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APPLICATION OF THE CD HOMOALLYLIC BENZOATE METHOD AS A CHIROPTICAL TOOL FOR DETERMINATION OF ABSOLUTE CONFIGURATION

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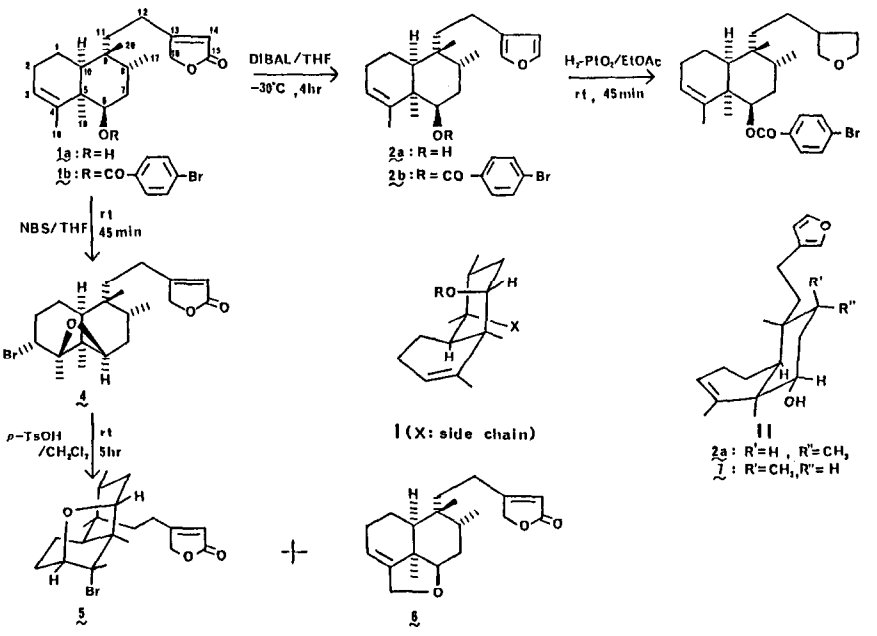
Summary: After the conformation I was clarified to 5α,10α-*cis*-solidagolactones by ^{1}H NMR measurement with Eu(dpm)$_3$ and chemical transformations, the CD homoallylic benzoate chirality method was applied to the homoallylic alcohol system of solidagolactone IV (1a) for a chiroptical determination of the absolute configuration. The result agreed with the absolute configuration elucidated by X-ray analysis, indicating the usefulness of the CD method.

The allylic benzoate chirality method, a CD exciton chirality method[1], has been successfully applied for determining absolute configurations of allylic alcohols[2]. Naya *et al.*[3] determined the absolute structure of the insect sesterterpene, 5-hydroxyfloridenol, in which the 5-OH functioned as both allylic and homoallylic alcohols. They observed, therefore, a positive Cotton effect composed of both allylic and homoallylic benzoate chiralities in the CD of 5-*p*-bromobenzoate derivative of the sesterterpene. This suggested that the homoallylic benzoate chirality may be arised from the same chiral exciton coupling mechanism as in the case of allylic benzoate chirality. In the present case, a 5α,10α-*cis*-solidagolactone, solidagolactone IV (1a) (clerodane diterpene) which was isolated from *Solidago altissima* L. as a piscicidal constituent[4] was considered to be a suitable example to show the significance of the homoallylic benzoate chirality method, since 1a contains a homoallylic alcohol system singly and the absolute stereochemistry has been established by X-ray analysis[4]. However, since the molecular conformation affects the sign and intensity of CD Cotton effect, before the CD work we determined the conformation of 5α,10α-*cis*-solidagolactones[5] on the basis of the induced shift in ^{1}H NMR added Eu(dpm)$_3$ and chemical conversion of 1a.

In ^{1}H NMR[6a] of 1a and related compounds (2a[7], 1b[8], 2b[9] and 3b[10]) including the other piscicidal 5α,10α-*cis*-solidagolactones[4], small coupling constants and triplet-like splittings of the H-6 signals [1a: δ 3.71 (1H, t, J=2.8) and the others: see notes[7-10]] indicated the axial configuration of the C-6 substituents. This was an essential point for elucidating the conformation. Solidagolactone IV (1a) was reduced to 2a (for reaction conditions, see Scheme 1) which was the C-8 epimer of compound 7 whose antipode 7' was isolated from other *Solidago* plant by McCrindle *et al.*[11] They applied Eu(dpm)$_3$ to ^{1}H NMR of 7' to give normalized ratio[12] values, 10 : 9.6 : 1.7 : 4.2, in the induced shifts of the C-4, C-5, C-8 and C-9 methyl resonances, respectively. These values were explainable for the relative configuration and the steroid-like conformation II[11]. In our similar ^{1}H NMR measurement with Eu(dpm)$_3$,



