A SYNTHESIS TOWARDS VIRANTMYCIN

A THESIS

PRESENTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

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by

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The Biologist and the Flea.

This particular researcher was studying the behaviour of a large and unusually cooperative flea. By virtue of years of practice and self denial, he had trained the flea to jump over a matchbox on command whenever he yelled the word "jump". Being a true scientist, he wondered what it was that gave the flea the ability to respond in that way, and decided it must be the first of its three pairs of legs. To test his theory, he tore off the front legs and again gave the command to jump. The flea jumped. Revising his hypothesis, he then tore off the middle two legs. He yelled "jump" and the flea once more successfully cleared the matchbox. Finally in a fervor of experimental zeal, he pulled off the last pair of legs, and once more issued the command. This time the flea remained immobile. So the researcher drew the inevitable conclusion that pulling off the flea's hind legs had made it deaf.

CONTENTS

SUMMARY

This thesis deals with a synthesis towards virantmycin (1). The synthetic strategy was designed in such a way as to also allow access to analogues of (1). The work was divided into three main parts: the construction of a suitably functionalised aromatic ring, cyclisation to give a tetrahydroquinoline and the synthesis of the appropriate sidechain.

Chapter 1 describes a method of preparing *ortho*-allylanilines cleanly and in good yield. Aryllithium reagents were formed in the presence of amide and carboxyl groups and arylcopper reagents were alkylated in the presence of amide and hydroxyl groups. The successful allylation of the trifunctional compound (59) represents the first step in the proposed synthetic strategy.

Chapter 2 assesses the reactions of *ortho*-allylanilines and their derivatives with various electrophiles. The amide derivatives of these compounds could not be cyclised with mercuric salts, however the free amines cyclised to form unstable organomercurials. These intermediates could not be halogenated to form the desired 3-halotetrahydroquinolines. The 3-iodotetrahydroquinolines (87) and (101) were prepared by treating *ortho*-allylanilines with iodine. The trifluoroacetamide (62)

gave the dihydroindole (94) under the same conditions. Treatment of *ortho*-allylanilines with either chlorine or bromine did not produce any halogenated tetrahydroquinolines. The epoxyamides (103) and (104) were treated with boron trifluoride but no cyclised products were obtained. Treatment of these compounds with potassium carbonate induced cyclisation to form the dihydroindoles (112) and (113).

Chapter 3 examines the synthetic approaches to the sidechain (8) required for the synthesis of virantmycin. The initial strategies were directed at a stereospecific synthesis of individual stereoisomers. The reaction of vinyloxirane (114) with allyllithium (116) or its diallylcuprate was considered but the allyllithium could not be prepared without it dimerising. Metallation of bromolactone (134) and subsequent alkylation with 1-bromo-2,3-dimethylbut-2-ene was attempted but this did not yield a sidechain precursor. Similarly coupling of the copper(I) enolate of E-methoxyacid (132) with this bromide could not be achieved. The lactone (128) was readily prepared by alkylation of the sulphone (140) followed by reduction of the sulphone moiety. However, the difficulties encountered in the hydrolysis of (128) prevented it from being elaborated to the sidechain (8). The reaction of the epoxide (146) with the lithium dialkylcuprate (161) was considered. Although this method seemed attractive, the epoxide was not

readily available. The enol ether (156) was also prepared, however reaction with methoxymethyllithium underwent demethylation rather than an addition-elimination sequence to give (155).

STATEMENT

This thesis contains no material previously submitted for a degree in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

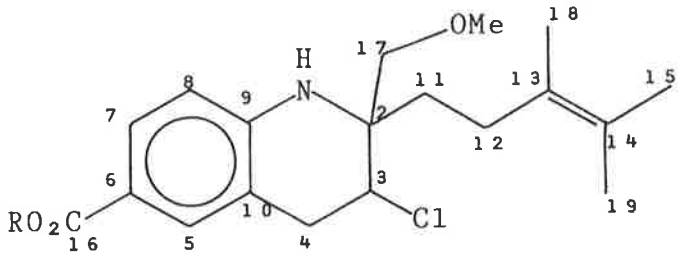
K.D. RANER

ACKNOWLEDGEMENTS

I would like to thank my supervisors Drs. A.D. Ward and R.H. Prager for their encouragement and guidance throughout the course of this work. I also wish to thank Dr. A. White (University of Western Australia) for providing the X-ray structures mentioned in this thesis. Also, I am indebted to my parents for their support and to my wife Anne for her understanding and encouragement.

INTRODUCTION

Virantmycin[1,2,3] (1), a novel antibiotic containing chlorine, has been isolated from the fermentation broth of *Streptomyces nitrosporeous*. The antibiotic has potent inhibitory action against RNA and DNA viruses and also possesses weak antifungal activity[3]. The active substance in the culture broth was isolated by high performance liquid chromatography as colourless needles of melting point 59^0 and with a specific rotation of $[\alpha]_D$ -0.05^0. The molecular formula was found to be $C_{19}H_{26}NO_3Cl$ by mass spectrometry and elemental analysis.



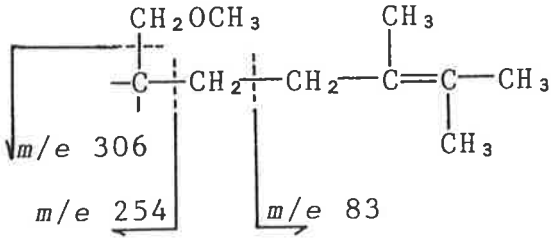
(1) R=H

(2) $R=CH_3$

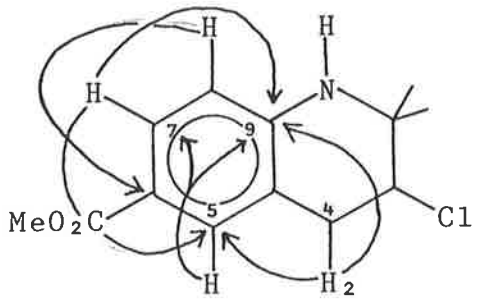
The following spectral data has been reported[2]. The mass spectrum showed the molecular ion at *m/e* 351 and characteristic fragment ions at *m/e* 316 (M^+-Cl), 306 (M^+-CH_2OCH_3), 270 (M^+-CH_2OCH_3-HCl), 254 (M^+-C_7H_{13}) and 83 (C_6H_{11}). The infrared spectrum had absorptions at 3440 cm^{-1} due to an N-H stretch and at 3400-2400, 1687 cm^{-1} arising from a carboxyl group.

The structural elucidation[2] was acheived by ^{1}H and ^{13}C spectroscopy. Selective proton decoupled ^{13}C experiments exhibited the presence of a trisubstituted aromatic ring (δ_H 6.56, d, *J* 8.5 Hz; 7.78, d, *J* 3.0 Hz and 7.82, dd, *J* 8.5, 3.0 Hz), a carboxyl carbon (δ_C 171.9), a methine (δ_H 4.36, t, *J* 6.0 Hz; δ_C 56.2) coupled with a methylene (δ_H 3.40, dd, *J* 16.4, 6.0 Hz and δ_H 3.08, dd, *J* 16.4, 6.0 Hz; δ_C 33.5), a methoxy methylene (δ_H 3.46, s; δ_C 59.4 for OCH_3 and δ_H 3.58, s; δ_C 74.1 for CH_2, two adjacent methylenes (δ_H 1.6, m; δ_C 27.8 and δ_H 2.0, m; δ_C 33.5), a quaternary carbon (δ_C 58.0) and three methyls (δ_H 1.60, s; δ_C 20.6, 19.9 and 18.4), which are attached to an isolated double bond (δ_C 124.8 and 126.5). Furthermore, two broad signals in the ^{1}H nmr spectrum were assigned to be the carboxylic (δ 8.0) and NH (δ 4.7) protons, which disappeared upon addition of D_2O. The higher field resonance of the aromatic proton at δ 6.56 suggests the location of the NH group to be *ortho* to this proton. The spectral evidences described above characterised the existence of the *p*-aminobenzoic acid skeleton as the chromophore and an alkyl side chain moiety [I].

The substitution pattern on the isolated double bond [I] and the aromatic ring [II] were well supported by the application of $^{13}C\{^{1}H\}$ long range decoupling (LSPD) technique to the methyl ester which was obtained by the treatment of virantmycin with diazomethane. The ester had nmr resonances at δ_H 3.80 and δ_C 51.5 due to the ester methyl and δ_C 167.2 arising from



[I]



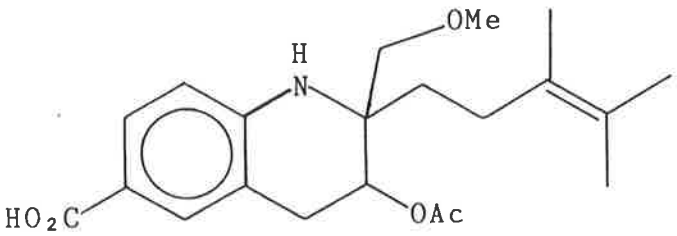
[II]

long range $^{13}C\{^{1}H\}$ coupling

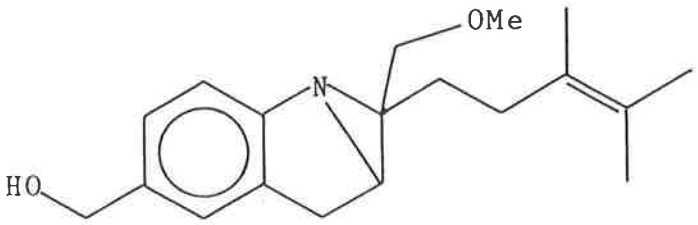
the carboxyl carbon. Long range decoupling of the methylene proton signal at C-4 (δ_H 3.34 corresponding to δ_C 33.4) collapsed the C-9 aromatic carbon resonance (δ_C 146.5, broad triplet) to a sharp triplet ($^{3}J_{CH}$ 9.0 Hz) and the C-5 aromatic carbon (δ_C 131.6, broad doublet) to a sharp doublet of doublets ($^{1}J_{CH}$ 160.0 Hz, $^{3}J_{CH}$ 6.4 Hz). Simultaneous irradiation of the C-5 (δ_H 7.63) and C-7 (δ_H 7.67) aromatic protons collapsed the C-5 and C-9 aromatic carbon resonances to broad singlets and the C-7 carbon (δ_C 129.6, $^{1}J_{CH}$ 163.0 Hz, $^{3}J_{CH}$ 7.1 Hz) to a singlet. These spectral data indicated that the C-4 methylene protons must be three bonds away from the C-5 and C-9 aromatic carbons.

Furthermore, the two olefinic carbon signals at δ_C 124.8 and 126.5 collapse from broad singlets to sharp singlets upon simultaneous irradiation of the methyl and methylene protons at δ_H 1.60 and 1.5-2.0, confirming that two methylene groups should be located adjacent to the double bond substituted with three methyl groups. Taking into consideration the two struc-

tural units [I] and [II] in addition to the location of a chlorine atom at the C-3 methine, the structure (1) was proposed.



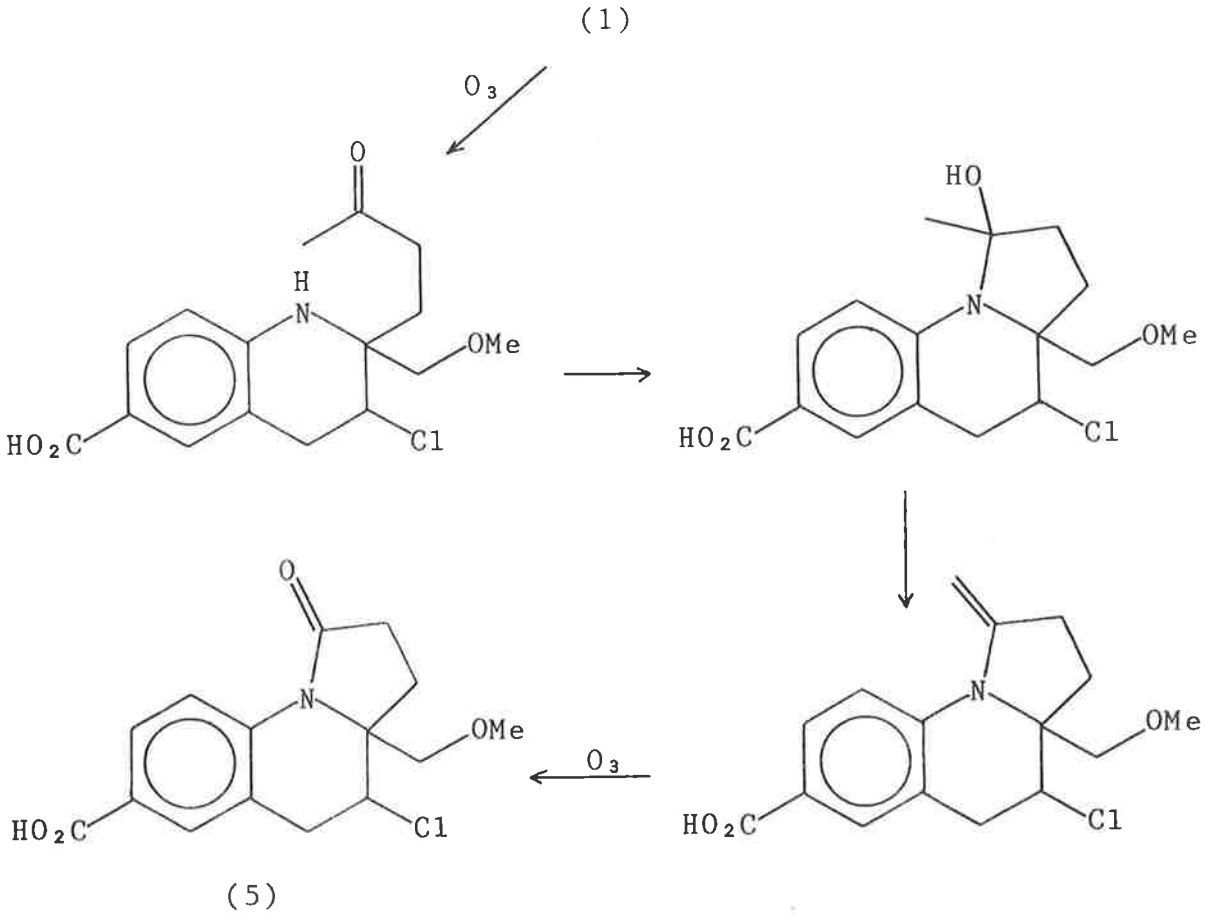
(3)



(4)

The validity of the structure (1) was also confirmed by the observed chemical reactions[2] of the antibiotic. The treatment of virantmycin with either zinc dust or sodium acetate in acetic acid afforded the acetoxy compound (3). This compound shows proton resonances at δ 2.03 arising from the acetoxy methyl group and a triplet at δ 5.23 due to the C-3 methine proton. Lithium aluminium hydride reduction of (1) gave the aziridine (4) arising from internal displacement of the chlorine atom. The aziridine ring proton at C-3 resonates at δ_H 2.80, and the carbon atoms produce resonances at δ_C 49.8 (C-2) and 50.1 (C-3).

Ozonolysis of (1) in chloroform at -12^0 gave a five membered ring lactam (5). The infrared spectrum of this compound shows a carbonyl stretch at 1700 cm^{-1} due to the lactam and another at 1687 cm^{-1} due to the carboxyl group. The ^1H nmr spectrum included a doublet of doublets at δ 4.20 due to the C-3 methine proton, resonances at δ 3.18 and 3.25 due to the C-4 methylene protons and a pair of doublets at δ 3.44 and 3.76 arising from the non-equivalent protons at C-17. The structure of this lactam was evidenced by the application of $^{13}C\{^1H\}$ long range decoupling. The formation of (5) was speculated to proceed *via* an enamine intermediate as shown in scheme 1.



Scheme 1

The assignment of ^{13}C nmr chemical shifts for compounds (1), (2), (4) and (5) was accomplished by selective $^{13}C\{^{1}H\}$ decoupling and long range decoupling experiments and is shown in table 1.

^{13}C Chemical Shifts of compounds (1), (2), (4), and (5).

Carbon No.	(1)	(2)	(4)	(5)
-NH-				
2	58.0 (s)	57.9	49.8	66.6
3	56.2 (d)	56.4	50.1	61.2
4	33.5 (t)	33.4b	30.2	35.8
5	132.4 (d)	131.6	122.6	131.3
6	117.7 (s)	118.6	138.0	126.8
7	130.4 (d)	129.6	126.2	129.3
8	113.5 (d)	113.5	120.7	119.8
9	147.2 (s)	146.5	150.1	125.5
10	116.0 (s)	115.9	139.5	139.3
11	33.5 (t)	33.6b	30.2	28.4
12	27.8 (t)	27.8	33.9	32.4
13	124.8 (s)	124.6	124.2	175.4
14	126.5 (s)	126.5	127.1	
15	18.8 (q)a	19.9a	20.0a	
16	171.9 (s)	167.2	64.5	167.9
17	74.1 (t)	73.9	66.4	72.3
17-OCH_3	59.4 (q)	73.9(?)	58.8	60.3
18	18.4 (q)	18.4a	18.3a	
19	20.6 (q)a	20.6a	20.6a	
OCH_3		51.5		

a,b These assignments within any vertical column may be reversed.

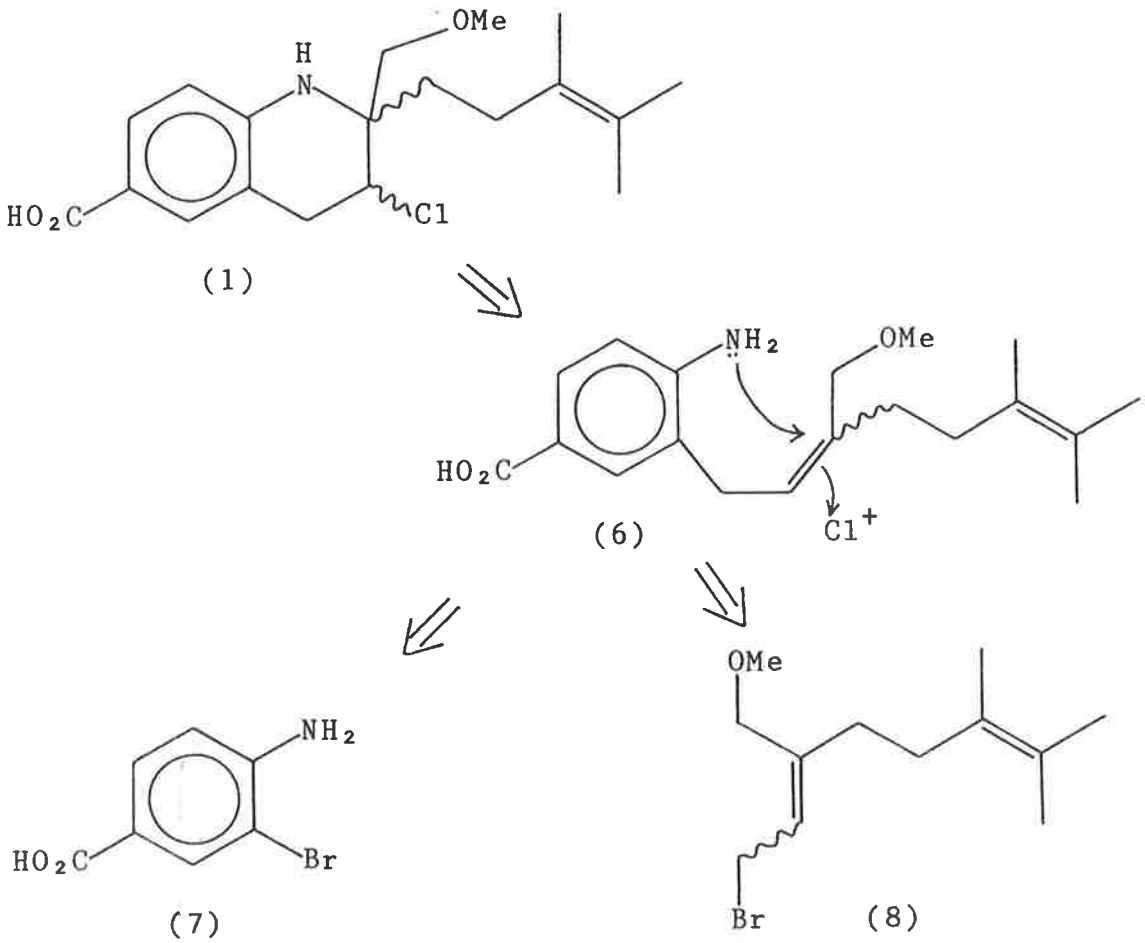
Compounds (1), (2), (4) were measured in $CDCl_3$.

Compound (5) was measured in CD_3SOCD_3.

Table 1

The authors report that the determination of the absolute stereochemistry at C-2 and C-3 by X-ray crystallography of (2) is in progress, however at this time no results have been published. It is hoped that our work towards the synthesis of virantmycin may provide stereochemical grounds for such an assignment.

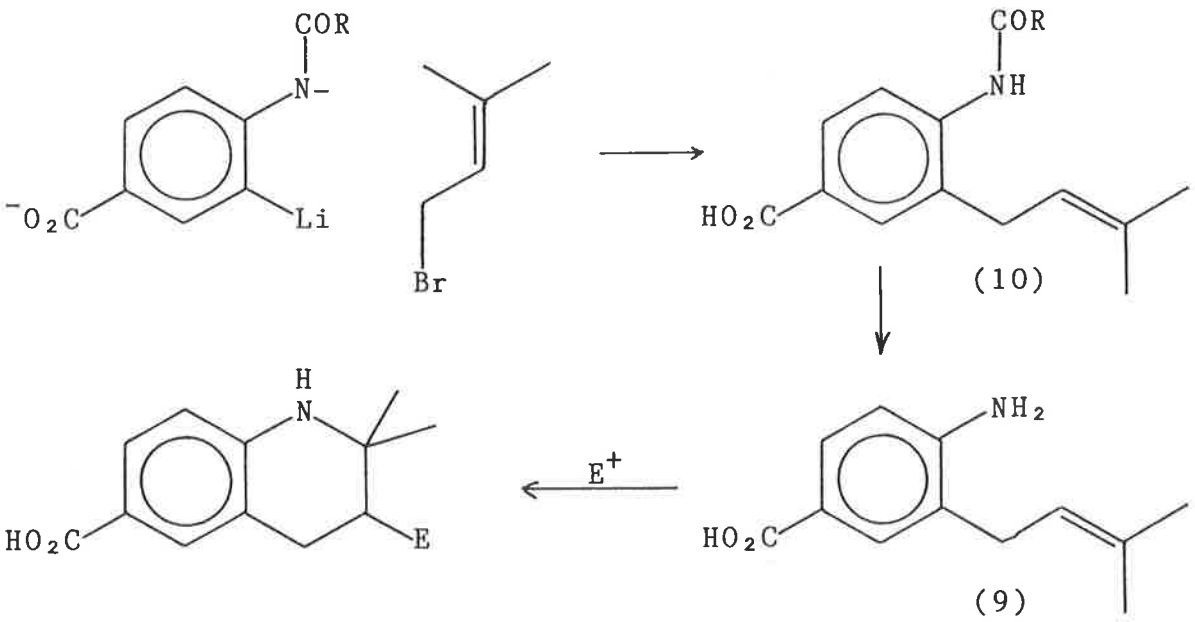
Our retrosynthetic analysis of virantmycin regards the molecule as being derived from two subunits as shown in



Scheme 2

scheme 2. Coupling of the subunits (7) and (8) could be achieved through metallation of (7) and subsequent reaction with (8) to give the allylbenzene (6). Electrophile promoted cyclisation of (6) should furnish virantmycin or a derivative thereof.

The work described in this thesis is presented in three main parts. Firstly, the coupling of (7) and (8) was investigated. Much of the work was carried out using 3,3-dimethylallyl bromide as a model compound for the sidechain (8) (scheme 3).

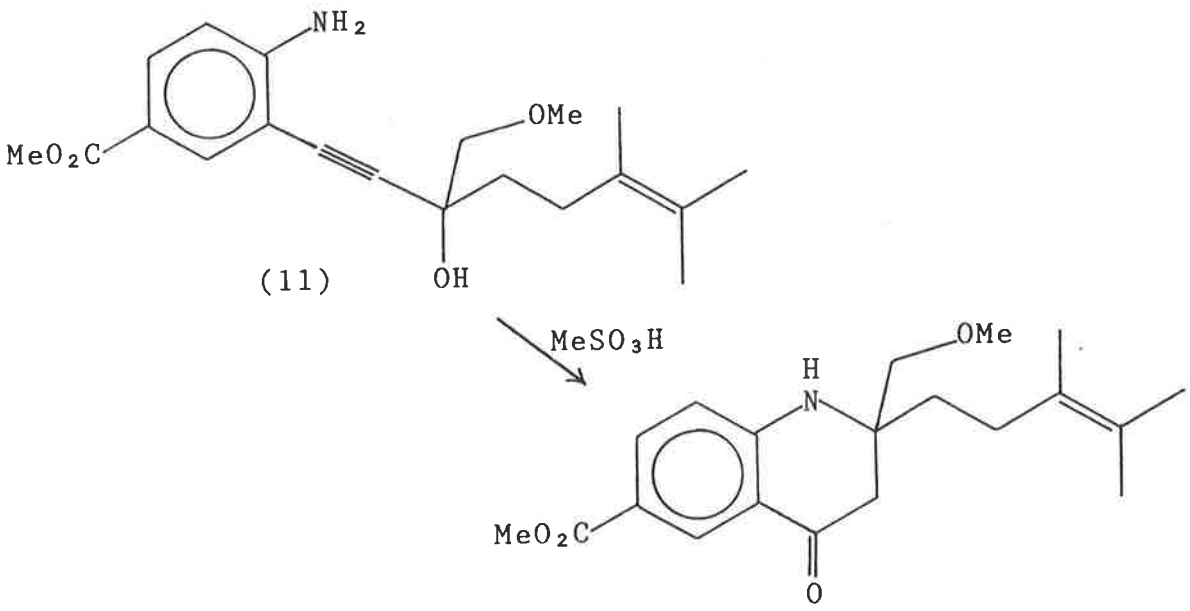


Scheme 3

Secondly, the cyclisation step was assessed. Amine (9) and its derivatives (10) were reacted with various electrophiles. Finally, work was directed towards the synthesis of the sidechain (8), and ultimately virantmycin.

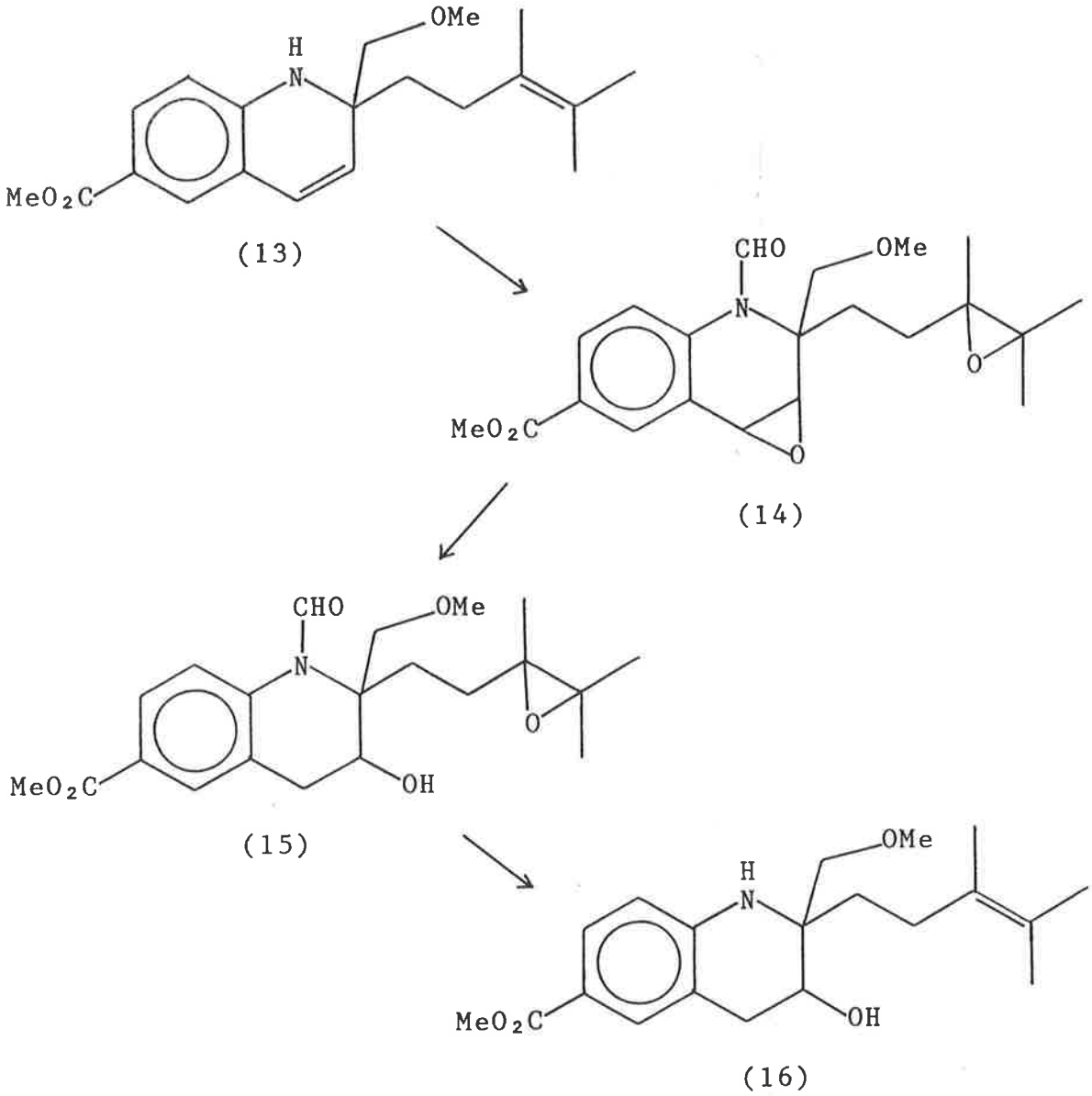
The stereochemical consequences of the cyclisation processes are of particular importance for the ultimate success of the project. Access to the individual stereoisomers of the cyclised product may be possible using the methods of chiral induction. As the stereochemistry at C-2 and C-3 of virantmycin is currently unkown, this approach will provide chemical evidence for a stereochemical assignment.

Towards the conclusion of this work, a total synthesis of virantmycin was published[4]. The key step in this synthesis was the cyclisation of the amino-ester (11) to give compound (12). The functionality in the heterocyclic ring was then manipulated to give virantmycin methyl ester. This approach differs from our intended synthesis where the functionality is directly introduced to the C-3 carbon at the time of cyclisation in the one step. Our approach should hasten the elaboration to virantmycin.



(11) (12)

The ketone (12) was reduced with sodium borohydride and the resulting alcohol was dehydrated using triphenylphosphine/ carbon tetrachloride to give the olefin (13). This compound was unstable and readily lost the elements of dimethyl ether

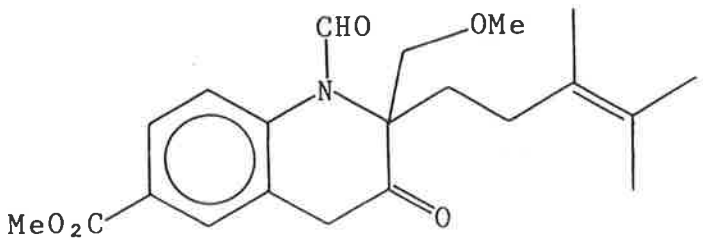


to form the corresponding quinoline. The synthesis was continued using the stable N-formyl derivative.

The formamide of (13) was converted to a diastereoisomeric mixture of epoxides (14) with excess *m*-chloroperbenzoic acid. This mixture was subjected to hydrogenolysis to yield the hydroxy-epoxide (15). De-epoxidation was carried out

by treatment with tungsten hexachloride/*n*-butyllithium, the product of which, after deformylation, gave a single pure diastereoisomer of the amino-alcohol (16).

Treatment of (16) with thionyl chloride gave a chloro-ester which was hydrolysed to the chloro-acid. This acid was identical to virantmycin in all chromatographic and spectroscopic respects. Oxidation of the N-formyl derivative of (16) with dimethylsulphoxide/oxalyl chloride gave the ketone (17)



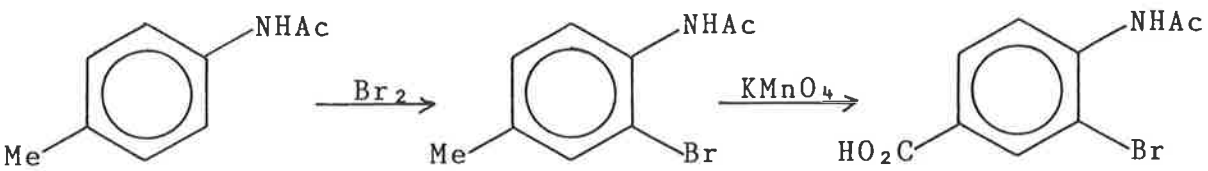
(17)

which was reduced with sodium borohydride and was deformylated to give predominantly the C-3 epimer of (16). Chlorination of this compound gave the C-3 epimer of (2) whose ^{1}H nmr spectrum was significantly different from that of authentic virantmycin methyl ester.

However the spectroscopic properties of these compounds give no unambiguous indication of the relative stereochemistry at C-2 and C-3. The authors are currently attempting to solve this problem by growing crystals of (2) suitable for X-ray diffraction. Until these results are published the stereochemistry of virantmycin is still unknown.

RESULTS AND DISCUSSION

The preparation of the *ortho*-substituted anilines (9),(10) *etc.* was first attempted by reaction of an aryllithium with an allyl halide. The readily available amidoacid (19) was prepared, according to the literature procedure[5], by the oxidation

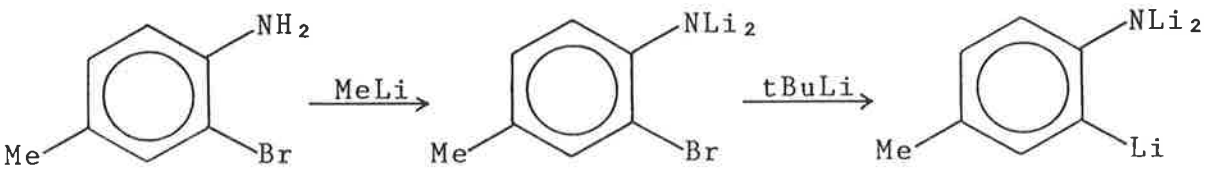


(18) (19)

of the bromotoluidide (18). A brominated substrate was chosen as this would produce the aryllithium by a facile lithium-bromine exchange[6] at low temperatures thereby minimising any possible side reactions of the carboxyl group with alkyllithium reagents. The amidoacid (19) was treated with two equivalents of methyllithium, in tetrahydrofuran at -78°, to remove the acidic carboxyl and amide (NH) protons. Methyllithium[6] does not undergo lithium-bromine exchange and so by using this reagent first, followed by *n*-butyllithium, the problems of deprotonation competing with lithium-bromine exchange can be avoided. If this competition was to occur, then metallation would proceed whilst there are still acidic protons in solution and this would lead to protonation of the newly formed aryllithium reagent. Unfortunately treatment of

the deprotonated amide with one equivalent of *n*-butyllithium followed by allyl chloride gave an intractable mixture as indicated by tlc and nmr. Treatment of (19) with two equivalents of methyllithium alone also gave decomposition products which possibly arose from base promoted aldol type condensations involving the acidic methyl protons of the acetyl group.

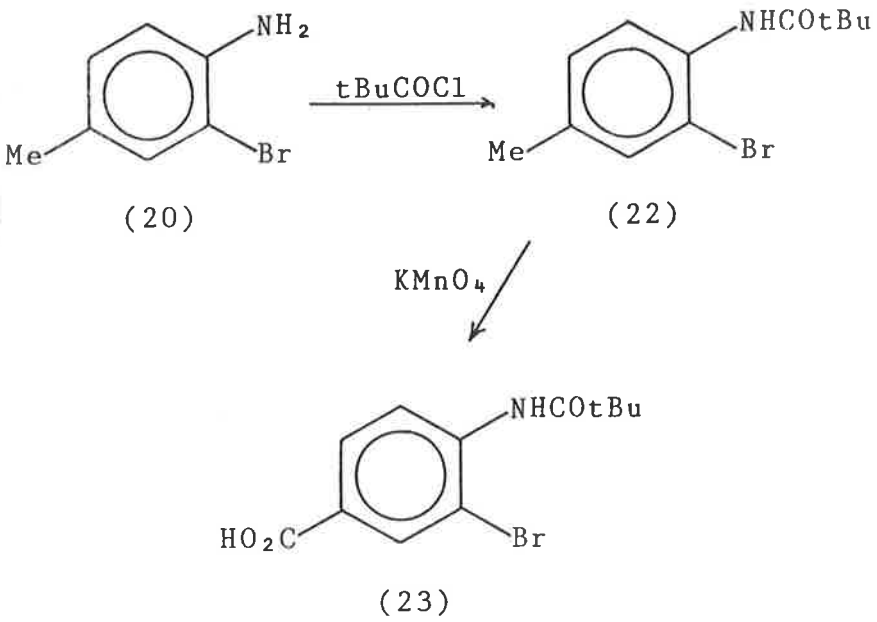
The commercially available bromotoluidine (20) was investigated to establish whether or not it was necessary to protect the amino group during the course of metallation. It



(20) (21)

was found that treatment of (20) with two equivalents of methyllithium followed by two equivalents of *tert*.-butyllithium, in tetrahydrofuran at -78^{0}, did not form the aryllithium species since the bromoamine was recovered quantitatively after workup with saturated ammonium chloride. Presumably the trilithio species (21) was reluctant to form due to adverse electrostatic interactions in what is formally a trianion.

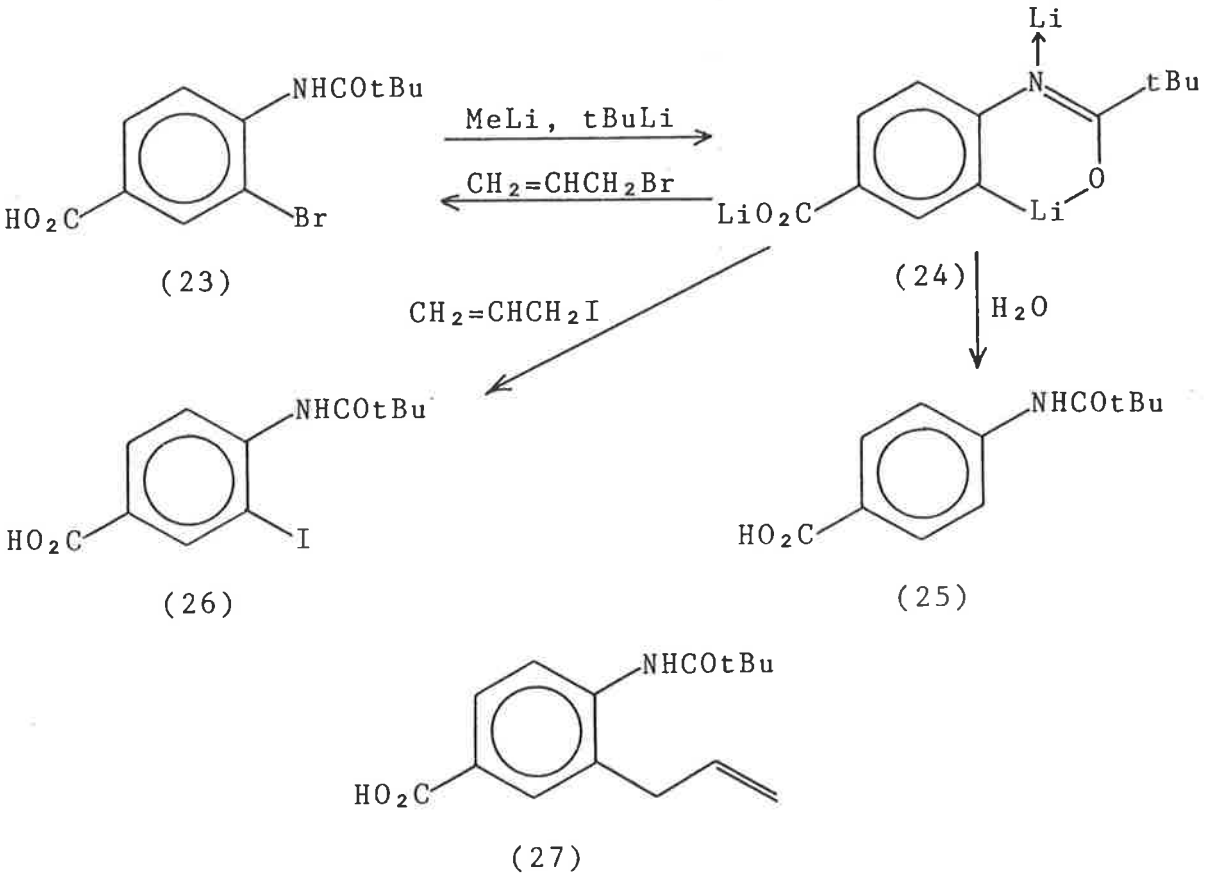
It was then decided to protect the amino group as a pivalanilide as metallations of *ortho*-bromopivalanilides have



(20) (22) (23)

been descibed in the literature[7]. The absence of acidic α-protons meant that the problem of undesirable aldol type condensations could be avoided. The aryllithium species (24) was generated in tetrahydrofuran at -78° by treatment of (23) with two equivalents of methyllithium then two equivalents of *tert.*-butyllithium to give a yellow suspension. Only *tert.*-butyllithium was reactive enough to effect the lithium-bromine exchange and two equivalents were required for complete metallation. The extent of metallation was estimated by quenching aliquots with water, followed by solvent extraction and analysis by nmr spectroscopy. The bromobenzene (23) and the corresponding reduced compound (25) are readily distinguished: (25) has a second order AA'BB' system with two doublets at δ 7.80 and 7.73 each with 8 Hz coupling, whilst (23) has a doublet of doublets at δ 7.88 with 2 and 8 Hz coupling;

a doublet at 8.11, 2 Hz coupling, and a doublet at 8.31 with 8 Hz coupling. In this manner it was found that metallation was complete within one minute.



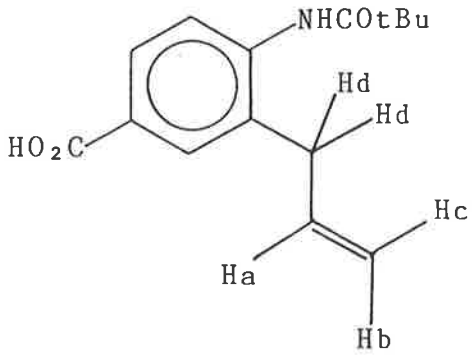
Scheme 4

Addition of allyl chloride to the aryllithium suspension failed to give any of the desired allylbenzene (27), only the reduced compound (25) was obtained when the aryllithium was quenched. Addition of allyl bromide also failed to give any allyl compound, and the bromobenzene (23) was recovered. It is thought that (23) is reformed by a second lithium-bromine exchange (scheme 4) as an aliquot of the aryllithium suspension

was quenched with water and was found to be completely metallated. Similarly, when the aryllithium (24) was treated with allyl iodide a second lithium-halogen exchange occurred producing the iodobenzene (26). The structure of (26) was confirmed by nmr, mass spectrometry and elemental analysis. This type of lithium-halogen exchange has been observed by Beak[8] who showed that *ortho*-lithio-N,N-di*iso*propylbenzamide reacted with allyl bromide to give the corresponding bromobenzene.

Since the desired allylbenzene (27) could not be obtained from the aryllithium (24), it was decided to try the corresponding organocopper reagent as these are known[9] to be more reactive towards nucleophilic substitution. The aryllithium was generated in tetrahydrofuran at -78^0 and the soluble cuprous iodide phosphine complex[10] $[CuI(n Bu_3P)]_4$ was added, followed ten minutes later by allyl chloride. Continued stirring did not result in the loss of yellow colour due to the organocopper species and quenching the reaction mixture with water gave mainly the reduced compound (25). Analysis of the crude product by nmr spectroscopy revealed weak resonances characteristic of an allyl system, namely a multiplet centered at δ 5.9 arising from Ha (figure 1), a multiplet at 5.1-4.9 due to Hb, Hc and a doublet with 7 Hz coupling (and also long range coupling) at 3.40 due to the methylene protons. When the reaction was repeated with excess $[CuI(n Bu_3P)]_4$ (to allow for possible complexation with the carboxyl group) the major pro-

duct was still the reduced compound (25) and no more than a trace of (27) could be found. Reactions at higher temperatures were no more productive.



(27)

a δ 5.9, m

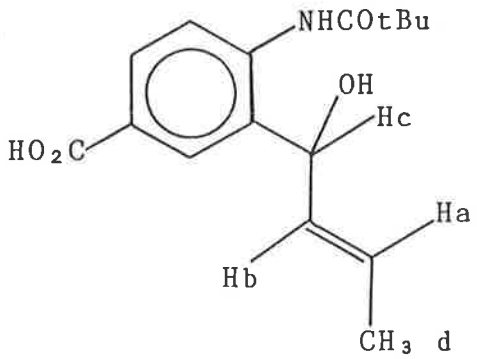
b,c δ 5.1-4.9, m

d δ 3.40, br d, *J* 7 Hz

Figure 1

The reaction of an aryllithium with an unsaturated aldehyde such as crotonaldehyde was considered as an alternative approach to aromatic systems with unsaturated side chains. Addition of crotonaldehyde to the aryllithium derived from (23) gave mainly the reduced compound (25) upon workup, and only a trace of the desired product (28) could be observed in the nmr spectrum (figure 2) of the crude product mixture.

It was surprising that the aryllithium species did not react with a simple aldehyde like crotonaldehye, and the lack of reactivity may have been due to insolubility of the lithio species which may be regarded as a trianion. It was then decided to study the chemistry of more soluble dilithio reagents in order to assess their reactivity towards electrophiles.



a,b δ 5.6, m

c δ 5.2, m

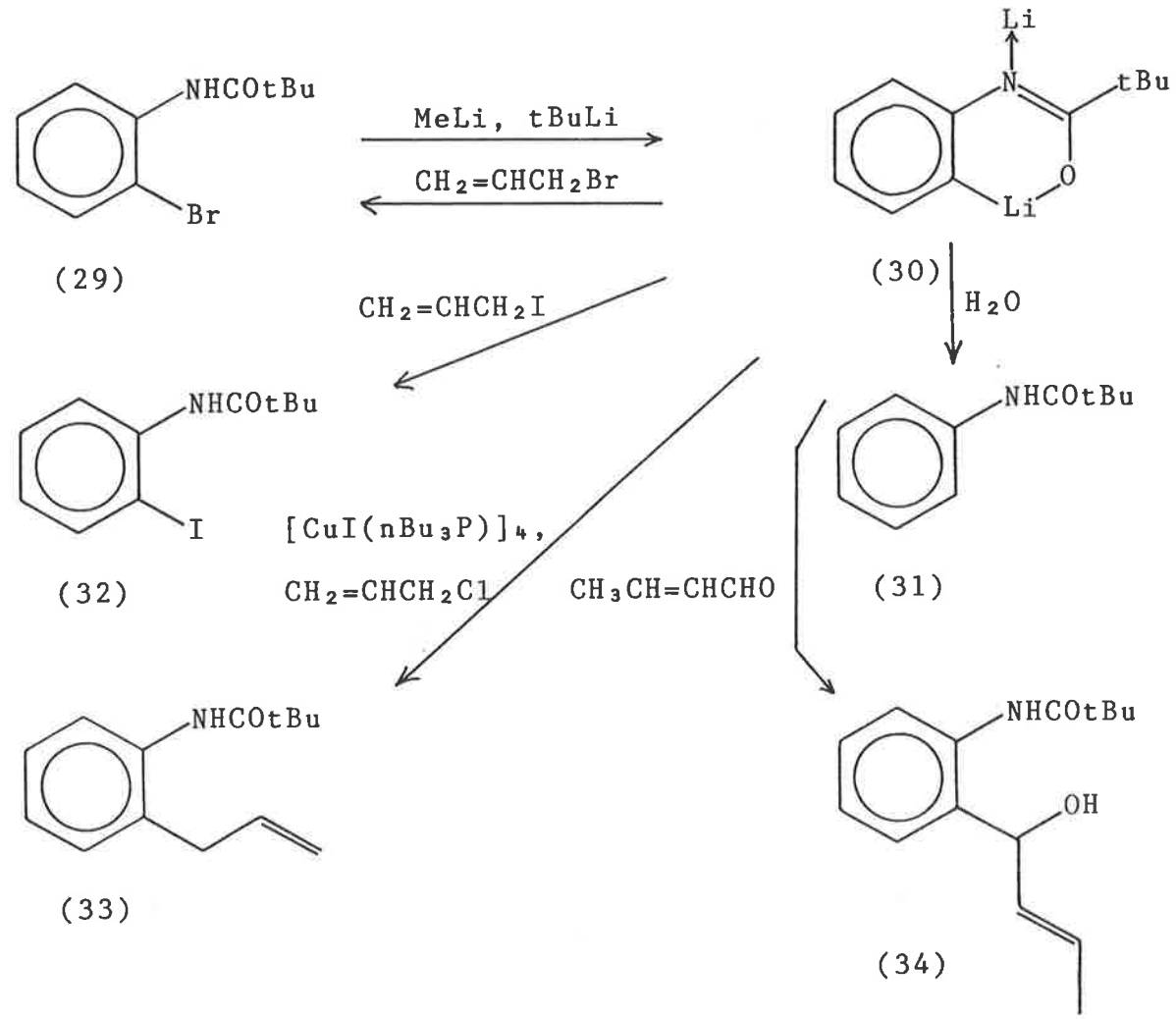
d δ 1.67, br d, *J* 4 Hz

(28)

Figure 2

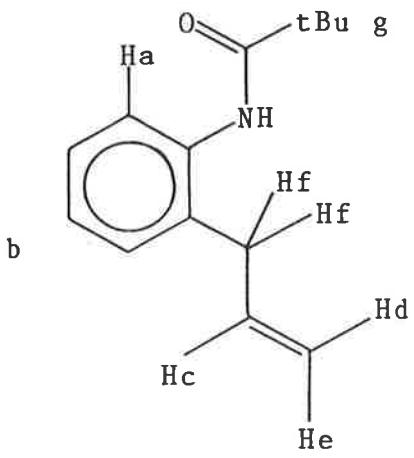
The bromoamide[11] (29) was prepared from *ortho*-bromoaniline and pivaloyl chloride, and was metallated following the literature procedure[7]. Treatment with one equivalent of methyllithium followed by two equivalents of *tert.*-butyllithium in tetrahydrofuran at -78^0 effected complete metallation within one minute (as was found by quenching aliquots with water and subjecting them to nmr analysis). Regarding the reaction with allyl halides, the dilithio reagent (30) exhibited similar reactivity to the carboxylic acid derived trilithio species (24). Thus with allyl bromide or iodide, a second lithium-halogen exchange occurred to give the corresponding halobenzene (scheme 5) whereas allyl chloride underwent no reaction and the reduced compound (31) was obtained upon workup. Even at higher temperatures there was no reaction between the dilithio species and allyl chloride.

