Diterpenoids from *Euphorbia pithyusa* subsp. *cupanii*

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The aerial parts of *Euphorbia pithyusa* subsp. *cupanii* collected in Sardinia afforded eleven novel diterpenoids belonging to the lathyrane (**1a**), premyrsinane (**4a**−**g**), and tigliane (**5a**−**c**) types. Compounds **4a**−**g** and **5a** are esters of two new parent alcohols, named premyrsinol and 4,12,20-trideoxyphorbol, respectively. Structures were elucidated by spectroscopic and chemical methods. Puzzling differences between the NMR data of lathyrol (**1c**) and its esters were rationalized in terms of flipping of the exomethylene around the mean plane of the macrocycle.

A spurge named *pityusa* was held in great esteem in the Greek, Latin, and medieval systems of medicine and was mentioned in many ancient medical treatises.[1] Traditionally, this plant has been identified as *Euphorbia pithyusa* L. (Euphorbiaceae), a species native to the Western Mediterranean region.[2] The name *pithyusa* refers to its resemblance to a small pine,[2] and the latex and seeds of this plant were prescribed for a bewildering array of conditions, some typical of spurges (constipation, removal of warts), but others peculiar for this drug (breast ailments, general tonic).[1,2] The roots were also used as a cheap substitute for turbith (*Convolvolus turpethum* L.), a practice which caused dramatic and often lethal effects in patients.[3] *Euphorbia pithyusa* bears no obvious morphological similarity with the other spurges of the Mediterranean area and is considered a paleoendemism.[4] Despite this, and the historical relevance of this plant in medicine and pharmacy, no chemical study has been performed so far on its constituents. We report here the isolation of eleven novel diterpenoids from *E. pithyusa* L. subsp. *cupanii* (Guss.) A. R. Sm. (= *E. cupanii* Guss. ex Bertol.), a plant endemic to the dry areas of Sardinia, Corsica, and Sicily.[2,4]

Results and Discussion

The plant material (aerial parts) came from the area of Gennargentu, in central Sardinia. An acetone extract was separated by column chromatography to afford three major (yield > 0.02%) crystalline constituents. The isolation of the minor compounds required further purification by HPLC, owing to their very similar chromatographic behavior.

Compound **1a** ($C_{32}H_{40}O_7$, HRMS) was the least polar of the three major constituents. Its ^{1}H NMR spectrum was similar to that of the *Euphorbia* factor L_1 (**2**),[5] the first *Euphorbia* diterpenoid obtained in pure form (Table 1).[6] The major difference between the ^{1}H NMR spectra of **1a** and **2** was the replacement of the AB system of the epoxide protons of **2** by two olefin protons (δ 4.99 and 4.72, s). This suggested that **1a** was the deoxy derivative of **2**, an observation in accordance with the molecular formula and the ^{13}C NMR spectrum, where the resonances of the oxyrane carbons (δ 58.98, s and 55.43, t) were replaced by two signals in the double bond region (δ 144.3, s, and 115.6, t). To confirm that **1a** was an ester of lathyrol, **1a** and the known lathyrol ester *Euphorbia* factor L_3 (**1b**)[7] were hydrolyzed, affording an identical triol (**1c**), having the melting point of lathyrol.[7] Deoxygenation of **2** with I_2-and polymer-supported triphenylphosphine[8] afforded a compound identical to **1a**, confirming the results of the hydrolysis and establishing that the esterification patterns of **1a** and **2** are identical. Despite the important role of lathyrol (**1c**) in the chemistry of the genus *Euphorbia*, no data besides its melting point[7] have been reported, prompting us to characterize lathyrol also from the spectroscopic point of view. The ^{1}H- and ^{13}C NMR spectra of **1c**, the hydrolysis product of **1a** and **1b**, confirmed the atom connectivity and the configuration expected for lathyrol (Table 1), but several unexpected and puzzling differences with **1a** and **1b** were noticed. Thus, in the ^{1}H NMR spectrum of **1c**, the olefinic proton H-12 resonated ca. 0.50 ppm upfield than in **1a** and **1b** (δ 6.04 vs δ 6.50 and 6.49, respectively), while the allylic methyl (H-20) was moved downfield (ca. 0.25 ppm), and $J_{4,5}$ decreased, in absolute value, from ca. 10 Hz to ca. 3 Hz. Shifts of this type are not uncommon in macrocyclic compounds, and the change in $J_{4,5}$ closely parallels that observed in $\Delta^{11,\,6(17)}$-jatrophadienes upon interconversion of "endo" and "exo" conforma-

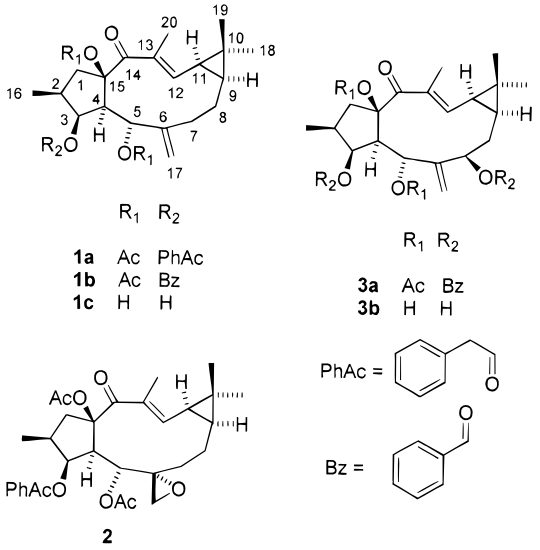

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Table 1. ^{1}H NMR Data for Compounds **1a**, **1c**, and **3b** (δ, $CDCl_3$ for **1a** and **1b**, CD_3OD for **3b**)[a–c]

position	1a	1c	3b[d]
1α	3.36 dd (14, 8)	2.80 dd (14, 10)	2.94 dd (13, 8.5))
1β	1.42 dd (14, 11)	1.81 dd (14, 10)	1.63 dd (13, 11)
2	2.20 m	2.17 m	1.93 m
3	5.58 t (3.5)	4.37 br d (3)	4.27 t (4)
4	2.76 dd (10, 3.5)	2.26 br t (3)	2.22 dd (8.5, 4)
5	6.11 d (10)	4.44 br s	4.86 d (8.5)
7α	2.20 m	2.53 m	4.20 dd (8.5, 4))
7β	2.06 m	1.73 m	–
8α	2.02 m	1.84 m	1.97 ddd (15, 4, 4)
8β	1.74 m	1.18 m	1.84 ddd (15, 12, 8.5)
9	1.14 m	1.12 m	1.32 ddd (12, 8.5, 4)
11	1.37 dd (11, 8)	1.39 dd (10, 8)	1.47 dd (11.5, 8.5)
12	6.49 d (11)	6.04 br d (10)	7.26 d (11.5)
16	0.71 d (6.5)	1.20 d (6.5)	1.08 d (7)
17a	4.99 br s	5.11 br s	5.11 br s
17b	4.72 br s	4.96 br s	4.90 br s
18	1.18 s	1.16 s	1.18 s
19	1.16 s	1.19 s	1.14 s
20	1.68 br s	1.99 br s	1.67 br s

