Carbohydrate Research xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Synthesis of benzyl protected β-D-GlcA-(1 → 2)-α-D-Man thioglycoside building blocks for construction of *Cryptococcus neoformans* capsular polysaccharide structures

Lorenzo Guazzelli, Rebecca Ulc, Stefan Oscarson *

Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland

ARTICLE INFO

Article history:
Received 25 November 2013
Received in revised form 24 January 2014
Accepted 30 January 2014
Available online xxxx

Keywords:
Oligosaccharide synthesis
Thiosaccharide blocks
Stereoselectivity
Uronic acid donors

ABSTRACT

In a project targeting the synthesis of large oligosaccharide structures corresponding to the *Cryptococcus neoformans* GXM capsular polysaccharide, an easy access to thiodisaccharide building blocks comprising a β-linked glucuronic acid moiety and a 6-*O*-acetyl group was required. Several pathways to such building blocks have been investigated, addressing the problem of constructing a β-linked glucuronic acid residue protected with groups that are orthogonal to a primary acetyl group. Two efficient routes have been developed, one using benzoylated glucosyl donors to form the β-linkage followed by a change of protecting groups to benzyls and subsequent introduction of the carboxyl function and the acetyl group. The second route explored the possibility to achieve β-selectivity using glucuronyl donors without acyl protecting groups. BF_3-etherate promoted glycosylations with benzyl (2,3,4-tri-*O*-benzyl-α-D-glucupyranosyl)uronate trichloroacetimidate in the presence of nitrile solvents and at low temperatures reproducibly gave good yields of disaccharides with high β-selectivity. Furthermore, the use of recently reported glucuronyl thioglycoside donors protected with a cyclic 2,4-silylene acetal was found to represent another efficient and completely β-selective way to desired disaccharide building blocks.

In a project aiming at developing glycoconjugate vaccines against the fungi *Cryptococcus neoformans*,[1,2] we are building a library of *Cryptococcus neoformans* oligosaccharide structures ranging from disaccharides up to octadecasaccharides using a building block approach. To accomplish this, access to large quantities of relevant disaccharide building blocks is essential. For the synthesis of *C. neoformans* Serotype A and D structures two variants of disaccharide blocks are required, a β-D-glucopyranosyluronic acid-(1 → 2)-D-mannose type and a β-D-xylopyranosyl-(1 → 2)-D-mannose type (Fig. 1). Of the two glucuronic acid-containing building blocks, the one containing a 6-*O*-acetate (R^1 = Ac) is the major target.

The presence of acetates in target structures severely complicates synthesis since it more or less excludes the use of ester protecting groups as permanent protecting groups. High-yielding methods have been developed for the synthesis of the xylose-containing disaccharide blocks on a large scale and with good reproducibility.[3] The β-xylopyranoside-linkage is constructed using benzoyl-protected xylosyl donors, followed by change of benzoyl to benzyl protecting groups and subsequent introduction of the 6-*O*-acetate. Synthesis of the β-glucuronic acid-containing blocks is however more difficult mainly due to the β-configuration in combination with the notoriously difficult benzylation of glucuronic acid derivatives. Applying the same procedure as for the xylosyl blocks, that is using an acylated glucuronyl donor, gave, after optimization of the benzylation step, acceptable yields of the desired blocks,[4] but there were problems with reproducibility of yields in the benzylation step and the reaction could not be performed on a large scale. Hence, another approach was developed in which a glucosyl donor was employed, and the carboxylic function, as well as the acetate, was introduced after the benzylation step.[5] We here report on further optimization of this route (Schemes 1 and 2) as well as new approaches utilizing non-acyl protected glucuronyl donors (Schemes 3–5) toward the target glucuronic acid-containing disaccharide building blocks.

For reasons relevant to the subsequent use of the disaccharide blocks in the construction of larger *Cryptococcus* structures, we changed the temporary protecting group from the allyl group used so far to a 2-naphtalenylmethyl (NAP) group, starting the synthesis from acceptor **2** instead of **1**. Since large scale synthesis was the target we decided to also change the glucosyl donor used from the bromide **3** to the trichloroacetimidate donor **4**, allowing the use of catalytic amount of promoter and avoiding the use of large

* Corresponding author. Tel.: +353 1 7162318; fax: +353 1 7162501.
E-mail address: stefan.oscarson@ucd.ie (S. Oscarson).

http://dx.doi.org/10.1016/j.carres.2014.01.022
0008-6215/

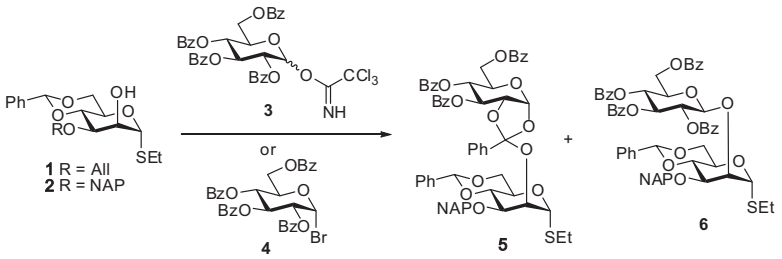
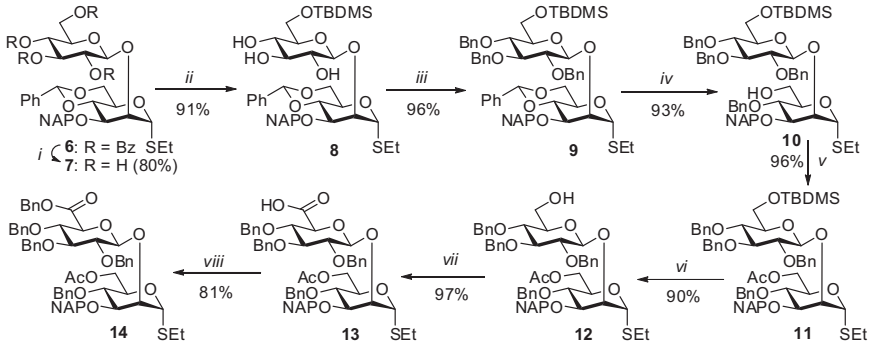


Figure 1. Required *C. neoformans* disaccharide building blocks.

