CANTABRIC ACIDS. TRIQUINANE SESQUITERPENOIDS FROM *ARTEMISIA CANTABRICA*

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ABSTRACT.—Four sesquiterpene acids with the silphiperfolane skeleton were isolated from extracts of *Artemisia cantabrica*. Their structures were determined by spectroscopic methods, mainly 2D-nmr techniques.

Artemisia cantabrica (Lainz) Lainz (Compositae, Anthemideae), formerly *Artemisia chamamaelifolia* subsp. *cantabrica* (1), is a small endemic plant from the "*Cordillera cantabrica*" (north of Spain) whose composition was hitherto unknown. Previously, the isolation of scopoletin, its β-glucoside scopolin, and an unidentified flavonoid glycoside from *A. chamamaelifolia* have been described (2).

We now report the results obtained from the study of sesquiterpene acids isolated from the hexane extract of the aerial parts of *A. cantabrica*. The structures of four new sesquiterpenoids, the cantabric acids, have been established through the analysis of their 2D-nmr spectra.

RESULTS AND DISCUSSION

The hexane extract was defatted and fractionated with aqueous NaOH. Treatment of the acid fraction with ethereal CH_2N_2 and repeated chromatographic separations lead to the isolation of the four methyl esters **1, 2, 3,** and **4.** The structural relationship between all of them has been established by careful study of their ir, ^1H- and ^{13}C-nmr properties. All of them have the ester group (1760 to 1725 cm^{-1}; CH_3O-: 3.8 ppm). In addition, **1** has a conjugate diene moiety (1640, 1605, and 890 cm^{-1}; 4.96, 5.63, and 6.67 ppm, one proton each), **2** contains a carbonyl (1760 cm^{-1}) and an additional epoxy group (1240, 980, 900, 780, and 755 cm^{-1}), **3** exhibits absorptions of a conjugated cyclopentenone (1715 and 1630 cm^{-1}), and **4** contains a secondary allylic alcohol (3500, 1645, and 1040 cm^{-1}; 4.53 ppm, one proton).

The ^{13}C-nmr spectra of substances **2, 3,** and **4** (Tables 1 and 2) exhibit, among others, three methyl, four methylene, and two methine signals which show only minor differences in their chemical shifts from one compound to another; this could be interpreted in terms of the existence of a different functionalized part of the molecule separated from the other which remains unchanged in all the cases. The ^{13}C-nmr spectrum of substance **1** shows an olefinic methylene instead of one of the methyl signals. The remaining ^{13}C-nmr signals of the four substances support the existence of the functional groups mentioned above.

In addition to the methyl signals, the 200 MHz ^1H-nmr spectra of the substances exhibit a very complex ten proton pattern in their high field region between 1.2 and 2.3 ppm with overlapping second order multiplets.

Due to its availability and the better resolution of its ^1H-nmr spectrum, substance **2** was first chosen for structural determination. Its structure was established through the study of its 2D ^1H-^{13}C heteronuclear and ^1H-^1H homonuclear correlation spectra and its stereochemistry was deduced from its 2D-nOe spectrum and from ^1H-^1H coupling constants.

The M^+ peak exhibited by **2** at *m/z* 278.1521 corresponds to the molecular formula $C_{16}H_{22}O_4$. Its ^1H nmr (200 MHz) (Table 1, Figure 1) contains, in addition to the methoxyl group absorption, two methyl singlets, one methyl doublet, and ten multi-

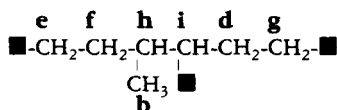TABLE 1. ^{1}H (500 MHz) and ^{13}C (50.3 MHz) Nmr Spectra of **2**

Atom No.	^{1}H ppm mult. (*J* in Hz)		^{13}C ppm	Type[a]	
1	1.89 dd (9.6, 6.9)	i[b]	56.22	CH	I[b]
2	1.30-1.45 m	d,d'	27.51	CH_2	D
3	2.11 m	g	37.61	CH_2	G
	1.41 m	g'			
4			58.79	C	J
5			210.25	C	
6			67.55	C	L
7			75.36	C	M
8			63.04	C	K
9	1.48 m	h	41.50	CH	H
10	1.84 dddd (12.3, 7.1, 5.2, 1.9)	f	36.24	CH_2	F
	1.22 dddd (12.3, 12.0, 12.0, 7.2)	f'			
11	1.96 ddd (14.0, 7.2, 1.9)	e	29.36	CH_2	E
	1.66 ddd (14.0, 12.1, 7.1)	e'			
12	1.06 s	c	21.48	CH_3	C
13			164.57	C	
14	1.50 s	a	12.81	CH_3	A
15	1.00 d (6.5)	b	18.89	CH_3	B
OMe	3.85 s		52.61	CH_3	

