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1→2 Migration and concurrent glycosidation of phenyl 1-thio-α-mannopyranosides via 2,3-*O*-cyclic dioxonium intermediates

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Abstract—Treatment of phenyl 2,3-*O*-cyclic ketene acetal- and 2,3-*O*-thionocarbonyl-1-thio-mannopyranosides with TMSOTf and MeOTf, respectively, gave the corresponding 2,3-*O*-cyclic dioxonium intermediates, which proceeded via 1→2 migration and concurrent glycosidation in the presence of alcohols to provide the corresponding 2-*S*-phenyl glycosides stereoselectively. While the former donors were too labile, the latter donors have proved superior for the present purpose. The X-ray crystallographic structures of phenyl 4-*O*-methyl-2,3-*O*-thiocarbonyl-1-thio-α-L-rhamnopyranoside (**1**), a typical donor for the present reaction, and its anomeric azide analogue (**6**), which could not undergo the present reaction under similar conditions, are provided.

1. Introduction

Based on the incidental finding that ethyl 1-thio-α-L-rhamnopyranoside 2,3-*O*-orthoesters undergo a 1→2 migration and concurrent glycosidation under the action of acids,[1,2] we developed a facile approach for the stereoselective syntheses of 2-thio-β-glucopyranosides by using ethyl(phenyl) 1-thio-α-mannopyranoside 2,3-*O*-ethoxyethylidenes as donors and TMSOTf as a promoter.[2] The resulting products are ready precursors to 2-deoxy-β-glycosides, which are important structural components in many natural products, and are otherwise difficult to synthesize. Although this method possess such advantages as easy accessibility of donors, convenient reaction conditions, and tolerance towards a variety of alcohol acceptors, an inherent drawback is that the ethoxy group resulting from the 2,3-*O*-ethoxyethylidene competes for glycosidation.[2] On mechanistic consideration (Scheme 1), 2,3-*O*-cyclic dioxonium IV was the key intermediate from 2,3-*O*-orthoester I, which then transformed into an 1,2-episulphonium, and finally led to the stereoselective 1→2 migration and concurrent glycosidation upon nucleophilic attack of an alcohol on the anomeric carbon. Therefore, any 1-thio-α-mannopyranosides which could generate 2,3-*O*-cyclic dioxonium IV would be possible donors. We have recently disclosed that phenyl 2,3-*O*-thionocarbonyl-1-thio-α-mannopyranosides (III) were ideal for this purpose.[3] This protocol has been successfully applied to the synthesis of the hexadeoxysaccharide fragment of Landomycine A, i.e., α-L-rhodinose-(1→3)-β-D-olivose-(1→4)-β-D-olivose-(1→4)-α-L-rhodinose-(1→3)-β-D-olivose-(1→4)-β-D-olivose→OMP.[4] Here we report the experimental results which have not been mentioned previously for the development of this successful glycosidation method.

2. Results and discussion

Shown in Scheme 2 is a representative example using phenyl 2,3-*O*-thionocarbonyl-1-thio-α-mannopyranosides for 1→2 migration and concurrent glycosidation.[3,4] While the expected product **2** was produced in excellent yield, a variable amount of **3** was always detected, which was conceivably produced via attack of the corresponding 2,3-*O*-cyclic dioxonium intermediate (IV) by any moisture that remains in the reaction, or water introduced in the workup procedure.

Nicolaou et al. disclosed that the 1→2 migration of an anomeric N_3 group took place as readily as that of the anomeric PhS group on the relevant 2-OH sugars under the promotion of DAST.[5] We thus explored the possibility of N_3 migration and concurrent glycosidation within the present subject (Scheme 3). Unfortunately, treatment of 2,3-*O*-thionocarbonyl azide **6**, which was readily prepared from **4**,[6] under similar conditions for the glycosidation of the 1-phenylthio counterpart **1**, did not produce the desired product **7**. In fact, no products other than the hydrolysis product **8** were detected.

Keywords: glycosidation; phenyl 1-thio-α-mannopyranoside; 2,3-*O*-cyclic dioxonium.

