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Note

Conversion of 2,6-anhydro-D-altrose and -mannose derivatives with 4-substituted phenyl thiols to prepare compounds with potential antithrombotic activity☆

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Abstract

Acetolysis of methyl 3,4-di-*O*-acetyl-2,6-anhydro-D-altropyranoside afforded a mixture containing, besides 1,3,4-tri-*O*-acetyl-2,6-anhydro-D-altropyranose, the (1*R*) and (1*S*) diastereomers of methyl 2,6-anhydro-D-altrose-tetraacetate. Treatment of this mixture with 4-cyanobenzenethiol in the presence of trimethylsilyl triflate resulted in a mixture containing the 3,4,5-tri-*O*-acetyl-2,6-anhydro-D-altrose bis(4-cyanophenyl) dithioacetal, the corresponding *O*-methyl *S*-aryl monothiohemiacetal diastereomers and the β-thiopyranoside, respectively. Acetolysis of methyl 3,4-di-*O*-acetyl-2,6-anhydro-D-mannopyranoside led to a mixture of the (1*R*) and (1*S*) diastereomers of methyl 2,6-anhydro-D-mannosetetraacetate, which was converted into the corresponding *O*-methyl *S*-aryl monothiohemiacetals. Treatment of 1,1,3,4,5-penta-*O*-acetyl-2,6-anhydro-*aldehydo*-D-altrose and -D-mannose with 4-cyano- and 4-nitrobenzenethiol, respectively, in the presence of trimethylsilyl triflate afforded the corresponding dithioacetal derivatives. All arylthio derivatives obtained after deacetylation were tested for their oral antithrombotic activity.

Keywords: *O*,*S*-Monothiohemiacetals; *S*,*S*-Dithioacetals; Thioglycosides; Oral antithrombotic activity

1. Introduction

During our search for thioglycosides with potential oral antithrombotic activity we found, that not only 5-thio-β-D-xylopyranosides (**1**),[2] but other 5-thio-pentopyranosides[3] and even glycosides with overbridged tricyclic[2,2,2] structures like **2** possess significant antithrombotic activity.[4] In the latter, the ring oxygen is not replaced by sulfur, but an additional sulfur atom is introduced into the molecule via a 2,6-thioanhydro bridge. In order to study the scope and limitations of this alteration, the synthesis of thioglycosides derived from 2,6-anhydro-D-altrose (**3a**) and -mannose (**3b**) was investigated (Scheme 1).

2. Results and discussion

Synthesis of the altrose derivatives.—For the synthesis of the corresponding thiogly-

☆ Orally active antithrombotic thioglycosides, Part XIII. For Part XII, see Ref. 1.

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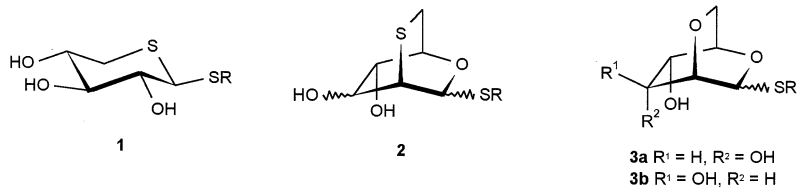
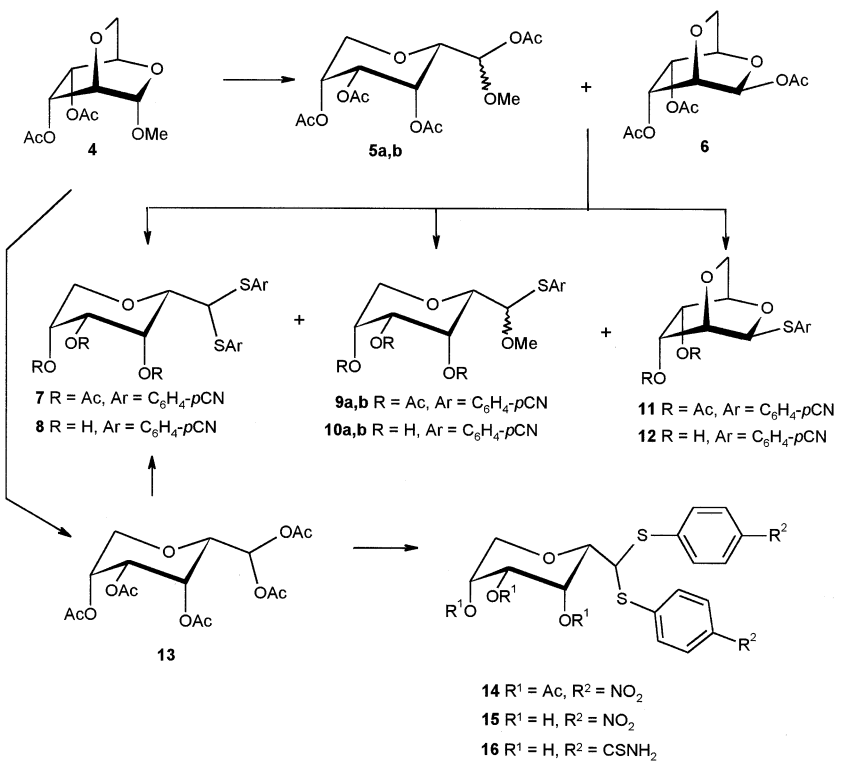


Scheme 1.



