Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Supporting Information

Synthesis of (*R*)-2-methyl-4-deoxy and (*R*)-2-methyl-4, 5-dideoxy analogues of 6-phosphogluconate as potential inhibitors of 6-phosphogluconate dehydrogenase

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Table of contents:

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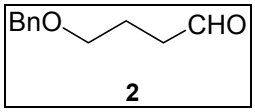
1- Preparation and spectroscopic datas (^{1}H NMR, ^{13}C NMR and DEPT) of 2, 12, 13, 14, 15 and 21b.

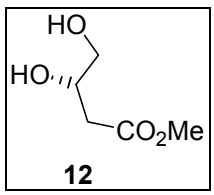
4-benzyloxy-butyraldehyde (2).



To a solution of DMSO (8.65 cm^3/ 122 mmol) in CH_2Cl_2 (150 cm^3) cooled to –70 ^oC was added oxalyl chloride (30.5 cm^3/ 61 mmol). After 5 min, 4-benzyloxy-1-butanol (9.75 cm^3, 55.5 mmol) was added neat at the same temperature. After 15 min, Et_3N (38 cm^3/ 277 mmol) was added to this thick white slurry. The reaction mixture was stirred another 15 min at –70 ^oC and 2 h at rt. The precipitated Et_3N.HCl was filtered off and the filtrate washed with CH_2Cl_2. The solution was concentrated to *ca* 150 cm^3 and washed with HCl 0.5M (100 cm^3). The aqueous phase was extracted with 50 cm^3 CH_2Cl_2. Combined organic extracts were washed with acidic brine, dried ($MgSO_4$) and concentrated. Chromatography on silica with Hexane/EtOAc (10%→ 30%) yielded the aldehyde **2** as a light yellow oil (8.64 g, 87 %); IR (film) υ_{max}/cm^{-1} 2933; 2861; 1720; 1102; 741; 698; δ_H ($CDCl_3$) 9.9 (1H, s); 7.5-7.35 (5H, m); 4.6 (2H, s); 3.6 (2H, t, *J* 6.1); 2.63 (2H, dt, *J* 7.1 and 1.5); 2.0 (2H, quint, *J* 6.1); δ_C ($CDCl_3$) 202.8; 160.5; 138.7; 128.8; 128.6; 128.3; 128.0; 73.4; 69.6; 41.4; 23.0.

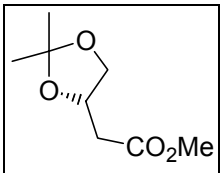
Preparation of 15.

***(S)*-3,4-Dihydroxy-butyric acid methyl ester (12).**



To a solution of *(L)*-malic acid dimethyl ester (7.6 g, 46.9 mmol) in THF (100 cm^3) under N_2 was added dropwise at rt over a 20 min period, BH_3-DMS complex (47 cm^3, 1M in CH_2Cl_2). After 30 min stirring, sodium borohydride (90 mg, 2.35 mmol) was added in portions to the flask cooled with a cold water bath. After 30 min, the reaction was quenched by the dropwise addition of MeOH (30 cm^3). After another 45 min stirring, the solvent was removed *in vacuo* and the crude oil was chromatographed on silica with 100% EtOAc to afford **12** as a light yellow oil (5.25 g, 83 %); R_f: 0.26 (EtOAc); $[\alpha]_D^{22}$= -26.9 (*c* 1.3, $CHCl_3$); δ_H ($CDCl_3$) 4.2 (1H, m); 3.8 (3H, s); 3.75 (1H, m); 3.6 (1H, m); 3.3 (1H, d, OH, exchange D_2O); 2.7-2.5 (2H, m); 2.2 (1H, br t, OH, exchange D_2O); δ_C ($CDCl_3$) 173.48; 68.93; 66.13; 52.4; 37.86; *m/z* (ES^+) 157 (M+Na).

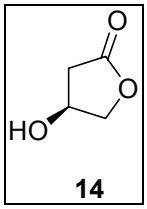
(2,2-Dimethyl-[*(S)*-1,3]dioxolan-4-yl)-acetic acid methyl ester (13).



