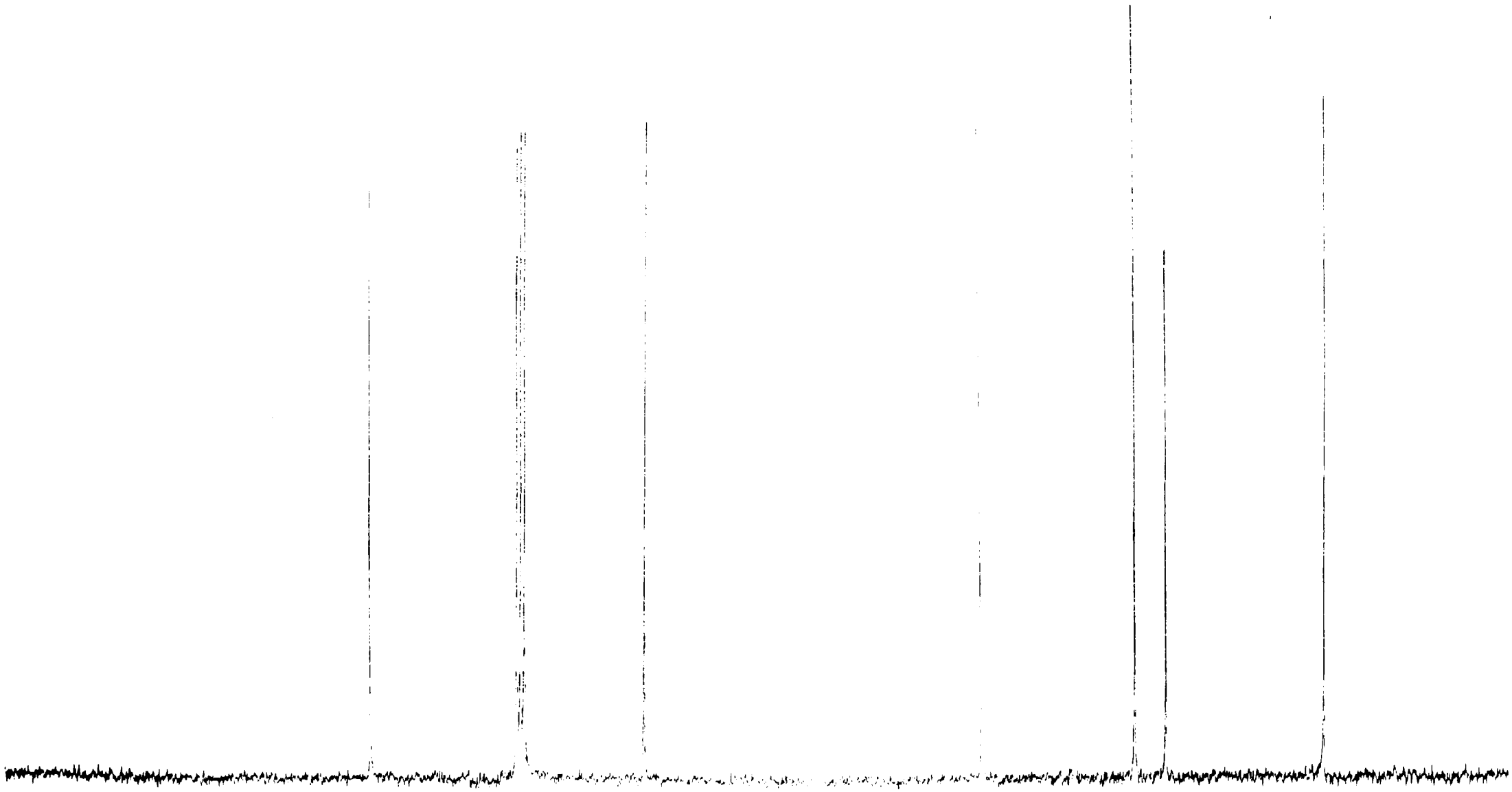


Figure 1

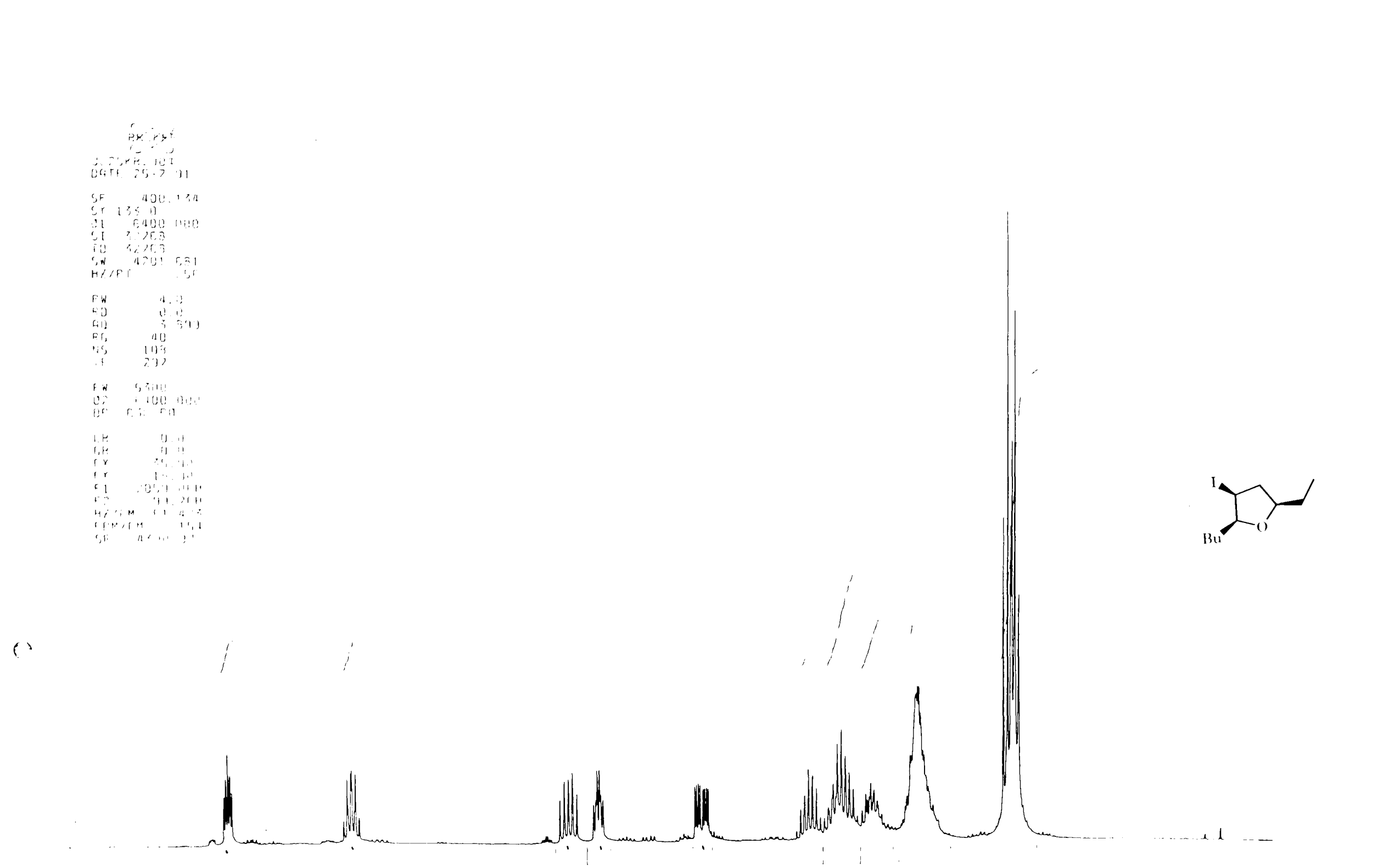


Figure 2a

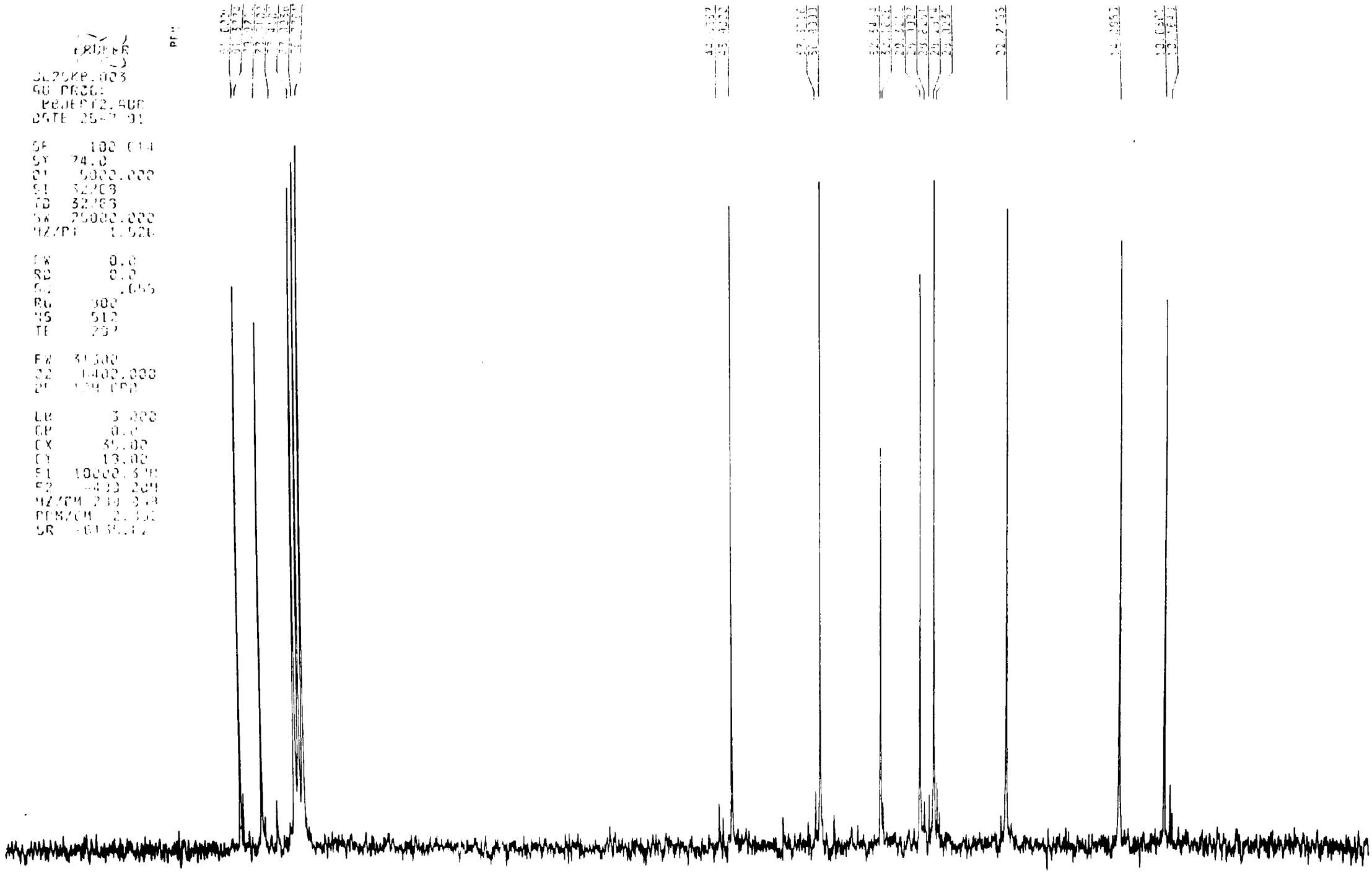


Figure 2b

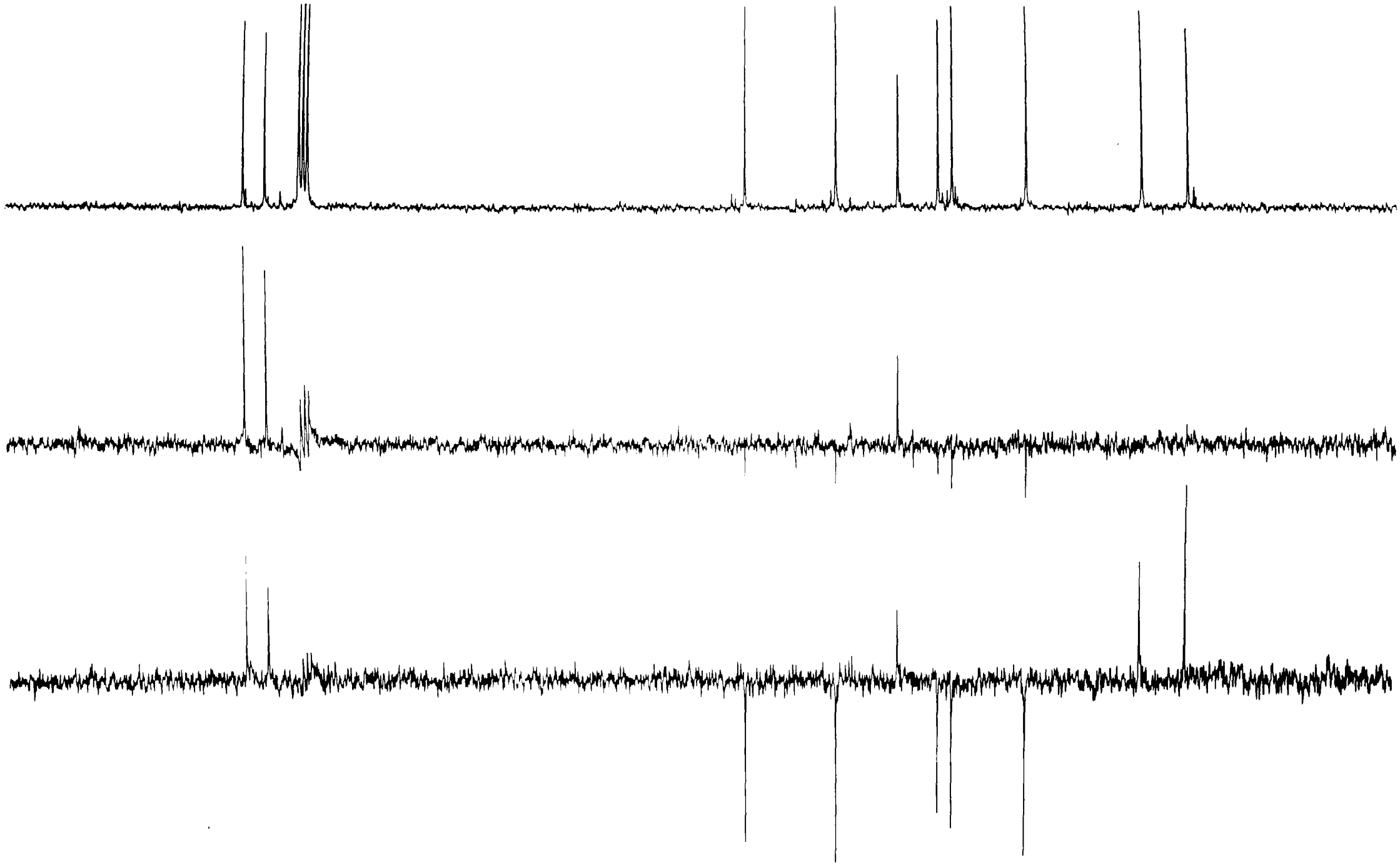


Figure 2c

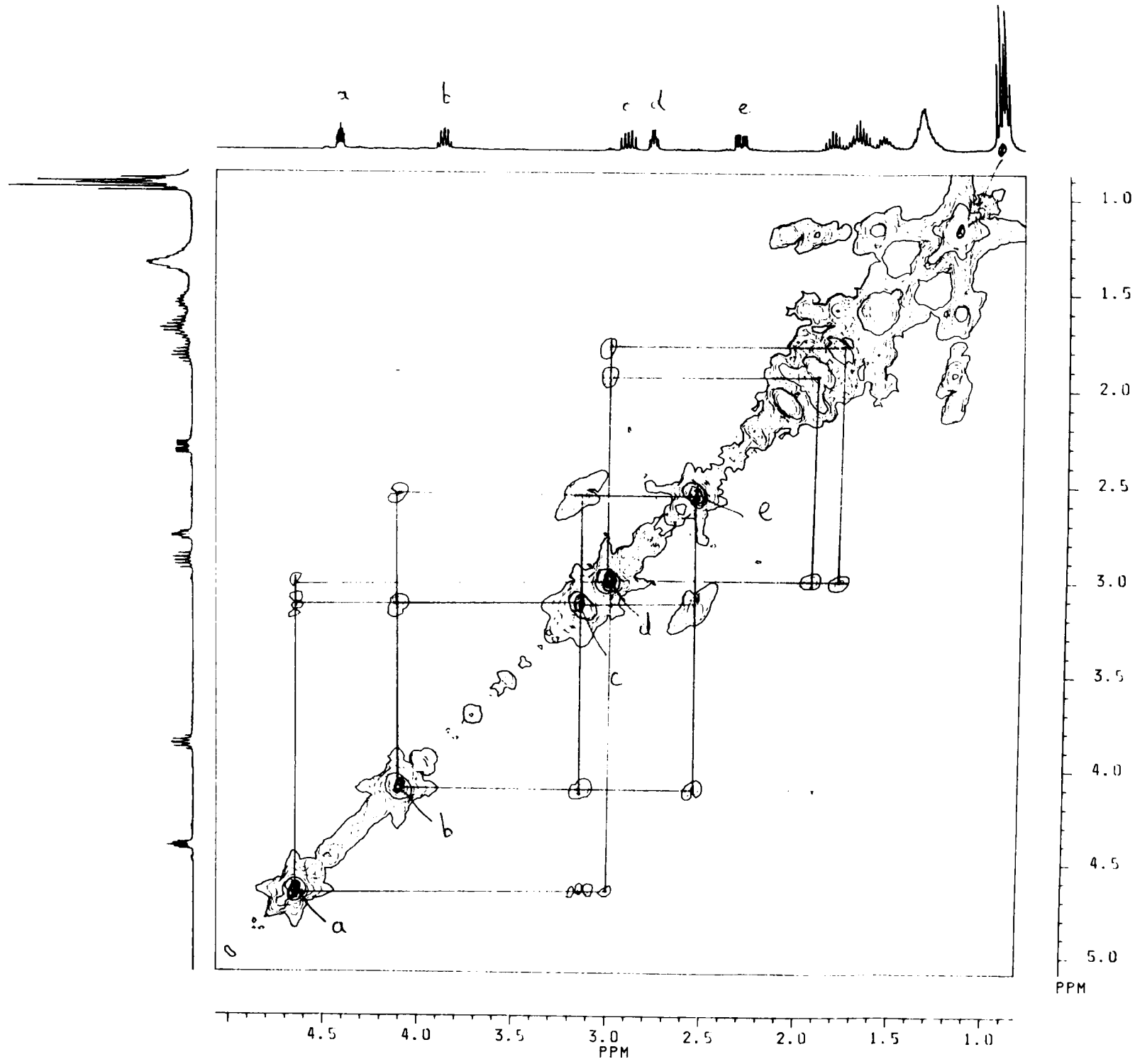


Figure 2d

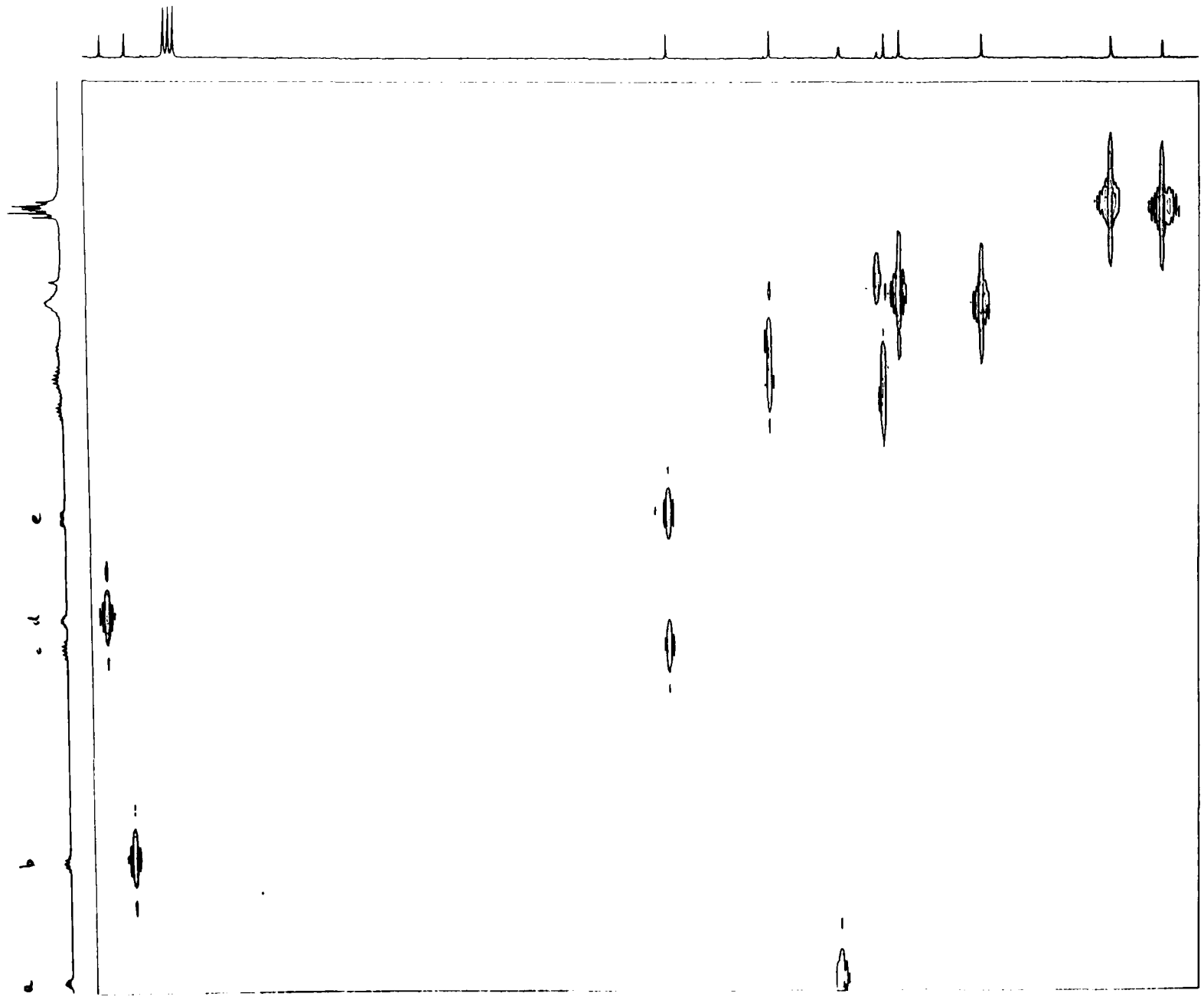


Figure 2e

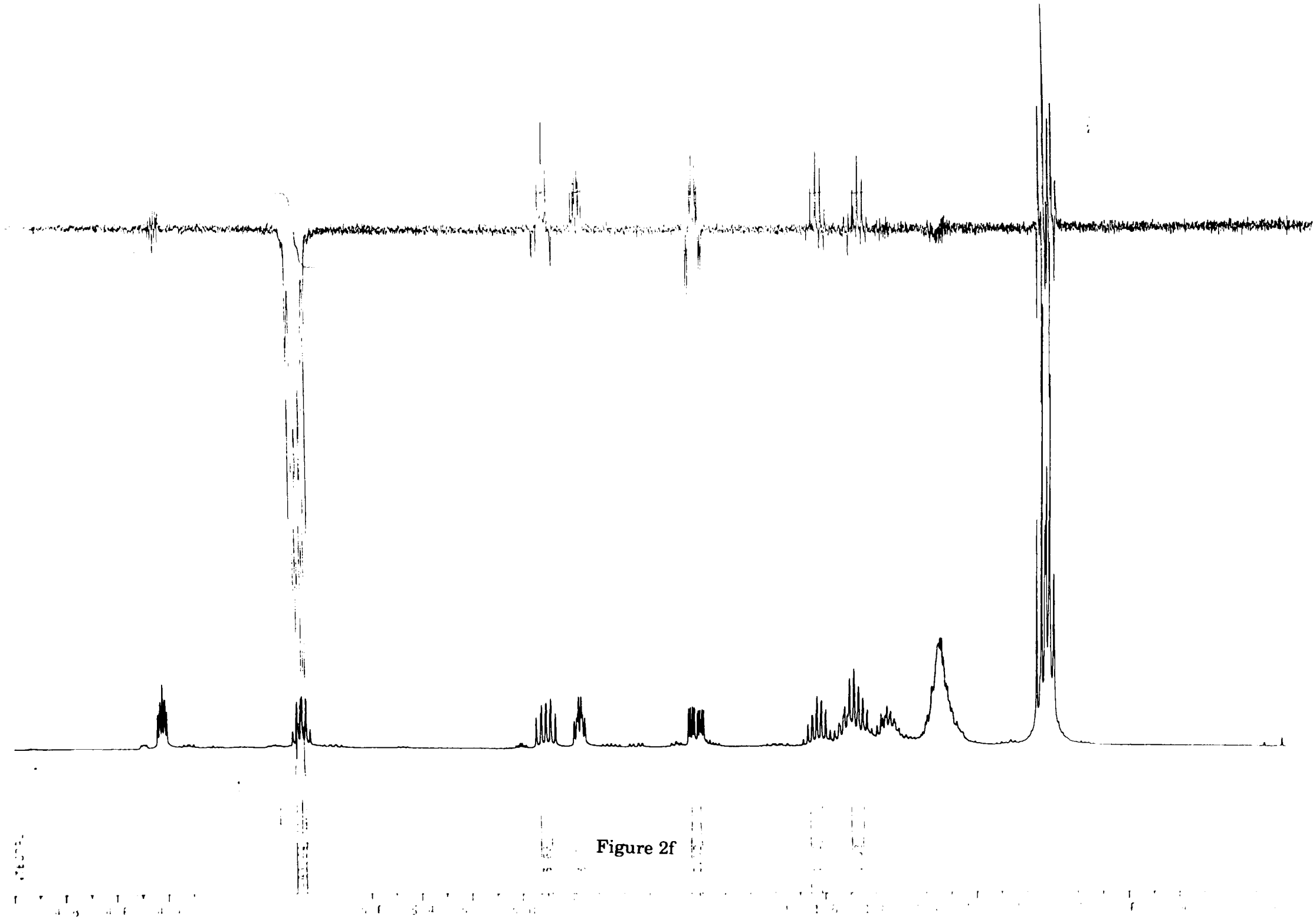


Figure 2f

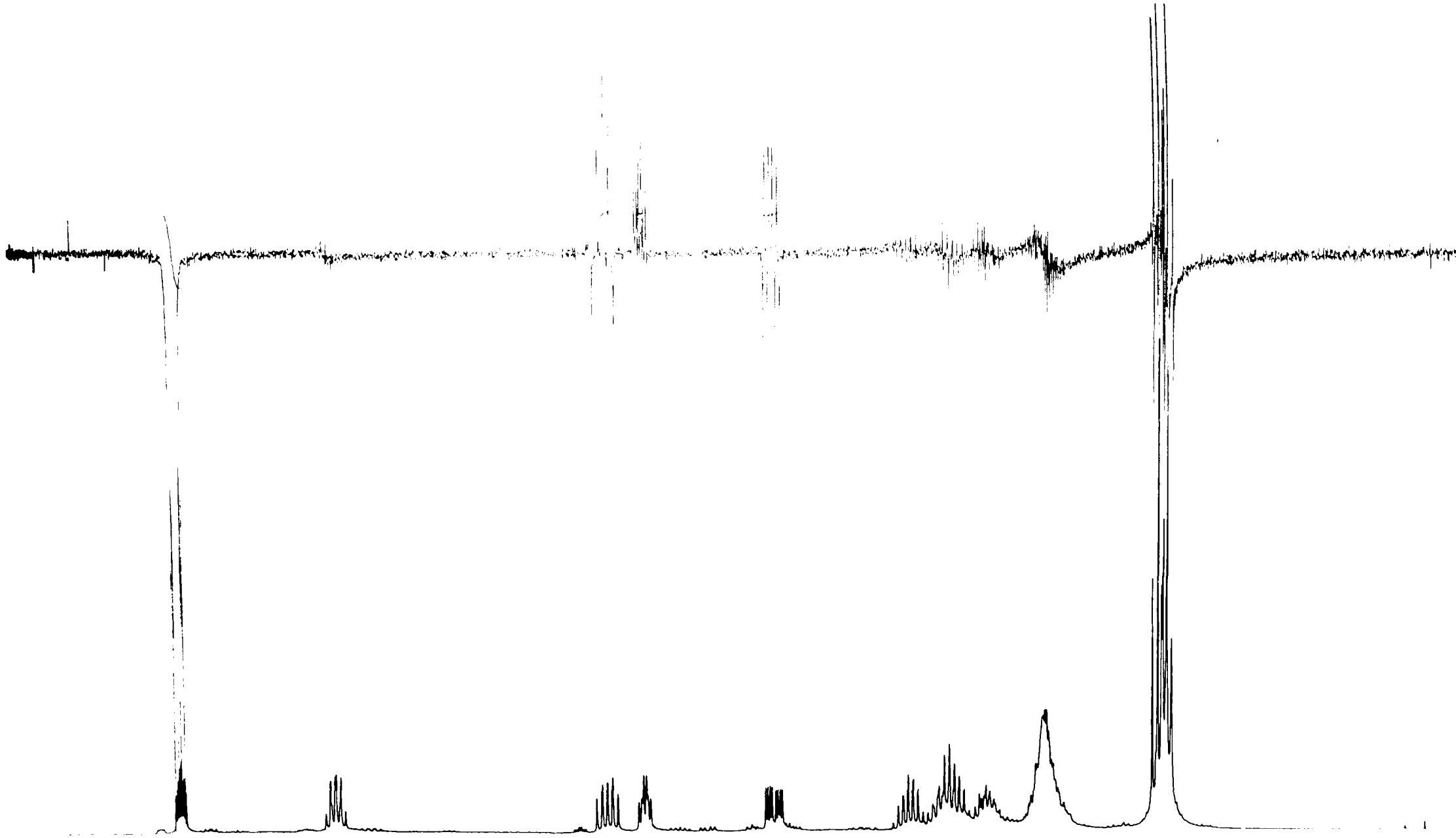


Figure 2g

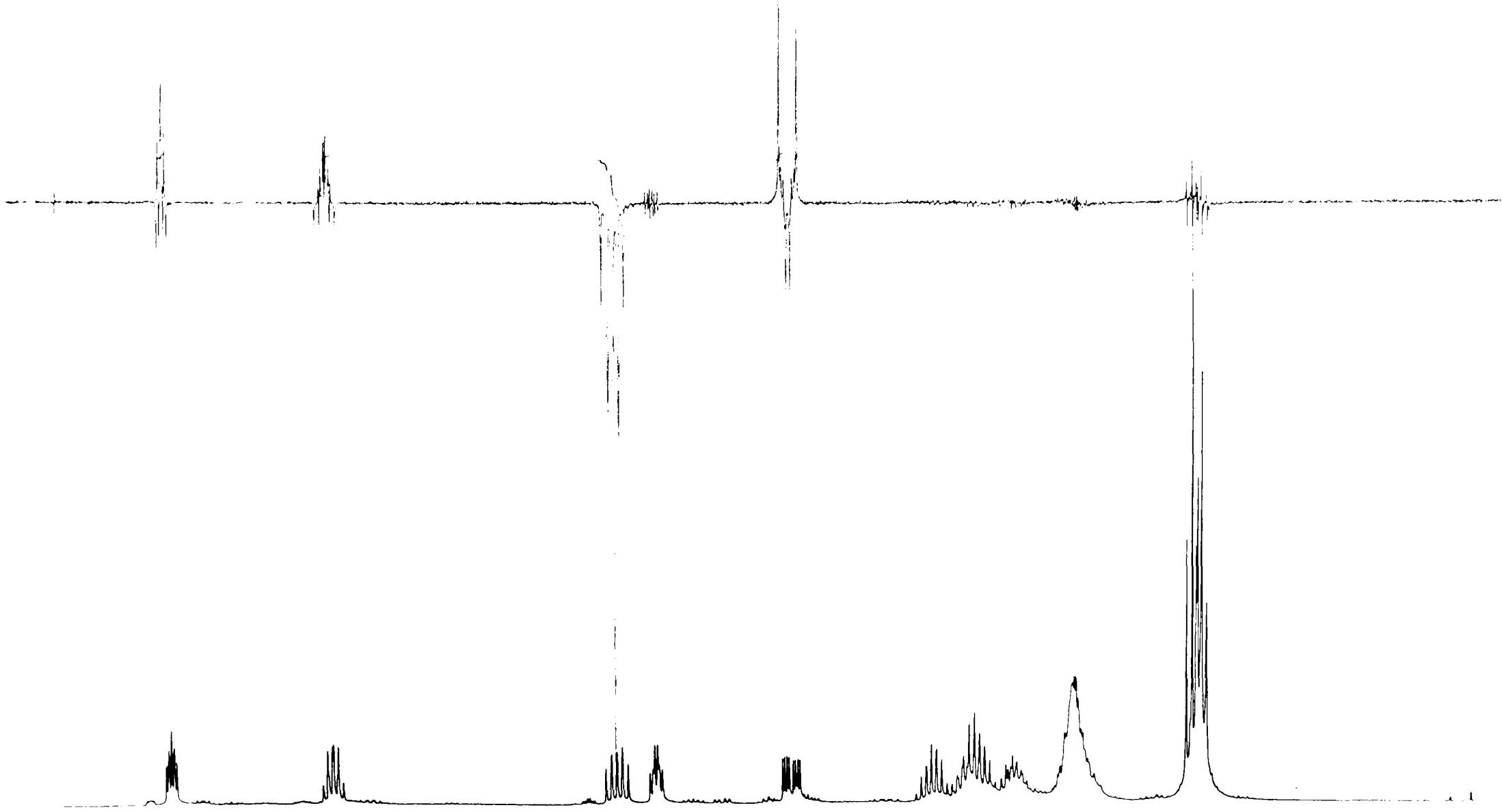


Figure 2h

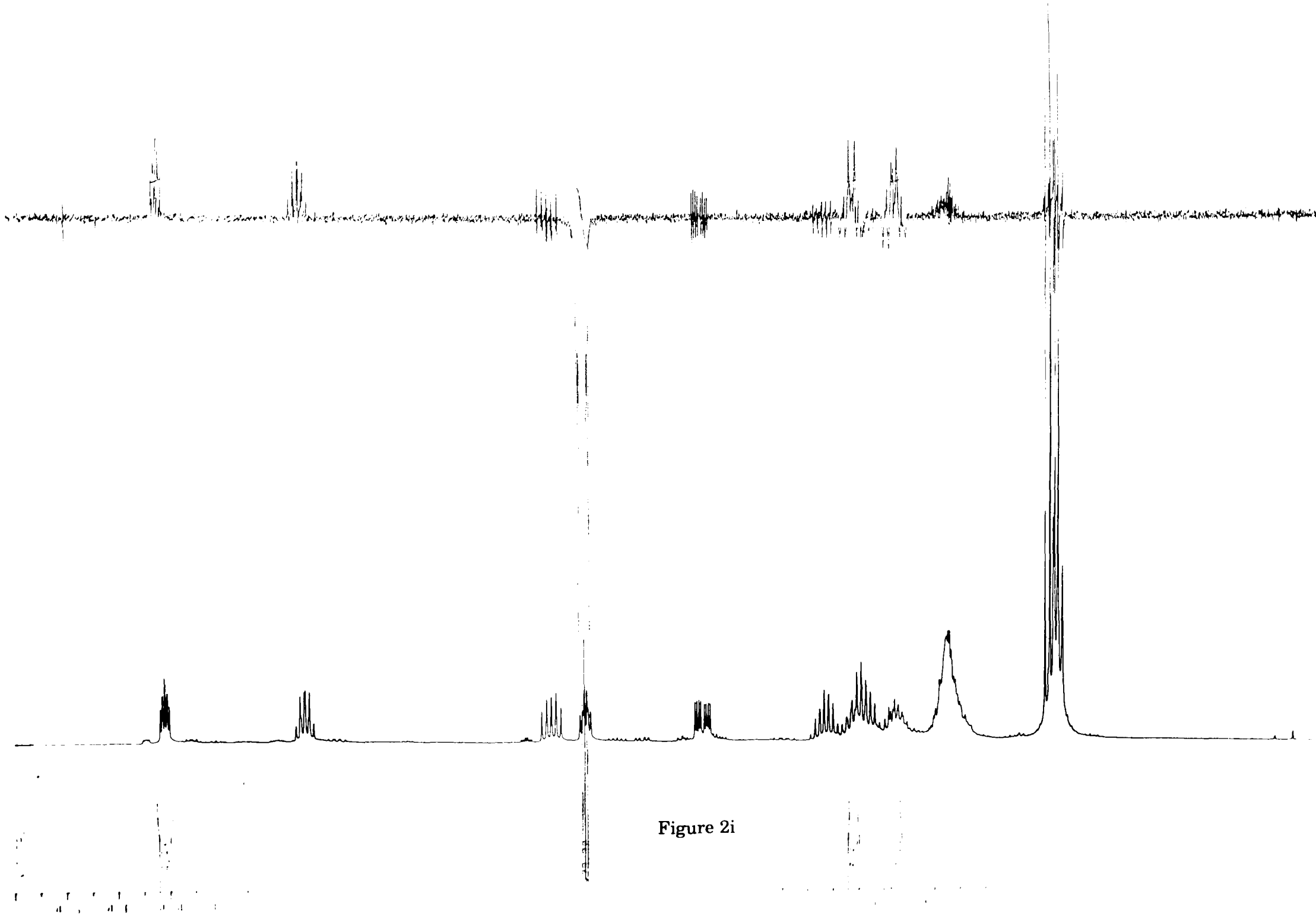


Figure 2i

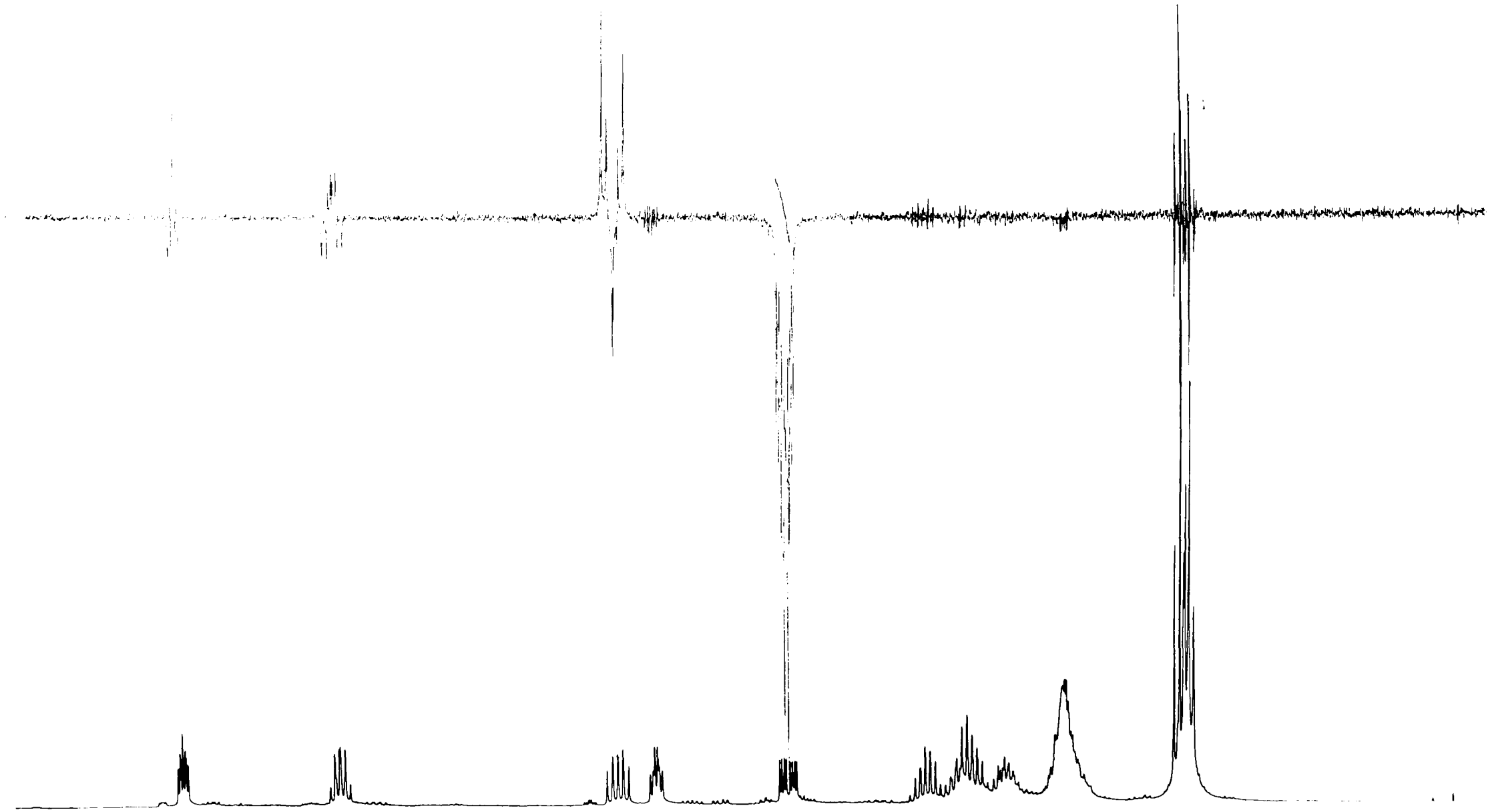


Figure 2j

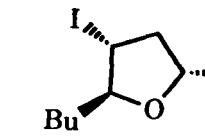
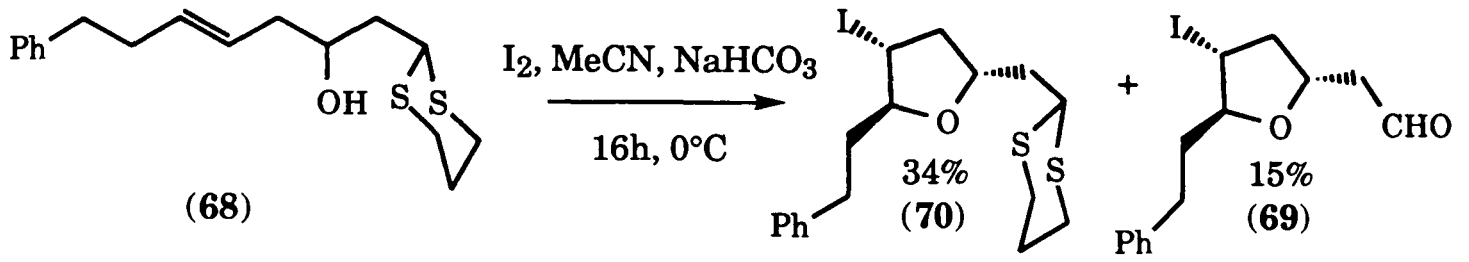


Figure 3

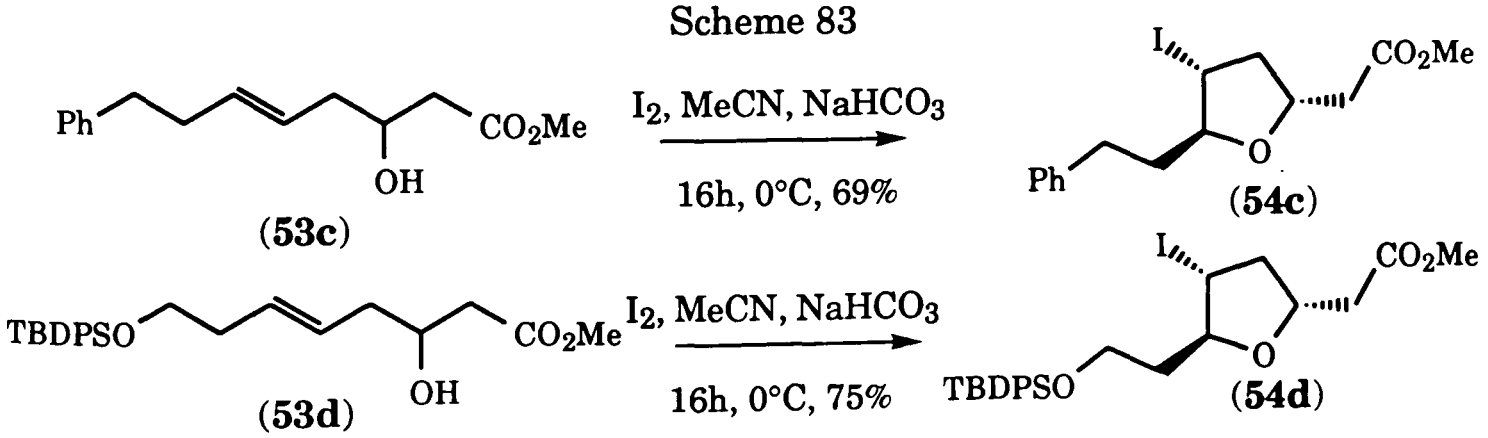
The dithiane derivative **68** cyclised smoothly but in somewhat lower yield due to *in situ* hydrolysis of the dithiane unit. This resulted in the formation of a significant proportion of the aldehyde **69** which was produced along with corresponding dithiane **70** in 49% overall yield (Scheme 82).

Scheme 82

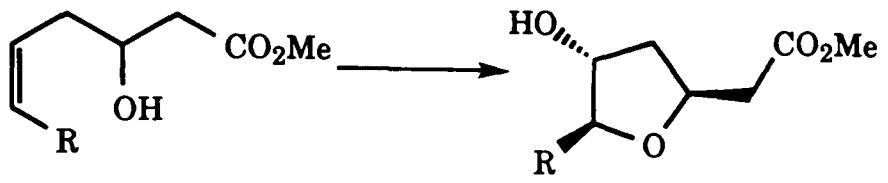


Further examples included various (E)-β-hydroxy-δ-alkenoates which were synthesised as part of the work towards a general synthesis of the cyclisation precursors. These molecules underwent fast cyclisation to give the iodo-THF esters with at least as good stereocontrol as in the cyclisation of ester **53b**. The ^{t}butyldiphenylsilyloxy group was shown to survive the cyclisation conditions, although a ^{t}butyldimethylsilyloxy group was cleaved. A THF containing a remote phenyl substituent **54c** was also synthesised; the aryl function could be a potential synthetic equivalent of an acid moiety upon oxidation (Scheme 76).[88] NOE data and comparison to the data from iodo-THF **54b** was used to confirm the stereochemistries shown.

Scheme 83



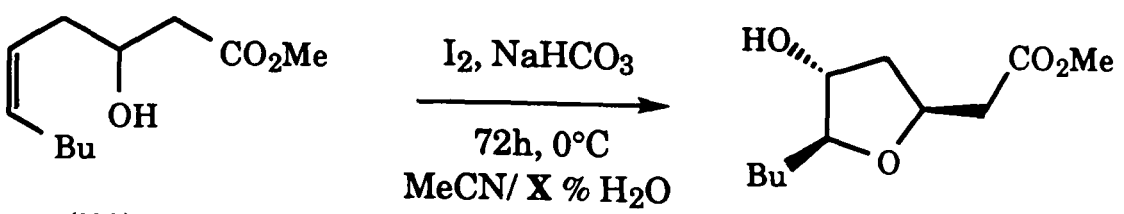
Scheme 84



When (Z)-β-hydroxy-δ-alkenoates were cyclised by stirring under the standard iodoetherification conditions using anhydrous acetonitrile for 72 hours, hydroxy-THFs were obtained in high yields (Scheme 84). Bedford[80] also cyclised (Z)-β-hydroxy-δ-alkenoates in dry conditions but obtained a mixture of hydroxy- and iodo-THFs. This result has since been attributed to impurities consisting of (E)-β-hydroxy-δ-alkenoates in the starting materials. Examples of the cyclisations were repeated as part of this present project using geometrically pure (Z)-methyl 3-hydroxy-dec-5-enoate **71** (one isomer by ^{13}C NMR) in 0%, 1%, 5%, 10% and 50% aqueous acetonitrile (Scheme 85) to give hydroxy-THF **72** but no iodo-THF products. The reactions proceed with good stereoselectivities for the isomer shown over its 3-epimer of around 10:1. [An exception was the case of R = Me where a stereoselection of around 8:1 was obtained in subsequent studies (see p 104).]

Various (Z)-methyl β-hydroxy-δ-alkenoates have been synthesised as part of this project and all the examples cyclise in high yields under these conditions [*eg* (Scheme 86)]. However, both the butyl and benzyl esters corresponding to the β-hydroxy-δ-alkenoate **71** underwent cyclisation in much lower yields (Scheme 87). This result has not been explained; there were no signs of valerolactone products from ester cleavage in the case of the benzyl ester, but there were various impurities, apparently resulting primarily from iodohydrin formation.

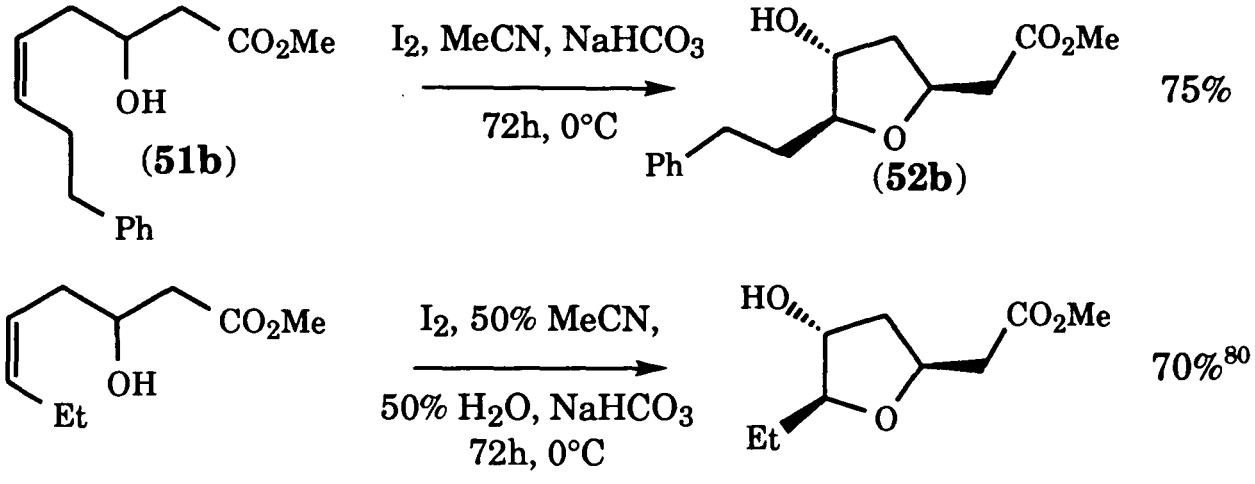
Scheme 85



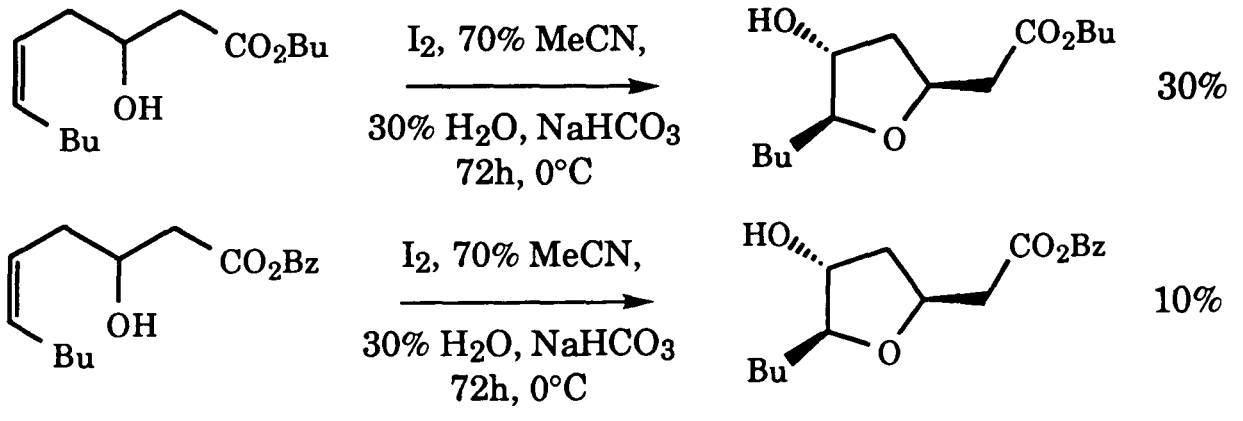
(71) (72)

X % H_2O	Yield
0%	83%
1%	85%
5%	75%
10%	75%
50%	60%

Scheme 86

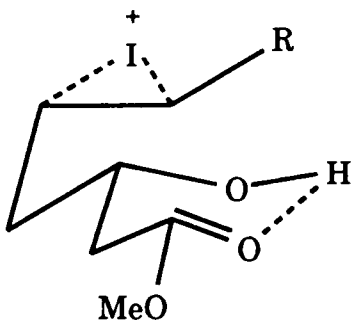


Scheme 87

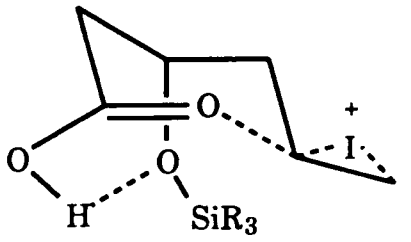


It is assumed that the cyclisation of (E)-β-hydroxy-δ-alkenoates proceeds through a 'chair like' transition state (Scheme 88). The reason that the cyclisations are insensitive to the presence of water could be that the hydroxyl function has increased nucleophilicity due to the fact that it is intramolecularly hydrogen bonded to the ester function. The electron donating effect of this hydrogen bonding, and the consequent weakening of the O-H bond, allows cyclisation to take preference over the attack of water upon the iodonium ion. This explanation is closely related to the explanation of the unusual stereochemical outcome of the iodo-lactonisation reactions (*cf* transition state **31**) (Scheme 89).

Scheme 88



Scheme 89

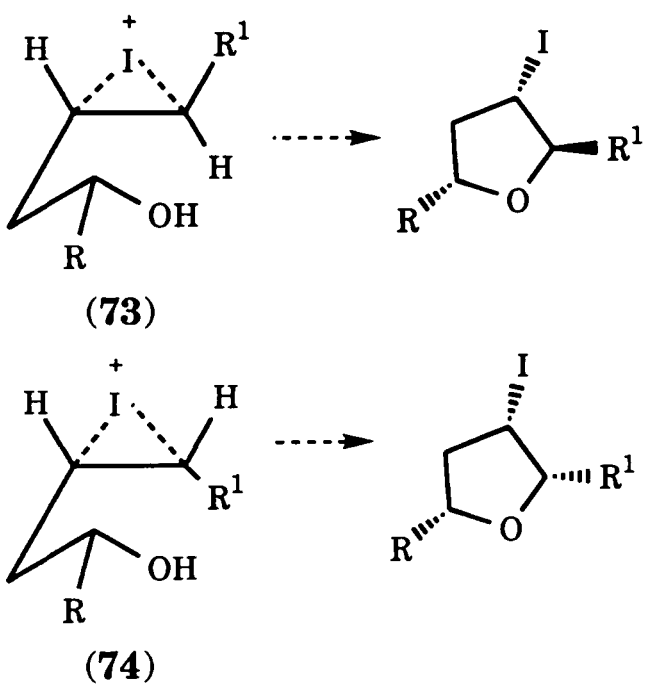


(31)

The proposed transition states for the 5-*endo*-trig cyclisations of general homoallylic alcohols in anhydrous acetonitrile are postulated to be 'chair like', and are related to the foregoing transition state for the cyclisation of (E)-β-hydroxy-δ-alkenoates (Scheme 90). The transition state for (E)-homoallylic alcohols **73** is favoured as there are no large steric interactions, whereas the corresponding transition state **74** for (Z)-homoallylic alcohols has a great deal of steric hindrance. This is consistent with the observation that the cyclisation of the *trans* isomers is

much smoother than that of the *cis* isomers. In transition state **74** the approach of the hydroxyl to the iodonium ion is blocked by the substituent R^1 and the transition state has a "boat" like eclipsed conformation. This would lead to a slow cyclisation, consistent with the observations made earlier. The stereochemistry of the substituents on the iodo-THF products are derived from the transition states as drawn and these also correspond to the products observed in these reactions. This provides good evidence for intermediacy of a "chair like" transition state.

Scheme 90



(73)

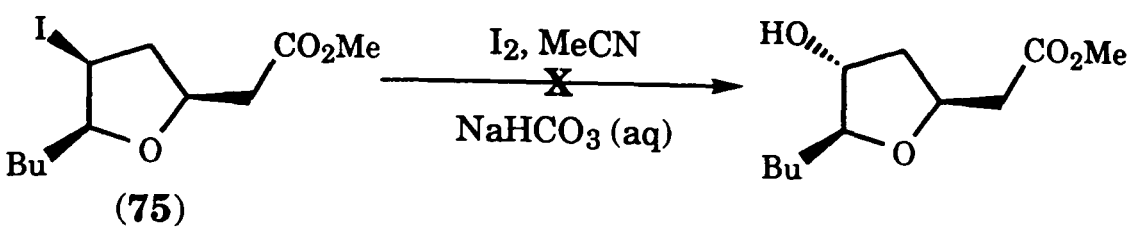
(74)

The hindered nature of transition state **74** also helps to explain perhaps the most unusual result in this field, namely the cyclisation of (Z)-β-hydroxy-δ-alkenoates to give hydroxy-THFs.

At first, the more obvious mechanistic explanations for the formation of hydroxy-THFs from the iodocyclisation of (Z)-β-hydroxy-δ-alkenoates were investigated, in two isolated studies by Bedford.[80] The

possibility of hydroxy-THFs arising from an S_N2 substitution at an initially formed iodo-THF was discounted because when the all-*cis*-iodo-THF **75** was subjected to the reaction conditions, no substitution was observed (Scheme 91).

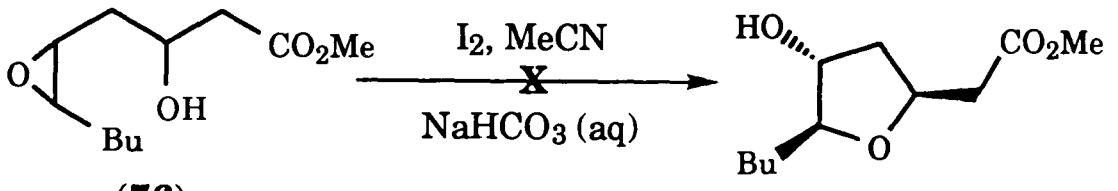
Scheme 91



(75)

A second possible explanation is the *in situ* formation and ring opening of epoxides **76** to give hydroxy-THFs. This was discounted because when such an epoxide was subjected to the reaction conditions, no THF products were observed (Scheme 92).

Scheme 92

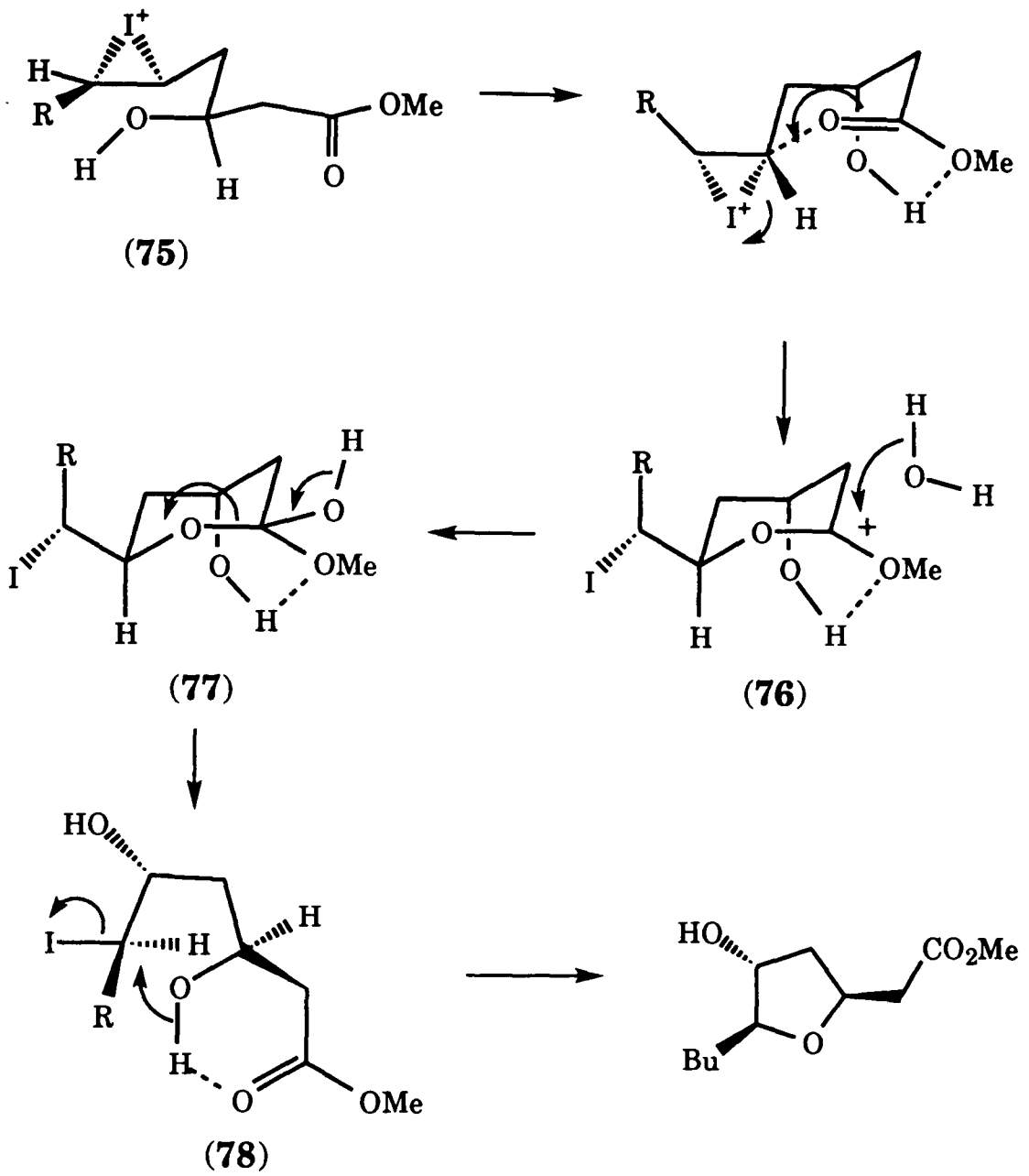


(76)

These results led to the consideration of the possible involvement of the ester function at an early stage of the cyclisation. The hindered nature of transition state **74** causes direct cyclisation to be a slow process, but in the case of general (Z)-homoallylic alcohols there are no alternative pathways. In the case of (Z)-β-hydroxy-δ-alkenoates, it is proposed that the

mechanism shown (Scheme 93) operates in preference to direct cyclisation due to the steric strain involved in transition state **74**.

Scheme 93



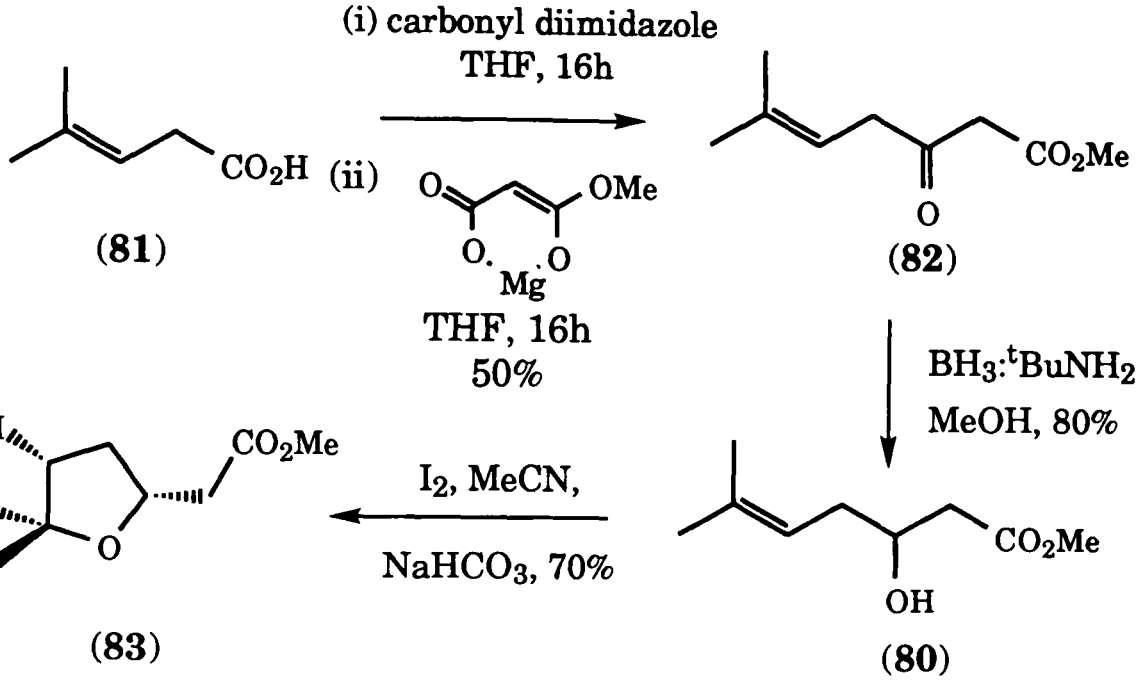
Attack of the ester function upon the iodonium ion **75** in an 6-*exo*-fashion, would yield the stabilised carbocation **76**. Attack of an external oxygen nucleophile (*eg* water) upon this carbocation would furnish the ortho-ester **77** which could then collapse, regenerating the methyl ester and giving rise to the iodo-diol **78**, as a single isomer. The enhanced nucleophilicity of the hydroxyl function in β-hydroxy-δ-

alkenoates, which is a key feature of the insensitivity of the cyclisation of (E)-β-hydroxy-δ-alkenoates to the presence of water, allows displacment of the iodine intramolecularly to give the hydroxy-THF **72**. When the cyclisation was stopped after 3 hours, an intermediate consistent by ^{1}H and ^{13}C NMR and IR with the iodo-diol **78**, was isolated as the major product. This intermediate was converted quantitatively into the hydroxy-THF **72** upon treatment with sodium carbonate in acetonitrile proving that iodine was unnecessary for this final step. Although the final step of the process has now been proven to be a fairly slow displacement of iodine, the mechanism of the iodo-diol formation remains somewhat open to speculation, although the proposed route certainly does account for the observed stereochemistry.

