EFFECTIVE SYNTHESIS OF 2,3-*seco*-2,3-DICARBOXYPLATANIC ACID

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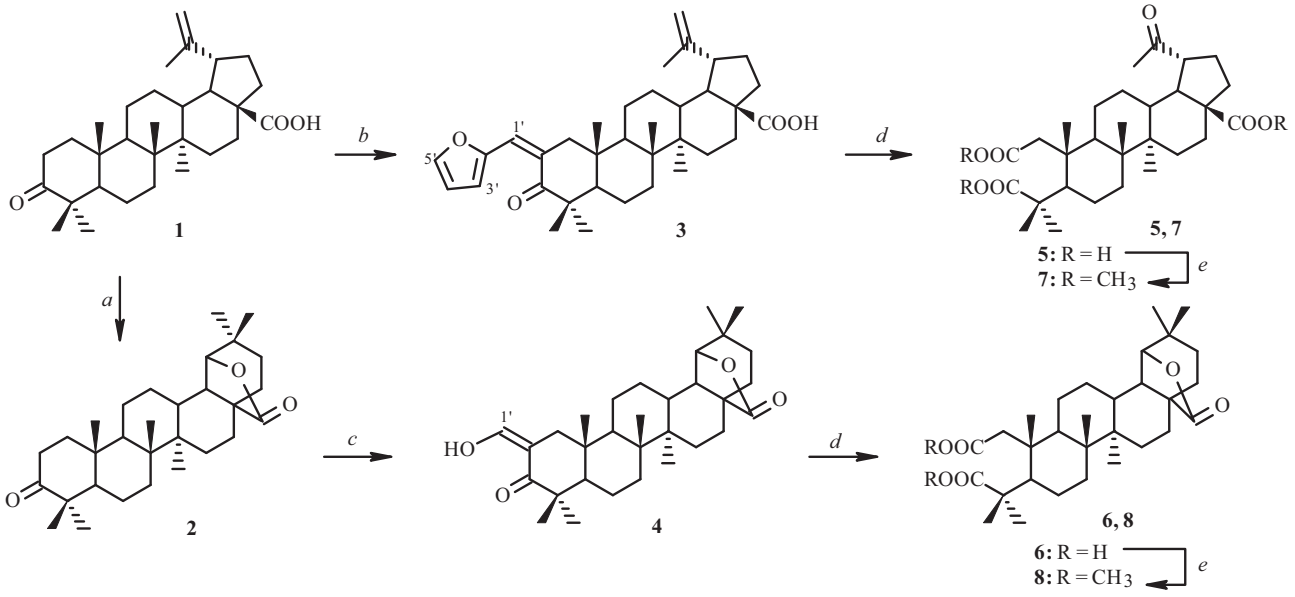
An effective method for preparing triterpene 2,3-seco-2,3-diacids by ozonolysis of 2-exomethylene-substituted derivatives of betulonic acid and 28-oxoallobetulone was proposed.

Keywords: betulin, platanic acid, 2,3-*seco*-triterpenoids, ozonolysis.

Platanic acid, which is isolated from bark of the tree *Platanus hypbrida* and exhibits anti-HIV-1 activity, is a promising target for modification and development of new antiviral agents [1]. Syntheses of several platanic acid amides have been reported [2, 3]. Platanic acid derivatives with a modified ring A have not been reported.

Herein we describe an effective synthesis of 2,3-*seco*-2,3-dicarboxyplatanic acid based on accessible betulin derivatives **1** and **2**. Known methods for preparing triterpene 2,3-*seco*-diacids are based on oxidative cleavage reactions of diosphenols [4, 5] in addition to oxidation of 2-hydroxymethylen-3-oxotriterpenoids by Cr(VI) oxide in AcOH, e.g., to **6** [6], or by H_2O_2 [7]. In the latter instance, the yield of diacid was less than 30%.