Scheme 1

the normalized ratio values, 3.9 : 5.3 : 2.0 : 3.3, were observed for the C-4, C-5, C-8 and C-9 methyl resonances of 2a, respectively, in which the value of 5.3[12] implied an *anti-trans* relation of the C-5 methyl to the axial C-6 hydroxy group. Our normalized ratio values were consistent only with the conformation I.

Solidagolactone IV (1a) quantitatively afforded 4[13], $C_{20}H_{29}O_3Br$ [*m/z* 398/396 (1:1, M^+)]; $[\alpha]_D$-42.2° (*c* 0.900)[6b]; ν_{max} (film): 1780, 1745, 1640 cm^{-1}; ^1H NMR: δ 0.86 (3H, d, *J*=6.8, H_3-17), 0.97 (3H, s, H_3-20), 1.16 (3H, s, H_3-19), 1.66 (3H, s, H_3-18), 4.09 (1H, dd, *J*=3.9, 5.6, H-3 or H-6), 4.46 (1H, dd, *J*=2.6, 3.3, H-6 or H-3), 4.75 (2H, d, *J*=1.8, H-16), 5.82 (1H, tt, *J*=1.5, 1.8, H-14); ^{13}C NMR[6c]: δ 59.55 (d, C-3), 79.81 (d, C-6), 84.62 (s, C-4). On treatment of 4 with *p*-toluenesulfonic acid, 5 (21% yield) was obtained with 6[14] (36%). The newly formed tetrahydrofuran ring of 5 was expected to be a thermodynamically more stable feature produced by the shift of the ether bond from C-4 of 4 to C-3 of 5 in acidic reaction condition; 5, $C_{20}H_{29}O_3Br$ [*m/z* 398/396 (1:1, M^+)]; $[\alpha]_D$-63.9° (*c* 0.360); ν_{max} (film): 1780, 1745, 1640 cm^{-1}; ^1H NMR: δ 0.88 (1H, d, *J*=6.8, H_3-17), 1.00 (3H, s, H_3-20), 1.14 (3H, s, H_3-19), 1.82 (3H, s, H_3-18), 3.75 (1H, dd, *J*=2.2, 3.1, H-6), 4.02 (1H, dd, *J*=1.7, 3.0, H-3), 4.76 (2H, d, *J*=1.8, H-16), 5.84 (1H, tt, *J*=1.5, 1.8, H-14); ^{13}C NMR: δ 74.66 (s, C-4), 76.77 (d, C-3), 81.63 (d, C-6). These data indicated that 5 takes the structure with a fixed non-steroidal conformation. Similar conformation was assignable to 1a (and the derivatives) because of the very close ^1H NMR properties for H-6, H_3-17, H_3-19 and H_3-20 of 5 to those of 1a [δ 3.71 (1H, t, *J*=2.8, H-6), 0.88 (3H, d, *J*=6.8, H_3-17), 1.15 (3H, s, H_3-19) and 1.03 (3H, s, H_3-20)][4]. The conformation I was, therefore, evaluated to 1a and the other 5α,10α-*cis*-solidagolactones[4].

For measuring the exciton chirality due to net homoallylic benzoates system, we reduced the butenolide chromophore (λ_{max} 205 nm) of 1a successively to furan (λ_{max} 200 nm) and tetrahydrofuran, and prepared the respective *p*-bromobenzoate derivatives (1b, 2b and 3b).

