AN *ENT*-SECO-ATISANE SKELETON DITERPENE FROM A NATURAL SOURCE, RHIZOMES OF *EUPHORBIA ACAULIS*[1]

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ABSTRACT.—*ent*-3,4-Seco-4,16α,17-trihydroxyatisan-3-oic acid [1] has been isolated and characterized as a minor constituent of rhizomes of *Euphorbia acaulis*. The structure determination is based on spectroanalytical, chemical, and X-ray diffraction data.

In earlier communications (1,2), we reported isolation and characterization of two novel atisane diterpenes, *ent*-3-oxo-atisane-16α,17-diol and *ent*-atisane-3β,16α,17-triol, from *Euphorbia acaulis* Roxb. (Euphorbiaceae). In the present manuscript we report the isolation and characterization data of a seco-atisane diterpene from this source; this constitutes the first report of the occurrence of a seco-atisane compound in nature.

The new isolate 1, a colorless crystalline solid, mp 170°, analyzed for $C_{20}H_{34}O_5$ and had a ^{13}C-nmr spectrum that showed resonances at 177.43 (s), 74.92 (s), 73.85 (s), and 69.58 (t). These data, together with its ir spectrum, suggested that 1 was a saturated trihydroxy acid. Four substituent groups are normally expected in such molecules. Compound 1 showed signals for three methyl groups (^{13}C nmr 19.01, 23.11, 28.66 ppm)

and one hydroxy-methyl group, and this indicated that the carboxyl group has originated by oxidative fission of a ring. The ^{13}C-nmr data of the compound compared well with those of compound 2 (2), except for the apparent difference in absorption frequencies of ring-A carbon atoms. These observations led to the hypothesis that ring A in 2 had undergone oxidative fission between C-3 and C-4 to yield 1, a hydroxy acid. The proposed structure of 1 was confirmed by X-ray analysis of a single crystal ($C_{20}H_{34}O_5$·MeOH) obtained by recrystallization from MeOH.

An ORTEP drawing (3) of the structure 1 is given in Figure 1. Taking the co-occurrence of the *ent*-atisane diterpene 2 into account, the stereochemistry
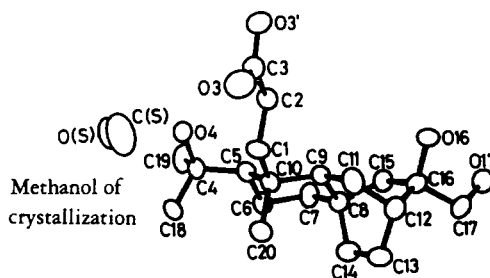

1

2

3
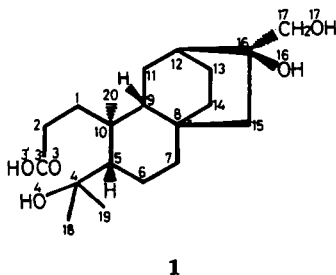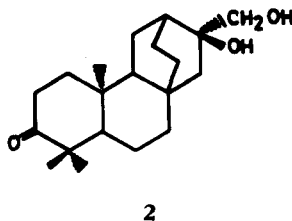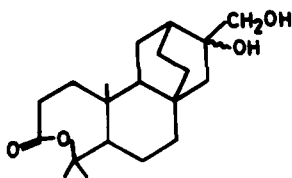
FIGURE 1.   ORTEP drawing of compound **1**.

of **1** is considered to be as shown. Fractional atomic coordinates and anisotropic thermal parameters, bond lengths and bond angles with their standard deviation are presented in Tables 1, 2, and 3. The absolute configuration of **1** was unequivocally determined by comparison of the optical rotation of its lactone **3** with that of the Baeyer-Villiger oxidation product of **2**, whose stereochemistry has previously been established by X-ray and cd spectral analysis (1,4).