The oxidation of 2-exomethylene-substituted 3-oxo-triterpenoids **3** and **4** by ozone provided a basis for the method proposed by us for preparing 2,3-*seco*-acids. Carrying out the reactions in CH_2Cl_2 at –60°C gave 2,3-*seco*-acids **5** and **6** in 87% yield (Scheme 1). The resulting peroxide products were unstable and decomposed in several hours to the diacids.



a. HCOOH, 100°C; *b*. 2-furylaldehyde, 40% KOH/EtOH; *c*. HCO_2Et, CH_3ONa, benzene, 22°C; *d*. O_3, CH_2Cl_2, –60°C; *e*. CH_2N_2/Et_2O

Scheme 1

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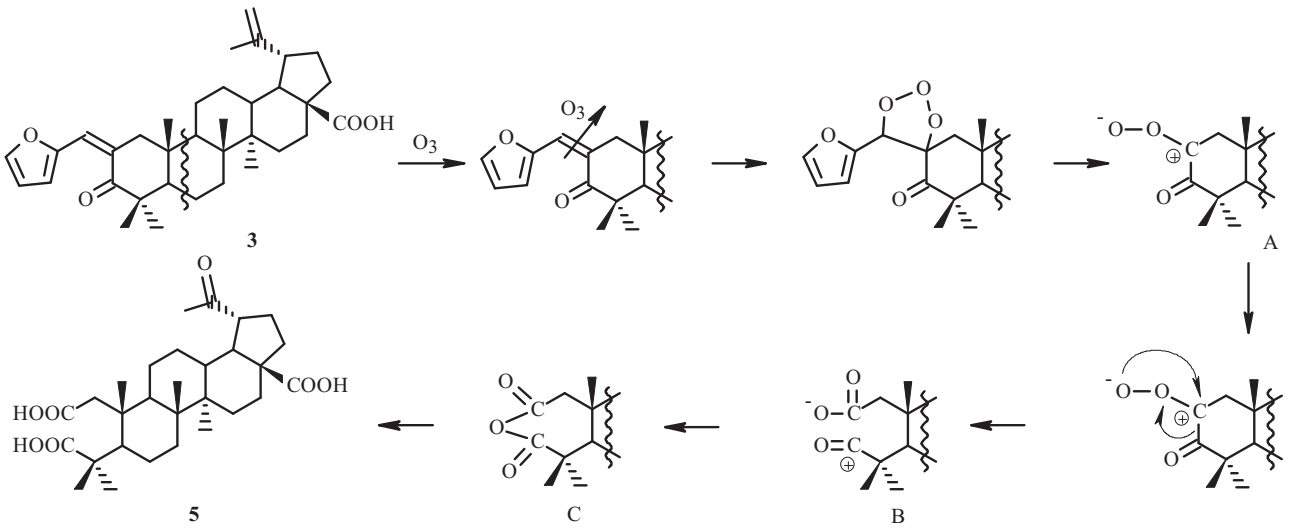
Scheme 2 shows a possible reaction mechanism based on 2-furfurylidenebetulonic acid **(3)**. Ozone attacks the exocyclic C2(C1′) double bond conjugated to the 3-ketone of **3**. The resulting Zwitter-ion A is instantaneously rearranged into secondary ion B, stabilization of which leads to formation of anhydride C, which converts into diacid **5**. In concert with cleavage of ring A, the isopropenyl group was oxidized to a C(20)-ketone. Esters **7** and **8** were synthesized via methylation of **5** and **6** by an ether solution of diazomethane.



Scheme 2

The structures of **5**-**8** were established based on NMR spectral data. Thus, resonances of the C2 and C3 carboxyls were observed at δ 174.5 and 183.4 ppm in the spectrum of **5** and 177.9 and 186.9 in that of **6**. Resonances of the methoxyl protons in spectra of **7** and **8** appeared as sharp singlets at 3.50–3.60 ppm.

Thus, an ecologically benign version for quantitative preparation of 2,3-*seco*-diacids via reaction of ozone with 2-exomethylene-substituted 3-oxo-triterpenoids is proposed using betulin derivatives as examples.