13

A solution of diol **12** (10 g, 75 mmol) and TsOH (145 mg, 0.75 mmol) in acetone (300 cm^3) was stirred 2 days at rt. Et_3N was added (0.5 cm^3) and the solvent was removed *in vacuo*. Chromatography with Hexane/EtOAc (3/2) yielded two products: the acetonide **13** was eluted first (9.08 g, 70 %), then the *(S)*-4-Hydroxy-dihydro-furan-2-one side-product **14** (1.21 g, 16 %). $R_{f\,(\mathbf{13})}$: 0.65 (50 % EtOAc in hexane); $[\alpha]_D^{21}$= + 30.77 (*c* 1.3, $CHCl_3$); δ_H ($CDCl_3$) 4.56 (1H, quint, *J* 6.4); 4.24 (1H, dd, J_{gem} 8.3; J_{vic} 6); 3.78 (3H, s); 3.73 (1H, dd, J_{gem} 8.3 and J_{vic} 6.4); 2.80 (1H, $1/2_{ABX}$, J_{AB} 15.9 and *J* 6.4,); 2.61 (1H, $1/2_{ABX}$, J_{AB} 15.9 and *J* 7); 1.49 (3H, s); 1.44 (3H, s); δ_C ($CDCl_3$) 171.5 (s); 109.7 (s); 72.4 (d); 69.6 (t); 52.5 (q); 39.2 (t); 27.3 (q); 25.9 (q).

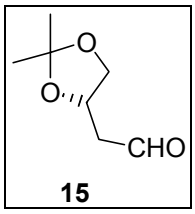
***(S)*-4-Hydroxy-dihydro-furan-2-one (14).**[1]



14

$R_{f(\mathbf{14})}$: 0.14 (50 % EtOAc in hexane); δ_H ($CDCl_3$) 4.55 (1H, br t); 4.42 (1H, td, *J* 2, *J* 9); 4.25 (1H, td, *J* 6 and 9.3); 4.1 (1H, s); 2.65 (1H, m); 2.3 (1H, m); δ_C ($CDCl_3$) 178.7 (s); 69.2 (d); 65.7 (t); 31.3 (t).

***(S)*-3,4-*O*-isopropylidene-3,4-dihydroxybutanal (15).**



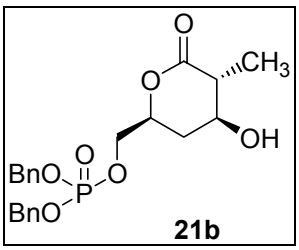
15

A solution of **13** (2.74 g, 15.7 mmol) in CH_2Cl_2 (60 cm^3) was flushed with N_2 and cooled to – 90 ^oC. DIBAL (1.5 M in toluene, 13.6 cm^3) was added dropwise over a 20 min period and the reaction was stirred 30 min at the same temperature. The cold bath was removed and the reaction was quenched with aqueous saturated NH_4Cl (4.2 cm^3) and 1M HCl (8 cm^3). The mixture was diluted with CH_2Cl_2 and was filtered on a path of silica. The aluminium salts were washed with CH_2Cl_2 and the filtrate was concentrated *in vacuo*. The crude yellow oil was chromatographed to afford the aldehyde **15** as a colourless volatile aromatic oil (1.89 g, 84 %). **15** should be stored a

[1] Wang, G.; Hollingsworth, R.I. *J. Org. Chem.* **1999**, *64*, 1036. And references cited therein.

0 ^{o}C; R_f: 0.33 (25 % EtOAc in hexane); $[\alpha]_D^{21}$ = + 19.1 (*c* 0.68, $CHCl_3$) (lit.,[2] + 8.3 (*c* 1.3, $CHCl_3$); lit.,[3] + 16.5 (*c* 5.32, $CHCl_3$)); δ_H ($CDCl_3$) 9.8 (1H, t, *J* 1.5); 4.55 (1H, quint, *J* 6.4); 4.22 (1H, dd, *J* 6 and 8.3); 3.6 (1H, dd, *J* 6.7 and 8.3); 2.88 (1H, ddd, *J* 1.8, 6.6 and 17.3); 2.68 (1H, ddd, *J* 1.2, 6.1 and 17.3); 1.44 (3H, s); 1.39 (3H, s); δ_C ($CDCl_3$) 200.4 (s); 109.7 (s); 71.0; 69.5; 48.2; 27.2 (q); 25.8 (q).