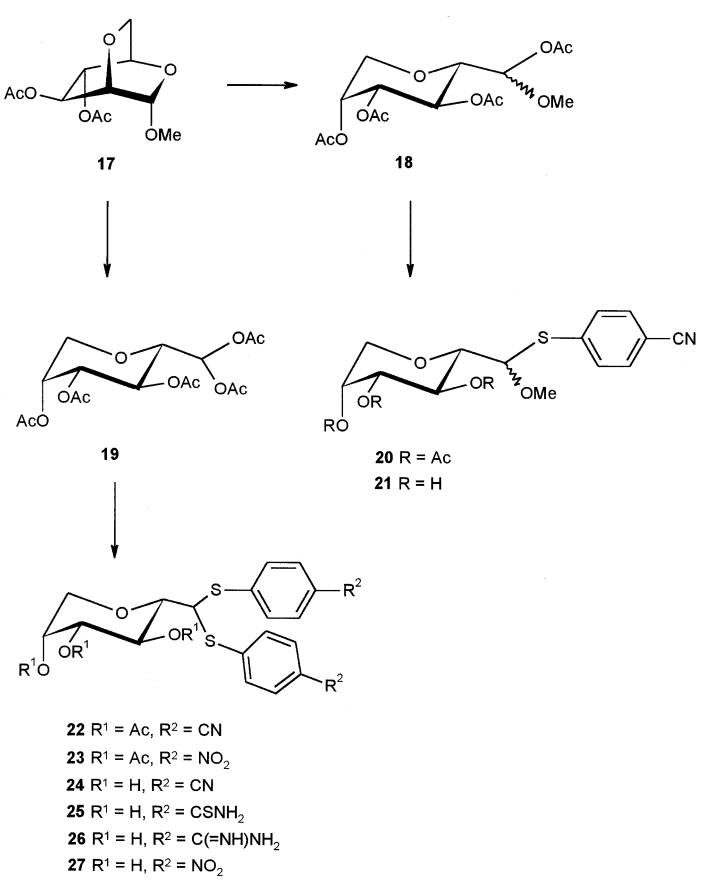
Scheme 2.

cosides, the bicyclic triacetate **6** was needed as a donor which could be obtained theoretically from the known[5] methyl 3,4-di-*O*-acetyl-2,6-anhydro-α-D-altropyranoside (**4**) by acetolysis. Treatment of **4** with acetic anhydride in the presence of sulfuric acid resulted however in an inseparable mixture containing, according to NMR spectroscopy and subsequent reactions, the two diastereomers of (1*R*) and (1*S*) methyl 2,6-anhydro-D-altrose-tetraacetate (**5**) and 1,3,4-tri-*O*-acetyl-2,6-anhydro-β-D-altropyranose (**6**) in a ratio of 3:2. Reaction of the above mixture of **5** and **6** with 4-cyanobenzenethiol in the presence of trimethylsilyl triflate resulted in a mixture, which could be partially separated by column chromatography affording, besides a 2:1 mixture of **7** + **9a** (28%), **9b** (14%) and **11** (18%), respectively. That suggests that while the two diastereomers of **5** afforded besides the dithioacetal **7** the two diastereomers of the *O*-methyl *S*-aryl monothioacetals **9a** and **9b**,[†] the triacetate **6** gave the β-thioglycoside **11** exclusively. The stereoselectivity of the glycosidation reaction is probably due to the presence of the two cis-related acetoxy groups at C-3 and C-4, which can either act as participating groups during the glycosidation reaction or as steric factors preventing the formation of the more crowded α-glycoside (Scheme 2).

[†] According to the NMR data, the anhydro ring of both diastereomers had the same configuration and conformation and differed only in the chirality of C-1. The configuration at C-1 could not, however, be established by NMR spectroscopy.

Zemplén deacetylation of **9b** and **11** afforded **10b** and **12**, respectively, while the mixture of **7** + **9a** gave a mixture of **8** + **10a**, which was separated by column chromatography. The configuration of C-1 in **10a** and **10b** could not be established by NMR spectroscopy. The obtained compounds **8**, **10a**, **10b** and **12** were submitted to biological testing and all of them showed antithrombotic activity. As among them the mercaptal type compound (**8**) possessed the highest activity, its large-scale synthesis became necessary. For this reason, **4** was converted into the known[6] pentaacetate (**13**) with acetic anhydride in the presence of trifluoromethanesulfonic acid and the resulting pentaacetate (**13**) was coupled with 4-cyanobenzenethiol and 4-nitrobenzenethiol in the presence of trimethylsilyl triflate to give **7** and **14** in 85 and 92% yield, respectively. Both dithioacetals were deacetylated according to Zemplén affording **8** and **15**, respectively. Compound **8**, containing the 4′-cyano group, could be converted by standard methods[7] into the 4′-aminothiocarbonyl derivative **16**.

