

Asymmetric Syntheses. Part VII.¹ † Asymmetric Reduction of Ketones and Alk-2-en-4-yn-1-ols with a Lithium Bismethoxyaluminium Hydride Complex; Determination of the Absolute Configurations of Allenic Alcohols

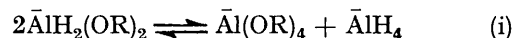
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(+)-Hexa- and (+)-hepta-3,4-dienols are readily obtained by reduction of hex- and hept-2-en-4-yn-1-ols with lithium bismethoxyaluminium hydride. Both dienols have been shown to have the (+)-*S*-configuration; this was confirmed by a synthesis of the former from (-)-(*S*)- α -chloroethyl 1-methylprop-2-ynyl ether involving elimination of hydrogen chloride followed by a Claisen sigmatropic rearrangement, and reduction of the resulting aldehyde. Asymmetric reduction of 4-methyl- and 4,4-dimethyl-pentan-2-ones with lithium bismethoxyaluminium hydride gave partially resolved (+)-4-methyl- and 4,4-dimethyl-pentan-2-ols.

In a preliminary communication² we reported that the asymmetric reduction of alk-2-en-4-yn-1-ols with a lithium bismethoxyaluminium hydride complex gave optically active allenic alcohols, whereas reduction of ketones gave only racemic alcohols. Further work with ketones has now shown that optically active alcohols are obtained in favourable cases but that with some ketones (*e.g.* methyl *t*-butyl ketone³) there is no stereoselectivity (see Table).

Maximum stereoselectivity in the reduction of both ketones and alkenynols was obtained by using a 2 : 1 molar proportion of menthol to lithium aluminium hydride. Although this provides evidence that the bismethoxyaluminium hydride complex is formed initially and must be reasonably stable, some disproportiona-

tion⁴ according to equation (i) cannot be ruled out and could account for the low stereoselectivity. However this is more likely to result from insufficient interaction



of the rather remote isopropyl substituent on the menthyl group with the bulkier substituent on the ketone or allene complex, leading to insufficient energy differences between the (*S*)- or (*R*)-transition states or the (*S*)- or (*R*)-intermediate complexes.

The asymmetric reduction of ketones must involve a kinetically controlled hydride transfer in which the sterically least hindered transition state (I) predominates (see Scheme 1). Both hydrogen atoms on the bismethoxyaluminium hydride complex are in equivalent surroundings in the preferred conformation and both should give the secondary alcohol (II) of (+)-*S*-

² R. J. D. Evans, S. R. Landor, and J. P. Regan, *Chem. Comm.*, 1965, 397.

³ S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc. (C)*, 1966, 1822.

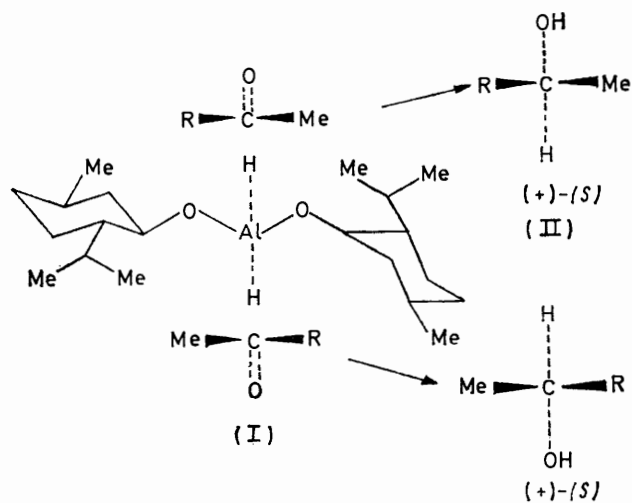
⁴ H. Haubenstock and E. L. Eliel, *J. Amer. Chem. Soc.*, 1962, **84**, 2363.

† This paper is also considered as Part XXIX in the series entitled Allenes; Part XXVIII, D. K. Black, Z. T. Fomum, P. D. Landor, and S. R. Landor, *J.C.S. Perkin I*, 1973, 1349.

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¹ Part VI, S. R. Landor, P. W. O'Connor, A. R. Tatchell, and I. Blair, *J.C.S. Perkin I*, 1973, 473.

