New Lupane Derivatives from the Leaves of *Licania pyrifolia*

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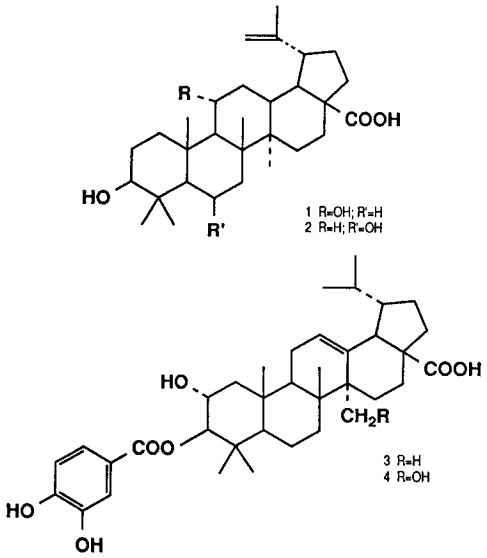
Received July 10, 1995[⊗]

Fractions of the dried leaves of *Licania pyrifolia* containing triterpenes were investigated, and four new compounds (**1**−**4**) were isolated. Their structures were established after detailed NMR spectral studies as 11α-hydroxybetulinic acid, 6*β*-hydroxybetulinic acid, 2α,3*β*-dihydroxyup-12-en-28-oic acid 3-(3′,4′-dihydroxybenzoyl ester), and 2α,3*β*,27-trihydroxylup-12-en-28-oic acid 3-(3′,4′-dihydroxybenzoyl ester), respectively.

As part of our study on the constituents of plants of the family Crysobalanaceae,[1] we report the results of a chemical investigation of the dried leaves of *Licania pyrifolia* Grisebach, a small tree widespread in Venezuela, where it is cultivated for the edible fruits.[2] No previous phytochemical investigation has been reported on this species, although previous studies have shown the presence of flavonoids in the genus *Licania*.[3−5] This paper deals with the isolation from the title plant of steroid and triterpenoid metabolites, of which four are new lupane derivatives **1**−**4**, whose structure elucidation was performed mainly by spectroscopic methods.



The plant material was powdered, defatted with *n*-hexane, and exhaustively extracted in a Soxhlet apparatus with $CHCl_3$ and a mixture of $CHCl_3$−MeOH (9:1).

The $CHCl_3$ extract yielded α-amyrin, *β*-sitosterol, lupeol, betulin, uvaol, ursolic acid, oleanolic acid, and betulinic acid.

The $CHCl_3$−MeOH extract was fractionated by column chromatography (CC) on Sephadex LH-20 with MeOH. The portion containing the bulk triterpenes was chromatographed over Si gel with $CHCl_3$/MeOH mixtures followed by low-pressure CC on Lichroprep RP-18 with MeOH/H_2O mixtures to yield four new compounds (**1**−**4**) and the following constituents of known structures *β*-sitosterol 3-*β*-D-glucoside, ursolic acid 3-α-L-arabinoside, euscapic acid 28-*β*-D-glucopyranosyl ester, tormentic acid 28-*β*-D-glucopyranosyl ester, 2α-hydroxyursolic acid, 2α,3α-dihydroxyurs-12-ene-28-oic acid, euscapic acid, tormentic acid, and maslinic acid.

The EIMS spectra of compounds **1** and **2** both showed a molecular peak $[M]^+$ at *m*/*z* 472 corresponding to the formula $C_{30}H_{48}O_4$ (confirmed by ^{13}C-NMR and DEPT analysis). These data indicated a triterpenoid skeleton with one carboxyl and two hydroxyl moieties and one double bond, confirmed by IR bands at 3450−3200 and 1065−1030 (hydroxyl), 1705 (carboxyl), and 1640 and 885 cm^{-1} (>C=CH_2) and *gem*-dimethyl signals at 1378−1363 cm^{-1}.

