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Note

A simple synthesis of sugar disulfides using tetrathiomolybdate as a sulfur-transfer reagent

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Disulfide bonds play an important role in the chemistry of many natural products [1,2]. The S–S linkage formed at cysteine residues influences local conformation and stability in folded proteins and polypeptides [3,4], and sugar disulfides are significant in metabolism and are also found to be useful as structural models in enzymology [5]. Although sugar disulfides have been known for a long time, there has been no systematic study for a convenient synthesis of these molecules, and, in general, long and circuitous procedures are employed. For example, octaacetyl β,β-diglucosyl disulfide was synthesised in three steps from tetra-*O*-acetyl-α-D-glucopyranosyl bromide via the formation of the xanthate, hydrolysis to the thiol, and then oxidation to the disulfide [6–8]. Even in the synthesis of 6,6′-dithiosucrose reported by two groups, Hough et al. [9] and Lees and Whitesides [10], an analogous procedure involving four steps was adopted.

We reported earlier that benzyltriethylammonium tetrathiomolybdate (**1**) is a useful sulfur-transfer reagent that converts a variety of alkyl halides to the corresponding disulfides with facility in inter- and intra-molecular reactions [11]. As part of our continuing interest in studying the scope and limitations of our methodology, we report herein a one-step, direct conversion of sugar halides to the corresponding sugar disulfides mediated by **1**. A number of anomeric bromides and primary bromides derived from carbohydrates were treated with a slight excess of tetrathiomolybdate **1** in CH_3CN or DMF (0–25 °C, 19–72 h), and the corresponding disulfides were obtained in good yields. The results are summarised in Table 1.

The anomeric bromides derived from glucose and xylose **2** [12] and **4** [12], respectively, on treatment with **1** yielded the corresponding disulfides **3** and **5** in the β configuration (established from chemical shifts and coupling constants), in moderate isolated yields. The primary bromide **6** [13], on treatment with **1**, afforded the corresponding disulfide **7** in 81% yield. The same reaction could also be carried out with facility on bromide **8** [13] containing unprotected hydroxy groups to give the disulfide **9** in 70% yield. Compound **9** could be converted to compound **7** by subjecting it to acetylation, and thus the identity was authenticated. The primary bromide **10** [14], derived from mannose, reacted with **1** to form the disulfide **11** in 78% yield. The dibromo compound **12** [9], derived from sucrose, also underwent a smooth sulfur-transfer reaction with **1** to form the cyclic disulfide in 30% isolated yield [9,10]. In this reaction, however, a considerable amount of starting material, which can be recycled, was recovered unchanged after chromatographic purification.

The present methodology, therefore, provides in a single step, direct access to a number of carbohydrate-derived disulfides that are otherwise made by circuitous routes. The easy accessibility of these sugar

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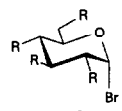
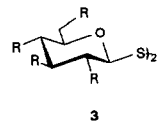
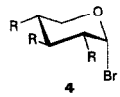
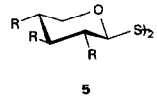
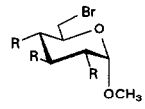
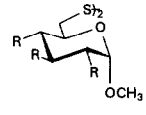
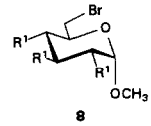
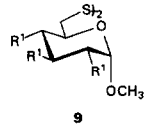
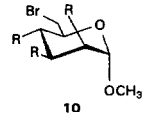
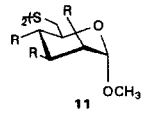
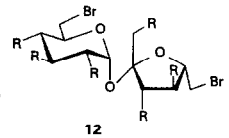
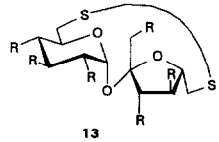
disulfides will pave the way for the synthesis of a number of thio sugars that will undoubtedly be of use in asymmetric synthesis.

1. Experimental

General methods.—Acetonitrile (CH_3CN) was distilled from P_2O_5. *N,N*-Dimethylformamide (Me_2NCHO) was dried according to the literature procedure [15]. TLC was performed on 0.25-mm precoated silica gel plates ($60F_{254}$). The mp's reported are uncorrected. Benzyltriethylammonium tetrathiomolybdate (**1**) was prepared as described earlier [11]. Sugar bromides were prepared according to the literature procedures [9,12–14]. For more reactive anomeric bromides **2** and **4**, procedure A was adopted, and for less reactive sugar bromides **6**, **8**, **10**, and **12**, procedure B was used.