[a] 500 MHz. *J* values are given in Hz in parentheses. [b] Other signals (δ), for **1a**: 7.33−7.21 (m, OPhAc), 3.63 (d, J = 15 Hz, OPhAc), 3.61 (d, J = 15 Hz, OPhAc). For **1c**: 4.53 (s, OH-1), 3.47 (s, OH-3), 3.38 (s, OH-5). [c] Selected NOEs, for **1c**: H-20, H-11; H-20, H-4; H-20−1α; H-18, H-11; H-19, H-12; H-5, H-7β; H-5, H-12; H-4, H-17a; H-4, H-17b. For **3b**: H-7, H-4; H-7, H-9; H-7, H-1; H-18, H-9; H-18, H-11; H-19, H-8β; H-19, H-12; H-20, H-11. [d] ^{1}H NMR data in $CDCl_3$: δ 3.10 (1H, dd, J = 14, 10 Hz, H-1α), 4.38 (1H, t, J = 3 Hz, H-3), 2.28 (1H, dd, J = 8.5, 3 Hz, H-4), 4.83 (1H, d, J = 8.5 Hz, H-5), 4.24 (1H, dd, J = 8.5, 4); 6.98 (1H, d, J = 11.4 Hz, H-12), 5.12 (1H, br s, H-17a), 4.93 (1H, br s, H-17b), 1.71 (3H, br s, H-20).

tions.[9] Yet, their detection in **1c** stands in sharp contrast to what was observed during the hydrolysis of the 7-hydroxylathyrol ester *Euphorbia* factor L_2 (**3a**).[10] In this case, no significant change was observed for $J_{4,5}$, while the chemical shift of the allylic methyl was moved *upfield* ($\Delta\delta$ −0.16, $CDCl_3$) and H-12 underwent a *downfield* shift (+ 0.43 ppm, $CDCl_3$) (Table 1). As a result of opposite shifts compared to their esters, overall differences of almost 1 ppm (δ 6.04 vs 6.98, $CDCl_3$) for the signal of H-12, and of almost 0.30 ppm (δ 1.99 vs 1.71, $CDCl_3$) for the signal of the allylic methyl were observed between lathyrol (**1c**) and its 7-hydroxy derivative (**3b**) (Table 1).

To rationalize these puzzling observations, a detailed investigation on the conformation of lathyrol (**1c**) was undertaken. The results of NOE difference experiments (Table 1) revealed that lathyrol adopts a conformation with the C-7 exomethylene on the mean plane of the macrocycle, and the allylic methyl perpendicular to it (Figure 1, A). The esters of lathyrol and 7-hydroxylathyrol, as well as 7-hydroxylathyrol itself (**3b**), adopt instead a conformation having these groups approximately perpendicular to the mean plane of the macrocycle, and *syn*-oriented on its α-face (Figure 1B). A similar geometry was found in the X-ray analysis of the *Euphorbia* factor L_1 (**1b**).[11] The changes in the NMR spectra of lathyrol and its esters are presumably related to a shielding effect of the C-15 ester carbonyl on H-12, and to a different extent of planarity within the enone moiety. Thus, removal of the C-15 ester carbonyl is expected to move the signal of H-12 downfield, as observed in the hydrolysis of 7-hydroxylathyrol esters, while in the hydrolysis of lathyrol esters this effect is offset by the reduced conjugation within the enone system, eventually resulting in an upfield shift for H-12. Pivotal to this effect is the flipping of the C-7 exomethylene from a perpendicular to a parallel orientation toward the mean plane of the macrocycle. This brings H-4 and H-5 into an

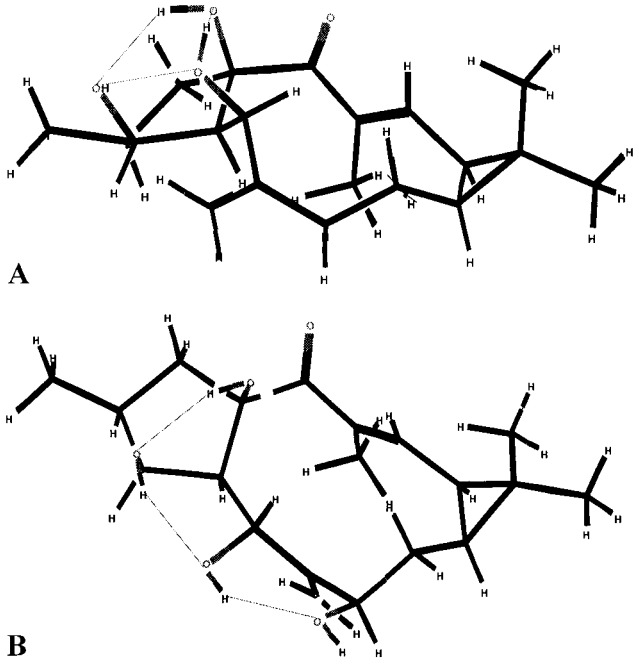


Figure 1. Calculated conformation of lathyrol (**1c**, A) and 7-hydroxylathyrol (**3b**, B).

almost orthogonal relationship, and makes possible the formation of a web of intramolecular hydrogen bondings which offsets the energy loss due to the decrease planarity within the enone system (Figure 1A). The observation that all the three hydroxyls of **1c** are involved in intramolecular hydrogen bonding is consistent with the observation that their chemical shift was not changed by dilution, while a decreased conjugation with the endocyclic double bond underlies the dramatic downfield shift of the ketone carbonyl in **1c** compared to **1a** and **1b** ($\Delta\delta$ ca. 10 ppm). Indeed, lathyrol (**1c**) behaves spectroscopically as an unconjugated ketone, as judged from the chemical shift of the enone β-proton (δ 6.04) and the enone carbonyl (δ 206.7).[12] In sharp contrast to lathyrol, 7-hydroxylathyrol (**2b**) retains the conformation of its ester, since in this conformation the 5-hydroxyl is ideally located to interact with the 7β-hydroxyl, and a 3,5,7-hydrogen bonding web can be formed (Figure 1B). This web is attained without decrease of conjugation within the enone system, and its formation is therefore favored over the 3, 5, 15 web.

