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# CYCLIZATION OF POLYENES XXII[1]
## SYNTHESIS AND STEREOCHEMISTRY OF THUNBERGOL

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Regio- and stereoselective synthesis of thunbergol(Vb) and its epimer(Va) was carried out starting from dl-epimukulol(IIb) and dl-mukulol(IIa), respectively. The present work establishes unequivocally the stereostructure of thunbergol which has remained unsolved.

An increasing number of macrocyclic cembrenoids has been elucidated recently from nature[2], in which thunbergol[3] is a typical example possessing hydroxylated skeleton. It is a constituent of pocket resin isolated from Douglas fir, Pseudotsuga menziesii(Mirb.) Franco, by Kimland and Norin. They have, however, not clarified the relative stereochemistry of the tertiary hydroxyl function with respect to the isopropyl group. Although trans nature( E form) of 1,2-double bond of thunbergol was demonstrated by NMR spectrum, geometry of the two other double bonds has remained unsolved. They proposed the structure(I) for thunbergol without any experimental evidence concerning the remaining double bonds. Here we report the synthesis of thunbergol and its epimer(Va) and reveal that the stereostructure of thunbergol should be shown by the formula(Vb).

Previously, we reported the synthesis of dl-mukulol(IIa) and its epimer(IIb) starting from geranyl geranyl acid chloride on the basis of biogenetical consideration[4]. Since double bonds of almost all the known cembrenoids have been demonstrated to have trans geometry, we started the synthesis from IIa and IIb by the assumption that the remaining double bonds in thunbergol are trans geometry. Regio- and stereoselective oxidation of 2,3-double bond of II(a and b) was achieved with t-$BuO_2H$ in the presence of $VO(acac)_2$ which was described to be an effective reagent for the conversion of allyl alcohol to the corresponding cis epoxy alcohol[5].

Treatment of IIa or IIb with t-$BuO_2H$( 1 mol eq.) in refluxing benzene containing catalytic amounts of $VO(acac)_2$ afforded the corresponding epoxy alcohol, IIIa or IIIb, in ca 70% yield[6]. IIIa, mp 49-51°, PMR($CCl_4$) 1.28($C_3$-Me), 1.59(C=C-Me x 2), 2.68(d, 8 Hz, $C_2$-H), 3.47(d, 8 Hz, $C_1$-H), and 5.0(C=C-H x 2)ppm. IIIb, oil, PMR 1.23($C_3$-Me), 1.59(C=C-Me x 2), 2.68(d, 7 Hz, $C_2$-H), 3.50(br d, 7 Hz, $C_1$-H), and 5.0(C=C-H x 2)ppm. Coupling mode of $C_1$-H indicates that dihedral angle of $C_1$-H with $C_{14}$-H is ca 90°. Secondary hydroxyl group of IIIa and IIIb was mesylated in ca 55% yield with MsCl in the mixed solvents of $CH_2Cl_2$-$Et_3N$( 1:1) to afford epoxy mesylates, IVa and IVb, respectively. IVa, oil, PMR 1.41($C_3$-Me), 1.59(C=C-Me x 2), 2.80(d, 10 Hz, $C_2$-H), 3.04(OMs), and 4.58(d, 10 Hz, $C_1$-H)ppm. IVb, mp 91° (decomp.), PMR 1.30($C_3$-Me), 1.59(C=C-Me x 2), 2.94(d, 10 Hz, $C_2$-H), 3.04(OMs), and 4.47(d, 10 Hz,

$C_1$-H)ppm.

Transformation of IVa and IVb into tertiary alcohols, Va and Vb, was performed by the method reported by Nozaki and his co-workers[7]. Each mesylate was treated with Na in $NH_3$ to give Va and Vb in ca 70% yield. Va, oil, PMR 0.81 and 0.84(each 3H, d, 6 Hz, CH$\underline{Me}_2$), 1.27($C_3$-Me), 1.52 and 1.59(C=C-Me x 2), 5.1(m, C=C-H x 2), 5.29 (dd, 16 and 7 Hz, $C_1$-H) and 5.59(d, 16 Hz, $C_2$-H)ppm. Vb, oil, PMR 0.83 and 0.85 (each 3H, d, 6 Hz, CH$\underline{Me}_2$), 1.34($C_3$-Me), 1.53 and 1.62(C=C-Me x 2), 5.1(m, C=C-H x 2), 5.27(dd, 16 and 8 Hz, $C_1$-H), and 5.73(d, 16 Hz, $C_2$-H)ppm.

PMR spectrum of Vb, thus obtained, was completely superimposable with that of natural thunbergol.[8] The present work means not only the total synthesis but also establishment of the stereochemistry of thunbergol.

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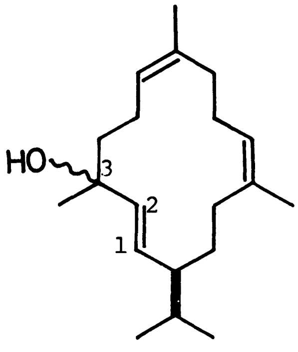
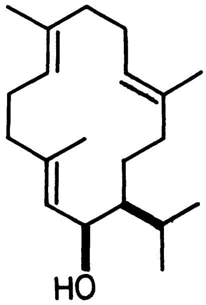
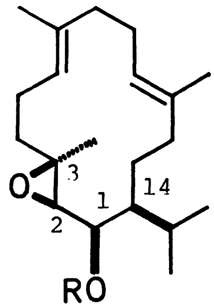


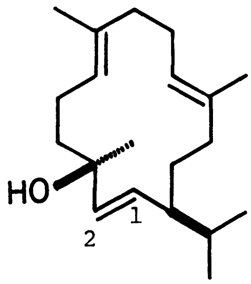
(I)



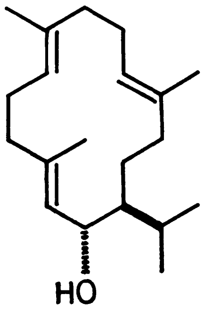
(IIa)



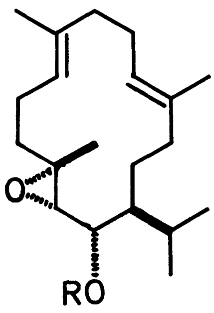
(IIIa) R=H
(IVa) R=Ms



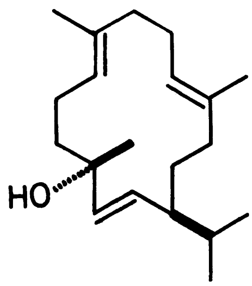
(Va)



(IIb)



(IIIb) R=H
(IVb) R=Ms



(Vb)

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