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TWO EPIMERIC, IRREGULAR DITERPENOID TOLUQUINOLS FROM THE BROWN ALGA *CYSTOSEIRA STRICTA*

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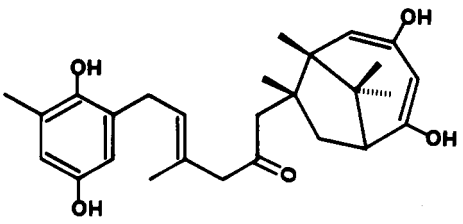
ABSTRACT.—Two novel, irregular tetraprenyltoluquinols have been isolated from the brown alga *Cystoseira stricta* and characterized by spectral methods.

Two groups of rearranged diterpenoids, mediterraneols (1), e.g., mediterraneol A [**1**] and cystoseirols (2), e.g., cystoseirol D [**2**], which possess an unprecedented bicyclo[4.2.1]nonane and an oxabicyclo[5.4.1]dodecane ring system, respectively, have been isolated by French authors from brown algae belonging to the genus *Cystoseira*: mediterraneols from *Cystoseira mediterranea*, and cystoseirols from the same alga as well as from the closely related *Cystoseira tamariscifolia* and *Cystoseira stricta* (Mont.) Sauv. (Cystoseiraceae).



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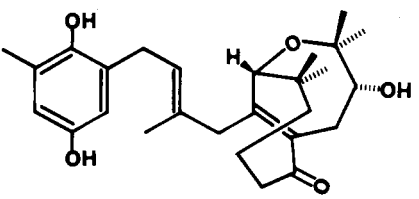

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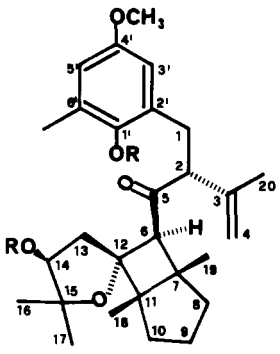
Previous work from our group on this last alga collected off the Sicilian coasts has resulted in the isolation of several metabolites of mixed biogenesis, all of them with a regular diterpenoid moiety (3–6). A meticulous re-examination of the minor components of the lipid extracts from *C. stricta* has now led to the isolation of two previously unreported diterpenoid toluquinols, neobalearone [**3**] and epineobalearone [**5**]. The compounds' very similar ir, uv, and mass spectra suggested stereochemical rather than structural differences between the two, while the presence in their ^{1}H-nmr spectra of resonances for five tertiary methyls and a terminal methylene revealed that they were irregular diterpenoids. However, a closer examination of the spectral characteristics excluded any relationship with the cystoseirols or the mediterraneols.

The more polar of the two compounds from *C. stricta*, neobalearone [**3**], $C_{28}H_{40}O_5$ (*m/z* 456.2877, calcd 456.2875), $[\alpha]^{25}D$ +120.0°, displayed uv absorptions for a hydroquinone nucleus (220 and 288 nm, ϵ = 10600 and 4600) and ir bands for hydroxyl(s) (3400 cm^{-1}) and a hydrogen-bonded carbonyl (1685 cm^{-1}). Acetylation of **3** (Ac_2O/pyridine) afforded diacetate **4**, $C_{32}H_{44}O_7$. The ^{1}H nmr of **3** contains an AB system (δ 6.54 and 6.41, J = 3 Hz) assignable to two meta-coupled aromatic protons and signals for a methoxyl (δ 3.72 s) and a methyl (δ 2.21 s) on aromatic ring. A benzylic methylene (AB part of an ABX system: δ 3.19 and 2.39) is coupled with a methine, whose low-field position (X part of an ABX system: δ 3.21) indicates that it is adjacent to the carbonyl function. This three-spin system could be completely analyzed in the spectrum run in C_6D_6 [AB part δ 3.61, dd (J = 12.5 and 11.4 Hz), 3.47, dd (J = 11.4 and 2.2



