

Synthesis and heterocyclization of triterpenic 1,3-diketones

Mikhail A. Nazarov, Irina A. Tolmacheva,* and Victoria V. Grishko

Perm Federal Scientific Center, Acad. Korolev St. 3, 614013 Perm, Russia

Email: tolmair@gmail.com

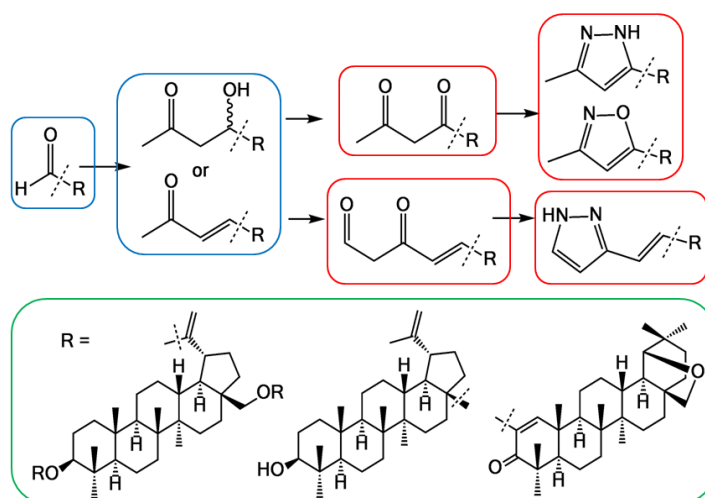
Received 08-28-2020

Accepted 11-15-2020

Published on line 11-29-2020

Abstract

Procedures for the synthesis of some new lupane and 18 α H-oleanane pyrazole and isoxazole derivatives from betulin are reported. The synthetic scheme for the preparation of 1,2-azoles involves aldol condensation of triterpenic aldehydes with acetone as a key stage.



Keywords: Triterpenoids; aldehydes; aldol condensation; 1,3-diketones; pyrazoles; isoxazoles

Introduction

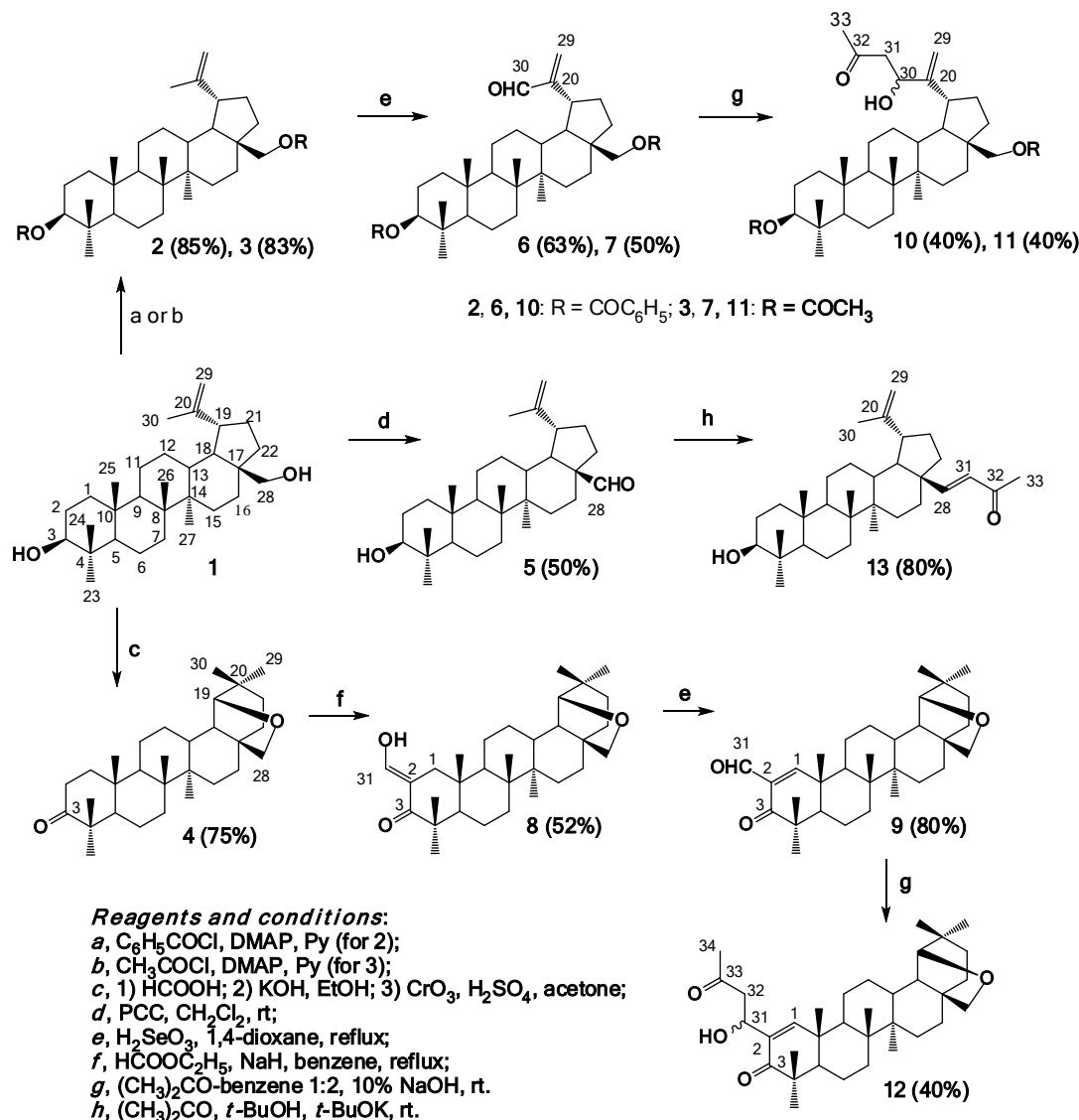
The strategy for the design of hybrid molecules, including those from natural compounds, is based on the methods of modern organic and medicinal chemistry and provides the preparation of chemical entities with two (or more than two) structural domains with different biological functions¹. In accord with the molecular hybridization concept, heterocyclic modification of triterpenic skeleton can provide new hybrid molecules with high biological potential and bioavailability²⁻⁵. Concurrently, β -dicarbonyl compounds have shown themselves as useful building blocks for the construction of heterocycles with one, two, or more heteroatoms⁶⁻⁸. So, 1,3-diketones obtained from 3-oxo derivatives of allobetulin, betulinic, dihydrobetulonic, 23-hydroxybetulinic, oleanolic, maslinic, and glycyrrhetic acids were successfully used as convenient and promising objects in the synthesis of *N,O*-based five-membered heterocycles, such as pyrazoles, oxazoles, and isoxazoles condensed with triterpenic skeleton at the 2,3-position⁹⁻¹⁹. Herein, we describe a convenient synthetic route for the preparation of lupane and oleanane 1,3-diketones with use of the aldol condensation. Further heterocyclization of the synthesized triterpenic 1,3-diketones to derivatives with a 1,2-azole fragment (pyrazole and isoxazole) in A or E cycles of triterpenoid has also been evinced as possible.

