Carotenoids and Related Compounds. Part 35.[1] Synthesis of (±)-Azafrin Methyl Ester and Other α-Glycols

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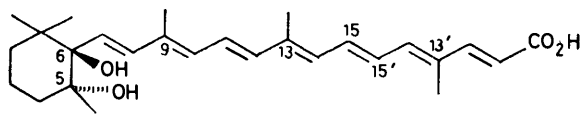
(±)-Azafrin methyl ester, and its retinoate and β-carotene analogues, have been synthesised both from β-ionone and from trimethylcyclohexanone.

AZAFRIN (1) is the principal pigment in the traditional yellow food colour, azafran, extracted in parts of South America from roots of the plant *Escobedia scabrifolia* and



(1)

related species.[2] It is accompanied by small amounts of the corresponding aldehyde.[3] Azafrin has also been reported in the rhizomes of the parasitic Indian plant, *Christisonia bicolor*,[2b] and in *Alectra parasitica* var. *chitrakutensis*.[2c] Recently an isomer of (C_{27}) azafrin, and two forms of a C_{25}-analogue, have been isolated from the root parasite *Aeginetia indica* Linn.[4a] The α-glycol end group, first revealed by conversion of azafrin into azafrinone and its methyl ester (2),[2a] has not been found in other natural carotenoids, though a similar feature has recently been proposed for the triol end group of the C_{40}-acetylenic carotenoid, heteroxanthin.[4b]

Our synthesis of azafrinone methyl ester (2),[5] by chromic acid oxidation of methyl 10'-apo-β-carotenoate (3) (for details see Experimental section), confirmed the gross structure assigned to azafrin by Kuhn and Deutsch.[2] Similar oxidation of the 15,15'-acetylenic analogue of (3) gave 15,15'-didehydroazafrinone methyl ester (5) which, on partial catalytic hydrogenation followed by stereomutation, also yielded azafrinone methyl ester (2). However, attempts to prepare an α-glycol closely related to azafrin by acid treatment of the 5,6-epoxide (6) were unsuccessful; under acidic conditions the main product was the expected 5,8-furanoid oxide (7).[6]

Since i.r. absorption studies on azafrin methyl ester,[5] and on the latter's monomethyl ether,[7] gave no evidence of intramolecular hydrogen bonding, it was concluded that the two hydroxy-groups in azafrin have a *trans*-diaxial arrangement, and hence the *threo*-configuration shown in (1). However, acidic hydrolysis of 5,6-epoxy-5,6-dihydro-10'-apocarotenoic acid by Schwieter *et al.*[8] gave a diastereoisomer of azafrin. Its methyl ester (4b) was distinguished [9] from the ester of the natural pigment by small, but significant, differences in the n.m.r. spectra (see Table 3). Though precedents are known for the formation of an *erythro*-glycol on hydrolysis of an epoxide, usually in systems capable of generating a benzylic or other relatively stable carbonium ion,[10a] this result cast some doubts on the *threo*-configuration assigned to azafrin. These were removed by the syntheses of (±)-azafrin methyl ester now described (for preliminary report see [6]). Recently it has been claimed that the structure shown in (1) also represents the absolute configuration of azafrin.[11]

Condensation of the β-ionone epoxide (18) [12] with the appropriate phosphonate gave the *cis*-9- and *trans*-9-esters (20) and (21), previously prepared in poor yield by

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[1] Part 34, R. Coman, A. P. Leftwick, and B. C. L. Weedon, *J.C.S. Perkin I*, 1976, 2140.

[2] (*a*) R. Kuhn and A. Deutsch, *Ber.*, 1933, **66**, 883, 891; F. W. Pennell, *Proc. Acad. Nat. Sci. Philadelphia*, 1931, **83**, 411; (*b*) S. P. Singh, S. Bhattacharji, and A. B. Sen, *J. Indian Chem. Soc.*, 1963, **40**, 925; (*c*) T. R. Rajagapolan and T. R. Seshadri, *Current Sci. (India)*, 1964, **33**(6), 174.

[3] A. Winterstein, A. Studer, and R. Rüegg, *Chem. Ber.*, 1960, **93**, 2951.

[4] (*a*) S. S. Dighe, S. V. Manerikar, and A. B. Kulkarni, *Indian J. Chem.*, 1977, **15B**, 550; (*b*) H. H. Strain, F. L. Benton, M. C. Grandolfo, K. Aitzetmüller, W. A. Svec, and J. J. Katz, *Phytochem.*, 1970, **9**, 2561.

[5] M. Akhtar and B. C. L. Weedon; quoted by B. C. L. Weedon in *Chemistry and Biochemistry of Plant Pigments*, 1st edn., pp. 86 and 101, ed. T. W. Goodwin, Academic Press, New York and London, 1965.

[6] *cf.* B. C. L. Weedon, *Pure Appl. Chem.*, 1973, **35**, 113.

[7] H. Müller and P. Karrer, *Helv. Chim. Acta*, 1965, **48**, 291.

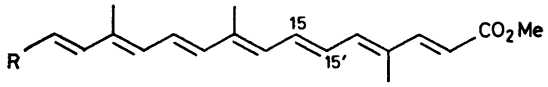
[8] Dr. U. Schwieter (Basle), personal communication.

[9] W. Vetter, G. Englert, N. Rigassi, and U. Schwieter, *Carotenoids*, ed. O. Isler, Birkhäuser Verlag, Basle, 1971, ch. 4.

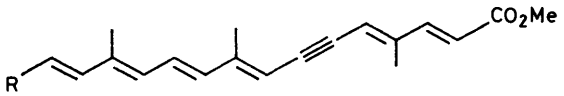
[10] (*a*) H. O. House, 'Modern Synthetic Reactions,' Benjamin Inc., Menlo Park, California, 1972, 2nd edn., p.301; (*b*) p. 283.

[11] W. Eschenmoser and C. H. Eugster, *Helv. Chim. Acta*, 1975, **58**, 1922.

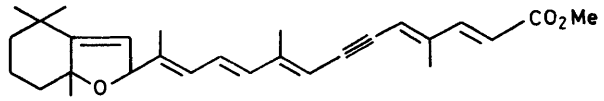
[12] Y. R. Naves, O. Schwarzkopf, and A. D. Lewis, *Helv. Chim. Acta*, 1947, **30**, 880.



(2) R = I; (3) R = II; (4a) R = III; (4b) R = IV



(5) R = I; (6) R = V



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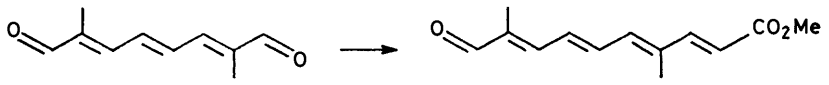
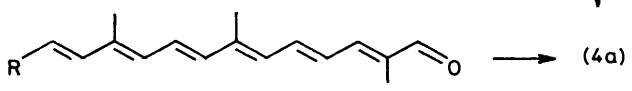
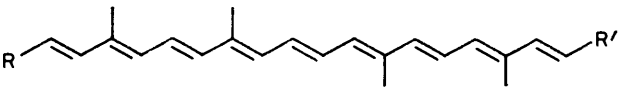


(8) (9)

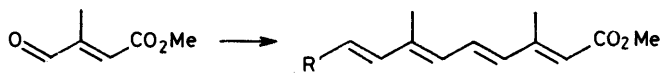


(4a)

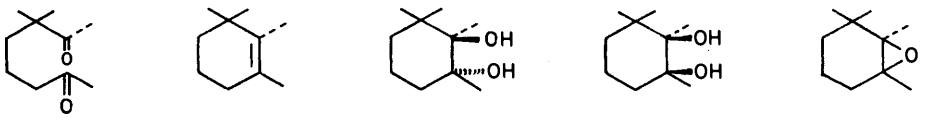
(10) R = III



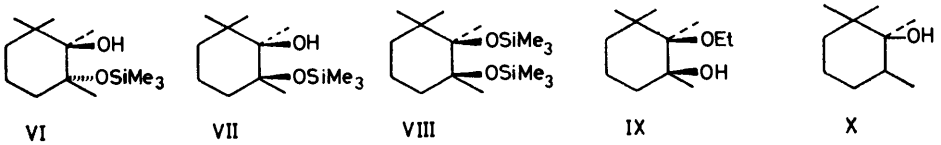
(11) R = R' = III; (12) R = III, R' = II



(13) (14a) R = III; (14b) R = IV
(15a) R = VI; (15b) R = VII; (16) R = VIII



I II III IV V



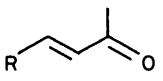
VI VII VIII IX X

a Wittig reaction.[13a] The esters were separated by chromatography and, on treatment with acid, gave dihydroxy-esters, provisionally assigned the *threo*-configurations (22) and (23), with properties in good agreement with those of the products reported by Tamura and Nagao.[13a] The *trans*-9-isomer of the corresponding ethyl ester was subsequently prepared by

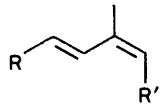
[13] (*a*) S. Tamura and M. Nagao, *Agric. Biol. Chem.*, 1970, **34**, 1393; (*b*) U. Schwieter, W. Arnold, W. E. Oberhänsli, N. Rigassi, and W. Vetter, *Helv. Chim. Acta*, 1971, **54**, 2447.

Schwieter *et al.*[13b] and Dighe *et al.*[14] have reported that aeginetic acid, from *Aeginetia indica* Linn., is the laevorotatory isomer of the corresponding carboxylic acid.

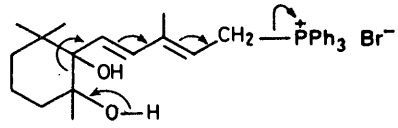
Aqueous tetrahydrofuran [13b] is to be preferred to aqueous alcohol [13a] as medium for the ring opening of the epoxide (21). When the ring opening of the corresponding ethyl ester was carried out in aqueous ethanol, hydroxy-ethoxy-esters were formed as minor by-products. Their n.m.r. properties indicate that they belong to the opposite diastereoisomeric series to the dihydroxy-esters. The by-products are provisionally formulated as (27) and (28).



(17) R = II
(18) R = V
(19) R = III



(20) R = V, R' = CO_2Me
(22) R = III, R' = CO_2Me
(24a) R = III, R' = CH_2OH
(24b) R = IV, R' = CH_2OH
(27) R = IX, R' = CO_2Et
(33) R = III, R' = CH_2PPh_3Br
(37) R = VI, R' = CH_2PPh_3Br
(52) R = X, R' = CH_2OH
(53) R = V R' = CH_2OH



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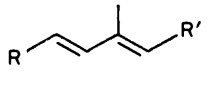
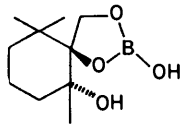


(21) R = V, R' = CO_2Me
(23) R = III, R' = CO_2Me
(25a) R = III, R' = CH_2OH
(25b) R = IV, R' = CH_2OH
(26) R = III, R' = CHO
(28) R = IX, R' = CO_2Et
(31) R = II, R' = CO_2H
(32) R = II, R' = CO_2Et
(34) R = III R' = CH_2PPh_3Br
(35) R = I R' = Me
(38) R = VI R' = CH_2PPh_3Br



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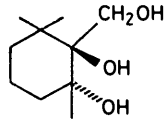


(30)

Reduction of the dihydroxy-esters (22) and (23) with lithium aluminium hydride gave the corresponding, crystalline, triols (24a) and (25a) respectively. Apart from differences due to the stereochemistry of the side chain, these had very similar n.m.r. spectra showing that both triols belong to the same diastereoisomeric series. Oxidation of the *trans,trans*-isomer in acetone with manganese dioxide gave the dihydroxy-aldehyde (26) which, on further oxidation in methanol in the presence of sodium cyanide, regenerated the dihydroxy-ester (23). Partial ozonolysis of the *cis,trans*-triol (24a) gave a dihydroxy-ketone (19) identical with that obtained [15] by hydrolysis of β-ionone epoxide (18), showing that, under the conditions used, ring opening of the epoxide group in (18) follows the same stereochemical course as that of the epoxide groups in (22) and (23). Prolonged ozonolysis of (24a), and reduction of the ozonide with sodium borohydride, gave a borate formulated as (29) which on hydrolysis yielded the known triol (30).[13b] Although the stereochemistry of the latter has been established by *X*-ray crystallographic analysis,[13b] this degradation does not provide conclusive proof of the stereochemistry of (24a) since it is conceivable that inversion occurs at C-1′ either during the formation of the borate or during its hydrolysis. However, as will be described in a separate publication,[16] the *threo*-configuration of the isomeric triol (25a) was established unambiguously by *X*-ray crystallographic analysis, and it has already been shown that (24a) and (25a) belong to the same diastereoisomeric series.