[a]Based on its DEPT spectrum (Figure 1).
[b]Letters used for structural discussion in the text (e.g., **E** for a carbon and **e,e'** for its protons).

plets in the range between 1.2 and 2.3 ppm. The ^{13}C-nmr spectrum (Table 1, Figure 1), apart from signals for carbonyl and carboxyl groups, shows a methoxyl carbon, three methyls (**A, B, C,** see Figure 1), four methylenes (**D, E, F, G**), two methines (**H, I**), and four quaternary carbons (**J, K, L, M**), two of which are bonded to an oxygen atom. In order to assign each carbon atom to its corresponding proton or group of protons, a 2D heteronuclear ^{1}H-^{13}C-nmr correlation experiment (H,C-COSY) (3) was performed. The results are shown in Figure 1.

Once the protons were located and differentiated in the one dimensional ^{1}H-nmr spectrum, a 2D homonuclear correlated experiment (COSY-90) (4) (Figure 2), allowed us to establish the connectivities between all the coupled protons in the molecule. Thus, methylene protons **e** and **e'** were connected to protons **f** and **f'**; these, to proton **h** (cross-peak **f-h**, not shown in Figure 2, was detected in a lower level contour plot), proton **h** to methyl protons **b** and to methine proton **i**; this, to methylene protons **d** and **d'** and, finally, these to methylene protons **g** and **g'**. As a result the coupled protonated part of the molecule should be:

$$\underset{\textbf{b}}{\overset{\displaystyle \quad\,\textbf{e}\quad\ \textbf{f}\quad\ \textbf{h}\quad \textbf{i}\quad\ \textbf{d}\quad\ \textbf{g}}{\blacksquare\text{-CH}_2\text{-CH}_2\text{-CH-CH-CH}_2\text{-CH}_2\text{-}\blacksquare}}$$

This proposal leads to the straightforward assignment of the corresponding proton and carbon signals in its 1D spectra.

According to the above mentioned spectroscopic data (ir, ^{1}H and ^{13}C nmr) and based on the fact that substance **2** was obtained by H_2O_2-NaOH epoxidation of the enone **3** (see Experimental), the other part of the molecule was proposed to be:
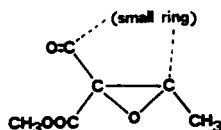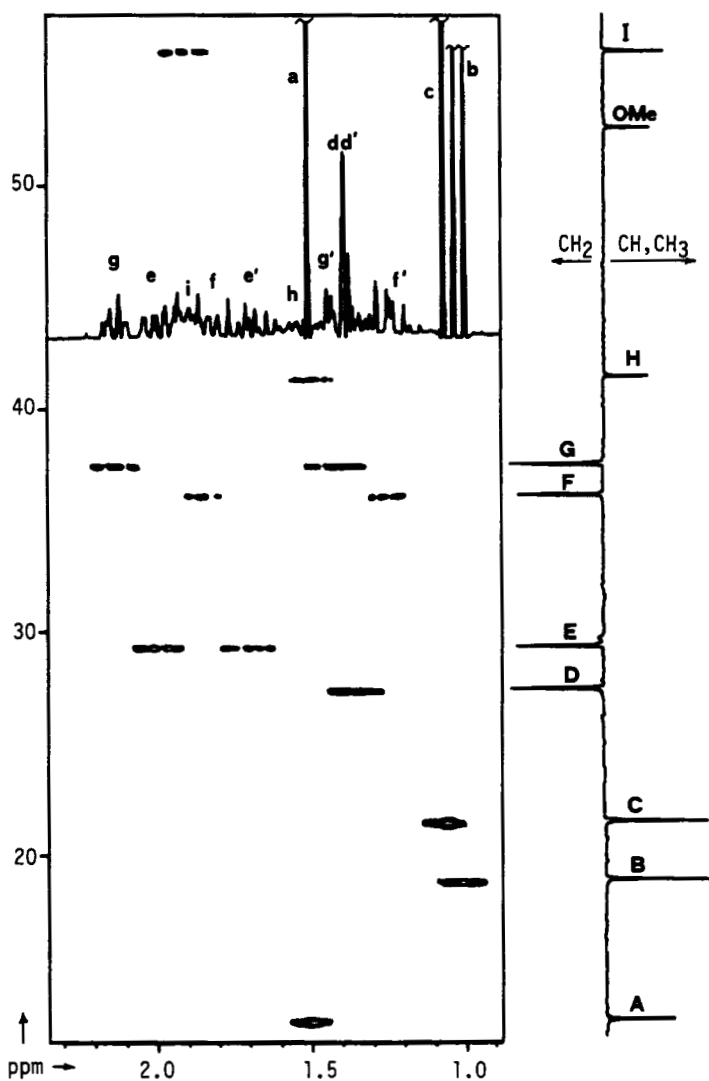
FIGURE 1.   Right: DEPT ^{13}C spectrum of **2**
Left: H,C-COSY spectrum with superimposed 200 MHz ^{1}H-nmr spectrum of **2**