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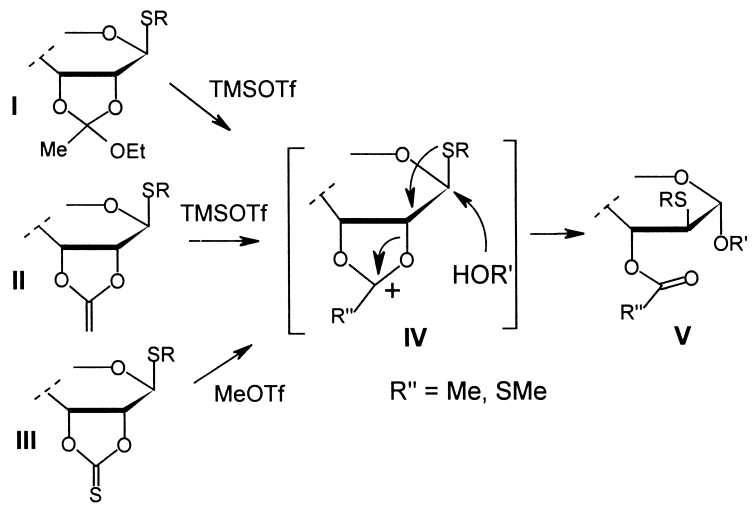
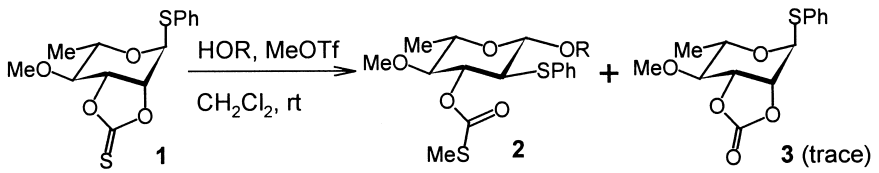


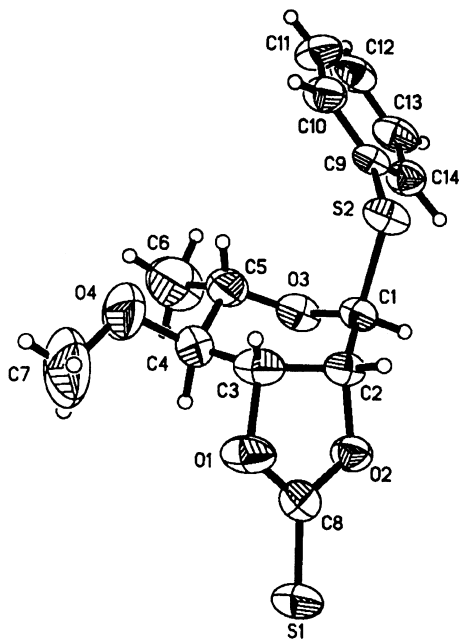
Scheme 1.



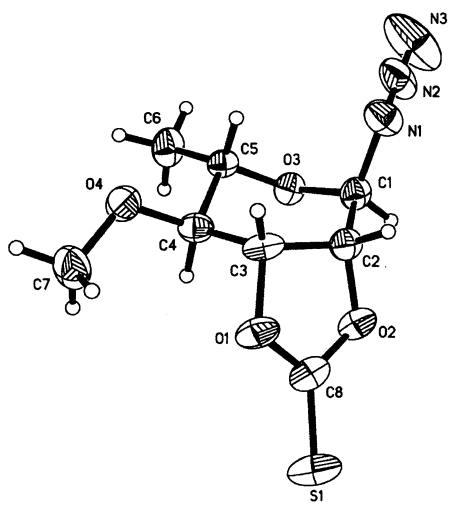
Scheme 2.

The single crystals of **1**, a typical donor, and the anomeric azide analogue **6** were obtained, which led to the X-ray structures as shown in the ORTEP drawings.[7] The fused-ring bicyclic systems of these two compounds adopt very similar conformations. The C9–S2–C1–C2–O2–C8–S1 atoms on **1** are orientated in such a way (i.e., the torsion angles of C9–S2–C1–C2, S2–C1–C2–O2, C1–C2–O2–C8, and C2–O2–C8–S1 are −163.5(2)°, −158.98(19)°, −147.3(2)°, and −171.5(2)°, respectively) that a ready 1⟶2 PhS migration would be facilitated. The similar conformation of **6** therefore could not explain why a 1⟶2 N_3 migration did not take place, the reason must lie in the different nuleophilicity of the phenylthio and the azide group.

