SOME REACTIONS OF ACETYLENIC ALCOHOLS

A thesis

presented for the degree

of

Doctor of Philosophy in Chemistry

in the

University of Canterbury

by

R. W. Vannoort

Christchurch, New Zealand

1983

TABLE OF CONTENTS

CHAPTER		PAGE
	ABSTRACT	1
1	GENERAL INTRODUCTION	2
	1.1 Background	2
	1.2 Allenic Compounds from Propargyl Alcohols	2
	1.3 Allylic Alcohols from Propargyl Alcohols	11
	1.4 Reduction of Propargyl Alcohols to give both Allenes and Alkenols -Solvent Effects	19
2	LITHIUM ALUMINIUM HYDRIDE REDUCTION OF 2,2-DI-(METHOXYMETHYL)-3-PHENYLHEX-4-YN-3-OL (98) AND 1-METHOXY-2,2-DIMETHYL-3-PHENYLHEX-4-YN-3-OL (90b)	35
	2.1 Introduction	35
	2.2 Synthesis of Alkynol (98)	36
	2.3 Reactions of Alkynol (98)	38
	2.4 Discussion of Alkynol (98) Reactions . .	45
	2.5 Synthesis of Alkynol (90b)	49
	2.6 Reactions of Alkynol (90b)	49
	2.7 Discussion of Alkynol (90b) Reactions. .	53

CHAPTER PAGE

3 LITHIUM ALUMINIUM HYDRIDE REDUCTIONS OF 1-METHOXY-2-PHENYLPENT-3-YN-2-OL (136), 1-METHOXY-3-PHENYLHEX-4-YN-3-OL (137), AND 7-METHOXY-4-PHENYLHEPT-2-YN-4-OL (138) . . . 57

3.1 Introduction 57

3.2 Synthesis of Alkynol (136) 58

3.3 Reactions of Alkynol (136) 58

3.4 Discussion of Alkynol (136) Reactions. . 62

3.5 Purification of Alkynol (137). 64

3.6 Reactions of Alkynol (137) 64

3.7 Discussion of Alkynol (137) Reactions. . 69

3.8 Synthesis of Alkynol (138) 71

3.9 Reactions of Alkynol (138) 72

3.10 Discussion of Alkynol (138) Reactions. . 75

4 LITHIUM ALUMINIUM HYDRIDE REDUCTION OF PROPARGYL ALCOHOLS IN BENZENE SOLVENT. 76

4.1 Introduction 76

4.2 Synthesis of Alkynol (90a) 77

4.3 Reactions of Alkynols (90a), (90b) and (98) 77

4.4 Discussion of Alkynol (90a), (90b) and (98) Reactions 78

4.5 Reactions of Alkynols (18), (136), (137) and (138). 79

4.6 Discussion of Alkynol (18), (136), (137) and (138) Reactions. 82

CHAPTER PAGE

5 EXPERIMENTAL

5.1 Apparatus, Materials and Instrumentation . 83

5.2 Experimental Relating to Chapter 2 85

5.3 Experimental Relating to Chapter 3 110

5.4 Experimental Relating to Chapter 4 140

APPENDIX 149

REFERENCES 152

ACKNOWLEDGEMENTS 177

TABLE OF ILLUSTRATIONS

	Page		Page
Scheme 1,3	24	Table 1	168
Scheme 2	25	Table 2	169
Scheme 4,5	26	Table 3	170
Scheme 6,7	27	Table 4	171
Scheme 8	28	Table 5	172
Scheme 9	29	Table 6	173
Scheme 10	30	Table 7	174
Scheme 11,14	31		
Scheme 12	32		
Scheme 13	33		
Table A	34		
Scheme 15,16	159	Block A	175
Scheme 17,18	160	Block B	176
Scheme 19,20	161		
Scheme 21,22	162		
Scheme 23,24,25	163		
Scheme 26	164		
Scheme 27,28,29	165		
Scheme 30	166		
Scheme 31,32,33	167		

ABSTRACT

The lithium aluminium hydride (deuteride) reduction of 2,2-di-(methoxymethyl)-3-phenylhex-4-yn-3-ol (98), in a range of ether solvents has been examined. Intramolecular solvation of the aluminium atom during the reduction process has been identified and the mode of formation of the reaction products discussed. Isolation and identification of the unexpected cyclopropane derivatives (115) and (116) resulted in extending studies to encompass the reaction of 1-methoxy-2,2-dimethyl-3-phenylhex-4-yn-3-ol (90b) with lithium aluminium hydride (deuteride). Cyclopropane derivatives were also isolated and the mode of formation of propenyl-cyclopropane (125) established.

In an attempt to determine the effect of ring size in intramolecular solvation, 1-methoxy-2-phenylpent-3-yn-2-ol (136), 1-methoxy-3-phenylhex-4-yn-3-ol (137) and 7-methoxy-4-phenylhept-2-yn-4-ol (138), were synthesized and their reactions with lithium aluminium hydride (deuteride) in diethyl ether, tetrahydrofuran or 2,5-dimethyltetrahydrofuran were studied. It was observed that intramolecular solvation occurs for methoxy compounds (136) and (137) but not for (138); these results are discussed.

A semi-quantitative rate comparison was made for the reactions of 2,2-dimethyl-3-phenylhex-4-yn-3-ol (90a), its 1-methoxy-(90b) and 1,1-dimethoxy-(98) derivatives, when reduced by lithium aluminium hydride (deuteride) in benzene solvent. Similar work was undertaken on 2-phenylpent-3-yn-2-ol (18), its 1-methoxy derivative (136), and methoxy alkynols (137) and (138). Rate enhancement was only observed when the alkynols contained an internal ether moiety.

CHAPTER 1

GENERAL INTRODUCTION

1.1 BACKGROUND

The field of complex metal hydride reductions has grown at a phenomenal rate since the appearance in 1947 of the first papers concerning the preparation and properties of lithium aluminium hydride[1] and its ability to reduce a range of organic functional groups.[2] Although other complex metal hydrides have since been reported, by far the greater number of applications in organic synthesis utilize lithium aluminium hydride, $LiAlH_4$. Its frequent use is undoubtedly related to its relative stability, ease of handling and availability.

The basis of this Ph.D. research is one such current area of interest and involves the study of propargyl alcohol reductions with lithium aluminium hydride in a variety of ether solvents. Two reaction paths may be followed in reactions of this type. The first, infrequently observed, type of reaction yields an allenic compound, while the second, more frequently observed reaction path, leads to the formation of allylic alcohols, in which the double bond may have the *cis* or *trans* stereochemistry.

1.2 ALLENIC COMPOUNDS FROM PROPARGYL ALCOHOLS

Allenes are compounds which contain the $\rangle C{=}C{=}C\langle$ grouping. The earliest authentic synthesis of an allenic compound was reported in 1888[3] and involved debromination of 2,3-dibromopropene with zinc, essentially the same technique as

is used today to create the parent, "allene"[4]. The fact that early allenic preparations involved numerous and often tedious experimental procedures, together with the mistaken belief that the cumulated double-bond system would prove to be relatively unstable, meant that interest in allenic syntheses diminished dramatically. Allenes came to be regarded as chemical curiosities mainly of interest for the chirality which van't Hoff had successfully predicted as long ago as 1875[5].

The presence of an optically active allene in nature was first shown in 1952, when Celmer and Solomons[6] characterized the fungal metabolite myomycin (1). It was

$$HC{\equiv}CC{\equiv}CCH{=}C{=}CCH\overset{c}{=}CHCH\overset{t}{=}CHCH_2CO_2H$$

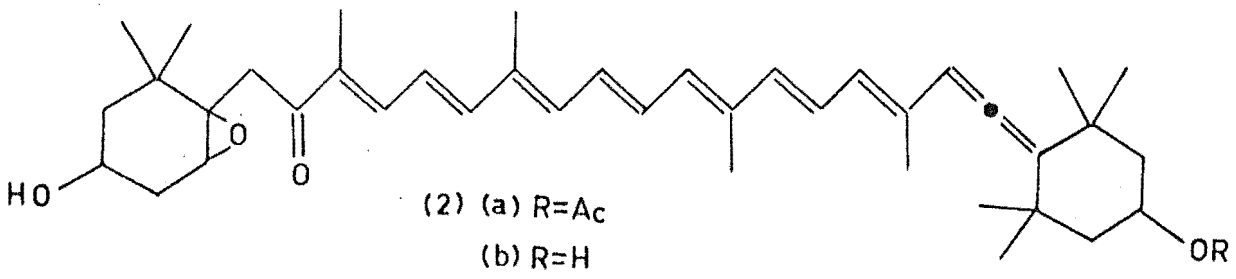
(1)

later recognised that many other optically active allenes occur in natural products, including other fungal

$$RC{\equiv}CC{\equiv}CCH{=}C{=}CR'$$

(1a)

metabolites (all of which contain the characteristic diyne-allene grouping (1a)); the carotenoid pigments



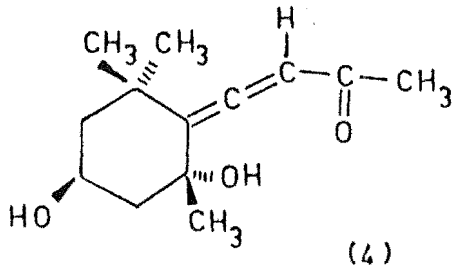
(2) (a) R=Ac
(b) R=H

of brown algae (fucoxanthin (2a)[7], neoxanthin (2b)[8]);

$$Me(CH_2)_{10}CH=C=CH(CH_2)_3CO_2H$$

(3)

labellenic acid (3) from the seed oil of *Leonotis nepetaefolia*[9], and an allenic sesquiterpenoid (4) from the grasshopper



(4)

Romalea Microptera[10]. The search for new allenic syntheses was thus rekindled.

One such technique developed, involved the reduction of propargyl alcohols of type (5) with lithium aluminium hydride. Common structural features are summarised in Scheme 1.*

In the reduction process, the initial hydride attack on the hydroxyl group of alkynol (5) results in the formation of an oxygen-aluminium bond with the concommittant evolution of hydrogen. The alkynyloxyaluminium hydride group (6) then functions as a hydride donor, donating a hydride ion intramolecularly to the near carbon of the acetylenic triple bond, coupled with a concerted shift of an electron pair and the departure of the group X. The group X may be a chlorine group (leaving as Cl^- [11,12]), a hydroxyl group (leaving as $^-OAlH_2$ [13,14]), a tetrahydropyranyloxy group (leaving as (9) [15,16,17]), a tertiary alkylammonium group (leaving as Me_3N [18] or $PhCH(CH_3)NMe_2$ [19]), an alkoxy group (leaving as ^-OR, R=n-C_3H_7, t-C_4H_9, $CH_2CH=CH_2$, or $(C_2H_5)N(CH_2)_2$ [20]) or an oxiran oxygen atom which leaves as an alkoxide[21]. The stereochemistry of the reaction allows

* Schemes 1-14 as foldouts at end of General Introduction.

the approaching hydride ion to attack either *syn* or *anti* to the displaced group X, resulting in the diastereomeric allenes (7) and (8) respectively.

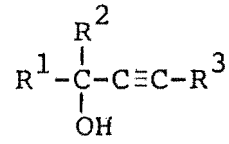
It continues to be a matter of debate whether the allene-forming reaction is synchronous S_Ni' as implied in Scheme 1, or whether the alternative S_N2' mechanism involving an *addition-elimination* process is in fact occurring. The S_N2' mechanism, analogous to the S_N2' reaction in allylic systems, is given in Scheme 2. The first step of the reduction involves the formation of the oxygen-aluminium bond with the resultant hydrogen evolution, and is identical with the first step of Scheme 1. The aluminium bound to the oxygen then serves to donate a hydride ion intramolecularly to the near carbon of the acetylenic function resulting in the formation of two carbanions (a) and (b) which are stabilized by the counterions in the reaction medium. Subsequent attack by the electron pair on C4 followed by the elimination of the group X yields the diastereomeric allenes (7) and (8). It is also possible for carbanion (a) to gain extra stabilization by the formation of the five-membered cyclic organoaluminium species (10) and (11); geometric constraints (trans double bond in five-membered ring) do not permit this stabilization to occur for carbanion (b). *Anti elimination* of (10) then results in the formation of allene (7) (overall *syn displacement*), while *syn elimination* of (11) gives allene (8) (overall *anti displacement*). Evidence for the existence of the alanate intermediates (10) and (11) has only recently been reported[22,23,24].

In an analogous manner to the aforementioned α-allenic alcohol production (Scheme 1), the reaction of propargyl

alcohols of type (12) with lithium aluminium hydride has been shown to afford high yields of the corresponding β-allenic alcohols. Their common structural features are summarised in Scheme 3, where the group X was an alkoxy group[22,25], a tetrahydropyranyloxy group[22,25], or a quaternary ammonium group[19,25].

After initial alkynyloxyaluminium hydride formation, both reaction mechanisms are again possible. The unusual stability of the six-membered ring intermediate (15) in the reduction of (12) (R^1=R^2=H, R^3=CH_3, R^4=H, X=Thp-O- [22]) with lithium aluminium hydride in diethyl ether at -10° confirmed the stepwise S_N2' nature of the reaction, whereas when the same reduction was carried out in refluxing diethyl ether, no intermediate (15) could be detected. For this reason, the alternative S_Ni' mechanism could not be excluded as it would have led to the same stereochemical result in the chiral systems studied thus far[19,22].

In 1969, it was reported[26] for the first time that allenes could also be formed by the reaction of lithium aluminium hydride on a propargyl alcohol of a slightly different structure (16).



(16)

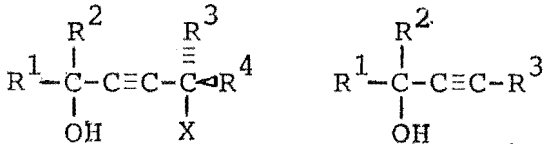
Since then many other propargyl alcohols of type (16), 1,1-diphenylbut-2-yn-1-ol (17)[27], 2-phenylpent-3-yn-2-ol (18)[28], and cholest-5-en-23-yn-3β, 25-diol (19)[29] (see Scheme 4), have all been shown to give allenes on reaction with lithium aluminium hydride in solvents such as diethyl ether, di-isopropyl ether or tetrahydrofuran.

The example which can best be used to illustrate the stereochemistry of this allene-forming mechanism is the reaction of the (R)-(+)-acetylenic alcohol, 2,2,3-trimethyl-hex-4-yn-3-ol (21) with lithium aluminium hydride (deuteride) in refluxing diglyme to give the (S)-(-)-allene, 4,5,5-trimethyl-hexa-2,3-diene (22)[30]. The mechanism is given in Scheme 5.

The initial step of the reaction is the same as in Scheme 1 and involves the formation of the oxygen-aluminium bond with the resultant emission of hydrogen. The single hydroxyl group which has been modified to $^{-}OAlH_3$ ($^{-}OAlD_3$) first donates a hydride (deuteride) ion to the far carbon of the alkyne function (C5) and subsequently leaves as $^{-}OAlH_2$ ($^{-}OAlD_2$) in the formation of the (S)-(-)-allene (22). For the synchronous S_Ni' mechanism described above, the formation of the (S)-allene (22) from the (R)-acetylenic alcohol (21) required that the hydride (deuteride) attack at C5 must have occurred *syn*-coplanar to the hydroxyl group. This stereochemical evidence did not, of course, exclude the alternative S_N2' mechanism in which *syn addition* could yield the possible labile organoaluminium intermediate (23) which on *syn elimination* would have again led to the same stereochemical result overall.

To date the apparent duality of S_Ni' and S_N2' allene-forming reactions has not been conclusively resolved. Claesson et al.[23,31] have tentatively suggested that for propargyl systems, the situation regarding concertedness may be more critical than in the analogous allylic systems, since the *addition-elimination* process may, in fact, be preferred with poor leaving groups.

In a similar vein, a variety of studies on the stereochemical course of the allene-forming 1,3-substitution reactions of chiral propargyl derivatives (of type 5 and 16) with lithium aluminium hydride have now shown that the whole



(5) (16)

spectrum of substitution, spanning between the *syn*(*cis*) and *anti*(*trans*) extremes, can be expected.

Hlubucek et al.[21] observed a *syn displacement* mechanism in the ring opening of a 4,5-epoxy-2-alkyn-1-ol derivative (24) with lithium aluminium hydride in refluxing tetrahydrofuran to afford the α-allenic alcohol (26), see Scheme 6. They postulated that an organoaluminium intermediate of type (25) was probably involved, and it was therefore predicted that in the final allenic product (26) the tertiary hydroxyl-group at C5 would be *trans* to the C3-hydroxyl and *anti* to the -CHOH-Me grouping on the allenic system. This expectation was proved conclusively by an X-ray crystallographic analysis of the p-bromo-benzoate (27) of the product[32]. Thus the reaction of lithium aluminium hydride with the acetylene (24) resulted in insertion of a hydrogen atom at the position α to the propargyl hydroxyl group, and *cis* to the departing propargyl oxygen substituent.

Work done by Damm et al.[30] (Scheme 5) has also shown the preference for the *syn* mechanism in the allene-forming reduction of propargyl alcohols (of type 16) with lithium aluminium hydride.

In contrast, the reverse stereoselectivity was recently reported by C. Elsevier et al.[33] who established, also by X-ray crystallography, that the stereospecific formation of allenes (29) and (31) by reduction of the corresponding 17-hydroxy-17-propynyl substituted steroids (28) and (30), (Scheme 7), was an *anti* instead of a *syn* 1,3-substitution reaction as previously reported[34]. (Aluminium chloride was found to increase the yield of allene production, without detectable loss of stereospecificity). This revision of literature data conclusively showed that the very speculative application[35] of the Lowe-Brewster rules[36,37] used to assign the absolute configuration of allenes directly attached to the steroid nucleus was indeed *not* valid.

The study undertaken by Claesson et al.[23] has now shown that several factors play a decisive role in the stereochemistry of 1,3-hydride substitutions in chiral propargyl systems. They include:

(a) The nature of the hydride reagent used. When lithium aluminium hydride-aluminium chloride was used to reduce (S)-dec-3-yn-2-ol, an increase in the *anti:syn* ratio was observed when the amount of aluminium chloride was decreased[23]. In their work on the reduction of chiral 1,3-di-tert-butylpropargyl alcohol with lithium aluminium hydride-aluminium chloride, Borden and Corey[38] noted a complete reversal of the predominant mode of substitution (*syn* → *anti*) as the mole ratio of lithium aluminium hydride-aluminium chloride was increased.

(b) The solvent used. It was noted[22] that the increasing donor properties of the solvent (isopropyl ether → diethylether → tetrahydrofuran) increased the degree of *syn*

displacement, when the α-allenic alcohol (33) was formed by reduction of (32) with lithium aluminium hydride (see Scheme 8).

(c) The nature of the leaving group. The chiral β-allenic alcohol 3,4-hexadien-1-ol (36) was prepared by the lithium aluminium hydride reduction of two propargyl derivatives (34) and (35) in tetrahydrofuran at 20°. Whereas the methanesulfonate (34) underwent an *anti displacement* reaction (see Scheme 8), it was observed[23] that the tertiary amine (35) was replaced via a *syn* mechanism.

(d) The neighbouring group. For the same leaving group, the position of the activating hydroxyl group relative to the acetylenic function appeared important[23]. The reduction of the chiral propargyl trialkyammonio derivative (35) with lithium aluminium hydride in tetrahydrofuran at -70° proceeded by a *syn displacement* to yield the β-allenic alcohol (36), whereas the conversion of (37) to the α-allenic alcohol (38) using the same solvent and temperature resulted in a predominant *anti displacement*.

(e) The temperature of the reaction mixture. The (R)-acetylenic alcohol (37) gave the (S)-allenic alcohol (38) (*syn displacement*) when reduced by lithium aluminium hydride in tetrahydrofuran at 20°, but at -70° a very high *anti:syn* ratio (85:15) was observed[23]. In contrast, however, the *syn:anti* stereoselectivity was apparently unaffected in the reduction of (S)-(39) → (R)-(38) with lithium aluminium hydride in diethyl ether at 0° and 35° and similarly for (R)-(35) → (S)-(36) at 20° and -70° in tetrahydrofuran. The conclusion was therefore drawn that the effect of temperature on the stereochemical course of the

allene-forming reaction was also dependent on either the type of leaving group, or the position of the hydroxyl group, or a combination of these factors.

1.3 ALLYLIC ALCOHOLS FROM PROPARGYL ALCOHOLS

Allylic alcohols, which may have the *cis* or *trans* stereochemistry, are the second and most common product resulting from the reaction of propargyl alcohols with lithium aluminium hydride. The first allylic alcohol isolated using this technique was, in fact, the conjugated dienol, trisnor-β-ionol (41) obtained in 70% yield from 1-(1'-cylohexenyl)-but-1-yn-3-ol (40)[39], (see Scheme 9). One year later, in 1950, Raphael and Sondheimer[40] reported that the lithium aluminium hydride reduction of (42) gave an 82% yield of the *trans*-allylic alcohol (43) in marked contrast to its catalytic hydrogenation over palladium on calcium-carbonate which gave an 87% yield of the *cis*-allylic alcohol (43). The realization that the lithium aluminium hydride reduction of propargyl alcohols now offered at facile means of producing the hitherto unobtainable *trans* ethylenic alcohols in high yields, meant that this technique became a much used tool in organic syntheses.

The first lithium aluminium hydride reduction of a non-conjugated acetylenic alcohol was reported in 1953 to involve the production of *trans*-crotyl alcohol (45) from but-2-yn-1-ol (44)[41] and was followed by the reduction of 1-phenylprop-2-yn-1-ol (46) with lithium aluminium hydride to give a 94% yield of *trans* 1-phenylprop-2-en-1-ol (47)[42] in 1954.

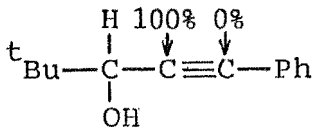
The first *cis* isomer isolated by this technique was reported by Attenburrow et al.[43] in their synthesis of

vitamin A from cyclohexanone. The C_{20} glycol (48) on reduction with lithium aluminium hydride in diethyl ether gave a crystalline polyene glycol (49), which was found to occur in two forms mp. 79° and 120°. Chemical tests indicated that the two forms were the respective *cis-trans* isomers about the newly formed double bond.

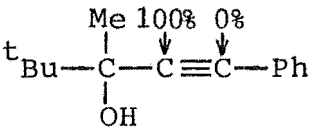
The mechanism which illustrates the formation of these allylic alcohols, obtained by the reduction of the corresponding propargyl alcohols (16) with lithium aluminium hydride, is given in Scheme 10. The first step of the reaction again involves the formation of an oxygen-aluminium bond with the concommittant evolution of hydrogen. The alkynyloxyaluminium hydride group then functions as a hydride donor, donating a hydride intramolecularly[44,45] to either the near (C2) and/or far (C3) carbon of the acetylenic linkage. The four stereochemically stable vinyl carbanions which result, may have either the *cis* [(51) and (53)] or *trans* [(50) and (52)] configuration, being stabilized by the available Li^+ counterions in the reaction medium. It is also possible for carbanions (50), (52) and (53) to gain extra stabilization by the formation of the five-membered (54) or four-membered cyclic organoaluminium species (55) and (56) prior to hydrolysis. Quenching the reaction with water then results in the formation of the *cis* [(58) and (60)] or *trans* alkenols [(57) and (59)] respectively.

The partitioning of the reaction pathways between the near and far carbon hydride attack has been shown to occur at the initial stage of the reaction[30] (as depicted in Scheme 10) and is dependent on three factors:

(a) The structure of alkynol (16). The relative yields of the carbanions (50), (51) and (52), (53), resulting from hydride attack at C2 or C3 respectively, will depend upon the nature of R^3. If R^3 is capable of stabilizing a carbanion at the far carbon (C3), e.g. R^3=phenyl, then the reaction pathway involving carbanions (50) and (51) will be favoured. Thus, in the reduction of 4,4-dimethyl-1-phenylpent-1-yn-3-ol (61)[45], and 2,2,3-trimethyl-5-phenyl-pent-4-yn-3-ol(62)[46] in either tetrahydrofuran (THF) or diethyl ether (Et_2O) as solvent, the sole site of hydride attack was

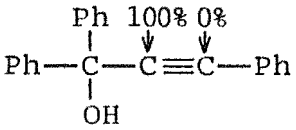


(61)

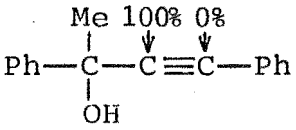


(62)

at the near carbon of the acetylenic group. Similarly, for the reduction of 1,1,3-triphenylprop-2-yn-1-ol (63)[47] and 2,4-diphenylbut-3-yn-2-ol (64)[47] in the same solvents,



(63)

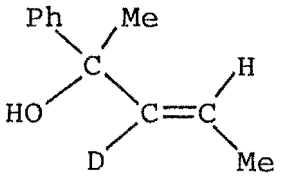


(64)

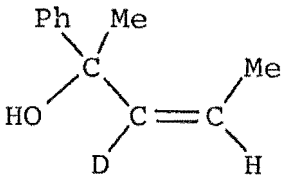
it was shown that all alkenol products arose by hydride (deuteride) attack solely at the near carbon of the acetylenic function.

When, however, R^3 is a group which is not able to stabilize an adjacent carbanion, e.g. R^3=alkyl, then there will be no marked bias in favour of one or other of the two carbanion-forming reaction pathways and products from both near and far carbon hydride-attack may be anticipated. This has been shown by the reduction of

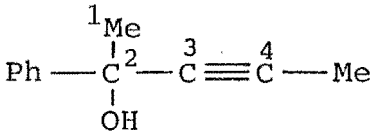
1,1-diphenylbut-2-yn-1-ol (17)[27] with lithium aluminium hydride (deuteride) in refluxing diethyl ether, which produced the *trans*-alkenol (71) and allene (69) both of which arose by hydride (deuteride) attack at C3, and the *trans* and *cis* alkenols, (67) and (68) respectively, formed from carbanion (65) (see Scheme 11). In the same solvent, reduction of 2-phenylpent-3-yn-2-ol (18)[28] with lithium aluminium deuteride gave a mixture (42% total) of *trans* and *cis*-3-deuteroalkenols, (72) and (73) respectively, and allene (74) (57%) with deuteriation on C4.



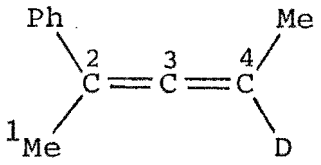
(72)



(73)



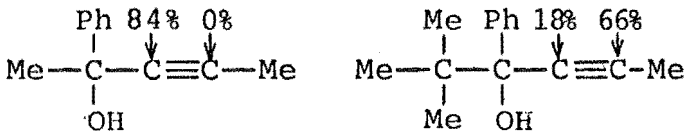
(18)



(74)

(b) <u>The steric size of R^1 and R^2</u>. The larger are R^1 and R^2, the more favoured is hydride attack at the far carbon resulting in carbanions (52) and (53) because of the increasing steric interaction that the alkynyloxy-aluminium hydride group is encountering. For example, it has been shown[28] that reduction of 2-phenylpent-3-yn-2-ol (18) with lithium aluminium deuteride in tetrahydrofuran (THF) as solvent gave the *trans*-alkenol (72) exclusively, arising by deuteride donation solely to the near carbon; whereas in the same solvent 2,2-dimethyl-3-phenylhex-4-yn-3-ol (75) gave 66% allene (which can only be formed by deuteride attack

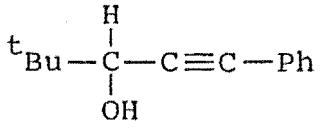
at the far carbon) and 18% *trans*-alkenol, formed totally



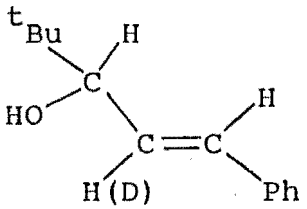
(18) (75)

by near carbon attack. Thus for R^1, R^2 the replacement of the methyl group by a more bulky tertiary butyl group increased the extent of far carbon attack significantly (0 → 66%).

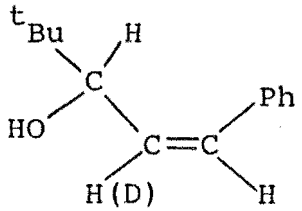
(c) The solvent used. Borden[45] was the first to notice that the *cis:trans* product ratio of the allylic alcohols, formed by the lithium aluminium hydride reduction of an acetylenic alcohol, was markedly solvent-dependent. In tetrahydrofuran as solvent, reduction of 4,4-dimethyl-1-phenylpent-1-yn-3-ol (61) gave the *trans*-alkenol (76) as the exclusive product while the use of diethyl ether as solvent led to the formation of some 25% *cis*-alkenol (77)



(61)



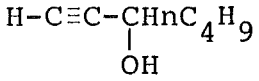
(76)



(77)

in addition to the expected *trans*-alkenol (76).

Investigation of the effect of solvents on the stereochemistry of acetylenic alcohol reductions of this type was extended further by Grant and Djerassi[48]. Their results, concerning the reduction of hept-1-yn-3-ol (78) with lithium aluminium hydride followed by D_2O quenching, indicated a strong inverse correlation between the Lewis



(78)

basicity of the solvent and the extent of *cis*-reduction. With dioxane or tetrahydrofuran as solvent the corresponding *trans*-alkenol was formed exclusively, but with diethyl ether or n-propyl ether *cis*-reduction occurred to about 50% and in the extreme case, isopropyl ether, *cis*-reduction predominated over *trans*-reduction to the extent of a 3:1 ratio. The data they obtained is summarised in the table below.

Per Cent Trans and Cis Reduction of Hept-1-yn-3-ol (78) as a Function of the Solvent

SOLVENT	% trans reduction	% cis reduction
Dioxane	100	0
Tetrahydrofuran	100	0
2,5-Dimethyltetrahydrofuran	55	45
2,2,5,5-Tetramethyltetrahydrofuran	33	67
Ethyl ether	60	40
n-Propyl ether	50	50
Isopropyl ether	25	75

It soon became apparent from their study of propargylic alcohols of general structure (79,R^3=H) that hydride transfer occurred exclusively to the alkyne carbon adjacent to the hydroxyl group (near carbon C2), presumably because of the greater stability of the primary vinyl carbanion over its

competing secondary vinyl counterpart. The general reaction mechanism was considered to be as given in Scheme 12. (Note that although R^3=H, it was labelled R^3 on this occasion to avoid ambiguity).

The *cis* reduction observed in these systems negated the possibility of intramolecular stabilization of the resulting vinylic carbanion (80) by the aluminium bound to oxygen, since this would have imposed unlikely geometrical constraints (*trans*-double bond in a 5-membered ring) on the resulting oxoaluminium species (the assumption that hydrolysis of the carbon-metal bond occurs with retention of configuration is quite common in the literature[45,49,50,51]). The stabilization of the vinyl carbanion (80) formed during the *cis* reduction was therefore assumed to be accomplished by other Lewis acids (Li^+ counterions) in the reaction medium. Since the extent of *cis* reduction varied inversely with the ability of the solvent to solvate Lewis acids in the reaction medium, it appeared reasonable to propose that these Lewis acids played an important role in the determination of the stereochemistry of the vinyl carbanion. In support of their views, recent experiments had indicated that vinyl carbanions exhibited a high degree of stereochemical stability[52,53], which had been attributed to either sufficiently long lifetimes of the anion in its trigonal configuration or the formation of stereochemically distinct intimate ion pairs with available counterions[53].

With this information in hand the mechanism outlined in Scheme 13 was presented, incorporating all the available data and providing a rational explanation of the observed results. Two transition states (83a) and (83b), which lead to the *trans* and *cis* vinyl carbanions (84a) and (84b)

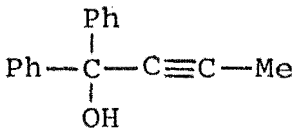
respectively, were postulated. In the weaker Lewis base solvents (e.g. ether, 2,5-dimethyltetrahydrofuran) the available Li^+ counterions are less solvated and hence readily available to stabilize existing anionic charges in the transition state (83a). This presumably would be best accomplished via pathway a. Conversely, in strong Lewis bases (e.g. dioxane, tetrahydrofuran) the highly solvated counterions would not be as available for stabilization of the developing anionic centres and the configuration yielding the greatest separation of these sites (83b) would be more energetically favourable (pathway b). Hydrolysis of the resulting ion pair (84a) or (84b) with retention of configuration[49] would result in the product of *cis* (86a) or *trans* (86b) reduction, respectively. On the basis of their results, a cyclic organoaluminium species (85b) could not be completely ruled out and would be involved prior to hydrolysis to the *trans* reduction product.

Two intersting observations were made which further supported the mechanism outlined above. When a small amount of the crown ether, dicyclohexyl-18-crown-6, was added to the reduction of hept-1-yn-3-ol (78) being performed in isopropyl ether, a dramatic reverse in the *cis:trans* reduction ratio, (30:70) instead of (75:25), was observed. Hence, as the proposed mechanism would have predicted, the addition of the crown ether, which complexes the lithium counterion[54] rendering it unavailable for stabilization of the developing anionic centres in the transition state, forced the reaction along pathway b. Conversely, by lowering the temperature of the reaction to -25° and

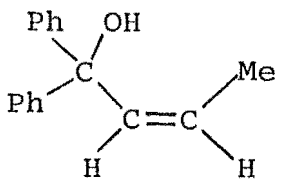
extending the reaction time in diethyl ether to 6 days, the extent of *cis* reduction (pathway a) predictably increased by approximately 15%.

1.4 REDUCTION OF PROPARGYL ALCOHOLS TO GIVE BOTH ALLENES AND ALKENOLS-SOLVENT EFFECTS.

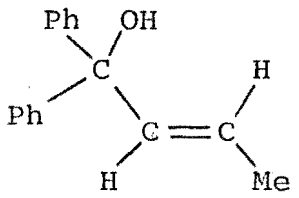
As studies were extended to tertiary propargyl alcohols, it became apparent that the allene and alkenol-forming reaction pathways were actually competitive. Hartshorn et al.[27], in their study of the reduction of 1,1-diphenylbut-2-yn-1-ol (17) with lithium aluminium hydride, observed in accord with earlier workers[45,48], that the alkenol-product ratio obtained was characteristic of



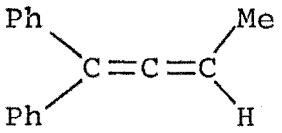
(17)



(87)



(88)



(89)

the solvent used for the reduction. For example reaction of alkynol (17) in diethyl ether at 35° for 22 h, followed by the addition of an equal volume of dry tetrahydrofuran and heating at 35° for a further 24 h, gave a product ratio essentially identical with that obtained simply by reaction in diethyl ether. Clearly, the reactions that occurred in diethyl ether were effectively irreversible, and the intermediate vinylic carbanions stereochemically

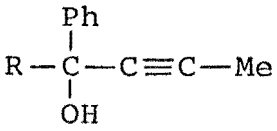
stable. When, however, mixtures of ether and tetrahydrofuran were used as the solvent for the reduction of alkynol (17) the ratios of products obtained were dependent on the solvent composition (see Table below). The mechanistic picture was further complicated by the isolation of allene (89), in addition to the expected (Z)-alkenol (87) and (E)-alkenol (88).

Solvent	Allene (89) % yield	(Z)-Alkenol (87) % yield	(E)-Alkenol (88) % yield
Et_2O	55	12	27
Et_2O/THF 9:1	39	6	36
3:1	15	2	48
1:1	-	-	66
THF	-	-	59

The extent of *cis* reduction was observed to increase gradually as the solvent mixture became richer in diethyl ether, whereas reaction in tetrahydrofuran (as well as in a 1:1 mixture of diethyl ether and tetrahydrofuran) yielded only the *trans*-alkenol (88).

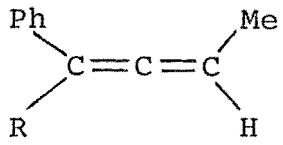
In their continuing work with tertiary propargyl alcohols, Hartshorn et al.[27] clearly established that the hydride transfer leading to alkenols is not site-specific and also that the ratio of hydride attack at the two alkyne carbons does not remain constant when the solvent is varied. The nature of the solvent-dependence in alkynol reductions has recently been illuminated further by Blunt et al.[55], in their comparative study of lithium aluminium hydride

(deuteride) reductions of 2,2-dimethyl-3-phenylhex-4-yn-3-ol

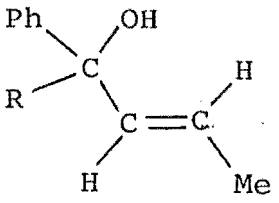


(90)a; R=^{t}Bu

b; R=CMe_2CH_2OMe



(91)



(92)

(90a) and its methoxy-derivative (90b). Their results are summarized in table A (as foldout p 34).

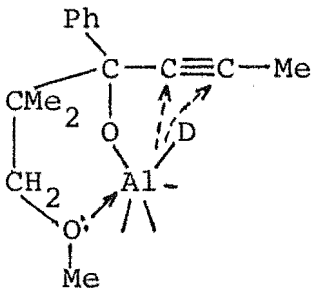
Reduction of (90a) in diethyl ether gave the corresponding allene (91a) as the sole product (i.e. hydride attack completely at far carbon), whereas in tetrahydrofuran under the same reaction conditions, near alkyne-carbon attack by hydride predominated over far alkyne-carbon attack by a 2:1 ratio. In the same solvent, tetrahydrofuran, it was observed that the near:far ratio decreased as the reaction temperature was elevated from 35° to 65°. In all reactions the (E)-alkenol (92a) formed was by hydride attack specifically at the alkyne carbon adjacent to the hydroxyl group.

The data obtained for alkynol (90a) thus demonstrated that the relative yields of product (91a) and (92a) varied considerably with the solvent used and, in the case of tetrahydrofuran (THF), with the reaction temperature. Further, the relative yields of products formed by deuteride attack at the near:far acetylenic carbon atoms also varied.

In contrast, for the reaction of alkynol (90b) (the 1-methoxy derivative of alkynol (90a)), although the relative yields of allene (91a) and (E)-alkenol (92b) were both solvent - and temperature-dependent, the relative

yields of products derived from near- and far-carbon deuteride attack were observed to be *independent* of both solvent and reaction temperature.

These results have been interpreted in terms of internal solvation of aluminium by the methoxy-substituent in the reacting alkoxyaluminium deuteride (93); in the absence of an internal ether, an external and potentially variable ether solvent molecule solvates the aluminium.



(93)

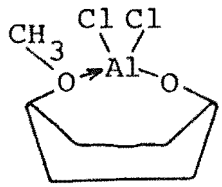
Given the consistent involvement of the methoxy-function as in (93), a constant near:far carbon attack was reasonable and, within the limit imposed by a near:far attack ratio of 1:3, the yield of allene (91b) was but a reflection of the extent to which the intermediate carbanion (94) (Scheme 14) was converted into allene (91b) prior to reaction quenching.

In support of this proposed mechanism, Wiberg et al.[56] have indicated that tetrahydrofuran is able to co-ordinate to the aluminium atom in the preparation of aluminium hydride (AlH_3) according to the equation given below.

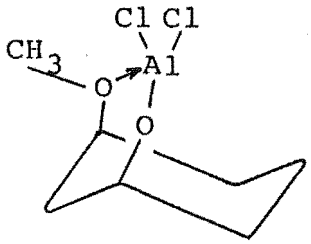
$$(AlH_3)_n + n\ THF \rightarrow n\ AlH_3.THF$$

Although aluminium hydride exists as a polymer in diethyl ether, they showed that the monomeric species could be stabilized in solution by the addition of tetrahydro-furan (THF), a stronger Lewis base. Evidence indicative

of the co-ordination of an internal ether to an aluminium atom has also been reported by Eliel and Brett[57] in the isolation of two chelates (95) and (96). Their report involved treatment of a mixture of *cis* and *trans*-4-methoxy-cyclohexanol with lithium aluminium hydride/aluminium chloride (1:4 mole ratio) to yield the *cis*-chelate (95).



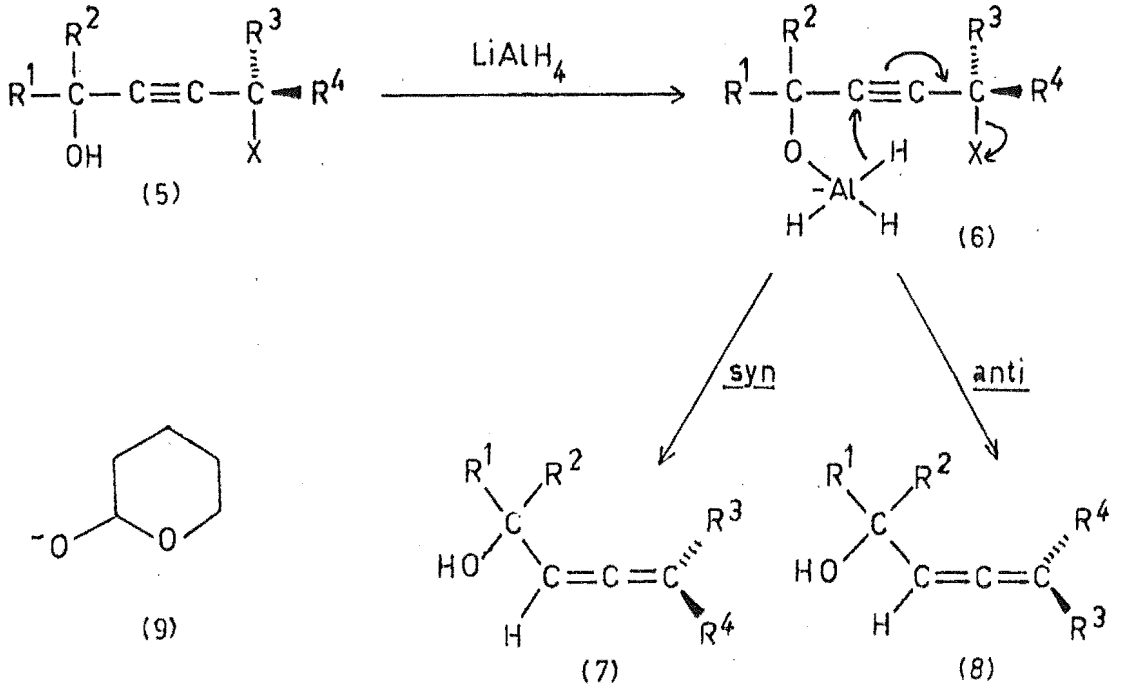
(95)



(96)

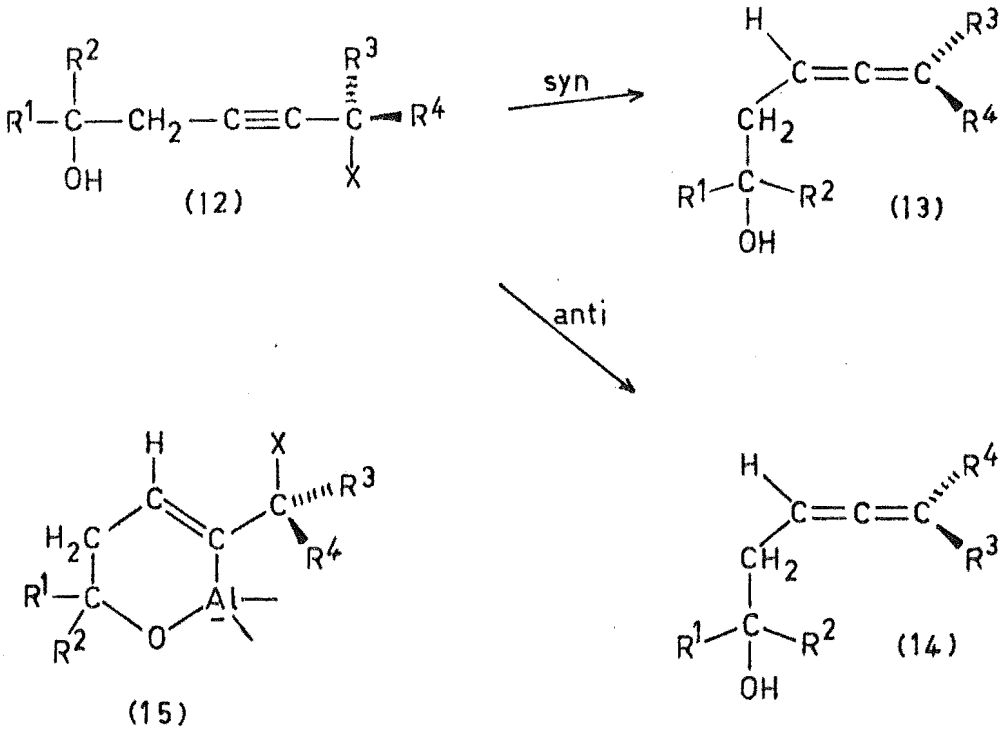
Similar treatment of *cis*- and *trans*-3-methoxycyclohexanol gave the *cis*-chelate (96).

The importance of aluminium solvation in the reduction process has thus been identified, whether it be by an internal or external ether solvent molecule. The need to investigate this work further is the reason why my Ph.D. research was undertaken. Chapter 2 of my thesis is devoted to the exploration of the effect of having two internal ethers within the substrate being reduced; Chapter 3 is a study aimed at determining the optimal ring size for intramolecular solvation to occur and Chapter 4 is designed to compare the kinetics, in a semi-quantitative manner, of the intramolecularly solvated alkynol reductions with their non-internal ether analogues in benzene solvent.