Synthesis of the mannose derivatives.—For their synthesis, the methyl pyranoside (**17**)[8] was used as starting material, but acetolysis of this compound in acetic anhydride in the presence of sulfuric acid led to the cleavage of the anhydro ring affording a 1:1 mixture of the (1*R*) and (1*S*) methyl 2,6-anhydro-D-mannose-tetraacetate (**18**). This inseparable mixture was coupled with 4-cyanobenzenethiol in the presence of trimethylsilyl triflate to give the two diastereomers of the *O*-methyl *S*-aryl acetals (**20**) in 95% yield containing the two isomers in a 3:1 ratio. This inseparable mixture was deacetylated according to Zemplén to furnish the mixture **21**, which was submitted to biological testing without separation. The pentaacetate (**19**) was obtained according to the literature[6] by treating **17** with trifluoromethanesulfonic acid in acetic anhydride. This pentaacetate (**19**) was coupled with 4-cyanobenzenethiol and 4-nitrobenzenethiol in the



Scheme 3.

presence of trimethylsilyl triflate to give **22** and **23** in 84 and 88% yield, respectively. These compounds were deacetylated according to Zemplén to afford **24** and **27**, and **24** could be converted by standard methods[7] into the 4′-aminothiocarbonyl derivative **25**, which gave **26** after methylation and subsequent treatment with ammonium acetate (Scheme 3).

Biological results.—The oral antithrombotic activity of **8**, **10a**, **10b**, **12**, **15**, **16**, **21**, **24**, **25**, **26** and **27** was determined on rats, using Pescador's model[9] and 4-cyanophenyl 2,6-anhydro-1,2-dithio-β-D-mannopyranoside (**2**-type compound)[4] as reference. All compounds were administered orally 3 h before ligation. From the data listed in Table 1, it can be seen that while **8**, **10** and **15** were as active as the reference compound, all other derivatives possessed a less pronounced biological activity. It is worth mentioning that the altro derivatives (**8**, **10**, **15** and **16**) were more active then the corresponding manno ones (**21**, **24**, **25** and **27**). Furthermore, these results question the general validity of the statement of the literature[2] that the presence of a ring-sulfur atom in the carbohydrate moiety is essential for the biological activity.

3. Experimental

General methods.—Organic solutions were dried over $MgSO_4$ and concentrated under diminished pressure at or below 40 °C. TLC: E. Merck precoated Silica Gel 60 F_{254} plates, with (A, 1:1; B, 2:1) hexane–EtOAc mixtures, EtOAc (C), (D, 4:1) toluene–MeOH mixtures and (E, 60:20:11:6) EtOAc–pyridine–water–AcOH mixtures; detection by spraying the plates with a 0.02 M solution of I_2 and a 0.30 M solution of KI in a 10% aq H_2SO_4 solution followed by heating at ca. 200 °C. For column chromatography, Kieselgel 60 was used. Melting points are uncorrected. Optical rotations were determined at 20 °C. NMR spectra were recorded with a Bruker AC 250 spectrometer at 250 MHz (^1H) and 62.9 MHz (^{13}C) for solutions in $CDCl_3$ (internal Me_4Si) unless stated otherwise. Multiplicities of the ^{13}C NMR spectra were obtained from DEPT experiments. The assignment of the protons was based on homonuclear decoupling. Connectivities between identified protons and protonated carbons were observed by means of HETCOR experiments (Tables 2 and 3).

Acetolysis of **4**.—To a solution of **4**[5] (2.35 g, 9 mmol) in Ac_2O (6 mL), concd H_2SO_4 (0.01 mL) was added at 0 °C. The mixture was stirred at 0 °C for 30 min and NaOAc (0.1 g) was added. The pH was adjusted to ~6 with ice-cold 6% aq $NaHCO_3$ and stirring was continued at rt for 2 h. Then the mixture was extracted with CH_2Cl_2, washed with water and concentrated to yield a syrupy mixture containing on the bases of ^1H NMR spectroscopy (1*R* and 1*S*) methyl 1,3,4,5-tetra-*O*-acetyl-2,6-anhydro-D-altrose hemiacetal (**5a**,**b**) and 1,3,4-tri-*O*-acetyl-2,6-anhydro-β-D-altropyranose (**6**) in a ratio of 3:2 (2.6 g, 87%): R_f 0.4 (solvent A). When the reaction was carried out at −10 °C, **4** was consumed after 90 min only, but the ratio of the formed **5a**,**b** and **6** remained unchanged.

