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Thioanhydro sugars. Part 9: Enantiospecific synthesis of a polyhydroxythiolane, key intermediate for the preparation of glycosidase inhibitors bearing inner thiosulfonium salt†

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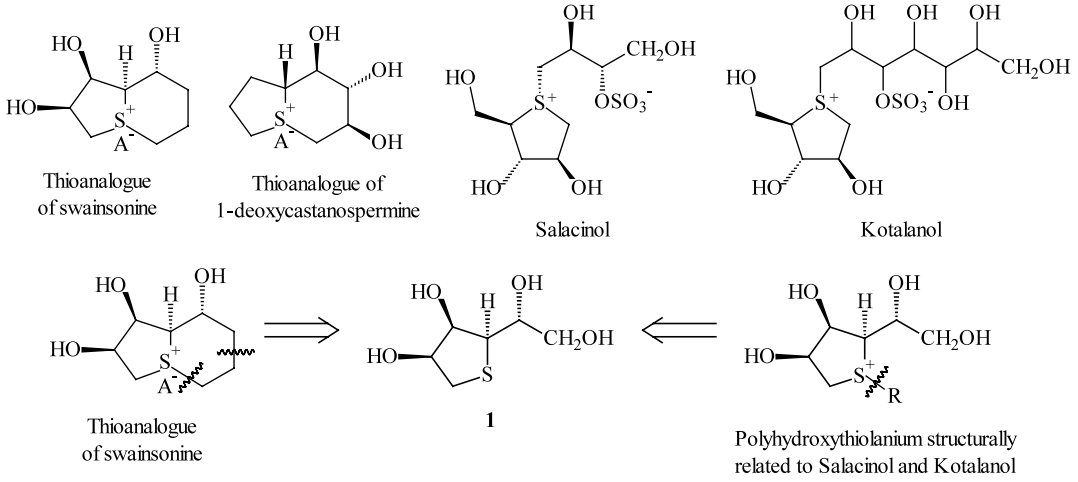
Abstract—(2*R*,3*R*,4*S*)-3,4-Dihydroxy-2-[(*R*)-1,2-dihydroxyethyl]thiolane (1,4-anhydro-4-thio-D-mannitol), **1** has been prepared from methyl 4,6-*O*-benzylidene-α-D-altropyranoside **2** in seven steps, the latter being readily available from commercial methyl α-D-glucopyranoside.

1. Introduction

In relation to the general interest of our group on the use of simple sugar derivatives as starting chiral templates for the stereospecific synthesis of complex molecules with biological activity (glycosidase inhibitors, pheromones, toxins, etc.), we have reported on the enantiospecific synthesis of compounds bearing the polyhydroxythiane,[1,2] thiolane[3] and other related moieties,[4] some of them being used as key intermediates for the stereocontrolled synthesis of a thioanalogue of swainsonine.[3c]

Despite the lack of reported work in the literature on these types of substances, over the last 2 years, different groups have reported, on the stereospecific synthesis of polyhydroxythiolanes[5] and thioanalogues of castanospermine,[6] These works mostly followed the isolation of the potent sucrase inhibitors salacinol[7] and kotalanol,[8] which bear a sulfonium salt-containing heterocycle in their skeletons, from *Salacia reticulata* Wight (Celastaceae), an antidiabetic treatment in popular Indian Ayurvedic traditional medicine.

The retrosynthetic analysis shown below, clearly indicated that (2*R*,3*R*,4*S*)-3,4-dihydroxy-2-[(*R*)-1,2-dihydroxyethyl]thiolane (1,4-anhydro-4-thio-D-mannitol) **1** could be an excellent chiral key intermediate for building-up in a stereocontrolled manner the skeleton of the showed target molecules (the stereochemistry of