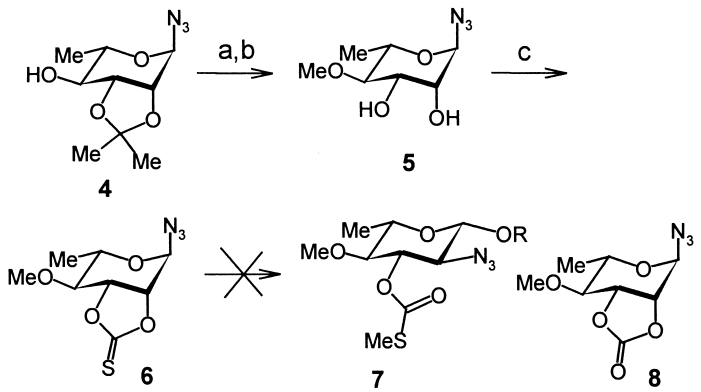
In the previous reports,[3,4] all the phenyl 2,3-*O*-thionocarbonyl-1-thio-α-mannopyranosides employed as donors were 6-deoxy derivatives. Thus, we further explored the utility of 6-hydroxylated sugars for glycosidation (Scheme 4). Subjecting phenyl 4,6-di-*O*-acetyl-2,3-*O*-thionocarbonyl-1-thio-α-D-mannopyranoside (**10**), which was readily prepared from diol **9**,[8] to the typical glycosidation conditions (1.2 equiv. MeOTf, alcohol **13**, 4 Å MS, CH_2Cl_2, room temperature, with or without 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP))[3,4] produced complex products.



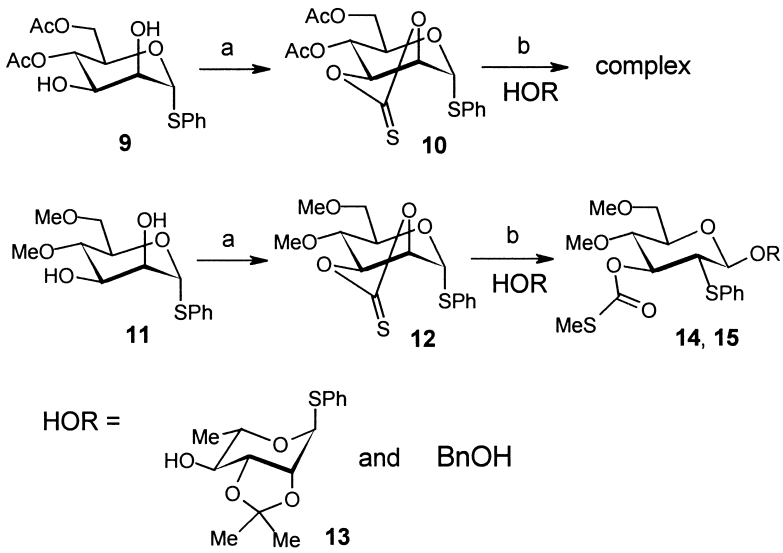
ORTEP drawing of **1**



ORTEP drawing of **6**



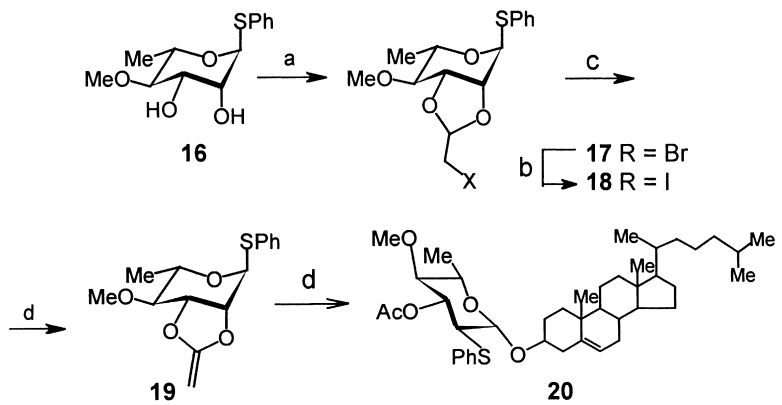
Scheme 3. *Reagents and conditions*: (a) MeI, NaH, DMF, room temperature; (b) *p*-TsOH·H_2O, 30°C, 92% (for two steps); (c) Im_2CS, THF, 60°C, 90%.



Scheme 4. *Reagents and conditions*: (a) Im_2CS, THF, 60°C, 80% (for **10**); 87% (for **12**); (b) **13** or BnOH, MeOTf (1.2 equiv.), DTBMP, 4 Å MS, CH_2Cl_2, room temperature, 85% (for **14**); 73% (for **15**).

The complexity might arise from the competitive attack on the nascent 2,3-*O*-cyclic dioxonium (IV) by the proximal carbonyl oxygen in the 6-OAc function. Thus, 4,6-di-*O*-methyl derivative **12** was prepared from diol **11**[8] and subjected toward glycosidation under similar conditions. Indeed, the expected glycosides **14** and **15** were obtained in satisfactory yields (89 and 73%, respectively) when sugar alcohol **13** and benzyl alcohol were used as acceptors, respectively.

