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Synthesis of 30-Bromo- and 30-Azido-20-oxo-29-nor-3β,28-diacylbetulin Derivatives

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Abstract—Ozonolysis of 3β,28-diacyloxylup-20,29-enes gave 20-oxo-29-nor-3β,28-diacyloxylup-20,29-enes, which were brominated with molecular bromine in AcOH to obtain a mixture of 30-bromo- and 30-dibromo derivatives. Ozonolysis of 30-bromo-3β,28-diacylbetulin produced 29-nor-30-bromoketones, whose reaction with sodium azide afforded 29-nor-30-azidoketones of the lupane series.

Keywords: betulin, ozonolysis, α-azidoketones

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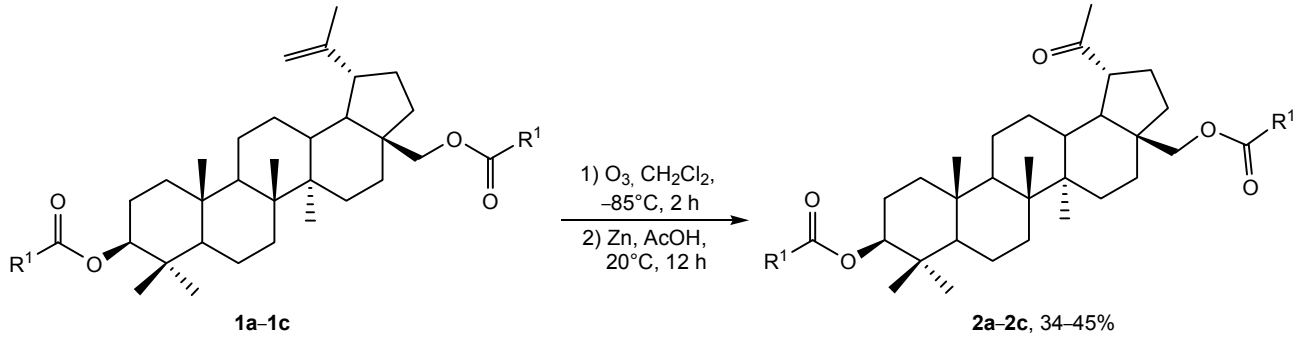
The recent discovery of the anticancer and cytotoxic activity of pentacyclic triterpenoids of the lupane series [1–3] gave new impetus to research into chemical modification of betulin and synthesis of its previously unknown derivatives [4–12]. We earlier synthesized conjugates of lupane triterpenoids and oleanan with ferrocene by aldol condensation and click chemistry [13–15]. The aim of the present work was to synthesize 30-bromo- and 30-azido-20-oxo-29-nor-3β,28-diacyl derivatives of betulin.

Ozonolysis is widely used for oxidative functionalization of pentacyclic triterpenoids [16–18]. By ozonolysis of 3β,28-diacetylbetulin **1a** [19–21], as well as dipropanoylbetulin **1b** [22, 23] and dibenzoylbetulin **1c** [24, 25] we obtained 20-oxo-29-nor derivatives **2a–2c** (Scheme 1).

Evidence for the formation of compounds **2a–2c** is provided by the appearance of an additional acetyl proton signal (δ 2.14–2.16 ppm) in the ^{1}H NMR spectra and the third, downfield (δ 210.8–211.5 ppm) carbonyl carbon signal in the ^{13}C NMR spectra.

The bromination of ketones **2a–2c** with molecular bromine in acetic acid at 10–15°C (Scheme 2, method *a*) gave a mixture of 30-bromo- (**3a**, **3b**) and 30,30-dibromo derivatives **4a–4c**, which was separated by column chromatography. With pyridinium perbromide in AcOH, the same result was obtained. It is interesting to note that the reaction with dibenzoyl derivative **2c**

