ISSN 1070-4280, Russian Journal of Organic Chemistry, 2011, Vol. 47, No. 4, pp. 589–601. © Pleiades Publishing, Ltd., 2011.
Original Russian Text © A.N. Antimonova, N.V. Uzenkova, N.I. Petrenko, M.M. Shakirov, E.E. Shul'ts, G.A. Tolstikov, 2011, published in Zhurnal Organicheskoi Khimii, 2011, Vol. 47, No. 4, pp. 586–596.

Synthetic Transformations of Higher Terpenoids: XXIV.* Synthesis of Cyanoethyl Derivatives of Lupane Triterpenoids and Their Transformation into 1,2,4-Oxadiazoles

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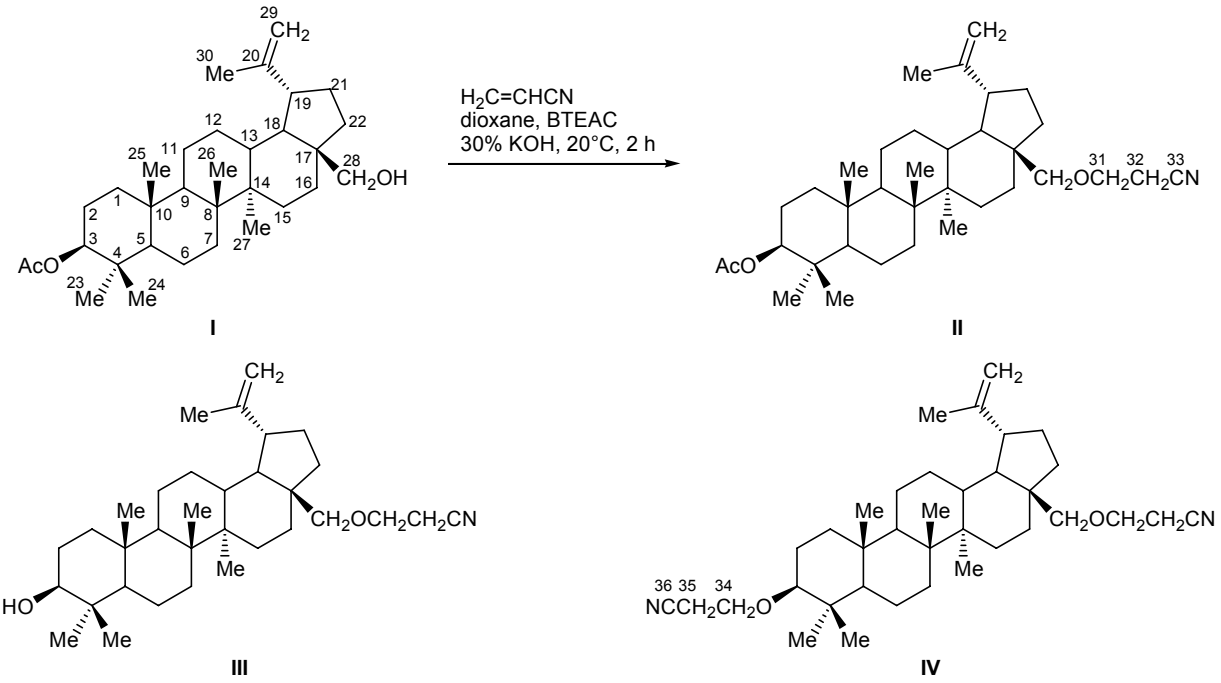
Received June 1, 2010

Abstract—Cyanoethylation of lupane triterpenoids was performed. Amide oximes of 3β-*O*-(2-cyanoethyl)-betulinic acid methyl ester and 3β-*O*-acetyl-28-*O*-(2-cyanoethyl)betulin and the corresponding *O*-[2-(1,2,4-oxadiazol-3-yl)ethyl] lupane derivatives were obtained.

DOI: 10.1134/S1070428011040208

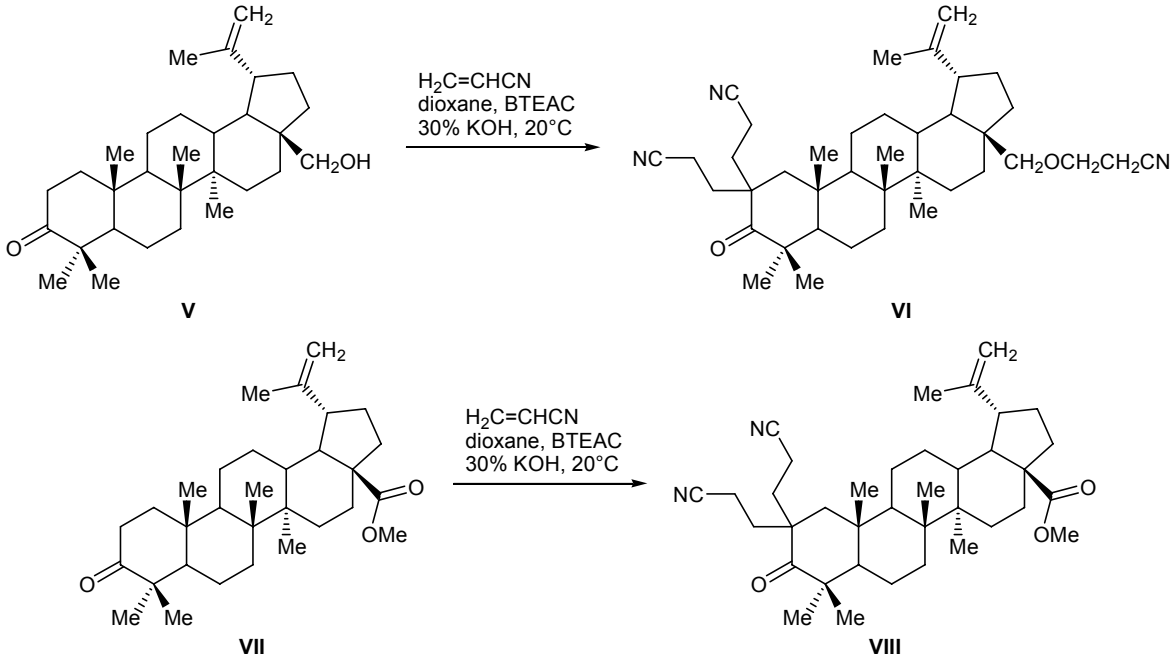
Pentacyclic triterpenoids of the lupane series attract researchers' attention as substrates for synthetic transformations due to their accessibility, as well as due to pharmacological importance of some semisynthetic derivatives which are often available via relatively simple modifications. In the past decade, particular emphasis was put on such pharmacological properties of lupane derivatives as antiviral (HIV-1) and antitumor activity [2]. While developing our studies on the transformations of plant metabolites produced by Sibe-

Scheme 1.



* For communication XXIII, see [1].

Scheme 2.

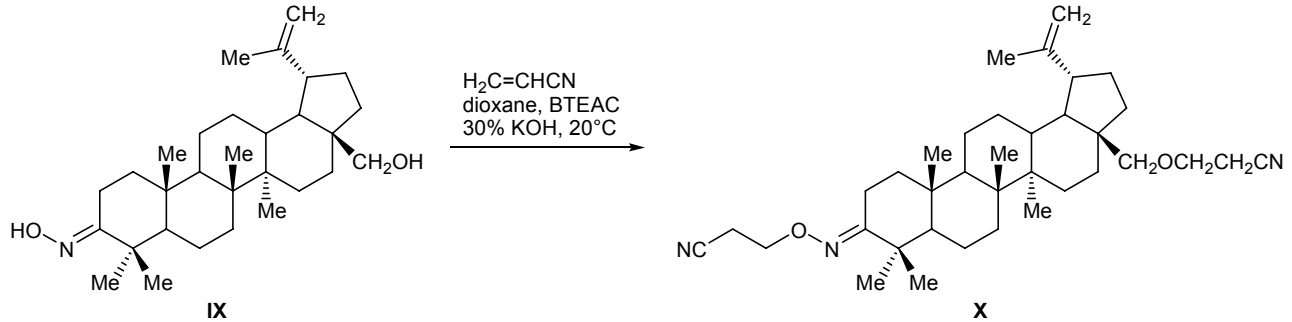


rian flora [3], we examined cyanoethylation of triterpenoids of the lupane series with a view to obtain homologous derivatives which can be used in the synthesis of polyamines, peptides, and various heterocycles. Cyanoethylation of 3β-*O*-acetylbetulin (**I**) having a primary hydroxy group on C^{28} with acrylonitrile smoothly afforded the corresponding cyanoethyl derivative **II** (Scheme 1). The reaction was carried out at room temperature in dioxane or methylene chloride in the presence of alkali and benzyl(triethyl)ammonium chloride (BTEAC). Addition of BTEAC to the reaction mixture made it possible to considerably shorten the reaction time (from 24 h [4] to 2–3 h) and improve the purity of the product. When the reaction was carried out in the absence of BTEAC, long reaction time (24 h) favored formation (though insignificant) of by-products **III** and **IV** as a result of hydrolysis of the acetate moiety.

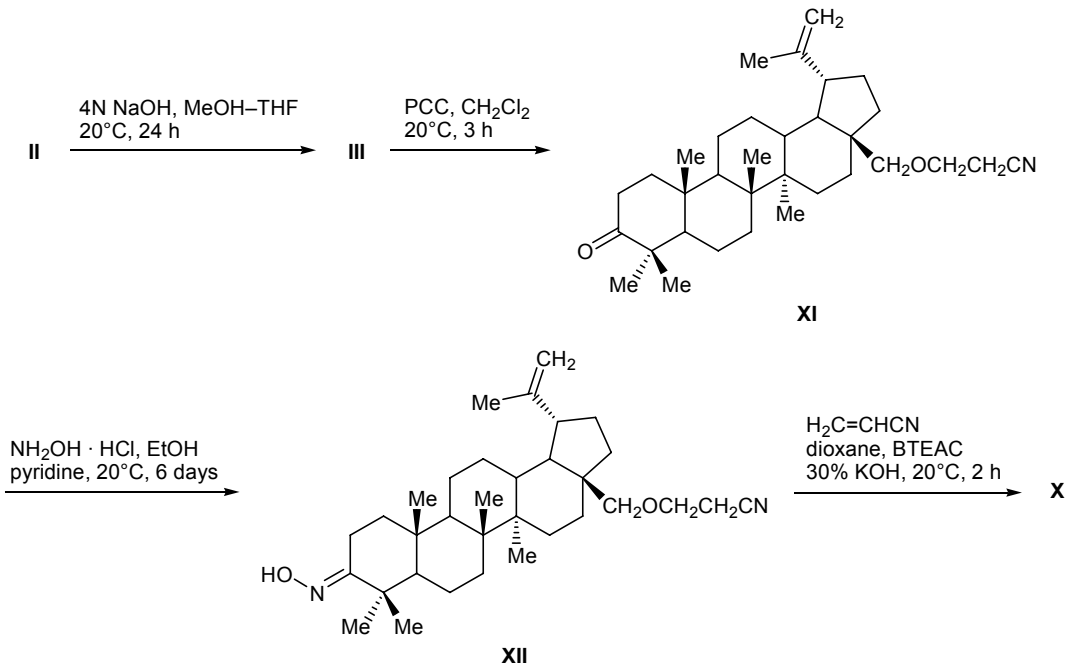
3-Oxobetulin (**V**) reacted with acrylonitrile under analogous conditions to give compound **VI** which was isolated as the only product in 84% yield (Scheme 2). In this case, cyanoethylation of the 28-OH group was accompanied by introduction of two cyanoethyl groups into the α-position with respect to the C^3=O group, which is consistent with published data [5]. In the reaction with betulonic acid methyl ester (**VII**), 2,2-bis-(cyanoethyl) derivative **VIII** was obtained in 60% yield. Compounds **VI** and **VIII** attract interest, taking into account that some 2-cyanolupane derivatives were found to exhibit high cytotoxic activity against a number of tumor cells [6].

