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Note

Regioselective synthesis of 6-*S*-alkyl and 6-*S*-glycosyl-6-thio-D-mannofuranose derivatives from 5,6-*O*-cyclic sulfate precursors

Anne Wadouachi,* Ludivine Lescureux, David Lesur and Daniel Beaupère

Laboratoire des Glucides UMR 6219, Université de Picardie Jules Verne, 33 Rue Saint-Leu, F-80039 Amiens, France

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Abstract—C-6 opening of 5,6-cyclic sulfate derivatives of mannofuranose with a thiolate anion followed by acidic hydrolysis of the acyclic sulfate gave 6-*S*-alkyl derivatives in good yields (70–95%) and short reaction times (10–15 min). This methodology was applied to the synthesis of methyl 2,3-*O*-isopropylidene-6-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-6-thio-α-D-mannofuranoside (70%), 2,3-*O*-isopropylidene-6-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-6-thio-α-D-mannofuranose (87%) and 2,3-*O*-isopropylidene-6-*S*-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl)-6-thio-α-D-mannofuranose (87%).

Keywords: Cyclic sulfates; Nucleophilic opening; 6-*S*-Alkyl-6-thio-D-mannofuranose; *S*-Alkyl-thiomannofuranose; Cyclic sulfite; Thiodisaccharides

Thiosugar derivatives have attracted wide attention for their use in both technical and biological applications.[1] For example, the introduction of fatty alkyl chains on carbohydrates leads to the formation of non-ionic surfactants or liquid crystals. *S*-Alkyl-1-thiopentitols and hexitols prepared from the corresponding glyconolactones have shown mesophasic and amphiphilic properties.[2] Moreover, heteroanalogues of oligosaccharides in which the glycosidic oxygen atoms have been replaced by sulfur (thiooligosaccharides) have also attracted attention due to their resistance to chemical and enzymatic hydrolyses and to their biological properties.[3] Recent evidence suggests that these sulfur derivatives may have therapeutic potential for the treatment of cancer and infectious diseases.[4]

The cyclic sulfate functionality of vicinal diols has been used as electrophile in a variety of nucleophilic displacement reactions.[5] We previously developed a simple method to access to 6-*O*-alkyl, 6-*C*-alkyl-6-deoxy and 6-*C*-alkynyl-6-deoxy carbohydrate derivatives from a 5,6-cyclic sulfate derivative.[6]

Here, we describe the synthesis of 6-*S*-alkyl-6-thio-D-mannofuranose derivatives and thiodisaccharides via a 5,6-cyclic sulfate.

Treatment of methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**1**),[7] with thionyl chloride in the presence of pyridine gave the corresponding 5,6-cyclic sulfite **3** in 94% yield.

The same reaction, applied to 2,3-*O*-isopropylidene-α-D-mannofuranose[8] (**2**) gave the expected 5,6-*O*-sulfinyl compound **4** in 75% yield accompanied by 1-chloro derivative **5** in 11% yield (Scheme 1).

Oxidation of these sulfite derivatives **3**, **4** and **5** was achieved with $RuCl_3/NaIO_4$[9] resulting in the corresponding cyclic sulfates **6**, **7** and **8** in 80%, 76% and 80% yield, respectively.

The latter products were characterized by NMR spectroscopy, which showed the anomeric protons at 5.41 and 6.21 ppm with a coupling constant $J_{1,2}$ 0 Hz and the anomeric carbons at 101.4 and 99.5 ppm, for **7** and **8**, respectively.

* Corresponding author. Tel.: +33 3 22 82 75 27; fax: +33 3 22 82 75 60; e-mail: anne.wadouachi@u-picardie.fr

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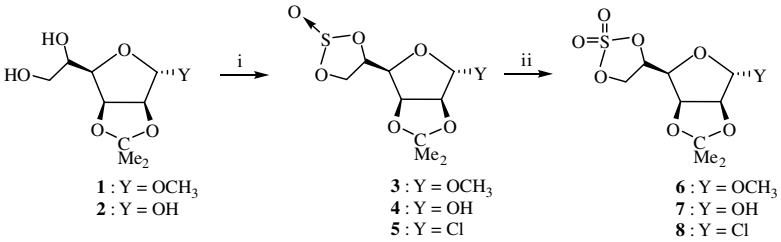


Scheme 1. Reagents and conditions: (i) $SOCl_2$, pyridine, THF 94%, 75% and 11% (**3**, **4** and **5**, respectively); (ii) $NaIO_4$, $RuCl_3{\cdot}3H_2O$, CH_2Cl_2/MeCN 80%, 76% and 80% (**6**, **7** and **8**, respectively).

Our initial study was carried out on methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside 5,6-*O*-cyclic sulfate (**6**). Nucleophilic opening of **6** was accomplished at C-6 by the action of alkylthiolate reagents generated in situ with NaH in 10–15 min reaction time. The acyclic sulfate intermediates were directly hydrolyzed with sulfuric acid–water to give **9a**–**d**. The introduction of alkyl chains such as butyl, octyl, dodecyl and hexadecyl gave the corresponding 6-*S*-alkyl-6-thio derivatives **9a**–**d** with good yields (90–95%) (Scheme 2, Table 1).

