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ABSOLUTE STEREOCHEMISTRIES AND CONFORMATIONS OF CLERODIN AND CARYOPTIN. WHY CONFLICTING RESULTS IN ABSOLUTE STEREOCHEMISTRY BASED ON CD AND ORD SPECTRA?

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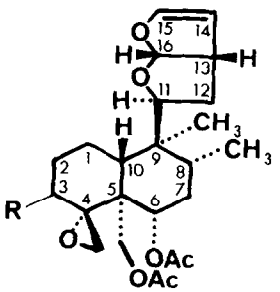
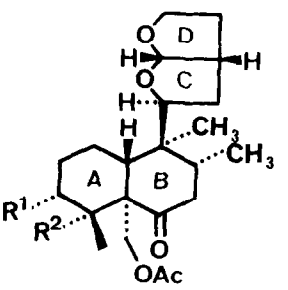
Summary: The reverse of absolute stereochemistries of clerodin and caryoptin means that the correct chirality conflict with the absolute stereochemistries based on Cotton effects. Molecular mechanics and X-ray studies confirmed that the B ring of the 6-keto derivatives retained the boat form as the stable conformer. Furthermore, the steric factors causing the conformational changes were proved by derivation to the strain-free derivatives. The conformation of the B ring in the derivatives changed to the chair form which is confirmed by the X-ray and CD.

Based on chiroptical data[1] and X-ray study[2], the absolute stereochemistries of specific insect antifeedants, clerodin, caryoptin, and 3-epicaryoptin, should be expressed as formulas 1, 2, and 3 which had earier been assigned the opposite chirality by Barton et al.[3] and the authors[4]. The reversal of their chirality, however, means that the correct chirality conflicts with the absolute stereochemistries which have been determined from Cotton effects[3,4]. Thus, the problem is why these compounds previouly exhibited unexpected Cotton effects.

In the present study, we report that the conflict of the Cotton effects on 6-keto derivatives 4 and 5 is attributable to conformational changes. Their absolute stereochemistries had been determined from the CD spectra with intense positive Cotton effects, 4: $\Delta\varepsilon_{301.5}$ +3.51 and 5: $\Delta\varepsilon_{301}$ +3.10[4], and the ORD spectrum of 6-keto clerodin derivative[3].



1, R=H
2, R=···OAc
3, R=◀OAc



4, R^1=H, R^2=OH
5, R^1,R^2= ·O ·O
6, R^1,R^2=OH
7, R^1=$O_2CC_6H_5Br$-p, R^2=OH

We attempted to clarify the conformations of 4 and 5 by energy minimization calculation[5] in studying the structure-activity relationships of 1 and its analog[6]. The results of the calculation were of interest in that the boat conformers of both compounds were more stable than the chair conformers on the B ring (Table 1). If they took the boat form on the B ring, the intense positive Cotton effects could not be concluded for them from the octant projections[7]. And the boat conformers of 4 and 5 seemed to have more steric interactions than the

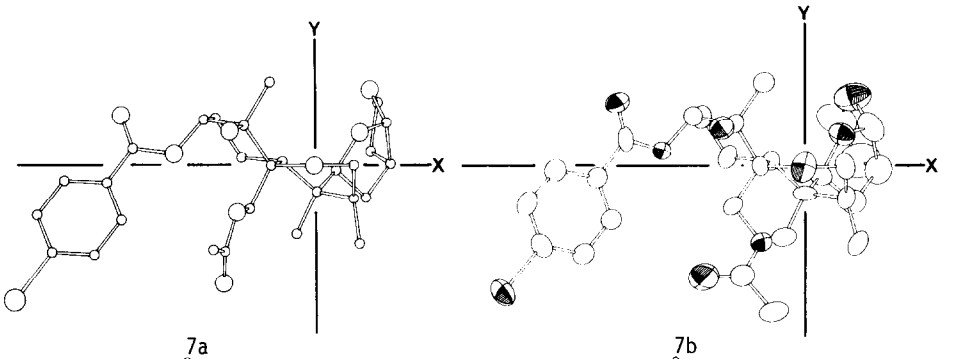
Table 1. Steric energies (E Kcal/mol) calculated for the chair and boat conformers on the B ring.