Results and Discussion

Betulin **1** and its derivatives – 3,28-betulin dibenzoate **2**, 3,28-betulin diacetate **3**, allobetulone **4**, and betulinol **5** – were used as easily available starting compounds for the synthesis of new triterpenic 1,3-diketone derivatives. First, via α,β -unsaturated aldehyde intermediates **6**, **7**, **9**²⁰⁻²³, compounds **2-4** were converted to β -hydroxyketones **10-12** according to the antecedently described method^{20,23} (Scheme 1).

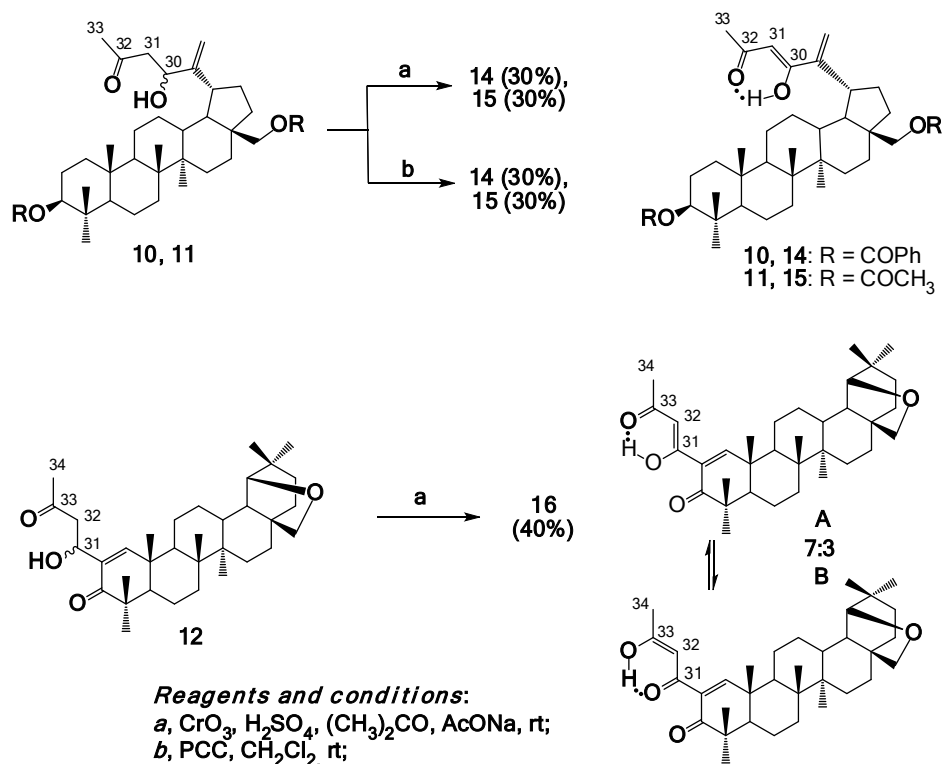
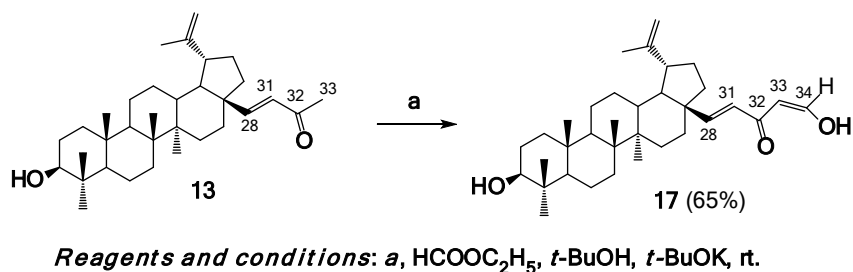
The aldol reaction of compounds **10-12** with acetone was discontinued at first signs of the formation (TLC) of a croton's by-product produced by the water elimination of their β -hydroxy ketone fragment. In turn, the aldol condensation of betulinol **5** with acetone carried out at room temperature and using *t*-BuOK–*t*-BuOH led to the formation of a new α,β -unsaturated methyl ketone **13** as a single product in an excellent 80% yield. The ¹H NMR spectrum of α,β -unsaturated methyl ketone **13** showed CH₃-33 protons of the methyl ketone moiety recorded as a singlet at 2.27 ppm. The *E*-configuration of the C-28–C-31 double bond was confirmed by a large coupling constant (16.5 Hz) between two olefinic protons at 6.16 and 7.07 ppm. The signals of C-28, C-31 carbon atoms and carbonyl group were observed in ¹³C NMR spectrum of compound **13** at 130.19, 149.62 and 198.58 ppm, respectively.

The different location of aldehyde group in the structure of compounds **5-9** enabled the introduction of a 1,3-diketone fragment at C-2, C-28 and C-30 positions of the triterpenic core. According to TLC, chromium (VI) oxide in anhydrous pyridine, normally used as an oxidation reagent, was not suitable for β -hydroxy ketones **10** and **11** because in both cases the reaction proceeded with the formation of a multicomponent hard-to-separate product mixture. Lupane 1,3-diketones **14**, **15** were obtained in 30% yields by treating compounds **10** and **11** with PCC in anhydrous CH₂Cl₂ or with the Jones reagent in acetone (Scheme 2). 18 α H-Oleanane 1,3-diketone **16** was obtained by oxidation of β -hydroxy ketone **12** with the Jones reagent (other oxidizing systems failed to lead to a good result).