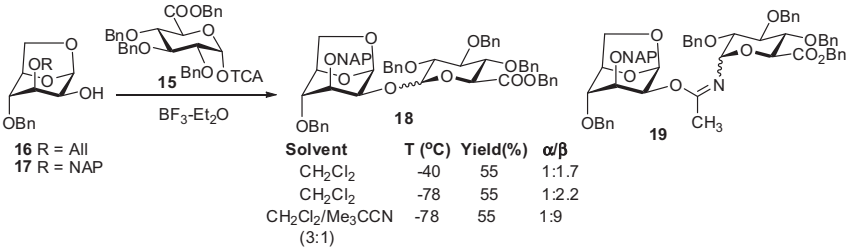
amounts of silver salts. Initially, this caused problems since the orthoester **5** was the product rather than the glycoside **6**. The standard solution to this problem, that is, using more acidic conditions (including acid-washed molecular sieves) and longer reaction times to allow any formed orthoester to rearrange in situ, worked well and after optimization (Scheme 1, Table 1) reproducible yields of ~90% of the β-linked disaccharide **6** were obtained even on 10 g scale glycosylations.

The continued transformation of **6** essentially followed the earlier published procedure[5] but by changing the order of some reaction steps and through optimization of each step it was possible to improve the overall yield in the synthesis of the target building block **14** from 15% up to a 40% overall yield over the eight steps and perform the synthesis on a gram scale (Scheme 2).The major part of this improvement in overall yield originated from the optimization of the benzylation step of compound **8**, where a 6 → 4 silyl migration was observed. By running the benzylation at 0 °C instead of at room temperature the migration could be prevented and the yield in this step raised to 97% from the 67% earlier reported.

Although efficient, a drawback of this pathway is the amount of steps (eight) required at the disaccharide level, why an alternative approach using already benzylated glucuronic acid donors has been pursued in parallel. Initial experiments were performed with the known α-trichloroacetimidate donor **15**,[6] which methyl ester equivalent, using BF_3-etherate as promoter, is reported to give good yields of β-linked product (S_N2-type glycosylation) in spite of the lack of a 2-*O*-participating group.[7] We have earlier used

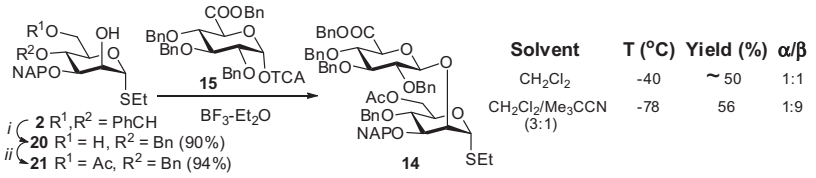


Scheme 1. Glycosylations with benzoylated glucosyl donors. Reaction conditions see Table 1.



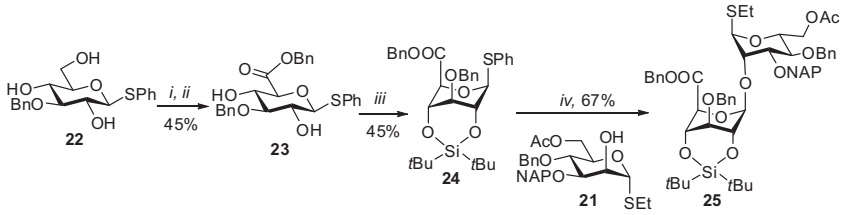
Solvent	T (°C)	Yield(%)	α/β
CH_2Cl_2	-40	55	1:1.7
CH_2Cl_2	-78	55	1:2.2
CH_2Cl_2/Me_3CCN (3:1)	-78	55	1:9

Scheme 2. Transformation of disaccharide **6** into target structure **14**. Key: Reagents and conditions: (i) NaOMe, MeOH; (ii) TBDMSCl, pyridine, DMAP; (iii) NaH, BnBr, DMF, 0 → 20 °C; (iv) Et_3SiH, $PhBCl_2$, CH_2Cl_2, −78 °C; (v) Ac_2O, pyridine; (vi) TBAF·3 H_2O, THF; (vi) TEMPO, BAIB, CH_2Cl_2/H_2O; (vii) Cs_2CO_3, BnBr, DMF, 0 → 20 °C.



Solvent	T (°C)	Yield (%)	α/β
CH_2Cl_2	-40	~ 50	1:1
CH_2Cl_2/Me_3CCN (3:1)	-78	56	1:9

Scheme 3. Glycosylations with 1,6-anhydro acceptors.



Scheme 4. Glycosylation using acceptor **21**. Key: Reagents and conditions: (i) BH_3-THF, Bu_2BOTf, THF/CH_2Cl_2, 0 °C; (ii) AcCl, collidine, CH_2Cl_2, −78 °C.

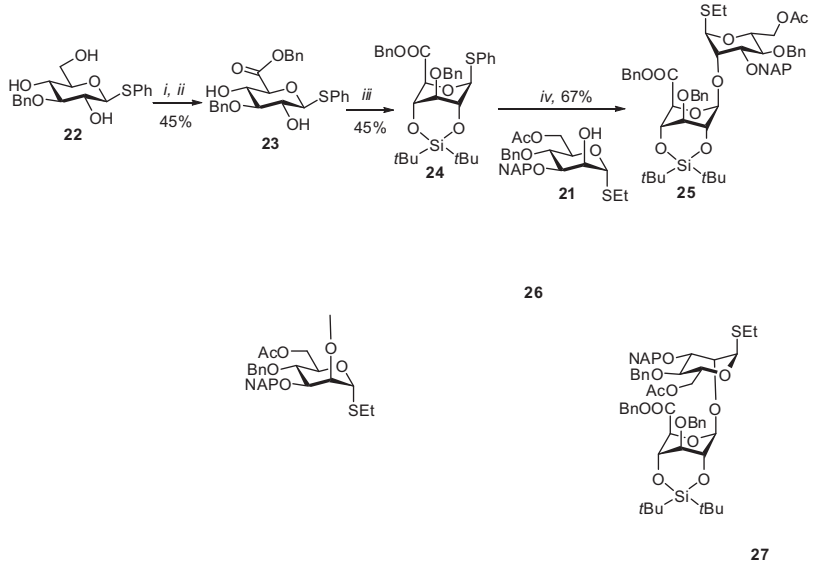
this approach successfully in the synthesis of β-linked glucuronosyl ester drug metabolites.[6] However, initial results were quite discouraging, a coupling in CH_2Cl_2 with compound **1** as the acceptor afforded a 58% yield of exclusively the α-linked disaccharide.[8]

We then investigated the effect of conformational changes in the acceptor on the stereochemical outcome of the glycosylation. The known 1,6-anhydro mannose derivatives **16**[9] and **17**[10] were prepared (Scheme 3), with an allyl or a naphtalenylmethyl group as 3-*O*-temporary protecting group, respectively. Acetolysis of the anhydro linkage in obtained β-linked disaccharides would effectively yield 1,6-diacetylated precursors to target building block.