Thioetherification was also carried out with 2,3-*O*-isopropylidene-α-D-mannofuranose 5,6-*O*-cyclic sulfate (**7**).

6-*S*-Butyl, -octyl, -dodecyl and -hexadecyl-6-thio-α-D-mannofuranose derivatives **10a**–**d** were prepared in 70–89% yields. NMR analysis showed that these compounds have the furanosidic structures with a coupling constant $J_{1,2}$ 0 Hz characteristic of the α-anomer. These examples illustrate that the free anomeric hydroxyl group did not undergo change when faced with these basic conditions.

2,3-*O*-Isopropylidene-α-D-mannofuranosyl chloride 5,6-*O*-cyclic sulfate (**8**) treated with octylthiolate gave the corresponding 6-*S*-octyl-6-thio-α-D-mannofuranosyl chloride **11** in 70% yield (Table 1). This example demonstrates that the reactivity of the cyclic sulfate was greater than that of the corresponding glycosyl chloride.

In the previous literature, thio-linked disaccharides have been reported from 3,4- and 4,6-cyclic sulfates of galactose and glucopyranose derivatives.[10] These thiosugars have been isolated as monosulfated compounds. We applied the methodology to anionic thiosugar derivatives to obtain thiodisaccharides.

Activation of commercial 1-thio-β-D-glucopyranose tetraacetate **12** with NaH, followed by the action of 5,6-cyclic sulfates **6** and **7** gave, after acidic hydrolysis of the acyclic sulfate intermediate, the corresponding thiodisaccharides **13** and **14** in 70% and 87% yields, respectively. The reaction was complete in 10 min (Scheme 3).

Table 1. Synthesis of 6-*S*-alkyl-6-thio-mannofuranose derivatives

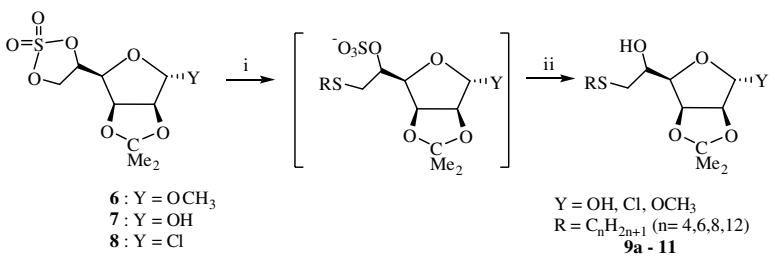
Entry	Starting cyclic sulfate	$C_nH_{2n+1}SH$	Reaction time (min)	Product Yield[a] (%)
1	**6**	$n = 4$	10	**9a** (93)
2	**6**	$n = 8$	10	**9b** (90)
3	**6**	$n = 12$	15	**9c** (95)
4	**6**	$n = 16$	15	**9d** (94)
5	**7**	$n = 4$	10	**10a** (89)
6	**7**	$n = 8$	10	**10b** (70)
7	**7**	$n = 12$	10	**10c** (77)
8	**7**	$n = 16$	10	**10d** (75)
9	**8**	$n = 8$	30[b]	**11** (70)

[a] Yields obtained after acidic hydrolysis of the acyclic sulfate.
[b] Reaction temperature was 55 °C.

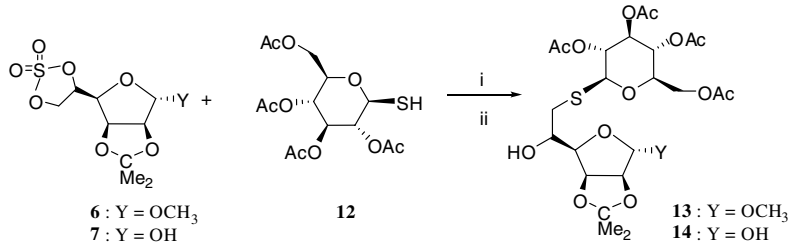
The non-anomerically linked thiodisaccharide D-Gal*p*-(6→6)-D-Man*f* **16** was prepared from 6-thio-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[11] (**15**) converted in situ into its thiolate anion. Compound **16** was isolated in 87% yield.

Further modification of the two free hydroxyls in **14** and **16** may be considered. This methodology allowed us to synthesize furanosidic and/or pyranosidic oligosaccharides (Scheme 4).

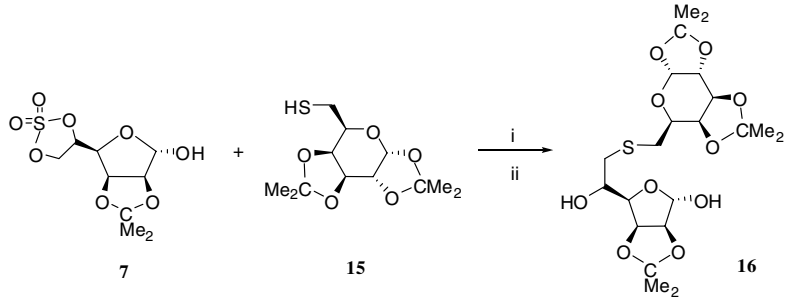
As we observed for **10a**–**d**, there is a possibility for furanose–pyranose interconversion for **14** and **16**, but NMR data showed a coupling constant $J_{1,2}$ 0 Hz for the mannofuranose moiety in agreement with retention of the five membered ring.



