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Synthetic Transformations of Higher Terpenoids: XI. Synthesis of A-Nor-5β*H*-19β,28-epoxy-18α-olean-3-one Derivatives

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Abstract—Starting with allobetulin triterpenoid A-nor-derivatives with a *cis*-junction of A/B rings were prepared for the first time.

Allobetulin (**I**) is a pentacyclic triterpenoid of the oleanane series contained in triterpene substances of the birch bark. It is easily formed from betulin by isomerization at treatment with acids [1, 2]. The allobetulin transformation is obviously advantageous taking into account its biological activity [3–7]. The allobetulin possesses a moderately pronounced activity with respect to influenza B virus [8]. We found that 28-oxo-allobetulone effectively inhibited the proliferation of influenza virus A/Rostock/34 (H7N1) [9]. A nor-derivative of allobetuline proved to be a highly active antifeedant for larva *Heliothis zea* [3]. Allobetulin derivatives are also known to be in some cases used as biomarkers [10].

Syntheses of certain A-nor-derivatives were formerly described for glycyrrhetic [11, 12] and oleanolic [15–17] acids, lupeol [6], and betulin [13, 14]. It is noteworthy that several examples are known [3,10, 18–20] of reactions on the A ring of allobetulin where the junctions of all rings remains intact The field of synthetic conversions to new derivatives with altered junction of A/B rings is not developed up till now. A preparation was recently described of allobetulin 3-isopropylidene derivative (**II**) involving treatment of 3-hydroxytriterpenoid **I** with PCl_5 [1], its isomerization into *endo*-isomer **III** under catalysis with acid was studied, and A-nor-ketone **IV** was synthesized [21].

Here we report for the first time on synthetic transformations of A-nor-5α*H*-19β,28-epoxy-18α-olean-3(4)-ene (**II**) resulting in allobetulin derivatives with a *cis*-junction of A/B rings. The latter compounds are interesting as new physiologically active substances.