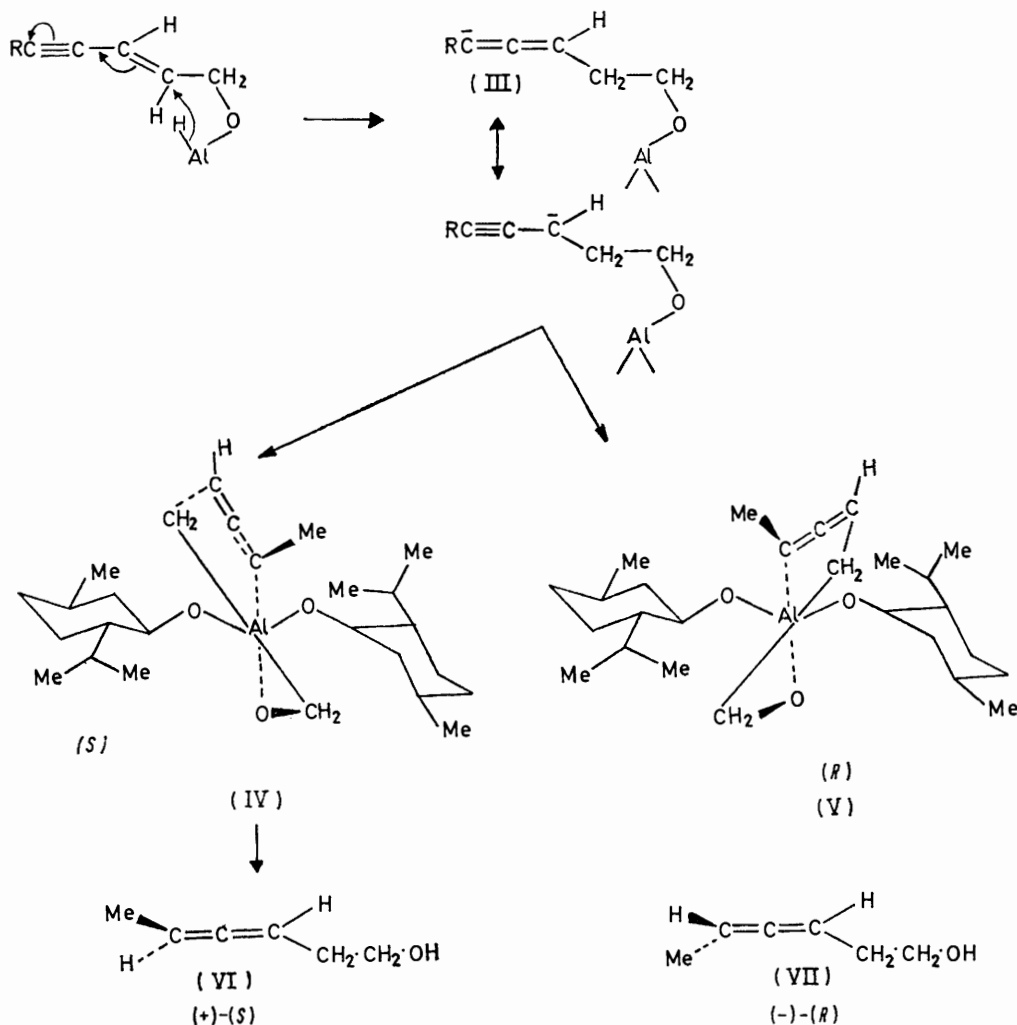
configuration. The data available (see Table) are in accord with this prediction.



SCHEME 1

The asymmetric synthesis of allenic alcohols from enynols must be thermodynamically controlled. Hydride transfer results in an achiral, delocalised anion (III) (see Scheme 2) which only shows chirality after complexing with trivalent aluminium as in (IV) and (V), the complexes then being hydrolysed to form the chiral β -allenic alcohols (VI) and (VII). This was confirmed by completing the reduction of the enynol with lithium aluminium hydride and then adding the chiral agent (menthol) to the aluminohydride-allene complex. Hydrolysis of the product gave chiral allene of the same sign of rotation and approximately the same optical purity as allene obtained from preformed bismenthyloxyaluminium hydride complex. Clearly the same thermodynamically more stable allene complex predominates whichever way it is formed, and on hydrolysis gives the (+)-(S)-allenic alcohol in excess.

