

Betulin, betulonic acid, 3-aminobetulinic acid. Improved extraction and preparative syntheses of derivatives

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We optimized the process of extraction and purification of betulin from birch bark and modified preparative syntheses of the simplest derivatives of betulin, namely, betulonic acid, betulonic aldehyde, and 3-aminobetulinic acid, as a platform for subsequent modifications.

Key words: triterpenes, betulin, betulonic acid, betulonic aldehyde, 3-aminobetulinic acid, extraction, synthesis.

Plant pentacyclic triterpenoids have a variety of biological activities: antitumor, antimicrobial, anti-inflammatory, antiviral, hepatoprotective, *etc.*^{1–5} These compounds are widely distributed in nature, in particular, they are found in the bark of white birch. Among triterpenoids, betulin (**1**), its derivatives, such as betulonic (**2**) and betulonic acids, betulonic aldehyde (**3**), as well as their modified analogs and so-called hybrid compounds, attract close attention.^{6–34} Relatively recently, after spread of SARS in 2003–2005, triterpenoids has been found to possess anti-coronavirus activity,⁶ which makes them very promising platforms for drug development, especially in connection with SARS-CoV-2 infection (see, for example, the review¹⁷).

We proposed an improved method for the isolation of betulin from natural raw materials and its purification, as well as modified methods for the synthesis of its simplest key derivatives, betulonic acid, betulonic anhydride, and 3-aminobetulinic acid (Scheme 1). The main attention was paid to the improvement of synthetic approaches so that they become more efficient and feasible for implementation in the scientific laboratory.

Results and Discussion

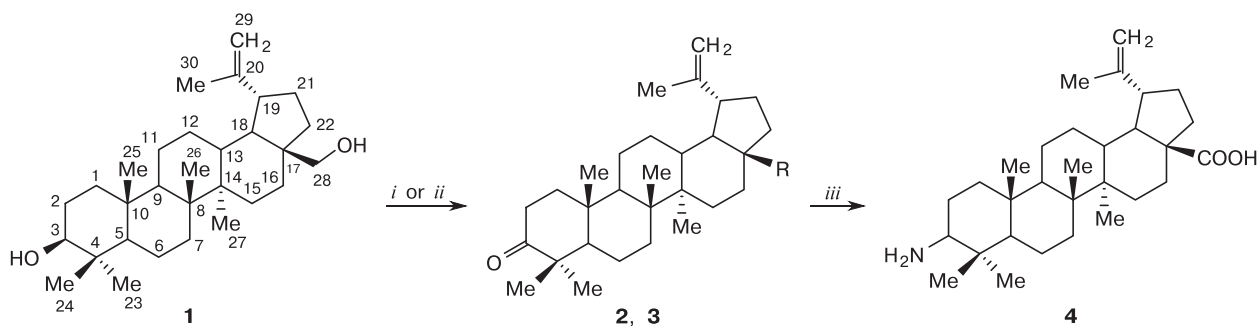
Betulin (3 β ,28-dihydroxy-20(29)-lupene, **1**) (see Scheme 1) is a pentacyclic triterpene alcohol with a lupane skeleton. Betulin **1** is contained mainly in the outer part of the birch bark (up to 30–40%), giving it a characteristic white color and protecting the wood from the penetration of various microorganisms and insects, as well as reflecting sunlight. The main method

for isolation of betulin is extraction from natural raw materials.^{19,20} To intensify the process, it was proposed to use extraction under microwave irradiation,²¹ thin-film vapor-phase extraction,²² as well as steam treatment of the feedstock under conditions of "explosive autohydrolysis".²³ An essential problem of the known methods is the contamination by compounds of the lupane series (lupeol, betulonic and betulonic acids).

In the present work, we propose an improved method for isolation and purification of betulin **1** from ground and preliminarily dried birch bark. For the isolation of betulin **1**, we used the extraction of plant raw materials with boiling aqueous propan-2-ol for 3 h. The degree of birch bark grinding significantly affects the yield of betulin isolated by extraction,⁹ therefore, the birch bark was ground to a particle size of 3×3 mm².