The detection of a small $J_{4,5}$ value in lathyrol (**1c**) and of a larger value in its esters might have contributed to the confusing situation regarding the configuration at C-5 of lathyrol and 5-hydroxyisocharaciol[13] derivatives. In the publications describing the X-ray analysis of *Euphorbia* factor L_1 (**1a**)[11] and 7-hydroxylathryol (**3b**),[10] no specific configurational data were in fact reported, and, even now, the configuration of the 5-oxygen function of **1a** is sometimes still incorrectly reported as β.[14] Overall, the conformational changes of $\Delta^{6(17),12}$-lathyradienes bear striking similarities with those detected in $\Delta^{6(17),11}$-jatrophadienes. Both are triggered by flipping of the exomethylene around the macrocycle, and exhibit as hallmark changes in the values of $J_{4,5}$.[9]

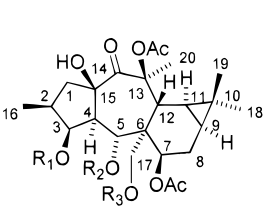
The crystalline alcohol **4a** had a molecular weight 636 daltons (HRMS), corresponding to the molecular formula $C_{35}H_{48}O_{12}$. The ^{1}H NMR spectrum (Table 2) showed signals diagnostic of three acetates (δ 2.08, 2.07, 2.05, s), one isobutyrate (δ 2.37, m; 1.09, d, J = 7 Hz; 1.06, d, J = 7 Hz), and one propionate residue (δ 2.33, q, J = 7 Hz; 1.08, t, J = 7 Hz), accounting for all the extra carbons of the

Table 2. ^{1}H NMR Data (δ, $CDCl_3$) for Compounds **4a**−**g**[a−c]

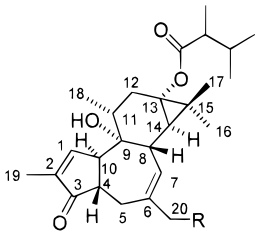
position	4a	4b	4c	4d	4e	4f	4g
1α	3.13 dd (14,8)	3.17 dd (14,8)	3.17 dd (14,8)	3.14 dd (14,8)	3.15 dd (14,8)	3.16 dd (14,8)	3.16 dd (14,8)
1*β*	1.60 dd (14,13)	1.63 dd (14,13)	1.62 dd (14,13)	1.60 dd (14,13)	1.60 dd (14,13)	1.64 dd (14,13)	1.60 dd (14,13)
2	1.80 m	1.85 m	1.80 m	1.78 m	1.78 m	1.80 m	1.80 m
3	5.25 t (3.5)	5.23 t (3.5)	5.26 t (3.5)	5.25 t (3.5)	5.26 t (3.5)	5.38 t (3.5)	5.25 t (3.5)
4	2.32 dd (11, 3.5)	2.38 dd (11, 3.5)	2.44 dd (11, 3.5)	2.41 m	2.40 m	2.39 dd (11, 3.5)	2.33 m
5	6.17 d (11)	6.23 d (11)	6.11 d (11)	6.18 d (11)	6.18 d (11)	6.38 d (11)	6.21 d (11)
7	4.50 d (7)	4.71 d (7)	4.42 d (7)	4.41 d (7)	4.48 d (7)	4.79 d (7)	4.53 d (7)
8α	2.07 m	2.09 m	2.06 m	2.07 m	2.05 m	2.05 m	2.00 m
8*β*	1.78 br d (17)	1.90 br d (17)	1.80 br d (17)	1.78 br d (17)	1.80 br d (17)	1.85 br d (17)	1.81 br d (17)
9	0.71 m	0.77 m	0.71 m	0.69 m	0.71 m	0.72 m	0.70 m
11	0.71 m	0.83 m	0.75 m	0.74 m	0.74 m	0.76 m	0.73 m
12	3.36 m	3.48 m	3.38 m	3.35 m	3.38 m	3.56 m	3.38 m
16	0.86 d (6.5)	0.92 d (6.5)	0.89 d (6.5)	0.86 d (6.5)	0.88 d (6.5)	0.86 d (6.5)	0.91 d (6.5)
17a	4.41 d (12)	4.88 d (12)	4.35 d (12)	4.34 d (12)	4.41 d (12)	4.69 d (12)	4.43 d (12)
17b	4.34 d (12)	4.51 d (12)	4.31 d (12)	4.31 d (12)	4.35 d (12)	4.31 d (12)	4.35 d (12)
18	1.03 s	1.07 s	1.05 s	1.03 s	1.04 s	1.05 s	1.05 s
19	0.89 s	0.95 s	0.89 s	0.89 s	0.91 s	0.94 s	0.92 s
20	1.67 s	1.74 s	1.72 s	1.69 s	1.69 s	1.71 s	1.69 s
15-OH	4.46 s	4.41 s	4.48 s	4.42 s	4.45 s	4.41 s	4.52 s