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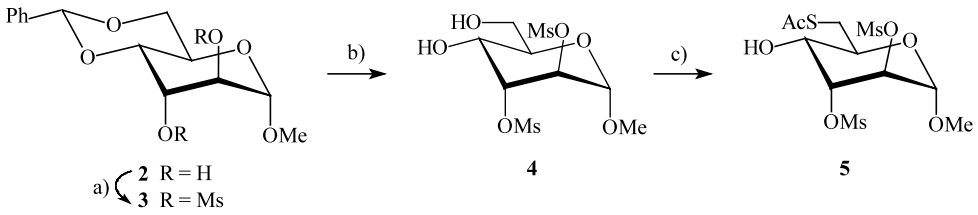
thioswainsonine totally matches that of **1**, only being necessary a chain-lengthening at the hydroxymethyl group followed by cyclisation.[3c] In the case of salacinol and kotalanol, structurally related stereoisomers could be prepared for future SAR analyses. Accordingly, we report herein on the enantiospecific synthesis of **1** from a suitably protected derivative of methyl α-D-altropyranoside, easily prepared from commercially available methyl α-D-glucopyranoside.

2. Results and discussion

According to Scheme 1 below, treatment of methyl 4,6-*O*-benzylidene-α-D-altropyranoside[9] **2** with methanesulfonyl chloride in dichloromethane gave the corresponding 2,3-di-*O*-methanesulfonyl derivative **3** in 80% yield. Compound **3** was easily transformed (80–83% yield) into methyl 2,3-di-*O*-methanesulfonyl-α-D-altropyranoside **4**, by removal of the 4,6-*O*-benzylidene group, and subsequently allowed to react under the thio-Mitsunobu reaction conditions[10] to afford, fast and regioselectively at C(6), methyl 6-*S*-acetyl-2,3-di-*O*-methanesulfonyl-6-thio-α-D-altropyranoside **5**.

The structure of **5** was determined on the basis of its analytical and spectroscopic data (see Tables 1 and 2 for the ^{1}H and ^{13}C NMR spectra), where marked upfield shifts were seen for H(6,6′) and C(6) with respect to their positions in **4**, indicating that an O→S interchange had occurred.



Scheme 1. *Reagents and conditions*: (a)MsCl/Et_3N/CH_2Cl_2; (b) AcOH/H_2O or I_2/MeOH; (c) Ph_3P/DEAD/AcSH.

Table 1. ^{1}H NMR chemical shifts (δ) and J (Hz) values for compound **1**, **3**–**7**, **9**, and **11**

Compound	H-1	H-1′	H-2	H-3	H-4	H-5	H-6	H-6′	OMe	OMs
1[a]	2.89t, $J_{1,2}=9.7$, $J_{1,1'}=9.7$	2.82dd, $J_{1',2}=6.7$	4.16ddd, $J_{2,3}=3.1$	4.25t	3.35dd, $J_{3,4}=3.7$, $J_{4,5}=9.7$	3.87ddd	3.60dd, $J_{5,6}=2.8$, $J_{6,6'}=11.6$	3.40dd, $J_{5,6'}=6.0$	–	–
3[b]	4.83s	–	4.88d, $J_{2,3}=3.0$	5.02t	4.03dd, $J_{3,4}=3.2$, $J_{4,5}=9.8$	4.24dt	4.36dd, $J_{5,6}=5.3$, $J_{6,6'}=10.4$	3.79t, $J_{5,6'}=10.4$	3.44s	3.14s, 2.99s
4[c]	4.82s	–	4.81d, $J_{2,3}=3.5$	4.96dd, $J_{3,4}=5.8$	3.91–3.74m	4.08ddd, $J=3.6$, $J=6.7$, $J=8.4$	3.91–3.74m		3.39s	3.22s, 3.16s
5[d]	4.75bs	–	4.81dd, $J_{1,2}=1.4$, $J_{2,3}=3.8$	4.91t, $J_{3,4}=3.7$	4.06bquin	3.78ddd, $J_{4,5}=9.5$	3.30dd, $J_{5,6}=5.3$, $J_{6,6'}=14.6$	3.25dd, $J_{5,6'}=3.9$	3.40s	3.14s, 3.12s
6[e]	4.71d, $J_{1,2}=6.9$	–	4.66dd, $J_{2,3}=3.0$	3.33dd, $J_{3,4}=4.7$	4.24bt	4.04m	2.81dd, $J_{5,6}=4.5$	2.58d, $J_{6,6'}=12.3$	3.27s	2.82s
7[f]	4.73d, $J_{1,2}=2.3$	–	4.69dd, $J_{2,3}=4.4$	4.86t, $J_{3,4}=3.8$	3.74ddd, $J_{4,5}=9.4$, $J_{4,OH}=6.6$	3.97dt, $J_{5,6}=2.8$	3.21dd	2.94dd, $J_{5,6'}=9.8$, $J_{6,6'}=13.8$	3.35s	3.28s, 3.21s
9[g]	4.65d, $J_{1,2}=6.6$	–	4.22m	3.47t, $J_{2,3}=4.0$	4.44dd, $J_{3,4}=4.4$, $J_{4,5}=2.9$	3.95m	3.05dd, $J_{5,6}=4.7$, $J_{6,6'}=12.6$	2.84d	3.54s	–
11[h]	3.13–3.05m		5.29–5.21m	5.70t, $J_{2,3}=3.6$	3.83dd, $J_{3,4}=4.0$, $J_{4,5}=10.7$	5.29–5.21m	4.40dd, $J_{5,6}=2.4$, $J_{6,6'}=12.5$	4.00dd, $J_{5,6'}=5.6$	–	–