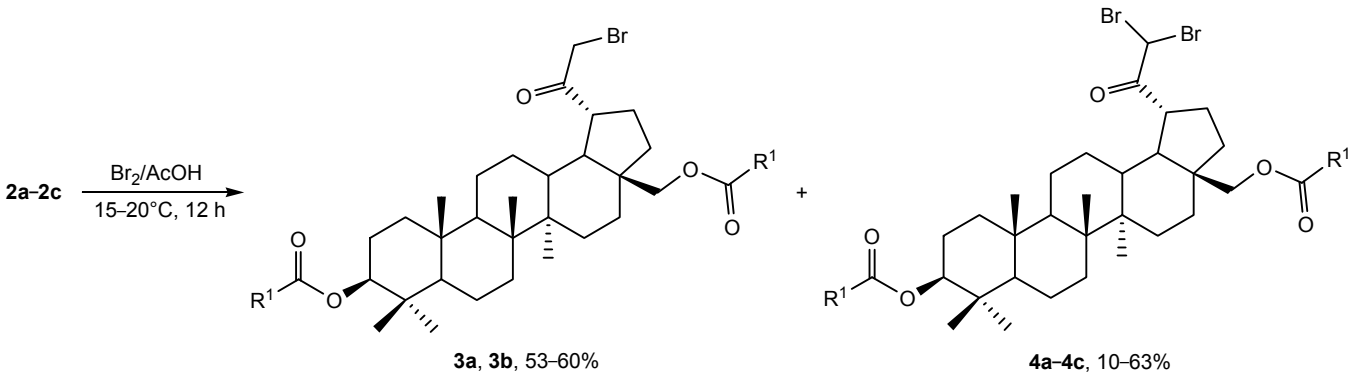
Scheme 1.



1a–1c **2a–2c**, 34–45%

1, **2**, R = Me (**a**), R = Et (**b**), R = Ph (**c**).

Scheme 2.

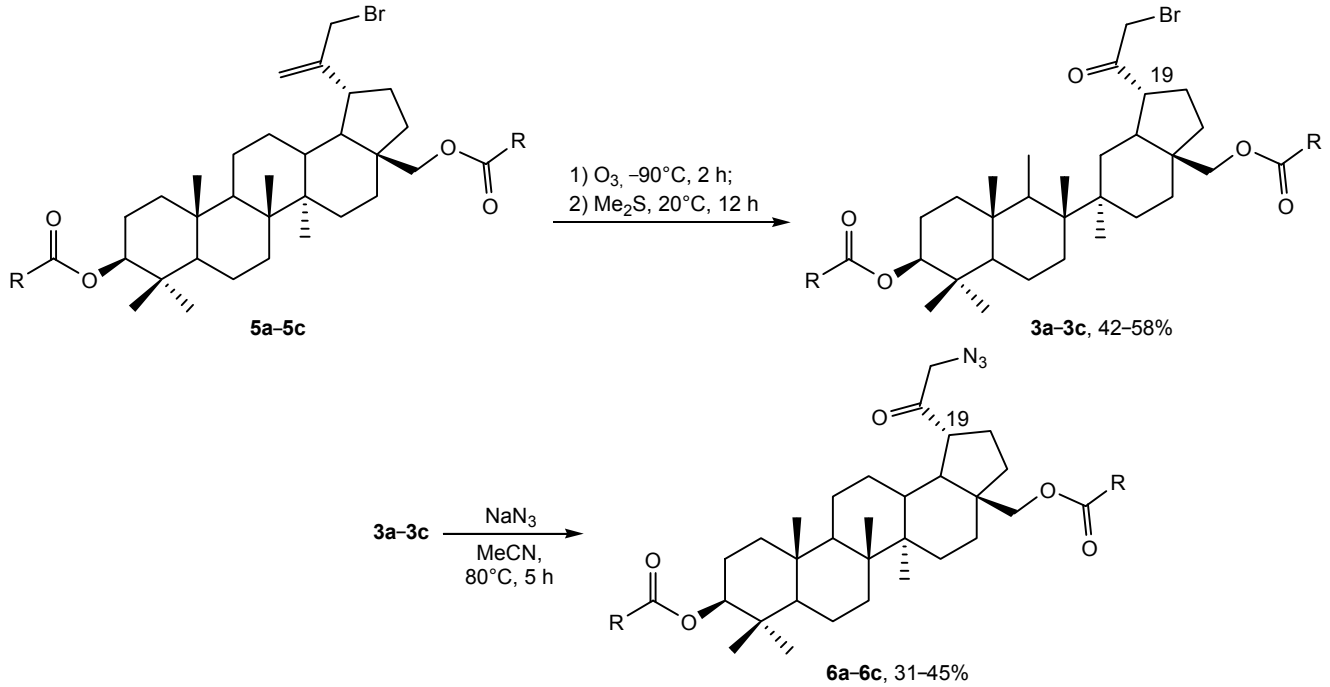


under these conditions resulted in the exclusive formation of dibromide **4c** (yield 63%).

