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REACTION OF 3-ACETOXY-(2,3),(19β,28)-DIEPOXYOLEANANE WITH CYCLIC AND LINEAR AMINES

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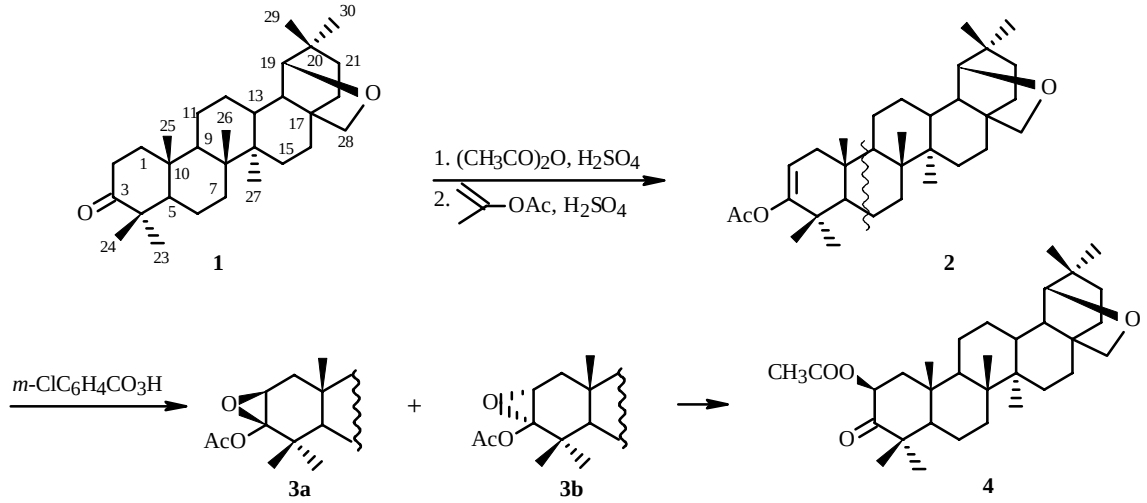
*A mixture of diastereomeric 3-acetoxy-(2,3),(19*β*,28)-diepoxyoleananes was prepared via reaction of 3-acetoxy-19*β*,28-epoxyolean-2-ene with m-chloroperbenzoic acid. Directed rearrangement of these formed 2*β*-acetoxy-19*β*,28-epoxyolean-3-one whereas heating of them in amines produced oleanane-type enamines.*

Key words: triterpenoids, oleanane, allobetulone, enamines, 2β-acetoxyketone.

Allobetulin and several of its derivatives belong to a group of pentacyclic triterpenoids that is promising for developing highly effective viricides and other medicinal preparations [1]. Allobetulin is highly active toward flu B virus [2]. 28-Oxoallobetulone prepared from it inhibits effectively flu A virus [3]. Among allobetulin derivatives, compounds with antifeedant [4] and biomarker [5] properties have been found.

In searches for compounds with antiviral and other activities, we synthesized new *N*-containing oleanane-type triterpenoids based on transformations of allobetulone (19β,28-epoxy-18α-olean-3-one).

Reaction of allobetulone (**1**) with acetic anhydride or isopropenylacetate in the presence of catalytic amounts of conc. H_2SO_4 [6] produced 3-acetoxy-19β,28-epoxyolean-2-ene (**2**), the PMR spectrum of which contained a singlet at 2.08 ppm and a doublet of doublets at 5.09 ppm corresponding to C-3 acetyl protons and the C-2 olefinic proton. Oxidation of **2** by *m*-chloroperbenzoic acid under standard conditions [7, 8] formed 3-acetoxy-(2,3),(19β,28)-diepoxyoleanane as a mixture of diastereomers **3a** and **3b**. This was confirmed by doubled signals in the PMR spectrum for the C-2 proton at 4.49 (**3b**) and 5.56 ppm (**3a**) and the acetyl protons at 2.03 (**3b**) and 2.09 ppm (**3a**). The integrated intensities of these signals established that the isomers **3a** and **3b** were synthesized in a 3:2 ratio.



