Chemistry of Natural Compounds, Vol. 48, No. 1, March, 2012 [Russian original No. 1, January-February, 2012]

SYNTHESIS OF C_2 SYMMETRIC TRITERPENE bis-ENAMINONES

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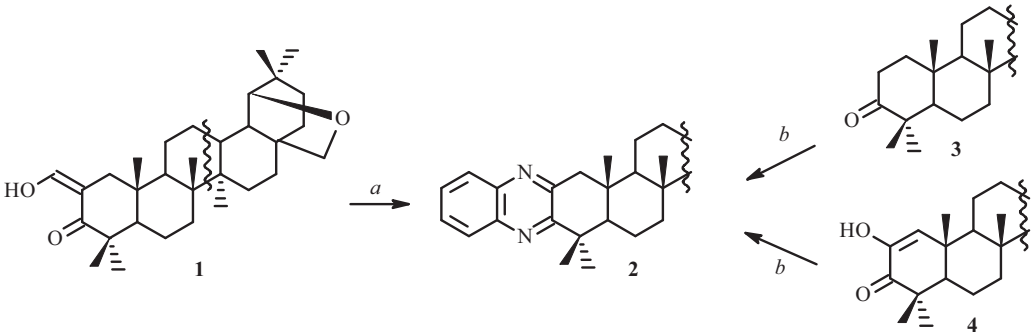
UDC 547.597:542.953.2

Mono- and dicondensed triterpene enaminones were prepared by reaction of oleanane- and lupane-type 2-hydroxymethylene derivatives with aliphatic and aromatic diamines in the presence of catalytic amounts of HOAc.

Keywords: triterpenoids, betulin, betulonic acid, allobetulone, diamines, enaminones, bis-enaminones, C_2 symmetric dimers.

The synthesis and biological properties of heteroatomic derivatives of betulin and betulinic acid have been the subject of many recent publications [1–5]. In particular, C-2 condensation reactions of triterpene 2-hydroxymethylene derivatives to form open and cyclic heteroatomic compounds that exhibit various biological activities were described [6–8]. We prepared previously *N*-containing triterpenoids with pronounced immunotropic activity [9–11] that were promising for modification by a stable C-2 enaminone [12, 13] via the reaction of lupane- and oleanane-type 2-hydroxymethylen-3-ones (**1** and **5**) with monoamines. An attempt to prepare symmetric condensation products of the triterpene 2-hydroxymethylene derivatives (**1** and **5**) with diamines under the published conditions [9] did not give the expected result. The resulting multi-component reaction mixture contained only traces of the mono- and dimeric products. That said, C_2 symmetric natural compounds and adducts with two triterpene moieties are interesting for medicinal chemistry [14–18].

The goal of the present work was to study the possibility of targeted synthesis of C_2 symmetric bis-enaminones based on 2-hydroxymethylen-19β,28-epoxy-18α-olean-3-one (**1**) and 2-hydroxymethylen-3-oxolup-20(29)-en-28-oic acid methyl ester (**5**).



a. $[1,2\text{-}(NH_2)_2C_6H_4)]_2Ni(NO_3)_2$, EtOH–MeOH; *b*. $1,2\text{-}(NH_2)_2C_6H_4$, S, morpholine

The possibility of using the template method for targeted synthesis of the *N*-containing triterpene dimers was examined. Chelate complexes of phenylenediamines with $Ni(NO_3)_2 \cdot 6H_2O$ [19] were tested for condensation with **1**. The desired product formed only if the chelate complex of *o*-phenylenediamine was used. According to spectral data, the obtained product was quinoxalino[2,3-*b*]-19β,28-epoxy-18α-oleanane (**2**), which was synthesized previously by reaction of *o*-phenylenediamine with allobetulone (**3**) [20] or allobetulone diosphenol (**4**) [21].

It was shown that condensation of *o*-phenylenediamine and oleanane diosphenol occurred most efficiently under acid-catalysis conditions [21]. In our instance, condensation of enolketones **1** and **5** with *o*-phenylenediamine formed monocondensed enaminones **6a** and **7a** in EtOH–PhH in the presence of catalytic amounts of AcOH regardless of the ratio of reagents (1:1 or 2:1).

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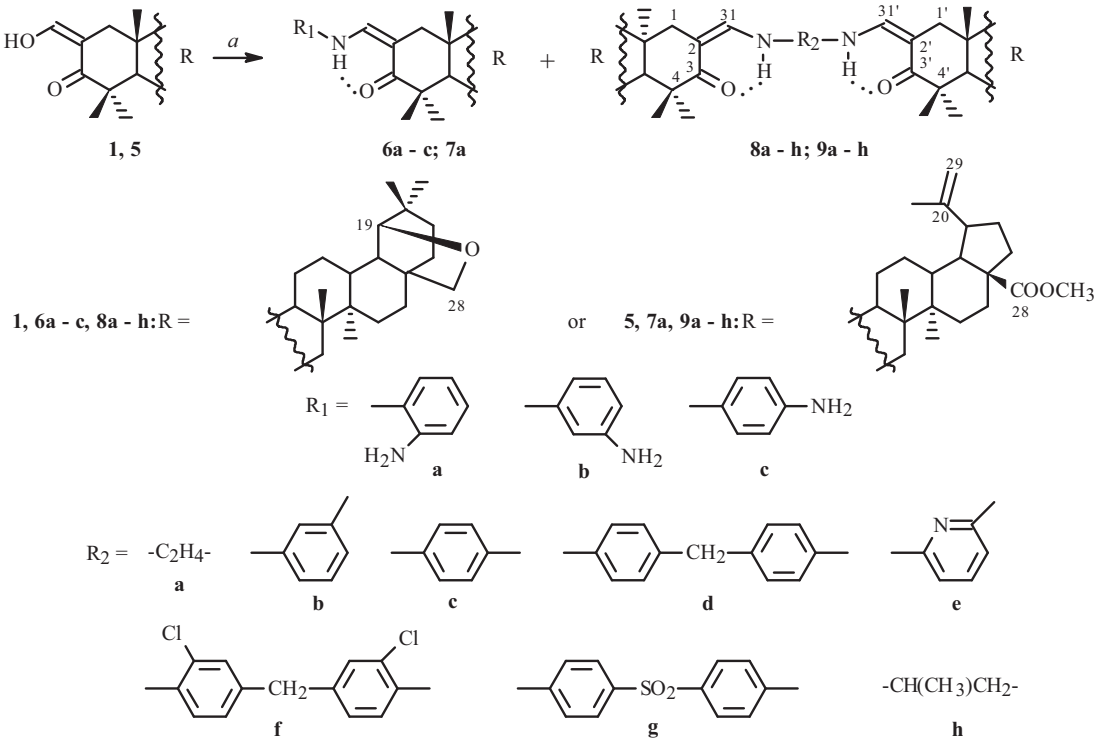

