THE MOLECULAR STRUCTURE OF SUBCORDATOLIDE C, A EUDESMANOLIDE FROM *CALEA SUBCORDATA*

ALFONSO G. OBER, FRANK R. FRONCZEK, and NIKOLAUS H. FISCHER*

Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803

ABSTRACT.—*Calea subcordata* yielded subcordatolide C, a new 12,8β-lactonized eudesmanolide type sesquiterpene lactone. Its structure was inferred from nmr and mass spectral data and the molecular structure determined by single-crystal X-ray diffraction.

We have recently reported the presence of guaianolide-type sesquiterpene lactones (1) and a 12,8α-lactonized eudesmanolide, subcordatolide B (2)(2), in *Calea subcordata* S.F. Blake. Further investigations of this species resulted in the isolation of a new eudesmanolide, subcordatolide C, which contains a 12,8β-lactonized γ-lactone moiety. The structure of the new compound was inferred from nmr and mass spectral data. The molecular structure was determined by single-crystal X-ray diffraction and its absolute configuration derived from chiroptical data.

RESULTS AND DISCUSSION

SPECTROSCOPIC CHARACTERIZATION.—Chromatographic procedures applied to the crude terpenoid extract of *C. subcordata* provided a colorless crystalline compound that we named subcordatolide C (**1**), $C_{19}H_{26}O_5$, mp 196-197° (dec.). The ir spectrum of **1** showed the presence of a hydroxyl group (3510 cm^{-1}), a γ-lactone (1765 cm^{-1}), and a saturated ester (1730 cm^{-1}). The α-methylene-γ-lactone moiety was further corroborated by the ^{1}H-nmr spectrum of **1**, which exhibited two one-proton doublets at δ 6.18 (H-13a) and 5.51 (H-13b), and a broadened doublet of doublets at δ 2.97 (H-7). The ester substituent was assigned to an isobutyrate group on the basis of diagnostic ^{1}H-nmr signals (a one-proton heptet at δ 2.51, and two three-proton doublets at δ 1.14 and 1.12), together with characteristic mass spectral peaks at *m/z* 246 (M-A), 71 (**A'**), and 43 (**A"**). Further assignments of the basic skeleton of subcordatolide C (**1**) were deduced from extensive double irradiation experiments, the results being summarized in Table 1.

The conclusions derived from spectroscopic analysis were further corroborated by the molecular structure obtained by single X-ray diffraction.

CRYSTAL STRUCTURE ANALYSIS.—The molecular structure of subcordatolide C, determined by X-ray diffraction, is illustrated in Figure 1. The α-methylene-γ-lactone

1

2
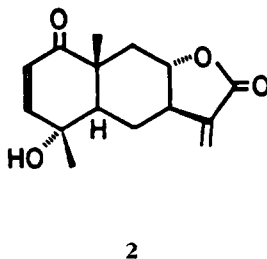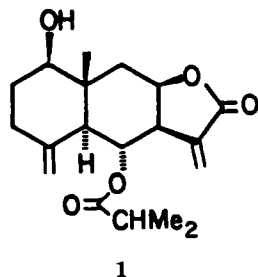
	A	A'	A"
m/z	88	71	43

HO—C—CHMe$_2$
  ‖
  O

TABLE 1.   ¹H-nmr Parameters[a] of Subcordatolide C (**1**)

H-1	3.43 dd	(12.0; 5.0)
H-2a	1.86 dddd	(13.0; 5.0; 5.0; 3.0)
H-2b	1.52 m	
H-3a	2.30 ddd	(14.0; 5.0; 3.0)
H-3b	2.05 ddd	(14.0; 14.0; 5.0)
H-5	2.18 d	(12.3)
H-6	5.18 dd	(12.3; 10.0)
H-7	2.97 br dd	(10.0; 5.8)
H-8	4.64 ddd	(5.8; 5.8; 2.0)
H-9a	2.68 dd	(16.8; 2.0)
H-9b	1.57 dd	(16.8; 5.8)
H-13a	6.18 d	(1.5)
H-13b	5.51 d	(1.3)
H-14	0.90 br s	
H-15a	4.86 br s	
H-15b	4.53 br s	
H-2′	2.51 h	(7.5)
2 C-2′-CH₃	1.14 d	(7.5)
	1.12 d	

[a]The spectrum was obtained at 200 MHz in $CDCl_3$. Chemical shifts are recorded in ppm relative to TMS. Multiplets are given by the usual symbols: s=singlet, d=doublet, h=heptet, m=multiplet, and br=broadened. Coupling constant (J) or line separations, in Hz, are given in parentheses.

ring is *cis*-fused to the eudesmane skeleton at C7-C8, unlike the co-occurring subcordatolide B, in which that fusion is *trans*. The conformation of the molecule is given by the torsion angles in Table 2. Both six-membered rings approximate the chair conformation, with this approximation being somewhat worse for the lactonized six-membered ring (mean deviation 10.8° from ideal 60° torsion angle) than for the other (mean deviation 3.2°). The conformation of this portion of the molecule adheres quite closely to that of the similar dihydropulchellin C diacetate (as the *p*-bromobenzenethiol adduct) (**3**); the 12 endocyclic torsion angles differ in magnitude by an average of only 2.8° between the two molecules.

