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3,6-Thioanhydro Sugars as Important Key Intermediates in the Enantiospecific Synthesis of Chiral Polyhydroxythiolanes[1]

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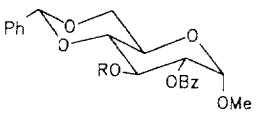
Abstract: Methyl 3,6-thioanhydro-α-D-glucopyranoside (**5**) was obtained in seven steps from the commercially available methyl α-D-glucopyranoside. Transformation of **5** into (2*R*,3*R*,4*S*)-3,4-dihydroxy-2-[(*S*)-1,2-dihydroxyethyl]thiolane (**9**) was achieved by acid hydrolysis and subsequent reduction without isolation of its formyl derivative (**8**).

The use of thioanhydro sugars as glycosyl donors in the synthesis of oligosaccharides containing deoxysugar units, has been recently reviewed by Tatsuta *et al.*[2], where the authors indicated the significance of these rigid systems not only in the stereocontrol of the glycosidation but in the regiospecificity of the deoxy functions, as well. On the other hand, the chemistry of the chiral polyhydroxythiolanes is an almost unexplored subject in the huge field of the sulphur heterocyclic chemistry. To the best of our knowledge, few examples are found in the literature[3] concerning the synthesis of these compounds. Polyhydroxythiolanes are in fact the thioanalogues of the important glycosidase inhibitors polyhydroxypyrrolidines[4], and finally, the close relationship that exists between chirality and biological activity is well known, thus the interest of our group in the enantiospecific synthesis of the aforementioned compounds using 3,6-thioanhydrohexosides as starting chiral templates.

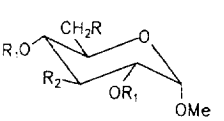
Although methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-methanesulfonyl-α-*D*-glucopyranoside (**2**) has been previously reported[5], our synthetic approach differs in the initial partial benzoylation at C-2 in which we used the highly regioselective Munavu method[6] followed by methanesulfonylation at C-3. The choice of the methanesulfonyl group will be crucial for the next step, since the *p*-toluenesulfonyl analogue would give a mixture of products by the radical bromination of the methyl group, in addition the NMR data for **2** are now included. Reaction of **2** with NBS yielded methyl 2,4-di-*O*-benzoyl-6-bromo-6-deoxy-3-*O*-methanesulfonyl-α-*D*-glucopyranoside (**3**) as could be demonstrated from its analytical and spectroscopic data. Reaction of **3** with potassium thioacetate in DMF proceeded smoothly and regiospecifically at C-6 to produce the corresponding 6-acetylthio-6-deoxy derivative **4**, since no nucleophilic substitution product at C-3 was detected. That

[1]Thioanhydro Sugar derivatives, Part III. For Part II, see Ref. 1.

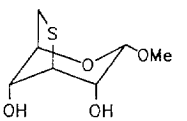
substitution at C-6 had occurred, was clearly demonstrated by the up-field shifts of the resonance signals showed by H-6,6' and C-6 in its NMR spectra respect to those in **3** (see Experimental).



1 R = H
2 R = Ms



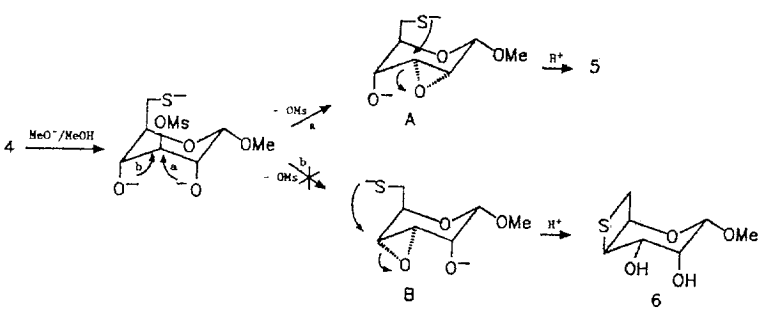
3 R = Br; R_1 = Bz; R_2 = OMs
4 R = SAc; R_1 = Bz; R_2 = OMs
7 R = R_1 = R_2 = H