1 **2** **3a** **3b** **4**

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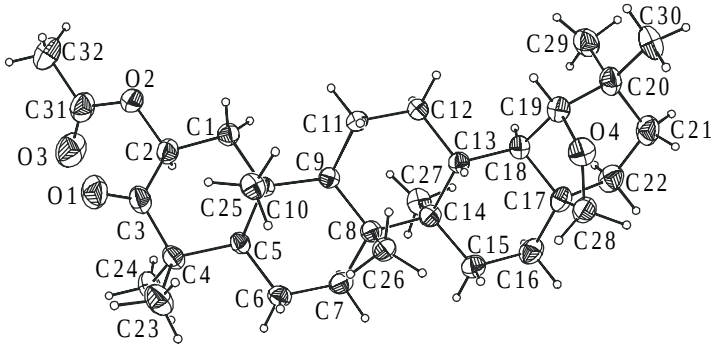
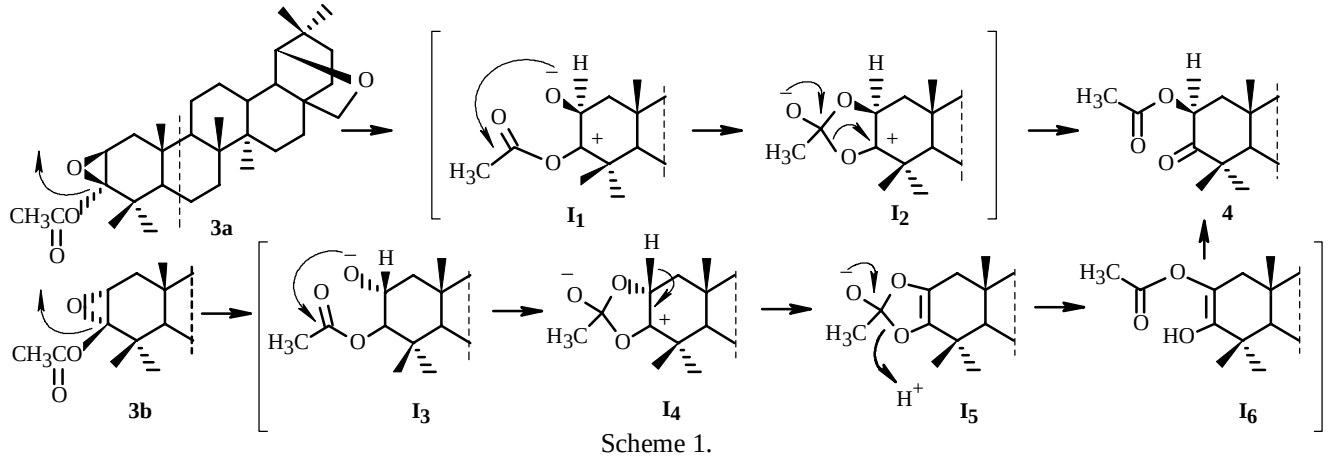


Fig. 1. Molecular structure of 2β-acetoxy-19β,28-epoxyolean-3-one (**4**).

New *N*-containing allobetulone derivatives were synthesized via reaction of a mixture of epoxides **3a** and **3b** with methyl esters of biogenic amino acids and cyclic and linear amines with heating in organic solvents. Regardless of the amine used and the solvent, the reaction proceeded under the given conditions to form a single rearrangement product of **3a** and **3b**, acetoxyketone **4**, the IR spectrum of which contained vibrational bands for carbonyl (1700 cm^{-1}) and ester (1740 cm^{-1}) groups. Fusion of **3a** and **3b** with amino-acid esters at 180-200°C also gave **4**.