EXPERIMENTAL

PMR and ^{13}C NMR spectra in $CDCl_3$ were recorded on a Bruker AM-300 spectrometer (300 and 75.5 MHz) with TMS internal standard. Melting points were determined on a Boetus microstage. Optical density was measured in a 1-dm tube on a Perkin–Elmer 241 MC polarimeter. An Ozon-2K ozonizer was used for the ozonation. TLC was performed on Sorbfil plates (ZAO Sorbpolimer, Russia) using $CHCl_3$:EtOAc (40:1). Compounds were detected with H_2SO_4 (10%) with subsequent heating to 100–120°C for 2–3 min. Betulonic acid (**1**) and 28-oxoallobetulone (**2**) were prepared as before [8, 9]. Compounds **5** and **6** were methylated by diazomethane in ether using the standard method [10].

2-Furfurylidenebetulonic Acid (3). A solution of betulonic acid (**1**, 1 mmol) in EtOH (20 mL) was stirred, cooled (≤ 10°C), treated with freshly distilled 2-furylaldehyde (0.18 mL, 2 mmol) in KOH solution (2.5 mL, 40%) in EtOH, cooled for 30 min, left overnight at room temperature, acidified with acetic acid until neutral, and poured into cold water (100 mL). The resulting solid was filtered off, washed wth water, dried, and recrystallized from EtOH. Yield 0.44 g (83%) of a cream-colored compound, mp 109°C, $C_{35}H_{48}O_4$ (MW 535.76).

PMR spectrum (δ, ppm, J/Hz): 0.84, 1.01, 1.05, 1.10, 1.16 (15H, 5s, $5CH_3$), 1.20-2.00 (22H, m, CH_2, CH), 1.76 (3H, s, H-30), 2.14–2.27 (1H, m, H-13), 2.93–3.02 (1H, m, H-19), 4.69 and 4.81 (2H, both br.s, H-29), 6.48 (1H, br.s, H-4′), 6.58 (1H, dd, J = 1.7, 3.4, H-3′), 7.27 (1H, s, H-5′), 7.55 (1H, br.s, H-1′).

^{13}C NMR spectrum: 14.5, 15.3, 16.1, 19.4, 20.3, 21.6, 22.1, 25.5, 29.5, 30.5, 31.6, 32.9, 35.8, 36.9, 38.4, 40.3, 42.4, 42.6, 44.6, 44.7, 46.7, 48.3, 49.0, 52.4, 56.4, 109.5, 112.1, 115.4, 124.2, 131.0, 144.3, 150.5, 152.4, 182.6 (C-28), 207.6 (C-3).

2-Hydroxymethylene-28-oxoallobetulone (4). A stirred suspension of sodium methoxide (0.35 g) in benzene (5 mL) at room temperature was treated with ethylformate (1 mL) that was freshly distilled over P_2O_5. After 20 min a solution

of **2** (1 mmol) in benzene (20 mL) was added. The mixture was stirred for 4 h (TLC monitoring). The organic layer was treated with cold water (30 mL) and separated. The aqueous layer was extracted with benzene (2 × 20 mL). The combined extracts were washed with HCl solution (5%, 20 mL) and water (20 mL) and dried over $MgSO_4$. Solvent was vacuum distilled. Yield 0.44 g (92%) of a cream-colored compound, mp 253–256°C, $[\alpha]_D^{20}$ +55° (*c* 0.2, $CHCl_3$), $C_{31}H_{46}O_4$ (MW 482.69).

PMR spectrum (δ, ppm): 0.82, 0.87, 0.95, 0.96, 1.00, 1.09, 1.15 (21H, 7s, $7CH_3$), 1.20–2.51 (22H, m, CH_2, CH), 3.99 (1H, s, H-19), 8.62 (1H, s, =C<u>H</u>OH), 14.35 (1H, br.s,=CHO<u>H</u>).