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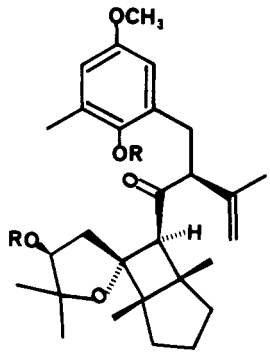
4 R=Ac



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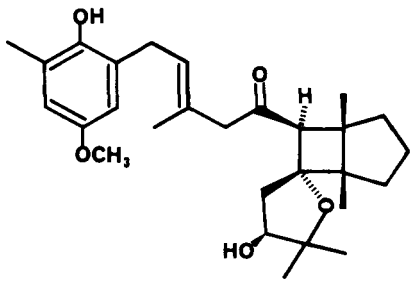
6 R=Ac



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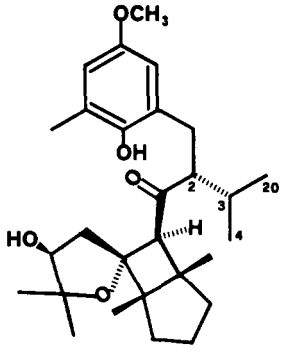

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Hz); X part δ 2.58, dd (J = 12.5 and 2.2 Hz)]. A broad singlet at δ 7.10 (D_2O-exchangeable), whose chemical shift is invariant regardless of dilution, was assigned to a phenolic hydroxyl involved in a hydrogen bond. The spectrum also shows resonances for an isopropenyl group (vinyl methyl at δ 1.76 long-range coupled to the terminal methylene, δ 5.02 and 4.89), which was located at C-2 on the basis of a long-range coupling between H-2 and H_2-4.

The rest of the spectrum consists of a methine singlet whose chemical shift (δ 3.12, H-6) indicates that it is α to the carbonyl group, an ABX system [AB part δ 3.04, dd (J = 12 and 6 Hz), 1.82, dd (J = 12 and 9 Hz), H_2-13; X part δ 3.90, dd (J = 9 and 6 Hz), H-14, shifted at 4.99 in the diacetate **4**], four tertiary methyls at δ 0.25, 0.79, 1.03, and 1.10, and a group of signals between δ 2.30 and 1.10, partly overlapped with other signals, assignable to three contiguous methylenes (H_2-8, H_2-9, and H_2-10) not further coupled with other protons. These data and the ^{13}C-nmr spectrum (Table 1), considered in comparison with that of balearone [**7**] (7) led us to formulate neobalearone as **3** (apart from stereochemistry). For clarity, the numbering system follows that for the related balearone. The proposed gross structure was unambiguously confirmed by long-range ^{1}H-^{13}C correlation (Table 1).

The relative stereochemistry at C-6, C-7, C-11, C-12, and C-14 was deduced from a NOESY spectrum (Table 2), which showed H_3-18 to be within nOe distance from H_3-14 and H_b-13, H_3-16 from H-6 and H-14, and H_3-17 from H_b-13. The relative configuration at the remaining chiral center (C-2) was assigned as depicted based on an nOe effect between H-6 and H_3-20, assuming a preferred conformation stabilized by

TABLE 1. ^1H and ^{13}C nmr Data for Neobalearone [3].[a]