The aryllithium could be converted to the arylcopper reagent by addition of $[CuI(nBu_3P)]_4$ and then subsequent



Scheme 5

addition of allyl chloride rapidly produced the desired allylbenzene (33). This was isolated by silica gel chromatography in 50% yield along with tri-*n*-butylphosphine and a small amount of the starting bromide (29). The allylbenzene was readily identified by the characteristic allyl resonances observed in the nmr spectrum (figure 3).

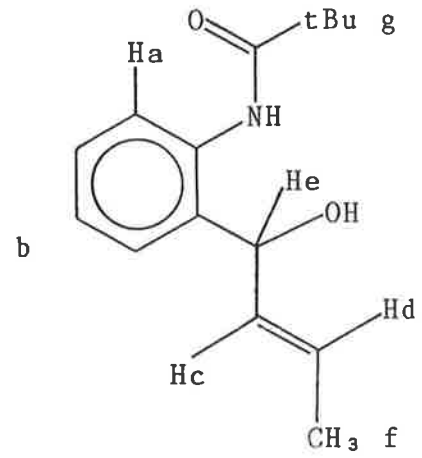


(33)

a	δ 7.80,	dd, *J* 2, 8 Hz
b	δ 6.9,	m
c	δ 5.9,	m
d,e	δ 5.1-4.9,	m
f	δ 3.38,	br d, *J* 7 Hz
g	δ 1.17,	s

Figure 3

The aryllithium (30) reacted rapidly and smoothly with crotonaldehyde to give the hydroxybutenyl compound (34) in 93% yield after purification by silica gel chromatography. The alcohol was an oil which decomposed on attempted distillation. The structure of (34) was verified by nmr (figure 4) and mass spectrometry.



(34)

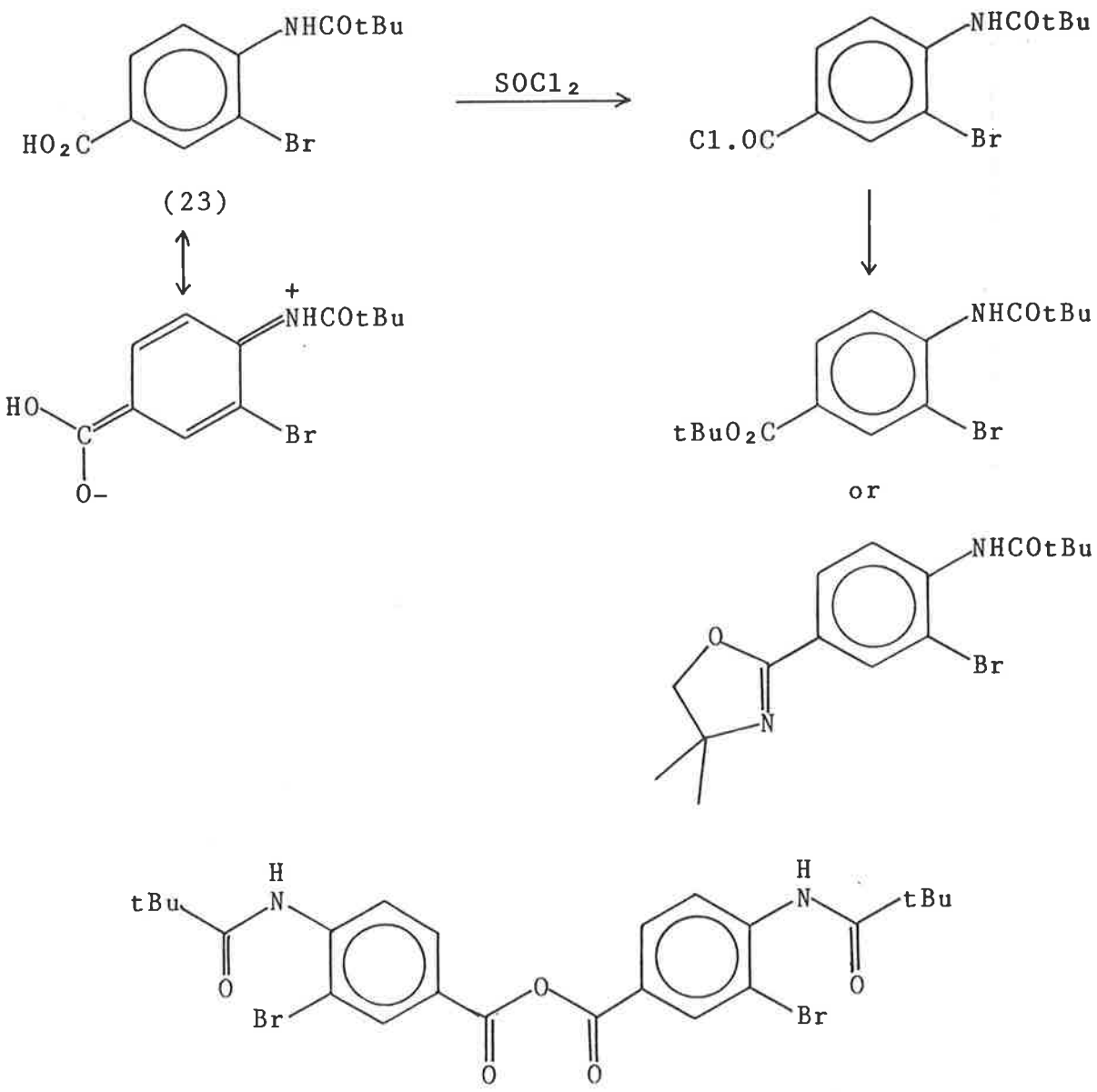
a	δ 7.96,	dd, *J* 2, 8 Hz
b	δ 6.9,	m
c,d	δ 5.6,	m
e	δ 5.2,	m
f	δ 1.63,	d, *J* 4 Hz
g	δ 1.20,	s

Figure 4

The large downfield shift of proton Ha is not unusual and is a feature of many pivalanilides where the *ortho* position is substituted[12]. In such cases, steric factors cause the carbonyl oxygen to lie in close proximity to this proton which therefore experiences a strong anisotropic effect.

Having established that the dilithio species (30) was sufficiently soluble and reactive enough to form an arylcopper reagent and hence give rise to allylbenzenes, it was decided to investigate systems where the carboxyl group of (23) was either masked or protected. Such compounds would be, for example, the oxazoline[13] or the hindered *tert.*-butyl ester[14] and were expected to form soluble and reactive dilithio species.

When the carboxylic acid (23) was treated with thionyl chloride at reflux, the acid chloride was not isolated but instead the symmetrical anhydride (35) was obtained. The infrared spectrum of the anhydride had absorptions at 1790 and 1740 cm^{-1} due to the anhydride linkage as well as an absorption at 1720 cm^{-1} due to the pivalamide moiety. The mass spectrum had the molecular ions at *m/e* 580/582/584. The reaction with thionyl chloride was repeated using a dilute solution of the acid (23) in thionyl chloride and still the anhydride formed. Similar results were obtained when the acid (23) was refluxed in oxalyl chloride.

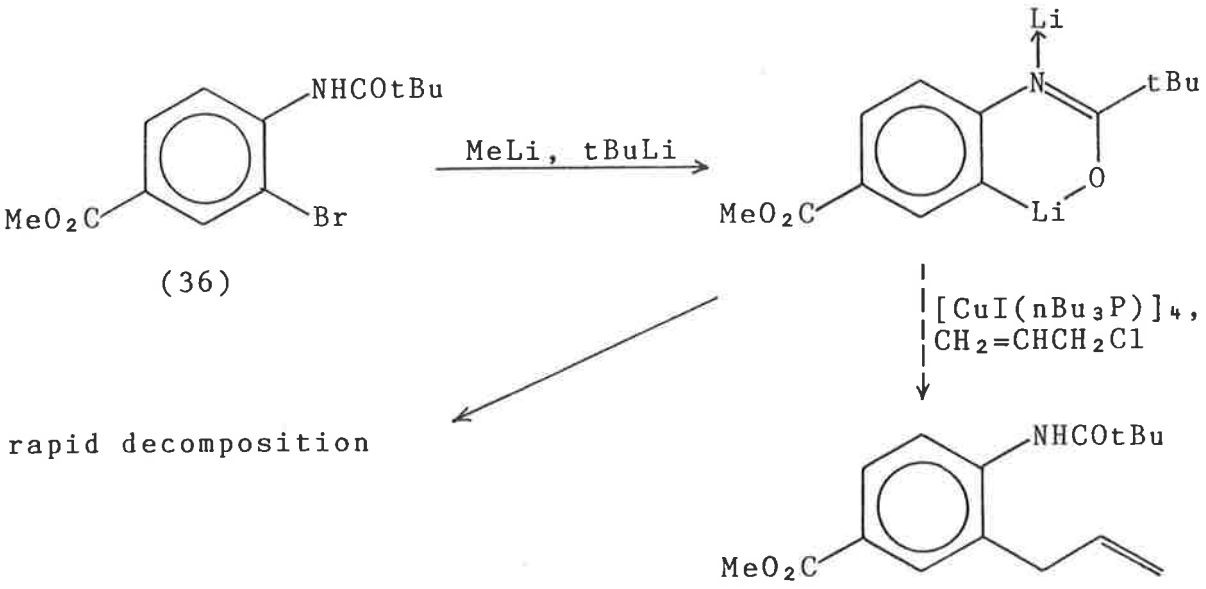


(35)

The preparation of the *tert.*-butyl ester was also attempted. Formation of the dicyclohexylcarbodiimide adduct in the presence of *tert.*-butanol gave only the anhydride (35). Following the procedure of Brewster[14], the anhydride (35) was prepared using *p*-toluenesulphonyl chloride in pyridine, however the addition of *tert.*-butanol to this mixture did not

yield any of the desired *tert.*-butyl ester. The favoured anhydride formation in the above reactions may possibly be a result of increased nucleophilicity of the carboxyl group arising from electron donation from the nitrogen lone pair.

Although the *tert.*-butyl ester and the oxazoline were not readily accessible, it was thought that at low temperature the simple methyl ester (36) may be compatible with metallation. This ester was readily prepared by treatment of a methanolic solution of the carboxylic acid (23) with diazomethane.



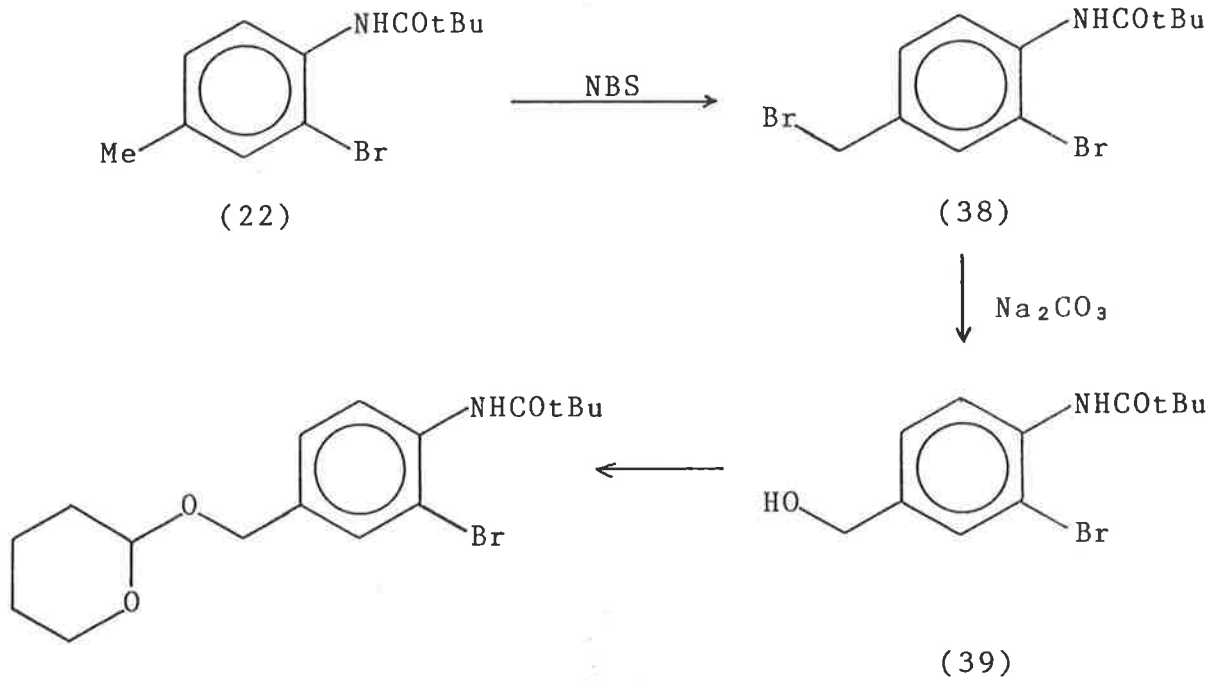
(36)

(37)

The amide proton of (36) was removed, in tetrahydrofuran at -78^0, by treatment with one equivalent of methyllithium. Subsequent addition of two equivalents of *tert.*-butyllithium gave an instant yellow colour which rapidly darkened, addition of $[CuI(nBu_3P)]_4$ followed by allyl chloride gave mainly poly-

meric material upon workup. Analysis of the crude reaction mixture by nmr spectroscopy showed very weak resonances which were attributable to the desired allylbenzene (37), however the amount was not large enough to allow isolation.

Since the carboxylic acid could not be conveniently protected it was decided to choose a group at the 4-position that was compatible with metallation and which could be elaborated to the carboxylic acid at a later stage. The benzyl alcohol (39) was selected since it may be possible to protect it as a tetrahydropyranyl ether for the purpose of metallation.

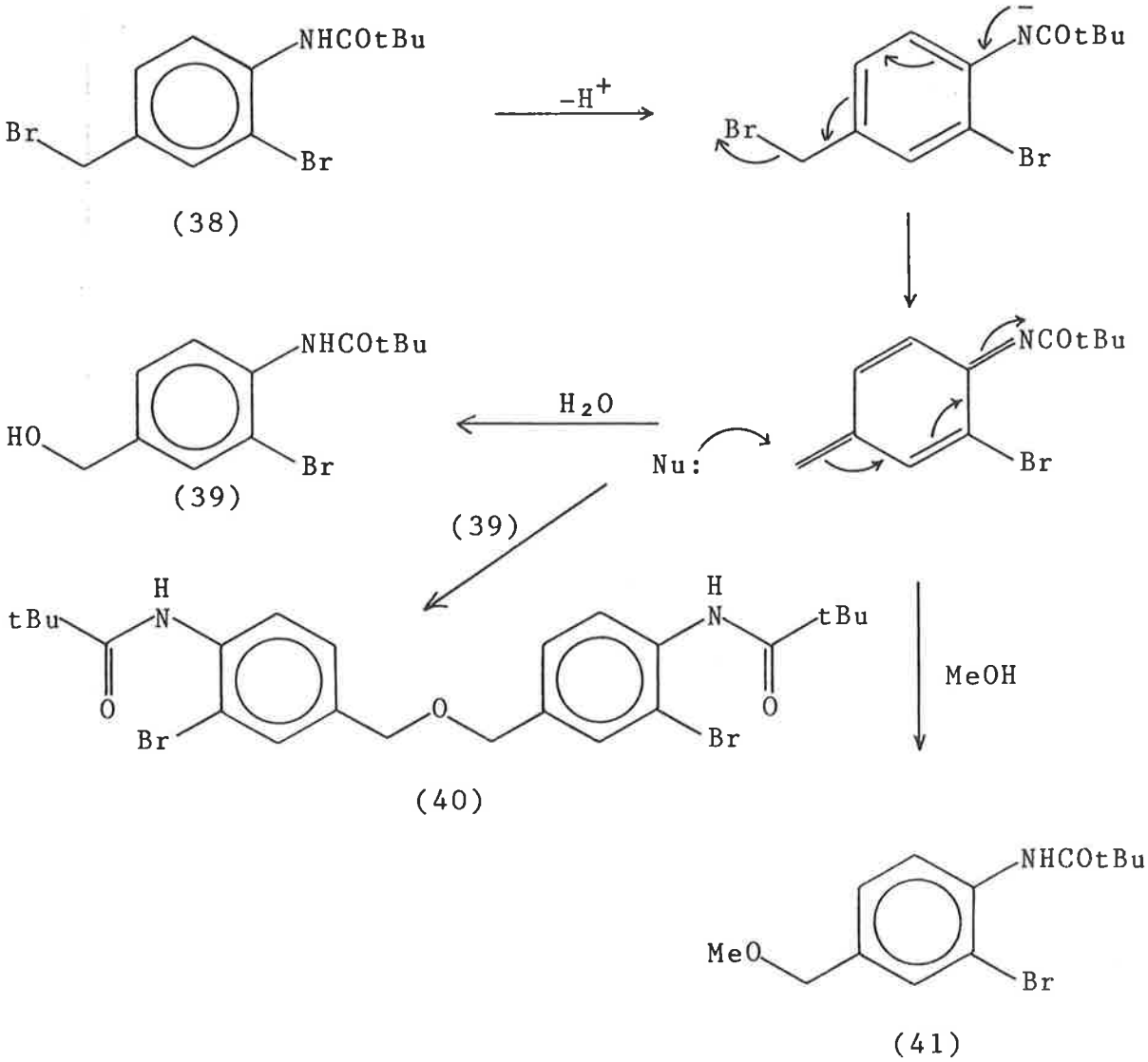


The toluidide (22) was converted to the benzyl bromide (38) in good yield using N-bromosuccinimide. Hydrolysis of (38) was first attempted by stirring the bromide in a two

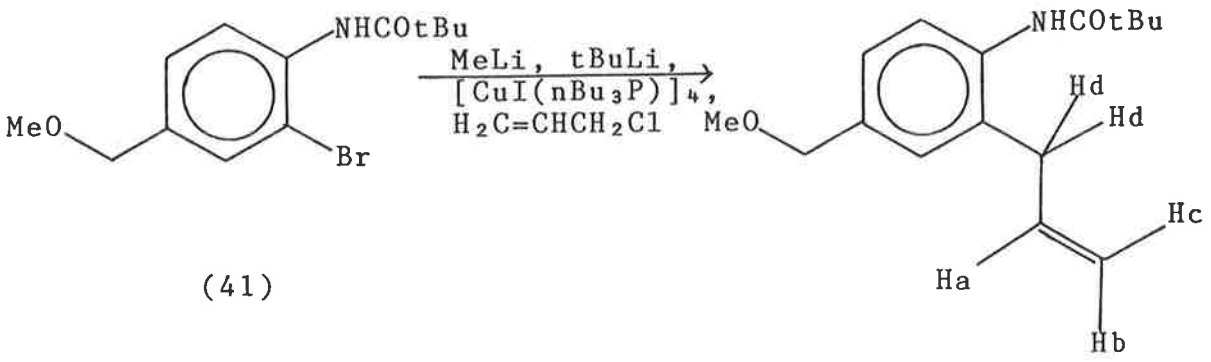
phase system of tetrahydrofuran and 10% aqueous sodium hydroxide at room temperature. The solution rapidly turned yellow and after ten minutes analysis by tlc showed that complex decomposition was occurring, and the nmr spectrum of the crude product mixture showed only a trace of the alcohol (39) to be present. When the bromide (38) was stirred in a mixture of tetrahydrofuran and saturated sodium carbonate, the yellow colour was again formed and slowly diminished over a period of sixteen hours. The crude product mixture was separated into two fractions by silica gel chromatography. The fraction of lower polarity consisted largely of the unreacted bromide (38) along with a small quantity of the symmetrical ether (40) as detected by mass spectrometry. The second fraction was the desired alcohol obtained in 50% yield after recrystallisation.

When the bromide (38) was stirred in methanol with solid sodium carbonate the resulting yellow colour faded within three hours and the single product isolated was the methyl ether (41) in 80% yield.

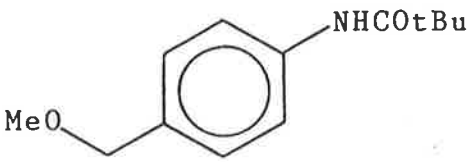
The ready solvolysis under mild conditions, the transient yellow colouration and the formation of the symmetrical ether (40) during the hydrolysis of the bromide suggest that the mechanism for these solvolysis reactions involves deprotonation followed by expulsion of a bromide ion. The resulting quinonoid intermediate may be expected to be coloured and would readily react with nucleophiles.



Having obtained the methyl ether (41) so conveniently it was decided to establish whether it was a suitable substrate for metallation. Lithiation of (41) by the method described earlier gave the dilithio species which was transmetallated by addition of $[CuI(n Bu_3P)]_4$. After five minutes at -78^0, allyl chloride was added and then the reaction was quenched with water. Solvent extraction and chromatography on silica gel gave the desired allylbenzene (42) in 38% yield along with the



(41) (42)



(43)

a δ 5.8, m

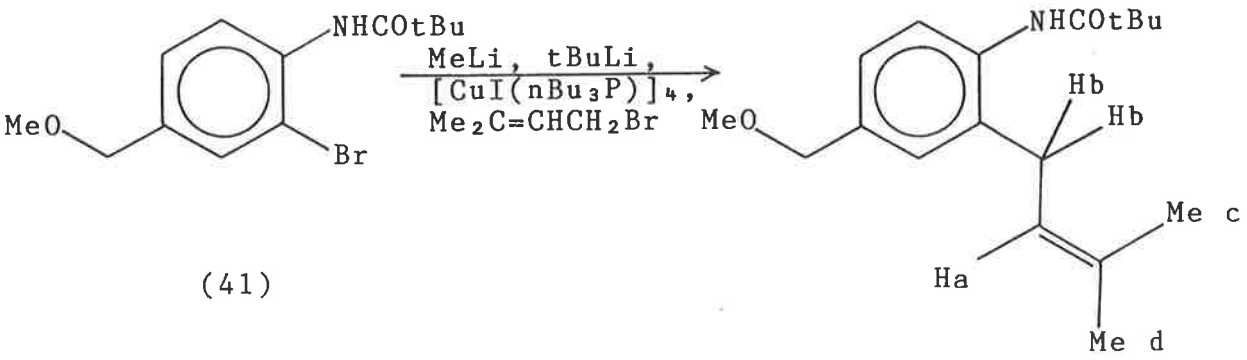
b,c δ 5.1-4.8, m

d δ 3.3, br d, *J* 7 Hz

Scheme 6

reduced compound (43) (35%) and a small quantity of the starting bromide (41). The allylbenzene (42) had resonances in the nmr spectrum that were characteristic of the allyl group (scheme 6) and the infrared spectrum also showed characteristic alkene absorptions at 1635 cm^{-1} (carbon-carbon double bond stretching) and at 990 cm^{-1} (bending).

Reaction of the arylcopper derived from (41) with 3,3-dimethylallyl bromide gave the dimethylallylbenzene (44) in 78% yield. This compound has the basic skeleton required for elaboration to the model compounds (9) and (10).



(41)

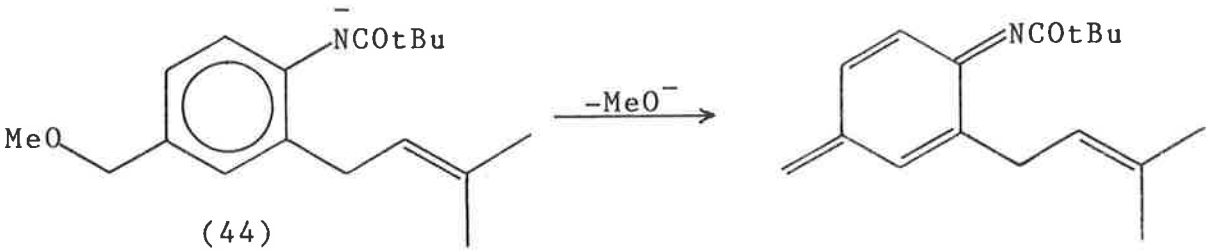
(44)

a δ 5.15, t, *J* 7 Hz

b δ 3.3, br d, *J* 7 Hz

c,d δ 1.73, br s

The results of a study of the behaviour of the allylbenzene (44) in basic media were disappointing. It was anticipated that treatment of (44) with base would lead to elimination of methoxide (scheme 7) and therefore allow hydrolysis via the quinonoid intermediate. However both the ether linkage and the amide were stable to 50% aqueous sodium hydroxide at

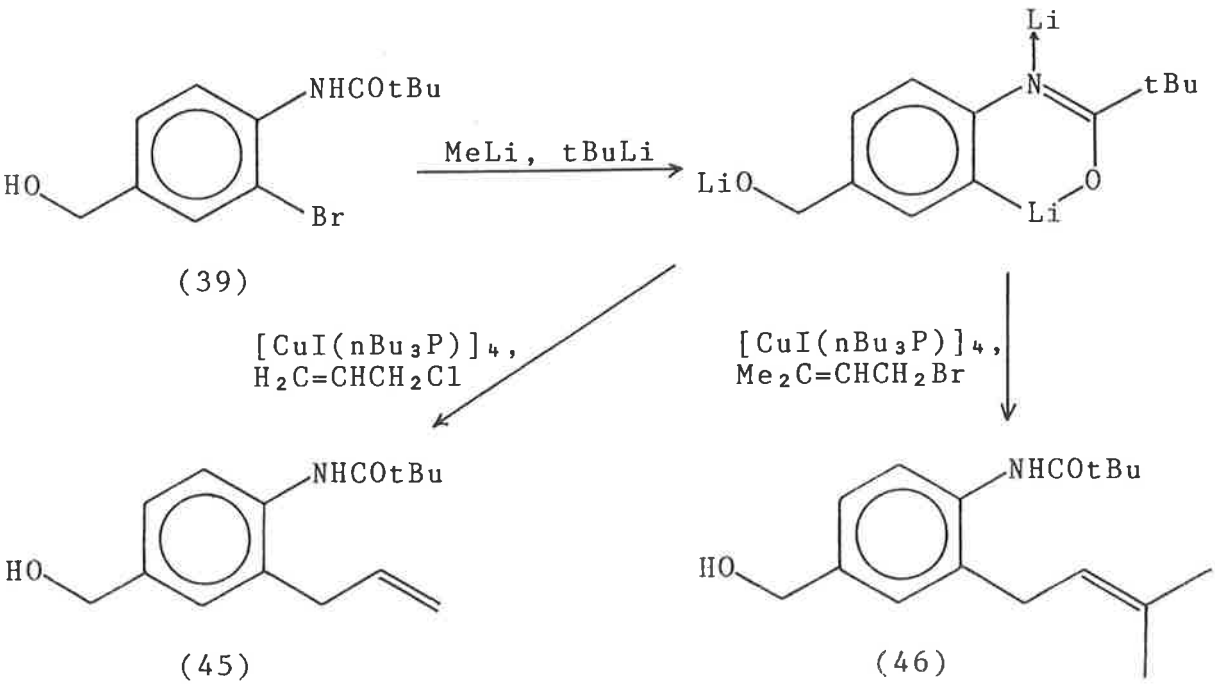


(44)

Scheme 7

reflux and the allylbenzene (44) was recovered quantitatively. An attempt at direct displacement of methoxide with the more nucleophilic hydroperoxide[15] anion also failed and again the allylbenzene was recovered quantitatively.

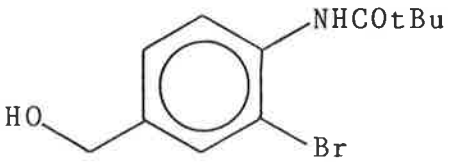
Since the ether linkage of (44) could not be cleaved, attention was turned to the bromoalcohol (39). It was found that the unprotected alcohol could be successfully metallated, this is presumably due to the benzyl alcohol (39) derived trilithio species being somewhat more soluble than the benzoic acid (23) derived analogue. Both the allylbenzene (45) and the 3,3-dimethyl analogue (46) could be prepared by reaction of the alcohol (39) derived organocopper reagent with the appro-



Scheme 8

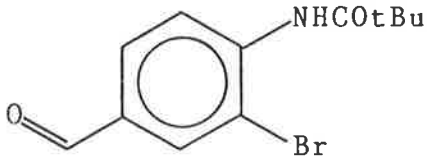
priate halide (scheme 8). The allylbenzenes had similar spectral data to that of the corresponding methyl ethers.

The next step was the oxidation of the benzyl alcohol (46) to the corresponding carboxylic acid (48). However when the alcohol was dissolved in acetone and titrated with Jones reagent the rapid oxidation gave the aldehyde (47) exclusively with no carboxylic acid being observed. When the bromoalcohol (39) was treated under the same conditions the products were the aldehyde (49) and the carboxylic acid (23) which were formed in equal amounts as determined by the nmr integration



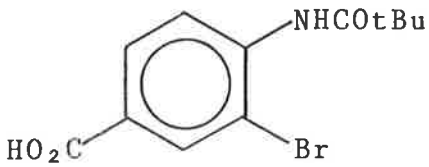
(39)

Jones Reagent

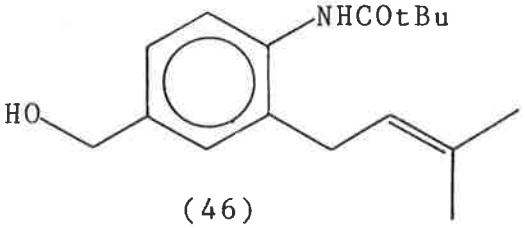


(49)

+

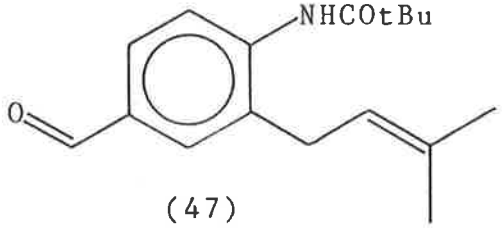


(23)



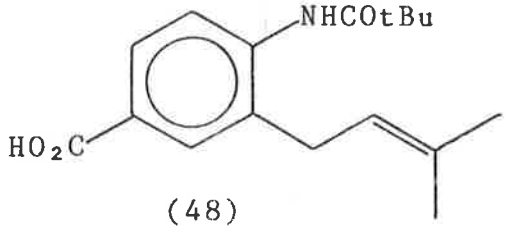
(46)

Jones Reagent



(47)

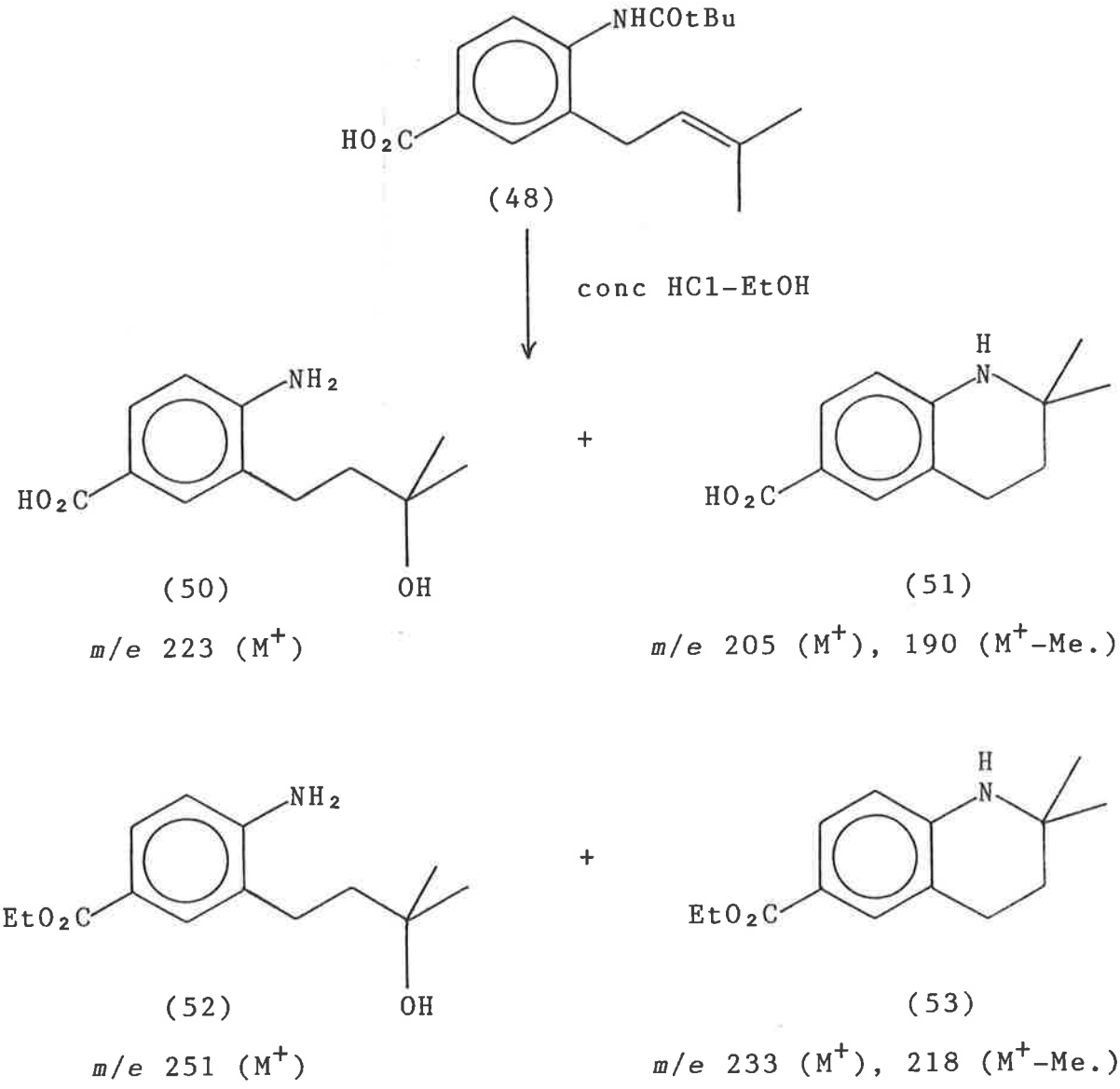
Ag_2O



(48)

of the crude product mixture. Complete oxidation of the alcohol (39) required two hours of stirring in acetone with excess Jones reagent. However when the alcohol (46) was stirred with excess Jones reagent for extended periods the required carboxylic acid was obtained in only low yield due to decomposition possibly arising through the reactivity of the olefinic side chain. The solution to the problem was a two step oxidation using Jones reagent to obtain the aldehyde in 95% yield followed by further oxidation with alkaline silver oxide[16] to give the desired carboxylic acid (48) in 75% yield after recrystallisation.

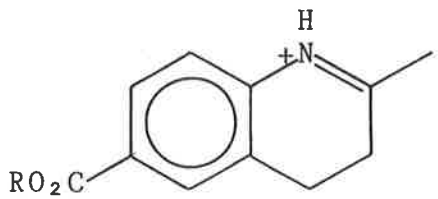
The final step to give the model compound (9) was the hydrolysis of the amide group of (48). It had already been observed that the amide group of the methyl ether (44) was inert to both refluxing in 50% aqueous sodium hydroxide and aqueous sodium peroxide, and similar results were found with the amide linkage of the carboxylic acid (48). It was expected that the hydrolysis would take place readily in acidic media as the carboxyl group would withdraw electron density from the amide carbonyl group rendering it more attractive to incoming nucleophiles. However refluxing the carboxylic acid in a mixture of ethanol and concentrated hydrochloric acid for two hours gave two fractions each in very low yield (<15%) after acid-base extraction. One fraction contained zwitterionic material and the other was basic.



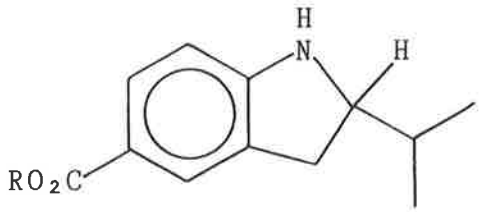
Scheme 9

The dark zwitterionic material was analysed by nmr spectroscopy which revealed that the dimethylallyl moiety was no longer present. Instead, higher field resonances were evident and in particular two singlets appeared at δ 1.23 and 1.30. The crude mixture had peaks in the mass spectrum at *m/e* 223, 205 and 190. This data suggests the presence of compounds

(50) and (51). These compounds are the most likely products to arise by protonation of the double bond in aqueous media. Further support for compound (51) being a six membered ring comes from the appearance of an (M^+-Me.) peak in the mass spectrum; the anti-Markownikoff product (54) would be expected to lose a hydrogen atom or an *iso*propyl radical (figure 5).



(M^+-Me.)

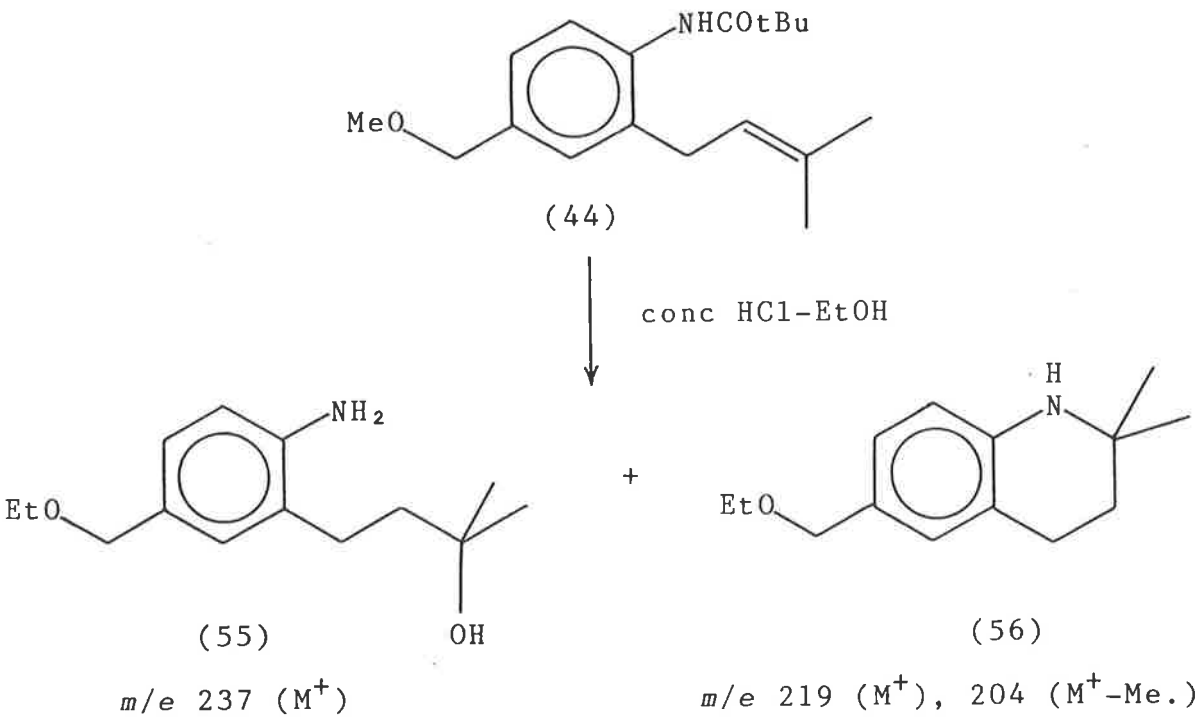


(54)

Figure 5

The basic material isolated from the hydrolysis of (48) had an almost identical nmr spectrum to that of the zwitterionic material but with the addition of a quartet at δ 4.30 and a triplet at 1.35. The mass spectrum had peaks at *m/e* 251, 233 and 218 which along with the nmr data suggests that the ethyl esters (52) and (53) were formed in the reaction of amide (48) with acid in ethanol (scheme 9).

In acidic media, the behaviour of the methyl ether (44) was similar to that of the carboxylic acid (48). Hydrolysis in a mixture of ethanol and concentrated hydrochloric acid at reflux for two hours gave the products shown in scheme 10.

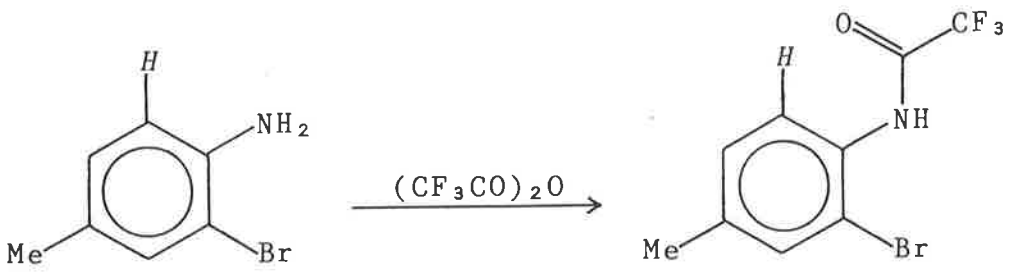


Scheme 10

Acid-base extraction gave a basic residue, the nmr spectrum of which showed that the dimethylallyl moiety was no longer present and that the methoxy group had been exchanged for an ethoxy group. The mass spectrum of this material showed peaks at *m/e* 237, 219 and 204 which confirms this ether exchange.

Owing to the difficulties associated with the removal of the pivalamide protecting group it was decided to consider an alternative protecting group. The trifluoroacetyl group was chosen because of its ease of removal under simple, mild conditions. The bromotoluidine (20) was converted to the trifluoroacetamide (57) in 93% yield by treatment with trifluoroacetic anhydride. As in the case of the pivalanilides the nmr

spectrum showed a large downfield shift in the *ortho* proton resonance due to the proximity of the carbonyl oxygen atom (scheme 11).

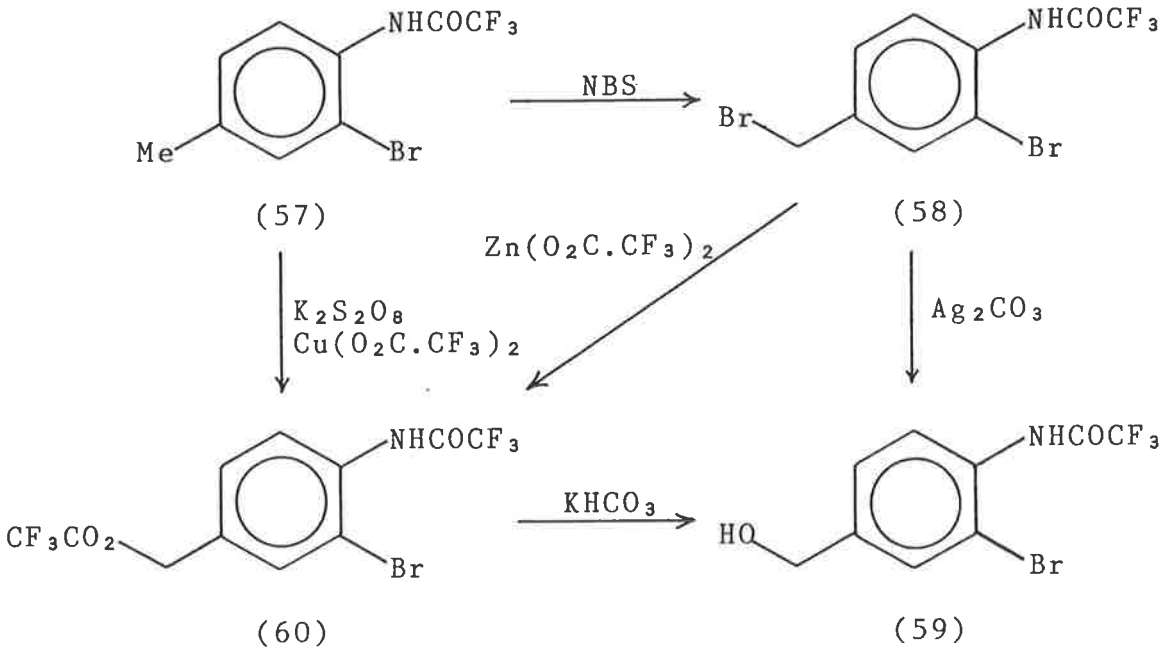


(20) (57)

δ 6.52 δ 8.03

Scheme 11

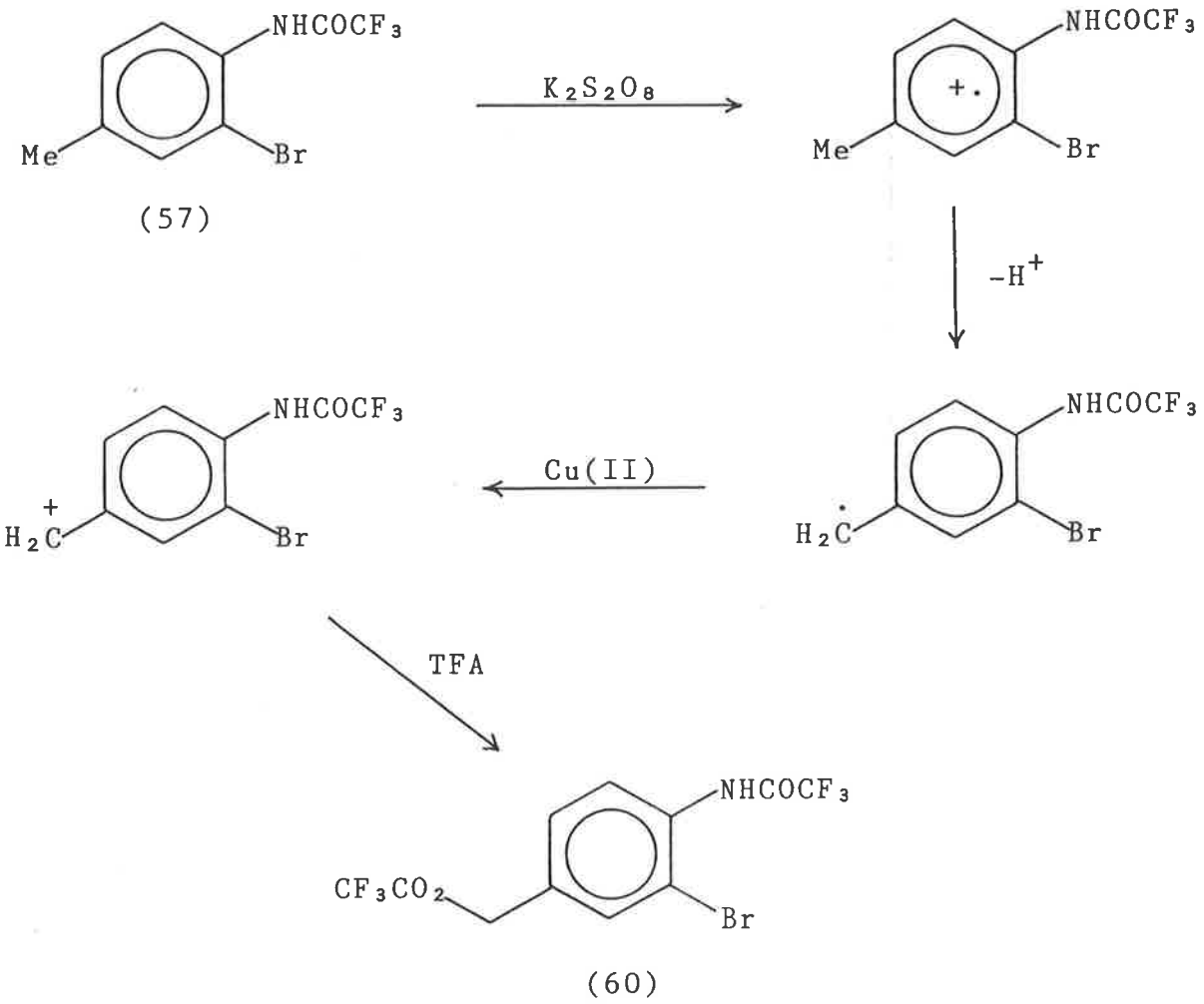
The reaction of the toluidide (57) with N-bromosuccinimide gave the benzyl bromide (58) in good yield, however the conditions for hydrolysis of the bromide to the alcohol (59) had to be chosen carefully. Basic media removed the trifluoroacetyl group and the free amino group then condensed with the unreacted benzyl bromide giving polymeric material. It was hoped that hydrolysis could be achieved using saturated sodium carbonate and tetrahydrofuran but these conditions were found to be too basic and led to decomposition of the starting material. Treatment of the benzyl bromide (58) with silver carbonate in wet acetone gave the alcohol (59) in 38% yield along with some more polar material. The yield of this reaction could not be improved and so a more efficient means of preparing the alcohol was sought (scheme 12).



Scheme 12

The bromide (58) could be converted to the trifluoroacetoxy compound (60) in high yield (92%) by stirring overnight with zinc trifluoroacetate[17], prepared *in situ* by dissolving zinc oxide in trifluoroacetic acid. The trifluoroacetate (60) could be hydrolysed to the alcohol (59) by treatment with potassium hydrogen carbonate in aqueous methanol. This procedure gave quantitative conversion within ten minutes.