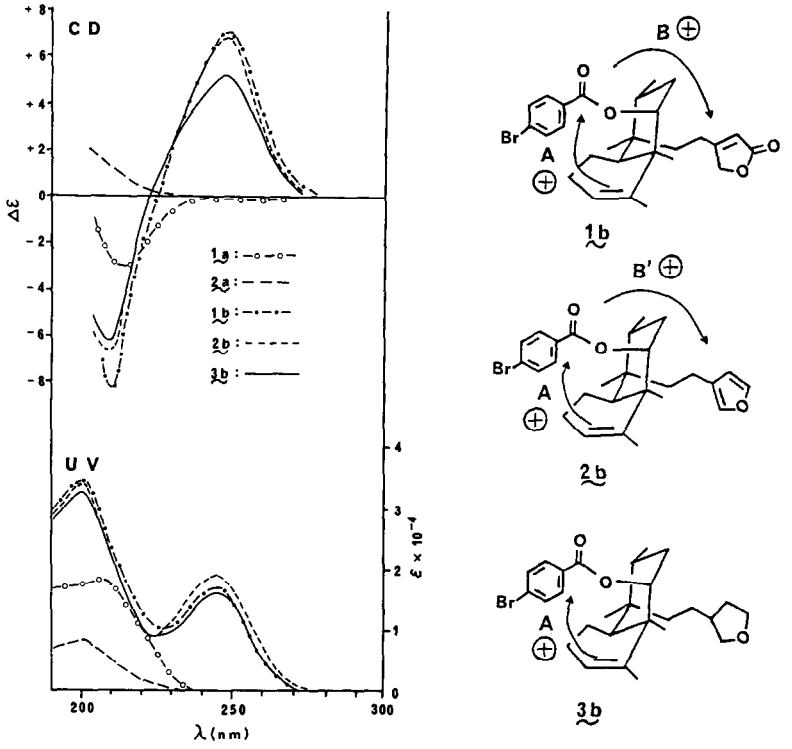


Fig. 1

The UV[6d] and CD[6d] curves of the benzoate derivatives are shown in Fig. 1 together with those of 1a[15] and 2a[7].

The CD of 3b exhibited a positive split Cotton effect with λ_{ext} 247.5 nm (Δε +5.34) (A in 3b of Fig. 1). This split was considered owing to the interaction of the homoallylic benzoate system of 3b, *ie.*, a coupled oscillator composed of the double bond ππ* transition at ca. 195 nm and the *p*-bromobenzoate ππ* transition at 244 nm. Furthermore, both 1b and 2b demonstrated positive Cotton effects at 247 (Δε +7.03) and 247.5 nm (Δε +6.87), respectively, in their CD. Either Δε value was anticipated to consist of two positive Cotton effects arising from the common 6-*p*-bromobenzoate/3-ene (A, Δε +5.34) interaction and 6-*p*-bromobenzoate/$\Delta^{\alpha\beta}$-butenolide (B in Fig. 1-1b, Δε +1.69) or 6-*p*-bromobenzoate/furan (B' in Fig. 1-2b, Δε +1.53) interaction by additive manner[16,17]. Exciton chiralities due to benzoate/remote chromophore, accordingly, would also contain respectable meaning[17] in the chiroptical determination. The positive sign of Cotton effect in 3b represents the clockwise relation (tortional angle around C3-C4-C6-OR: ca. +50°) between 6-*p*-bromobenzoate/3-ene (Fig. 1-3b). Hence, the absolute configuration of solidagolactone IV was assigned as illustrated in 1a, which agreed with the configuration by X-ray analysis[4].

The homoallylic benzoate chirality method was shown here to be a useful chiroptical tool for determining absolute configurations of homoallylic alcohols included abundantly in natural and synthetic organic compounds.

