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CYCLIZATION OF POLYENES XXIII[1]
SYNTHESIS AND STEREOCHEMISTRY OF ISOINCENSOLE-OXIDE

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In order to establish the stereochemistry of incensole(I) and isoincensole-oxide(II), which had remained unsolved, I and II were synthesized starting from dl-mukulol(III) and its epimer(IV). The detailed studies of physical and chemical evidences enabled us to determine the stereostructure of these highly oxygenated cembrenoids.

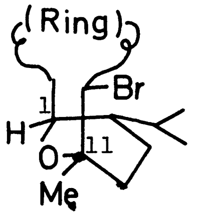
A few dozens of macrocyclic cembrenoids have been isolated recently from plants and animals[2], in which incensole(I)[3] and isoincensole-oxide(II)[4] are the typical examples having highly oxygenated skeleton. Both are the components from frankincense resin elaborated by Nicoletti and his coworkers who have, however, not clarified the stereochemistry covering asymmetric carbons as well as double bonds of these synthetically intriguing terpenoids.

For the sake of establishment of the stereochemistry, we have explored the regio- and stereoselective synthesis of I and II starting from dl-mukulol(III)[5] and reported previously the effective conversion of III into dl-incensole(I), lacking any stereochemical argument[6]. Our continuous studies enabled us to determine the stereostructure by performance of synthesis of both I and isoincensole-oxide(II).

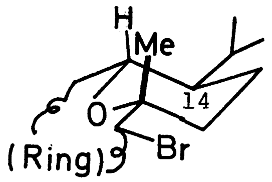
SYNTHESIS As described previously, treatment of dl-mukulol(III) with 2,4,4,6-tetrabromocyclohexadienone(TBCO) resulted in the formation of bromo-ether(V), which was transformed into isomeric five membered ether(VI) by the action of BF_3-etherate. VI was also obtained from epimukulol(IV) as follows. When IV was allowed to react with TBCO under the same conditions, the isomeric six membered bromo-ether (VIII) was gained in 53% yield after purification with SiO_2 chromatography. VIII, mp 111-113°, PMR 1.09(C_{11}-Me), 1.63(6H, C_3- and C_7-methyls), 4.32(C_{10}-H, d, 8 Hz), 4.45(C_1-H, bd, 11 Hz), 4.94(C_6-H, m), and 5.31(C_2-H, bd, 11 Hz)ppm. On rearrangement with BF_3-etherate, VIII was converted into the five membered bromo-ether(VI) in 47% yield, which was identical with that obtained from V by the same treatment[7]. Replacement of Br atom of VI with AgOAc in HOAc proceeded exclusively to give the corresponding acetate(VII) in 78% yield, from which dl-incensole(I) was derived by reduction with $LiAlH_4$.

When dl-incensole(I) was submitted to the reaction with TBCO, formation of an additional oxide bridge between C_7 and C_{10} positions was efficiently achieved with concomitant introduction of Br atom at C_6 position affording fairly unstable bromo-oxide(IX) in 70% yield. IX, mp 95-97°, PMR 1.00, 1.30 and 1.58(each 3H, C_{11}-, C_7-, and C_3-methyls), 3.79(C_6-H, bm), 4.22(C_{10}-H, bd, 8 Hz), and 5.90(C_2-H, bt, 6.4 Hz) ppm. Treatment of IX with AgOAc resulted in the isolation of two isomeric acetates, X, mp 113-114° and XI, mp 78-80°, after separation with SiO_2 chromatography, in 46 and 22% yields, respectively[8]. The former acetate was converted, upon treatment with $LiAlH_4$, to the corresponding hydroxy oxide(II), mp 123-124°, in 80% yield, PMR and IR(CCl_4) spectra[9] of which were completely identical with those of natural isoincensole-oxide. Reduction of XI afforded the epimer(XII), mp 121-122°. PMR X, 1.01, 1.13 and 1.59(C_{11}-, C_7-, and C_3-methyls), 4.68(C_6-H, bm), 4.10(C_{10}-H, dd, 7 and 2 Hz), and 5.73(C_2-H, bt, 8 Hz)ppm. XI, 1.04, 1.35, and 1.63(C_{11}-, C_7-, and C_3 methyls), 4.24(C_6-H, bd, 11 Hz), 3.30(C_{10}-H, bm), and 5.32(C_2-H, bm)ppm. XII, 1.00, 1.06, and 1.63(each 3H, Me x 3), and 5.25(C_2-H, bt, 8 Hz)ppm.