The formation of bromides **3a** and **3b** is accompanied by the disappearance of the acetyl singlet at δ 2.14–2.16 ppm and appearance of two doublets of the diastereotopic $C^{30}H_2$ protons at δ 3.80–3.81 and 3.89–3.94 ppm (^3J 12.0–12.8 Hz). The ^{1}H NMR spectra of dibromoketones **4a–4c** contain a characteristic $C^{30}\underline{H}Br_2$ singlet at δ 5.93–5.95 ppm

The R_f values of dibromides **4a–4c** are slightly larger compared to bromides **3a–3c**, but still very close to them, and, therefore, these groups of compounds are quite difficult to separate by column chromatography. To obtain pure bromoketones **3a–3c**, we developed a synthetic approach involving ozonolysis of allyl bromides **5a–5c** (Scheme 3, method *b*) [26]. The reaction of bromoketones **3a–3c** with sodium azide in MeCN under reflux gave azides **6a–6c** in yields of 31–45%. The R_f values of azidoketones **6a–6c** are slightly larger than those of bromides **3a–3c**. The IR spectra of compounds **6a–6c** contain a very strong absorption band of the azido group at 2105–2106 cm^{-1}. The ^{1}H NMR spectra of bromoketones **3a–3c** and azidoketones **6a–6c** are quite similar to each other; as a difference criterion, we can consider the upfield shift

Scheme 3.



1, **2**, R = Me (**a**), R = Et (**b**), R = Ph (**c**).

of the HC^{19} proton signal from δ 2.95–3.05 ppm in bromides **3a–3c** to δ 2.67–2.69 ppm in azides **6a–6c**.

Further on we undertook an attempt to involve azidoketones in a click reaction with ethynylferrocene, catalyzed by CuI/TMEDA [14, 15, 26]. However, under these conditions azidoketones **6a–6c** fail to react with ethynylferrocene. Attempts to perform the click reaction in "classical" conditions, specifically in aqueous *tert*-butanol at 40–50°C in the presence of a $CuSO_4$/sodium ascorbate catalytic system [27], too, have not met with success. Click reactions of α-azidoketones have been reported in the literature [28–30], though few in number. Obviously, the carbonyl group in our triterpenoid substrate so strongly deactivates the azide function that a copper-catalyzed click reaction becomes impossible.

Thus, our developed method of synthesis of pure bromoketones **3a–3c** allows further functionalization of such 29-nor-triterpenoids by C^{20} and C^{30} (azidoketones **6a–6c**, aminoketones, etc.) with the aim of preparing novel heterocyclic derivatives of the lupane series.

EXPERIMENTAL

The IR spectra were recorded on a Bruker VERTEX 80v spectrometer in thin films obtained by evaporation of chloroform solutions. The ^1H and ^{13}C NMR spectra in $CDCl_3$ were obtained on a Bruker Avance III HD 400 spectrometer at 400 and 100 MHz, respectively, using HMDS as internal references for ^1H NMR and the $CDCl_3$ signal (δ_C 77.0 ppm) as internal references for ^{13}C NMR. Elemental analysis was performed on an Elementar Vario EL cube analyzer. The melting points were determined on a PTP device. The specific rotation was measured on a Perkin–Elmer 341 polarimeter in chemical grade chloroform containing 0.5% of ethanol and reported in $10^{-1}\cdot deg\cdot g^{-1}\cdot cm^2$. Column chromatography was performed on an Alfa Aesar Silicagel 60 (0.060–0.2 mm, 70–230 mesh), eluent petroleum ether–ethyl acetate. The reaction progress was monitored, and the R_f values were measured by TLC on Sorbfil plates, eluent petroleum ether–ethyl acetate, 7 : 3; the spots were visualized by spraying 20% H_2SO_4 followed by heating. Dimethyl disulfide was purchased from Merck and pure grade petroleum ether and chemical grade ethyl acetate, dichloromethane, and glacial acetic acid were purchased from Russian producers.