The reaction of acrylonitrile with 3-oxobetulin oxime (**IX**) involved both alcoholic and oxime groups, and the product was di-*O*-(2-cyanoethyl) derivative **X** (yield 85%, Scheme 3).

Scheme 3.



Scheme 4.



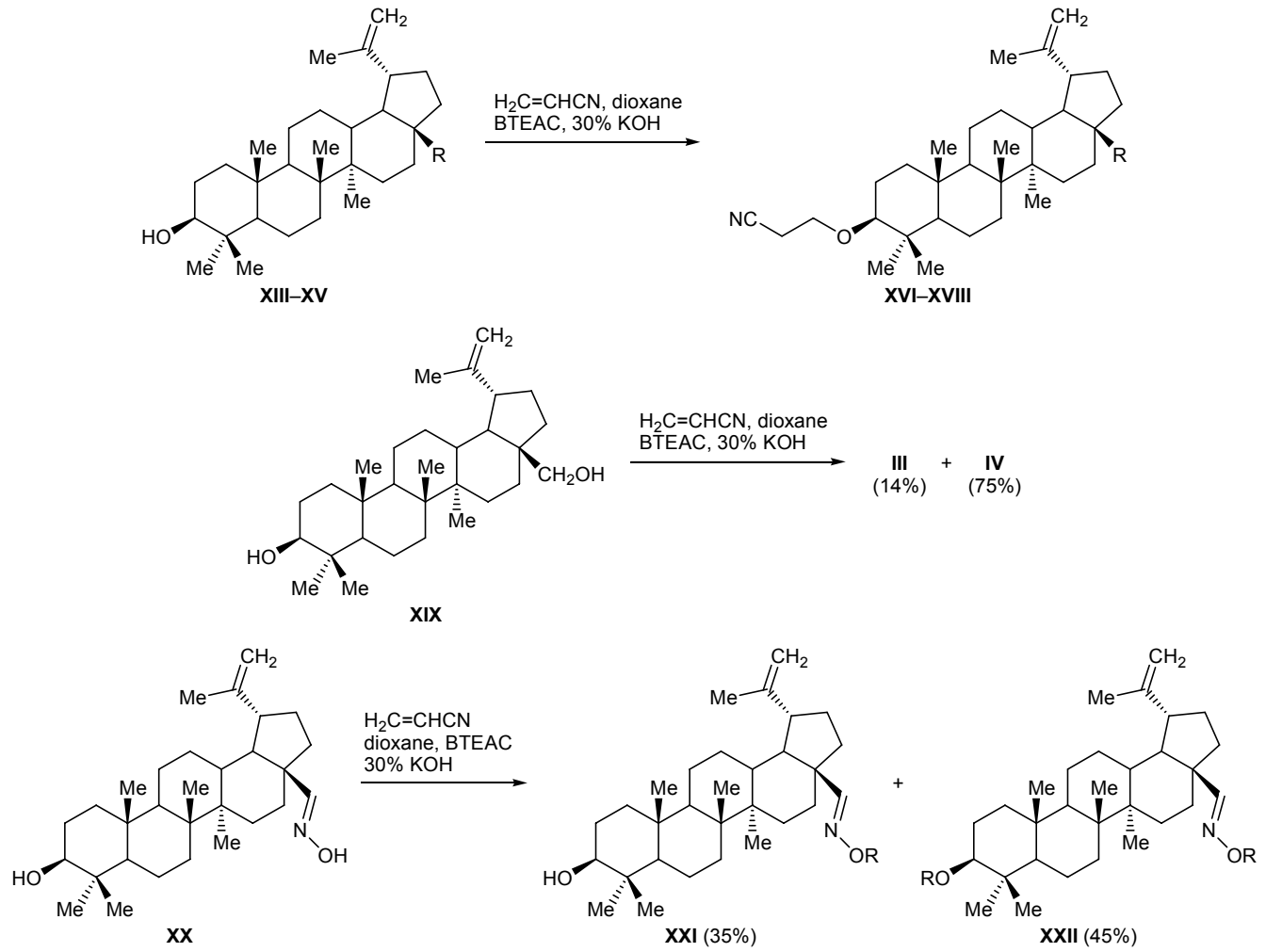
3-Oxo and 3-hydroxyimino lupane derivatives which cannot be obtained by direct cyanoethylation of the corresponding betulin derivatives **V** and **IX** were synthesized by chemical modification of 3-*O*-acetyl-28-*O*-(2-cyanoethyl)betulin (**II**) (Scheme 4). Alkaline hydrolysis of compound **II** by the action of 4 M NaOH in a mixture of methanol and tetrahydrofuran at room temperature smoothly afforded 96% of 3-hydroxy derivative **III** which was oxidized to 3-oxo derivative **XI** (yield 91%) with pyridinium chlorochromate (PCC) in methylene chloride. Ketone **XI** was treated with hydroxylamine hydrochloride in ethanol in the presence of pyridine at room temperature to obtain the corresponding oxime **XII** in almost quantitative yield. Oxime **XII** reacted with acrylonitrile in dioxane in the presence of alkali and BTEAC at room temperature to give 87% of **X**. The latter was identical to the product obtained by cyanoethylation of **IX** (Scheme 3).

Cyanoethylation of compounds having a secondary hydroxy group on C^3 (dioxane, 30% KOH, BTEAC, 20°C) always resulted in the formation of a mixture of products whose composition depended on the substituent on C^{28} (Scheme 5). In the reactions with compounds **XIII**–**XV**, cyanoethylation products **XVI**–**XVIII** were formed in 45, 53, and 57% yield, respectively; the conversion was not complete, and the initial compounds were present in the reaction mixtures. Cyanoethylation of betulin (**XIX**) and betulinaldehyde oxime (**XX**) gave mixtures of mono- and di-*O*-(2-cyanoethyl) derivatives **III**/**IV** and **XXI**/**XXII**. Longer reaction time, elevated temperature, or increased amount of acrylonitrile did not ensure complete conversion of the 3-OH group, which was consistent with our preliminary data on the cyanoethylation of betulin (**XIX**) [4]. The conversion of the secondary hydroxy group ranged from 45 to 75%, depending on the reaction conditions and structure of the initial compound.

Cyanoethylation of 28-*O*-acetylbetulin (**XXIII**) under standard conditions gave compound **XXIV** in 64% yield; in addition, compounds **III**, **IV**, and **XIX** were formed in 5, 9, and 22% yield, respectively (according to the GC–MS data), as a result of partial hydrolysis of the ester group and subsequent cyanoethylation. The yield of **XXIV** increased to 88% when the reaction was carried out in methylene chloride instead of dioxane (Scheme 6).

Successful synthesis of cyano derivatives of the lupane series both via cyanoethylation of appropriate triterpenoids and by chemical transformations of compounds already having a cyanoethyl group prompted us to perform their further modifications. We were interested in synthesizing heterocyclic lupane derivatives possessing an 1,2,4-oxadiazole substituent. Introduction of this structural fragment into molecules of triterpenoids seemed to be promising from the viewpoint of biological activity. It is known that compounds containing an 1,2,4-oxadiazole fragment exhibit antiphlogistic, antiviral, and other kinds of pharmacolog-

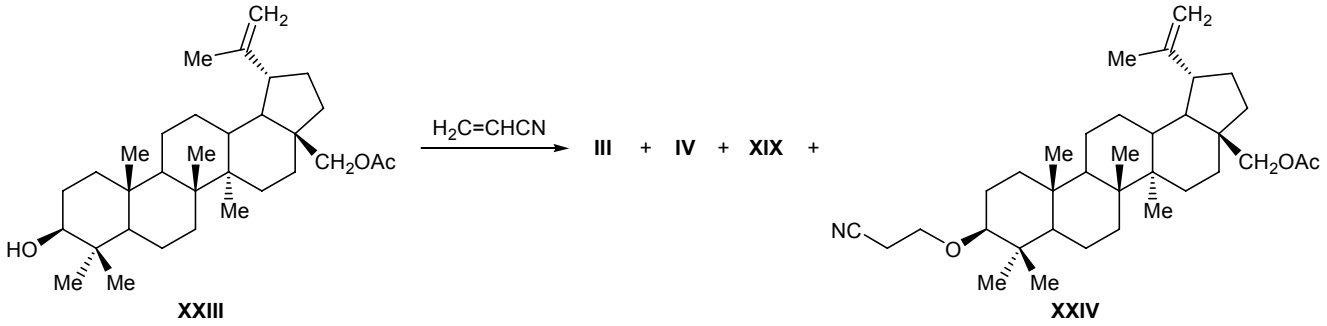
Scheme 5.