Position	δ_c	DEPT	δ_H (*J*)	H/C long range correlations[b]
1′	146.4	C		H-3′, H-5′, 6′-Me, 1′-OH
2′	127.0	C		H_2-1, 1′-OH
3′	113.2	CH	6.41 d (3)	H-5′, H_a-1
4′	153.2	C		H-3′, H-5′, -OMe
5′	114.9	CH	6.54 d (3)	H-3′, 6′-Me
6′	127.5	C		6′-Me
1	30.0	CH_2	H_a 3.19 m[c] H_b 2.39 dd (11, 1.6)	H-3′
2	64.8	CH	3.21 m[c]	H_2-4, H_3-20
3	142.4	C		H-2, H_3-20
4	115.5	CH_2	H_a 5.02 bs H_b 4.89 bs	H-2, H_3-20
5	211.7	C		H_2-1, H-2
6	60.1	CH	3.12 s	H_3-19
7	47.4	C		H-6, H_3-18, H_3-19
8	40.9	CH_2	1.30 m, 1.65 m	H-6, H_3-19
9	24.9	CH_2	1.75 m	
10	35.6	CH_2	1.10 m, 2.30 m	H_3-18
11	52.9	C		H_3-18, H_3-19
12	81.1	C		H-6, H_2-13, H_3-18
13	35.9	CH_2	H_a 3.04 dd (12, 6) H_b 1.82 dd (12, 9)	
14	78.4	CH	3.90 dd (9, 6)	H_b-13, H_3-16, H_3-17
15	79.8	C		H_3-16, H_3-17
16	27.6	Me	1.10 s	H_3-17
17	22.3	Me	1.03 s	H_3-16
18	18.8	Me	0.79 s	H_2-10
19	15.4	Me	0.25 s	H-6
20	20.9	Me	1.76 s	H_2-4
-OMe	55.8	Me	3.72 s	
6′-Me	16.7	Me	2.21 s	H-5′
1′-OH			7.10 bs	

[a]The ^1H- and ^{13}C-nmr spectra were run at 250 and 62.5 MHz, respectively, in $CDCl_3$ (ppm from TMS).

[b]Long range correlations were obtained by two experiments for optimum generation of polarization transfer with $J = 7.5$ and 10 Hz.

[c]Overlapped.

hydrogen bonding of the phenolic hydroxyl to the carbonyl group. To obtain a more detailed description of this conformation a computational analysis was carried out using the MacroModel program[1] (MM2 force field) and assigning 1.8 and 3.5 Å as the length of the hydrogen bond and the distance between H_3-20 and the geminal methyl at C-15, respectively (an interaction between these two groups is observed in the NOESY spectrum). A stereoscopic view of the conformation thus determined is shown in Figure 1 and allows the ascription of the unusual highfield position of the methyl at C-7 (δ 0.25) to the shielding effect of the double bond at C-3. In fact, the resonance for this methyl undergoes a large downfield shift following catalytic hydrogenation (δ 0.77 in the dihydroderivative **8**) as well as by suppression of the hydrogen bond (δ 0.54 in solution of CD_3OD and 0.56 in the acetate **4**).

[1]The MacroModel program, developed by Prof. W.C. Still, is a copyright of Columbia University, New York.

TABLE 2. NOESY Data for Neobalearone [**3**] and Epineobalearone [**5**].

Proton	Compound	
	3	**5**
	Protons correlated	Protons correlated
H-3′	H_2-1, -OMe, 1′-OH	H_b-1, H-2, -OMe
H-5′	6′-Me, -OMe	6′-Me, -OMe
H_a-1	H_3-20	
H_b-1		H_3-20
H-2	H_3-20	H-6, H_3-16
H_a-4	H_3-20	H_3-20
H_b-4	H_2-1, H-2, H-6	H-2, H-6
H-6	H_3-16	H_2-8, H_2-9, H_3-16
H_b-13	H_3-17, H_3-18	H_3-18
H-14	H_3-16	H_b-13
H_3-16	H_3-17	
H_3-18	H_3-19	H_2-10, H_3-19
H_3-19		H_2-8, H_3-18
H_3-20	H-6, H_3-16, H_3-17	H_3-19
-OMe	H-3′, H-5′, H_3-16	H-3′, H-5′, H_3-16
6′-Me		H_b-13
1′-OH	H_2-1, 6′-Me	H_a-1, 6′-Me

The second metabolite isolated from *C. stricta*, epineobalearone [**5**], $[\alpha]^{25}D$ −77.1°, has spectral properties similar to neobalearone, the main differences being observed in some of the proton resonances. In particular, the ^{1}H-nmr spectrum of **5** (Table 3) contains a hydroxymethine resonance at a value as high as δ 2.20, while a resonance assignable to the tertiary methyl at C-7 appears at a normal value (δ 0.96). That