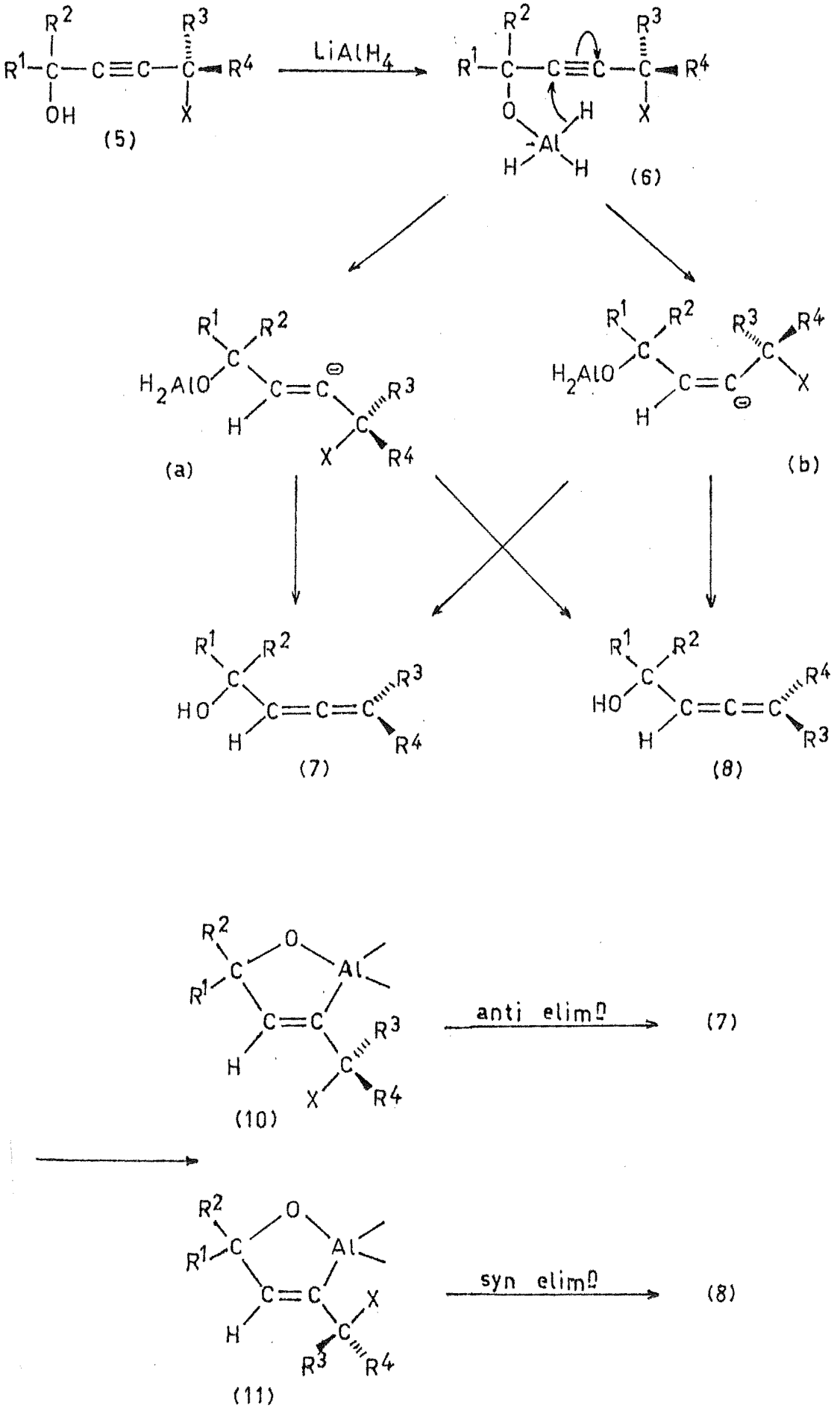
(5) (6) (9) (7) (8)

Scheme 1

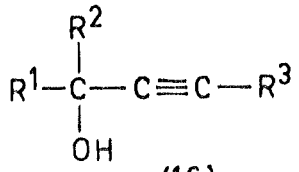


(12) (13) (15) (14)

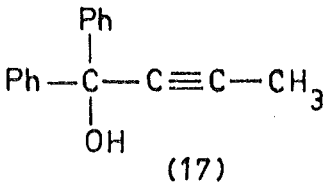
Scheme 3



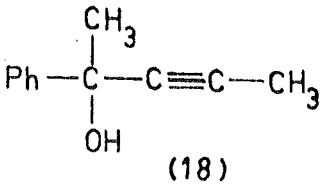
Scheme 2



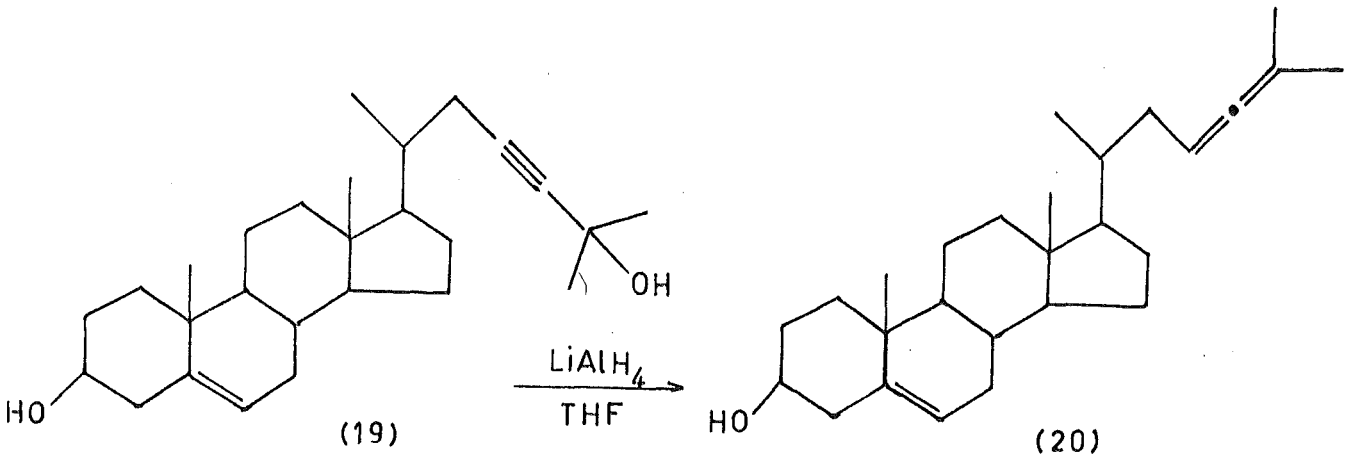
(16)



(17)

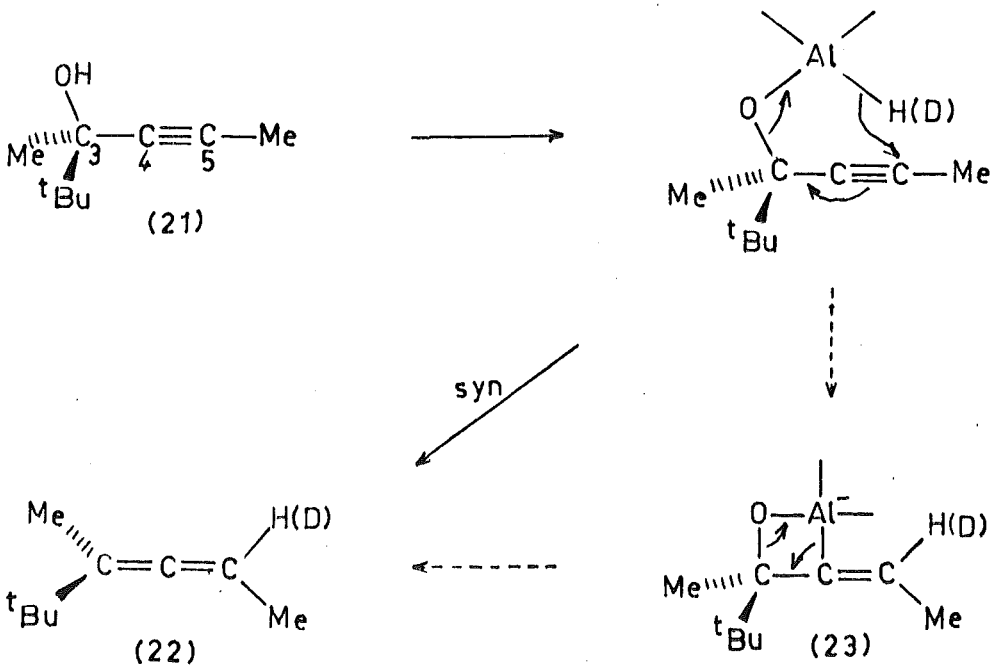


(18)



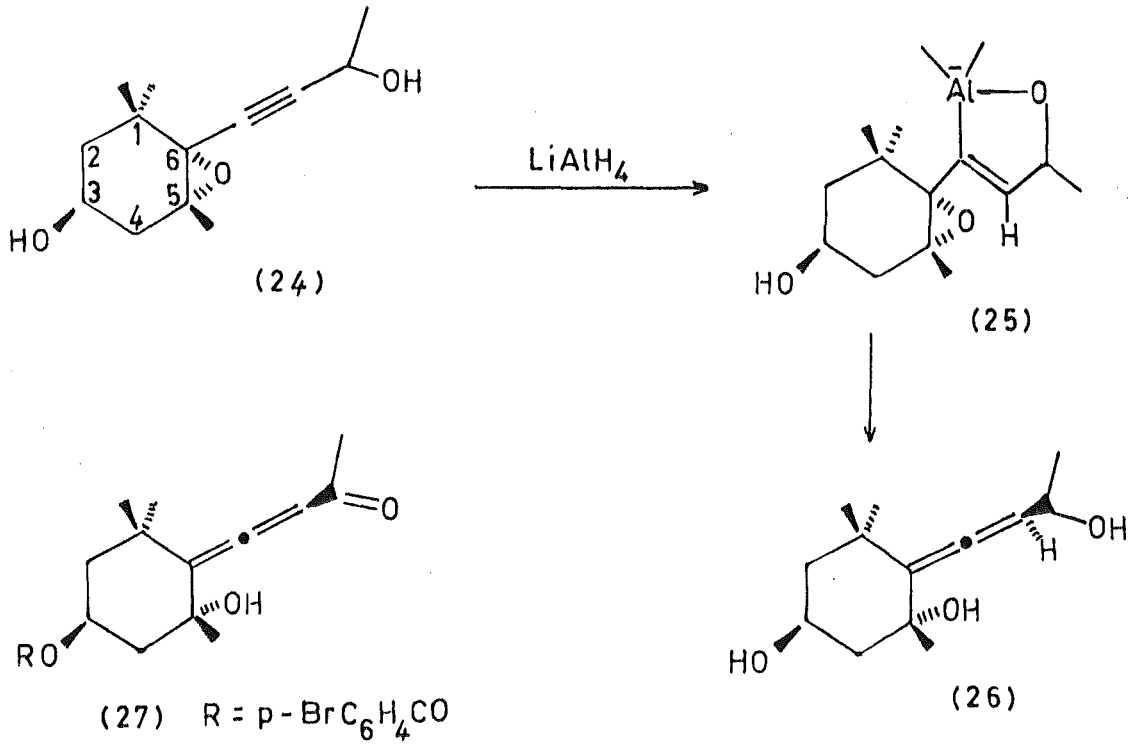
(19) (20)

Scheme 4

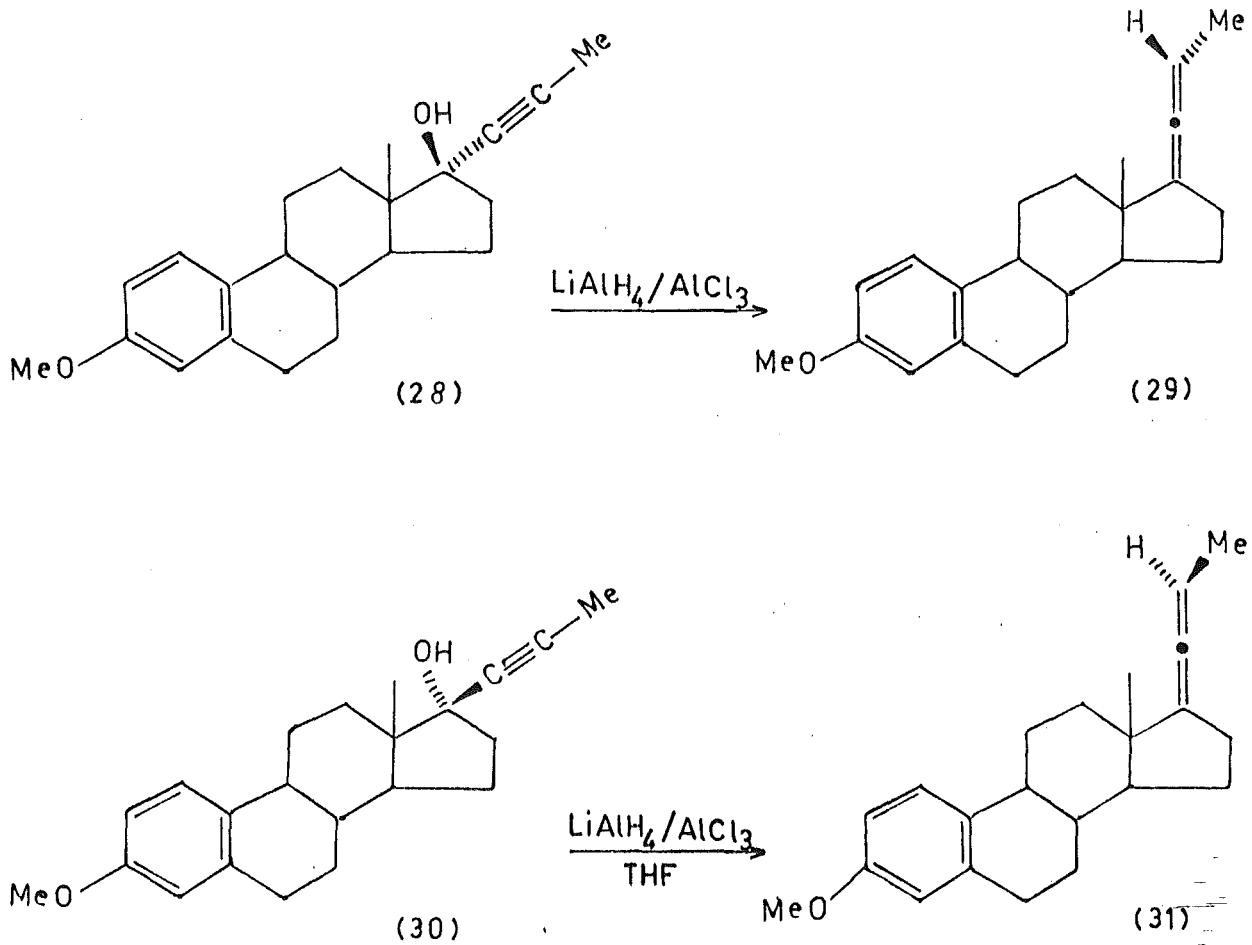


(21) (22) (23)

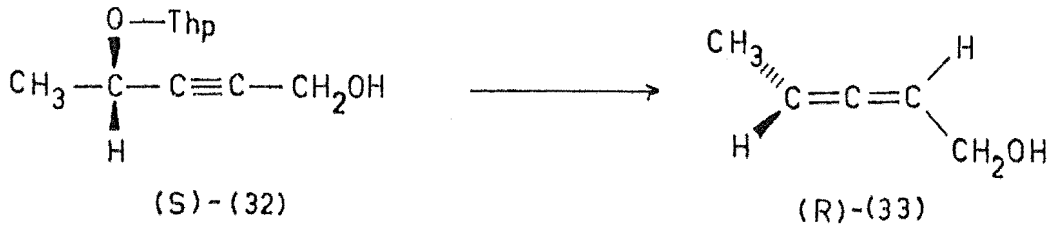
Scheme 5



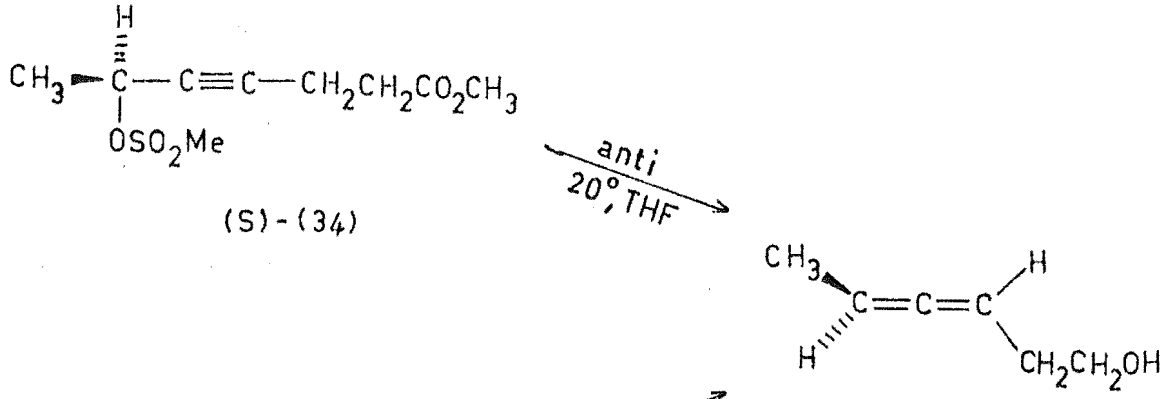
Scheme 6



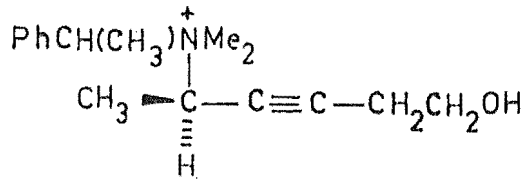
Scheme 7



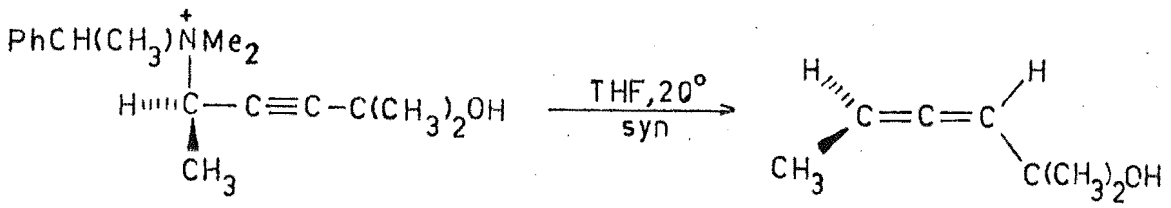
(S)-(32) (R)-(33)



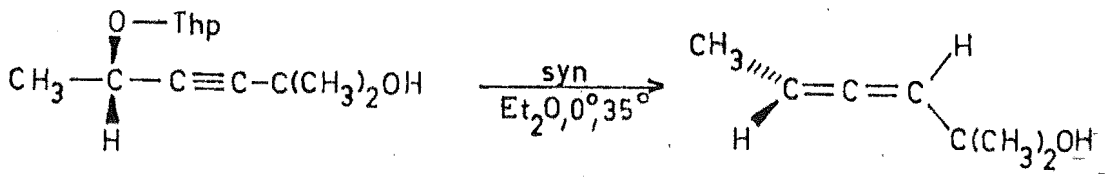
(S)-(34) (S)-(36)



(R)-(35)

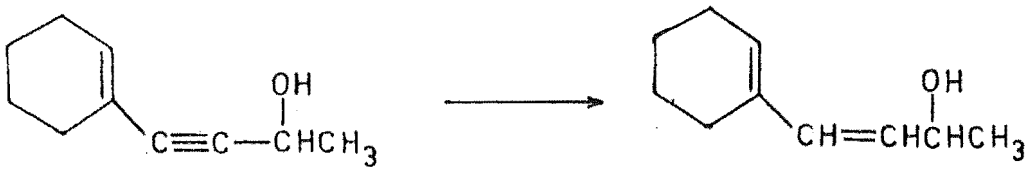


(R)-(37) (S)-(38)

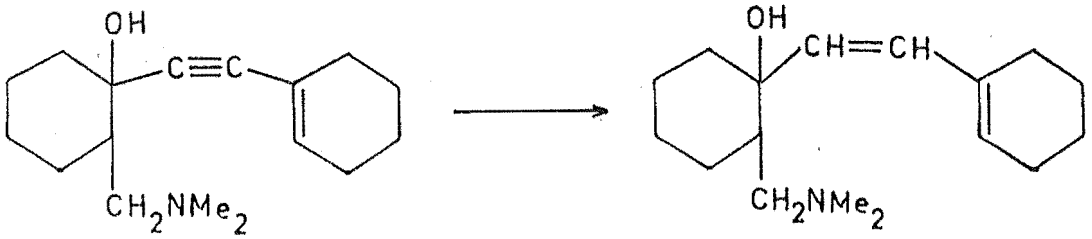


(S)-(39) (R)-(38)

Scheme 8



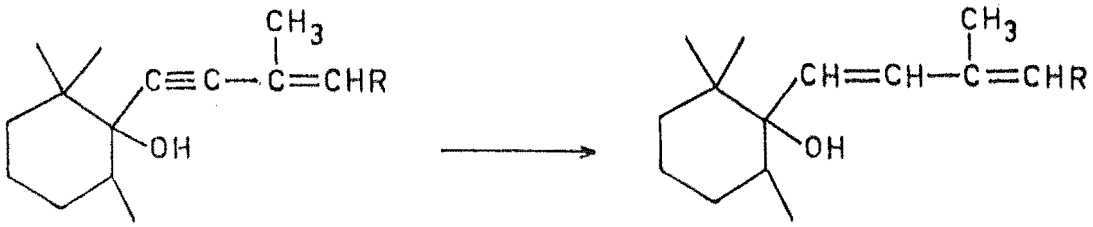
(40) (41)



(42) (43)

(44) (45)

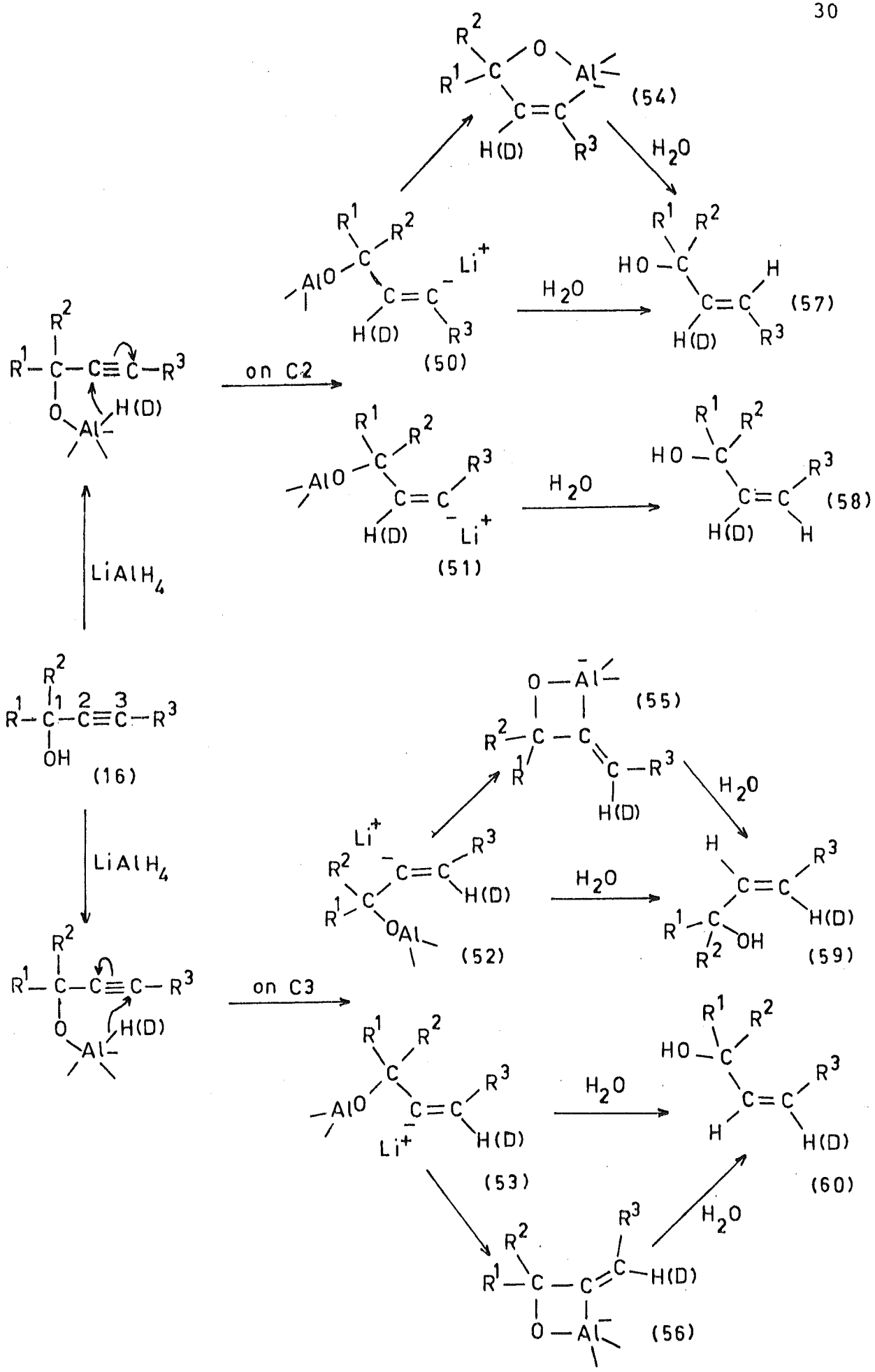
(46) (47)



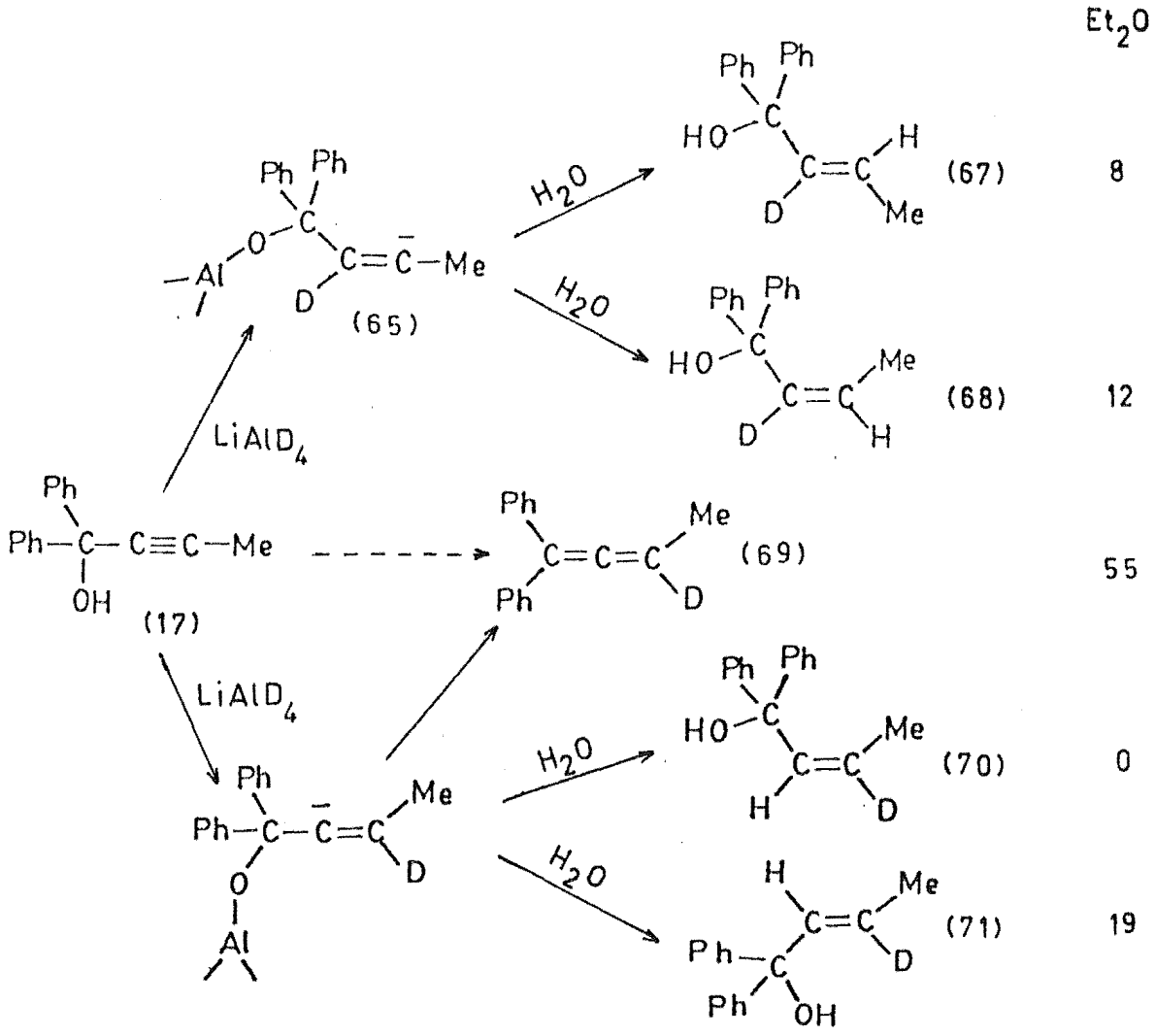
(48) (49)

R = $CH{=}CHC(CH_3){=}CHCH_2OH$

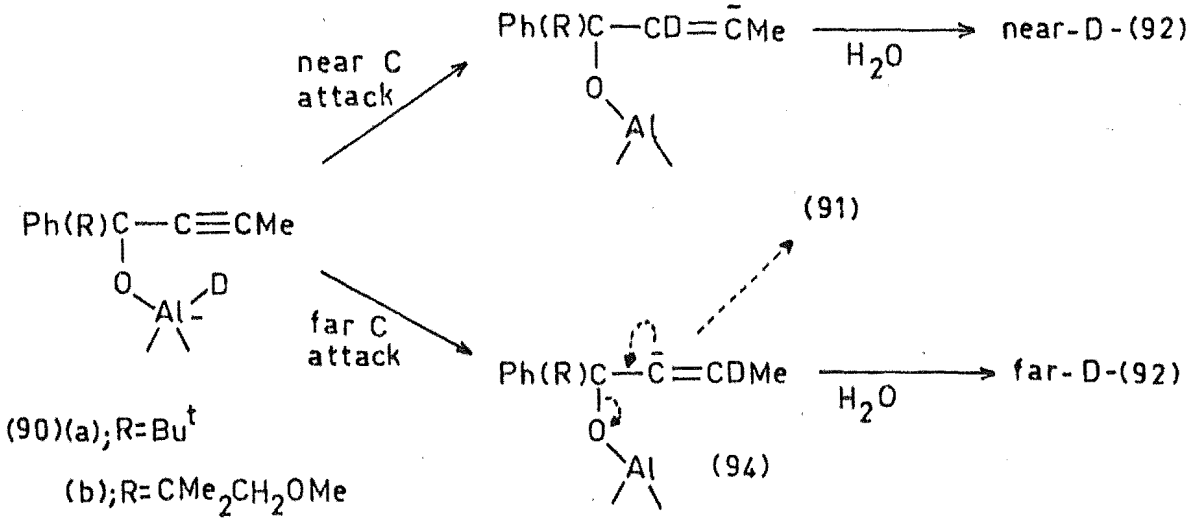
Scheme 9



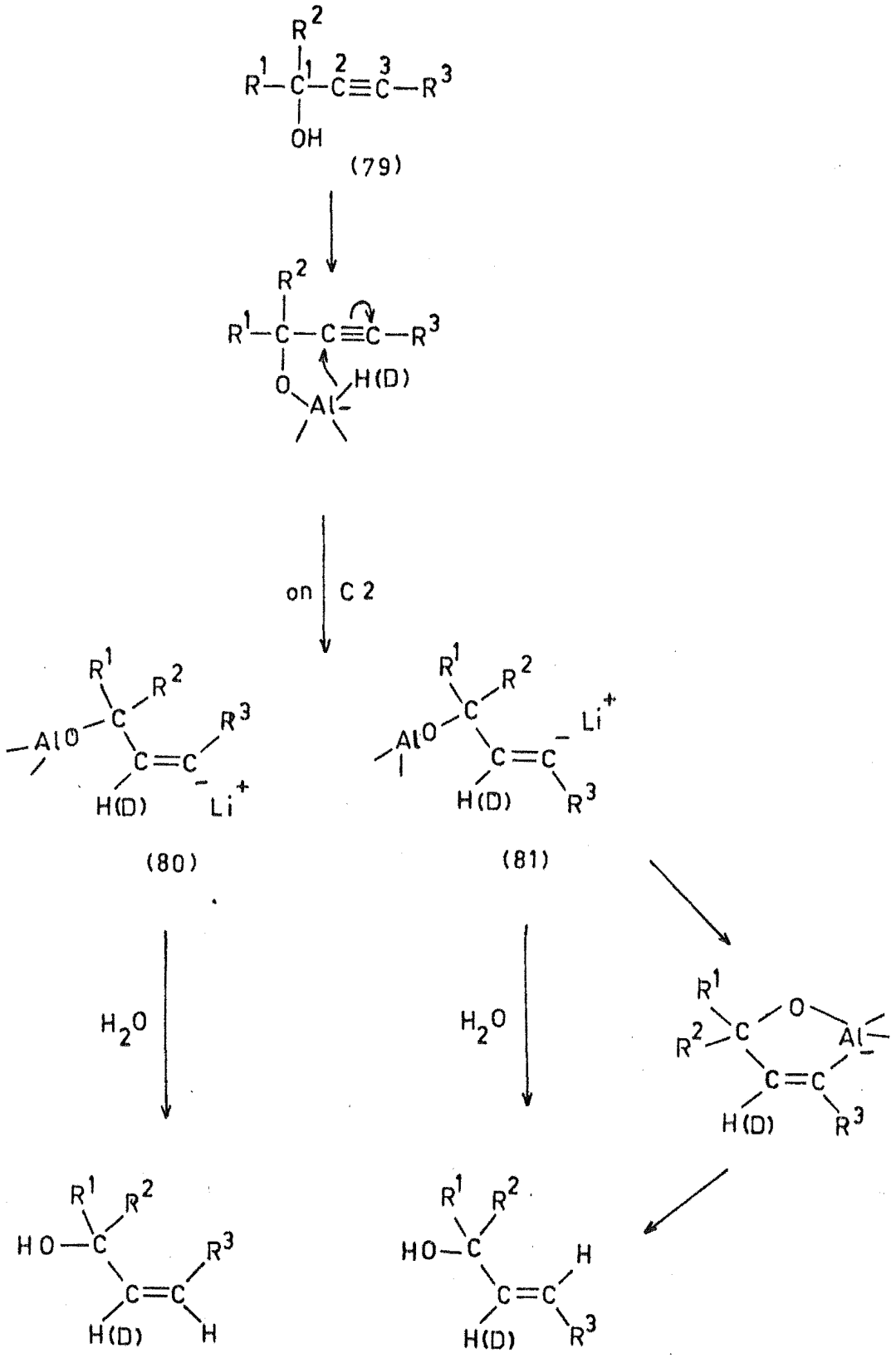
Scheme 10



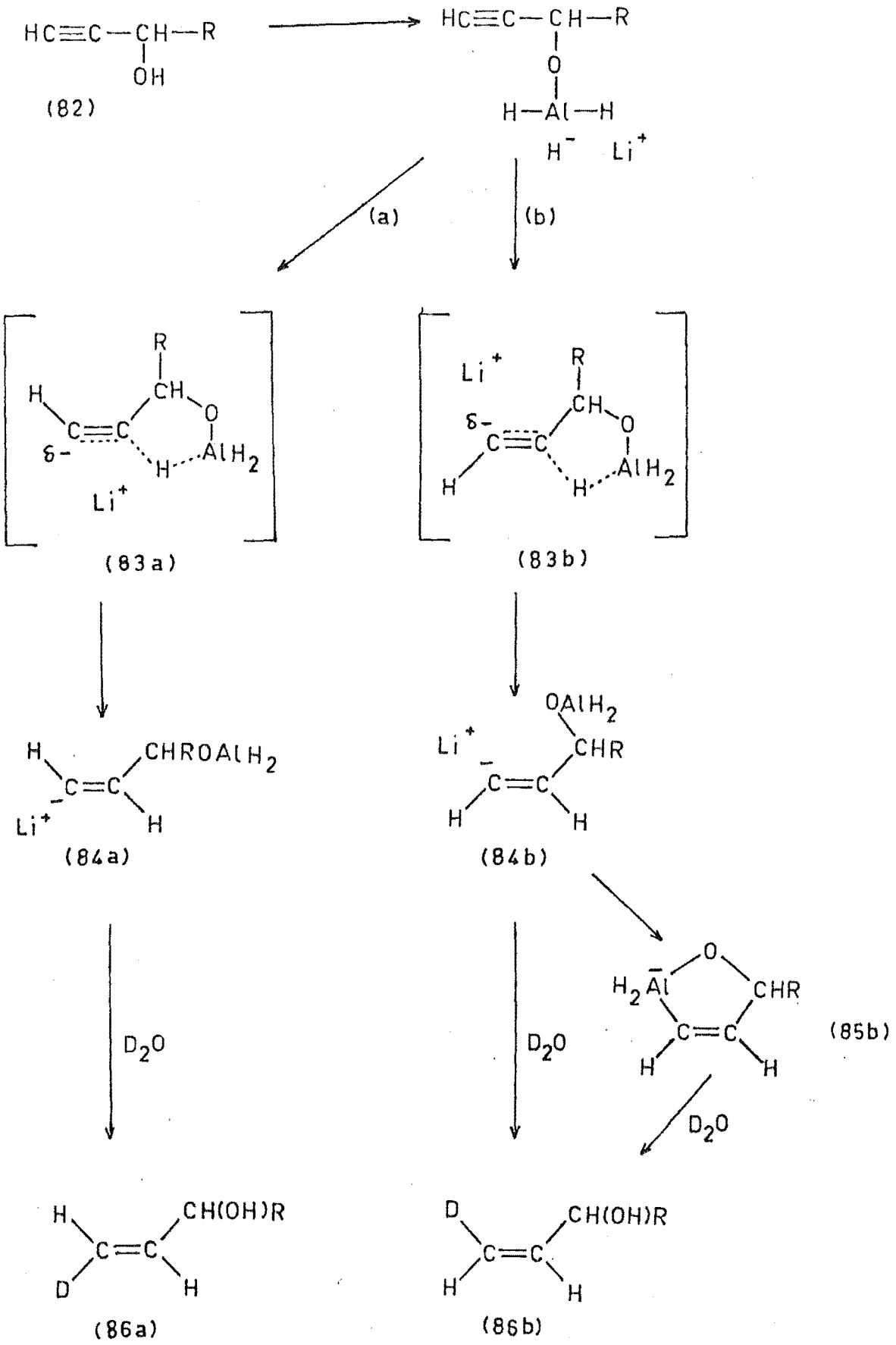
Scheme 11



Scheme 14



Scheme 12



Scheme 13

Product yields of reactions of alkynol (90) with lithium aluminium deuteride

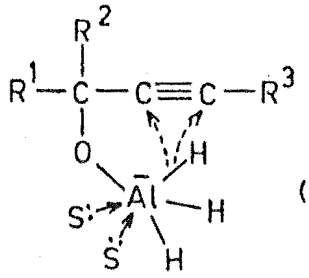
Alkynol	Solvent	% Yield		Attack by D^- at near:far carbon	
	temp.(°C), time(h)	Allene (91)	(E)-Alkenol (92)	Leading to (92)	Overall
90a	Et_2O,35,89	84	Trace	-	ca 0:84
	THF,35,89	30	60	60:0	60:30
	THF,65,2.5	66	18	18:0	18:66
	2,5-Me_2THF,65,2.5	92	2	2:0	2:92
90b	Et_2O,35,16	69	27	24:3	24:72
	THF,35,16	29	70	30:40	30:69
	THF,65,2.5	57	42	25:17	25:74
	2,5-Me_2THF,35,16	54	44	26:18	26:72
	2,5-Me_2THF,65,2.5	67	30	23:7	23:74
	2,5-Me_2THF,91,0.5	75	25	25:0	25:75

CHAPTER 2

LITHIUM ALUMINIUM HYDRIDE REDUCTION OF 2,2-DI-(METHOXYMETHYL)-3-PHENYLHEX-4-YN-3-OL (98) AND 1-METHOXY-2,2-DIMETHYL-3-PHENYLHEX-4-YN-3-OL (90b).

2.1 INTRODUCTION

The obvious importance of the solvent in propargyl alcohol reductions has now redirected attention to the state of the aluminium atom in the reacting alkynyloxyaluminium hydride. With its known preference for six-fold over five-fold co-ordination with highly electronegative atoms, the implication is that aluminium, as depicted in structure (97) below, is



(97)

actually co-ordinated to two solvent molecules, during the reduction process. Direct evidence of at least one ether molecule being attached to the aluminium atom has now been established[55] (making it at least five-fold co-ordinate prior to hydride transfer).

In an attempt to gain further information about the solvent function, an acetylenic alcohol modified to contain two internal ethers was synthesised, 2,2-di-(methoxymethyl)-3-phenylhex-4-yn-3-ol (98), Block A, and its reactions with lithium aluminium hydride (deuteride) studied in a range of ether solvents.

2.2 SYNTHESIS OF 2,2-DI-(METHOXYMETHYL)-3-PHENYLHEX-4-YN-3-OL (98)

The synthesis of alkynol (98) involved reaction of propynyllithium with the corresponding ketone, 2,2-Di-(methoxymethyl)-1-phenylpropan-1-one (104). The synthetic route to the dimethoxy ketone (104) is outlined in Scheme 15. Aldol condensation of propiophenone (99) with formaldehyde gave an equilibrium mixture of products (30%) and starting material (69%). The majority of unreacted propiophenone was extracted from the crude product with petroleum ether. The di-(hydroxymethyl)-ketone (101) was isolated in 12% yield overall from the mono-aldol (100;8%), the crossed Cannizzaro product (102;10%) and residual starting material by chromatography on silica gel[58]. The methylation of di-(hydroxymethyl)-ketone (101) with an ethereal solution of diazomethane was catalyzed by boron-trifluoride etherate. The required di-(methoxymethyl)-ketone (104;84%) was separated from the mono-(methoxymethyl)-ketone (103;15%) by column chromatography on 5% deactivated alumina. Previous attempts with conventional methylation techniques such as Purdie's[59] silver oxide-methyl iodide, modified to utilize the accelerating effect of dimethylformamide[60], or Haworth's alkali-methyl sulphate method[61], were shown to be ineffective as yields were either extremely poor or product mixtures complicated by retro-aldol impurities[62]. Diazomethane was first used in conjunction with boron-trifluoride etherate in 1958[63] and has since been recognised as an extremely useful methylating agent for compounds containing base-labile substituents[64]. The preparation of diazomethane followed conventional procedures; conversion of acetamide (105) to

acetyl methylurea (106), to nitrosomethylurea (107)[65], to diazomethane (108)[66]; as depicted in Scheme 16.

Reaction of propyne with freshly prepared 1-butyllithium gave the required propynyllithium[67]. 1-Butyllithium[68] was obtained by adding lithium strips[69] to a solution of 1-butyl bromide in ether at -15°[70] with stirring. The concentration of 1-butyllithium was determined by titrating two aliquots of the solution with standard acid (1M)[71]. The first titration was carried out after the solution had been hydrolysed with distilled water and this determined the total alkali content. To the second aliquot benzyl chloride was added, subsequently hydrolysed with distilled water and then titrated. This determined the alkali present other than the 1-butyllithium. The difference between the two titration values represented the concentration of 1-butyllithium in the aliquots taken; total concentration thus followed. The production of propyne (112) is outlined in Scheme 17 in which dehydration of isopropanol (109) at 260°-270° by phosphoric acid gave propene (110)[72], followed by bromination to give the propylene bromide (111)[73] which was distilled off as a colourless liquid. On addition of propylene bromide (111) to a rapidly stirred solution of potassium hydroxide in refluxing n-butanol, a good yield of propyne gas was obtained; condensed to a liquid by a trap immersed in an isopropanol/dry-ice bath[74].

The reaction of propynyllithium with di-(methoxymethyl)-ketone (104) gave a high yield of 2,2-di-(methoxymethyl)-3-phenylhex-4-yn-3-ol (98) (94%) after purification by chromatography on 5% deactivated alumina.

2.3 REACTIONS OF 2,2-DI-(METHOXYMETHYL)-3-PHENYLHEX-4-YN-3-OL (98)

Reduction of 2,2-di-(methoxymethyl)-3-phenyhex-4-yn-3-ol (98) with lithium aluminium hydride (1.1 mole) in refluxing tetrahydrofuran for 2.5 h gave, on water quenching, a crude product from which 5,5-di-(methoxymethyl)-4-phenylhexa-2,3-diene (113), (E)-2,2-di-(methoxymethyl)-3-phenylhex-4-en-3-ol (114) and a mixture of 1-methyl-1-methoxymethyl-2-phenyl-2-(1'-propenyl)-cyclopropanes (115) and (116) were isolated. (See Block A for structures; Table 1 for yield data).* The products were identified through their spectroscopic data.

The absorption band at 1965 and 1100 cm^{-1} in the infrared spectrum of allene (113) confirmed the presence of the allenic and internal ether functions, respectively. In the ^{1}H n.m.r. spectrum of (113) the C6-H_3 protons appeared as a singlet at δ 0.98, while the C1-H_3 protons appeared as a doublet centred at δ 1.68 with coupling to the allenic H2-signal (J 7 Hz), itself a quartet centred at δ 5.09. Decoupling centred at δ 1.68 collapsed the H2 signal (δ 5.09) to the expected singlet, and vice-versa. The aromatic protons were a five proton singlet at δ 7.15. The ^{13}C n.m.r., mass spectra and micro-analyses were also in accord with structure (113).

The alkenol (114) exhibited infrared absorptions at 3500, 1670 and 970 cm^{-1}, which was consistent with its assignment as an alcohol with a *trans*-disubstituted double bond, while the strong 993 cm^{-1} absorption again confirmed internal ether presence. In its ^{1}H n.m.r. the vinyl C6-H_3

---

* All Tables and Blocks as fold-outs at end of this thesis.

group appeared as a doublet centred at δ 1.75 with coupling to the vinylic C5 proton (J 6 Hz), in contrast to the saturated C1-H_3 signal which appeared as a singlet at δ 0.78. The hydroxyl proton appeared as a sharp singlet at δ 4.40, and was removed by deuterium oxide shake. The vinylic C5 proton, centred at δ 5.81, appeared as doublet of quartets, with coupling to the C6-H_3 protons (J 6 Hz), and to the C4-proton (J 14.5 Hz), itself a doublet (J 14.5 Hz) centred at δ 6.22. Irradiation of the $(H6)_3$ signal (δ 1.75) reduced the H5 signal (δ 5.81) to a doublet ($J_{5,4}$ 14.5 Hz), while irradiation at δ 5.81 reduced $(H6)_3$ signal (δ 1.75) to an expected singlet. The signal at δ 17.96 in its ^{13}C n.m.r. was assigned to C6, by comparison with C6 (δ 17.90) of the analogous alkenol (92b), Block A. By elimination, therefore, the C1 peak was assigned to δ 16.39, being observed at higher field than the analogous C2-methyls (δ 20.93, 21.66) of alkenol (92b), due to its increased steric compression. The methoxy peaks were coincident at δ 59.08, while those of $-CH_2-O-$ were not so (δ 75.02, 74.47). Mass spectra and micro-analyses were also consistent with its assigned structure.

The mixture of propenylcyclopropane derivatives consisted mainly of the two (E)-1'-isomers (115a) and (116a) (1:1), with the corresponding (Z)-1'-isomers (115b) and (116b) present in only trace quantities. These latter compounds were not isolated.

The less polar propenylcyclopropane derivative (115a) was isolated by preparative layer chromatography on alumina, and the more polar compound (116a) by repeated h.p.l.c. Both compounds (115a) and (116a) exhibited infrared absorptions at 1655 and 960 cm^{-1}, characteristic of a compound containing a *trans*-disubstituted double bond. In the ^1H n.m.r. spectrum

of (115a), the $(H3')_3$ protons appeared as a doublet of doublets centred at δ 1.60 with coupling to H2' (J 6 Hz) and H1' (J 1.5 Hz). The H2' signal (δ 5.13) was itself an overlapping doublet of quartets with coupling to H1' (J 15.5 Hz) and $(H3')_3$ (J 6 Hz). The signal centred at δ 5.61 was also a doublet of quartets and assigned to H1', with coupling to H2' (J 15.5 Hz) and $(H3')_3$ (J 1.5 Hz). Irradiative decoupling at $(H3')_3$ (δ 1.60) reduced the H1' and H2' signals to an expected AB quartet ($J_{1',2'}$ 15.5 Hz), while decoupling at H1' collapsed the signal of $(H3')_3$ (δ 1.60) to a doublet ($J_{Me',2'}$ 6 Hz) and the H2' peak (δ 5.13) to a quartet ($J_{2',Me'}$ 6 Hz). Similar treatment at δ 5.13 (H2') resulted in reduction of $(H3')_3$ signal to a doublet ($J_{Me',1'}$ 1.5 Hz) and H1' (δ 5.61) to a quartet ($J_{1',Me'}$ 1.5 Hz). The *trans*-propenyl system was confirmed in a similar manner from the ^1H n.m.r. of (116a). The aromatic protons appeared as a singlet at δ 7.21 and 7.23 respectively for the two propenylcyclopropane derivatives (115a) and (116a).

The assignments of stereochemistry of the substituents on the cyclopropane ring for stereoisomers (115a) and (116a) are based on the expected shielding effect of the phenyl group on the ^1H n.m.r. signals of groups *cis* to the phenyl. The relevant ^1H n.m.r. signals were: (115a), δ 1.30, 1-$\underline{CH_3}$; 2.80, 2.88, $-CH_2-O-$; 3.11, CH_3-O-; (116a), δ 0.84, 1-$\underline{CH_3}$; 3.36, 3.46, $-CH_2-O-$; 3.37, CH_3-O-. Having thus assigned the stereochemistry of the two propenylcyclopropanes (115a) and (116a), and recognised that the C3' signal of the *trans*-propenyl systems will be far less dependent on changes in stereochemistry than a methyl directly attached to the cyclopropane ring, it became possible to assign the relevant ^{13}C n.m.r. signals: (115a), δ 17.42, 1-CH_3; 17.91, C3': (116a),

δ 17.82, C3'; 20.05, 1-$\underline{CH}_3$. The C3' values thus assigned compare favourably with those of the (E)-2,2-dimethyl-1-phenyl-(1'-propenyl)-cyclopropane (125a) (C3', δ 17.92) isolated in later work.

Lithium aluminium deuteride reduction of the dimethoxy-alkynol (98) in refluxing tetrahydrofuran for 2.5 h, followed by H_2O reaction quenching, gave a crude product with a composition essentially identical to that obtained above. The ^1H n.m.r. spectrum of the 2-deutero allene (113) showed a singlet $(H1)_3$ signal at δ 1.68, and the absence of any peaks in the δ 4.5-5.5 region reflected the presence of deuterium at C2. The absence of the peak at δ 86.59 in its ^{13}C n.m.r. confirmed this assignment. The remainder of the spectroscopic data taken for this compound was in accord with a mono-deuteriated allene. The ^1H n.m.r. spectrum of the (E)-alkenol (114) revealed a mixture of the 4-deutero and 5-deutero structures. The major component had the 5-deutero structure. For this isomer the C4-proton was a broad singlet centred at δ 6.22, and the $(H6)_3$ group gave rise to a broadened singlet at δ 1.75. For the 4-deutero isomer the $(H6)_3$ group appeared as a doublet (J 6 Hz) centred at δ 1.75, while the C5 proton gave rise to a quartet (J 6 Hz) centred at δ 5.81, each component of which was broadened. The 4-deutero/5-deutero isomeric ratio (15:26) was measured from a comparison of the peak intensities of the protonated alkene-carbons in its repetitive pulse, Fourier transform ^{13}C n.m.r. spectrum (see Appendix). The ^1H n.m.r. spectrum of the methoxy propenylcyclopropane derivatives (115a) and (116a) revealed a singlet $(H3')_3$ at δ 1.60 and no signals in the olefinic region, indicative of deuterium substitution at C1' and C2'.