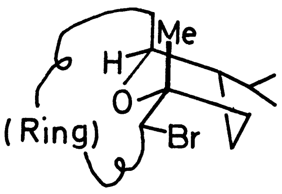
STEREOCHEMISTRY Due to the macrocyclic nature of the starting mukulol(III), four stereoisomers(Ca,b and Ta,b) are possible for the bromo-ether(V). C and T are cis and trans with respect to C_1-H and C_{11}-Me, respectively.[10] Assuming that the isopropyl group possesses an equatorial configuration on the six membered ether ring, partial stereostructures of these possible candidates are shown below.



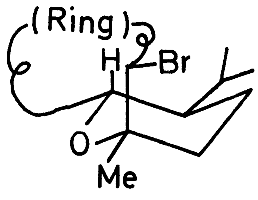
(Ca)



(Cb)



(Ta)



(Tb)

In the PMR spectrum of V, C_3-Me shows 20% nOe with C_1-H, while exhibiting no nOe with C_2-, C_6-, and C_{10}-protons. On the meanwhile, C_7- and C_{11}-methyls have no nOe with C_1-, C_2-, C_6-, and C_{10}-protons. These nOe experiments indicate that all the olefinic methyls occupy uncrowded positions and hence rule out the possibility of trans forms(Ta and b) since Dreiding model suggests that both of the trans forms are sterically crowded due to the tendency of the olefinic methyls extending inside the ring.[11] Of the remaining candidates(Ca and b), Ca is more plausible since C_{11}-Me shows no nOe with C_1-proton. Small coupling of C_1-H with neighbouring C_{14}-H(2 Hz) supports the above deduction.

The rearrangement of V into VI might proceed through the conjugated diene intermediate(XIII) and hence isomer(VIa) is equally possible. During the rearrangement reaction, possibility of trans/cis isomerization of 2,3-double bond should be considered. Trans nature of 2,3-double bond of the rearranged ether was demonstrated by the comparison of CMR spectra(Table 1) of original(V) and rearranged(VII) ethers. Similar chemical shifts of olefinic methyls in both compounds indicate that the geometry of the double bonds is same.[12] This deduction is supported by the observation of no nOe between C_2-H and C_3-Me in the PMR spectrum of dl-isoincensole-oxide(II).

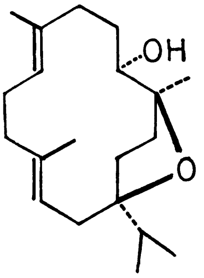
It is noteworthy that the signal of C_{10}-protons of V and its rearranged ethers (VI, VII, and I) appears as doublet with the coupling constant of ca 10 Hz, indicating that the macrocyclic ring is rigidly fixed and the dihedral angle between C_{10}-

Table 1

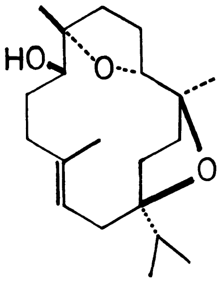
CMR spectra of V and VII[13]

Compds C_n	V	VII	C_n	V	VII	C_n	V	VII	C_n	V	VII
1	72.5	32.1	6	124.9	121.1	11	75.9	83.1[a]	16	15.0	16.1
2	132.6	125.4	7	135.7	133.2	12	39.9	38.5	17	20.3	21.4
3	135.7	135.5	8	36.4	33.4	13	20.3	27.8	18	32.7	35.0
4	34.8	35.6	9	31.5	30.4	14	47.8	89.2[a]	19	19.7[a]	18.1
5	25.9	24.8	10	64.6	76.6	15	17.2	17.7	20	20.0[a]	18.1