The cationic nature of these processes means that they are only formally exceptions to Baldwin's rules, which were not intended for use in cationic processes. An interesting test case was chosen as part of the initial work of this project. The *gem*-dimethyl-β-hydroxy-δ-alkenoate **80** was synthesised in order to see whether steric hindrance would make it behave like a (Z)-β-hydroxy-δ-alkenoate or whether the extra electron donation to the iodonium ion would stabilise a positive charge sufficiently to favour a direct cyclisation in a 5-*endo*-trig fashion. Unsaturated acid **81** was prepared by a literature procedure[89] and was converted into its acyl imidazole derivative before being treated with the magnesium chelate Grignard reagent from methyl hydrogen malonate to give the β-keto ester **82**. The ester was then reduced using borane-^{t}butylamine complex to give the hydroxy ester **80**. To our surprise, this molecule underwent

iodocyclisation to give the iodo-THF **83** in good yield, despite the effects of steric hindrance. This serves to emphasise the pronounced effect that stabilisation of a cation can have upon the cyclisation of β-hydroxy-δ-alkenoates (Scheme 94).

Scheme94



(III) Generation of the Cyclisation Precursors

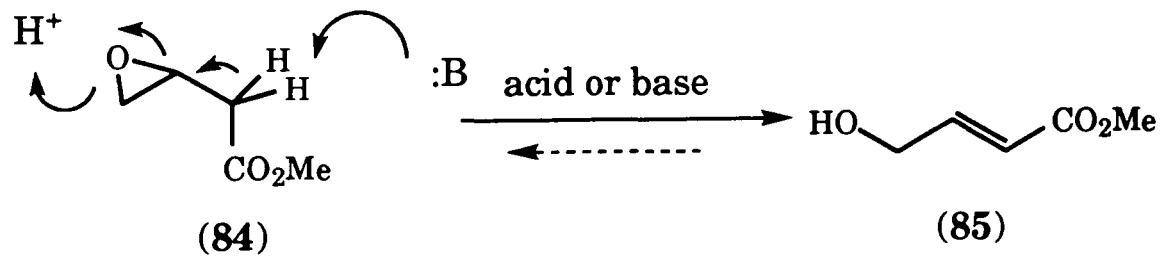
Prior to the beginning of this project, various different routes had been used by previous researchers in our group to synthesise the homoallylic alcohols required as cyclisation precursors; there was, however, no general or particularly efficient route available.[80]

The potential sensitivity of the β-hydroxy-δ-alkenoates to acid and base meant that a mild route for their preparation was required. It was decided to seek routes to these compounds which would not only yield pure geometrical isomers, to ensure the results of the cyclisations were clear

and to maximise the synthetic utility of the products, but which would also prove amenable to the incorporation of chirality into the system, which would be vital in later projected natural product target syntheses. An appropriate approach would therefore involve the generation of the chiral centre in the cyclisation precursor in a controlled way.

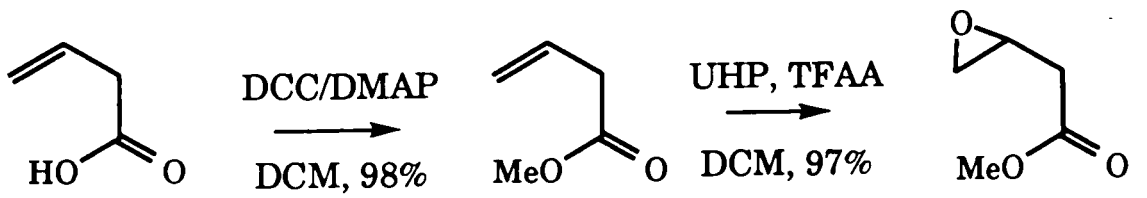
The use of methyl 3,4-epoxybutanoate **84** has allowed all of these goals to be achieved. Previous workers[80] had found this molecule difficult to prepare in usable quantities due to its high volatility (bp =110°C) and its extreme acid and base sensitivity (Scheme 95). As shown below, the acidity of the α protons is reasonably high and even treatment with carbonate will cause rearrangement to the unsaturated ester **85**. Acid also triggers ring opening of the epoxide. However, it was found that with the use of low boiling solvents and mild conditions, the epoxide could be prepared in 90% overall yield in 2 steps, in quantities of up to 20 g. Vinyl acetic acid was esterified using the DCC/DMAP method[90] in dichloromethane and the resulting ester epoxidised using buffered urea-hydrogen peroxide complex and trifluoroacetic anhydride (Scheme 96).[91]

Scheme 95



(**84**) (**85**)

Scheme 96

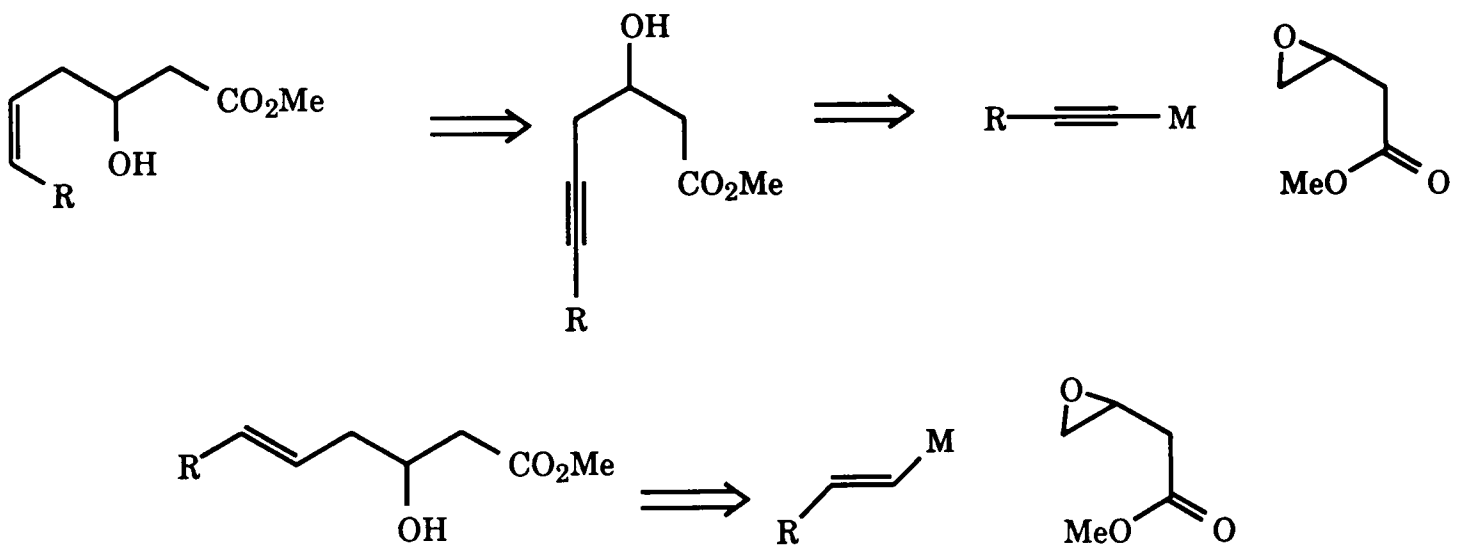


± (**84**)

The corresponding butyl ester was prepared as part of the early work of this present project, in order to reduce the volatility problems, but the failure of the (Z)-butyl β-hydroxy-δ-alkenoates formed to cyclise in high yield meant that this approach was not continued.

Treatment of the epoxide **84** with an appropriate nucleophile then leads to a convergent route to the required β-hydroxy esters. The use of (E)-vinyl anions would give the (E)-β-hydroxy-δ-alkenoates whilst treatment with acetylide anions, and subsequent Lindlar reduction would lead to the (Z)-β-hydroxy-δ-alkenoates (Scheme 97).

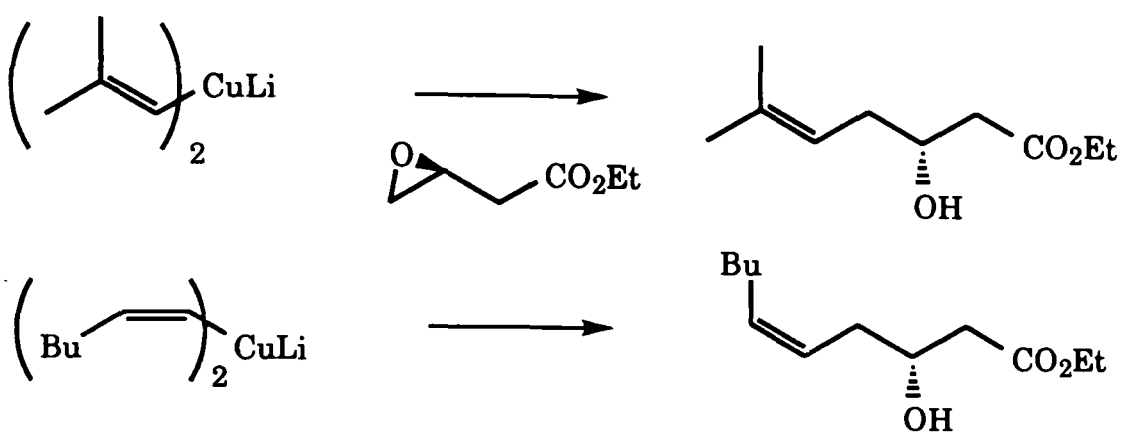
Scheme 97



Possible viable sources of non-basic vinyl anions appropriate for epoxide opening include vinyl alanate complexes[92] and vinyl cuprates, whereas simple lithio acetylides can be used to open epoxides.

Chiral ethyl 3,4-epoxybutanoate has been synthesised in 5 steps from (S)-malic acid by Larchevêque[93,94] who demonstrated that it was opened highly regioselectively by various nucleophiles, especially vinyl cuprates (Scheme 98).

Scheme 98

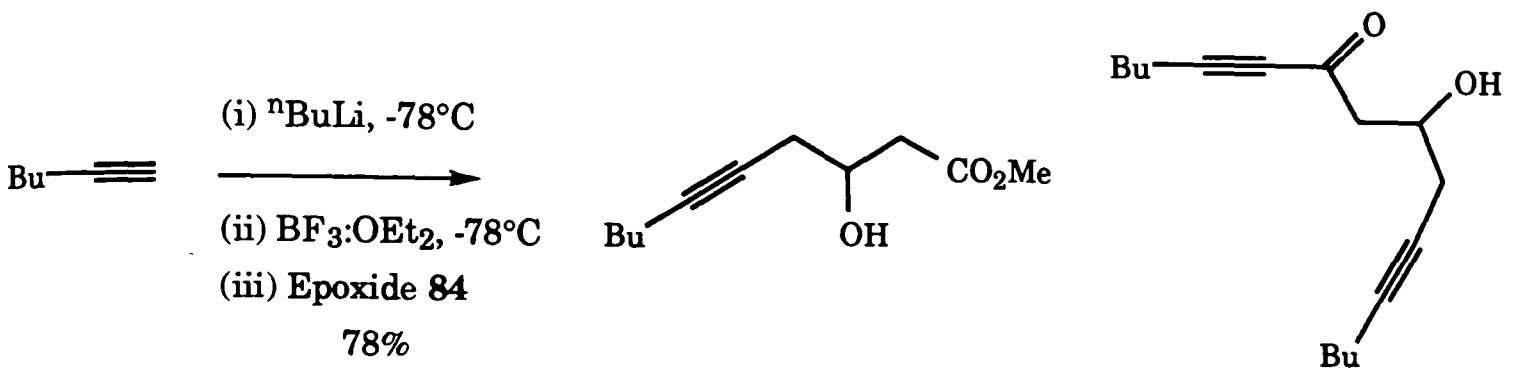


The methyl ester has also been resolved using pig liver esterase.[95]

(A) (Z)-β-Hydroxy-δ-alkenoates

The general approach adopted to all the (Z)-β-hydroxy-δ-alkenoates synthesised in this project has been the coupling of acetylide anions, generated using butyl lithium, with the (±)-epoxy ester **84** in the presence of a stoichiometric amount of boron trifluoride etherate. The original procedure was developed by Yamaguchi.[96] The approach used during this project was adapted because the excess acetylene used in the original procedure also attacked the ester function of the substrate at the carbonyl site to give the dialkynyl ketone **86** as a side product. The coupling was carried out for 15-20 minutes at -78°C which gave high yields of the β-hydroxy-δ-alkynoate **87** and minimal ketone formation (Scheme 99).

Scheme 99



Lindlar reduction of these acetylenes was accomplished in high yield to give the (Z)-β-hydroxy-δ-alkenoates as single isomers according to ^{13}C NMR spectroscopy. The commercially supplied Lindlar catalyst (Aldrich) proved unreliable and so the catalyst was prepared from 5% palladium on barium sulphate by poisoning with quinoline, prior to each reduction.[82]

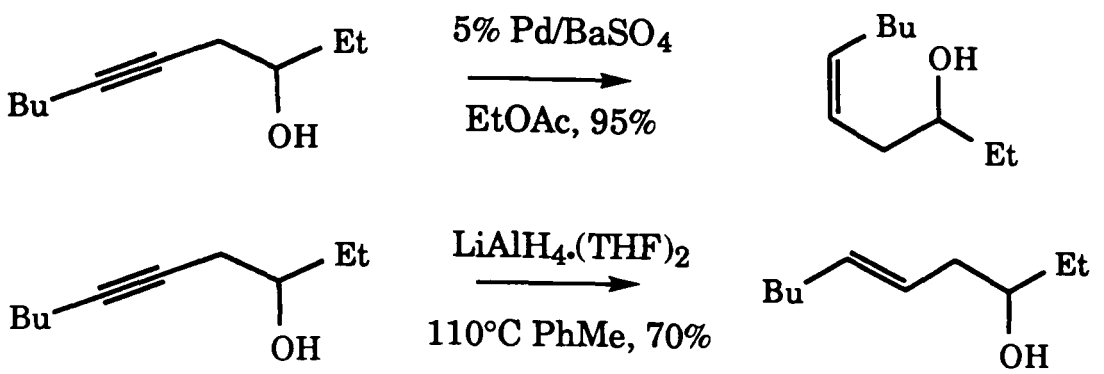
(B) (E)- and (Z)- Homoallylic alcohols

These molecules can generally be accessed by a coupling reaction of an acetylene and an epoxide under boron trifluoride catalysis, as described by Yamaguchi.[96]

The acetylenes produced can be reduced specifically to give (E)- or (Z)-homoallylic alcohols as single geometric isomers. Lindlar reduction, as previously described, gave the (Z)-isomers in high yield, pure by ^{13}C NMR spectroscopy, whereas reduction by refluxing with lithium aluminium hydride *bis*-tetrahydrofuran in toluene over 48 hours,

afforded the corresponding (E)-isomers in approximately 75% yield, again as single isomers according to ^{13}C NMR spectroscopy (Scheme 100).

Scheme 100



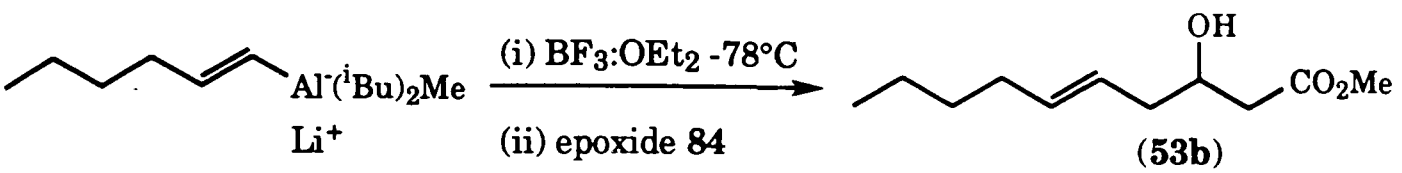
Overall, this provides routes to homoallylic alcohols which are applicable to many systems and can be applied to asymmetric synthesis.

(C) (E)-β-Hydroxy-δ-alkenoates

The synthesis of (E)-β-hydroxy-δ-alkenoates has provided many more problems than the routes to the other homoallylic alcohols. The use of lithium aluminium hydride to reduce an acetylene is obviously not compatible with the ester function. The work of Alexakis[97] led to the consideration of the use of vinyl alanates as the source of vinyl anions. This work comprised the first use of vinyl alanates in the synthesis of β-hydroxy-esters. The (±)-epoxy-ester **84** was treated with the vinyl alanate complex derived from 1-hexyne [by treatment with diisobutylaluminium hydride in hexane at 50°C for 2 hours, and reaction of the resulting vinyl alane with methyl lithium] in the presence of boron trifluoride etherate, to give the (E)-β-hydroxy-δ-alkenoate **53b** in high yield, as a single isomer,

according to ^{13}C NMR spectroscopy (Scheme 101). This pure hydroxy-ester **53b** proved extremely useful in the investigations of the iodocyclisations (Scheme 80).

Scheme 101



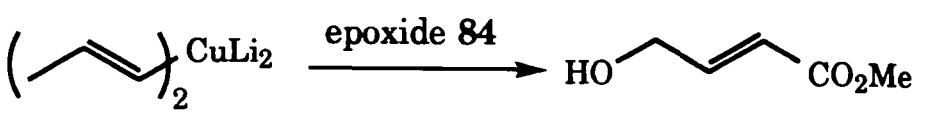
(**53b**)

However, when this new approach was extended to the alkylation of 4-phenylbutyne, smooth vinyl alane formation was not observed, except over 48 hours at 50°C in the presence of diisobutylaluminium hydride. Subsequent vinyl alanate formation in this system was not observed. Although this methodology is probably extendable to the coupling of enynes[98] to the (±)-epoxy-ester **84**, it is also limited in that smooth (E)-vinyl alane formation is not observed in the presence of heteroatoms.[99] Other methods of coupling to the (±)-epoxy-ester **84** were therefore sought.

Vinyl cuprate chemistry proved very unreliable in the generation of vinyl anions and in the subsequent coupling reactions required. The results obtained by Larchevêque[94] could not be repeated. (E)-1-Iodo-hexene was prepared[92] and used in the formation of the corresponding vinyl lithium *via* halogen metal exchange. This vinyl lithium was used in the attempted cuprate formation with copper (I) iodide and with copper (I) cyanide and also in the formation of higher cuprates using lithium 2-thienylcyanocuprate.[100] However, none of these reagents were found to couple with the epoxy-ester **84**. One reason for this could be the extreme base sensitivity of the epoxide; the major product isolated from these

attempted couplings was the ester **85** (Scheme 102). This simply results from the potential nucleophile acting as a base rather than as a nucleophile. Further work on the use of vinyl cuprates is decribed later (p. 130).

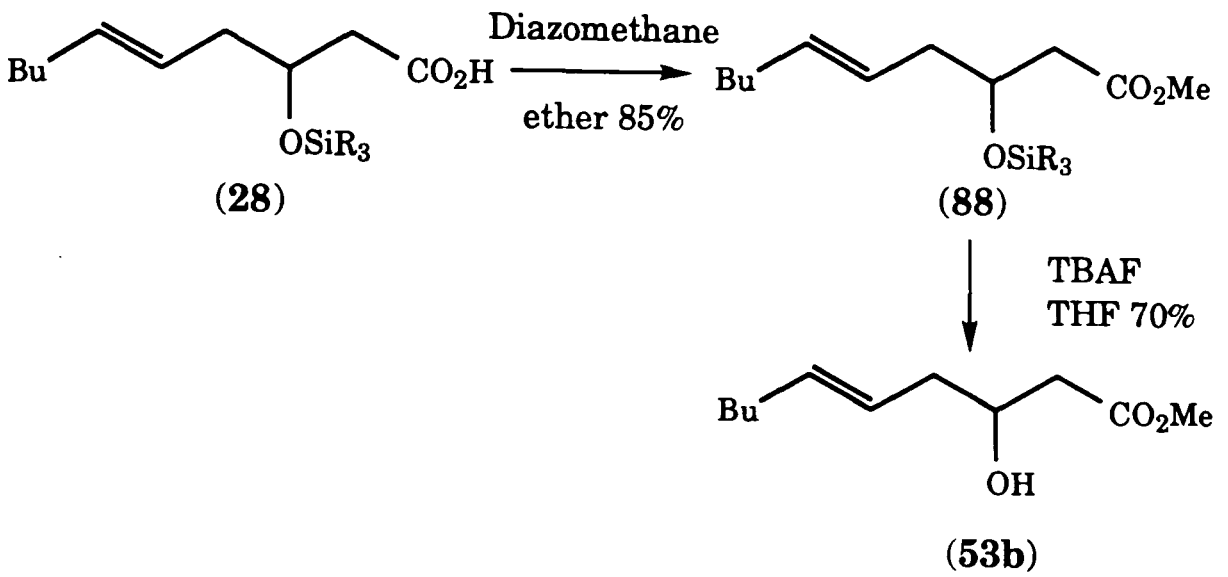
Scheme 102



(85)

Direct transformation of vinyl alanes into vinyl cuprates was advocated by Ireland[101] but this method carries with it the restrictions which apply to the generation of vinyl alanates. At this point, it was decided that the adoption of less elegant routes to the (E)-β-hydroxy-δ-alkenoates was necessary. The first approach considered was the use of the aforementioned acid **28** (p. 48); this compound was treated with diazomethane to give the silyl ether **88** in good yield. Deprotection of this molecule with tetrabutyl-ammonium fluoride in tetrahydrofuran gave the (E)-β-hydroxy-δ-alkenoate **53b** (Scheme 103) which was easily identified by comparison to earlier samples. Although this method is fairly general, it is relatively lengthy and is also incompatible with aromatic functionality which would be reduced (Birch) during the lithium in ammonia step, which is used to generate the (E)-double bond.

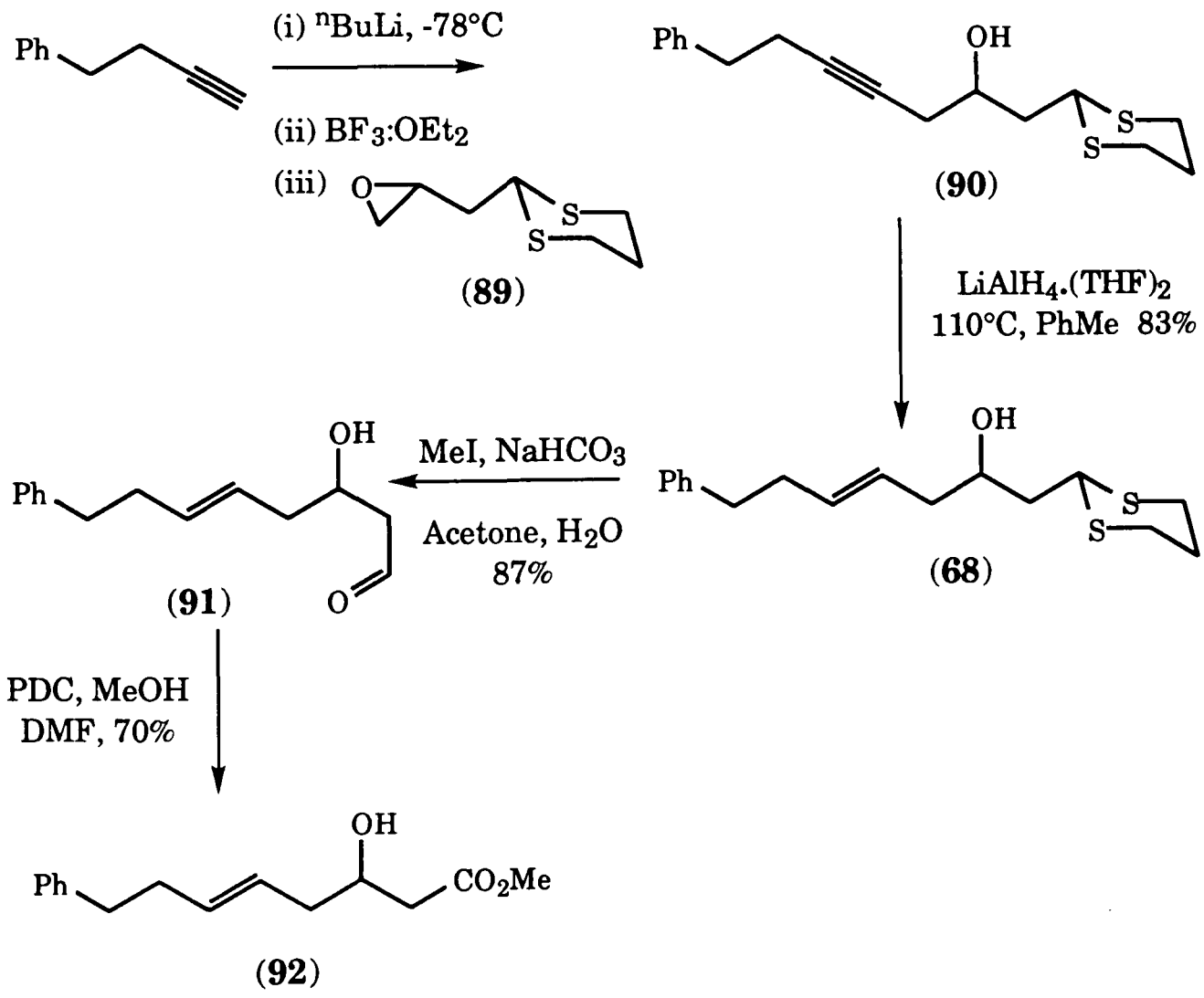
Scheme 103



It was necessary to find a functional group to act as an equivalent of the ester grouping. This group needed to be simply convertible into a methyl ester group, and also needed to be stable to lithium aluminium hydride reduction at high temperatures. The dithiane group was investigated with this in mind, because the epoxide **89** had been prepared in homochiral form by Bênechie.[102] The racemic epoxide **89** was prepared by literature methods[103] and was coupled in reasonable yield to 4-phenylbutyne under standard Yamaguchi conditions[96] to give the dithianyl acetylene **90**. This was reduced using lithium aluminium hydride *bis*-tetrahydrofuran in toluene to furnish the alkene **68**, in high yield, as a single geometrical isomer by ^{13}C NMR. This alkene was treated with excess methyl iodide in wet acetone, at reflux in the presence of sodium carbonate, to give the aldehyde **91** in good yield. Addition of further portions of methyl iodide to the mixture was necessary in order to obtain a good conversion. Hydrolysis of the dithiane group with N-chlorosuccinimide[104] was attempted without success; the dithiane

appeared to be stable to these reaction conditions. The aldehyde **91** was oxidised directly to the methyl ester **92** using pyridinium dichromate in dimethylformamide in the presence of methanol (Scheme 104).[105] This involves direct oxidation of the dimethyl acetal which occurs rapidly; the methanol solvent is only oxidised slowly under the reaction conditions and there was no oxidation of the secondary hydroxyl present in the substrate. The data for this pure geometrical isomer were compared to that of the pure (Z)-isomer (Scheme 86) and the two compounds were shown to be different.

Scheme 104



Oxidation of the aldehyde to the corresponding acid was also attempted using potassium permanganate in ^{t}butanol[106] and also with

silver(I) oxide,[107] but with little success. The dithiane based approach proved to be fairly general but it is by no means ideal and other routes to accomplish the synthesis also need to be investigated.

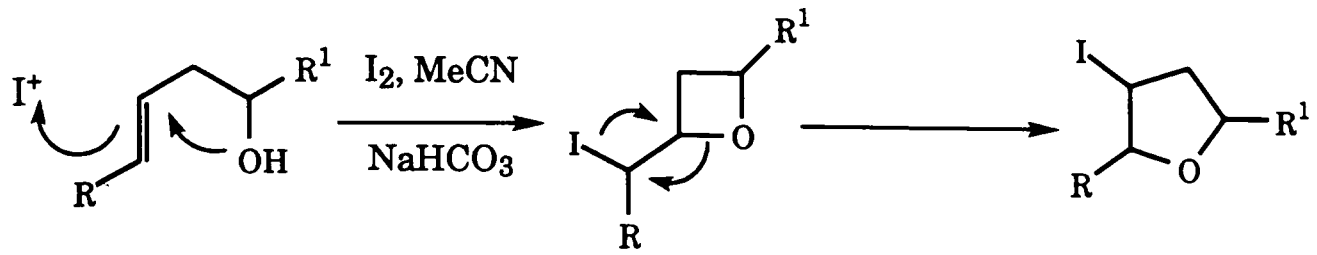
In conclusion, the synthetic importance of these reactions makes it slightly surprising that the iodocyclisation of homoallylic alcohols has not been explored before. The susceptability of these systems to solvolysis of the iodonium ion, and the fact that the cyclisation is formally a 5-*endo*-trig process, goes some way to explaining this. The processes are, however, not strictly governed by Baldwin's rules due to their cationic nature, so the term 5-*endo*-trig is only an approximate description of the reactions.

The synthetic utility of the iodoetherification of homoallylic alcohols is extensive. However, the cyclisation of the (Z)-isomers needs further optimisation because the water which is generated during the course of the reaction causes some solvolysis to occur. This leads to the somewhat lower yields. Higher yields may well be obtained if the water produced can be removed, perhaps by the inclusion of molecular sieves.

The possibility that these processes occur *via* an initial 4-*exo*-trig cyclisation to give an iodomethyl oxetane and subsequent dyotropic rearrangement to give the tetrahydrofuran, has been considered (Scheme 105). These processes are known in lactone systems under Lewis acid catalysis; indeed Black[108] has investigated them extensively. However, no evidence for the proposed oxetane intermediates has been seen, even when the reactions have been stopped after less than five minutes. Therefore, if these intermediates exist, their rearangement must be almost

instantaneous.

Scheme 105



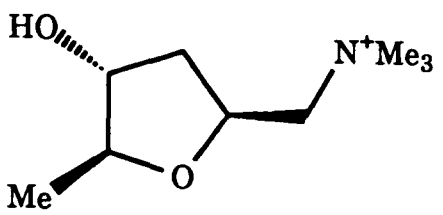
The cyclisation of (Z)-β-hydroxy-δ-alkenoates is also a very synthetically useful process. An overall stereospecific *trans*-dihydroxylation of a double bond, controlled by a remote hydroxyl group, is achieved. This is in many ways complementary to the chiral *cis*-dihydroxylations introduced by Sharpless and others.[109] The limitation of this process to β-hydroxy-esters is still under investigation, but at this stage it does present a restriction of the synthetic utility of the process. The comparison of this technique to the Sharpless epoxidation of homoallylic alcohols is favourable, as only approximately 30% enantiomeric excess is obtained from such an epoxidation.[110]

CHAPTER THREE

The Total Synthesis of Muscarine

The Total Synthesis of Muscarine

(I) Introduction

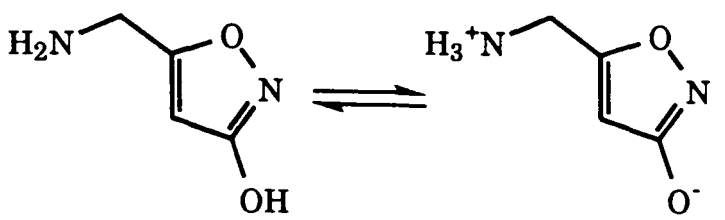


(93)

L-(+)-Muscarine **93** was the subject of intense interest[111] long before its structure was first determined by X-ray crystallography in 1957.[112] Indeed, the plot of a murder mystery novel, published in 1930, turned upon the difference between natural and synthetic muscarine.[113]

Muscarine is the major toxic principle found in the well known mushroom *Amanita muscaria* (Fly agaric), a common, but dangerous feature of deciduous woodland in autumn. It is, however, not the only biologically active alkaloid isolated from this species. In fact, the related alkaloid muscimol **94** (Scheme 106) is responsible for the notorious hallucinogenic effects of the mushroom, which have led to its ritualistic use by the Shamen and medicine men of Siberian tribes, and to the cults of mushroom worship among South American indians.[114] Muscarine has also been isolated from *Amanita phalloides* (death cap mushroom) and certain species of *Inocybe* and *Clitocybe*.

Scheme 106

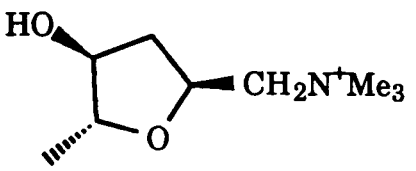


(**94**)

The pharmacological action of muscarine upon smooth muscle so resembles that of acetyl choline that direct action on cholinergic receptors in the autonomic nervous system has come to be known as "muscarinic" action. Muscarine is a selective agonist of acetyl choline in the smooth muscles of the gastro-intestinal tract, eye, exocrine glands and heart. Recently, pharmacological investigations with selective antagonists evidenced distinct sub-types of muscarinic receptors. The receptors in the central nervous system and peripheral ganglia (M_1), are distinguishable from the receptors of the cardiac cells (M_2) and also from those of the smooth muscles and exocrine glands (M_3). There is renewed interest in the muscarinic field because of the discovery of a relationship between cholinergic deficits in cortical and hippocampal areas and the pathology of Alzheimer's disease. Current activity in exploring compounds which may be specific agonists or antagonists of individual muscarinic receptors is intense. This means that a readily adaptable synthesis of muscarine and its analogues, particularly those where changes are made at C-2 (*ie* where the methyl group at C-2 is exchanged for another functional group) and which retain activity, would be of great synthetic value.

Muscarine isolated from natural sources is frequently

contaminated with *allo*-muscarine **95** and its purification is tedious and impractical. For this reason, pharmacological studies are generally carried out using synthetic material. This means that short and efficient syntheses of L-(+)-muscarine are of utilitarian value.



(95)

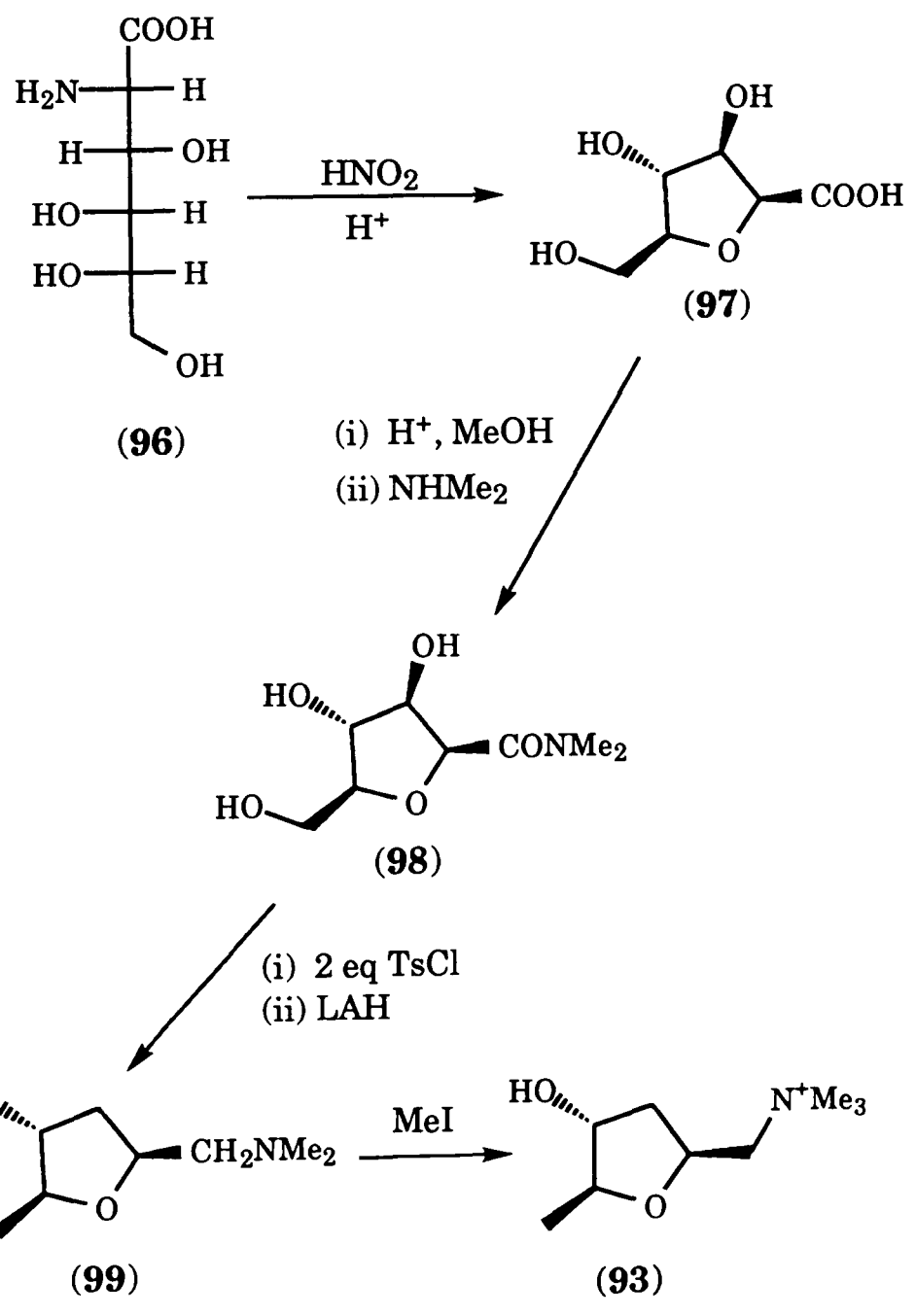
(II) Approaches to Muscarine

There have been numerous asymmetric total syntheses of muscarine, some of which are genuinely asymmetric while others involve the separation of enantiomers. There have also been a number of achiral syntheses. A wide ranging review of the area was published in 1984.[115] As part of this chapter, all the syntheses of muscarine published to date will be evaluated in terms of flexibility (*ie* ease of incorporation of new functional groups to the muscarine skeleton), practicality (*ie* number of synthetic operations involved and the scale upon which these operations can be carried out), overall yield and stereo/enantioselectivity. A new synthesis of muscarine utilising the iodocyclisation of (Z)-β-hydroxy-δ-alkenoates carried out as part of this project will also be described.

L-(+)-Muscarine was synthesised, and its absolute

configuration finally proven, in 1957, as the culmination of an extensive amount of work in the field by Hardeggar and his colleagues in a twelve step synthesis starting from L-arabinose.[116] This pioneering synthesis used the diazotisation of glucose amino acid **96** to give the tetrahydrofuran **97**, which was esterified and then converted into the amide **98**. Amide **98** is a key intermediate, analogues of which have been used in a number of subsequent approaches to muscarine.

Scheme 107



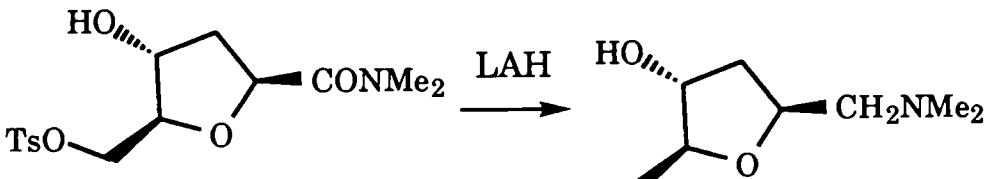
Regiospecific tosylation followed by lithium aluminium

hydride (LAH) reduction gave the amine **99**, which were then methylated to give muscarine **93** in a low overall yield (Scheme 107).

There is some scope for the synthesis of C-2 analogues of muscarine by this or by many of the subsequent carbohydrate-based approaches because the C-2 methyl group is obtained by degradation of a CH_2OH function in the original sugar. This functionality could be utilised to synthesise C-2 analogues, but this has not been attempted.

Since 1957, a variety of other carbohydrate based syntheses have been developed: Pochet and Huynh-Dinh[117] also synthesised one of the stereoisomers of the amine **99**, this time in four steps from 2-deoxyribose. The key reaction was again the reduction of an amide, this time compound **100**. Both enantiomers of muscarine and *allo*-muscarine were synthesised individually, but the number of steps required to synthesise 2-deoxyribose compromised the overall yield in each case (Scheme 108).

Scheme 108

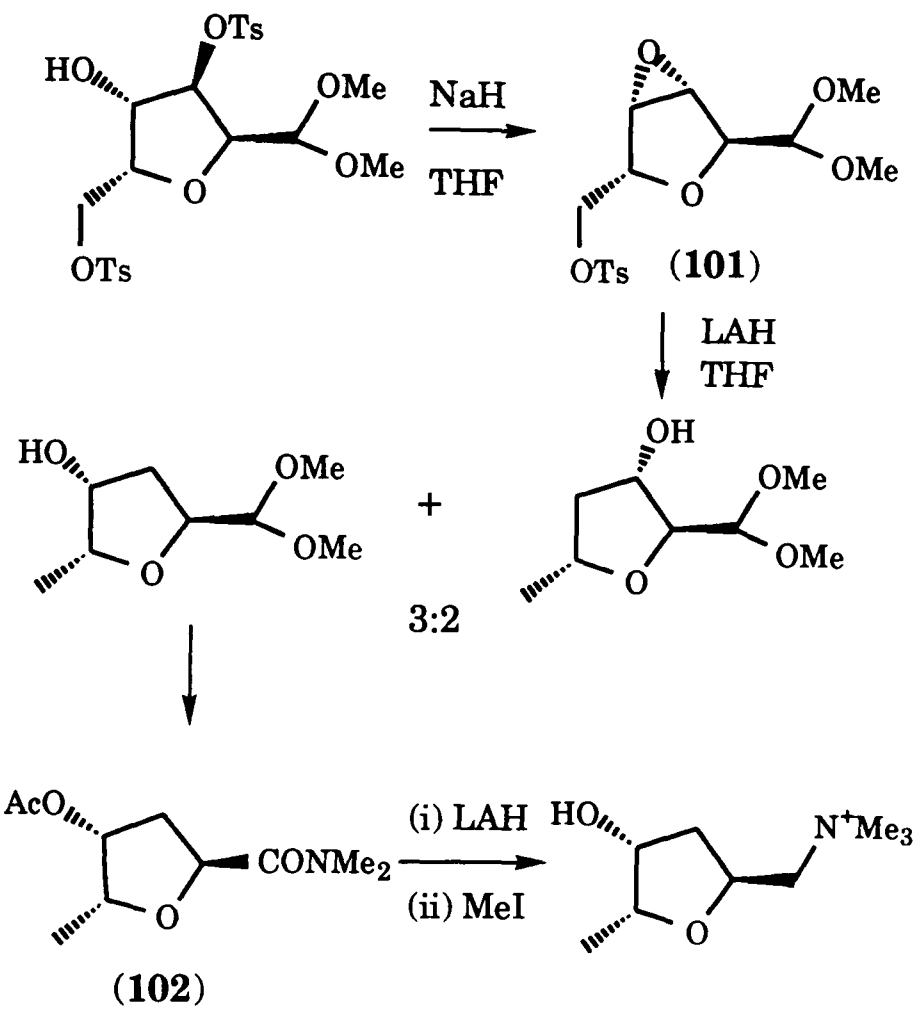


(100)

Joullie *et al*[118] synthesised D-*epi*-*allo*-muscarine from D-glucose in thirteen steps with a reasonable overall yield. The carbohydrate derived epoxide **101** was ring opened using a moderately regioselective LAH reduction. After a number of steps, the amide **102**

was synthesised, and another LAH reduction followed by methylation, furnished D-*epi-allo*-muscarine (Scheme 109).

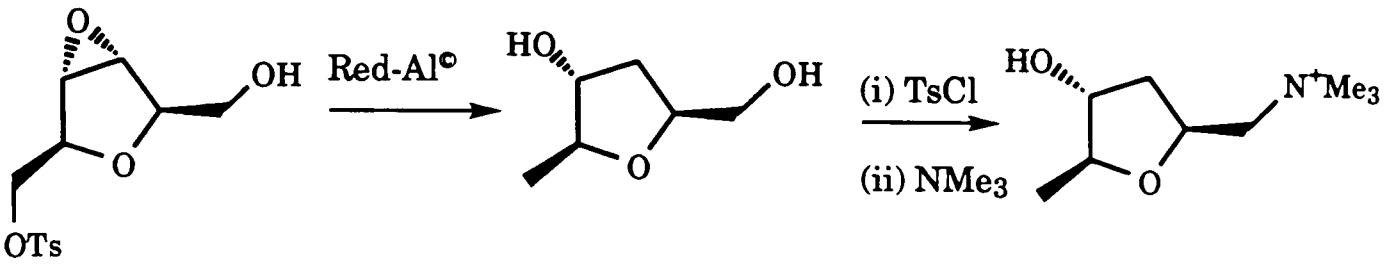
Scheme 109



Mubarek and Brown[119] improved this approach by synthesising the epoxide **103** in seven steps from D-mannitol and effecting a regiospecific ring opening using Red-Al©. Monotosylation of the diol **104** thus produced, and treatment of the resulting tosylate with trimethylamine, gave muscarine in a good overall yield of 30% for the last seven steps of the synthesis (Scheme 110). The use of diol **104** to access muscarine as first seen here, has become a common feature of

many of the more recent approaches to muscarine.

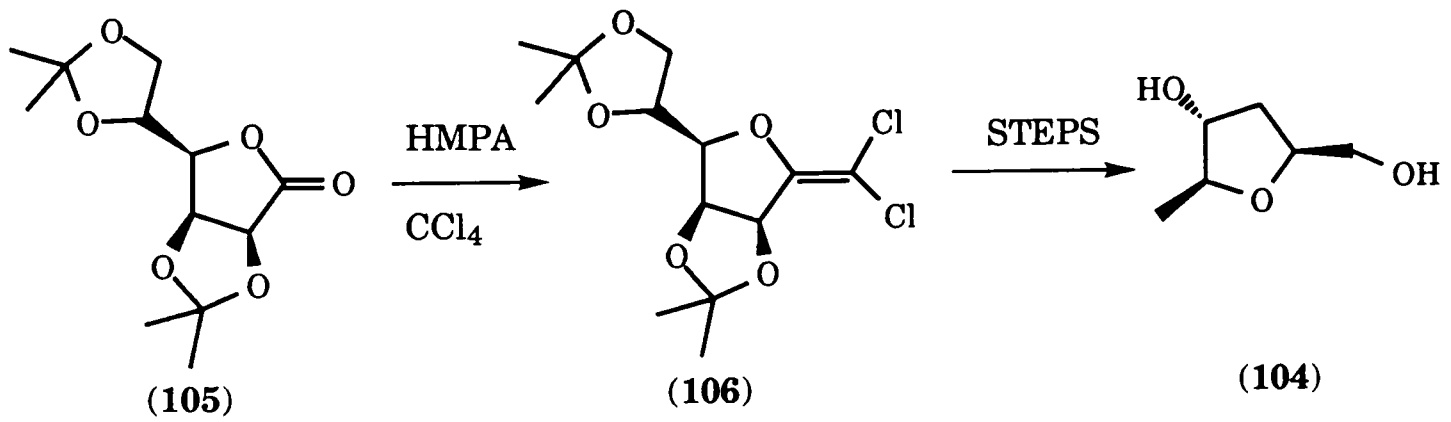
Scheme 110



(103) **(104)**

Bandouzzi and Chapleur[120] also synthesised the diol **104**, this time in nine steps from D-gluconolactone **105**. This approach featured the homologation of lactones using hexamethylphosphoramide (HMPA) in carbon tetrachloride to give the dichloride **106** (Scheme 111) which was converted into the diol **104**. The toxicity of these reagents precludes their use on larger scales and this synthesis is again not amenable to the production of C-2 analogues of muscarine.

Scheme 111

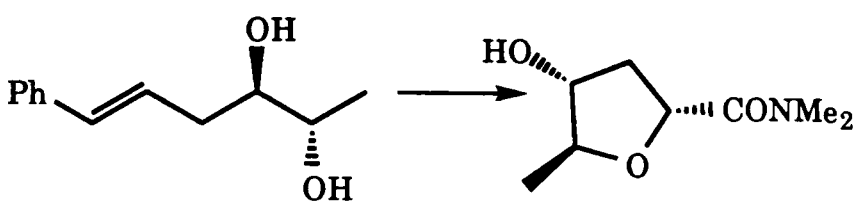


(105) **(106)** **(104)**

The first non-carbohydrate based synthesis of D-(-)-*allo*-muscarine was published by Fronza *et al.*[121] The fermentation of cinnamaldehyde with baker's yeast gave the chiral diol **107** which was converted into the amide **108** in ten steps with low overall yield. The

amide was then converted into muscarine as before (Scheme 112). Again this approach is not easily adaptable to the synthesis of C-2 analogues of muscarine because the methyl group originates from the ethanol produced by the fermentation process.

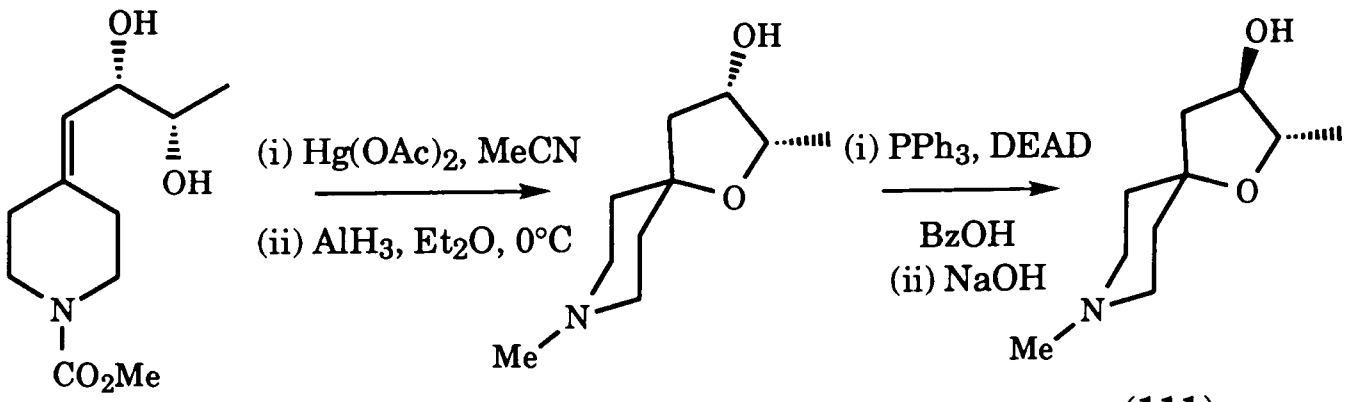
Scheme 112



(107) **(108)**

Shapiro *et al*[122] identified the problem that there were "no general syntheses of analogues of muscarine with the natural (S) stereochemistry at C-2" which is required for biological activity. The large scale synthesis of analogues of muscarine was then addressed. The piperidine **109** was cyclised in a 5-*endo*-trig fashion using mercury(II) acetate to give the THF derivative **110**, which furnished the C-5 analogue of muscarine **111** after a Mitsunobu inversion (Scheme 113).

Scheme 113



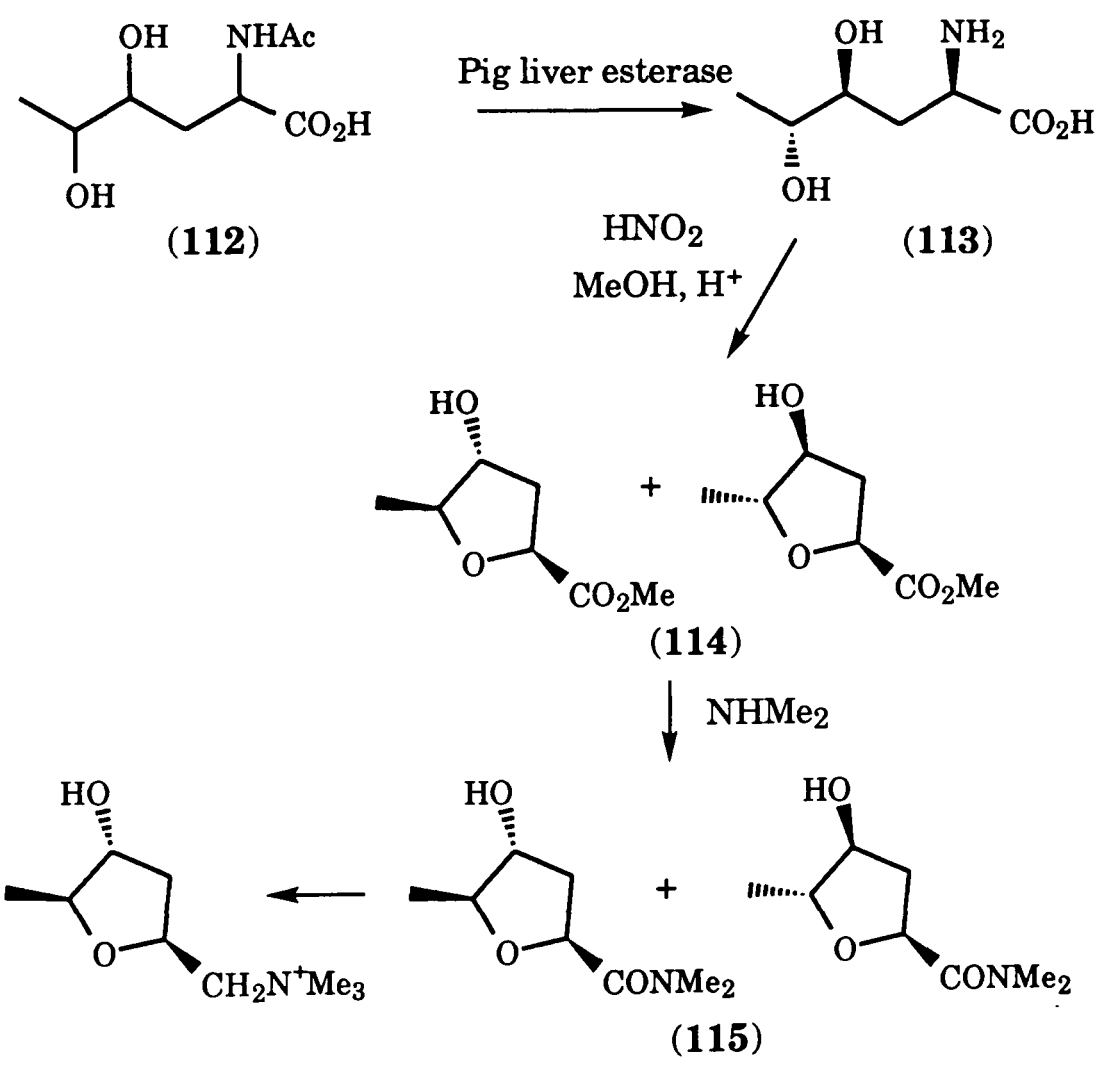
(109) **(110)** **(111)**

These compounds are potentially highly biologically active because unlike muscarine itself, they have been shown to penetrate the blood/brain barrier. These authors did not however address the

synthesis of C-2 analogues.

Whiting *et al*[123] developed a potentially flexible synthesis of L-(+) muscarine in 1972, *via* the pig liver esterase resolution of the N-acyl amino acid **112** to give the chiral amino acid **113**. Diazotisation of the amino acid **113** in the presence of methanol gave the methyl esters **114** which were converted to the corresponding amides **115**. These were then separated and individually converted as before to give a moderate overall yield of L-(+)-muscarine and L-(+)-*allo*-muscarine (Scheme 114).

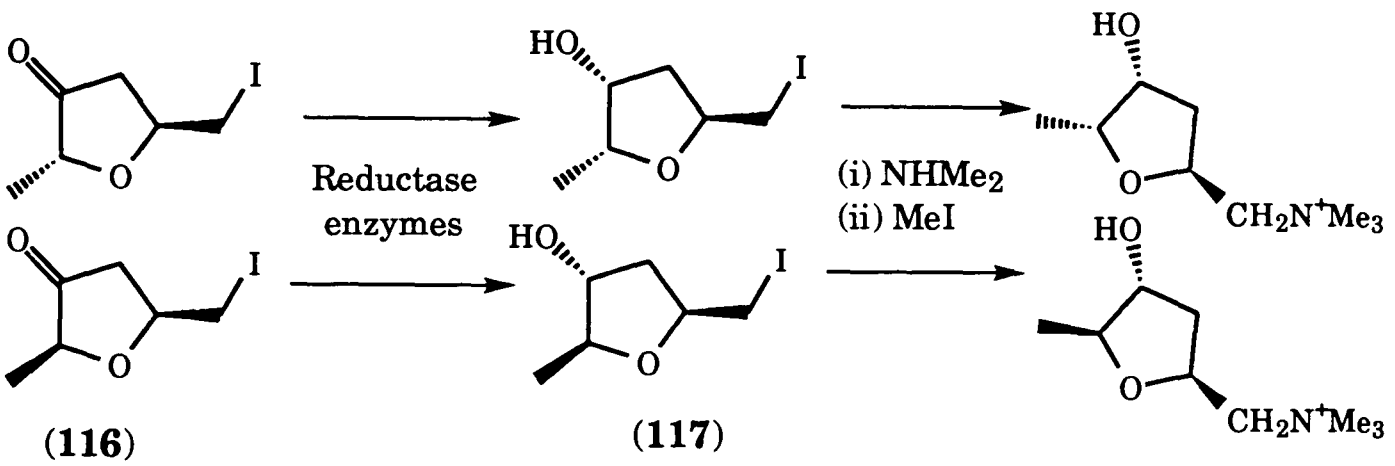
Scheme 114



Micheli *et al*[124] synthesised all 8 enantiomers of muscarine

and *allo*-muscarine by using a chemoenzymatic reduction to resolve the iodoketones **116**. The iodoalcohols **117** produced were converted in two steps into muscarines (Scheme 115). The iodoketones were synthesised using an extended reaction sequence in which the C-2 methyl group was derived from methyl lactate. Obviously this substituent would be difficult to change without taking a higher homologue of lactate through the entire sequence.

Scheme 115

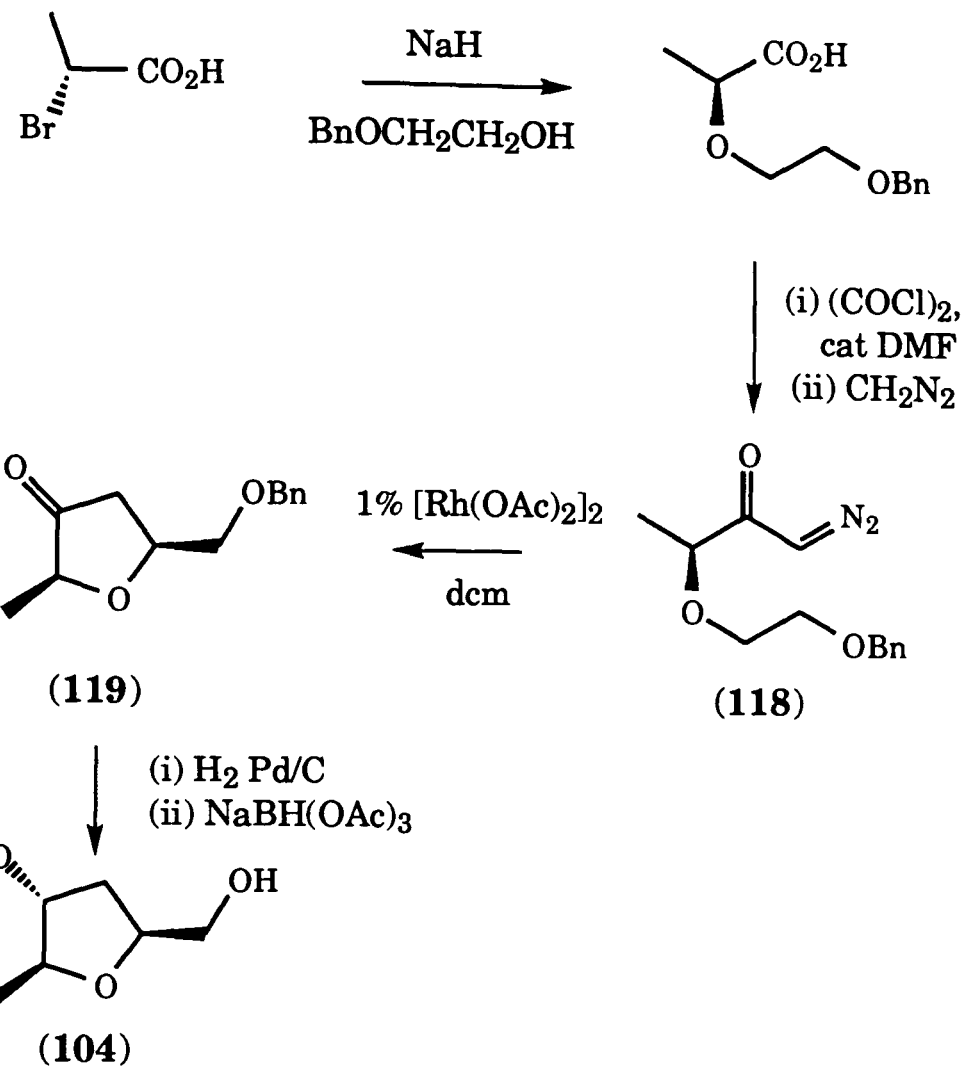


(116) **(117)**

Adams *et al*[125] devised an elegant nine step route to the diol **104** using alanine as the starting material and utilising a rhodium carbenoid insertion. The diazoketone **118** was obtained in good yield over three steps from homochiral bromopropionic acid, derived from alanine. Rhodium catalysed insertion into the C-H bond gave the ketone **119** in good yield. Removal of the benzyl protecting group was followed by a highly stereoselective reduction of the ketone using sodium triacetoxy borohydride to invoke the directing effect of the 3-hydroxyl. This procedure gives muscarine in an acceptable 7.3% overall yield and it is theoretically extendable to the synthesis of C-2 analogues by using a different amino acid as the starting material

(Scheme 116).

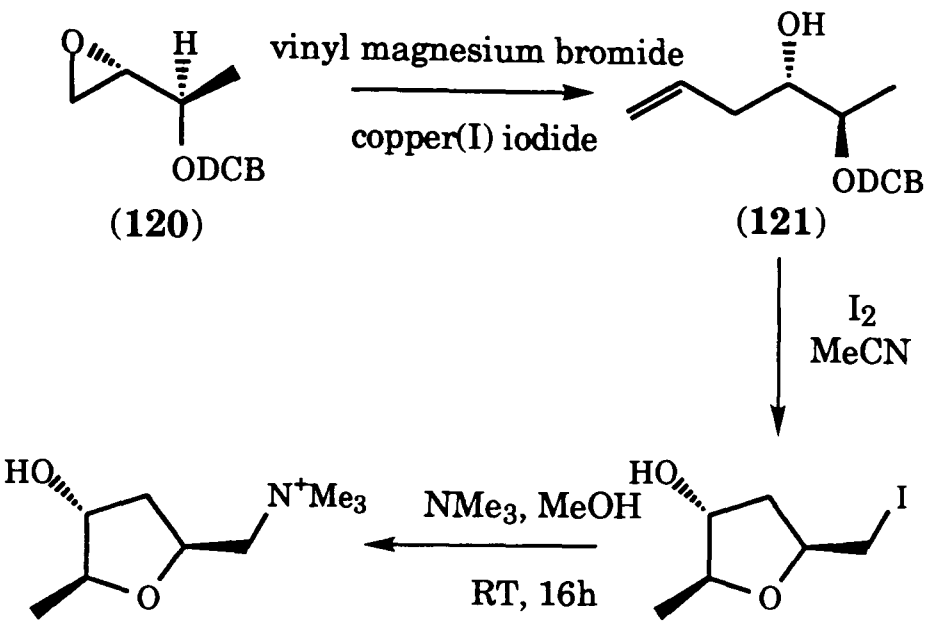
Scheme 116



A second, somewhat less flexible amino acid-based approach to muscarine, was developed by Chastrette *et al.*[126] The epoxide **120** was synthesised in six steps from threonine and treated with vinyl magnesium bromide to give the homoallylic alcohol **121**. Using the methodology for 5-*exo*-trig iodoetherification developed by Bartlett,[30] the alcohol was cyclised to give the iodide **122** in a highly stereoselective fashion. This compound was used to alkylate trimethylamine in a single step to give muscarine iodide (Scheme 117).

The rather unsatisfactory synthesis of epoxide **120** gives a rather low overall yield and does not allow the incorporation of C-2 substituents other than methyl, except by the use of substituted threonines.

Scheme 117

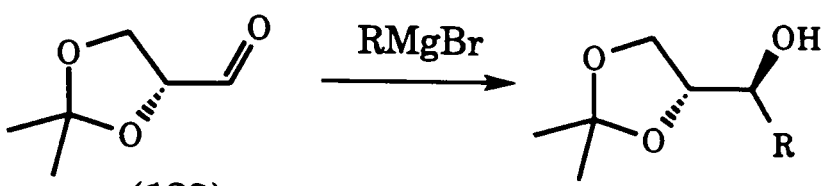


(120) **(121)** **(122)**

Mulzer[127] greatly improved this approach when he synthesised the epoxide **120** in five steps from (R)-2,3-O-isopropylidine glyceraldehyde **123**, which allowed the molecule to be accessed routinely in quantities greater than 10 g. Consequently, muscarine iodide was obtained in multigram quantities. The C-2 substituent is incorporated using a stereoselective Grignard addition to the aldehyde **123** (Scheme 118) and therefore the incorporation of C-2 substituents is potentially easy. This is a comparatively long route to muscarines and the separation of stereoisomers at the early stages of the synthesis reduces the overall yield. It does however rate as one of the most

practical routes to muscarine to date.

