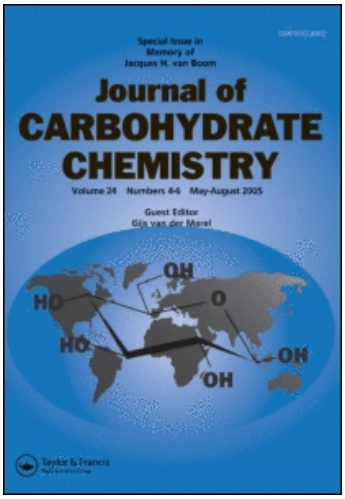

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis of 2-Deoxy-2-thiophenylglucosyl Azides through 1,2 Thio Migration of Thiophenyl Mannosides

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To cite this Article Maiereanu, Carmen , Kanai, Akira , Weibel, Jean-Marc and Pale, Patrick(2005) 'Synthesis of 2-Deoxy-2-thiophenylglucosyl Azides through 1,2 Thio Migration of Thiophenyl Mannosides', Journal of Carbohydrate Chemistry, 24: 8, 831 — 842

To link to this Article: DOI: 10.1080/07328300500409150

URL: http://dx.doi.org/10.1080/07328300500409150

Journal of Carbohydrate Chemistry, 24:831–842, 2005

ISSN: 0732-8303 print 1532-2327 online
DOI: 10.1080/07328300500409150

Synthesis of 2-Deoxy-2-thiophenylglucosyl Azides through 1,2 Thio Migration of Thiophenyl Mannosides

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2-Deoxy-2-thio glucosyl azides bearing or not bearing an azido group at the 6-position can be conveniently obtained through a 1,2-thio migration from thiophenyl mannoside derivatives.

Keywords Glucosyl azides, Thiophenyl mannosides, 1,2-Thio migration

INTRODUCTION

Carbohydrates play crucial roles in important biological recognition processes, including bacterial and viral infections, cell adhesion in inflammation and metastasis, differentiation, development, regulation, and other intercellular communication and signal transduction events.[1,2] Since natural oligosaccharides are easily degraded in vivo, development of biologically stable oligosaccharide analogs is very important for studying such recognition processes and for the elaboration of carbohydrate-based therapeutics and vaccines.[3] In this context, we are investigating 6-amino-6-deoxyglycosides, glycosyl amines, and the corresponding deoxy derivatives as building blocks for some oligosaccharide mimics (Fig. 1).[4,5]

Received August 2005; accepted September 2005.
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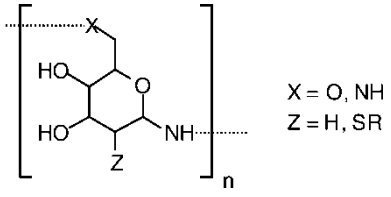


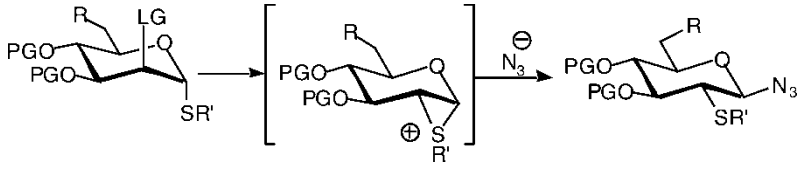
Figure 1: Oligosaccharides mimics based on glycosyl amines, 6-amino-6 deoxyglycosyl amines and their corresponding 2-thio and 2-deoxy analogs.

In order to have convenient access to this family of compounds, we realized that 2-deoxy-2-thio glycosyl azides, with or without an azido group at the 6 position, would offer a key entry to several series of derivatives. The azido group can indeed be reduced to the amine, and the thio group can also be reduced leading to the 2-deoxy series. A literature survey revealed that 6-amino-2,6-dideoxy-2-thioglycosyl azides are unknown and that even 2-deoxy-2-thioglycosyl azides surprisingly are almost unknown. A single paper mentioned 2-deoxy-2-thioglucosyl azides in multicomponent reactions leading to carbohydrate combinatorial libraries;[6] they were obtained as mixtures through electrophilic addition of dibenzyl disulfide-antimony pentachloride to glucals in the presence of trimethylsilyl azide and alcohols.

We thus designed and described here an alternative and more convenient route to 2-deoxy-2-thio glucosyl azides bearing or not bearing an azido group at the 6-position through a 1,2-migration of thio mannose derivatives (Sch. 1).

