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STEREOCHEMICAL IMPLICATIONS IN SESQUITERPENE BIOGENESIS

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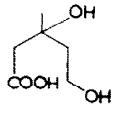
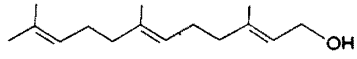
Abstract—The biogenesis of the sesquiterpenes is envisioned as a displacement of the allylic hydroxyl of farnesol by either of the isolated double bonds, giving rise to versatile 6-, 10-, or 11-membered ring intermediates. The medium-ring intermediates possess unique conformations which dictate the structure as well as stereochemistry of the sesquiterpenes derived from them by a variety of simple further reactions, notably double-bond cyclizations.

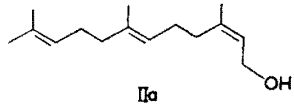
THE domain of terpene biogenesis, which was for too long a haven for undisciplined speculation, has been brilliantly codified and extended in recent years by the Swiss group of Ruzicka, first in an original and authoritative presentation of the entire field in 1953,[1] and then in the elegant conception of triterpene and steroid biogenesis[2] which must rank as a model of the critical approach to this speculative realm which is made possible by the application of modern reaction theory and the stereochemical limits implicit in it. An attempt is made here to apply this approach to sesquiterpene biogenesis, extending the ideas of Ruzicka[1] and Barton[3] on the involvement of large rings in order to incorporate stereochemical features.

It now seems clear that the actual isoprenoid unit utilized in terpene biosynthesis is mevalonic acid (I),[4] three molecules of which (or an appropriately activated simple derivative) can self-condense with decarboxylation directly to farnesol (II),* the simplest acyclic sesquiterpene. It should be noted that this conversion yields farnesol





II



IIa

without any change in oxidation state and with its double bonds all anchored at the tertiary carbons initially occupied by the hydroxyl in mevalonic acid. Farnesol is isolated from natural sources as a complex mixture of double bond isomers, but it is assumed here by analogy with squalene that the original farnesol produced from

* Unless otherwise indicated, all structures herein are taken from Sir John Simonsen, *The Terpenes* (2nd Ed.), Vols. III and V, Cambridge University Press (1952, 1957) and reference (3), and original references contained therein.

[1] L. Ruzicka, *Experientia* **9**, 357 (1953).

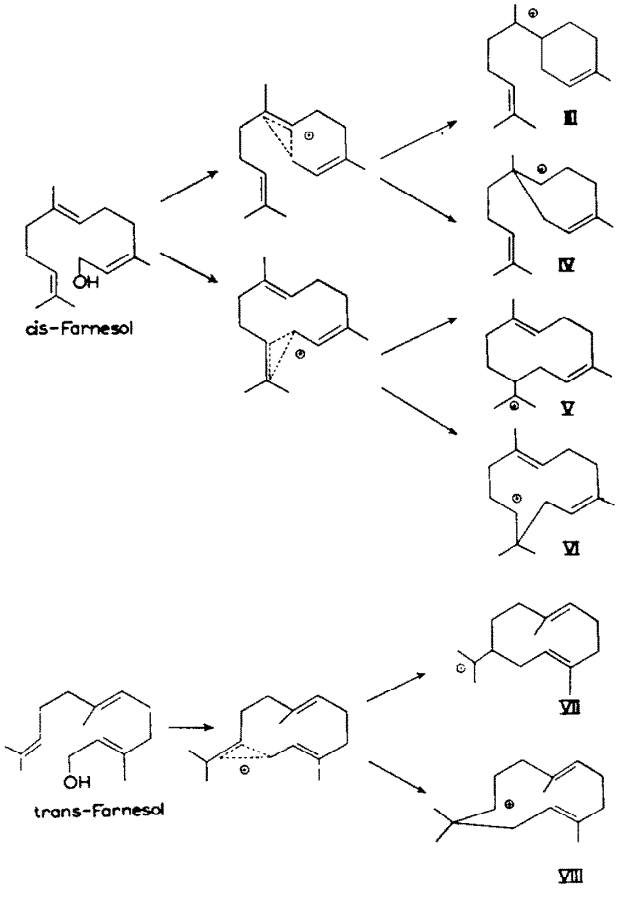
[2] A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, *Helv. Chim. Acta* **38**, 1890 (1955); L. Ruzicka in *Perspectives in Organic Chemistry* (ed. by A. Todd) pp. 265. Cambridge University Press (1956).

[3] D. H. R. Barton and P. de Mayo, *Quart. Rev.* **11**, 189 (1957).