Scheme 2. Reagents and conditions: (i) RSH, NaH, THF/HMPA; (ii) H_2SO_4/H_2O (1 equiv).



Scheme 3. Reagents and conditions: (i) NaH, THF/HMPA, 10 min; (ii) H_2SO_4/H_2O (1 equiv), 70% and 87% (**13** and **14**, respectively).



Scheme 4. Reagents and conditions: (i) NaH, THF/HMPA, 10 min; (ii) H_2SO_4/H_2O (1 equiv), 87%.

To summarize, we have described an easy access to 6-*S*-alkyl-6-thio-D-mannofuranose derivatives in good yields (70–95%) with a short reaction time (10–15 min). The 5,6-*O*-cyclic sulfate mannofuranose compound is a convenient precursor for thiodisaccharide synthesis with furanosidic and/or pyranosidic structures.

1. Experimental

1.1. General

All chemicals were purchased from Aldrich or Acros (France). Thin-layer chromatography (TLC) was performed on Silica Gel 60 F_{254} (E. Merck) plates with visualization by UV light (254 nm) and/or charring with the vanillin–H_2SO_4 reagent. Preparative column chromatography for cyclic sulfite compounds was performed using 230–400 mesh E. Merck silica gel. Optical rotations were determined with a Jasco Dip 370 electronic micropolarimeter (10 cm cell). ^{1}H NMR spectra were recorded on a Bruker 300 WB spectrometer at 300 MHz and ^{13}C were recorded at 75 MHz. Chemical shifts are given as δ values with reference to tetramethylsilane (TMS) as internal standard. Low resolution electrospray mass spectra (ESIMS) in the positive ion mode were obtained on a Waters-Micromass ZQ quadrupole instrument, equipped with an electrospray (Z-spray) ion source (Waters-Micromass, Manchester, UK). High resolution electrospray experiments (HRESIMS) were performed on a Waters-Micromass Q-TOF *Ultima Global* hybrid quadrupole time-of-flight instrument, equipped with an electrospray (Z-spray) ion source (Waters-Micromass, Manchester, UK). All solvents were distilled before use. THF was distilled from $LiAlH_4$ and thionyl chloride from triphenylphophite (10% v/v). All reactions were performed in dried glassware under argon atmosphere.

1.2. General procedure for the synthesis of 5,6-cyclic sulfate mannofuranose derivatives 7 and 8

Thionyl chloride (1.5 equiv) was added dropwise to a soln of the mannofuranose derivative (500 mg, 1 equiv) in anhyd THF (30 mL) and pyridine (3 equiv) cooled at −10 °C. This soln was stirred for 20 min at this temperature, then filtered to eliminate the pyridinium salt formed and concentrated to give a residue, which was dissolved in water (25 mL) and extracted with CH_2Cl_2 (2×25 mL). The organic layer was successively dried, concentrated, and flash chromatography on silica gel (CH_2Cl_2) gave the corresponding *endo*/*exo* mixture of 5,6-cyclic sulfite. The latter was dissolved in 1:1 CH_2Cl_2–CH_3CN (10 mL) and stirred for 20 min at room temperature with sodium periodate (2 equiv), a catalytic amount of ruthenium trichloride hydrate and water (10 mL). The reaction mixture was filtered on Celite and washed with satd aq NaCl. The organic layer was treated as above to give the 5,6-cyclic sulfate mannofuranose derivative.

1.2.1. 2,3-*O*-Isopropylidene-α-D-mannofuranose 5,6-*O*-cyclic sulfate (7). Syrup; 403 mg (76%); R_f 0.65 (9:1 CH_2Cl_2–acetone); $[\alpha]_D$ +25.5 (*c* 1.45, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.41 (s, 1H, $J_{1,2}$ 0 Hz, H-

1), 5.20 (m, 1H, H-5), 4.82 (dd, 1H, $J_{5,6a}$ 7.2 Hz, $J_{6a,6b}$ 8.8 Hz, H-6a), 4.79 (dd, 1H, $J_{3,4}$ 3.8 Hz, H-3), 4.69 (dd, 1H, $J_{5,6b}$ 6.8 Hz, H-6b), 4.59 (d, 1H, $J_{2,3}$ 5.8 Hz, H-2), 4.55 (t, 1H, $J_{3,4}$ 3.8 Hz, H-4), 1.40, 1.25 (2s, 6H, CMe_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 113.2 (C-*iso*), 101.4 (C-1), 85.3 (C-2), 79.2 (C-3), 78.8 (C-4), 77.7 (C-5), 69.6 (C-6), 25.4, 23.9 (CMe_2). ESIMS: *m*/*z* 305.16 $[M+Na]^+$.