The rearrangement of thio derivatives through thiiranium intermediates is a well-known process often used in organic chemistry.[7] This process has been extended in carbohydrate chemistry and applied to the synthesis of 2-thioglycosides,[8] 2-deoxyglycosides,[9–11] sugar 2-*C*-sulfonic acids,[12] and 1,2-thio-linked disaccharides.[13] It has also been used in the total synthesis of apoptolidin.[14] This rearrangement was also detected in various works as an undesirable side reaction.[15–18]

Based on these precedents, we anticipated that α-thio mannosides bearing an electron-withdrawing group at the 2-position should have the right geometrical and electronic requirements for a facile 1-2-thio migration. In the presence of an azide source, the thiiranium intermediate, which should be formed, might be opened, leading to 2-deoxy-2-thioglucosyl azides (Sch. 1).

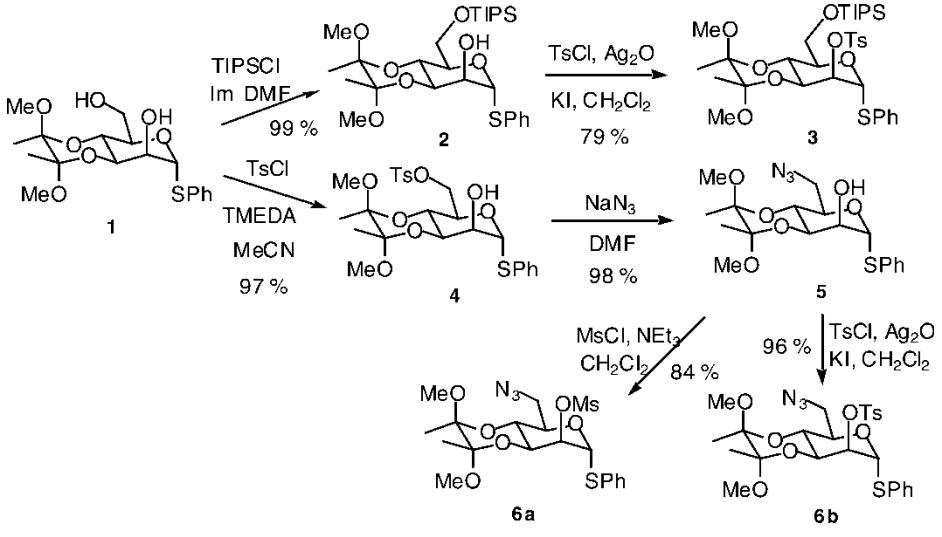


Scheme 1: Anticipated synthesis of 2-deoxy-2-thioglucosyl azides by 1,2-thio migration of thio mannosides (R = OPG, N_3).

RESULTS AND DISCUSSION

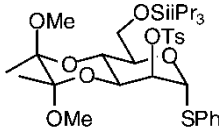
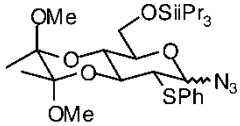
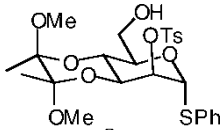
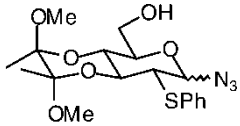
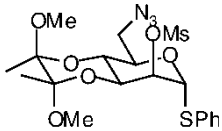
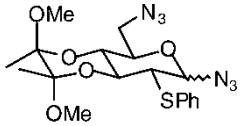
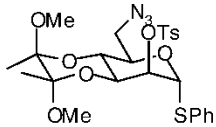
To validate this route, we started from the known[19] α-D-thiophenyl mannoside protected by the Ley acetal[20] at the 3, 4 position (**1** in Sch. 2). Due to this selective protecting group, the 2, 6-positions of the sugar remained free but are easily distinguishable, the 6 being a primary hydroxyl group. Indeed, selective silylation[21] with tri-*iso*propylsilyl chloride in the presence of imidazole provided exclusively the 6-silylated compound **2**, which was then tosylated at the 2-position with the Bouzide's method,[22] giving **3** in excellent overall yields. Alternatively, selective tosylation at the 6 position can be achieved using Yoshida's method[23] (**4** in Sch. 2). The resulting primary tosylate was then displaced by sodium azide, leading to the azido compound **5**, which was then mesylated and tosylated (**6a**–**b**), thus providing an entry to the 6-amino-6-deoxyglucosyl series.

