A Facile Synthesis of (*S*)-5-Benzyloxymethyl-2-oxo-2,5-dihydrofuran via D-5-*O*-Benzyl-2-deoxyxylono-1,4-lactone

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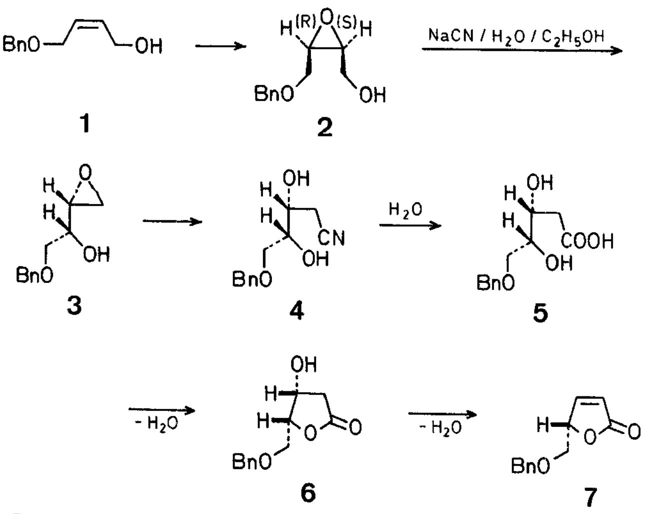
In spite of its potential value as chiral building block, optically active 5-hydroxymethyl-2-oxo-2,5-dihydrofuran and its derivatives have so far been utilized only in a limited number of syntheses of natural products[1-4], probably owing to dificulties in their preparation. Three syntheses of chiral 5-alkoxymethyl-2-oxo-2,5-dihydrofurans[1,2,3,5,6] require optically active naturally occurring precursors such as L-glutamin acid[1,2] or D-ribonolactone[3,5,6], the availability of which is limited to particular enantiomeric forms. We report here a simple and efficient preparation of (*S*)-5-benzyloxymethyl-2-oxo-2,5-dihydrofuran (**7**) via D-5-*O*-benzyl-2-deoxyxylono-1,4-lactone (**6**), starting from the known chiral epoxyalcohol 4-benzyloxy-(2*S*, 3*R*)-epoxybutanol (**2**)[7,8] which is easily prepared from (*Z*)-4-benzyloxy-2-butenol (**1**)[9] by a known oxidation procedure using naturally occuring L-tartrate ester as the chirality-controlling agent[8]. The procedure described may be extended to the preparation of the L-enantiomer of lactone **6** since both (2*R*, 3*S*)- and (2*R*, 3*R*)-forms of 4-benzyloxy-2,3-epoxybutanol (**2**) have already been prepared from **1** by asymmetric epoxidation[8].

It is known that substitution occurs at C-1 when a 2,3-epoxyalcohol is treated with a nucleophile to produce a secondary 1,2-glycol[10].This reaction has been successfully applied to an enantiocontrolled synthesis of sugars[8,11,12] and a chiral synthesis of the mycotoxin vertinolide[13]. We have now applied this reaction to the synthesis of (*S*)-5-benzyloxymethyl-2-oxo-2,5-dihydrofuran (**7**) using sodium cyanide as nucleophile[12]. Treatment of **2** with 3 molecular equivalents of sodium cyanide in boiling 40% aqueous ethanol for 8 h allowed the expected substitution at C-1; spontaneous hydrolysis[13] of the resultant cyanide **4** afforded crude D-5-*O*-benzyl-2-deoxyxylic acid (**5**) in one reaction. The crude compound **5** was then azeotropically refluxed with toluene to give pure crystalline D-5-*O*-benzyl-2-deoxyxylono-1,4-lactone (**6**) in 38% overall yield from epoxide **2**, after recrystallization. We assigned the relative configuration between C-4 and C-5 of the product to be *threo* as the ^{1}H-N.M.R. spectrum of **6** exhibits signals of 3,3-H_2 (of the furan ring system) as patterns which are quite similar to those of 3,5-di-*O*-methyl-2-deoxyxylono-1,4-lactone[14] but not to those of 3,5-di-*O*-

methyl-2-deoxyribono-1,4-lactone[14]. Dehydration of xylonolactone **6** was simply carried out by treating **6** with 1.2 molecular equivalents of methanesulfonyl chloride in the presence of 2 molecular equivalents of triethylamine at 0 °C for 1 h to give (*S*)-5-benzyloxymethyl-2-oxo-2,5-dihydrofuran (**7**)[1,5,6] in 94% yield.