1.2.2. 2,3-*O*-Isopropylidene-α-D-mannofuranosyl chloride 5,6-*O*-cyclic sulfate (8). Syrup; 423 mg (80%); R_f 0.64 (CH_2Cl_2); $[\alpha]_D$ +25.3 (*c* 1.5, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 6.21 (s, 1H, $J_{1,2}$ 0 Hz, H-1), 5.23 (m, 1H, H-5), 4.95 (d, 1H, $J_{2,3}$ 5.8 Hz, H-2), 4.90 (dd, 1H, $J_{5,6a}$ 4.1 Hz, $J_{6a,6b}$ 8.3 Hz, H-6a), 4.85 (dd, 1H, $J_{3,4}$ 3.8 Hz, H-3), 4.62 (dd, 1H, $J_{3,4}$ 3.9 Hz, H-4), 4.60 (dd, 1H, $J_{5,6b}$ 5.0 Hz, H-6b), 1.54, 1.38 (2s, 6H, CMe_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 115.2 (C-*iso*), 99.5 (C-1), 91.4 (C-2), 82.8 (C-4), 78.8 (C-3), 80.4 (C-5), 70.6 (C-6), 26.9, 25.5 (CMe_2). ESIMS: *m*/*z* 323.11 $[M+Na]^+$.

1.3. General procedure for the synthesis of 6-thio mannofuranose derivatives 9a–16

To a soln of NaH (2 equiv) in THF (10 mL) and HMPA (0.5 mL) was added the thiol reagent (2 equiv) at room temperature under argon atmosphere. This soln was stirred for 30 min, then added rapidly to a soln of the 5,6-cyclic sulfate derivative (250 mg, 1 equiv) in THF (5 mL). The mixture was stirred until all the starting sugar had disappeared, as checked by TLC (1:1 hexane–EtOAc). H_2SO_4 (1 equiv) and water (1 equiv) were added, the mixture was stirred for 10 min and poured into a cold molar soln of $NaHCO_3$. The aq soln was extracted with EtOAc and the combined extracts were dried (Na_2SO_4) and concentrated under diminished pressure. The residue was chromatographed over silica gel (95:5 hexane–EtOAc) to yield the 6-thio derivative.

1.3.1. Methyl 6-*S*-butyl-2,3-*O*-isopropylidene-6-thio-α-D-mannofuranoside (9a). Syrup; 240 mg (93%); R_f 0.4 (9:1 hexane–EtOAc); $[\alpha]_D$ +59.6 (*c* 1.2, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.78 (s, 1H, $J_{1,2}$ 0 Hz, H-1), 4.76 (dd, 1H, $J_{3,4}$ 3.7 Hz, H-3), 4.45 (d, 1H, $J_{2,3}$ 5.7 Hz, H-2), 3.90 (m, 1H, H-5), 3.74 (dd, 1H, $J_{4,5}$ 8 Hz, H-4), 3.19 (s, 3H, CH_3O), 2.86 (dd, 1H, $J_{5,6a}$ 3.2 Hz, $J_{6a,6b}$ 13.9 Hz, H-6a), 2.51 (dd, 1H, $J_{5,6b}$ 3.3 Hz, H-6b), 2.60–1.42 (m, 4H, $2CH_2$), 1.36, 1.34 (2s, 6H, CMe_2), 1.3–1.13 (m, 2H, CH_2), 0.6 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 112.4 (C-*iso*), 107.0 (C-1), 84.6 (C-2), 81.0 (C-4), 79.7 (C-3), 67.9 (C-5), 54.4 (CH_3O), 37.1 (C-6), 32.1, 31.6 ($2CH_2$), 25.8, 24.5 (CMe_2), 21.7 (CH_2), 13.5 (CH_3). HRESIMS: *m*/*z* 329.1407. Calcd for $C_{14}H_{26}O_5NaS$: 329.1399. Anal. Calcd for $C_{14}H_{26}O_5S$: C, 54.88; H, 8.55; S, 10.46. Found: C, 54.74; H, 8.61; S, 10.40.

1.3.2. Methyl 2,3-*O*-isopropylidene-6-*S*-octyl-6-thio-α-D-mannofuranoside (9b). Syrup; 275 mg (90%); R_f 0.41 (9:1 hexane–EtOAc); $[\alpha]_D$ +62.6 (*c* 1.2, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.75 (s, 1H, $J_{1,2}$ 0 Hz, H-1), 4.71 (dd, 1H, $J_{3,4}$ 3.5 Hz, H-3), 4.43 (d, 1H, $J_{2,3}$ 5.9 Hz, H-2), 3.88 (m, 1H, H-5), 3.72 (dd, 1H, $J_{4,5}$ 8.3 Hz, H-4), 3.17 (s, 3H, CH_3O), 2.84 (dd, 1H, $J_{5,6a}$ 3.3 Hz, $J_{6a,6b}$ 13.8 Hz, H-6a), 2.51 (dd, 1H, $J_{5,6b}$ 3.3 Hz, H-6b), 2.50–1.42 (m, 8H, $4CH_2$), 1.35, 1.33 (2s, 6H, CMe_2), 1.25–1.10 (m, 6H, $3CH_2$), 0.76 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 112.3 (C-*iso*), 107.0 (C-1), 84.6 (C-2), 81.0 (C-4), 79.7 (C-3), 67.9 (C-5), 54.3 (CH_3O), 37.1 (C-6), 32.5, 30.1, 29.6, 29.0, 28.7 ($6CH_2$), 25.6, 24.5 (CMe_2), 22.4 (CH_2), 13.9 (CH_3). HRESIMS: *m*/*z* 385.2039. Calcd for $C_{18}H_{34}O_5NaS$: 385.2025. Anal. Calcd for $C_{18}H_{34}O_5S$: C, 59.64; H, 9.45; S, 8.84. Found: C, 54.74; H, 9.51; S, 8.78.