20-Oxo-29-norlupane-3β,28-diyl diacetate (2a) was obtained by the ozonolysis of 4.0 g (7.5 mmol) of betulin 3β,28-diacetate (**1a**) [19–21] in 150 mL of anhydrous dichloromethane at ~ –90°C (a mixture of 50% aqueous ethanol and liquid nitrogen) for 2 h by the procedure in [31, 32]. After ozonolysis was complete, 4 mL of AcOH, 2 mL of conc. HCl, and 2 g of Zn dust were added to the reaction mixture, and it was stirred and left to stand for 12 h at room temperature to decompose ozonide. The solution was then decanted from residual zinc, washed with water and $NaHCO_3$ solution, and dried over $MgSO_4$. The solvent was removed by distillation, and the residue was subjected to column chromatography. Yield 1.90 g (48%), colorless crystals, mp 183–185°C (190–191°C [32]; 188–189°C [33]), R_f 0.38. The ^1H NMR spectrum coincides with that in [33]. ^{13}C NMR spectrum, δ, ppm: 14.57, 15.87, 16.02, 16.39, 18.03, 20.70, 20.90, 21.19, 23.55, 26.88, 27.12, 27.40, 27.83, 29.26, 29.56, 33.93, 34.33, 36.33, 36.95, 37.68, 38.22, 40.68, 42.44, 46.24, 49.26, 50.01, 51.56, 55.21, 62.39, 80.70, 170.79 ($C=O_{ester}$), 171.35, ($C=O_{ester}$), 211.49 ($C=O_{ketone}$).

20-Oxo-29-norlupane-3β,28-diyl dipropanoate (2b) was obtained by the ozonolysis of 2.2 g (3.9 mmol) of betulin 3β,28-dipropanoate **1b** [22, 23] in 150 mL of anhydrous dichloromethane. Further workup was performed as described for compound **2a**. Yield 505 mg (23%), colorless crystals, mp 125–127°C. $[\alpha]_D^{25}$ –11.5 (*c* 1, $CHCl_3$), R_f 0.50. IR spectrum, ν, cm^{-1} (thin film): 2945, 2874, 1733 (C=O), 1462, 1423, 1390, 1378, 1365, 1277, 1216, 1187, 1083, 1017, 970, 735. ^1H NMR spectrum, δ, ppm: 0.81 s (6H, 2Me), 0.83 s (3H, Me), 0.97 s (3H, Me), 1.00 s (3H, Me), 1.09–1.14 m (6H, 2Me), 2.12 s [3H, $CH_3C(O)$], 2.27–2.35 m (4H, OCH_2), 2.63 m (1H, H^{19}), 3.77 d (1H, H^{28}, ^2J 12.0 Hz), 4.21 d (1H, H^{28}, ^2J 12.0 Hz), 4.44 m (1H, H^3). ^{13}C NMR spectrum, δ, ppm: 8.63, 8.80, 14.16, 15.45, 15.84, 17.62, 20.30, 23.15, 26.51, 26.68, 26.99, 27.11, 27.40, 27.49, 28.95, 33.55, 33.93, 35.96, 36.57, 37.34, 37.83, 40.31, 42.05, 45.96, 48.88, 49.64, 51.23, 54.84, 61.73, 79.94, 173.49 ($C=O_{ester}$), 174.08 ($C=O_{ester}$), 210.76 ($C=O_{ketone}$). Found, %: C 75.90; H 10.23. $C_{35}H_{56}O_5$. Calculated, %: C 75.50; H 10.14.

20-Oxo-29-norlupane-3β,28-diyl dibenzoate (2c) was obtained by the ozonolysis of 3.03 g (4.65 mmol) betulin 3β,28-dibenzoate **1c** [24, 25] in 170 mL of anhydrous dichloromethane. Further workup was performed as described for compound **2a**. Yield 1.31 g (43%), colorless crystals, mp 143–147°C, R_f 0.60,

$[\alpha]_D^{24}$ +21.3 (*c* 1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2947, 2873, 1716, 1635, 1451, 1391, 1315, 1275, 1176, 1114, 1070, 1026, 972, 757, 712. ^1H NMR spectrum, δ, ppm: 0.89 s (3H, Me), 0.90 s (3H, Me), 0.99 s (3H, Me), 1.04 s (3H, Me), 1.07 s (3H, Me), 2.16 s [3H, $CH_3C(O)$], 2.73 m (1H, H^{19}), 4.03 d (1H, H^{28}, ^2J 12.0 Hz), 4.48 d (1H, H^{28}, ^2J 12.0 Hz), 4.71 m (1H, H^3), 7.40–7.44 m ($4H_{arom}$), 7.50–7.56 m ($2H_{arom}$), 8.02 m ($4H_{arom}$). ^{13}C NMR spectrum, δ, ppm: 14.77, 16.05, 16.13, 16.77, 18.19, 20.88, 23.74, 27.11, 27.28, 27.57, 28.11, 29.59, 29.63, 34.09, 34.60, 36.61, 37.16, 38.22, 38.40, 40.89, 42.68, 46.78, 49.48, 50.20, 51.79, 55.45, 62.97, 80.79, 166.21 (O–C=O), 166.83 (O–C=O), 211.42 ($C=O_{ketone}$). Found, %: C 78.87; H 8.60. $C_{43}H_{56}O_5$. Calculated, %: C 79.10; H 8.65.