The tosylated thiophenyl α-D-mannoside **3** was used as a model to find the right conditions for the expected 1,2-thio migration. Treatment of **3** with sodium azide in polar solvents such as DMF, MeCN, THF, etc., at various temperatures led mostly to the recovery of the starting material if the temperature did not reach 100°C. DMF proved to be the best solvent, but its effect seemed mainly correlated with its boiling point. Indeed, nothing happened after 24 h at 50°C and only 15% of starting material was converted at 80°C (Table 1; entries 1–2), but at 100°C, 50% of the expected product **7** was formed (entry 3). A better yield was obtained at 130°C but decomposition started occurring (entry 4). The structure of **7** was easily deduced from changes in NMR spectra. As expected, the signal corresponding to H_2 was



Scheme 2: Synthesis of the starting materials.

Table 1: Formation of glucosyl azides upon treatment of α-thiophenyl mannosides by NaN_3 in DMF.

Entry	Glycosides	Products	Temperature (°C)	Time (h)	Ratio α:β [a]	Yield (%) [b]
1	 **3**	 **7**	50	24	1:2.5	0
2			80	15	1:2.5	11
3			100	15	1:2.5	50
4			130	15	1:2.5	64
5	 **8**	 **9**	80	24	—	0[c]
6			130	15	1:2	46
7	 **6a**	 **10**	130	15	2:1	45
8			130	24	2.5:1	76
9	 **6b**	**10**	130	15	1.2:1	62

[a]The ratio was derived from integration of the H^1 NMR anomeric signals of the crude mixture.
[b]Yields of pure isolated product.
[c]Starting material recovered.

shifted from 4.88 ppm in **3** to 3.27 ppm in **7α** (2.97 in **7β**) and its multiplicity changed from a massif in **3** to a doublet of doublet in **7**, clearly reflecting profound modifications in the atomic environment of this proton and in its stereochemistry. Similarly, the signal of the anomeric proton H_1 was shielded, especially for the β-anomer of **7** (5.55 ppm in **3**, 5.38 in **7α**, and 4.58 ppm in **7β**). The multiplicity was also different: Appearing as a broad singlet in **3**, the anomeric proton in **7** is a doublet with typical constant either for axial-equatorial coupling in **7α** ($J = 4.0$ Hz) or for axial-axial coupling in **7β** ($J = 9.5$ Hz).

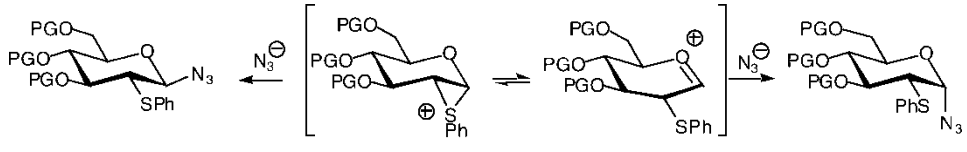
It is worth noting that the α/β ratio did not change whatever the conditions in this series of experiments, and that it was in favor of the β isomer as expected from nucleophilic opening of a thiiranium intermediate (see Sch. 1). Further control experiments showed that this ratio did not change either

upon prolonged heating. These results are thus in agreement with the intermediate formation of a thiiranium species.

During preliminary experiments to form **4** using standard tosylation procedures, we obtained mixtures of products, among which the mannoside monotosylated at position 2 (**8**) was isolated (<15%). This analog of **3** bearing a free hydroxyl group at position 6 (**8**) was also submitted to the above-mentioned conditions (Table 1, entries 5–6). Although disaccharide formation could be a competitive process via a nucleophilic attack of the free 6-alcohol to the thiiranium intermediate, the corresponding thioglucosyl azide **9** was cleanly obtained but in moderate yields. Here again, a higher temperature was required (entry 6 vs. 5) and the α/β ratio observed was similar to the one obtained from the 6-protected **3** (entry 6 vs. 3, 4). Interestingly enough, no disaccharide can be detected, reflecting the better nucleophilicity of the azide ion over the hydroxyl group. Compound **9** exhibited NMR data similar to **7** with H_1 appearing as a doublet at 5.38 ppm ($J = 4.0$ Hz) in **7α** and 4.61 ppm ($J = 9.6$ Hz) in **7β** and with H_2 as a doublet of doublet at 3.30 ppm ($J = 4.0$, 11.3 Hz) in **7α** and 2.98 ppm ($J = 9.6$, 11.2 Hz) in **7β**.