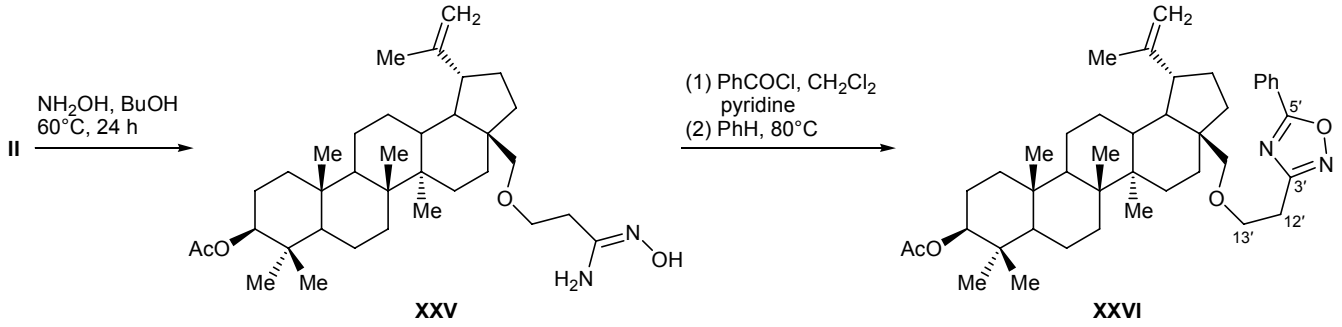
XIII, **XVI**, R = CHO; **XIV**, **XVII**, R = HOCO; **XV**, **XVIII**, R = MeOCO; **XXI**, **XXII**, R = $NCCH_2CH_2$.

ical activity [7]. The key precursors of 1,2,4-oxadiazoles are amide oximes which are generally prepared by reaction of nitriles with hydroxylamine hydrochloride in the presence of bases [8]. However, by treatment of lupane nitrile **II** with hydroxylamine hydrochloride under standard conditions we obtained only ~10% of the corresponding amide oxime. We succeeded in improving the yield of amide oxime **XXV** to 55% by carrying out the reaction of nitrile **II** with hydroxylamine as free base in butyl alcohol (instead of ethanol). The reaction of **XXV** with benzoyl chloride in the presence of pyridine, followed by

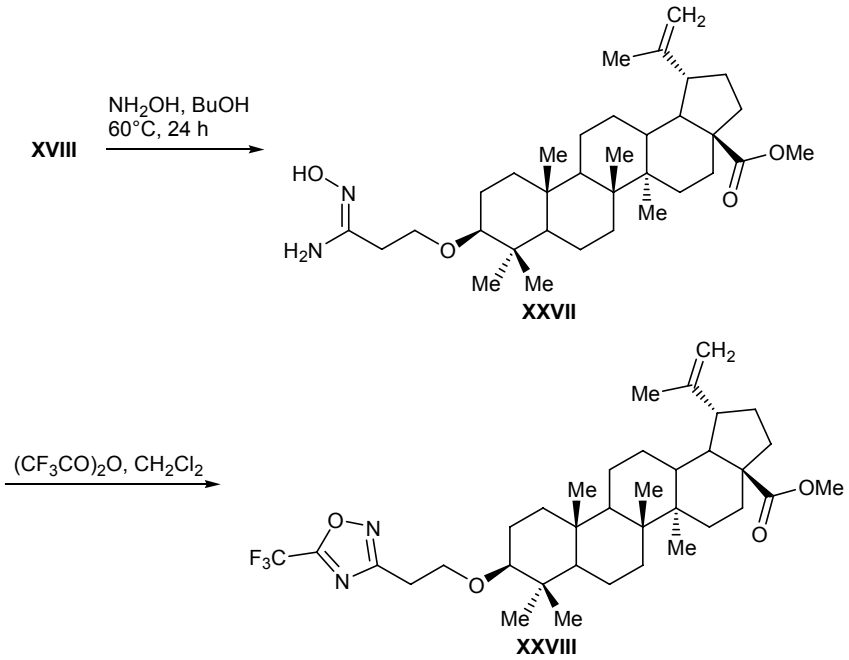
Scheme 6.



Scheme 7.



Scheme 8.



heating in benzene afforded 59% of 1,2,4-oxadiazole **XXVI** (Scheme 7). Likewise, amide oxime **XXVII** obtained from nitrile **XVIII** smoothly reacted with trifluoroacetic anhydride in methylene chloride at room temperature to produce oxadiazole **XXVIII** in 85% yield (Scheme 8).

The structure of the isolated compounds was confirmed by their elemental compositions and IR, NMR, and mass spectra. The IR spectra of the cyanoethyl derivatives contained an absorption band in the region 2200–2252 cm^{-1} due to stretching vibrations of the C≡N group. In the ^1H NMR spectra of the products we observed characteristic signals from the 3-H, 28-H, and 29-H protons, as well as signals typical of protons in the CH_2CH_2CN group. The IR spectra of amide oximes **XXV** and **XXVII** and oxadiazoles **XXVI** and **XXVIII** lacked C≡N absorption band at 2200–2252 cm^{-1}, but an absorption band appeared in the region 1650–1660 cm^{-1} due to stretching vibrations of the C=N bond.

The NH_2 protons resonated in the ^1H NMR spectra of amide oximes **XXV** and **XXVII** at δ 5.00–5.05 ppm. Complete assignment of signals in the ^1H and ^{13}C NMR spectra was made using two-dimensional proton–proton and carbon–proton correlation techniques with account taken of published data for betulin and its derivatives [9]. The ^1H and ^{13}C NMR spectra of oxime **XII**, as well as of 3-(2-cyanoethoxyimino)-lupane derivative **XI** indicated that these compounds were formed as a single isomer with respect to the C=N bond. Compound **XII** displayed in the ^1H NMR spectrum one one-proton signal at δ 9.30 ppm. *E*-Configuration of the double C=N bond followed from comparison of the chemical shifts of C^2 and C^4 in the ^{13}C NMR spectra of **XI** and **XII** and the corresponding carbonyl compound. The C^2 signal of **XI** and **XII** ap-

pears in a considerably stronger field ($\Delta\delta_C \approx 16$ ppm) relative to the C^2 signal of 3-oxo analog, while the difference in the chemical shifts of C^4 does not exceed 6.0 ppm. These findings suggest that the N–OH group is oriented toward C^2 (*E* isomer) rather than C^4 (*Z*). Compounds **XXI** and **XXII** having a 2-cyanoethoxyimino group on C^{28} were also formed as a single isomer. In the ^{1}H NMR spectra of **XXI** and **XXII**, the 28-H proton resonated as a singlet at δ 7.50–7.51 ppm (cf. δ 7.51 ppm for initial oxime **XX**), which corresponds to *E* configuration of the double C^{28}=N bond. The ^{13}C NMR spectra of heterocyclic derivatives **XXVI** and **XXVIII** contained singlets at δ_C 164.08, 169.76 ($C^{3'}$) and 65.49, 65.82 ppm ($C^{5'}$), respectively, which are typical of 1,2,4-oxadiazole ring.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Bruker Vector-22 spectrometer. The NMR spectra were measured from solutions in $CDCl_3$ on Bruker AV-300 (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) and AV-400 instruments (400.13 MHz for ^{1}H and 100.78 MHz for ^{13}C). Multiplicities of signals in the ^{13}C NMR spectra were determined using standard *J*-modulation (JMOD) technique with off-resonance decoupling from protons. The two-dimensional ^{1}H–^{1}H (COSY) and ^{13}C–^{1}H NMR spectra (HXCO 125 Hz, COLOC 7 Hz) were recorded on a Bruker DRX-500 spectrometer (500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C) from solutions in $CDCl_3$ using standard Bruker procedures. The chemical shifts were determined relative to the carbon and residual proton signals of the solvent ($CDCl_3$, δ_C 76.90; $CHCl_3$, δ 7.24 ppm). The mass spectra (electron impact, 70 EV) were obtained on a Finnigan MAT 8200 high-resolution mass spectrometer. The specific optical rotations $[\alpha]_D^{20}$ were measured on Polamat A and PolAAr3005 polarimeters in chloroform at room temperature (20–25°C). The product mixture obtained by cyanoethylation of compound **XXIII** was analyzed by gas chromatography–mass spectrometry on a Hewlett–Packard HP 5890 Series II chromatograph coupled with an HP 5971 quadrupole mass-selective detector (HP-5MS quartz capillary column, 30 m × 0.25 mm, 5% diphenyl–95% dimethylpolysiloxane, film thickness 0.25 μm; oven temperature programming from 50 to 280°C at a rate of 4 deg × min^{-1}, 15 min at 280°C). The components were quantitated by peak areas with no correction factors.

The elemental compositions were determined on a Carlo Erba 1106 CHN analyzer. The melting points were measured on a Kofler hot stage. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using chloroform–acetonitrile (15 : 1) as eluent; spots were developed by spraying with 20% sulfuric acid and subsequent heating to 100°C. Aluminum oxide was used as sorbent for column chromatography.

Betulin (**XIX**) was isolated by extraction of *Betula pendula Roth* birch bark. 3β-*O*-Acetylbetulin (**I**) and betulonic acid were synthesized as described in [10], betulinic acid and its methyl ester were prepared as reported in [11], and triterpenoid oximes were obtained according to [12].

28-*O*-(2-Cyanoethyl)lup-20(29)-en-3β-yl acetate (II). A mixture of 1.0 g (2.07 mmol) of compound **I**, 2.7 ml (41.4 mmol) of acrylonitrile, 0.23 g (1.06 mmol) of BTEAC, and 2.7 ml of 30% KOH in 25 ml of dioxane was stirred for 2 h at room temperature under argon. The mixture was poured into a mixture of ice with hydrochloric acid, the precipitate was filtered off, washed with water until neutral washings, dried in air, and dissolved in methylene chloride, the solution was filtered, and the filtrate was evaporated. Yield 1.07 g (97%). An analytical sample was obtained by chromatography on aluminum oxide using hexane–chloroform (1 : 1) as eluent; mp 135–137°C (from methanol); $[\alpha]_D^{20}$ = +23° (*c* = 1.32, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2251 (C≡N), 1730 (C=O, ester). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.75 m (1H, 5-H), 0.80 s (9H, $C^{23}H_3$, $C^{24}H_3$, $C^{25}H_3$), 0.92 s (3H, $C^{27}H_3$), 0.94–0.96 m (1H, 1-H), 0.99 s (3H, $C^{26}H_3$), 1.00–1.04 m (3H, 12-H, 15-H, 22-H), 1.11–1.21 m (2H, 11-H, 16-H), 1.23–1.29 m (1H, 9-H), 1.31–1.41 m (5H, 6-H, 7-H, 11-H, 21-H), 1.44–1.54 m (2H, 6-H, 18-H), 1.55–1.63 m (6H, 1-H, 2-H, 12-H, 13-H, 15-H), 1.64 s (3H, $C^{30}H_3$), 1.84–1.96 m (3H, 16-H, 21-H, 22-H), 1.99 s (3H, $C^{35}H_3$), 2.31–2.38 m (1H, 19-H), 2.55 t (2H, 32-H, *J* = 6.4), 3.13 d and 3.54 d (1H each, 28-H, *J* = 8.8), 3.61 t (2H, 31-H, *J* = 6.5), 4.43 d.d (1H, 3-H, *J* = 10.4, 4.8), 4.54 br.s and 4.63 br.s (1H each, 29-H). ^{13}C NMR spectrum, δ_C, ppm: 14.53 q (C^{27}), 15.79 q (C^{26}), 15.95 q (C^{25}), 16.29 q (C^{24}), 17.96 t (C^6), 18.64 t (C^{32}), 18.70 q (C^{30}), 20.63 t (C^{11}), 21.08 q (C^{35}), 23.48 t (C^2), 24.92 t (C^{12}), 26.95 t (C^{15}), 27.73 q (C^{23}), 29.63 t (C^{21}), 29.67 t (C^{16}), 33.91 t (C^7), 34.48 t (C^{22}), 36.84 s (C^{10}), 37.33 d (C^{13}), 37.57 s (C^4), 38.16 t (C^1), 40.70 s (C^8), 42.45 s (C^{14}), 47.10 s (C^{17}), 47.77 d (C^{19}), 48.51 d (C^{18}), 50.06 d (C^9), 55.14 d (C^5), 65.98 t (C^{31}), 69.58 t (C^{28}), 80.65 d (C^3), 109.48 t (C^{29}), 117.70 s (C^{33}), 150.20 s (C^{20}), 170.69 s (C^{34}). Mass spectrum:

m/*z* 537.41814 $[M]^+$. Found, %: C 78.15; H 10.50; N 2.68. $C_{35}H_{55}NO_3$. Calculated, %: C 78.16; H 10.31; N 2.61. *M* 537.31817.