EXPERIMENTAL

TABLE 1.   Fractional Atomic Coordinates ($\times 10^4$) and Anisotropic Thermal Parameters ($\times 10^3$).[a]

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C-1	4338(4)	9202(6)	5113(11)	33(4)	42(5)	27(5)	3(4)	−4(4)	−10(5)
C-2	5035(4)	8928(7)	4644(12)	34(4)	41(5)	30(5)	1(4)	−3(4)	−7(5)
C-3	5515(4)	9331(7)	5956(12)	43(5)	42(5)	30(5)	1(4)	−10(5)	5(5)
C-4	3901(4)	10431(7)	1653(13)	35(5)	32(5)	55(6)	3(4)	−3(5)	−4(5)
C-5	3844(4)	9248(6)	1949(11)	35(4)	35(5)	32(5)	4(4)	0(4)	−1(4)
C-6	3299(4)	8793(7)	811(12)	44(5)	38(5)	38(5)	3(5)	−12(5)	1(5)
C-7	3376(5)	7638(7)	658(12)	55(6)	32(5)	33(5)	−4(5)	−17(5)	−3(5)
C-8	3382(4)	7108(6)	2455(12)	33(4)	33(5)	37(5)	−1(4)	−9(5)	2(5)
C-9	3862(4)	7651(6)	3740(11)	30(4)	32(5)	31(5)	3(4)	−5(4)	1(4)
C-10	3797(4)	8832(6)	3890(12)	34(4)	33(5)	37(5)	4(4)	6(4)	−4(4)
C-11	3867(5)	7097(7)	5557(11)	58(6)	40(5)	21(5)	6(5)	−5(5)	−2(4)
C-12	3453(4)	6145(7)	5460(11)	40(5)	44(5)	24(4)	−3(4)	−3(4)	7(5)
C-13	2736(4)	6454(7)	5076(14)	37(5)	52(6)	51(6)	3(5)	12(5)	−1(6)
C-14	2692(4)	6976(8)	3249(14)	32(5)	50(6)	59(7)	−2(5)	−6(5)	0(6)
C-15	3657(4)	6026(7)	2184(12)	38(5)	38(5)	32(5)	−1(4)	−7(4)	3(5)
C-16	3707(4)	5460(6)	3981(12)	33(5)	36(5)	32(5)	−4(4)	1(4)	3(4)
C-17	3341(4)	4441(7)	3966(14)	45(5)	38(5)	52(6)	−11(5)	2(5)	7(5)
C-18	3350(4)	11046(5)	2498(15)	41(5)	33(5)	74(7)	10(5)	−1(6)	8(6)
C-19	3941(5)	10664(7)	−338(13)	66(7)	46(6)	43(6)	−3(5)	−11(6)	11(5)
C-20	3145(4)	9138(7)	4852(13)	42(5)	45(6)	43(6)	5(5)	8(5)	−4(5)
O-3	5349(3)	9730(6)	7316(9)	56(4)	79(5)	45(4)	−7(4)	−14(4)	−20(4)
O-3'	6137(3)	9172(5)	5628(9)	36(3)	57(4)	53(4)	−8(3)	−12(3)	3(4)
O-4	4493(3)	10792(4)	2456(8)	37(3)	34(3)	45(4)	−1(3)	−3(3)	−9(3)
O-16	4386(3)	5236(4)	4299(8)	26(3)	49(4)	43(4)	2(3)	−2(3)	6(3)
O-17	3634(3)	3746(4)	2745(9)	38(4)	50(4)	50(4)	−4(3)	−2(3)	−2(4)
O(S)	4581(4)	12564(5)	4133(9)	85(5)	41(4)	54(4)	10(4)	−12(5)	0(4)
C(S)	4650(7)	12330(9)	5967(16)	147(13)	70(8)	43(7)	12(9)	−6(9)	−15(7)

[a]The anisotropic thermal parameters are expressed in the form: exp $-2\pi^2(U_{11}h^2a^{*2} + \ldots + 2U_{23}klb^*c^*)$. The standard deviation for the last digit is given in parentheses.

TABLE 2.   Bond Lengths and their Standard Deviations (Å).