Another route to the trifluoroacetoxy compound (60) involves direct oxidation of the toluidide (57) with potassium persulphate and copper(II) trifluoroacetate as shown in scheme 13. During the course of acetoxylation of toluenes it has been demonstrated[18,19] that only a catalytic amount of copper(II) is required to oxidise the benzyl radical as the copper(I) is



(57)

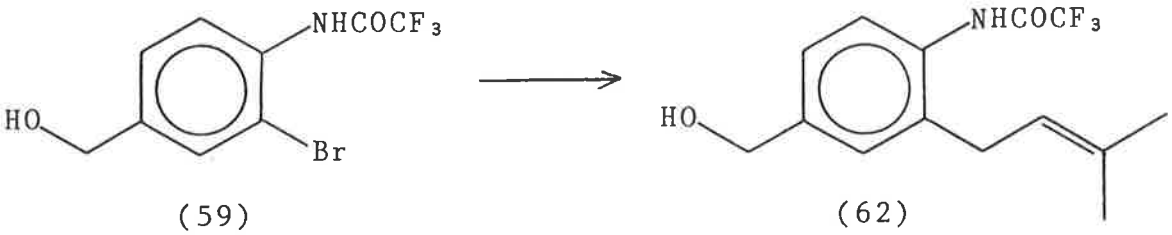
(60)

Scheme 13

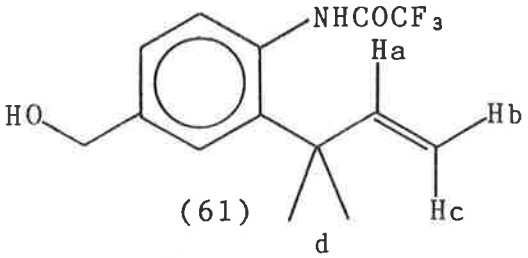
oxidised back to copper(II) by excess persulphate. However, the trifluoroacetoxylation of (57) was not catalytic with respect to copper(II) possibly due to the differences in the redox potentials of copper(I) trifluoroacetate and copper(I) acetate. Copper(I) trifluoroacetate presumably requires a stronger oxidising agent to convert it to copper(II) than does copper(I) acetate. In performing this reaction one equivalent of potassium persulphate and 1.2 equivalents of copper(II)

trifluoroacetate (prepared *in situ* from copper(II) carbonate) were used.

Having found an efficient path to the bromoalcohol (59) it was lithiated and converted to the organocopper species in exactly the same manner as for the corresponding pivalanilide (39). Reaction of the organocopper reagent with 3,3-dimethyl-allyl bromide at -78^0 gave a mixture of allylbenzenes (61) and (62) in the ratio of 3:7 respectively (scheme 14) which could not be separated by chromatography. The nmr spectrum of the mixture showed resonances due to (62) which were similar to the corresponding pivalanilide (46). The presence of (61) was inferred by a sharp singlet at δ 1.43 due to methyl groups on an sp^3 carbon atom, a doublet of doublets at 6.13 arising from the vinylic proton Ha (scheme 14) and a multiplet resonance for protons Hb and Hc occurring at 5.2.



(59) (62)



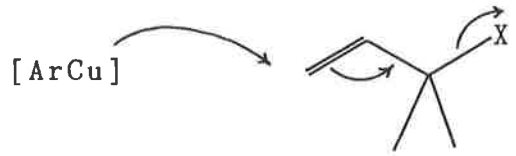
(61)

a δ 6.13, dd, *J* 10, 17 Hz

b,c δ 5.2, m

d δ 1.43, s

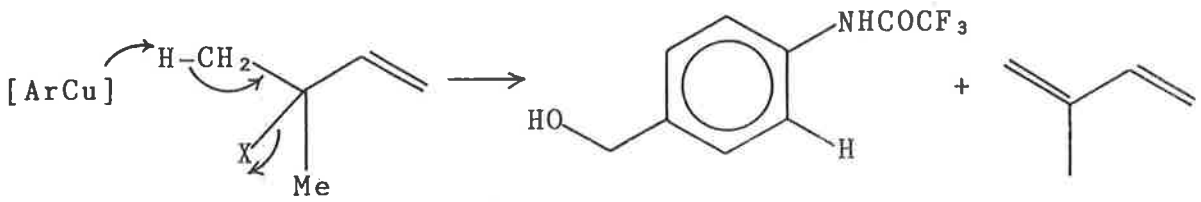
Scheme 14



(63) X=OAc

(64) X=$O_2C.pC_6H_4.NO_2$

The formation of (61) by an S_N2' attack of the organocopper species on the allyl halide was unfortunate in that pure (62) could not be obtained, but raised the question of whether (62) could be obtained by reaction of the arylcopper reagent with allyl systems of the type (63). It was hoped that this type of substrate would be less likely to undergo direct displacement (S_N2) as the halide is on a tertiary carbon atom but should allow ready S_N2' attack at the terminal methylene carbon atom[20]. Treatment of the arylcopper reagent with (63)[21a] resulted in protonation of the organometallic species leading to the formation of the reduced compound (65) (scheme 15). It was initially thought that the proton source may be

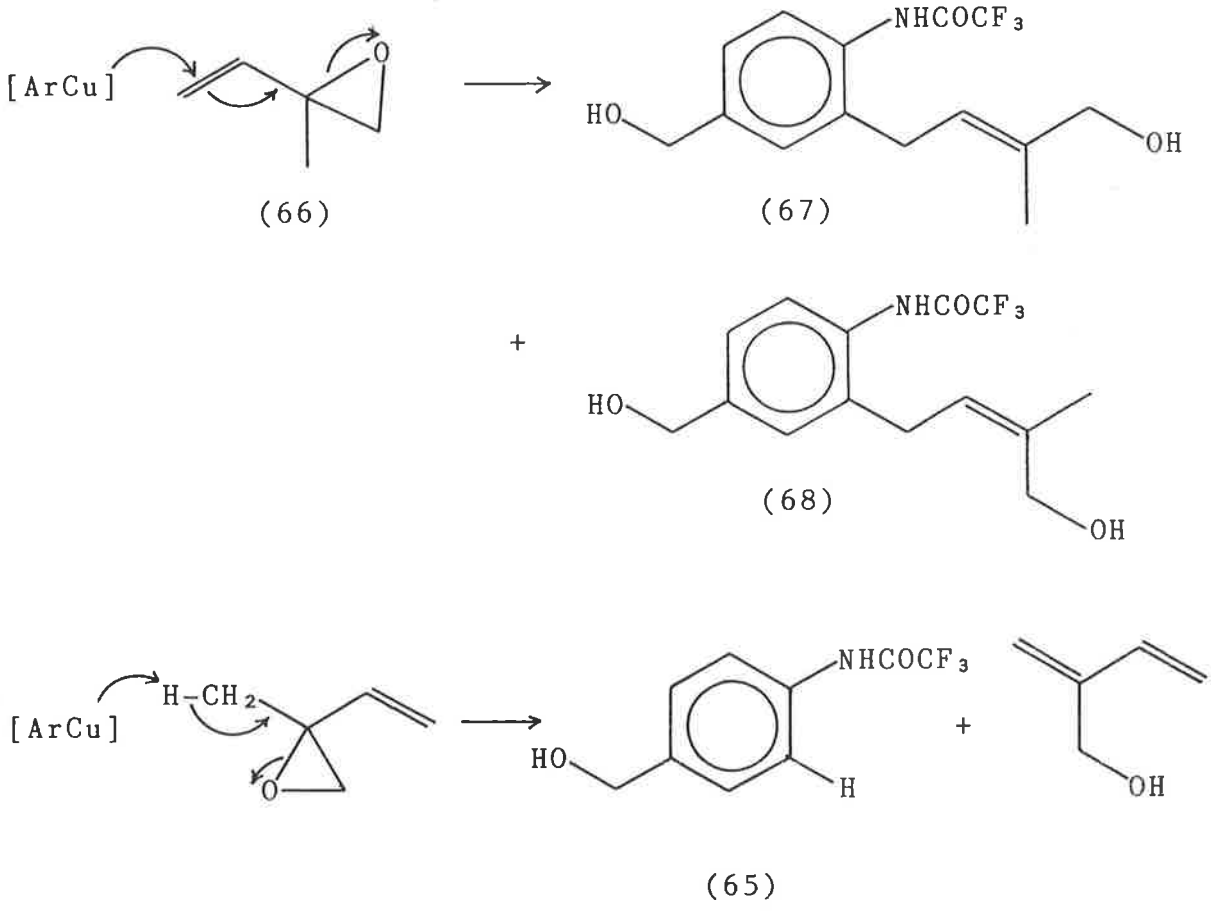


(65)

Scheme 15

the α-proton of the acetoxy group but similar results were obtained when (64)[21b] was used as the electrophile, suggesting that the allyl system was undergoing elimination to produce isoprene.

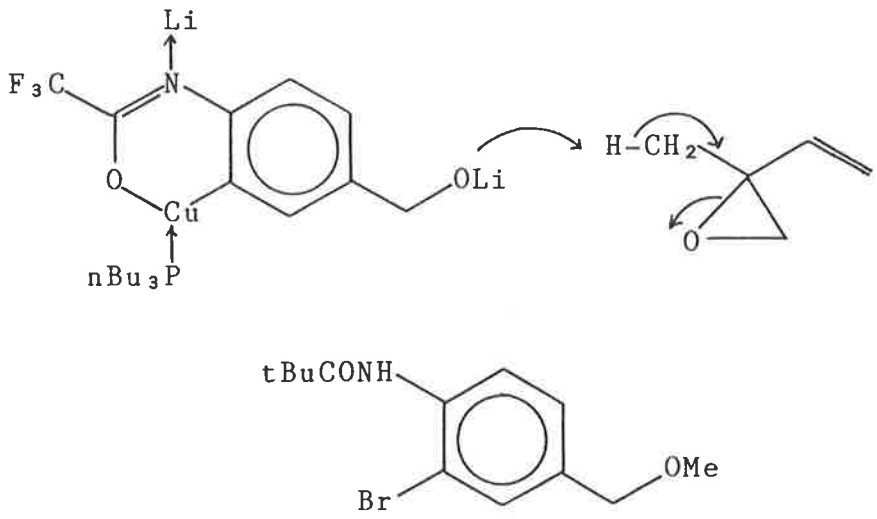
Isoprene oxide[21c] (66) was also considered as a potentially useful electrophile as reports[22,23] in the literature suggested that this might lead (scheme 16) to the hydroxyallylbenzenes (67) and (68) which would also serve as useful model compounds of (6) for the cyclisation studies. The reaction of the arylcopper species with the vinyloxirane (66)



Scheme 16

followed the same course as it did with the allylic esters (63),(64) that is, the organocopper reagent caused elimination in the vinyloxirane system (scheme 16) as indicated by the formation of the *protonated* material even when worked up with *deuterium* oxide.

Tamura[23] has shown that *n*-butyllithium reacts with isoprene oxide (66) through the S_N2' mechanism in 76% yield. It is therefore very surprising to find that the arylcopper reagent derived from (59) is so basic as to cause elimination whilst *n*-butyllithium does not. One possible explanation for this was that the alkoxide group in the organocopper reagent was acting as the base in the first instance, and promoting the elimination (scheme 17). However when the methyl ether (41) derived arylcopper reagent was treated with isoprene

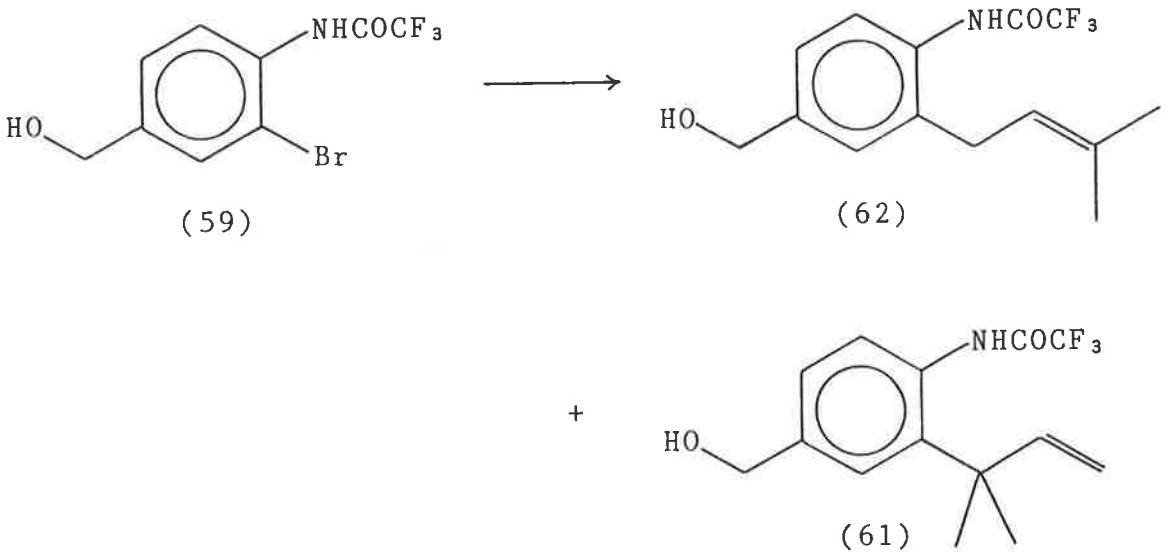


(41)

Scheme 17

oxide the result was again elimination of the vinyloxirane thus ruling out the possibility that the alkoxide was chiefly responsible for elimination.

Due to the lack of success using (63), (64) and (66) as electrophiles it was decided to further investigate the reaction of the organocopper reagent derived from (59) with 3,3-dimethylallyl bromide. When this reaction was carried out at -100^0 it was found that the ratio of (61) to (62) was even less favourable at 4:6 respectively. Reaction at higher



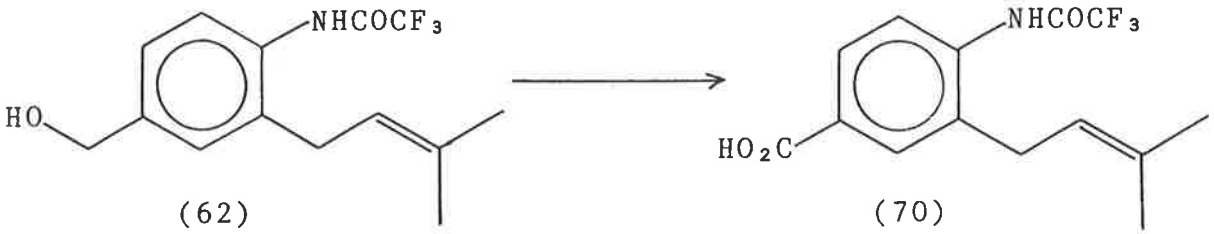
Scheme 14

temperature favoured the formation of (62) and at -50^0 the ratio was 1:9 (this temperature was optimum for the reaction). Above -40^0 isomerically pure allylbenzene (62) was formed but was accompanied by an unacceptable amount (20%) of the reduced compound (65) arising from adventitious proton sources. Iso-

merically pure (62) was best obtained from reaction at -50^0 followed by recrystallisation from dichloromethane / light petroleum.

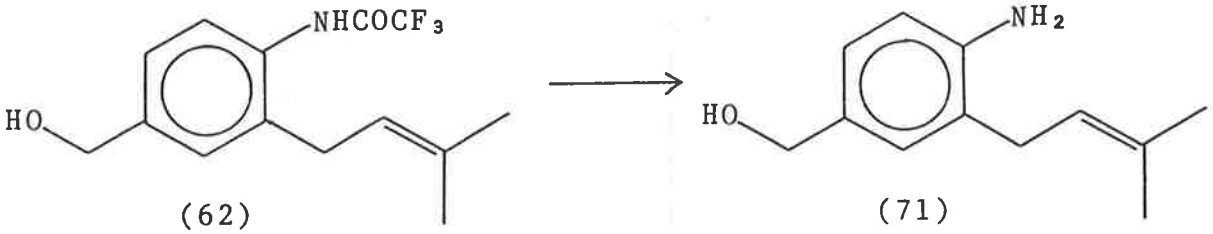
The oxidation of the benzyl alcohols (59) and (62) proved to be much easier than that of the corresponding pivalanilides (39) and (46). The bromoalcohol (59) was rapidly oxidised to the carboxylic acid (69) with Jones reagent in less than two minutes whilst similar treatment of the allylbenzene (62) resulted in complete oxidation to the corresponding acid (70) after twenty five minutes.

(59) (69)

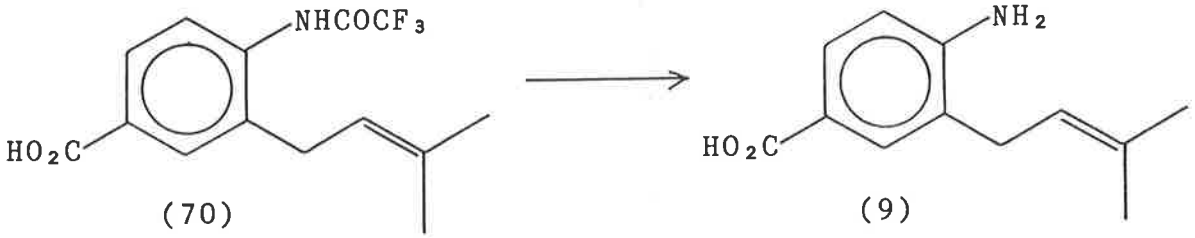


(62) (70)

The amides (62) and (70) were hydrolysed to the free amines (71) and (9) by refluxing for one hour in 10% methanolic potassium hydroxide.



(62) (71)

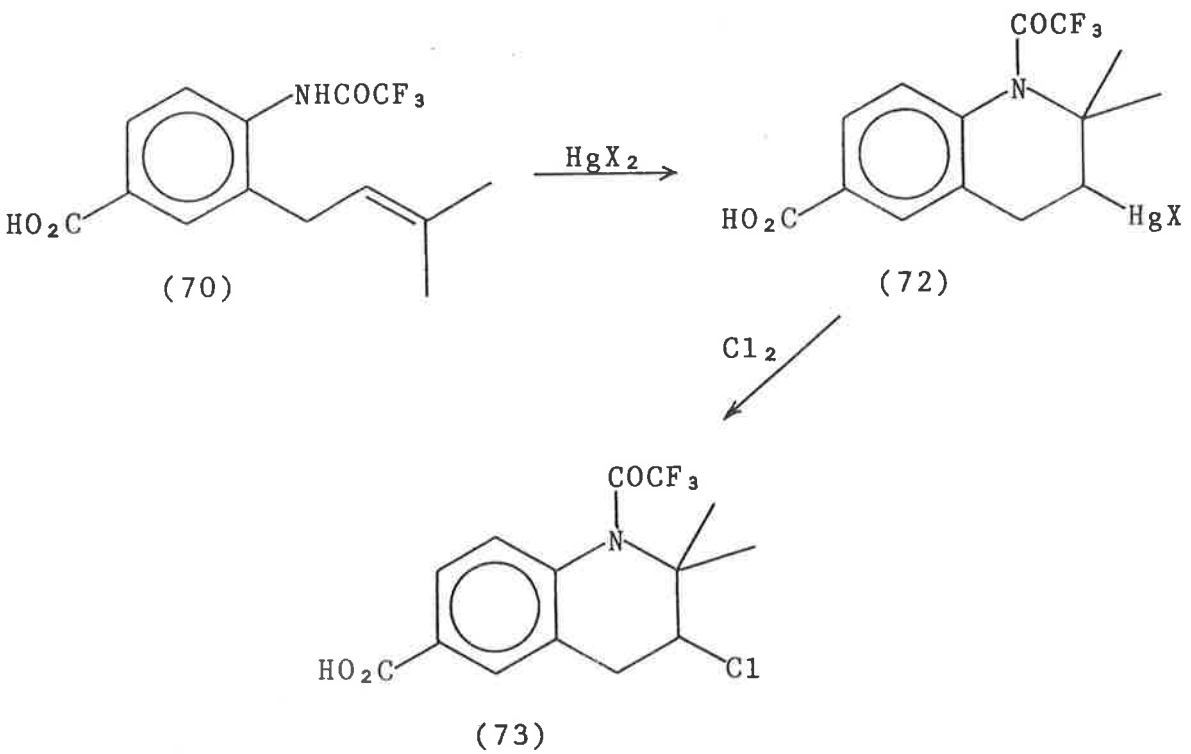


(70) (9)

Having established a route to the desired 4-substituted allylanilines and anilides, a study of electrophile promoted cyclisation could now be undertaken.

Chapter 2.

The initial studies of the cyclisation process were carried out using the amidoacid (70) as it was more convenient to prepare and handle than the less stable aminoacid (9). It was expected that (73) could be formed by amidomercuration[24,25] of (70) followed by halogenation[26,27] of the resulting organomercurial (scheme 18).



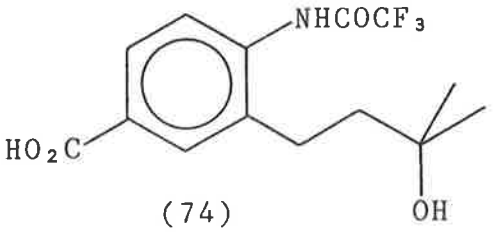
(70) (72) (73)

Scheme 18

When the amidoacid (70) was stirred with one equivalent of mercuric chloride in tetrahydrofuran at room temperature, no reaction occurred and workup with alkaline sodium boro-

hydride returned the amidoacid almost quantitatively as evidenced by nmr spectroscopy which showed the vinyl proton and the adjacent methylene protons. Neither mercuric acetate nor mercuric chloride gave any mercurated products when the reaction mixture was heated to reflux. In order to understand the failure of this reaction, a study of the oxymercuration reaction was undertaken.

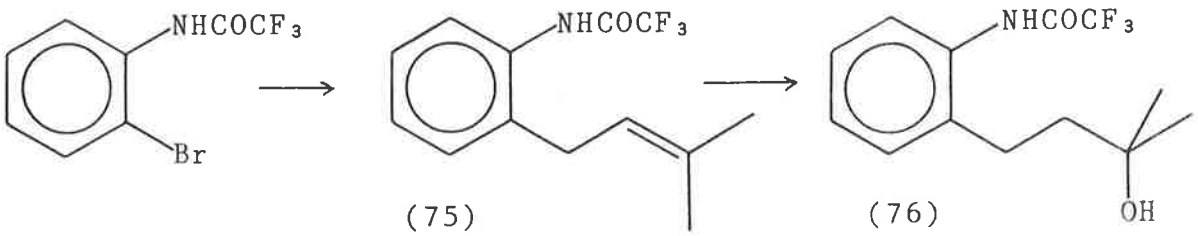
The amidoacid (70) could be smoothly oxymercurated at room temperature by stirring with two equivalents of mercuric acetate in aqueous tetrahydrofuran. Reductive workup with alkaline sodium borohydride gave the hydroxy compound (74) whose structure was confirmed by the upfield shift of the geminal dimethyl resonance to δ 1.08 and the appearance of two mutually coupled triplets at δ 1.75 and 2.72. When this reac-



(74)

tion was carried out using only one equivalent of mercuric acetate, no oxymercurated product was formed and the starting material was recovered quantitatively. The requirement for two equivalents of mercuric acetate suggests that the first equivalent of the mercury complexes to the molecule at a site other than the double bond. Therefore a second equivalent of

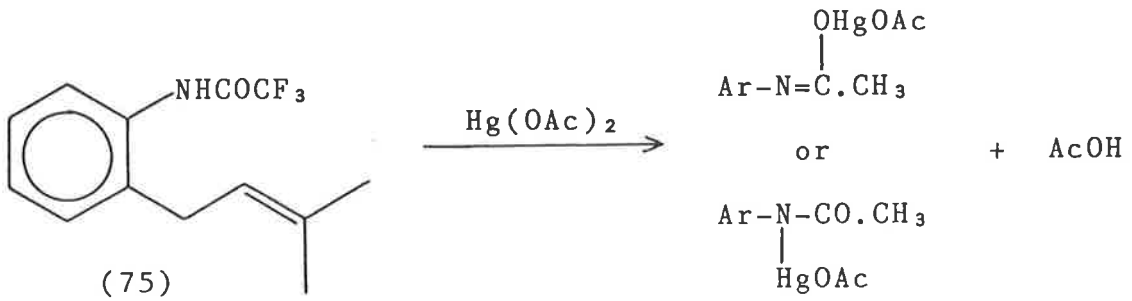
mercury is required in order for the double bond to mercurate and yield products. The other possible sites for mercury complexation within the molecule are the carboxyl group and the amide moiety. Bearing this in mind, the cyclisation reaction was again attempted by refluxing (70) with excess (three equivalents) mercuric acetate in dry tetrahydrofuran. However, only the starting material was recovered after reductive workup with alkaline sodium borohydride. It was then considered that the cyclisation reaction may have failed due to electronic reasons. The presence of the carboxyl group may have withdrawn so much electron density from the nitrogen atom as to leave it insufficiently nucleophilic to undergo cyclisation. If this carboxyl moiety was absent from the molecule then the cyclisation reaction may proceed and so attention was turned to the amide (75).



(75) (76)

The amide (75) was prepared, from *ortho*-bromotrifluoroacetanilide[28], by the same procedure as that used to prepare the allylbenzene (62). Unfortunately, the amide (75) failed to cyclise when refluxed with excess mercuric acetate in dry tetrahydrofuran. Amide (75) underwent oxymercuration with two equivalents of mercuric acetate in aqueous tetra-

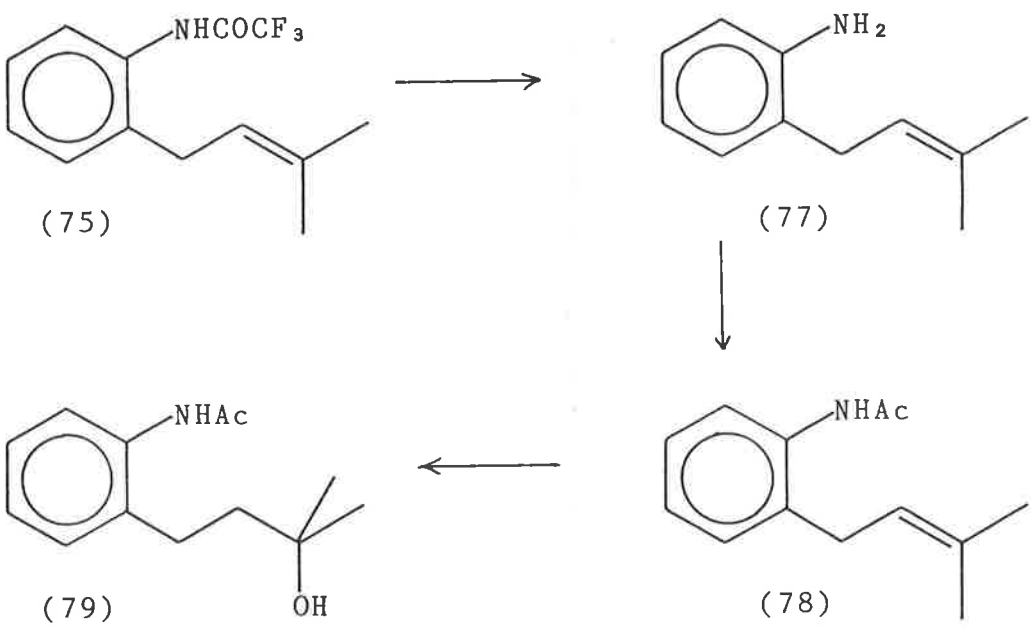
hydrofuran to give (76), the nmr spectum of which was similar to that of (74). However, treatment of (75) with one equivalent of mercuric acetate under the same conditions gave no oxymercurated product. This suggests that the first equivalent of mercury complexes not to the double bond but to the amide moiety and this would both sterically and electronically hinder cyclisation.



(75)

In order to try and prevent the complexation of mercury to the amide moiety, attention was turned to the acetamide (78). The acidity of the amide (NH) proton of the acetamide would be less than that of the corresponding trifluoroacetamide, and so (78) would be presumably less likely to form a mercuric amide salt.

The trifluoroacetamide (75) was hydrolysed using 10% methanolic potassium hydroxide at reflux. This procedure gave the aniline (77) which was acetylated using acetyl chloride/ pyridine in dichloromethane. The acetamide (78) was stirred with one equivalent of mercuric acetate in aqueous tetrahydrofuran at room temperature and was then worked up with alkaline

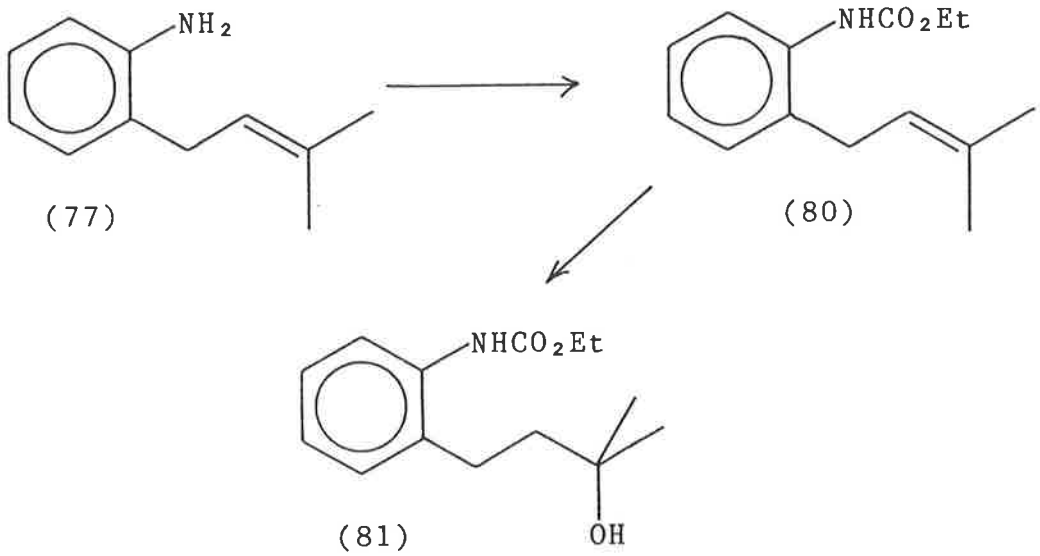


(75) (77) (78) (79)

sodium borohydride. This gave the hydroxyamide (79) as evidenced by nmr which showed an upfield shift for the geminal dimethyl resonances and two mutually coupled triplets corresponding to the adjacent methylenes. The observation that only one equivalent of mercuric acetate was required shows that the amide moiety of (78) does not complex to mercury. It was unfortunate that despite this fact, the treatment of the acetamide even with excess mercuric acetate in refluxing tetrahydrofuran failed to produce any cyclised material. It appears that the acetamide is simply not nucleophilic enough to undergo cyclisation.

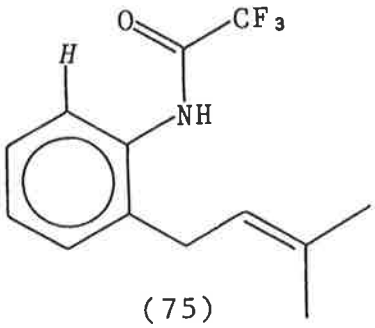
Our interest was then directed towards the carbamate (80) as there was literature precedence[25,29] for carbamates participating as nucleophiles in mercuration reactions.

The carbamate was prepared from the aniline (77) by treatment with ethyl chloroformate/pyridine in dichloromethane. The carbamate behaved similarly to the acetamide (78), undergoing oxymercuration with only one equivalent of mercuric acetate but alas failing to participate in the cyclisation reaction.



(77) (80) (81)

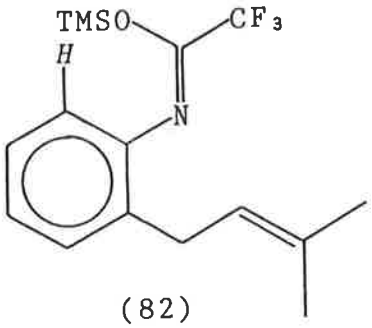
It was thought that the electron density on the amide nitrogen atom could be increased by preparing the silylamide (82). This was done by stirring the amide (75) with N,O-*bis*-(trimethylsilyl)acetamide in dichloromethane. The decrease in the carbonyl stretching frequency from 1740 to 1690 cm^{-1} indicated that silylation occurred on the oxygen atom to give the thermodynamically more stable product[30]. Further evidence for silylation on oxygen is the upfield shift of the *ortho* proton resonance from δ 7.92 to *ca.* 7.1, indicating that this proton is no longer being influenced by a carbonyl group. However,



(75)

ν_{max} 1740 cm^{-1}

δ_H 7.92



(82)

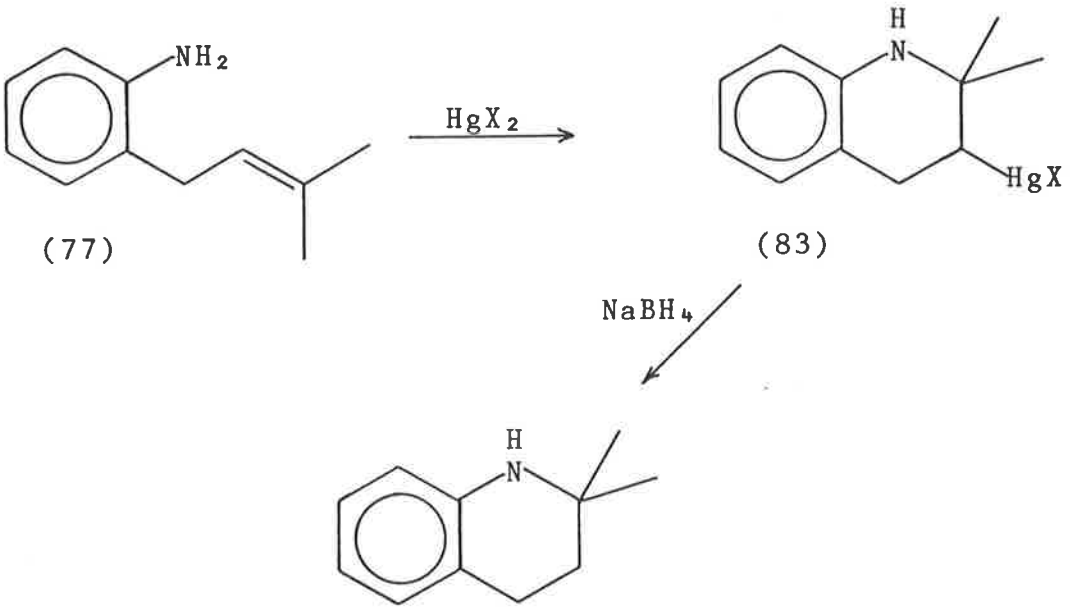
ν_{max} 1690 cm^{-1}

δ_H 7.1, m, 4H

when this silylamide was stirred with mercuric acetate in tetrahydrofuran at room temperature no cyclisation occurred and reductive workup with alkaline sodium borohydride gave only the desilylated starting material (75) as indicated by nmr spectroscopy. It is uncertain whether desilylation ocurred *in situ* or upon workup.

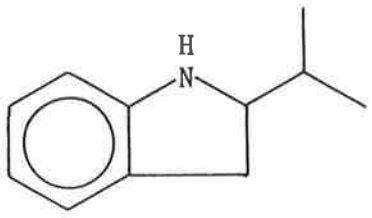
Having had little success with the cyclisation of the amide derivatives of (77), attention was turned to the free amine. The more nucleophilic amine was expected to be more likely to cyclise and (77) served as a suitable model for aminoacid (9) which was less tractable.

Treatment of the allylaniline with one equivalent of mercuric acetate in tetrahydrofuran at room temperature for fifteen minutes followed by reduction with alkaline borohydride gave a mixture of the known tetrahydroquinoline[31] (84) and the starting material (77) in the ratio 1:1 as assessed by the nmr integration of the mixture. The identity of the



(77) (83) (84)

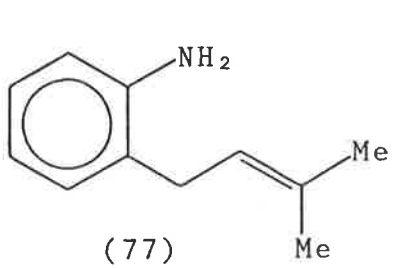
tetrahydroquinoline (84) was confirmed by the singlet resonance at δ 1.15 due to the geminal dimethyl groups and the appearance of two mutually coupled triplets at δ 2.72 and 1.63 arising from adjacent methylene groups in the heterocyclic ring. This data rules out the alternative (anti-Markownikoff) dihydroindole structure (85).



(85)

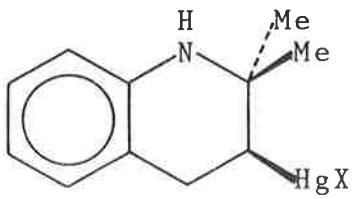
However, when the aminomercuration reaction time was extended to one hour, analysis of the crude reduction products

by nmr spectroscopy and tlc showed that the cyclisation was still incomplete and there was a considerable amount of very polar material arising from the decomposition of the organomercurial. An investigation of the aminomercuration reaction was undertaken by following the reaction of (77) with various mercuric salts, in d^6-acetone, by nmr spectroscopy. Reaction with one equivalent of mercuric acetate resulted in the gradual disappearance of the starting material dimethyl resonances at δ 1.71 and the appearance of two methyl resonances at δ 1.35 and 1.23 (figure 6). By following the course of the



(77)

δ_{Me} 1.71, br s



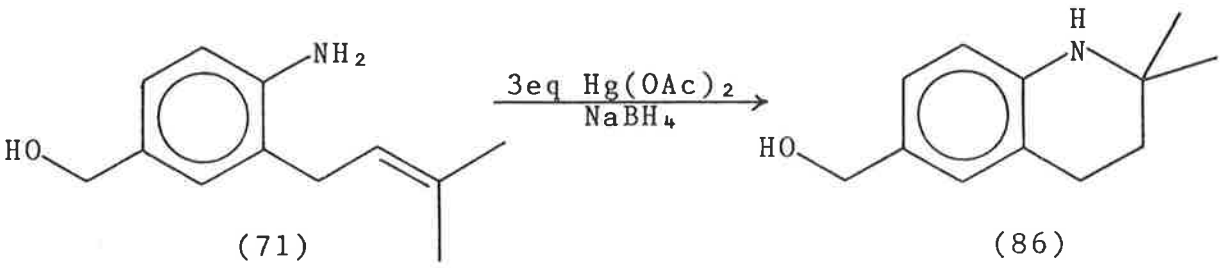
(83)

δ_{Me} 1.35, 1.23, both s

Figure 6

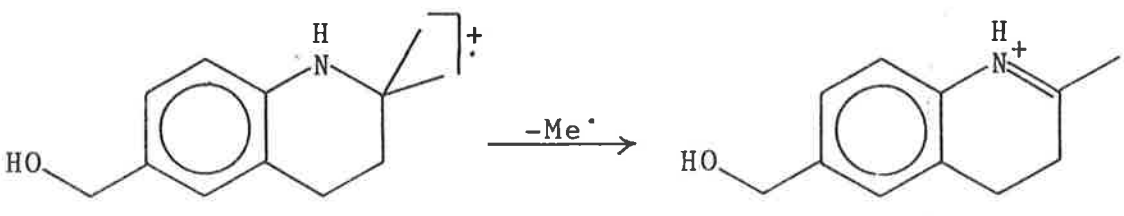
reaction in this manner it could be seen that after fifteen minutes, the extent of decomposition of the mercurated product (83) was significant even though the cyclisation was still incomplete. Reaction of (77) with one equivalent of mercuric chloride resulted in a considerably slower reaction and even after seven hours there was still 50% of the starting material remaining. Mercuric nitrate failed to give any cyclised material, possibly due to complexation with the amino group.

It was found that by using three equivalents of mercuric acetate, the rate of formation of the organomercurial (83) could be increased. In this manner, complete cyclisation was achieved in ten minutes and before any significant amount of decomposition of the organomercurial (83) was observed. When the reaction was carried out on a larger scale, reductive workup with alkaline borohydride gave an 88% yield of (84). In a similar fashion, treatment of the allylaniline (71) with three equivalents of mercuric acetate in methanol gave a 90% yield of the corresponding tetrahydroquinoline (86). The nmr



(71) (86)

spectrum of this compound showed a singlet resonance at δ 1.16 due to the geminal dimethyl groups and two mutually coupled triplets at δ 1.63 and 2.71 arising from adjacent methylene groups in the heterocyclic ring. The mass spectrum had the

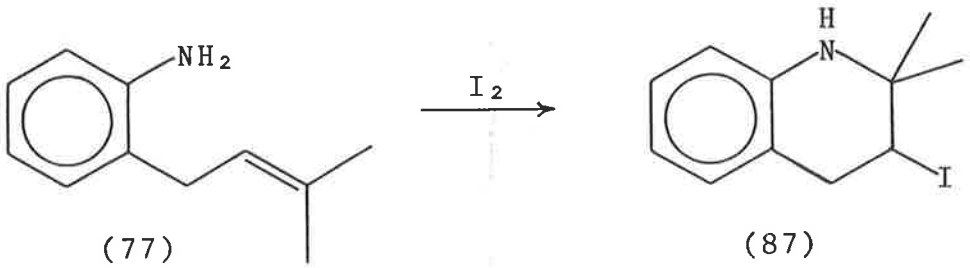


M^+ $M^+-Me\cdot$

molecular ion at *m/e* 191 and also showed the loss of a methyl radical thus supporting the tetrahydroquinoline structure.

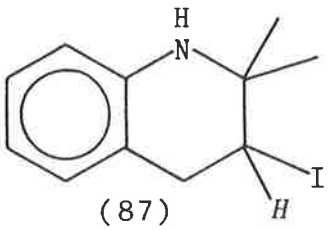
Having successfully cyclised the allylanilines, it was of importance to investigate the halogenation[26,27] of the organomercurials. Due to the instability of these intermediates, isolation was impractical and the halogen had to be introduced directly into the crude reaction mixture. When the organomercurial derived from (77) was treated with one equivalent of chlorine in carbon tetrachloride under irradiation, only a dark intractable mixture was obtained as was evidenced by nmr spectroscopy and tlc. Attempted bromination and iodination were found to be no more productive.

Attention was then directed to the assessment of other electrophiles which would provide routes to the desired halotetrahydroquinolines. One such electrophile was iodine and it was anticipated that this would complex to the alkene sidechain of a suitable allylaniline causing cyclisation in the Markownikoff sense.

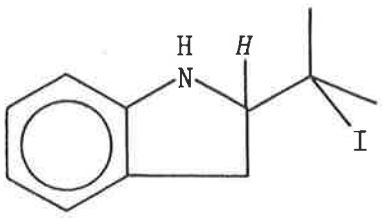


(77) (87)

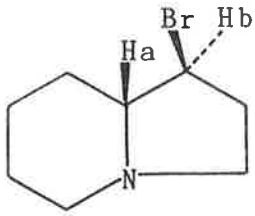
The allylaniline (77) was stirred with iodine and sodium carbonate in dichloromethane for four hours during which time the iodine colour of the reaction faded. Analysis of the product by nmr spectroscopy showed a singlet resonance at δ 1.35 due to the geminal dimethyl group, a broad doublet at δ 3.47 due to the benzylic methylene and a doublet of doublets at δ 4.38 arising from the methine proton next to iodine being coupled to the nonequivalent benzylic protons. It was expected that the methyl groups would be magnetically nonequivalent but this was not the case (nor is it so with the parent allylaniline). The chemical shift of δ 4.38 for the methine proton suggests that the product is the tetrahydroquinoline (87) rather than the dihydroindole (88) (figure 7) as the latter would be expected to have the methine resonance further upfield (as in the compound[24] (89)).



(87)



(88)



(89)

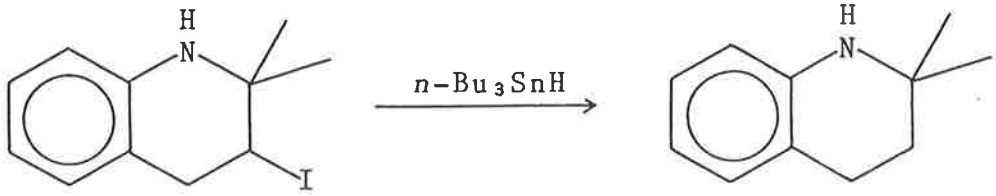
a δ 3.75

b δ 4.38

Figure 7

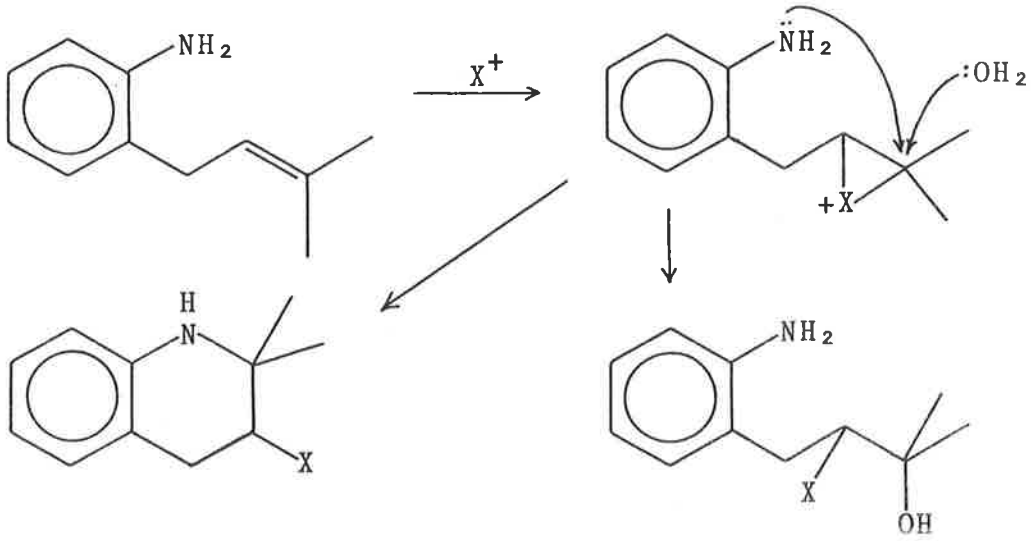
Chemical evidence for the assignment of structure (87) comes from the reduction of the iodinated product. When the iodide was refluxed with tri-*n*-butylstannane in benzene under

irradiation, the single product was the known tetrahydroquinoline[31] (84) thus showing the cyclisation to have occurred in the Markownikoff sense.



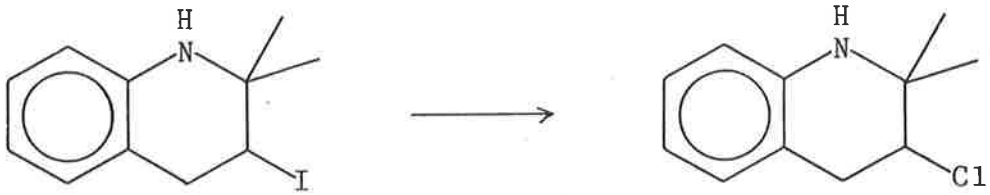
(87) (84)

The possibility of using chlorine or bromine as electrophiles was also briefly investigated. However, treatment of (77) even with a low concentration of these halogens led to a complex mixture of aromatic ring halogenated products as well as dihalides arising from simple addition of the halogen to the alkene sidechain, as was found by nmr spectroscopy and tlc.



Scheme 19

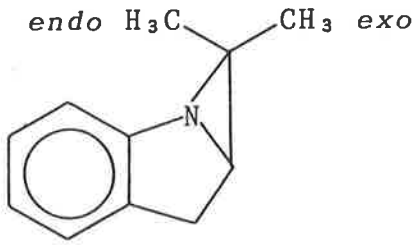
Conditions that were conducive to halohydrin formation were considered as intramolecular cyclisation should be favoured over intermolecular attack by water (scheme 19). Precedence for this idea was the fact that aminomercuration reactions could be carried out in methanol or aqueous acetone without solvent participation. Unfortunately, treatment of (77) with either N-bromosuccinimide or N-chloroacetamide in aqueous tetrahydrofuran led to a complex product mixture which included aromatic ring halogenated material. It was therefore considered that the best way to prepare the chloride (90) might be by nucleophilic substitution of the iodide (87).



(87) (90)

The iodide was heated to 50^0 with lithium chloride in dimethyl sulphoxide but no substitution occurred even over prolonged periods of time. Since the iodide did not undergo substitution by direct displacement, it was decided to abstract the iodide ion by the use of a silver salt. The iodide (87) was stirred with silver chloride in acetone however the product was not the expected chloride (90) but the aziridine (91) arising from intramolecular substitution. The aziridine was identified by the very different chemical shifts of the

two methyl groups indicating quite different environments (figure 8), and the upfield shift of the methine resonance to δ 2.75. The ^{13}C nmr spectrum showed a methine carbon at



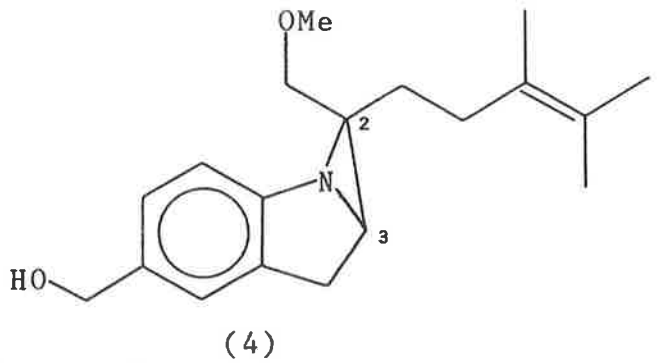
(91)

endo δ_H 0.73; δ_C 12.7

exo δ_H 1.30; δ_C 26.8

Figure 8

δ 51.9 and a quaternary carbon at δ 44.7 both being consistent with aziridine ring carbons. The lithium aluminium hydride reduction product[2] (4) of virantmycin shows similar resonances (figure 9).



(4)

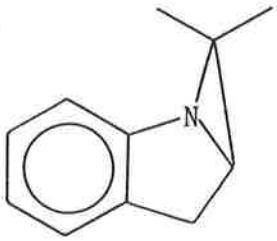
C-2 δ_C 49.8

C-3 δ_C 50.1

Figure 9

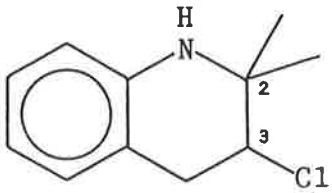
It was found that the most convenient way to prepare the aziridine was to treat the iodide with one equivalent of sodium hydride in tetrahydrofuran at 0^0. This procedure was better as it was more rapid and gave a cleaner product.

