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The Synthesis and Stereochemistry of Allenes,

Acetylenes and Related Compounds.

Thesis Presented for

the Degree of

Doctor of Philosophy

in the

University of Durham

by

John Patrick Regan

September 1967

ABSTRACT

(±)-Marasin, claimed to be the product from the
reduction of non-2-en-4,6,8-triyn-1-ol with lithium aluminium
hydride, has been shown to be a minor product only, the
major product being the allenene. Reduction with dialk-
oxylithium aluminium hydride gave improved yields of
allenynes together with allenenes whereas the lithium
aluminium hydride-butane-2,3-diol complex gave allenynes
only. Reduction with the asymmetric complexes of lithium
aluminium hydride with menthol, and 3-0-benzyl-1,2-0-
cyclohexylidene-α-D-glucofuranose gave the optically active
allenynes. A consideration of the stereochemistry of
these reductions enabled the configuration of the product
to be predicted. The absolute configurations of four allenynes,
including the naturally occurring marasin and its next
higher homologue (9-methyl marasin) were determined. The
lithium aluminium hydride-active amyl alcohol (2-methyl-
butan-1-ol) complex was found to be unsuitable for prod-
ucing optically active allenynes. The kinetically controlled
reduction of 4-chloro-2-yn-1-ols and the corresponding
acetates with an asymmetric complex has been investigated.

The absolute configuration of (+)-hexa-3,4-dienol
has been determined by application of the Claisen rearrange-
ment to optically active (-)-chloroethyl but-1-yn-3-yl

ether. Trace impurities in 3-0-benzyl-1,2-0-cyclohexylidene-
α-D-glucofuranose have been isolated and identified and the
analytically pure compound prepared for the first time.

3,3,5-Trimethylcyclohexanone has been reduced with
cyclic complexes of lithium aluminium hydride. The axial/
equatorial ratio of the cyclohexanols obtained from these
and other reductions has been interpreted by postulating
the participation of the flexible form of the ketone in
the reduction.

Bromopropargyl aldehyde has been synthesised for the
first time and attempts to use this compound as an inter-
mediate are described.

ACKNOWLEDGMENTS

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I

INTRODUCTION

INTRODUCTION

Naturally Occurring Allenes

The discovery and isolation of penicillin from the mould Penicillium notatum just before the last war, stimulated great interest in the possibility of isolating other powerful antibiotics from mould and plant species. During the post war years, a great amount of effort has therefore been put into the screening of mould and plant extracts in the search for more potentially useful natural products.

The isolation of a naturally occurring diacetylene compound was reported by Sorensen and Stene[145] who obtained methyl dec-2-ene-4,6-diynoate from Matricaria indora L in 1941. By 1950 seven natural acetylenic compounds were known, and since then the number isolated, principally by the schools of Sir E. R. H. Jones and F. Bohlmann, has increased to about three hundred. The rapid increase in the rate of development in this field during the last seventeen years is a consequence of the introduction of automatic recording ultra-violet and, to a lesser extent, infra-red spectrophotometers. The polyacetylene system has a highly characteristic absorption pattern in the ultra-violet region and this, together with the high sensitivity of the ultra-violet spectrophotometer, makes its detection in plant or mould extracts relatively easy. After purification by counter-current distribution and

chromatography, the assignment of detailed structures to the compounds is made largely on the basis of spectral evidence.

(-)-Mycomycin (I), the first naturally occurring allene to be isolated, was discovered in 1947 by Johnson and Burdon[96] and shown to be active against the bacilli of human tuberculosis. In 1952 Celmer and Solomon[85] showed it to be the (-)-3(trans), 5(cis),7,8-tridecatetraene-10,12-diynoic acid, (I).

$$\overset{c}{} \quad \overset{t}{}$$
$$HC\equiv C\text{-}C\equiv C\text{-}CH=C=CH\text{-}CH=CH\text{-}CH=CH\text{-}CH_2COOH \qquad (I)$$
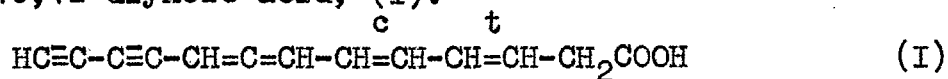
The allenic system was shown to be present in this compound by absorption at 1930 cm.$^{-1}$ in the infra-red spectrum. The ultra-violet spectrum showed the presence of isolated triene, and endiyne chromophores and thus enabled the position of the allene grouping to be decided, since the central carbon in the allene separates the two conjugated systems. The compound is very unstable and shows the high optical activity characteristic of asymmetric conjugated allenes.

Under alkaline conditions mycomycin rearranges to trans-trans-trideca-3,5-diene-7,9,11-triynoic acid (isomycomycin) (II).

$$CH_3C\equiv C\text{-}C\equiv C\text{-}C\equiv C\text{-}CH\overset{t}{=}CH\text{-}CH\overset{t}{=}CH\text{-}CH_2COOH \qquad (II)$$

This compound was synthesised by Bohlmann and Viehe[86] in 1954.

Several synthetic routes to ($\pm$)-mycomycin were tried by Bohlmann and Sucrow[88] in 1964. They considered it necessary to use alkali free conditions to avoid rearrangement of the allene group,[*] and their approach was therefor somewhat limited. An attempt by these workers to apply the lithium aluminium hydride reduction of enynols to allenes[2] to the system

$$H(C\equiv C)_3(CH=CH)_2-\overset{\overset{\displaystyle OH}{|}}{C}H-CH_2R$$
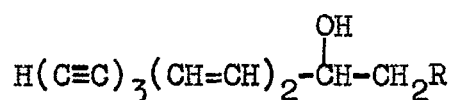
failed for the naturally occurring allenynes although model compounds were successfully reduced to allenes.[**]

An attempt to apply the Chodkiewicz[89] method of extending compounds with terminal triple bonds, by coupling with bromopropiolic acid and then removing the carboxylic acid group by copper bronze in boiling dioxan was used as follows:[‡]

---

[*]It has been shown by Baker, Landor, and Landor[87] that allenynols can be prepared under basic conditions, however. This synthesis is mentioned later.

[**]It is reported in this thesis that allenynols cannot be prepared by lithium aluminium hydride reduction of enynols since further reduction to allenenol occurs (p.39).

[‡]The lithium aluminium hydride reduction in the last stage of this reaction sequence would again be expected to produce mainly allenenol.

$$HC \equiv C - CH = CH - CH(OH)CH = CH - CH_2 R$$

$$\Big\downarrow BrC \equiv C - COOH$$

$$HOOC - C \equiv C - C \equiv C - CH = CH - CH(OH) - CH = CH - CH_2 R$$

$$\Big\downarrow Cu/dioxan$$

$$HC \equiv C - C \equiv C - CH = CH - CH(OH)CH = CHCH_2 R$$

$$\Big\downarrow Repeat$$

$$H(C \equiv C)_3 CH = CH - CH(OH) - CH = CHCH_2 R$$

$$\Big\downarrow LiAlH_4$$

$$H(C \equiv C)_2 - CH = C = CH - CH_2 CH(OH) - CH = CHCH_2 R \qquad (III)$$
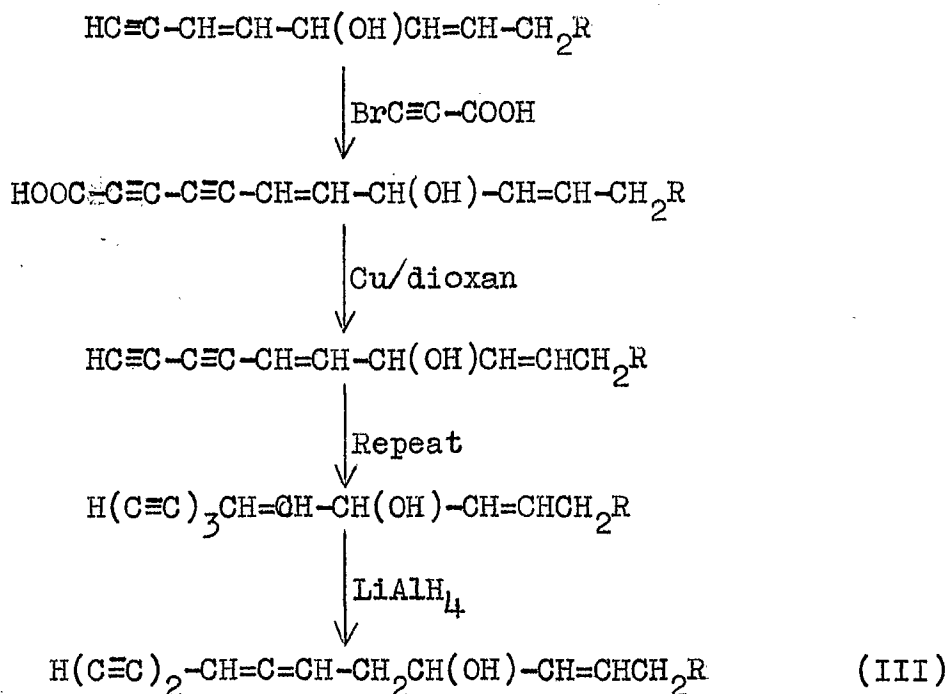
It was hoped that elimination of water from (III) would give a certain amount of the 5-_cis_ double bond. No elimination of water from (III) could be induced, however, using known acids and neutral reagents.

Kuhn and Winterstein[90] have reduced ω,ω-diphenyl-polyenes with aluminium amalgam in wet ether as follows:

$$Ph(CH=CH)_3 Ph \longrightarrow PhCH_2(CH=CH)_2 CH_2 Ph$$
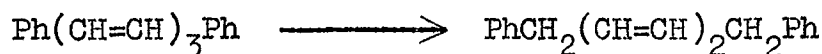
Bohlmann and Sucrow[88] tried to apply this reduction to the preparation of mycomycin as follows:

$$H(C{\equiv}C)_2\text{-}C{\equiv}C\text{-}CH{=}CH\text{-}CH{=}CH\text{-}CH{=}CH\text{-}COOR$$

$$\downarrow$$

$$H(C{\equiv}C)_2\text{-}CH{=}C{=}CH\text{-}(CH{=}CH)_2CH_2COOR \qquad\qquad (IV)$$
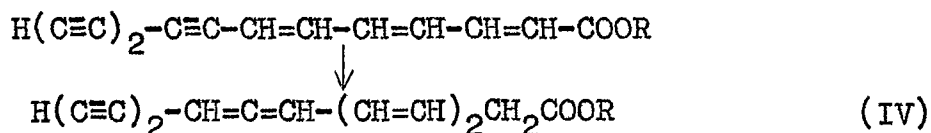
It was claimed that this method produced the methyl ester
having spectra identical with the methyl ester of the
naturally occurring material of Celmer and Solomons[85] but
it could not be crystallised. In an attempt to produce
crystallisable trans,trans-mycomycin the tert butyl ester
of the precursor of (IV) was prepared* and the trans,trans,trans-
isomer isolated by crystallisation. However, the tert-
butyl ester produced by aluminium amalgam reduction (con-
sidered by Bohlmann and Sucrow to be the ester of mycomycin)
could not be crystallised. Saponification with sulphuric
acid in dioxan gave a solution considered to contain a
small quantity of trans,trans-mycomycin. Attempts to
crystallise this after purification by counter-current
distribution were unsuccessful.** Two new polyacetylenic

---

*Tert butyl esters are usually more stable than methyl
esters.

**It has been shown in this thesis (p.48) that the ultra-
violet spectra of allenene and allenyne are very similar.
Attempts to separate mixtures of these compounds during
the course of the present work and by other workers in
these laboratories have proved unsuccessful (cf. Section II
p.45). The inability of Bohlmann and Sucrow to crystal-
lise their reduction product, even after attempted purific-
ation by the counter-current technique, suggests that the
reducing agent used here had also caused further reduction
of allenyne to allenene, and that these workers were
unwittingly dealing with such a mixture.

antibiotics, nemotinic acid and nemotin, were isolated

by Anchel, Palatnic, and Kavanagh[93] in 1950; the structures

of these compounds were shown to be 4-hydroxyundeca-5,6-

diene-8,10-diynoic acid and the corresponding lactone

respectively by Bu'Lock, Jones, and Leeming.[94] These

workers also isolated the related compounds odyssic acid

and odyssin from the same source.[95] Nemotinic acid and

nemotin undergo prototropic rearrangement on treatment with

alkali with the loss of the allene groups to give (-)-4-

hydroxyundeca-6,8,10-triynoic acid (isonemotinic acid), and

undec-4-ene-6,8,10-triynoic acid (nemotin A) respectively.

Nemotin A is also obtainable by treating the lactone of

isonemotinic acid with alkali. These reactions are rep-

resented in the following scheme:

$$H(C\equiv C)_2-CH=C=CH-CH-(CH_2)_2COOH \longrightarrow H(C\equiv C)_2-CH=C=CHCHCH_2CH_2$$

Nemotinic Acid $\quad$ OH $\qquad\qquad\qquad\qquad\qquad$ O——C=O

$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad$ Nemotin

$\qquad\qquad\qquad$ OH$^-$ $\qquad\qquad\qquad\qquad\qquad$ OH$^-$

$$H(C\equiv C)_3-CH_2-CH-(CH_2)_2COOH \qquad H(C\equiv C)_3-CH=CH-(CH_2)_2COOH$$

$\qquad\qquad\qquad$ OH $\qquad\qquad\qquad\qquad\qquad\qquad$ Nemotin A

Isonemotinic

Acid

$\qquad\qquad\qquad$ OH$^-$

$$H(C\equiv C)_3CH_2CHCH_2CH_2$$

$\qquad\quad$ O——C=O

$\qquad\qquad\qquad$ OH$^-$
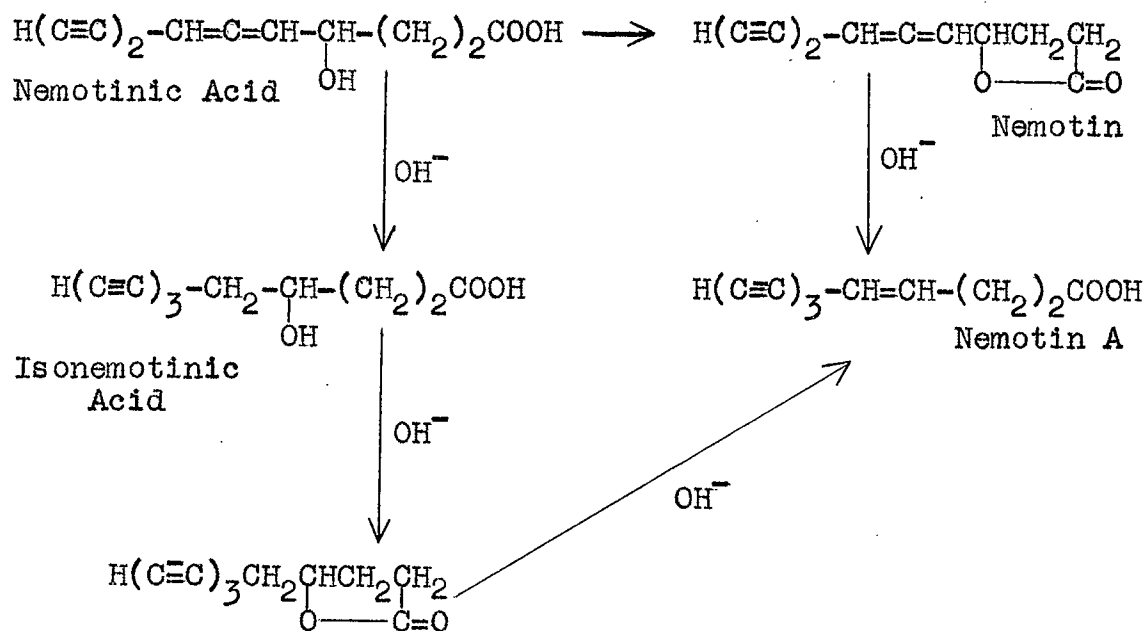
Isomerisations of this type in which the allene group is

lost are accompanied by a very large decrease in the optical activity which indicates that the allenic system with the highly polar diacetylene substituent is largely responsible for the high rotations observed.

In a study of some Marasmius species in 1959, G. Bendz[97] isolated marasin, an unstable, light-sensitive antibiotic, active in vitro against Staphylococcus aureous H, and Mycobacterium tuberculosis. He showed it to be nona-3,4-diene-6,8-diyn-1-ol, (V).

$$HC{\equiv}C-C{\equiv}C-CH{=}C{=}CH-CH_2CH_2OH \qquad \text{(V)}$$
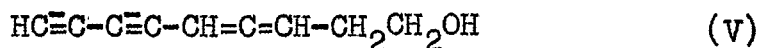
The compound was separated from other polyacetylenes using the counter-current distribution technique, with carbon tetrachloride and water as the two liquid phases. Bendz[143] found that in the presence of alkali isomerisation to isomarasin (VI) occurred, the allene group being lost.

$$HC{\equiv}C-C{\equiv}C-CH{=}C\underset{O}{\overset{CH_2-CH_2}{\diagup}}CH_2 \qquad \text{(VI)}$$
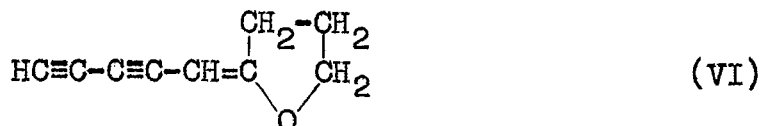
This was accompanied by a loss in antibiotic activity and Bendz suggested that this activity was a property of the allene group in conjugation with the acetylene groups. Support for this suggestion came from Baker, Landor, and Landor[87] in 1963. A number of allenynes were synthesised by coupling 1-bromo- and 1-iodo-allenes with terminal acetylenic compounds in the presence of cuprous ions and

a suitable base, and found to exhibit a high level of

activity in vitro against mycobacterium tuberculosis.

A synthesis of marasin in high yield was claimed by

Bohlmann, Herbst, and Gleinig[5] in 1961, but work described

in this thesis demonstrated that this synthesis yields

mainly the dihyromarasin, having similar ultra-violet

absorption spectra to marasin, and produces only traces

of pure marasin. Other naturally occurring allenic poly-

acetylenes which have recently been isolated are shown in

Table I, (p. 16).

Recently (1964) Bonnett, Spark, Tee, and Weedon[98]

have shown that the carotenoid pigment fucoxanthin, present

in brown algae, is an allenic polyene, (VII).

(VII)
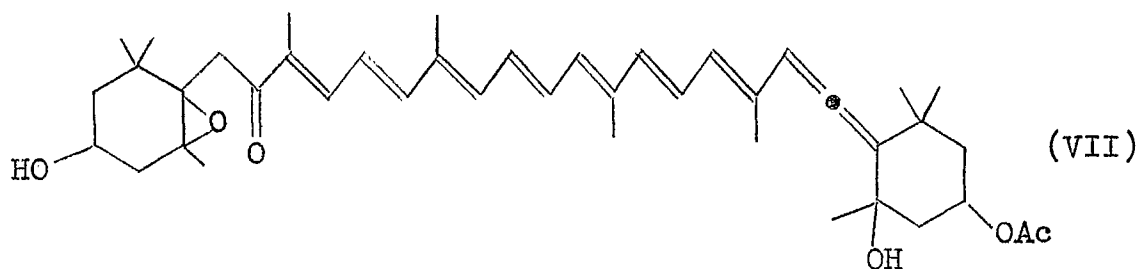
In 1966 the same workers[99] showed that foliaxanthin

which was first isolated from paprika[100] and has since

been found in lucerne, maple and other leaves,[99] has

structure (VIII). This is the first allenic carotenoid

to be reported. Neoxanthin, first described by Strain[101]

in 1938 has now been shown to be identical with

foliaxanthin.[102]

<u>TABLE I</u>[92]

<u>Natural Allenic Polyacetylenes</u>

$HC{\equiv}CC{\equiv}CCH{=}C{=}CHX$ $\qquad\qquad [\alpha]_D^{20}$

X = CH_2OH	-380
CH_2CH_2OH	±385
$CH_2CH_2CH_2OH$	-290
$CH_2CH_2CH_2CH_2OH$	-300
$CH(OH)CH_2CH_2OH$	-210
$CH(OH)CH_2CH_2CH_2OH$	-
$CH_2CH(OH)CH_2CH_2OH$	-210
$CH_2COOMe(H)$	+285
$CH(OH)CH_2CH_2COOH(Me)$	+380
$CH{=}CH{-}CH{=}CH{=}CH_2COOH$	-
$CHCH_2CH_2CO$ (O-bridge)	+320
$CHCH_2CH_2COOH$ O-xylose	+237

$CH_3C{\equiv}CC{\equiv}CCH{=}C{=}CHX$

X = CH_2CH_2OH	+340
$CH(OH)CH_2CH_2COOH$	+360
$CHCH_2CH_2CO$ (O-bridge)	+300
$CHCH_2CH_2COOH$ O-xylose	-

$H(C{\equiv}C)_2CH{\equiv}CC{\equiv}(CH)_2{\overset{c}{=}}(CH)_2{\overset{t}{=}}CHCH_2COOH$ $\qquad$ -310

$H_2C{=}C{=}CHC{\equiv}CC{\equiv}CCH{\overset{c}{=}}CHCH_2COOH$ $\qquad$ -

(VIII)
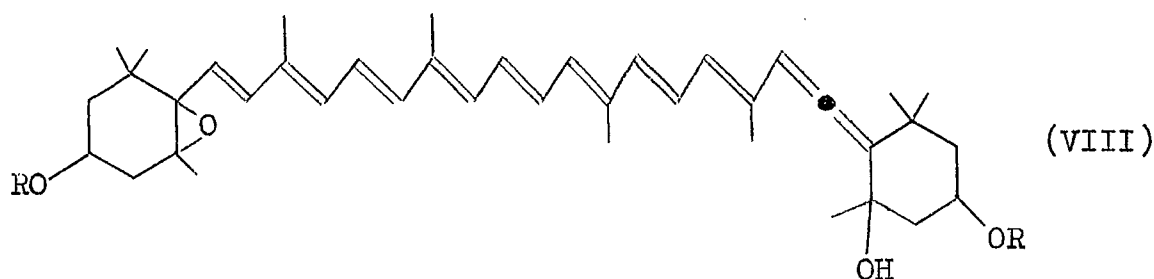
The first naturally occurring allenic fatty acid was isolated in 1964 from sapium sebiferum seed oil and was first believed to be the allenic cyclopropane carboxylic acid, 2,3-methylene-heptadeca-4,5-dienoic acid.[103] Later work showed it to be octadeca-5,6-dienoic acid.[104] (IX)

$$CH_3(CH_2)_{10}CH=C=CH(CH_2)_3COOH$$ (IX)
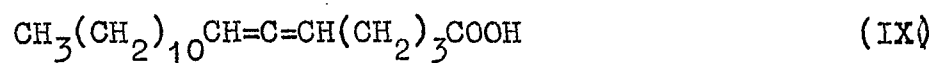
This compound has just been synthesised and its absolute configuration determined by Landor and Punja.[105]

The Stereochemistry of Allenes

The stereochemical significance of the allenic system was first discussed by van't Hoff in his famous thesis of 1874. The original concept of van't Hoff was based on the representation of the carbon atom as a tetrahedron: double bonds between carbon atoms were shown by joining tetrahedra edge to edge, and this has been much discussed in elementary texts. The salient feature about such a model of the allenic system, is that the pairs of substituents on C_1 and C_3 lie in planes which are mutually perpendicular. Modern wave mechanics supports this feature of the early model, and indicates that the planes occupied by the two π bonds of the central carbon atom are also muthally perpendicular. A more up to date representation of the allene system is the following:

Figure 1
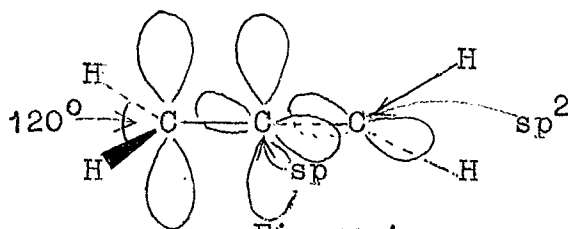
Van't Hoff realised that the orthogonal arrangement of the substituents on C_1 and C_3 of the allene system led to the possibility of optical activity in allenes if no one carbon contained the same two substituents. Although 1,1-dimethyl-allene was made three years later, sixty years elapsed

before Maitland and Mills[106] were able to prepare the first optically active allene although many other attempts had been made. These workers prepared the (+) and (-) enantiomers of 1,3-diphenyl-1,3-di-∝-naphthylallene by dehydration of the corresponding prop-2-en-1-ol derivative with (+)- or (-)-camphor-10-sulphonic acid respectively.
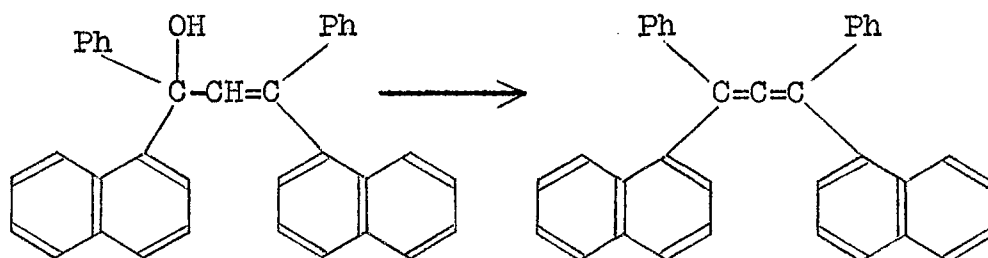
The product from the asymmetric dehydration was only slightly enriched in one enantiomer and this was increased by fractional crystallisation.

The first successful resolution of an allenic compound was carried out in 1935 by Kohler, Walker and Tischler.[107] These workers converted 1-∝-naphthylallene-3-carboxylic acid into its glycollic acid ester, via the acid chloride and resolved this by forming the crystalline diastereoisomeric (-)-brucine salts which were separable by fractional crystallisation.

Brucine salt
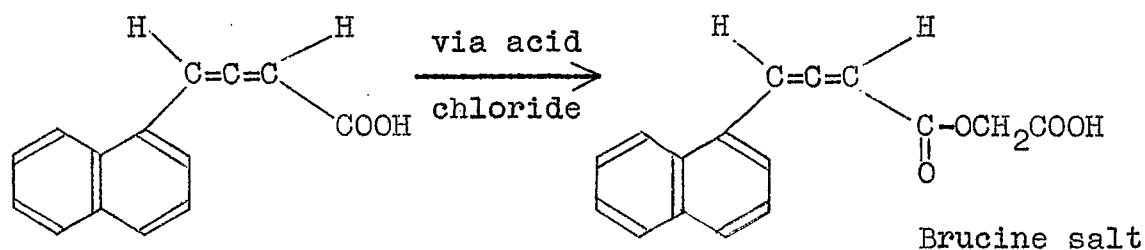
Resolution of an allenic acid was also accomplished by Watiz and Palchak[108] in 1951. Octa-2,3-dien-4-carboxylic acid was prepared by the reaction of the Grignard derivative of 2-bromo-oct-3-yne with carbon dioxide and this was resolved via its diastereoisomeric strychnine salts which were separable by fractional crystallisation.

$$CH_3-\underset{\underset{MgBr}{|}}{CH}-C\equiv C-(CH_2)_3CH_3 \xrightarrow{CO_2} CH_3-CH=C=C\underset{(CH_2)_3CH_3}{\overset{CO_2H}{<}} \xrightarrow{} \text{Strychnine salts}$$
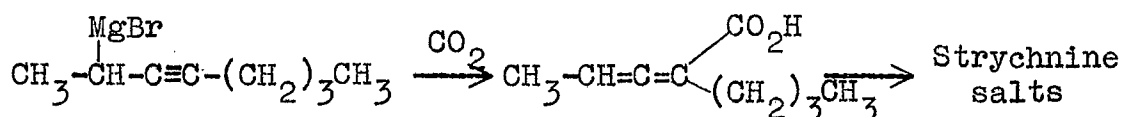
In 1957 Jacobs and Dankner[109] achieved an asymmetric synthesis of 1,3-diphenylallene and of 1-(p-biphenyl)-3-phenylallene, by prototropic rearrangement of their corresponding propynes with optically active bases adsorbed on alumina. The propynes were passed through columns containing the base impregnated alumina, pentane being used as the eluting solvent. The optically active allenic hydrocarbons were eluted and these were subsequently recrystallised to constant specific rotations. The stereoselectivity obtained by this method was low.

The (+)-enantiomer of 1,3-diphenylallene was also prepared in a much purer state than that obtained by the previous workers by Jones, Wilson, and Tutweiler.[110] These workers prepared the (+)-enantiomer by the action of lithium ethoxide on (+)-N-nitroso-N-(trans-2,3-diphenyl-cyclopropyl)-urea. The latter compound was prepared by

the following reaction sequence from (-)-trans-2,3-diphenyl-

cyclopropane-carboxylic acid.
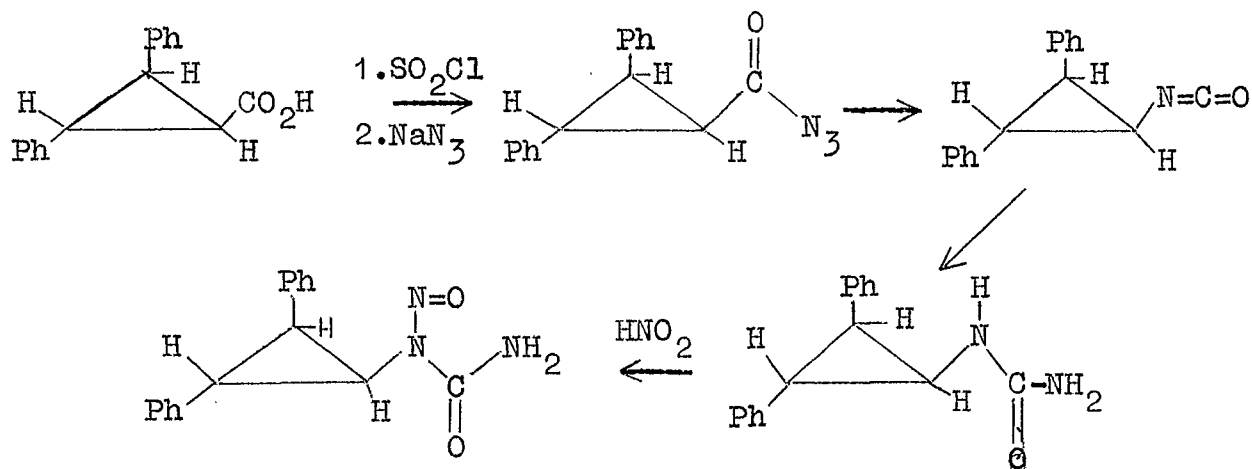
The reaction with lithium ethoxide may involve the

intermediate formation of diazocyclopropane which decomposes

to the allene either directly or via the carbene.[111]
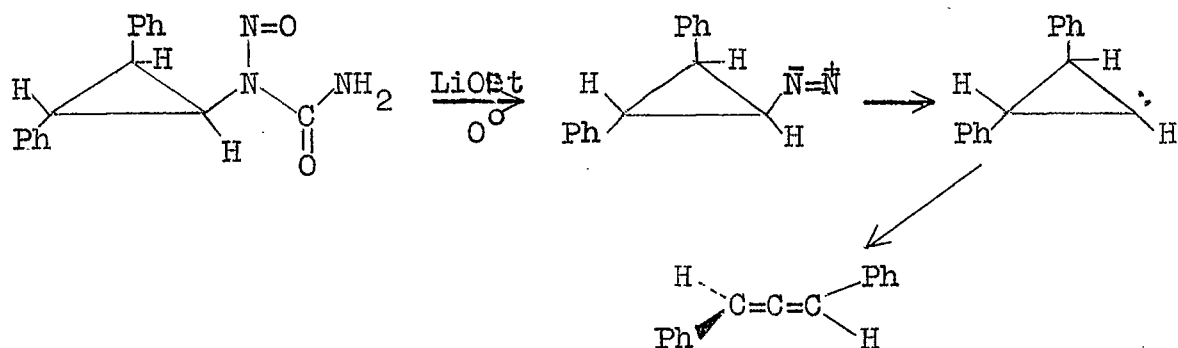
The stereochemical course of this conversion has

recently been analysed by Jones and Wilson[123] from which

it was deduced that (+)-1,3-diphenylallene has the S

configuration. This is in agreement with the result

obtained recently by Mason and Vane[124] from a study of

the electronic absorption and circular dichroism spectra of

the compound.

It was shown by Landor, Taylor-Smith, and Evans[112,113] that optically active 1-chloro-3,4,4-trimethylpenta-1,2-diene could be prepared from optically active 3,4,4-trimethylpent-1-yn-3-ol by reaction with thionyl chloride. These authors considered that this reaction could go by either an $S_N i'$ or an $S_N 2'$ mechanism. They found that under conditions favouring an $S_N i'$ mechanism, optically active allenic chloride, having the same sign of rotation as that obtained under conditions favouring an $S_N 2'$ mechanism, was produced from optically active acetylenic carbinol of given sign of rotation. The $S_N 2'$ mechanism requires the loss of oxygen at the asymmetric centre (C_3) and concerted attack by Cl^- at the terminal acetylenic carbon atom (C_1) from the same side of the molecule.[*] This appears quite reasonable on the basis of the stereo-electronic requirements[28a] of the system. (Cf. p. 90).

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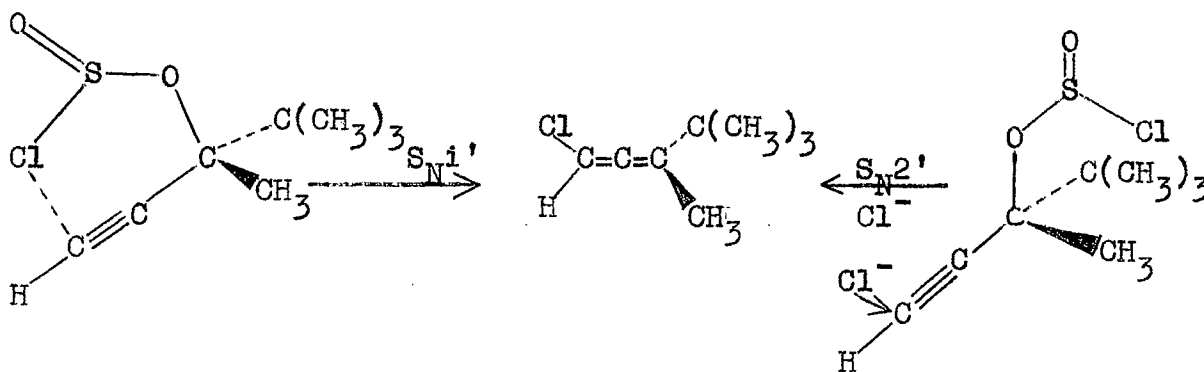
[*]Stork and White[114] observed the same effect in allylic rearrangements.

The absolute configuration of the acetylenic carbinol[**]
was determined by Landor and Evans[117] as R(-) by relating
it to S-(+)-2-t-butyl lactic acid which was synthesised
by reacting menthyl pyruvate with t-butylmagnesium chloride
(application of Prelog's rule[40]). It was shown that
conversion of acetylenic alcohol to allenic chloride
proceeds by an S_Ni' mechanism with retention of config-
uration and the absolute configuration of the allenic
chloride was therefore assigned as S(-) by these workers.

Later work by Landor and Evans (unpublished) showed
that the corresponding optically active allenic bromide
could be prepared in good yield from the optically active
acetylenic carbinol by use of a cuprous bromide-copper
catalyst initially developed by Black, Landor, Patel, and
Whiter.[118] The absolute configuration of 1-bromo-3,4,4-
trimethylpenta-1,2-diene was assigned by a correlative
method in which the (-)-chloroallene (S)- configuration
and the (+)-bromoallene were converted by carbonation of
their Grignard derivatives to mixtures of the allenic
and acetylenic acids. These acids were separated by
elution chromatography using silica gel and found in each
case to be dextrorotatory. These results are summarised
below.

[**]Subsequently deduced by Eliel[115] from a consideration of
the polarisability of the substituents based on Brewster's
theory.

$$
\underset{\substack{\text{Me} \\ }}{\overset{\substack{\text{Bu}^t \\ }}{}}\!\!\!\!C=C=C\!\!\!\!\underset{\text{MgX}}{\overset{\text{H}}{}} \quad \xrightarrow{\ CO_2\ } \quad \underset{\substack{\text{Me} \\ }}{\overset{\substack{\text{Bu}^t \\ }}{}}\!\!\!\!C=C=C\!\!\!\!\underset{CO_2H}{\overset{\text{H}}{}} \quad + \quad \underset{\text{Me}}{\overset{\text{Bu}^t}{}}\!\!CH\text{-}C\equiv C\text{-}CO_2H
$$

<div align="center">2 : 1</div>

X = Cl or Br   ratio of products

R-(-)acetylenic   ⟶   S-(-)allenic   ⟶ (+)-allenic acid
       alcohol   chloride   and
                                                  (+)-acetylenic acid

R-(-)acetylenic   ⟶   (+)-allenic   ⟶ (+)-allenic acid
       alcohol   bromide   and
                                                  (+)-acetylenic acid
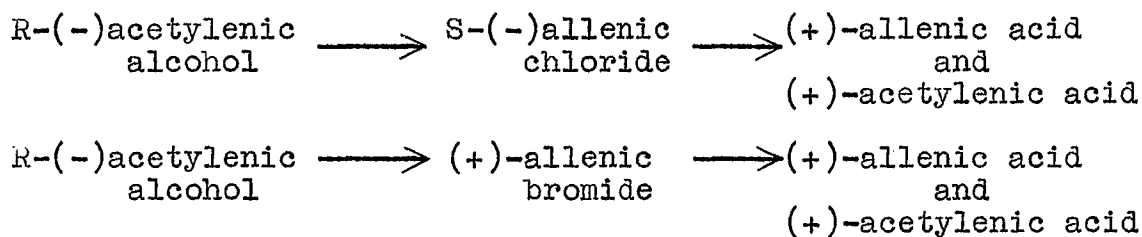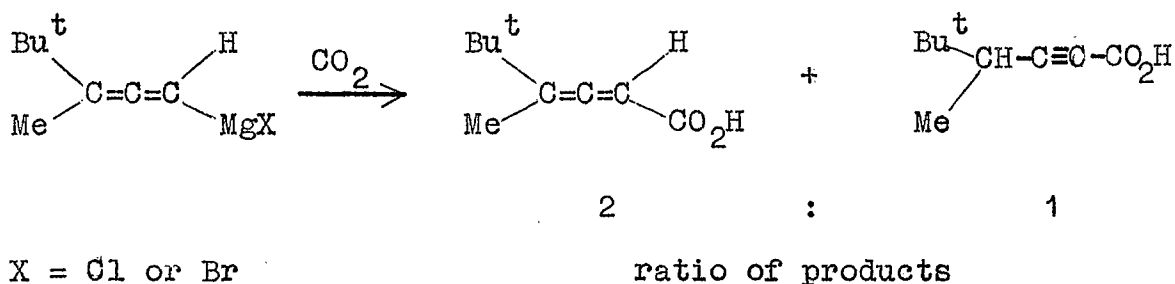
The configuration of the (+)-allenic bromide was therefore

deduced to be S.[*]

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*It is at first sight surprising that the allenic chloride
is S(-) whilst the corresponding allenic bromide is S(+).
This observation is no doubt due to the optical rotatory
dispersion curve of one (or possibly both) of these compounds
crossing the zero axis of rotation, as in figure (a) or (b).

figure (a)   figure (b)
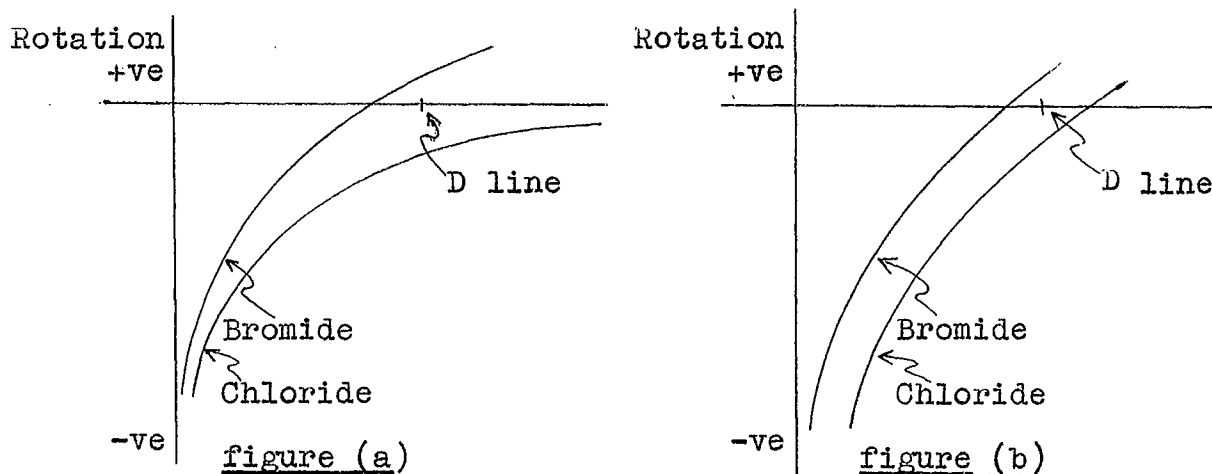
This situation is not unique. For example Sjoberg[119]
observed that for a given configuration at the asymmetric
carbon the meta- and para-iodophenyl ethers of lactic acid
were dextrorotatory at the D line whilst the orthoisomer
was laevorotatory.