a. $R(NH_2)_2$, EtOH – C_6H_6, AcOH

The reaction of **1** or **5** with the other diamines was carried out with a 2:1 ratio of reagents for targeted synthesis of the symmetric *N*-containing triterpene dimers. Enolketones **1** and **5** underwent double condensation with the diamines to form C_2 symmetric bis-enaminones **8a**–**h** and **9a**–**h** under acid-catalysis conditions. The influence of steric factors, which prevented the formation of bis-enaminones in the case of *o*-phenylenediamine, was only partially extended to *m*- and *p*-phenylenediamines. These reacted with **1** to form both mono- (**6b** and **6c**) and dicondensed (**8b** and **8c**) adducts. Only diconjugates **9b** and **9c** were found in the reaction products of **5**. The structures of the compounds were confirmed by spectral data. Thus, PMR spectra of monocondensed enaminones **6a**–**c** and **7a** contained characteristic resonances of vinyl, amine, and C-1 methylene protons. PMR spectra of dimers **8a**–**h** and **9a**–**h** differed from those of monocondensation products by the lack of a resonance for a free amine and resonances that were relatively twice as strong for protons of the enaminone and triterpene framework.

In contrast with PMR spectra of the symmetric *bis*-enaminones, those of dicondensed **8h** and **9h** that were prepared using an asymmetric 1,2-diaminopropane linker showed amine protons and vinyl protons on C-31 and C-31′ with different chemical shifts for each triterpene moiety of the dimer. The observation in PMR spectra of bis-enaminones **8h** and **9h** of four sets of amine and vinyl proton resonances was explained by the formation of (*S*)- and (*R*)-diastereomeric species (1:1) at the C-2″ atom of the asymmetric linker (Fig. 1).

Thus, double condensation of C-2 hydroxymethylene-substituted triterpenoids and diamines to form C_2 symmetric bis-enaminones incorporating two pharmacophoric triterpene moieties was carried out under acid-catalysis conditions. The products were of interest as new biologically active compounds.

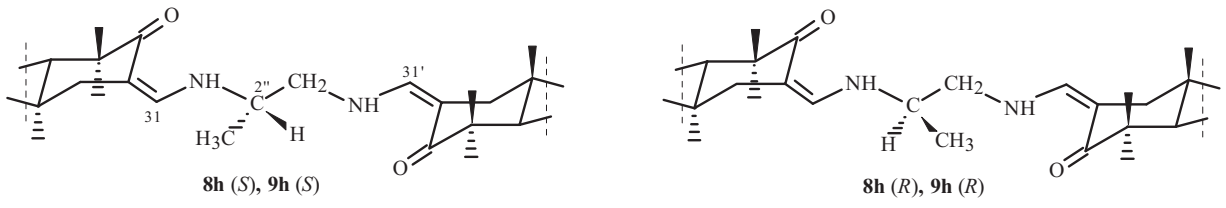

Fig. 1. (*S*)- and (*R*)-Diastereomeric forms at C-2″ of **8h** and **9h**.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded from $CDCl_3$ solutions with HMDS internal standard on a Mercury+ spectrometer (Varian, USA) at operating frequency 300 and 75.5 MHz. UV spectra of EtOH solutions were taken on a Model Lambda EZ201 spectrophotometer (Perkin–Elmer, USA). IR spectra were recorded in mineral oil mulls on a Specord M80 spectrophotometer (Germany). Melting points were measured on a PTP instrument (Russia). Specific optical rotation was recorded from $CHCl_3$ solutions at wavelength 589 nm on a Model 341 polarimeter (Perkin–Elmer, USA). Elemental analyses (C, H, N) were performed using a Leco CHNS-9321P elemental analyzer (Netherlands) and agreed with those calculated. Compounds were detected using TLC on Sorbfil plates (Russia) after spraying with phosphomolybdic acid solution (20%) in EtOH and subsequent heating at 100–120°C for 2–3 min. Column chromatography used silica gel (60-200 μm, Merck, Germany) with an ~1:50 compound:sorbent ratio. The eluent was selected individually for each compound. 2-Enolketones **1** and **5** were synthesized as before [22].

Quinoxalino[2,3-*b*]-19β,28-epoxyoleanane (2). The complex bis(*o*-phenylenediamine)nickel(II) dinitrate (1.1 mmol) [19] in MeOH (50 mL) was treated with 2-hydroxymethylen-19β,28-epoxyolean-3-one (0.5 mol) in MeOH (20 mL) and stirred with heating for 2–3 h. The solvent was distilled in vacuo (water aspirator). The solid was dissolved in EtOAc and treated with aqueous disodium EDTA (2.2 mmol). The organic layer was separated and dried over anhydrous $MgSO_4$. The solvent was distilled in vacuo (water aspirator). The solid was purified by column chromatography. Yield of **2** (0.31 g, 55%), $C_{36}H_{50}N_2O$, R_f 0.3 (hexane:EtOAc, 5:1), mp 263–267°C (EtOH) (lit. [20] mp 277–279; [21] 272–293), $[\alpha]_D^{22}$ +59° (*c* 0.5, $CHCl_3$) (lit. [20] $[\alpha]_D$ +66°).