Thus hex-2-en-4-yn-1-ol with lithium bismenthyloxyaluminium hydride gave hexa-3,4-dienol with $[\alpha]_D^{20} +8.3^\circ$; complete reduction with lithium aluminium hydride followed by equilibration with menthol, gave



SCHEME 2

the same allenol with $[\alpha]_D^{20} +9.3^\circ$. Similarly hept-2-en-4-yn-1-ol, with pre-formed complex, gave hepta-3,4-dienol with $[\alpha]_D^{20} +2.3^\circ$.

The strained seven-membered cyclic allene complex

The absolute configuration of (+)-hexa-3,4-dienol was independently determined as follows. But-1-yn-3-ol was resolved as previously described⁷ and converted into (-)-(S)- α -chloroethyl 1-methylprop-2-ynyl ether

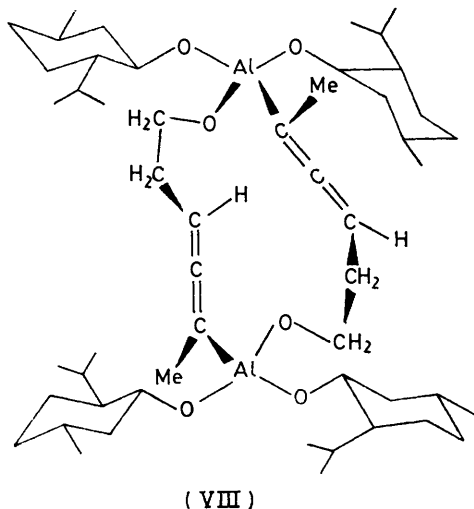
Reduction of ketones with aluminohydride complexes of (-)-menthol

	Ketone		Menthol		LiAlH ₄		Yield		Secondary alcohol	
	g	mol	g	mol	g	mol	g	%	B.p. (°C)	$[\alpha]_D^{20} (^\circ)$
Bu ^t COMe	5.0	0.05	15.6	0.1	2.85	0.075	4.0	78	129—130	+0.60
Bu ^t COMe	5.0	0.05	15.6	0.1	1.9	0.05	4.2	82		+0.64
Bu ^t COMe	2.5	0.025	25.0	0.16	2.85	0.075	2.0	78		+0.44
Bu ^t COMe	2.5	0.025	25.8	0.165	2.85	0.075	2.0	78		+0.42
Bu ^t COMe†	5.0	0.05	15.6	0.1	1.9	0.05	3.5	69	119—121	0.00
neo-C ₈ H ₁₇ COMe	5.7	0.05	15.6	0.1	1.9	0.05	4.8	83	137—138	+0.33

† Varying the proportion of menthol to LiAlH₄ in a further four experiments all gave product with $[\alpha]_D^{20} 0.00^\circ$.

(IV) or (V) (see Scheme 2) is the most convenient representation of the intermediate. The alternative fourteen-membered ring (VIII) is strainless and its formation would have the same stereochemical outcome. A polymeric complex, though theoretically possible, is unlikely to be present as it would be expected to precipitate from solution; no precipitation is observed.

Asymmetric reduction of non-2-ene-4,6,8-triyn-1-ol with a four-fold excess of lithium bismethyloxyaluminum hydride at room temperature for 2 h gave 15% of



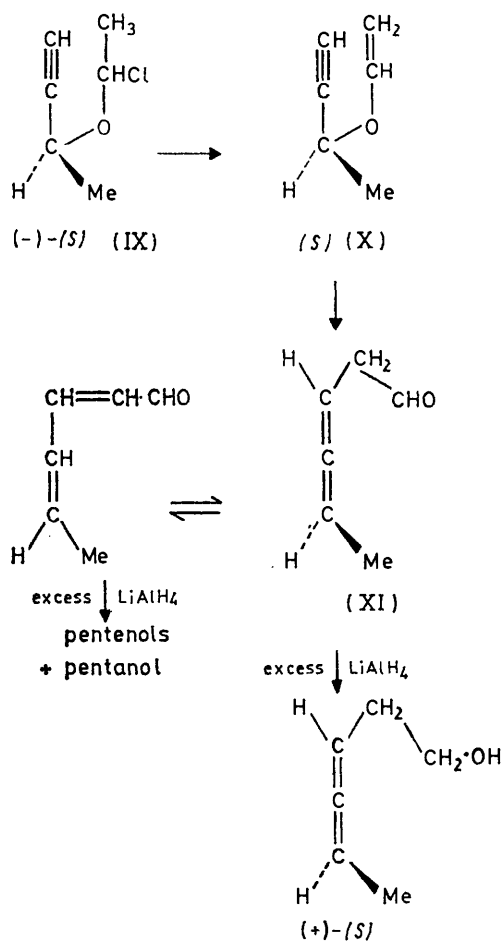
optically active marasin (nona-3,4-diene-6,8-diyn-1-ol)⁵ free from further reduction products (allenenes mixed with allenyne were obtained when diethoxyaluminum hydride complexes were used⁶). However g.l.c. monitoring of the fractions showed that the two alcohols, marasin and menthol, could not be separated completely by careful chromatography, and although separation was achieved on a small scale by a two-way counter-current distribution between carbon tetrachloride and water, insufficient marasin was obtained for the determination of optical activity (marasin⁵ decomposes rapidly in concentrations >0.5%).