This conformational change in the acceptor improved β-selectivity in couplings with donor **15**. Early attempts with BF_3-promoted glycosylations in CH_2Cl_2 with acceptor **16** afforded exclusively the β-linked disaccharide product in 78% yield.[11] However, the stereochemical outcome proved to be most sensitive to reaction conditions and efforts to reproduce the initial results (now in a new laboratory in Dublin), with either acceptor **16** or **17**, failed and lower yields and (especially) stereoselectivities were obtained (Scheme 3). Lowering the temperature (−78 instead of −40 °C) in the glycosylation had only a marginal effect on the α/β-selectivity (1:1.7 → 1:2.2). Therefore, solvent effects were explored and couplings were performed in CH_2Cl_2/CH_3CN mixtures. The well-documented β-directing effect of nitrile solvents in glycosylations[12] has been rarely investigated with uronic acid donors and an initial paper reports opposite results.[13] In the glycosylation between donor **15** and acceptor **17** using a 3:1 CH_2Cl_2/CH_3CN mixture at −78 °C the β-selectivity was enhanced, but the major product was compound **19** in which the acetonitrile donor adduct has been captured by the acceptor. This type of side product has been reported and also the use of more sterically hindered nitrile solvents to prevent their formation.[14,15] Accordingly, the glycosylation was tried in a 3:1 CH_2Cl_2/trimethylacetonitrile mixture yielding product **18** with high β-selectivity (α/β 1:9) and acceptable yield (55%). The separation of the anomers, however, proved to be not possible and this problem prevailed also after subsequent acetolysis of the 1,6-anhydro bridge. For characterization purposes pure **18β** was prepared using an acetylated methyl ester glucuronic acid donor followed by exchange of acetates and methyl ester with benzyl groups in the obtained disaccharide (Method A in Section 1, 26% yield over 3 steps).

While looking for ways to solve this separation problem, the nitrile solvent effect was explored in glycosylations using the earlier $^4C_1$ type acceptors. Partly due to the discouraging glycosylation results obtained with acceptor **1** and partly to minimize reaction steps at the disaccharide level, acceptor **21** was prepared from **2** (Scheme 4). Coupling between donor **15** and acceptor **21** in CH_2Cl_2 at −40 °C gave a 1:1 α/β-mixture, which was encouraging considering the complete α-selectivity obtained in the earlier coupling with acceptor **1**. Also, it was found that these two anomers were easy to separate by silica gel chromatography. Subsequent glycosylation using a 3:1 CH_2Cl_2/trimethylacetonitrile mixture at −78 °C afforded disaccharide **14** in a 56% yield as a *separable* 9:1 β:α-mixture, constituting a very direct way to this building block with no reaction steps required at the disaccharide level (Scheme 4).

We have also looked into the possibility of using other donors with a protecting group pattern claimed to be β-directing although not using 2-*O*-acyl participating groups. A 2-*O*-picolinyl group was introduced by Demchenko and coworkers as a non-acyl participating protecting group.[16,17] We prepared the 2-*O*-picolinyl analogue



Scheme 5. Glycosylation using the cyclic silylene acetal protected glucuronyl donor **24**. Key: Reagents and conditions: (i) TEMPO, BAIB, CH_2Cl_2/H_2O (2:1); (ii) Cs_2CO_3, BnBr, DMF; (iii) Lutidine, DTBSDT, $(CH_2Cl)_2$; (iv) (1) Ph_2SO, TTBP, CH_2Cl_2, −60 °C, (2) Tf_2O, −60 °C → 0 °C.

Table 1
Reaction conditions used in the glycosylation between donor **3**/**4** and acceptor **2**

Entry	Donor	Acceptor	Reaction conditions	Yield (**5**/**6**)
1	**3**	**1**	TMSOTf/CH_2Cl_2/−78 °C → 20 °C/overnight/no MS/argon	0%/22%
2	**3**	**1**	TBDMSOTf/CH_2Cl_2/−78 °C → 20 °C/overnight/no MS/argon	0%/26%
3	**3**	**1**	TBDMSOTf/CH_2Cl_2/−78 °C/4 h/no MS/argon	97%/0%
4	**3**	**1**	TBDMSOTf/CH_2Cl_2/−78 °C → 20 °C/overnight/basic MS 4 Å/argon	85%/0%
5	**3**	**1**	TBDMSOTf/CH_2Cl_2/−78 °C → 20 °C/overnight/acidic MS 4 Å/argon	0%/88%
6	**4**	**1**	AgOTf, DTBP/CH_2Cl_2/−50 °C/overnight/basic MS 4 Å/argon	0%/52%

of donor **15** but this was found to be too unreactive in glycosylations with acceptor **1** and gave no product at all.[18] Recently Furukawa, Hinou, and Nishimura reported on a β-selective methyl (phenyl 1-thio-D-glucopyranoside)uronate donor without a 2-*O*-participating group.[19] The β-stereoselectivity was accredited to the use of a sterically large cyclic 2,4-*O*-silyl acetal which forced the change of donor conformation to $^1C_4$ and which was argued to shield the α-side of the activated donor from attack by the acceptor. To change this type of donor into one that fulfilled our requirements for a glucuronic acid donor (β-selective with protecting groups orthogonal to an acetate) the corresponding benzyl ester protected donor **24** was synthesized and tried in couplings with acceptor **21** (Scheme 5). Since both acceptor **21** and donor **24** are thioglycosides, a protocol involving pre-activation of the donor was employed. In agreement with the results reported in the paper for the methyl ester donor, the glycosylation proceeded with complete β-selectivity and good yield (67%) affording an easy access to a variant glucuronic acid-containing *Cryptococcus* disaccharide building block.

As a conclusion we now have two functional routes to *Cryptococcus* β-D-glucuronic acid-containing building block targets, both pathways are reproducible and can be performed on a large scale. One comprises a very easily accessible glucosyl donor as well as mannose acceptor but requires a number of (high-yielding) steps at the disaccharide levels whereas the other employs more elaborate glucuronyl donors and mannose acceptors but do not require any steps at the disaccharide level. Both routes are being used in the lab to produce glucuronic acid-containing building blocks for continued synthesis of *C. neoformans* CPS structures. It is possible to get good β-selectivity with perbenzylated glucuronyl donors, that is, without a 2-*O*-participating group, but the outcome is dependent on a number of factors. Glycosylation with perbenzylated glucuronyl donor **15** in the presence of nitrile solvents and at low temperatures reproducibly gave high but not complete β-selectivity. We further confirmed that glycosylations with recently reported 2,4-cyclic silylene acetal protected glucuronyl donors yielded complete β-selectivity also with our type of acceptor.