IR spectrum (ν, cm^{-1}): 1720 (C–N=C), 1370 (C–O–C).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.82, 0.86, 0.94, 0.98, 1.06, 1.41, 1.42 (3H each, s, CH_3), 2.63 and 3.33 (1H each, d, J_{AB} = 16.5, AB-system, H_2-1), 3.46 and 3.79 (1H each, d, J = 8.1, AB-system, H_2-28), 3.56 (1H, s, H-19), 7.59–7.66 (2H, m, arom.), 7.91–8.02 (2H, m, arom.) [20].

Preparation Method for 6a–c, 7a, 8a–h, and 9a–h. A solution of **1** (1.07 mmol) in EtOH (5 mL) and benzene (3 mL) was treated in the presence of catalytic amounts of HOAc with diamine (0.53 mmol; for *o*-phenylenediamine, 0.53 or 1.07 mmol) and left at room temperature (for **8e**, **8g**, and **9e**, the reaction mixture was refluxed). The reaction was monitored by TLC. The solvent was distilled in vacuo (water aspirator). The solid was purified by column chromatography using $CHCl_3$:EtOAc (10:1).

2-*N*′-(1′,2′-Diaminophenyl)methylen-19β,28-epoxy-18α-olean-3-one (6a). Yellow crystals, 78% yield, $C_{37}H_{54}N_2O_2$, R_f 0.48 ($CHCl_3$:EtOAc, 10:1), mp 126–128°C (hexane:EtOAc:$CHCl_3$), $[\alpha]_D^{20}$ +69.6° (*c* 0.3, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3350 (NH), 3280 (NH_2), 1644 (C=O). UV spectrum (THF, λ_{max}, nm, ε): 246 (9806), 272 (4724), 310 (4311), 379 (15,435), 395 (14,282).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.80, 0.88, 1.03, 1.08, 1.15 (3H each, s, CH_3), 0.93 (6H, s, $2CH_3$), 2.11 and 2.40 (1H each, d, J_{AB} = 13.8, AB-system, H_2-1), 3.44 and 3.78 (1H each, d, J_{AB} = 7.8, AB-system, H_2-28), 3.54 (1H, s, H-19), 3.65 (2H, br.s, NH_2), 6.75 and 6.99 (2H, 2d, J = 7.8, arom.), 6.77 and 6.89 (2H, 2t, J = 7.8, arom.), 7.07 (1H, d, J = 11.6, H-31), 12.05 (1H, d, J = 11.1, NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.47, 15.33, 15.55, 20.21, 21.62, 22.30, 24.58, 26.32, 26.51, 26.55, 28.83, 29.12, 32.82, 33.17, 34.41, 36.32, 36.84, 36.99, 40.48, 40.84, 41.53, 44.35, 44.79, 46.90, 49.00, 53.50, 71.32 (C-28), 87.94 (C-19), 103.05 (C-2), 116.71, 117.16, 119.86 124.22, 129.15, 136.62, 145.56 (C-31), 204.95 (C-3).

2-*N*′-(1′,3′-Diaminophenyl)methylen-19β,28-epoxy-18α-olean-3-one (6b). Yellow crystals, 13% yield, $C_{37}H_{54}N_2O_2$, R_f 0.48 ($CHCl_3$:EtOAc, 10:1), mp 149–151°C (hexane:EtOAc:$CHCl_3$), $[\alpha]_D^{20}$ +94.4° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3356 (NH), 3220 (NH_2), 1644 (C=O). UV spectrum (THF, λ_{max}, nm, ε): 236 (10,832), 270 (4442).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.80, 0.87, 1.02, 1.06, 1.13 (3H each, s, CH_3), 0.93 (6H, s, $2CH_3$), 2.09 and 2.37 (1H each, d, J_{AB} = 14.1, AB-system, H_2-1), 3.44 and 3.78 (1H each, d, J_{AB} = 7.7, AB-system, H_2-28), 3.54 (1H, s, H-19), 3.63 (2H, s, NH_2), 6.30–6.32 (2H, m, arom.), 6.4 (1H, d, J = 8.1, arom.), 7.01–7.06 (2H, m, arom., H-31), 11.94 (1H, d, J = 12.0, NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.45, 15.30, 15.51, 20.16, 21.55, 22.30, 24.55, 26.25, 26.44, 26.49, 28.80, 29.02, 32.73, 33.08, 34.32, 36.27, 36.74, 36.92, 40.39, 40.77, 41.48, 44.34, 44.80, 46.80, 48.86, 53.30, 71.27 (C-28), 87.89 (C-19), 102.47 (C-2), 106.27, 109.88, 130.42 (2C), 141.74, 143.63 (C-31), 147.69 (2C), 205.22 (C-3).

2-*N*′-(1′,4′-Diaminophenyl)methylen-19β,28-epoxy-18α-olean-3-one (6c). Yellow crystals, 12% yield, $C_{37}H_{54}N_2O_2$, R_f 0.48 ($CHCl_3$:EtOAc, 10:1), mp 178–180°C (hexane:EtOAc:$CHCl_3$), $[\alpha]_D^{20}$ +10.3° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3352 (NH), 3116 (NH_2), 1636 (C=O).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.80, 0.87, 1.02, 1.06, 1.13 (3H each, s, CH_3), 0.93 (6H, s, $2CH_3$), 2.05 and 2.35 (1H each, d, J_{AB} = 14.3, AB-system, H_2-1), 3.44 and 3.78 (2H, 2d, J_{AB} = 7.5, AB-system, H_2-28), 3.55 (1H, s, H-19), 6.63 and 6.85 (2H each, d, J = 8.9, arom.), 7.02 (2H, d, J = 11.9, H-31), 12.16 (1H, d, J = 11.9, NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.43, 15.27, 15.47, 20.13, 21.55, 22.16, 24.52, 26.21, 26.40, 26.46, 28.77, 29.00, 30.83, 32.68, 33.04, 34.28, 36.23, 36.70, 36.86, 40.34, 40.71, 41.44, 44.03, 44.64, 46.75, 48.87, 53.23, 71.23 (C-28), 87.85 (C-19), 101.23 (C-2), 116.19 (2C), 117.60 (2C), 132.66, 142.35, 145.06 (C-31), 204.08 (C-3).

