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Pentodialdose Mercaptal Derivatives: New Chiral C_5 Synthetic Building Blocks

Imre Kovács, Zoltán Tóth, Pál Herczegh,* Ferenc Sztaricskai

Research Group for Antibiotics of the Hungarian Academy of Sciences, Lajos Kossuth University

H-4010 Debrecen, P.O. Box 20., Hungary

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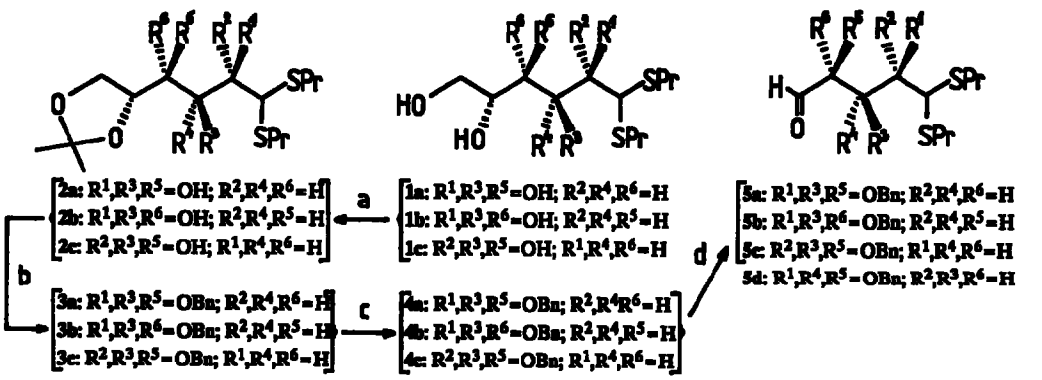
Abstract: Three tribenzyloxy derivatives of the title compounds with D-*xylo*, L-*arabino* and D-*lyxo* configuration were prepared from naturally abundant hexoses in five steps.

The title compounds **5a** and **5d** proved to be versatile intermediates in our studies on Diels-Alder and other cycloaddition reactions.[1-3] The D-*xylo* isomer **5a** could be prepared[1] from the pentose 2,3,4-tri-*O*-benzyl ether and the D-*ribo* derivarive **5d** has been synthesized[2] from D-ribose mercaptal 2,3,4-tri-*O*-benzyl ether.[4] For further synthetic studies we needed all pentodialdose mercaptal diastereoisomers. Therefore we elaborated a simple synthetic route to them. D-Glucose, D-galactose and D-mannose di(*n*-propyl)dithioacetals **1a**[5], **1b**[6] and **1c**[6] were monoisopropylidenated under kinetic control using 2,2-dimethoxypropane in acetone and pyridinium *p*-toluenesulfonate catalyst,[7] obtaining the 5,6-dioxolanes **2a**, **2b** and **2c**, respectively. Kinetic monoisopropylidenation of hexose mercaptals has been studied recently by Grindley et al.[8] utilizing 2-methoxypropene and *p*-toluenesulfonic acid catalyst. Our method seems to be more advantageous giving better yields and in several cases avoiding chromatographic separation. Subsequently, **2a**, **2b** and **2c** were benzylated with benzyl bromide (**3a**[9], **3b**, **3c**) and the dioxolane protective groups were removed hydrolytically giving rise to hexose mercaptal 2,3,4-tri-*O*-benzyl ethers **4a**, **4b** and **4c**, respectively. Finally, glycol cleaving reaction of the latter derivatives with lead(IV)acetate resulted in the formation of the desired compounds (**5a**, **5b**, **5c**).



(a) DMP, PyH^+OTs^- (10 mol%), acetone, rt, 1-1.5 h; (b) NaH, BnBr, DMF (dioxane, Bu_4NI (cat.) for **2c**), rt, 20 h; (c) $AcOH/H_2O$ (3:1), 60°C, 2.5 h; (d) $Pb(OAc)_4$, benzene, rt, 2 h.

