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Conformational Behavior and Epoxidation of the Dolabella-3*E*,7*E*-dienoid

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Conformational analysis of the dolabellane diterpenoid, 6β-acetoxy-12β-hydroxydolabella-3*E*,7*E*-diene containing 1,5-undecadiene, has been achieved by means of molecular mechanics calculations, ^{1}H NMR, and CD spectrometry. The epoxidation products of the diene can be rationalized in terms of the calculated equilibrium conformations.

Previously, we isolated the antifungal dolabellane diterpenoid, (+)-acetoxyodontoschismenol (1), from the liverwort *Odontoschisma denudatum* (Nees) Dum. to establish its structure and absolute configuration as (1R,6R,11R,12R)-6-acetoxy-12-hydroxydolabella-3*E*,7*E*-diene (1).[1] The conformational analysis of the dolabellane diterpenoid consisting of a 1,5-undecadiene system offers a great worth in postulating a stereoselective transannular cyclization to the tricyclic dolastane and fusicoccane diterpenoids. The present paper deals with its conformational aspects as well as the relationship between the conformational equilibrium and the epoxidation products.

It is generally known that the endocyclic *trans* double bonds in medium ring compounds should be almost perpendicular to the average plane of the rings to minimize the transannular nonbonding interaction.[2] Thus, for the dolabella-3*E*,7*E*-dienoid (1) four variations of the strain minimum conformers, αα, αβ, βα, and ββ,[3] are expected by a combination of orientations of the two double bonds. Additional rotational freedom around the C9-C10 bond confers a further flexibility on the molecule, giving two forms to each of the four basic conformers. First of all, in order to obtain the conformational informations the most popular program, Allinger's MM2,[4] for empirical force field calculations was applied to the compound (1): the three conformers, P-αα, M-αα, and P-αβ,[5] were judged to be stable in the eight possible conformers. ORTEP drawings of the three stable conformers are summarized in Fig. 1 along with their steric energies and energy barriers

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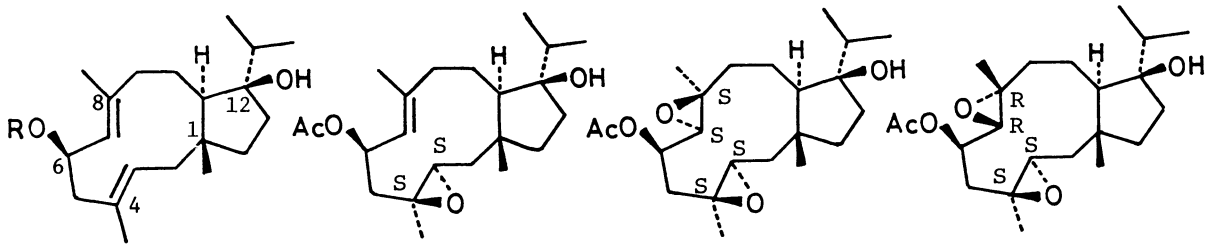

1 R=Ac
2 R=*p*-BrC_6H_4CO

3 4 5

between the conformers.[6,7] In addition to the P-αα conformer, which corresponds to the crystal structures of the two derivatives 2 and 3 determined previously by X-ray analysis,[1] the M-αα and P-αβ conformers now turned out to be important; the P-αα and M-αα conformers are equally stable and are more stable than the P-αβ conformer. The M-αα type is also a common conformer as crystal structures of the other liverwort dolabellanoids,[8] but P-αβ is not known yet as a plausible conformer in natural dolabellanoids.