Having obtained the aziridine, it was of interest to see if it could be converted to the chloride (90). The aziridine was dissolved in dichloromethane and was treated with gaseous hydrogen chloride at room temperature. This gave rise to two products as was shown by hplc. The components could not be



(91)

HCl



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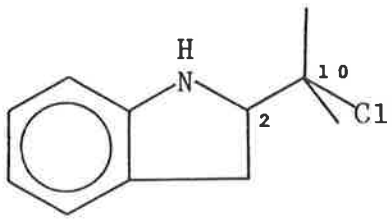


(90)

C-2 δ 53.1, s

C-3 δ 61.7, d

(92)

C-2 δ 45.6, d

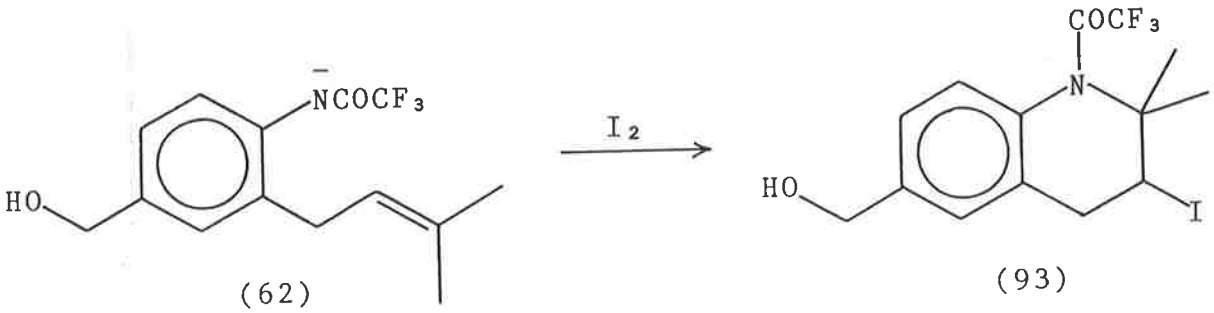
C-10 δ 62.7, s

(Virantmycin has C-2 δ 58.0; C-3 δ 56.2)

separated by preparative chromatography but the ^{13}C nmr spectrum of the mixture showed resonances which could be assigned to the structures (90) and (92). Accurate mass measurement on the molecular ion also verified the formula of the products.

The iodination and aziridine chemistry seemed very useful methods to prepare halotetrahydroquinolines but these procedures were found to be incompatible with the 4-substituted aniline (71). When this compound was stirred with iodine and sodium carbonate in dichloromethane it underwent decomposition giving rise to very polar material as shown by tlc and analysis by nmr spectroscopy. The decomposition probably arises due to the formation of hydroiodic acid as a byproduct of the reaction. This presumably converts the benzylic alcohol to an iodide which would then react with the amine thus undergoing undesirable condensation reactions. The reaction was attempted using triethylamine as a buffer and also aqueous sodium carbonate as a two phase system but decomposition was still observed.

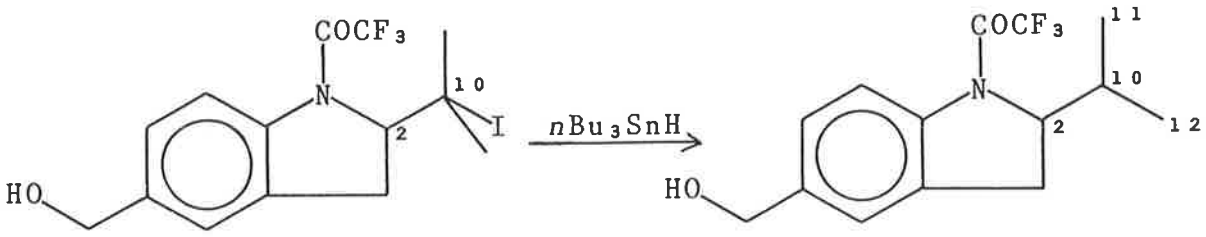
An alternative procedure was required for the cyclisation of the acid sensitive hydroxyamine (71) and so the possibility of cyclising the amide anion of (62) was considered. In this manner, the problem of acid promoted decomposition might be alleviated.



(62) (93)

The allylbenzene (62) was treated with one equivalent of sodium hydride in tetrahydrofuran and the anion thus formed was stirred overnight with excess iodine. The ^{1}H nmr spectrum of the product revealed that the cyclisation had occurred as the vinyl proton resonance had disappeared, the geminal dimethyl groups resonated individually as two singlets at δ 2.07 and 1.53, and a doublet of doublets at δ 5.17 had arisen which was due to a heteroatom-bearing methine proton adjacent to the benzylic protons. However the methine resonance in the ^{13}C nmr occurred at δ 71.8 which was too high[32] for a carbon bearing iodine and was therefore bonded to the acylamino group. Furthermore the carbon bearing iodine resonated at δ 50.9 as a singlet indicating that this carbon was quaternary and hence the cyclised material was the dihydroindole (94).

This assignment was confirmed by the tri-*n*-butylstannane reduction of (94) to give the hydrocarbon (95) whose structure was assigned by ^{1}H nmr spectoscopy. The nonequivalent methyl groups of the *iso*propyl moiety each resonated as a doublet at δ 0.97 and 0.63 being coupled to a multiplet at δ



(94)

C-2 δ_C 71.8, d

C-10 δ_C 50.9, s

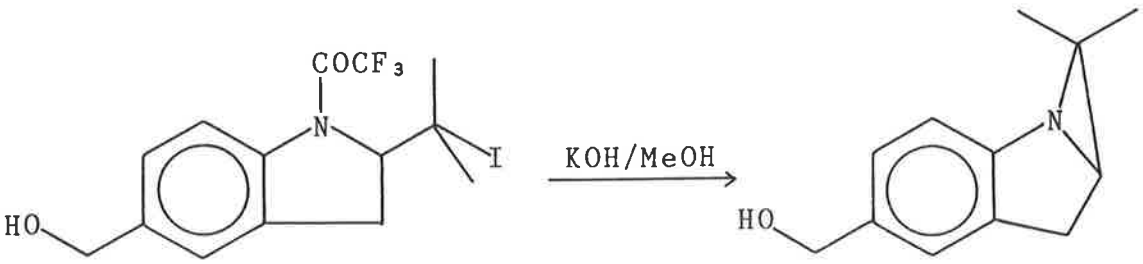
(95)

C-2 δ_H 3.1, m

C-10 δ_H 1.2, m

C-11, 12 δ_H 0.97, 0.63, both d, J 7 Hz

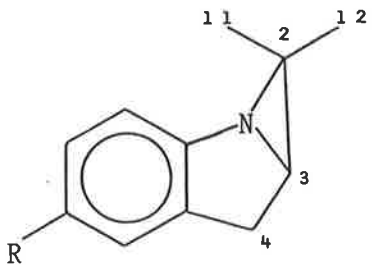
1.2 due to the proton at C-10. The methine proton at C-2 resonated as a multiplet at δ 3.1 which was coupled to the benzylic methylene protons and the proton at C-10. This spectral data is compatible with structure (95) and is quite different to that of tetrahydroquinoline (84).



(94) (96)

Despite the opposite regiochemistry of cyclisation, the iodine induced cyclisation of the amide anion was found to be useful as (94) could be readily converted to an aziridine. Treatment of the iodide (94) with 10% methanolic potassium

hydroxide gave the aziridine (96) in quantitative yield after fifteen minutes. The amide first hydrolyses and then the base causes deprotonation of the unusually acidic amine which undergoes an internal nucleophilic substitution reaction to give the aziridine. The spectral data for (96) was consistent with that of aziridine (91) as is shown in table 2.



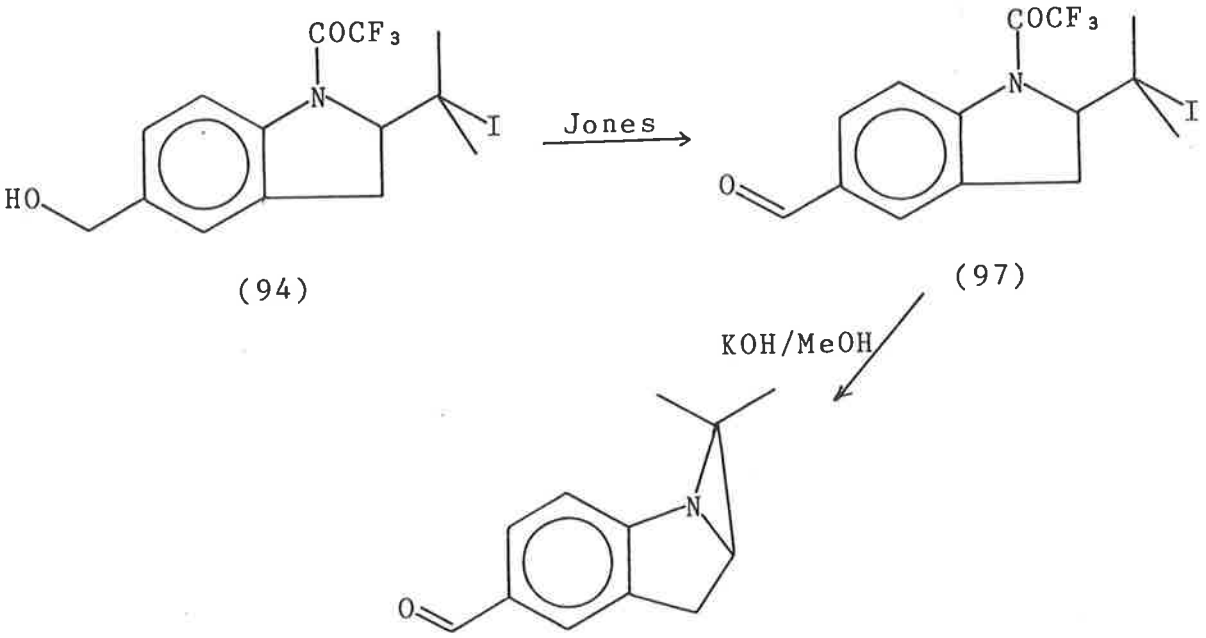
Nmr Data.

		R=H	$R=CH_2OH$	R=CHO
C-2	δ_C	44.7	44.5	40.9
C-3	δ_C	51.9	51.9	53.2
	δ_H	2.75	2.75	2.83
C-4	δ_C	30.2	30.3	30.0
	δ_H	3.4	3.1	3.3
C-11	δ_C	12.7	12.9	13.1
	δ_H	0.73	0.73	0.84
C-12	δ_C	26.8	26.8	27.0
	δ_H	1.30	1.30	1.40

Table 2

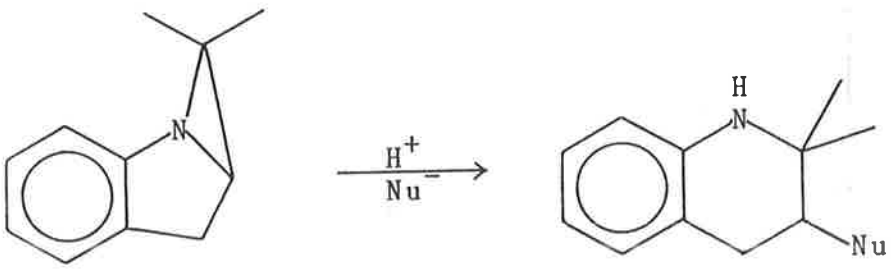
The aldehyde-aziridine (98) could also be prepared by this procedure. Oxidation of the iodobenzyl alcohol (94) with

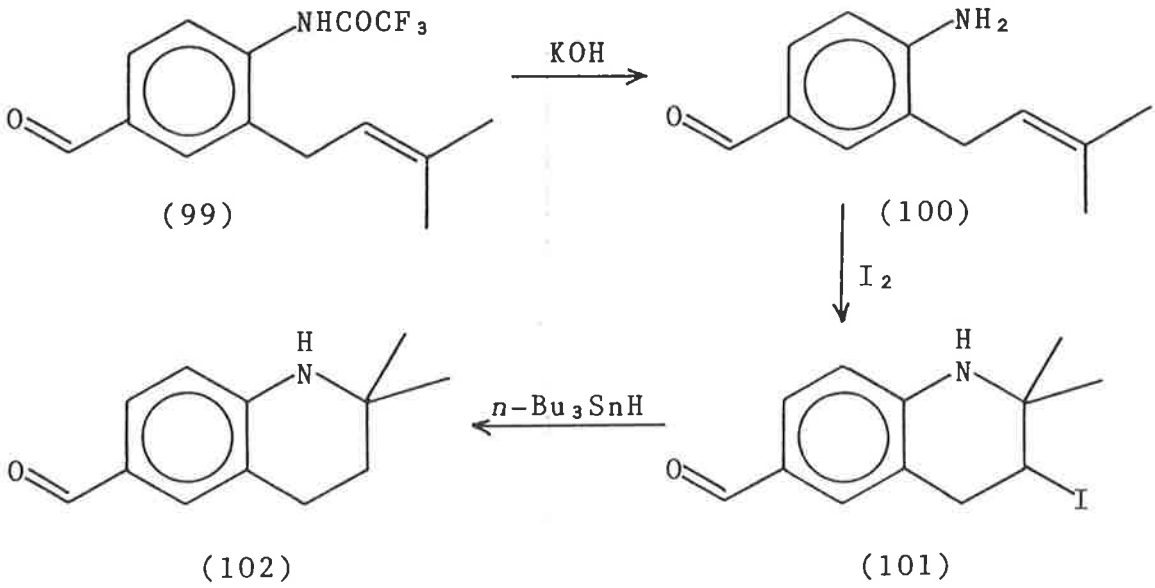
Jones reagent yielded the iodoaldehyde (97) which could then be converted to (98). This aziridine also had spectral data similar to that of (91) and (96) (see table 2).



(94) (97) (98)

The establishment of a route to aziridines such as (91), (96) and (98) was important as these compounds may serve as useful precursors to virantmycin analogues due to their ability to add nucleophiles under acidic conditions, as was suggested by the reaction of (91) with hydrogen chloride.



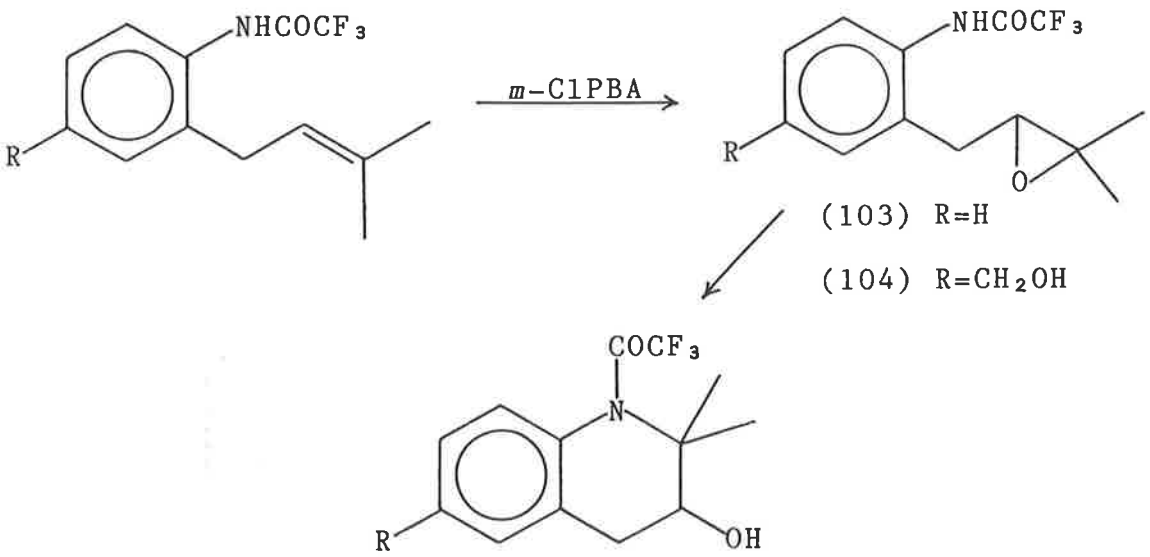


Since neither the aminoalcohol (71) nor its amide derivative (62) could be cyclised to an iodotetrahydroquinoline, it was of importance to find a 4-substituted amino compound which could be cyclised to give a six membered ring. The cyclisation of aminoaldehyde (100) with iodine might provide a possible route to the iodo-analogue of virantmycin. Aminoaldehyde (100) could be prepared by rapid treatment of (62) with Jones reagent to give the amidoaldehyde (99) which was hydrolysed to the free amine. This compound was more suitable for cyclisation than the aminoacid (9) as it was more tractable.

Although the aminoalcohol (71) could not be cyclised by stirring with iodine, the aminoaldehyde (100) was not too sensitive to the hydroiodic acid formed and thus yielded the iodotetrahydroquinoline (101). This compound had a doublet of doublets at δ 4.37 due to the methine proton next to the iodine atom and a singlet at δ 1.41 arising from the geminal

dimethyl group. The regiochemistry of the product was revealed by reduction with tri-*n*-butylstannane to give (102). The nmr spectrum of this compound was similar to that of (84); two mutually coupled triplets were seen at δ 2.75 and 1.68 arising from two adjacent methylene groups and the geminal dimethyl group resonated as a singlet at δ 1.05.

Another method of cyclisation considered was the ring closure of epoxides such as (103). It has been recently reported[33] that under acid catalysis, nucleophiles add to the more substituted carbon atom of epoxides in a concerted fashion. In this manner, treatment of the epoxides with boron trifluoride might be expected to produce tetrahydroquinolines such as (105). These compounds might then be converted to chlorides and hence to virantmycin.



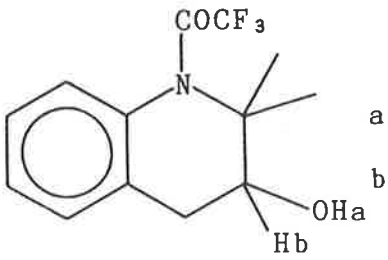
(103) R=H

(104) R=CH_2OH

(105) R=H

(106) R=CH_2OH

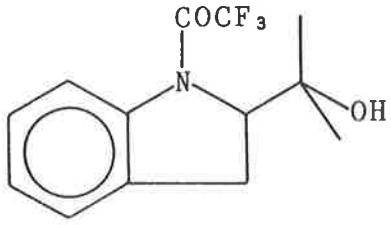
The allylbenzenes (62) and (75) were epoxidised by stirring with *meta*-chloroperbenzoic acid in dichloromethane. This procedure gave the epoxides (103) and (104) the nmr spectra of which had two singlet resonances due to the nonequivalent methyl groups on the epoxide ring and a three proton multiplet arising from the benzylic methylene and the epoxide ring proton.



a δ 5.55, d, *J* 4 Hz

b δ 3.85, m

(105)

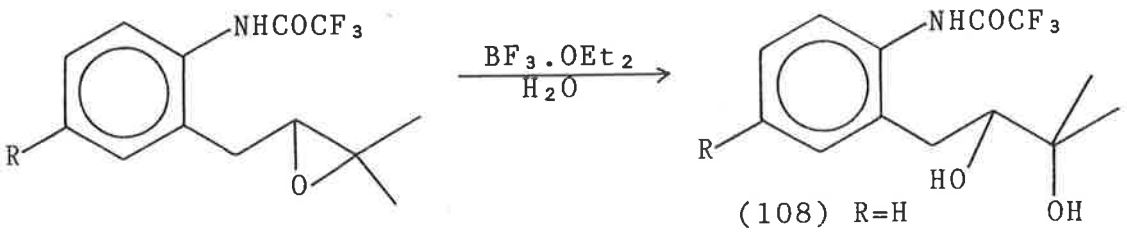


(107)

Figure 10

Treatment of these epoxides with excess boron trifluoride in ether gave crystalline solids with the following spectral data. The mass spectrum of the product derived from (103) had a peak at *m/e* 273 corresponding to the molecular ion of (105). The nmr spectrum of this material showed two singlet resonances at δ 1.30 and 1.57 due to nonequivalent methyl groups and a doublet arising from the benzylic methylene group. In deuterochloroform the methine resonance appeared as a triplet at δ 3.68 however this shift is compatible with both possible structures (105) and (107) as the chemical shift arising from a hydroxyl group is comparable to that from an acylamino group. However the spectrum in d^6-acetone showed additional

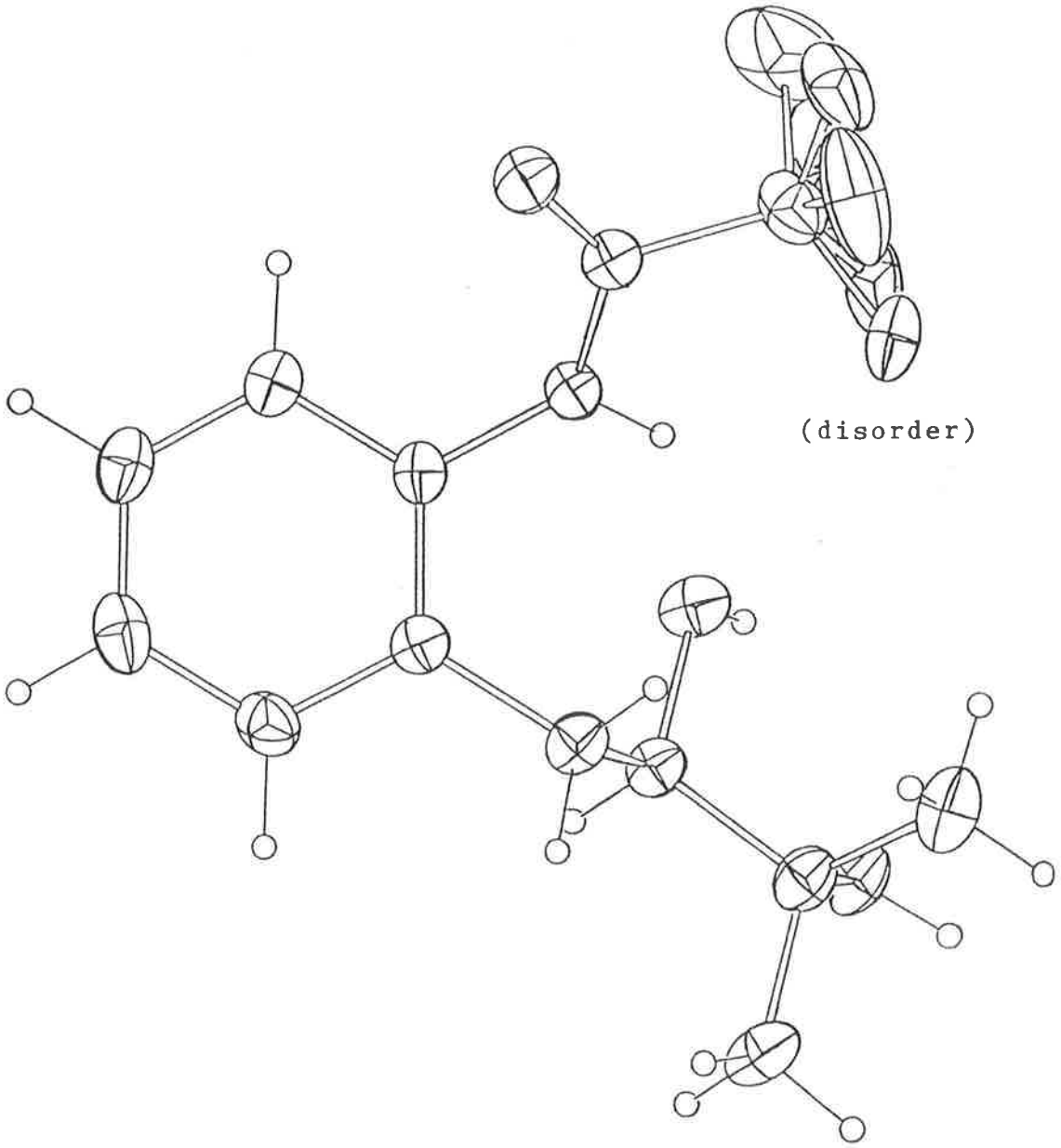
coupling of the hydroxyl proton to the methine resonance. This observation suggested that the product was the desired tetrahydroquinoline (figure 10). Contrary to this, the microanalytical data for the product was not in agreement with either of the structures (105) or (107). The product was finally assigned the stucture (108) by X-ray diffraction (figure 11). This compound presumably forms, not during the attempted cyclisation reaction, but afterwards when water is added during workup.



(108) R=H

(109) R=CH_2OH

It is interesting to note that the ^{13}C nmr spectra of glycols (108) and (109) show two sets of resonances for the carbon atoms in the sidechain (figure 12). Also the high field (300 MHz) ^{1}H nmr spectrum reveals that (108) has two singlet resonances for each methyl group (figure 13). It was initially thought that the glycols might exist as orthoamides when in solution and the two diastereoisomers thus formed would give rise to two sets of resonances (figure 14). However the solution infrared spectra show a stong carbonyl stretch ruling out this possibility. The two sets of resonances are thought to be due to the hydroxyl groups presumably holding the sidechain in different orientations.



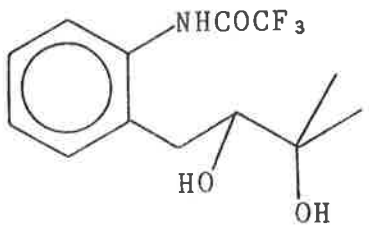


Figure 11

X-Ray structure of (108).

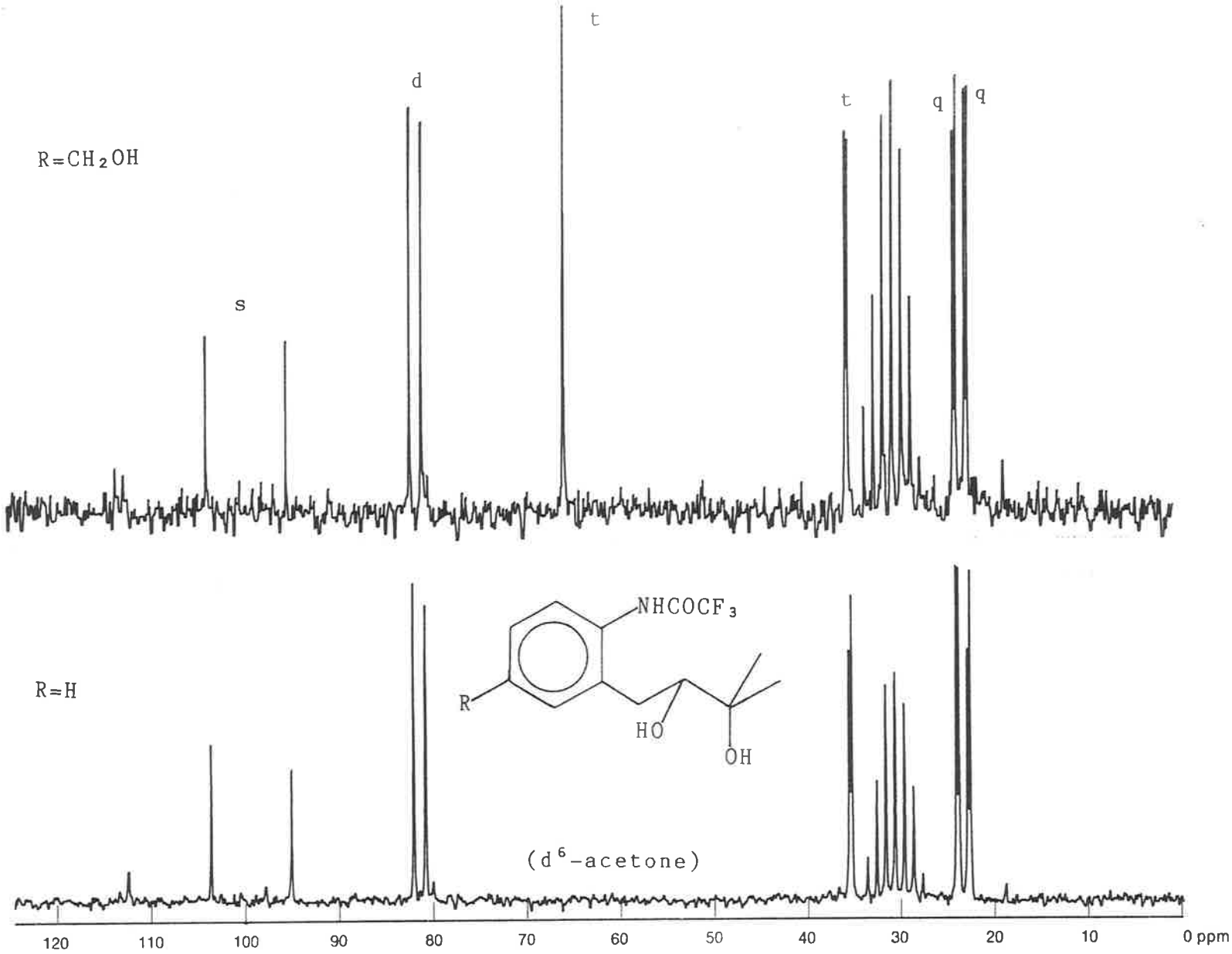
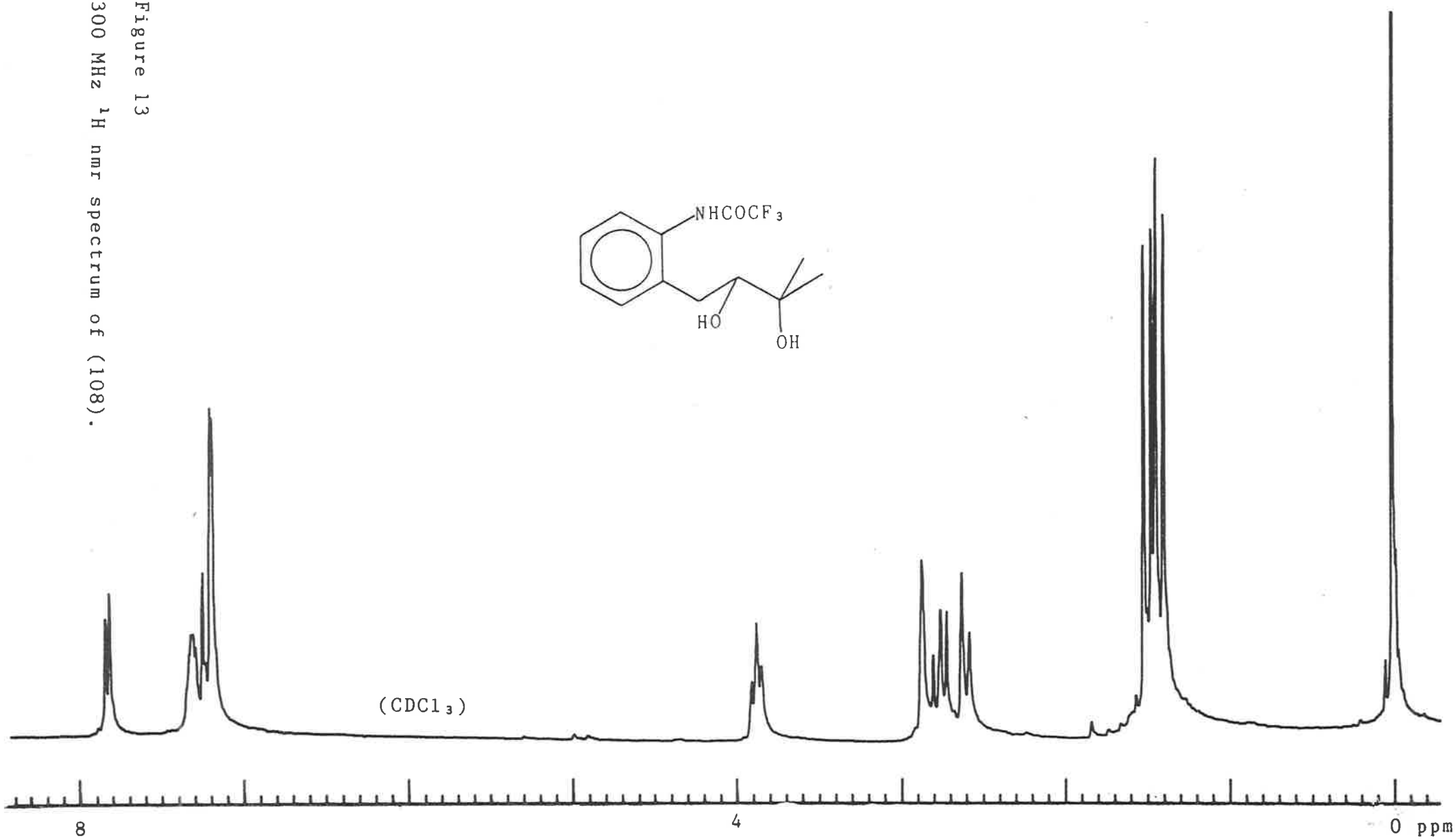


Figure 12

20.1 MHz ^{13}C nmr spectra of (108) and (109).

Figure 13

300 MHz ^1H nmr spectrum of (108).



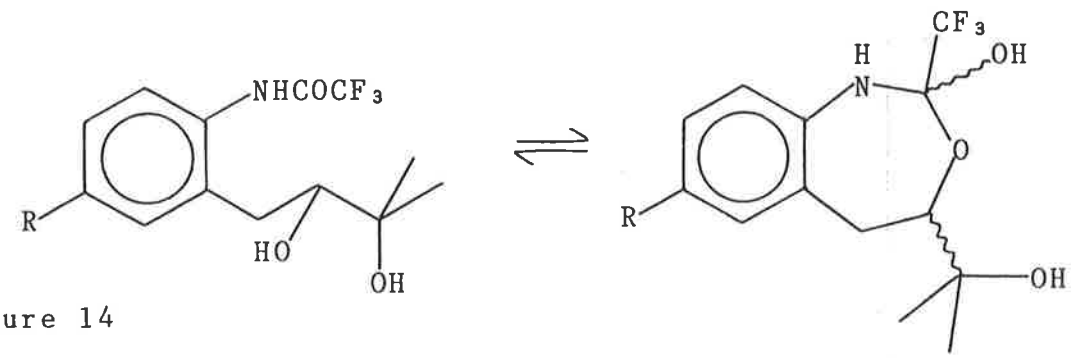
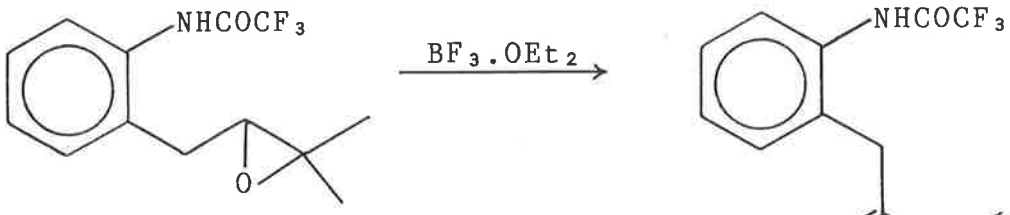


Figure 14

In another attempt to cyclise the epoxide (103) it was stirred with boron trifluoride for a longer period. However no cyclisation product was obtained, only a rearrangement product was isolated which was assigned the structure (110) on the



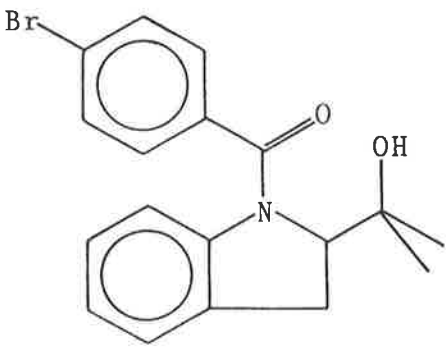
(103) (110)

basis of its spectral data. The infrared spectrum showed carbonyl absorptions at 1720 cm^{-1} due to the amide and a ketone stretch at 1700 cm^{-1}. The nmr spectrum showed a singlet at δ 3.75 due to the benzylic methylene group, a septet at δ 2.75 and a doublet at 1.17 due to the *iso*propyl ketone moiety.

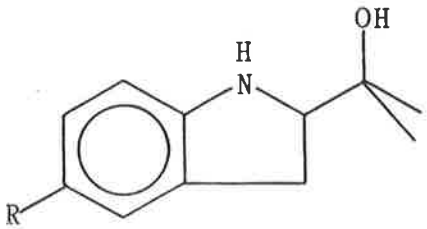
The epoxides were also treated with base to ascertain whether the compounds could be cyclised by using the amide anion as the internal nucleophile. A methanolic solution of

the epoxide (103) was stirred over potassium carbonate for fifteen minutes after which time addition of water and solvent extraction afforded a solid. The infrared spectrum did not possess a carbonyl absorption and the nmr spectrum showed a doublet resonance at δ 6.53 due to the aromatic proton *ortho* to the amino group. The chemical shift of this proton confirmed that the amino group was not acylated. The proton spectrum also showed a doublet at δ 2.63 arising from the benzylic methylene protons which were coupled to a methine proton appearing as a triplet at δ 3.77.

The amine was converted to the *para*-bromobenzamide and was assigned the structure (111) on the basis of X-ray diffraction (figure 15). This shows that the cyclisation under basic conditions gives rise to the dihydroindole system (112). Similarly, the 4-substituted epoxide (104) was found to give the dihydroindole (113) in almost quantitative yield.



(111)



(112) R=H

(113) R=CH_2OH

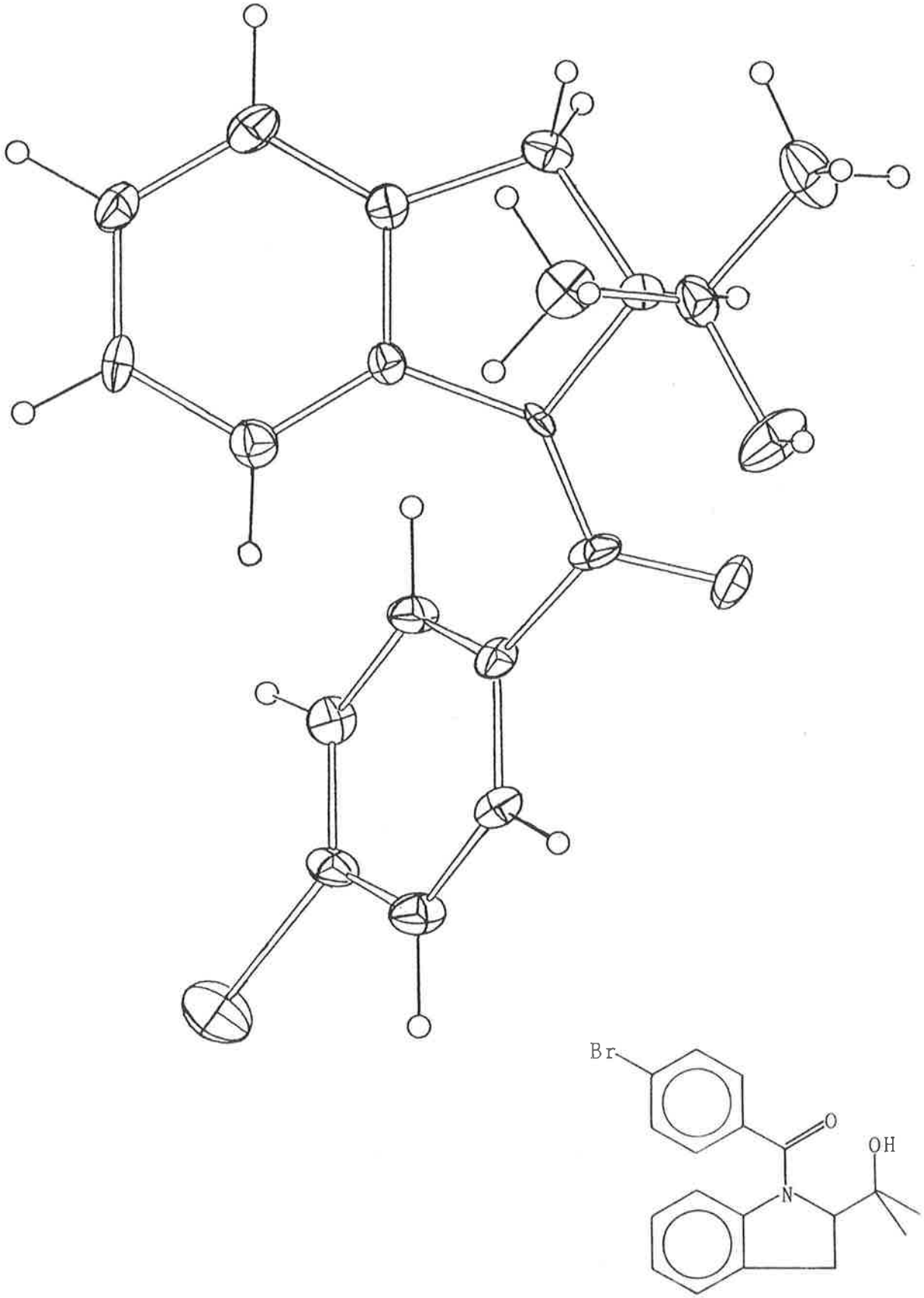


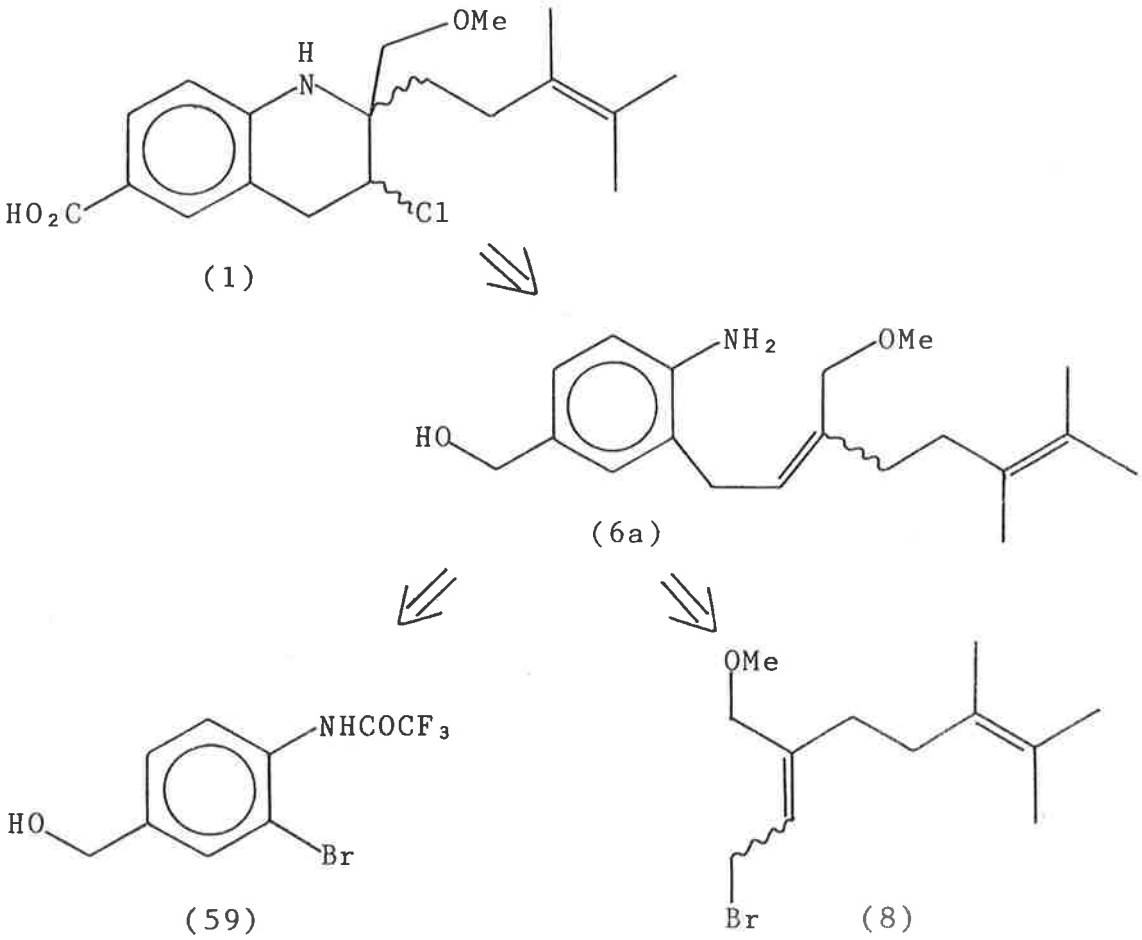
Figure 15

X-Ray structure of (111).

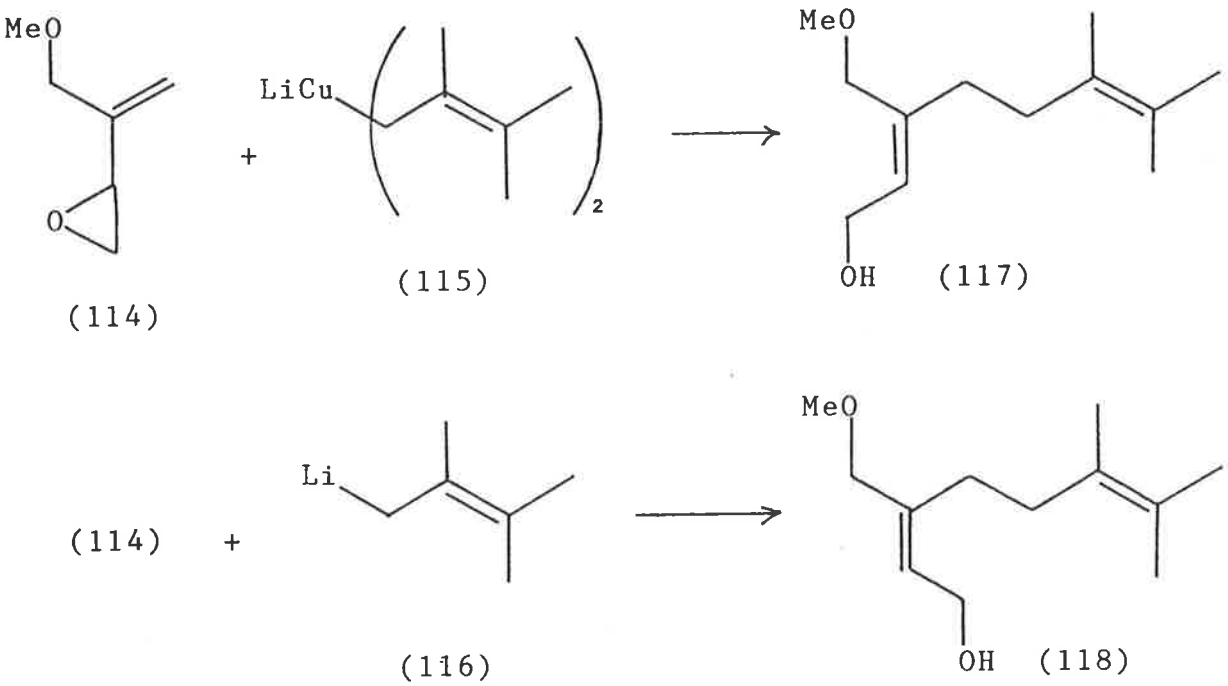
Although the cyclisation of epoxides failed to give tetrahydroquinoline systems, these compounds could be obtained from the iodination and aziridine chemistry. With this in mind, no further cyclisation studies were undertaken and attention was directed towards the synthesis of the sidechain (8).

Chapter 3.

The synthesis of virantmycin is complicated by the unknown stereochemistry at C-2 and C-3. To establish the stereochemistry would necessitate the unambiguous synthesis of both diastereomers and subsequent comparison of these compounds with an authentic sample of the antibiotic. It was therefore of interest to synthesise both geometric isomers of (6a) and hence both isomers of (8) were required (scheme 2a).



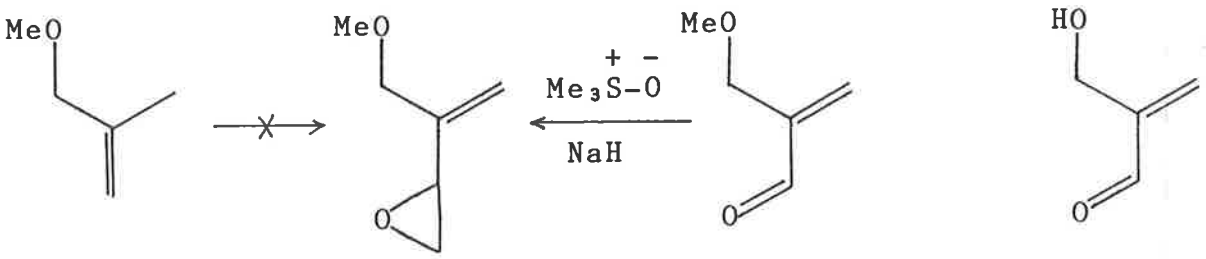
Scheme 2a



Scheme 20

A potential route to the sidechain (8) was the coupling of the vinyloxirane (114) with an organometallic species such as (115) or (116). Although this reaction gives mixtures of geometric isomers[22], the use of lithium dialkycuprates has been shown[34] to give the trans-addition product almost exclusively. Furthermore, Tamura[23] reports that the presence of a tertiary amine or a lithium alkoxide promotes cis-addition with a high degree of selectivity. This approach therefore offers a method of obtaining the alcohols (117) and (118) individually which may then be converted to the individual isomers of the sidechain (8).

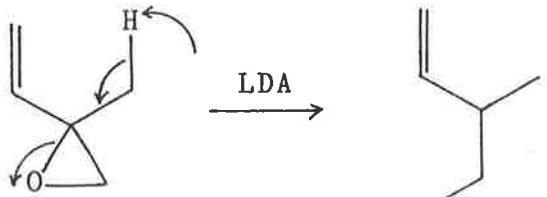
Epoxidation of methoxyisoprene would lead to reaction of the more substituted double bond. Therefore the aldehyde (119) was chosen as a precursor as treatment of this with a sulphur ylide[35] would furnish the desired epoxide (scheme 21).



