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New conformationally locked thioderivatives of mannose: synthesis, applications, and mechanistic studies

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Abstract—Tetrathiomolybdate has been used as an efficient sulfur-transfer reagent in the synthesis of a number of thiolevomannosan derivatives having an axial-rich $^1C_4$ conformation. An unprecedented synthesis of a novel thioorthoester and its synthetic utility in glycosylation has been demonstrated. This is a general and efficient method for the synthesis of conformationally locked thiosugars.

Keywords: Glycosylation; Conformational locking; Thiolevomannosan; X-ray studies

1. Introduction

Thioglycosides have gained prominence as reliable glycosyl donors in the preparation of oligosaccharides.[1] The stability of thioglycosides to a broad range of reagents and conditions makes them ideal starting materials for the preparation of diversely functionalized glycosyl donors. Furthermore, sulfonated thiooligosaccharides have been found to activate lymphocytes that destroy certain tumors and virus-infected cells.[2]

Thiolevoglucosan has been known for many years,[3a,b] and efficient synthesis of thiolevoglucosan has been reported by Stick and co-workers.[4a–c] Recent work from our laboratory has shown that a number of derivatives of thiolevoglucosan[5] can be synthesized in high yield from glucosyl bromides using benzyltriethylammonium tetrathiomolybdate, $[BnNEt_3]_2MoS_4$ (**1**) as an efficient sulfur-transfer reagent.[6]

2. Results and discussion

It was of interest to extend this study to D-mannose (**2**) having an axial hydroxyl group at the C-2 position, which is likely to dictate an unexpected reactivity profile with tetrathiomolybdate **1**. In this article, we disclose an unprecedented synthesis of thioorthoester **6** and its utility in glycosylation reactions and also an efficient synthesis of thiolevomannosan derivatives using tetrathiomolybdate **1**. D-Mannose was initially converted into its per-*O*-acetyl-6-*O*-tosyl derivative **3**, which on treatment with HBr/AcOH under standard conditions led to the formation of mannosyl bromide **4**.[7] Treatment of **4** with tetrathiomolybdate **1** (2 equiv, CH_3CN, ultrasonic cleaning bath 25 kHz, 3 h) led to the formation of two products, thiolevomannosan derivative **5** and thioorthoester **6** (55:45), respectively, in 90% yield (Scheme 1). Their structures were confirmed by X-ray studies (Fig. 1).

The likely mechanism for the formation of thiolevomannosan derivative **5** is depicted in Scheme 2, which is analogous to the one reported by Stick and co-workers.[4d] Initial nucleophilic attack of **1** at the anomeric position of **4** leads to the formation of the intermediate **4a**, which can then undergo ring flipping leading to

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intermediate **4b**. Intramolecular displacement of tosylate as depicted then leads to thiolevomannosan derivative **5**.

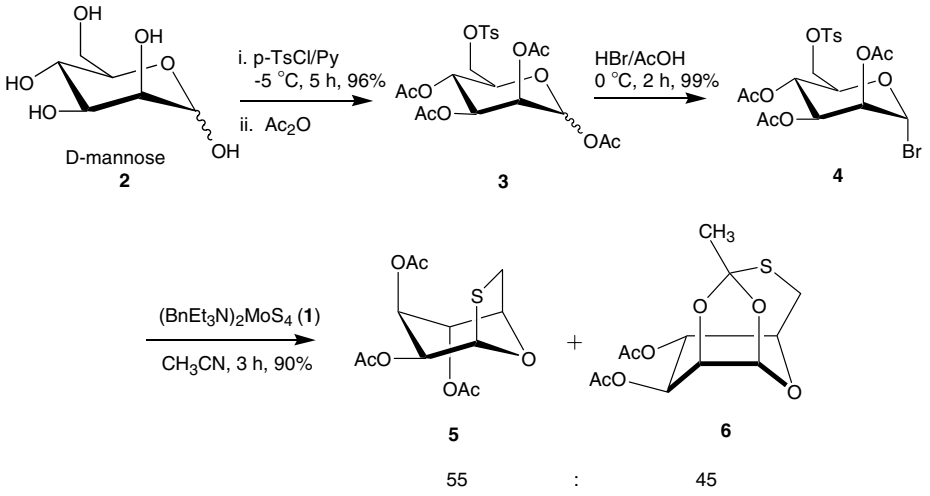
A tentative mechanism for the formation of thioorthoester **6** involving anchimeric assistance of the C-2 acetate in **4** is delineated in Scheme 3. Nucleophilic attack by tetrathiomolybdate **1** can lead to the formation of the intermediate **6a**, which can displace the tosylate as depicted to furnish the thioorthoester **6**.