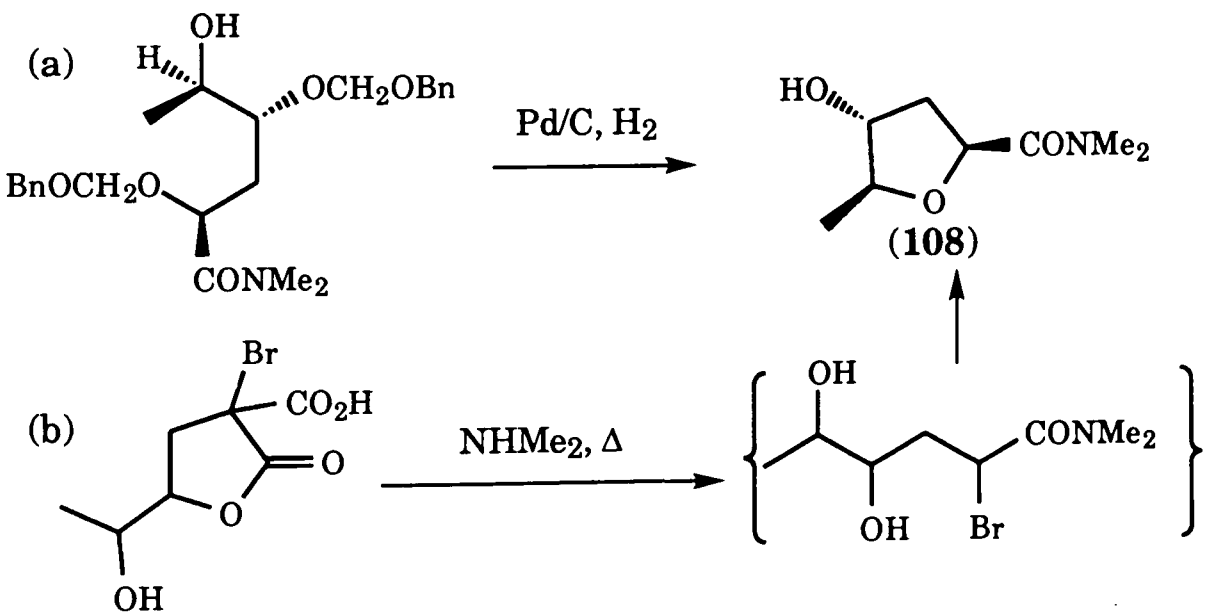
Scheme 118



(123)

Achiral syntheses of muscarine have been used by several groups to illustrate the utility of their own methodology. Still *et al*[128] [(a)] and Matsumoto *et al*[129] [(b)] both synthesied the (±) amide **108** by related cyclisations and converted it, as previously, into muscarine (Scheme 119). Although both of these syntheses illustrate new methodology, they represent relatively lengthy approaches to muscarine.

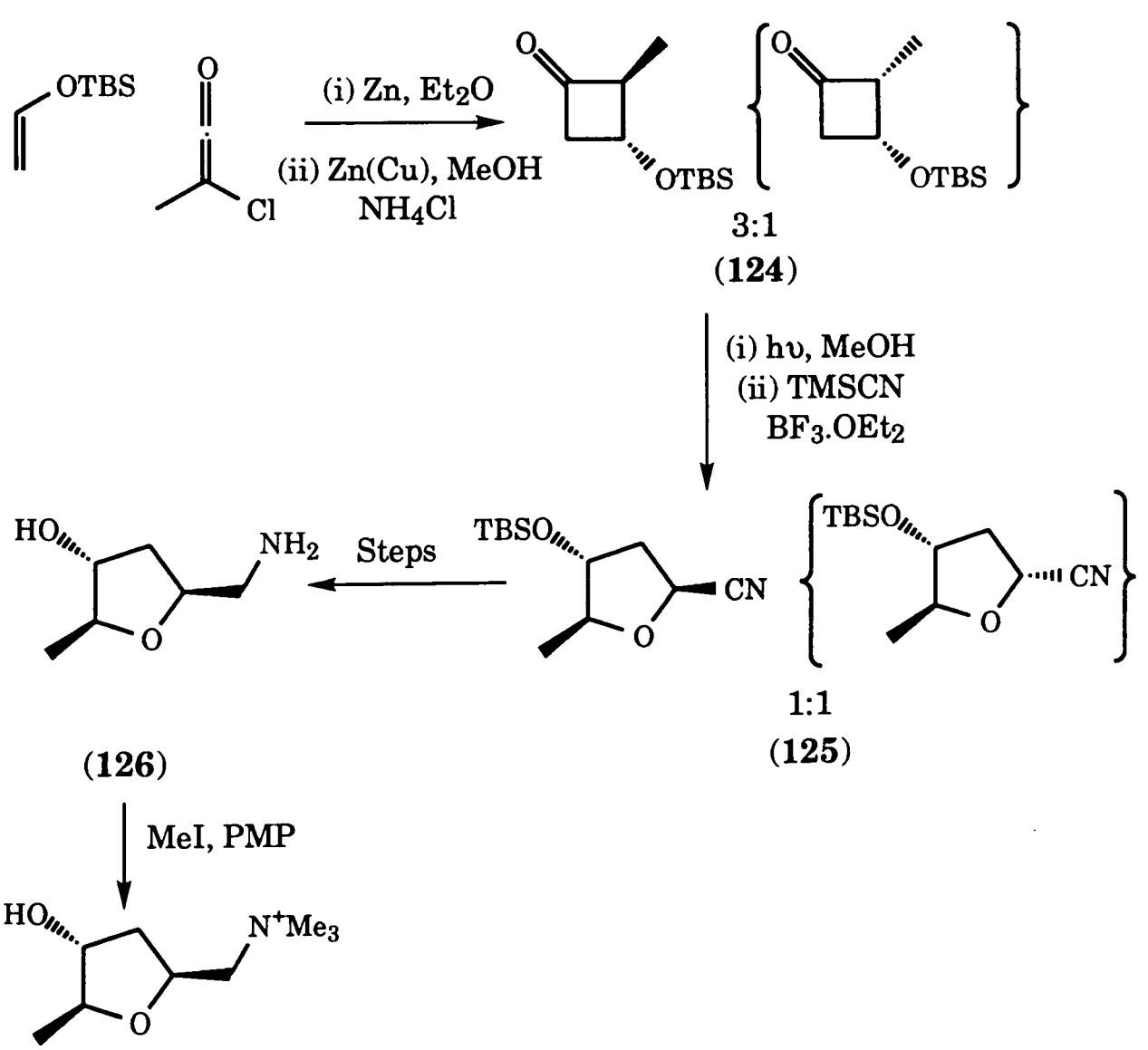
Scheme 119



Pirrung[130] synthesised (±)-muscarine using the ring expansion of cyclobutanones. The cycloaddition of a silyl enol ether

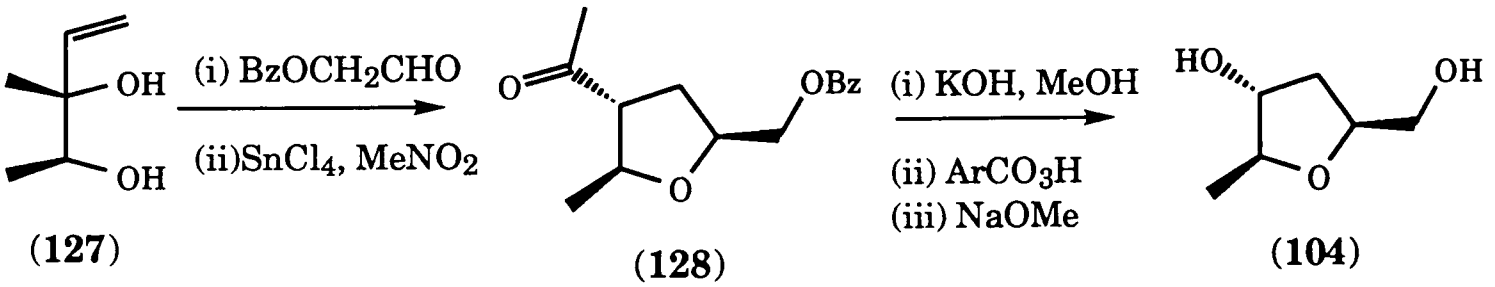
with chloromethylketene followed by the removal of the halogen group, gave the cyclobutanones **124**, which were separated. After a non-stereoselective ring expansion, and treatment with cyanotrimethylsilane, the mixture of THFs **125** was obtained. Separation and reduction gave the amine **126** which was methylated to give muscarine iodide using methyl iodide and 1,2,2,5,5-pentamethyl piperidine (PMP). The low yields and lack of stereospecificity rather tends to reduce this to an illustration of the use of ring expansion methodology (Scheme 120).

Scheme 120



Overmann[131] *et al* used the synthesis of L-(+)-muscarine to illustrate the acid promoted rearrangement of allylic diols as a route to THFs. It was found that the lactate derived allylic diol **127** rearranged to give the ketone **128** stereospecifically. After cleavage of the benzyl ether, this ketone was oxidised using the Baeyer-Villiger reaction to give the corresponding acetate, which was cleaved to give the diol **104** (Scheme 121). This compound was converted into muscarine as previously described. The overall yield for this synthesis was not high but its adaptability to allow the incorporation of a variety of functional groups makes this a potentially important route to THFs in general, and to the muscarines in particular.

Scheme 121

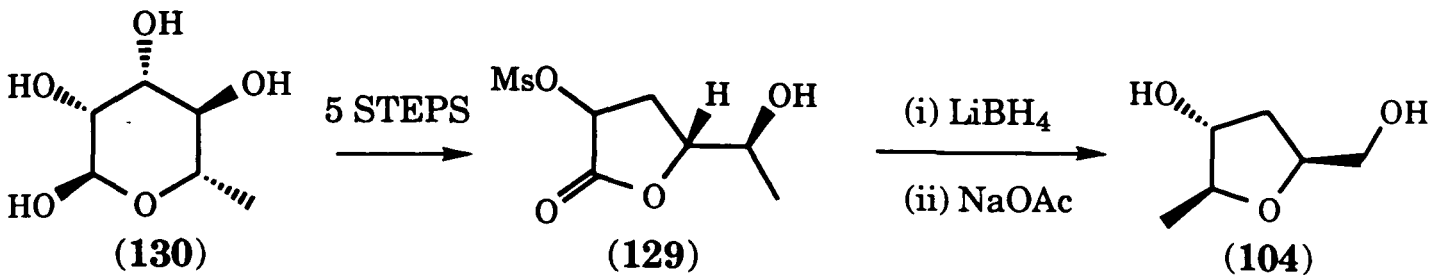


(127) **(128)** **(104)**

Fleet *et al*[132] also synthesised the diol **104** as part of an approach to L-(+)-muscarine. This synthesis involved the ring contraction of lactones **129** to give the diol **104** stereospecifically. They achieved a total synthesis of L-(+)-muscarine from L-rhamnose **130** in nine steps and an overall yield of 10%; no protecting groups were used and remarkably 5.01 g of L-(+)-muscarine tosylate was isolated (Scheme 122). Although this is most certainly one of the most

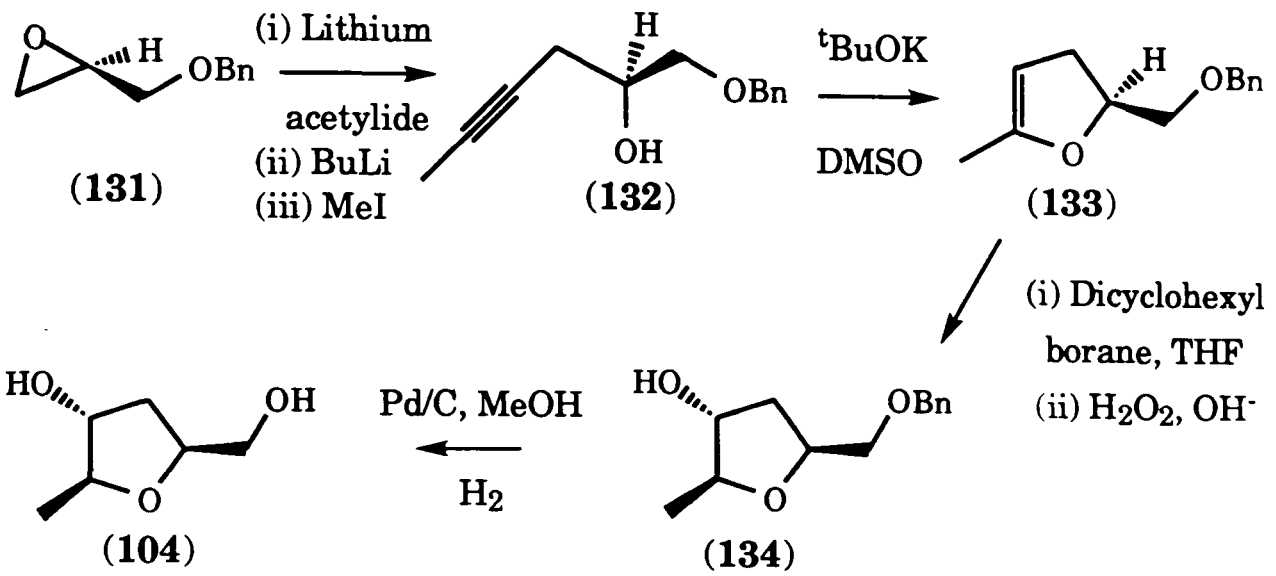
practical routes to muscarine, it does not allow for easy expansion into syntheses of C-2 analogues.

Scheme 122



Takano *et al*[133] devised a highly flexible route to muscarine starting from (R)-O-benzyl glycidol **131**; overall, 8 steps were used to access the natural product. The homochiral acetylene **132** was cyclised using potassium ^{t}butoxide in dimethyl sulphoxide to give the 2,3-dihydrofuran **133**. Subsequent hydroboration and oxidative cleavage gave the alcohol **134**, which was deprotected to give the known diol **104** (Scheme 123). This approach would allow the access of various C-2 analogues of muscarine but the overall yield is lower than the other comparable approaches.

Scheme 123

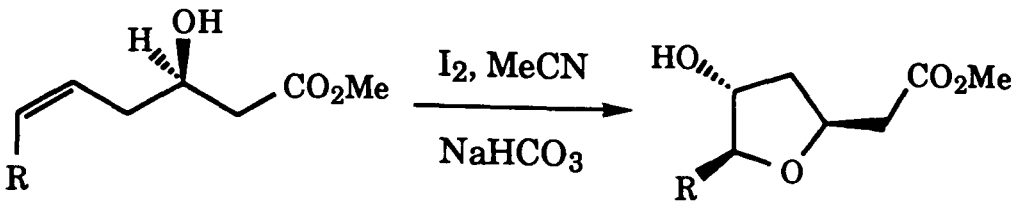


(III) (Z)-β-hydroxy-δ-alkenoates in the Synthesis of Muscarine

Despite the extensive amounts of work in this field, a gap still exists. The asymmetric synthesis of C-2 analogues of muscarine by a short synthetic procedure in high overall yield remains an exceedingly desirable target. The availability of hydroxy-THFs of the desired stereochemistry from the iodocyclisation of (Z)-β-hydroxy-δ-alkenoates, as shown in Scheme 124, offers such a route. The efficiency with which these cyclisations occur has been demonstrated in Chapter Two. Multigram quantities of a variety of hydroxy-THF esters have been routinely obtained in a highly stereoselective manner. All of these facts pointed to the use of these hydroxy THFs to synthesise muscarine and its analogues. Such a synthesis would also be useful further proof of the structure and stereochemistry of the hydroxy-THFs formed in the cyclisation reaction, by what appears to be a

rather odd mechanism (p 68).

Scheme 124



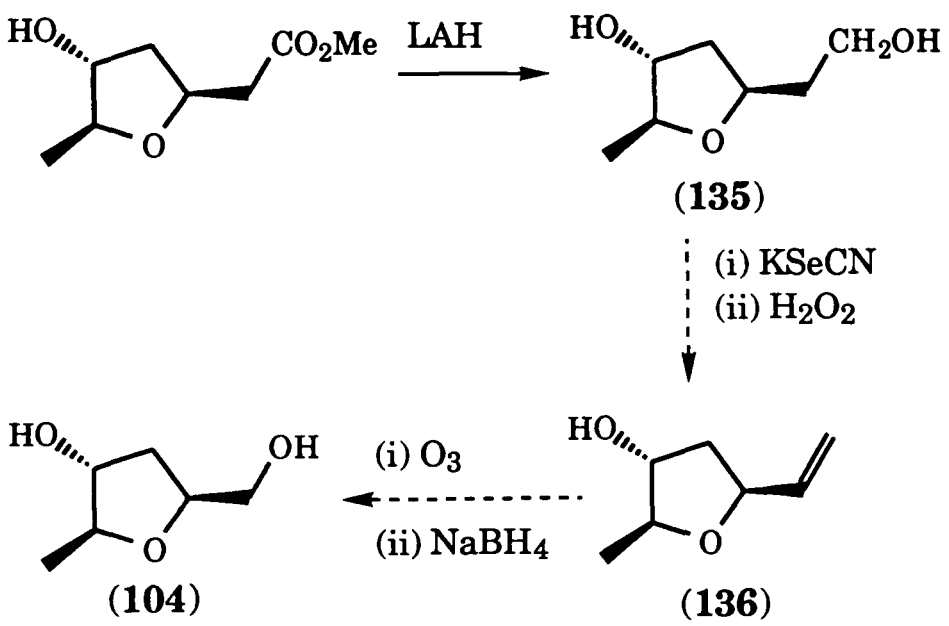
The conversion of the cyclisation products into muscarine requires a one carbon degradation of the methyl acetate side chain as shown in Scheme 125.

Scheme 125

Problems reported in the saponification of these ester groups by a previous researcher in this group[80] at first led to the consideration of the use of (Z)-benzyl β-hydroxy-δ-alkenoates, which after cyclisation could be hydrogenolysed to give the corresponding THF-acids. These acids were considered to be vital intermediates in the approach to one carbon degradation. The outstandingly poor yields obtained from the attempted cyclisation of these benzyl esters caused this approach to be abandoned [see earlier (p. 64)]. A second approach also considered was reduction of the initial ester products to give the diol **135**. Displacement of the primary alcohol with a selenocyanide function,[134]

and subsequent elimination, should then result in the formation of the olefin **136**. Ozonolysis with reductive ($NaBH_4$) work up would then furnish the known diol **104** (Scheme 126). This approach was abandoned because the displacement of the primary alcohol was not effected efficiently. Information obtained in a concurrent part of this project (p. 123), showed that the saponification of these THF acetic acid esters proceeded in good yield, without epimerisation.

Scheme 126

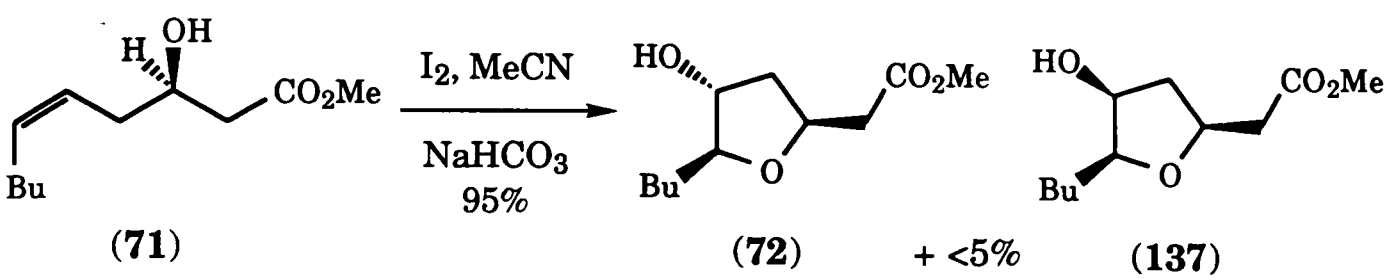


As the earlier results[80] turned out to be misleading, the way was left open to use the (Z)-methyl β-hydroxy-δ-alkenoates in the cyclisations. This allowed the high yielding reactions which were developed in the early part of this project to be utilised.

Model studies towards the synthesis of muscarine then began in earnest. The alkene **71** was available in geometrically pure form according to ^{13}C NMR spectroscopy, *via* the Lindlar reduction of the corresponding acetylene **36**, in turn obtained in high yield by the alkylation of the epoxy ester (±) **84**. Large scale cyclisations of the

alkene proceeded in high yield, as in the earlier experiments. The hydroxy-THF **72** was obtained with very high stereoselectivity; less than 5% of what was assumed to be the 3-epimer **137** was obtained (Scheme 127).

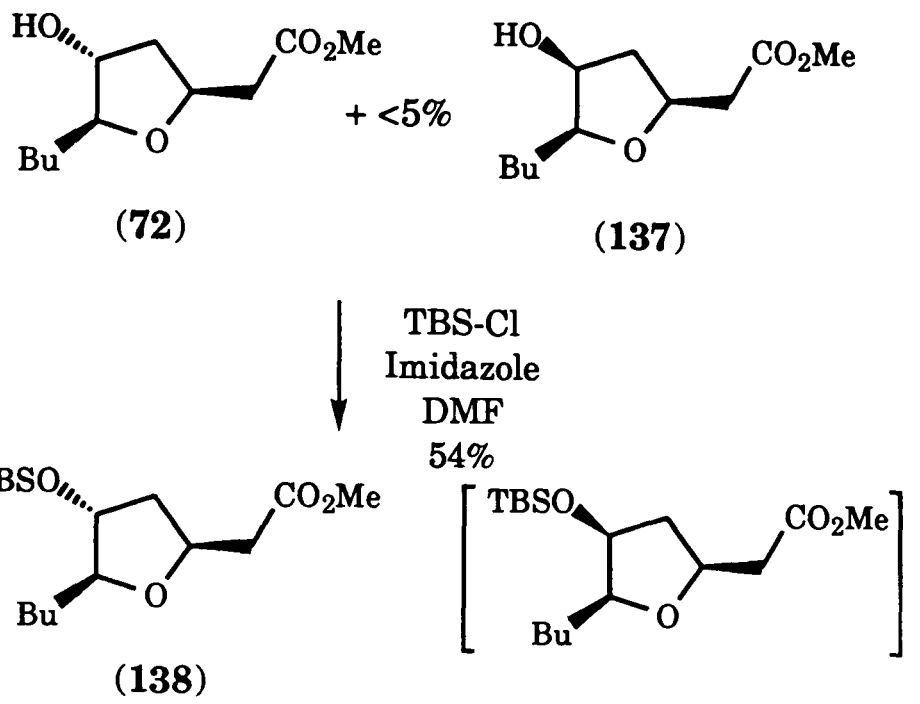
Scheme 127



(**71**) (**72**) + <5% (**137**)

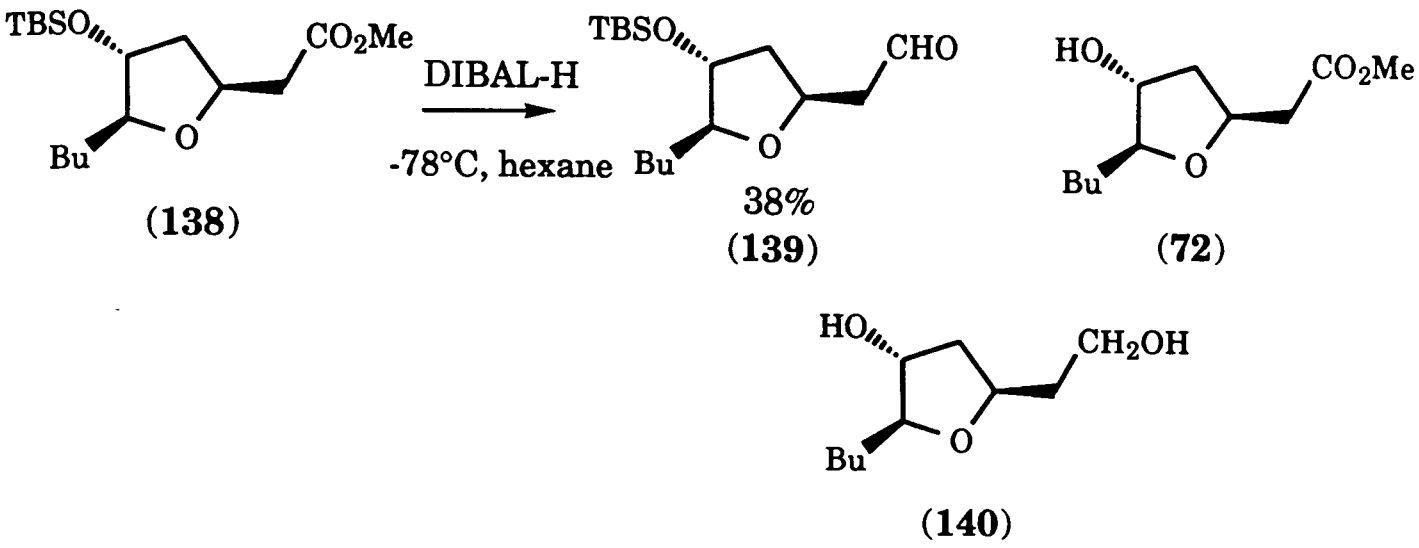
When the hydroxy-THF produced was purified by column chromatography, consistently high losses were observed. For this reason and since all the spectroscopic data had been obtained, it became common practice to silicon protect the crude reaction mixture with ^{t}butyldimethylsilyl chloride (TBS-Cl) and imidazole in DMF. Even when an extended reaction time of over 72 hours was used, the yield of the silyl ether **138** was generally low; typically around 55% (in this case 54%). However, chromatographical purification of the silyl ether **138** was facile. Disappearance of the (OH) stretch in the infra red spectrum was noted (Scheme 128).

Scheme 128



Direct saponification was not attempted here for reasons described earlier. Instead, the silyl ether **138** was reduced using diisobutylaluminium hydride in hexanes,[135] at -78°C, over 2 hours. The aldehyde **139** was obtained in a low yield of 38% after chromatography. This was the result of cleavage of the silicon-oxygen bond during the reaction. Not only did this reduce the reductant available, but it also caused the substrate to be effectively removed from the reaction, by the insolubility of the aluminium complex formed in hexane, and this caused both deprotected starting material and over reduced diol **140** to be formed (Scheme 129).

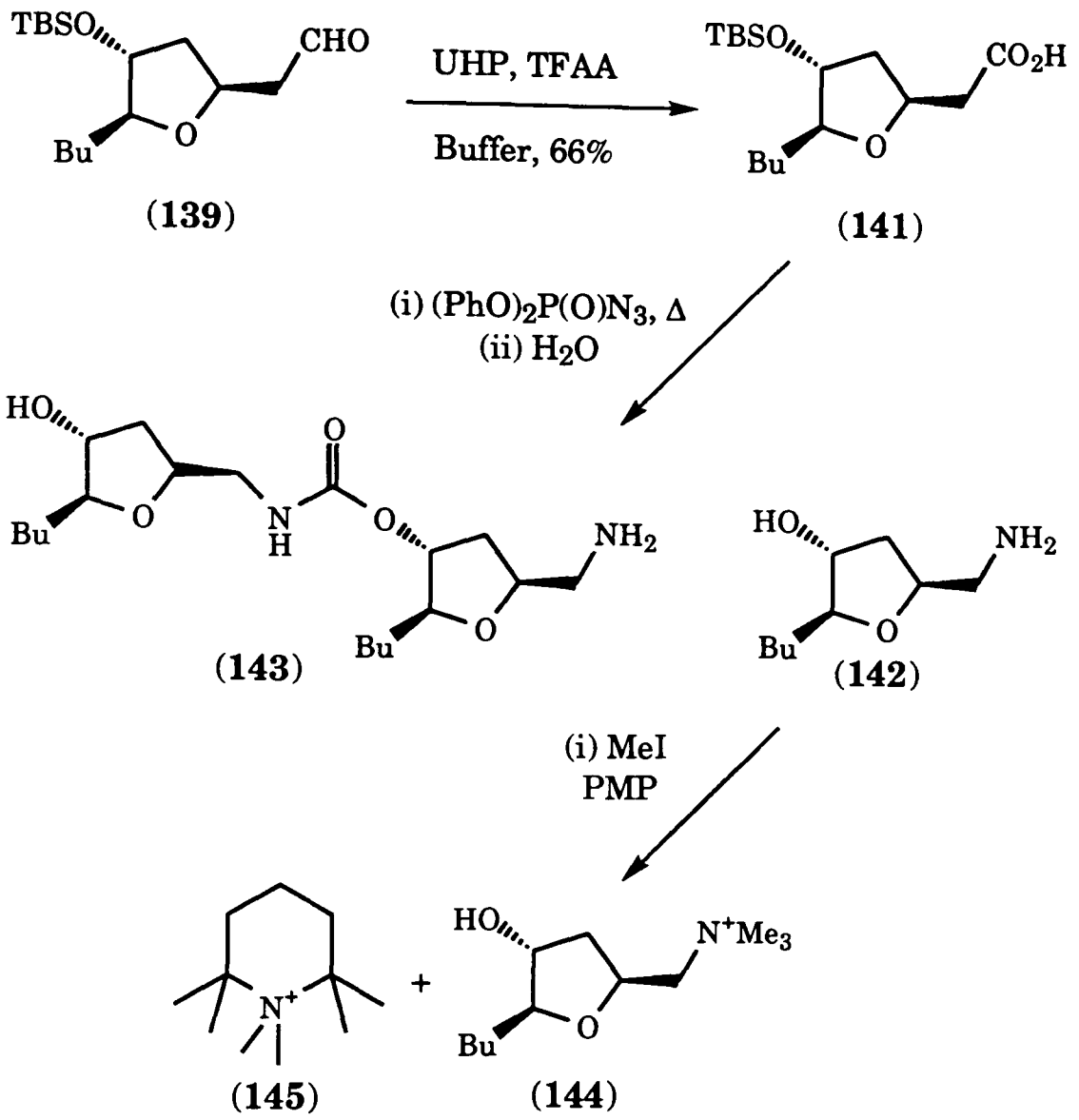
Scheme 129



The aldehyde **139** was then oxidised using the urea-hydrogen peroxide/TFAA method,[91] to give the acid **141** in a reasonable 66% yield in what amounts to a Baeyer-Villiger rearrangement in which the proton migrates. One carbon degradation of this acid was first approached using the Curtius rearrangement. Incorporation of nitrogen at this stage of the synthesis seemed to be a favourable route to approach muscarine, particularly considering the work of Pirrung[130] who converted the amine **126** into muscarine. The acid **141** was treated with diphenylphosphoranyl azide[136] to furnish the acyl azide which was heated in refluxing toluene to give the expected isocyanate. This intermediate was then hydrolysed by the addition of water to give the amine **142**. Surprisingly, the reaction was found to proceed with concomitant desilylation. The loss of the silicon must occur at a late stage in the reaction because no products from the alcoholysis of the isocyanate by the free hydroxyl leading to the dimerisation product **143** were observed. Although the yield for the process was a moderate 38%, the effective accomplishment of two steps

in one offers some compensation for this shortcoming.

Scheme 130



The amino alcohol **142** was treated with methyl iodide and PMP according to the procedure of Pirrung[130] but the separation of the muscarine analogue **144** formed from the hydrogen iodide salts of the quaternised base **145** did not prove possible; no details of how this could be achieved have been given by Pirrung (Scheme 130).

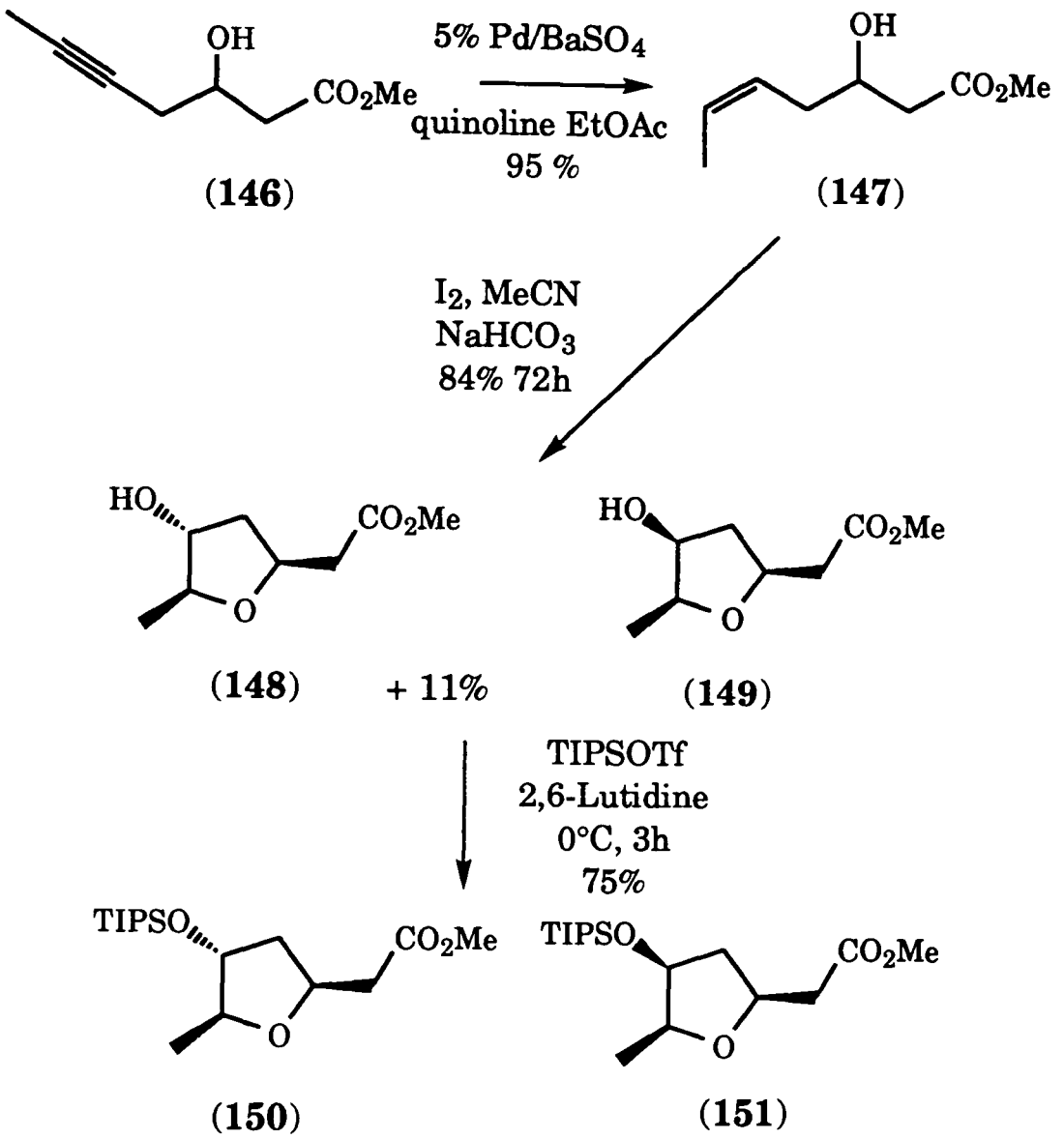
The studies then continued with incorporation of the methyl side chain required for the synthesis of muscarine; in addition, necessary improvements were incorporated into the route. Alkylation

of the (±) epoxide **84** using propynyl lithium was carried out using the Yamaguchi procedure.[96] Certain modifications were made to the procedure to take into account the fact that propyne is a gas at ambient temperature. A large excess of propyne was condensed at -78°C and a measured amount of it was then distilled into cooled THF. Excess propyne was used to compensate for evaporative losses. A good yield of the acetylene **146** was obtained after chromatography. Lindlar reduction of this acetylene was carried out in the dark as ^{13}C NMR analysis of samples hydrogenated using the normal procedure showed that greater than 50% isomerisation to the (E)-alkene had occurred. This has only been observed in the case of the methyl substituted alkene, so it may be that the energy barrier to isomerisation is lower in this case. However, excluding light during the reduction allowed the (Z)-alkene **147** to be isolated as a single geometrical isomer in excellent yield. Cyclisation of this alkene under the standard conditions led to an excellent 84% yield of the hydroxy-THF **148**. The stereoselectivity however was somewhat reduced and 11% of another hydroxy-THF **149** were observed (Scheme 131), perhaps due to the smaller methyl substituent exerting less stereocontrol. The corresponding silyl ether **151** of this compound was proven to be the 3-epimer by NOE experiments, and was shown to differ as expected from the corresponding silyl ether **150** of the hydroxy-THF **148**.

Silicon protection of the crude cyclisation product was achieved in high yield using triisopropylsilyl triflate and 2,6-lutidine in dichloromethane[137] over 3 hours at 0°C. The silyl ethers **150** and **151**

were readily separated by column chromatography. The triisopropylsilyl protecting group was chosen as it was thought likely that it would survive the Curtius rearrangement and lead to a higher yield from that step.

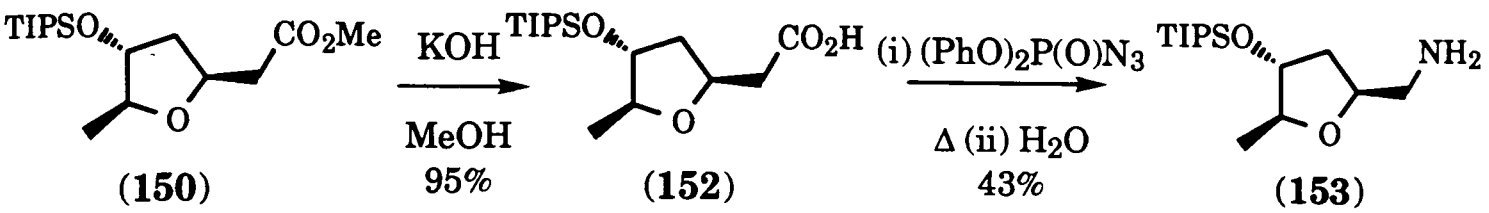
Scheme 131



Direct saponification, using potassium hydroxide in methanol, led to the acid **152** in high yield, contrary to the results of an earlier project.[80] The loss of the methyl ester resonances in the ^{1}H and ^{13}C NMR and the change in the infra red spectrum confirmed this. There was no sign of any epimerisation by ring opening of the THF. Curtius rearrangement of this acid following the earlier procedure

yielded the amine **153** without loss of the silicon group; disappointingly though, there was little increase in yield (Scheme 132).

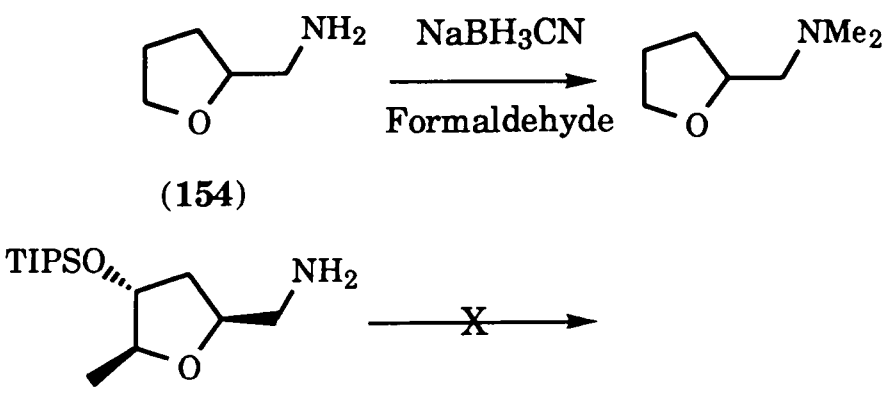
Scheme 132



(150) **(152)** **(153)**

The dimethylation of this amine using the Eschweiler-Clarke reaction with sodium cyanoborohydride and formaldehyde[138] was unsuccessful despite the success of this reaction on the model compound tetrahydrofurfurylamine **154** (Scheme 133).

Scheme 133



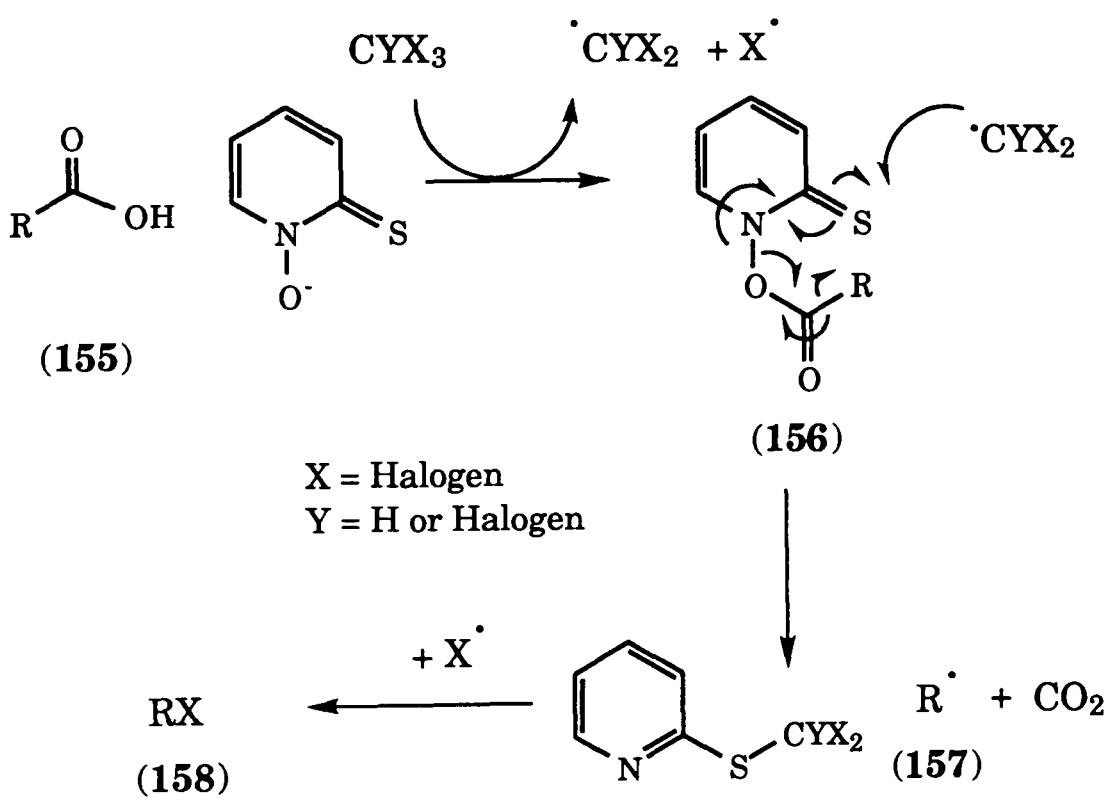
(154)

(153)

The low yields obtained in this way led to the consideration of other methods to effect decarboxylation of the acid **152**. It was then concluded that a Hunsdieker type decarboxylation was the most hopeful alternative. The traditional Hunsdieker reaction is

notoriously low yielding and inefficient; however, the modern approach features the use of the methodology for decarboxylation developed by Barton *et al.*[139] The acid **155** concerned is converted to the corresponding thiohydroxamic acid ester **156** in the presence of a source of radicals. The decomposition of the ester formed leads to the carbon centered radical **157**, which is trapped with the halogen radical to give the halide **158** (Scheme 134).

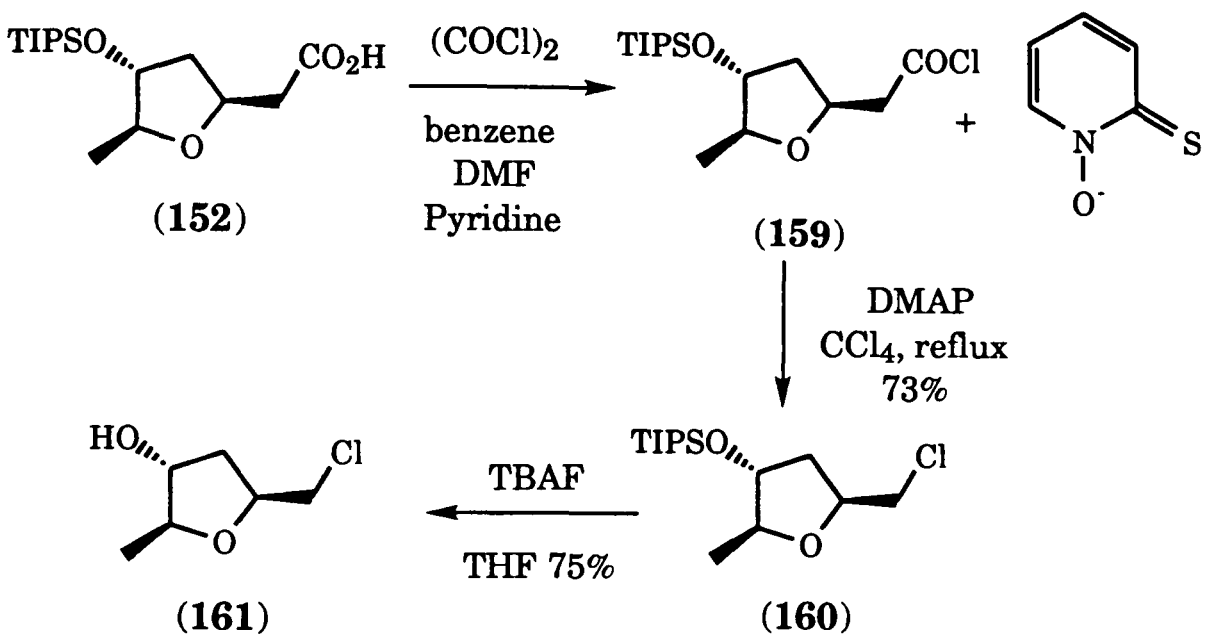
Scheme 134



The acid **152** was converted into the acid chloride **159** using oxalyl chloride in benzene in the presence of catalytic DMF and pyridine,[140] without any of the expected acid catalysed ring opening. Treatment of this acid chloride with 2-mercaptopyridine-N-oxide, sodium salt and 4-dimethylaminopyridine (DMAP) in carbon tetrachloride at reflux, gave the chloride **160** in a good yield after

chromatographic isolation. Treatment of the chloride **160** with TBAF in THF for 24 hours then gave the chloro-alcohol **161** which showed a characteristic infra red stretch at 3450 cm^{-1}, together with appropriate NMR data (Scheme 135).

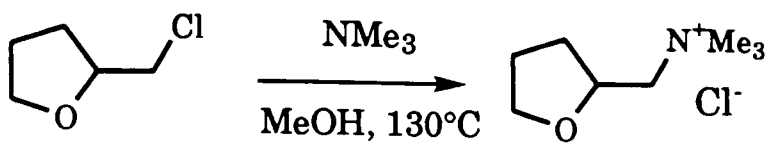
Scheme 135



Treatment of the chloro-alcohol **161** with trimethylamine in methanol in a sealed tube at 90°C, 130°C and 150°C was unsuccessful in forming muscarine chloride. At temperatures of up to 130°C, no reaction was observed, and at 150°C the alcohol decomposed. This was disappointing, as trimethylamine had been successfully alkylated with tetrahydrofurfuryl chloride under the same conditions at 130°C (Scheme 136). The fact that the chloro-alcohol **161** is a β-chloro ether may explain its lack of reactivity. Alkylations using chlorides are known to occur under the conditions used in other circumstances.[141] The chloro-alcohol **161** is much more prone to decomposition than tetrahydrofurfuryl chloride, as it can be dehydrated at higher

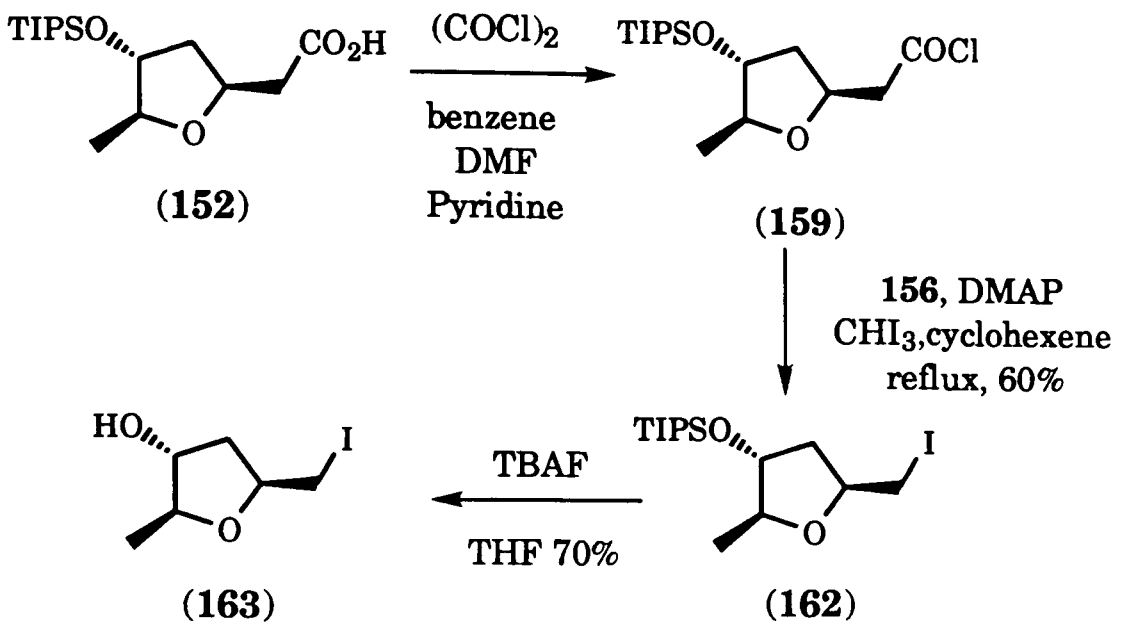
temperatures.

Scheme 136



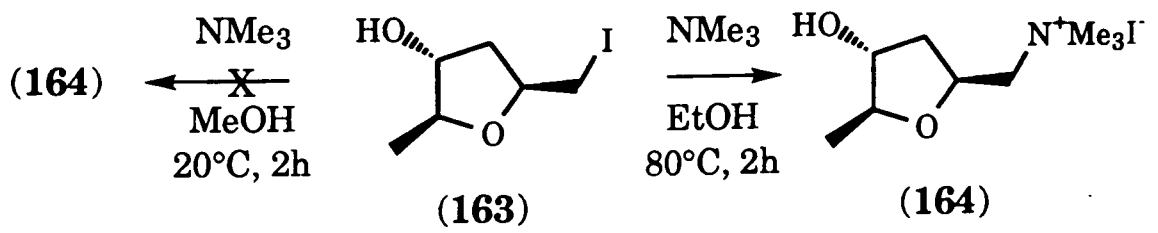
The unreactivity of the chloride led to the consideration of the synthesis of the iodo-alcohol **163**. This compound has been converted into muscarine by two previous groups.[126,127] Two approaches were available for the synthesis of the iodo-alcohol; firstly a Finkelstein[142] reaction of the chloro-alcohol **161** or alternatively, adaption of the Barton decarboxylation step to incorporate an iodine atom instead of a chlorine. The second option was thought to be preferable because it allowed the composition of the final product (*ie* muscarine iodide) to be certain; if some of the chloride was also converted into muscarine, the data for the final product would be confused. When the acid chloride **159** was refluxed in cyclohexene in the presence of DMAP, iodoform and 2-mercaptopyridine-N-oxide, sodium salt, the iodide **162** was formed in reasonable yield.[139] Iodoform is used in the reaction because it decomposes to give the important chain carrying diiodomethyl radical ($CHI_2^{\bullet}$) and an iodine radical upon heating. Cyclohexene is used as solvent because it acts as a trap for the molecular iodine which is a major by-product of this radical process. The iodide was again smoothly desilylated by treatment with TBAF in THF to give the pure iodo-alcohol **163** after chromatography (Scheme 137).

Scheme 137



The data found for the iodo-alcohol **163** corresponded exactly to that quoted by Mulzer.[127] Treatment of the iodo-alcohol **163** with trimethylamine in ethanol, at 80°C, for 2 hours, according to the literature procedure[127] gave (±) muscarine iodide **164**, the data for which corresponded to that quoted in the literature.[127] The final step as described by Chastrette *et al*[126] [*ie* treatment of the iodo-alcohol with trimethylamine in methanol for 16 hours at RT] however, could not be repeated (Scheme 138).

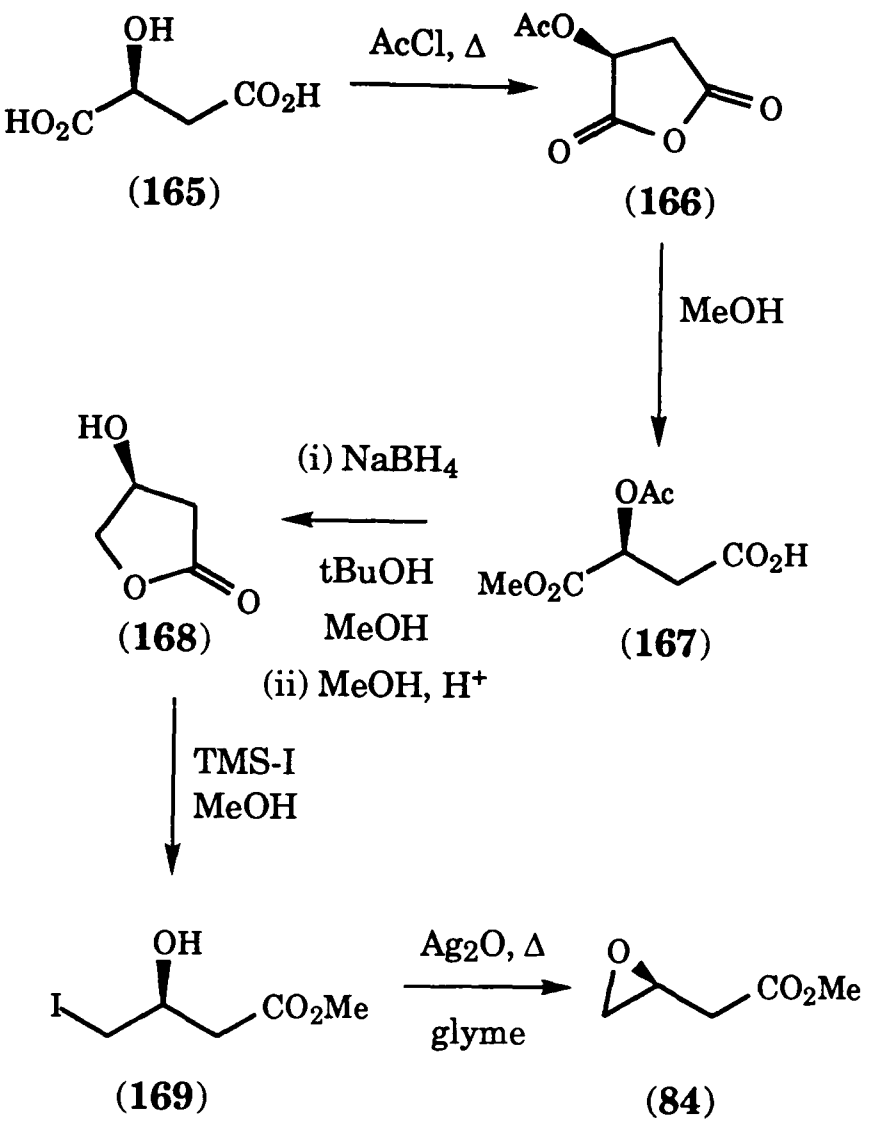
Scheme 138



The sequence was then repeated using the (S)-epoxy ester **84**

which was obtained in five steps from (S)-malic acid following the procedure of Larchêveque *et al.*[93,94] (S)-Malic acid **165** was mono-esterified by conversion into the anhydride **166** followed by methanolysis to give the half-ester **167**.

Scheme 139



This was reduced using sodium borohydride in ^{t}butanol/methanol to give the (S)-lactone **168** which is now commercially available as either enantiomer. Ring opening of the lactone with iodotrimethylsilane and methanol gave the iodohydrin **169** which, upon treatment with silver(I) oxide in glyme, at reflux, for 8 hours in the dark, ring closed to give the (S)-epoxide **84** (Scheme 139).

Extremely careful distillation afforded the epoxide free from

Extremely careful distillation afforded the epoxide free from the solvent, although losses were incurred during this process. The conversion of this epoxide into D-(-)-muscarine proceeded smoothly, exactly as described for the racemate above. The chiral iodo-alcohol **162** exhibited optical rotation close to that reported in the literature.[127] The (S)-epoxide **84** from (S)-malic acid was synthesised rather than the (R)-epoxide **84** from (R)-malic acid simply on the grounds of cost, because the starting material (S)-malic acid is significantly cheaper. The synthesis of natural L-(+)-Muscarine from (R)-malic acid or the (R)-epoxide **84**, obtained by enzymatic resolution, would be equally possible to achieve.

In summary, the route that has been developed provides the required flexible, and reasonably brief, 8 step route to muscarine, and possible C-2 analogues. The final product was isolated in a 14.3% overall yield from the (S)-epoxide **84**. This route was found to be good in many respects, but the selectivity of the key cyclisation was disappointing, compared to the examples investigated in Chapter Two. This is probably due to the reduced steric influence of the methyl substituent with respect to the model reactions. A better overall yield could therefore be expected in the preparation of C-2 analogues of muscarine. The relatively low yield in the Barton decarboxylation step was also slightly disappointing, but further optimisation of this step has not been carried out. The easy incorporation of C-2 analogues makes this a useful synthesis of muscarines. Further improvement of this synthesis is still possible; for example, the use of a cheaper oxygen protecting group (*eg* benzyloxy) is under consideration.

CHAPTER FOUR

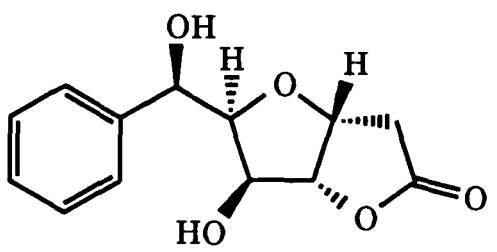
Approaches to Goniofufurone

Approaches To Goniofufurone

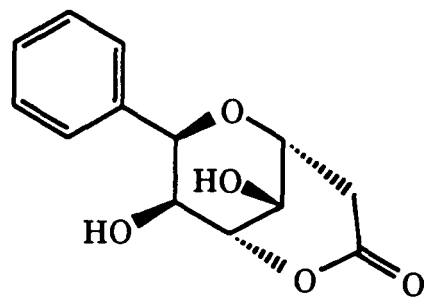
(I) Introduction

In 1990, McLaughlin *et al*[143] isolated three novel styryl lactones; (+)-goniofufurone **170**, (+)-goniopypyrone **171** and (+)-8-acetyl goniotriol **172** (Scheme 140).

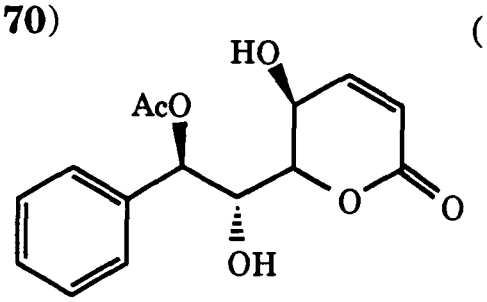
Scheme 140



(170)



(171)

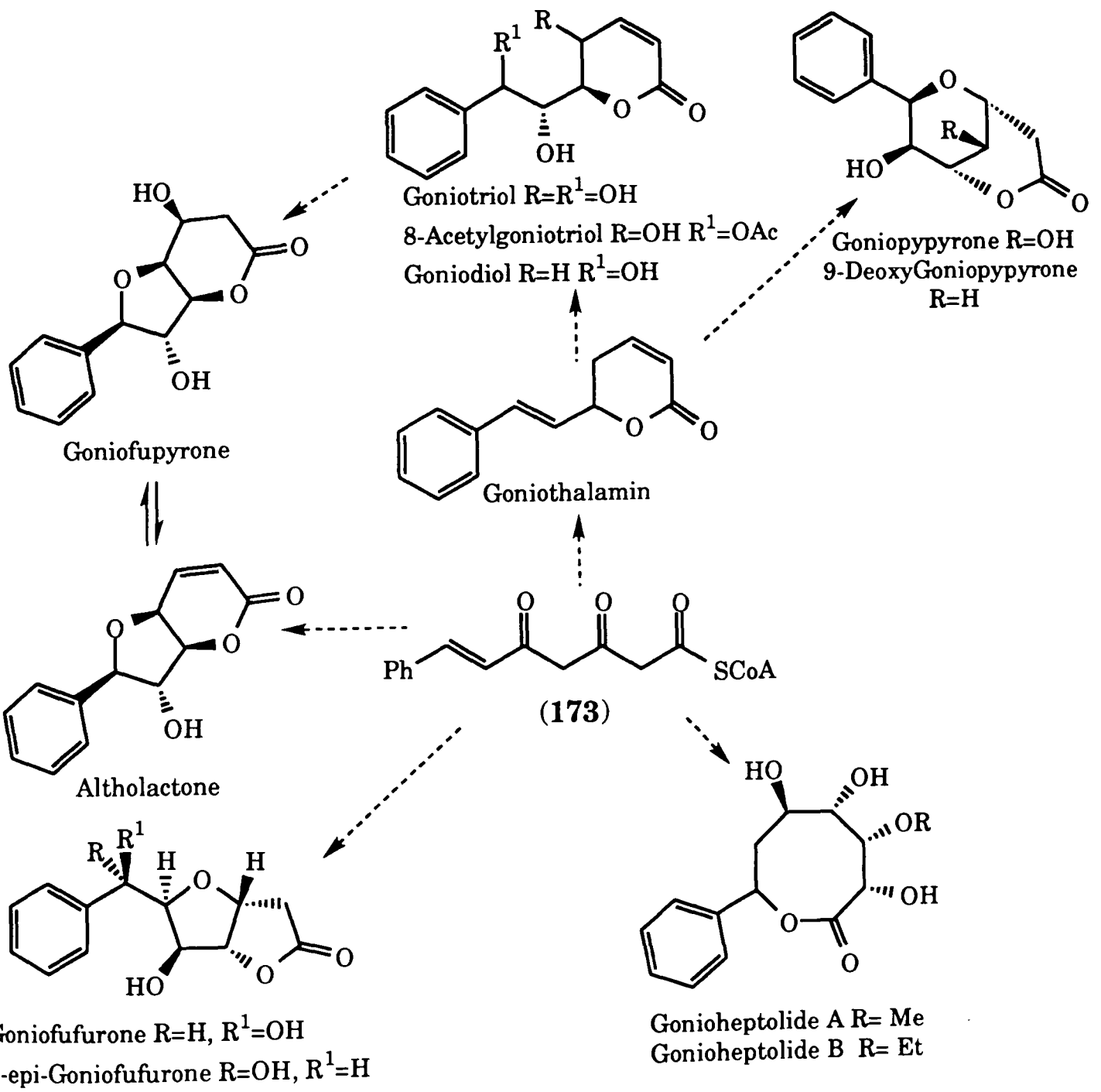


(172)

The lactones were isolated from ethanolic extracts of the stem bark of *Goniothalamus giganteus* (Hook. f., Thomas), a Taiwanese lily, and the X-ray structures of (+)-goniofufurone **170** and (+)-goniopypyrone **171** were determined. The three compounds exhibited activity against human tumor cell lines; (+)-goniopypyrone **171** was the most bioactive, showing ED_{50} values

of about 0.67 μg/ml. These compounds form part of a family of styryl lactones isolated from the stem bark of this plant. It has been proposed[143] that they all originate from a single parent molecule **173** derived *in vivo* from a combination of shikimate and polyketide pathways (Scheme 141).

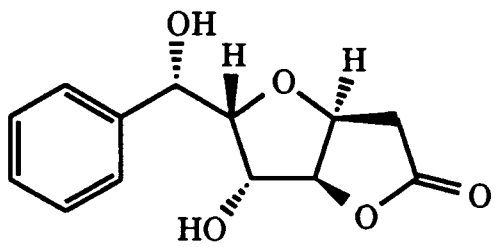
Scheme 141



(II) Synthetic Approaches to Goniofufurone

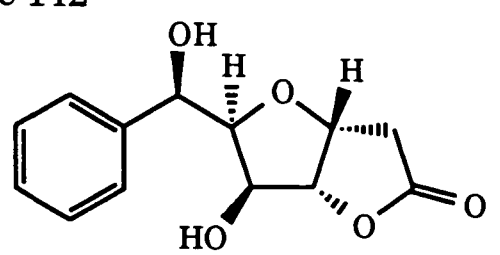
(-)-Goniofufurone **174** was synthesised by two groups of researchers during early 1992. This enabled the configuration of the natural enantiomer to be established as that shown in Scheme 142.

Scheme 142



(174)

Synthetic
(-)-Goniofufurone

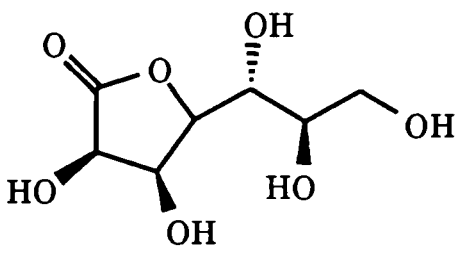


(170)

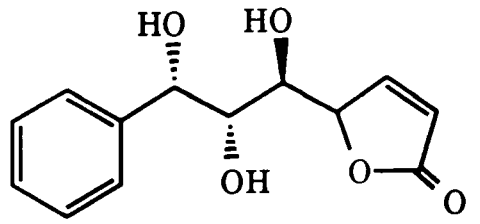
Natural
(+)-Goniofufurone

Shing and Tsui[144] synthesised the unsaturated lactone **175** in eleven steps from D-glycero-D-gulo-heptonolactone **176**, and then converted it into (-)-goniofufurone **174** by a 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU)-catalysed Michael-type cyclisation (Scheme 143).

Scheme 143

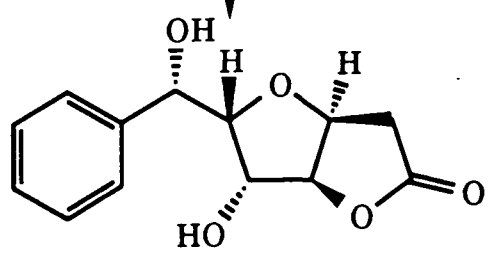


(176)



(175)

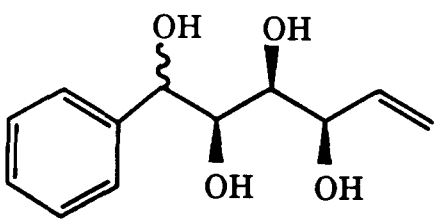
0.05%
w/v DBU



(174)

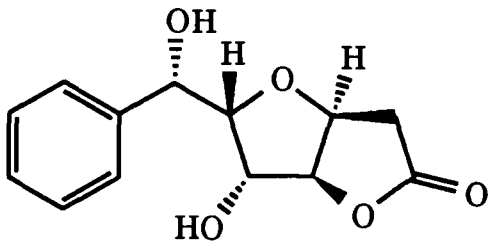
By contrast, Jäger and Gracza[145] took the tetrol mixture **177**, available in five steps from monoacetone D-glucose, and converted it into a readily separable mixture of (-)-goniofufurone **174** and (-)-7-epi-goniofufurone **178**, by a palladium(II)-catalysed cyclisation-carbonylation reaction (Scheme 144).