These two fragments account for 13 carbons, 19 protons, and all of the oxygen atoms in the molecule, leaving only two quaternary carbons and one methyl group for the structure to be completed. The analysis of the long-range ^{1}H-^{1}H couplings observed in the COSY spectrum (Figure 2) lead to the establishment of how the principal fragments are fused. Based on the small coupling of methyl protons **c** with methylene protons **g, g'**, and **e'** and the methine proton **i**, structures **I** and **II** are proposed.

To differentiate between **I** and **II** a 2D long-range heteronuclear ^{1}H/^{13}C experiment, tuned for couplings of value $^nJ_{C,H}=6.3$ Hz, was performed. The 2D correlated spectrum clearly showed that the carbonyl carbon at 215.25 ppm was coupled with protons of the methyl **C** and with those of the methylene **G**; certain other long-range correlations (e.g. proton/carbon:**c/J, c/K, a/L, a/M**) (Table 3) were also observed. These results allowed us to propose structure **I** for substance **2**.

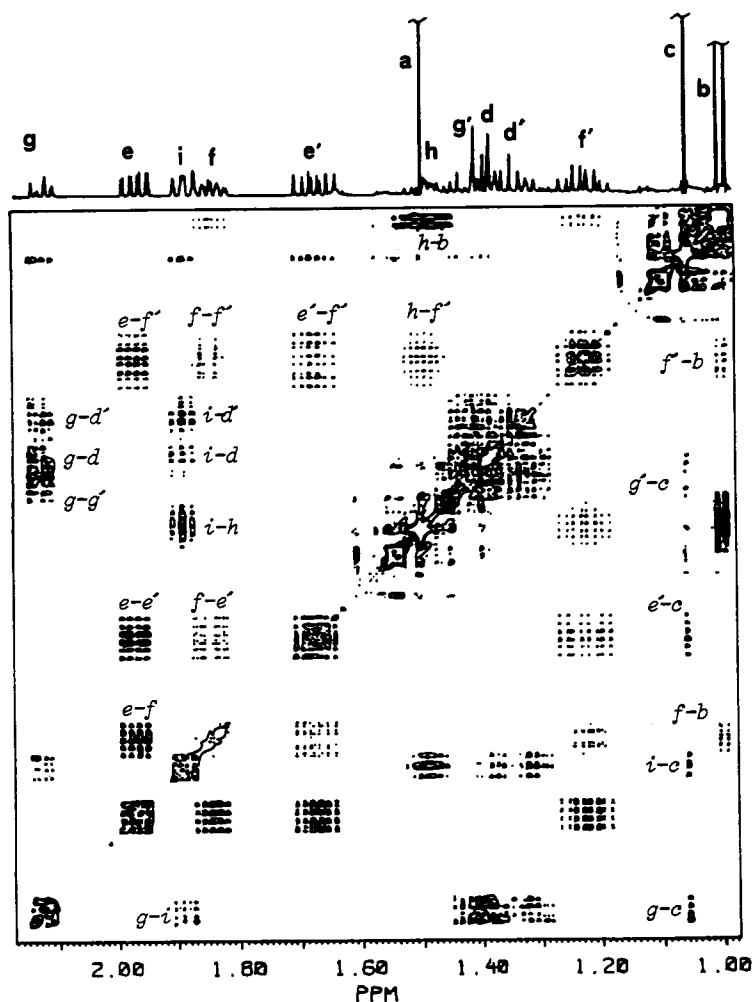The relevant peaks in its high resolution eims could be consistently interpreted as depicted in scheme 1.