5

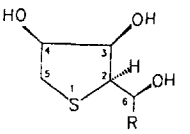
Treatment of **4** with sodium methoxide in an organic solvent (benzene or dichloromethane) caused the loss of the protecting acyl groups and a ring closure to afford methyl 3,6-thioanhydro-α-*D*-glucopyranoside (**5**). Formation of **5** must take place *via* 2,3-anhydroglycoside intermediate (**A**) (see Scheme I) formed by a regiospecific internal nucleophilic displacement of the mesylate by the alkoxide ion produced in the methanolysis of the benzoyl group at C-2, followed by a regiospecific diaxial opening of the oxirane ring at C-3 by the thiolate ion located at C-6 concomitant with a favourable 5-*exo*-tet[7] ring closure. Formation of intermediate epoxide **B** seems to be precluded since no compound **6** was detected as a product of the reaction. In a related example[1], involving cyclisation of a 6-thio-3,4(α)-epoxide, where the position of the epoxide ring was unambiguously knwon, only a 4,6-thioanhydrosugar was formed.

Scheme I



The structure of **5** was established on the basis of its analytical and spectroscopic data, but due to the all equatorial dispositions for H-2,3,4,5 some troubles were found in the assignments of their resonance signals which could be solved by running its 2D ^{1}H-^{1}H-homo and ^{13}C-^{1}H-heteronuclear shift-correlation spectra. In addition, desulphurization of **5** by Raney nickel to the well known methyl 3,6-dideoxy-α-*D*-*ribo*-pyranoside[8] (methyl α-*D*-paratoside) (**7**), also assured the proposed structure for **5**.

When methanolysis of **4** was performed in dichloromethane with a more concentrated (3 *M*) sodium methoxide solution a minor product was isolated but its spectroscopic data have not allowed the elucidation of its structure so far, thus further investigations are being carried out and will be communicated in due course. Finally, hydrolysis of **5** and reduction of the not isolated aldehyde **8** gave the required (2*R*,3*R*,4*S*)-3,4-dihydroxy-2-[(*S*)-1,2-dihydroxyethyl]thiolane (**9**).



8 R = CHO
9 R = CH_2OH

Experimental

General: Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300, and WP-80 WC spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin-Elmer 782 instrument and mass spectra with a Hewlett-Packard HP-5988-A mass spectrometer. Optical rotations were measured for solutions in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated silica gel 60 F_{254} aluminium sheets and detection by charring with H_2SO_4. Column chromatography was performed on silica gel (Merck, 7734). The noncrystalline compounds, for which elemental analyses were not obtained were shown to be homogeneous by chromatography and characterised by NMR and mass spectrometry.

Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-3-*O*-methanesulfonyl-α-*D*-glucopyranoside (2)

To an ice-water and stirred solution of methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-*D*-glucopyranoside (**1**)[6] (8.1 g, 21 mmol) in dry pyridine (25 mL) that contained DMAP (150 mg) methanesulfonyl chloride (2.3 mL, 30 mmol) was added dropwise and the mixture kept at room temperature for 24 h. TLC (Cl_2CH_2) then revealed the presence of a sligltly faster-running compound. The mixtured was poured into ice-water, extracted with Cl_2CH_2 (3 x 20 mL) and the extracts washed with aqueous 10% hydrochloric acid, water, saturated $NaHCO_3$ solution, water and then concentrated to give crystalline **2** (8.1 g, 78%), m.p. 162-164°C (from Cl_2CH_2), $[\alpha]_D^{26}$: +118.5 (c 1.4). [lit.[5], m.p. 169-171°C (from acetone-ether-pentane), $[\alpha]_D$: +123 (c 1.06]; ν_{max}^{KBr} 3030 and 3088 (C-H, aromatic), 2941 and 2879 (C-H), 1726 (C=O, benzoate), 716 and 698 cm^{-1} (aromatic). NMR data: ^1H, δ 8.20-8.15 and 7.60-7.35 (2 m, 10 H, 2 Ph), 5.59 (s, 1 H, C<u>H</u>Ph), 5.29 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9.7 Hz, H-3), 5.21 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.09 (dd, 1 H, H-2), 4.35 (dd, 1 H, $J_{5,6eq}$ 4.6, $J_{6ax,6eq}$ 10.2 Hz, H-6*eq*), 3.98 (dt, 1 H, H-5), 3.83 (t, 1 H, $J_{4,5}$ 9.4 Hz, H-4), 3.83 (t, 1 H, $J_{5,6ax}$ 10.3 Hz, H-6*ax*), 3.39 (s, 3 H, OMe), and 2.93 (s, 3 H, OMs); ^{13}C, δ 165.93 (C=O), 136.60, 133.61, 130.23, 129.42, 128.95, 128.56, 128.45, and 126.08 (2 Ph), 101.91 (<u>C</u>HPH), 97.91 (C-1), 79.01 (C-4), 77.58 (C-3), 71.81 (C-2),