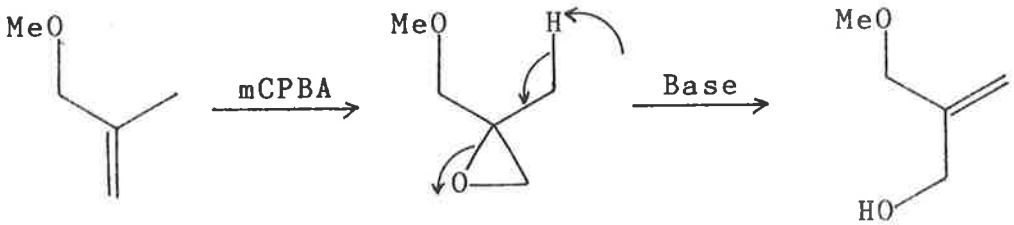
(114) (119) (120)

Scheme 21

The hydroxyaldehyde (120) has been reported[36] in the literature, however, its preparation is very tedious. We felt that the methoxyaldehyde (119) could be prepared more directly (scheme 22). It has been reported in the literature[21c] that lithium di*iso*propylamide causes elimination in the isoprene oxide system to give the alcohol (121). If elimination of this type could be induced in epoxide (123) then the alcohol (124)



(66) (121)



(122) (123) (124)

Scheme 22

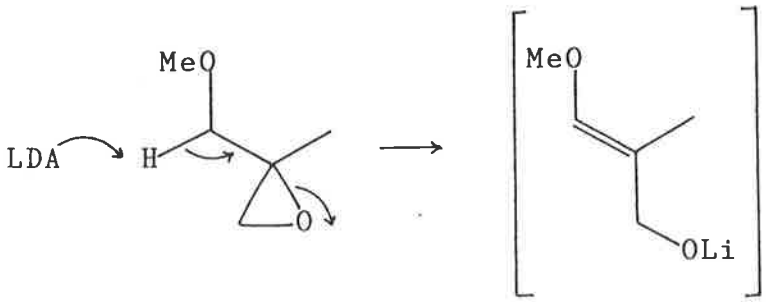
could be obtained. Alcohol (124) could then be presumably oxidised with pyridinium chlorochromate to give the aldehyde (119).

β-Methallyl alcohol was treated with sodium hydride in ether and was methylated, using methyl iodide, to give the methyl ether (122). The epoxide (123) was prepared by treatment of this ether with *meta*-chloroperbenzoic acid in dichloromethane. The epoxide ring protons are non-equivalent and resonate as two doublets at δ 2.07 and 2.18 with a coupling constant of 6 Hz.

The epoxide (123) was treated with one equivalent of lithium di*iso*propylamide in tetrahydrofuran for ten minutes at 0^0. Solvent extraction recovered the epoxide unchanged as was indicated by nmr spectroscopy. This reaction was repeated for thirty minutes at room temperature yet again the epoxide was recovered, although accompanied by a small amount of polar material arising from decomposition. When this reaction was left for an hour at room temperature there was extensive decomposition of the epoxide, although some starting material was still detected by nmr spectroscopy.

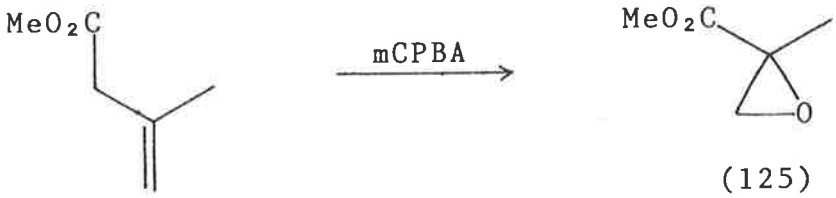
After this lack of success, a stronger base was thought to be necessary and so the reaction of the epoxide with methyllithium was investigated. Since nucleophilic attack by methyllithium was to be avoided, low temperature conditions were tried. Surprisingly, the epoxide was found to be inert to

methyllithium in tetrahydrofuran at -90° and even at -35° no reaction was observed.



Scheme 23

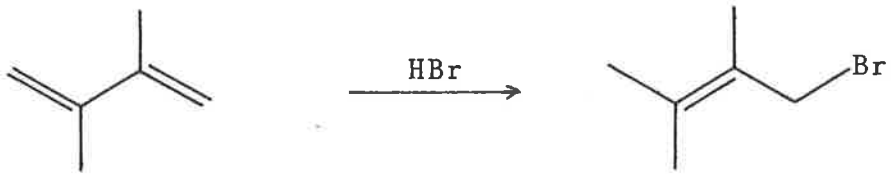
It was thought that the decomposition that was observed in the reaction of the epoxide (123) with lithium di*iso*propylamide at room temperature, might be due to removal of a methylene proton adjacent to the methoxy group (scheme 23). The enol ether formed in this manner may be undergoing decomposition in the reaction mixture or upon workup. If adverse deprotonation at this site could be stopped then deprotonation of the methyl group might proceed thus giving the required product. For this reason, the epoxyester (125) was prepared.



(125)

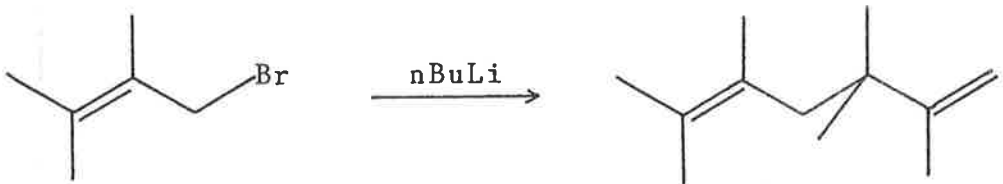
Methyl methacrylate was treated with *meta*-chloroperbenzoic acid to give epoxide (125), according to a literature procedure[37]. This compound also showed mutual coupling of the epoxide ring protons which resonated at δ 2.73 and 3.08.

Unfortunately, when this epoxide was treated with lithium di*iso*propylamide in tetrahydrofuran, at either room temperature or at -20^0, extensive decomposition was observed as was indicated by tlc and nmr spectroscopy. This approach to the methoxyaldehyde (119) was then discontinued. No other efforts to prepare this compound were made as other work revealed that the allylithium (116) was not readily accessible.



(126)

The trimethylallyl bromide (126) was prepared by the hydrobromination of 2,3-dimethyl-1,3-butadiene according to the literature procedure[38]. The allyl bromide was treated with one equivalent of *n*-butyllithium, in tetrahydrofuran at -78^0, and subsequent treatment with carbon dioxide gave no carboxylic acid products after workup. This indicated that no active alkyllithium reagent had been formed. The material recovered from this reaction was found to be the 1,5-diene[39]



(126) (127)

(127) which had been formed by the coupling of the allyl moieties.

The head to tail nature of the coupling reaction was indicated by the nmr spectrum which showed two vinyl protons resonating as a broad singlet at δ 4.84, an allylic methylene group at 2.03, an allylic methyl group at 1.80, three magnetically equivalent allylic methyl groups at 1.63 and a geminal dimethyl group at 1.05. The mass spectrum showed a molecular ion at *m/e* 166 and had the base peak at 83 which corresponded to the most favourable fragmentation process (figure 16).

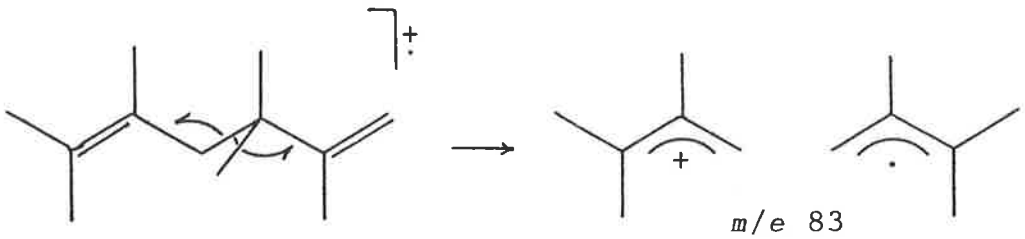
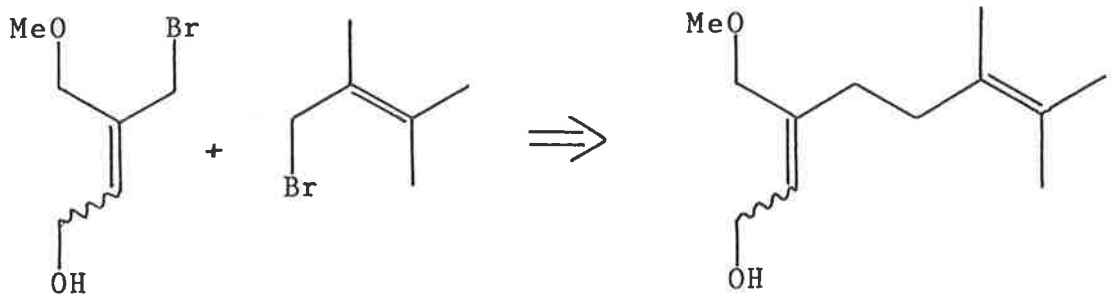


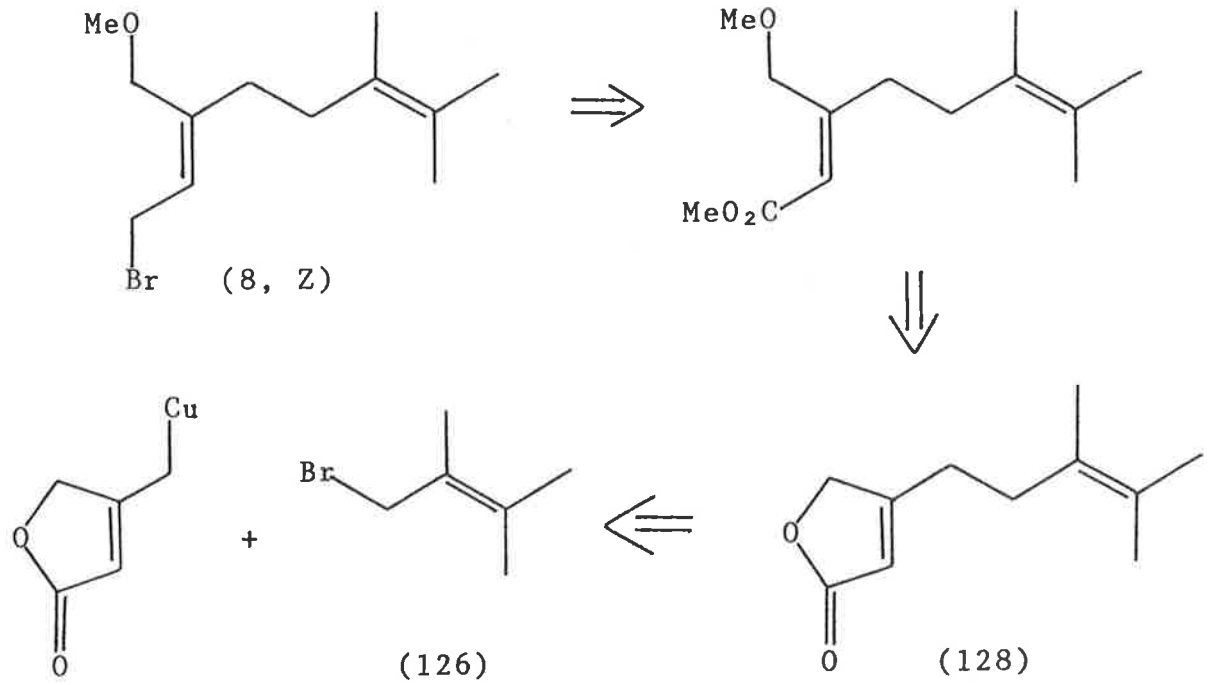
Figure 16

The problems associated with preparing the allylithium (116) meant that a new approach to the sidechain had to be sought. The sidechain (8) is essentially a 1,5-diene and therefore it might be prepared by the coupling of two allyl bromides (scheme 24). This type of reaction can be effected by the use of organometallic compounds such as palladium(II) complexes. However the problems[40] of cross-coupling, and regiochemical and stereochemical scrambling led us to consider other options first.



Scheme 24

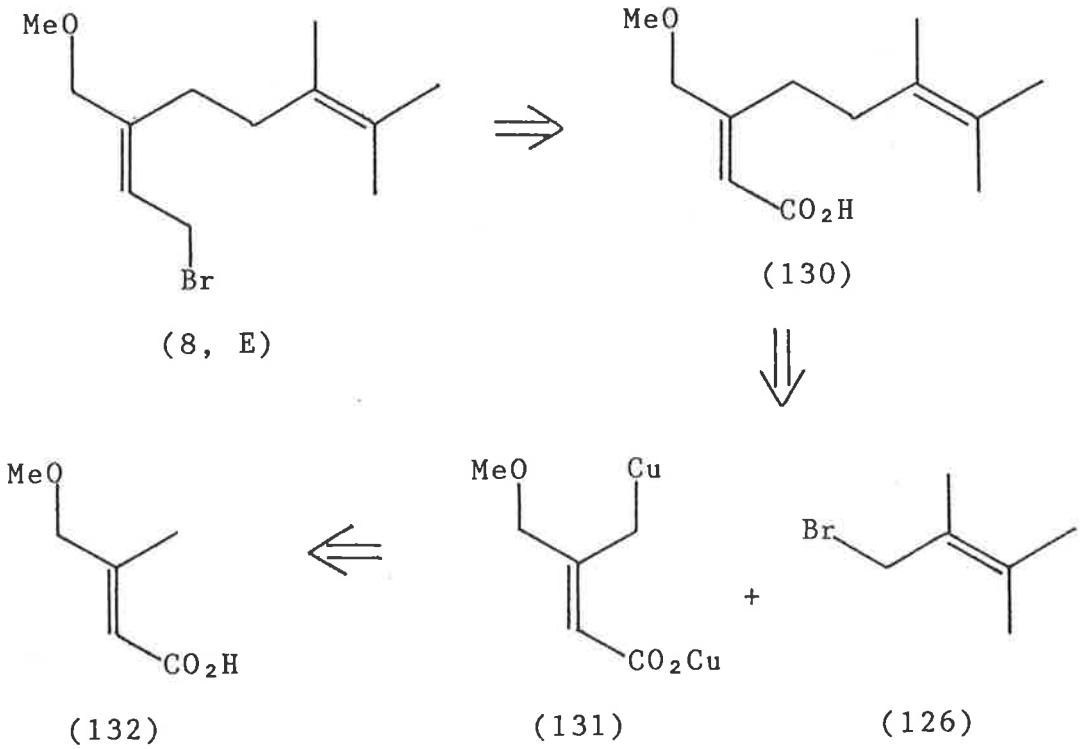
We decided to investigate the possibility of preparing the sidechain by coupling an allylcopper reagent with an allylbromide as outlined in schemes 25 and 26. The Z-isomer was envisaged as arising from the lactone (128) which was to be prepared by alkylating the allylcopper reagent (129). The lactone was selected as this would give a product of known



(129)

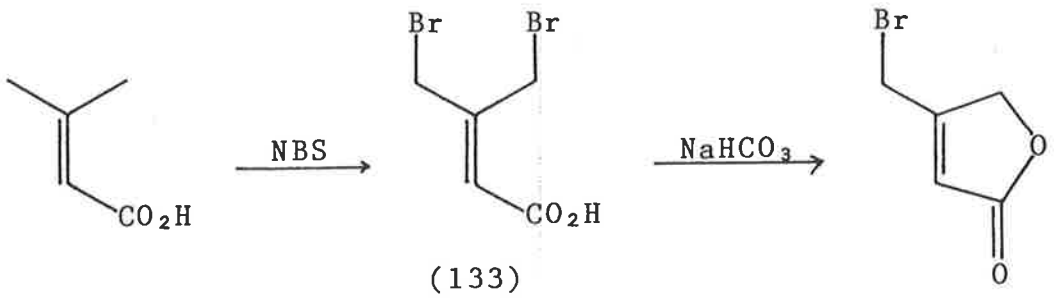
Scheme 25

stereochemistry about the double bond. It was also thought that the E-isomer of (8) could be prepared by the γ-alkylation[41] of the copper(I) enolate of the methoxyacid[42] (132).



Scheme 26

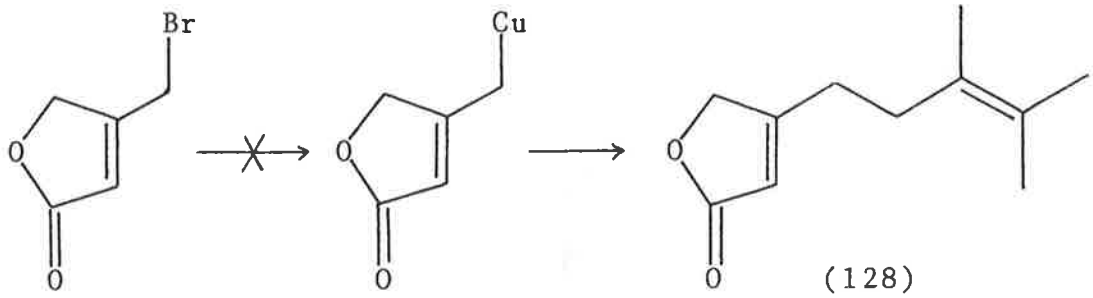
It was intended that the lactone allylcopper reagent (129) would be prepared by metallation of the bromolactone (134) at low temperature. The bromolactone (134) was prepared by a modification of the literature method[43]. 3,3-Dimethylacrylic acid was converted, using N-bromosuccinimide, to the dibromoacid (133) which was cyclised to the desired bromolactone (134) by treatment with aqueous sodium bicarbonate (scheme 27).



(133) (134)

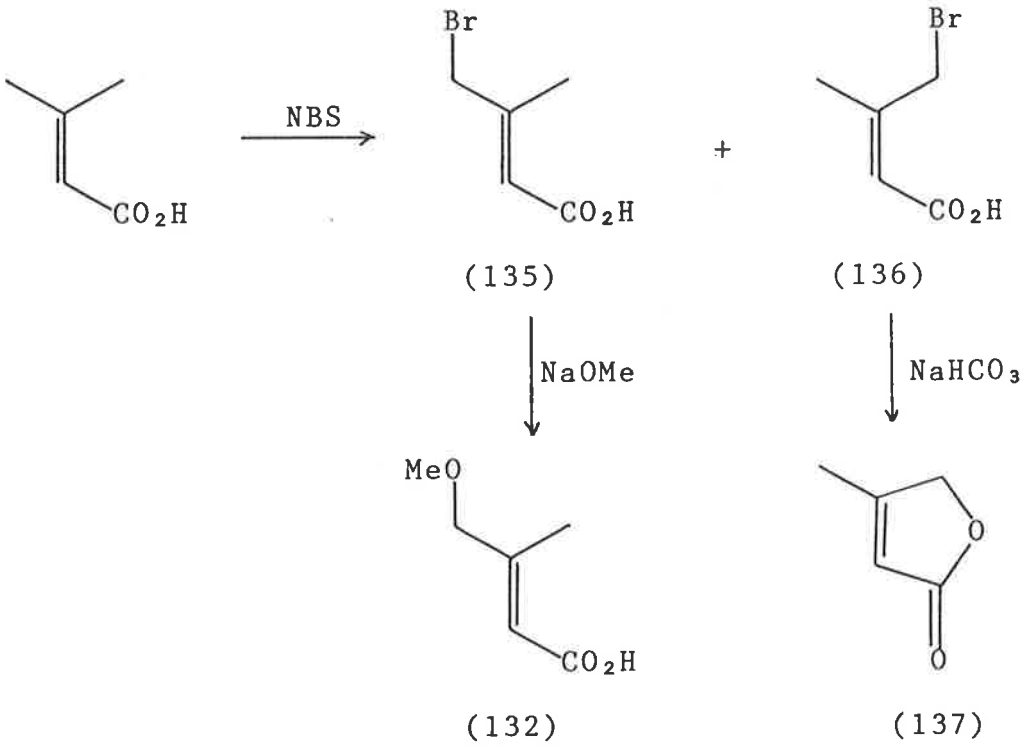
Scheme 27

The bromolactone (134) was treated with one equivalent of *n*-butyllithium, in tetrahydrofuran at -78°, to give the lithiated material. One equivalent of copper(I) (as $[CuI(nBu_3P)]_4$) was added and then the trimethylallyl bromide (126) was introduced into the reaction mixture. This resulted in a complex product mixture as shown by tlc and nmr spectroscopy. The metallated lactone probably undergoes reaction with the carbonyl group of other molecules of itself. The bromolactone thus seemed incompatible with metallation chemistry and so attention was turned to the γ-alkylation of the methoxyacid (132).



(134) (128)

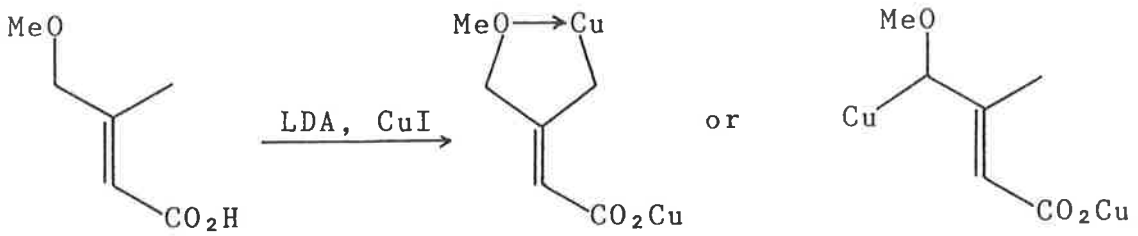
It has been reported[41] in the literature that the copper(I) enolates of α,β-unsaturated carboxylic acids undergo alkylation predominantly at the γ-carbon atom when treated with allyl halides. Therefore the methoxyacid (132) was prepared as it was expected that this would lead to the sidechain precursor (130) (scheme 26).



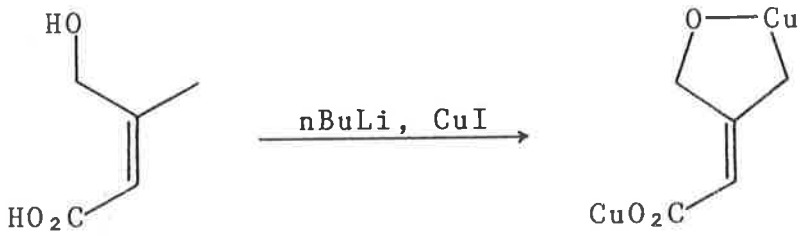
The (E)-methoxyacid (132) was prepared by an analogous method[42,44] to that described in the literature for the preparation of a mixture of geometric isomers. 3,3-Dimethylacrylic acid was brominated using N-bromosuccinimide to give a mixture of bromoacids[44] (135) and (136). When this mixture was treated with aqueous sodium bicarbonate, the bromoacid (136) cyclised to the lactone[42] (137) whereas the bromoacid[44]

(135) was unchanged and could be isolated as a pure isomer. This was then converted to the methoxyacid (132) by stirring with sodium methoxide in methanol for one hour at room temperature. The pure E-isomer obtained in this manner had an nmr spectrum which agreed with the nmr data[42] quoted in the literature for the E-isomer from the isomeric mixture.

The methoxyacid (132) was deprotonated in tetrahydrofuran by treatment with two equivalents of lithium di*iso*propylamide at 0°. The addition of two equivalents of cuprous iodide, followed later by the trimethylallyl bromide (126), gave only an intractable oil upon workup. The alkylation was also attempted



(132)



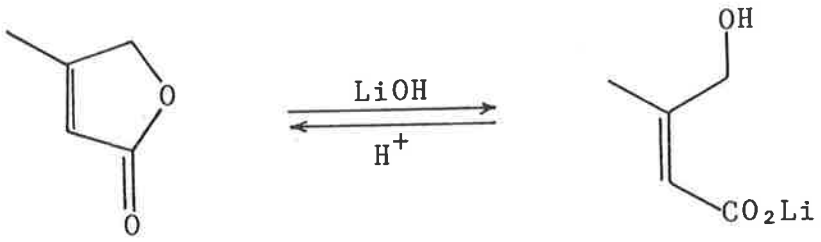
(138)

Scheme 28

using $[CuI(nBu_3P)]_4$ as a source of copper(I) but still a complex mixture was obtained as indicated by tlc and nmr spectroscopy.

It was uncertain which proton of (132) was being removed by the lithium di*iso*propylamide (scheme 28) and so it was decided to investigate the hydroxyacid (138) as a substrate as it was unlikely to form a carbanion adjacent to the alkoxide anion. The hydroxyacid (138) might be formed from the lactone (137) and because of the transoid arrangement of the enolate the stability of the system might be increased by the greater p-orbital overlap.

The lactone (137) was refluxed in 2M sulphuric acid for two hours but unfortunately solvent extraction returned the lactone unchanged as indicated by nmr spectroscopy. However, the lactone rapidly dissolved in aqueous lithium hydroxide to give a solution of the carboxylate salt (139) but the hydroxyacid (138) could not be isolated as acidification resulted in re-lactonisation to give the starting material. The lithium salt of the hydroxyacid was isolated by removal of the water *in vacuo* to give a crystalline solid. The infrared spectrum showed two bands at 1560 and 1380 cm^{-1} which was consistent with the antisymmetric and symmetric carbonyl stretches of a carboxylate salt. The nmr spectrum in deuterium oxide showed a singlet resonance at δ 1.88 due to the methyl group, a singlet at δ 4.32 due to the methylene adjacent to the oxygen atom and a broad singlet at δ 5.73 arising from the vinyl proton.

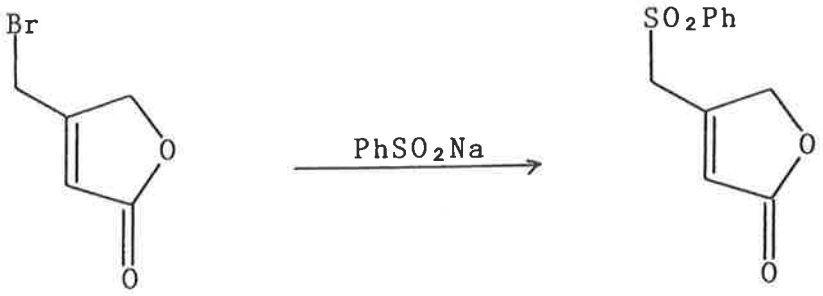


(137) (139)

Since deprotonation of (139) would lead to a trianion it was necessary to use *n*-butyllithium as a sufficiently strong base. The salt (139) was treated with two equivalents of *n*-butyllithium in tetrahydrofuran at -78° and then three equivalents of cuprous iodide were added. However addition of trimethylallyl bromide (126) followed by acidic workup conditions gave a complex mixture of products with some of the lactone (137) being present as shown by nmr spectroscopy.

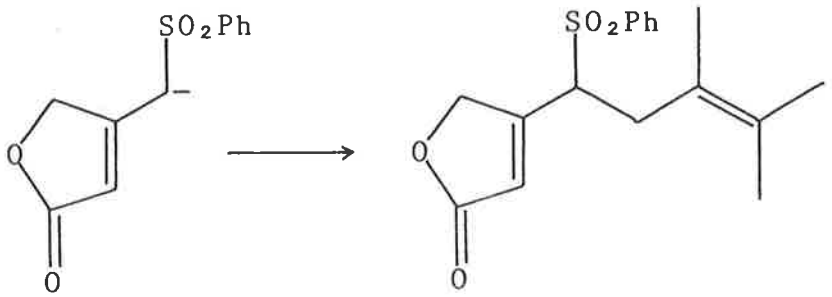
Since the copper(I) enolates (129) and (131) (schemes 25 and 26) were too unstable to undergo clean alkylations, it was decided to introduce a stabilising group. γ-Alkylation of α,β-unsaturated systems has been accomplished by introducing a directing group such as a carbonyl[45], sulphoxide[46] or a sulphone[47,48,49,50] group *etc*. The sulphone group was considered because of its ease of introduction and removal under mild conditions.

The sulphone (140) was prepared by stirring the bromolactone (134) with sodium benzenesulphinate in tetrahydrofuran according to the literature procedure[51]. The alkylation was



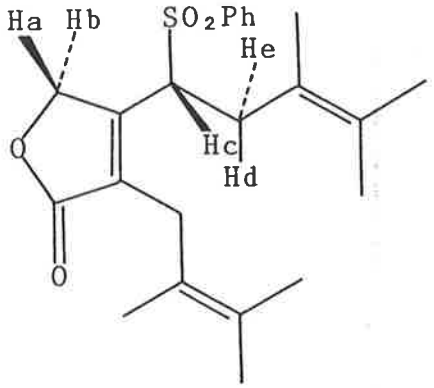
(134) (140)

carried out by generating the anion with sodium hydride in N,N-dimethylformamide and then treating the solution with the trimethylallyl bromide (126). Addition of water and solvent extraction gave the sulphone (141) in 29% yield, after chromatography, along with a small amount (9%) of dialkylated material (142).



(140) (141)

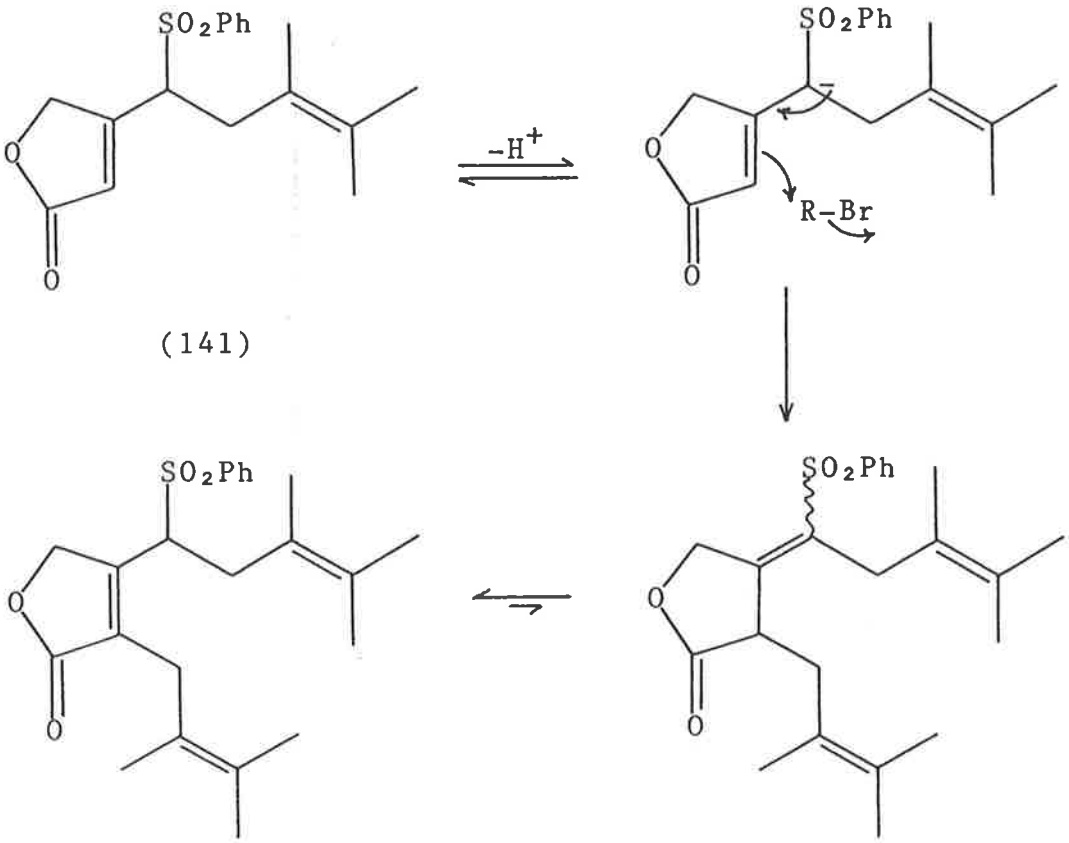
The nmr spectrum of the sulphone (141) showed a broad singlet at δ 1.62 due to the three methyl groups on the alkene moiety, a vinyl proton at δ 5.92 and a triplet at δ 4.18 arising from the methine proton next to the sulphone group. This proton was coupled to the adjacent methylene group which resonated at δ 2.82 as a doublet.



(142)

Figure 17

The nmr spectrum of the dialkylated material showed a broad peak at δ 1.5 which integrated for six methyl groups. The absence of a vinyl proton indicated that the second alkyl moiety was connected to the α-position (figure 17). The lactone methylene protons (Ha, Hb) were nonequivalent and appeared as a pair of doublets due to the carbon bearing the sulphone group being chiral. The proton (Hc) attached to this chiral carbon atom resonated as a doublet of doublets showing coupling to the nonequivalent protons (Hd, He) of the vicinal methylene group. This compound arises by sulphone (141) being deprotonated [by the anion of (140)] and undergoing alkylation at the α-position. This second alkylation does not occur at the γ-carbon atom presumably due to steric hindrance. The first formed dialkylation product then tautomerises to the more stable (142) (scheme 29).

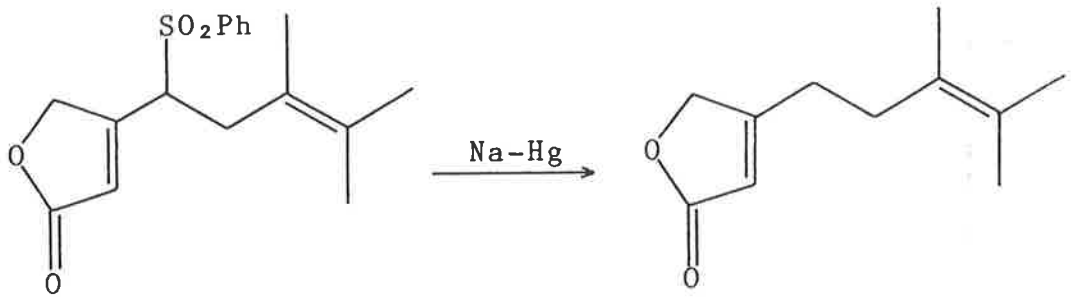


(141)

(142)

Scheme 29

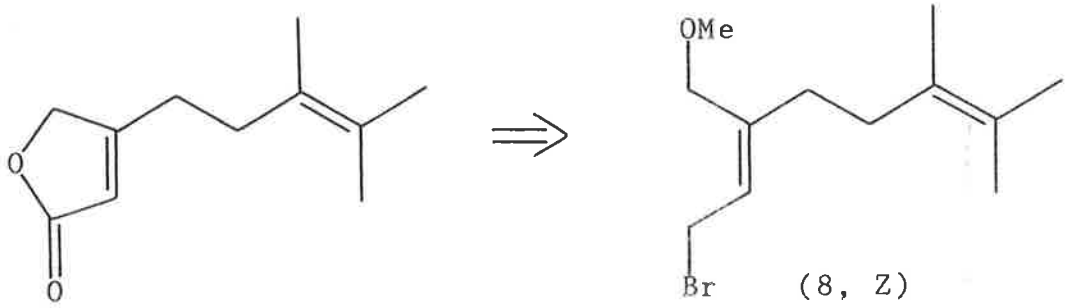
Due to the low yield (29%) of the desired product (141), more favourable reaction conditions were sought. In order to prevent the dialkylation, the addition mode was reversed. A solution of the sulphone (140) anion was added slowly to an excess of the alkyl bromide, in this manner the sulphone (140) anion was rapidly alkylated and its concentration was kept to a minimum thereby preventing deprotonation and further alkylation of the product. This procedure stopped the dialkylation and increased the yield of (141) to 57%.



(141) (128)

The sulphone moiety of (141) was removed by reduction[51] with 5% sodium amalgam in methanol at -20^0 to give the lactone (128). The nmr spectrum of the crude product showed no phenyl proton reonances, indicating that this reduction was quantitative. The two adjacent methylene groups of (128) gave rise to a broad singlet resonance due to the protons being in very similar environments.

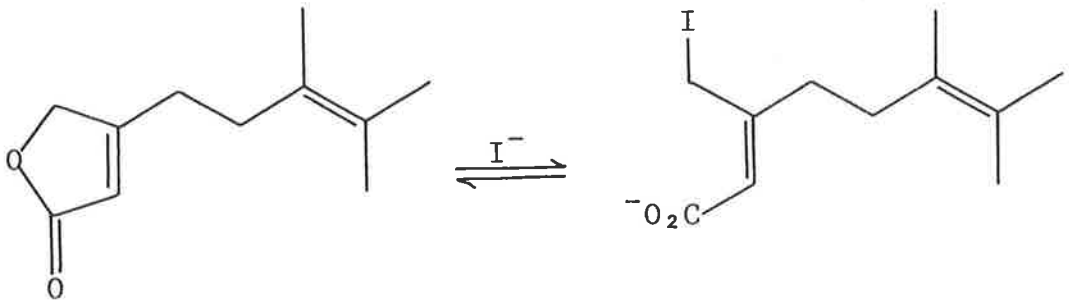
The use of sulphone chemistry had enabled us to successfully couple the allylic bromides (134) and (126) to produce the lactone (128) (scheme 25). Our next concern was the elaboration of this lactone to give the Z-isomer of the sidechain (8), however difficulty was encountered at this stage.



(128)

As was found with lactone (137), attempted acid hydrolysis failed to cleave the lactone ring. Since lactone (137) could be cleaved with aqueous lithium hydroxide at room temperature, it was thought that these conditions might promote hydrolysis of (128). Contrary to this, lactone (128) was found to be inert towards this treatment, possibly because of its low water solubility. The use of methanol as a cosolvent led to decomposition as did attempted hydrolysis with lithium hydroxide in dimethoxyethane.

Owing to the difficulties in effecting an O-acyl cleavage in the lactone ring, reagents capable of inducing O-alkyl cleavage[52] were investigated.

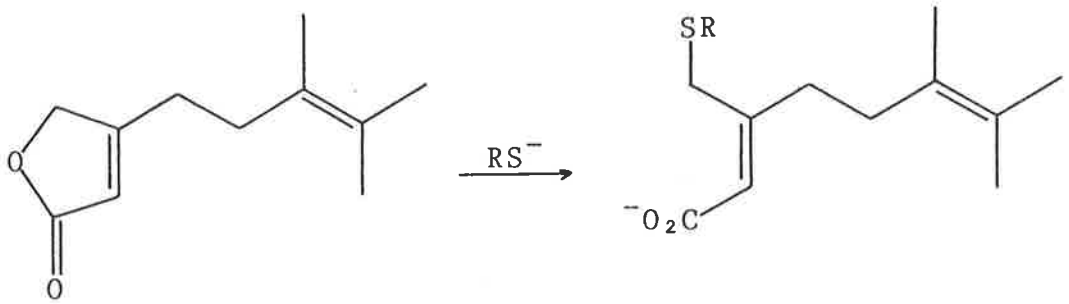


(128)

Scheme 30

The lactone (128) was refluxed with lithium iodide in N,N-dimethylformamide for 24 hours, however, only starting material was recovered. Since the O-alkyl cleavage by iodide ion is potentially reversible (Scheme 30), it was uncertain whether this reaction failed to proceed or established an

equilibrium favouring the starting material. If trimethylsilyl iodide could be used to cleave the lactone ring, then the product would be O-protected and might be isolated without the reverse reaction occurring. Consequently, the lactone (128) was stirred in acetonitrile with trimethylsilyl iodide (which was prepared *in situ*[53] from the silyl chloride and sodium iodide). However, this procedure failed to cleave the lactone ring even after reflux for three days.

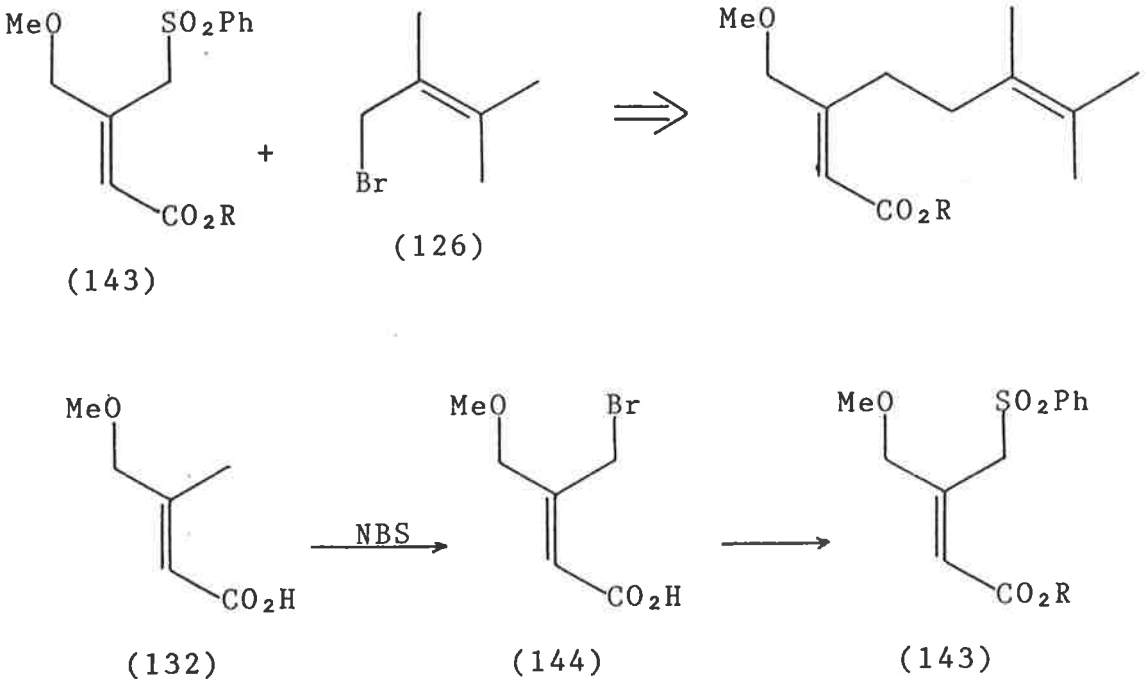


(128)

Lithium thiolates[54,55] were also investigated for their ability to promote O-alkyl cleavage of the lactone. The lactone (128) was stirred overnight with excess lithium thiophenoxide in N,N-dimethylformamide but workup returned the starting material quantitatively as was shown by nmr spectroscopy. Similarly, treatment with excess lithium thioethoxide failed to cause ring openning.

Since the lactone (128) could not be elaborated to the Z-isomer of the sidechain (8), attention was turned to the E-isomer. It was thought that sulphone chemistry might again be

employed to couple the allyl units (143) and (126) (scheme 31). In order to gain success from this approach it would be necessary to be able to differentiate between the methyl groups of 3,3-dimethylacrylic acid.

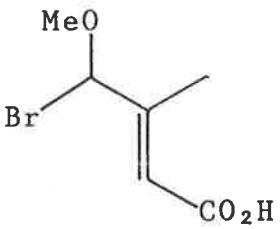


(143) (126)

(132) (144) (143)

Scheme 31

It was hoped that the sulphone (143) might be obtained *via* the bromination of the (E)-methoxyacid (132). However, bromination of this compound with N-bromosuccinimide gave the product (145) arising from bromination at the carbon atom



(145)

bearing the methoxyl group. The nmr spectrum of this material displayed a one proton resonance at δ 5.57 due to the methine group bearing the bromine atom and the methoxyl group. The methyl group resonated δ 2.07, indicating that no bromination had occurred at this position. The crude product reaction mixture contained none of the desired bromide (144).

The anticipated difficulty involved with the differentiation of the methyl groups of 3,3-dimethylacrylic acid meant that the sulphone (143) would not be easily synthesised. For this reason, an alternative synthetic scheme was sought.

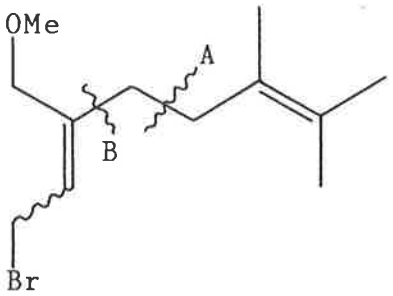
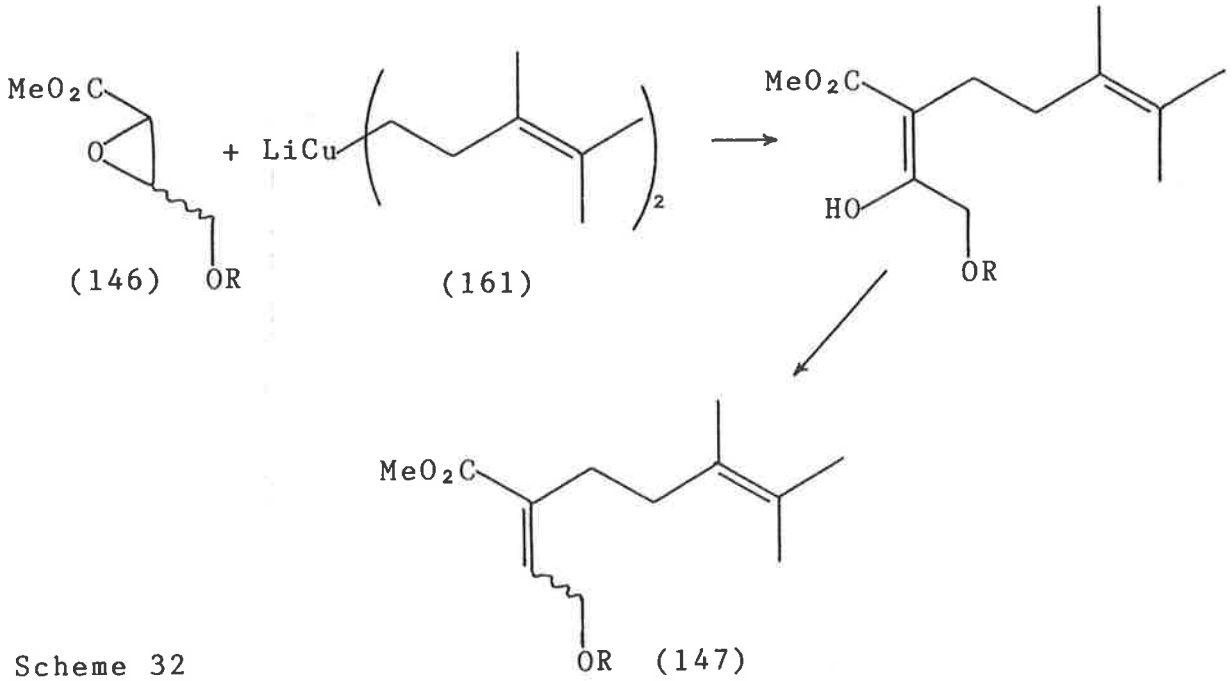


Figure 18

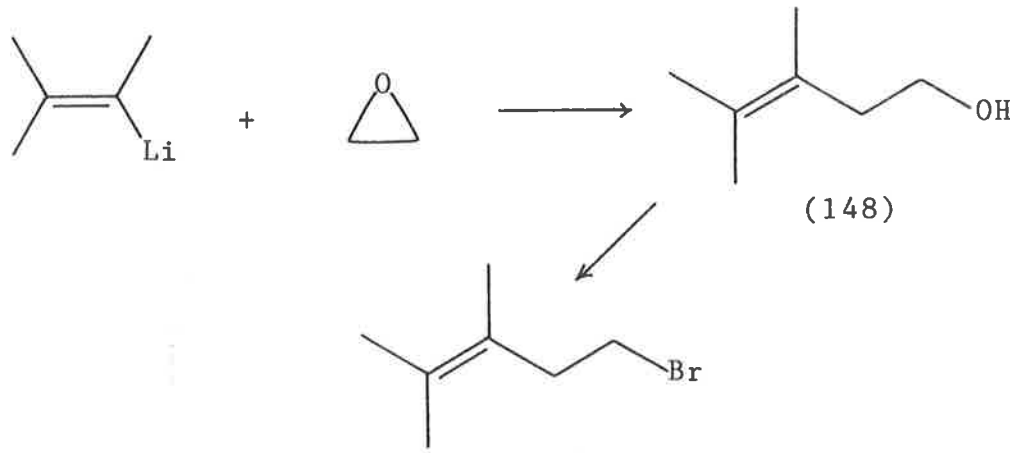
The previous allyl-allyl coupling strategy was concerned with the formation of bond A (figure 18). An alternative approach might be the formation of bond B, this can be envisaged as shown in scheme 32.

If epoxide (146) was treated with a suitable lithium dialkylcuprate the organometallic reagent may be expected to attack at the α-carbon atom as there is literature precedence[56,57,58] for this regiochemistry. The first formed aldol product could then give rise to the desired ester (147) by

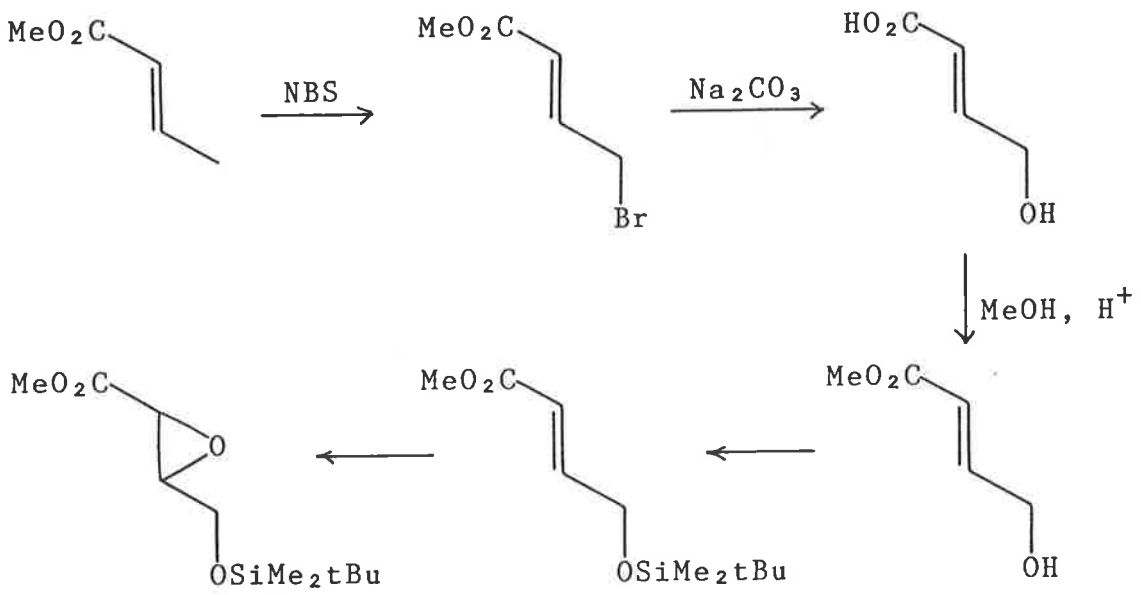


Scheme 32

undergoing dehydration. The lithium dialkylcuprate required for this reaction could be prepared from the homoallylic bromide (149) which might be prepared by reaction of trimethylvinyllithium[59] with ethylene oxide, followed by treatment with phosphorus tribromide (scheme 33).



