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BIOGENETIC-TYPE CONVERSION OF AGEROL INTO AGERATRIOL

F. Bellesia, U.M.Pagnoni and R. Trave°

Istituto di Chimica Organica - Università di Modena

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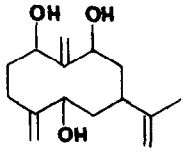
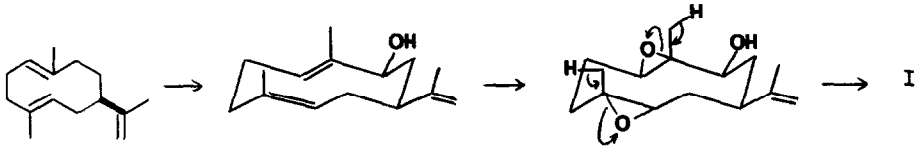
We have previously suggested the hypothesis that ageratriol I, a sesquiterpene triol isolated[1] from Achillea ageratum, is derived biogenetically



I

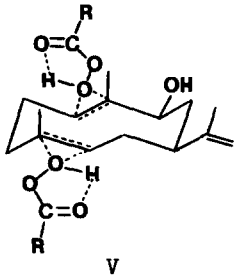
from germacrene A (II). This hypothesis was then confirmed by the finding in the flowers of the same plant of agerol III[2], which may be considered the first product of enzymatic hydroxylation from II.



II III IV

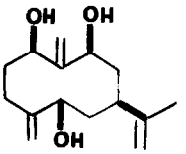
Although it has not as yet been possible to isolate the supposed intermediate diepoxide (IV) from extracts of A. ageratum, we set out to discover whether it was possible to reproduce the route indicated (III ⟶ I) in vitro. A positive result could also have provided information regarding the absolute configuration[3] of ageratriol, for, in view of the trans configuration and of the crossed orientation[2] of the endocyclic double bonds, of their greater reactivity and, finally, of the greater probability of an at-

tack of the peroxyacid on the less hindered side of the molecule (V), the attack of a peroxyacid on agerol III should give[4] a diepoxide with the stereostructure reported (IV).



V

IV $\xrightarrow{LiN(C_2H_5)_2}$



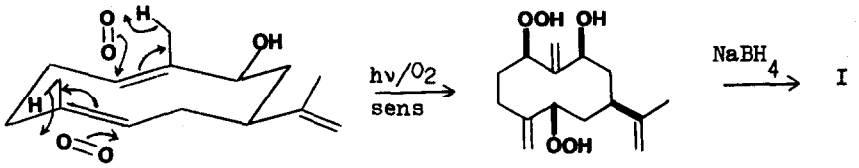
Ia

The reaction of agerol III with m-chloroperbenzoic acid (2 equiv.) in CH_2Cl_2 at 0°C gives acceptable yields (50%) only if carried out in the presence of pyridine[5], for the diepoxide IV is extremely sensitive to the acid medium. IV, isolated by preparative TLC (silica gel) and purified by crystallisation (diisopropylether), is perfectly homogeneous in TLC and GLC (after acetylation), m.p. 190-192°; $[\alpha]_D^{20}$ -62.3° (c 0.9 CH_3OH); IR (nujol): 3400 cm^{-1}; 100 MHz NMR ($CDCl_3$): 1.27, 1.34 (3H each,s,CH_3-C-O); 1.73 (3H,s, CH_3-C=); 2.60 (1H,d (J 8Hz),H-C—C); 2.89 (1H,d (J 10Hz),H-C—C); 3.20 (1H, dd (J 3.5 and 8Hz),H-C-OH) and 4.59, 4.65 δ (1H each,br.s, H-C=C).

Lithium diethylamide[6] (5 equiv.) in boiling benzene (2 hr) induced in the diepoxide IV a double, Hoffmann-like elimination to give a triol, which was purified by preparative TLC and crystallisation (yield ca. 25%), m.p. 194° (undepressed in admixture with ageratriol from A. ageratum), $[\alpha]_D^{20}$ +30.1° (c 1.9 CH_3OH); its IR and NMR spectra are exactly superimposable with those of ageratriol I[1].

It follows, therefore, that ageratriol probably has the absolute configuration reported in Ia.

The similarity between oxidation of the type described above and oxygenations with singlet oxygen[7,8,9,10], often associated with certain biological oxidations[11,12,13] (linked, for example, to photochemical processes occurring in the chloroplasts), led us to consider also the route of the "ene" reaction[14] for the in vitro conversion of III into ageratriol I, according to the following scheme:



III VI

It was found that the photosensitised oxygenation[12,15] (24 hr, Pyrex apparatus thermostatted at 20°C, 125 w high pressure Hg lamp) of III, using methylene blue as a photosensitizer according to the method of Schenck[16], gave a crude dihydroperoxide (VI) which on reduction with sodium borohydride gave (total yield 60%) the corresponding alcohol which, isolated by preparative TLC (silica gel) was found to have identical specific optical rotation and IR and NMR spectra with those of the material isolated from A. ageratum and from the base-promoted reaction of IV.

Since it is known[12] that in these reactions oxygen approaches from the least-hindered side of the skeleton, the configuration of the dihydroperoxide is presumably that shown in formula VI. It follows that, by this route too, the final product should have the configuration Ia.
Biosynthetic experiments are being carried out in vivo starting also from the labelled diepoxide IV.

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(3) The absolute configuration of ageratriol is now being determined chemically.

(4) These observations are supported by the fact that germacrone yields both microbiologically and chemically a diepoxide (H.Hikino,C.Konno,T.Nagashima,T.Kohama,T.Takemoto, Tetrahedron Letters, 337 (1971)) with a configuration of the oxyranic groups identical to that given by us for IV.

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