SYNTHESIS OF 30-AMINO DERIVATIVES OF LUPANE TRITERPENOIDS

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New derivatives of betulin and betulinic acid containing various amines on C-30 that are of interest as potentially biologically active agents were prepared.

Key words: betulin, betulin diacetate, methyl esters of betulinic and 3-acetylbetulinic acids, amines, NMR spectra.

Natural triterpenoids of the lupane group are of great interest because of their availability and broad spectrum of biological activities [1-3]. Chemical transformations of these compounds at the C-3, C-20, and C-28 positions produced synthetic derivatives that were more effective compared with the starting ones and possessed selective action [4-7]. Recent achievements suggest that preparations based on lupane triterpenoids are promising for application to the therapy of certain diseases [8,9].

We previously described the synthesis of amides and peptides of betulonic acid that contain amino acids or their methyl esters on C-28 [10]. It has been shown that the compounds actively inhibit reproduction of the immunodeficiency virus HIV-1 and possess other properties [11-17]. Herein we prepare derivatives containing various amines on C-30 for subsequent studies of their pharmacological properties.

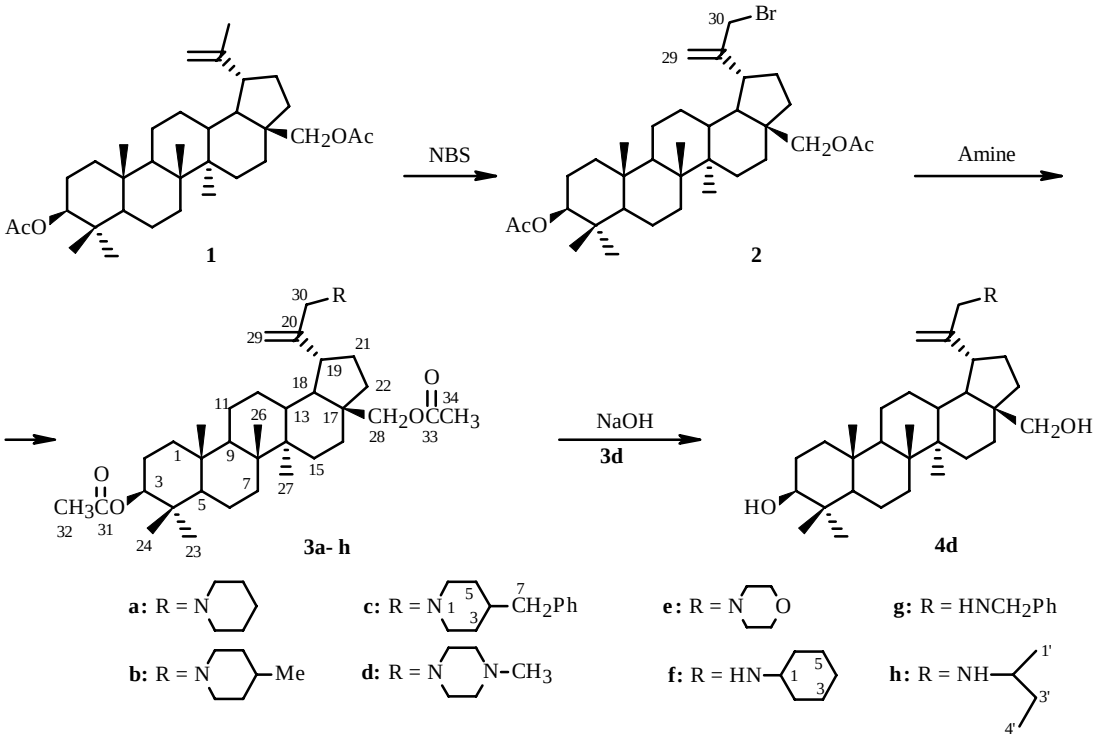

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TABLE 1. C log P Data for Betulin and Betulinic Acid Methyl Ester and Their 30-Amino Derivatives

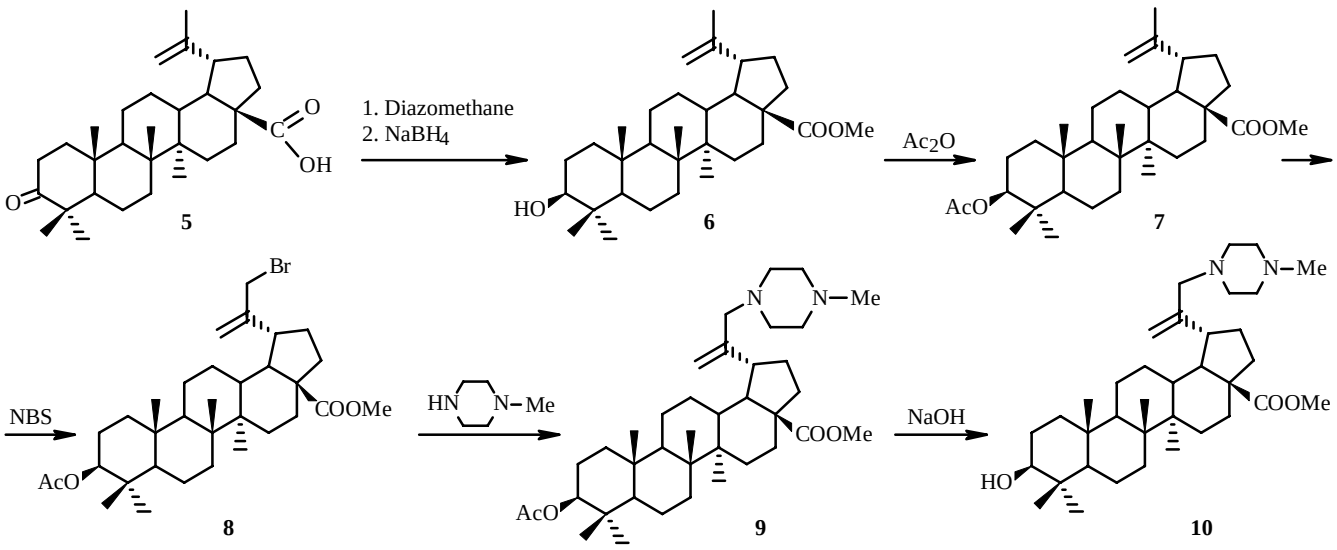
Compound	C log P	Compound	C log P
Betulin	8.53	**4g**	9.01
4a	8.88	**4h**	8.86
4b	9.23	**6**	8.85
4c	10.82	**10**	7.07
4d	6.74	**10e**	8.00
4e	7.67	**10a**	9.21
4f	9.01		

10a: Methyl ester of 3β-hydroxy-30-(piperidin-1′-yl)lup-20(29)-en-28-oic acid.
10e: Methyl ester of 3β-hydroxy-30-(morpholin-1′-yl)lup-20(29)-en-28-oic acid.