1. Experimental

1.1. General methods

TLC was carried out on precoated 60 F_{254} silica gel alumina plates (Merck) using UV-light and/or 8% H_2SO_4 and/or AMC-solution (ammonium molybdate, cerium(IV) sulfate, 10% H_2SO_4 [5:0.1:100, w/w/v]) for visualization. Flash column chromatography was performed on silica gel (Merck, pore size 60 Å, particle size 40–63 μm). NMR spectra were recorded in $CDCl_3$ (internal Me_4Si δ = 0.00 ppm) at 25 °C on a Varian instrument (500 MHz for ^1H and 125 MHz for ^{13}C). Coupling constants are given in Hertz (Hz). Assignments were aided by DEPT, ^1H–^1H, and ^1H–^{13}C correlation spectroscopies. HRMS spectra were recorded on a micromass LCT instrument. Optical rotations were measured with a Perkin-Elmer 343 polarimeter in a 1 dm cell. Organic phases were dried over $MgSO_4$ before evaporation, which was performed under reduced pressure at temperatures not exceeding 40 °C.

1.2. Ethyl [3,4,6-tri-*O*-benzoyl-[1,2-*O*-(1-phenylmethylene)]-α-D-glucopyranosyl]-(1 → 2)-4,6-*O*-benzylidene-3-*O*-(2-naphthalenylmethyl)-1-thio-α-D-mannopyranoside (5)

A catalytic amount of TBDMSOTf (50 μL, 0.22 mmol) was added to a solution of donor **3** (1.64 g, 2.21 mmol) and acceptor **2** (1.0 g, 2.21 mmol) in dry CH_2Cl_2 (20 mL) containing crushed molecular sieves (4 Å) kept at −78 °C in an atmosphere of nitrogen (TLC, toluene–EtOAc, 6:1). After 4 h, the reaction mixture was neutralized with Et_3N (185 μL, 1.33 mmol), the solids were removed by filtration, and the filtrate was concentrated in vacuo to a yellowish foam. Purification by silica gel flash column chromatography (toluene–EtOAc, 100:0 → 86:14) gave **5** (2.67 g, 97%); R_f 0.61 (toluene–EtOAc, 9:1); ^1H NMR (500 MHz, $CDCl_3$): δ 8.02–7.17 (m, 32H, ArH), 6.05 (d, 1H, $J_{1',2'}$ = 5.5 Hz, H-1′), 5.69 (m, 1H, H-3′), 5.65 (s, 1H, C_6H_5CH), 5.41 (d, 1H, J = 8.5 Hz, H-4′), 4.92 (m, 1H, H-2′), 4.82 (m, 2H, NAPCH_2), 4.61 (d ≈ s, 1H, H-1), 4.52 (m, 1H, H-6a′), 4.35 (dd, 1H, $J_{5',6b'}$ = 5.5 Hz, $J_{6a',6b'}$ = 12.5 Hz, H-6b′), 4.22 (m, 1H, H-2), 4.19–4.13 (m, 2H, H-4, H-6a), 4.10 (m, 1H, H-5′), 4.06–4.01 (m, 1H, H-5), 3.87 (m, 2H, H-3, H-6b), 2.32–2.23 (m, 2H, SCH_2CH_3), 0.97 (t, 3H, SCH_2CH_3); NMR (125 MHz, $CDCl_3$): δ 165.9, 165.0, 165.6 (3 × CO), 135.5–125.3 (ArC and ArCH), 121.0 ($C_{orthoester}$), 101.6 (C_6H_5CH), 97.6 (C-1′), 83.7 (C-1), 78.7 (C-4), 75.2 (C-3), 72.8 (C-2), 72.5 (CH_2, C-2′), 69.0 (C-3′), 68.5 (C-6), 68.3 (C-4′), 67.6 (C-5′), 64.8 (C-5), 64.0 (C-6′), 25.2 (SCH_2CH_3), 14.7 (SCH_2CH_3); HRMS (ESI): $[M+Na]^+$ Calcd for $C_{60}H_{54}O_{14}NaS$, 1053.3132; found, 1053.3157.

1.3. Ethyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1 → 2)-4,6-*O*-benzylidene-3-*O*-(2-naphthalenylmethyl)-1-thio-α-D-mannopyranoside (6)

Method A: A catalytic amount of TBDMSOTf (102 μL, 0.44 mmol) was added to a solution of donor **3** (3.27 g, 4.42 mmol) and acceptor **2** (2.0 g, 4.42 mmol) in dry CH_2Cl_2 (40 mL) containing crushed acid-washed molecular sieves (AW-300) kept at −78 °C under an atmosphere of nitrogen. The temperature was then allowed to rise to 20 °C overnight (TLC, toluene–EtOAc, 6:1). The reaction mixture was neutralized with Et_3N (370 μL, 2.65 mmol), the solids were removed by filtration, and the filtrate was concentrated. Purification by silica gel flash column chromatography (toluene–EtOAc, 100:0 → 86:14) afforded **6** (4.08 g, 88%).

Method B: A solution of AgOTf (1.13 g, 4.42 mmol) in dry toluene was added to a stirred solution of donor **4** (2.91 g, 4.42 mmol), acceptor **2** (1.00 g, 2.21 mmol), 2,6-di-*tert*-butylpyridine (0.24 mL, 1.11 mmol), and crushed molecular sieves (4 Å) in dry CH_2Cl_2 (10 mL) kept at −50 °C in an atmosphere of nitrogen. The reaction was protected from light. The temperature was then allowed to rise to 20 °C overnight (TLC, toluene–EtOAc, 6:1). The reaction was diluted with CH_2Cl_2, and neutralized with Et_3N at 0 °C. The solution was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. Purification by silica gel flash column chromatography (toluene–EtOAc, 100:0 → 86:14) afforded **6** (1.19 g, 52%); R_f 0.52 (toluene/EtOAc 9:1); $[\alpha]_D$ +32 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.96 (m, 4H, ArH), 7.87 (m, 4H, ArH),

