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SYNTHESIS AND MOLECULAR STRUCTURE OF 3*β*,28-DIACETOXY-(20*R*)-LUPAN-29-OIC ACID

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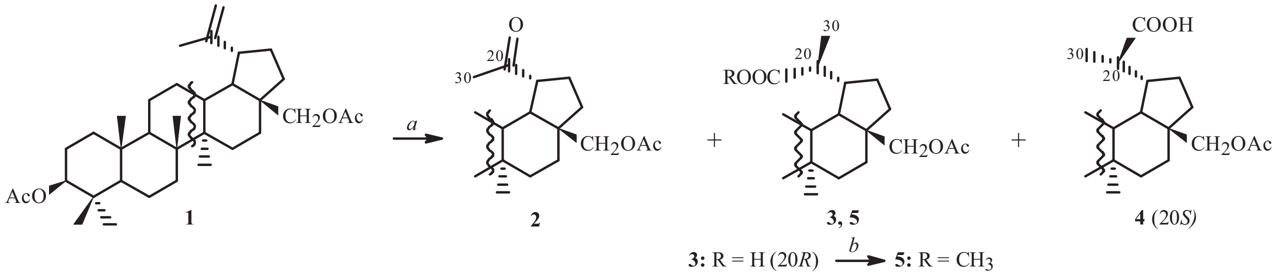
The methyl ester of 3β,*28-diacetoxy-(20*R*)-lupan-29-oic acid was synthesized and its molecular structure was determined.*

Keywords: betulin, oxidation, 3*β*,28-diacetoxy-(20*R*)-lupan-29-oic acid, x-ray structure analysis.

Oxidation is an effective method for modifying the isopropenyl group of lupane-type triterpenoids. The reaction of lupane derivatives with ozone and dimethyldioxirane has been studied [1, 2]. It was shown that oxidation of betulin and its acetates by Cr(VI) oxide produced derivatives with keto- and carboxylic groups [3–6]. Thus, the formation of epimeric C20-acids from the reaction of betulin diacetate (**1**) with CrO_3 in acetic acid at 70°C was reported [5]. On the other hand, the product from the reaction of **1** with CrO_3 was purported to be a norketone (**2**) [6]. Herein data on the product composition from the oxidation of **1** by CrO_3 in refluxing acetic acid and an x-ray structure analysis (XSA) of one of the acids as the methyl ester are reported.

The reaction of **1** and CrO_3 in acetic acid at 100°C for 3 h produced a mixture of the norketone (**2**) and two epimeric acids (**3** and **4**), which were isolated pure using column chromatography in yields of 50, 20, and 15%, respectively (Scheme 1). NMR spectra of **3** and **4** were identical. The structure of ketone **2** was confirmed previously by an XSA [7].



a. CrO_3, AcOH, 100°C, 3 h; *b*. CH_2N_2/Et_2O

Scheme 1

Methylation of acid **3** by diazomethane solution gave ester **5**. An XSA established its molecular and crystal structure (Fig. 1). All six-membered rings had the chair conformation. The five-membered ring had a slightly distorted envelope conformation. This is usually observed for such compounds [8]. The absolute configuration of **5** was determined from the retention of configuration of the chiral atoms during the reaction (Fig. 1). This suggested that C20 had the *R*-configuration. According to the XSA of **5**, it can be concluded that acids **3** and **4** were the 20*R* and 20*S*-epimers.

Thus, the structure of the methyl ester of 3*β*,28-diacetoxy-(20*R*)-lupan-29-oic acid was determined. Pure (20*R*)- and (20*S*)-lupane acids are interesting as a platform for synthesizing triterpenoid derivatives at the C3, C28, and C29 positions.

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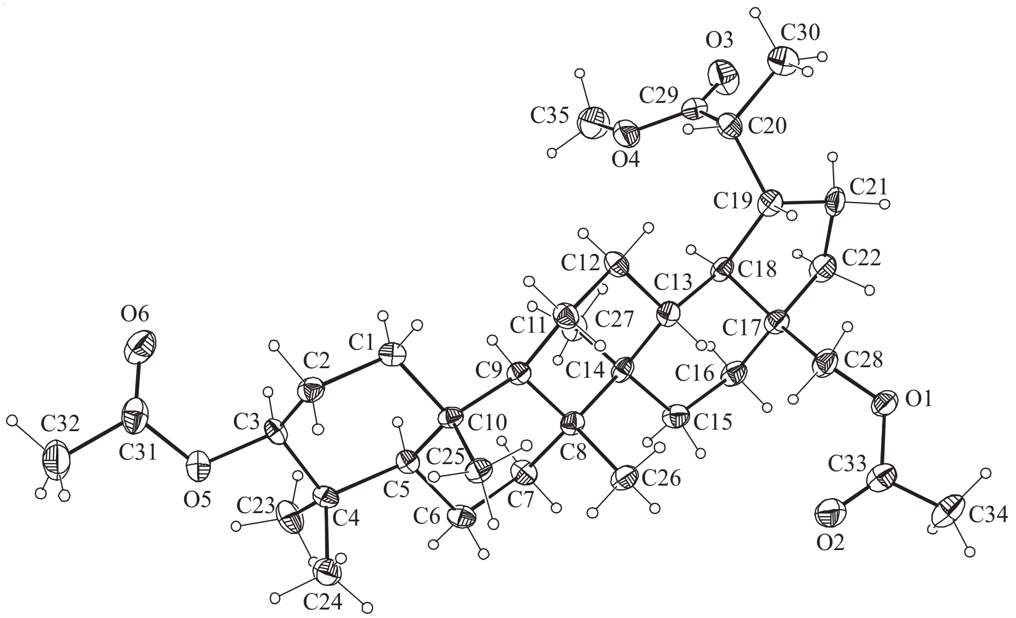