Melting points are uncorrected. Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter. Mass spectra were measured with a JEOL-D 300 spectrometer. I.R. spectra were measured with a JASCO A-102 spectrometer. ^{1}H-N.M.R. spectra were measured with a JEOL-PMX 60 or a JEOL-FX 100 spectrometer.

All reactions are carried out under argon.

D-5-*O*-Benzyl-2-deoxyxylono-1,4-lactone (6):

4-Benzyloxy-(2*S*, 3*R*)-epoxybutanol[8,15] (**2**; 4.85 g, 25 mmol) is heated to reflux with sodium cyanide (3.68 g, 75 mmol) in aqueous 40% ethanol (40 ml) for 8 h. Most of the ethanol is then removed in vacuo and the aqueous residue is washed with ether (2 × 20 ml). The aqueous phase is carefully acidified to pH 3–4 with concentrated hydrochloric acid, with icecooling in a hood. The aqueous phase is then extracted with dichloromethane (3 × 30 ml), and the extract dried with magnesium sulfate. Evaporation of the solvent gives the crude D-*O*-benzyl-2-deoxyxylic acid (**5**; 4.06 g) as a dark oil. This product heated in boiling toluene (60 ml) for 12 h with removal of water using a Dean-Stark trap. After cooling, the mixture is washed with aqueous 5% sodium hydrogen carbonate (50 ml) and saturated sodium chloride solution (50 ml), and dried with magnesium sulfate. Evaporation of the solvent gives a pale yellow solid (2.80 g) which is recrystallized from hexane/ether (1/1) to give the pure product **6** as colorless leaflets; yield: 2.14 g (38% from **2**); m.p. 74.5–75.5 °C; $[\alpha]_D$: +48.9° (*c* 1.53, ethanol).

$C_{12}H_{14}O_4$	calc.	C 64.85	H 6.35
(222.2)	found	64.55	6.50

M.S. (high resolution): *m/e* = 222.0891 (calc. 222.0891).

I.R. (film): ν = 3450, 1780 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): δ = 2.6 (m, 2H); 3.1 (d, 1H, exchangeable); 3.8 (d, 2H); 4.4 (m, 1H); 4.5 (s, 2H); 7.3 ppm (s, 5H).

(*S*)-5-Benzyloxymethyl-2-oxo-2,5-dihydrofuran (7):

A mixture of xylonolactone **6** (220 mg, 1 mmol) and triethylamine (200 mg, 2 mmol) in dichloromethane (5 ml) is stirred and cooled to 0 °C, and methanesulfonyl chloride (136 mg, 1.2 mmol) is added dropwise. Stirring is continued for 1 h at 0 °C. Then, dichloromethane (10 ml) is added, the mixture is washed with water (10 ml), 5% hydrochloric acid (2 × 5 ml), and saturated sodium chloride solution (2 × 10 ml), and dried with magnesium sulfate. The solvent is evaporated in vacuo to give the essentially pure product **7** as an oil which is distilled in vacuo to give pure **7**; yield: 190 mg (94%); b.p. 140 °C/0.03 torr (Kugelrohr) (Lit.[6], b.p. 140 °C/0.06 torr); $[\alpha]_D$: −117.1° (*c* 1.47, ethanol) [Lit., $[\alpha]_D$: −107° (ethanol)[1]; $[\alpha]_D$: −10.6° (*c* 2.1, ethanol)[5]; $[\alpha]_D$: −10.7° (*c* 1.6, ethanol)[6]].

M.S.: *m/e* = 204 (M$^+$), 91 (100%).

I.R. (neat): ν = 1780, 1745 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): δ = 3.7 (d, 2H, *J* = 5 Hz); 4.5 (s, 2H); 5.1 (m, 1H); 6.1 (dd, 1H *J* = 6 and 2 Hz); 7.2 (s, 5H); 7.4 ppm (dd, 1H, *J* = 6 and 2 Hz).

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