TABLE 2. Physicochemical Properties of **3a-h**, **4d**, **9**, **10**

Compound	Yield, %	$[\alpha]_D$, °, (*c*)	Empirical formula	Found (M)
3a	63	+5 (3.38)	$C_{39}H_{63}NO_4$	609.47846
3b	61	-7 (3.72)	$C_{40}H_{65}NO_4$	623.49346
3c	52	+4 (2.59)	$C_{46}H_{69}NO_4$	700
3d	60	+4 (3.6)	$C_{39}H_{64}N_2O_4$	624.48808
3e	61	+4 (3.72)	$C_{38}H_{61}NO_5$	611.45526
3f	68	-6 (3.04)	$C_{40}H_{65}NO_4$	623.49326
3g	45	-2 (2.93)	$C_{41}H_{61}NO_4$	631.45413
3h	60	-9 (3.27)	$C_{38}H_{63}NO_4$	597.47495
4d	93	-8 (3.6)	$C_{35}H_{60}N_2O_2$	540.46012
9	69	-5 (2.36)	$C_{38}H_{62}N_2O_4$	610.47111
10	95	-20 (3.49)	$C_{36}H_{60}N_2O_3$	568.45983

*Data for M^+ of all compounds agreed with those calculated.



Reaction of betulin diacetate (**1**) with *N*-bromosuccinimide (NBS) in CCl_4 as before [18] produced the 30-bromo derivative **2**. Boiling **2** with various amines in alcohol gave **3a-h** with secondary or tertiary amines on C-30. The product yields were 45-68%. Thus, we prepared a series of compounds with an identical triterpene skeleton and various amines on C-30 of the triterpenoid.

TABLE 3. Chemical Shifts of C Atoms in ^{13}C NMR Spectra of **3a-h**, **4d**, **9**, **10** (δ, ppm)

C atom	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**4d**	**9**	**10**
C-1	38.26 t	38.21	38.20	38.17	38.12	38.17	38.24	38.26	38.80	38.21	38.52
C-2	23.51 t	23.49	23.46	23.43	23.36	23.48	23.53	23.56	27.38	23.48	27.18
C-3	80.76 d	80.70	80.65	80.62	80.48	80.65	80.96	80.61	78.68	80.71	78.32
C-4	37.62 s	37.60	37.56	37.53	37.45	37.58	37.63	37.67	38.80	37.59	38.60
C-5	55.23 d	55.18	55.17	55.14	55.06	55.18	55.22	55.27	55.33	55.22	55.11
C-6	18.00 t	17.98	17.95	17.92	17.86	17.98	17.99	18.04	18.28	17.97	18.03
C-7	34.04 t	33.99	33.98	33.95	33.90	33.98	34.01	34.05	33.82	34.07	34.07
C-8	40.78 s	40.73	40.72	40.69	40.66	40.73	40.76	40.61	40.94	40.49	40.37
C-9	50.16 d	50.10	50.09	50.05	50.01	50.09	50.10	50.17	50.40	50.27	50.27
C-10	36.89 s	36.86	36.84	36.81	36.76	36.85	36.89	36.94	37.11	36.89	36.88
C-11	20.76 t	20.74	20.87	20.67	20.62	20.69	20.73	20.77	20.93	20.80	20.69
C-12	26.29 t	26.28	26.28	26.31	26.33	26.27	26.31	26.50	26.60	26.21	26.16
C-13	37.38 d	37.31	37.31	37.26	37.25	37.32	37.35	37.40	37.23	38.06	37.96
C-14	42.52 s	42.48	42.45	42.43	42.38	42.47	42.48	42.55	42.65	42.17	42.08
C-15	26.95 t	26.91	26.89	26.85	26.79	26.87	26.91	26.94	27.09	29.55	29.46
C-16	29.69 t	29.64	29.64	29.60	29.54	29.58	29.62	29.66	29.31	31.92	31.87
C-17	46.12 s	46.08	46.07	46.05	46.02	46.10	46.14	46.19	47.70	56.40	56.28
C-18	49.30 d	49.27	49.31	49.32	49.35	49.21	49.26	49.33	49.52	49.78	49.68
C-19	44.52 d	44.50	44.38	44.31	44.30	45.06	44.83	44.80	44.79	44.22	44.08
C-20	151.16 s	151.16	151.14	150.67	150.38	153.00	152.61	153.00	150.87	150.78	150.75
C-21	31.24 t	31.21	31.23	31.23	31.18	31.17	31.25	31.28	31.58	31.76	31.65
C-22	34.29 t	34.26	34.22	34.19	34.10	34.26	34.24	34.35	34.31	36.68	36.57
C-23	27.76 q	27.75	27.72	27.69	27.48	27.75	27.77	27.82	27.97	27.74	27.79
C-24	16.29 q	16.31	16.25	16.24	16.01	16.29	16.31	16.35	15.33	16.29	15.21
C-25	15.97 q	15.97	15.91	15.90	15.70	15.97	15.96	16.04	16.02	15.99	15.87
C-26	15.89 q	15.87	15.84	15.81	15.62	15.86	15.87	15.94	16.02	15.77	15.68
C-27	14.63 q	14.60	14.56	14.57	14.37	14.57	14.54	14.61	14.77	14.61	14.54
C-28	62.62 t	62.59	62.55	62.48	62.27	62.42	62.44	62.52	59.95	176.42	176.30
C-29	109.57 t	109.49	109.80	109.89	109.93	107.14	107.72	107.38	109.73	109.88	109.65
C-30	64.15 t	63.82	63.50	63.32	63.71	49.80	52.53	48.80	63.28	62.80	62.80
C-1′	-	-	-	-	-	56.09 t	53.33 t	19.66 q	-	-	-
								19.54 q			
C-2′	54.87 t	54.00[a] t	53.85[a] t	53.25[a] t	53.28[a] t	33.48[a] t	-	54.02 d	53.31 t	53.29	53.24
							-	54.92 d			
C-3′	25.88 t	34.26 t	32.11 t	55.00 t	66.68 t	24.90 t		29.35 t	55.21 t	55.05	54.96
							-	29.49 t			
C-4′	24.39 t	30.75 t	37.81 t	-	-	26.05 t		10.16 q	-	-	-
C-5′	25.88 t	34.26 t	32.11 t	55.00 t	66.68 t	24.90 t	-	-	55.21 t	55.05	54.96
C-6′	54.87 t	54.53[a] t	54.34[a] t	53.25[a] t	53.78[a] t	33.37[a] t	-	-	53.31 t	53.29	53.24
C-7′	-	21.79 q	43.04 t	45.81 q	-	-	-	-	45.96 q	45.88	45.82
Ph	-	-	125.43	-	-	-	126.70	-	-	-	-
			127.85				127.88				
			128.84				128.15				
			140.64				140.31				
$CH_3\underline{C}O$ at C-3	170.72 s	170.74	170.60	170.59	170.35	170.68	170.69	170.90	-	170.78	-
$CH_3\underline{C}O$ at C-28	171.36 s	171.39	171.24	171.23	170.98	171.28	171.26	171.51	-	-	-
$\underline{C}H_3CO$ at C-3	21.13 q	21.10	20.99	20.99	20.74	21.09	21.06	21.18	-	21.12	-
$\underline{C}H_3CO$ at C-28	20.88 q	20.84	20.74	20.74	20.48	20.82	20.79	20.91	-	-	-
COO<u>Me</u>	-	-	-	-	-	-	-	-	-	51.04 q	51.04