Fig. 1. Molecular structure of the methyl ester of 3*β*,28-diacetoxy-(20*R*)-lupan-29-oic acid (**5**) with 50% probability atomic ellipsoids.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in CDCl$_3$ with TMS internal standard on a Bruker AM-300 spectrometer (300 and 75.5 MHz). Melting points were determined on a Boetius microstage. Optical density was measured on a Perkin–Elmer 241 MC polarimeter in a 1-dm tube. An Ozon-2K ozonizer was used for the ozonation. TLC was performed on Sorbfil plates (Sorbpolimer, Russia) using CHCl$_3$:EtOAc (40:1). Compounds were detected by H$_2$SO$_4$ solution (10%) with subsequent heating at 100–120°C for 2–3 min. Betulin diacetate (**1**) was prepared as before [9].

3*β*,28-Diacetoxy-29-norlupan-20-one (2), 3*β*,28-Diacetoxy-(20*R*)-lupan-29-oic Acid (3), 3*β*,28-Diacetoxy-(20*S*)-lupan-29-oic Acid (4). A solution of **1** (10 mmol, 5.15 g) in acetic acid (150 mL) was treated with CrO$_3$ (0.1 mol, 1.0 g), refluxed at 100°C for 3 h, and poured into water (300 mL). The precipitate was filtered off, washed until neutral, dried in air, and chromatographed over a column with elution successively by petroleum ether, benzene, CHCl$_3$, and CHCl$_3$:MeOH mixtures (100:1, 50:1, 10:1). Yield of **2**, 2.43 g (50%); **3**, 1.02 g (20%); **4**, 0.75 g (15%). The physicochemical properties and NMR spectra of **2** agreed with those published [7]. Compound **3**: R_f 0.22, mp 238–240°C, $[\alpha]_D^{20}$ –56° (*c* 1.00, CHCl$_3$) {lit. [5] mp 239–241°C, $[\alpha]_D^{22}$ –44° (*c* 0.68)}, C$_{34}$H$_{54}$O$_6$ (MW 558.789).

Compound **4**: R_f 0.14, mp 248–251°C, $[\alpha]_D^{20}$ +8° (*c* 1.00, CHCl$_3$) {lit. [5] mp 254–259°C, $[\alpha]_D^{22}$ +11° (*c* 0.65)}. NMR spectra of **3** and **4** were identical.

PMR spectrum of **3**/**4** (δ, ppm, J/Hz): 0.65, 0.65, 0.70, 0.90, 1.05 (3H each, s, CH$_3$), 1.15–1.85 (29H, m, CH, CH$_2$), 2.01 and 2.03 (3H each, s, OAc), 2.70–2.80 (1H, br.s, H-3), 3.55 and 4.20 (1H each, d, J = 7.8, H-28), 4.50 (1H, t, H-19).

^{13}C NMR spectrum of **3**/**4** (δ, ppm): 14.5, 16.1, 16.1, 16.5, 17.1, 18.1, 20.8, 21.0, 21.2, 23.5, 23.7, 27.0, 27.9, 27.9, 29.8, 34.0, 34.2, 37.0, 37.0, 37.8, 38.4, 40.9, 42.0, 42.9, 43.3, 46.3, 49.0, 49.8, 55.3, 62.5 (C-28), 80.9 (C-3), 171.0, 171.6, 181.1 (C-20).

Methyl Ester of 3*β*,28-Diacetoxy-(20*R*)-lupan-29-oic Acid (5). A solution of **3** (1 mmol, 0.58 g) in MeOH was stirred and treated with an Et$_2$O solution of diazomethane until the starting material disappeared completely (TLC monitoring). The solvent was evaporated in vacuo. The product was crystallized from benzene. Yield 0.56 g (97%), R_f 0.82, mp 203–205°C, $[\alpha]_D^{20}$ –69° (*c* 3, CHCl$_3$), C$_{35}$H$_{56}$O$_6$.

