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Synthesis and heterocyclization of triterpenic 1,3-diketones

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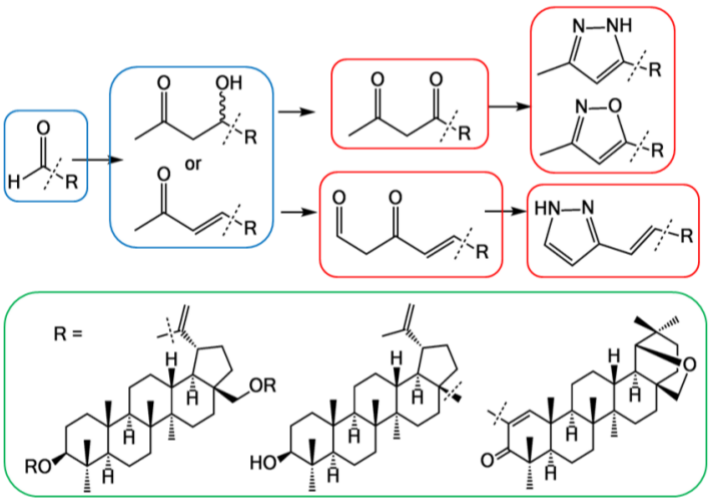
Abstract

Procedures for the synthesis of some new lupane and 18αH-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

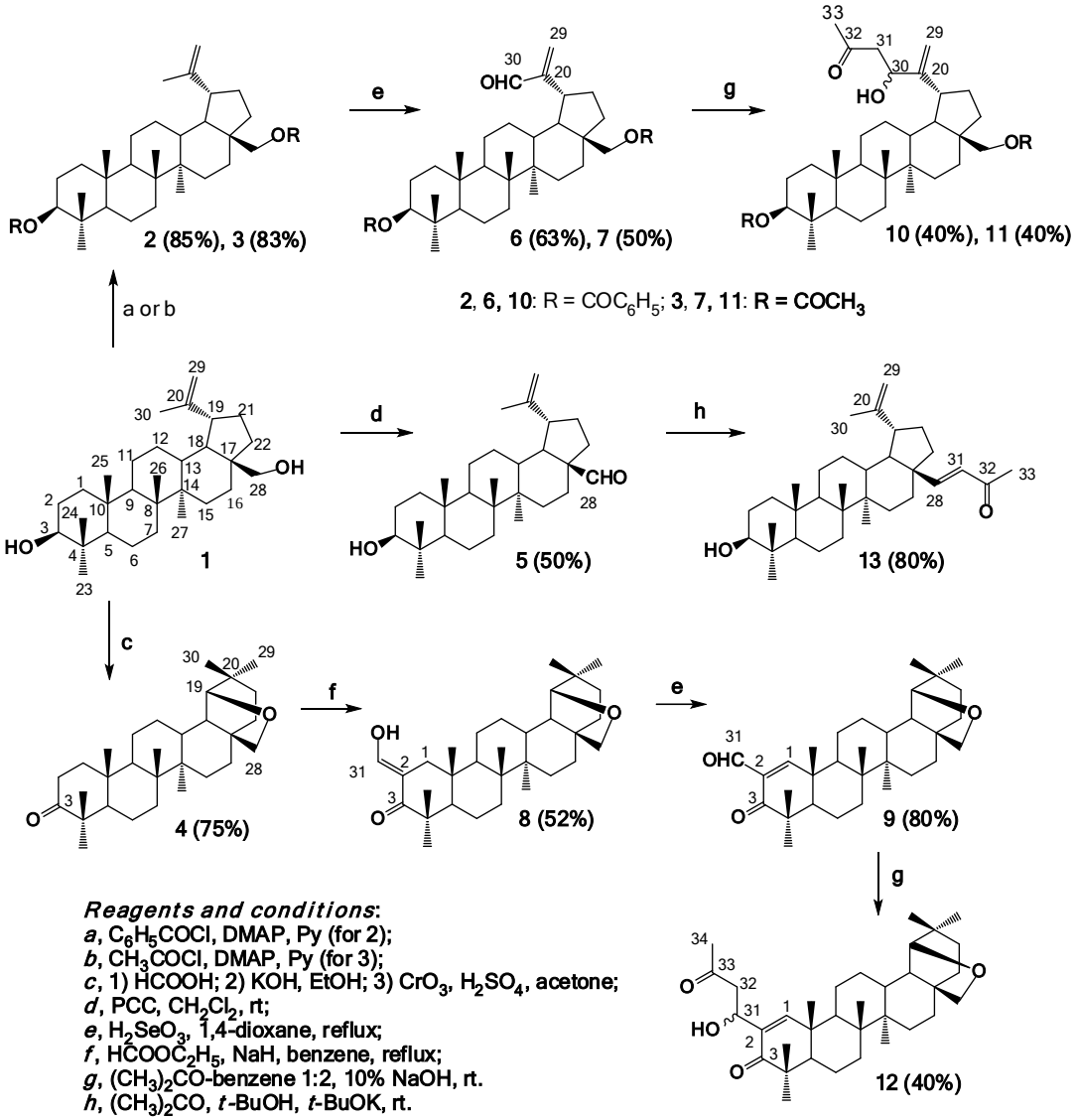
The strategy for the design of hybrid molecules, including those from natural compounds, is based on the methods of modern organic and medicinal chemistry and provides the preparation of chemical entities with two (or more than two) structural domains with different biological functions[1]. In accord with the molecular hybridization concept, heterocyclic modification of triterpenic skeleton can provide new hybrid molecules with high biological potential and bioavailability[2-5]. Concurrently, β-dicarbonyl compounds have shown themselves as useful building blocks for the construction of heterocycles with one, two, or more heteroatoms[6-8]. So, 1,3-diketones obtained from 3-oxo derivatives of allobetulin, betulinic, dihydrobetulonic, 23-hydroxybetulinic, oleanolic, maslinic, and glycyrrhetinic 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-position[9-19]. 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 betulinal **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).