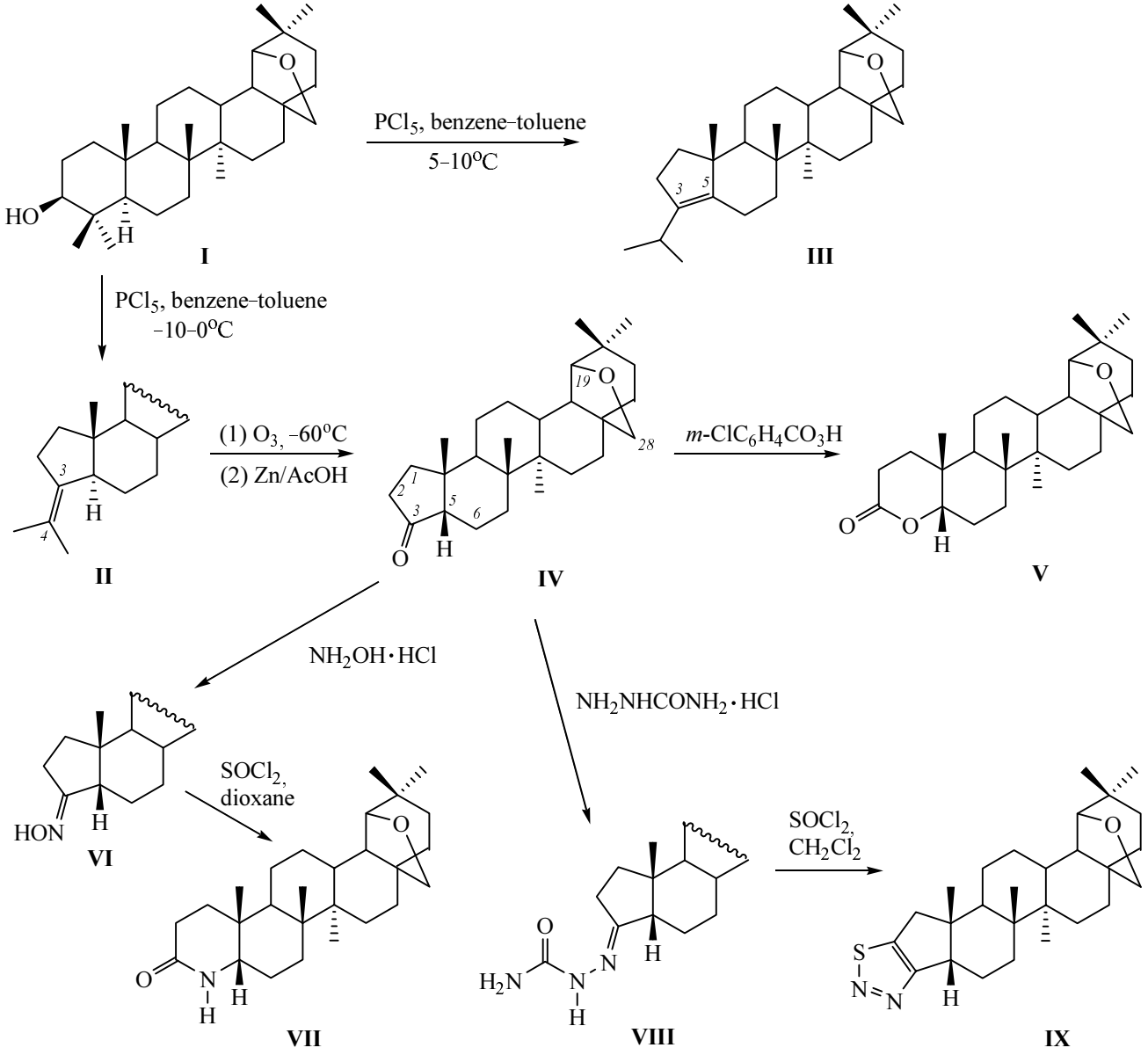
The treatment with PCl_5 of 3-hydroxytriterpenoids and steroids is known to be the most common method for A ring contraction [22–25]. Allobetulin (**I**) dehydration effected by PCl_5 in a benzene–toluene mixture at –10–0°C occurred with the Wagner–Meerwein rearrangement and afforded 3-isopropylidene derivative (**II**) in 82% yield (after recrystallization). In the ^{13}C NMR spectrum the signals from atoms C^3 and C^4 appeared at δ 120.6 and 135.5 ppm respectively. The reaction carried out at higher temperature (5–10°C) gave rise in a quantitative yield to isomeric A-nor-triterpene (**III**) with an *endo*-cyclic $\Delta^{3,5}$-bond containing in the ^1H NMR spectrum a signal of H^4 proton as a septet at δ 2.65 ppm (*J* 6.8 Hz).

The ozonolysis of 3-isopropylidene derivative (**II**) in dichloromethane furnished A-nor-5β*H*-3-ketone **IV** in 63% yield. As a result of acid catalysis in the course of ozonides reduction with zinc in acetic acid the configuration of H^5 hydrogen changed from α to β, and the junction of A/B rings from the *trans*-state into the more stable *cis*-state [21]. Similarly to the case of methyl-3-oxo-A-nor-5β*H*-oleanoate [14] in the ^{13}C NMR spectrum of A-nor-ketone **IV** the signals from atoms C^3 and C^5 are observed at δ 220.8 and 56.9 ppm and are in the chemical shift unlike the signals of the same atoms in the spectrum of αH^5-analog (δ 217.0 and 62.0 ppm respectively [14]). We carried out the assignment of proton and carbon signals in the spectra of A-nor-5β*H*-3-ketone **IV** using calculations by additive schemes and ^{13}C NMR spectra registered with modulation of the CH-coupling constant and two-dimensional spectra with CH-correlation (CHCORR). It follows from the CHCORR

spectrum that the protons of the cyclopentanone fragment and its close surrounding (H^{1a}, H^2, H^5, H^6 attached to atoms C^1, C^2, C^5, C^6 with chemical shifts 34.7, 36.1, 57.2, 17.2 ppm respectively) appear as a multiplet in the region 1.85–2.30 ppm. The signals of protons linked to atoms C^1, C^7, C^{11}, C^{13}, C^{18} are present in the region 1.40–1.75 ppm, and the signals of protons at atoms C^9, C^{12}, C^{15}, C^{16}, C^{21}, C^{22} give rise to peaks at 1.10–1.40 ppm.

