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ENT-KAURANE DITERPENOIDS FROM *EUPHORBIA WANGII*

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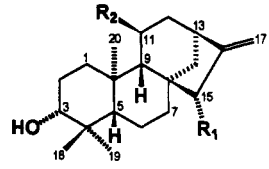
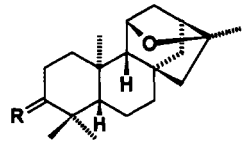
ABSTRACT.—Four new diterpenoids having the *ent*-kaurane skeleton, euphoranginol A 11-acetate [**1**], euphoranginol B [**2**], euphoranginol C [**3**], and euphoranginone D [**4**], together with a known compound *ent*-kaur-16-en-3β-ol [**5**], were isolated from the whole plant of *Euphorbia wangii*. Their structures were elucidated by spectroscopic methods and chemical transformations.

Recently, we reported the isolation and structural determination of a new diterpenoid from *Euphorbia micractina* (1). In a continuation of our phytochemical studies of diterpenoids from the genus *Euphorbia*, we now describe the isolation and characterization of four new *ent*-kaurane diterpenoids, euphoranginol A 11-acetate [**1**], euphoranginol B [**2**], euphoranginol C [**3**], and euphoranginone D [**4**], as well as a known compound *ent*-kaur-16-en-3β-ol [**5**] (2,3), which were obtained from the whole plants of *E. wangii* Oudejans (Euphorbiaceae).



1 R_1=H, R_2=OAc
2 R_1=OH, R_2=H
5 R_1=H, R_2=H
6 R_1=H, R_2=OH



3 R=α-OH, β-H
4 R=O
7 R=α-OAc, β-H

Euphoranginol A 11-acetate [**1**] was obtained as colorless needles from Me_2CO. The ir spectrum of **1** showed the presence of a hydroxy group (3537 cm^{-1}), an acetoxyl group (1720 and 1264 cm^{-1}), and an exocyclic methylene group (3069, 1660, and 874 cm^{-1}). The eims of **1** showed an $[M]^+$ at *m/z* 346, and elemental analysis gave a molecular formula of $C_{22}H_{34}O_3$. The characteristic fragment ions at *m/z* 286 $[M-HOAc]^+$ and 43 $[Ac]^+$ indicated the presence of an acetoxyl group. The ^{1}H-nmr spectrum (δ_H 1.92, 3H, s) and ^{13}C-nmr spectrum (δ_C 169.7 and 21.6) confirmed the presence of an acetoxyl group. A combination of the ^{13}C-nmr and DEPT spectra indicated signals for three Me, seven CH_2, five CH (two CH-O), three quaternary carbons, and an exocyclic methylene group (δ 155.0 and 103.1). The ^{1}H-nmr spectrum of **1** exhibited signals for three tertiary methyl groups at δ 0.98, 0.95, and 0.76 (each 3H, s), an exocyclic methylene group at δ 4.81 and 4.67 (each 1H, br s), two oxymethine protons at δ 5.03 (1H, t, J=3.4 Hz) and 3.20 (1H, dd, J=11.5 and 4.9 Hz), and an allylic proton at δ 2.62 (1H, m) characteristic for H-13. From these data **1** was assigned as a tetracyclic diterpene with an *ent*-kaur-16-ene skeleton (4,5). The locations of the two oxygenated functional groups were deduced as follows. In the ^{1}H-^{1}H COSY nmr spectrum of **1**, there were couplings between H-11 (δ 5.03) and H-12 (δ 1.85, 2H, m), with the latter signal in turn being coupled to H-13 (δ 2.62). Comparison of the ^{13}C-nmr spectrum of **1** with that of the hydrolyzed product **6** indicated that the C-11 signal of **6** was shifted upfield from δ 69.0 to δ 67.0, while the C-9 and C-12 resonances were shifted downfield from δ 61.7 and 39.1 to