The triol (25a) was also prepared in 16% overall yield from *trans,trans* β-ionylideneacetic acid (31) by adaptation of the procedures described above, and in 21% overall yield from a mixture of ethyl *cis*-9- and *trans*-9-β-ionylideneacetate (32) without purification of the

[14] S. S. Dighe, S. V. Manerikar, and A. B. Kulkarni, *Indian J. Chem.*, 1977, **15B**, 546.
[15] D. L. Roberts, U.S. Patent 3 400 158 (1968) (*Chem. Abs.*, 1968, **69**, 9085).
[16] M. Flo, M. B. Hursthouse, G. P. Moss, and B. C. L. Weedon, forthcoming publication.

intermediates. Though not detected at this stage, it is probable that bulk samples of (24a) and (25a) contained small amounts of the *erythro*-isomers (24b) and (25b) since traces of the *erythro*-dihydroxycarotenoid were isolated in one of the syntheses described later. Evidently, under the acidic conditions required to form the dihydroxy-esters from the epoxides, a side reaction occurs to a small extent involving the formation of a (planar) tertiary carbonium ion, with subsequent solvolysis to give both *erythro*- and *threo*-products.

When treated with triphenylphosphonium bromide in methanol, both triols (24a) and (25a) gave the same 'C_{15}-Wittig salt', presumably as a mixture of *cis*-(33) and *trans*-isomers (34) about the tri-substituted double bond since subsequent condensations gave *cis*-9- and *trans*-9-carotenoids.

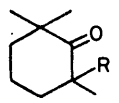
Reaction of methoxycarbonylmethyltriphenylphosphorane with the C_{10}-triene dial (8) [17] gave the aldehydo-ester (9), first obtained by Kuhn and Brockmann [18] by degradation of natural azafrin. Condensation of (9) with the 'C_{15}-Wittig salt', and stereomutation of the mixture of *cis–trans* isomers thus formed, yielded (±)-azafrin methyl ester (4a). Its chromatographic and n.m.r. properties were indistinguishable from those of the methyl ester prepared from natural azafrin. Condensation of the 'C_{15}-Wittig salt' with the C_{10}-triene dial (8) gave the C_{25}-aldehyde (10) with light absorption properties indicating a *cis*-9-structure. On reaction with either methoxycarbonyltriphenylphosphorane or the corresponding phosphonate, and stereomutation of the initial product, (±)-azafrin methyl ester was again obtained.

Condensation of the C_{25}-aldehyde (10) with the 'C_{15}-Wittig salt' led to a previously unknown tetrahydroxy-derivative (11) of β-carotene, whilst with the appropriate β-ionylidene Wittig salt [19] it yielded the *threo*-glycol (12). The latter exhibited no *cis*-peak, and was therefore assigned the all-*trans*-structure. Though its light absorption properties were similar to those reported by Kuhn and Brockmann [20] for the glycol formed initially on oxidation of β-carotene with chromic acid, the melting points of the two products differ markedly. This suggests that the product prepared by Kuhn and Brockmann had the *erythro*-configuration (IV), as might be expected from its mode of formation.[10b]

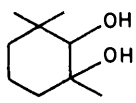
The recognition that vitamin A acid, and its 5,6-epoxide,[21] are effective in the treatment and prevention of certain epithelial papillomas and carcinomas has renewed interest in analogues of vitamin A acid (retinoic acid). We therefore condensed the 'C_{15}-Wittig salt' with the aldehydo-ester (13) [22] and obtained the all-*trans*-dihydroxy-dihydro-retinoate (14a) in *ca.* 40% yield. Its stereochemistry was fully confirmed by its n.m.r. spectrum. When tested biologically it proved to be considerably less active than vitamin A acid. The *erythro*-isomer (14b) was also isolated as a minor by-product (*ca.* 2%). Trimethylsilylation of the *threo*-isomer gave only a mono-derivative (15a), whereas the *erythro*-isomer gave a mixture of both the mono- (15b) and the di-derivative (16).

Another by-product in the synthesis of the retinoate (14a) was identified as the diketone (35). Its formation from the 'C_{15}-Wittig salt' is rationalised in (36). Trimethylsilylation of the Wittig salt gave a mixture of (37) and (38) which on condensation with the aldehydo-ester (13) gave the retinoate derivative (15a) in *ca.* 60% yield together with traces of the di-derivative (16) of the *erythro*-isomer, again confirming the presence of small amounts of the *erythro*-compounds in bulk samples of the dihydroxy-esters (22) and (23) and their derivatives.

The above syntheses are all based on β-ionone (17). As an alternative starting material, we also examined 2,2,6-trimethylcyclohexanone (39) [23] which was readily converted into the α-hydroxy-ketone (40) by the method of Stevens and Weinheimer.[23] Reaction with the *cis*-2-methylpentenynol (42),[24] an intermediate in the manufacture of vitamin A, gave a mixture of two



(39) R = H
(40) R = OH
(41) R = $OSiMe_3$



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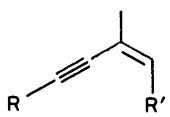
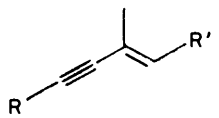


(42) R = H, R′ = CH_2OH
(44a) R = III, R′ = CH_2OH
(44b) R = IV, R′ = CH_2OH
(46) R = X, R′ = CH_2OH
(47) R = X, R′ = CH_2OAc
(48) R = II, R′ = CH_2OAc
(49) R = V, R′ = CH_2OAc
(50) R = V, R′ = CH_2OH
(51a) R = III, R′ = CH_2OAc
(51b) R = IV, R′ = CH_2OAc
(54) R = VII, R′ = CH_2OH
(56a) R = VI, R′ = CH_2OAc
(56b) R = VII R′ = CH_2OAc



(43) R = H, R′ = CH_2OH
(45a) R = III, R′ = CH_2OH
(45b) R = IV, R′ = CH_2OH
(55) R = VII, R = CH_2OH

[17] P. Mildner and B. C. L. Weedon, *J. Chem. Soc.*, 1953, 3294; H. H. Inhoffen and G. von der Bey, *Annalen*, 1953, **583**, 100.
[18] R. Kuhn and H. Brockmann, *Annalen*, 1935, **516**, 139.
[19] W. Sarnecki and H. Pommer, Ger. Pat. 1,060,386 (*Chem. Abs.*, 1961, **55**, 4577).
[20] R. Kuhn and H. Brockmann, *Annalen*, 1935, **516**, 95.
[21] W. Bollag, *Cancer Chemother. Rep.* 1971, **55**, 53 (*Chem. Abs.* 1971, **75**, 67486e); F. Chytil and D. E. Ong, *Nature*, 1976, **260**, 49; A. Matter and W. Bollag, *European J. Cancer*, 1977, **13**, 831.
[22] K. Sisido, K. Kondo, H. Nozaki, M. Tuda, and Y. Udo, *J. Amer. Chem. Soc.*, 1960, **82**, 2286.
[23] C. L. Stevens and A. J. Weinheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 4072.
[24] C. von Planta, U. Schwieter, L. Chopard-dit-Jean, R. Rüegg, M. Kofler, and O. Isler, *Helv. Chim. Acta*, 1962, **45**, 548.

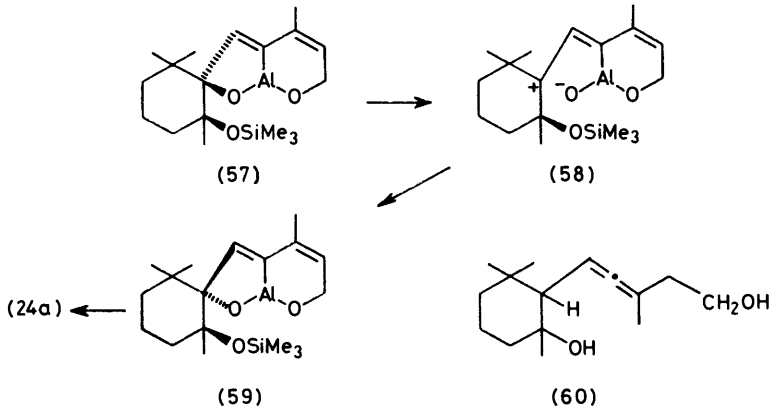
diastereoisomers, (44a) and (44b). The higher-melting isomer predominated in the product from a Grignard reaction, and the lower-melting form in that from a Nef reaction. Since preferential formation of the *threo*-isomer would be expected in a Grignard reaction with the OMgBr complex from (40), this configuration was assigned to the high-melting form, and the *erythro*-configuration to the other. A Grignard reaction between (40) and the *trans*-2-methylpentenynol (43) [24] gave a crystalline product which, on the basis of n.m.r. comparisons, was also assigned the *threo*-configuration (45a). Support for these configurations is given later.

A Grignard reaction between the *cis*-2-methylpentenynol (42) and 2,2,6-trimethylcyclohexanone (39) gave the glycol (46). The latter, on treatment with acetic anhydride, was converted into the enynene acetate (48) which, on reaction with monoperphthalic acid, yielded the acetylenic epoxide (49). This, when heated with acid, gave an α-glycol (51b) with n.m.r. properties similar to those of the low-melting triol (44b), and apparently affords an example of the isolation of an *erythro*-glycol after hydrolytic ring opening of an epoxide.

Although reduction of the two models (46) and (50) proceeded normally with lithium aluminium hydride to give the expected *cis*, *trans*-dienes (52) and (53) respectively, attempts to reduce (44a) gave very erratic results. In one experiment the main product was the diene triol (24a). Though of little value for synthetic purposes, this result is consistent with the *threo*-assignment to the parent enyne (44a). The diastereoisomeric enyne (44b) was not reduced by lithium aluminium hydride, probably because of complexing of the *erythro*-α-glycol function with the reagent, and the isomer (45a) gave little if any conjugated diene; presumably the *trans*-double bond in the side chain precludes the formation of the necessary complex (see discussion below).

To circumvent these difficulties, the α-hydroxy-ketone (40) was converted into its trimethylsilyl derivative (41). Grignard reactions with (42) and (43) gave essentially one product in each case. Since it has been demonstrated that the $OSiMe_3$ group has a lower conformational preference for the equatorial position than the methyl group,[25] these products were assigned the *erythro*-configurations (54) and (55) respectively. That (54) was in the opposite diastereoisomeric series to the triol (44a) was confirmed by acetylation to give (56b). This had n.m.r. properties different from those of the isomer (56a) which, as expected from the proposed *threo*-configuration, was the only product formed on trimethylsilylation of the acetate (51a) derived from the triol (44a).

Reduction of the *trans*-2-isomer (55) with lithium aluminium hydride gave a complex mixture of products containing little if any conjugated diene. This was not unexpected since it is known that similar reduction of related *trans*-enyne alcohols gives allenes rather than conjugated dienes.[26-28] However, vigorous treatment of the *cis*-2-(*erythro*) isomer (54) readily and consistently gave the *cis*-2-(*threo*) triol (24a) in 45% yield. To explain the ease of reduction, and the stereochemical inversion, it is suggested that a tricyclic intermediate such as (57) is involved which rearranges *via* a carbonium ion (58), with rotation about the adjacent acyclic carbon–carbon bond, to give a more stable intermediate (59) as the precursor of the *threo*-product. The loss of the protecting group can be attributed to reductive fission of the O–Si bond by hydride ion, a typical reaction of alkoxysilanes.[29,30] The possibility that loss of the protecting group and the stereochemical inversion result from hydrolytic fission at C-2′ can be discounted; both (54) and (55) when subjected to conditions similar to those used in the work-up of the reduction product underwent partial hydrolysis to the *erythro*-triols (44b) and (45b), but with only *ca.* 20% inversion to the *threo*-triols (44a) and (45a) respectively. Eaborn [31] has previously shown that base-catalysed hydrolysis of alkoxysilanes generally proceeds by nucleophilic attack of hydroxy ion on silicon, not carbon. Partial inversion



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[31] C. Eaborn, *J. Chem. Soc.*, 1952, 2840.

was also observed on mild acid hydrolysis of (54) and (55).

Support for tricyclic intermediates such as (57) in the reduction of (54) came from the detection of two isomers of the allenic by-product (60). Their n.m.r. properties show that they have the same relative configuration about the ring but differ in the relative configuration about the allene group. Their formation may be attributed to hydride ion attack at C-1′ on either (57) or (59).