FIGURE 2.   500 MHz COSY-90 spectrum of **2**. Upper left part: geminal and vicinal connectivities; bottom right part: long-range connectivities.

To determine the stereochemistry of **2**, two different 2D-nOe (NOESY) (5) experiments at 200 and 500 MHz were performed. The corresponding 2D spectra showed the cross peaks **a-f′, a-i, a-e, b-i, c-g′**, and **c-e′** which, together with the exhibited ^{1}H-^{1}H coupling constants (Table 1), allowed us to establish the structure and conformation of **2** as depicted below.

The structures of compounds **1, 3,** and **4** were easily deduced from their spectral comparison (ms, ir, uv, nmr) with substance **2**. As has been stated above, **2** was ob-
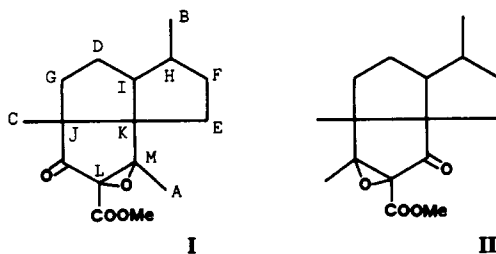
TABLE 2. ^{13}C-nmr (50.3 MHz) Spectra of Compounds **1, 3, 4, 5, 7**, and **8**[a]

Carbon No.	Compounds					
	1	**3**	**4**	**5**	**7**	**8**
1	65.15	59.32	54.11	54.61	58.08	57.58
2	28.30	26.25	29.91	29.56	28.75	29.69
3	37.23	37.05	40.26	38.85	36.64	39.63
4	57.55	59.32	58.44	97.46	59.43	54.78
5	107.02	208.11	81.71	163.33	214.43	85.08
6	133.62	129.29	127.12	58.09	127.73	128.92
7	164.68	188.74	166.69	70.79	182.21	157.37
8	66.18	68.28	73.45	62.71	68.49	71.49
9	41.79	40.01	42.38	44.23	39.65	41.83
10	36.16	35.51	37.08	35.29[b]	35.02	36.73
11	33.62	29.23	31.58	36.33[b]	29.62	33.33
12	21.14	20.72	19.52	22.35	20.78	19.61
13	159.18	164.04	164.90	165.28	—	58.85
14	104.89	15.22	13.54	18.06	15.42	10.94
15	19.29	18.91	17.04	19.53	19.05	17.26
OMe	51.27	51.55	51.00	52.95	—	—

[a]The number of protons attached to each carbon atom has been ascertained by means of DEPT experiments performed for all these substances.
[b]Interchangeable assignments.

tained by epoxidation of **3**, thus confirming the structure of the latter compound. In excess of the oxidant the γ-lactone **5**, expected from a Baeyer-Villiger reaction, was obtained, and its structure established through spectral comparison with substance **2** (Tables 1 and 2, Experimental). As could be deduced from their ^{13}C-nmr data the ketone carbonyl C_5 (210.25 ppm) and the quaternary C_4 (58.79 ppm) in substance **2** changed to the lactone carbonyl (163.33 ppm) and the oxygenated C_4 (97.46 ppm) in compound **5**, respectively.

Hydrolysis of the ester **3** followed by decarboxylation of the acid **6** with LiI/collidine yielded the norsesquiterpenoid ketone **7**. The cd spectrum of **7** showed enone associated Cotton effects $\Delta\epsilon_{338} = -0.18$, $\Delta\epsilon_{265} = +0.20$, which, according to the empirical rules for cyclopentenones (6), could support the absolute stereochemistries represented for these sesquiterpenoids. Conformational differences observed using Dreiding models are rather too small to ensure this assignment, however.

TABLE 3.   Long-Range ^{1}H/^{13}C Connectivities for **2**[a]

| Section at Proton	Long-Range Connected Carbons
a	**L, M**
b	**F, I**
c	**G, J, K, CO**
d and/or d′	**H, K**
e′	**M**
f and/or f′	**B, E, (H)**[b]**, (K)**
g and/or g′	**D, I, J, K, CO**
h	**K**
i	**E, J, (B), (H), (K), (M)**

[a]See Experimental for details about this 2D-experiment.
[b]Connectivities in parentheses are not totally sure due to overlapping of signals.