In 1960, Jones, Loder, and Whiting[57] established the

absolute configuration of 2,2-dimethylhexa-3,4-dienal by

pyrolysis of optically active isobutyraldehydedibut-1-ynyl

acetal. Elimination of but-1-yn-3-ol was postulated to

give the vinyl ether which was not isolated and this

by Claisen rearrangement gave the corresponding allenic

aldehyde.

$$(CH_3)_2CHCH \begin{array}{c} O-CH-C\equiv CH \\ | \\ CH_3 \\ \\ O-CH-C\equiv CH \\ | \\ CH_3 \end{array} \longrightarrow \quad \longrightarrow$$
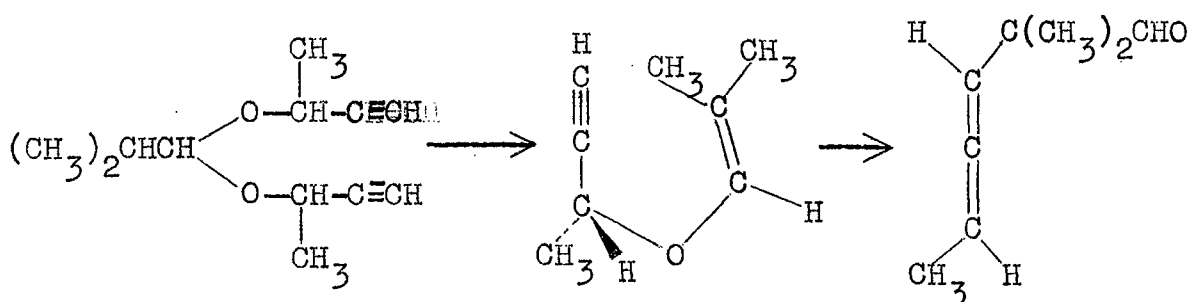
The absolute configuration of (+)-but-1-yn-3-ol was est-

ablished by hydrogenation to (+)-butan-2-ol of known

configuration and this was confirmed by the detailed

work* of Baker, Landor, Landor, and Patel.[78]

In 1961 Gianni[120] synthesised the glycolic acid ester

of 1,3-diphenyl-3-(1-naphthyl)allene-1-carboxylic acid

(X) by the method of Kohler, Walker, and Tischler[107] and

resolved this via the brucine salts. The glycolic acid ester

*In their preliminary account, Jones, Loder, and Whiting[57]
state that they are "relating the butynol $[\alpha]_D^{20}$ -12.6°
(homogeneous l=1 dm.) to the corresponding hydrogen phthalate
$[\alpha]_D^{23}$ -6.6° (c 10.0 in CHCl$_3$)." According to Baker, Landor,
Landor, and Patel,[78] however, (+)-but-3-yn-2-yl hydrogen
phthalate $[\alpha]_D^{20}$ +7.7° gave (-)-but-3-yn-2-ol $[\alpha]_D^{20}$ -17.4°.

was then converted stereospecifically by bromine to 1,3-diphenyl-3-(1-naphthyl)-2-bromocrotono lactone(XI).
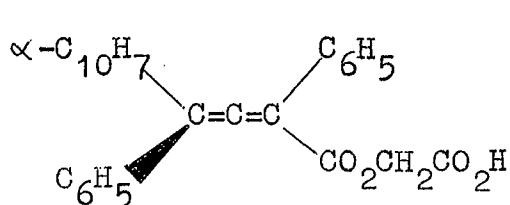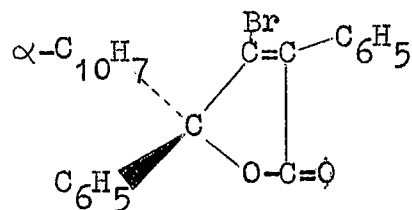
(X)   (XI)

Attempted ozonolysis of this lactone to ∝-naphthyl-mandelic acid (XIII) failed. The lactone was reduced to 1,3-diphenyl-1-(∝-naphthyl)-2-bromo-2-butene-1,4-diol (XII), ozonolysis of which also failed to give ∝-napthyl-mandelic acid.
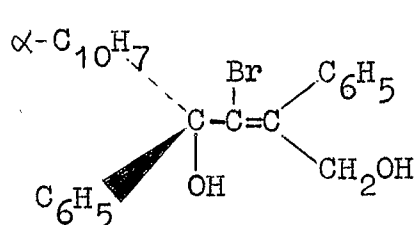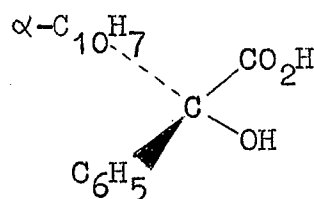
(XII)   (XIII)

The optical rotatory dispersion curves of the lactone (XI) and diol (XII) were compared with that of an authentic sample of R(+)-∝-naphthylmandelic acid (XIII). It was found that the dextrorotatory isomers of all three compounds showed a single positive Cotton effect. On the basis of the R(+) assignment to (XIII), the R(+) configuration was assigned to (XI) and (XII). As (XI) was formed from the allene (X) stereospecifically, the R(+) configuration was assigned to the allene.

In 1962 Agosta[121] deduced the configuration of

(+)-pentadiendioic acid (XIV) by forming a Diels Alder

adduct with cyclopentadiene and converting this into the

2,4-dinitrophenylhydrazone of (+)-norcamphor of established

configuration.

$$\begin{array}{ccc} \text{HOOC} & & \text{H} \\ & \diagdown \quad \diagup & \\ & \text{C=C=C} & \\ & \diagup \quad \diagdown & \\ \text{H} & & \text{COOH} \end{array}$$

(XIV)
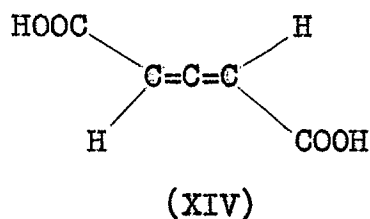
In 1965 it was shown by Lowe[125] that the absolute

configuration of allenes could be predicted by an applic-

ation of Brewster's[126] theory. According to Brewster[126]

a centre of optical activity can be described as an

asymmetric screw pattern of polarizability. Lowe applied

this concept to allenes by viewing the allene system from

one end so that the near substituents are in a vertical plane

and the far substituents are then necessarily in a horiz-

ontal plane. Then, if when the more polarizable substituent

in the vertical plane is uppermost and the more polarizable

substituent in the horizontal plane is to the right, the

polarizability will have a clockwise screw pattern and

the enantiomer will be dextrorotatory. If the more polar-

izable substituent in the horizontal plane is to the left,

the polarizability will have an anti-clockwise screw pattern

and the enantiomer will be laevorotatory.
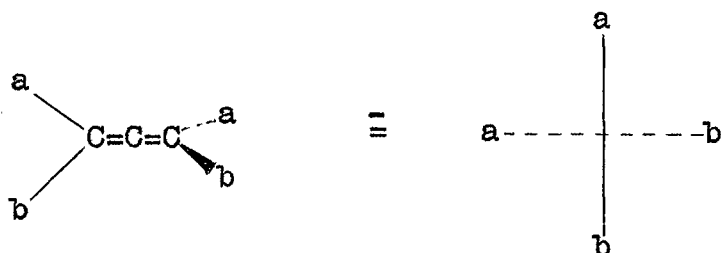
e.g. in Figure 2 if the polarizability of "a" is greater than
that of "b", the compound is laevorotatory.

It follows therefore that the sign of rotation together
with the above rule can be used to predict the absolute
configuration of allenes.

On the basis of this rule, Lowe predicted that the
naturally occurring fungal allenes containing the rigid
diyne-allene system (R.C≡C-C≡C-CH=C=CHR') (where R = H
or Me, and R' does not introduce conformational asymmetry)
should have the R(-) and S(+) configuration. The deter-
mination of the absolute configuration of these compounds
by a method described in this thesis has confirmed this
prediction.

The Claisen Rearrangement

The Claisen rearrangement[41] was discovered in 1912 and has since undergone extensive investigation; it is the subject of several reviews.[59,63,64] Claisen and Tietze[67] put forward an intramolecular mechanism for the arrangement and this has now been well established. Thus Ryan and O'Conner[73] synthesised phenyl allyl ether with the terminal carbon marked by radioactive C^{14} and traced the path of C^{14} through the rearrangement by degradation of the product.
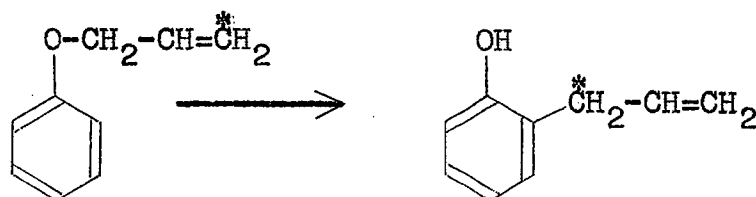
It was shown that migration with inversion of the allyl group was the only reaction which had occurred, thus supporting a cyclic mechanism.

Kincaid and Tarbell,[65] studied the rearrangement of allyl 4-methylphenyl ether and confirmed that the reaction was strictly first order over a fivefold change in concentration in diphenyl ether solution, and that the initial rate in pure liquid was the same as the rate in solution. These results, as well as those of Alexander and Kluiber[134] in which high stereospecificity in the rearrangement of (-)-1,3-dimethylallyl ether was observed, also support

the cyclic mechanism.

The Claisen rearrangement is not confined to ethers of phenols. Thus vinyl allyl ether, first synthesised in 1938 by Hurd and Pollack[77a] was found to undergo rearrangement to pent-4-enol when heated in the liquid phase to 200-250°.

$$H_2C=CH-O-CH_2CH=CH_2 \longrightarrow CH_2=CH(CH_2)_2CHO$$

A similar rearrangement of 1-methylvinyl allyl ether was found to occur at a lower reaction temperature.

The kinetics of the rearrangement of vinyl allyl ether and iso-propenylallyl ether was studied by Murphy, Schuler[77b] and Stein[77c] during the early 1950s and it was concluded that the reactions were homogeneous, first order and accompanied by a large negative entropy of activation. The observations led to the proposal of a cyclic mechanism for these rearrangements.
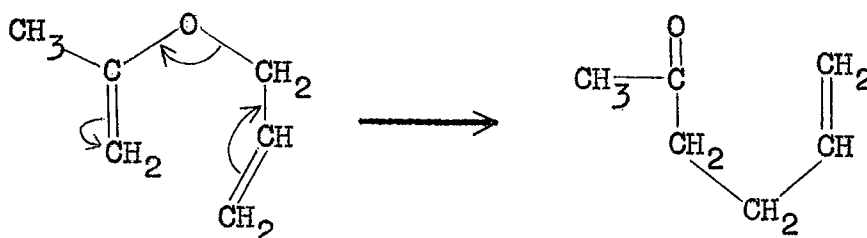
It has recently been demonstrated by Landor and Black[54] that propargyl vinyl systems of type $RC\equiv C-CH_2-O-CH=CH_2$ can be rearranged to the allenic aldehydes by pyrolysis under special conditions. A series of these ethers were

rearranged and it was observed that as methyl substitution
on the propargyl vinyl ether increased, the temperature
at which rearrangement occurred decreased. Since increas-
ing methyl substitution of the propargyl vinyl ether should
not favour a two electron shift (I) ──➤ (II) Landor and
Black rationalised this observation by postulating a one
electron shift as in (III).

    (I)   (II)   (III)   (IV)
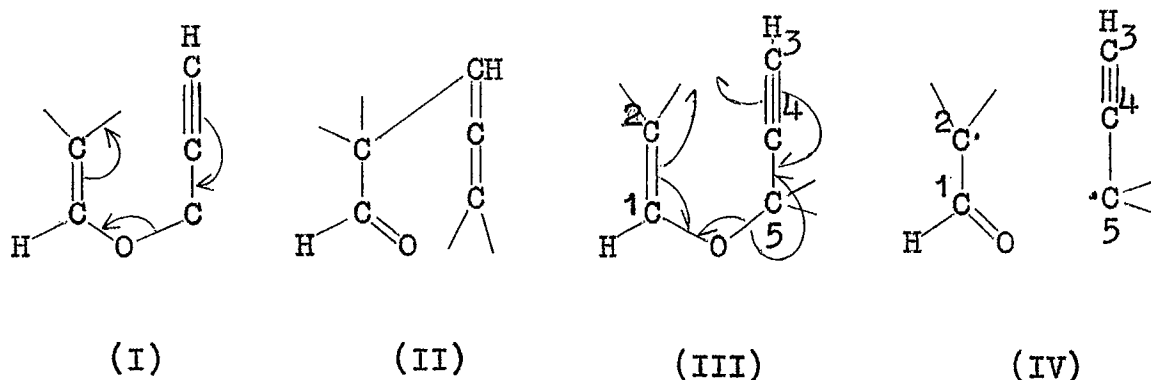
Partial radical formation at C_2 and C_5 (viz. (IV)) is
helped by increasing substitution at these points.

An independent investigation by Jones, Loder, and
Whiting[57] has established the direct conversion of iso-
butyraldehyde dipropargyl and dibut-1-ynyl acetals to the
corresponding allenic aldehydes without isolation of the
ether. Starting with optically active but-1-yn-3-ol of
known absolute configuration, the absolute configuration of
the optically active allenic aldehyde was deduced, postulat-
ing the ether as an intermediate (cf. p. 82).

The Stereochemistry of the Reduction of Cyclohexanones

It is well established that the reduction of alkyl-
cyclohexanones gives mixtures of cis and trans alkylcyclo-
hexanols.[36,146] The introduction of conformational concepts[147]
permitted a detailed analysis of the mechanism of such
reductions. All such analyses start with the assumption
that cyclohexanones are predominantly in the chair form
which is thermodynamically more stable than the boat
(flexible) form. The attacking entity, e.g. a metal hydride,
may then approach the carbonyl group either from the axial
side or the equatorial side of the chair form of a cyclo-
hexanone. Axial attack gives equatorial alcohols, whereas
equatorial attack gives axial alcohols.[25] Although mixtures
of the axial and equatorial alcohols are usually obtained,
it has been observed that reduction of unhindered[*] ketones
usually gives predominantly the more stable equatorial
alcohols[36] whereas hindered ketones give predominantly the
unstable axial alcohols.[25] This is at first sight sur-
prising since the axial alcohols from hindered ketones are
considerably less stable than the corresponding equatorial
alcohols.

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[*]The term "hindered ketone" is now accepted as meaning a
cyclohexanone having an axial substituent (other than a
hydrogen) in the 3 and/or 5 position of the ring.

Dauben[25] discussed this problem in 1956 and proposed that the ratio of equatorial to axial alcohol produced in the reduction of a cyclohexanone depended on the relative importance of two opposing effects. These he termed "steric approach control" and "product development control".

In the case of a hindered ketone, approach from the axial side of the ring is hindered by the axial substituent in the 3 and/or 5 position of the ring. This favours attack from the equatorial side and thus favours the formation of axial alcohol.
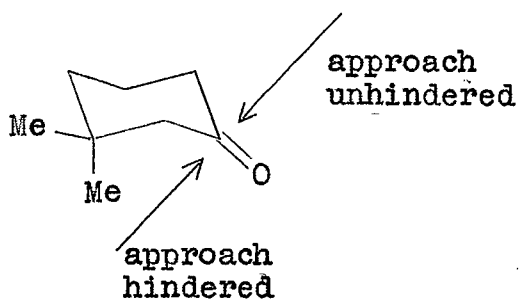
It is this effect that Dauben has termed "steric approach control".

In describing the opposing effect, "product development control", Dauben made the assumption that for an unhindered ketone approach of the attacking entity is equally likely from either equatorial or axial side, and he accepted the earlier proposal by Cram and Green[38] that the first step in the reduction of ketones by lithium aluminium hydride is the formation of a co-ordination

complex between the hydride and the carbonyl oxygen atom.
The formation of an axial alcohol thus requires the intro-
duction of the O-Al-group into an axial position, (I).

(I)
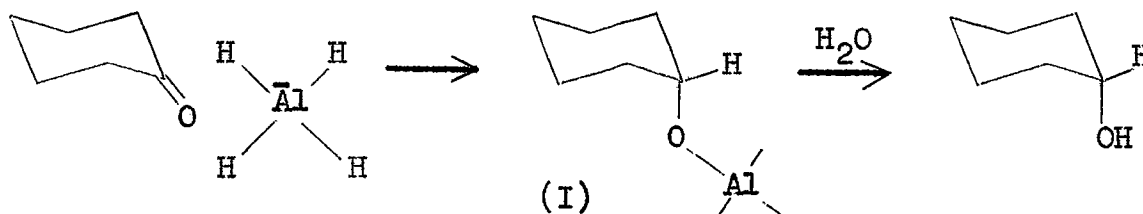
The formation of equatorial alcohol, on the other
hand, requires the introduction of the O-Al- group into
an equatorial position, (II).

(II)
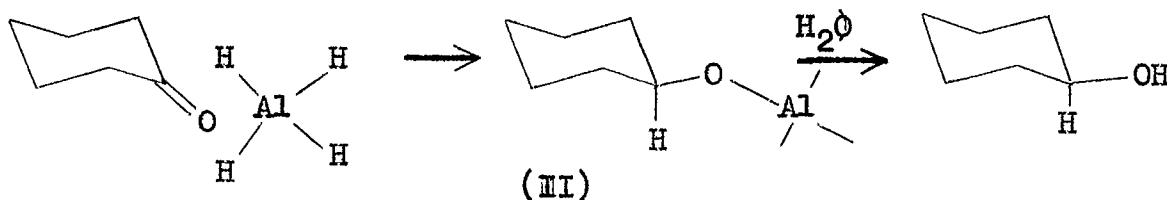
The formation of isomer (I) requires the expenditure
of more energy than does the formation of isomer (II) due
to the axial/axial interaction that is set up in the
former, and this favours the formation of equatorial
alcohol.

According to Dauben, therefore, the ratio of equatorial
to axial alcohol in the product depends on the relative
importance of steric approach control and product devel-
opment control in the reduction of any substituted cyclo-
hexanone. In this way he interpreted the product ratios

(axial/equatorial alcohol) produced in the reduction of menthone, 4-methylcyclohexanone and 2-methylcyclohexanone by metal hydrides as shown in Table II.

TABLE II[25]

Distribution of Isomers Formed by Reduction of Ketones

Reagent	Menthone		4-Methyl Cyclo- hexanone		2-Methyl Cyclo- hexanone	
	Menthol %	Neo- men- thol %	% trans	% cis	% trans	% cis
LiAlH$_4$	71	29	81	19	82	18
NaBH$_4$ in methanol	49	51	75	25	69	31
NaBH$_4$ in Pyridine	-	-	60	40	56	44
Al(O-Pr^i)$_3$	30	70	67	33	42	58
NaBH(OCH$_3$)$_3$	-	-	-	-	70	30
Equilibrium	mostly	-	88	12	99	1

In the light of Dauben's work, Haubenstock and Eliel[22,23] investigated the reduction of 3,3,5-trimethylcyclohexanone using alkoxy complexes of lithium aluminium hydride and sodium borohydride. They showed that there is some cor-relation (qualitative) between reagent size and axial/ equatorial ratio of the alcohols produced and interpreted this on the basis of the concepts discussed by Dauben. However, some anomalous results with complexes of secondary

alcohols were obtained, which gave lower axial/equatorial
ratios than expected. These were explained by postulating
that lithium aluminium hydride complexes obtained from
secondary alcohols disproportionate to give lithium aluminium
hydride and lithium tetra-alkoxyaluminium so that some
reduction was due to lithium aluminium hydride itself.

$$2LiAlH_2(OR)_2 \rightleftharpoons LiAl(OR)_4 + LiAlH_4$$
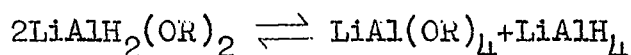
In the case of very bulky secondary alcohols and tertiary
alcohols, however, the equilibrium lies well to the left.

Some of the results obtained by Haubenstock and
Eliel are shown in Table III (p.112).

The concept of product development control has been
attacked by Richer.[35] Richer maintains that as additions
to acyclic ketones are regulated only by steric factors such
as Cram's rule[39] and Prelog's rule,[40] there is no need to
postulate the concept of product development control.
Dauben postulated product development control in order to
explain the relatively small amount of axial alcohols
produced from unhindered ketones, but in other cases axial
alcohols of low stability are produced in large amounts
from highly hindered ketones. According to Richer, "the
stereochemical results of all the additions to unhindered
ketones by groups small enough not to interfere with the
axial hydrogens in positions 3 and 5, will be directed
exclusively by the presence of the axial hydrogens in

positions 2 and 6 which hinder attack from the equatorial side". Some of Richer's results are shown in Table IV (p. 126).

These conflicting views are further discussed later in this thesis, (p. 112).

Preparation of Allenynols with Deactivated Lithium Aluminium Hydride.

In 1960 an investigation was started in this laboratory[1,2] into the reduction of diynenols with lithium aluminium hydride as a potential route to naturally occurring allenynols. It was shown that simple alkyl- and aryl-penta-3,4-dienols of type $R-C\equiv C-CH=CH-CH_2OH$ of molecular weight similar to that of the naturally occurring allenes could be prepared pure, in good yield. Alkynylpenta-3,4-dienols (allenynols) of type $R-C\equiv C-CH=C=CH-CH_2CH_2OH$ underwent further reduction to allenenols, however, and since the complete separation of allenenol from allenynol was seldom possible, only very small yields of pure allenynol could be obtained by this procedure.

$$RC\equiv C-CH=C=CH-CH_2CH_2OH \xrightarrow{\text{LiAlH}_4} RCH=CH-CH=C=CHCH_2CH_2OH$$
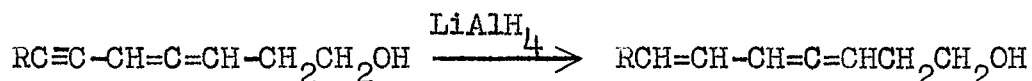
The mechanism of the first stage of the reduction of an enynol to the corresponding allenic alcohol is now reasonably well established by deuteration experiments[3] and a seven-membered cyclic allene complex (I) has been used as a convenient representation of the reaction intermediate.[4]*

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*See the later discussion of this, however, (p.55).

R–C≡C–CH=CH ... Al—O ... H ... CH₂ ⟶ structure (I)

$$(I)$$
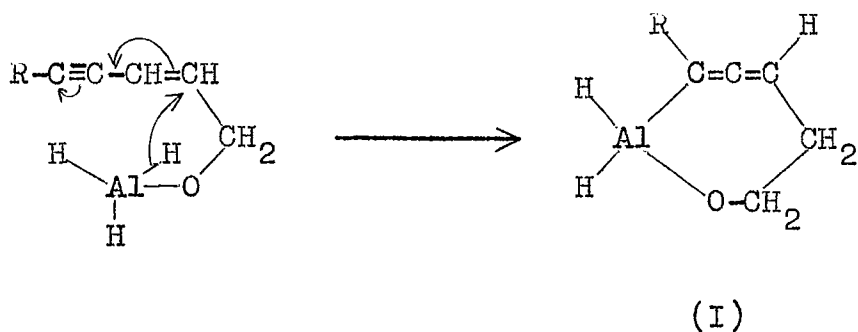
It had already been shown by Bohlmann, Enkelmann, and Plettner[122] that the reduction of the diynol, 6-phenyl-hexa-3,5-diyn-1-ol to the corresponding enynol by lithium aluminium hydride was prevented if the hydroxyl group was protected by formation of the tetrahydropyranyl ether. This indicated that the aluminium atom must be attached to the oxygen of the diynol in order to donate a hydride ion to C_2 of the latter. To establish whether or not this also applied to reduction of enynols 1-tetrahydropyranyl-oxypent-2-en-4-yne was treated with lithium aluminium hydride. No reaction occurred and the starting material was recovered quantitatively. This indicated that the aluminium atom must be attached to the oxygen of the enynol in order to facilitate hydride transfer to C_2 of a diynenol of type R–C≡C–C≡C–CH=CH–CH₂OH with lithium aluminium hydride. The first stage of the reduction, therefore, is the formation of the allenic aluminium hydride complex which will be represented here as the seven-membered ring, (II).

R–C≡C–C≡C–CH=CH ... Al—O ... H ... CH₂ ⟶ structure (II)

$$(II)$$
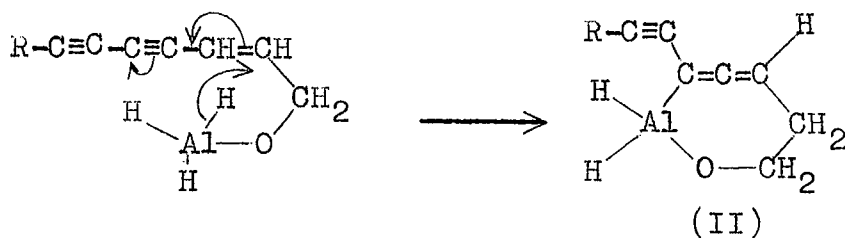
It was considered likely that the next stage of the reduction which gives the allenene, was also likely to go by an intramolecular mechanism. Since transfer of another hydride ion to (II) would produce a double negatively charged complex ion, it was considered preferable to postulate that (II) picks up a proton first. Allenene could then be produced by intramolecular hydride ion transfer as in (III) to produce a new mesomeric allene anion.

$$R-C{\equiv}C-CH{=}C{=}C\begin{smallmatrix}H\\CH_2\\CH_2\end{smallmatrix} \quad \longrightarrow \quad R-C{=}C{=}CH-CH{=}C\begin{smallmatrix}H\\CH_2\\CH_2\end{smallmatrix}$$

(III)
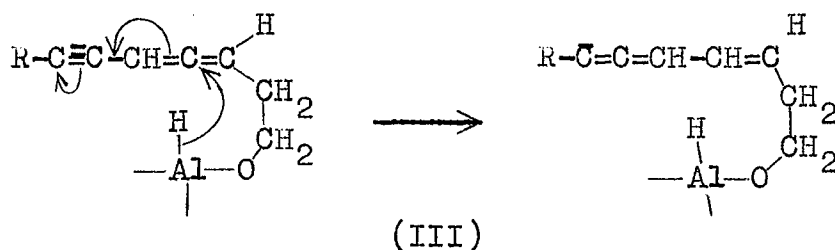
It was reasoned that if this mechanism is correct then removal of two hydride ions from the lithium aluminium hydride by reaction with a suitable primary alcohol, should suppress the second stage of the reduction. Landor and Pepper[1] showed that reduction of alkynylpent-2-en-4-yn-1-ols with dimethoxy- and diethoxy-lithium aluminium hydride did give less reduction of allenyne to allenene, but did not suppress the formation of the latter completely.

At about this time, Bohlmann, Herbst, and Gleinig[5] claimed to have obtained (±)-nona-3,4-diene-6,8-diyn-1-ol ((±)-marasin) in 83% yield by the reduction of non-2-ene-4,6,8-triyn-1-ol with an excess of lithium aluminium hydride. Their product was described as showing a band at 968 cm.$^{-1}$

in the infra-red spectrum, typical of the trans-double

bond in the allenene system,[1] and absent in natural marasin.[6]

This work was repeated under the conditions described by

the previous workers.

Non-2-en-4,6,8-triyn-1-ol was prepared by coupling

5-bromopent-2-en-4-yn-1-ol with diacetylene in the presence

of base and cuprous ions* (p. 147), reduced with lithium

aluminium hydride under the conditions specified by the

previous workers[5] and isolated by the same procedure. The

product was eluted from acid alumina in fractions 14 to 19

in approximately 85% theoretical yield (based on non-2-en-

4,6,8-triyn-1-ol). This is similar to the yield obtained

by Bohlmann, Herbst, and Gleinig. The approximate dis-

tribution of the product in these fractions was as follows:

fraction 14, 34%; fraction 15, 18%; fraction 16, 15%;

fraction 17, 11%; fraction 18, 4%; fraction 19, 0.6%.

The main fraction, fraction 14, and fraction 15 had

maxima in the ultra-violet spectrum at λ_{max} 212 (ϵ47,000),

265 mμ(15,000), λ_{sh} 253 (ϵ12,400), 272 mμ(ϵ12,600);

(U.V.No. 2) and bands in the infra-red spectrum at

ν_{max}3,450 m. (OH), 3,350 m (R-C≡CH), 2,210 m (R-C≡C-R),

1,950 w (-C=C=C-), 965 cm.$^{-1}$ m (trans-double bond in

---

*Non-2-en-4,6,8-triyn-1-ol was prepared using the conditions
specified by Bohlmann, Herbst, and Gleinig. A considerable
improvement in yield was later achieved, however.

allenene system); (I.R. No. 1). The material absorbed five

molar equivalents of hydrogen. The band at λ265 in the

ultra-violet spectrum was 2 mμbelow the equivalent band

(λ 263) in the marasin spectrum. Such a bathochromic shift

in the ultra-violet spectra has been shown to accompany

reduction of allenynes to allenenes.[1] The band at 965 cm.$^{-1}$

in the infra-red spectrum is also typical of allenenes,[1]

and it seems reasonable on the above evidence to propose

that fractions 14 and 15 consisted of an allenene. The

presence of both terminal and internal acetylenes in the

infra-red spectrum indicated that more than one allenene

was present and mechanistic considerations led to the con-

clusion that two isomeric trienynols might be present, nona-

3,4,8-trien-6-yn-ol (IV), and nona-3,4,6-trien-8-yn-1-ol (V).

$$CH_2=CH-C\equiv C-CH=C=CH-CH_2CH_2OH \qquad\qquad (IV)$$

$$HC\equiv C-CH=CH-CH=C=CH-CH_2CH_2OH \qquad\qquad (V)$$
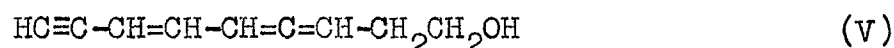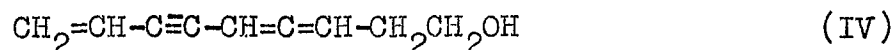
The following mechanisms for formation of compounds

(IV) and (V) seems plausible:

$$H(C\equiv C)_3-CH=CHCH_2OH \xrightarrow{\text{LiAlH}_4} H(C\equiv C)_2CH=C=CH(CH_2)_2OH$$

$$H(C\equiv C)_2CH=C=CH(CH_2)_2OH$$

$$\text{LiAlH}_4 \swarrow \qquad\qquad \searrow \text{LiAlH}_4$$

$$HC\equiv C-CH=\bar{C}-CH=C=CH(CH_2)_2OH \quad + \quad CH_2=\bar{C}-C=C-CH=C=CH(CH_2)_2OH$$

$$\downarrow H_2O \qquad\qquad\qquad\qquad \downarrow H_2O$$

$$HC\equiv C-CH=CH-CH=C=CH(CH_2)_2OH \quad + \quad CH_2=CH-C\equiv C-CH=C=CH(CH_2)_2OH$$
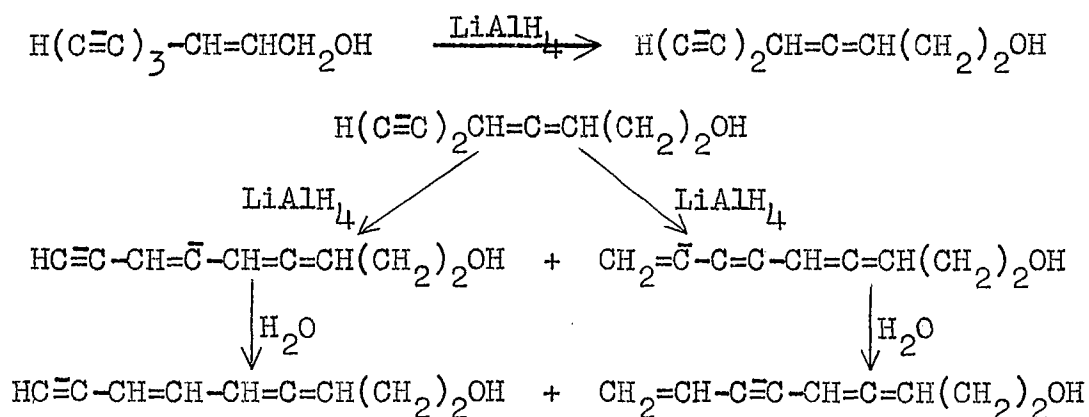
The ultra-violet spectra showed that fractions 16, 17 and

18 contained allenenes (LV) and (VI) together with increasing quantities of marasin as shown by a shift in the ultraviolet band towards λ263 for successive fractions, (U.V. No. 3). The last fraction, fraction 19, contained a small amount (0.6%) of pure marasin with typical ultra-violet spectrum.

It was desirable to have some idea of the total quantity of marasin formed but which could not be separated from the allenene. This could not be computed from extinction coefficients as these are approximately the same for marasin and the allenenes, (cf. figure 1[a] p.48). A graphical method in which the percentage of reduction product in each fraction is plotted against the fraction number was therefore employed. Based on the fact that fraction 14 and fraction 15 contained only allenene and that fraction 19 contained no allenene, a fairly accurate curve representing percentage of allenene against fraction number could be drawn, (graph I). The percentages of reduction product in fractions 16, 17 and 18, representing the mixture of marasin and allenene, were also plotted on the curve enabling the percentages of marasin in these fractions to be computed. The total yield of marasin, obtained by the repetition of the procedure of Bohlmann, Herbst, and Gleinig, and computed in this way was approximately 16%; the yield of allenene was approximately 65%. Only a small quantity

%

40

30   Total reduction product
                                       Allenene
                                       Marasin

20

10

0

14   15   16   17   18   19
                                       Fraction Nos.
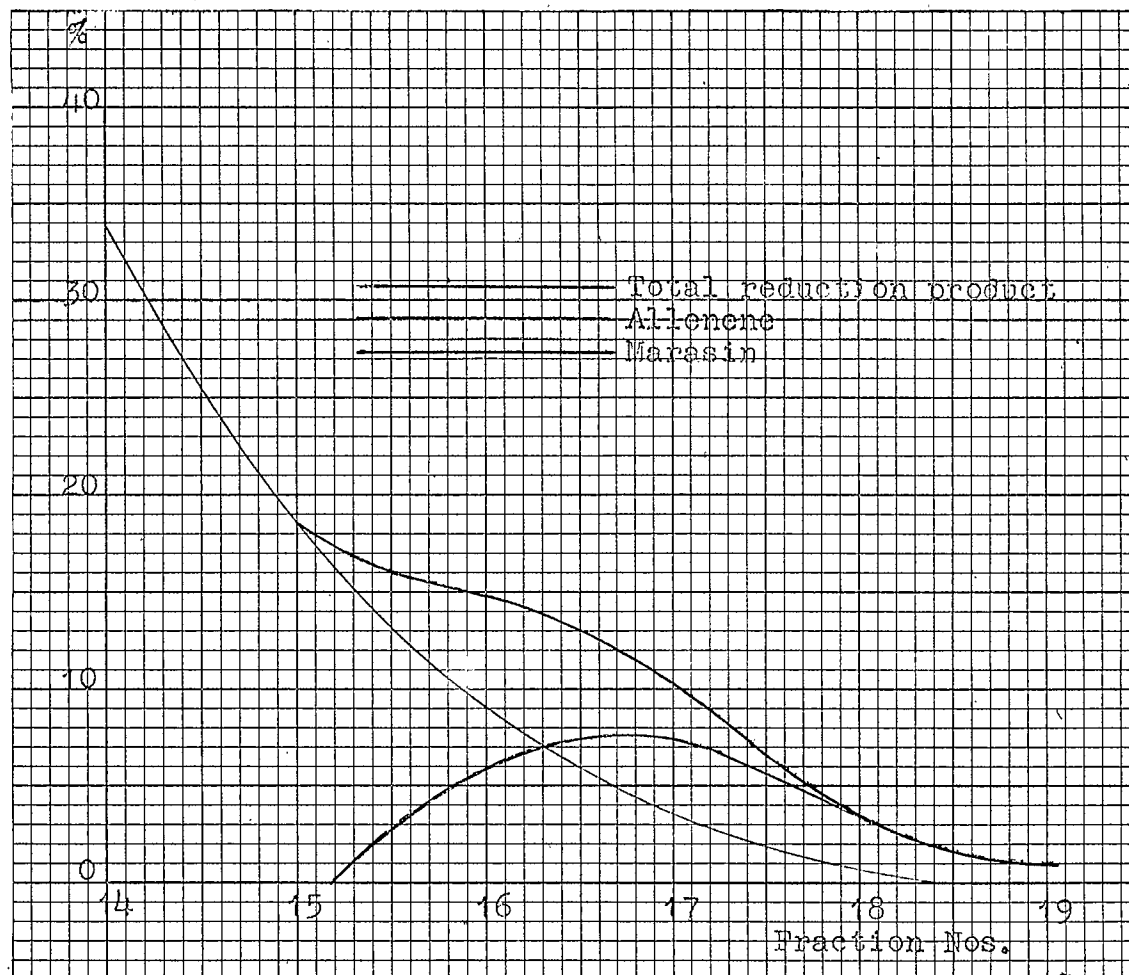
Graph I

Percentage of reduction product in each fraction is plotted
against fraction number.

of marasin (0.6%) could be obtained pure by chromatography,
however. Further chromatography of fractions 16-18 yielded
small additional amounts of pure marasin (0.1% on non-2-en-
4,6,8-triyn-1-ol) but the bulk of the marasin was still
eluted as a mixture with allenene. This work was in

agreement with earlier work by Landor and Pepper,[1] these

workers also being unable to effect complete separation of

allenene and allenyne by chromatography. In the light of this

work it is suggested that most of the material prepared by

Bohlmann, Herbst, and Gleinig was in fact a mixture of

allenenes (IV) and (VI) and that this was mistaken for

impure marasin by these workers.

As is well-known,[143] marasin undergoes isomerisation

under alkaline conditions to produce isomarasin, (VII).

$$H(C{\equiv}C)_2CH{=}C{=}CH(CH_2)_2OH \longrightarrow HC{\equiv}C{-}C{\equiv}C{-}CH{=}C\underset{O}{\overset{CH_2{-}CH_2}{\diagdown\diagup}}CH_2 \quad (VII)$$
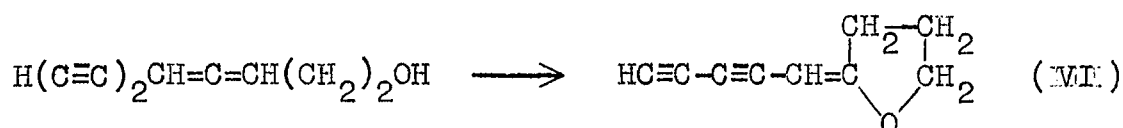
Bohlmann, Herbst, and Gleinig[5] claimed to have isomerised

their product to isomarasin in 29% yield (based on marasin).

Fraction 17, which from the graph was known to contain approx-

imately 70% of marasin (based on the total reduction product

in fraction 17 only) and 30% of allenene was subjected to the

alkaline treatment specified by the previous workers and the

products separated by their procedure using chromatography on

acid alumina. Isomarasin in 45% yield (based on total

reduction product in fraction 17 only)[*] was obtained having

[*]Due to the volatility of isomarasin the amount obtained was
calculated from the extinction coefficients due to Bendz.
Bendz had calculated the extinction coefficients of this
volatile compound by partially isomerising a number of samples
of marasin solution. Knowing the extinction coefficients of
marasin he calculated the quantity of isomarasin produced and
hence was able to obtain the extinction coefficients of the
compound as: λ_{max} 224 (20,900), 266 (10,700), 279.5 (14,500),
295 (11,200). Bohlmann, Herbst, and Gleinig give both the
weight of material produced in their experiment and extinction
coefficients which are very close to those of Bendz. They
do not indicate how these were calculated, however.

ultra-violet spectrum similar to that obtained by Bendz.[143]

This was a higher yield than was reported by Bohlmann,
Herbst, and Gleinig (29%), and is no doubt due to the fact
that the fraction containing the highest proportion of
marasin was deliberately chosen for this experiment.

It was anticipated that the allenenes (dihydromarasin)
would isomerise under basic conditions to the furan deriv-
atives, having similar ultra-violet absorption spectra
to that of isomarasin. In order to check this, fraction
14, containing only pure allenenes (i.e. no marasin), was
subjected to the alkaline treatment as used for marasin and
chromatographed as before on acid alumina. Surprisingly,
no material having an ultra-violet spectrum similar to
isomarasin was eluted. A material eluted in the fractions
expected to contain the dihydroisomarasin (by analogy with
the earlier chromatography of isomarasin) contained a compound
having absorption maxima at λ 220 and at much lower intensity
at λ 268, (U.V. No. 5). The experiment was repeated using
fraction 15, containing only allenenes, and the isolation
procedure described by Bendz.[143] Following Bendz the
isomerisation product was subjected to a counter-current
distribution in eight funnels between pentane as the
stationary phase and ethanol containing 30% water as the
mobile phase. After fifteen transfers the material prev-
iously described was found in the aqueous/ethanolic solutions

in funnels 2,3 and 4.[*] No material having an ultra-
violet absorption spectrum similar to isomarasin was found,
and it was concluded that the allenenes do not isomerise
under basic conditions to the same type of conjugated furan
derivative that is obtained with marasin. The isomerisation
product obtained was probably a mixture since fractions
14 and 15 had contained two allenenes (IV) and (V). An
attempt to obtain an infra-red spectrum of the material
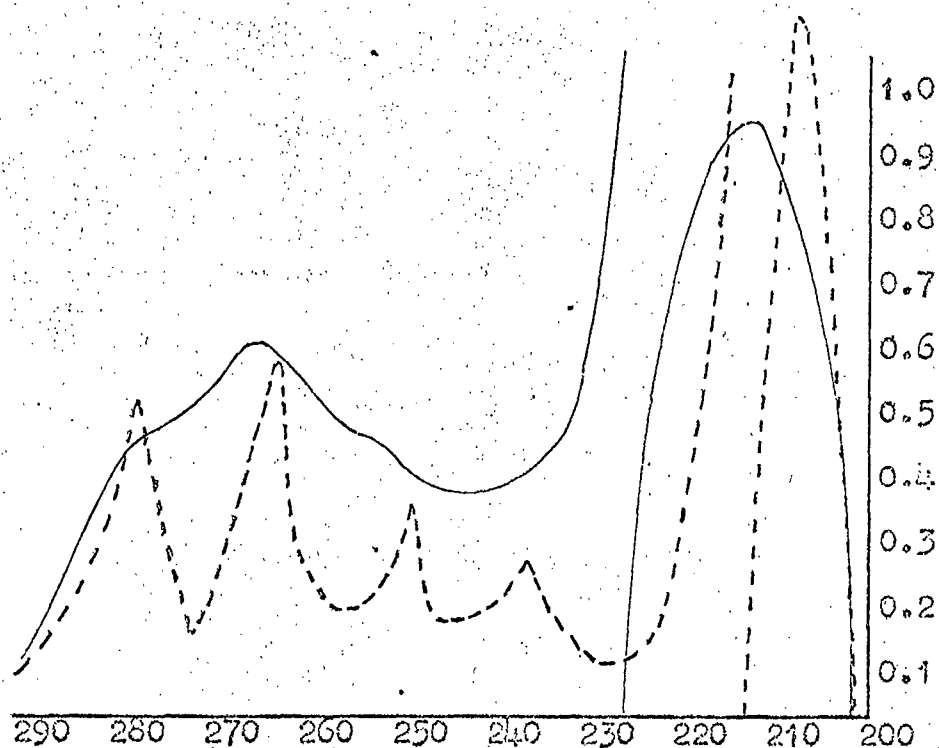
Figure 1[a]
The ultra-violet spectra of (-) marasin (-----) and
dihydromarasin (IV) and (V) (————).

[*]Bendz had found isomarasin in the aqueous/ethanolic
solutions in funnels 2, 3, 4 and 5.

was unsuccessful due to its volatility.[*]

An attempt was made to suppress the formation of
allenene and increase the yield of marasin by using lithium
diethoxy-aluminium hydride to reduce non-2-ene-4,6,8-triyn-
1-ol. Preparation of the lithium diethoxyaluminium hydride
complex was carried out by the dropwise addition of the
calculated quantity of ethanol to a previously standardised[7]
ethereal solution of lithium aluminium hydride, followed
by heating of the reaction mixture under reflux for 1 hr.
This procedure would be expected to give mainly diethoxy
lithium aluminium hydride with a minimum of the triethoxy
compound. The reduction of non-2-en-4,6,8-triyn-1-ol was
then carried out for 2 hr. at room temperature and the
aluminium complexes decomposed with 10% sulphuric acid
to prevent isomerisation of the product under basic
conditions. It was found that the yield of pure marasin
obtained was increased to approximately 6% indicating that
further reduction of marasin to allenene had been suppressed
to some extent. Ultra-violet spectra showed that allenene
formation was still occurring, however, and an estimate
by the graphical method previously described showed that
the yield of allenene was approximately 45% (based on
non-2-en-4,6,8-triyn-1-ol) and marasin approximately 30%

---

[*]The material was lost in attempting to concentrate the
dilute solution from the chromatography and the counter-
current experiment by evaporation.