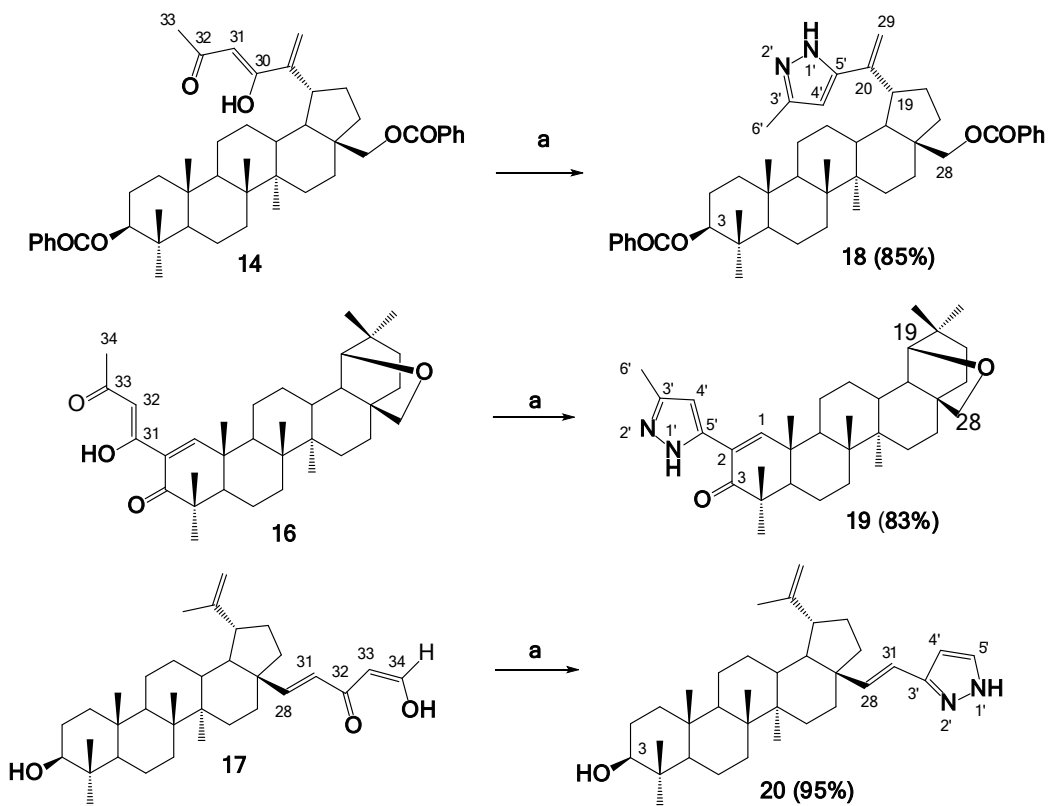
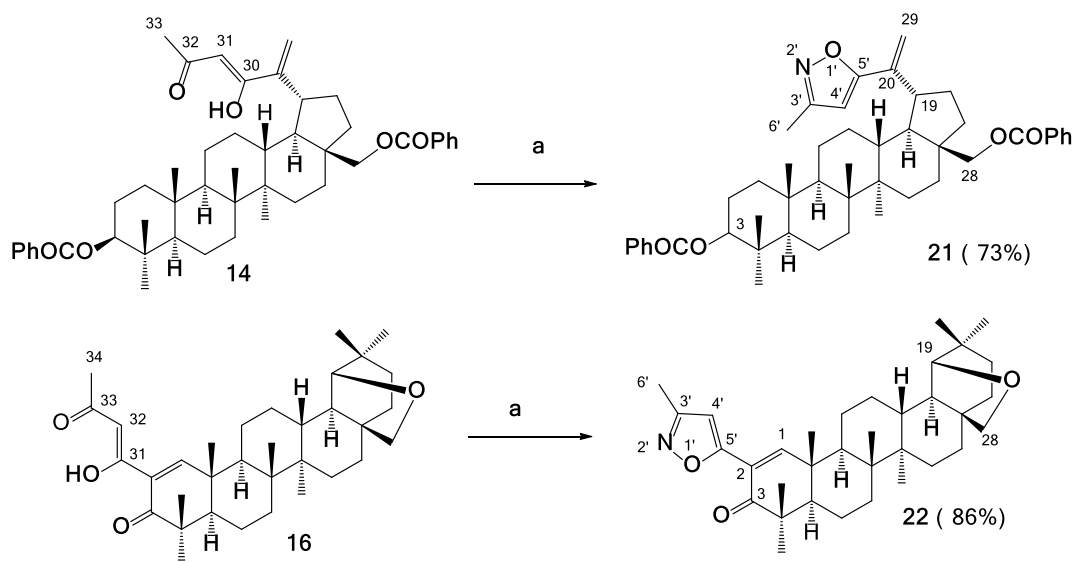
Scheme 1. Synthesis of triterpenic β -hydroxy ketones **10-12** and α,β -unsaturated methyl ketone **13** from betulin **1**.

Lupane 1,3-diketones **14** and **15** are completely enolized at the C-30 atom; that was confirmed by the data of ¹H and ¹³C NMR spectra with characteristic signals: (1) a singlet of protons H₃-33 at 2.11-2.12 ppm and a signal of the carbon atom C-32 at 193.13-193.17 ppm were assigned to the methyl ketone fragment; (2) a singlet of enol hydroxyl in the downfield area at 15.65-15.67 ppm and a signal of proton H-31 at 5.85-5.87 ppm were identified as an enol fragment. Two enol forms A and B for 18 α H-oleanane 1,3-diketone **16** in solution at the ratio 7:3 were registered on the basis of the integrated intensity of the signals of protons H₃-34 (1.94 and 2.13 ppm) and proton H-19 (3.53 and 3.54 ppm), as well as the proton of enolic hydroxyl (15.63 and 15.70 ppm) in the ¹H NMR spectrum. Lupane 1,3-diketone **17** was obtained by the Claisen condensation of α,β -unsaturated methyl ketone **13** with HCOOC₂H₅ in 65% yield (Scheme 3). The enolization of the ketone group C-34 of compound **17** was confirmed by the registration of doublet signals of olefinic protons H-28 and H-31 (5.97 and 7.19 ppm) and protons H-33 and H-34 (5.57 and 8.46 ppm), a signal of carbonyl atom carbon C-32 at 182.99 ppm, and a signal of C-34 atom at 182.52 ppm in the ¹H and ¹³C NMR spectra.

Scheme 2. Synthesis of triterpenic 1,3-diketones **14-16**.Scheme 3. Synthesis of triterpenic 1,3-diketone **17**.

