Novel Stereoselective Reaction of Levoglucosenone with Furfural

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Levoglucosenone reacted with furfural in the presence of an aqueous base to give a product in high yield with high stereoselectivity. The structure, including the stereochemistry of the product, was elucidated by NMR analyses.

Key words: levoglucosenone; furfural; stereoselective reaction; conjugate addition

Levoglucosenone (1), a readily available carbohydrate from the pyrolysis of cellulose, has been attracting attention as a chiral starting material with multifunctional groups. Its unique structure, being highly oxygenated but with no hydroxy groups, provides a great advantage for multi-step synthesis. Levoglucosenone (1) requires none of the protection-deprotection steps of hydroxy groups that are required with other carbohydrates. The enone face is differentiated by 1,6-anhydro-bridge and is useful for stereoselective processes such as conjugate addition, the Diels-Alder reaction, hydroxylation. We have already demonstrated in our laboratory the usefulness of 1 as a chiron for the syntheses of complex natural products such as allo-yohimban, reserpine, tautomycin, and tetrodotoxin. We describe here a novel highly stereoselective reaction between 1 and furfural (2), which was accidentally found during a large-scale preparation of 1.

Levoglucosenone was prepared in our laboratory by reported procedure. Pyrolysis of micro-crystals of cellulose (Avicell® from Asahi Kasei Co.) in the presence of an acid under reduced pressure gave a crude acidic distillate, this then being alkalized and left to stand at rt without extraction. After several weeks, we surprisingly found that levoglucosenone (1) had completely disappeared, and a new compound was apparent by TLC. NMR analyses indicated that the new compound (3) was produced from 1 and furfural (2), another major product of the pyrolysis of cellulose. Compound 3 could be synthesized from pure 1 and 2 in a saturated NaHCO₃ solution in a good yield (Scheme 1). No other isomeric products were isolated. The stereochemistry of the hydroxy group and the geometry of the olefin in 3 were established as shown in Fig. 1 on the basis of NOE data (for the corresponding acetate 4) between the H₆-6 and H-4 protons and between the H-4 and furan protons.

The mechanism for this novel reaction is proposed as shown in Scheme 2. Conjugate addition of a hydroxide ion gave the resulting enolate, which reacted with furfural to give the thermodynamically more stable olefin. The stereospecificity of the C-4 hydroxy group was due to sterio shielding of the endo face of the pyranose ring by the anhydro bridge. The proposed mechanism is similar to that of the Baylis-Hillman reaction, but different in the direction of dehydration.

Reduction of acetate 4 with sodium borohydride exclusively gave 2,6-β-alcohol 5, which was acetylated to afford 6. Similarly, diacetate 6 was synthesized from 3 as shown in Scheme 3. These easily operable reactions could provide an access to some C-branched-hexose derivatives.

![Fig. 1. NOEs Observed in Compound 4.](image)

![Scheme 2. Proposed Mechanism for the Reaction of Levoglucosenone and Furfural.](image)

![Scheme 3. Reagents and Conditions: a) NaBH₄, CeCl₃ (H₂O)₃ /MeOH; b) Ac₂O, Py.](image)
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E-(1R, 2S, 4S, 5S)-3-(2-furfurylmethylene)-4-acetoxy-8-oxabicyclo[3.2.1]octan-2-one (3). A mixture of levoglucosone (500 mg, 3.79 mmol) and furfural (0.66 ml, 7.94 mmol) in a saturated NaHCO₃ solution (5.0 ml) was stirred vigorously overnight at rt. The mixture was acidified by 1 N HCl and extracted with CH₂Cl₂ (3×). The combined organic layer was dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The resulting residue was purified by column chromatography (silica gel (35 g), ether:hexane=4:1) to give 3 (737 mg, 84%) as an oil. [α]D³⁴ = 475 (c 1.0, CHCl₃). IR ν (KBr) cm⁻¹: 3447, 1698, 1601. ¹H-NMR (300 MHz, CDCl₃) δ: 2.80 (1H, d, J = 7 Hz, -OH), 3.77 (1H, dd, J = 8, 1.5 Hz, H-6), 3.98 (1H, dd, J = 7.5, 6 Hz, H-6), 4.88 (1H, dt, J = 6.0, 1.5 Hz, H-5), 4.94 (1H, br d, J = 7 Hz, H-4), 5.35 (1H, s, H-1), 6.59 (1H, dd, J = 3.5, 2 Hz, H-4'), 6.96 (1H, d, J = 3.5 Hz, H-3'), 7.61 (1H, s, olefinic), 7.67 (1H, s, J = 2 Hz, H-5'). ¹³C-NMR (75 MHz, CDCl₃) δ: 64.8, 69.1, 78.1, 100.9, 113.2, 120.2, 126.8, 130.0, 146.9, 150.7, 188.1. EI-MS m/z: 222 (M⁺), 194 (M+CO). Anal. Found: C, 52.46; H, 4.50%. Calcd. for C₁₁H₁₀O₃: C, 52.56; H, 4.53%.