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References and Notes

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6. a: In $CDCl_3$ at 90 MHz. J in Hz; b: In EtOH at 25°C unless otherwise stated; c: In $CDCl_3$ at 22.5 MHz; d: Measured with a 0.45×10^{-4} molar solution in EtOH in an 1-cm cell at 25°C.
7. 2a: $C_{20}H_{30}O_2$; exact MS: *m/z* 302.2235 (M^+); $[\alpha]_D$+12.6° (*c* 0.950); λ_{max} 200.0 nm (ε 8400); CD: no clear extremum at 205-300 nm; ν_{max} (film): 3560, 3470 (sh.), 878 cm^{-1}; ^{1}H NMR: δ 0.86 (3H, d, *J*=6.6, H_3-17), 1.05 (3H, s, H_3-20), 1.21 (3H, s, H_3-19), 1.70 (3H, brs, H_3-18), 3.69 (1H, t, *J*=2.5, H-6) 5.83 (1H, m, H-3), 6.25 (1H, m, furanoid), 7.19 (1H, m, furanoid), 7.33 (1H, t, *J*=1.5, furanoid); δ [with 0.84 mol. equiv. of Eu(dpm)$_3$] 2.73 (3H, d, *J*=6.6, H_3-17), 4.20 (3H, s, H_3-20), 5.36 (3H, brs, H_3-18), 6.22 (3H, s, H_3-19).
8. 1b: $C_{27}H_{33}O_4Br$ (Anal. Calcd: C, 64.67; H, 6.63; Br, 15.93. Found: C, 64.20; H, 6.55; Br, 15.80); MS: *m/z* 502/500 (1:1, M^+); mp 157-159°; $[\alpha]_D$+22.1° (*c* 0.452); λ_{max} 243.7 (ε 16600), 200.8 nm (34300); CD: λ_{ext} 247.0 (Δ +7.03), 224.5 (0.0), 208.5 nm (-8.41); ν_{max} (KBr): 1785, 1750, 1715, 1640, 1595, 1490, 1275 cm^{-1}; ^{1}H NMR δ 0.87 (3H, d, *J*=6.2, H_3-17), 1.09 (3H, s, H_3-20), 1.26 (3H, s, H_3-19), 1.56 (3H, brs, H_3-18), 4.76 (2H, d, *J*=1.8, H-16), 5.16 (1H, brt, *J*=2.6, H-6), 5.50 (1H, m, H-3), 5.86 (1H, tt, *J*=1.5, 1.8, H-14), 7.56 (2H, dm, *J*=8.8, *p*-bromobenzoyl), 7.81 (2H, dm, *J*=8.8, *p*-bromobenzoyl).
9. 2b: $C_{27}H_{33}O_3Br$; exact MS: *m/z* 486.1592/484.1613 (1:1, M^+); mp 122-123.5°; $[\alpha]_D$+24.3° (*c* 0.740), +44.2° (*c* 0.430, $CHCl_3$); λ_{max} 243.8 (ε 18600), 199.4 nm (33700); CD: λ_{ext} 247.5 (Δε +6.87), 222.0 (0.0), 207.5 nm (-6.73); ν_{max} (KBr): 1715, 1595, 1490, 1270, 875 cm^{-1}; ^{1}H NMR: δ 0.85 (3H, d, *J*=6.2, H_3-17), 1.11 (3H, s, H_3-20), 1.32 (3H, s, H_3-19), 1.56 (3H, brs, H_3-18), 5.16 (1H, brt, *J*=2.6, H-6), 5.51 (1H, m, H-3), 6.28 (1H, m, furanoid), 7.22 (1H, m, furanoid), 7.36 (1H, t, *J*=1.7, furanoid), 7.55 (2H, dm, *J*=8.8, *p*-bromobenzoyl), 7.82 (2H, dm, *J*=8.8, *p*-bromobenzoyl).
10. 3b (a mixture of two epimers at C-13): exact MS: *m/z* 490.1939/488.1890 (M^+); $[\alpha]_D$+55.0° (*c* 0.220, $CHCl_3$); λ_{max} 243.7 (ε 16200), 200.0 nm (32300); CD: λ_{ext} 247.5 (Δε +5.34), 221.0 (0.0), 208.8 nm(-6.42); ν_{max} (film): 1715, 1595, 1490, 1275 cm^{-1}; ^{1}H NMR: δ 0.84 (3H, d, *J*=6.5, H_3-17), 1.03 (3H, s, H_3-20), 1.27 (3H, s, H_3-19), 1.57 (3H, brs, H_3-18), 3.34 (1H, m, tetrahydrofuranoid), 3.62-4.03 (3H, complex, tetrahydrofuranoid), 5.14 (1H, brt, *J*=2.4, H-6), 5.49 (1H, m, H-3), 7.55 (2H, dm, *J*=8.8, *p*-bromobenzoyl), 7.81 (2H, dm, *J*=8.8, *p*-bromobenzoyl).
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14. 6; $C_{20}H_{28}O_3$; exact MS: *m/z* 316.1672 (M^+); $[\alpha]_D$-56.6° (*c* 0.530); ν_{max} (film): 1780, 1745, 1640 cm^{-1}; ^{1}H NMR: δ 0.91 (3H, d, *J*=7.0, H_3-17), 1.06 (3H, s, H_3-20), 1.22 (3H, s, H_3-19), 4.08 (1H, dd, *J*=8.1, 9.5, H-6), 4.29 (1H, dm, *J*=13.0, H-18a), 4.50 (1H, dm, *J*=13.0, H-18b), 4.76 (2H, d, *J*=1.8, H-16), 5.45 (1H, brt, *J*=3.1, H-3), 5.85 (1H, tt, *J*=1.5 , 1.8, H-14); ^{13}C NMR: δ 67.75 (t, C-18), 82.57 (d, C-6), 115.95 (d, C-3), 143.29 (s, C-4).
15. λ_{max} 204.9 nm (ε 18100); CD: λ_{ext} 213.0 nm (Δε -2.91).
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