2
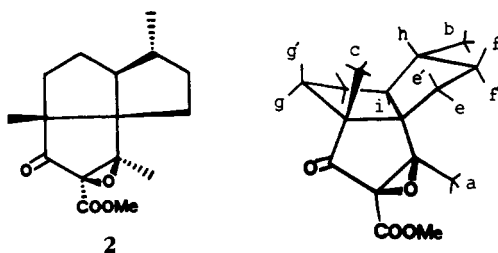
Substances **1** and **4** were isolated as oily products and they are unstable in atmospheric conditions. The structural relationship between these substances was also confirmed by ms. The eims of **4** showed most of the peaks observed in **1**, which could be readily explained on the basis of the dehydration of the first compound. The configuration of C_5 in substance **4** was established from the $+0.21$ ppm pyridine induced shift on the methyl H_{12} resonance, which implies a *synclinal* disposition of this methyl with respect to the hydroxyl group (7). The LiAlH$_4$ reduction of hydroxyester **4** yielded the crystalline diol **8**, which on attempted ketalization with 2,2-dimethoxypropane and trimethylsilyl chloride was transformed into the diene alcohol **9**.

The names of cantabradienic, epoxycanbtabronic, cantabrenonic, and cantabrenolic acids are proposed for the new natural acids corresponding to esters **1, 2, 3,** and **4**, respectively. They are the first substances with a triquinane skeleton to be isolated from *Artemisia*, and they have the silphiperfolane skeleton which was previously described for some compounds isolated from *Silphium* (8) and *Espeletiopsis* (9) spp.

SCHEME 1

1   R=COOMe
9   R=CH₂OH

3   R=COOMe
6   R=COOH
7   R=H

4   R=COOMe
8   R=CH₂OH

5
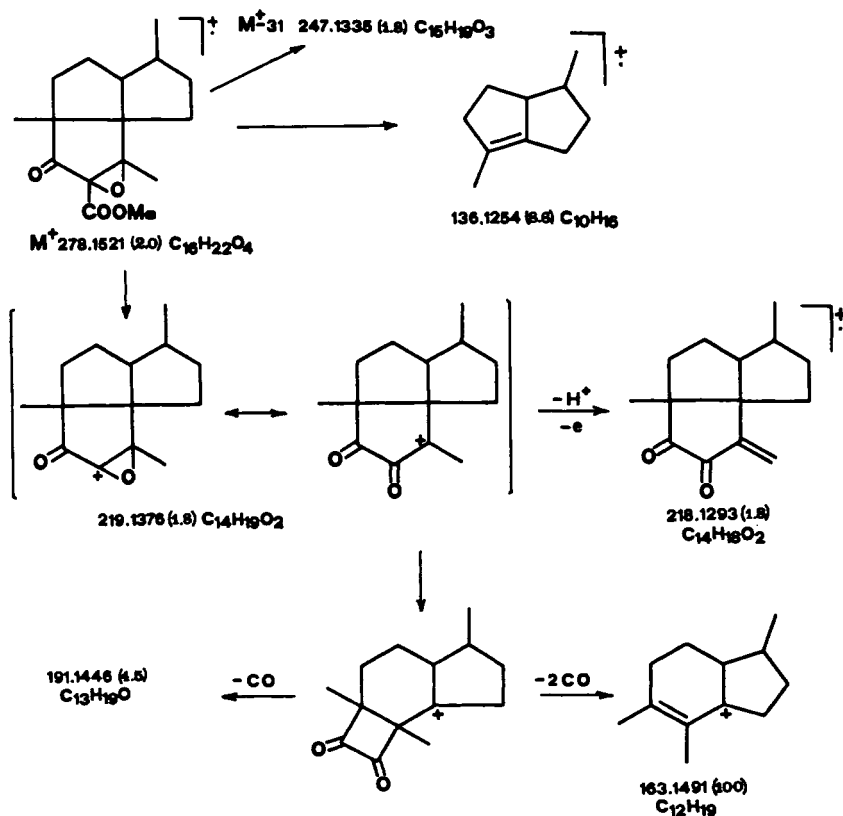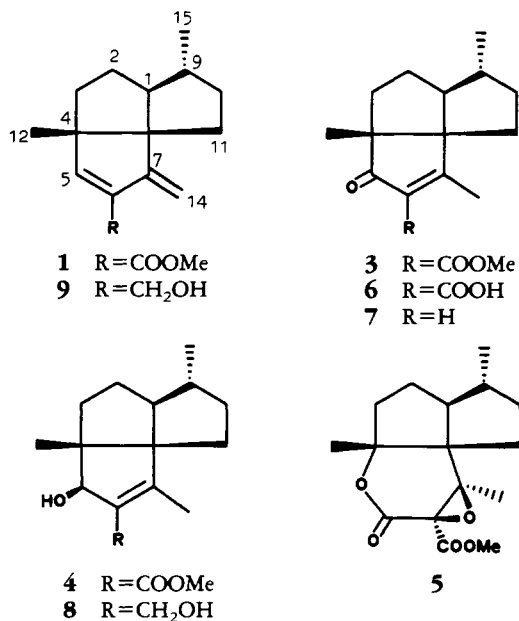
EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were determined in capillaries on a Buchi 510 instrument and are uncorrected. Optical rotations were measured in CHCl₃ on a Perkin-Elmer 241 polarimeter. Uv spectra were recorded in EtOH on a Hitachi 100-60 spectrometer. Ir spectra were obtained on a Beckman AccuLab VIII spectrophotometer. ¹H-nmr (200.13 MHz) and ¹³C-nmr (50.3 MHz) spectra were measured in CDCl₃ with TMS as internal standard on a Bruker WP 200 SY and ¹H-nmr (500 MHz) spectra on a Bruker WM 500 spectrometer. Eims were obtained on a AEI MS-50 spectrometer and high resolution eims on a VG Micromass ZAB-2F at 70 ev. Cd was measured in EtOH on a Jobin-Yvon Dichrograph III. Flash chromatography was run on silica gel (Merck No. 9385) in an Eyela EF-10 chromatograph.