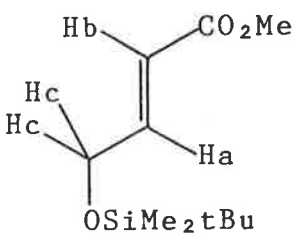
Scheme 33



(151) (150)

Scheme 34

It was thought that the epoxide (151) could be prepared from methyl crotonate (scheme 34). Treatment of methyl crotonate with N-bromosuccinimide gave methyl 4-bromocrotonate. This was refluxed in aqueous sodium carbonate for 2 hours to give the hydroxyacid which was re-esterified by refluxing it in methanol containing *p*-toluenesulphonic acid. The hydroxyester thus formed was converted to the *tert.*-butyldimethylsilyl ether (150) with *tert.*-butyldimethylsilyl chloride and using 4-dimethylaminopyridine as a catalyst[60], in a mixture of triethylamine and dichloromethane. The silyl ether (150) was characterised by the following spectral data. The infrared spectrum showed a carbonyl peak at 1720 cm^{-1} and another at 1660 due to the double bond in conjugation. The nmr spectrum showed three mutually coupled signals. The vinyl protons Ha



Ha δ 6.77, dt, *Jd* 15, *Jt* 4 Hz

Hb δ 5.83, dt, *Jd* 15, *Jt* 2 Hz

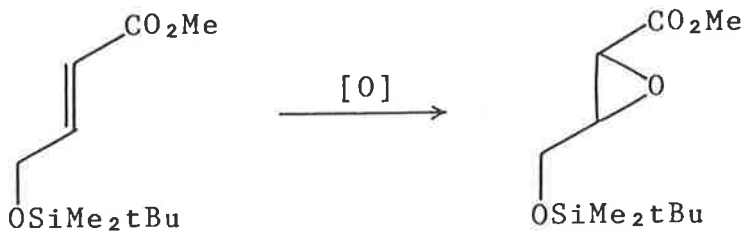
Hc δ 4.20, m

Figure 19 (150)

and Hb (figure 19) appear as a pair of doublets at δ 6.77 and 5.83 with a coupling constant of 15 Hz. Ha is further coupled to the methylene protons Hc with a coupling constant of 4 Hz and Hb also shows 2 Hz coupling to Hc. The methylene protons Hc appear as a multiplet at δ 4.20, being split into a doublet by each of Ha and Hb. The ester methyl group resonates at δ 3.58 and the silyl group has resonances at δ 0.87 and 0.05 due to the *tert.*-butyl and methyl groups respectively.

The epoxidation of α,β-unsaturated esters with *meta*-chloroperbenzoic acid has been described[37,61] in the literature. These reactions proceed very slowly yet give the epoxides in acceptable yield. The unsaturated ester (150) was treated with *meta*-chloroperbenzoic acid in dichloromethane at reflux for twenty hours, however no epoxidation was observed and only the starting material was recovered as was found by nmr spectroscopy.

Other reagents were then investigated in order to prepare the epoxyester (151). Basic hydrogen peroxide has been used successfully to epoxidise unsaturated aldehydes[62]. α,β-Un-

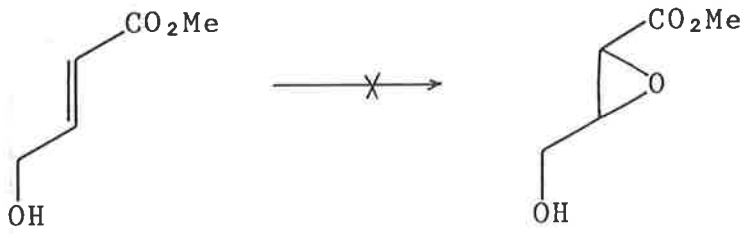


(150) (151)

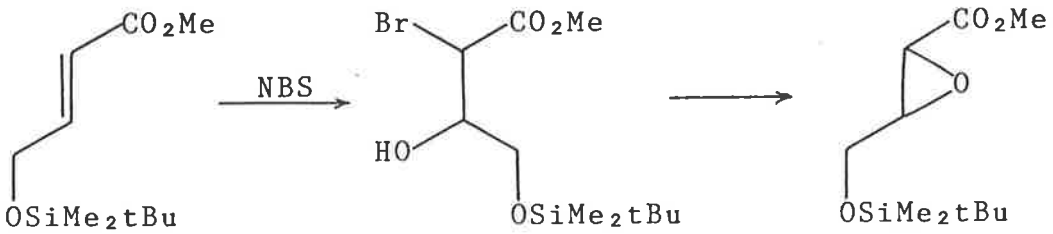
saturated ketones have also been epoxidised with hydrogen peroxide. The procedure described by Yamazaki[63] involves oxidation with hydrogen peroxide, in methanol, using potassium carbonate as a mild base. This procedure gives epoxides in high yield. However, when the unsaturated ester (150) was treated with hydrogen peroxide and potassium carbonate in methanol for sixteen hours, no reaction was observed.

Basic *tert.*-butylhydroperoxide is another reagent that has also been used to epoxidise α,β-unsaturated aldehydes[64] and ketones[65]. Ketones are oxidised using benzyltrimethylammonium hydroxide (Triton B) as a catalyst in dry benzene. Treatment of (150) with freshly distilled *tert.*-butylhydroperoxide in the presence of Triton B for sixteen hours, failed to yield the required epoxide.

Allylic alcohols[66] are known to react very rapidly with *tert.*-butylhydroperoxide using vanadyl acetylacetonate as a catalyst. Therefore, it was considered that methyl 4-hydroxycrotonate may be epoxidised more readily than the silyl ether (150). Methyl 4-hydroxycrotonate was refluxed in benzene with



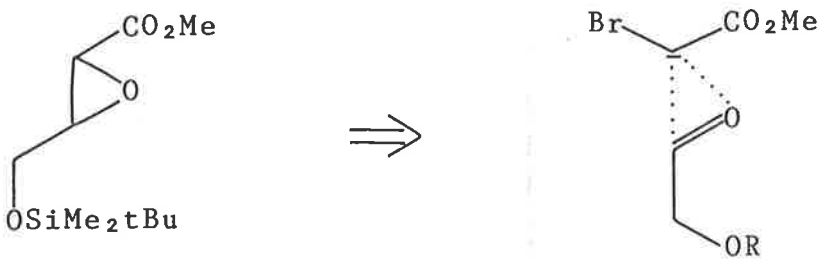
tert.-butylhydroperoxide and vanadyl acetylacetonate for four days yet epoxidation could still not be effected and the starting material was recovered.



(150) (151)

The unsaturated ester (150) was also treated with N-bromosuccinimide in aqueous tetrahydrofuran to ascertain whether the bromohydrin could be formed, since this may lead to the epoxide. The ester (150) was inert to N-bromosuccinimide under these conditions and no further attempts were made to epoxidise the ester (150).

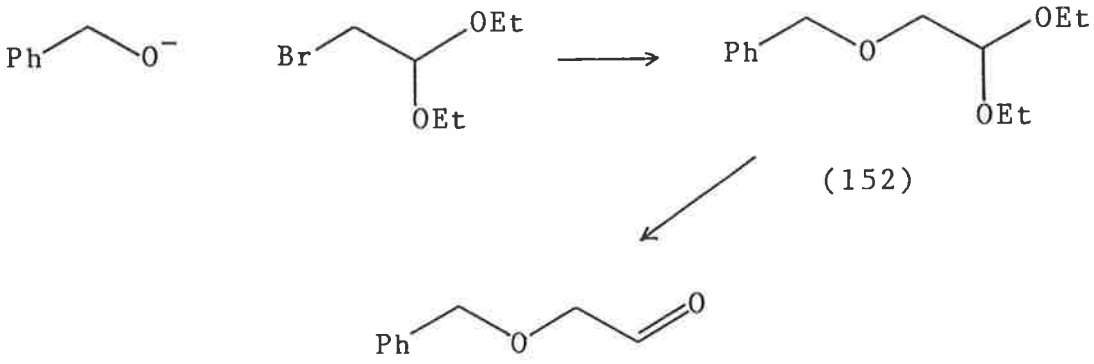
An alternative approach to the epoxyester (151) was offered by the Darzen's glycidic ester synthesis[67] (scheme 35). Reaction of a protected hydroxyacetaldehyde with methyl chloroacetate under basic conditions might yield the epoxy-ester directly. The protecting group chosen was the benzyl



(151)

Scheme 35

ether as this would be stable to base and would be easily removable with acid. The literature preparation[68] of benzyloxyacetaldehyde involves the oxidative cleavage of glycerol 1-benzyl ether[69], the preparation of which is lengthy. For this reason, a more direct method of preparation was attempted (scheme 36).



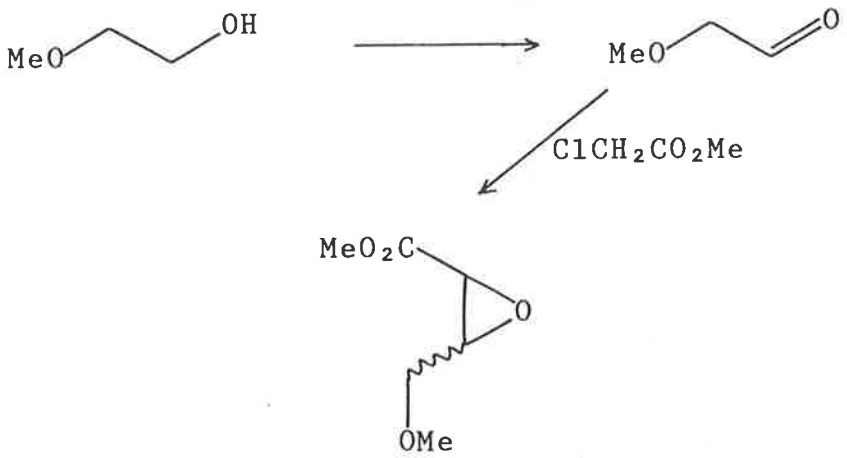
Scheme 36

Benzyl alcohol was deprotonated with sodium hydride, in tetrahydrofuran, and was alkylated with bromoacetaldehyde diethyl acetal to give the desired benzyloxyacetaldehyde as the acetal. The nmr spectrum of (152) showed a mutually coupled (6 Hz) doublet at δ 3.28 and a triplet at δ 4.57 arising

from the adjacent methylene and methine groups, respectively, of the acetaldehyde moiety. The spectrum also showed two quartets at δ 3.58 and 3.54 revealing that the ethoxy groups are magnetically non-equivalent. (This was also observed with the bromoacetaldehyde diethyl acetal.) The aromatic and methylene protons of the benzyl group resonated at δ 7.18 and 4.53 respectively.

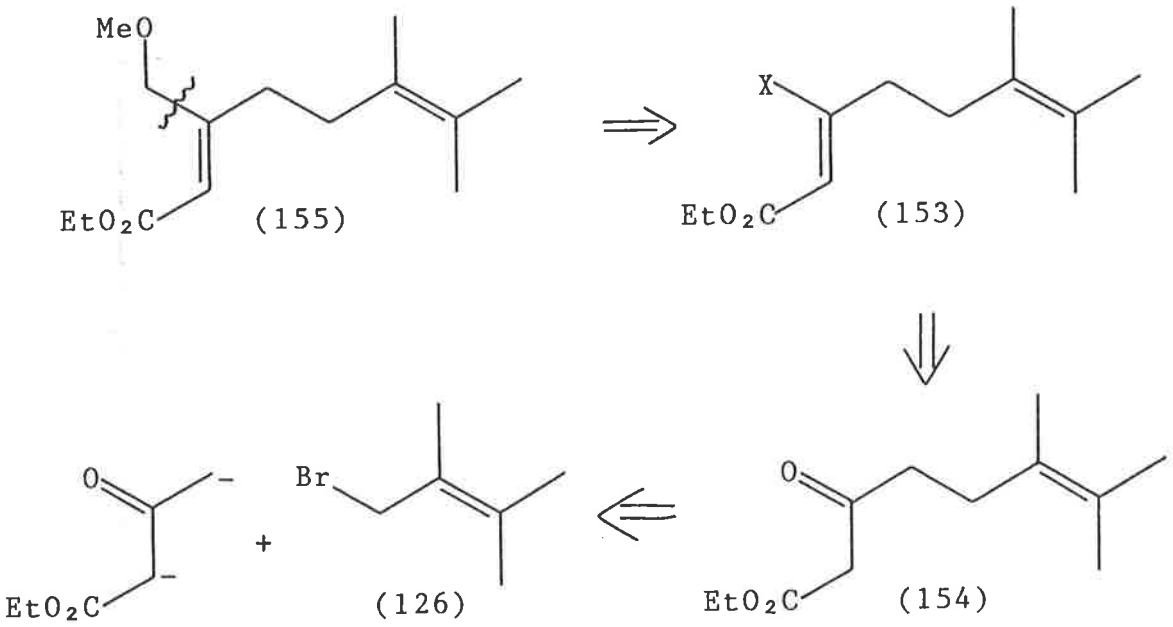
Unfortunately, the acetal moiety of (152) could not be hydrolysed without the benzyl ether also being cleaved. When the ether-acetal was stirred in a mixture of ethanol and 10% sulphuric acid (2:1), for sixteen hours at room temperature, neither the acetal nor the benzyl ether was hydrolysed and the starting material was recovered as was indicated by nmr spectroscopy. However, treatment of the ether-acetal with a mixture of ethanol and 10% sulphuric acid (1:3), for the same period of time, hydrolysed the benzyl ether and only benzyl alcohol was recovered (neither hydroxyacetaldehyde nor its acetal could be recovered from the aqueous phase). When the ether-acetal was stirred in a mixture of methanol and 10% sulphuric acid (1:1), benzyl alcohol was recovered showing that the ether had undergone partial hydrolysis. The starting material and its corresponding dimethyl acetal were also recovered showing that the acetal was undergoing exchange, yet no hydrolysis of the acetal was observed.

Benzyloxyacetaldehyde could not be prepared by the above method, and so to assess the Darzen's reaction, methoxyacetaldehyde was prepared by the oxidation[70] of 2-methoxyethanol.



Ethanolic sodium ethoxide was added to a mixture of methyl chloroacetate and methoxyacetaldehyde at -20°. The ratio of ethoxide to chloroester and aldehyde was 1.6:1.6:1.0 respectively as this has been reported[67] to be optimum. However workup gave an intractable mixture and no epoxide was isolated. The use of ether as a cosolvent proved to be no more fruitful and again only dark polymeric material was obtained.

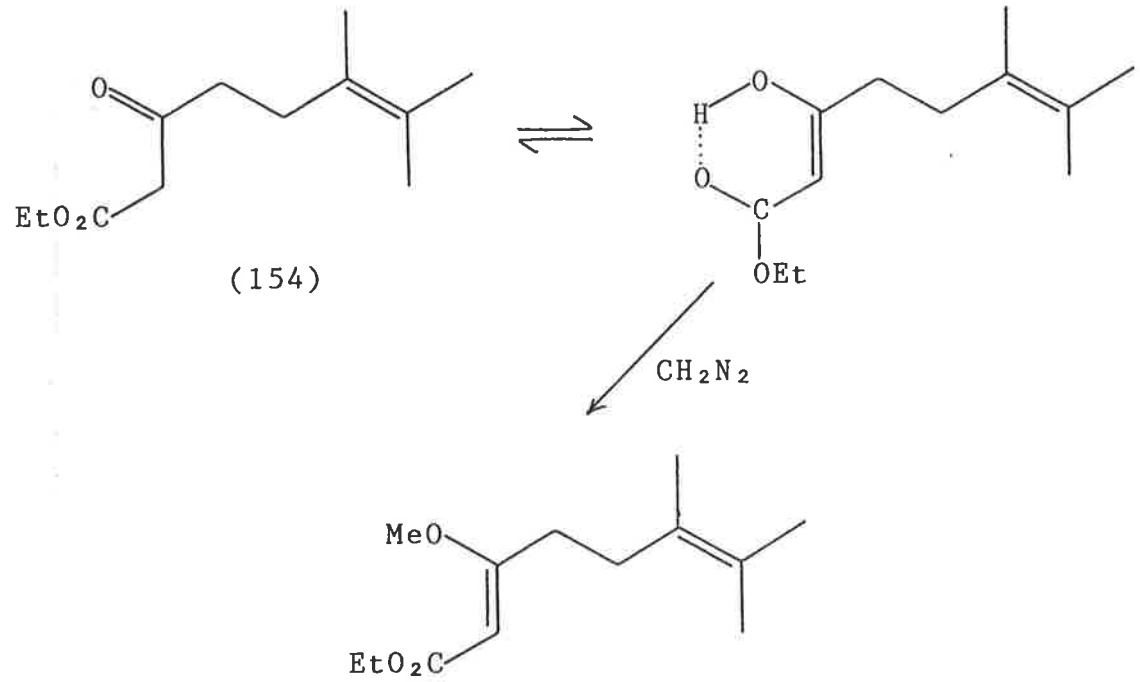
The final retrosynthetic analysis of the sidechain to be considered was that shown in scheme 37. The methoxymethyl moiety might be introduced by a suitable anion undergoing an addition-elimination sequence, replacing the leaving group X in compound (153). Examples of such addition-elimination sequences have been reported[71] in the recent literature. Compound (153) could be obtained from the corresponding β-ketoester.



Scheme 37

Ethyl acetoacetate was treated with sodium hydride in tetrahydrofuran followed by *n*-butyllithium to generate the dianion[72]. Alkylation with allyl bromide (126) gave the keto-ester (154) in 83% yield. The nmr spectrum showed a nine proton signal at δ 1.64 due to the methyl groups on the carbon-carbon double bond. The two adjacent methylene groups resonated as a multiplet at δ 2.46, and the methylene group between the two carbonyl groups resonated at δ 3.43. The mass spectrum showed the molecular ion at *m/e* 212.

Ketoester (154) could be converted to the methyl enol ether (156) by treatment with excess ethereal diazomethane over sixteen hours. The alkylation proceeded very slowly but cleanly to give one geometric isomer, which was assigned the Z-stucture. This assignment was made on the basis that it is

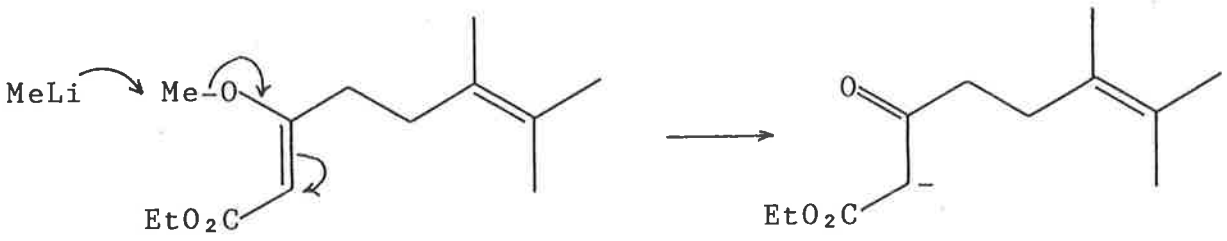


Scheme 38

the hydrogen bonded Z-enol that undergoes alkylation[73] (scheme 38). The slow rate of this reaction is probably due to the low enol content of compound (154), as its nmr spectrum shows no indication of any enol being present.

The nmr spectrum of enol ether (156) shows a sharp singlet at δ 4.85 due to the vinyl proton and another at δ 3.80 due to the methoxyl group. The two adjacent methylene groups also resonated as a singlet at δ 2.20 due to the protons being magnetically equivalent.

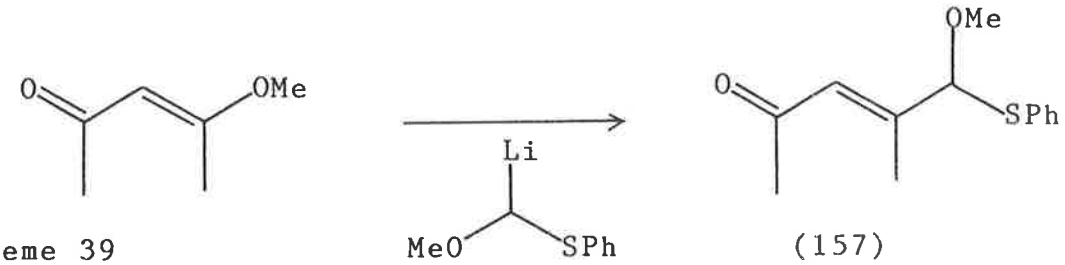
The initial investigation of the addition-elimination sequence used methyllithium and lithium dimethylcuprate as model systems. The enol ether (156) was treated with one equivalent of methyllithium in tetrahydrofuran at -70^0. The solution was



(156)

allowed to warm to room temperature and then acidic workup gave the ketoester (154). This product was formed by the methyllithium attacking the methoxyl carbon atom and thus displacing the stable enolate anion of (154). This demethylation does not occur by simple hydrolysis during workup as a small sample of the enol ether was subjected to the workup conditions and was recovered intact.

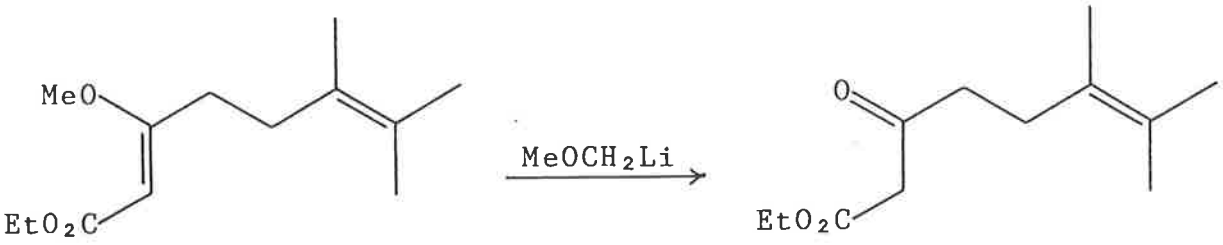
When this reaction was repeated with lithium dimethylcuprate, in tetrahydrofuran at low temperature, no reaction occurred and the enol ether was recovered after workup. Treatment of the enol ether with lithium dimethylcuprate at room temperature caused demethylation and the ketoester (154) was obtained.



Scheme 39 (157)

The methyl enol ethers of β-diketones have been reported[71] to react with heteroatom substituted alkyllithium reagents to give systems such as (157) (scheme 39). The

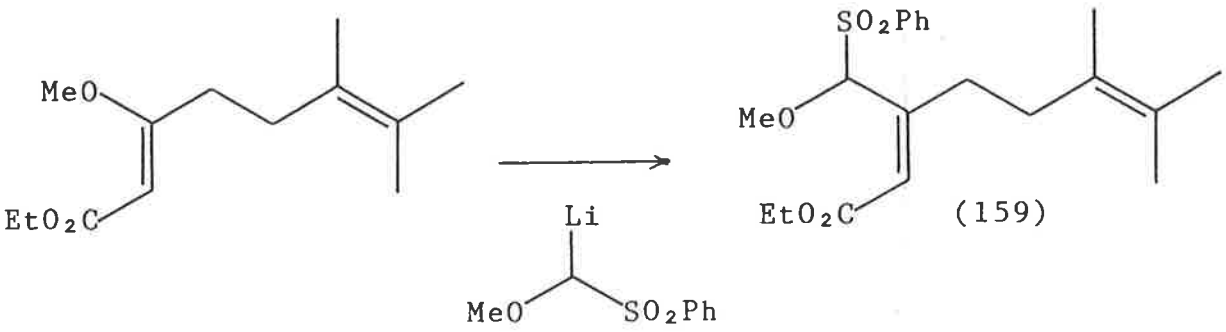
authors do not report any competing demethylation and so the heteroatom substituted methoxymethyllithium was hoped to behave similarly and undergo the desired addition-elimination sequence.



(156) (154)

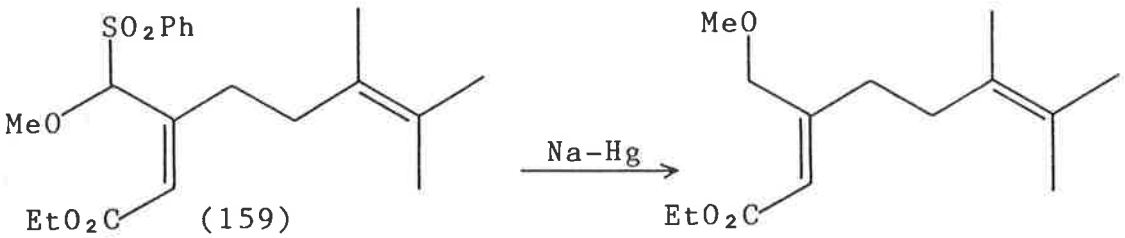
Methoxymethyllithium was prepared from methoxymethyl chloride by treatment with lithium in dimethoxymethane, according to a literature procedure[74]. Treatment of the enol ether (156) with methoxymethyllithium, in dimethoxymethane at low temperature, effected demethylation and the ketoester (154) was recovered. This reaction was repeated in the presence of cuprous iodide in an attempt to form the lithium dialkylcuprate. Treatment of methoxymethyllithium with cuprous iodide followed by subsequent addition of the enol ether at low temperature returned the starting material upon workup. It is uncertain whether the dialkylcuprate was formed, as previous work[75] in this department has met with no success in attempts at generating α-methoxycuprates.

Another alternative considered was the use of a less reactive alkyllithium reagent, for example, the sulphone stabilised alkyllithium (158). This softer anion would hopefully



(158) (159)

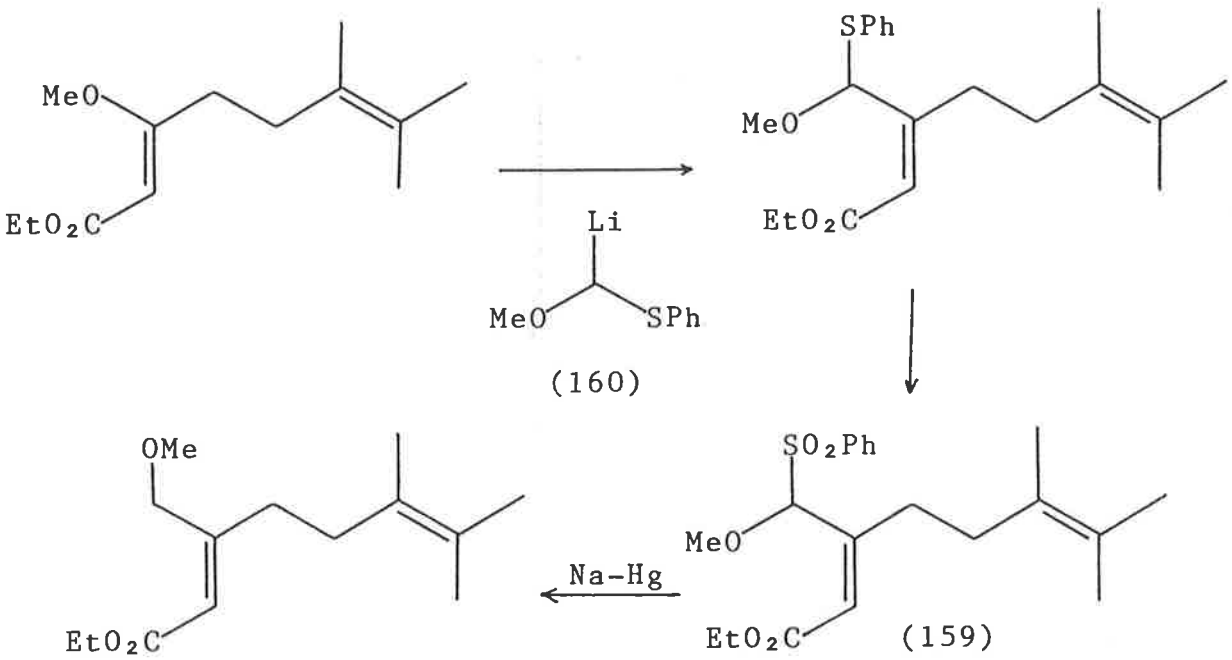
react with the unsaturated ester moiety rather than attack the methoxy carbon atom. The sulphone moiety of (159) might then be reductively cleaved using sodium amalgam.



(159)

(Methoxymethyl)sulphonylbenzene[76] was prepared by reacting methoxymethyl chloride with sodium benzensulphinate in tetrahydrofuran. The sulphone was deprotonated with *n*-butyllithium, in tetrahydrofuran at -70^0, and then the enol ether (156) was added. The solution was stirred at room temperature for two days whereupon workup returned the sulphone and the enol ether intact.

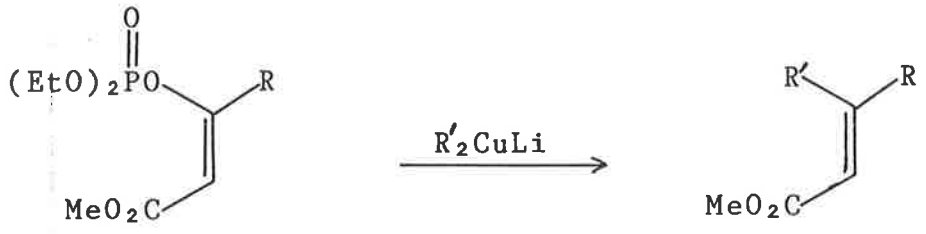
Since the methoxy(phenylthio)methyllithium (160) has been reported[71] to undergo the addition-elimination sequence (scheme 40), it was decided to investigate the reaction of



this reagent with enol ether (156). It was considered that this reagent should be the one most likely to bring success and the phenylsulphide moiety could, in principle, be converted to the sulphone and hence be reductively cleaved to give the desired sidechain.

Methoxymethyl phenyl sulphide was prepared by the alkylation of thiophenol with methoxymethyl chloride as described[77] in the literature. This sulphide was deprotonated with *sec.*-butyllithium, in tetrahydrofuran at -78^0, and was introduced to the enol ether (156). This procedure caused demethylation of the enol ether and the ketoester (154) was recovered.

The enol phosphate esters of β-ketoesters have also been used as substrates[51] for the addition-elimination sequence. These enol phosphates react with lithium dialkylcuprates to



Scheme 41

give β-alkylated unsaturated esters stereoselectively (scheme 41). The enol phosphate ester of (154) may be a better substrate for this process but unfortunately this could not be investigated in the time available.

EXPERIMENTAL

General.

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Microanalyses were performed by the Australian Microanalytical Service, Melbourne. Light petroleum refers to a fraction of boiling point 60-70°. Preparative thin layer chromatography plates were prepared from Merck Kieselgel GF_{254} and analytical thin layer chromatography was performed using Merck DC-Alufolein Kieselgel $60F_{254}$. Column chromatography was performed on Sorbsil silica. Drying and other purification of organic solvents was accomplished by standard laboratory procedures[78]. All organic extracts were dried over anhydrous sodium sulphate.

Infrared (ir) spectra were recorded on a Jasco IRA-1 grating spectrometer in carbon tetrachloride solutions unless otherwise stated. The 1602 cm^{-1} band of polystyrene was used for calibration. ^{1}H Nuclear magnetic resonance (nmr) spectra were recorded on a Jeol PMX-60 spectrometer operating at 60 MHz. ^{13}C and some ^{1}H nmr spectra were recorded using a Bruker WP80DS spectrometer operating at 20.1 or 80 MHz respectively. Deuterochloroform was used for solvent unless otherwise specified and tetramethylsilane was used as an internal standard; all chemical shifts are quoted as δ in parts per million and coupling constants are given in Hertz. Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-7D double focusing mass spectrometer or an AEI MS 3074 spectrometer, both operating at 70 eV.

4-(N-Acetylamino)-3-bromobenzoic Acid (19).

This compound was prepared by a literature procedure[5]. M.p. 214-215° (lit.[5] m.p. 230°). ν_{max} (nujol mull) 3200-2600, 1710, 1660, cm^{-1}. N.m.r. δ (CD_3COCD_3) 8.54, d, *J* 8 Hz, ArH; 8.06, d, *J* 2 Hz, ArH; 7.61, dd, *J* 8, 2 Hz, ArH; 2.14, s, $COCH_3$. Mass spectrum *m/e* 257/259 (M^+), 215/217, 197/199.

N-(2-Bromo-4-methylphenyl)-2,2-dimethylpropanamide (22).

2-Bromo-4-toluidine (5.00 g, 27 mmol) in ether (25 ml) was added dropwise to a solution of pivaloyl chloride (3.25 g, 27 mmol) in ether (100 ml) and the solution was stirred for 1 h. The solution was washed with 3 N hydrochloric acid (2 x 50 ml), then with saturated sodium hydrogen carbonate (50 ml) and the solvent was evaporated. The residue was recrystallised from light petroleum to give colourless prisms (6.50 g, 89%), m.p. 65-66° (Found: C, 53.5; H, 6.0. $C_{12}H_{16}BrNO$ requires C, 53.4; H, 6.0%). ν_{max} 3440, 1700, 1610, 1580, 1510 cm^{-1}. N.m.r. δ 8.10, d, *J* 8 Hz, ArH; 7.8, br, NH; 7.27, d, *J* 2 Hz, ArH; 7.00, dd, *J* 8, 2 Hz, ArH; 2.25, s, CH_3; 1.32, s, tBu. Mass spectrum *m/e* 269/271 (M^+), 268/270, 190, 185/187, 57.

3-Bromo-4-(2,2-dimethylpropanoylamino)-benzoic Acid (23).

The toluidide (22) (0.50 g, 1.85 mmol), potassium permanganate (1.00 g, 6.3 mmol) and magnesium sulphate (0.80 g) were refluxed in water (15 ml) for 1 h. Addition of sodium metabisulphite (0.50 g), filtration, acidification of the filtrate and extraction with ethyl acetate (2 x 30 ml) gave the *carboxylic acid* (23) (0.22 g, 40%) which was recrystallised from dichloromethane/light petroleum. M.p. 170-171.5° (Found: C, 47.7; H, 4.5. $C_{12}H_{14}BrNO_3$ requires C, 48.0; H, 4.7%). ν_{max} (nujol mull) 3440, 3000-2600, 1700, 1600, 1580, 1530 cm^{-1}. N.m.r. δ (CD_3COCD_3) 8.31, d, *J* 8 Hz, ArH; 8.2, br, NH; 8.11, d, *J* 2 Hz, ArH; 7.88, dd, *J* 8, 2 Hz, ArH; 1.33, s, tBu. Mass spectrum *m/e* 299/301 (M^+), 220, 215/217, 205, 57.

Lithiation of the Carboxylic Acid (23).

The carboxylic acid (0.100 g, 0.33 mmol) in dry tetrahydrofuran (5 ml) was cooled to -78° under nitrogen. Methyllithium (1.00 ml, 0.72 mmol) was added followed by *tert.*-butyllithium (0.35 ml, 0.67 mmol) which produced a yellow solution after stirring for 1 min. Allyl iodide (170 mg, 1.01 mmol) was then added and stirring was continued for a further 5 min at -78°. Water (5 ml) was added, the mixture was washed with ethyl acetate (5 ml) and the aqueous layer was acidified and extracted with ethyl acetate (3 x 10 ml) to give *4-(2,2-dimethylpropanoylamino)-3-iodobenzoic acid* (26) which was re-

crystallised from dichloromethane/light petroleum to give colourless needles (63 mg, 54%), m.p. 209-211° (Found: C, 41.8; H, 4.1. $C_{12}H_{14}INO_3$ requires C, 41.5; H, 4.1%). ν_{max} (nujol mull) 3400, 3000-2600, 1690, 1600, 1590, 1570, 1510 cm^{-1}. N.m.r. δ (CD_3COCD_3) 9.2, br, NH; 8.4-7.6, m, ArH, 3H; 1.23, s, tBu. Mass spectrum *m/e* 347 (M^+), 304, 263, 57.

N-(2-Bromophenyl)-2,2-dimethylpropanamide[11] *(29).*

2-Bromoaniline (3.00 g, 17 mmol) in ether (20 ml) was added dropwise to a solution of pivaloyl chloride (2.20 g, 18 mmol) and pyridine (2.00 g, 25 mmol) in ether (50 ml) and the solution was stirred for 1 h. The solution was washed with 3 N hydrochloric acid (2 x 30 ml), then with saturated sodium hydrogen carbonate (30 ml) and the solvent was evaporated. The residue was recrystallised from light petroleum to give a white crystalline solid (2.55 g, 59%), m.p. 56-57° (lit.[11] 60-61.5°). ν_{max} 3440, 1700, 1590, 1520 cm^{-1}.

Tetrakis*[iodo(tri*-n-*butylphosphine)copper(I)].*

This compound was prepared by a literature procedure[10b]. M.p. 72-73° (lit.[10b] m.p. 75°).

Lithiation[7] *of the Bromoamide (29).*

The bromoamide (0.50 g, 1.95 mmol) in dry tetrahydrofuran (25 ml) was cooled to -78° under nitrogen. Methyllithium (2.80 ml, 2.0 mmol) was added followed by *tert.*-butyllithium (2.10 ml, 4.0 mmol) which produced a yellow solution after stirring for 1 min. The electrophile (6.00 mmol) was then added and stirring was continued for a further 5 min at -78°. Saturated ammonium chloride (25 ml) was added and the mixture was extracted with ethyl acetate (3 x 25 ml). Purification of the product was achieved by chromatography on silica gel and/or recrystallisation.

By this procedure the following compounds were prepared:

A. *N-(2-Iodophenyl)-2,2-dimethylpropanamide* (32), using allyl iodide and chromatography on silica gel [ethyl acetate/light petroleum (20:80)] gave the *iodide* (32) (355 mg, 60%) then the *reduced compound* (31) (75 mg, 22%). The iodide was recrystallised from light petroleum to give colourless needles, m.p. 75.5-76° (Found: C, 43.8; H, 4.7. $C_{11}H_{14}INO$ requires C, 43.6; H, 4.7%). ν_{max} 3430, 1700, 1590, 1520 cm^{-1}. N.m.r. δ 8.18, dd, *J* 8, 2 Hz, ArH; 7.67, dd, *J* 8, 2 Hz, ArH; 7.25, td, *J*t 8, *J*d 2 Hz, ArH; 6.73, td, *J*t 8, *J*d 2 Hz, ArH; 1.30, s, tBu. Mass spectrum *m/e* 303 (M^+), 219, 176, 57.

B. *(E)-N-[2-(1-Hydroxybut-2-en-1-yl)-phenyl]-2,2-dimethyl-propanamide* (34), using *trans*-2-butenal and chromatography on silica gel [ethyl acetate/light petroleum (30:70)] gave (34) (0.45 g, 93%) as an oil. (Found: M^+ 247.1578. $C_{15}H_{21}NO_2$ requires 247.1572). ν_{max} 3360, 1680, 1610, 1590, 1520 cm^{-1}. N.m.r. δ 9.2, br, NH; 7.96, dd, *J* 8, 2 Hz, ArH; 6.9, m, ArH, 3H; 5.6, m, HC=CH; 5.18, m, *H*COH; 5.1, br, OH; 1.63, d, *J* 4 Hz, C=C.CH_3; 1.20, s, tBu. Mass spectrum *m/e* 247 (M^+), 162, 57. The compound decomposed on attempted distillation, (dec. 120°/0.01 mm).

C. *N-[2-(Prop-2-en-1-yl)-phenyl]-2,2-dimethylpropanamide* (33). This compound was prepared by lithiation of the bromoamide (29) followed by addition of *tetrakis*[iodo(tri-*n*-butylphosphine)copper(I)] (0.77 g, 1.95 mmol Cu) and then allyl chloride (0.46 g, 6.01 mmol) at -78°. Chromatography on silica gel and elution with ethyl acetate/light petroleum (30:70) gave *tri-n-butylphosphine* (0.37 g, 94%), *bromoamide* (29) (0.14 g, 28%) and then the *allylbenzene* (33) (0.20 g, 47%) which was recrystallised from light petroleum. M.p. 98-98.5° (Found: C, 77.6; H, 8.9. $C_{14}H_{19}NO$ requires C, 77.4; H, 8.8%). ν_{max} 3440, 1700, 1600, 1590, 1530 cm^{-1}. N.m.r. δ 7.80, dd, *J* 8, 2 Hz, ArH; 6.9, m, ArH, 3H; 5.9, m, CH=C; 5.1-4.9, m, $C=CH_2$; 3.38, br d, *J* 7 Hz, CH_2; 1.17, s, tBu. Mass spectrum *m/e* 217 (M^+), 177, 160, 132, 93, 57.

Reaction of the Carboxylic Acid (23) with Thionyl Chloride.

The carboxylic acid (23) (0.40 g, 1.33 mmol) was refluxed in thionyl chloride (10 ml) for 30 min. Evaporation of the volatile components gave a solid which was recrystallised from carbon tetrachloride to give *2-bromo-4-(2,2-dimethylpropanoylamino)-benzoic anhydride* (35) as colourless prisms (0.31 g, 79%), m.p. 130-131° (Found: C, 49.4; H, 4.7. $C_{24}H_{26}Br_2N_2O_5$ requires C, 49.5; H, 4.5%). ν_{max} 3440, 1790, 1740, 1720, 1600, 1580, 1520 cm^{-1}. N.m.r. δ 8.57, d, *J* 8 Hz, ArH; 8.20, d, *J* 2 Hz, ArH; 7.97, dd, *J* 8, 2 Hz, ArH; 1.37, s, tBu. Mass spectrum *m/e* 580/582/584 (M^+), 501/503, 282/284, 220, 198/200, 57.

Attempted Formation of the tert.*-Butyl Ester of (23).*

The carboxylic acid (23) (0.20 g, 0.67 mmol) was dissolved in dichloromethane (1.0 ml) containing dimethylformamide (0.1 ml) and the solution was cooled to 0°. 4-Dimethylaminopyridine[79] (5 mg), *tert.*-butanol (0.20 g, 2.7 mmol) and dicyclohexylcarbodiimide (0.15 g, 0.73 mmol) were added and the reaction mixture was stirred overnight at room temperature. The mixture was filtered, diluted with more dichloromethane (10 ml) and was washed with 0.5 N hydrochloric acid (5 ml). Removal of the solvent and recrystallisation of the residue from carbon tetrachloride gave the *anhydride* (35) (0.17 g, 85%) which was identical to that prepared earlier.

Methyl 2-Bromo-4-(2,2-dimethylpropanoylamino)-benzoate (36).

The carboxylic acid (23) (1.00 g, 3.33 mmol) was dissolved in methanol (20 ml) and an ethereal solution of diazomethane[80] (10 ml, *ca.* 10 mmol) was added. Removal of the volatile components *in vacuo* and recrystallisation of the residue from light petroleum gave the *ester* (36) as colourless prisms (0.95 g, 91%), m.p. 57-58° (Found: C, 49.5; H, 5.2. $C_{13}H_{16}BrNO_3$ requires C, 49.7; H, 5.1%). ν_{max} 3440, 1740, 1720, 1600, 1570, 1510 cm^{-1}. N.m.r. δ 8.33, d, *J* 8 Hz, ArH; 7.98, d, *J* 2 Hz, ArH; 7.77, dd, *J* 8, 2 Hz, ArH; 3.80, s, OCH_3; 1.30, s, tBu. Mass spectrum *m/e* 313/315 (M^+), 234, 229/231, 57.

N-[2-Bromo-4-(bromomethyl)phenyl]-2,2-dimethylpropanamide (38).

The toluidide (22) (2.00 g, 7.4 mmol) was refluxed with N-bromosuccinimide (1.35 g, 7.6 mmol) and benzoyl peroxide (50 mg) in carbon tetrachloride (80 ml) for 1 h. The mixture was filtered and the filtrate evaporated. Recrystallisation of the residue from light petroleum gave colourless prisms (2.10 g, 81%), m.p. 89-90° (Found: C, 41.5; H, 4.3. $C_{12}H_{15}Br_2NO$ requires C, 41.3; H, 4.3%). ν_{max} 3440, 1700, 1600, 1570, 1510 cm^{-1}. N.m.r. δ 8.17, d, *J* 8 Hz, ArH; 7.8, br, NH; 7.35, d, *J* 2 Hz, ArH; 7.10, dd, *J* 8, 2 Hz, ArH; 4.27, s, CH_2Br; 1.30, s, tBu. Mass spectrum *m/e* 347/349/351 (M^+), 346/348/350, 268/270, 190, 57.

Hydrolysis of the Benzyl Bromide (38).

The benzyl bromide (38) (0.80 g, 2.3 mmol) was dissolved in tetrahydrofuran (30 ml) and was stirred for 16 h with saturated sodium carbonate (30 ml). The layers were separated and the organic phase was washed with saturated sodium chloride (30 ml), evaporated and chromatographed on silica gel. Elution with ethyl acetate/light petroleum (50:50) gave a fraction containing the *benzyl bromide* (38) (0.25 g, *ca.* 30%) and some of the *ether* (40). Mass spectrum *m/e* M^+ 552.0639 ($C_{24}H_{30}{}^{79}Br_2N_2O_3$ requires 552.0624); 552/554/556 (ether, M^+), 473/475 (ether, M^+-Br.), 347/349/351 (benzyl bromide, M^+), 268/270 (benzyl bromide, M^+-Br.).

Further elution gave *N-[2-bromo-4-(hydroxymethyl)-phenyl]-2,2-dimethylpropanamide* (39) (0.34 g, 52%) which was recrystallised from dichloromethane/light petroleum to give colourless prisms, m.p. 90-91° (Found: C, 50.1; H, 5.7. $C_{12}H_{16}BrNO_2$ requires C, 50.4; H, 5.6%). ν_{max} ($CHCl_3$) 3640, 3500, 3440, 1690, 1610, 1580, 1520 cm^{-1}. N.m.r. δ 7.98, d, *J* 8 Hz, ArH; 7.9, br, NH; 7.35, d, *J* 2 Hz, ArH; 7.05, dd, *J* 8, 2 Hz, ArH; 4.45, s, CH_2OH; 3.9, br, OH; 1.28, s, tBu. Mass spectrum *m/e* 285/287 (M^+), 242/244, 206, 201/203, 57.

N-[2-Bromo-4-(methoxymethyl)-phenyl]-2,2-dimethylpropanamide (41).

The benzyl bromide (38) (0.50 g, 1.4 mmol) was stirred with sodium carbonate (0.30 g) in methanol (40 ml) for 3 h. The solvent was evaporated and the residue was extracted with dichloromethane (50 ml) to give a colourless oil (0.37 g, 86%) which was microdistilled. B.p. 110°/0.01 mm (Found: C, 51.9; H, 5.9. $C_{13}H_{18}BrNO_2$ requires C, 52.0; H, 6.0%). ν_{max} 3440, 1700, 1610, 1590, 1510 cm^{-1}. N.m.r. δ 8.27, d, *J* 8 Hz, ArH; 7.9, br, NH; 7.45, d, *J* 2 Hz, ArH; 7.17, dd, *J* 8, 2 Hz, ArH; 4.35, s, OCH_2; 3.35, s, OCH_3; 1.37, s, tBu. Mass spectrum *m/e* 299/301 (M^+), 298/300, 220, 57.

1-Bromo-3-methylbut-2-ene.

This compound was prepared by a literature procedure[81]. B.p. 78-80°/140 mm (lit.[81] b.p. 77-78.5°/135 mm). ν_{max} (film) 2960, 1660, 1440, 1370, 1200, 840 cm^{-1}. N.m.r. δ 5.45, br t, *J* 7 Hz, C=CH; 3.92, d, *J* 7 Hz, $C=C.CH_2$; 1.75, 1.72, both s, $C(CH_3)_2$.

Allylation of Bromoamides (39) and (41).

The bromoamide (2.00 mmol) was dissolved in dry tetrahydrofuran (30 ml) and was cooled to -78° under nitrogen. Methyllithium [2.10 mmol, for (41) or 4.20 mmol, for (39)]

was added followed by *tert.*-butyllithium (4.00 mmol). After stirring for 1 min, *tetrakis*[iodo(tri-*n*-butylphosphine)-copper(I)] (0.77 g, 2.00 mmol Cu) was added, followed 5 min later by the allyl halide (6.00 mmol). After stirring for a further 5 min, saturated ammonium chloride (30 ml) was added and the mixture was extracted with ethyl acetate (3 x 30 ml). Purification of the product was achieved by chromatography on silica gel.

By this procedure the following allylbenzenes were prepared:

A. *N-[4-Methoxymethyl-2-(prop-2-en-1-yl)-phenyl]-2,2-dimethylpropanamide* (42) using bromoamide (41) and allyl chloride, followed by chromatography on silica gel. Elution with ethyl acetate / light petroleum (30:70) gave *tri*-n-*butylphosphine* (0.33 g, 82%), *bromoamide* (41) (30 mg, 5%), *reduced compound* (43) (0.155 g, 35%) and then the *allylbenzene* (42) (0.198 g, 38%) which was microdistilled to give a colourless oil, b.p. 140°/0.01 mm (Found: C, 73.3; H, 8.4. $C_{16}H_{23}NO_2$ requires C, 73.5; H, 8.9%). ν_{max} 3460, 1690, 1630, 1590, 1510 cm^{-1}. N.m.r. δ 7.80, d, *J* 8 Hz, ArH; 7.0, m, ArH, 2H; 5.8, m, CH=C; 5.1-4.8, m, $C=CH_2$; 4.33, s, OCH_2; 3.30, br, OCH_3, $ArCH_2C=C$; 1.27, s, tBu. Mass spectrum *m/e* M^+ 261.1726 ($C_{16}H_{23}NO_2$ requires 261.1729), 204, 177, 57.

B. *N-[4-Methoxymethyl-2-(3-methylbut-2-en-1-yl)-phenyl]-2,2-dimethylpropanamide* (44) using bromoamide (41) and 1-bromo-3-methylbut-2-ene, followed by chromatography on silica gel. Elution with ethyl acetate/light petroleum (30:70) gave *tri-n-butylphosphine* (0.31 g, 77%), *bromoamide* (41) (55 mg, 9%) and then the *allylbenzene* (44) (0.45 g, 78%) which was microdistilled to give a colourless oil, b.p. 150°/0.01 mm (Found: C, 75.0; H, 9.6. $C_{18}H_{27}NO_2$ requires C, 74.7; H, 9.4%). ν_{max} 3440, 1700, 1590, 1510 cm^{-1}. N.m.r. δ 7.82, d, *J* 8 Hz, ArH; 7.1, m, ArH, 2H; 5.15, br t, *J* 7 Hz, CH=C; 4.32, s, OCH_2; 3.28, br, OCH_3, $ArCH_2C=C$; 1.73, s, $C=C(CH_3)_2$; 1.23, s, tBu. Mass spectrum *m/e* 289 (M^+), 220, 204, 57.