[4] D. E. Wolf, C. H. Hoffman, P. E. Aldrich, H. R. Skeggs, L. D. Wright and K. Folkers, *J. Amer. Chem. Soc.* **78**, 4499 (1956); B. H. Amdur, H. Rilling and K. Bloch, *Ibid.* **79**, 2646 (1957); A. J. Birch, R. J. English, R. A. Massy-Westropp and H. Smith, *Proc. Chem. Soc.* 233 (1957).

mevalonic acid has the trans central bond. However, it is known that the allylic double bond can be found in both *cis*- and *trans*-orientations, via anionotropic conversion through nerolidol, the corresponding tertiary allylic alcohol. It will be argued below that *cis*-farnesol (IIa) or *trans*-farnesol (II) is a reasonable precursor for cyclization to all the cyclic sesquiterpenes.

The lowest and most common oxidation state of the cyclic sesquiterpenes is the same as that of farnesol, implying that the cyclization proceeds without oxidation and hence is a different process from that occurring in squalene cyclization to the triterpenes. The biogenesis of the sesquiterpenes from farnesol is considered[1] to involve ionization of the allylic hydroxyl and cyclization of one of the other double bonds to the cation thus formed. Thus, we may envision that one of the isolated double bonds can assist in the ionization of the allylic hydroxyl if its π-electrons can be oriented by coiling the chain so that they overlap with the generating π-orbital of the allylic cation.* Such species can then collapse by solvent attack or deprotonation to give the products expected from neutralization of the simple cations (III) through (VIII).

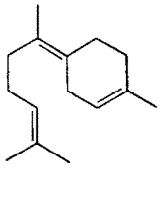


* The detailed mechanism is not germane to our purpose, for even if the cyclization is considered to be a simple displacement of —OH by the π-electrons of the double bond, the stereochemical requirements to be discussed will be the same.

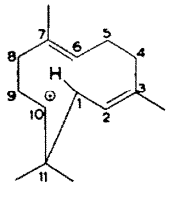
If we now consider in detail the various possibilities of cyclizing *cis*- and *trans*-farnesol, we can see that utilization of the central double bond is only possible with *cis*-farnesol, and that both electronic and steric factors combine to favor the intermediacy of the cation (III) rather than (IV). The monocyclic 6-ring sesquiterpenes do in fact all have this skeleton and generally possess the same pattern of oxidized sites on the skeleton, as in bisabolene (IIIa), which simply derives from (III) by deprotonation.

The question of utilization of the terminal double bond is more interesting. Models make it clear that *cis*- and *trans*-farnesol can each fold in such a way as to allow cyclization to products of the four intermediate cations (V), (VI), (VII) and (VIII). Furthermore, each of these ions has a *single, unique conformation dictated by maximum π-overlap and minimum steric interference* in the process of attack by the isolated double bond on the allylic alcohol. The *cis*, 10-ring cation (V) is, however, much more strained than the 11-ring cation (VI) and the models suggest that the latter will form by preference, i.e., steric rather than electronic control of the cyclization. From *trans*-farnesol, the cation (VII) is sterically as well as electronically favored over its rival (VIII). Thus the large body of sesquiterpenes which arise by cyclization involving the terminal bond can be shown to arise either from *cis*-farnesol via (VI) or from *trans*-farnesol via (VII).

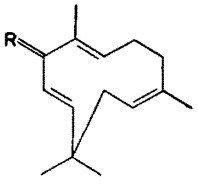
Models of the *cis*-cation (VIa) reveal two interesting features: (a) the double bonds are not very close to each other for internal cyclization; and (b) one of the hydrogens on C_1 is turned inside the ring, lying somewhat between C_6 and the cationic C_{10}. Examining the various ways in which the *cis*-cation can be neutralized, we find first that simple loss of a proton yields (IX), R = H_2, which fits the known facts for the sesquiterpene, humulene, and suggests the *cis* and *trans* orientation of the double bonds as well, the models indicating clearly a *trans* double bond at C_{9-10} as shown. The ketone (IX), R = O, is thus zerumbone, with the same *cis-trans-trans* geometry predicted for the double bonds. The *cis*-cation can also be neutralized by attack of a double bond on the C_{10} cation; the conformation of (VIa) allows this *only* with the Δ^{2-3} double bond (the Δ^{6-7} bond is blocked by the "inside" hydrogen at C_1) and a