The ^{13}C-NMR spectra of both compounds **1** and **2** revealed 30 carbon signals which were sorted by DEPT ^{13}C-NMR as six methyls, nine methylenes, five methines, five quarternary carbons, two alcoholic methines, one carboxylic acid, and two olefinic carbons (one =CH_2 and one quarternary). The $\Delta^{20,29}$-functionality of a lupene skeleton was inferred for both compounds from the resonances of the sp^2 carbons at C-29 (secondary carbon signal deduced by DEPT pulse sequence) at ca. 109 ppm and C-20 (quarternary carbon) at ca. 150 ppm.[6,7]

A detailed analysis of the ^{1}H-NMR of **1** confirmed the characteristic features for a betulinic acid parent structure bearing one α-OH group at C-11. This spectrum was characterized by signals for five tertiary methyls (*δ* 0.78−1.04, Me-23−Me-27) and one vinylic methyl (*δ* 1.67, Me-30), two protons of an isopropenyl moiety at *δ* 4.59 and 4.72 (1H each, d, J = 2.1 Hz, H_a-29 and H_b-29), and two carbinolic protons. One of these was observed as a signal at *δ* 3.38 (dd with J = 11.5 and 4.5 Hz) due to coupling with two methylene protons. The values of the chemical shift and J couplings (diaxial and axial/equatorial interactions) suggested the presence of *β*-OH substitution at C-3.[8] In the same region of the ^{1}H-NMR spectrum of **1** a signal at *δ* 3.85 (1H, ddd, J = 10.5, 10.5, and 5.0 Hz) was also present. The J values (two diaxial couplings and one axial/equatorial spin−spin coupling) were in accordance with an α-hydroxyl moiety. The substitution at C-11 was revealed by a shift of the carbon signal at *δ* 20.9 (C-11) of betulinic acid to

[⊗] Abstract published in *Advance ACS Abstracts,* February 1, 1996.

0163-3864/96/3259-0297$12.00/0

δ 69.8 (d) and by the downfield shifts of signals of C-1 (2.9 ppm), C-9 (2.0 ppm), and C-12 (1.6 ppm) due to δ and γ steric effects of the α configuration of this hydroxyl moiety. This conclusion was confirmed by the downfield shift in the ^{1}H-NMR spectrum of the methyl protons linked at C-10 (Me-25) due to the same steric effects. Therefore, **1** was deduced as 11α-hydroxybetulinic acid, a new compound.

The ^{1}H-NMR spectrum of compound **2**, as in **1**, showed signals attributable to a betulinic acid derivative where the signal at δ 3.85 was replaced by a multiplet at δ 4.51 whose splitting and chemical shift were characteristic for a geminal proton on an oxygen-bearing C-6 atom of a triterpene.[9] The 6β-hydroxy substitution was suggested by the downfield shifts in the ^{1}H-NMR spectrum of Me-24 (0.28 ppm), Me-25 (0.34 ppm), and Me-26 (0.29 ppm) due to 1,3 diaxial interactions of the β-OH linked to C-6 when compared with the same signals of betulinic acid. The substitution at C-6 was confirmed by a shift of the ^{13}C-NMR signal at 19.7 ppm (C-6) of betulinic acid to δ 69.6 (d) and by the downfield shifts due to a β-effect of this substituent at C-7 (8.3 ppm) and C-5 (1.7 ppm). In addition, the diaxial interaction (δ effect) of the OH with Me-24, Me-25, and Me-26 whose resonances were shifted downfield between 1.0 and 2.7 ppm when compared with those of betulinic acid[10] confirmed the 6β-OH substitution. Compound **2** was thus deduced as 6β-hydroxybetulinic acid, another new derivative.

The IR spectra of **3** and **4** showed bands similar to those found in **1** and **2** except that the signal of the $>C{=}CH_2$ function was replaced by a trisubstituted double bond (1665 and 850 cm^{-1}). In addition, one ester carbonyl signal (1710 and 1100 cm^{-1}) and signals of an aromatic moiety at 1645 and 1680 cm^{-1} were also present. The EIMS of compounds **3** and **4** showed molecular peaks $[M]^+$ at *m/z* 608 and 624 corresponding to the formulas $C_{37}H_{52}O_7$ and $C_{37}H_{52}O_8$, respectively (confirmed by ^{13}C-NMR and DEPT analysis). The ^{13}C-NMR spectrum of both compounds revealed 37 carbon signals. Those of **3** were sorted by DEPT ^{13}C-NMR as seven methyls, eight methylenes, five methines, five quaternaries, two alcoholic methines, one carboxylic acid, one −COOR, and two olefinic carbons (one =CH and one quaternary). Furthermore, a nonsymmetrically trisubstituted aromatic ring was also present. The signals of **4** were similar to those of **3** except that one $-CH_3$ was replaced by a $-CH_2OH$.