PLANT MATERIAL, EXTRACTION, AND ISOLATION.—The plant material was collected in September 1984, at Peña de las Agujas, Palencia, Spain. Voucher specimens are deposited in the Botany Department (register number SALAF No. 7647). Air-dried material (1.3 kg) was extracted with hexane (room temperature) for 20 h to give 35.7 g of crude extract. This extract was fractionated by its solubility in cold MeOH (3 liters), and the soluble part (20.0 g) was treated with urea saturated MeOH (500 ml) to remove linear compounds (10). The resulting defatted product was dissolved in Et₂O and extracted with an aqueous NaOH (4%) solution to yield a neutral (10.0 g) and an acidic (3.8 g) part. After methylation of acids with ethereal CH₂N₂, compounds 1 (30 mg), 2 (86 mg), 3 (330 mg), and 4 (139 mg) were isolated by repeated chromatographic separations (column chromatography and tlc on Si gel and Si gel-20% AgNO₃) and crystallization (compounds 2 and 3 only).

METHYL CANTABRADIENATE (1).—Pale yellow oil eluted from Si gel-20% AgNO₃ column with hexane-Et₂O (98:2); uv λ max 267 nm, [α]²⁴ (λ nm): −22.3° (589), −23.1° (578), −26.4° (546), −39.0° (436), 40.8° (365), (*c* 0.5); ir ν max 1725, 1640, 1605, 1250, 890 cm⁻¹; ¹H nmr δ 0.98 (3H, d, J=6.5 Hz, Me₁₅), 1.04 (3H, s, Me₁₂), 1.1-1.9 (10H, m), 3.77 (3H, s, COOCH₃), 4.96 (1H, d, J= 1.8 Hz, H₁₄), 5.63 (1H, s, H₅), 6.67 (1H, d, J=1.8 Hz, H₁₄) ppm; ¹³C nmr see Table 2; eims *m/z* (%) 246 (87), 231 (30), 218 (28), 215 (11), 203 (31), 187 (65), 159 (58), 145 (60), 128 (71), 115 (100).

METHYL EPOXYCANTABRONATE (2).—Eluted from Si gel column with hexane-EtOAc (9:1). White crystals, mp 63° (hexane), uv λ max 205 (ε=2790) nm, [α]²⁴ (λ nm) −5.2° (589), −4.5° (578), −3.5° (546), +1.8° (436),(*c*, 0.8); ir ν max 2960, 1760, 1380, 1310, 1240, 1085, 980, 900, 780, 755 cm⁺¹; ¹H nmr see Table 1; eims *m/z* (%) 278 M⁺ (2) (Found: *m/z* 278.1521, C₁₆H₂₂O₄ requires: *m/z* 278.1518), 247 (1.8), 219 (1.8), 218 (1.8), 191 (4.5), 163 (100), 136 (8.6).