The structure of **4** was proposed based on PMR and ^{13}C NMR data (Table 1), which were integrated using two-dimensional (2D) $^{1}H—^{1}H$ (COSY) and $^{13}C—^{1}H$ (TOCSY, ROESY, HSQC, HMBC) NMR. Thus, PMR and $^{1}H—^{1}H$ (COSY) NMR spectra identified the protons on C-28 (3.78 and 3.46 ppm) and C-19 (3.54 ppm). The $^{1}H—^{1}H$ (COSY) NMR spectrum identified the signals of the C-1 protons in ring A with chemical shifts (CS) 2.20 and 1.67 ppm by their correlation with the C-2 proton, which appeared as a weak-field doublet of doublets with CS 5.65 ppm (J_{aa} = 11.5 Hz, J_{ac} = 8.3 Hz). The nature of the splitting of the H-2 signal, which was geminal to the acetoxy, indicated that the acetoxy was oriented equatorially because the observed SSCC were typical of an axial proton of a cyclohexyl ring with the boat or slightly distorted boat conformation. The 2D $^{1}H—^{1}H$ (COSY) NMR spectrum of **4** contained cross peaks due to spin—spin coupling of protons through two or three σ-bonds and cross peaks due to through-space spin—spin couplings H(19)/H(21), H(19)/H(22), and H(28)/H(22). The 2D $^{13}C—^{1}H$ (HMBC) NMR spectrum showed cross peaks consistent with the proposed structure C(2)/H(1), C(3)/H(1), H(3)/H(23), C(3)/H(24), C(4)/H(2), C(9)/H(25), C(9)/H(26), C(15)/H(27), C(18)/H(28), C(28)/H(19), C(19)/H(28), C(19)/H(29), C(22)/H(28), C(29)/H(30), C(31)/H(32). The absolute configuration of 2β-acetoxy-19β,28-epoxyolean-3-one was confirmed by an x-ray structure analysis (Fig. 1).

Examples of kinetic separation of racemic epoxides of enol esters of monocyclic compounds with formation of enantiomerically enriched α-acyloxyketones in the presence of chiral Lewis acids have been reported [9]. In our instance, rearrangement of lupane derivatives **3a** and **3b** into the corresponding acetoxyketone **4** occured at elevated temperatures. This process typically was highly stereoselective. Because of steric hindrances from the geminal C-4 methyls, the final product 2β-acetoxyketone **4** was formed exclusively. The observed high (76%) chemical yield of **4** indicated that both diastereomeric epoxides **3a** and **3b** were involved in the rearrangement. If it is assumed that **4** formed from **3a** through intermediates I_1 and I_2, then transformation of the second diastereomer **3b** gave the analogous product **4**, most probably through enolization involving formation of the corresponding intermediates I_3-I_6.



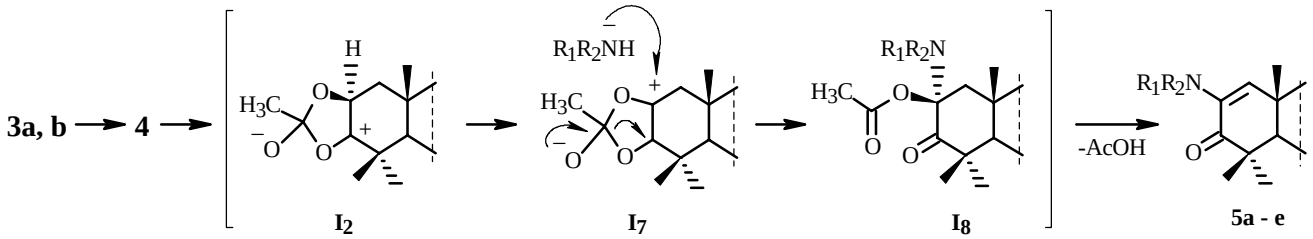
Scheme 1.