	E_{chair}	E_{boat}	Δ^a		E_{chair}	E_{boat}	Δ
4	71.2105	70.7709	0.4396	7	82.3930	80.7588	1.6342
5	89.2744	88.4923	0.7821	8	64.3601	67.0583	-2.6982
6	75.1541	74.4208	0.7333	10	68.9847	69.7139	-0.7292

[a] $E_{chair} - E_{boat}$

chair conformers from molecular models although clerodin and caryoptin themselves retained the chair conformation on the B ring[2,8]. Furthermore, minimized steric energies were also calculated for strainless 3,4-dihydroxy and 3-p-bromobenzoyl-6-keto derivatives 6 and 7 (Table 1). Although the steric energies of both compounds decrease in comparison with that of 5, the stable conformers leave the boat form on the B ring (Fig. 1. 7a). Both compounds were experimentally derived from 2[9], and the CD spectra showed 6: $\Delta\varepsilon_{300}$ +5.07 and 7: $\Delta\varepsilon_{299}$ +2.55. Further increase in intensities of the Cotton effects with positive sign may be attributed to the disappearance of the contribution of the 3,4-acetonide group to the minus front octant and to the retention of the boat conformation on the B ring. The X-ray study presented a definitive evidence of the conformation and the absolute stereochemistry of 7 (Fig. 1. 7b)[10]

Fig. 1

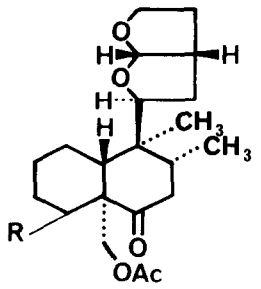


7a 7b

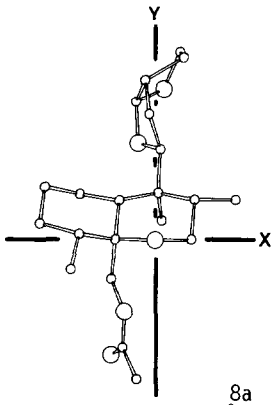
and proved the validity of prediction for the stable boat conformation of 4 ∿ 7 by molecular mechanics. Thus, it is concluded that the Cotton effects of the 6-keto derivatives were in conflict with the correct absolute stereochemistry of 1 and 2 because of converting to the boat conformation of the B ring, which was entirely unexpected from the conformation of the C-6 acetyl derivatives[2,8].

The result may be accepted as a general concept by proof of factors causing the unusual conformational change. The steric factors were predicted by molecular mechanics and the derivation of strain-free compounds 8 and 9 was demonstrated. Steric forces responsible for the conformational changes were predicted from detailed studies of steric and VDW interaction energies for 4 ∿ 9 and the compounds replaced by hydrogen(s) of C-4, 5, 8, and 9 substituent group(s). It is striking that the compound 8 with a 4-α-methyl group assumed the chair conformation on the B ring as the stable conformer (Table 1; Fig. 2. 8a). Therefore, the 4-α-methyl derivative 8 was derived from 1 stereospecifically[11], and the CD spectrum with positive sign and low intensity showed $\Delta\varepsilon_{301}$ +0.89. The marked decrease in the intensity over

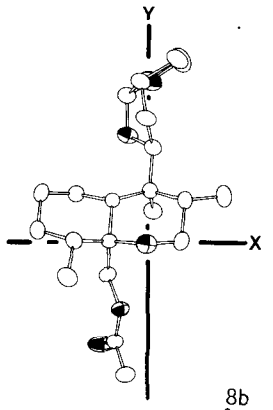
Fig. 2



8, R= ···CH3
9, R= ◄CH3



8a



8b

that of 4 would be attributable to the eq orientation of C-4 methyl group, and further corroborating evidence for the chair conformation was provided by the X-ray study of 8 (Fig. 2. 8b)[12]. The X-ray analysis showed that the B ring of 8 was transformed into the chair conformation by deletion of the steric strain on the C-4 ax substituent group. Thus, one of the steric factors causing the conformational change on the B ring is 1,3-interactions due to participation by the C-4 ax substituent group for the carbonyl group and C-10 proton.