1.3.3. Methyl 6-*S*-dodecyl-2,3-*O*-isopropylidene-6-thio-α-D-mannofuranoside (9c). Syrup; 335 mg (95%); R_f 0.37 (9:1 hexane–EtOAc); $[\alpha]_D$ +68.6 (*c* 1.4, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.80 (s, 1H, $J_{1,2}$ 0 Hz, H-1), 4.76 (dd, 1H, $J_{3,4}$ 3.4 Hz, H-3), 4.48 (d, 1H, $J_{2,3}$ 5.8 Hz, H-2), 3.90 (m, 1H, H-5), 3.77 (dd, 1H, $J_{4,5}$ 7.9 Hz, H-4), 3.22 (s, 3H, CH_3O), 2.84 (dd, 1H, $J_{5,6a}$ 3.2 Hz, $J_{6a,6b}$ 13.7 Hz, H-6a), 2.57 (dd, 1H, $J_{5,6b}$ 3.5 Hz, H-6b), 2.50–1.40 (m, 14H, $7CH_2$), 1.39, 1.38 (2s, 6H, CMe_2), 1.37–1.00 (m, 8H, $4CH_2$), 0.80 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 112.3 (C-*iso*), 107.0 (C-1), 84.6 (C-2), 81.0 (C-4), 79.7 (C-3), 67.9 (C-5), 54.3 (CH_3O), 37.1 (C-6), 32.5, 30.1, 29.6, 29.0, 28.7 ($10CH_2$), 25.6, 24.5 (CMe_2), 22.4 (CH_2), 13.9 (CH_3). HRESIMS: *m*/*z* 441.2655. Calcd for $C_{22}H_{42}O_5NaS$: 441.2651. Anal. Calcd for $C_{22}H_{42}O_5S$: C, 63.12; H, 10.11; S, 7.66. Found: C, 63.06; H, 10.09; S, 7.53.

1.3.4. Methyl 6-*S*-hexadecyl-2,3-*O*-isopropylidene-6-thio-α-D-mannofuranoside (9d). Syrup; 376 mg (94%); R_f 0.36 (9:1 hexane–EtOAc); $[\alpha]_D$ +75.7 (*c* 1.5, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.75 (s, 1H, $J_{1,2}$ 0 Hz, H-1), 4.70 (dd, 1H, $J_{3,4}$ 3.3 Hz, H-3), 4.43 (d, 1H, $J_{2,3}$ 5.9 Hz, H-2), 3.92 (m, 1H, H-5), 3.72 (dd, 1H, $J_{4,5}$ 7.9 Hz, H-4), 3.22 (s, 3H, CH_3O), 2.84 (dd, 1H, $J_{5,6a}$ 3.2 Hz, $J_{6a,6b}$ 13.5 Hz, H-6a), 2.45 (dd, 1H, $J_{5,6b}$ 3.3 Hz, H-6b), 2.50–1.42 (m, 22H, $11CH_2$), 1.38, 1.37 (2s, 6H, CMe_2), 1.37–1.00 (m, 8H, $4CH_2$), 0.80 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 112.3 (C-*iso*), 107.0 (C-1), 84.6 (C-2), 81.0 (C-4), 79.7 (C-3), 67.9 (C-5), 54.4 (CH_3O), 37.1 (C-6), 32.5, 30.1, 29.6, 29.0, 28.7 ($14CH_2$), 25.6, 24.5 (CMe_2), 22.4 (CH_2), 13.9 (CH_3). HRESIMS: *m*/*z* 497.3259. Calcd for $C_{26}H_{50}O_5NaS$: 497.3277. Anal. Calcd for $C_{26}H_{50}O_5S$: C, 65.78; H, 10.62; S, 6.75. Found: C, 65.85; H, 10.55; S, 6.61.