68.81 (C-6), 62.46 (C-5), 55.67 (OMe), and 38.89 (OMs).

Methyl 2,4-di-*O*-benzoyl-6-bromo-6-deoxy-3-*O*-methanesulfonyl-α-*D*-glucopyranoside (3)

A stirred suspension of **2** (637 mg, 1.37 mmol), NBS (280 mg, 1.57 mmol) and $BaCO_3$ (560 mg, 2.83 mmol) in dry CCl_4 (20 mL) was heated under reflux and illuminated for 30 min. During this time the initially red solution became colourless. The reaction mixture was filtered and the filtrate washed with 10% aqueous sodium thiosulfate and brine, then concentrated. Column chromatography (1:2 EtOAc-hexane) of the residue gave **3** (619 mg, 83%) as a colourless solid foam; $[\alpha]_D^{26}$: +65 (c 1.7); ν_{max}^{KBr} 3066 and 3036 (C-H, aromatic), 2945 and 2847 (C-H), 1739 and 1733 (C=O, benzoate), 1357, 1264, 1200, 1179, and 1097 (C-O-C), and 711 cm^{-1} (aromatic). NMR data: ^1H, δ 8.15-8.08 and 7.63-7.42 (2 m, 10 H, relative intensity 2:3, 2 Bz), 5.55-5.46 (m, 1 H, H-3), 5.37 (t, 1 H, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4), 5.23-5.18 (m, 2 H, H-1,2), 4.18 (ddd, 1 H, H-5), 3.54 (dd, 1 H, $J_{5,6}$ 3, $J_{6,6'}$ 11.3 Hz, H-6), 3.48 (s, 3 H, OMe), 3.47 (dd, 1 H, $J_{5,6'}$ 7.5 Hz, H-6'), and 2.75 (s, 3 H, OMs); ^{13}C, δ 165.62 and 165.32 (2 PhCO), 133.97, 133.78, 130.21, 130.19, 128.91, 128.74, and 128.67 (2 COPh), 96.96 (C-1), 76.88 (C-3), 71.24 (C-2), 71.03 (C-4), 69.22 (C-5), 55.89 (OMe), 38.94 (OMs), and 31.12 (C-6). Anal. Calcd. for $C_{22}H_{23}BrO_9S$: C, 48.63; H, 4.26; S, 5.90. Found: C, 48.93; H, 4.28; S, 5.46.

Methyl 6-*S*-acetyl-2,4-di-*O*-benzoyl-6-deoxy-3-*O*-methanesulfonyl-6-*thio*-α-*D*-glucopyranoside (4)