(based on non-2-en-4,6,8-triyn-1-ol). Most of the marasin
was thus not separated from the allenene by the chromatography.

It was considered likely that allenene formation was
due to the presence of lithium monoethoxyaluminium hydride
resulting from the initial formation of a mixture in
preparing the reducing agent. A cyclic complex would be
expected to be more stable than the acyclic complex[*] and it
was therefore predicted that the use of a cyclic complex
of lithium aluminium hydride should suppress allenene
formation to a minimum. The cyclic complex chosen for.
investigation was the lithium aluminium hydride-butane-
2,3-diol complex. The preparation of this complex and its
use in the reduction of alka-4,6-diyn-2-en-1-ols was
carried out as described for the diethoxy complex, (p. 49).
Three molar equivalents of complex per mole of diynenol
was used for the reduction. As marasin is very unstable
and difficult to handle, two model compounds, trans-8,8-
dimethylnon-2-en-4,6-diyn-1-ol[1] and trans-hept-2-en-4,6-
diyn-1-ol,[10] were chosen for preliminary experiments.
It was found that formation of allenene was completely
suppressed; however, substantial amounts of the starting
material were also recovered. This was completely separated
from allenyne by chomatography on acid alumina. Pure

---

[*]E.g. Cyclic acetals are more stable than acyclic ones.

8,8-dimethylnona-3,4-dien-6-yn-1-ol was obtained in 14%
yield and pure hepta-3,4-dien-6-yn-1-ol in 9% yield.
Both these compounds were shown to be free of allenene
by the absence of bands in the region of 955 cm.$^{-1}$ in
their infra-red spectra, (I.R. Nos. 8 and 10). This was
in contrast to the earlier work of Landor and Pepper[1]
in which the lithium dialkoxyaluminium hydride complex was
used to reduce the above two model compounds. In both
cases the formation of some allenene was observed, and
although some hepta-3,4-dien-6-yn-1-ol was obtained pure
by chromatography, the 8,8-dimethylnona-3,4-dien-6-yn-1-ol
could not be completely freed from allenene, as shown by a
band at 955 cm. $^{-1}$ in its infra-red spectrum, (cf. ref. 1).

It may thus be concluded that in the reduction of
alka-4,6-diyn-2-en-1-ols with lithium aluminium hydride, the
first product, the allenyne, is further reduced to an
allenene. Formation of allenene can be partially sup-
pressed by using a dialkoxyaluminiumhydride complex as
the reducing agent, and may be completely eliminated by
using a cyclic lithium aluminium hydride complex. In the
latter case, however, a substantial quantity of unreduced
alka-4,6-diyn-2-en-1-ol is recovered even though excess
reducing agent is used. This may be completely separated
from the allenyne by chromatography.

The Asymmetric Synthesis and Determination of the Absolute
Configuration of Allenic Alcohols

The successful preparation of allenynols with deactivated
lithium aluminium hydride complexes (pp. 50, 51) led to the
interesting possibility that if an asymmetric complex of
lithium aluminium hydride were used as the reducing agent,
an asymmetric allenynol could be produced. Further, if it
could be deduced theoretically whether the asymmetric
reduction should give rise to the R or the S form of the
allenic alcohol, it would be possible to determine the
absolute configuration of these compounds. A preliminary
investigation into the use of lithium dimenthoxyaluminium
hydride as an asymmetric reducing agent was initiated by
Evans and Landor,[11] and further work is described in this
thesis.

The procedure used for preparing the complex was to
add the calculated quantity of menthol in ether to the
calculated quantity of an ethereal solution of lithium
aluminium hydride and to heat the reaction mixture under
reflux for 2 hr.; this was to ensure as far as possible
that equilibration was complete and a dimenthoxyaluminium
hydride complex had been formed. The enynol in ethereal
solution was then added to the ethereal solution of the
complex and stirred for 2 hr.; usually at room temperature.
The complex was decomposed by dropwise addition of water,

or by pouring into dilute acid and, in the case of simple

allenic alcohols, the products purified by careful fraction-

ation under reduced pressure. The allenic alcohols were

checked for the presence of traces of menthol by g.l.c.

and rotations measured. Three preliminary experiments

on these lines were carried out and the results are tabulated

below:

Table I

Asymmetric Reduction of Alk-2-en-4-yn-1-ols with
Menthoxyaluminium-hydride Complexes[11]

$LiAlH_4$ Mole	(-)-Menthol Mole	Alkenynol Mole	Allenic Alcohol $RCH=C=CHCH_2CH_2OH$	
			$R=CH_3$	$R=C_2H_5$
0.05	0.05	0.033	+1.68°	
0.13	0.26	0.065	+8.27	
0.125	0.25	0.075		+2.29°

Eliel[8] postulated disproportionation of complexes of

lithium aluminium hydride with secondary alcohols, to explain

his stereochemical results. The following equilibrium

can occur, although in the case of bulky alcohols the

equilibrium lies well to the left:

$$2LiAl(OR)_2H_2 \rightleftharpoons LiAl(OR)_4 + LiAlH_4$$
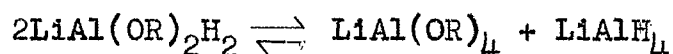
The production of optically active allenic alcohols (cf.

Table I) by the dimenthoxyaluminium hydride complex indicates

that the menthoxy groups are sufficiently large to inhibit

disproportionation of the complex. A consideration of

the stereochemistry of the complex ion is therefore

appropriate.

Examination of a Dreiding model shows that the pre-
ferred conformation of the dimenthoxyaluminium hydride
ion may be readily predicted. The most important inter-
actions are between the two hydrogens on the aluminium
atom and the equatorial hydrogens at C_2 and C'_2 and
between the aluminium hydrogens and the hydrogens on the
isopropyl groups. The menthyl chairs will also tend to
position themselves so that the aluminium is staggered
between the C_2 carbon and the axial hydrogen on C_1.
Figure 1 represents the preferred conformation of the complex
ion. The model shows that in this conformation the two
remaining hydrogens on the aluminium are exactly equivalent
and that each hydrogen is in an asymmetric environment
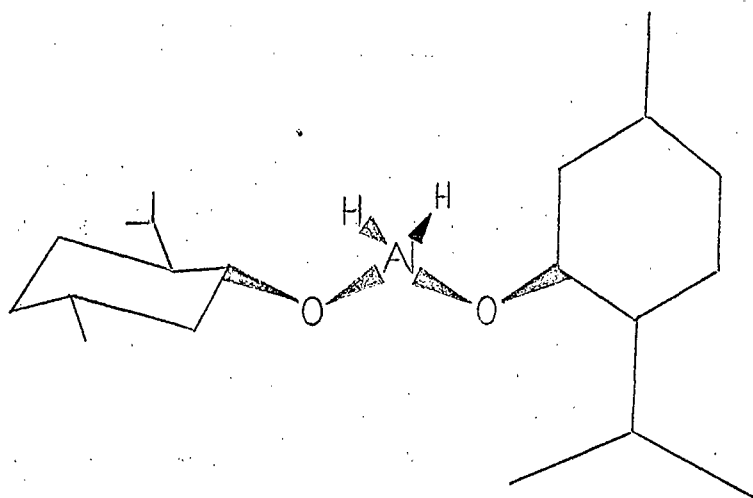
Figure 1
The dimenthoxyaluminium hydride complex in the
preferred conformation.

being shielded on one side by an isopropyl group.

It has already been shown (p. 40) that the aluminium
hydride ion must be attached to the oxygen of the enynol
in order to transfer a hydride ion to C_2 of the enynol.
After hydride ion transfer the aluminium is formally neutral
but has the characteristics of a Lewis acid; at the same
time an allenic mesomeric anion is formed. The allenic
anion can co-ordinate with a trivalent aluminium either
intramolecularly or intermolecularly. Intramolecular
co-ordination would lead to the formation of a seven-
membered cyclic allene complex (figure 2).
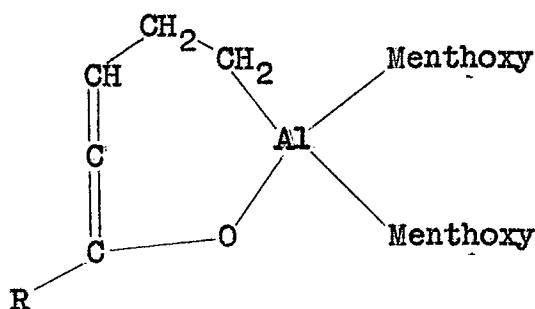
Figure 2
The seven-membered cyclic allene complex.

Intermolecular co-ordination could lead to either a poly-
meric complex (figure 3) or a dimeric fourteen-membered
cyclic complex (figure 4).

The seven-membered cyclic allene complex is used
as a convenient representation of the reaction inter-
mediate although its formation in practice is doubtful
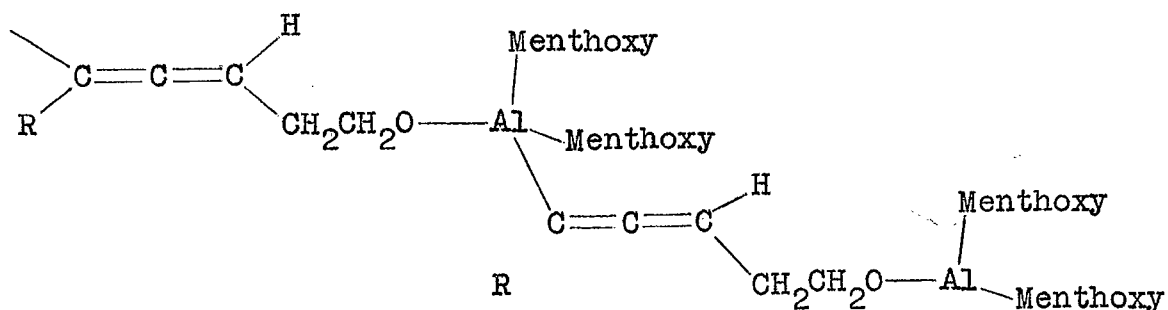
Figure 3
The polymeric complex.
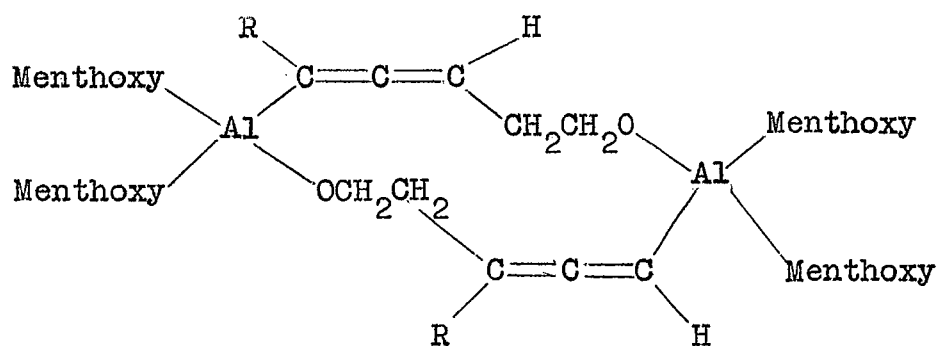
Figure 4
The dimeric fourteen-membered cyclic complex.

since seven- or eight-membered cyclic allene compounds are
highly strained and not usually stable.[12] On the other
hand, if a polymeric complex is formed it would be expected
to precipitate* and no such precipitation has been observed
during these reductions. It is for these reasons that
the fourteen-membered cyclic allene complex is suggested
as a third alternative. Such a complex appears to be
unstrained and models can be readily constructed. In any

---

*Short polymer chains may be soluble, however.

case, an examination of models shows that whichever of
these three possible intermediate complexes is formed, the
stereochemistry of the reduction product will be the same.

Before discussing the stereochemistry of these inter-
mediate complexes, it is pertinent to consider whether
the reaction is under kinetic or thermodynamic control
and any stereochemical consequences.

The concepts of kinetic control, and thermodynamic
control may be conveniently explained by considering a
chemical reaction in which two products, A and B are
possible.[*] If A is formed faster than B, then if the
reaction is stopped after a short time, A will predominate
in the reaction products. Product A is then said to be the
product of kinetic control, i.e., it is the product of
the faster of the two reactions. It may happen, however,
that the formation of A and B is reversible under the reaction
conditions employed. In this event, if the reaction is
allowed sufficient time to attain equilibrium, the thermo-
dynamically more stable compound (say B) will predominate
in the reaction products. Product B is then said to be
the product of thermodynamic control.

If the observed optical activity of the products of
this asymmetric reduction were a consequence of kinetic

---

[*]For the present case the two possible products are the S
and R forms of the allenic alcohol. The concepts are not
restricted to the formation of enantiomeric forms, however.

control, then it would follow that the rate of formation

of the R and the S forms of the allene must differ. An

examination of models was therefore made to determine whether

such a difference in rates would be expected. Since the

enynol has a plane of symmetry, any asymmetry introduced

into the reduction cannot involve the formation of the

O-Al bond and this stage of the reduction will therefore

be assumed to have taken place. In the second stage of

the reduction, the donation of a hydride ion to C_2 of the

enynol, however, two possible approach orientations are

possible. Although one approach orientation may be favoured

over the other, the anion produced is mesomeric[*] and this

mechanism would therefore be expected to lead to a racemic

product. Therefore a reduction under kinetic control should

not give optically active allenic alcohols. The illustration

of these arguments on paper is difficult, however, an

attempt is made to demonstrate this point in figure 5.

After formation of the mesomeric anion a reversible

co-ordination with a trivalent aluminium can occur as

previously outlined. As no acetylene is formed on decom-

position of the complex with water it is assumed that only

the allenic anion participates in such a complex. If

one form of the co-ordinated allene, i.e., R or S, is

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[*]In resonance terminology, the two canonical forms, i.e.,
the allenic anion and the propargylic anion are both linear.
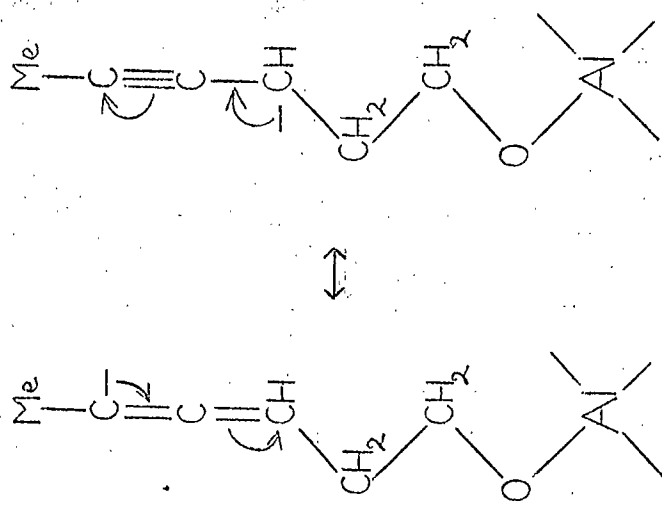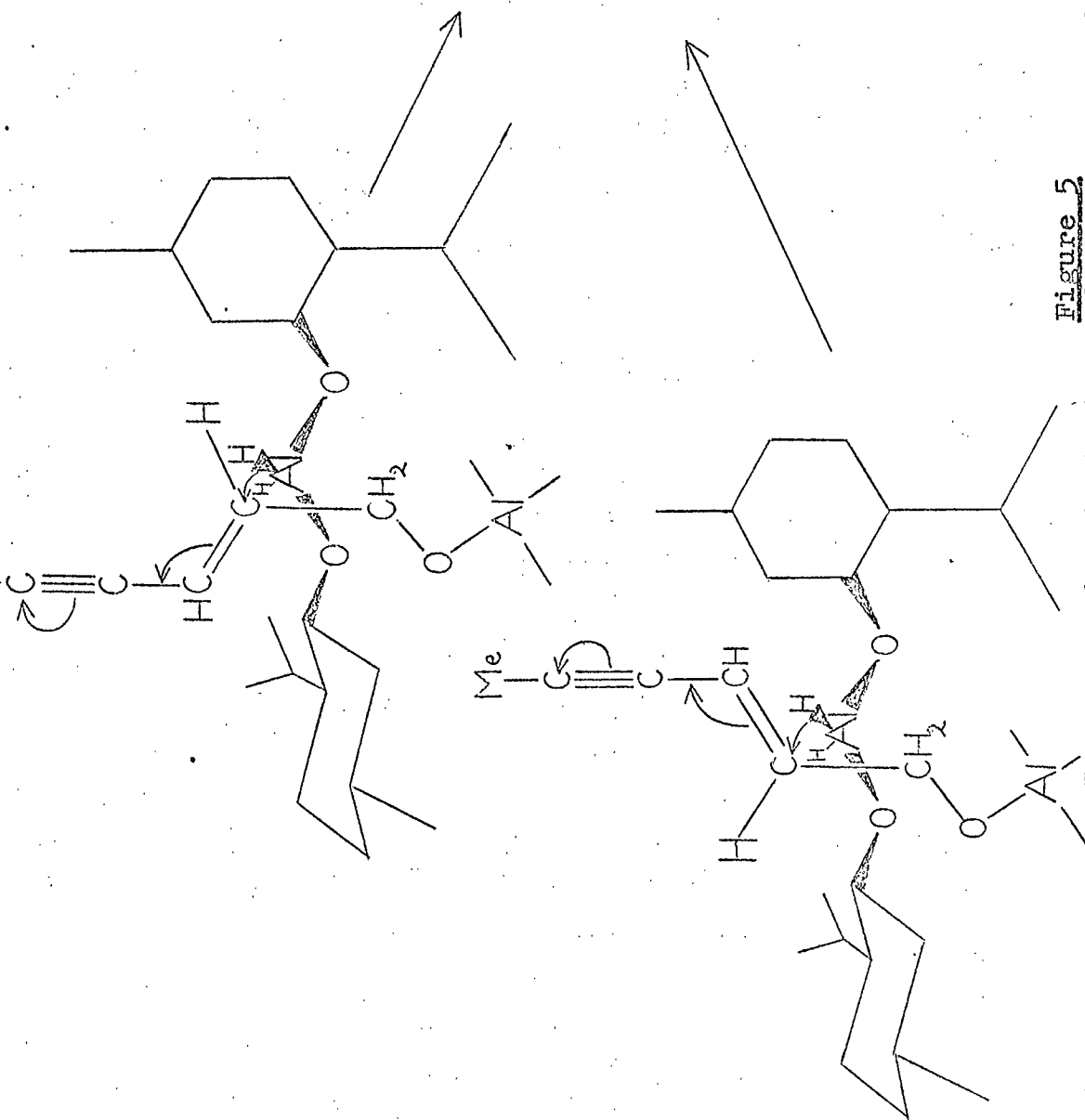
Figure 5

Two approach orientations of the enyne to the dimenthoxyaluminium
hydride complex leading to the same mesomeric anion.

more thermodynamically stable than the other, then a pre-
ponderance of this enantiomer would be expected in the red-
uction products. An examination of models of the seven-
membered cyclic allene complex, the fourteen-membered
dimeric cyclic allene complex and the polymeric allene
complex shows that in all cases the interactions between
non-bonded atoms are at a minimum when the allene is in the
S form. The S forms of these allenic complexes therefore
have greater thermodynamic stability than the R forms. Thus
thermodynamic control of this reduction would be expected
to lead to an excess of the S form of the allenic alcohol in
the product. This is illustrated in figures 6-8.
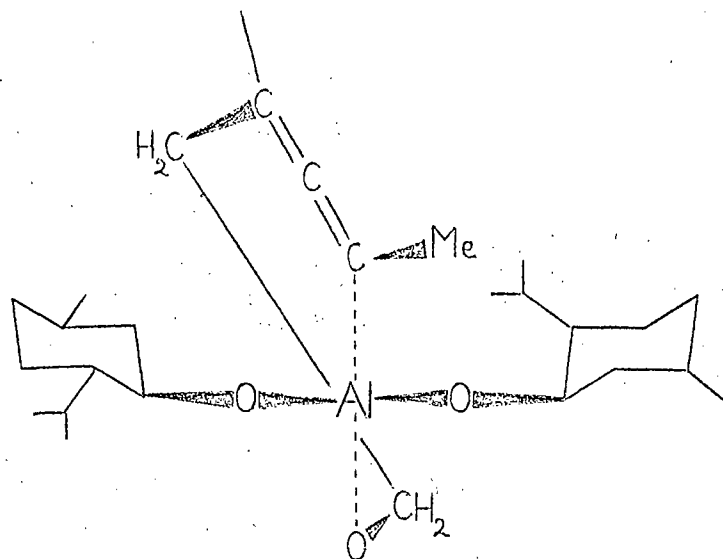
Figure 6
The seven-membered cyclic allene/dimenthoxyaluminium
hydride complex in the more stable S form.
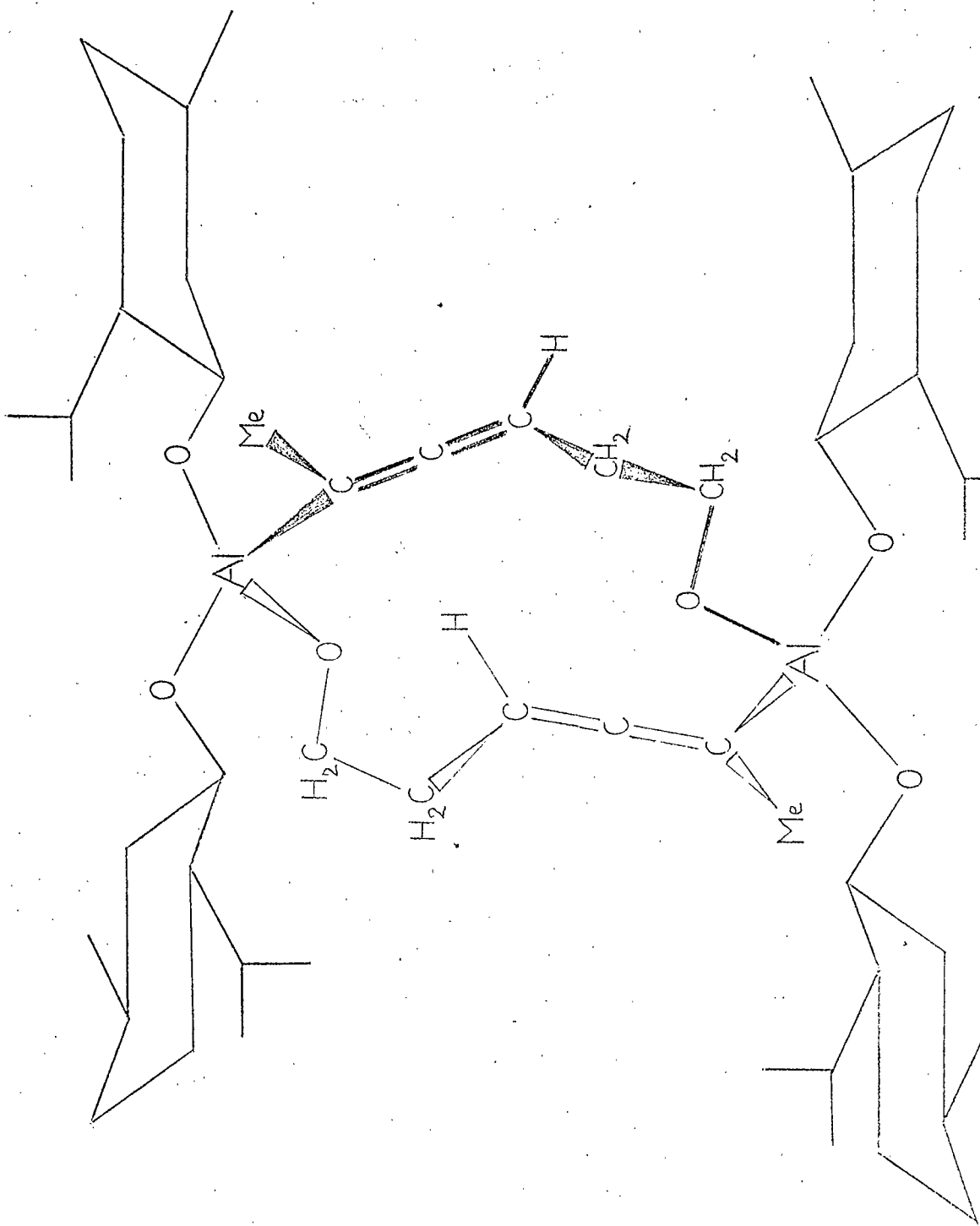
Figure 7

The fourteen membered dimeric cyclic allene-dimenthoxyaluminium hydride complex in the more stable S form.
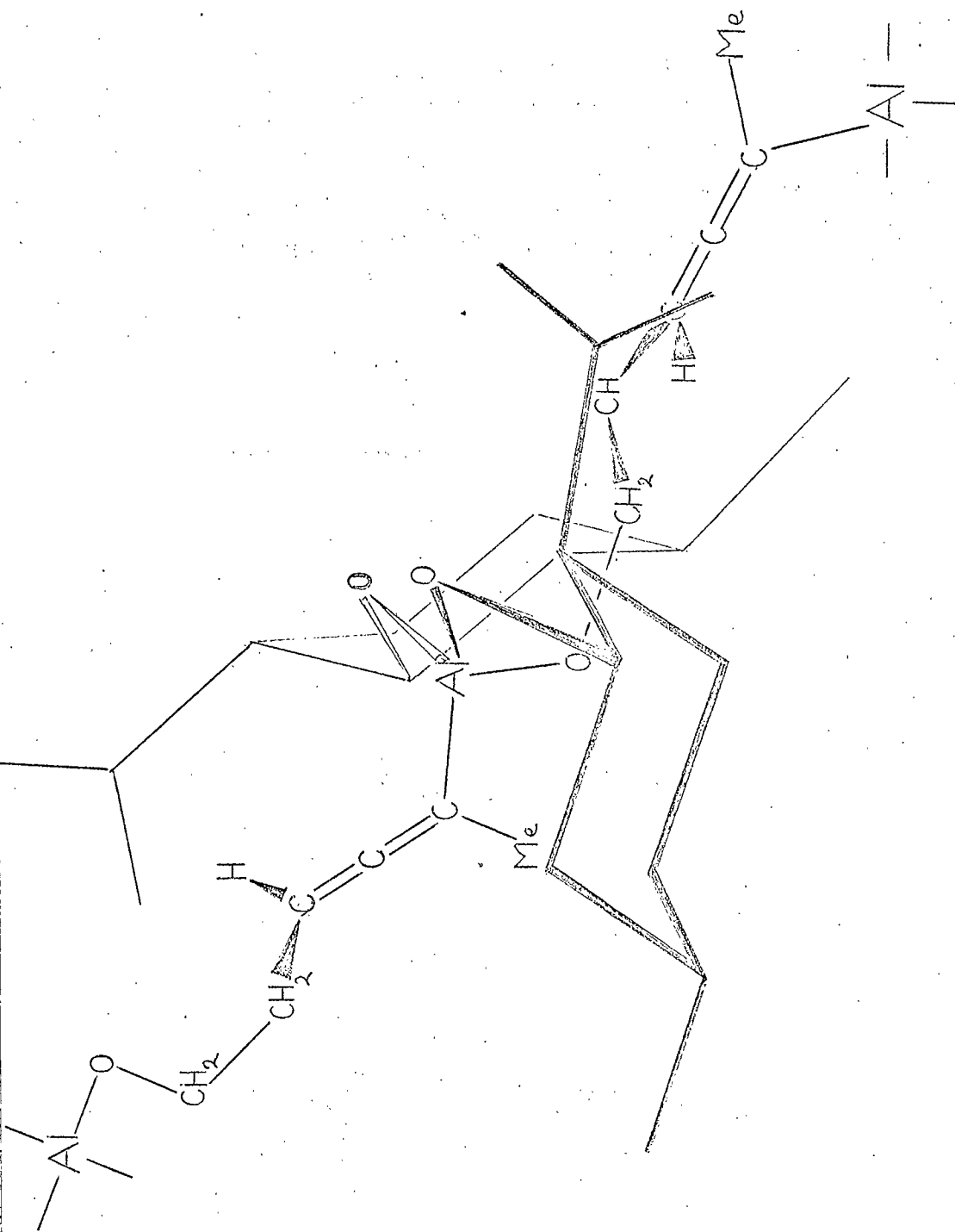
Figure 8

The polymeric allene–dimenthoxyaluminium hydride complex in the more stable S form.

The formation of an optically active product is therefore in no way connected with the actual reduction process (i.e. hydride transfer) of enynol to allenic alcohol. It was reasoned that if this was so, then addition of the optically active agent (e.g. menthol) after completion of the reduction stage should give an excess of the more stable S allene dimenthoxyaluminium complex and, after decomposition with water, excess S allenic alcohol just as it had done in the previous experiments with preformed menthylate complex. Accordingly, hex-2-en-4-yn-1-ol was stirred in ethereal solution with lithium aluminium hydride for 0.5 hr., an ethereal solution of menthol added and the reaction mixture stirred for a further 2 hr. After working up (+)hexa-3,4-dien-1-ol[*] $\left[\alpha\right]_D^{25} +9.3^{o}$ was obtained, thus supporting the conclusion that the reaction was thermodynamically controlled.

The theoretical prediction that reduction of an enynol of type $R-C \equiv C-CH=CH-CH_2OH$ with the lithium dimenthoxyaluminium hydride complex leads to excess of the S form of the corresponding allenic alcohol, constitutes a method for the determination of the absolute configuration of allenic alcohols. In principle, it is only necessary to prepare the allenic alcohol by use of the complex, observe its sign of rotation and assign the S configuration to the predominant

---

[*](+)Hexa-3,4-dien-1-ol prepared by adding hex-2-en-4-yn-1-ol to the previously formed lithium dimenthoxyaluminium hydride complex had $\left[\alpha\right]_D^{25} +8.27^{o}$.

enantiomorph. On this basis the configuration of the allenic

alcohols listed in Table I (p. 53) is S(+).[*]

An attempt was made to use the lithium dimenthoxyaluminium

hydride complex to determine the absolute configuration of

the naturally occurring antibiotic nona-3,4-diene-6,8-diyn-

1-ol (marasin). Preparation of non-2-ene-4,6,8-triyn-1-ol

by the method used by Bohlmann, Herbst, and Gleinig[5,1] gave

the pure product in only 5% yield. By modifying the reaction

conditions (pp. 147-150) the yield was increased to 23.5%.

The time-consuming chromatographic purification of the

crude product was avoided by precipitating the compound

as its silver salt in mildly basic solution. The highly

explosive, shock-sensitive, silver salt was separated and

washed several times with ether using a refrigerated centri-

fuge at $-20°$. Reduction of non-2-ene-4,6,8-triyn-1-ol was

achieved by using a three-fold excess of lithium dimenthoxy-

aluminium hydride complex (prep. p. 52). About 0.1 g.

of marasin was required for an accurate determination of

rotation and this necessitated the use of approximately

7 g. of menthol in the preparation of the complex.[**]

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[*]The absolute configuration of these alcohols has also been
assigned as S(+) by a completely independent method described
in this thesis (p. 82). The S(+) configuration has also been
predicted[125] by an application of Brewster's theory[126] (cf.p. 27)

[**]In this reduction only 10-15% of marasin (based on non-2-ene-
4,6,8-triyn-1-ol) was obtained, the unreduced starting material
being recovered. This was completely separated from the
marasin by chromatography. No Allenene was formed.

Thus after decomposition of the complex with acid, the marasin had to be separated from this relatively large quantity of menthol. Although an exhaustive effort was made to achieve this, traces of this ten carbon alcohol persisted in the nine carbon marasin. Chromatography on Spence type H alumina deactivated with from 2-15% of 10% aqueous acetic acid and elution with ether/n-pentane mixtures was unsuccessful, as was chromatography on Woelm acid alumina deactivated with 3% water and elution with ether/n-pentane.

An attempt was also made to purify the marasin on a small hand-operated 50 tube counter-current apparatus (Quickfit) using 40-60° pet ether/butanol/water and carbon tetrachloride water systems (p. 152). Although separation was achieved using only 25 ml. of the dilute marasin solution, (∿ 0.05%) it was not practical to use the method for the separation of the large bulk of the marasin solution.[*]

During these experiments the photosensitive marasin was at all times protected from light by working in dim red light and by wrapping chromatography columns in brown paper. The traces of menthol in the marasin solution were readily detectable by gas/liquid chromatography on a silicon oil column.

By about this time, Landor, Miller, and Tatchell[13,14]

---

[*]The decomposition of marasin is rapid if the concentration is much above 0.6% (cf. G. Bendz[97]). Solutions were therefore necessarily very dilute, and optical rotations could not be determined.

had developed a method of asymmetric reduction using a
complex prepared from lithium aluminium hydride and 3-O-
benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose. Attempts
by these workers to obtain the monosaccharide analytically
pure by chromatography had been unsuccessful and they had
therefore used the slightly impure complex, containing
approximately 1% of impurity, to reduce a series of ketones.
The optically active alcohols produced were distilled from
the high boiling monosaccharide which together with the
impurities remained in the residue and was recovered for
further use. During the course of this work, these workers
introduced the use of titrated lithium aluminium hydride
solutions[7] for the preparation of the complex so as to
ensure accuracy in the stoichiometry. A number of alk-
enynols were also reduced with the slightly impure complex
and optically active allenic alcohols produced.[15] Thus
for example, reduction of hex-2-en-4-yn-1-ol gave (-)-hexa-
3,4-dien-1-ol $[\alpha]_D^{20}$-10^0, hept-2-en-4-yn-1-ol gave (-)-hepta-
3,4-dien-1-ol $[\alpha]_D^{20}$-8.9^0, and non-2-en-4-yn-1-ol gave
(-)-nona-3,4-dien-1-ol $[\alpha]_D^{20}$-7.4^0. The allenic alcohols
could be distilled off and separated from the monosaccharide
derivative without difficulty. It was therefore decided to
attempt the preparation of optically active marasin using
the complex prepared from the slightly impure monosaccharide
derivative and lithium aluminium hydride.

The preparation of the monosaccharide complex and the
reduction of enynols with this complex was carried out in
a similar manner to that already described for the menthylate
complex (p.52). Following Landor, Miller, and Tatchell,
titrated solutions of lithium aluminium hydride[7] were used
throughout this work.

After decomposition of the complex with acid and
working up, the solution was chromatographed on Woelm acid
alumina deactivated with 3% water using ether/n-pentane
1/4 as the eluting solvent. The marasin solution so obtained
($[\alpha]_D^{25}$-31°) was examined for the presence of traces of
sugar derivatives by thin layer chromatography. After
development of the t.l.c. plates with 2% methanol in benzene
and spraying with a solution of naphthoresorcinol in
ethanol/phosphoric acid the plates were placed in an oven
at 110° for $\frac{1}{2}$ hr. when monosaccharide derivatives showed
as blue spots. Marasin gave a brownish spot at R_F 0.6.
A second light blue spot at R_F 0.25 revealed the presence
of an impurity suspected at the time of being a monosac-
charide derivative due to the characteristic blue colour
of the spot. Re-chromatography of the solution on deact-
ivated alumina failed to remove this impurity. Examination
of the 3-0-benzyl-1,2-0-cyclohexylidene-α-D-glucofuranose
by thin layer chromatography showed a heavy blue spot at
R_F 0.20 and faint blue spots at R_F values of 0.0, 0.25

and 0.95 and supported the conclusion that the impurity in
the marasin was a monosaccharide derivative introduced as
an impurity in the 3-O-benzyl-1,2-O-cyclohexylidene-α-D-
glucofuranose.[*] As monosaccharide derivatives are optically
active the optical rotation of marasin could not be deter-
mined in the presence of these impurities.

An unsuccessful attempt was made to remove the mono-
saccharide derivative by passing the marasin solution
through a silica column impregnated with boric acid. This
removes viscinal diols such as the 3-O-benzyl-1,2-O-cyclo-
hexylidene-α-D-glucofuranose but did not remove the impurity
having R_F 0.25 in the marasin solution, suggesting that
it was probably a mono-ol. An attempt to hydrolyse the
monosaccharide derivative contaminating the marasin solution
with methanolic hydrochloric acid for 2 hr. at room tem-
perature and then remove the hydrolysed sugar by further
chromatography on silica impregnated with boric acid was
successful. However, the marasin was apparently racemised
by the acid treatment which defeated the purpose of the
experiment.[**] As a last resort, an attempt was made to

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[*]This was later confirmed and the monosaccharide identified
(pp. 99-106).

[**]Evans, Landor and Taylor Smith[113] had shown that optically
active allenic chloride is racemised by hydrochloric
acid.

separate the marasin as the silver salt, but as expected the marasin underwent rapid polymerisation and isomerisation under the mild alkaline conditions used.

It was realised at this point that a complete re-investigation of the preparation of the 3-0-benzyl-1,2-0-cyclohexylidene-α-D-glucofuranose would have to be undertaken with a view to removing the trace impurities. The separation of the trace impurities and their identification, and the preparation of 3-0-benzyl-1,2-0-cyclohexylidene-α-D-glucofuranose in an analytically pure form is described later in this thesis (pp. 99-106).

Using the pure glucofuranose, optically active (-)-marasin (11.5% on non-2-ene-4,6,8-triyn-1-ol) $\left[\alpha\right]_D^{25} -26.6^{\circ}$ was obtained (p. 156) by the chromatography of the crude product on deactivated alumina and silica/boric acid. The marasin solution was shown to be free of monosaccharide derivatives by thin layer chromatography[*] and its ultra-violet spectrum was in agreement with those of Bendz[6,97] and Cambie, Hirschberg, Jones and Lowe[16] (U.V. No. 15). Since the lithium aluminium hydride-3-0-benzyl-1,2-0-cyclohexylidene-α-D-glucofuranose complex gives allenes of the R configuration, (-)-marasin has the R configuration.

Having thus established a method for preparing optically active allenynols of known configuration, the method was

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[*]Determination of the minimum quantity of monosaccharide detectable by t.l.c. (p. 178).

applied to three other examples. (-)-Deca-3,4-diene-6,8-

diyn-1-ol ((-)-9-methylmarasin)[91]was prepared as follows:

penta-1,3-diyne was prepared by a modification of the

literature method[17] (p.157), and coupled under modified

Chodkiewicz[18,1] (p.157) conditions with 5-bromopent-2-

en-4-yn-1-ol[144] to give dec-2-ene-4,6,8-triyn-1-ol.[20]

This was reduced with an excess of the lithium aluminium

hydride-3-0-benzyl-1,2-0-cyclohexylidene-α-D-glucofuranose

complex (p.158) to give (-)-9-methylmarasin (14.0% on

dec-2-ene-4,6,8-triyn-1-ol) $[\alpha]_D^{25}$-11.3°. (-)-9-Methyl-

marasin therefore has the R configuration.

7-Phenylhept-2-ene-4,6-diyn-1-ol was prepared by

coupling phenylacetylene with 5-bromopent-2-en-4-yn-1-ol[144]

(p.160) and reduction of this with excess of the lithium

aluminium hydride-3-0-benzyl-1,2-0-cyclohexylidene-α-D-

glucofuranose complex gave (-)-7-phenylhepta-3,4-dien-6-

yn-1-ol (14.4% on 7-phenylhept-2-ene-4,6-diyne-1-ol)

$[\alpha]_D^{25}$-3.1° (p.161). (-)-7-Phenylhepta-3-4-dien-6-yn-

1-ol therefore has the R configuration.

8,8-Dimethylnon-2-ene-4,6-diyn-1-ol was prepared by

coupling of 3,3-dimethylbut-1-yne[21] with 5-bromopent-2-en-

4-yn-1-ol[144] (p. 139) and reduction with the lithium

aluminium hydride-3-0-benzyl-1,2-0-cyclohexylidene-α-D-

glucofuranose complex gave (-)-8,8-dimethylnona-3,4-dien-

6-yn-1-ol (32% on 8,8-dimethylnon-2-ene-4,6-diyn-1-ol)

$\left[\alpha\right]_D^{25}$ -12.5°.   (-)-8,8-Dimethylnona-3,4-dien-6-yn-1-ol

therefore has the R configuration.

Samples of the above optically active allenynols were

sent to Dr. L. Verbit at the State University of New York

for optical rotatory dispersion measurements. Unfortunately,

with the exception of the (-)-8,8-dimethylnona-3,4-dien-6-

yn-1-ol, all the compounds had decomposed by the time they

were received. The circular dichroism curve of (-)-8,8-

dimethylnona-3,4-dien-6-yn-1-ol showed unambiguously the

presence of a negative Cotton effect (p.221).

It has already been deduced theoretically that the

configuration of allenic alcohols produced by the lithium

dimenthoxyaluminium hydride complex is S(+). Since the

monosaccharide complex produced laevorotatory allenic

alcohols it follows that this complex produces predomin-

antly the R(-) form of the allenic alcohol. If this con-

clusion could be confirmed by an independent consideration

of the stereochemistry of reduction with the monosaccharide

complex, then the force of the whole argument would be

increased considerably. This may be demonstrated by an

examination of models which predict that the monosaccharide

complex should produce the R form of the allenic alcohol.

A Dreiding model of the lithium aluminium hydride-3-

O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose complex

in its preferred conformation is shown in figure 9.
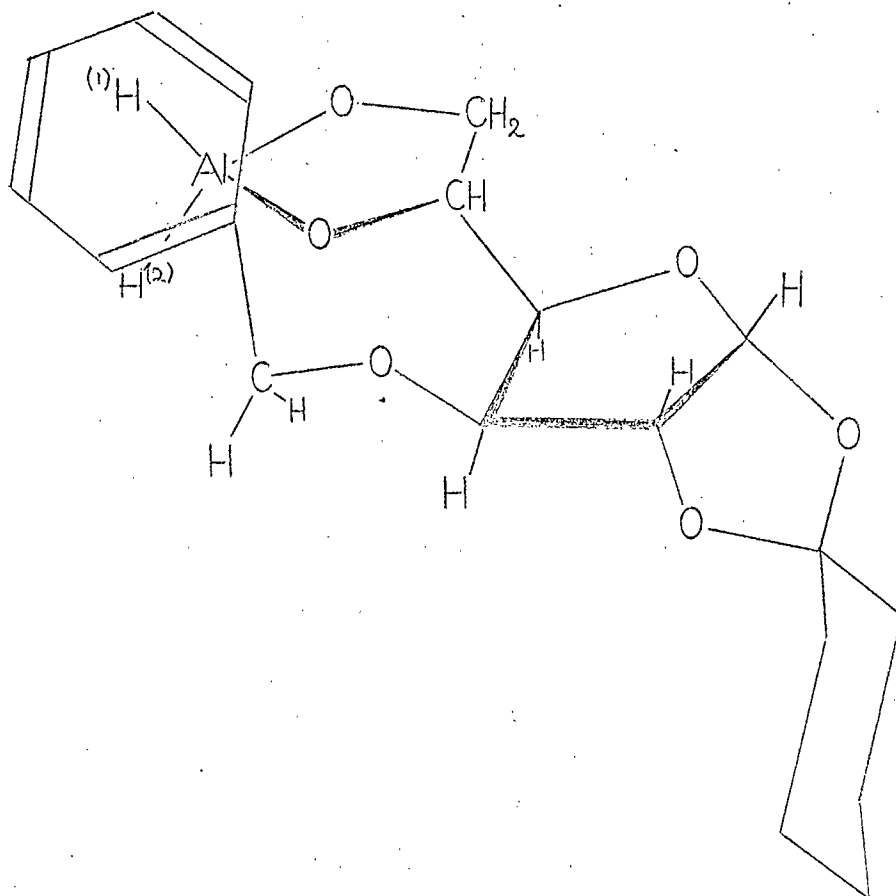
Figure 9

The 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose-
aluminium hydride complex ion in the preferred conformation.