Scheme 144

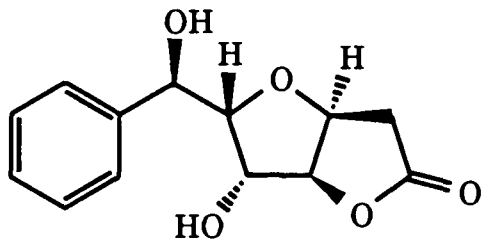


(**177**)

$PdCl_2$ (0.1 eq), $CuCl_2$ (3eq)
NaOAc (3eq), CO, AcOH
21h, RT



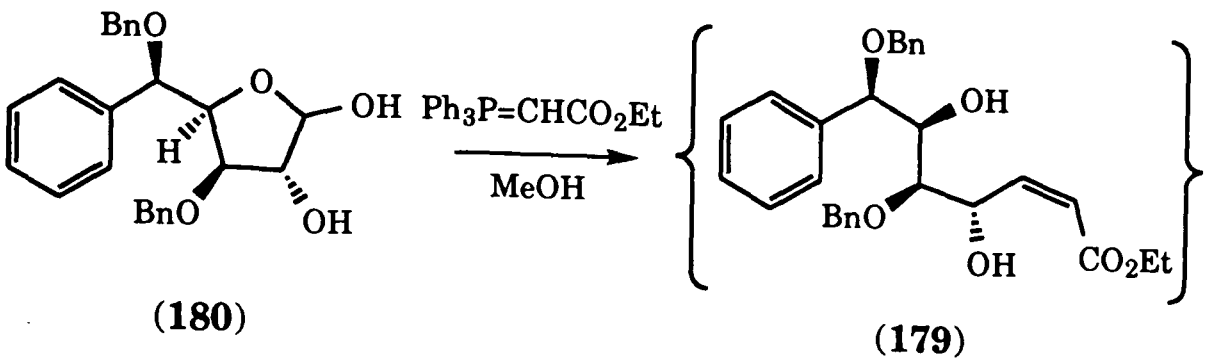
(**174**)



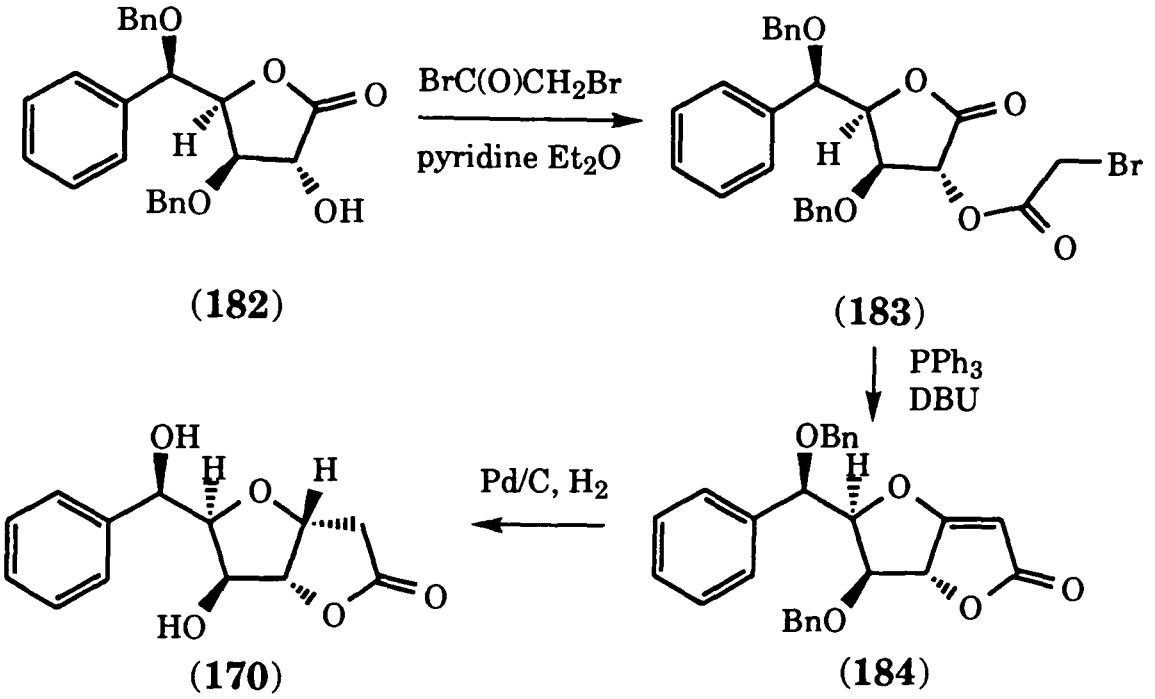
(**178**)

Four further approaches to goniofufurone have since been reported. The first of these was that developed by Prakash and Rao[146] in which (+)-Goniofufurone was synthesised from D-glucose in eleven steps. The unsaturated lactone **179** was synthesised by a stereocontrolled Wittig addition to the lactol **180**. This ester then cyclised spontaneously to give dibenzylgoniofufurone **181**, which was deprotected by hydrogenation to give the natural product (Scheme 145).

Scheme 145



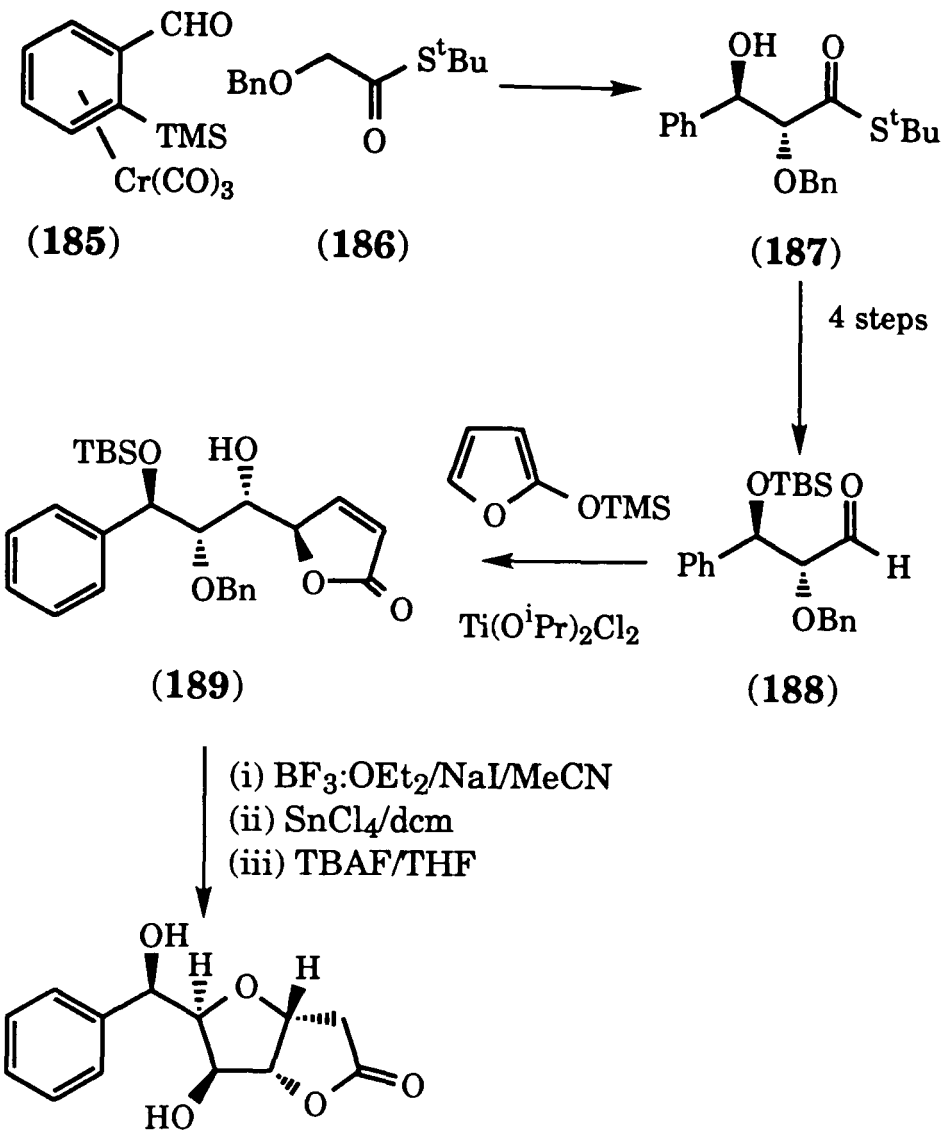
Scheme 146



Murphy and Dennison[147] used a very similar approach, generating the lactone **182**, also from D-glucose, and acylating to give the bromoacetate **183**. Intramolecular Wittig reaction gave the unsaturated lactone **184**,

hydrogenation of which furnished (+)-goniofufurone **170** in thirteen steps overall from D-glucose (Scheme 146).

Scheme 147

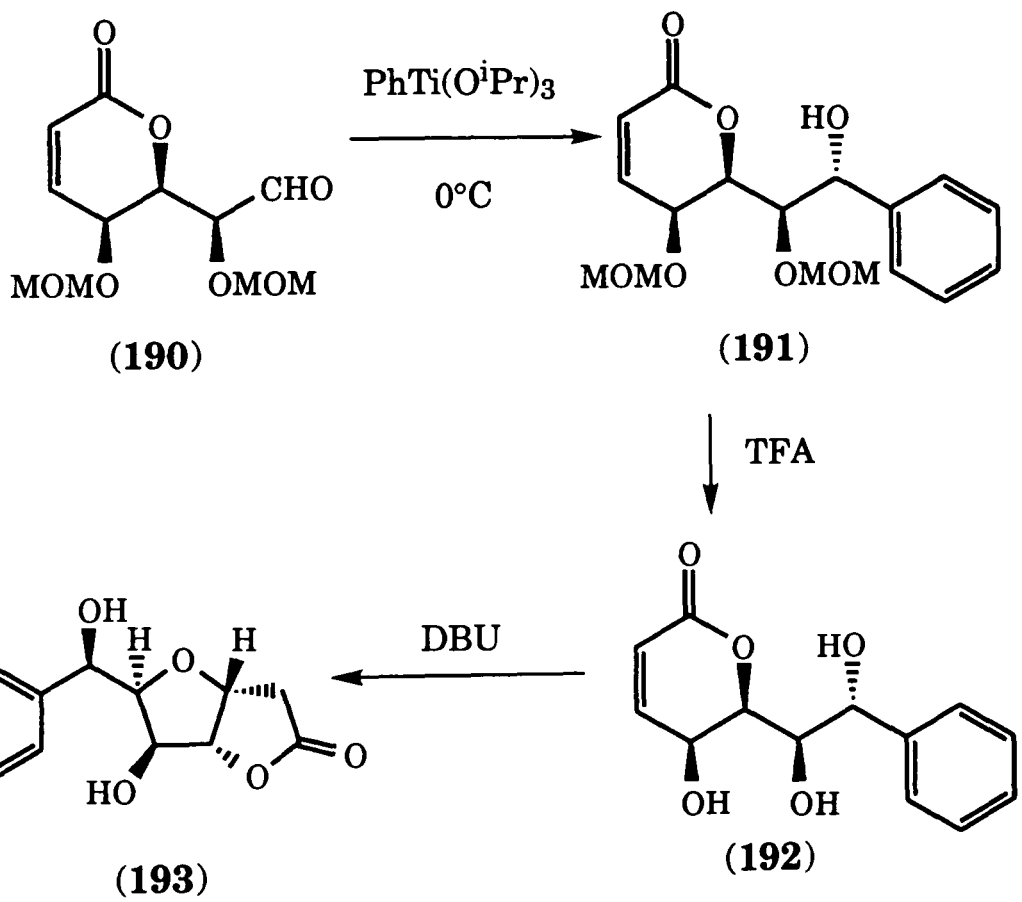


Hanaoka *et al*[148] used the homochiral chromium complex **185** in an efficient route to (+)-goniofufurone, the first non-carbohydrate based synthesis. The titanium enolate of thioester **186** was reacted with the complex **185** to give the aldol product **187**. This was converted into the aldehyde **188** and reacted with trimethylsilyloxyfuran under chelation controlled conditions, to give the lactone **189** which, upon deprotection, cyclised spontaneously to give (+)-goniofufurone **170** (Scheme 147).

Honda *et al*[149] have used the chiral lactonic aldehyde **190** to effect

elegant syntheses of (+)-goniofufurone (+)-goniopypyrone, (+)-goniotriol, (+)-8-acetylgoniotriol and (+)-altholactone. The aldehyde **190** was treated with an equivalent of phenyl anion, under chelation control, to give the alcohol **191.** This was deprotected with trifluoroacetic acid (TFA) to give the triol **192**, which was cyclised, *via* an unexplained base initiated rearrangement, to give (+)-goniofufurone **193** (Scheme 148).

Scheme 148



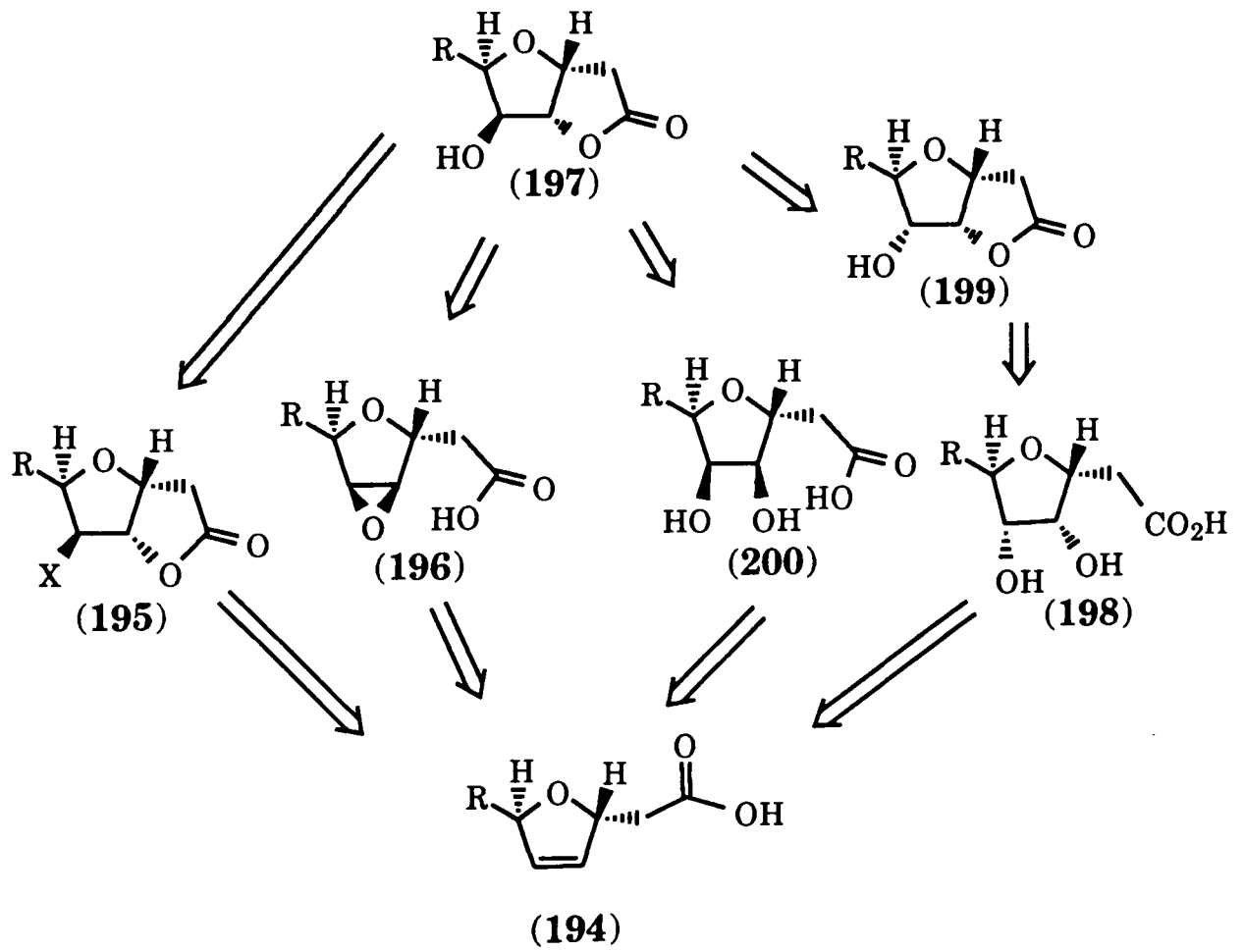
(190) **(191)** **(192)** **(193)**

(III) Retrosynthetic Analysis of Goniofufurone

Retrosynthetic analysis of goniofufurone, soon after its isolation in 1991, led to the consideration of a synthesis of this molecule using the methodology developed earlier in this project (see Chapter Two). At first

glance, the hydroxy-THF with an acetic acid ester side chain as the 2-substituent present in the molecule, makes it look ideally set up for an approach using the cyclisation of (Z)-β-hydroxy-δ-alkenoates. However, the cyclisation of these molecules gives a high selectivity for the 2,5-*cis*-stereochemistry. The natural product has a 2,5-*trans*-stereochemistry so an approach *via* this route is not a viable prospect. The cyclisation of (E)-β-hydroxy-δ-alkenoates however, gives a very good selectivity for the 2,5-*trans*-stereochemistry required. Thus an approach to goniofufurone was planned using the iodocyclisation of (E)-β-hydroxy-δ-alkenoates to give iodo-THF acetic acid esters of the desired stereochemistry. This left open a number of routes to the natural product skeleton.

Scheme 149



It became clear that a dihydrofuran of the type **194** could be a key intermediate in such an approach (Scheme 149).

Simple lactonisation of the acid would allow the skeleton **195** to be assembled directly, and it would only remain to alter the functionality at the 5-position. Stereocontrolled oxidation of the acid to give the epoxide **196** would allow acid-catalysed cyclisation to give the target molecule **197**. Stereoselective osmylation, on either face, would also allow elaboration to the target molecule. Osmylation on the same face of the acid moiety, to give the dihydroxy acid **198**, would allow the specific lactonisation to give the alcohol **199**, which could be inverted by a Mitsunobu reaction to give the target ring system **197**. Alternatively, osmylation on the opposite face to the acid moiety, to give the dihydroxy acid **200**, and subsequent formation of the bidentate sulphonate ester,[150] would yield the target molecule, upon ring opening.

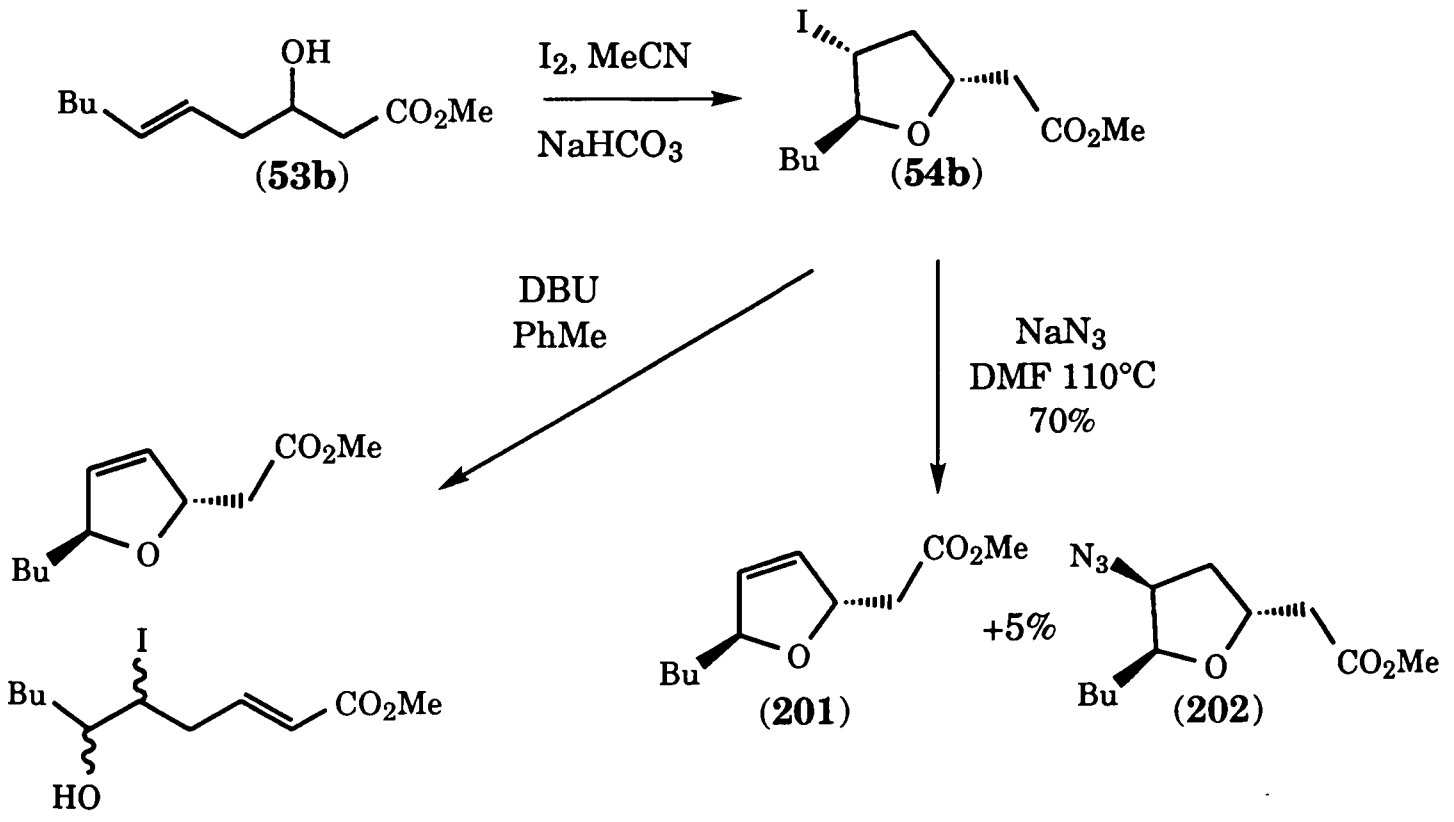
(IV) Model Reactions

Considering the potential usefulness of the unsaturated acid **194** in the approach to the natural product, model work began with the development of a route to these acids and then proceeded with investigations of the synthesis of the natural product skeleton.

The β-hydroxy ester **53b** was readily available in large quantities from the vinyl-alanate chemistry described earlier (p 76). Iodocyclisation of this molecule was smooth and stereospecific following the earlier procedures,

and yielded large quantities of the iodo-THF **54b**. Earlier experiments by Bedford[80] suggested that when the iodo-THFs were heated at too high a temperature with sodium azide and 18-crown-6 in DMF, the olefin **201** was produced along with the expected azide **202** resulting from S_N2 substitution. These results were unexplained, but nevertheless these findings were investigated as part of these model reactions. Pleasingly, a high yield of the olefin **201** was obtained when the iodo-THF **54b** was heated with sodium azide in DMF at 110°C for 16 hours; only traces of the azide **202** were isolated. DBU was also used to initiate this elimination reaction, but the olefin was isolated in much lower yields; this was because ring opening elimination reactions competed with the 2,5-dihydrofuran formation (Scheme 150).

Scheme 150

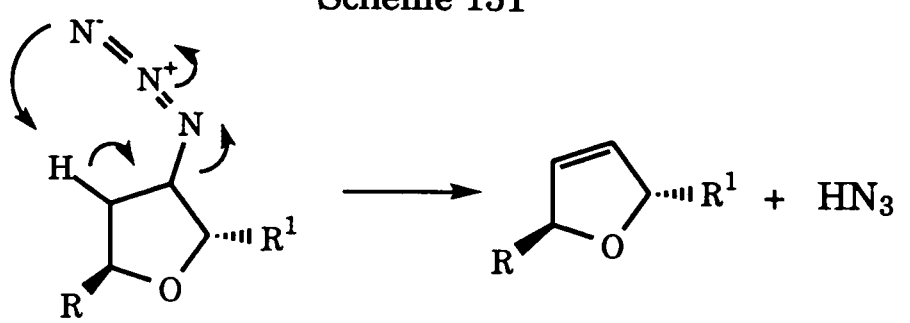


2,5-Dihydrofurans of controlled stereochemistry are useful synthetic intermediates. For example, they have been used in [3+2]

cycloadditions to give tetrasubstituted THFs.[151]

There appear to be two possible explanations for this unexpected elimination reaction. It is conceivable that sodium azide acts as a mild base, abstracting a proton to initiate the elimination. However, the regiospecificity of this process suggests that the cyclic decomposition of the azide is also a viable mechanism (Scheme 151).

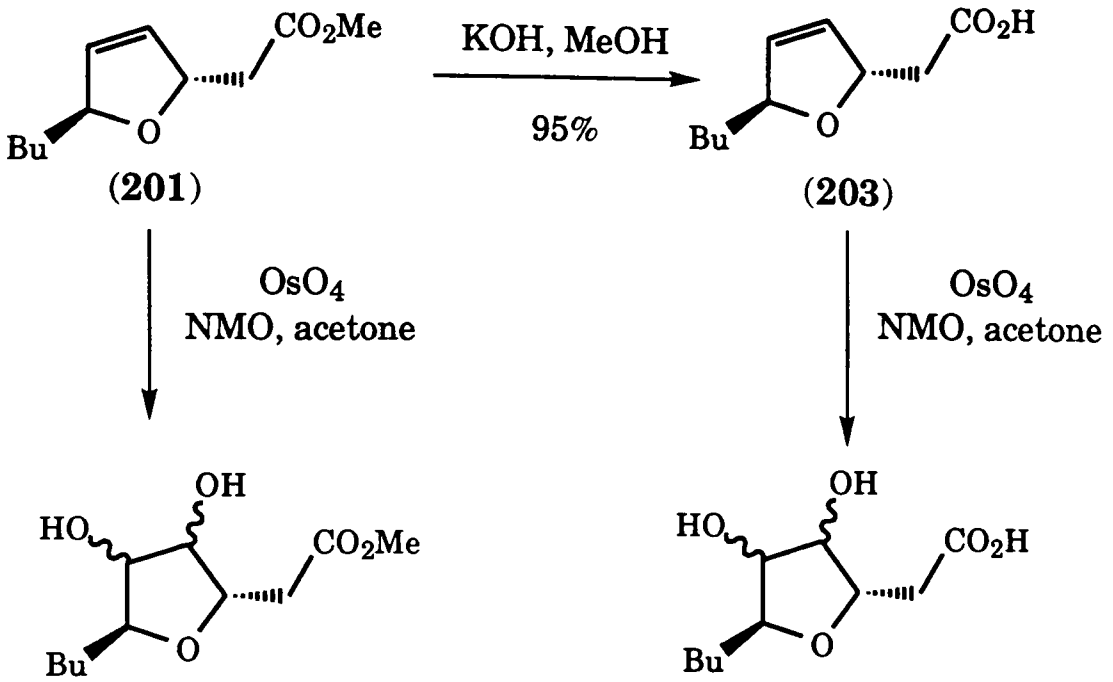
Scheme 151



West[152] has also observed a similar reaction using sodium azide. Unfortunately, further investigation of this process was prohibited by time considerations.

The olefinic ester **201** was saponified successfully using potassium hydroxide in methanol to give the acid **203** in high yield. This was a very pleasing result as epimerisation and ring opening had been observed in a similar system by a previous researcher.[80] This result also had implications in the synthesis of muscarine (see p 99). Both the ester **201** and the acid **203** were treated with osmium(VIII) tetroxide, under standard conditions.[153] It was hoped that face selective dihydroxylation might take place in the case of the ester **201** on steric grounds or, in the case of the acid **203**, by co-ordination of the approaching osmium species. Disappointingly, there was little stereoselectivity observed in either case (Scheme 152).

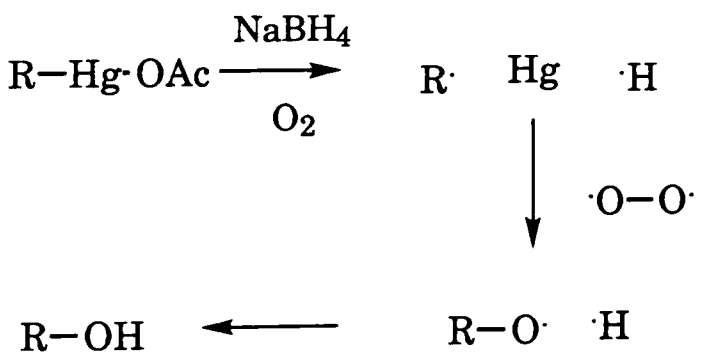
Scheme 152



Selective epoxidation of the acid **203** was considered, possibly by formation of the peracid at low temperature followed by intramolecular delivery of oxygen.[154] However, selective delivery of the oxygen atom from below to give the epoxide (the epimer of the epoxide **196**) would not allow easy elaboration to the natural product.

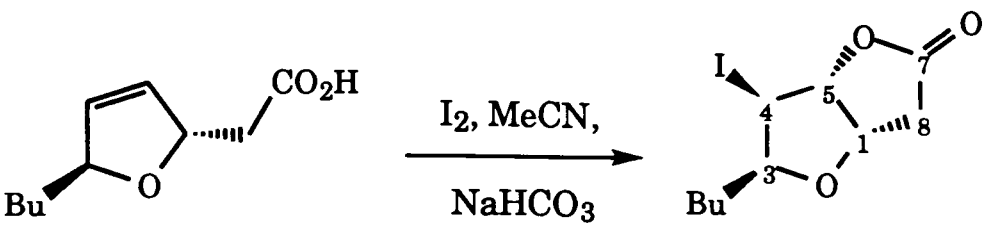
Lactonisation of the acid **203** was the next approach adopted. Mercury mediated lactonisation was considered, but as the replacement of the alkyl mercury function generated to give an alcohol is a radical process (Scheme 153), the stereocentre produced would be expected to be largely stereorandom, and therefore of little use in the context of this sequence.

Scheme 153



Halolactonisation seemed the most reliable alternative, and indeed, smooth iodolactonisation of the acid **203** furnished the iodolactone **204** in excellent yield (Scheme 154).

Scheme 154

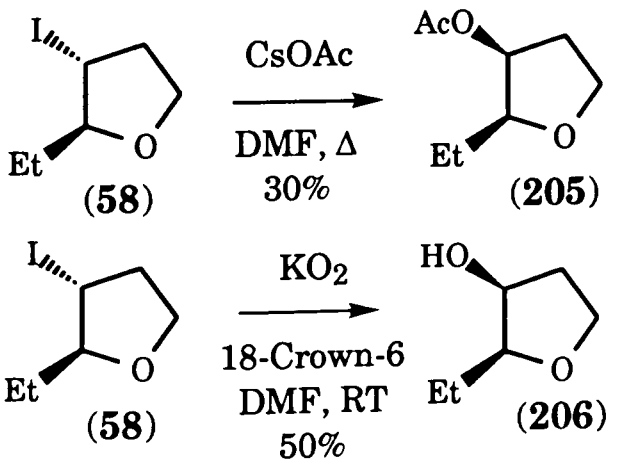


(203) **(204)**

The iodolactone **204** showed considerable similarities to the natural product in the ^{1}H and ^{13}C NMR spectra. The resonances for the 1-H, 4-H, 5-H and 8-CH_2, for example, showed similar coupling patterns and chemical shifts to those reported by McLaughlin[143] for goniofufurone. The ^{13}C NMR signals for the 1-CH, 3-CH, 5-CH, 7-C and 8-CH_2 were again consistent with the corresponding signals in the natural product.

Investigations of the possible introduction of oxygen functionality began with model reactions on the easily accessible iodo-THF **58**. Cesium acetate at 100°C in DMF[155] was used to give the acetate **205** in moderate yield. Slightly better results were obtained using potassium superoxide and 18-crown-6 in DMF, at RT, to give the alcohol **206** (Scheme 155).

Scheme 155



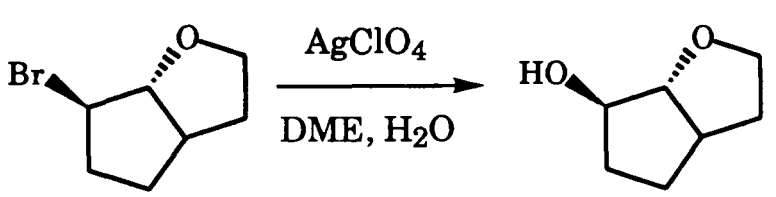
(58) **(205)**

(58) **(206)**

Corey[156] used this latter method in the presence of an ester group. The yields from these reactions are, of course, related to pure compounds after chromatography. In the case of these model reactions, the yields were possibly reduced by the volatility of the products.

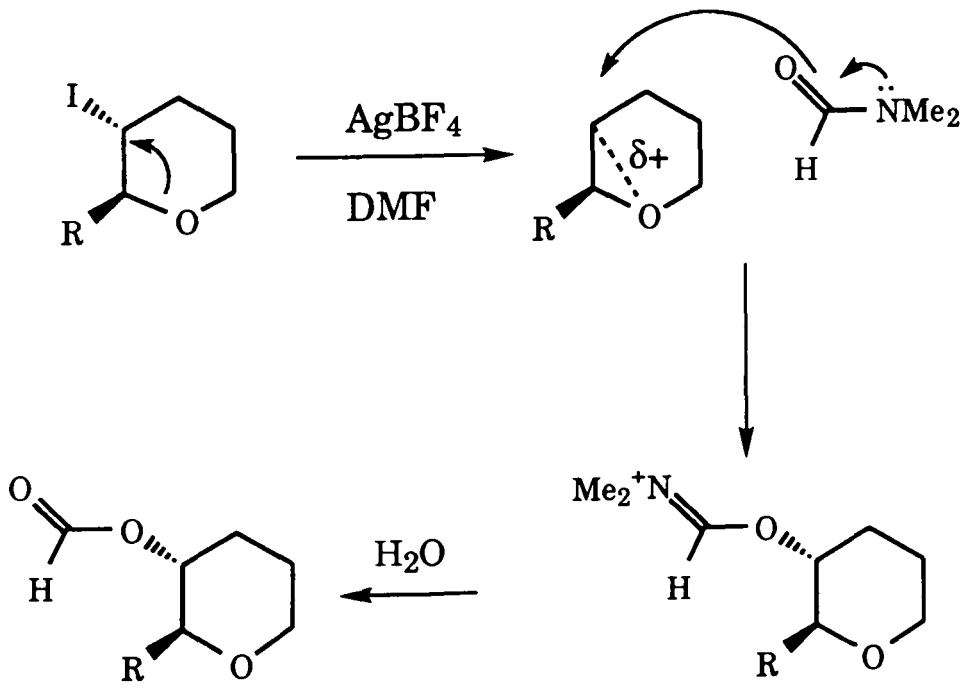
Kocovsky[157] used silver salts with non-nucleophilic counter anions to effect substitution of a bromine atom by an oxygen function with overall retention of configuration, in the presence of anchimeric assistance from a proximal oxygen atom (Scheme 156).

Scheme 156



Bartlett[158] observed the formation of formate esters, with retention of configuration, using silver tetrafluoroborate in DMF on a similar system to that used by Kocovsky (Scheme 157).

Scheme 157

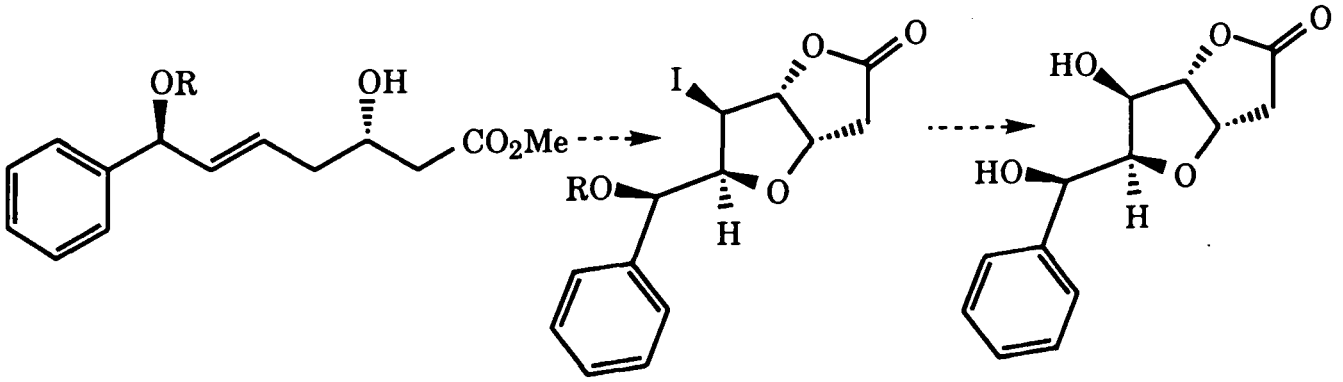


Overall retention of configuration would be ideal in our system in that it would give the required configuration of the natural product directly. The examples which Bartlett used to perform this reaction were six-membered rings, but, in principle, the use of five-membered rings is not precluded. The iodolactone **204** was treated with both potassium superoxide/18-crown-6 in DMF, and with silver tetrafluoroborate in DMF. The results were promising in that there was good evidence for substitution in both cases (*ie* formation of a single, more polar spot by tlc). However, there was insufficient material to prove this conclusively.

(V) Incorporation of the Natural Side Chain

The first approach adopted to the synthesis of natural goniofufurone was the elaboration of mandelic acid **207**, the (R)- and (S)-enantiomers of which are both commercially available and relatively inexpensive. It was thought that mandelic acid could be an ideal starting material with which to attempt the homochiral synthesis of the β-hydroxy-ester **208**. This could be converted into (+)-goniofufurone by following the foregoing model work (Scheme 158).

Scheme 158

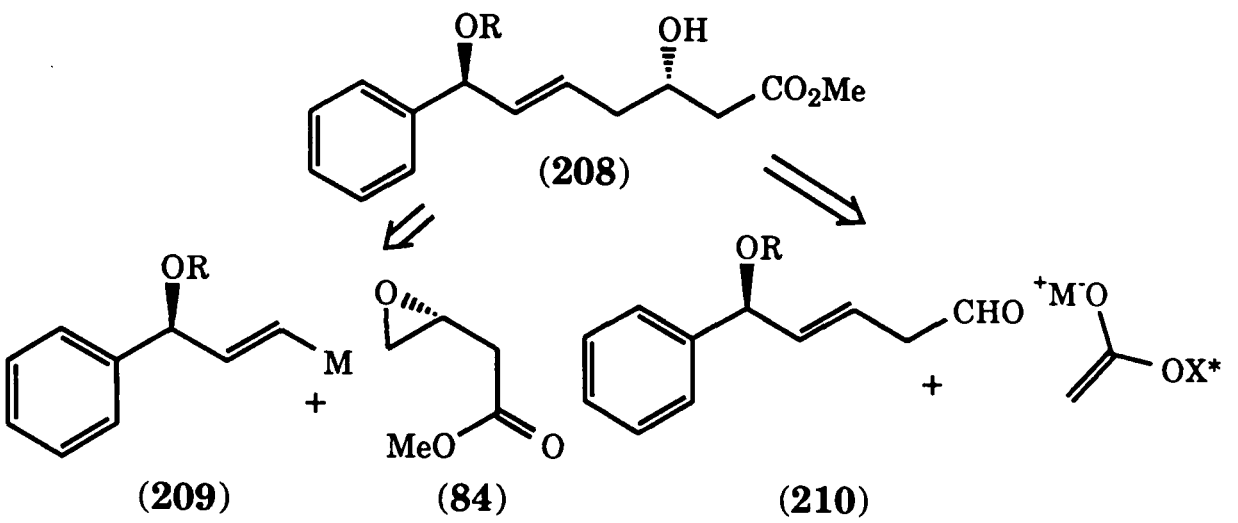


(208) **(170)**

Retrosynthetic analysis shows that two of the possible approaches

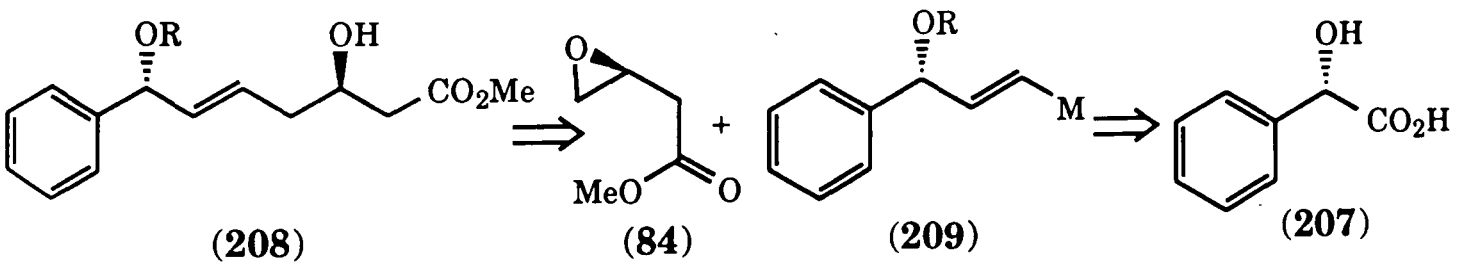
to the ester **208** are: (i) coupling of the vinyl anion **209** to a single enentiomer of the epoxy ester **84**, and (ii) stereochemically controlled chiral aldol reaction of the aldehyde **210** with a chiral acetate enolate (Scheme 159).

Scheme 159



Natural (+)-goniofufurone would arise from elaboration of the (3R,7R)-ester **208** (*ie* from the coupling of the (R)-mandelic acid derivative with the (R)-enantiomer of the epoxy ester **84**). Bearing in mind that the (S)-enantiomer of the epoxy ester **84** had already been synthesised, and was derived from the cheaper (S)-enantiomer of malic acid, it was decided to begin work on the synthesis of (-)-goniofufurone from the (3S,7S)-ester **208** (*ie* by the coupling of the (S)-mandelic acid derivative with the (S)-enantiomer of the epoxy ester **84** (Scheme 160).

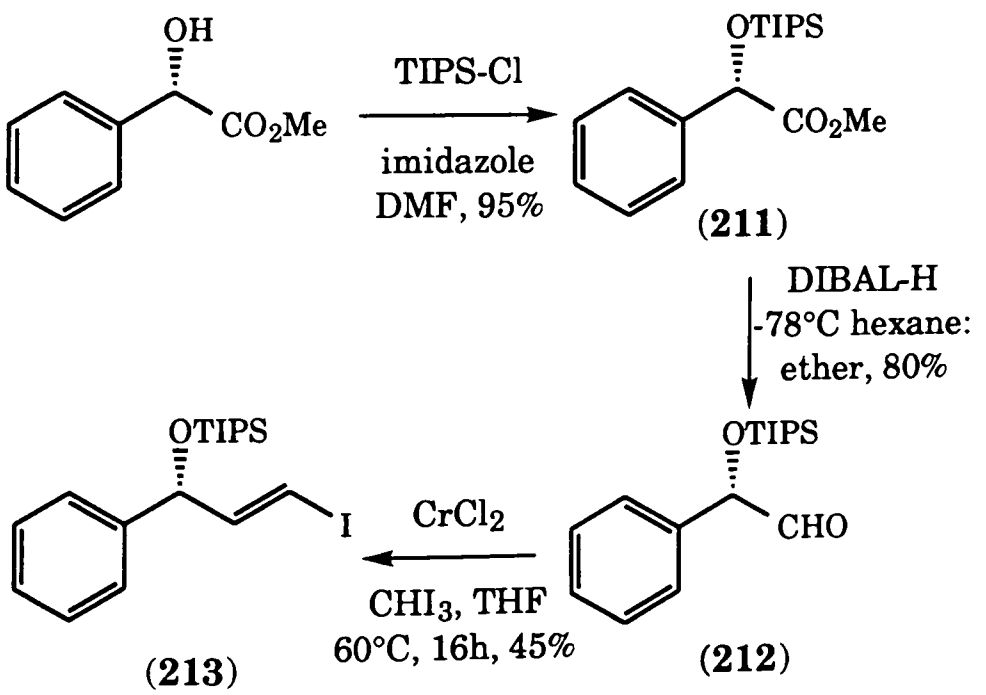
Scheme 160



The first work in this area was the synthesis of the vinyl anion **209** (M = Li) by derivatisation of (S)-mandelic acid. (S)-Methyl mandelate,

prepared by literature methods,[159] was silylated using TIPS chloride, in dry DMF in the presence of imidazole, to give the silyl ether **211**. Reduction of this silyl ether at -78°C with diisobutylaluminium hydride in hexane:ether[160] gave the aldehyde **212** in high yield. This aldehyde was then homologated using the Takai procedure,[161] to give the (E)-vinyl iodide **213** exclusively. However, extensive modifications to the literature procedure were required as the aldehyde **212** reacts much less readily than the examples given by Takai, possibly due to the steric effect of the TIPS protecting group. A standard procedure, as used by Takai, involved stirring the given aldehyde with chromium(II) chloride and iodoform, at 0°C, in THF. However, homologation of the aldehyde **212** required 16 hours at 60°C. Interestingly, this slower reaction gave better stereoselection for the (E)-isomer than that quoted by Takai. Separation of the extremely non-polar vinyl iodide **213** from iodoform proved difficult, but after two separations eluting with cyclohexane, the pure iodide was obtained in 45% yield (Scheme 161).

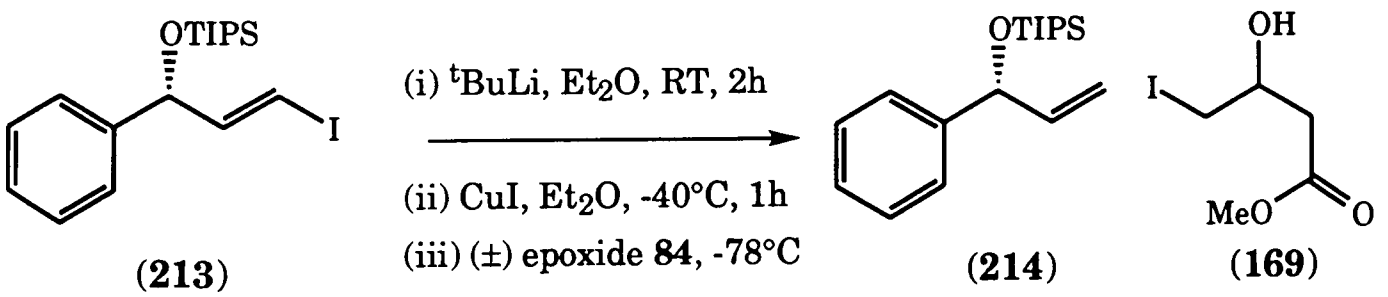
Scheme 161



Extensive studies of the halogen-lithium exchange of this molecule

with two equivalents of ^{t}butyl lithium showed that, although this process normally occurs at -78°C in less than 15 minutes, the lithium exchange of the vinyl-iodide **213** only occurs after warming to RT and stirring for 2 hours. Quenching of the reaction before this point resulted in recovery of starting material; in fact, the molecule did not react with ^{t}butyl lithium at all at -78°C. It is essential that diethyl ether, and not THF, is used as solvent for this reaction as at 0°C ^{t}butyl lithium and THF react together. Once the conditions for halogen-lithium exchange had been established, cuprate formation was attempted using lithium 2-thienyl-cyanocuprate[162] and also using copper(I) iodide but in both cases, although it was not shown whether cuprate formation had occurred, the major product from the exposure of the resulting solutions to the (±)-epoxide **84** was the (±)-iodohydrin **169**. It seems that the iodide anion is more nucleophilic than the anionic species generated by these procedures. The vinyl iodide was exclusively converted into the terminal olefin **214** (Scheme 162).

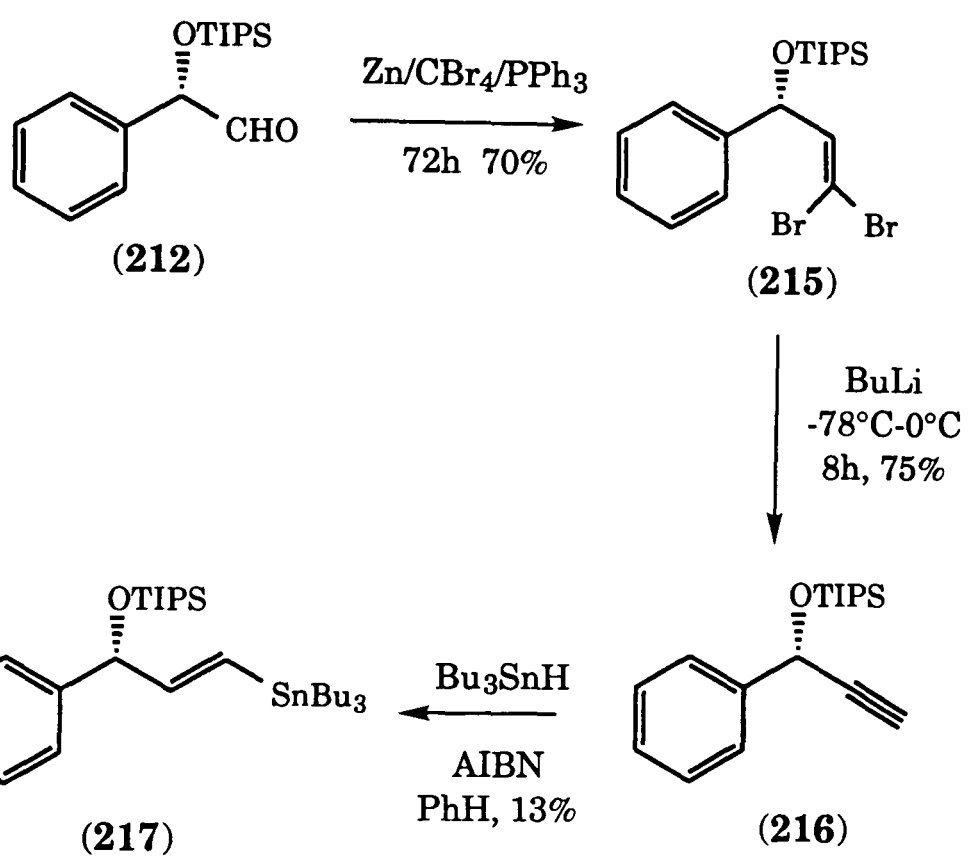
Scheme 162



With these results in mind, the aldehyde **212** was converted by the Corey procedure[163] into the dibromide **215**, and subsequently the acetylene **216**, in reasonable overall yield. Again, reaction times far in excess of those

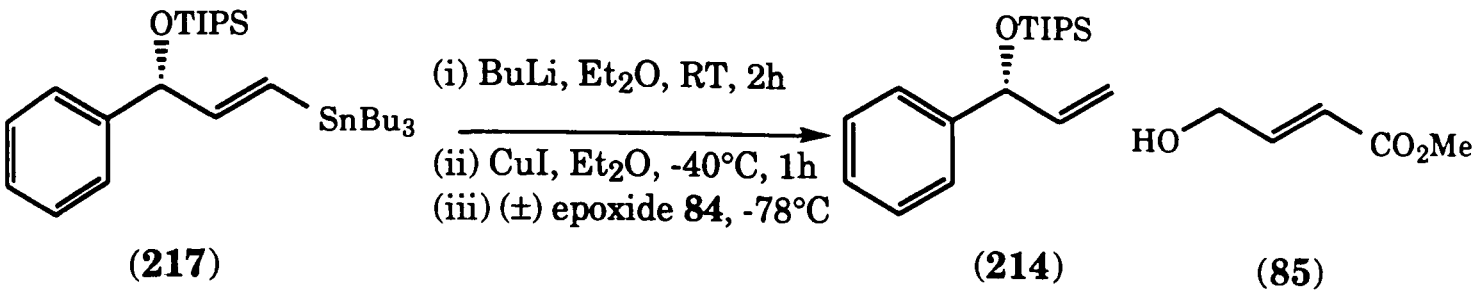
used in the literature were required. Hydrostannylation of this acetylene proceeded in low yield to give exclusively the (E)-vinyl-stannane **217** which was purified by column chromatography (Scheme 163). The recently developed Hodgson route to (E)-vinyl-stannanes[164] directly from aldehydes was not used, as the steric restraints of our system seemed likely to prevent this method from being appropriate.

Scheme 163



The (E)-vinyl stannane **217** was treated with butyl lithium, for two hours at RT, to effect tin-lithium exchange. The vinyl lithium thus formed was reacted with copper(I) iodide at -40°C, and then treated with the (±)-epoxide **84**. This time the products were the terminal olefin **214** and the ester **85** from the action of base upon the epoxy-ester (Scheme 164). This suggests that the required cuprate complex was not formed (*ie* the basic vinyl-organometallic extracted a proton from the (±)-epoxide **84**).

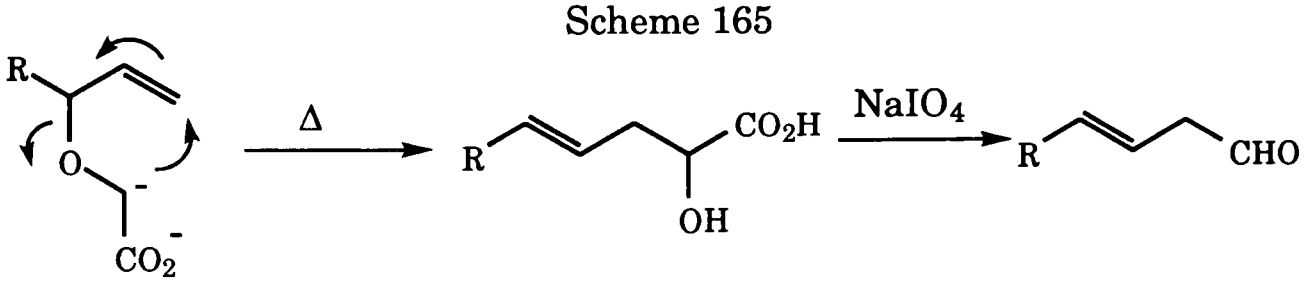
Scheme 164



(217) **(214)** **(85)**

With this discouraging result, investigation of the second disconnection of the hydroxyester **208** began. The required aldehyde **210** was thought to be accessible by following the work of Nakai *et al*,[165] who used a [2.3]-sigmatropic rearrangement to give an unsaturated hydroxy-acid, which was cleaved with sodium periodate to give a β,γ-unsaturated aldehyde, as shown in Scheme 165.

Scheme 165

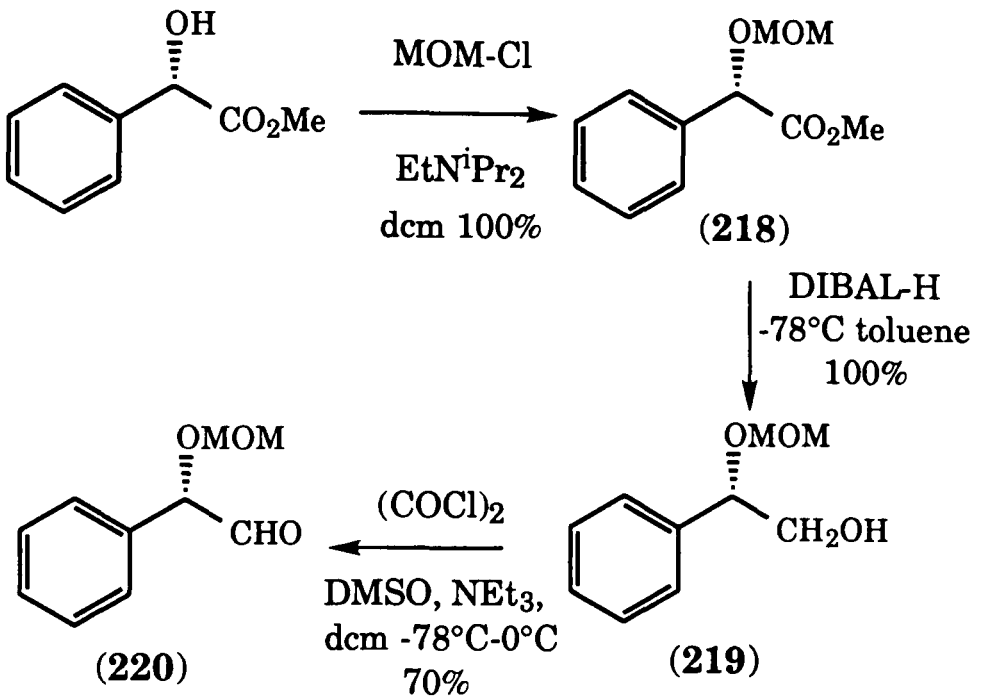


The known aldehyde **220** was synthesised by a route which differed from that used by Corey.[166] Although the route as described by Corey was also attempted, it yielded less of the desired compound than the route which is shown in Scheme 166.

The methoxymethoxy (MOM) ether **218** of (S)-methyl mandelate was formed in quantitative yield by treatment with chloromethyl methyl ether and ethyldiisopropylamine in dcm. The ester was then reduced to the

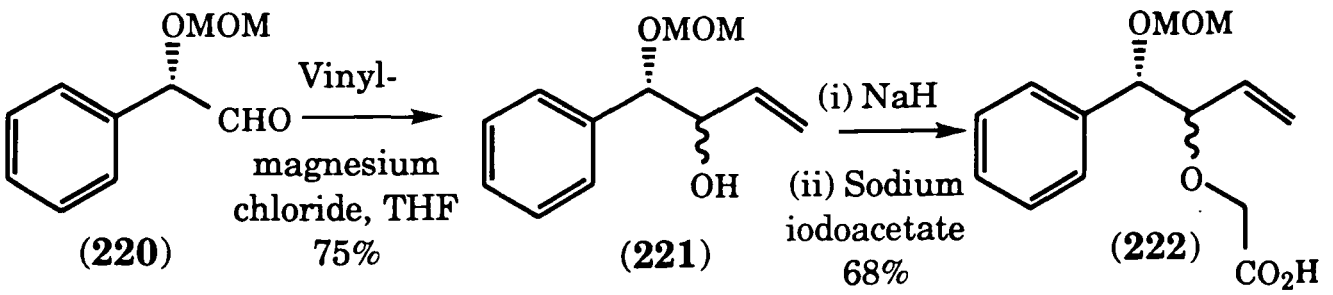
known diol derivative **219**,[167] using diisobutylaluminium hydride in toluene, in essentially quantitative yield. Swern oxidation[168] of the unprotected primary alcohol gave the aldehyde **220** in reasonable yield.

Scheme 166



The aldehyde **220** was then treated with vinylmagnesium chloride to give the allylic alcohols **221**, by a partially stereoselective addition reaction (approximately 3:1 ratio of isomers). Alkylation of the allylic alcohols **221**, using sodium hydride in THF to form the alkoxide and treating the resulting solution with sodium iodoacetate, gave the acids **222** (Scheme 167).

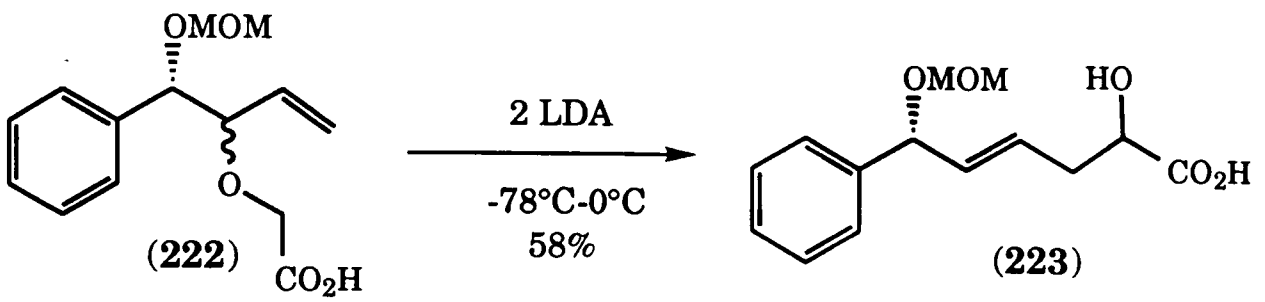
Scheme 167



These acids are precursors to the Wittig rearrangement, as described by Nakai;[165] formation of an anion α to the carboxylate function, at

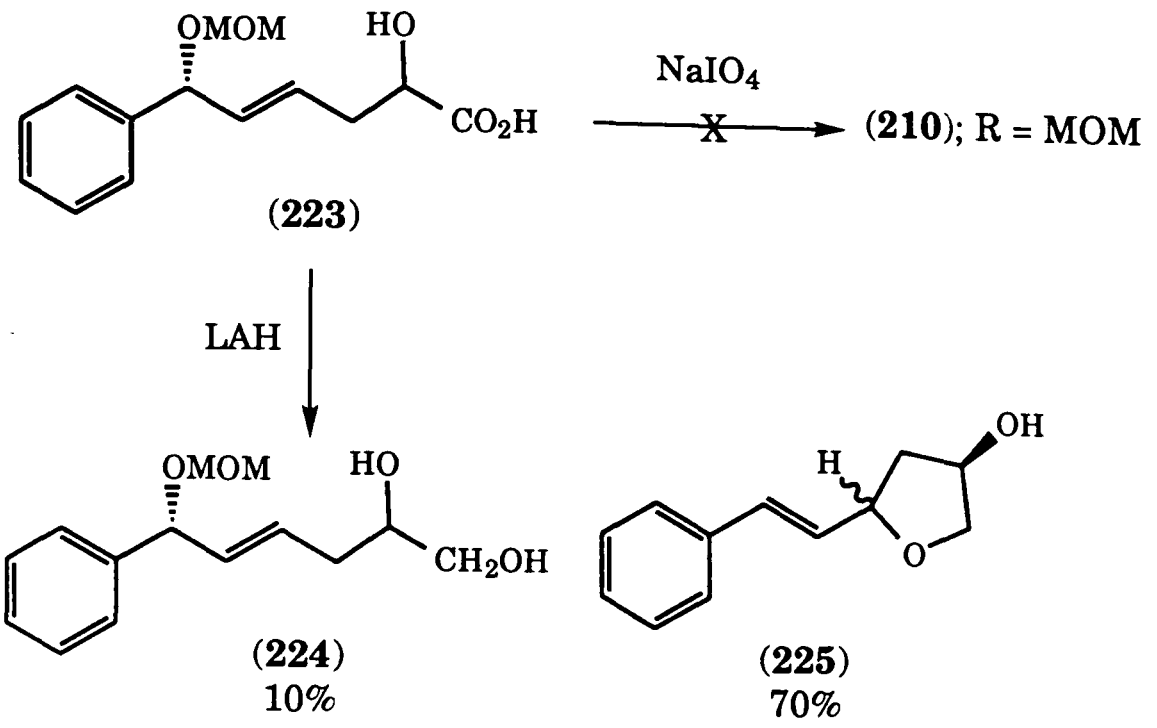
-78°C, using two equivalents of lithium diisopropylamide, allows the thermal rearrangement to occur upon warming to room temperature. The hydroxy-acid **223** was obtained in reasonable yield (Scheme 168).

Scheme 168

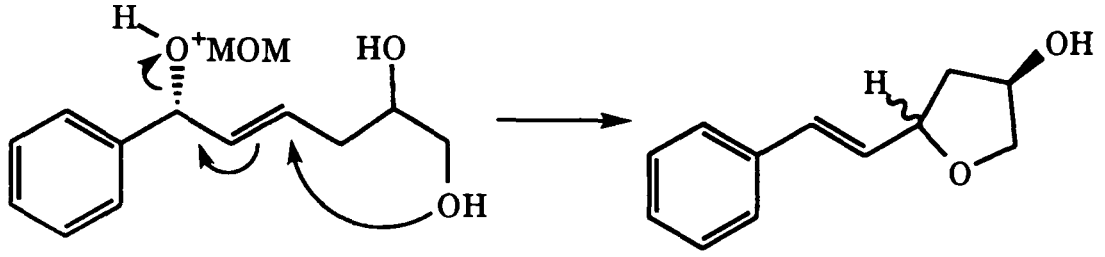


This hydroxy-acid was treated with sodium periodate but there was no aldehyde formation, and significant amounts of the starting material decomposed. Reduction of the hydroxy-acid to the diol **224** was then attempted, as it was thought that periodate cleavage of this would be more facile. However, attempted reduction using LAH gave only a 10% yield of the desired diol **224** and the majority of the product was the undesired hydroxy-THF **225** (Scheme 169). This hydroxy-THF is presumably formed by an S_N1' cyclisation as shown in Scheme 170. The reason for this cyclisation is the fact that the benzylic centre is now also allylic and this allows great stabilisation of a carbocation at this centre. Consequently, loss of the methoxymethoxy group is extremely facile under even mildly (Lewis) acidic conditions. The extra stability of a conjugated double bond relative to an isolated double bond also causes migration to be extremely facile, giving the cyclisation observed. Unfortunately, there is little stereoselectivity in this process, otherwise it would comprise an interesting new route to THFs.