Extension of the reaction time to 4 and 22 h for the reduction of dimethoxyalkynol (98) with lithium aluminium hydride (water and deuterium oxide quenching, respectively) in tetrahydrofuran gave reduced yields of the allene (113) and the (E)-alkenol (114) and noticeably increased yields of the mixture of propenylcyclopropane derivatives (115) and (116) (Table 1).

In diethyl ether as solvent, lithium aluminium hydride reduction of the dimethoxyalkynol (98) at 35° for 16 h gave the allene (113), the (E)-alkenol (114) and two minor components tentatively assigned the (E)- and (Z)-alkene structures (117a) and (117b), Block A. Unfortunately the latter pair of compounds could not be separated, nor could a mixture of them be obtained free from allene (113). The structural assignment for compound (117a) is based on spectroscopic data for a mixture rich in that component. The infrared absorptions at 1655 and 966 cm^{-1} were consistent with the assignment of a *trans*-disubstituted double bond. The presence of two $-CH_2-O-CH_3$ groups and a mono-substituted aromatic system was unequivocably confirmed by infrared, ^1H and ^{13}C n.m.r. Further, the $(H1)_3$ appeared as a doublet, in its ^1H n.m.r., centred at δ 1.68 with coupling to the H2 proton (J 6 Hz). The H2 signal gave rise to an overlapping doublet of quartets centred at δ 5.41 with coupling to the C3 proton (J 15 Hz) and to the $(H1)_3$ group (J 6 Hz). The H3 signal appeared as a doublet of doublets centred at δ 5.85 with coupling to H2 (J 15 Hz) and to H4 (J 9 Hz), itself a doublet (J 9 Hz) centred at δ 3.40. On irradiation at δ 3.40 (H4), the H3 doublet of doublets reduced to a doublet ($J_{3,2}$ 15 Hz) centred at δ 5.85. Similarly, when irradiated at δ 5.85 (H3) the H4 doublet reduced to a singlet

centred at δ 3.40 in addition to the H2 doublet of quartets collapsing to a quartet ($J_{2,Me}$ 6 Hz). Decoupling of the C1-H_3 group (δ 1.68) reduced the H2 doublet of quartets to a doublet ($J_{2,3}$ 15 Hz) centred at δ 5.41, while conversely, irradiation at δ 5.41 (H2) reduced the C1-H_3 doublet to a singlet at δ 1.68 and the H3 (δ 5.85) doublet of doublets to a doublet ($J_{3,4}$ 9 Hz). In the ^{13}C n.m.r., δ 16.36 and 18.06 were assigned to C6 and C1, respectively by analogy to alkenol (114). The benzyl allylic carbon C4 occurred at δ 52.06, distinguishable from C5 by relative intensity and confirmed by broad band gated decoupling. The accurate parent ion and the observed mass spectrometric fragmentation pattern were in accord with the expected structure (117a). No traces of the methoxy propenylcyclopropanes (115) and (116) could be detected among the products from this reaction.

On reduction of the dimethoxyalkynol (98) with lithium aluminium deuteride, under the above reaction conditions, with water quenching, similar yields of allene (113), (E)-alkenol (114) and alkene (117) were obtained. The allene was confirmed to be the 2-deutero structure (113) by ^1H n.m.r., while ^1H n.m.r. analysis of the mono-deuteriated alkenol (114) indicated a mixture of the 4-deutero and 5-deutero isomers, in the ratio (14:42) as determined from its ^{13}C n.m.r. spectrum. Unexpectedly the spectroscopic and mass spectrometric data for the deuteriated alkenes (117) pointed to the presence of <u>three</u> deuterium atoms at C2, C3 and C4. In particular, the deuteriated alkene (117) gave a parent ion corresponding to a molecular formula, $C_{16}H_{21}D_3O_2$; the ^1H n.m.r. spectrum signals associated with H2 (δ 5.41), H3 (δ 5.85) and H4 (δ 3.40) were absent, the C1-H_3 peak was now a singlet (centred at δ 1.67); and the normal C2 (δ 127.06), C3 (δ 130.32) and

C4 (δ 51.95) resonances were not present in the ^{13}C n.m.r. of the deuteriated material. The major fragmentation pathway of alkene (117) involved cleavage of the C4-C5 bond; see Scheme 18; thus for the deuteriated alkene, fragments were observed corresponding to this fragmentation, i.e. $C_{10}H_8D_3$ and $C_6H_{13}O_2$ confirming that the three deuteriums were all on the same side of the C4-C5 bond cleavage.

When the reaction of dimethoxyalkynol (98) with lithium aluminium hydride was carried out in 2,5-dimethyltetrahydrofuran at 91° for 0.5 h, the products formed were allene (113), (E)-alkenol (114), propenylcyclopropanes (115) and (116), alkene (117) and a new acetylenic compound (118), Block A. The near identical R_f values of compounds (113), (115), (116) and (117) meant that complete chromatographic separation was impossible and that yields had to be ascertained from comparative integrals of the non-vinylic methyl protons of each compound. The structural assignment for compound (118) is based on its spectroscopic data. The absorptions at 2250 and 1106 cm^{-1} in its infrared spectrum were consistent with a compound containing both alkyne and internal ether functions. The ^{13}C n.m.r. signal observed at δ 3.59 is highly indicative of a methyl grouping adjacent to an acetylenic function, the latter being confirmed by presence of alkyne carbons in the expected region, at δ 78.77 and 79.02. The C4 peak is assigned to δ 41.04 [coupling the known 5-15 ppm upfield shift of acetylenic substituents[75] with the chemical shift (δ 52.06) of the corresponding carbon (C4) in the analogous alkene (117)] and is distinguished from C5 by its relative intensity. In the ^1H n.m.r., the C1-H_3 signal is a doublet (J 2 Hz) centred at δ 1.85, coupled through the acetylenic function to the C4 proton, itself a quartet (J 2 Hz) centred at δ 3.62.

Irradiative decoupling at C1-H_3 (δ 1.85) collapsed the H4 quartet to a singlet centred at δ 3.62, while irradiation at H4 (δ 3.62) reduced the C1-H_3 doublet to a singlet at δ 1.85. The parent ion corresponded to the assigned molecular formula $C_{16}H_{22}O_2$ and fragments ($C_6H_{13}O_2$ and $C_{10}H_9$) were observed corresponding to cleavage of the C4-C5 bond, the major fragmentation pathway of alkyne (118), see Scheme 19.

The use of deuterium oxide to quench the above reaction instead of water gave a crude product essentially identical to that obtained above. As expected, no deuterium substitution was evident in the allene (113), propenylcyclopropanes (115) and (116), alkene (117) or alkyne (118) and their ^1H n.m.r. were identical with the fully protonated spectra on file. For the monodeutero (E)-alkenol (114) the C4:C5 distribution of hydride attack was shown to be (7:23) as determined by ^{13}C n.m.r. In each of the above two reactions, a series of minor products were also isolated by chromatography but their structures could not be identified.

Reduction of dimethoxy alkynol (98) with lithium aluminium hydride (or deuteride) in 2,5-dimethyltetrahydrofuran at the lower temperature of 65° for 2.5 h gave, on water quenching, a mixture of allene (113), (E)-alkenol (114) and alkene (117). No trace of propenylcyclopropanes (115) and (116) or alkyne (118) could be detected among the products from the reaction on this temperature or time scale.

2.4 DISCUSSION OF 2,2-DI-(METHOXYMETHYL)-3-PHENYLHEX-4-YN-3-OL (98) REACTIONS.

The reaction of dimethoxyalkynol (98) with lithium aluminium hydride (deuteride) in tetrahydrofuran at 65° for 2.5 h produced in addition to allene (113) and (E)-alkenol (114)

the unexpected propenylcyclopropane derivatives (115) and (116). The extent and location of deuterium labelling in (115) and (116) from the lithium aluminium deuteride reaction are consistent with their formation *via* deuteride ion attack on the intermediate allene (113) to form the carbanion (119), Scheme 20. Internal displacement of methoxide ion from carbanion (119) *via* pathway (a) or (b) would then yield the propenylcyclopropane stereoisomers (115) and (116), respectively. In agreement with this proposal, it is observed that extension of the reaction time in tetrahydrofuran gave increased yields of propenylcyclopropane derivatives (115) and (116) at the expense of both allene (113) and (E)-alkenol (114). From a study of the C4:C5 ratios leading to (114), entries 5 and 7 (Table 1) clearly show that the decrease in yield of (E)-alkenol (114) is specifically at the expense of far carbon (C5) attack supporting the proposal that (115) and (116) result from further reaction on the initially formed far carbon attack product, allene (113). It is noteable, however, that in spite of these changes in product distribution, the overall ratio of hydride (deuteride) ion attack at C4:C5 is essentially constant, indicative of intramolecular solvation of the alkynyloxyaluminium hydride group by at least one of the internal ethers of dimethoxyalkynol (98), during the reduction process.

Lowering the tetrahydrofuran temperature from 65° to 35° was accompanied by an absence of propenylcyclopropane products (115) and (116), an appreciable decrease in allene (113) yield and a large increase in the yield of (E)-alkenol (114). This indicates that the extent to which intermediate carbanion (122), see Scheme 21, is converted into deutero allene (113) prior to reaction quenching is drastically diminished at the lower

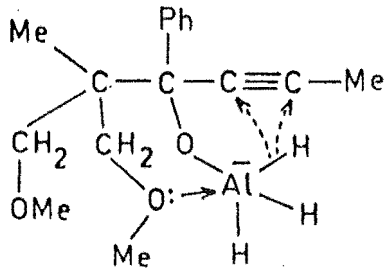
temperature and also, that insufficient energy remains to activate second deuteride attack on allene (113) present in the reaction mixture.

In diethyl ether, reduction of dimethoxy alkynol (98) produced alkene (117) in addition to allene (113) and (E)-alkenol (114). When lithium aluminium deuteride/water quenching was used for the reduction, it was revealed by spectroscopic and mass spectrometric techniques that alkene (117) actually contained three deuterium atoms. The mechanism of formation of alkene (117) is not obvious, but it seems likely that the deuterium atoms at C2 and C3 arise by deuteride ion attack at C3 of the 2-deutero allene (113), see Scheme 22. The mode of introduction of the C4-deuterium is not yet understood, but it must be introduced prior to reaction quenching (H_2O).

Carrying out the reduction of dimethoxyalkynol (98) in refluxing 2,5-dimethyltetrahydrofuran gave a profuse range of products, including the new alkyne (118). Its mode of formation, as shown in Scheme 23, has been elucidated by the use of lithium aluminium hydride with deuterium oxide quenching. It is presumably initiated by hydride attack on the C2-hydrogen of allene (113) to give the alkynyl carbanion (123), which then abstracts a hydride from the reaction mixture prior to quenching with deuterium oxide. Base-catalyzed prototropic rearrangements of this type are well documented and known to proceed *via* a carbanionic intermediate[76]. A lowering of reaction temperature from 91° to 65° produced a much smaller range of products, as expected, with a resultant increase in allene (113) and (E)-alkenol (114) yields. Percentage accountability of products for the 91° reaction was somewhat lower than usual (85% vs 98% av.), but quite understandable in light of the unidentified

compounds isolated.

Inspection of the ratios of overall hydride (deuteride) ion attack on the dimethoxy alkynol (98) accurring at C4:C5, given in Table 1, reveal that they are essentially independent of the reaction solvent, reaction time or reaction temperature. These results parallel those observed for methoxy alkynol (90b) and confirm that intramolecular solvation of the aluminium atom by at least one of the methoxy-substituents in the reacting alkynyloxyaluminium hydride (120) is occurring.



(120)

Considering the reactions of dimethoxy alkynol (98) (THF and Me_2 THF) both at 65° for 2.5 h, a definite solvent effect can still be observed in the product distribution. This variation in product yields can be accounted for in terms of the extent of conversion of the carbanionic intermediate (122), Scheme 21, into the allene (113) prior to reaction quenching. Variation of solvent or reaction temperature would be expected to affect the extent of this reaction, as is observed.

The involvement of the second internal ether of (98) during the reduction process cannot be rigorously proven from an inspection of the results given in Table 1. It may well be that the stereochemical constraints introduced by the first intramolecular solvation of the aluminium atom are such that insufficient flexibility remains for co-ordination of the second internal ether. However, the surprising ease with

which allene (113) undergoes second hydride (deuteride) attack does seem to imply participation of the second internal ether. To pursue this avenue further, it was deemed necessary to synthesize 1-methoxy-2,2-dimethyl-3-phenylhex-4-yn-3-ol (90b), Block A, and extend investigations of its lithium aluminium hydride reactions to see if any cyclopropane compounds could likewise be formed by the loss of its internal ether function, known to participate in intramolecular solvation of the aluminium atom during the reduction process.

2.5 SYNTHESIS OF 1-METHOXY-2,2-DIMETHYL-3-PHENYLHEX-4-YN-3-OL (90b)

The reaction of propynyllithium with 3-methoxy-2,2-dimethyl-1-phenylpropan-1-one (124)[77] gave a 75% yield of methoxyalkynol (90b), see Scheme 24, after chromatography on 5% deactivated alumina and crystallisation from petroleum ether.

2.6 REACTIONS OF 1-METHOXY-2,2-DIMETHYL-3-PHENYLHEX-4-YN-3-OL (90b)

Lithium aluminium hydride reduction of the methoxyalkynol (90b) in refluxing tetrahydrofuran for an extended reaction time (116 h) gave, on quenching with water, in addition to 6-methoxy-5,5-dimethyl-4-phenylhexa-2,3-diene (91b) and (E)-1-methoxy-2,2-dimethyl-3-phenylhex-4-en-3-ol (92b), an inseparable mixture (9:1) of the (E)-(125a) and (Z)-(125b)-2,2-dimethyl-1-phenyl-1-(1'-propenyl)-cyclopropanes, and 2,2-dimethyl-1-phenyl-1-(1'-propynyl)-cyclopropane (126) (see Block A for structures; Table 2 for yield data)*. The isolated products were identified through their spectroscopic data.

---

* Blocks and Tables appear as foldouts at the end of this thesis.

The presence of the allene function in (91b) was indicated by a band at 1960 cm^{-1} in its infrared spectrum, as was the central allenic carbon (C3) at δ 203.61 in its ^{13}C n.m.r. In the ^{1}H n.m.r. of (91b) the allenic proton (H2) appeared as a quartet (J 7 Hz) centred at δ 5.08 and coupled to the C1-H_3 protons at δ 1.68, this signal itself a doublet (J 7 Hz). Irradiation at firstly δ 1.68, then δ 5.08 confirmed their coupled relationship. Mass spectra, microanalyses and the other signals observed in its infrared, ^{13}C and ^{1}H n.m.r. spectra were also in accord with structure (91b).

The allylic alcohol (92b) exhibited absorptions at 3475, 1668 and 970 cm^{-1} in its infrared spectrum, consistent with its assignment as an alcohol with a *trans*-disubstituted double bond. In the ^{1}H n.m.r. of (92b) the C5-proton signal appeared as a doublet of quartets centred at δ 5.78 with coupling to the C4-protons (J 14.5 Hz) and to the C6-H_3 protons (J 6 Hz). The C4-proton signal, centred at δ 6.20, appeared as a doublet, with coupling to H5 (as above) as did the vinylic C6-H_3 group (δ 1.76), also coupled to H5 (J 6 Hz). On irradiation at the C6-H_3 signal (δ 1.76), the C5-proton signal (δ 5.78) reduced to a doublet ($J_{5,4}$ 14.5 hz). Similar decoupling confirmed the other coupled relationships detailed above. The assignment of the ^{13}C n.m.r. of (92b) was unambiguous when based on expected chemical shifts and relative peak height intensities.

The characterization of the two propenylcyclopropanes was necessarily somewhat incomplete, but on the basis of spectroscopic information the structure of the major (E)-propenyl isomer (125a) appears certain. The high resolution mass spectrum obtained for (125a) gave a parent ion corresponding to the correct molecular formula, $C_{14}H_{18}$, while infrared

absorptions at 3075-3045 and 1659, 965 cm^{-1} were indicative of cyclopropane and the assignment of a *trans*-disubstituted double bond within the molecule. On the basis of the expected shielding effect of the phenyl group on the ^1H n.m.r. signals of groups *cis* to the phenyl, the relevant ^1H n.m.r. signals were assigned for (125a): δ 0.77, C2-$(\underline{CH_3})_A(CH_3)_B$, *cis* to phenyl and δ 1.23, C2-$(CH_3)_A(\underline{CH_3})_B$, *trans* to phenyl. The noticeable absence of a methoxy ^1H n.m.r. signal, in conjunction with the AB quartet observed at δ 0.86, 0.99 and aromatic singlet at δ 7.20 in its ^1H n.m.r., all with correct relative integrals, confirmed a phenylcyclopropane assignment. The vinylic C3'-H_3 protons appeared as a doublet of doublets, centred at δ 1.60 in the ^1H n.m.r. of (125a), with coupling to H2' (J 6 Hz) and H1' (J 1.4 Hz). The C2' proton signal was a doublet of quartets centred at δ 5.09, with coupling to H1' (J 15 Hz) and to C3'-H_3 (J 6 Hz), while the H1' signal (δ 5.62) also appeared as a doublet of quartets with coupling to H2' (J 15 Hz) and to C3'-H_3 (J 1.4 Hz). On irradiation at the centre of the C3'-H_3 (δ 1.60) doublet of doublets, the H1' and H2' signals were reduced to an AB quartet ($J_{1',2'}$ 15 Hz) the respective halves centred at δ 5.62 and δ 5.09 respectively. Spin-tickling at H1' (δ 5.62) reduced the C3'-H_3 signal (δ 1.60) from a doublet of doublets to a doublet ($J_{Me',2'}$ 6 Hz) and reduced H2' (δ 5.09) from a doublet of quartets to a quartet ($J_{2',Me'}$ 6 Hz). Similar spin-tickling at H2' (δ 5.09) collapsed the H1' (δ 5.62) signal from a doublet of quartets to a quartet ($J_{1',Me'}$ 1.4 Hz) and collapsed the C3'-H_3 (δ 1.60) from a doublet of doublets to a doublet ($J_{Me,1'}$ 1.4 Hz). The ambiguous ^{13}C n.m.r. signals for the propenylcyclopropane (125a) were assigned by analogy with propenylcyclopropanes (115) and (116) making appropriate

allowance for the methoxy group in (115a) and (116a). The relevant ^{13}C n.m.r. signals are: δ 17.92, C3'; 22.05, C2-Me, *trans* to phenyl; 24.76, C2-Me, *cis* to phenyl.

The evidence in support of the minor (Z)-propenyl isomer (125b) is limited; the structural assignment rests on the closing similar chromatographic and spectroscopic properties of (125a) and (125b), and on the coupling constant ($J_{1',2'}$ 9 Hz) identifiable in the ^{1}H n.m.r. from the C1'-H signal for the minor (Z)-isomer (125b).

The structure of the propynylcyclopropane (126) was assigned on the basis of its spectroscopic data. In particular, the presence of the acetylenic function was indicated by the infrared spectrum (ν_{max} 2245 cm^{-1}), the ^{1}H n.m.r. chemical shift of the $(H3')_3$ signal (δ 1.77), the absence of ^{1}H n.m.r. signals due to olefinic or paraffinic hydrogens, unaccounted for elsewhere in the structure, the ^{13}C n.m.r. chemical shift of C3' (δ 3.68), C2' (δ 73.69), C1' (δ 83.19) and also the 5-15 p.p.m. upfield shift of C1 (δ 27.36) due to the alkyne substituent[75], relative to C1 (δ 37.70) of propenylcyclopropane (125). The mass spectral parent ion was in accord with a molecular formula of $C_{14}H_{16}$, the presence of a mono-substituted benzene was also verified by infrared, ^{1}H and ^{13}C n.m.r. spectra.

When deuterium oxide was used to quench the above reaction instead of water, a product distribution essentially identical with that above was obtained. The ^{1}H n.m.r. spectrum of the mono-deuteriated alkenol (92b) revealed it to be a mixture of the 4-deutero and 5-deutero structures. The major component had the 5-deutero structure. For this isomer the C4-proton appeared as a multiplet ($W_{h/2}$ 6 Hz) centred at δ 6.17, and the C6-H_3 gave rise to a broadened singlet at δ 1.73. For the 4-deutero isomer the C6-H_3 group appeared as

a doublet (J 7 Hz) centred at δ 1.73, while the C5-proton gave rise to a quartet (J 7 Hz) centred at δ 5.79, each component of which was broadened. The 5-deutero/4-deutero isomeric ratio (20:4) was determined by ^{13}C n.m.r.

2.7 DISCUSSION OF 1-METHOXY-2,2-DIMETHYL-3-PHENYLHEX-4-YN-3-OL (90b) REACTIONS

The absence of deuterium in the propenylcyclopropane (125) and the propynylcyclopropane (126) when the lithium aluminium hydride reaction was quenched with deuterium oxide is consistent with their formation *via* further hydride attack on the allene (91b) (Scheme 25). In each pathway, reaction is initiated by hydride ion attack, either at C3 in the allene (91b) to give a carbanion (127) which may ring close to give the propenylcyclopropane (125), or on the C2-hydrogen to give the alkynyl carbanion (128) which may ring close to give the propynylcyclopropane (126). In support of this scheme, inspection of Table 2 reveals that for the long term reaction in tetrahydrofuran (THF) solvent at 65°, the propenyl and propynylcyclopropanes (125) and (126) are, in fact, formed at the expense of allene (91b) and far carbon attack (E)-alkenol (92b).

The mode of formation of the propenylcyclopropane (125) was able to be established by the reaction of H-allene (91b) with lithium aluminium deuteride in refluxing tetrahydrofuran to give the D_1-propenylcyclopropane (125), deuteriated specifically at C1'. This was evident from the high resolution mass spectrum which gave a parent ion corresponding to the molecular formula $C_{14}H_{17}D$, the ^1H n.m.r. where C3'-H_3 was now a broad doublet (J 6 Hz) centred at δ 1.60, coupled to H2', itself a broadened quartet (J 6 Hz) centred at δ 5.09,

and the notable absence in its ^{13}C n.m.r. spectrum of the Cl' signal at δ 135.64, in conjunction with the small upfield shift of the Cl signal (δ 37.58 reduced peak height) due to the adjacent Cl'-deuterium.

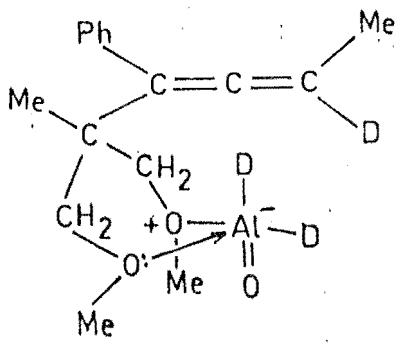
Unfortunately, no evidence regarding the formation of the propynylcyclopropane (126) was found in the above reaction; the proposed mechanism must, therefore, be regarded as speculative.

It should be noted that, if it is assumed the propenyl-(125) and propynyl-(126) cyclopropanes arise from the allene (91b), formed by initial hydride (deuteride) attack at C5, then the overall C4:C5 attack ratio for the long-term reaction in tetrahydrofuran is 20:70, extremely similar (Table 2) to the overall C4:C5 attack ratios obtained for the other reactions of methoxyalkynol (90b).

Coupling the results of this study, therefore, with the evidence obtained from the reaction of the dimethoxy-alkynol (98), it can be concluded that the implicit constant value of the near:far ratios obtained in Tables 1 and 2 is the result of internal solvation of the aluminium atom by the well-placed methoxy substituent(s) during the reduction process. With the knowledge that allenes, in general, do not react with lithium aluminium hydride[78], it is also evident from this study that the presence of an internal ether within the substrate serves to promote the second hydride (deuteride) attack, such that when two internal ethers are present, attack by hydride (deuteride) on allene (113) is able to occur even in short-term reactions (THF) or at low temperature (Et_2O). In light of the results obtained from both alkynol (90b) and its structural analogue (98) with lithium aluminium hydride (deuteride) the conclusion may be drawn that both of the

internal ethers of dimethoxy alkynol (98) are participating in solvation of the aluminium atom during the reduction process; the first is definitely involved in intramolecular solvation (constant C4:C5 ratio of attack by hydride), while the second apparently enhances second hydride (deuteride) attack [semi-quantitative comparison of rates of propenylcyclopropane formation in tetrahydrofuran at 65° for alkynols (90b) and (98)].

Dreiding models reveal that intramolecular hydride donation would be virtually impossible if both internal ethers co-ordinate concurrently during initial hydride donation. Assuming that both internal ethers do co-ordinate *intra*molecularly to the aluminium atom, then a progressive co-ordination would seem to be likely; the first internal ether co-ordinates during initial hydride donation, while the other internal ether co-ordinates during the second hydride attack on allene (113). Dreiding models reveal that this may actually offer some explanation for the rate enhancement of second hydride attack because co-ordination of the second internal ether actually fixes the orientation of the aluminium atom such that the hydride (deuteride) is proximate to the allene (113) as depicted below. When only one internal ether



is co-ordinated to the aluminium atom the aluminium atom is not conformationally constrained, only approaching the central allenic carbon close enough to donate a hydride (deuteride) when thermally excited.

From the information presently at hand from the study of 2,2-di-(methoxymethyl)-3-phenylhex-4-yn-3-ol (98), the only statement that can be made with conviction regarding the co-ordination state of aluminium during this reduction process is that it is at least five-fold. Further conclusions must remain speculative.

CHAPTER 3

LITHIUM ALUMINIUM HYDRIDE REDUCTION OF 1-METHOXY--2-PHENYLPENT-3-YN-2-OL (136), 1-METHOXY-3-PHENYLHEX-4-YN-3-OL (137) AND 7-METHOXY-4-PHENYLHEPT-2-YN-4-OL (138)

3.1 INTRODUCTION

In the reduction of acetylenic alcohols (16) with lithium aluminium hydride (deuteride), the ether solvent molecule is known to have a marked directing power on the alkynyloxyaluminium hydride (deuteride) group (97), and is therefore a deciding factor between the two reaction pathways leading to carbanions (129) and (130), Scheme 26. Blunt et al.[55] have shown that the incorporation of a well-placed internal ether within the substrate is able to solvate the aluminium atom during the reduction process, thus making the near:far hydride (deuteride) ion attack ratio independent of the solvent used. In Chapter 2 it has been further demonstrated that the same internal ether is able to promote a second hydride (deuteride) attack during the reduction, this process is markedly accelerated when two internal ethers are incorporated in the reacting alkynol. Studies also revealed that the aluminium atom is in at least a five-fold co-ordination state during the reduction process.

As part of a continuing study on the influence of alkynol structure and of the solvent on the reduction of alkynols with lithium aluminium hydride, an attempt to determine the optimal transition-state ring size for intramolecular solvation of aluminium to occur was made, by synthesizing 1-methoxy-2-phenylpent-3-yn-2-ol (136),

1-methoxy-3-phenylhex-4-yn-3-ol (137) and 7-methoxy-4-phenylhept-2-yn-4-ol (138), Block B, and examining their reactions with lithium aluminium hydride (deuteride) in a range of ether solvents.

3.2 SYNTHESIS OF 1-METHOXY-2-PHENYLPENT-3-YN-2-OL (136)

Methoxyalkynol (136), Block B, was prepared by reaction of propynyllithium with the corresponding ketone, ω-methoxyacetophenone (141). Its synthesis is outlined in Scheme 27. The reaction of formaldehyde with sodium cyanide gave hydroxymethylcyanide (139), which was methylated "in situ" by methylsulphate to give methoxyacetonitrile (140), purified by fractional distillation[79]. Addition of (140) to phenyl magnesium bromide gave an adduct, which was decomposed by the addition of cold aqueous acid to produce the required precursor, ω-methoxyacetophenone (141) in 71% yield, after distillation under diminished pressure[80].

3.3 REACTIONS OF 1-METHOXY-2-PHENYLPENT-3-YN-2-OL (136)

The reduction of 1-methoxy-2-phenylpent-3-yn-2-ol (136) with lithium aluminium hydride (1.1 mole) in refluxing 2,5-dimethyltetrahydrofuran with stirring for 0.5 h gave, on water quenching, a crude product from which (E)-1-methoxy-2-phenylpent-3-en-2-ol (142) and an inseparable mixture (1:1) of (E)- and (Z)-2-phenylpenta-1,3-dienes (143), Block B, was isolated (see Table 3 for yield data). The products were identified through their spectroscopic data.

The (E)-alkenol (142) gave infrared absorptions at 3500, 1673 and 967 cm^{-1} which revealed it to be an alcohol with a *trans*-disubstituted double bond. The vinylic region

in its ^{1}H n.m.r. spectrum appeared to be part of a degenerate ABX_3 system centred at δ 5.65. It showed only two lines of equal intensity, ca. 2 Hz apart, with a very small satellite close on either side. The C5-H_3 signal appeared as a doublet, with a half-height singlet in between, centred at δ 1.69 with coupling to the C4-proton (J 5 Hz) and the C3-proton. On irradiation at the centre of the tight ABq region, the C5-H_3 signal became a singlet centred at δ 1.69. Similarly, when irradiated at δ 1.69 (C5-H_3) the ABq reduced to a singlet centred at δ 5.65. The ^{13}C n.m.r., mass spectrum, micro-analyses and remainder of the infrared and ^{1}H n.m.r. spectra were also in accord with structure (142).

The (E)- and (Z)-dienes (143) were obtained as an inseparable mixture (1:1), easily identifiable by its extremely characteristic, pungent odour. Notable in the infrared, ^{1}H and ^{13}C n.m.r. spectra was the absence of signals corresponding to a methoxymethyl group. The diene nature of these compounds was indicated by absorptions at 1643 and 1596 cm^{-1} in the infrared spectrum. The olefinic methylene group and *trans*-disubstituted double bond gave infrared absorptions at 893 and 967 cm^{-1}, respectively. The expected medium to strong band due to a *cis* CH wag in the region 650-730 cm^{-1}, characteristic of a *cis*-disubstituted alkene[81], was obscured by the strong aromatic band at 705 cm^{-1}. The ^{13}C n.m.r. confirmed a mixture of comparatively identical compounds, with all peak positions appearing twinned. The most characteristic ^{13}C n.m.r. signals were for the C1 methylene carbon of each isomer, appearing in their expected position at δ 114.28 and 114.98, and the C5 signals at δ 14.73(Z) and δ 18.23(E). The ^{13}C n.m.r. was complicated somewhat by the presence of polymer peaks, formed from the unstable dienes during the running of the

carbon spectrum. High resolution mass spectra confirmed that not only was the correct molecular parent ion present, $C_{11}H_{12}$, but that of its dimer $C_{22}H_{24}$ also. The ^1H n.m.r. spectrum of the mixture was broken up into its (E)-(143a) and (Z)-(143b) segments by decoupling experiments. Spin-tickling at δ 1.66 (the C5-H_3 group) collapsed the doublet of quartets at δ 5.75 (H4) to a doublet, with coupling to H3 ($J_{4,3}$ 10.5 Hz) centred at δ 6.10; this vinylic coupling constant verified that these signals do belong to the (Z)-(143b) isomer. By elimination, the other similar ^1H n.m.r. signals could be assigned to the (E)-(143a) isomer: δ 1.77, C5-H_3; 5.57, H4; and 6.24, H3. Similar spin-tickling confirmed this to be the case. Irradiation at δ 5.57 (H4) collapsed the H3 doublet to a singlet at δ 6.24, and also reduced the C5-H_3 doublet, centred at δ 1.77, to a singlet, whereas irradiation at δ 1.77 (C5-H_3) reduced the H4 doublet of quartets to a doublet ($J_{4,3}$ 15 Hz) centred at δ 5.57, with coupling to H3, itself a doublet ($J_{3,4}$ 15 Hz) centred at δ 6.24. This coupling constant is characteristic of a *trans* vinylic system. The olefinic methylene protons appeared in the ^1H n.m.r. at their expected positions, although assignment of the respective peaks to the (E)-(143a) or (Z)-(143b) isomer was not possible. Using the 10-proton singlet of the aromatic system as a reference, the ^1H n.m.r. integrals were shown to be consistent with (E)- and (Z)-dienes (143) in a 1:1 ratio.

When deuterium oxide was used to quench the above reaction, a product distribution essentially identical with that above was obtained. The spectroscopic data of the (E)- and (Z)-diene (143) mixture (1:1) was identical with the fully protonated spectra on file. The (E)-alkenol (142) was on the other hand, mono-deuteriated (mass spectrum) and shown

by ^{1}H n.m.r. to be, in fact, a mixture of the 4-deutero and 3-deutero structures, their 25:52 isomeric ratio being determined by ^{13}C n.m.r. (see Appendix).

The use of lithium aluminium deuteride in the reduction of methoxyalkynol (136) in refluxing 2,5-dimethyltetrahydrofuran for 0.5 h, gave on water quenching, similar product yields to those previously obtained. The spectroscopic data for the mixture (1:1) of the (E)- and (Z)-dienes (143) reflected the presence of two deuteriums (mass spectrum) at C3 and C4 (^{1}H and ^{13}C n.m.r.). The deuteriated dienes (143) gave a parent ion corresponding to a molecular formula, $C_{11}H_{10}D_2$ while the normal ^{13}C n.m.r. signals at δ 128.37, 129.04, 129.92 and 132.89 in conjunction with the ^{1}H n.m.r. peaks associated with vinylic protons, H3 and H4 at δ 5.57, 5.75, 6.10 and 6.24 were notably absent. The vinylic C5-H_3 groups at δ 1.66 and 1.77 were singlets as expected in the ^{1}H n.m.r. The ratio of deuteride attack at C4:C5 in the (E)-alkenol (142) was shown by ^{13}C n.m.r. to be 27:48, essentially identical to the ratio obtained when lithium aluminium hydride/deuterium oxide was used, as would be expected to be the case.

Reduction of 1-methoxy-2-phenylpent-3-yn-2-ol (136) with lithium aluminium hydride (deuteride) in diethyl ether, tetrahydrofuran or 2,5-dimethyltetrahydrofuran under a variety of reaction conditions continued to give the mixture (1:1) of (E)-(143a) and (Z)-(143b) dienes and the (E)-alkenol (142), their relative yields being both solvent- and, for tetrahydrofuran and 2,5-dimethyltetrahydrofuran reactions, temperature dependent (see Table 3). Their spectroscopic data was consistent with that already obtained.

3.4 DISCUSSION OF 1-METHOXY-2-PHENYLPENT-3-YN-2-OL (136) REACTIONS

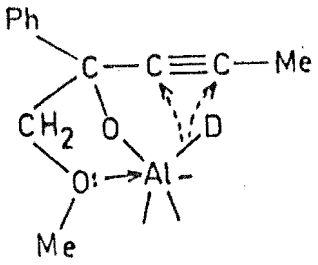
The reaction of methoxyalkynol (136) with lithium aluminium hydride (deuteride) in 2,5-dimethyltetrahydrofuran, tetrahydrofuran or diethyl ether produced in addition to the expected (E)-alkenol (142), the (E)- and (Z)- pentadienes (143). The extent and location of deuterium labelling in the isomeric dienes (143) when lithium aluminium deuteride was used is consistent with their formation *via* further deuteride ion attack on the allene (144), Scheme 28. Assuming a two-step mechanism, this is then followed by elimination from the intermediate carbanion (145) to yield the conjugated dienes (143). Spectra obtained when lithium aluminium hydride/deuterium oxide was used were identical with those of fully protonated samples; this is also in accord with Scheme 28. The mechanism proposed is, in fact, analogous to that established in Chapter 2 for the D_2-propenylcyclopropane derivatives (125) on reduction of methoxyalkynol (90b) with lithium aluminium deuteride, Scheme 25.

This mechanism is, in itself, very important when placed against the backdrop that allenes, in general, are totally insensitive to attack by lithium aluminium hydride[78]. Claesson et al[82] have shown that allenes become reactive only when activated, by such as a hydroxyl group. The relevant part of their work, outlined in Scheme 29, demonstrated that treatment of α-allenic alcohol (146) with lithium aluminium hydride in tetrahydrofuran gave the corresponding diene (148) in 80% yield, *via* transition state (147). Their concerted mechanism involved the intramolecular donation of hydride to the central allenic carbon of (146), followed by migration of the double bond and elimination of the alkoxyaluminium hydride group.

In light of this information, and from a comparative study of alkynol (18)[28], Block B, Table 7, the structural analogue of alkynol (136) but lacking the methoxy substituent, it is apparent that the driving force for the second hydride (deuteride) attack on allene (144) is the presence of the internal ether; presumably due to its ability to co-ordinate to aluminium to promote further hydride (deuteride) attack and/or also due to its good leaving group properties. Unfortunately time did not permit ascertainment of whether this second hydride (deuteride) attack was, in fact, an *intra*- or *inter*molecular process.

The other observation worth noting is that, although second hydride (deuteride) attack on allene (144), Block B, was to be expected in the light of the results obtained in Chapter 2, the failure to isolate or detect the intermediate allene (144) in these reactions was not so. This would seem to indicate that in the ethereal solvents used, the activation energy for second hydride (deuteride) ion attack to occur for methoxyalkynol (136) is indeed very small and that the dienes (143) thus act as a long-term "sink" for initial hydride attack at C4.

Assuming that the dienes (143) are formed *via* the allene (144), and thus by hydride (deuteride) ion attack initially at C4 in alkynol (136), coupled with the ratios of deuteride ion attack at C3:C4 on the alkynol (136) to yield (E)-alkenol (142), the overall attack ratio C3:C4 can be determined; these results are also given in Table 3. It is clear that, although the relative yields of dienes (143) and (E)-alkenol (142) are solvent - and temperature-dependent in Table 3, the overall ratio of hydride (deuteride) ion



(149).

attack at C3:C4 in alkynol (136) is independent of the reaction conditions. These results point towards methoxy group participation (149) in the reduction process.

3.5 PURIFICATION OF 1-METHOXY-3-PHENYLHEX-4-YN-3-OL (137)

The crude methoxyalkynol (137)[83], Block B, was purified for use by column chromatography on 10% deactivated alumina. The spectroscopic data obtained (Experimental Section) was consistent with its assignment to structure (137).

3.6 REACTIONS OF 1-METHOXY-3-PHENYLHEX-4-YN-3-OL (137)

Reduction of 1-methoxy-3-phenylhex-4-yn-3-ol (137) with lithium aluminium hydride at 35° in either diethyl ether or tetrahydrofuran gave the corresponding 6-methoxy-4-phenylhexa-2,3-diene (151) and (E)-1-methoxy-3-phenylhex-4-en-3-ol (150), Block B, the spectroscopic data for which were in accord with their assigned structures (see Table 4 for yield data).

The characteristic infrared absorption at 1955 cm^{-1} indicated the presence of the allene function in (151), confirmed by the distinguishing ^{13}C n.m.r. shifts at δ 89.28 (C2) and δ 204.71 (C3). The ^{13}C, ^{1}H n.m.r. and infrared spectra unambiguously indicated an internal ether and mono-substituted benzene within the structure. In the ^{1}H n.m.r. spectrum the allenic C1-H_3 group appeared as a doublet centred at δ 1.79 with coupling (J 7 Hz) to the allenic C2-proton, itself an overlapping triplet of quartets centred at δ 5.43. The C2-proton (δ 5.43) is coupled to the C1-H_3 group (J 7 Hz), with

additional long-range coupling to the C5-H_2 protons (J 3 Hz), itself an overlapping doublet of triplets centred at δ 2.62, with coupling to H2 (as above) and additional coupling to the C6-H_2 group (J 7 Hz) centred at δ 3.48. Long-range coupling through five bonds (as encountered in this allenic system), is not uncommon in the literature[30,35,84,85,86] with typical coupling constants in the range 2.5 - 3.5 Hz. Spin decoupling centred at δ 5.43 (H2) collapsed the C1-H_3 doublet at δ 1.79 to a singlet and the doublet of triplets at δ 2.62 (C5-H_2) to a triplet ($J_{5,6}$ 7 Hz) as expected. Irradiation at δ 2.62 (C5-H_2) reduced the triplet of C6-H_2 (δ 3.48) to a singlet, as well as collapsing the apparent nine-peak signal of H2 (δ 5.43) to a quartet ($J_{2,1}$ 7 Hz). On irradiation at δ 3.48 (C6-H_2), the C5-H_2 (δ 2.62) doublet of triplets was reduced to a doublet ($J_{5,2}$ 3 Hz), while decoupling centred at δ 1.79 (C1-H_3) resulted in collapsing the overlapping doublet of quartets of H2 (δ 5.43) to a doublet ($J_{2,5}$ 3 Hz). The allene (151) was, unfortunately, insufficiently stable for accurate micro-analyses to be taken, although an accurate parent ion corresponding to $C_{13}H_{16}O$ was obtained by high resolution mass spectroscopy.

The assignment of the *trans* configuration to alkenol (150) was based on its infrared absorptions at 1670 and 965 cm^{-1}. The alcohol and internal ether ether functions appeared at 3475 and 1104 cm^{-1}, respectively in the infrared. The ^{13}C n.m.r. assignment was unambiguous, and with mass spectra and micro-analyses, were in accord with structure (150). In its ^{1}H n.m.r. spectrum, the vinylic region appeared to be part of a degenerate ABX_3 system, analogous to (E)-alkenol (142). It showed only two lines of equal intensity, ca. 2 Hz apart, centred at δ 5.62 with a satellite on either side. H4 and H5

were coupled to each other with a coupling constant ca. 16 Hz, derived from a computer simulation of the AB portion of the spectrum[87]. The C6-H_3 appeared as a doublet (J ≃ 5 Hz), with a half-length singlet superimposed, centred at δ 1.66. The C2-H_2 triplet was centred at δ 2.03, being coupled to the C1-protons (J 6 Hz), itself a multiplet ranging from δ 3.05 - 3.50. Exhaustive irradiative decoupling confirmed beyond doubt the coupling relationships described above.

For reductions using lithium aluminium deuteride, followed by reaction quenching with water, the allene (151) produced gave spectroscopic data consistent with the expected presence of deuterium at C2. In its ^{1}H n.m.r., no signal was observed in the vinylic region, the C1-H_3 group at δ 1.75 was now a singlet and the C5-H_2 signal at δ 2.60 a triplet ($J_{5,6}$ 7 Hz), while the normal ^{13}C n.m.r. signal for C2 (δ 89.28) was also missing in the spectrum of the deuteriated material. The location of the deuterium atom in the mono-deutero (E)-alkenol (150) was determined from the ^{13}C n.m.r spectra of the samples (see Appendix), the ratios of deuteride ion attack at C4:C5 on the alkynol (137) are given in Table 4.

At higher temperatures (65°) in tetrahydrofuran, or in 2,5-dimethyltetrahydrofuran (65° or 91°), lithium aluminium hydride reduction of methoxyalkynol (137) gave two additional products, 1-phenyl-1-(1'-propenyl)-cyclopropane (152) and 8-methoxy-4-methyl-6-phenyl-3-(1'-phenylcyclopropyl)-octa-2,5-diene (153), Block B, the formation of which have been reported in the preliminary communication[88]. The spectroscopic data for these two compounds, (152) and (153), are in accord with their assigned structures (see Table 4 for yield data).

The cyclopropane derivative (152) exhibited infrared spectrum absorptions at 1664 and 967 cm^{-1}, which was consistent with its assignment as a compound having a *trans*-disubstituted double bond. Notably absent from the infrared, ^{1}H or ^{13}C n.m.r. were any signals which would indicate the remaining presence of the methoxy substituent within the structure. Assignment of the low field region of the ^{13}C n.m.r. spectrum was unambiguous, the high field peaks at δ 14.46, 17.67 and 27.62 were assigned to C2, C3; C3' and C1 respectively on the basis of relative intensities and expected shifts. In its ^{1}H n.m.r. spectrum, the C2'-proton appeared as an overlapping doublet of quartets centred at δ 4.96 with coupling to the C1'-proton (J 15.5 Hz) itself a doublet centred at δ 5.28, and to the C3'-protons (J 5.5 Hz) itself a doublet centred at δ 1.58. Irradiative decoupling confirmed the above relationships. The mass spectrum and ultraviolet spectrum were also consistent with structure (152).

The methoxy diene (153) was shown by infrared absorptions at 1600 and 1110 cm^{-1} to contain diene and methoxy functions. The assignment of its ^{13}C n.m.r. was only possible with the assistance of single-frequency-off-resonance decoupling. The vinylic methyl (C1) was assigned to δ 14.89, at slightly higher field than usual (≃ δ 18.00) because of its obvious greater steric compression; the other quartet occurred at δ 26.39, and was assigned to the saturated C4-Me. The high field triplets at δ 17.74, 18.39 and 26.39 could unambiguously be assigned to C2'/C3' and C7 respectively. The signals of C1' (δ 26.39) and C4 (δ 38.65) were observed as a singlet and doublet, respectively in the SFORD spectrum of methoxy diene (153). The C8 and methoxy signals appeared with correct multiplicities in their expected positions. The olefinic carbons, C2 (δ 123.67)

and C5 (δ 136.32), were of doublet multiplicity and designated on the expected greater downfield shift for C5 due to its extra β carbons, other factors being approximately equal. Two aromatic systems were definitely evident in the ^{13}C n.m.r., but could not be distinguished. The remaining unassigned peaks were both singlets, at δ 134.34 and at δ 142.79. Using the formula based on the number of α,β,γ,α',β' and γ' carbons to determine the approximate shifts of olefinic carbons, it could be shown that C3 was to be expected at a lower field than C6 and assignment was made accordingly. In its ^{1}H n.m.r. the cyclopropane protons appeared as a singlet, overlapping with the C4-CH_3 signal, itself a doublet ($J_{Me,4}$ 7 Hz) also centred at δ 1.13. The C8-H_2 signal was a triplet, its centre at ca. δ 3.15 (obscured by the methoxy signal at δ 3.13) with coupling to the C7-H_2 protons (J 7 Hz). The C1-H_3 signal appeared as a doublet at δ 1.75 with coupling to H2 (J 7 Hz), itself a quartet centred at δ 5.67. The C5-proton appeared as a doublet centred at δ 5.48 with coupling to H4 (J 10 Hz), itself a doublet of quartets centred at δ 3.47 with coupling to H5 (as above) and additional coupling to the C4-CH_3 (J 7 Hz). The coupling relationships detailed above were confirmed by exhaustive spin-decoupling experiments. The micro-analyses and ultraviolet spectra were also in accord with structure (153).

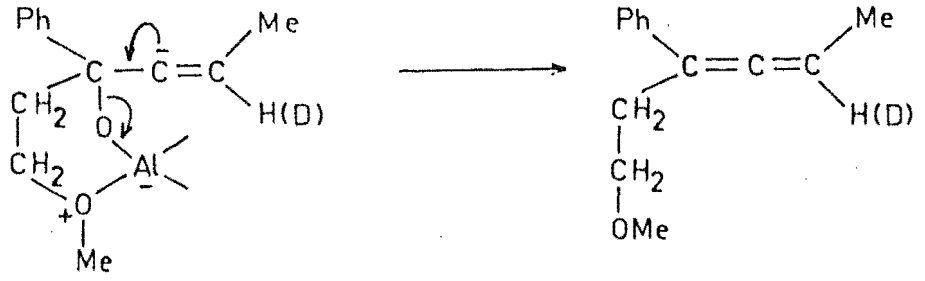
For reductions using lithium aluminium deuteride, followed by reaction-quenching with water, the spectroscopic data was consistent with deuteriation at C1' and C2' in the cyclopropane derivative (152) and C2, C4 and C5 in the methoxy diene (153). In the ^{1}H n.m.r. spectrum of the 1',2'-dideutero cyclopropane derivative (152) there was no detectable signal in the δ 5-6 region, and the C1-H_3 signal had collapsed to a singlet centred at δ 1.73. In the ^{1}H n.m.r. spectrum of methoxy

diene (153) the signals centred at δ 3.47, 5.67 and 5.48 were absent, the C1-H_3 and C4-CH_3 signals gave rise to singlets centred at δ 1.12 and 1.73 respectively. The normal ^{13}C n.m.r. signals at δ 38.65, 123.67 and 136.32 were also notably absent for the deuteriated material, thus indicating substitution by deuterium at C4, C2 and C5 respectively. The relative yields of the allene (151), cyclopropane derivative (152) and methoxy diene (153) on reduction of alkynol (137) were markedly dependent on reaction conditions (see Table 4).