64.7 and 43.2 ppm, respectively. Hence the acetoxyl group was placed at C-11. An α-orientation of the acetoxyl group occurring in an axial configuration was assigned by the coupling constant of H-11 (t, J=3.4 Hz). The location of the acetoxyl group at C-11 was further confirmed from the fact that H-11 showed cross-peaks with Me-20 (δ 0.95) and H-14 (δ 1.92) in the ^{1}H-^{1}H NOESY nmr spectrum of **1**. In an nOe difference nmr experiment, irradiation of the H-11 signal gave enhancements of the Me-20 (16%) and H-14 (11%) signals. The hydroxy group was located at C-3 (4,6) according to the coupling pattern of the H-3 proton at δ 3.20 (dd, J=11.5 and 4.9 Hz) which showed a cross-peak in the ^{1}H-^{1}H NOESY nmr spectrum of **1** with Me-18 (δ 0.98). An nOe difference nmr experiment showed that irradiation of the H-3 signal gave enhancements of the H-1 (δ 1.94) (10%), H-5 (δ 0.80) (8%), and Me-18 (5%) signals. Consequently, the structure of euphoranginol A 11-acetate [**1**] was assigned as *ent*-11α-acetoxykaur-16-en-3β-ol.

Euphoranginol B [**2**] was obtained as white needles from Me_2CO. The eims of **2** gave a strong molecular ion peak at *m/z* 304 $[M]^+$, and CH analysis for the molecular formula of $C_{20}H_{32}O_2$, and a pair of eims fragments at *m/z* 286 $[M-H_2O]^+$ and *m/z* 268 $[M-2H_2O]^+$ for the successive loss of two H_2O molecules. The ir spectrum showed an absorption band for one or more hydroxy groups (3304 cm^{-1}) and an exocyclic methylene group (3077, 1661, and 894 cm^{-1}). The nmr spectral data of **2** indicated the presence of three tertiary methyl groups (^{1}H nmr δ 1.02, 0.99, and 0.78, each 3H, s; ^{13}C nmr δ 28.4, 17.7, and 15.5), an exocyclic methylene group (^{1}H nmr δ 5.02 and 5.07, each 1H, br s; ^{13}C nmr δ 160.3 and 108.2) and two CH-OH groups (^{1}H nmr δ 3.20, 1H, dd, J=11.2 and 5.2 Hz; 3.79, 1H, br s; ^{13}C nmr δ 78.9 and 82.9). Comparison of the ^{1}H- and ^{13}C-nmr data of **2** with those of **1** showed that **1** and **2** are based on the same *ent*-kaurane skeleton, and therefore **2** was established as *ent*-kaur-16-ene diol.

A hydroxymethine proton at δ 3.79 (br s) showed cross-peaks for allylic coupling with the exocyclic methylene protons in the ^{1}H-^{1}H COSY nmr spectrum of **2**, and this fixed one hydroxy group at C-15. For *ent*-kaurenoids, the 15α-hydroxymethine proton appears as a triplet with a J value of 2–3 Hz (4,7,8), and the 15β-hydroxymethine proton appears as a singlet (9,10). The H-15 methine proton of **2** appeared as a broad singlet and thus established the 15β-configuration. This was further confirmed by the ^{1}H-^{1}H NOESY spectrum of **2** which showed a strong cross-peak between H-15 and H-9 (δ 0.88). Irradiation of the H-15 signal gave an enhancement of the H-9 signal (16%) in an nOe difference nmr experiment. Also the ^{13}C-nmr chemical shifts reported for an exo-(15β-OH) functionality (11) are nearly the same as observed ($\Delta\delta<0.3$ ppm), but the reported shifts for the endo-15-hydroxy group (4,7,11) are rather different from those observed, particularly for C-8, C-9, C-13, C-14, C-16, and C-17 ($\Delta\delta$ 2–8 ppm). Comparison of the ^{1}H- and ^{13}C-nmr spectra of **2** with those of **1** or **6** indicated that the remaining hydroxy group of **2** should be present at the 3β position. Moreover, the ^{1}H-^{1}H NOESY nmr spectrum of **2** indicated a cross-peak between H-3 and Me-18 (δ 0.98). A nOe difference nmr experiment with irradiation of the H-3 signal gave enhancements of the H-1 (δ 1.85) (8%), H-5 (δ 0.76) (10%), and Me-18 (4%) signals. Hence the positions and configurations of the two hydroxy groups were deduced as 15β and 3β, respectively. Accordingly, the structure of euphoranginol B [**2**] was assigned as *ent*-kaur-16-en-3β,15β-diol.