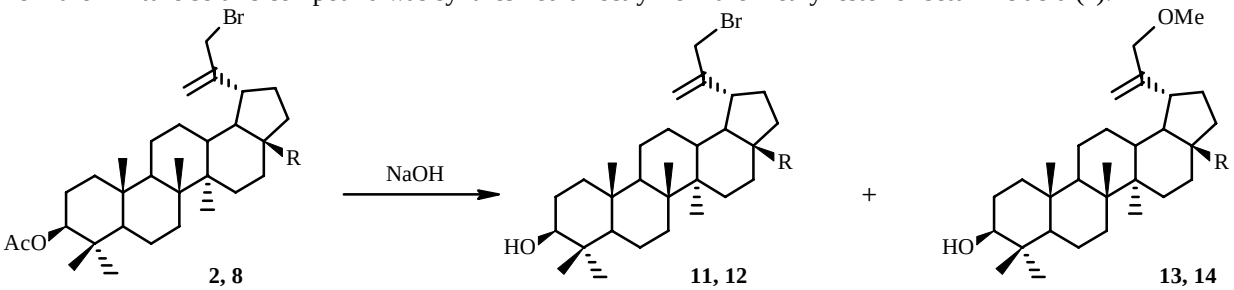
[a]Chemical shifts denoted with the same letters within a single column should possibly be switched.

The next stage of our work was to synthesize compounds containing various lupane triterpenes but the same amino group in the 30-position in order to study the effect of the triterpene part of the aminotriterpene on the biologial activity. After analyzing C log P of the amino derivatives of betulin and betulinic acid (Table 1), we focused on the N-methylpiperazine group.

Alkaline hydrolysis of **3d** by NaOH solution (4 M) in a MeOH:THF mixture at room temperature led smoothly to 30-N′-methylpiperazino derivative **4d** in 93% yield.

We also prepared N′-methylpiperazino derivatives of the methyl esters of 3-acetylbetulinic and betulinic acids. The methyl ester of 3-acetylbetulinic acid (**7**) was synthesized from betulonic acid (**5**) in 55% yield. The N′-methylpiperazino derivative **9** was prepared in 69% yield analogously to the amino derivative of betulin diacetate (**2**). Alkaline hydrolysis of **9** led smoothly to the corresponding 3-hydroxy-30-amino derivative **10** in 95% yield.

It should be noted that hydrolysis of the 30-bromo derivatives of **2** and the methyl ester of 3-acetylbetulinic acid (**8**) was nonselective. In addition to the expected 30-bromo derivatives of betulin (**11**) and the methyl ester of betulinic acid (**12**), the 30-methoxy derivatives **13** and **14**, respectively, were formed. The ratio of 30-bromo derivatives **11** (**12**) and 30-methoxy derivatives **13** (**14**) depended on the reaction conditions. Thus, after 3 d of hydrolysis at room temperature, the ratios of **11** to **13** and **12** to **14** were 1:1 and 1:2, respectively, according to PMR spectra. Increasing the hydrolysis time to 15 d gave practically the 30-methoxy derivative. The 30-bromo derivative of the methyl ester of betulinic acid (**12**) could not be isolated pure from the mixture so this compound was synthesized directly from the methyl ester of betulinic acid (**6**).



2, 8 **11, 12** **13, 14**

2: R = CH_2OAc
8: R = COOMe

11: R = CH_2OH
12: R = COOMe

13: R = CH_2OH
14: R = COOMe

The structures of all newly synthesized compounds (**2**, **3a**-**h**, **4d**, **9**-**14**) were confirmed by elemental analyses and mass and NMR spectra. Signals in the ^{13}C NMR spectra were assigned based on 2D spectra of **2**, **3a**, **b**, **d**, **f**, **4d**, **9**, **10**, and **14** and the literature [10].

EXPERIMENTAL

NMR spectra were recorded on Bruker AC-200 and AM-400 instruments at working frequencies 200.13 and 400.13 MHz for ^1H and 50.32 and 100.61 MHz for ^{13}C in $CDCl_3$. The multiplicity of signals in ^{13}C NMR spectra was determined by standard methods of recording spectra with *J*-modulation (JMOD) and off-resonance. Two-dimensional NMR $^1H—^1H$ (COSY) and $^{13}C—^1H$ (COSY 125 Hz, COLOC 7 Hz) of **2**, **3a**, **b**, **d**, **f**, **4d**, **9**, **10**, and **14** were obtained on a Bruker DRX-500 instrument at working frequencies 500.13 MHz for ^1H and 125.76 MHz for ^{13}C in $CDCl_3$ using standard Bruker programs. The internal standards were $CDCl_3$ signals (δ_C = 76.90) and residual ^1H in $CDCl_3$ (δ_H = 7.24 ppm). Mass spectra were obtained in a Finnigan MAT 8200 high-resolution mass spectrometer with 70 eV ionzing potential. Specific rotations ($[\alpha]_{580}$) were measured on a Polamat A polarimeter in $CHCl_3$ at room temperature (20-25°C). Melting points were determined on a Kofler microheating stage. Elemental analyses were carried out in a Carlo Erba 1106 model CHN-analyzer.

The course of reactions and purity of products were monitored by TLC on Silufol UV-254 plates using solvent systems CH_2Cl_2:MTBE (20:1) for **1**, **2**, and **5**-**8** and $CHCl_3$:CH_3OH (10:1) for **3a**-**h**, **4d**, and **9**-**14**. Spots were developed by spraying plates with H_2SO_4 (20%) and heating subsequently to 100°C. Column chromatography was carried out on aluminum oxide (activity II, CH_2Cl_2 eluent).

