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SYNTHESIS OF THE *Rhodiola rosea* GLYCOSIDE ROSAVIN

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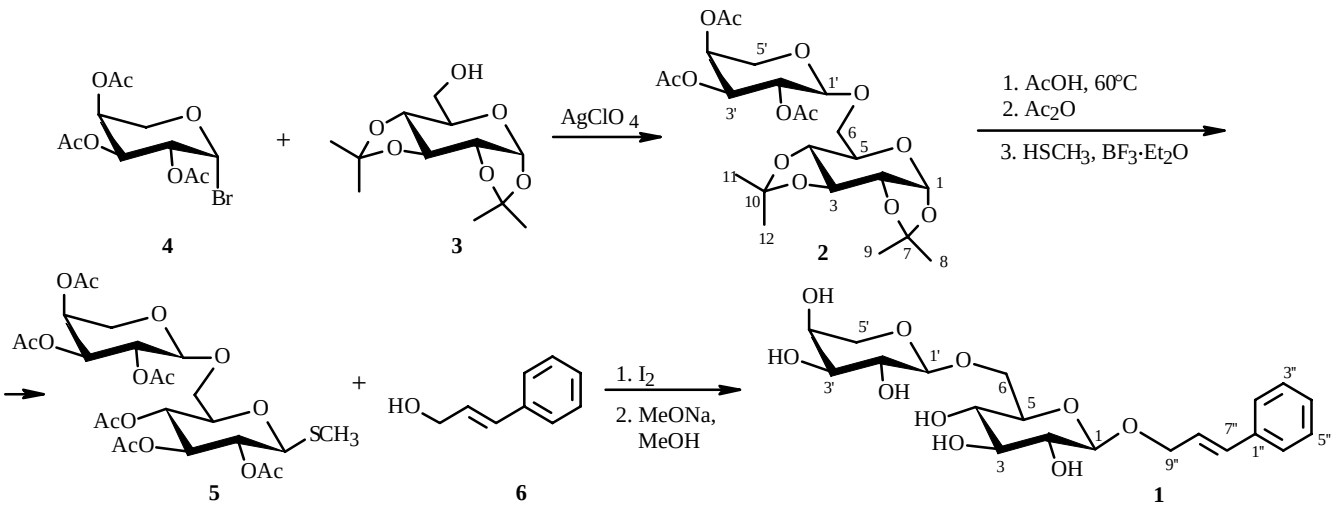
A synthetic scheme was proposed for the glycoside rosavin that includes a one-step glycosylation of cinnamyl alcohol with a disaccharide. The structure of the product was confirmed by PMR and ^{13}C NMR spectroscopy.

Key words: *Rhodiola rosea*, rosavin, glycoside synthesis.

The principal biologically active compounds in the extract of *Rhodiola rosea* are glycosides of *trans*-cinnamyl alcohol (rosin, rosavin, rosarin, and salidroside) [1-4].

We proposed a synthetic scheme for rosavin (**1**) because the glycoside is difficult to isolate from the plant material. The scheme included preparation of the disaccharide 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl-(1→6′)-(1′,2′,3′,4′-diisopropylidene-D-glucopyranose) (**2**) and its subsequent addition to the aglycon [5].

Disaccharide **2** was prepared by first synthesizing 1,2,3,4-diisopropylidene-D-glucopyranose (**3**) with a free hydroxyl on C_6. Glycosylation of **3** with 2,3,4-tri-*O*-acetyl-β-L-arabinopryanosylbromide (**4**) in the presence of a mixture of silver perchlorate and calcium carbonate ($AgClO_4$, $CaCO_3$) produced **2**. The IR spectrum of **2** contained bands characteristic of ν C–O–C at 1670 cm^{-1} and δ C–O–C (α-L-glycoside bond) at 824. The ^{13}C NMR spectrum exhibited signals for C_7 and C_{10} of the isopropylidene groups at 110.3 and 111.7 ppm, respectively; for methyls $C_{8,9}$ and $C_{11,12}$ at 26-28 ppm; for the α-L-glycoside bond between C_6 of glucose and $C_{1'}$ of arabinose at 102.3 ppm; and for C_1 of glucose at 92.7 ppm. Signals for C atoms of arabinose and glucose were found at 62.4-72.2 ppm; of acetates, at 169.7-170.8 ppm (O=C–O) and 20.5-20.7 ppm (OCH_3).



The glycosylating agent was isolated from **2** by removing the protecting isopropylidene groups by heating to 50°C in dilute acetic acid. This approach did not affect the acetates and did not decompose the disacccharide at the glycoside bond.

The resulting 2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl-(1→6)-(β-D-glucopyranose) was acylated with acetic anhydride in the presence of a catalytic amount of $HClO_4$ and then dissolved in a small amount of $CHCl_3$ with added methylmercaptan and boron trifluoride etherate ($BF_3 \cdot Et_2O$) to produce glycosylating agent **5**.

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Mercaptan derivative **5** was purified and added to cinnamyl alcohol (**6**). The synthesis was performed in anhydrous CH_2Cl_2 using a solution of I_2 in CH_3CN as a catalyst. Acylated rosavin was hydrolyzed using the Zemplen reaction.

The product was purified in a concentrating cartridge filled with reversed-phase sorbent (Diasorb 130-C16T) to remove residual cinnamyl alcohol and carbohydrates. The effluent from the cartridge contained chromatographically pure (HPLC monitoring) rosavin. The structure of the synthetic rosavin was confirmed by NMR spectroscopy.