With the conditions in hand for the expected 1,2-thio migration and azidation, we started investigating the azido mannosides **6a–b**. Both gave the expected rearranged product **10** in good yields (Table 1, entries 7–9). The azido mesylated compound **6a** proved to be less reactive than its tosylated counterpart **6b**. Indeed, heating **6a** at 130°C for 1 day was required to get a satisfactory yield (entry 8 vs. 7), while heating overnight was enough for **6b** (entry 9). The new product formed **10** exhibited NMR spectra very similar to **7** and **9** and was also a mixture of anomers (H_1: doublet at 5.41 ppm ($J = 4.2$ Hz) in **10α** and 4.59 ppm ($J = 9.6$ Hz) in **10β**; H_2: doublet of doublet at 3.29 ppm ($J = 4.2$, 11.5 Hz) in **10α** and 3.00 ppm ($J = 9.6$, 10.8 Hz) in **10β**).

Surprisingly, the anomeric ratio of the azidoglucosyl azide so formed **10** was in favor of the α isomer when starting from the mesyl derivative **6a**, but did not show any significant preference for one anomer or the other when starting from the tosyl derivatives **6b**. Such differences obviously reflect some isomerization of the thiiranium intermediate to a thia-carbenium intermediate, but the role of the leaving group in this process is unclear (Sch. 3).



Scheme 3: Isomerization of the thiiranium intermediate, leading to an α/β mixture of products.

CONCLUSION

This work demonstrated that concomitant 1,2-thio migration and azidation of α-thiophenyl mannosides can be achieved and offer a convenient synthesis of various glucosyl azides, substituted or not. The compounds so obtained could then be reduced to the corresponding glycosyl amines and to their 2-deoxy derivatives. Such compounds may find broad applications as building blocks and tools in glycoscience. Progress in this area is under way.

EXPERIMENTAL

General

Reactions were monitored by TLC on silica gel MERCK DC Alufolien Kieselgel 60 PF_{254} with detection by UV absorption (254 nm). All moisture-sensitive reactions were carried out under an atmosphere of argon in oven-dried glassware. Solvents were freshly distilled; THF was distilled from Na/benzophenone; C_6H_6, MeCN, and CH_2Cl_2 were distilled from CaH_2. Column chromatographies were performed with Merck silica gel (0.040–0.063 mesh). Yields were based on isolated products. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer. For ^1H NMR, TMS was used as internal standard; for ^{13}C NMR, the solvent peak at 77.00 ppm ($CDCl_3$) was used. IR spectra were recorded on a spectrafile IR™ Plus MIDAC spectrophotometer. Mass Spectra were recorded on a Bruker Daltonis Data Analysis 3.1 mass spectrometer. Specific rotations were measured at 589 nm with an ADP 220 Bellingham-Stanley polarimeter or a Perkin Elmer 241 polarimeter. Melting points were determined on a Bibby Sterilin Stuart Scientific melting point apparatus and are uncorrected.

Phenyl 6-*O*-tri*iso*propylsilyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-1-thio-α-D-mannopyranoside (2)

A solution of diol **1**[19] (0.04 g, 0.104 mmol), tri*iso*propylsilylchloride (0.034 mL, 0.156 mmol), and imidazole (0.011 g, 0.156 mmol) in DMF (1 mL) was stirred for 7 h at rt. After quenching with water, the mixture was extracted three times with EtOAc. The combined organic layers were then washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuo and the resulting crude solid was grossly purified by column chromatography (cyclohexane/EtOAc, 4/1), leading to a white solid (0.059 g; quantitative yield), which was directly engaged in the next step.

Phenyl 6-*O*-tri*iso*propylsilyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-2-*O*-toluenesulfonyl-1-thio-α-D-mannopyranoside (3)