Hecht and co-workers have reported the preparation of sugar 1,2-*O*-cyclic ketene acetals (1,2-*O*-vinylidene acetals) and the reaction of the resulting 1,2-*O*-cyclic acetoxoniums upon treatment with proton donors.[9] The 1,2-*O*-cyclic acetoxoniums are always the putative key intermediates in the glycosylation reaction employing sugar donors with a neighbouring acetyl group.[10] We thus envisioned phenyl 1-thio-α-L-rhamnopyranoside 2,3-*O*-cyclic ketene acetals, which would readily lead to 2,3-*O*-cyclic dioxoniums (IV), as good donors for the present 1→2 migration and concurrent glycosidation (Scheme 5). Treatment of 2,3-diol **16**[3,11] with 2-bromo-1,1-dimethoxyethane in the presence of a catalytic amount of 10-camphorsulphonic acid (CSA) gave 2,3-*O*-acetal **17** in 81% yield.[12] Dehydrobromination of **17** under the action of bases (KOH or *t*-BuOK) in the presence or absence of phase transfer agents (TBAB or Aliquat 336) in THF or DMF at various temperatures led to no product or complex products,[12,13] including the decomposed product **16**. Thus bromide **17** was converted into the corresponding iodide **18** (KI, Aliquat 336 (2%), DMF, 80°C, 90%). Applying the iodide **18** to the typical elimination conditions ($KOBu^t$, DMF, room temperature) gave clean reaction as monitored by TLC; the starting iodide disappeared within 2 h and two new spots appeared. However, flash chromatography on a silica gel column, even using Et_3N containing elutes, only afforded the more polar product. The ^1H NMR spectrum of the resulting product correlated clearly to a mixture of the 2-OAc and 3-OAc derivatives, which are conceivably derived from the desired 2,3-cyclic ketene acetal.[12] Therefore, the reaction mixture, after concentration under vacuum, was passed through a short basic alumina column (pH~9.5) with 15:1 petroleum ether–Et_3N as elutes. Removal of the elutes under vacuum provided a white syrup, whose ^1H NMR spectrum was still complicated due to the appearance of the mono-acetyl derivatives. Fortunately, direct utilization of the resulting syrup for the glycosidation conditions (cholesterol, 0.2 equiv. TMSOTf,



Scheme 5. *Reagents and conditions*: (a) $BrCH_2CH(OMe)_2$, CSA (cat.), 60°C, 81%; (b) KI, Aliquat 336, DMF, 80°C, 90%; (c) $KOBu^t$, DMF, room temperature; (d) cholesterol, TMSOTf (0.2 equiv.), 4 Å MS, CH_2Cl_2, room temperature, 76%.

4 Å MS, CH_2Cl_2, room temperature) afforded the desired 1→2 migration and concurrent glycosidation product **20** in satisfactory yield (78%).

In conclusion, under the scope of 2,3-*O*-cyclic dioxonium initiated 1→2 migration and concurrent glycosidation of 1-thio-α-mannopyranosides, we developed 2,3-*O*-ortho-esters,[2] 2,3-*O*-ketene acetals, and 2,3-*O*-thionocarbonates as donors. While the 2,3-*O*-orthoesters inhere a competing glycosidation of the ethoxy group and the 2,3-*O*-ketene acetals are unstable, the 2,3-*O*-thionocarbonates demonstrate optimal donor characteristics.[3,4]

3. Experimental

3.1. General remarks[14]

3.1.1. Phenyl 2,3-*O*-carbonyl-4-*O*-methyl-1-thio-α-L-rhamnopyranoside (3). Trace amount of **3** was obtained as a white amorphous solid in the glycosidation reaction of 2,3-*O*-thionocarbonyl donor **1**,[3,4] under similar conditions for preparation of **14** and **15**. **3**: $[\alpha]_D^{20}=-248.5$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.46–7.34 (m, 5H, Ph), 5.77 (s, 1H, H-1), 4.86 (d, 1H, *J*=6.9 Hz, H-2), 4.75 (t, 1H, *J*=6.9 Hz, H-3), 4.15 (m, 1H, H-5), 3.57 (s, 3H, OMe), 3.14 (dd, 1H, *J*=9.7, 6.9 Hz, H-4), 1.28 (d, 3H, *J*=6.2 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.26 (C=O), 132.56, 131.67, 129.33, 128.43, 82.66, 82.22, 78.81, 77.56, 65.66, 59.62, 17.54; EIMS (*m*/*z*, %): 296 (M^+, 25.6), 187 (100), 110 (38.0). IR (ν_{max}): 2979, 2939, 2897, 1805 (C=O) cm^{-1}. Anal. calcd for $C_{14}H_{16}O_5S$: C, 56.72; H, 5.44. Found: C, 56.83; H, 5.62.