A-Nor-5β*H*-3-ketone **IV** is a convenient intermediate for syntheses of various derivatives with a modified A ring. Oxidation of A-nor-5β*H*-3-ketone **IV** with *m*-chloroperbenzoic acid by Bayer–Williger reaction furnished lactone **V**, and a complete conversion of the initial compounds was attained in 7 days. The chemical shift values for resonances of H^1, H^2 , and H^5 (δ 2.30–2.50 and 4.00 ppm) in the ^1H NMR spectrum and of C^5 and C^3 in the ^{13}C NMR spectrum (δ 82.4 and 173.8 ppm) unambiguously evidence the formation of A-nor-5β*H*-A-homo-4-oxa-19β,28-epoxy-18α-olean-3-one (**V**). The preparation of the αH^5-analog of lactone **V** was described in [18, 26].

The reaction of A-nor-5β*H*-3-ketone **IV** with hydroxylamine hydrochloride in pyridine afforded oxime **VI**. No evidence on Beckmann rearrangement was published for triterpene A-nor-ketoximes, and in the series of pentacyclic triterpenes the data are limited to several compounds (for instance, for lupenone oxime [27], allobetulin oxime [28], and glycyrrhetic acid oxime [29, 30]). In the



most cases the oxime rearrangement under standard conditions yielded a mixture of lactams and ω-ketonitriles apparently due to the presnce of a gem-dimethyl moiety in the α-position with respect to the oximino group [12]. The rearrangement of oxime **VI** in the presence of $SOCl_2$ in anhydrous dioxane [31] occurred with a quantitative yield of lactam **VII** and without ring opening. The structure of lactam was derived from spectral data. In the IR spectrum a strong band was observed characteristic of amide carbonyl (1670–1640 cm^{-1}), and absorption bands at 1610 and 3240–3230 cm^{-1} corresponding to the bending and stretching vibrations of NH bond. The peaks in the NMR spectra correspond-ing to CONH group appear at δ 172.8 ppm (^{13}C) and δ 6.30 ppm (^{1}H). The formation of A-nor-5β*H*-A-homo-4-aza-19β,28-epoxy-18α-olean-3-one (**VII**) is confirmed by the chemical shifts and signal patterns of H^2 (d.d, δ 2.25 ppm) and H^5 (br.s, 3.22 ppm) peaks in the ^{1}H NMR spectrum. In compounds **V** and **VII** the *cis*-junction of A/B rings is retained as confirmed by the remaining pattern of the H^5 signal looking as a broadened singlet with small coupling constants.

We attempted to synthesize 1,2,3-thiadiazole fuzed with A-nor-3-ketone **IV**. The thiadiazole fragment is known to be present in the structure of some important biologically active substances (e.g., cephalosporin antibiotics) [32], and the synthesis of 1,2,3-thiadiazoles with the use of naturally-occurring compounds was reported only for steroid from androstane series [33] and ω-ketonitrile derivatives of (+)-carene and α-pinene [34]. 1,2,3-Thiadiazole **IX** was prepared by Hard–Mowry procedure from semicarbazone **VIII** obtained by treating ketone **IV** with semicarbazide hydrochloride in a water–ethanol mixture. The heterocyclization occurred in anhydrous methylene chrloride at room temperature in the presence of 10-fold excess of $SOCl_2$. Yield of 1,2,3-thiadiazole **IX** was 74% after column chromatography on aluminum oxide. In the ^{13}C NMR spectrum the signals of the thiadiazole fragment appeared at δ 153.9 (C^2) and 173.8 ppm (C^3).