In order to get an insight into the mechanism of this reaction, the 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide (**7**, having an acetate group instead of tosylate at C-6) was treated with tetrathiomolybdate **1** (CH_3CN, rt, 6 h), resulting in the formation of thiocarbonyl derivative **8** as the major product and disulfide **9** as the minor product in a ratio of 4:1 (Scheme 4). The formation of compound **8** may be visualized to take place as depicted in Scheme 4 (path a). In the absence of a tosylate as a good leaving group at C-6, the oxycarbenium ion **7a** can react with tetrathiomolybdate **1** to yield intermediate **7b**, which collapses to give the thiocarbonyl derivative **8** (Scheme 4).

The oxycarbenium ion **7a** can also react with **1** to give the alkylated intermediate **7c** (path b), which can lead to the disulfide **9** by a pathway established earlier.[6] The structure of **8** was confirmed by X-ray crystallography (Fig. 2).

The formation of novel thioorthoester **6** in the reaction of **4** with **1** provides an attractive opportunity to use this stable compound as a key partner in glycosylation reactions. A model glycosylation with **6** was carried out with *N*-iodosuccinimide (MeOH, 0 °C, 10 min) to furnish the glycosylated product **10** in good yield (Scheme 5). Encouraged by the success of this glycosylation reaction, a few more substrates were studied to test the general utility of the thioorthoester **6** as a good glycosyl donor, and in all cases the glycosylated products were obtained in good yields (Scheme 5).

It is important to note that, unlike other glycosylation reactions in which activators such as CF_3SO_3H were



Scheme 1.

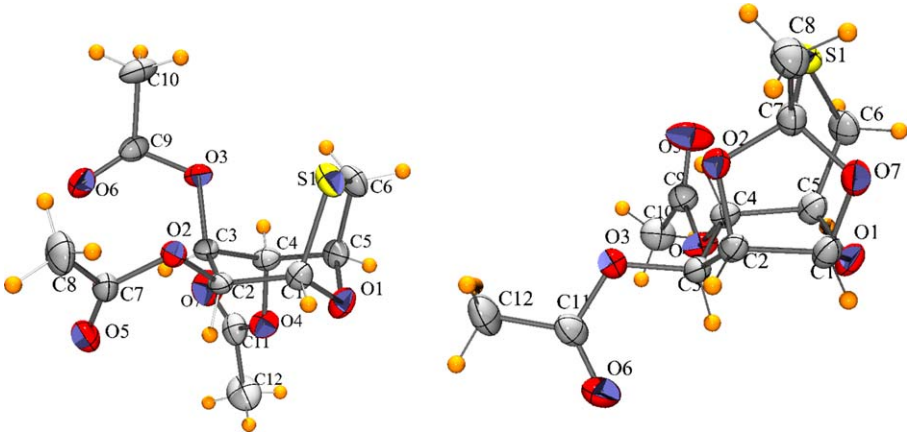
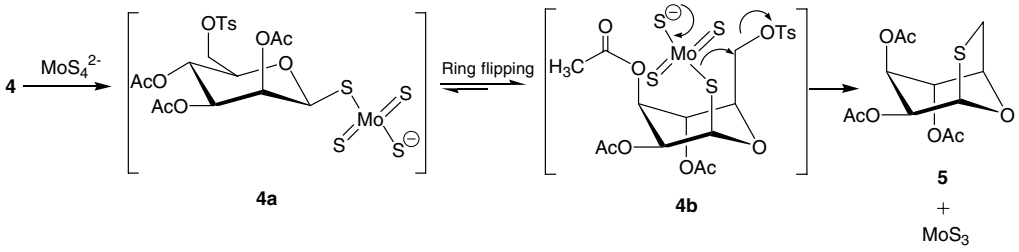
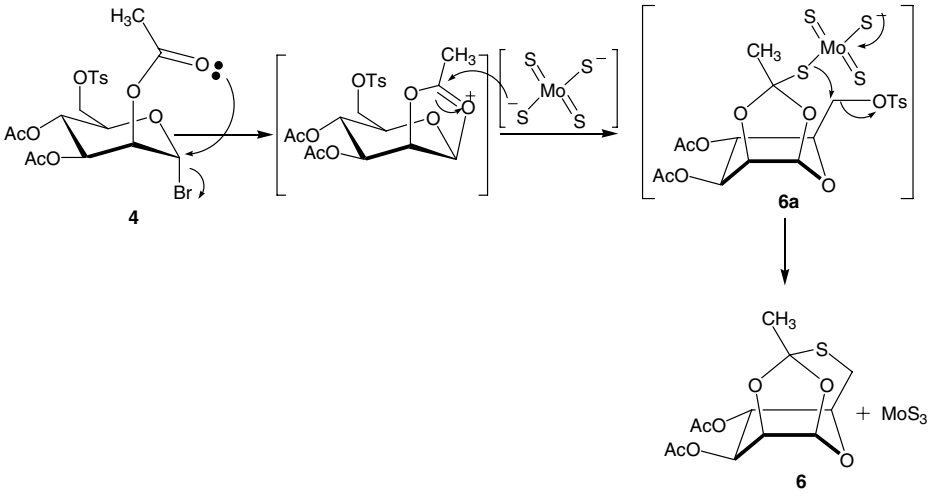


