2,5-Dimethyl-4-hydroxy-3(2H)-furanone (Furaneol®) from Methyl α-β-Glucopyranoside

François Mazenod*, François Delay, and Ferdinand Naf

Abstract. An efficient synthesis of 2,5-dimethyl-4-hydroxy-3(2H)-furanone (Furaneol®) [1], an important strawberry flavour, starting from the readily available and cheap methyl α-β-glucopyranoside is described.

Introduction

Furaneol (2,5-dimethyl-4-hydroxy-3(2H)-furanone, 1), an important aroma compound, was first identified in 1965 as a constituent of strawberry [2] and pineapple [3].

Later, it was found to occur not only in innumerable other fruits, but also in various cooked, roasted, and fermented foods [4]. As a result of Furaneol's increasing importance as a general food flavour of extremely broad application, several syntheses were elaborated [5], all of which possess minor or major drawbacks. The first synthesis, an Amadori-type rearrangement of L-rhamnose (2) [5a] suffers from the limited availability of the starting material. Apart from rhamnose, other 6-deoxyhexoses such as α-quinovose (3) [6] and L-fucose (4) [7], which again cannot be found easily, have also been transformed efficiently into Furaneol (1).

*Correspondence: Dr. F. Mazenod
Firmenich SA
P.O. Box 239
CH-1211 Geneva 8

In the present publication, we focused on methyl α-β-glucopyranoside (5) as a cheap starting material, which is manufactured on a large scale from β-glucose [8], and developed an efficient access to 1 in four steps via β-quinovose (6-desoxy-β-glucose, 3) as key intermediate.

α-β-Glucose itself has been used by Hardegger and Montavon [9] as starting material for the preparation of β-quinovose-tetraacetate which is readily hydrolysed to β-quinovose (3) [10]. However, the number of steps involved (five), combined with the low overall yield with additional lowering of yield upon scale-up, are severe limitations and preclude industrial application.

On the other hand, the Scheme by Evans and Parrish [11] seemed more attractive, since it is shorter and looked amenable to improvement.
The chlorination step uses a five-fold excess of MsCl as a reagent and produces MsOH in stoichiometric quantities as a by-product. We, therefore, tried phosgene (1.5 mol-equiv.) in DMF as an alternative chlorinating agent and obtained, in 80–90% yield, the crude chloride 6 which could be directly used as such for the next step. The reduction method of the original procedure, using LiAlH₄ in a four-fold molar excess, was also improved by employing catalytic hydrogenation over Raney-Ni in the presence of a base. As the chloride 6 was reduced only sluggishly to methyl α-quinovoside (8) (45 h at 200 bar, see Table, entry 1), we also looked at the corresponding iodide (7) obtained by exchange reaction with NaI, THF/acetone, 66 h at 100°C.

As expected, the iodide 7 reacted much faster (Table, entry 2), and in order to avoid an extra step and stoichiometric amounts of the expensive NaI, we decided to examine the hydrolysis with in situ substitution of iodine for chlorine, using catalytic amounts of NaI. And indeed, the reduction of chloride 6 in the presence of catalytic amounts of NaI as low as 1 mol-% became economically feasible in 11–21 h at only 5 bars, 150°C (Table, entries 3–6). As solvent we preferred a ketone such as dipropylketone.

Instead of hydrolysing methyl α-quinovoside (8) to quinovose (3) usingaq. HCl as described earlier [11a], we employed a strongly acidic macroreticular resin in H₂O. With Dowex 50 W-H⁺X 4 for 22 h at 100°C, a 97% yield of quinovoside (3) was obtained, which could be directly used as such for its transformation into Furaneol (1). As reported earlier [6], piperidine/AcOH in EtOH for 13 h at 80°C transformed quinovoside (3) in 75% yield into Furaneol (1).

### Experimental

**General.** Solvents were removed with a Büchi Rotovopper R. Kugelrohr distillation; Buchi GKR-50 apparatus with internal temp. reading. GC: Vario 3700 dual column instrument, glass capillary columns (SE-30 12 m and Carbowax 20M 50 m). HPLC: Spectra-Physics SP 8700XR extended range LC pump, using an SP 8750 organizer, refractive index detector ERC-7510 (Erma Optical Works Ltd), programmable multichannel detector Waters M-490, column Aminex HPX 87C carbohydrate (30 cm, BioRad) at 80°C with H₂O as eluent. Column chromatography: silicagel Merck (particle size 0.063–0.2 mm) at atmospheric pressure. Flask and Merck reagents were used with the purity indicated. Catalysts: Raney-Ni from Dowaco, washed with MeOH before use. Nickel en support [Na/SiO₂–Al₂O₃ (Ni-G-96)] from Oiltimer Südt-Chemie. IR: Perkin Elmer spectrometer 720. NMR: Bruker AM 260 instrument. ¹H at 360 MHz and ¹C at 90 MHz using H₂O as solvent with TSP (sodium 3-trimethylsilyl)etrahydropropionate) as internal reference, unless otherwise stated. Chemical shift in ppm. Coupling constant in Hz. Suppression of the HO signal by relaxation time technique. MS: Finsigan 1020 automated GC/MS instrument, electron energy 70 eV, signal in m/z (rel. %).

**Methyl 6-Chloro-6-deoxy-α-D-glucopyranoside (8).** A. From Chloride 6 Compound 6 (4.47 mmol) and KOH (263 mg, 4.7 mmol) are diluted in 200 ml of H₂O and hydrogenated with H₂ at 200 bar and 60°C for 92 h using Raney-Ni as catalyst. The reaction can be followed by HPLC using an Aminex HPX 87C carbohydrate column operating at 80°C with H₂O as eluent (0.5 ml/min). The starting material, eluted at 25.37 min, is progressively replaced by 8, eluted at 19.51 min.