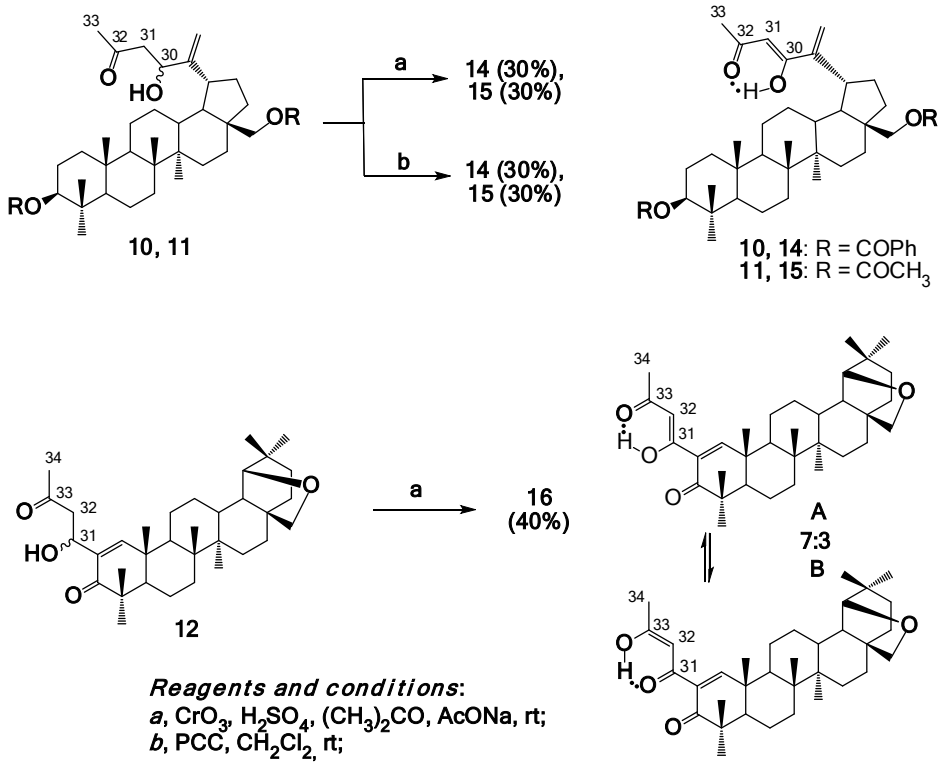
The aldol reaction of compounds **10-12** with acetone was discontinued at first signs of the formation (TLC) of a croton's by-product produced by the water elimination of their β-hydroxy ketone fragment. In turn, the aldol condensation of betulinal **5** with acetone carried out at room temperature 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 ^{1}H NMR spectrum of α,β-unsaturated methyl ketone **13** showed CH_3-33 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 ^{13}C 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 CH_2Cl_2 or with the Jones reagent in acetone (Scheme 2). 18αH-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).