Scheme 169



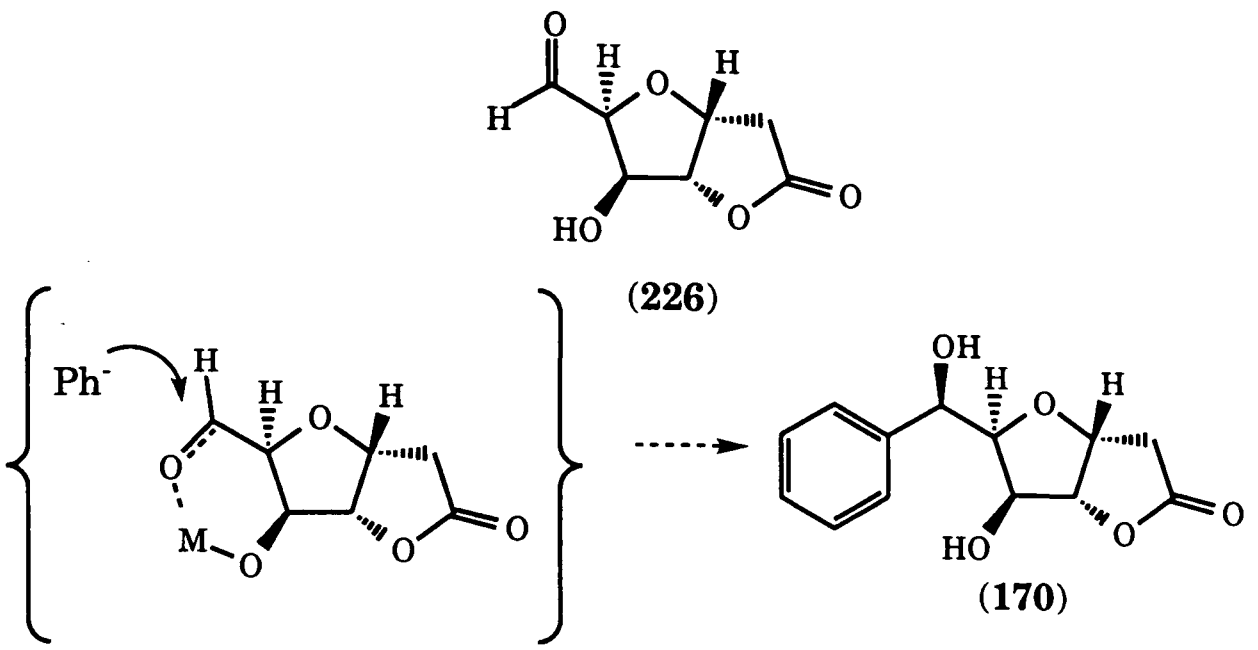
Scheme 170



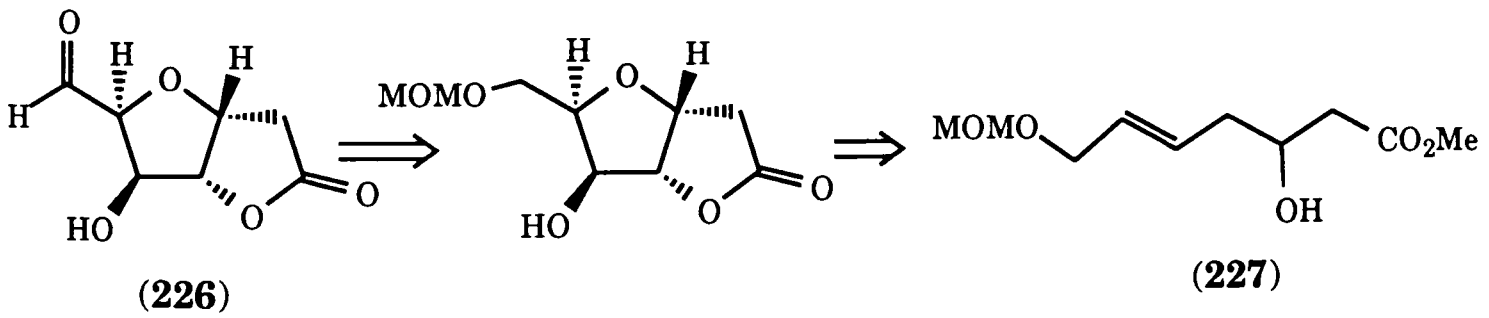
This result gave cause for doubts about whether the iodocyclisation of the ester **208** would be a smooth reaction, or whether the same process as we observed here would occur under the attempted iodocyclisation conditions.

These problems led to the consideration of the use of another disconnection to access the natural product. It was anticipated that the addition of a phenyl anion to the aldehyde **226** would give potentially good chelation control (Scheme 171).

Scheme 171

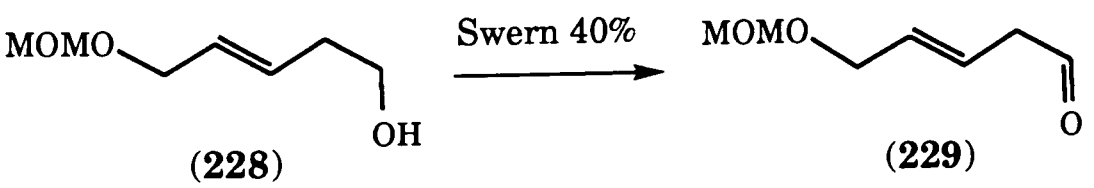


The synthesis of the aldehyde **226** then became a desirable target. It was envisaged that this could be approached using the successful model chemistry described earlier. The β-hydroxy ester **227** became the initial target because it was considered that the oxidation of the primary alcohol would allow the synthesis of the aldehyde **226**.



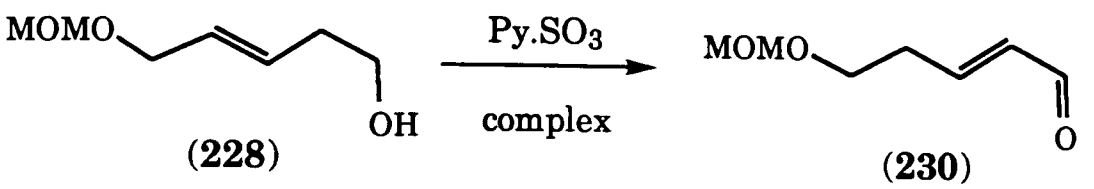
The alcohol **228** was synthesised following the methods of Momose *et al*[169] and was subsequently oxidised to give the aldehyde **229** in a disappointing yield of 40% by the use of a Swern oxidation (Scheme 172).

Scheme 172



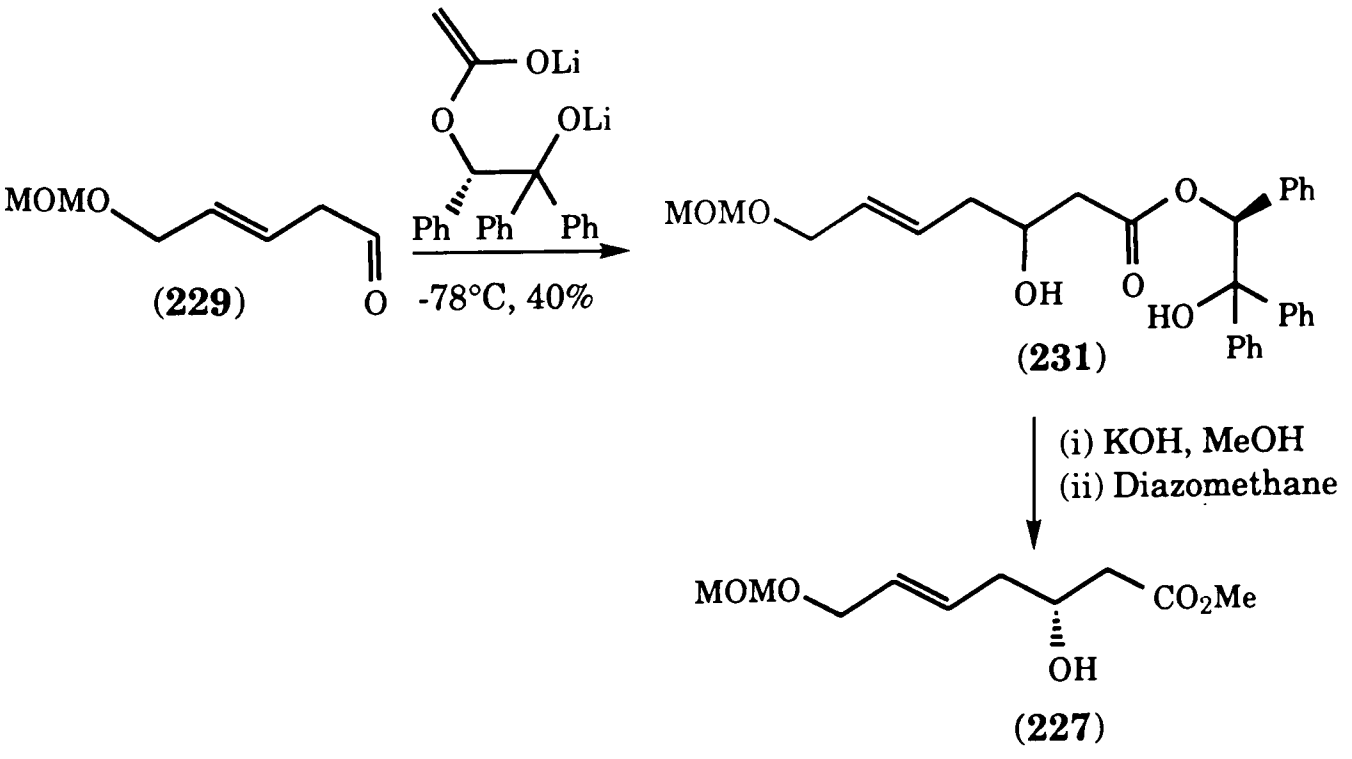
Unfortunately, Moffat oxidation[170] gave only the conjugated aldehyde **230**, and other techniques failed to give any reaction (Scheme 173).

Scheme 173



Chiral aldol reaction of the aldehyde **229** was eventually effected using the methodology first described by Braun.[171] The lithium enolate of (S)-1,1,2-triphenyl-1,2-ethandiol-2-acetate reacted with the aldehyde to give a moderate yield of the β-hydroxy ester **231** on a small scale. Subsequent hydrolysis of this ester and treatment with diazomethane[172] furnished what appeared to be a small quantity of the desired β-hydroxy ester **227**. Time restrictions have not allowed these reactions to be repeated on a larger scale to confirm these results (Scheme 174).

Scheme 174



This synthesis may well be feasible if the phenyl group is introduced at a late stage as shown in Scheme 171, but otherwise the intermediates seem to be too sensitive to undergo the desired transformations.

CHAPTER FIVE

Radical Reactions of Tetrahydrofurans

Radical Reactions of Tetrahydrofurans

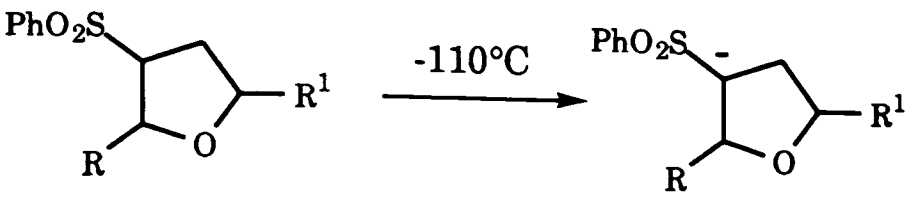
(I) Introduction

As part of the ongoing investigation into methods for the elaboration of the initial products of the iodocyclisations described in Chapter Two, some aspects of the radical chemistry of these tetrahydrofurans were investigated. One of the important considerations in the design of homologation methods for these trisubstituted THF systems is the difficulty in the formation of β-anions. The anticipated facile β-elimination reaction (Scheme 175) which would be expected to occur, allows the stabilisation of the negative charge by transfering it from a carbon atom to an oxygen centre.

Scheme 175

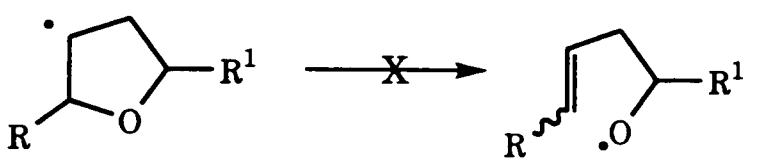
This is a significant limitation in the chemistry of β-iodo-THF systems. Although there are examples of the generation of kinetically stable β-anions in THF systems at extremely low temperatures[173] (Scheme 176), the usefulness of this process has so far been limited.

Scheme 176



The generation of a β-radical, however, is a potentially extremely useful process, as the anticipated kinetic stability of carbon centered radicals, relative to oxygen centered species, means that the β-elimination process does not take place (Scheme 177).

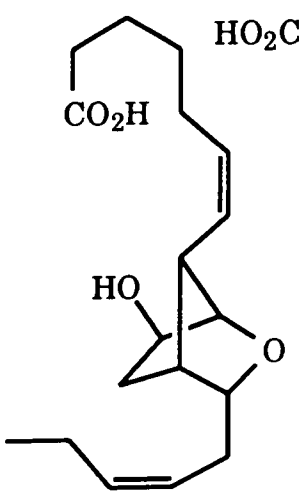
Scheme 177



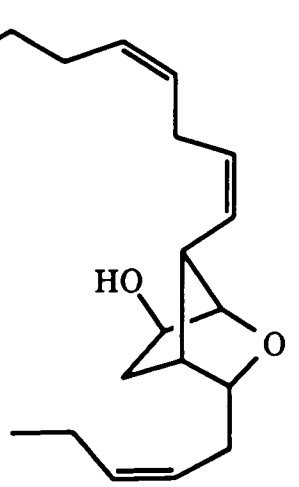
With this knowledge, it was decided to exploit the products of the cyclisation reactions described in Chapter Two to attempt to generate 2,5-disubstituted β-radicals from these THF systems. It has proven possible to illustrate the synthetic potential of this type of intermediate in a new approach to the 2-oxabicyclo-[2.2.1]-heptane ring system **232**.

Scheme 178

(**232**)



Cymathere ether A

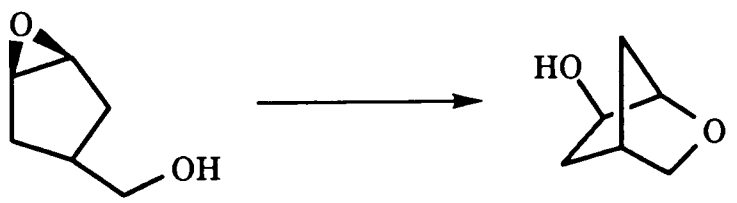


Cymathere ether B

During the last decade, much attention has been focused on

various physiological activities of cyclopentanoids and derivatives of related fused ring systems, especially those of prostacyclines and thromboxanes. Expectations of possible biological activity in this area are high. The 2-oxabicyclo-[2.2.1]-heptane ring system **232** has recently been brought to prominence by the isolation of two fatty acid derived oxylipin natural products, the Cymathere ethers A and B shown in scheme 178.[174] These molecules were isolated from the Marine brown algae *Cymathere triplicata* and appear to be derived by oxidative cyclisation of fatty acids. There are only a very few isolated examples of ring systems of the 2-oxabicyclo-[2.2.1]-heptane type to be found in the chemical literature. The cyclsation of 1-hydroxy-methyl-3,4-epoxycyclopentanes has been used in two cases to generate the ring system (Scheme 179).[175-178]

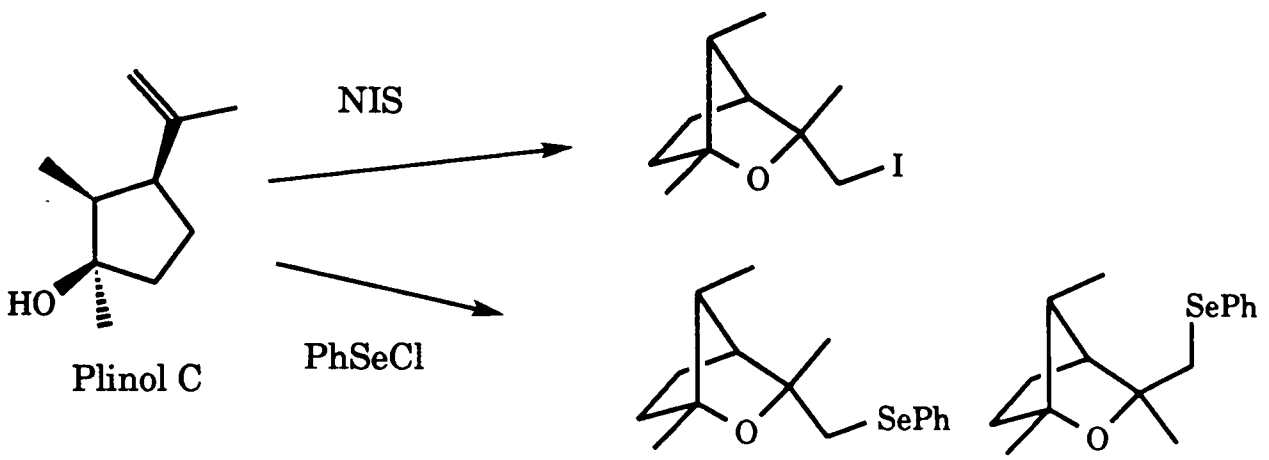
Scheme 179



Kakimuna[177] used the electrophilic 5-*exo*-trig cyclisation of Plinol C by both halo- and selenoetherification procedures to obtain the substituted 2-oxabicyclo-[2.2.1]-heptanes shown in Scheme 180. The stereoselectivity of the thermodynamically controlled iodoetherification, is excellent, but the kinetically controlled selenoetherification shows little selectivity. The difficulty of obtaining other cyclopentanes suitable for

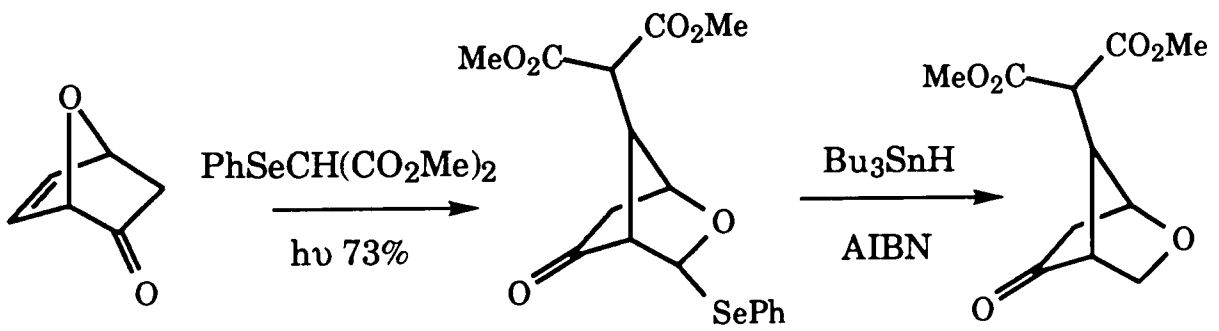
this reaction has meant that only these examples have been carried out.

Scheme 180



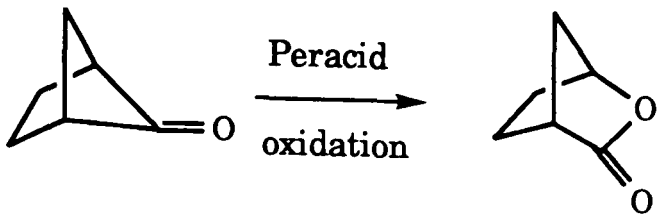
Renaud has used a radical addition to 7-oxabicyclo-[2.2.1]-heptane to generate this ring system in an isolated example (Scheme 181).[178]

Scheme 181



Elaboration of these systems was carried out, but only to a limited extent, and there appear to have been no examples of the generation of 3,5-disubstituted 2-oxabicyclo-[2.2.1]-heptane systems. The related lactone and hemi-acetal ring systems **233** and **234** are somewhat better known. The lactone **233** has been generated by the Baeyer-Villiger oxidation of the ketone **235** (Scheme 182).

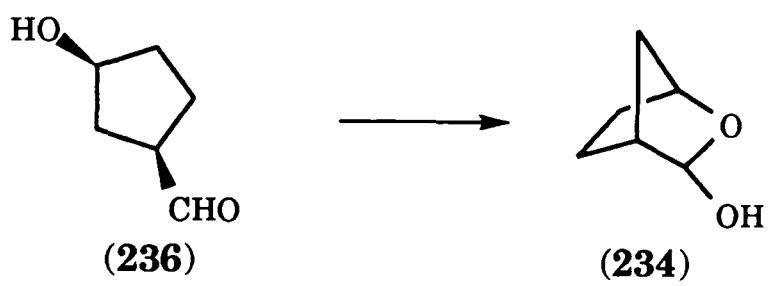
Scheme 182



(235) **(233)**

By contrast the hemi-acetal **234** is derived from ring closure of the *cis*-cyclopentane aldehyde **236** (Scheme 183).[179]

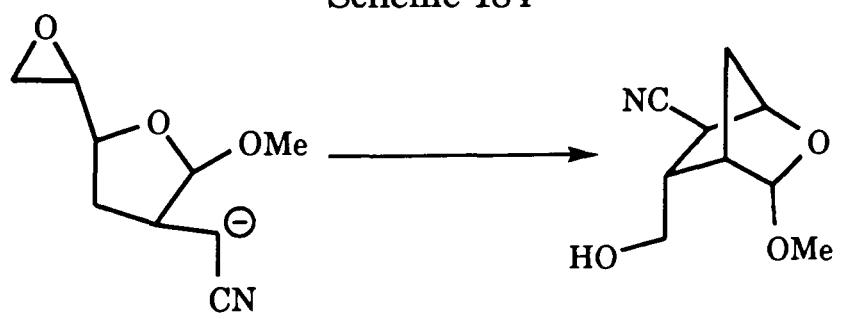
Scheme 183



(236) **(234)**

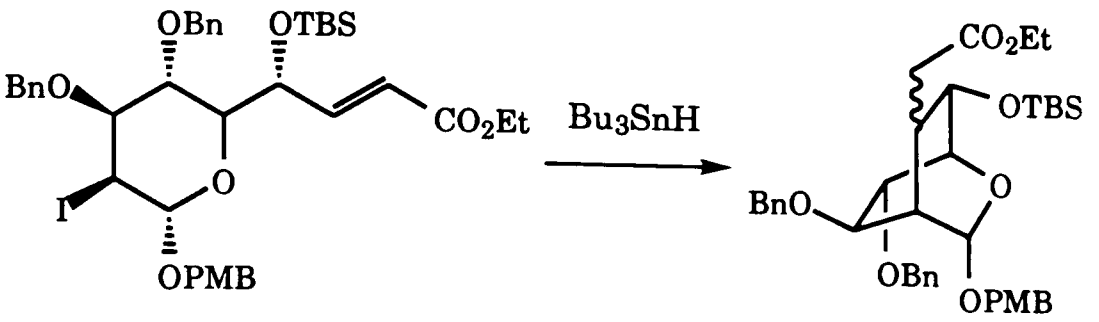
Bicyclic hemi-acetals of the type described above have also been generated by the cyclisation of the cyano-epoxide shown in Scheme 184.[180]

Scheme 184



An interesting radical cyclisation of carbohydrate derived iodo-hemi-acetals has been used by Fraser-Reid to generate bicyclic hemi-acetals, in a related ring system, as shown in Scheme 185.[181]

Scheme 185

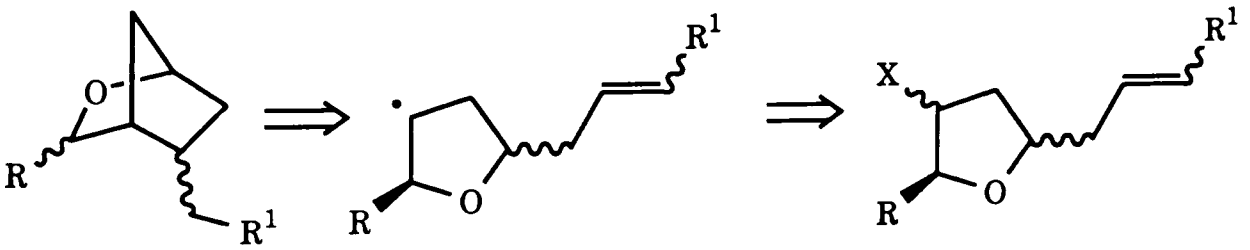


With these exceptions, the ring system has not been approached by organic chemists.

(II) Radical Chemistry of 2,3,5-Trisubstituted THFs

It was anticipated that this ring system would be accessible from the cyclisation of the α-alkenyl-THF radicals **237**, available from the 2,3,5-trisubstituted THFs **238**. These THFs would, in turn, be available from simple elaboration of the cyclisation products described in Chapter Two (Scheme 186).

Scheme 186

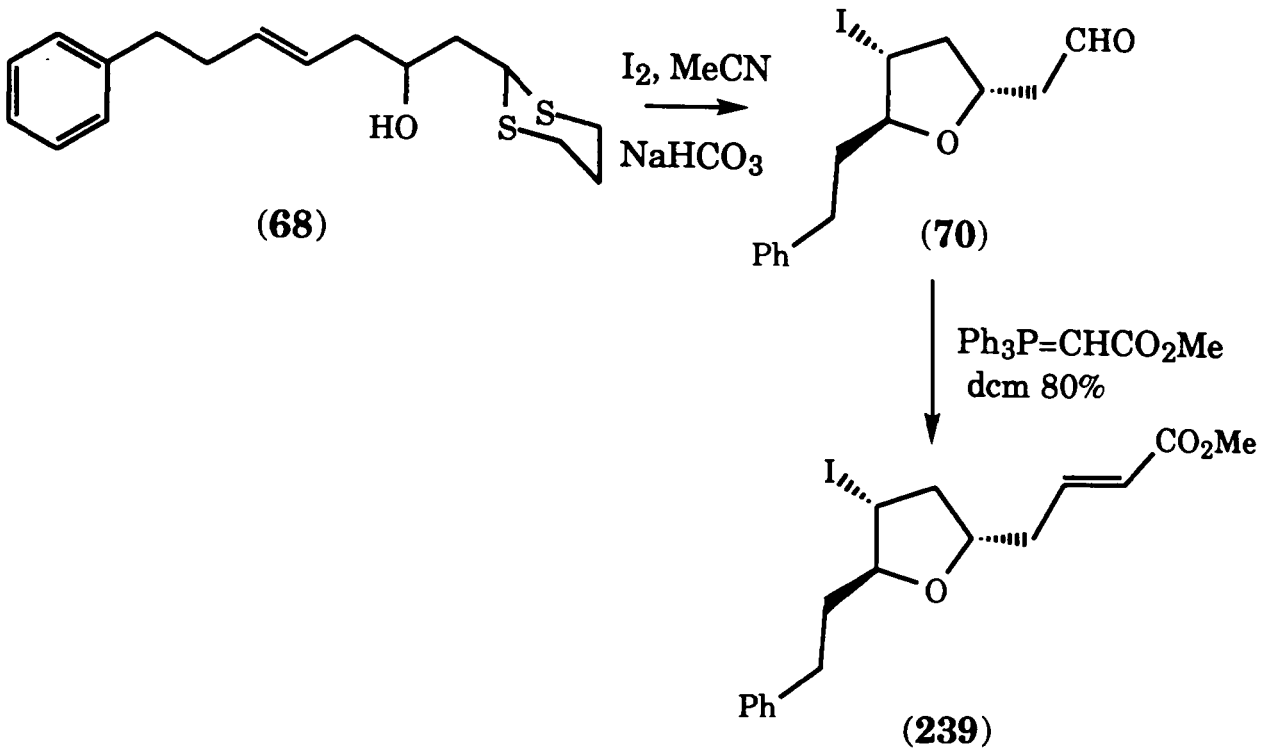


(237) **(238)**

Consequently, when the aldehyde **70** was isolated as a side product from the iodocyclisation of the dithiane **68**, the opportunity to

investigate such cyclisations was presented. The aldehyde **70** was homologated using methyl triphenylphosphoranylideneacetate in dichloromethane to give the (E)-ester **239** in good yield (Scheme 187).

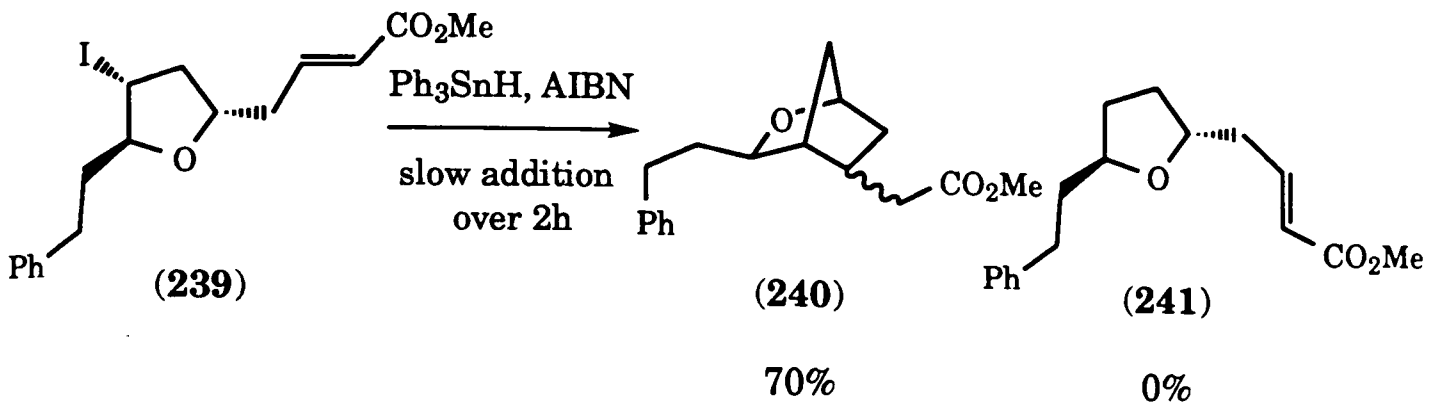
Scheme 187



(68) **(70)** **(239)**

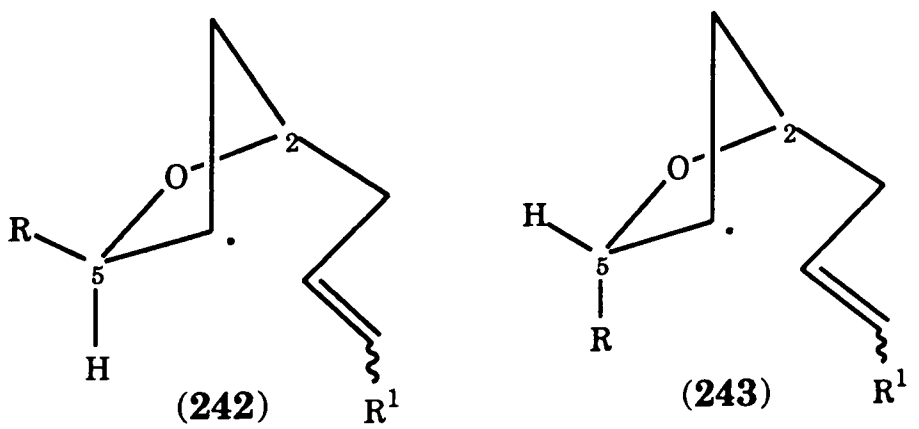
When this ester was subsequently treated, on a small scale, with triphenyltin hydride and azo-*bis*-isobutyronitrile (AIBN) in benzene, at reflux, using the slow addition conditions recommended by Motherwell and Crich,[182] the desired ring system **240** was isolated in a 70% yield as a 3:1 mixture of isomers, the stereochemistry of which was not proven (Scheme 188). No sign of reduced starting material **241** was observed. Slow addition conditions were used to ensure a low concentration of hydride radicals, therefore maximising the chance of cyclisation occurring. The final product of this reaction sequence was fully characterised, but insufficient data were obtained for the intermediates to allow their inclusion in the experimental section.

Scheme 188



To investigate this encouraging preliminary result, a variety 2-alkenyl-4-iodo-THFs and 2-alkenyl-4-hydroxy-THFs were synthesised containing both conjugated and unconjugated double bonds. The cyclisation of the *trans*-2,5-disubstituted-THF radical **242** showed only moderate stereoselectivity. However, upon consideration of the transition state from this and from the cyclisation of the corresponding *cis*-2,5-disubstituted THF radical **243**, it was postulated that the cyclisation of the *cis*-2,5-disubstituted THF radicals might be expected to proceed with greater stereoselectivity (Scheme 189), assuming the departed iodine atom does not influence these conformations.

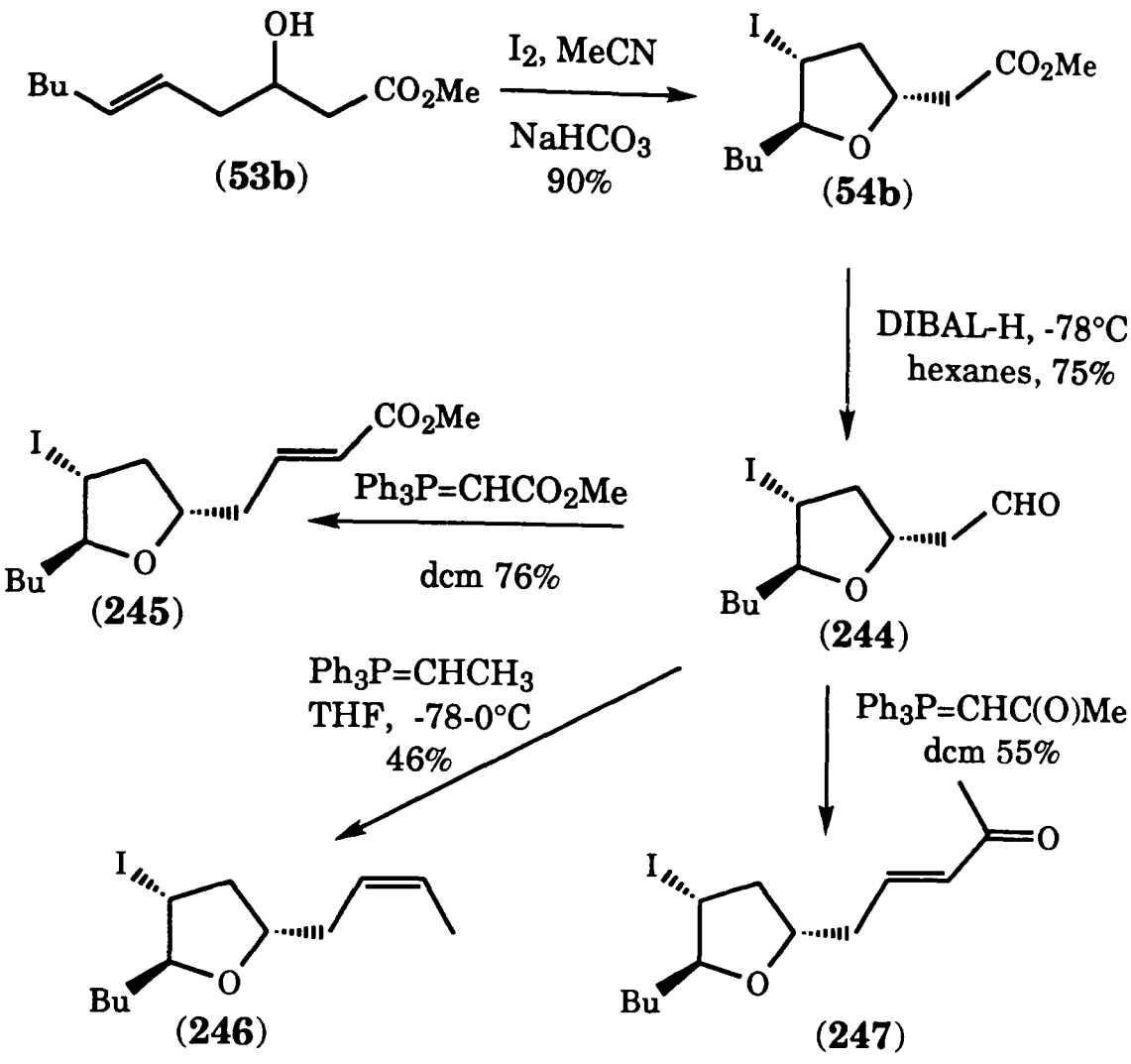
Scheme 189



The 2-substituent containing the radical acceptor is constrained to be in a pseudo-equatorial position so that it is able to cyclise. This means that in the case of the *trans*-2,5-disubstituted-THF radical, the 5-substituent is in a pseudo-equatorial position and therefore little steric effect is exerted upon the cyclisation. In contrast, in the case of the *cis*-2,5-disubstituted-THF radical, the 5-substituent is constrained to be in a pseudo-axial position for cyclisation to take place. This means that this substituent could exert a steric effect upon the cyclisation causing a higher stereoselectivity to be observed. The availability of both *trans*-2,5-disubstituted-THF radicals (from the iodo-THFs) and *cis*-2,5-disubstituted-THF (from the Barton deoxygenation of the hydroxy-THFs) allowed this theory to be investigated.

The iodotetrahydrofuran **54b** was easily available in multigram quantities from the iodoetherification of the β-hydroxy-δ-alkenoate **53b**. Treatment of this compound with diisobutylaluminium hydride in hexanes at -78°C over 2 hours gave the aldehyde **244** in good yield. This aldehyde was then homologated with various Wittig reagents. Methyl triphenylphosphoranylideneacetate in dichloromethane gave a 76% yield of the (E)-alkenoate ester **245**. Ethyl triphenylphosphonium iodide was treated with butyl lithium at -78°C to generate the corresponding ylid, which reacted with the aldehyde **244** to give a 46% yield of the (Z)-alkene **246**. Triphenyl-phosphoranylidine-2-propanone reacted with the aldehyde to give a 55% yield of the (E)-ketone **247** (Scheme 190).

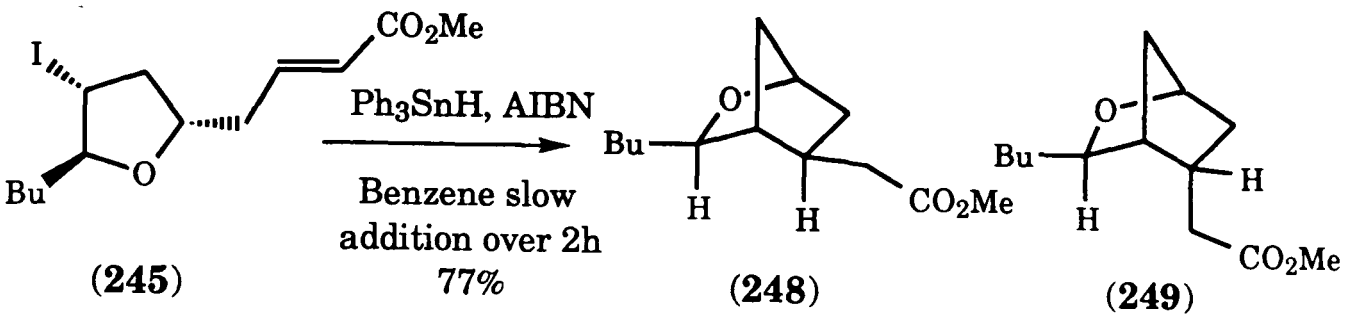
Scheme 190



The cyclisations of these molecules were carried out under similar conditions to those specified for the preliminary cyclisation of the ester **239**. In the case of the cyclisation of the ester **245**, the earlier conditions were closely followed. In the case of the cyclisation of the alkene **246**, which was carried out on a larger scale, the addition of reagents was carried out using a syringe pump. To facilitate the removal of non-polar tin residues from the products, which are themselves non-polar, an aqueous potassium fluoride work up was used in the cyclisations of the alkene **246** and the ketone **247**, to enable the isolation of the products in a pure form.[182]

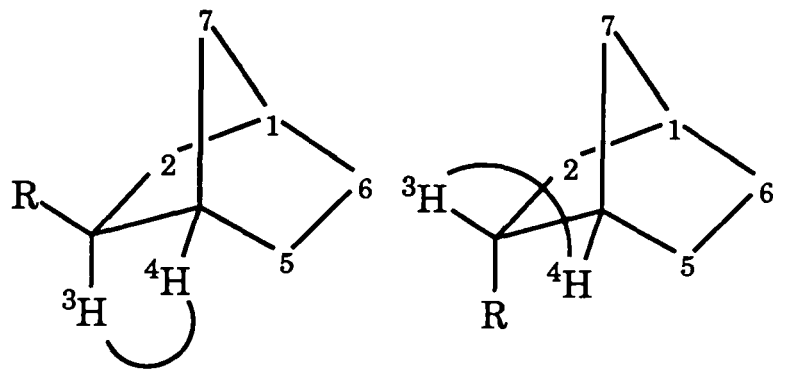
The cyclisation of the ester **245** furnished a 3:1 mixture of the two isomeric 2-oxabicyclo-[2.2.1]-heptanyl esters **248** and **249** (Scheme 191), in a satisfying 77% combined yield.

Scheme 191



(245) **(248)** **(249)**

Scheme 192



$J_{3,4}$ = 0-2 Hz where 3-H is *endo*

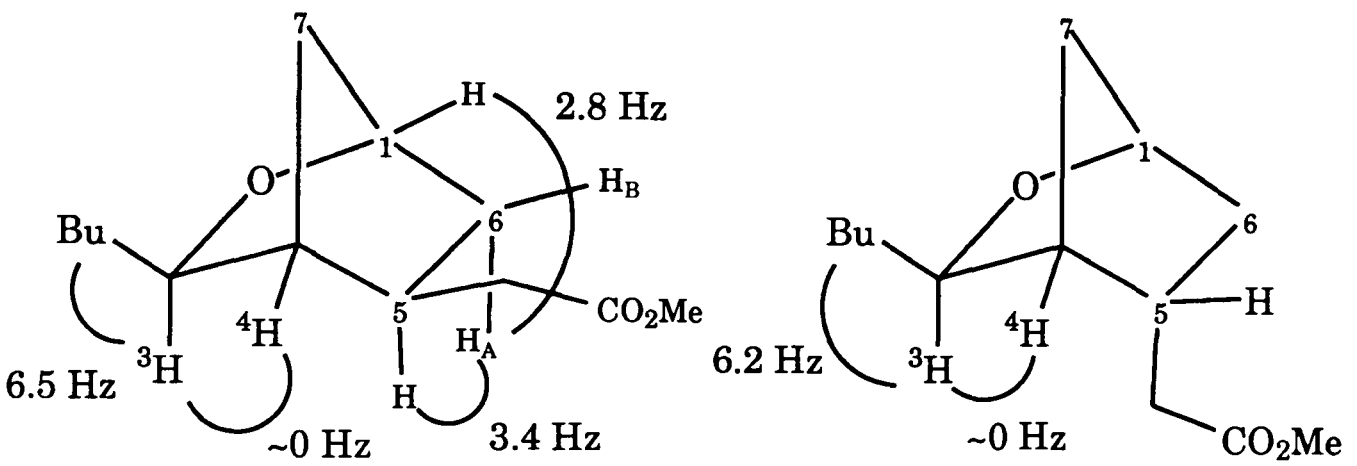
$J_{3,4}$ = 3-5 Hz where 3-H is *exo*

Comparative coupling constant data from norbornane systems were used to assign the stereochemistries of these products (Scheme 192).[183]

^{1}H-^{1}H and ^{1}H-^{13}C COSY NMR spectra allowed the assignment of the NMR resonances of both isomers. Both exhibited a broad triplet due to the 3'-H resonance (assigned by ^{1}H-^{1}H COSY NMR spectrum) with J = 6.5 Hz (major isomer **248**) and 6.2 Hz (minor isomer **249**) due to coupling to the butyl side chain. In neither case was coupling to the 4'-H

observed. This suggested the assignment of a 3'-*exo* configuration of the butyl side chain in both isomers. In both isomers, the 1'-H occurred as a broad singlet in accordance to the literature precedent;[174-176] the 4'-H was also a broad singlet at δ_H = ~2 in both isomers. Both the 7'-H resonances occured separately between δ = 1.10-1.70, as observed in previous examples.[176]

Scheme 193

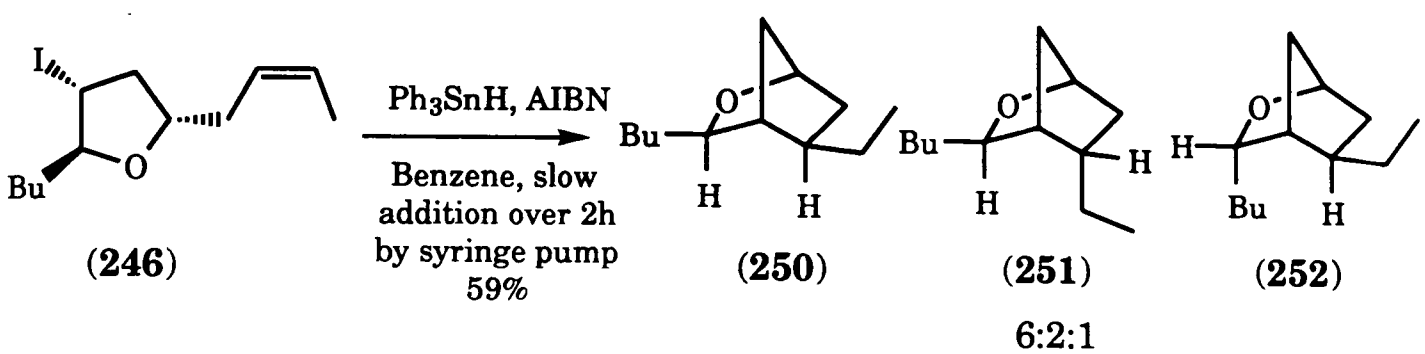


(248) **(249)**

A coupling of 3.4 Hz is observed from the 5'-H to the 6'-H_A in the major isomer; since a coupling of 2.8 Hz is also observed in the resonance for the 6'-H_A, almost certainly to the 1'-H, this indicates that the 6'-H_A is *endo*, the 1'-H fixed and the 5'-H also *endo* (*ie* the major isomer **248** has the 3'-*exo*, 5'-*exo* conformation). The relevant resonances for the 5'-H, 6'-H_A and 6'-H_B of the minor isomer **249** are obscured but as the 3'-*exo* conformation is suggested by the lack of coupling from the 3'-H to the 4'-H, the 3'-*exo*, 5'-*endo* conformation is the only likely possibility remaining (Scheme 193).

In the cyclisation of the alkene **246** under the same conditions three isomeric 2-oxabicyclo-[2.2.1]-heptanes **250**, **251** and **252** were isolated (Scheme 194).

Scheme 194



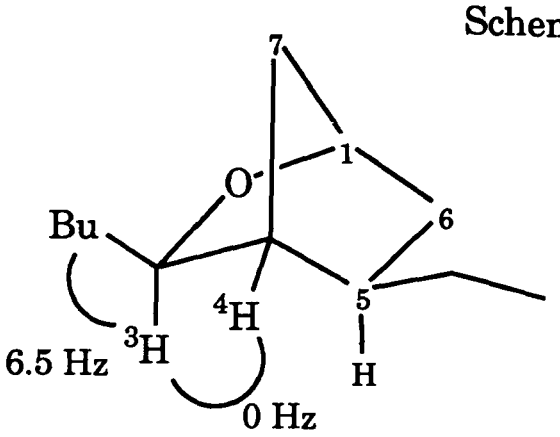
(**246**) (**250**) (**251**) (**252**)

6:2:1

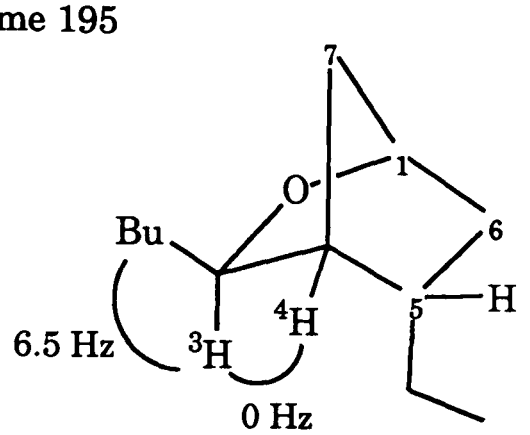
A ratio of 6:2:1 was observed; careful chromatography allowed the minor third isomer **252** to be separated from the two others. Mass spectrometry confirmed that these were indeed isomers of the same molecular formula, whilst ^{13}C NMR showed that the three isomers had discernable differences. Again, in the cases of isomers **250** and **251**, ^{1}H-^{1}H and ^{1}H-^{13}C COSY NMR spectra allowed the assignment of the resonances for both isomers. The 3-H resonance in both cases was a broad triplet of coupling constant 6.5 Hz to the butyl side chain, with no coupling apparent to the 4-H, suggesting the assignment of a 3-*exo* configuration to both the isomers **250** and **251**. The 4-H again appeared as a broad singlet at δ = ~2 in both isomers. As expected from the literature data of these systems, both the 7-H resonances occurred separately between δ_H = 1.20-1.50.[176] The resonances relating to the 5-H, 6-H_A and 6-H_B of both the isomers occur together and are therefore obscured. However, since the 3-H has been assigned to the *endo*

position, the 3-*exo* configuration for the butyl substituent has been demonstrated. This means that the isomers **250** and **251** represent the 3-*exo*, 5-*exo* and the 3-*exo*, 5-*endo* isomers respectively. By analogy to the similar cyclisation products, it seems reasonable that the major isomer **250** has the 3-*exo*, 5-*exo* configuration.

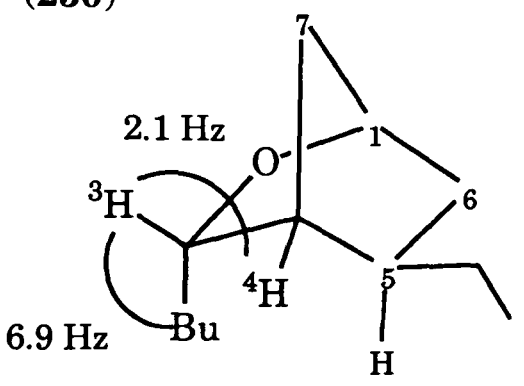
Scheme 195



(250)



(251)



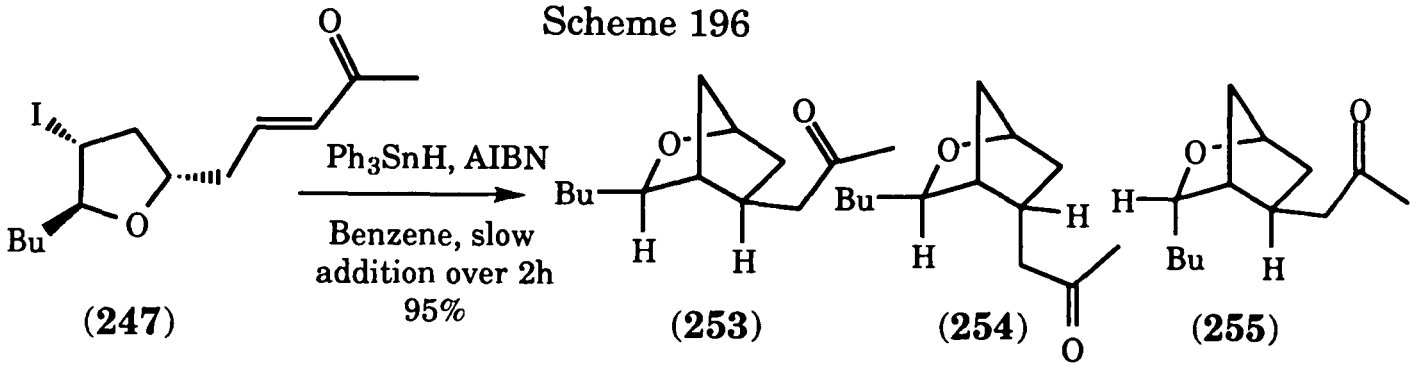
(252)

The third isomer **252** exhibited a resonance at δ_H = 3.78 for the 3-H which was a triplet of doublets containing couplings of 6.9 Hz to the butyl side chain and 2.1 Hz to the 4-H. This suggested that in the isomer **252**, the butyl group has the 3-*endo* configuration. The other information derived from the ^{1}H NMR spectrum did not allow a firm assignment of the 5-H stereochemistry of this single isomer; however, the

assumption is made that it is unlikely to be the 3-*endo*, 5-*endo* isomer due to the steric constraints involved in the cyclisation. The fact that this isomer is formed to the exclusion of the other possible isomer, suggests that this has the 3-*endo*, 5-*exo* configuration (Scheme 195).

The cyclisation of the ketone **247** under the earlier conditions led to the formation of the three isomeric ketones **253**, **254**, and **255** in a high combined yield (Scheme 196). A ratio of 3:1:1 was observed; separation of the third isomer **255** was achieved by careful chromatography.

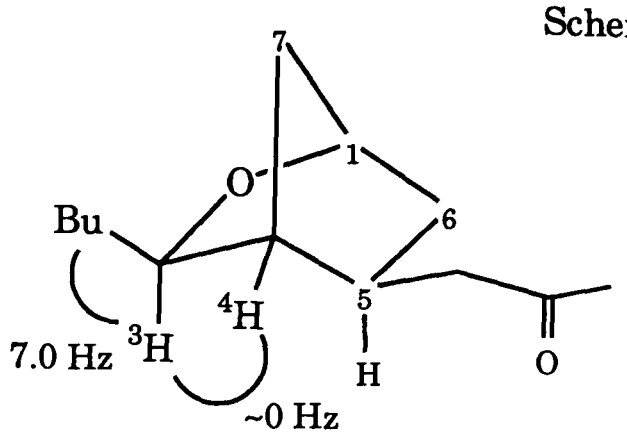
Scheme 196



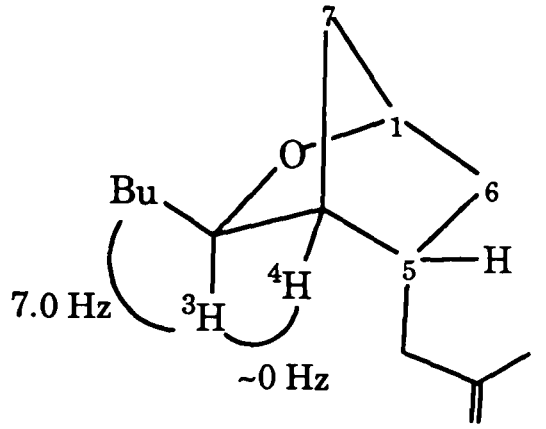
The reduced stereoselectivity of this cyclisation may be due to the fact that the cyclisation is faster, as the conjugated ketone used is the best radical acceptor tried in this series. This may also explain the high overall yield. Mass spectrometry showed that these compounds had the same molecular formula, whilst ^{13}C NMR was used to demonstate that the three isomers had discernable differences. The 3-H resonance for the isomers **253** and **254**, was a broad triplet of coupling constant 7.0 Hz to the butyl side chain, with no apparent coupling to the 4-H, in either case. This suggested the assignment of a 3-*exo* conformation for the butyl substituent in both the isomers **250** and **251**. The 4-H again appeared as a broad singlet at δ = ~2 in both isomers. Both the 7-H

resonances occurred separately between δ_H = 1.50-1.60, as in the literature examples.[176] The resonances relating to the 5-H, 6-H_A and 6-H_B of both the isomers occur as overlapping multiplets and are therefore obscured. However, since the 3-H has been assigned to the *endo* position, the 3-*exo* configuration has been demonstrated.

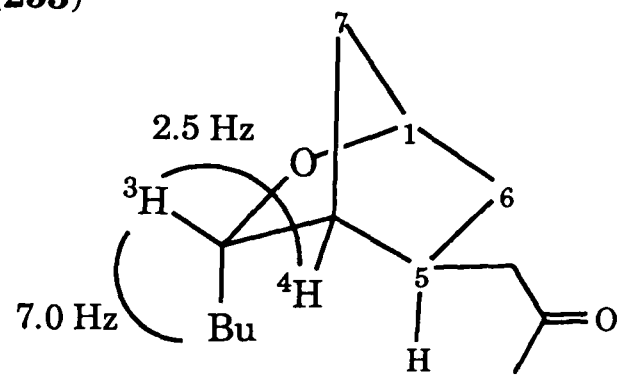
Scheme 197



(253)



(254)



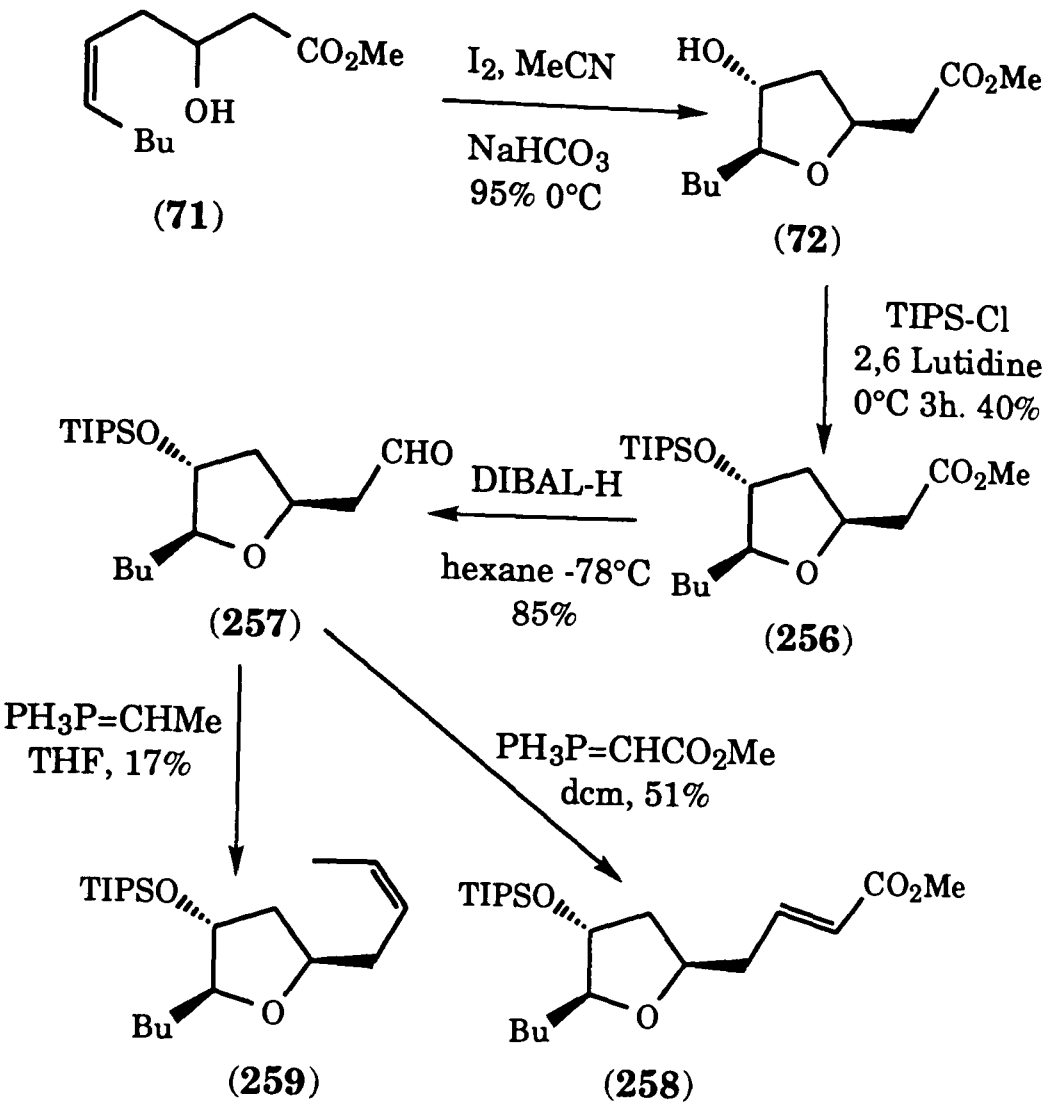
(255)

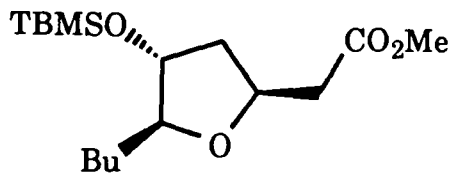
This means that the isomers **253** and **254** represent the 3-*exo*, 5-*exo* and the 3-*exo*, 5-*endo* isomers respectively. By analogy to the similar cyclisation products, it can be assumed that the major isomer **253** has the 3-*exo*, 5-*exo* configuration. The third isomer **255** exhibited a resonance at δ_H = 3.81 for the 3-H which was a triplet of doublets containing couplings of 7.0 Hz to the butyl side chain and 2.5 Hz to the 4-

H, indicating that the isomer **255** had the 3-*endo* conformation. The other information derived from the ^{1}H NMR spectrum did not allow a firm assignment of the 5-H stereochemistry of this single isomer; as before the assumption is made that it is unlikely to be the 3-*endo*, 5-*endo* isomer due to the steric constraints involved in the cyclisation. The formation of the isomer **255** without the formation of the other possible isomer suggests that this product has the 3-*endo*, 5-*exo* configuration (Scheme 197).

The hydroxy-THF **72** used in the earlier model work, is easily obtained in multigram quantities from the iodocyclisation of (Z)-methyl 3-hydroxydec-5-enoate **71**. This hydroxy-THF was silylated in exactly the same manner as the corresponding 5'-methyl hydroxy-THF **148**, (*ie* using TIPS triflate, and 2,6-lutidine in dichloromethane) to give the silyl ether **256**. A somewhat lower yield was obtained, but as this was an isolated occurrence the reaction was not optimised further. The TIPS protecting group was used in preference to the corresponding TBS function as low yields were obtained in the reduction of the silyl ether **138**, due to the cleavage of the silicon group. However, reduction of the silyl ether **256** with diisobutylaluminium hydride in hexane, at -78°C, proceeded without removal of the protecting group, to give the aldehyde **257**, in an excellant yield of 85%. This aldehyde was then homologated with various Wittig reagents. Methyl triphenylphosphoranylideneacetate in dcm gave a 51% yield of the alkenoate ester **258** (Scheme 198).

Scheme 198





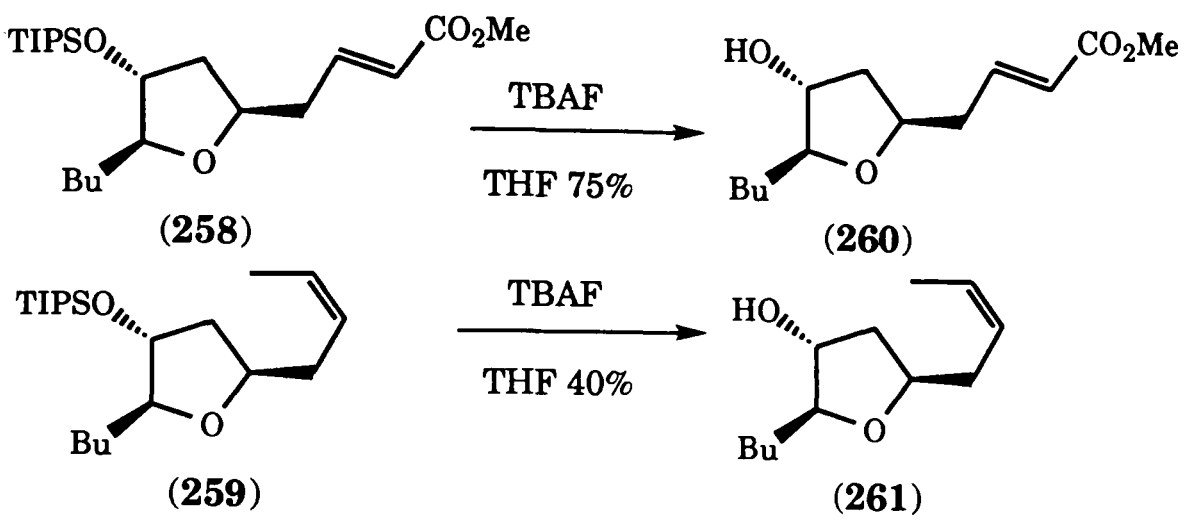
(138)

Ethyl triphenylphosphonium iodide was treated with butyl lithium at -78°C to generate the corresponding ylid, which reacted with the aldehyde **257** to give only a 17% yield of the alkene **259**. These yields are again unoptimised (from a single experiment) and consequently disappointing; however, if significantly improved they would offer a

comprehensive route to these cyclisation precursors.

Desilylation of these Wittig products proceeded in relatively good yields to give the hydroxy-THFs **260** and **261** (Scheme 199).

Scheme 199



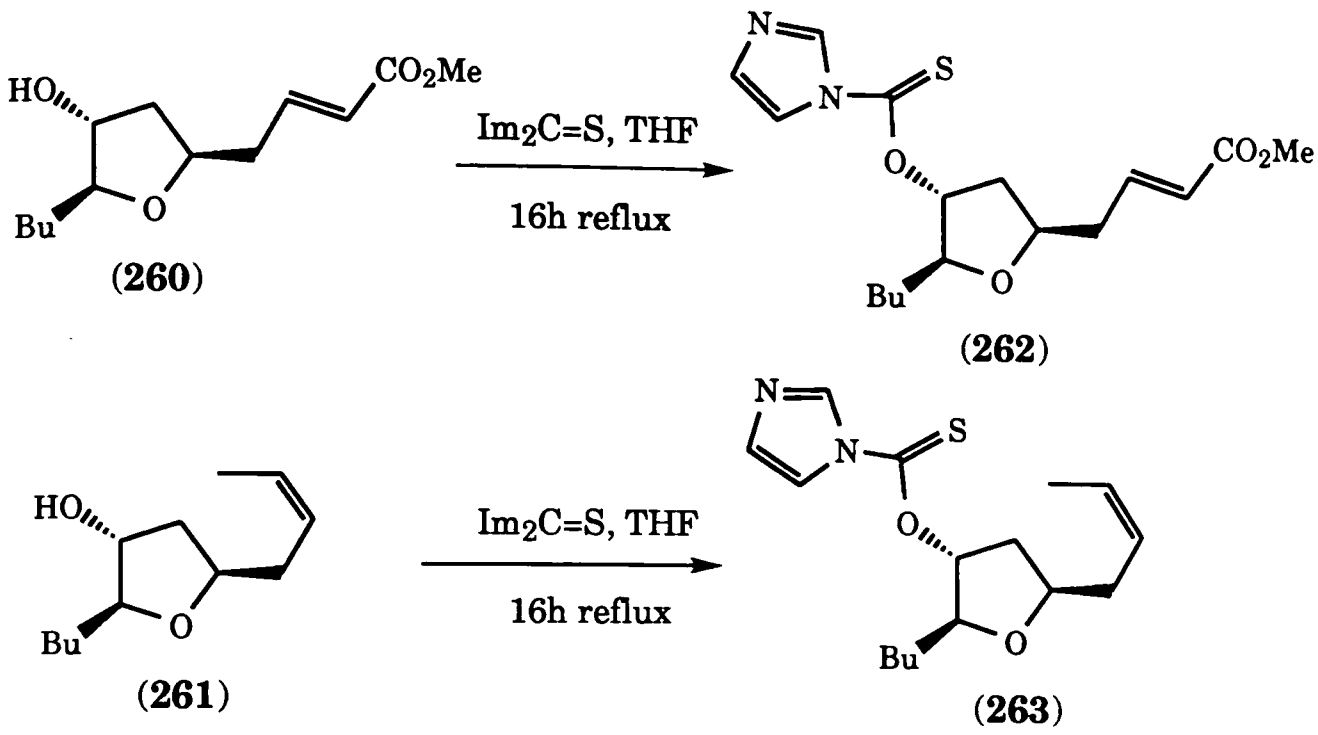
(**258**) (**260**)

(**259**) (**261**)

The Barton deoxygenation of these alkenes gives the 2,5 *cis*-disubstituted-THF radicals which are the direct analogues of the 2,5 *trans*-disubstituted THF radicals generated from the iodo-THFs **245** and **246**. This provides an opportunity to test the proposal made earlier in this chapter, *ie* that a better stereoselection would be obtained from the 2,5 *cis*-disubstituted THF radicals.