^{13}C NMR spectrum: 13.7, 15.4, 15.6, 19.4, 20.7, 21.5, 24.0, 25.6, 26.6, 28.0, 28.3, 28.8, 32.0, 32.4, 32.8, 33.6, 36.2, 36.7, 40.0, 40.1, 40.3, 40.5, 46.2, 46.7, 49.5, 52.3, 86.0 (C-19), 105.7 (C-2), 180 (C-28), 189.0 (C-1′), 190.3 (C-3).

Ozonolysis of 3 and 4. A solution of **3** or **4** (2 mmol) in CH_2Cl_2 (50 mL) at –60°C was purged with ozone until starting material disappeared (TLC monitoring). The temperature was raised to ambient. After 1 d solvent was vacuum distilled. The solid was washed on a filter with water and dried. The solid was recrystallized from $CHCl_3$:MeOH.

2,3-*seco*-Lup-29-nor-20-oxo-2,3,28-trioic Acid (5). Yield 0.73 g (87%) of a cream-colored compound, mp 152–153°C, $[\alpha]_D^{20}$ +9° (*c* 0.1, $CHCl_3$), $C_{29}H_{44}O_7$ (MW 423.8).

PMR spectrum (δ, ppm): 0.85, 1.01, 1.05, 1.10, 1.16 (15H, 5s, $5CH_3$), 1.20–2.10 (22H, m, CH_2, CH), 2.12 (3H, s, H-30), 2.18-2.40 (1H, m, H-13), 2.40-3.58 (1H, m, H-19), 10.50 and 10.60 (1H each, both br.s, COO<u>H</u>).

^{13}C NMR spectrum: 14.3, 15.6, 19.6, 20.6, 21.7, 23.4, 26.8, 27.2, 28.2, 29.5, 31.3, 33.0, 36.6, 37.3, 40.3, 42.4, 43.6, 46.1, 48.0, 48.9, 49.0, 49.3, 49.7, 51.4, 56.0, 174.5 (C-2), 178.9 (C-28), 183.0 (C-3), 213.6 (C-20).

2,3-*seco*-19β,28-Epoxy-28-oxo-18α-olean-2,3-dioic Acid (6). Yield 0.87 g (87%) of a white compound, mp 260–263°C, $[\alpha]_D^{20}$ +17° (*c* 0.1, $CHCl_3$) (lit. [6] mp 265–266°C), $C_{30}H_{46}O_6$ (MW 502.68).

PMR spectrum (δ, ppm): 0.75, 0.80, 0.86, 0.93, 0.98, 0.10, 0.11 (21H, 7s, $7CH_3$), 1.18–1.49 (23H, m, CH_2, CH), 2.95–3.04 (1H, m), 4.41 (1H, br.s, H-19).

^{13}C NMR spectrum: 13.7, 15.5, 16.1, 19.5, 20.9, 21.5, 21.9, 23.9, 25.4, 26.4, 27.8, 28.7, 31.9, 32.2, 32.9, 33.5, 36.0, 40.3, 40.4, 41.4, 42.0, 42.5, 45.8, 46.1, 46.6, 48.4, 85.9, 177.9 (C-2), 179.8 (C-28), 186.9 (C-3).

2,3-*seco*-Lup-29-nor-20-oxo-2,3,28-trioic acid trimethyl ester (7), mp 189–190°C, $[\alpha]_D^{20}$ +23° (*c* 0.1, $CHCl_3$), $C_{32}H_{50}O_7$ (MW 546.9).

PMR spectrum (δ, ppm): 0.89, 1.01, 1.18, 1.20, 1.21 (15H, 5s, $5CH_3$), 1.28–2.41 (23H, m, CH_2, CH), 2.12 (3H, s, H-30), 3.69 [3H, s, C(2)$O_2C\underline{H}_3$], 3.65 [3H, s, C(3)$O_2C\underline{H}_3$], 3.69 [3H, s, C(2)$O_2C\underline{H}_3$].

