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SYNTHESIS OF 2,11-DIOXO-NOROLEAN A(1)-12,18(19)-DIEN-30-OIC ACID

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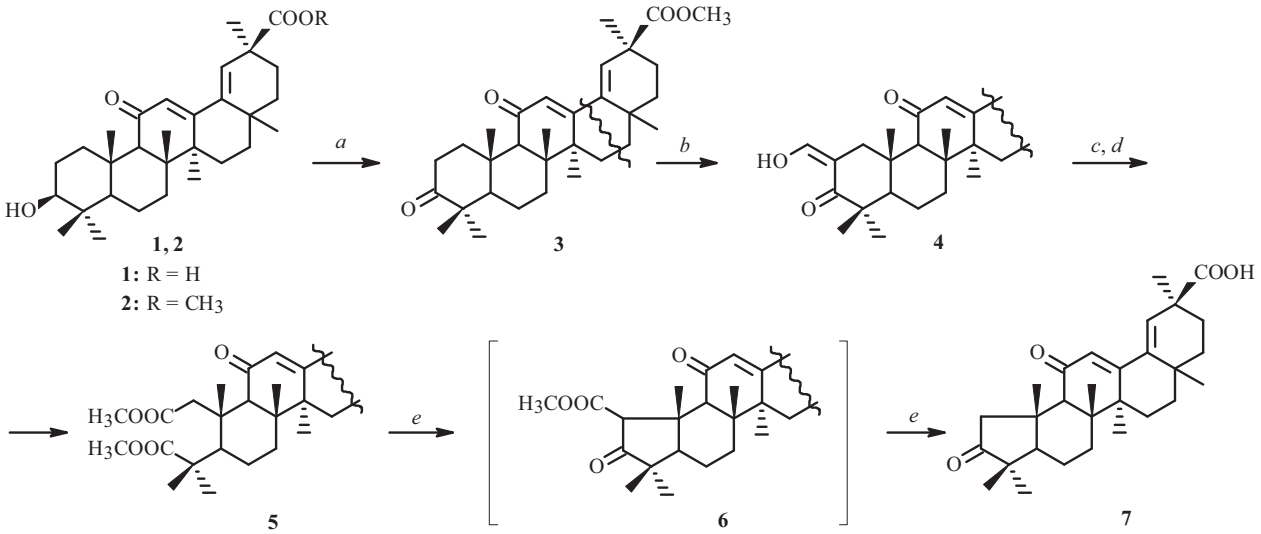
A new A-noroleanane triterpenoid with an altered pentacyclic skeleton of 2,11-dioxo-norolean A(1)-12,18(19)-dien-30-oic acid based on 18,19-dehydroglycyrrhetic acid was synthesized.

Keywords: triterpenoids, 2,11-dioxo-norolean A(1)-12,18(19)-dien-30-oic acid, 18,19-dehydroglycyrrhetic acid.

The development of triterpenoid chemistry during the last decade has led to the preparation of several unique biologically active compounds of interest to medicine as potential antiviral and antitumor drugs. Certain betulinic, oleanolic, and moronic acid derivatives are among the leading candidates with high anti-HIV and anticancer activity [1–5].

In continuation of our research on skeletal and oxidative transformations of triterpenoids from licorice roots (*Glycyrrhiza glabra* L. and *G. uralensis* Fisher) (Leguminosae) [6–9], we synthesized a new 18,19-dehydroglycyrrhetic acid (18,19-dehydro-GLA) derivative with an altered pentacyclic skeletion, 2,11-dioxo-A-norolean-12,18(19)-dien-30-oic acid (**7**) (Scheme 1).



a. PDC/CH_2Cl_2; *b*. HCO_2Et, 28% MeONa/MeOH; *c*. 30% H_2O_2, 28% NaOMe/MeOH; *d*. CH_2N_2/MeOH/Et_2O; *e*. *t*-BuOK/C_6H_6.

Scheme 1

We used pharmaceutical 18,19-dehydro-GLA (**1**) as the base structure for the synthetic transformations. It was converted to methyl ester **2** and oxidized by pyridinium dichromate (PDC) in CH_2Cl_2 into 3-oxo-18,19-dehydro-GLA (**3**) (75% yield).