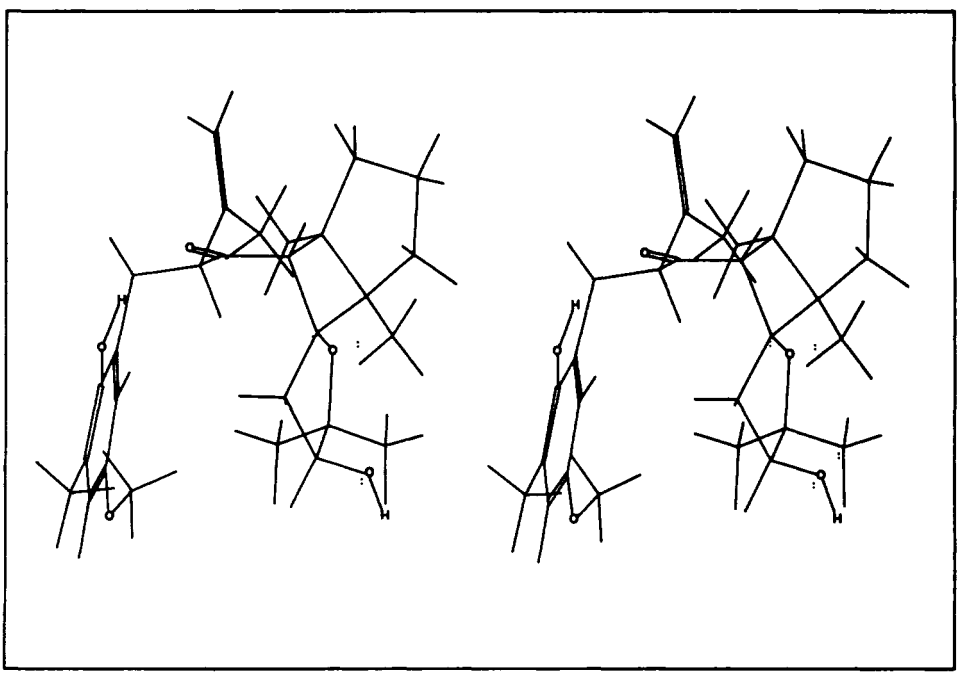

FIGURE 1. Stereoscopic drawings of the preferred conformation of compound **3**.

5 has the same gross structure as **3**, suspected from the similarity of the spectral properties, has been firmly established by long-range heteronuclear correlation (Table 3). In alkaline solution an equilibrium mixture, in which **3** predominates in the ratio 3:2, was obtained from either **3** or **5**; therefore, they must differ only in the chirality of a carbon atom adjacent to the carbonyl. When the equilibration was performed in CD_3OD in the presence of NaOD, the disappearance of the signal of H-2 was observed in the ^{1}H-nmr spectrum, while that of H-6 remained unmodified, thus showing that the chiral center at C-2 was the one involved in the epimerization. An nOe interaction was observed between the methoxyl group and one of the geminal methyls at C-15 (Table 2), and in addition hydrogen bonding of the phenolic hydroxyl to the carbonyl was noted (the chemical shift of the OH-1′ signal in the ^{1}H-nmr spectrum of **5** is in fact independent of concentration). Based on these findings, it was possible to determine the preferred conformation of **5** by the use of the MacroModel computer program. A stereoview of this conformation is shown in Figure 2. From this conformation it could be deduced that the exceptionally high-field value of the chemical shift for the hydroxymethine proton at C-14 (δ 2.20) is due to the shielding effect of the aromatic ring. Acetylation of **5** gave the diacetate **6**, in which the acetoxymethine resonates at δ 4.55 owing to the increased flexibility of the molecule when intramolecular hydrogen bonding is no longer feasible.