EXPERIMENTAL

IR spectra were recorded on spectrophotometer Specord M-80 from samples as mulls with mineral oil. NMR spectra of ^{13}C and ^{1}H were registered on spectrometer Bruker AM-300 at operating frequencies 75.5 and 300 MHz respectively from solutions in deuterochloroform, internal reference TMS. The melting points were measured on a Boëtius heating block. TLC was carried out on Silufol plates (Chemapol, Czechia), eluent chloroform–methanol, 25 : 1 , development with. 10% solution of phosphotungstic acid in ethanol followed by heating to 100–120°C for 2–3 min. Allobetulin (**I**) was obtained by procedure [1].

A-Nor-5α*H*-19β,28-epoxy-18α-olean-3-ene (δ-apo-allobetulin) (II). To a solution of 1 mmol (0.44 g) of allobetulin (**I**) in 100 ml of anhydrous benzene–toluene mixture (1:1) at –10–0°C was added in a single portion 5.5 mmol (0.50 g) of PCl_5, and the mixture was stirred for 30 min (TLC monitoring). Then 30 ml of saturated water solution of Na_2CO_3 was added, and the stirring was continued for 30 min allowing the reaction mixture to warm to room temperature. The organic layer was separated, washed with water, dried with Na_2SO_4, and evaporated in a vacuum. The residue was crystallized from 2-propanol. Yield 0.35 g (82%). White substance, mp 211–213°C, $[\alpha]_D^{20}$ 58° (*c* 0.01, $CHCl_3$). IR spectrum, cm^{-1}: 1750, 1630, 1530, 1470, 1380, 1320, 1270, 1240, 1150, 1050, 1020, 910, 780, 730 ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.61 c, 0.71 c, 0.93 c, 0.97 c, 1.58 c, 1.73 c (21H, $7CH_3$), 1.00–1.80 m (CH_2, CH), 2.10–2.20 m (2H, H^2), 3.45 d, 3.80 d (1H, H^{28}, *J* 7.8 Hz), 3.55 c (1H, H^{19}). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.5, 15.1, 15.7, 19.4, 22.8, 23.3, 23.5, 24.6, 26.3, 26.4, 26.7, 28.3, 28.9, 32.8, 33.7, 34.3, 36.3, 36.9, 39.8, 40.4, 40.7, 41.6, 44.5, 46.9, 48.9, 56.4, 71.3 (C^{28}), 88.0 (C^{19}), 120.6 (C^3), 135.5 (C^4). Found, %: C 84.55; H 11.10. $C_{30}H_{48}O$. Calculated, %: C 84.84; H 11.39.Publ.: mp 210–212°C [1], mp 216–218°C, $[\alpha]_D^{22}$ +48.2° (*c* 1.31) [21].

A-Nor-5α*H*-19β,28-epoxy-18α-olean-3(5)-ene (III) was prepared in the same way as compound **II**, maintaining the reaction mixture temperature at 5–10°C. The product was crystallized from ethanol Yield 0.34 g (80%). Yellow substance, mp 199–201°C, $[\alpha]_D^{20}$ +82° (*c* 0.01, $CHCl_3$). IR spectrum, cm^{-1}: 1760, 1620, 1530, 1460, 1360, 1310, 1280, 1240, 1160, 1040, 910, 790, 720. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.79 c, 0.85 c, 0.86 c, 0.92 c, 0.98 c, 1.00 c, 1.03 c (21H, $7CH_3$), 1.10–2.30 m (CH_2, CH), 2.65 s (1H, H^4, *J* 6.8 Hz), 3.42 d, 3.80 d (1H, H^{28}, *J* 7.8 Hz), 3.54 C (1H, H^{19}). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.4, 14.2, 19.0, 19.7, 21.3, 21.8, 23.6, 24.5, 26.2, 26.3, 26.5, 26.7, 27.3, 28.7, 32.4, 32.6, 34.5, 36.2, 36.7, 40.6, 40.8, 41.4, 42.1, 46.7, 49.8, 50.0, 71.2 (C^{28}), 87.9 (C^{19}), 136.1 (C^4), 139.8 (C^3). Found, %: C 85.12; H 10.98. $C_{30}H_{48}O$. Calculated, %: C 84.84; H 11.39. Publ.: mp 200–201°C, $[\alpha]_D^{22}$ +81° (*c* 1.23) [21].