EXPERIMENTAL

General: Melting points were determined on a Kofler melting point apparatus and are reported uncorrected. Thin-layer chromatography (TLC): precoated aluminum-backed plates (Silica gel $60F_{254}$, Merck), layer thickness: 0.2 mm. Column chromatography: Merck silica gel 60, 0.063 to 0.2 mm. Specific rotations were measured in chloroform at room temperature on a Perkin-Elmer 141 MC polarimeter. ^1H NMR (200 MHz): Bruker WP-200SY instrument, tetramethylsilane (TMS) as internal standard, $CDCl_3$ as solvent. Mass spectra were obtained using a VG-7035 GC/MS/D5 instrument (70 eV).

General procedure for isopropylidenation of 1a-c (2a-c)

To a well stirred suspension of 1 (20.0 g, 63.3 mmol) in dry acetone (250 mL) 2,2-dimethoxypropane (16 mL, 127.3 mmol) and pyridinium *p*-toluenesulfonate (1.5 g, 6.3 mmol) were added, and the reaction was monitored by TLC (hexane/EtOAc 1:1). After 1-1.5 h the reaction was complete, the reaction mixture became homogeneous. The reaction was quenched with saturated $NaHCO_3$ solution, the solvent was evaporated, and the residue taken up in CH_2Cl_2 (300 mL). The organic layer was washed with $NaHCO_3$ solution (3x50 mL), dried ($MgSO_4$), evaporated and coevaporated with toluene to give crude 2 which was purified as shown below.

5,6-*O*-Isopropylidene-D-glucose 1,1-di(*n*-propyl)dithioacetal (2a):

Column chromatography (hexane/EtOAc 7:3). Yield: 65%. - m.p. 55°C; $[\alpha]_D$ = +56.9 (*c* = 0.9); ^1H NMR: δ(ppm) = 0.96-1.10 (t, 6H, $SCH_2CH_2CH_3$), 1.38 and 1.42 (2s, 6H, CH_3), 1.64 (d, 1H, O*H*), 1.54-1.78 (m, 4H, $SCH_2CH_2CH_3$), 2.54-2.85 (m, 4H, $SCH_2CH_2CH_3$), 3.14 (d, 1H, O*H*), 3.62 (d, 1H, O*H*), 3.56-4.28 (m, 7H); MS (*m/z*): 354 [M^+], 163 [$(PrS)_2CH^+$]. Anal. Calcd for $C_{15}H_{30}O_5S_2$: C, 50.79; H, 8.46; S, 18.05. Found: C, 50.55; H, 8.40; S, 17.91.

5,6-*O*-Isopropylidene-D-galactose 1,1-di(*n*-propyl)dithioacetal (2b):

Crystallized from hexane. Yield: 70%. - m.p. 100-101°C, $[\alpha]_D$ = +73.0 (*c* = 1.1); ^1H NMR: δ(ppm)= 0.94-1.12 (2t, 6H, $SCH_2CH_2CH_3$), 1.38 and 1.45 (2s, 6H, CH_3), 1.54-1.78 (m, 4H, $SCH_2CH_2CH_3$), 2.48 (d, 1H, O*H*), 2.54 (d, 1H, O*H*), 2.58-2.80 (m, 4H, $SCH_2CH_2CH_3$), 3.35 (d, 1H, O*H*), 3.52-4.45 (m, 7H); MS (*m/z*): 354 [M^+], 163 [$(PrS)_2CH^+$]. Anal. Calcd for $C_{15}H_{30}O_5S_2$: C, 50.79; H, 8.46; S, 18.05. Found: C, 50.60; H, 8.39; S, 17.83.