Euphoranginol C [**3**] gave white needles with Me_2CO. It gave ir absorption bands for a hydroxy group (3260 cm^{-1}) and an ether bond (1030, 1091, and 1115 cm^{-1}). The molecular formula of **3** was established as $C_{20}H_{32}O_2$ by its ^{13}C-nmr data (Table 1) and the molecular

TABLE 1. ^{13}C-Nmr Spectral Data of Compounds **1–4**, **6**, and **7**.

Carbon	Compound									
	1[a]		**2**[a]		**3**[a]		**4**[a]		**6**[b]	**7**[b]
	^{13}C	DEPT	^{13}C	DEPT	^{13}C	DEPT	^{13}C	DEPT	^{13}C	^{13}C
1	38.1	CH_2	38.7	CH_2	39.0	CH_2	39.0	CH_2	38.0	38.6
2	27.2	CH_2	27.3	CH_2	27.1	CH_2	34.0	CH_2	27.2	23.5
3	78.7	CH	78.9	CH	78.9	CH	217.3	C	78.7	80.9
4	38.9	C	39.2	C	38.8	C	47.2	C	38.8	37.6
5	55.0	CH	55.0	CH	55.7	CH	55.3	CH	55.0	55.9
6	19.8	CH_2	19.1	CH_2	19.7	CH_2	21.2	CH_2	19.8	19.6
7	41.0	CH_2	35.2	CH_2	37.8	CH_2	37.1	CH_2	40.9	37.6
8	42.8	C	47.5	C	44.7	C	44.7	C	42.7	44.6
9	61.7	CH	54.2	CH	59.0	CH	57.9	CH	64.7	58.8
10	37.9	C	38.8	C	36.6	C	35.9	C	37.6	36.4
11	69.0	CH	18.1	CH_2	76.8	CH	76.8	CH	67.0	76.7
12	39.7	CH_2	32.7	CH_2	40.4	CH_2	40.4	CH_2	43.2	40.3
13	42.3	CH	42.3	CH	45.6	CH	45.4	CH	42.1	45.5
14	39.1	CH_2	36.2	CH_2	43.7	CH_2	43.3	CH_2	39.4	43.9
15	47.8	CH_2	82.9	CH	57.1	CH_2	56.8	CH_2	48.7	57.0
16	155.0	C	160.3	C	85.6	C	85.8	C	156.0	85.5
17	103.1	CH_2	108.2	CH_2	23.2	CH_3	23.1	CH_3	105.3	23.1
18	28.4	CH_3	28.4	CH_3	28.8	CH_3	27.5	CH_3	28.4	28.8
19	15.5	CH_3	15.5	CH_3	16.0	CH_3	21.6	CH_3	15.5	17.1
20	17.4	CH_3	17.7	CH_3	18.4	CH_3	18.6	CH_3	17.1	18.4
Ac	169.7	C								170.8
	21.6	CH_3								21.2

[a]Assignments from ^{1}H-^{13}C COSY experiments.
[b]Assignments by comparison with **1** and **3**.

ion peak at *m/z* 304 in the eims, and by CH analysis. The ^{13}C-nmr and DEPT spectra of **3** indicated carbon signals for four Me groups, seven CH_2 units, three quaternary carbons, two oxygenated methine carbons (δ 79.9 and 76.8) and one oxygenated quaternary carbon (δ 85.6). Its ^{1}H-nmr spectrum exhibited four tertiary methyls at δ 1.33, 1.06, 0.98, and 0.80 (each 3H, s) and two downfield protons at δ 4.32 (1H, t, J=3.1 Hz) and 3.22 (1H, dd, J=11.3 and 5.0 Hz). By comparing the above spectral data of **3** with those of **1** and **2**, it was found that a methyl group (δ_H 1.33; δ_C 23.2) and an oxygenated quaternary carbon (δ 85.6) replaced an exocyclic methylene group. In the ^{1}H-^{1}H COSY spectrum of **3**, the H-11 proton (δ 4.32) and the characteristic H-13 proton (δ 2.20, t J=6.4 Hz) showed cross-peaks with two intermediary methylene protons (H_2-12, δ 1.89, 1H, m, and 2.04, 1H, d, J=11.2 Hz), so that an oxygen function was located at C-11. Furthermore, the coupling constant of H-11 (t, J=3.1 Hz) indicated that the oxygen function is axial (12). Acetylation of **3** with Ac_2O in pyridine gave a monoacetate, **7**. The eims of **7** exhibited a molecular ion peak at *m/z* 346, which was 42 mass units higher than that of **3**, which established the presence of one hydroxy group in the molecule of **3**. Comparison of the ^{13}C-nmr spectrum of **7** with that of **3** indicated that the C-3 resonance of **7** was shifted downfield from δ 78.9 to 80.8, while the C-2 and C-4 signals were shifted upfield from δ 27.1 to 23.5 and 38.8 to 37.6, respectively, confirming a hydroxy group at C-3. The coupling pattern of H-3 (J=11.5 and 5.0 Hz) indicated the hydroxy group is in the β-orientation. The above-mentioned data indicated that