Reaction of **3** with ethylformate in benzene in the presence of 28% NaOMe/MeOH produced the methyl ester of 2-hydroxymethylen-3,11-dioxo-olean-12(13),18(19)-dien-30-oic acid (**4**), the PMR spectrum of which exhibited a weak-field chemical shift (CS) of the HO–C<u>H</u>= group at 8.60 ppm and the ^{13}C NMR spectrum of which contained an additional weak-field resonance at 187.7 ppm (C-31a). Oxidation of **4** by H_2O_2 (30%) in the presence of NaOMe/MeOH (28%) gave the 2,3-*seco*-derivative, which was isolated in 55% yield as the dimethyl ester **5** after work up of the ether solution with diazomethane in MeOH. The PMR spectrum of this compound had protons of the three methoxyls with CS 3.57, 3.60, and 3.68 ppm. The

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^{13}C NMR spectrum exhibited new resonances for two OCH_3 groups at 48.5 and 50.5 ppm. The molecular ion determined by liquid-chromatography–mass-spectrometry (LCMS) had *m*/*z* 558 $[M + H]^+$ and agreed with empirical formula $C_{33}H_{48}O_7$.

Refluxing **5** with an excess of potassium *tert*-butoxide (*t*-BuOK) in benzene produced 2,11-dioxo-A-noroleanene **7** in 53% yield after column chromatography. Cyclization of **5** by *t*-BuOK should form 1-methoxycarbonyl derivative **6**, which could not be isolated from the reaction mixture. Apparently simultaneous decarboxylation and hydrolysis of the C-30 ester occurred in the presence of an excess of base (*t*-BuOK) during refluxing. The structure of the new nortriterpenoid with a pentacyclic ring A was confirmed by NMR spectra and LCMS. The ^{13}C NMR spectrum of the product contained resonances for 29 C atoms. A new resonance for C^2=O appeared at 224.3 ppm. The molecular ion with *m*/*z* 453 $[M + H]^+$ corresponded to empirical formula $C_{29}H_{40}O_4$.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS internal standard on a Bruker AM-300 spectrometer at operating frequency 300 MHz (^1H) and 75.5 (^{13}C). Resonances in NMR spectra in normal mode were assigned using the ACD LABS program set and literature data for GLA derivatives [6, 7, 10]. IR spectra were taken as mineral-oil mulls on an IR Prestige-21 (Shimadzu) spectrometer. UV spectra were recorded on a UF-400 spectrophotometer. Molecular ions were determined by LCMS on a Shimadzu LCMS-2010 with atmospheric-pressure chemical ionization of MeOH solutions. Optical activity was measured on a Perkin–Elmer 341 polarimeter in a 1-dm tube at 20–22°C (λ_{Na} 546 nm). Melting points were determined on a Boetius microstage.

Column chromatography (CC) was carried out over KSK silica gel (SG) (50–150 fraction) (Sorbpolimer) or Al_2O_3 (Brockmann neutral). TLC used Sorbfil plates (Sorbpolimer). Spots were detected by H_2SO_4 solution (5%) in EtOH with subsequent heating at 110–120°C for 2–3 min. Solvents were purified by standard methods [11]. Solvents were evaporated in vacuo at <50°C. We used pharmaceutical 18,19-dehydro-GLA (Chimkentbiofarm). The methyl ester of 18,19-dehydro-GLA (**2**) was prepared by refluxing in MeOH in the presence of H_2SO_4 as before [12], mp 208–210°C (EtOH); $[\alpha]_D^{20}$ +268±1° (*c* 0.03, $CHCl_3$), lit. [12] mp 207–209°C, $[\alpha]_D^{20}$ +270±2° (*c* 1.0, $CHCl_3$).

Methyl Ester of 3,11-Dioxo-olean-12,18(19)-dien-30-oic Acid (3). A solution of the methyl ester of 18,19-dehydro-GLA (**2**, 1.92 g, 4 mmol) in CH_2Cl_2 (20 mL) was stirred, treated with PDC (1.4 g, 6.4 mmol), stirred at 20–22°C for 3 h with TLC monitoring, diluted with CH_2Cl_2, and washed with H_2O, saturated $NaHCO_3$ and NaCl solutions, and again with H_2O. The organic layer was filtered through a thin layer of Al_2O_3 and evaporated. The solid was recrystallized from aqueous EtOH. Yield 1.44 g (75%), R_f 0.68 (toluene:EtOAc, 3:1), mp 192–194°C.