^{13}C NMR spectrum: 14.7, 15.7, 19.6, 20.7, 21.9, 23.8, 27.4, 27.7, 28.3, 29.7, 29.9, 31.3, 33.2, 36.5, 37.5, 40.5, 41.6, 41.9, 42.0, 42.5, 46.3, 48.3, 49.3, 50.8, 51.2, 51.3, 51.6, 56.5, 171.8 (C-2), 176.5 (C-28), 179.9 (C-3), 212.1 (C-20).

2,3-*seco*-19β,28-Epoxy-28-oxo-18α-olean-2,3-dioic acid dimethyl ester (8), mp 108–111°C, $[\alpha]_D^{20}$ +59° (*c* 0.1, $CHCl_3$), $C_{32}H_{50}O_6$ (MW 530.7).

PMR spectrum (δ, ppm): 0.87, 0.88, 0.90, 0.91, 0.99, 1.10, 1.23 (21H, 7s, $7CH_3$), 1.25–2.49 (22H, m, CH_2, CH), 3.59 [3H, s, C(2)$O_2C\underline{H}_3$], 3.62 [3H, s, C(3)$O_2C\underline{H}_3$], 3.91 (1H, s, H-19).

^{13}C NMR spectrum: 13.6, 15.5, 16.3, 19.5, 20.0, 20.6, 21.3, 21.8, 23.8, 23.9, 25.5, 26.5, 27.8, 28.7, 31.9, 32.6, 33.5, 34.0, 39.8, 40.2, 41.8, 42.1, 46.6, 48.4, 50.5, 50.8, 51.7, 55.0, 85.8 (C-19), 171.4 (C-2), 180.6 (C-28), 182.3 (C-3).

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REFERENCES

1. T. Fujioka, Y. Kashiwada, R. Kilkuskie, L. Cosentino, L. Ballas, J. Jiang, W. Janzen, I. Chen. and K.-H. Lee, *J. Nat. Prod.*, **57**, No. 2, 243 (1994).
2. M. Evers, C. Poujade, F. Soler, Y. Ribeill, C. James, Y. Lelievre, J. C. Gueguen, D. Reisdorf, I. Morize, R. Pauwels, E. De Clercq, Y. Henin, A. Bousseau, J. F. Mayaux, J. B. LePecq, and N. Dereu, *J. Med. Chem.*, **39**, No. 5, 1056 (1996).

3. O. B. Flekhter, N. I. Medvedeva, G. A. Tolstikov, O. V. Savinova, E. I. Boreko, and F. M. Dolgushin, *Bioorg. Khim.*, **35**, No. 1, 129 (2009).
4. M. Endova, E. Klinotova, J. Sejbal, and B. Maca, *Collect. Czech. Chem. Commun.*, **59**, 1420 (1994).
5. M. Urban, J. Sarek, J. Klinot, G. Korinkova, and M. Hajduch, *J. Nat. Prod.*, **67**, 1100 (2004).
6. L. Ruzicka, G. F. Frame, H. M. Leicester, M. Liguori, and H. Brunger, *Helv. Chim. Acta*, **17**, 426 (1934).
7. T. Konoike, K. Takahashi, and Y. Kitaura, *Tetrahedron*, **55**, 14901 (1999).
8. O. B. Flekhter, L. R. Nigmatullina, L. A. Baltina, L. T. Karachurina, F. Z. Galin, F. S. Zarudii, G. A. Tolstikov, E. I. Boreko, N. I. Pavlova, S. N. Nikolaeva, and O. V. Savinova, *Khim.-farm. Zh.*, **36**, No. 9, 26 (2002).
9. O. B. Flekhter, E. I. Boreko, L. R. Nigmatullina, N. I. Pavlova, N. I. Medvedeva, S. N. Nikolaeva, E. V. Tret′yakova, O. V. Savinova, L. A. Baltina, L. T. Karachurina, F. Z. Galin, F. S. Zarudii, and G. A. Tolstikov, *Khim.-farm. Zh.*, **38**, No. 3, 31 (2004).
10. *Practicum in Organic Chemistry* [in Russian], Vol. II, Mir, Moscow, 1979, pp. 247–250.