TABLE 1. PMR and ^{13}C NMR Data for **4** and **5b** (500 MHz, $CDCl_3$, δ, ppm, J/Hz)

C atom	**4**		**5**	
	δ_C	δ_H	δ_C	δ_H
1	47.24	1.67 (1H, dd, J_1 = 13.2, J_2 = 8.0); 2.20 (1H, br.t, J = 13.4)	134.73	5.99 (1H, s)
2	71.31	5.65 (1H, dd, J_1 = 11.5, J_2 = 8.3)	144.65	-
3	212.40	-	201.60	-
4	46.38	-	45.41	-
5	52.05	1.80 (1H, dd, J_1 = 9.9, J_2 = 3.1)	52.38	1.46-1.50 (1H)
6	19.86	1.42-1.50 (2H)	19.44	1.42-1.50 (2H)
7	32.42	1.39-1.51 (2H)	32.66	1.22-1.25 (1H); 1.54-1.56 (1H)
8	40.42	-	40.97	-
9	50.40	1.57 (1H, dd, J_1 = 13.2, J_2 = 2.5)	45.76	1.60 (1H, br.d, J = 13.0)
10	37.38	-	38.18	-
11	22.13	1.29-1.33 (1H); 1.38-1.43 (1H)	21.78	1.33-1.43 (1H); 1.65 (1H, dm, J = 15.0)
12	26.41	0.91-0.96 (1H); 1.64-1.70 (1H)	26.47	0.98-1.08 (1H); 1.74 (2H, dm, J = 14.0)
13	34.47	1.48-1.52 (1H)	34.42	1.51-1.55 (1H)
14	40.78	-	41.22	-
15	26.41	1.15 (1H, dm, J = 10.9); 1.56 (1H)	26.36	1.00-1.08 (1H); 1.53-1.62 (1H)
16	26.19	1.31-1.36 (1H); 1.42-1.50 (1H)	26.23	1.31-1.37 (1H); 1.42-1.51 (1H)
17	41.47	-	41.44	-
18	46.75	1.48-1.53 (1H)	46.72	1.48-1.54 (1H)
19	87.90	3.54 (1H, s)	87.82	3.55 (1H, s)
20	36.28	-	36.24	-
21	32.71	1.25 (1H, dd, J_1 = 13.9, J_2 = 6.1); 1.48-1.55 (1H)	33.07	1.39-1.52 (2H)
22	36.73	1.28-1.34 (1H); 1.41-1.46 (1H)	36.70	1.27-1.34 (1H); 1.37-1.46 (1H)
23	29.09	1.19 (3H, s)	29.05	1.16 (3H, s)
24	19.35	1.09 (3H, s)	20.83	1.06 (3H, s)
25	18.76	0.81 (3H, s)	20.99	0.98 (3H, s)
26	15.05	0.97 (3H, s)	15.91	1.03 (3H, s)
27	13.42	0.96 (3H, s)	13.35	0.96 (3H, s)
28	71.25	3.46 (1H, d, J = 7.8); 3.78 (1H, d, J = 7.8)	71.23	3.46 (1H, d, J = 8.0); 3.77 (1H, d, J = 8.0)
29	24.56	0.81 (3H, s)	24.51	0.80 (3H, s)
30	28.79	0.94 (3H, s)	28.76	0.94 (3H, s)
31	170.26	-	49.38	2.52-2.56 (1H, m); 2.86-2.89 (1H, m)
32	20.78	2.15 (3H, s)	66.68	3.75-3.84 (2H, m)
33	-	-	66.68	3.75-3.84 (2H, m)
34	-	-	49.38	2.52-2.56 (1H, m); 2.86-2.89 (1H, m)

When a cyclic or linear amine was used simultaneously as the reagent and solvent [8], heating caused the reaction with **3a** and **3b** to form enamines **5a-e** (Scheme 2). The PMR spectra of **5a-e** contained signals characteristic of protons of the *N*-containing substituent and the C-1 vinyl proton. The structures of the enamines were confirmed by 2D ^1H—^1H (COSY) and ^{13}C—^1H (HSQC, HMBC) NMR spectra using the morpholine derivative **5b** as an example (Table 1). Thus, according to the ^1H—^1H (COSY) PMR spectrum of **5b**, signals with CS 2.53-2.56, 2.86-2.89, and 3.75-3.84 ppm corresponded to protons of

the morpholine substituent. The singlet characteristic of the vinyl proton (CH-1) appeared at 5.98 ppm. Cross peaks were found in the 2D $^{13}C—^{1}H$ (HMBC) NMR spectrum for through-space spin—spin couplings C(5)/H(1), C(9)/H(1), C(13)/H(27), C(17)/H(19), C(18)/H(28), C(19)/H(29), C(19)/H(30), C(21)/H(19), C(22)/H(28), C(26)/H(24).