To obtain pyrazole derivatives, compounds **14**, **16**, **17** were heated with hydrazine hydrate in an alcohol–acetic acid mixture (1:1) for 1.5 h (Scheme 4).

The ¹H NMR spectra of compounds **18** and **19** showed the presence of two singlet signals at 2.28 and 6.12–6.23 ppm which conjointly with a broad signal at 8.20–8.22 ppm were assigned to protons H₃–6', H–4' and the proton of NH group of a substituted pyrazole cycle, respectively, whereas the ¹³C NMR spectra revealed the characteristic signals of heterocyclic fragment at 102.02–102.62 and 141.25–147.12 ppm. In the ¹H NMR spectrum of compound **20**, the signals of H–4' and H–5' protons of the pyrazole fragment were recorded as two doublets at 6.33 and 7.49 ppm with a coupling constant of 1.7 Hz and the NH proton signal at 5.79 ppm. The treatment of triterpenic 1,3-diketones **14**, **16** with hydroxylamine hydrochloride in aqueous EtOH in the presence of CH₃COONa at reflux afforded isoxazole derivatives **21**, **22** in 86% and 73% yields, respectively (Scheme 5). In the ¹H NMR spectra of the compounds **21** and **22**, the characteristic singlet signals of protons H₃–6' and H–4' of isoxazole fragment were recorded at 2.30–2.31 and 6.12–6.61 ppm, respectively.

Scheme 4. Synthesis of triterpenic pyrazoles **18-20**.Scheme 5. Synthesis of triterpenic isoxazoles **21, 22**.

Conclusions

Triterpenic derivatives with a pyrazole or isoxazole fragment in the A or E cycle of triterpenoids were synthesized from the lupane and 19 β ,28-epoxy-18 α H-oleanane 1,3-diketones obtained from commercially available pentacyclic triterpenoid betulin. The synthetic route to triterpenic 1,2-azoles involved the reaction of aldol condensation of α , β -unsaturated aldehydes with acetone, the products of which as β -hydroxyketone and methyl ketone were converted to 1,3-diketones, whose participation in reaction with hydrazine hydrate and hydroxylamine led to target heterocyclic derivatives.

Experimental Section

General. The ^1H , ^{13}C and 2D NMR spectra (HMBC) (δ , ppm; J , Hz) were recorded for solutions in CDCl_3 using a Bruker AVANCE II spectrometer (400 MHz and 100 MHz, respectively), relative to HMDS. IR spectra (ν , cm^{-1}) were recorded on a Bruker 66/S IFS Fourier spectrometer using a thin film obtained by evaporation from the solution of the substance in CHCl_3 . Melting points were determined on an OptiMelt MPA100 device at the heating rate $1^\circ\text{C}/\text{min}$. Optical rotation was measured on a Perkin-Elmer 341 polarimeter using sodium D for CHCl_3 solutions at 589 nm. Elemental analysis was preformed using a vario EL cube elemental analyzer. Chromato-mass spectra were analyzed using Agilent Technologies 6890N, capillary column HP-5ms 15000 \times 0.25 mm, electronic ionization as sample ionization method. Thin layer chromatography (TLC) on “Sorbfil” plates was used to control the reaction course and substance purity by visualization under UV light (254 nm). The samples were then subjected to treatment with a 5% solution of H_2SO_4 and heating at 95–100 $^\circ\text{C}$ for 2–3 min. Column chromatography (CC) procedure was performed using Macherey-Nagel 60 Silica (0.063–0.2 mm) as an adsorbent. For each compound, eluents were selected individually. 3,28-Betulin dibenzoate **2** and 3,28-betulin diacetate **3** synthesized by treating technical betulin with an acylating agent (benzoyl chloride or acetic anhydride) in pyridine^{21,24}. Betulinal **5** was obtained by oxidation of the C28 hydroxyl group of betulin by PPC in pyridine²⁵.

3 β -Hydroxy-28-(2-oxopropylidene)lup-20(29)-ene (13). *t*-BuOK (4 mmol) was added to a solution of aldehyde **5** (2.3 mmol) in *t*-BuOH (50 ml) and acetone (2 ml). The reaction mixture was stirred for 2 h at rt. With 10% HCl added, the reaction mixture was extracted with ethyl acetate (30 mL \times 2). The organic layer was separated, washed with H_2O (5 \times 10 ml), and dried over anhydrous MgSO_4 . The solvent was evaporated, and the residue was subjected to CC (eluent: light petroleum–ethyl acetate, 10:1). Yield: 80%, m.p. 191.6 $^\circ\text{C}$, $[\alpha]_D^{21}$ –24.0 (*c* 0.5, CHCl_3). IR (cm^{-1}): 3447, 1672. ^1H NMR (400 MHz, CDCl_3): δ_{H} 7.07 and 6.16 (2H, 2d, J 16.5 Hz, 28-H, 31-H), 4.72 and 4.60 (2H, 2s, 29-H₂), 3.16 (1H, dd, J 5.1, 11.2 Hz, 3-H), 2.45 (1H, td, J 11.1, 5.3 Hz, 19-H), 2.27 (3H, s, 33-H₃), 1.68 (3H, s, 30-H₃), 0.97, 0.95, 0.93, 0.81, 0.74 (15H, 5s, 5CH₃). ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 198.58, 152.72, 149.62, 130.19, 110.06, 78.93, 55.33, 50.38, 50.06, 49.70, 47.85, 42.79, 40.82, 38.99, 38.84, 38.76, 38.72, 37.17, 34.29, 33.52, 29.79, 27.97, 27.85, 27.39, 27.13, 25.27, 20.76, 19.25, 18.25, 16.02, 15.90, 15.32, 14.69. MS: m/z 480.35 (M^+); Anal. Calcd. for $\text{C}_{33}\text{H}_{52}\text{O}_2$: C, 82.44; H, 10.90. Found: C, 82.61; H, 10.99.

