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Note

Stereoselective syntheses of 1,2-*trans*-related 1-thioglycoses*

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Thioglycosides and thioglycosyl-oligosaccharides are known as valuable substrate analogs for studies of glycosidases and glycanases acting as inducers[4,5], specific inhibitors[6], ligands for affinity chromatography[7], and model substrates for evaluation of the catalytic activity of glycanases[8]. Nucleophilic sulfur substitutions at anomeric center of glycosyl halides or acid-mediated thiolysis of peracetylated sugars are hitherto the main-established methods for the synthesis of thioglycoses and thioglycosides[9]. Recent improvements include the use of hexamethylphosphotriamide as solvent, which allows a complete anomeric stereocontrol in the displacement of 1,2-*cis* as well as 1,2-*trans*-related acylglycosyl halides with sulfur nucleophiles[10,11]. Comparable results were obtained with the tetrabutylammonium salt of thioacetic acid in toluene for the preparation of 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-α-D-glucopyranose from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl chloride[1]. The boron trifluoride-catalyzed reaction of 1,2-*trans*-related glycosyl acetates[12] is another convenient improvement of the acid-mediated thiolysis technique; however this reaction is still not totally stereoselective and yields small proportions of 1,2-*cis*-related 1-thioglycosides**. In contrast with this behavior, zirconium chloride, a moderately hygroscopic Lewis acid, yields exclusively 1,2-*trans*-related 1-thioglycoses when applied to the reaction of thioacetic acid with a peracetylated sugar in dichloromethane.

Reaction of thioacetic acid with the following 1,2-*trans*, per-*O*-acetylated glycosyl esters, 1,2,3,4-tetra-*O*-acetyl-β-D-xylopyranose[14], 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose[15], 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose[16], and 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranose[17], in dichloromethane with zirconium chloride as catalyst, led in excellent yields to the corresponding 1,2-*trans*-

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**A recent report points out, however, that similar treatment of *O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glycosyl)trichloroacetimidate yields exclusively 1,2-*trans* related 1-thioglycosides[13].

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TABLE I

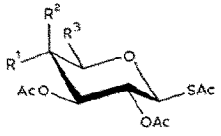
YIELDS AND PHYSICAL CONSTANTS OF PER-*O*-ACETYLATED 1-*S*-ACETYL-1-THIOGLYCOPYRANOSES

Per-O-acetyl-1-S-acetyl-1-thio-	R_F *(solvent)*[a]	*Yield (%)*	*Characterization*				
			Found		*Ref.*	*Lit*	
			M.p. (degrees) (crist. solvent)	$[\alpha]_D^{22}$ *(c, $CHCl_3$) (degrees)*		*M.p. (degrees)*	$[\alpha]_D$ *(c, $CHCl_3$) (degrees)*
-β-D-xylopyranose (**1**)	0.33 (A)	90	99–103 (ethanol)	−7.0 (1.1)	18	103	−7.7 (1.4)
-β-D-glucopyranose (**2**)	0.54 (B)	77	115–116 (ether)	+11.0 (1.08)	19	119–120	+10.5 (0.6)
-β-D-galactopyranose (**3**)	0.57 (B)	69	112-114 (ether)	+32 (1.25)	18	115–116	+31.3 (1.9)
-α-D-mannopyranose[b,c] (**4**)	0.44 (C)	88	70–71 (ether)	+73 (1.17)			
-β-D-mannopyranose (**5**)	0.53 (B)	79	127–128 (ether)	−29 (1.0)	21	130–131	−29.1 (1.7)

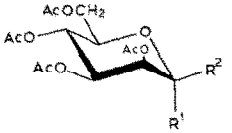
[a]A, 2:1 (v/v) ether–hexane; B, 1:2 (v/v) toluene–ether; C, 3:1 (v/v) ether–hexane. [b]Calc. for $C_{16}H_{22}O_{10}S$: C, 47.28; H, 5.45; S, 7.88. Found: C, 47.49; H, 5.53; S, 8.04. [c]^{1}H-N.m.r.: δ 5.95 (d, $J_{1,2}$ 2.0 Hz, H-1), 5.35 (t, $J_{4,5}$ 10 Hz, H-4), 5.33 (dd, $J_{2,3}$ 4.0 Hz, H-2), 5.1 (dd, $J_{3,4}$ 10 Hz, H-3), 4.29 (dd, $J_{5,6b}$ 5.0 Hz, H-6*b*), 4.08 (dd, $J_{6a,6b}$ 12 Hz, H-6*a*), 3.94 (ddd, $J_{5,6a}$ 2.5 Hz, H-5), 2.44 (s, 3 H, $SCOCH_3$), 2.20, 2.08, 2.06, and 2.00 (4 s, 12 H, $OCOCH_3$); ^{13}C-n.m.r.: δ 80.2 ($J_{C\text{-}1,H\text{-}1}$ 169 Hz, C-1), 72.5 (C-5), 71.1, 69.9, 65.8, 62.2 (C-6), 31.2 ($SCOCH_3$), 20.8 ($OCOCH_3$), and 20.6.