Figure 1. ORTEP diagrams for **5** and **6**.



Scheme 2. Mechanism for the formation of **5**.



Scheme 3. Mechanism for the formation of **6**.

used, the reactions with thioorthoester **6** do not need any activators. This is due to the enhanced reactivity of **6** compared to other glycosyl donors. These glycosylated products provide an additional opportunity to extend the oligosaccharide chain at the primary carbon since the disulfide bond can be cleaved by tetrathiomolybdate **1**.[6]

It was anticipated that, if the hydroxyl groups in mannose **2** are protected as benzoate or pivaloate in the reaction of anomeric bromides, it would be possible to obtain the corresponding thiolevomannosan as the only product. Accordingly, benzoate **13a** and pivaloate esters **13b** were synthesized using reported procedures.[8a,b] The esters were converted into the corresponding bromides **14a**,**b** using HBr/AcOH. Treatment of **14a**,**b** with tetrathiomolybdate **1** gave the corresponding thiolevomannosan derivative **15a** and **15b** as exclusive products in high yield (Scheme 6). In particular, the reaction of benzoate-protected bromide **14a** with tetrathiomolybdate **1** was very clean and high yielding (93%), and the structure of **15a** was confirmed by X-ray crystallography.

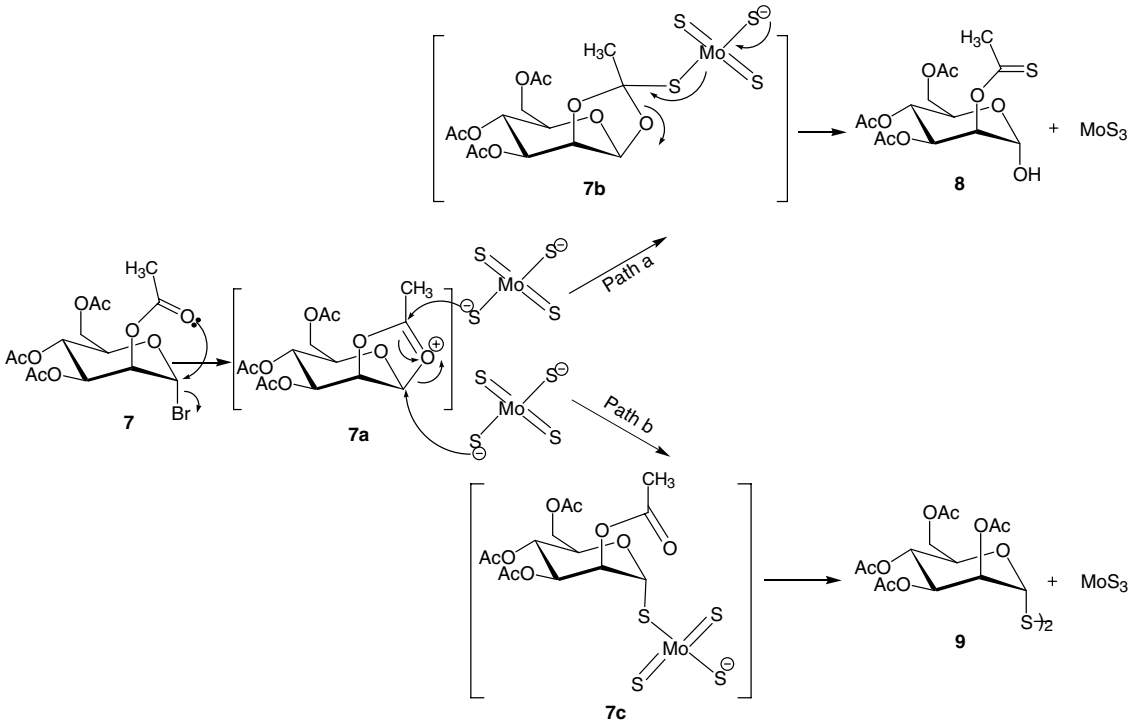
The starting mannose **2** has the $^4C_1$ conformation, but the final products **5** and **15** have the axial-rich $^1C_4$ conformation. These (1→6)-linked sugars can serve as important precursors for oligosaccharide synthesis.