7.73–7.64 (m, 4H, ArH), 7.50-7.24 (m, 20H, ArH), 5.94 (dd ≈ t, 1H, $J_{2',3'} = J_{3',4'} = 9.5$ Hz, H-3′), 5.69 (m, 2H, H-2′, H-4′), 5.52 (s, 1H, C_6H_5CH), 5.19 (d ≈ s, 1H, H-1), 5.01 (d, 1H, $J_{1',2'} = 8.0$ Hz, H-1′), 4.87 (d, 1H, $J_{gem} = 12.0$ Hz, NAPCH_2), 4.78 (d, 1H, $J_{gem} = 12.0$ Hz, NAPCH_2), 4.66 (dd, 1H, $J_{5',6a'} = 3.5$ Hz, $J_{6a',6b'} = 12.0$ Hz, H-6a′), 4.51 (dd, 1H, $J_{5',6b'} = 5.5$ Hz, H-6b′), 4.30 (dd ≈ d, 1H, H-2), 4.19–4.15 (ddd, 1H, H-5′), 4.10 (dd ≈ t, 1H, $J = 10.0$ Hz, H-4), 3.96 (ddd, 1H, H-5), 3.89–3.84 (m, 2H, H-3, H-6a), 3.48 (dd ≈ t, 1H, $J = 10.0$ Hz. H-6b), 2.39–2.34 (m, 1H, SCH_2CH$_3$), 1.09 (t, 3H, SCH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 165.8, 165.1, 164.8 (4 × CO), 137.6, 135.6, 133.4, 133.3, 133.2, 133.1, 132.9 (ArC), 129.8–125.3 (ArCH), 101.5 (C_6H_5CH), 100.0 (C-1′), 82.5 (C-1), 78.3 (C-4), 77.9 (C-2), 74.3 (C-3), 72.7 (C-3′), 72.6 (C-5′), 71.8 (C-2′), 71.5 (NAPCH$_2$), 69.7 (C-4′), 68.3 (C-6), 64.5 (C-5), 63.3 (C-6′), 25.4 (SCH$_2$CH$_3$), 14.7 (SCH$_2$CH$_3$); HRMS (ESI): $[M+Na]^+$ Calcd for $C_{60}H_{54}O_{14}NaS$, 1053.3132; found, 1053.3125. Anal. Calcd for $C_{60}H_{54}O_{14}S$: C, 69.89; H, 5.28; S, 3.11. Found: C, 69.31; H, 5.11; S, 3.37.

1.4. Ethyl β-D-glucopyranosyl-(1 → 2)-4,6-*O*-benzylidene-3-*O*-(2-naphthalenylmethyl)-1-thio-α-D-mannopyranoside (7)

A catalytic amount of NaOMe (10 mg, 0.17 mmol) was added to a solution of **6** (1.77 g, 1.71 mmol) in dry MeOH (15 mL). The mixture was stirred at ambient temperature overnight (TLC, CH_2Cl_2/MeOH 9:1). After complete conversion, Dowex (H^+) acidic ion exchange resin was added for neutralisation, the resin was filtered off, washed with MeOH, and the filtrate was concentrated under reduced pressure. Purification by silica gel flash chromatography (CH_2Cl_2/MeOH, 100:0 → 90:10) gave **7** (0.83 g, 80%); R_f 0.34 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$ +64.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD): δ 7.87 (m, 1H, ArH), 7.82–7.78 (m, 2H, ArH), 7.70 (m, 1H, ArH), 7.54–7.49 (m, 3H, ArH), 7.45–7.41 (m, 2H, ArH), 7.38–7.35 (m, 3H, ArH), 5.64 (s, 1H, C_6H_5CH), 5.55 (s, 1H, H-1), 4.97 (d, 1H, $J_{gem} = 12.0$ Hz, NAPCH_2), 4.80 (d, 1H, $J_{gem} = 12.0$ Hz, NAPCH_2), 4.48 (m, 2H, H-1′, H-2), 4.23-4.13 (m, 3H, H-6a), 3.96-3.85 (m, 3H, H-6a, H-6b), 3.70-3.67 (dd, 1H, $J_{5,6b} = 5.5$ Hz, $J_{6a,6b} = 11.5$ Hz, H-6b), 3.43-3.31 (m, 4H), 2.69–2.60 (m, 2H, SCH_2CH$_3$), 1.27 (t, 3H, SCH$_2$CH_3); ^{13}C NMR (125 MHz, CD_3OD): δ 137.8, 135.3, 133.3, 133.1 (ArC), 128.5–125.5 (ArCH), 101.7 (C_6H_5CH), 101.6 (C-1′), 83.5 (C-1), 78.1, 77.0, 76.4, 75.6, 74.9, 73.0, 71.1 (NAPCH$_2$), 70.2, 68.1 (C-6), 64.5, 61.6 (C-6′), 25.0 (SCH$_2$CH$_3$), 14.0 (SCH$_2$CH$_3$); HRMS (ESI): $[M+Na]^+$ Calcd for $C_{32}H_{38}O_{10}NaS$, 637.2083; found, 637.2071. Anal. Calcd for $C_{32}H_{38}O_{10}S$: C, 62.52; H, 6.23; S, 5.22. Found: C, 61.36; H, 6.16; S, 4.98.

1.5. Ethyl 6-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosyl-(1 → 2)-4,6-*O*-benzylidene-3-*O*-(2-naphthalenylmethyl)-1-thio-α-D-mannopyranoside (8)