2-*N*′-(1′,2′-Diaminophenyl)methylen-3-oxolup-20(29)-en-28-oic Acid Methyl Ester (7a). Yellow crystals, 39% yield, $C_{38}H_{54}N_2O_3$, R_f 0.34 (hexane:EtOAc, 10:1), mp 165–167°C (hexane:EtOAc), $[\alpha]_D^{20}$ +39.7° (*c* 0.4, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3435, 3359 (NH_2), 3242 (NH), 1722 ($COOCH_3$), 1636 (C=O). UV spectrum (THF, λ_{max}, nm, ε): 246 (9806), 272 (4724), 310 (4311), 379 (15,435), 395 (14,282).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.85, 0.97, 0.99, 1.07, 1.13 (3H each, s, CH_3), 1.69 (3H, s, H_3-30), 2.06 and 2.35 (1H each, d, J_{AB} = 14.4, AB-system, H_2-1), 3.02 (1H, m, H-19), 3.63 (2H, br.s, NH_2), 3.67 (3H, s, $COOCH_3$), 4.61 and 4.75 (1H each, s, H_2-29), 6.79 and 7.00 (1H each, d, J = 7.8, arom.), 6.75 and 6.88 (1H each, t, J = 7.8, arom.), 7.03 (1H, d, J = 12.0, H-31), 12.04 (1H, d, J = 11.4, NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.67, 15.01, 15.69, 19.40, 20.20, 21.47, 22.31, 25.64, 29.04, 29.69, 30.60, 32.12, 33.50, 36.82, 36.95, 38.41, 40.46, 42.45, 44.26, 44.49, 46.93, 48.40, 49.42, 51.26, 53.18, 56.57, 103.05 (C-2), 109.58 (C-29), 116.57, 117.12, 119.86, 124.17, 129.05, 136.51, 145.49 (C-31), 150.55 (C-20), 176.64 (C-28), 204.99 (C-3).

1,2-Bis-(2-aminomethylen-3-oxo-19β,28-epoxy-18α-oleanyl)ethane (8a). Yellow crystals, 37% yield, $C_{64}H_{100}N_2O_4$, R_f 0.22 ($CHCl_3$:EtOAc, 10:1), mp 268–271°C (EtOH), $[\alpha]_D^{20}$ –5.3° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3252 (NH), 1644 (C=O).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.80, 0.81, 0.91, 0.93, 1.01, 1.02, 1.09 (6H each, s, $2CH_3$), 1.95 and 2.19 (4H, 2d, J_{AB} = 13.7, AB-system, $2H_2$-1), 3.22 and 3.29 (4H, 2t, J = 6.8, $NHC\underline{H}_2C\underline{H}_2NH$), 3.44 and 3.78 (4H, 2d, J_{AB} = 7.7, AB-system, $2H_2$-28), 3.53 (2H, s, 2H-19), 6.42 (2H, 2d, J = 12.0, 2H-31), 10.11-10.25 (2H, m, J = 11.6, 2NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.49, 15.29, 15.53, 20.15, 21.51, 22.13, 24.56, 26.27, 26.45, 28.80, 28.90, 32.75, 33.13, 34.33, 36.27, 36.76, 36.81, 40.37, 40.73, 40.74, 41.49, 43.83, 44.51, 46.81, 49.02, 49.86, 53.41 (2C each), 71.26 (2C-28), 87.88 (2C-19), 99.68 (2C-2), 154.31 (2C-31), 203.63 (2C-3).

1,3-Bis-(2-aminomethylen-3-oxo-19β,28-epoxy-18α-oleanyl)benzene (8b). Yellow crystals, 33% yield, $C_{68}H_{100}N_2O_4$, R_f 0.30 (hexane:EtOAc, 5:1), mp 258–260°C (hexane:EtOAc:$CHCl_3$), $[\alpha]_D^{20}$ +125.3° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3200 (NH), 1636 (C=O). UV spectrum (THF, λ_{max}, nm, ε): 234 (14,404), 265 (4727), 345 (33,686).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.81, 0.88, 1.03, 1.07, 1.14 (6H each, s, $2CH_3$), 0.94 (12H, s, $4CH_3$), 2.10 and 2.40 (4H, 2d, J_{AB} = 14.1, AB-system, $2H_2$-1), 3.45 and 3.78 (4H, 2d, J_{AB} = 8.0, AB-system, $2H_2$-28), 3.55 (2H, s, 2H-19), 6.60–6.63 (3H, m, arom.), 7.05 (2H, d, J = 12.0, 2H-31), 7.16 (1H, t, J = 6.8, arom.), 12.05 (2H, d, J = 12.0, 2NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.79, 15.34, 15.52, 20.16, 21.56, 22.36, 24.56, 26.27, 26.44, 26.49, 28.80, 29.02, 32.73, 33.06, 34.32, 36.28, 36.78, 36.94, 40.40, 40.77, 41.49, 44.49, 44.74, 46.80, 48.85, 53.30 (2C each), 71.28 (2C-28), 87.89 (2C-19), 102.64 (2C-2), 103.41, 110.35 (2C), 130.77, 142.02 (2C), 142.88 (2C-31), 205.94 (2C-3).