Reaction of the triol (24a) prepared by the acetylenic route, with triphenylphosphonium bromide gave the same ' C_{15}-Wittig salt ' as that described earlier from β-ionone.

The n.m.r. properties of the majority of the compounds reported in this paper are summarised in the Tables. Azafrin methyl ester, the two *threo*-triols (24a) and (25a), and the derived C_{20}-, C_{25}-, and C_{40}-polyene α-glycols all exhibit an unsymmetrical pattern of three bands at δ 0.84, 1.14, and 1.19 due to the methyl groups attached to the ring. A very similar set of signals is observed with the *threo*-dihydroxy-esters (22) and (23), and with the dihydroxy-ketone (19). However, in the spectra of the *erythro*-isomer (4b) of azafrin methyl ester, and its retinoate analogue (14b), the corresponding bands are more evenly spaced. The *erythro*- and *threo*-triols in the acetylene series are also readily distinguished by the methyl bands in their n.m.r. spectra.

TABLE 1

Principal ^{1}H n.m.r. bands (δ values) of enones and dienes.[a]

Compound	1-Me_2 (6′-Me_2)	5-Me (2′-Me)	9-Me (3-Me)	Other bands
β-Ionone epoxide (18)	0.94 1.15	1.15	2.27	6.28 (d, *J* 15.5, 8-H), 7.03 (d, *J* 15.5, 7-H)
threo-Dihydroxy ketone (19)	0.84 1.24 *	1.15 *	2.33	6.37 (d, *J* 16, 8-H), 7.38 (d, *J* 16, 7-H)
cis,trans-*Dienes*				
Epoxy-ester (20)	0.97 1.10 *	1.12 *	2.01 (d, *J* 1.3)	3.70 (CO_2Me), 5.70 (m, 10-H), 5.26 (d, *J* 16, 7-H), 7.63 (d, *J* 16, 8-H)
threo-Dihydroxy-ester (22)	0.88 1.22 *	1.07 *	2.04	3.60 (CO_2Me), 5.71 (10-H), 6.67 (d, *J* 15, 7-H), 7.77 (d, *J* 15, 8-H)
threo-Triol (24a)	0.85 1.18 *	1.14 *	1.91	4.33br (d, J_1 7, 11-H_2), 5.59br (t, J_1 7, 10-H), 6.24 † (d, *J* 15.5, 7-H), 6.73 † (d, *J* 15.5, 8-H)
Diol (52), more polar	0.80 1.08	1.75 (d, *J* 7)	1.87	4.30 (d, *J* 7, 11-H_2), 5.54 (t, *J* 7, 10-H), 5.97 † (d, *J* 15.5, 7-H), 6.67 (d, *J* 15.5, 8-H)
Diol (52), less polar	0.84 0.98	1.75 (d, *J* 7)	1.86	4.30 (d, *J* 7, 11-H_2), 5.53 (t, *J* 7, 10-H), 5.66 † (d, *J* 15.5, 7-H), 6.60 † (d, *J* 15.5, 8-H)
Epoxy-alcohol (53)	1.03 1.08	1.21	1.90	4.02 (d, *J* 7, 11-H_2), 6.13 * (d, *J* 13, 7-H), 5.62 * (d, *J* 13, 8-H)
trans,trans-*Dienes*				
Epoxy-ester (21)	0.93 1.12 *	1.14 *	2.30 (d, *J* 1.3)	3.71 (CO_2Me), 5.81 (q, *J* 1.3, 10-H), 6.32 (7-H and 8-H)
threo-Dihydroxy-ester (23)	0.83 1.21 *	1.14 *	2.31 (d, *J* 1.2)	3.74 (CO_2Me), 5.85 (m, 10-H), 6.52 † (d, *J* 16.5, 7-H), 6.72 † (d, *J* 16.5, 8-H)
Methyl aeginetate (23) [b]	0.83 1.22 *	1.13 *	2.30	3.66 (CO_2Me), 5.86 (10-H), 6.26 (d, *J* 16), 6.66 (d, *J* 16)
threo-Triol (25a)	0.84 1.19 *	1.14 *	1.86 (m)	4.33br (d, J_1 7, 11-H_2), 5.76br (t, J_1 7, 10-H), 6.15 † (d, *J* 16, 7-H), 6.47 † (d, *J* 16, 8-H)
Aldehyde (26)	0.86 1.22 *	1.12 *	2.32 (d, *J* 1.5)	9.76 (d, *J* 8, 11-H)
erythro-Hydroxy-ethoxy-ester (28)	0.80 1.20 *	0.99 *	2.32	1.17 (t, *J* 7, OCH_2CH_3), 1.29 (t, *J* 7, $CO_2CH_2CH_3$), 3.37 (q, *J* 7, OCH_2CH_3), 4.18 (q, *J* 7, $CO_2CH_2CH_3$), 5.80 (10-H), 6.28 † (d, *J* 16, 7-H), 6.75 † (d, *J* 16, 8-H)
Wittig salt (34) [c]	0.77 1.13	1.13	2.14	4.65 (dd, J_1 8, J_2 16, 11-H_2), 5.40 (10-H), 6.20 (7-H and 8-H), 7.3—8.1 (Ar-H)
Diketone (35) [d]	1.09 1.09	2.00	1.80 *	1.86 * (11-H_3), 5.98 (q, *J* 7, 10-H), 6.32 (d, *J* 16, 7-H), 7.16 (d, *J* 16, 8-H)
Allene (60), more polar	0.91 1.00	1.24	1.74 (d, *J* 3)	1.92 (d, *J* 10, 6-H), 2.21 (dt, J_1 3, J_2 6, 10-H), 3.71 (t, *J* 6, 11-H), 5.03 (d sextet, J_1 10, J_2 3, 7-H)
Allene (60), less polar	0.91 0.98	1.24	1.71 (d, *J* 3)	1.93 (d, *J* 10, 6-H), 2.15 (dt, J_1 3, J_2 6, 10-H), 3.74 (t, *J* 6, 11-H), 5.00 (d sextet, J_1 10, J_2 3, 7-H)

[a] Spectra were determined in deuteriochloroform, unless the contrary is indicated, at 60 or 100 MHz. For ease of comparison, carotenoid numbering [see formula (1)] is used in the Tables; the numbering given in parentheses at the head of the columns in Tables 1 and 2 corresponds to the conventional numbering used in the Experimental section for all compounds with C_{15}-carbon skeletons, except (35), (46), (47), and (52) for which the standard conventions require a different numbering of the end group. For the C_{13}-compounds (18) and (20), the standard conventions used in the Experimental section also number the ring positions as shown in parentheses at the head of the columns; however, the conventional numbering of the side chain is again different. The assignment of pairs of signals marked with an asterisk (*) or dagger (†) for any one compound is arbitrary and the two assignments may need to be exchanged. All signals had the expected relative intensities. [b] See ref. 14; the Indian authors assign the band at 1.22 to the 5-Me. [c] Probably contains the *cis*-isomer (33). [d] Additional small signals at δ 2.06, 6.43 (d, *J* 16), and 7.63 (d, *J* 16) were attributed to the presence of small amounts of an isomer with the *cis*-configuration about the methyl substituted carbon–carbon double bond.

EXPERIMENTAL

Unless indicated to the contrary, the following general points apply.

All operations involving polyenes or acetylenes were carried out in an atmosphere of nitrogen. Solutions were dried over anhydrous sodium or magnesium sulphate, and solvents were evaporated under reduced pressure. Light petroleum refers to the fraction, b.p. 60—80 °C.

Alumina for chromatography was graded according to Brockmann and Schodder.[32] Thin layer chromatograms (t.l.c.) were performed on Kieselgel with the eluants indicated in parentheses.

N.m.r. spectra were determined on dilute solutions in deuteriochloroform using tetramethylsilane as an internal reference. The results are quoted as δ values; doublets are indicated by d, triplets by t, quartets by q, multiplets by m, and a broad signal by br. Coupling constants (J) are given in Hz. Selected bands only are cited for mass spectra and i.r. light absorption spectra.

Melting points were determined in evacuated capillary tubes and are uncorrected, except those marked K which were determined on a Kofler block and are corrected.

15,15′-Didehydroazafrinone Methyl Ester (5).—A solution (4.5 ml) of chromic acid (prepared by dissolving 1.6 g of chromium trioxide in 250 ml of water) was added at 20 °C during 7 min to a stirred solution of methyl 10′-apo-15,15′-didehydro-β-carotenoate [33] (60 mg) in acetic acid (36 ml) and benzene (12 ml). Water was added and the product isolated with benzene in the usual way. Crystallisation from methanol gave the *diketone* (20 mg) as yellow plates, m.p. (K) 135—137 °C; $\lambda_{max.}$ (light petroleum) 430 and 405 nm (ε 80 000 and 85 000 respectively); $\nu_{max.}$ ($CHCl_3$) 2 160, 1 706, 1 672, 929, and 959 cm^{-1} (Found: C, 77.0; H, 8.25. $C_{28}H_{36}O_4$ requires C, 77.0; H, 8.3%).

Azafrinone Methyl Ester (2).—(i) A solution (1.5 ml) of chromic acid (prepared as in the preceding experiment) was mixed slowly (20 min) at 20 °C with one of methyl 10′-apo-β-carotenoate [33] (40 mg) in benzene (25 ml). Dilution with water, isolation of the product in the usual way, chromatography on alumina (Grade IV) using benzene–light petroleum as eluant, and crystallisation from light petroleum gave azafrinone methyl ester (5 mg), m.p. (K) 115—117 °C; $\lambda_{max.}$ 452, 425, and 402 nm (ε 88 000, 88 000, and 57 000 respectively); $\nu_{max.}$ (KBr) 1 695, 1 667, 980, 976, and 961 cm^{-1}. The m.p. was not depressed on admixture with an authentic specimen which had the same light absorption properties.

(ii) The acetylenic analogue (20 mg) in ethyl acetate (5 ml) was shaken with Lindlar catalyst [34] (45 mg, containing a trace of quinoline) in hydrogen until 1.1 mol of hydrogen had been absorbed. Removal of catalyst and solvent, stereomutation in benzene, chromatography on alumina, and crystallisation from light petroleum gave azafrinone methyl ester (4 mg), identical with an authentic specimen.

Methyl 5,6-Epoxy-5,6-dihydro-15,15′-didehydro-10′-apo-β-carotenoate (6).—Ethereal monoperphthalic acid (0.5M;

TABLE 2

Principal ^1H n.m.r. bands (δ values) of enynes.[a]

Compounds	1-Me_2 (6′-Me_2)	5-Me (2′-Me)	9-Me (3-Me)	Other bands
cis-*Series*				
threo-Triol (44a) [b]	1.12 1.19 *	1.41 *	1.86 (dt, J_1 1.5)	4.24 (dq, J_1 7, J_2 1.5, 11-H_2), 5.82 (tq, J_1 7, J_2 1.5, 10-H)
erythro-Triol (44b) [b]	1.07 1.30 *	1.37 *	1.87 (dt. J_1 1.5)	4.25 (dq, J_1 7, J_2 1.5, 11-H_2), 5.85 (tq, J_1 7, J_2 1.5, 10-H)
threo-Dihydroxy acetate (51a) [b]	1.14 1.20 *	1.42 *	1.90 (dt, J_1 1.5)	2.00 (OAc), 4.75br (d, J 7, 11-H_2), 5.84 (tq, J_1 7, J_2 1.5, 10-H)
erythro-Dihydroxy acetate (51b) [b]	1.08 1.32 *	1.37 *	1.91 (dt, J_1 1.5)	4.77 (dq, J_1 7, J_2 1.5, 11-H_2), 5.84 (tq, J_1 7, J_2 1.5, 10-H)
Diol (46)	1.07 1.10	1.01 (d, J 7)	1.87 (d, J 1.5)	4.29 (d, J 7, 11-H_2), 5.83 (tq, J_1 7, J_2 1.5, 10-H)
Hydroxy-acetate (47), more polar	1.06 1.06	1.04 (d, J 7)	1.87	2.03 (OAc), 4.71 (d, J 7, 11-H_2), 5.77 (tq, J_1 7, J_2 1.5, 10-H)
Hydroxy-acetate (47), less polar	1.00 1.10	1.03 (d, J 7)	1.90 (dt, J_1 1.5)	2.03 (OAc), 4.72 (d, J 7, 11-H_2), 5.76 (tq, J_1 7, J_2 1.5, 10-H)
Enynene acetate (48)	1.08 1.08	1.87 (m)	1.92 (m)	2.03 (OAc), 4.74 (d, J 7, 11-H_2), 5.70 (tq, J_1 7, J_2 1.5)
Epoxy-acetate (49)	1.13 1.13	1.43	1.87	2.02 (OAc), 4.68 (d, J 7, 11-H_2), 5.75 (tq, J_1 7, J_2 1.5, 10-H)
Epoxy-alcohol (50)	1.12 1.15	1.44	1.87 (dq, J_1 1.5)	4.29 (dq, J_1 6.5, J_2 1.5, 11-H_2), 5.87 (tq, J_1 6.5, J_2 1.5, 10-H)
erythro-Silyl ether (54)	1.06 1.24 *	1.43 *	1.92 (dt, J_1 1.5)	0.15 ($SiMe_3$), 4.34 (dq, J_1 7, J_2 1.5, 11-H_2), 5.88 (tq, J_1 7, J_2 1.5, 10-H)
erythro-Silyl ether acetate (56b)	1.06 1.24 *	1.43 *	1.93 (dt, J_1 1.5)	0.14 ($SiMe_3$), 2.05 (OAc), 4.80 (dq, J_1 7, 11-H_2), 5.81 (tq, J_1 7, J_2 1.5, 10-H)
threo-Silyl ether acetate (56a)	1.13 1.13	1.51	1.91 (dt, J_1 1.5)	0.27 ($SiMe_2$, 2.05 (OAc), 4.78 (dq, J_1 7, 11-H_2), 5.80 (bt, J_1 7, 10-H)
trans-*Series*				
threo-Triol (45a) [b]	1.10 1.18 *	1.38 *	1.78 (dt, J_1 1)	4.11 (dq, J_1 7, J_2 1, 11-H_2), 5.89 (tq, J_1 7, J_2 1, 10-H)
erythro-Triol (45b) [b,c]	1.07 1.31 *	1.36 *	1.81 (dt, J_1 1.2)	4.16 (dq, J_1 7, J_2 1.2, 11-H_2), 5.96 (tq, J_1 7, J_2 1,2, 10-H)
erythro-Silyl ether (55)	1.04 1.23 *	1.41 *	1.85 (dt, J_1 1)	0.13 ($SiMe_3$), 4.21br (d, J 7, 11-H_2), 5.95 (tq, J_1 7, J_2 1, 10-H)

