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BIOGENETIC TYPE SYNTHESIS OF 10-BROMO-α-CHAMIGRENE[1]

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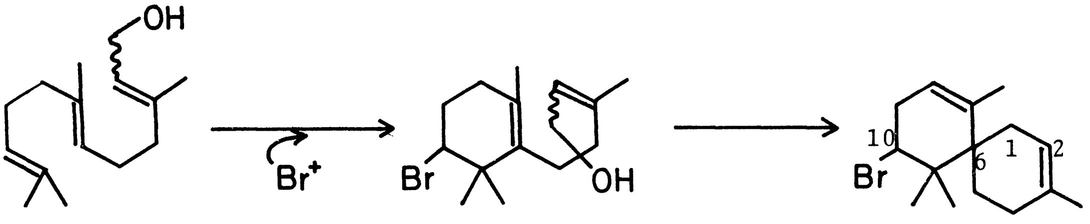
Bromonium ion induced cyclization of methyl 2,3-cis-farnesoate (III) was achieved by the action of 2,4,4,6-tetrabromocyclohexadienone (II) to give monocyclic bromoester (IV), which was converted into dl-10-bromo-α-chamigrene (I), a naturally occurring brominated sesquiterpenoid.

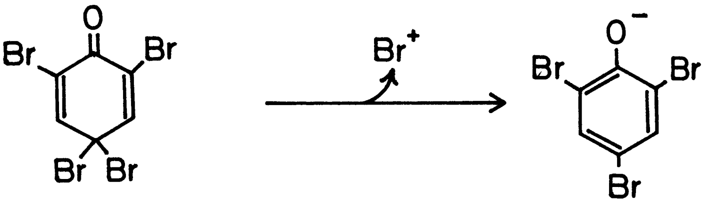
An increasing number of bromine-containing terpenoids has been accumulated from nature, particularly from sea weeds and sea animals[2], in which 10-bromo-α-chamigrene (I)[3] is a typical example belonging to sesquiterpenoids. I is a metabolite of <u>Laurencia</u> species and is attributed to be a plausible key intermediate in the biosynthesis of other bromine-containing terpenoids isolated from the same and relevant species[4]. Here we wish to report a biogenetic type synthesis of dl-10-bromo-α-chamigrene which is presumed to be biosynthesized through the bromonium ion induced cyclization of farnesol as shown below.



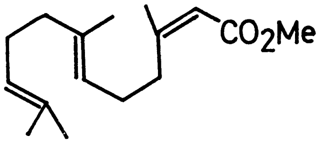
(I)

As reported previously[5], 2,4,4,6-tetrabromocyclohexadienone (II, abbreviated as TBCO) has been revealed to be an efficient reagent for the generation of Br^+ when reacted with polyene systems, resulting in the formation of bromine-containing products. The present synthetic study was started using methyl-2,3-cis-farnesoate (III) prepared easily from geranylacetone by the Wittig reaction followed by separation with SiO_2 column chromatography. A mixture of the ester (III)(1.19 g) and an equimolar amount of TBCO in CH_3NO_2 (48 ml) was stirred at room temperature for 2.5 h and the resulting neutral fraction was passed through a short SiO_2 column affording a monocyclic bromoester (IV) in 76% yield as an isomeric mixture concerning a double bond. The crystalline tetra-substituted olefinic isomer was isolated in 28% yield[6] from n-pentane solution of the mixture. IV($\Delta^{6,7}$), mp 61-62°, M^+ 328 and 330 ($C_{16}H_{25}BrO_2$)[7], PMR (CCl_4) 1.22 and 1.28 (C_{11}-Me x 2)[8], 1.75 (C_7-Me), 1.98 (d, 1.5 Hz, C_3-Me), 3.72 (CO_2Me), 4.28 (m, C_{10}-H), and 5.72 ppm (q, 1.5 Hz, C_2-H).

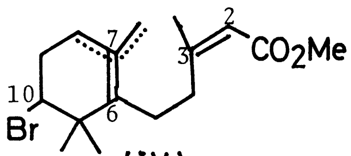
Treatment of IV($\Delta^{6,7}$) with AlH_3 followed by purification with SiO_2 column chromatography and then recrystallization from n-pentane afforded the corresponding



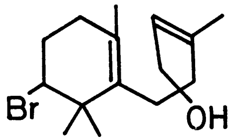
(II, TBCO)



(III)



(IV)



(V)

bromo-alcohol (V) in 62% yield, mp 41-42°, M^+ 300 and 302 ($C_{15}H_{25}BrO$), PMR (CCl_4) 1.16 and 1.21 (C_{11}-Me x 2), 1.66 (C_7-Me), 1.78 (C_3-Me), 4.02 (3H, bd, 7 Hz, C_1-$\underline{H}_2$ overlapping with C_{10}-H), and 5.33 ppm (bt, 7 Hz, C_2-H).

The final cyclization of V (180 mg) with simultaneous dehydration was achieved when treated[9] at room temperature with iodine (670 mg) in benzene (60 ml) containing Molecular Sieves 3A. The resultant crude products were separated by repeated high pressure liquid chromatography using a μ-Porasil column with n-hexane as an eluent. The PMR and IR (CCl_4) spectra as well as mass spectrum of the pure product, thus obtained in ca 6% yield, were completely identical[10] with those of natural 10-bromo-α-chamigrene[11,12].

References

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6. The composition of the olefinic isomers of IV depends on the reaction conditions and exocyclic isomer was isolated in 62% yield when CH_2Cl_2 was used as solvent.
7. All the compounds described herein have the satisfactory analytical data.
8. Numbering is based on that of 10-bromo-chamigrene.
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10. We deeply thank Dr. W. H. Fenical for his giving the copies of physical data of natural 10-bromo-α-chamigrene.
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12. The exact stereochemistry of natural product remains unsolved concerning C_{10}-Br and C_1-C_6 bond. The present study gives no solution on this stereochemical aspect although only one of the possible isomers was isolated.

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