Chemistry of Natural Compounds, Vol. 45, No. 2, 2009

GLYCOSYLATION OF SHIKONIN BY THE HELFERICH METHOD

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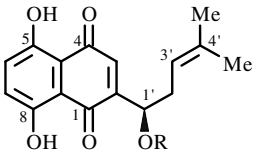
UDC 547.655.6

Shikonin (**1**) is a natural pigment that has been isolated from plants of the family *Boraginaceae* [1] and is produced biosynthetically [2]. In nanomolar concentrations *in vitro*, it suppresses replication of drug-resistant HIV-1 [3].



1 - 4

1: R = H; **2:** R = α-D-Glc(Ac)$_4$
3: R = β-D-Glc(Ac)$_4$; **4:** R = β-D-Glc

New lipid- and water-soluble derivatives were prepared by glucosylation of natural **1** by the Helferich method.

A mixture of **1** (288 mg, 1.0 mmol), $Hg(CN)_2$ (252 mg, 1.0 mmol), and molecular sieves 4A (1.0 g) in anhydrous nitromethane (20 mL) was refluxed for 1.5 h, treated with α-acetobromoglucose (820 mg, 2.0 mmol), and cooled. The precipitate was filtered off. The filtrate was evaporated. The solid was chromatographed over SiO_2 (40-63 μ) using hexane:acetone (10:1→2:1) to isolate **2** (78 mg, 12%) and **3** (346 mg, 56%). Saponification of **3** (MeONa/MeOH) under an Ar atmosphere followed by chromatography under the same conditions gave **4** (75%).

2-[1′(*R*)-(Tetra-*O*-acetyl-α-D-glucopyranosyloxy)-4′-methylpent-3′-en-1′-yl)]-5,8-dihydroxy-1,4-naphthoquinone (2). mp 97-99°C (hexane:acetone). PMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.72 and 1.74 (2 × Me), 2.04, 2.06, 2.12, and 2.21 (4 × OAc), 2.42 (2H, m, 2H-2′), 4.08 (1H, dd, $J_{5″,6″}$ = 3.7, $J_{6″,6″}$ = 13.7, H-6″), 4.28 (2H, m, 1H-5″, 1H-6″), 4.84 (1H, d, $J_{1″,2″}$ = 3.7, H-1″), 4.92 (1H, dd, $J_{2″,3″}$ = 10.3, H-2″), 5.04 (1H, m, H-3′), 5.09 (1H, dd, $J_{3″,4″}$ = 9.6, $J_{4″,5″}$ = 9.6, H-4″), 5.29 (1H, m, H-1′), 5.56 (1H, dd, H-3″), 7.16 (2H, s, arom.), 7.25 (1H, s, arom.), 12.41 and 12.57 (2 × 1H, s, C_5-OH or C_8-OH). IR spectrum ($CHCl_3$, ν, cm^{-1}): 1752 (CH_3COO), 1610 (C=O), 1570, 1455, 1433, 1345, 1247, 1038.

2-[1′(*R*)-(Tetra-*O*-acetyl-β-D-glucopyranosyloxy)-4′-methylpent-3′-en-1′-yl)]-5,8-dihydryxo-1,4-naphthoquinone (3). mp 140-141°C (hexane:acetone). PMR spectrum (250 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.56 and 1.59 (2 × Me), 1.92, 2.01, 2.02, and 2.08 (4 × OAc), 2.34 (1H, ddd, $J_{1′,2α′}$ = 7.5, $J_{2α′,2β′}$ = 14, $J_{2α′,3′}$ = 4, H-2α′), 2.52 (1H, ddd, $J_{1′,2β′}$ = 4, $J_{2β′,3′}$ = 7.5, H-2β′), 3.61 (1H, ddd, $J_{4″,5″}$ = 9.5, $J_{5″,6α″}$ = 2.5, $J_{5″,6β″}$ = 4.5, H-5″), 3.98 (1H, dd, $J_{6α″,6β″}$ = 12.0, H-6α″), 4.06 (1H, dd, H-6β″), 4.66 (1H, d, $J_{1″,2″}$ = 7.5, H-1″), 4.94 (1H, dd, H-3′), 5.04 (1H, dd, $J_{3″,4″}$ = 9.0, H-4″), 5.06 (1H, dd, $J_{2″,3″}$ = 9.5, H-2″), 5.12 (1H, m, H-1′), 5.21 (1H, t, H-3″), 7.17, 7.20, and 7.22 (3 × 1H, s, arom.), 12.50 and 12.58 (2 × 1H, s, C_5-OH or C_8-OH). IR spectrum ($CHCl_3$, ν, cm^{-1}): 1757 (CH_3COO), 1609 (C=O), 1570, 1455, 1435, 1410, 1367, 1249, 1065, 1040.

2-[1′(*R*)-(β-D-Glucopyranosyloxy)-4′-methylpent-3′-en-1′-yl)]-5,8-dihydroxy-1,4-naphthoquinone (4). mp 193-195°C (hexane:acetone). PMR spectrum (300 MHz, DMSO-d_6, δ, ppm, J/Hz): 1.44 and 1.60 (2 × Me), 2.37 (1H, m, H-2α′), 2.58 (1H, m, H-2β′), 3.06 (3H, m, H-2″, H-3″, H-5″), 3.15 (1H, m, H-4″), 3.35 (1H, m, H-6α″), 3.53 (1H, m, H-6β″), 4.31 (1H, br.t, J = 5.7, $C_{6′}$H-OH), 4.36 (1H, d, $J_{1″,2″}$ = 7.7, H-1″), 4.89 (1H, br.s, C-OH), 4.96 (1H, br.s, C-OH), 5.01 (1H, m, H-3′), 5.12 (1H, br.s, C-OH), 5.23 (1H, m, H-1′), 7.16 (1H, s, arom.), 7.35 (2H, s, arom.), 12.32 and 12.37 (2 × 1H, s, C_5-OH or C_8-OH). IR spectrum (KBr, ν, cm^{-1}): 3418 (OH), 1633 (C=O), 1616 (C=O), 1456, 1384, 1348, 1273, 1200, 1159, 1073, 1033.

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0009-3130/09/4502-0247

Proton resonances for the newly synthesized glucosides were assigned based on two-dimensional COSY H^1—H^1 experiments. Elemental analyses of all compounds agreed with those calculated.

ACKNOWLEDGMENT

The work was supported by a grant of the FEB RAS 09-II-CU-05-001.

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