30-Bromo-20-oxo-29-norlupane-3β,28-diyl diacetate (3a). *a*. A solution of 113 mg (0.71 mmol) of bromine in 8 mL of AcOH was added to a solution of 350 mg (0.65 mmol) of compound **2a** in 30 mL of glacial AcOH at 10–15°C. The mixture was stirred for 12 h at room temperature and then poured into water and extracted with dichloromethane. The organic extract was washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and subjected to column chromatography. The first fraction contained dibromide **4a**, and the second fraction contained bromide **3a**.

b. Compound **3a** was prepared by the ozonolysis of 5.509 g (9 mmol) of compound **5a** [34] in 180 mL of anhydrous dichloromethane at ~ −90°C (a mixture of 50% aqueous ethanol and liquid nitrogen) for 2 h, the flow rate of air through the ozone generator was 1.3–1.4 L/min. The reaction progress was monitored by TLC. After the reaction had been complete, 0.88 mL (745 mg, 11.9 mmol) of dimethyl sulfide was added, and the mixture was left to stand for 12 h at room temperature. The solvent was then removed by distillation, and the residue was purified on a silica gel column (eluent petroleum ether–ethyl acetate, 20 : 1) to obtain 2.46 g (45%) of bromoketone **3a**, colorless crystals, mp 163–167°C (from MeOH), R_f 0.54, $[\alpha]_D^{24}$ –13.7 (*c* 1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2947, 2873, 1732 (C=O), 1458, 1390, 1367, 1246, 1031, 980, 757. ^1H NMR spectrum, δ, ppm: 0.83 s (3H, Me), 0.84 s (6H, 2Me), 0.98 s (3H, Me), 1.01 s (3H, Me), 2.02 s [3H, $CH_3C(O)$], 2.06 s [3H, $CH_3C(O)$], 2.95 m (1H, H^{19}), 3.80 d (1H, H^{30}, ^2J 12.0 Hz), 3.94 d (1H, H^{30}, ^2J 12.0 Hz), 4.21 d (1H, H^{28}, ^2J 12.0 Hz), 4.45 m (1H, H^3). ^{13}C NMR spectrum, δ, ppm: 14.61, 15.98, 16.08, 16.46, 18.14, 20.83, 20.92, 21.22, 23.65, 26.96, 27.55, 27.92, 29.03, 29.45, 34.06, 34.64, 34.67, 36.39, 37.09, 37.79, 38.36, 40.82, 42.66, 46.35, 48.13, 49.98, 50.09, 55.33, 62.55, 80.79, 170.73 (O–C=O), 171.37 (O–C=O), 204.89 ($C=O_{ketone}$). Found, %: C 65.78; H 9.03. $C_{33}H_{51}BrO_5$. Calculated, %: C 65.23; H 8.46.

30-Bromo-20-oxo-29-norlupane-3β,28-diyl dipropanoate (3b). *a*. A solution of 139 mg (0.87 mmol) of bromine in 10 mL of glacial AcOH was added over the course of 2 h at 10–15°C to a solution of 440 mg (0.79 mmol) of compound **2b** [26], in 40 mL of glacial AcOH. The mixture was left to stand for 12 h at room temperature and then poured into water and extracted with dichloromethane. The organic extract was washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and subjected to column chromatography. The first fraction contained dibromide **4b** (R_f 0.62), and the second fraction contained bromide **3b** (R_f 0.57). Yield 266 mg (53%). Colorless crystals, mp 70–73°C, $[\alpha]_D^{24}$ –13.3 (*c* 1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2944, 2874, 1732, 1462, 1390, 1357, 1276, 1216, 1188, 1083, 1017, 972, 756. ^1H NMR spectrum, δ, ppm: 0.83 s (6H, 2Me), 0.84 s (3H, Me), 0.99 s (3H, Me), 1.02 s (3H, Me), 1.13–1.15 m (6H, 2Me), 2.27–2.37 m [4H, 2C(O)CH_2], 2.95 m (1H, H^{19}), 3.81 d (1H, H^{28}, ^2J 12.0 Hz), 3.89 d (NCH, ^2J 12.8 Hz), 3.94 d (NCH, ^2J 12.8 Hz), 4.22 m (1H, H^{28}, ^2J 12.0 Hz), 4.46 m (1H, H^3). ^{13}C NMR spectrum, δ, ppm: 9.14, 9.27, 14.49, 15.95, 16.05, 16.48, 18.11, 20.80, 23.36, 23.65, 25.11, 26.99, 27.52, 27.63, 27.91, 28.01, 29.02, 29.46, 34.02, 34.66, 36.35, 37.07, 37.85, 38.32, 40.79, 42.61, 46.43, 48.14, 49.99, 50.06, 55.31, 62.27, 80.43, 174.08 ($C=O_{ester}$), 174.58 ($C=O_{ester}$), 204.68($C=O_{ketone}$). Found, %: C 65.84; H 9.02. $C_{35}H_{55}BrO_5$. Calculated, %: C 66.13; H 8.72.