[a] 500 MHz. *J* are given in Hz in parentheses. [b] Other signals (δ), for **4a**: *O*-prop: 2.33 (q, $J = 7$ Hz), 1.08 (t, $J = 7$ Hz); 5-*O*-iBu, 2.37 (m), 1.09 (d, $J = 7$ Hz), 1.06 (d, $J = 7$ Hz); OAc-7, 2.07 (s); OAc-13, 2.08 (s); OAc-17, 2.05 (s). For **4b**: *O*-prop, 2.33 (q, $J = 7$ Hz), 1.09 (t, $J = 7$ Hz); *O*-iBu, 2.38 (m), 0.88 (d, $J = 7$ Hz); OAc-7, 2.11 (s); OAc-13, 2.11 (s); *O*-Nic, 9.16 (d, $J = 1.5$ Hz), 8.82 (dd, $J = 6, 1.1$ Hz), 8.19 (dt, $J = 8, 1.5$ Hz), 7.44 (dd, $J = 8.5, 1.5$ Hz). For **4c**: *O*-prop, 2.35 (q, $J = 7$ Hz), 1.10 (t, $J = 7$ Hz); *O*-MeBu, 2.52 (m), 1.35 (m), 1.10 (t, $J = 6.5$ Hz), 1.06 (d, $J = 6.5$ Hz); OAc-7, 2.09 (s); OAc-13, 2.11 (s)); *O*-iBu, 2.35 (m), 1.19 (d, $J = 7$ Hz), 1.17 (d, $J = 7$ Hz). For **4d**: *O*-prop, 2.32 (m), 1.08 (t, $J = 7$ Hz); 5-*O*-iBu, 2.37 (m); 1.09 (d, $J = 7$ Hz); 1.07 (d, $J = 7$ Hz); OAc-7, 2.07 (s); OAc-13, 2.08 (s): 17-*O*-iBu, 2.50 (m), 1.17 (d, $J = 7$ Hz), 1.14 (d, $J = 7$ Hz); 2.05 (s). **For 4e**: *O*-prop, 2.36 (q, $J = 7$ Hz), 2.34 (q, $J = 7$ Hz), 1.16 (t, $J = 7$ Hz), 1.10 (t, $J = 7$ Hz); *O*-iBu, 2.37 (m); 1.09 (d, $J = 7$ Hz); 1.07 (d, $J = 7$ Hz); OAc, 2.10 (s), 2.08 (s). For **4f**: *O*-Prop, 2.30 (q, $J = 7$ Hz), 0.96 (t, $J = 7$ Hz); OBz, 7.87 (AA′), 7.50 (C), 7.37 (BB′); OAc, 2.15 (s), 2.12 (s), 2.12 (s). For **4g**: *O*-iBu, 2.41 (m), 1.12 (2 x Me, d, $J = 6.5$ Hz); OAc, 2.11 (s), 2.11 (s), 2.09 (s), 2.03 (s). [c] Selected NOEs for **4a**: H-12, OAc-13; H-3, H-4; H-17a, H-20; H-17a,b−H-7; H-5, H-12.

diterpenoid skeleton. One exchangeable proton at δ 4.46 showed the presence of a free hydroxyl, confirmed by the presence of a IR absorption band at 3475 cm^{-1}. Apart from the signals of the ester groups and of three methyl singlets, the ^{1}H NMR spectrum could be interpreted in terms of three independent aliphatic spin systems. One started from a pair of diastereotopic methylene protons (δ 3.13, dd, $J =$ 14, 8 Hz, H-1α, δ 1.60, dd, $J = 14$, 13 Hz, H-1*β*), and continued with one methine adjacent to a methyl (δ 1.80, m, H-2), and with three additional methines (δ 5.25, t, J = 3.5 Hz, H-3; δ 2.32, m, H-4; δ 6.17, d, $J = 11$ Hz, H-5), two of which were oxygenated on account of their downfield resonance. The second spin system was an isolated AB system of an oxygenated methylene (δ, 4.41 and 4.34, d, J = 12 Hz, H-17a,b), while the last spin system started from an oxymethine (δ 4.50, d, $J = 7$ Hz, H-7), and proceeded through a methylene (δ 2.07, m, H-8α; δ 1.78, br d, $J =$ 17, H-8*β*) to three aliphatic methines (δ 0.71, m, H-9; δ 0.71, m, H-11; δ 3.36, m, H-12). The high-field chemical shift of two of them suggested the presence of a cyclopropane moiety. Three methyl singlets (δ 1.03, C-18; δ 0.89, C-19 and δ 1.67, C-20) and one methyl doublet (δ 0.86, d, $J = 6.5$ Hz) were also present. The remaining nonprotonated carbons were one carbonyl (δ 204.3, C-14), two aliphatic oxygenated quaternary carbons (δ 85.9 and 83.9, s, C-13 and C-15), and one aliphatic quaternary carbon (δ 47.3, s, C-6). HMBC correlations allowed the assembly of these features into a premyrsinane topology. In this context, the most relevant feature was the detection of HMBC correlations between the methine H-12 and both C-6 and C-7, an observation requiring the connection of C-12 to the quaternary carbon C-6. Location of the ester groups was assessed by analysis of the HMBC correlations between the ester carbonyls and the oxymethine (oxymethylene) protons, while the remaining ester group (an acetate) was located at C-13 on account of a NOE effect between H-12 and the acetyl signal at δ 2.07. NOE effects, summarized in Table 2, were also pivotal to assess the configuration as depicted in **4a**. The polyol corresponding

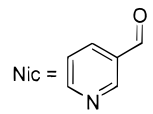


	R_1	R_2	R_3
4a	Prop	iBu	Ac
4b	Prop	iBu	Nic
4c	Prop	MeBu	iBu
4d	Prop	iBu	iBu
4e	Prop	iBu	Prop
4f	Prop	Bz	Ac
4g	Ac	iBu	Ac



R

5a H
5b OH
5c OAc



to this structure is new, and we have named it premyrsinol. The third crystalline product obtained by column chromatography of the extract (**4b**) was closely related to **4a**, the only differences being related to the replacement of one acetyl with one nicotinate group. Differences in the chemical shift of the diastereotopic methylene at C-17, backed up by HMBC measurements, showed that the nicotinate group was located at this position.

^{1}H NMR spectroscopic analysis of the noncrystalline fractions of *E. pithyusa* subsp. *cupanii* revealed the presence of mixtures of premyrsinanes containing small amounts of phorbol-related compounds (characteristic broad singlet for H-1 around 7.50 ppm). HPLC separation of these mixtures afforded five additional premyrsinanes (**4c**−**g**) and three tiglianes (**5a**−**c**). Compounds **4c**−**g** showed the same spin-systems of the diterpenoid core of **4a**,**b**, and differed only for the esterification pattern, which contained, besides acetyl residues, various combinations of propionic-, α-methylbutyric, isobutyric, and benzoic acids. In all cases, location of the ester groups could be assessed in a straightforward way by the inspection of diagnostic HMBC cor-

relations between the carbonyl carbons and their corresponding oxymethines (oxymethylene), and by NOE-difference experiments for the tertiary ester groups. The results showed that compounds **4a**−**g** shared the same esterification pattern at C-7 and C-13, while various combinations of aliphatic and aromatic acids were present at the oxygenated carbons C-3, C-5, and C-17.