The first stage of the proposed method for purification of betulin **1** was the treatment of the extract with 20% aqueous NaOH, which allowed us to remove impurities of betulonic and betulonic acids as their soluble Na salts. Betulin **1** itself does not react with alkalis. Next, resinous, slightly colored impurities were removed using silica gel chromatography. At the last stage, the impurities of lupeol and other compounds soluble in hexane were removed by extraction with boiling hexane. Such a purification gave chemically pure betulin **1**. The ¹H NMR spectrum of betulin **1** exhibits singlets for six methyl groups and multiplets for cycloalkyl CH and CH₂ groups in the region of δ 0.7–2.0. The signals for other protons are found in the region of δ 2.0–4.7 and fully correspond to the structure of betulin **1**.

Scheme 1



R = C(O)OH (**2**), CHO (**3**)

Reagents and conditions: *i* (for **2**). acetone, $K_2Cr_2O_7$, H_2SO_4 (conc.), Al_2O_3 , 0 °C, 2 h; *ii* (for **3**). CH_2Cl_2 , PCC, 25 °C, 2 h; *iii*. 1) **2**, methanol, NH_3 —methanol, $AcONH_4$, 25 °C, 3 h, 2) $NaBH_4$, 0 °C, 3) 2 h, 25 °C.

The proposed method for the isolation of betulin **1** does not require its purification by recrystallization from alcohols and the use of highly toxic benzene, instead of which we used hexane. The proposed method is convenient for scaling and application under laboratory conditions.

Betulin **1** was oxidized to betulonic acid **2** with a mixture of potassium bichromate and sulfuric acid supported on alumina in acetone at 0 °C for 2 h (see Scheme 1) according to a modified known procedure.¹¹ The use of Al_2O_3 as a substrate allowed us to selectively oxidize betulin **1** to betulonic acid **2**. In contrast to the procedure described in the work,¹¹ we did not use ultrasonic dispersion of betulin in acetone and changed the order of mixing the components. The 1H and ^{13}C NMR spectra, as well as the IR spectrum of betulonic acid **2** confirm its structure. The oxidation of the primary hydroxy group at atom C(28) of betulin **1** to the carboxy group is evidenced by the absence of signals for the $C(28)H_2$ protons at δ 3.36 and 3.80 in the 1H NMR spectrum of acid **2**, which are observed in the 1H NMR spectrum of betulin **1**. The ^{13}C NMR spectrum of compound **2** exhibits two downfield signals at δ 218.35 (C(3)) and 182.61 (C(28)), confirming the oxidation of secondary and primary hydroxy groups. In addition, the presence in the IR spectrum of compound **2** of a strong absorption band in the region of 1705 cm^{-1} related to the stretching vibrations of carbonyl groups and the absence of a broad absorption band of stretching vibrations of hydroxy groups in the region of 3390 cm^{-1} , which is present in the IR spectrum of betulin **1**, also confirm the formation of betulonic acid **2**.

For the oxidation of the hydroxy groups of betulin **1** at atoms C(28) and C(3) to the aldehyde and carbonyl groups, respectively, we used a selective oxidizing agent, pyridinium chlorochromate (PCC). The reaction was

carried out according to a modified known procedure¹² in anhydrous dichloromethane at room temperature for 2 h (see Scheme 1). To increase the conversion of betulin, we used an excess of PCC, which made it possible to increase the yield of betulonic aldehyde **3** to 93% and eliminate purification of the product by recrystallization from hexane. The appearance in the 1H NMR spectrum of aldehyde **3** of the singlet at δ 9.69 reliably confirms the presence of an aldehyde group. In the ^{13}C NMR spectrum of aldehyde **3**, the signal for the C(28) atom is observed in a lower field (δ 206.53) than the corresponding signal for acid **2** (δ 182.61). Very strong absorption corresponding to the stretching vibrations of the C=O bond in the IR spectrum of aldehyde **3**, like in the case of betulonic acid **2**, is observed at 1705 cm^{-1} . It should be noted that in the 1H NMR spectra of betulin **1**, betulonic acid **2**, and betulonic aldehyde **3**, the $C(29)H_2$ methylene protons of the isopropenyl group resonate as two singlets at δ 4.60–4.65 and 4.70–4.78. In addition, the presence of the signals for atoms C(29) (δ ~109) and C(20) (δ ~150) in the ^{13}C NMR spectra of compounds **1**, **2**, and **3** also indicates that the transformations we carried out do not affect the double bond.