E-(1R, 2S, 4S, 5S)-3-(2-furfurylmethylene)-4-acetoxy-8-oxabicyclo[3.2.1]octan-2-one (4). A mixture of 3 (202 mg, 0.91 mmol) in pyridine (3 ml) and acetic anhydride (3 ml) was stirred overnight at rt. After adding toluene, the mixture was evaporated in vacuo. The residue was purified by column chromatography (silica gel (15 g), ether:hexane=1:1) to give 4 (222 mg, 93%) as an oil. [α]D³⁵ = 305 (c 1.14, CHCl₃). IR ν (KBr) cm⁻¹: 3125, 2972, 2904, 1737, 1704, 1604, 1231, 1120. ¹H-NMR (400 MHz, CDCl₃) δ: 2.09 (3H, s, Ac), 3.86 (1H, dd, J = 8, 1.5 Hz, H-6), 3.98 (1H, dd, J = 8, 6 Hz, H-6), 4.92 (1H, dt, J = 6, 1.5 Hz, H-5), 5.36 (1H, s, H-1), 6.02 (1H, br s, H-4), 6.56 (1H, dd, J = 3.5, 2 Hz, H-4'), 6.86 (1H, d, J = 3.5 Hz, H-3'), 7.58 (1H, d, J = 2 Hz, H-5'), 7.65 (1H, s, olefinic). ¹³C-NMR (75 MHz, CDCl₃) δ: 21.2, 64.9, 70.7, 75.5, 100.9, 113.2, 121.3, 121.7, 130.8, 147.4, 150.7, 171.1, 187.3. EI-MS m/z: 264 (M⁺), 236 (M-CO). Anal. Found: C, 59.06; H, 4.67%. Calcd. for C₁₃H₁₂O₆: C, 59.09; H, 4.58%.

E-(1R, 2S, 4S, 5S)-2-hydroxy-3-(2-furfurylmethylene)-7,8-oxabicyclo[3.2.1]oct-2-yl acetate (5). To a solution of acetate 4 (214 mg, 0.81 mmol) in MeOH (6.5 ml) was added CeCl₃(H₂O)₃ (302 mg, 0.81 mmol), and the mixture was cooled to 0°C. NaBH₄ (30 mg, 0.81 mmol) was then added portionwise. After stirring at 0°C for 15 min, the mixture was quenched with a saturated NH₄Cl solution and extracted with AcOEt (× 3). The combined organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel (10 g), ether:hexane=3:1) to give 5 (180 mg, 84%), mp 160.5-160.7°C. [α]D³⁵ = 292 (c 1.08, CHCl₃). IR ν (KBr) cm⁻¹: 3456, 2964, 2899, 1732, 1240, 1088. ¹H-NMR (400 Hz, CDCl₃) δ: 2.14 (3H, s, Ac), 3.69 (1H, dd, J = 8, 1.5 Hz, H-6), 3.81 (1H, dd, J = 8, 6 Hz, H-6), 4.35 (1H, br s, -OH), 4.78 (1H, dt, J = 6, 1.5 Hz, H-5), 5.43 (1H, d, J = 2 Hz, H-1), 6.06 (1H, d, J = 2 Hz, H-4), 6.35 (1H, d, J = 3.5 Hz, H-3'), 6.40 (1H, dd, J = 3.5, 2 Hz, H-4'), 6.84 (1H, d, J = 2 Hz, olefinic), 7.40 (1H, d, J = 2 Hz, H-5'). ¹³C-NMR (75 MHz, CDCl₃) δ: 21.1, 66.2, 69.7, 71.0, 74.9, 102.5, 111.5, 112.2, 120.5, 130.0, 143.3, 151.1, 170.9. EI-MS m/z: 266 (M⁺). Anal. Found: C, 58.54; H, 5.20; N, 0.02%. Calcd. for C₁₃H₁₄O₅: C, 58.65; H, 5.30; N, 0.00%.

E-(1R, 2S, 4S, 5S)-4-acetoxy-3-(2-furfurylmethylene)-7,8-oxabicyclo[3.2.1]oct-2-yl acetate (6). To a solution of 3 (91 mg, 0.41 mmol) and CeCl₃(H₂O)₃ (152 mg, 0.40 mmol) that had been cooled to 0°C was added NaBH₄ (15 mg, 0.40 mmol). After stirring at 0°C for 30 min, the mixture was quenched with 1 N HCl and extracted with AcOEt (× 3). The combined organic extract was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was dissolved in pyridine (2 ml) and Ac₂O (2 ml). After stirring at rt overnight, the mixture was evaporated in vacuo. Purification of the residue by silica gel chromatography (ether:hexane = 1:2→1:1) gave 6 (101 mg, 80% in 2 steps).
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References
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10) In a preliminary experiment, the reaction of levoglucosenone (1) with benzaldehyde failed under the same conditions as those used with furfural.