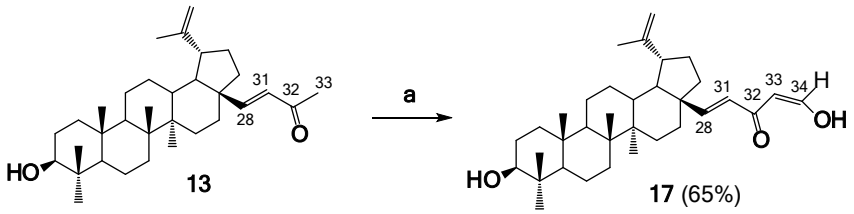


Scheme 1. Synthesis of triterpenic β-hydroxy ketones **10-12** and α,β-unsaturated methyl ketone **13** from betulin **1**.

Lupane 1,3-diketones **14** and **15** are completely enolized at the C-30 atom; that was confirmed by the data of ^{1}H and ^{13}C NMR spectra with characteristic signals: (1) a singlet of protons H_3-33 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 18αH-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 H_3-34 (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 ^{1}H NMR spectrum. Lupane 1,3-diketone **17** was obtained by the Claisen condensation of α,β-unsaturated methyl ketone **13** with $HCOOC_2H_5$ 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 ^{1}H and ^{13}C NMR spectra.