TABLE 2. ^{1}H-Nmr Spectral Data of Compounds **1–4**, **6**, and **7**.[a]

Proton	Compound					
	1[b]	**2**[b]	**3**[b]	**4**[b]	**6**[c]	**7**[c]
1	1.03 dt (13.5,3.5)	0.91 dt (12.5,3.3)	1.17 dt (13.0,4.2)	1.26 m	1.14 dt (12.4,3.7)	1.22 m
	1.93 m	1.85 m	1.78 t (13.0,4.0)	1.98 m	1.93 m	1.76 dt (13.2,3.4)
2	1.64 m	1.64 m	1.59 m	2.46 m	1.64 m	1.62 m
3	3.20 dd (11.5,4.9)	3.20 dd (11.2,5.2)	3.22 dd (11.3,5.0)	—	3.22 dd (11.5,4.9)	4.46 dd (11.4,4.9)
5	0.80 br d (11.8)	0.76 br d (12.7)	0.77 br d (11.8)	1.01 m	0.82 br d (12.4)	0.84 dd (11.2,1.6)
6	1.35 m	1.33 m	1.32 m	1.31 m	1.33 m	1.32 m
	1.53 m	1.52 m	1.50 m	1.50 m	1.52 m	1.50 m
7	1.58 m	1.73 m	1.47 m	1.45 m	1.56 m	1.47 m
9	1.26 br s	0.88 m	1.42 m	1.42 m	1.37 brs	1.42 m
11	5.03 t (3.4)	1.56 m	4.32 t (3.1)	4.33 t (3.5)	3.83 t (3.4)	4.29 t (3.1)
12	1.85 m	1.60 m	1.89 m	1.87 m	1.94 m	1.87 m
	1.85 m	1.60 m	2.04 d (11.2)	2.03 d (11.4)	1.94 m	2.01 d (11.2)
13	2.62 m	2.74 m	2.20 t (6.4)	2.23 t (6.5)	2.69 m	2.18 t (6.4)
14	1.14 m	1.31 m	1.25 m	1.26 m	1.15 m	1.25 m
	1.92 m	1.87 br d (12.0)	1.93 dd (11.6,3.4)	1.93 dd (11.6,3.6)	1.86 m	1.92 dd (11.4,3.5)
15	2.04 dt (16.7,3.0)	3.79 br s	1.33 d (11.1)	1.37 d (11.2)	2.09 dt (16.9,2.8)	1.33 d (11.1)
	2.45 br d (16.7)	—	1.35 m	1.42 m	2.44 br d (16.9)	1.39 m
17	4.67 br s	5.07 br s	1.31 s	1.34 s	4.84 br s	1.31 s
	4.8 br s	5.20 br s	—	—	5.02 br s	—
18	0.98 s	0.98 s	0.98 s	1.10 s	0.98 s	0.85 s
19	0.76 s	0.78 s	0.80 s	1.03 s	0.76 s	0.83 s
20	0.95 s	1.02 s	1.06 s	1.07 s	0.88 s	1.07 s
Ac	1.92 s					2.01 s

[a]Coupling constants (J in Hz) are given in parentheses.
[b]Assignments from ^{1}H-^{1}H COSY and ^{1}H-^{13}C COSY experiments.
[c]Assignments by comparison with **1** and **3**.

euphoranginol C [**3**] had a structure corresponding to *ent*-11α,16α-epoxykauran-3β-ol.