⁵ G. Bendz, *Arhiv Kemi*, 1959, **14**, 305.

⁶ S. R. Landor, E. S. Pepper, and J. P. Regan, *J. Chem. Soc. (C)*, 1967, 189.

⁷ C. S. L. Baker, P. D. Landor, S. R. Landor, and A. N. Patel, *J. Chem. Soc.*, 1965, 4348.

with acetaldehyde and boron trichloride.⁸ This ether was converted into a mixture of hexa-3,4-dienal and hexa-2,4-dienal by passing it through an electrically



SCHEME 3

heated glass tube at 200° in a stream of nitrogen. This reaction is likely to be a concerted [3,3] sigmatropic Claisen rearrangement⁹ of the optically active 1-methyl-

⁸ D. K. Black and S. R. Landor, *J. Chem. Soc.*, 1965, 5225.

⁹ D. K. Black, and S. R. Landor, *J. Chem. Soc.*, 1965, 6784; E. R. H. Jones, J. D. Loder, and M. C. Whiting, *Proc. Chem. Soc.*, 1960, 180.

prop-2-ynyl vinyl ether intermediate (X); the stereochemistry of the product hexa-3,4-dienal is thus predictable.¹⁰ Immediate reduction of the aldehydes with lithium aluminium hydride, chromatography, and distillation gave (+)-hexa-3,4-dienol, $[\alpha]_D^{20} +5.3^\circ$, which therefore must have the *S*-configuration.

The mechanistic argument was strengthened by isolating the vinyl ether (X) and carrying out its rearrangement to the allenic aldehyde (XI) as a separate step. However, the vinyl ether (X) was only isolated in poor yield, together with 70% of dimer, by treating the 2-chloroethyl methylpropynyl ether (IX) with triethylamine and heating the resulting quaternary ammonium salt *in vacuo* at 120°. On pyrolysis at 200° it gave a mixture of hexa-2,3-dienal and hexa-2,4-dienal similar to that obtained directly from the chloroethyl ether. The poor yields made it impracticable to use the optically active vinyl ether (X) for the rearrangement.

EXPERIMENTAL

I.r. spectra were determined for liquid films (0.025 mm cell) and for 5% solutions in chloroform, with Perkin-Elmer 237 and 337 spectrophotometers. U.v. spectra were obtained for ethanolic solutions with a Bausch and Lomb Spectronic 505 spectrometer. G.l.c. was carried out with a Griffin and George instrument (6 ft glass columns with nitrogen as carrier gas at a flow rate of 2 l h⁻¹) or with a Pye 104 instrument (5 ft glass columns with nitrogen at 2.5 l h⁻¹). Columns were packed with 10% silicone oil SE-30 or 20% Carbowax 20M on Chromosorb W. Solutions in organic solvents were dried with anhydrous magnesium sulphate, except where stated otherwise.

Reduction of Ketones with Aluminohydride Complexes of (-)-Menthol (with B. J. MILLER and A. R. TACHELL).—A solution of (-)-menthol in dry ether was added dropwise to a measured volume of a standardised ethereal solution of lithium aluminium hydride.¹¹ The mixture was stirred for 30 min, an ethereal solution of the ketone was added, and the resulting mixture was refluxed for 3 h, then cooled. Water (50 ml) was added cautiously, followed by sufficient aqueous 10% hydrochloric acid to dissolve the precipitated hydroxides. The ethereal layer was separated, the aqueous layer was extracted with ether (3 × 50 ml), and the combined ether layer and extracts were dried and evaporated. The residue was distilled under reduced pressure. The distillates were all strongly laevorotatory owing to the presence of substantial quantities of menthol. Redistillation (spinning-band column) furnished the pure alcohols, possessing low dextrorotations (see Table). Purity was established by g.l.c. (Apiezon L; 90°; N₂ 1.5 l h⁻¹) and by i.r. spectra (if the products are free from menthol, bands at 930 and 845 cm⁻¹ are absent).