Phosphoric acid dibenzyl ester 4-hydroxy-5-methyl-6-oxo-tetrahydro-pyran-2-ylmethyl ester (21b).



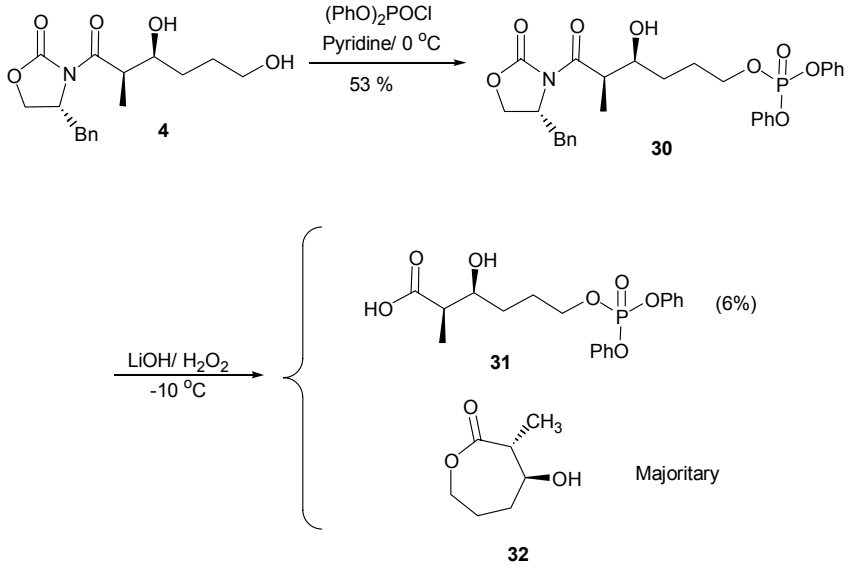
21b

δ_H ($CDCl_3$) 7.5 (10H, s); 5.21 (2H, m); 5.18 (2H, m); 4.45 (1H, m), 4.2 (2H, m); 3.85 (1H, m); 3.45 (1H, d); 2.45 (1H, m); 2.2 (1H, dt); 1.85 (1H, m); 1.5 (3H, d); δ_C ($CDCl_3$) 173.2 (s); 135.9 (s); 135.8 (s); 129.2 (d); 129.1 (d); 128.5 (d); 128.3 (d); 74.7 (CH, d, *J* 7.5); 70.2 (CH_2, d), 70.1 (CH_2, d); 69.6 (d); 68.8 (t, *J* 7.5); 45.3 (d); 33.9 (t); 13.9 (q); δ_P ($CDCl_3$) – 0.12; *m/z* (ES^+) 443 (M+Na); *m/z* (ES^+) 421.1426 (M+H. $C_{21}H_{26}O_7P$ requires 421.1416).

[2] André, C.; Bolte, J.; Demuynck, C, *Tetrahedron: Asymmetry* **1998**, *9*, 1359.

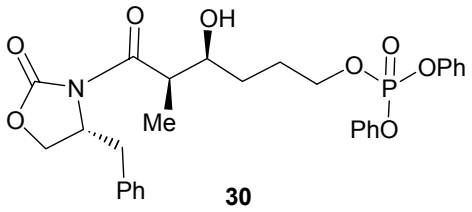
[3] Meyers, A.I.; Lawson, J.P.; Walker, D.G.; Linderman, R.J. *J. Org. Chem*. **1986**, *51*, 5111.

2- Previous synthetic approach tried for the synthesis of (*R*)-2-methyl-4,5-dideoxy analogues of 6PG.



Scheme S1

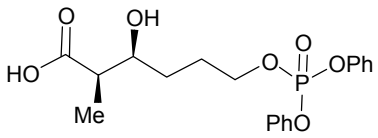
Phosphoric acid 6-[(R)-4-benzyl-2-oxo-oxazolidin-3-yl]-(S)-4-hydroxy-(R)-5-methyl-6-oxo-hexyl ester diphenyl ester (30).