2,2,28-*O*-Tris(2-cyanoethyl)lup-20(29)-en-3-one (VI). A mixture of 0.3 g (0.68 mmol) of compound **V**, 0.89 ml (1.36 mmol) of acrylonitrile, 0.072 g (0.34 mmol) of BTEAC, and 0.89 ml of 30% KOH in 10 ml of dioxane was stirred for 7 h at room temperature under argon. The mixture was then poured into a mixture of ice with hydrochloric acid, and the precipitate was filtered off, washed with water until neutral washings, dried in air, and purified by chromatography on Al_2O_3 using hexane–chloroform (1:1) as eluent. Yield 0.34 g (84%), mp 116–118°C. IR spectrum, ν, cm^{-1}: 2249 (C≡N), 1689 (C=O). ^{1}H NMR spectrum (only characteristic signals are given), δ, ppm (*J*, Hz): 0.67 s (3H, $C^{25}H_3$), 0.99 s (3H, $C^{26}H_3$), 1.01 s (3H, $C^{27}H_3$), 1.05 s (3H, $C^{24}H_3$), 1.11 s (3H, $C^{23}H_3$), 1.65 s (3H, $C^{30}H_3$), 2.57 t (2H, 32-H, *J* = 6.2), 3.15 d (1H, 28-H, *J* = 8.3), 3.56 t (1H, 28-H, *J* = 8.6), 4.55 br.s and 4.65 br.s (1H each, 29-H). ^{13}C NMR spectrum, δ_C, ppm: 12.23 t and 12.36 t (C^{35}, C^{38}), 14.61 q (C^{25}), 15.25 q (C^{27}), 17.53 q (C^{26}), 18.80 t (C^{32}), 18.96 q (C^{30}), 20.05 t (C^6), 21.60 t (C^{11}), 24.97 q (C^{24}), 25.04 t (C^{12}), 26.97 t (C^{15}), 29.63 t (C^{21}), 29.67 t (C^{16}), 30.02 q (C^{23}), 32.21 t and 32.44 t (C^{34}, C^{37}), 34.58 t (C^{22}), 36.65 s (C^{10}), 37.27 t (C^7), 37.55 d (C^{13}), 40.62 s (C^8), 42.74 s (C^{14}), 46.00 s (C^{17}), 47.18 s (C^4), 47.81 d (C^{19}), 48.06 t (C^2), 48.47 d (C^{18}), 49.52 d (C^9), 50.98 d (C^5), 51.49 t (C^1), 66.12 t (C^{31}), 69.70 t (C^{28}), 109.80 t (C^{29}); 117.90 s, 118.60 s, and 119.46 s (C^{33}, C^{36}, C^{39}); 150.15 s (C^{20}), 218.64 s (C^3). Mass spectrum: *m*/*z* 599.4567 $[M]^+$. $C_{39}H_{57}N_3O_2$. Calculated: *M* 599.4589.

Methyl 2,2-bis(2-cyanoethyl)-3-oxolup-20(29)-en-28-oate (VIII). A mixture of 0.5 g (1.07 mmol) of compound **VII**, 1.40 ml (21.37 mmol) of acrylonitrile, 0.11 g (0.54 mmol) of BTEAC, and 1.4 ml of 30% KOH in 10 ml of dioxane was stirred for 7 h at room temperature under argon. The mixture was then poured into a mixture of ice with hydrochloric acid and treated as described above. Yield 0.4 g (60%), mp 109–111°C, $[\alpha]_D^{20}$ = +17.4° (*c* = 2.38, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2248 (C≡N), 1725 (C=O, ester), 1689 (C=O). ^{1}H NMR spectrum (only characteristic signals are given), δ, ppm: 0.65 s (3H, $C^{25}H_3$), 0.89 s (3H, $C^{26}H_3$), 0.97 s (3H, $C^{27}H_3$), 1.03 s (3H, $C^{24}H_3$), 1.10 s (3H, $C^{23}H_3$), 1.65 s (3H, $C^{30}H_3$), 2.95 m (1H, 19-H), 3.63 s (3H, $C^{37}H_3$), 4.56 br.s and 4.70 br.s (1H each, 29-H). ^{13}C NMR spectrum, δ_C, ppm: 12.16 t and 12.29 t (C^{32}, C^{35}), 14.46 q (C^{25}), 15.15 q (C^{27}), 17.47 q (C^{26}), 19.20 q (C^{30}), 20.00 t (C^6), 21.61 t (C^{11}), 22.89 q (C^{24}), 25.33 t (C^{12}), 29.40 t (C^{15}), 29.40 q (C^{23}), 30.38 t (C^{21}), 31.87 t (C^{16}), 32.19 t (C^7), 32.56 t and 37.22 t (C^{31}, C^{34}), 36.64 s (C^{10}), 36.74 t (C^{22}), 38.13 d (C^{13}), 40.36 s (C^8), 42.40 s (C^{14}), 45.91 s (C^4), 46.74 d (C^{19}), 48.00 s (C^2), 49.16 d (C^{18}), 49.69 d (C^9), 51.00 d (C^5), 51.15 q (C^{37}), 51.48 t (C^1), 56.32 s (C^{17}), 109.60 t (C^{29}), 118.51 s and 119.31 s (C^{33}, C^{36}), 150.15 s (C^{20}), 176.39 s (C^{28}), 218.51 s (C^3). Mass spectrum: *m*/*z* 574.4138 $[M]^+$. $C_{37}H_{54}N_2O_3$. Calculated: *M* 574.4129.

3-[3-(2-Cyanoethoxyimino)lup-20(29)-en-28-yloxy]propanenitrile (X). A mixture of 1 g (1.78 mmol) of compound **IX**, 0.19 g (0.89 mmol) of BTEAC, 2.3 ml (35.65 mmol) of acrylonitrile, and 2.3 ml of 30% KOH in 25 ml of dioxane was stirred for 2 h at room temperature under argon. The mixture was poured into a mixture of ice with hydrochloric acid, the precipitate was filtered off, washed with water until neutral washings, dried in air, and washed with methylene chloride, the washings were evaporated, and the residue was subjected to chromatography on aluminum oxide using hexane–chloroform (1:1) as eluent. Yield 1.05 g (85%), mp 127–131°C, $[\alpha]_D^{20}$ = +9° (*c* = 3.6, $CDCl_3$). IR spectrum, ν, cm^{-1}: 2250 (C≡N), 1641 (C=C). ^{1}H NMR spectrum (only characteristic signals are given), δ, ppm (*J*, Hz): 0.86 s (3H, CH_3), 0.92 s (3H, CH_3), 0.99 s (3H, CH_3), 1.01 s (3H, CH_3), 1.02 s (3H, CH_3), 1.63 s (3H, $C^{30}H_3$), 2.21 (1H, 2-H), 2.34 m (1H, 19-H), 2.55 t (2H, 32-H, *J* = 6.3), 2.64 t (2H, 35-H, *J* = 6.3), 2.79 d.t (1H, 2-H, *J* = 4.2, 13.9), 3.13 d and 3.54 d (1H each, 28-H, *J* = 8.6), 3.61 t (2H, 31-H, *J* = 6.3), 4.15 t (2H, 34-H, *J* = 6.3), 4.53 br.s and 4.63 br.s (1H each, 29-H). ^{13}C NMR spectrum, δ_C, ppm: 14.48 q (C^{27}), 15.53 q (C^{26}), 15.68 q (C^{25}), 17.80 t (C^2), 18.13 t (C^{32}), 18.61 t (C^{35}), 18.83 t (C^6), 18.86 q (C^{30}), 20.93 t (C^{11}), 22.78 q (C^{24}), 24.98 t (C^{12}), 26.94 t (C^{15}), 27.03 q (C^{23}), 29.63 t (C^{21}), 29.68 t (C^{16}), 33.51 t (C^7), 34.47 t (C^{22}), 36.85 s (C^{10}), 37.40 d (C^{13}), 38.41 t (C^1), 40.05 s (C^4), 40.71 s (C^8), 42.50 s (C^{14}), 47.10 s (C^{17}), 47.71 d (C^{19}), 48.48 d (C^{18}), 49.68 d (C^9), 47.10 d (C^5), 65.98 t (C^{34}), 67.08 t (C^{31}), 69.60 t (C^{28}), 109.47 t (C^{29}), 117.72 s (C^{33}), 118.33 s (C^{36}), 150.13 s (C^{20}), 167.91 s (C^3). Mass spectrum: *m*/*z* 561.42574 $[M]^+$. $C_{36}H_{55}N_3O_2$. Calculated: *M* 561.42940.