1.3.5. 6-*S*-Butyl-2,3-*O*-isopropylidene-6-thio-α-D-mannofuranose (10a). Syrup; 230 mg (89%); R_f 0.33 (7:3 hex-

ane–EtOAc); $[\alpha]_D$ +27.1 (*c* 1.5, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.25 (s, 1H, $J_{1,2}$ 0 Hz, H-1), 4.80 (dd, 1H, $J_{3,4}$ 3.6 Hz, H-3), 4.51 (d, 1H, $J_{2,3}$ 5.9 Hz, H-2), 3.95 (m, 1H, H-5), 3.74 (dd, 1H, $J_{4,5}$ 8 Hz, H-4), 2.90 (dd, 1H $J_{5,6a}$ 3.3 Hz, $J_{6a,6b}$ 13.2 Hz, H-6a), 2.58 (dd, 1H, $J_{5,6b}$ 3.3 Hz, H-6b), 2.50–1.41 (m, 4H, $2CH_2$), 1.40, 1.39 (2s, 6H, CMe_2), 1.38–1.11 (m, 2H, CH_2), 0.7 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 112.5 (C-*iso*), 100.9 (C-1), 85.3 (C-2), 81.2 (C-4), 79.9 (C-3), 68.1 (C-5), 37.4 (C-6), 32.1, 31.6 ($2CH_2$), 25.8, 24.5 (CMe_2), 21.7 (CH_2), 13.5 (CH_3). ESIMS: *m*/*z* 315.10 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{24}O_5S$: C, 53.40; H, 8.27; S, 10.97. Found: C, 53.65; H, 8.42; S, 10.76.

1.3.6. 2,3-*O*-Isopropylidene-6-*S*-octyl-6-thio-α-D-mannofuranose (10b). Syrup; 216 mg (70%); R_f 0.35 (7:3 hexane–EtOAc); $[\alpha]_D$ +28.1 (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.28 (s, 1H, $J_{1,2}$ 0 Hz, H-1), 4.79 (dd, 1H, $J_{3,4}$ 3.5 Hz, H-3), 4.49 (d, 1H, $J_{2,3}$ 5.8 Hz, H-2), 4.01 (m, 1H, H-5), 3.91 (dd, 1H, $J_{4,5}$ 8.3 Hz, H-4), 2.84 (dd, 1H, $J_{5,6a}$ 3.0 Hz, $J_{6a,6b}$ 13.8 Hz, H-6a), 2.55 (dd, 1H, $J_{5,6b}$ 3.2 Hz, H-6b), 2.50–1.42 (m, 8H, $4CH_2$), 1.38, 1.36 (2s, 6H, CMe_2), 1.32–1.10 (m, 6H, $3CH_2$), 0.80 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 112.4 (C-*iso*), 100.9 (C-1), 85.4 (C-2), 81.2 (C-4), 79.9 (C-3), 68.1 (C-5), 37.0 (C-6), 32.3, 31.7, 29.6, 29.0, 28.7 ($6CH_2$), 25.8, 24.7 (CMe_2), 22.4 (CH_2), 14.0 (CH_3). HRESIMS: *m*/*z* 371.1863. Calcd for $C_{17}H_{32}O_5NaS$: 371.1868. Anal. Calcd for $C_{17}H_{32}O_5S$: C, 58.59; H, 9.26; S, 9.20. Found: C, 58.42; H, 9.18; S, 9.32.

1.3.7. 6-*S*-Dodecyl-2,3-*O*-isopropylidene-6-thio-α-D-mannofuranose (10c). Syrup; 275 mg (77%); R_f 0.32 (7:3 hexane–EtOAc); $[\alpha]_D$ +28.9 (*c* 1.4, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.31 (s, 1H, $J_{1,2}$ 0 Hz, H-1), 4.77 (dd, 1H, $J_{3,4}$ 3.4 Hz, H-3), 4.50 (d, 1H, $J_{2,3}$ 5.8 Hz, H-2), 3.92 (m, 1H, H-5), 3.90 (dd, 1H, $J_{4,5}$ 7.9 Hz, H-4), 2.85 (dd, 1H, $J_{5,6a}$ 3.3 Hz, $J_{6a,6b}$ 13.6 Hz, H-6a), 2.56 (dd, 1H, $J_{5,6b}$ 3.4 Hz, H-6b), 2.50–1.39 (m, 14H, $7CH_2$), 1.39, 1.37 (2s, 6H, CMe_2), 1.36–1.00 (m, 8H, $4CH_2$), 0.81 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 112.5 (C-*iso*), 100.9 (C-1), 85.5 (C-2), 81.3 (C-4), 79.8 (C-3), 66.7 (C-5), 37.1 (C-6), 33.8, 32.5, 31.8, 29.5, 29.3, 29.1, 28.7, 28.5, 28.3 ($10CH_2$), 25.8, 24.5 (CMe_2), 22.4 (CH_2), 14.0 (CH_3). HRESIMS: *m*/*z* 427.2494. Calcd for $C_{21}H_{40}O_5NaS$: 427.2491. Anal. Calcd for $C_{21}H_{40}O_5S$: C, 62.34; H, 9.96; S, 7.93. Found: C, 62.12; H, 9.86; S, 7.78.