1-Tetrahydropyran-2-yloxy-pent-2-en-4-yne.—Concentrated hydrochloric acid (0.3 ml) was added to a mixture of 2,3-dihydropyran (63.0 g, 0.75 mol) and pent-2-en-4-yn-1-ol (41.0 g, 0.5 mol). The reaction commenced immediately on shaking and was moderated by cooling in a water-bath. The mixture was shaken for a further 30 min, left overnight, and diluted with ether (150 ml). The solution was washed twice with aqueous sodium hydrogen carbonate, dried, and evaporated, and the residue was distilled under reduced

pressure to give the *product* (77 g, 93%), b.p. 86–88° at 3 mmHg (Found: C, 71.5; H, 8.2. C₁₀H₁₄O₂ requires C, 72.2; H, 8.2%), ν_{\max} 3300 (C≡CH), 2100 (C≡CH), 1730 (C=O), 1630 (C=C), and characteristic tetrahydropyranyl ether bands at 1195, 1175, 1120, 1015, 870, and 814 cm⁻¹.

1-Tetrahydropyran-2-yloxyhex-2-en-4-yne.—Iron(III) nitrate (0.1 g), was added with stirring to liquid ammonia (2 l) contained in a Dewar vessel. Sodium (128.0 g, 5.6 g atom) was then added; the mixture was stirred for a further 4 h, then set aside overnight. The foregoing ether (66.4 g, 0.4 mol) was added dropwise over 30 min, followed (3 h later) by dimethyl sulphate (151 g, 1.2 mol) over 1 h. Stirring was continued for a further 8 h, and the mixture was left overnight. The ammonia was allowed to evaporate, the residue was extracted with ether, and the extract was dried and evaporated. The residue was distilled under reduced pressure to give the *product* (32.5 g, 45%), b.p. 103–107° at 3 mmHg (Found: C, 72.6; H, 8.4. C₁₁H₁₅O₂ requires C, 73.3; H, 8.9%), ν_{\max} 2220 (C≡C-) and 1640 cm⁻¹ (C=C), and characteristic tetrahydropyranyl ether bands.

Hex-2-en-4-yn-1-ol.—(a) *1-Tetrahydropyran-2-yloxyhex-2-en-4-yne* (32.5 g, 0.18 mol) was dissolved in methanol (200 ml) and concentrated hydrochloric acid (30 ml). The mixture was heated under reflux for 2 h, cooled, neutralised with an excess of solid sodium hydrogen carbonate, diluted with ether, and filtered. The solvent was evaporated off under reduced pressure, the residue was dissolved in ether, and the solution was washed twice with water and dried (MgSO₄). Removal of the ether followed by distillation of the residue under reduced pressure gave hex-2-en-4-yn-1-ol (12.9 g, 74.5%), b.p. 65° at 3 mmHg, ν_{\max} 3400–3300 (OH), 2230 (C≡C-), 1640 (C=C), and 1085, 1010, and 950 cm⁻¹, g.l.c. t_R 7 min (silicone oil; 148°).

(b) A similar experiment, in which the crude products from the methylation were hydrolysed with methanolic hydrochloric acid, gave 58% overall yield.

1-Tetrahydropyran-2-yloxyhept-2-en-4-yne.—*1-Tetrahydropyran-2-yloxy-pent-2-en-4-yne* (41.5 g, 0.25 mol) was added over 30 min to sodamide [from sodium (23.0 g, 1.0 g atom)] in liquid ammonia (2 l). Stirring was continued for 3 h, then diethyl sulphate (154 g, 1.0 mol) was added dropwise. After a further 4 h stirring, the mixture left overnight and the ammonia evaporated. The residue was extracted with ether, the extracts were dried, and the residue was distilled to give *1-tetrahydropyran-2-yloxyhept-2-en-4-yne* (38.2 g, 79%), b.p. 115–120° at 3 mmHg, ν_{\max} 2230 (C≡C-), and 1640 cm⁻¹ (C=C), and tetrahydropyranyl ether bands.