METHYL CANTABRENONATE (3).—Eluted from Si gel column with hexane-EtOAc (7:3). White crystals, mp 70° (hexane); uv λ max 239 nm (ε=16160); [α]²⁴ (λ nm) −36.9° (589), −38.0° (578), −37.3° (546), −59.0° (436), 21.3° (365) (*c*, 1.0); ir ν max 3040, 1745, 1715, 1630, 1240, 1070, 1000

cm^{-1}; ^{1}H nmr δ 1.03 (3H, d, J=6.6 Hz, Me$_{15}$), 1.05 (3H, s, Me$_{12}$), 1.2-2.3 (10H, m), 2.37 (3H, s, Me$_{14}$), 3.82 (3H, s, COOCH$_3$) ppm; ^{13}C nmr see Table 2; eims m/z (%): 262 M$^+$ (35), (Found: m/z 262.1569, C$_{16}$H$_{22}$O$_3$ requires: m/z 262.1569), 231 (100), 204 (33), 175 (73), 136 (10), 105 (41).

METHYL CANTABRENOLATE (**4**).—Viscous oil eluted from Si gel column with hexane-EtOAc (7:3); [α]^{24} (λ nm) −47.9° (589), −50.0° (578), −57.2° (546), −101.0° (436), −167.9° (365), (c, 1.2); ir ν max 3500, 1720, 1645, 1250, 1130, 1070, 1040, and 980 cm^{-1}; ^{1}H nmr δ 0.99 (3H, d, J=6.5 Hz, Me$_{15}$), 1.05 (3H, s, Me$_{12}$), 1.2-2.0 (10H, m), 2.08 (3H, d, J=1.4 Hz, Me$_{14}$), 3.77 (3H, s, COOCH$_3$), 4.53 (1H, br s, H$_5$) ppm; ^{13}C nmr see Table 2; eims m/z (%): 264 (8), 263 (32), 246 (14), 231 (38), 218 (7), 215 (10), 203 (9), 187 (14), 159 (13), 145 (21), 115 (29), 41 (100).

OXIDATION OF METHYL CANTABRENONATE.—To a solution of **3** (100 mg) in MeOH (5 ml), 0.1 ml of H$_2$O$_2$ (30%) and 0.5 ml of 6 N NaOH were added, and the mixture was allowed to react for 12 h at room temperature, then poured into H$_2$O, extracted with Et$_2$O and flash chromatographed on Si gel yielding 30 mg of **2** (identical mp and tlc; superimposable ir and nmr spectra with those of the natural product) and 60 mg of lactone **5** eluted with hexane-EtOAc (9:1). Compound **5**, white crystals, showed mp 98° (hexane); [α]^{24} (λ nm) −3.3° (589), −3.3° (578), −2.1° (546), +6.0° (436), (c, 0.7); ir ν max 1760, 1730, 1390, 1360, 1270, 1150, 1120, 1090 cm^{-1}; ^{1}H nmr δ 1.03 (3H, d, J=6.5 Hz, Me$_{15}$), 1.31 (3H, s, Me$_{12}$), 1.1-2.2 (10H, m), 1.47 (3H, s, Me$_{14}$), 3.62 (3H, s, COOCH$_3$) ppm; ^{13}C nmr see Table 2.

CANTABRENONIC ACID (**6**).—Compound **3** (100 mg) were refluxed with 20% KOH in EtOH-H$_2$O (1:1) for 5 h. H$_2$O addition and Et$_2$O extraction afforded 77 mg of **6**. Mp 119° (hexane); [α]^{24} (λ nm) −20.1° (589), −20.6 (578), −22.2° (546), −28.3° (436), (c, 1.6); ir ν max 3450-2700, 1750, 1660, 1620, 1370, 1175, 1130, 960, 860 cm^{-1}; ^{1}H nmr δ 1.06 (3H, d, J=6.5 Hz, Me$_{15}$), 1.11 (3H, s, Me$_{12}$), 1.3-2.4 (10H, m), 2.60 (3H, s, Me$_{14}$) ppm.