The ^{13}C NMR and PMR spectra of rosavin exhibited chemical shifts that were consistent with the formation of a β-D-glycoside bond between glucose and the aglycon (102.3, dd, and 4.5 ppm) and an α-L-glycoside bond between arabinose and glucose (103.5 and 4.5 ppm, dd).

The angle of rotation $[\alpha]_D^{20}$ -56.3° ($CHCl_3$:MeOH) of the synthesized rosavin also confirmed that it had been prepared {lit. $[\alpha]_D^{20}$ -56.5° ($CHCl_3$:MeOH) [6]}.

EXPERIMENTAL

Materials and Methods. PMR and ^{13}C NMR spectra were recorded on a Bruker DRX 400 spectrometer at working frequency 400 and 100 MHz, respectively, in DMSO-d_6 with TMS.

HPLC was performed on a Millichrom-2 chromatograph with a 2/60-mm column packed with Silasorb C18 and elution by CH_3OH:C_4H_9OH:H_2O (35:1:14) with UV detection at 252 nm and flow rate 50 μL/min; TLC, on Silufol plates (Czech Rep.) using toluene:ethylacetate (6:1 and 4:1). The developer was phosphotungstic acid (20%) in ethanol with heating to 120°C for 1 min. Column chromatography was carried out over silica gel L (100/160 μm) using toluene:ethylacetate (10:1-4:1) as eluent.

Diisopropylideneglucose (**6**) was prepared by the literature method [7]; 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosylbromide (**5**), by the literature method [7], silver carbonate, by reacting silver nitrate with saturated Na_2CO_3 solution in the dark and drying the resulting yellow powder with anhydrous acetone and then in vacuo. Boron trifluoride etherate ($BF_3 \cdot OEt_2$) was vacuum distilled. Crystalline iodine was purified by sublimation. Acetic anhydride (chemically pure, Russia), silver perchlorate (Sigma, USA) and methylmercaptan (Sigma, USA) were purchased commercially.

2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl-(1→6′)-(1′,2′,3′,4′-diisopropylidene-D-glucopyranose) (2). A solution of 1,2,3,4-diisopropylidene-α-D-glucopyranose (100 mg, 0.42 mmol) in anhydrous acetone (25 mL) was stirred, treated with an equimolar amount of glycosylating agent 2,3,4-tri-*O*-acetyl-β-L-arabinopyranosylbromide (172.6 mg, 0.42 mmol) and a two-fold excess of silver prechlorate (176 mg, 0.84 mmol) with $CaCO_3$ (84 mg, 0.84 mmol), irradiated for 15 min in an ultrasonic bath, and stirred for 1 d at room temperature. After the reaction was finished, the mixture was filtered. The solvent was evaporated. The solid was chromatographed over a silica-gel column using toluene:ethylacetate (9:1-4:1). Yield of **2**, 44.5 mg (18%). The IR and NMR spectra are described in the text.

2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl-(1→6′)-(2′,3′,4′-tri-*O*-acetyl-β-methyl-1′-thio-D-glucopyranoside) (5). 2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl-(1→6′)-(1′,2′,3′,4′-tetra-*O*-acetyl-β-D-glucopyranoside) (1 g, 1.6 mmol) was dissolved in $CHCl_3$ (10 mL) and treated with methylmercaptan (92 mg, 1.9 mmol) and then boron trifluoride etherate (542 mg, 8 mmol). The mixture was stirred for 6 h, washed with saturated Na_2CO_3 solution and water, and dried over anhydrous Na_2SO_4 to afford **5** in 64% yield.

Total Acetate of Rosavin. 2,3,4-Tri-*O*-acetyl-α-L-arabinopyranosyl-(1-6′)-(2′,3′,4′-tri-*O*-acetyl-β-methyl-1′-thio-D-glucopyranoside) was dissolved in dry CH_3CN (5 mL), stirred, and treated with cinnamic alcohol (33.5 mg, 0.25 mmol) and iodine (64.5 mg, 0.25 mmol). The mixture was stirred and cooled with ice for 1 h and then stirred at room temperature for 7 h. After the reaction was finished the reaction mixture was dissolved in $CHCl_3$ (20 mL) and washed with water (3 × 100 mL) and saturated $Na_2S_2O_3$ solution (50 mL) and again with water (100 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated. The resulting product was separated over a column of silica gel using toluene:ethylacetate (9:1-4:1), yield 34.8 mg (30% of theoretical).

Rosavin (1). A solution of protected glycoside (186 mg, 0.4 mmol) in anhydrous methanol (25 mL) was treated with clean Na (10 mg, 0.4 mmol) dissolved in methanol (25 mL), stirred at room temperature for 5 h, and neutralized by adding cation-exchanger KU-2 (1 g) in the H-form [8]. Yield of **1**, 113 mg (95%).

^{13}C NMR spectrum (ppm): 136.7, 126.3, 127.4, 128.5, 131.5, 127.5, 70.5, 102.3, 103.5, 64.8-74.5.

PMR spectrum (ppm, J/Hz): 7.45 d, 7.34 t, 6.35 m, 3.17 d, 6 (d, J = 16), 7.25 t, 4.3 (dd, J = 7), 3.3 (t, C-2′), 3.15 (t, C-3′), 3.05 (t, C-4′), 3.37 (q, C-5′), 3.05 (t, C-6′), 3.35 (t, C-2″), 3.15 (t, C-3″), 3.95 (dd, C-4″), 3.35 (m, C-5″).

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