Hydrolysis of 28-*O*-(2-cyanoethyl)lup-20(29)-en-3β-yl acetate (II). A solution of 0.20 g (0.37 mmol) of compound **II** in a mixture of 2 ml of THF and 4 ml of methanol was cooled to 0°C, 0.4 ml (1.6 mmol) of a 4 M solution of sodium hydroxide was added under argon, and the mixture was kept for 24 h at room temperature and poured into a mixture of ice with hydrochloric acid. The precipitate was filtered off, washed

with water, and dried in air. Yield of 3-[3β-hydroxylup-20(29)-en-28-yloxy]propanenitrile (**III**) 0.18 g (96%), mp 200–202°C (from methanol), $[\alpha]_D^{20}$ = +9.1° (*c* = 1.32, $CHCl_3$) (cf. [4]). IR spectrum: ν 2200 cm^{-1} (C≡N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.63 m (1H, 5-H), 0.70 s (3H, $C^{24}H_3$), 0.77 s (3H, $C^{25}H_3$), 0.80–0.89 m (1H, 1-H), 0.91 s (6H, $C^{23}H_3$, $C^{27}H_3$), 0.99 s (3H, $C^{26}H_3$), 1.00–1.06 m (3H, 12-H, 15-H, 22-H), 1.08–1.18 m (2H, 11-H, 16-H), 1.19–1.24 m (1H, 9-H), 1.28–1.39 m (5H, 6-H, 7-H, 11-H, 21-H), 1.45–1.65 m (8H, 1-H, 2-H, 6-H, 12-H, 13-H, 15-H, 18-H), 1.62 s (3H, $C^{30}H_3$), 1.83–1.94 m (3H, 16-H, 21-H, 22-H), 2.30–2.36 m (1H, 19-H), 2.55 t (2H, 32-H, *J* = 6.5), 3.09–3.14 m (2H, 3-H, 28-H), 3.52 d (1H, 28-H, *J* = 8.6), 3.59 t.d (2H, 31-H, *J* = 6.5, 1.6), 4.52 br.s and 4.62 br.s (1H each, 29-H). ^{13}C NMR spectrum, δ_C, ppm: 14.52 q (C^{27}), 15.16 q (C^{24}), 15.73 q (C^{26}), 15.85 q (C^{25}), 18.02 t (C^6), 18.58 t (C^{32}), 18.65 q (C^{30}), 20.55 t (C^{11}), 24.89 t (C^{12}), 26.89 t (C^{15}), 27.08 t (C^2), 27.74 q (C^{23}), 29.57 t (C^{21}), 29.60 t (C^{16}), 33.92 t (C^7), 34.42 t (C^{22}), 37.85 s (C^{10}), 37.26 d (C^{13}), 38.43 t (C^1), 38.57 s (C^4), 40.61 s (C^8), 42.38 s (C^{14}), 47.03 s (C^{17}), 47.67 d (C^{19}), 48.44 d (C^{18}), 50.07 d (C^9), 54.98 d (C^5), 65.89 t (C^{31}), 69.47 t (C^{28}), 78.55 d (C^3), 109.41 t (C^{29}), 117.72 s (C^{33}), 150.16 s (C^{20}). Mass spectrum: *m*/*z* 495.40688 $[M]^+$. $C_{33}H_{53}NO_2$. Calculated: *M* 495.40761.

28-*O*-(2-Cyanoethyl)lup-20(29)-en-3-one (XI). Pyridinium chlorochromate, 2.90 g (13.46 mmol), was added under argon to 100 ml of anhydrous methylene chloride, the solution was stirred for 10 min at room temperature, and 2.22 g (4.48 mmol) of compound **III** was added. The mixture was stirred for 2.5 h at room temperature and filtered through a thin layer of Al_2O_3, and the filtrate was evaporated. Yield 2.02 g (91%), mp 160–163°C, $[\alpha]_D^{20}$ = +45° (*c* = 4.3, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2249 (C≡N), 1705 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.85 s (3H, $C^{25}H_3$), 0.91 s (3H, $C^{27}H_3$), 0.95 s (3H, $C^{24}H_3$), 0.99 s (6H, $C^{26}H_3$, $C^{23}H_3$), 0.99–1.07 m (3H, 12-H, 15-H, 22-H), 1.09–1.15 m (1H, 16-H), 1.16–1.21 m (1H, 21-H), 1.23–1.28 m (1H, 5-H), 1.28–1.42 m (8H, 1-H, 6-H, 7-H, 9-H, 11-H), 1.48 t (1H, 18-H, *J* = 11.7), 1.55–1.64 m (3H, 5-H, 12-H, 13-H), 1.60 s (3H, $C^{30}H_3$), 1.78–1.95 m (4H, 1-H, 16-H, 21-H, 22-H), 2.29–2.36 m (2H, 2-H, 19-H), 2.37–2.45 m (1H, 2-H), 2.55 t (2H, 32-H, *J* = 6.4), 3.10 d and 3.52 d (1H each, 28-H, *J* = 8.8), 3.59 t (1H, 31-H, *J* = 6.4), 4.50 br.s and 4.61 br.s (1H each, 29-H). ^{13}C NMR spectrum, δ_C, ppm: 14.39 q (C^{27}), 15.47 q (C^{26}), 15.68 q (C^{25}), 18.56 t (C^{32}), 18.77 q (C^{30}), 19.31 t (C^6), 20.73 q (C^{24}), 21.01 t (C^{11}), 24.80 t (C^{12}), 26.32 q (C^{23}), 26.80 t (C^{15}), 29.44 t (C^{21}), 29.50 t (C^{16}), 33.10 t (C^7), 33.81 t (C^2), 34.36 t (C^{22}), 36.51 s (C^{10}), 37.29 d (C^{13}), 39.25 t (C^1), 40.48 s (C^8), 42.38 s (C^{14}), 46.96 s (C^{17}), 46.99 s (C^4), 47.59 d (C^{19}), 48.29 d (C^{18}), 49.35 d (C^9), 54.47 d (C^5), 65.84 t (C^{31}), 69.36 t (C^{28}), 109.45 t (C^{29}), 117.75 s (C^{33}), 150.04 s (C^{20}), 217.81 s (C^3). Mass spectrum: *m*/*z* 493.39156 $[M]^+$. $C_{33}H_{51}NO_2$. Calculated: *M* 493.39196.

28-*O*-(2-Cyanoethyl)lup-20(29)-en-3-one oxime (XII). Compound **IX**, 0.40 g (0.81 mmol), was dissolved in 13 ml of ethanol, 0.11 g (1.58 mmol) of hydroxylamine hydrochloride, and 2.6 ml of pyridine were added, and the mixture was kept for 6 days at room temperature with intermittent stirring. The mixture was then poured into a mixture of ice with hydrochloric acid, and the precipitate was filtered off, washed with water, and dried in air. Yield 0.39 g (96%), mp 197–203°C, $[\alpha]_D^{20}$ = –3° (*c* = 4.84, $CDCl_3$). IR spectrum, ν, cm^{-1}: 2252 (C≡N), 1641 (C=C). ^1H NMR spectrum (only characteristic signals are given), δ, ppm (*J*, Hz): 0.89 s (3H, CH_3), 0.92 s (3H, CH_3), 1.02 s (6H, CH_3), 1.11 s (3H, CH_3), 1.64 s (3H, $C^{30}H_3$), 2.22 m (1H, 2-H), 2.35 m (1H, 19-H), 2.57 t (2H, 32-H, *J* = 6.4), 2.95 d.t (1H, 2-H, *J* = 14.4, 4.1), 3.14 d and 3.55 d (1H each, 28-H, *J* = 8.9), 3.62 t (2H, 31-H, *J* = 6.4), 4.54 br.s and 4.64 br.s (2H, 29-H), 9.30 br.s (1H, NOH). ^{13}C NMR spectrum, δ_C, ppm: 14.47 q (C^{27}), 15.62 q (C^{26}), 15.75 q (C^{25}), 17.00 t (C^2), 18.67 t (C^{32}), 18.73 t (C^6), 18.83 q (C^{30}), 20.91 t (C^{11}), 22.69 q (C^{24}), 24.97 q (C^{12}), 26.93 t (C^{15}), 27.05 q (C^{23}), 29.61 t (C^{21}), 29.66 t (C^{16}), 33.58 t (C^7), 34.49 t (C^{22}), 37.00 s (C^{10}), 37.39 d (C^{13}), 38.56 t (C^1), 40.17 s (C^4), 40.72 s (C^8), 42.49 s (C^{14}), 47.12 s (C^{17}), 47.75 d (C^{19}), 48.47 d (C^{18}), 49.75 d (C^9), 55.29 d (C^5), 65.99 t (C^{31}), 69.58 t (C^{28}), 109.52 t (C^{29}), 117.76 t (C^{33}), 150.21 s (C^{20}), 166.72 s (C^3). Mass spectrum: *m*/*z* 508.40324 $[M]^+$. $C_{33}H_{52}N_2O_2$. Calculated: *M* 508.40286.

Cyanoethylation of 28-*O*-(2-cyanoethyl)lup-20(29)-en-3-one oxime (XII). A mixture of 0.2 g (0.39 mmol) of compound **XII**, 0.2 g (0.88 mmol) of BTEAC, 0.5 ml (7.53 mmol) of acrylonitrile, and 0.5 ml of 30% KOH in 5 ml of dioxane was stirred for 2 h at room temperature under argon. The mixture was then poured into a mixture of ice with hydrochloric acid, the precipitate was filtered off, washed with water until neutral washings, dried in air, and washed with methylene chloride, and the washings were evaporated to isolate 0.19 g (87%) of compound **X** whose spectral parameters were identical to those of a sample of **X** obtained by cyanoethylation of oxime **IX**.

3-*O*-(2-Cyanoethyl)lup-20(29)-en-28-al (XVI). A mixture of 0.5 g (1.14 mmol) of betulinaldehyde (**XIII**), 0.12 g (0.57 mmol) of BTEAC, 1.5 ml (22.8 mmol) of acrylonitrile, and 1.5 ml of 30% KOH in 25 ml of dioxane was stirred for 24 h at room temperature. The mixture was poured into a mixture of ice with hydrochloric acid, the precipitate was filtered off, washed with water until neutral washings, dried in air, and washed with methylene chloride, the washings were evaporated, and the residue containing (according to the ^{1}H NMR data) 45% of aldehyde **XVI** and 55% of initial compound **XIII** was subjected to chromatography on aluminum oxide using hexane–chloroform (1:1) as eluent. Yield 0.2 g (36%), mp 155–157°C, $[\alpha]_D^{20}$ = +33.9° (*c* = 2.25, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2253 (C≡N), 1725 (CHO), 1641 (C=C). ^{1}H NMR spectrum (only characteristic signals are given), δ, ppm (*J*, Hz): 0.63 (1H, 5-H), 0.72 s (3H, CH_3), 0.79 s (3H, CH_3), 0.88 s (3H, CH_3), 0.93 s (3H, CH_3), 0.94 s (3H, $C^{23}H_3$), 1.66 s (3H, $C^{30}H_3$), 2.53 t (2H, 32-H, *J* = 6.6), 2.75–2.87 m (2H, 3-H, 19-H), 3.49 m and 3.77 m (1H each, 31-H), 4.59 br.s and 4.72 br.s (1H each, 29-H), 9.64 s (1H, 28-H). ^{13}C NMR spectrum, δ_C, ppm: 14.15 q (C^{27}), 15.82 q (C^{26}), 16.04 q (C^{24}, C^{25}), 18.08 t (C^6), 18.93 q (C^{30}), 19.18 t (C^{32}), 20.68 t (C^{11}), 22.84 t (C^2), 25.43 t (C^{12}), 27.98 q (C^{23}), 28.69 t (C^{15}), 29.14 t (C^{16}), 29.76 t (C^{21}), 33.11 t (C^{22}), 34.21 t (C^7), 37.00 s (C^{10}), 38.38 t (C^1), 38.56 d (C^{13}), 38.76 s (C^4), 40.77 s (C^8), 42.45 s (C^{14}), 47.42 d (C^{19}), 47.95 d (C^{18}), 50.35 d (C^9), 55.62 d (C^5), 59.21 s (C^{17}), 64.04 t (C^{31}), 87.56 d (C^3), 110.06 t (C^{29}), 118.10 s (C^{33}), 149.62 s (C^{20}), 206.48 s (C^{28}). Mass spectrum: *m*/*z* 493.3918 $[M]^+$. $C_{33}H_{51}NO_2$. Calculated: *M* 493.3914.