Reaction of (**5ab** + **6**) *with 4-cyanobenzenethiol.*—Under Ar, to a stirred solution of a 3:2 mixture of **5ab** + **6** (2.0 g, 6 mmol) and 4-cyanobenzenethiol (1.88 g, 13.9 mmol) in 1,2-dichloroethane (100 mL), TMSOTf (1.34 mL, 7.4 mmol) was added at −10 °C. After stirring at −10 °C for 30 min, the reaction was quenched with Et_3N, concentrated and

Table 1
Oral antithrombotic activity of 4-substituted phenyl *S*-acetals of 2,6-anhydro-D-altrose and -mannose in rats using Pescador's model[9]

Compound	Reference [a]	**8**	**10a**	**10b**	**12**	**15**	**16**	**21**	**24**	**25**	**26**	**27**
C-4′-R	CN	CN	CN	CN	CN	NO_2	$CSNH_2$	CN	CN	$CSNH_2$	$C(NH)NH_2$	NO_2
Inhibition [b] (%)	50	56	52	53	39	53	43	43	44	35	25	33

[a] 4-Cyanophenyl 2,6-anhydro-1,2-dithio-β-D-mannopyranoside[4] was chosen as reference compound.
[b] Inhibition % at an oral dose of 2 mg/kg.

Table 2
Selected ^{1}H NMR data for solutions in $CDCl_3$

Compound	Chemical shifts (δ)							
	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	Others
5a	5.80	3.50–4.40	5.30–5.50	5.05–5.25		3.50–4.40		3.41 (OMe)
5b	5.90	3.50–4.40	5.30–5.50	5.05–5.25		3.50–4.40		3.52 (OMe)
6	6.27	4.00	5.39	5.10	4.14	3.91	4.35	2.10, 2.11, 2.19 (OAc)
7	4.75	3.60	5.72	5.04	5.14	3.68	4.20	2.03, 2.06, 2.17 (OAc)
8[a]	5.35	3.50	3.47	4.03	3.67	3.50	3.86	4.85, 4.98, 5.06 (OH)
9a	4.82	3.58	5.60	4.92	5.10	3.66	4.20	2.00, 2.08, 2.16 (OAc)
9b	4.66	3.35	5.46	4.99	5.12	3.50	4.15	3.45 (OMe) 1.96, 2.11, 2.12 (OAc)
10a [a]	5.17	3.48	3.98	3.42	3.66	3.45	3.91	3.37 (OMe) 4.68, 4.93, 5.30 (OH)
10b [a]	5.01	3.19	3.76	3.44	3.64	3.33	3.83	3.41 (OMe) 4.69, 4.86, 5.12 (OH)
11	5.81	4.16	5.39	5.12	4.14	3.95	4.69	2.12, 2.15 (OAc)
12 [a]	5.95	3.87	4.04	3.87	3.87	3.82	4.33	4.98, 5.40 (OH)
14	4.87	3.71	5.76	5.09	5.17	3.75	4.22	2.01, 2.09, 2.20 (OAc)
15 [a]	5.48	3.60	3.55	4.08	3.72	3.52	3.90	4.90, 5.03, 5.28 (OH)
16 [a]	5.14	3.42	3.52	4.08	3.68	3.50	3.90	4.80, 4.96, 5.24 (OH) 9.50, 9.85 (NH_2)
20a	4.99	3.78	5.53	5.07	5.32	3.67	4.10	3.47 (OMe) 2.14, 2.08, 2.17 (OAc)
20b	4.90	3.65	5.48	5.06	5.29	3.59	4.05	3.44 (OMe) 2.05, 2.07, 2.18 (OAc)
21a [a]	5.46	3.25–3.50	3.56–3.83	3.25–3.50	3.56–3.83	3.25–3.50	3.56–3.83	3.35 (OMe) 4.56, 4.76, 5.04 (OH)
21b [a]	5.45	3.25–3.50	3.56–3.83	3.25–3.50	3.56–3.83	3.25–3.50	3.56–3.83	3.33 (OMe) 4.53, 4.78, 5.20 (OH)
22	4.57	3.85	5.72	5.07	5.30	3.64	4.10	2.04, 2.07, 2.20 (OAc)
23	4.69	3.92	5.75	5.08	5.32	3.68	4.10	2.05, 2.11, 2.20 (OAc)
24 [a]	5.47	3.55	3.85	3.40	3.73	3.48	3.86	4.65, 5.00, 5.60 (OH)
25 [a]	5.30	3.50	3.86	3.38	3.72	3.50	3.84	4.60, 4.84, 5.47 (OH)
26 [a]	5.44	3.35–3.52	3.82	3.35–3.52	3.68	3.35–3.52	3.82	
27 [a]	5.56	3.55	3.81	3.38	3.70	3.46	3.83	4.65, 4.86, 5.56 (OH)