In this conformation the two hydrogens on the aluminium
atom are shielded on one side by the benzyl group and it
is clear from the model that H-1 (figure 9) is shielded
more than H-2. H-2 would therefore be expected to react
preferentially to H-1.*

*The validity of this theory has now been confirmed by Landor,
Miller, and Tatchell.[24] These workers predicted the S con-
figuration for alcohols obtained by the reduction of a series
of ketones, on the basis that H-2 reacted preferentially with
the ketone. It was then reasoned that if H-2 was removed by
reaction with a primary alcohol H-1 would have to be utilised
in the reduction, and this should lead to the R form of the
alcohol. These predictions were realised experimentally.

The mechanism of the reduction of an enynol with the monosaccharide complex will be similar to that discussed for the dimenthoxy complex (p. 55). The seven-membered cyclic allene complex will again be used as the most convenient demonstration of the stereochemical argument, although the polymeric allene complex or the fourteen-membered dimeric allene complex are more realistic possibilities.

The possibility that the reduction was under kinetic control was rejected on the same theoretical grounds as before (p. 58) and an experiment (cf. p. 63) in which hex-2-en-4-yn-1-ol was first reduced with lithium aluminium hydride and monosaccharide was then added to the mixture gave optically active hexa-3,4-dienol[*] $[\alpha]_D^{25}$ -8.2° and confirmed that the formation of optically active alcohol was due to a thermodynamic control of the reaction.

In considering the stereochemistry of the monosaccharide/allenic complexes an important difference between these and the previously considered dimenthoxy/allenic complexes is immediately apparent. Whereas in the earlier case the two hydrogens on the aluminium were equivalent to each other, in the present case H-1 is not equivalent to H-2.

The initial reaction of the monosaccharide complex

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[*]Preformed complex produced hexa-3,4-dien-1-ol $[\alpha]_D^{20}$ -10°.

with the hydroxyl group on the enynol will undoubtedly

involve H-2, the more reactive hydrogen. After donation of

the hydride ion and formation of the mesomeric allene anion,

however, the formally neutral aluminium atom will adopt

a planar arrangement. In co-ordinating with this aluminium

atom to form the seven-membered cyclic complex, therefore,

the anion can approach from either side of the planar

aluminium.
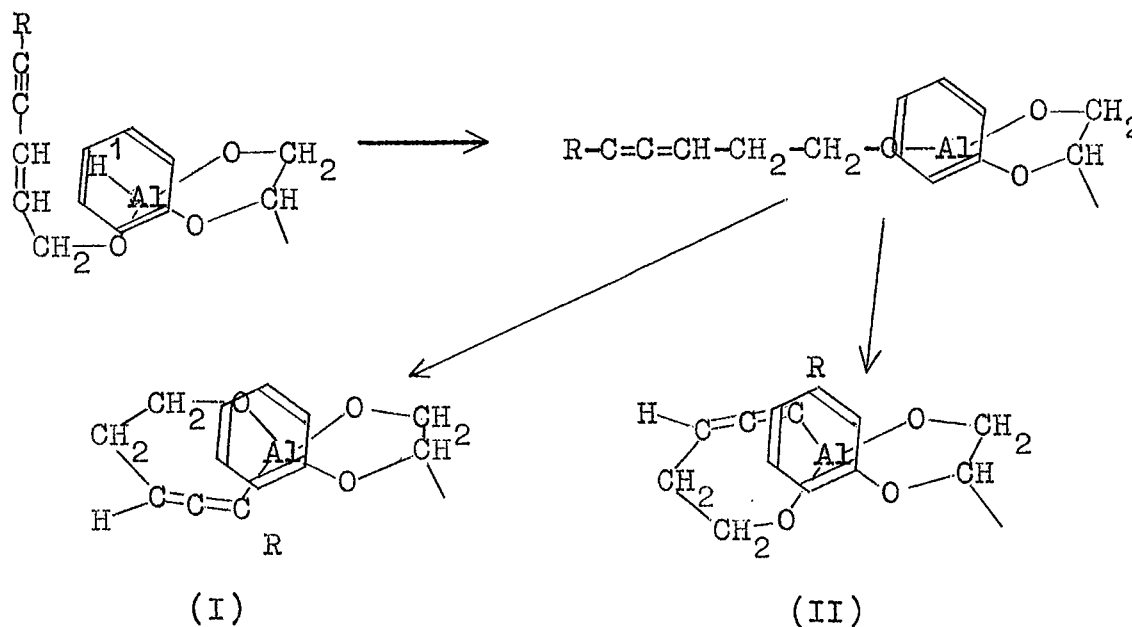
Figure 10
Only partial glucofuranose structures are shown.

Two factors favour approach such that in the final cyclic

complex the oxygen of the enynol will replace H-1 as shown

in figure 10 (I). The first factor is steric approach

control. Approach from the H-2 side of the aluminium is

easier than approach from the H-1 side due to differential
shielding by the benzyl group, (cf. Landor, Miller, and
Tatchell[14]). The second factor is the greater thermodynamic
stability of the complex in which the oxygen replaces H-1
indicated by fewer interactions between non-bonded atoms
in this complex compared with the alternative. With the
seven-membered cyclic allene complex no conformational
variations are possible, the only other variant being
whether the allene is in the R or the S configuration.
There is no doubt that the R configuration is subject to
less steric interference by the benzyl group than the S
configuration and the R form would therefore be expected
to predominate in the reaction products. This is illustrated
in figure 11, (p. 76).

In considering the fourteen-membered cyclic complex
and the polymeric allene complex the arguments used for the
seven-membered cyclic complex also apply but are further
complicated by the greater flexibility of the system. There
are six possible conformations for the R allene and six
for the S allene; these are represented schematically in
figure 12 (p. 77). Steric interactions with the benzyl
group make conformations b_1, b_2, c_1, and c_2 unfavourable
and these may be ignored. A model of conformation a_1 shows
that the R form of the allene would be thermodynamically
more stable and a model of conformation a_2 shows that the
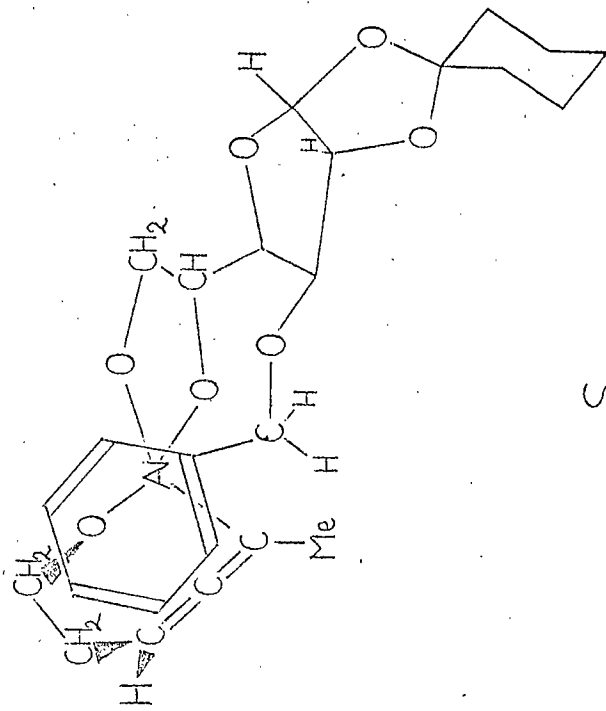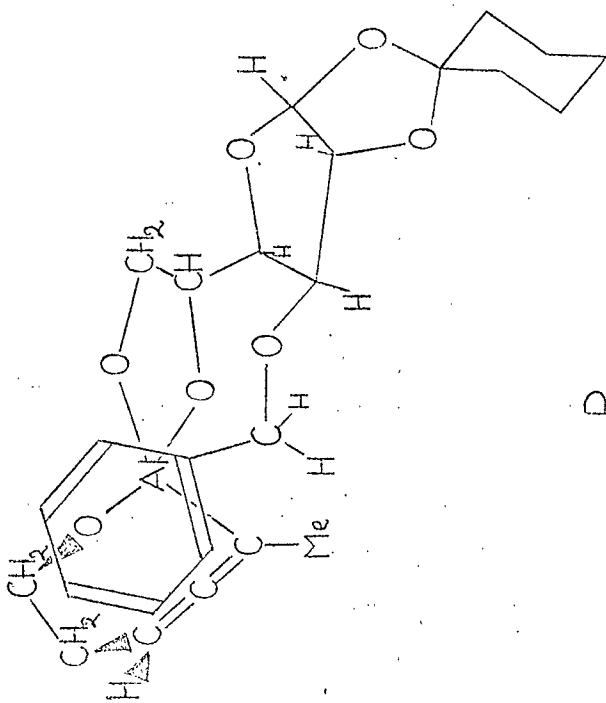
Figure 11
Braiding model of the seven-membered cyclic allene-monosaccharide complex in the R and S forms.

S

R
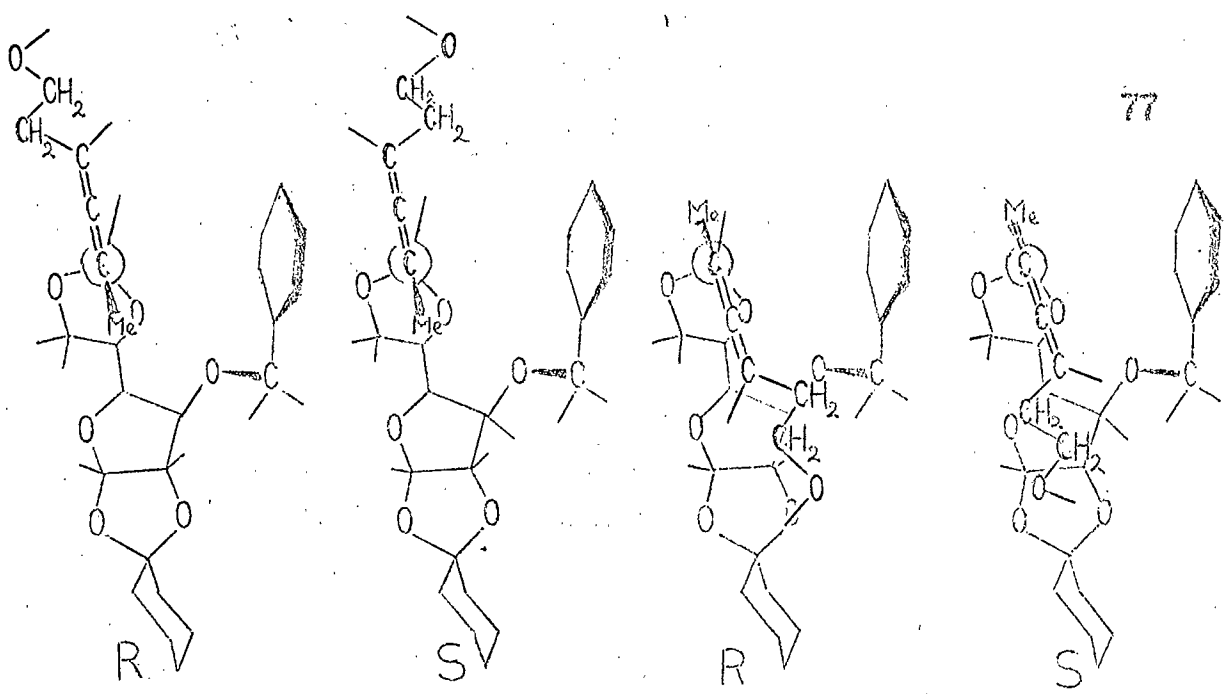
a₁ R form more stable   a₂ S form more stable
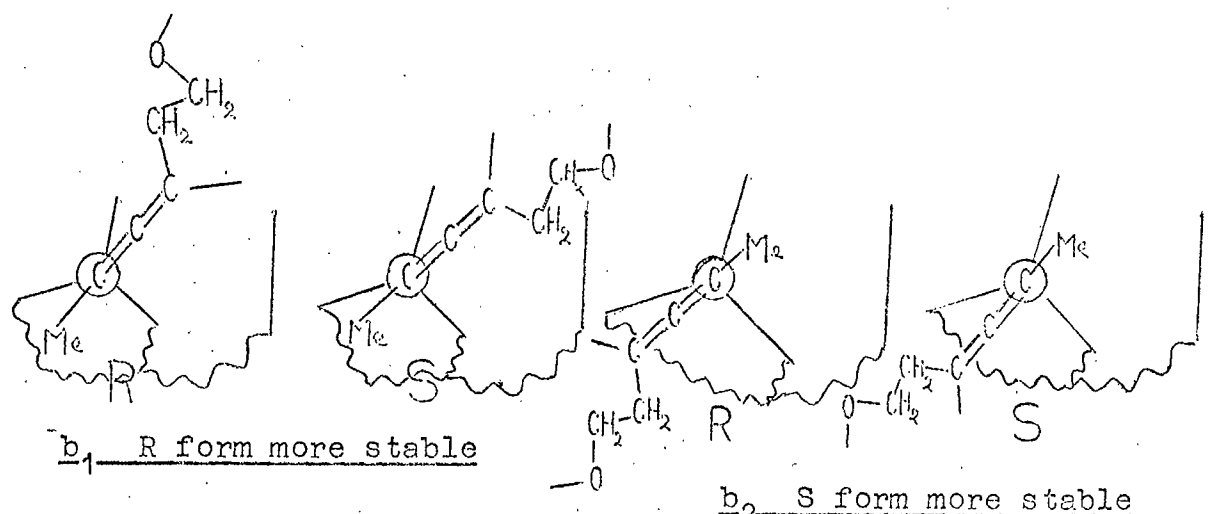
b₁ R form more stable

b₂ S form more stable
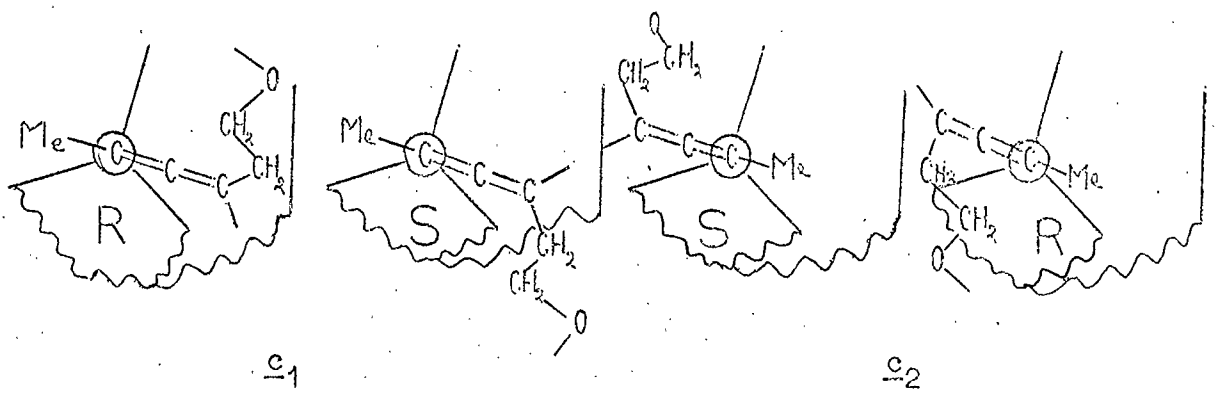
c₁   c₂

Figure 12
Conformations of the monosaccharide-olivose complex drawn
as Newman projections.

S form of the allene would be more stable. Models of
conformation a_2 cannot be constructed for the dimeric
fourteen-membered cyclic complex. Models of conformation
a_1 are readily constructed for this complex and the dimeric
fourteen-membered cyclic complex would therefore be expected
to give an excess of the R form of the allene. Models of
conformation a_2 can be constructed for the polymeric complex
although it appears less stable than conformation a_1 due
to interference of the two monosaccharide molecules. The
polymeric complex would also be expected to give excess of
the R form of the allene therefore. The stereochemistry
of the dimeric fourteen-membered cyclic complex and the
polymeric allene complex are shown in figures 13 and 14,
(pp. 79 and 80).

To summarise, it has been deduced theoretically in
this section that reduction of alkenynols with the lithium
dimenthoxyaluminium hydride complex should produce pre-
dominantly S allenic alcohols. As all the allenic alcohols
which have so far been prepared by this method are dextro-
rotatory they must have the S(+) configuration. Independent
theoretical deductions led to the conclusion that reduction
of alkenynols with the lithium aluminium hydride-3-O-benzyl-
1,2-O-cyclohexylidene-α-D-glucofuranose complex should
give predominantly the R form of the allenic alcohols.
The observation that all allenic alcohols produced in this
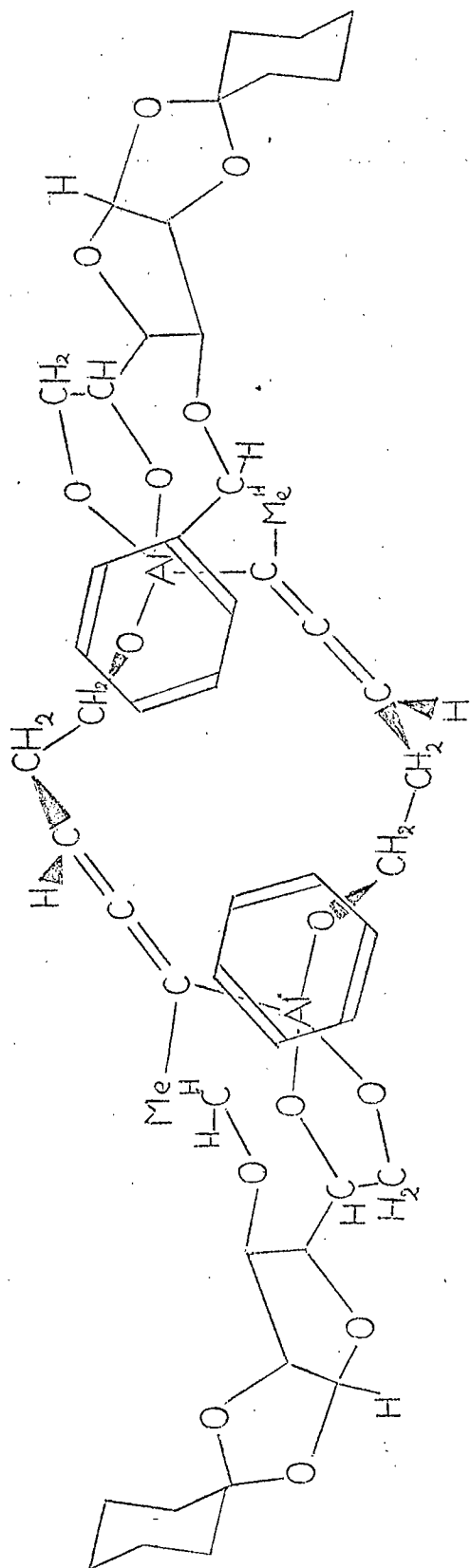
Figure 3.17
Desiring model of the dimeric cyclic ...
... in the ... functions
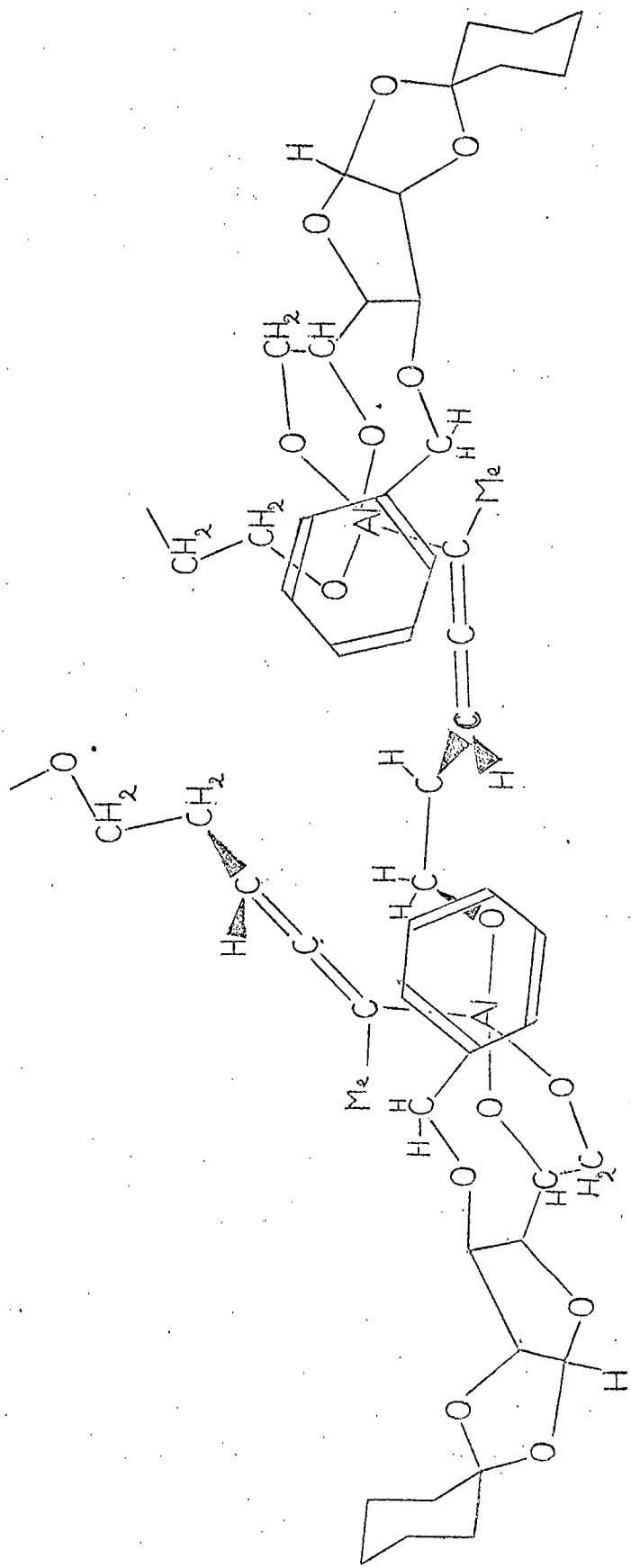
Figure 14

Idealizing model of the polymeric alleno-oligosaccharide complex in the Z configuration.

way are laevorotatory confirms that they have the R(-)
configuration.

The configuration of an allenic alcohol has also been
assigned as S(+) by a completely different experimental
method described later in this thesis (p. 82).

An application of Brewster's theory[126] predicts that
allenynols (e.g. marasin) should have the S(+) configuration.[125]

The Determination of the Absolute Configuration of Allenic

Alcohols by use of the Claisen Rearrangement

There is considerable evidence[77] (p.30) that the
Claisen rearrangement of allyl vinyl ethers involves a
six-membered cyclic transition state, C-C bond formation
occurring simultaneously with C-O bond fission. With
propargyl vinyl ethers, the formation of a cyclic trans-
ition state is less favourable since the group $C-C\equiv C-$
must be linear. It has been demonstrated[54] that under
suitable conditions, however, these systems can be made
to undergo Claisen type rearrangements and by analogy with
the allyl vinyl systems it seems reasonable to suppose that
this rearrangement also goes via a cyclic transition state.
The rearrangement of optically active propargyl vinyl
ethers described in this thesis and the independent work
by Jones, Loder and Whiting[76] on the direct conversion of
optically active isobutyraldehyde dibut-1-ynyl acetal to
the corresponding optically active allenic aldehydes,*
corroborates this conclusion.

On the basis of a cyclic transition state for this
rearrangement, Jones, Loder and Whiting deduced the absolute
configuration of 2,2-dimethylhex-3,4-dienal by using

---

*These workers postulated the ether as a necessary inter-
mediate although this was not isolated.

optically active but-1-yn-3-ol of known configuration[I]

in the preparation of the acetal and converting[*] this to

the optically active allenic aldehyde.

By similar argument, it was proposed to deduce the

absolute configuration of straight chain allenic aldehydes,

and of the corresponding allenic alcohols. The argument

depends on the fact that in the cyclic transition state,

rotation about bonds is not possible. In the transition

state the molecule takes up the conformation shown in

figure 15 and as indicated there, if S-but-1-yn-3-ol is

used in the preparation of the ether the S form of the

allenic aldehyde should be produced.
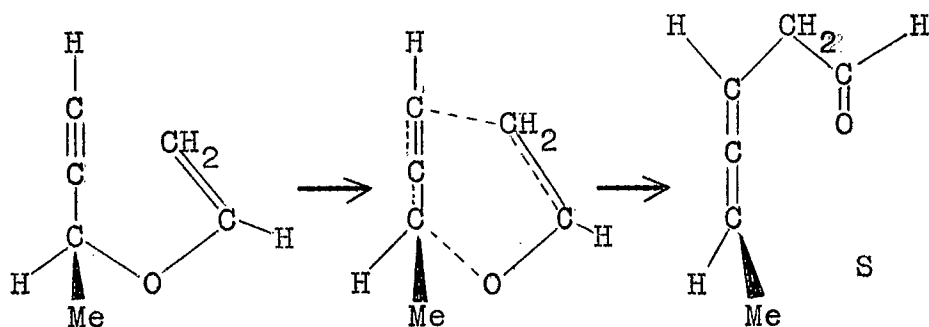
Figure 15

[I]The absolute configuration of but-1-yn-3-ol was shown to
be S(-) by Jones, Loder and Whiting[76] by reducing (-)
but-1-yn-3-ol to (+)-butan-2-ol of known absolute con-
figuration. This was confirmed in our laboratories.[78]

[*]These workers postulated an elimination of but-1-yn-3-ol
to give the isobutenylbut-1-yn-3-yl ether as a necessary
intermediate although this was not isolated. It was
proposed that this intermediate then rearranged intra-
molecularly to the optically active allene.

The absolute configuration of the allenic aldehyde may
thus be determined and by reducing this to the corresponding
alcohol with lithium aluminium hydride, which does not
affect the π bond system, the absolute configuration of
the allenic alcohol too, may be deduced.

Black and Landor[56] have prepared a number of 1-chloro-
alkyl and vinyl ethers, and the preparation of α-chloroethyl
but-1-yn-3-yl ether was undertaken by the method introduced
by these workers. The procedure used was as follows
(cf. p. 165): a mixture of freshly redistilled dry acet-
aldehyde (1 equiv.) and dry but-1-yn-3-ol (2 equiv.) was
added dropwise with stirring under anhydrous conditions to
boron trichloride (1.3 equiv.), cooled to -15° and stirred
for 3 hr. at -15°. The mixture was then allowed to warm
to room temperature, stand for 3 days and the chloro ether
distilled in vacuo into a cold trap. After refractionation
the required 1-chloro ether was obtained.

Following the procedure of Black and Landor, the
chloro ether was treated in dry diethyl ether solution
at 0° with excess anhydrous triethylamine to give the
corresponding quaternary ammonium salt as a hygroscopic
solid. This was decomposed at 120° in vacuo to give the
impure vinyl ether, having identical infra-red spectrum,
(ν_{max} 3,320 (C≡CH), 2,110 (C≡C), 1,680 and 1,630 cm.$^{-1}$
(C=C)), to that obtained by the previous workers, but the

gas liquid chromatogram of this material showed three peaks (t=14 min. 60%), (t=9 min. 2%) and(t=85 min. 38%) (dinonylphthalate 84°, nitrogen 2 1/h). On distillation only a very small amount of pure vinyl ether was obtained and a large residue. The infra-red spectrum of the residue was similar to the crude product and its g.l.c. showed that the peak at (t=85 min.) had increased in size to represent 70% of the material.

It is well-known that vinylic ethers dimerise[81] and Landor and Black[79] have previously observed that 3-carboxylpropargyl vinyl ether undergoes a ready dimerisation, viz.

$$CH_2=CH-O-CH_2C\equiv C-COOH \longrightarrow \begin{array}{c} CH_2-CH-O-CH_2C\equiv C-COOH \\ | \quad | \\ CH_2-CH-O-CH_2C\equiv C-COOH \end{array}$$
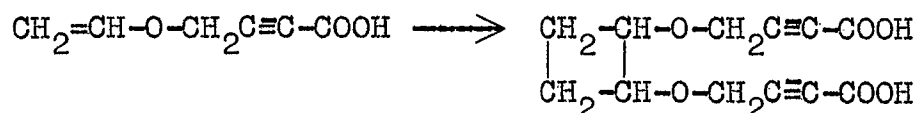
It is therefore probable that a similar dimerisation (or polymerisation) had occurred with the 1-methylprop-2-ynyl vinyl ether. (This being responsible for the g.l.c. peak at t=85 min.) Attempts to purify the vinyl ether were therefore abandoned.

The pyrolysis of the impure ether gave as main product hexa-2,4-dienal identified from its infra-red spectrum ν_{max} 1,750 (C=O), 1,640 and 1,680 cm.$^{-1}$ (C=C) and its ultra-violet spectrum λ_{max} 273 mμ (Σ 14,400) (pure hexa-2,4-dienal λ_{max} 271 mμ (Σ 25,000)).[80] It is probable that traces of base in the impure vinyl ether had caused

rearrangement of the hexa-3,4-dienal to the conjugated hexa-2,4-dienal during the pyrolysis.

It is known that α-chloro ethers eliminate HCl on pyrolysis,[82] and Black and Landor[54] had shown that a number of α-dichloroalkyl propargyl ethers could be converted directly to allenic aldehydes by heating under reflux. It was therefore considered, that under carefully controlled conditions, pyrolysis of the α-chloroethyl but-1-yn-3-yl ether should result in elimination of HCl followed by the Claisen rearrangement. This was achieved by passing the chloro ether in a stream of nitrogen through an electrically heated glass tube packed with glass wool at 200°. The unstable hexa-3,4-dienal together with some hexa-2,4-dienal was collected in a trap at -60° (I.R. No. 16). The amount of conjugated diene in the mixture was estimated to be 20-50% from the ultra-violet spectrum (U.V. No. 20). The mixture of aldehydes was added to an excess of lithium aluminium hydride and stirred at room temperature overnight. Excess lithium aluminium hydride was destroyed with dilute sulphuric acid and the mixture of alcohols produced was ether extracted, dried and separated by chromatography on alumina to give pure hexa-3,4-dienol (I.R. No. 17).

Repetition of this procedure using optically active (-)-α-chloroethyl but-1-yn-3-yl ether, $[\alpha]_D^{20}$ -44.5°

(prepared from acetaldehyde, boron trichloride and S-(-)-

but-1-yn-3-ol $[\alpha]_D^{20}$ -5.3°) gave (+)-hexa-3,4-dienol, $[\alpha]_D^{20}$

+5.3°. (+)-Hexa-3,4-dienol therefore has the S

configuration.

The Attempted Asymmetric Reduction of Acetophenone with the Lithium Aluminium Hydride-Active Amyl Alcohol Complex.

The preparation of a complex of lithium aluminium hydride with active amyl alcohol (2-methylbutan-1-ol) and its use in reducing acetophenone to 1-phenylethyl alcohol was carried out as previously described (p. 52); experimental details (p. 170) for the menthoxy complex. After decomposition of the complex with dilute acid, ether extraction, drying and fractionation on a spinning band fractionating column, the 1-phenylethyl alcohol was still contaminated with traces of active amyl alcohol. This was readily shown by gas liquid chromatography on silicon oil. The last trace of active amyl alcohol was removed by dissolving the impure 1-phenylethyl alcohol in n-pentane/ether (4/1) and passing water through the solution in a continuous extraction apparatus overnight. Evaporation of solvent and redistillation gave the pure 1-phenyl ethyl alcohol. This compound was found to be optically inactive, ($\pm 0.001^{\circ}$ Bendix photoelectric polarimeter.)

In the light of this it was considered most unlikely that other ketones would undergo asymmetric reduction with this complex since the difference in bulk between the phenyl group, and the methyl group on acetophenone is quite substantial.

An examination of a model of the lithium aluminium

hydride-active amyl alcohol complex shows that the lack of

asymmetric reduction with this complex is not surprising.

The asymmetric centres are too far from the aluminium atom

to play an important part in the shielding of the remaining

two hydrogens on the aluminium atom, (figure 16). The

approaching ketone molecule thus sees these hydrogens in an

approximately symmetrical environment and the reduction

product is therefore racemic.
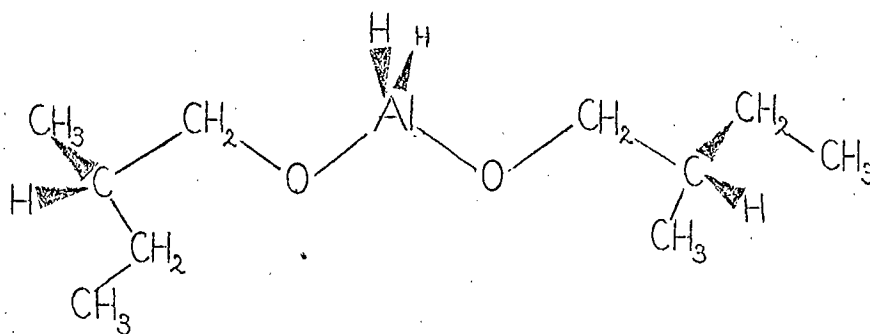
Figure 16
The lithium aluminium hydride-active amyl alcohol complex in
the preferred conformation.

Preparation of 4-Cholorhept-2-yn-1-ol and 4-Chlorohept-2-
ynyl acetate and the Reduction of These Compounds with the
Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-
α-D-Glucofuranose Complex.

Following the work of Landor, Landor, and Pepper[72]
on the preparation of allenic alcohols by the reduction of
propynyl halides with lithium aluminium hydride, it was of
interest to carry out the reduction using the lithium
aluminium hydride-monosaccharide complex. An unconjugated
chloracetylenic alcohol would be expected to be reduced to
the allene by the following mechanism (cf. ref. 72):

$$\text{R-CH-C}\equiv\text{C-CH}_2 \qquad \longrightarrow \qquad \text{R-CH=C=CHCH}_2\text{OH}$$
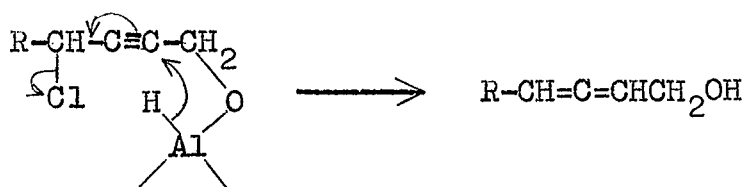
Due to stereoelectronic[28a] requirements (i.e. trans
movement of electrons) the elimination of the chlorine would
normally be expected to take place from the same side of
the propynyl halide as the hydride ion is introduced, (cf.
p. 22). If an asymmetric reducing agent is used, such
as the lithium aluminium hydride monosaccharide complex, the
two stereoisomers would not be expected to undergo reduction
at the same rate, since the R group on one enantiomorph
would give rise to more steric interaction with the benzyl

group on the monosaccharide than would the R group on the other

enantiomorph. This is illustrated in figure 17, p. 92.

If the reduction was stopped before completion, optically

active allenic alcohol should therefore be obtained. This

would constitute an example of a kinetically controlled

asymmetric reduction.

An examination of models showed that the stereospecificity

of the reaction was likely to increase with increasing size

of the R group on the acetylenic halide since this would

increase interference with the benzyl group on the monosac-

charide (cf. figure 17). 4-Chlorohept-2-yn-1-ol was considered

a suitable compound for investigation. Preparation of this

compound was carried out by the following method. 3-Tetra-

hydropyranyloxyprop-1-yne was reacted with ethyl magnesium

bromide in tetrahydrofuran, and the resulting Grignard reagent

reacted with n-butyraldehyde to give 1-tetrahydropyranyloxy-

hept-2-yn-4-ol, (VII). Chlorination of (VII) with thionyl

chloride in the presence of pyridene followed by hydrolysis

of the OTp derivative with methanolic hydrochloric acid

afforded the required 4-chlorohept-2-yn-1-ol, (VIII).

$$HC\equiv C-CH_2OTp \quad \xrightarrow[\text{2. } C_3H_7CHO]{\text{1. EtMgBr}} \quad C_3H_7-\underset{\underset{OH}{|}}{C}H-C\equiv C-CH_2OTp \quad (VII)$$

$$\Big\downarrow SOCL_2$$

$$C_3H_7-\underset{\underset{Cl}{|}}{C}H-C\equiv C-CH_2OH \quad \xleftarrow{\text{HCl/MeOH}} \quad C_3H_7-\underset{\underset{Cl}{|}}{C}H-C\equiv C-CH_2OTp$$

(VIII)
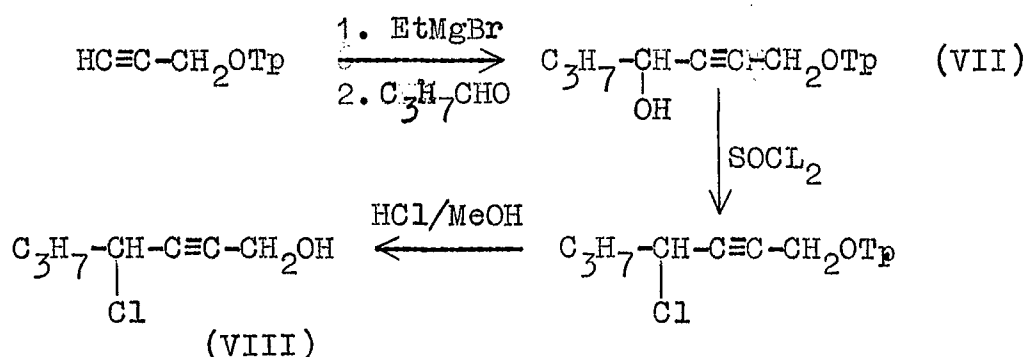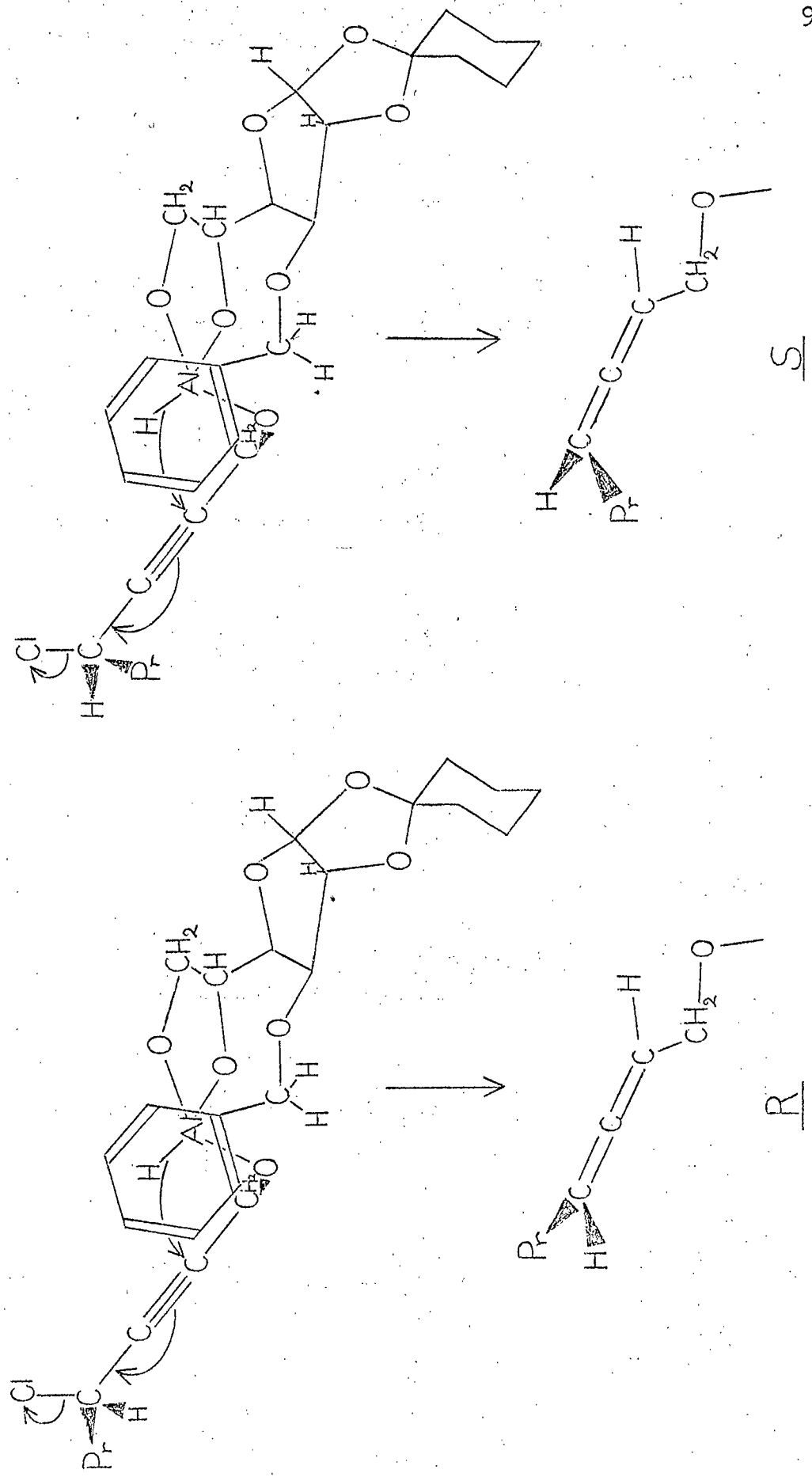
Figure 17

Reduction of the chloracetylenic alcohol with the lithium aluminium hydride-mono-saccharide complex. Both chloracetylenic alcohol enantiomorphs are shown.

The compounds prepared in the course of this synthesis
were identified by infra-red spectra and analysis.

The lithium aluminium hydride-monosaccharide complex
(.01 mole in ether) was prepared as described earlier in
this thesis (p. 67) and the 4-chlorohept-2-yn-1-ol (.01 mole)
added in one portion at room temperature and stirred for
0.5 hr. The product showed a single peak on g.l.c. (silicon
oil) and was optically inactive ($\pm 0.001^{\circ}$). It was identi-
fied as hept-2,3-dien-1-ol by its infra-red spectrum.
Clearly the reduction to the allenic alcohol had gone to
completion.

The reduction was repeated using a deficiency of the
reducing complex, but it was found that although some
starting material was recovered, the allenic alcohol produced
was still optically inactive.

Repetition of the reduction at -40° for 10 min. with
one equivalent of reducing complex still resulted in com-
plete reduction of the acetylenic chloride to allenic
alcohol, and it was concluded that this reaction was too
fast for kinetic control to be effective.