b. The ozonolysis of 2.13 g (3.84 mmol) of compound **5b** in dichloromethane at –90°C by the procedure described for compound **3a**, followed by decomposition with 1.1 mL (0.93 g, 14.9 mmol) of dimethyl sulfide gave 1.415 g (58%) of compound **3b**.

30-Bromo-20-oxo-29-norlupane-3β,28-diyl dibenzoate (3c) was prepared by method *b* similarly to compound **3a** by the ozonolysis of 1.028 g (1.4 mmol) of compound **5c** [26] in dichloromethane at –90°C followed by decomposition with 0.4 mL (5.5 mmol) of dimethyl sulfide. The solvent was then removed by distillation, and the residue was subjected to column chromatography, eluent petroleum ether–ethyl acetate (the fraction of ethyl acetate was gradually increased from 0 to 10%). Yield 0.90 g (42%), white powder, mp

148–152°C (from MeOH), R_f 0.60, $[\alpha]_D^{24}$ –14.7 (*c* 1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2947, 2873, 1732, 1458, 1390, 1367, 1246, 1031, 980, 757. ^1H NMR spectrum, δ, ppm: 0.90 s (3H, Me), 0.92 s (3H, Me), 0.99 s (3H, Me), 1.04 s (3H, Me), 1.07 s (3H, Me), 3.05 m (1H, HC^{19}), 3.92 d (1H, $BrCCH_2$, ^2J 12.0 Hz), 3.97 d (1H, $BrCCH_2$, ^2J 12.0 Hz), 4.06 d (1H, H^{28}, ^2J 12.0 Hz), 4.48 d (1H, H^{28}, ^2J 12.0 Hz), 4.71 m (1H, H^3), 7.43 m ($4H_{arom}$), 7.55 m ($2H_{arom}$), 8.03 m ($4H_{arom}$). ^{13}C NMR spectrum, δ, ppm: 14.68, 16.02, 16.10, 16.75, 18.16, 20.86, 23.70, 27.04, 27.57, 28.06, 29.10, 29.65, 34.06, 34.66, 34.79, 36.48, 37.14, 38.19, 38.37, 40.86, 42.74, 46.71, 48.20, 50.07, 50.11, 55.40, 63.01, 81.38, 128.25, 128.40, 129.49, 129.53, 130.23, 131.03, 132.61, 132.99, 166.21 (C=O), 166.81 (C=O), 204.70 (C=O). Found, %: C 70.32; H 7.60; Br 10.78. $C_{43}H_{55}BrO_5$. Calculated, %: C 70.57; H 7.58; Br 10.92.

30,30-Dibromo-20-oxo-29-norlupane-3β,28-diyl diacetate (4a) formed as an admixture (~10–15%) to bromide **6a** in the experiment on the bromination of ketone **2a** with bromine or pyridinium perbromide in AcOH. Colorless oil, R_f 0.56 (bromide **3a**: R_f 0.54). ^1H NMR spectrum, δ, ppm: 0.82 s (3H, Me), 0.84 s (6H, 2Me), 0.98 s (3H, Me), 1.01 s (3H, Me), 2.02 s [3H, $CH_3C(O)$], 2.07 s [3H, $CH_3C(O)$], 3.10 m (1H, H^{19}), 3.81 d (1H, H^{28}, ^2J 12.0 Hz), 4.21 d (1H, H^{28}, ^2J 12.0 Hz), 4.45 m (1H, H^3), 5.93 s (1H, H^{30}). ^{13}C NMR spectrum, δ, ppm: 14.60, 15.98, 16.08, 16.46, 18.15, 20.81, 20.93, 21.22, 23.65, 26.92, 27.34, 27.93, 29.46, 31.47, 34.06, 34.90, 36.48, 37.09, 37.80, 38.39, 40.83, 42.77, 43.25, 45.93, 46.24, 50.08, 50.78, 55.33, 62.61, 80.79, 170.86 (O–C=O), 171.39 (O–C=O), 199.23 ($C=O_{ketone}$). $C_{33}H_{50}Br_2O_5$. Satisfactory elemental analysis could not be obtained.