A solution of diol **4** (359 mg, 1.12 mmol) and pyridine (0.27 ml, 3.36 mmol) in CH_2Cl_2 (5 ml) was cooled to 0 °C with an ice-bath. Diphenylchlorophosphate was added dropwise with a syringe. The reaction was stirred at 0 °C for 2.5 h and then partitioned between saturated NH_4Cl solution and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. Organic extracts were dried ($MgSO_4$) and concentrated.

Chromatography on silica with Hexane/EtOAc 50 %. The diphosphorylated product (R_f: 0.4, 50 % EtOAc in Hexane) was eluted first (45 mg, 5 %) then, the monophosphorylated product **30** was obtained as a colourless oil (327 mg, 53 %). R_f: 0.32 (50 % EtOAc in Hexane); $[\alpha]_D^{24} = -20$ (*c* 0.1, CH_2Cl_2); υ_{max} (neat)/cm^{-1} 3440; 2973; 1778; 1698; 1489; 1194; 1024; 955; 765; 693; δ_H ($CDCl_3$) 7.5-7.2 (m, 15H, aro); 4.76 (m, 1H); 4.4 (m, 2H); 4.3-4.15 (m, 2H); 4.02 (dt, 1H, *J* 3.3 and 8.6); 3.78 (qd, 1H, *J* 2.8 and 7); 3.3 (dd, 1H, *J* 3.3 and 13.4); 2.8 (dd, 1H, *J* 9.4 and 13.4); 2.75 (br, OH); 2.0 (m, 1H); 1.85 (m, 1H); 1.75-1.45 (m, 2H); 1.35 (d, 3H, *J* 7.1); δ_C ($CDCl_3$) 177.2 (s); 153.5 (s); 151.0 (s, J_{C-P} 7.5); 135.5 (d); 130.2 (d); 129.8; 129.4; 129.3; 127.7; 125.7; 120.5 (s, J_{C-P} 7.5); 71.3 (d); 69.7 (t, J_{C-P} 7.5); 66.5 (t); 55.5 (d); 43.1 (d); 38.0 (t); 30.3 (t); 27.3 (t, J_{C-P} 7.5); 11.3 (q); δ_P ($CDCl_3$) –10.66; *m/*z (ES) 576 (M+Na, 100%).

6-(Diphenoxy-phosphoryloxy)-3-hydroxy-2-methyl-hexanoic acid (31).



31

To a solution of the aldol **30** (130 mg, 0.23 mmol) in THF/H_2O (4/1, 5 ml) cooled with an ice-bath was added H_2O_2 (30% in water, 0.1 ml, 0.94 mmol). A solution of LiOH (7 mg, 0.3 mmol) in water (2 ml) was added at such a rate to keep the internal temperature between –10 and –3 ^oC. The reaction was stirred 1.5 h at the same temperature and quenched with a solution of sodium sulfite (150 mg) in water (4 ml). THF was removed *in vacuo* and the aqueous phase was extracted with EtOAc. The organic extracts were dried ($MgSO_4$) and concentrated. Chromatography with

CH_2Cl_2/MeOH: 4→10%. The lactone **32** was eluted first, then **31** was obtained as an oil (6 mg, 6%); δ_H ($CDCl_3$) 7.4-7.0 (m, 10 H); 4.3 (m, 2H); 3.85 (m, 1H); 2.45 (m, 1H); 2.0-1.35 (m, 4H); 1.2 (m, 1H); 1.1 (d, 3H, *J* 7); δ_C ($CDCl_3$) 179.7 (s); 150.9 (2xs); 130.3 (d); 125.9 (d); 120.5 (2xd); 71.5 (d); 69.7 (t, $J_{C\text{-}P}$ 5.6); 44.6 (d); 29.5 (t); 27.3 (t, $J_{C\text{-}P}$ 5.6); 11.1 (q); *m/*z (ES) 417(M+Na, 100%).