Betulin diacetate (**1**) and betulonic acid (**5**) were prepared as before [10]. Table 2 lists the physicochemical properties of **3a**-**h**, **4d**, **9**, and **10** (yields, constants, mass spectra). Compounds **3a**-**h**, **4d**, **9**, and **10** were obtained as amorphous powders. Chemical shifts of characteristic protons in PMR spectra of **3c**, **e**, **g**, and **h** are given. Table 3 lists ^{13}C NMR data for **3a**-**h**, **4d**, **9**, and **10**. Elemental analyses of the compounds agreed with those calculated.

3β,28-Diacetoxy-30-bromolup-20(29)-ene (2). **1** (5.00 g, 9.50 mmol) in CCl_4 (200 mL) was treated with NBS (3.40 g, 19.10 mmol), stirred at room temperature for 5 d, and filtered through filter paper. The filtrate was evaporated. The solid was dissolved in CH_3OH. The resulting solid was filtered off, washed with CH_3OH, and dried in a vacuum desiccator over P_2O_5 to afford **2** (3.70 g, 64%), mp 190-196°C, lit. [18] mp 185°C.

PMR spectrum (δ, ppm, J/Hz): 0.73 (1H, m, H-5), 0.77 (3H, s, Me-24), 0.78 (3H, s, Me-23), 0.79 (3H, s, Me-25), 0.91 (1H, m, H-1), 0.92 (3H, s, Me-27), 0.98 (3H, s, Me-26), 1.00 (2H, m, H-12, 15), 1.03 (1H, m, H-11), 1.10 (1H, m, H-22), 1.21 (1H, m, H-9), 1.23 (1H, m, H-16), 1.29 (1H, m, H-12), 1.32 (1H, m, H-21), 1.34 (2H, m, H-7), 1.36 (1H, m, H-11), 1.43 (2H, m, H-6), 1.55 (2H, m, H-2), 1.60 (1H, m, H-1), 1.64 (1H, m, H-13), 1.65 (1H, m, H-15), 1.70 (1H, t, J = 11.9, H-18), 1.74 (1H, ddd, J_1 = 12.4, J_2 = 8.6, J_3 = 1.2, H-22), 1.80 (1H, ddd, J_1 = 13.6, J_2 = 4.7, J_3 = 2.3, H-16), 1.98 (3H, s, AcO on C-3), 2.01 (3H, s, AcO on C-28), 2.16 (1H, td, J_1 = 11.2, J_2 = 5.4, H-21), 2.39 (1H, td, J_1 = 11.3, J_2 = 5.4, H-19), 3.78 (1H, dd, J_1 = 11.2, J_2 = 1.1, H_A-28), 3.92 (2H, AB-system, J = 10.3, H-30), 4.20 (1H, dd, J_1 = 11.2, J_2 = 1.8, H_B-28), 4.40 (1H, dd, J_1 = 10.4, J_2 = 6.0, H-3), 4.97 and 5.07 (2H, both br.s, H-29).

^{13}C NMR spectrum (δ, ppm): 14.50 (q, C-27), 15.83 (q, C-26), 15.94 (q, C-25), 16.27 (q, C-24), 17.92 (t, C-6), 20.69 (t, C-11), 20.81 (q, C-34), 21.08 (q, C-32), 23.44 (t, C-2), 26.74 (t, C-12), 26.78 (t, C-15), 27.71 (q, C-23), 29.57 (t, C-16), 32.27 (t, C-21), 33.92 (t, C-7), 34.06 (t, C-22), 36.81 (s, C-10), 37.13 (t, C-30), 37.21 (d, C-13), 37.54 (s, C-4), 38.14 (t, C-1), 40.68 (s, C-8), 42.43 (s, C-14), 43.00 (d, C-19), 46.13 (s, C-17), 49.98 (d, C-9), 50.03 (d, C-18), 55.10 (d, C-6), 62.33 (t, C-28), 80.64 (d, C-3), 113.05 (t, C-29), 150.56 (s, C20), 170.75 (s, C-31), 171.30 (s, C-33). The compound was used further without additional purification.

General Method for Preparing 30-Amino Derivatives of 1 (3a-h). **2** (1.00 g, 1.65 mmol) in alcohol (25 mL) was treated with amine (8.25 mmol), boiled for 10 h, and poured onto ice. The resulting solid was filtered off, washed with water, dried in a vacuum desiccator over P_2O_5, and chromatographed over Al_2O_3.

3β,28-Diacetoxy-30-(piperidin-1′-yl)lup-20(29)-ene (3a). PMR spectrum (δ, ppm, J/Hz): 0.74 (1H, m, H-5), 0.79 (3H, s, Me-24), 0.80 (6H, s, Me-23,25), 0.93 (3H, s, Me-27), 0.94 (1H, m, H-1), 0.99 (3H, s, Me-26), 1.00 (1H, m, H-15), 1.05 (1H, m, H-12), 1.10 (1H, m, H-22), 1.15 (1H, m, H-11), 1.22 (1H, m, H-16), 1.24 (1H, m, H-9), 1.29-1.42 (9H, m, H-6,7,7,11,12,21,3′,4′,5′), 1.46 (1H, m, H-6), 1.50 (3H, m, H-3′,4′,5′), 1.57 (2H, m, H-2), 1.60 (1H, m, H-13), 1.62 (1H, m, H-1), 1.65 (1H, m, H-15), 1.69 (1H, m, H-18), 1.71 (1H, m, H-22), 1.80 (1H, m, H-16), 1.99 (3H, s, AcO on C-3), 2.01 (1H, m, H-21), 2.02 (3H, s, AcO on C-28), 2.32 (5H, br.s, H-19,2′,2′,6′,6′), 2.75 (2H, AB-system, J = 14.0, H-30), 3.80 (1H, dd, J_1 = 11.0, J_2 = 1.9, H_A-28), 4.21 (1H, dd, J_1 = 11.0, J_2 = 1.3, H_B-28), 4.42 (1H, dd, J_1 = 10.3, J_2 = 5.8, H-3), 4.80 and 4.81 (2H, both br.s, H-29).