To a stirred solution of **3** (5.26 g, 9.7 mmol) in dry DMF (15 mL) was added potassium thioacetate (1.1 g, 9.6 mmol) portionwise, under argon, and the mixture left at room temperature for 1 1/2 h. TLC (1:1 EtOAc-hexane) then revealed a new compound of slightly lower mobility. The solvent was evaporated and the residue in CH_2Cl_2 (25 mL) washed with brine and water, then concentrated. Column chromatography (1:4 → 1:2 EtOAc-hexane) of the residue gave **4** (4.56 g, 88%) as a solid foam; $[\alpha]_D^{25}$: +115 (c 0.6); ν_{max}^{KBr} 3068 (C-H, aromatic), 2984, 2942, and 2847 (C-H), 1740 and 1732 (C=O, benzoate), 1697 (C=O, thioacetate), 1373, 1358, 1264, 1179, 1108, 1047, 960, 911, and 841 (C-O-C and C-S-C), and 713 cm^{-1} (aromatic). NMR data: ^1H, δ 8.16-8.11 and 7.63-7.43 (2 m, 10 H, relative intensity 2:3, 2 Bz), 5.45 (t, 1 H, $J_{2,3} = J_{3,4} = 9.4$ Hz, H-3), 5.35 (t, 1 H, $J_{4,5}$ 9.4 Hz, H-4), 5.17 (dd, 1 H, $J_{1,2}$ 3.7 Hz, H-2), 5.13 (d, 1 H, H-1), 4.07 (ddd, 1 H, H-5), 3.41 (s, 3 H, OMe), 3.34 (dd, 1 H, $J_{5,6}$ 3.1, $J_{6,6'}$ 14.2 Hz, H-6), 3.05 (dd 1 H, $J_{5,6'}$ 8 Hz, H-6'), 2.74 (s, 3 H, OMs), and 2.32 (s, 3 H, SAc); ^{13}C, 194.41 (COMe), 165.70 and 165.57 (2 COPh), 133.74, 133.69, 130.25, 130.15, 129.14, 129.05, 128.69, and 128.62 (2 COPh), 96.96 (C-1), 77.22 (C-3), 71.44 (C-2), 71.36 (C-4), 68.74 (C-5), 55.66 (OMe), 38.94 (OMs), 30.46 (COMe), and 30.42 (C-6). Anal. Calcd. for $C_{24}H_{26}O_{10}S_2$; C, 53.52; H, 4.87; S, 11.91. Found: C, 53.38; H, 4.77; S, 11.79.

Methyl 3,6-*thioanhydro*-α-*D*-glucopyranoside (5)

a).- To a stirred solution of **4** (4.33 g, 8.04 mmol) in dry Cl_2CH_2 (20 mL), 3 *M* methanolic sodium methoxide (8 mL) was added dropwise, and the mixture maintained at room temperature for 30 min. TLC

(2:1 EtOAc-hexane) of the deep brown solution showed the absence of **4** and the presence of two slower-running products. The mixtures was neutralised with acetic acid, concentrated and the residue extracted with EtOAc. The combined extracts were concentrated to give a residue that was chromatographed (4:1 ether-hexane → ether) to afford first syrupy **5** (662 mg, 45.6%) that crystallised on standing, mp 83-84°C (from ether); $[\alpha]_D^{25}$: +11.6 (c 1); ν_{max}^{film} 3414 (OH), 2942 (C-H), 1445, 1218, 1141, 1087, 1083, 1020, and 873 cm^{-1} (C-O-C and C-S-C). NMR data (D_2O exchanged): ^1H, δ 5.13 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 4.46 (bt, 1 H, H-5), 3.99 (ddd, 1 H, $J_{3,4}$ 4, $J_{4,5}$ 3, $J_{2,4}$ 1.2 Hz, H-4), 3.90 (m, 1 H, H-2), 3.60 (s, 3 H, OMe), 3.55 (bt, 1 H, $J_{2,3}$ 4 Hz, H-3), 3.01 (dd, 1 H, $J_{5,6exo}$ 4.5, $J_{6exo,6endo}$ 12.3 Hz, H-6*exo*), and 2.91 (d, 1 H, H-6*endo*); ^{13}C, δ 96.12 (C-1), 76.52 (C-5), 75.47 (C-4), 71.73 (C-2), 57.01 (OMe), 42.42 (C-3), and 30.19 (C-6). Mass spectrum: *m/z* 194 (1.1%, M^++2), 193 (1.6, M^++1), 192 (17.4, M^+), 174 (11.7, M^+-H_2O), 160 (18.8, M^+-MeOH), 132 (14.9), 114 (13.3), 88 (52.4), 86 (42.1), 85 (85.5), 73 (66.8), and 45 (100). Anal. Calcd. for $C_7H_{12}O_4S$: C, 43.73; H, 6.29. Found: C, 43.15; H, 6.31.