Euphoranginone D [**4**], colorless prisms (Me_2CO), showed a strong ir absorption band for a keto group (1701 cm^{-1}) and bands for an ether bond (1036 and 1114 cm^{-1}). Its eims exhibited a molecular ion peak at *m/z* 302. The ^{1}H-nmr, ^{13}C-nmr, and DEPT spectra of **4** (Tables 1 and 2) resembled those of **3** except that the hydroxy of **3** was replaced by a keto group in the case of **4**. The structure of **4** was confirmed by the fact that reduction of **4** with $NaBH_4$ afforded **3**. Thus the structure of **4** is *ent*-11α,16α-epoxykauran-3-one.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were determined on an X-4 micro-melting point apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ with a Rudolph Research Autopol III automatic polarimeter. Ir spectra were recorded on KBr plates as films using a Nicolet 170 SX ir spectrophotometer. Eims were run on a VG ZAB-HS mass spectrometer, and ^{1}H- and ^{13}C-nmr spectra were recorded on a Bruker AM 400 spectrometer in $CDCl_3$ using TMS as internal reference.

PLANT MATERIAL.—*Euphorbia wangii* Oudejans (Euphorbiaceae) was collected in Zhouqu County, Gansu Province, People's Republic of China in September 1990. It was identified by Mr. Zhao Zhi-Li, Associate Professor of Plant Taxonomy, Lanzhou Medical College, Lanzhou, People's Republic of China, and a voucher specimen (No. 9046) is deposited at the Herbarium of the Department of Pharmacy, Lanzhou Medical College.

EXTRACTION AND ISOLATION.—Air-dried and powdered whole plants (10 kg) were repeatedly extracted (4×) with Me_2CO at room temperature. The combined extracts were evaporated to give a concentrated solution, which was decolorized with activated charcoal in the usual fashion. The decolorized filtrate was concentrated to yield a syrup (374 g). The syrupy extract was absorbed on Si gel and chromatographed (cc), eluting with petroleum ether (60–90°), Et_2O, EtOAc, and Me_2CO, successively. The Et_2O eluate (82 g) was subjected to cc on Si gel and eluted with a gradient of cyclohexane and EtOAc to give 7 fractions. Fraction 2 was purified by Si gel cc with petroleum ether-EtOAc (8:1) to afford the known compound **5** (27 mg); fraction 3 was purified by Si gel cc with petroleum ether-EtOAc (5:1) to give **4** (50 mg); fraction 4 was purified by Si gel cc with petroleum ether-Me_2CO (5:1) to yield **1** (123 mg); and fraction 5 was further separated by repeated Si gel cc with petroleum ether-Me_2CO (3:1) to afford **2** (18 mg) and **3** (95 mg).

Euphoranginol A 11-acetate [**1**].—Mp 204–206°; $[\alpha]^{24.5}D$ −55.6° (c=0.45, $CHCl_3$); ir (KBr) ν max 3537, 3069, 2927, 1721, 1660, 1442, 1382, 1366, 1264, 1036, 960, 874 cm^{-1}; eims m/z (70 eV) $[M]^+$ 346 (4), $[M-H_2O]^+$ 328 (5), 313 (2), $[M-HOAc]^+$ 286 (68), 271 (66), 268 (60), 253 (94), 225 (15), 199 (17), 148 (43), 135 (63), 105 (70), 91 (84), 79 (45), 69 (50), 55 (53), 43, (100); ^1H nmr, see Table 2; ^{13}C nmr, see Table 1; *anal.* calcd for $C_{22}H_{34}O_3$, C 76.26, H 9.89; found C 76.28, H 9.93.

HYDROLYSIS OF EUPHORANGINOL A 11-ACETATE [**1**].—A solution of **1** (37 mg) in MeOH (2 ml) was treated with 5% NaOH-MeOH solution (5 ml) at room temperature. After 3 h the mixture was worked up in the usual way to give **6** (20 mg), which was then recrystallized from Me_2CO. Colorless needles, mp 170–172°; $[\alpha]^{24.5}D$ −54.5° (c=0.45, $CHCl_3$); ir (KBr) ν max 3554, 3466, 3058, 2934, 1657, 1434, 1384, 1366, 1041, 1001 cm^{-1}; eims m/z (70 eV) $[M]^+$ 304 (14), $[M-H_2O]^+$ 286 (36), 271 (60), 268 (65), 261 (7), 253 (72), 244 (18), 225 (19), 148 (59), 135 (67), 132 (74), 105 (70), 91 (97), 79 (49), 69 (58), 55 (60), 41 (100); ^{13}C nmr, see Table 1; ^1H nmr, see Table 2.