1,4-Bis-(2-aminomethylen-3-oxo-19β,28-epoxy-18α-oleanyl)benzene (8c). Yellow crystals, 23% yield, $C_{68}H_{100}N_2O_4$, R_f 0.16 (hexane:EtOAc, 5:1), mp >295°C (EtOH), $[\alpha]_D^{20}$ +128.6° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3340 (NH), 1634 (C=O). UV spectrum (THF, λ_{max}, nm, ε): 235 (7929), 250 (6636), 320 (8283), 380 (29,980).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.80, 0.87, 1.02, 1.07, 1.13 (6H each, s, $2CH_3$), 0.93 (12H, s, $4CH_3$), 2.09 and 2.37 (4H, 2d, J_{AB} = 14.1, AB-system, $2H_2$-1), 3.44 and 3.78 (4H, 2d, J_{AB} = 7.8, AB-system, $2H_2$-28), 3.54 (2H, s, 2H-19), 6.70 and 7.25 (4H, 2s, arom.), 7.05 (2H, d, J = 11.9, 2H-31), 12.16 (2H, d, J = 11.9, 2NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.46, 15.32, 15.52, 20.15, 21.55, 22.28, 24.55, 26.26, 26.44, 26.49, 28.80, 29.03, 32.72, 33.06, 34.31, 36.27, 36.74, 36.92, 40.38, 40.76, 41.48, 44.30, 44.70, 46.79, 48.86, 53.27 (2C each), 71.27 (2C-28), 87.89 (2C-19), 102.60 (2C-2), 117.18, 128.30, 136.15 (2C each), 143.63 (2C-31), 205.20 (2C-3).

4,4′-Bis-(2-aminomethylen-3-oxo-19β,28-epoxy-18α-oleanyl)diphenylmethane (8d). Yellow crystals, 28% yield, $C_{75}H_{106}N_2O_4$, R_f 0.55 (hexane:EtOAc, 5:1), mp 254–256°C (EtOH), $[\alpha]_D^{20}$ +97.8° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3470 (NH), 1642 (C=O). UV spectrum (THF, λ_{max}, nm, ε): 241 (13,680), 310 (9130).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.80, 0.87, 1.02, 1.06, 1.13 (6H each, s, $2CH_3$), 0.93 (12H, s, $4CH_3$), 2.09 and 2.37 (4H, 2d, J_{AB} = 14.1, AB-system, $2H_2$-1), 3.44 and 3.78 (4H, 2d, J_{AB} = 7.8, AB-system, $2H_2$-28), 3.54 (2H, s, 2H-19), 3.84 (2H, s, -C_6H_4-C<u>H</u>$_2$-C_6H_4-), 6.91–7.08 (10H, m, 2H-31, arom.), 12.07 (2H, d, J = 11.7, 2NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.45, 15.31, 15.51, 20.15, 21.55, 22.28, 24.55, 26.24, 26.43, 26.48, 28.80, 29.01, 32.71, 33.05, 34.30, 36.27, 36.73, 36.90, 40.37, 40.75, 41.47, 44.31, 44.74, 46.78, 48.85, 53.26 (2C each), 71.87 (2C-28), 87.89 (2C-19), 102.59 (2C-2), 116.02 (4C), 129.95 (4C), 135.71 (2C), 138.86 (2C), 143.75 (2C-31), 205.33 (2C-3).

1,5-Bis-(2-aminomethylen-3-oxo-19*β*,28-epoxy-18*α*-oleanyl)pyridine (8e). Yellow crystals, 28% yield, $C_{67}H_{99}N_3O_4$, R_f 0.26 (hexane:EtOAc, 5:1), mp 264–266°C (hexane:EtOAc:$CHCl_3$), $[\alpha]_D^{20}$ +181.2° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3370 (NH), 1642 (C=O). UV spectrum (THF, λ_{max}, nm, ε): 233 (8424), 269 (4313), 310 (13,131), 349 (21,556), 380 (26,879).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.78, 0.88, 0.92, 0.95, 1.03, 1.08, 1.14 (6H each, s, $2CH_3$), 2.13 and 2.52 (4H, 2d, J_{AB} = 14.1, AB-system, $2H_2$-1), 3.45 and 3.78 (4H, 2d, J_{AB} = 7.8, AB-system, $2H_2$-28), 3.54 (2H, s, 2H-19), 6.30 (2H, d, J = 7.8, arom.), 7.41 (1H, t, J = 7.8, arom.), 7.66 (2H, d, J = 11.3, 2H-31), 12.19 (2H, d, J = 11.3, 2NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.47, 15.31, 15.51, 20.17, 21.63, 22.43, 24.59, 26.24, 26.42, 26.51, 28.78, 29.08, 32.67, 33.00, 34.29, 36.25, 36.71, 36.96, 40.39, 40.76, 41.46, 44.68, 44.76, 46.78, 48.74, 53.27 (2C each), 71.28 (2C-28), 87.90 (2C-19), 104.75, 104.39 (2C-2), 140.01 (2C), 140.76 (2C), 151.40 (2C-31), 207.13 (2C-3).

4,4′-Bis-(2-aminomethylen-3-oxo-19*β*,28-epoxy-18*α*-oleanyl)-3,3′-dichlorodiphenylmethane (8f). Yellow crystals, 23% yield, $C_{75}H_{100}Cl_2N_2O_4$, R_f 0.14 (hexane:EtOAc, 5:1), mp 210–211°C (hexane:EtOAc:$CHCl_3$), $[\alpha]_D^{20}$ +74.4° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3570 (NH), 1644 (C=O). UV spectrum (THF, λ_{max}, nm, ε): 242 (14,553), 314 (10,787).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.80, 0.87, 1.02, 1.09, 1.15 (6H each, s, $2CH_3$), 0.93 (12H, s, $4CH_3$), 2.12 and 2.42 (4H, 2d, J_{AB} = 13.8, AB-system, $2H_2$-1), 3.44 and 3.78 (4H, 2d, J_{AB} = 8.6, AB-system, $2H_2$-28), 3.54 (2H, s, 2H-19), 6.98 and 7.07 (4H, 2d, J = 8.4, arom.), 7.04 (2H, d, J = 11.7, 2H-31), 7.13 and 7.14 (4H, 2s, arom.), 12.20 (2H, d, J = 11.7, 2NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.46, 15.36, 15.51, 20.14, 21.56, 22.41, 24.56, 26.24, 26.43, 26.48, 28.80, 29.00, 32.72, 33.05, 34.31, 36.27, 36.73, 36.94, 39.78, 40.39, 40.77, 41.48, 44.67, 44.96, 46.79, 48.82, 53.44 (2C each), 71.28 (2C-28), 87.89 (2C-19), 104.69 (2C-2), 113.84 (2C), 122.24 (2C), 128.11 (2C), 130.18 (2C), 135.13 (2C), 136.21 (2C), 141.15 (2C-31), 206.14 (2C-3).