3.1.2. 4-*O*-Methyl-α-L-rhamnopyranosyl azide (5). To a solution of 2,3-*O*-isopropylidene-α-L-rhamnopyranosyl azide (**4**)[6] (1.89 g, 8.23 mmol) in DMF was added NaH (0.82 g, 20.5 mmol, 60% suspension in paraffin oil). After stirring at room temperature for 0.5 h, MeI (2.6 mL, 41.15 mmol) was added to the suspension at 0°C. The mixture was stirred for an additional 3.5 h at room temperature. TLC (3:1 hexane–EtOAc) indicated completion of the reaction. The mixture was quenched with water and diluted with CH_2Cl_2 (80 mL). The organic layer was washed successively with 2 M HCl (20 mL), aq. $NaHCO_3$ (20 mL), and brine, and then dried over $MgSO_4$. After evaporation of the solvent, the residue oil was dissolved in MeOH (30 mL), and *p*-TsOH·H_2O (210 mg, 1.2 mmol) was added to the solution. The mixture was stirred at 30°C for 5 h, and then quenched with Et_3N. After concentration the residue was purified by flash silica gel column chromatography (1:2 hexane–EtOAc) to afford **5** (1.54 g, 92%) as a white solid mp 93.3°C; $[\alpha]_D^{20}=-262.1$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 5.32 (s, 1H, H-1), 3.85 (br s, 1H, H-2), 3.76 (m, 2H, H-3, H-5), 3.56 (s, 3H, OMe), 3.12 (t, 1H, *J*=9.1 Hz, H-4), 2.51 (m, 2H, OH), 1.38 (d, 3H, *J*=6.1 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 89.4, 82.4, 70.6, 70.3, 69.6, 60.6, 17.8. ESIMS (*m*/*z*): 226.0 ($M+Na^+$). IR (ν_{max}): 3261 (br), 2120 (N_3) cm^{-1}. Anal. calcd for $C_7H_{13}N_3O_4$: C, 41.38; H, 6.45; N, 20.68. Found: C, 41.39; H, 6.39; N, 20.53.

3.1.3. 4-*O*-Methyl-2,3-*O*-thionocarbonyl-α-L-rhamnopyranosyl azide (6). To a solution of the diol **5** (200 mg, 0.98 mmol) in dry THF (5 mL) was added a solution of 1,1′-thiocarbonyl diimidazole (234 mg, 1.18 mmol) in dry THF (5 mL). The mixture was stirred at reflux under an atmosphere of Ar for 3.5 h. TLC indicated completion of the reaction. Then the mixture was concentrated and purified by a silica gel column chromatography (6:1 hexane–EtOAc) to provide **6** (227 mg, 94%) as a white solid. Recrystallization in petroleum ether and CH_2Cl_2 gave **6** as colourless prisms.[7] mp 76.8°C; $[\alpha]_D^{20}=-176.7$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 5.70 (s, 1H, H-1), 4.87 (t, 1H, *J*=7.0 Hz, H-3), 4.60 (d, 1H, *J*=7.0 Hz, H-2), 3.81 (m, 1H, H-5), 3.57 (s, 3H, OMe), 3.10 (dd, 1H, *J*=9.9, 7.0 Hz, H-4), 1.39 (d, 3H, *J*=6.3 Hz, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.3, 84.6, 82.8, 81.1, 79.7, 66.2, 59.8, 17.5. ESIMS (*m*/*z*): 246.0 ($M+H^+$). IR (ν_{max}): 2164, 2121, 1328 cm^{-1}. Anal. calcd for $C_8H_{11}N_3O_4S$: C, 39.18; H, 4.52; N, 17.13; S, 13.07. Found: C, 39.19; H, 4.50; N, 17.19; S, 13.03.

3.1.4. 2,3-*O*-Carbonyl-4-*O*-methyl-α-L-rhamnopyranosyl azide (8). Trace amount of **8** was obtained as a white solid in the attempted glycosidation reaction of 2,3-*O*-thionocarbonyl azide **6** under the similar conditions for the preparation of **14** and **15**; mp 78.8°C; $[\alpha]_D^{20}=-204.8$ (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 5.63 (s, 1H, H-1), 4.66 (t, 1H, *J*=7.0 Hz, H-3), 4.48 (d, 1H, *J*=7.0 Hz, H-2), 3.83–3.78 (m, 1H, H-5), 3.54 (s, 3H, OMe), 3.09 (dd, 1H, *J*=9.6, 7.0 Hz, H-4), 1.38 (d, 3H, *J*=6.3 Hz, H-6). ESIMS

(*m*/*z*): 252.1 ($M+Na^+$). IR (ν_{max}): 2121, 1847 (C=O) cm^{-1}. Anal. calcd for $C_8H_{11}N_3O_5$: C, 41.92; H, 4.84; N, 18.33. Found: C, 42.36; H, 5.03; N, 17.96.