[a] See footnote *a* to Table 1. [b] In [$^2H_6$]acetone. [c] Sample contained *ca.* 25% of the *threo*-isomer according to the minor bands observed.

[32] H. Brockmann and H. Schodder, *Ber.*, 1941, **74**, 73.
[33] O. Isler, W. Guex, R. Rüegg, G. Ryser, G. Saucy, U. Schwieter, M. Walter, and A. Winterstein, *Helv. Chim. Acta*, 1959, **42**, 862.
[34] H. Lindlar, *Helv. Chim. Acta*, 1952, **35**, 446.

4 ml) was added to methyl 10′-apo-15,15′-didehydro-β-carotenoate (200 mg) in ether (80 ml), and the mixture was kept at 20 °C in the dark for 21 h. Isolation of the product in the usual way and crystallisation from light petroleum gave the *epoxide* (140 mg) m.p. (K) 150—152 °C; $\lambda_{max.}$ (light petroleum) 425 and 402 nm (ε 62 000 and 74 000 respectively); $\nu_{max.}$ (CCl_4) 2 151, 1 712, 974, and 958 cm^{-1} (Found: C, 80.1; H, 8.5. $C_{28}H_{36}O_3$ requires C, 79.95; H, 8.65%).

Methyl 5,8-*Epoxy*-5,8-*dihydro*-15,15′-*didehydro*-10′-*apo*-β-*carotenoate* (7).—Chloroformic hydrogen chloride (1 ml) was added to a solution of the above 5,6-epoxide (40 mg) in ether (10 ml), and the mixture was kept at 20 °C for 15 min. Isolation of the product in the usual way, and crystallisation from methanol gave the *furanoid oxide* (20 mg), m.p. (K) 131—133 °C; $\lambda_{max.}$ (light petroleum) 404 and 383 nm (ε 60 000 and 66 000 respectively); $\nu_{max.}$ (CCl_4) 2 151, 1 709, 1 639, 994, 976, and 956 cm^{-1} (Found: C, 80.0; H, 8.55. $C_{28}H_{36}O_3$ requires C, 79.95; H, 8.65%).

furan (10 ml). The mixture was kept at 20 °C for 20 h and then poured onto ice containing an excess of sodium hydrogen carbonate. Isolation of the product with ether and crystallisation from a mixture of hexane and ethyl acetate gave the *trans,trans*-diene glycol (75 mg), m.p. 112—113 °C; $\lambda_{max.}$ (EtOH) 271.5 nm; $\nu_{max.}$ 3 570, 3 520, 1 695, 1 630, 1 610, 1 440, 1 257, and 1 180 cm^{-1}; δ see Table 1 (lit.,[13] m.p. 114—116 °C).

(ii) A solution of the *trans*-2,*trans*-4-triol (25a) (135 mg) in acetone (5 ml) was stirred with manganese dioxide (500 mg) at 0 °C for 48 h. The dioxide and solvent were removed, and the resulting crude aldehyde in methanol (5.0 ml) containing sodium cyanide (133 mg) and acetic acid (50 μl) was stirred with manganese dioxide at 20 °C for 18 h. The dioxide was filtered off, water was added to the filtrate, and the product was isolated with ether. Preparative t.l.c. (20% acetone in light petroleum) and crystallisation gave the *trans,trans*-diene glycol ester (65 mg), identical in all respects with a sample from (i).

TABLE 3

Principal ^1H n.m.r. bands (δ values) of carotenoids and retinoates.[a]

Compound	1-Me_2	5-Me	9-Me	13-Me	13′-Me	9′-Me	5′-Me	1′-Me_2	Other bands
9-*cis*-Azafrinal (10)	0.85 1.20 *	1.14 *	2.03	1.99	1.87				0.55 (CHO)
Natural azafrin methyl ester	0.84 1.19 *	1.14 *	1.98	1.98	1.91				3.73 (CO_2Me), 5.84 (d, *J* 16, 11′-H), 7.36 (d, *J* 16, 12′-H)
(±) Azafrin methyl ester (4a)	0.84 1.19 *	1.14 *	1.98	1.98	1.91				3.73 (CO_2Me), 5.84 (d, *J* 16, 11′-H), 7.36 (d, *J* 16, 12′-H)
erythro-Isomer (4b) [b]	0.89 1.20 *	1.09 *	1.99 †	1.95 †	1.92				3.76 (CO_2Me), 5.87, 7.38
threo-Retinoate (14a)	0.84 1.20 *	1.14 *	2.00	2.36					3.70 (CO_2Me), 5.79 (14-H), 6.18 (d, *J* 12, 10-H), 6.27 (d, *J* 14, 12-H), 6.36 (7-H and 8-H), 7.01 (dd, J_1 12, J_2 14, 11-H)
erythro-Retinoate (14b)	0.84 1.16 *	1.02 *	1.98	2.34					3.68 (CO_2Me)
C_{40}-Diol (12)	0.84 1.20 *	1.14 *	1.97	1.97	1.97	1.97	1.71	1.03 1.03	
Acetylenic analogue of (12)	0.84 1.20 *	1.14 *	1.98	2.11	2.11	1.98	1.71	1.03 1.03	5.70 (14-H and 14′-H)
C_{40}-Tetraol (11)	0.85 1.20 *	1.14 *	1.97	1.97	1.97	1.97	1.14 †	0.85 1.20 †	

[a] See footnote [a] to Table 1. [b] Vetter *et al.* (see ref. 9).

Methyl 5-(1′,2′-*Epoxy*-2′,6′,6′-*trimethylcyclohexyl*)*penta*-cis-2,trans-4-(*and* trans-2,trans-4-)*dienoate* (20) *and* (21).—Diethyl ethoxycarbonylmethylphosphonate (12.1 g) in methanol (30 ml) was added to a stirred solution of sodium methoxide (from 1.33 g of sodium) in methanol (16 ml). After 75 min β-ionone γ,δ-epoxide [12] (8.34 g) in methanol (10 ml) was added slowly and the mixture was refluxed for 20 h. The mixture was then cooled, diluted with water, and the product was isolated with ether. Chromatography on neutral alumina (1 kg; Merck Grade III) using gradient elution with ethyl acetate in light petroleum gave, in order of elution the following. (i) The *trans,trans*-ester (5.0 g), $\lambda_{max.}$ (EtOH) 267 nm (ε 25 300); $\nu_{max.}$ 1 710, 1 630, and 1 615 cm^{-1}; δ see Table 1 (lit.[13] $\lambda_{max.}$ 267 nm and $\nu_{max.}$ 1 710, 1 632, and 1 613 cm^{-1}). (ii) The *cis,trans*-ester (2.6 g) $\lambda_{max.}$ 267 nm (ε 18 500); $\nu_{max.}$ 1 710, 1 630, and 1 605 cm^{-1}; δ see Table 1 (lit.[13] $\lambda_{max.}$ 267 nm and $\nu_{max.}$ 1 710, 1 632, and 1 602 cm^{-1}). (iii) β-Ionone γ,δ epoxide (0.9 g).

Methyl 5-(1′,2′-threo-1′,2′-*Dihydroxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpenta*-trans-2,trans-4-*dienoate* (23).—(i) Sulphuric acid (0.1 ml) in water (0.15 ml) was added to the preceding *trans,trans*-epoxy-ester (100 mg) in tetrahydro-

Preparative t.l.c. of the crude aldehyde gave the *trans*-2-*trans*-4-isomer (26); δ see Table 1.

Methyl 5-(1′,2′-threo-1′,2′-*Dihydroxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpenta*-cis-2,trans-4-*dienoate* (22).—Hydrolysis of the *cis,trans*-epoxy-ester, as described for the *trans,trans*-isomer, gave the *cis,trans*-diene glycol, m.p. 148—149 °C; $\lambda_{max.}$ (EtOH) 272 nm; $\nu_{max.}$ (Nujol) 3 520, 1 695, 1 635, 1 600, 1 243, and 1 175 cm^{-1}; δ see Table 1 (Tamura, lit.[13] m.p. 151—153 °C).

5-(1′,2′-threo-1′,2′-*Dihydroxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpenta*-cis-2,trans-4-*dienol* (24a).—(i) Lithium aluminium hydride (220 mg) was added slowly to the above *cis*,-*trans*-glycol (1.1 g) in ether (50 ml). After the mixture had been kept at 20 °C for 18 h, a saturated solution of sodium potassium tartrate in water was added. Isolation with ether gave the *triol* as a colourless glass (1.0 g); $\lambda_{max.}$ (EtOH) 237.5 nm (ε 14 200); $\nu_{max.}$ 3 520, 2 970, 2 910, 1 640, 1 460, 1 380, 1 055, and 925 cm^{-1}; δ see Table 1; *m/e* 254 ($M^{+\cdot}$; $C_{15}H_{26}O_3$ requires *m/e* 254).

(ii) A solution of (1′,2′-*erythro*-1′-hydroxy-2′,6′,6′-trimethyl-2′-trimethylsiloxycyclohexyl)-3-methylpent-*cis*-2-en-4-yn-1-ol (54) (6.7 g) in tetrahydrofuran (100 ml) was added

slowly to a cooled solution of lithium aluminium hydride (5.4 g). The mixture was boiled under reflux for 1 week, then cooled, and the excess of hydride was decomposed by the addition of saturated aqueous potassium sodium tartrate. Isolation of the product with ether, and preparative t.l.c. (30% acetone in light petroleum), gave the 1′,2′-*threo*-triol (2.4 g) as a colourless glass; *m/e* 254.189 ($M^{+\cdot}$; calc. for $C_{15}H_{26}O_3$: 254.188); its t.l.c., i.r. and n.m.r. properties were identical with those of a sample from (i). Two allenic by-products in the reaction are described below.

5-(2′-*Hydroxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpenta*-3,4-*dien*-1-*ol* (60).—Further t.l.c. of the minor fractions from the preceding reduction, and crystallisation from ether–light petroleum, gave two diastereoisomers of the *allenic glycol*. (i) The more-polar isomer (100 mg), as colourless prisms, had m.p. 116—118 °C, which (in EtOH) exhibited no u.v. light absorption maximum above 220 nm; $\nu_{max.}$ (Nujol) 3 305, 1 973 (weak), 965, 915, and 865 cm^{-1}; δ see Table 1; *m/e* 238.192 ($M^{+\cdot}$; 20%; $C_{15}H_{26}O_2$ requires *m/e* 238.193), 220 (M − 18, 30%), 207 (M − 31, 10%), 205 (M − 18 − 15, 20%; *m** 191.00, $205^2/220$ = 191.00), and 193 (M − 45, 8%) (Found: C, 75.8; H, 10.7. $C_{15}H_{26}O_2$ requires C, 75.65; H, 10.9%). (ii) A mixture (30 mg), m.p. 95—98 °C, *m/e* 238, of the above isomer (*ca.* 30%) with a slightly less polar isomer (*ca.* 70%). The mixture exhibited no u.v. light absorption maximum above 220 nm. Its n.m.r. spectrum indicated that the less-polar isomer was associated with the bands given in Table 1.