PMR spectrum ($CDCl_3$, δ, ppm): 0.99, 1.09, 1.11, 1.18, 1.20, 1.30, 1.32 (21H, all s, $7CH_3$), 1.45–1.70 (12H, m, H-6, H_a-21, H_a-22, H_a-2, H_2-7, H_2-8, H_2-15, H_2-16), 2.04–2.14 (2H, m, H_b-21, H_b-22), 2.33 (2H, m, H-10, H_b-2), 2.65 (1H, m, H_a-3), 2.88 (1H, m, H_b-3, 2H), 3.65 (3H, s, OCH_3), 5.82 (2H, s, H-12, H-19).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 39.7 (C-1), 33.3 (C-2), 217.2 (C-3), 47.7 (C-4), 55.5 (C-5), 18.9 (C-6), 34.2 (C-7), 45.3 (C-8), 60.1 (C-9), 36.1 (C-10), 199.75 (C-11), 129.9 (C-12), 163.1 (C-13), 44.4 (C-14), 25.9 (C-15), 34.9 (C-16), 34.8 (C-17), 142.7 (C-18), 124.0 (C-19), 43.3 (C-20), 27.9 (C-21), 36.6 (C-22), 26.5 (C-23), 21.4 (C-24), 16.0 (C-25), 18.3 (C-26), 19.7 (C-27), 24.4 (C-28), 25.0 (C-29), 176.7 (C-30), 52.2 (C-31).

Methyl Ester of 2-Hydroxymethylene-3,11-dioxo-olean-12(13),18(19)-dien-30-oic Acid (4). A solution of **3** (1.05 g, 2.2 mmol) in benzene (20 mL) was treated dropwise with a solution of NaOMe/MeOH (28%, 1.8 mL) and ethylformate (17 mL), stirred periodically at room temperature for 48 h, cooled in an ice bath, and treated with HCl (1 M, 10 mL) and EtOAc (10 mL). The organic layer was separated, washed with saturated NaCl solution and H_2O, dried, and evaporated. The solid was recrystallized twice from aqueous EtOH. Yield 0.94 g (82.4%). IR spectrum (ν, cm^{-1}): 1726 ($COOCH_3$), 1651 (C=O), 1600, 1589 (C=C). UV spectrum (MeOH, λ_{max}, nm): 280 (log ε 5.09); mp 182–184°C (EtOH); $[\alpha]_D^{20}$ +214° (*c* 0.04, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm): 0.96, 1.14, 1.18, 1.20, 1.22, 1.25, 1.30 (21H, all s, $7CH_3$), 1.45-1.65, 1.85–2.10 (CH, m, CH_2), 3.35 (3H, s, OCH_3), 5.82 (2H, s, H-12, H-19), 8.60 (1H, s, HO—C<u>H</u>=).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 39.7 (C-1), 105.7 (C-2), 189.7 (C-3), 45.2 (C-4), 58.7 (C-5), 19.7 (C-6), 34.3 (C-7), 40.0 (C-8), 60.8 (C-9), 28.4 (C-10), 199.6 (C-11), 124.0 (C-12), 142.6 (C-13), 44.3 (C-14), 27.9 (C-15), 34.3 (C-16), 36.0 (C-17), 163.4 (C-18), 130.1 (C-19), 43.1 (C-20), 32.9 (C-21), 36.1 (C-22), 25.9 (C-23), 20.9 (C-24), 15.1 (C-25), 18.2 (C-26), 18.8 (C-27), 24.4 (C-28), 25.0 (C-29), 176.2 (C-30), 52.4 (C-31), 187.7 (C-31a). LCMS (*m*/*z*): 522 $[M + H]^+$, $C_{33}H_{44}O_5$, MW 520.7.