C. *N-[4-Hydroxymethyl-2-(prop-2-en-1-yl)-phenyl]-2,2-dimethylpropanamide* (45) using bromoamide (39) and allyl chloride, followed by chromatography on silica gel. Elution with ethyl acetate / light petroleum (50:50) gave *tri-n-butylphosphine* (0.39 g, 97%), *N-(4-hydroxymethylphenyl)-2,2-dimethylpropanamide* (50 mg, 12%) and then the *allylbenzene* (45) (0.375 g, 76%) which was microdistilled, b.p. 160°/0.01 mm to give a colourless oil which crystallised on standing. M.p. 72-73° (Found: C, 72.6; H, 8.3. $C_{15}H_{21}NO_2$ requires C, 72.8; H, 8.6%). ν_{max} ($CHCl_3$) 3640, 3440, 1680, 1630, 1590, 1520 cm^{-1}. N.m.r. δ 7.63, d, *J* 8 Hz, ArH; 7.4, br, NH; 7.0, m, ArH, 2H; 5.8, m, CH=C; 5.1-4.8, m, $C=CH_2$; 4.50, s, CH_2OH; 3.28, br d, *J* 6 Hz, $ArCH_2C=C$; 1.23, s, tBu. Mass spectrum *m/e* 247 (M^+), 162, 57.

D. *N-[4-Hydroxymethyl-2-(3-methylbut-2-en-1-yl)-phenyl]-2,2-dimethylpropanamide* (46) using bromoamide (39) and 1-bromo-3-methylbut-2-ene, followed by chromatography on silica gel. Elution with ethyl acetate/light petroleum (50:50) gave *tri-n-butylphosphine* (0.36 g, 89%), *bromoamide* (39) (40 mg, 7%) and then the *allylbenzene* (46) (0.48 g, 87%) which was microdistilled, (b.p. 190°/0.05 mm) to give a colourless oil which crystallised on standing. M.p. 102-103° (Found: C, 73.8; H, 9.0. $C_{17}H_{25}NO_2$ requires C, 74.1; H, 9.2%). ν_{max} 3650, 3450, 1700, 1620, 1600, 1580 cm^{-1}. N.m.r. δ 7.55, d, *J* 8 Hz, ArH; 7.5, br, NH; 7.1, m, ArH, 2H; 5.08, br t, *J* 7 Hz, CH=C; 4.50, s, CH_2OH; 3.25, d, *J* 7 Hz, $ArCH_2C{=}C$; 1.73, s, $C{=}C(CH_3)_2$; 1.25, s, tBu. Mass spectrum *m/e* 275 (M^+), 196, 57.

Oxidation of the Alcohol (39).

The alcohol (0.20 g, 0.70 mmol) was dissolved in acetone (20 ml) and was titrated with Jones Reagent until an orange colour persisted. The mixture was diluted with water (20 ml) and extracted with ethyl acetate (3 x 20 ml) to give an oil which was chromatographed on silica gel. Elution with ethyl acetate / light petroleum (30:70) gave *N-(2-bromo-4-formylphenyl)-2,2-dimethylpropanamide* (49) which was recrystallised from light petroleum to give colourless prisms (100 mg, 51%), m.p. 118-119° (Found: C, 50.5; H, 4.9. $C_{12}H_{14}BrNO_2$ requires C, 50.7; H, 5.0%). ν_{max} 3440, 2850, 2720, 1700, 1590, 1570, 1510

cm^{-1}. N.m.r. δ 9.75, s, CH=O; 8.57, d, *J* 8 Hz, ArH; 7.98, d, *J* 2 Hz, ArH; 7.72, dd, *J* 8, 2 Hz, ArH; 1.35, s, tBu. Mass spectrum *m/e* 283/285 (M^+), 204, 199/201, 198/200, 57.

Further elution with ethanol/dichloromethane (10:90) gave the *carboxylic acid* (23) (88 mg, 42%) which was identical to that prepared earlier.

Oxidation of the Alcohol (46).

The alcohol (0.20 g, 0.73 mmol) was treated as above to give *N-[4-formyl-2-(3-methylbut-2-en-1-yl)-phenyl]-2,2-dimethylpropanamide* (47) (0.19 g, 95%) which was microdistilled to give a colourless oil, b.p. 155°/0.05 mm (Found: C, 74.4; H, 8.3. $C_{17}H_{23}NO_2$ requires C, 74.7; H, 8.5%). ν_{max} ($CHCl_3$) 3400, 2740, 1690, 1620, 1590 cm^{-1}. N.m.r. δ 9.98, s, CH=O; 8.40, d, *J* 8 Hz, ArH; 7.88, dd, *J* 8, 2 Hz, ArH; 7.70, d, *J* 2 Hz, ArH; 5.28, br t, *J* 7 Hz, CH=C; 3.43, br d, *J* 7 Hz, $ArCH_2C{=}C$; 1.83, s, $C{=}C(CH_3)_2$; 1.33, s, tBu. Mass spectrum *m/e* 273 (M^+), 216, 204, 188, 57.

4-(2,2-Dimethylpropanoylamino)-3-(3-methylbut-2-en-1-yl)-benzoic acid (48).

A solution of silver nitrate (0.70 g, 4.1 mmol) in water (1.0 ml) was added to a solution of the aldehyde (47) (0.50 g, 1.8 mmol) in ethanol (20 ml). 1.0 M Aqueous potassium hydroxide (10 ml) was then added and the resulting suspension was

stirred for 4 h. The mixture was filtered and the filtrate was washed with ether (20 ml). The aqueous phase was then acidified and extracted with ether (2 x 20 ml) to give the *carboxylic acid* (48) (0.39 g, 75%). Recrystallisation from dichloromethane/light petroleum gave colourless prisms, m.p. 175-177° (Found: C, 70.5; H, 8.1. $C_{17}H_{23}NO_3$ requires C, 70.6; H, 8.0%). ν_{max} (nujol mull) 3380, 3000-2600, 1700, 1680, 1610, 1590, cm^{-1}. N.m.r. δ (CD_3COCD_3) 7.80, m, ArH, 3H; 5.18, br t, *J* 7 Hz, CH=C; 3.40, br d, *J* 7 Hz, $ArCH_2C=C$; 1.75, s, $C=C(CH_3)_2$; 1.27, s, tBu. Mass spectrum *m/e* 289 (M^+), 204, 57.

Hydrolysis of the Amide (48).

The amide (75 mg, 0.26 mmol) was refluxed in a mixture of concentrated hydrochloric acid (2 ml) and ethanol (2 ml) for 2 h. The solution was washed with ether (5 ml), basified and then extracted with ether (2 x 5 ml) to give a dark oil (9 mg) containing the *ethyl esters* (52) and (53). N.m.r. δ 7.6, m, ArH, 2H; 6.53, br d, *J* 8 Hz, ArH; 4.30, q, *J* 7 Hz, OCH_2CH_3; 2.6, m, $ArCH_2CH_2$; 1.7, m, $ArCH_2CH_2$; 1.35, t, *J* 7 Hz, OCH_2CH_3; 1.30, 1.23, both s, $C(CH_3)_2$. Mass spectrum *m/e* M^+ (52) 251.1474 ($C_{14}H_{21}NO_3$ requires 251.1521), M^+ (53) 233.1415 ($C_{14}H_{19}NO_2$ requires 233.1416), (M^+-Me.) (53) 218.1175 ($C_{13}H_{16}NO_2$ requires 218.1181).

The aqueous phase was then neutralised and extracted with ether (2 x 5 ml) to give a dark oil (11 mg) containing the

carboxylic acids (50) and (51). N.m.r. δ (CD_3COCD_3) 7.8, m, ArH, 3H; 6.52, br d, *J* 8 Hz, ArH; 2.8, m, $ArCH_2CH_2$; 1.8, m, $ArCH_2CH_2$; 1.30, 1.23, both s, $C(CH_3)_2$. Mass spectrum *m/e* M^+ (50) 223.1196 ($C_{12}H_{17}NO_3$ requires 223.1208), M^+ (51) 205.1099 ($C_{12}H_{15}NO_2$ requires 205.1103), (M^+-Me.) (51) 190.0864 ($C_{11}H_{12}NO_2$ requires 190.0868).

Hydrolysis of the Amide (44).

The amide (60 mg, 0.21 mmol) was refluxed in a mixture of concentrated hydrochloric acid (2 ml) and ethanol (2 ml) for 2 h. The solution was washed with ether (5 ml), basified and then extracted with ether (2 x 5 ml) to give a dark oil (6 mg) containing the *ethyl ethers* (55) and (56). N.m.r. δ 7.0, m, ArH, 2H; 6.60, br d, *J* 8 Hz, ArH; 3.50, q, *J* 7 Hz, OCH_2CH_3; 2.5, m, $ArCH_2CH_2$; 1.7, m, $ArCH_2CH_2$; 1.32, 1.28, both s, $C(CH_3)_2$; 1.30, t, *J* 7 Hz, OCH_2CH_3. Mass spectrum *m/e* M^+ (55) 237.1731 ($C_{14}H_{23}NO_2$ requires 237.1729), M^+ (56) 219.1595 ($C_{14}H_{21}NO$ requires 219.1623), (M^+-Me.) (56) 204.1383 ($C_{13}H_{18}NO$ requires 204.1389).

N-(2-Bromo-4-methylphenyl)-trifluoroacetamide (57).

Trifluoroacetic anhydride (1.20 g, 5.7 mmol) was added dropwise, over 5 min, to a stirred solution of 2-bromo-4-toluidine (1.00 g, 5.4 mmol) in dichloromethane (20 ml). After

stirring for a further 5 min, the solution was washed with saturated sodium hydrogen carbonate (2 x 20 ml), the solvent was evaporated and the residue was recrystallised from light petroleum to give colourless prisms (1.41 g, 93%), m.p. 67-67.5° (Found: C, 38.4; H, 2.5. $C_9H_7BrF_3NO$ requires C, 38.3; H, 2.5%). ν_{max} 3420, 1755, 1615, 1590, 1540 cm^{-1}. N.m.r. δ 8.2, br, NH; 8.03, d, *J* 8 Hz, ArH; 7.40, d, *J* 2 Hz, ArH; 7.07, dd, *J* 8, 2 Hz, ArH; 2.30, s, CH_3. Mass spectrum *m/e* 281/283 (M^+), 202.

N-[2-Bromo-4-(bromomethyl)-phenyl]-trifluoroacetamide (58).

The toluidide (57) (1.00 g, 3.5 mmol) was refluxed with N-bromosuccinimide (0.70 g, 3.9 mmol) in carbon tetrachloride (40 ml) for 30 min whilst being irradiated by a 40 W sun lamp. The mixture was filtered, the filtrate evaporated and the residue was recrystallised from light petroleum to give colourless prisms (1.12 g, 89%), m.p. 101-102° (Found: C, 30.1; H, 1.8. $C_9H_6Br_2F_3NO$ requires C, 30.0; H, 1.7%). ν_{max} 3400, 1750, 1600, 1580, 1530 cm^{-1}. N.m.r. δ 8.13, d, *J* 8 Hz, ArH; 7.52, d, *J* 2 Hz, ArH; 7.27, dd, *J* 8, 2 Hz, ArH; 4.35, s, CH_2Br. Mass spectrum *m/e* 359/361/363 (M^+), 280/282.

Hydrolysis of the Benzyl Bromide (58).

The benzyl bromide (2.00 g, 5.5 mmol) was dissolved in acetone (5 ml) containing water (0.1 ml) and was cooled to 0^0. Silver carbonate[82] (1.60 g, 5.8 mmol) was added over 5 min and then the reaction mixture was stirred for 1 h at room temperature. The suspension was filtered, the filtrate evaporated and the residue was chromatographed on silica gel. Elution with ethyl acetate / light petroleum gave *N-[2-bromo-4-(hydroxymethyl)-phenyl]-trifluoroacetamide* (59) (0.63 g, 38%) which was recrystallised from dichloromethane / light petroleum to give colourless prisms, m.p. 73-73.5^0 (Found: C, 36.4; H, 2.6. $C_9H_7BrF_3NO_2$ requires C, 36.3; H, 2.4%). ν_{max} 3400, 1750, 1610, 1580, 1530 cm^{-1}. N.m.r. δ 7.73, d, *J* 8 Hz, ArH; 7.37, d, *J* 2 Hz, ArH; 7.07, dd, *J* 8, 2 Hz, ArH; 4.46, s, CH_2OH. Mass spectrum *m/e* 297/299 (M^+), 280/282, 268/270, 218.

Solvolysis of the Benzyl Bromide (58) in Trifluoroacetic Acid.

The benzyl bromide (2.00 g, 5.5 mmol) was added to a solution of zinc oxide (1.0 g, 12 mmol) in trifluoroacetic acid (20 ml) and the solution was stirred for 16 h. The trifluoroacetic acid was evaporated and the residue was extracted with dichloromethane (30 ml). The extract was washed with saturated sodium hydrogen carbonate (25 ml) and the solvent was evaporated to give *N-[2-bromo-4-(trifluoroacetoxymethyl)-phenyl]-trifluoroacetamide* (60) (2.02 g, 92%) which was recrystallised

from dichloromethane / light petroleum to give colourless prisms, m.p. 81-82° (Found: C, 33.8; H, 1.6. $C_{11}H_6BrF_3NO_3$ requires C, 33.5; H, 1.5%). ν_{max} 3410, 1790, 1750, 1610, 1580, 1530 cm^{-1}. N.m.r. δ 8.23, d, *J* 8 Hz, ArH; 7.53, d, *J* 2 Hz, ArH; 7.28, dd, *J* 8, 2 Hz, ArH; 5.23, s, OCH_2. Mass spectrum *m/e* 393/395 (M^+), 314, 280/282.

Trifluoroacetoxylation of the Toluidide (57).

The toluidide (1.00 g, 3.5 mmol), potassium persulphate (1.00 g, 3.7 mmol) and copper(II) carbonate (0.50 g, 4.0 mmol) were refluxed in trifluoroacetic acid (20 ml) for 16 h. The trifluoroacetic acid was evaporated and the residue was extracted with dichloromethane (30 ml). The extract was washed with water (25 ml), saturated sodium hydrogen carbonate (25 ml) and the solvent was evaporated to give the *trifluoroacetate* (60) (1.15 g, 83%) which was identical to that prepared earlier.

Hydrolysis of the Trifluoroacetate (60).

10% Aqueous potassium hydrogen carbonate (10 ml) was added to a stirred solution of the trifluoroacetate (0.50 g, 1.3 mmol) in methanol (15 ml). After stirring for 10 min, the reaction mixture was diluted with water (20 ml) and was extracted with dichloromethane to give the *alcohol* (59) (0.37 g, 98%) which was identical to that prepared earlier.

N-[4-Hydroxymethyl-2-(3-methylbut-2-en-1-yl)-phenyl]-trifluoroacetamide (62).

The bromoamide (59) (0.50 g, 1.7 mmol) was dissolved in dry tetrahydrofuran (25 ml) and was cooled to -50° under nitrogen. Methyllithium (3.50 ml, 3.5 mmol) was added followed by *tert.*-butyllithium (1.80 ml, 3.4 mmol). After stirring for 1 min, *tetrakis*[iodo(tri-*n*-butylphosphine)copper(I)] (0.67 g, 1.7 mmol Cu) was added, followed 5 min later by 1-bromo-3-methylbut-2-ene. After stirring for a further 5 min, 5% hydrochloric acid (25 ml) was added and the mixture was extracted with ethyl acetate (3 x 25 ml) to give an oil which was chromatographed on silica gel. Elution with ethyl acetate / light petroleum (50:50) gave *tri*-n-*butylphosphine* (0.27 g, 79%) and then the *allylbenzenes* (61) and (62) (10:90, respectively) as a mixture which was recrystallised from dichloromethane/light petroleum to give pure (62), m.p. 61-62° (Found: C, 58.3; H, 5.7. $C_{14}H_{16}F_3NO_2$ requires C, 58.5; H, 5.6%). ν_{max} 3360, 1750, 1600, 1530 cm^{-1}. N.m.r. δ 8.4, br, NH; 7.70, d, *J* 8 Hz, ArH; 7.1, m, ArH, 2H; 5.08, br t, *J* 7 Hz, CH=C; 4.50, s, CH_2OH; 3.7, br, OH; 3.27, br d, *J* 7 Hz, $ArCH_2C=C$; 1.73, s, $C=C(CH_3)_2$. Mass spectrum *m/e* 287 (M^+), 218.

2-Methylbut-3-en-2-yl Acetate (63).

This compound was prepared according to a literature procedure[21a]. B.p. 75°/60 mm (lit[21a] b.p. 50°/55 mm). N.m.r. δ

6.00, dd, *J* 18, 10 Hz, C*H*=CHaHb; 5.05, dd, *J* 18, 2 Hz, HC=C*Ha*Hb; 4.95, dd, *J* 10, 2 Hz, CH=CHa*Hb*; 1.90, s, OAc; 1.48, s, $C(CH_3)_2$.

2-Methylbut-3-en-2-yl 4-Nitrobenzoate[21b] *(64).*

2-Methylbut-3-en-2-ol (1.00 g, 11.6 mmol) was dissolved in dry tetrahydrofuran (20 ml) and was treated with sodium hydride (280 mg 11.7 mmol) under nitrogen. After 5 min, 4-nitrobenzoyl chloride (2.16 g, 11.6 mmol) was added and the solution was stirred for a further 30 min. The mixture was diluted with water (20 ml) and extracted with dichloromethane (3 x 25 ml) to give the *ester* (2.29 g, 84%) which was recrystallised from dichloromethane/light petroleum to give pale yellow crystals, m.p. 114-115° (lit[21b] m.p. 115.5-116.5°). N.m.r. δ 8.08, br s, ArH, 4H; 6.15, dd, *J* 17, 10 Hz, C*H*=CHaHb; 5.20, dd, *J* 17, 2 Hz, CH=C*Ha*Hb; 5.08, dd, *J* 10, 2 Hz, CH=CHa*Hb*; 1.67, s, $C(CH_3)_2$.

2-Methyl-2-vinyloxirane (66)

This compound was prepared according to a literature procedure[21c]. B.p. 80-82°/760 mm (lit[21c] b.p. 78-82°/760 mm). N.m.r. δ 5.7-5.0, m, C*H*=CH_2; 2.73, d, *J* 5 Hz, C*Ha*HbO; 2.63, d, *J* 5 Hz, CHa*Hb*O; 1.42, s, CH_3.

Metallation and Attempted Alkylation of Bromides (59) and (41) with Electrophiles (63), (64) and (66).

The bromoamide (1.00 mmol) was dissolved in dry tetrahydrofuran (15 ml) and was metallated as before at -78°. The electophile (3.00 mmol) was added and the reaction mixture was stirred for 10 min. The reaction mixture was quenched with deuterium oxide and then was diluted with 10% hydrochloric acid (20 ml). The mixture was extracted with ethyl acetate (3 x 30 ml) to give an oil which was chromatographed on silica gel using ethyl acetate/light petroleum (50:50) as solvent.

A. Bromoamide (59) was metallated and reacted with (63). Chromatography gave *tri*-n-*butylphosphine* (182 mg) and then the *protonated* compound (65) (190 mg, 87%) which was recrystallised from dichloromethane / light petroleum to give colourless prisms, m.p. 118-119° (Found: M^+ 219.0504. $C_9H_8F_3NO_2$ requires M^+ 219.0507). N.m.r. δ 7.83, d, *J* 8 Hz, ArH, 2H; 7.20, d, *J* 8 Hz, ArH, 2H; 4.58, s, CH_2OH.

B. Bromoamide (59) was metallated and reacted with (64). Chromatography gave *tri*-n-*butylphosphine* (176 mg) and then the *protonated* compound (65) (176 mg, 80%). Mass spectrum *m/e* 219 (M^+).

C. Bromoamide (59) was metallated and reacted with (66). Chromatography gave *tri*-n-*butylphosphine* (184 mg) and then the *protonated* compound (65) (183 mg, 84%). Mass spectrum *m/e* 219 (M^+).

D. Bromoamide (41) was metallated and reacted with (66). Elution with ethyl acetate/light petroleum (30:70) gave *tri-n-butylphosphine* (166 mg) and then the *protonated* compound (43) (168 mg, 76%) as a pale yellow oil. (Found: M^+ 221.1423. $C_{13}H_{19}NO_2$ requires M^+ 221.1416). N.m.r. δ 7.63, d, *J* 8 Hz, ArH, 2H; 7.37, d, *J* 8 Hz, ArH, 2H; 4.18, s, CH_2O; 3.17, s, CH_3; 1.08, s, tBu.

Oxidation of the Alcohol (59).

The alcohol (0.50 g, 1.7 mmol) was dissolved in acetone (20 ml) and was titrated with Jones Reagent until an orange colour persisted. The mixture was diluted with water (20 ml) and extracted to give *3-bromo-4-(trifluoroacetylamino)-benzoic acid* (69) which was recrystallised from dichloromethane/light petroleum to give colourless prisms, m.p. 188-190° (Found: C, 34.8; H, 1.7. $C_9H_5BrF_3NO_3$ requires C, 34.6; H, 1.6%). ν_{max} (nujol mull) 3300, 3000-2600, 1720, 1680, 1600, 1580, 1530 cm^{-1}. N.m.r. δ (CD_3COCD_3) 8.1, m, ArH, 3H. Mass spectrum *m/e* 311/313 (M^+), 294/296, 232.

Oxidation of the Alcohol (62).

The alcohol (0.50 g, 1.7 mmol) was dissolved in acetone (20 ml) and was stirred with Jones Reagent (2 ml) for 25 min. Dilution with water (20 ml) and extraction with ethyl acetate

(3 x 20 ml) gave *3-(3-methylbut-2-en-1-yl)-4-(trifluoroacetyl-amino)-benzoic acid* (70) (0.39 g, 74%) which was recrystallised from dichloromethane/light petroleum to give colourless needles, m.p. 175-177° (Found: C, 55.7; H, 4.7. $C_{14}H_{14}F_3NO_3$ requires C, 55.8; H, 4.7%). ν_{max} (nujol mull) 3320, 2700, 1700, 1610, 1590, 1540 cm^{-1}. N.m.r. δ (CD_3COCD_3) 7.92, m, ArH, 2H; 7.58, d, *J* 8 Hz, ArH; 5.22, br t, *J* 7 Hz, CH=C; 3.45, br d, *J* 7 Hz, $ArCH_2C$=C; 1.70, s, C=$C(CH_3)_2$. Mass spectrum *m/e* 301 (M^+), 232.

Hydrolysis of the Trifluoroacetamide (62).

The amide (0.50 g, 1.7 mmol) was dissolved in 10% methanolic potassium hydroxide (20 ml) and was heated to reflux for 1 h. The solution was diluted with water (20 ml) and extracted with dichloromethane (3 x 20 ml) to give *4-amino-3-(3-methyl-but-2-en-1-yl)-benzyl alcohol* (71) (0.28 g, 84%) as a pale yellow oil. (Found: M^+ 191.1307. $C_{12}H_{17}NO$ requires 191.1310). ν_{max} ($CHCl_3$) 3630, 3480, 3400, 1620, 1500 cm^{-1}. N.m.r. δ 7.2-6.7, m, ArH, 2H; 6.37, d, *J* 8 Hz, ArH; 5.07, br t, *J* 7 Hz, C=CH; 4.30, s, CH_2OH; 3.07, br d, *J* 7 Hz, $ArCH_2C$=C; 1.67, s, C=$C(CH_3)_2$. Mass spectrum *m/e* 191 (M^+), 146, 136. The amine distilled with partial decomposition. B.p. 120°/0.01 mm.

Hydrolysis of the Trifluoroacetamide (70).

The amide (70 mg, 0.23 mmol) was refluxed in 10% methanolic potassium hydroxide (5 ml) for 1 h. The solution was diluted with water (5 ml), neutralised and extracted with ethyl acetate (3 x 10 ml) to give *4-amino-3-(3-methylbut-2-en-1-yl)-benzoic acid* (9) (40 mg, 84%) as a pale yellow solid, m.p. 126-129° (Found: M^+ 205.1101. $C_{12}H_{15}NO_2$ requires 205.1103). ν_{max} 3520, 3420, 2640, 1680, 1610 cm^{-1}. N.m.r. δ (CD_3COCD_3) 7.7, m, ArH, 2H; 6.65, d, *J* 8 Hz, ArH; 5.28, br t, *J* 7 Hz, CH=C; 3.25, br d, *J* 7 Hz, $ArCH_2C=C$; 1.82, s, $C=C(CH_3)_2$. Mass spectrum *m/e* 205 (M^+), 150.

N-(2-Bromophenyl)-trifluoroacetamide[28].

Trifluoroacetic anhydride (6.50 g, 0.031 mol) was added dropwise to a stirred solution of 2-bromoaniline (5.00 g, 0.029 mol) in dichloromethane (50 ml). After stirring for a further 5 min, the solution was washed with saturated sodium hydrogen carbonate (3 x 50 ml) and the solvent was evaporated to give a colourless solid (7.32 g, 94%) which was recrystallised from light petroleum. M.p. 69-70° (lit.[28] 70-71°). ν_{max} 3400, 1750, 1590, 1530 cm^{-1}. N.m.r. δ (CCl_4) 8.33, dd, *J* 8, 2 Hz, ArH; 7.6-6.9, m, ArH, 3H.

N-[2-(3-Methylbut-2-en-1-yl)-phenyl]-trifluoroacetamide (75).

N-(2-Bromophenyl)-trifluoroacetamide (1.00 g, 3.73 mmol) was dissolved in dry tetrahydrofuran (50 ml) and was cooled to -50° under nitrogen. Methyllithium (3.80 ml, 3.8 mmol) was added followed by *tert.*-butyllithium (4.00 ml, 7.6 mmol). After stirring for 1 min, *tetrakis*[iodo(tri-*n*-butylphosphine)-copper(I)] (1.50 g, 3.8 mmol Cu) was added, followed 5 min later by 1-bromo-3-methylbut-2-ene. After stirring for a further 5 min, 5% hydrochloric acid (50 ml) was added and the mixture was extracted with ethyl acetate (3 x 25 ml) to give an oil which was chromatographed on silica gel. Elution with

ethyl acetate/light petroleum (15:85) gave *tri-n-butylphosphine* (0.71 g, 92%), the *allylbenzene* (75) (0.75 g, 78%) and then *N-phenyltrifluoroacetamide* (56 mg, 8%). The allylbenzene was recrystallised from light petroleum to give colourless prisms, m.p. 49-50° (Found: C, 60.6; H, 5.5. $C_{13}H_{14}F_3NO$ requires C, 60.7; H, 5.5%). ν_{max} 3360, 1740, 1610, 1590 cm^{-1}. N.m.r. δ 7.92, dd, *J* 8, 2 Hz, ArH; 7.9, br, NH; 7.2, m, ArH, 3H; 5.22, br t, *J* 7 Hz, C=CH; 3.35, br d, *J* 7 Hz, $ArCH_2C=C$; 1.95, s, $C=C(CH_3)_2$. Mass spectrum *m/e* 257 (M^+), 242, 188, 160.

2-(3-Methylbut-2-en-1-yl)-aniline[83] *(77).*

The amide (75) (0.50 g, 1.95 mmol) was dissolved in 10% methanolic potassium hydroxide (20 ml) and was heated to reflux for 1 h. The solution was diluted with water (20 ml) and was extracted with dichloromethane (3 x 20 ml) to give the *allylaniline* (71) (0.28 g, 89%) which was microdistilled to give a colourless oil, b.p. 130°/10 mm (lit.[83] b.p. 130-132°/12 mm). ν_{max} 3460, 3375, 1620, 1590, 1500 cm^{-1}. N.m.r. δ 7.2-6.4, m, ArH, 4H; 5.15, br t, *J* 7 Hz, C=CH; 3.5, br, NH_2; 3.15, br d, *J* 7 Hz, $ArCH_2C=C$; 1.68, s, $C=C(CH_3)_2$.

N-[2-(3-Methylbut-2-en-1-yl)-phenyl]-acetamide (78).

This compound was prepared from the amine (77) using acetyl chloride, according to a standard procedure[80]. B.p.

$90^0/0.1$ mm (Found: M^+ 203.1306. $C_{13}H_{17}NO$ requires 203.1310). ν_{max} (film) 3400, 1710, 1580, 1520 cm^{-1}. N.m.r. δ 7.2, m, ArH, 4H; 5.10, br t, *J* 7 Hz, C=CH; 3.13, br d, *J* 7 Hz, $ArCH_2C=C$; 2.23, s, NHAc; 1.77, s, $C=C(CH_3)_2$. Mass spectrum *m/e* 203 (M^+), 202, 188, 160.

Ethyl N-[2-(3-Methylbut-2-en-1-yl)-phenyl]-carbamate (80).

Ethyl chloroformate (140 mg, 1.29 mmol) in dichloromethane (1 ml) was added to a stirred solution of the amine (77) (200 mg, 1.24 mmol) and pyridine (100 mg, 1.27 mmol) in dichloromethane (5 ml) and the solution was stirred for a further 10 min. The solution was then washed with 5% hydrochloric acid (2 x 15 ml) and the solvent was evaporated to give the *carbamate*. Recrystallisation from dichloromethane/light petroleum gave a colourless oil (252 mg, 87%). B.p. $90^0/0.08$ mm (Found: M^+ 233.1413. $C_{14}H_{19}NO_2$ requires 233.1416). ν_{max} (film) 3300, 1700, 1590, 1520 cm^{-1}. N.m.r. δ 7.67, dd, *J* 8, 2 Hz, ArH; 7.7, m, ArH, 3H; 5.02, br t, *J* 7 Hz, C=CH; 4.15, q, *J* 7 Hz, OCH_2; 3.23, br d, *J* 7 Hz, $ArCH_2C=C$; 1.73, s, $C=C(CH_3)_2$; 1.25, t, *J* 7 Hz, OCH_2CH_3. Mass spectrum *m/e* 233 (M^+), 218, 160, 144, 106.

Attempted Amidomercuration of Amides (70), (75), (78) and Carbamate (80).

The compound (0.20 mmol) and the mercuric salt (0.60 mmol) were refluxed in tetrahydrofuran (5 ml) for 16 h. Sodium borohydride (25 mg, 0.68 mmol) in 2.5 M sodium hydroxide (1 ml) was added and the mixture was stirred for 1 min and then filtered. Water (5 ml) was added to the filtrate, acidification and extraction with ethyl acetate (3 x 10 ml) returned the starting material (*ca.* 90%).

Oxymercuration of Amides (70), (75), (78) and Carbamate (80).

The compound (0.20 mmol) and mercuric acetate (0.20 or 0.40 mmol) were stirred in a mixture of water (1 ml) and tetrahydrofuran (4 ml) for 2 h. Sodium borohydride (10 mg, 0.27 mmol or 20 mg, 0.54 mmol) in 2.5 M sodium hydroxide (1 ml) was added and the mixture was stirred for 1 min and then filtered. Water (5 ml) was then added to the filtrate, acidification and extraction with ethyl acetate (3 x 10 ml) gave the *hydroxyamide*.

By this procedure the following compounds were prepared:

A. *3-(3-Hydroxy-3-methylbutyl)-4-(trifluoroacetylamino)-benzoic acid* (74), using two equivalents of mercuric acetate

to give a colourless oil (46 mg, 72%). (Found: M^+ 319.1022. $C_{12}H_{16}F_3NO_4$ requires 319.1031). ν_{max} (film) 3600, 3400-2600, 1700, 1610, 1590 cm^{-1}. N.m.r. δ (CD_3COCD_3) 7.7, m, ArH, 3H; 2.72, t, *J* 7 Hz, $ArCH_2CH_2$; 1.75, t, *J* 7 Hz, $ArCH_2CH_2$; 1.08, s, $C(CH_3)_2$. Mass spectrum *m/e* 319 (M^+), 301, 232.

B. *N-[2-(3-Hydroxy-3-methylbutyl)-phenyl]-trifluoroacetamide* (76), using two equivalents of mercuric acetate to give a colourless oil (47 mg, 85%). (Found: M^+ 275.1129. $C_{13}H_{16}F_3NO_2$ requires 275.1134). ν_{max} (film) 3300, 1720, 1590, 1550 cm^{-1}. N.m.r. δ 7.67, dd, *J* 8, 2 Hz, ArH; 7.0, m, ArH, 3H; 2.67, t, *J* 7 Hz, $ArCH_2CH_2$; 1.73, t, *J* 7 Hz, $ArCH_2CH_2$; 1.20, s, $C(CH_3)_2$. Mass spectrum *m/e* 275 (M^+), 255, 241, 146.

C. *N-[2-(3-Hydroxy-3-methylbutyl)-phenyl]-acetamide* (79), using one equivalent of mercuric acetate to give a colourless oil (34 mg, 77%). (Found: M^+ 221.1409. $C_{13}H_{19}NO_2$ requires 221.1416). ν_{max} (film) 3300, 1710, 1590, 1530 cm^{-1}. N.m.r. δ 7.1, m, ArH, 4H; 2.68, t, *J* 7 Hz, $ArCH_2CH_2$; 1.73, t, *J* 7 Hz, $ArCH_2CH_2$; 1.22, s, $C(CH_3)_2$. Mass spectrum *m/e* 221 (M^+), 203, 146.

D. *Ethyl N-[2-(3-Hydroxy-3-methylbutyl)-phenyl]-carbamate* (81), using one equivalent of mercuric acetate to give a colourless oil (41 mg, 82%). (Found: M^+ 251.1517. $C_{14}H_{21}NO_3$ requires 251.1521). ν_{max} (film) 3300, 1700, 1590, 1520 cm^{-1}. N.m.r. δ 7.65, dd, *J* 8, 2 Hz, ArH; 7.0, m, ArH, 3H; 4.18, q, *J*

7 Hz, OCH_2; 2.68, t, *J* 7 Hz $ArCH_2CH_2$; 1.73, t, *J* 7 Hz, $ArCH_2CH_2$; 1.27, br t, *J* 7 Hz, OCH_2CH_3 and $C(CH_3)_2$. Mass spectrum *m/e* 251 (M^+), 233, 218, 160.

Silylation of the Amide (75).

The amide (200 mg, 0.78 mmol) was stirred with N,O-*bis*-(trimethylsilyl)-acetamide (190 mg, 0.94 mmol) in dichloromethane (10 ml) for 16 h. The solvent was then evaporated and the residue was microdistilled to give the *silylamide* (82) as an unstable colourless oil (190 mg, 74%), b.p. $60^0/0.1$ mm. ν_{max} 1690, 1590, 1630 cm^{-1}. N.m.r. δ 7.1, m, ArH, 4H; 5.22, br t, *J* 7 Hz, C=CH; 3.25, br d, *J* 7 Hz, $ArCH_2C=C$; 1.75, s, $C=C(CH_3)_2$.

Attempted Amidomercuration of the Silylamide (82).

The silylamide (100 mg, 0.30 mmol) was stirred with mercuric acetate (100 mg, 0.31 mmol) in dry tetrahydrofuran (3 ml) for 1 h. Sodium borohydride (15 mg, 0.41 mmol) in 2.5 M sodium hydroxide (1 ml) was added and the mixture was stirred for 1 min and then filtered. Water (5 ml) was added to the filtrate and extraction with ethyl acetate (3 x 10 ml) gave the *amide* (75) (60 mg, 78%).

2,2-Dimethyl-1,2,3,4-tetrahydroquinoline[31] *(84).*

The allylaniline (77) (170 mg, 1.13 mmol) in acetone (1 ml) was added to a stirred suspension of mercuric acetate (1.05 mg, 3.30 mmol) in a mixture of water (1 ml) and acetone (4 ml). This suspension was stirred for 10 min and then sodium borohydride (130 mg, 3.51 mmol) in 2.5 M sodium hydroxide (1 ml) was added. After stirring for a further 1 min, the mixture was filtered and the filtrate was diluted with water (5 ml) and extracted with dichloromethane to give the *tetrahydroquinoline* (84) as a colourless oil (150 mg, 88%). N.m.r. δ 7.1-6.4, m, ArH, 4H; 2.72, t, *J* 7 Hz, $ArCH_2CH_2$; 1.63, t, *J* 7 Hz, $ArCH_2CH_2$; 1.15, s, $C(CH_3)_2$.

The *picrate salt* was prepared by a standard procedure[80]. M.p. 150-151° (lit.[31] m.p. 152°).

2,2-Dimethyl-1,2,3,4-tetrahydroquinoline-6-methanol (86).

The allylaniline (71) (400 mg, 2.1 mmol) in methanol (2 ml) was added to a stirred suspension of mercuric acetate (2.0 g, 6.3 mmol) in methanol (10 ml). This suspension was stirred for 10 min and then alkaline workup with sodium borohydride (0.30 g, 8.1 mmol) as described above gave an oil which was crystallised from dichloromethane/light petroleum to give pale yellow crystals (360 mg, 90%). M.p. 102-103° (Found: M^+ 191.1276. $C_{12}H_{17}NO$ requires 191.1310). ν_{max} 3640, 3420, 1620,

1500 cm^{-1}. N.m.r. δ (CD_3COCD_3) 6.8, m, ArH, 2H; 6.41, d, *J* 9 Hz, ArH; 4.40, s, CH_2OH; 2.71, t, *J* 7 Hz, $ArCH_2CH_2$; 1.63, t, *J* 7 Hz, $ArCH_2CH_2$; 1.16, s, $C(CH_3)_2$. Mass spectrum *m/e* 191 (M^+), 176, 160.

The *diacetate* was prepared by a standard procedure[80] using acetyl chloride, and was crystallised from dichloromethane/light petroleum. M.p. 65-66° (Found: C, 69.9; H, 7.5. $C_{16}H_{21}NO_3$ requires C, 69.8; H, 7.7%). ν_{max} 1735, 1650, 1610, 1580 cm^{-1}. N.m.r. δ (CCl_4) 7.1-6.7, m, ArH, 3H; 4.90, s, CH_2OAc; 2.55, t, *J* 7 Hz, $ArCH_2CH_2$; 2.00, br s, OAc, NAc; 1.67, t, *J* 7 Hz, $ArCH_2CH_2$; 1.53, s, $C(CH_3)_2$. Mass spectrum *m/e* 275 (M^+), 260, 218.

Attempted Halogenation of the Organomercury Intermediate derived from (77).

The allylaniline (77) (50 mg, 0.31 mmol) was stirred with mercuric acetate (300 mg, 0.94 mmol) in methanol (2 ml) for 15 min. A solution of the halogen (0.35 mmol) in carbon tetrachloride (0.5 ml) was added and the resulting solution was irradiated with a 40 W sun lamp for 10 min. The mixture was diluted with dichloromethane (10 ml), washed with 10% sodium metabisulphite (5 ml) and the solvent was evaporated to give a dark intractable oil (*ca.* 30 mg).

Attempted Cyclisation of Amine (77) using Chlorine or Bromine as Electrophiles.

A solution of the halogen (3.5 mmol) in carbon tetrachloride (1 ml) was added to the allylaniline (500 mg, 3.11 mmol) in carbon tetrachloride (5 ml). The solution was washed with 10% sodium metabisulphite (5 ml) and was evaporated to give an intractable oil (*ca.* 60 mg).

Attempted Cyclisation of Amine (77) using N-Chloroacetamide or N-Bromosuccinimide as Electrophiles.

The allylaniline (50 mg, 0.31 mmol) was stirred with the N-haloamide (0.35 mmol) in a mixture of water (1 ml) and tetrahydrofuran (4 ml) for 16 h. The solution was exracted with dichloromethane (2 x 10 ml) and the extract was evaporated to give an intractable oil (*ca.* 70 mg).

3-Iodo-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (87).

The allylaniline (77) (240 mg, 1.49 mmol), iodine (400 mg, 0.57 mmol) and sodium carbonate (0.5 g) were stirred in dichloromethane (15 ml) for 4 h. The mixture was washed with 10% sodium thiosulphate (20 ml) and the solvent was evaporated to give the *iodoamine* (87) (380 mg, 89%) as a pale yellow oil. (Found: M^+ 287.0177. $C_{11}H_{14}IN$ requires 287.0173). ν_{max} ($CHCl_3$) 3400, 1600, 1580 cm^{-1}. ^1H n.m.r. δ 7.2-6.8, m, ArH, 3H; 6.47,

dd, *J* 8, 2 Hz, ArH; 4.38, dd, *J* 7, 9 Hz, CHI; 3.47, br d, *J* 7 Hz, CH_2CHI; 1.35, s, $C(CH_3)_2$. ^{13}C n.m.r. δ 137.1, 136.0, 116.9, all d, aromatic CH; 52.7, s, C.N; 37.7, t, CH_2; 36.3, d, CHI; 28.8, 27.2, both q, CH_3. Mass spectrum *m/e* 287 (M^+), 272, 159, 144, 78.

The iodoamine decomposed on attempted distillation (90°/ 0.001 mm).

*Reduction of the Iodoamine (87) with Tri-*n*-butylstannane.*

The iodoamine (350 mg, 1.22 mmol) and tri-*n*-butylstannane (360 mg, 1.24 mmol) were stirred in benzene (1 ml) at 50° for 1 h, whilst being irradiated by a 40 W sun lamp. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with ethyl acetate/light petroleum (20:80) gave the *tetrahydroquinoline* (84) (115 mg, 59%), which was identical to the material prepared earlier.

*1,1-Dimethyl-7,7a-dihydro-1*H*-azirino[1,2-a]indole (91).*

The iodoamine (350 mg, 1.22 mmol) was stirred with sodium hydride (30 mg, 1.25 mmol) in dry tetrahydrofuran (10 ml) for 1.5 h at 0°. Saturated sodium carbonate (5 ml) was added and the mixture was extracted with dichloromethane (2 x 20 ml) to give the *aziridine* (91) (187 mg, 96%) as an orange oil. (Found: M^+ 159.0987. $C_{11}H_{13}N$ requires 159.1048). ν_{max} 1600,

1580, 1460, 1150 cm^{-1}. ^1H n.m.r. δ 7.3-6.7, m, ArH, 4H; 3.4, m, $ArCH_2$; 2.75, dd, *J* 3, 7 Hz, CHN; 1.30, 0.73, both s, $C(CH_3)_2$. ^{13}C n.m.r. δ 136.2, 133.1, 123.0, all d, aromatic CH; 51.9, d, CHN; 44.7, s, C.N; 30.2, t, CH_2; 26.8, 12.7, both q, CH_3. Mass spectrum *m/e* 159 (M^+).

Hydrochlorination of the Azirdine (91).

Dry hydrogen chloride was bubbled through a solution of the aziridine (200 mg, 1.26 mmol) in dichloromethane (2 ml) for 15 min at 0^0. The solution was washed with saturated sodium hydrogen carbonate (2 x 10 ml) and was evaporated to give a mixture of *chlorides* (90) and (92) (187 mg, 76%). B.p. 85^0/0.05 mm (Found: M^+ 195.0829. $C_{11}H_{14}{}^{35}ClN$ requires 195.0815). ν_{max} 3400, 1600, 1580, 1480 cm^{-1}. ^1H n.m.r. δ 7.2-6.2, m, ArH, 4H; 4.4, m, CHCl and CHN; 3.3-3.1, m, $ArCH_2$; 1.22, s, $C(CH_3)_2$. ^{13}C n.m.r. δ 137.7, 136.0, 127.7, 116.7, all d, aromatic CH; 62.7, s, C.Cl; 61.7, d, CHCl; 53.1, s, C.N; 45.6, d, CHN; 34.8, 34.2, both t, CH_2; 28.5, 28.1, 27.3, 23.3, all q, CH_3. Mass spectrum *m/e* 195 (M^+), 180, 160, 144.

*2-(1-Iodo-1-methylethyl)-1-trifluoroacetyl-2,3-dihydro-*1H*-indole-5-methanol (94).*

The amide (62) (500mg, 1.74 mmol) was dissolved in dry tetrahydrofuran (50 ml) and was cooled to 0^0. Sodium hydride

(42 mg, 1.75 mmol) was added to the stirred solution and after 15 min iodine (0.89 g, 3.5 mmol) was added and the mixture was stirred for 16 h at room temperature. 10% Sodium thiosulphate (30 ml) was then added and the mixture was extracted with dichloromethane (2 x 75 ml). The extract was evaporated to give a colourless solid (570 mg, 79%) which was recrystallised from dichloromethane/light petroleum. M.p. 103-104^0 (Found: C, 40.8; H, 3.7. $C_{14}H_{15}F_3INO_2$ requires C, 40.7; H, 3.7%). ν_{max} 3400, 1680, 1600, 1490, 1210, 1160 cm^{-1}. ^1H n.m.r. δ 7.3, m, ArH, 3H; 5.17, dd, *J* 10, 2 Hz, CHN; 4.68, s, C*H*$_2$OH; 3.3, m, ArCH$_2$; 2.07, 1.53, both s, CH$_3$. ^{13}C n.m.r. δ 126.3, 123.6, 116.9, all d, aromatic CH; 71.8, d, CHN; 64.6, t, CH$_2$OH; 50.9, s, C.I; 35.5, q, CH$_3$; 32.2, t, CH$_2$; 19.8, q, CH$_3$. Mass spectrum *m/e* 413 (M^+), 186, 144.

*Reduction of the Iodoamide (94) with Tri-*n*-butylstannane.*

The iodoamide (200 mg, 0.48 mmol) and tri-*n*-butylstannane (145 mg, 0.50 mmol) were stirred in benzene (1 ml) at 50^0 for 1h, whilst being irradiated by a 40 W sun lamp. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with ethyl acetate/light petroleum (20:80) gave *2-(1-methylethyl)-1-trifluoroacetyl-2,3-dihydro*-1H-*indole-5-methanol* (95) (93 mg, 68%). B.p. 120^0/0.03 mm (Found: C, 58.0; H, 5.7. $C_{14}H_{16}F_3NO_2$ requires C, 58.5; H, 5.6%). ν_{max} 3350, 1680, 1610, 1590 cm^{-1}. N.m.r. δ 7.90, dd, *J* 8, 2 Hz, ArH; 7.2,

m, ArH, 2H; 4.58, s, CH_2OH; 3.1, m, CHN; 2.3, m, $ArCH_2$; 1.2, m, $CHMe_2$; 0.97, d, *J* 7 Hz, CH_3; 0.63, d, *J* 7 Hz, CH_3. Mass spectrum *m/e* 287 (M^+), 244, 214.

2-(1-Iodo-1-methylethyl)-1-trifluoroacetyl-2,3-dihydro-1H-*indole-5-carboxaldehyde (97).*

The alcohol (94) (500 mg, 1.21 mmol) was dissolved in acetone (20 ml) and was titrated with Jones Reagent until an orange colour persisted. The mixture was diluted with water (20 ml) and was extracted with ethyl acetate (3 x 20 ml) to give the *aldehyde* (467 mg, 94%) as an oil. (Found: M^+ 410.9948. $C_{14}H_{13}F_3INO_2$ requires 410.9943). ν_{max} 2850, 2750, 1690, 1580 cm^{-1}. N.m.r. δ 9.80, s, CHO; 7.7, m, ArH, 3H; 5.03, dd, *J* 7, 3 Hz, CHN; 3.4, m, $ArCH_2$; 2.03, s, CH_3; 1.55, s, CH_3. Mass spectrum *m/e* 411 (M^+), 300, 284.

The Conversion of Iodoamides (94) and (97) to Aziridines.

The iodoamide (0.50 mmol) was stirred in 10% methanolic potassium hydroxide (2 ml) at room temperature for 15 min. Water (5 ml) was added and the mixture was extracted with dichloromethane (3 x 10 ml) to give the *aziridine.*

By this procedure the following compounds were prepared:

A. *1,1-Dimethyl-7,7a-dihydro-1H-azirino[1,2-a]indole-5-methanol* (96) (84 mg, 89%). (Found: M^+ 189.1159. $C_{21}H_{15}NO$ requires 189.1154). ν_{max} 3300, 1490, 1450, 1260, 1110, 740 cm^{-1}. ^1H n.m.r. δ 6.9, m, ArH; 4.48, s, CH_2OH; 3.12, br d, $ArCH_2$; 2.75, dd, *J* 7, 3 Hz, CHN; 1.30, s, CH_3; 0.73, s, CH_3. ^{13}C n.m.r. δ 152.3, 140.2, 137.3, s, aromatic C; 126.3, 123.2, 120.8, all d, aromatic CH; 65.2, t, CH_2OH; 51.9, d, CHN; 44.5, s, C.N; 30.3, t, CH_2; 26.8, q, CH_3; 12.9, q, CH_3. Mass spectrum *m/e* 189 (M^+), 174, 144.

B. *1,1-Dimethyl-7,7a-dihydro-1H-azirino[1,2-a]indole-5-carboxaldehyde* (98) (79 mg, 84%). (Found: M^+ 187.0990. $C_{12}H_{13}NO$ requires 187.0997). ν_{max} 2850, 2750, 1690, 1610, 1580, 1260, 1240, 1100 cm^{-1}. ^1H n.m.r. δ (CCl_4) 9.75, s, CHO; 7.5, m, ArH, 2H; 7.15, d, *J* 8 Hz, ArH; 3.3, m, $ArCH_2$; 2.83, dd, *J* 7, 3 Hz, CHN; 1.40, s, CH_3; 0.84, s, CH_3. ^{13}C n.m.r. δ 191.2, d, CHO; 131.2, 124.6, 121.4, all d, aromatic CH; 53.2, d, CHN; 40.9, s, C.N; 30.0, t, CH_2; 27.0, q, CH_3; 13.1, q, CH_3. Mass spectrum *m/e* 187 (M^+), 172, 144.

N-[4-Formyl-2-(3-Methylbut-2-en-1-yl)-phenyl]-trifluoroacetamide (99).