3.1.5. Phenyl 4,6-di-*O*-acetyl-2,3-*O*-thionocarbonyl-1-thio-α-D-mannopyranoside (10). To the diol **9**[8] (1.12 g, 3.14 mmol) in dry tetrahydrofuran (8 mL) was added a solution of 1,1′-thiocarbonyldiimidazole (840 mg, 4.72 mmol) in THF (8 mL) while at reflux under an atmosphere of Ar. After being stirred for 2 h, the reaction mixture was diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and then filtered and concentrated in vacuum. The residue was purified by flash chromatography (10:1 petroleum ether–EtOAc) to give **10** (1.0 g, 80%) as a white amorphous solid. $[\alpha]_D^{20}=162.2$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.51–7.36 (m, 5H, Ph), 5.93 (s, 1H, H-1), 5.20–5.05 (m, 3H), 4.52–4.44 (m, 1H), 4.26 (dd, 1H, *J*=12.4, 5.5 Hz, H-6), 4.09 (dd, 1H, *J*=12.4, 2.5 Hz, H-6′), 2.16, 2.02 (s each, 3H each, 2 Ac). ESIMS (*m*/*z*, %): 338 (M^+-60, 0.6), 261 (12.6), 247 (16.3). IR (ν_{max}): 1751, 1737, 1319, 1302, 1242 cm^{-1}. Anal. calcd for $C_{17}H_{18}O_7S_2\cdot 1/2H_2O$: C, 50.11; H, 4.70. Found: C, 50.29; H, 4.79.

3.1.6. Phenyl 4,6-di-*O*-methyl-2,3-*O*-thionocarbonyl-1-thio-α-D-mannopyranoside (12). A similar procedure for the preparation of **10** from diol **9** was employed for the synthesis of **12** from diol **11**.[8] Compound **12** was obtained as a white solid (87%); mp 92.9°C; $[\alpha]_D^{20}=203.0$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.55–7.38 (m, 5H, Ph), 5.93 (s, 1H, H-1), 5.05–5.03 (m, 2H), 4.24–4.18 (m, 1H), 3.71–3.54 (m, 6H), 3.40 (s, 3H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.6, 132.5, 131.2, 129.3, 128.5, 83.0, 82.1, 81.1, 75.9, 70.4, 68.9, 59.5, 59.2. IR (ν_{max}): 3004, 2968, 2931, 1368, 1377, 1345, 1302, 1285, 1101 cm^{-1}; ESIMS (*m*/*z*): 360.1 ($M+NH_4^+$). Anal. calcd for $C_{15}H_{18}O_5S_2\cdot 1/2H_2O$: C, 51.26; H, 5.45. Found: C, 51.51; H, 5.43.

3.2. Typical procedure for the glycosidation reaction of phenyl 2,3-*O*-thionocarbonyl-1-thio-α-mannopyranoside donors with alcohols

To a stirred solution of an alcohol (1.0 equiv.), 2,6-di-*tert*-butyl-4-methylpyridine (1.5 equiv.), and 4 Å MS in anhydrous CH_2Cl_2 at room temperature under argon, was added a solution of the donor in CH_2Cl_2 (1.2 equiv.), followed by the addition of a solution of MeOTf (1.2 equiv.) in CH_2Cl_2. After being stirred for 6 h, the mixture was quenched with Et_3N, and then filtered through a pad of Celite™. The filtrates were concentrated. The residue was applied to a silica gel column chromatography (5:1 petroleum ether–EtOAc) to give the corresponding 2-thioglycosides as amorphous solids.

3.2.1. Phenyl 4,6-di-*O*-methyl-3-*O*-(methylthio)carbonyl-2-*S*-phenyl-β-D-glucopyranosyl-(1→4)-2,3-*O*-isopropylidene-1-thio-α-L-rhamnopyranoside (14). $[\alpha]_D^{20}=-159.7$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.56–7.25 (m, 10H, 2×SPh), 5.70 (s, 1H, H-1), 5.12 (dd, 1H, *J*=11.4, 8.7 Hz, H-3′), 4.95 (d, 1H, *J*=9.0 Hz, H-1′), 4.31–4.29 (m, 2H), 3.90–3.82 (m, 1H), 3.76–3.70 (m, 1H), 3.68–3.54 (m, 2H), 3.46 (s, 3H, OMe), 3.44–3.36 (m, 4H, OMe), 3.34–3.28 (m, 1H), 3.07 (dd, 1H, *J*=11.4, 8.7 Hz, H-2), 2.40 (s, 3H, MeS), 1.50, 1.36 (s each, 3H each, Me_2C), 1.07 (d, 3H, *J*=6.0 Hz, H-6); IR (ν_{max}): 2986, 2935, 1722, 1144, 1122 cm^{-1}; ESIMS (*m*/*z*): 670.3 ($M+NH_4^+$). Anal. calcd for $C_{31}H_{40}O_9S_3$: C, 57.03; H, 6.18. Found: C, 56.61; H, 6.19.