5a: R_1R_2 = -$(CH_2)_5$-; **5b:** R_1R_2 = -$(CH_2)_2O(CH_2)_2$-; **5c:** R_1 = $C_6H_5CH_2$-, R_2 = H; **5d:** R_1 = C_6H_{13}-, R_2 = H; **5e:** R_1 = C_6H_{11}-, R_2 = H

Scheme 2.

Assuming that the reaction of **3a** and **3b** with the more nucleophilic aliphatic amines also occurred through formation of rearrangement product **4**, we synthesized enamine **5b** starting from 2*β*-acetoxy-19*β*,28-epoxyolean-3-one (**4**). Boiling **4** in morpholine produced 2-morpholino-19*β*,28-epoxyolean-1-en-3-one (**5b**) in the same chemical yield as for the reaction with epoxides **3a** and **3b**. Apparently the synthesis of the *N*-containing derivatives **5a-e** (Scheme 2) from **3a** and **3b** occurred through formation from the rearrangement product **4** of intermediates I_2, I_7, and I_8 and final elimination of acetic acid to form the oleanane enamines **5a-e**.

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer in mineral oil; 2D $^{1}H—^{1}H$ (COSY) and $^{13}C—^{1}H$ (TOCSY, ROESY, HSQC, HMBC) NMR spectra of **4** and **5b** in $CDCl_3$, on a Bruker DRX-500 spectrometer (working frequency 500 MHz, internal standard HMDS). PMR spectra in $CDCl_3$ were recorded on a Varian Mercuryplus-300 spectrometer (working frequency 300 MHz, internal standard HMDS). Melting points were measured on PTP instrument. Specific optical rotations in $CHCl_3$ were determined on a Perkin—Elmer model 341 polarimeter at 589 nm. X-ray structure analysis of **4** was performed on a Syntex $P2_1$ automated four-circle diffractometer (Mo Kα-radiation, λ = 0.71073 Å, graphite monochromator, $\theta/2\theta$ scanning, $2\theta < 54°$). Elemental analyses (C, H, N) were carried out using a Carlo Erba Model 1106 analyzer. Elemental analyses agreed with those calculated.

Column chromatography was performed over silica gel (Merck 60-200 μm) at a 1:50 compound:sorbent ratio with individual eluents for each compound. TLC used Sorbfil (Russia) plates. Compounds were developed by spraying with phosphomolybdic acid (20%) in ethanol with subsequent heating at 100-120°C for 2-3 min. Anhydrous solvents were prepared by standard methods [10]. Allobetulone (**1**) was prepared by oxidation of allobetulin [11] using standard Jones reagent [12] in acetone.

3-Acetoxy-19*β*,28-epoxyolean-2-ene (2) was prepared by two methods. a) A solution of **1** (2 g, 4.5 mmol) in anhydrous CCl_4 (50 mL) was treated with acetic anhydride (2 mL) and conc. H_2SO_4 (2 drops). The mixture was stirred at room temperature with TLC monitoring. Solvent was distilled in vacuo. The solid was recrystallized from ethanol:chloroform, yield 1.4 g (70%).

b) A solution of **1** (2 g, 4.5 mmol) in anhydrous CCl_4 (50 mL) was treated with isopropenylacetate (4 mL) and conc. H_2SO_4 (2 drops). The mixture was stirred at room temperature with TLC monitoring. Solvent was distilled in vacuo. The solid was recrystalized from ethanol:chloroform, yield 1.5 g (73%), mp 262-264°C (ethanol:chloroform), R_f 0.56 (hexane:ethylacetate, 5:1), $[\alpha]_D^{22}$ +56.2° (*c* 1.5, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1750 ($OCOCH_3$).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.74, 0.87, 0.90 (3H each, s, CH_3), 0.85, 0.94 (6H each, s, $2CH_3$), 2.08 (3H, s, $OCOCH_3$), 3.39 and 3.73 (1H each, d, J = 7.8, CH_2-28), 3.48 (1H, s, CH-19), 5.09 (1H, dd, J_1 = 6.6, J_2 = 1.8, CH-2).