Euphoranginol B [**2**].—Mp 180–182°; $[\alpha]^{24.5}D$ −32.1° (c=0.25, $CHCl_3$); ir (KBr) ν max 3304, 3077, 2929, 1661, 1455, 1388, 1366, 1099, 1059, 996, 894 cm^{-1}; eims m/z (70 eV) $[M]^+$ 304 (19), $[M-CH_3]^+$ 289 (20), $[M-H_2O]^+$ 286 (24), 271 (52), 268 (13), 253 (20), 246 (50), 229 (18), 203 (25), 147 (30), 135 (42), 121 (41), 107 (50), 91 (64), 79 (57), 67 (51), 55 (74), 41 (100); ^{13}C nmr, see Table 1; ^1H nmr, see Table 2; *anal.* calcd for $C_{20}H_{32}O_2$, C 78.90, H 10.59; found C 78.68, H 10.37.

Euphoranginol C [**3**].—Mp 210–211°; $[\alpha]^{24.5}D$ −8.3° (c=0.48, $CHCl_3$); ir (KBr) ν max 3260, 2939, 1442, 1382, 1367, 1115, 1091, 1030, 972, 940, 821 cm^{-1}; eims m/z (70 eV) $[M]^+$ 304 (100), $[M-Me]^+$ 289 (7), $[M-H_2O]^+$ 286 (14), 271 (12), 261 (93), 243 (12), 189 (19), 149 (52), 135 (31), 119 (29), 107 (38), 91 (38), 79 (28), 69 (38), 55 (39); ^{13}C nmr, see Table 1; ^1H nmr, see Table 2; *anal.* calcd for $C_{20}H_{32}O_2$, C 78.90, H 10.59; found C 78.82, H 10.58.

ACETYLATION OF EUPHORANGINOL C.—Compound **3** (27 mg) was dissolved in Ac_2O-pyridine (1:1). The solution was left overnight at room temperature and worked up in the usual way to yield **7** (21 mg). White needles, mp 166–168°; $[\alpha]^{24.5}D$ −11.3° (c=0.57, $CHCl_3$); ir (KBr) ν max 2948, 1722, 1451, 1381, 1370, 1241, 1113, 1024, 980, 943, 902, 822 cm^{-1}; eims m/z (70 eV) $[M]^+$ 436 (81), $[M-CH_3]^+$ 331 (4), $[M-Ac]^+$ 303 (84), $[M-HOAc]^+$ 286 (19), 271 (12), 243 (18), 227 (7), 189 (17), 149 (37), 135 (20), 107 (25), 91 (24), 79 (15), 69 (30), 55 (22), 43 (100); ^{13}C nmr, see Table 1; ^1H nmr, see Table 2.

Euphoranginone D [**4**].—Mp 154–156°; $[\alpha]^{24.5}D$ −49.0° (c=0.50, $CHCl_3$); ir (KBr) ν max 2958, 1701, 1482, 1443, 1381, 1360, 1114, 1036, 968, 819 cm^{-1}; eims m/z (70 eV) $[M]^+$ 302 (88), $[M-CH_3]^+$ 287 (10), $[M-H_2O]^+$ 284 (12), 259 (100), 244 (15), 229 (10), 149 (52), 107 (35), 91 (24), 79 (32), 69 (26), 55 (34); ^{13}C nmr, see Table 1; ^1H nmr, see Table 2; *anal.* calcd for $C_{20}H_{30}O_2$, C 79.42, H 10.00; found C 79.46, H 10.13.

REDUCTION OF EUPHORANGINONE D [**4**] WITH $NaBH_4$.—A solution of **4** (28 mg) in MeOH (10 ml) was treated with $NaBH_4$ (45 mg) and stirred for 30 min at room temperature. The mixture was diluted with H_2O (25 ml) and extracted with CH_2Cl_2 (25 ml×2). The combined CH_2Cl_2 extracts were concentrated to dryness, then crystallized from Me_2CO to give **3** (20 mg).

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