3.2.2. Benzyl 4,6-di-*O*-methyl-3-*O*-(methylthio)carbonyl-2-*S*-phenyl-β-D-glucopyranosides (15). $[\alpha]_D^{20}=-14.4$ (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.52–7.20 (m, 10H, Ph), 5.11 (dd, 1H, *J*=11.4, 8.7 Hz, H-3), 4.91 (d, 1H, *J*=12.0 Hz), 4.60 (d, 1H, *J*=12.0 Hz), 4.34 (d, 1H, *J*=9.0 Hz, H-1), 3.64–3.61 (m, 2H), 3.47, 3.42 (s each, 3H each, 2×OMe), 3.40–3.27 (m, 2H), 3.05 (dd, 1H, *J*=11.4, 8.7 Hz, H-2), 2.40 (s, 3H, MeS); IR (ν_{max}): 2934, 2839, 1720, 1146, 1112 cm^{-1}; ESIMS (*m*/*z*): 482.2 ($M+NH_4^+$); HRMS (*m*/*z*): calcd for $C_{23}H_{28}O_6S_2$: 464.1327. Found: 464.1345.

3.2.3. Phenyl 2,3-*O*-bromoethylidene-4-*O*-methyl-1-thio-α-L-rhamnopyranoside (17). In a 25 mL flask fitted with a Claisen distillation apparatus were heated diol **16**[3,11] (344 mg, 1.27 mmol), bromoacetaldehyde dimethyl acetal (0.3 mL, 2.54 mmol), and CSA (89 mg, 0.38 mmol) at 70°C for 7 h while being stirred. The methanol was continuously removed during the reaction by distillation into a receiver. The crude product was purified by a silica gel column chromatography (12:1 petroleum ether–EtOAc) to give **17** (387 mg, 81%) as a yellow syrup. $[\alpha]_D^{20}=-153.8$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.56–7.28 (m, 5H, SPh), 5.79 (s, 1H, H-1), 5.22 (dd, *J*=4.7, 3.6 Hz, 1H), 4.34–4.22 (m, 2H), 4.06–4.02 (m, 1H), 3.56 (s, 3H, OMe), 3.54–3.44 (m, 2H), 3.18–3.12 (m, 1H), 1.25 (d, *J*=6.3 Hz, 3H, H-6). EIMS (*m*/*z*, %): 374 (M^+-1, 3.0), 265 ($M^+-SPh-1$, 99.6).

3.2.4. Phenyl 2,3-*O*-iodoethylidene-4-*O*-methyl-1-thio-α-L-rhamnopyranoside (18). To a mixture of **17** (893 mg, 2.38 mmol) and KI (4.74 g, 28.55 mmol) in dry DMF (2 mL) at 80°C under Ar, was added phase-transfer catalyst Aliquat 336 (1.1 mL). After being stirred for two days, the mixture was diluted with EtOAc, and then filtered through a pad of Celite™. The filtrates were concentrated. The residue was purified by a silica gel column chromatography (16:1 petroleum ether–EtOAc) to give **18** (800 mg, 90%) as a yellow syrup. $[\alpha]_D^{20}=-142.3$ (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.56–7.28 (m, 5H, SPh), 5.79 (s, 1H, H-1), 5.03 (t, *J*=4.7 Hz, 1H), 4.34–4.27 (m, 2H), 4.12–4.04 (m, 1H), 3.56 (s, 3H, OMe), 3.38–3.18 (m, 3H), 1.25 (d, *J*=6.1 Hz, 3H, H-6); EIMS (*m*/*z*, %): 422 (M^+, 0.4), 313 (M^+-SPh, 100); HRMS calcd for $C_{15}H_{19}O_4IS$: 422.0049. Found: 422.0013.

