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Cyclization of Polyenes XVI[1]. Biogenetic Type Synthesis of Cembrene Type Compounds

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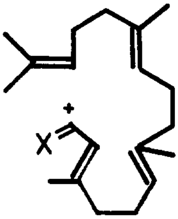
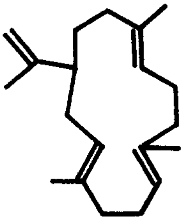
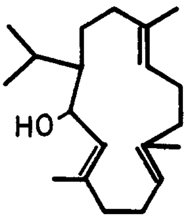
After the year 1965 when Dauben[2] and his co-workers reported on the discovery of cembrene, a fourteen membered macrocyclic diterpene, more than a dozen of this type of natural products[3] appeared in the literature and constitute a family of diterpenoid skeletons. Among them are inclusive of cembrene-A (II)[4,5] and mukulol (III)[5], the former of which is of special interest due to its pheromone activity toward a kind of termite[6]. The biogenesis of this family is properly considered to be resulted from the bond formation between the terminal double bond and C_1 cation of geranyl geraniol (Ia) or its biogenetical equivalent (Ib).



Ia X = H_2
Ib X = O



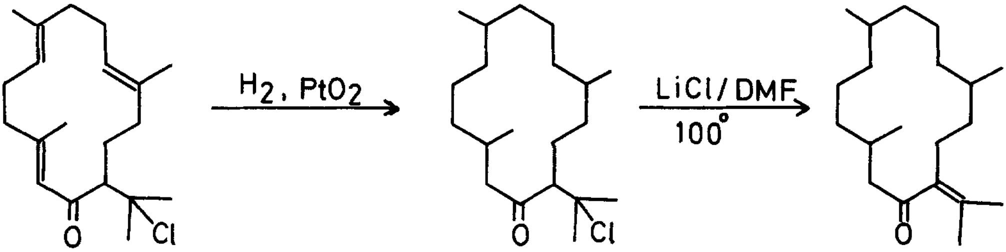
(II)



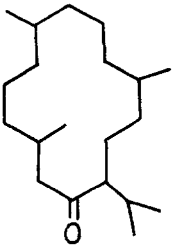
(III)

Our continuous interest in the biogenetic type synthesis of terpenoids[7] has prompted us to find the reaction conditions promoting the intramolecular cyclization which is induced by the cation in a polyene molecule and we found recently that cis farnesic acid chloride is effectively converted[8] to bisabolane skeleton by the action of $SnCl_4$ or $AlCl_3$. In this communication we describe the selective conversion of geranyl geranic acid chloride which corresponds to Ib into the macrocyclic cembrene skeleton by the application of our method.

To a stirred mixture of trans geranyl geranic acid chloride (1.5g) in CH_2Cl_2 (1ℓ) was added dropwise 1 mol equivalent of $SnCl_4$ in CH_2Cl_2 (10 mℓ) at -78° and the mixture was kept for 1.5 hrs at the same temperature. After usual work up and purification with SiO_2 chromatography and subsequent recrystallization, IV. mp 71-73°, (Found C, 74.40; H, 9.72) was obtained in 71% yield. UV λ_{max} 247 nm (9462), IR 1670 and 1605 cm^{-1}; NMR 1.51 (6H, s), 1.54 and 1.63 (each 3H, bs), 2.09 (3H, d, 1 Hz), 2.75 (1H, m), 4.85 (2H, bm), and 5.88 (1H, q, 1 Hz). Structure of the cyclized product was confirmed as follows. IV was submitted to catalytic hydrogenation giving hexahydro derivative (V), IR



(IV) (V) (VI)



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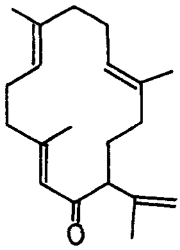

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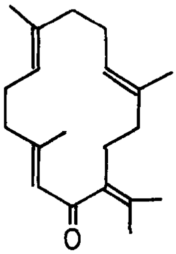

(IX)

1700 cm^{-1}; NMR 1.60 (3H x 2, s). Dehydrochlorination (LiCl in DMF, 100°, 4 hr) to the conjugated ketone (VI) [UV λ_{max} 247 nm (2859), IR 1680 cm^{-1}; NMR 1.65 and 1.75 (each 3H)] and subsequent hydrogenation afforded the saturated ketone (VII). All the prominent peaks (signals) of mass, nmr and ir spectra described in the literature[5] were consistently observed in our compound (VII).

Treatment of IV with LiCl in DMF (100°, 24 hr) furnished two isomeric mixture (VIII + IX, 2:3), which were separated by SiO_2 chromatography with n-hexane-AcOEt (20:1). VIII [UV 244 nm (7216), IR 1680 and 1610 cm^{1}; NMR 1.55, 1.63, 1.66, and 2.06 (each 3H), 4.83 (2H, bs), 4.95 (2H, bm), and 5.93 (1H, bs)]. IX [UV λ_{max} 254 nm (9072), IR 1660 and 1610 cm^{-1}; NMR 1.55 (3H x 2), 1.74 (3H x 2), 2.10 (3H), 4.90 (2H, bm), and 5.95 (1H, bs)].

All the evidence described herein strongly support the structure of IV and our result proclaims that cembrene skeleton is effectively and biogenetically constracted by cation cyclization[9] of Ib. Finally, chlorine atom of IV was quantitatively reduced with Bu_3SnH to provide X[UV λ_{max} 242 nm (4508)], which was reduced with $LiAlH_4$ to give ca 1:1 mixture of saturated ketone (XI) and alcohols (II). XI [IR 1700 cm^{-1}; NMR three methyls near 0.9 ppm and no proton at 5.95 ppm]. IR, nmr and mass fragmentation of both X and the major alcohol (II), which was further purified by SiO_2 chromatography, were identical with those described by S. Dev.[5,10] It is of interest to note that 2,3-double bond is susceptible to reduction with $LiAlH_4$ in this series. For another example, XII and XIII (ca 1:1) were isolated when IX was successively treated with $LiAlH_4$ and SiO_2 chromatography. XII [UV λ_{max} 251 nm (4356), NMR 0.91 (3H, d), 1.56 (3H x 2, bs), 1.75 (3H x 2, s), 5.0 (2H, bm). XIII [UV 252 nm (12548), NMR 1.31 (3H x 2, s), 1.54, 1.60, and 1.73 (each 3H, bs), 4.93 (2H, m), 5.77 (1H, bd, 12 Hz), and 6.24 (1H, d, 12 Hz). The rearranged alcohol (XIII) corresponds to dehydro nephthenol.

** Acknowledgement

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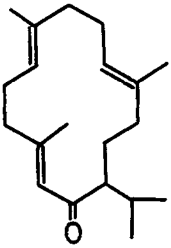
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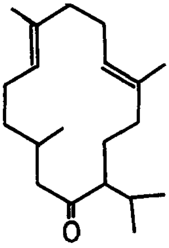
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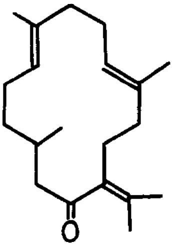
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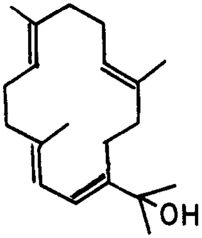
(XIII)

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9. M. Kodama, Y. Matsuki, and S. Ito carried out the synthesis of II and nephthenol by anion initiated cyclization of epoxy geranyl geraniol derivative. We are acknowledged to them for their kind supply of their manuscript before publication.

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