Biogenetic-type Synthesis of (±)-Farnesiferol A and (±)-Farnesiferol C

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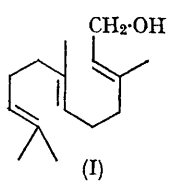
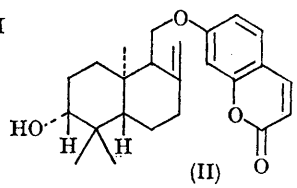
BECAUSE of the propitious structural relationship between farnesol (I) and the naturally occurring farnesiferols A, B, and C (II, III, and IV, respectively),[1] the biogenetic-type, laboratory conversion of the former, simple and available acyclic terpene into the latter, oxidized and cyclized systems was attempted, using synthetic methods under development in this laboratory.[2,3] Herein we report the total synthesis of (±)-farnesiferol A and (±)-farnesiferol C, proceeding along such lines.

Umbelliprenin (V),[4] the natural product required as a starting material, was prepared as the known[5,6] *trans, trans*-isomer (Va) by the action of umbelliferone sodium salt on *trans, trans*-farnesyl bromide in dimethylformamide. By similar means, the *trans, cis*-isomer[7] (Vb) was obtained from *trans,-cis*-farnesyl bromide, itself made by treatment of *trans, cis*-farnesol with phosphorus tribromide in petroleum. Each ether (Va or b) was ostensibly free from its geometrical isomer.[8] Terminal oxidation was realized by the reaction of (Va or b) with *N*-bromosuccinimide in aqueous ethylene



(I)



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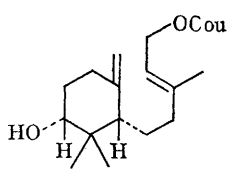

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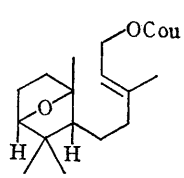
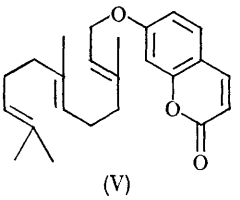
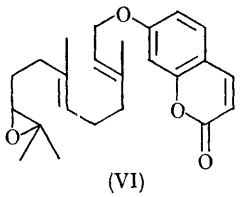


(IV)

glycol methyl ether,[2,9] and resulting halogenohydrins were separately converted by potassium carbonate–methanol into the *trans, trans*-(VIa) and *trans, cis*-umbelliprenin terminal epoxides.



(V)



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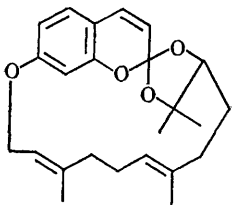
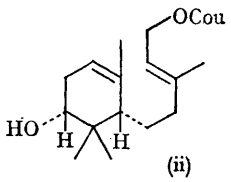
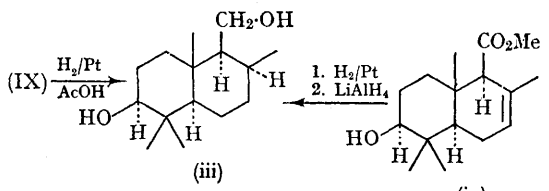


(i)

On being subjected to the action of 1·2 moles of boron trifluoride etherate[10] in benzene for 40 seconds at room temperature, the *trans*, *trans*-epoxide (VIa) gave rise to six identifiable products in a total yield of 65%. These include: acyclic ketone (m.p. 57—59·5°) formed by simple rearrangement of the starting epoxide (28%); fluorohydrin (non-crystalline) formed by ring-opening of the epoxide (7%); mixture of monocyclized alcohols (VII), m.p. 100—111° (9%);[11] rearranged, cyclized ketone (VIII), m.p. 141—143·5° (4%); mixture of bicyclized alcohols (IX), m.p. 91—109° (9%);[12] and bridged ether (IV), m.p.

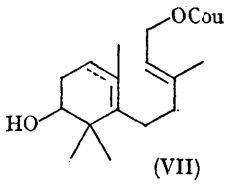


(ii)



(iii) (iv)

85—87·5° (8%), generated presumably by sequence (A).[13] Infrared and n.m.r. spectral, as well as t.l.c. (three solvent systems) comparison showed the synthetic bridged ester to be (±)-farnesiferol C. This identification was substantiated by lithium–ethylamine[14] reduction of synthetic and natural material: the hydrogenolysis products (IV, -OCou replaced by -H) were again indistinguishable by v.p.c. and i.r.