Compound **5a** ($C_{26}H_{38}O_4$, HRMS) displayed NMR signals indicative of a diterpenoid esterified with 2,3-dimethylbutyric acid. The olefinic signals at δ 7.56 (s, H-1) and 5.22 (br s, H-7) were typical of a tigliane derivative. No other nonexchangeable downfield signals were present in the ^{1}H NMR spectrum, in accordance with the quaternary nature of the two oxygenated sp^3 carbons detected in the ^{13}C NMR spectrum (δ 75.2 and 62.8, s, C-9 and C-13, respectively). Since a signal diagnostic for H-4 (δ 2.40, ddd, J = 10, 9, 4 Hz) could be detected, and H-20, resonated as an allylic methyl (δ 1.71, br s), **5a** was a derivative of 4,12,20-trisdeoxyphorbol, a new type of tigliane polyol representing the most deoxygenated form of phorbol reported to date. It is not known whether this compound and the other less oxygenated analogues of phorbol are derived from the parent polyol by removal of oxygen atoms, or, alternatively, from the transannular cyclization of less oxygenated lathyrane precursors. The β-configuration of H-4 was evident from its splitting pattern and the chemical shift of H-1,[15] while the site of esterification was located at the 13-hydroxyl by comparison of the ^{13}C NMR resonances of the ring C carbons and those of known 12-deoxyphorbol esters.[15] This was further supported by the detection of a low-field ^{1}H NMR signal for the 9-hydroxyl (δ 5.54, s), a feature diagnostic of an intramolecular hydrogen bonding between the carbonyl of the C-13 ester group and the tertiary 9-hydroxyl.[16] The two remaining tiglianes (**5b** and **5c**) were isolated in trace amounts (less than 0.1% w/w of the purified extract), and could not be obtained completely free of cyclomyrsinane impurities (ca. 15% in both cases). Their structure elucidation was based on MS and ^{1}H NMR data alone, but was helped greatly by the similarity of the spectra with those of **5a**. Indeed, the differences could be rationalized in terms of oxygenation of C-20 to an hydroxymethyl-(**5b**) and to an acetoxymethyl group (**5c**).The detection of a downfield singlet for the 9-hydroxyl (δ 5.70 in **5b** and δ 5.68 in **5d**) is in accordance with the location of the ester group at C-13, as is the virtual identity of all the proton resonances around ring C. The presence of a hydroxyl at C-20, and of the 13-acyloxy-9-hydroxy group on ring C make **5b** a potential protein kinase C (PKC) ligand, while **5c** should be considered its corresponding "cryptic" form.[17] These compounds are presumably responsible for the cathartic activity of the plant mentioned in the ancient literature.[1,3]

Compounds **4a**−**g** belong to the premyrsinane group of diterpenoids. Nine examples were previously known,[18] but the presence of an acyloxy group at C-17 in place of an intramolecular ether function[18a−c] or a methyl group,[18d] sets **4a**−**g** apart from all the other compounds of this class.

The detection of structurally unique diterpenoids in *E. pithyusa* subsp. *cupanii* is not surprising on account of the unique taxonomic position of this species and the geographical isolation of Sardinia. The detection of new diterpene polyols shows that spurges are a source of structurally diverse isoprenoids much richer than assumed from bioactivity-directed fractionation with the mouse ear erythema assay, which selectively targets compounds with phorbol ester-like activity. This skeletal diversity is further amplified by esterification with a diverse array of acids, as exemplified very well by the structure of compounds **4a**−**g**.

Experimental Section

General Experimental Procedures. Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer model 237 spectrophotometer. ^{1}H and ^{13}C NMR spectra were taken on a Bruker DRX instrument (500 and 125 MHz, respectively). ^{1}H and ^{13}C NMR chemical shifts refer to C*H*Cl$_3$ at 7.26 ppm, and to *C*DCl$_3$ at 77.0 ppm, respectively. HRMS were obtained on a MAT 95ST Finnigan-MAT apparatus (70 eV, EI mode). CIMS were carried out on a Finnigan-MAT apparatus TSQ 70 using isobutane as a reactant gas. Si gel 60 (70−230 mesh) was used of open column chromatography. A Hibar Lichrosorb column (2.5 × 25 cm, Merck) was used for HPLC separations. Figure 1 was generated with PCMODEL, Serena Software, Version 4.0 (Serena Software, Bloomington, IN). Compounds **1b**, **2**, and **3a** were available from previous work on *E. lathyris* L.[5b]

Plant Material. Aerial parts (leaves and stems) of *E. pithyusa* subsp. *cupanii* were collected around Arzana (Nuoro, Sardinia, Italy) in June 1998. The plant material was identified by Mauro Ballero, and a voucher specimen (1212) is kept at the Dipartimento di Scienze Botaniche, University of Cagliari.

Extraction and Isolation. Dried and powdered plant material (400 g) was extracted with Me_2CO at room temperature (1 × 1.5 L, 2 × 1 L). The pooled extracts were evaporated in vacuo, and the residue was suspended in EtOH (400 mL) and treated with an equal volume of 3% Pb(OAc)$_2$. After about 3 h, the suspension was filtered on a bed of Celite, and the clear filtrate was concentrated in vacuo to remove most of the EtOH, and then extracted with EtOAc. After washing with brine, drying (Na_2SO_4), and evaporation, a brown residue (4.2 g) was obtained. The latter was purified by open column chromatography on Si gel (ca. 30 g), using mixtures of hexane and EtOAc (from 9:1 to 3:7). According to differences in composition indicated by TLC, 10 crude fractions were obtained. Fractions A−C contained triterpenoids and fats and were not further investigated. Fractions D, G, and I crystallized from diethyl ether, affording 275 mg **1a** (0.069%), 171 mg **4a** (0.043%), and 99 mg **4b** (0.025%). The mother liquors from the crystallization of **1a** were further separated by HPLC (hexanes−EtOAc 7:3) to give 5 mg **5a**. After HPLC (hexanes−EtOAc 7:3), fraction E afforded 3 mg **4c** and 36 mg **4d**, and fraction F 3 mg **5c** and 23 mg **4e**. Fraction H was further purified by HPLC (hexanes−EtOAc 6:4) to afford **4f** (12 mg) and **4g** (6 mg). Fraction L (120 mg) was first chromatographed on Sephadex LH-20 (5 g). Elution with hexanes−EtOAc 4:6 afforded 19 mg of a colorless gum, which was further purified by HPLC (hexanes−EtOAc 4:6) to afford 2 mg **5b**.

Lathyrol-3-phenylacetate-5,15-diacetate (= deoxy *Euphorbia* factor L$_1$) (1a): white powder, mp 125−127 °C; $[\alpha]_D^{25}$ +195° (*c* 0.9, $CHCl_3$); IR (KBr) ν_{max} 1740, 1728, 1647, 1622, 1263, 1238, 1128, 1010, 1005 cm^{-1}; ^{1}H NMR data, see Table 1; ^{13}C NMR ($CDCl_3$) δ 48.3 (t, C-1), 37.4 (d, C-2), 80.5 (d, C-3), 52.2 (d, C-4), 65.8 (d, C-5), 144.3 (s, C-6), 35.0 (t, C-7), 21.3 (t, C-8), 35.3 (d, C-9), 25.2 (d, C-10), 28.4 (d, C-11), 146.7 (d, C-12), 134.1 (s, C-13), 196.8 (s, C-14), 92.3 (s, C-15), 13.7 (q, C-16), 115.6 (t, C-17), 29.0 (q, C-18), 16.8 (q, C-19), 12.4 (q, C-20); PhAc: 169.8 (s), 135.4 (s), 129.5 (d), 128.5 (d), 127.1 (d), 41.5 (t); OAc: 171.3 (s), 170,7 (s), 22.0 (q), 22.0 (q); EIMS *m*/*z* 536.2780 [M]$^+$ (5) (calcd for $C_{32}H_{40}O_7$, 536.2774).

