Chimia 46 (1992) 403–405

ISSN 0009–4293

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

François Mazenod*, **François Delay**, and **Ferdinand Näf**

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

Introduction

Furaneol (2,5-dimethyl-4-hydroxy-3(2*H*)-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 D-quinovose (**3**) [6] and L-fucose (**4**) [7], which again cannot be found easily, have also been transformed efficiently into Furaneol (**1**).

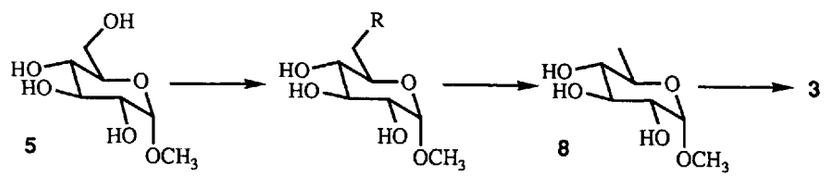
**Correspondence*: Dr. F. Mazenod
Firmenich SA
P.O. Box 239
CH-1211 Geneva 8

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

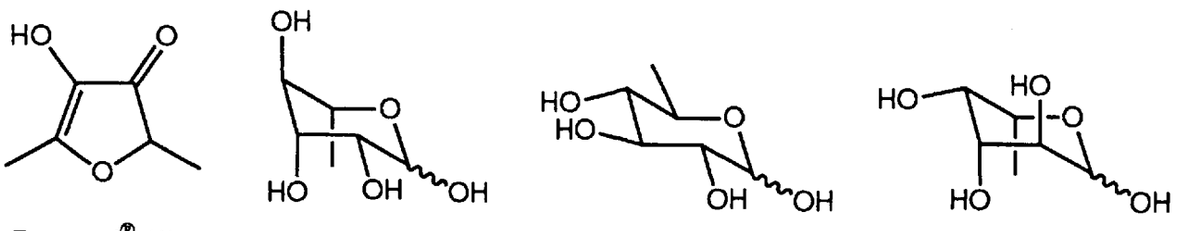
α-D-Glucose itself has been used by *Hardegger* and *Montavon* [9] as starting material for the preparation of D-quinovose-tetraacetate which is readily hydrolysed to D-quinovose (**3**) [10]. However, the number of steps involved (five), combined with the low overall yield with additional lowering of 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.

Scheme



	Evans & Parrish [11]	This work (see Exper. Part)
5 → **6**	CH_3SO_2Cl/DMF	$COCl_2$/DMF
6 → **7**	—	NaI, THF/acetone
6 → **8**	$LiAlH_4$/THF	– H_2, Ra-Ni, KOH – Cat. NaI, Ra-Ni or Ra-G96, Na_2CO_3
7 → **8**	—	H_2, Ra-Ni, Na_2CO_3
8 → **3**	1N aq. HCl	Dowex 50 W-H⊕ X



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 $LiAlH_4$ 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 D-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°.

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 hydrogenolysis 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° (*Table*, entries *3–6*). As solvent we preferred a ketone such as dipropylketone.

Instead of hydrolysing methyl D-quinovoside (**8**) to quinovose (**3**) using aq. HCl as described earlier [11a], we employed a strongly acidic macroreticular resin in H_2O. With *Dowex 50 W-H⁺ X 4* for 22 h at 100°, a 97% yield of quinovose (**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° transformed quinovose (**3**) in 75% yield into Furaneol (**1**).