3 β ,28-Dibenzoyloxy-30-oxo-30-(2-oxopropyl)lup-20(29)-ene (14). A solution of **10** (1.4 mmol) and CH_3COONa (0.7 mmol) in acetone (100 ml) was cooled to 0–5 $^\circ\text{C}$, then the Jones reagent (0.8 ml) was added slowly, with subsequent stirring of the reaction mixture for 15 min. The progress of the reaction was monitored by TLC. The reaction mixture was extracted with ethyl acetate, washed with H_2O (5 \times 10 ml), and dried over anhydrous MgSO_4 . The solvent was evaporated, and the residue was subjected to CC (eluent: light petroleum–ethyl

acetate, 10:1). Yield: 30%, m.p. 142.1 °C, $[\alpha]_D^{21} +18.4$ (c 0.6, CHCl₃). IR (cm⁻¹): 1716. ¹H NMR (400 MHz, CDCl₃): δ_H 15.67 (1H, br s, OH), 8.05-8.00 (4H, m, Ph), 7.55-7.49 (2H, m, Ph), 7.44-7.38 (4H, m, Ph), 5.87 (1H, s, 31-H), 5.79 and 5.47 (2H, 2s, 29-H₂), 4.69 (1H, dd, *J* 5.1, 11.0 Hz, 3-H), 4.53 and 4.13 (2H, 2d, *J* 11.1 Hz, 28-H₂), 2.73 (1H, td, *J* 11.2, 5.4 Hz, 19-H), 2.11 (3H, s, 33-H₃), 1.07, 0.99, 0.98, 0.90, 0.87 (15H, 5s, 5CH₃). ¹³C NMR (100 MHz, CDCl₃): δ_C 193.13, 185.30, 166.86, 166.22, 151.62, 132.86, 132.62, 131.00, 130.42, 129.53 (2C), 129.47 (2C), 128.35 (2C), 128.25 (2C), 118.64, 97.22, 81.51, 63.17, 55.46, 51.45, 50.21, 46.76, 42.71, 40.95, 40.92, 38.42, 38.17, 37.45, 37.11, 34.55, 34.18, 33.04, 30.11, 28.08 (2C), 27.58, 27.15, 25.73, 23.71, 21.01, 18.16, 16.73, 16.07, 14.75. Anal. Calcd. for C₄₇H₆₀O₆: C, 78.30; H, 8.39. Found: C, 78.13; H, 8.54.

3β,28-Diacetoxy-30-oxo-30-(2-oxopropyl)lup-20(29)-ene (15). A solution of **11** (1.7 mmol) and CH₃COONa (0.8 mmol) in acetone (100 ml) was cooled to 0-5 °C, then the Jones reagent (1.0 ml) was added slowly, with subsequent stirring of the reaction mixture for 15 min. The progress of the reaction was monitored by TLC. The reaction mixture was extracted with ethyl acetate, washed with H₂O (5 × 10 ml), and dried over anhydrous MgSO₄. The solvent was evaporated, and the residue was subjected to CC (eluent: light petroleum–ethyl acetate, 10:1). Yield: 30%, m.p. 100.3 °C, $[\alpha]_D^{21} +2.4$ (c 0.59, CHCl₃). IR (cm⁻¹): 1733. ¹H NMR (400 MHz, CDCl₃): δ_H 15.65 (1H, br s, OH), 5.85 (1H, s, 31-H), 5.77 and 5.44 (2H, 2s, 29-H₂), 4.45 (1H, dd, *J* 5.7, 10.8 Hz, 3-H), 4.27 and 3.88 (2H, 2d, *J* 10.8 Hz, 28-H₂), 2.65 (1H, td, *J* 11.3, 5.5 Hz, 19-H), 2.12 (3H, s, 33-H₃), 2.06 and 2.02 (6H, 2s, 2CH₃COO-), 1.03, 0.95, 0.82, (9H, 3c, 3CH₃), 0.83 (6H, s, 2CH₃). ¹³C NMR (100 MHz, CDCl₃): δ_C 193.17, 185.34, 171.50, 170.94, 151.68, 118.64, 97.24, 80.91, 62.66, 55.42, 51.46, 50.22, 46.40, 42.66, 40.93, 38.44, 37.81, 37.38, 37.09, 34.39, 34.21, 33.01, 29.88, 27.94 (2C), 27.57, 27.08, 25.77, 23.68, 21.24, 21.01, 20.97, 18.17, 16.46, 16.11, 16.05, 14.70. Anal. Calcd. for C₃₇H₅₆O₆: C, 74.46; H, 9.46. Found: C, 74.73; H, 9.12.

2-(1,3-Dioxobut-1-yl)-19β,28-epoxyolean-1(2)-en-3-one (16). A solution of **12** (1.4 mmol) and CH₃COONa (0.95 mmol) in acetone (100 ml) was cooled to 0-5 °C, then the Jones reagent (1.0 ml) was added slowly, with subsequent stirring of the reaction mixture for 15 min. The progress of the reaction was monitored by TLC. The reaction mixture was extracted with ethylacetate, washed with H₂O (5 × 10 ml), and dried over anhydrous MgSO₄. The solvent was evaporated, and the residue was subjected to CC (eluent: light petroleum–ethylacetate, 10:1). Yield: 40%, m.p. 114.4 °C. $[\alpha]_D^{21} +2.7$ (c 0.6). IR (cm⁻¹): 1684, 1615. For form A. ¹H NMR (400 MHz, CDCl₃): δ_H 15.70 (1H, br s, OH), 7.92 (1H, s, 1-H), 6.20 (1H, s, 32-H), 3.78 and 3.45 (2H, 2d, *J* 7.8 Hz, 28-H₂), 3.54 (1H, s, 19-H), 2.13 (3H, s, 34-H₃), 1.16, 1.09, 1.05, 1.02, 0.80 (15H, 5s, 5CH₃), 0.92 (6H, s, 2CH₃). ¹³C NMR (100 MHz, CDCl₃): δ_C 202.97, 196.88, 176.62, 163.63, 131.17, 100.35, 87.88, 71.25, 52.21, 46.73, 46.00, 44.81, 41.58, 41.48, 41.04, 39.56, 36.73, 36.27, 34.51, 32.92, 32.71, 28.77, 28.67, 26.58, 26.41, 26.28, 26.23, 24.52, 21.86, 21.07, 19.51, 18.83, 16.15, 13.29. Anal. Calcd. for C₃₄H₅₀O₄: C, 78.12; H, 9.64. Found: C, 78.22; H, 9.85.