The lactone ring is distinctly nonplanar (sum of endocyclic torsion angle magnitude = 117°) and exists in the half-chair conformation, with the local twofold axis passing through C12 and bisecting C7-C8. Interestingly, the *trans*-fused lactone ring in subcordatolide B (**2**) exhibits a half-chair conformation almost identical to that of the *cis*-fused lactone in subcordatolide C, except that the sense of the twist about the local
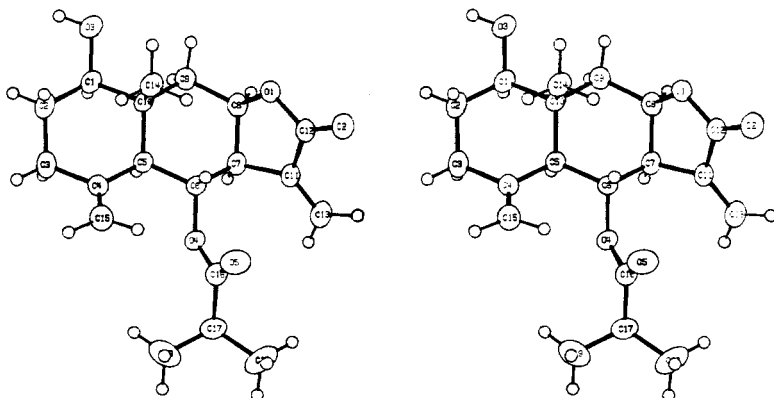

FIGURE 1.   Stereoscopic representation of subcordatolide C.

TABLE 2. Selected Torsion Angles

Atom 1	Atom 2	Atom 3	Atom 4	Angle (degree)
C1	C2	C3	C4	53.4
C2	C3	C4	C5	−57.2
C3	C4	C5	C6	−172.3
C4	C5	C6	C7	173.8
C5	C6	C7	C8	53.4
C6	C7	C8	C9	−41.9
C7	C8	C9	C10	39.7
C8	C9	C10	C1	−160.8
C9	C10	C1	C2	175.1
C10	C1	C2	C3	−55.8
C3	C4	C5	C10	62.0
C4	C5	C10	C1	−59.3
C5	C10	C1	C2	57.0
C8	C9	C10	C5	−45.4
C9	C10	C5	C6	55.5
C10	C5	C6	C7	−60.8
C7	C8	O1	C12	29.7
C8	O1	C12	C11	−10.9
O1	C12	C11	C7	−12.6
C12	C11	C7	C8	29.1
C11	C7	C8	O1	−35.1
O2	C12	C11	C13	−15.7
C2	C1	O3	H3OH	−43.7

twofold axis is enantiomeric. Thus, the exocyclic torsion angle C13-C11-C12-O2 has a value of −15.7° in subcordatolide C, and the corresponding angle in subcordatolide B is +22.0°. The cd spectrum of **1** exhibited a negative band at 255 nm, indicative of a negative Cotton effect of the n↦π* transition of the α-methylene-γ-lactone ring. The crystal structure showed the lactone group to have a left-handed chirality with a negative torsion angle (C13=C11-C12=O2, −15.7) for the lactone chromophore if the absolute configuration is that given in Figure 1. Application of Beecham's rule (4) correlates the left-handed chirality of this torsion angle with a negative Cotton effect. It was also shown by Cox and Sims (5) that the exocyclic C13=C11-C12=O2 and the endocyclic C12-C7-C8-O1 torsion angles correlated well and the authors suggested that the latter torsion angle might correlate better with the sign of the Cotton effect. Since in the case of subcordatolide C the above torsion angles (−15.7 and −35.1, respectively) are in accord with the cd data, by application of Beecham's rule and its extension