A suspension of **2**, silver oxide (0.104 g, 0.448 mmol), potassium iodide (0.074 g, 0.448 mmol), and *p*-toluenesulfonyl chloride (TsCl) (0.085 g, 0.448 mmol) in CH_2Cl_2 was refluxed for 11 h, then cooled down to rt. The mixture was filtered with Celite. The residue was evaporated in vacuo and then purified by column chromatography (cyclohexane/EtOAc, 4/1), yielding a colorless oil (0.062 g, 79% yield). $[\alpha]_D^{24}$ +113.1 (c 1.23, $CHCl_3$). ^{1}H NMR: 7.83 (d, $J = 8.3$, 2H, Ph), 7.44–7.46 (m, 2H, Ph), 7.27–7.29 (m, 3H, Ph), 5.55 (br.s, 1H, H_1), 4.88 (m, 1H, H_2), 4.15 (br.dt, $J = 3.4$ and 10.1 Hz, 1H, H_5), 4.04 (dd, $J = 10.0$ and 10.2 Hz, 1H, H_4), 3.95 (dd, $J = 3.0$ and 10.0 Hz, 1H, H_3), 3.90–3.91 (m, 2H, H_6), 3.20 (s, 3H, OCH_3), 3.14 (s, 3H, OCH_3), 2.42 (s, 3H, $PhCH_3$), 1.25 (s, 3H, CH_3), 1.07 (s, 3H, Me), 1.03 (s, 21H, TIPS). ^{13}C NMR: 144.3, 133.9, 133.7, 131.7, 129.3, 129.0, 128.2, 127.6, 100.1, 99.6, 86.8, 78.6, 72.9, 66.7, 62.7, 61.6, 21.6, 17.9, 17.8, 17.7, 17.4, 12.3, 11.9. IR (KBr): 3017, 2944, 2867, 1597, 1463, 1370, 1112, 921, 756. HR-MS: calcd for $C_{34}H_{52}O_9NaSiS_2$ ($[M + Na]^+$): 719.2714. Found: 719.2734.

Phenyl 3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-6-*O*-toluenesulfonyl-1-thio-α-D-mannopyranoside (4)

To a stirred solution of **1** (1.878 g, 4.86 mmol) in acetonitrile (50 mL) was added TsCl (1.85 g, 9.72 mmol) and TMEDA (1.5 μL, 9.72 mmol). The mixture was then stirred at 1.5 h at rt, poured into ice water, and then extracted with methylene chloride. The organic layer was dried ($MgSO_4$) and evaporated under vacuum. The residue was chromatographied on silica gel using EtOAc/cyclohexane 3/2 as eluent giving **4** (2.556 g, 2.63 mmol; 97%). $[\alpha]_D^{25}$ +216.6 (c 2.19, $CHCl_3$). IR (neat): 3465, 3015, 2951, 2835, 1638, 1599, 1366, 1177, 755. ^{1}H NMR (300 MHz, $CDCl_3$): 7.7 (d, $J = 8.1$ Hz, 2H, Har), 7.41–7.37 (m, 2H, Har), 7.30–7.24 (m, 5H, Har), 5.37 (br.s, 1H, H_1), 4.40 (m, 1H, H_5), 4.26–4.01(m, 4H, H_2, H_3, H_4, H_6), 3.94 (dd, $J = 2.8$ and 11.1 Hz, 1H, H_6), 3.29 (s, 3H, -OCH_3), 3.22 (s, 3H, -OCH_3), 2.49 (d, $J = 1.8$ Hz, 1H, -OH), 2.41 (s, 3H, -$PhCH_3$), 1.31 (s, 3H, CH_3), 1.29 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 144.5 (1C, Cq), 133.4 (1C, Cq), 132.7 (1C, Cq), 131.7 (1C, CHar), 129.5 (1C, CHar), 128.9 (1C, CHar), 127.9 (1C, CHar), 127.5 (1C, CHar), 100.4 (1C, Cq), 100.0 (1C, Cq), 87.9 (1C, C1), 70.8 (1C), 69.2 (1C), 68.6 (1C), 67.6 (1C), 62.9 (1C), 48.1 (1C, -OCH_3), 48.0 (1C, -OCH_3), 21.5 (PhMe), 17.6 (1C, -CH_3), 17.5 (1C, -CH_3). HR-MS: calcd for $C_{25}H_{32}O_9NaS_2$ ($[M + Na]^+$): 563.1379. Found: 563.1393.