3β-Hydroxy-28-(2,4-dioxobutylidene)lup-20(29)-ene (17). *t*-BuOK (4 mmol) was added to a solution of **13** (2 mmol) and HCOOC₂H₅ (6 mmol) in *t*-BuOH (50 ml). The reaction mixture stirred for 4 h at rt. With 10% HCl added, the reaction mixture was extracted with ethyl acetate. The organic layer was separated, washed with H₂O (2 × 10 ml), and dried over anhydrous MgSO₄. The solvent was evaporated, and the residue was subjected to CC (eluent: light petroleum–ethyl acetate, 5:1). Yield: 65%, m.p. 153.0 °C, $[\alpha]_D^{21} -25.5$ (c 1.0, CHCl₃). IR (cm⁻¹): 3447, 1717, 1642, 1613. ¹H NMR (400 MHz, CDCl₃): δ_H 8.46 and 5.57 (2H, 2d, *J* 3.5 Hz, 33-H, 34-H), 7.19 and 5.97 (2H, 2d, *J* 16.1 Hz, 28-H, 31-H), 4.71 and 4.60 (2H, 2s, 29-H₂), 3.16 (1H, dd, *J* 5.0, 11.2 Hz, 3-H), 2.47 (1H, td, *J* 11.2, 5.4 Hz, 19-H), 1.68 (3H, s, 30-H₃), 0.97, 0.95, 0.94, 0.80, 0.74 (15H, 5s, 5CH₃). ¹³C NMR (100 MHz, CDCl₃): δ_C 182.99, 182.59, 150.84, 149.69, 125.25, 110.05, 101.17, 78.97, 55.35, 50.42, 50.28, 49.91, 47.80, 42.82, 40.84, 38.96, 38.85, 38.79, 38.73, 37.19, 34.34, 33.54, 29.82, 27.98, 27.89, 27.40, 25.29, 20.77, 19.27, 18.27, 16.03, 15.99, 15.33, 14.69. Anal. Calcd. for C₃₄H₅₂O₃: C, 80.26; H, 10.30. Found: C, 80.41; H, 10.55.

3 β ,28-Dibenzoyloxy-20-(3'-methyl-1H-pyrazol-5'-yl)-30-norlup-20(29)-ene (18). Compound **14** (0.14 mmol) was dissolved in 2 mL of ethanol, and hydrazine hydrate (0.17 mmol) was added. Then, 2 ml of CH₃COOH were added under stirring. The mixture was refluxed and monitored by TLC until the starting material completely disappeared (1.5 h). The product was extracted with ethyl acetate. The organic layer was separated, washed with H₂O, and dried over anhydrous MgSO₄. The solvent was evaporated, and the residue was subjected to CC (eluent: light petroleum–ethyl acetate, 5:1). Yield: 85%, m.p. 129.0 °C, $[\alpha]_D^{21} +16.0$ (c 0.5, CHCl₃). IR (cm⁻¹): 3324, 3206, 1717. ¹H NMR (400 MHz, CDCl₃): δ_H 8.20 (1H, br s, NH), 8.05-7.99 (4H, m, Ph), 7.55-7.49 (2H, m, Ph), 7.43-7.37 (4H, m, Ph), 6.12 (1H, s, 4'-H), 5.39 and 5.11 (2H, 2s, 29-H₂), 4.69 (1H, dd, *J* 5.1, 11.0 Hz, 3-H), 4.58 and 4.15 (2H, 2d, *J* 11.1 Hz, 28-H₂), 2.88 (1H, td, *J* 11.2, 5.5 Hz, 19-H), 2.28 (3H, s, 6'-H₃), 1.06, 0.98, 0.97, 0.89, 0.86 (15H, 5c, 5CH₃). ¹³C NMR (100 MHz, CDCl₃): δ_C 166.86, 166.23, 149.63, 145.74, 143.99, 132.81, 132.60, 131.02, 130.51, 129.54 (2C), 129.47 (2C), 128.33 (2C), 128.24 (2C), 109.71, 102.62, 81.55, 63.25, 55.45, 50.55, 50.24, 46.80, 42.74, 40.95, 38.39, 38.18, 37.57, 37.10, 34.54, 34.18, 32.56, 30.10, 29.63, 28.09, 27.20, 27.06, 23.72, 20.97, 18.17, 16.73, 16.10, 16.08, 14.81, 12.07. Anal. Calcd. for C₄₇H₆₀N₂O₄: C, 78.73; H, 8.43; N, 3.91. Found: C, 78.67; H, 8.58; N, 3.88.

19 β ,28-Epoxy-2-(3'-methyl-1H-pyrazol-5'-yl)-18 α H-olean-1(2)en-3-one (19). Compound **16** (0.2 mmol) was dissolved in 1 mL of ethanol with subsequent addition of hydrazine hydrate (0.22 mmol). Then, 1 ml of CH₃COOH was added under stirring. The mixture was refluxed and monitored by TLC until the starting material completely disappeared (1.5 h). The product was extracted with ethyl acetate. The organic layer was separated, washed with H₂O, and dried over anhydrous MgSO₄. The solvent was evaporated, and the residue was subjected to CC (eluent: light petroleum–ethyl acetate, 7:3). Yield: 83%, m.p. 139.5 °C. $[\alpha]_D^{21} +42.4$ (c 0.5, CHCl₃). IR (solution in CHCl₃, cm⁻¹): 3427, 3206, 1672. ¹H NMR (400 MHz, CDCl₃): δ_H 8.22 (1H, br s, NH), 7.51 (1H, s, 1-H), 6.23 (1H, s, 4'-H), 3.78 and 3.45 (2H, 2d, *J* 7.9 Hz, 28-H₂), 3.54 (1H, s, 19-H), 2.28 (3H, s, 6'-H₃), 1.17, 1.14, 1.10, 1.06, 0.80 (15H, 5s, 5CH₃), 0.94 (6H, s, 2CH₃). Спектр ¹³C NMR (100 MHz, CDCl₃): δ_C 204.82, 156.49, 147.12, 141.25, 124.55, 102.02, 87.87, 71.24, 52.62, 46.75, 45.40, 45.04, 41.62, 41.48, 41.07, 39.34, 36.73, 36.27, 34.43, 33.15, 32.70, 28.78, 28.66, 26.39, 26.31, 26.24, 24.53, 21.55, 21.50, 19.62, 19.19, 16.21, 13.33, 12.97. MS: *m/z* 518.3 (M⁺); Anal. Calcd. for C₃₄H₅₀N₂O₂: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.96; H, 9.64; N, 5.57.