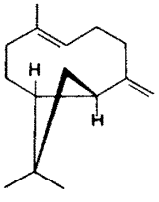
IIIa



VIa

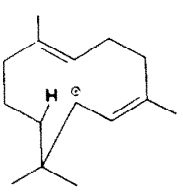


IX

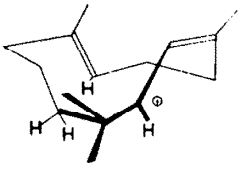


X

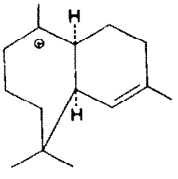
concerted loss of hydrogen from the C_3-methyl group yields carophyllene (X) directly, its known stereochemistry (*trans*-fused four-membered ring and *trans* double bond at C_{6-7}) a direct consequence of the conformation of (VI). Finally, the "inside" hydrogen at C_1 can undergo a 1,3-migration* to relieve its strain, yielding the ion (XI). The conformation of (XI), depicted in (XIa), is such as to provide considerable overlap of the π-electrons at C_6 with those of the allylic carbonium ion at C_1, so that collapse to the *cis*-fused bicyclic ion (XII) will be facile. The geometry of (XII) is such that C_7 is close to the double bond at C_2–C_3; although the electronic preference would now dictate the formation of a C_2–C_7 bond, this process would yield a highly strained four-membered ring in a polycyclic system. Hence we may reasonably expect instead



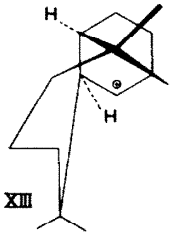
XI



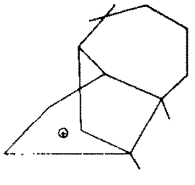
XIa



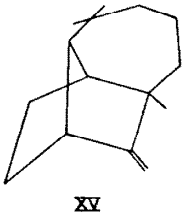
XII



XIII

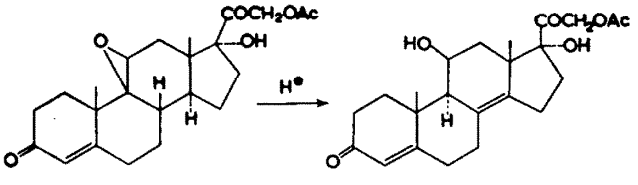


XIV



XV

* Migrations of this sort are known in rigid systems, cf. the familiar cases in the [2,2,1]-bicycloheptane series[5] and the steroid case of Wendler,[6] given below. The rigidity of (VI) and the close proximity of the involved atoms therein strongly suggest it as a comparable example.

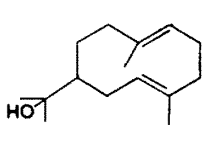


[5] J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., *J. Amer. Chem. Soc.* **76**, 4501 (1954), and references therein.

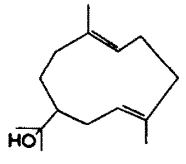
[6] N. L. Wendler, R. P. Graber, C. S. Snoddy, Jr. and F. W. Bollinger, *J. Amer. Chem. Soc.* **79**, 4476 (1957).

a cyclization to the ion (XIII), which, rewritten as (XIV), will be recognized as a [2,2,1]-bicycloheptane derivative capable of neutralizing the cation by rearrangement and deprotonation to the sesquiterpene, longifolene (XV). Thus the conformation of (VI) can be seen to proceed uniquely to these complex substances in all stereochemical detail. It should be remarked that caryophyllene and humulene occur together in *Eugenia caryophyllata* and that caryophyllene and longifolene are the only sesquiterpenes known to date to be found in pines (*Pinus* spp.).[4]

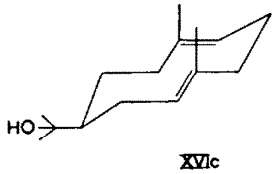
Models of the *trans*-cation (VII) reveal that the two-double bonds are extremely close to each other, by contrast with (VI), and that there are no "inside" hydrogens. The cationic center now resides out on the pendent isopropyl group where it may be hydrated or suffer the further extensive oxidation characteristic of the sesquiterpene lactones, all of which can be shown to derive from (VII). Taking simple hydration as an example of the fate of the *trans*-cation, let us examine the resultant alcohol, of which the various pictorializations (XVIa–d) are entirely equivalent. It will be seen at once that this alcohol (XVI) possesses two double bonds uniquely situated for concerted cyclizations, with complete *trans* anti-parallel additions to the double bonds, to yield the bicyclic products (XVIIa,b) and (XVIIIa,b) with R=H for a simple acid-catalyzed cyclization or R=OH for an oxidative cyclization reminiscent of those in the triterpene series. As the geometry of such a concerted cyclization requires,