[a] MeOH-d_4 (sugar numbering).
[b] Signal for PhC*H* at 5.63s.
[c] Me_2CO-d_6, signal for OH-4 at 4.70d (J 6.7 Hz).
[d] Signal for *Me*COS and HO-4 at 2.40s and 3.69d (J 6.2 Hz), respectively.
[e] Signal for OH-4 at 4.48d (J 4.6 Hz).
[f] DMSO-d_6.
[g] Signals for HO-2,4 at 2.92bs and 2.40dd.
[h] Signals (sugar numbering) for OAc at 2.10s, 2.08s, 2.02s, and 1.99s.

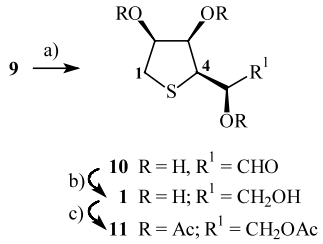
Table 2. ^{13}C NMR chemical shifts (δ) for compound **1**, **3**–**7**, **9**, and **11**

Compound	C-1	C-2	C-3	C-4	C-5	C-6	OMe	OMs	Others
1	33.42	73.37	74.79	49.60	77.49	65.79	–	–	–
3	99.05	75.20*	73.65*	73.23*	56.01	68.97	58.10	38.60, 38.18	Ph*C*H, 102.32
4	99.68	77.81*	76.81*	71.17*	64.83	62.34	55.50	38.30, 38.16	–
5	98.72	76.11*	75.21*	67.06*	64.99*	30.77	55.87	38.53, 38.21	AcS, 198.52, 30.63
6	98.73	76.81	48.51	76.32	75.09	29.83	56.32	37.71	–
7	97.59	76.35[a]	75.32[a]	67.66[b]	65.44[b]	39.80	55.10	37.88, 37.57	–
9	103.10	67.66	50.40	76.47	75.87	30.26	57.52	–	–
11	30.72	74.69*	71.69*	44.46	70.33*	63.70	–	–	AcO, 170.02, 170.01, 20.77, 20.74, 20.65

*,[a,b] Interchangeable assignments.

Treatment of **5** with sodium methoxide (see Scheme 2) effected clean removal of the *S*-acyl group producing a mercaptide anion, which promoted an intramolecular and regioselective nucleophilic attack at C(3) to afford methyl 2-*O*-methanesulfonyl-3,6-thioanhydro-α-D-mannopyranoside **6**, according to its chiroptical, analytical and spectroscopic data (see Tables 1 and 2). When the reaction was scaled up to multigrams, the corresponding *S*-deacylation product **7** could be isolated in minute quantity. The structure of **6** was also confirmed by desulfuration with Raney-nickel in refluxing ethanol, that surprisingly afforded the unexpected methyl 2,3,6-trideoxy-α-D-*erythro*-hexopyranoside **8**,[11] where not only C(3,6)-desulfuration, but also deoxygenation at C(2), had occurred. On the other hand, in order to complete the synthesis of **1** (see Scheme 3), compound **6** was 2-*O*-demesylated by treatment with $LiAlH_4$ in anhydrous refluxing 1,2-dimethoxyethane (DME) to **9**.