4,4′-Bis-(2-aminomethylen-3-oxo-19*β*,28-epoxy-18*α*-oleanyl)diphenylsulfone (8g). Yellow crystals, 24% yield, $C_{74}H_{104}N_2O_4S$, R_f 0.48 (hexane:EtOAc, 7:3), mp 261–263°C ($CHCl_3$:EtOAc), $[\alpha]_D^{20}$ +88° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3470 (NH), 1642 (C=O), 1148 (SO_2), 1100.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.80, 0.85, 1.01, 1.06, 1.12 (6H each, s, $2CH_3$), 0.93 (12H, s, $4CH_3$), 2.10 and 2.42 (4H, 2d, J_{AB} = 14.3, AB-system, $2H_2$-1), 3.44 and 3.77 (4H, 2d, J_{AB} = 7.8, AB-system, $2H_2$-28), 3.54 (2H, s, 2H-19), 6.70–7.05 (6H, m, 2H-31, arom.), 7.79 (4H, d, J = 9.3, arom.), 12.05 (2H, d, J = 11.1, 2NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.41, 14.07, 15.33, 15.46, 20.07, 22.42, 22.59, 24.52, 26.19, 26.39 28.77, 28.95, 31.53, 32.66, 34.25, 36.23, 36.68, 36.88, 40.34, 40.73, 41.43, 44.70, 44.77, 46.73, 48.70, 53.18 (2C each), 71.21 (2C-28), 87.85 (2C-19), 105.79 (2C-2), 115.31 (4C), 129.40 (4C), 134.73 (2C), 140.70 (2C), 144.66 (2C-31), 207.37 (2C-3).

1,2-Bis-(2-aminomethylen-3-oxo-19*β*,28-epoxy-18*α*-oleanyl)-1-methylethane (8h). White crystals, 35% yield, $C_{65}H_{102}N_2O_4$, R_f 0.36 ($CHCl_3$:EtOAc, 10:1), mp 264–266°C (EtOH), $[\alpha]_D^{20}$ –5.8° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3312 (NH), 1646 (C=O).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.80, 0.82, 1.08, 1.11 (3H each, s, CH_3), 0.81, 0.91 (6H each, s, $2CH_3$), 0.93, 1.01 (18H, 2s, $6CH_3$), 1.02 (3H, d, J = 6.6, CH_3), 1.64 and 1.94 (4H, 2d, J_{AB} = 13.5, AB-system, $2H_2$-1), 2.85–2.95 [1H, m, $NHCH_2C\underline{H}(CH_3)NH$], 3.08–3.33 [2H, m, $NHC\underline{H}_2CH(CH_3)NH$], 3.44 and 3.78 (4H, 2d, J_{AB} = 7.8, AB-system $2H_2$-28), 3.53 (2H, s, 2H-19), 6.34, 6.41, 6.43, 6.53 (2H, 4d, J = 12.1, 2H-31), 9.97–10.04 and 10.16–10.36 (2H, 2m, 2NH).

1,2-Bis-[2-aminomethylen-28-methoxy-3,28-dioxolup-20(29)-enyl]ethane (9a). White crystals, 57% yield, $C_{66}H_{100}N_2O_6$, R_f 0.54 ($CHCl_3$:MeOH, 20:1), mp 183–185°C (hexane:EtOAc:$CHCl_3$), $[\alpha]_D^{20}$ +10.2° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3340 (NH), 1726 ($COOCH_3$), 1642 (C=O).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.79, 0.96, 0.99, 1.01, 1.08 (6H each, s, $2CH_3$), 1.68 (6H, s, $2H_3$-30), 1.92 and 2.14 (4H, 2d, J_{AB} = 14.1, AB-system, $2H_2$-1), 2.95–3.04 (2H, m, 2H-19), 3.19–.31 (4H, m, $NHC\underline{H}_2C\underline{H}_2NH$), 3.66 (6H, s, $2COOCH_3$), 4.61 and 4.74 (4H, 2s, $2H_2$-29), 6.38 (2H, d, J = 9.9, 2H-31), 10.19 (2H, br.s, 2NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.69, 14.94, 15.68, 19.42, 20.16, 21.40, 22.11, 25.58, 28.84, 29.68, 30.60, 32.12, 33.53, 36.67, 36.92, 38.40, 40.40, 42.39, 43.75, 44.29, 46.89, 48.46, 49.40, 49.76, 51.24, 53.14, 56.56 (2C each), 99.68 (2C-2), 109.53 (2C-29), 150.50 (2C-20), 154.25 (2C-31), 176.62 (2C-28), 203.53 (2C-3).