	Coupling constants (Hz)						
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
5a	7.9	nd [b]	nd	nd	nd	nd	nd
5b	8.1	nd	nd	nd	nd	nd	nd
6	1.8	4.6	8.5	1.4	~1	2.1	10.4
7	8.7	<1	3.6	3.6	1.0	1.6	13.3
8 [a]	9.4	~0	~3	~3.5	~1	1.9	12.2
9a	8.2	<1	3.7	3.7	1.0	1.2	13.6
9b	8.7	1.4	3.6	3.8	1.5	1.6	13.4
10a [a]	9.1	<1	3.5	3.6	1.3	1.5	12.1
10b [a]	9.0	<1	3.1	3.1	1.0	1.7	12.0
11	1.2	4.4	8.6	1.1	~1.5	2.1	10.5
12 [a]	~1	~4.5	~8.8	nd	~1	1.7	10.0
14	8.7	0.9	3.7	3.7	1.1	1.3	13.4
15 [a]	9.3	~0	~3	~3.5	~1	1.7	12.0
16 [a]	9.5	~0	13	~3.5	~1	~1.5	12.0
20a	2.3	9.7	10.0	3.5	1.0	~1.5	12.1
20b	4.0	9.6	9.6	3.5	~1	2.2	12.0
21a [a]	~1	nd	nd	nd	nd	nd	nd

Table 2 (*Continued*)

	Coupling constants (Hz)						
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
21b [a]	~3	nd	nd	nd	nd	nd	nd
22	1.4	9.5	9.8	3.4	~1	1.4	13.1
23	1.2	9.3	9.8	3.4	~1	1.5	13.2
24 [a]	~1	9.0	9.3	3.4	<1	~0	12.0
25 [a]	~1	~9	9.0	3.2	~1	~1	~12
26 [a]	~1	~9	~9	~3	~1	~1	12.0
27 [a]	~1	9.3	9.0	3.1	<1	~0	12.0

[a] Me_2SO-d_6.
[b] nd, not determined.

Table 3
Selected ^{13}C NMR data for solutions in $CDCl_3$

Compound	Chemical shifts (δ)						
	C-1	C-2	C-3	C-4	C-5	C-6	Others
7	56.7	78.4	66.2 [a]	68.1	66.3 [a]	69.4	118.1, 118.2 (CN)
8 [b]	54.9	79.6	68.4 [a]	70.0	69.2 [a]	71.5	118.8, 118.8 (CN)
9a	88.3	78.3	66.2 [a]	68.1	66.3 [a]	69.3	56.4 (OMe); 118.2 (CN)
9b	87.9	76.5	66.2 [a]	76.8	66.5 [a]	69.0	56.2 (OMe); 118.0 (CN)
10a [b]	89.4	78.6	68.5 [a]	70.3	69.3 [a]	71.0	55.0 (OMe); 118.8 (CN)
10b [b]	89.0	78.1	68.3 [a]	69.7 [a]	69.6 [a]	71.2	56.0 (OMe); 118.9 (CN)
11	83.8	65.6 [a]	67.4 [a]	68.4 [a]	69.4 [a]	66.4	118.1 (CN)
12 [b]	82.7	65.1 [a]	70.8 [a]	71.8 [a]	65.6 [a]	66.4	119.0 (CN)
14	56.2	78.4	66.1 [a]	68.4	66.3 [a]	69.4	
20a	88.0	81.8	66.6 [a]	68.2 [a]	71.7 [a]	68.4	56.2 (OMe); 118.4(CN)
21a [b]	88.5	84.9	67.8 [a]	69.5 [a]	74.7 [a]	71.2	56.0 (OMe); 118.5 (CN)
22	57.4	80.4	67.8 [a]	68.2 [a]	71.4 [a]	68.0	118.0, 118.1 (CN)
23	57.0	80.5	67.9 [a]	68.2 [a]	71.3 [a]	68.1	
24 [b]	54.2	82.4	68.2 [a]	68.8 [a]	73.7 [a]	70.7	118.8, 118.8 (CN)

[a] Arbitrary assignment.
[b] Me_2SO-d_6.

submitted to column chromatography (solvent B, then A). Concentration of the first fraction gave 4-cyanophenyl 3,4-di-*O*-acetyl-2,6-anhydro-1-thio-β-D-altropyranoside (**11**, 0.45 g, 18%): mp 165–167 °C (ether); $[\alpha]_D$ −153° (*c* 0.4, $CHCl_3$); R_f 0.6 (solvent A); Anal. Calcd for $C_{17}H_{17}NO_6S$: C, 56.19; H, 4.72; N, 3.85; S, 8.82. Found: C, 56.02; H, 4.58; N, 3.90; S, 8.73.