5-(1′,2′-threo-1′,2′-*Dihydroxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpenta*-trans-2,trans-4-*dienol* (25a).—(i) Lithium aluminium hydride (500 mg) was added slowly to the *trans,trans*-dihydroxy ester (23) (3.5 g) in ether (150 ml) at 0 °C, and the mixture was kept at 20 °C for 18 h. Isolation of the product as described for the geometrical isomer, and crystallisation from a mixture of ethyl acetate and light petroleum, gave the *triol* (2.2 g) as prisms, m.p. 116—117 °C; $\lambda_{max.}$ (EtOH) 236 nm (ε 14 700); $\nu_{max.}$ (Nujol) 3 360, 1 625, 1 302, 1 280, 1 113, 1 068, 1 025, and 976 cm^{-1}. δ see Table 1; *m/e* 254.189 ($M^{+\cdot}$; $C_{15}H_{26}O_3$ requires *m/e* 254.188).

(ii) β-Ionylideneacetic acid (300 mg) was added slowly to a solution (22.5 ml) of perbenzoic acid in chloroform (9.11 g l^{-1}). The solution was kept at 5 °C for 24 h and then evaporated. The residue was dissolved in ether (0.4 ml), and aqueous sulphuric acid (20%, 0.1 ml) was added. The mixture was kept at 20 °C for 68 h, then diluted with water and the product isolated with ether in the usual way. Treatment with an excess of ethereal diazomethane gave the crude glycol ester which was reduced with lithium aluminium hydride as described above. Isolation gave the triol (53 mg), m.p. 116—117 °C, with spectroscopic properties identical with those reported above.

(iii) *m*-Chloroperbenzoic acid (26 g) was added slowly at 0 °C to a mixture (31 g) of ethyl *cis,trans*- and *trans,trans*-β-ionylideneacetate in dichloromethane (480 ml). The mixture was stirred at 0 °C for 2.5 h and then poured onto ice and aqueous sodium hydroxide (3M; 40 ml). Isolation of the product in the usual way gave the crude epoxide (30 g) which was dissolved in ethanol (240 ml). Aqueous sulphuric acid (20%; 60 ml) was added dropwise and the mixture was kept at 20 °C for 65 h, then diluted with water and neutralised with saturated aqueous sodium hydrogen carbonate. Most of the ethanol was evaporated and the crude glycol (33 g) isolated with ether. Reduction in ether (350 ml) with lithium aluminium hydride (7.7 g), isolation of the product, and crystallisation from benzene–light petroleum, gave the triol (6.2 g) as prisms, m.p. 114—117 °C, with spectroscopic properties identical with those reported above. The bulk sample was probably contaminated with traces of the *erythro*-isomer.

Ethyl 5-(1′,2′-erythro-2′-*Ethoxy*-1′-*hydroxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpenta*-trans-2,trans-4-*dienoate* (28).—A small amount of the above crude glycol was subjected to t.l.c. (12% acetone in light petroleum) and gave as a minor by-product (*ca.* 8%) the erythro *monoethyl ether*; $\lambda_{max.}$ (EtOH) 271 nm; δ see Table 1.

5-(1′,2′-threo-1′,2′-*Dihydroxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpenta*-2,4-*dienyltriphenylphosphonium Bromide* (33) *and* (34).—(i) Triphenylphosphonium bromide (6.6 g) was added slowly to a solution of the above crystalline triol (5.0 g) in methanol (260 ml). The mixture was kept at 20 °C for 20 h and then evaporated. Trituration of the residue with ether gave the Wittig salt (11.6 g), m.p. 75—85 °C with decomposition; $\lambda_{max.}$ (EtOH) 229 nm; δ see Table 1. Hexamethyldisilazane (0.6 ml) and trimethylchlorosilane (0.5 ml) were added to a solution of the Wittig salt (87 mg) in pyridine (0.8 ml). After the mixture had been kept at 20 °C for 7 h, carbon tetrachloride was added, and the solution was evaporated in a stream of nitrogen to give the 2-trimethylsilyl derivative as a solid (57 mg) which was used without purification.

(ii) Similar reaction of the 1′,2′-*threo-cis*-2,*trans*-4-diene triol (24a) with triphenylphosphonium bromide gave the same dihydroxy Wittig salt. Both products probably consisted of a mixture of the *cis*- and *trans*-isomers (33) and (34).

Methyl 9-*Formyl*-4-*methyldeca*-2,4,6,8-*tetraenoate* (9).—Methoxycarbonylmethyltriphenylphosphorane (1.0 g) in benzene (150 ml) was added over a period of 4 h to a solution of 2,7-dimethylocta-2,4,6-triene-1,8-dial [17] (0.5 g) in benzene (50 ml). The mixture was stirred at 20 °C for 3 h and finally under reflux for 3 h. The mixture was then cooled and poured into water. The benzene layer was separated, dried, and evaporated. Preparative t.l.c. and crystallisation from methanol gave a mixture of isomers (260 mg), m.p. 85—100 °C. A portion (100 mg) was dissolved in benzene (10 ml) containing a trace of iodine, and the solution was refluxed for 18 h in front of a 100 W tungsten filament light. Isolation of the product in the usual way gave the all-*trans* aldehydo-ester (90 mg) as yellow needles, m.p. 106—107 °C; $\lambda_{max.}$ (hexane) 366, 347, and 333 nm (ε 75 000, 77 000, and 46 500 respectively); $\nu_{max.}$ 1 718, 1 660, 1 611, and 984 cm^{-1}; δ 1.91 (3 H), 2.00 (3 H), 3.78 (3 H), 6.01 (1 H, d, J = 15.5 Hz), 6.3—7.2 (4 H, m), 7.40 (1 H, d, J = 15.5 Hz), and 9.49 (1 H); $\nu_{max.}$ (KBr) 1 667, 1 709, 995, and 985 cm^{-1} (Kuhn and Brockmann [18] give m.p. 106 °C for a sample prepared by degradation of azafrin. The previously reported [35] synthetic product, m.p. 129 °C, despite attempted stereomutation by u.v. irradiation for 2.5 h, was evidently the *cis*-6-isomer. It exhibited a *cis*-peak at 257 nm and on iodine-catalysed stereomutation in boiling benzene for 9 h in front of a 60 W tungsten filament lamp gave the all-*trans*-isomer, m.p. 104—106 °C. The oxime crystallised from methanol and had m.p. 192—193 °C (Found: C, 66.4; H, 7.25. Calc. for $C_{13}H_{17}NO_3$: C, 66.35; H, 7.25%) (Kuhn and Brockmann [18] give m.p. 194 °C).

Reduction with sodium borohydride in methanol gave the hydroxy-ester, $\lambda_{max.}$ (EtOH) 344 nm; $\nu_{max.}$ (CCl_4) 3 620,

[35] R. Ahmad and B. C. L. Weedon, *J. Chem. Soc.*, 1953, 3299.

3 500, 2 950, 1 723, 1 623, and 980 cm^{-1}; δ 1.85 (3 H), 1.91 (3 H), 3.78 (3 H), 5.85 br (2 H), 5.88 (d, *J* 16, 1 H), 6.1—7.35 (m, 4 H), and 7.40 (d, *J* 16, 1 H). Reaction with triphenylphosphonium bromide gave a Wittig salt which was condensed, on a spectroscopic scale, with the aldehyde (26) to give a product with visible light absorption properties similar to those of azafrin methyl ester.

12′-*Apo-azafrinal* (5,6-threo-5,6-*Dihydroxy*-5,6-*dihydro*-10′-*apo*-β-*caroten*-10′-*al*) (10).—The ' C_{15}-Wittig salt ' (600 mg), 2,7-dimethylocta-2,4,6-trienedial [17] (270 mg), and 1,2-epoxy-butane (5.0 ml) were heated in a sealed tube at 90 °C for 2 h. The mixture was cooled and evaporated. Preparative t.l.c. of the residue, using 20% acetone in light petroleum as eluant, gave the product as a red gum (120 mg). Crystallisation from benzene–hexane gave 12′-apo-azafrinal as needles, m.p. 183—185 °C; $\lambda_{max.}$ (benzene) 437, 415, 395, and 298 nm (ε_{415} 57 100, ε_{298} 8 100); $\lambda_{max.}$ (hexane) 422, 400, 358, and 290; $\nu_{max.}$ (KBr) 3 600, 3 440, 3 038, 2 920, 2 870, 1 648, and 1 608 cm^{-1}; δ see Table 3; *m/e* 384.266 ($M^{+\cdot}$; $C_{25}H_{36}O_3$ requires 384.266). From a consideration of the light absorption spectra, which included a *cis*-peak, and of the method of formation, it was concluded that the product had the *cis*-9-configuration. The same product was isolated after attempted iodine-catalysed stereomutation.

5,6-threo-5′,6′-threo-5,6,5′,6′-*Tetrahydroxy*-5,6,5′,6′-*tetrahydro*-β,β-*carotene* (11).—The preceding aldehyde (45 mg), the parent phosphonium salt (100 mg), and 1,2-epoxybutane (2.5 ml) were heated in a sealed tube at 90 °C for 1 h. Further phosphonium salt (100 mg) was added and the mixture heated at 90 °C for 40 min. Isolation of the product in the usual way, iodine-catalysed stereomutation, and t.l.c. on Kieselgel and on basic magnesium carbonate gave the all-*trans* isomer of the *tetraol* (3 mg) which crystallised from benzene–hexane as needles, m.p. 220—222 °C; $\lambda_{max.}$ (benzene) 479, 450, and 423 nm (ε 108 000, 108 000, and 70 000 respectively); $\nu_{max.}$ (KBr) 3 480, 3 030, 3 920, and 3 865 cm^{-1}; δ see Table 3; *m/e* 604.448 ($M^{+\cdot}$; $C_{40}H_{60}O_4$ requires 604.449).

(±)-*Azafrin Methyl Ester* (*Methyl* 5,6-threo-5,6-*Dihydroxy*-5,6-*dihydro*-10′-*apo*-β-*caroten*-10′-*oate*) (4a).—(i) A suspension of the aldehyde (10) (32 mg) in propan-2-ol (0.2 ml) was added to a solution of the ' C_{15}-Wittig salt ' (85 mg), prepared from either the *trans,trans*-(25a) or the *cis,trans*-triol (24a), in propan-2-ol (0.6 ml) at −30 °C. A solution (0.1 ml) of potassium hydroxide (7.6 g) in water (100 ml) was added during 10 min whilst the temperature of the mixture was allowed to rise to −10 °C. The mixture was stirred at 20 °C for 15 min and then diluted with water. The ethereal layer was separated, washed with water, dried, and evaporated. Preparative t.l.c. (20% acetone in light petroleum), and isolation of the major orange band, gave the product as a mixture of geometrical isomers (15 mg). A solution of the isomers in benzene (9 ml) containing a trace of iodine was illuminated with a 100-W tungsten filament lamp for 19 h. The solution was then washed with aqueous sodium thiosulphate, dried, and evaporated. Preparative t.l.c. on basic magnesium carbonate using 50% benzene in light petroleum as eluant, isolation of the main product, and crystallisation from benzene–light petroleum gave *all*-trans-(±)-*azafrin methyl ester* (10 mg) as prisms, m.p. 187—188 °C; $\lambda_{max.}$ (benzene) 453, 428.5, and (inflexion) 418 nm, (ε_{453} 68 500, $\varepsilon_{428\cdot5}$ 81 000); $\nu_{max.}$ (KBr) 3 620, 3 490, 3 040, 2 920, 1 692, 1 615, 974, and 958 cm^{-1}; δ see Table 3; *m/e* 440.293 ($M^{+\cdot}$; $C_{28}H_{40}O_4$ requires *m/e* 440.293). A sample of the methyl ester of natural azafrin had $\lambda_{max.}$ (benzene) 453.5, 428.5, and (inflexion) 418 nm; $\nu_{max.}$ (KBr) 3 600, 3 480, 2 910, 1 685, 1 610, 973, and 956 cm^{-1}; δ see Table 3 (for the laevorotatory isomer Kuhn and Brockmann [36] give m.p. 191 °C). The two samples did not separate on mixed t.l.c. on Kieselgel (20% acetone in light petroleum; R_F 0.45) or on basic magnesium carbonate (70% benzene in light petroleum; R_F 0.35); on iodine-catalysed stereomutation both gave an indistinguishable mixture of two isomers.