related peracetylated 1-thio-β-D-xylose[18] (**1**), -β-D-glucose[19] (**2**), -β-D-galactose[18] (**3**), and -α-D-mannose (**4**) (Table I). No anomerized product could be detected at any stage of the reactions (which were monitored by t.l.c.), or in the mother liquors.

The structure of the hitherto unknown 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-α-D-mannopyranose (**4**) was further confirmed by comparison with its β-D-anomer **5**. This derivative was obtained by application of the previously described technique for the preparation of 1,2-*cis*-related 1-thioglycoses[1] involving the displacement of the halide of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide[20] with the tetrabutylammonium salt of thioacetic acid in toluene, in the



1 $R^1 = OAc, R^2 = R^3 = H$
2 $R^1 = OAc, R^2 = H, R^3 = CH_2OAc$
3 $R^1 = H, R^2 = OAc, R^3 = CH_2OAc$



4 $R^1 = SAc, R^2 = H$
5 $R^1 = H, R^2 = SAc$
6 $R^1 = Cl, R^2 = H$

presence of barium carbonate. This reaction proceeded as efficiently as in the D-glucopyranose series[1] and led to 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-mannopyranose[21] (**5**) with a 79% yield. The increment (+12 Hz) in $^1J_{^{13}C,H\text{-}1}$ couplings from the β (**5**) to the α anomer (**4**) is in agreement with values found for several anomeric pairs of pyranoses and derivatives[22].

The zirconium chloride-catalyzed thiolysis of glycose peresters appeared to proceed faster with 1,2-*trans*, diequatorially related configurational isomers, as compared with their 1,2-*cis*, axial–equatorial counterparts, and this confirms a displacement mechanism involving an anchimeric assistance by the ester group at C-2. Thus, at room temperature, a 54% conversion of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose into its β-D-1-thioacetate **2** was reached after 6 h when, in a comparative assay, the corresponding α-D anomer required one week for a similar level of conversion into **2**. Such rate of conversion appeared to be comparatively faster for 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranose; however, a 26% yield of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl chloride (**6**) was isolated together with the expected α-D-1-thioacetate **4** (39% yield) after 4 days at room temperature. Such a reactivity is in agreement with previous results of Lemieux and Brice[23] concerning the rate of exchange of acetoxy-1 groups of pentaacetates of D-glucose and D-mannose catalyzed by Lewis acids.

EXPERIMENTAL

General methods. — Melting points were determined with a Zeiss hot-stage

equipped with a microscope and correspond to "corrected melting-points". Optical rotations were determined with a Perkin–Elmer model 241 polarimeter. ^{1}H-N.m.r. spectra were recorded at 250 MHz with a Cameca spectrometer (Thomson C.S.F., Paris) and assignments were confirmed by double irradiation or INDOR techniques (s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet). Spectra of compounds **1–3** are in agreement with previous literature data[18]. ^{13}C-N.m.r. spectra were recorded at 25.18 MHz with a Bruker WP 100 instrument. Both n.m.r. techniques used (^{2}H)chloroform as solvent; chemical shifts are reported relative to the signal of tetramethylsilane and coupling constants in Hz. Reactions were followed by t.l.c. on silica gel plates (Merck F-254, Darmstadt, Germany) with respective eluants given in Table I. Preparative chromatography was performed on columns of silica gel (Merck 60, 70–230 mesh) with eluants indicated. Solutions were dried with anhydrous sodium sulfate and were evaporated under reduced pressure at bath temperatures not exceeding 45°.