Furthermore, the steric energies suggested the participation of a C-5 carbinol group in the conformational change and, for a decarbinol derivative 10, showed the chair conformation on the B ring as a stable conformer (Table 1). This prediction was actually proved by derivation of 10 from 2[13]. The derivative 10 with trans juncture[13,14] showed the CD spectrum with positive sign, $\Delta\varepsilon_{303}$ +2.20. The determination of its conformation based on the Cotton effect is logically deduced from the fact that, although the C-5 carbinol group of 5 contributes much to negative amplitude at the third quardrant in any conformation, the Cotton effect of 10 has a lower intensity than that of 5. Thus, it is concluded that the conformation on the B ring of 10 could only be the chair form (Fig. 3) and the other steric factor causing the conformational change is the C-5 carbinol group.

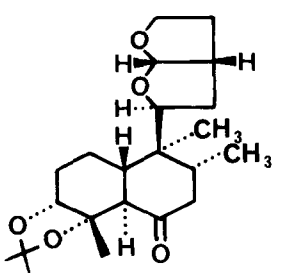


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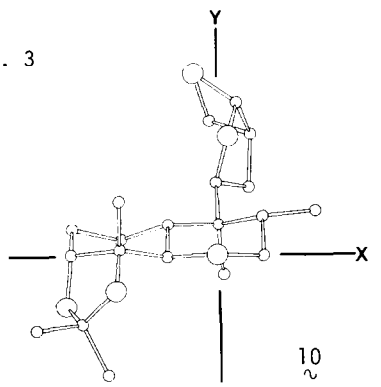
Fig. 3



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There have been many arguments against the absolute stereochemistries of neo-clerodane diterpenes[3,4,15]. Complications may arise from the fact that the conformational changes in many cases depended on the delicate balance among bisectional steric interactions above and below the decalone ring.

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References and Footnotes

1, Harada, N.; Uda, H. J. Am. Chem. Soc. 1978, 100, 8022.

2, Rogers, D.; Unal, G.G.; Williams, D.J.; Ley, S.V.; Sim, G.A.; Joshi, B.S.; Ravindranath, K.R. J. Chem. Soc. Chem. Comm. 1979, 97.

3, Barton, D.H.R.; Cheung, H.T.; Cross, A.D.; Jackman, L.M.; Martin-Smith, M. J. Chem. Soc. 1961, 5061.

4, Hosozawa, S.; Kato, N.; Munakata, K. Phytochemistry 1974, 13, 308; Tetrahedron Lett. 1974, 3753.

5, Allinger, N.L. Program MM2: 77-Force Field 1980. QCPE No. 318. Computation was performed at the computer center of Institute for Molecular Science and Nagoya University.

6, Kojima, Y.; Kato, N. Tetrahedron Lett. 1980, 21, 5033; Tetrahedron 1981, 37, 2527.

7, Moffit, W.; Woodward, R.B.; Moscowitz, A.; Klyne, W.; Djerassi, C. J. Am. Chem. Soc. 1961, 83, 4013.

8, Paul, I.C.; Sim, G.A.; Hamor, T.A.; Robertson, J.M. J. Chem. Soc. 1962, 4133.