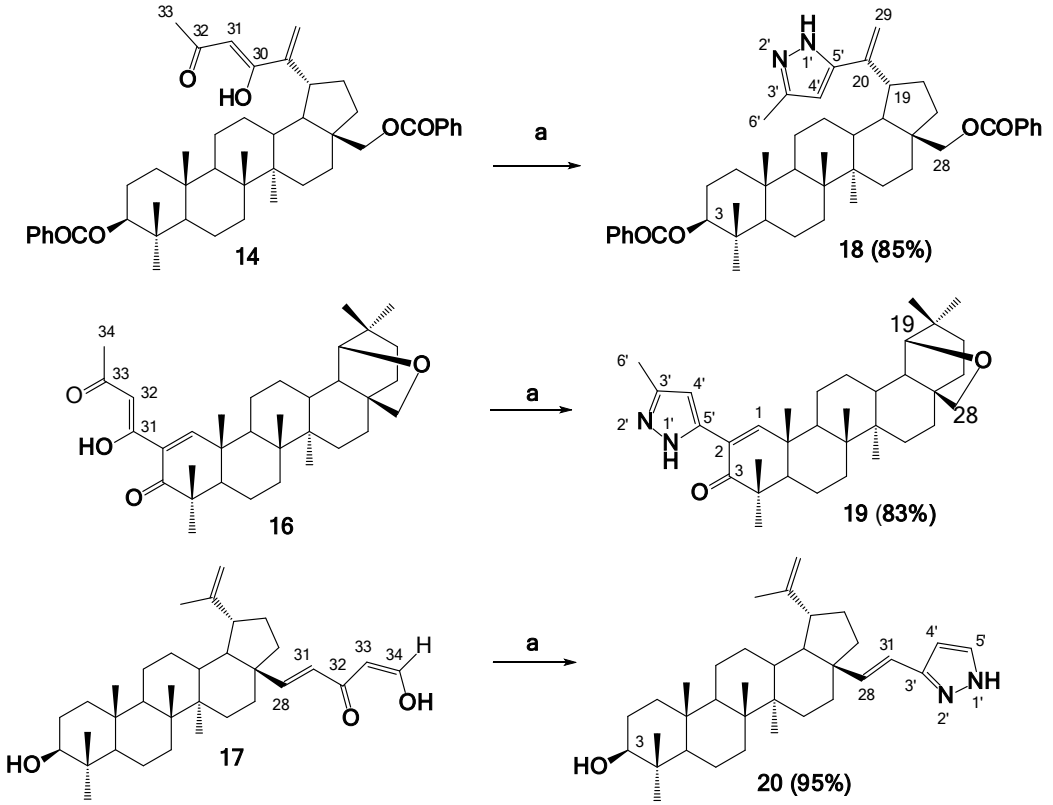
Scheme 2. Synthesis of triterpenic 1,3-diketones **14-16**.



Scheme 3. Synthesis of triterpenic 1,3-diketone **17**.

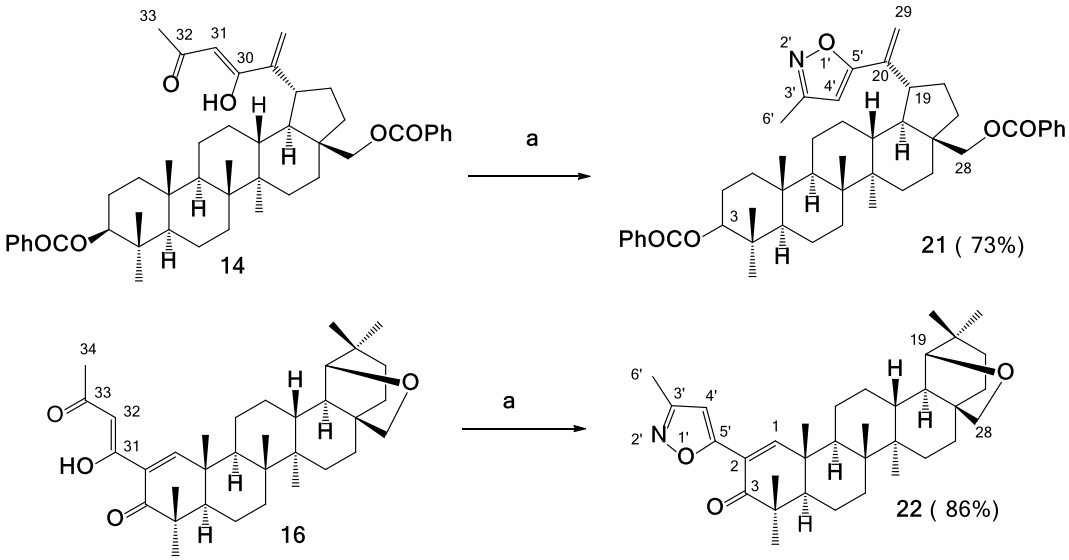
To obtain pyrazole derivatives, compounds **14**, **16**, **17** were heated with hydrazine hydrate in an alcohol–acetic acid mixture (1:1) for 1.5 h (Scheme 4).