Experimental

General. Solvents were removed with a *Büchi Rotavapor-R*. Kugelrohr distillation: *Büchi GKR-50* apparatus with external temp. reading. GC: *Varian 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 multiwavelength detector *Waters M-490*, column *Aminex HPX 87C* carbohydrate (30 cm, *BioRad*) at 80° with H_2O as eluent. Column chromatography: silicagel *Merck* (particle size 0.063–0.2 mm) at atmospheric pressure. *Fluka* and *Merck* reagents were used with the purity indicated. Catalysts: *Raney*-Ni from *Doduco*, washed with MeOH before use. Nickel on support (Ni/SiO_2–Al_2O_3) (Ni G-96) from *Girdler Süd-Chemie*. IR: *Perkin-Elmer spectrometer 720*. NMR: *Bruker AM 360* instrument. ^1H at 360 MHz and ^{13}C at 90 MHz using H_2O as solvent with TSP (sodium 3-(trimethylsilyl)tetradeutero propionate) as internal reference, unless otherwise stated. Chemical shift in ppm. Coupling constant *J* in Hz. Suppression of the HOD signal by relaxation time technique. MS: *Finnigan 1020* automated GC/MS instrument, electron energy 70 eV, signal in *m/z* (rel. %).

Methyl 6-Chloro-6-deoxy-α-D-glucopyranoside (**6**). A soln. of methyl α-D-glucopyranoside (**5**; 120 g, 0.62 mol) in anh. DMF (2.3 l) was treated dropwise under mechanical stirring at 0–10° with a 20% soln. of phosgene in toluene (490 ml, 0.93 mol). The resulting soln. was subsequently stirred for 6 h at 25° and 6 h at 80°. After concentration at 10 Torr, a viscous material, which partly crystallized, was obtained. This material was dissolved in a mixture of AcOEt/EtOH/H_2O 45:5:3, rapidly washed to neutrality by 2N NaOH, and filtered over a column of silica gel (600 g).

After evaporation of the solvent, **6** (111.5 g, 0.53 mol, 85% yield) was obtained as a yellowish solid. Recrystallization from AcOEt. M.p. 112–113°. ^1H-NMR: 3.44 (*s*, CH_3O); 3.51 (*t*, *J* = 9.5, H–C(3)); 3.59 (*dd*, *J* = 10.1, 3.6, H–C(2)); 3.69 (asym. *t*, *J* = 10, H–C(4)); 3.87 (*m*, H–C(6)); 3.89 (*m*, H–C(6')); 3.95 (*m*, H–C(5)); 4.82 (*d*, *J* = 3.6, H–C(1)). ^{13}C-NMR: 46.99 (*t*, C(6)); 57.91 (*q*, CH_3O); 72.94 (*d*, C(4)); 73.29 (*d*, C(5)); 73.86 (*d*, C(2)); 75.53 (*d*, C(3)); 102.1 (*d*, C(1)). Anal. calc. for $C_7H_{13}O_5Cl$: C 39.53, H 6.12, Cl 16.70; found: C 39.62, H 6.27, Cl 16.50.

Methyl 6-Deoxy-α-D-glucopyranoside (**8**). *A) From Chloride* **6**. Compound **6** (1 g, 4.7 mmol) and KOH (263 mg, 4.7 mmol) are diluted in 200 ml of H_2O and hydrogenated with H_2 at 200 bar and 60° 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° with H_2O 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 501 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°. 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*, CH_3O); 3.6 (*m*, 2 H); 3.72 (sym. *m*, H–C(5)); 4.75 (*d*, *J* = 3.6, H–C(1)). ^{13}C-NMR: 19.34 (*q*, C(6)); 57.76 (*q*, CH_3O); 70.24 (*d*, C(5)); 74.18 (*d*, C(2)); 75.53 (*d*, C(3)); 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 **7** (0.3 g, 1 mmol), Na_2CO_3 (0.106 g, 1 mmol) and with *Raney*-Ni (30 mg, *Doduco*) in MeOH (15 ml). The bottle is flushed, then pressurized with 1 bar of H_2, by means of a syringe connected to a hydrogen line. The reaction is carried out at 40° for 16 h.

At the end of the reaction, the soln. is diluted with H_2O and the salts are removed on a mixed resin. After evaporation of the solvent, a syrup is obtained whose HPLC trace shows a purity of 93.5%; **8** is eluted after 18.62 min. Yield: 95.8%.