Premyrsinol-3-propanoate-5-isobutyrate-7,13,17-triacetate (4a): white powder, mp 176−178 °C; $[\alpha]_D^{25}$ −15° (*c* 1.1, MeOH); IR (KBr) ν_{max} 3475, 1736, 1728, 1653, 1367, 1289, 1245, 1159, 1038 cm^{-1}; ^{1}H NMR data, see Table 2; ^{13}C NMR data, see Table 3; EIMS *m*/*z* 636.3137 [M]$^+$ (1) (calcd for $C_{35}H_{48}O_{12}$, 636.3145), 71 (100).

Premyrsinol-3-propanoate-5-isobutyrate-7,13-diacetate-17-nicotinate (4b): white powder, mp 179−181 °C; $[\alpha]_D^{25}$ −18° (*c* 1.2, MeOH); IR (KBr) ν_{max} 3470, 1732, 1714, 1650,

Table 3. ^{13}C NMR (δ, $CDCl_3$) Data for Compounds **4a**−**g**[a,b]

position	4a	4b	4c	4d	4e	4f	4g
C-1	42.8 t	42.8 t	42.8 t	42.8 t	42.8 t	42.8 t	42.7 t
C-2	37.3 d	37.4 d	37.4 d	37.3 d	37.3 d	37.2 d	37.3 d
C-3	78.2 d	78.3 d	78.2 d	78.2 d	78.2 d	78.1 d	78.2 d
C-4	50.2 d	50.5 d	50.5 d	50.4 d	50.4 d	50.3 d	50.1 d
C-5	68.7 d	69.0 d	68.6 d	68.6 d	68.7 d	69.8 d	68.7 d
C-6	47.3 s	47.6 s	47.2 s	47.2 s	47.4 s	47.7 s	47.4 s
C-7	70.5 d	70.7 d	71.2 d	71.1 d	70.8 d	70.6 d	70.5 d
C-8	22.0 t	22.3 t	21.9 t	21.9 t	22.0 t	22.0 t	22.1 t
C-9	18.7 d	18.9 d	18.7 d	18.8 d	18.8 d	18.9 d	18.8 d
C-10	18.0 s	18.3 s	18.1 s	18.0 s	18.1 s	18.2 s	18.1 s
C-11	23.8 d	23.8 d	24.0 d	23.7 d	24.3 d	23.8 d	23.8 d
C-12	34.7 d	35.0 d	34.7 d	34.7 d	34.7 d	35.0 d	34.7 d
C-13	85.9 s	85.7 s	86.0 s	86.0 s	86.0 s	85.7 s	85.9 s
C-14	204.3 s	204.3 s	204.5 s	204.4 s	204.4 s	204.3 s	204.3 s
C-15	83.9 s	84.1 s	84.1 s	84.0 s	84.0 s	84.1 s	84.0 s
C-16	14.0 q	14.1 q	14.1 q	14.0 q	14.0 q	13.8 q	14.0 q
C-17	63.4 t	64.3 t	63.7 t	63.5 t	63.3 t	62.8 t	63.4 t
C-18	29.4 q	29.4 q	29.5 q	29.4 q	29.4 q	29.4 q	29.5 q
C-19	14.7 q	14.8 q	15.0 q	14.8 q	14.8 q	14.8 q	14.8 q
C-20	24.5 q	24.5 q	23.9 q	24.5 q	23.8 q	24.8 q	24.5 q

[a] 125 MHz; assignments aided by HMBC and HMQC experiments. Selected HMBC for **4a** as representative: H-12, C-5; H-12, C-7; H-12, C-17; H-3, C-15; H-5, C-15; H-3, C═O (Prop, δ 174.1), H-5, C═O (iBu, δ 175.0); H-7, C═O (Ac, δ 169.8)); H-17a,b, C═O (Ac, δ 170.2). [b] Other signals (δ): for **4a**: *O*-Prop, 174.1 (s), 27.7 (t), 8.8 (q); *O*-iBu, 175.0 (s), 34.0 (d), 18.7 (q), 18.5 (q); OAc-7, 169.8 (s), 21.2 (q); OAc-13, 170.5 (s), 21.2 (q); OAc-17, 170.2 (s), 21.1 (q). For **4b**, *O*-Prop: 174.0 (s), 27.7 (t), 8.8 (q); *O*-iBu, 174.9 (s), 33.9 (d), 18.4 (q), 18.3 (q); *O*-Nic, 164.8 (s), 153.9 (d), 150.5 (d), 136.7 (d), 126.0 (s), 123.7 (d); OAc-7, 169.9 (s), 21.2 (q); OAc-13: 170.6 (s), 21.3 (q). For **4c**: *O*-Prop, 174.1 (s), 27.7 (t), 8.8 (q); *O*-iBu, 174.7 (s), 34.1 (d), 18.8 (q), 18.7 (q); *O*-MeBu, 176.4 (s), 40.9 (d), 27.2 (t), 11.6 (q), 18.8 (q); OAc-7, 169.9 (s), 21.2 (q); OAc-13, 170.7 (s), 21.3 (q). For **4d**: *O*-Prop, 174.1 (s), 27.7 (t), 8.8 (q); *O*-iBu, 175.1 (s), 34.1 (d), 18.7 (q), 18.5 (q); 7-OAc, 169.8 (s), 21.2 (q); OAc-13, 170.6 (s), 21.3 (q); 17-*O*-iBu, 176.4 (s), 34.1 (d), 19.3 (q), 18.6 (q). For **4e**: *O*-Prop, 174.1 (s), 173.7 (s), 27.7 (t), 27.7 (t), 9.0 (q), 8.8 (q); *O*-iBu, 175.1 (s), 34.1 (d), 18.7 (q), 18.5 (q); OAc-7, 169.7 (s), 21.3 (q); OAc-13, 170.6 (s), 21.3 (q). For **4f**: *O*-Prop, 173.5 (s), 25.7 (t), 8.7 (q); *O*-Bz, 165.1 (s), 132.0 (d), 129.8 (s), 129.6 (d), 128.2 (d); OAc, 170.7 (s), 170.6 (s), 170.1 (s), 21.3 (q), 21.3 (q), 20.5 (q). For **4g**: *O*-iBu, 175.2 (s), 34.1 (d), 18.7 (q), 18.5 (q); OAc, 171.0 (s), 170.7 (s), 170.3 (s), 170.0 (s), 21.3 (q), 21.3 (q), 21.2 (q), 21.1 (q).