30,30-Dibromo-20-oxo-29-norlupane-3β,28-diyl dipropanoate (4b) could not be isolated pure and characterized; it formed as a hardly separable admixture (~20%) to bromide **3b** in the bromination of ketone **2b** with bromine un AcOH.

30,30-Dibromo-20-oxo-29-norlupane-3β,28-diyl dibenzoate (4c). A solution of compound **2c**, dissolved in 50 mL of glacial AcOH, was brominated at 10–15°C in a solution of 0.79 mL (1.53 mmol) of bromine in 10 mL of glacial AcOH for 12 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic extract was washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and subjected to column chromatography. Yield 0.71 g (73%), colorless crystals, mp 220–222°C, R_f 0.52, $[\alpha]_D^{24}$ –1.4 (*c* 1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2947, 2873, 1715, 1602, 1584, 1451, 1390, 1316, 1275, 1176, 1115, 1070, 1026, 973, 757, 712. ^1H NMR spectrum, δ, ppm: 0.90 s (3H, Me), 0.92 s (3H, Me), 0.99 s (3H, Me), 1.04 s (3H, Me), 1.07 s (3H, Me), 3.19 m (1H, H^{19}), 4.08 d (1H, H^{28}, ^2J 12.0 Hz), 4.49 d (1H, H^{28}, ^2J 12.0 Hz), 4.71 m (1H, H^3), 5.95 s (1H, H^{30}), 7.40–7.45 m ($4H_{arom}$), 7.50–7.57 m ($2H_{arom}$), 8.01–8.05 m ($4H_{arom}$). ^{13}C NMR spectrum, δ, ppm: 14.68, 16.02, 16.10, 16.75, 18.16, 20.86, 23.70, 27.04, 27.39, 28.11, 29.76, 31.62, 34.08, 35.11, 36.60, 37.17, 38.22, 38.42, 40.90, 42.88, 43.30, 46.04, 46.62, 540.11, 50.90, 55.42, 63.20, 81.45, 128.28, 128.45, 129.51, 129.56, 130.21, 131.06, 132.64, 133.06, 166.22, 166.84, 199.25. Found, %: C 64.16; H 7.16. $C_{43}H_{54}Br_2O_5$. Calculated, %: C 63.71; H 6.71; Br 19.71.

30-Azido-20-oxo-29-norlupane-3β,28-diyl diacetate (6a). A mixture of bromoketone **3a**, 725 mg (1.23 mmol) and 240 mg (3.69 mmol, three-fold excess) of sodium azide was heated under reflux in 150 mL of acetonitrile for 5 h. The solvent was removed in a vacuum, and the residue was subjected to column chromatography, eluent petroleum ether–ethyl acetate (the fraction of ethyl acetate was gradually increased from 0 to 10%). Yield 306 mg (45%), white foam, decomp. point 120–123°C, $[\alpha]_D^{22}$ –17.0 (*c* 0.5, $CHCl_3$), R_f 0.61. IR spectrum, ν, cm^{-1}: 2947, 2873, 2106 (N_3), 1732 (C=O), 1458, 1390, 1367, 1246, 1031, 979, 756. ^1H NMR spectrum, δ, ppm: 0.86 s (6H, 2Me), 0.87 s (3H, Me), 1.02 s (3H, Me), 1.05 s (3H, Me), 2.05 s [3H, C(O)Me], 2.09 s [3H, C(O)Me], 2.69 m (1H, H^{19}), 3.81 d (1H, H^{28}, ^2J 12.0 Hz), 3.94 d (NCH, ^2J 16.0 Hz), 4.00 d (NCH, ^2J 16.0 Hz), 4.22 d (1H, H^{28}, ^2J 12.0 Hz), 4.49 m (1H, H^3). ^{13}C NMR spectrum, δ, ppm: 13.78, 15.19, 15.40, 15.96, 17.90, 20.40, 20.70, 23.16, 26.48, 27.44, 28.67, 33.53, 35.85, 36.61, 37.23, 37.66, 40.35, 42.13, 42.77, 45.91, 47.54, 48.93, 49.60, 50.28, 54.86, 56.86, 61.90, 80.22, 170.29 ($C=O_{ester}$), 170.81 ($C=O_{ester}$), 206.51 ($C=O_{ketone}$). Found, %: C 69.49; H 8.92; N 7.35. $C_{33}H_{51}N_3O_5$. Calculated, %: C 69.56; H 9.02; N 7.37.