The ^{1}H 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 H_3-6′, H-4′ and the proton of NH group of a substituted pyrazole cycle, respectively, whereas the ^{13}H NMR spectra revealed the characteristic signals of heterocyclic fragment at 102.02-102.62 and 141.25-147.12 ppm. In the ^{1}H 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 CH_3COONa at reflux afforded isoxazole derivatives **21, 22** in 86% and 73% yields, respectively (Scheme 5). In the ^{1}H NMR spectra of the compounds **21** and **22,** the characteristic singlet signals of protons H_3-6' and H-4' of isoxazole fragment were recorded at 2.30-2.31 and 6.12-6.61 ppm, respectively.



Reagents and conditions: *a*, $NH_2NH_2*H_2O$, EtOH; AcOH, reflux.

Scheme 4. Synthesis of triterpenic pyrazoles **18**-**20**.



Reagents and conditions: *a*, $NH_2OH*HCl$, EtOH, AcONa, reflux.

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 19β,28-epoxy-18αH-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 ^{1}H, ^{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°C/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 x 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 °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 pyridine[25].

3β-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 x 2). The organic layer was separated, washed with H_2O (5 × 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 °C, $[\alpha]_D^{21}$ -24.0 (*c* 0.5, $CHCl_3$). IR (cm^{-1}): 3447, 1672. ^{1}H 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-H_2), 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-H_3), 1.68 (3H, s, 30-H_3), 0.97, 0.95, 0.93, 0.81, 0.74 (15H, 5s, 5CH_3). ^{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 $C_{33}H_{52}O_2$: C, 82.44; H, 10.90. Found: C, 82.61; H, 10.99.

3β,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 °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 × 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, $CHCl_3$). IR (cm^{-1}): 1716. ^1H NMR (400 MHz, $CDCl_3$): 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-H_2), 4.69 (1H, dd, *J* 5.1, 11.0 Hz, 3-H), 4.53 and 4.13 (2H, 2d, *J* 11.1 Hz, 28-H_2), 2.73 (1H, td, *J* 11.2, 5.4 Hz, 19-H), 2.11 (3H, s, 33-H_3), 1.07, 0.99, 0.98, 0.90, 0.87 (15H, 5s, 5CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{47}H_{60}O_6$: 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 CH_3COONa (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 H_2O (5 × 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. 100.3 °C, $[\alpha]_D^{21}$ +2.4 (*c* 0.59, $CHCl_3$).IR (cm^{-1}): 1733. ^1H NMR (400 MHz, $CDCl_3$): δ_H 15.65 (1H, br s, OH), 5.85 (1H, s, 31-H), 5.77 and 5.44 (2H, 2s, 29-H_2), 4.45 (1H, dd, *J* 5.7, 10.8 Hz, 3-H), 4.27 and 3.88 (2H, 2d, *J* 10.8 Hz, 28-H_2), 2.65 (1H, td, *J* 11.3, 5.5 Hz, 19-H), 2.12 (3H, s, 33-H_3), 2.06 and 2.02 (6H, 2s, 2CH_3COO-), 1.03, 0.95, 0.82, (9H, 3c, 3CH_3), 0.83 (6H, s, 2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{37}H_{56}O_6$: 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 CH_3COONa (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 H_2O (5 × 10 ml), and dried over anhydrous $MgSO_4$. 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, $CDCl_3$): 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-H_2), 3.54 (1H, s, 19-H), 2.13 (3H, s, 34-H_3), 1.16, 1.09, 1.05, 1.02, 0.80 (15H, 5s, 5CH_3), 0.92 (6H, s, 2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{34}H_{50}O_4$: 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 $HCOOC_2H_5$ (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 H_2O (2 × 10 ml), and dried over anhydrous $MgSO_4$. 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, $CHCl_3$). IR (cm^{-1}): 3447, 1717, 1642, 1613. ^1H NMR (400 MHz, $CDCl_3$): 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-H_2), 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-H_3), 0.97, 0.95, 0.94, 0.80, 0.74 (15H, 5s, 5CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{34}H_{52}O_3$: C, 80.26; H, 10.30. Found: C, 80.41; H, 10.55.