3.7 DISCUSSION OF 1-METHOXY-3-PHENYLHEX-4-YN-3-OL (137) REACTIONS

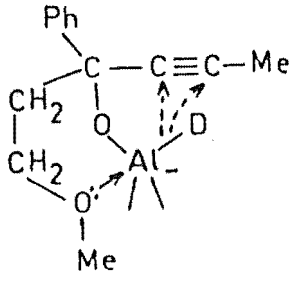
The reactions of methoxy alkynol (137) with lithium aluminium hydride (deuteride) in tetrahydrofuran (at 65°) or 2,5-dimethyltetrahydrofuran (65° or 91°) gave in addition to the expected allene (151) and (E)-alkenol (150), the propenyl-cyclopropane (152) and methoxy diene (153). Both the cyclo-propane derivative (152) and methoxy diene (153) are envisaged as being formed by further reduction of the allene (151), Scheme 30. Deuteride ion attack at the central allenic carbon gives the delocalised carbanion (154), which may then undergo ring formation and internal displacement of methoxide (155) to give the cyclopropane derivative (152). Alternatively the delocalised carbanion (154) may react with a second molecule of allene (151), followed by ring formation and elimination of methoxide (156), to give the methoxy diene (153). This reaction scheme is in accord with the observed deuteriation pattern in products (152) and (153) from the lithium aluminium deuteride reaction. In keeping with the intermolecular mechanism proposed for the formation of the methoxy diene (153), a reaction of methoxy alkynol (137) in tetrahydrofuran carried

carried out at greater dilution (10x) gave a sharply reduced yield of (153) and the allene (151) was isolable (Table 4). Unfortunately allene (151) proved to be too unstable for a convincing conversion into compounds (152) and (153) by reaction with lithium aluminium hydride (deuteride). The higher yields of 5-deutero (E)-alkenol (150), which arises by deuteride attack at C5, was but a reflection of incomplete conversion of carbanion (157) into deutero allene (151) prior to reaction quenching.



(157) (151)

Given that the cyclopropane derivative (152) and the methoxy diene (153) are formed *in situ* from the allene (151), the overall ratio of hydride (deuteride) ion attack at C4:C5 can be determined, these data are given in Table 4. With the possible exception of the diethyl ether reaction, where the product accountability was less satisfactory, the ratio of attack at C4:C5 in methoxy alkynol (137) was essentially independent of the ether solvent used or the reaction temperature, and consistent with intramolecular solvation in the reacting alkynyloxyaluminium hydride (158) by the methoxy group.



(158)

3.8 SYNTHESIS OF 7-METHOXY-4-PHENYLHEPT-2-YN-4-OL (138)

The reaction of propynyllithium with the corresponding ketone, 4-methoxy-1-phenylbutan-1-one (164) gave methoxy alkynol (138), Block B, in 65% yield, after purification by fractional distillation under diminished pressure and chromatography on 10% deactivated alumina. The synthesis of ketone (164) is outlined in Scheme 31. Bromination of 2-methoxyethanol with phosphorus tribromide produced 1-bromo-2-methoxyethane (159) in 46% yield[89]. The reaction of diethyl malonate with 1-bromo-2-methoxyethane but using sodium hydride in 1,2-dimethoxyethane[90] under nitrogen gave diethyl (2-methoxyethyl) malonate (160) in 51% yield. Base hydrolysis of (160), followed by acidification with HCl gave two possible results. In attempting to combine the acidification and decarboxylation processes, in a similar manner to Reibosomer et al.[91], an unwanted acid promoted cyclization took place in conjunction with methanol and carbon dioxide elimination to produce a quantitative yield of γ-butyrolactone (161), identical with authentic data (^{1}H n.m.r.[92], ^{13}C n.m.r.[93], infrared spectrum[94] and b.p.[95]), Scheme 32. To avoid this complication the acidification temperature was not permitted to rise above 20°, the dicarboxylic acid (162) was extracted immediately from the acidic medium with ether, the solvent removed and then decarboxylation begun, to give 4-methoxybutyric acid (163) in a quantitative yield. Addition of (163) to phenyl-lithium in ether, followed by hydrolysis with water gave the required precursor, 4-methoxy-1-phenylbutan-1-one (164).

3.9 REACTIONS OF 7-METHOXY-4-PHENYLHEPT-2-YN-4-OL (138)

In 2,5-dimethyltetrahydrofuran, the reaction of 7-methoxy-4-phenylhept-2-yn-4-ol (138) with lithium aluminium hydride gave 7-methoxy-4-phenylhepta-2,3-diene (165), and the (Z)- and (E)-alkenols (166), Block B, the spectroscopic data for which were consistent with their assigned structures (see Table 5 for yield data).

The allene function was confirmed by the infrared absorption at 1951 cm^{-1}, and the ^{13}C n.m.r. signals at δ 89.29 (C2), 104.70 (C4) and 204.65 (C3). The allenic C2-proton appeared as a triplet of quartets centred at δ 5.40 in the ^{1}H n.m.r., with coupling to C1-H_3 (J 6.7 Hz) itself a doublet centred at δ 1.73, and additional long-range coupling through the allenic system to C5-H_2 (J 3.4 Hz). The C5-H_2 signal, centred at δ 2.43, appeared as a doublet of triplets with coupling to H2 (as above) and C6-H_2 (J 7.2 Hz), itself a triplet of triplets centred at δ 1.78. The C7-H_2 signal was a triplet centred at δ 3.43, with coupling to C6-H_2 (J 6.3 Hz). The respective integrals were correct, the coupling relationships exhaustively confirmed by spin-decoupling. The mass spectrum and micro-analyses were also in accord with structure (165).

The (E)-alkenol (166b) gave infrared absorptions at 3450, 1664 and 964 cm^{-1} consistent with its assignment as an alcohol with a *trans*-disubstituted double bond. Although assignment of the ^{13}C n.m.r. was unambiguous, the ^{1}H n.m.r. was not so. As for (E)-alkenols (142) and (150), the vinylic protons (H2,H3) appeared as a multiplet δ 5.27-5.93, the AB portion of a degenerate ABX_3 pattern. Irradiation at the centre of the vinylic region confirmed coupling between H2 and C1-H_3, previously a disproportionated doublet (appearing superimposed on the C5-H_2, C6-H_2 multiplet at δ 1.20-2.05)

which visibly collapsed to a singlet centred at δ 1.69. Reverse decoupling also confirmed this. The saturated nature of the C5- and C6-protons meant their overlapping coupled peaks appeared as a multiplet (see above). The C7-H_2 protons attached to oxygen were thus deshielded as a result and occurred as a triplet at much lower field; their coupling (J 6 Hz) to C6-H_2 was confirmed by irradiation in the region δ 1.20-2.05. Micro-analyses and mass spectra were both in agreement with structure (166b).

The (Z)-alkenol (166a), giving a mass spectral parent ion corresponding to the same molecular formula $C_{14}H_{20}O_2$ as expected, was easily distinguishable from its (E)-counterpart (166b) by its spectroscopic data. In its infrared, the alcohol absorption occurred at 3460 cm^{-1}, but the disubstituted double bond absorption now occurred at 1652 cm^{-1} [12 cm^{-1} lower than (E)-alkenol (166b)], there was no 964 cm^{-1} absorption and unfortunately, the expected *cis* CH wag in the region 650-730 cm^{-1}, characteristic of a *cis*-disubstituted alkene[81], was obscured by a strong aromatic band at 718 cm^{-1}. Notably different in the ^{13}C n.m.r. was the upfield shift of the C1 carbon in the more sterically congested (Z)-isomer (δ 14.65) in relation to the (E)-isomer (δ 17.72); there was also a downfield shift of C2 ((E):δ 123.48, (Z):δ 128.02) in the (Z) isomer, which proved to be most unfortunate in the necessary calculation of ^{13}C n.m.r. ratios for mixtures of the mono-deuteriated (Z)-alkenol (166a) (the problem and solution are explained in the Appendix). In the ^{1}H n.m.r. of (Z)-alkenol (166a) the vinylic region could be readily resolved, in contrast to the (E)-alkenol (166b). H3 appeared as a doublet at δ 5.80, with coupling (J 11.5 Hz) to H2, itself a "pseudo-quintet" (overlapping doublet of quartets) centred at δ 5.54 with coupling to H3 (as above) and to

$C1\text{-}H_3$ (J 6 Hz), itself a doublet (J 6 Hz) centred at δ 1.57. This higher field signal [δ 1.57-(Z) c.f. δ 1.69-(E)] proved to be an excellent means of verifying if only one, or both isomers were actually present. Irradiative decoupling at δ 1.57 ($C1\text{-}H_3$) reduced H2 (δ 5.54) to a doublet ($J_{2,3}$ 11.5 Hz), a coupling constant indicative of a *cis*-disubstituted alkene. On irradiation at δ 5.54 (H2), the $C1\text{-}H_3$ doublet at δ 1.57 collapsed to a singlet, as did H3 centred at δ 5.80.

For reductions using lithium aluminium deuteride, followed by reaction quenching with water, under the above conditions, the relative yields of the allene (165) and two alkenols (166) were similar. As expected, the ^1H n.m.r. spectrum of the 2-deuteroallene (165) showed no signal in the δ 5-6 region, the $C5\text{-}H_2$ group now appeared as a triplet ($J_{5,6}$ 7.2 Hz), and the appearance of the $C1\text{-}H_3$ signal as a singlet at δ 1.73 all reflected the substitution by deuterium at C2. This was confirmed by the absence of the normal ^{13}C n.m.r. signal for C2 (δ 89.29) in the deuteriated allene (165). The monodeutero (E)- and (Z)-alkenols (166) were shown by ^1H n.m.r. and ^{13}C n.m.r. to be deuteriated specifically at C3.

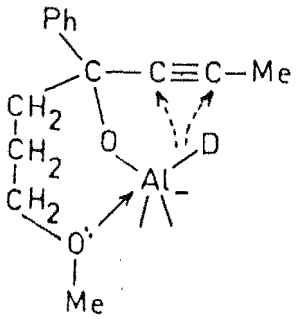
When methoxy alkynol (138) was reduced with lithium aluminium hydride (deuteride) in tetrahydrofuran or diethyl ether, the relative product yields varied considerably with both reaction solvent and temperature. (Z)-alkenol (166a) was formed only in the long-term reaction in diethyl ether (entry 2, Table 5). When deuteriated reagents were used, the distribution of deuterium (C3:C2) in the mono-deutero (E)-alkenol (166b) was determined by ^{13}C n.m.r. (Appendix) (see Table 5).

3.10 DISCUSSION OF 7-METHOXY-4-PHENYLHEPT-2-YN-4-OL (138)

When methoxy alkynol (138) is reduced with lithium aluminium hydride (deuteride) the (Z)-alkenol is formed, in addition to the expected allene (165) and (E)-alkenol (166b); only in poor Lewis bases (2,5-dimethyltetrahydrofuran or diethyl ether), in a manner which is, interestingly enough, analogous to the observations made by Grant and Djerassi[48].

It is clear from an inspection of Table 5 that the ratio of hydride (deuteride) ion attack at C3:C2 for methoxy alkynol (138) is dependent on both the reaction temperature and the ether solvent used. It appears, therefore, that intramolecular solvation by the methoxy group in the reacting alkoxyaluminium hydride is unimportant in product formation and that solvation of the aluminium atom involves predominantly the variable ether solvent molecule.

As has been noted previously, for methoxy alkynols (136) and (137) evidence for the participation of the methoxy function in the reduction process was found, but no so for the methoxy alkynol (138) where participation would have involved a seven-membered ring (167). In this connection it is notable that, for the diethyl ether or tetrahydrofuran reactions at 35°, the rates of reaction (seen as the extent of reaction; Tables 3-5) of alkynols (136) and (137) are similar, and are faster than the corresponding rates of reaction of alkynol (138).



(167)

CHAPTER 4

LITHIUM ALUMINIUM HYDRIDE REDUCTION OF PROPARGYL ALCOHOLS IN BENZENE SOLVENT

4.1 INTRODUCTION

The very high reactivity of lithium aluminium hydride (deuteride) has severely restricted the choice of suitable solvents to ethers, hydrocarbons or tertiary amines[96]. Ethereal solvents are generally utilized because of their inertness towards attack by lithium aluminium hydride and the good solubility they offer. The reported solubilities for diethyl ether and tetrahydrofuran are, in grams per 100 g of solvent, 25-30 and 13, respectively[97]. In contrast, lithium aluminium hydride is insoluble in hydrocarbon solvents and as a result, when reducing acetylenic alcohols, the extent of reaction is extremely low, if at all. For this reason no systematic study of this reagent has been undertaken in hydrocarbon solvents.

The results obtained in Chapter 2 and Chapter 3, indicated the participation of suitably well placed internal ether functions in intramolecular solvation of the aluminium atom during the reduction process, such that solvation by an ether solvent molecule was no longer crucial and consequently no solvent effect was observed in the near:far deuteride ion attack ratio. In light of these results, it seemed reasonable to assume that in a non-ethereal solvent, that the rate of reduction of an acetylenic alcohol containing such an internal ether would be significantly enhanced over its structural analogue lacking such assistance. It was thus decided to

make a comparison in a semi-quantitative manner, of the rates of the intramolecularly solvated alkynol reductions with their non-internal ether analogues, in a solvent such as benzene. To this end it was necessary (a) to synthezize 2,2-dimethyl-3-phenylhex-4-yn-3-ol (90a), see Block A, the non-internal ether analogue of alkynols (90b) and (98); (b) to purify 2-phenylpent-3-yn-2-ol (18), Block B, the non-internal ether analogue of alkynol (136); and (c) to observe their reactions and those of their methoxy analogues with lithium aluminium hydride (deuteride) in benzene solvent.

4.2 SYNTHESIS OF 2,2-DIMETHYL-3-PHENYLHEX-4-YN-3-OL (90a)

To an ethereal solution of pivaloyl chloride (168) was added phenyl magnesium bromide[98] slowly, the reaction quenched with water and the required precursor (169)[99] purified by column chromatography. Alkynol (90a) was then obtained in 92% yield by reaction of propynyllithium with a precursor ketone, pivalophenone (169), Scheme 33.

4.3 REACTIONS OF 2,2-DIMETHYL-3-PHENYLHEX-4-YN-3-OL (90a), 1-METHOXY-2,2-DIMETHYL-3-PHENYLHEX-4-YN-3-OL (90b) AND 2,2-DI-(METHOXYMETHYL)-3-PHENYLHEX-4-YN-3-OL (98) WITH LITHIUM ALUMINIUM HYDRIDE (DEUTERIDE) IN BENZENE SOLVENT.

The reduction of 2,2-dimethyl-3-phenylhex-4-yn-3-ol (90a), Block A, with lithium aluminium hydride in refluxing benzene for 0.75 h gave, on water quenching, a quantitative yield of unreacted starting material.

Reaction of 1-methoxy-2,2-dimethyl-3-phenylhex-4-yn-3--ol (90b), with lithium aluminium hydride in refluxing benzene for 0.75 h gave, on water quenching, the allene (91b),

(E)-alkenol (92b) and 30% of unreacted alkynol (90b), Block A, each compound was shown by spectroscopic techniques to be identical with material isolated earlier (see Table 6 for yield data).

When deuterium oxide was used to quench the above reaction, a similar product distribution was obtained. The 5-deutero/4-deutero isomeric ratio for the mono-deuteriated (E)-alkenol(92b) was shown by ^{13}C n.m.r. to be 10:18.

Lithium aluminium hydride reduction of 2,2-di-(methoxymethyl)-3-phenylhex-4-yn-3-ol (98), in refluxing benzene for 0.75 h gave, on water quenching, the alkene (117), allene (113), (E)-alkenol (114) and 10% unreacted alkynol (98), Block A, each compound identical with authentic material isolated earlier (see Table 6 for yield data).

The use of lithium aluminium deuteride, with water quenching in the above reaction gave essentially identical product yields. The C4:C5 (10:45) deuteride ion attack ratio for the mono-deuteriated (E)-alkenol was determined by ^{13}C n.m.r.

4.4 DISCUSSION OF 2,2-DIMETHYL-3-PHENYLHEX-4-YN-3-OL (90a), 1-METHOXY-2,2-DIMETHYL-3-PHENYLHEX-4-YN-3-OL (90b) AND 2,2-DI-(METHOXYMETHYL)-3-PHENYLHEX-4-YN-3-OL (98) REACTIONS WITH LITHIUM ALUMINIUM HYDRIDE (DEUTERIDE) IN BENZENE SOLVENT

The reactions of 2,2-dimethyl-3-phenylhex-4-yn-3-ol (90a), and its 1-methoxy-(90b) and 1,1-dimethoxy-(98) derivatives with lithium aluminium hydride (deuteride) were performed in benzene solution at 80° for 0.75 h. For alkynol (90a), the structure which does not contain an internal ether function, no reaction

was observable after 45 minutes at 80° and the organic reactant was recovered essentially quantitatively. In contrast, under the same reaction conditions considerable conversion of methoxy alkynols (90b) and (98) into products occurred. The yields of products are given in Table 6, each compound obtained was identical with authentic material isolated earlier.

A comparison of reaction rates (seen as the extent of reaction) between alkynol (90a) and its 1-methoxy-derivative (90b) clearly shows the expected rate enhancement attributable to the presence of the internal ether function. The addition of a second internal ether, as in alkynol (98), appears to enhance reaction rate even further.

4.5 REACTION OF 2-PHENYLPENT-3-YN-2-OL (18)[100], 1-METHOXY-2-PHENYPENT-3-YN-2-OL (136), 1-METHOXY-3-PHENYLHEX-4-YN-3-OL (137) AND 7-METHOXY-4-PHENYLHEPT-2-YN-4-OL (138) WITH LITHIUM ALUMINIUM HYDRIDE (DEUTERIDE) IN BENZENE SOLVENT

In benzene at 80° the reduction of 2-phenylpent-3-yn-2-ol (18), with lithium aluminium hydride (water quenching) gave 2-phenylpenta-2,3-diene (74), (E)-2-phenylpent-3-en-2-ol (72) and unreacted alkynol (18), Block B, as the reaction products (see Table 7 for yield data). The compounds were identified through their spectroscopic data.

The allene (74) gave a correct mass spectrum parent ion; showed the characteristic allenic infrared absorption at 1958 cm^{-1}; and a ^{13}C n.m.r. in accord with structure (74). In the ^{1}H n.m.r., the C5-H_3 signal at δ 1.79 appeared as a doublet with coupling (J 6 Hz) to H4, itself an overlapping quartet of quartets centred at δ 5.38, with coupling to C5-H_3 (as above) and additional long-range coupling to C1-H_3 (J 3 Hz), itself

a doublet (J 3 Hz) centred at δ 2.08. Irradiation at H4 (δ 5.38) collapsed both doublets at δ 1.79 and δ 2.08 to the expected singlet. Similarly, irradiation at either δ 1.79 (C5-H_3) or δ 2.08 (C1-H_3) resulted in collapsing the H4 quartet of quartets at δ 5.38 to a quartet, with ($J_{4,1}$ 3 Hz) or ($J_{4,5}$ 6 Hz) respectively.

The (E)-alkenol (72) was assigned on the basis of the infrared absorptions at 3400, 1665 and 965 cm^{-1}, its unambiguous ^{13}C n.m.r. or its ^{1}H n.m.r. The vinylic region was a multiplet, obviously part of a degenerate ABX_3 system. Irradiation at ca. δ 5.60 collapsed the doublet at δ 1.68 to a singlet, confirming it to belong to C5-H_3. The C1-H_3 signal appeared as a three proton singlet at δ 1.58. The mass spectrum was in accord with structure (72).

When deuterium oxide was used to quench the reaction, a similar product distribution was obtained. The allene (74) was identical, as expected, with that obtained above. The monodeutero (E)-alkenol (72) was shown by ^{1}H n.m.r. to be deuteriated solely at the C4 position, the C5-H_3 signal at δ 1.72 appearing as a singlet. The infrared and mass spectra were in accord with monodeutero structure (72).

Reaction of 1-methoxy-2-phenylpent-3-yn-2-ol (136) with lithium aluminium hydride in benzene for 0.75 h gave, on water quenching, in addition to the previously characterized dienes (143) and (E)-alkenol (142), the corresponding allene, 1-methoxy-2-phenylpenta-2,3-diene (144), Block B; its structure was assigned on the basis of its spectroscopic data.

The characteristic absorption at 1950 cm^{-1} in its infrared spectrum confirmed the presence of the allenic function. The allenic carbons were evident in the ^{13}C n.m.r. at δ 88.63 (C4), 101.78 (C2) and 206.08 (C3). In its ^{1}H n.m.r.,

the coupling between the C5-H_3 doublet (J 7 Hz) centred at δ 1.82 and the H4 quartet centred at δ 5.46 was confirmed unequivocably by decoupling experiments. The mass spectrum gave a parent ion corresponding to the correct molecular formula, $C_{12}H_{14}O$.

The use of deuterium oxide to quench the above reaction gave similar product yields. The C4:C5 ratio of the monodeuteriated (E)-alkenol (142) was shown to be 35:44 by ^{13}C n.m.r.

On repeating the above reaction with lithium aluminium deuteride, the allene (144) obtained was deuteriated as expected at C4, confirmed by the absence in its ^{13}C n.m.r. of δ 88.63 (C4), the absence of any signal in the vinylic region of its ^{1}H n.m.r. and the singlet present at δ 1.82 for the C5-H_3 group. The ratio of deuteride ion attack in the monodeutero (E)-alkenol (142) was 32:47, as determined by ^{13}C n.m.r. (see Appendix).

The reaction of 1-methoxy-3-phenylhex-4-yn-3-ol (137) with lithium aluminium hydride in benzene at 80° for 0.75 h gave, on quenching with deuterium oxide, allene (151) and monodeutero (E)-alkenol (150), Block B, identical with authentic material isolated earlier. The product yields are given in Table 4, where it can be observed that the ^{13}C n.m.r. determination of C4:C5 for monodeutero (E)-alkenol (150) was 27:21.

When 7-methoxy-4-phenylhept-2-yn-4-ol (138) was reduced with lithium aluminium hydride (deuteride) in benzene at 80° for 0.75 h, isolated from the crude was allene (165), (Z)-alkenol (166a) and (E)-alkenol (166b), Block B, identical with authentic material isolated earlier. The product distribution is given in Table 5. Both monodeuteriated

alkenols (166) were shown by ^{13}C n.m.r. to undergo attack at C3 predominantly over C2.

4.6 DISCUSSION OF 2-PHENYLPENT-3-YN-2-OL (18), 1-METHOXY-2-PHENYLPENT-3-YN-2-OL (136), 1-METHOXY-3-PHENYLHEX-4-YN-3-OL (137) AND 7-METHOXY-4-PHENYLHEPT-2-YN-4-OL (138) REACTIONS WITH LITHIUM ALUMINIUM HYDRIDE (DEUTERIDE) IN BENZENE SOLVENT.

A comparison of the lithium aluminium hydride (deuteride) reaction rates in benzene (seen as the extent of reaction) between alkynol (18), see Table 7, and its 1-methoxy derivative (136) (Table 3) (both Block B), clearly shows the rate enhancement which is attributable to the presence of the internal ether function.

Noteworthy is the isolation of allene (144), for the first time, in the study of the lithium aluminium hydride (deuteride) reaction of 1-methoxy-2-phenylpent-3-yn-2-ol (136) in benzene.

On examination of the reactions of methoxy alkynols (136), (137) and (138) with lithium aluminium hydride (deuteride) in benzene at 80° for 0.75 h, extensive reaction was seen to occur for each substrate; yield data are given in Tables 3-5. The promotion of lithium aluminium hydride reduction is explained in terms of the presence of the solvating internal ether.

It is evident, therefore, from these studies that the reduction of acetylenic alcohols with lithium aluminium hydride (deuteride) in benzene are significantly accelerated by the presence of an internal ether within the substrate.

CHAPTER 5

EXPERIMENTAL METHODS

5.1 APPARATUS, MATERIALS AND INSTRUMENTATION

Infrared spectra were recorded on a Shimadzu IR-27G spectrophotometer for liquid films or nujol mulls. Ultraviolet absorptions were determined for cyclohexane or ethanol solutions on a Varian Superscan 3 spectrophotometer.

Routine ^{1}H n.m.r. spectra were obtained for carbon tetrachloride solutions, with tetramethylsilane as an internal reference on a Varian T60 or EM360 spectrometer. ^{1}H n.m.r. and ^{13}C n.m.r. spectra were recorded on a Varian CFT-20 Fourier Transform NMR spectrometer for $CDCl_3$ solutions with $CHCl_3$ and $SiMe_4$ as internal standards. N.M.R. spectral parameters were derived by first-order analyses and wherever possible confirmed by double irradiation experiments. All chemical shifts are expressed as parts per million (ppm) downfield from TMS and are quoted as position (δ), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet), relative integral and coupling constants (J, Hz).

High resolution mass spectrometry was performed on an AEI-MS902 instrument in the electron impact (EI) mode. Microanalyses were carried out by Professor A.D. Campbell and associates, University of Otago. Melting points were determined in open capillaries and are uncorrected.

Analytical thin layer chromatography (t.l.c.) was performed on 190 x 50 x 0.5 mm alumina fluka (Type H) plates and the chromatograms developed by spraying with phosphomolybdic acid in ethanol (10% w/v) and baking at 100 °C. Preparative t.l.c. was carried out on 200 x 200 x 1 mm plates

of alumina fluka (Type H) and visualised under ultraviolet light. Column chromatography was routinely carried out using Laporte Grade H alumina (100-300 mesh) deactivated by the addition of 5% v/v of 10% aqueous acetic acid; less frequently used was 2.5% or 10% acid-deactivated alumina, and occasionally florosil (100-200 mesh) or silica gel (Grace 923).

High performance liquid chromatography (h.p.l.c.) was performed on a Varian Model 5020 Liquid Chromatograph connected to a Varian UV-50 variable wavelength spectrophotometric detector, and traces were taken with a Hewlett Packard 3390 A recording integrator. The column used for h.p.l.c. was an analytical Zorbax-NH_2 (4.6 mm I.D. x 25 cm), and the solvents employed for normal phase work were hexane/isopropanol.

All solvents used were either of analytical grade (AR) or were purified and dried according to standard procedures. "Ether" refers to commercial diethyl ether distilled off sodium hydride, and "Petroleum Ether" refers to petroleum ether (50-70 °C) distilled off phosphorus pentoxide. All solvents used for reactions were dried by refluxing over lithium aluminium hydride followed by distillation under an atmosphere of nitrogen.

5.2 EXPERIMENTAL RELATING TO CHAPTER 2

2,2-Di-(hydroxymethyl)-1-phenylpropan-1-one (101)[58]

Propiophenone (58 g, 0.43 mole) in dimethylsulphoxide (100 ml) was added dropwise over 1.5 h to a suspension of paraformaldehyde (30 g, 1 mole) in dimethylsulphoxide (150 ml) containing potassium hydroxide (1.5 g) dissolved in ethanol (20 ml) (see Scheme 15). The reaction mixture was stirred at room temperature for 1.5 h, diluted to 1.5 ℓ with water, and neutralized with dilute hydrochloric acid. After saturation with sodium chloride, the crude product was extracted with ethyl acetate (3 x 300 ml), washed with saturated sodium chloride solution and dried over anhydrous calcium sulphate. Removal of solvent left a colourless oil (70 g). The majority of the unreacted propiophenone (38.4 g) was extracted from the crude product with petroleum ether (3 x 200 ml). The crude 2,2-di-(hydroxymethyl)-1-phenylpropan-1-one (27 g) was mixed with silica gel (50 g) in diethyl ether (100 ml). The ether was removed and the silica gel added in a petroleum ether slurry to a silica column (700 g).

Elution with petroleum ether/ether (70:30) yielded unreacted propiophenone (99) (1.935 g), identical (^{1}H n.m.r) with an authentic sample.

Elution with petroleum ether/ether (40:60) yielded 2-(hydroxymethyl)-1-phenylpropan-1-one (100) (5.610 g; 8%); a yellow oil; ν_{max} (liquid film) 3450, 1040, OH; 1680, aryl ketone; 1600, 1580, 710 cm^{-1}, mono-substituted benzene; ^{1}H n.m.r. ($CDCl_3$) δ 1.18, d, $J_{Me,2}$ 6 Hz, 3H, $(H3)_3$; 2.83, s, 1H, OH; 3.50-4.00, m, 3H, H2, $-CH_2-O-$; 7.25-7.60, m, 3H, meta and para aromatic protons; 7.87-8.03, m, 2H, ortho aromatic protons.

Elution with petroleum ether/ether (35:65) yielded 2,2-di-(hydroxymethyl)-1-phenylpropan-1-one (101) (10.444 g; 12%); a white solid (crystallised from CCl_4); m.p. 78-80° (lit.[58] m.p. 79-80°); ν_{max}(nujol mull) 3320, 1057, 1040, OH; 1670, aryl ketone; 1600, 1581, 700 cm^{-1}, mono-substituted benzene; ^1H n.m.r. ($CDCl_3$) δ 1.13, s, 3H, $(H3)_3$; 3.57, s, 2H, OH; 3.79, 4.03, AB system, J 12 Hz, 4H, $-CH_2-O-$; 7.27-7.50, m, 3H, meta and para aromatic protons; 7.57-7.78, m, 2H, ortho aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 17.69, C3; 54.40, C2; 68.84, $-CH_2-O-$; 127.64, 128.37, C2'/C3'; 131.50, C4'; 138.31, C1'; 208.84, C1.

Elution with petroleum/ether (15:85) yielded 2,2-di-(hydroxymethyl)-1-phenylpropan-1-ol (102) (8.483 g; 10%); a white solid; m.p. 95-97° (lit.[101] m.p. 96-97°); ν_{max}(nujol mull) 3375, 1034, 1025, OH; 1600, 744, 708 cm^{-1}, mono-substituted benzene; ^1H n.m.r. ($CDCl_3$) δ 0.62, s, 3H, $(H3)_3$; 2.95, s, 3H, OH; 3.41-4.09, m, 5H, H1, $-CH_2-O-$; 7.33, s, 5H, aromatic protons.

Production of Diazomethane

(i) Acetyl Methylurea[65]

To a solution of acetamide (295 g; 5 mole) and bromine (440 g; 142 ml; 2.75 mole) in a 3 ℓ beaker was added, dropwise and with stirring, a solution of sodium hydroxide (200 g; 5 mole) in water (500 ml) (see Scheme 16). The resulting yellow reaction mixture was then poured into two 5 ℓ beakers in approximately equal portions, and with continued stirring, gently heated on a steam bath until effervescence set in, after which time heating was continued for three further minutes. Crystallisation of product from the yellow to red solution commenced immediately and was completed by cooling in an ice

bath for one hour. The residual bromine was removed from the filtered product by washing with cold ethanol. The weight of crude white crystalline acetyl methylurea obtained after oven drying was 456 g (reaction below showed NaBr (165-190 g) to be present); ^{1}H n.m.r. ($CDCl_3$) δ 2.12, s, 3H, CH_3-CO-; 2.85, d, $J_{Me,H}$ 4.5 Hz, $\underline{CH_3}$-NH-; 8.43, s, $W_{h/2}$ 16 Hz, 1H, CH_3-$\underline{NH}$-; 10.25, s, $W_{h/2}$ 14 Hz, 1H, -CO-$\underline{NH}$-CO-.

(ii) Nitrosomethylurea[65]

Acetyl methylurea (370 g), as prepared above, and concentrated hydrochloric acid (200 ml) were heated, with stirring, on a steam bath until it was apparent that no more solid was dissolving (the residual solid was sodium bromide). Heating was continued for 3 or 4 min. longer (total time on steam bath 8-12 min.) after which the solution was diluted with an equal volume of ice-cold water and cooled below 10° in an ice-bath. A cold saturated solution of sodium nitrite (172 g, 2.45 mole) in water (250 ml) was run in slowly with vigorous stirring. The frothy mixture was allowed to remain in the ice bath for several minutes after which time the nitrosomethylurea was filtered and washed with cold water (200 ml) to remove any residual sodium bromide. Air drying gave the pale yellow product, nitrosomethylurea, (190 g; 92%), (lit.[65] 76-82%), m.p. 122-124° (d), (lit.[65] m.p. 123-124° (d)); ^{1}H n.m.r. ($CDCl_3$) δ 3.19, s, 3H, CH_3-N(NO)-; 6.00, bs, $W_{h/2}$ 60 Hz, 2H, $-NH_2$.

(iii) Diazomethane[66]

In a 2 ℓ Erlenmyer round-bottom flask was placed aqueous potassium hydroxide solution (40%; 300 ml) and diethyl ether (1 ℓ). The mixture was then cooled to -25°

with an isopropanol/dry ice bath. To the cooled mixture was added with agitation, small portions of finely powdered nitrosomethylurea (100 g; 0.97 mole) over a five minute period, during which time the temperature was maintained between -30° and -20°. The resulting deep yellow ether layer was decanted into a 2 ℓ conical flask. The residual nitrosomethylurea was decomposed by further shaking and the diazomethane produced extracted with more ether (2 x 250 ml). The ether extracts were combined and dried over potassium hydroxide pellets for 3 h while maintaining the temperature at approximately -50°. The strength of the diazomethane solution was determined by the following titration method: (1) a 5 ml aliquot of the solution was diluted to approx. 20 ml at 0° with dry ether. To this was added, an ethereal solution of benzoic acid (0.2 M) until the solution was decolourised and excess acid was present (25 ml sufficed). (2) Water (10 ml) was added and the excess benzoic acid back-titrated with sodium hydroxide solution (0.1 M), with phenolphthalein as indicator. The difference between the molar quantities of benzoic acid and sodium hydroxide used represented the molar quantity of CH_2N_2 in the 5 ml aliquot. The yield of diazomethane thus obtained was 74% (lit.[66] 63-70%).

2,2-Di-(methoxymethyl)-1-phenylpropan-1-one (104)[58]

An ethereal solution of diazomethane (1.5 ℓ; 0.72 mole) at -60°, prepared as above, was added to a solution of boron trifluoride etherate (2.4 ml; 2.7 g; 0.021 mole) and 2,2-di-(hydroxymethyl)-1-phenylpropan-1-one[59] (101) (7.0 g, 0.036 mole) in dry diethyl ether (300 ml) at -60° (see Scheme 15). The yellow reaction mixture was stored first at -60° for 1 h and then allowed to rise to room temperature overnight. Excess

diazomethane was removed by washing with ethereal acetic acid (100 ml; 10%) until gas was no longer evolved. Subsequent washing with saturated sodium bicarbonate solution (3 x 150 ml) removed remaining boron trifluoride and hydrogen fluoride. The amorphous polymethylene, inevitably formed in the methylation process, was filtered off and the remaining ethereal solution dried over anhydrous magnesium sulphate. Removal of solvent left a yellow oil (7.8 g). The crude 2,2-di-(methoxymethyl)-1-phenylpropan-1-one was dissolved in petroleum ether (200 ml) and adsorbed onto 5% deactivated alumina (450 g).

Elution with petroleum ether/ether (93:7) gave the dimethoxy ketone (104) (6.68 g; 84%); a colourless oil; ν_{max} (liquid film) 1680, aryl ketone; 1095, C-O-CH_3; 1600, 1580, 704 cm^{-1}, mono-substituted benzene; ^1H n.m.r. ($CDCl_3$) δ 1.28, s, 3H, CH_3; 3.27, s, 6H, CH_3-O-; 3.55, s, 4H, -CH_2-O-; 7.18-7.62, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 18.53, C3; 53.53, C2; 59.17, CH_3-O-; 75.33, -CH_2-O-; 126.82, 127.94, C2'/C3'; 130.31, C4'; 139.91, C1'; 207.80, C1.

Elution with ether gave impure 2-hydroxymethyl-2-methoxymethyl-1-phenylpropan-1-one (103) (1.10 g). Careful rechromatography of this material on 5% deactivated alumina (100 g) gave pure material as a colourless oil; ν_{max} (liquid film) 3455, 1050, OH; 1674, aryl ketone; 1600, 1580, 712, mono-substituted benzene; 1103 cm^{-1}, C-O-CH_3; ^1H n.m.r. ($CDCl_3$) δ 1.27, s, 3H, CH_3; 2.88, s, 1H, OH; 3.28, s, 3H, CH_3-O-; 3.45-4.06, m, 4H, -CH_2-O-; 7.28-7.77, m, 5H, aromatic protons.

Preparation of Propyne

(i) Propene[72]

To well-stirred phosphoric acid (150 ml) at 260-270° was added dropwise isopropyl alcohol (200 ml) (see Scheme 17). The hydrocarbon produced was passed through two traps, the first cooled in ice and the second filled with aqueous sodium hydroxide (5%). The propene gas was dried by passage through a tube of calcium chloride and collected in a graduated trap immersed in an isopropyl alcohol/dry ice bath. The yield of propene obtained was 130 ml; 1.56 mole.

(ii) 1,2-Dibromopropane[73]

Liquid propene (130 ml; 1.56 mole) was poured into sodium-dried ether (350 ml) at -50° and bromine (256 g, 83 ml, 1.60 mole) was added with stirring at -40° to -60° until a brown colour persisted. The ether was removed under reduced pressure to leave the colourless propylene bromide (145 ml; 88%).

(iii) Propyne[74]

In a 1-ℓ three-necked round-bottom flask fitted with a dropping funnel, mechanical stirrer, and a double surface reflux condenser was placed potassium hydroxide (180 g; 3.21 mole) and 1-butanol (400 ml). This solution was maintained at boiling point (≃ 155°) and well-agitated as the 1,2-dibromopropane (80 ml; 0.77 mole) was added dropwise. The alcohol vapour which passed through the exit tube (attached to the top of the condenser) was removed from the unsaturated hydrocarbon by a trap cooled in ice. The propyne gas was then bubbled through a second trap containing aqueous sodium hydroxide solution (5%), dried through a length of calcium chloride

tubing and collected in a graduated trap immersed in an isopropyl alcohol/dry ice bath. The yield of propyne obtained was 30 ml; 0.51 mole; 67%.

Preparation of 1-butyllithium[68]

In a 1-ℓ three necked round-bottom flask fitted with a mechanical stirrer, dropping funnel and low-temperature thermometer was placed dry ether (300 ml) and lithium strips[69] (12 g, 1.7 mole). The flask was flushed with nitrogen, and about one fifth of the ethereal 1-bromobutane added to the stirred suspension to initiate the reaction. Within 2 or 3 min. a white turbidity appeared and the black coating on the lithium pieces partially disappeared. The temperature of the mixture was maintained below -15°[70]. When after 15-20 min. the exothermic reaction had subsided, the remainder of the 1-bromobutane (96 g in total; 75 ml; 0.7 mole) in dry ether (100 ml in total) was added slowly while maintaining the temperature between -15° to -25°. After the addition was complete, the temperature of the greyish reaction mixture was allowed to rise gradually to -5° over a period of 1 h. The mixture was again cooled to -25° and then poured through a funnel plugged with a wad of glass wool into a measuring cylinder previously filled with nitrogen. After the volume had been measured, the cold solution was transferred into a 500-ml round-bottom blask filled with nitrogen, the stepper well-greased, and the flask stored at 0-5°. The strength of the solution was determined by the double-titration method[71] as follows: (1) A 5 ml aliquot of the solution was hydrolysed with 10 ml of distilled water. It was then titrated with hydrochloric acid (1M) to determine the total alkali present, using phenolphthalein as indicator. (2) A second 5 ml aliquot

of the solution was reacted with a solution of benzyl chloride (1 ml) in dry ether (10 ml). The resulting mixture was allowed to stand for 1 min. and then hydrolysed with 10 ml of distilled water. It was then titrated with hydrochloric acid (1M) to determine the alkali present other than the 1-butyllithium. The difference between the two titration values represented the concentration of 1-butyllithium. The yield of 1-butyllithium determined in this manner was 0.28 mole; 40% (lit.[68] 90%).

Propynyllithium[67]

Dry ether (100 ml) at -60° was added to propyne (30 ml, 0.51 mole) at -70° and poured with stirring into an ethereal solution of 1-butyllithium (0.15 mole; 214 ml), as quickly as possible at -20° or lower temperature in a stream of nitrogen.

2,2-Di-(methoxymethyl)-3-phenylhex-4-yn-3-ol (98)

A solution of the dimethoxy ketone (104) (17.6 g; 0.079 mole) in dry ether (80 ml) was added dropwise to excess propynyllithium at -30° (prepared from propyne (30 ml, 0.51 mole) and 1-butyllithium (0.15 mole) in dry ether (400 ml)), and the resulting mixture was stirred at room temperature for 64 h. Saturated ammonium chloride solution (200 ml) was added carefully and the crude product (25 g), extracted with ether (3 x 300 ml), was adsorbed onto 5% acid deactivated alumina (1 kg).

Elution with petroleum ether/ether (90:10) gave the dimethoxy alkynol (98) (19.5 g; 94%) as a viscous, colourless oil; ν_{max} (liquid film) 3350, 1035, OH; 2240, alkyne; 1600, 758, 707, mono-substituted benzene; 1100, 1090 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 0.77, s, 3H, $(H1)_3$; 1.93, s, 3H, $(H6)_3$;

3.03-3.77, m, 4H, $-CH_2-O-$; 3.28, s, 3H, CH_3-O-; 3.37, s, 3H, CH_3-O-; 4.77, s, 1H, OH; 7.00-7.57, m, 5H, aromatic protons; ^{13}C n.m.r. (CCl_4) δ 3.38, C6; 16.65, C1; 45.97, C2; 58.84, CH_3-O-; 73.81, $-CH_2-O-$; 76.11, $-CH_2-O-$; 77.99, 80.14, 82.17, C3/C4/C5; 126.57, 127.57, C2'/C3'; 126.78, C4'; 141.40, C1'; (Found: M^+, 262.1534. Calc. for $C_{16}H_{22}O_3$; M^+, 262.1569); (Found: C, 73.42; H, 8.68. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%).

Reduction of 2,2-Di-(methoxymethyl)-3-phenylhex-4-yn-3-ol (98) with Lithium Aluminium Hydride in Tetrahydrofuran.

(a) To a suspension of lithium aluminium hydride (80 mg) in tetrahydrofuran was added a solution of the alkynol (98) (500 mg) in tetrahydrofuran (5 ml). More solvent (10 ml) was added and the mixture refluxed for 2.5 h under an atmosphere of nitrogen. The reaction was quenched with water and the crude product, isolated by means of ether, was subsequently adsorbed onto 5% deactivated alumina (50 g).

Elution with petroleum ether/ether (98:2) gave a mixture (39 mg) (≃1:1; ^1H n.m.r.) of the (E)-propenylcyclopropane derivatives (115a) and (116a), Block A, and traces of the (Z)-double bond isomers. Repetitive development of an alumina thick-layer chromatography plate using pentane gave the pure (n.m.r., h.p.l.c.) 1-methyl-1-methoxymethyl-2-phenyl-2-((E)-1'-propenyl)-cyclopropane (115a) as a mobile colourless oil; (Found: M^+, 216.1521. Calc. for $C_{15}H_{20}O$; M^+, 216.1514); ν_{max} (liquid film) 3100-3050, cyclopropane; 1655, 960, *trans* -CH=CH-; 1600, 700, mono-substituted benzene; 1100 cm^{-1}, C-O-CH_3; λ_{max} (EtOH) 202.5 nm (ε 11,750); ^1H n.m.r. (CFT 20, $CDCl_3$) δ 0.92, d, $J_{A,B}$ 5 Hz, 1H, 3-H_AH_B; 1.16, d, $J_{B,A}$ 5 Hz, 1H, 3-H_AH_B; 1.30, s, 3H, 1-CH_3; 1.60, dd, $J_{Me,2'}$ 6 Hz,

$J_{Me,1'}$ 1.5 Hz, 3H, $(H3')_3$; 2.80, 2.88, AB quartet, $J_{A,B}$ 10 Hz, 2H, $-CH_2-O-$; 3.11, s, 3H, CH_3-O-; 5.13, dq, $J_{2',1'}$ 15.5 Hz, $J_{2',Me}$ 6 Hz, 1H,H2'; 5.61, dq, $J_{1',2'}$ 15.5 Hz, $J_{1',Me}$ 1.5 Hz, 1H, H1'; 7.21, s, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 17.42, 1-$\underline{CH_3}$; 17.91, C3'; 22.98, C3; 26.99, C1; 37.50, C2; 58.53, CH_3-O-; 78.94, $-CH_2-O-$; 125.67, C2'; 126.11, C4"; 128.01, 130.17, C3"/C2"; 134.76, C1'; 142.37, C1".

The second propenylcyclopropane derivative, 1-methyl--1-methoxymethyl-2-phenyl-2-((E)-1'-propenyl)-cyclopropane (116a) was isolated from the mixture after four successive series of injections on the High Performance Liquid Chromatograph, where in each isocratic run (100% hexane, 0.6 ml/min, 220 nm), the tail portion of the trailing peak was shaved off until ≃97% purity was achieved; (Found: M^+, 216.1494. Calc. for $C_{15}H_{20}O$: M^+, 216.1514); ν_{max} (liquid flim) 3100-3050, cyclopropane; 1655, 960, *trans* -CH=CH-; 1600, 700, mono-substituted benzene; 1100 cm^{-1}, $C-O-CH_3$; ^1H n.m.r. (CFT 20, $CDCl_3$) δ 0.84, s, 3H, $1-CH_3$; 1.00, d, $J_{A,B}$ 5 Hz, 1H, $3-H_AH_B$; 1.06, d, $J_{B,A}$ 5 Hz, 1H, $3-H_AH_B$; 1.60, dd, $J_{Me,2'}$ 6 Hz, $J_{Me,1'}$ 1.5 Hz, 3H, $(H3')_3$; 3.36, 3.46, AB quartet, $J_{A,B}$ 10 Hz, 2H, $-CH_2-O-$; 3.37, s, 3H, CH_3-O-; 5.20, dq, $J_{2',1'}$ 15.5 Hz, $J_{2',Me}$ 6 Hz, 1H, H2'; 5.64, dq, $J_{1',2'}$ 15.5 Hz, $J_{1',Me}$ 1.5 Hz, 1H, H1'; 7.23, s, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 17.82, C3'; 20.05, 1-$\underline{CH_3}$; 22.16, C3; 26.90, C1; 37.79, C2; 58.64, CH_3-O-; 77.15, $-CH_2-O-$; 125.36, 125.96, C2'/C4"; 128.07, 130.02, C2"/C3"; 134.27, C1'; 142.28, C1". The (Z)-double bond isomers presumably (115b) and 116b), could not be isolated.

Elution with petroleum ether/ether (98:2) contained a mixture (total 115 mg) of the two propenylcyclopropane derivatives (115) and (116) and the allene (113), (see overleaf).

This mixture was separated by chromatography on 5% deactivated alumina (12 g) and gave the propenylcyclopropane derivatives (115) and (116) (16 mg; 1:1) and the allene (113) (99 mg).

Continued elution with petroleum ether/ether (98:2) gave pure 5,5-di-(methoxymethyl)-4-phenylhexa-2,3-diene (113) (102 mg) as a viscous, colourless oil; ν_{max} (liquid film) 1965, allene; 1600, 762, 706, mono-substituted benzene; 1100 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 0.98, s, 3H, $(H6)_3$; 1.68, d, $J_{Me,2}$ 7 Hz, 3H, $(H1)_3$; 3.18, s, 3H, CH_3-O-; 3.25, s, 3H, CH_3-O-; 3.15-3.50, m, 4H, $-CH_2$-O-; 5.09, q, $J_{2,Me}$ 7 Hz, 1H, H2; 7.15, s, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 14.76, C1; 20.28, C6; 42.84, C5; 59.04, CH_3-O-; 76.21, $-CH_2$-O-; 86.59, C2; 109.14, C4; 126.62, C4'; 127.75, 129.65, C3'/C2'; 137.41, C1'; 203.95, C3; (Found: M^+, 246.1618. Calc. for $C_{16}H_{22}O_2$:M^+, 246.1620); (Found: C, 78.21; H, 9.05. $C_{16}H_{22}O_2$ requires C, 78.01; H, 9.00%).

Elution with petroleum ether/ether (95:5) gave (E)-2,2-di-(methoxymethyl)-3-phenylhex-4-en-3-ol (114) (182 mg) as a viscous, colourless oil; ν_{max} (liquid film) 3500, OH; 1670, 970, *trans* -CH=CH-; 1600,774, 744, 704, mono-substituted benzene; 993 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 0.78, s, 3H, $(H1)_3$; 1.75, d, $J_{Me,5}$ 6 Hz, $(H6)_3$; 3.07-3.47, m, 4H, $-CH_2$-O-; 3.23, s, 3H, CH_3-O-; 3.28, s, 3H, CH_3-O-; 4.40, s, 1H, OH; 5.81, dq, $J_{5,4}$ 14.5 Hz, $J_{5,Me}$ 6 Hz, 1H, H5; 6.22, d, $J_{4,5}$ 14.5 Hz, 1H, H4; 7.00-7.50, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 16.39, C1; 17.96, C6; 45.62, C2; 59.08, CH_3-O-; 75.02, $-CH_2$-O-; 75.47, $-CH_2$-O-; 79.85, C3; 124.34, C5; 126.42, C4'; 127.16, 127.26, C3'/C2'; 133.79, C4; 144.03, C1'; (Found: M^+, 264.1725. Calc. for $C_{16}H_{24}O_3$: M^+, 264.1725); (Found: C, 72.96; H, 9.31. $C_{16}H_{24}O_3$ requires C, 72.69; H, 9.15%).