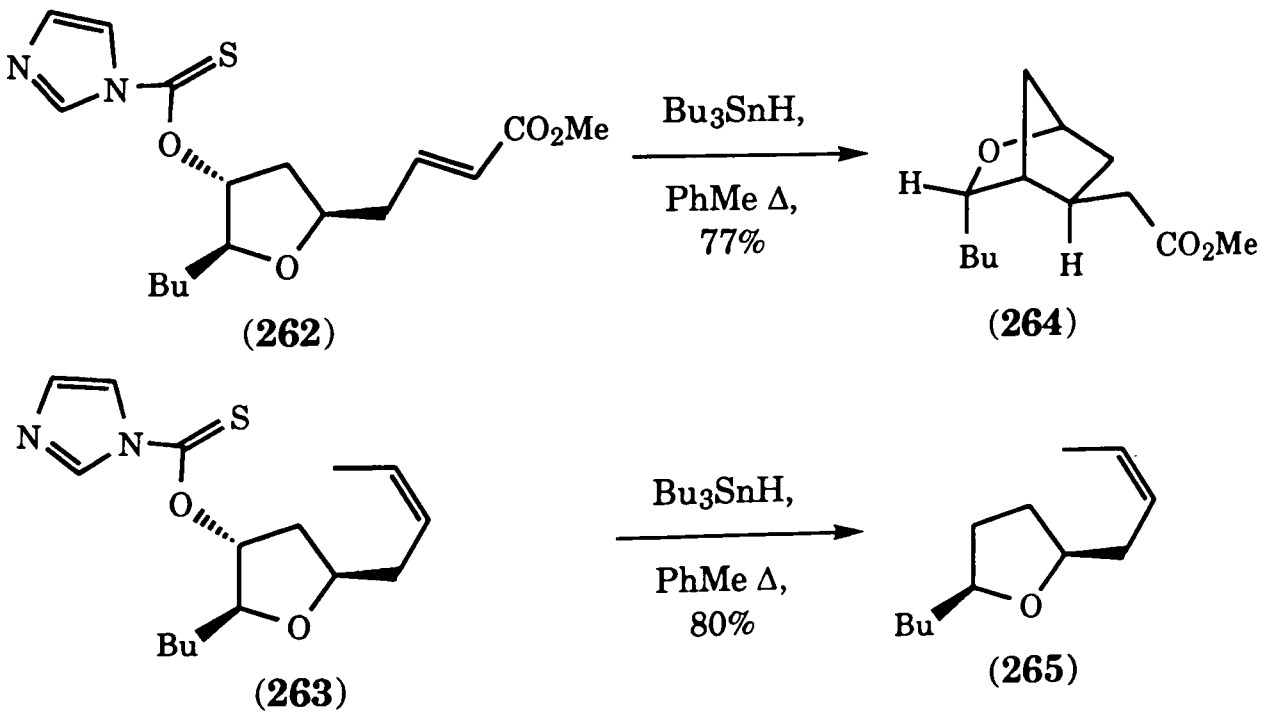
The thioimidazole esters **262** and **263** of the alcohols **260** and **261** were formed quantitatively using thiocarbonyldiimidazole in THF at reflux (Scheme 200).

Scheme 200



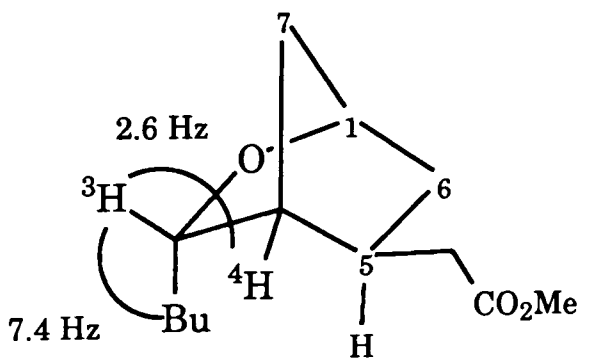
Treatment of these derivatives with tributyltin hydride in refluxing toluene resulted in deoxygenation, forming the required radicals.[184] The alkenoate ester **260** cyclised to give the substituted 2-oxabicyclo-[2.2.1]-heptanyl ester **264** as the only product in 77% yield, whereas the alkene **261** was simply deoxygenated to give the 2,5-*cis*-THF **265** in 80% yield (Scheme 201).

Scheme 201



The cyclisation of the alkenoate ester **260** was stereospecific giving a single isomer. This result is especially pleasing as it provides evidence that the reaction path follows that discussed earlier, as greater selectivity was predicted on the basis of the transition states described in Scheme 189. The substituted 2-oxabicyclo-[2.2.1]-heptanyl ester **264** exhibited the broad singlet in the ^1H NMR spectrum at $\delta_H = 4.26$ corresponding to the 1'-H. It also showed the characteristic broad singlet at $\delta_H = 2.04$ from the 4'-H. Mass spectrometry demonstrated that the isomer had the same molecular formula and major fragmentation pattern as the two isomeric products from the cyclisation of the corresponding 2,5-*trans*-THF radical from ester **245**. The ^{13}C NMR spectrum showed that the isomers **248**, **249** and **264** were similar but showed distinct differences. Crucially, the 3'-H shows a resonance at $\delta_H = 3.81$, which is a triplet of doublets showing coupling constants of 7.4 Hz to the butyl side chain and 2.6 Hz to the 4'-H.

Scheme 202

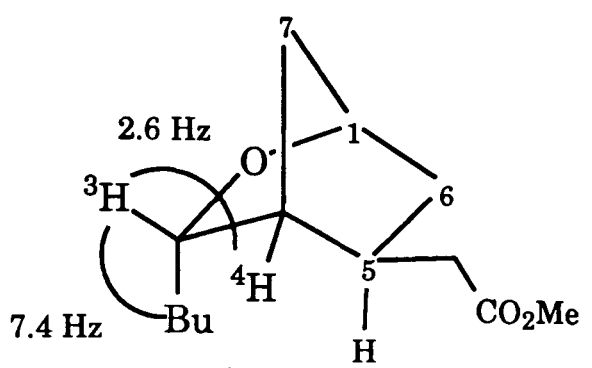


(**264**)

By analogy to the earlier systems, this suggests a 3'-*endo* configuration; although the rest of the coupling constants in this isomer

are difficult to analyse, the 5'-*exo* configuration is thought to be more likely as the stereoselectivity is almost certain to arise from the steric strain involved in the formation of the 3'-*endo*, 5'-*endo* isomer (Scheme 202).

Scheme 202



(264)

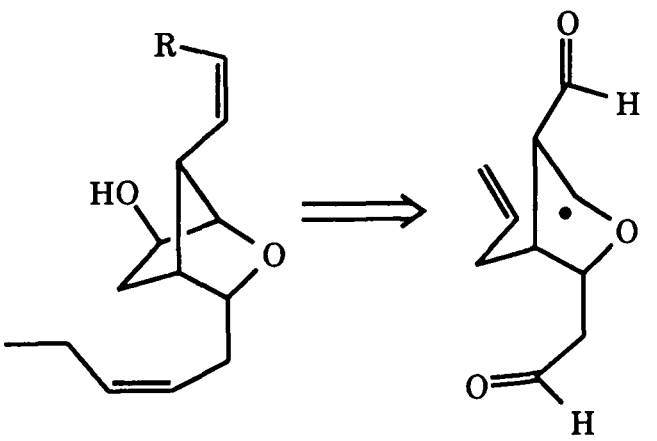
The deoxygenation of the alkene **261** could perhaps be avoided by the use of lower temperatures for the cyclisation process (*ie* allowing less collisions and favouring intramolecular reaction), or by further increasing dilution or slowing down the speed of addition of the tributyltin hydride. However, time constraints did not allow these trial reactions to be carried out.

Atom transfer cyclisation of the ester **245** was attempted using the procedure developed by Curran[185] which consists of irradiation of the molecule with a 275 W sun lamp, in the presence of 0.1 mol% hexabutylditin in benzene. Cyclisation was <u>not</u> observed, but the iodine atom was epimerised to give a 1:1 mixture of the ester **245** and its 7-epimer **263** (Scheme 203).

I thank Dr J. A. Murphy and others for helpful discussion at this

point, suggesting that there is a low driving force for the cyclisation, which can be considered to be an equilibrium process. It is possible that upon formation of a small concentration of THF radicals during this process, the tributyltin iodide which is also produced can trap the radical before it cyclises. This would regenerate the iodo-THF, but without stereoselectivity (*ie* epimerisation at the 7-position would be observed). Alternatively, this could occur by a simple Finkelstein exchange between the starting material and the tributyltin iodide generated under the reaction conditions.

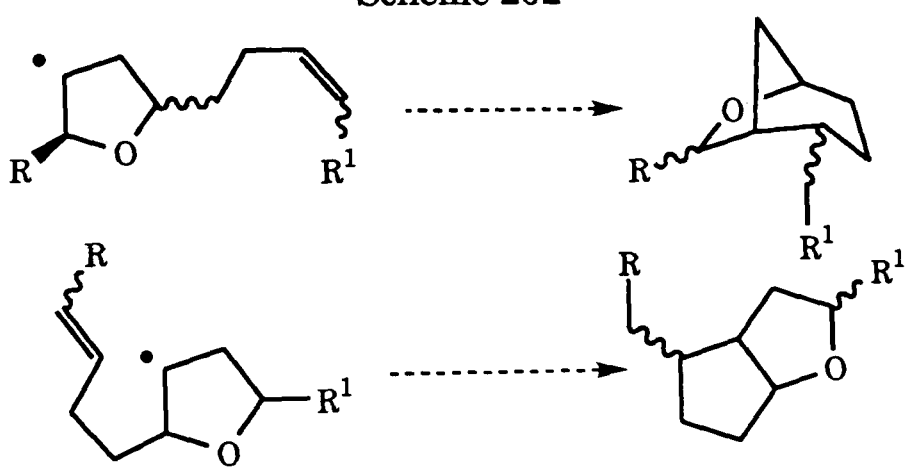
Scheme 204



In conclusion, it has been shown that the radical cyclisation of 2,5-disubstituted-THF radicals having alkenyl side chains provides an efficient and, in some cases, highly stereoselective route to the 2-oxabicyclo-[2.2.1]-heptane ring system. This could, therefore possibly, be developed into a viable approach to the Cymathere ethers A and B (Scheme 204). There is however a lot of development of the methodology required.

Similar radical cyclisations could be used to generate other interesting ring systems (Scheme 205). This would provide an interesting combination of ionic and radical processes in the preparation of bicyclic systems.

Scheme 202



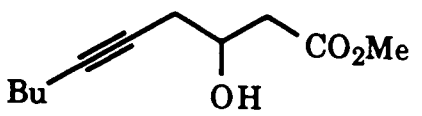
CHAPTER SIX

Experimental

General Experimental

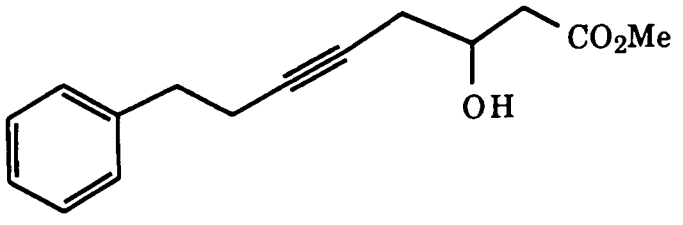
Melting Points were determined on a Kofler hot stage apparatus and are uncorrected. Infra red spectra were recorded on a Perkin Elmer 1720 FTIR as liquid films or as chloroform solutions. ^{1}H NMR spectra were measured on Brüker WM 250 (250 MHz, PFT), Brüker AM 400 (400 MHz, PFT), and JEOL EX270 (270 MHz, PFT) instruments. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad and dt; doublet of triplets, etc. ^{13}C NMR spectra were recorded on Brüker AM 400 (101 MHz, PFT) [indicated by (400)] and JEOL EX270 (68 MHz, PFT) [indicated by (270)] instruments. Chemical shifts are reported in ppm from tetramethylsilane (or chloroform) and are corrected to 0.00 (TMS) and 7.27 ($CHCl_3$) ppm for ^{1}H NMR and 77.30 ($CDCl_3$) ppm for ^{13}C NMR. Deuteriochloroform was used as solvent for NMR measurements unless otherwise stated. Where no clear resonances for the OH function of alcohols or acids were observed the values have not been quoted. Mass spectra and molecular weights were determined using a VG MM7070E or AEI MS 902 spectrometer. Molecular formulae quoted for molecular fragment ions are converted to ±3 mmu. Optical rotations (α_D) were measured on a JASCO DIP 370 polarimeter. All reactions using air/moisture sensitive reagents were performed in oven-dried or flame-dried apparatus, under atmospheres of argon or nitrogen. All solvents and reagents were purified according to procedures laid down in "Purification of Laboratory Chemicals" by D. D. Perrin and W. L. F. Armarego. All organic solutions were dried by brief exposure to anhydrous magnesium sulphate. Chromatography was performed using silica gel SORBSIL® C60-H (40-60 μm).

(±)-Methyl 3-hydroxydec-5-ynoate (**36**)



Hexyne (5.31 g, 64.7 mmol, 1.5 eq) was dissolved in dry tetrahydrofuran (80 ml) and treated exactly as in the preparation of compound **146** using the racemic epoxide **84** (2.5 g, 21 mmol, 1.0 eq), to give an oil (7.7 g) which was chromatographed on silica (eluting with 20% ethyl acetate in petrol) to give the *alkyne* **36** as a pale yellow oil (3.5 g, 70%), υ_{MAX} 3448 (OH), 1738 (C=O), 1437, 1162 and 1058 cm^{-1}; δ_H (250) 0.91 (3H, t, J = 7.1, 10-CH_3), 1.37-1.48 (4H, m, 8- and 9-CH_2), 2.14-2.19 (2H, m, 7-CH_2), 2.39-2.42 (2H, m, 4-CH_2), 2.52 (1H, dd, J = 16.3 and 8.7, 2-C$\underline{H}_A H_B$), 2.67 (1H, dd, J = 16.3 and 3.8, 2-$CH_A\underline{H}_B$), 3.78 (3H, s, OMe) and 4.05-4.20 (1H, m, 3-CH); δ_C (270) 13.46 (10-Me), 18.23 (CH_2), 21.84 (CH_2), 26.70 (CH_2), 30.89 (4-CH_2), 40.73 (2-CH_2), 51.68 (OMe), 66.83 (3-CH), 75.06 (5-C), 83.36 (6-C) and 172.78 (C=O); m/z 180 (7%, M^+-H_2O), 103 (100), 81 (18), 71 (51) and 61 (23) [Found: M^+-H_2O, 180.1157. $C_{11}H_{16}O_2$ requires M, 180.1350].

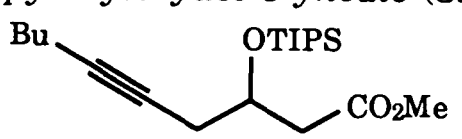
(±)-Methyl 3-hydroxy-8-phenyl-oct-5-ynoate (**36b**)



4-Phenylbutyne (0.70 ml, 5 mmol, 1.0 eq) was alkylated with the (±)-epoxide **84** (580 mg, 5 mmol, 1.0 eq) exactly as in the preparation of compound **146**, to give a brown oil (2 g) which was

chromatographed on silica (eluting with 25% ethyl acetate in petrol) to give, as a colourless oil, the *alkyne* **36b** (0.66 g, 56%), υ_{MAX} 3515 (OH), 1738 (C=O), 1437, 1173 and 1058 $c\,m^{-1}$; δ_H (250), 2.38-2.42 (2H, m, 4-CH_2), 2.43-2.51 (1H, m, 7-CH_2), 2.67-2.86 (2H, m, 2-CH_2), 2.81 (2H, t, J = 10.0, 8-CH_2), 3.74 (3H, s, OMe), 4.06-4.12 (1H, m, 3-CH) and 7.19-7.32 (5H, m, Ph); δ_C (270) 29.25 (CH_2), 34.03 (CH_2), 35.93 (CH_2), 41.05 (CH_2), 51.75 (OMe), 66.83 (3-CH), 76.43 (5-C), 82.10 (6-C), 125.43 (CH), 128.76 (CH), 128.83 (CH), 135.67 (C) and 173.29 (C=O); m/z 246 (5%, M^+), 228 (10%, M^+-H_2O), 154 (45), 144 (47) and 129 (100) [Found: M^+, 246.3032. $C_{15}H_{18}O_2$ requires M, 246.1256].

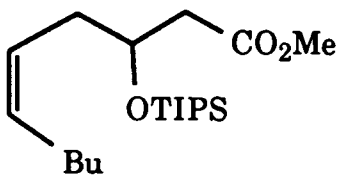
(±)-Methyl 3-triisopropylsilyloxydec-5-ynoate (**37**)



Triisopropylsilyl chloride (366 mg, 1.9 mmol, 1.5 eq) was added to a stirred solution of the alkyne **36** (238 mg, 1.2 mmol, 1.0 eq) and imidazole (211 mg, 3.1 mmol, 2.5 eq) in dimethylformamide (6 ml). The resulting solution was stirred at RT for 72h and water (100 ml) was added. The resulting mixture was extracted with ether (3 x 100 ml) and the combined organic layers dried and evaporated to give a yellow oil (600 mg), which was chromatographed on silica (eluting with 9% ethyl acetate in petrol) to give the *silyl derivative* **37** as a colourless oil (426 mg, 98%), υ_{MAX} 1736 (C=O), 1465, 1109 and 1069 $c\,m^{-1}$; δ_H (250) 0.89 (3H, t, J = 7.1, 10-CH_3), 0.91-1.15 (21H, m, TIPS), 1.31-1.72 (4H, m, 8- and 9-CH_2),

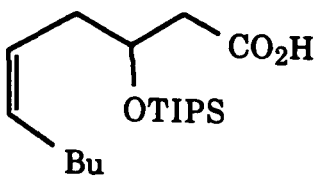
2.10-2.21 (2H, m, 7-CH_2), 2.41-2.43 (2H, m, 4-CH_2), 2.60 (1H, dd, J = 15.0 and 6.3, 2-C$\underline{H}_A H_B$), 2.79 (1H, dd, J = 15.0 and 5.1, 2-$CH_A\underline{H}_B$), 3.74 (3H, s, OMe) and 4.10-4.30 (1H, m, 3-H); δ_C (270) 12.41 (3 x CH, TIPS), 13.58 (10-Me), 17.80 (6 x Me, TIPS), 18.42 (CH_2), 21.80 (CH_2), 28.01 (CH_2), 30.51 (CH_2), 40.01 (2-CH_2), 51.37 (OMe), 68.31 (3-CH), 75.60 (5-C), 84.10 (6-C) and 171.01 (C=O); m/z 311 (7%, M^{+}-^{i}Pr), 131 (35), 103 (29), 71 (100) and 61 (30)

(±)-(Z)-Methyl 3-triisopropylsilyloxydec-5-enoate (**38**)



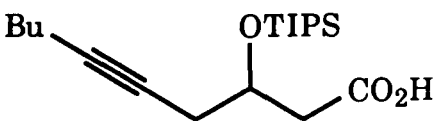
The silyl derivative **37** (420 mg, 1.2 mmol) was reduced exactly as in the preparation of compound **147**, to give the *alkene* **38** as a pale yellow oil (400 mg, 94%), υ_{MAX} 1741 (C=O), 1465 and 1103 cm^{-1}; δ_H (250) 0.89 (3H, t, J = 7.1, 10-CH_3), 0.92-1.17 (21H, m, TIPS), 1.31-1.71 (4H, m, 8- and 9-CH_2), 2.10-2.13 (2H, m, 7-CH_2), 2.41-2.44 (2H, m, 4-CH_2), 2.60 (1H, dd, J = 15.0 and 6.7, 2-C$\underline{H}_A H_B$), 2.79 (1H, dd, J = 15.0 and 4.1, 2-$CH_A\underline{H}_B$), 3.74 (3H, s, OMe), 4.01-4.09 (1H, m, 3-H), 5.35-5.42 (1H, m, 5-H) and 5.55-5.60 (1H, m, 6-H); δ_C (270) 12.44 (3 x CH, TIPS), 13.91 (10-Me), 18.00 (6 x Me, TIPS), 22.43 (CH_2), 27.24 (CH_2), 31.86 (CH_2), 35.54 (CH_2), 42.08 (2-CH_2), 51.63 (OMe), 66.31 (3-CH), 124.35 (5-CH), 132.79 (6-CH) and 171.73 (C=O); m/z 313 (4%, M^{+}-^{i}Pr), 131 (100), 71 (65), 61 (41) and 55 (47) [Found: M^{+}-^{i}Pr, 313.2180. $C_{16}H_{31}O_3Si$ requires M, 313.2199].

(±)-(Z)-3-Triisopropylsilyloxydec-5-enoic acid (**32**)



The alkene **38** (400 mg, 1.2 mmol) was saponified exactly as in the preparation of compound **152**, to give the *(Z)-acid* **32** as a pale yellow oil (380 mg, 95%), υ_{MAX} 3664 (OH), 1713 (C=O) and 1103 cm^{-1}; δ_H (250) 0.90 (3H, t, J = 7.1, 10-CH_3), 1.10-1.13 (21H, m, TIPS), 1.31-1.71 (4H, m, 8- and 9-CH_2), 1.93-2.25 (2H, m, 7-CH_2), 2.45-2.46 (2H, m, 4-CH_2), 2.60 (1H, dd, J = 15.3 and 8.0, 2-C$\underline{H}_A H_B$), 2.65 (1H, dd, J = 15.3 and 5.9, 2-$CH_A\underline{H}_B$), 4.01-4.09 (1H, m, 3-H), 5.35-5.42 (1H, m, 5-H) and 5.55-5.60 (1H, m, 6-H); δ_C (270) 12.47 (3 x CH, TIPS), 13.98 (10-Me), 18.08 (6 x Me, TIPS), 22.39 (CH_2), 27.22 (CH_2), 31.79 (CH_2), 40.71 (CH_2), 41.51 (2-CH_2), 69.52 (3-CH), 124.13 (5-CH), 132.99 (6-CH) and 175.53 (C=O); m/z 299 (87%, M^{+}-^{i}Pr), 201 (20), 157 (44), 131 (80) and 71 (30) [Found: M^{+}-^{i}Pr, 299.2017. $C_{16}H_{31}O_3Si$ requires M, 299.2041].

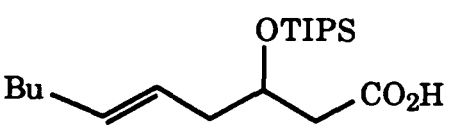
(±)-3-Triisopropylsilyloxydec-5-ynoic acid (**39**)



The silyl derivative **37** (0.52 g, 1.47 mmol, 1 eq) was saponified exactly as in the preparation of compound **152**, to give the *alkynoic acid* **39** as a colourless oil (500 mg, 95%), υ_{MAX} 3500 (OH), 1714 (C=O), 1465, 1109 and 1069 cm^{-1}; δ_H (250) 0.89 (3H, t, J = 7.0, 10-

CH_3), 1.05-1.10 (21H, m, TIPS), 1.31-1.47 (4H, m, 8- and 9-CH_2), 2.11-2.17 (2H, m, 7-CH_2), 2.43-2.46 (2H, m, 4-CH_2), 2.58 (1H, dd, J = 15.1 and 6.6, 2-C$\underline{H}_A H_B$), 2.78 (1H, dd, J = 15.1 and 5.0, 2-$CH_A\underline{H}_B$) and 4.26-4.30 (1H, m, 3-H); δ_C (270) 12.40 (3 x CH, TIPS), 13.53 (10-Me), 17.95 (6 x Me, TIPS), 18.39 (CH_2), 21.89 (CH_2), 27.82 (7-CH_2), 30.91 (4-CH_2), 41.62 (2-CH_2), 68.56 (3-CH), 75.62 (5-C), 83.09 (6-C) and 177.18 (C=O); m/z 297 (10%, M^+-^{i}Pr), 131 (65), 85 (45), 71 (100) and 61 (37) [Found: M^+-^{i}Pr, 297.1902. $C_{16}H_{29}O_3Si$ requires M, 297.1886].

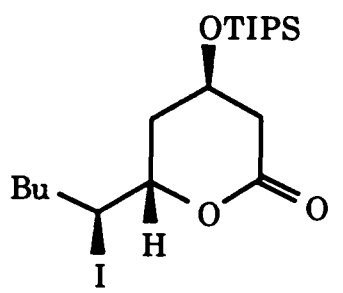
(±)-(E)-3-Triisopropylsilyloxydec-5-enoic acid (**28**)



^{t}Butanol (120 mg, 1.47 mmol, 1 eq) was added to a suspension of ammonium sulphate (1.94 g,14.7 mmol, 10 eq) and the alkynoic acid **39** (420 mg, 1.2 mmol) in tetrahydrofuran (25 ml). Ammonia (50 ml) was condensed into the solution at -78°C and the resulting mixture was stirred at -40°C during the addition of lithium chips (54 mg, 8.9 mmol, 6 eq). The reaction was stirred at this temperature for 2h and then allowed to warm to RT over 16h. Water (100 ml) was added and the resulting solution was extracted with chloroform (3 x 50 ml) and the combined organic layers dried and evaporated to give, as a colourless oil, the *(E)-acid* **28** (475 mg, 95%), υ_{MAX} 3500 (OH), 1713 (C=O), 1464 and 1106 cm^{-1}; δ_H (250) 0.89 (3H, t, J = 7.1, 10-CH_3), 1.05-1.07 (21H, m, TIPS), 1.31-1.40 (4H, m, 8-

and 9-CH_2), 1.95-1.98 (2H, m, 7-CH_2), 2.20-2.29 (2H, m, 4-CH_2), 2.47 (1H, dd, J = 15.2 and 5.9, 2-C$\underline{H}_A H_B$), 2.57 (1H, dd, J = 15.2 and 4.1, 2-$CH_A\underline{H}_B$), 4.17-4.27 (1H, m, 3-H), 5.30-5.42 (1H, m, 5-H) and 5.55-5.60 (1H, m, 6-H); δ_C (270) 12.42 (3 x CH, TIPS), 13.89 (10-Me), 18.01 (6 x Me, TIPS), 22.19 (CH_2), 31.47 (CH_2), 32.33 (7-CH_2), 40.75 (4-CH_2), 41.48 (2-CH_2), 69.44 (3-CH), 124.64 (5-CH), 134.52 (6-CH) and 177.45 (C=O); m/z 299 (2%, M^+-^{i}Pr), 131 (45), 89 (51), 85 (100) and 71 (52) [Found: M^+-^{i}Pr, 299.2035. $C_{16}H_{31}O_3Si$ requires M, 299.2041].

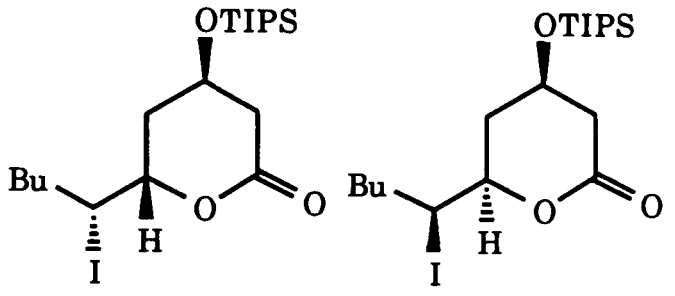
(3RS,4SR,6SR)-6-Iodo-3-triisopropylsilyloxydecan-5-olide (**40**)



The (Z)-acid **32** (130 mg, 0.38 mmol, 1 eq) was iodocyclised exactly as in the preparation of compound **54b**,but using 3:1 acteonitrile:water as solvent, to give a yellow oil (140 mg), which, upon chromatography on silica (eluting with 15% ether in petrol), gave the *lactone* **40** as a colourless oil (100 mg, 57%), υ_{MAX} 1748 (C=O), 1464, 1342 and 1248 cm^{-1}; δ_H (250) 0.92 (3H, t, J = 6.7, 10-CH_3), 1.05-1.08 (21H, m, TIPS), 1.22-1.45 (4H, m, 8- and 9-CH_2), 1.50-1.65 (1H, m, 7-H_A), 1.87 (1H, ddd, J = 14.4, 9.9 and 4.9, 4-C$\underline{H}_A H_B$), 2.06 (1H, ddd, J = 14.4, 8.3 and 2.6, 4-$CH_A\underline{H}_B$), 2.09-2.13 (1H, m, 7-H_B), 2.61 (1H, dd, J = 17.5 and 3.7, 2-C$\underline{H}_A H_B$), 2.65 (1H, dd, J = 17.5 and 5.1, 2-$CH_A\underline{H}_B$), 4.12 (1H, ddd, J = 9.9, 4.7 and 2.6, 5-

H) and 4.39-4.50 (2H, m, 3- and 6-H); δ_C (270) 12.29 (3 x CH, TIPS), 13.93 (10-Me), 17.72 (6 x Me, TIPS), 21.89 (CH_2), 31.91 (CH_2), 35.88 (CH_2), 35.93 (CH_2), 38.96 (6-CH), 39.41 (2-CH_2), 63.59 (3-CH), 77.23 (5-CH) and 169.41 (C=O); m/z 425 (5%, M^{+}-^{i}Pr), 297 (10), 157 (100), 99 (45) and 57 (40) [Found: M^{+}-^{i}Pr, 425.0986. $C_{16}H_{30}IO_3Si$ requires M, 425.1011].

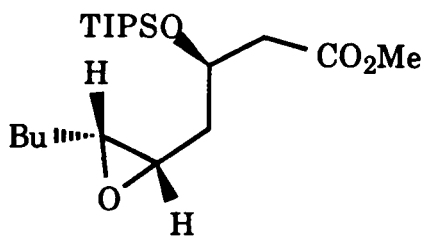
(3RS,4SR,6RS)-6-Iodo-3-triisopropylsilyloxy-decan-5-olide (**41**) and *(3RS,4RS,6SR)-6-iodo-3-triisopropylsilyloxy-decan-5-olide* (**42**)



The (E)-acid **28** (504 mg, 1.47 mmol, 1 eq) was iodocyclised exactly as in the preparation of compound **40**, to give a yellow oil (900 mg), which, upon chromatography on silica (eluting with 15 % ether in petrol), gave the trans-*lactone* **41** as a colourless oil (540 mg, 78%), υ_{MAX} 1748 (C=O), 1464, 1342 and 1248 cm^{-1}; δ_H (250) 0.92 (3H, t, J = 7.0, 10-CH_3), 1.05-1.07 (21H, m, TIPS), 1.13-1.42 (6H, m, 7-, 8- and 9-CH_2), 1.70- 1.90 (2H, m, 4-CH_2), 2.67 (2H, app. dd, J = 17.5 and 5.1, 2-CH_2), 4.27-4.37 (2H, m, 6- and 3-H) and 4.48 (1H, ddd, J = 6.8, 6.8 and 3.5, 5-H); δ_C (270) 12.31 (3 x CH, TIPS), 14.14 (10-Me), 18.24 (6 x Me, TIPS), 22.12 (CH_2), 31.81 (CH_2), 35.65 (7-CH_2), 35.77 (4-CH_2), 39.66 (2-CH_2), 41.04 (6-CH), 63.83 (3-CH), 77.79 (5-H) and 169.34 (C=O); and, as a colourless oil, the cis-*lactone* **42** (50 mg,

8%), υ_{MAX} 1748 (C=O), 1464, 1342 and 1248 c m^{-1}; δ_H (250) 0.93 (3H, t, *J* = 6.7, 10-CH_3), 1.05-1.10 (21H, m, TIPS), 1.26-1.36 (4H, m, 8- and 9-CH_2), 1.55-1.62 (2H, m, 4-H_A), 1.72-1.87 (2H, m, 7-CH_2), 2.09 (2H, dd, *J* = 17.3 and 8.3, 2-CH_2), 2.85 (1H, ddd, *J* = 17.1, 5.2 and 1.2, 4-H_B), 3.97 (1H, ddd, *J* = 11.1, 6.0 and 3.0, 5-H), 4.29 (1H, td, *J* = 6.2 and 3.0, 6-H) and 4.30 (1H, app. tt, *J* = 8.6 and 5.2, 3-H); δ_C (270) 12.19 (3 x CH, TIPS), 13.97 (10-Me), 16.02 (6 x Me, TIPS), 21.91 (CH_2), 31.55 (CH_2), 35.04 (7-CH_2), 38.13 (4-CH_2), 39.11 (6-CH), 40.37 (2-CH_2), 64.25 (3-CH), 78.90 (5-CH) and 169.41 (C=O).

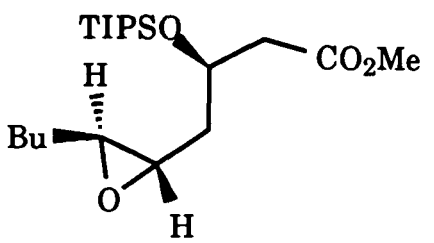
(3RS,5SR,6RS)-Methyl 5,6-epoxy-3-triisopropylsilyloxydec-anoate (**43**)



Sodium carbonate (16.1 mg, 0.16 mmol, 1.7 eq) was added to a stirred solution of the lactone **40** (45 mg, 0.09 mmol, 1 eq) in dry methanol (1.6 ml) and the resulting mixture was stirred for 16h in the dark. The solvent was removed *in vacuo* and the residue partitioned between water (1 ml) and ether (3 ml). The organic phase was dried and evaporated to give, as a colourless oil, the *epoxide* **43** (18 mg, 76%), υ_{MAX} 1741 (C=O), 1463, 1381, 1170 and 1096 c m^{-1}; δ_H (250) 0.92 (3H, t, *J* = 6.9, 10-CH_3), 1.10-1.27 (21H, m, TIPS), 1.35-1.60 (6H, m, 7-, 8- and 9-CH_2), 1.68 (1H, ddd, *J* = 14.4, 7.8 and 4.1, 4-C$\underline{H}_A H_B$), 1.94 (1H, ddd, *J* = 14.4, 6.1 and 3.9, 4-$CH_A\underline{H}_B$), 2.65

(2H, app. dd, J = 6.4 and 2.2, 2-CH_2), 2.92 (1H, ddd, J = 7.8, 4.1 and 3.9, 5-H), 3.13 (1H, td, J = 7.9 and 4.1, 6-H), 3.67 (3H, s, OMe) and 4.55 (1H, tdd, J = 6.4, 6.1 and 4.1, 3-H); δ_C (270) 12.45 (3 x CH, TIPS), 14.00 (10-Me), 18.06 (6 x Me, TIPS), 22.59 (CH_2), 27.35 (CH_2), 27.65 (7-CH_2), 35.31 (4-CH_2), 41.83 (2-CH_2), 51.50 (OMe), 53.05 (5-CH), 56.26 (6-CH), 67.78 (3-CH) and 171.59 (C=O); m/z 329 (90%, M^+-^{i}Pr), 227 (77), 131 (85), 131 (75) and 75 (100) [Found: M^+-^{i}Pr, 329.2916. $C_{17}H_{33}O_4Si$ requires M, 329.2148].

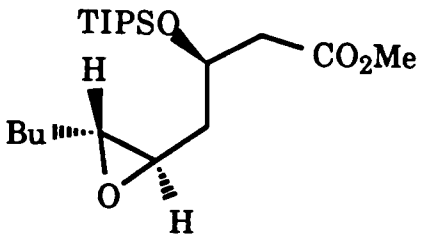
(3RS,5SR,6SR)-Methyl 5,6-epoxy-3-triisopropylsilyloxydecanoate (**44**)



The *trans*-lactone **41** (400 mg, 0.85 mmol, 1 eq) was treated as in the preparation of compound **43**, to give, as a colourless oil, the *epoxide* **44** (190 mg, 75%), υ_{MAX} 1741 (C=O), 1463, 1371, 1176 and 1060 cm^{-1}; δ_H (250) 0.91 (3H, t, J = 6.9, 10-CH_3), 1.05-1.07 (21H, m, TIPS), 1.36-1.44 (4H, m, 8- and 9-CH_2), 1.51-1.62 (2H, m, 7-CH_2), 1.68 (1H, ddd, J = 14.3, 7.1 and 3.8, 4-C$\underline{H}_A$H$_B$), 1.94 (1H, ddd, J = 14.3, 6.4 and 4.3, 4-CH$_A\underline{H}_B$), 2.58-2.71 (3H, m, 6-H and 2-CH_2), 2.86 (1H, ddd, J = 7.1, 4.3 and 2.2, 5-H), 3.66 (3H, s, OMe) and 4.47 (1H, dddd, J = 6.4, 6.4, 3.8 and 2.6, 3-H); δ_C (270) 12.71 (3 x CH, TIPS), 14.25 (10-Me), 18.33 (6 x Me, TIPS), 22.81 (CH_2), 28.39 (CH_2), 31.97 (7-CH_2), 39.97 (4-CH_2), 42.07 (2-CH_2), 51.79 (OMe), 55.10 (5-CH), 58.55 (6-CH), 67.80

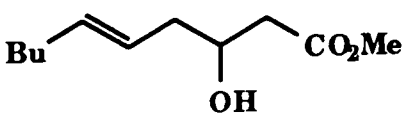
(3-CH) and 172.22 (C=O); m/z 329 (90%, $M^{+-i}Pr$), 227 (77), 131 (85), 131 (75) and 75 (100).

(3RS,5RS,6RS)-Methyl 5,6-epoxy-3-triisopropyl-silyloxydecanoate (**45**)



The *cis*-lactone **42** (40 mg, 0.8 mmol, 1 eq) was treated exactly as in the preparation of compound **43** to give, as a colourless oil, the *epoxide* **45** (15 mg, 70%) υ_{MAX} 1741 (C=O), 1463, 1371, 1174 and 1095 cm^{-1}; δ_H (250) 0.92 (3H, t, J = 6.9, 10-CH_3), 1.07-1.17 (21H, m, TIPS), 1.27-1.45 (6H, m, 7-, 8- and 9-CH_2), 1.70-1.72 (1H, m, 4-CH), 1.82-1.85 (1H, m, 4-CH), 2.53 (2H, dd, J = 6.3 and 1.7, 2-CH_2), 2.66 (1H, td, J = 5.3 and 2.2, 6-H), 2.79 (1H, ddd, J = 5.6, 4.1 and 2.2, 5-H), 3.67 (3H, s, OMe) and 4.54 (1H, m, 3-H); δ_C (270) 12.46 (3 x CH, TIPS), 13.91 (10-Me), 18.05 (6 x Me, TIPS), 22.48 (CH_2), 27.98 (CH_2), 31.63 (7-CH_2), 40.07 (4-CH_2), 42.70 (2-CH_2), 51.48 (OMe), 58.89 (5-CH), 56.26 (6-CH), 67.91 (3-CH) and 171.68 (C=O); m/z 329 (90%, $M^{+-i}Pr$), 227 (77), 131 (85), 131 (75) and 75 (100).

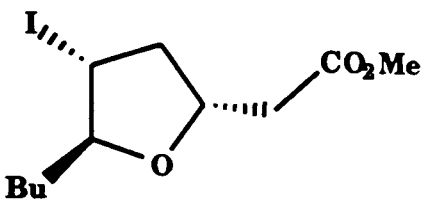
(±)-(E)-Methyl 3-hydroxydec-5-enoate (**53b**)



Diisobutylaluminium hydride (27 ml of a 1M solution, 27

mmol, 1 eq) was added to 1-hexyne (3.1 ml, 27 mmol, 1eq) in hexane (91 ml) at -78°C and the resulting solution was then heated at 50°C for 2h, before cooling to -30°C. Methyl lithium (18.5 ml of a 1.4M solution in ether, 26 mmol, 0.96 eq) and then ether (90 ml) were added. The resulting suspension was stirred at 0°C for 0.5h and then cooled to -78°C. The (±)-epoxide **84** (3 g, 26 mmol, 0.96 eq) followed by boron trifluoride etherate (3.18 ml, 26 mmol, 0.96 eq) were added. The solution was stirred at -78°C for 0.75h. Methanol (15 ml) was added and after 10 min, 1M hydrochloric acid (60 ml). The resulting mixture was extracted with ethyl acetate (3 x 50 ml) and the combined organic phases were dried and evaporated to give a colourless oil (6.4 g). Chromatography on silica (eluting with 15% ethyl acetate in petrol gave *alkene* **53b** as a colourless oil (3.28 g, 63%), υ_{MAX} 3417 (OH) and 1732 (C=O) c m^{-1}; δ_H (250) 0.90 (3H, t, J = 6.4, 10-CH_3), 1.20-1.40 (4H, m, 8- and 9-CH_2), 2.01-2.05 (2H, m, 7-CH_2), 2.10-2.14 (2H, m, 4-CH_2), 2.45 (1H, dd, J = 15.7 and 9.8, 2-$C\underline{H}_AH_B$), 2.52 (1H, dd, J = 15.7 and 3.8, 2-$CH_A\underline{H}_B$), 3.71 (3H, s, OMe), 4.05-4.20 (1H, m, 3-CH), 5.35-5.45 (1H, m, 5-CH) and 5.55-5.65 (1H, m, 6-CH); δ_C (270) 13.92 (10-Me), 22.22 (CH_2), 31.55 (CH_2), 32.32 (CH_2), 39.91 (4-CH_2), 40.44 (2-CH_2), 51.80 (OMe), 67.75 (3-CH), 124.82 (5-C), 138.70 (6-C) and 173.26 (C=O); m/z [NH_4-CI] 218 (85%, M^+ + NH_4), 201 (20%, MH^+), 183 (100), 169 (5) and 151 (10); [Found: C, 65.4; H, 9.9. $C_{11}H_{20}O_3$ requires C, 66.0; H, 10.1%].

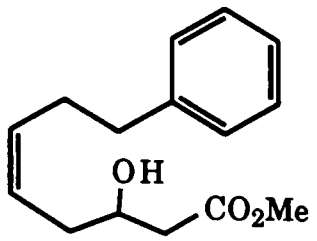
(2'SR,4'SR,5'RS) Methyl (5'-butyl-4'-iodotetrahydrofuran-2'-yl) acetate (**54b**)



Sodium hydrogencarbonate (4.11 g, 48.9 mmol, 3 eq) was added to an ice-cold solution of the alkene **53b** (3.26 g, 16.3 mmol, 1 eq) in dry acetonitrile (66 ml) and the suspension stirred for 5 mins. Iodine (12.42 g, 48.9 mmol, 3eq) was added and the resulting mixture was stirred at 0-5 °C in the dark for 16 h. Ether (100 ml) was added and the solution was washed with saturated aqueous sodium thiosulphate (120 ml). The separated aqueous phase was extracted with ether (3 x 50 ml). The combined organic phases were dried and evaporated to give the *iodotetrahydrofuran* **54b** as a colourless oil (3.98 g, 75%), υ_{MAX} 1732 (C=O) c m^{-1}; δ_H (250) 1.06 (3H, t, J = 6.7, CH_3), 1.38-1.90 (6H, m, 3 x CH_2), 2.05 (1H, ddd, J = 12.6, 5.6 and 3.7, 3'-CH), 2.39 (1H, dd, J = 15.5 and 6.5, 2-C$\underline{H}_A H_B$), 2.45 (1H, ddd, J = 12.6, 6.7 and 6.4, 3'-CH), 2.70 (1H, dd, J = 15.5 and 7.0, 2-C$H_A\underline{H}_B$), 3.49 (1H, ddd, J = 6.7, 3.7 and 3.5, 4'-CH), 3.51 (3H, s, OMe), 4.20 (1H, ddd, J = 6.7, 6.7 and 3.5, 5'-CH) and 4.39 (1H, dddd, J = 7.0, 6.5, 6.4 and 5.6, 2'-CH); δ_C (270, C_6D_6) 14.11 (Me), 22.50 (4'-CH), 22.94 (CH_2), 28.34 (CH_2), 32.27 (CH_2), 40.59 (3'-CH_2), 44.76 (2-CH_2), 51.06 (OMe), 74.47 (2'-CH), 86.75 (5'-CH) and 170.56 (C=O); m/z [NH_4-CI] 327 (15%, MH^+), 281 (30), 221 (43), 207 (36) and 147

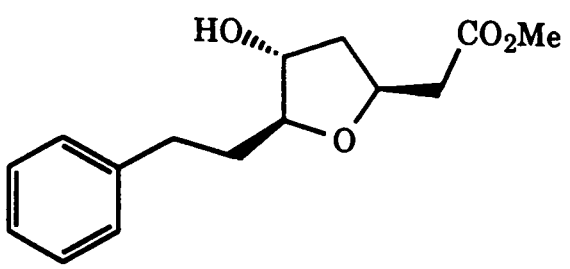
(100) [Found: C, 40.8; H, 5.9. $C_{11}H_{19}IO_3$ requires C, 40.5, 6.0%].

(±)-(Z)-Methyl 3-hydroxy-8-phenyloct-5-enoate (**51b**)



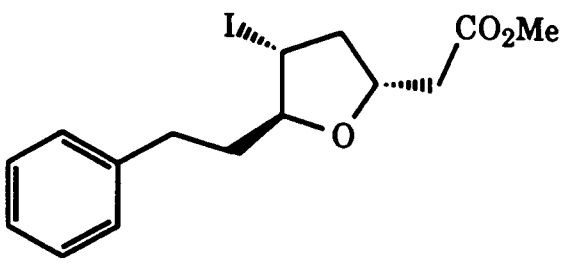
The alkyne **36b** (600 mg, 2.4 mmol) was reduced exactly as in the preparation of compound **147** to give the *alkene* **51b** as a pale yellow oil (510 mg, 85%), υ_{MAX} 3505 (OH), 1737 (C=O), 1437, 1201 and 1172 cm^{-1}; δ_H (250) 2.15-2.20 (2H, m, 4-CH_2), 2.30-2.40 (2H, m, 6-CH_2), 2.40-2.51 (2H, m, 2-CH_2), 2.57 (2H, t, J = 10.1, 8-CH_2), 3.70 (3H, s, OMe), 3.92-4.00 (1H, m, 3-CH), 5.38-5.45 (1H, m, 5-CH), 5.55-5.62 (1H, m, 6-CH) and 7.15-7.31 (5H, m, Ph); δ_C (270) 29.37 (CH_2), 34.31 (CH_2), 35.74 (CH_2), 40.38 (CH_2), 51.74 (OMe), 67.85 (3-CH), 125.37 (5-CH), 128.36 (CH), 128.39 (CH), 128.46 (CH), 133.80 (6-CH), 141.75 (C) and 173.25 (C=O); m/z [NH_4-CI] 266 (75%, M^++NH_4), 249 (100%, MH^+), 199 (23), 134 (27) and 91 (24). [Found: C, 72.3; H, 8.0. $C_{15}H_{20}O_3$ requires C, 72.6; H, 8.1%].

(2'SR,4'RS,5'SR) Methyl (4'-hydroxy-5'-phenylethyltetrahydrofuran-2'-yl) acetate (**52b**)



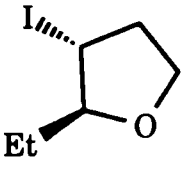
The alkene **51b** (80 mg, 0.32 mmol, 1 eq) was treated exactly as in the preparation of the preparation **148**, to give the *hydroxytetrahydrofuran* **52b** as a colourless oil (60 mg, 70%), υ_{MAX} 3570 (OH), 1736 (C=O), 1157 and 1084 cm^{-1}; δ_H (250) 1.83 (1H, ddd, J = 13.5, 9.6 and 6.1, 3'-CH_A), 2.03 (1H, ddd, J = 13.5, 5.6 and 2.0, 3'-CH_B), 2.52 (1H, dd, J = 15.6 and 6.2, 2-C$\underline{H}_A$$CH_B$), 2.63 (1H, dd, J = 15.6 and 6.9, 2-CH_AC$\underline{H}_B$), 2.48-2.51 (2H, m, 7-CH_2), 2.78-2.80 (2H, m, 6-CH_2), 3.70 (3H, s, OMe), 3.75 (1H, ddd, J = 6.1, 5.6 and 3.1, 4'-CH), 4.10 (1H, td, J = 6.3 and 3.1, 5'-CH) and 4.50 (1H, dddd, J = 9.6, 6.9, 6.2 and 2.0, 2'-CH); δ_C (270) 32.14 (CH_2), 36.14 (CH_2), 40.72 (CH_2), 40.85 (CH_2), 51.74 (OMe), 74.16 (4'-CH), 76.57 (2'-CH), 86.43 (5'-CH), 128.51 (CH), 128.52 (CH), 128.54 (CH), 141.78 (C) and 172.71 (C=O); m/z 246 (25%, M^+-H_2O), 191 (37), 104 (65), 98 (95) and 91 (100) [Found: M^+-H_2O, 246.1261. $C_{15}H_{18}O_3$ requires M, 246.1259].

(2'RS,4'SR,5'RS) Methyl (4'-iodo-5'-phenylethyltetrahydro-furan-2'-yl)-acetate (**54c**)



The methyl ester **92** (60 mg, 0.24 mmol, 1 eq) was iodocyclised exactly as in the preparation of compound **54b**, to give an oil (100 mg) which was chromatographed on silica (eluing with 10% ethyl acetate in petrol) to give, as a colourless oil, the *iodotetrahydrofuran* **54c** (170 mg, 69%), υ_{MAX} 1736 (C=O), 1438, 1202 and 1030 c m^{-1}; δ_H (250) 1.71 (1H, ddd, *J* = 13.8, 4.7 and 3.5, 3'-CH), 2.05 (1H, m, 3'-CH), 2.48 (1H, dd, *J* = 15.5 and 6.4, 2-C$\underline{H}_A H_B$), 2.60-2.85 (5H, m, 2-C$H_A\underline{H}_B$, 6- and 7-CH_2), 3.64 (3H, s, OMe), 3.70 (1H, ddd, *J* = 7.4, 3.5 and 3.4, 4'-H), 3.94 (1H, dt, *J* = 8.5 and 3.5, 5'-H), 4.35 (1H, dddd, *J* = 6.9, 6.4, 4.7 and 1.4, 2'-H) and 7.08-7.25 (5H, m, Ph); δ_C (270) 21.52 (4'-CH), 32.18 (CH_2), 33.93 (CH_2), 40.67 (3'-CH_2), 44.52 (2-CH_2), 51.83 (OMe), 74.48 (2'-CH), 85.88 (5'-CH), 125.96 (CH), 128.44 (CH), 128.46 (CH), 134.45 (C), 141.63 (C=O) and 170.45 (C=O); m/z 246 (2%, M^+-HI), 186 (43), 160 (36), 91 (100) and 55 (100).

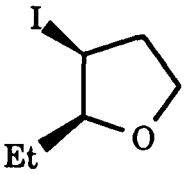
(2RS,3SR)-2-Ethyl-3-iodotetrahydrofuran (**58**)



(E)-3-Hexen-1-ol **57** (0.37 ml, 3 mmol, 1 eq) was iodocyclised

(over various times: 5-45 mins) exactly as in the preparation of compound **54b**, to give the *iodotetrahydrofuran* **58** as a colourless oil (0.54 g, 80%), which showed data which was identical to literature values,[36] υ_{MAX} 1462, 1384, 1164, 1069 and 1023 cm^{-1}; δ_H (250) 0.99 (3H, t, J = 7.4, CH_3), 1.49 (1H, ddq, J = 13.9 and 7.4, 7.4, 1'-H_A), 1.72 (1H, ddq, J = 13.9, 7.4 and 7.4, 1'-H_B), 2.23-2.27 (1H, m, 4-H_A), 2.46-2.50 (1H, m, 4-H_B), 3.79 (1H, ddd, J = 6.9, 5.9 and 4.2, 3-H), 3.89 (2H, dt, J = 7.1 and 1.2, 5-CH_2) and 3.97 (1H, td, J = 7.4 and 4.2, 2-H); δ_C (400) 10.23 (Me), 23.35 (3-CH), 25.91 (CH_2), 38.59 (4-CH_2), 66.92 (5-CH_2) and 89.48 (2-CH); m/z 198 (16%, M^+), 156 (37), 91 (61), 85 (100) and 57 (92).

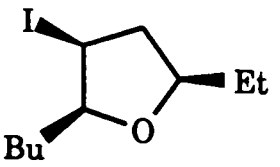
(2SR,3SR)-2-Ethyl-3-iodotetrahydrofuran (**60**)



(Z)-3-Hexen-1-ol **59** (0.37 ml, 3 mmol, 1 eq) was iodocyclised over 72h in the same way as in the preparation of compound **54b** to give the *iodotetrahydrofuran* **60** as a colourless oil (0.41 g, 60%), υ_{MAX} 1462, 1384, 1164 and 1023 cm^{-1}; δ_H (250) 0.93 (3H, t, J = 7.5, CH_3), 1.50 (1H, dqd, J = 13.7 and 7.5, 6.6, 1'-H_A), 1.76 (1H, dqd, J = 13.9, 7.5 and 6.5, 1'-H_B), 2.47 (1H, dddd, J = 14.2, 7.1, 2.9 and 1.4, 4-H_A), 2.73 (1H, ddt, J = 14.2, 9.2 and 5.6, 4-H_B), 2.80 (1H, dt, J = 6.5 and 3.2, 2-H), 3.79 (1H, ddd, J = 6.9, 5.9 and 4.2, 3-H), 3.91 (1H, ddd, J = 9.2, 8.3 and 2.9, 5-CH_A), 4.14 (1H, ddd, J = 9.2, 8.3 and 7.2, 5-CH_B) and 4.48 (1H, ddd, J = 5.6, 3.2 and 1.4, 2-H); δ_C (270) 10.24

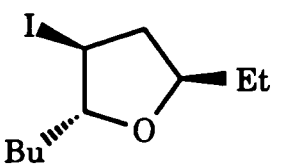
(Me), 30.46 (CH_2), 34.16 (3-CH), 39.10 (4-CH_2), 66.00 (5-CH) and 83.49 (2-CH); m/z 226 (10%, M^+), 197 (15), 99 (100), 71 (28) and 57 (95).

(2SR,3SR,5RS) 2-Butyl-5-ethyl-3-iodotetrahydrofuran (**62**)



(Z)-Dec-5-en-3-ol (230 mg, 1.6 mmol, 1 eq) was iodocyclised exactly as in the preparation of **54b**, to give the *iodo-tetrahydrofuran* **62** (270 mg, 60%) as a colourless oil which showed, υ_{MAX} 1463 and 1168 cm^{-1}; δ_H (250) 0.92 (3H, t, J = 7.1, CH_3), 0.95 (3H, t, J = 7.4, CH_3), 1.23-1.39 (4H, m, 2 x CH_2), 1.50-1.83 (4H, m, 2 x CH_2), 2.31 (1H, ddd, J = 14.6, 6.4 and 3.0, 4-H_B), 2.76 (1H, ddd, J = 6.4, 6.4 and 4.0, 2-H), 2.92 (1H, ddd, J = 14.6, 8.0 and 7.0, 4-H_A), 3.86 (1H, dddd, J = 8.0, 6.4, 6.4 and 6.4, 5-H) and (1H, ddd, J = 7.0, 4.0 and 3.0, 3-H); δ_C (400) 10.63 (Me), 14.09 (Me), 22.72 (CH_2), 28.02 (CH_2), 29.32 (CH_2), 30.95 (CH_2), 32.35 (3-CH), 43.90 (4-CH_2), 81.38 (2-CH) and 81.60 (5-CH); m/z 253 (M^+-Et, 4%), 225 (50), 155 (91), 85 (69) and 69 (100) [Found: M^+-Et, 253.0172. $C_8H_{14}IO$ requires M, 253.0089].

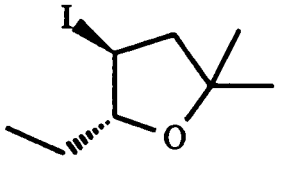
(2RS,3SR,5RS) 2-Butyl-5-ethyl-3-iodotetrahydrofuran (**63**)



(E)-Dec-5-en-3-ol (160 mg, 1.02 mmol, 1 eq) was iodocyclised exactly as in the preparation of **54b**, to give the *iodotetrahydro-furan* **63** (250 mg, 90%) as a colourless oil which showed, υ_{MAX} 1680, 1540

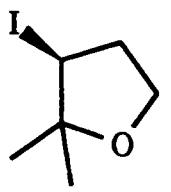
and 1403 cm^{-1}; δ_H (250) 0.92 (6H, app. t, J = 7.5, 2 x CH_3), 1.22-1.47 (4H, m, 2 x CH_2), 1.51-1.85 (4H, m, 2 x CH_2), 1.99 (1H, ddd, J = 12.8, 10.3 and 8.5, 4-H_A), 2.65 (1H, ddd, J = 12.8, 7.3 and 6.2, 4-H_B), 3.75 (1H, ddd, J = 8.7, 7.5 and 3.3, 2-H), 3.89 (1H, dddd, J = 8.5, 6.4, 6.4 and 6.2, 5-H) and (1H, ddd, J = 10.3, 7.3 and 3.3, 3-H); δ_C (400) 10.23 (Me), 14.28 (Me), 23.05 (CH_2), 23.35 (3-CH), 28.48 (CH_2), 29.22 (CH_2), 32.32 (CH_2), 44.78 (4-CH_2), 79.93 (2-CH) and 86.50 (5-CH); m/z 267 (1%, M^+-Me), 239 (5), 222 (15), 155 (10) and 125 (100).

(2SR,3RS)-5,5-Dimethyl-2-ethyl-3-iodotetrahydrofuran (**65**)



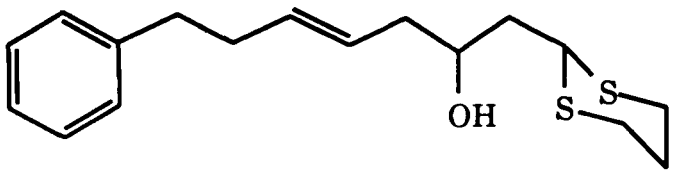
(E)-2-Methylhept-5-en-2-ol **64** (1 g, 7.8 mmol, 1 eq) was iodocyclised exactly as in the preparation of compound **54b**, to give the *iodotetrahydrofuran* **65** (1.5 g, 76%) as a colourless oil which showed, υ_{MAX} 1453, 1367, 1182 and 1099 cm^{-1}; δ_H (250) 0.99 (3H, t, J = 7.5, CH_3), 1.23 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.42-1.58 (1H, m, $C\underline{H}_AH_BCH_3$), 1.76-1.88 (1H, m, $CH_A\underline{H}_BCH_3$), 2.18 (1H, dd, J = 12.9 and 9.9, 4-H_A), 2.39 (1H, dd, J = 12.9 and 6.9, 4-H_B), 3.79 (1H, ddd, J = 9.9, 6.9 and 3.4, 3-H) and 4.00 (1H, ddd, J = 8.9, 6.9 and 3.4, 2-H); δ_C (270) 9.76 (Me), 22.51 (4-CH), 24.91 (CH_2), 28.75 (Me), 29.46 (Me), 51.34 (3-CH_2) and 81.11 (2-CH); m/z 239 (7%, M^+-Me), 225 (59), 127 (33), 98 (100) and 69 (85) [Found: M^+-Me, 238.9940. $C_7H_{12}IO$ requires M, 238.9933].

(±)-2,2-Dimethyl-3-iodotetrahydrofuran (**67**)



5-Methylpent-4-en-1-ol **66** (1 g, 10 mmol, 1 eq) was iodocyclised exactly as in the preparation of compound **54b** to give the *iodotetrahydrofuran* **67** (1.94 g, 85%) as a colourless oil, υ_{MAX} 1455, 1384, 1370, 1246, 1126 and 1038 cm^{-1}; δ_H (250) 1.33 (3H, s, CH_3), 1.39 (3H, s, CH_3), 2.18-2.46 (1H, m, 4-H_A), 2.54-2.67 (1H, m, 4-H_B), 3.79-3.98 (3H, m, 4-H and 2-CH_2); δ_C (270) 25.00 (Me), 26.36 (Me), 31.00 (4-CH), 37.65 (3-CH_2), 65.79 (2-CH) and 82.03 (5'-C); m/z 226 (8%, M^+), 211 (31), 99 (89), 84 (41) and 41 (100) [Found: M^+, 225.9850. $C_6H_{10}IO$ requires M, 225.9854].

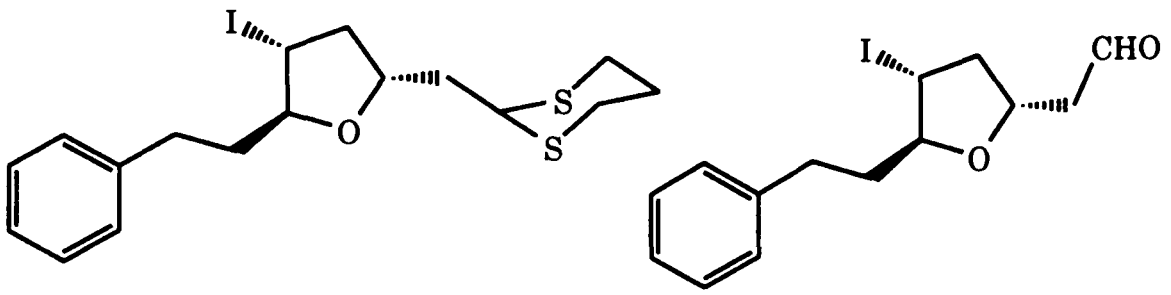
(±)-(E)-2-(2'-Hydroxy-7'-phenylhept-4'-enyl)-1,3-dithiane (**68**)



Lithium aluminium hydride bis-tetrahydrofuran (37.7 ml of a 1M solution in toluene, 37.7 mmol, 2.6 eq) was added to a solution of the dithiane **90** (4.45 g, 14.5 mmol, 1 eq) in glyme (80 ml). The solution was heated at reflux for 16h and then cooled to RT. Water (25 ml) was added very cautiously and the resulting mixture was extracted with ethyl acetate (3 x 50 ml). The combined organic phases were dried and evaporated to give the *alkene* **68** as a

colourless oil (3.71 g, 83 %), υ_{MAX} 3430 (OH), 1313, 1147, 1052 and 1030 c m^{-1}; δ_H (250) 1.80-1.82 (2H, m, 5-CH_2), 1.85-1.93 (2H, m, 1'-CH_2), 2.05-2.25 (2H, m, 3'-CH_2), 2.32-2.40 (2H, m, 6'-CH_2), 2.70 (2H, t, J = 9.0, 7'-CH_2), 2.80-2.97 (4H, m, 4 and 6-CH_2), 3.82-3.91 (1H, m, 2'-H), 4.27 (1H, t, J = 8.0, 2-H), 5.32-5.60 (2H, m, 3' and 4'-H) and 7.20-7.35 (5H, m, Ph); δ_C (270) 25.96 (CH_2), 30.02 (CH_2), 30.36 (CH_2), 34.40 (CH_2), 36.58 (CH_2), 40.69 (CH_2), 42.01 (CH_2), 44.18 (2-CH), 67.58 (2'-CH), 125.87 (4-CH), 125.87 (CH), 126.03 (CH), 128.32 (CH), 133.86 (3-CH) and 141.71 (C); m/z [NH_4-CI] 326 (63%, M^++NH_4), 309 (MH^+, 60), 291 (MH^+-H_2O, 40), 119 (100) and 91 (75) [Found: C, 66.1; H, 8.0. $C_{17}H_{24}OS_2$ requires C, 66.2, H, 7.8%].

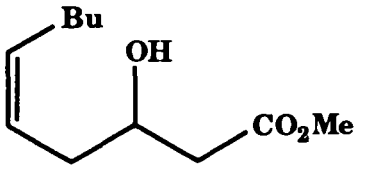
(2RS,4RS,5RS)-2-(1,3-Dithiane-2-ylmethyl)-4-iodo-5-(2-phenylethyl)tetrahydrofuran (**69**) and *(2'RS,4'RS,5'SR)-(4'-iodo-5'-phenylethyl-tetrahydrofuran-2'-yl)acetaldehyde* (**70**)



The alkene **68** (1.0 g, 3.24 mmol, 1 eq) was treated exactly as in the preparation of compound **54b**, to give a brown oil (1.9 g) which was chromatographed on silica (eluting with 10% ethyl acetate in petrol) to give the *iodotetrahydrofuran* **69** as a colourless oil (270 mg, 34%), υ_{MAX} 1602, 1496, 1454, 1422, 1376, 1276, 1144, 1074 and 1031 c m^{-1}; δ_H (250) 1.70-1.80 (2H, m, 5'-CH_2), 1.82-2.05 (6H, m,

1-, 3- and 6-CH_2), 2.47-2.95 (6H, m, 4'-,6'- and 7-CH_2), 3.72 (1H, ddd, J = 6.2, 4.0 and 3.0, 3-H), 3.95 (1H, td, J = 7.0 and 3.0, 5-H), 4.20 (1H, dd, J = 12.0 and 8.0, 2'-H), 4.32 (1H, m, 2-H) and 7.15-7.30 (5H, m, Ph); δ_C (270) 21.75 (CH_2), 29.98 (CH_2), 30.32 (CH_2), 31.93 (CH), 32.24 (CH_2), 33.67 (CH_2), 41.71 (CH_2), 44.05 (4-CH), 44.58 (CH_2), 66.39 (2'-CH), 74.57 (2-CH), 85.23 (5-CH), 125.80 (CH), 128.30 (CH), 128.36 (CH) and 141.60 (C); and also the *aldehyde* **70** (100 mg, 15%) as a colourless oil which showed, δ_H (250) 1.75 (1H, ddd, J = 13.0, 4.7 and 3.5, 3'-H), 2.05 (1H, ddd, J = 13.0, 6.0 and 2.1, 3-H), 2.70-2.90 (6H, m, 2-, 6- and 7-CH_2), 3.73 (1H, ddd, J = 6.2, 4.0 and 3.0, 4'-H), 4.03 (1H, dd, J = 7.0 and 3.0, 5'-H), 4.42-4.52 (1H, m, 2'-H) and 7.15-7.30 (5H, m, Ph).

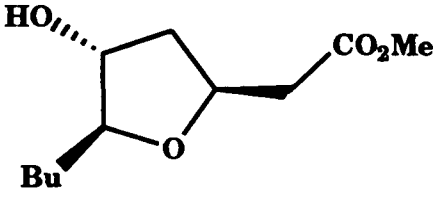
(±)-(Z)-Methyl 3-hydroxydec-5-enoate (**71**)



The alkyne **36** (430 mg, 2.1 mmol) was reduced exactly as in the preparation of compound **147**, to give the *alkene* **71** as a pale yellow oil (410 mg, 97%), υ_{MAX} 3442 (OH), 1736 (C=O), 1438, 1163 and 1060 cm^{-1}; δ_H (250) 0.90 (3H, t, J = 7.1, 10-CH_3), 1.27-1.40 (m, 6H, 3 x CH_2), 2.0-2.1 (2H, m, 7-CH_2), 2.20-2.37 (2H, m, 4-CH_2), 2.45 (1H, dd, J = 16.2 and 8.7, 2-C$\underline{H}_A$H$_B$), 2.76 (1H, dd, J = 16.2 and 3.8, 2-CH$_A\underline{H}_B$), 3.25 (1H, br, OH), 3.71 (3H, s, OMe), 4.01-4.09 (1H, m, 3-CH), 5.35-5.42 (1H, m, 5-CH) and 5.55-5.60 (1H, m, 6-CH); δ_C (270)

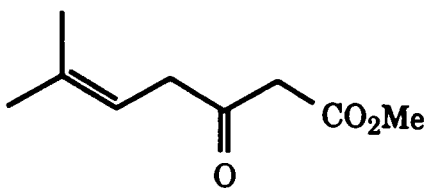
14.23 (10-Me), 22.63 (CH_2), 27.41 (CH_2), 32.02 (CH_2), 34.65 (4-CH_2), 40.72 (2-CH_2), 52.01 (OMe), 68.25 (3-CH), 124.40 (5-CH), 133.80 (6-CH) and 173.55 (C=O); m/z 182 (6%, M^+-H_2O), 103 (100), 71 (95), 61 (44) and 55 (95) [Found: M^+-H_2O, 182.2469. $C_{11}H_{18}O_2$ requires M, 182.2469].