Trimethyl Ester of 3,11-Dioxo-2,3-*seco*-olean-12,18(19)-dien-2,3,30-trioic Acid (5). A solution of **4** (0.52 mg, 1.0 mmol) in MeOH (100 mL) was treated with a solution of NaOMe/MeOH (28%), cooled on an ice bath, treated with H_2O_2 (14 mL, 30%), stirred with cooling for 1 h, diluted with CH_2Cl_2, washed with H_2O, dried over $MgSO_4$, and evaporated. The dry solid was dissolved in MeOH and treated with diazomethane in Et_2O at 5–10°C until the yellow color was stable. The solvent was evaporated. The solid was chromatographed over a column of SG with elution by C_6H_6:EtOAc (200:1 and 100:1, v/v). Fractions that were homogeneous according to TLC were combined to afford pure **5** (0.30 g, 55.4%) (amorphous yellow solid), R_f 0.74 (toluene:EtOAc, 3:1), $[\alpha]_D^{20}$ +232±1° (*c* 0.08, $CHCl_3$). UV spectrum (MeOH, λ_{max}, nm): 282 (log ε 4.72).

PMR spectrum ($CDCl_3$, δ, ppm): 0.90, 1.11, 1.19, 1.22, 1.24, 1.26, 1.31 (21H, all s, $7CH_3$), 1.52–2.40 (CH, m, CH_2), 3.57, 3.60, 3.68 (9H, all s, $COOCH_3$), 5.71, 5.78 (2H, both s, H-12, H-19).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 44.3 (C-1), 173.2 (C-2), 179.4 (C-3), 41.5 (C-4), 45.6 (C-5), 34.8 (C-6), 45.5 (C-7), 35.9 (C-8), 52.2 (C-9), 40.8 (C-10), 200.8 (C-11), 124.2 (C-12), 142.4 (C-13), 52.0 (C-14), 19.7 (C-15), 33.0 (C-16), 34.9 (C-17), 162.6 (C-18), 129.8 (C-19), 43.3 (C-20), 25.6 (C-21), 28.6 (C-22), 27.7 (C-23), 23.0 (C-24), 18.5 (C-25), 19.5 (C-26), 24.3 (C-27), 24.9 (C-28), 27.9 (C-29), 176.2 (C-30), 51.8 (C-31), 48.5 (C-32), 50.5 (C-33). LCMS (*m*/*z*): 558 $[M + H]^+$, $C_{33}H_{48}O_7$, MW 556.7.

2,11-Dioxo-norolean A(1)-12,18(19)-dien-30-oic Acid (7). A solution of **5** (0.28, g, 0.5 mmol) in benzene (10 mL) was treated with a suspension of *t*-BuOK (2 mL, 1 M) in THF in two portions, refluxed for 1.5 h, acidified with HCl solution (1 M), and extracted with EtOAc. The extract was washed with saturated NaCl solution and H_2O, dried, and evaporated. The solid was chromatographed over a column of SG with elution by C_6H_6:EtOH (100:1→10:1, vol%). Fractions that were homogeneous according to TLC were combined and evaporated. Yield 0.12 g (53.1%), R_f 0.62 (benzene:alcohol, 5:1), $[\alpha]_D^{20}$ +255±2° (*c* 0.22, MeOH).

PMR spectrum ($CDCl_3$, δ, ppm): 0.99, 0.99, 1.03, 1.14, 1.24, 1.26, 1.36 (21H, all s, $7CH_3$), 1.40–1.72, 1.60–2.25 (CH, m, CH_2), 5.90, 5.95 (2H, all s, H-12, H-19).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 56.5 (C-1), 224.3 (C-2), 44.1 (C-4), 58.7 (C-5), 18.6 (C-6), 33.2 (C-7), 45.4 (C-8), 59.7 (C-9), 38.4 (C-10), 199.2 (C-11), 129.9 (C-12), 164.5 (C-13), 43.6 (C-14), 27.6 (C-15), 29.5 (C-16), 34.7 (C-17), 142.5 (C-18), 123.1 (C-19), 34.6 (C-20), 33.0 (C-21), 36.0 (C-22), 28.1 (C-23), 24.1 (C-24), 17.4 (C-25), 19.8 (C-26), 20.7 (C-27), 24.7 (C-28), 26.0 (C-29), 180.5 (C-30). LCMS (*m*/*z*): 453 $[M + H]^+$, $C_{29}H_{40}O_4$, MW 452.6.

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