(b) The alkynol (98) (500 mg) was treated as above with lithium aluminium hydride (80 mg) in tetrahydrofuran (25 ml),

except the reaction time was extended to 4 h. Water quenching gave a crude product, extracted with ether, which was adsorbed onto 5% deactivated alumina (120 g).

Elution with petroleum ether gave the propenylcyclopropane derivatives (115) and (116) (79 mg) (1:1), identical (^{1}H n.m.r.) with an authentic sample.

Further elution with petroleum ether gave a mixture (total 18 mg; 1:1:7; ^{1}H n.m.r.) of the propenylcyclopropane derivatives (115) and (116) and allene (113).

Elution with petroleum ether/ether (99:1) gave the allene (113) (175 mg), identical (^{1}H n.m.r., infrared spectra) with an authentic sample.

Elution with petroleum ether/ether (85:15) gave (E)-alkenol (114) (183 mg), identical (^{1}H n.m.r.) with authentic material.

(c) The alkynol (98) (500 mg) was treated in the same manner as above except the reaction time was extended further to 22 h and the mixture quenched with deuterium oxide, instead of water. The crude product, isolated by means of ether, was adsorbed onto 5% deactivated alumina (120 g).

Elution with pentane gave the propenylcyclopropane derivatives (115) and (116) (168 mg) (1:1, ^{1}H n.m.r.).

Elution with petroleum ether gave allene (113) (130 mg) identical (^{1}H n.m.r., I.R.) with authentic material.

Elution with petroleum ether/ether (95:5) gave the 5-deutero and 4-deutero (E)-2,2-di-(methoxymethyl)-3-phenylhex-4-en-3-ols (114) (142 mg) as a mixture (17:11; ^{13}C n.m.r); a viscous, colourless oil; (Found: M^+, 265.1785. Calc. for $C_{16}H_{23}DO_3$: M^+, 265.1788); ν_{max} (liquid film) 3495, OH; 1655,

$\rangle C=C\langle$; 1600, 770, 737, 710, mono-substituted benzene; 1100 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) (5-deutero) δ 0.78, s, 3H, $(H1)_3$; 1.75, s, 3H, $(H6)_3$; 3.07-3.47, m, 4H, -CH_2-O-; 3.23, s, 3H, CH_3-O-; 3.28, s, 3H, CH_3-O-; 5.00, s, 1H, OH; 6.22, s, 1H, H4; 7.00-7.50, m, 5H, aromatic protons; ^1H n.m.r. (CCl_4) (4-deutero) δ 0.78, s, 3H, $(H1)_3$; 1.75, d, $J_{Me,5}$ 6H, 3H, $(H6)_3$; 3.07-3.47, m, 4H, -CH_2-O-; 3.23, s, 3H, CH_3-O-; 3.28, s, 3H, CH_3-O-; 5.00, s, 1H, OH; 5.81, q, $J_{5,Me}$ 6 Hz, 1H, H5; 7.00-7.50, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 16.39, C1; 17.81, C6; 45.62, C2; 59.08, CH_3-O-; 75.02, -CH_2-O-; 75.47, -CH_2-O-; 79.85, C3; 124.34, C5; 126.42, C4'; 127.16, 127.26, C3'/C2'; 133.79, C4; 144.03, C1'.

Reduction of 2,2-Di-(methoxymethyl)-3-phenylhex-4-yn-3-ol (98) with Lithium Aluminium Deuteride in Tetrahydrofuran.

(a) The alkynol (98) (500 mg) in tetrahydrofuran (5 ml) was added to a suspension of lithium aluminium deuteride (88 mg) in tetrahydrofuran (10 ml). More solvent was added (10 ml) and the mixture heated under reflux for 2.5 h under an atmosphere of nitrogen. The reaction was quenched with water and the crude product, isolated by means of ether, was adsorbed onto 5% deactivated alumina (55 g).

Elution with pentane gave a mixture of the 1',2'-dideutero propenylcyclopropane derivatives (115) and (116) (24 mg, 1:1 ratio); ν_{max} (liquid film) 3100-3050, cyclopropane; 1655, *trans* $\rangle C=C\langle$; 1600, 700, mono-substituted benzene; 1100 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CFT 20, $CDCl_3$) δ 0.85, s, 3H, $(H1)_3$, (116); 0.92, d, $J_{A,B}$ 5 Hz, 1H, 3-H_AH_B, (115); 1.00 d, $J_{A,B}$ 5 Hz, 1H, 3-H_AH_B, (116), 1.06, d, $J_{B,A}$ 5 Hz, 1H, 3-H_AH_B, (116); 1.16, d, $J_{B,A}$ 5 Hz, 1H, 3-H_AH_B, (115); 1.30, s, 3H, $(H1)_3$, (115); 1.60, s, 6H, $(H3')_3$, (115) and (116); 2.80,

2.88, AB system, J 10 Hz, $-CH_2-O-$, (115); 3.11, s, 3H, CH_3-O-, (115); 3.37, s, 3H, CH_3-O-, (116); 3.36, 3.46, AB system, J 10 Hz, $-CH_2-O-$, (116); 7.25, s, 10H, aromatic protons, (115) and (116).

Continued elution with pentane gave a mixture of the 1',2'-dideutero propenylcyclopropane derivatives (115) and (116) and the 2-deutero allene (113) (79 mg, in a ratio 1:1:4).

Elution with petroleum ether gave the pure 2-deutero allene (113) (159 mg); (Found: M^+, 247.1673. Calc. for $C_{16}H_{21}DO_2$: M^+, 247.1682); ν_{max} (liquid film) 1959, allene; 1600, 766, 709, mono-substituted benzene; 1103 cm^{-1}; $C-O-CH_3$; ^1H n.m.r. (CCl_4) δ 1.00, s, 3H, $(H6)_3$; 1.68, s, 3H, $(H1)_3$; 3.18, s, 4H, $-CH_2-O-$; 3.25, s, 6H, CH_3-O-; 7.18, s, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) 14.64,C1; 20.29, C6; 42.86, C5; 58.99, CH_3-O-; 76.15, $-CH_2-O-$; 109.09, C4; 126.64, C4'; 127.76, C3'; 129.62, C2'; 137.38, C1', 188.07, C3.

Elution with petroleum ether/ether (95:5) gave the 5-deutero and 4-deutero (E)-alkenols (114) (208 mg) as a mixture (15:26).

Reduction of 2,2-Di-(methoxymethyl)-3-phenylhex-4-yn-3-ol (98) with Lithium Aluminium Hydride in Diethyl Ether.

A solution of the alkynol (98) (500 mg) in diethyl ether (15 ml) was added to a suspension of lithium aluminium hydride (80 mg) in the same solvent (10 ml) and the stirred mixture refluxed for 16 h under an atmosphere of nitrogen. The reaction was cooled and quenched with water, and the crude product, isolated by means of ether, was adsorbed onto 5% deactivated alumina (50 g).

Elution with pentane gave a mixture (33 mg) ($\simeq$12:1:6) of the (E)-(117a) and (Z)-(117b) 5,5-di-(methoxymethyl)-4-phenylhex-2-enes and allene (113), the components of which

could not be separated. Data for the major component, (E)-alkene (117a), are as follows: (Found: M^+, 248.1786. $C_{16}H_{24}O_2$ requires M^+, 248.1776; M^+-32, 216.1510 ($C_{15}H_{20}O$, 216.1514); M^+-64, 184.1247 ($C_{14}H_{16}$,184.1252); M^+-117, 131.0860 ($C_{10}H_{11}$, 131.0861); M^+-131, 117.0842 ($C_6H_{13}O_2$, 117.0915) base peak, detector overloaded); ν_{max} (liquid film) 1655, 966, *trans* -CH=CH-; 1600, 750, 705, mono-substituted benzene; 1103 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 0.80, s, 3H, $(H6)_3$; 1.68, d, $J_{Me,2}$ 6 Hz, 3H, $(H1)_3$; 2.90, s, 2H, -CH_2-O-; 3.09, AB quartet, 2H, -CH_2-O-; 3.22, s, 3H, CH_3-O-; 3.28, s, 3H, CH_3-O-; 3.40, d, $J_{4,3}$ 9 Hz, 1H, H4; 5.41, dq, $J_{2,3}$ 15 Hz, $J_{2,Me}$ 6 Hz, 1H, H2; 5.85, dd, $J_{3,2}$ 15 Hz, $J_{3,4}$ 9 Hz, 1H, H3; 7.15, s, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 16.36, C6; 18.06, C1; 41.95, C5; 52.06, C4; 58.84, CH_3-O-; 59.05, CH_3-O-; 75.55, -CH_2-O-; 76.01, -CH_2-O-; 126.03, C4'; 127.06, C2; 127.83, 129.39, C3'/C2'; 130.32, C3; 141.97, C1'.

Further elution with pentane gave a mixture (53 mg) of the allene (113) (85%) and the (E)- and (Z)-alkenes (117a) and (117b).

Continued elution with pentane gave the allene (113) (100 mg), identical in all respects with authentic material.

Elution with petroleum ether/ether (96:4) gave the (E)-alkenol (114) (270 mg), identical in all respects with an authentic sample.

Finally, elution with petroleum ether/ether (70:30) gave unreacted alkynol (98) (21 mg).

Reduction of 2,2-Di-(methoxymethyl)-3-phenylhex-4-yn-3-ol (98) with Lithium Aluminium Deuteride in Diethyl Ether.

Reaction of alkynol (98) (500 mg) with lithium aluminium deuteride (88 mg) was carried out in the same manner as above. Water quenching and ether extraction gave a crude product, the

components of which were separated by chromatography on 5% deactivated alumina (50 g).

Elution with pentane gave a mixture (21 mg) (≃12:1:8) of the (E)-(117a) and (Z)-(117b) 2,3,4-trideutero-5,5-di-(methoxymethyl)-4-phenylhex-2-enes and D-allene (113). Spectral data for the major alkene (117a) component are as follows: (Found: M^+, 251.1928. $C_{16}H_{21}D_3O_2$ requires M^+, 251.1965; M^+-33, 218.1682 ($C_{15}H_{18}D_2O$, 218.1640); M^+-66, 185.1324 ($C_{14}H_{15}D$, 185.1315); M^+-117, 134.1020 ($C_{10}H_8D_3$, 134.1049); M^+-134, 117.0801 ($C_6H_{13}O_2$, 117.0915) base peak, detector overloaded); ν_{max} (liquid film) 1600, 733, 710, mono-substituted benzene; 1106 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 0.77, s, 3H, $(H6)_3$; 1.67, s, 3H, $(H1)_3$; 2.88, s, 2H, $-CH_2-O-$; 3.08, AB q, 2H, $-CH_2-O-$; 3.20, s, 3H, CH_3-O-; 3.27, s, 3H, CH_3-O-; 7.10, s, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 16.40, C6; 17.91, C1; 41.89, C5; 51.95 (very small triplet), C4; 58.84, CH_3-O-; 59.06, CH_3-O-; 75.56, $-CH_2-O-$; 76.01, $-CH_2-O-$; 126.02, C4; 127.86, 129.36, C3'/C2'; 142.00, C1'.

Elution with more pentane gave a mixture (47 mg) (12:1:33) of the trideutero (E)- and (Z)-alkenes (117a) and (117b) and the monodeutero allene (113).

Continued elution with petroleum ether gave pure mono-deutero allene (113) (125 mg), identical (^1H n.m.r.) with an authentic sample.

Elution with petroleum ether/ether (96:4) gave the 4-deutero and 5-deutero (E)-alkenols (114) (273 mg) as a mixture (14:42), identical (^1H n.m.r., ^{13}C n.m.r., infrared spectra) with authentic material.

Elution with petroleum ether/ether (70:30) liberated starting alkynol (98) (14 mg), identical (^1H n.m.r.) with an authentic sample.

Reduction of 2,2-Di-(methoxymethyl)-3-phenylhex-4-yn-3-ol (98) with Lithium Aluminium Hydride in 2,5-Dimethyltetrahydrofuran.

(a) A mixture of alkynol (98) (500 mg) and lithium aluminium hydride (80 mg) in 2,5-dimethyltetrahydrofuran (25 ml) was heated under reflux for 0.5 h, after which time water was added to the cooled reaction mixture. The crude product, isolated by means of ether, was adsorbed onto 5% deactivated alumina (50 g).

Elution with pentane gave the propenylcyclopropane derivatives (115) and (116) (8 mg) (6:2; ^{1}H n.m.r.).

Elution with more pentane gave a complex mixture (48 mg) (≃5:12:23:8) of the propenylcyclopropane derivatives (115) and (116), alkene (117) and allene (113).

Further elution with pentane gave a mixture (50 mg) (31:19) of alkene (117) and allene (113).

Continued elution with pentane gave allene (113) (97 mg), identical in all respects with authentic material.

Elution with petroleum ether gave pure 5,5-di-(methoxymethyl)-4-phenylhex-2-yne (118) (48 mg) a viscous, colourless oil; (Found: M^+, 246.1613. Calc for $C_{16}H_{22}O_2$:M^+, 246.1620; M^+-32, 214.1355 ($C_{15}H_{18}O$, 214.1358); M^+-45, 201.1278 ($C_{14}H_{17}O$, 201.1279); M^+-117, 129.0663; ($C_{10}H_9$, 129.0704) detector overloaded; M^+-129, 117.0864 ($C_6H_{13}O_2$, 117.0915) base peak, detector overloaded); ν_{max} (liquid film) 2250, alkyne; 1608, 753, 710, monosubstituted benzene; 1106 cm^{-1}, C-O-CH_3; ^{1}H n.m.r. (CCl_4) δ 0.82, s, 3H, $(H6)_3$; 1.85, d, $J_{Me,4}$ 2 Hz, 3H, $(H1)_3$; 2.76, 3.00, AB quartet, $J_{A,B}$ 9 Hz, 2 Hz, -CH_2-O-; 3.23, s, 3H, CH_3-O-; 3.33, s, 5H, -CH_2-O-CH_3; 3.62, q, $J_{4,Me}$ 2 Hz, 1H, H4; 7.23, s, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 3.59, C1; 15.90, C6; 41.04, C4; 42.84, C5; 58.81, CH_3-O-; 59.30,

CH_3-O-; 74.46, -CH_2-O-; 76.04, -CH_2-O; 78.77, 79.02, C2/C3; 126.69, C4'; 127.68, 129.75, C3'/C2'; 138.63, C1'.

Elution with petroleum ether/ether (98:2) gave (E)-alkenol (114) (156 mg), identical in all respects with an authentic sample.

Elution with petroleum ether/ether (95:5) gave a series of unidentified compounds (78 mg in total).

(b) Alkynol (98) (500 mg) was reacted with lithium aluminium hydride (80 mg) in 2,5-dimethyltetrahydrofuran (25 ml) as in (a) above, except the reaction was quenched with deuterium oxide, instead of water. The crude product was chromatographed on 5% deactivated alumina (40 g).

Elution with petroleum ether gave the propenylcyclopropane derivatives (115) and (116) as a mixture (13 mg) (≃9:4; ^{1}H n.m.r.).

Continued elution with petroleum ether gave a complex mixture (43 mg) (≃2:5:28:8; ^{1}H n.m.r.) of the propenylcyclopropane derivatives (115) and (116), alkene (117) and allene (113).

Further elution with petroleum ether gave a mixture (37 mg) (27:10; ^{1}H n.m.r.) of the alkene (117) and allene (113).

Elution with more petroleum ether gave a mixture (24 mg) (6:18; ^{1}H n.m.r.) of alkene (117) and allene (113).

Continued elution with petroleum ether gave pure allene (113) (64 mg); identical (^{1}H n.m.r., I.R.) with authentic material.

Elution with petroleum ether/ether (99:1) gave a mixture (42 mg) (15:27; ^{1}H n.m.r.) of allene (113) and alkyne (118).

Further elution with petroleum ether/ether (99:1) gave pure alkyne (118) (27 mg), identical (^{1}H n.m.r.) with authentic material.

Elution with petroleum ether/ether (98:2) gave a mixture (36 mg) (9:27; ^{1}H n.m.r.) of alkyne (118) and mono-deutero

alkenol (114).

Elution with petroleum ether/ether (96:4) gave 5-deutero and 4-deutero (E)-alkenols (114) (125 mg) as a mixture (7:23), identical (^{1}H n.m.r., ^{13}C n.m.r.) with authentic material.

Elution with petroleum ether/ether (94:6) gave a series of unidentified compounds (66 mg).

(c) To a suspension of lithium aluminium hydride (64 mg) in 2,5-dimethyltetrahydrofuran (5 ml) was added a solution of the alkynol (98) (400 mg) in 2,5-dimethyltetrahydrofuran (15 ml) and the stirred mixture heated at 65° for 2.5 h under an atmosphere of nitrogen. After quenching with water, the crude product was chromatographed on 5% deactivated alumina (30 g). The products were: (1) alkene (117) (20 mg); (2) allene (113) (184 mg); (3) (E)-alkenol (114) (161 mg); identical in all respects with authentic samples; and (4) unknown (18 mg).

Reduction of 2,2-Di-(methoxymethyl)-3-phenylhex-4-yn-3-ol (98) with Lithium Aluminium Deuteride in 2,5-Dimethyltetrahydrofuran.

(a) Alkynol (98) (500 mg) was reacted with lithium aluminium deuteride (88 mg) in 2,5-dimethyltetrahydrofuran (25 ml) under the same conditions as (c) above. The crude product was then adsorbed onto 5% deactivated alumina (30 g) and separated into its components. These were: (1) Trideutero alkene (117) (6 mg); (2) monodeutero allene (113) (249 mg); (3) 4-deutero and 5-deutero (E)-alkenols (114) (204 mg) as a mixture (8:34); (4) Alkynol (98) (20 mg); all compounds identical in all respects with authentic samples.

1-Methoxy-2,2-dimethyl-3-phenylhex-4-yn-3-ol (90b).

A solution of the methoxy ketone (124) (9 g; 0.047 mole) in dry ether (70 ml) was added dropwise to excess propynyllithium at -30° [prepared from 1-butyllithium (0.19 mole) in dry ether (400 ml) and propyne (35 ml, 0.6 mole) in dry ether (50 ml)], and the resulting mixture was stirred for 20 h at room temperature. It was then treated with saturated aqueous ammonium chloride and the crude product, isolated by means of ether, was adsorbed onto 5% deactivated alumina (700 g).

Elution with petroleum ether/ether (50:50) gave the methoxy alkynol (90b) (8.2 g; 75%); a white solid (recrystallisation solvent: pet ether); m.p. 44.5-46°; ν_{max} (liquid film) 3455, OH, 2225, alkyne; 1600, 755, 707, mono-substituted benzene; 1089 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 0.80, s, 3H, 2-$(CH_3)_A$ $(CH_3)_B$; 0.87, s, 3H, 2-$(CH_3)_A$ $(CH_3)_B$; 1.92, s, 3H, $(H6)_3$; 3.13, d, $J_{A,B}$ 9 Hz, 1H, CH_3-O-CH_AH_B-; 3.38, s, 3H, CH_3-O-; 3.75, d, $J_{B,A}$ 9 Hz, 1H, CH_3-O-CH_AH_B-; 4.31, s, 1H, OH; 7.05-7.62, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 3.63, C6; 19.69, 22.41, 2-$(CH_3)_2$; 42.33, C2; 59.34, CH_3-O-; 79.44, 81.11, C3/C4/C5; 82.08, C1; 126.91, C2'; 127.10, C4'; 127.85, C3'; 141.94, C1'; (Found: M^+, 232.1473. Calc. for $C_{15}H_{20}O_2$: M^+, 232.1463); (Found: C, 77.37; H, 8.98. $C_{15}H_{20}O_2$ requires: C, 77.55; H, 8.68%).

Reduction of 1-Methoxy-2,2-dimethyl-3-phenyhex-4-yn-3-ol (90b) with Lithium Aluminium Hydride in Tetrahydrofuran.

(a) To a suspension of lithium aluminium hydride (90 mg) in tetrahydrofuran (10 ml) was added a solution of the alkynol (90 b) (500 mg) in the same solvent (5 ml). More tetrahydrofuran (10 ml) was added and the mixture refluxed for 116 h under an atmosphere of nitrogen. The reaction was quenched

with deuterium oxide and the crude product, isolated by means of ether, was adsorbed onto 2.5% deactivated alumina (60 g).

Elution with pentane gave an inseparable (t.l.c., h.p.l.c) mixture (9:1, ^{1}H n.m.r.) of the (E)-(125a) and (Z)-(125b) 2,2-dimethyl-1-phenyl-1-(1'-propenyl)-cyclopropanes (36 mg), Block A, as a mobile, colourless oil; (Found: M^+, 186.1412. Calc. for $C_{14}H_{18}$: M^+, 186.1408); ν_{max} (liquid film) 3075-3045, cyclopropane; 1659, 965, *trans*-CH=CH-; 1603, 706 cm^{-1}, mono-substituted benzene; λ_{max} (cyclohexane) 211 nm (ε 11,200); n.m.r. data for the major component, (E)-propenylcyclopropane derivative (125a) as follows, ^{1}H n.m.r. (CFT 20, $CDCl_3$) δ 0.77, s, 3H, 2-$(CH_3)_A$ $(CH_3)_B$, *cis* to phenyl; 0.86, 0.99, AB quartet, $J_{A,B}$ 5 Hz, 2H, $(H3)_2$; 1.23, s, 3H, 2-$(CH_3)_A$ $(CH_3)_B$, *trans* to phenyl; 1.60, dd, $J_{Me,2'}$ 6 Hz, $J_{Me,1'}$ 1.4 Hz, 3H, $(H3')_3$; 5.09, dq, $J_{2',1'}$ 15 Hz, $J_{2',Me}$ 6 Hz, 1H, H2'; 5.62, dq, $J_{1',2'}$ 15 Hz, $J_{1',Me}$ 1.4 Hz, 1H, H1'; 7.20, s, 5H, aromatic protons; ^{13}C n.m.r ($CDCl_3$) δ 17.92, C3'; 22.05, 2-$(CH_3)_A$ $(CH_3)_B$, *trans* to phenyl; 23.00, C2; 24.76, 2-$(CH_3)_A$ $(CH_3)_B$, *cis* to phenyl; 25.44, C3; 37.70, C1; 124.71, C2'; 125.73, C4''; 127.94, 130.27, C3'/C2'; 135.64, C1'; 143.01, C1''; n.m.r. evidence for the presence of minor component, (Z)-propenyl-cyclopropane derivative as follows, ^{1}H n.m.r. (CFT 20, $CDCl_3$) signals visible δ 0.75, s, 2-Me, *cis* to phenyl; 1.21, s, 2-Me, *trans* to phenyl; 1.62, ?d, $J_{Me,2'}$ 6 Hz, $(H3')_3$; 5.83, 5.94, downfield pair of signals of AB quartet, $J_{1',2'}$ 9 Hz, H1'; upfield signals due to H2' were obscured.

Continued elution with pentane gave a mixture (87 mg) (80:7) of the propenylcyclopropane derivatives (125a) and (125b), and the propynylcyclopropane derivative (126), see below.

Further elution with pentane gave pure (t.l.c., n.m.r., h.p.l.c.) 2,2-dimethyl-1-phenyl-1-(1'-propynyl)-cyclopropane (126)

(26 mg); a colourless oil; (Found: M^+, 184.1252. Calc. for $C_{14}H_{16}$: M^+, 184.1252); ν_{max} (liquid film) 3100-3040, cyclopropane; 2245, -C≡C-; 1603, 765, 705 cm^{-1}, mono-substituted benzene; λ_{max} (cyclohexane) 206.5 nm (ε 6500); ^1H n.m.r. (CFT20, $CDCl_3$) δ 0.72, s, 3H, 2-$(\underline{CH_3})_A$ $(CH_3)_B$, *cis* to phenyl; 0.94, 1.22, AB quartet, $J_{A,B}$ 4.5 Hz, 2H, $(H3)_2$; 1.40, s, 3H, 2-$(CH_3)_A$ $(\underline{CH_3})_B$, *trans* to phenyl; 1.77, s, 3H, $(H3')_3$; 7.26, s, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 3.68, C3'; 22.28, 2-$(\underline{CH_3})_A$ $(CH_3)_B$, *trans* to phenyl; 23.79, 2-$(CH_3)_A$ $(\underline{CH_3})_B$, *cis* to phenyl; 24.87, C2; 26.76, C3; 27.36, C1; 73.69, C2'; 83.19, C1'; 126.23, C4''; 128.08, 129.10, C2''/C3''; 140.97, C1''.

Continued elution with pentane gave a mixture (11 mg) (6:5) of the propynylcyclopropane derivative (126) and the allene (91b), see below.

Later fractions eluted by pentane gave pure <u>6-methoxy-5,5-dimethyl-4-phenylhexa-2,3-diene</u> (91b) (116 mg); a mobile colourless oil; ν_{max} (liquid film) 1960, allene; 1600, 760, 705, mono-substituted benzene; 1100 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 1.03, s, 6H, 5-$(CH_3)_2$; 1.68, d, $J_{Me,2}$ 7 Hz, 3H, $(H1)_3$; 3.07, s, 2H, $(H6)_2$; 3.23, s, 3H, CH_3-O-; 5.08, q, $J_{2,Me}$ 7 Hz, 1H, H2; 7.10, s, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 14.81, C1; 25.16, 5-$(\underline{CH_3})_2$; 38.60, C5; 59.02, CH_3-O-; 80.67, C6; 86.34, C2; 112.15, C4; 126.53, C4', 127.75, 129.57, C3'/C2'; 137.99, C1'; 203.61, C3; (Found: M^+, 216.1506. Calc. for $C_{15}H_{20}O$: M^+, 216.1514); (Found: C, 83.28; H, 9.24. $C_{15}H_{20}O$ requires C, 83.28; H, 9.32%).

Elution with petroleum ether (95:5) gave a mixture (33 mg) of unidentified compounds.

Finally, elution with petroleum ether/ether (70:30) gave a mixture (119 mg) (20:4) of the <u>5-deutero and 4-deutero (E)-alkenols</u> (92b) as a viscous colourless oil; ν_{max} (liquid film)

3500, OH; 1658, C=C; 1600, 765, 730, 705, mono-substituted benzene; 1090 cm^{-1}, C-O-CH_3; ^1H n.m.r. (4-deutero) (CCl_4) δ 0.85, s, 6H, 2-$(Me)_2$; 1.73, d, $J_{Me,5}$ 7 Hz, 3H, $(H6)_3$; 2.96, 3.26, AB quartet, $J_{A,B}$ 9 Hz, 2H, $(H1)_2$; 3.27, s, 3H, CH_3-O-; 4.03, s, 1H, OH; 5.79, q, $J_{5,Me}$ 7 Hz, 1H, H5; 7.0-7.4, m, 5H, aromatic protons; ^1H n.m.r. (CCl_4) (5-deutero) δ 0.85, s, 6H, 2-$(Me)_2$; 1.73, s, 3H, $(H6)_3$, 2.96, 3.26, AB quartet, $J_{A,B}$ 9 Hz, 2H, $(H1)_2$; 3.27, s, 3H, CH_3-O-; 4.03, s, 1H, OH; 6.17, m, $W_{h/2}$ 6 Hz, 1H, H4; 7.0-7.4, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 17.90, C6; 20.93, 21.66, 2-$(\underline{CH_3})_2$; 41.65, C2; 59.03, CH_3-O-; 80.29, C3; 81.44, C1; 124.60, C5; 126.28, C4'; 127.09, 127.35, C3'/C2'; 133.36, C4; 144.51, C1'; (Found: M^+, 235.1681. Calc. for $C_{15}H_{21}DO_2$: M^+, 235.1682).

(b) The alkynol (90b) (500 mg) was treated in the same manner as (a) above except the reaction mixture was quenched with water, not deuterium oxide. The crude product, isolated by means of ether, was adsorbed onto active alumina (55 g) with pentane (40 ml).

Elution with pentane gave an inseparable mixture (9:1) of the (E)-(125a) and (Z)-(125b) propenylcyclopropane derivatives (113 mg), identical (^1H n.m.r., ^{13}C n.m.r., infrared spectra) with authentic material.

Elution with petroleum ether/ether (98:2) gave a mixture (48 mg) (31:17) of the propynylcylopropane derivative (126) and allene (91b). The propynylcyclopropane derivative was isolated after successive series of injections on the High Performance Liquid Chromatograph, where in each isocratic run (100% hexane, 0.6 ml/min, 220 nm), the portion of the leading peak was shaved off until the propynylcyclopropane derivative (126) was enriched to 96%, identical (^1H n.m.r.,

^{13}C n.m.r.) with an authentic sample.

Further elution with petroleum ether/ether (98:2) gave allene (91b) (119 mg), identical (^{1}H n.m.r.) with authentic material.

Elution with ether gave (E)-1-methoxy-2,2-dimethyl-3-phenylhex-4-en-3-ol (92b) (141 mg) as a viscous, colourless oil; ν_{max} (liquid film) 3475, OH; 1668, 970, *trans*-CH=CH-; 1600, 772, 728, 705, mono-substituted benzene; 1090 cm^{-1}, C-O-CH_3; ^{1}H n.m.r. (CCl_4) δ 0.87, s, 6H, 2-$(CH_3)_2$; 1.76, d, $J_{Me,5}$ 6 Hz, 3H, $(H6)_3$; 2.99, 3.29, AB quartet, $J_{A,B}$ 9 Hz, 2H, $(H1)_2$; 3.30, s, 3H, CH_3-O-; 4.08, s, 1H, OH; 5.78, dq, $J_{5,4}$ 14.5 Hz, $J_{5,Me}$ 6 Hz, 1H, H5; 6.20, d, $J_{4,5}$ 14.5 Hz, 1H, H4; 7.03-7.31, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 17.98, C6; 20.94, 21.67, 2-$(CH_3)_2$; 41.67, C2; 59.03, CH_3-O-; 80.32, C3; 81.45, C1; 124.75, C5; 126.27, C4'; 127.09, 127.35, C2'/C3'; 133.46, C4; 144.53, C1'; (Found: M^+, 234.1626. Calc. for $C_{15}H_{22}O_2$: M^+, 234.1620); (Found: C, 76.87; H, 9.58. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%).

Reduction of 6-Methoxy-5,5-dimethyl-4-phenylhexa-2,3-diene (91b) with Lithium Aluminium Deuteride in Tetrahydrofuran.

To a suspension of lithium aluminium deuteride (81 mg; 1.1 mol) in tetrahydrofuran (10 ml) was added a solution of the allene (91b) (380 mg) in tetrahydrofuran (15 ml). The mixture was heated under reflux for 133 h under an atmosphere of nitrogen. The reaction was quenched with water, and the crude product, isolated by means of ether, was adsorbed onto 2.5% deactivated alumina (40 g).

Elution with petroleum ether gave a mixture (9:1) of the monodeutero-(E)-(125a) and (Z)-(125b) propenylcyclopropane derivatives (5 mg).

Further elution with petroleum ether gave a complex mixture (123 mg) from which, on rechromatography, was obtained further monodeutero-(E)-(125a) and (Z)-(125b) propenylcyclopropane derivatives (42 mg) (9:1) as a mobile colourless oil; (Found: M^+, 187.1474. $C_{14}H_{17}D$ requires M^+, 187.1471); n.m.r. data for the major component, (E)-1'-deutero-propenylcyclopropane derivative as follows: ^1H n.m.r. (CFT20, $CDCl_3$) δ 0.77, s, 3H, 2-$(CH_3)_A$ $(CH_3)_B$, *cis* to phenyl; 0.86, 0.99, AB quartet, $J_{A,B}$ 5 Hz, 2H, $(H3)_2$; 1.23, s, 3H, 2-$(CH_3)_A$ $(CH_3)_B$, *trans* to phenyl; 1.60, d, $J_{Me,2'}$ 6 Hz, 3H, $(H3')_3$; 5.09, tq, $J_{2',Me}$ 6 Hz, $J_{2',D}$ 1 Hz, 1H, H2'; 7.20, s, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) as for all -H compound except for the absence of C1' signal (δ 135.64) and small upfield shift of C1 signal (δ 37.58, reduced peak height) due to the adjacent C1'-deuterium.

Continued elution with petroleum ether gave slightly impure (≃10%) allene (91b) (222 mg), identified by ^1H n.m.r., ^{13}C n.m.r. and infrared spectra.

5.3 EXPERIMENTAL RELATING TO CHAPTER 3

Methoxyacetonitrile (140)[79]

In a 500 ml three-necked round-bottom flask, fitted with a mechanical stirrer, a thermometer for reading low temperatures, and a dropping funnel was placed pulverized sodium cyanide (49 g; 1 mole) and water (100 ml), see Scheme 27. The stirrer was started and some of the paraformaldehyde (30 g; 1 mole) was added in small quantities until the temperature rose to 20-25° and the sodium cyanide had dissolved. The flask was then cooled by an ice-bath, and the temperature kept below 25° during the completion of the addition of the paraformaldehyde.

Technical methyl sulphate (135 g; 100 ml; 1.05 mole) was placed in a dropping funnel, and when the temperature inside the flask had dropped to 13°, a portion of the sulphate (10-15 ml) was added. An exothermic reaction set in; initiated by removal of the ice-bath. When the temperature began to fall, the remainder of the methyl sulphate was admitted at such a rate as to keep the temperature at 12-15°. When the addition was complete, the mixture was stirred an additional forty minutes, during which time the temperature dropped to about 5°. The stirrer was stopped, and the oily, upper layer separated at once. The lower aqueous layer was returned to the flask and methylated as before with a second portion of methyl sulphate (100 ml).

The oily, upper layer was dried with anhydrous sodium sulphate and distilled under diminished pressure, using an efficient fractionating column. The portion boiling below 70° at 15 mm was mainly methoxyacetonitrile. The upper oily layer from the second methylation was treated in a similar

manner.

The crude fractions were combined and distilled at atmopsheric pressure through a 20 cm Vigreux column; about 95% distilled at 118-122° as a colourless liquid. The methoxyacetonitrile so prepared weighed 31 g; 43%, (lit.[79] 70-77%); ν_{max} (liquid film) 2000, nitrile; 1110 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 3.47, s, 3H, CH_3-O-; 4.18, s, 2H, -CH_2-O-.

ω-Methoxyacetophenone (141)[80]

In a 2-ℓ three-necked round-bottom flask fitted with a dropping funnel, a reflux condenser and a mechanical stirrer was placed magnesium (12.6 g; 0.52 mole) and the whole system was flushed with dry nitrogen for about ¼ h. One hundred millilitres of a mixture of bromobenzene (81.2 g; 55 ml; 0.52 mole) and sodium-dried ether (400 ml) was then run in and the flask warmed gently to initiate the reaction. Stirring was then started, and the vessel cooled by a water bath. The remainder of the bromobenzene/ether mixture was added at such a rate as to keep the reaction refluxing gently. When the addition was complete, the whole was stirred for an extra 15 minutes.

To the Grignard solution, cooled in an ice-salt bath, a mixture of methoxyacetonitrile (30.6 g; 0.43 mole) in dry ether (75 ml) was slowly added with stirring. The white, tar-like addition product separated at once. After stirring at room temperature for 2 h, the mixture was again cooled and then decomposed, by adding with stirring, ice-water (500 ml) and then cold dilute sulphuric acid (100 ml) (one volume of concentrated sulphuric acid was added to two volumes of water and the mixture cooled in an ice-salt bath). When the

decomposition was complete (the two layers were light yellow in colour with only a small amount of tarry material present), the ether layer was separated and the aqueous layer extracted with a little ether. This ether extract was combined with the ether layer, the whole was then washed with aqueous sodium carbonate (5%) and then with water. The solution was dried with anhydrous sodium sulphate.

The ether was removed by rotary-evaporator, and the residue distilled under diminished pressure. ω-Methoxyacetophenone was a colourless liquid which boiled at 118°-120° (15 mm), [lit.[80] b.p. 118-120° (15 mm)]. The yield was 46 g; 71% based on the methoxyacetonitrile, (lit[80] 71-78%, based on the methoxyacetonitrile); ν_{max} (liquid film) 1704, aryl ketone; 1602, 763, 703, mono-substituted benzene; 1128 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 3.48, s, 3H, CH_3; 4.67, s, 2H, -CH_2-O-; 7.23-7.63, m, 3H, meta and para aromatic protons; 7.80-8.07, m, 2H, ortho aromatic protons; ^{13}C n.m.r. (neat + dioxan) δ 56.56, CH_3-O-; 72.73, -CH_2-O-; 125.63, 126.56, C2'/C3'; 131.25, C4'; 132.85, C1'; 194.15, C1.

1-Methoxy-2-phenylpent-3-yn-2-ol (136)

A solution of ω-methoxyacetophenone (141) (4.5 g; 0.03 mole) in dry ether (50 ml) was added in small portions to propynyllithium [prepared from 1-butyllithium (0.035 mole) in dry ether (55 ml) and propyne (10 ml; 0.17 mole)] at -70°, and the resulting mixture was stirred for 60 h at room temperature. It was then carefully hydrolysed with saturated ammonium chloride solution (100 ml) and the crude product, extracted with ether (3 x 100 ml), was then dried over anhydrous magnesium sulphate. Solvent removal left a yellow oil (6.7 g). The alkynol (136) was purified by fractional

distillation under diminished pressure b.p. 132-135° (5 mm), followed by chromatography on 10% deactivated alumina (200 g).

Elution with petroleum ether/ether (50:50) gave 1-methoxy-2-phenylpent-3-yn-2-ol (136)(3.2 g, 56%) as a white solid; m.p. 28.5-29.5°; ν_{max} (liquid film) 3455, OH, 2250, alkyne; 1603, 767, 703, mono-substituted benzene; 1110 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 1.87, s, 3H, $(H5)_3$; 3.37, s, 3H, CH_3-O-; 3.24-3.59, m, 3H, -CH_2-O-, OH; 7.18-7.66, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 3.73, C5; 59.67, CH_3-O-; 72.15, C1; 80.59, 81.48, 81.82, C4/C2/C3; 125.86, 128.06, C2'/C3'; 127.82, C4'; 141.82, C1'; (Found: M^+, 190.0960. Calc. for $C_{12}H_{14}O_2$: M^+, 190.0994; M^+ -32, 158.0725 ($C_{11}H_{10}O$, 158.0732); M^+ -45, 145.0655 ($C_{10}H_9O$, 145.0653) base peak); (Found: C, 75.99; H, 7.50. $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42%).

Reaction of Alkynols* with Lithium Aluminium Hydride (Deuteride) in an Ether Solvent.

General Procedure: The total volume of an ether solvent used was 5 ml per 100 mg of alkynol. To a suspension of lithium aluminium hydride (deuteride) (1.1 molar equivalents) in the ether solvent was added the alkynol in the same solvent at a rate such that the evolution of hydrogen was not vigorous. The reaction mixture was either stirred at a certain temperature or heated under reflux with stirring for a specific period of time in an atmosphere of nitrogen. The cooled reaction mixture was quenched by the addition of water or deuterium oxide, sodium potassium tartrate added, the crude product isolated by means of ether, dried over magnesium sulphate and the ether solvent removed by water aspirator.

---

* Can be any of compounds (90a, 90b, 98, 18, 136, 137 or 138), see Blocks A and B.

Reduction of 1-Methoxy-2-phenylpent-3-yn-2-ol (136) with Lithium Aluminium Hydride in 2,5-Dimethyltetrahydrofuran (refer to general procedure).

(a) Reaction of the alkynol (136) (400 mg) with lithium aluminium hydride (89 mg) in 2,5-dimethyltetrahydrofuran (20 ml) was carried out at 91°/0.5 h, then quenched with water. The components of the crude product were separated by chromatography on 5% deactivated alumina (25 g).

Elution with petroleum ether gave a mixture (1:1) of the (E)-(143a) and (Z)-(143b) 2-phenylpenta-1,3-dienes (61 mg); see Block B, a pungent smelling, mobile, colourless oil which readily dimerized; (Found: M^+, 144.0938. Calc. for $C_{11}H_{12}$: M^+, 144.0939; Found: M^+, 288.1878. Calc. for $C_{22}H_{24}$: M^+, 288.1878); ν_{max} (liquid film) 3100-3040, 893, $R_2C{=}CH_2$; 1643, 1596, diene; 1596, 778, 705, mono-substituted benzene; 1494, 1448, C-H; 967 cm^{-1}, *trans*-CH=CH-; λ_{max} (cyclohexane) 218.5 nm (ε 12,600), 238.5 nm (ε 8,600); ^1H n.m.r. (CCl_4) for (E)-isomer (143a) δ 1.77, d, $J_{Me,4}$ 6.5 Hz, 3H, $(H5)_3$; part of three doublets (each J 1.5 Hz) 4.98, 1H; 5.08, 2H; 5.49, 1H, $(H1)_2$; 5.57, dq, $J_{4,3}$ 15 Hz, $J_{4,Me}$ 6.5 Hz, 1H, H4; 6.24, d, $J_{3,4}$ 15 Hz, 1H, H3; 7.21, s, 5H, aromatic protons; ^1H n.m.r. (CCl_4) for (Z)-isomer (143b) δ 1.66, d, $J_{Me,4}$ 6.5 Hz, 3H, $(H5)_3$; part of three doublets (each J 1.5 Hz) 4.98, 1H; 5.08, 2H; 5.49, 1H, $(H1)_2$; 5.75, dq, $J_{4,3}$ 10.5 Hz, $J_{4,Me}$ 6.5 Hz, 1H, H4; 6.10, d, $J_{3,4}$ 10.5 Hz, 1H, H3; 7.21, s, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 14.73, 18.23, C5; 114.28, 114.98, C1; 126.64, 127.29, 127.48, 128.06, 128.10, 128.29, C4'/C3'/C2'; 128.37, 129.04, 129.92, 132.89, C3/C4; 140.85, 141.05, C1'; 148.28, C2.

Elution with petroleum ether/ether (70:30) gave (E)-1-methoxy-2-phenylpent-3-en-2-ol (142) (308 mg), a viscous, colourless oil; ν_{max} (liquid film) 3500, OH; 1673, 967,

trans -CH=CH-; 1603, 763, 703, mono-substituted benzene; 1102 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 1.69, d, $J_{Me,4}$ 5 Hz, 3H, $(H5)_3$; 2.93, s, 1H, OH; 3.30, s, 3H, CH_3-O-; 3.48, s, 2H, $(H1)_2$; 5.55-5.74, ABq, 2H, olefinic protons; 7.07-7.47, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 17.79, C5; 59.17, CH_3-O-; 75.93, C2; 79.63, C1; 125.64, C4; 125.72, C2'; 126.81, C4'; 127.84, C3'; 134.57, C3; 143.90, C1'; ^{13}C n.m.r. (acetone) δ 17.80, C5; 59.18, CH_3-O-; 76.16, C2; 80.37, C1; 124.84, C4; 126.40, C2'; 127.00, C4'; 128.21, C3'; 135.84, C3; 145.26, C1'; (Found: M^+, 192.1150. Calc. for $C_{12}H_{16}O_2$: M^+, 192.1150); (Found: C, 74.92; H, 8.28. $C_{12}H_{16}O_2$ requires C, 74.97; H, 8.39%).

(b) The alkynol (136) (300 mg) was treated in the same manner as above except that the reaction mixture was quenched with deuterium oxide. The crude product isolated by means of ether, was adsorbed onto 5% deactivated alumina (25 g).

Elution with petroleum ether gave a mixture (1:1) of the (E)-(143a) and Z-(143b) dienes (51 mg), identical (^1H n.m.r., ^{13}C n.m.r., ultraviolet spectra) with an authentic sample.

Elution with petroleum ether/ether (70:30) gave 4-deutero and 3-deutero (E)-alkenols (142) (234 mg) as a mixture (25:52); ν_{max} (liquid film) 3475, OH; 1655, >C=C<; 1600, 763, 703, mono-substituted benzene; 1100 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) (3-deutero) δ 1.69, d, $J_{Me,4}$ 6.5 Hz, 3H, $(H5)_3$; 3.15, s, 1H, OH; 3.28, s, 3H, CH_3-O-; 3.49, s, 2H, $(H1)_2$; 5.68, q, $J_{4,Me}$ 6.5 Hz, 1H, H4; 7.43-7.83, m, 5H, aromatic protons; ^1H n.m.r. (CCl_4) (4-deutero) δ 1.69, s, 3H, $(H5)_3$; 3.15, s, 1H, OH; 3.28, s, 3H, CH_3-O-; 3.49, s, 2H, $(H1)_2$; 5.68, bs, $W_{h/2}$ 8 Hz, 1H, H3; 7.43-7.83, m, 5H, aromatic protons; ^{13}C n.m.r. (d_6-acetone) δ 17.75, C5; 59.23, CH_3-O-; 76.20, C2; 80.52, C1; 124.71, C4; 126.51, C2'; 127.06, C4'; 128.29, C3'; 135.94, C3; 145.52, C1'; (Found: M^+, 193.1213. Calc. for $C_{12}H_{15}DO_2$:

M^+, 193.1213).

(c) Reaction of alkynol (136) (300 mg) with lithium aluminium hydride (66 mg) in 2,5-dimethyltetrahydrofuran (15 ml) was carried out at 65°/1.25 h, then quenched with water. The crude product was chromatographed on 5% deactivated alumina (25 g).

Elution with petroleum ether gave a mixture (1:1) of the (E)-(143a) and (Z)-(143b) dienes (10 mg), identical (^{1}H n.m.r.) with an authentic sample.

Elution with petroleum ether/ether (70:30) gave (E)-alkenol (142) (288 mg), identical (^{1}H n.m.r., infrared spectra) with an authentic sample.

Reduction of 1-Methoxy-2-phenylpent-3-yn-2-ol (136) with Lithium Aluminium Deuteride in 2,5-Dimethyltetrahydrofuran (refer to page 113).

(a) Reaction of the alkynol (136) (400 mg) with lithium aluminium deuteride (97 mg), as in (a) above, gave a crude product which was separated into its components by chromatography on 5% deactivated alumina (25 g).

Elution with petroleum ether gave a mixture (1:1) of the (E)-(143a) and (Z)-(143b) 3,4-dideutero-2-phenylpenta-1,3-dienes (65 mg); a pungent smelling, mobile, colourless oil; (Found: M^+, 146.1065. Calc. for $C_{11}H_{10}D_2$: M^+, 146.1065; Found: M^+, 292.2129. Calc. for $C_{22}H_{20}D_4$: M^+, 292.2129); ν_{max} (liquid film) 3100-3040, 898, $R_2C{=}CH_2$; 1600, diene; 1492, 1445, C-H; 1575, 762, 700 cm^{-1}, mono-substituted benzene; ^{1}H n.m.r. (CCl_4) for (E)-isomer (143a) δ 1.78, s, 3H, $(H5)_3$; part of three doublets (each J 1.5 Hz) 4.98, 1H; 5.11, 2H; 5.50, 1H, $(H1)_2$; 7.25, s, 5H, aromatic protons; ^{1}H n.m.r. (CCl_4) for (Z)-isomer (143b) δ 1.67, s, 3H, $(H5)_3$; part of

three doublets (each J 1.5 Hz) 4.98, 1H; 5.11, 2H; 5.50, 1H, $(H1)_2$; 7.25, s, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 14.55, 18.03, C5; 114.22, 115.00, C1; 126.60, 127.28, 127.46, 128.04, 128.10, 128.25, C2'/C4'/C3'; 140.73, C1'.

Elution with petroleum ether/ether (70:30) gave 3-deutero and 4-deutero (E)-alkenols (142) (304 mg) as a mixture (27:48), identical (^1H n.m.r., ^{13}C n.m.r., infrared spectra) with an authentic sample.

(b) The alkynol (136) (400 mg) was reduced by lithium aluminium deuteride (97 mg) in the same manner as (c) above, the reaction being quenched with water. Chromatography of the crude product on 5% deactivated alumina (25 g) gave:

(1) a 1:1 mixture of (E)-(143a) and Z-(143b) dideutero-dienes (16 mg), identical (^1H n.m.r.) with an authentic sample.

(2) 3-deutero and 4-deutero (E)-alkenols (142) (382 mg) as a mixture (23:71), identical (^1H n.m.r., ^{13}C n.m.r., infrared spectra) with an authentic sample.

Reduction of 1-Methoxy-2-phenylpent-3-yn-3-ol (136) with Lithium Aluminium Hydride in Tetrahydrofuran (refer to general method).

(a) For a tetrahydrofuran solvent reaction (25 ml, 65°, 2.5 h) quenched with water, alkynol (136) (500 mg) reduced by lithium aluminium hydride (110 mg) gave a crude product, the components of which were separated by chromatography on 5% deactivated alumina (25 g): (1) (E)-(143a) and (Z)-(143b) dienes (26 mg), and (2) (E)-alkenol (142) (464 mg); all of which were identical (^1H n.m.r., infrared spectra) with authentic samples.

(b) Reaction of alkynol (136) (300 mg) with lithium aluminium hydride (66 mg) in tetrahydrofuran (15 ml) was carried out at 35° for 2.75 h under an atmosphere of nitrogen,

and then quenched with water. The crude product, isolated by means of ether, was chromatographed on 5% deactivated alumina (25 g) to yield (E)-(143a) and (Z)-(143b) dienes (3 mg) and (E)-alkenol (142) (294 mg).