30-Azido-20-oxo-29-norlupane-3β,28-diyl dipropanoate (6b) was prepared similarly to azide **6a** from 1.00 g (1.57 mmol) of bromoketone **3b** and 0.307 g (4.7 mmol) of sodium azide in 250 mL of acetonitrile. Yield 310 mg (33%), colorless crystals, mp 78–80°C. $[\alpha]_D^{25}$ –18.8 (*c* 0.25, $CHCl_3$), R_f 0.63. IR spectrum, ν, cm^{-1}: 2945, 2874, 2105 (N_3), 1731 (C=O), 1462, 1390, 1357, 1277, 1188, 1083, 1017, 969, 757. ^1H NMR spectrum, δ, ppm: 0.83 s (6H, 2Me), 0.84 s (3H, Me), 0.99 s (3H, Me), 1.01 s (3H, Me), 1.13 t (3H, Me),

1.14 t (3H, Me), 2.27–2.37 m [4H, 2C(O)CH_2], 2.67 m (1H, H^{19}), 3.78 d (1H, H^{28}, ^2J 12.0 Hz), 3.92 d (NCH, ^2J 16.0 Hz), 3.97 d (NCH, ^2J 16.0 Hz), 4.21 m (1H, H^{28}, ^2J 12.0 Hz), 4.46 m (1H, H^3). ^{13}C NMR spectrum, δ, ppm: 9.15, 9.28, 14.66, 16.01, 16.08, 16.51, 18.17, 20.88, 23.71, 27.04, 27.66, 27.76, 27.97, 28.02, 28.05, 29.50, 34.11, 34.59, 36.40, 37.16, 37.93, 38.42, 40.89, 42.70, 46.55, 48.18, 49.55, 50.14, 55.41, 57.37, 62.60, 80.50, 174.07 ($C{=}O_{ester}$), 174.65 ($C{=}O_{ester}$), 206.99 ($C{=}O_{ketone}$). Found, %: C 70.05; H 9.30; N 6.94. $C_{35}H_{55}N_3O_5$. Calculated, %: C 70.32; H 9.27; N 7.03.

30-Azido-20-oxo-29-norlupane-3β,28-diyl dibenzoate (6c) was prepared similarly to azide **6a** from 400 mg (0.546 mmol) of bromoketone **3c** and 106 mg (1.64 mmol) of sodium azide in 150 mL of acetonitrile. Yield 118 mg (31%), colorless foam, mp 140–143°C. $[\alpha]_D^{25}$ –1.6 (*c* 0.25, $CHCl_3$), R_f 0.64, IR spectrum, ν, cm^{-1}: 2948, 2873, 2105 (N_3), 1715, 1602, 1584, 1452, 1390, 1316, 1275, 1176, 1115, 1070, 1026, 972, 757, 712. ^{1}H NMR spectrum, δ, ppm: 0.90 s (3H, Me), 0.92 s (3H, Me), 0.99 s (3H, Me), 1.04 s (3H, Me), 1.07 s (3H, Me), 2.75 m (1H, H^{19}), 3.97 s (2H, CH_2N_3), 4.03 d (1H, H^{28}, ^2J 12.0 Hz), 4.47 d (1H, H^{28}, ^2J 12.0 Hz), 4.73 m (1H, H^3), 7.40–7.45 m ($4H_{arom}$), 7.50–7.57 m ($2H_{arom}$), 8.01–8.05 m ($4H_{arom}$). ^{13}C NMR spectrum, δ, ppm: 14.71, 16.05, 16.13, 16.78, 18.18, 20.89, 23.73, 27.07, 27.79, 28.04, 28.12, 29.42, 29.60, 30.83, 34.08, 34.71, 36.45, 37.18, 38.23, 40.89, 42.75, 46.80, 48.14, 49.56, 50.12, 55.43, 57.40, 62.84, 81.44, 128.28, 128.45, 129.52, 129.55, 130.24, 131.07, 132.64, 133.06, 166.22 (C=O), 166.84 (C=O), 207.04 (C=O). Found, %: C 74.26; H 8.16; N 5.89. $C_{43}H_{55}N_3O_5$. Calculated, %: C 74.43; H 7.99; N 6.06.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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