C-1–C-2 . . . . . . 1.52 (1)	C-1–C-10 . . . . . 1.53 (1)	C-2–C-3 . . . . . . 1.50 (1)
C-3–O-3 . . . . . . 1.21 (1)	C-3–O-3' 1.32 (1)	C-4–C-5 . . . . . . 1.59 (1)
C-4–C-18 . . . . 1.54 (2)	C-4–C-19 . . . . 1.54 (1)	C-4–O-4 . . . . . . 1.44 (1)
C-5–C-6 . . . . . . 1.54 (1)	C-5–C-10 . . . . 1.58 (1)	C-6–C-7 . . . . . . 1.55 (1)
C-7–C-8 . . . . . . 1.53 (1)	C-8–C-9 . . . . 1.56 (1)	C-8–C-14 . . . . . . 1.55 (1)
C-8–C-15 . . . . 1.56 (1)	C-9–C-10 . . . . 1.58 (1)	C-9–C-11 . . . . . . 1.56 (1)
C-10–C-20 . . . . 1.58 (1)	C-11–C-12 . . . . 1.53 (1)	C-12–C-13 . . . . 1.56 (1)
C-12–C-16 . . . . 1.54 (1)	C-13–C-14 . . . . 1.55 (2)	C-15–C-16 . . . . 1.56 (1)
C-16–C-17 . . . . 1.55 (1)	C-16–O-16 . . . . 1.45 (1)	C-17–O-17 . . . . . 1.44 (1)
O(S)–C(S) 1.43 (2)		

Pradesh, India. A voucher specimen is preserved at NBRI, Lucknow.

EXTRACTION AND ISOLATION.—Compound **1** (30 mg) was isolated from $CHCl_3$-MeOH (9:1) fractions, by cc of the MeOH extract of *E. acaulis* over Si gel, as a colorless crystalline solid: mp 170°, analyzed for $C_{20}H_{34}O_5$ on the basis of elemental analysis (calcd C 67.79, H 9.60; found C 67.89, H 9.55) and $[M]^+$ at *m/z* 354 in eims; ir ν max (KBr) 3300–3450 (-OH), 1690 (-COOH), 1395, 1285 cm^{-1} (acid dimer); ^{1}H nmr (pyridine-d_5), δ 1.24, 1.45, and 1.46 (3s for 3H each), 2.04 (1H, t, $J = 10$ Hz), 2.24 (1H, s), 2.49 (1H, t, $J = 10$ Hz), 2.62 (1H, dt, $J = 10, 4$ Hz), 2.88 (1H, dt, $J = 10, 4$ Hz), 3.09 (1H, dt, $J = 10, 4$ Hz), 3.87 (AB$_q$, $J = 12$ Hz), 8.52 (1H, s); ^{13}C nmr (pyridine-d_5) δ 39.601 (C-1), 33.482 (C-2), 177.431 (C-3), 73.851 (C-4), 52.755 (C-5), 23.771 (C-6), 35.164 (C-7), 41.919 (C-8),

44.617 (C-9), 33.823 (C-10), 23.568 (C-11), 33.863 (C-12), 27.568 (C-13), 33.594 (C-14), 53.698 (C-15), 74.928 (C-16), 69.588 (C-17), 28.658 (C-18), 23.144 (C-19), 19.015 (C-20). Compound **1** on treatment with CH_2N_2 yielded a crystalline ester, mp 179°, analyzed for $C_{21}H_{36}O_5$ on the basis of elemental analysis (calcd C 68.47, H 9.78; found C 68.55, H 9.72) and $[M]^+$ at *m/z* 368 in eims.

BAEYER-VILLIGER OXIDATION OF **2**.—Pure **2** (4 mg) was dissolved in moist $CHCl_3$, and perbenzoic acid was added to the solution in a twofold excess. The reaction mixture was allowed to stand at room temperature with frequent shaking for 24 h. Usual workup yielded product **3** which was purified by crystallization from EtOAc: mp 159° $[\alpha]^{25}$D −24.9 (*c* = 1.0%, MeOH); analyzed for $C_{20}H_{32}O_4$ on the basis of elemental analysis (calcd C 71.42, H 9.52; found

TABLE 3.   Bond Angles and Their Standard Deviations (deg).