1,3-Bis-[2-aminomethylen-28-methoxy-3,28-dioxolup-20(29)-enyl]benzene (9b). Light-yellow crystals, 29% yield, $C_{70}H_{100}N_2O_6$, R_f 0.43 (petroleum ether:EtOAc, 5:1), mp 167–169°C (petroleum ether:EtOAc:$CHCl_3$), $[\alpha]_D^{20}$ +112.4° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3277 (NH), 1727 ($COOCH_3$), 1642 (C=O). UV spectrum (THF, λ_{max}, nm, ε): 234 (14,404), 265 (4727), 345 (33,686).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.84, 0.98, 1.00, 1.06, 1.13 (6H each, s, $2CH_3$), 1.7 (6H, s, $2H_3$-30), 2.07 and 2.37 (4H, 2d, J_{AB} = 14.0, AB-system, $2H_2$-1), 2.99–3.05 (2H, m, 2H-19), 3.66 (6H, s, $2COOCH_3$), 4.62 and 4.76 (4H, 2s, $2H_2$-29), 6.58-6.62 (3H, m, arom.), 7.01 (2H, d, J = 12.0, 2H-31), 7.16 (1H, t, J = 7.8, arom.), 12.04 (2H, d, J = 12.0, 2NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.68, 15.02, 15.69, 19.40, 20.21, 21.49, 22.39, 25.63, 29.00, 29.68, 30.60, 32.12, 33.47, 36.85, 36.95, 38.41, 40.46, 42.46, 44.45, 46.94, 48.34, 49.43, 51.26, 53.13, 56.57 (2C each), 102.24, 103.42 (2C-2), 109.63 (2C-29), 110.52 (2C), 130.76, 141.99 (2C), 142.78 (2C-31), 150.51 (2C-2), 150.55 (2C-20), 176.63 (2C-28), 205.93 (2C-3).

1,4-Bis-[2-aminomethylen-28-methoxy-3,28-dioxolup-20(29)-enyl]benzene (9c). Yellow crystals, 33% yield, $C_{70}H_{100}N_2O_6$, R_f 0.40 (petroleum ether:EtOAc, 5:1), mp 100–102°C (hexane:EtOAc:$CHCl_3$), $[\alpha]_D^{20}$ +68.5° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3432 (NH), 1728 ($COOCH_3$), 1640 (C=O). UV spectrum (THF, λ_{max}, nm, ε): 235 (7929), 250 (6636), 320 (8283), 380 (28,980).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.84, 0.97, 0.99, 1.06, 1.12 (6H each, s, $2CH_3$), 1.70 (6H, s, $2H_3$-30), 2.05 and 2.33 (4H, 2d, J_{AB} = 13.8, AB-system, $2H_2$-1), 2.98–3.04 (2H, m, 2H-19), 3.67 (6H, s, $2COOCH_3$), 4.62 and 4.75 (4H, 2s, $2H_2$-29), 6.94 (4H, s, arom.), 6.99 (2H, d, J = 12.0, 2H-31), 12.14 (2H, d, J = 11.7, 2NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.66, 14.99, 15.67, 19.39, 20.19, 21.45, 22.92, 25.62, 29.00, 29.67, 30.60, 32.10, 33.46, 36.81, 36.92, 38.39, 40.44, 42.43, 44.25, 44.50, 46.92, 48.35, 49.40, 51.25, 53.09, 56.56 (2C each), 102.61 (2C-2), 109.55 (2C-29), 117.16 (4C), 136.11 (2C), 143.60 (2C-31), 150.54 (2C-20), 176.62 (2C-28), 205.20 (2C-3).

4,4′-Bis-[2-aminomethylen-28-methoxy-3,28-dioxolup-20(29)-enyl]diphenylmethane (9d). Yellow crystals, 40% yield, $C_{77}H_{106}N_2O_6$, R_f 0.49 (hexane:EtOAc, 5:1), mp 155–157°C (hexane:EtOAc:$CHCl_3$), $[\alpha]_D^{20}$ +75.4° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 1727 ($COOCH_3$), 1640 (C=O). UV spectrum (THF, λ_{max}, nm, ε): 241 (13,680), 310 (9130).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.84, 0.97, 0.99, 1.06, 1.12 (6H each, s, $2CH_3$), 1.69 (6H, s, $2H_3$-30), 2.05 and 2.33 (4H, 2d, J_{AB} = 13.8, AB-system, $2H_2$-1), 2.98–3.04 (2H, m, 2H-19), 3.66 (6H, s, $2COOCH_3$), 3.85 (2H, s, -C_6H_4-C$\underline{H}_2$-C_6H_4-), 4.61 and 4.75 (4H, 2s, $2H_2$-29), 6.91 and 7.07 (8H, 2d, J = 8.4, arom.), 7.02 (2H, d, J = 14.1, 2H-31, arom.), 12.10 (2H, d, J = 11.7, 2NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.66, 14.99, 15.67, 19.38, 20.19, 21.47, 22.31, 25.61, 29.00, 29.68, 30.57, 32.10, 33.47, 36.80, 36.94, 38.38, 40.43, 42.43, 44.28, 44.55, 46.91, 48.34, 49.39, 51.27, 53.08, 56.55, 78.94 (2C each), 102.60 (2C-2), 109.58 (2C-29), 115.99 (4C), 129.94 (4C), 135.70 (2C), 138.83 (2C), 143.69 (2C-31), 150.55 (2C-20), 176.62 (2C-28), 205.32 (2C-3).

1,5-Bis-[2-aminomethylen-28-methoxy-3,28-dioxolup-20(29)-enyl]pyridine (9e). Yellow crystals, 57% yield, $C_{69}H_{99}N_3O_6$, R_f 0.51 (hexane:EtOAc, 5:1), mp 190–192°C (petroleum ether:EtOAc:$CHCl_3$), $[\alpha]_D^{20}$ +172.2° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3155 (NH), 1727 ($COOCH_3$), 1638 (C=O). UV spectrum (THF, λ_{max}, nm, ε): 233 (8424), 269 (4313), 310 (13,131), 349 (21,556), 380 (26,879).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.97, 0.99, 1.06, 1.12, 1.24 (6H each, s, $2CH_3$), 1.71 (6H, s, $2H_3$-30), 2.06 and 2.43 (4H, 2d, J_{AB} = 13.8, AB-system, $2H_2$-1), 2.96–3.08 (2H, m, 2H-19), 3.68 (6H, s, $2COOCH_3$), 4.64 and 4.77 (4H, 2s, $2H_2$-29), 6.30 (2H, d, J = 8.1, arom.), 7.40 (1H, t, J = 7.8, arom.), 7.72–7.50 (2H, m, 2H-31), 12.28 (2H, d, J = 10.2, 2NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.65, 14.93, 15.69, 19.34, 20.25, 21.45, 22.48, 25.59, 29.09, 29.68, 30.55, 32.13, 33.40, 36.90, 38.36, 40.47, 42.54, 44.41, 44.66, 47.00, 48.18, 49.40, 51.28, 53.11, 56.56, 65.54 (2C each), 104.91 (2C-2), 109.71 (2C-29), 130.88 (2C), 139.93, 140.76 (2C-31), 150.51 (2C-20), 151.50 (2C), 176.65 (2C-28), 207.15 (2C).