General procedure for the preparation of O-*acetylated 1*-S-*acetyl-1-thioglycoses* (**1**), (**2**), (**3**), *and* (**4**). — 1,2-*trans*-Related per-*O*-acetylated aldoses (1.5 g, 3.84 mmol) were dissolved in dichloromethane (25 mL), and a mixture of zirconium chloride (0.97 g, 4.16 mmol) and thioacetic acid (0.3 mL, 4.2 mmol) was added. After 6 h at 50°, additional zirconium chloride (0.4 g, 1.7 mmol) and thioacetic acid (0.2 mL, 2.8 mmol) in dichloromethane (10 mL) were added, and the solution was heated for further 15 h at 50°. The mixture was poured into ice-cold water (200 mL) and extracted with dichloromethane (200 mL). The organic phase was successively washed with ice-cold, saturated sodium hydrogencarbonate solution (2 × 200 mL) and ice-cold water (200 mL). After drying (sodium sulfate) and evaporation, the expected *O*-acetylated 1-*S*-acetyl-1-thio-glycoses **1–4** (Table I) were crystallized from either ethanol (**1**) or ether (**2–4**).

2,3,4,6-Tetra-O-*acetyl-1*-S-*acetyl-1-thio-β*-D-*mannopyranose* (**5**). — To tetrabutylammonium hydroxide (25% w/v in methanol, 5.7 mL, 4.6 mmol) in 6:1 (v/v) toluene–methanol (80 mL) was added thioacetic acid (0.5 mL, 7 mmol), the mixture was evaporated at a bath temperature <40°, and the residual solvent co-evaporated with toluene (3 × 200 mL). 2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl bromide[20] (obtained from 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranose[17], 1.5 g, 3.84 mmol) was added to the prepared tetrabutylammonium thioacetate in toluene (70 mL) containing barium carbonate (1 g, 5 mmol). After being kept for 15 h at room temperature, the mixture was filtered through Celite and the toluene evaporated. The residue was dissolved in dichloromethane (200 mL), and successively washed with a cold saturated sodium hydrogencarbonate solution (200 mL) and water (200 mL). The resulting 1-thioacetate **5** (1.1 g, 71%) was crystallized from ether. The mother liquors were purified on a silica gel column (150 g, 1:2, v/v, toluene–ether) and additional pure **5** was recovered (0.12 g, total yield 79%); for physical constants and lit.[21], see Table I; ^{1}H-n.m.r.: δ 5.53 (d, $J_{1,2}$ 1.5 Hz, H-1), 5.49 (dd, $J_{2,3}$ 3.0 Hz, H-2), 5.27 (t, $J_{4,5}$ 9.5 Hz, H-4), 5.18 (dd, $J_{3,4}$ 9.5 Hz, H-3), 4.29 (dd, $J_{5,6b}$ 5.0 Hz, H-6*b*), 4.12 (dd, $J_{6a,6b}$ 12 Hz, H-6*a*), 3.86

(ddd, $J_{5,6a}$ 2.5 Hz, H-5), 2.38 (s, 3 H, SAc), 2.20 2.09, 2.06, and 1.98 (4 s, 12 H, OAc); ^{13}C-n.m.r.: δ 79.3 ($J_{C\text{-}1,H\text{-}1}$ 157 Hz, C-1), 76.9 (C-5), 71.7, 70.7, 65.4, 62.4 (C-6), 30.6 ($SCOCH_3$), 20.6, and 20.5 ($OCOCH_3$).

*Treatment of 2,3,4,6-penta-*O*-acetyl-α-*D*-mannopyranose with thioacetic acid and zirconium chloride at room temperature; formation of 2,3,4,6-tetra-*O*-acetyl-α-*D*-mannopyranosyl chloride* (**6**). — To 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranose[17] (2.5 g, 6.4 mmol) in dichloromethane (25 mL) were added zirconium chloride (0.75 g, 3.2 mmol) and thioacetic acid (2.5 mL, 35.1 mmol). After 4 days at room temperature, usual work-up led to a syrup that showed on t.l.c. (3:1, v/v ether–hexane), three spots corresponding to the starting material (R_F 0.39), α-D-1-thioacetate **4** (R_F 0.44), and chloride **6** (R_F 0.62). Separation of this mixture on a silica gel column with the same eluant led, in the order of elution, to 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl chloride (**6**, 0.6 g, 26%), m.p. 75–77° (ether), $[\alpha]_D^{22}$ +92° (*c* 1, chloroform), lit.[24] m.p. 81°, $[\alpha]_D^{20}$ +90.6° (*c* 0.8, chloroform); and then to 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-α-D-mannopyranose (**4**, 10.2 g, 39%), m.p. 70–71°, $[\alpha]_D^{22}$ +72.5° (*c* 1.1, chloroform), after a further purification on a column of silica gel (1:2, v/v toluene–ether).

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