5,6-*O*-Isopropylidene-D-mannose 1,1-di(*n*-propyl)dithioacetal (2c):

Crystallized from hexane. Yield: 92%. - m.p. 69°C, $[\alpha]_D$ = -7.9 (*c* = 1.0); ^1H NMR: δ(ppm)= 0.95-1.10 (t, 6H, $SCH_2CH_2CH_3$), 1.34 and 1.46 (s, 6H, CH_3), 1.54-1.76 (m, 4H, $SCH_2CH_2CH_3$), 2.56-2.78 (m, 4H, $SCH_2CH_2CH_3$), 2.88 (d, 2H, O*H*), 3.12 (d, 1H, O*H*), 3.84-4.34 (m, 7H); MS (*m/z*): 354 [M^+], 163 [$(PrS)_2CH^+$]. Anal. Calcd for $C_{15}H_{30}O_5S_2$: C, 50.79; H, 8.46; S, 18.05. Found: C, 50.67; H, 8.37; S, 18.10.

General procedure for benzylation of 2a-c (3a-c)[10]

To 50% NaH (3.36 g, 70.0 mmol) freed from oil a solution of 2 in dry DMF (50 mL) was added. When the evolution of H_2 was complete, benzyl bromide (8.3 mL, 70.0 mmol) was dropped to the reaction mixture and it was stirred at room temperature. After 20 h the solvent was evaporated under reduced pressure and the mixture was dissolved in CH_2Cl_2 (200 mL) and washed with water (3x50 mL). The organic layer was dried ($MgSO_4$), concentrated and the residue was purified by chromatography (hexane/EtOAc 19:1)

2,3,4-Tri-*O*-benzyl-5,6-*O*-isopropylidene-D-glucose 1,1-di(*n*-propyl)dithioacetal (3a):
Yield: 86%. - Oil, $[\alpha]_D$ = +18.5 (*c* = 1.2); ^{1}H NMR: δ(ppm)= 0.84-1.04 (2t, 6H, $SCH_2CH_2CH_3$), 1.28 and 1.44 (2s, 6H, CH_3), 1.42-1.62 (m, 4H, $SCH_2CH_2CH_3$), 2.38-2.76 (m, 4H, $SCH_2CH_2CH_3$), 3.70-4.30 m, 7H), 4.54-4,95 (m, 6H, CH_2Ph), 7.16-7.42 (m, 15H, aromatic); MS (*m/z*): 609 [M^+-CH_3], 549 [M^+-SPr], 163 [$(PrS)_2CH^+$]. Anal. Calcd for $C_{36}H_{48}O_5S_2$: C, 69.17; H, 7.58; S, 10.25. Found: C, 69.01; H, 7.50; S, 10.16.

2,3,4-Tri-*O*-benzyl-5,6-*O*-isopropylidene-D-galactose 1,1-di(*n*-propyl)dithioacetal (3b):
Yield: 75%. - Oil, $[\alpha]_D$ = -6.8 (*c* = 1.0); ^{1}H NMR: δ(ppm)= 0.88-1.04 (2t, 6H, $SCH_2CH_2CH_3$), 1.36 and 1.42 (2s, 6H, CH_3), 1.46-1.66 (m, 4H, $SCH_2CH_2CH_3$), 2.52-2.76 (m, 4H, $SCH_2CH_2CH_3$), 3.60-4.40 (m, 7H), 4.60-4.88 (m, 6H, CH_2Ph), 7.18-7.42 (m, 15H, aromatic); MS (*m/z*): 609 [M^+-CH_3], 163 [$(PrS)_2CH^+$]. Anal. Calcd for $C_{36}H_{48}O_5S_2$: C, 69.17; H, 7.68; S, 10.25. Found: C, 68.95; H, 7.70; S, 10.26.