Concentration of the second fraction gave on the basis of ^1H NMR spectroscopy a 2:1 mixture of 3,4,5-tri-*O*-acetyl-2,6-anhydro-D-altrose bis(4-cyanophenyl) dithioacetal (**7**) and 3,4,5-tri-*O*-acetyl-2,6-anhydro-D-altrose *S*-4-cyanophenyl *O*-methyl monothiohemiacetal (**9a**) (1.0 g, 28%): R_f 0.5 (solvent A).

Concentration of the third fraction gave 3,4,5-tri-*O*-acetyl-2,6-anhydro-D-altrose *S*-4-cyanophenyl *O*-methyl monothiohemiacetal (**9b**) (0.42 g, 14%): mp 138–143 °C (ether); $[\alpha]_D$ −34° (*c* 0.5, $CHCl_3$); R_f 0.3 (solvent A); Anal. Calcd for $C_{20}H_{23}NO_8S$: C, 54.91; H, 5.30; N, 3.20; S, 7.33. Found: C, 54.87; H, 5.22; N, 3.27; S, 7.43.

2,6-Anhydro-D-*altrose bis(4-cyanophenyl) dithioacetal* (**8**) *and 2,6-anhydro*-D-*altrose* S-*4-cyanophenyl* O-*methyl monothiohemiacetal* (**10a**).—To a solution of a 2:1 mixture of **7** and **9a** (1.42 g, 2.8 mmol) in MeOH (20 mL) and CH_2Cl_2 (10 mL), 3 M methanolic NaOMe (0.1 mL) was added and the mixture was kept at rt for 1 h. Thereafter it was neutralized with

solid CO_2, concentrated and the residue was submitted to column chromatography (solvent C). Concentration of the first fraction gave **8** (0.7 g, 60%) as an oil: $[\alpha]_D$ +4° (*c* 0.5, MeOH); R_f 0.3 (solvent C); Anal. Calcd for $C_{20}H_{18}N_2O_4S_2$: C, 57.95; H, 4.38; N, 6.76; S, 15.47. Found: C, 57.88; H, 4.46; N, 6.82; S, 15.55.

Concentration of the second fraction gave **10a** (0.25 g, 29%): mp 132–135 °C (ether); $[\alpha]_D$ −104° (*c* 0.5, MeOH); R_f 0.2 (solvent C); Anal. Calcd for $C_{14}H_{17}NO_5S$: C, 54.01; H, 5.50; N, 4.50; S, 10.30. Found: C, 54.13; H, 5.44; N, 4.61; S, 10.33.

2,6-Anhydro-D-*altrose* S-*4-cyanophenyl* O-*methyl monothiohemiacetal* (**10b**).—Deacetylation of **9b** (0.42 g, 0.96 mmol) was carried out as described for **8** to give after column chromatography (solvent D) **10b** (0.25 g, 83%) as an oil: $[\alpha]_D$ −21° (*c* 0.5, MeOH); R_f 0.3 (solvent D); Anal. Calcd for $C_{14}H_{17}NO_5S$: C, 54.01; H, 5.50; N, 4.50; S, 10.30. Found: C, 54.07; H, 5.43; N, 4.55; S, 10.37.

4-Cyanophenyl 2,6-anhydro-1-thio-β-D-*altropyranoside* (**12**).—Deacetylation of **11** (0.45 g, 1.2 mmol) was carried out as described for **8** to give **12** (0.3 g, 87%): mp 125–130 °C (ether); $[\alpha]_D$ −211° (*c* 0.5, MeOH); R_f 0.3 (solvent D); Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.01; S, 11.48. Found: C, 55.83; H, 4.77; N, 5.11; S, 11.54.

Reaction of **13** *with 4-cyanobenzenethiol.*—Under Ar, to a stirred solution of **13**[6] (1.15 g, 2.9 mmol) and 4-cyanobenzenethiol (0.95 g, 7 mmol) in 1,2-dichloroethane (30 mL), TMSOTf (0.75 mL, 4 mmol) was added at 0 °C. After stirring at rt for 24 h, the reaction was quenched with Et_3N, concentrated and submitted to column chromatography (solvent A) to give **7** (1.35 g, 85%) as an oil: $[\alpha]_D$ +65° (*c* 0.5, $CHCl_3$); R_f 0.5 (solvent A); Anal. Calcd for $C_{26}H_{24}N_2O_7S_2$: C, 57.77; H, 4.47; N, 5.18; S, 11.86. Found: C, 57.81; H, 4.38; N, 5.23; S, 11.90.