(2'SR,4'RS,5'SR) Methyl (5'-butyl-4'-hydroxytetrahydrofuran-2'-yl)acetate (**72**)



The alkene **71** (1.75g, 8.75 mmol, 1 eq) was iodocyclised exactly as in the preparation of compound **148**, to give the *hydroxy-tetrahydrofuran* **72** as a colourless oil (1.80 g, 95%), υ_{MAX} 3500 (OH) and 1738 (C=O) $c m^{-1}$; δ_H (250) 0.90 (3H, t, J = 6.3, Me), 1.1-1.5 (6H, m, 3 x CH_2), 1.76 (1H, ddd, J = 12.7, 9.6 and 6.1, 3'-CH), 1.97 (1H, ddd, J = 12.7, 6.6 and 3.9, 3'-CH), 2.50 (1H, dd, J = 15.6 and 6.2, 2-C$\underline{H}_A$CH_B), 2.62 (1H, dd, J = 15.6 and 6.9, 2-CH_AC$\underline{H}_B$), 3.75 (3H, s, OMe), 3.85 (1H, td, J = 6.3 and 3.1, 5'-CH), 4.01 (1H, ddd, J = 6.6, 6.1 and 3.1, 4'-CH) and 4.49 (1H, dddd, J = 9.6, 6.9, 6.2 and 3.9, 2'-CH); δ_C (270) 13.99 (Me), 22.71 (CH_2), 27.96 (CH_2), 34.10 (CH_2), 40.78 (2-CH_2), 51.69 (OMe), 73.90 (2'-CH), 76.28 (4'-CH), 87.10 (5'-CH) and 171.62 (C=O); m/z 198 (2%, M^+-H_2O), 130 (19), 117 (18), 98 (100) and 57 (61) [Found: M^+-H_2O, 198.2640. $C_{11}H_{18}O_3$ requires M, 198.2643].

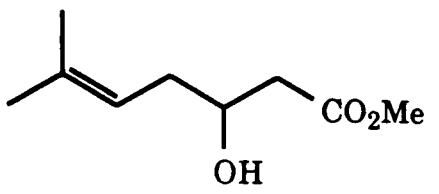
(±)-Methyl 6-methyl-3-oxahept-6-enoate (**80**)



1,1'-Carbonyldiimidazole (4.36 g, 27 mmol, 1.01 eq) was added to a stirred solution of 4-methylpent-3-enoic acid **81** (3.0 g, 26 mmol, 1.0 eq), prepared following the procedure of Smith,[88] in tetrahydrofuran (20 ml) and the resulting solution was stirred for 16h at RT. The resulting solution was then added dropwise to the magnesium chelate form of the methyl hydrogen malonate dianion (27 ml of a 1M solution in tetrahydrofuran, 27 mmol, 1eq). The resulting mixture was stirred for 24h and saturated aqueous ammonium chloride was added (50 ml). The resulting solution was extracted with ethyl acetate (3 x 100 ml) and the combined organic phases were washed with saturated aqueous sodium bicarbonate (50 ml) and brine (50 ml), dried and evaporated to give a brown oil (2 g) which was chromatographed on silica (eluting with 15% ethyl acetate in petrol), to give the *keto-ester* **80** as a colourless oil (1.05 g, 45%), which showed, υ_{MAX} 1750 (C=O), 1438, 1377 and 1108 cm^{-1}; δ_H (250) 1.38 (6H, d, J = 9.0, 2 x CH_3), 1.65-1.80 (2H, m, 4-CH_2), 2.41-2.60 (2H, m, 2-CH_2), 3.75 (3H, s, OMe) and 5.10-5.15 (1H, m, 5-H); δ_C (400) 25.61 (Me), 29.20 (Me), 30.71 (4-CH_2), 45.23 (2-CH_2), 51.54 (OMe), 125.39 (5-CH), 131.95 (6-C), 173.61 (C=O) and 200.91 (C=O); m/z 170 (2%, M^+), 143 (46), 101 (39), 97 (69) and 69

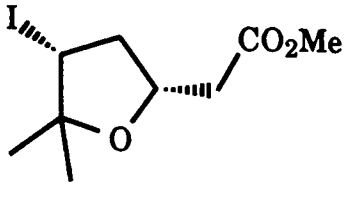
(100).

(±)-Methyl 3-hydroxy-6-methylhept-6-enoate (**82**)



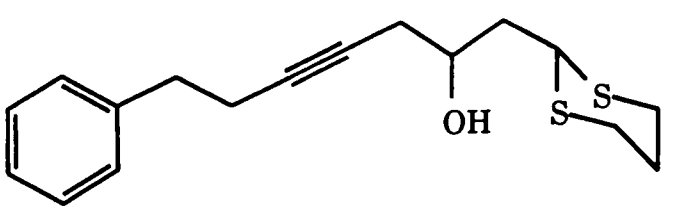
Butylamine-borane complex (502 mg, 10, mmol, 1.05 eq) was added to a stirred solution of the keto-ester **80** (1.7 g, 10 mmol, 1 eq) and 1M citric acid (7ml) in methanol (30 ml) and the resulting solution was stirred for 1h at RT. The solution was then diluted with water (30 ml) and extracted with ether (3 x 100 ml). The combined organic phases were dried and evaporated to give a brown oil (1.9 g), which was chromatographed on silica (eluting with 20% ethyl acetate in hexane) to give the *hydroxy-ester* **82** as a colourless oil (1.37 g, 80%), υ_{MAX} 3490 (OH), 1744 (C=O) and 1643 cm^{-1}; δ_H (250) 1.64 (6H, d, J = 4.6, 2 x CH_3), 2.20-2.43 (2H, m, 4-CH_2), 2.46 (2H, dd, J = 15.1 and 8.7, 2-$C\underline{H}_AH_B$), 2.51 (2H, dd, J = 15.1 and 6.3, 2-$CH_A\underline{H}_B$), 3.72 (3H, s, OMe), 4.02-4.05 (1H, m, 3-H) and 5.23-5.24 (1H, m, 5-H); δ_C (400) 25.64 (Me), 29.30 (Me), 31.57 (4-CH_2), 42.10 (2-CH_2), 51.59 (OMe), 63.91 (3-CH), 126.00 (5-CH), 131.49 (6-C) and 172.59 (C=O); m/z 172 (1%, M^+), 154 (30), 101 (100), 70 (64) and 55 (43).

(2'SR,4'SR) Methyl (5',5'-dimethyl-4'-iodotetrahydrofuran-2'-yl)acetate (**83**)



The hydroxy-ester **82** (150 mg, 0.9 mmol, 1 eq) was iodocyclised exactly as in the preparation of compound **54b**, to give the *iodo-tetrahydrofuran* **83** as a colourless oil (160 mg, 59%) which showed, υ_{MAX} 1462, 1384, 1164 and 1023 cm^{-1}; δ_H (250) 1.64 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.83-1.91 (1H, m, 3-H_A), 2.22 (1H, ddd, J = 13.0 and 10.8, 9.1, 3'-H_B),2.53 (1H, dd, J = 15.4, and 6.7, 2-H_A), 2.65 (1H, dd, J = 15.4, and 6.5, 2-H_B), 3.69 (3H, s, OMe), 4.02 (1H, dd, J = 10.8 and 6.8, 4'-H_B) and 4.33 (1H, dddd, J = 9.1, 6.7, 6.7 and 6.5, 2'-H); δ_C (400) 25.66 (Me), 29.23 (Me), 29.96 (4'-CH), 41.58 (3'-CH_2), 43.66 (4-CH_2), 51.79 (OMe), 73.93 (2'-CH), 82.74 (5'-C) and 171.46 (6-C).

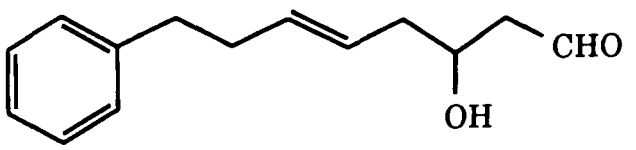
(±)-2-(2'-Hydroxy-7'-phenylhept-4'-ynyl)-1,3-dithiane (**90**)



A solution of 4-phenylbutyne (6.67 g, 0.05 mol,1.5 eq) in tetrahydrofuran (60 ml) was alkylated exactly as in the preparation of

146 with 2-(2,3-epoxypropan-1-yl)-1,3-dithiane **89** (6.02g, 0.033 mol, 1.0 eq), prepared by the method of Seebach,[103] to give a yellow oil (9 g), which was chromatographed on silica (eluting with 10% ethyl acetate in petrol), to give, as a pale yellow oil, the *dithiane* **90** (5.8 g, 55%), υ_{MAX} 3437 (OH), 1453, 1423, 1276, 1075 and 1030 cm^{-1}; δ_H (250) 1.85-1.95 (2H, m, 5-CH_2), 2.10-2.20 (2H, m, 1'-CH_2), 2.30 (1H, ddt, J = 14.7, 6.3 and 2.0, 3'-$C\underline{H}_AH_B$), 2.40 (1H, ddt, J = 14.7, 4.0 and 2.0, 3'-$CH_A\underline{H}_B$), 2.48 (2H, tt, J = 9.0 and 2.0, 6'-CH_2), 2.81 (2H, t, J = 9.0, 7'-CH_2), 2.85-2.94 (4H, m, 4 and 6-CH_2), 3.95-4.03 (1H, m, 2'-H), 4.25 (1H, dd, J = 11.0 and 9.2, 2-H) and 7.20-7.35 (5H, m, Ph); δ_C (270) 20.85 (CH_2), 25.89 (CH_2), 27.65 (CH_2), 29.84 (CH_2), 30.22 (CH_2), 35.14 (CH_2), 41.47 (CH_2), 43.86 (2'-CH), 66.75 (2-CH), 76.37 (4'-C), 82.70 (3'-C), 126.25 (CH), 128.36 (CH), 128.38 (CH) and 140.62 (C); m/z [NH_4-CI] 324 (100%, M^++ NH_4), 307 (MH^+, 90), 199 (87), 161 (65) and 119 (91), [Found: C, 66.3; H, 7.3; S, 20.5. $C_{17}H_{22}OS_2$ requires C, 66.6; H, 7.2; S, 20.9%].

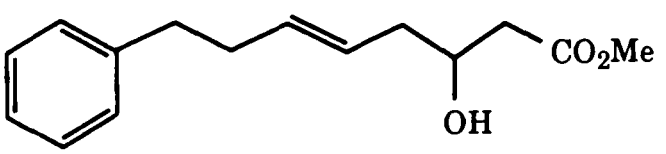
(±)-(E)-3-Hydroxy-8-phenyloct-5-enal (**91**)



Methyl iodide (4.4 ml, 70.2 mmol, 8 eq) was added to a suspension of the alkene **68** (2.71 g, 8.8 mmol, 1 eq) and sodium hydrogencarbonate (5.9 g, 70.2 mmol, 8 eq) in acetone (300 ml) and

water (15 ml). The resulting suspension was refluxed for 5h. Further portions of methyl iodide were added, until the reaction was complete by tlc., water (500 ml) was added, and the cooled mixture extracted with ethyl acetate (3 x 300 ml). The combined organic phases were dried and evaporated to give an oil (1.6 g), which was chromatographed on silica (eluting with 40% ethyl acetate in petrol), to give the *aldehyde* **91** (1.6 g, 87%) υ_{MAX} 1721 (C=O) cm^{-1}; δ_H (250) 2.12-2.21 (2H, m, 4-CH_2), 2.30-2.41 (2H, m, 7-CH_2), 2.47-2.50 (2H, m, 2-CH_2), 2.62-2.73 (2H, m, 8-CH_2), 4.05-4.12 (1H, m, 3-H), 5.30-5.60 (2H, m, 5- and 6-H), 7.15-7.31 (5H, m, Ph) and 9.80 (1H, t, J = 0.7, 1-H); δ_C (270) 34.42 (CH_2), 35.67 (CH_2), 40.33 (CH_2), 40.95 (CH_2), 68.04 (3-CH), 125.76 (5-CH), 128.45 (CH), 128.56 (CH), 128.95 (CH), 134.67 (6-CH), 141.54 (C) and 200.14 (C=O).

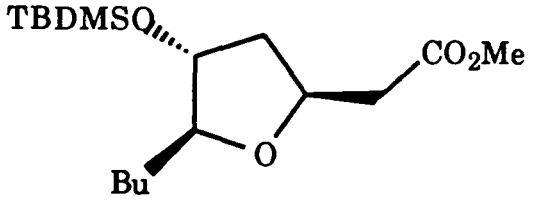
(±)-(E)-Methyl 3-hydroxy-8-phenyloct-5-enoate (**92**)



Pyridinium dichromate (2.27 g, 6 mmol, 6 eq) was added to a solution of the aldehyde **91** (218 mg, 1 mmol, 1 eq) in dimethyl-formamide (2 ml) and methanol (2.0 ml, 6 mmol, 6 eq).[105] The resulting suspension was stirred for 16h before being diluted with water (100 ml) and extracted with ether (3 x 25 ml). The combined organic phases were dried and evaporated to give an oil (300 mg) which was chromatographed on silica (eluing with 40% ethyl

acetate in petrol) to give, as a colourless oil, the *methyl ester* **92** (170 mg, 69%) υ_{MAX} 1737 (C=O) c m^{-1}; δ_H (250) 2.14 (2H, t, J = 6.5, 7-CH_2), 2.31 (1H, dd, J = 16.5 and 8.0, 2-C$\underline{H}_A H_B$), 2.35 (2H, m, 4-CH_2), 2.63 (2H, t, J = 6.5, 8-CH_2), 2.67 (1H, dd, J = 16.5 and 3.3, 2-$CH_A\underline{H}_B$), 3.65 (3H, s, OMe), 3.91-3.93 (1H, m, 3-H), 5.27-5.55 (2H, m, 5- and 6-H) and 7.09-7.25 (5H, m, Ph); δ_C (270) 34.43 (CH_2), 35.79 (CH_2), 39.63 (CH_2), 40.44 (CH_2), 51.79 (OMe), 67.71 (3-CH), 125.89 (CH), 128.36 (CH), 128.53 (CH), 134.54 (C), 141.80 (CH) and 173.22 (C=O); m/z 230 (15%, M^+-H_2O), 199 (27), 146 (40) 134 (30) and 91 (100)

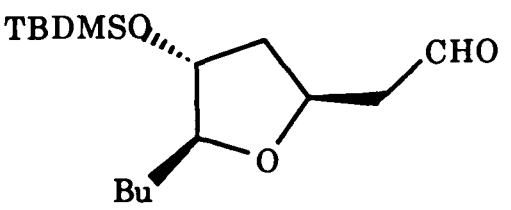
(2'SR,4'RS,5'SR) Methyl (5'-butyl-4'-^{t}butyldimethylsilyloxy-tetrahydrofuran-2'-yl) acetate (**138**)



Imidazole (1.79 g, 26 mmol, 2.5 eq) was added to a stirred solution of the hydroxytetrahydrofuran **72** (2.22 g, 10.5 mmol, 1 eq) and ^{t}butyldimethylsilyl chloride (3.95 g, 26 mmol, 2.5 eq) in dry dimethylformamide (12 ml). The resulting solution was stirred at RT for 72h. Water (200 ml) was added and the resulting solution was extracted with hexane (3 x 80 ml). The combined organic phases were dried and evaporated to give an oil (5 g), which was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the *silyloxytetrahydrofuran* **138** as a colourless oil (4.2 g,

54%), υ_{MAX} 1738 (C=O); δ_H (250) 0.05 (6H, m, 2 x MeSi), 0.85 (9H, s, ^{t}BuSi), 0.9 (3H, t, *J* = 6.4, Me), 1.23-1.50 (6H, m, 3 x CH_2), 1.71 (1H, ddd, *J* = 12.7, 9.2 and 6.4, 3'-CH), 1.97 (1H, ddd, *J* =12.7, 5.9 and 2.7, 3'-CH), 2.45 (1H, dd, *J* = 15.2 and 6.4, 2-C$\underline{H}_A$CH$_B$), 2.60 (1H, dd, *J* = 15.2 and 6.6, 2-CH$_A$C$\underline{H}_B$), 3.75 (3H, s, OMe), 3.6-3.7 (1H, td, *J* = 6.4 and 3.1, 5'-CH), 3.95 (1H, ddd, *J* = 6.4, 5.9 and 3.1, 4'-CH) and 4.42 (1H, dddd, *J* = 9.2, 6.6, 6.4 and 2.7, 2'-CH); δ_C (270) -4.58 (MeSi), -4.78 (MeSi), 13.95 (Me), 17.91 (Me$_3\underline{C}$Si), 22.70 (CH_2), 25.73 (^{t}Bu), 28.00 (CH_2), 33.77 (CH_2), 40.60 (3'-CH_2), 41.06 (2-CH_2), 51.57 (OMe), 73.84 (CH), 76.53 (CH), 86.88 (5'-CH) and 171.55 (C=O); m/z 261 (47%, M$^+$-^{t}Bu), 187 (37), 173 (87), 147 (100) and 89 (52)

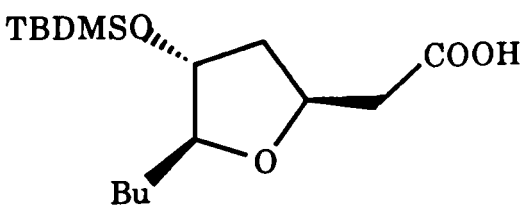
(2'SR,4'RS,5'SR)-5'-Butyl-4'-^{t}butyldimethylsilyloxytetrahydro-furan-2'-yl) acetaldehyde (**139**)



Diisobutylaluminium hydride (3.7 ml of a 1.0 M solution in hexanes, 3.7 mmol, 1 eq) was added to a solution of the silyloxytetrahydrofuran **138** (1.17 g, 3.7 mmol, 1 eq) in hexane (2 ml) at -78°C, and the resulting solution was stirred at this temperature for 2h. Methanol (2 ml) was then added and after 10 min, 2M hydrochloric acid (20 ml). The resulting mixture was extracted with ethyl acetate (3 x 50 ml) and the combined organic

phases dried and evaporated. The resulting oil (1.1 g) was chromato-graphed over silica (eluting with 5% ethyl acetate in hexane) to give the *aldehyde* **139** as a colourless oil (400 mg, 38%), υ_{MAX} 1735 (C=O); δ_H (250) 0.10 (6H, 2 x MeSi), 0.90 (12H, m, ^tBu), 1.2-1.5 (6H, m, 3 x CH_2), 1.72 (1H, ddd, J = 12.7, 9.0 and 6.3, 3'-CH), 1.95 (1H, ddd, J = 12.7, 5.7 and 2.4, 3'-CH), 2.61 (1H, dd, J = 10.2 and 5.6, 2-C$\underline{H}_A$CH$_B$), 2.63 (1H, dd, J = 10.2 and 3.4, 2-CH$_A$C$\underline{H}_B$), 3.68 (1H, td, J = 6.3 and 3.2, 5'-CH), 3.98 (1H, ddd, J = 6.3, 3.2 and 2.4, 4'-CH), 4.51 (1H, dddd, J = 9.0, 5.7, 5.6 and 3.4, 2'-CH) and 9.55 (1H, s, CHO); δ_C (270) -4.62 (MeSi), -4.81 (MeSi), 13.91 (Me), 17.90 (Me_3CSi), 22.63 (CH_2), 25.70 (^tBu), 28.02 (CH_2), 33.73 (CH_2), 41.28 (3'-CH_2), 49.29 (2-CH_2), 72.62 (CH), 76.48 (CH), 87.05 (5'-CH) and 201.13 (C=O); m/z 286 (13%, M^+-Me), 216 (100), 173 (87), 99 (50) and 75 (52).

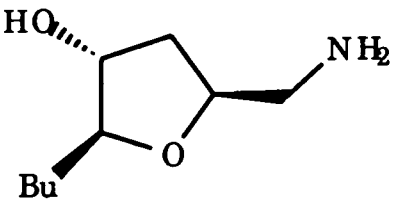
(2'SR,4'RS,5'SR)-5'-Butyl-4-^{t}butyldimethylsilyloxytetrahydro-furan-2'-yl) acetic acid (**141**)



Trifluoroacetic anhydride (0.12 ml, 87 mmol, 2.5 eq) was added dropwise to a stirred solution of urea-hydrogen peroxide[91] (0.325 g, 3.46 mmol, 10 eq), disodium hydrogen phosphate (0.368g, 8.7 eq, 2.7 mmol) and the aldehyde **139** in dichloromethane (2.2 ml). The resulting suspension was refluxed for 1h and then poured into

saturated aqueous sodium carbonate (10 ml). The resulting mixture was then neutralised with 1M hydrochloric acid (5 ml) and extracted with dichloromethane (3 x 25 ml), and the combined organic phases were dried and evaporated. The *acid* **141** was obtained as a pale yellow oil (70 mg, 66%), υ_{MAX} 3400 (OH) and 1712 (C=O); δ_H (250) 0.02 (6H, 2 x MeSi), 0.82 (12H, s, ^tBu), 1.15-1.40 (6H, m, 3 x CH_2), 1.81 (1H, ddd, J = 12.8, 9.6 and 6.0, 3'-CH), 2.02 (1H, ddd, J = 12.8, 5.8 and 2.3, 3'-CH), 2.65 (2H, d, J = 5.6, 2-CH_2), 3.91 (1H, td, J = 6.3 and 2.9, 5'-CH), 4.06 (1H, ddd, J = 6.0, 2.9 and 2.3, 4'-CH) and 4.48 (1H, dddd, J = 9.6, 5.8, 5.6 and 5.6, 2'-CH); δ_C (270) -4.56 (MeSi), -4.78 (MeSi), 13.96 (Me), 17.95 (Me_3CSi), 22.70 (CH_2), 25.75 (^tBu), 28.03 (CH_2), 33.78 (CH_2), 40.54 (2-CH_2), 41.04 (3'-CH_2), 73.80 (CH), 76.44 (CH), 87.24 (5'-CH) and 175.01 (C=O); m/z 259 (47%, M^+-^tBu), 187 (100), 131 (60), 75 (60) and 57 (70) [Found: M^+-^tBu, 259.1289. $C_{12}H_{23}O_4Si$ requires M, 259.1366].

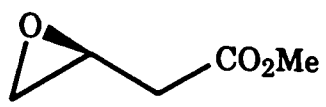
(2'SR,4'RS,5'SR)-2-Aminomethyl-5-butyl-4-hydroxytetrahydrofuran (**142**)



Triethylamine (0.032 ml, 0.23 mmol, 1 eq) was added to a solution of the acid **141** (63 mg, 0.23 mmol, 1 eq) in dry toluene (5 ml) and diphenylphosphoranyl azide (0.049 ml, 0.23 mmol, 1 eq) was added. The resulting solution was slowly warmed to 80°C and

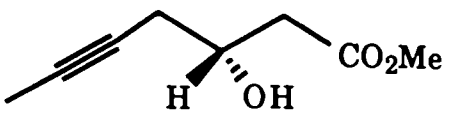
stirred at this temperature for 2h. The solution was then cooled to RT, water (5 ml) was added and the mixture was stirred for a further 16h at this temperature. The resulting mixture was extracted with chloroform (3 x 10 ml) and the combined organic phases were dried and evaporated to give a brown oil (70 mg). The oil was chromatographed on silica (eluting with 50% ethyl acetate in hexane) to give the *amino-alcohol* **142** as a pale yellow oil (16 mg, 38%), υ_{MAX} 3530 (NH_2/OH); δ_H (250) 0.85 (3H, t, J = 6.6, Me), 1.20-1.50 (6H, m, 3 x CH_2), 1.73 (1H, ddd, J =13.3, 9.6 and 6.2, 3-CH), 1.82 (1H, ddd, J = 13.3, 6.2 and 2.7, 3-CH), 3.18 (1H, dd, J = 14.0, and 6.1 $C\underline{H}_AH_BNH_2$), 3.49 (1H, dd, J = 14.0, and 6.2 $CH_A\underline{H}_BNH_2$), 3.66 (1H, td, J = 6.6 and 3.1, 5-CH), 4.02 (1H, ddd, J = 6.2, 6.2 and 3.1, 4-CH) and 4.16 (1H, dddd, J = 9.6, 6.1, 6.2 and 2.7, 2-CH); δ_C (270) 13.98 (Me), 22.64 (CH_2), 28.02 (CH_2), 33.95 (CH_2), 37.68 (CH_2NH_2), 44.44 (3-CH_2), 76.13 (CH), 76.29 (CH) and 86.97 (5-CH); m/z 173 (5%, M^+), 143 (100), 99 (66), 81 (87) and 69 (58)

(S)-Methyl 3,4,-epoxybutanoate (**84**)



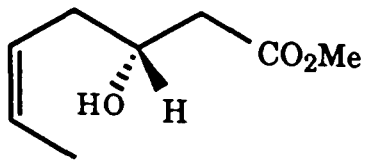
The *epoxide* **84** was obtained in quantities from 0.5-2.5g following exactly the methods of Larcheveque *et al.*[93] for the preparation of the corresponding ethyl epoxy-ester from (S)-malic acid the epoxide **84** showed, $[\alpha]_D$ = -11.0 [c, 1.3 (CH_2Cl_2)]. (lit) $[\alpha]_D$ = +10.7 [c, 1.8 ($CHCl_3$)].; the intermediate iodohydrin **116** showed, υ_{MAX} 3471 (OH), 1732, 1434 and 1372 cm^{-1}; δ_H (250) 2.54 (1H, dd, J = 16.3 and 7.9, 4-C$\underline{H}_A$H$_B$I), 2.65 (1H, dd, J = 16.3 and 4.3, 4-CH$_A\underline{H}_B$I), 3.24 (1H, dd, J = 14.4 and 10.3, 2-C$\underline{H}_A$H$_B$), 3.24 (1H, dd, J = 14.4 and 5.7, 2-CH$_A\underline{H}_B$), 3.67 (3H, s, OMe) and 3.9-4.1 (1H, m, 3-CH); δ_C (270) 12.20 (4-CH_2), 40.83 (2-CH_2), 51.30 (OMe), 67.49 (3-CH) and 171.79 (CH); m/z 226 (5%, M^+- H_2O), 117 (100), 99 (18), 85 (25) and 71 (22) [Found: M^+-H_2O, 225.9507. $C_5H_7IO_2$ requires M, 225.9490]; $[\alpha]_D$ = -9.6 [c, 1.3 (CH_2Cl_2)].

(R)-Methyl 3-hydroxyhept-5-ynoate (**146**)



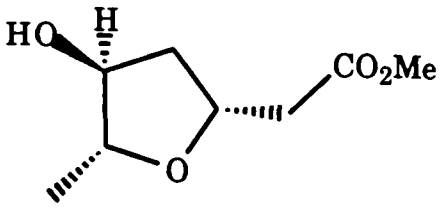
Propyne (~8 ml) was condensed under an atmosphere of nitrogen, dissolved in dry tetrahydrofuran (60 ml), and the solution cooled to -78°C before butyl lithium (21.5 ml of a 1.6M solution in hexanes, 34.4 mmol, 1.5 eq) was added. The resulting solution was stirred for 0.5 h at this temperature and then boron trifluoride etherate (2.83 ml, 23.0 mmol, 1.0 eq) was added. After a further 10 min at -78°C, (S)-methyl 3,4,-epoxybutanoate **84** (2.64 g, 23 mmol, 1.0 eq) was added. The mixture was stirred at this temperature for 4h and then poured into saturated aqueous ammonium chloride (200 ml). The resulting mixture was extracted with ethyl acetate (3 x 50 ml), and the combined organic phases were dried and evaporated to give a pale yellow oil (4.4 g), which was chromatographed on silica (eluting with 15% ether in petrol) to give the *alkyne* **146** as a pale yellow oil (2.9 g, 80%), υ_{MAX} 3452 (OH), 2221, 1736 (C=O), 1672, 1439, 1162 and 1059 $c\,m^{-1}$; δ_H (250) 1.79 (3H, t, J = 2.6, 7-CH_3), 2.38-2.40 (2H, m, 4-CH_2), 2.47 (1H, dd, J = 16.2 and 8.6, 2-C$\underline{H}_A H_B$), 2.71 (1H, dd, J = 16.2 and 3.8, 2-$CH_A\underline{H}_B$), 3.71 (3H, s, OMe) and 4.12-4.20 (1H, m, 3-CH); δ_C (270) 3.22 (7-Me), 26.54 (4-CH_2), 39.91 (2-CH_2), 51.56 (OMe), 66.65 (3-CH), 74.31 (5-C), 78.35 (6-C) and 172.67 (C=O); m/z 138 (7%, M^+-H_2O), 103 (100), 81 (15), 71 (56) and 61 (22) [Found: M^+-H_2O, 138.0685. $C_8H_{10}O_2$ requires M, 138.0681]; $[\alpha]_D$ = -13.16 [c, 7.1 (CH_2Cl_2)] .

(R)-(Z)-Methyl 3-hydroxyhept-5-enoate (**147**)



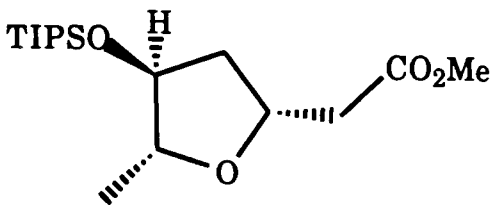
5% Palladium on barium sulphate (63.2 mg) was suspended in dry ethyl acetate (2.1 ml) and quinoline (58μl) was added.[82] The suspension was stirred for 10 min before the acetylene **146** (329 mg, 2.1 mmol) in ethyl acetate (2.1 ml) was added. The mixture was stirred in the dark under an atmosphere of hydrogen until no more gas was absorbed (0.75h) and then filtered through celite. The filtrate was washed with 1M hydrochloric acid (10ml), saturated aqueous sodium bicarbonate (10 ml) and brine (10 ml), before being dried and evaporated to give the *alkene* **147** as a pale yellow oil (290 mg, 87%), υ_{MAX} 3417 (OH), 1732 (C=O), 1438, 1371, 1259, 1202, 1163 and 1058 cm^{-1}; δ_H (250) 1.84 (3H, dd, J = 7.3 and 0.5, 7-CH_3), 2.40 (2H, m, 4-CH_2), 2.52 (1H, dd, J = 16.2 and 8.7, 2-$C\underline{H}_AH_B$), 2.76 (1H, dd, J = 16.2 and 3.9, 2-$CH_A\underline{H}_B$), 3.25 (1H, d, J = 4.2, OH), 3.73 (3H, s, OMe), 4.15 (1H, m, 3-CH), 5.43 (1H, m, 5-CH) and 5.64 (1H, m, 6-CH); δ_C (270) 12.99 (7-Me), 34.16 (4-CH_2), 40.70 (2-CH_2), 51.77 (OMe), 68.01 (3-CH), 125.41 (5-CH), 127.15 (6-CH) and 173.29 (C=O); m/z 140 (11%, M-H_2O), 103 (100), 81 (22), 71 (95) and 61 (41) [Found: M^+-H_2O, 140.0846. $C_8H_{12}O_2$ requires M, 140.0837]; $[\alpha]_D$ = -22.70 [c, 2.7 (CH_2Cl_2)].

(2'R,4'S,5'R)-Methyl (5'-methyl-4'-hydroxytetrahydrofuran-2'-yl) acetate (**148**)



Sodium hydrogencarbonate (810 mg, 9.6 mmol, 3 eq) was added to an ice-cold solution of the alkene **147** (450 mg, 3.2 mmol, 1 eq) in dry acetonitrile (7 ml) and the suspension stirred for 5 mins. Iodine (2.44 g, 9.6 mmol, 3eq) was added and the resulting mixture was stirred at 0-5°C, in the dark, for 72 h. Ether (10 ml) was added and the solution was washed with saturated aqueous sodium thiosulphate (120 ml). The separated aqueous phase was extracted with ether (3 x 50 ml). The combined organic phases were dried and evaporated to give the *hydroxytetrahydrofuran* **148** as a colourless oil (350 mg, 63 %), υ_{MAX} 3402 (OH) and 1734 (C=O), 1653, 1440, 1371, 1163 and 1078 cm^{-1}; δ_H (250) 1.27 (3H, d, J = 6.4, 5'-CH_3), 1.87 (1H, ddd, J = 13.2, 9.4 and 6.4, 3'-CH), 2.02 (1H, ddd, J =13.2, 6.0 and 2.6, 3'-CH), 2.52 (1H, dd, J= 15.6 and 6.2, 2-C$\underline{H}_A$CH_B), 2.66 (1H, dd, J= 15.6 and 6.9, 2-CH_AC$\underline{H}_B$), 3.69 (3H, s, OMe), 3.87 (1H, qd, J = 6.4 and 3.4, 5'-CH), 4.00-4.03 (1H, m, 2'-CH) and 4.47 (1H, ddd, J = 9.4, 6.0 and 3.4, 4'-CH); δ_C (270) 19.75 (5'-Me), 40.47 (3'-CH_2), 40.68 (2-CH_2), 51.74 (OMe), 73.99 (2'-CH), 77.21 (4'-CH), 82.08 (5'-CH) and 173.29 (C=O); m/z 156 (5%, M^+-H_2O), 101 (51), 98 (100), 74 (57) and 57 (61) [Found: M^+-H_2O, 156.0791. $C_8H_{12}O_3$ requires M, 156.0786]; $[\alpha]_D$ = +14.8 [c, 0.4 (CH_2Cl_2)].

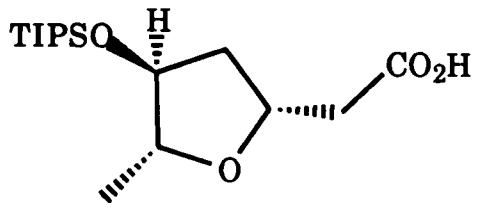
(2'R,4'S,5'R)-Methyl (5'-methyl-4'-triisopropylsilyloxy-tetrahydrofuran-2'-yl) acetate (**150**)



2,6-Lutidine (154 mg, 1.44 mmol, 2.5 eq) was added to a solution of the hydroxytetrahydrofuran **148** (100 mg, 0.57 mmol, 1 eq) in dry dichloromethane (0.63 ml) maintained at 0°C. Triisopropylsilyl trifluoromethanesulphonate (0.23 ml, 0.86 mmol, 1.5 eq) was added dropwise and the resulting mixture stirred at 0°C for 3 h. Brine (20 ml) was added and the resulting mixture extracted with dichloromethane (2 x 25 ml). The combined organic phases were dried and evaporated to give a colourless oil (360 mg) which was chromatographed on silica (eluting with 7% ethyl acetate in petrol) to give the *silyloxytetrahydrofuran* **150** as a clear oil (140 mg, 74%), υ_{MAX} 1729 (C=O), 1464, 1382, 1268, 1163, 1108 and 1040 cm^{-1}; δ_H (250) 1.09-1.11 (21H, m, TIPS) 1.27 (3H, d, J = 6.4, 5'-CH_3), 1.80 (1H, ddd, J = 13.6, 9.3 and 6.4, 3'-CH), 2.05 (1H, ddd, J = 13.6, 5.9 and 2.7, 3'-CH), 2.54 (1H, dd, J = 15.3 and 6.6, 2-C$\underline{H}_A$CH_B), 2.65 (1H, dd, J = 15.3 and 6.4, 2-CH_AC$\underline{H}_B$), 3.67 (3H, s, OMe), 3.85 (1H, qd, J = 6.4 and 3.1, 5'-CH), 4.05 (1H, ddd, J = 6.4, 3.1 and 2.7, 4'-CH) and 4.50 (1H, dddd, J = 9.3 6.6, 6.4 and 5.9, 2'-CH); δ_C (270) 12.04 (6 x Me, TIPS), 17.92 (3 x CH, TIPS), 19.87 (5'-Me), 40.60 (3'-CH_2), 41.24 (2-CH_2), 51.63 (OMe), 74.11 (2'-CH), 78.17 (4'-CH), 83.36

(5'-CH) and 171.50 (C=O); m/z 287 (14%, M^{+}-^{i}Pr), 187 (100), 113 (21), 103 (31) and 75 (35) [Found: M^{+}-^{i}Pr, 287.1669. $C_{14}H_{27}O_4Si$ requires M, 287.1679]; $[\alpha]_D$ = +16.2 [c, 1.6 (CH_2Cl_2)].

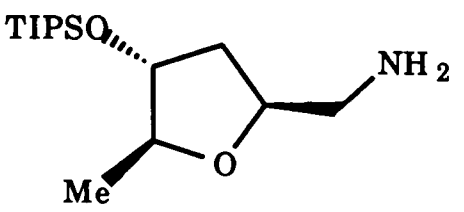
(2'R,4'S,5'R)-(5'-Methyl-4'-triisopropylslyloxytetrahydrofuran-2'-yl)acetic acid (**152**)



Potassium hydroxide (2.04 g, 36.4 mmol, 8 eq) was added to a solution of the methyl ester **150** (1.5 g, 4.4 mmol, 1 eq) in methanol (18.2 ml). The resulting solution was stirred at room temperature for 16h. The solvent was removed under vacuum, the oil obtained was dissolved in water, and the solution washed with ether (25 ml). 2M Hydrochloric acid (16 ml) was added to the solution which was then extracted with chloroform (3 x 50 ml). The combined organic phases were dried and evaporated to give the *acid* **152** as a clear oil (1.40 g, 97%), υ_{MAX} 3368 (OH), 1717 (C=O), 1507, 1419, 1163, 1109 and 1040 cm^{-1}; δ_H (250) 1.03-1.05 (21H, m, TIPS), 1.20 (3H, d, *J* = 6.2, 5'-CH_3), 1.80 (1H, ddd, *J* = 12.8, 9.6 and 6.0, 3'-CH), 2.02 (1H, ddd, *J* = 12.8, 5.8 and 2.3, 3'-CH), 2.65 (2H, d, *J* = 6.3, 2-CH_2), 3.91 (1H, qd, *J* = 6.2 and 2.9, 5'-CH), 4.06 (1H, ddd, *J* = 6.0, 2.9 and 2.3, 4'-CH) and 4.48 (1H, dddd, *J* = 9.6, 6.3, 6.3 and 5.8, 2'-CH); δ_C (270) 12.51 (6 x CH_3-TIPS), 18.45 (3 x CH-TIPS), 20.38 (5'-Me), 40.90 (3'-CH_2), 41.69 (2-CH_2), 74.45 (2'-CH), 78.56 (4'-CH), 84.29 (5'-CH) and

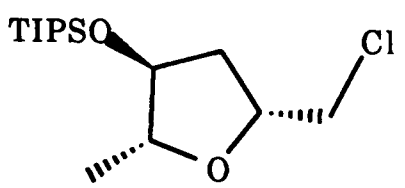
175.97 (C=O); m/z 317 (11%, M^+), 273 (24%, $M^{+-i}Pr$), 187 (100), 131 (58) and 75 (64) [Found: $M^{+-i}Pr$, 273.1517. $C_{13}H_{25}O_4Si$ requires M, 273.1522]; $[\alpha]_D$ = +17.1 [c, 1.0 (CH_2Cl_2)].

(2'SR,4'RS,5'SR)-2-Aminomethyl-5-methyl-4-triisopropylsilyl-oxytetrahydrofuran (**153**)



The acid **152** (130 mg, 0.41 mmol) was treated exactly as in the preparation of the amine **142**, to give a brown oil (300 mg), which was chromatographed on silica (eluting with 30% ethyl acetate in hexane) to give the *amine* **153** as a pale yellow oil (106 mg, 90%), υ_{MAX} 3430 (NH_2); δ_H (250) 1.10 (21H, m, TIPS), 1.27 (3H, t, J = 6.4, 5-Me), 1.73 (1H, ddd, J = 13.1, 9.4 and 6.2, 3-CH), 1.82 (1H, ddd, J = 13.1, 6.1 and 2.7, 3-CH), 3.18 (1H, ddd, J = 14.0 and 6.1, $C\underline{H}_AH_BNH_2$), 3.49 (1H, dd, J = 14.0,and 6.4, $CH_A\underline{H}_BNH_2$), 3.66 (1H, td, J = 6.4 and 3.1, 5-CH), 4.02 (1H, ddd, J = 6.2, 6.1 and 3.1, 4-CH) and 4.16 (1H, dddd, J = 9.4, 6.4, 6.1 and 2.7, 2-CH); δ_C (270) 12.02 (5-Me), 17.90 (6x Me-TIPS), 19.84 (3x CH-TIPS), 37.95 (3-CH_2), 44.42 (CH_2NH_2), 76.52 (CH), 78.11 (CH) and 83.88 (5-CH); m/z 234 (5%, $M^{+-i}Pr$), 143 (100), 81 (93), 57 (70) and 49 (32).

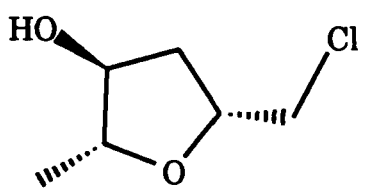
(2SR,4RS,5SR)-2-Chloromethyl-5-methyl-4-triisopropylsilyl-oxytetrahydrofuran (**160**)



The racemic acid **152** (100 mg, 0.32 mmol, 1 eq) was dissolved in dry benzene (5 ml) and the resulting solution was cooled to 0°C before pyridine (1 drop) and dimethylformamide (1 drop) were added. The resulting solution was stirred during the dropwise addition of oxalyl chloride (0.15 ml, 0.32 mmol, 1eq) and stirring was continued for a further 3h. The solvent was then removed *in vacuo*. The crude oil thus obtained was azeotroped with dry benzene (5 ml) before being dissolved in dry carbon tetrachloride (3 ml) and added to a refluxing suspension of 2-mercaptopyridine-N-oxide sodium salt (57 mg, 0.38 mmol, 1.2 eq) and catalytic 4-dimethylaminopyridine (2 mg) in carbon tetrachloride (15 ml). The resulting suspension was heated for 1.5h before being cooled and filtered through celite. The filtrate was evaporated to give a brown oil (300 mg), which was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the *chloride* **160** as a clear oil (72 mg, 73%), υ_{MAX} 1402, 1371, 1249, 1106 and 1058 cm^{-1}; δ_H (250) 1.05-1.07 (21H, m, TIPS), 1.20 (3H, d, J = 6.2, 5-CH_3), 1.93-1.96 (2H, m, 3-CH_2), 3.59 (2H, d, J = 4.8, CH_2Cl), 3.95 (1H, qd, J = 6.4 and 3.1, 5-CH), 4.07 (1H, ddd, J = 4.1, 3.6 and 3.1, 4-CH) and 4.39 (1H, tdd, J

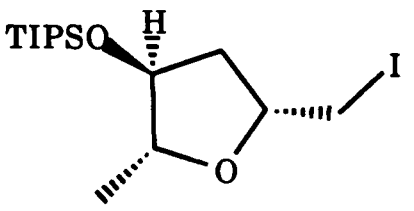
= 6.2, 4.8 and 2.1, 2-CH); δ_C (270) 11.97 (6 x CH_3, TIPS), 17.94 (3 x CH, TIPS), 20.46 (5-Me), 38.83 (3-CH_2), 47.17 (CH_2Cl), 77.34 (CH), 77.92 (CH), 83.52 (5-CH); m/z 263 (29%, M^+-^{i}Pr), 187 (77), 131 (100), 97 (40) and 75 (33) [Found: M^+-^{i}Pr, 263.1198. $C_{12}H_{24}ClO_2Si$ requires M, 263.1234].

(2SR,4RS,5SR) 2-Chloromethyl-4-hydroxy-5-methyltetrahydrofuran (**161**)



The chloride **160** (48 mg, 0.15 mmol, 1eq) was dissolved in dry tetrahydrofuran (1 ml) and tetrabutylammonium fluoride (0.3 ml of a 1M solution in tetrahydrofuran, 0.3 mmol, 2 eq) was added. The resulting solution was stirred at RT for 40h, before the solvent was removed *in vacuo* to give a viscous oil, which was chromatographed on silica (eluting with 20% ethyl acetate in petrol) to give the *chloro-alcohol* **161** as a clear oil (15 mg, 60%), υ_{MAX} 3430 (OH), 1645, 1444, and 1350 cm^{-1}; δ_H (250) 1.25 (3H, d, J = 6.2, 5-CH_3), 2.05 (2H, m, 3-CH_2), 3.59 (2H, d, J = 5.0, CH_2Cl), 4.02-4.05 (2H, m, 4- and 5-CH) and 4.39 (1H, tdd, J = 5.0, 2.8 and 2.0, 2-CH); δ_C (270) 19.52 (5-Me), 38.08 (3-CH_2), 46.99 (CH_2Cl), 77.21 (CH), 77.34 (CH) and 82.93 (5-CH); m/z 115 (17%, M^+-Cl), 101 (71), 71 (53), 70 (32) and 57 (100). [Found: M^+-Cl, 115.0078. $C_6H_{11}O_2$ requires M, 115.0759].

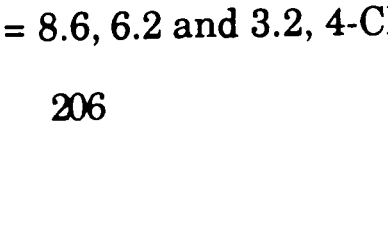
(2R,4S,5R)-2-Iodomethyl-5-methyl-4-triisopropylsilyloxytetrahydrofuran (**162**)



The acid **152** (20.5 mg, 0.065 mmol, 1 eq) was dissolved in dry benzene (1 ml) and the resulting solution was cooled to 0°C before pyridine (1 drop) and dimethylformamide (1 drop) were added. The resulting solution was stirred during the dropwise addition of oxalyl chloride (0.03 ml, 0.065 mmol, 1eq) and stirring was continued for a further 3h. The solvent was then removed *in vacuo*. The crude oil thus obtained was azeotroped with dry benzene (1 ml) before being dissolved in cyclohexene (2 ml) and added to a refluxing suspension of iodoform (28 mg, 0.07 mmol, 1.1 eq), 2-mercaptopyridine-N-oxide sodium salt (11 mg, 0.07 mmol, 1.1 eq) and catalytic 4-dimethylaminopyridine (1 mg) in cyclohexene (5 ml). The resulting suspension was heated for 15h before being cooled and filtered through celite. The filtrate was evaporated to give a brown oil (60 mg), which was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the *iodide* **163** as a clear oil (8.9 mg, 40%), υ_{MAX} 1445, 1250, 1156 and 1071 cm^{-1}; δ_H (250) 1.00-1.02 (21H, m, TIPS), 1.25 (3H, d, J = 6.3, 5-CH_3), 1.74 (1H, ddd, J = 12.7, 6.5 and 2.9, 3-CH), 1.93 (1H,

ddd, J = 12.7, 6.0 and 2.9, 3-CH), 3.22 (2H, d, J = 4.8, CH_2I), 3.92 (1H, qd, J = 6.3 and 3.2, 5-CH), 4.02 (1H, ddd, J = 6.0, 3.2 and 2.9, 4-CH) and 4.39 (1H, dtd, J = 6.5, 4.8 and 2.9, 2-CH); δ_C (270) 11.04 (CH_2I), 12.00 (6 x CH_3-TIPS), 17.92 (3 x CH-TIPS), 19.88 (5-Me), 41.78 (3-CH_2), 77.00 (CH), 78.10 (CH) and 83.86 (5-CH); m/z 355 (3%, M^+-^{i}Pr), 187 (100), 141 (35), 127 (40) and 75 (15) [Found: M^+-^{i}Pr. 355.0512. $C_{12}H_{24}IO_2Si$ requires M, 355.0590]; $[\alpha]_D$ = +24.6 [c, 8.7 (CH_2Cl_2)].

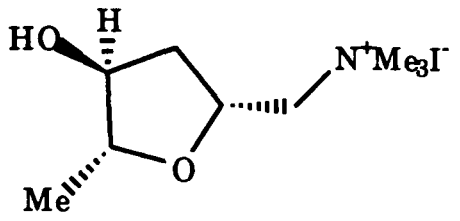
(2R,4S,5R) 4-Hydroxy-2-iodomethyl-5-methyltetrahydrofuran (**163**)



The iodide **162** (32 mg, 0.10 mmol, 1 eq) was dissolved in dry tetrahydrofuran (0.5 ml) and tetrabutylammonium fluoride (0.2 ml of a 1M solution in tetrahydrofuran, 0.2 mmol, 2 eq) was added. The resulting solution was stirred at RT for 40h, before the solvent was removed *in vacuo* to give a viscous oil, which was chromatographed on silica (eluting with 20% ethyl acetate in petrol) to give the *iodo-alcohol* **163** as a clear oil (10 mg, 60%), υ_{MAX} 3400 (OH), 1447, 1353, 1061 and 1028 cm^{-1}; δ_H (250) 1.26 (3H, d, J = 6.4, 5-CH_3), 1.91 (1H, ddd, J = 13.3, 8.6 and 6.2, 3-CH), 2.05 (1H, ddd, J = 13.3, 6.2 and 3.0, 3-CH), 3.34 (1H, dd, J = 10.2 and 6.2, $C\underline{H}_AH_BI$), 3.31 (1H, dd, J = 10.2 and 4.9, $CH_A\underline{H}_BI$), 3.97 (1H, qd, J = 6.4 and 3.2, 5-CH), 4.05 (1H, ddd, J = 8.6, 6.2 and 3.2, 4-CH) and 4.16 (1H, dddd,

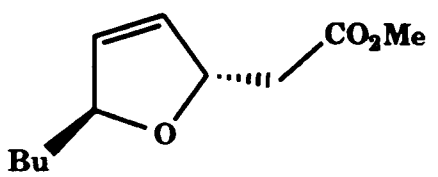
J = 6.2, 6.2, 4.9 and 3.0, 2-CH); δ_C (270) 10.42 (CH_2I), 19.79 (5-Me), 41.06 (3-CH_2), 77.17 (CH), 77.59 (CH), 83.34 (5-CH); m/z 242 (2%, M^+), 115 (31), 101 (100), 71 (70) and 57 (49); $[\alpha]_D$ = +20.5 [c, 2.0 ($CHCl_3$)]; (lit) $[\alpha]_D$ = +26.5 [c, 1.8 ($CHCl_3$)] for the enantiomer.

(-)- Muscarine iodide (**164**)



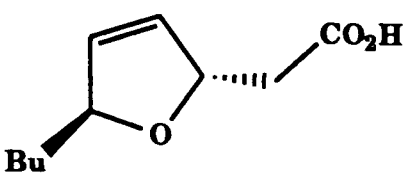
Trimethylamine (0.05 ml) was added to a solution of the iodo-alcohol **163** (10 mg, 0.04 mmol, 1 eq) in ethanol (0.2 ml) and the resulting solution was heated at 70°C in a sealed tube over 4h. Cooling was allowed over 16h. and the solvent was evaporated to give a solid residue (8 mg) which was crystallised from acetone to give muscarine iodide **164** (5 mg, 60%) which showed spectral data identical to the literature values: m.p. 135-137°C [lit[127] m.p. 138-142°C; δ_H (250) 1.23 (3H, d, J = 6.5, 5-CH_3), 2.04 (1H, ddd, J = 14.0, 10.0 and 5.5, 3-CH), 2.17 (1H, ddd, J = 14.0, 6.0 and 2.0, 3-CH) 3.29 (9H, s, NMe_3), 3.49 (1H, dd, J = 14.0 and 9.2, $C\underline{H}_AH_BN$), 3.63 (1H, dd, J = 14.0 and 2.0, $CH_A\underline{H}_BI$), 4.13 (1H, qd, J = 6.5 and 2.5, 5-CH), 4.24 (1H, ddd, J = 5.5, 2.5 and 2.0) and 4.72 (1H, m, 2-CH).

(2'R,5'RS)-Methyl (5'-butyl-2',5'-dihydrofuran-2'-yl)acetate (**201**)



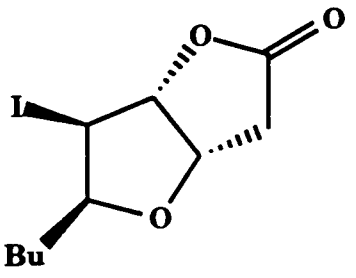
Sodium azide (1.32 g, 20.2 mmol, 2 eq) was added to a solution of the iodotetrahydrofuran **54b** (3.31 g, 10.1 mmol, 1 eq) in dry dimethylformamide (35 ml) and the solution was heated to 110°C for 16h and then cooled to RT before diluting with water (150 ml). The resulting mixture was extracted with ether (3 x 100 ml). The combined organic phases were dried and evaporated to give an oil (2 g) which was chromatographed on silica (eluting with 10% ethyl acetate in hexane) to give the *dihydrofuran* **201** as a colourless oil (0.93 g, 47%), υ_{MAX} 1736 (C=O), 1437, 1163 and 1068 cm^{-1}; δ_H (250) 0.87 (3H, t, J = 6.8, CH_3), 1.20-1.60 (6H, m, 3 x CH_2), 2.47 (1H, dd, J = 15.3 and 6.2, 2-$C\underline{H}_AH_B$), 2.59 (1H, dd, J = 15.3 and 7.0, 2-$CH_A\underline{H}_B$), 3.68 (3H, s, OMe), 4.85 (1H, dt, J = 5.9 and 0.5, 5'-CH), 5.19 (1H, ddd, J = 7.0, 6.2 and 0.5, 2'-CH) and 5.80 (2H, m, 3'- and 4'-CH); δ_C (270) 14.02 (Me), 22.77 (CH_2), 27.19 (CH_2), 35.55 (CH_2), 41.04 (2-CH_2), 51.65 (OMe), 81.76 (2'-CH), 85.85 (5'-CH), 128.75 (3'-CH), 131.05 (4'-CH) and 171.45 (C=O); m/z 198 (16%, M^+), 156 (37), 91 (61), 85 (100) and 57 (92) [Found: M^+, 198.1236. $C_{11}H_{18}O_3$ requires M, 198.1256].

'2'SR,5'RS)-5'-Butyl-2',5'-dihydrofuran-2'-yl) acetic acid (**203**)



The dihydrofuran **201** (500 mg, 2.52 mmol, 1 eq) was treated exactly as in the preparation of compound **152** to give the *acid* **203** as a colourless oil (400 mg, 86%), υ_{MAX} 3300 (OH), 1715 (C=O), 1424, 1259 and 1069 $c m^{-1}$; δ_H (250) 0.87 (3H, t, J = 6.5, CH_3), 1.30-1.70 (6H, m, 3 x CH_2), 2.60 (1H, d, J = 7.0, 2-CH_2), 4.85 (1H, dt, J = 5.9 and 0.7, 5'-CH), 5.20 (1H, dt, J = 7.0 and 0.7, 2'-CH) and 5.90 (2H, m, 3' and 4'-CH); δ_C (270) 14.02 (Me), 22.75 (CH_2), 27.19 (CH_2), 35.44 (CH_2), 40.77 (2-CH_2), 81.51 (2'-CH), 86.16 (5'-CH), 128.36 (3'-CH), 131.27 (4'-CH) and 176.10 (C=O); m/z 184 (10%, M^+), 139 (41), 127 (43), 81 (44) and 57 (57) [Found : M^+, 184.1509. $C_{10}H_{16}O_3$ requires M, 184.1099].

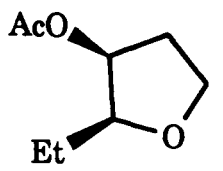
3-Butyl-4-iodo-2,6-dioxabicyclo-[3,3,0]-7-one (**204**)



The acid **203** (15 mg, 0.1 mmol, 1 eq) was treated exactly as in the preparation of compound **54b**, to give the *iodo-ester* **204** as a colourless oil (21 mg, 75%), υ_{MAX} 1787 (C=O), 1467, 1185, 1148 and 1047 $c m^{-1}$; δ_H (250) 0.91 (3H, t, J = 7.0, CH_3), 1.20-1.80 (6H, m, 3 x CH_2), 2.73 (1H, dd, J = 17.8 and 8.4, 8-$C\underline{H}_A H_B$), 2.59 (1H, dd, J = 17.8 and 6.2, 8-$CH_A\underline{H}_B$), 3.18 (1H, dt, J = 6.4 and 3.0, 3-CH), 4.51 (1H, d,

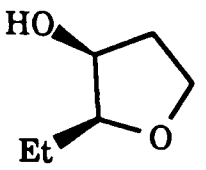
J = 3.0, 4-CH), 5.10 (1H, ddd, J = 8.4, 6.2 and 4.4, 1-CH) and 5.37 (1H, d, J = 4.4, 5-CH); δ_C (270) 13.91 (Me), 22.52 (CH_2), 27.68 (CH_2), 34.77 (4-CH), 46.08 (8-CH_2), 75.68 (CH), 77.12 (CH), 90.60 (5-CH), and 176.59 (C=O); m/z 310 (3%, M^+), 253 (100), 183 (99), 127 (30), 85 (31) and 57 (73) [Found: M^+, 310.0146. $C_{10}H_{15}IO_3$ requires M, 310.0066].

(2RS,3RS)-3-Acetoxy-2-ethyltetrahydrofuran (**205**)



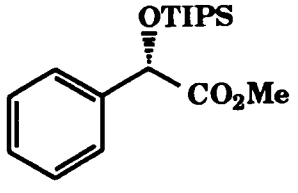
Cesium acetate (127 mg, 0.66 mmol, 1.5 eq) was added to a stirred solution of the iodotetrahydrofuran **58** (100 mg, 4.4 mmol, 1 eq) in dimethylformamide (0.5 ml). The resulting mixture was heated at 80°C for 14h and then water (25 ml) was added. The mixture was extracted with ether (3 x 20 ml) and the combined organic phases were dried and evaporated to give a brown oil (50 mg) which was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give, as a colourless oil, the *acetoxytetrahydrofuran* **205** (20 mg, 35%), which showed data identical to literature values,[186] υ_{MAX} 1741 (C=O), 1242, 1106 and 1025 cm^{-1}; δ_H (250) 0.87 (3H, t, J = 7.6, CH_3), 1.40-1.55 (2H, m, 1'-CH_2), 1.85-2.03 (1H, m, 4-H_A), 2.17-2.29 (1H, m, 4-H_B), 3.57 (1H, td, J = 7.3 and 3.7, 2-H), 3.72 (1H, td, J = 8.7 and 5.3, 5-H_A), 3.95 (1H, dt, J = 8.0 and 7.6 , 5-H_B) and 5.23 (1H, ddd, J = 6.0, 4.3 and 1.5, 3-H).

(2RS,3RS)-2-Ethyl-3-hydroxytetrahydrofuran (**206**)



Potassium superoxide (344 mg, 4.8 mmol, 1.1 eq) was added to a stirred solution of the iodotetrahydrofuran **58** (1 g, 4.4 mmol, 1 eq) and 18-crown-6 (0.1 ml) in dimethylformamide (1 ml). The resulting mixture was stirred for 16h at RT and water (50 ml) was added. The mixture was extracted with ether (3 x 20 ml) and the combined organic phases were dried and evaporated to give a brown oil (500 mg), which was chromatographed on silica (eluting with 20% ethyl acetate in petrol) to give the *hydroxy-tetrahydrofuran* **206** as a colourless oil (104 mg, 25%), which showed data identical to literature values,[109] υ_{MAX} 3542 (OH), 1375, 1150 and 1023 cm^{-1}; δ_H (250) 0.94 (3H, t, J = 7.6, CH_3), 1.40-1.55 (2H, m, 1'-CH_2), 1.84-1.90 (1H, m, 4-H_A), 2.09-2.18 (1H, m, 4-H_B), 3.42 (1H, td, J = 6.8 and 3.1, 2-H), 3.79 (1H, td, J = 8.9 and 4.6, 5-H_A), 3.97 (1H, m, 5-H_B) and 4.16-4.17 (1H, m, 3-H).

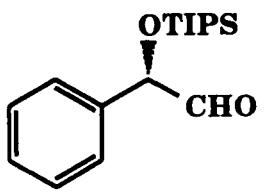
(S)-Methyl 2-phenyl-2-(triisopropylsilyloxy)acetate (**211**)



Triisopropylsilyl chloride (10.6 ml, 50 mmol, 1.1 eq) was added dropwise to a stirred solution of (S)-methyl mandelate (7.5 g, 45.1 mmol, 1.0 eq) and imidazole (6.14 g, 90.2 mmol, 2 eq) in

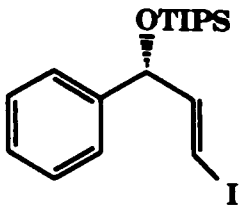
dimethylformamide (25 ml) at RT. The resulting solution was stirred for 26h and then poured into water (300 ml). The resulting mixture was extracted with petrol (3 x 100 ml) and the combined organic phases dried and evaporated to give the *silyl ether* **211** as a colourless oil (14.95 g, 97%), υ_{MAX} 1732 (C=O), 1465, 1206 and 1074 $c\,m^{-1}$; δ_H (250) 0.90-1.10 (21H, m, TIPS), 3.70 (3H, s, OMe), 5.32 (1H, s, 2-H) and 7.30-7.60 (5H, m, Ph); δ_C (270) 11.88 (TIPS, 3 x CH), 17.54 (TIPS, 6 x CH_3), 51.67 (OMe), 74.36 (2-CH), 126.13 (CH), 127.89 (CH), 128.07 (CH), 139.27 (C) and 172.31 (C=O), m/z 279 (76%, M^+-^{i}Pr), 202 (15), 77 (100), 71 (56) and 51 (53); $[\alpha]_D$ = + 80.2 [c, 1.0 (CH_2Cl_2)].

(S)-Methyl 2-phenyl-2-(triisopropylsilyloxy)acetaladehyde (**212**)



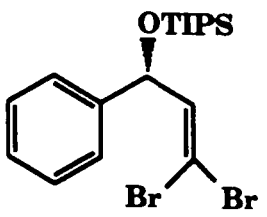
The silyl ether **211** (1.0 g, 3.1 mmol, 1 eq) was dissolved in dry hexane (10 ml) and dry ether (10 ml) and was reduced as in the preparation of compound **244** to give the *aldehyde* **212** as a colourless oil (0.57 g, 63%), υ_{MAX} 1730 (C=O), 1464, 1291 and 1117 $c\,m^{-1}$; δ_H (250) 1.00-1.30 (21H, m, TIPS), 5.32 (1H, d, J = 1.0, 2-H), 7.30-7.60 (5H, m, Ph) and 9.55 (1H, d, J = 1.0, CHO); δ_C (270) 12.04 (TIPS, 3 x CH), 17.81 (TIPS, 6 x CH_3), 80.09 (2-CH), 126.43 (CH), 128.34 (CH), 128.41 (CH), 132.85 (C) and 199.64 (C=O); $[\alpha]_D$ = + 11.5 [c. 1.1 (CH_2Cl_2)].

(1E,3S)-1-Iodo-3-phenyl-3-triisopropylsilyloxyprop-1-ene (**213**)



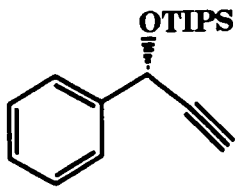
To a suspension of chromium(II) chloride (5 g, 40.7 mmol, 6 eq) in dry tetrahydrofuran (100 ml) was added dropwise a solution of iodoform (5.34 g, 13.6 mmol, 2 eq) and aldehyde **212** (1.98 g, 6.78 mmol, 1 eq) in dry tetrahydrofuran (8 ml). The resulting solution was refluxed in the dark for 24h, under an atmosphere of argon, before being cooled and poured into water (250 ml). The resulting mixture was extracted with ether (3 x 200 ml), and the combined organic phases were dried and evaporated to give a purple oil, which was chromatographed twice on silica (eluting with cyclohexane) to give the *vinyl iodide* **213** as a colourless oil (1.10 g, 42%), υ_{MAX} 1600, 1463, 1197 and 1114 cm^{-1}; δ_H (250) 0.90-1.20 (21H, m, TIPS), 5.20 (1H, dd, J = 5.5 and 1.1, 3-H), 6.37 (1H, dd, J = 14.4 and 1.1, 1-H), 6.45 (1H, dd, J = 14.4 and 5.5, 2-H) and 7.30-7.60 (5H, m, Ph); δ_C (270) 12.11 (TIPS, 3 x CH), 17.85 (TIPS, 6 x CH_3), 75.65 (3-CH), 77.34 (1-CH), 125.89 (CH), 127.39 (CH), 128.27 (CH), 137.24 (C) and 148.95 (2-CH); m/z 416 (5%, M^+), 373 (100%, M^{+}-^{i}Pr), 245 (29), 213 (35) and 116 (57) [Found: M^{+}-^{i}Pr, 373.0536. $C_{15}H_{22}IOSi$ requires M, 373.0485]; $[\alpha]_D$ = - 15.4 [c. 1.0 (CH_2Cl_2)].

(S)-1,1-Dibromo-3-phenyl-3-triisopropylsilyloxyprop-1-ene (**215**)



Zinc dust (3.58 g, 55 mmol, 2 eq) was added to a stirred solution of carbon tetrabromide (18.17 g, 55 mmol, 2 eq) and triphenylphoshine (14.4 g, 55 mmol, 2 eq)[163] in dry dichloromethane (200 ml) at RT, and the resulting solution was stirred for 24h. The aldehyde **212** (8 g, 27 mmol, 1 eq) was added and the resulting solution was stirred for 80h at RT and then poured into petrol (300 ml) and the mixture filtered. The filtrate was evaporated to give a clear oil, which was chromatographed on silica (eluting with 10% dichloromethane in petrol) to give the *dibromide* **215** as a colourless oil (9.2 g, 75%), υ_{MAX} 1630, 1464 and 1063 cm^{-1}; δ_H (250) 1.00-1.40 (21H, m, TIPS), 5.40 (1H, d, J = 14.0, 3-H), 6.55 (1H, d, J = 14.0, 1-H), and 7.20-7.60 (5H, m, Ph); δ_C (270) 12.11 (3 x CH-TIPS), 17.85 (3 x CH_3-TIPS), 74.89 (3-CH), 88.62 (1-C), 128.25 (CH), 128.34 (CH), 128.41 (CH), 136.75 (C) and 141.96 (2-CH); $[\alpha]_D$ = - 62.3 [c, 1.0 (CH_2Cl_2)].