3-Aminobetulinic acid **4** was obtained from betulonic acid **2** by treatment with a solution of ammonia in methanol in the presence of ammonium acetate, followed by reduction with sodium borohydride (see Scheme 1). To remove the unreacted betulonic acid **2** as its soluble sodium salt, the crude product was treated with 1 M NaOH. Note that 3-aminobetulinic acid **4** does not form Na salt under these conditions. This method makes it possible to obtain 3-aminobetulinic acid from commercially available reagents in good yield. In this version of the synthesis, the reaction proceeds *via* an intermediate formation of a Schiff base, while

the literature sources^{28,34} show obtaining of compound **4** *via* an intermediate oxime.

The ¹H NMR spectrum of compound **4** exhibits a signal for the C(3)H proton at δ 3.13, which is absent in the spectrum of the starting betulonic acid **2**. In addition, two singlets for the protons of the C(29)H₂ group are present at δ 4.55 and 4.68 in the ¹H NMR spectrum of aminobetulonic acid **4**, like in the spectrum of the starting betulonic acid **2**. The signal for carbon atom C(3), which in the ¹³C NMR spectrum of betulonic acid **2** is observed at δ 218.35, in the case of 3-aminobetulonic acid **4** is significantly shifted to the upfield region to δ 77.90, confirming the formation of the C—N bond. At the same time, the chemical shifts for carbon atom C(28) of betulonic acid **2** (δ 182.61) and 3-aminobetulonic acid **4** (δ 181.90) are very close, which confirms the presence of the carboxy group.

In conclusion, in the present work we proposed an improved method for the isolation and purification of betulin from birch bark, which does not require the use of special equipment and can be implemented under laboratory conditions. Betulin was converted to betulonic acid, betulonic aldehyde, and 3-aminobetulonic acid in good yields, which were characterized by spectral methods.

In the future, we plan to synthesize hybrid betulin-ferrocene structures and study their pharmacological activity.

Experimental

¹H and ¹³C NMR spectra were recorded on a Bruker Avance 400 instrument (400.13 and 100.925 MHz, respectively). Chemical shifts are given relative to the residual signals of protons and carbon atoms of the solvent. IR spectra were recorded on a Bruker TEM37 IR Fourier-transform spectrophotometer. Specific rotation was determined on a P3000 polarimeter (A.KRÜSS Optronic). Melting points were measured on a Stuart SMP30 apparatus. Solvent were purified using standard procedures. Reaction progress was monitored by TLC. Dichloromethane, methanol, diethyl ether, hexane, and propan-2-ol (Acros Organics) were dehydrated before use. Ammonia was used as a 7 N solution in methanol (Acros Organics). The birch bark was collected in the Bitsevsky forest park in Moscow.

Lup-20(29)-ene-3 β ,28-diol (betulin, 1). A mixture of air-dried and ground birch bark (50 g, particle size 3×3 mm²) and an azeotropic mixture of propan-2-ol—water (9 : 1, 300 mL) was refluxed for 3 h with stirring and filtered, the filtrate was kept for 24 h in a freezer (−18 °C). The white flocculent precipitate was collected by filtration and washed with propan-2-ol. Then, it was dissolved in chloroform, washed with 20% aqueous NaOH and brine. The resulting solution was passed through a short layer of silica gel, eluting