4,4′-Bis-[2-aminomethylen-28-methoxy-3,28-dioxolup-20(29)-enyl]-3,3′-dichlorodiphenylmethane (9f). Yellow crystals, 23% yield, $C_{77}H_{104}Cl_2N_2O_6$, R_f 0.20 (hexane:EtOAc, 5:1), mp 154–156°C (hexane:EtOAc), $[\alpha]_D^{20}$ +47.9° (*c* 0.3, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3471 (NH), 1728 ($COOCH_3$), 1639 (C=O). UV spectrum (THF, λ_{max}, nm, ε): 242 (14,553), 314 (10,787).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.84, 0.97, 0.99, 1.08, 1.14 (6H each, s, $2CH_3$), 1.70 (6H, s, $2H_3$-30), 2.07 and 2.38 (4H, 2d, J_{AB} = 14.1, AB-system, $2H_2$-1), 2.98–3.04 (2H, m, 2H-19), 3.67 (6H, s, $2COOCH_3$), 3.74 (2H, s, -C_6H_4-C$\underline{H}_2$-C_6H_4-), 4.61 and 4.74 (4H, 2s, $2H_2$-29), 6.68 and 6.84 (4H, 2d, J = 8.1, arom.), 6.98–7.14 (4H, m, 2H-31, arom.), 12.18 (2H, d, J = 12.0, 2NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.67, 15.03, 15.68, 19.39, 20.18, 21.48, 22.43, 25.62, 28.98, 29.68, 30.59, 32.10, 33.47, 36.83, 36.94, 38.39, 39.67, 40.45, 42.45, 44.61, 44.76, 46.92, 48.32, 49.41, 51.27, 53.27, 56.56 (2C each), 104.55 (2C-2), 109.57 (2C-29), 113.77, 122.24, 128.08, 130.10, 135.95, 141.19 (2C each), 141.26 (2C-31), 150.56 (2C-20), 176.63 (2C-28), 206.07 (2C-3).

4,4′-Bis-[2-aminomethylen-28-methoxy-3,28-dioxolup-20(29)-enyl]diphenylsulfone (9g). Yellow crystals, 66% yield, $C_{74}H_{104}N_2O_8S$, R_f 0.49 (petroleum ether:EtOAc, 1:1), mp 198–200°C (hexane:EtOAc:$CHCl_3$), $[\alpha]_D^{20}$ +65° (*c* 0.5, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3471 (NH), 1725 ($COOCH_3$), 1642 (C=O), 1148 (SO_2), 1104.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.82, 0.97, 0.98, 1.05, 1.11 (6H each, s, $2CH_3$), 1.69 (6H, s, $2H_3$-30), 2.06 and 2.38 (4H, 2d, J_{AB} = 14.4, AB-system, $2H_2$-1), 2.96–3.04 (2H, m, 2H-19), 3.67 (6H, s, $2COOCH_3$), 4.61 and 4.74 (4H, 2s, $2H_2$-29), 6.63, 7.65, and 7.77 (6H, 3d, J = 9.0, arom.), 6.99 (4H, d, J = 9.0, 2H-31, arom.), 12.02 (2H, d, J = 11.7, 2NH).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.64, 15.03, 15.67, 19.40, 20.15, 21.50, 22.45, 25.60, 28.96, 29.67, 30.61, 32.10, 33.42, 36.83, 36.92, 38.38, 40.47, 42.47, 44.58, 44.75, 46.93, 48.28, 49.42, 51.25, 53.11, 56.57 (2C each), 105.59 (2C-2), 109.58 (2C-29), 114.17, 115.28, 129.16, 129.52, 135.78 (2C each), 140.95 (2C-31), 144.32 (2C), 150.51 (2C-20), 176.62 (2C-28), 207.27 (2C-3).

1,2-Bis-[2-aminomethylen-28-methoxy-3,28-dioxolup-20(29)-enyl]-1-methylethane (9h). White crystals, 47% yield, $C_{67}H_{102}N_2O_6$, R_f 0.35 ($CHCl_3$:EtOAc, 10:1), mp 167–169°C ($CHCl_3$:EtOAc), $[\alpha]_D^{20}$ +13.5° (*c* 0.2, $CHCl_3$).

IR spectrum (ν, cm^{-1}): 3372 (NH), 1728 ($COOCH_3$), 1641 (C=O).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.75 and 0.81 (3H, s, CH_3), 0.79, 1.01 (3H each, s, CH_3), 0.95, 0.96, 0.97, 1.08 (24H, 4s, $8CH_3$), 1.00 (3H, d, J = 6.0, CH_3), 1.69 (6H, s, $2H_3$-30), 1.87 and 2.15 (4H, 2d, J_{AB} = 14.1, AB-system, $2H_2$-1), 2.92–3.07 [3H, m, 2H-19, $NHCH_2C\underline{H}(CH_3)NH$], 3.15–3.34 [2H, m, $NHC\underline{H}_2CH(CH_3)NH$], 3.66 (6H, s, $2COOCH_3$), 4.60 and 4.74 (4H, 2s, $2H_2$-29), 6.38 (2H, br.s, 2H-31), 10.19 (2H, br.s, 2NH).

ACKNOWLEDGMENT

The work was supported by the Federal Targeted Program "Research and Development in Priority Areas for Development of the Russian Science and Technology Complex for 2007-2013" (State Contract No. 11.519.11.2033) and RFBR Grant No. 10-03-96044-r-_ural_a.

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