These data indicated the presence in both **3** and **4** of a triterpenoid skeleton with two secondary hydroxyls (plus one primary OH in **4**) and one carboxyl moiety, one double bond, and a 3,4-hydroxybenzoic unit. A $\Delta^{12,13}$-double bond and the fact that both derivatives had a lup-12-ene skeleton was indicated by resonances of the sp^2 carbons C-12 (methine) at 126.3 ppm and C-13 (quaternary carbon) at 138.0 ppm and by the analysis of the methine and methylene resonances.[6,7]

A detailed analysis of the ^{1}H-NMR spectrum of **3** confirmed the characteristic features for a lup-12-en-28-oic acid derivative bearing an α-OH at C-2 and a β-OH at C-3.[11] This spectrum showed seven methyl groups of which five were tertiary (δ 0.80, 0.96 × 2, 0.99, 1.02) and two secondary (δ 0.87 and 0.94, d, J = 5.9 Hz). A triplet at δ 5.10 (J = 3.6 Hz) due to H-12 was also present. The carbinolic region revealed a doublet of doublets at δ 3.82 (1H, J = 4.5, 9.6 and 10.8 Hz) and a doublet at δ 4.63 (1H, J = 9.6 Hz), whose chemical shifts and J couplings were typical for a 2α,3β-dihydroxyl substitution pattern.[12−14] Furthermore, the ^{1}H-NMR spectrum revealed the presence of a 3,4-dihydroxybenzoic unit by the presence of signals at δ 6.90 (2H, m, H-5′ and H-6′) and δ 7.02 (1H, br s, H-2′). Furthermore, the linkage of this moiety to C-3 of the triterpene was derived from the downfield shift (1.6 ppm) of C-3 when compared with other derivatives with the same substitution pattern.[15,16] Therefore, **3** was assigned as the new compound, 2α,3β-dihydroxyup-12-en-28-oic acid 3-(3′,4′-dihydroxybenzoyl ester).

Table 1. Interactions Observed in the NOESY NMR Spectrum of 4

		correlated signal	
proton	δ_H	proton	δ_H
5	0.72	9	1.56
5	0.72	23	1.04
5	0.72	6α	1.52
9	1.56	6α	1.52
9	1.56	23	1.04
9	1.56	27a	3.18
9	1.56	27b	3.52
18	1.38	19	1.40
27b	3.52	20	0.88

Compound **4** had resonances similar to those apparent in the ^{1}H-NMR spectrum of **3** for a 2α,3β-dihydroxylup-12-en-28-oic acid derivative.[9] In addition, two signals for an oxymethylene group [doublets (J = 10.8 Hz) at δ 3.18 and 3.52] replaced the signal due to a *tert*-methyl of the aliphatic region (Me-27). Further support for this additional substitution was obtained from NOESY experiments (Table 1). Thus, NOEs were observed between H-5 and H-9, H-23 and H-6α; between H-9 and H-23, H-3, H-27$_a$, and H-27$_b$; between H-27$_b$ and H-20; as well as between H-18 and H-19. These results showed that the primary hydroxyl and isopropyl groups both had α-dispositions, whereas the OH function at C-3 was β-oriented.[17] Therefore, **4** was a new compound determined as 2α,3β,27-trihydroxylup-12-en-28-oic acid 3-(3′,4′-dihydroxybenzoyl ester).

This is the first report dealing with triterpenes in plants of the family Chrysobalanaceae. Previously, only *ent*-kaurenoid diterpenes have been isolated from *Chrysobalanus icao* L., and these were shown to exhibit anti-HIV activity.[18] Furthermore, since α- and β-amyrin and lupane derivatives are common constituents of the plants of the family Rosaceae,[19−25] their presence could be of significance in establishing the equivocal taxonomy of the Chrysobalanaceae. In fact, this family, constituted by the genera *Acioa*, *Chrysobalanus*, *Couepia*, *Hexellodendrum*, *Hirtella*, *Licania*, and *Parinari*, was previously included in the family Rosaceae and later separated due to the different morphology of the sexual organs.[3]

Experimental Section

General Experimental Procedures. The following instruments were used: NMR, Bruker AC-200 Spectrospin spectrometer; EIMS, VG ZAB instrument; LPCC, Duramat pump using a Lichroprep RP-18 column. IR spectra were determined with a Perkin-Elmer spectrophotometer Model 684. TLC was carried out on silica 60 F_{254} gel-coated Al sheets and RP-18 HPTLC plates

(Merck). Compounds were visualized by spraying with cerium sulfate/sulfuric acid reagent. One- and two-dimensional NMR spectra were measured as described previously.[26]

Plant Material. The dried powered leaves of *L. pyrifolia* (350 g) were collected and identified in July 1992 by Prof. A. Cardoso (Universidad Central de Venezuela, Facultad de Agraria), and a voucher sample was deposited in the Escuela de Quimica, Universidad Central de Venezuela.