Reaction of **13** *with 4-nitrobenzenethiol.*—Under Ar, to a stirred solution of **13** (1.8 g, 4.6 mmol) and 4-nitrobenzenethiol (2.2 g, 14 mmol) in 1,2-dichloroethane (40 mL), TMSOTf (1.2 mL, 6.4 mmol) was added at 0 °C. After stirring at rt for 24 h, the reaction was quenched with Et_3N, concentrated and submitted to column chromatography (solvent B) to give 3,4,5-tri-*O*-acetyl-2,6-anhydro-D-altrose bis(4-nitrophenyl) dithioacetal (**14**, 2.46 g, 92%) as an oil: $[\alpha]_D$ +70° (*c* 0.58, $CHCl_3$); R_f 0.5 (solvent A); Anal. Calcd for $C_{24}H_{24}N_2O_{11}S_2$: C, 49.65; H, 4.17; N, 4.82; S, 11.05. Found: C, 49.74; H, 4.08; N, 4.90; S, 11.15.

2,6-Anhydro-D-*altrose bis(4-nitrophenyl) dithioacetal* (**15**).—Deacetylation of **14** (1.7 g, 2.9 mmol) was carried out as described for **8** to give **15** (0.97 g, 73%): mp 166–168 °C (ether); $[\alpha]_D$ +14° (*c* 0.5, pyridine); R_f 0.3 (solvent D); Anal. Calcd for $C_{18}H_{18}N_2O_8S_2$: C, 47.57; H, 3.99; N, 6.16; S, 14.11. Found: C, 47.51; H, 4.01; N, 6.10; S, 14.22.

2,6-Anhydro-D-*altrose bis[4-(aminothiocarbonyl)phenyl] dithioacetal* (**16**).—A stirred solution of **8** (0.4 g, 0.96 mmol) in dry pyridine (10 mL) and Et_3N (10 mL) was saturated with a slow stream of dry H_2S for 1 h. The mixture was kept at rt overnight and was then concentrated. The residue was recrystallized from MeOH to yield **16** (0.33 g, 72%): mp 112–116 °C (MeOH); $[\alpha]_D$ −15° (*c* 0.5, pyridine); R_f 0.2 (solvent D); Anal. Calcd for $C_{20}H_{22}N_2O_4S_4$: C, 49.77; H, 4.59; N, 5.80; S, 26.57. Found: C, 49.85; H, 4.48; N, 5.91; S, 26.65.

Acetolysis of **17**.—To a solution of **17**[8] (1.0 g, 3.8 mmol) in Ac_2O (5 mL), concd H_2SO_4 (0.01 mL) was added at 0 °C. The mixture was stirred at 0 °C for 30 min and NaOAc (0.1g) was added. The pH was adjusted to ~6 with ice-cold 6% aq $NaHCO_3$ and stirring was continued at rt for 2 h. Then the mixture was extracted with CH_2Cl_2, washed with water and concentrated to yield a 1:1 diastereomeric mixture of (1*R* and 1*S*) methyl 1,3,4,5-tetra-*O*-acetyl-2,6-anhydro-D-mannose hemiacetal (**18**, 1.08 g, 78%) as syrup: R_f 0.4 (solvent A), identical with lit.[6]

Reaction of **18** *with 4-cyanobenzenethiol.*—Condensation of **18** (0.4 g, 1.1 mmol) with 4-cyanobenzenethiol (0.3 g, 2.2 mmol) was carried out as described for **13** to give after column chromatography (solvent B) 3:1 diastereomeric mixture of 3,4,5-tri-*O*-acetyl-2,6-anhydro-D-mannose *S*-4-cyanophenyl *O*-methyl monothiohemiacetal (**20**, 0.46 g, 95%) as syrup: R_f 0.6 (solvent A); Anal. Calcd for

$C_{20}H_{23}NO_8S$: C, 54.91; H, 5.30; N, 3.20; S, 7.33. Found: C, 54.85; H, 5.28; N, 3.13; S, 7.41.

2,6-Anhydro-D-*mannose* S-*4-cyanophenyl* O-*methyl monothiohemiacetal* (**21**).—To a solution of **20** (0.46 g, 1.0 mmol) in MeOH (15 mL), 3 M methanolic NaOMe (0.1 mL) was added and the mixture was kept at rt for 1 h. Thereafter it was neutralized with solid CO_2, concentrated and the residue was submitted to column chromatography (solvent D) to give a 3:1 diastereomeric mixture of **21** (0.24 g, 74%) as an oil: R_f 0.3 (solvent D); Anal. Calcd for $C_{14}H_{17}NO_5S$: C, 54.01; H, 5.50; N, 4.50; S, 10.30. Found: C, 53.96; H, 5.47; N, 4.44; S, 10.41.