At the end of the reaction, the salts are removed on a mixed resin (BioRad type AG 50 W-X 8 D) and lyophilization gives a viscous material. This material, when evacuated under 1 Torr for 2 d, becomes crystalline. M.p. 83–85°C. Yield: 0.78 g (94%). ¹H-NMR: 1.28 (d, J = 6.5, 3-H(C(6))); 3.15 (t, J = 9, H-C(3)); 3.41 (s, CH₃O); 3.6 (m, 2 H); 3.72 (sym. m, H-C(5)); 4.75 (d, J = 3.6, H-C(1)). ¹C-NMR: 19.34 (q, C(6)); 57.76 (q, CH₃O); 70.24 (d, C(5)); 75.53 (d, C(7)); 77.78 (d, C(4)); 101.93 (d, C(1)).

**B) From Iodide 7.** A pressure bottle, equipped with a crown cap and a septum and with a magnet bar, is charged with 0.3 g (1 mmol) Na₂CO₃ (0.106 g, 1 mmol) and with Raney-Ni (30 mg, Dowaco) in MeOH (15 ml). The bottle is flushed, then pressurized with 1 bar of H₂, by means of a syringe connected to a hydrogen line. The reaction is carried out at 40°C for 16 h. At the end of the reaction, the solution is diluted with H₂O and the salts are removed on a mixed resin. After evaporation of the solvent, the syrup is obtained whose HPLC trace shows a purity of 93.5%; 8 is eluted after 18.62 min. Yield: 95.8%.

**Methyl 6-halo-6-deoxy-α-D-glucopyranoside (7).** A 100-ml flask, equipped with a reflux condenser connected to an Ar line and with a magnet bar, is charged with 6 (1.0 g, 4.7 mmol) and NaI (1.45 g, 9.6 mmol) in diethyl ketone (40 ml). After 48 h at reflux, the mixture is concentrated, redissolved in acetone/H₂O and filtered first on a Dowex 3 OH⁺ column then twice on a Dowex 50

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**Table. Hydrolysis of Methyl 6-Halo-6-deoxy-α-D-glucopyranosides to Methyl α-Quinovoside (7)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Conc.</th>
<th>Solvent</th>
<th>NaI*</th>
<th>Base*</th>
<th>Catalyst*</th>
<th>Press./Temp./Time</th>
<th>Yield, isof.*</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>2</td>
<td>H₂O</td>
<td>1 KOH</td>
<td>10 Ra-Ni</td>
<td>200/60/94</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>2</td>
<td>MeOH</td>
<td>1</td>
<td>1 KOH</td>
<td>10 Ra-Ni</td>
<td>1/40/16</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>10</td>
<td>DMF</td>
<td>0.5</td>
<td>1 Na₂CO₃</td>
<td>5/150/11</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>2.5</td>
<td>Diethyl ketone</td>
<td>1</td>
<td>1 Na₂CO₃</td>
<td>5/100/65</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>0.1</td>
<td>Dipropyl ketone</td>
<td>0.1</td>
<td>0.1 Na₂CO₃</td>
<td>5/95/21</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>10</td>
<td>Diglyme</td>
<td>0.1</td>
<td>0.1 Na₂CO₃</td>
<td>5/150/13.5</td>
<td>74</td>
<td></td>
</tr>
</tbody>
</table>

*In % (g/ml) of halosugar in the solvent. * Equivalents of NaI per chlorosugar. * Equivalent of base relative to the halosugar. * Amount of catalyst in % (wt./wt.) relative to the halosugar. * Hydrogen pressure. * Bath temperature. * Isolated yield corrected for purity.
W-H+ column, to remove all the salts. After concentration, a viscous material was obtained (1.37 g) with an HPLC purity of 80%. The yield obtained is 77%. Recrystallization from AcOEt. M.p. 115-125°C. *H-NMR: 3.33 (s, J = 9, H = C(6)); 3.42 (m); 3.48 (s, CH$_2$O); 3.59 (m); 3.62 (m); 3.67 (sym. m); 3.71 (sym. s); 4.81 (d, J = 3.6, H-C(1)). C(3)-NMR: 95.1 (C(6)); 58.2 (g, CH$_2$O); 73.0 (d); 74.0 (d); 75.3 (d); 76.29 (d) 102.2 (d, C(1)).

Methyl-6-deoxy-α-glucopyranose (o-Quinovose, 3). Compound 8 (5 g, 92%, 25.8 mmol), Dowex 50 W-H+ X 4 (5 g), and H$_2$O (50 ml) are heated with stirring at 100°C overnight. After filtration and basification to pH 10 with NaOH, 9 was extracted with CH$_2$Cl$_2$. After concentration, 1 g of yellow liquid was obtained which was distilled in a Kugelrohr (120/0.3 Torr). IR (neat): 1700, 1625, 1215. *H-NMR (in CDC$_3$, with TMS): 1.40 (d, J = 7.2, CH$_3$); 1.48 (m, 2H); 1.58 (quint, 4H); 2.20 (s, CH$_2$); 2.94 (br. s, H-C(1)); 3.42 (q, J = 7.2, 1H); C(3)-NMR: 14.4 (g), 16.4 (g); 24.0 (t); 26.7 (2r); 52.2 (2r); 80.3 (d) 128.5 (s); 183.9 (s); 203.0 (s). MS: 195 (66, M$^+$), 194 (25), 180 (24), 152 (28), 130 (104), 124 (13), 110 (15), 96 (18), 84 (12), 69 (13), 58 (17), 43 (35).

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[1] Registered trademark of Firmenich SA.