In summary, the reactivity and utility of the reagent, tetrathiomolybdate **1** has been studied extensively with D-mannosyl bromides. An unprecedented synthesis of a novel thioorthoester **6** and its synthetic utility in glycosylation have been extensively studied with different acceptors. A facile and efficient synthesis of derivatives of thiolevomannosan from D-mannose has been reported. Reasonable mechanisms have been postulated for the formation of thio derivatives of mannose with reagent **1**. Efforts toward the synthesis of higher oligosaccharides using the thioorthoester **6** are under progress.

3. Experimental

3.1. General methods

Melting points reported were recorded on a BÜCHI B540 melting point apparatus, and melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL-300 MHz and 75 MHz spectrometer, respectively. Chemical shifts (δ) are reported in parts per million downfield from the internal reference, tetramethylsilane. Coupling constants are reported wherever it is necessary



Scheme 4. Mechanism for the formation of **8** and **9**.

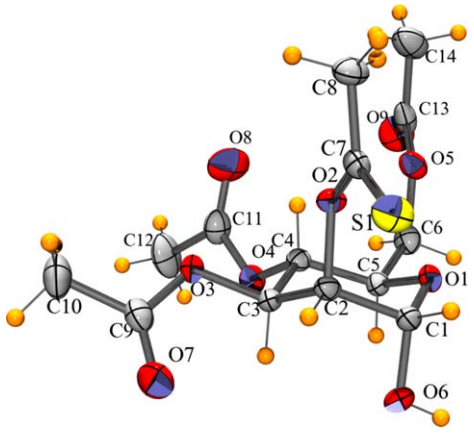


Figure 2. ORTEP diagram of **8**.

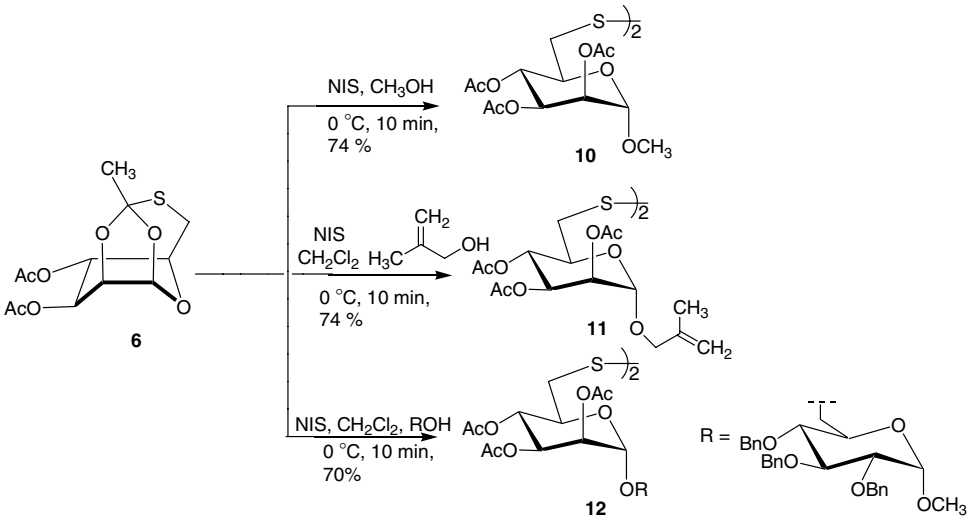
in hertz (Hz). Flash column chromatography was performed on silica gel (230–400 mesh). Mass spectra were recorded on a Q-TOF electrospray instrument. Data collections were recorded in BRUKER-SMART APEX CCD-Single-Crystal Diffractometer.

