Synthesis of betulonic acid *S*,*S*′-bis(carboxymethyl) dithioketal

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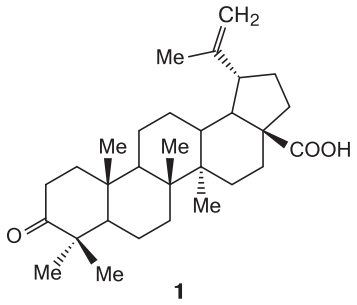
Betulonic acid *S*,*S*′-bis(carboxymethyl) dithioketal was obtained by condensation of betulonic and thioglycolic acids.

Key words: betulonic acid, thioglycolic acid, thioketals.

White birch bark has long been known as a practically inexhaustible source of a family of five-membered triterpene compounds with a wide range of biological activity. The most well-known of them are compounds of the lupane group (betulin, lupeol, betulinic and betulonic acids), which showed high hepatoprotective,[1] antiviral,[2—6] or antibacterial properties.[4,7] The directed transformation of functional groups of these triterpenoids is used in the search for new drugs.[2,8] Thus, the modification of betulonic acid **1** with fragments containing an alkyne function has proved to be promising for the design of new antioxidant and antiinflammatory agents[9] due to the complex compounds with biogenic metals, for example, cobalt, zinc, and copper. Such complexes are of interest as radioprotectors, antidotes of cyanides and carbon monoxide.[10]

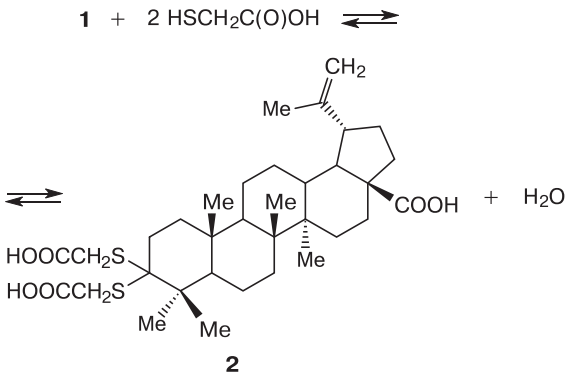


1

In the present work, in order to further obtain zinc-chelating β-lactamase inhibitors, we synthesized a new derivative of betulonic acid (**1**), namely, the corresponding dithioketal **2** containing two fragments of thioglycolic acid (Scheme 1). According to the literature,[11] *S*-derivatives of mercaptoacetates and their hydrolyzate (thioglycolic acid) co-inhibit metallo-β-lactamase L1, which can be used to regulate the efficiency of β-lactam antibiotics.

Betulonic acid **1** was obtained by the oxidation of betulin with potassium dichromate in an acidic medium according to the procedure described earlier.[12] The progress of the formation of dithioketal **2** was monitored by circular dichroism (CD) method. The CD spectrum of betulonic acid (Fig. 1) exhibits a small negative maximum of the Cotton effect (CE) at 320 nm and a significant positive maximum of CE in the region of shorter wavelengths (λ_{max} = 298 nm) corresponding to the n—π*-electronic transition in the keto group; therefore, the course of the reaction is easily monitored by decreasing intensity of the large peak. Similar CD pattern is characteristic of some other 3-keto terpenes having saturated six-membered rings, as well as two *gem*-methyl groups at position C(4) of ring A, which is in a distorted *chair* conformation, for example, lup-20(29)-en-3-one.[13]

Scheme 1



2

Conditions: $CHCl_3$, 20 °C, 48 h, then reflux with a Dean—Stark trap.