3β-*O*-(2-Cyanoethyl)lup-20(29)-en-28-oic acid (XVII). A mixture of 0.87 g (1.9 mmol) of betulinic acid (**XIV**), 0.2 g (0.95 mmol) of BTEAC, 2.5 ml (38 mmol) of acrylonitrile, and 2.5 ml of 30% KOH in 25 ml of dioxane was stirred for 24 h at room temperature. The mixture was poured into a mixture of ice with hydrochloric acid, the precipitate was filtered off, washed with water until neutral washings, dried in air, and washed with methylene chloride, the washings were evaporated, and the residue containing (according to the ^{1}H NMR data) compounds **XIV** and **XVII** at a ratio of 1:4 was subjected to chromatography on aluminum oxide using hexane–chloroform (1:1) as eluent. Yield 0.51 g (53%), mp 271–274°C. IR spectrum, ν, cm^{-1}: 2250 (C≡N), 1725 (C=O), 1641 (C=C). ^{1}H NMR spectrum (only characteristic signals are given), δ, ppm (*J*, Hz): 0.66 m (1H, 5-H), 0.74 s (3H, CH_3), 0.81 s (3H, CH_3), 0.91 s (3H, CH_3), 0.92 s (6H, CH_3), 1.60 t (1H, 18-H, *J* = 11.5), 1.68 s (3H, $C^{30}H_3$), 2.55 t (2H, 32-H, *J* = 6.3), 2.81 d.d (1H, 3-H, *J* = 11.0, 3.0), 2.98 m (1H, 19-H), 3.51 m and 3.80 m (1H each, 31-H), 4.60 br.s and 4.72 br.s (1H each, 29-H). ^{13}C NMR spectrum, δ_C, ppm: 14.65 q (C^{27}), 16.02 q and 16.09 q (C^{24}, C^{25}, C^{26}), 18.16 t (C^{32}), 19.26 t (C^6), 19.37 q (C^{30}), 20.84 t (C^{11}), 22.94 t (C^2), 25.48 t (C^{12}), 28.07 q (C^{23}), 29.66 t (C^{15}), 30.57 t (C^{21}), 32.15 t (C^{16}), 34.28 t (C^7), 36.03 t (C^{22}), 37.12 s (C^{10}), 38.40 d (C^{13}), 38.44 t (C^1), 38.86 s (C^4), 40.70 s (C^8), 42.40 s (C^{14}), 46.90 d (C^{19}), 49.27 d (C^{18}), 50.45 d (C^9), 55.75 d (C^5), 56.37 s (C^{17}), 64.12 t (C^{31}), 87.72 d (C^3), 109.64 t (C^{29}), 118.16 s (C^{33}), 150.40 s (C^{20}), 182.01 s (C^{28}). Mass spectrum: *m*/*z* 509.3860 $[M]^+$. $C_{33}H_{51}NO_3$. Calculated: *M* 509.3864.

Methyl 3β-*O*-(2-cyanoethyl)lup-20(29)-en-28-oate (XVIII). A mixture of 1.0 g (2.13 mmol) of compound **XV**, 0.23 g (1.06 mmol) of BTEAC, 2.8 ml (42.6 mmol) of acrylonitrile, and 2.8 ml of 30% KOH in 25 ml of dioxane was stirred for 24 h at room temperature under argon. The mixture was poured into a mixture of ice with hydrochloric acid, the precipitate was filtered off, washed with water until neutral washings, dried in air, and washed with methylene chloride, the washings were evaporated, and the residue was subjected to chromatography on aluminum oxide using hexane–chloroform (1:1) as eluent. Yield 0.82 g (57%), mp 183–185°C, $[\alpha]_D^{20}$ = +24° (*c* = 3.38, $CDCl_3$). IR spectrum, ν, cm^{-1}: 2250 (C≡N), 1715 (C=O), 1640 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.62 m (1H, 5-H), 0.72 s (3H, $C^{24}H_3$), 0.78 s (3H, $C^{25}H_3$), 0.82 m (1H, 1-H), 0.87 s (3H, $C^{26}H_3$), 0.92 s (3H, $C^{27}H_3$), 0.93 s (3H, $C^{23}H_3$), 0.98 m (1H, 12-H), 1.08–1.12 m (1H, 15-H), 1.17–1.24 m (2H, 9-H, 11-H), 1.28–1.40 m (8H, 6-H, 7-H, 11-H, 15-H, 16-H, 21-H, 22-H), 1.42–1.47 m (2H, 2-H, 4-H), 1.53 t (1H, 18-H, *J* = 12.3), 1.64 s (3H, $C^{30}H_3$), 1.65–1.69 m (3H, 1-H, 2-H, 12-H), 1.81–1.89 m (2H, 21-H, 22-H), 2.12–2.21 m (2H, 13-H, 16-H), 2.52 t (2H, 32-H, *J* = 6.5), 2.78 d.d (1H, 3-H, *J* = 12.2, 3.8), 2.95 m (1H, 19-H), 3.48 m (1H, 31-H), 3.62 s (3H, $C^{34}H_3$), 3.78 m (1H, 31-H), 4.56 br.s and 4.69 br.s (1H each, 29-H). ^{13}C NMR spectrum, δ_C, ppm: 14.48 q (C^{27}), 15.75 q (C^{26}), 15.91 q and 15.93 q (C^{24}, C^{25}), 17.99 t (C^6), 19.06 t (C^{32}), 19.19 q (C^{30}), 20.71 t (C^{11}), 22.73 t (C^2), 25.31 t (C^{12}), 27.87 q (C^{23}), 29.45 t (C^{15}), 30.40 t (C^{21}), 31.95 t (C^{16}), 34.10 t (C^7), 36.74 t (C^{22}), 36.91 s (C^{10}), 38.03 d (C^{13}), 38.26 t (C^1), 38.65 s (C^4), 40.50 s (C^8), 42.17 s (C^{14}), 46.75 d (C^{19}), 49.26 d (C^{18}), 50.33 d (C^9), 51.05 q (C^{34}), 55.57 d (C^5), 56.33 s (C^{17}), 63.92 t (C^{31}), 87.47 d (C^3), 109.38 t (C^{29}), 117.99 s (C^{33}),

150.34 s (C^{20}), 176.38 s (C^{28}). Mass spectrum: *m*/*z* 523.40325 $[M]^+$. $C_{34}H_{53}NO_3$. Calculated: *M* 523.40252.

Cyanoethylation of betulin (XIX). A mixture of 0.5 g (1.13 mmol) of compound **XIX**, 0.1 g (0.44 mmol) of BTEAC, 1.5 ml (22.6 mmol) of acrylonitrile, and 1 ml of 30% KOH in 20 ml of dioxane was kept for 24 h at room temperature under argon. The mixture was poured into a mixture of ice with hydrochloric acid, and the precipitate was filtered off, washed with water until neutral washings, and dried in air. According to the ^{1}H NMR data, the product contained 21% of monosubstituted compound **III** and 79% of disubstituted derivative **IV** which were separated by chromatography on aluminum oxide using hexane–chloroform (1 : 1) as eluent. Yield of 3β,28-di-*O*-(2-cyanoethyl)lup-20(29)-ene (**IV**) 0.45 g (75%), mp 178–180°C (from methanol), $[\alpha]_D^{20}$ = +27° (*c* = 0.81, $CHCl_3$) (cf. [4]). IR spectrum: ν 2250 cm^{-1} (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.64 m (1H, 5-H), 0.74 s (3H, $C^{24}H_3$), 0.75–0.78 m (1H, 1-H), 0.80 s (3H, $C^{25}H_3$), 0.94 s (3H, $C^{27}H_3$), 0.95 s (3H, $C^{23}H_3$), 1.00 s (3H, $C^{26}H_3$), 1.01–1.04 m (3H, 12-H, 15-H, 22-H), 1.16 t.d (1H, 16-H, *J* = 13.2, 3.2), 1.20–1.26 m (2H, 9-H, 11-H), 1.31–1.41 m (5H, 6-H, 7-H, 7-H, 11-H, 21-H), 1.46–1.50 m (2H, 2-H, 6-H), 1.51 t (1H, 18-H, *J* = 11.3), 1.57–1.70 m (5H, 1-H, 2-H, 12-H, 13-H, 15-H), 1.64 s (3H, $C^{30}H_3$), 1.86–1.96 m (3H, 16-H, 21-H, 22-H), 2.32–2.39 m (1H, 19-H), 2.53 t (2H, 35-H, *J* = 6.5), 2.56 t (2H, 32-H, *J* = 6.5), 2.79 d.d (1H, 3-H, *J* = 12.1, 3.8), 3.14 d (1H, 28-H, *J* = 8.9), 3.47–3.52 m (1H, 34-H), 3.55 d (1H, 28-H, *J* = 8.9), 3.62 t.d (2H, 31-H, *J* = 6.5, 1.6), 3.74–3.80 m (1H, 34-H), 4.55 br.s and 4.65 br.s (1H each, 29-H). ^{13}C NMR spectrum, δ_C, ppm: 14.60 q (C^{27}), 15.85 q (C^{26}), 15.92 q (C^{25}), 15.96 q (C^{24}), 18.03 t (C^6), 18.68 t (C^{32}), 18.94 q (C^{30}), 19.10 t (C^{35}), 20.71 t (C^{11}), 22.80 t (C^2), 25.06 t (C^{12}), 27.02 t (C^{15}), 27.92 q (C^{23}), 29.73 t (C^{21} or C^{16}), 29.77 t (C^{16} or C^{21}), 34.05 t (C^7), 34.54 t (C^{22}), 36.93 s (C^{10}), 37.41 d (C^{13}), 38.31 t (C^1), 38.71 s (C^4), 40.80 s (C^8), 42.52 s (C^{14}), 47.17 s (C^{17}), 47.80 d (C^{19}), 48.61 d (C^{18}), 50.21 d (C^9), 55.55 d (C^5), 63.98 t (C^{34}), 66.04 t (C^{31}), 69.67 t (C^{28}), 87.51 d (C^3), 109.45 t (C^{29}), 117.71 s (C^{33}), 117.98 s (C^{36}), 150.29 s (C^{20}). Mass spectrum: *m*/*z* 548.43521 $[M]^+$. Found, %: C 78.72; H 10.21; N 4.90. $C_{36}H_{56}N_2O_2$. Calculated, %: C 78.72; H 10.21; N 5.11. *M* 548.43415. Further elution gave 0.08 g (14%) of compound **III** whose spectral parameters were identical to those of a sample obtained by hydrolysis of compound **II**.