3.2. 2,3,4-Tri-*O*-acetyl-1,6-thioanhydro-β-D-mannose (5) and 3,4-di-*O*-acetyl-1,2-*O*-(6-thio-orthoacetyl)-β-D-mannopyranose (6)

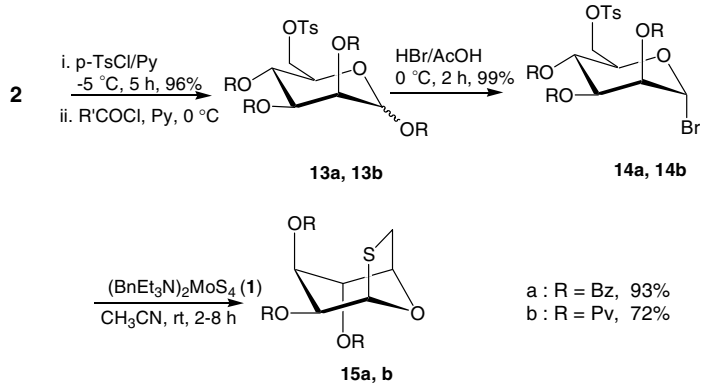
To a stirred solution of 2,3,4-tri-*O*-acetyl-6-*O*-(*p*-toluenesulfonyl)-α-D-mannopyranosyl bromide (**4**)[8] (0.49 g, 0.937 mmol) in CH_3CN (10 mL), benzyltriethylammonium tetrathiomolybdate (**1**)[6] (1.14 g, 1.183 mmol) was added, and the reaction mixture was sonicated for 3 h (ultrasonic cleaning bath; 25 kHz). After completion of the reaction (TLC), the solvent was removed in vacuo, and the black residue was extracted with 1:9 CH_2Cl_2–Et_2O (5 × 20 mL) and filtered through a Celite pad. The filtrate was concentrated, and the crude product was purified by flash column chromatography on silica gel (230–400 mesh, eluting with 1:1 hexane–EtOAc) to furnish compound **5** as shiny white crystals (0.13 g, 49.7%) and compound **6** (0.125 g, 40%) as colorless crystals.

3.2.1. Data for compound 5. Mp 125 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.46 (dd, 1H, J_1 4.2 Hz, J_2 1.2 Hz), 5.30 (t, 1H, J 5.4 Hz), 5.21–5.17 (m, 1H), 4.84 (dd, 1H, J_1 7.2 Hz, J_2 1.5 Hz), 4.76 (t, 1H, J 1.8 Hz), 3.30–3.18 (m, 2H), 2.16 (s, 3H), 2.14 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 169.6, 169.5, 81.6, 77.8, 72.7, 66.9, 66.4, 32.7, 20.9, 20.8, 20.7; HRESIMS: calcd for $C_{12}H_{16}O_7S$ ($M+Na^+$): m/z 327.0514; observed ($M+Na^+$): m/z 327.0512.

3.2.2. Data for compound 6. Mp 145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.76 (d, 1H, J 5.7 Hz), 5.43 (dd, 1H, J_1 9 Hz, J_2 2.1 Hz), 5.14 (dd, 1H, J_1 8.7 Hz, J_2 2.4 Hz), 4.63 (dd, 1H, J_1 6 Hz, J_2 2.7 Hz), 4.45 (dd, 1H, J 6 Hz), 3.43 (dd, 1H, J 12.6 Hz), 3.08 (dd, 1H, J_1 14.4 Hz, J_2 5.7 Hz), 2.16 (s, 3H), 2.08 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 170.5, 120.3, 98.9, 79.6, 73.9, 70.9, 69.2, 35.9, 28.6, 21.2, 20.8;



Scheme 5.



Scheme 6.

HRESIMS: calcd for $C_{12}H_{16}O_7S$ ($M+Na^+$): m/z 327.0514; observed ($M+Na^+$): m/z 327.0527.