Dithioketal **2** was obtained by a modified procedure,[14] excluding the use of standard acid catalysts. The process of thioketalization of betulonic acid, like other related reactions, is an equilibrium one (see Scheme 1). A high,

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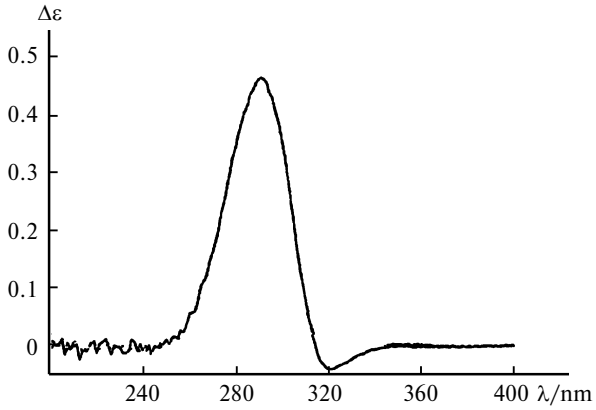

Fig. 1. CD spectrum of betulonic acid in methanol (C = 0.008 mol L^{-1}.

practically quantitative, yield of the target product **2** was achieved completely removing the formed water using a Dean—Stark trap.

The composition and structure of betulonic acid *S*,*S′*-bis(carboxymethyl) dithioketal **2** were established based on elemental analysis results, IR and ^{1}H NMR spectroscopy data.

Experimental

^{1}H NMR spectrum was recorded on a Bruker Avance 400 spectrometer (400.13 MHz, ^{1}H). CD spectra were obtained on an SKD-2 automatic recording dichrograph (a joint development of the V. A. Engelgardt Institute of Molecular Biology of the RAS and the Institute of Spectroscopy of the RAS). The extreme intensities of the Cotton effect (CE) in the CD spectra were calibrated using an aqueous solution of camphor-10-sulfonic acid based on the value of Δε (L mol^{-1} cm^{-1}) at 291 nm. The measurements were carried out in a MeOH or CH_2Cl_2 solution in a 1 cm thick quartz cell with a spectral resolution of 3 nm, 2.4 nm accumulation, and a scanning speed of 35 nm min^{-1}. The range of spectrum measurements was from 200 to 400 nm. Figure 1 shows the measurement results described by the value of molecular dichroism Δε/L mol^{-1} cm^{-1}. Betulonic acid **1** was obtained as described[12] in 96% yield, white crystals, m.p. 248—250 °C. IR (KBr), ν/cm^{-1}: 1706 (C=O), 1646 (C=C), 884 (=CH_2). CD (MeOH), λ_{max}/nm (Δε): +298 (0.45), −320 (0.05). Thioglycolic acid used was of reagent grade.

3,3-Bis[(carboxymethyl)thio]lup-20(29)-en-28-oic acid (2). Thioglycolic acid (1.02 g, 10.90 mmol) was added to a solution of betulonic acid **1** (2.48 g, 5.45 mmol) in anhydrous chloroform (10 mL) with stirring. The homogeneous reaction solution was allowed to stand at 20 °C for 48 h, after which chloroform was distilled off using a Dean—Stark trap to remove water formed during the reaction. The residue was concentrated to dryness *in vacuo* at 50 °C. The reaction progress was monitored measuring CD spectra of the reaction mixture. The completion of the process was marked by the disappearance of a positive CE maximum at 298 nm in the CD spectrum. The resulting dense oil was dissolved in CH_2Cl_2 (5 mL), and the solution was poured into *n*-hexane (50 mL) with stirring. The solid precipitate formed was separated and dried to constant weight in a vacuum desiccator over P_2O_5. The yield of betulonic acid dithioketal **2** was 3.05 g (95%), cream fine crystals with m.p. 98—99 °C. IR (KBr), ν/cm^{-1}: 3412 br (OH in COOH), 2951 (CH_3), 1734 and 1706 (C=O in COOH), 1380, 1280, 1194 and 1161 (C—O), 580 br (C—S). CD (dioxane), λ_{max}/nm: –215, –286, –344. ^{1}H NMR (DMSO-d_6), δ: 0.90 (s, 3 H, C(24)H_3); 0.95 (s, 3 H, C(23)H_3); 0.98 (s, 3 H, C(27)H_3); 1.00 (s, 3 H, C(25)H_3); 1.02 (s, 3 H, C(26)H_3); 1.60 (s, 3 H, C(30)H_3); 3.54, 3.56 (both s, 2 H each, CH_2S); 4.56, 4.68 (both m, 2 H each, C(29)H_2). Found (%): C, 65.50; H, 8.47; S, 10.40. $C_{34}H_{52}O_6S_2$. Calculated (%): C, 65.77; H, 8.44; S, 10.33.

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