(ii) A solution of 12′-apo-azafrinal (27 mg) and methoxycarbonylmethyltriphenylphosphorane (50 mg) in benzene (5 ml) was refluxed in the dark for 18 h. Evaporation of the solvent and preparative t.l.c. of the residue gave the required product as a mixture of isomers (15 mg). Stereomutation, t.l.c. and crystallisation gave the all-*trans*-(±)-ester identical with the sample described above.

(iii) Sodium methoxide (from 365 mg of sodium) in methanol (1 ml) was added to diethyl methoxycarbonylmethylphosphonate (33 mg) in methanol (5 ml). After 5 min 12′-apo-azafrinal (43 mg) in methanol (1 ml) was added and the mixture was stirred at 20 °C for 2 h and then under reflux for 16 h. The mixture was cooled, diluted with water, and the product was isolated with ether. Preparative t.l.c. gave the required product as a mixture of isomers (20 mg). Stereomutation, t.l.c., and crystallisation gave the all-*trans*-(±)-ester identical with the samples described above.

5,6-threo-5,6-*Dihydroxy*-5,6-*dihydro*-β,β-*carotene* (12).—(i) A solution of β-ionylidene-ethyltriphenylphosphonium bromide [19] (100 mg) and 12′-apo-azafrinal (35 mg) in 1,2-epoxybutane (0.5 ml) was heated in a sealed tube at 90 °C for 45 min. More phosphonium salt (100 mg) was added, and the mixture was again heated at 90 °C for 45 min, and then cooled. Isolation in the usual way, stereomutation, preparative t.l.c. on basic magnesium carbonate using a mixture of benzene, light petroleum, and acetone (20 : 79 : 1) as eluant, and crystallisation from methanol–benzene–water of the product from the more polar of the two bands, gave the 5,6-*dihydroxy*-5,6-*dihydro*-β,β-*carotene*, m.p. 151—152 °C; $\lambda_{max.}$ (benzene) 484, 455.5, and (inflexion) 432 nm (ε_{484} 169 000, $\varepsilon_{455\cdot5}$ 195 000); $\lambda_{max.}$ (hexane) 470, 442, and (inflexion) 430 nm; $\nu_{max.}$ (KBr) 3 600, 3 480, 3 025, 2 920, 2 860, and 963 cm^{-1}; δ see Table 3; *m/e* 570.443 ($M^{+\cdot}$; $C_{40}H_{58}O_2$ requires *m/e* 570.444).

(ii) A solution of 12′-apo-azafrinal (23 mg) and the phosphonium salt (37 mg) in propan-2-ol (1.6 ml) was cooled to −30 °C. A solution (0.1 ml) of potassium hydroxide (11.5 g) in water (100 ml) was added during 10 min. The mixture was stirred at −20 °C for 20 min and then at 20 °C for 4 h. Isolation of the product in the usual way, stereomutation, and preparative t.l.c. gave the all-*trans*-glycol (8 mg), m.p. 150 °C, with spectroscopic properties and chromatographic behaviour identical with those of the product from (i).

5,6-threo-5,6-*Dihydroxy*-15,15′-*didehydro*-5,6-*dihydro*-β,β-*carotene*.—A similar condensation of the phosphonium salt (33) and (34) (140 mg) and 12′-apo-15,15′-didehydro-β-caroten-12′-al [37] (75 mg) in 1,2-epoxybutane (2.0 ml) gave the *all*-trans-*acetylenic glycol* (30 mg) which crystallised from aqueous ethanol–benzene and had m.p. 150—152 °C; $\lambda_{max.}$ (benzene) 465, 436, and (inflexion) 416 nm (ε_{465} 134 000,

[36] R. Kuhn and H. Brockmann, *Ber.*, 1931, **64**, 338.

[37] R. Rüegg, H. Lindlar, M. Montavon, G. Saucy, S. F. Schaeren, U. Schwieter, and O. Isler, *Helv. Chim. Acta*, 1959, **42**, 847.

ε_{436} 165 000); $\lambda_{max.}$ (hexane) 450, 423, and 404 nm; $\nu_{max.}$ (KBr) 3 585, 3 550, 3 040, 2 930, 2 867, 2 150, 960, and 810 cm^{-1}; δ see Table 3; *m/e* 568.430 ($M^{+\cdot}$; $C_{40}H_{56}O_2$ requires *m/e* 568.428).

Methyl 5,6-threo-5,6-*Dihydroxy*-5,6-*dihydroretinoate* (14a).—A solution of methyl (*E*)-3-methyl-4-oxobut-2-enoate (13) [21] (2.76 g) and the Wittig salt (33) and (34) (11.6 g) in 1,2-epoxybutane (20 ml) was stirred at 40—50 °C for 6 h, and then evaporated. Chromatography of the residue on silica gel (1 kg, 10% deactivated), using gradient elution with acetone (1—16%) in light petroleum, gave *methyl all*-trans-5,6-*threo*-5,6-*dihydroxy*-5,6-*dihydroretinoate* which crystallised from benzene–light petroleum as yellow needles (1.0 g), m.p. 135—137 °C; $\lambda_{max.}$ (EtOH) 347 nm (ε 50 000); $\nu_{max.}$ (KBr) 3 600, 3 520, 2 940, 1 685, 1 605, 970, and 963 cm^{-1}; δ see Table 3; *m/e* 348.229 ($M^{+\cdot}$; $C_{21}H_{32}O_4$ requires 348.230, 40%), 330 (3%), 317 (6%), 316 (10%), 221 (34%), 189 (23%), 178 (13%), 161 (50%), 127 (70%), 109 (100%), and 106 (34%).

The eluate preceding that containing the all-*trans* isomer, on evaporation followed by preparative t.l.c. (12% acetone in light petroleum) of the residue, yielded a mixture (1.5 g) of the *cis*-9- and *trans*-9-isomers; $\lambda_{max.}$ (EtOH) 344 and 246 nm; in addition to the bands due to the all-*trans* isomer, the n.m r. spectrum contained signals at δ 1.96 (s, 9-Me) and 5.86br (s, 1 H, 14-H) attributable to the *cis*-9-isomer. Repeated stereomutation in boiling benzene, containing a trace of iodine, in front of a tungsten filament lamp, evaporation, and trituration of the residue with light petroleum, gave a solid which was crystallised from benzene–light petroleum to give more of the all-*trans*-isomer (1.2 g).

Methyl 5,6-erythro-5,6-*Dihydroxy*-5,6-*dihydroretinoate* (14b).—Elution of the more-polar yellow band from the silica gel chromatogram described above, evaporation, and preparative t.l.c. (15% acetone in light petroleum) of the residue gave a gum (140 mg, 2%) which crystallised from benzene–light petroleum to give the all-*trans* isomer of the erythro-*glycol*, m.p. 128—133 °C; $\lambda_{max.}$ (EtOH) 346 nm; $\nu_{max.}$ (film) 3 470, 2 940, 1 700, 970, and 956 cm^{-1}; δ see Table 3: *m/e* 348.230 ($M^{+\cdot}$; $C_{21}H_{32}O_4$ requires 348.230, 62%), 330 (5%), 317 (11%), 316 (16%), 273 (18%), 255 (9%), 205 (18%), 191 (25%), 183 (38%), 165 (43%), 159 (43%), 125 (100%), and 106 (80%).

6,6,10-*Trimethyldodeca*-8,10-*diene*-2,7-*dione* (35).—Elution of the least-polar product from the preparation of the retinoates described above gave the *dienedione* which consisted mainly of the *trans*,*trans*-isomer; $\lambda_{max.}$ (EtOH) 284 nm; $\nu_{max.}$ (film) 2 955, 1 710, 1 675, 1 620, and 980 cm^{-1}; δ see Table 1; *m/e* 236 ($M^{+\cdot}$; $C_{15}H_{24}O_2$ requires 236, 6%), 211 (1%), 208 (2%), 152 (13%), 127 (7%), 109 (100%), 81 (40%), and 69 (18%). The formation of the dienedione was enhanced when the Wittig reaction was carried out at 100 °C.

Methyl 5,6-threo-6-*Hydroxy*-5-*trimethylsilyloxy*-5,6-*dihydroretinoate* (15a).—(i) Hexamethyldisilazane (0.6 ml) and trimethylchlorosilane (0.4 ml) were added to a solution of crystalline methyl all-*trans*-5,6-*threo*-5,6-dihydroxy-5,6-dihydroretinoate (6 mg) in pyridine (0.7 ml). T.l.c. indicated that conversion into the mono-derivative was complete after 2 h. The mixture was kept at 20 °C for 7 days but there was no evidence (t.l.c.) of the formation of a bis-derivative. The mixture was evaporated, and the residue was extracted with ether. Evaporation of the ethereal extract, and preparative t.l.c. (8% acetone in light petroleum) gave the *monotrimethylsilyl ether* as a pale yellow gum; *m/e* 420 ($M^{+\cdot}$; $C_{24}H_{40}O_4Si$ requires 420, 100%), 405 (2.5%), 330 (3%), 265 (9%), 186 (24%), 161 (28%), 159 (16%), 156 (20%), 143 (28%), 133 (26%), and 109 (35%).

Hydrolysis. A solution (0.4 ml) of dilute hydrochloric acid (2 M; 0.3 ml) in methanol (2 ml) was added to the ether (1 mg) and the mixture was shaken for 15 min. T.l.c. revealed the formation in high yield of a polar product which did not separate on mixed t.l.c. from an authentic sample of methyl *threo*-5,6-dihydroxy-5,6-dihydroretinoate.

(ii) A mixture of the trimethylsilyl derivative (57 mg) of the Wittig salt (33) and (34) and methyl (*E*)-2-methyl-4-oxobut-2-enoate [21] (16 mg) in 1,2-epoxybutane (1 ml) was stirred at 50—60 °C for 4 h. Evaporation, and preparative t.l.c. (7% acetone in light petroleum) of the residue gave the required monotrimethylsilyl ether (24 mg) as the main product; its t.l.c. properties were identical with a sample from (i). A small amount of a much less polar yellow product was observed which was identified by mixed t.l.c. (1% acetone in light petroleum) as the *erythro*-bistrimethylsilyl derivative. Hydrolysis gave (mixed t.l.c.) methyl 5,6-*erythro*-5,6-dihydroxy-5,6-dihydroretinoate.

Methyl 5,6-erythro-6-*Hydroxy*-5-*trimethylsilyloxy*- *and* 5,6-*Bistrimethylsilyloxy*-5,6-*dihydroretinoate* (15b) *and* (16).—Trimethylsilylation of methyl *erythro*-5,6-dihydroxy-5,6-dihydroretinoate (6 mg) for 7 days as described above for the *threo*-isomer, and preparative t.l.c. (8% acetone in light petroleum) gave two major yellow products. The more polar was identified as the *monotrimethylsilyl ether*; *m/e* 420 (M^+; 100%), 405 (6%), 402 (4.5%), 289 (12%), 388 (18%), 377 (14%), 345 (9%), 330 (2.5%), 287 (14%), 255 (40%), 197 (28%), 161 (34%), 159 (60%), 147 (34%), 145 (34%), 143 (34%), 125 (62%), 117 (44%), and 107 (44%). Further t.l.c. of the less polar product, using 1% acetone in light petroleum as eluant, gave the *bistrimethylsilyl ether*; *m/e* 492 ($M^{+\cdot}$; $C_{27}H_{42}O_4Si_2$ requires 492; 100%), 477 (4%), 461 (3%), 402 (2%), 387 (1.5%), 285 (4%), 231 (4%), 197 (4%), 173 (4.5%), 171 (3.5%), 159 (7.5%), 147 (12%), and 117 (13%). Both ethers on hydrolysis, as described above for the *threo*-mono-ether, regenerated the *erythro*-glycol (no separation on mixed t.l.c. with an authentic specimen).