Reduction of 1-Methoxy-2-phenylpent-3-yn-2-ol (136) with Lithium Aluminium Deuteride in Tetrahydrofuran (refer to page 113).

(a) Reaction of the alkynol (136) (250 mg) with lithium aluminium deuteride (61 mg) in tetrahydrofuran (12.5 ml) was carried out at 65°/1.25 h, and then quenched with water. Chromatography of the crude product on 5% deactivated alumina (25 g) gave: (1) (E)-(143a) and (Z)-(143b) dideutero dienes (13 mg); and (2) 3-deutero and 4-deutero (E)-alkenols (142) (234 mg) as a mixture (30:62).

(b) The reaction of alkynol (136) (250 mg) was carried out under reflux, as above, except the reaction time was extended to 4 h. The products were: (1) (E)-(143a) and (Z)-(143b) dideutero dienes (22 mg) (in 1:1 ratio), identical (^{1}H n.m.r., infrared spectra) with an authentic sample and (2) 3-deutero and 4-deutero (E)-alkenols (142) (219 mg) as a (28:58) mixture.

(c) Reaction of alkynol (136) (400 mg) with lithium aluminium deuteride (97 mg) in tetrahydrofuran (20 ml) at 35° was quenched with water after 2.75 h. The components of the crude product were separated by chromatography and were: (1) (E)-(143a) and (Z)-(143b) dideutero dienes (2 mg); (2) a (29:67) mixture of 3-deutero and 4-deutero (E)-alkenols (142) (389 mg), identical (^{1}H n.m.r., ^{13}C n.m.r., infrared spectra) with an authentic sample.

Reduction of 1-Methoxy-2-phenylpent-3-yn-2-ol (136) with Lithium Aluminium Hydride in Diethyl Ether (refer to page 113).

The reaction of alkynol (136) (300 mg) with lithium aluminium hydride (66 mg) in refluxing diethyl ether (15 ml) was quenched with water after 2.75 h. The crude product, isolated by means of ether, was separated into its components on 5% deactivated alumina (25 g): (1) (E)-(143a) and (Z)-(143b) dienes (3 mg); (2) (E)-alkenol (142) (270 mg); identical (^{1}H n.m.r., infrared spectra) with an authentic sample, and (3) the starting alkynol (136) (30 mg), identical (^{1}H n.m.r.) with an authentic sample.

Reduction of 1-Methoxy-2-phenylpent-3-yn-2-ol (136) with Lithium Aluminium Deuteride in Diethyl Ether (refer to page 113).

Reaction of alkynol (136) (400 mg) with lithium aluminium deuteride (97 mg) as above gave (E)-(143a) and (Z)-(143b) dideutero dienes (3 mg), 3-deutero and 4-deutero (E)-alkenols (142) (383 mg) as a mixture (25:71), and the unreacted alkynol (136) (7 mg).

1-Methoxy-3-phenylhex-4-yn-3-ol (137)[83]

Crude alkynol (137)[83] (5 g) was purified by chromatography on 10% deactivated alumina (250 g).

Elution with petroleum ether/ether (80:20) gave the pure alkynol (137) as a viscous colourless oil; ν_{max} (liquid film) 3450, OH; 2250, alkyne; 1603, 764, 708, mono-substituted benzene; 1105 cm^{-1}, C-O-CH$_3$; ^{1}H n.m.r. (CCl_4) δ 1.83, s, 3H, $(H6)_3$; 1.88-2.15, m, 2H, $(H2)_2$; 3.23, s, 3H, CH_3-O-; 3.10-3.72, m, 2H, $(H1)_2$; 3.88, s, 1H, OH; 7.03-7.63, m, 5H, aromatic protons; ^{13}C n.m.r. (CCl_4) δ 3.38, C6; 44.28, C2; 58.38, CH_3-O-; 70.30, C1; 71.98, C3; 80.34, 82.31, C5/C4; 125.14, C2'; 126.73, C4'; 127.53, C3'; 145.52, C1'; (Found: M$^+$, 204.1152.

Calc. for $C_{13}H_{16}O_2$: M^+, 204.1150); (Found: C, 76.11; H, 8.13. $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90%).

Reduction of 1-Methoxy-3-phenylhex-4-yn-3-ol (137) with Lithium Aluminium Hydride in 2,5-Dimethyltetrahydrofuran (refer to general procedure, page 113).

(a) To lithium aluminium hydride (62 mg) in 2,5-dimethyltetrahydrofuran (5 ml) was added a solution of the alkynol (300 mg) in 2,5-dimethyltetrahydrofuran (10 ml) and the mixture heated under reflux in an atmosphere of nitrogen for 0.5 h. The crude product, isolated by means of ether, was adsorbed onto 5% deactivated alumina (30 g).

Elution with petroleum ether gave 1-phenyl-1-(1'-propenyl)-cyclopropane (152) (14 mg), Block B, as a mobile, pungent smelling, colourless liquid; (Found: M^+, 158.1093. Calc. for $C_{12}H_{14}$: M^+, 158.1095); ν_{max} (liquid film) 3100-3040, 1495, cyclopropane, C-H; 1664, 967, *trans* -CH=CH-; 1600, 765, 706 cm^{-1}, mono-substituted benzene; λ_{max} (cyclohexane) 209 nm (ε 8370); ^1H n.m.r. (CCl_4) δ 0.75-1.00, m, 4H, cyclopropane protons; 1.58, d, $J_{Me,2'}$ 5.5 Hz, 3H, $(H3')_3$; 4.96, dq, $J_{2',1'}$ 15.5 Hz, $J_{2',Me}$ 5.5 Hz, 1H, H2'; 5.28, d, $J_{1',2'}$ 15.5 Hz, 1H, H1'; 7.10, s, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 14.46, C2, C3; 17.67, C3'; 27.62, C1; 123.32, C2'; 126.10, C4"; 128.10, 129.47, C3"/C2"; 137.82, C1'; 144.26, C1".

Continued elution with petroleum ether gave unidentified material (7 mg).

Continued elution with petroleum ether gave a fraction (11 mg) containing an unidentified compound (7 mg) and allene (151) (4 mg) (see below).

Continued elution with petroleum ether gave a fraction containing pure 6-methoxy-4-phenylhexa-2,3-diene (151) (11 mg)

as a mobile, colourless oil; (Found: M^+, 188.1201. Calc. for $C_{13}H_{16}O$: M^+, 188.1201); ν_{max} (liquid film) 1950, allene; 1600, 789, 753, 700, mono-substituted benzene; 1113 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 1.79, d, $J_{Me,2}$ 7 Hz, 3H, $(H1)_3$; 2.62, dt, $J_{5,6}$ 7 Hz, $J_{5,2}$ 3 Hz, 2H, $(H5)_2$; 3.28, s, 3H, CH_3-O-; 3.48, t, $J_{6,5}$ 7 Hz, 2H, $(H6)_2$; 5.43, tq, $J_{2,Me}$ 7 Hz, $J_{2,5}$ 3 Hz, 1H, H2; 7.02-7.43, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 14.27, C1; 30.05, C5; 58.65, CH_3-O-; 71.41, C6; 89.28, C2; 101.79, C4; 125.91, C2'; 126.55, C4'; 128.37, C3'; 137.17, C1'; 204.71, C3.

Continued elution with petroleum ether gave two fractions (25 mg in total), shown by ^1H n.m.r. to contain allene (151) (13 mg) and dimer (153) (12 mg) (see below).

Elution with petroleum ether/ether (99:1) gave 8-methoxy-4-methyl-6-phenyl-3-(1'-phenylcyclopropyl)-octa-2,5-diene (153) (51 mg) as a mobile, colourless oil; ν_{max} (liquid film) 3100-3040, 1495, cyclopropane, C-H; 1600, diene; 760, 705, mono-substituted benzene; 1110 cm^{-1}, C-O-CH_3; λ_{max} (cyclohexane) 224 nm (ε 19,500), 256 nm (ε 10,000); ^1H n.m.r. (CCl_4) δ 1.13, s, 4H, cyclopropane protons; 1.13,d, $J_{Me,4}$ 7 Hz, 3H, 4-CH_3; 1.75, d, $J_{Me,2}$ 7 Hz, 3H, $(H1)_3$; 2.50-2.71, m, 2H, $(H7)_2$; 3.03-3.27, t, $J_{8,7}$ 7 Hz, 2H, $(H8)_2$; 3.13, s, 3H, CH_3-O-; 3.47, dq, $J_{4,5}$ 10 Hz, $J_{4,Me}$ 7 Hz, 1H, H4; 5.48, d, $J_{5,4}$ 10 Hz, 1H, H5; 5.67, q, $J_{2,Me}$ 7 Hz, 1H, H2; 7.08, s, 10 H, aromatic protons; ^{13}C n.m.r. (CCl_4) δ 14.89, C1; 17.74, 18.39, C2'/C3'; 21.49, 4-Me; 26.39, C1'; 30.29, C7; 38.65, C4; 57.91,CH_3-O-; 70.89, C8; 123.67, C2; 124.72, 125.09, 126.17, 127.77, 128.07, C3"/C3"' /C2"/C2"' /C4"/C4"' ; 134.34, C6; 136.32, C5; 142.79, 144.46, 144.94, C3/C1"/C1"' ; (Found: C, 86.78; H, 8.88. $C_{25}H_{30}O$ requires C, 86.66; H, 8.73%).

Elution with petroleum ether/ether (70:30) gave (E)-1-methoxy-3-phenylhex-4-en-3-ol (150) (161 mg) as a viscous, colourless oil; ν_{max} (liquid film) 3475, OH; 1670, 965, *trans* -CH=CH-; 1600, 765, 752, 704, mono-substituted benzene; 1104 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 1.66, d, $J_{Me,5}$ 5 Hz, 3H, $(H6)_3$; 2.03, t, $J_{2,1}$ 6 Hz, 2H, $(H2)_2$; 3.15, s, 3H, CH_3-O-; 3.05-3.50, m, 2H, $(H1)_2$; 3.70, s, 1H, OH; 5.52-5.72, AB q, 2H, vinylic protons; 7.00-7.40, m, 5H, aromatic protons; ^{13}C n.m.r. (CCl_4) δ 17.50, C6; 40.83, C2; 58.31, CH_3-O-; 69.88, C1; 76.04, C3; 122.57, C5; 125.21, C2'; 125.94, C4'; 127.62, C3'; 137.75, C4; 146.46, C1'; (Found: M^+, 206.1304. Calc. for $C_{13}H_{18}O_2$: M^+, 206.1307); (Found: C, 75.46, H, 9.10. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%).

(b) Alkynol (137) (150 mg) was reduced by lithium aluminium hydride (31 mg) in 2,5 dimethyltetrahydrofuran (7.5 ml) heated at 65° for 1.25 h. The crude product was separated into its components by chromatography on 5% deactivated alumina to yield: (1) allene (151) (36 mg); (2) dimer (153) (2 mg); (3) an unidentified compound (10 mg); (4) (E)-alkenol (150) (99 mg); all identical with authentic material by ^1H n.m.r., infrared spectra.

Reduction of 1-Methoxy-3-phenylhex-4-yn-3-ol (137) with Lithium Aluminium Deuteride in 2,5-Dimethyltetrahydrofuran (refer to page 113).

(a) Reaction of alkynol (137) (400 mg) with lithium aluminium deuteride (91 mg) in 2,5-dimethyltetrahydrofuran (20 ml), as in (a) above, gave a crude product which was adsorbed onto 5% deactivated alumina (30 g).

Elution with petroleum ether gave 1',2'-dideutero-1-phenyl-1-(1'-propenyl)-cyclopropane (152) (15 mg) as a mobile, pungent smelling, colourless oil; ν_{max} (liquid film) 3080-3000,

1495, cyclopropane, C-H; 1603, 762, 703, mono-substituted benzene; ^{1}H n.m.r. (CCl_4) δ 0.75-1.00, m, 4H, cyclopropane protons; 1.57, s, 3H, $(H3')_3$; 7.10, s, 5H, aromatic protons.

Elution with more petroleum ether gave an unidentified material (8 mg).

Continued elution with petroleum ether gave a fraction containing further unidentified material (5 mg) and deutero allene (151) (5 mg) (see below).

Continued elution with petroleum ether gave a fraction containing pure 2-deutero-6-methoxy-4-phenylhexa-2,3-diene (151) (15 mg) as a mobile, colourless oil; (Found: M^+, 189.1267. Calc. for $C_{13}H_{15}DO$: M^+, 189.1264); ν_{max} (liquid film) 1943, allene; 1598, 766, 700, mono-substituted benzene; 1115 cm^{-1}, C-O-CH_3; ^{1}H n.m.r. (CCl_4) δ 1.75, s, 3H, $(H1)_3$; 2.60, t, $J_{5,6}$ 7 Hz, 2H, $(H5)_2$; 3.27, s, 3H, CH_3-O-; 3.45, t, $J_{6,5}$ 7 Hz, 2H, $(H6)_2$; 6.98-7.32, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 14.15, C1; 30.05, C5; 58.64, CH_3-O-; 71.41, C6; 101.93, C4; 125.94, C2'; 126.55, C4'; 128.36, C3'; 137.17, C1'; 204.75, C3.

Elution with petroleum ether next gave 3 fractions (61 mg in total), shown by ^{1}H n.m.r. to contain deutero allene (151) (24 mg) and trideutero dimer (153) (37 mg) (see below).

Elution with petroleum ether/ether (99:1) gave 2,4,5-trideutero-8-methoxy-4-methyl-6-phenyl-3-(1'-phenylcyclopropyl)-octa-2,5-diene (153) (59 mg) as a mobile, colourless oil; (Found: M^+, 349.2460. Calc. for $C_{25}H_{27}D_3O$: M^+, 349.2485); ν_{max} (liquid film) 3100-3040, 1496, cyclopropane, C-H; 1600, 759, 705, mono-substituted benzene; 1109 cm^{-1}, C-O-CH_3; ^{1}H n.m.r. (CCl_4) δ 1.12, s, 7H, cyclopropane protons and 4-CH_3; 1.73, s, 3H, $(H1)_3$; 2.45-2.70, m, 2H, $(H7)_2$; 3.12, t, $J_{8,7}$ 7 Hz, 2H, $(H8)_2$; 3.12, s, 3H, CH_3-O-; 7.07,

s, 10H, aromatic protons; ^{13}C n.m.r. (CCl_4) δ 14.72, C1; 17.69, 18.31, C2'/C3'; 21.35, 4-Me; 26.29, C1'; 30.25, C7; 57.28, CH_3-O-; 70.86, C8; 124.72, 125.03, 126.09, 127.71, C3"/C3"' /C2"/C2"' /C4"/C4"' ; 134.17, C6; 142.62, 144.29, 144.77, C3/C1"/C1"' .

Elution with petroleum ether/ether (90:10) gave (E)-4-deutero-and 5-deutero-1-methoxy-3-phenylhex-4-en-3-ols (150) (206 mg) as a mixture (47:4) as a viscous,colourless oil; (Found: M^+, 207.1370. Calc. for $C_{13}H_{17}DO_2$: M^+, 207.1369); ν_{max} (liquid film) 3500, OH; 1655, >C=C<; 1601, 768, 705, mono-substituted benzene; 1106 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) (4-deutero) δ 1.68, d, $J_{Me,5}$ 6 Hz, 3H, $(H6)_3$; 2.05, t, $J_{2,1}$ 6 Hz, 2H, $(H2)_2$; 3.22, s, 3H, CH_3-O-; 3.10-3.50, m, 2H, $(H1)_2$; 3.60, s, 1H, OH; 5.63, m, $W_{h/2}$ 8 Hz, 1H, H5; 6.93-7.47, m, 5H, aromatic protons; ^1H n.m.r. (CCl_4) (5-deutero) δ 1.68, s, 3H, $(H6)_3$; 2.05, t, $J_{2,1}$ 6 Hz, 2H, $(H2)_2$; 3.08-3.55, m, 2H, $(H1)_2$; 3.22, s, 3H, CH_3-O-; 3.66, s, 1H, OH; 5.65, bs, $W_{h/2}$ 8 Hz, 1H, H4; 7.08-7.45, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 17.60, C6; 40.82, C2; 58.67, CH_3-O-; 70.12, C1; 76.61, C3; 123.48, C5; 125.38, C2'; 126.38, C4'; 128.00, C3'; 137.29, C4; 146.36, C1'.

(b) Reaction of alkynol (137) (300 mg) by lithium aluminium deuteride (68 mg) in 2,5-dimethyltetrahydrofuran (15 ml), as in (b) above, gave when quenched with water and extracted with ether, a crude product the components of which were separated by chromatography on 5% deactivated alumina (30 g). The products isolated were: (1) deutero allene (151) (72 mg), identical (^1H n.m.r., infrared spectra) with authentic material; (2) trideutero dimer (153) (10 mg), identical (^1H n.m.r.) with authentic material; (3) unidentified compound(s)

(21 mg); (4) 4-deutero and 5-deutero (E)-alkenols (150) (195 mg), as a mixture (48:16), identical (^{1}H n.m.r., ^{13}C n.m.r., infrared spectra) with authentic material.

Reduction of 1-Methoxy-3-phenylhex-4-yn-3-ol (137) with Lithium Aluminium Hydride in Tetrahydrofuran (see page 113 for general method).

(a) Reaction of alkynol (137) (150 mg) with lithium aluminium hydride (31 mg) in tetrahydrofuran (7.5 ml) at 35° for 2.75 h, gave a crude product the components of which were separated by chromatography on 5% deactivated alumina (30 g). The products isolated were: (1) allene (151) (4 mg), identical (^{1}H n.m.r.) with authentic material; (2) (E)-alkenol (150) (123 mg), confirmed by ^{1}H n.m.r., infrared spectra; (3) unreacted starting alkynol (137) (20 mg), identical (^{1}H n.m.r.) with an authentic sample.

(b) Reaction of alkynol (137) (500 mg) with lithium aluminium hydride (100 mg) in refluxing tetrahydrofuran (250 ml) was quenched with water after 4 h, and the crude product adsorbed onto 5% deactivated alumina (50 g). Its components were: (1) (E)-propenylcyclopropane (152) (17 mg); identified by ^{1}H n.m.r., infrared spectra; (2) allene (151) (45 mg), identical (^{1}H n.m.r., infrared spectra) with authentic material; (3) dimer (153) (31 mg), identical (^{1}H n.m.r.) with authentic material; (4) (E)-alkenol (150) (348 mg), identical (^{1}H n.m.r., infrared spectra) with authentic material; (5) two unidentified compounds (33 mg).

Reduction of 1-Methoxy-3-phenylhex-4-yn-3-ol (137) with Lithium Aluminium Deuteride in Tetrahydrofuran (refer to page 113).

(a) Alkynol (137) (300 mg) was reduced by lithium aluminium deuteride (68 mg), as in (a) above, and the components of the crude product separated by chromatography on 5% deactivated alumina (30 g). The products isolated were: (1) deutero allene (151) (13 mg); (2) 4-deutero and 5-deutero (E)-alkenols (150) (264 mg) as a mixture (51:41) and (3) alkynol (137) (18 mg); all identical (^{1}H n.m.r.) with authentic material.

(b) Lithium aluminium deuteride (115 mg) reduction of alkynol (137) (500 mg) was carried out in tetrahydrofuran under the dilution conditions of (b) above. The products isolated were: (1) (E)-dideutero propenylcyclopropane (152) (25 mg); (2) deutero allene (151) (35 mg); (3) trideutero dimer (153) (34 mg); (4) unidentified compound(s) (23 mg); (5) 4-deutero and 5-deutero (E)-alkenols (150) (350 mg) as a mixture (47:20); all compounds gave ^{1}H n.m.r. data identical with those for authentic materials.

(c) Reaction of alkynol (137) (500 mg) with lithium aluminium deuteride (115 mg) in refluxing tetrahydrofuran (25 ml) was quenched with water after 4 h, and the crude product, isolated by means of ether, chromatographed on 5% deactivated alumina (50 g). The products isolated were: (1) (E)-dideutero propenylcyclopropane (152) (29 mg); (2) trideutero dimer (153) (128 mg); (3) unidentified compound(s) (33 mg); (4) 4-deutero and 5-deutero (E)-alkenols (150) (259 mg) as a mixture (46:5); all compounds were identical (^{1}H n.m.r.) with authentic samples.

1-Bromo-2-methoxyethane (159)[89]

In a 1-ℓ three-necked round-bottom flask, fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel 2-methoxyethanol (266 g; 276 ml; 3.5 mole) was placed (see Scheme 31). The stirrer was started, and phosphorus tribromide (300 g; 105 ml; 1.1 mole) added from the dropping funnel over a period of 1.5-2 h. The temperature was allowed to rise until the reaction mixture refluxed gently.

The mixture was then distilled, the distillate boiling below 130° collected in a 1-ℓ flask filled with 500 ml of water. The lower layer of crude 1-bromo-2-methoxyethane (159), was separated and dried over calcium chloride. The liquid was decanted off and distilled through a 25 cm fractionating column, the fraction boiling at 109-110° (760 mm) was collected, [lit.[102] b.p. 110.3° (759.4 mm)]. The yield of pure colourless product was 213 g, 46% based on the phosphorus tribromide, (lit. [89] 65-66% on PBr_3 basis); ν_{max} (liquid film) 1119, C-O-CH_3; 600 cm^{-1}, C-Br; ^1H n.m.r. ($CDCl_3$) δ 3.38, s, 3H, CH_3-O-; 3.47-3.83, m, 4H, CH_2.

Preparation of [2-methoxyethyl] malonic ester (160)[90]

In a 2-ℓ three-necked round-bottom flask, fitted with a mechanical stirrer, dropping funnel and reflux condenser was placed dry dimethoxyethane (650 ml) and sodium hydride (46 g; 1.52 mole; 80% dispersion in oil). The stirrer was started and diethyl malonate (274 g; 260 ml; 1.71 mole) added dropwise over a 1 h period. On completion, sodium iodide (3.5 g; 0.023 mole) was added, followed by 1-bromo-2-methoxyethane (213 g; 1.53 mole) in small portions over a 15 minute period. The milky reaction mixture (NaBr in suspension) was stirred under reflux for 2 days.

As much solvent as possible was then removed by distillation. Five hundred millilitres of water was added to the cooled remnant, stirred and then extracted with ether (3 x 250 ml). All ether extracts were combined, dried over magnesium sulphate, and the ether removed by water aspirator. Fractional distillation of the red oil under diminished pressure yielded 169 g of clear oil, 51% based on 1-bromo-2-methoxyethane, (lit.[89] 48%), b.p. 123-125° (15 mm), [lit.[89] b.p. 110-111° (6 mm)]; ν_{max} (liquid film) 1751, 1739, saturated ester; 1112 cm^{-1}, C-O-CH_3; ^{1}H n.m.r. ($CDCl_3$) δ 1.27, t, J 7 Hz, 6H, CH_3; 2.13, dt, $J_{CH_2,CH}$ 6 Hz, J_{CH_2,CH_2} 6 Hz, 2H, -$CH_2\underline{CH_2}$ $\underline{CH}$; 3.28, s, 3H, CH_3-O-; 3.42, t, J_{CH_2,CH_2} 6 Hz, 2H, CH_3-O-$\underline{CH_2}$-; 3.52, t, J_{CH,CH_2} 6 Hz, 1H, -CO-$\underline{CH}$-CO-; 4.18, q, J 7 Hz, 4H, $CH_3\underline{CH_2}$-O-.

Hydrolysis of [2-methoxyethyl] malonic ester (160)

A solution of potassium hydroxide (220 g; 4.0 mole) in water (220 ml) was placed in a 2-ℓ three-necked round-bottom flask, fitted with a reflux condenser, a mechanical stirrer and a dropping funnel. The stirrer was started and to this hot solution [2-methoxyethyl] malonic ester (214 g; 0.98 mole) was added slowly. The solution refluxed gently owing to the heat of saponification. After completion, the clear solution was heated under reflux for 4 h.

The solution was then diluted with water (200 ml) and 200 ml of liquid was distilled from the solution to remove all the alcohol formed during the saponification.

The residual liquid in the flask was allowed to cool and a cold solution of concentrated hydrochloric acid (37%; 440 ml; 5.0 mole) was slowly added with stirring, while maintaining the temperature below 20° with an ice bath. The

resultant solution (with heavy potassium chloride precipitation) was strongly acidic to litmus paper.

Production of γ-butyrolactone (161)

The acidic hydrolysis solution above was then refluxed for 3 days, after which time there was no further evidence that carbon dioxide was escaping. On cooling, the homogeneous solution was extracted with ether (10 x 100 ml), dried over anhydrous magnesium sulphate and the ether removed by distillation. The residue was distilled under diminished pressure to yield the pungent smelling colourless liquid, γ-butyrolactone (161) (17 g; 20%); b.p. 90-92° (15 mm), [lit.[95] b.p. 89° (12 mm)]; ν_{max} (liquid film) 1777, five-membered ring lactone; 1166 cm^{-1} C-O; ^{1}H n.m.r. ($CDCl_3$) δ 1.93-2.63, m, 4H, $(H2)_2$,$(H3)_2$; 4.33, t, $J_{4,3}$ 7 Hz, 2H, $(H4)_2$; ^{13}C n.m.r. ($CDCl_3$) δ 22.32, C3; 27.91, C2; 69.02, C4; 178.45, C1.

4-Methoxybutyric acid (163)

The acidic hydrolysis solution (0.1 x scale) mentioned previously was heated to 80° for 0.5 h, then cooled below 20° and extracted with 25 x 20 ml portions of ether (previously washed with calcium chloride solution to remove alcohol impurities so that esterification with the dicarboxylic acid would not occur in the prevailing acidic conditions). The ether extracts were combined, dried over magnesium sulphate and the ether distilled off. The residue was decarboxylated by heating at 100° for 3 h. Purification by fractional distillation under diminished pressure gave the pungent smelling, colourless 4-methoxybutyric acid (163) (10.9 g; 96%), (lit.[89] 25%); b.p. 97-100° (10 mm), [lit.[89] b.p. 105.0-105.5° (7 mm)]; ν_{max} (liquid film) 3300-2500, H-bonded OH; 1711, saturated carboxylic acid; 1110 cm^{-1}, C-O-CH_3; ^{1}H n.m.r. ($CDCl_3$) δ 1.88, tt,

$J_{3,2}$ 7 Hz, $J_{3,4}$ 6 Hz, 2H, $(H3)_2$; 2.42, t, $J_{2,3}$ 7 Hz, 2H, $(H2)_2$; 3.33, s, 3H, CH_3-O-; 3.43, t, $J_{4,3}$ 6 Hz, 2H, $(H4)_2$; 11.13, s, 1H, COOH; ^{13}C n.m.r. (neat + TMS) δ 30.68, C3; 36.43, C2 ; 63.89, CH_3-O-; 77.59, C4; 183.72, C1.

4-Methoxy-1-phenylbutan-1-one (164)[90]

In a 2-ℓ three-necked round-bottom flask fitted with a mechanical stirrer, a dropping funnel and a reflux condenser was placed lithium (8.3 g; 1.2 mole; flattened with a rubber hammer and cut into strips) and sodium-dried ether (750 ml). The system was flushed with nitrogen, the stirrer started and bromobenzene (63 ml; 94.2 g; 0.6 mole) was added at such a rate as to maintain gentle reflux of the reaction mixture. On completion, the reaction mixture was stirred at room temperature for 3 h, all of the metal now having been consumed. A solution of 4-methoxybutyric acid (36 g; 0.30 mole) in dry ether (70 ml) was added to the stirred reaction mixture dropwise. The white, gel-like addition product separated at once. After the addition of the ethereal 4-methoxyburyric acid was complete, stirring was continued for 20 h. The ethereal solution of crude ketone was liberated by careful water hydrolysis. The yellow ether layer was separated, the aqueous layer extracted with further ether (3 x 100 ml) and the combined ether extracts dried over magnesium sulphate. Removal of solvent gave crude ketone (164), which was purified by fractional distillation under diminished pressure, b.p. 141-143 ° (14 mm), [lit.[103] b.p. 140-145° (14 mm)]; followed by chromatography on 5% deactivated alumina (450 g), to remove the biphenyl impurity which eluted in petroleum ether.

Elution with petroleum ether/ether (90:10) gave pure 4-methoxy-1-phenylbutan-1-one (164) (12.1 g, 22%) as a colourless liquid; ν_{max} (liquid film) 1690, aryl ketone; 1600, 1581,

759, 741, 694, mono-substituted benzene; 1112 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 1.90, tt, $J_{3,2}$ 6.8 Hz, $J_{3,4}$ 6.5 Hz, 2H, $(H3)_2$; 3.10, t, $J_{2,3}$ 6.8 Hz, 2H, $(H2)_2$; 3.20, s, 3H, CH_3-O-; 3.33, t, $J_{4,3}$ 6.5 Hz, 2H, $(H4)_2$; 7.0-7.6, m, 3H, meta and para aromatic protons; 7.7-8.1, m, 2H, ortho aromatic protons; ^{13}C n.m.r. (neat + TMS) δ 24.53, C3; 35.14, C2; 58.26, CH_3-O-; 71.94, C4; 128.25, 128.81, C2'/C3'; 133.04, C4'; 137.50, C1'; 199.08, C1.

7-Methoxy-4-phenylhept-2-yn-4-ol (138)

A solution of 4-methoxy-1-phenylbutan-1-one (164) (11 g; 0.062 mole) in dry ether (100 ml) was added dropwise to propynyllithium [prepared from 1-butyllithium (0.100 mole) in dry ether (166 ml) and propyne (28 ml; 0.047 mole)] at -70°, and the resulting mixture stirred for 84 h at room temperature. Saturated ammonium chloride solution (100 ml) was then carefully added and the crude product, isolated by means of ether (3 x 100 ml), was purified by fractional distillation under diminished pressure b.p. 133-136° (2 mm), followed by chromatography on 10% deactivated alumina (500 g).

Elution with petroleum ether/ether (70:30) gave 7-methoxy-4-phenylhept-2-yn-4-ol (138) (8.8 g; 65%); a viscous, colourless oil; ν_{max} (liquid film) 3420, OH; 2240, -C≡C-; 1600, 762, 699, mono-substituted benzene; 1107 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 1.42-2.02, m, 4H, $(H5)_2$, $(H6)_2$; 1.88, s, 3H, $(H1)_3$; 3.01, s, 1H, OH; 3.18, s, 3H, CH_3-O-; 3.25, t, $J_{7,6}$ 6 Hz, 2H, $(H7)_2$; 7.13-7.61, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 3.53, C1; 24.94, C6; 42.69, C5; 58.16, CH_3-O-; 72.65, C7; 81.50, 82.23, C2/C3/C4; 125.51, C2'; 127.20, C4'; 127.89, C3'; 145.56, C1'; (Found: M^+ -32, 186.1051. Calc. for $C_{13}H_{14}O$: M^+, 186.1045; M^+ -73, 145.0602. Calc. for $C_{10}H_9O$: M^+, 145.0653,

base peak, detector overloaded); (Found: C, 76.70; H, 8.24. $C_{14}H_{18}O_2$ requires C, 77.03; H, 8.31%).

Reduction of 7-Methoxy-4-phenylhept-2-yn-4-ol (138) with Lithium Aluminium Hydride in 2,5-Dimethyltetrahydrofuran (refer to general procedure, page 113).

(a) The mixture of alkynol (138) (300 mg) and lithium aluminium hydride (57 mg) in 2,5-dimethyltetrahydrofuran (15 ml) was heated under reflux for 0.5 h. The crude product, isolated by means of ether, was adsorbed onto 5% deactivated alumina (30 g).

Elution with petroleum ether gave 7-methoxy-4-phenylhepta-2,3-diene (165) (145 mg), a colourless liquid; ν_{max} (liquid film) 1951, allene; 1599, 781, 748, 695, mono-substituted benzene; 1111 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CFT 20, $CDCl_3$) δ 1.73, d, $J_{Me,2}$ 6.7 Hz, 3H, $(H1)_3$; 1.78, tt, $J_{6,5}$ 7.2 Hz, $J_{6,7}$ 6.3 Hz, 2H, $(H6)_2$; 2.43, dt, $J_{5,6}$ 7.2 Hz, $J_{5,2}$ 3.4 Hz, 2H, $(H5)_2$; 3.32, s, 3H, CH_3-O-; 3.43, t, $J_{7,6}$ 6.3 Hz, 2H, $(H7)_2$; 5.40, tq, $J_{2,Me}$ 6.7 Hz, $J_{2,5}$ 3.4 Hz, 1H, H2; 7.06-7.43, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 14.35, C1; 26.32, C6; 28.02, C5; 58.56, CH_3-O-; 72.33, C7; 89.29, C2; 104.70, C4; 125.97, C2'; 126.41, C4'; 128.29, C3'; 137.39, C1'; 204.65, C3; (Found: M^+, 202.1359. Calc. for $C_{14}H_{18}O$: M^+, 202.1358); (Found: C, 83.19; H, 9.01. $C_{14}H_{18}O$ requires C, 83.12; H, 8.97%).

Elution with petroleum ether/ether (75:25) gave a fraction (33 mg) from which, on rechromatography, was obtained (Z)-7-methoxy-4-phenylhept-2-en-4-ol (166a) (25 mg) and the corresponding (E)-isomer (166b) (8 mg). The (Z)-alkenol (166a) (25 mg) was a viscous, colourless liquid; (Found: M^+, 220.1451. Calc. for $C_{14}H_{20}O_2$: M^+, 220.1463); ν_{max} (liquid film) 3460, OH; 1652, *cis*-CH=CH-; 1603, 765, 718, mono-substituted benzene;

1115, C-O-CH_3; ^{1}H n.m.r. (CCl_4) δ 1.27-2.07, m, 4H, $(H5)_2$, $(H6)_2$; 1.57, d, $J_{Me,2}$ 6 Hz, 3H, $(H1)_3$; 2.48, s, 1H, OH; 3.25, s, 3H, CH_3-O-; 3.28, t, $J_{7,6}$ 6 Hz, 2H, $(H7)_2$; 5.54, dq, $J_{2,3}$ 11.5 Hz, $J_{2,Me}$ 6 Hz, 1H, H2; 5.80, d, $J_{3,2}$ 11.5 Hz, 1H, H3; 7.07-7.53, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 14.44, C1; 23.99, C6; 42.44, C5; 58.46, CH_3-O-; 73.11, C7; 76.24, C4; 125.55, C2'; 126.26, C4'; 127.90, C3'; 128.02, C2; 136.97, C3; 147.52, C1'; ^{13}C n.m.r. (CD_3COCD_3) δ 14.65, C1; 24.72, C6; 42.69, C5; 58.31, CH_3-O-; 73.54, C7; 76.60, C4; 126.37, C2'; 126.66, 127.34, C2/C4', 128.42, C3'; 138.42, C3; 149.17, C1'; ^{13}C n.m.r. (CH_3OD) δ 14.79, C1; 24.91, C6; 42.52, C5; 58.57, CH_3-O-; 74.11, C7; 77.09, C4; 126.71, C2'; 127.17, 128.46, C2/C4'; 128.75, C3'; 138.03, C3; 148.80, C1'.

Continued elution with petroleum ether/ether (75:25) gave pure (E)-7-methoxy-4-phenylhept-2-en-4-ol (166b) (108 mg) as a viscous, colourless liquid; ν_{max} (liquid film) 3450, OH; 1664, 964, *trans* -CH=CH-; 1601, 764, 704, mono-substituted benzene; 1106 cm^{-1}, C-O-CH_3; ^{1}H n.m.r. (CCl_4) δ 1.20-2.05, m, 4H, $(H5)_2$, $(H6)_2$; 1.69, d, $J_{Me,2}$? Hz, 3H, $(H1)_3$; 2.86, s, 1H, OH; 3.20, s, 3H, CH_3-O-; 3.27, t, $J_{7,6}$ 6 Hz, 2H, $(H7)_2$; 5.27-5.93, degen. ABX_3, 2H, H2, H3; 7.08-7.50, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 17.72, C1; 23.92, C6; 39.55, C5; 58.29, CH_3-O-; 73.04, C7; 75.92, C4; 123.48, C2; 125.53, C2'; 126.34, C4'; 127.92 C3'; 137.91, C3; 146.56, C1'; (Found: M^+, 220.1459. Calc. for $C_{14}H_{20}O_2$: M^+, 220.1463); (Found: C, 76.54; H, 8.98. $C_{14}H_{20}O_2$ requires C, 76.33; H, 9.15%).

(b) Reaction of the alkynol (138) (300 mg) with lithium aluminium hydride (57 mg) in 2,5-dimethyltetrahydrofuran (15 ml) was stirred with heating at 65° for 1.25 h, then quenched with water. Chromatography of the crude product on 5% deactivated alumina (30 g) followed:

Elution with petroleum ether/ether (99:1) gave allene (165) (102 mg); identical (^{1}H n.m.r., infrared spectra) with an authentic sample.

Elution with petroleum ether/ether (70:30) gave a fraction containing (Z)-alkenol (166a) (11 mg), identical (^{1}H n.m.r., infrared spectra) with authentic material.

Continued elution with petroleum ether/ether (70:30) gave a fraction (54 mg), shown by ^{1}H n.m.r. to contain (Z)-alkenol (166a) (16 mg) and (E)-alkenol (166b) (38 mg).

Continued elution with petroleum ether/ether (70:30) gave pure (E)-alkenol (166b) (120 mg), identical (^{1}H n.m.r., infrared spectra) with authentic material.

Reduction of 7-Methoxy-4-phenylhept-2-yn-4-ol (138) with Lithium Aluminium Deuteride in 2,5-Dimethyltetrahydrofuran (refer to page 113).

(a) Reaction of alkynol (138) (400 mg) with lithium aluminium deuteride (85 mg), as in (a) above, gave a crude product which was separated into its components by chromatography on 5% deactivated alumina (30 g).

Elution with petroleum ether gave 2-deutero-7-methoxy-4-phenylhepta-2,3-diene (165) (186 mg) as a mobile, colourless liquid; (Found: M^+, 203.1422. Calc. for $C_{14}H_{17}DO$: M^+, 203.1420); ν_{max} (liquid film) 1942, allene; 1599, 763, 700, mono-substituted benzene; 1113 cm^{-1}, C-O-CH_3; ^{1}H n.m.r. (CFT 20, $CDCl_3$) δ 1.73, s, 3H, $(H1)_3$; 1.78, tt, $J_{6,5}$ 7.2 Hz, $J_{6,7}$ 6.3 Hz, 2H, $(H6)_2$; 2.45, t, $J_{5,6}$ 7.2 Hz, 2H, $(H5)_2$; 3.33, s, 3H, CH_3-O-; 3.43, t, $J_{7,6}$ 6.3 Hz, 2H, $(H7)_2$; 7.08-7.40, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) 14.24, C1; 26.34, C6; 28.08, C5; 58.56, CH_3-O-; 72.36, C7; 104.80, C4; 125.98, C2'; 126.44, C4'; 128.29, C3'; 137.42, C1'; 204.62, C3.

Elution with petroleum ether/ether (80:20) gave (Z)-3-deutero-7-methoxy-4-phenylhept-2-en-4-ol (166a) (6 mg) as a viscous, colourless oil; (Found: M^+, 221.1526. Calc. for $C_{14}H_{19}DO_2$: M^+, 221.1526); ν_{max} (liquid film) 3460, OH; 1642, >C=C<; 1604, 770, 708, mono-substituted benzene; 1111 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 1.27-2.07, m, 4H, $(H5)_2$, $(H6)_2$; 1.54, d, $J_{Me,2}$ 7 Hz, 3H, $(H1)_3$; 2.63, s, 1H, OH; 3.23, s, 3H, CH_3-O-; 3.28, t, $J_{7,6}$ 6 Hz, 2H, $(H7)_2$; 5.55, q, $J_{2,Me}$ 7 Hz, 1H, H2; 7.12-7.55, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 14.40, C1; 23.95, C6; 42.34, C5; 58.43, CH_3-O-; 73.09, C7; 76.14, C4; 125.52, C2'; 126.24, C4'; 127.89, C3' + C2; 147.52, C1'; ^{13}C n.m.r. (CH_3OD) δ 14.72, C1; 24.91, C6; 42.47, C5; 58.55, CH_3-O-; 74.11, C7; 77.03, C4; 126.70, C2'; 127.17, C4'; 128.31, C2; 128.76, C3'; 138.00, small triplet; 148.79, C1'.

Continued elution with petroleum ether/ether (80:20) gave a mixture (93 mg) shown by ^1H n.m.r. to contain (Z)-deutero-alkenol (166a) (30 mg) and (E)-deutero-alkenol (166b) (63 mg) (see below).

Continued elution with petroleum ether/ether (80:20) gave (E)-3-deutero-7-methoxy-4-phenylhept-2-en-4-ol (166b) (104 mg) as a viscous, colourless liquid; (Found: M^+, 221.1526. Calc. for $C_{14}H_{19}DO_2$: M^+, 221.1526); ν_{max} (liquid film) 3455, OH; 1656, >C=C<; 1603, 767, 704, mono-substituted benzene; 1110 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 1.20-2.07, m, 4H, $(H5)_2$, $(H6)_2$; 1.69, d, $J_{Me,2}$ 6.5 Hz, 3H, $(H1)_3$; 2.93, s, 1H, OH; 3.20, s, 3H, CH_3-O-; 3.25, t, $J_{7,6}$ 6 Hz, 2H, $(H7)_2$; 5.59, q, $J_{2,Me}$ 6.5 Hz, 1H, H2; 7.08-7.50, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 17.64, C1; 23.89, C6; 39.47, C5; 58.22, CH_3-O-; 73.01, C7; 75.81, C4; 123.30, C2; 125.51, C2'; 126.29, C4'; 127.92, C3'; 137.81, very small triplet; 146.54, C1'.

(b) Reduction of alkynol (138) (400 mg) with lithium aluminium deuteride (85 mg), as in (b) above, gave a crude product which was chromatographed on 5% deactivated alumina (30 g).

Elution with petroleum ether gave deutero-allene (165) (126 mg), identical (^{1}H n.m.r., infrared spectra) with authentic material.

Elution with petroleum ether/ether (80:20) gave 3 initial fractions (77 mg in total), shown by ^{1}H n.m.r. to be mixtures of (Z)-3-deutero alkenol (166a) (34 mg) and (E)-3-deutero alkenol (166b) (43 mg).

Continued elution with petroleum ether/ether (80:20) gave (E)-3-deutero alkenol (166b) (187 mg), identical (^{1}H n.m.r., ^{13}C n.m.r.) with an authentic sample.

Reduction of 7-methoxy-4-phenylhept-2-yn-4-ol (138) with Lithium Aluminium Hydride in Tetrahydrofuran (refer to page 113).

(a) Lithium aluminium hydride (77 mg) reduction of alkynol (138) (400 mg) was carried out in refluxing tetrahydrofuran, and quenched with water after 1.25 h. Chromatography of the crude product on 5% deactivated alumina (30 g) gave the following products: (1) allene (165) (81 mg), eluted with petroleum ether, identical with an authentic sample; (2) two unidentified compounds (total 10 mg), eluted with petroleum ether/ether (90:10); (3) unidentified compound (8 mg), eluted with petroleum ether/ether (80:20); (4) (E)-alkenol (166b) (300 mg), identical (^{1}H n.m.r.) with authentic material, eluted with petroleum ether/ether (70:30).

(b) The alkynol (138) (400 mg) was treated in the same manner as above except that the reaction time was extended to 4 h. The crude product, isolated by means of ether, was

adsorbed onto 5% deactivated alumina (25 g). The products were (1) allene (165) (48 mg), identical (^{1}H n.m.r. infrared spectra) with an authentic sample; (2) two unidentified compounds (total 45 mg), eluted with petroleum ether/ether (98:2); (3) unidentified compound (27 mg), eluted with petroleum ether/ether (90:10); (4) (E)-Alkenol (166b) (285 mg), identical (^{1}H n.m.r., infrared spectra) with an authentic sample, eluted in petroleum ether/ether (70:30).

(c) Alkynol (138) (400 mg) was reduced by lithium aluminium hydride (77 mg) in tetrahydrofuran (20 ml) at 35° for 2.75 h, after which time the reaction mixture was quenched with deuterium oxide. Chromatography of the crude product on 5% deactivated alumina gave the following materials: (1) allene (165) (7 mg), identical (^{1}H n.m.r.) with an authentic sample, eluted in petroleum ether/ether (99:1); (2) unidentified ccmpound(s) (9 mg), eluted in petroleum ether/ether (90:10); (3) 2-deutero and 3-deutero (E)-alkenols (166b) (83 mg) as a mixture (61:24) as a viscous, colourless liquid; (Found: M^+, 221.1526. Calc. for $C_{14}H_{19}DO_2$: M^+ 221.1526); ν_{max} (liquid film) 3455, OH; 1656, >C=C<; 1603, 767, 704, mono-substituted benzene; 1110 cm^{-1}, C-O-CH_3; ^{13}C n.m.r. ($CDCl_3$) (2-deutero) δ 17.60, C1; 23.99, C6; 39.70, C5; 58.39, CH_3-O-; 73.09, C7; 75.92, C4; 123.51, small triplet; 125.51, C2'; 126.37, C4'; 127.98, C3'; 137.76, C3; 146.54, C1'; ^{1}H n.m.r. (CCl_4) (2-deutero) δ 1.22-2.07, m, 4H, $(H5)_2$, $(H6)_2$; 1.70, s, 3H, $(H1)_3$; 2.52, s, 1H, OH; 3.22, s, 3H, CH_3-O-; 3.27, t, $J_{7,6}$ 6 Hz, 2H, $(H7)_2$; 5.62, s, 1H, H3; 6.98-7.42, m, 5H, aromatic protons; (4) continued elution with petroleum ether/ether (70:30) gave unreacted alkynol (138) (303 mg), identical (^{1}H n.m.r.) with authentic sample.

Reduction of 7-methoxy-4-phenylhept-2-yn-4-ol (138) with Lithium Aluminium Deuteride in Tetrahydrofuran (refer to page 113).

(a) Reaction of alkynol (138) (400 mg) with lithium aluminium deuteride, as in (a) above, gave a crude product which was chromatographed on 5% deactivated alumina (30 g) to give: (1) deutero allene (165) (58 mg), identical (^{1}H n.m.r., infrared spectra) with an authentic sample; (2) unidentified compound(s) (13 mg); (3) (E)-3-deutero alkenol (166b) (319 mg), identical (^{1}H n.m.r., infrared spectra, ^{13}C n.m.r.) with an authentic sample.

(b) Alkynol (138) (400 mg) was reduced in tetrahydrofuran by lithium aluminium deuteride, as in (b) above, gave a crude product which on chromatography on 5% deactivated alumina (30 g) yielded: (1) deutero allene (165) (48 mg); (2) unidentified compound(s) (28 mg); (3) unidentified compound (30 mg); (4) (E)-3-deutero alkenol (166b) (301 mg), identical (^{1}H n.m.r., ^{13}C n.m.r., infrared spectra) with authentic material.

Reduction of 7-methoxy-4-phenylhept-2-yn-4-ol (138) with Lithium Aluminium Hydride in Diethyl Ether (refer to page 113).

(a) Alkynol (138) (450 mg) was reduced by lithium aluminium hydride (87 mg) in diethyl ether (22.5 ml) refluxed for 2.75 h, when the reaction was quenched with deuterium oxide. The components of the crude product, after chromatography on 5% deactivated Al_2O_3 (40 g) were: (1) allene (165) (40 mg), identical (^{1}H n.m.r., infrared spectra) with authentic material; (2) (E)-2-deutero alkenol (166b) (22 mg), identity confirmed by ^{1}H n.m.r.; (3) unreacted alkynol (138) (377 mg), identical (^{1}H n.m.r.) with authentic material.

(b) Reaction of alkynol (138) (300 mg) with lithium aluminium hydride (57 mg) in refluxing diethyl ether (15 ml) was quenched after 93 h with water. The crude product was separated into its components by chromatography on 5% deactivated alumina (35 g): (1) unidentified compound (31 mg); (2) allene (165) (67 mg); (3) unidentified compound (5 mg); (4) (Z)-alkenol (166a) (43 mg); (5) (E)-alkenol (166b) (157 mg); identities confirmed by ^{1}H n.m.r. and infrared spectra.

5.4 EXPERIMENTAL RELATING TO CHAPTER 4

Reduction of 2,2-Di-(methoxymethyl)-3-phenylhex-4-yn-3-ol (98) with Lithium Aluminium Hydride in Benzene.

A solution of alkynol (98) (500 mg) in benzene (15 ml) was added to a suspension of lithium aluminium hydride (80 mg) in benzene (10 ml) and the mixture refluxed for 0.75 h under nitrogen. The reaction was cooled and quenched with water, the crude product isolated be means of ether and separated into its components by chromatography on 5% deactivated alumina (40 g). The products were: (1) alkene (117) (12 mg); (2) allene (113) (196 mg); (3) (E)-alkenol (114) (234 mg); (4) alkynol (98) (44 mg); all compound identities, Block A, authentic by ^{1}H n.m.r., infrared spectra.