Phenyl 6-azido-6-deoxy-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-1-thio-α-D-mannopyranoside (5)

To a solution of **4** (125 mg, 0.23 mmol) in DMF (3 mL) was added at rt sodium azide (45 mg, 0.69 mmol). The resulting mixture was heated at 80°C for 40 h. The mixture was then poured in ice water and extracted three times with EtOAc. The organic solvent was dried ($MgSO_4$) and evaporated under vacuum. The residue was chromatographied on silica gel with EtOAc/cyclohexane 1/2 as eluent giving **5** (93 mg, 0.22 mmol; 98%). $[\alpha]_D^{25}$ +249 (c 1.62, $CHCl_3$). IR (neat): 3447, 2993, 2948, 2833, 2100, 1583, 1480, 1376, 1281, 1140, 1049, 753. ^{1}H NMR (300 MHz, $CDCl_3$): 7.48–7.44 (m, 2H, Har), 7.30 = 7.21 (m, 3H, Har), 5.53 (d, $J = 0.5$ Hz, 1H, H_1), 4.40 (m, 1H, H_5), 4.20 (m, 1H, H_2), 4.05 (dd, $J = 9.8$ and 10.1 Hz, 1H, H_4), 3.96 (dd, $J = 2.8$ and 10.1 Hz, 1H, H_3), 3.44 (s, 1H, OH), 3.42–3.36 (m, 2H, H_6), 3.27 (s, 3H, -OCH_3), 3.19 (s, 3H, -OCH_3), 2.49 (d, $J = 1.8$ Hz, 1H, -OH), 2.41 (s, 3H, -PhC*H*$_3$), 1.32 (s, 3H, CH_3), 1.27 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 133.6 (1C, Cq), 131.6 (2C, CHar), 129 (2C, CHar), 127.5 (1C, CHar), 100.4 (1C, Cq), 100.0 (1C, Cq), 88.1 (1C, C_1), 71.0 (1C), 70.9 (1C), 68.7 (1C), 64.3 (1C), 50.6 (1C, C_6), 48.1 (1C, -O*C*H$_3$), 47.9 (1C, -O*C*H$_3$), 17.7 (1C, -CH_3), 17.5 (1C, -CH_3). HR-MS: calcd for $C_{18}H_{25}O_6NaS$ ($[M + Na]^+$): 434.1356. Found: 434.1359.

Phenyl 6-azido-6-deoxy-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-2-*O*-methylsulfonyl-1-thio-α-D-mannopyranoside (6a)

To a stirred solution of alcohol **5** (112 mg, 0.27 mmol) in CH_2Cl_2 (3 mL) was added MsCl (0.33 μL, 3.99 mmol) and triethylamine (0.57 mL, 4.1 mmol). The mixture was stirred for 1 day and then quenched with ice water. The water layer was extracted with dichloromethane. The organic layers were dried ($MgSO_4$) filtrated and the solvent evaporated in vacuo. The product was purified by flash chromatography, using cyclohexane/EtOAc 3/1 as eluent giving **6a** (112 mg, 0.23 mmol; 84%). $[\alpha]_D^{25}$ +162.5 (c 2.00, $CHCl_3$). IR (neat): 2994, 2948, 2835, 2101, 1583, 1364, 1177, 1142, 1109, 923. ^{1}H NMR (300 MHz, $CDCl_3$): 7.50–7.46 (m, 2H, Har), 7.35–7.29 (m, 3H, Har), 5.58 (d, $J = 1.0$ Hz, 1H, H_1), 5.09 (dd, $J = 1.5$ and 2.7 Hz, 1H, H_2), 4.38 (m, 1H, H_5), 4.11 (dd, $J = 2.7$ and 10.3 Hz, 1H, H_3), 3.99 (dd, $J = 10.0$ and 10.3 Hz, 1H, H_4), 3.55–3.40 (m, 2H, H_6), 3.31 (s, 3H), 3.24 (s, 3H), 3.16 (s, 3H), 1.29 (s, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 132.5 (1C, Cq), 132.2 (2C, CHar), 129.3 (2C, CHar), 128.3 (1C, CHar), 100.5 (1C, Cq), 100.0 (1C, Cq), 87.5 (1C, C_1), 79.4 (1C), 71.3 (1C), 67.0 (1C), 64.1 (1C), 50.4 (1C, C_6), 48.4 (1C, -O*C*H$_3$), 48.2 (1C, -O*C*H$_3$), 39.0 (1C, -SO_2CH$_3$), 17.6 (1C, -CH_3), 17.5 (1C, -CH_3). HR-MS: calcd for $C_{19}H_{27}O_8NaS_2$ ($[M + Na]^+$): 512.1131. Found: 512.1107.