The possibility that only one of the isolated compounds is an algal constituent, the other one being an artifact, could be ruled out because in the experimental conditions of the isolation procedure epimerization does not occur to any extent.

Neobalearone and epineobalearone can hypothetically derive from the attack to an aromatic precursor of an activated form of geranyllavandulol, followed by modifications possibly catalyzed by the same enzyme systems that are involved in the biosynthesis of the regular diterpenoid counterpart, balearone.

EXPERIMENTAL

GENERAL METHODS.—Eims were determined at 70 eV on a Kratos MS-50S instrument. Uv and ir

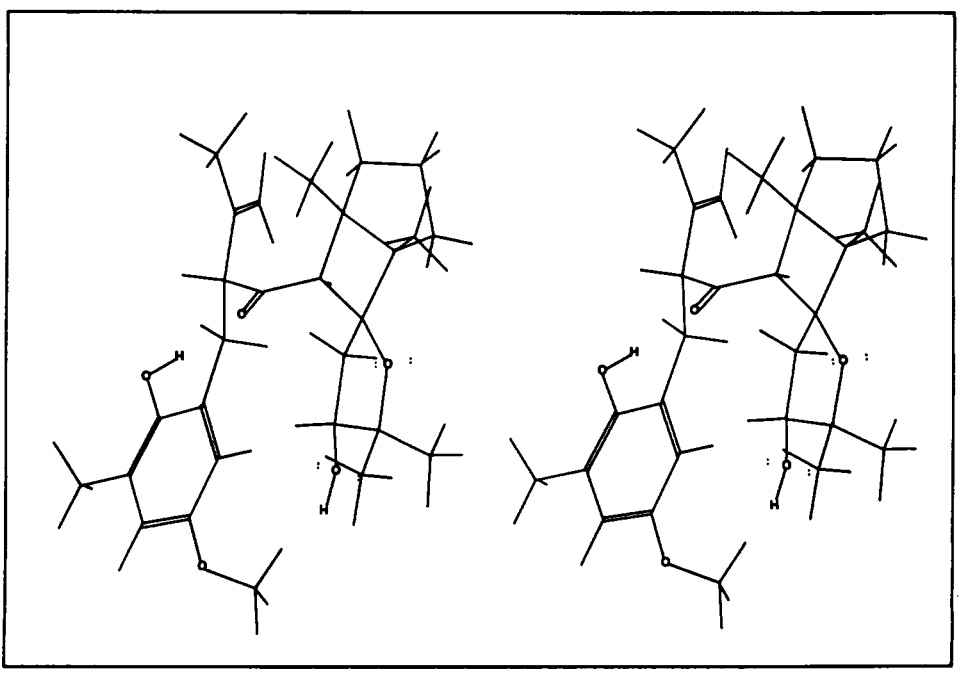

FIGURE 2. Stereoscopic drawings of the preferred conformation of compound **5**.

TABLE 3. ^1H and ^{13}C Data for Epineobalearone [**5**].[a]

Position	δ_c	DEPT	δ_H (*J*)	H/C long range correlations[b]
1′	146.5	C		H-3′, H-5′, H_b-1, 6′-Me
2′	127.6	C		H_2-1, 1′-OH
3′	113.2	CH	6.46 d (3)	H-5′, H_2-1
4′	153.4	C		-OMe
5′	114.5	CH	6.56 d (3)	H-3′, 6′-Me
6′	127.9	C		6′-Me
1	29.8	CH_2	H_a 3.22 dd (13.5, 11.3) H_b 2.37 dd (13.5, 2.3)	
2	66.9	CH	3.34 dd (11.3, 2.3)	H_a-1, H_2-4, H_3-20
3	141.3	C		H-2, H_3-20
4	115.5	CH_2	5.05 bs 4.89 bs	H-2, H_3-20
5	210.8	C		H_2-1, H-2, H-6
6	62.5	CH	3.08 s	H_b-13, H_3-19
7	44.6	C		H-6, H_3-18, H_3-19
8	41.2	CH_2	1.17 m, 1.51 m	H-6, H_3-19
9	24.2	CH_2	1.64 m	
10	36.0	CH_2	1.09 m, 2.22 m	H_3-18
11	52.9	C		H_b-13, H_3-18, H_3-19
12	82.5	C		H-6, H_b-13, H_3-18
13	34.6	CH_2	H_a 2.13 dd (11.3, 6.8) H_b 1.68 dd (11.3, 10)	
14	76.7	CH	2.20 dd (10, 6.8)	H_b-13, H_3-16, H_3-17
15	79.0	C		H_3-16, H_3-17
16	27.2	Me	0.72 s	H_3-17
17	21.7	Me	0.84 s	H_3-16
18	18.7	Me	0.64 s	
19	17.2	Me	0.96 s	H-6
20	20.7	Me	1.76 s	H_2-4
-OMe	55.6	Me	3.70 s	
6′-Me	16.7	Me	2.25 s	
1′-OH			7.40 bs	

