Some Aspects of Terpene Biosynthesis—A Model

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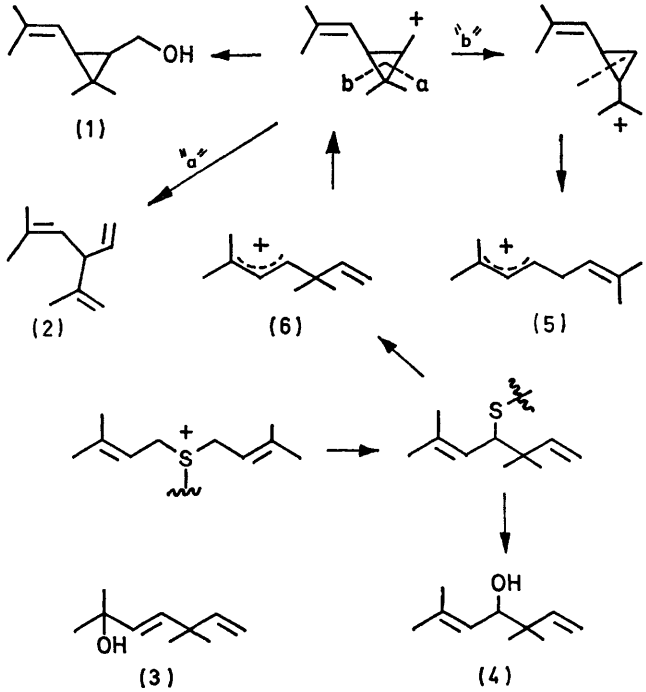
Summary A model for non-head to tail monoterpene biosynthesis involving conversion of the artemisyl skeleton into the chrysanthemyl skeleton is proposed and supported by the solvolytic conversion of an artemisyl sulphonium salt into a chrysanthemic derivative; the relationship to squalene biogenesis is discussed.

MUCH speculation centres around the conversion of farnesyl pyrophosphate into squalene.[1] With the isolation of a cyclopropylcarbinol as an intermediate in the biosynthesis,[2] an obvious link between the non-head to tail monoterpenes, chrysanthemol (**1**), santolinatriene (**2**), yomogi alcohol (**3**), artemisia alcohol (**4**), and lavandulal, is established.[1e,3] Scheme 1 presents a unified proposal for the biogenetic relationships of these compounds and their conversion into a head to head monoterpene (**5**). The transformation of the chrysanthemyl skeleton to (**5**) represents the monoterpene equivalent of the presqualene alcohol to squalene conversion.

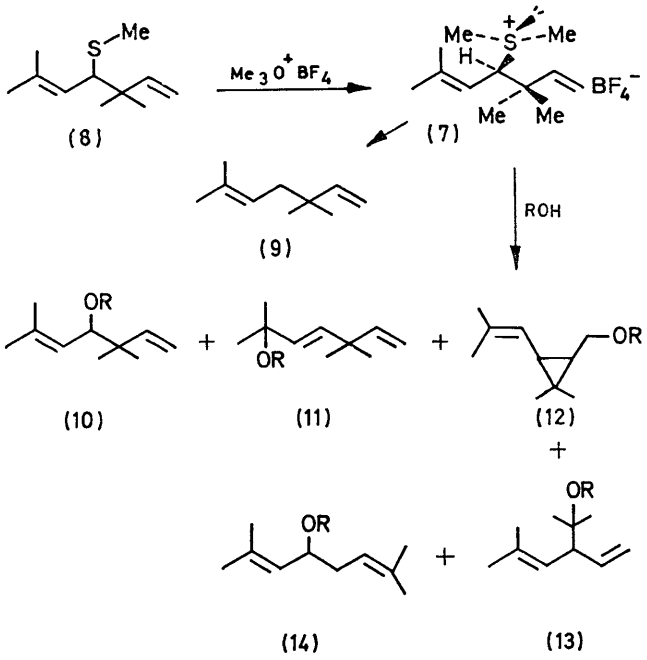
To test this proposal, generation of cation (**6**) from a mimic of the biological precursor, sulphonium salt (**7**) (Scheme 2), was undertaken. Alkylation of artemisylmethyl thioether (**8**) with trimethyloxonium fluoroborate generates an exceedingly labile sulphonium salt. Keeping it below −40° allowed its isolation as a crystalline white solid. Its structure was supported by the n.m.r. spectrum. In particular the diastereotopic S–Me and saturated C–Me groups appear as singlets at δ 2·75, 2·62, 1·35, and 1·16, respectively. The methine proton (H_e) appears as a triplet ($J \sim 7$ Hz) at δ 4·32. Confirmation that no skeletal rearrangement occurred was obtained by sodium in liquid ammonia reduction to diene (**9**).



SCHEME 1. *Proposed monoterpene biogenesis*[a,b]

[a] Classical carbonium ions are written only for clarification.

[b] It should be noted that the two dimethylallyl units of the bis-(γ,γ-dimethylallyl)-sulphonium salt precursor are enantiotopic and would be treated nonequivalently by an enzymatic system. Thus, the observation that the two halves of artemesia ketone are enzymatically differentiated is fully accounted for by this proposal.



SCHEME 2. *Generation and solvolysis of* SS-*dimethyl*-S-*artemisylsulphonium fluoroborate*

Solvolysis in aqueous acetone generated (**11**) (R=H) almost exclusively. In fact, this sequence serves as an excellent synthetic route to yomogi alcohol. Alternatively, alcoholic solvolysis generates a plethora of products. The major product(s) in all cases arises by direct trapping of the allyl cation (**6**). In methanol (**10**) (R=Me) and (**11**) (R=Me) account for over 70% of the product.

The identification of the minor constituents was hampered by the small quantities available. Synthetic samples of (**12**), (**13**), and (**14**) (R=Me) were made available by independent unambiguous routes.† By gas chromatographic and spectral comparisons, the synthetically available compounds were identified in the solvolysis mixture. Thus, the presence of (**12**), (**13**), and (**14**) (R=Me), although present in only less than 2% yield each, was confirmed.

The observation of the conversion of an artemisyl skeleton into chrysanthemyl and santolinyl skeletons does necessitate consideration being given to a similar sequence *in vivo*.[4] Such a proposal is in contrast to the presently considered pathways invoking the chrysanthemyl skeleton as the precursor of the artemisyl and santolinyl systems.[3] Furthermore, the presence of (**14**), the product of net head to head coupling of two γ,γ-di-methylallyl units, requires consideration to a similar pathway being operative in the farnesol to squalene conversion.

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† The independent synthetic routes will be reported in our full account of this work.

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[2] W. W. Epstein and H. C. Rilling, *J. Biol. Chem.*, 1970, **245**, 4597; H. C. Rilling and W. W. Epstein, *J. Amer. Chem. Soc.*, 1969, **91**, 1041.

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[4] For an alternative approach, see A. F. Thomas, *Chem. Comm.*, 1970, 1054.