Hydrolysis of **9** gave the intermediate aldehyde **10** (which was not investigated), which was subsequently reduced with sodium borohydride to **1**, whose structure was determined on the basis of its analytical and spectroscopic data, as well as those of its peracetylated derivative **11**.

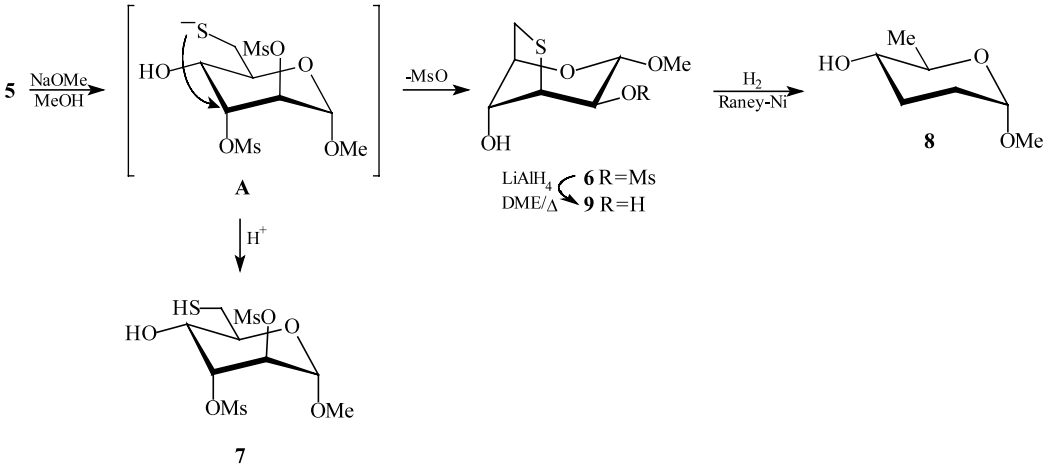


Scheme 3. *Reagents and conditions*: (a) 70% TFAA/H_2O; (b) $NaBH_4$/MeOH; (c) Ac_2O/Pyr/DMAP.

3. Experimental

3.1. 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 ARX-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin–Elmer 782 instrument and mass spectra with a Micromass Mod. Platform II and Autospec-Q mass spectrometers. Optical rotations were measured for solutions in $CHCl_3$ (1 dm tube) with a



Scheme 2.

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 non-crystalline compounds, for which elemental analyses were not obtained were shown to be homogeneous by chromatography and characterised by NMR and HRMS.

3.2. Methyl 4,6-*O*-benzylidene-2,3-di-*O*-methanesulfonyl-α-D-altropyranoside, 3

To a stirred and cooled (ice-water) solution of methyl 4,6-*O*-benzylidene-α-D-altropyranoside[9] **2** (3.95 g, 14 mmol) and triethylamine (6.5 mL, 46.2 mmol) in dry dichloromethane (70 mL) a solution of methanesulfonyl chloride (2.4 mL, 30.8 mmol) in the same solvent (40 mL) was added dropwise and the reaction mixture allowed to warm to rt and then left for 1 h. TLC (ether/hexane/ethanol, 6:0.5:0.2) then revealed the presence of a less polar product. The mixture was filtered and the filtrate treated with ethanol (5 mL), washed with brine, water, then concentrated to a solid foam that was recrystallised from ethanol to afford pure **3** (4.91 g, 80%): mp 162–164°C; $[\alpha]_D^{22}=+44$ (*c* 1.1); ν_{max}^{KBr} 3034, 3019, 703, and 684 cm^{-1} (aromatic). For NMR data, see Tables 1 and 2. Anal. calcd for $C_{16}H_{28}O_{10}S_2$: C, 43.82; H, 5.06; S, 14.63. Found: C, 43.80; H, 5.47; S, 15.10.