[a]The ^1H- and ^{13}C-nmr spectra were run at 250 MHz and 62.5 MHz, respectively, in $CDCl_3$ (ppm from TMS).

[b]Long range correlations were obtained by two experiments for optimum generation of polarization transfer with $J = 7.5$ and 10 Hz.

spectra were recorded on Perkin-Elmer model 330 and model 684 spectrophotometers, respectively. Nmr spectra were measured on a Bruker AC-250 instrument, operating at 250 and 62.9 MHz for ^1H and ^{13}C, respectively. Multiplicities of ^{13}C-nmr resonances were determined by DEPT experiments. COSY, long-range heteronuclear correlations (performed with maximum polarization for 7.5 and 10 Hz, leading to ^2J and ^3J signals in the same spectrum) and NOESY experiments on compounds **3** and **5** were run using the standard Bruker microprograms. Optical rotations were determined with a Perkin-Elmer 141 polarimeter using a 10-cm microcell. Preparative liquid chromatography (plc) was carried out on a Jobin-Yvon LC Miniprep (LiChroprep Si 60, 25-40 μ as the stationary phase).

PLANT MATERIAL.—*C. stricta* was collected on rocks at about 1 m depth in October 1987 at Acicastello, Sicily. A voucher specimen is deposited at the Herbarium of the Department of Botany, Catania, Italy.

EXTRACTION AND PURIFICATION.—Shade-dried and ground plant material (500 g) was extracted three times with CH_2Cl_2 at room temperature with continuous stirring. The extracts were pooled and evaporated to give a dark green oil (15 g), which was applied to an open column (3 × 100 cm) of Si gel using eluents of increasing polarity from hexane to Et_2O. Fractions of 200 ml were collected, and those exhibiting similar tlc profiles were combined. Fractions 30–33 were pooled and subjected to plc [$CHCl_3$-Et_2O (97:3)] to yield **5** (50 mg, 0.01% dry wt of the alga). Fractions 34–36 were evaporated to give a viscous residue which was purified by plc [iPrOH-C_6H_{12} (2:98)] to give **3** (67 mg, 0.013% dry wt).