Cyanoethylation of 3β-hydroxylup-20(29)-en-28-al oxime (XX). A mixture of 0.5 g (1.13 mmol) of compound **XX**, 0.1 g (0.44 mmol) of BTEAC, 7 ml (105.35 mmol) of acrylonitrile, and 1 ml of 30% KOH in 20 ml of dioxane was kept for 24 h at room temperature under argon. The mixture was poured into a mixture of ice with hydrochloric acid, and the precipitate was filtered off, washed with water until neutral washings, and dried in air. According to the ^{1}H NMR data, the product contained 45% of monosubstituted compound **XXI** and 55% of disubstituted derivative **XXII** which were separated by chromatography on aluminum oxide using hexane–chloroform (1 : 1) as eluent. Yield of 3-{28-[(*E*)-(2-cyanoethoxyimino)]lup-20(29)-en-3β-yloxy}propanenitrile (**XXII**) 0.16 g (45%), mp 178–180°C. IR spectrum, ν, cm^{-1}: 2250 (C≡N), 1646 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.63 (1H, 5-H), 0.72 s (3H, $C^{25}H_3$), 0.78 s (3H, $C^{26}H_3$), 0.79–0.82 m (1H, 1-H), 0.94 s (9H, $C^{23}H_3$, $C^{24}H_3$, $C^{27}H_3$), 1.00–1.05 m (1H, 21-H), 1.15–1.23 m (2H, 9-H, 11-H), 1.26–1.49 m (9H, 2-H, 6-H, 7-H, 11-H, 15-H, 16-H, 22-H), 1.58 t (1H, 18-H, *J* = 11.8), 1.65 s (3H, $C^{30}H_3$), 1.63–1.80 m (7H, 1-H, 2-H, 12-H, 13-H, 15-H, 22-H), 1.84–1.96 m (2H, 16-H, 21-H), 2.45 t.d (1H, 19-H, *J* = 5.7, 11.1), 2.53 t (2H, 35-H, *J* = 6.5), 2.68 t (2H, 32-H, *J* = 6.3), 2.78 d.d (1H, 3-H, *J* = 4.3), 3.48 m and 3.77 m (1H, 34-H), 4.19 t (2H, 31-H, *J* = 6.3), 4.57 br.s and 4.68 br.s (2H, 29-H), 7.50 s (1H, 28-H). ^{13}C NMR spectrum, δ_C, ppm: 14.56 q (C^{27}), 15.88 q (C^{24}), 15.97 q (C^{25}), 16.01 q (C^{26}), 17.99 t (C^6), 18.33 t (C^{32}), 19.03 q (C^{30}), 19.14 t (C^{35}), 20.60 t (C^{11}), 22.75 t (C^2), 24.97 t (C^{12}), 27.70 t (C^{21}), 27.93 q (C^{23}), 29.53 t (C^{15}), 31.91 t (C^{16}), 34.09 t (C^7), 36.87 t (C^{22}), 36.91 s (C^{10}), 38.25 t (C^1), 38.46 d (C^{13}), 38.69 s (C^4), 40.71 s (C^8), 42.67 s (C^{14}), 47.66 d (C^{19}), 49.16 d (C^{18}), 49.92 s (C^{17}), 50.14 d (C^9), 55.50 d (C^5), 63.97 t (C^{34}), 67.40 t (C^{31}), 87.47 s (C^3), 110.01 t (C^{29}), 117.59 s (C^{33}), 118.18 s (C^{36}), 149.55 s (C^{20}), 155.89 t (C^{28}). Mass spectrum: *m*/*z* 561.42574 $[M]^+$. $C_{36}H_{55}N_3O_2$. Calculated: *M* 561.42940.

Further elution gave 0.12 g (35%) of 28-[(*E*)-(2-cyanoethoxyimino)]lup-20(29)-en-3β-one (**XXI**), mp 197–199°C. IR spectrum, ν, cm^{-1}: 2252 (C≡N), 1648 (C=C). ^{1}H NMR spectrum (only characteristic signals are given), δ, ppm (*J*, Hz): 0.89 s (3H, Me), 0.92 s (3H, Me), 1.02 s (3H, Me), 1.11 s (3H, Me), 1.64 s (3H, $C^{30}H_3$), 2.22 m (1H, 2-H), 2.35 m (1H, 19-H), 2.57 t (2H, 32-H, *J* = 6.4), 2.95 d.t (1H, 2-H, *J* = 14.4, 4.1), 3.62 t (2H, 31-H, *J* = 6.4), 4.54 br.s and 4.64 br.s (1H each, 29-H), 7.50 s (28-H), 9.30 br.s (1H, NOH). ^{13}C NMR spectrum, δ_C, ppm: 14.47 q (C^{27}),

15.62 q (C^{26}), 15.75 q (C^{25}), 17.00 t (C^{2}), 18.67 t (C^{32}), 18.23 t (C^{6}), 18.80 q (C^{30}), 20.91 t (C^{11}), 22.69 q (C^{24}), 24.97 q (C^{12}), 26.93 t (C^{15}), 27.05 q (C^{23}), 29.61 t (C^{21}), 29.66 t (C^{16}), 33.58 t (C^{7}), 34.49 t (C^{22}), 37.00 s (C^{10}), 37.39 d (C^{13}), 38.56 t (C^{1}), 40.17 s (C^{4}), 40.72 s (C^{8}), 42.49 s (C^{14}), 47.12 s (C^{17}), 47.75 d (C^{19}), 48.47 d (C^{18}), 49.75 d (C^{9}), 55.29 d (C^{5}), 65.99 t (C^{31}), 69.58 t (C^{28}), 109.52 t (C^{29}), 117.76 t (C^{33}), 150.21 s (C^{20}), 166.72 s (C^{3}).

3β-*O*-(2-Cyanoethyl)lup-20(29)-en-28-yl acetate (XXIV). *a*. A mixture of 0.5 g (1.03 mmol) of compound **XXIII**, 1.35 ml (20.6 mmol) of acrylonitrile, 0.11 g (0.51 mmol) of BTEAC, and 1.35 ml of 30% KOH in 20 ml of dioxane was kept for 24 h at room temperature under argon. The mixture was poured into a mixture of ice with hydrochloric acid, and the precipitate was filtered off, washed with water until neutral washings, and dried in air. According to the GC–MS data, the product contained 64% of compound **XXIV**, 22% of betulin (**XIX**), 9% of **IV**, and 5% of **III**.

b. A mixture of 0.5 g (1.03 mmol) of compound **XXIII**, 1.35 ml (20.6 mmol) of acrylonitrile, 0.11 g (0.51 mmol) of BTEAC, and 1.35 ml of 30% KOH in 20 ml of methylene chloride was stirred for 2 h at room temperature under argon. The mixture was washed with 10% hydrochloric acid and water, dried over $MgSO_4$, and evaporated. According to the GC–MS data, the product contained 88% of **XXIV**, 7% of **IV**, and 5% of **III**. Compound **XXIV** was isolated from the product mixture by chromatography on aluminum oxide using hexane–chloroform (1 : 1) as eluent. Yield 0.45 g (84%). IR spectrum, ν, cm^{-1}: 2251 (C≡N), 1735 (C=O), 1642 (C=C). ^{1}H NMR spectrum (only characteristic signals are given), δ, ppm (*J*, Hz): 0.64 m (1H, 5-H), 0.74 s (3H, CH_3), 0.80 (3H, CH_3), 0.95 s (3H, CH_3), 0.99 s (3H, CH_3), 1.65 s (3H, $C^{30}H_3$), 1.99 s (3H, $C^{34}H_3$), 2.35 m (1H, 19-H), 2.52 t (2H, 32-H, *J* = 6.4), 3.47 m and 3.74 m (1H each, 31-H), 3.79 d and 4.20 d (1H each, 28-H, *J* = 8.9), 4.52 br.s and 4.62 br.s (2H, 29-H). ^{13}C NMR spectrum, δ_C, ppm: 14.50 q (C^{27}), 15.78 q (C^{24}), 15.91 q (C^{26}), 15.92 q (C^{25}), 17.98 t (C^{26}), 18.89 q (C^{30}), 19.04 t (C^{32}), 20.64 t (C^{11}), 20.82 q (C^{34}), 22.72 q (C^{12}), 24.98 t (C^{15}), 26.82 t (C^{2}), 27.86 q (C^{23}), 28.97 t (C^{21}), 29.55 t (C^{16}), 33.77 t (C^{7}), 34.99 t (C^{22}), 36.84 s (C^{10}), 37.04 d (C^{13}), 38.22 t (C^{1}), 38.63 s (C^{4}), 40.72 s (C^{8}), 42.46 s (C^{14}), 47.53 s (C^{17}), 47.53 d (C^{19}), 48.53 d (C^{18}), 50.14 d (C^{9}), 55.47 d (C^{5}), 60.09 t (C^{31}), 63.91 t (C^{28}), 87.45 d (C^{3}), 109.42 t (C^{29}), 118.01 t (C^{33}), 150.29 s (C^{20}), 171.29 s (C^{34}). Mass spectrum: *m*/*z* 537.8345 $[M]^+$. $C_{35}H_{55}NO_3$. Calculated: *M* 537.8252.