Phenyl 6-azido-6-deoxy-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-2-*O*-toluenesulfonyl-1-thio-α-D-mannopyranoside (6b)

To a stirred solution of alcohol **5** (49 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) was added Ag_2O (110 mg, 0.48 mmol), TsCl (91 mg, 0.48 mmol), and KI (79 mg, 0.48 mmol). The mixture was refluxed for 48 h. After cooling at rt, the mixture was filtered and a large excess of TMEDA was added. After stirring for 10 min, the solvent was evaporated in vacuo. The product was purified by flash chromatography, using cyclohexane/EtOAc 4/1 as eluent giving **6b** (65 mg, 0.11 mmol; 96%). IR (neat): 3060, 2993, 2952, 2835, 2101, 1738, 1597, 1444, 1370, 918. ^{1}H NMR (300 MHz, $CDCl_3$): 7.84–7.80 (m, $J = 8.3$ Hz, 2H, Har), 7.47–7.34 (m, 2H, Har), 7.34–7.25 (m, 5H, Har), 5.57 (d, $J = 1.0$ Hz, 1H, H_1), 4.86 (dd, $J = 1.4$ and 2.4 Hz, 1H, H_2), 4.29 (m, 1H, H_5), 3.94–3.90 (m, 2H, H_3 and H_4), 4.28 (dd, $J = 2.6$ and 13.2 Hz, 1H, H_6), 4.19 (dd, $J = 6.4$ and 13.2 Hz, 1H, H_6), 3.18 (s, 3H, -OCH_3), 3.11 (s, 3H, -OCH_3), 2.02 (s, 3H, -C_6H_4-C*H*$_3$), 1.22 (s, 3H, CH_3), 1.04 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 144.6 (1C, Cq), 133.6 (1C, Cq), 132.7 (1C, Cq), 132.1, 129.4, 129.3, 128.3, and 128.2 (CHar), 100.2 (1C, Cq), 99.8 (1C, Cq), 87.2 (1C, C_1), 78.5 (1C), 71.3 (1C), 66.3 (1C), 64.1 (1C), 50.5 (1C, C_6), 48.0 (2C, -O*C*H_3), 21.6 (1C, Ar-Me), 17.6 (1C, -CH_3), 17.3 (1C, -CH_3). HR-MS: calcd for $C_{25}H_{31}O_8NaS_2$ ($[M + Na]^+$): 588.1444. Found 588.1401.

Procedure for 1,2-Thio Migration/Azidation

To a solution of thiophenyl · α-D-mannoside (1 eq.) in DMF (0.05 M) was added at rt sodium azide (3 eq). The resulting mixture was heated at 130°C for several hours until disappearance of the starting material as judged from TLC. The mixture was then poured in ice water and extracted three times with CH_2Cl_2. The combined organic layers were washed with water are brine, dried over $MgSO_4$, and concentrated in vacuum. The residue was chromatographied on silica gel with EtOAc/cyclohexane 7/1 as eluent.

2-Deoxy-6-*O*-tri*iso*propylsilyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-2-thiophenyl-D-mannopyranosyl azide (7)

(Mixture α/β) ^{1}H NMR (300 MHz, $CDCl_3$): 7.60–7.53 (m, 2H, Har), 7.29–7.24 (m, 3H, Har), 5.38 (d, $J = 4.0$ Hz, 1H, H_1 minor), 4.58 (d, $J = 9.5$ Hz, 1H, H_1 major), 3.95–3.89 (m, two H_6 major; H_3, H_4, H_5, and H_6 minor), 3.82 (dd, $J = 9.6$ and 9.9 Hz, 1H, H_4 major), 3.67 (dd, $J = 9.6$ and 11.4 Hz, 1H, H_3 major), 3.48 (ddd, $J = 2.2$, 3.1 and 9.5 Hz, 1H, H_5 major), 3.38 (s, 3H, -OCH_3 major), 3.35 (s, 3H, -OCH_3 minor), 3,27 (dd, $J = 4.0$ and 11.2 Hz, 1H, H_2

minor), 3.28 (s, 3H, -OCH_3 major), 3.26 (s, 3H, -OCH_3 minor), 2,97 (dd, $J = 9.5$ and 11.4 Hz, 1H, H_2 major), 1.35 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.05 (s, 21H, TIPS).