Methyl 6-Iodo-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 anh. NaI (1.45 g, 9.6 mmol) in diethyl ketone (40 ml). After 48 h at reflux, the mixture was concentrated, rediluted in acetone/H_2O and filtered first on a *Dowex 3 OH⁻* column then twice on a *Dowex 50*

Table. *Hydrogenolysis of Methyl 6-Halo-6-desoxy-α-D-glucosides to Methyl* D-*Quinovoside* (**7**)

Entry	Starting material	Conc.[a])	Solvent	NaI[b]) [equiv.]	Base[c]) [equiv.]	Catalyst[d]) [% weight]	Press.[e])/Temp.[f])/Time [bar/°C/h]	Yield, isol.[g]) [%]
1	**6**	2	H_2O	–	1 KOH	10 *Ra*-Ni	200 / 60 / 92	94
2	**8**	2	MeOH	–	1 Na_2CO_3	10 *Ra*-Ni	1 / 40 / 16	96
3	**6**	10	DMF	0.5	1 Na_2CO_3	10 *Ra*-Ni	5 / 150 / 11	87
4	**6**	2.5	Diethyl ketone	1	1 Na_2CO_3	10 *Ra*-Ni	5 / 100 / 65	95
5	**6**	10	Dipropyl ketone	0.01	1 Na_2CO_3	5 Ni G-96	5 / 150 / 21	83
6	**6**	10	Diglyme	0.1	1 Na_2CO_3	1.5 Ni G-96	5 / 150 / 13.5	74

[a]) In % (g/ml) of halosugar in the solvent. [b]) Equivalents of NaI per chlorosugar. [c]) Equivalent of base relative to the halosugar. [d]) Amount of catalyst in % (wt./wt.) relative to the halosugar. [e]) Hydrogen pressure. [f]) Bath temperature. [g]) 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°. ^{1}H-NMR: 3.33 (*'t'*, *J* = 9, H_2–C(6)); 3.42 (*m*); 3.48 (*s*, CH_3O); 3.59 (*m*); 3.62 (*m*); 3.67 (sym. *m*); 3.71 (asym. *t*); 4.81 (*d*, *J* = 3.6, H–C(1)). ^{13}C-NMR: 9.51 (*t*, C(6)); 58.2 (*q*, CH_3O); 73.01 (*d*); 74.05 (*d*); 75.33 (*d*); 76.29 (*d*); 102.22 (*d*, C(1)).

*Methyl 6-Deoxy-*D*-glucopyranose* (D-*Quinovose*, **3**). Compound **8** (5 g, 92% pure, 25.8 mmol), *Dowex 50 W-H*$^+$ *X* 4 (5 g), and H_2O (50 ml) are heated with stirring at 100°.

The progression of the hydrolysis is followed by HPLC (*Aminex HPX-87C* carbohydrate column, *BioRad*, at 80° with refractive index detection). After 2 h, the ratio between hydrolyzed and non-hydrolyzed sugar is 55:45. The ratio becomes 78:22 after 4.25 h, 86:14 after 7.25 h and 98.3:1.7 after 22 h.

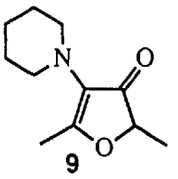
After removal of the resin by filtration, the soln. is lyophilized to give 4.6 g of a viscous (almost solid) brownish material (90% pure by HPLC). Yield: 97.2% (corrected for purity). Recrystallization in 20 ml of AcOEt gives 2.79 g of a white solid. Yield: 66% (recrystallized). M.p. 135–140°. Spectral data of a $\beta/\alpha = 2.3$ mixture: ^{1}H-NMR: 1.26 (*d*, *J* = 6.5, 3 H–C(6) of α-isomer); 1.28 (*d*, *J* = 6.5, 3 H–C(6) of β-isomer); 3.15 (*m*); 3.24 (*t*); 3.43 (*t*); 3.50 (*m*); 3.65 (*t*); 3.90 (sym. *m*); 4.62 (*d*, *J* = 7.6, H–C(1) of β-isomer); 5.18 (*d*, *J* = 3.6, H–C(1) of α-isomer). ^{13}C-NMR: 19.59 (*q*, C(6) of α and β-isomers); 70.20 (*d*, C(5) of α-isomer); 74.53 (*d*, C(2) of α-isomer); 74.72 (*d*, C(5) of β-isomer); 75.27 (*d*, C(3) of α-isomer); 77.18 (*d*, C(2) of β-isomer); 77.69 (*d*, C(3) of β-isomer); 78.00 (*d*, C(4) of α-isomer); 78.26 (*d*, C(4) of β-isomer); 94.76 (*d*, C(1) of α-isomer); 98.53 (*d*, C(1) of β-isomer).