TABLE 3. Coordinates for Nonhydrogen Atoms

Atom	x	y	z	Atom	x	y	z
O1	0.3206(3)	−0.0824(2)	0.04393(8)	C8	0.1427(5)	0.0051(3)	0.0324(1)
O2	0.3643(4)	−0.3002(2)	0.05934(8)	C9	0.1890(6)	0.1521(3)	0.0408(1)
O3	0.3319(4)	0.4108(2)	0.06625(10)	C10	0.1795(5)	0.2024(3)	0.0920(1)
O4	−0.2223(3)	−0.0520(2)	0.13534(7)	C11	0.0182(5)	−0.1998(3)	0.0597(1)
O5	−0.0548(4)	−0.2068(2)	0.17899(8)	C12	0.2481(5)	−0.2048(3)	0.0545(1)
C1	0.1551(5)	0.3575(3)	0.0907(1)	C13	−0.1031(6)	−0.3063(3)	0.0605(1)
C2	0.1252(6)	0.4183(3)	0.1395(1)	C14	0.3797(5)	0.1636(3)	0.1191(1)
C3	−0.0591(6)	0.3581(3)	0.1659(1)	C15	−0.0243(7)	0.1388(3)	0.2071(1)
C4	−0.0378(5)	0.2060(3)	0.1672(1)	C16	−0.2151(5)	−0.1549(3)	0.1661(1)
C5	−0.0213(5)	0.1476(3)	0.1173(1)	C17	−0.4313(6)	−0.1938(3)	0.1823(1)
C6	−0.0284(5)	−0.0042(3)	0.1144(1)	C18	−0.4537(9)	−0.3411(4)	0.1874(2)
C7	−0.0347(5)	−0.0533(3)	0.0621(1)	C19	−0.4817(9)	−0.1191(5)	0.2267(2)

Estimated standard deviations in the least significant digits are shown in parentheses

by Cox and Sim, we suggest an absolute configuration for the molecule as shown in Figure 1.

Bond distances are normal with individual standard deviations of 0.003 to 0.005 Å. Molecules are linked in the solid state by hydrogen bonds involving hydroxyl group O3 as donor and lactone carbonyl O2 as acceptor. This intermolecular interaction has O . . . O distance 2.899 Å and is nearly linear, with O-H . . . O angle 163°.

EXPERIMENTAL

C. subcordata was collected on December 12, 1979, in the state of Tachira, Venezuela, 13.5 km from Delicias along the road toward Villa Paez (L. Urbatsch, No. 3427, voucher specimen deposited at Louisiana State University, Baton Rouge). The air-dried plant material was extracted and worked up as previously described (2).

Fractions 29-34 (370 mg) were rechromatographed on a silica gel column with $CHCl_3$-Me_2CO mixtures of increasing polarity; 50 fractions of 50 ml each were collected. From these, fractions 27-31 (48 mg) were further purified by tlc on silica gel with $CHCl_3$-Me_2CO (7:3) yielding 15 mg of subcordatolide C (**1**), $C_{19}H_{26}O_5$, mp 196-197° (dec.); uv λ max (MeOH) 213 nm (ϵ 1.04$\times$10^4); cd (MeOH, c 2.08=10^{-4}): $[\theta]_{206}+4.34=10^4$, $[\theta]_{255}-2.81\times10^3$; ir ν max (film) 3510 (br, OH), 1765 (γ-lactone), 1730 (ester); ms 70 eV, *m/z* (rel. int.) 246 (34.6, M-A), 231 (6.6, M-A-Me), 229 (10.2, M-A-OH), 228 (45.0, M-A-H_2O), 202 (12.5, M-A-CO_2), 185 (43.6, M-A-H_2O-Me-CO), 71 (68.9, **A'**), 43 (100.0, **A''**).

X-RAY DATA.—A crystal of dimensions 0.28$\times$0.64$\times$0.72 mm was used for data collection on an Enraf-Nonius CAD4 diffractometer equipped with MoKα radiation (λ=0.71073Å) and a graphite monochromator. Crystal data are: $C_{19}H_{26}O_5$, MW=334.4, orthorhombic space group P2$_1$2$_1$2$_1$, a=6.387(3), b=9.980(2), c=27.992(6)Å, Z=4, d_c=1.245 gcm^{-3}, μ(MoKα)=0.83 cm^{-1}. Data were collected by ω-2θ scans of variable speed, designed to yield I$\simeq$50σ(I) for all significant reflections. One octant of data having 1°<θ<25° was measured, yielding 1837 unique reflections, of which 1401 had I>3σ(I) and were used in the refinement. Data reduction included corrections for background, Lorentz, and polarization effects; absorption was negligible.

The structure was solved by direct methods (MULTAN 78) (6) and refined by full-matrix, weighted-least-squares methods. Nonhydrogen atoms were refined anisotropically, while hydrogen atoms were located in difference maps and included as fixed contributions with B=5.0Å^2 (9.0Å^2 for isobutyrate methyl groups). Convergence was achieved with R=0.041, R$_w$=0.055 based on observed reflections, and residual electron density was less than 0.20 eÅ^{-3}. Coordinates are given in Table 3; hydrogen atom coordinates, anisotropic thermal parameters, bond distances, bond angles, and structure factors are available as supplementary material.

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