2-Deoxy-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-2-thiophenyl-D-mannopyranosyl azide (9)

(Mixture α/β) ^{1}H NMR (300 MHz, $CDCl_3$): 7.60–7.52 (m, 2H, Har), 7.29–7.24 (m, 3H, Har), 5.38 (d, $J = 4.0$ Hz, 1H, H_1 minor), 4.61 (d, $J = 9.6$ Hz, 1H, H_1 major), 4.05–3,68 (m, H_6, H_4, and H_3 of both anomers, H_5 minor), 3.55 (m, 1H, H_5 major), 3.38 (s, 3H, -OCH_3 major), 3.35 (s, 3H, -OCH_3 minor), 3.30 (dd, $J = 4.0$ and 11.3 Hz, 1H, H_2 minor), 3.26 (s, 3H, -OCH_3), 2.98 (dd, $J = 9.6$ and 11.2 Hz, 1H, H_2 major), 1.34 (s, 3H, CH_3 major), 1.31 (s, 3H, CH_3 minor), 1.30 (s, 6H, CH_3 major and minor).

6-Azido-2,6-dideoxy-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-2-thiophenyl-α-D-mannopyranosyl azide (10α)

$[\alpha]_D^{24}$ +268 (c 0.51, $CHCl_3$). IR (neat): 2993, 2948, 2833, 2107, 1440, 1379, and 1136. ^{1}H NMR (300 MHz, $CDCl_3$): 7.55 (m, 2H, Har), 7.29 (m, 3H, Har), 5.41 (d, $J = 4.2$ Hz, 1H, H_1), 4.09 (m, 1H, H_5), 3.92 (dd, $J = 9.6$ and 11.5 Hz, 1H, H_3), 3.71 (dd, $J = 9.6$ and 9.8 Hz, 1H, H_4), 3.58 (dd, $J = 2.5$ and 13.3 Hz, 1H, H_6), 3.40 (dd, $J = 4.8$ and 13.3 Hz, 1H, H_6), 3.35 (s, 3H, -OCH_3), 3.29 (dd, $J = 4.2$ and 11.5 Hz, 1H, H_2), 3.26 (s, 3H, -OCH_3), 1.31 (s, 3H, CH_3), 1.29 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 133.9 (1C, Cq ar), 132.7 (2C, CHar), 128.9 (2C, CHar), 127.7 (1C, CHar), 100.2 (1C, Cq), 100.1 (1C, Cq), 90.1 (1C, C_1), 71.3 (1C, C_5), 68.2 (1C, C_3), 68.1 (1C, C_4), 51.7 (1C, C_2), 50.1 (1C, C_6), 48.2 (1C, -OCH_3), 48.1 (1C, -OCH_3), 17.6 (1C, -CH_3), 17.5 (1C, -CH_3). HR-MS: calcd for $C_{18}H_{24}N_6O_5NaS$ ($[M + Na]^+$): 459.1426. Found: 459.1413.

6-Azido-2,6-dideoxy-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-2-thiophenyl-β-D-mannopyranosyl azide (10β)

$[\alpha]_D^{24}$ +116 (c 0.52, $CHCl_3$). IR (neat): 2995, 2948, 2836, 2116, 1441, 1376, and 1136. ^{1}H NMR (300 MHz, $CDCl_3$): 7.58 (m, 2H, Har), 7.28 (m, 3H, Har), 4.59 (d, $J = 9.6$ Hz, 1H, H_1), 3.64 (m, 4H, H_3, H_4, H_5, H_6), 3.37 (m, 1H, H_6), 3.38 (s, 3H, -OCH_3), 3.26 (s, 3H, -OCH_3), 3.00 (dd, $J = 9.6$ and 10.8 Hz, 1H, H_2), 1.34 (s, 3H, CH_3), 1.29 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): 133.6 (1C, Cq ar), 133.2 (2C, CHar), 128.9 (2C, CHar), 127.8 (1C, CHar), 100.4 (1C, Cq), 99.9 (1C, Cq), 91.5 (1C, C_1), 75.4 (1C, C_3), 70.5 (1C, C_4), 67.8 (1C, C_5), 53.5 (1C, C_2), 50.2 (1C, C_6), 48.4 (1C, -OCH_3), 48.1 (1C, -OCH_3), 17.6

(1C, -CH_3), 17.5 (1C, -CH_3). HR-MS: calcd for $C_{18}H_{24}N_6O_5NaS$ ($[M + Na]^+$): 459.1426. Found: 459.1445.

ACKNOWLEDGMENT

The authors thank the CNRS for financial support. C.M. thanks the ANRS for financial support; A.K. thanks the Science University of Tokyo for fellowship.

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