*2,5-Dimethyl-4-hydroxy-3(2*H*)-furanone (Furaneol,* **1***) from* D-*quinovose* (**3**). A 1-l flask, equipped with a reflux condenser connected to an Ar line and with a magnet bar, was charged with piperidine (12.96 g, 0.152 mol), abs. EtOH (250 ml), AcOH (21.04 g, 0.35 mol) and cryst. **3** (50 g, 0.305 mol). The mixture was heated at reflux. After 13 h, the EtOH was evaporated and the crude mixture extracted with AcOEt (2 x 200 ml), washed with brine (5 x), dried, and concentrated to give 37.9 g of a yellow-brown material containing 90% **1** and 10% enamine **9** [12] by GC (*SE-30* 12 m, 100–220°). The quantification of **1** using triglyme as internal standard gave a 75% yield. A first crystallization from toluene (29 g) gave 17.7 g of pure **1** (45% yield). After distillation of the mother liquor (18.2 g) in a Kugelrohr (150–160°/10 Torr), 12.2 g of distillate (80% **1** and 20% **9** by GC) was obtained. After dilution with H_2O and acidification with H_3PO_4 to pH 2, this mixture was passed through a *Dowex 50 W-H*$^+$ (25 g wet) column to remove the enamine. Extraction of the percolate with AcOEt gave 8.3 g of **1** (after recryst. from toluene 4.11 g). 56% total yield of pure **1** being identical in all respects (mixed m.p., spectral data) with an authentic sample [5e].

*2,5-Dimethyl-4-(1'-piperidyl)-3(2*H*)-furanone* (**9**). The macroreticular sulfonic resin (*Dowex 50 W*) used in the previous experiment to retain the enamine was placed in a flask and triturated with 10% aq. HCl (150 ml) at 25° overnight. After filtration and basification to pH 10 with NaOH, **9** was extracted with CH_2Cl_2. After concentration, 1 g of a yellow liquid was obtained which was distilled in a Kugelrohr (120°/0.3 Torr). IR (neat): 1700, 1625, 1215. ^{1}H-NMR (in $CDCl_3$ with TMS): 1.40 (*d*, *J* = 7.2, CH_3); 1.48 (*m*, 2 H); 1.58 (*quint*, 4 H); 2.20 (*s*, CH_3); 2.94 (br. *t*, 4 H); 4.32 (*q*, *J* = 7.2, 1 H). ^{13}C-NMR: 14.4 (*q*); 16.4 (*q*); 24.0 (*t*); 26.7 (2*t*); 52.2 (2*t*); 80.3 (*d*); 128.5 (*s*); 183.9 (*s*); 203.0 (*s*). MS: 195 (66, M^+), 194 (25), 180 (24), 152 (28), 138 (100), 124 (13), 110 (15), 96 (18), 84 (12), 69 (13), 68 (13), 55 (17), 43 (35).