The alcohol (62) (1.00 g, 3.48 mmol) was dissolved in acetone (25 ml) and was titrated with Jones Reagent until an orange colour persisted. The mixture was diluted with water (20 ml) and extracted with ethyl acetate (3 x 20 ml) to give

the *aldehyde* (0.91 g, 92%) as a colourless oil. B.p. 120°/0.05 mm (Found: M^+ 285.0988. $C_{14}H_{14}F_3NO_2$ requires 285.0977). ν_{max} 3400, 2860, 2740, 1760, 1715, 1600, 1530 cm^{-1}. N.m.r. δ 9.72, s, CHO; 8.0-7.2, m, ArH, 3H; 5.25, br t, *J* 7 Hz, C=CH; 3.43, br d, *J* 7 Hz, $ArCH_2C=C$; 1.77, $C=C(CH_3)_2$. Mass spectrum *m/e* 285 (M^+), 146, 69.

4-Amino-3-(3-Methylbut-2-en-1-yl)-benzaldehyde (100).

The amide (99) (0.70 g, 2.46 mmol) was dissolved in 10% methanolic potassium hydroxide (20 ml) and was heated to reflux for 45 min. The solution was diluted with water (20 ml) and was extracted with dichloromethane (3 x 20 ml) to give the *allylaniline* (0.41 g, 88%) as a pale yellow oil. B.p. 110°/0.05 mm (Found: M^+ 189.1157. $C_{12}H_{15}NO$ requires 189.1154). ν_{max} 3450, 3350, 2820, 2740, 1670, 1620, 1590 cm^{-1}. N.m.r. δ 9.57, CHO; 7.5-7.0, m, ArH, 2H; 6.52, d, *J* 8 Hz, ArH; 5.02, br t, *J* 7 Hz, C=CH; 3.15, br d, *J* 7 Hz, $ArCH_2C=C$; 1.72, s, $C=C(CH_3)_2$. Mass spectrum *m/e* 189 (M^+), 174, 160, 132.

2,2-Dimethyl-3-iodo-1,2,3,4-tetrahydroquinoline-6-carboxaldehyde (101).

The allylaniline (100) (410 mg, 2.17 mmol), iodine (1.10 mg, 4.33 mmol) and sodium carbonate (0.5 g) were stirred in dichloromethane (15 ml) for 4 h. The mixture was washed with

10% sodium thiosulphate (20 ml) and the solvent was evaporated to give the *iodoamine* (500 mg, 73%) as a yellow oil. (Found: M^+ 315.0115. $C_{12}H_{14}INO$ requires 315.0120). ν_{max} 3350, 2820, 2750, 1670, 1600, 1510 cm^{-1}. ^1H n.m.r. δ 9.67, s, CHO; 7.5, m, ArH, 2H; 6.52, d, *J* 8 Hz, ArH; 4.37, dd, *J* 7, 5 Hz, CHI; 3.5, m, $ArCH_2$; 1.41, s, $C(CH_3)_2$. ^{13}C n.m.r. δ 190.2, d, CHO; 131.7, 130.3, 114.0, all d, aromatic CH; 52.7, s, C.N; 37.6, t, CH_2; 35.0, d, CHI; 28.8, 28.1, both q, CH_3. Mass spectrum *m/e* 315 (M^+), 188, 173.

Reduction of the Iodoamine (101) with Tri-n-butylstannane.

The iodoamine (200 mg, 0.63 mmol) and tri-*n*-butylstannane (185 mg, 0.64 mmol) were stirred in benzene (1 ml) at 50^0 for 1 h, whilst being irradiated by a 40 W sun lamp. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with ethyl acetate/light petroleum (30:70) gave *2,2-dimethyl-1,2,3,4-tetrahydroquinoline-6-carboxaldehyde* (102) (76 mg, 64%). B.p. 90^0/0.03 mm (Found: M^+ 189.1155. $C_{12}H_{15}NO$ requires 189.1154). ν_{max} 3350, 2740, 1670, 1600, 1510 cm^{-1}. N.m.r. δ 9.37, s, CHO; 7.3, m, ArH, 2H; 6.28, d, *J* 8 Hz, ArH; 2.75, t, *J* 7 Hz, $ArCH_2CH_2$; 1.68, t, *J* 7 Hz, $ArCH_2CH_2$; 1.05, s, $C(CH_3)_2$. Mass spectrum *m/e* 189 (M^+), 174, 143.

Epoxidation of the Allylbenzenes (62) and (75).

The allylbenzene (1.70 mmol) and *m*-chloroperbenzoic acid (0.35 g, 2.0 mmol) were stirred in dichloromethane (25 ml) for 3 h. The solution was washed with 10% sodium metabisulphite (20 ml), saturated sodium hydrogen carbonate (2 x 30 ml) and the solvent was evaporated to give the *epoxide*.

By this procedure the following epoxides were prepared:

A. *N-[2-(2,3-Epoxy-3-methylbutyl)-phenyl]-trifluoroacetamide* (103) which was recrystallised from dichloromethane / light petroleum to give colourless prisms (0.43 g, 93%), m.p. 80-81° (Found: C, 57.1; H, 5.3. $C_{13}H_{14}F_3NO_2$ requires C, 57.1; H, 5.2%). ν_{max} 3270, 1740, 1615, 1590 cm^{-1}. N.m.r. δ (CCl_4) 7.77, dd, *J* 8, 2 Hz, ArH; 7.0, m, ArH, 3H; 2.8, m, CH_2CH; 1.72, 1.27, both s, $C(CH_3)_2$. Mass spectrum *m/e* 273 (M^+), 118.

B. *N-[2-(2,3-Epoxy-3-methylbutyl)-4-(hydroxymethyl)-phenyl]-trifluoroacetamide* (104) which was recrystallised from dichloromethane/light petroleum to give colourless prisms (0.38 g, 74%), m.p. 59-60° (Found: C, 55.2; H, 5.6. $C_{14}H_{16}F_3NO_3$ requires C, 55.5; H, 5.3%). ν_{max} ($CHCl_3$) 3600, 3250, 1720, 1600, 1540 cm^{-1}. N.m.r. δ 7.83, d, *J* 8 Hz, ArH; 7.4-7.2, m, ArH, 2H; 4.62, s, CH_2OH; 3.2-2.6, m, CH_2CH; 1.48, 1.37, both s, $C(CH_3)_2$. Mass spectrum *m/e* 303 (M^+), 245, 232.

Attempted Cyclisation of Epoxides (103) and (104) using Boron Trifluoride.

The epoxide (0.67 mmol) was dissolved in dry ether (15 ml) and boron trifluoride etherate (0.30 g, 2.1 mmol) was added and the solution was stirred for 5 min. The solution was washed with water (10 ml) and the solvent was evaporated to give the *dihydroxyamide*.

By this procedure the following compounds were prepared:

A. *N-[2-(2,3-Dihydroxy-3-methylbutyl)-phenyl]-trifluoroacetamide* (108) which was recrystallised from dichloromethane/light petroleum to give colourless prisms (165 mg, 90%), m.p. 113-114° (Found: C, 53.4; H, 5.4. $C_{13}H_{16}F_3NO_3$ requires C, 53.6; H, 5.5%). ν_{max} 3600, 1735, 1590 cm^{-1}. ^1H n.m.r. δ (CD_3COCD_3) 7.80, dd, *J* 8, 2 Hz, ArH; 7.4, m, ArH, 3H; 5.55, d, *J* 4 Hz, CHO*H*; 3.85, m, C*H*OH; 2.85, d, *J* 6.5 Hz, CH_2CH; 1.57, 1.30, both s, $C(CH_3)_2$. ^{13}C n.m.r. δ (CD_3COCD_3) 136.0, 133.7, both s, aromatic C; 132.1, 128.1, 127.5, 124.6, all d, aromatic CH; 101.8, 93.4, both s, COH; 80.3, 79.1, both d, CHOH; 34.7, 34.4, both t, CH_2; 23.4, 23.2, both q, CH_3; 22.2, 22.0, both q, CH_3. Mass spectrum *m/e* 273 (M^+-H_2O), 203, 134.

B. *N-[2-(2,3-Dihydroxy-3-methylbutyl)-4-(hydroxymethyl)-phenyl]-trifluoroacetate* (109) which was recrystallised from dichloromethane/light petroleum to give colourless prisms (168 mg, 83%), m.p. 126-128° (Found: C, 51.9; H, 5.7. $C_{14}H_{18}F_3NO_4$

requires C, 52.3; H, 5.7%). ν_{max} ($CHCl_3$) 3600, 3300, 1730, 1600, 1540 cm^{-1}. ^1H n.m.r. δ (CD_3COCD_3) 7.73, d, *J* 8 Hz, ArH; 7.3, m, ArH, 2H; 5.50, d, *J* 4 Hz, CHO*H*; 4.61, d, *J* 5.5 Hz, C*H*$_2$OH; 4.32, t, *J* 5.5 Hz, CH_2O*H*; 3.8, m, C*H*OH; 2.81, d, *J* 6.5 Hz, C*H*$_2$CH; 1.57, 1.30, both s, $C(CH_3)_2$. ^{13}C n.m.r. δ (CD_3COCD_3) 141.7, 134.6, 133.5, all s, aromatic C; 130.3, 126.3, 124.5, all d, aromatic CH; 101.6, 93.3, both s, COH; 80.3, 79.0, both d, CHOH; 64.2, t, CH_2OH; 34.7, 34.4, both t, CH_2; 23.4, 23.1, both q, CH_3; 22.2, 21.9, both q, CH_3. Mass spectrum *m/e* 303 (M^+-H_2O), 288.

Boron Trifluoride Induced Rearrangement of the Epoxide (103).

The epoxide (250 mg, 0.92 mmol) and boron trifluoride etherate (0.30 g, 2.1 mmol) were stirred in dry ether (15 ml) for 3 h. The solution was washed with water (10 ml) and the solvent was evaporated to give *N-[2-(3-methyl-2-oxobutyl)-phenyl]-trifluoroacetamide* (110) (162 mg, 65%) which was recystallised from dichloromethane/light petroleum to give colourless prisms, m.p. 60-62° (Found: C, 57.0; H, 5.0. $C_{13}H_{14}F_3NO_2$ requires C, 57.1; H, 5.2%). ν_{max} ($CHCl_3$) 3250, 1720, 1700, 1610, 1600, 1540 cm^{-1}. N.m.r. δ 7.77, dd, *J* 8, 2 Hz, ArH; 7.1, m, ArH, 3H; 3.75, s, $ArCH_2CO$; 2.75, septet, *J* 7 Hz, CO.CH; 1.17, d, *J* 7 Hz, $C(CH_3)_2$. Mass spectrum *m/e* 273 (M^+), 202, 176.

Base Promoted Cyclisation of the Epoxides (103) and (104).

The epoxide (0.67 mmol) was dissolved in methanol (15 ml) and was stirred over potassium carbonate (200 mg) for 15 min. The solution was diluted with water (15 ml) and was extracted with dichloromethane (3 x 20 ml) to give the *dihydroindole*.

By this procedure the following compounds were prepared:

A. *2,3-dihydro*-1H-*indole-2-propan-2-ol* (112) (125 mg, 96%) which was recrystallised from dichloromethane/light petroleum to give colourless prisms, m.p. 82-84° (Found: M^+ 177.1152. $C_{11}H_{15}NO$ requires 177.1154). ν_{max} ($CHCl_3$) 3500, 3400, 1600, 1490 cm^{-1}. N.m.r. δ 6.9, m, ArH, 3H; 6.53, d, *J* 8 Hz, ArH; 3.77, t, *J* 9 Hz, CH_2CH; 2.63, d, *J* 9 Hz, CH_2CH; 1.23, 1.17, both s, $C(CH_3)_2$. Mass spectrum *m/e* 177 (M^+), 118.

The *acetamide* was prepared by a standard procedure[80] using acetyl chloride, and was crystallised from dichloromethane/light petroleum. M.p. 134-135° (Found: C, 71.0; H, 7.9. $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.8%). ν_{max} ($CHCl_3$) 3350, 1620, 1590 cm^{-1}. ^1H n.m.r. δ (CD_3COCD_3) 7.1, m, ArH, 4H; 4.60, dd, *J* 1.5, 9 Hz, C*Ha*.CHbHc; 3.36, dd, *J* 9, 15 Hz, CHa.C*Hb*Hc; 2.90, dd, *J* 1.5, 15 Hz, CHa.CHb*Hc*; 2.36, s, NAc; 1.17, 0.88, both s, $C(CH_3)_2$. ^{13}C n.m.r. δ (CD_3COCD_3) 127.6, 125.2, 124.4, 117.8, all d, aromatic CH; 74.3, s, COH; 69.3, d, CHN; 27.1, 24.5, 24.0 all q, CH_3. Mass spectrum *m/e* 219 (M^+), 161, 118.

B. *5-Hydroxymethyl-2,3-dihydro*-1H-*indole-2-propan-2-ol* (113) (115 mg, 76%) which was isolated as an oil. ν_{max} ($CHCl_3$) 3600, 3500, 3380, 1600, 1490 cm^{-1}. ^1H n.m.r. δ 7.1-6.9, m, ArH, 2H; 6.60, d, *J* 8 Hz, ArH; 4.54, s, CH_2OH; 3.85, t, *J* 9 Hz, CH_2CH; 2.99, d, *J* 9 Hz, CH_2CH; 1.26, 1.19, both s, $C(CH_3)_2$. ^{13}C n.m.r. δ 126.9, 124.2, 109.2, all d, aromatic CH; 71.0, s, COH; 68.6, d, CHN; 65.3, t, CH_2OH; 30.8, t, CH_2; 27.8, 24.2, both q, CH_3. The mass spectrum could not be obtained due to instability.

The *diacetate* was prepared by a standard procedure[80] using acetyl chloride to give a pale yellow oil (153 mg, 78%). (Found: M^+ 291.1475. $C_{16}H_{21}NO_4$ requires 291.1470). ν_{max} 3400, 1740, 1640, 1610, 1490 cm^{-1}. N.m.r. δ 7.2, m, ArH, 3H; 5.06, s, CH_2OAc; 4.70, dd, *J* 1.5, 9 Hz, CHa.CHbHc; 3.39, dd, *J* 9, 15 Hz, CHa.CHbHc; 2.80, dd, *J* 1.5, 15 Hz, CHa.CHbHc; 2.44, s, NAc; 2.10, s, OAc; 1.27, 0.88, both s, $C(CH_3)_2$. Mass spectrum *m/e* 291 (M^+), 233, 130.

1-(4-bromobenzoyl)-2,3-dihydro-1H-*indole-2-propan-2-ol (111).*

4-Bromobenzoyl chloride (155 mg, 0.71 mmol) in dichloromethane (1 ml) was added to a stirred solution of the dihydroindole (112) (130 mg, 0.67 mmol) and pyridine (55 mg, 0.70 mmol) in dichloromethane (5 ml) and the solution was stirred for a further 15 min. The solution was then washed with 5% hydrochloric acid (2 x 15 ml) and the solvent was evaporated

to give the *dihydroindole amide* (111) (144 mg, 94%). Recrystallisation from dichloromethane/light petroleum gave colourless prisms, m.p. 144-145° (Found: C, 59.8; H, 4.9. $C_{18}H_{18}BrNO_2$ requires C, 60.0; H, 5.0%). ν_{max} 3500, 1655, 1620, 1510 cm^{-1}. N.m.r. δ 7.40, d, *J* 8 Hz, Ar'H, 2H; 7.23, d, *J* 8 Hz, Ar'H, 2H; 7.2-6.9, m, ArH, 3H; 6.17, br d, *J* 8 Hz, ArH; 4.80, dd, *J* 1.5, 9 Hz, C*Ha*.CHbHc; 3.47, dd, *J* 9, 15 Hz, CHa.C*Hb*Hc; 2.83, dd, *J* 1.5, 15 Hz, CHa.CHb*Hc*; 1.30, 0.90, both s, $C(CH_3)_2$. Mass spectrum *m/e* 359/361 (M^+), 344/346, 183/185.

1-Methoxy-2-methylprop-2-ene[84] *(122).*

2-Methylprop-2-en-1-ol (5.0 g, 69 mmol) was stirred with sodium hydride (1.67 g, 69 mmol) in ether (50 ml). After 5 min, iodomethane (10.0 g, 70 mmol) was added and the solution was stirred for 4 h. The mixture was diluted with water (50 ml) and was extracted with ether (3 x 50 ml) to give the *methoxyalkene* (4.63 g, 78%) as a colourless oil which was distilled, b.p. 68° (lit.[84] b.p. 66.2°). N.m.r. δ 4.73, br s, $C=CH_2$; 3.65, s, CH_2; 3.16, s, OCH_3; 1.67, s, CH_3.

2-(Methoxymethyl)-2-methyloxirane[85] *(123).*

The alkene (122) (4.00 g, 47 mmol) was stirred with 3-chloroperbenzoic acid (8.5 g, 49 mmol) in dichloromethane (50 ml) for 16 h. The solution was washed with 10% sodium metabisulphite (25 ml) then with saturated sodium hydrogen carbonate (2 x 25 ml) and was fractionally distilled to give the *epoxide* (3.88 g, 81%), b.p. 113-115°. N.m.r. δ 3.27, s, OCH_3, CH_2; 2.18, d, *J* 6 Hz, OC*Ha*Hb; 2.07, d, *J* 6 Hz, OCHa*Hb*; 1.60, s, CH_3.

Treatment of Epoxide (123) with Lithium Diisopropylamide.

n-Butyllithium (1.7 ml, 2.0 mmol) was added to a solution of di*iso*propylamine (200 mg, 1.98 mmol) in dry tetrahydrofuran (5 ml) under nitrogen at 0^0. The epoxide (200 mg, 1.96 mmol) was added to this solution which was stirred continuously for 10 min. The solution was diluted with 5% hydrochloric acid (5 ml) and was extracted with ether (2 x 10 ml) and the extract was fractionally distilled to return the *epoxide* (123) (159 mg, 80%).

Treatment of Epoxide (123) with Methyllithium.

The epoxide (200 mg, 1.96 mmol) was disolved in dry tetrahydrofuran (5 ml) under nitrogen at -90^0. Methyllithium (1.9 ml, 1.9 mmol) was added and the solution was sirred and was allowed to warm to -35^0 over 30 min. The solution was diluted with 5% hydrochloric acid (5 ml) and was extracted with ether (2 x 10 ml) and the extract was fractionally distilled to return the *epoxide* (123) (147 mg, 74%).

Methyl 2-Methyloxirane-2-carboxylate (125).

This compound was prepared according to a literature procedure[37]. B.p. $68-70^0/20$ mm. N.m.r. δ 3.70, s, OCH_3; 3.08, d, *J* 6 Hz, OC*Ha*Hb; 2.73, d, *J* 6 Hz, OCHa*Hb*; 1.55, s, CH_3.

The Treatment of Epoxide (125) with Lithium Diisopropylamide.

n-Butyllithium (1.45 ml, 1.7 mmol) was added to a solution of di*iso*propylamine (174 mg, 1.72 mmol) in dry tetrahydrofuran (5 ml) under nitrogen at 0^0. The solution was cooled to -20^0 and the epoxide (200 mg, 1.72 mmol) was added and the solution was allowed to warm to room temperature over 30 min. The solution was diluted with 5% hydrochloric acid (5 ml) and was extracted with ether (2 x 10 ml). The extract was concentrated to give an orange intractable oil (140 mg).

1-Bromo-2,3-dimethylbut-2-ene (126).

This compound was prepared by a literature procedure[38], b.p. $53-55^0/20$ mm (lit.[38] b.p. $51-54^0/20$ mm). ν_{max} (film) 2990, 2900, 1650, 1440, 1370, 1200, 1180 cm^{-1}. N.m.r. δ (CCl_4) 3.87, s, CH_2Br; 1.72, br s, 3 x CH_3.

Attempted Lithiation of the Allyl Bromide (126).

The allyl bromide (200 mg, 1.23 mmol) was dissolved in dry tetrahydrofuran (10 ml) and was cooled to -78^0 under nitrogen. *n*-Buthyllithium (1.1 ml, 1.3 mmol) was added and then carbon dioxide was bubbled through the solution for 5 min. Addition of 5% hydrochloric acid (10 ml) and extraction with ether (2 x 20 ml) gave *2,3,3,5,6-pentamethylhepta-1,5-diene*[39] (87 mg, 86%) which was microdistilled to give a colourless

oil. B.p. $100^0/20$ mm (lit[39] b.p. $68^0/2.7$ mm). ν_{max} (film) 1460, 1440, 1370, 1150, 890, 790 cm^{-1}. N.m.r. δ 4.84, br s, $C=CH_2$; 2.03, s, $C=C.CH_2$; 1.80, s, $C=C.CH_3$; 1.63, s, $(CH_3)_2C=C.CH_3$; 1.05, s, $C(CH_3)_2$. Mass spectrum *m/e* 166 (M^+), 83.

4-Bromo-3-bromomethylbut-2-enoic Acid (133)

This compound was prepared by a literature procedure[43]. N.m.r. δ 5.98, s, C=CH; 4.65, 4.15, both s, both CH_2Br.

4-Bromomethylfuran-2(5H)-one[42,43] *(134).*

The dibromoacid (133) (10.0 g, 39 mmol) was dissolved in ether (100 ml) and was rapidly stirred with saturated sodium hydrogen carbonate (100 ml) for 20 min. Evaporation of the solvent from the organic phase gave the *bromolactone* as a pale yellow oil (5.83 g, 85%), b.p. $124-126^0/0.1$ mm (lit.[42] b.p. $120^0/0.1$ mm). ν_{max} (film) 2910, 1780, 1750, 1640 cm^{-1}. N.m.r. δ 6.03, s, C=CH; 4.87, s, CH_2O; 4.20, s, CH_2Br.

Attempted Metallation of the Bromolactone (134).

The bromolactone (0.25 g, 1.41 mmol) was dissolved in dry tetrahydrofuran (10 ml) and was cooled to -78^0 under nitrogen. *n*-Butyllithium (1.20 ml, 1.4 mmol) was added and then, after

stirring for 2 min, *tetrakis*[iodo(tri-*n*-butylphosphine)copper (I)] (0.60 g, 1.53 mmol Cu). After stirring for a further 2 min, the trimethylallyl bromide (126) (300 mg, 1.84 mmol) was added and stirring was continued for another 20 min. Addition of 5% hydrochloric acid (10 ml) and extraction with ethyl acetate (3 x 20 ml) gave a dark intractable oil (0.76 g).

(E)- and (Z)-4-Bromo-3-methylbut-2-enoic Acids[44] *(135) and (136).*

3,3-Dimethylacrylic acid (5.00 g, 50 mmol) and N-bromosuccinimide (10.7 g, 60 mmol) were refluxed in carbon tetrachloride (100 ml) for 1 h whilst being irradiated by a 40 W sun lamp. The mixture was filtered and the filtrate was evaporated to give a mixture of (135) and (136) (6.90 g, 77%) as an oil. N.m.r. δ 5.92, s, C=CH, (E); 5.73, s, C=CH, (Z); 4.47, s, CH_2Br, (Z); 3.92, s, CH_2Br, (E); 2.25, s, CH_3, (E); 2.08, s, CH_3, (Z). Integration showed (E):(Z), *ca.* 60:40.

The mixture of bromoacids (6.90 g, 38.5 mmol) was dissolved in ether (100 ml) and was rapidly stirred with saturated sodium hydrogen carbonate (100 ml) for 20 min. Removal of the solvent from the organic phase gave the *lactone*[42] (137) (1.25 g, 83% from the (Z)-bromoacid) as an oil. ν_{max} (film) 1780, 1750, 1640 cm^{-1}. N.m.r. δ 5.82, s, C=CH; 4.73, s, CH_2O; 2.13, s, CH_3.

The aqueous phase was acidified and extracted with ether (3 x 50 ml) to give the *(E)-bromoacid* (3.23 g, 78% recovery) which was recrystallised from light petroleum. M.p. 74-75° (lit.[44] m.p. 73-74°). ν_{max} 3400-2600, 1690, 1640, 1420, 1250, 880 cm^{-1}. N.m.r. δ 5.92, s, C=CH; 3.92, s, CH_2Br; 2.25, s, CH_3.

(E)-4-Methoxy-3-methylbut-2-enoic Acid[42] *(132).*

A solution of sodium methoxide (from sodium 0.39 g, 17 mmol) in methanol (15 ml) was added to a stirred solution of the (E)-bromoacid (135) (1.50 g, 8.4 mmol) in methanol (20 ml) and stirring was continued for 1 h. Water (50 ml) was added, and the solution was acidified and extracted with ether (3 x 10 ml) to give the *(E)-methoxyacid* (0.84 g, 77%) which was recrystallised from dichloromethane/light petroleum. M.p. 78-79°. ν_{max} 3400-2600, 1680, 1640, 1420, 1240, 1110, 920 cm^{-1}. N.m.r. δ 5.87, s, C=CH; 3.87, s, CH_2OMe; 3.32, s, OCH_3; 2.07, s, CH_3.

The Attempted γ-Alkylation of the Methoxyacid (132).

n-Butyllithium (1.30 ml, 1.6 mmol) was added to a stirred solution of di*iso*propylamine (0.160 g, 1.6 mmol) in dry tetrahydrofuran (5 ml) under nitrogen at -78°. The solution was warmed to 0° and the methoxyacid (100 mg, 0.77 mmol) in dry tetrahydrofuran (1 ml) was added and stirring was continued

for 30 min. The solution was then cooled to -78°, cuprous iodide (0.30 g, 1.57 mmol) was added and the suspension was stirred for a further 1 h. The trimethylallyl bromide (126) (0.25 g, 1.53 mmol) was added and the solution was stirred for 1 h at -50°. 10% Hydrochloric acid (10 ml) was then added and the mixture was extracted with ether (3 x 20 ml) to give a dark intractable oil (0.16 g).

Attempted Acid Hydrolysis of Lactone (137).

The lactone (300 mg, 3.06 mmol) was refluxed in 2M sulphuric acid (10 ml) for 2 h. The solution was cooled, diluted with water (20 ml) and was extracted with dichloromethane (3 x 25 ml) to return the *lactone* (137) (282 mg, 94%).

Lithium 4-Hydroxy-3-methylbut-2-enoate (139).

The lactone (137) (1.00 g, 10 mmol) was added to a stirred solution of lithium hydroxide (0.48 g, 20 mmol) in water (10 ml). After stirring for 10 min, the water was removed *in vacuo* to give the *lithium carboxylate* salt as a pale yellow powder (1.20 g, 98%), m.p. 107° (dec.). ν_{max} 1560, 1380 cm^{-1}. N.m.r. δ (D_2O) 5.73, br s, C=CH; 4.32, s, CH_2OH; 1.88, s, CH_3.

Attempted γ-Alkylation of the Lithium Carboxylate (139).

n-Butyllithium (2.80 ml, 3.4 mmol) was added to a stirred solution of the lithium carboxylate (200 mg, 1.64 mmol) in dry tetrahydrofuran (5 ml) under nitrogen at -78°. After stirring for 10 min, cuprous iodide (0.90 g, 4.72 mmol) was added and stirring was continued for a further 1 h at -78°. The trimethylallyl bromide (126) (0.53 g, 3.25 mmol) was added and then after 1 h, 10% hydrochloric acid (10 ml) was added and the mixture was extracted with ether (3 x 20 ml) to give an intractable oil (0.37 g).

4-(Phenylsulphonylmethyl)-furan-2(5H)-one (140).

This compound was prepared by a literature procedure[51]. M.p. 122-123° (lit.[51] m.p. 125°). N.m.r. δ 7.4-7.9, m, ArH, 5H; 5.87, br s, C=CH; 4.90, br s, CH_2O; 4.20, s, CH_2SO_2.

Alkylation of the Sulphone (140).

A. The sulphone (350 mg, 1.47 mmol) was dissolved in dry N,N-dimethylformamide (15 ml) and was stirred with sodium hydride (35 mg, 1.46 mmol) for 15 min at 0°. The trimethylallyl bromide (126) (240 mg, 1.47 mmol) was then added and the mixture was stirred for a further 2 h. 5% Hydrochloric acid (10 ml) was added, and the mixture was extracted with ethyl

acetate (3 x 30 ml) to give an oil which was chromatographed on silica gel. Elution with ethyl acetate/light petroleum (30:70) gave *3-[2,3-dimethylbut-2-en-1-yl]-4-[3,4-dimethyl-1-(phenylsulphonyl)-pent-3-en-1-yl]-furan*-2(5H)-*one* (142) (51 mg, 9%). Recrystallisation from dichloromethane / light petroleum gave a colourless solid, m.p. 142-144° (Found: M^+ 402.1874. $C_{23}H_{30}O_4S$ requires 402.1865). ν_{max} 1755, 1650, 1580, 1460 cm^{-1}. N.m.r. δ 7.5, m, ArH, 5H; 5.15, d, *J* 18 Hz, C*Ha*HbO; 4.75, d, *J* 18 Hz, CHa*Hb*O; 4.32, dd, *J* 9, 4 Hz, HC.SO_2; 2.7, m, 2 x CH_2; 1.5, br s, 6 x CH_3. Mass spectrum *m/e* 402 (M^+), 260, 245, 227.

Further elution gave *4-[3,4-dimethyl-1-(phenylsulphonyl)-pent-3-en-1-yl]-furan*-2(5H)-*one* (141) (136 mg, 29%) which was recrystallised from dichloromethane/light petroleum. M.p. 100-101° (Found: C, 63.3; H, 6.2. $C_{17}H_{20}O_4S$ requires C, 63.7; H, 6.3%). ν_{max} ($CHCl_3$) 1780, 1750, 1630, 1590, 1360, 1140 cm^{-1}. N.m.r. δ 7.62, m, ArH, 5H; 5.92, s, C=CH; 4.63, s, CH_2O; 4.18, t, *J* 8 Hz, HC.SO_2; 2.82, d, *J* 8 Hz, C=C.CH_2; 1.62, br s, 3 x CH_3. Mass spectrum *m/e* 179, 178, 147, 119, 117.

B. The sulphone (4.00 g, 16.8 mmol) was dissolved in a mixture of dry tetrahydrofuran (150 ml) and N,N-dimethylformamide (50 ml) and was stirred with sodium hydride (400 mg, 16.7 mmol) for 10 min at room temperature. This mixture was then added dropwise to a stirred solution of the trimethylallyl bromide (126) (5.70 g, 35.0 mmol) in tetrahydrofuran (50 ml) over 1 h. 5% Hydrochloric acid (50 ml) was added and the mix-

ture was extracted with ethyl acetate (3 x 100 ml) to give the *sulphone* (141) (3.074 g, 57%).

Reduction of the Sulphone (141).

The sulphone (340 mg, 1.06 mmol) and sodium dihydrogen phosphate (0.51 g, 4.25 mmol) were dissolved in methanol (15 ml) and the solution was stirred with 5% sodium amalgam (1.95 g, 4.24 mmol Na) at -20^0 for 1 h. Saturated ammonium chloride (10 ml) was added and the mixture was extracted with dichloromethane (3 x 15 ml) to give an oil which was chromatographed on silica gel. Elution with ethyl acetate/light petroleum (30:70) gave *(3,4-dimethylpent-3-en-1-yl)-furan-2(5H)-one* (128) as a colourless oil (180 mg, 94%) which was microdistilled, b.p. $95^0/0.04$ mm. (Found: M^+ 180.1155. $C_{11}H_{16}O_2$ requires 180.1150). ν_{max} (film) 1780, 1750, 1670, 1640 cm^{-1}. N.m.r. δ 5.77, s, C=CH; 4.70, s, CH_2O; 2.38, br s, CH_2CH_2; 1.63, br s, 3 x CH_3. Mass spectrum *m/e* 180 (M^+), 165, 83, 55, 41.

Attempted Acid Hydrolysis of Lactone (128).

The lactone (200 mg, 2.04 mmol) was refluxed in 2M sulphuric acid (10 ml) for 1 h. The solution was cooled, diluted with water (20 ml) and was extracted with dichloromethane (3 x 20 ml) to return the *lactone* (128) (115 mg, 58%).

Attempted Base Hydrolysis of Lactone (128).

The lactone (200 mg, 2.04 mmol) was added to a stirred solution of lithium hydroxide (49 mg, 2.04 mmol) in aqueous methanol (1:1) (3 ml). After stirring for 5 min, the solvent was removed from the brown solution to give a black intractable solid (250 mg).

This reaction was also carried out using dimethoxyethane as solvent, and an intractable solid was again obtained.

Attempted Cleavage of Lactone (128) with Lithium Iodide.

The lactone (110 mg, 0.61 mmol) and lithium iodide (246 mg, 1.84 mmol) were refluxed in N,N-dimethylformamide (3 ml) for 24 h. The solution was diluted with water (5 ml), acidified and was extracted with dichloromethane (3 x 10 ml) to return the *lactone* (128) (97 mg, 88%).

Attempted Cleavage of Lactone (128) with Trimethyliodosilane.

The lactone (110 mg, 0.61 mmol), sodium iodide (300 mg, 2.0 mmol) and trimethylchlorosilane (220 mg, 2.0 mmol) were refluxed in acetonitrile (2 ml) under nitrogen for 3 days. The solution was cooled, filtered and evaporated to return the *lactone* (128) (64 mg, 58%).

Attempted Cleavage of Lactone (128) with Lithium Thiolates.

A. Lithium hydride (60 mg, 7.5 mmol) was added to thiophenol (820 mg, 7.5 mmol) in N,N-dimethylformamide (20 ml) and the solution was stirred for 10 min. The lactone (670 mg, 3.7 mmol) was then added and the solution was stirred for 16 h. The solution was diluted with water (20 ml), acidified and was extracted with dichloromethane (3 x 25 ml). The extract was evaporated and the residue was chromatographed on silica gel. Elution with ethyl acetate/light petroleum (30:70) gave *thiophenol* (750 mg) then the *lactone* (128) (560 mg, 84%).

B. The above reaction was repeated with the lactone (200 mg, 1.1 mmol) and lithium thioethoxide (2.2 mmol) in N,N-dimethylformamide (5 ml) at room temperature for 16 h. Workup as above returned the *lactone* (167 mg, 84%).

Bromination (E)-Methoxyacid (132) with N-Bromosuccinimide.

The methoxyacid (300 mg, 2.31 mmol) and N-bromosuccinimide (410 mg, 2.30 mmol) were refluxed for 30 min in carbon tetrachloride (30 ml) whilst being irradiated with a 40 W sun lamp. The mixture was filtered and the filtrate was evaporated to give the *bromoacid* (145) (350 mg, 72%) as a yellow oil. (Found: M^+-CO_2H 162.9761. $C_5H_8{}^{79}BrO$ requires 162.9759). ν_{max} (film) 3400-2600, 1720, 1640, 1430, 1260, 1110 cm^{-1}. N.m.r. δ 5.83, q, *J* 2 Hz, C=CH; 5.57, s, MeOC*H*Br; 3.33, s, OCH_3; 2.07, s, CH_3. Mass spectrum *m/e* 178/180, 163/165.

Methyl (E)-4-Bromo-2-butenoate.

This compound was prepared by a literature procedure[86]. B.p. 89-90°/20 mm (lit.[86] b.p. 83-85°/13 mm). N.m.r. δ 7.08, dt, *Jd* 15, *Jt* 6 Hz, C=C*H*.CH_2; 6.13, br d, *J* 15 Hz, HC=C; 4.08, br d, *J* 6 Hz, CH_2Br; 3.50, s, CO_2CH_3.

(E)-4-Hydroxy-2-butenoic Acid.

This compound was prepared by a literature procedure[87]. M.p. 104-106° (lit.[87] m.p. 107-108°). N.m.r. δ (CD_3COCD_3) 7.08, dt, *Jd* 16, *Jt* 4 Hz, C=C*H*.CH_2; 6.07, br d, *J* 16 Hz, HC=C; 4.37, m, CH_2OH.

Methyl (E)-4-Hydroxy-2-butenoate.

(E)-4-Hydroxy-2-butenoic acid (2.00 g, 19.6 mmol) and 4-toluenesulphonic acid (100 mg) were refluxed in methanol (100 ml) for 1 h. The solution was diluted with water (60 ml) and was extracted with dichloromethane (3 x 75 ml). The extract was washed with saturated sodium hydrogen carbonate (50 ml) and was evaporated to give the *methyl ester* (1.87 g, 82%). B.p. 123-125°/20 mm (lit.[88] b.p. 118°/15 mm). ν_{max} (film) 3450, 2950, 1720, 1660, 1430 cm^{-1}. N.m.r. δ 6.92, dt, *Jd* 15, *Jt* 4 Hz, C=C*H*CH_2; 5.97, dt, *Jd* 15, *Jt* 2 Hz, HC=C; 4.27, m, CH_2OH; 3.70, s, CO_2CH_3.

Methyl (E)-4-(2,2-dimethylethyl)dimethylsilyloxy-2-butenoate (150).

Methyl (E)-4-hydroxy-2-butenoate (1.00 g, 8.6 mmol) was added to a stirred solution of *tert.*-butyldimethylsilyl chloride (1.30 g, 8.6 mmol) and 4-dimethylaminopyridine (1.05 g, 8.6 mmol) in a mixture of triethylamine (10 ml) and dichloromethane (20 ml) and stirring was continued for 16 h. The mixture was diluted with water (25 ml) and was extracted with dichloromethane (3 x 30 ml). The extract was washed with 5% hydrochloric acid (2 x 40 ml) then with water (30 ml) and was evaporated to give the *silyl ether* (1.76 g, 89%) which was distilled, b.p. $70^0/0.2$ mm. (Found: M^+ 230.1336. $C_{11}H_{22}O_3Si$ requires M^+ 230.1338). ν_{max} 1720, 1660, 1470, 1460, 1430 cm^{-1}. N.m.r. δ 6.77, dt, *Jd* 15, *Jt* 4 Hz, C=C*H*.CH_2; 5.83, dt, *Jd* 15, *Jt* 2 Hz, HC=C; 4.20, m, CH_2OSi; 3.58, s, CO_2CH_3; 0.87, s, tBu; 0.05, s, $Si(CH_3)_2$. Mass spectrum *m/e* 230 (M^+), 220, 199, 187, 173, 99.

Attempted Epoxidation of Ester (150) with 3-Chloroperbenzoic Acid.

The ester (0.50 g, 2.17 mmol) was stirred with 3-chloroperbenzoic acid (0.45 g, 2.61 mmol) in dichloromethane (25 ml) at reflux for 20 h. The solution was washed with 10% sodium metabisulphite (10 ml), then with saturated sodium hydrogen carbonate (2 x 20 ml) and was evaporated to return the *ester* (150) (0.43 g, 86%).

Attempted Epoxidation of Ester (150) with Basic Hydrogen Peroxide.

The ester (250 mg, 1.09 mmol), 30% aqueous hydrogen peroxide (0.5 ml) and 5% aqueous potassium carbonate (0.5 ml) were stirred in methanol (20 ml) for 16 h. The solution was diluted with water (20 ml) and was extracted with dichloromethane (3 x 25 ml). The extract was washed with 10% sodium metabisulphite (20 ml) and was evaporated to return the *ester* (150) (216 mg, 86%).

Attempted Epoxidation of Ester (150) with tert.-*Butylhydroperoxide.*

The ester (250 mg, 1.09 mmol) was stirred with freshly purified *tert.*-butylhydroperoxide (200 mg, 2.22 mmol) and 35% methanolic benzyltrimethylammonium hydroxide (0.25 ml) in benzene (10 ml) for 16 h. The solution was washed with 10% sodium metabisulphite (10 ml), then with water (10 ml) and was evaporated to return the *ester* (150) (197 mg, 79%).

Attempted Epoxidation of Methyl (E)-4-Hydroxy-2-butenoate with tert.-*Butylhydroperoxide.*

The ester (250 mg, 2.16 mmol), vanadyl acetylacetonate (5 mg, 0.018 mmol) and freshly purified *tert.*-butylhydroperoxide (200 mg, 2.2 mmol) were stirred in benzene (10 ml) for 4

days. The solution was washed with water (10 ml) and was evaporated to return the *ester* (173 mg, 69%).

Attempted Epoxidation of Ester (150) via the Bromohydrin.

The ester (250 mg, 1.09 mmol) was stirred with N-bromosuccinimide (195 mg, 1.10 mmol) in a mixture of water (2 ml) and tetrahydrofuran (8 ml) for 16 h. The mixture was diluted with carbon tetrachloride (30 ml) and was dried, filtered and evaporated to return the *ester* (150) (224 mg, 90%).

1,1-Diethoxy-2-benzyloxyethane (152).

Benzyl alcohol (5.00 g, 46.3 mmol) was dissolved in dry tetrahydrofuran (150 ml) and was stirred with sodium hydride (1.11 g, 46.3 mmol) at 0^0. After 5 min, 1,1-diethoxy-2-bromoethane (9.10 g, 46.3 mmol) was added and the solution was stirred at room temperature for 1.5 h. The solution was diluted with water (100 ml) and was extracted with dichloromethane (3 x 75 ml) to give a colourless oil (7.88 g, 76%). ν_{max} (film) 2960, 2860, 1490, 1450, 1050 cm^{-1}. N.m.r. δ 7.18, s, ArH, 5H; 4.57, t, *J* 6 Hz, $CHCH_2$; 4.53, s, $ArCH_2$; 3.58, 3.54, both q, *J* 7 Hz, both OCH_2CH_3; 3.28, d, *J* 6 Hz, $CHCH_2$; 1.18, t, *J* 7 Hz, OCH_2CH_3. Mass spectrum *m/e* 91.

Attempted Hydrolysis of Acetal (152).

A. The acetal (250 mg, 1.12 mmol) was stirred, for 16 h, in a mixture of ethanol (10 ml) and 10% sulphuric acid (5 ml). Addition of water (10 ml) and extraction with dichloromethane (3 x 20 ml) returned the *acetal* (152) (223 mg, 89%).

B. The acetal (250 mg, 1.12 mmol) was stirred, for 16 h, in a mixture of ethanol (5 ml) and 10% sulphuric acid (15 ml). Workup as above gave *benzyl alcohol* (102 mg, 84%).

C. The acetal (250 mg, 1.12 mmol) was stirred, for 16 h, in a mixture of methanol (5 ml) and 10% sulphuric acid (5 ml). Workup as above gave a mixture (160 mg) of *benzyl alcohol* (60%), *diethyl acetal* (152) (15%) and the *dimethyl acetal* (25%). (The composition of this mixture is based on the nmr integration.) N.m.r. δ 7.22, br, ArH, 5H; 4.55, br, $ArCH_2$, $CHCH_2$; 3.58,3.54, both q, *J* 7 Hz, both OCH_2CH_3; 3.32, s, OCH_3; 3.28, d, *J* 6 Hz, $CHCH_2$; 1.18, t, *J* 7 Hz, OCH_2CH_3.

2-Methoxyacetaldehyde.

This compound was prepared according to a literature procedure[70]. B.p. 89-90° (lit.[89] b.p. 92.3°). ν_{max} (film) 2850, 2720, 1720, 1350, 1240 cm^{-1}. N.m.r. δ 9.72, t, *J* 2 Hz, CH=O; 3.95, d, *J* 2 Hz, CH_2; 3.36, s, OCH_3.

Attempted Darzen's Condensation of 2-Methoxyacetaldehyde with Methyl Chloroacetate.

Ethanolic sodium ethoxide [prepared from sodium (0.49 g, 21.3 mmol) and ethanol (10 ml)] was added dropwise, over 1h, to a stirred mixture of methyl chloroacetate (2.35 g, 21.7 mmol) and 2-methoxyacetaldehyde (1.00 g, 13.5 mmol) at -20^0. The mixture was then warmed to 50^0 and stirring was continued for 3 h. Addition of water (50 ml) followed by extraction with dichloromethane (3 x 75 ml) gave a dark intractable mixture.

The reaction was repeated using ether (30 ml) as a cosolvent and again an intractable mixture was obtained.

Ethyl 2,3-Dimethyl-6-oxooctanoate (154).

Ethyl acetoacetate (1.16 g, 10 mmol) was added dropwise to a suspension of sodium hydride (0.27 g, 11 mmol) in tetrahydrofuran (25 ml) under nitrogen at 0^0. After stirring for 10 min, *n*-butyllithium (6.2 ml, 10 mmol) was added and the solution was stirred for an additional 10 min. 4-Bromo-2,3-dimethylbut-2-ene (1.80 g, 11 mmol) in tetrahydrofuran (2 ml) was added and the reaction mixture was warmed slowly to room temperature over 15 min. A mixture of concentrated hydrochloric acid (2 ml), water (5 ml) and ether (15 ml) was added and the reaction mixture was extracted with dichloromethane (3 x 25 ml) to give an oil (2.36 g, 83%) which was distilled,

b.p. 60°/0.15 mm. (Found: M^+ 212.1396. $C_{12}H_{20}O_3$ requires M^+ 212.1412). ν_{max} 2900, 1740, 1710, 1620 cm^{-1}. N.m.r. δ 4.20, q, *J* 7 Hz, OCH_2; 3.43, s, $CO.CH_2.CO$; 2.46, m, CH_2CH_2; 1.64, s, 3 x CH_3; 1.28, t, *J* 7 Hz, OCH_2CH_3. Mass spectrum *m/e* 212 (M^+), 194, 83.

Ethyl 2,3-Dimethyl-6-methoxy-6-octenoate (156).

The ketoester (154) (700 mg, 3.30 mmol) was stirred with diazomethane[80] (10 mmol) in ether (10 ml) for 16 h. The solution was evaporated to give the *methyl enol ether* (709 mg, 95%). (Found: M^+ 226.1564. $C_{13}H_{22}O_3$ requires M^+ 226.1569). ν_{max} (film) 2950, 1710, 1630, 1460, 1370 cm^{-1}. N.m.r. δ 4.85, s, C=CH; 4.03, q, *J* 7 Hz, OCH_2; 3.80, s, OCH_3; 2.20, s, CH_2CH_2; 1.67, s, 3 x CH_3; 1.23, t, *J* 7 Hz, OCH_2CH_3.

Treatment of Enol Ether (156) with Methyllithium.

The enol ether (100 mg, 0.44 mmol) was dissolved in dry tetrahydrofuran (10 ml) and was cooled to -70° under nitrogen. Methyllithium (0.44 ml, 0.44 mmol) was added to the solution which was allowed to warm to room temperature over 1.5 h. The reaction mixture was poured into 10% sulphuric acid (20 ml) and was extracted with dichloromethane (3 x 25 ml) to give the *ketoester* (154) (72 mg, 77%).

Treatment of Enol Ether (156) with Lithium Dimethylcuprate.

A. Methyllithium (0.88 ml, 0.88 mmol) was added to a stirred suspension of copper(I) iodide (84 mg, 0.44 mmol) in dry tetrahydrofuran (10 ml) under nitrogen at 0^0. This solution was stirred for 5 min and was then cooled to -70^0. The enol ether (100 mg, 0.44 mmol) was added and the solution was allowed to warm to room temperature over 1.5 h. The reaction mixture was poured into 10% sulphuric acid (20 ml) and was extracted with dichloromethane (3 x 25 ml) to return the *enol ether* (156) (79 mg, 79%).

B. The above reaction was repeated and stirring was continued for 2 h at room temperature. Workup as above gave the *ketoester* (154) (76 mg, 81%).

Methoxymethyllithium.

0.72 M Methoxymethyllithium in dimethoxymethane was prepared according to a literature procedure[74].

Treatment of Enol Ether (156) with Methoxymethyllithium.

The enol ether (100 mg, 0.44 mmol) was dissolved in dry dimethoxymethane (10 ml) and was cooled to -70^0 under nitrogen. Methoxymethyllithium (0.63 ml, 0.44 mmol) was added to the solution which was allowed to warm to room temperature

over 1.5 h. The reaction mixture was poured into 10% sulphuric acid (20 ml) and was extracted with dichloromethane (3 x 25 ml) to give the *ketoester* (154) (69 mg, 74%).

Attempted Formation of Lithium Bis*(methoxymethyl)cuprate and Reaction with Enol Ether (156).*

Methoxymethyllithium (1.25 ml, 0.88 mmol) was added to a stirred suspension of copper(I) iodide (84 mg, 0.44 mmol) in dry dimethoxymethane (10 ml) under nitrogen at 0^0. This solution was stirred for 5 min and then the enol ether (100 mg, 0.44 mmol) was added and stirring was continued for a further 1 h at room temperature. The reaction mixture was poured into 10% sulphuric acid (20 ml) and was extracted with dichloromethane (3 x 25 ml) to return the *enol ether* (78 mg, 84%).

(Methoxymethyl)sulphonylbenzene.

This compound was prepared according to a literature procedure[90]. M.p. 68-69^0 (lit.[76] m.p. 69-70^0). N.m.r. δ 7.8-7.3, m, ArH, 5H; 4.40, s, CH_2; 3.57, s, OCH_3.

Treatment of Enol Ether (156) with Methoxy(phenylsulphonyl)-methyllithium.

(Methoxymethyl)sulphonylbenzene (82 mg, 0.44 mmol) was dissolved in dry tetrahydrofuran (10 ml) and was cooled to -70^0 under nitrogen. *n*-Butyllithium (0.29 ml, 0.44 ml) was added and the solution was stirred for 5 min. The enol ether (100 mg, 0.44 mmol) was then added and the solution was warmed to room temperature and stirred for 2 days. The solution was poured into 10% sulphuric acid (20 ml) and was extracted with dichloromethane (3 x 25 ml) to give an oil which was chromatographed on silica gel. Elution with ethyl acetate / light petroleum (30:70) gave the *enol ether* (68 mg, 68%) followed by the *sulphone* (66 mg, 80%).

[(Methoxymethyl)thio]benzene.

This compound was prepared according to a literature procedure[77]. N.m.r. δ 7.4-7.0, m, ArH, 5H; 4.80, s, CH_2; 3.30, s, OCH_3.

Treatment of Enol Ether (156) with Methoxy(phenylthio)-methyllithium[71].

[(Methoxymethyl)thio]benzene (68 mg, 0.44 mmol) and TMEDA (51 mg, 0.44 mmol) were dissolved in dry tetrahydrofuran (10

ml) and the solution was cooled to -78° under nitrogen. *sec.*-Butyllithium (0.25 ml, 0.44 ml) was added and the solution was stirred for 2 h. The enol ether (100 mg, 0.44 mmol) was then added and the solution was allowed to warm to room temperature over 1.5 h. The solution was poured into 10% sulphuric acid (20 ml) and was extracted with dichloromethane (3 x 25 ml) to give an oil which was chromatographed on silica gel. Elution with ethyl acetate/light petroleum (30:70) gave the *thioether* (60 mg, 88%) followed by the *keto ester* (154) (77 mg, 83%).

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