3 β -Hydroxy-28-[(1H-pyrazol-3'-yl)methylylidene]lup-20(29)-ene (20). Compound **17** (0.58 mmol) was dissolved in 2 mL of ethanol with subsequent addition of hydrazine hydrate (0.88 mmol). Then, 2 ml of CH₃COOH were added under stirring. The mixture was refluxed and monitored by TLC until the starting material completely disappeared (1.5 h). The product was extracted with ethyl acetate. The organic layer was separated, washed with H₂O, and dried over anhydrous MgSO₄. The solvent was evaporated, and the residue was subjected to CC (eluent: light petroleum–ethyl acetate, 7:3). Yield: 95%, m.p. 158.8 °C, $[\alpha]_D^{21} -18.8$ (c 0.6, CHCl₃). IR (cm⁻¹): 3209, 1718, 1642. ¹H NMR (400 MHz, CDCl₃): δ_H 7.49 and 6.33 (2H, 2d, *J* 1.7 Hz, 4'-H, 5'-H), 6.48 and 6.44 (2H, 2d, *J* 16.6 Hz, 28-H, 31-H), 5.79 (1H, s, NH), 4.70 and 4.58 (2H, 2s, 29-H₂), 3.17 (1H, dd, *J* 5.1, 11.0 Hz, 3-H), 2.46 (1H, td, *J* = 11.0, 4.8 Hz, 19-H), 1.68 (3H, s, 30-H₃), 0.97, 0.95, 0.94, 0.79, 0.74 (15H, 5c, 5CH₃). ¹³C NMR (100 MHz, CDCl₃): δ_C 150.24, 147.12, 136.88, 134.18, 118.66, 109.72, 101.88, 78.97, 55.35, 50.45, 49.78, 49.41, 47.95, 42.82, 40.87, 38.93, 38.85, 38.74, 38.44, 37.19, 34.32, 34.16, 29.98, 28.02, 27.84, 27.38, 25.28, 20.85, 19.32, 18.30, 16.05, 16.01, 15.40, 14.74. Anal. Calcd. for C₃₄H₅₂N₂O: C, 80.90; H, 10.38; N, 5.55. Found: C, 81.01; H, 10.22; N, 5.34.

3 β ,28-Dibenzoyloxy-20-(3'-methylisoxazol-5'-yl)-30-norlup-20(29)-ene (21). Compound **14** (0.14 mmol) was dissolved in 4 mL of ethanol with subsequent addition of hydroxylamine hydrochloride (0.14 mmol) and CH₃COONa (0.14 mmol). The mixture was refluxed and monitored by TLC until the starting material completely disappeared (1.5 h). The product was extracted with ethyl acetate. The organic layer was separated, washed

with H₂O, and dried over anhydrous MgSO₄. The solvent was evaporated, and the residue was subjected to CC (eluent: light petroleum–ethyl acetate, 10:1). Yield: 73%, m.p. 69.0 °C, $[\alpha]_D^{21} +12.0$ (c 0.5, CHCl₃). IR (cm⁻¹): 1716, 1451. ¹H NMR (400 MHz, CDCl₃): δ_H 8.06-8.00 (4H, m, Ph), 7.56-7.49 (2H, m, Ph), 7.44-7.38 (4H, m, Ph), 6.12 (1H, s, 4'-H), 5.41 and 5.14 (2H, 2s, 29-H₂), 4.69 (1H, dd, *J* 5.2, 10.9 Hz, 3-H), 4.58 and 4.16 (2H, 2d, *J* 11.1 Hz, 28-H₂), 2.87 (1H, td, *J* 11.2, 5.7 Hz, 19-H), 2.30 (3H, s, 6'-H₃), 1.07, 0.99, 0.97, 0.90, 0.87 (15H, 5s, 5CH₃). ¹³C NMR (100 MHz, CDCl₃): δ_C 166.92, 166.27, 149.17, 144.79, 144.10, 132.87, 132.63, 131.05, 130.50, 129.58 (2C), 129.50 (2C), 128.37 (2C), 128.27 (2C), 106.42, 102.91, 81.59, 63.20, 55.48, 50.67, 50.26, 46.86, 42.78, 41.00, 38.42, 38.21, 37.58, 37.14, 34.53, 34.21, 32.60, 30.10, 28.11 (2C), 27.21 (2C), 23.74, 21.00, 18.20, 16.76, 16.13 (2C), 14.83, 11.97. Anal. Calcd. for C₄₇H₅₉NO₅: C, 78.62; H, 8.28; N, 1.95. Found: C, 78.81; H, 8.41; N, 2.11.

19 β ,28-Epoxy-2-(3'-methylisoxazol-5'-yl)-18 α H-olean-1(2)en-3-one (22). Compound **16** (0.2 mmol) was dissolved in 2 mL of ethanol with subsequent addition of hydroxylamine hydrochloride (0.22 mmol) and CH₃COONa (0.22 mmol). The mixture was refluxed and monitored by TLC until the starting material completely disappeared (1.5 h). The product was extracted with ethyl acetate. The organic layer was separated, washed with H₂O, and dried over anhydrous MgSO₄. The solvent was evaporated, and the residue was subjected to CC (eluent: light petroleum–ethyl acetate, 5:1). Yield: 86%, m.p. 79.8 °C. $[\alpha]_D^{21} +36.7$ (c 0.8, CHCl₃). IR (cm⁻¹): 1681, 1626, 1453. ¹H NMR (400 MHz, CDCl₃): δ_H 7.85 (1H, s, 1-H), 6.61 (1H, s, 4'-H), 3.80 and 3.49 (2H, 2d, *J* 7.8 Hz, 28-H₂), 3.59 (1H, s, 19-H), 2.31 (3H, s, 6'-H₃), 1.21, 1.17, 1.15, 1.10, 0.97, 0.96, 0.85 (21H, 7s, 7CH₃). ¹³C NMR (100 MHz, CDCl₃): δ_C 201.56, 164.21, 160.35, 158.48, 123.72, 104.16, 87.87, 71.21, 52.50, 46.70, 45.29, 44.97, 41.63, 41.46, 41.04, 39.40, 36.71, 36.25, 34.44, 33.10, 32.70, 29.64, 28.75, 28.55, 26.37, 26.22, 24.52, 21.59, 21.46, 19.35, 19.23, 16.21, 13.29, 11.41. MS: *m/z* 519.35 (M⁺); Anal. Calcd. for C₃₄H₄₉NO₃: C, 78.57; H, 9.50; N, 2.69. Found: C, 78.63; H, 9.39; N, 2.78.