In view of the rapidity of the reduction of the
chloracetylenic alcohol it was decided to try reducing
the corresponding acetate since it was considered that
this reduction might be a slower process, and kinetic
control might then be effective. 4-Chlorohept-2-ynyl

acetate was prepared by the following method. 3-Tetra-
hydropyranyloxyhex-1-yne was converted to the Grignard
reagent by reaction with ethyl magnesium bromide in tetra-
hydrofuran, and this reacted with formaldehyde gas to give
4-tetrahydropyranyloxyhept-2-yn-1-ol, (IX). Acetyl-
ation of (IX) with a mixture of acetic anhydride and dry
pyridene gave 4-tetrahydropyranyloxyhept-2-ynyl acetate
and hydrolysis of the OTp derivative followed by chlorin-
ation with thionyl chloride in the presence of dry pyridene
afforded the required 4-chlorohept-2-ynyl acetate (X)
identified by infra-red spectrum and analysis.

$$C_3H_7\underset{\underset{OTp}{|}}{CH}-C\equiv CH \xrightarrow[\text{2. CH}_2O]{\text{1. EtMgBr}} C_3H_7\underset{\underset{OTp}{|}}{CH}-C\equiv C-CH_2OH \xrightarrow{(CH_3CO)_2O} C_3H_7\underset{\underset{OTp}{|}}{CH}-C\equiv C-CH_2OAc$$

(IX)

$$H^+$$

$$C_3H_7\underset{\underset{Cl}{|}}{CH}-C\equiv C-CH_2OAc \xleftarrow{SOCl_2} C_3H_7\underset{\underset{OH}{|}}{CH}-C\equiv C-CH_2OAc$$

(X)
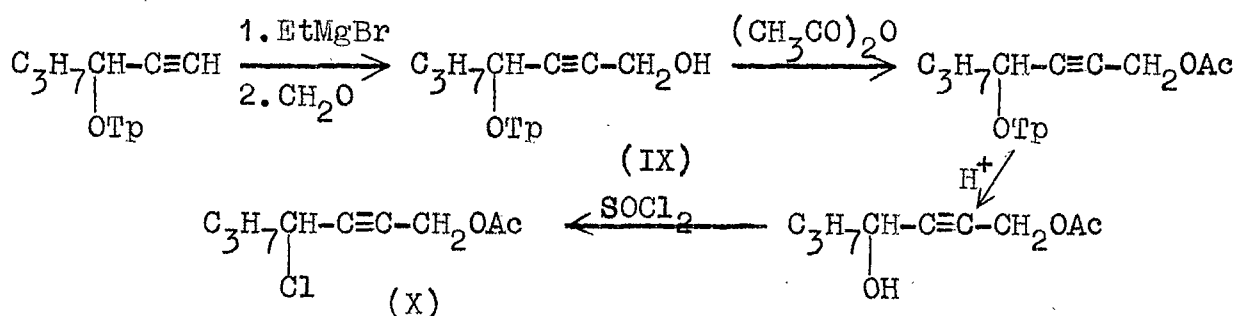
4-Chlorohept-2-ynyl acetate (0.01 mole) added in one
portion to lithium aluminium hydride-monosaccharide complex
(0.01 mole) in ether and stirred for 0.5 hr. at room
temperature gave hepta-2,3-dien-1-ol $[\alpha]_D^{25}+1.6°$, identified
by its infra-red spectrum, and gas/liquid chromatography.

The production of dextrorotatory allenic alcohol
was somewhat unexpected. Examination of models show that
if the hydride ion is donated by an aluminium already.

attached to the oxygen of the chloracetylenic alcohol in the

usual way then the R form of the allenic alcohol should be

formed more rapidly than the S form (cf. figure 17, p. 92).

If the reaction is interrupted before completion the product

would therefore be expected to be laevorotatory.[*] It may be

inferred from this that the mechanism of the reduction of the

chloracetate (X) is more complex than is indicated on p. 90[**]

and the following scheme is put forward as a plausible

alternative.

(XI)

(XII)

(XIII)

(XIV)
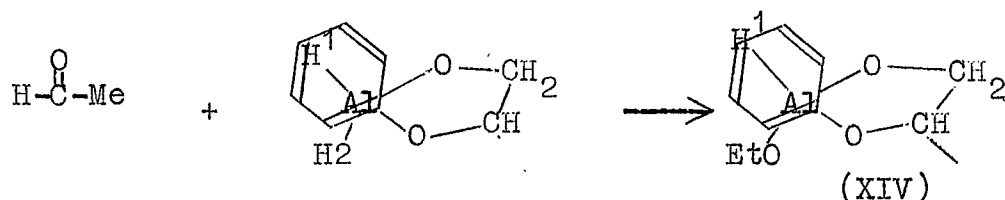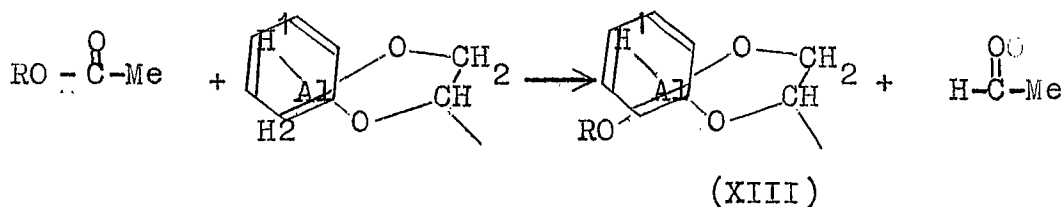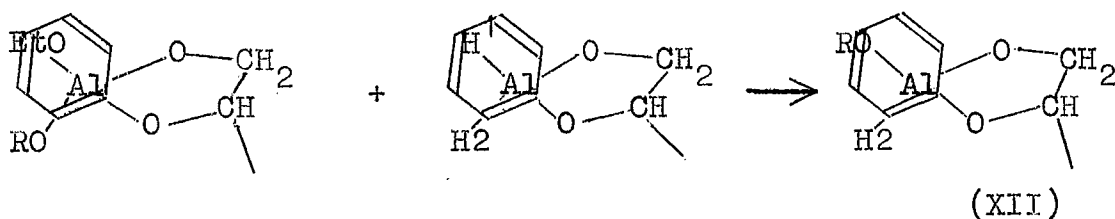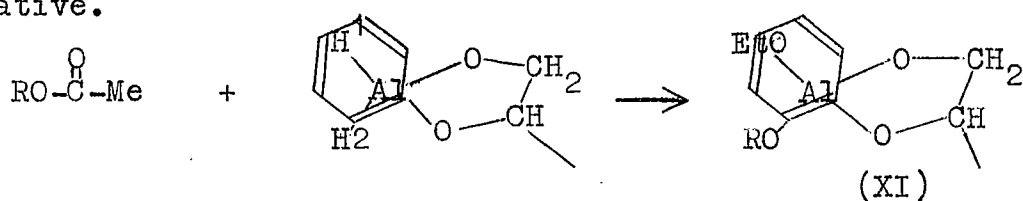
Only partial monosaccharide structures are shown.

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[*]The absolute configuration of allenic alcohols has been shown
to be R(-) earlier in this thesis (p. 52 et seq.)

[**]The mechanism depicted on p. 90 is still considered to
apply to the reduction of the corresponding alcohol.

Reaction of the lithium aluminium hydride-monosaccharide
complex with the chloracetate may give rise to species
(XI), (XII) or (XIII). Species (XI) can react by inter-
molecular reduction only. Since a deficiency of reducing
complex was used in these experiments this must involve
the less active hydrogen H-1 (cf. p. 72) on the attacking
complex molecule as H-2 will already have been used up
preferentially in formation of species such as (XIV). A
model shows that if such a reduction was interrupted before
completion, the S form of the allenic alcohol (i.e. dextro-
rotatory) should predominate in the products. This is
illustrated in figure 18.

The larger OR group would be expected to predominate
in the less shielded position, i.e. replacing H-2, in
species (XI) with the smaller OEt group replacing H-1
(cf. p. 74). If hydride exchange occurs between another
molecule of complex and species (XI) attack will be pre-
dominantly from the H-2 side of the aluminium in species
(XI) (cf. p. 74). This will be accompanied by inversion
of the aluminium to give species (XII) with the OR group
predominating in the more shielded position, replacing H-1.

Species (XII) can undergo intramolecular reduction and
a model shows that, if interrupted before completion, this
would also result in a predominance of the S form of the
allenic alcohol in the products. This is illustrated in
figure 18, p. 97.
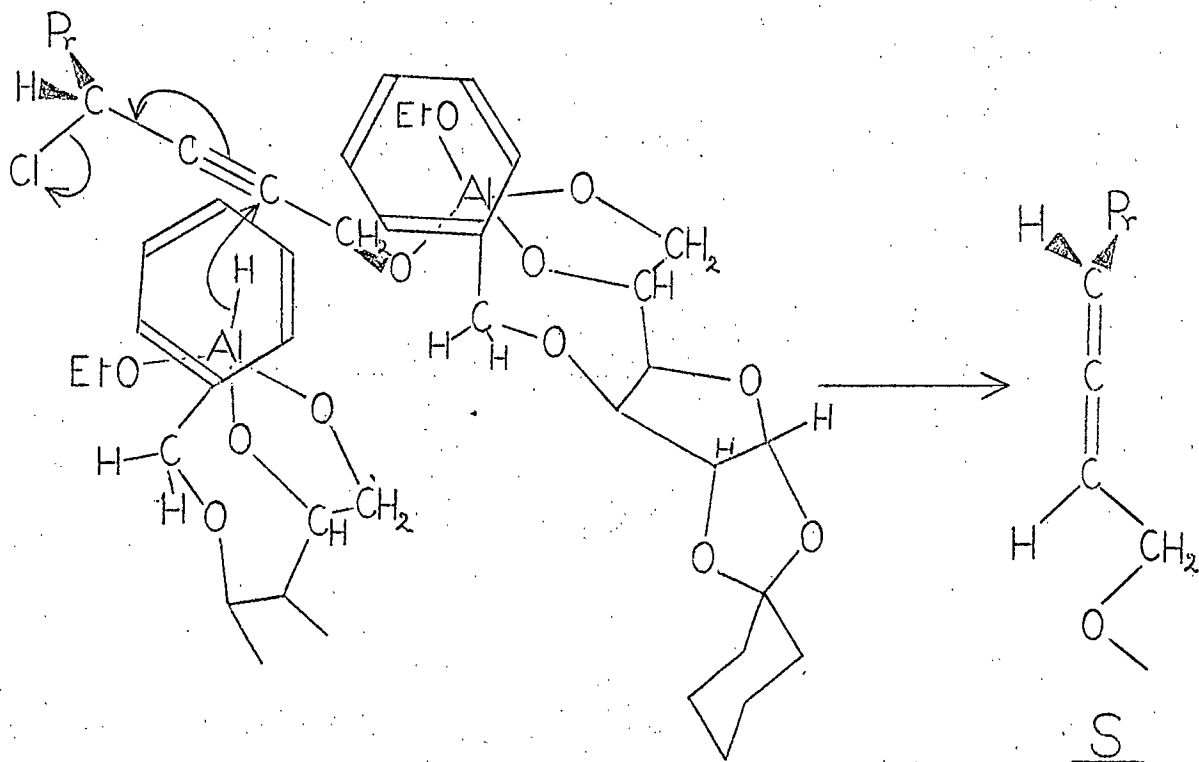
Intermolecular reduction of species (XI).
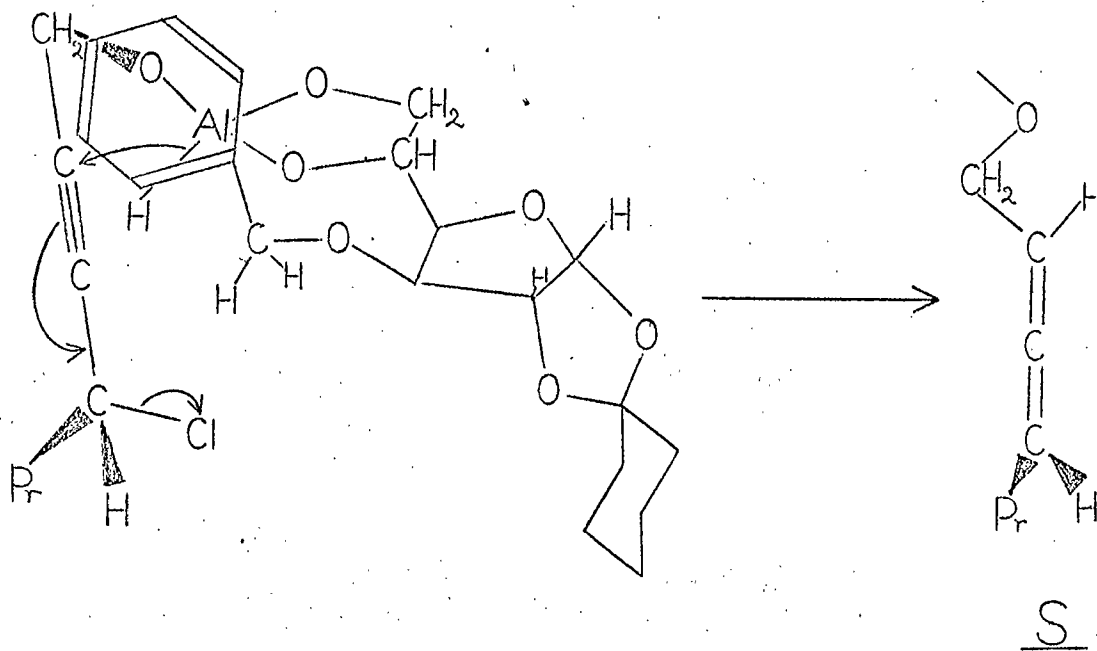
Intramolecular reduction of species (XII).
Figure 18

Species (XIII) in which the OR group replaces the less

shielded hydrogen could also be formed as shown on p. 95.

Intramolecular reduction of (XIII) would lead to the R

form of the allenic alcohol (cf. figure 17, p. 92), but

since the S form (dextrorotatory) is found to predominate

experimentally, species (XIII) must play a minor part.

The Isolation and Identification of Trace Impurities in 3-O-

Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose and the

Preparation of the Pure Compound.

The method introduced by Landor, Miller, and Tatchell[13]

for the preparation of 3-O-benzyl-1,2-O-cyclohexylidene-

α-D-glucofuranose is represented very briefly by the

following reaction scheme:

(XV)

(XVI)

(XVIII)

(XVII)
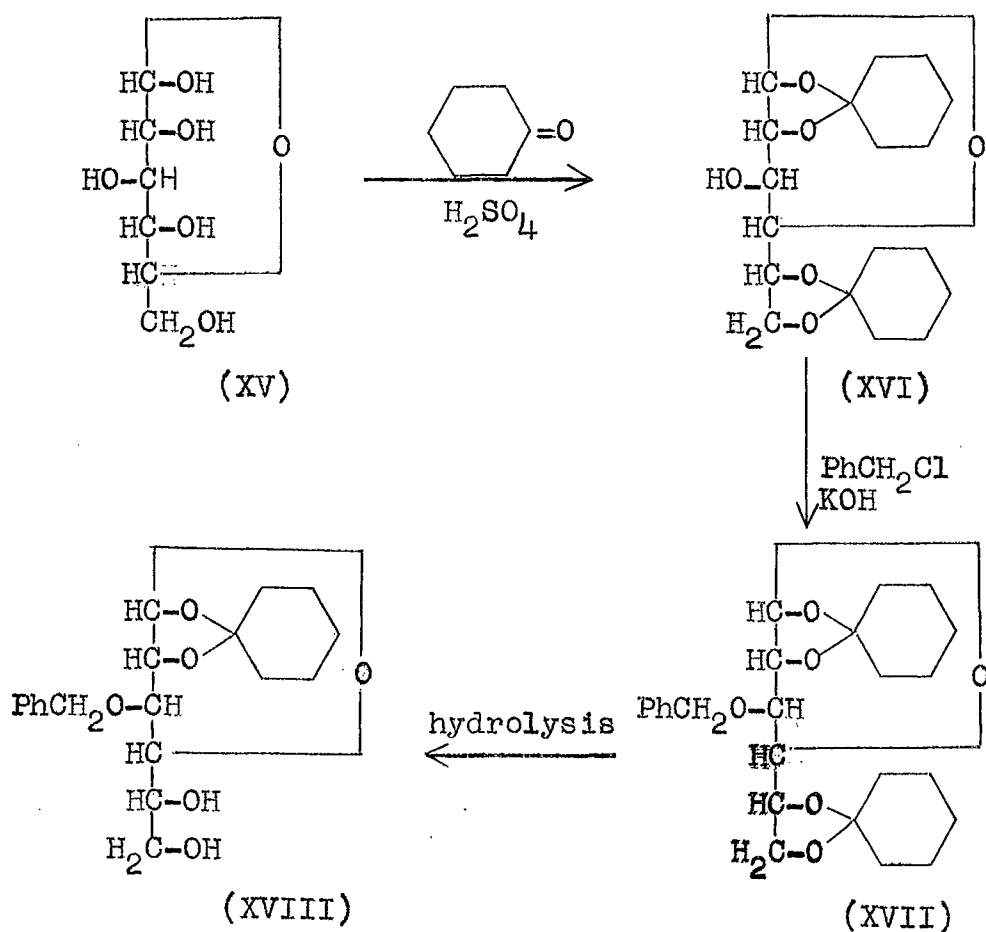
These workers had shown by thin layer chromatography

on silica gel, using 2% methanol in benzene as

eluant,*that their product contained small amounts of

impurities. Attempts to purify the compound by chromato-

graphy on activated alumina using benzene/chloroform (3/1)

as eluant had been unsuccessful.[83] They therefore used the

slightly impure monosaccharide to prepare the complex

with lithium aluminium hydride, and used this in the

preparation of optically active alcohols and simple allenic

alcohols by reduction of ketones and enynols.[13,14] The

impurities did not interfere in these reductions, and,

being high boiling, were easily removed from the products

by distillation.

The monosaccharide was prepared by the method of

Landor, Miller, and Tatchell and thin layer chromatography

confirmed the presence of trace amounts of impurities.

Attempts to remove the impurities by chromatography on

activated alumina, or silica gel impregnated with boric

acid solution using benzene/chloroform or n-pentane/ether

solvent mixtures as eluant were unsuccessful. It was

therefore decided to go back to the start of the synthesis

and to check each stage by thin layer chromatography to

establish where the impurities were introduced.

1,2:5,6-Di-O-cyclohexylidene-α-D-glucofuranose was

---

*After development the plates were sprayed with a 0.2%
solution of naphthoresorcinol in ethanol to which 0.1 vol.
of H_3PO_4 had been added for every volume of ethanol.
Monosaccharides show up as light blue spots on heating at
110° for 0.5 hr.

prepared by the literature method,[84] (p.179) and after

three recrystallisations from n-heptane, melted sharpày at

132° (lit. 132°). Thin layer chromatography of this material,

however, revealed the presence of a minute quantity of

impurity at R_F 0.10; the main spot was at R_F 0.20. The

impurity was not removed by further recrystallisation.

Glucose, on thin layer chromatography, gave a single

spot at R_F 0.00. It was considered probable, therefore,

that the impurity at R_F 0.10 was 1,2-O-cyclohexylidene-α-

D-glucofuranose (XIX) or an isomer of this.
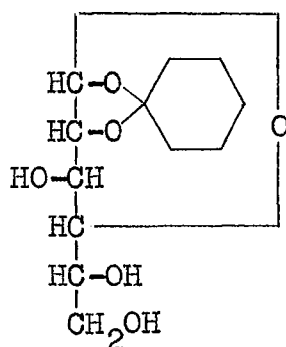
(XIX)

It was realised that in the next stage of the synthesis

the free -OH groups would become benzylated and then be

resistant to hydrolysis in the final stage. It was con-

sidered likely that these benzylated derivatives were the

impurities encountered in the final product, and it was

therefore imperative to remove the monosaccharide deriv-

ative (XIX) at this stage. This was achieved by dissolving

the crystals in the minumum volume of hot heptane (60°)

and washing the resulting solution repeatedly with hot

water (60°) in which the monosaccharide derivative (XIX)

is slightly soluble. On refrigeration of the heptane

solution the required 1,2:5,6-di-O-cyclohexylidene-α-D-

glucofuranose crystallised out and showed only one spot

R_F 0.20 on t.l.c.; the crystals had m.pt. 132.0°.

Benzylation of the 1,2:5,6-di-O-cyclohexylidene-α-D-

glucofuranose was carried out with excess benzyl chloride

at 150° in the presence of potassium hydroxide. The reaction

was followed by withdrawal of small portions at 1 hr.

intervals and t.l.c. examination of these. After 4 hr. the

reaction was complete as shown by obtaining one spot on

t.l.c. R_F 0.95. The solution was allowed to cool and the

organic layer separated from solid inorganic salts.

Distillation using a mercury vapour pump gave 3-O-benzyl-

1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose, $\left[\alpha\right]_D^{20}$ -17.4°

(c. 19.68 in $CHCl_3$), as a brittle glass identified by its

infra-red spectrum and analysis. The compound showed one

spot on t.l.c. R_F 0.95.

The final stage of the synthesis, hydrolysis of one

of the cyclohexylidene groups, was carried out using 75%

acetic acid at 80° in a water bath. The reaction was followed

by withdrawing small samples at 0.5 hr. intervals and

examining these by t.l.c. as before. The formation of the

required monocyclohexylidene derivative was marked by the

gradual appearance of a spot at R_F 0.25 accompanied by a
corresponding diminishing of the spot at R_F 0.95 for
successive samples. Before hydrolysis of the dicyclo-
hexylidene derivative was complete, however, the gradual
appearance of a third spot at R_F 0.00 was observed. This
clearly corresponded to the formation of 3-0-benzylglucose
by hydrolysis of the second cyclohexylidene group. To
prevent substantial hydrolysis of the 3-0-benzyl-1,2-0-
cyclohexylidene-α-D-glucofuranose it was necessary to stop
the hydrolysis with a small amount (ca. 4%) of the dicyclo-
hexylidene derivative still remaining. The solution was
cooled, water and chloroform added, the organic layer
separated and the aqueous layer extracted several times
with chloroform. The combined chloroform layers were
washed with sodium bicarbonate solution to remove acetic
acid and with hot water (60°) to remove 3-0-benzylglucose.
T.l.c. on the chloroform solution showed only two spots,
R_F 0.25 (3-0-benzyl-1,2-0-cyclohexylidene-α-D-glucofuranose)
and R_F 0.95 (unhydrolysed 3-0-benzyl-1,2:5,6-di-0-cyclo-
hexylidene-α-D-glucofuranose).

Removal of the unhydrolysed material was achieved on
a small scale (ca. 1. g.) by chromatography* on acid alumina

---

*This is not the same impurity that was present in the
3-0-benzyl-1,2-0-cyclohexylidene-α-D-glucofuranose prepared
by Landor, Miller and Tatchell.

identification of the impurities present in the monosac-
charide prepared by the original method of Landor, Miller,
and Tatchell. A sample of the slightly impure monosaccharide
that had been used in early attempts at preparing optically
active marasin (p. 67 et seq.) was available and was used
for this purpose.

Preparative size t.l.c. plates of silica gel were
prepared, a 10% solution of the impure monosaccharide in
chloroform applied using an automatic applicator (supplied
by Desaga Ltd.), and the plates developed with 2% methanol
in benzene. The bands were located by spraying just the
ends of the t.l.c. plates with the naphthoresorcinol
spray mentioned earlier (p. 100), each band removed and
extracted with chloroform. Evaporation of the solvent gave
the monosaccharide derivatives which were identified by
infra-red spectra and analysis. The compounds present in
the monosaccharide prepared by the method of Landor, Miller,
and Tatchell, and the R_F values are listed on p. 106. The
compound at R_F 0.25 which could not be removed from marasin
solution by chromatography, was found to be a mono-ol as
suspected earlier (cf. p. 68). The impurities in the
3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose amounted
to approximately 1% by weight.

R_F 0.95 PhCH$_2$O-CH

HC-O
HC-O
PhCH$_2$O-CH
HC
HC-OCH$_2$Ph
H$_2$C-OCH$_2$Ph

HC-O
HC-O
PhCH$_2$O-CH
HC
HC-O
H$_2$C-O

mixture

R_F 0.25 PhCH$_2$O-CH

HC-O
HC-O
PhCH$_2$O-CH
HC
HCCH$_2$OPh
CH$_2$OH

or isomers

R_F 0.20 PhCH$_2$O-CH

HC-O
HC-O
PhCH$_2$O-CH
HC
HC-OH
CH$_2$OH

R_F 0.00 PhCH$_2$O-CH

HC-OH
HC-OH
PhCH$_2$O-CH
HC-OH
HC
CH$_2$OH
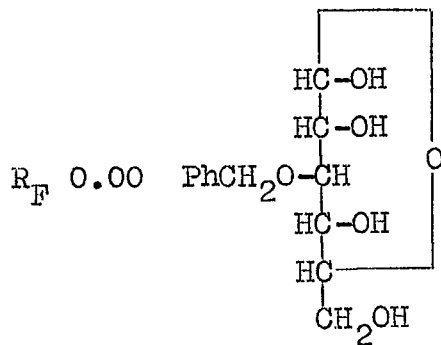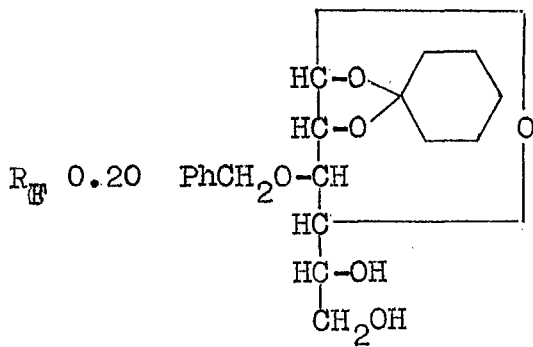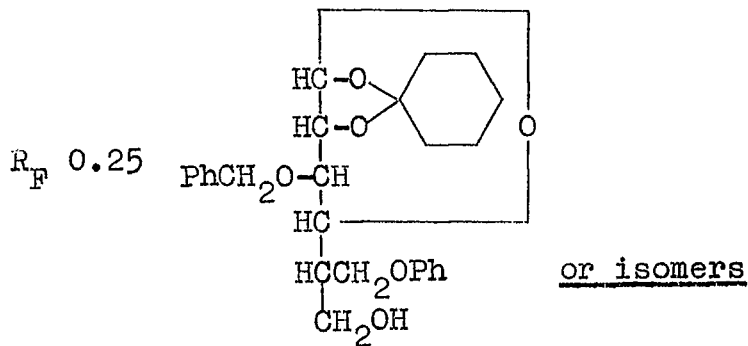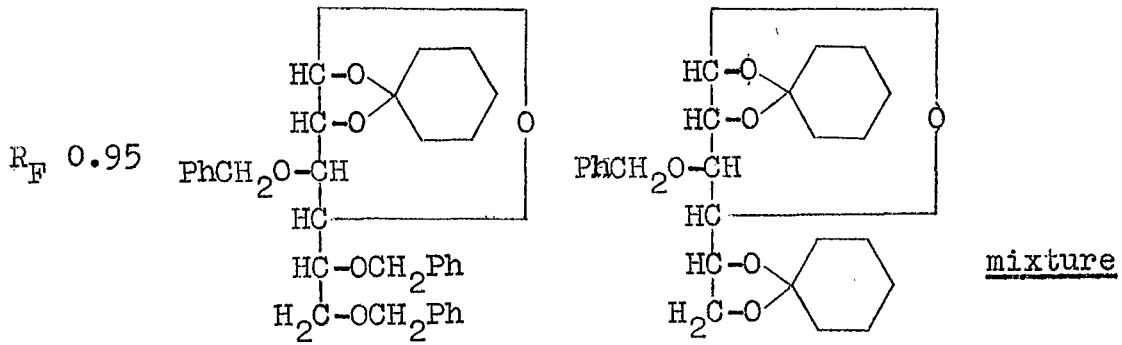
Preparation and Reactions of Bromopropargyl Aldehyde

Propargyl aldehyde was prepared in 1950 by Wille and Saffer[130] and their method has since been considerably improved by Landor and Pepper.[131] The method consists of oxidizing propargyl alcohol to the aldehyde which is distilled from the reaction sphere under reduced pressure as it is formed to prevent further oxidation.

$$HC\equiv CH_2OH \xrightarrow{\text{[O]}} HC\equiv C-CHO$$
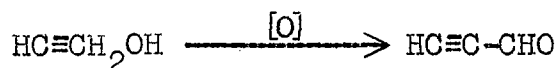
Landor and Pepper prepared one acetylenic alcohol and two diacetylenic alcohols from propargyl aldehyde via the Grignard reagents, (table II).[131]

TABLE II[131]

Reagent	Product	Yield %
$(CH_3)_3CMgCl$	$(CH_3)_3C-CH(OH)-C\equiv CH$	25
$HC\equiv CMgBr$	$HC\equiv C-CH(OH)-C\equiv CH$	66
$(CH_3)_3C-C\equiv CMgBr$	$(CH_3)_3C-C\equiv C-CH(OH)-C\equiv CH$	72

Penta-1,4-diyn-3-ol had been previously prepared by a different method by Jones, Skattebol, and Whiting,[132] and since Landor and Pepper's work, Wille and Strasser[133] have also used propargyl aldehyde to prepare the compound.

One of the disadvantages of using propargyl aldehyde in syntheses is the high reactivity of the acetylenic hydrogen which is often involved in side reactions. Thus

Landor and Pepper attributed the low yield of 4,4-dimethyl-

pent-1-yn-3-ol in Table II to side reactions of type:

$$(CH_3)_3CMgCl + HC\equiv C-CHO \longrightarrow (CH_3)_3CH + ClMgC\equiv C-CHO.$$

It was considered possible that these side reactions

could be inhibited by the use of bromopropargyl aldehyde

instead of propargyl aldehyde. The preparation of bromo-

propargyl aldehyde and an examination of its properties

was therefore undertaken.

The first attempted synthesis was to convert propargyl

aldehyde to the diethyl acetal and to brominate this with

sodium hypobromite. Accordingly, propargyl aldehyde was

prepared by the method of Landor and Pepper (p.185) and

this was added to an ice cold mixture of anhydrous calcium

chloride and ethyl alcohol. The propargyl aldehyde underwent

rapid polymerisation under these conditions, however, and

none of the required acetal could be prepared by this method.

A similar result was obtained when hydrochloric acid was

used as the catalyst, and an alternative approach was

therefore tried.

Bromopropargyl alcohol was prepared by the action

of sodium hypobromite on propargyl alcohol, (p. 185).

This was oxidised to the aldehyde by the slow addition

of an acidic solution of chromium trioxide. During the

addition nitrogen was bubbled through the reaction mixture

and the pressure reduced to 4 mm. Hg. The volatile

bromopropargyl aldehyde was thus swept from the oxidising

mixture and collected in a trap at -60° as it was formed.

Further oxidation of the aldehyde was thus reduced to a

minimum. After drying $(MgSO_4)$, the material was identified

as bromopropargyl aldehyde (11%) by comparison of its

infra-red spectrum with that of an authentic sample of

propargyl aldehyde, (I.R. No.4 and 2). An attempt to

distil the compound resulted in an explosion after a small

amount of distillate had been collected. The infra-red

spectrum of the distillate (I.R. No.26) was much more

complex than that of the undistilled material and it was

concluded that polymerisation had occurred.

In view of the low yield (11%) obtained by the previous

method, an alternative synthesis was sought. Propargyl

aldehyde diethylacetal had been prepared in 1949 by a

rather roundabout route by Sheehan and Robinson.[129] It

was decided to prepare this compound by their method and to

try brominating it with sodium hypobromite solution. The

synthesis of propargyl aldehyde diethylacetal is represented

very briefly by the following reaction scheme (experimental

details p.187 et seq.).

$$CH_2=CH-CHO \xrightarrow{\quad Br_2 \quad} CH_2(Br)CH(Br)-CHO$$

$$\downarrow EtOH/HCl$$

$$HC\equiv C-CH(OEt)_2 \xleftarrow{\quad KOH/EtOH \quad} CH_2(Br)CH(Br)-CH(OEt)_2$$
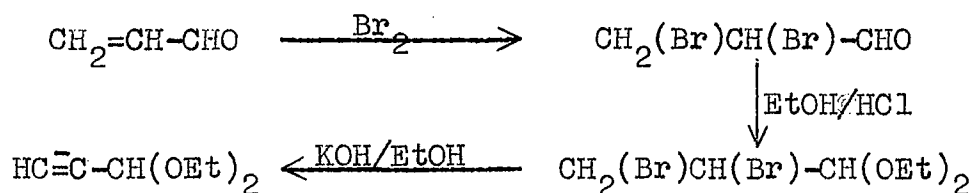
Bromination of the acetylenic acetal was carried out

with sodium hypobromite and the brominated acetal obtained,
hydrolysed to the aldehyde with dilute sulphuric acid,
ether extracted, and dried. Removal of the ether gave
bromopropargyl aldehyde (45% on acrolein) identified by
its infra-red spectrum as before. Another attempt to
distil the compound, again resulted in an explosion and
it was therefore decided to use the compound without
further purification. The material polymerised in a
few hours at room temperature and throughout this work
was prepared in small batches as required.

Bromopropargyl aldehyde was reacted with one equiv-
alent of tbutylmagnesium chloride (experimental details
p.189). A large amount of polymer was formed during the
reaction. After working up, an attempt to distil the
material resulted in further polymerisation and only a small
quantity of distillate was obtained. The infra-red spectrum
of the distillate showed bands at ν_{max} 3,450 (OH), 2,220
and 2,185 (RC$\equiv$CR) and 1,700 cm.$^{-1}$ (C$=$O), (I.R. No.36).
The absence of a band in the region of 685 cm.$^{-1}$ indicated
that the bromine had been lost and it was therefore con-
sidered that the acetylenic bromine had undergone reaction
with the Grignard reagent, and that the product was probably
a mixture of tBuC$\equiv$C-CH(OH)tBu and tBuC$\equiv$C-CHO. Since the
primary object of this work was to inhibit reaction at the
acetylene and the yield of distillate was so low (ca. 6%)

the experiment was abandoned at this stage.

An attempt was made to react bromopropargyl aldehyde with 2-tetrahdropyranyloxyethyl lithium. A large amount of polymeric material was again formed during the reaction and only a very small amount of material could be distilled after working up the reaction products. The infra-red spectrum of the distillate showed bands at $_{max}$ 3,400 (OH) and 2,220 cm.$^{-1}$ (RC≡CR), (I.R. No. 37). Absence of a band in the region 685 cm.$^{-1}$ indicated that the acetylenic bromine had again been lost and the small quantity of distillate obtained was probably TpO$(CH_2)_2$C≡C-CH(OH)$(CH_2)_2$OTp. This experiment was also abandoned.

An attempt to carry out a Reformatsky reaction between bromopropargyl aldehyde and ethyl bromoacetate was also unsuccessful. Difficulty was caused by a very rapid polymerisation of the bromopropargyl aldehyde under reaction conditions.

In the light of this work it was concluded that bromination of the acetylene in propargyl aldehyde was of no advantage in inhibiting reactions of the acetylene group.

The Stereochemistry of the Reduction of Cyclohexanones

Reductions with cyclic complexes of lithium aluminium hydride have been described earlier in this thesis (pp. 50, 66 et seq.). To obtain further information on the mechanism of these reductions, 3,3,5-trimethylcyclohexanone was reduced with the complexes shown in table III and the ratio of axial/equatorial alcohol produced determined by g.l.c. on "Tide" detergent. Results obtained by Haubenstock and Eliel[22,23] (cf. p. 35) are also included in table III for convenience.

TABLE III
The reduction of 3,3,5-trimethylcyclohexanone with lithium aluminium hydride complexes

	Addend	$\dfrac{\text{Moles addend}}{\text{Mole LiAlH}_4}$	$\dfrac{\text{Moles of complex}}{\text{Mole ketone}}$	Axial alcohol %(Trans)
1	$CH_2(OH)CH_2(OH)$	1	3	54
2	$CH_3CH(OH)CH(OH)CH_3$	1	3	53
3	3-O-Benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose	1	2	58
4	3-O-Benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose/EtOH	1/1	2	70
5	EtOH	3	3	85
6	EtOH	2	3	81
7	EtOH[22]	3	1.20	83
8	t-Butyl alc.[22]	3	1.07	73
9	None[22]	–	1.24	52
10	None[22]	–	8.40	55

Reagent	Solvent	Mole Reagent Mole ketone	Axial alcohol % (Trans)
11 NaBH$_4$[23]	Anhyd. isopropyl alc.	0.53	55
12 NaBH$_4$[23]	Anhyd. isopropyl alc.	0.25	56
13 NaBH$_4$[23]	Anhyd. t-butyl alc.	0.52	55
14 NaBH$_4$[23]	Anhyd. diglyme	0.52	55

As described earlier in this thesis, in the preparation
of allenynols by reduction of enynols, further reduction
of the product to allenene was prevented by using a cylic
complex of lithium aluminium hydride as the reducing agent
(p. 50). Reduction of enynols with the cyclic 3-O-benzyl-
1,2-O-cyclohexylidene-α-D-glucofuranose complex with lithium
aluminium hydride, gave optically active allenic alcohols
(p. 66 et seq.). These observations led to the conclusion
that the cyclic complexes used were stable under the
experimental conditions; the other cyclic complexes shown
in table III would also be expected to be stable under the
conditions used. It was found that reduction of 3,3,5-
trimethylcyclohexanone with the cyclic complexes listed
gave products with similar axial/equatorial ratios as did
lithium aluminium hydride and sodium borohydride.

Prior to the present work, the reduction of cyclohex-
anones was assumed to involve only the chair form of the
ketone, and in the case of 3,3,5-trimethylcyclohexanone
the reduction was considered to be subject to steric approach

control[25,26] (cf. p. 33). It was shown by Landor, Miller,
and Tatchell[24] that in the asymmetric reduction of ketones
with optically active complexes of lithium aluminium hydride,
the stereochemistry of the resulting alcohols was correctly
predicted if the approach of the ketone towards the complex
occurred so that minimum interaction of the non-bonded
oxygen atoms occurred.

An examination of Dreiding models shows that the
experimental results obtained (table III) are inconsistent
with these points. It is clearly untenable that a cyclic
complex of lithium aluminium hydride should experience
roughly the same steric interaction by the axial methyl
group during its approach from the axial side to the carbonyl
of 3,3,5-trimethylcyclohexanone as does lithium aluminium
hydride and the sodium borohydride complexes. This therefore
leads to the conclusion that axial attack of 3,3,5-trimethyl-
cyclohexanone by lithium aluminium hydride or its complexes,
and by sodium borohydride or its complexes, does not occur.[*]
An examination of a Catalin model of 3,3,5-trimethylcyclo-
hexanone shows that this conclusion is quite reasonable,
since the carbonyl group is effectively shielded to attack
from the axial side.[**] The only way of producing the equatorial

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[*]If axial attack did occur the reaction would be subject
to steric approach control and results 1, 2, 3, 10, 11,
13 and 14 in table III would be much more divergent.

[**]This applies to any hindered cyclohexanone (cf. footnote p. 32).

alcohol by reduction of 3,3,5-trimethylcyclohexanone, there-
fore, is by equatorial attack on the flexible form of the
ketone with nearly simultaneous flip to the chair form.
It is proposed that this reaction competes with equatorial
attack of the chair form. The ratio axial/equatorial
alcohols produced in the products thus depends on the rel-
ative rates of these two competing reactions. A re-examination
of some results cited in the literature which have up to
the present time appeared anomalous, may also be rationalised
by assuming the participation of flexible forms.

Although flexible forms have not previously been
considered to be of importance in this type of reaction,
it has been estimated that in cyclohexanone the energy
difference between the chair and flexible forms is only
2.7 K cal/mole,[27] i.e. about half as much as in cyclohexane.
This means that about 1% of the ketone is in the flexible
form.[28a] Attempts have been made to measure the barrier
height to chair-chair and chair-flexible forms in cyclo-
hexanones[26] from low temperature NMR spectra of cyclohexanone
and some of its simple alkyl derivatives down to -75°, but
it has not yet been possible to reach sufficiently low
temperatures to freeze the conformational inversions. It
may be implied from this that the barrier is substantially
lower than in cyclohexane. It seems a reasonable proposal,
therefore, that a ketone with an axial methyl group such

as 3,3,5-trimethylcyclohexanone should be capable of
existing to considerably greater than 1% in the flexible
form. Consideration of some observations reported in the
literature leads to the conclusion that even for ketones
having no axial substituents, flexible forms can be important
participants in reactions. It will be shown that in some
cases, the participation of the flexible form in a reaction
of a ketone may have a marked affect on the stereochemistry
of the products, even though the concentration of flexible
form in the chair-flexible form equilibrium is extremely
low.

The equation derived by Eliel, Ro and Lukach[28a,29]
for reactions of equatorial and axial conformers present
in an equilibrium mixture, may be applied to reactions of
chair-flexible form mixtures:

$$k=(k_cK+k_f)/(K+1)$$

where k is the overall rate constant, k_c is the rate constant
of reaction of the chair form and k_f is the rate constant
of reaction of the flexible form. If about 5% of the
flexible form* is present at 25° then $K = 19$ and we must
assume that $k_f = 17k_c$ to account for the formation of
about equal amounts of equatorial and axial alcohol with

---

*For a 95:5 equilibrium the difference in energy between
chair and flexible form is 1.7 K cal/mole; it is assumed
that the energy due to relief of axial Me:H interaction
is about 1 K cal/mole which seems not unreasonable.

lithium aluminium hydride.[*] Such a difference in reaction rate of chair and flexible form may be accounted for by a detailed consideration of the mechanism of the reduction process.

A broad-side attack of the carbonyl group (i.e. simultaneous donation of the hydride ion and formation of the new O-Al bond) by the aluminium hydride complex ion is unlikely since this would involve an unstable four centred cyclic transition state. The reduction is more likely to go in two stages, the initial donation of hydride ion by the complex being followed by formation of the oxygen-aluminium bond, possibly by reaction with a different molecule of complex.[*]
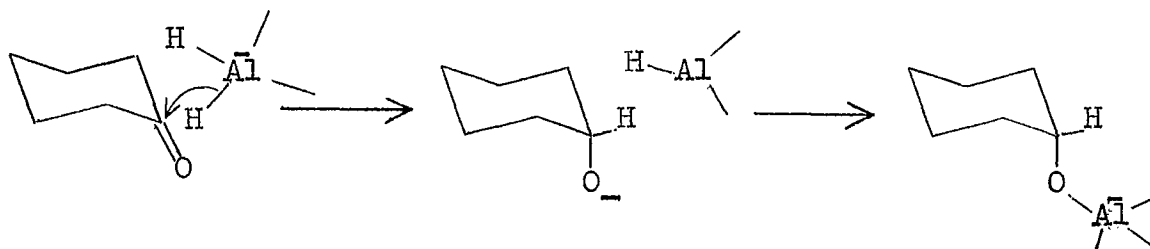
Clearly, the concept of product development control as originally introduced by Dauben,[25,26] in which the bulk of the group being introduced into the axial position

---

[*] $\dfrac{\text{axial}}{\text{equatorial}} = \dfrac{k_c \times 95}{k_f \times 5} = \dfrac{k_c \times 95}{17k_c \times 5} = \dfrac{95}{85} = 1.117$

[*]Such a mechanism is consistent with the observed stereochemical results. This mechanism is also supported by the work of Landor, Miller, and Tatchell[14] on the asymmetric reduction of ketones.

was considered to exert a retarding effect on the reaction,
must be modified in the present case. If the proposed
mechanism for this reaction is correct, the substituent
being introduced into the axial position is always a neg-
atively charged oxygen atom, no matter what lithium aluminium
hydride complex is used. In the case of attack of the
flexible form this might lead to interaction (i.e. attraction)
between flagpole hydrogen and O^- and between the isoclinal[*]
methyl group on C_3 and O^-. This would thus cause an
acceleration of the reaction (i.e. a lowering of the
activation energy of the reaction) and this reaction could
thus be regarded as being subject to "positive product
development control".[*] This is shown in figure 19, p. 119.