3β,28-Diacetoxy-30-(4′-methylpiperidin-1′-yl)lup-20(29)-ene (3b). PMR spectrum (δ, ppm, J/Hz): 0.73 (1H, m, H-5), 0.79 (9H, s, Me-23,24,25), 0.87 (3H, d, J = 6.5, Me-7′), 0.91 (1H, m, H-1), 0.92 (3H, s, Me-27), 0.98 (3H, s, Me-26), 1.00 (1H, m, H-15), 1.04 (1H, m, H-12), 1.08 (1H, m, H-22), 1.15 (2H, m, H-3′,5′), 1.16 (1H, m, H-11), 1.21 (1H, m, H-16), 1.23 (2H, m, H-9,4′), 1.26-1.41 (6H, H-6,7,7,11,12,21), 1.45 (1H, m, H-6), 1.51 (2H, m, H-3′,5′), 1.55 (2H, m, H-2), 1.58 (1H, m, H-13), 1.61 (1H, m, H-1), 1.64 (1H, m, H-15), 1.68 (1H, m, H-18), 1.70 (1H, m, H-22), 1.77 (1H, m, H-2′ or 6′), 1.79 (1H, m, H-16), 1.85 (1H, m, H-2′ or 6′), 1.99 (3H, s, AcO on C-3), 2.00 (1H, m, H-21), 2.02 (3H, s, AcO on C-28), 2.33 (1H, m, H-19), 2.79 (4H, m, H-30,30,2′,6′), 3.79 (1H, d, J = 11.0, H_A-28), 4.20 (1H, d, J = 11.4, H_B-28), 4.42 (1H, dd, J_1 = 10.4, J_2 = 6.0, H-3), 4.80 (2H, br.s, H-29).

3β,28-Diacetoxy-30-(4′-benzylpiperidin-1′-yl)lup-20(29)-ene (3c). PMR spectrum (δ, ppm, J/Hz): 0.76 (1H, m, H-5), 0.81 (9H, s, Me-23,24,25), 0.93 (3H, s, Me-27), 1.01 (3H, s, Me-26), 2.00 (3H, s, AcO on C-3), 2.03 (3H, s, AcO on C-28), 2.34 (1H, m, H-19), 2.50 (2H, m, CH_2), 2.79 (4H, m, H-30, C<u>H</u>$_2$Ph), 3.81 (1H, d, J = 11.0, H_A-28), 4.20 (1H, d, J = 11.0, H_B-28), 4.44 (1H, dd, J_1 = 10.5, J_2 = 6.1, H-3), 4.84 (2H, br.s, H-29), 7.20 (5H, m, Ph).

3β,28-Diacetoxy-30-(4′-methylpiperazin-1′-yl)lup-20(29)-ene (3d). PMR spectrum (δ, ppm, J/Hz): 0.70 (1H, m, H-5), 0.75 (3H, s, Me-24), 0.76 (3H, s, Me-23), 0.77 (3H, s, Me-25), 0.89 (3H, s, Me-27), 0.95 (3H, s, Me-26), 0.90 (1H, m, H-1), 0.97 (1H, m, H-15), 1.01 (1H, m, H-12), 1.05 (1H, m, H-22), 1.12 (1H, m, H-11), 1.18 (1H, m, H-16), 1.20 (1H, m, H-9), 1.24-1.37 (6H, m, H-6,7,7,11,12,21), 1.43 (1H, m, H-6), 1.54 (2H, m, H-2), 1.56 (1H, m, H-13), 1.58 (1H, m, H-1), 1.60 (1H, m, H-15), 1.64 (1H, m, H-18), 1.68 (1H, m, H-22), 1.77 (1H, m, H-16), 1.96 (3H, s, AcO on C-3), 1.97 (1H, m, H-21), 1.99 (3H, s, AcO on C-28), 2.20 (3H, s, N-Me), 2.29 (1H, m, H-19), 2.36 (8H, m, H-2′,3′,5′,6′), 2.76 (2H, AB-system, J = 14.0, H-30), 3.76 (1H, d, J = 11.2, H_A-28), 4.17 (1H, d, J = 11.1, H_B-28), 4.39 (1H, dd, J_1 = 10.5, J_2 = 5.8, H-3), 4.78 and 4.80 (2H, both br.s, H-29).

3β,28-Diacetoxy-30-(morpholin-1′-yl)lup-20(29)-ene (3e). PMR spectrum (δ, ppm, J/Hz): 0.72 (1H, m, H-5), 0.76 (6H, s, Me-23,24), 0.78 (3H, s, Me-25), 0.91 (3H, s, Me-27), 0.96 (3H, s, Me-26), 1.93 (3H, s, AcO on C-3), 1.96 (3H, s, AcO on C-28), 2.32 (5H, m, H-19,2′,6′), 2.76 (2H, m, H-30), 3.57 (4H, m, H-3′,5′), 3.78 (1H, d, J = 10.6, H_A-28), 4.18 (1H, d, J = 10.6, H_B-28), 4.46 (1H, dd, J_1 = 10.8, J_2 = 6.0, H-3), 4.79 and 4.81 (2H, both br.s, H-29).

3β,28-Diacetoxy-30-cyclohexylaminolup-20(29)-ene (3f). PMR spectrum (δ, ppm, J/Hz): 0.73 (1H, m, H-5), 0.77 (3H, s, Me-24), 0.78 (3H, s, Me-23), 0.79 (3H, s, Me-25), 0.90 (1H, m, H-1), 0.91 (3H, s, Me-27), 0.97 (3H, s, Me-26), 0.99 (1H, m, H-15), 1.04 (1H, m, H-12), 1.08 (1H, m, H-22), 1.12 (4H, m, H-2′,3′,5′,6′), 1.16 (2H, m, H-11,4′), 1.20 (1H, m, H-16), 1.23 (1H, m, H-9), 1.28-1.40 (6H, m, H-6,7,7,11,12,21), 1.45 (1H, m, H-6), 1.56 (2H, m, H-2), 1.57 (2H, m, H-13,4′), 1.60 (1H, m, H-1), 1.64 (1H, m, H-15), 1.67 (2H, m, H-3′,5′), 1.69 (1H, m, H-18), 1.71 (1H, m, H-22), 1.79 (1H, m, H-16), 1.82 (2H, m, H-2′,6′), 1.98 (3H, s, AcO on C-3), 2.00 (1H, m, H-21), 2.01 (3H, s, AcO on C-28), 2.28 (1H, m, H-19), 2.37 (1H, m, H-1′), 3.15 (2H, AB-system, J = 15.3, H-30), 3.78 (1H, d, J = 11.0, H_A-28), 4.18 (1H, d, J = 11.1, H_B-28), 4.40 (1H, dd, J_1 = 10.6, J_2 = 5.8, H-3), 4.76 and 4.79 (2H, both br.s, H-29).

3β,28-Diacetoxy-30-benzylaminolup-20(29)-ene (3g). PMR spectrum (δ, ppm, J/Hz): 0.70 (1H, m, H-5), 0.82 (9H, s, Me-23,24,25), 0.90 (3H, s, Me-27), 1.00 (3H, s, Me-26), 2.00 (3H, s, AcO on C-3), 2.03 (3H, s, AcO on C-28), 2.30 (1H, m, H-19), 3.18 (2H, m, C$\underline{H}_2$Ph), 3.80 (3H, m, H-28,30), 4.22 (1H, d, J = 10.8, H-28), 4.44 (1H, dd, J_1 = 10.8, J_2 = 6.0, H-3), 4.85 and 4.89 (2H, both br.s, H-29), 7.25 (5H, m, Ph).