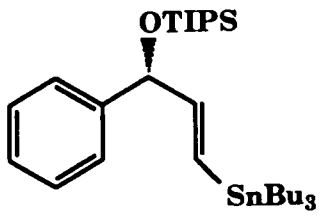
(S)-3-Phenyl-3-triisopropylsilyloxypropyne (**216**)



Butyl lithium (7.4 ml of a 1.6 M solution in hexane, 11.9

mmol, 2 eq) was added to a solution of the dibromide **215** (2.68 g, 5.95 mmol, 1 eq) in dry tetrahydrofuran (25 ml) at -78°C. The resulting solution was stirred at this temperature for 8h, and then allowed to warm to RT over 20h. Saturated aqueous ammonium chloride (10 ml) was added and the mixture was extracted with ethyl acetate (2 x 20 ml). The combined organic phases were dried and evaporated to give a brown oil (2.7 g), which was chromatographed on silica (eluting with petrol) to give *acetylene* **216** as a colourless oil (900 mg, 53%), υ_{MAX} 2200, 1630, 1464, and 1063 cm^{-1}; δ_H (250) 1.00-1.20 (21H, m, TIPS), 2.52 (1H, d, J = 2.3, 1-H), 5.55 (1H, d, J = 2.3, 3-H) and 7.26-7.60 (5H, m, Ph); δ_C (270) 12.11 (3 x CH, TIPS), 17.85 (6 x Me, TIPS), 76.45 (2-C), 74.89 (3-CH), 88.62 (1-C), 128.25 (Ph-CH), 128.34 (Ph-CH), 128.41 (CH) and 136.75 (C); m/z 245 (100%, M^+-^{i}Pr), 220 (27), 131 (60), 71 (35) and 55 (100) [Found: M^+-^{i}Pr, 245.1367. $C_{15}H_{21}OSi$ requires M, 245.1361].

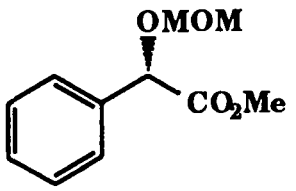
(3S,1E)-3-Phenyl-3-triisopropylsilyloxy-1-tributyl-stannylprop-1-ene (**217**)



A solution of azo-*bis*-isobutyronitrile (49.8 mg, 0.028 mmol, 0.28 eq) in dry benzene (3 ml) was added slowly to a refluxing solution of acetylene **216** (292 mg, 1.01 mmol, 1 eq) and tributyltin hydride (0.3 ml, 1.12 mmol, 1.1 eq) in dry benzene (15 ml). The resulting solution was refluxed in the dark for 15h, under an

atmosphere of argon, before the solvent was evaporated to give an oil, which was chromatographed on silica (eluting with petrol) to give the *vinyl stannane* **217** as a colourless oil (100 mg, 17%), υ_{MAX} 1596, 1463, 1096 and 1067 $c m^{-1}$; δ_H (250) 0.70 (9H, t, J = 7.0, 3 x Me), 1.00-1.05 (21H, m, TIPS), 1.20-1.70 (18H, m, 9 x CH_2), 5.20 (1H, dd, J = 5.5 and 0.8, 3-H), 5.99 (1H, dd, J = 18.9 and 5.5, 2-H), 6.23 (1H, dd, J = 18.9 and 0.8, 1-H) and 7.20-7.40 (5H, m, Ph); δ_C (270) 9.44 (3 x CH_2Sn), 13.70 (3 x CH, TIPS), 14.35 (3 x Me), 18.06 (6 x CH_3, TIPS), 27.23 (3 x CH_2), 29.08 (3 x CH_2), 78.85 (3-CH), 77.34 (1-CH), 125.97 (CH), 126.34 (CH), 126.65 (CH), 127.96 (C) and 151.36 (2-C); m/z 523 (100%, M^+-Bu), 521 (75%, M^+-Bu), 117 (88), 115 (48) and 55 (59); $[\alpha]_D$ = - 7.1 [c, 0.7 (CH_2Cl_2)].

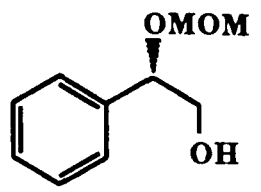
(S)-Methyl 2-methoxymethoxyphenylacetate (**218**)



Chloromethyl methyl ether (6 ml, 78.9 mmol, 5 eq) was added dropwise to a stirred solution of (S)-methyl mandelate (2.62 g, 15.8 mmol, 1.0 eq) and ethyldiisopropylamine (4.12 ml, 23.7 mmol, 1.5 eq) in dichloromethane (10 ml) at RT. The resulting mixture was stirred for 19h and the poured into water (50 ml). The resulting solution was extracted with dichloromethane (3 x 30 ml) and the combined organic phases were dried and evaporated to give the *ether* **218** as a yellow oil (3.58 g, 100%), which showed data corresponding exactly to literature values,[167] υ_{MAX} 1735 (C=O) $c m^{-1}$;

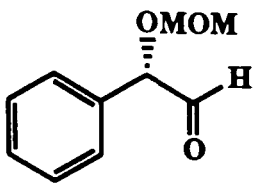
δ_H (250) 3.46 (3H, s, OMe), 3.79 (3H, s, CO_2Me), 4.80 (2H, s, $OC\underline{H}_2OMe$), 5.26 (1H, s, 2-CH) and 7.40-7.60 (5H, m, Ph); δ_C (270) 52.60 (MeO), 56.22 (Me ester), 76.89 (2-CH), 95.25 ($O\underline{C}H_2OMe$), 127.71 (CH), 128.94 (CH), 129.03 (CH), 136.35 (C) and 171.50 (C=O).

(S)-2-Methoxymethoxy-2-phenylethanol (**219**)



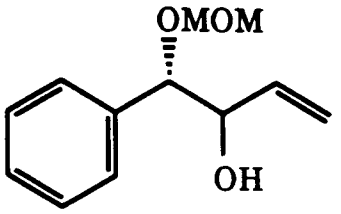
Diisobutylaluminium hydride (38.1 ml of a 1.5 M solution in toluene, 57 mmol, 4 eq) was added to a stirred solution of the ester **218** in dry toluene (10 ml) at -78°C and the resulting solution allowed to warm to RT over 1.75h. The resulting solution was cooled to 0°C during the cautious addition of 2M hydrochloric acid (15 ml). The resulting mixture was then extracted with ethyl acetate (3 x 25 ml) and the combined organic phases were dried and evaporated to give the pure *alcohol* **219** as a colourless oil (2.45 g, 94%), which showed data in accordance with literature values,[167] υ_{MAX} 3600 (OH) cm^{-1}; δ_H (250) 2.80-3.05 (1H, br, OH), 3.38 (3H, s, OMe), 3.64 (1H, dd, J = 11.9 and 4.0, $C\underline{H}_AH_BOH$), 3.73 (1H, dd, J = 11.9 and 8.0, $CH_A\underline{H}_BOH$), 4.63 (2H, dd, J = 8.0 and 4.0, 2-H), 5.26 (1H, s, $OC\underline{H}_2OMe$) and 7.20-7.40 (5H, m, Ph); δ_C (270) 55.33 (OMe), 67.01 (CH_2OH), 79.93 (2-CH), 94.74 ($O\underline{C}H_2OMe$), 126.83 (CH), 127.98 (CH), 128.35 (CH) and 138.26 (C); $[\alpha]_D$ = + 190 [c, 2.0 (CH_2Cl_2)]; (lit); +196 [c. 2.7 ($CHCl_3$)].

(S)-2-Methoxymethoxyphenylacetaldehyde (**220**)



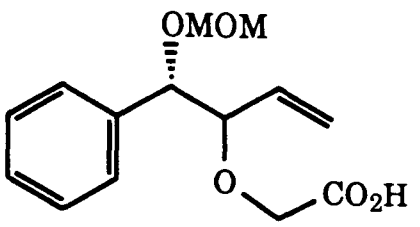
A solution of dimethyl sulphoxide (1.25 ml, 17.5 mmol, 2.5 eq) in dichloromethane (6 ml) was added dropwise to a solution of oxalyl chloride (0.8 ml, 8.7 mmol, 1.1 eq) in dichloromethane at -60°C at such a rate that the temperature was kept below -55°C. After 0.25h, the alcohol **219** (1.45 g, 8 mmol, 1 eq) was added and after a further 5 min, triethylamine (5.6 ml, 40 mmol, 5 eq) was added slowly and the resulting mixture allowed to warm to 10°C over 0.5h before water (12 ml) was added. The resulting mixture was extracted with dichloromethane (2 x 30 ml) and the combined organic phases were washed with brine (20 ml), 1M hydrochloric acid (3 x 30 ml) and brine (30 ml) and then dried and evaporated to give the *aldehyde* **220** as a yellow oil (1.02 g, 71%), which showed data in accordance to literature values,[166] υ_{MAX} 1730 (C=O) c m^{-1}; δ_H (250) 3.35 (3H, s, OMe), 4.65 (2H, s, OCH_2OMe), 5.26 (1H, d, J = 0.4, 2-H), 7.20-7.40 (5H, m, Ph) and 9.53 (1H, d, J = 0.4, 1-H); δ_C (270) 56.01 (OMe), 73.16 (2-CH), 94.72 (OCH_2OMe), 127.61 (CH), 128.94 (CH), 129.03 (CH), 133.49 (C) and 195.88 (C=O); $[\alpha]_D$ = + 105 [c, 2.0 (CH_2Cl_2)]; (lit) +112 [c, 1.0 ($CHCl_3$)].

(3RS, 4S)-4-Methoxymethoxy-4-phenylbut-1-en-3-ol (**221**)



Vinylmagnesium chloride (10 ml of a 1.7 M solution in tetrahydrofuran, 17 mmol, 3 eq) was added to a solution of the aldehyde **220** (1.02 g, 5.6 mmol, 1 eq) in dry tetrahydrofuran (5 ml) at 0°C. The resulting solution was stirred at RT for 16h. Saturated aqueous ammonium chloride (10 ml) was added and the mixture was extracted with ethyl acetate (2 x 20 ml). The combined organic phases were dried and evaporated to give a brown oil (1 g), which was chromatographed on silica (eluting with 20% ethyl acetate in petrol) to give the *alcohols* **221** as a yellow oil (1.02 g, 71%), υ_{MAX} 3300 (OH) c m^{-1}; δ_H (250) 3.46 (3H, s, OMe), 4.37 (1H, dd, J = 7.5 and 6.6, 3-H), 4.51 (1H, d, J = 7.5, 4-H), 4.69 (2H, s, O$\underline{C}H_2$OMe), 5.17 (1H, dd, J = 10.5 and 1.5, 1-H), 5.30 (1H, dd, J = 17.2 and 1.5, 1-H), 5.73 (1H, ddd, J = 17.2, 10.5 and 6.6, 2-H) and 7.30-7.42 (5H, m, Ph); δ_C (270) 55.41 (OMe), 75.60 (4-CH), 81.80 (3-CH), 94.56 (O$\underline{C}H_2$OMe), 116.41 (1-CH_2), 127.51 (CH), 127.91 (CH), 128.01 (CH), 135.81 (2-CH) and 137.36 (C); and also the 3-epimer which showed, δ_H (250) 3.45 (3H, s, OMe) and 5.80 (1H, ddd, J = 16.6, 9.4 and 6.0, 2-CH) [other peaks obscured]; a ratio of ca. 3:1 between the two isomers was observed.

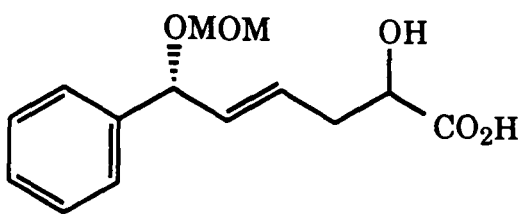
(4RS,5S)-4-Ethenyl-5-methoxymethoxy-5-phenyl-3-oxapentanoic acid (**222**)



Sodium hydride (249 mg of a 60% suspension in mineral oil, 6.5 mmol, 1.5 eq) was added to a solution of the alcohols **221** (900 mg, 4.3 mmol, 1 eq) in dry tetrahydrofuran (5 ml) at 0°C. The resulting solution was stirred at RT for 1h before solid sodium iodoacetate (1.87, 6.5 mmol, 1.5 eq) was added. The resulting suspension was refluxed for 16h. 2M Sodium hydroxide (30 ml) was added to the cooled mixture which was then washed with ethyl acetate (2 x 30 ml). The aqueous phase was acidified with 2M hydrochloric acid and extracted with chloroform (2 x 30 ml). The combined chloroform phases were dried and evaporated to give the *acids* **222** as a yellow oil (0.75 g, 68%), υ_{MAX} 3450 (OH) and 1715 (C=O) cm^{-1}; δ_H (250) 3.41 (3H, s, OMe), 3.96 (1H, dd, J = 9.6 and 7.4, 4-H), 4.02 (1H, d, J = 17.4, 2-C$\underline{H}_A$H$_B$), 4.30 (1H, d, J = 17.4, 2-CH$_A\underline{H}_B$), 4.62 (2H, s, OC$\underline{H}_2$OMe), 4.65 (1H, d, J = 9.6, 5-H), 5.05-5.15 (2H, m, 2'-CH_2), 5.45 (1H, ddd, J = 17.5, 10.0 and 6.6, 1'-H), and 7.20-7.42 (5H, m, Ph); δ_C (270) 55.74 (OMe), 66.54 (4-CH), 79.91 (5-CH), 85.62 (2-CH_2), 93.80 (O$\underline{C}$H$_2$OMe), 119.62 (2'-CH_2), 127.89 (CH), 128.36 (CH), 128.49 (CH), 132.49 (1'-CH), 136.32 (C) and 172.76; and also the 4-

epimer which showed, δ_H (250) 3.38 (3H, s, OMe), 5.20-5.25 (2H, m, 2'-CH_2) and 5.66 (1H, ddd, J = 17.8, 10.4 and 2.7, 1'-H) [other peaks obscured].

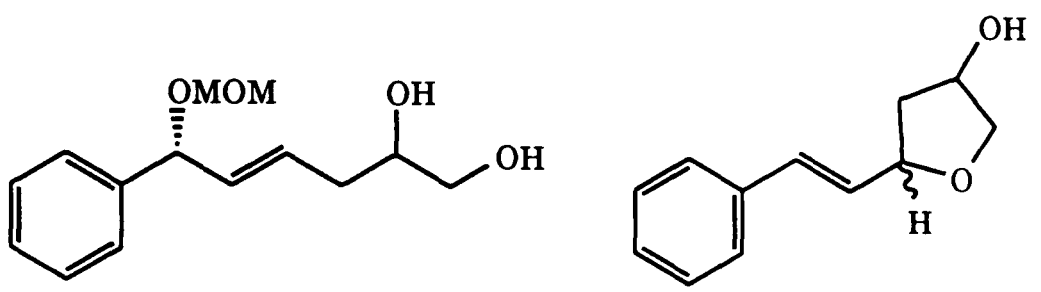
(4E,2RS,6S)-2-Hydroxy-6-methoxymethoxy-6-phenylhex-4-enoic -acid (**223**)



Butyl lithium (3.76 ml of a 1.6M solution in hexane, 6.02 mmol, 2.0 eq) was added to a solution of diisopropylamine (1.05 ml, 7.52 mmol, 3 eq) in dry tetrahydrofuran (5 ml) at -78°C. The resulting solution was stirred at -10°C for 0.5h before being cooled to -78°C. A solution of the acids **222** (800 mg, 3.01 mmol, 1 eq) in dry tetrahydrofuran (5 ml) was added. After 8h at -78°C, the mixture was allowed to warm to RT before adding saturated aqueous ammonium chloride (50 ml). The resulting mixture was extracted with chloroform (3 x 50 ml) and the combined organic phases were dried and evaporated to give, as a brown oil (460 mg, 58%), the *hydroxy-acid* **223** (460 mg, 58%), υ_{MAX} 3400 (OH) and 1709 cm^{-1}; δ_H (250) 2.41-2.43 (1H, m, 3-H_A), 4.30 (1H, m, 3-H_B), 3.29 (3H, s, OMe), 2.53-2.60 (1H, m, 2-H), 4.70 (2H, s, O$C\underline{H}_2$OMe), 5.20 (1H, d, J = 6.0, 6-H), 5.60-5.75 (2H, m, 4 and 5-H) and 7.20-7.52 (5H, m, Ph); δ_C (270) 36.50 (3-CH_2), 54.50 (OMe), 69.75 (2-CH), 77.50 (6-CH), 93.50

($OC\underline{H}_2OMe$), 119.27 (5-CH), 126.76 (CH), 127.9 (CH), 128.34 (CH), 128.48 (C), 141.29 (4-CH) and 176.05 (C=O).

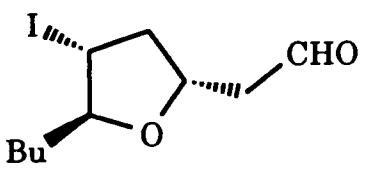
(4E,2RS,6S)-6-Methoxymethoxy-6-phenylhex-4-en-1,2-diol (**224**) *and (2RS,4RS) and (2RS,4SR)-4-hydroxy-2-[(1E)-2-styryl]-tetrahydrofuran* (**225**)



Lithium aluminium hydride *bis*-tetrahydrofuran (0.97 ml of a 1.0M solution in toluene, 0.97 mmol, 2.6 eq) was added to a solution of the hydroxy-acid **223** (100 mg, 0.37 mmol, 1 eq) in dry toluene (1 ml) and the resulting solution stirred at RT for 1.5h. Saturated aqueous ammonium chloride (5 ml) was added and the resulting mixture was extracted with chloroform (3 x 60 ml). The combined organic phases were dried and evaporated to give a brown oil (120 mg) which was chromatographed on silica (eluting with 50% ethyl acetate in petrol) to give, as a colourless oil, the *diol* **224** (14 mg, 15%), υ_{MAX} 3455 (OH) $c\,m^{-1}$; δ_H (250) 2.40-2.46 (2H, m, 3-CH_2), 3.40 (3H, s, OMe), 3.55-3.60 (1H, m, 2-H), 3.70-3.73 (1H, m, $C\underline{H}_AH_BOH$), 3.80-3.82 (1H, m, $CH_A\underline{H}_BOH$), 4.68-4.70 (1H, m, 6-CH), 4.80 (2H, s, $OC\underline{H}_2OMe$), 5.75-5.80 (2H, m, 4 and 5-H) and 7.15-7.30 (5H, m, Ph); and also, as a colourless oil, the

hydroxytetrahydrofurans **225** (87 mg, 74%), υ_{MAX} 3420 c m^{-1}; δ_H (250) 2.17 (1H, ddd, *J* = 13.3, 5.7 and 1.2, 3'-H_A), 2.48 (1H, ddd, *J* = 13.3, 6.2 and 1.9, 3'-H_B), 3.63 (1H, dddd, *J* = 6.2, 3.4, 2.2, 1.2, CH and 1.9, 4'-H), 3.93 (1H, dd, *J* = 8.4 and 1.6, 5'-H), 4.15 (1H, dd, *J* = 9.8 and 4.3, 5'-H), 6.21 (1H, dd, *J* = 16.0 and 6.9, 2-H), 6.63 (1H, d, *J* = 16.0, 1-H) and 7.20-7.50 (5H, m, Ph); δ_C (270) 42.87 (3'-CH_2), 57.63 (2'-CH), 76.31 (5'-CH_2), 79.81 (4'-CH), 126.97 (2-CH), 128.16 (Ph-CH), 128.27 (Ph-CH), 129.00 (1-CH), 129.76 (Ph-CH), 131.75 (C) and 148.95 (2-C); m/z 190 (61%, M^+), 151 (37), 104 (58), 91 (40) and 45 (100); [Found: M^+, 190.1001. $C_{12}H_{14}O_2$ requires M, 190.0993].

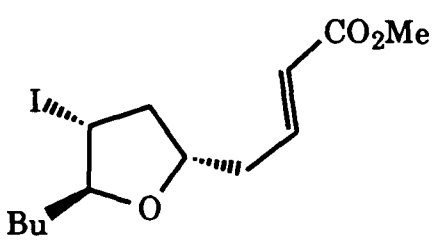
(2'SR,4'RS,5'SR)-2-(5'-Butyl-4'-iodotetrahydrofuran-2'-yl)acetaldehyde (**244**)



Diisobutylaluminium hydride (8.8 ml of a 1.0M solution in hexanes, 8.8 mmol, 1 eq) was added quickly to a solution of the iodotetrahydrofuran **54b** (2.88 g, 8.78 mmol, 1 eq) in petrol (10 ml) at -78°C and the resulting solution was stirred at this temperature for 3h. Methanol (3 ml) was added followed by 1M hydrochloric acid (8 ml) and the resulting mixture extracted with ethyl acetate (3 x 50 ml). The combined organic phases were dried and evaporated to give the *iodo-aldehyde* **244** as a colourless oil (2.15 g, 82%), υ_{MAX} 1725 (C=O), 1454, 1379 and 1068 c m^{-1}; δ_H (250) 0.81 (3H, t, *J* = 7.0, CH_3),

1.19-1.43 (6H, m, 3 x CH_2), 1.91 (1H, m, 3'-H_A), 2.50-2.70 (3H, m, 2-CH_2 and 3'-H_B), 3.71- 3.91 (1H, m, 4'-H), 4.02 (1H, td, J = 7.8 and 3.0, 5'-H), 4.30-4.42 (1H, m, 2'-H) and 9.30 (1H, br-s, 1-H); δ_C (270) 13.87 (CH_3), 21.49 (4'-CH), 22.59 (CH_2), 28.00 (CH_2), 31.93 (CH_2), 44.73 (3'-CH_2), 49.62, (2-CH_2), 72.83 (2'-CH), 86.23 (5'-CH) and 200.27 (C=O); m/z 239 (33%, M^+-Bu), 125 (43), 84 (41), 68 (27) and 55 (100) [Found: M^+-Bu, 238.9566. $C_6H_8IO_2$ requires M, 239.8569].

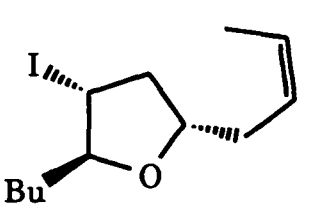
(5SR,7RS,8SR,2E)-Methyl 7-iodo-5,8-oxadodec-2-enoate (**245**)



Methyl triphenylphosphoranylidineacetate (271 mg, 0.8 mmol, 1.2 eq) was added to a solution of the iodo-aldehyde **244** (200 mg, 0.67 mmol, 1 eq) in dichloromethane (5 ml) at RT and the resulting solution stirred at this temperature for 16h. The solvent was removed *in vacuo* and the solid residue was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the *iodo-alkene* **245** as a colourless oil (180 mg, 76%), υ_{MAX} 1723 (C=O), 1659, 1436, 1326, 1274 and 1175 cm^{-1}; δ_H (250) 0.82 (3H, t, J = 7.0, 12-CH_3), 1.23-1.48 (6H, m, 9-, 10- and 11-CH_2), 1.99 (1H, ddd, J = 14.5, 3.0 and 1.0, 6-H_A), 2.30-2.52 (2H, m, 4-H_A and 6-H_B), 2.63 (1H, ddd, J = 14.0, 6.6, 1.3, 4-H_B), 3.69 (3H, s, OMe), 3.68-3.71 (1H, m, 7-H), 3.90-4.10 (2H, m, 5- and 8-H), 5.84 (1H, dt, J = 15.7 and 1.3, 2-H) and 6.88 (1H,

dt, J = 15.7 and 6.6 3-H); δ_C (270) 14.22 (12-Me), 22.19 (7-CH), 22.95 (CH_2), 28.32 (CH_2), 32.24 (CH_2), 38.82 (6-CH_2), 44.67 (4-CH_2), 51.72 (OMe), 76.78 (5-CH), 86.96 (8-CH), 123.68 (2-CH), 144.65 (3-CH) and 166.85 (C=O); m/z 239 (51%, M^+-CH_2CH=$CHCO_2Me$), 125 (45), 107 (18), 74 (64) and 55 (100) [Found: M^+-CH_2CH=$CHCO_2Me$, 253.0106. $C_8H_{14}IO$ requires M, 253.0089].

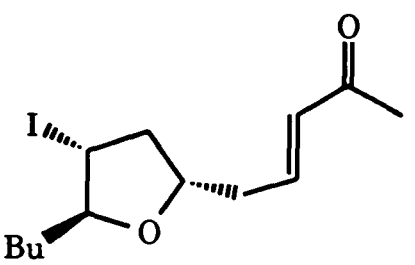
(5SR,7RS,8SR,2Z)-7-Iodo-5,8-oxadodec-2-ene (**246**)



Butyl lithium (5.03 ml of a 1.6 M solution, 8.14 mmol, 1.2 eq) was added to a solution of ethyltriphenylphosphonium iodide (3.36 g, 8.1 mmol, 1.2 eq) in dry tetrahydrofuran (10 ml) at -78°C and the resulting solution stirred at 0°C for 0.5h and then recooled to -78°C. A solution of the iodo-aldehyde **244** (2 g, 6.7 mmol, 1 eq) in dry tetrahydrofuran (5 ml) was added and the resulting solution was allowed to warm to RT over 16h. The solvent was removed *in vacuo* and the solid residue obtained was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the *iodo-alkene* **246** as a colourless oil (1.10 g, 46%), υ_{MAX} 1436, 1377, 1264, 1149, 1057 and 1015 cm^{-1}; δ_H (250) 0.89 (3H, t, J = 6.8, CH_3), 1.21-1.47 (5H, m, 9-H_A and 10- and 11-CH_2), 1.61 (3H, d, J = 6.8, 1-CH_3), 1.72-1.98 (1H, m, 9-H_B), 2.01 (1H, ddd, J = 8.9, 2.6 and 1.9, 6-H_A), 2.11-2.44 (2H, m, 4-H_A

and 6-H_B), 2.60 (1H, m, 4-H_B), 3.68-3.72 (1H, m, 7-H), 3.90-4.15 (2H, m, 5- and 8-H), 5.25-5.41 (1H, m, 2-H) and 5.47-5.62 (1H, m, 3-H); δ_C (270) 12.99 (CH_3), 14.16 (1-CH_3), 23.06 (7-CH), 23.25 (CH_2), 28.18 (CH_2), 32.17 (CH_2), 33.48 (6-CH_2), 44.62 (4-CH_2), 77.93 (5-CH), 86.52 (8-CH), 125.57 (2-CH) and 126.77 (3-CH); m/z 308 (1%, M^+), 253 (100), 125 (47), 81 (50) and 69 (57) [Found: M^+, 308.0688. $C_{12}H_{21}IO$ requires M, 308.0637]; and also 5% of the (E)-isomer which showed, δ_C (270) 125.51 (CH) and 128.21 (CH).

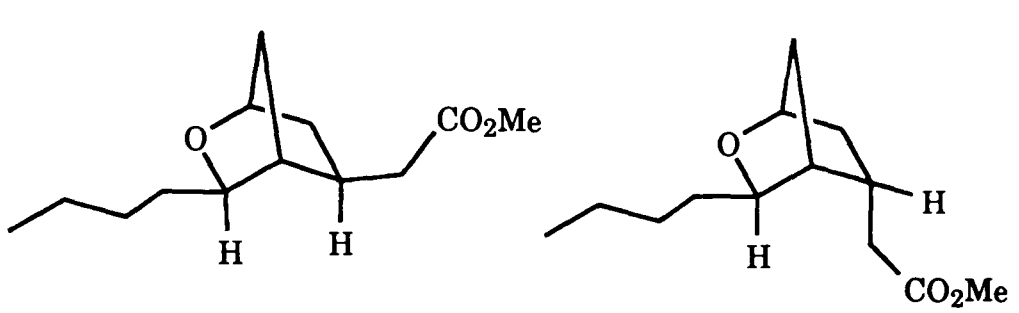
(6SR,8RS,9SR,3E)-8-Iodo-6,9-oxatridec-3-en-2-one (**247**)



Triphenylphosphoranylidine-2-propanone (152 mg, 0.47 mmol, 1.5 eq) was added to a solution of the iodo-aldehyde **244** (95 mg, 0.32 mmol, 1 eq) in dichloromethane (0.5 ml) at RT and the resulting solution was stirred at this temperature for 16h. The solvent was removed *in vacuo* and the solid obtained was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the *ketone* **247** as a colourless oil (53 mg, 55%), υ_{MAX} 1675 (C=O), 1629, 1455, 1360, 1254 and 1176 cm^{-1}; δ_H (250) 0.89 (3H, t, J = 7.0, 13-CH_3), 1.23-1.43 (6H, m, 9-, 10- and 11-CH_2), 2.04 (1H, ddd, J = 13.2, 9.8 and 1.5, 7-H_A), 2.16 (1H, ddd, J = 13.2, 6.1 and 2.6, 7-H_B),

2.27 (3H, s, 1- CH_3), 2.29-2.74 (2H, m, 5-CH_2), 3.77 (1H, ddd, J = 11.2, 9.8 and 2.6, 8-H), 4.01-4.29 (2H, m, 6- and 9-H), 6.14 (1H, dt, J = 16.0 and 1.3, 3-H) and 6.78 (1H, dt, J = 16.0 and 7.2, 4-H); δ_C (270) 13.95 (CH_3), 21.87 (CH_2), 22.19 (8-CH), 26.96 (1-CH_3), 28.07 (CH_2), 31.95 (7-CH_2), 38.78 (CH_2), 44.39 (5-CH_2), 51.72 (OMe), 76.53 (6-CH), 86.81 (9-CH), 133.44 (3-CH), 144.23 (4-CH) and 199.72 (C=O); m/z 337 (1%, M^+), 125 (100), 107 (36), 81 (64) and 55 (95) [Found: M^+, 337.0625. $C_{13}H_{22}IO_2$ requires M, 337.0664].

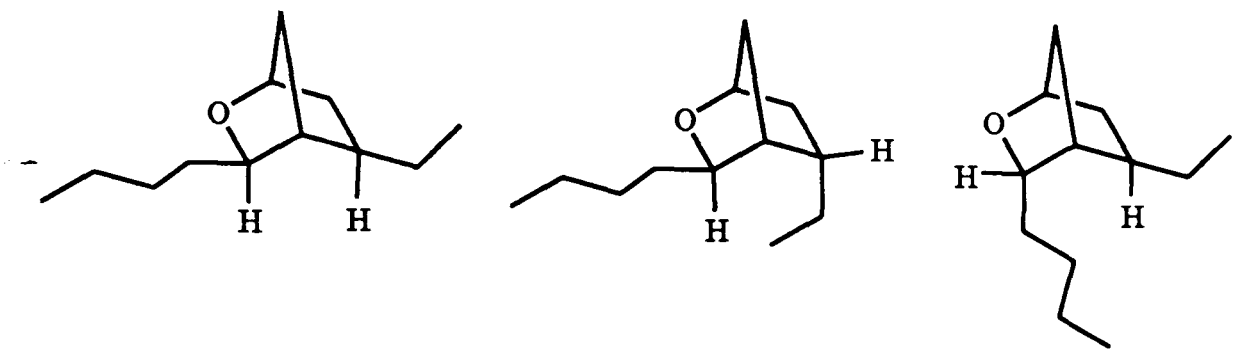
(3'-exo,5'-exo)-Methyl 2-(3'-butyl-2'-oxabicyclo-[2.2.1]-heptan-5'-yl) acetate (**248**) and *(3'-exo,5'-endo)-methyl 2-(3'-butyl-2'-oxabicyclo-[2.2.1]-heptan-5'-yl) acetate* (**249**)



Triphenyltin hydride (17 ml of a 0.02M solution in dry benzene, 0.34 mmol, 1.5 eq) and azo-*bis*-isobutyronitrile (11.3 ml of a 0.006M solution in dry benzene, 0.068 mmol, 0.3 eq) were added to a solution of the iodo-alkene **245** (80 mg, 0.23 mmol, 1 eq) in dry benzene (27 ml) at 80°C, over a period of 2h, under an atmosphere of argon. The resulting solution was heated for a further 2h and then cooled to RT before evaporating to give a clear oil (150 mg), which was chromatographed on silica (eluting with 5% ethyl acetate in

petrol) to give the *esters* **248** and **249** as a colourless oil (40 mg, 77%, as a 3:1 ratio), which showed υ_{MAX} 1738 (C=O), 1434 and 1153 cm^{-1}; m/z 226 (3%, M^+), 169 (45), 137 (100), 125 (33) and 67 (41) [Found: M^+, 226.1549. $C_{13}H_{22}O_3$ requires M, 226.1569]; for the isomer **248** δ_H (250) 0.82 (3H, t, J = 6.8, CH_3), 1.08 (1H, ddd, J = 13.8, 3.4 and 2.8, 6'-H_A), 1.21-1.34 (7H, m, 7'-H_A and 3 x CH_2), 1.53 (1H, br s, 7'-H_B), 1.92-2.01 (1H, m, 6'-H_B), 2.01 (1H, br s, 4'-H), 2.16 (1H, ddd, J = 8.4, 8.0 and 3.4, 5'-H), 2.31 (1H, dd, J = 14.9 and 8.0, 2-H_A), 2.46 (1H, dd, J = 14.9 and 8.4, 2-H_B), 3.43 (1H, t, J = 6.5, 3'-H), 3.61 (3H, s, OMe) and 4.22 (1H, br s, 1'-H); δ_C (270) 13.68 (CH_3), 22.35 (CH_2), 27.65 (CH_2), 31.17 (7'-CH_2), 34.91 (CH_2), 39.59 (2-CH_2), 44.72 (4'-CH), 51.19 (OMe), 75.91 (1'-CH), 83.27 (3'-CH) and 173.42 (C=O); for the isomer **249** δ_H (250) 0.82 (3H, t, J = 6.8, CH_3), 1.08 (1H, ddd, J = 13.8, 3.4 and 2.8, 6'-H_A), 1.21-1.34 (7H, m, 7'-H_A and 3 x CH_2), 1.53 (1H, br s, 7'-H_B), 1.92 (1H, m, 6'-H_B), 2.01 (1H, br s, 4'-H), 2.16 (1H, ddd, J = 8.4, 8.0 and 3.4, 5'-H), 2.29 (1H, dd, J = 14.9 and 8.0, 2-H_A), 2.45 (1H, dd, J = 14.9 and 8.4, 2-H_B), 3.60 (3H, s, OMe), 3.68 (1H, t, J = 6.2, 3'-H) and 4.18 (1H, br s, 1'-H); δ_C (270) 13.68 (CH_3), 22.35 (CH_2), 27.65 (CH_2), 31.17 (7'-CH_2), 34.70 (5-CH), 34.98 (CH_2), 35.25 (6'-CH_2), 37.14 (2-CH_2), 44.05 (4'-CH), 51.19 (OMe), 75.57 (1'-CH), 76.58 (3'-CH) and 173.42 (C=O).

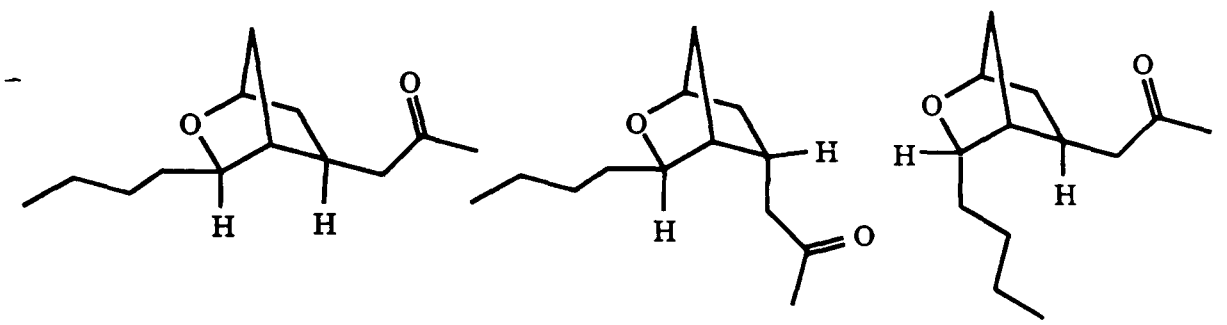
(3-exo,5-exo)-3-Butyl-5-ethyl-2-oxabicyclo-[2.2.1]-heptane (**250**), *(3-exo,5-endo)-3-butyl-5-ethyl-2-oxabicyclo-[2.2.1]-heptane* (**251**) and *(3-endo,5-exo)-3-butyl-5-ethyl-2-oxabicyclo-[2.2.1]-heptane* (**252**)



Triphenyltin hydride (146 ml of a 0.02M solution in dry benzene, 2.93 mmol, 1.5 eq) and azo-*bis*-isobutyronitrile (97 ml of a 0.006M solution in dry benzene, 0.58 mmol, 0.3 eq) were added by syringe pump to a solution of the iodo-alkene **246** (600 mg, 1.95 mmol, 1 eq) in dry benzene (240 ml) at 80°C, under an atmosphere of argon, over a period of 2h. The resulting solution was heated for a further 2h and then cooled to RT. Carbon tetrachloride (100 ml) was added and the resulting solution was treated with iodine (~100 mg) until the colour just persisted. Evaporation gave a clear oil (400 mg) which was dissolved in ethyl acetate (50 ml) and washed with saturated aqueous potassium fluoride until there was no further precipitation. The combined organic phases were dried and evaporated to give a colourless oil (200 mg), which was chromatographed on silica (eluting with 1% ethyl acetate in petrol) to give the *alkanes* **250** and **251** as a colourless oil (151 mg, 43%, as a 3:1 ratio) which showed υ_{MAX} 1468, 1327 and 1063 c m^{-1}; m/z 181 (8%, M+), 155 (29), 77 (17), 69 (24) and 57 (23); for isomer **250**, δ_H (250) 0.83

(6H, t, J = 6.8, 2 x CH_3), 1.15-1.20 (1H, m, 6-H_A), 1.21-1.34 (10H, m, 5-H, 7-H_A and 4 x CH_2), 1.52 (1H, br s, 7-H_B), 1.79-1.82 (1H, m, 6-H_B), 2.03 (1H, br s, 4-H), 3.41 (1H, t, J = 6.4, 3-H) and 4.25 (1H, br s, 1-H); δ_C (270) 12.69 (CH_3), 14.28 (CH_3), 23.02 (CH_2), 28.39 (CH_2), 28.86 (CH_2), 31.74 (CH_2), 35.64 (7-CH_2), 38.83 (6-CH_2), 43.63 (5-CH), 45.03 (4-CH), 76.55 (1-CH) and 84.21 (3-CH); and for isomer **251**, δ_H (250) 0.83 (6H, t, J = 6.8, 2 x CH_3), 1.11-1.13 (1H, m, 6-H_A), 1.21-1.34 (10H, m, 4 x CH_2), 1.40-1.42 (1H, m, 7-H_A), 1.70 (1H, br s, 7-H_B), 1.78-1.82 (2H, m, 5-H and 6-H_B), 2.17 (1H, br s, 4-H), 3.77 (1H, t, J = 6.5, 3-H) and 4.23 (1H, br s, 1-H); δ_C (270) 13.40 (CH_3), 14.28 (CH_3), 24.17 (CH_2), 29.76 (CH_2), 31.51 (CH_2), 35.76 (CH_2), 36.41 (7-CH_2), 37.81 (6-CH_2), 40.95 (5-CH), 44.08 (4-CH), 75.85 (1-CH) and 77.40 (3-CH); and b) the *alkane* **252** (46 mg, 13%), which showed, υ_{MAX} 1468, 1327 and 1063 cm^{-1}; δ_H (250) 0.85 (3H, t, J = 6.9, CH_3), 0.87 (3H, t, J = 7.0, CH_3), 1.05 (1H, dd, J = 12.1 and 2.0, 6-H_A), 1.15-1.40 (10H, m, 7'-CH_2 and 4 x CH_2), 1.78-1.80 (1H, m, 5-H), 1.87 (1H, dd, J = 12.1 and 1.0, 6-H_B), 2.13 (1H, br s, 4-H), 3.78 (1H, td, J = 6.9 and 2.1, 3-H) and 4.24 (1H, br s, 1-H); δ_C (270) 12.08 (CH_3), 14.05 (CH_3), 22.31 (CH_2), 28.64 (CH_2), 31.76 (CH_2), 34.12 (CH_2), 34.62 (5-CH), 35.77 (7-CH_2), 39.23 (6-CH_2), 43.85 (4-CH), 77.22 (1-CH) and 81.66 (3-CH); m/z 182 (1%, M^+), 125 (42%, M^+-Bu), 96 (22), 67 (100) and 55 (30) [Found: M^+-Bu, 125.0965. $C_8H_{13}O$ requires M, 125.0966].

(3-exo,5-exo)-3-Butyl-5-(2-oxapropyl)-2-oxabicyclo-[2.2.1]-heptane (**253**), *(3-exo,5-endo)-3-butyl-5-(2-oxapropyl)-2-oxabi-cyclo-[2.2.1]-heptane* (**254**) and *(3-endo,5-exo)-3-butyl-5-(2-oxa-propyl)-2-oxabicyclo-[2.2.1]-heptane* (**255**)

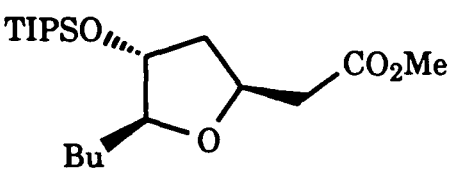


Triphenyltin hydride (12 ml of a 0.02M solution in dry benzene, 0.24 mmol, 1.5 eq) and azo*bis* isobutyronitrile (8 ml of a 0.006M solution in dry benzene, 0.047 mmol, 0.3 eq) were added to a solution of the iodo-alkene **247** (53 mg, 0.16 mmol, 1 eq) in dry benzene (18 ml) at 80°C, under an atmosphere of argon, over a period of 2h. The resulting solution was heated for a further 2h and then cooled to RT. Carbon tetrachloride (20 ml) was added and the resulting solution was treated with iodine (~15 mg) until the colour just persisted. Evaporation gave a clear oil (100 mg) which was dissolved in ethyl acetate (20 ml) and washed with saturated aqueous potassium fluoride until there was no further precipitation. The combined organic phases were dried and evaporated to give a colourless oil (90 mg) which was chromatographed on silica (eluting with 4% ethyl acetate in petrol) to give a) the *ketones* **253** and **254** as a colourless oil (26 mg, 77%, as a 3:1 ratio), which showed υ_{MAX} 1713 (C=O), 1462, 1357, 1155 and 1041

cm^{-1}; m/z 210 (8%, M^+), 153 (35), 135 (34), 95 (41), 66 (46) and 43 (100) [Found: M^+, 210.1602. $C_{13}H_{22}O_2$ requires M, 210.1620]; for isomer **253**, δ_H (250) 0.87 (3H, t, J = 6.7, CH_3), 1.00-1.40 (7H, m, 6-H_A and 3 x CH_2), 1.53-1.65 (2H, m, 7-CH_2), 1.83-1.89 (2H, m, 5-H and 6-H_B), 2.04 (1H, br s, 4-H), 2.13 (3H, s, 1'- CH_3), 2.41-2.47 (1H, m, 3'-CH_A), 2.64 (1H, dd, J = 6.5 and 1.6, 3'-CH_B), 3.49 (1H, t, J = 7.0, 3-H) and 4.23 (1H, br s, 1-H); δ_C (270) 14.29 (CH_3), 22.97 (CH_2), 25.39 (CH_2), 28.23 (CH_2), 31.84 (1'-CH_3), 35.49 (CH_2), 36.46 (5-CH), 38.87 (6-CH_2), 45.24 (4-CH), 49.95 (3-CH_2), 76.46 (1-CH) and 83.95 (3-CH); and for isomer **254**, δ_H (250) 0.89 (3H, t, J = 6.7, CH_3), 1.00-1.40 (7H, m, 6-H_A and 3 x CH_2), 1.53-1.65 (2H, m, 7-CH_2), 1.83-1.89 (2H, m, 5-H and 6-H_B), 2.01 (1H, br s, 4-H), 2.15 (3H, s, 1'-Me), 2.32-2.52 (2H, m, 3'-CH_2), 3.70 (1H, t, J = 7.0, 3-H) and 4.26 (1H, br s, 1-H); δ_C (270) 14.28 (CH_3), 24.00 (CH_2), 28.29 (CH_2), 30.24 (CH), 31.94 (CH_3), 35.60 (CH_2), 36.40 (CH_2), 38.41 (CH_2), 45.03 (CH), 76.42 (1-CH) and 77.46 (3-CH); and b) the *ketone* **255** (6 mg, 20%), which showed υ_{MAX} 1713 (C=O), 1462, 1357, 1155 and 1041 cm^{-1}; δ_H (250) 0.92 (3H, t, J = 6.8, CH_3), 1.06 (1H, m, 6-H_A), 1.25-1.40 (4H, m, 2 x CH_2), 1.52-1.68 (5H, m, 5'-H, 7-CH_2 and 1 x CH_2), 1.91 (1H, m, 6-H_B), 2.11 (1H, br s, 4-H), 2.14 (3H, s, 1'- CH_3), 2.39 (1H, dd, J = 12.4 and 4.3, 3'-CH_A), 2.47 (1H, dd, J = 12.4 and 4.8, 3'-CH_B), 3.81 (1H, td, J = 7.0 and 2.5, 3-H) and 4.25 (1H, br s, 1'-H); δ_C (270) 14.05 (Me), 22.84 (CH_2), 27.87 (CH_2), 28.55 (CH_2), 30.19 (Me), 31.31 (CH_2), 35.97 (CH_2), 39.30 (5-CH), 44.13 (4-CH), 49.81 (3-CH_2), 77.20 (1-CH) and 81.38 (3-CH); m/z 210 (3%, M^+), 124 (41%, M^+-Bu), 95

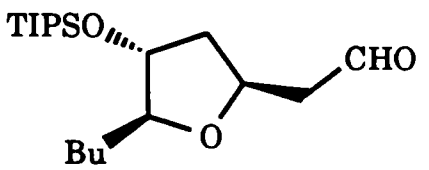
(38), 66 (75) and 43 (100); [Found: M^+, 210.1602. $C_{13}H_{22}O_2$ requires M, 210.1619].

(2'SR,4'RS,5'SR)-Methyl (5'-butyl-4'-triisopropylsilyloxytetrahydrofuran-2'-yl) acetate (**256**)



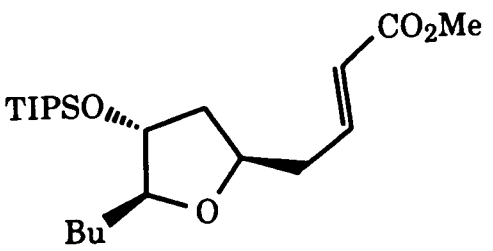
The hydroxytetrahydrofuran **72** (3.50 g, 16.5 mmol, 1 eq) was silylated exactly as in the preparation of compound **150**, to give an oil (5 g) which was chromatographed on silica (eluting with 3% ethyl acetate in petrol) to give the *silyloxy-tetrahydrofuran* **256** as a colourless oil (2.33 g, 40%), υ_{MAX} 1739 (C=O), 1464, 1437, 1382, 1329, 1246, 1107 and 1048 cm^{-1}; δ_H (250) 0.87 (3H, t, J = 6.4, CH_3), 1.00-1.10 (21H, m, TIPS), 1.21-1.47 (6H, m, 3 x CH_2), 1.67 (1H, ddd, J = 12.7, 9.8 and 5.7, 3'-H), 1.94 (1H, ddd, J =12.7, 6.2 and 2.8, 3'-H), 2.45 (1H, dd, J = 15.2 and 6.3, 2-C$\underline{H}_A$CH_B), 2.59 (1H, dd, J = 15.2 and 6.6, 2-CH_AC$\underline{H}_B$), 3.63 (3H, s, OMe), 3.70 (1H, td, J = 6.4 and 3.1, 5'-H), 4.07 (1H, ddd, J = 9.8, 3.1 and 2.8, 4'-H) and 4.42 (1H, dddd, J = 6.6, 6.3, 6.2 and 5.7, 2'-H); δ_C (270) 12.20 (3 x CH, TIPS), 13.80 (CH_3), 17.56 (6 x CH_3, TIPS), 22.54 (CH_2), 27.89 (CH_2), 34.09 (CH_2), 40.41 (3'-CH_2), 41.24 (2-CH_2), 51.39 (OMe), 73.93 (CH), 77.46 (CH), 87.35 (5'-CH) and 171.46 (C=O); m/z 329 (20%, $M^{+-i}Pr$), 229 (31), 131 (92), 103 (83) and 75 (100) [Found: $M^{+-i}Pr$, 329.2158. $C_{17}H_{33}O_4Si$ requires M, 329.2148].

(2'SR,4'RS,5'SR)-(5'-Butyl-4'-triisopropylsilyloxytetrahydro-furan-2'-yl)acetaldehyde (**257**)



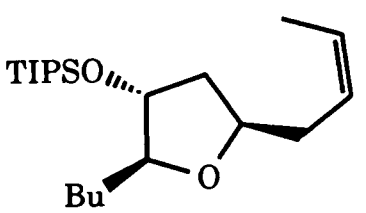
The silyloxytetrahydrofuran **256** (2.33 g, 6.3 mmol, 1 eq) was reduced exactly as in the preparation of compound **244**, to give the *aldehyde* **257** as a colourless oil (1.83 g, 85%), υ_{MAX} 1731 (C=O) c m^{-1}; δ_H (250) 0.87 (3H, t, J = 6.4, CH_3), 1.00-1.10 (21H, m, TIPS), 1.21-1.47 (6H, m, 3 x CH_2), 1.52 (1H, ddd, J = 12.7, 8.7 and 6.3, 3'-H), 2.02 (1H, ddd, J = 12.7, 6.0 and 2.4, 3'-H), 2.61 (1H, dd, J = 10.2 and 5.6, 2-$C\underline{H}_ACH_B$), 2.61 (1H, dd, J = 10.2 and 3.4, 2-$CH_AC\underline{H}_B$), 3.68 (1H, td, J = 6.3 and 3.2, 5'-H), 4.09 (1H, ddd, J = 6.3, 3.2 and 2.4, 4'-H), 4.51 (1H, dddd, J = 8.7, 6.0, 5.6 and 3.4, 2'-H) and 9.55 (1H, br.s, CHO); δ_C (270) 12.58 (3 x CH, TIPS), 14.23 (CH_3), 17.97 (6 x CH_3, TIPS), 22.93 (CH_2), 28.36 (CH_2), 34.49 (CH_2), 41.92 (3'-CH_2), 49.58 (2-CH_2), 73.17 (CH), 77.05 (CH), 87.82 (5'-CH) and 201.65 (C=O); m/z 299 (44%, M^{+}-^{i}Pr), 229 (100), 131 (93), 99 (74) and 75 (81) [Found: M 329.2158. $C_{17}H_{33}O_4Si$ requires M, 329.2148].

(5SR,7RS,8SR,2E)-Methyl 7-triisopropylsilyloxy-5,8-oxadodec-2-enoate (**258**)



The aldehyde **257** (800 mg, 2.34 mmol, 1 eq) was treated exactly as in the preparation of compound **245**, to give the *alkenoate* **258** as a colourless oil (475 mg, 51%), υ_{MAX} 1729 (C=O), 1659, 1463, 1270, 1161 and 1056 $c m^{-1}$; δ_H (250) 0.85 (3H, t, J = 7.0, CH_3), 1.01-1.10 (21H, m, TIPS), 1.25-1.47 (6H, m, 3 x CH_2), 1.63 (1H, ddd, J = 12.6, 5.8 and 3.0, 6-H), 1.87 (1H, ddd, J =12.6, 5.5 and 2.1, 6-H), 2.44 (1H, m, 4-CH_2), 3.72 (3H, s, Me ester), 3.73-3.82 (1H, m, 8-H), 4.08-4.12 (1H, m, 7-H), 4.13-4.28 (1H, m, 5-H), 5.84 (1H, dd, J = 15.7 and 1.3, 2-H) and 6.88 (1H, dt, J = 15.7 and 7.2, 3-H); δ_C (270) 12.11 (3 x CH, TIPS), 13.96 (CH_3), 17.97 (6 x CH_3, TIPS), 22.54 (CH_2), 27.89 (CH_2), 34.09 (CH_2), 40.41 (6-CH_2), 41.24 (4-CH_2), 51.39 (OMe), 73.93 (CH), 77.46 (CH), 87.35 (8-CH), 122.97 (3-CH), 145.43 (2-CH) and 171.46 (C=O); m/z 355 (25%, M^{+}-^{i}Pr), 229 (100), 131 (34), 103 (38) and 75 (53) [Found: M^{+}-^{i}Pr, 355.2358. $C_{19}H_{35}O_4Si$ requires M, 355.2304].

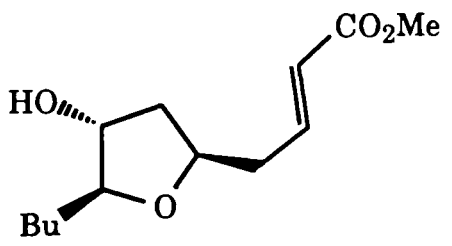
(5SR,7RS,8SR,Z)-7-Triisopropylsilyloxy-5,8-oxadodec-2-ene (**259**)



The aldehyde **257** (800 mg, 2.34 mmol, 1 eq) was subjected to Wittig olefination exactly as in the preparation of compound **246**, to give the *alkene* **259** as a colourless oil (140 mg, 17%), υ_{MAX} 1464, 1245, 1118 and 1091 $c m^{-1}$; δ_H (250) 0.87 (3H, t, J = 7.0, 12-CH_3), 0.97-1.12 (21H, m, TIPS), 1.20-1.47 (6H, m, 9-, 10- and 11-CH_2), 1.61 (3H, d, J =

6.5, 1-CH_3), 1.75 (1H, ddd, J = 10.7, 5.7 and 1.7, 6-H_A), 1.80-2.03 (1H, m, 6-H_B), 2.12-2.49 (2H, m, 4-CH_2), 3.65-3.73 (1H, m, 8-H), 4.01-4.19 (2H, m, 5- and 7-H) and 5.27-5.69 (2H, m, 2- and 3-H); δ_C (270) 12.11 (3 x CH, TIPS), 12.96 (1-CH_3), 13.96 (CH_3), 17.95 (6 x CH_3, TIPS), 22.67 (CH_2), 28.14 (CH_2), 34.22 (CH_2), 40.99 (6-CH_2), 41.23 (4-CH_2), 76.52 (CH), 77.14 (CH), 87.10 (8-CH), 125.84 (2-H) and 126.07 (3-H); m/z 311 (20%, M^{+}-^{i}Pr), 229 (100), 131 (73), 81 (25) and 59 (21) [Found: M^{+}-^{i}Pr, 311.2424. $C_{18}H_{35}O_2Si$ requires M, 311.2406].

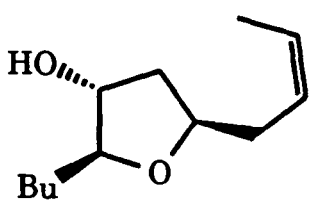
(5SR,7RS,8SR,2E)-Methyl 7-hydroxy-5,8-oxadodec-2-enoate (**260**)



The silyl-alkenoate **258** (374 mg, 0.94 mmol, 1 eq) was treated exactly as in the preparation of compound **163**, to give the *hydroxy-alkenoate* **260** as a colourless oil (171 mg, 75%), υ_{MAX} 3414 (OH), 1726 (C=O), 1659, 1437, 1271, 1163 and 1091 cm^{-1}; δ_H (250) 0.90 (3H, t, J = 6.4, 12-CH_3), 1.20-1.47 (6H, m, 9-, 10- and 11-CH_2), 1.80 (1H, ddd, J = 13.2, 6.8 and 3.8, 6-H), 1.92 (1H, ddd, J =13.2, 5.7 and 2.2, 6-H), 2.41 (1H, ddd, J = *7.4*, 6.1 and 1.0, 4-CH_2), 3.60 (3H, s, Me ester), 3.90-4.22 (3H, m, 5-, 7- and 8-H), 5.86 (1H, dt, J = 15.4 and 1.0, 2-H) and 6.91 (1H, dt, J = 15.4 and 7.4, 3-H); δ_C (270) 14.45 (CH_3), 23.15 (CH_2), 28.47 (CH_2), 34.45 (CH_2), 38.58 (6-CH_2), 41.24 (4-CH_2), 51.36 (OMe), 76.95 (CH), 77.42 (CH), 88.43 (8-CH), 123.59 (2-H), 143.21 (3-H) and 171.46

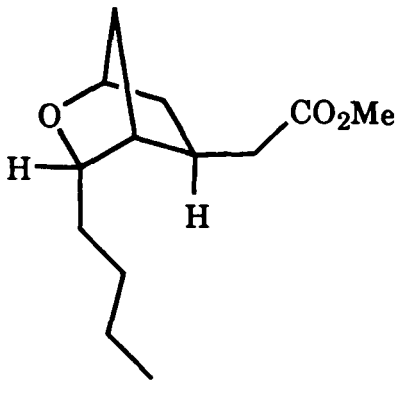
(C=O); m/z 144 (100%, M^+-$CH_2CH{=}CHCO_2Me$), 100 (43), 99 (47), 81 (40) and 55 (34) [Found: M^+-$CH_2CH{=}CHCO_2Me$, 142.0997. $C_8H_{14}O_2$ requires M, 142.0993].

(5RS,7RS,8SR,2Z)-7-Hydroxy-5,8-oxadodec-2-ene (**261**)



The silyl-alkene **259** (136 mg, 0.38 mmol, 1 eq) was treated exactly as in the preparation of compound **163**, to give the *hydroxy-alkene* **261** as a colourless oil (30 mg, 40%), υ_{MAX} 3445 (OH), 1659, 1462, 1260, 1158 and 1050 c m^{-1}; δ_H (250) 0.93 (3H, t, J = 6.5, 12-CH_3), 1.21-1.52 (6H, m, 9-, 10- and 11-CH_2), 1.62 (3H, dd, J = 6.2 and 0.8, 1-CH_3), 1.72 (1H, ddd, J = 13.2, 9.7 and 6.4, 6-H_A), 1.88 (1H, ddd, J = 13.2, 5.7 and 2.3, 6-H_B), 2.13-2.30 (1H, m, 4-H_A), 2.37-2.53 (1H, m, 4-H_B), 3.69 (1H, td, J = 6.1 and 3.1, 8-H), 4.01-4.19 (2H, m, 7- and 5-CH) and 5.33-5.63 (2H, m, 2- and 3-H); δ_C (270) 12.96 (1-CH_3), 13.98 (CH_3), 22.72 (CH_2), 28.02 (CH_2), 32.94 (CH_2), 34.07 (6-CH_2), 40.49 (4-CH_2), 76.53 (CH), 77.47 (CH), 86.81 (8-CH), 125.75 (2-H) and 126.11 (3-CH); m/z 143 (100%, M^+-Bu), 99 (69), 81 (76), 57 (71) and 55 (65) [Found: M^+-Bu, 142.1035. $C_8H_{14}O_2$ requires M, 142.0993].

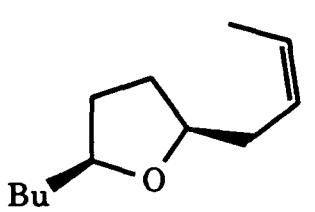
(3'-endo,5'-exo)-Methyl 2-(3'-butyl-2'-oxabicyclo[2.2.1]-heptan-5'-yl) acetate (**264**)



Thiocarbonyldiimidazole (378 mg, 2.1 mmol, 3 eq) was added to a solution of the hydroxy-alkenoate **260** (171 mg, 0.71 mmol, 1eq) in dry tetrahydrofuran (5 ml) and the resulting solution was heated at reflux for 16h. The resulting solution was cooled and evaporated and the residue filtered through silica (eluting with dichloromethane), to give the thioimidazole ester **262** (220 mg). This derivative was dissolved in toluene (70 ml) and the solution heated at reflux while a solution of tributyltin hydride (280µl, 1.05 mmol, 1.5 eq) in toluene (15 ml) was added dropwise over 8h. The solution was then cooled and evaporated to give an oil (500 mg), which was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the *ester* **264** as a colourless oil (121 mg, 77%), υ_{MAX} 1738 (C=O), 1434 and 1153 $c m^{-1}$; δ_H (250) 0.89 (3H, t, J = 6.8, CH_3), 1.05-1.12 (1H, m, 6'-H_A), 1.21-1.53 (8H, m, 7'-CH_2 and 3 x CH_2), 1.82-1.95 (1H, m, 6'-H_B), 2.04 (1H, br s, 4'-H), 2.17 (1H, br s, 5'-H), 2.29 (2H, dd, J = 7.8 and 4.5, 2-CH_2), 3.68 (3H, s, Me ester), 3.81 (1H, td, J = 7.0 and 2.6, 3'-H) and 4.26 (1H, br s, 1'-H); δ_C (270) 13.85 (CH_3), 17.85 (CH_2),

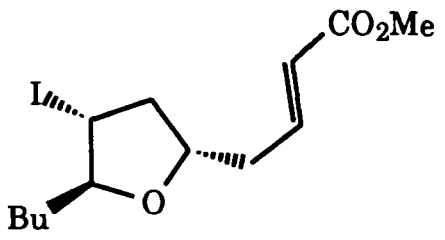
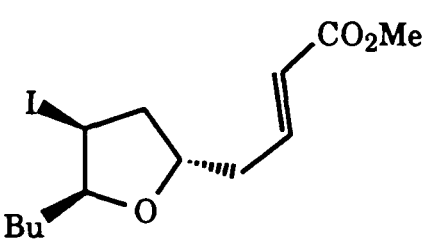
23.31 (CH_2), 27.85 (CH_2), 28.14 (CH_2), 29.85 (CH_2), 36.15 (CH), 39.90 (2-CH_2), 40.03 (4'-CH), 51.54 (OMe), 77.10 (1'-CH), 81.31 (3'-CH) and 173.41 (C=O); m/z 226 (6%, M^+), 169 (66), 140 (62), 108 (92) and 67 (100) [Found: M^+, 226.1632. $C_{13}H_{22}O_3$ requires M, 226.1569].

(5SR,8SR,Z)-5,8-Oxadodec-2-ene (**265**)



The hydroxy-alkene **261** (30 mg, 0.15 mmol, 1 eq), was treated exactly as in the preparation of compound **264**, to give a clear oil (90 mg) which was chromatographed on silica (eluting with 5% ethyl acetate in petrol) to give the *tetrahydrofuran* **265** as a clear oil (23 mg, 80%), υ_{MAX} 1462, 1378 and 1090 c m^{-1}; δ_H (250) 0.93 (3H, t, J = 6.8, 12- CH_3), 1.25-1.54 (6H, m, 9-, 10- and 11-CH_2), 1.65 (3H, d, J = 6.2, 1-CH_3), 1.83-1.96 (4H, m, 6- and 7-CH_2), 2.12-2.49 (2H, m, 4-CH_2), 3.72-3.92 (2H, m, 5- and 8-CH) and 5.35-5.63 (2H, m, 2- and 3-H); δ_C (270) 12.98 (CH_3), 14.03 (CH_3), 22.81 (CH_2), 28.36 (CH_2), 29.99 (CH_2), 30.48 (CH_2), 33.44 (CH_2), 35.80 (CH_2), 76.52 (8-CH), 77.18 (5-CH), 125.71 (2-H) and 126.36 (3-CH); m/z 127 (100%, M+-Pr), 109 (100), 83 (29), 67 (58) and 57 (33) [Found: M+-Pr, 127.1112. $C_8H_{15}O$ requires M, 127.1123].

(5SR,7RS,8SR,2E)-Methyl 7-iodo-5,8-oxadodec-2-enoate (**245**) and *(5SR,7SR,-8SR,2E)-methyl 7-iodo-5,8-oxadodec-2-enoate* (**265**)

A stirred solution of the iodo-alkene **245** (180 mg, 0.51 mmol, 1 eq) and hexabutylditin (30 mg, 0.026 ml, 0.1 eq) in dry, degassed benzene (20 ml), at reflux, was irradiated from a distance of 14 cm with a 275 W sun lamp for 65 mins, under an atmosphere of argon. 1,8-Diazabicyclo-[5,4,0]-undec-7-ene (0.15 ml) was added and, after 5 mins, iodine was added until the colour just persisted. The resulting solution was filtered through silica (washing with ether) and evaporated to give the *iodo-alkenes* **245** and **265**, free of tin residues, as a colourless oil (180 mg, 76%), υ_{MAX} 1723 (C=O), 1659, 1436, 1326, 1274 and 1175 cm^{-1}; δ_H (250) 0.82 (3H, t, J = 7.0, 12-CH_3), 1.23-1.48 (6H, m, 9-, 10- and 11-CH_2), 1.99 (1H, ddd, J = 14.5, 3.0 and 1.0, 6-H_A), 2.30-2.52 (2H, m, 4-H_A and 6-H_B), 2.63 (1H, ddd, J = 14.0, 6.6, 1.3, 4-H_B), 3.69 (3H, s, Me ester), 3.68-3.71 (1H, m, 7-H), 3.90-4.10 (2H, m, 5- and 8-H), 5.84 (1H, dt, J = 15.7 and 1.3, 2-H) and 6.88 (1H, dd, J = 15.7 and 6.6 3-H); δ_C (270) 14.22 (12-Me), 22.19 (7-CH), 22.95 (CH_2), 28.32 (CH_2), 32.24 (CH_2), 38.82 (6-CH_2), 44.67 (4-CH_2), 51.72 (OMe), 76.78 (5-CH), 86.96 (8-CH), 123.68 (2-CH), 144.65 (3-CH) and 166.85 (C=O) and for *iodo-alkene* **265**, δ_C (270) 13.89 (12-Me), 22.63 (CH_2), 23.47 (7-CH), 27.93 (CH_2), 31.92 (CH_2), 37.67 (6-CH_2), 43.13 (4-CH_2), 51.43 (OMe), 76.35 (5-CH), 88.98 (8-CH), 123.38 (2-CH), 144.33 (3-CH) and 166.58 (C=O).

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