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SYNTHESIS OF LYCOPERSENE-2,3-EPOXIDE AND LYCOPERSENE-2,3:30,31-DIEPOXIDE

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The close parallel in the initial stages of triterpenoid and carotenoid biosynthesis is now known to extend as far as presqualene alcohol (5b)[1] and prephytoene alcohol (5c).[2] Although the C_{40} analogue of squalene (1) namely lycopersene (3) was early postulated[3] to be involved in the biosynthesis of the carotenoids, the natural occurence of lycopersene (3) was questioned by later careful investigations[4] which failed to identify it as a natural product. Furthermore, use[5] of [2-^{14}C]-MVA as a substrate in the presence of diphenylamine (inhibitor of carotenogenesis) resulted in accummulation of phytoene ($\Delta^{16,17}$ lycopersene) without detection of lycopersene (3). Recently there has been a claim[6] that (3) is an intermediate in carotenoid biosynthesis, however the current balance of opinion would support phytoene as being the first-formed acyclic tetraterpene. Goodwin and Britton[7] have isolated a number of epoxides of acyclic carotenoids from tomatoes but of particular relevance is the occurence of phytoene-2,3-epoxide ($\Delta^{16,17}$ lycopersene-2,3-epoxide) in which *in vivo* cyclisations[8,9] of the type undergone by squalene-2,3-epoxide (2) are precluded by the central double bond.

It was thus decided to synthesise lycopersene-2,3-epoxide (4) and the corresponding bis-terminal epoxide in order to compare them with the squalene analogues under both *in vitro* and *in vivo* cyclisation conditions. Lycopersene-2,3-epoxide (4) has the correct alignment of trisubstituted double bonds requisite for cyclisation to the carbonium ion (6c) having the apo-euphol ring system whereas acid treatment of squalene-2,3-epoxide (2) has been shown[10] to afford products derived from the malabaracane ion (7b).

All *trans*-geranylgeraniol (8) was transformed into the chloride (CCl_4-Ph_3P), without affecting the configuration of the double bonds, followed

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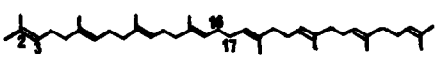

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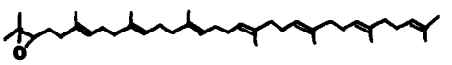

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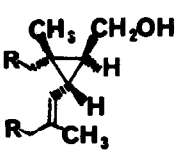

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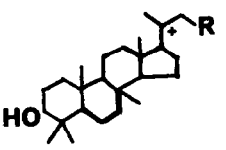

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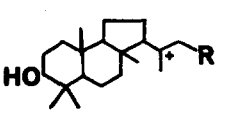

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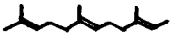

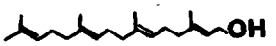

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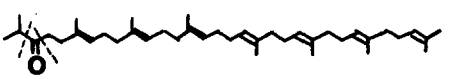

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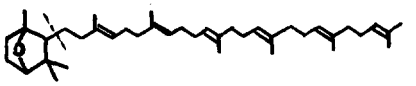

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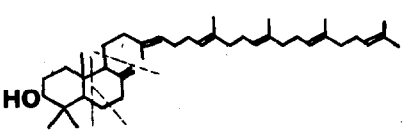

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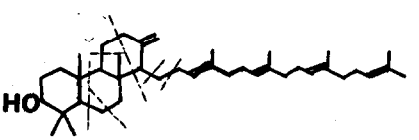

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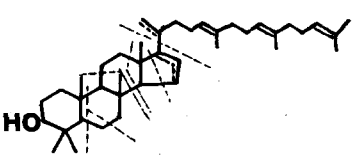

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by Wurtz coupling (Li-THF/100° C) to give all trans lycopersene (3) in 25% yield after purification via the thiourea clathrate. N.M.R. distinguishes [11] the 8 Me groups trans to the olefinic H (1.5ppm) from the 2 Me groups cis to the olefinic H (1.65ppm). Treatment of all trans-lycopersene (3) with NBS in aqueous glyme [12] gave 2-hydroxy-3-bromo-lycopersene [$Me_2C(OH)$-6H, s; 1.28ppm] and the bisbromohydrin resulting from attack at both terminal double bonds [$Me_2C(OH)$-12H, s; 1.28ppm]. These were separately converted (K_2CO_3-MeOH) into lycopersene-2,3-epoxide (4) and lycopersene-2,3:30,31-diepoxide whose structures were assigned from N.M.R., high resolution mass spectral data and comparison with the corresponding squalene epoxides.

Cyclisation (picric acid-nitromethane) [13] of lycopersene-2,3-epoxide (4) and squalene-2,3-epoxide (2) in parallel gave a similar range of products by TLC comparison. Preparative TLC (SiO_2, 5% EtOH in benzene) effected a separation of the 5 major isomeric acid transformation products of (4), $C_{40}H_{66}O$. The least polar compound (6%) was a ketone (ν max 1713cm^{-1}, no - OH) and assigned the structure (9) on the basis of mass spectral fragmentation [4] and N.M.R., which clearly showed a $(CH_3)_2CH$- grouping together with the expected signals due to the polyisoprene system. The second compound (7%) was neither an alcohol or a ketone, and was assigned the bicyclic ether structure (10) on the basis of N.M.R. and mass spectrometry [*], using accurate mass of the fragment ions, which showed the loss of the bicyclic moiety in addition to progressive fragmentation of allylic bonds. IR, NMR and mass spectral data supported the assignment of structures (11) and (12) to the two major alcohols obtained in 2% and 9% respectively. In the case of bicyclic alcohol (11), loss of the intact bicyclic moiety (m/e 207) was observed together with fragmentation of successive isoprene units. A complication in the case of the alcohol products, in contrast to (9) and (10), was the elimination of H_2O followed by an analogous fragmentation pattern, or retro Diels-Alder cleavage of ring A. With the alcohol (12) a fragment due to the tricyclic system was

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[*] Significant mass spectral fragmentations are indicated on the formulae.

observed together with an intense ion due to loss of the side chain and H_2O. The third alcohol obtained in 1% yield was assigned the structure (13) on the basis of IR and mass spectral data which exhibited a very intense ion at m/e 315 due to loss of the side chain and also a fragmentation involving loss of the side chain plus 39 mass units characteristic of C_{17} substituted steriods, although it was not possible to assign unambiguously the position of the double bond produced in the cyclisation process by deprotonation of (6c).

Further detailed examination of the cyclisation of lycopersene-2,3-epoxide leading to isolation of polycyclic tetraterpenes could prove valuable in an attempt to isolate lycopersene-derived tetraterpenes from natural sources.

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