5-(1′,2′-*Dihydroxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpent*-cis-2-*en*-4-*yn*-1-*ol* (44a) *and* (44b).—(i) To a solution of ethylmagnesium bromide (from 3.45 g of magnesium and 16.4 g of ethyl bromide) in ether (150 ml), one of 3-methylpent-*cis*-2-en-4-yn-1-ol [24] (4.8 g) in dichloromethane (100 ml) was added during 1 h at 20 °C, and the mixture was then stirred for a further hour. A solution of 2-hydroxy-2,6,6-trimethylcyclohexanone [23] (5.2 g) in dichloromethane (100 ml) was added during 20 min and the mixture was stirred under reflux for 16 h and then cooled. Saturated aqueous ammonium chloride was added to decompose the Grignard complex and the product was isolated with ether. Preparative t.l.c. (Kieselgel HF_{254}), using 33% acetone in light petroleum (b.p. 60—80 °C) as eluant, gave the triols as a colourless oil (7.4 g). When kept for 3 weeks the oil partially crystallised. The crystals were separated, washed with chloroform, and recrystallised from ether–light petroleum (b.p. 40—60 °C) to give the 1′,2′-threo-*triol* as colourless prisms, m.p. 136—137 °C; $\lambda_{max.}$ (EtOH) 229 nm (ε 12 500); $\nu_{max.}$ (CCl_4) 3 619, 2 940, 1 638, and 960 cm^{-1}; δ see Table 2 (Found: C, 71.3; H, 9.75. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.6%).

(ii) To a solution of lithium amide (from 2.7 g of lithium in the presence of 300 mg of ferric nitrate) in liquid ammonia (300 ml), 3-methylpent-*cis*-2-en-4-yn-1-ol [24] (15.0 g) in ether

(60 ml) was added. The ammonia was allowed to evaporate whilst ether (120 ml) was slowly added. A solution of 2-hydroxy-2,6,6-trimethylcyclohexanone [23] (5.0 g) in ether (50 ml) was added slowly during 20 min and the mixture was stirred for 2 h at 20 °C. Saturated aqueous ammonium chloride was added and the product isolated with ether. The excess of methylpentenynol was evaporated at 40 °C/0.02 mmHg. Chromatography of the residue as described above gave the triols as a colourless oil (5.0 g). Crystallisation from a mixture of ether and light petroleum (b.p. 40—60 °C) gave the 1′,2′-erythro-*triol*, m.p. 75—76 °C; $\lambda_{max.}$ (EtOH) 229 nm (ε 12 500); $\nu_{max.}$ (CCl_4) 3 626, 3 412, 2 940, 1 635, and 980 cm^{-1} (Found: C, 71.3; H, 9.6. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.6%).

1-*Acetoxy*-5-(1′,2′-threo-1′,2′-*dihydroxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpent*-cis-2-*en*-4-*yne* (51a).—Acetic anhydride (0.2 ml) was added to a solution of the triol (44a) (46 mg) in pyridine (0.5 ml), and the mixture was kept at 20 °C for 90 h. Water was added and the product was isolated with ether to give the *acetate* as a colourless glass; $\lambda_{max.}$ (EtOH) 229 nm (ε 13 000); $\nu_{max.}$ 3 470, 2 920, 1 743, 1 452, 962, and 930 cm^{-1}; δ see Table 2; *m/e* 294 ($M^{+\cdot}$) and 234 (M − 60) (Found: *m/e* 234.161. $C_{15}H_{22}O_2$ requires *m/e* 234.162).

5-(1′,2′-threo-1′,2′-*Dihydroxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpent*-trans-2-*en*-4-*yn*-1-*ol* (45a).—A Grignard condensation between 2-hydroxy-2,6,6-trimethylcyclohexanone (2.5 g) and 3-methylpent-*trans*-2-en-4-yn-1-ol [24] (4.0 g) was carried out as described above for the *cis*-isomer. Chromatography of the crude product on a column of alumina (Grade IV, pH 4.5), using gradient elution from 60% ether to 20% acetone in light petroleum (b.p. 40—60 °C), gave a mixture of triols (2.0 g). Crystallisation from a mixture of ethyl acetate and light petroleum (b.p. 40—60 °C) gave the 1′,2′-threo-*triol* (300 mg), m.p. 156—157 °C; $\lambda_{max.}$ (EtOH) 229.5 nm (ε 13 000); $\nu_{max.}$ (KBr) 3 460, 3 270, 2 940, 2 220, 1 637, 940, 932, 860, and 805 cm^{-1}; δ see Table 2 (Found: C, 71.2; H, 9.75. $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.6%).

5-(1′-*Hydroxy*-2′,2′,6′-*trimethylcyclohexyl*)-3-*methylpent*-cis-2-*en*-4-*yn*-1-*ol* (46).—A solution of 3-methylpent-*cis*-2-en-4-yn-1-ol (28.8 g) in dichloromethane (300 ml) was added during 1 h at 20 °C to a solution of ethylmagnesium bromide (from 14.7 g of magnesium and 65.4 g of ethyl bromide) in ether (300 ml), and the mixture was stirred for a further hour. 2,2,6-Trimethylcyclohexanone (28.0 g) in dichloromethane (80 ml) was added during 30 min and the mixture was then stirred under reflux for 16 h. Decomposition of the complex, isolation of the product in the usual way, and distillation gave the glycol as a pale yellow viscous oil (35 g), b.p. 132—133 °C/0.1 mmHg, n_D^{22} 1.519 1; $\lambda_{max.}$ (EtOH) 228 nm (ε 12 000); $\nu_{max.}$ (film) 3 400, 2 930, 2 260, 1 635, 968, 850, and 798 cm^{-1}; δ see Table 2. A sample kept at 0 °C solidified and, after recrystallisation from ether–light petroleum had m.p. 87—89 °C (Found: 75.9; H, 10.0. Calc. for $C_{15}H_{24}O_2$: C, 76.2; H, 10.2%) (Inhoffen and Erdmann [38] give b.p. 121—123 °C/0.01 mmHg; m.p. 88—89 °C). Acetylation of the diols with acetic anhydride in pyridine gave (86%) a mixture of the primary monoacetates (Found: C, 73.6; H, 9.5. Calc. for $C_{17}H_{26}O_3$: C, 73.3; H, 9.4%).

5-(1′-*Hydroxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpenta*-cis-2,trans-4-*dien*-1-*ol* (52).—The preceding glycol (800 mg) in ether (10 ml) was added slowly to a stirred solution of lithium aluminium hydride (500 mg) in ether (60 ml) at 20 °C. The mixture was stirred for 6 h at 20 °C, and the excess of hydride was decomposed by the addition of saturated aqueous ammonium chloride. Isolation of the product with ether, and preparative t.l.c. (Kieselgel HF_{254}; 20% acetone in light petroleum), gave the two diastereoisomers of the *cis,trans*-diene. The more polar (186 mg) and the less polar (102 mg) had different n.m.r. spectra (see Table 1).

1-*Acetoxy*-3-*methyl*-5-(2′,6′,6′-*Trimethylcyclohex*-1′-*enyl*)-*pent*-cis-2-*en*-4-*yne* (48).—Acetic anhydride (16.0 g) was added to the preceding enyne glycol (46) (30.0 g) in acetic acid (70 ml). The mixture was boiled under reflux and the reaction was monitored by u.v. light absorption spectroscopy. After 7 h the mixture was cooled, poured onto crushed ice, and the product was isolated with ether. Preparative t.l.c. (8% acetone in light petroleum), and distillation gave the enynene acetate as an oil (17.0 g), b.p. (bath temp.) 85—90 °C/0.05 mmHg; $\lambda_{max.}$ (EtOH) 274 nm (ε 11 000); $\nu_{max.}$ (film) 2 900, 2 210, 1 735, 1 610, and 943 cm^{-1}; δ see Table 2 (Found: C, 77.7; H, 9.4. $C_{17}H_{24}O_2$ requires C, 78.4; H, 9.3%). Hydrolysis of a small sample with 20% methanolic potassium hydroxide for 2 h at 20 °C gave (90%) the corresponding alcohol which had the expected spectral properties.

Further chromatography of the polar fractions from the above t.l.c. yielded both diastereoisomers of 1-acetoxy-5-(1′-hydroxy-2′,2′,6′-trimethylcyclohexyl)-3-methylpent-*cis*-2-en-4-yne. The less polar had b.p. (bath temp.) 90 °C/0.05 mmHg; $\nu_{max.}$ (film) 3 540, 1 740, 1 680, 1 640, and 1 245 cm^{-1}; δ see Table 2. The more polar had b.p. (bath temp.) 90 °C/0.05 mmHg; $\nu_{max.}$ (film) 3 540, 1 742, 1 640, and 1 243 cm^{-1}; δ see Table 2.

1-*Acetoxy*-5-(1′,2′-*Epoxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpent*-cis-2-*en*-4-*yne* (49).—The preceding enynene acetate (5.0 g) in benzene (15 ml) was added to monoperphthalic acid in benzene (260 ml containing 0.02 g-atom of active oxygen), and the mixture was kept at 15 °C for 48 h. The solution was washed with saturated aqueous sodium hydrogen carbonate, dried, and evaporated. Preparative t.l.c. (Kieselgel HF_{254}: 10% acetone in light petroleum), and distillation gave the epoxide as an oil (2.2 g), b.p. (bath temp.) 125—130 °C/0.05 mmHg; $\lambda_{max.}$ (EtOH) 233 nm (ε 13 700); $\nu_{max.}$ (film) 2 950, 2 250, 1 735, 1 635, 978, and 897 cm^{-1}; δ see Table 2; *m/e* 276 ($M^{+\cdot}$; $C_{17}H_{24}O_3$ requires 276; 4%), 260 (1%), 233 (18%), and 216 (18%).

1-*Acetoxy*-5-(1′,2′-erythro-1′,2′-*dihydroxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpent*-cis-2-*en*-4-*yne* (51b).— A dilute solution (6 ml) of perchloric acid (1 drop of 60% perchloric acid in 25 ml of water) was added to the preceding epoxide (90 mg) in tetrahydrofuran (1 ml) and diglyme (1 ml). Acetone (5 ml) was added and the solution was heated at 70 °C for 3 h and then cooled. Isolation of the product in the usual way, and preparative t.l.c. (Kieselgel HF_{254}; 33% acetone in light petroleum as eluant) gave the erythro-*glycol* as an oil (60 mg); $\lambda_{max.}$ 229.5 nm (ε 13 000); $\nu_{max.}$ (CCl_4) 3 630, 3 585, 3 540, 2 958, 2 936, 2 875, 1 750, and 970 cm^{-1}; δ see Table 2; *m/e* 294 ($M^{+\cdot}$; $C_{17}H_{26}O_4$ requires 294).

5-(1′,2′-*Epoxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpent*-cis-2-*en*-4-*yn*-1-*ol* (50).—The preceding epoxide (1.27 g) was added slowly to a stirred suspension of lithium aluminium hydride (173 mg) in ether (30 ml) at −70 °C. The mixture was allowed to warm to 20 °C and the excess of

[38] H. H. Inhoffen and D. Erdmann, *Annalen*, 1956, **598**, 51.

hydride was decomposed by the addition of 20% aqueous potassium sodium tartrate. Isolation of the product in the usual way, t.l.c. (Kieselgel HF_{254}), and distillation gave the *alcohol* as a colourless oil (800 mg), b.p. (bath temp.) 135—140 °C/0.05 mmHg, $n_D^{17.5}$ 1.511 9; $\lambda_{max.}$ (EtOH) 231.5 nm (ε 10 000); $\nu_{max.}$ (film) 3 410, 2 975, 2 870, 2 210, 1 630, and 897 cm^{-1}; δ see Table 2; *m/e* 234.161 3 ($M^{+\cdot}$; $C_{15}H_{22}O_2$ requires 234.161 4).

5-(1′2′-*Epoxy*-2′,6′,6′-*trimethylcyclohexyl*)-3-*methylpenta*-cis-2,trans-4-*dien*-1-*ol* (53).—The preceding enyne alcohol (265 mg) in ether (20 ml) was added slowly to a stirred suspension of lithium aluminium hydride (100 mg) in ether (40 ml) at −70 °C. The mixture was allowed to warm to 20 °C and then the ether was distilled off whilst tetrahydrofuran (40 ml) was added. The mixture was stirred under reflux for 1.5 h, and then cooled. The excess of hydride was decomposed by the addition of 20% aqueous potassium sodium tartrate, and the product was isolated with ether. Preparative t.l.c. (Kieselgel HF_{254}; 15% acetone in light petroleum) gave the *diene alcohol* (35 mg); δ see Table 2; *m/e* 236 ($M^{+\cdot}$; $C_{15}H_{24}O_2$ requires *m/e* 236).