Reduction of 2,2-Di-(methoxymethyl)-3-phenylhex-4-yn-3-ol (98) with Lithium Aluminium Deuteride in Benzene.

The alkynol (98) (500 mg) was reacted in benzene (25 ml) with lithium aluminium deuteride (88 mg) in the same manner as above. The crude product was chromatographed on 5% deactivated alumina (45 g). The products isolated were: (1) Trideutero alkene (117) (8 mg); (2) monodeutero allene (113) (168 mg); (3) 4-deutero and 5-deutero (E)-alkenols (114) (248 mg) as a mixture (10:45); (5) unreacted alkynol (98) (54 mg); all samples identical (^{1}H n.m.r., infrared spectra) with authentic compounds.

Reduction of 1-Methoxy-2,2-dimethyl-3-phenylhex-4-yn-3-ol (90b) with Lithium Aluminium Hydride in Benzene.

(a) A solution of alkynol (90b) (400 mg) in benzene (15 ml) was added to a suspension of lithium aluminium hydride (72 mg) in benzene (5 ml) and the mixture refluxed for 0.75 h

under an atmosphere of nitrogen. The reaction was quenched with water and the crude product, isolated by means of ether, adsorbed onto 5% deactivated alumina (35 g).

Elution with petroleum ether gave allene (91b), Block A, (185 mg), identical (^{1}H n.m.r., infrared spectra) with authentic material.

Elution with petroleum ether/ether (95:5) gave (E)-alkenol (92b) (80 mg), identical (^{1}H n.m.r., infrared spectra) with authentic material.

Elution with ether gave unreacted alkynol (90b) (120 mg), identical (^{1}H n.m.r., infrared spectra) with an authentic sample.

(b) Alkynol (90b) (500 mg) was reduced by lithium aluminium hydride (90 mg) in the same manner as (a) above, except the reaction was quenched by deuterium oxide after 0.75 h, not water. The crude product was separated into its components by chromatography on 5% deactivated alumina (35 g). The products were: (1) allene (91b) (244 mg); (2) 5-deutero and 4-deutero (E)-alkenols (92b) (103 mg) as a mixture (10:18); (3) unreacted alkynol (90b) (136 mg).

Preparation of Pivalophenone (169)[99]

(1) Phenyl Magnesium Bromide[98]

In a 250 ml three-necked round-bottom flask fitted with a reflux condenser, a dropping funnel and a nitrogen gas inlet was added magnesium (4.8 g, 0.2 mole) and the whole system flushed with dried nitrogen for about 10 min. A crystal of iodine and sodium dried ether (25 ml) was added to cover the magnesium. Approximately twenty millilitres of a mixture of bromobenzene (31.4 g; 21 ml; 0.2 mole) and Na-dried ether (80 ml) was then run in and the flask swirled and warmed gently to initiate the reaction. Magnetic stirring was started

and the remainder of the ethereal bromo-benzene added at such a rate as to keep the reaction boiling gently without external heating. When the addition was complete, the reaction mixture was refluxed gently on a water bath for 15 minutes, after which time most of the magnesium had disappeared.

(2) Pivalophenone (169)[99]

In a 500 ml three-necked round-bottom flask fitted with a dropping funnel was placed pivaloyl chloride (24.1 g; 24 ml; 0.2 mole) and dry ether (50 ml), (see Scheme 33). Phenyl magnesium bromide (0.2 mole) [prepared as above] was added slowly with stirring and ice-bath cooling. When the addition was complete (approx. 20 min) the mixture was stirred for 6 hours at room temperature. Workup involved washing the ethereal layer with ice-water (2 x 100 ml), saturated sodium bicarbonate (3 x 100 ml), water (100 ml) and drying over magnesium sulphate. The crude ketone (29 g) was purified by chromatography on 5% deactivated alumina (1.5 kg).

Elution with petroleum ether/ether (98:2) gave pivalophenone (169) (17.8 g; 55%), (lit.[99] 40%) as a colourless oil; ν_{max} (liquid film) 1680, aryl ketone; 1600, 720, 701 cm^{-1}, mono-substituted benzene; ^1H n.m.r. (CCl_4) δ 1.32, s, 9H, $C(CH_3)_3$; 7.19-7.38, m, 3H, meta and para aromatic protons; 7.56-7.73, m, 2H, ortho aromatic protons.

2,2-Dimethyl-3-phenylhex-4-yn-3-ol (90a)

To a solution of propynyllithium at -30° [prepared from propyne (32 ml, 0.54 mole) and 1-butyllithium (0.14 mole) in dry ether (350 ml)] was added dropwise pivalophenone (169) (17 g; 0.11 mole) in dry ether (50 ml) and the resulting mixture was stirred at room temperature for 20 h. Treatment of the cooled reaction mixture with saturated ammonium

chloride (200 ml), and isolation by means of ether (3 x 300 ml) gave a crude product (30 g) which was purified by chromatography on 5% deactivated alumina (1.4 kg).

Elution with petroleum ether/ether (80:20) gave the pure alkynol (90a) (20.5 g; 92%) as a viscous, colourless oil; ν_{max} (liquid film) 3500, OH; 2240, alkyne; 1602, 752, 706 cm^{-1}, mono-substituted benzene; ^{1}H n.m.r. (CCl_4) δ 1.10, s, 9H, C-$(CH_3)_3$; 1.91, s, 4H, $(H6)_3$, OH; 7.08-7.58, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 3.52, C6; 25.49, C-$(CH_3)_3$; 39.41, C2; 78.96, C3; 81.54, 82.51, C5/C4; 126.89, C2'; 127.09, C4'; 127.73, C3'; 142.76, C1'; (Found: C, 83.09; H, 8.64. $C_{14}H_{18}O$ requires C, 83.17; H, 8.91%).

Reduction of 2,2-Dimethyl-3-phenylhex-4-yn-3-ol (90a) with Lithium Aluminium Hydride in Benzene.

The alkynol (90a) (500 mg) in benzene (15 ml) was added to a suspension of lithium aluminium hydride (103 mg) in the same solvent (10 ml). The mixture was stirred and heated under reflux for 2.5 h. Quenching with water gave a crude product which was essentially pure unreacted starting alkynol (90a) (500 mg); identical (^{1}H n.m.r., ^{13}C n.m.r., infrared spectra) with authentic material, (see Block A).

2-Phenylpent-3-yn-2-ol (18)

Crude alkynol (18)[100] was purified by crystallization from hexane to yield pure 2-phenylpent-3-yn-2-ol (18), white crystals, m.p. 40.5-42° (lit.[104] m.p. 41-42.5°); ν_{max} (liquid film) 3450, OH; 2250, alkyne; 1602, 770, 705 cm^{-1}, mono-substituted benzene; ^{1}H n.m.r. (CCl_4) δ 1.63, s, 3H, $(H1)_3$; 1.88, s, 3H, $(H5)_3$; 2.10, s, 1H, OH; 7.17-7.65, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 3.39, C5; 33.43, C1; 69.82, C2; 80.70, C4; 83.41, C3; 125.06, C2'; 127.25, C4'; 128.03, C3'; 146.37, C1'.

Reduction of 2-Phenylpent-3-yn-2-ol (18) with Lithium Aluminium Hydride in Benzene.

(a) A solution of alkynol (18) (500 mg) in benzene (15 ml) was added to a suspension of lithium aluminium hydride (130 mg) in benzene (10 ml). The stirred mixture was refluxed under an atmosphere of nitrogen for 0.75 h, after which time it was quenched with water. Extraction with ether gave a crude product which was subsequently adsorbed onto florisil (70 g).

Elution with petroleum ether gave 2-phenylpenta-2,3-diene (74) (44 mg); Block B, a pungent smelling, mobile, colourless oil; (Found: M^+, 144.0939. Calc. for $C_{11}H_{12}$: M^+, 144.0936); ν_{max} (liquid film) 1958, allene; 1600, 782, 753, 700, mono-substituted benzene; 1493, 1445 cm^{-1}, C-H; ^1H n.m.r. (CCl_4) δ 1.79, d, $J_{Me,4}$ 6 Hz, 3H, $(H5)_3$; 2.08, d, $J_{Me',4}$ 3 Hz, 3H, $(H1)_3$; 5.38, qq, $J_{4,Me}$ 6 Hz, $J_{4,Me'}$ 3 Hz, 1H, H4; 7.10-7.36, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 14.26, C5 ; 17.09, C1; 87.50, C4; 99.80, C2; 125.71, C2'; 126.36, C4'; 128.34, C3'; 137.85, C1' ; 205.03, C3.

Elution with petroleum ether/ether (98:2) gave (E)-2-phenylpent-3-en-2-ol (72)(10 mg) as a viscous, colourless, oil; (Found: M^+, 162.1045. Calc. for $C_{11}H_{14}O$: M^+, 162.1045); ν_{max} (liquid film) 3400, OH; 1665, 965, *trans* -CH=CH-; 1600, 765, 701 cm^{-1}, mono-substituted benzene; ^1H n.m.r. (CCl_4) δ 1.58, s, 3H, $(H1)_3$; 1.68, d, $J_{Me,4}$ approx. 5 Hz, 3H, $(H5)_3$; 2.23, s, 1H, OH; 5.25-5.95, m, 2H, H3 and H4; 7.05-7.50, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 17.67, C5; 29.84, C1; 74.41, C2; 123.71, C4; 125.25, C2'; 126.74, C4'; 128.10, C3'; 138.31, C3 ; 147.35, C1'.

Continued elution with petroleum ether/ether (98:2) gave 2 fractions containing (E)-alkenol (72) (14 mg) and unreacted

alkynol (18) (35 mg).

Continued elution with petroleum ether/ether (98:2) gave unreacted alkynol (18) (266 mg), identical (^{1}H n.m.r., ^{13}C n.m.r., infrared spectra) with an authentic sample.

(b) Reaction of alkynol (18) (500 mg) in the same manner as (a) above, except with deuterium oxide quenching gave a crude product which was separated into its components by similar chromatography on florisil (70 g) to yield:

(1) allene (74) (45 mg); identical (^{1}H n.m.r., infrared spectra) with an authentic sample.

(2) (E)-4-deutero-2-phenylpent-3-en-2-ol (72) (23 mg); a viscous, colourless oil; (Found: M^+, 163.1107. Calc. for $C_{11}H_{13}DO$: M^+, 163.1107); ν_{max} (liquid film) 3470, OH; 1655, C=C; 1600, 762, 700 cm^{-1}, mono-substituted benzene; ^{1}H n.m.r. (CCl_4) δ 1.50, s, 1H, OH; 1.55, s, 3H, $(H1)_3$; 1.72, s, 3H, $(H5)_3$; 5.78, s, 1H, H3; 7.13-7.45, m, 5H, aromatic protons.

Reduction of 1-Methoxy-2-phenylpent-3-yn-2-ol (136) with Lithium Aluminium Hydride in Benzene.

(a) To a suspension of lithium aluminium hydride (66 mg) in benzene (6 ml) was added a solution of the alkynol (136) (300 mg) in benzene (3 ml). More solvent was added (6 ml) and the mixture heated under reflux for 0.75 h under an atmosphere of nitrogen. The reaction was quenched with water and the crude product, isolated by means of ether, was subsequently adsorbed onto 5% deactivated alumina (25 g).

Elution with petroleum ether gave a 1:1 mixture of (E)-(143a) and (Z)-(143b) dienes (44 mg), identical (^{1}H n.m.r., ultraviolet spectra) with an authentic sample, see Block B.

Elution with petroleum ether/ether (95:5) gave 1-methoxy-2-phenylpenta-2,3-diene (144) (6 mg), a mobile,

colourless oil; (Found: M^+, 174.1046. Calc. for $C_{12}H_{14}O$: M^+, 174.1045); ν_{max} (liquid film) 1950, allene; 1600, 763, 700, mono-substituted benzene; 1093 cm^{-1}, C-O-CH_3; ^1H n.m.r. (CCl_4) δ 1.82, d, $J_{Me,4}$ 7 Hz, 3H, $(H5)_3$; 3.28, s, 3H, CH_3-O-; 4.28, s, 2H, $(H1)_2$; 5.46, q, $J_{4,Me}$ 7 Hz, 1H, H4; 7.10-7.48, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 14.05, C5; 57.33, CH_3-O-; 72.38, C1; 88.63, C4; 101.78, C2; 126.33, C2'; 126.75, C4'; 128.39, C3'; 135.45, C1'; 206.08, C3.

Elution with petroleum ether/ether (80:20) gave (E)-alkenol (142) (215 mg), identical (^1H n.m.r., infrared spectra) with an authentic sample.

Elution with petroleum ether/ether (50:50) gave unreacted alkynol (136) (20 mg), identical (^1H n.m.r.) with an authentic sample.

(b) The alkynol (136) (400 mg) was treated in the same manner as above except that the reaction mixture was quenched with deuteride oxide. The crude product was chromatographed on 5% deactivated alumina (25 g) and gave: (1) (E)-(143a) and (Z)-(143b) dienes (40 mg) as a (1:1) mixture, identical (^1H n.m.r., infrared and ultraviolet spectra) with an authentic sample; (2) allene (144) (12 mg), identical (^1H n.m.r., infrared spectra) with an authentic sample; (3) 4-deutero and 3-deutero (E)-alkenols (142) (280 mg) as a mixture (35:44), identical (^1H n.m.r., ^{13}C n.m.r., infrared spectra) with an authentic sample; (4) unreacted starting alkynol (136) (50 mg), identical (^1H n.m.r.) with an authentic sample.

Reduction of 1-Methoxy-2-phenylpent-3-yn-2-ol (136) with Lithium Aluminium Deuteride in Benzene.

The alkynol (136) (400 mg) in benzene (6 ml) was added to a suspension of lithium aluminium deuteride (97 mg) in

benzene (8 ml). The volume of solvent was made up to 20 ml, and the reaction mixture heated under reflux for 0.75 h. The reaction quenched with water and the crude product adsorbed onto 5% deactivated alumina (25 g).

Elution with petroleum ether gave a (1:1) mixture of (E)-(143a) and (Z)-(143b) dideutero dienes (3 mg), (^{1}H n.m.r.).

Elution with petroleum ether/ether (95:5) gave 4-deutero-1-methoxy-2-phenylpenta-2,3-diene (144) (43 mg) as a mobile, colourless oil; (Found M^+, 175.1101. Calc. for $C_{12}H_{13}DO$: M^+, 175.1107); ν_{max} (liquid film) 1950, allene; 1603, 773, 703, mono-substituted benzene; 1097 cm^{-1}, C-O-CH_3; ^{1}H n.m.r. (CCl_4) δ 1.82, s, 3H, $(H5)_3$; 3.28, s, 3H, CH_3-O-; 4.29, s, 2H, $(H1)_2$; 7.08-7.48, m, 5H, aromatic protons; ^{13}C n.m.r. ($CDCl_3$) δ 13.96, C5; 57.30, CH_3-O-; 72.36, C1; 87.14, (small triplet); 101.83, C2; 126.33, C2'; 126.76, C4'; 128.39, C3'; 135.41, C1'; 206.09, C3.

Elution with petroleum ether/ether (80:20) gave 3-deutero and 4-deutero (E)-alkenols (142) (227 mg) as a mixture (32:47), identical (^{1}H n.m.r., ^{13}C n.m.r., infrared spectra) with an authentic sample.

Elution with petroleum ether/ether (50:50) gave unreacted alkynol (136) (120 mg), identical (^{1}H n.m.r.) with an authentic sample.

Reduction of 1-Methoxy-3-phenylhex-4-yn-3-ol (137) with Lithium Aluminium Hydride in Benzene.

To a suspension of lithium aluminium hydride (124 mg) in benzene (10 ml) was added a solution of the alkynol (137) (600 mg) in benzene (20 ml). The mixture was stirred under reflux for 0.75 h under an atmosphere of nitrogen. The reaction was quenched with deuterium oxide, and the crude product, isolated by means of ether, was chromatographed on

5% deactivated alumina (30 g). The products isolated were: see Block B, (1) allene (151) (125 mg), identical (^{1}H n.m.r., infrared spectrum) with authentic material; (2) 5-deutero and 4-deutero (E)-alkenols (150) (144 mg) as a mixture (27:21), identical (^{1}H n.m.r., ^{13}C n.m.r., infrared spectra) with authentic material; (3) unreacted alkynol (137) (306 mg); identical (^{1}H n.m.r.) with authentic material.

Reduction of 7-Methoxy-4-phenylhept-2-yn-4-ol (138) with Lithium Aluminium Hydride in Benzene.

To a suspension of lithium aluminium hydride (57 mg) in benzene (5 ml) was added a solution of the alkynol (138) (300 mg) in benzene (10 ml). After 0.75 h heating under reflux, the reaction was quenched with water. Chromatography of the crude product on 5% deactivated alumina (30 g) gave: (1) allene (165) (123 mg); (2) (Z)-alkenol (166a) (30 mg); (3) (E)-alkenol (166b) (100 mg); (4) unreacted alkynol (138) (45 mg); identities confirmed by ^{1}H n.m.r. and infrared spectra, see Block B for structures.

Reduction of 7-Methoxy-4-phenylhept-2-yn-4-ol (138) with Lithium Aluminium Deuteride in Benzene.

Reaction of alkynol (138) (400 mg) with lithium aluminium deuteride (85 mg) in refluxing benzene (20 ml) was quenched with water after 0.75 h. The components of the crude product, isolated by means of ether, were separated by chromatography on 5% deactivated alumina (30 g): (1) deutero allene (165) (140 mg); (2) 3-deutero and 2-deutero (Z)-alkenols (166a) (35 mg) as a mixture (10:1); (3) 3-deutero and 2-deutero (E)-alkenols (166b) (130 mg) as a mixture (36:4); (4) unreacted alkynol (138) (80 mg); identities confirmed by ^{1}H n.m.r. and infrared spectra.

APPENDIX

For monodeutero alkenols, arising from reactions of alkynols either with lithium aluminium deuteride followed by H_2O quenching or with lithium aluminium hydride followed by D_2O quenching, the ratios of deuterium present on near C:far C* were determined from a comparison of the peak intensities of the protonated alkene-carbons in the repetitive-pulse Fourier-transform ^{13}C n.m.r. spectra of monodeuteriated products, all obtained under near-identical conditions to minimize effects due to possible differences in relaxation times. The ratios of hydride (deuteride) attack at near:far of the alkynol in the formation of the alkenols are given in Tables 1-7, as are overall near:far attack ratios.

Intensity variations in ^{13}C FT spectra are attributable to four major causes:[105]

(a) There may be variations in the relaxation times of the carbon atoms in the molecule.

(b) There may be differential NOE for the different carbon resonances in the molecule.

(c) The RF pulse may not have sufficient power to irradiate all the nuclei equally effectively.

(d) The computer may have insufficient storage (i.e. data points) to completely define all the peaks.

The fact that both carbons were olefinic and protonated meant that their comparative Nuclear Overhauser Effects could be considered to be identical, as would be their relaxation times. For the ^{13}C n.m.r. FT instrument used,

---

* Near-C; alkyne carbon adjacent to carbinol carbon.
Far-C; more remote alkyne carbon.

point (c) above represented no problem. The fourth cause of error represented a more significant problem. The computer used had 16 K data points but only 8 K are, in fact, real in an FT run. For the fully protonated (E)-alkenol (114), Block A, the peak heights of the olefinic carbons at δ 133.79 and 124.34 should be identical. It was discovered, however, that on two separate occasions, using identical computer parameters, that the respective ratios varied from 3:4 to 2:1 on the other extreme. This problem was overcome by using:

(1) zero filling so that 16 K data points were now available to describe the spectrum, and

(2) the sensitivity enhancement value was changed from its usual value of -1.0 to -0.2.

The net result of these changes in technique was such that all fully protonated alkenols subsequently run gave, as should be expected, olefinic carbons of equal intensity.

It is fortunate that this technique has, in fact, been utilized rather than that of determining ^{1}H n.m.r. integrals, for although the alkenols (114) and (92b), Block A, gave olefinic protons of sufficient separation for ^{1}H n.m.r. integration to be useful, similar evaluation of alkenols (142), (150) and (166), Block B, would have been impossible.

It must be noted that in almost all instances the ^{13}C n.m.r. spectra were run in $CDCl_3$. Unfortunately, for (E)-alkenol (142), the C4 signal at δ 125.64 was in such close proximity to the aromatic carbons at δ 125.72 that its intensity could not be measured with confidence. For this reason a solvent change to d_6-acetone was employed, which served to shift the C4 olefinic peak sufficiently to be clear of the aromatic carbons. Similarly, D1-methanol was required to shift

the C2 olefinic peak of (Z)-alkenol (166a), Block B, sufficiently from the proximate aromatic carbons. Fortunately any ambiguity which may have arisen was resolved by the fact that the monodeutero alkenol (166a) was almost always deuteriated exclusively at C3, the olefinic carbon at δ 138.03 being no longer apparent in the deuteriated material.

REFERENCES

(1) A.E. Finholt, A.C. Bond, Jr., and H.I. Schlesinger, *J. Am. Chem. Soc.*, 1947, 69, 1199.

(2) R.F. Nystrom, and W.G. Brown, *J. Am. Chem. Soc.*, 1947, 69, 1197, 2548.

(3) G. Gustavson, and N. Demjanof, *J. Prakt. Chem.*, 1888, 38(2), 202.

(4) H.N. Cripps, and E.F. Kiefer, *Org. Syn.*, 1962, 42, 12.

(5) J.H. van't Hoff, "La Chemie dans l'Espace," P.M. Bazendijk, Rotterdam, 1875, p29.

(6) W.D. Celmer, and I.A. Solomons, *J. Am. Chem. Soc.*, 1952, 74, 1870.

(7) R. Bonnett, A.A. Spark, J.L. Tee, and B.C.L. Weedon, *Proc. Chem. Soc.*, 1964, 419.

(8) A.K. Mallams, E.S. Waight, B.C.L. Weedon, L. Cholnoky, K. Györgyfy, J. Szabolcs, N.I. Krinsky, B.P. Schimmer, C.O. Chichester, T. Katayama, L. Lowry, and H. Yokayama, *J. Chem. Soc. Chem. Commun.*, 1967, 484.

(9) M.O. Bagby, C.R. Smith, and I.A. Wolff, *Chem. and Ind.*, 1964, 1861.

(10) J. Meinwald, K. Erickson, M.P. Hartshorn, Y.C. Meinwald, and T. Eisner, *Tetrahedron Lett.*, 1968, 2959.

(11) W.J. Bailey, and C.R. Pfeifer, *J. Org. Chem.*, 1955, 20, 1337.

(12) P.D. Landor, S.R. Landor, and E.S. Pepper, *J. Chem. Soc. C*, 1967, 185.

(13) T. Miki, and Y. Hara, *Chem. Pharm. Bull.*, 1956, 4, 85.

(14) A.C. Day, and M.C. Whiting, *J. Chem. Soc. B*, 1967, 991.

(15) J.S. Cowie, P.D. Landor, and S.R. Landor, *J. Chem. Soc. Chem. Commun.*, 1969, 541.

(16) A. Claesson, and C. Bogentoft, *Acta Chem. Scand. B*, 1972, 26, 2540.

(17) J.S. Cowie, P.D. Landor, and S.R. Landor, *J. Chem. Soc., Perkin Trans. I*, 1973, 720.

(18) E. Galantay, I. Basco, and R.V. Coombs, *Synthesis*, 1974, 344.

(19) A. Claesson, L-I. Olsson, G.R. Sullivan, and H.S. Mosher, *J. Am. Chem. Soc.*, 1975, 97, 2919.

(20) A. Claesson, L-I. Olsson, and C. Bogentoft, *Acta Chem. Scand.*, 1973, 27, 2941.

(21) J.R. Hlubucek, J.Hora, S.W. Russell, T.P. Toube, and B.C.L. Weedon, *J.Chem.Soc., Perkin Trans. I*, 1974, 848.

(22) L-I. Olsson, and A. Claesson, *Acta Chem. Scand. B*, 1977, 31, 614.

(23) A. Claesson, and L-I. Olsson, *J. Am. Chem. Soc.*, 1979, 101, 7303.

(24) G.E. Keck, and R.R. Webb, *Tetrahedron Lett.*, 1982, 23 (30), 3051.

(25) L-I. Olsson, A. Claesson, and C. Bogentoft, *Acta Chem. Scand. B*, 1974, 28, 765.

(26) L.A. Van Dijck, K.H. Schönemann, and F.J. Zeelen, *Recl. Trav. Chim. Pays-Bas*, 1969, 88, 254.

(27) M.P. Hartshorn, R.S. Thompson, and J. Vaughan, *Aust. J. Chem.*, 1977, 30, 865.

(28) M.P. Hartshorn, R.S. Thompson, and J. Vaughan, unpublished results.

(29) Y. Fujimoto, M. Morisaki, and N. Ikekawa, *J. Chem. Soc., Perkin Trans. I*, 1975, 2303.

(30) L.G. Damm, M.P. Hartshorn, and J. Vaughan, *Aust. J. Chem.*, 1976, 29, 1017.

(31) The S_N2' reactions of certain allylic ethers with $LiAlH_4$ should have carbanion-like transition states; A. Claesson, *Acta Chem. Scand. B*, 1974, 28, 993.

(32) T.E. De Ville, M.B. Hursthouse, S.W. Russell, and B.C.L. Weedon, *J. Chem. Soc. Chem. Commun.*, 1969, 754.

(33) C.J. Elsevier, J. Meijer, H. Westmijze, P. Vermeer, and L.A. Van Dijck, *J. Chem. Soc. Chem. Commun.*, 1982, 84.

(34) L.A. Van Dijk, B.J. Lankwerden, and J.G.C.M. Vermeer, *Recl. Trav. Chim. Pays-Bas*, 1979, 98, 553.

(35) L.A. Van Dijk, B.J. Lankwerden, J.G.C.M. Vermeer, and A.J.M. Weber, *Recl. Trav. Chim. Pays-Bas*, 1971, 90, 801.

(36) G. Lowe, *J. Chem. Soc. Chem. Commun.*, 1965, 411.

(37) J.H. Brewster, *J. Am. Chem. Soc.*, 1959, 81, 5475.

(38) W.T. Borden, and E.J. Corey, *Tetrahedron Lett.*, 1969, 5, 313.

(39) J.D. Chanley, and H. Sabotka, *J. Am. Chem. Soc.*, 1949, 71, 4140.

(40) R.A. Raphael, and F. Sondheimer, *J. Chem. Soc.*, 1950, 153, 3185.

(41) K.R. Bharucha, and B.C.L. Weedon, *J. Chem. Soc.*, 1953, 156, 1584.

(42) E.B. Bates, E.R.H. Jones, and M.C. Whiting, *J. Chem. Soc.*, 1954, 157, 1854.

(43) J. Attenburrow, A.F.B. Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A.B.A. Jansen, and T. Walker, *J. Chem. Soc.*, 1952, 155, 1095.

(44) W.T. Borden, *J. Am. Chem. Soc.*, 1968, 90, 2197.

(45) W.T. Borden, *J. Am. Chem. Soc.*, 1970, 92, 4898.

(46) J. Ralph, B.Sc. Hons. report, 1976, University of Canterbury.

(47) T.S. Lee, Masters Thesis, 1976, University of Canterbury.

(48) B. Grant, and C. Djerassi, *J. Org. Chem.*, 1974, 39, 968.

(49) H.G. Kuivila, W. Rahman, and R.H. Fish, *J. Am. Chem. Soc.*, 1965, 87, 2835.

(50) B. Franzus, and E.I. Snyder, *J. Am. Chem. Soc.*, 1965, 87, 3423.

(51) E.I. Snyder, *J. Org. Chem.*, 1967, 32, 3531.

(52) G. Maccagnani, and F. Taddei, *Boll. Sci. Fac. Chim. Ind. Bologna*, 1968, 26, 83; *Chem. Abstr.*, 1968, 69, 86143 h.

(53) D.H. Hunter, and D.J. Cram, *J. Am. Chem. Soc.*, 1966, 88, 5765.

(54) J.J. Christensen, J.O. Hill, and R.M. Izatt, *Science*, 1971, 174, 459.

(55) J.W. Blunt, M.P. Hartshorn, M.H.G. Munro, T.S. Lee, R.S. Thompson, and J. Vaughan, *J. Chem. Soc. Chem. Commun.*, 1980, 820.

(56) E. Wiberg, and W. Gosel, *Z. Naturforsch.*, 1956, 11b, 485.

(57) E.L. Eliel, and T.J. Brett, *J. Org. Chem.*, 1963, 28, 1923.

(58) B. Wesslen, *Acta Chem. Scand.*, 1967, 21, 713.

(59) T. Purdie, and J.C. Irvine, *J. Chem. Soc.*, 1903, 83, 1021.

(60) R. Kuhn, H. Trischman, and I. Löw, *Angew. Chem.*, 1955, 67, 32.

(61) W.N. Haworth, *J. Chem. Soc.*, 1915, 107, 8.

(62) P.R. Trebilco, B.Sc. Hons. project, 1979, University of Canterbury.

(63) E. Müller, and W. Rundel, *Angew. Chem.*, 1958, 70, 105.

(64) E.G. Gros, and S.M. Flematti, *Chem. and Ind.*, 1966, 1556.

(65) A.H. Blatt, *Org. Syn., Coll. Vol. II*, p462.

(66) A.H. Blatt, *Org. Syn., Coll. Vol. II*, p165.

(67) L. Brandsma, "Preparative Acetylenic Chemistry", Elsevier, 1971, p25.

(68) H. Gilman, J.A. Beel, C.G. Brannen, M.W. Bullock, G.E. Dunn, and L.S. Miller, *J. Am. Chem. Soc.*, 1949, 71, 1499.

(69) H. Gilman, W. Langham, and F.W. Moore, *J. Am. Chem. Soc.*, 1940, 62, 2327.

(70) R.G. Jones, and H. Gilman, *Organic Reactions*, 1951, 6, 352.

(71) H. Gilman, and A.H. Haubein, *J. Am. Chem. Soc.*, 1944, 66, 1515.

(72) G.S. Newth, *J. Chem. Soc.*, 1901, 79, 915.

(73) L. Brandsma, "Preparative Acetylenic Chemistry", Elsevier, 1971, p187.

(74) G.B. Heisig, H.M. Davis, *J. Am. Chem. Soc.*, 1935, 57, 339.

(75) G.C. Levy, R.L. Lichter, and G.L. Nelson, Carbon-13 Nuclear Magnetic Resonance Spectroscopy, Second Edition, John Wiley and Sons,Inc., 1980, p91.

(76) W. Smadja, *Ann. Chim.* (Paris) 1965, 10 (3-4), 105-44 (Fr); *Chem. Abstr.*, 1965, 63(2), 6834 g.

(77) Prepared by R.W. Vannoort, B.Sc. Hons. project,1979, University of Canterbury.

(78) R. Badouy, and J. Gore, *Tetrahedron*, 1975, 31, 383.

(79) *Org. Syn., Coll. Vol. II*, 1943, p387.

(80) R.B. Moffett, and R.L. Shriner, *Org. Syn.*, 1941, 21, 79.

(81) W.J. Potts, R.A. Nyquist, *Spectrochim. Acta.*,1959, 15, 679.

(82) A. Claesson, and C. Bogentoft, *Acta. Chem. Scand.*, 1972, 26, 2540.

(83) Prepared by T.S. Lee, Ph.D. work 1981, University of Canterbury.

(84) E.I. Snyder, and J.D. Roberts, *J. Am. Chem. Soc.*, 1962, 84, 1582.

(85) S.R. Landor, A.N. Patel, P.F. Whiter, and P.M. Greaves, *J. Chem. Soc. C*, 1966, 1224.

(86) S. Hoff, L. Brandsma, and J.F. Arens, *Recl. Trav. Chim. Pays-Bas*, 1968, 87, 916.

(87) Private communication, T.S. Lee, University of Canterbury, 1981.

(88) J.W. Blunt, M.P. Hartshorn, M.H.G. Munro, Lee Tin Soong, and R.W. Vannoort, *Tetrahedron Lett.*, 1981, 2143.

(89) M.H. Palomaa, and A. Kenetti, *Chem. Ber.*, 1931, 64, 797; *Chem. Abstr.*, 1931, 25, 3958.

(90) P.C. Loewen, L.P. Makhubu, and R.K. Brown, *Can. J. Chem.*, 1972, 50, 1510.

(91) J.L. Riebosomer, J. Irvine, and R. Andrews, *J. Am. Chem. Soc.*, 1938, 60, 1015.

(92) C.J. Pouchert, and J.R. Campbell, The Aldrich Library of NMR Spectra, Aldrich Chemical Company, Inc., 1974, 3, 72B.

(93) W. Bremser, L. Ernst, B. Franke, R. Gerhards, and A. Hardt, Carbon-13 N.M.R. Spectral Data, Verlag Chemie, Weinheim; Deerfield Beach, Florida; Basel 1981, Microfiche Spectrum 0485.

(94) C.J. Pouchert, The Aldrich Library of Infrared Spectra, Second Edition, Aldrich Chemical Company, Inc., 1975, 360 H.

(95) CRC Handbook of Chemistry and Physics, 61st Edition, CRC Press, Inc., 1980-81, C-214.

(96) H.C. Brown, and S. Krishnamurthy, *Tetrahedron*, 1979, 35, 567.

(97) N.G. Gaylord, Reduction with Complex Metal Hydrides, 1956, Interscience, New York.

(98) A.I. Vogel, Elementary Practical Organic Chemistry, Longmans, Green and Co., 1958, p305.

(99) F.H. Hon, H. Matsumura, H. Tanida, and T.T. Tidwell, *J. Org. Chem.*, 1972, 37, 1778.

(100) Prepared by R.S. Thompson during work on ref. 28, 1980.

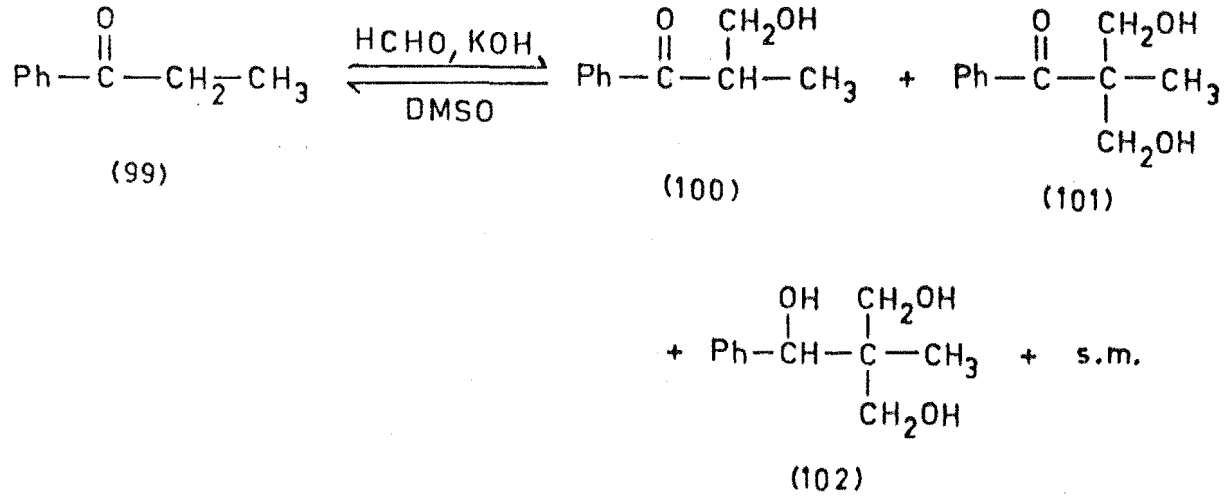
(101) J. Manta, *J. prakt. Chim.*, 1935, 142, 11; *Chem. Abstr.*, 1935, 29(1), 2155 h.

(102) A. Karnoven, *Acad. Sci. Fennicae.*, 3A, 1; *Chem. Abstr.*, 1920, 14(2), 2175.

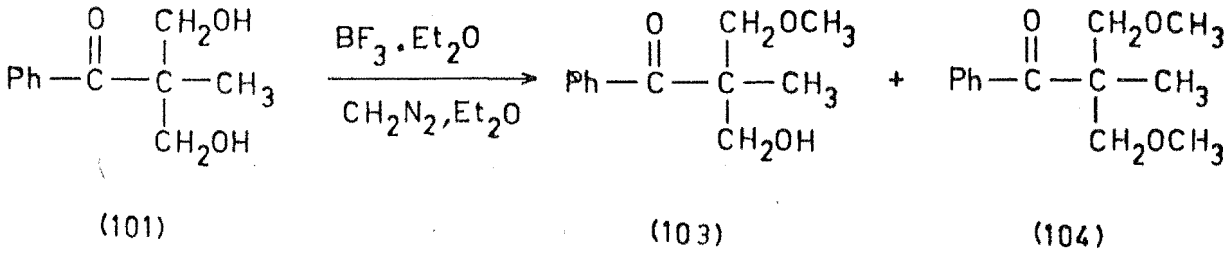
(103) E. Polla, S. Borcic, and D.E. Sunko, *J. Org. Chem.*, 1979, 44, 4091.

(104) C. Shoepf, H.J. Strauss, M. Hoehn, and A. Hutzler, *Monatsch. Chem.*, 1967, 98, 1274.

(105) G.C. Levy, and G.L. Nelson, Carbon-13 Nuclear Magnetic Resonance for Organic Chemists, John Wiley and Sons,Inc., 1972, p30.

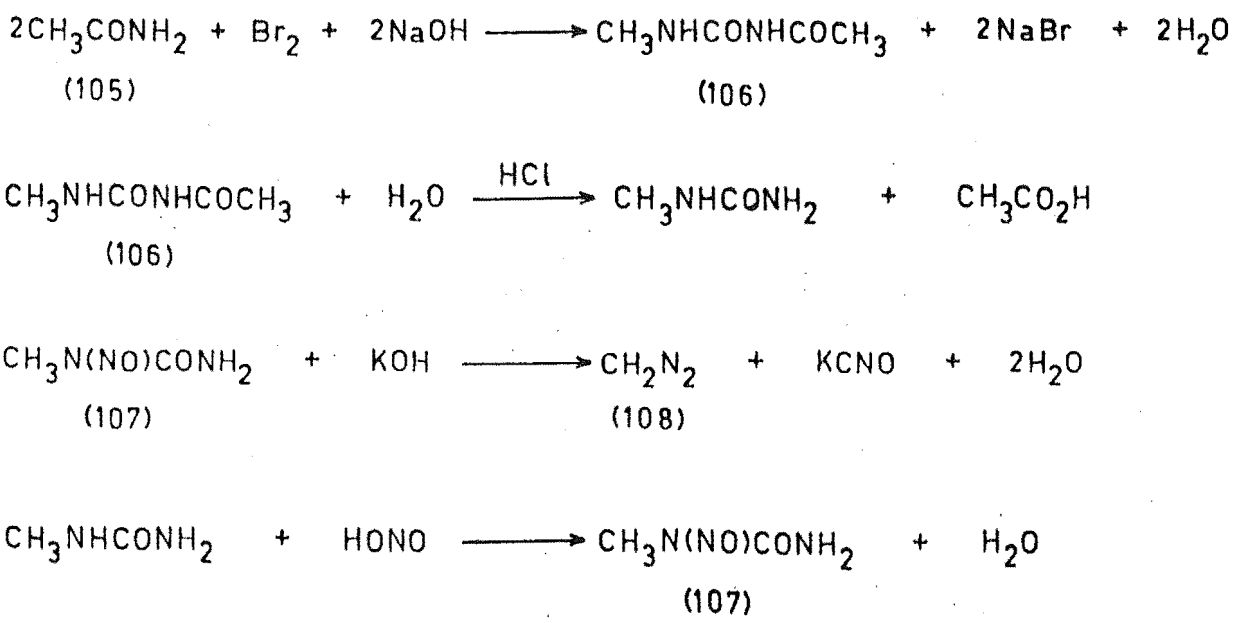


(99) (100) (101) (102)



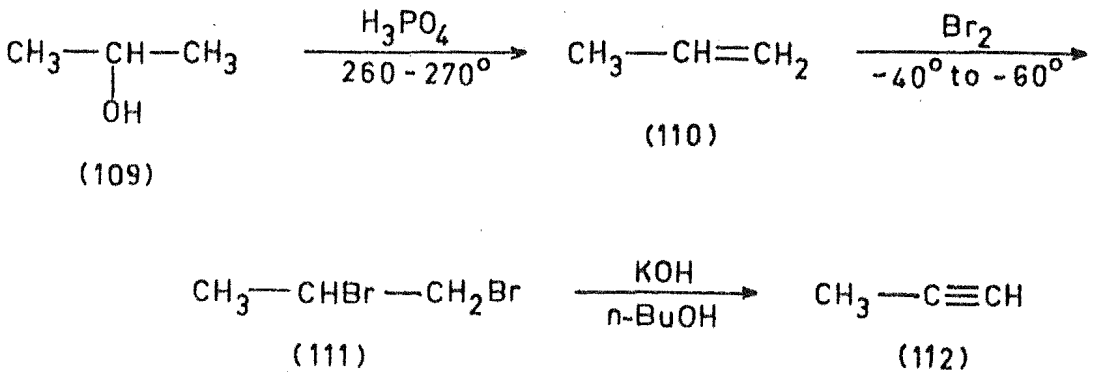
(101) (103) (104)

Scheme 15

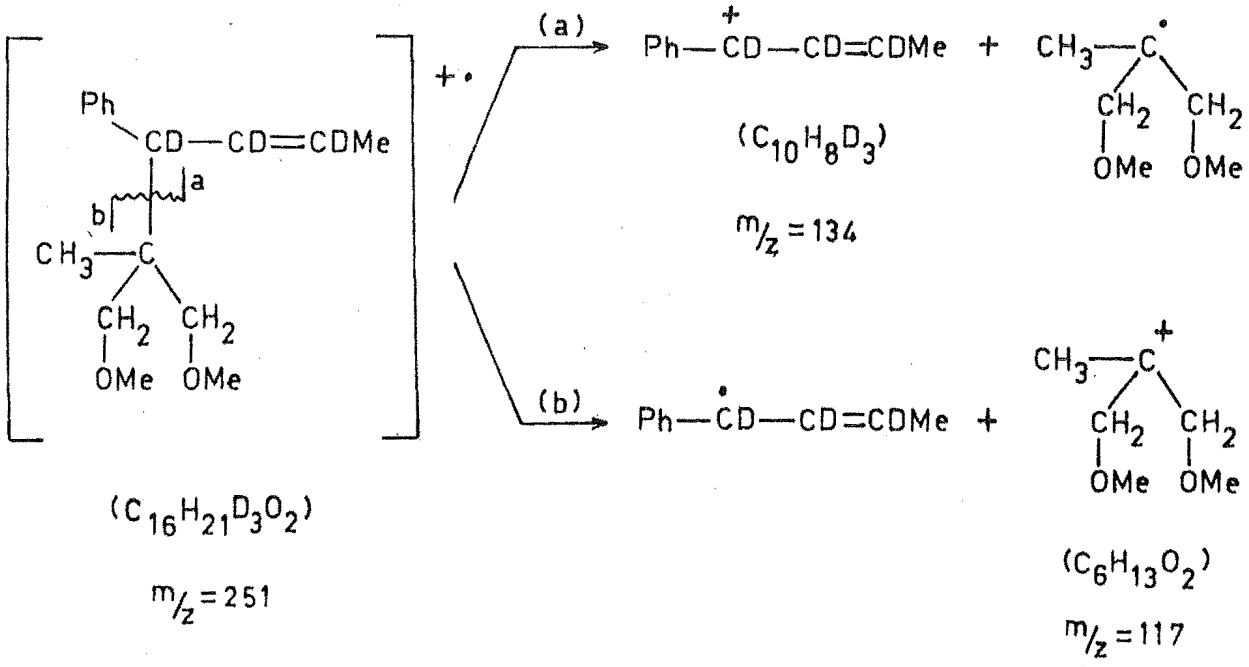


(105) (106) (106) (107) (108) (107)