Received: August 4, 1992

[1] Registered trademark of *Firmenich SA*.
[2] B. Willhalm, E. Palluy, M. Winter, *Helv. Chim. Acta* **1966**, *49*, 65.
[3] J.O. Rodin, C.M. Himel, R.M. Silverstein, R.W. Leepe, W.A. Gortner, *J. Food Sci.* **1965**, *30*, 280.
[4] For some recent references, see: a) A. Sen, P. Schieberle, W. Grosch, *Lebensm.-Wiss. Technol.* **1991**, *24*, 364; b) G. Bruche, H.-G. Schmarr, A. Bauer, A. Mosandl, A. Rapp, E. Lorenz, *Z. Lebensm.-Unters. Forsch.* **1991**, *193*, 115; c) I. Lesschaeve, D. Langlois, P. Etievant, *J. Food Sci.* **1991**, *56*, 1393; d) A.F. Pisarnitskii, G.G. Okroperidze, T.G. Tabatadze, O.V. Gamova, L.S. Kazinyan, I.A. Egorov, *Prikl. Biokhim. Mikrobiol.* **1991**, *27*, 394; e) W. Holscher, G.O. Vitzthum, H. Steinhart, *Café, Cacao, Thé* **1990**, *34*, 205; f) G. Ziegleder, *Z. Lebensm.-Unters. Forsch.* **1991**, *192*, 521; g) I. Pons, Ch. Garrault, J.-N. Jaubert, J. Morel, J.-C. Fenyo, *Food Chem.* **1991**, *39*, 311; h) A. Pabst, D. Barron, P. Etievant, P. Schreier, *J. Agric Food Chem.* **1991**, *39*, 173. For a recent comprehensive review see: S. van Straten, H. Maarse, C.A. Visscher, 'List of Volatile Compounds in Food', Central Institute of Nutrition and Food Research, Zeist, Holland 1983 – Suppl. 4, 1987, 6th edn., Qualitative and Quantitative Data, 1989.
[5] a) J.E. Hodge, B.E. Fisher, E.C. Nelson, *Am. Assoc. Brewing Chemists Proc.* **1963**, 84; b) B. Willhalm, M. Stoll, A.F. Thomas, *Chem. Ind.* **1965**, 1629; c) R.M. Silverstein, *J. Org. Chem.* **1966**, *31*, 2351; d) G. Büchi, E. Demole, A.F. Thomas, *ibid.* **1973**, *38*, 123; e) L. Ré, B. Maurer, G. Ohloff, *Helv. Chim. Acta* **1973**, *56*, 1882; f) G.A.M. van den Ouweland, S.B. Tjan, *Recl. J. R. Netherl. Chem. Soc.* **1974**, 312; g) D. De Rijke, H. Boelens, *Recl. Trav. Chim. Pays-Bas* **1973**, 731; h) L. Bassignoni, A. Brandt, V. Caciagli, L. Ré, *J. Org. Chem.* **1978**, *43*, 4246; i) M. Baumann, W. Hoffmann, *Synthesis* **1981**, 709; k) G.M. Whitesides, F. Mazenod, C.H. Wong, *J. Org. Chem.* **1983**, *48*, 3493; l) M.A. Briggs, A.H. Haines, *J. Chem. Soc., Perkin Trans. 1* **1985**, 795; m) S. Torii, T. Inokuchi, Y. Hirata, *Synthesis* **1987**, 377; n) H.J. Wild, *Chem. Ind.* **1988**, 580; U. Huber, H.J. Wild, US Pat. 4,208,338 (prior. LU, Aug. 11, 1977, to *Givaudan*); *Chem. Abstr.* **1983**, *98*, 107 146.
[6] M. Matsui, T. Ogawa, K. Tagaki, Jpn. Kokai Tokkyo Koho 79 19 962, 1979, *Chem. Abstr.* **1979**, *91*, 20309q.
[7] a) T. Doornbos, G.A.M. van den Ouweland, S.B. Tjan, *Prog. Food Nutr. Sci.* **1981**, *5*, 57; b) H.G. Peer, G.A.M. van den Ouweland, G.N. de Groot, *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1011.
[8] a) G.N. Bollenback, *Meth. Carbohydr. Chem.* **1963**, *2*, 326; b) B. Helferich, W. Schäfer, *Org. Synth. Coll. Vol. I* **1941**, 364.
[9] E. Hardegger, R.M. Montavon, *Helv. Chim. Acta* **1946**, *29*, 1199.
[10] M.L. Wolfrom, A. Thompson, *Meth. Carbohydr. Chem.* **1963**, *2*, 211, 215.
[11] a) M.E. Evans, F.W. Parrish, *Meth. Carbohydr. Chem.* **1972**, *6*, 177; b) *ibid.* **1972**, *6*, 193.
[12]



9