In the case of equatorial attack of the chair form,
the O^- being introduced into the axial position could
interact (attraction) with the axial methyl group on C_3,
so that this reaction too is subject to positive product

---

[*] The classical boat form of 3,3,5-trimethylcyclohexanone
may be twisted so that the two methyl groups on C_3 are
orientated at equal angles above and below the plane of
the ring. Following a suggestion by Professor M. C.
Whiting, methyl groups thus orientated have been called
isoclinal. Interactions in the boat (flexible) form
appear to be at a minimum in this conformation.

[*] The type of effect envisaged by Dauben in which the bulk
of the substituent (uncharged) being introduced into the
axial position causes steric crowding of axial substituents
(thus increasing the activation energy) could be termed
"negative product development control".
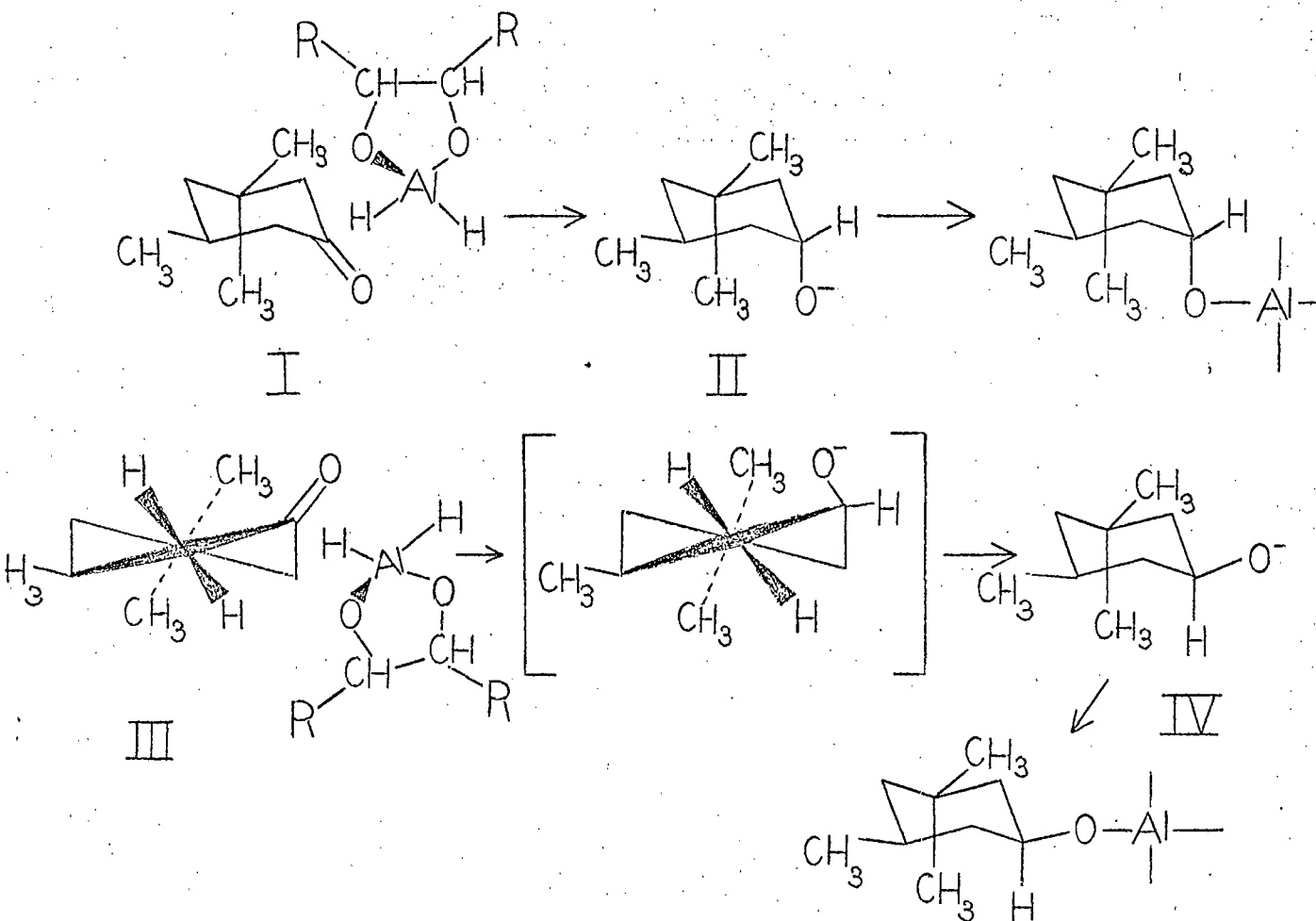
Figure 19

development control. The difference in reaction rates of
flexible and chair forms of 3,3,5-trimethylcyclohexanone
may thus be attributed to a difference in the magnitude
of the positive product development control in the two
cases.

Examination of models show that during equatorial
attack of both chair and flexible forms of 3,3,5-trimethyl-
cyclohexanone by lithium aluminium hydride or sodium

borohydride, and by moderately sized complexes of these
hydrides in which not more than two of the aluminium hydrogens
have been replaced, steric interactions between reactants
are comparitively unimportant. The axial/equatorial
ratios of alcohols produced by these complexes are therefore
insensitive to the size of the reducing complex (cf. table III).
With a very bulky complex of this type however, (and a
critical size seems to be reached with the monosaccharide
complex) equatorial attack on the flexible form experiences
more steric retardation both by the 2,6-hydrogens and the
isoclinal 3-methyl group, than does equatorial attack on
the chair form, and this leads to slightly more axial
alcohol in the product.

When the third hydrogen on the complex hydride is
replaced by an alkoxy group, approach of the complex
hydride towards the carbonyl is much more unfavourable
(if overlap of non-bonded oxygens is kept at a minimum,
cf. p. 114). This causes the reaction to be much more
sensitive to steric interactions. Models show that reaction
of flexible form is retarded more than reaction of chair form
by steric interactions of the 2,6-hydrogen and isoclinal
3-methyl and more axial alcohol is therefore observed in
the products, (cf. results 3 and 4, table III).

The result obtained by Haubenstock and Eliel for the
triethoxyaluminiumhydride complex, and confirmed during

the present work, indicates that this effect is more enhanced with a non-cyclic tri-alkoxy complex. This may be due to the fact that an alkoxy modified cyclic complex is a more rigid structure than the non-cyclic tri-alkoxy complex. Random movements of the three alkoxy groups on the non-cyclic tri-alkoxy complex may increase the interference with the 2,6-hydrogens and isoclinal 3-methyl group as attack occurs. Reduction with the tri-_t_-butoxy aluminium hydride complex gives a lower amount of axial alcohol in the products than would be expected. It has recently been suggested[30] that tri-_t_-butoxyaluminium hydride may not be the operative reducing agent however, and this may account for this result.

The participation of flexible forms in reactions of some cyclohexanones enables some observations reported in the literature to be rationalised, which prior to the present work have appeared anomalous. Thus it is reported by Lansbury and MacLeay[31] that reduction of 4-_t_-butylcyclohexanone with both lithium aluminium hydride and sodium borohydride gives predominantly the equatorial alcohol and is influenced only very slightly by temperature differences, the amount of equatorial alcohol increasing slightly at lower reaction temperature. Similar reductions of 3,3,5-trimethylcyclohexanone give substantially larger amounts of axial alcohol at lower temperature, however.

Normally, in a system in which two reaction paths are

possible, the proportion of the product derived from the
reaction path of lower activation energy increases as the
reaction temperature is lowered. Thus in the present case,
lowering the reaction temperature should increase the
proportion of equatorial alcohol produced (from equatorial
attack of flexible form). Opposing this effect however, is
the fact that as reaction temperature is lowered, the amount
of flexible form present in the flexible form/chair form
equilibrium decreases. This second temperature effect thus
tends to decrease the proportion of equatorial alcohol
produced at lower reaction temperature. The net result
observed thus depends on which of these two opposing temp-
erature effects is dominant for the particular compound
concerned. In the case of 4-t-butylcyclohexanone the first
effect is dominant and in the case of 3,3,5-trimethylcyclo-
hexanone the second effect is dominant. The observations
of Lansbury and MacLeay are thus explained.

The stereochemistry of catalytic reduction may also
be interpreted on the basis of flexible form participation.
Such reductions have been considered to involve steric
approach control (absorption on the catalyst and approach
of hydrogen from the less hindered equatorial side) and
yield mainly axial alcohols (von Auwers-Skita hydrogenation
rule[28a]). The equatorial alcohols produced in smaller
quantities in these reductions were considered to result

from absorption on catalyst and approach of hydrogen from
the axial side. Examples are the reduction of cholestan-
3-one over active platinum to give cholestan-3-α- and
-3β-ol[32] in a ratio of 3:1 and reduction of 4-$\underline{t}$-butyl-
cyclohexanone[33] over platinum in acetic acid-hydrochloric
acid to give cis and trans-4-$\underline{t}$-butylcyclohexanol in a
ratio of 4:1. These reductions are not completely stereo-
selective and it has been observed that catalytic hydrogen-
ation gives the greatest amount of axial alcohol when
carried out under conditions where hydrogenation is fast.
Thus hydrogenation of 4-$\underline{t}$-butylcyclohexanone[33] is more
stereoselective in the presence of hydrochloric acid (4:1)
than in its absence (2:1); use of an aged and not very
active platinum catalyst reduced selectivity even more
(1.2:1).

If the equatorial alcohols produced in these catalytic
reductions resulted from reduction of chair forms of the
ketones, then absorption of ketone onto the catalyst would
have to take place from the axial side. If this were the
mechanism of the formation of equatorial alcohol, then
slowing down the reaction by use of old catalyst should
lead to more axial alcohol, not less, as the less active
catalyst would be more selective in absorbing molecules in
favourable orientation (i.e. from the equatorial side).
The observed decrease in the amount of axial alcohol produced

with the use of old catalyst therefore implies that another

mechanism must be operative. This conclusion is supported

by an examination of models which show that absorption of

these ketones onto a catalyst surface from the axial side

is very difficult due to the angle of the carbonyl group.

It is proposed therefore, that in these catalytic reductions

no axial absorption of ketone onto the catalyst occurs. Any

equatorial alcohol produced in the reductions must therefore

be a result of the equatorial absorption of flexible forms

onto the catalyst surface. Use of an aged catalyst (with

a not very active surface) results in preferred absorption

of flexible form[*] from the equatorial side, and will thus

give larger amounts of equatorial alcohol in the products

as observed.

An exception to the hydrogenation rule is the reduction

of cholestan-1-one[34] which is reduced to the (equatorial)

1-β-ol over platinum in acetic acid in over 90% yield.

This observation would be predicted since in cholestan-1-one

equatorial absorption of the ketone when the A ring has the

chair conformation is prevented by the methyl group in the

C_{10} position. The reduction therefore goes completely

---

[*]Models show that equatorial absorption of flexible form
takes up less room on the catalyst surface than does
equatorial absorption of chair form. With an aged and not
very active catalyst the surface is presumably contaminated
and the slightly different spatial requirements of chair
and flexible forms become important.

by the equatorial absorption and reduction of the flexible

form to give the equatorial alcohol. This is illustrated

in figure 20.

equatorial attack
hindered

Me

Me

O

C$_8$H$_{17}$
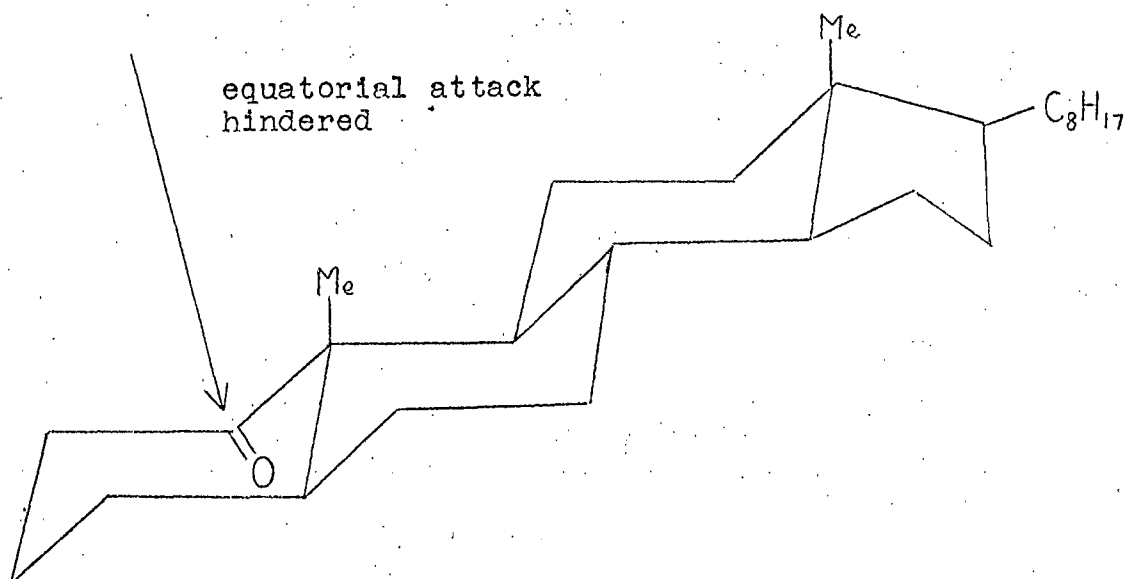
Figure 20

The proposal by Richer[35](cf. p. 36) that "the stereo-

chemical results of all the additions on unhindered ketones

by groups small enough not to interfere with the axial

hydrogen in positions 3 and 5, are directed exclusively

by the axial hydrogens on positions 2 and 6 which hinder

attack from the equatorial side", appears dubious on exam-

ination of models. Due to the angle of the carbonyl group,

approach to the carbonyl appears to be always easier from

the equatorial side no matter what size the attacking entity.

Richer's[35] results from reductions of different substituted cyclohexanones with lithium tri-t-butoxy aluminium hydride (table IV) may be interpreted by postulating the participation of chair and flexible forms. (There is some doubt whether the reducing entity is tri-t-butoxy aluminium hydride[30]).

TABLE IV[35]

Reduction of cyclic ketones by LiAlH(O-t-Bu)$_3$ in tetrahydrofuran.

Ketone	% Stable Isomer
1. 2-Methylcyclohexanone	63.2
2. 3-Methylcyclohexanone	86.0
3. 4-Methylcyclohexanone	82.6
4. 4-t-Butylcyclohexanone	89.7
5. 4-t-Butyl-2,2-dimethylcyclohexanone	100.0
6. 3,3,5-Trimethylcyclohexanone	12.2

1.   2-Methylcyclohexanone gives less of the stable (trans) isomer than any of the other monosubstitued cyclohexanones in table IV.   Axial attack on chair* produces the stable (trans)isomer:
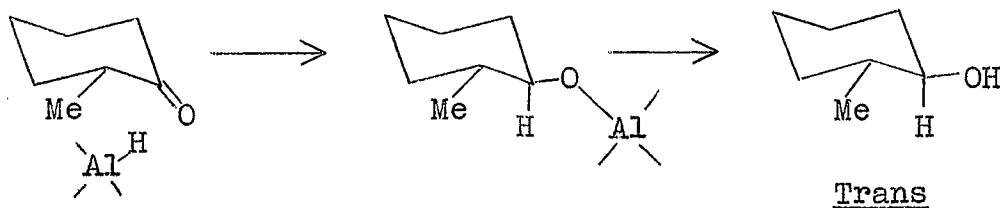
equatorial attack on chair gives the cis isomer, but so does equatorial attack on flexible form in this case.

---

*Axial attack on chair is possible in this case since there are no axial substituents in positions 3 and 5.

axial Me

Al
O
H

Me

Me
axial Me
O
Al
H

isoclinal
Me

isoclinal
Me

O—Al
Me
equatorial Me

OH
Me
cis
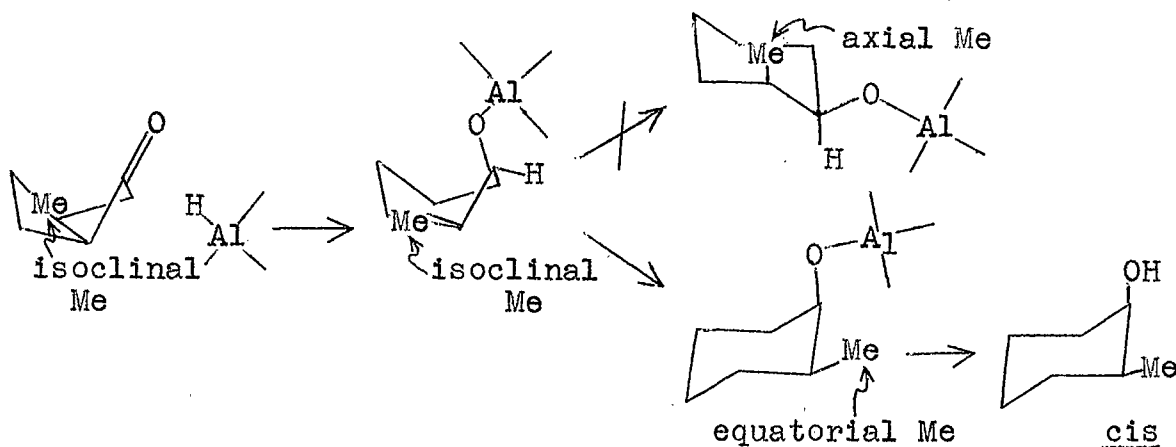
2, 3 and 4. Both axial attack on chair form and equatorial attack on flexible form give the more stable isomer. Equatorial attack on the flexible form would be expected to play a bigger part with tri-$\underline{t}$-butoxy aluminium hydride as reducing agent than with lithium aluminium hydride.

5. Equatorial attack on both chair and flexible form is prevented by the 2,2-dimethyl group. Axial attack on chair[*] form gives only the stable (trans) isomer. The fact that no axial alcohol is formed indicates that axial attack of flexible form does not occur. This may be due to shielding by the flagpole hydrogen.

6. Equatorial attack by the bulky reagent on the flexible form experiences steric interference from the 2,6-hydrogens and isoclinal 3-methyl group and gives the equatorial

[*]Axial attack on chair is possible in this case since there are no axial substituents on positions 3 and 5.

cyclohexanol. Equatorial attack on the chair form gives the axial cyclohexanol which predominates in the product.

There are therefore four possible reaction paths to be considered for reductions of cyclohexanones:

(a) axial attack of chair form to give equatorial alcohol, (for unhindered cyclohexanones);

(b) equatorial attack of chair form to give axial alcohol;

(c) axial attack of flexible form to give axial alcohol (appears to be relatively unimportant due to steric hindrance of the flagpole hydrogen);

(d) equatorial attack of flexible form to give equatorial alcohol.

The axial/equatorial ratio of products from these four reaction paths should be interpreted in the light of steric approach control and product development control for the particular compound concerned; e.g. in the case of a hindered cyclohexanone having no substituents in positions 2 and 6 (such as 3,3,5-trimethylcyclohexanone) mechanism (a) is eliminated by steric approach control. Mechanisms (b) and (d) are both favoured by positive product development control and the relative magnitude of this factor in the two cases is important in determining the axial/equatorial ratio of products.

In a different cyclohexanone, however, e.g. 4-t-butyl-2,2-dimethylcyclohexanone (table IV) mechanisms (b) and (d) are eliminated by steric approach control and the

reaction goes entirely by mechanism (a). Mechanism (c) appears to be unimportant, possibly due to shielding of the carbonyl by the flagpole hydrogen.

The products from the reduction of 3,3,5-trimethyl-cyclohexanone with the lithium aluminium hydride-mono-saccharide complex were found to be optically inactive. Whilst the chair form of 3,3,5-trimethylcyclohexanone is undergoing equatorial attack, the axial methyl group on C_3 is on the side of the ring remote from the attacking complex hydride. From the point of view of the attacking entity, therefore, the ketone appears to be symmetrical. A model of the flexible form of 3,3,5-trimethylcyclohexanone shows that the steric interference of the two isoclinal methyl groups on C_3 with the benzyl group on the monosac-charide, is about the same as that of the lone methyl group on C_5 with the benzyl group of the monosaccharide. (This is illustrated in figure 20.) Optically inactive alcohol would therefore be expected from both these mech-anisms. The observation that optically inactive alcohol is obtained experimentally is further support for the proposal that axial attack of the chair form of 3,3,5-trimethyl-cyclohexanone does not occur. If axial attack did occur the steric interaction of the axial methyl group on C_3, with the benzyl group of the monosaccharide, would differ

for the two ketone enantiomorphs. (This is illustrated

in figure 22). The alcohol produced would thus be optically

active.

Attempts to measure experimentally the relative rates

of formation of axial and equatorial alcohol were unsuc-

cessful due to the rapidity of the reactions. Even at

$-40°$ the reaction was found to be complete after about two

minutes.

chair form - symmetrical
to equatorial attack

Flexible form - 3,3-isoclinal methyl groups cause about the
same steric interference to the benzyl group as the 5-equatorial
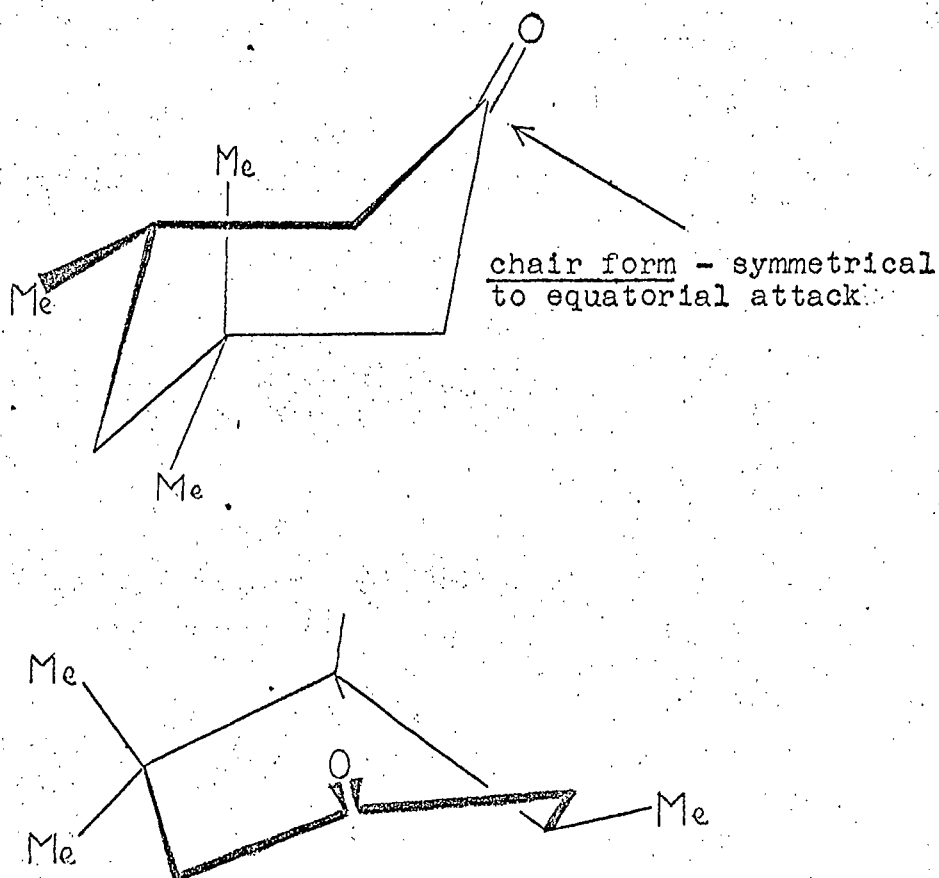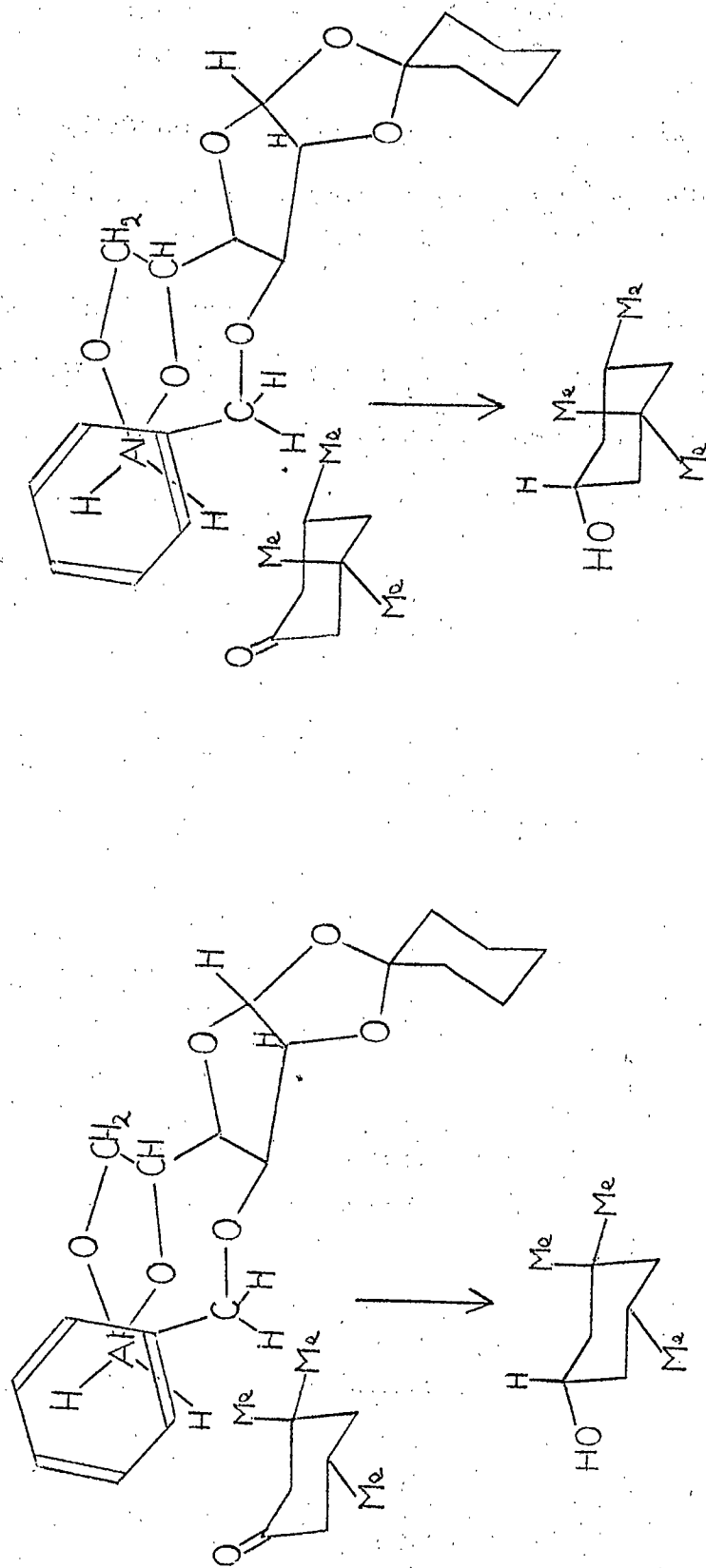methyl group.

Figure 21

Figure 22

If axial attack occurred as shown, the rate of reduction of the two ketone enantiomorphs would differ.

III
EXPERIMENTAL

5-Bromopent-2-en-4-yn-1-ol[19].-Sodium hydroxide (60 ml.

10 N. 0.6 mole) and ice (100 g.) were placed in a 250 ml.

two-necked flask cooled in an ice bath and bromine (40 g.,

0.24 mole) added dropwise with stirring over 0.5 hr. The

solution was stirred for 0.5 hr. at 0° after the addition

of bromine was complete. The sodium hypobromite so prod-

uced was then added dropwise with stirring over 1 hr. to

pent-2-en-4-yn-1-ol[19] (16.4 g., 0.2 mole) contained in a

second 250 ml. two-necked flask cooled in an ice bath.

Stirring was continued for 3 hr. at 0° after completion

of the sodium hypobromite addition. The cream-coloured

precipitate was filtered off using a cooled sintered glass

filter, and recrystallised from chloroform/40°-60° pet

ether (1/4) to yield whitish crystals (25 g., 78%) m.p.

38°-39°. The material was identified as 5-bromopent-2-en-

4-yn-1-ol by its infra-red spectrum,[2,19] ν_{max} 3,350 s (OH),

2,220 m (RC$\equiv$CR).

Buta-1,3-diyne(diacetylene)[127].-1,4-Dichlorobut-2-yne (46 g.,

0.38 mole) was placed in a 500 ml. flask with potassium

hydroxide (45 g., 0.80 mole,) dioxan (20 ml.) and water

(300 ml.). Nitrogen was bubbled through the reaction

mixture which was heated to reflux temperature with rapid

stirring. The diacetylene vapour evolved was passed through

two double surface condensers in series, dried by passing

over anhydrous calcium chloride and collected in a trap at

-60° (13.7 g., 73%), identified by its infra-red spectrum

in chloroform, I.R. No. 5. (One sample of this material

exploded violently and throughout this work was used

immediately after preparation, being diluted with dimethyl

formamide at -60°).

Non-2-ene-4,6,8-triyn-1-ol (Bohlmann Procedure)[5].-Hydroxylamine

hydrochloride (0.6 g.) and aqueous ethylamine solution

(12 ml., 50%) followed by cuprous chloride (0.1 g.) were

added to a solution of diacetylene (1.4 g., 0.03 mole) in

dimethyl formamide (50 ml.) and methanol (40 ml.) at 0°.

This was immediately followed by the addition of a solution

of 5-bromopent-2-en-4-yn-1-ol (1.6 g., 0.01 mole) in

dimethyl formamide (40 ml.). The reaction mixture was

stirred for 2 hr. at 0° and then the complex decomposed

by the addition of potassium cyanide (5 g.) in water (50 ml.),

followed by extraction with ether (3 x 200 ml.). The

combined ethereal extracts were washed with water (2 x 100 ml.),

2.5 N. HCl (2 x 100 ml.) and water (3 x 100 ml.) and dried

(MgSO$_4$). The ultra-violet spectrum of the crude solution

showed peaks clearly discernable at λ 231, 240, 271, 288,

306, 327 mμ(U.V. No. 1a). The ethereal solution was

evaporated down to 50 ml. in vacuo without heating, 100 ml.

n-pentane added and the solution again evaporated to 50 ml.

After three repetitions of this procedure the solution

(50 ml.) was chromatographed on Woelm acid alumina

(200 g.,), deactivated with water (6 ml., 3%), eluted with

n-pentane (5 x 400 ml.) and then ether/n-pentane 1/4

(20 x 400 ml.). Non-2-ene-4,6,8-triyn-1-ol was eluted

in fractions 14 to 16 (0.053 g., 4.7% on 5-bromopent-

2-en-4-yn-1-ol) λ_{max} 229 (Σ62,500), 240 (Σ86,600), 272

(Σ6,400), 288 (Σ12,400), 306.5 (Σ16,250) and 328 m/μ(Σ11,150)

(U.V. No. 1).

Nona-3,4-6-trien-8-yn-1-ol, Nona-3,4,8-trien-6-yn-1-ol

and Nona-3,4-dien-6,8-diyn-1-ol (Bohlmann Procedure[5]).-A

solution of non-2-ene-4,6,8-triyn-1-ol (1.070 g.) in

ether (50 ml.) was added at room temperature over 0.25 hr.

with stirring, to a standardised ethereal solution of

lithium aluminium hydride (75.5 ml. of 0.4 molar solution

0.03 mole). The reaction mixture was stirred for 2 hr.

at room temperature and then the complex decomposed by

pouring into 10% sulphuric acid (150 ml.) with rapid

stirring, and extracted into ether (3 x 200 ml.). The

combined extracts were washed with water (3 x 100 ml.)

and dried ($MgSO_4$). The ultra-violet spectrum of this

crude solution is shown (U.V. No. 2a). The ethereal

solution was evaporated to 50 ml. in vacuo without heating,

100 ml. n-pentane added and the solution again evaporated

to 50 ml. After three repetitions of this procedure the
solution (50 ml.) was chromatographed on Woelm acid alumina
(200 g.) deactivated with water (6 ml. 3%), eluted with
n-pentane (5 x 400 ml.) and then ether/n-pentane 1/4
(21 x 400 ml.). Fraction 14 contained a mixture of nona-3,4,8-
trien-6-yn-1-ol (IV) and nona-3,4,6-trien-8-yn-1-ol (V)
(0.36 g., 33.7%) λ_{max} 212 (Σ47,500), 265 mμ(Σ15,200),
λ_{sh} 253 (Σ12,400), 272 mμ(Σ12,600)(U.V. No. 2)ν_{max} 3,500,
3,300, 2,210, 1,950, 1,650, 965 and 935 cm.$^{-1}$ (I.R. No. 1).
The product 0.11 g. absorbed hydrogen (102.6 ml., 5 mole
(PtO$_2$)). Fraction 15 (0.19 g., 18%) also contained a
mixture of (IV) and (V), having the same ultra-violet and
infra-red spectra as before. Fractions 16 (0.17 g., 15%),
17 (0.12 g., 11%), and 18 (0.05 g., 4%) consisted of (IV)
and (V) with increasing proportions of nona-3,4-dien-6,8-
diyn-1-ol; (U.V. No. 3). Fraction 19 gave nona-3,4-dien-
6,8-diyn-1-ol (±marasin) (0.006 g., 0.6%) λ_{max} 208 (Σ51,000),
237 (Σ5,000), 239.5 (Σ8,900), 263 (Σ14,100) 278 mμ(Σ12,500)
(cf. U.V. No.15);ν_{max} 3,450, 3,320, 2,210, 1,950 cm.$^{-1}$
(I.R. No. 6).

Use of lithium diethoxyaluminium hydride.-Similarly, 0.4 M
lithium aluminium hydride solution (75.5 ml., 0.03 mole)
with added ethanol (2.76 g., 0.06 mole) and non-2-ene-4,6,8-
triyn-1-ol (0.26 g., 0.002 mole) at room temperature for
2 hr. gave a mixture of (IV) and (V) with (±)marasin, and

pure (±) marasin (0.016 g., 6%) with the same ultra-violet
and infra-red spectra as before.

2-(Penta-2,4-diyn-1-ylidene)-Tetrahydrofuran (isomarasin).[143]

Fraction 17 from the preceeding experiment (containing
0.08 g. marasin and 0.04 g. dihydromarasin) was repeatedly
evaporated to 50 ml. with addition of methanol. Sodium
hydroxide (50 ml. 4 N.) was then added and the solution
allowed to stand for 24 hr. in the dark. The solution
was then extracted with n-pentane (4 x 10 ml.), the combined
extracts washed with water (1 x 10 ml.) and dried ($MgSO_4$).
Chromatography on Woelm acid alumina (100 g.) deactivated
with water (3 ml., 3%) and eluted with n-pentane (6 x 100 ml.)
gave isomarasin in fraction 4 (0.054 g., 45% based on
total weight of fraction 17 - calculated from extinction
coefficients, cf. p. 46) identified by its ultra-violet
spectrum λ 224, 266, 279.5, 295[143] (U.V. No. 6).

Isomerisation of Nona-3,4,6-trien-8-yn-1-ol and Nona-3,4,8-trien-6-yn-1-ol.-(a) Sodium hydroxide (50 ml., 4 N.) was

added to a mixture of nona-3,4,6-trien-8-yn-1-ol and
nona-3,4,8-trien-6-yn-1-ol (total 0.36 g.) in methanol
(50 ml.) and the solution allowed to stand for 24 hr. in
the dark. The solution was then extracted with n-pentane
(4 x 10 ml.) the combined extracts washed with water

(1 x 10 ml.),dried (MgSO$_4$) and chromatographed on Woelm

acid alumina (100 g.) deactivated with water (3 ml., 3%)

and eluted with n-pentane (12 x 100 ml.) and then ether

(3 x 100 ml.). The product λ_{max} 220, 268 (U.V. No. 5)

was eluted in fraction 4.

(b) The experiment was repeated on a fresh solution of the

allenenes but the isolation procedure described by Bendz[143]

was used. The isomerisation product was subjected to a

counter-current distribution in eight 500 ml. funnels

between n-pentane as the stationary phase and ethanol

containing 30% water as the mobile phase (200 ml. of each

phase in each funnel). After fifteen transfers the product

λ_{max} 220,268 (as before) was found in the aqueous ethanolic

solutions in funnels 2, 3 and 4.

<u>2,2-Dichloro-3,3-dimethylbutane and 2-chloro-3,3-dimethylbut-</u>

<u>1-ene[21].-</u>Pinacolone (48 g., 0.48 mole) was added with stirring

over 1 hr. to phosphorous pentachloride (100 g., 0.48 mole)

with ice cooling. Stirring was continued for 6 hr., and

the reaction mixture allowed to stand overnight. It was

then poured onto crushed ice and the solid produced was

filtered off, washed with water and dried in a dessicator

giving 2,2-dichloro-3,3-dimethylbutane (40 g., 54%).

The filtrate consisted of two layers, a lower aqueous

layer which was separated and rejected, and an upper

organic layer, which was dried (Mg SO_4) to give crude

2-chloro-3,3-dimethylbut-1-ene (24 g., 41%). The combined

yield of products was 95% (lit. 91%).

3,3-Dimethylbut-1-yne[21].-Potassium hydroxide pellets

(102.8 g.) were crushed using a pestle and mortar in a

dry box and mixed thoroughly with 2,2-dichloro-3,3-dimethyl-

butane (30 g., 0.2 mole);the powder was transferred to a

1 litre two-necked flask fitted with two double surface

reflux condensers and a trap at -50° in series. Absolute

ethanol (10.2 ml.) was added, the flask heated in an oil

bath over 1 hr. to 165° and maintained at this temperature

for 5 hr. The reflux condensers were then replaced by a

still head and condenser fitted for distillation, and the

reaction flask heated in the oil bath to 200°. A colourless

distillate was collected which on refractionation gave

3,3-dimethylbut-1-yne (13 g., 82%) ν_{max} 3,330 s $(C\equiv C-H)$,

2,110 m $(C\equiv CH)$, 1,390 m and 1,360 s $(CMe_3$ doublet) (I.R.

No. 7).

The compound was obtained in a similar manner from

2-chloro-3,3-dimethylbut-1-ene.

trans-8,8-Dimethylnon-2-en-4,6-diyn-1-ol.-Cuprous chloride

(1.65 g., 0.016 mole), hydroxylamine hydrochloride (20 mg.),

dimethylformamide (20 ml.) and 70% aqueous ethylamine

(2.68 ml., 0.033 mole) were placed in a dropping funnel

under oxygen free nitrogen and shaken for 0.5 min. The

light green suspension was then immediately added in

one portion to a solution of 3,3-dimethylbut-1-yne

(8.2 g., 0.1 mole) in dimethylformamide (20 ml.) contained

under nitrogen and cooled in an ice bath. The reaction

mixture remained light green in colour. After 0.5 min.

a solution of trans-5-bromopent-2-en-4-yn-1-ol (2.68 g.,

0.017 mole) in dimethylformamide (15 ml.) was added in

one portion and the mixture stirred under nitrogen for

2 hr. The complex was then decomposed by addition of a

solution of potassium cyanide (20 g.) in water (50 ml.)

and extracted with ether (3 x 75 ml.). The combined extracts

were washed with water (2 x 50 ml.), 2.5 N. HCl (2 x 75 ml.),

water (3 x 200 ml.) and dried (MgSO$_4$). A band at

λ_{max} 230 m/μin the ultra-violet spectrum (U.V. No. 7)

showed that the product contained 5-bromopent-2-en-4-

yn-1-ol. The solution was therefore evaporated in vacuo

without heating, to 50 ml. and pet ether (100 ml., 40-60°)

added, resulting in precipitation of 5-bromopent-2-en-4-

yn-1-ol. This was removed by filtration and the filtrate

washed with water (6 x 100 ml.). Methanol (100 ml.)

was then added and the solution evaporated in vacuo to 100 ml.

Ammoniacle silver nitrate solution (75 ml., 10%*) was

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*Preparation of ammoniacle silver nitrate solution: 17 g. silver nitrate was dissolved in 100 ml. water and 0.880 ammonium hydroxide solution added until the initial dark brown precipitate had just redissolved. This solution was used immediately.

then added and the solution refrigerated for 1 hr. with

occasional shaking. Excess 3,3-dimethylbut-1-yne was

filtered off as the silver salt and rejected. The fil-

trate contained trans-8,8-dimethylnon-2-en-4,6-diyn-1-ol

(1.1 g., 41% on bromopentenynol) λ_{max} 207 (Σ33,000),

212 (Σ38,000), 229 (Σ3,000), 240 (Σ5,100), 252 (Σ12,100),

267 (Σ18,000) and 282 mμ (Σ14,000) (U.V. No. 11). (Found

C 81.5, H 8.9; $C_{11}H_{14}O$ requires C 81.6, H 8.7%).

In subsequent preparations purification was also

carried out by chromatography on Woelm acid alumina (100 g.)

deactivated with water (3 ml., 3%) eluted with n-pentane

(5 x 200 ml.) and then ether/n-pentane 1/4 (10 x 200 ml.).

trans-8,8-Dimethylnon-2-ene-4,6-diyn-1-ol was eluted in

fractions 9 and 10 and had the same ultra-violet spectrum

as before.

8,8-Dimethylnona-3,4-dien-6-yn-1-ol (Use of Lithium

Aluminium Hydride-Butane-2,3-diol Complex).-Butane-2,3-

diol (3.6 g., 0.04 mole) was added dropwise with stirring

to a standardised solution of lithium aluminium hydride

(0.04 mole) in ether (100 ml.) and the reaction mixture

heated under reflux for 2 hr. The reaction mixture was

then allowed to cool to room temperature, a solution of

8,8-dimethylnon-2-ene-4,6-diyn-1-ol (1.62 g., 0.01 mole)

in ether (40 ml.) was added and the mixture stirred at

room temperature for a further 2 hr. The complex was then

decomposed by pouring into 10% sulphuric acid extracted

into ether (3 x 150 ml.), washed with water (3 x 100 ml.)

and dried ($MgSO_4$). Ether was removed in vacuo and the

yellowish oil remaining distilled using a mercury vapour

pump to give 8,8-dimethylnona-3,4-dien-6-yn-1-ol

(0.7 g., 43%) b.p. 60°/ 5 x 10^{-3} mm. λ_{max} 219 mμ (Σ14,700)

(U.V. No. 8) ν_{max} 3,400 m (OH), 2,120 w (C≡C-R), 1,950 mμ

(C=C=CH) and 868 cm.$^{-1}$ m (allene CH deformation) (I.R. No. 8).