Extractiom and Isolation. The plant material was defatted with *n*-hexane and exhaustively extracted for 28 h in a Soxhlet apparatus with $CHCl_3$ and $CHCl_3$−MeOH (9:1), successively. Sephadex LH-20 (Pharmacia Fine Chemicals) CC of the $CHCl_3$ extract (3.1 g) gave, on elution with MeOH−$CHCl_3$ (9:1), fractions containing impure compounds. Further flash or gravity CC on Si gel (Merck) of these mixtures yielded α-amyrin (29 mg), β-sitosterol (59 mg), lupeol (39 mg), betulin (65 mg), uvaol (15 mg), and the following acids as pure metabolites: ursolic (38 mg), oleanolic (59 mg), and betulinic (63 mg).

The $CHCl_3$−MeOH extract (6.2 g) was fractionated by CC on Sephadex LH-20 with MeOH. Fractions 1−6 contained the bulk triterpenes. Fraction 1 gave by flash CC β-sitosterol 3-β-D-glucoside (29 mg), while ursolic acid 3-α-L-arabinoside (27 mg), euscapic acid 28-β-D-glucopyranosyl ester (19 mg), and tormentic acid 28-β-D-glucopyranosyl ester (14 mg) were isolated by LPLC on Lichroprep RP-18 with MeOH/H_2O (4:1). The new derivatives **1** (13 mg) and **2** (200 mg) were isolated from fraction 3 by flash CC. Fraction 4, by combination of gravity and flash CC over Si gel, yielded four compounds: 2α-hydroxyursolic acid (23 mg), 2α,3α-dihydroxyurs-12-en-28-oic acid (19 mg), euscapic acid (59 mg), and tormentic acid (63 mg). Preparative TLC of the residue of fraction 5 gave maslinic acid (9 mg). Finally, the new derivatives **3** (13 mg) and **4** (17 mg) were obtained by a combination of gravity and flash CC over Si gel.

The following known compounds were isolated in this investigation: α-amyrin, β-sitosterol, lupeol, betulin, ursolic acid, oleanolic acid, betulinic acid, β-sitosterol 3-β-D-glucoside, euscapic acid 28-β-D-glucosyl ester, tormentic acid 28-β-D-glucosyl ester, 2α-hydroxyursolic acid, 2α,3α-dihydroxyurs-12-en-28-oic acid, euscapic acid, tormentic acid, and maslinic acid. These compounds were identified by comparison TLC and ^{1}H- and ^{13}C-NMR data with authentic samples. Ursolic acid 3-α-L-arabinose was identified by comparing its ^{1}H- and ^{13}C-NMR data with published values.[27]

11α-Hydroxybetulinic acid (1): white crystals ($CHCl_3$−MeOH); mp 253−254 °C; $[\alpha]^{25}_D$ + 3.4° (*c* 0.1, $CHCl_3$); IR (Nujol) *ν* max 3540−3200 (OH), 3029−2933 (CH, aliphatic and olefinic), 1705 (C=O, carboxyl), 1640 (>C=CH_2), 1458, 1381, 1149, 1065, 1030, 970, 885 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.59 and 4.72 (2H, each d, J = 2.1 Hz, H_2-29), 3.85 (1H, ddd, J = 5.0, 10.5, and 10.5 Hz, H-11), 3.38 (1H, dd, J = 4.5 and 11.5 Hz, H-3), 1.67 (3H, s, Me-30), 1.04, 1.01, 0.90, 0.86, 0.78 (3H each, s, Me-23, Me-24, Me-25, Me-26, Me-27); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 181.0 (s, C-28), 150.6 (s, C-20), 109.7 (t, C-29), 78.8 (d, C-3), 69.8 (d, C-11), 55.4 (d, C-5), 52.4 (d, C-9), 48.8 (d, C-19), 48.0 (d and s, C-17 and C-18), 42.5 (s, C-14), 40.7 (s, C-8), 38.9 (s, C-4), 38.7 (t, C-1), 38.5 (d, C-13), 37.2 (s, C-10), 34.5 (t, C-7), 34.2 (t, C-22), 30.6 (t, C-15), 30.0 (t, C-21), 29.4 (t, C-16), 28.0 (q, C-23), 27.5 (t, C-2), 27.2 (t, C-12), 19.6 (q, C-30), 18.5 (t, C-6), 16.2 (q, C-26), 15.8 (q, C-25), 15.0 (q, C-24), 14.8 (q, C-27); EIMS (70 eV) *m/z* [M]$^+$ 472 (8), 454 (18), 436 (21), 421 (15), 300 (22), 264 (15), 259 (22), 246 (35), 237 (40), 234 (99), 219 (45), 189 (84), 175 (86), 152 (83), 147 (73), 135 (100), 107 (83).