2,3,4-Tri-*O*-benzyl5,6-*O*-isopropylidene-D-mannose 1,1-di(*n*-propyl)dithioacetal (3c):
Yield: 82%. - Oil, $[\alpha]_D$ = -5.1 (*c* = 1.1); ^{1}H NMR: δ(ppm)= 0.82-1.04 (2t, 6H, $SCH_2CH_2CH_3$), 1.30 and 1.42 (2s, 6H, CH_3), 1.46-1.68 (m, 4H, $SCH_2CH_2CH_3$), 2.50-2.78 (m, 4H, $SCH_2CH_2CH_3$), 3.35-4.43 (m, 7H), 4.43-5.16 (m, 6H, CH_2Ph), 7.14-7.40 (m, 15H, aromatic); MS (*m/z*): 549 [M^+-SPr], 163 [$(PrS)_2CH^+$]. Anal. Calcd. for $C_{36}H_{48}O_5S_2$: C, 69.17; H, 7.68; S, 10.25. Found: C, 69.20; 7.75; S, 10.38.

Hydrolysis of isopropylidene groups of 3a-c (4a-c)

3 (5.0 g, 8.0 mmol) was stirred for 2.5 h at 60°C in 75% aqueous acetic acid (75 mL). The reaction mixture was evaporated and coevaporated three times with toluene. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with saturated $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and evaporated to dryness to give crude 4 which was pure enough for the next reaction step. Analytically pure material was isolated by column chromatography (hexanes/EtOAc 4:1).

2,3,4-Tri-*O*-benzyl-D-glucose 1,1-di(*n*-propyl)dithioacetal (4a):
Yield: 79%. - m.p. 86-7°C, $[\alpha]_D$ = +17.5 (*c* = 1.0); ^{1}H NMR: δ(ppm)= 0.88-1.02 (2t, 6H, $SCH_2CH_2CH_3$), 1.45-1.64 (m, 4H, $SCH_2CH_2CH_3$), 2.48-2.68 (m, 4H, $SCH_2CH_2CH_3$), 1.67-2.10 (br, 1H, O*H*), 3.25-3.54 (br, 1H, O*H*), 5.54-4.34 (m, 7H) 4.46-4.88 (m, 6H, CH_2Ph), 7.20-7.44 (m, 15H, aromatic); MS (*m/z*): 566 [M^+-H_2O], 163 [$(PrS)_2CH^+$]. Anal. Calcd for $C_{33}H_{44}O_5S_2$: C, 67.76; H, 7.53; S, 10.95. Found: C, 67.82; H, 7.50; S, 11.08.

2,3,4-Tri-*O*-benzyl-D-galactose 1,1-di(*n*-propyl)dithioacetal (4b):
Yield: 98%. - Light yellow oil, $[\alpha]_D$ = -16.7 (*c* = 1.2); ^{1}H NMR: δ(ppm)= 0.82-1.06 (2t, 6H, $SCH_2CH_2CH_3$), 1.45-1.75 (m, 4H, $SCH_2CH_2CH_3$), 2.20-2.35 (t, 1H, O*H*), 2.50-2.78 (m, 4H, $SCH_2CH_2CH_3$), 3.48 (d, 1H, O*H*), 3.44-4.44 (m, 7H) 4.45-4.94 (m, 6H, CH_2Ph), 7.18-7.45 (m, 15H, aromatic); MS (*m/z*): 509 [M^+-SPr], 163 [$(PrS)_2CH^+$]. Anal. Calcd for $C_{33}H_{44}O_5S_2$: C, 67.76; H, 7.53; S, 10.95. Found: C, 67.60; H, 7.50; S, 10.81.

2,3,4-Tri-*O*-benzyl-D-mannose 1,1-di(*n*-propyl)dithioacetal (4c):
Yield: 99%. - Light yellow oil, $[\alpha]_D$ = -1.9 (*c* = 1.0); ^{1}H NMR: δ(ppm)= 0.88-1.05 (t, 6H, $SCH_2CH_2CH_3$), 1.46-1.70 (m, 4H, $SCH_2CH_2CH_3$), 1.94-2.06 (t, 1H, O*H*), 2.50-2.70 (m, 4H, $SCH_2CH_2CH_3$), 2.94 (d, 1H, O*H*), 3.60-4.25 (m, 7H), 4.46-5.12 (m, 6H, CH_2Ph), 7.15-7.42 (m, 15H, aromatic); MS (*m/z*): 509 [M^+-SPr], 163 [$(PrS)_2CH^+$]. Anal. Calcd for $C_{33}H_{44}O_5S_2$: C, 67,76; H, 7.53; S, 10.95. Found: C, 67.45; H, 7.39; S, 10.67.