COMPOUND **3**.—Oily, $[\alpha]^{25}D + 120.0°$ ($c = 1.60$, EtOH); ir ν max (film) cm^{-1} 3395, 1685, 1614, 1605; uv λ max (EtOH) 288 nm ($\epsilon = 4600$), 220 ($\epsilon = 10600$); hreims $[M]^+$ 456.2877, calcd for $C_{28}H_{40}O_5$, 456.2875; ms *m/z* (%) 456 (1), 438 (11), 289 (8), 264 (11), 233 (7), 232 (6), 230 (11), 206 (6), 205 (4), 190 (8), 189 (8), 151 (19), 150 (50), 138 (27), 97 (38), 95 (38), 93 (34), 91 (30), 83 (46), 82 (27), 81 (42), 80 (31), 79 (50), 69 (65), 67 (61), 57 (42), 55 (100), 43 (54), 41 (77); ^1H and ^{13}C nmr see Table 1; ^1H nmr (250 MHz, TMS, δ in CD_3OD) 6.53 and 6.50 (AB system, each 1 H, d, $J = 3$ Hz, H-5′ and H-3′), 4.89 and 4.84 (each 1H, 2bs, H_a-4 and H_b-4), 3.91 (1H, dd, $J = 10.2$ and 7 Hz, H-14), 3.70 (3H, s, OMe), 3.50 (1H, dd, $J = 8.2$ and 5.6 Hz, H-2), 3.12 (1H, s, H-6), 3.08 (1H, dd, $J = 11.5$ and 7 Hz, H_a-13), 3.05 (1H, dd, $J = 14$ and 8.2, H_a-1), 2.63 (1H, dd, $J = 14$ and 5.6 Hz, H_b-1), 2.20 (3H, s, 6′-Me), 1.81 (1H, dd, $J = 11.5$ and 10.2 Hz, H_b-13), 1.73 (3H, s, H-20), 1.13 and 1.00 (each 3H, 2s, H-16 and H-17), 0.86 and 0.54 (each 3H, 2s, H-18 and H-19); ^1H nmr (250 MHz, TMS, δ in C_6D_6) 7.66 (1H, bs, 1′-OH), 6.90 and 6.84 (AB system, each 1H, d, $J = 3$ Hz, H-5′ and H-3′), 5.01 (2H, bs, H-4), 4.06 (1H, dd, $J = 10$ and 6 Hz, H-14), 3.65 (3H, s, OMe), 3.61 (1H, dd, $J = 12.5$ and 11.4 Hz, H_a-1), 3.52 (1H, s, H-6), 3.47 (1H, dd, $J = 11.4$ and 2.2 Hz, H-2), 3.33 (1H, dd, $J = 12.5$ and 6 Hz, H_a-13), 2.63 (3H, s, 6′-Me), 2.58 (1H, dd, $J = 12.5$ and 2.2 Hz, H_b-1), 2.01 (1H, dd, $J = 12.5$ and 10 Hz, H_b-13), 1.77 (3H, s, H-20), 1.38 and 1.33 (each 3H, 2s, H-16 and H-17), 0.94 and 0.66 (each 3H, 2s, H-19 and H-18).

Compound **5**.—Oily, $[\alpha]^{25}D -77.1°$ ($c = 1.86$, EtOH); ir ν max (film) cm^{-1} 3400, 1675, 1640, 1605; uv λ max (EtOH) 291 nm ($\epsilon = 3300$), 219 ($\epsilon = 10800$); hreims $[M]^+$ 456.2871, calcd for $C_{28}H_{40}O_5$, 456.2875; ms *m/z* (%) 456 (13), 438 (38), 420 (6), 360 (21), 342 (13), 288 (29), 286 (15), 273 (13), 246 (17), 233 (29), 232 (40), 228 (19), 206 (12), 205 (11), 191 (13), 190 (27), 189 (21), 168 (31), 155 (75), 151 (38), 150 (100), 139 (11), 137 (44), 123 (15), 113 (23), 109 (15), 96 (11), 95 (25), 91 (11), 83 (11), 81 (15), 79 (11), 71 (42), 69 (17), 67 (15), 55 (11), 43 (30), 41 (15); ^1H and ^{13}C nmr ($CDCl_3$) see Table 3; ^1H nmr (250 MHz, TMS, δ in CD_3OD) 6.53 (2H, bs, H-5′ and H-3′), 4.99 and 4.84 (each 1H, 2bs, H_a-4 and H_b-4), 3.70 (3H, s, OMe), 3.56 (1H, dd, $J = 9.5$ and 5 Hz, H-2), 3.11 (1H, s, H-6), 3.02 (1H, dd, $J = 14$ and 9.5 Hz, H_a-1), 2.97 (1H, dd, $J = 9.5$ and 7 Hz, H-14), 2.63 (1H, dd, $J = 14$ and 5 Hz, H_b-1), 2.45 (1H, dd, $J = 11.8$ and 7 Hz, H_a-13), 2.19 (3H, s, 6′-Me), 1.77 (1H, dd, $J = 11.8$ and 9.5 Hz, H_b-13), 1.72 (3H, s, H-20), 0.97 and 0.92 (each 3H, 2s, H-16 and H-17), 0.92 and 0.89 (each 3H, 2s, H-19 and H-18).