3β,28-Diacetoxy-30-(*sec*-butyl)aminolup-20(29)-ene (3h). PMR spectrum (δ, ppm, J/Hz): 0.75 (1H, m, H-5), 0.81 (9H, s, Me-23,24,25), 0.88 (3H, t, J = 7.6, Me-4′), 0.94 (3H, s, Me-27), 1.00 (3H, s, Me-26), 1.04 (3H, d, J = 6.1, Me-1′), 2.04 (3H, s, AcO on C-3), 2.05 (3H, s, AcO on C-28), 2.32 (1H, m, H-19), 2.57 (1H, m, H-2′), 3.16 (2H, m, H-30), 3.80 (1H, d, J = 10.6, H_A-28), 4.23 (1H, d, J = 10.6, H_B-28), 4.43 (1H, dd, J_1 = 10.8, J_2 = 5.8, H-3), 4.83 (2H, br.s, H-29).

3β,28-Hydroxy-30-(4′-methylpiperazin-1′-yl)lup-20(29)-ene (4d). 3d (0.20 g, 0.32 mmol) in MeOH (4 mL) and THF (2 mL) under Ar at 0°C was treated with NaOH solution (0.32 mL, 1.32 mmol, 4 N), held at room temperature for 2 d, and poured onto ice. The resulting solid was filtered off, washed with water, and dried in air.

PMR spectrum (δ, ppm, J/Hz): 0.61 (1H, m, H-5), 0.70 (3H, s, Me-24), 0.76 (3H, s, Me-25), 0.90 (3H, s, Me-23), 0.92 (3H, s, Me-27), 0.96 (3H, s, Me-26), 0.97 (1H, m, H-15), 0.99 (1H, m, H-22), 1.02 (1H, m, H-12), 1.13 (1H, m, H-16), 1.15 (1H, m, H-11), 1.20 (1H, m, H-9), 1.25-1.40 (6H, m, H-6,7,7,11,12,21), 1.46 (1H, m, H-6), 1.52 (2H, m, H-2), 1.54 (1H, m, H-13), 1.57 (1H, m, H-1), 1.60 (1H, m, H-18), 1.64 (1H, m, H-15), 1.80 (1H, m, H-22), 1.89 (1H, m, H-16), 1.99 (1H, m, H-21), 2.20 (3H, s, N-Me), 2.23 (1H, m, H-19), 2.38 (8H, br.s, H-2′,3′,5′,6′), 2.79 (2H, AB-system, J = 14.2, H-30), 3.10 (1H, dd, J_1 = 11.0, J_2 = 5.4, H-3), 3.23 (1H, d, J = 10.7, H_A-28), 3.69 (1H, d, J = 10.7, H_B-28), 4.79 and 4.81 (2H, both br.s, H-29).

Methyl Ester of 3β-Acetoxylup-20(29)-en-28-oic Acid (7). **5** (3.88 g, 8.55 mmol) was dissolved in anhydrous diethylether (235 mL), cooled to 0°C, stirred vigorously, treated dropwise with diazomethane until a yellow color was stable, held at 0°C for 48 h, dried over anhydrous $MgSO_4$, and evaporated. The solid was washed with MeOH and chromatographed over Al_2O_3 (CH_2Cl_2 eluent). The purified methyl ester of betulonic acid (2.81 g, 6.00 mmol) was dissoslved in dry THF (140 mL), cooled to 0°C, treated in portions with $NaBH_4$ (0.98 g, 25.79 mmol), stirred with cooling for 3 h, held at room temperature for 1 d, and poured onto ice with dilute HCl. The resulting solid was filtered off, washed with water, dried in a desiccator over P_2O_5, and chromatographed over Al_2O_3. A mixture of purified methyl ester of betulinic acid (**6**, 2.30 g, 4.90 mmol), Ac_2O (18 mL), and pyridine (70 mL) was held at room temperature, periodically stirred during 3 d, and poured onto ice with conc. HCl. The resulting solid was filtered off, washed with water, and dried over P_2O_5 to afford the methyl ester of 3-acetylbetulinic acid (**7**, 2.40 g, 55%), mp 201-203°C, lit. [19] mp 202-203°C.

Methyl Ester of 3β-Acetoxy-30-bromolup-20(29)-en-28-oic Acid (8). A mixture of **7** (2.40 g, 4.69 mmol) and NBS (1.67 g, 9.38 mmol) in CCl_4 (96 mL) was held at room temperature, periodically stirred during 3 d, and filtered through filter paper. The filtrate was evaporated. The solid was dissolved in MeOH. The resulting solid was filtered off, washed with MeOH, and dried in a vacuum desiccator over P_2O_5 to afford **8** (1.47 g, 53%), mp 218-220°C, $[\alpha]_D$ -5° (*c* 2.93), lit. [20] mp 235-236°C, $[\alpha]_D$ +42.55. Found, %: Br 13.60; M-Br (mass spectrometry) 511.38024. $C_{33}H_{51}O_4Br$. Calc., %: Br 13.51; M-Br 511.37871.

PMR spectrum (δ, ppm, J/Hz): 0.72 (1H, m, H-5), 0.77 (3H, s, Me-24), 0.78 (6H, s, Me-23,25), 0.85 (3H, s, Me-26), 0.91 (3H, s, Me-27), 1.97 (3H, s, AcO), 2.98 (1H, td, J_1 = 11.7, J_2 = 4.6, H-19), 3.61 (3H, s, OMe), 3.93 (2H, br.s, H-30), 4.40 (1H, dd, J_1 = 10.5, J_2 = 5.8, H-3), 4.98 and 5.08 (2H, both br.s, H-29).

^{13}C NMR spectrum (δ, ppm): 14.49 (q, C-27), 15.79 (q, C-26), 15.98 (q, C-25), 16.30 (q, C-24), 18.00 (t, C-6), 20.84 (t, C-11), 21.06 (q, C-32), 23.50 (t, C-2), 26.63 (t, C-12), 27.76 (q, C-23), 29.49 (t, C-15), 31.84 (t, C-16), 32.91 (t, C-21), 34.13 (t, C-7), 36.45 (t, C-22), 36.74 (t, C-30), 36.93 (s, C-10), 37.60 (s, C-4), 38.07 (d, C-13), 38.24 (t, C-1), 40.54 (s, C-8), 42.17

(s, C-14), 42.97 (d, C-19), 50.26 (d, C-9), 50.86 (d, C-18), 51.10 (q, OMe), 55.26 (d, C-5), 56.37 (s, C-17), 80.67 (d, C-3), 113.20 (t, C-29), 151.14 (s, C-20), 170.65 (s, C-31), 176.13 (s, C-28). The compound was used further without additional purification.