Eluted second was unexpected syrupy product (255 mg, 17.6%) that was not investigated.

b).- To a stirred solution of **4** (8 g, 14 mmol) in dry benzene (25 mL), 1 *M* methanolic sodium methoxide (28 mL) was added dropwise, and the mixture maintained at room temperature for 2 h. TLC (2:1 EtOAc-hexane) then showed only the presence of **5**. Work-up of the reaction mixture as above afforded **5** (2.17 g, 80.4%).

Methyl 3,6-dideoxy-α-*D-ribo*-hexopyranoside (7)

A solution of **5** (60 mg, 0.3 mmol) in anhydrous ethanol (10 mL) was refluxed with Raney-nickel (4 g), for 20 min. TLC (EtOAc) then revealed the presence of a new slower-running product. The catalyst was filtered off, washed with ethanol and the combined filtrate and washing concentrated. Column chromatography (30:1 ether-methanol) gave syrupy **7** (33 mg, 65%), $[\alpha]_D^{25}$: +153 (c 1.7). NMR data: ^1H, δ 4.56 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 3.74-3.61 (bm, 1 H, H-2), 3.47 (dq, 1 H, $J_{4,5}$ 9.2, $J_{5,6}$ 6.3 Hz, H-5), 3.41 (s, 3 H, OMe), 3.24 (ddd, 1 H, $J_{3ax,4}$ 11.1, $J_{3eq,4}$ 4.5 Hz, H-4), 2.29 (bs, 2 H, HO-2,4), 2.15 (dt, 1 H, $J_{2,3eq}$ 4.7, $J_{3ax,3eq}$ 11.5, Hz, H-3*eq*), 1.62 (q, 1 H, $J_{2,3ax}$ 11.5 Hz, H-3*ax*), and 1.22 (d, 3 H, H-6,6,6); ^{13}C, δ 98.43 (C-1), 70.77 (C-5), 68.71 and 67.64 (C-2,4), 55.07 (OMe), 36.94 (C-3), and 17.38 (C-6).

(2*R*,3*R*,4*S*)-3,4-dihydroxy-2-[(*S*)-1,2-dihydroxyethyl]thiolane (9)

A solution of **5** (400 mg, 2.1 mmol) in aqueous 75% trifluoroacetic acid (9 mL) was left at room temperature overnight. TLC (5:1 ether-methanol) then revealed a slower running compound. The mixture was concentrated and the residue disolved in dry methanol (10 mL), neutralised (K_2CO_3) and filtered. The filtrate was treated with $NaBH_4$ (200 mg) portionwise. After 4 h TLC (5:1 ether-methanol) then showed the presence of a slower running product. The mixture was neutralised with acetic acid, filtered, cocentrated and the residue subjected to column chromatography (10:1 ether-methanol) to yield pure **9** (300 mg, 79%) as a syrup that crystallised on standing, m.p. 128-130°C, $[\alpha]_D^{25}$: -49 (c 0.26, methanol). NMR data (Methanol-d_4): ^1H, δ 4.20-4.13 (m,

2 H, H-3,4), 3.94 (dt, 1 H, $J_{2,6}$ 6.6, $J_{6,7} = J_{6,7'} = 5.5$ Hz, H-6), 3.60 (dd, 1 H, $J_{7,7'}$ 11.2 Hz, H-7), 3.55 (dd, 1 H, H-7'), 3.52 (dd, 1 H, $J_{2,3}$ 4.8 Hz, H-2), and 2.88-2.78 (m, 2 H, H-5,5') ; ^{13}C, δ 77.14 (C-6), 75.81 (C-3), 72.91 (C-4), 65.70 (C-7), 51.42 (C-2), and 33.23 (C-5). Anal. Calcd. for $C_6H_{12}O_4S$: C, 39.99; H, 6.71; S, 17.79. Found: C, 39.73; H, 6.82; S, 18.07.

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