A-Nor-5β*H*-19β,28-epoxy-18α-olean-3-one (IV). Through a solution containing 2 mmol (0.85 g) of compound **II** in 50 ml of CH_2Cl_2 an ozone flow was passed at –60°C till complete consumption of the initial compound (TLC monitoring). The mixture was warmed to 0°C, 10 ml of glacial AcOH and 1 g of zinc dust were added, and the mixture was stirred for 1 h. The reaction mixture was filtered, the filtrate was washed with saturated water solution of Na_2CO_3 (2 × 20 ml), with water (2 × 20 ml), dried on Na_2SO_4, and evaporated in a vacuum. The residue was subjected to purification by column chromatography on aluminum oxide (eluent benzene). Yield 0.49 g (62%). Colorless substance, mp 213°C, $[\alpha]_D^{20}$ +159° (*c* 1, $CHCl_3$). IR spectrum, cm^{-1}: 1730, 1670, 1500, 1420, 1390, 1300, 1200, 1120, 1030, 970, 890, 710. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.68 C (3H, CH_3, H^{27}), 0.70 C (3H, CH_3, H^{25}), 0.83 C (3H, CH_3, H^{30}), 0.92 C (3H, CH_3, H^{26}), 1.20 C (3H, CH_3, H^{29}), 1.10–1.40 μ (11H, H^9, H^{12}, H^{15}, H^{16}, H^{21}, H^{22}), 1.40–1.75 μ (7H, H^{1a}, H^7, H^{11}, H^{13}, H^{18}), 1.85–2.30 m (6H, H^{1b}, H^2, H^5, H^6), 3.35 d, 3.65 d (1H, H^{28}, *J* 7.8 Hz), 3.42 C (1H, H^{19}). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.0 (C^{27}), 14.7 (C^{26}), 17.2 (C^6), 23.0 (C^{11}), 24.4 (C^{29}), 24.7 (C^{25}), 26.0 (C^{12}), 26.2 (C^{15}), 26.4 (C^{22}), 27.7 (C^7), 28.7 (C^{30}), 32.5 (C^{21}), 34.5 (C^9), 34.7 (C^1), 35.6 (C^{16}), 36.1 (C^2), 36.5 (C^{20}), 39.0 (C^{13}), 39.5 (C^{10}), 40.5 (C^8), 41.3 (C^{17}), 41.7 (C^{14}), 46.6 (C^{18}), 57.2 (C^5), 70.9 (C^{28}), 87.4 (C^{19}), 220.8 (C^3). Found, %: C 81.15; H 10.12. $C_{27}H_{42}O_2$. Calculated, %: C 80.90; H 10.62. Publ.: mp 215–216°C, $[\alpha]_D^{22}$ +151.6° (*c* 1.22) [21].

A-Nor-5β*H*-A-homo-4-oxa-19β,28-epoxy-18α-olean-3-one (V). To a solution of 1 mmol (0.40 g) of compound **IV** in 20 ml of anhydrous CH_2Cl_2 was added 0.8 g of *m*-chloroperbenzoic acid. The reaction was kept in the dark for 7 days (TLC monitoring), then it was washed with 5% KI solution (2 × 20 ml), with 5% Na_2S solution (2 × 20 ml), with water (3 × 40 ml), dried on Na_2SO_4, evaporated in a vacuum, and subjected to column chromatography on Al_2O_3 (eluent chloroform). Yield 0.32 g (77%). Colorless substance, mp 118–120°C, $[\alpha]_D^{20}$ +34° (*c* 0.01, $CHCl_3$). IR spectrum, cm^{-1}: 1760, 1720, 1660, 1440, 1380, 1250, 1130, 1110, 1020, 930, 820, 780, 710. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.82 C, 0.86 C, 0.89 C, 0.98 C, 1.03 C (15H, $5CH_3$), 1.10–1.90 m (CH_2, CH), 2.30–2.50 m (4H, H^1, H^2), 3.40 d, 3.73 d (1H, H^{28}, *J* 7.9 Hz), 3.48 C (1H, H^{19}), 4.00 br.s (1H, H^5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.2, 14.6, 14.8, 21.6, 21.7, 23.1, 24.4, 24.7, 25.9, 26.2, 27.1, 28.7, 32.5, 33.4, 34.3, 35.0, 36.2, 36.5, 39.5, 40.2, 40.8, 41.3, 46.4, 71.1 (C^{28}), 82.4 (C^5), 87.7 (C^{19}), 173.8 (C^3). Found, %: C 78.45; H 10.02. $C_{27}H_{42}O_3$. Calculated, %: C 78.21; H 10.21.