9, The 3,4-dihydroxy caryoptin derivative 6 was derived by methanolysis from 5 and 7 was obtained by treatment of 6 with p-bromobenzoyl chloride.
6: mp 112-114°C; $[\alpha]_D$ +95° (c 0.34, $CHCl_3$); CD $\Delta\varepsilon_{300}$ +5.07 (c 0.46, EtOH)
7: mp 168-170°C; $[\alpha]_D$ +26° (c 0.35, $CHCl_3$); CD $\Delta\varepsilon_{299}$ +2.55 (c 0.57, EtOH)
Satisfactory spectroscopic data (NMR, MS, high resolution MS, IR) were obtained for these compounds.

10, The crystallographic data were collected on a Rigaku fourcircle diffractometer RU-200, using ω-2θ scan technique and graphite-monochromatized MoKα radiation. All the data were corrected for Lorentz and polarization factors. The structure was solved by the heavy atom method and refined using the block-diagonal least-square program; HBLS VI. Both set of F(hkl) and F($\bar{h}\bar{k}\bar{l}$) were refined including the anormalous dispersion terms of Br and with anisotropic temperature factors for C, O, and Br atoms. The final weighted agreement factors were R_{W+}=0.076 and R_{W-}=0.045. The absolute configuration was confirmed by the ratio R_{W+}/R_{W-}=1.69. Crystal data: $C_{29}H_{37}O_8Br$, mol wt 593.5; orthorhombic, space group $P2_12_12_1$; a=24.144(6)Å, b=7.313(6)Å, c=15.961(6)Å; F(000)=1232; (MoKα)=16.0cm^{-1}; number of reflections=2017($2\theta \leqq 44°$).

11, The α-4-methyl derivative 8 was derived in five steps from 1. 8: mp 108-110°C; $[\alpha]_D$ -33.4° (c 0.39, $CHCl_3$); CD $\Delta\varepsilon_{301}$ +0.89 (c 0.22, EtOH). Satisfactory spectroscopic data (NMR, MS, high resol. MS, IR) were obtained for this compound.

12, The crystallographic data was collected on CuKα radiation. The structure was solved by the direct method program MULTAN 78 and refined by HBLS VI programs with anisotropic temperature factors for all C and O atoms. Crystal data: $C_{22}H_{34}O_5$, mol wt 378.4; monoclinic, space group $P2_1$; a=13.678(1)Å, b=8.172(1)Å, c=10.091(1)Å, β=113.55(1)°; F(000)=412, (CuKα)=7.2cm^{-1}; number of reflections=1670. R=0.043 and R_W=0.056.

13, The decarbinol derivative 10 was derived in six steps from 2. 10: mp 115-117°C; $[\alpha]_D$ +28.1° (c 0.10, $CHCl_3$); CD $\Delta\varepsilon_{303}$ +2.20 (c 0.38, EtOH); NMR ($CDCl_3$) 5·H δ2.42 (d, J=11.9 Hz). Satisfactory spectroscopic data (NMR, MS, high resol. MS, IR) were obtained for this compound.

14, Franklin, N.C.; Feltkamp, H. Angew. Chem. Internat. Edit. 1965, 4, 774.

15, Kubo, I.; Lee, Y.-W.; Balogh-Nair, V.; Nakanishi, K.; Chapya, A. J. Chem. Soc. Chem. Comm. 1976, 949; Trivedi, G.; Komura, H.; Kubo, I.; Nakanishi, K. J. Chem. Soc. Chem. Comm. 1979, 885; Kubo, I.; Kido, M.; Fukuyama, Y. J. Chem. Soc. Chem. Comm. 1980, 897; Savona, G.; Passannanti, S.; Paternostro, M.; Piozzi, F.; Hanson, J.R.; Hitchcook, P.B.; Siverns, M. J. Chem. Soc. Perkin I 1978, 356; Savona, G.; Paternostro, M.; Piozzi, F.; Rodriguez, B. Tetrahedron Lett. 1979, 897; Gács-Baitz, E.; Radics, L.; Oganessian, G.B.; Minatsakanian, V.A. Phytochemistry 1978, 17, 1967.

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