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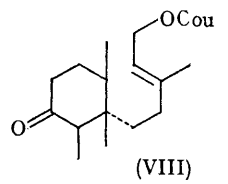
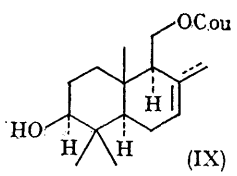
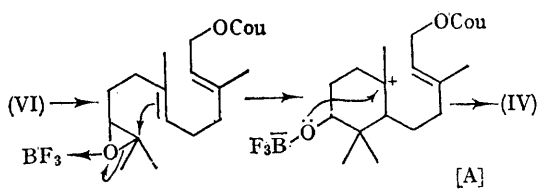


(VIII)

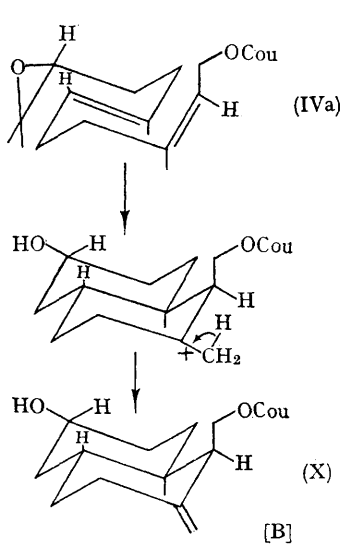


(IX)



[A]

In an experiment designed (scheme B) to produce farnesiferol A, *trans*,*cis*-umbelliprenin terminal epoxide (VIb) was subjected to reaction conditions approximating those described above for the cyclization of (VIa). After column-chromato-

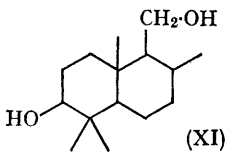


(IVa) (X)

[B]

graphic and t.l.c. isolation and purification, (±)-farnesiferol A (m.p. 152—156°) was obtained

in ~2% yield. Satisfactory comparison between synthetic and natural substances was again achieved by means of i.r., n.m.r., and t.l.c. (three solvent systems) techniques.[15] Furthermore, after catalytic hydrogenolysis,[1] the same (except for optical activity) saturated diol (XI), m.p. 179—181°, was obtained from both synthetic racemic and natural farnesiferol A.



(XI)

Ordinarily, when a low yield level is encountered, stereochemical arguments based on product isolation are unjustified. However, it is pertinent to note that, although (±)-farnesiferol A is produced from *trans*, *cis*-epoxide (VIb), this substance is *not* generated detectably from the *trans*, *trans*-epoxide (VIa). Rather, there is produced (by means of BF_3 etherate in benzene alone, or better, with added dimethylformamide–water[16]) exocyclic, bicyclic product (*ca.* 1% yield) which is *not* identical with farnesiferol A, but which is best regarded as the C-9 epimer of (II). Because of this particular set of results, we tentatively regard our experimental findings as supporting the stereochemistry shown in (X). This representation was established securely by Caglioti, Naef, Arigoni, and Jeger,[1] in all respects save one, the C-9 stereochemistry, which was provisionally assigned as indicated. The particular point is an important one, since the "*trans–syn*" arrangement in (X) is highly unusual in the terpene series.[17]

(*Received, April 26th*, 1966; *Com.* 278.)

[1] T. Caglioti, H. Naef, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, 1958, **41**, 2278; *ibid.*, 1959, **42**, 2557.
[2] E. E. van Tamelen and T. J. Curphey, *Tetrahedron Letters*, 1962, 121.
[3] E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *J. Amer. Chem. Soc.*, 1963, **85**, 3295.
[4] E. Späth and F. Vierhapper, *Ber.*, 1938, **71**, 1667.
[5] R. B. Bates, D. M. Gale, and B. J. Gruner, *J. Org. Chem.*, 1963, **28**, 1086.
[6] R. B. Bates, J. H. Schauble, and M. Souček, *Tetrahedron Letters*, 1963, 1683.
[7] In this paper "*cis*-" geometry refers to the allyl ether site.
[8] By n.m.r. spectroscopy.
[9] As indicated by the number of saturated (two) and olefinic (two) methyl groups appearing in the n.m.r. spectrum.
[10] When 0·1 mole of this reagent was used, there was formed a variety of products, including fluorohydrin (as above) and an isomer of (VI), which spectral and chemical characteristics, as well as molecular-weight data, indicated to possess structure (i).
[11] On the basis of only superficial comparison, farnesiferol D, for which structure (ii) has been entertained (personal communication from Professor D. Arigoni, Eidg. Technische Hochschule, Zurich), appears to be identical with a (±)-component of this synthetic mixture.
[12] Chemical proof for this assignment was gained by positive comparison of the hydrogenation–hydrogenolysis product (iii) with the diol resulting from hydrogenation, followed by lithium aluminium hydride reduction, of hydroxy-ester (iv), a substance of established structure and stereochemistry. (E. E. van Tamelen, M. Schwartz, E. J. Hessler, and A. Storni, *Chem. Comm.*, 1966, 409.
[13] Satisfactory elemental analyses were secured on all products described. Structural assignments are based largely on n.m.r. spectral properties, *per se* and by comparison with those of authentic model or related compounds.
[14] A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1957, 1969.
[15] Among other products formed, a bicyclic alcohol, distinctly different from that (IX) derived from the *trans*, *trans*-epoxide (VIa), was isolated in 5% yield. Although almost certainly the C-9 epimer of (IX), the product was not subject to close scrutiny.
[16] G. Ohloff and G. Schade, *Angew. Chem.*, 1962, **74**, 944.
[17] A. I. Scott, F. McCapra, F. Comer, S. A. Sutherland, D. W. Young, G. A. Sim, and G. Ferguson, *Tetrahedron*, 1964, **20**, 1339.