3.3. 2-Thiocarbonyl-3,4,6-tri-*O*-acetyl-α-D-mannose (8) and bis-(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-manno-pyranosyl) 1,1′-disulfide (9)

To a stirred solution of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide (**7**) (0.34 g, 0.80 mmol) in CH_3CN (5 mL), benzyltriethylammonium tetrathiomolybdate **1** (0.58 g, 0.96 mmol) was added, and the reaction mixture was stirred for 6 h at 25 °C. After disappearance of starting material (TLC), solvent was removed in vacuo, and the black residue was extracted with 1:9 CH_2Cl_2–Et_2O (5 × 20 mL) and filtered through a Celite pad. The filtrate was concentrated, and the crude product was purified by flash column chromatography on silica gel (3:2 hexane–EtOAc) to furnish white crystals of compound **8** (0.22 g, 74%). Compound **9** was obtained as a gummy solid (0.22 g, 22%).

3.3.1. Data for compound 8. Mp 127 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.99 (dd, 1H, J_1 2.1 Hz, J_2 3.3 Hz), 5.56 (dd, 1H, J_1 3.6 Hz, J_2 10.2 Hz), 5.40–5.31 (m,1H), 4.30–4.09 (m, 4H), 3.69 (br s, 1H) 2.67 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 219.7, 170.7, 170.0, 169.9, 169.8, 91.3, 71.8, 69.0, 68.6, 68.5, 66.4, 66.1, 62.5, 53.7, 34.7, 29.2, 20.7; HRESIMS: calcd for $C_{14}H_{20}O_9S$ ($M+Na^+$): m/z 387.0726; observed ($M+Na^+$): m/z 387.0727.

3.3.2. Data for compound 9. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.99 (dd, 1H, J_1 3.3 Hz, J_2 1.8 Hz), 5.55 (dd, 1H, $J_1 = 10.2$ Hz, J_2 3.3 Hz), 5.4–5.33 (m, 2H), 4.29–4.24 (m, 2H), 3.37 (d, 1H, J 3.9 Hz), 2.67 (s, 3H), 2.11 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 169.6, 169.5, 81.6, 77.8,

72.7, 66.9, 66.4, 32.7, 20.9, 20.8, 20.7; HRESIMS: calcd for $C_{28}H_{38}O_{18}S_2$ ($M+Na^+$): m/z 749.1397, observed ($M+Na^+$): m/z 749.1469.

3.4. General experimental procedure for glycosylation with 6: synthesis of compounds 10, 11, and 12

3.4.1. Bis-(methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-thio-α-D-mannopyranoside) 6,6′-disulfide (10). To a stirred solution of thioorthoester **6** (0.03 g, 0.1 mmol) in CH_3OH (1 mL), *N*-iodosuccinimide (0.03 g, 0.118 mmol) was added at 0 °C. There was an immediate color change from colorless to deep purple. After completion of the reaction (10 min) CH_3OH was evaporated, and the crude product was dissolved in CH_2Cl_2 (30 mL). This mixture was washed with sodium thiosulfate solution (2×10 mL) and then with water (2×10 mL). The organic layer was dried over anhyd Na_2SO_4, and the filtrate was concentrated. The residue was then purified by flash column chromatography on silica gel (3:7 hexane–EtOAc) to furnish compound **10** as a gummy solid (0.05 g, 74%).

3.4.2. Data for compound 10. ^1H NMR (300 MHz, $CDCl_3$): δ 5.48 (d, 1H, J 3 Hz), 5.21 (br d, 1H, J 2.4 Hz), 5.17 (dd, 1H, J_1 6.3 Hz, J_2 3.3 Hz), 4.61 (br dd, 1H, J 2.7 Hz), 3.75 (m, 1H), 3.27 (s, 3H), 3.01 (m, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 169.8, 124.3, 97.5, 77.2, 76.4, 75.4, 71.9, 70.4, 69.5, 68.5, 53.8, 49.9, 41.7, 31.7, 29.3, 24.2, 20.8, 20.7; HRESIMS: calcd for $C_{28}H_{44}O_{16}S_2$ ($M+Na^+$): m/z 693.1499; observed ($M+Na^+$): m/z 693.1454.