with a 9 : 1 mixture of chloroform—methanol. The solvent was vacuum evaporated to dryness on a rotary evaporator, the residue was diluted with hexane and refluxed for 1 h, the precipitate was collected by filtration to obtain compound **1** (5.6 g, 37% based on the 30% content of betulin in birch bark), a white crystalline substance. M.p. 251 °C (*cf.* Ref. 8: m.p. 250—252 °C). ¹H NMR (CDCl₃), δ : 0.78 (s, 3 H, C(24)H₃); 0.84 (s, 3 H, C(27)H₃); 0.99 (s, 3 H, C(25)H₃); 1.00 (s, 3 H, C(23)H₃); 1.04 (s, 3 H, C(24)H₃); 1.07—1.95 (m, 24 H, CH₂, CH), 1.70 (s, 3 H, C(30)H₃); 2.41 (m, 1 H, C(19)H); 3.21 (m, 1 H, H(3)); 3.36 (d, 1 H, H(28)); 3.80 (d, 1 H, H(28)); 4.60 (s, 1 H, H(29)); 4.70 (s, 1 H, H(29)). ¹³C NMR (CDCl₃), δ : 150.51 (C(20)), 109.41 (C(29)), 78.62 (C(3)), 59.67 (C(28)), 55.2 (C(5)), 50.27 (C(9)), 47.67 (C(19)), 47.56 (C(17)), 42.55 (C(14)), 40.76 (C(18)), 38.69 (C(4)), 38.64 (C(1)), 37.16 (C(10)), 36.98 (C(13)), 34.09 (C(7)), 33.81 (C(22)), 29.58 (C(21)), 29.02 (C(16)), 27.74 (C(23)), 26.82 (C(2)), 25.09 (C(15)), 20.7 (C(11)), 18.09 (C(30)), 18.17 (C(16)), 15.92 (C(25)), 15.75 (C(26)), 15.22 (C(24)), 14.57 (C(27)). IR (KBr), ν /cm^{−1}: 3390 (O—H), 3082—2869 (CH, CH₂, CH₃), 1644 (C=C).

Lup-20(29)-en-3-oxo-28-oic acid (betulonic acid, 2). A mixture of K₂Cr₂O₇ (3 g, 10 mmol), H₂SO₄ (5 mL), and water (7 mL) was added to a solution of betulin **1** (1.50 g, 3.38 mmol) and Al₂O₃ (9.2 g) in acetone (150 mL). The mixture was stirred for 2 h at 0 °C, the alumina was filtered off. Water (1 L) was added to the filtrate, and the resulting white flocculent precipitate was collected by filtration and dried. Then, the precipitate was dissolved in benzene and the undissolved, unreacted betulin **1** was filtered off. A 10% aqueous NaOH (30 mL) was added to the filtrate, the resulting precipitate of the sodium salt was collected by filtration and dried. After its dissolution in methanol, a 15% aqueous HCl was added dropwise to the resulting solution until pH 1 was reached. The precipitate formed was collected by filtration, washed with water, and dried to obtain acid **2** (1.22 g, 81%), white crystals, m.p. 247 °C (*cf.* Ref. 26: m.p.: 245—248 °C). ¹H NMR (CDCl₃), δ : 0.94 (s, 3 H, C(26)H₃); 0.99 (s, 3 H, C(27)H₃); 1.01 (s, 3 H, C(25)H₃); 1.03 (s, 3 H, C(23)H₃); 1.09 (s, 3 H, C(24)H₃); 1.20—2.56 (m, 24 H, CH₂, CH); 1.71 (s, 3 H, H(30)); 3.03 (m, 1 H, H(19)); 4.63 (s, 1 H, H(29)); 4.76 (s, 1 H, H(29)). ¹³C NMR (CDCl₃), δ : 218.35 (C(3)), 182.61 (C(28)), 150.32 (C(20)), 109.78 (C(29)), 56.4, 54.90, 49.83, 49.17, 47.34, 46.90, 42.48, 40.62, 39.60, 38.51, 37.05, 36.91, 34.12, 33.58, 32.10, 30.55, 29.68, 26.64, 25.47, 21.37, 21.00, 19.62, 19.37, 15.96, 15.81, 14.62. IR (KBr), ν /cm^{−1}: 3073—2870 (CH, CH₂, CH₃), 1705 (C=O), 1643 (C=C).