tert-Butyldimethylchlorosilane (1.44 g, 9.56 mmol) and DMAP (9 mg, 80 μmol) were added to a solution of **7** (4.90 g, 7.97 mmol) in dry pyridine (50 mL) at 20 °C and the mixture was stirred overnight. The progress of the reaction was followed by TLC (CH_2Cl_2/MeOH 9:1). The mixture was concentrated and purified by silica gel flash chromatography (CH_2Cl_2/MeOH, 100:0 → 91:9) to yield **8** (5.33 g, 91%); R_f 0.51 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$ +62.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83–7.75 (m, 4H, ArH), 7.53 (m, 3H, ArH), 7.47 (m, 2H, ArH), 7.40 (m, 3H, ArH), 5.66 (s, 1H, C_6H_5CH), 5.29 (s, 1H, H-1), 5.02 (d, 1H, $J_{gem} = 12.0$ Hz, NAPCH_2), 4.91 (d, 1H, $J_{gem} = 12.0$ Hz, NAPCH_2), 4.55 (d, 1H, $J_{1',2'} = 8.0$ Hz, H-1′), 4.26–4.22 (m, 4H, H-2, H-4, H-5, H-6a), 4.02 (dd, 1H, $J_{2,3} = 3.0$ Hz, $J_{3,4} = 9.5$ Hz, H-3), 3.96 (d, 1H, $J = 2.3$ Hz, 2-OH), 3.94–3.89 (m, 2H, H-6b, H-6a′), 3.81 (dd, 1H, $J_{5',6b'} = 5.0$ Hz, $J_{6a',6b'} = 10.5$ Hz, H-6b′), 3.58–3.53 (m, 2H, H-3′, H-4′), 3.49 (m, 1H, H-2′), 3.39 (m, 1H, H-5′), 3.20 (d, 1H, $J = 1.5$ Hz, 4-OH), 2.84 (d, 1H, $J = 1.7$ Hz, 3-OH), 2.62–2.57 (m, 2H, SCH_2CH$_3$), 1.26 (t, 3H, SCH$_2$CH_3), 0.90 (s, 9H, (CH_3)$_3$C(CH$_3$)$_2$Si), 0.08 (s, 6H, (CH$_3$)$_3$C(CH_3)$_2$Si); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.7, 134.7, 133.5, 133.4 (ArC), 128.6–126.2 (ArCH), 101.9 (C_6H_5CH), 101.5 (C-1′), 85.7 (C-1), 79.8 (C-4), 75.9 (C-3′), 75.7 (C-5′), 75.1 (C-3), 74.3 (NAPCH$_2$), 74.0 (C-2), 72.3 (C-4′), 70.5 (C-2′), 68.8 (C-6), 64.7 (C-5), 64.4 (C-6′), 26.0 ((CH_3)$_3$C(CH$_3$)$_2$Si), 25.8 (SCH_2CH$_3$), 18.4 ((CH$_3$)$_3$C(CH$_3$)$_2$Si), 15.2 (SCH$_2$CH_3), −5.2 ((CH$_3$)$_3$C(CH_3)$_2$Si); HRMS (ESI): $[M+Na]^+$ Calcd for $C_{38}H_{52}O_{10}NaSSi$, 751.2948; found, 751.2956. Anal. Calcd for $C_{38}H_{52}O_{10}SSi$: C, 62.61; H, 7.19; S, 4.40. Found: C, 61.81; H, 7.10; S, 4.84.

1.6. Ethyl (2,3,4-tri-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosyl)-(1 → 2)-4,6-*O*-benzylidene-3-*O*-(2-naphthalenylmethyl)-1-thio-α-D-mannopyranoside (9)

NaH (1.04 g, 25.9 mmol, 60% oil dispersion) was washed with *n*-hexane (3 × 30 mL) prior to use. The washed NaH was added portionwise to a solution of **8** (4.20 g, 5.76 mmol) in dry DMF (40 mL) at 0 °C under an atmosphere of argon. After 15 min, BnBr (2.74 mL, 23.05 mmol) was added dropwise at 0 °C and the solution was stirred for 2 h at rt (TLC, toluene/EtOAc 5:1). To quench residual NaH, MeOH (40 mL) was carefully added, followed by H_2O (40 mL). The product was extracted into EtOAc (1 × 200 mL), the organic phase was washed with sat. NaCl (2 × 200 mL), dried over $MgSO_4$, and concentrated. Purification on a silica gel flash column (toluene/EtOAc, 100:0 → 88:12) gave **9** (5.53 g, 96%); R_f 0.64 (toluene/EtOAc 9:1); $[\alpha]_D$ +32 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (1H, ArH), 7.84–7.78 (m, 2H, ArH), 7.69–7.67 (m, 1H, ArH), 7.55–7.52 (m, 3H, ArH), 7.48–7.26 (m, 20H, ArH), 5.60 (s, 1H, C_6H_5CH), 5.51 (d ≈ s, 1H, H-1), 5.14 (d, 1H, $J_{gem} = 10.0$ Hz, PhCH_2), 5.05 (d, 1H, $J_{gem} = 13.0$ Hz, NAPCH_2), 4.97 (d, 1H, $J_{gem} = 10.5$ Hz, PhCH_2), 4.89 (d, 1H, $J_{gem} = 11.0$ Hz, PhCH_2), 4.85–4.74 (m, 3H, PhCH_2, NAPCH_2), 4.69 (d, 1H, $J_{gem} = 11.0$ Hz, PhCH_2), 4.56 (d, 1H, $J_{1',2'} = 8.0$ Hz, H-1′), 4.46 (d, 1H, $J_{2,3} = 3.0$ Hz, H-2), 4.29–4.20 (m, 3H, H-4, H-5, H-6a), 3.99 (dd, 1H, $J_{3,4} = 9.5$ Hz, H-3), 3.93 (dd ≈ d, 1H, $J = 10.5$ Hz, H-6a′), 3.86 (dd, 1H, $J_{5',6b'} = 5.0$ Hz, $J_{6a',6b'} = 11.5$ Hz, H-6b′), 3.81 (dd ≈ t, 1H, $J_{5,6b} = J_{6a,6b} = 9.5$ Hz, H-6b), 3.70 (dd ≈ t, 1H, $J_{2',3'} = J_{3',4'} = 9.3$ Hz, H-3′), 3.73–3.60 (m, 2H, H-2′, H-4′), 3.39 (m, 1H, H-5′), 2.64–2.61 (m, 2H, SCH_2CH$_3$), 1.27 (t, 3H, SCH$_2$CH_3), 0.88 (s, 9H, (CH_3)$_3$C(CH$_3$)$_2$Si), 0.06, 0.05 (2 s, 6H, (CH$_3$)$_3$C(CH_3)$_2$Si); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.9, 138.7, 138.5, 137.9, 135.9, 133.5, 133.2 (ArC), 129.2–125.5 (ArCH), 101.9 (C-1′), 101.8 (C_6H_5CH), 85.1 (C-3′), 83.0 (C-1), 82.4 (C-2′), 78.8 (C-4), 77.8 (C-4′), 76.8 (C-5′), 76.3 (C-2), 76.0, 75.4, 75.3 (3 × PhCH$_2$), 74.1 (C-3), 70.9 (NAPCH$_2$), 69.0 (C-6), 64.8 (C-5), 62.8 (C-6′), 26.2 ((CH_3)$_3$C(CH$_3$)$_2$Si), 25.9 (SCH_2CH$_3$), 18.5 ((CH$_3$)$_3$C(CH$_3$)$_2$Si), 15.2 (SCH$_2$CH_3), −4.8 ((CH$_3$)$_3$C(CH_3)$_2$Si), −5.0 ((CH$_3$)$_3$C(CH_3)$_2$Si); HRMS (ESI): $[M+Na]^+$ Calcd for $C_{59}H_{70}O_{10}NaSSi$, 1021.4357; found, 1021.4351. Anal. Calcd for $C_{59}H_{70}O_{10}SSi$: C, 70.91; H, 7.06; S, 3.21. Found: C, 70.48; H, 7.17; S, 3.30.