3-Acetoxy-(2,3),(19β,28)-diepoxyoleanane (3a and 3b). A solution of **2** (2.5 g, 5.2 mmol) in CH_2Cl_2 (30 mL) was stirred on a magnetic stirrer and treated with *m*-chloroperbenzoic acid (2.5 g, 14.5 mmol) in diethylether (20 mL). The mixture was stirred for 24 h at room temperature with TLC monitoring. When the reaction was finished the mixture was washed with aqueous NaOH (10%) to remove residual *m*-chloroperbenzoic acid. The organic layer was separated and dried over Na_2SO_4. The solvent was removed in vacuo. The product was purified by column chromatography with elution by hexane:ethylacetate:chloroform (10:1:2), yield 2 g (77%), mp 258-260°C (ethanol:chloroform), R_f 0.4 (hexane:ethylacetate:chloroform, 10:1:2), $[\alpha]_D^{18}$ +20.23° (*c* 1.7, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1750 ($OCOCH_3$).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.73, 0.83, 0.87, 0.97, 1.04 (5 × 3H, 5s, $5CH_3$), 1.07 (1.8H, s, CH_3 of isomer **3a**), 1.09 (1.2H, s, CH_3 of isomer **3b**), 1.13 (1.2H, s, CH_3 of isomer **3b**), 1.16 (1.8H, s, CH_3 of isomer **3a**), 2.03 (1.2H, s, $OCOCH_3$ of isomer **3b**), 2.09 (1.8H, s, $OCOCH_3$ of isomer **3a**), 2.26 (0.6H, dd, J_1 = 12.2, J_2 = 6.0, CH-1 of isomer **3a**), 2.46 (0.4H, dd, J_1 = 12.5, J_2 = 6.6, CH-1 of isomer **3b**), 3.39 and 3.71 (2H, 2d, J = 7.8, CH_2-28), 3.47 (1H, s, CH-19), 4.49 (0.4H, dd, J_1 = 12.3, J_2 = 6.6, CH-2 of isomer **3b**), 5.56 (0.6H, dd, J_1 = 13.2, J_2 = 6.0, CH-2 of isomer **3a**).

2β-Acetoxy-19β,28-epoxyolean-3-one (4). A mixture of **3a** and **3b** (0.5 g, 1 mmol) and morpholine (0.1 mL, 1.15 mmol) in benzene (50 mL) was refluxed with TLC monitoring. Solvent was distilled in vacuo. The solid was recrystallized from ethanol:chloroform, yield 0.38 g (76%), mp 284-286°C (ethanol:chloroform), R_f 0.25 (hexane:ethylacetate, 5:1), $[\alpha]_D^{18}$ +60.8° (*c* 1, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1700 (C=O), 1740 ($COOCH_3$). Mass spectrum (EI, 70 eV, *m*/*z*, I_{rel}, %): 498 (53) $[M]^+$, 456 (47), 438 (25), 427 (100), 205 (53), 204 (33), 191 (48), 190 (22), 189 (33), 187 (41), 177 (44), 175 (30), 163 (31), 161 (28), 150 (20), 149 (70), 147 (30), 137 (29), 135 (55), 133 (35), 123 (34), 122 (21), 121 (66), 119 (41), 109 (58), 108 (23), 107 (64), 105 (34), 95 (84), 93 (46), 83 (30), 82 (28), 81 (81), 79 (26), 69 (91), 55 (57).

Table 1 gives the PMR and ^{13}C NMR spectral data for **4**.

General Method for Preparing C-2-Substituted 19β,28-Epoxyolean-1-en-3-ones (5a-e). Epoxide (**3a** and **3b**, 1 mmol) was added to an amine (30 mmol) and refluxed for 16-20 h with TLC monitoring. The mixture was diluted with water. The resulting precipitate was filtered off, dried, and purified by column chromatography with an individual eluent for each compound. The products were crystallized from hexane:ethylacetate (10:1).