1360, 1281, 1249, 1150, 1010 cm^{-1}; ^1H NMR data, see Table 2; ^{13}C NMR data, see Table 3; EIMS *m/z* 699.3255 $[M]^+$ (0.5) (calcd for $C_{37}H_{49}NO_{12}$, 669.3255), 124 (100).

Premyrsinol-3-propanoate-5(α-methyl)butyrate-7,13-diacetate-17-isobutyrate (4c): gum, $[\alpha]_D^{25}$ −16° (*c* 0.9, MeOH); IR (liquid film) ν_{max} 3450, 1740, 1729, 1650, 1376, 1295, 1245, 1150, 1030 cm^{-1}; ^1H NMR data, see Table 2; ^{13}C NMR data, see Table 3; EIMS *m/z* 678.3622 $[M]^+$ (1) (calcd for $C_{36}H_{54}O_{12}$, 678.3615), 57 (100).

Premyrsinol-3-propanoate-5,17-diisobutyrate-7,13-diacetate (4d): white powder, mp 72−75 °C; $[\alpha]_D^{25}$ −11° (*c* 0.9, MeOH); IR (KBr) ν_{max} 3496, 1740, 1729, 1372, 1230, 1192, 1063, 670 cm^{-1}; ^1H NMR data, see Table 2; ^{13}C NMR data, see Table 3; EIMS *m/z* 664.3457 $[M]^+$ (2) (calcd for $C_{35}H_{52}O_{12}$, 664.3459), 71 (100).

Premyrsinol-3,17-dipropanoate-5-isobutyrate-7,13-diacetate (4e): gum, $[\alpha]_D^{25}$ −16° (*c* 0.9, MeOH); IR (liquid film) ν_{max} 3470, 1736, 1729, 1380, 1290, 1250, 1100, 1039 cm^{-1}; ^1H NMR data, see Table 2; ^{13}C NMR data, see Table 3; EIMS *m/z* 650.3301 $[M]^+$ (1) (calcd for $C_{34}H_{50}O_{12}$, 650.3302), 57 (100).

Premyrsinol-3-propanoate-5-benzoate-7,13,17-triacetate (4f): gum, $[\alpha]_D^{25}$ −15° (*c* 1.3, MeOH); IR (liquid film) ν_{max} 3450, 1745, 1719, 1660, 1370, 1297, 1241, 1136, 1031 cm^{-1}; ^1H NMR data, see Table 2; ^{13}C NMR data, see Table 3; EIMS *m/z* 670.2989 $[M]^+$ (1) (calcd for $C_{36}H_{46}O_{12}$, 670.2989), 105 (100).

Premyrsinol-3-propanoate-5-isobutyrate-7,13,17-triaacetate (4g): gum, $[\alpha]_D^{25}$ −14° (*c* 0.9, MeOH); IR (liquid film) ν_{max} 3470, 1737, 1380, 1291, 1225, 1158, 1050 cm^{-1}; ^1H NMR data, see Table 2; ^{13}C NMR data, see Table 3; EIMS *m/z* 622.2981 $[M]^+$ (2) (calcd for $C_{32}H_{46}O_{12}$, 622.2989), 71 (100).

4,12,20-Trideoxyphorbol-13-(2,3-dimethyl)butyrate (5a): gum, $[\alpha]_D^{25}$ +35° (*c* 0.5, MeOH); IR (liquid film) ν_{max} 3510, 1715, 1660, 1390, 1119, 1100, 1016, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (1H, br s, H-1), 5.54 (1H, s, OH-9), 5.22 (1H, br s, H-7), 3.29 (1H, br s, H-10), 2.81 (1H, dd, *J* = 18, 9 Hz, H-5b), 2.40 (1H, ddd, *J* = 10, 9, 4 Hz, H-4), 2.19 (1H, m, H-2′), 2.10 (1H, dd, *J* = 15, 6 Hz, H-12a), 2.07 (1H, br dd, *J* = 6.5, 4 Hz, H-8), 1.98 (1H, dd, *J* = 18, 10 Hz, H-5a), 1.93 (1H, m, H-3′), 1.71 (3H, br s, H-20), 1.53 (1H, dd, *J* = 15, 4, H-12b), 1.19 (3H, s, H-17), 1.09 (3H, d, *J* = 6.5 Hz, Me-2′), 1.02 (3H, s, H-16), 0.93 (3H, d, *J* = 6.5 Hz, Me-3′), 0.91 (3H, d, *J* = 6.5 Hz, H-18), 0.90 (3H, d, *J* = 6.5 Hz, Me-3′), 0.75 (1H, d, *J* = 5 Hz, H-14); ^{13}C NMR ($CDCl_3$) δ 161.0 (d, C-1), 138.3 (s, C-2), 203.0 (s, C-3), 44.4 (d, C-4), 34.0 (t, C-5), 136.2 (s, C-6), 126.8 (d, C-7), 41.9 (d, C-8), 75.2 (s, C-9), 53.9 (d, C-10), 46.2 (d, C-11), 31.8 (t, C-12), 62.8 (s, C-13), 32.0 (d, C-14), 22.5 (d, C-15), 15.2 (q, C-16), 22.9 (q, C-17), 19.0 (q, C-18), 10.0 (q, C-19), 25.2 (q, C-20), 178.0 (s, C-1′), 35.3 (d, C-2′), 30.5 (d, C-3′), 20.7 (d, C-4′), 19.1 (q, C-5′), 13.3 (q, C-6′); EIMS *m/z* 414.2981 $[M]^+$ (1) (calcd for $C_{26}H_{38}O_4$, 414.2982), 281 (100).