General procedure for cleavage of diols 4a-c (5a-c)

To a well stirred solution of 4 (4.2 g, 7.2 mmol) in dry benzene (50 mL) lead(IV)acetate (3.2 g, 7.2 mmol) was added. After 2 h the reaction mixture was filtered through a Celite pad, washed with benzene (2x10 mL). The combined organic layers were washed with $NaHCO_3$ solution (3x10 mL) and dryed ($MgSO_4$). The solvent was removed and the residue was purified by column chromatography (hexane/EtOAc 4:1) to afford 5 as an oil.

2,3,4-Tri-*O*-benzyl-D-*xylo*-pentodialdose 1,1-di(*n*-propyl)dithioacetal (5a):

Yield: 62%. - Oil, $[\alpha]_D$ = -17.0 (*c* = 1.4); ^1H NMR: δ(ppm)= 0.85-1.05 (2t, 6H, $SCH_2CH_2CH_3$), 1.38-1.68 (m, 4H, $SCH_2CH_2CH_3$), 2,48-2.66 (m, 4H, $SCH_2CH_2CH_3$), 3.30-3.98 (m, 4H), 4.35-4.88 (m, 6H, CH_2Ph), 7.18-7.42 (m, 15H, aromatic), 9.72 (s, 1H, *CH*O); MS (*m/z*): 552 [M^+], 477 [M^+-SPr], 163 [$(PrS)_2CH^+$]. Anal. Calcd for $C_{32}H_{40}O_4S_2$: C, 69.47; H, 7.23; S, 11.58. Found: C, 69.23; H, 7.20; S, 11.42.

2,3,4-Tri-*O*-benzyl-L-*arabino*-pentodialdose 1,1-di(*n*-propyl)dithioacetal (5b):

Yield: 71%. - Oil, $[\alpha]_D$ = -1.0 (*c* = 1.1); ^1H NMR: δ(ppm)= 0.88-1.02 (t, 6H, $SCH_2CH_2CH_3$), 1.45-1.68 (m, 4H, $SCH_2CH_2CH_3$), 2.50-2.68 (m, 4H, $SCH_2CH_2CH_3$), 3.90-4.38 (m, 4H), 4.45-4.94 (m, 6H, CH_2Ph), 7.22-7.38 (m, 15H, aromatic), 9.70 (s, 1H, *CH*O); MS (*m/z*): 477 [M^+-SPr], 163 [$(PrS)_2CH^+$]. Anal. Calcd for $C_{32}H_{40}O_4S_2$: C, 69.47; H, 7.23; S, 11.58. Found: C, 69.17; H, 7.11; S, 11.54.

2,3,4-Tri-*O*-benzyl-D-*lyxo*-pentodialdose 1,1-di(*n*-propyl)dithioacetal (5c):

Yield: 96%. - Oil, $[\alpha]_D$ = -45.2 (*c* = 1.0); ^1H NMR: δ(ppm)= 0.88-1.02 (2t, 6H, $SCH_2CH_2CH_3$), 1.45-1.68 (m, 4H, $SCH_2CH_2CH_3$), 2.48-2.70 (m, 4H, $SCH_2CH_2CH_3$), 4.02-4.38 (m, 4H), 4.38-5.05 (m, 6H, CH_2Ph), 7.20-7.40 (m, 15H, aromatic), 9.65 (s, 1H, *CH*O); MS (*m/z*): 477 [M^+-SPr], 163 [$(PrS)_2CH^+$]. Anal. Calcd for $C_{32}H_{40}O_4S_2$: C, 69.47; H, 7.23; S, 11.58. Found: C, 69.66; H, 7.40; S, 11.71.

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