3.4.3. Bis-(methacrylyl 2,3,4-tri-*O*-acetyl-α-D-mannopyranoside) 6,6′-dithiodianhydride (11) and bis-{methyl (2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)-[1→6]-2,3,4-tri-*O*-acetyl-α-D-mannopyranoside} 6,6′-dithiodianhydride (12). To a stirred solution of thioorthoester **6** (0.03 g, 0.1 mmol) in CH_2Cl_2 (1 mL), *N*-iodosuccinimide (0.03 g, 0.118 mmol) was added at 0 °C, followed by the addition of appropriate acceptor (0.118 mmol). The same color change to purple was observed, and after the reaction (TLC) the products were isolated as described in the previous experiment. Compounds **11** (74%) and **12** (70%) were both obtained as gummy solids.

3.4.4. Data for compound 11. ^1H NMR (300 MHz, $CDCl_3$): δ 5.30 (s, 1H), 5.01 (br d, 1H), 4.95 (br s, 1H), 4.80 (br s, 1H), 4.06 (dd, J_1 11.4 Hz, 1H), 2.90 (br d, 2H), 2.77 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H), 1.99 (s, 3H); HRESIMS: calcd for $C_{32}H_{46}O_{16}S_2$ ($M+Na^+$): m/z 773.2125; observed ($M+Na^+$): m/z 773.2177.

3.4.5. Data for compound 12. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.30 (aromatic, 15H), 5.30 (s, 1H), 3.37 (s, 3H), 2.16 (s, 3H), 2.09 (s, 3H), 2.01 (s, 3H); HRESIMS: calcd for $C_{80}H_{94}O_{26}S_2$ ($M+Na^+$): m/z 1558.7188; observed ($M+Na^+$): m/z 1558.877.

3.5. General procedure: 2,3,4-tri-*O*-benzoyl-1,6-thioanhydro-β-D-mannose (15a) and 2,3,4-tri-*O*-pivaloyl-1,6-thioanhydro-β-D-mannose (15b)

To a stirred solution of the bromide **14a** (0.28 g, 0.395 mmol) in CH_3CN (4 mL), benzyltriethylammonium tetrathiomolybdate **1** (0.5 g, 0.83 mmol) was added at 28 °C. After completion of the reaction (TLC, 2 h) the solvent was evaporated in vacuo, and the black residue was extracted with 1:9 CH_2Cl_2–Et_2O (5×20 mL) and filtered through a Celite pad. The filtrate was concentrated, and the crude products were purified by flash column chromatography on silica gel (7:3 hexane–EtOAc) to furnish the products. Compound **15a** was obtained as a white crystalline solid (0.18 g, 93%).

3.5.1. Data for compound 15a. Mp 75 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 5.50 (dd, 15H, aromatic), 3.40–3.48 (m, 2H), 5.10 (dd, 1H, J 1.2 Hz), 5.20 (s, 1H), 5.72–5.79 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 67.3, 67.4, 73.1, 77.9, 81.7, 128.3, 128.6, 128.6, 129.8, 130.0, 130.1, 133.4, 133.5, and 133.7; HRESIMS: calcd for $C_{27}H_{22}O_7S$ ($M+Na^+$): m/z 513.1086; observed ($M+Na^+$): m/z 513.0984.

3.5.2. Data for compound 15b. Colorless gummy solid (0.13 g, 72%); ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–8.19 (dd, 1H, J_1 3.9 Hz, J_2 1.5 Hz), 5.25–5.22 (m, 1H), 5.20–5.17 (m, 1H), 4.81–4.77 (m, 1H), 4.64 (t, 1H, J 1.8 Hz), 3.30–3.15 (m, 2H), 2.27 (s, 9H), 1.25 (s, 9H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176, 175.8, 174.6, 80.1, 76.2, 75, 73.8, 71.0, 36.3, 42.5, 26.2. HRESIMS: calcd for $C_{21}H_{34}O_7S$ ($M+Na^+$): m/z 453.2025; observed ($M+Na^+$): m/z 453.1923.

Acknowledgements

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Supplementary data

Supplementary data [characterization data (^1H, ^{13}C, HRMS) for compounds **5**, **6**, **8**–**12**, and **15**, and the crystallographic information file (CIF) for compounds **5**, **6**, **8**, **15a**] associated with this article can be found in the online version at doi:10.1016/j.carres.2006.06.001. Crystallographic data for all the above reported compounds

have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. (a) Compound-**5** CCDC-287582, (b) Compound-**6** CCDC-282454, (c) Compound-**8** CCDC-287584, (d) Compound-**15a** CCDC-282453. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK, +44 1223 336408; email: deposit@ccdc.cam.ac.uk.

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