4,12-Dideoxyphorbol-13-(2,3-dimethyl)butyrate (5b): gum, IR (liquid film) ν_{max} 3600, 1713, 1660, 1375, 1120, 1060, 1011, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (1H, br s, H-1), 5.70 (1H, s, OH-9), 5.24 (1H, br s, H-7), 4.06 (1H, br d, *J* = 11 Hz, H-20a), 4.03 (1H, br d, *J* = 11 Hz, H-20b) 3.28 (1H, br s, H-10), 3.16 (1H, dd, *J* = 18, 9 Hz, H-5*β*), 2.42 (1H, ddd, *J* = 10, 9, 4 Hz, H-4), 2.19 (1H, m, H-2′), 1.94 (1H, m, H-3′), 1.71 (1H, br s, H-19), 1.61 (1H, dd, *J* = 15, 4 Hz, H-12b), 1.20 (3H, s, H-17), 1.09 (3H, d, *J* = 6.5 Hz, Me-2′), 1.06 (3H, s, H-16), 0.97 (3H, d, *J* = 6.5 Hz, Me-3′), 0.91 (3H, d, *J* = 6.5 Hz, Me-3′), 0.77 (1H, d, *J* = 5 Hz, H-14); CIMS *m/z* 431 $[M]^+$ $[C_{26}H_{38}O_5 + H]^+$ (31).

4,12-Dideoxyphorbol-13-(2,3-dimethyl)butyrate-20-acetate (5c): gum, IR (liquid film) ν_{max} 3600, 1718, 1660, 1380, 1150, 1061, 1090, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (1H, br s, H-1), 5.68 (1H, s, OH-9), 5.56 (1H, br s, H-7), 4.42 (1H, br d, *J* = 12 Hz, H-20a), 4.35 (1H, br d, *J* = 12 Hz, H-20b) 3.26 (1H, br s, H-10), 3.15 (1H, dd, *J* = 18, 9 Hz, H-5*β*), 2.40 (1H, m, H-4), 2.19 (1H, m, H-2′), 2.04 (3H, s, OAc), 1.93 (1H, m, H-3′), 1.69 (3H, br s, H-19), 1.56 (1H, dd, *J* = 15, 4 Hz, H-12b), 1.19 (3H, s, H-17), 1.09 (3H, d, *J* = 6.5 Hz, Me-2′), 1.03 (3H, s, H-16), 0.93 (3H, d, *J* = 6.5 Hz, Me-3′), 0.90 (3H, d, *J* = 6.5 Hz, Me-3′), 0.75 (1H, d, *J* = 5 Hz, H-14); CIMS *m/z* 475 $[M]^+$ $[C_{28}H_{40}O_6 + H]^+$, (10).

Deoxygenation of *Euphorbia* Factor L_1 (2). To a solution of iodine (270 mg, 1.07 mmol, 3.7 mol equiv) in CH_2Cl_2 (20 mL) was added polymer-supported triphenylphosphine (350 mg, 1.10 mmol, 3.8 mol equiv), resulting in the decoloration of the solution and the formation of a black precipitate. After stirring at room temperature for 15 min, a solution of *Euphorbia* factor L_1 (**2**) (160 mg, 0.29 mmol) in CH_2Cl_2 (5 mL) was added. After further stirring for 10 min, the reaction mixture was worked up by filtration, and the filter cake was washed with CH_2Cl_2 (10 mL). The pooled filtrates were washed sequentially with 5% $Na_2S_2O_3$ and brine. After drying (Na_2SO_4) and removal of the solvent, a yellowish solid was obtained. Washing with diethyl ether gave 81 mg (82%) **1a** as a white powder, identical (^1H NMR, TLC) to the natural product.

Hydrolysis of Deoxy *Euphorbia* Factor L_1 (1a). Compound **1a** (200 mg, 0.37 mmol) was suspended in 5% KOH in MeOH (2 mL). After stirring at room temperature for 4 h, the reaction was worked up by dilution with water (8 mL) and extraction with EtOAc. The organic phase was washed with brine and dried (Na_2SO_4). The residue was crystallized from ether to give 68 mg (55%) lathyrol (**1c**) as a white powder, identical to the compound obtained from the hydrolysis of *Euphorbia* factor L_3 (**1b**): mp 168−170 °C (lit.: 168−169 °C);[7] $[\alpha]_D^{25}$ +101° (*c* 1.3, MeOH): IR (KBr) ν_{max} 3389, 3261, 1653, 1641, 1444, 1269, 1047, 910, 904 cm^{-1}; ^1H NMR data, see Table 1; ^{13}C NMR ($CDCl_3$) δ 46.8 (t, C-1), 38.1 (d, C-2), 77.2 (d, C-3), 53.2 d (C-4), 69.6 (d, C-5), 147.8 (s, C-6), 33.7 (t, C-7), 23.2 (t, C-8), 34.8 (d, C-9), 24.0 (s, C-10), 26.0 (d, C-11), 139.9 (d, C-12), 137.0 (s, C-13), 206.7 (s, C-14), 87.9 (s, C-15), 13.9 (q, C-16), 110.9 (t, C-17), 28.6 (q, C-18), 15.5 (q, C-19), 13.6 (q, C-20); EIMS *m/z* 334.2160 $[M]^+$ (10) (calcd for $C_{20}H_{30}O_4$, 334.2144).

Hydrolysis of *Euphorbia* factor L_2 (3a). Compound **3a** (300 mg) was hydrolyzed as described for **1a**, giving 89 mg (54%) 7β-hydroxylathyrol (**3b**) as a white powder, mp 220−222 °C; $[\alpha]_D^{25}$ +52° (*c* 0.9, MeOH): IR (KBr) ν_{max} 3435, 1676, 1615, 1153, 1076, 1059, 1007, 922 cm^{-1}; ^1H NMR data, see Table 1; ^{13}C NMR ($CDCl_3$−DMSO-d_6 1:1) δ 47.2 (t, C-1), 35.8 (d, C-2), 76.9 (d, C-3), 53.2 d (C-4), 63.4 (d, C-5), 147.8 (s, C-6), 76.2 (d, C-7), 22.8 (t, C-8), 30.3 (d, C-9), 26.6 (s, C-10), 27.4 (d, C-11), 147.8 (d, C-12), 132.2 (s, C-13), 199.8 (s, C-14), 87.2 (s, C-15), 12.8 (q, C-16), 111.3 (t, C-17), 30.0 (q, C-18), 14.8 (q, C-19), 11.1 (q, C-20); EIMS *m/z* 350.2083 $[M]^+$ (10) (calcd for $C_{20}H_{30}O_4$, 350.2093).

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References and Notes

(1) Pliny's opening of the paragraph on *pityusa* in his *Naturalis Historia* has often been quoted: *Cum honore et pityusa simile de causa dicetur, quamdam in tithymali genere numerant* (Honorable mention will now be made of pityusa, which some include in the same class as tithymalus) (XXIV, XXXI).
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