DECARBOXYLATION OF CANTABRENONIC ACID (**6**).—Compound **6** (72 mg) in collidine (10 ml) with LiI (61 mg) was stirred under N$_2$ for 20 h at room temperature. The reaction mixture was extracted with EtOAc and washed with HCl 2N and saturated NaHCO$_3$ to give 52 mg of reaction material, which after chromatography on Si gel yielded 22 mg of **7** (eluted with hexane-EtOAc, 9:1). Cd λ max 338 nm (Δε= −0.18), 265 nm (Δε= +0.20); ir ν max 2850, 1700, 1610, 1370, 1140, 1060, 850 cm^{-1}; ^{1}H nmr δ 1.00 (3H, d, J=5.9 Hz, Me$_{15}$), 1.02 (3H, s, Me$_{12}$), 1.2-2.2 (10H, m), 2.07 (3H, d, J=1.0 Hz, Me$_{14}$), 5.78 (1H, d, J=1.0 Hz, H$_6$) ppm; ^{13}C nmr see Table 2.

CANTABRENEDIOL (**8**).—Reduction of **4** (70 mg) with LiAlH$_4$ (15 mg) afforded 55 mg of product which, after column chromatography on Si gel (hexane-EtOAc, 7:3) and crystallization, yielded 32 mg of diol **8**. Mp 74° (hexane); [α]^{24} (λnm) −9.4° (589), −9.1° (578), −10.9° (546), −19.7° (436), −33.3° (365), (c, 0.9); ir ν max 3380, 1650, 1380, 1270, 1050, 1000 cm^{-1}; ^{1}H nmr δ 0.97 (3H, d, J=6.1 Hz, Me$_{15}$), 0.99 (3H, s, Me$_{12}$), 1.1-1.8 (10H, m) 1.66 (3H, s, Me$_{14}$), 4.17 (1H, d, J=12.2 Hz, H$_{13}$), 4.30 (1H, d, J=12.2, H$_{13}$), 4.38 (1H, brs, H$_5$) ppm; ^{13}C nmr see Table 2.

CANTABRADIENOL (**9**).—A solution of **8** (30 mg) in Me$_2$CO (20 ml) with 2,2-dimethoxypropane (1 ml) and a small amount of trimethylsilyl chloride were allowed to react at room temperature for 10 min yielding 24 mg of **9** (unstable oil). Ir ν max 3410, 3080, 3020, 1640, 1370, 1220, 1020, 860 cm^{-1}; ^{1}H nmr δ 0.98 (3H, d, J=6.5 Hz, Me$_{15}$), 1.01 (3H, s, Me$_{12}$), 1.1-2.0 (10H, m), 4.30 (2H, s, H$_{13}$), 4.71 (2H, s, H$_{14}$), 5.69 (1H, brs, H$_5$) ppm.

2D-NMR EXPERIMENTS.—*Heteronuclear ^{1}H-^{13}C correlations (200/50.3 MHz).*—Pulse sequence XHDEPT.AU. 128 FIDs of 96 scans each, with 1.1 sec recycle delay and incrementing t$_1$ from 3 μsec to 184 msec, were acquired over a 1M solution of **2** at 25°. Polarization transfer was tuned for a value of $^1J_{C,H}$=135 Hz. After sine-bell filtration in both domains FT with one degree of zero-filling in F$_1$ a matrix sized 256×1024 data points with digital resolution (DR)=2.5 Hz/pt in F$_1$ and 4.8 kHz/pt in F$_2$ was obtained (Figure 1).

The long-range ^{1}H/^{13}C correlation was performed on the same conditions except in tuning reponse for $^nJ_{C,H}$=6.3 Hz. DR was 4.7 Hz/pt in F$_1$ and 20.8 Hz/pt in F$_2$. Number of scans per FID was 192, and the F$_1$ carrier was placed at the end of the ^{1}H spectrum to avoid folding.

Homonuclear ^{1}H-^{1}H correlation (500 MHz).—COSY.AU pulse sequence from Bruker DISNMR 85 program library was used. 256 FIDs of 16 scans each with 1 sec recycle delay and incrementing from 3 μsec to 427 msec the delay between both 90° pulses, were acquired over a 50 mmol solution of **2** at 37°. Fourier transform was performed after sine-bell filtration in both domains leading to a 256×1024 data points matrix, with DR=1.7 Hz/pt, which was symmetrized (Figure 2).

2D-nOe (500 MHz).—NOESY.AU pulse sequence was applied on the same sample as COSY experiment, to obtain 256 FIDs of 16 scans each with a recycle delay of 2 sec, incrementing t$_1$ from 2 to 102.4

msec and with a variable (10%) mixing delay of 1 sec. The carrier was placed at the end of the spectrum to avoid ghost peaks. Fourier transform was performed after sine-bell filtration, leading to a 256×1024 data point matrix, with DR$=4.8$ Hz/pt, which was symmetrized.

ACKNOWLEDGMENTS

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