A-Nor-5β*H*-19β,28-epoxy-18α-olean-3-oxime (VI). To a solution of 1 mmol (0.40 g) of compound **IV** in 30 ml of anhydrous pyridine was added 0.5 g of $NH_2OH{\cdot}HCl$, and the mixture was boiled for 2 h. On cooling the reaction mixture was poured into 150 ml of 5% HCl solution, the separated precipitate was filtered off, washed with water, and dried. Yield 0.35 g (85%). Colorless substance, mp 195–197°C, $[\alpha]_D^{20}$ +58° (*c* 0.01, $CHCl_3$). IR spectrum, cm^{-1}: 3300–3150, 1760, 1710, 1670, 1470, 1380, 1280, 1240, 1150, 1120, 1040, 950, 840, 820, 780, 730. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.79 C, 0.82 C, 0.93 C, 1.02 C, 1.09 C (15H, $5CH_3$), 1.10–1.80 m (CH_2, CH), 1.90–2.00 m (2H, H^1), 2.30 br.s (1H, H^5), 2.45–2.55 m (2H, H^2), 3.43 d, 3.78 d (1H, H^{28}, *J* 7.8 Hz), 3.56 C (1H, H^{19}). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.2, 15.2, 18.9, 23.1, 23.5, 24.5, 25.1, 26.2, 26.3, 26.4, 26.6, 28.8, 32.7, 34.6, 36.2, 36.7, 37.3, 38.0, 39.7, 40.8, 41.4, 43.7, 46.8, 49.9, 71.3 (C^{28}), 87.8 (C^{19}), 167.6 (C^3). Found, %: C 78.85; H 10.15; N 3.53. $C_{27}H_{43}NO_2$. Calculated, %: C 78.40; H 10.47; N 3.38.

A-Nor-5β*H*-A-homo-4-aza-19β,28-epoxy-18α-olean-3-one (VII). To a solution of 1 mmol (0.41 g) of compound **VI** in 50 ml of anhydrous dioxane 1 ml of a freshly-distilled $SOCl_2$ was added, and the mixture was stirred for 5 h at room temperature. Then it was poured into 100 ml of water, the separated precipitate was filtered off, washed with water till neutral washings, and dried. Yield 0.36 g (87%). Colorless substance, mp 227–229°C, $[\alpha]_D^{20}$ +12° (*c* 0.01, $CHCl_3$). IR spectrum, cm^{-1}: 3240–3230, 1760, 720, 1670–1640, 1610, 1430, 390, 1250, 1110, 1040, 930, 830, 710. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.76 C, 0.87 C, 0.89 C, 0.95 C, 1.01 C (15H, $5CH_3$), 1.10–1.95 (CH_2, CH), 2.25 d.d (2H, H^2, *J* 5.9, *J* 9.3 Hz), 3.22 br.s (1H, H^5), 3.42 d, 3.73 d (1H, H^{28}, *J* 7.8 Hz), 3.48 C (1H, H^{19}), 6.30 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.4, 15.4, 21.1, 22.8, 24.4, 24.5, 24.7, 26.0, 26.3, 26.4, 27.8, 28.7, 32.6, 33.8, 34.1, 34.2, 34.4, 36.1, 36.6, 39.7, 41.0, 46.7, 58.0, 71.1 (C^{28}), 87.7 (C^{19}), 172.8 (CONH). Found, %: C 78.08; H 10.35; N 3.25. $C_{27}H_{43}NO_2$. Calculated, %: C 78.40; H 10.47; N 3.38.