Procedure A: Reaction of 2,3,4-tri-O-acetyl-α-D-xylopyranosyl bromide (**4**) *with tetrathiomolybdate* (**1**).—To a soln of anomeric bromide **4** (0.514 g, 1.51 mmol) in CH_3CN (10 mL) was added tetrathiomolybdate **1** (1.01 g, 1.67 mmol), and the mixture was stirred at 0 °C for 19 h. Most of the solvent was evaporated under reduced pressure, and the black residue was slurried with CH_2Cl_2 (2 mL) and ether (10 mL), then filtered through a pad of Celite and washed with ether (6 × 20 mL). The combined filtrate on removal of solvent yielded a crude product, which on recrystallisation (4:1 ether–hexane) afforded the pure disulfide **5** (0.19 g, 43%) as a white solid: mp 142–145 °C; $[\alpha]_D^{25}$ −262° (*c* 2.04, $CHCl_3$); IR (Nujol): ν 1720, 1440, 1350, 1230, 1190 cm^{-1};

Table 1
Formation of sugar disulfides using benzyltriethylammonium tetrathiomolybdate (**1**) [a]

Entry	Substrate	Product	Time (h)	Yield (%)
1	 **2**	 **3**	24	65
2	 **4**	 **5**	19	43
3	 **6**	 **7**	72	81 (86)
4	 **8**	 **9**	72	70 (80)
5	 **10**	 **11**	72	78 (84)
6	 **12**	 **13**	72	30 (80)

[a] R = Oac; R^1 = OH. Yields in parentheses are based on recovered starting materials.

^{1}H NMR (270 MHz, $CDCl_3$): δ 5.27–5.05 (m, 4 H, H-5ax, 5eq, 5'ax, 5'eq), 5.05–4.88 (m, 2 H, H-4, 4'), 4.71 (d, 2 H, $J_{1,2}$ 8.0 Hz, H-1ax, 1'ax), 4.26 (dd, 2 H, $J_{3,4}$ 4.8, $J_{2,3}$ 11.8 Hz, H-3, 3'), 3.49 (dd, 2 H, $J_{1,2}$ 8.0, $J_{2,3}$ 11.8 Hz, H-2, 2'), 2.09 (s, 6 H, Ac), 2.07 (s, 6 H, Ac), 2.06 (s, 6 H, Ac); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 170.3 (C=O), 170.2 (C=O), 169.6 (C=O), 88.9 (C-1, C-1'), 72.4 (C-2, C-2'), 69.9 (C-4, C-4'), 68.9 (C-3, C-3'), 65.9 (C-5, C-5'), 21.1 (3 × CH_3). Anal. Calcd for $C_{22}H_{30}O_{14}S_2$ (582.59): C, 45.36; H, 5.15. Found: C, 44.91; H, 5.12.

*Procedure B: Reaction of methyl 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-α-*D*-mannopyranoside* (**10**) with tetrathiomolybdate (**1**).—To a soln of **1** (2.4 mmol, 1.44 g) in CH_3CN (9 mL) and Me_2NCHO (0.9 mL) was added the bromodeoxy compound **10** (0.83 g, 2.15 mmol), and the reaction mixture was stirred for 72 h at room temperature (25 °C). Two additional equiv of tetrathiomolybdate (2 × 1.44 g) were added during the reaction at 24-h intervals. Once the reaction was over (TLC), it was worked up as described in the previous section. Column chromatography of the material on silica gel using 65:35 petroleum ether–EtOAc afforded the unreacted starting material **10** (8%, 0.063 g) and the disulfide **11** (0.56 g, 78%) as a white solid: mp 71–73 °C; $[\alpha]_D^{25}$ +171° (*c* 1.1, $CHCl_3$); IR (Nujol): ν 1740, 1450, 1360, 1230, 1210 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.31 (dd, 2 H, $J_{2,3}$ 1.5, $J_{3,4}$ 10.5 Hz, H-3, 3'), 5.21 (m, 2 H, H-2, 2'), 5.12 (t, 2 H, $J_{3,4} = J_{4,5} = 10.5$ Hz, H-4, 4'), 4.68 (s, 2 H, H-1ex, 1'ex), 4.08–3.94 (m, 2 H, H-5, 5'), 3.43 (s, 6 H, OCH_3), 2.90 (d, 4 H, $J_{5,6}$ 5.3 Hz, H-6, 6'), 2.14 (s, 6 H, Ac), 2.07 (s, 6 H, Ac), 1.99 (s, 6 H, Ac); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.0 (3 × C=O), 98.4 (C-1, C-1'), 69.6, 69.2, 68.9 (C-2, C-2', C-3, C-3', C-4, C-4', C-5, C-5') 55.3 (OCH_3), 41.4 (C-6, C-6'), 20.8 (3 × CH_3); FABMS (*m/z*) 670 (M^+, 38), 639 (45), 303 (16), 155 (30), 99 (40), 43 (100); Anal. Calcd for $C_{26}H_{38}O_{16}S_2$ (670.69): C, 46.57; H, 5.67. Found: C, 46.83, H, 5.81.