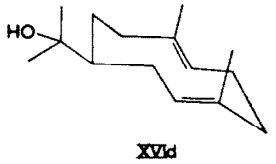
XVIa



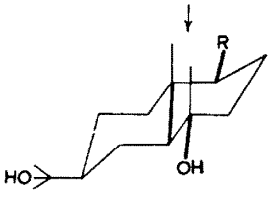
XVIb



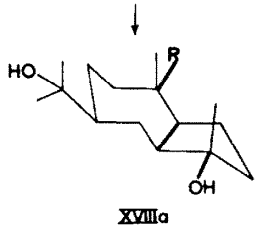
XVIc



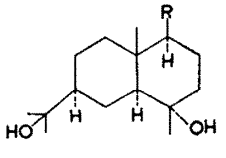
XVId



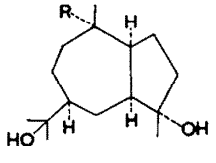
XVIIa



XVIIIa



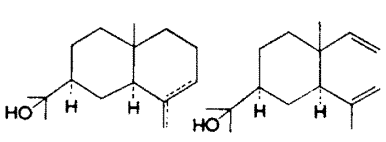
XVIIb



XVIIIb

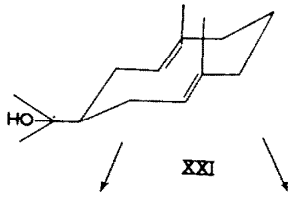
all the new bonds formed are parallel, as indicated by the heavier lines in (XVIIa) and (XVIIIa). The product (XVII) derives from a completely Markownikoff-oriented polarization of the two double bonds, whereas one double bond must polarize in an anti-Markownikoff fashion for the production of (XVIII), a situation akin to the C-ring cyclization of lanosterol from squalene[2] and allowable here because of the compelling proximity of the double bonds.

Product (XVII) is the direct precursor of eudesmol (XIX) and the other sesquiterpenes of that skeleton (santonin, cyperone, etc.) and is in complete accord with the stereochemistry of that group in all cases in which this is known. Furthermore, a direct six-membered-ring cycling of the electrons in (XVIa) yields elemol (XX). Product (XVIII) is the precursor of the large body of sequiterpenes with the guaiazulene skeleton and predicts their stereochemistry, although this is not at present known for any example. Alternatively, a simple double bond isomerization from (XVIc)

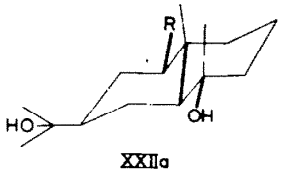


XIX XX XXIV

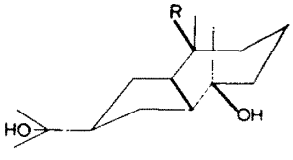
to (XXI) can occur with negligible steric complaint, followed by entirely analogous cyclizations to (XXa,b) and (XXIIIa, b). It is tempting to consider the possibility that since this involves an extra biogenetic step, fewer sesquiterpenes will arise by this route. This seems to be borne out by the examples presently known: (XXIII)



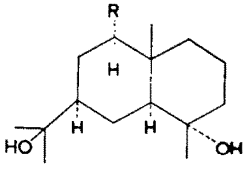
XXI



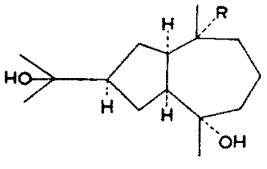
XXIIa



XXIIIa

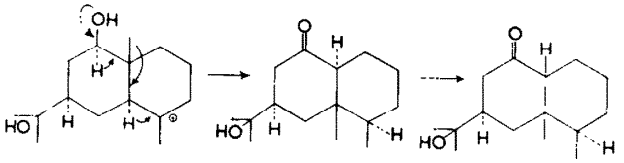


XXIIb

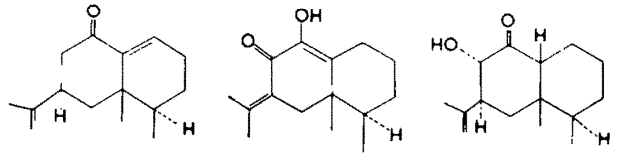


XXIIIb

represents the known stereochemistry of β-vetivone (XXIV) and presumably yields the few other vetivazulene skeletons in nature, whereas (XXII) yields only the eremophilones, by the following means. (XXII) is considered as (XXV) (oxidative cyclization) which reveals the ideal anti-parallel geometry for a multi-group rearrangement (indicated by arrows) of the sort so dramatically exemplified in friedelin chemistry.[7] Such a migration yields (XXVI), which may isomerize to the more stable ketone (XXVII). This in turn, by side-chain dehydration as well as oxidation of either enol, yields eremophilone (XXVIII), hydroxy-eremophilone (XXIX), and hydroxydihydro-eremophilone (XXX), all three of which are found to co-exist in nature; the stereochemisty of (XXX) is known to be as indicated.