1.3.8. 6-*S*-Hexadecyl-2,3-*O*-isopropylidene-6-thio-α-D-mannofuranose (10d). Syrup; 315 mg (75%); R_f 0.3 (7:3 hexane–EtOAc); $[\alpha]_D$ +31.5 (*c* 1.5, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.28 (s, 1H, $J_{1,2}$ 0 Hz, H-1), 4.81 (dd, 1H, $J_{3,4}$ 3.4 Hz, H-3), 4.55 (d, 1H, $J_{2,3}$ 5.9 Hz, H-2), 4.10 (dd, 1H, $J_{4,5}$ 8.0 Hz, H-4), 3.95 (m, 1H, H-5), 2.91 (dd, 1H, $J_{5,6a}$ 3.3 Hz, $J_{6a,6b}$ 13.2 Hz, H-6a), 2.65 (dd, 1H, $J_{5,6b}$ 3.3 Hz, H-6b), 2.60-1.41 (m, 22H, $11CH_2$), 1.38, 1.37 (2s, 6H, CMe_2), 1.35–1.00 (m, 8H, $4CH_2$), 0.80 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 112.6 (C-*iso*), 101.1 (C-1), 85.3 (C-2), 81.4 (C-4), 80.0 (C-3), 68.1 (C-5), 37.1 (C-6), 32.5, 31.8, 29.6, 29.3, 29.0, 28.8 ($14CH_2$), 25.8, 24.5 (CMe_2), 22.6 (CH_2), 13.9 (CH_3). ESIMS: *m*/*z* 483.30 $[M+Na]^+$: Anal. Calcd for $C_{25}H_{48}O_5S$: C, 65.17; H, 10.50; S, 6.96. Found: C, 65.28; H, 10.32; S, 6.84.

1.3.9. 2,3-*O*-Isopropylidene-6-*S*-octyl-6-thio-α-D-mannofuranosyl chloride (11). Syrup; 213 mg (70%); R_f 0.26 (4:1 hexane–EtOAc); $[\alpha]_D$ +24.6 (*c* 1, CH_2Cl_2), ^1H NMR ($CDCl_3$, 300 MHz): δ 6.01 (s, 1H, $J_{1,2}$ 0 Hz, H-1), 4.90 (dd, 1H, $J_{4,5}$ 8.4 Hz, H-4), 4.20 (d, 1H, $J_{3,4}$ 2.0 Hz, H-3), 4.14 (m, 1H, H-5), 4.12 (d, 1H, $J_{2,3}$ 4.3 Hz, H-2), 3.91 (dd, 1H, $J_{4,5}$ 8.3 Hz, H-4), 2.80 (dd, 1H, $J_{5,6a}$ 3.2 Hz, $J_{6a,6b}$ 14.0 Hz, H-6a), 2.60 (dd, 1H, $J_{5,6b}$ 3.4 Hz, H-6b), 2.51–1.40 (m, 8H, $4CH_2$), 1.39, 1.37 (2s, 6H, CMe_2), 1.31–1.10 (m, 6H, $3CH_2$), 0.80 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 113.2 (C-*iso*), 97.4 (C-1), 88.8 (C-2), 83.2 (C-4), 78.7 (C-3), 67.0 (C-5), 36.8 (C-6), 32.5, 31.7, 29.6, 29.0, 28.7 ($6CH_2$), 25.8, 24.7 (CMe_2), 22.5 (CH_2), 13.9 (CH_3).

1.3.10. Methyl 2,3-*O*-isopropylidene-6-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-6-thio-α-D-mannofuranoside (13). Syrup; 340 mg (70%); R_f 0.37 (9:1 hexane–EtOAc); $[\alpha]_D$ +70.8 (*c* 1.2, CH_2Cl_2), ^1H NMR ($CDCl_3$, 300 MHz): δ 5.20 (d, 1H, $J_{1',2'}$ 9.8 Hz, H-1′), 5.10 (t, 1H, $J_{3',4'}$ 9.3 Hz, H-3′), 4.90 (dd, 1H, $J_{2',3'}$ 9.8 Hz, H-2′), 4.75 (s, 1H, $J_{1,2}$ 0 Hz, H-1), 4.70 (dd, 1H, $J_{3,4}$ 3.5 Hz, H-3), 4.60 (dd, 1H, $J_{4',5'}$ 9.8 Hz, H-4′), 4.22 (dd, 1H, $J_{5',6a'}$ 2.5 Hz, H-6a′), 4.20 (dd, 1H, $J_{5',6b'}$ 4.8 Hz, $J_{6a',6b'}$ 12.5 Hz, H-6b′), 4.00 (m, 1H, H-5), 3.80 (dd, 1H, $J_{4,5}$ 8.5 Hz, H-4), 3.70 (m, 1H, H-5), 3.19 (s, 3H, OCH_3), 2.91 (dd, 1H, $J_{5,6a}$ 4.1 Hz, H-6a), 2.90 (dd, 1H, $J_{5,6b}$ 4.0 Hz, $J_{6a,6b}$ 14.6 Hz, H-6b), 1.99–1.89 (4s, 12H, $4CH_3CO$), 1.35 (s, 6H, CMe_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.0, 169.9, 169.1 (C=O), 112.3 (C-*iso*), 106.9 (C-1), 84.6 (C-2), 80.5 (C-4), 79.5 (C-3), 79.0 (C-1′), 75.6 (C-2′), 73.5 (C-4′), 69.7 (C-3′), 68.0 (C-5′), 67.9 (C-5), 61.8 (C-6′), 54.4 (OCH_3), 36.5 (C-6), 25.8, 24.5 (CMe_2), 20.6, 20.4 (CH_3CO). Anal. Calcd for $C_{24}H_{36}O_{14}S$: C, 49.65; H, 6.25; S, 5.52. Found: C, 49.48; H, 6.12; S, 5.64.