Acknowledgements

This research was financially supported by the State Contractual Order Nr. AAAA-A19-119031890083-9. Analytical and spectroscopic studies were performed at the "Research of materials and substances" collective Center of PFRC UB RAS.

Supplementary Material

Supplementary data related to this article, such as the ¹H and ¹³C NMR spectrums for compounds **13-22** can be found in the online version of the text.

References

1. Meunier B. *Acc. Chem. Res.* **2008**, *41*, 69.
<https://doi.org/10.1021/ar7000843>
2. Kvasnica, M., Urban, M. Dickinson, N.J., Sarek, J. *Nat. Prod. Rep.* **2015**, *32*, 1303.
<https://doi.org/10.1039/c5np00015g>

3. Zhou, M., Zhang, R.-H., Wang, M., Xu, G.-B., Liao, S.-G. *Eur. J. Med. Chem.* **2017**, 131, 222.
<http://dx.doi.org/10.1016/j.ejmech.2017.03.005>
4. Borkova, L., Hodon, J., Urban, M. *Asian J. Org. Chem.* **2018**, 7, 1542.
<http://dx.doi.org/10.1002/ajoc.201800163>
5. Sousa, C. J. L., Freire, C. S. R., Silvestre, A. J. D., Silva, A. M. S. *Molecules*. **2019**, 24, 355.
<https://doi.org/10.3390/molecules24020355>
6. Kel'in, A. V., Maioli A. *Curr. Org. Chem.* **2003**, 7, 1855.
<https://doi.org/10.1002/chin.200432286>
7. Shokova, E. A., Kim, J. K., Kovalev, V. V. *Russ. J. Org. Chem.* **2015**, 51, 755.
<https://doi.org/10.1134/S1070428015060019>
8. Bondarenko, O. B., Zyk, N. V. *Chem. Heterocycl. Compd.* **2020**, 56, 694.
<https://doi.org/10.1007/s10593-020-02718-0>
9. You, Y.-J., Kim, Y., Nam, N.-H., Ahn, B.-Z. *Bioorg. Med. Chem. Lett.* **2003**, 13, 3137.
[https://doi.org/10.1016/S0960-894X\(03\)00724-8](https://doi.org/10.1016/S0960-894X(03)00724-8)
10. Chen, J., Gong, Y., Liu, J., Hua, W., Zhang, L., Sun, H. *Chem. Biodiversity* **2008**, 5, 1304.
<https://doi.org/10.1002/cbdv.200890117>
11. Qiu, W.-W., Shen, Q., Yang, S. F., Wang, B., Zou, H., Li, J.-Y., Li, J., Tang, J. *Bioorg. Med. Chem. Lett.* **2009**, 19, 6618.
<https://doi.org/10.1016/j.bmcl.2009.10.017>
12. Li, H., Zou, H., Gao, L., Liu, T., Yang, F., Li, J., Li, J., Qiu, W.-W., Tang, J. *Heterocycles* **2012**, 85, 1117.
<https://doi.org/10.3987/COM-12-12445>
13. Xu, J., Li, Z., Luo, J., Yang, F., Liu, T., Liu, M., Qiu, W.-W., Tang, J. *J. Med. Chem.* **2012**, 55, 3122.
<https://dx.doi.org/10.1021/jm201540h>
14. Urban, M., Vlk, M., Dzubak, P., Hajduch, M., Sarek, J. *Bioorg. Med. Chem.* **2012**, 20, 3666.
<http://dx.doi.org/10.1016/j.bmc.2012.03.066>
15. Kang, X., Hu, J., Gao, Z., Ju, Y., Xu, C. *Med. Chem. Commun.* **2012**, 3, 1245.
<https://doi.org/10.1039/c2md20051a>
16. Gao, C., Dai, F.-J., Cui, H.-W., Peng, S.-H., He, Y., Wang, X., Yi, F.-Z., Qiu, W.-W. *Chem. Biol. Drug. Des.* **2014**, 84, 223.
<https://doi.org/10.1111/cbdd.12308>
17. Zhang, H., Zhu, P., Liu, J., Lin, Y., Yao, H., Jiang, J., Ye, W., Wu, X., Xu, J. *Bioorg. Med. Chem. Lett.* **2015**, 25, 728.
<http://dx.doi.org/10.1016/j.bmcl.2014.11.058>
18. Zhang, H., Li, F., Zhu, P., Liu, J., Yao, H., Jiang, J., Ye, W., Wu, X., Xu, J. *Chem. Biol. Drug. Des.* **2015**, 86, 424.
<https://doi.org/10.1111/cbdd.12543>
19. Laavola, M., Haavikko, R., Hamalainen, M., Leppanen, T., Nieminen, R., Alakurtti, S., Moreira, V. M., Yli-Kauhaluoma, J., Moilanen, E., *J. Nat. Prod.* **2016**, 79, 274.
<https://doi.org/10.1021/acs.inatprod.5b00709>
20. Nazarov, M. A., Tolmacheva I. A., Grishko, V. V. *AIP Conference Proceedings*. **2020**, 2280, 050035.
<https://doi.org/10.1063/5.0018052>
21. Ghosh, P., Mandal, A., Ghosh, J., Pal, C., Nanda, A. K. J. *J. Asian Nat. Prod. Res.* **2012**, 14, 141.
<http://dx.doi.org/10.1080/10286020.2011.640774>
22. Nazarov, M. A., Zhikina, L. A., Tolmacheva I. A., Grishko, V. V. *Bashkir Chem. J.* **2017**, 24, 28.

23. Nazarov, M. A., Tolmacheva, I. A., Eroshenko, D. V., Mayorova, O. A., Dmitriev, M. V., Grishko, V. V. *Chem. Heterocycl. Compd.* **2020**, 56, 1321.
<https://doi.org/10.1007/s10593-020-02817-y>
24. Glushkov, V. A., Shemyakina, D. A., Zhukova, N. K., Pavlogradskaia, L. V., Dmitriev, M. V., Eroshenko, D. V., Galeev, A. R., Mokrushin, I. G. *Russ. J. Org. Chem.* **2019**, 55, 1690.
<https://doi.org/10.1134/s1070428019110083>
25. Komissarova, N. G., Belenkova, N. G., Spirikhin, L. V., Shitikova, O. V., Yunusov, M. S. *Chem. Nat. Compd.* **2002**, 38, 58.
<https://doi.org/10.1023/A:1015733832373>

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>)