A-Nor-5β*H*-19β,28-epoxy-18α-olean-3-one semicarbazone (VIII). To a solution of 1 mmol (0.40 g) of compound **IV** in 10 ml of ethanol was added at stirring 10 ml of 1.2 M water solution of semicarbazide

hydrochloride and 0.5 g of $NaAc·3H_2O$. The mixture was stirred at 40°C for 6 h. Then the reaction mixture was poured into 100 ml of water, the separated precipitate was filtered off, washed with water, dried, and crystallized from ethanol. Yield 0.39 g (86%). Colorless substance, mp >280°C. IR spectrum, cm^{-1}: 3160–3120, 1700, 1680, 1570, 1450, 1340, 1210, 1060, 970, 720. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.71 c, 0.76 c, 0.93 c, 1.03 c, 1.12 c (15H, $5CH_3$), 1.20–2.00 m (CH_2, CH), 2.20–2.30 m (3H, H^2, H^5), 3.43 d, 3.77 d (1H, H^{28}, *J* 7.7 Hz), 3.55 C (1H, H^{19}), 7.49 br.s (3H, NH, NH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.1, 15.1, 18.7, 23.0, 23.6, 24.5, 25.5, 26.1, 26.3, 26.5, 28.8, 29.7, 32.7, 34.6, 36.3, 36.7, 37.1, 38.1, 39.8, 40.7, 41.4, 43.2, 46.7, 51.0, 71.7 (C^{28}), 87.8 (C^{19}), 157.4 ($C^{1'}$), 160.7 (C^3). Found, %: C 74.21; H 10.10; N 9.42. $C_{28}H_{45}N_3O_2$. Calculated, %: C 73.80; H 9.95; N 9.22.

A-Nor-5β*H*-19β,28-epoxy-18α-olean-2-eno-[3,2-*d*][1,2,3]thiadiazole (IX). To a dispersion of 1 mmol (0.46 g) of compound **VIII** in 20 ml of anhydrous CH_2Cl_2 was added at stirring in one portion 10 equiv (1.45 ml) of freshly-distilled $SOCl_2$. The mixture was left overnight, then 20 ml of water was added, the organic layer was washed with 10% Na_2CO_3 solution (3×20 ml), with water (3×20 ml), dried on $MgSO_4$, and evaporated in a vacuum. The residue was subjected to column chromatography on alumina, eluent benzene. Yield 0.33 g (75%). Light-brown substance, mp 210–212°C, $[\alpha]_D^{20}$ +69° (*c* 0.01, $CHCl_3$). IR spectrum, cm^{-1}: 1730, 1700, 1480, 1430, 1360, 1300, 1260, 1250, 1230, 1180, 1130, 1070, 1020, 980, 940, 880, 770, 730. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.55 c, 0.75 c, 0.90 c, 1.03 c, 1.22 c (15H, $5CH_3$), 1.10–2.20 m (CH_2, CH), 2.30–2.40 m (2H, H^1), 3.45 d, 3.72 d (1H, H^{28},*J* 7.7 Hz), 3.56 C (1H, H^{19}). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 12.9, 14.9, 18.5, 22.9, 23.4, 24.3, 25.4, 25.9, 26.2, 26.4, 28.5, 32.5, 34.5, 36.0, 37.0, 38.0, 39.7, 40.5, 41.2, 43.1, 46.6, 50.9, 71.0 (C^{28}), 87.9 (C^{19}), 153.9 (C^2), 173.8 (C^3). Found, %: C 73.78; H 8.97; N 6.22; S 7.01. $C_{27}H_{40}N_{20}OS$. Calculated, %: C 73.58; H 9.15; N 6.35; S 7.27.

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