<u>Trans-hept-2-en-4,6-diyn-1-ol and 1-(2-Furyl)prop-1-yne</u>[10].-

1,4-Dichlorobut-2-yne (123.0 g., 1.00 mole) was added

dropwise to a suspension of sodamide prepared from sodium

(69.0 g., 3.00 g-atom) in liquid ammonia (3 litres) and

a crystal of ferric nitrate. This was immediately followed

by the dropwise addition of epichlorohydrin (46.3 g.,

0.50 mole). The mixture was stirred for 3 hr. and left

to stand overnight. The complex was then decomposed by

the addition of ammonium chloride (53.5 g., 1.00 mole)

with stirring and the ammonia allowed to evaporate off.

The residue was extracted with ether (4 x 150 ml.) and

the combined extracts dried ($MgSO_4$). The ethereal solution

was then evaporated to 60 ml. in vacuo without heating,

petroleum ether (100 ml., 40-60°) added and the solution

again evaporated to 60 ml. After repetition of this

procedure a further two times the material was chromato-
graphed on Spence type H alumina (750 g.,) deactivated with
acetic acid (37.5 ml., 10% aqueous solution) eluted with
40-60° petroleum ether (17 x 350 ml.) and then ether/40-60°
pet ether 1/3 (5 x 350 ml.). 1-(2-Furyl)prop-1-yne (13.4 g.,
25%) having infra-red spectrum identical to that of the
known compound was eluted in fractions 1 to 7. Trans-
hept-1-en-4,6-diyn-1-ol was eluted in fractions 10 to
18. Removal of solvent gave the crystalline material
(2.4 g., 5%) m.p. 48° (lit.[149] 48-49): λ_{max} 279 (ε14,300),
264 (ε18,600), 250 (ε12,800), 238 (ε6,500), 227 (ε3,300)
and 211 m/μ(ε39,800) and 205.5 $_{sh}$ (ε32,300) (U.V. No. 9)
and I.R. spectrum in chloroform: ν_{max} 3,400 m (OH), 3,300
m (C≡C-H), 2,050 w, 1,630 w (C=C), and 948 m (trans CH=CH)
(I.R. No. 9).

Hepta-3,4-dien-6-yn-1-ol (use of the Lithium Aluminium
Hydride-Butane-2,3-diol Complex).-Butane-2,3-diol (3.6 g.,
0.04 mole) was added dropwise with stirring to a standard-
ised solution of lithium aluminium hydride (0.04 mole)
in ether (100 ml.) and the reaction mixture heated under
reflux for 2 hr. The reaction mixture was then allowed to
cool to room temperature and a solution of trans-hept-2-en-
4,6-diyn-1-ol (1.06 g., 0.01 mole) in ether (40 ml.) added
dropwise with stirring and the reaction mixture stirred

at room temperature for 2 hr. The complex was then

decomposed by pouring into 10% sulphuric acid (150 ml.),

ether extracted (3 x 150 ml.) and washed with water (3 x 150 ml.)

and dried ($MgSO_4$). The ethereal solution was then evaporated

down in vacuo without heating to 50 ml., 40-60° pet ether

(100 ml.) added and the solution again evaporated to

50 ml. After repetition of this procedure three times the

material was chromatographed on Spence type H alumina

(200 g.) deactivated with acetic acid (10 g., of 10%

solution) eluted with 40-60° pet ether (7 x 200 ml.) and

then ether/pet ether 1/4 (7 x 200 ml.). Unchanged starting

material was eluted in fractions 6 to 8, identified by

its ultra-violet spectrum. Fraction 10 contained hepta-

3,4-dien-6-yn-1-ol (0.896 g., 9%) identified by its infra-

red spectrum (in $CHCl_3$): λ_{max} 3,450 s (OH), 3,300 v s

(C≡C-H), 2,100 m (C≡CH), 1,955 s (C=C=C) and 868 cm.$^{-1}$ m

(allene CH deformation (I.R. No. 10 cf. ref. 10) and

λ_{max} 211 m (11,00) (U.V. No. 10).

1-Tetrahydropyranyloxypent-2-en-4-yne (Action of Lithium

Aluminium Hydride (a).-Concentrated hydrochloric acid (1 ml.)

was added to a mixture of pent-2-en-4-yn-1-ol (8.2 g.,

0.1 mole) and 2,3-dihydropyran (10.9 g., 1.3 mole) with

ice cooling, the mixture allowed to warm to room temperature

over 1 hr. and then heated to 70° in a water bath for 3 hr.

Ether (100 ml.) was added and the solution washed with

water (50 ml.), saturated sodium bicarbonate solution

(50 ml.) and dried (MgSO$_4$). Solvent was removed and the

material distilled to give 1-tetrahydropyranyloxypent-

2-en-4-yne (13.6 g., 82%) b.p. 66°/3 mm., identified

by its infra-red spectrum ν_{max} 3,250 m (-C≡C-H),

2,110 w (RC≡CH). The compound gave one peak on g.l.c.

(silicone oil 120°) t = 9.5 min.

Action of Lithium Aluminium Hydride (b). -1-Tetrahydrop-

yranyloxypent-2-en-4-yne (1.7 g., 0.01 mole) was added

dropwise over 0.25 hr. to a standardised solution of

lithium aluminium hydride (0.02 mole) in ether (104 ml.)

and the reaction mixture stirred at room temperature for

2 hr. The complex was then decomposed by addition of water,

the precipitated solids removed by filtration, the filtrate

extracted with ether (3 x 25 ml.) and the combined extracts

dried (MgSO$_4$). Removal of solvent gave 1-tetrahydrop-

yranyloxypent-2-en-4-yne (1.7 g., 100% recovery) identified

by its infra-red spectrum as before (I.R. No. 11). G.l.c.

(silicone oil 120°) gave one peak t = 9.5 min.

Hex-2-en-4-yn-1-ol. -1-Tetrahydropyranyloxypent-2-en-4-yne

(16.6 g., 0.1 mole) was added dropwise to sodamide prepared

from sodium (4.6 g., 0.2 g. atom) liquid ammonia (700 ml.)

and ferric nitrate (0.1 g.) and stirred for 1 hr.

Dimethyl sulphate(25.3 g., 0.2 mole) was then added dropwise
over 0.5 hr. and the mixture stirred for a further 3 hr.
and left overnight. Ammonium chloride (11 g., 0.2 mole)
was then added and the ammonia allowed to evaporate. The
solid was extracted with ether (4 x 100 ml.) and the
combined extracts heated under reflux for 0.5 hr. with
added methanol (50 ml.) and concentrated hydrochloric
acid (2 ml.). The solution was then washed with water
(2 x 50 ml.), saturated sodium hydrogen carbonate sol-
ution (1 x 50 ml.), and dried. Solvent was removed and
the residue distilled to give hex-2-en-4-yn-1-ol (5.5 g.,
58%) b.p. 90°/20 mm. identified by its infra-red spectrum.
ν_{max} 3,500 s (OH), 2,200 m (RC≡CR).

(±)-Hexa-3,4-dien-1-ol (Menthol added at end of Reaction).-
A solution of hex-2-en-4-yn-1-ol (1.0 g., 0.01 mole) in
ether (50 ml.) was added dropwise over 0.5 hr. at room
temperature, with stirring, to a standardised solution
of lithium aluminium hydride (0.015 mole) in ether (67.2 ml.)
and the reaction mixture then heated under reflux for
2 hr. A solution of menthol (5.1 g., 0.03 mole) in ether
(50 ml.) was then added dropwise over 0.5 hr. and the
refluxing continued for a further 2 hr. The complex was
then decomposed by pouring into 10% sulphuric acid (150 ml.),
ether extracted (3 x 100 ml.), washed with water (2 x 50 ml.)

and dried ($MgSO_4$). Solvent was removed and the material distilled to give hexa-3,4-dien-1-ol (0.7 g., 70%).. G.l.c.. on silicone oil at 120° showed two peaks at t = 4.5 min. (menthol) and t = 7 min. The material was refractionated using a 12" column packed with Fenske rings, giving hexa-3,4-dien-1-ol $[\alpha]_D^{20}$ + 9.3° (0.3 g., 30%) having infra-red spectrum identical with an authentic sample. ν_{max} 3,340 s (OH), 1,960 w (C=C=C) and 1,040 cm.$^{-1}$ (cf. I.R.. No.17).. The material gave one peak on g.l.c. t = 7 min.

Non-2-ene-4,6,8-triyn-1-ol[5](a).-Cuprous chloride (1.2 g., 0.012 mole) was placed in a 250 ml. three-necked flask under oxygen free nitrogen. Hydroxylamine hydrochloride (0.02 g.) was added followed by dimethylformamide (4 ml.), 70% aqueous ethylamine solution (2.0 ml., 0.024 mole) and a solution of diacetylene (4.4 g., 0.88 mole) in dimethylformamide (40 ml.). A solution of 5-bromopent-2-en-4-yn-1-ol (2.0 g., 0.012 mole) in dimethylformamide (4 ml.) was then added and the mixture stirred for 0.5 hr. The complex was decomposed by addition of a solution of potassium cyanide (10 g.) in water (100 ml.) and the solution was extracted with ether (3 x 100 ml.), washed with 2.5 N. HCl (3 x 100 ml.) water (3 x 100 ml.), and dried ($MgSO_4$). The crude product (0.16 g., 10%) showed

λ_{max} 229 (Σ26,900), 240 (Σ31,500), 257 (Σ4,100), 272 (Σ4,100),

288 (Σ5,000), 306 (Σ5,800) and 327 mμ(Σ4,500) (U.V. No. 12).

(b)   Attempt to Increase Yield of Non-2-en-4,6,8-triyn-

1-ol.-Cuprous chloride (1.2 g., 0.012 mole) was placed

in a 250 ml. three-necked flask under oxygen free nitrogen.

Hydroxylamine hydrochloride (0.02 g.) was added followed

by dimethylformamide (4 ml.), 70% aqueous ethylamine solu-

tion (2.0 ml., 0.024 mole), and a solution of diacetylene

(4.4 g., 0.88 mole) in dimethylformamide (40 ml.). A

solution of 5-bromopent-2-en-4-yn-1-ol (2.0 g., 0.012 mole)

in dimethylformamide (4 ml.) was then added and the mixture

stirred for 0.5 hr.

A second flask was prepared containing cuprous chloride

(1.2 g., 0.012 mole), hydroxylamine hydrochloride (0.02 g.)

dimethylformamide (4 ml.), 70% aqueous ethylamine solution

(2.0 ml., 0.024 mole), and a solution of diacetylene (4.4

g., 0.88 mole) in dimethylformamide (40 ml.) under oxygen

free nitrogen. The contents of the first reaction flask

were then added to the second (keeping the reaction mixture

under oxygen free nitrogen during the transfer) and the

reaction mixture stirred for a further 0.5 hr. The complex

was decomposed by addition of a solution of potassium

cyanide (10 g.) in water (100 ml.). The solution was

extracted with ether (3 x 100 ml.), washed with 2,5 N. HCl

(3 x 100 ml.), water(3 x 100 ml.) and dried ($MgSO_4$).

The ultra-violet spectrum of the crude product (0.15 g.,

10%) was the same as before (a). No improvement in yield

was obtained.

(c) Cuprous chloride (4.95 g., 0.05 mole), hydroxylamine

hydrochloride (0.02 g.), dimethylformamide (40 ml.) and

70% aqueous ethylamine solution (8.05 ml., 0.1 mole)

were placed in a dropping funnel under oxygen free nitrogen

and shaken for 0.5 min. The light green suspension was

then immediately added in one portion to a solution of

diacetylene (13.7 g., 0.27 mole) in dimethylformamide

(80 ml.) contained under nitrogen in a 500 ml. three necked

flask fitted with stirrer and nitrogen inlet and cooled

in an ice bath. A deep red precipitate formed which

started to darken in colour almost immediately. After

0.5 min. a solution of 5-bromopent-2-en-4-yn-1-ol (8.05 g.,

0.05 mole) in dimethylformamide (30 ml.) was added in

one portion and the mixture stirred under nitrogen at

0° for 2 hr. The complex was decomposed by addition of

a solution of potassium cyanide (30 g.) in water (150 ml.),

extracted with ether (3 x 200 ml.) and the combined extracts

washed with water (2 x 100 ml.), 2.5 N. HCl (2 x 100 ml.),

water (3 x 200 ml.) and dried ($MgSO_4$). The ultra-violet

spectrum of the crude material (2.01 g., 31%) showed

peaks clearly defined at λ230, 240, 272, 288, 306 and

328 mμ.

<u>Silver Salt Separation.</u>-The solution was evaporated to
200 ml. (without heating) methanol (100 ml.) added followed
by ammoniacle silver nitrate solution[*] (100 ml.) and the
mixture refrigerated for 1 hr. with occasional shaking.
The silver salt formed was separated by refrigerated
centrifuge at -20° and washed with ether (3 x 100 ml.).
It was shock-sensitive and detonated violently if allowed
to dry. The solid salt was decomposed by shaking with
potassium cyanide (30 g.) in water (200 ml.) and ether
(200 ml.). The ether layer was separated and the aqueous
layer extracted with ether (2 x 75 ml.). The combined
ethereal extracts were washed with water (2 x 50 ml.),
dilute HCl (2 x 50 ml.), water (3 x 100 ml.) and dried
($MgSO_4$). The solution contained non-2-ene-4,6,8-triyn-
1-ol (1.52 g., 23.5% based on bromopentenynol).

λ_{max} 229 (Σ61,000), 240 (Σ86,500), 271.5 (Σ7,100),
288 (Σ13,200), 306.5 (Σ17,000) and 327.5 mμ(Σ12,600)
U.V. No. 13) (cf. Jones and Stephenson's values for
the naturally occurring product: λ_{max} 229 (Σ60,500),
239.5 (Σ86,500), 271.5 (Σ6,500), 288 (Σ13,000), 306
(Σ17,000) and 327.5 mμ(Σ12,500).

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[*]See footnote on p. 140;

(+)-Nona-3,4-dien-6,8-diyn-1-ol ((+)-Marasin) with the
Dimenthoxyaluminium Hydride Complex.-Lithium aluminium
hydride (0.4 g., 0.01 mole) was suspended in ether (100 ml.)
and a solution of menthol (3.3 g., 0.02 mole) in ether
(10 ml.) added dropwise with stirring at room temperature
over 0.5 hr. The reaction mixture was heated under reflux
with stirring for 1 hr. and then allowed to cool to
room temperature. A solution of non-2-ene-4,6,8-triyn-1-ol
(0.3 g., 0.002 mole) in ether (60 ml.) was added and the
reaction mixture stirred for 2 hr. at room temperature.
The complex was decomposed by adding water dropwise from
a burette, followed by dilute sulphuric acid until all the
precipitated solid had dissolved. The ether layer was
separated and the aqueous layer extracted with ether
(2 x 75 ml.), the combined extracts were washed with water
(4 x 100 ml.). The solution of the crude product gave
λ_{max} 238 (ϵ2,000), 250.5 (ϵ4,400), 264 (ϵ10,100), and
279 mμ (ϵ6,100).

Attempts to remove menthol from the marasin by chroma-
tography on Woelm acid alumina (200 g.) deactivated with
water (3; 4; 5; and 6 ml.) or on Spence type H alumina
(200 g.) deactivated with 10% aqueous acetic acid (2; 4;
6; 8; 10; 15; 20; and 30 ml.) eluting with n-pentane or
ether/n-pentane (1/10; 1/8; 1/6; 1/4) were unsuccessful;
mixtures were invariably obtained. The following experiment

is typical: the solution of marasin and menthol was rep-
eatedly evaporated to 50 ml. with addition of n-pentane
and then chromatographed on Woelm acid alumina (200 g.)
deactivated with water (6 ml., 3%) (column wrapped in
brown paper). The polarity of the eluting solvent was
increased very slowly, the total continuous chromatography
taking 54 hr., however, the marasin eluted in fractions
60-69 still contained menthol as shown by g.l.c. (silicone
oil 110° menthol t = 9.5 min.).

Counter-Current Distribution.-Attempts were also made to
remove the menthol by counter-current distribution using
a hand-operated 50 tube (each tube 50 ml.) apparatus. In
a typical experiment a small sample (25 ml.) of the solution
of marasin and menthol was placed in tube 19 and using
water/carbon tetrachloride as the two phases the apparatus
was worked by the "steady state method" (upper and lower
phases transferred in opposite directions). After forty
transfers the marasin (0.005 g.) was found in tubes 16-32
and was shown to be free of menthol by g.l.c. on silicone
oil at 110° (menthol t = 9.5 min.).

Attempts to separate the bulk of the marasin solution
using carbon tetrachloride/water and ether/butanol/water
systems were unsuccessful as marasin was washed from the
apparatus before removal of menthol was complete.

(-)-Nona-3,4-dien-6,8-diyn-1-ol ((-)-Marasin) with the

Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-

α-D-Glucofuranose Complex (a).-A solution of the slightly

impure 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose

(11.2 g., 0.032 mole) in ether (50 ml.) was added drop-

wise with stirring to lithium aluminium hydride (1.67 g.,

0.044 mole) in ether (50 ml.) and the reaction mixture

heated under reflux for 2 hr. The solution was then

allowed to cool to room temperature and a solution of

non-2-ene-4,6,8-triyn-1-ol (1 g.) in ether (60 ml.) added

dropwise and stirring continued for 2 hr. at room temperature.

The complex was decomposed by pouring into 10% sulphuric

acid (140 ml.) with rapid stirring, ether extracted (3 x 200 ml.),

washed with water (3 x 100 ml.) and dried ($MgSO_4$). The

ethereal solution was repeatedly evaporated down to 50 ml.,

n-pentane (100 ml.) added, and again evaporated to 50 ml.

The solution was then chromatographed on Woelm acid alumina

(200 g.) deactivated with water (6 ml., 3%) and eluted

with n-pentane (5 x 400 ml.) and then ether/n-pentane

1/4 (20 x 400 ml.). Marasin (0.098g., 10%) was eluted

in fractions 12 to 16 and was detected by ultra-violet

scanning of each fraction. Fractions 12 to 16 were com-

bined and evaporated down to 20 ml. and the rotation of

the solution found to be $[\alpha]_D^{25}$-31°(c 0.49 in n-pentane).

Examination of the solution by thin layer chromatography,[*]

showed two spots, R_F 0.25 (blue - monosaccharide derivative)

and R_F 0.6 (brown - marasin). The solution was diluted to

50 ml. with n-pentane and rechromatographed on alumina

as before. The marasin (0.030 g., 3.2%) solution obtained

was examined by t.l.c. and showed two spots, R_F 0.25 (blue)

and R_F 0.6 (brown) as before.

(b) <u>Chromatography on Boric Acid-Silica</u>.-Marasin was prepared

by the method described in (a). After the chromatography

on acid alumina the fractions containing marasin (12-16)

were evaporated to 50 ml. and chromatographed on silica

(400 g.) impregnated with boric acid (120 ml. of 0.1 M

solution) eluted with n-pentane (10 x 100 ml.) Marasin

(0.1 g., 10%) was eluted in fractions 4-8. Examination

by t.l.c. as before showed two spots R_F 0.25 (blue) and

R_F 0.6 (brown).

(c) <u>Attempt to Remove Traces of Monosaccharide by Hydrolysis</u>

<u>and Chromatography</u>.-The preparation of marasin was repeated

by the method described in (a). Before the chromatography

on alumina, however, an attempt was made to hydrolyse the

monosaccharide by the following procedure: to the ethereal

solution of marasin was added methyl alcohol (100 ml.) and

the solution evaporated to 100 ml. without heating.

Concentrated hydrochloric acid (60 ml.) was then added

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[*]Details of thin layer chromatography p.178 .

and the solution stirred for 2 hr. at room temperature. Water
(400 ml.) was added, the mixture extracted with ether
(5 x 100 ml.), and the combined extracts dried $(MgSO_4)$.
The solution was then repeatedly evaporated down with
n-pentane to 50 ml. and chromatographed on alumina as in
(a) to yield pure marasin (0.1 g., 10%) identified by its
ultra-violet spectrum: λ_{max} 208 (Σ51,000), 224 (Σ3,200),
327 (Σ5,000), 249.5 (Σ8,900), 263 (Σ14,100) and 278 mμ
(Σ12,500), (U.V. No. 15) (cf. ref. 97). On evaporation
to 20 ml. t.l.c. as before gave one spot R_F 0.6 (brown).
The solution was optically inactive however ($\pm$0.001°).

The above experiment was repeated four times in an
attempt to increase the rotation without success. It
was concluded that the acid hydrolysis of the monosaccharide
was also causing racemisation of the marasin.

(d) <u>Attempt to Purify Marasin by Precipitation as the
Silver Salt.</u>-Marasin was prepared by the procedure described
in (a) and repeatedly evaporated down to 50 ml. with added
methanol. Ammoniacle silver nitrate solution[*] (75 ml.)
was added and the solution refrigerated for 1 hr. with
occasional shaking. The precipitated silver salt was
separated and washed with ether using a refrigerated
centrifuge at -20°. A solution of potassium cyanide (10 g.)

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in water (100 ml.) and ether (100 ml.) was added, the
ether layer separated and the aqueous layer extracted with
ether (3 x 75 ml.). The combined ethereal extracts were
washed with water (2 x 50 ml.), dilute HCl (2 x 50 ml.)
and water (3 x 100 ml.) and dried ($MgSO_4$). The ultra-
violet spectrum of this solution showed end absorption and
a broad band centred on 280 mμ .

(e) A solution of the complex of lithium aluminium hydride
with analytically pure 3-O-benzyl-1,2-cyclohexylidene-α-D-
glucofuranose was prepared and used to reduce non-2-ene-
4,6,8-triyn-1-ol (1 g.) in ether (60 ml.) as described in
(a). Chromatography on Woelm acid alumina as previously
described in (a) was followed by chromatography on Boric
acid-silica as described in (b) to yield a solution of
marasin (0.12 g., 12%), λ_{max} 208 ($\gtrsim$51,000), 224 ($\gtrsim$3,200)
237 ($\gtrsim$5,000), 249.5 ($\gtrsim$8,900), 263 ($\gtrsim$14,100) and 278 mμ
($\gtrsim$12,500) (U.V. No. 16); ν_{max} 3,330, 2,220, and 1,960 cm.$^{-1}$;
(I.R. No. 12). The solution was evaporated to 20 ml.,
without heating, and the rotation found to be $[\alpha]_D^{20}$-26.6°
(c, 0.6 in n-pentane) (Stanley visual polarimeter). After
further evaporation to 2 ml. the rotation was found to be
$[\alpha]_D^{20}$-20.301° (c, 0.6 in n-pentane) (Bendix photoelectric
polarimeter ±0.001°). This concentrated solution was
examined by t.l.c. and gave one spot R_F 0.6 (brown).

Penta-1,3-diyne[17].-1,4-Dichlorobut-2-yne (29.6 g., 0.24 mole)
was added dropwise with stirring to a suspension of sodamide
in liquid ammonia prepared from sodium (16.56 g., 0.72 g.atom),
liquid ammonia (600 ml.) and a crystal of ferric nitrate.
After stirring for 0.25 hr., methyl iodide (34.08 g.,
0.24 mole) was added dropwise, and the reaction mixture
stirred for 3 hr. The solution was then allowed to evaporate
to 200 ml. and n-pentane (300 ml.) was cautiously added.
The remaining ammonia was then allowed to evaporate from
the solution overnight, and this solution then used without
further purification for the preparation of dec-2-ene-
4,6,8-triyn-1-ol.

Dec-2-ene-4,6,8-triyn-1-ol[20].-Cuprous chloride (1.66 g.,
0.016 mole) hydroxylamine hydrochloride (0.02 g.), dimethyl-
formamide (40 ml.) and 70% aqueous ethylamine solution
(2.8 ml., 0.032 mole) were placed in a dropping funnel
under oxygen free nitrogen and shaken for 0.5 min. The
light green suspension was then added in one portion to
the solution of penta-1,3-diyne prepared in the preceding
experiment and contained in a 500 ml. three necked flask
fitted with stirrer and nitrogen inlet and cooled in
an ice bath. A bright yellow precipitate formed. After
0.5 min. a solution of 5-bromopent-2-en-4-yn-1-ol (8.05 g.,
0.05 mole) in dimethyl formamide (30 ml.) was added in

one portion. The mixture was stirred under nitrogen at
0° for 2 hr. The complex was then decomposed by addition
of a solution of potassium cyanide (30 g.) in water (150 ml.),
extracted with ether (3 x 200 ml.) washed with water
(2 x 100 ml.), 2.5 N. HCl (2 x 100 ml.) and water (3 x 200 ml.)
and dried ($MgSO_4$). The solution was repeatedly evaporated
down to 60 ml. without heating with added n-pentane and
chromatographed on Woelm acid alumina (200 g.) deactivated
with water (6 ml., 3%) eluted with n-pentane (6 x 400 ml.)
and then ether/n-pentane 1/4 (20 x 400 ml.). Fractions
13 to 16 contained dec-2-ene-4,6,8-triyn-1-ol (2.05 g.,
28.6% on bromopentenynol) λ_{max} 205 (ε99,500), 230
(ε67,000), 241.5 (ε87,000), 272 (ε6,800), 288.5 (ε12,500),
307.5 (ε17,000), 329 mμ (ε12,000).

<u>(-)-Dec-3,4-diene-6,8-diyn-1-ol ((-)-9-Methylmarasin)</u> [91]
<u>with the Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-</u>
<u>Cyclohexylidene-α-D-Glucofuranose Complex.</u>-A solution of
analytically pure 3-O-benzyl-1,2-O-cyclohexylidene-α-D-
glucofuranose (12.36 g., 0.035 mole) in ether (50 ml.)
was added dropwise with stirring to a standardised solution
of lithium aluminium hydride (0.035 mole) in ether (57.6 ml.)
over 0.5 hr. and the reaction mixture heated under reflux
for 2 hr. The solution was then allowed to cool to room
temperature and dec-2-ene-4,6,8-triyn-1-ol (1.05g., 0.007 mole)

in ether (60 ml.) added over 0.5 hr. and stirring continued

at room temperature for a further 2 hr. The complex was

decomposed by pouring into 10% sulphuric acid (200 ml.)

with rapid stirring, ether extracted (3 x 200 ml.) and the

combined extracts washed with water (2 x 50 ml.) and dried

($MgSO_4$). The ethereal solution was repeatedly evaporated

down to 60 ml. in vacuo with added n-pentane and chromato-

graphed on Woelm acid alumina (200 g.) deactivated with

water (6 ml., 3%) eluted with n-pentane (4 x 400 ml.)

and then ether/n-pentane 1/4 (25 x 400 ml.). 9-Methyl-

marasin was eluted in fractions 19 to 21. These fractions

were combined, evaporated to 60 ml. and the solution

chromatographed on silica gel (200 g.) impregnated with

boric acid (120 ml. of 0.1 M solution) eluted with n-pentane

(10 x 100 ml.). Fractions 2 and 3 contained 9-methylmarasin

(0.15 g., 10%) λ_{max} 208 ($\mathcal{E}$56,000), 224.5 ($\mathcal{E}$3,900), 237

($\mathcal{E}$6,500), 250.5 ($\mathcal{E}$12,100), 264 ($\mathcal{E}$16,000) and 280 mμ ($\mathcal{E}$12,900)

(U.V. No. 16). The solution was evaporated to 20 ml.

and the rotation found to be $\left[\alpha\right]_D^{25}$-11.3° (c 0.75, n-pentane).

(Stanley visual polarimeter). After further evaporation to

2 ml. the rotation was $\left[\alpha\right]_D^{25}$-11.012° Bendix photoelectric

polarimeter ±0.001°). Examination of this concentrated

solution by t.l.c.* showed one spot R_F 0.6 (brown).

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*Details of thin layer chromatography p. 178.

<u>7-Phenylhept-2-en-4,6-diyn-1-ol</u>.-Cuprous chloride (1.65 g.,
0.016 mole), hydroxylamine hydrochloride (0.02 g.),
dimethylformamide (20 ml.) and 70% aqueous ethylamine
solution (2.68 ml., 0.033 mole) were placed in a dropping
funnel under oxygen free nitrogen and shaken for 0.5 min.
The light green suspension was then added in one portion
to a solution of phenylacetylene (10.2 g., 0.1 mole) in
dimethylformamide (40 ml.) under nitrogen at 0°. A bright
yellow precipitate formed. After 0.5 min. a solution of
5-bromopent-2-en-4-yn-1-ol (8.05 g., 0.05 mole) in dimethyl-
formamide (30 ml.) was added in one portion. The solution
turned a light green colour. The mixture was stirred
under nitrogen at 0° for 2.5 hr. and the complex then
decomposed by addition of a solution of potassium cyanide
(30 g.) in water (150 ml.), extracted with ether (3 x 200 ml.),
washed with water (2 x 200 ml.) and dried ($MgSO_4$). The
solution was repeatedly evaporated to 50 ml. with added
n-pentane and chromatographed on Spence type H alumina
(100 g.) deactivated with 10% aqueous acetic acid (5 ml.),
eluted with n-pentane (4 x 400 ml.) and then ether/n-pentane
1/4 (6 x 400 ml.). 1,4-Diphenyldiacetylene, having infra-red
spectrum identical to an authentic sample was eluted in
fraction 1. Fraction 5 gave 7-phenylhept-2-en-4,6-diyn-1-ol
(5.8 g., 70%) λ_{max} 210 ($\mathcal{E}$55,000), 230 ($\mathcal{E}$37,800),

240 (Σ36,000), 252 (Σ27,000), 265 (Σ15,000), 299 (Σ31,800) and 319 m/μ (Σ25,600) (U.V. No. 17).

(-)-7-Phenylhepta-3,4-dien-6-yn-1-ol with the Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose Complex.-A solution of analytically pure 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose (8.5 g., 0.024 mole) in ether (25 ml.) was added dropwise with stirring over 0.5 hr. to a standardised solution of lithium aluminium hydride (0.024 mole) in ether (41 ml.) and the reaction mixture heated under reflux with stirring for 2 hr. The solution was then allowed to cool to room temperature and a solution of 7-phenylhept-2-en-4,6-diyn-1-ol (0.9 g., 0.005 mole) in ether (50 ml.) added over 0.5 hr. and stirring continued for 2 hr. at room temperature. The complex was then decomposed by pouring into 10% sulphuric acid (200 ml.) with rapid stirring, and ether extracted (3 x 100 ml.). The combined extracts were washed with water (3 x 50 ml.) and dried (MgSO$_4$). The ethereal solution was repeatedly evaporated to 50 ml. with added n-pentane and chromatographed on Spence type H alumina (100 g.) deactivated with 10% aqueous acetic acid solution (5 ml.) eluted with n-pentane (4 x 200 ml.) and then ether/n-pentane 1/4 (6 x 200 ml.). Ultra-violet scanning of each fraction

showed that 7-phenylhepta-3,4-dien-6-yn-1-ol was eluted

in fractions 8 to 10. These were combined and evaporated

without heating to 60 ml. and chromatographed on silica gel

(200 g.) impregnated with boric acid (60 ml. of 0.1 M

solution). 7-Phenylhepta-3,4-dien-6-yn-1-ol (0.13 g.,

14.4% on 7-phenylhept-2-ene-4,6-diyne-1-ol) having

λ_{max} 205 ($\mathcal{E}$41,500), 257 ($\mathcal{E}$13,600), 273.5 ($\mathcal{E}$19,300),

288 m/μ ($\mathcal{E}$14,800) λ_{sh} 218 m/μ ($\mathcal{E}$29,000) (U.V. No. 18) and

ν_{max} 3,300 m (OH) and 1,950 m (C=C=C) (I.R. No. 13).

The solution was evaporated to 20 ml. and the rotation

found to be $[\alpha]_D^{25}$-3.1° (c 0.65, n-pentane) (Stanley

visual polarimeter). After further evaporation to 2 ml.

the rotation was found to be $[\alpha]_D^{20}$-2.805° (Bendix photo-

electric polarimeter $\pm$0.001°). This concentrated solution

gave one spot on t.l.c. R_F 0.75 (yellow).

(-)-8,8-Dimethylnona-3,4-dien-6-yn-1-ol with the Lithium

Aluminium Hydride-3-0-Benzyl-1,2-0-Cyclohexylidene-α-D-

Glucofuranose Complex.-A solution of analytically pure

3-0-benzyl-1,2-0-cyclohexylidene-α-D-glucofuranose (9 g.,

0.026 mole) in ether (50 ml.) was added dropwise with

stirring over 0.5 hr. to a standardised solution of lithium

aluminium hydride (0.026 mole) in ether (62.5 ml.) and the

reaction mixture heated under reflux with stirring for 2 hr.

The solution was allowed to cool to room temperature, a

solution of 8,8-dimethylnon-2-ene-4,6-diyn-1-ol (1.67 g.,
0.01 mole) (preparation, p. 139) in ether (50 ml.) added
over 0.5 hr. and stirring continued at room temperature
for 2 hr. The complex was then decomposed by pouring into
10% sulphuric acid (200 ml.) with rapid stirring, and
ether extracted (3 x 150 ml.). The combined extracts
were washed with water (2 x 50 ml.) and dried (MgSO$_4$).
Ether was removed and the residual yellowish oil distilled
to give 8,8-dimethylnona-3,4-dien-6-yn-1-ol (0.55 g., 32%)
b.p. 79°/2 x 10^{-3} mm. λ $_{max}$ 219 (Σ14,690), (U.V. No. 19);
$\mathcal{V}$ $_{max}$ 3,300 m (OH) 2,200 w (C≡C) and 1,600 w (C=C=C)
(I.R. No. 14). (Found C, 80.51; H, 9.80 C$_{11}$H$_{16}$O requires
C, 80.60; H, 9.82%); $[\alpha]_D^{25}$-12.5° (neat) (Stanley visual
polarimeter).

(-)-Hexa-3,4-dien-1-ol (Monosaccharide added at end of

Reaction).-A solution of hex-2-en-4-yn-1-ol (1.0 g., 0.01 mole)
in ether (50 ml.) was added dropwise over 0.5 hr. at room
temperature, with stirring to a standardised solution of
lithium aluminium hydride (0.015 mole) in ether (59.0 ml.)
and the reaction mixture heated under reflux for 2 hr.
A solution of analytically pure 3-O-benzyl-1,2-O-cyclo-
hexylidene-α-D-glucofuranose (5.3 g., 0.015 mole) in
ether (50 ml.) was then added dropwise over 0.5 hr. and
the refluxing continued for a further 2 hr. The complex

was then decomposed by pouring into 10% sulphuric acid

(150 ml.),ether extracted (3 x 100 ml.) washed with water

(2 x 50 ml.) and dried (MgSO$_4$). Solvent was removed and

the material distilled to give hexa-3,4-dien-1-ol (0.4 g.,

40%) $[\alpha]_D^{25}$-8.2^0 (neat) b.p. 60^0/4 mm. having infra-red

spectrum identical with an authentic sample ν_{max} 3,340 s (OH),

1,960 w (C=C=C) and 1,040 cm.$^{-1}$ (cf. I.R. No. 17). The

compound was shown to be free of monosaccharide derivatives

by examination on t.l.c.

Claisen Rearrangement

1-Chloroethyl but-1-yn-3-yl ether.-[56]A mixture of but-1-
yn-3-ol (28.0 g., 0.40 mole) and freshly distilled
acetaldehyde (8.8 g., 0.20 mole) was added dropwise with
stirring to boron trichloride (31.2 g., 0.27 mole) cooled
to -15° in an ice salt bath. After stirring for 3 hr. at
-15° the reaction mixture was allowed to warm to room
temperature and left to stand for 2 days. The product was
distilled in vacuo (1 mm.), using a 12 cm. column packed
with Fenske rings to give 1-chloroethyl but-1-yn-3-yl
ether (9.5 g., 36%) b.p. 64-68°/120 mm. ν_{max} 3,320 (C≡C)
2,130 (C≡C), 1,135 (C-O-C)(I.R. No. 15.)

Hexa-3,4-dienal and Hexa-2,4-dienal.- 1-Chloroethyl but-
1-yn-3-yl ether (0.3 ml.) was injected into a stream of
nitrogen passing through an electrically heated glass tube
clamped vertically and packed with glass wool at 200°.
The pyrolysis products having ν_{max} 3,300 (C≡C-H), 2,112 (C≡CH),
1,960 (C=C=C) (I.R. No. 16) and λ_{max} 228 (Σ23,000) and
271 mμ(Σ12,000) (U.V. No. 20) were collected in a trap
at -60° and contained approximately 50% of hexa-3,4-dienal
and 50% of hexa-2,4-dienal.[*]

[*]From absorption coefficient; pure hexa-2,4-dienal has
λ_{max} 271 mμ(Σ25,000).[80]

Hexa-3,4-dien-1-ol.-The mixture of aldehydes resulting from

the pyrolysis of 1-chloroethyl but-1-yn-3-yl ether (1.5 g.)

was rapidly transferred to a solution of lithium aluminium

hydride (2 g.) in ether (30 ml.) and stirred at room

temperature overnight. Excess lithium aluminium hydride

was decomposed by the dropwise addition of water, the

ether layer separated and the aqueous layer extracted

with ether (2 x 50 ml.). The combined ether extracts

were evaporated to 5 ml., 40-60° petroleum ether (10 ml.)

added and the solution chromatographed on Spence type H

alumina (100 g.), deactivated with acetic acid (10 ml.

of 10% aqueous solution). Elution with ether/40-60°

petroleum ether (1/4) (12 x 100 ml.) gave hexa-3,4-dien-

1-ol (0.4 g., 26%) in fraction 9. ν_{max} 3,350 (OH)

1,960 (C=C=C) (I.R. No. 17) identical with the infra-red

spectrum of an authentic sample.

(+)-Hexa-3,4-dien-1-ol.-The procedure given in the pre-

ceeding three experiments was repeated starting with

(-)-but-1-yn-3-ol $[\alpha]_D^{20}$-5.3°. Reaction of this with

acetaldehyde in the presence of boron trichloride as

before gave (-)-1-chloroethyl but-1-yn-3-yl ether

$[\alpha]_D^{20}$-44.5°. Pyrolysis of this and reduction of the

unstable allenic aldehyde, followed by chromatography

of the alcohol as before gave (+)-hexa-3,4-dienol $[\alpha]_D^{20}$+5.3°.

Resolution of But-1-yn-3-ol[127]

<u>But-1-yne-3-hydrogenphthalate</u>.-But-1-yn-3-ol (28 g.,

0.4 mole) and recrystallised phthalic anhydride[*]

(88.8 g., 0.60 mole) were placed in a conical flask and

ice cold 10% sodium hydroxide solution (240 ml., 0.6 mole)

was added in three portions with vigorous shaking. The

reaction mixture became warm and after shaking for a

further 5 minutes was transferred to a beaker and carefully

rendered acid by the addition of 5 N hydrochloric acid.

The crude phthalate separated as an oil, and on extraction

with chloroform (200 ml.) phthalic acid (12 g.,) was

precipitated. After filtration the chloroform layer

was separated, dried ($MgSO_4$) evaporated in vacuo and

the crude phthalate recrystallised from chloroform/40-60°

petroleum ether giving a small residue of phthalic acid

and but-1-yne-3-hydrogenphthalate (67 g., 77%) m.p. 92°.

<u>Brucine Salt of But-1-yne-3-hydrogenphthalate</u>.- Anhydrous

brucine (157 g., 0.4 mole) was added to a solution of

but-1-yn-3-hydrogenphthalate (86.1 g., 0.4 mole) in

acetone (1,150 ml.), the mixture refluxed for 3 hr. and

allowed to cool. No crystallisation occurred. Acetone

(300 ml.) was distilled off and the solution again cooled

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[*]Recrystallised from chloroform.

when heavy crystallisation occurred. A small sample of

the crystals were debasified (cf. next experiment) and

the phthalate (20% solution in ether) examined in the

polarimeter and found to be optically inactive. The bulk

of the brucine salt was therefore again recrystallised

from acetone[*] until a small sample when debasified produced

but-1-yne-3-hydrogenphthalate $[\alpha]_D^{20}+5.3^o$ (c 4.3 in

ether). The bulk of the brucine salt (49 g.) was then

debasified.

Debasification of the Brucine Salt of (+)-but-1-yne-3-

hydrogenphthalate.-The brucine salt of (+)-but-1-yne-3-

hydrogenphthalate (49 g.) was shaken with hydrochloric

acid (100 ml., 2.5 N) and ether (400 ml.), and the ether

layer separated and dried (MgSO$_4$). Ether was removed

in vacuo and the crude but-1-yne-3-hydrogenphthalate

recrystallised from chloroform/40-60° petroleum ether

(1/4) giving a small residue of phthalic acid and

(+)-but-1-yne-3-hydrogenphthalate (8.1 g., 45%) m.p.

91° $[\alpha]_D^{20}+5.3^o$ (c 3.4 in ether).

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[*]It was found difficult to obtain the right conditions to
precipitate the brucine salt of (+)-but-1-yne-3-hydrogen-
phthalate the first time. In subsequent preparations,
however, the solution was seeded with the optically active
salt and no trouble was experienced.

<u>Recovery of Brucine.</u>-The acid solution from hydrolysis
was made alkaline by the addition of potassium hydroxide
solution and the precipitated brucine filtered and washed
with water.   After drying in a dessicator for one week the
brucine hydrate was dissolved in benzene and the water
separated by azeotropic distillation using a Dean and
Stark apparatus.   On removal of 70% of the benzene by
distillation the anhydrous brucine crystallised on cooling.
Recovery was 85%.

<u>(-)-But-1-yn-3-ol from (+)-But-1-yne-3-hydrogenphthalate.</u> -
But-1-yn-3-hydrogenphthalate (25 g., 0.1 mole) was dis-
solved in 40% sodium hydroxide solution (25 ml., 0.25 mole)
and continuously extracted with ether for 48 hr.   The
ether layer was removed, dried $(MgSO_4)$, and the solvent
removed by distillation.   Distillation of the residue gave
(-)-but-1-yn-3-ol (4.0 g., 47%) b.p. $50^\circ/120$ mm.
$[\alpha]_D^{20}$ -5.3° (neat) ν_{max} 3,300 (OH) 2,130 cm.$^{-1}$ $(C\equiv C)$.

Reduction of Acetophenone with the Lithium Aluminium
Hydride-Active Amyl Alcohol Complex. -Active amyl alcohol
(5.3 g., 0.06 mole) was added dropwise over 0.5 hr. to
a standardised solution of lithium aluminium hydride
(0.03 mole) in ether (120 ml.) and the resulting solution
heated under reflux for 2 hr. Acetophenone (1.2 g., 0.01
mole) in dry ether (10 ml.) was then added, the solution
refluxed for a further 2 hr., allowed to cool to room
temperature, poured into 10% sulphuric acid, and ether
extracted (3 x 50 ml.). After drying ($MgSO_4$) and removal
of ether, the residue was distilled using a spinning band
column. 1-Phenylethyl alcohol (1.0 g.) b.p. $74^\circ/10$ mm.
was obtained. G.l.c. on silica at 110° showed two peaks
t = 7 minutes (amyl alcohol 10%) and t = 12 minutes
(1-phenylethyl alcohol 90%). The mixture of alcohols was
added to a mixture of n-pentane (30 ml.) and ether (5 ml.)
and washed with water for 48 hr. on a continuous extraction
apparatus. Evaporation of solvent gave 1-phenylethyl
alcohol (0.8 g.) identical with an authentic sample. The
compound was examined on visual and photoelectric polarimeters
($\pm0.001^\circ$) and found to be optically inactive.