Methyl Ester of 3β-Acetoxy-30-(4′-methylpiperazin-1′-yl)lup-20(29)-en-28-oic Acid (9). A solution of **8** (0.90 g, 1.52 mmol) in alcohol (23 mL) was treated with 1-methylpiperazine (0.84 mL, 7.59 mmol), boiled for 10 h, and poured onto ice. The resulting solid was filtered off, washed with water, dried in a desiccator over P_2O_5, and chromatographed over Al_2O_3.

PMR spectrum (δ, ppm, J/Hz): 0.72 (1H, m, H-5), 0.76 (3H, s, Me-24), 0.78 (6H, s, Me-23,25), 0.84 (3H, s, Me-26), 0.90 (3H, s, Me-27), 0.92 (1H, m, H-1), 0.98 (1H, m, H-12), 1.08 (1H, m, H-15), 1.17 (1H, m, H-11), 1.22 (1H, m, H-9), 1.25-1.36 (7H, m, H-6,7,7,11,15,16,21), 1.38 (1H, m, H-22), 1.40-1.47 (2H, m, H-6,12), 1.55 (2H, m, H-2), 1.61 (1H, m, H-1), 1.66 (1H, t, J = 11.3, H-18), 1.77 (1H, dd, J_1 = 12.3, J_2 = 7.7, H-22), 1.88 (1H, m, H-21), 1.97 (3H, s, AcO), 2.10 (1H, td, J_1 = 12.1, J_2 = 3.6, H-13), 2.18 (1H, m, H-16), 2.23 (3H, s, N-Me), 2.37 (8H, br.s, H-2′,3′,5′,6′), 2.80 (2H, AB-system, J = 14.3, H-30), 2.86 (1H, td, J_1 = 11.0, J_2 = 4.4, H-19), 3.60 (3H, s, OMe), 4.40 (1H, dd, J_1 = 10.3, J_2 = 6.1, H-3), 4.80 and 4.84 (2H, both br.s, H-29).

Methyl Ester of 3β-Hydroxy-30-(4′-methylpiperazin-1′-yl)lup-20(29)-en-28-oic Acid (10). A solution of **9** (0.22 g, 0.36 mmol) in MeOH (4.4 mL) and THF (2.2 mL) under Ar at 0°C was treated with NaOH solution (0.36 mL, 1.44 mmol, 4 N), held at room temperature for 2 d, and poured onto ice. The resulting solid was filtered off, washed with water, and dried in air.

PMR spectrum (δ, ppm, J/Hz): 0.57 (1H, m, H-5), 0.65 (3H, s, Me-24), 0.71 (3H, s, Me-25), 0.79 (1H, m, H-1), 0.80 (3H, s, Me-26), 0.86 (6H, s, Me-23,27), 0.94 (1H, m, H-12), 1.05 (1H, m, H-15), 1.14 (2H, m, H-9,11), 1.20-1.33 (7H, m, H-6,7,7,11,15,16,21), 1.33-1.45 (3H, m, H-6,12,22), 1.48 (2H, m, H-2), 1.56 (1H, m, H-1), 1.61 (1H, t, J = 11.4, H-18), 1.73 (1H, m, H-22), 1.84 (1H, m, H-21), 2.06 (1H, td, J_1 = 12.0, J_2 = 2.6, H-13), 2.14 (1H, m, H-16), 2.18 (3H, s, N-Me), 2.35 (8H, br.s, H-2′,3′,5′,6′), 2.77 (2H, AB-system, J = 14.3, H-30), 2.82 (1H, td, J_1 = 11.2, J_2 = 4.0, H-19), 3.05 (1H, dd, J_1 = 10.3, J_2 = 5.8, H-3), 3.56 (3H, s, OMe), 4.76 and 4.80 (2H, both br.s, H-29).

General Method for Hydrolysis of 30-Bromo Derivatives (2, 8). A solution of **2** (**8**) (1.9 mmol) in MeOH (26 mL) and THF (12 mL) under Ar at 0°C was treated with NaOH solution (1.2 mL, 4.8 mmol, 4 N), held at room temperature for 3 d, and poured onto ice with dilute HCl. The resulting solid was filtered off, washed with water, and dried over P_2O_5 to afford a mixture of **11** and **13** or **12** and **14** in ~1:1 or 1:2 ratios, respectively, according to PMR spectra. Chromatography over Al_2O_3 produced analytically pure compounds.

3β,28-Hydroxy-30-bromolup-20(29)-ene (11). Mp 201-204°C, $[\alpha]_D$ -2° (*c* 3.49). Mass spectrum, *m*/*z*: 520.29120 $[M]^+$. $C_{30}H_{49}O_2Br$. Calc.: 520.29162 $[M]^+$.

PMR spectrum (δ, ppm, J/Hz): 0.66 (1H, m, H-5), 0.73 (3H, s, Me-24), 0.80 (3H, s, Me-25), 0.94 (3H, s, Me-23), 0.96 (3H, s, Me-27), 1.08 (3H, s, Me-26), 3.14 (1H, dd, J_1 = 10.1, J_2 = 5.2, H-3), 3.29 (1H, d, J = 10.8, H_A-28), 3.76 (1H, d, J = 10.9, H_B-28), 3.99 (1H, m, H-30), 5.00 and 5.09 (2H, both br.s, H-29).

^{13}C NMR spectrum (δ, ppm): 14.64 (q, C-27), 15.24 (q, C-24), 15.95 (q, C-25,26), 18.30 (t, C-6), 20.85 (t, C-11), 26.92 (t, C-12,15), 27.25 (t, C-2), 27.88 (q, C-23), 29.15 (t, C-16), 32.54 (t, C-21), 33.59 (t, C-22), 34.19 (t, C-7), 37.04 (t, C-30), 37.11 (s, C-10), 37.20 (d, C-13), 38.62 (t, C-1), 38.73 (s, C-4), 40.86 (s, C-8), 42.59 (s, C-14), 43.38 (d, C-19), 47.70 (s, C-17), 50.22 (d, C-9,18), 55.19 (d, C-5), 60.13 (t, C-28), 78.81 (d, C-3), 113.12 (t, C-29), 150.92 (s, C-20).

3β,28-Hydroxy-30-methoxylup-20(29)-ene (13). Mp 212-214°C, $[\alpha]_D$ -13° (*c* 3.38). Mass spectrum, *m*/*z*: 472.40779 $[M]^+$. $C_{31}H_{52}O_3$. Calc.: 472.39162 $[M]^+$.