2-Piperidino-19β,28-epoxyolean-1-en-3-one (5a). Yield 0.25 g (47%), mp 79-81°C, R_f 0.15 (chloroform:ethylacetate, 10:1), $[\alpha]_D^{18}$ +147.41° (*c* 1.3, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1680 (C=O).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.74, 0.88, 0.89, 0.90, 0.96, 0.98, 1.08 (7 × 3H, 7s, $7CH_3$), 2.39-2.47 (2H, m, piperidine), 2.68-2.75 (2H, m, piperidine), 3.39 and 3.72 (2H, 2d, J = 8.1, CH_2-28), 3.49 (1H, s, CH-19), 5.90 (1H, s, CH-1).

2-Morpholino-19β,28-epoxyolean-1-en-3-one (5b). $C_{37}H_{54}NO_3$, yield 0.35 g (62%), mp 197-199°C, R_f 0.15 (hexane:ethylacetate, 5:1), $[\alpha]_D^{18}$ +118.47° (*c* 2.1, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1685 (C=O).

Table 1 gives the PMR and ^{13}C NMR data for **5b**.

Synthesis of 2-Morpholino-19β,28-epoxyolean-1-en-3-one (5b) from Acetoxyketone 4. A mixture of **4** (0.1 g, 0.2 mmol) and morpholine (2.5 mL, 30 mmol) was refluxed for several hours with monitoring by TLC. The mixture was diluted with water. The resulting precipitate was filtered off, dried, and purified by column chromatography with elution by hexane:ethylacetate (5:1), yield 0.063 g (60%).

2-Benzylamino-19β,28-epoxyolean-1-en-3-one (5c). $C_{37}H_{54}NO_2$, yield 0.35 g (64%), mp 296-298°C, R_f 0.25 (chloroform:ethylacetate, 10:1), $[\alpha]_D^{18}$ +41.70° (*c* 1.5, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1680 (C=O), 3400 br (NH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.71, 0.85, 0.95 (3 × 3H, 3s, $3CH_3$), 0.80, 0.84 (2 × 6H, s, $4CH_3$), 3.38 and 3.71 (2H, 2d, J = 7.5, CH_2-28), 3.44 (1H, s, CH-19), 5.00 (2H, s, $\underline{CH_2}C_6H_5$), 6.91 (1H, d, J = 7.2, CH-1), 7.23-7.44 (5H, m, arom.).

2-*n*-Hexylamino-19β,28-epoxyolean-1-en-3-one (5d). Yield 0.35 g (66%), mp 130-132°C, R_f 0.6 (hexane:ethanol, 10:1), $[\alpha]_D^{18}$ +72.8° (*c* 1.0, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1680 (C=O), 3350 br (NH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.74, 0.87, 0.88, 0.97, 1.02, 1.05, 1.09 (7 × 3H, 7s, $7CH_3$), 2.63-2.79 (2H, m, $NH\underline{CH_2}C_5H_{11}$), 3.40 and 3.72 (2H, 2d, J = 8.1, CH_2-28), 3.49 (1H, s, CH-19), 3.88 (1H, br.s, NH), 5.65 (1H, s, CH-1).

2-Cyclohexylamino-19β,28-epoxyolean-1-en-3-one (5e). $C_{36}H_{58}NO_2$, yield 0.3 g (59%), mp 180-181°C, R_f 0.4 (hexane:ethanol, 10:1), $[\alpha]_D^{18}$ +53.1° (*c* 1.0, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1680 (C=O), 3400 br (NH).

PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.75, 0.87, 0.88, 0.97, 1.02, 1.04, 1.08 (7 × 3H, 7s, $7CH_3$), 2.74-2.88 (1H, m, $NH\underline{CH}C_5H_{10}$), 3.39 and 3.72 (2H, 2d, J = 8.1, CH_2-28), 3.50 (1H, s, CH-19), 3.88 (1H, br.s, NH), 5.69 (1H, s, CH-1).

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