28-[3-Amino-3-(hydroxyimino)propoxy]lup-20(29)-en-3β-yl acetate (XXV). A solution of 0.054 g (1.63 mmol) of hydroxylamine in 5 ml of butan-1-ol was added to 0.29 g (0.54 mmol) of compound **II**. The mixture was heated for 10 h at 60°C and poured into a mixture of ice with hydrochloric acid, and the precipitate was filtered off, washed with water until neutral washings, and dried in air. According to the ^{1}H NMR data, the product was a mixture of initial compound **II** and amide oxime **XXV** at a ratio of 1:5. Compound **XXV** was isolated by chromatography on silica gel using chloroform–methanol (10:1) as eluent. Yield 0.17 g (55%), mp 141–143°C. IR spectrum, ν, cm^{-1}: 1730 (C=O), 1671 (C=N), 1642 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.77 m (1H, 5-H), 0.81 s (3H, $C^{23}H_3$), 0.82 s (6H, $C^{24}H_3$, $C^{25}H_3$), 0.94 s (3H, $C^{27}H_3$), 0.99 s (3H, $C^{26}H_3$), 1.65 s (3H, $C^{30}H_3$), 2.02 (3H, $C^{35}H_3$), 2.38 t (2H, 32-H, *J* = 5.4), 3.09 d (1H, 28-H, *J* = 9.1), 3.53 d (1H, 28-H, *J* = 8.9), 3.60 t (2H, 31-H, *J* = 5.64), 4.45 m (1H, 3-H), 4.56 br.s and 4.65 br.s (2H, 29-H), 5.00 br.s (2H, NH_2). ^{13}C NMR spectrum, δ_C, ppm: 14.73 q (C^{27}), 15.97 q (C^{26}), 16.14 q (C^{25}), 16.47 q (C^{24}), 18.14 t (C^{6}), 19.05 q (C^{30}), 20.80 t (C^{11}), 21.30 q (C^{35}), 23.65 t (C^{2}), 25.10 t (C^{12}), 27.09 t (C^{15}), 27.91 q (C^{23}), 29.80 t (C^{16}), 30.08 t (C^{21}), 31.24 t (C^{32}), 34.09 t (C^{7}), 34.82 t (C^{22}), 37.03 s (C^{10}), 37.47 d (C^{13}), 37.76 s (C^{4}), 38.33 t (C^{1}), 40.88 s (C^{8}), 42.64 s (C^{14}), 47.11 s (C^{17}), 47.92 d (C^{19}), 48.71 d (C^{18}), 50.24 d (C^{9}), 55.33 d (C^{5}), 69.57 t (C^{31}), 69.67 s (C^{28}), 80.89 d (C^{3}), 109.71 t (C^{29}), 150.39 s (C^{20}), 154.31 s (C^{33}), 171.01 s (C^{34}). Mass spectrum: *m*/*z* 570.8525 $[M]^+$. $C_{35}H_{58}N_2O_4$. Calculated: *M* 570.8382.

28-[2-(5-Phenyl-1,2,4-oxadiazol-3-yl)ethoxy]lup-20(29)-en-3β-yl acetate (XXVI). Pyridine, 0.021 ml (0.26 mmol), and benzoyl chloride, 0.02 ml (0.17 mmol), were added under argon to a solution of 0.1 g (0.17 mmol) of compound **XXV** in 3 ml of methylene chloride. The mixture was stirred for 24 h at room temperature, washed with 10% hydrochloric acid and water, dried over anhydrous $MgSO_4$, and evaporated. The residue was heated for 6 h in boiling benzene, the solvent was distilled off, and the residue was purified by chromatography on silica gel using chloroform as eluent. Yield 0.07 g (59%), mp 118–120°C. IR spectrum, ν, cm^{-1}: 1733 (C=O), 1640 (C=C). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.75 m (1H, 5-H), 0.81 s (3H, $C^{23}H_3$), 0.82 s (6H, $C^{24}H_3$, $C^{25}H_3$), 0.94 s (3H, $C^{27}H_3$), 1.00 s (3H, $C^{26}H_3$), 1.66 s (3H, $C^{30}H_3$), 2.01 s (3H, $C^{32}H_3$), 2.36 t.d (1H, 19-H, *J* = 5.8, 10.7), 2.60 t

(2H, 12′-H, J = 5.4), 3.15 d (1H, 28-H, J = 9.0), 3.57 d (1H, 28-H, J = 8.8), 3.70 t (2H, 13′-H, J = 5.5), 4.45 m (1H, 3-H), 4.56 br.s and 4.66 br.s (1H each, 29-H), 7.39–7.47 m (2H, H_{arom}), 7.51–7.58 m (1H, H_{arom}), 7.99–8.05 m (2H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 14.74 q (C^{27}), 15.99 q (C^{26}), 16.13 q (C^{25}), 16.45 q (C^{24}), 18.12 t (C^{6}), 19.06 q (C^{30}), 20.78 t (C^{11}), 21.30 q (C^{32}), 23.65 t (C^{2}), 25.09 t (C^{12}), 27.10 t (C^{15}), 27.90 q (C^{23}), 29.77 t (C^{16}), 30.11 t (C^{21}), 31.00 t ($C^{12'}$), 34.09 t (C^{7}), 34.83 t (C^{22}), 37.03 s (C^{10}), 37.49 d (C^{13}), 37.76 s (C^{4}), 38.34 t (C^{1}), 40.88 s (C^{8}), 42.65 s (C^{14}), 47.11 s (C^{17}), 47.87 d (C^{19}), 48.70 d (C^{18}), 50.24 d (C^{9}), 55.33 d (C^{5}), 65.82 s ($C^{5'}$), 69.33 t ($C^{13'}$), 69.75 s (C^{28}), 80.87 d (C^{3}), 109.82 t (C^{29}), 128.42 d (C^{m}), 129.38 d (C^{o}), 132.86 d (C^{p}), 150.20 s (C^{20}), 159.05 s (C^{i}), 164.08 s ($C^{3'}$), 171.01 s (C^{31}). Mass spectrum: m/z 656.4654 $[M]^+$. $C_{42}H_{60}N_2O_4$. Calculated: M 6561.4638.

Methyl 3β-[3-amino-3-(hydroxyimino)propoxy]-lup-20(29)-en-28-oate (XXVII). A solution of 0.093 g (2.81 mmol) of hydroxylamine in 10 ml of butan-1-ol was added to 0.49 g (0.94 mmol) of compound **XVIII**, the mixture was heated for 10 h at 60°C and poured into a mixture of ice with hydrochloric acid, and the precipitate was filtered off, washed with water until neutral washings, and dried in air. The product was isolated by preparative thin-layer chromatography on silica gel using chloroform–methanol (20:1) as eluent. Yield 0.28 g (53%), mp 191–194°C. IR spectrum, ν, cm^{-1}: 1716 (C=O), 1665 (C=N), 1642 (C=C). ^1H NMR spectrum (only characteristic signals are given), δ, ppm (J, Hz): 0.64 (1H, 5-H), 0.72 s (3H, $C^{24}H_3$), 0.79 s (3H, $C^{25}H_3$), 0.88 s (3H, $C^{26}H_3$), 0.91 s (3H, $C^{23}H_3$), 0.92 s (3H, $C^{27}H_3$), 1.55 t (1H, 18-H, J = 11.3), 1.65 s (3H, $C^{30}H_3$), 1.81–1.92 m (2H, 21-H, 22-H), 2.10–2.24 m (2H, 13-H, 16-H), 2.35 m (2H, 32-H), 2.74 d.d (1H, 3-H, J = 4.1), 2.96 t.d (1H, 19-H, J = 4.5, 10.8), 3.45 m (1H, 31-H), 3.64 s (3H, $C^{30}H_3$), 3.77 m (1H, 31-H), 4.57 br.s and 4.71 br.s (1H each, 29-H), 5.04 br.s (2H, NH_2). ^{13}C NMR spectrum, δ_C, ppm: 14.23 q (C^{27}), 15.50 q (C^{26}), 15.61 q (C^{25}), 15.93 q (C^{24}), 17.77 t (C^{6}), 18.93 q (C^{30}), 20.45 t (C^{11}), 22.36 t (C^{2}), 25.06 t (C^{12}), 27.75 q (C^{23}), 29.20 t (C^{32}), 30.15 t (C^{15}), 31.19 t (C^{21}), 31.72 t (C^{16}), 33.85 t (C^{7}), 36.51 t (C^{22}), 36.68 s (C^{10}), 37.80 d (C^{13}), 38.04 t (C^{1}), 38.26 s (C^{4}), 40.24 s (C^{8}), 41.92 s (C^{14}), 46.51 d (C^{19}), 49.02 d (C^{18}), 50.07 d (C^{9}), 50.82 q (C^{34}), 55.30 d (C^{5}), 56.10 s (C^{17}), 66.98 t (C^{31}), 87.03 d (C^{3}), 109.13 t (C^{29}), 150.12 s (C^{20}), 154.06 s (C^{33}), 176.21 s (C^{28}). Mass spectrum: m/z 556.4274 $[M]^+$. $C_{34}H_{56}N_2O_4$. Calculated: M 556.4264.

Methyl 3β-[2-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)ethoxy]lup-20(29)-en-28-oate (XXVIII). Trifluoroacetic anhydride, 0.018 ml (0.13 mmol), was added under argon to a solution of 0.073 g (0.13 mmol) of compound **XVIII** in 3 ml of methylene chloride. The mixture was kept for 24 h at room temperature, washed with 10% hydrochloric acid and water, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by chromatography on silica gel using chloroform as eluent. Yield 0.07 g (85%), mp 128–131°C. IR spectrum, ν, cm^{-1}: 1735 (C=O), 1643 (C=C). ^1H NMR spectrum, δ, ppm (J, Hz): 0.59 m (1H, 5-H), 0.65 s (3H, $C^{24}H_3$), 0.76 s (3H, $C^{25}H_3$), 0.78 s (3H, $C^{26}H_3$), 0.88 s (3H, $C^{27}H_3$), 0.93 s (3H, $C^{23}H_3$), 1.55 t (1H, 18-H, J = 11.3), 1.66 (3H, $C^{30}H_3$), 2.74 d.d (1H, 3-H, J = 4.1), 2.93–3.15 m (3H, 7-H, 19-H) 3.64 s (3H, $C^{31}H_3$), 3.99 m (1H, 8-H), 4.58 br.s and 4.72 br.s (1H each, 29-H). ^{13}C NMR spectrum, δ_C, ppm: 14.67 q (C^{27}), 15.94 q (C^{26}), 16.08 q (C^{25}, C^{24}), 18.18 t (C^{6}), 19.37 q (C^{30}), 20.90 t (C^{11}), 22.89 t (C^{2}), 25.53 t (C^{12}), 27.34 q (CF_3), 27.73 q (C^{23}), 29.66 t (C^{15}), 30.61 t (C^{21}), 32.17 t (C^{16}), 27.26 t ($C^{7'}$) 34.30 t (C^{7}), 36.97 t (C^{22}), 37.13 s (C^{10}), 38.25 d (C^{13}), 38.49 s (C^{1}), 38.76 t (C^{4}), 40.70 s (C^{8}), 42.38 s (C^{14}), 46.97 d (C^{19}), 49.48 d (C^{18}), 50.53 d (C^{9}), 51.24 q (C^{31}), 55.75 d (C^{5}), 56.55 s (C^{17}), 65.49 t ($C^{8'}$), 65.49 s ($C^{5'}$), 87.46 d (C^{3}), 109.55 t (C^{29}), 150.60 s (C^{20}), 169.76 s ($C^{3'}$), 176.63 s (C^{28}). ^{19}F NMR spectrum: δ_F 96.25 ppm (3F, CF_3). Mass spectrum: m/z 634.3954 $[M]^+$. $C_{36}H_{53}F_3N_2O_4$. Calculated: M 634.3952.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 09-03-00183).

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