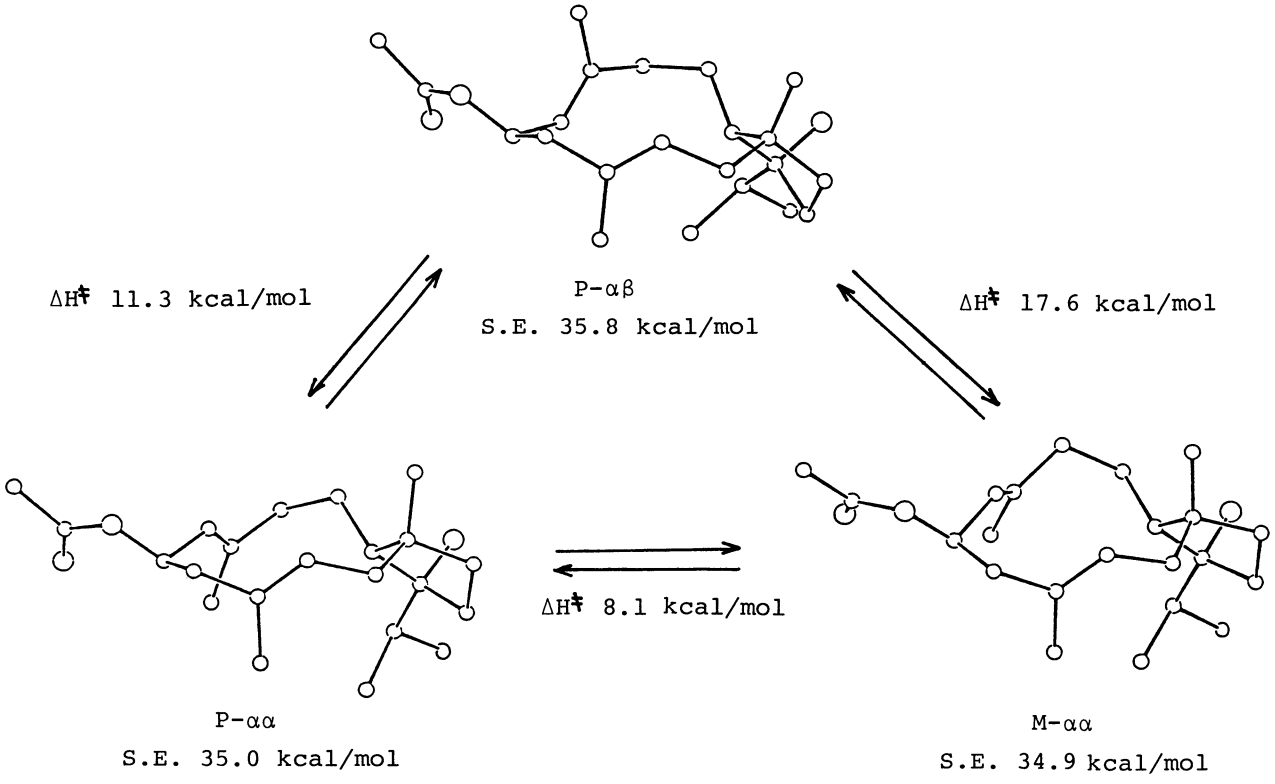

Fig. 1. Three stable conformers of the dolabellanoid (1) and their steric energies (S.E.) and energy barriers (ΔH‡).

The ^1H NMR (400 MHz) and ^{13}C NMR (22.63 MHz) spectra of the dolabellanoid (1) showed an average set of signals with no broadening. The observed vicinal coupling constants of the ^1H NMR,[9] however, gave a good agreement with the weighted average values of those of the above three conformers,[10] calculated by the

Karplus equation using the Bother-By's parameter.[11,12] These phenomena are explained by a rapid exchange between the three stable conformers owing to their low energy barriers (see Fig. 1). Moreover, the variable temparature CD spectra of the benzoate (2) resulted in an increase of negative Cotton effect at low temperature,[13] revealing that the most stable conformer gave a negative Cotton effect.[14] The difference of free energy ($\Delta G°$ = 0.6 kcal/mol) between the major conformers showing a negative curve and the minor conformer giving a positive one was calculated by the method of Moscowitz *et al.*,[15] and this value was in conformity with the difference of steric energy ($\Delta H°$ = 0.9 kcal/mol) for the compound (1).

Mono-epoxidation of the diene (1) using *m*-chloroperbenzoic acid (MCPBA) in $CHCl_3$ resulted in a regioselective reaction of the C3-C4 double bond. Since the C4-methyl group of the above three conformers has the same α orientation, formation of the 3S,4S-epoxide (3) is expected by considering peripheral attack of the peracid to the double bond. In the event the 3S,4S-epoxide (3) was produced as a single product in 80% yield.[1] However, when 1 was submitted to bis-epoxidation using two equivalents of MCPBA in $CHCl_3$, two stereoisomeric products (4), $C_{22}H_{36}O_5$, mp 109-110 °C, and (5), $C_{22}H_{36}O_5$, mp 220-221 °C, were obtained.[16] Their stereochemistries were elucidated by the ^1H NMR spectra as 3S,4S;7S,8S-diepoxide (4) and 3S,4S;7R,8R-diepoxide (5), and crystal structure of the minor (5) was confirmed by X-ray analysis as shown in Fig. 2.[17,18] The major 3S,4S;7S,8S-diepoxide (4) arises from the P-αα and/or M-αα conformers, while the minor 3S,4S;7R,8R-diepoxide (5) from the P-αβ conformer. The ratio of the two products (4 and 5) (4 : 1 at reflux; 5 : 1 at room temperature) is reasonably related to the above conformational populations of the original diene (1).