3β,28-Dibenzoyloxy-20-(3′-methyl-1*H*-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 CH_3COOH 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 H_2O, and dried over anhydrous $MgSO_4$. 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, $CHCl_3$). IR (cm^{-1}): 3324, 3206, 1717. ^{1}H NMR (400 MHz, $CDCl_3$): 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-H_2), 4.69 (1H, dd, *J* 5.1, 11.0 Hz, 3-H), 4.58 and 4.15 (2H, 2d, *J* 11.1 Hz, 28-H_2), 2.88 (1H, td, *J* 11.2, 5.5 Hz, 19-H), 2.28 (3H, s, 6′-H_3), 1.06, 0.98, 0.97, 0.89, 0.86 (15H, 5c, 5CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{47}H_{60}N_2O_4$: C, 78.73; H, 8.43; N, 3.91. Found: C, 78.67; H, 8.58; N, 3.88.

19β,28-Epoxy-2-(3′-methyl-1*H*-pyrazol-5′-yl)-18αH-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 CH_3COOH 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 H_2O, and dried over anhydrous $MgSO_4$. 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, $CHCl_3$). IR (solution in $CHCl_3$, cm^{-1}): 3427, 3206, 1672. ^{1}H NMR (400 MHz, $CDCl_3$): 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-H_2), 3.54 (1H, s, 19-H), 2.28 (3H, s, 6′-H_3), 1.17, 1.14, 1.10, 1.06, 0.80 (15H, 5s, 5CH_3), 0.94 (6H, s, 2CH_3). Спектр ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{34}H_{50}N_2O_2$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.96; H, 9.64; N, 5.57.

3β-Hydroxy-28-[(1*H*-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 CH_3COOH 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 H_2O, and dried over anhydrous $MgSO_4$. 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, $CHCl_3$). IR (cm^{-1}): 3209, 1718, 1642. ^{1}H NMR (400 MHz, $CDCl_3$): 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-H_2), 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-H_3), 0.97, 0.95, 0.94, 0.79, 0.74 (15H, 5c, 5CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{34}H_{52}N_2O$: C, 80.90; H, 10.38; N, 5.55. Found: C, 81.01; H, 10.22; N, 5.34.

3β,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 CH_3COONa (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 H_2O, 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: 73%, m.p. 69.0 °C, $[\alpha]_D^{21}$ +12.0 (*c* 0.5, $CHCl_3$). IR (cm^{-1}): 1716, 1451. ^1H NMR (400 MHz, $CDCl_3$): 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-H_2), 4.69 (1H, dd, *J* 5.2, 10.9 Hz, 3-H), 4.58 and 4.16 (2H, 2d, *J* 11.1 Hz, 28-H_2), 2.87 (1H, td, *J* 11.2, 5.7 Hz, 19-H), 2.30 (3H, s, 6′-H_3), 1.07, 0.99, 0.97, 0.90, 0.87 (15H, 5s, $5CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{47}H_{59}NO_5$: C, 78.62; H, 8.28; N, 1.95. Found: C, 78.81; H, 8.41; N, 2.11.

19β,28-Epoxy-2-(3′-methylisoxazol-5′-yl)-18α*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 CH_3COONa (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 H_2O, and dried over anhydrous $MgSO_4$. 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, $CHCl_3$). IR (cm^{-1}): 1681, 1626, 1453. ^1H NMR (400 MHz, $CDCl_3$): 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-H_2), 3.59 (1H, s, 19-H), 2.31 (3H, s, 6′-H_3), 1.21, 1.17, 1.15, 1.10, 0.97, 0.96, 0.85 (21H, 7s, $7CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{34}H_{49}NO_3$: C, 78.57; H, 9.50; N, 2.69. Found: C, 78.63; H, 9.39; N, 2.78.

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Supplementary Material

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

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