Hept-2-en-4-yn-1-ol.—The foregoing ether (38.2 g, 0.2 mol) was dissolved in methanol (200 ml) and concentrated hydrochloric acid (30 ml); the mixture was refluxed for 2 h, then cooled, neutralised with an excess of solid hydrogen carbonate, diluted with ether (200 ml), filtered, and evaporated. The residue was dissolved in ether, and the solution was washed twice with water and dried. Removal of the ether, followed by distillation, gave *hept-2-en-4-yn-1-ol* (14.4 g, 66%), b.p. 79–82° at 1.5 mmHg (Found: C, 76.0; H, 9.2. C₇H₁₀O requires C, 76.3; H, 9.2), ν_{\max} 3400–3300 (OH), 2220 (C≡C-), 1640 (C=C), 1090, 1010, and 955 cm⁻¹, g.l.c. t_R 9 min (silicone oil; 148°).

(+)-*Hexa-3,4-dien-1-ol* (VI).—(a) *Use of lithium monomethylaluminum hydride*. A solution of (-)-menthol (7.8 g, 0.05 mol) in dry ether (120 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.9 g,

¹⁰ R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry,' Verlag Chemie, Academic Press, 1970.

¹¹ S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc. (C)*, 1966, 2280.

0.05 mol) in dry ether (120 ml). After 1 h, a solution of hex-2-en-4-yn-1-ol (3.2 g, 0.033 mol) in dry ether (120 ml) was added slowly and the mixture was refluxed for 3 h, then cooled. The excess of reagent was decomposed by careful addition of water (50 ml). Dilute hydrochloric acid was added to dissolve the solid and the ether layer was separated, washed with aqueous sodium hydrogen carbonate, dried, and distilled. The fraction with b.p. 37–55° at 1.0 mmHg was collected and redistilled, giving (+)-hexa-3,4-dien-1-ol (VI) (1.4 g, 44%), b.p. 38–40° at 1 mmHg, d_4^{20} 0.8955, $[\alpha]_D^{20} +1.68^\circ$, ν_{\max} 3300 (OH), 1950 (C=C=C), and 1430, 1360, 1270, 1170, 1040, and 870 cm^{-1} , identical with an authentic sample.¹² There were no i.r. bands at 920 and 845 cm^{-1} (characteristic of menthol). The g.l.c. trace showed a single peak, t_R 5 min (silicone oil; 128°).

(b) *Use of lithium bismenthylaluminium hydride.* The procedure of method (a) was used, with dry ethereal solutions of menthol (41 g, 0.26 mol) and hex-2-en-4-yn-1-ol (6.3 g, 0.067 mol). Redistillation of the products afforded hexa-3,4-dien-1-ol, b.p. 38–40° at 1.0 mmHg (2.0 g, 31%), $[\alpha]_D^{20} +9.27^\circ$, g.l.c. one peak, t_R 5 min (silicone oil; 128°), otherwise identical with the product from method (a).

(c) *Menthol added at the end of the reduction.* A solution of hex-2-en-4-yn-1-ol (1.0 g, 0.01 mol) in ether (50 ml) was added dropwise over 0.5 h at room temperature with stirring to a standardised solution of lithium aluminium hydride (0.015 mol) in ether (67.2 ml), and the mixture was then heated under reflux for 2 h. A solution of (–)-menthol (5.1 g, 0.03 mol) in ether (50 ml) was added dropwise over 0.5 h and the refluxing was continued for a further 2 h. The complex was decomposed by pouring into 10% sulphuric acid (150 ml). The mixture was extracted with ether (3 × 100 ml) and the extracts were washed with water (2 × 50 ml) and dried. Solvent was removed and the material was twice distilled to give hexa-3,4-dien-1-ol (0.3 g, 30%), $[\alpha]_D^{20} +9.3^\circ$, g.l.c. t_R 7 min (silicone oil; 120°), otherwise identical with sample from (a).