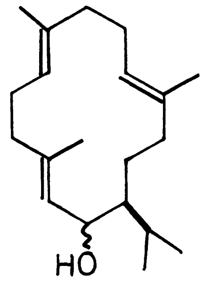
a Values in each vertical column may be reversed



(I)

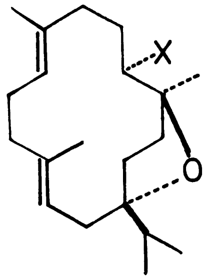


(II)



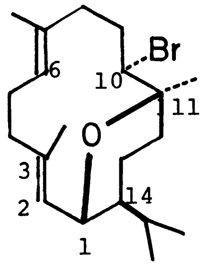
(III) β OH

(IV) α OH

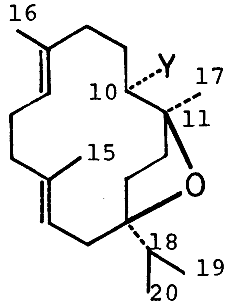


(Ia) X = OH

(VIa) X = Br

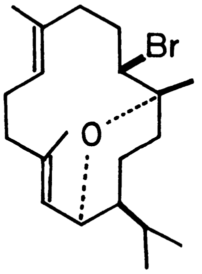


(V)

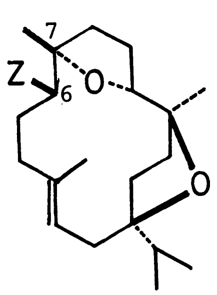


(VI) Y = Br

(VII) Y = OAc

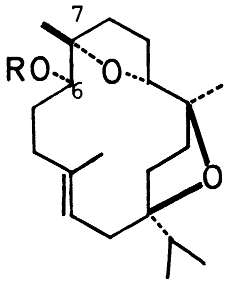


(VIII)



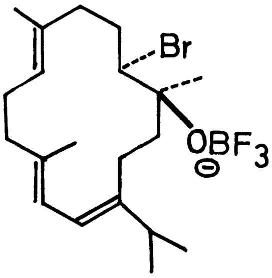
(IX) Z = Br

(X) Z = OAc



(XI) R = Ac

(XII) R = H



(XIII)

proton and one of the neighbouring C_9-protons is ca 90° in each compound.

Coupling mode of C_{10}-proton of VI and VII also reveals that replacement of Br atom with OAc group proceeded exclusively with retention of the configuration. Dreiding model clearly demonstrates that an ether bridging between C_7- and C_{10}-positions of dl-incensole is only possible when C_{11}-Me is cis to C_{14}-isopropyl group, thus ruling out the possibility of trans isomers(Ia and VIa).

In the PMR spectra, C_7- and C_{11}-methyls of IX exhibit no nOe with the neighbouring C_6-, and C_{10}-protons, respectively. An olefinic proton of IX, X and II is fairly downfield shifted as compared with that of epimeric isomers, XI and XII. These observations as well as the similar reaction mode of bromo etherification of I by TBCO lead to the demonstration of the favourable stereochemistry at C_6-, C_7-, C_{10}-, and C_{11}-positions of dl-isoincensole-oxide(II) and its epimer(XII), respectively.

References

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6. T. Kato, C. C. Yen, T. Kobayashi, and Y. Kitahara, Chem. Lett., 1191(1976).
7. One enantiomer of the dl-forms is depicted.
8. Mixed solvents of n-hexane-EtOAc(20 : 1) were used for the elution of column chromatography.
9. Authors deeply thank Dr. Nicoletti for his sending PMR and IR spectra of natural isoincensole-oxide.
10. Numbering of all the compounds described herein is based on that of geranyl geraniol.
11. Details of the conformational analyses of cembrenoids will be published elsewhere.
12. M. Baranyal, J. Szabolcs, and G. Toth, Tetrahedron, 32, 867(1976).
13. Authors deeply thank Dr. T. Suzuki of Eizai Co. Ltd., for his measuring CMR spectra.

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