3.3. Methyl 2,3-di-*O*-methanesulfonyl-α-D-altropyranoside, 4

(a) A suspension of compound **3** (440 mg, 1 mmol) in aqueous 70% acetic acid (12 mL) was vigorously stirred at rt until a homogeneous solution was obtained. TLC (ether/hexane/ethanol, 6:1:0.1), then showed a slower-running product. The mixture was concentrated and repeatedly co-distilled with toluene–ethanol to remove water and acetic acid. The residue was crystallised from ethanol/hexane to give **4** (290 mg, 83%): mp 176–178°C; $[\alpha]_D^{27}=+50$ (*c* 1.2, acetone); ν_{max}^{KBr} 3566 cm^{-1} (OH). For NMR data, see Tables 1 and 2. Anal. calcd for $C_9H_{18}O_{10}S_2$: C, 30.85; H, 5.18; S, 18.30. Found: C, 31.22; H, 5.58; S, 17.96%.

(b) To a well stirred solution of iodine (1.9 g) in methanol (190 mL) compound **3** (3.8 g, 8.7 mmol) was added and the mixture heated under reflux for 30 min. TLC (ether/hexane/ethanol, 6:1:0.1) then showed the presence of **4**. Saturated aqueous sodium thiosulfate solution was added to reduce iodine and then concentrated to a residue that was extracted with ethyl acetate (3×100 mL). The solvent was removed and the residue purified by chromatography (ether–ethanol 10:1→5:1) to afford crystalline **4** (2.43 g, 80%).

3.4. Methyl 6-*S*-acetyl-2,3-di-*O*-methanesulfonyl-6-thio-α-D-altropyranoside, 5

To a stirred and cooled (ice-water) solution of triphenylphosphine (2.8 g, 10.5 mmol) in dry THF (20 mL) was added diethyl azodicarboxylate (DEAD, 1.9 g, 10.5 mmol). After 10 min, thioacetic acid (0.85 g, 11.2 mmol) and compound **4** (2.45 g, 7 mmol) were added, and after 10 min the mixture allowed to reach rt and then left for 4 h. TLC (ether/hexane/ethanol, 6:0.5:0.2) then revealed a less polar product. The solvent was evaporated and the residue purified by silica gel chromatography (ether/hexane, 6:1→ether/hexane/ethanol, 6:1:0.2) to afford syrupy **5** (2.32 g, 81%): $[\alpha]_D^{23}=+32$ (*c* 1.1); ν_{max}^{film} 3523 (OH) and 1696 cm^{-1} (AcS). For NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): *m*/*z*: 431.0111 [M^++Na] for $C_{11}H_{20}O_{10}NaS_3$ 431.0116 (deviation 1.3 ppm).

3.5. Methyl 2-*O*-methanesulfonyl-3,6-thioanhydro-α-D-mannopyranoside, 6

To a stirred solution of **5** (2.59 g, 6.35 mmol) in dry methanol (40 mL), 1 M methanolic sodium methoxide (10 mL) was added dropwise and the mixture maintained at room temperature for 5 h. TLC (ether/hexane/ethanol, 6:1:0.1) then showed the presence of a slightly more polar product. The mixture was neutralised (AcOH) and concentrated. Column chromatography (ether/hexane/ethanol, 6:1:0.1→ether/ethanol 5:2) of the residue afforded first crystalline **6** (1.53 g, 90%): mp 178–179°C (from ether/hexane); $[\alpha]_D^{25}=+113$ (*c* 0.8). For NMR data, see Tables 1 and 2. Anal. calcd for $C_8H_{14}O_6S_2$: C, 35.54; H, 5.22; S, 23.72. Found: C, 35.80; H, 5.71; S, 23.30%.

Eluted second was crystalline methyl 6-deoxy-2,3-di-*O*-methanesulfonyl-6-thio-α-D-altropyranoside (**7**, 133 mg): mp 115–117°C (from ether/ethanol); $[\alpha]_D^{25}=+142$ (*c* 0.5, ethyl acetate); ν_{max}^{KBr} 3516 and 3507 cm^{-1} (SH and OH). For NMR data, see Tables 1 and 2. Anal. calcd for $C_9H_{18}O_9S_3$: C, 29.50; H, 4.95; S, 26.25. Found: C, 29.87; H, 5.20; S, 26.65%.