PMR spectrum (CDCl$_3$, δ, ppm, J/Hz): 0.74, 0.75, 0.76, 0.83, 0.94 (3H each, s, CH$_3$), 1.02 (3H, d, J = 7, H-30), 1.10–1.80 (22H, m, CH$_2$, CH), 1.94 and 1.95 (3H each, s, OAc), 2.65-2.67 (2H, m, H-19, H-20), 3.56 (3H, s, OCH$_3$), 3.67 and 3.78 (1H each, d, H-28), 4.35–4.40 (1H, m, H-3).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.4, 16.0, 16.1, 16.5, 17.2, 18.1, 20.8, 21.0, 21.3, 23.3, 23.6, 26.8, 26.9, 27.9, 29.8, 33.9, 34.2, 36.9, 37.0, 37.8, 38.3, 40.9, 42.0, 42.8, 43.5, 46.2, 49.0, 49.9, 51.0, 55.3, 62.4 (C-28), 80.9 (C-3), 171.0, 171.6, 176.0 (C-30).

XSA of 5. Colorless thin needle-like crystals, $C_{35}H_{56}O_6$ (MW = 572.80), were orthorhombic, $a = 7.4502(12)$, $b = 11.8528(18)$, $c = 35.658(6)$ Å, $V = 3148.8(8)$ Å^3, space group $P2_12_12_1$, $Z = 4$, $d_{\text{calcd}} = 1.124$ g/cm^3. A data set of 32,322 reflections was obtained on a Bruker SMART APEX2 CCD diffractometer at 100 K (λ Mo Kα-radiation, $\theta_{\max} = 27°$) from a single crystal of size 0.14 × 0.03 × 0.01 mm. The initial data set of measured intensities was processed using the SAINT and SADABS programs included in the APEX2 programs [10]. The structure was solved by direct methods and refined by anisotropic full-matrix least-squares methods for nonhydrogen atoms over F^2_{hkl}. Hydrogen atoms were placed in geometrically calculated positions and refined using a rider model [$U_{iso}(\text{H}) = nU_{eq}(\text{C,O})$, where $n = 1.5$ for methyl H atoms and 1.2 for other C atoms]. A total of 3904 independent reflections was used in the refinement. The refinement converged over all independent reflections for $wR_2 = 0.1023$ [$R_1 = 0.0504$ over 2667 reflections with $I > 2\sigma(I)$]. All calculations were performed on an IBM PC using the SHELXTL program set [11]. Atomic coordinates and thermal factors were deposited in the Cambridge Crystallographic Data Centre (CCDC No. 793691).

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REFERENCES

1. O. B. Flekhter, N. I. Medvedeva, O. S. Kukovinets, L. V. Spirikhin, E. G. Galkin, F. Z. Galin, D. G. Golovanov, N. I. Pavlova, O. V. Savinova, E. I. Boreko, and G. A. Tolstikov, *Bioorg. Khim.*, **33**(6), 629 (2007).
2. O. Yu. Ashavina, N. N. Kabal′nova, O. B. Flekhter, L. V. Spirikhin, F. Z. Galin, L. A. Baltina, Z. A. Starikova, M. Yu. Antipin, and G. A. Tolstikov, *Mendeleev Commun.*, **14**(5), 221 (2004).
3. L. Ruzicka, A. H. Lamberton, and E. W. Christie, *Helv. Chim. Acta*, **21**, 1706 (1938).
4. Z. Kitasato and M. Sinkai, *Acta Phytochim.*, **11**, 231 (1940).
5. A. Vystrcil, V. Pouzar, and V. Krecek, *Collect. Czech. Chem. Commun.*, **38**, 3902 (1973).
6. R. S. Ludwiczak, U. Wrzeciono, K. Szczawinska, and A. Mroczkiewicz, *Rocz. Chem.*, **45**, 1009 (1971).
7. O. B. Flekhter, G. V. Giniyatullina, F. Z. Galin, N. Zh. Baschenko, N. S. Makara, F. S. Zarudii, E. I. Boreko, O. V. Savinova, N. I. Pavlova, Z. A. Starikova, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 582 (2005).
8. O. B. Kazakova, N. I. Medvedeva, E. V. Salimova, and K. Yu. Suponitskii, *Zh. Strukt. Khim.*, **51**, 810 (2010).
9. G. A. Tolstikov, M. I. Goryaev, H. O. Kim, and R. A. Hegai, *Zh. Prikl. Khim.*, **40**(4), 920 (1967).
10. APEX2 and SAINT, Bruker AXS Inc., Madison, Wisconsin, USA, 2005.
11. G. M. Sheldrick, *Acta Crystallogr. Sect. A: Found. Crystallogr.*, **64**, 112 (2008).