3.2.5. Cholesteryl 3-*O*-acetyl-6-deoxy-4-*O*-methyl-2-*S*-phenyl-β-L-glucopyranoside (20). In a conical flask potassium *t*-butoxide (50 mg, 0.45 mmol) was dissolved in anhydrous DMF (2 mL) at 0°C under Ar. After being stirred for 0.5 h, a solution of iodide **18** (190 mg, 0.45 mmol) in DMF (1 mL) was added, the reaction mixture was then allowed to warm to room temperature. After 2 h, TLC showed the reaction to be complete. After the solvent had been removed by evaporation, the residue was applied to a basic alumina column (pH~9.5) chromatography (15:1

petroleum ether–triethylamine) to give the crude ketene acetal **19** (119 mg) as a colourless syrup, which was used immediately in the next step without characterization. To a stirred solution of cholesterol (65 mg, 0.17 mmol) and 4 Å MS (200 mg) in anhydrous CH_2Cl_2 (2 mL) at room temperature under argon was added a solution of TMSOTf in CH_2Cl_2 (0.1 M, 0.2 equiv.), followed by the addition of a solution of the crude ketene acetal **19** (119 mg, 0.40 mmol) in CH_2Cl_2 (1 mL). After being stirred for 2 h, the mixture was quenched with Et_3N, and then filtered through a pad of Celite™. The filtrates were concentrated. The residue was applied to a silica gel column chromatography (10:1 petroleum ether–EtOAc) to provide **20** (87 mg, 76%) as a white amorphous solid. $[\alpha]_D^{20}=-29.0$ (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.58–7.27 (m, 5H, SPh), 5.34 (m, 1H), 5.05 (dd, 1H, *J*=11.3, 9.1 Hz), 4.45 (d, 1H, *J*=8.8 Hz, H-1), 3.58–3.46 (m, 1H), 3.44 (s, 3H, OMe), 3.42–3.33 (m, 1H, H-5), 3.13 (dd, 1H, *J*=11.3, 8.8 Hz), 2.93 (t, 1H, *J*=9.1 Hz, H-2), 2.40–2.20 (m, 2H), 2.07 (s, 3H, OAc), 2.06–0.64 (m, 44H); EIMS (*m*/*z*, %): 680 (M^+-H), 369 (100). IR: (ν_{max}) 2937, 2868, 1750, 1238 cm^{-1}. Anal. calcd for $C_{42}H_{64}O_5S$: C, 74.07; H, 9.47. Found: C, 74.16; H, 9.42.

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References

1. (a) Auzanneau, F.-I.; Bundle, D. R. *Carbohydr. Res.* **1991**, *212*, 13–24. (b) Pozsgay, V. *Carbohydr. Res.* **1992**, *235*, 295–302.
2. (a) Yu, B.; Yang, Z. *Tetrahedron Lett.* **2000**, *41*, 2961–2964. (b) Yang, Z.; Yu, B. *Carbohydr. Res.* **2001**, *333*, 105–114.
3. Yu, B.; Yang, Z. *Org. Lett.* **2001**, *3*, 377–379.
4. Yu, B.; Wang, P. *Org. Lett.* **2002**, *4*, 1919–1922.
5. Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466–2467.
6. Györgydeak, Z.; Szilagyi, L. *Liebigs Ann. Chem.* **1985**, 103–112.
7. Full crystallographic details of compounds **1** and **6** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 190419 and 191703, respectively). Copies of these data may be obtained free of charge from the director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).
8. Similar procedure for the preparation of ethyl 4,6-di-*O*-acetyl-1-thio-α-D-mannopyranoside was used for the preparation of diols **9** and **11**, see Ref. 2b.
9. Sznaidman, M. L.; Johnson, S. C.; Crasto, C.; Hecht, S. M. *J. Org. Chem.* **1995**, *60*, 3942–3943.
10. Yang, Z.; Lin, W.; Yu, B. *Carbohydr. Res.* **2000**, *329*, 879–884, and references cited therein.
11. Nicolaou, K. C.; Li, Y.; Fylaktakidou, K. C.; Mitchell, H. J.; Wei, H. X.; Weyershausen, B. *Angew. Chem. Int. Ed.* **2001**, *40*, 3849–3854.
12. Zhu, P. C.; Lin, J.; Pittman, Jr. C. U. *J. Org. Chem.* **1995**, *60*, 5729–5731.
13. (a) Bailey, W. J.; Zhou, L.-L. *Tetrahedron Lett.* **1991**, *32*, 1539–1540. (b) Díez-Ortiz, A.; Díez-Barra, E.; de la Hoz, A.; Prieto, P. *Synth. Commun.* **1993**, *23*, 1935–1942.
14. Yu, B.; Zhu, X.; Hui, Y. *Tetrahedron* **2001**, *57*, 9403–9413.