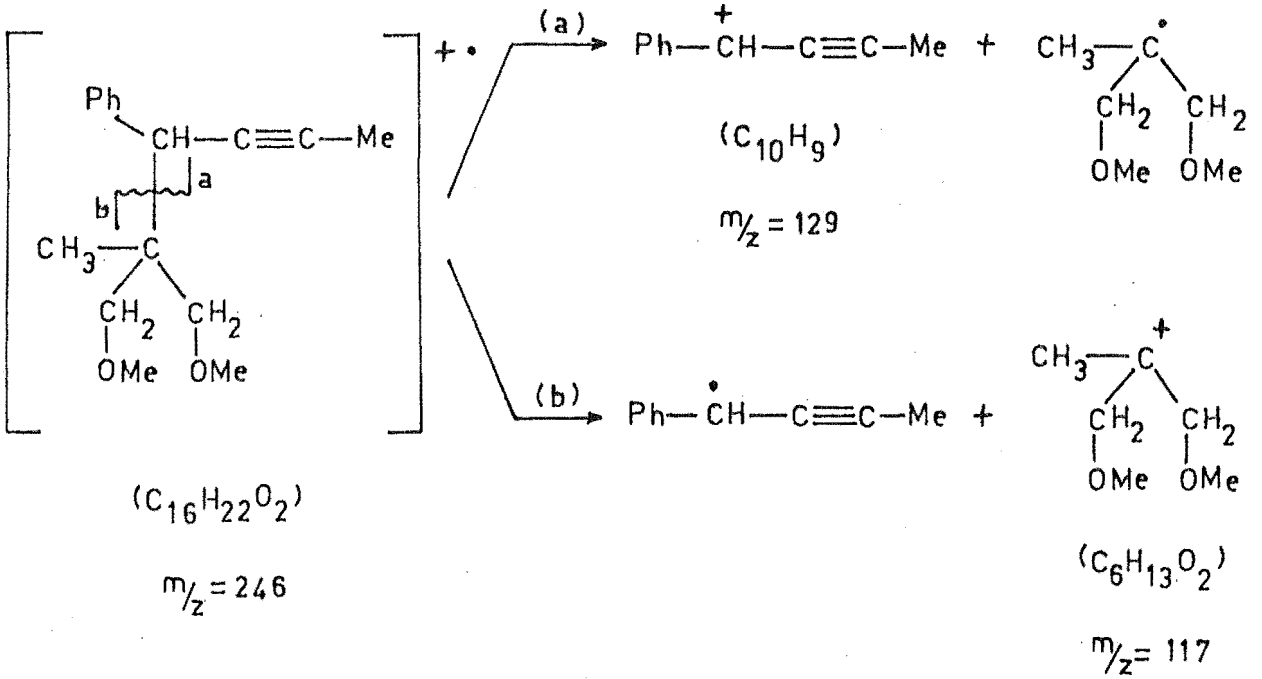
Scheme 16



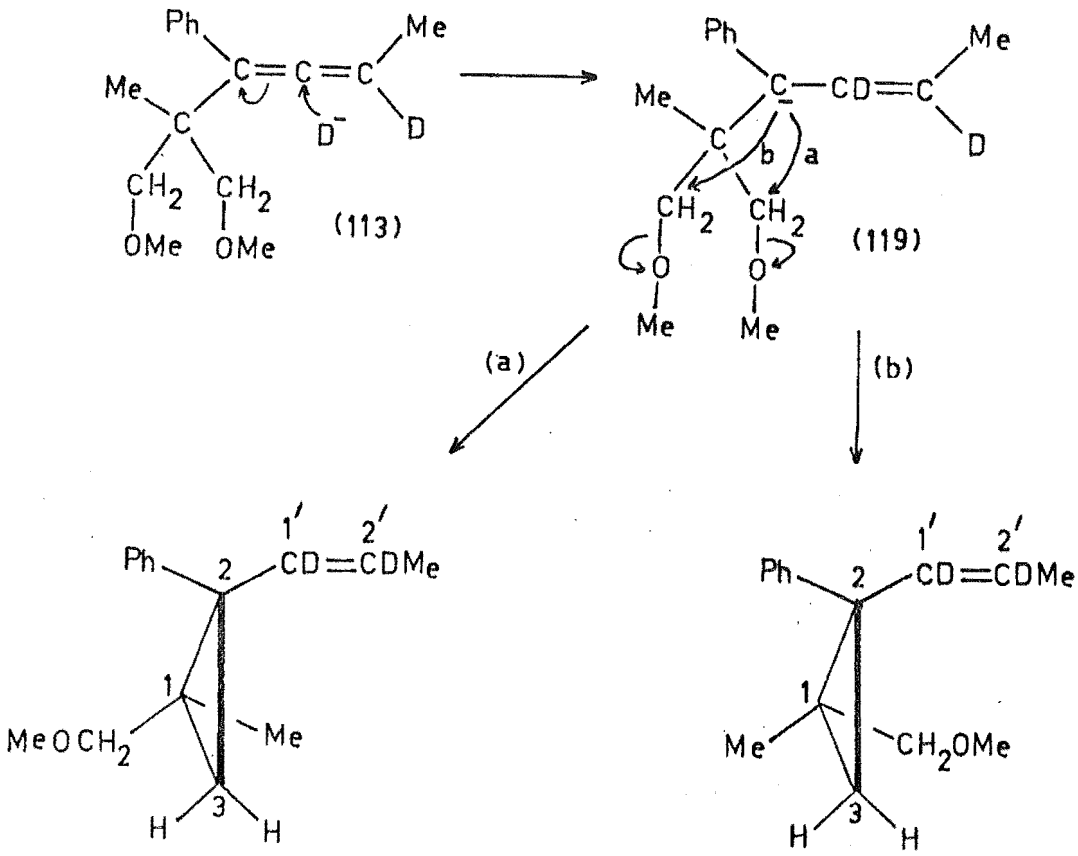
Scheme 17



Scheme 18



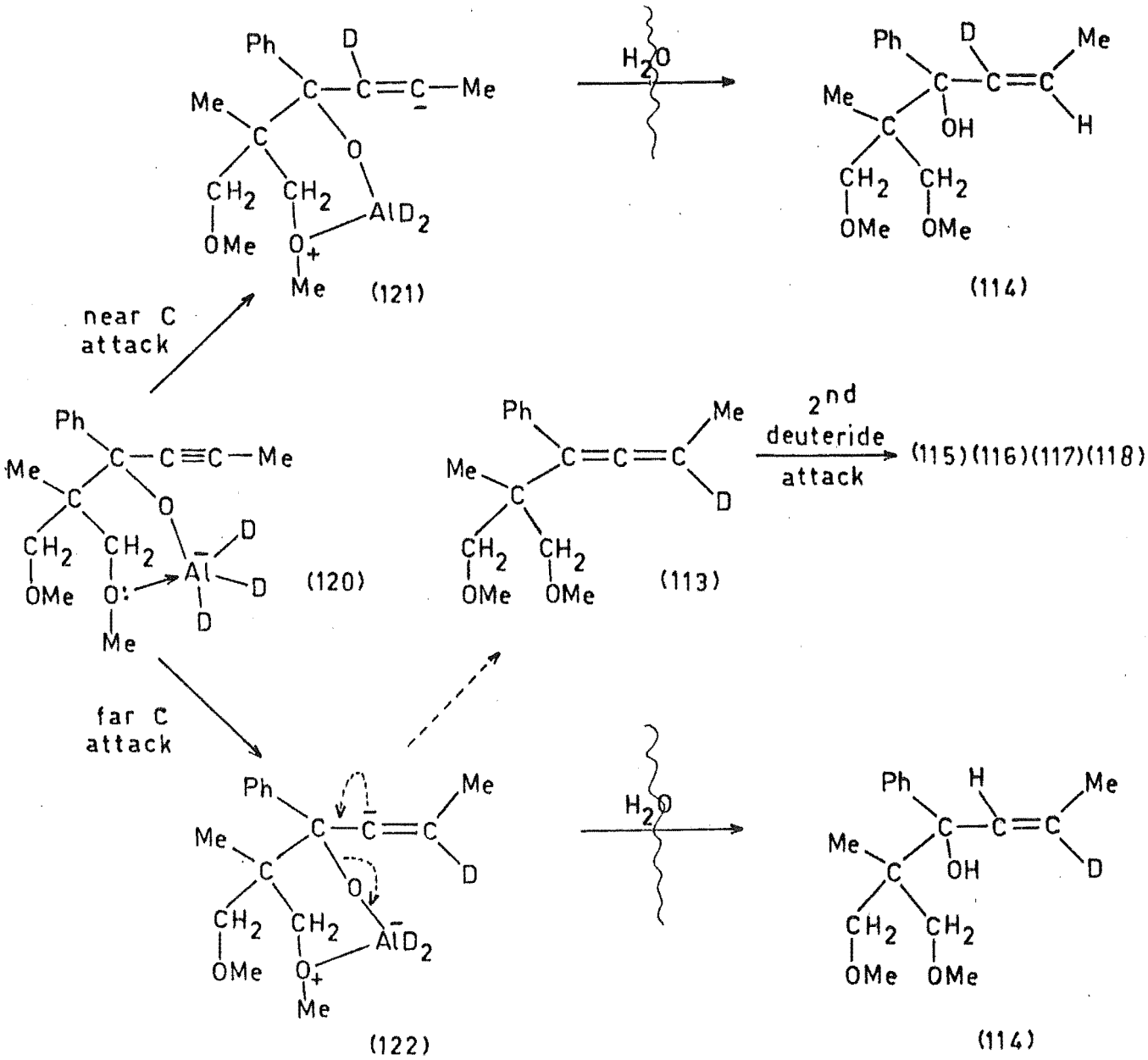
Scheme 19



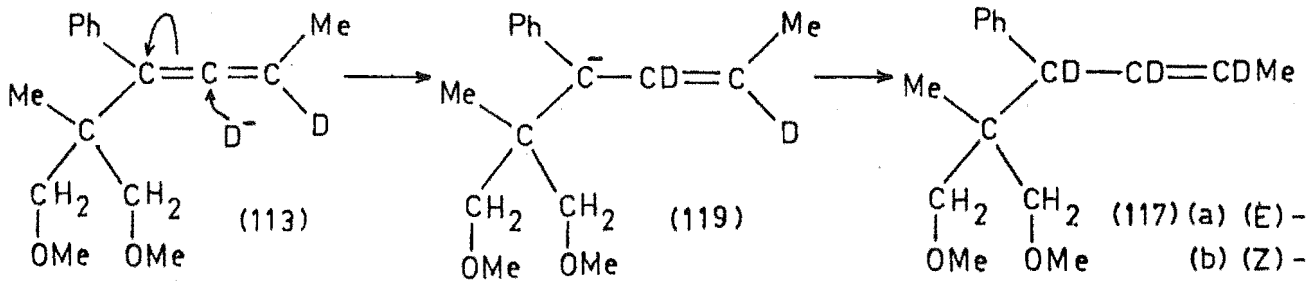
(115) (a) (E) –
(b) (Z) –

(116) (a) (E) –
(b) (Z) –

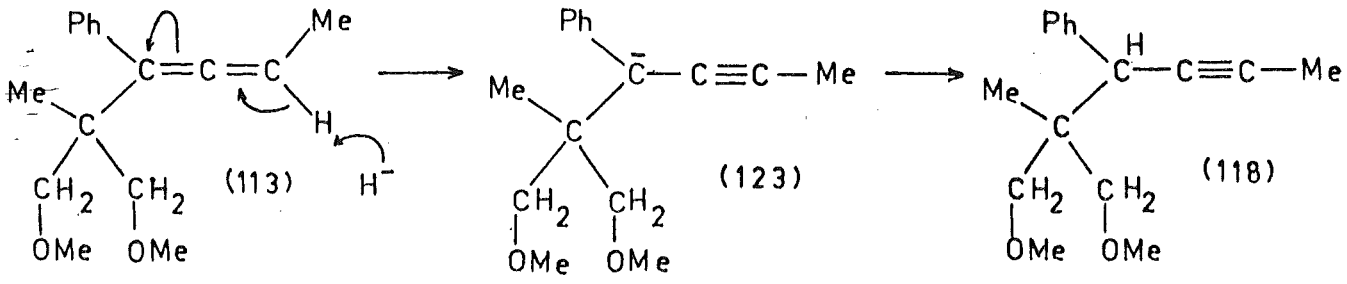
Scheme 20



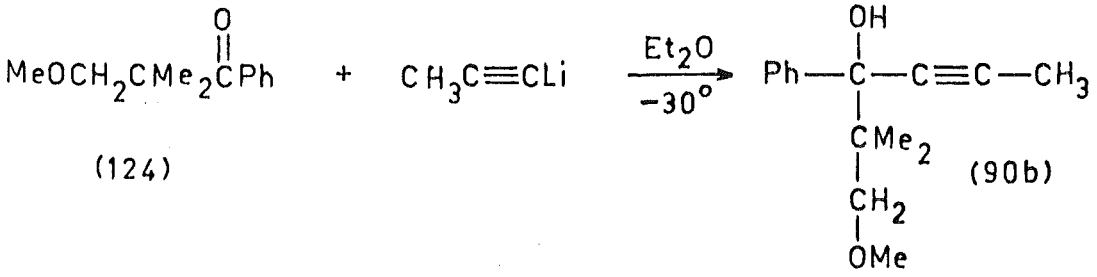
Scheme 21



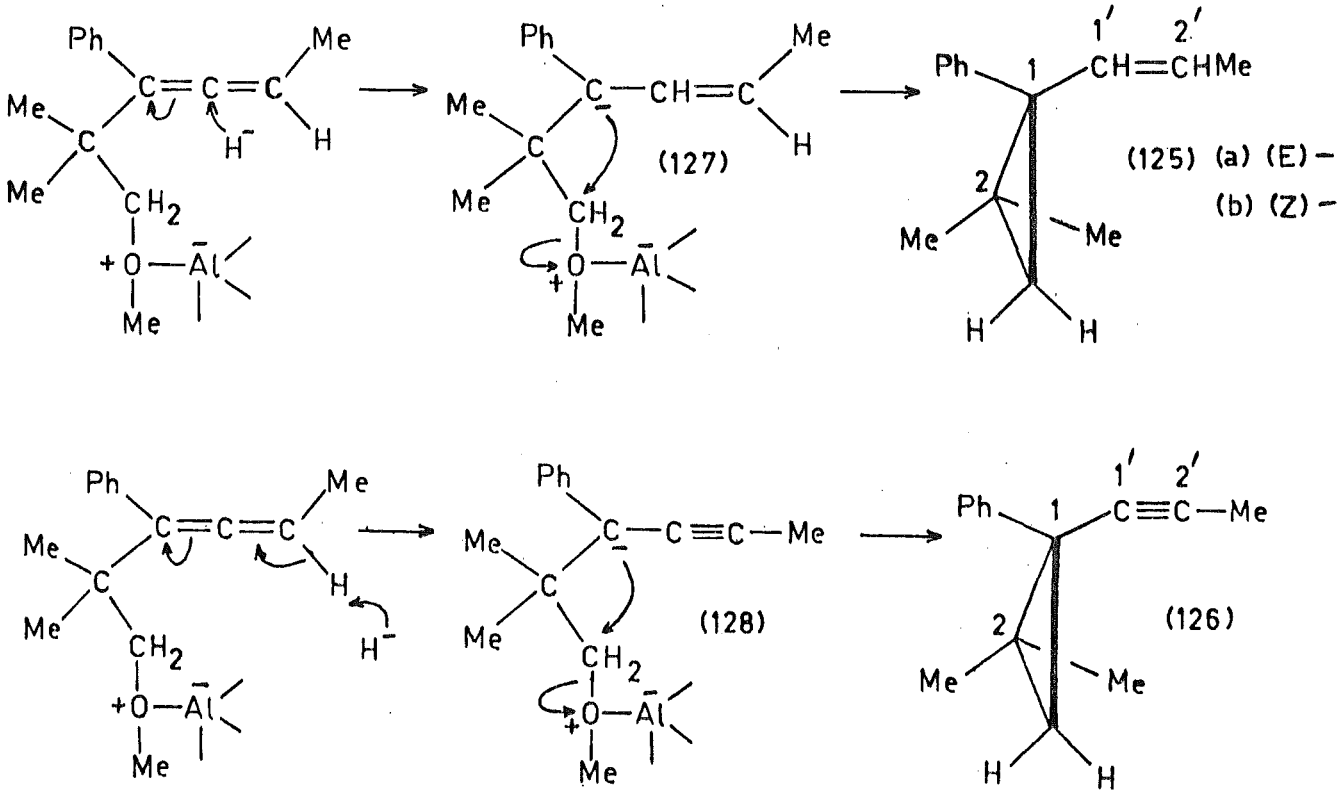
Scheme 22



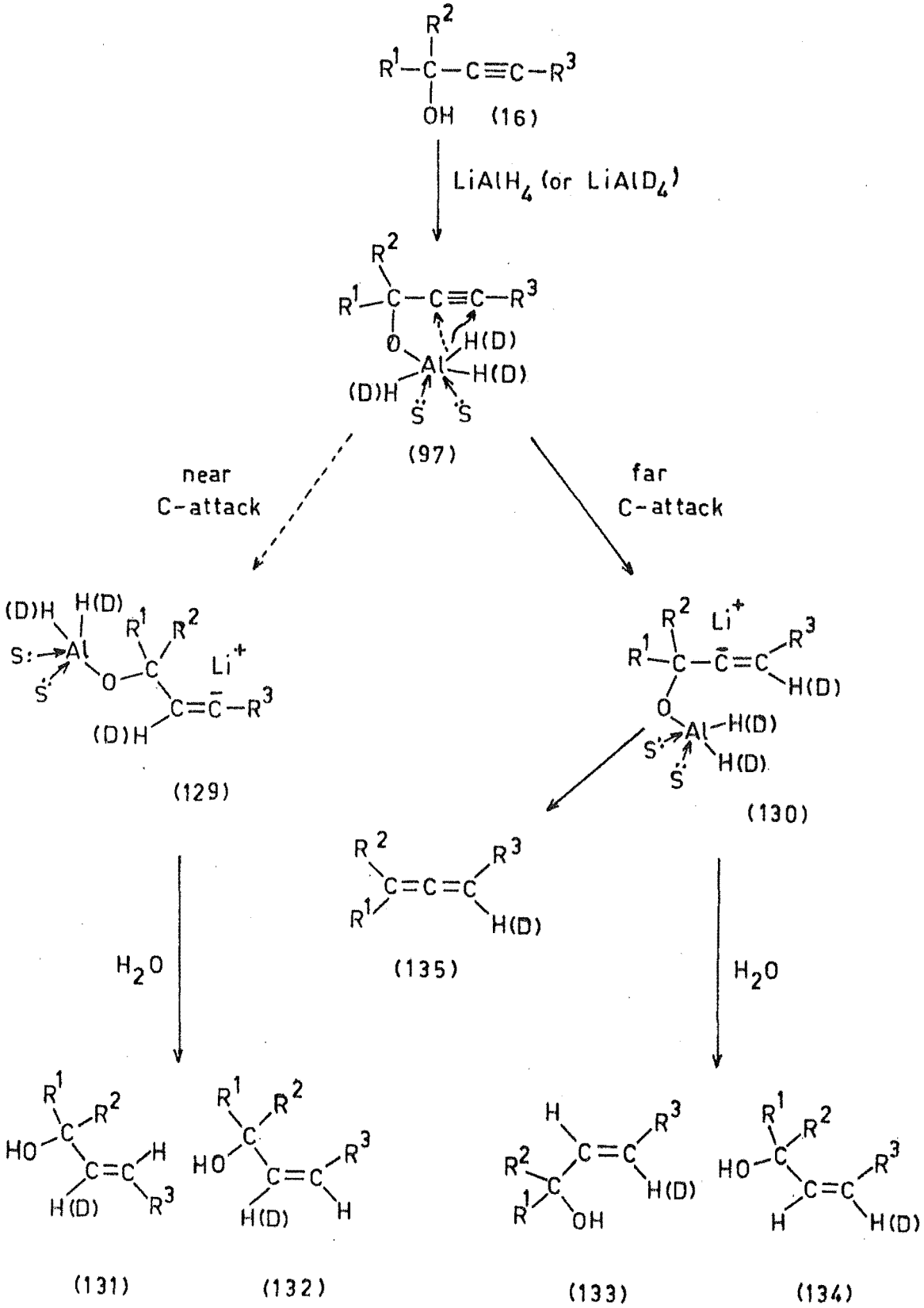
Scheme 23



Scheme 24

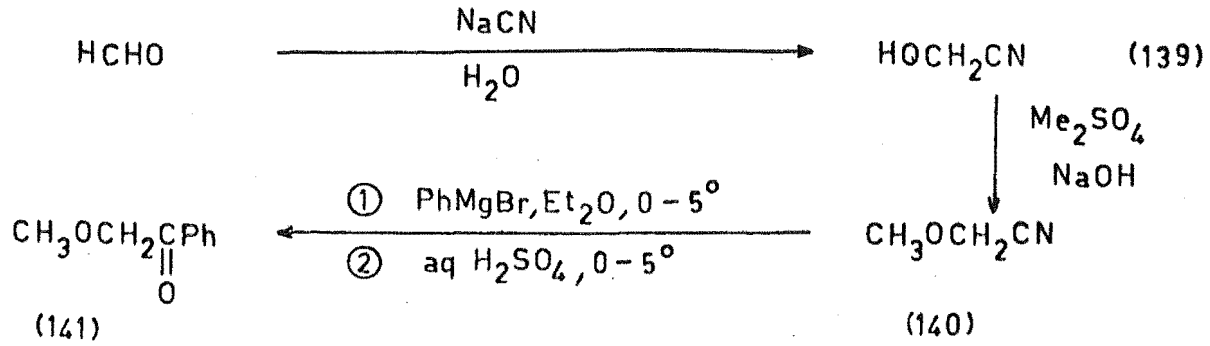


Scheme 25

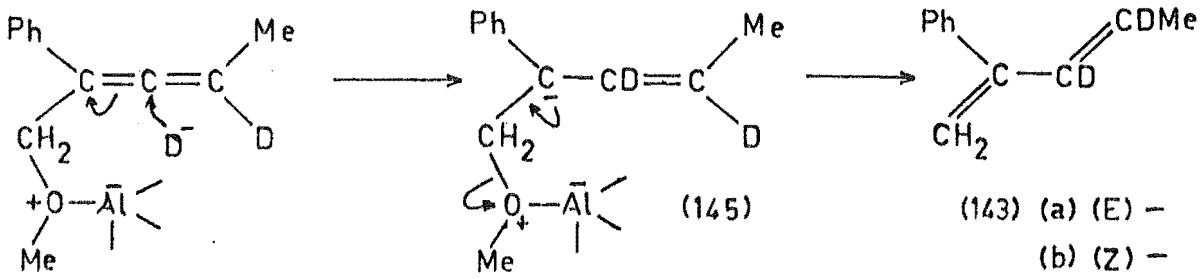


(16) (97) (129) (130) (135) (131) (132) (133) (134)

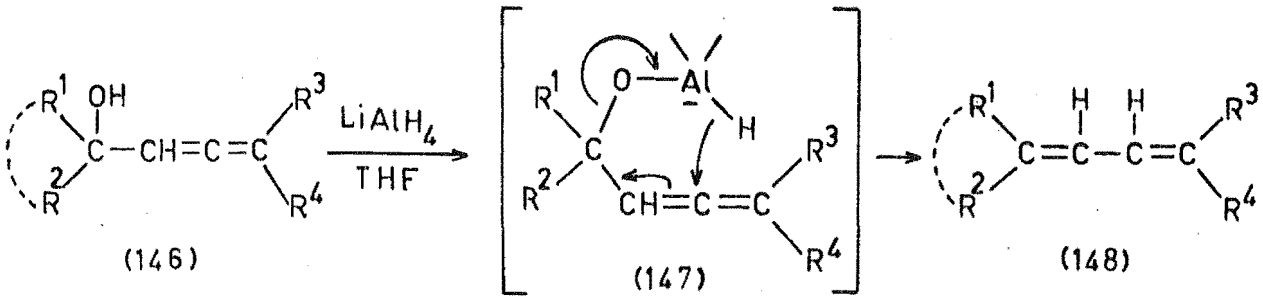
Scheme 26



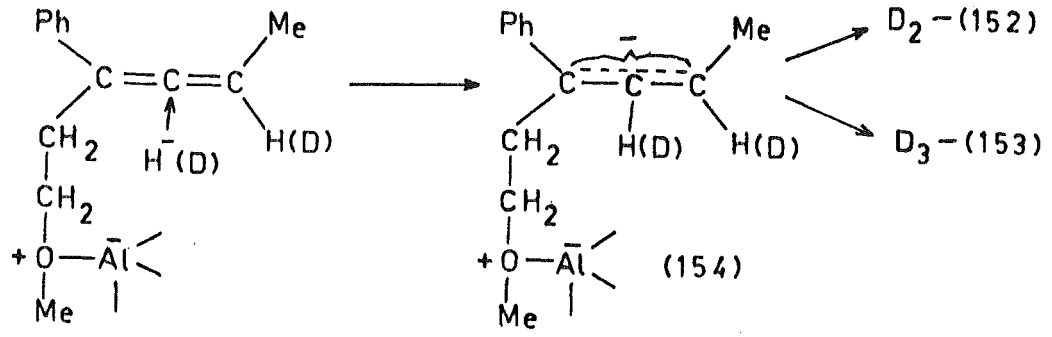
Scheme 27

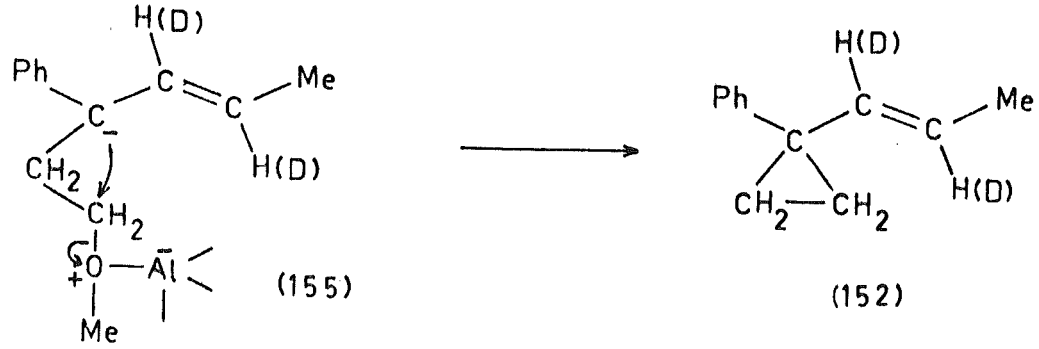


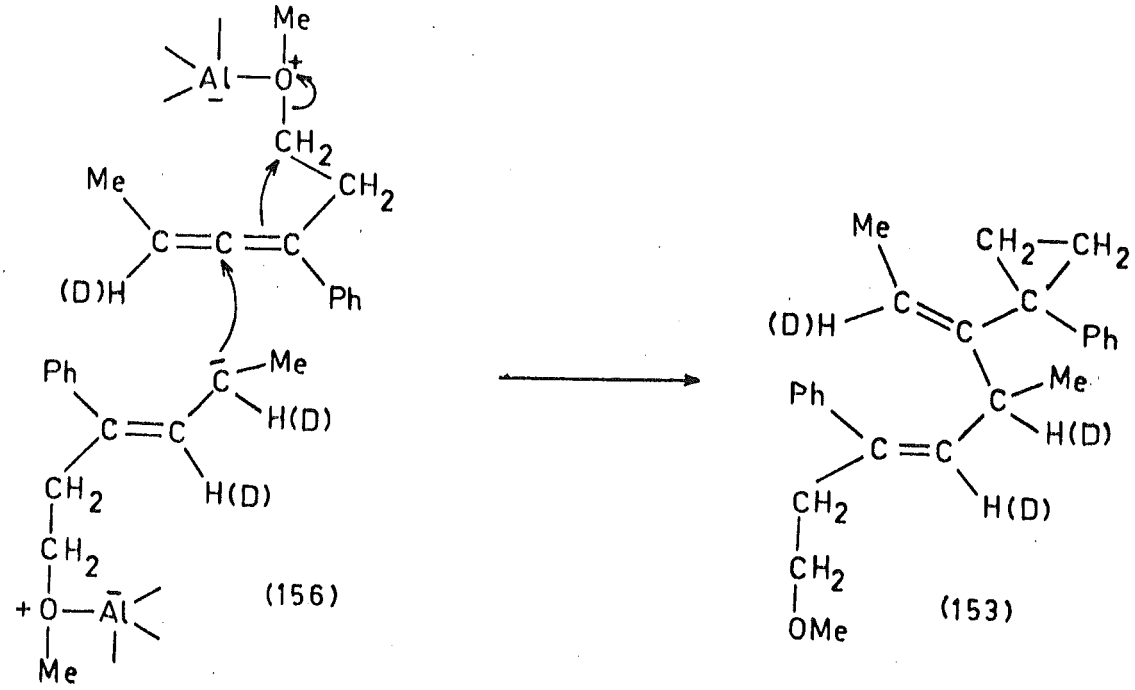
Scheme 28



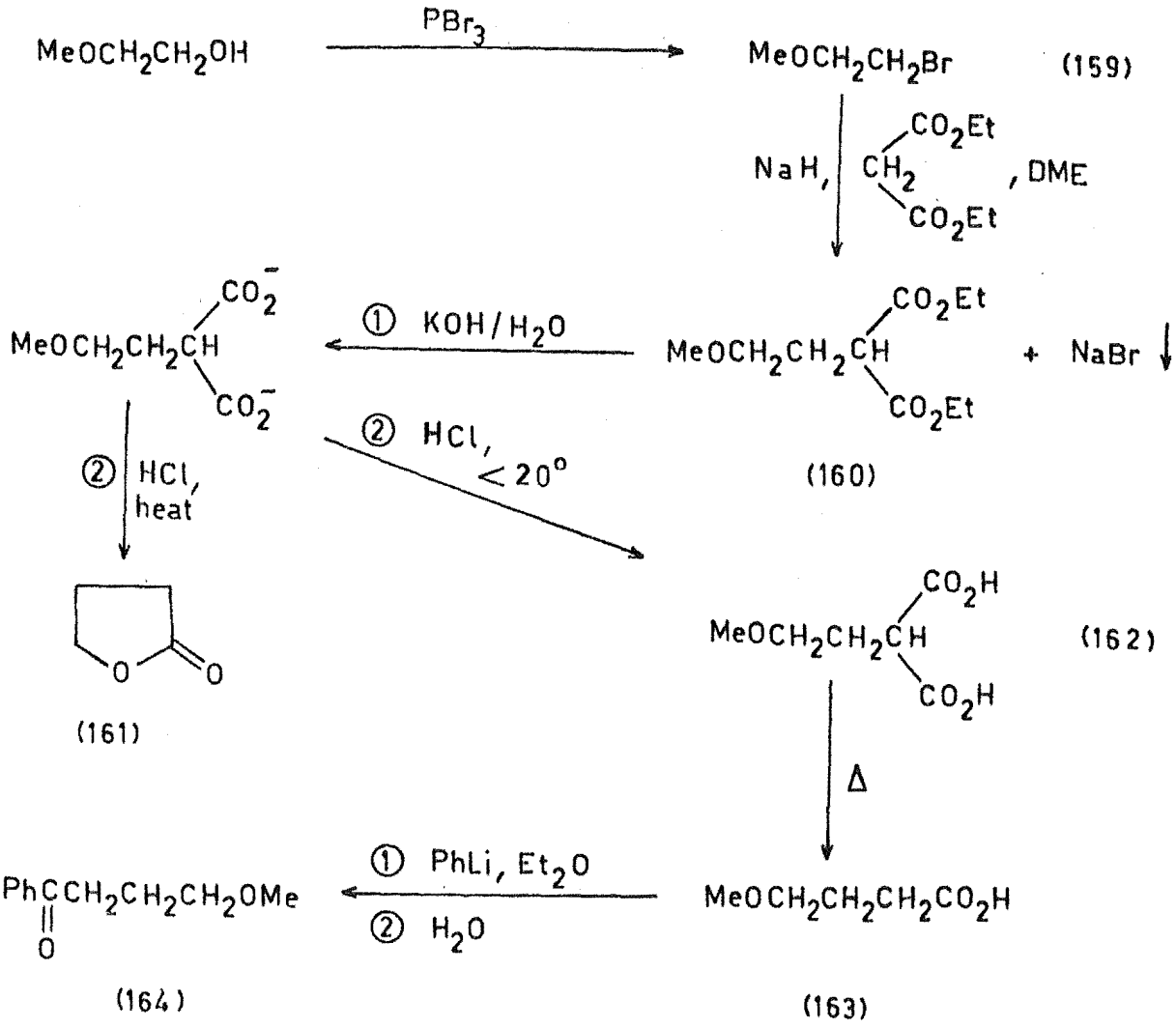
Scheme 29


Ph
Me
H(D)
Me
D2 – (152)
D3 – (153)
(154)

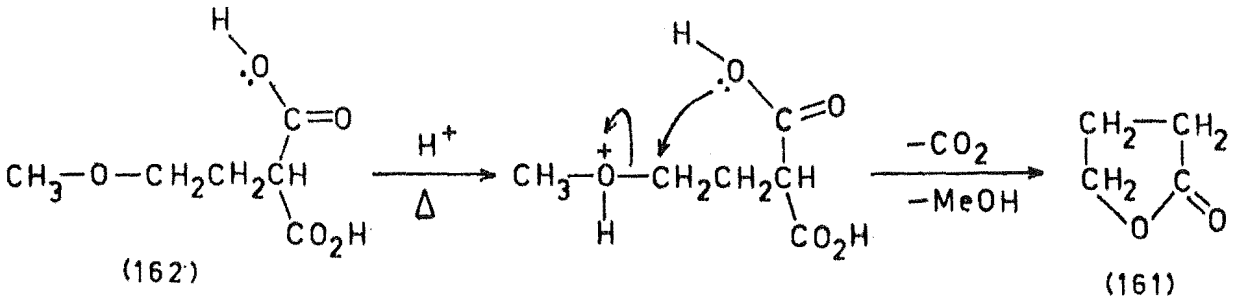

H(D)
Ph
Me
H(D)
(155)
(152)


Me
CH2
CH2
Me
(D)H
Ph
Ph
Me
H(D)
H(D)
(156)
(153)
OMe

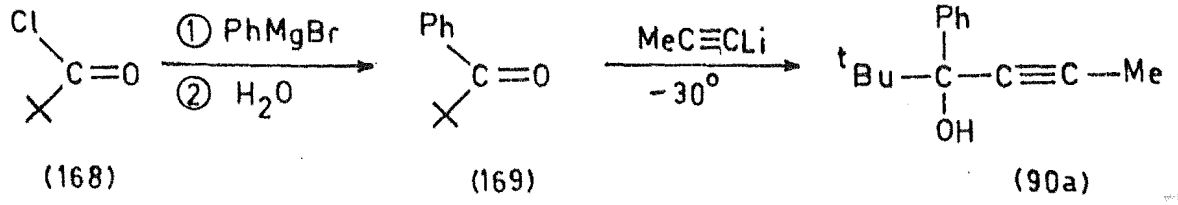
Scheme 30



Scheme 31



Scheme 32



Scheme 33

TABLE 1

PRODUCT YIELDS FOR REACTIONS OF ALKYNOL (98) WITH LITHIUM ALUMINIUM HYDRIDE (DEUTERIDE)

% Reaction	Reaction Conditions		Product Yields (%)					Ratio of Attack by H^- (D^-) at C4:C5	
	Solvent	Temp. (°C) time (h)	Propenylcyclo-propanes (115) and (116)[a]	Alkene (117)[a]	Allene (113)	Alkyne (118)[a]	(E)-alkenol (114)	Leading to (E)-alkenol (114)	Overall
96	Et_2O	35,2.75	-	6	35	-	56	-	-
97	Et_2O	35,2.75	-	6	36	-	56	14:42	14:83[b]
72	THF	35,16	-	-	15	-	80	-	-
100	THF	65,2.5	13	-	43	-	36	-	-
100	THF	65,2.5	12	-	45	-	41	15:26	15:83
100	THF	65,4	20	-	40	-	36	-	-
100	THF	65,22	41	-	28	-	28	17:11	17:80
100	Me_2THF	91,0.5	6	11	26	10	31	-	-
100	Me_2THF	91,0.5	5	13	24	13	30	7:23	7:78
100	Me_2THF	65,2.5	-	5	49	-	40	-	-
96	Me_2THF	65,2.5	-	1	55	-	42	8:34	8:90
91	Benzene	80,0.75	-	3	46	-	51	-	-
89	Benzene	80,0.75	-	2	42	-	55	10:45	10:89

[a] Assumed to arise *via* Allene (113)

[b] These values are estimated to be ±3

TABLE 2

PRODUCT YIELDS FOR REACTIONS OF ALKYNOL (90b) WITH LITHIUM ALUMINIUM HYDRIDE (DEUTERIDE)

% Reaction	Reaction Conditions		Isolated Product Yields (%)				Ratio of Attack by H^- (D^-) at C4:C5	
	Solvent	Temp. (°C) time (h)	Propenylcyclo-propane (125)	Propynylcyclo-propane (126)[a]	Allene (91b)	(E)-Alkenol (92b)	Leading to (E)-alkenol (92b)	Overall
90	Et_2O	35,16	-	-	69	27	24:3	24:72[b,c]
97	THF	35,16	-	-	29	70	30:40	30:69[c]
100	THF	65,2.5	-	-	57	42	25:17	25:74[c]
100	THF	65,116	28	8	29	28	-	-
100	THF	65,116	30	10	26	24	20:4	20:70
100	Me_2THF	35,16	-	-	54	44	26:18	26:72[c]
100	Me_2THF	65,2.5	-	-	67	30	23:7	23:74[c]
100	Me_2THF	91,0.5	-	-	75	25	25:0	25:75[c]
70	Benzene	80,0.75	-	-	71	28	-	-
73	Benzene	80,0.75	-	-	72	28	10:18	10:90

[a] Assumed to arise *via* allene (91b)

[b] These values are estimated to be ±3

[c] Reference 55

TABLE 3

PRODUCT YIELDS FOR REACTIONS OF ALKYNOL (136) WITH LITHIUM ALUMINIUM HYDRIDE (DEUTERIDE)

% Reaction	Reaction Conditions		Product Yields (%)			Ratio of Attack by $H^-(D^-)$ at C3:C4	
	Solvent	Temp.(°C) time (h)	Dienes (143)[b]	Allene (144)	(E)-Alkenol (142)	Leading to (E)-alkenol (142)	Overall
90	Et_2O	35,2.75	1	-	89	-	-[a]
98	Et_2O	35,2.75	1	-	96	25:71	25:72
100	THF	35,2.75	1	-	96	-	-
100	THF	35,2.75	1	-	97	29:67	29:68
100	THF	65,1.25	7	-	92	30:62	30:69
100	THF	65,2.5	7	-	92	-	-
100	THF	65,4	11	-	86	28:58	28:69
100	Me_2THF	65,1.25	4	-	95	-	-
100	Me_2THF	65,1.25	5	-	94	23:71	23:76
100	Me_2THF	91,0.5	20	-	76	-	-
100	Me_2THF	91,0.5	22	-	77	25:52	25:74
100	Me_2THF	91,0.5	21	-	75	27:48	27:69
93	Benzene	80,0.75	21	2	76	-	-
88	Benzene	80,0.75	15	4	79	35:44	35:63
70	Benzene	80,0.75	1	17	79	32:47	32:65

[a] These values are estimated to be ±3

TABLE 4

PRODUCT YIELDS FOR REACTIONS OF ALKYNOL (137) WITH LITHIUM ALUMINIUM HYDRIDE (DEUTERIDE)

% Reaction	Reaction Conditions		Isolated Product Yields (%)				Ratio of Attack by H^- (D^-) at C4:C5	
	Solvent	Temp. (°C) time (h)	Propenyl-cyclopropane (152)[d]	Allene (151)	Methoxy diene (153)[d]	(E)-alkenol (150)	Leading to (E)-alkenol (150)	Overall
67	Et_2O	35,2.75	-	10	-	78	-	-[a,b]
74	Et_2O	35,2.75	-	10	-	73	48:25	48:35[b]
87	THF	35,2.75	-	3	-	94	-	-
94	THF	35,2.75	-	5	-	92	51:41	51:46
100	THF	65,4	9	-	20	54	-	-
100	THF	65,4	7	-	30	51	46:5	46:45
100	THF	65,4	4	10	7	69	-	-[c]
100	THF	65,4	6	8	8	67	47:20	47:42[c]
100	THF	65,17	4	-	22	48	48:0	48:26[b]
100	Me_2THF	65,1.25	-	26	2	65	-	-
100	Me_2THF	65,1.25	-	26	4	64	48:16	48:46
100	Me_2THF	91,0.5	6	10	25	53	-	-
100	Me_2THF	91,0.5	5	12	28	51	47:4	47:49
49	Benzene	80,0.75	-	46	-	48	27:21	27:67

[a] These values are estimated to be ±3

[c] 10 x dilution of solvent

TABLE 5

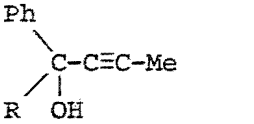
PRODUCT YIELDS FOR REACTIONS OF ALKYNOL (138) WITH LITHIUM ALUMINIUM HYDRIDE (DEUTERIDE)

Reaction Conditions			Product Yields (%)			Ratio of Attack by H^- (D^-) at C3:C2		
% Reaction	Solvent	Temp. (°C) time (h)	Allene (165)	(Z)-alkenol (166a)	(E)-alkenol (166b)	Leading to (Z)-alkenol (166a)	Leading to (E)-alkenol (166b)	Overall
16	Et_2O	35,2.75	59	-	30	-	30:0	30:59[a]
100	Et_2O	35,93	24	14	52	-	-	-
24	THF	35,2.75	8	-	85	-	61:24	61:32
100	THF	65,1.25	22	-	74	-	-	-
100	THF	65,1.25	16	-	79	-	79:0	79:16
100	THF	65,4	13	-	71	-	-	-
100	THF	65,4	13	-	74	-	74:0	74:13
100	Me_2THF	65,1.25	37	9	52	-	-	-
100	Me_2THF	65,1.25	34	8	57	8:0	57:0	65:34
100	Me_2THF	91,0.5	52	8	38	-	-	-
100	Me_2THF	91,0.5	50	9	40	9:0	40:0	49:50
85	Benzene	80,0.75	50	11	37	-	-	-
80	Benzene	80,0.75	47	11	40	10:1	36:4	46:52

[a] These values are estimated to be ±3

TABLE 6

PRODUCT YIELDS FOR REACTIONS OF ALKYNOLS (90a), (90b) and (98) WITH LITHIUM ALUMINIUM HYDRIDE (DEUTERIDE) IN BENZENE FOR 45 MIN AT 80°

Alkynol		Extent of Reaction	Product Yields (%)			Ratio of Attack by H^- (D^-) at C4:C5	
			Alkene	Allene	(E)-Alkenol	Leading to (E)-Alkenol	Overall
(90a)	R=^{t}Bu	0%	-	-	-	-	-
(90b)	R=-CMe_2CH_2OMe	73%	-	(91b) 72	(92b) 28	10:18	10:90[a]
(98)	R=-$CMe(CH_2OMe)_2$	90%	(117) 2	(113) 42	(114) 55	10:45	10:89

[a] These values are estimated to be ±3

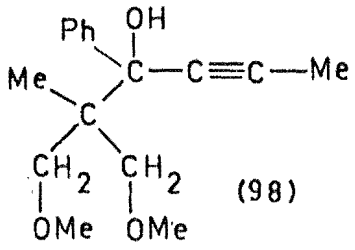
TABLE 7

PRODUCT YIELDS FOR REACTIONS OF ALKYNOL (18) WITH LITHIUM ALUMINIUM HYDRIDE (DEUTERIDE)

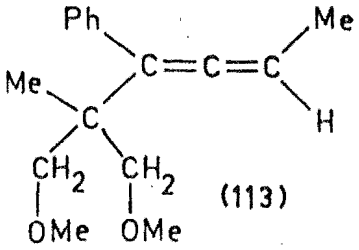
	Reaction Conditions		Isolated Product Yield (%)			Ratio of Attack by H^- (D^-) at C3:C4		
% Reaction	Solvent	Temp. (°C) time (h)	Allene (74)	(Z)-Alkenol (73)	(E)-Alkenol (72)	Leading to (Z)-Alkenol (73)	Leading to (E)-Alkenol (72)	Overall
73	Et_2O	35,44	57	13	29	13:0	29:0	42:57[a,b]
100	THF	35,48	-	-	83	-	83:0	83:0[b]
100	THF	65,4	-	-	84	-	84:0	84:0[b]
100	Me_2THF	65,4	61	6	21	6:0	21:0	27:61[b]
14	Benzene	80,0.75	65	-	33	-	-	-
15	Benzene	80,0.75	65	-	33	-	33:0	33:65

[a] These values are estimated to be ±3

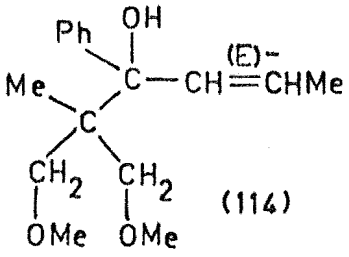
[b] Reference 28



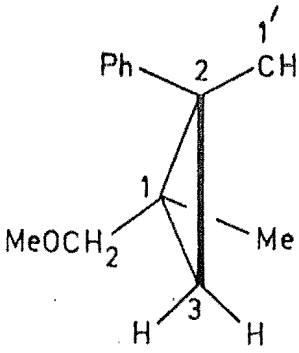
(98)



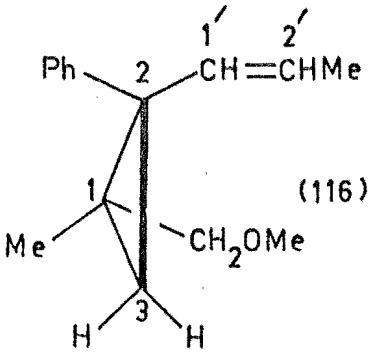
(113)



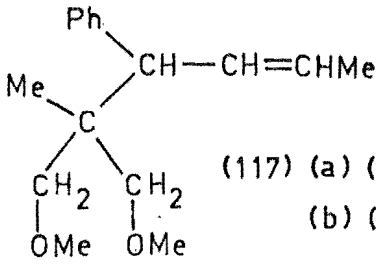
(114)



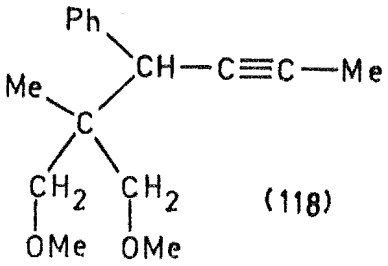
(115) (a) (E)-
(b) (Z)-



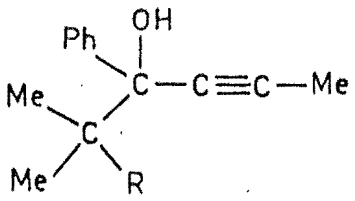
(116) (a) (E)-
(b) (Z)-



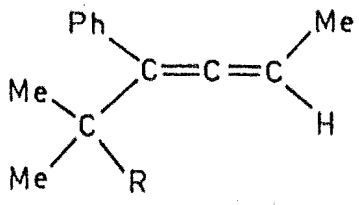
(117) (a) (E)-
(b) (Z)-



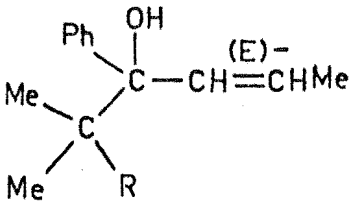
(118)



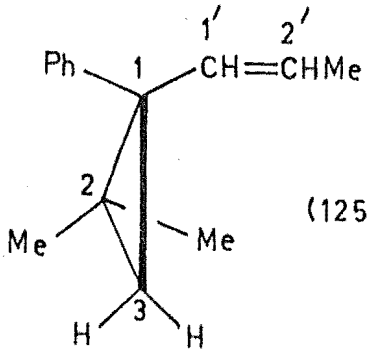
(90) (a) R = Me
(b) R = CH_2OMe



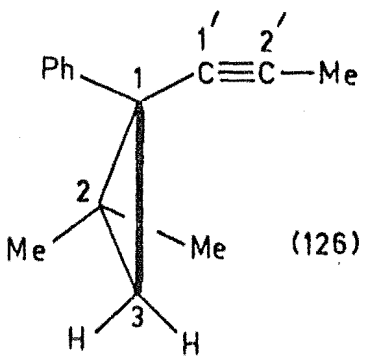
(91) (a) R = Me
(b) R = CH_2OMe



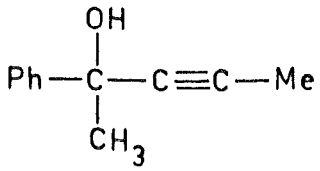
(92) (a) R = Me
(b) R = CH_2OMe



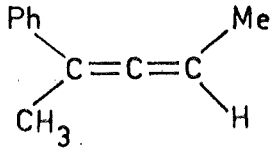
(125) (a) (E)-
(b) (Z)-



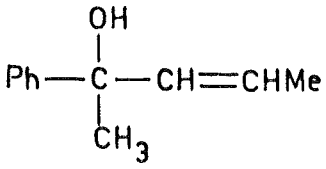
(126)



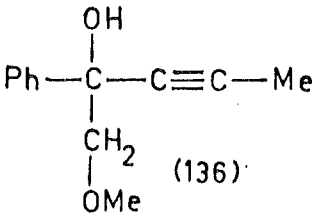
(18)



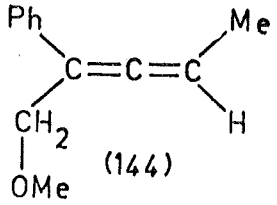
(74)



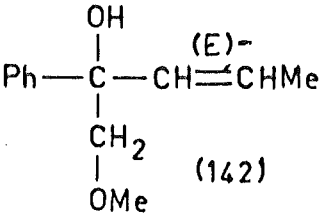
(72) (E)-
(73) (Z)-



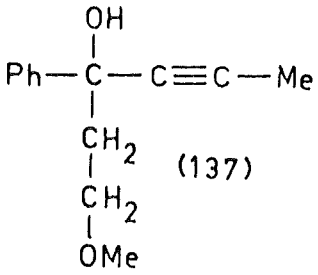
(136)



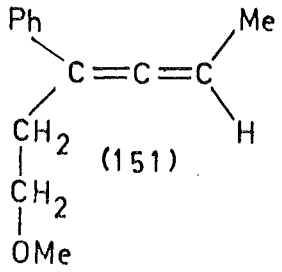
(144)



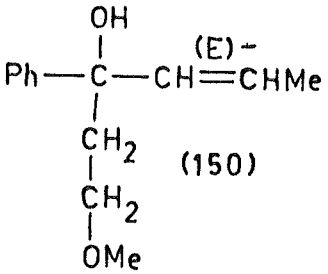
(142)



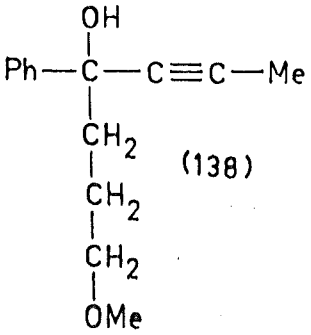
(137)



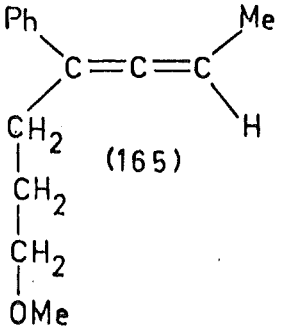
(151)



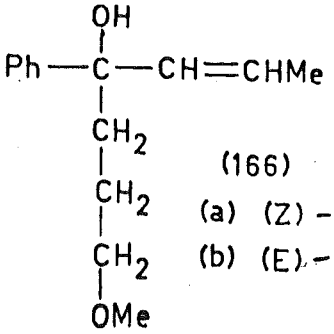
(150)



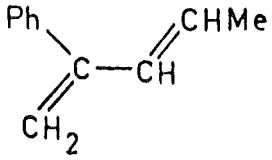
(138)



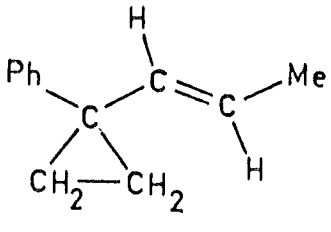
(165)



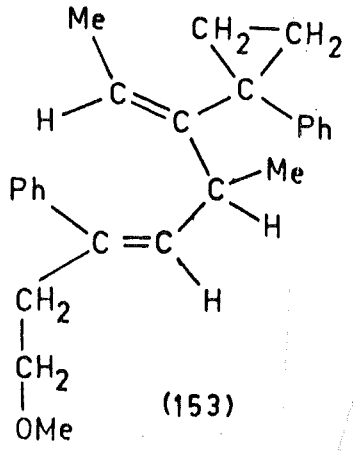
(166)
(a) (Z)-
(b) (E)-



(143) (a) (E)-
(b) (Z)-



(152)



(153)

ACKNOWLEDGEMENTS

I wish to express my extreme indebtedness to my supervisor, Professor Michael P. Hartshorn, for his encouragement and direction throughout the duration of this work.

In addition, my thanks are due to staff and technicians of the Chemistry Department of the University of Canterbury for their assistance, to Mrs. M.E. Boswell for typing this thesis and to Mr. K.H. Sutton for proof reading the type-script.

The award of a Teaching Fellowship (1980-1983) by the Chemistry Department, University of Canterbury, is also gratefully acknowledged.

Last, but by no means least, I would like to extend a special word of thanks to my parents, and to my wife, Margreet, without whose love and support this thesis would not have been possible.