1.7. Ethyl (2,3,4-tri-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosyl)-(1 → 2)-3-*O*-(2-naphthalenylmethyl)-4-*O*-benzyl-1-thio-α-D-mannopyranoside (10)

A solution of **9** (80 mg, 0.08 mmol) in dry CH_2Cl_2 (8 mL) containing crushed 4 Å molecular sieves was cooled to −78 °C and Et_3SiH (38 μL, 0.24 mmol) and $PhBCl_2$ (40 μL, 0.30 mmol) were added. The reaction mixture was stirred at −78 °C for 2 h (TLC, toluene/EtOAc, 10:1). Then Et_3N (312 μL, 2.24 mmol) was added and the mixture was allowed to attain rt. The molecular sieves were filtered off, the filtrate was concentrated, and the oily residue was purified by silica gel flash chromatography (toluene/EtOAc, 100:0 → 79:21) to give **10** (74 mg, 93%); R_f 0.44 (toluene/EtOAc 9:1); $[\alpha]_D$ +35 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87

(m, 2H, ArH), 7.82 (m, 1H, ArH), 7.75 (m, 1H, ArH), 7.58 (dd, 1H, ArH), 7.50 (m, 2H, ArH), 7.44 (m, 2H, ArH), 7.38–7.30 (m, 18H, ArH), 5.53 (s, 1H, H-1), 5.16 (d, 1H, J_{gem} = 11.5 Hz, PhCH_2), 5.10 (d, 1H, J_{gem} = 11.5 Hz, NAPCH_2), 5.04 (d, 1H, J_{gem} = 11.0 Hz, PhCH_2), 4.98 (d, 1H, J_{gem} = 11.0 Hz, PhCH_2), 4.92 (d, 1H, J_{gem} = 10.5 Hz, PhCH_2), 4.85 (d, 1H, J_{gem} = 11.0 Hz, PhCH_2), 4.78 (d, 1H, J_{gem} = 10.5 Hz, PhCH_2), 4.71–4.68 (m, 2H, 2 PhCH_2), 4.64 (d, 1H, J_{gem} = 10.5 Hz, PhCH_2), 4.60 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1′), 4.49 (dd ≈ m, 1H, H-2), 4.04–3.96 (m, 4H, H-3, H-4, H5, H-6a′), 3.84 (dd, 1H, $J_{5',6b'}$ = 5.5 Hz, $J_{6a',6b'}$ = 11.5 Hz, H-6b′), 3.81–3.72 (m, 3H, H-3′, H-6a, H-6b), 3.68 (dd ≈ t, 1H, $J_{2',3'}$ = 8.0 Hz, H-2′), 3.60 (dd ≈ t, 1H, $J_{3',4'} = J_{4',5'}$ = 8.0 Hz, H-4′), 3.47–3.43 (m, 1H, H-5′), 2.65–2.62 (m, 2H, SCH_2CH$_3$), 1.30 (t, 3H, SCH$_2$CH_3), 0.89 (s, 9H, (CH_3)$_3$C(CH$_3$)$_2$Si), 0.07, 0.04 (2 s, 6H, (CH$_3$)$_3$C(CH_3)$_2$Si); ^{13}C NMR (125 MHz, CDCl$_3$): δ 138.9, 138.7, 138.5, 135.7, 133.6, 133.4 (ArC), 128.7–126.0 (ArCH), 102.1 (C-1′), 85.2 (C-3′), 82.1 (C-1), 82.0 (C-2′), 78.3 (C-3), 77.8 (C-4′), 76.9 (C-5′), 75.9, 75.4, 75.2, 75.1, 74.9, 74.8 (C-2, C-4, 4 × PhCH$_2$), 72.3 (C-5), 70.5 (NAPCH$_2$), 63.1 (C-6′), 62.8 (C-6), 26.2 ((CH_3)$_3$C(CH$_3$)$_2$Si), 25.8 (SCH$_2$CH$_3$), 18.5 ((CH$_3$)$_3$C(CH$_3$)$_2$Si), 15.1 (SCH$_2$CH$_3$), −4.9 ((CH$_3$)$_3$C(CH$_3$)$_2$Si), −5.0 ((CH$_3$)$_3$C(CH$_3$)$_2$Si); HRMS (ESI): [M+Na]$^+$ Calcd for $C_{59}H_{72}O_{10}NaSSi$, 1023.4513; found, 1023.4520; Anal. Calcd for $C_{59}H_{72}O_{10}SSi$: C, 70.77; H, 7.25; S, 3.20. Found: C, 70.62; H, 7.33; S, 3.40.

1.8. Ethyl (2,3,4-tri-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosyl)-(1 → 2)-6-*O*-acetyl-4-*O*-benzyl-3-*O*-(2-naphthalenylmethyl)-1-thio-α-D-mannopyranoside (11)