3,4,5-Tri-O-*acetyl-2,6-anhydro*-D-*mannose bis(4-cyanophenyl) dithioacetal* (**22**).—Under Ar, to a stirred solution of **19**[6] (2.1 g, 5.4 mmol) and 4-cyanobenzenethiol (1.73 g, 12.8 mmol) in 1,2-dichloroethane (50 mL), TMSOTf (1.33 mL, 7.1 mmol) was added at 0 °C. After stirring at rt for 24 h, the reaction was quenched with Et_3N, concentrated and submitted to column chromatography (solvent A) to give **22** (2.45 g, 84%) as an oil: $[\alpha]_D$ −145° (*c* 0.5, $CHCl_3$); R_f 0.6 (solvent A); Anal. Calcd for $C_{26}H_{24}N_2O_7S_2$: C, 57.77; H, 4.47; N, 5.18; S, 11.86. Found: C, 57.69; H, 4.39; N, 5.26; S, 11.92.

3,4,5-Tri-O-*acetyl-2,6-anhydro*-D-*mannose bis(4-nitrophenyl) dithioacetal* (**23**).—Under Ar, to a stirred solution of **19** (1.3 g, 3.3 mmol) and 4-nitrobenzenethiol (1.28 g, 8.25 mmol) in 1,2-dichloroethane (25 mL), TMSOTf (0.85 mL, 4.5 mmol) was added at 0 °C. After stirring at rt for 24 h, the reaction was quenched with Et_3N, concentrated and submitted to column chromatography (solvent B) to give **23** (1.7 g, 88%) as an oil: $[\alpha]_D$ −159° (*c* 0.5, $CHCl_3$); R_f 0.7 (solvent A); Anal. Calcd for $C_{24}H_{24}N_2O_{11}S_2$: C, 49.65; H, 4.17; N, 4.82; S, 11.05. Found: C, 49.71; H, 4.12; N, 4.89; S, 11.10.

2,6-Anhydro-D-*mannose bis(4-cyanophenyl) dithioacetal* (**24**).—Deacetylation of **22** (1.15 g, 2.1 mmol) was carried out as described for **21** to give, after column chromatography (solvent D), **24** (0.67 g, 76%): mp 96–98 °C (ether); $[\alpha]_D$ −145° (*c* 0.5, MeOH); R_f 0.3 (solvent D); Anal. Calcd for $C_{20}H_{18}N_2O_4S_2$: C, 57.95; H, 4.38; N, 6.76; S, 15.47. Found: C, 57.88; H, 4.31; N, 6.82; S, 15.53.

2,6-Anhydro-D-*mannose bis[4-(aminothiocarbonyl)phenyl] dithioacetal* (**25**).—A stirred solution of **24** (0.4 g, 0.96 mmol) in dry pyridine (10 mL) and Et_3N (10 mL) was saturated with a slow stream of dry H_2S for 1 h. The mixture was kept at rt overnight and was then concentrated. The residue was recrystallized from MeOH to yield **25** (0.34 g, 74%): mp 165–168 °C (MeOH); $[\alpha]_D$ −282° (*c* 0.5, pyridine); R_f 0.2 (solvent D); Anal. Calcd for $C_{20}H_{22}N_2O_4S_4$: C, 49.77; H, 4.59; N, 5.80; S, 26.57. Found: C, 49.83; H, 4.53; N, 5.87; S, 26.61.

2,6-Anhydro-D-*mannose bis(4-amidinophenyl) dithioacetal* (**26**).—To a stirred solution of **25** (0.2 g, 0.4 mmol) in dry acetone (20 mL), MeI (0.2 mL) was added and the mixture was refluxed for 2 h. After cooling to rt, the precipitated crystals were filtered off and washed with ether to give 2,6-anhydro-D-mannose bis(4-[(imino)(methylthio)methyl]phenyl) dithioacetal (0.25 g, 79%). The resulting compound was dissolved in EtOH (25 mL), NH_4OAc (0.2 g) was added and the mixture was stirred at 60 °C for 2 h. Then the reaction mixture was concentrated, the residue was dissolved in 10% aq AcOH (20 mL) and purified on an ion-exchange resin (Varion AD, H^+ form) using 5% aq AcOH as eluent. The fractions having the desired compound were freeze dried to yield the diacetate of **26** (0.1 g, 54%) as a foam: $[\alpha]_D$ −90° (*c* 0.34, MeOH); R_f 0.6 (solvent E); Anal. Calcd for $C_{24}H_{32}N_4O_8S_2$: C, 50.69; H, 5.67; N, 9.85; S, 11.28. Found: C, 50.73; H, 5.59; N, 9.87; S, 11.33.

2,6-Anhydro-D-*mannose bis(4-nitrophenyl) dithioacetal* (**27**).—Deacetylation of **23** (1.7 g, 2.9 mmol) was carried out as described for **21** to give, after column chromatography (solvent D), **27** (1.06 g, 80%): mp 197–199 °C (ether); $[\alpha]_D$ −271° (*c* 0.5, pyridine); R_f 0.3 (solvent D); Anal. Calcd for $C_{18}H_{18}N_2O_8S_2$: C, 47.57; H, 3.99; N, 6.16; S, 14.11. Found: C, 47.59; H, 4.03; N, 6.11; S, 14.19.

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