1,2-*Dihydroxy*-1,3,3-*trimethylcyclohexane* (61).—(i) The recrystallised *cis*-2-threo-glycol (24a), m.p. 136—137 °C, (100 mg) was heated at 100 °C under reduced pressure (12 mm). The *diol* was formed as a crystalline sublimate (55 mg), m.p. 128 °C; $\nu_{max.}$ (KBr) 3 430, 3 320, 2 930, 1 451, 1 364, 1 318, 1 147, 1 061, 943, and 801 cm^{-1}; δ 0.98 (s, 3 H), 1.01 (s, 3 H), 1.24 (s, 3 H), *ca.* 1.40 (m, 6 H), and 3.00 (m, but singlet after deuteriation, 1 H) (Found: C, 68.2; H, 11.3. $C_9H_{18}O_2$ requires C, 68.3; H, 11.5%).

(ii) The recrystallised *cis*-2-*threo*-glycol (24a) (95 mg) in acetone (8 ml) was shaken with manganese dioxide (500 mg) for 16 h. The dioxide and solvent were removed. N.m.r. analysis showed the major product to be the diol described in (i).

4-(1′,2′-threo-1′,2′-*Dihydroxy*-2′,6′,6′-*trimethylcyclohexyl*)-*but*-trans-3-*en*-2-*one* (19).—Ozonised oxygen (*ca.* 3% O_3) was passed through a solution of the *cis*-2,*trans*-4-triol (24a) (200 mg) in methanol (5 ml) at −70 °C for 45 min. The solution was flushed with nitrogen, warmed to 0 °C and a solution of sodium borohydride (700 mg) in 50% aqueous methanol (20 ml) was added. The mixture was stirred at 20 °C for 2 h and then diluted with water. Isolation of the product with ether gave a colourless gum (140 mg). Crystallisation from ether–light petroleum gave the threo-*dihydroxy*-*ketone* (100 mg) as needles, m.p. 107.5—108.5 °C; $\lambda_{max.}$ (EtOH) 233 nm; $\nu_{max.}$ (CCl_4) 3 620, 3 460, 2 922, 2 870, 1 680, 1 628, and 990 cm^{-1}; δ see Table 1); *m/e* 226.156 ($C_{13}H_{22}O_3$ requires *m/e* 226.157). The product was identical with a sample obtained by hydration of 5,6-epoxy-5,6-dihydro-β-ionone.[15]

1,2-threo-1,2-*Dihydroxy*-2-*hydroxymethyl*-1,3,3-*trimethylcyclohexane* (30).—(i) The *cis*-2-,*trans*-4-triol (24a) (135 mg) in methanol (4 ml) was ozonised for 6 h at −18 °C to 0 °C. A solution of sodium borohydride (700 mg) in 50% aqueous methanol (8 ml) was added and the mixture stirred at 20 °C for 18 h. Isolation of the product with ether, and preparative t.l.c. (Kieselgel; 30% acetone in light petroleum), gave the *borate ester* (30 mg) of the required triol as prisms, m.p. 127—129 °C; $\nu_{max.}$ (Nujol) 3 400 cm^{-1}; δ ([$^2H_6$]DMSO) 0.80 (s, 3 H, Me), 1.00 (s, 3 H, Me), 1.03 (s, 3 H, Me), 1.20—1.90 (m, 7 H, $CH_2{\cdot}CH_2{\cdot}CH_2$ and OH), 3.83 (d, J = 10 Hz, 1 H, CH_2O), 4.09 (d, J = 10 Hz, 1 H, CH_2O) and 4.37 (s, 1 H, OH); δ ([$^2H_6$]acetone) 0.89 (s, 3 H), 1.10 (s, 3 H), 1.17 (s, 3 H), 1.20—1.90 (m, 6 H), 2.84br (s, 2 H), 3.99 (d, J = 10 Hz, 1 H), and 4.28 (d, J = 10 Hz, 1 H); *m/e* 214.137 ($M^{+\cdot}$; $C_{10}H_{19}{}^{11}BO_4$ requires *m/e* 214.138).

(ii) The triol (24a) (100 mg) was ozonised as in the previous experiment. A solution of the crude product (after hydride reduction) and sodium hydroxide (250 mg) in ether was boiled under reflux for 45 min and then kept at 20 °C for 18 h. Isolation of the product, preparative t.l.c. (Kieselgel, 20% acetone in light petroleum), and crystallisation from ether–light petroleum, gave the C_{10}-triol (10 mg) as monoclinic crystals, m.p. 96 °C; δ([$^2H_6$]DMSO) 0.85 (s, 3 H, Me), 1.10 (s, 3 H, Me), 1.13 (s, 3 H, Me), 1.40—1.90 (m, 6 H, $CH_2{\cdot}CH_2{\cdot}CH_2$), 3.65 (ABX multiplet, J_{AB} = *ca.* 11 Hz, $J_{AX} = J_{BX}$ = *ca.* 5 Hz, 2 H, CH_2OH) and 5.00 (t, J = 5 Hz, 1 H, $CH_2{\cdot}OH$). The m.p. was undepressed on admixture with an authentic sample, m.p. 98—100 °C, which had identical n.m.r. and t.l.c. properties, prepared from β-cyclocitral (lit.,[13b] m.p. 101—103 °C).

2,6,6-*Trimethyl*-2-*trimethylsiloxycyclohexanone* (41).—2,2,-6-Trimethylcyclohexanone was converted into 2-hydroxy-2,6,6-trimethylcyclohexanone, b.p. 110—120 °C/18 mmHg; $\nu_{max.}$ (film) 3 480, 1 700, and 1 160 cm^{-1}; δ 1.15 (s, 3 H, 6-Me), 1.22 (s, 3 H, 6-Me), 1.40 (s, 3 H, 2-Me), 1.60—1.90 (m, 6 H, $CH_2{\cdot}CH_2{\cdot}CH_2$), and 5.90br (s, 1 H, OH) (lit.,[23] b.p. 93 °C/15 mmHg).

Hexamethyldisilazane (6 ml) and trimethylsilyl chloride (4 ml) were added to a solution of the hydroxy-ketone (3.0 g) in pyridine (20 ml). The mixture was kept at 20 °C for 18 h, then cooled to 0 °C. Water was added and the product was extracted with light petroleum (b.p. 40—60°). The extract was dried and evaporated, and the residue was distilled to give the *trimethylsiloxy-ketone* as a colourless oil (3.2 g), b.p. 100—110 °C/18 mmHg; $\nu_{max.}$ (film) 2 950, 1 710, 1 455, 1 375, 2 150, 1 177, 1 135, 1 085, 1 050, 990, 870, 850, and 755 cm^{-1}; δ 0.10 (s, 9 H, $SiMe_3$), 1.07 (s, 3 H, 6-Me), 1.27 (s, 3 H, 6-Me), 1.33 (s, 3 H, 2-Me), 1.50—1.90 (m, 6 H, $CH_2{\cdot}CH_2{\cdot}CH_2$); *m/e* 228.154 ($M^{+\cdot}$; $C_{12}H_{24}O_2Si$ requires *m/e* 228.155).

5-(1′,2′-erythro-1′-*Hydroxy*-2′,6′,6′-*trimethyl*-2′-*trimethylsiloxycyclohexyl*)-3-*methylpent*-cis-2-*en*-4-*yn*-1-*ol* (54).—A solution of 3-methylpent-*cis*-2-en-4-yn-1-ol (3.6 g) in dichloromethane (60 ml) was added during 1 h to ethylmagnesium bromide (from magnesium and 8.5 g of ethyl bromide) in ether (100 ml). The mixture was boiled for 5 min and then stirred at 20 °C for 1 h. 2-Trimethylsiloxy-2,6,6-trimethylcyclohexanone (4.0 g) in dichloromethane (50 ml) was added during 20 min. The mixture was boiled under reflux for 18 h and then cooled. Saturated aqueous ammonium chloride was added and the product isolated with ether. Excess of methylpentenynol was evaporated at 40 °C/0.1 mmHg, leaving the *glycol* (7.5 g) as a pale yellow solid; δ see Table 2; *m/e* 324 ($M^{+\cdot}$; $C_{18}H_{32}O_3Si$ requires *m/e* 324). The same product was obtained in a Nef reaction.

5-(1′,2′-erythro-1′-*Hydroxy*-2′,6′,6′-*trimethyl*-2′-*trimethylsiloxycyclohexyl*)-3-*methylpent*-trans-2-*en*-4-*yn*-1-*ol* (55).—A Grignard reaction between 2-trimethylsiloxy-2,6,6-trimethylcyclohexanone (1.75 g) and 3-methylpent-*trans*-2-en-4-yn-1-ol (1.6 g), as described above for the *cis*-isomer, gave a yellow solid (3.0 g). Preparative t.l.c. (20% acetone in light petroleum) and crystallisation from ether–light petroleum gave the *glycol* (2.01 g) as colourless needles, m.p. 80—82 °C; $\lambda_{max.}$ (EtOH) 230 nm (ε 14 000); δ see Table 2; *m/e* 324.211 ($M^{+\cdot}$; $C_{18}H_{32}O_3Si$ requires *m/e* 324.212).

1-*Acetoxy*-5-(1′-*hydroxy*-2′,6′,6′-*trimethyl*-2′-*trimethylsiloxycyclohexyl*)-3-*methylpent*-cis-2-*en*-4-*yne* (56a) *and*

(56b).—(i) Hexamethyldisilazane (0.3 ml) and trimethylsilyl chloride (0.2 ml) were added to the glycol acetate (51a) (20 mg) in pyridine (1 ml). The mixture was kept at 20 °C for 18 h, then cooled to 0 °C and diluted with water. Isolation of the product with light petroleum (b.p. 40—60 °C) gave the threo-*derivative* (56a) as a colourless gum; $\lambda_{max.}$ (EtOH) 229.5 nm (ε 13 000); $\nu_{max.}$ ($CHCl_3$) 3 520, 3 450, 1 735, 1 456, 963, 891, and 840 cm^{-1}; δ see Table 2; *m/e* 366.222 ($M^{+\cdot}$; $C_{20}H_{35}O_4Si$ requires *m/e* 366.223).

(ii) Acetic anhydride (0.5 ml) was added to a solution of the trimethylsiloxy-diol (54) (50 mg) in chloroform (1 ml) and pyridine (1 ml), and the mixture was kept at 20 °C for 4 h. Ice cold water and ether were added and the mixture was shaken vigorously for 5 min to decompose the excess of anhydride. Isolation of the product in the usual way, and t.l.c. (15% acetone–light petroleum) gave the erythro-*derivative* (56b) as a colourless gum; $\lambda_{max.}$ (EtOH) 229.5 nm (ε 13 000); $\nu_{max.}$ (film) 3 690, 2 990, 1 744, 1 635, 1 453, 970, 893, 868, 840, and 755 cm^{-1}; δ see Table 2; *m/e* 366 ($M^{+\cdot}$; $C_{20}H_{35}O_4Si$ requires *m/e* 366).

Hydrolysis of the 5-(1′,2′-erythro-1′-*Hydroxy*-2′,6′,6′-*trimethyl*-2-*trimethylsiloxycyclohexyl*)-3-*methylpent*-2-*en*-4-*yn*-1-*ols* (54) and (55).—(i) The *trans*-2-1′,2′-*erythro*-trimethylsilyl derivative (55) (100 mg) was dissolved in tetrahydrofuran (4 ml), and a small excess of lithium aluminium hydride was added. The mixture was kept at 20 °C for 2 min, excess of saturated aqueous potassium sodium tartrate was added slowly, and the mixture was stirred for 30 min. Isolation of the product with ether, and preparative t.l.c. (25% acetone in light petroleum) gave a crystalline solid (65 mg), m.p. 79—81 °C, with t.l.c. and spectral properties identical with those of the starting material, and a more-polar colourless gum (25 mg); n.m.r. analysis indicated that this consisted of 75% of the 1′,2′-*erythro*-triol (45b) and 25% of the 1′,2′-*threo*-triol (45a).

(ii) Repetition of the above experiment with the *cis*-2-isomer (54) resulted in *ca.* 30% hydrolysis to give a mixture containing (n.m.r. analysis) 80% of the 1′,2′-*erythro*-triol (44b) and 20% of the 1′,2′-*threo*-triol (44a).

(iii) The *trans*-2-trimethylsilyl derivative (100 mg) was shaken with 2M-hydrochloric acid for 20 h at 20 °C. Isolation of the product in the usual way gave a mixture containing (n.m.r. analysis) 60% of the 1′,2′-*erythro*-triol (44b) and 40% of the *threo*-isomer (44a).

(iv) Repetition of the preceding experiment with the *cis*-2-isomer (54) gave a mixture containing (n.m.r. analysis) 80% of the 1′,2′-*erythro*-triol and 20% of the *threo*-isomer.

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