1.3.11. 2,3-*O*-Isopropylidene-6-*S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-6-thio-α-D-mannofuranose (14). Syrup; 436 mg (87%); R_f 0.27 (7:3 hexane–EtOAc); $[\alpha]_D$ +31.5 (*c* 1.5, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.25 (s, 1H, $J_{1,2}$ 0 Hz, H-1), 5.16 (d, 1H, $J_{1',2'}$ 9.9 Hz, H-1′), 4.95 (t, 1H, $J_{3',4'}$ 9.3 Hz, H-3′), 4.90 (dd, 1H, $J_{2',3'}$ 9.4 Hz, H-2′), 4.70 (dd, 1H, $J_{3,4}$ 3.5 Hz, H-3), 4.50 (dd, 1H, $J_{4',5'}$ 9.8 Hz, H-4′), 4.52 (dd, 1H, $J_{2,3}$ 5.7 Hz, H-2), 4.17 (dd, 1H, $J_{5',6a'}$ 2.5 Hz,

H-6a′), 4.15 (dd, 1H, $J_{5',6b'}$ 4.8 Hz, $J_{6a',6b'}$ 12.5 Hz, H-6b′), 4.10 (dd, 1H, $J_{4,5}$ 8.1 Hz, H-4), 4.00 (m, 1H, H-5), 3.70 (m, 1H, H-5′), 2.91 (dd, 1H, $J_{5,6a}$ 3.8 Hz, H-6a), 2.89 (dd, 1H, $J_{5,6b}$ 3.8 Hz, $J_{6a,6b}$ 14.0 Hz, H-6b), 2.10–1.90 (4s, 12H, $4CH_3CO$), 1.37 (s, 6H, CMe_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.7, 170.0, 169.4, 169.3 (C=O), 112.3 (C-*iso*), 100.8 (C-1), 85.4 (C-2), 83.9 (C-4), 80.6 (C-3), 79.7 (C-1′), 75.6 (C-2′), 73.6 (C-4′), 69.7 (C-3′), 68.0 (C-5′), 67.9 (C-5), 61.6 (C-6′), 36.6 (C-6), 25.8, 24.7 (CMe_2), 20.5, 20.4 (CH_3CO). ESIMS: *m*/*z* 589.20 $[M+Na]^+$. Anal. Calcd for $C_{23}H_{34}O_{14}S$: C, 48.76; H, 6.05; S, 5.66. Found: C, 48.84; H, 6.12; S, 5.75.

1.3.12. 2,3-*O*-Isopropylidene-6-*S*-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl)-6-thio-α-D-mannofuranose (16). Syrup. Yield: 368 mg (87%); R_f 0.25 (7:3 hexane–EtOAc); $[\alpha]_D$ +31.5 (*c* 1.5, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz): δ 5.50 (d, 1H, $J_{1',2'}$ 5.0 Hz, H-1′), 5.28 (s, 1H, $J_{1,2}$ 0 Hz, H-1), 4.80 (dd, 1H, $J_{3,4}$ 4.0 Hz, H-3), 4.65 (dd, 1H, $J_{2,3}$ 5.7 Hz, H-2), 4.52 (dd, 1H, $J_{4',5'}$ 1.8 Hz, H-4′), 4.25 (dd, 1H, $J_{2',3'}$ 2.5 Hz, H-2′), 4.23 (dd, 1H, $J_{3',4'}$ 8.0 Hz, H-3′), 4.05 (dd, 1H, $J_{4,5}$ 6.1 Hz, H-4), 4.02 (m, 1H, H-5′), 3.85 (m, 1H, H-5), 3.02 (m, 2H, H-6a′, H-6b′), 2.08 (m, 2H, H-6a, H-6b), 1.4, 1.37, 1.27, 1.25 (4s, 12H, $4CH_3$), 1.48 (s, 6H, CMe_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 112.5, 109.2, 108.7 (C-*iso*), 100.9 (C-1), 96.5 (C-1′), 85.4 (C-2), 80.9 (C-4), 79.8 (C-3), 71.3 (C-2′), 70.7 (C-4′), 70.4 (C-3′), 68.0 (C-5′), 67.5 (C-5), 36.6 (C-6), 31.9 (C-6′), 25.8, 24.8, 24.6, 24.3 ($3CMe_2$). HRESIMS: *m*/*z* 501.1772. Calcd for $C_{21}H_{34}O_{10}NaS$: 501.1770. Anal. Calcd for $C_{21}H_{34}O_{10}S$: C, 52.71; H, 7.16; S, 6.70. Found: C, 52.89; H, 7.25; S, 6.58.

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