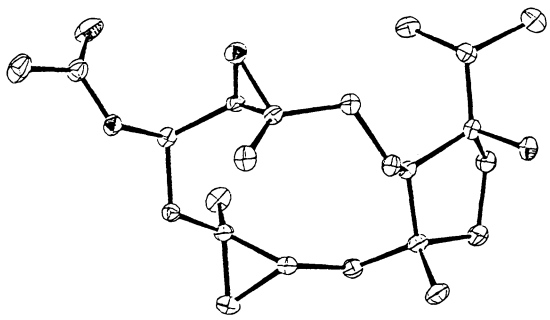

Fig. 2. A perspective view of 5.

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References

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2) For example: H. Shirahama, E. Osawa, and T. Matsumoto, J. Am. Chem. Soc., 102, 3208 (1980); W. C. Still and I. Galynker, Tetrahedron, 37, 3981 (1981).
3) The four conformers are expressed by a combination of directions of the C4-methyl and C8-methyl (α or β orientation).
4) N. L. Allinger, J. Am. Chem. Soc., 99, 8127 (1977).
5) The twisting signs (P:plus and M:minus) are used as the signs of dihedral angle of the C8-C9-C10-C11 bond.
6) Steric energy (kcal/mol) of the other five conformers is as given below: M-αβ 38.5; P-ββ 39.9; M-ββ 47.3; P-βα 39.1; M-βα 44.0.

7) The barrier to the conformational exchange was calculated by using the dihedral driver routine of MM2.

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9) The characteristic coupling constants of 1 are as follows: $J_{2\alpha-3}$=12.5 Hz (calcd. J=12.7 Hz), $J_{2\beta-3}$=0 (4.3), $J_{5\alpha-6}$=5.3 (5.9), $J_{5\beta-6}$=10.7 (12.2), J_{6-7}= 10.2 (12.7), $J_{9\alpha-10\alpha}$=3.7 (4.9), and $J_{9\alpha-10\beta}$=6.1 (8.2).

10) The relative populations of the three conformers (P-αα 41%, M-αα 48%, and P-αβ 11%) were calculated from the steric energies obtained in Fig. 1, assuming they are in an equilibrium.

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16) The new compounds 4 and 5 gave satisfactory combustion and mass spectrometric analysis and spectroscopic data consistent with the assigned structures; 4: δ 2.50 (dd, J=13.2 and 3.7 Hz: 5-Hα), 2.89 (d, J=9.5 Hz: 7-H), 3.07 (dd, J=8.8 and 1.1 Hz: 3-H), and 4.91 (ddd, J=11.9, 9.5, and 3.7 Hz: 6-H);[8] 5: δ 2.47 (dd, J=12.8 and 5.9 Hz: 5-Hα), 2.88 (d, J=8.4 Hz: 3-H), 3.00 (d, J=4.4 Hz: 7-H), and 5.48 (ddd, J=12.1, 5.9, and 4.4 Hz: 6-H).

17) Crystal data of 5: $C_{22}H_{36}O_5$, M=380.5, monoclinic, space group $P2_1$, a=11.314(2), b=7.931(1), c=12.434(2) Å, β=108.87(1)°, U=1055.7(3) Å^3, Z=2, D_c=1.20 g/cm^3, F(000)=416, Mo-Kα radiation, λ=0.7107 Å, μ(Mo-Kα)=0.9 cm^{-1}.

The diffraction intensities with $2\theta \leqslant 50°$ were collected in the variable speed ω scan mode with graphite-monochromated Mo-Kα radiation on a Syntex R3 four-circle diffractometer. Of 2115 independent reflections, 1852 having $Fo \geqslant 2\sigma(Fo)$ were judged to be observed after correction for Lorentz, polarization, and background effects. The structure was solved by direct methods (MULTAN 78),[19] and refinement by block diagonal least-squares using anisotropic thermal parameters for the non-hydrogen atoms and isotropic ones for the hydrogen atoms with UNICS III program system[20] led to a final R-value of 0.034.

18) The atomic co-ordinates for this work have been deposited with Cambridge Crystallographic Data Centre.

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