6β-Hydroxybetulinic acid (2): white crystals ($CHCl_3$−MeOH); mp 220−225 °C; $[\alpha]^{25}_D$ +2.8° (*c* 0.1, $CHCl_3$); IR (Nujol) *ν* max 3540−3220 (OH), 3035−2930 (CH, aliphatic and olefinic), 1705 (C=O, carboxyl), 1640 (>C=CH_2), 1470, 1381, 1065, 1030, 990, 885; ^{1}H NMR ($CDCl_3$, 200 MHz), δ 4.60 and 4.70 (2H, each d, J = 1.9 Hz, H-29a, and H-29b), 4.51 (1H, m, H-6), 3.20 (1H, dd, J = 10.4 and 4.6 Hz, H-3), 2.98 (1H, ddd, J = 5.6, 11, and 11 Hz, H-19), 1.68 (3H, br s, Me-30), 1.64 (3H, s, Me-26), 1.46 (3H, s, Me-25), 0.96 (3H, s, Me-27), 0.92 (3H, s, Me-23), 0.75 (3H, s Me-24); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 181.1 (s, C-28), 150.7 (s, C-20), 109.8 (t, C-29), 78.9 (d, C-3), 69.6 (d, C-6), 57.1 (d, C-5), 50.4 (d, C-9), 48.8 (d, C-19), 48.0 (d and s, C-17 and C-18), 42.6 (t, C-7), 42.3 (s, C-14), 40.7 (s, C-8), 38.9 (s, C-4), 38.7 (t, C-1), 38.5 (d, C-13), 37.2 (s, C-10), 34.0 (t, C-22), 30.6 (t, C-15), 30.0 (t, C-21), 29.3 (t, C-16), 28.0 (q, C-23), 27.3 (t, C-2), 25.6 (t, C-12), 21.2 (t, C-11), 19.4 (q, C-30), 18.7 (q, C-26), 16.8 (q, C-25), 16.2 (q, C-24), 14.9 (q, C-27); EIMS (70 eV) *m/z* [M]$^+$ 472 (4), 454 (21), 436 (28), 327 (18), 285 (20), 280 (18), 262 (25), 244 (38), 234 (80), 222 (40), 201 (57), 189 (84), 152 (100). 147 (70), 121 (65).

2α,3β-Dihydroxylup-12-en-28-oic acid 3-(3′,4′-dihydroxybenzoyl ester) (3): white crystals ($CHCl_3$); mp 280−284 °C; $[\alpha]^{25}_D$ + 8.7° (*c* 0.4, $CHCl_3$); IR (Nujol) *ν* max 3540−3200 (OH), 3029 (CH, aliphatic), 2933 (CH, olefinic), 1710 (C=O, carboxyl ester), 1665 (>CH=C<), 1680 and 1645 (aromatic moiety), 1458, 1380, 1363, 1100, 1065, 1030, 970, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.02 (1H, br s, H-2′), 6.90 (2H, m, H-5′ and H-6′), 5.13 (1H, t, J = 3.6 Hz, H-12), 4.63 (1H, d, J = 9.6 Hz, H-3), 3.82 (1H, ddd, J = 4.5, 9.6, and 10.8 Hz, H-2), 1.02 (3H, s, Me-23), 0.99 (3H, s, Me-25), 0.96 (6H, s, Me-26 and Me-24), 0.94 (3H, d, J = 5.9 Hz, Me-29), 0.87 (3H, d, J = 5.9 Hz, Me-30), 0.80 (3H, s, Me-27); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 181.2 (s, C-28), 163.7 (s, OC=O), 146.5 (s, C-4′), 143.8 (s, C-3′), 139.1 (s, C-13), 126.9 (s, C-1′), 126.3 (d, C-12), 122.3 (d, C-6′), 115.2 (d, C-2′), 114.9 (d, C-5′), 83.1 (d, C-3), 67.9 (d, C-2), 55.4 (d, C-5), 52.6 (d, C-18), 48.3 (s, C-17), 47.9 (t, C-1), 47.2 (d, C-9), 42.2 (s, C-14), 39.7 (s, C-8), 39.6 (s, C-4), 39.3 (d, C-19), 39.0 (d, C-20), 38.0 (s, C-10), 36.7 (t, C-22), 33.1 (t, C-7), 30.8 (t, C-21), 28.7 (t, C-15), 28.2 (q, C-23), 24.3 (t, C-16), 24.0 (t, C-11), 23.8 (q, C-29), 21.2 (q, C-30), 18.8 (t, C-6), 18.6 (q, C-24), 17.3 (q, C-30), 17.2 (q, C-26), 16.8 (q, C-25); EIMS (70 eV); *m/z* [M]$^+$ 608 (6), 590 (9), 575 (10), 564 (8), 443(9), 425 (10), 360 (18), 342 (33), 248 (2), 223 (58), 217 (19), 208 (18), 205 (56), 178 (23), 143 (29), 137 (78), 97 (21), 95 (54), 83 (65), 55 (100).