ACETYLATION OF **3** AND **5**.—Compounds **3** and **5** (10 mg each) were acetylated separately overnight at room temperature with Ac_2O/pyridine. Purification of plc [Et_2O-C_6H_{14} (1:8)] gave the pure acetyl derivative.

Neobalearone diacetate [**4**].—Hreims $[M]^+$ 540.3085, calcd for $C_{32}H_{44}O_7$, 540.3087; ^1H nmr (250 MHz, TMS, δ in $CDCl_3$, selected values) 4.99 (1H, t, $J = 6$ Hz), 3.18 (1H, dd, $J = 14$ and 6.25 Hz, H_a-13), 3.17 (1H, s, H-6), 3.16 (1H, t, $J = 7$, H-2), 2.96 (1H, dd, $J = 13$ and 7.5, H_a-1), 2.50 (1H, dd, $J = 13$ and 6.5, H_b-1), 2.08 and 2.05 (each 3H, 2s, AcO-), 1.97 (1H, dd, $J = 14$ and 6 Hz, H_b-13), 0.56 (3H, s, H-19).

Epineobalearone diacetate [**6**].—Hreims $[M]^+$ 540.3082, calcd for $C_{32}H_{44}O_7$, 540.3087; ^1H nmr (250 MHz, TMS, δ in $CDCl_3$, selected values) 4.55 (1H, bm, H-14), 3.33 (1H, dd, $J = 8$ and 4 Hz, H-2), 3.02 (1H, dd, $J = 13.3$ and 8 Hz, H_a-1), 2.44 (1H, dd, $J = 13.3$ and 4 Hz, H_b-1), 2.38 (1H, m overlapped, H_a-13) 2.06 and 2.01 (each 3H, 2s, CH_3CO-), 2.0 (1H, m overlapped, H_a-13).

CATALYTIC HYDROGENATION OF **3** TO GIVE **8**.—A solution of **3** (15 mg) in EtOH (2 ml) was hydrogenated at room temperature under atmospheric pressure in the presence of Pd-C for 24 h. Removal of the catalyst by filtration followed by concentration under vacuum yielded **8** (9 mg): hreims $[M]^+$ 458.3030, calcd for $C_{28}H_{42}O_5$, 458.3032; ^1H nmr (250 MHz, TMS, δ in $CDCl_3$) 1.16 and 0.81 (each 3H, 2d, $J = 7$ Hz, H-4 and H-20), 0.77 (3H, s, H-19).

EPIMERIZATION.—Neobalearone (20 mg) dissolved in EtOH was treated with 0.1 M NaOH in MeOH (0.4 ml) and the solution kept at room temperature for 4 h. After addition of H_2O (2 ml) and neutralization with 0.1 M HCl the mixture was extracted with Et_2O. The organic layer was dried (Na_2SO_4) and evaporated to give a residue which was subjected to Si gel cc [Et_2O-CH_2Cl_2 (1:99) as solvent]. Two compounds were thus obtained, which were identified (nmr, ir, [α], ms) as neobalearone and epineobalearone. When the reaction was performed by treating a solution of neobalearone (5 mg) in CD_3OD (0.5 ml) with 0.1 M NaOD in CD_3OD (0.1 ml), the epimerization could be followed by running ^1H-nmr spectra at time intervals (20 min) until the equilibrium between **3** and **5** (3:2) was reached (4 h). Compound **5** in the same conditions afforded a mixture of the identical composition.

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