*Bis-(2,3,4,6-tetra-*O*-acetyl-1-deoxy-1-thio-β-*D*-glucopyranosyl) 1,1'-disulfide* (**3**).—mp 140–142 °C, lit. 142–143 °C [6]; $[\alpha]_D^{25}$ −149.8° (*c* 2.3, $CHCl_3$), lit. −156° (*c* 2, $CHCl_3$) [6]; IR (Nujol): ν 1720, 1435, 1350, 1200 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.36–5.02 (m, 6 H, H-2, 2', 3, 3', 4, 4'), 4.66 (d, 2 H, $J_{1,2}$ 9.4 Hz, H-1ax, 1'ax), 4.28 (pair of dd, 4 H, $J_{5,6b}$ 1.8, $J_{5,6a}$ 4.2, $J_{6a,6b}$ 12.5 Hz, H-6, 6'), 3.81 (td, 2 H, $J_{5,6}$ 1.8, $J_{4,5}$ 9.9 Hz, H-5, 5'), 2.13 (s, 6 H, Ac), 2.1 (s, 6 H, Ac), 2.03 (s, 6 H, Ac), 2.0 (s, 6 H, Ac); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 170.2, 169.5, 168.9 (4 × C=O), 86.6 (C-1, C-1'), 75.6 (C-2, C-2'), 73.4 (C-5, C-5'), 69.2 (C-3, C-3'), 67.4 (C-4, C-4'), 61.2 (C-6, C-6'), 20.1 (4 × CH_3); FABMS (*m/z*) 727 ([M + 1]$^+$, 3), 667 (3), 547 (5), 331 (45), 169 (100), 109 (52). Anal. Calcd for $C_{28}H_{38}O_{18}S_2$ (726.71): C, 46.28, H, 5.23. Found: C, 45.85, H 5.25.

*Bis-(methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-thio-α-*D*-glucopyranoside) 6,6'-disulfide* (**7**).—mp 156–157 °C, lit. 156 °C [16]; $[\alpha]_D^{25}$ +255° (*c* 0.35, $CHCl_3$), lit. +259° (*c* 0.37, $CHCl_3$) [16]; IR (Nujol): ν 1735, 1450, 1360, 1240, 1210 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.46 (t, 2 H, $J_{3,4} = J_{4,5} = 9.7$ Hz, H-4, 4'), 5.00–4.81 (m, 6 H, H-1, 1', 2, 2', 3, 3'), 4.02 (td, 2 H, $J_{5,6}$ 3.2, $J_{4,5}$ 8.6 Hz, H-5, 5'), 3.44 (s, 6 H, OCH_3), 2.86 (a pair of dd, 4 H, $J_{5,6b}$ 3.2, $J_{5,6a}$ 8.5, $J_{6a,6b}$ 13.8 Hz, H-6, 6'), 2.07 (s, 6 H, Ac), 2.06 (s, 6 H, Ac), 2.00 (s, 6 H, Ac); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.7, 169.6 (3 × C=O), 96.5 (C-1, C-1'), 71.7 (C-4, C-4'), 70.8 (OCH_3), 69.8 (C-2, C-2'), 67.5 (C-5, C-5'), 55.4 (C-3, C-3'), 41.4 (C-6, C-6'), 20.4 (3 × CH_3); FABMS (*m/z*): 670 (M^+, 12), 638 (12), 477 (7). Anal. Calcd for $C_{26}H_{38}O_{16}S_2$ (670.69): C, 46.6, H, 5.71. Found: C, 46.1, H, 5.49.

*Bis-(methyl 6-deoxy-6-thio-α-*D*-glucopyranoside) 6,6'-disulfide* (**9**) *[16]*.—Compound **9** was isolated as a viscous liquid after the usual work-up and was additionally confirmed by acetylation, the product of which was identical to compound **7**.

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