2α,3β,27-Trihydroxylup-12-en-28-oic acid 3-(3′,4′-dihydroxybenzoyl ester) (4): white crystals ($CHCl_3$); mp 298−303 °C; $[\alpha]^{25}_D$ +12.5° (*c* 0.2, $CHCl_3$); IR (Nujol) *ν* max 3540−3200 (OH), 3029 (CH, aliphatic), 2933 (CH, olefinic), 1710 (C=O, carboxyl ester), 1665 (>CH=C<), 1680 and 1645 (aromatic moiety), 1458, 1380, 1363, 1100, 1065, 1030, 970, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200

MHz) δ 7.09 (1H, br s, H-2′), 6.93 (2H, m, H-5′ and H-6′), 5.10 (1H, t, J = 3.6 Hz, H-12), 4.63 (1H, d, J = 9.8 Hz, H-3), 3.80 (1H, ddd, J = 4.5, 9.8 and 11.0 Hz, H-2), 3.18 and 3.52 (1H each, d, J = 10.8 Hz, H_2-27), 1.56 (1H, H-9), 1.51 (1H, H-6α), 1.40 (1H, H-19), 1.38 (1H, H-18), 1.04 (3H, s, Me-23), 1.00 (3H, s, Me-24), 0.95 (3H, s, Me-26), 0.93 (3H, d, J = 5.9 Hz, Me-29), 0.88 (1H, H-20), 0.80 (3H, d, J = 5.8 Hz, Me-30), 0.78 (3H, s, Me-25), 0.72 (1H, H-5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 179.8 (s, C-28), 163.7 (s, OC=O), 146.5 (s, C-4′), 144.0 (s, C-3′), 138.8 (s, C-13), 126.9 (s, C-1′), 125.3 (d, C-12), 122.1 (d, C-6′), 115.5 (d, C-2′), 114.7 (d, C-5′), 83.7 (d, C-3), 69.9 (t, C-27), 69.0 (d, C-2), 55.4 (d, C-5), 53.8 (d, C-18), 48.6 (t, C-1), 47.8 (d, C-9), 44.9 (s, C-17), 42.2 (s, C-14), 39.9 (s, C-8), 39.8 (s, C-4), 39.5 (d, C-19), 39.2 (d, C-20), 38.0 (s, C-10), 33.3 (t, C-7), 32.7 (t, C-22), 31.0 (t, C-21), 28.2 (q, C-23), 24.0 (t, C-15), 22.0 (t, C-16), 23.9 (t, C-11), 23.0 (q, C-29), 18.7 (t, C-6), 18.4 (q, C-24), 17.3 (q, C-30), 17.1 (q, C-26), 16.7 (q, C-25); EIMS (70 eV) m/z $[M]^+$ 624 (8), 606 (6), 591 (8), 588 (9), 580 (14), 459 (10), 441 (10), 360 (21), 342 (35), 264 (22), 246 (32), 233 (15), 190 (44), 163 (22), 143 (32), 137 (81), 109 (78), 83 (63), 57 (100), 55 (87), 43 (89).

Acknowledgment. This work was supported in part by a grant from MURST (Ministero dell' Universita' e della Ricerca Scientifica e Tecnologica, Roma) and by a grant from CNR (Consiglio Nazionale delle Ricerche, Roma).

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NP960134J