3.6. Methyl 2,3,6-trideoxy-α-D-erythrohexopyranoside, 8

To a solution of **6** (160 mg, 0.6 mmol) in ethanol (10 mL) Raney-nickel (1 g, Fluka) was added and the mixture heated under reflux for 1 h. TLC (ethyl acetate/hexane 3:1) then revealed the presence of a slightly less polar product. The catalyst was filtered off, washed with ethanol and the filtrate and washings concentrated to a residue that was submitted to chromatography (ethyl acetate/hexane 2:1) to yield **8** (30 mg, 21%) as a colourless syrup: $[\alpha]_D^{23}=+150$ (*c* 0.5) (lit.[11b] $[\alpha]_D^{20}=+154$ (*c* 1). NMR data were in accordance with those found in the literature.[11]

3.7. Methyl 3,6-thioanhydro-α-D-mannopyranoside, 9

To a stirred suspension of $LiAlH_4$ (220 mg, 5.8 mmol) in anhydrous refluxing DME (10 mL) was added dropwise a solution of **6** (610 mg, 2.26 mmol) in the same solvent (20 mL) under argon and the refluxing continued for 3 h. TLC (ethyl acetate) then showed the presence of a more polar product. Ethyl acetate saturated with an aqueous solution of potassium bisulfate was cautiously added, the mixture was filtered through

a Celite pad, and the filtrate concentrated to a residue that was supported on silica gel, then chromatographed (ether→ether/ methanol, 20:1) to give first starting material **6** (45 mg) and then syrupy **9** (320 mg, 80%); $[\alpha]_D^{23}=+66$ (*c* 0.5). For NMR data, see Tables 1 and 2. Mass spectrum (LSIMS): *m*/*z*: 215.0352 [M^++Na] for $C_7H_{12}O_4NaS$ 215.0354 (deviation 0.7 ppm).

3.8. (2*R*,3*R*,4*S*)-3,4-Dihydroxy-2-[(R)-1,2-dihydroxyethyl]thiolane (1,4-anhydro-4-thio-D-mannitol), 1

A solution of **9** (320 mg, 1.67 mmol) in aqueous 70% trifluoroacetic acid (5 mL) was heated at 60°C for 4 h. TLC (ether/methanol, 10:1) then revealed the presence of a more polar product (presumably aldehyde **10**). The mixture was concentrated and repeatedly co-distilled with toluene. The residue was dissolved in methanol (5 mL) and neutralised with saturated aqueous sodium bicarbonate solution. $NaBH_4$ (70 mg) was added and the mixture left for 30 min, when TLC (ether/methanol 4:1) showed the presence of a slower-running compound. The mixture was again neutralised (Amberlite IR-120, H^+ form) concentrated to a residue and purified by column chromatography (ether/methanol 10:1) to afford crystalline **1** (200 mg, 67%), mp 98–100°C (from ether/methanol/hexane); $[\alpha]_D^{23}=+64$ (*c* 1, methanol). For NMR data, see Tables 1 and 2. Anal. calcd for $C_6H_{12}O_4S$: C, 39.99; H, 6.71; S, 17.79. Found: C, 40.47; H, 7.12; S, 17.59%.

Compound **1** (200 mg, 1.1 mmol) was acetylated in dry pyridine (3 mL) with acetic anhydride (1 mL) and catalytic amount of DMAP for 24 h. Conventional work-up and column chromatography (ether/hexane, 3:2) gave the peracetylated derivative of **1** (**11**, 230 mg, 88%) as white crystals, mp 112–114°C (from ether/hexane); $[\alpha]_D^{24}=+81$ (*c* 1). For NMR data, see Tables 1 and 2. Anal. calcd for $C_{14}H_{20}O_8S$: C, 48.27; H, 5.79; S, 9.20. Found: C, 48.79; H, 6.22; S, 9.09%.

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