PMR spectrum (δ, ppm, J/Hz): 0.66 (1H, m, H-5), 0.74 (3H, s, Me-24), 0.80 (3H, s, Me-25), 0.94 (3H, s, Me-23), 0.96 (3H, s, Me-27), 1.00 (3H, s, Me-26), 3.16 (1H, dd, J_1 = 10.3, J_2 = 5.1, H-3), 3.29 (1H, d, J = 10.8, H_A-28), 3.33 (3H, s, OMe), 3.76 (1H, d, J = 10.9, H_B-28), 3.84 (1H, m, H-30), 4.88 and 4.90 (2H, both br.s, H-29).

^{13}C NMR spectrum (δ, ppm): 14.62 (q, C-27), 15.23 (q, C-24), 15.96 (q, C-25,26), 18.20 (t, C-6), 20.86 (t, C-11), 26.62 (t, C-12), 26.98 (t, C-15), 27.29 (t, C-2), 27.88 (q, C-23), 29.18 (t, C-16), 31.44 (t, C-21), 33.70 (t, C-22), 34.22 (t, C-7), 37.07 (s, C-10), 37.15 (d, C-13), 38.64 (t, C-1), 38.74 (s, C-4), 40.88 (s, C-8), 42.59 (s, C-14), 43.61 (d, C-19), 47.67 (s, C-17), 49.37 (d, C-18), 50.31 (d, C-9), 55.21 (d, C-5), 58.12 (q, OMe), 60.14 (t, C-28), 74.86 (t, C-30), 78.81 (d, C-3), 108.99 (t, C-29), 150.97 (s, C-20).

Methyl Ester of 3β-Hydroxy-30-methoxylup-20(29)-en-28-oic Acid (14). Amorphous powder, $[\alpha]_D$ -20° (*c* 8.11). Mass spectrum, *m*/*z*: 500.39376 $[M]^+$. $C_{32}H_{52}O_4$. Calc.: 500.38654 $[M]^+$.

PMR spectrum (δ, ppm, J/Hz): 0.62 (1H, m, H-5), 0.71 (3H, s, Me-24), 0.77 (3H, s, Me-25), 0.85 (1H, td, J_1 = 12.4, J_2 = 4.6, H-1), 0.86 (3H, s, Me-26), 0.91 (3H, s, Me-23), 0.92 (3H, s, Me-27), 1.05 (1H, m, H-15), 1.10 (1H, m, H-12), 1.20 (2H, m, H-9,11), 1.25-1.40 (6H, m, H-7,7,11,15,16,21), 1.40-1.53 (4H, m, H-6,6,12,22), 1.55 (2H, m, H-2) 1.61 (1H, td, J_1 = 13.0, J_2 = 3.6, H-1), 1.65 (1H, t, J = 11.4, H-18), 1.81 (1H, dd, J_1 = 11.9, J_2 = 7.9, H-22), 1.92 (1H, m, H-21), 2.12 (1H, td, J_1 = 12.8, J_2 = 3.6, H-13), 2.20 (1H, dd, J_1 = 8.9, J_2 = 2.7, H-16), 2.83 (1H, td, J_1 = 11.3, J_2 = 4.5, H-19), 3.12 (1H, dd, J_1 = 11.3, J_2 = 5.0, H-3), 3.30 (3H, s, OMe), 3.61 (3H, s, COOMe), 3.82 (1H, br.s, H-30), 4.88 and 4.89 (2H, both br.s, H-29).

^{13}C NMR spectrum (δ, ppm): 14.53 (q, C-27), 15.21 (q, C-24), 15.81 (q, C-26), 15.95 (q, C-25), 18.14 (t, C-6), 20.83 (t, C-11), 26.48 (t, C-12), 27.25 (t, C-2), 27.84 (q, C-23), 29.56 (t, C-15), 31.94 (t, C-16,21), 34.22 (t, C-7), 36.62 (t, C-22), 37.04 (s, C-10), 38.11 (d, C-13), 38.59 (t, C-1), 38.69 (s, C-4), 40.55 (s, C-8), 42.20 (s, C-14), 42.94 (d, C-19), 49.92 (d, C-18), 50.40 (d, C-9), 51.08 (q, OMe), 55.23 (d, C-5), 56.40 (s, C-17), 58.14 (q, COOMe), 74.86 (t, C-30), 78.73 (d, C-3), 108.61 (t, C-29), 151.13 (s, C-20), 176.37 (s, C-28).

Methyl Ester of 3β-Hydroxy-30-bromolup-20(29)-en-28-oic Acid (12). A mixture of **6** (0.55 g, 1 mmol) and NBS (0.36 g, 2 mmol) in CCl_4 (22 mL) was held at room temperature, periodically stirred during 1.5 d, and filtered through filter paper. The filtrate was evaporated. The solid was chromatographed over Al_2O_3 to afford **12** (0.25 g, 39%) as an amorphous powder, $[\alpha]_D$ -12° (*c* 4.05).

PMR spectrum (δ, ppm, J/Hz): 0.64 (1H, m, H-5), 0.72 (3H, s, Me-24), 0.78 (3H, s, Me-25), 0.87 (3H, s, Me-26), 0.92 (3H, s, Me-23), 0.94 (3H, s, Me-27), 3.00 (1H, td, J_1 = 11.0, J_2 = 4.8, H-19), 3.14 (1H, dd, J_1 = 11.0, J_2 = 5.2, H-3), 3.64 (3H, s, OMe), 3.95 (2H, s, H-30), 5.00 and 5.10 (2H, both br.s, H-29).

^{13}C NMR spectrum (δ, ppm): 14.58 (q, C-27), 15.21 (q, C-24), 15.84 (q, C-26), 15.95 (q, C-25), 18.16 (t, C-6), 20.87 (t, C-11), 26.71 (t, C-12), 27.25 (t, C-2), 27.86 (q, C-23), 29.55 (t, C-15), 31.92 (t, C-16), 32.92 (t, C-21), 34.26 (t, C-7), 36.52 (t, C-22), 36.67 (t, C-30), 37.08 (s, C-10), 38.17 (d, C-13), 38.63 (t, C-1), 38.71 (s, C-4), 40.59 (s, C-8), 42.24 (s, C-14), 43.11 (d, C-19), 50.42 (d, C-9), 50.92 (d, C-18), 51.15 (q, COOMe), 55.26 (d, C-5), 56.44 (s, C-17), 78.82 (d, C-3), 113.26 (t, C-29), 151.20 (s, C-20), 176.22 (s, C-28).

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