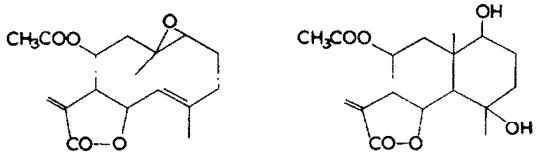


XXV XXVI XXVII



XXVIII XXIX XXX

Finally, we might reasonably expect examples of uncyclized (VII) to be found in natural sources; such monocyclic sesquiterpenes would be predicted to undergo facile cyclizations *in vitro* of the sort postulated here for biogenesis, to bicyclic derivatives of (XVII) and (XVIII). This expectation has recently been realized. Thus, pyrethrosin has been shown to possess structure (XXXI) and to cyclize under a variety of acidic conditions to give such products as (XXXII). Two other sesquiter-



XXXI XXXII

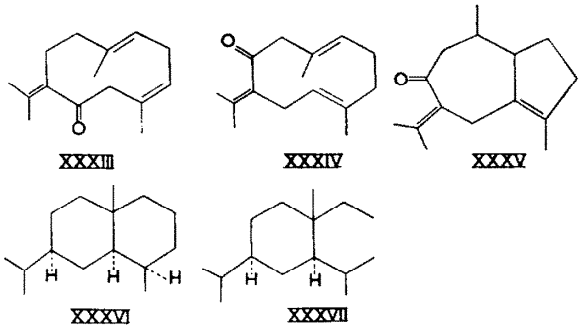
penes, unequivocably monocyclic, deserve attention here. The first is germacrone, said to possess structure (XXXIII).[8] The biogenetic hypothesis outlined here dictates (XXXIV) as the simplest structure for germacrone consistent with the experimental evidence. In accord with the views developed above, this accommodates readily the observation of Treibs[9] that germacrone yields (XXXV) on acid catalysis and

[7] E. J. Corey and J. J. Ursprung, *J. Amer. Chem. Soc.* **78**, 5041 (1956).

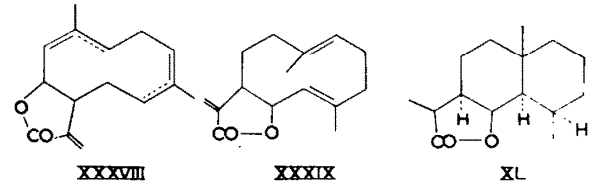
[8] I. Ognjanoff, D. Ivanoff, V. Herout, M. Horák, J. Pliva and F. Sorm, *Chem. & Ind.* 820 (1957); *Coll. Czech. Chem. Comm.* **23**, 2033 (1958); V. Herout and M. Suchy, *Ibid.* **23**, 2169 (1958); M. Suchy and F. Sorm, *Ibid.* **23**, 2175 (1958).

[9] W. Treibs, *Liebigs Ann.* **576**, 116 (1952).

the obtention[8] of selinane (XXXVI) on catalytic hydrogenation, in acid, of the alcohol corresponding to germacrone. Of similar interest is the observation that dehydration of the latter alcohol followed by hydrogenation yields elemane (XXXVII).



Both pyrethrosin and germacrone afford cham- or guaiazulene on dehydrogenation, as does the final example, costunolide, recently formulated as (XXXVIII).[10] The hypothesis implies instead the structure (XXXIX). Costunolide yields on catalytic



hydrogenation in acid a saturated tetrahydro-lactone, m.p. 154°, which we would formulate as (XL), analogous to (XVII) above. The lactone (XL) is in fact the structure of tetrahydrodeoxy-santonin, which is known to possess m.p. 153–154°. These examples will serve to indicate the utility of the hypothesis in considerations of sesquiterpene structures.

Note added in proof: The absolute stereochemistry is in fact enantiomeric with the structures drawn here, in those cases in which this is known.

[10] A. Somasekar Rao, G. R. Kelkar and S. C. Bhattacharyya, *Chem. & Ind.* 1359 (1958).