3-Tetrahydropyranyloxyprop-1-yne.-Concentrated hydrochloric

acid (1.1 ml.) was added to propargyl alcohol (56.0 g.,

1.0 mole) and 2,3-dihydropyran (109 g., 1.3 mole), with

ice cooling, the mixture allowed to warm to room temperature

with stirring over 1 hr. and then heated at 70° in a

water bath for 2 hr. Ether (100 ml.) was added and the

resulting solution washed with saturated sodium hydrogen

carbonate solution (50 ml.), water (50 ml.), dried and the

solvent removed in vacuo. The residue was distilled to

give 3-tetrahydropyranyloxyprop-1-yne (120 g., 86%) b.p.

$90^{\circ}/29$ mm. ν_{max} 3,300 and 2,110 cm.$^{-1}$ (C≡CH).

1-Tetrahydropyranyloxyhept-2-yn-4-ol. - 3-Tetrahydropyranyl-

oxyprop-1-yne (120 g., 0.86 mole) dissolved in dry tetra-

hydrofuran (120 ml.) was added dropwise, with ice cooling,

to ethylmagnesium bromide (prepared under nitrogen from

ethyl bromide (98 g., 0.90 mole), magnesium (21.8 g.,

0.90 g. atom), and dry tetrahydrofuran, (300 ml.)).

After stirring for 1.5 hr., n-butyraldehyde (67.7 g., 0.94

mole) dissolved in dry tetrahydrofuran (60 ml.) was added

dropwise to the reaction mixture at 0°. Stirring was

continued for 3 hr., then the ice bath was removed and

the stirring continued at room temperature overnight. The

mixture was then poured into saturated ammonium chloride

solution (200 ml.), ether extracted (4 x 100 ml.), washed

with saturated sodium chloride solution (2 x 50 ml.), and
dried. Solvent was removed in vacuo and the residue
distilled to give 1-tetrahydropyranyloxyhept-2-yn-4-ol
(108 g., 60%), b.p. 136-140°/4 mm. (I.R. No. 18).

4-Chloro-1-Tetrahydropyranyloxyhept-2-yne.-Thionyl chloride
(80.0 g., 0.63 mole) was added dropwise over 1 hr. to a
stirred mixture of 1-tetrahydropyranyloxyhept-2-yn-4-ol
(117.9 g., 0.56 mole), dry pyridene (53.0 g., 0.63 mole)
and dry ether (450 ml.) cooled to 0°. The mixture was
stirred to room temperature for 3 hr. and left to stand
over the weekend. The mixture was then washed with water
(100 ml.), dilute hydrochloric acid (100 ml.), saturated
sodium hydrogen carbonate solution (100 ml.), dried, the
solvent removed and the residue distilled to give 4-chloro-
1-tetrahydropyranyloxyhept-2-yne (85.0 g., 70%), b.p.
110-115/1.5 mm. ν_{max} 700 cm.$^{-1}$ (C-Cl) (I.R. No. 19).

4-Chlorohept-2-yn-1-ol. - 4-Chloro-1-tetrahydropyranyl-
oxyhept-2-yne (30 g., 0.8 mole) in absolute methanol
(60 ml.) and concentrated hydrochloric acid (3 ml.) was
refluxed for 3 hr. After cooling the mixture was added
to water (200 ml.), the aqueous layer extracted with ether
(3 x 40 ml.), the combined organic layers treated with
potassium carbonate, dried, and the solvent removed.

Distillation of the residue gave 4-chlorohept-2-yn-1-ol

(7 g., 60%), b.p. 70°/1 mm. (Found C, 57.49; H, 7.60%

$C_7H_{11}OCl$ requires C 57.40 H 7.56%). ν_{max} 3,300 (OH)

700 cm.$^{-1}$ (C-Cl) (I.R. No. 20).

3-Tetrahydropyranyloxyhex-1-yne.-Concentrated hydrochloric

acid (0.6 ml.) was added to hex-1-yn-3-ol (50.0 g., 0.51

mole) and 2,3-dihydropyran (59.5 g., 0.71 mole), with ice

cooling, the mixture stirred for 2 hr. and allowed to warm

to room temperature. The mixture was then heated at 70°

for 2 hr., ether (100 ml.) was added, the resulting solution

was washed with saturated sodium hydrogen carbonate solution

(50 ml.), water (50 ml.), dried (MgSO$_4$), the solvent

removed and the residue distilled to give 3-tetrahydro-

pyranyloxyhex-1-yne (66.8 g., 78%), b.p. 70-75°/3 mm.

ν_{max} 3,300 (C≡CH), 2,100 cm.$^{-1}$ (C≡C) (I.R. No. 21).

4-Tetrahydropyranyloxyhept-2-yn-1-ol.- 3-Tetrahydropyranyloxy-

hex-1-yne (66.8 g., 0.34 mole) in dry tetrahydrofuran

(60 ml.) was added dropwise with stirring and ice cooling

to ethylmagnesium bromide (prepared under nitrogen from

ethyl bromide (43.0 g., 0.4 mole), magnesium (9.0 g.,

0.4 g. atom) and dry tetrahydrofuran (200 ml.). The

reaction mixture was allowed to warm to room temperature

and formaldehyde gas, generated by heating paraformaldehyde

(18.0 g.), was passed through a heated glass tube onto the
surface of the well stirred reaction mixture. Stirring
was continued overnight, and the reaction mixture was poured
into saturated ammonium chloride solution, ether extracted,
and dried. The solvent was removed and the residue distilled
to give 4-tetrahydropyranyloxyhept-2-yn-1-ol (55.0 g.,
70%) b.p. 140°/3 mm. (Found, C, 67.73; H, 9.67 $C_{12}H_{20}O_3$
requires C, 67.80; H, 9.48%) ν_{max} 3,400 (OH) 2,200 cm.$^{-1}$
(-C≡C-) (I.R. No. 22).

4-Tetrahydropyranyloxyhept-2-ynyl Acetate.-A mixture of
acetic anhydride (23.4 g., 0.23 mole), and dry pyridene
(18.2 g., 0.23 mole), was added to 4-tetrahydropyranyloxyhept-
2-yn-1-ol (45.7 g., 0.23 mole) at 0°. The resulting sol-
ution was heated at 70° for 3 hr., diluted with ether
(200 ml.), washed with dilute hydrochloric acid (3 x 50 ml.),
water (3 x 50 ml.), saturated sodium hydrogen carbonate
solution (3 x 50 ml.), dried, and the solvent removed.
The residue was distilled to give 4-tetrahydropyranyloxyhept-
2-ynyl acetate (33 g., 60%) b.p. 135-140°/3 mm. (Found
C, 65.97; H, 8.70; $C_{14}H_{22}O_4$ requires C, 66.1; H, 8.72%)
ν_{max} 2,240 (-C≡C-) 1,760 cm.$^{-1}$ (C=O) (I.R. No. 23).

1-Acetoxyhept-2-yn-4-ol.- 4-Tetrahydropyranyloxyhept-2-ynyl
acetate (35.2 g., 0.15 mole) and 5 N hydrochloric acid

(100 ml.), were mechanically shaken for 0.5 hr., extracted

several times with ether, the combined ether extracts

dried and the solvent removed. Distillation of the residue

gave 1-acetoxyhept-2-yn-4-ol (12.0 g., 47%) b.p. 119°/4 mm.

4-Chlorohept-2-ynyl Acetate.-Redistilled thionyl chloride

(8.33 g., 0.07 mole) was added dropwise with stirring, to

a mixture of 1-acetoxyhept-2-yn-4-ol (11.6 g., 0.07 mole),

dry pyridine (5.5 g., 0.07 mole) and anhydrous ether

(50 ml.) cooled in ice. Stirring was continued for 1 hr.

and the mixture left overnight. Pyridinium chloride

was filtered off, washed with ether, and the filtrate

washed with dilute hydrochloric acid (3 x 50 ml.), water

(3 x 50 ml.), saturated sodium hydrogen carbonate solution

(2 x 50 ml.), dried and the solvent removed to give

4-chlorohept-2-ynyl acetate (11.7 g., 70%) ν_{max} 2,210

(-C≡C-), 1,750 cm.$^{-1}$ (C=O) (I.R. No. 24).

Reduction of 4-Chlorohept-2-yn-1-ol with the Lithium

Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-

Glucofuranose Complex (a).- 4-Chlorohept-2-yn-1-ol (1.46 g.,

0.01 mole) in ether (10 ml.) was added as rapidly as pos-

sible to the lithium aluminium hydride-monosaccharide

complex (prepared from lithium aluminium hydride (0.01 mole)

in ether (93.5 ml. standardised) and 3-O-benzyl-1,2-O-

cyclohexylidene-∝-D-glucofuranose (3.5 g., 0.01 mole)

by the method described on p. 153) at room temperature

and stirred for 0.5 hr. The complex was decomposed by

the dropwise addition of water, filtered, ether extracted

and dried. The solution on g.l.c. on silica at 70° gave

solvent peaks and a single peak at t = 7.5 minutes.

Removal of solvent from the bulk of the solution and

distillation of the residue gave hepta-2,3-dien-1-ol

(1.0 g., 89%) b.p. $60^o/20$ mm. (Found C, 74.5; H, 10.8;

$C_7H_{12}O$ requires C, 74.90: H, 10.78%). ν_{max} 3,350 (OH)

1,970 cm.$^{-1}$ (-C=C=C-) (I.R. No. 25). The compound was

optically inactive ($\pm0.001^o$).

(b).-The above reduction was repeated at -40° for 10 min.

After decomposition of the complex as in (a), g.l.c. on

the ether solution on silica at 70° gave solvent peaks

and a single peak at t = 7.5 minutes. Removal of solvent

and distillation of the residue gave the optically inactive

hepta-2,3-dien-1-ol as in (a).

(c).-The reaction was again repeated using 4-chlorohept-2-

yn-1-ol (2.92 g., 0.02 mole) and lithium aluminium hydride-

monosaccharide complex (0.01 mole prepared as in (a)).

After decomposition of the complex as in (a), g.l.c. on

the ethereal solution as before showed solvent peaks, a

peak at t = 7.5 minutes (hepta-2,3-dien-1-ol) and a peak

at t = 11 minutes. Fractionation gave hepta-2,3-dien-1-ol

b.p. $60^o/20$ mm. and 4-chlorohept-2-yn-1-ol as residue

identified by its infra-red spectrum. The hepta-2,3-dien-1-ol was optically inactive ($\pm$0.001°).

Reduction of 4-Chlorohept-2-ynyl Acetate with the Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose Complex. - 4-Chlorohept-2-ynyl acetate (3.6 g., 0.02 mole) in ether (10 ml.) was added as rapidly as possible to the lithium aluminium hydride-monosaccharide complex (prepared from lithium aluminium hydride (0.017 mole)in ether (56.6 ml. standardised) and 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose (5.9 g., 0.017 mole) by the method described on p. 153). After decomposition of the complex and work up as in (a) (p. 175), g.l.c. on silica at 70° gave solvent peaks, a peak at t = 7.5 minutes (hepta-2,3-dien-1-ol) and a peak at t = 8 minutes (4-chloro-hept-2-ynyl acetate). Fractionation gave pure hepta-2,3-dien-1-ol (0.9 g., 40%) b.p. 60°/20 mm. identified by its infra-red spectrum. This material had $[\alpha]_D^{25}$=+1.6° (neat).

The Isolation and Identification of Trace Impurities in
3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-Glucofuranose and
the Preparation of the Pure Compound.

Preparation and use of Thin Layer Chromatography Plates. -
Silica gel[*] (30 g.,) was made into a paste with distilled
water (60 ml.) and spread on five 20 x 20 cm. plates to
a thickness of 250 μ . The solution of the monosaccharide
in chloroform or ether was applied using a glass capilliary
and the solvent allowed to evaporate from the spot before
placing the plate in the development solvent (2% methanol
in benzene). After development (a 10 cm. run was used in
all cases) the plates were sprayed with a 0.2% solution of
naphthoresorcinol in ethanol to which 0.1 volume of phos-
phoric acid had been added for every volume of ethanol.
The plates were then placed in an oven at 110° for 15
minutes when the monosaccharides showed up as blue spots.

Determination of Minimum Quantity of Monosaccharide
Detectable.-The impure monosaccharide (5 g.) was dissolved
in chloroform and made up to 10 ml. in a standard flask.
1 ml. of this solution was diluted with chloroform to
10 ml. in a second standard flask. Repetition of this
procedure gave a range of solutions of concentrations

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[*]"Kieselgel G" - suppliers: E. Merck AG., Darmstadt.

ranging from 0.5 g./ml. to 0.0005 g./ml. These were

applied to a t.l.c. plate, developed and sprayed. The

monosaccharide could just be detected as a blue smudge

on the solution of strength 0.0005 g./ml. On application

of allenyne solutions to t.l.c. plates, several spots

(up to 10) were superimposed so as to increase the

sensitivity.

1,2:5,6-Di-O-Cyclohexylidene-α-D-Glucofuranose. -[84]

Cyclohexanone (400 ml., 4.0 mole) was placed in a 1 l.

flask cooled in an ice bath and concentrated sulphuric acid

(26 ml.) added over 10 minutes with rapid stirring. This

was immediately followed by the rapid addition of D-glucose

(180 g., 1.0 mole). The mixture was allowed to warm up

to room temperature over 1 hr. with stirring and stirring

continued until the mixture solidified (ca 6 hr.).

n-Heptane (600 ml.) was added and the mixture heated in

a water bath to 80° when two layers formed. The lower

dark coloured layer was separated and rejected and the

upper n-heptane layer refrigerated overnight when heavy

crystallisation occurred. The crystals were removed by

filtration, dissolved in the minimum volume of near boiling

n-heptane and the solution washed with hot water (5 x 200 ml.

at 60°) and dried ($MgSO_4$). Refrigeration of the n-heptane

layer overnight gave 1,2:5,6-di-O-cyclohexylidene-α-D-

glucofuranose as white crystals, (272 g., 80%) m.p. 132°

giving one spot on t.l.c. R_F 0.20.

3-O-Benzyl-1,2:5,6-Di-O-Cyclohexylidene-α-D-Glucofuranose. -

Potassium hydroxide (74 g.) was added.to freshly redistilled

benzyl chloride (110 ml.) followed by 1,2:5,6-di-O-cyclo-

hexylidene-α-D-glucofuranose (32 g., 0.09 mole) with stirring,

and the temperature of the reaction mixture increased to 150°

over 1.5 hr. The temperature was maintained at 150° and a

small sample of the reaction mixture withdrawn at intervals

of 1 hr. and examined by t.l.c. After 4.0 hr. only one spot,

R_F 0.95, was obtained, and the reaction mixture was allowed

to cool to room temperature. The organic layer was sep-

arated from solid inorganic salts. Water (150 ml.) was then

added to dissolve the inorganic salts and the resulting

solution extracted with chloroform (3 x 50 ml.). The

organic layer and chloroform extracts were combined and

dried ($CaCl_2$). Chloroform and benzyl chloride were then

distilled off to leave a light amber coloured viscous oil

(43 g.). Distillation of this on a mercury vapour pump

gave 3-O-benzyl-1,2:5,6-di-O-cyclohexylidene-α-D-gluco-

furanose as a brittle glass, (30 g., 82%) b.p. 190-195°/

2 x 10^{-3} mm. $[\alpha]_D^{20}$-17.4° (C 19.68 in $CHCl_3$), (Found:

C, 69.7; H, 7.8 $C_{25}H_{34}O_6$ requires C, 69.7; H, 7.9%);

t.l.c. gave one component R_F 0.95. (I.R. No. 27).

3-0-Benzyl-1,2-0-Cyclohexylidene-∝-D-Glucofuranose. -

3-0-Benzyl-1,2:5,6-di-0-cyclohexylidene-∝-D-glucofuranose

(16 g.) was added to acetic acid (62 ml. of 75% v.v) and

the solution heated to 70-80° in a water bath with stirring.

Small samples were withdrawn at intervals of 0.5 hr. and

examined by t.l.c. After 3.0 hr. blue spots showed at

R_F 0.95 (light), R_F 0.25 (heavy), and R_F 0.0 (faint).

After 4.0 hr. t.l.c. showed spots as follows: R_F 0.95

(faint), R_F 0.25 (heavy), R_F 0.0 (light). The reaction

mixture was cooled, water (50 ml.) added and chloroform

extracted (5 x 75 ml.). The combined chloroform extracts

were shaken with saturated sodium hydrogen carbonate

solution till no further effervescence was observed,

washed with hot water (60°, 4 x 100 ml.), and dried

(MgSO$_4$). Removal of chloroform and distillation of the

residue gave 3-0-benzyl-1,2-0-cyclohexylidene-∝-D-gluco-

furanose (9.8 g., 75%) as a pale coloured very viscous

oil, b.p. 195-200°/5 x 10^{-3} mm. (Found: C, 66.0; H, 7.8

$C_{19}H_{26}O_6$ requires C, 65.1; H, 7.4%). T.l.c. showed one

main component at R_F 0.25 and a minor component at

R_F 0.95.

Analytically pure 3-0-Benzyl-1,2-0-Cyclohexylidene-∝-D-

Glucofuranose (cf. p. 104).-The slightly impure monosaccharide

(40 g.) was stirred for 2 hr. with chloroform/n-heptane

1/20 (200 ml.). A portion of the monosaccharide remained
undissolved. After refrigerating overnight the solvent
was removed by decanting and the remaining oil washed
with n-heptane (2 x 50 ml.) by decanting and distilled
to give 3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose
(11.5 g., 29%) b.p. 200°/5 x 10^{-3} mm. $[\alpha]_D^{20}$-34.8°
(C 4.3 in CHCl$_3$). (Found: C, 65.3; H, 7.6 C$_{19}$H$_{26}$O$_6$
requires C, 65.1; H, 7.4%) as a pale yellow brittle glass
(I.R. No. 28).

Identification of Trace Impurities in 3-O-Benzyl-1,2-O-
Cyclohexylidene-α-D-Glucofuranose.-Preparative t.l.c.
plates (20 x 40 cm.) were prepared as previously described
(p. 178). The impure monosaccharide (5 g.) was dissolved
in chloroform (30 ml.), the whole of this solution applied
to ten t.l.c. plates using an automatic applicator[*] and
the plates eluted with 2% methanol in benzene. The bands
were located at R$_F$ values 0.00; 0.20; 0.25; and 0.95 by
spraying just the ends of the plates, then each band was
removed, the silica slurried with chloroform to dissolve
the monosaccharide and the silica removed by filtration.
Evaporation of the chloroform afforded the monosaccharide.
Earlier work had inferred that the impurities were benzylated

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[*]Supplied by Desaga Ltd.

glucose derivatives (cf. p. 101).

(a) Band at R_F 0.00.-The infra-red spectrum of this material showed a strong band at 3,400 cm.$^{-1}$ (OH) (I.R. No. 29) and the low R_F value indicated more than two -OH groups.[*] Analysis gave C, 57.56; H, 6.97%. These facts are best accounted for if the material at R_F 0.00 is 3-0-benzyl-glucose (requires C, 56.40 H, 6.61).

(b) Band at R_F 0.25.-The infra-red spectrum of this material showed extremely weak absorbance in the 3,400 cm.$^{-1}$ region (I.R. No. 39) and the R_F value indicated that less than two hydroxyl groups were present.[**] Analysis gave C, 70.90; H, 7.69%. These facts are best accounted for if the material at R_F 0.25 is a di-0-benzylated-1,2-0-cyclo-hexylidene glucose derivative (requires C, 70.20; H, 7.24%). An example is shown on page 106, but the position of the free -OH group cannot be definitely decided.

(c) Band at R_F 0.95.-The infra-red spectrum of this material showed no absorbance in the 3,400 cm.$^{-1}$ region (I.R. No. 31) indicating a complete absence of hydroxyl groups, a

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[*]By comparison with analytically pure 3-0-benzyl-1,2-0-cyclohexylidene-α-D-glucofuranose of R_F ·20.

[**]By comparison with analytically pure 3-0-benzyl-1,2-0-cyclohexylidene-α-D-glucofuranose of R_F 0.20.

conclusion supported by the high R_F value.[*] Analysis

gave C, 72.88; H, 7.63%. These facts are best accounted

for if the material at R_F 0.95 is a mixture of 3-O-benzyl-

1,2:5,6-di-O-cyclohexylidene-α-D-glucofuranose (requires

C, 69.70; H, 7.90%.) and 3,5,6-tri-O-benzyl-1,2-O-cyclo-

hexylidene-α-D-glucofuranose (requires C, 73.8; H, 7.14%).

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[*]By comparison with analytically pure 3-O-benzyl-1,2:5,6-
di-O-cyclohexylidene-α-D-glucofuranose of R_F 0.95.

Propargyl Aldehyde.[130,131]A solution of chromium trioxide

(105 g.), concentrated sulphuric acid (68 ml.) and water

(165 ml.) was added dropwise to a mixture of concentrated

sulphuric acid (68 ml.), water (100 ml.) and propargyl

alcohol (60 g., 1.07 mole) cooled in an ice bath. During

the addition, the reaction flask was evacuated to 50-20 mm.

pressure by a vacuum pump connected via two traps at

-60° in series. A mixture of propargyl aldehyde, water,

and propargyl alcohol collected in the traps. The total

trap contents were fractionated using a 25 cm. column filled

with Raschig rings, to give propargyl aldehyde (21 g.)

b.p. $54-55^\circ/760$ mm. from which all the propargyl alcohol

and most of the water had been removed. Drying $(CaCl_2)$

gave pure propargyl aldehyde (18.0 g., 31%), ν max 3,320,

2,130 (C≡C-H) 1,700 (C=O) (I.R. No. 2).

Bromopropargyl Alcohol.-Bromine (11 ml., 0.2 mole) was

added dropwise to sodium hydroxide (50 ml. 1 0N.) and ice

(100 g.) cooled in an ice bath and stirred at 0° for

0.5 hr. The sodium hypobromite solution so formed was

added dropwise over 3 hr. to propargyl alcohol (11.2 g.,

0.2 mole) cooled in an ice bath and stirred for 1 hr.

The mixture was then extracted with chloroform (3 x 100 ml.)

and dried $(MgSO_4)$. Evaporation of solvent gave bromopropargyl

alcohol[*] (11.5 g., 48%) ν_{max} 3,360 (OH), 2,260 cm.$^{-1}$

(R-C≡C-R). (I.R. No. 3).

Bromopropargylaldehyde.-A solution of chromium trioxide

(4.2 g.) and concentrated sulphuric acid (2.7 ml.) in

water (20 ml.) was added dropwise to a stirred mixture of

bromopropargyl alcohol (5.0 g.), concentrated sulphuric

acid (2.6 ml.) and water (9.0 ml.), cooled in an ice salt

bath. During the addition the reaction flask was evacuated

to 4 mm. pressure and nitrogen bubbled through the reaction

mixture. Bromopropargylaldehyde (0.6 g., 11%) was collected

by means of a trap cooled to -60°, and dried (MgSO$_4$).

ν_{max} 2,200 (RC≡CR), 1,680 (C=O) and 685 cm.$^{-1}$ (C-Br)

(I.R. No. 4).

2,3-Dibromopropanaldehyde Diethyl Acetal.-[128]Bromine

(32.0 g., 0.4 mole) was added dropwise with ice cooling

to redistilled acrolein (11.0 g., 0.2 mole) in chloro-

form (50 ml.) and the reaction mixture stirred for 1 hr.

Solvent was removed in vacuo and the residue distilled

to give 2,3-dibromopropanal (28.0 g., 0.13 mole, 65%)

b.p. 63°/5 mm. (I.R. No. 32).

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[*]A previous attempt to distil bromopropargyl alcohol
resulted in an explosion.

(a).-This was added to absolute ethyl alcohol (30 g.,
0.65 mole) containing hydrogen chloride (1% by weight)[*]
and allowed to stand with occasional shaking for three
days. The acid was then neutralised by the addition of
sodium hydrogen carbonate, water added, and the acetal
ether extracted, dried ($MgSO_4$), solvent removed and the
residue distilled to give 2,3-dibromopropanaldehyde diethyl
acetal (28.0 g., 77%) b.p. 80°/2 mm.(I.R. No. 33).

(b).-The acetal was also prepared as follows: anhydrous
calcium chloride (10.0 g.) was added to absolute ethyl
alcohol (23.0 g., 0.5 mole) and stirred for 0.5 hr.,
2,3-dibromopropanal (21.6 g., 0.1 mole) was then added
and the reaction mixture allowed to stand for two days
with occasional shaking. Sodium hydrogen carbonate solution
(100 ml., 10%) was then added and the acetal ether extracted
and dried ($MgSO_4$). Evaporation of ether and distillation
gave 2,3-dibromopropanaldehyde diethyl acetal (16.2 g.,
75%) as before.

Propargyl Aldehyde Diethyl Acetal.-[129]2,3-Dibromoprop-
analdehyde diethyl acetal (17.5 g., 0.06 mole) was added
dropwise to a solution of potassium hydroxide (8.5 g)

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[*]Dry HCl gas was bubbled into the absolute alcohol until
its weight had increased by 1%.

in absolute ethyl alcohol (58 ml.) the temperature being allowed to rise to 50-55°. The reaction mixture was cooled to 10°, precipitated potassium bromide removed by filtration and washed with absolute alcohol (10 ml.). The combined filtrate and washings was heated under reflux for 2.5 hr. cooled to 20° and the pale yellow solution containing crystallised potassium bromide was poured into water (500 ml.) and extracted with chloroform (3 x 60 ml.). The chloroform solution was washed with water (2 x 20 ml.), dried (MgSO$_4$) solvent removed and the residue distilled to give propargyl aldehyde diethyl acetal (6.4 g., 83%) b.p. 139-142°/750 mm. ν max 3,320 (C≡CH), 2,140 (C≡CH), 1,060 (C-O-C) (I.R. No. 34).

Bromopropargylaldehyde Diethyl Acetal.-Bromine (5.5 ml., 0.1 mole) was added dropwise with stirring to sodium hydroxide (25 ml., 1 ON solution) and ice (50 g.) with ice cooling and the mixture stirred at 0° for 0.5 hr. The sodium hypobromite solution so formed was added dropwise over 1.5 hr. to propargyl aldehyde diethyl acetal (12.8 g., 0.1 mole) with ice cooling and the reaction mixture stirred at 0° for 2 hr. and extracted with ether (3 x 75 ml.), dried (MgSO$_4$) and the solvent evaporated to yield bromopropargylaldehyde diethyl acetal (16.5 g., 80%) ν max 2,220 (RC≡CR), 1,060 (C-O-C) (I.R. No. 35).

Bromopropargylaldehyde.-Bromopropargylaldehyde diethyl

acetal (18.0 g.) was stirred for 2 hr. with 10% sulphuric

acid (150 ml.) at 35° and ether extracted using a cont-

inuous extraction apparatus. The ether solution was

dried ($MgSO_4$), and ether removed in vacuo to give crude

bromopropargylaldehyde (11.0 g., 95%). ν_{max} 2,200

($RC\equiv CR$), 1,680 (C=O) and 685 cm.$^{-1}$ (C-Br). (I.R. No. 4).

The material was distilled at $42^{\circ}/1.5$ mm. Polymerisation

occurred in the distilling flask. Infra-red spectrum

of distillate ν_{max} 2,200 ($RC\equiv CR$, 1,700, 1,660 and

1,580 cm.$^{-1}$ (I.R. No. 26).

Reaction of Bromopropargylaldehyde with t-Butylmagnesium

Chloride.-Bromopropargylaldehyde (6.6 g., 0.05 mole) in

dry ether (8.0 ml.) was added dropwise with stirring and

cooling in an ice salt bath to t-butylmagnesium chloride

(prepared from magnesium (1.2 g., 0.05 g. atom) and

t-butylchloride (4.6 g., 0.05 mole) in dry ether (14 ml.)).

The reaction mixture was stirred for 0.25 hr. and then

poured onto crushed ice (18.0 g.), ether extracted and

dried ($MgSO_4$). Removal of solvent and distillation gave

the product (0.6 g.) b.p. $40^{\circ}/1.2$ mm. ν_{max} 3,450 (OH),

2,230 and 2,170 ($RC\equiv CR$) and 1,700 cm.$^{-1}$ (C=O) (I.R. No. 36).

2-Tetrahydropyranyloxyethylbromide.-Ice cold 2,3-dihydropyran

(10.8 g., 0.12 mole) was added portionwise to ice cold
ethylene bromohydrin (12.5 g., 0.1 mole) and shaken with
cooling in an ice bath for 0.25 hr. Concentrated hydro-
chloric acid (1 drop) was then added and the mixture
allowed to warm up to room temperature and stand overnight.
The mixture was shaken with sodium hydroxide solution
(20 ml., 10%), ether extracted (3 x 100 mL), washed with
water (2 x 50 ml.) and dried ($MgSO_4$). Removal of solvent
and distillation gave 2-tetrahydropyranyloxyethylbromide
(16.5 g., 75%), b.p. 86°/6 mm.

Reaction of Bromopropargylaldehyde with 2-Tetrahydro-
pyranyloxyethyl Lithium.-Bromopropargylaldehyde (5.0 g.,
0.4 mole) in dry ether (20 ml.) was added with ice cooling
to 2-tetrahydropyranyloxyethyl lithium (prepared from
lithium (0.56 g., 0.08 g. atom) and 2-tetrahydropyranyloxy-
ethyl bromide (8.6 g., 0.04 mole) in dry tetrahydrofuran
(30 ml.)) and the reaction mixture stirred for 3 hr.
The complex was decomposed with iced ammonium chloride
solution (100 ml.), ether extracted, and dried ($MgSO_4$).
Removal of solvent in vacuo and distillation gave the
product (0.5 g.) b.p. 71-74°/2 mm. ν_{max} 3,400 (OH)
and 2,210 cm.$^{-1}$ (RC≡CR) (I.R. No. 37).

Reduction of 3,3,5-Trimethylcyclohexanone with Lithium
Aluminium Hydride Complexes.

Reactions were carried out using titrated solutions
of lithium aluminium hydride[7] and the reaction mixtures
heated under reflux for 3 hr. Solvents were removed from
the products which were analysed directly by gas chromato-
graphy (g.l.c.) using a 12 ft. "Tide" detergent column
at 167°. Ether was dried (Na wire) and distilled from
lithium aluminium hydride before use. All alcohols and
diols were distilled from calcium hydride.

Reduction of 3,3,5-Trimethylcyclohexanone with the Lithium
Aluminium Hydride-Ethylene Glycol Complex.-Ethylene glycol
(1.86 g., 0.03 mole) was added to an ethereal solution of
lithium aluminium hydride (120 ml. containing 0.03 mole)
and the mixture heated under reflux for 2 hr., 3,3,5-tri-
methylcyclohexanone (1.4 g., 0.01 mole) in ether (20 ml.)
was then added and the mixture refluxed for a further
3 hr. Excess complex was destroyed with 10% sulphuric acid
and the aqueous layer extracted with ether. The combined
ether solution was washed with saturated sodium bicarbonate
solution, salt solution, and dried (MgSO$_4$). Distillation
of ether gave the product; g.l.c. on "Tide" detergent at
167° gave two components t = 105 min. (54% axial alcohol,

identical with an authentic specimen) and t = 175 min.

(46% equatorial alcohol identical with an authentic

specimen).

Reduction of 3,3,5-Trimethylcyclohexanone with the Lithium

Aluminium Hydride-Butane-2,3-diol Complex.[*] Butane-2,3-

diol (2.7 g., 0.03 mole) in dry ether (20 ml.) was added

dropwise to an ethereal solution of lithium aluminium

hydride (120 ml. containing 0.03 mole) and the mixture

heated under reflux for 2 hr. 3,3,5-Trimethylcyclohexanone

(1.4 g., 0.01 mole) in dry ether (20 ml.) was then added

and the mixture refluxed for a further 3 hr. The excess

complex was decomposed and the material worked up as before.

G.l.c. gave two components t = 105 min. (53% axial alcohol

and t = 175 min. (47% equatorial alcohol).

Reduction of 3,3,5-Trimethylcyclohexanone with the Lithium

Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclohexylidene-α-D-

Glucofuranose Complex.- 3-O-Benzyl-1,2-O-cyclohexylidene-

α-D-glucofuranose (7 g., 0.02 mole) in dry ether (20 ml.)

was added dropwise to an ethereal solution of lithium

aluminium hydride (80 ml. containing 0.02 mole) and the

mixture heated under reflux for 2 hr; 3,3,5-trimethyl-

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cyclohexanone (1.4 g., 0.01 mole) in dry ether (20 ml.) was then added and the mixture refluxed for a further 3 hr. The excess complex was decomposed and the material worked up as before. G.l.c. gave two components t = 105 min. (58% axial alcohol) and t = 175 min. (42% equatorial alcohol). The products, separated from monosaccharide derivative by distillation, showed no optical activity ($\pm$0.001°).

Reduction of 3,3,5-Trimethylcyclohexanone with the Ethanol Modified Lithium Aluminium Hydride-3-O-Benzyl-1,2-O-Cyclo-hexylidene-α-D-Glucofuranose Complex.-3-O-Benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose (7 g., 0.02 mole) in dry ether (20 ml.) was added dropwise to an ethereal solution of lithium aluminium hydride (66.6 ml. containing 0.02 mole) and the mixture heated under reflux for 1.5 hr. Dry ethyl alcohol (0.92 g., 0.02 mole) was then added and heating continued for a further 1 hr. 3,3,5-Trimethyl-cyclohexanone (1.4 g., 0.01 mole) was added and heating continued for a further 3 hr. The excess complex was decomposed and the material worked up as before. G.l.c. gave two components t = 105 min. (70% axial alcohol) and t = 175 min. (30% equatorial alcohol). The products, separated from the monosaccharide derivative by distillation, showed no optical activity ($\pm$0.001°).

Reduction of 3,3,5-Trimethylcyclohexanone with the Lithium Aluminium Hydride-Diethoxy Complex.-Ethyl alcohol (2.76 g., 0.06 mole) in dry ether (10 ml.) was added to an ethereal solution of lithium aluminium hydride (99.9 ml. containing 0.03 mole) and the mixture heated under reflux for 2 hr. 3,3,5-Trimethylcyclohexanone (1.4 g., 0.01 mole) in dry ether (20 ml.) was then added and the mixture heated for a further 3 hr. The excess complex was decomposed and the material worked up as before. G.l.c. gave two components t = 105 min. (81% axial alcohol) and t = 175 min. (19% equatorial alcohol). A repeat experiment gave 82% axial alcohol and 18% equatorial alcohol.

Reduction of 3,3,5-Trimethylcyclohexanone with the Lithium Aluminium Hydride-Triethoxy Complex.-Ethyl alcohol (4.1 g., 0.09 mole) in dry ether (10 ml.) was added to an ethereal solution of lithium aluminium hydride (120 ml. containing 0.03 mole) and the mixture heated under reflux for 2 hr. 3,3,5-Trimethylcyclohexanone (1.4 g., 0.01 mole) in dry ether (20 ml.) was then added and the mixture heated for a further 3 hr. The excess complex was decomposed and the material worked up as before. G.l.c. gave two components t = 105 min. (85% axial alcohol) and t = 175 min. (15% equatorial alcohol).

Standardisation of Lithium Aluminium Hydride Solution[7]

Solutions (a).-Lithium aluminium hydride (10 g.) was stirred
with dry ether (400 ml.) for 2 hr. and the solution
filtered at the pump. The residue was decomposed with
absolute alcohol.[*]

(b).-Iodine (50 g.) was dissolved in analar benzene (1,000 ml.,
Na dried) to give an approximately 0.4 N solution. This
solution was standardised against standard sodium thio-
sulphate solution (0.1 N) as follows: iodine solution
(10 ml.) pipetted into water (50 ml.) and glacial acetic
acid (1 ml.) and titrated against standard thiosulphate
using starch indicator.

Titration of Lithium Aluminium Hydride Solution.-Lithium
aluminium hydride solution (5 ml.) was added to iodine
solution (50 ml.) and the flask shaken for 4 minutes.
Water (50 ml.) and acetic acid (1 ml.) was added and the
excess iodine titrated with standard thiosulphate using
starch indicator.

---

[*]Residue sometimes catches fire on being decomposed.

SPECTRA

IR N° 1

WAVELENGTH (MICRONS)

IR N° 1   HC≡CH—CH=CH—CH₂C≡CH—CH=CH—CH₂CH₂OH
and
HC≡C—C≡C—CH=C≡CH—CH=CH—CH₂CH₂OH

in CHCl₃ soln 0·1 mm cell

ABSORBANCE

CM⁻¹

INFRACORD

WAVELENGTH (MICRONS)

IR N° 2   HC≡C—CHO

ABSORBANCE

CM⁻¹

INFRACORD

WAVELENGTH (MICRONS)

IR N° 3   Br—C≡C—CH₂OH

ABSORBANCE

CM⁻¹

INFRACORD

I.R. Nº 4   Br-C≡C-CHO

I.R.Nº 5   HC≡C-C≡CH   in CHCl₃   0·1 mm cell

I.R. Nº 6   HC≡C-C≡C-CH=C≡CH-CH₂-CH₂OH
in CHCl₃   0·1 mm   cell
(Bohlmann reduction)

I R Nº 7 CH₃–C(CH₃)(CH₃)–C≡CH

I R Nº 8 CH₃–C(CH₃)(CH₃)–C≡C–CH=C=C–CH₂–CH₂–OH   in CHCl₃ soln   0·1 mm cell

I R Nº 9 HC≡C–C≡C–CH=CH–CH₂OH   in CHCl₃   0·1 mm cell

IR Nº 10 HC≡C—CH=C=CH—CH₂CH₂OH
in CHCl₃ soln 0·1 mm cell

IR Nº 11 HC≡C—CH=CH—CH₂OTp

IR Nº 12 HC≡C—C≡C—CH=C=CH—CH₂CH₂OH
in CCl₄ 0·1mm cell

I.R. Nº 13   Ph C≡C-CH=C=CH-CH₂CH₂OH
in CHCl₃   0·1 mm cell

I.R. Nº 14.
CH₃-C-C≡C-CH=C-CH₂-CH₂OH
      CH₃
Thin Film

I.R. Nº 15
CH₃CH-O-CH-C≡CH
         CH₃

I R Nº 16, $CH_3-CH=C=CH-CH_2CH_2OH$
and.
$CH_3-CH=CH-CH=CH-CH_2OH$

I R Nº 17 $CH_3-CH=C=CH-CH_2CH_2OH$

I R Nº 18 $C_3H_7CH-C\equiv C-CH_2OT_p$
                          OH

IR N° 19 $C_3H_7CH-C\equiv C-CH_2OT_p$
                    Cl

IR N° 20 $C_3H_7CH-C\equiv C-CH_2OH$
                    Cl

IR N° 21 $C_3H_7CH-C\equiv CH$
                    OT_p

Spectrum 1

WAVELENGTH (MICRONS)

I R Nº 22   CH$_3$CH$_2$CH$_2$CH-C≡C-CH$_2$OH
OTp

ABSORBANCE

CM⁻¹

INFRACORD

Spectrum 2

WAVELENGTH (MICRONS)

I R Nº 23   C$_3$H$_7$CH-C≡C-CH$_2$OAc
OTp

ABSORBANCE

CM⁻¹

INFRACORD

Spectrum 3

WAVELENGTH (MICRONS)

I R Nº 24   C$_3$H$_7$C-C≡C-CH$_2$OAc

ABSORBANCE

CM⁻¹

INFRACORD

IR Nº 25   C₃H₇ CH=C=CHCH₂OH

IR Nº 26   BrC≡C-CHO (polymerised)

IR Nº 27.

3-O-Benzyl-1,2:5,6-Di-O-Cyclohexylidene-
α-D-glucofuranose   in   CHCl₃   0·1 mm cell

WAVELENGTH (MICRONS)

I.R. Nº 28.
3-O-Benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose
in CHCl₃ 0·25 mm cell

WAVELENGTH (MICRONS)

I.R. Nº 29
Monosaccharide at R_F 0·00 in CHCl₃ 0·25 mm cell

WAVELENGTH (MICRONS)

I.R. Nº 30
Monosaccharide at R_F 0·25 in CHCl₃ 0·25 mm cell

207

I.R. N° 31
Monosaccharide n° R_f 0.75 in CHCl_3 0.25 mm cell

I.R. N° 32 $CH_2Br \cdot CH_2Br \ CHO$

I R N° 33 $CH_2-CH-CH \begin{smallmatrix} OEt \\ OEt \end{smallmatrix}$
            $\quad Br \quad Br$

IR N° 34 $HC \equiv C - CH \big\langle^{OEt}_{OEt}$

IR N° 35 $Br C \equiv C - CH \big\langle^{OEt}_{OEt}$

IR N° 36

IR N° 37

ABSORBANCE

UV Nr 2(a)

(Bohlmann procedure, crude reduction product)

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ALOG NO. 33-28-15

ABSORBANCE

UV Nr 2

HC≡C-C≡C-CH=CH=CH-CH₂-OH
and
HC≡C-CH=CH=C≡C-CH=CH-CH₂-OH

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ALOG NO. 33-28-15

ABSORBANCE

UV Nº 15

Distillation product from dihydrocoumarin

ALOG NO. 33-28-15

ABSORBANCE

UV Nº 8

ALOG NO. 33-28-15

UV n° 7

ALOG NO. 33-28-15

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UV N° 6   D. manosia

ALOG NO. 33-28-15

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ABSORBANCE

U.V. N° 9

HC≡C-CH₂-C≡C-CH=CH-CH₂OH

TALOG NO. 33-28-15

ABSORBANCE

U.V. N° 6

CH₃
CH≡C-C≡C-CH=CHCH₂OH
CH₃

TALOG NO. 33-28-15

ABSORBANCE

UV N° 11

CH₃
|
CH₃—C≡C—C≡C—CH=CH—CH₂—OH
|
CH₃

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ALOG NO. 33-28-15

ABSORBANCE

UV N° 10

HC≡C—CH=C=CH—CH₂—CH₂OH

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ALOG NO. 33-28-15

ABSORBANCE

UV N° 13

HC≡C-C≡C-C≡C-CH=CH-CH₂-OH

ALOG NO. 33-28-15

ABSORBANCE

UV N° 12

ALOG NO. 33-28-15

BAUSCH & LOMB INCORPORATED

U V N° 15

HC≡C—C≡C—CH=C≡H—CH₂—CH₂—OH

ABSORBANCE

U V N° 14

CH₃—C≡C—C≡C—CH=CH=CH=CH₂—OH

ABSORBANCE

IR N° 12

$Ph-C≡C-C≡C-CH=CH-CH_2OH$

TALOG NO. 33-28-15

ABSORBANCE

UV N° 16

$CH_2=C=C-C≡C-CH=CH-CH-CH_2OH$

TALOG NO. 33-28-15

ABSORBANCE

UV N° 19

[ALOG NO. 33-28-15

ABSORBANCE

UV N° 18

$PhC \equiv C - CH = C = CH - CH = CH_2 \cdot OH$

[ALOG NO. 33-28-15

F 59

uv N° 20

ABSORBANCE

221

ABSORBANCE

ROTATION ANGLE (°)

0.0002 ΔA

U.V	SCALE	SOLVENT	CONC.	CELL LENGTH	TEMPERATURE	SPEED CONTROL	λ EXPANSION
ORD							
C.D	0.002	96% EtOH	12.02 mg/ml	0.98 mm	27°	1 mμ/min	× 2

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