C-2–C-1–C-10 . . . . 117.9 (7)	C-1–C-2–C-3 . . . . 112.3 (7)
C-2–C-3–O-3 . . . . 122.5 (8)	C-2–C-3–O-3' 117.2 (8)
O-3–C-3–O-3' 120.2 (8)	C-5–C-4–C-18 . . . . 114.3 (8)
C-5–C-4–C-19 . . . . 109.9 (7)	C-5–C-4–O-4 . . . . 109.4 (7)
C-18–C-4–C-19 . . . . 109.8 (8)	C-18–C-4–O-4 . . . . 105.7 (8)
C-19–C-4–O-4 . . . . 107.5 (8)	C-4–C-5–C-6 . . . . 111.3 (7)
C-4–C-5–C-10 . . . . 118.9 (7)	C-6–C-5–C-10 . . . . 110.0 (7)
C-5–C-6–C-7 . . . . 111.0 (7)	C-6–C-7–C-8 . . . . 113.0 (8)
C-7–C-8–C-9 . . . . 110.3 (7)	C-7–C-8–C-14 . . . . 112.9 (8)
C-7–C-8–C-15 . . . . 108.1 (7)	C-9–C-8–C-14 . . . . 112.8 (8)
C-9–C-8–C-15 . . . . 106.2 (7)	C-14–C-8–C-15 . . . . 106.2 (8)
C-8–C-9–C-10 . . . . 116.8 (7)	C-8–C-9–C-11 . . . . 109.6 (7)
C-10–C-9–C-11 . . . . 113.9 (7)	C-1–C-10–C-5 . . . . 114.1 (7)
C-1–C-10–C-9 . . . . 107.6 (7)	C-1–C-10–C-20 . . . . 104.8 (7)
C-5–C-10–C-9 . . . . 106.0 (7)	C-5–C-10–C-20 . . . . 113.2 (7)
C-9–C-10–C-20 . . . . 111.2 (7)	C-9–C-11–C-12 . . . . 110.2 (7)
C-11–C-12–C-13 . . . . 108.6 (8)	C-11–C-12–C-16 . . . . 109.7 (7)
C-13–C-12–C-16 . . . . 110.0 (8)	C-12–C-13–C-14 . . . . 109.8 (8)
C-8–C-14–C-13 . . . . 110.1 (8)	C-8–C-15–C-16 . . . . 110.7 (7)
C-12–C-16–C-15 . . . . 109.2 (7)	C-12–C-16–C-17 . . . . 111.0 (8)
C-12–C-16–O-16 . . . . 109.2 (7)	C-15–C-16–C-17 . . . . 112.5 (8)
C-15–C-16–O-16 . . . . 107.9 (7)	C-17–C-16–O-16 . . . . 106.9 (7)
C-16–C-17–O-17 . . . . 111.2 (8)	

C 71.49, H 9.48) and $[M]^+$ at m/z 336 in eims: ir ν max (KBr) 3300–3400 (primary and tertiary -OH groups), 1740 (lactone C=O).

LACTONIZATION OF **1**.—An MeOH solution of **1** was heated to reflux in the presence of tosic acid, and the product was purified by crystallization from EtOAc, mp 158° (undepressed in admixture with **3**), $[\alpha]^{25}D$ −24.7 (c = 1.0%, MeOH).

X-RAY DATA.[2]—A single crystal of **1** ($C_{20}H_{34}O_5 \cdot MeOH$) obtained by recrystallization from MeOH was subjected to single crystal analysis. The crystal data are as follows: size ca. $0.13 \times 0.13 \times 0.65$ mm; orthorhombic; space group $P2_12_12_1$ (Z=4); cell dimensions a = 20.580 (3), b = 13.296 (3), c = 7.579 (1) Å, V = 2073.8 (6) Å^3, D observed = 1.24 g/cm^3, D calcd = 1.24 g/cm^3. The 1793 unique intensities were collected by 2θ–ω scan method within 2θ<120 on a Rigaku AFC-5 FOS four-circle diffractometer using graphite monochromated Cu-Kα (λ = 1.5418A) radiation. All the nonhydrogen atomic positions, including those of the solvent (MeOH), were revealed by direct methods (MULTAN) (5). After refinement by several cycles of isotropic and anisotropic least squares, the calculated positions of hydrogen atoms, except those of hydroxy and carboxy groups, and those of the solvent were introduced. The refinement of the positions with thermal parameters anisotropic for nonhydrogen atoms and isotropic for hydrogen atoms by the block diagonal least squares (UNICS III) (6) converged to an R-value of 0.063 for the 1330 reflections ($F_o \gtreqless 2 \cdot OF_o$). Calculations were performed on a Tosbac DS-600 computer.

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[2]Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.