(+)-*Nona-3,4-diene-6,8-diyne-1-ol* [(+)-*Marasin*].—Lithium aluminium hydride (0.4 g, 0.01 mol) was suspended in ether (100 ml) and a solution of (–)-menthol (3.3 g, 0.0 mol) in ether (10 ml) was added dropwise with stirring at room temperature over 0.5 h. The mixture was heated under reflux with stirring for 1 h and then allowed to cool to room temperature. A solution of non-2-ene-4,6,8-triyn-1-ol⁶ (0.3 g, 0.002 mol) in ether (60 ml) was added and the mixture was stirred for 2 h at room temperature. The complex was decomposed by dropwise addition of water, 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 × 75 ml); the combined extracts were washed with water (4 × 100 ml). The solution of the crude product showed λ_{\max} 238 (ϵ 2000), 250.5 (4400), 264 (10,100), and 279 nm (6100).

Attempts to remove menthol from the marasin by chromatography on Woelm acid alumina (200 g) deactivated with water (3, 4, 5, or 6 ml) or on Spence type H alumina (200 g) deactivated with aqueous 10% acetic acid (2, 4, 6, 8,

10, 15, 20, or 30 ml), with n-pentane or ether–n-pentane (1 : 10, 1 : 8, 1 : 6, or 1 : 4) as eluant were unsuccessful. In a typical experiment a solution of marasin and menthol was repeatedly evaporated to 50 ml with addition of n-pentane and then chromatographed in the dark on Woelm acid alumina (200 g) deactivated with water (6 ml, 3%). The polarity of the eluting solvent was increased very gradually, the total continuous chromatography taking 54 h; marasin was eluted in fractions 60–69, which still contained traces of menthol as shown by g.l.c. (silicone oil; 110°; menthol t_R 9.5 min).

Counter-current Distribution.—A hand-operated 50-tube (tube capacity 50 ml) apparatus was used with a water-carbon tetrachloride system. Application of the 'steady-state two-way distribution method' gave marasin (0.005 g) after forty transfers in tubes 16–32, shown to be free of menthol by g.l.c.

(–)-1-Chloroethyl 1-Methylprop-2-ynyl Ether (IX).—A mixture of but-1-yn-3-ol (28.0 g, 0.40 mol), $[\alpha]_D^{20} -5.30^\circ$, and freshly distilled acetaldehyde (8.8 g, 0.20 mol) was added dropwise with stirring to boron trichloride (31.2 g, 0.27 mol) cooled to –15° in an ice-salt bath. The mixture was stirred for 3 h at –15°, then allowed to warm to room temperature and left for 2 days. The product was distilled at 1 mmHg (12 cm column packed with Fenske rings) to give the ether (IX) (9.5 g, 36%), b.p. 64–68° at 120 mmHg, $[\alpha]_D^{20} -44.5^\circ$, ν_{\max} 3320 (C≡CH) 2130 (C≡C), and 1135 cm^{-1} (C–O–C).

Hexa-3,4-dienal (XI) and *Hexa-2,4-dienal*.—(–)-1-Chloroethyl 1-methylprop-2-ynyl ether (0.3 ml; $[\alpha]_D^{20} -44.5^\circ$) 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, collected in a trap at –60°, consisted of hexa-3,4-dienal (XI) and hexa-2,4-dienal (ca. 50 : 50), ν_{\max} 3300 (C≡C–H), 2112 (C≡CH), and 1960 cm^{-1} (C=C=C), λ_{\max} 228 (ϵ 23,000) and 271 nm (12,000) [hexa-2,4-dienal, λ_{\max} 271 nm (ϵ 25,000)].

Hexa-3,4-dien-1-ol.—The mixture of aldehydes resulting from pyrolysis of the foregoing 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. The excess of lithium aluminium hydride was decomposed by dropwise addition of water, the ether layer was separated, and the aqueous layer was extracted with ether (2 × 50 ml). The combined extracts were evaporated to 5 ml, petroleum (b.p. 40–60°; 10 ml) was added, and the solution was chromatographed on Spence type H alumina (100 g), deactivated with acetic acid (10 ml of aqueous 10% solution). Elution with ether–petroleum (b.p. 40–60°) (1 : 4; 12 × 100 ml), evaporation of eluates, and distillation gave hexa-3,4-dien-1-ol (0.4 g, 26%), b.p. 38–40° at 1 mmHg $[\alpha]_D^{20} +5.3^\circ$ (neat), ν_{\max} 3350 (OH) and 1960 cm^{-1} (C=C=C), identical with an authentic sample.

[3/1101 Received, 30th May, 1973]

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