Lup-20(29)-en-3-on-28-al¹² (betulonic aldehyde, 3). A mixture of betulin **1** (0.40 g, 0.9 mmol), dichloromethane (7 mL), and pyridinium chlorochromate (0.645 g, 3.0 mmol) was stirred for 2 h at room temperature, followed by the addition of diethyl ether (7 mL). The product was isolated by column chromatography on alumina, eluent diethyl ether. The yield was 0.37 g (93%), a white crystalline compound. M.p. 160 °C (*cf.* Ref. 12: m.p. 160—162 °C). ¹H NMR (CDCl₃), δ : 0.94 (s, 3 H, CH₃); 0.97 (s, 3 H, CH₃); 1.00 (s, 3 H, CH₃); 1.03 (s, 3 H, CH₃); 1.08 (s, 3 H, CH₃); 1.21—2.49 (m, 24 H, CH₂, CH); 1.71 (s, 3 H, C(30)H₃); 2.89 (t, 1 H,

C(19)H); 4.65 (s, 1 H, C(29)H₂); 4.78 (s, 1 H, C(29)H₂); 9.69 (s, 1 H, C(28)HO). ¹³C NMR (CDCl₃), δ: 218.12 (C(3)), 206.53 (C(28)), 149.61 (C(20)), 110.22 (C(29)), 59.30 (C(17)), 54.89 (C(5)), 49.79 (C(9)), 47.92 (C(18)), 47.46 (C(19)), 47.31 (C(4)), 42.58 (C(14)), 40.74 (C(8)), 39.61 (C(1)), 38.73 (C(13)), 36.86 (C(10)), 34.10 (C(2)), 33.59 (C(7)), 33.14 (C(16)), 29.82 (C(15)), 29.11 (C(21)), 28.78 (C(22)), 26.60 (C(23)), 25.50 (C(12)), 21.26 (C(11)), 21.02 (C(24)), 19.59 (C(6)), 19.00 (C(30)), 15.97 (C(26)), 15.71 (C(25)), 14.18 (C(27)). IR (KBr), ν/cm⁻¹: 3075–2867 (CH, CH₂, CH₃); 1705 (C=O), 1642 (C=C), 894 (=C–H).

3-Aminolup-20(29)-en-28-oic acid (3-amino-3-deoxy-betulonic acid, 4). A 7 N ammonia in methanol (1.0 mL) was added to a solution of betulonic acid **2** (500 mg, 1.1 mmol) and AcONH₄ (20 mg) in methanol (20 mL) cooled to 0 °C. The mixture was stirred for 8 h at room temperature and cooled to ~0 °C (ice–water), followed by the addition of NaBH₄ (166 mg, 4.4 mmol) and stirring for another 6 h. The solvent was evaporated, dichloromethane (20 mL) was added. The resulting solution was washed with aqueous NaHCO₃, then 1 M solution of NaOH was added to the aqueous phase until pH 11 was reached. The precipitate was collected by filtration, washed with water, and dried to obtain a white crystalline compound (0.39 g, 79%). M.p. 275–277 °C (cf. Ref. 28: m.p. 271–274 °C). [α]_D²² +14.44 (c 0.6, THF). ¹H NMR (pyridine-d₅), δ: 0.51 (s, 3 H, C(26)H₃); 0.69 (s, 3 H, C(27)H₃); 0.74 (s, 3 H, C(25)H₃); 0.75 (s, 3 H, C(23)H₃); 0.89 (s, 3 H, C(24)H₃); 0.98–1.71 (22 H, CH, CH₂); 1.47 (s, 3 H, C(30)H₃); 1.97 (m, 3 H); 2.40 (m, 1 H, C(9)H); 2.62 (m, 1 H, C(18)H); 3.13 (m, 1 H, C(3)H); 3.34 (m, 1 H, C(19)H); 4.55 (s, 1 H, C(29)H); 4.68 (s, 1 H, C(29)H). ¹³C NMR (pyridine-d₅), δ: 181.90, 152.11, 109.21, 77.90, 57.11, 55.73, 50.85, 49.84, 47.72, 42.70, 40.90, 39.31, 39.09, 38.24, 38.19, 37.32, 34.68, 33.68, 31.41, 30.28, 28.47, 28.08, 26.06, 21.10, 19.39, 18.63, 16.47, 16.29, 16.18, 14.72. IR (KBr), ν/cm⁻¹: 3381 (N–H), 3072–2867 (CH, CH₂, CH₃); 1641 (C=C), 1546 (C=O), 1452 (N–H), 1389, 1375, 882 (=C–H).

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