Ac_2O (0.88 mL, 9.27 mmol) was added at 20 °C to a solution of **10** (1.16 g, 1.16 mmol) in dry pyridine (20 mL), and the mixture was stirred for 3 h (TLC, toluene–EtOAc, 9:1). The reaction mixture was concentrated, and the residue re-dissolved and co-evaporated with toluene (3 × 50 mL). Purification by silica gel flash column chromatography (toluene–EtOAc, 100:0 → 85:15) gave **11** (1.19 g, 96%); R_f 0.53 (toluene/EtOAc 9:1); $[\alpha]_D$ +33 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (m, 2H, ArH), 7.79 (d, 1H, ArH), 7.73 (m, 1H, ArH), 7.59 (d, 1H, ArH), 7.49–7.45 (m, 4H, ArH), 7.38–7.27 (m, 18H, ArH), 5.51 (s, 1H, H-1), 5.20 (d, 1H, J_{gem} = 10.5 Hz, PhCH_2), 5.11 (d, 1H, J_{gem} = 12.0 Hz, NAPCH_2), 5.03 (d, 1H, J_{gem} = 11.0 Hz, PhCH_2), 4.99 (d, 1H, J_{gem} = 11.0 Hz, PhCH_2), 4.90 (d, 1H, J_{gem} = 11.5 Hz, PhCH_2), 4.83 (d, 1H, J_{gem} = 10.5 Hz, PhCH_2), 4.70–4.66 (m, 3H, NAPCH_2, PhCH_2), 4.57 (m, 2H, H-1′, PhCH_2), 4.46 (m, 1H, H-2), 4.38 (dd, 1H, $J_{5,6a}$ = 4.5 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6a), 4.29 (dd ≈ d, 1H, H-6b), 4.22 (m, 1H, H-5), 4.04–3.95 (m, 3H, H-3, H-4, H-6a′), 3.82 (dd, 1H, $J_{5',6b'}$ = 6.5 Hz, $J_{6a',6b'}$ = 11.5 Hz, H-6b′), 3.73–3.67 (m, 2H, H-2′, H-3′), 3.57 (dd ≈ t, 1H, H-4′), 3.43 (m, 1H, H-5′), 2.68–2.61 (m, 2H, SCH_2CH$_3$), 1.73 (s, 3H, COCH_3), 1.29 (t, 3H, SCH$_2$CH_3), 0.88 (s, 9H, (CH_3)$_3$C(CH$_3$)$_2$Si), 0.05, 0.02 (2 s, 6H, (CH$_3$)$_3$C(CH_3)$_2$Si); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9 (CO), 138.9, 138.5, 138.4, 135.5, 133.5, 133.3 (ArC), 129.2-126.0 (ArCH), 102.5 (C-1′), 85.2 (C-3′), 82.4 (C-1), 82.1 (C-2′), 78.3 (C-3), 77.8 (C-4′), 76.9 (C-5′), 75.9 (PhCH$_2$), 75.4, 75.3, 75.3, 75.2 (C-2, 3 × PhCH$_2$), 74.3 (C-4), 70.5 (NAPCH$_2$), 70.1 (C-5), 63.7 (C-6), 63.2 (C-6′), 26.2 ((CH_3)$_3$C(CH$_3$)$_2$Si), 25.9 (SCH$_2$CH$_3$), 20.7 (COCH$_3$), 18.5 ((CH$_3$)$_3$C(CH$_3$)$_2$Si), 15.2 (SCH$_2$CH$_3$), −4.9 ((CH$_3$)$_3$C(CH$_3$)$_2$Si), −5.0 ((CH$_3$)$_3$C(CH$_3$)$_2$Si); HRMS (ESI): [M+Na]$^+$ *m/z* Calcd for $C_{61}H_{74}O_{11}NaSSi$, 1065.4619; found, 1065.4624; Anal. Calcd for $C_{61}H_{74}O_{11}SSi$: C, 70.22; H, 7.15; S, 3.07. Found: C, 70.18; H, 7.20; S, 3.38.

1.9. Ethyl (2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl)-(1 → 2)-6-*O*-acetyl-4-*O*-benzyl-3-*O*-(2-naphthalenylmethyl)-1-thio-α-D-mannopyranoside (12)

TBAF trihydrate (0.52 g, 1.65 mmol) was added to a solution of **11** (1.28 g, 1.23 mmol) in dry THF (50 mL) and the mixture was stirred at 20 °C (TLC, toluene/EtOAc, 10:1). After 3 h, the reaction mixture was concentrated and purified by silica gel flash column chromatography (toluene–EtOAc, 100:0 → 76:24) to give **12** (1.03 g, 90%); R_f 0.22 (toluene/EtOAc 6:1); $[\alpha]_D$ +38 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (m, 3H, ArH), 7.76 (m, 1H, ArH), 7.54 (dd, 1H, ArH), 7.46 (m, 2H, ArH), 7.40 (m, 2H, ArH), 7.33-7.25 (m, 18H, ArH), 5.43 (d ≈ s, 1H, H-1), 5.15 (d, 1H, J_{gem} = 10 Hz, PhCH_2), 5.00–4.95 (m, 3H, PhCH_2, NAPCH_2), 4.86 (d, 1H, J_{gem} = 10.8 Hz, PhCH_2), 4.82 (d, 1H, J_{gem} = 10.8 Hz, PhCH_2), 4.75 (d, 1H, J_{gem} = 11 Hz, NAPCH_2), 4.63 (m, 2H, PhCH_2), 4.58 (d, 1H, J_{gem} = 11 Hz, PhCH_2), 4.52 (d, 1H, $J_{1',2'}$ = 7.2 Hz, H-1′), 4.36 (dd, 1H, $J_{5,6a}$ = 4.2 Hz, $J_{H\text{-}6a,H\text{-}6b}$ = 12 Hz, H-6a), 4.30–4.27 (m, 2H, H-2, H-6b), 4.24–4.21 (m, 1H, H-5), 4.00 (dd ≈ t, 1H, H-4), 3.96 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.6 Hz, H-3), 3.84 (m, 1H, H-6a′), 3.72 (m, 1H, H-6b′), 3.68–3.60 (m, 3H, H-2′, H-3′, H-4′), 3.38 (m, 1H, H-5′), 2.65–2.55 (m, 2H, SCH_2CH$_3$), 1.76 (m, 1H, OH), 1.71 (s, 3H, COCH_3), 1.26 (t, 3H, SCH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6 (CO), 138.6, 138.2, 138.1, 137.9, 135.1, 133.3, 133.1 (ArC), 129.0–125.9 (ArCH), 102.8 (C-1′), 84.5 (C-3′), 82.5 (C-1), 81.8 (C-2′), 78.8 (C-3), 77.2 (C-4′), 76.6 (C-2), 75.7 (PhCH$_2$), 75.4 (C-5′), 75.2, 75.1, 75.0 (3 × PhCH$_2$), 74.3 (C-4), 71.3 (NAPCH$_2$), 70.0 (C-5), 63.3 (C-6), 62.2 (C-6′), 25.8 (SCH$_2$CH$_3$), 20.5 (COCH$_3$), 15.0 (SCH$_2$CH$_3$); HRMS (ESI): [M+Na]$^+$ Calcd for $C_{55}H_{60}O_{11}NaS$, 951.3754; found, 951.3758. Anal. Calcd for $C_{55}H_{60}O_{11}S$: C, 71.10; H, 6.51; S, 3.45. Found: C, 70.76; H, 6.42; S, 3.43.

1.10. Ethyl (2,3,4-tri-*O*-benzyl-β-D-glucopyranosyluronic acid)-(1 → 2)-6-*O*-acetyl-4-*O*-benzyl-3-*O*-(2-methylnaphthalenyl)-1-thio-α-D-mannopyranoside (13)

TEMPO (83 mg, 0.53 mmol) and BAIB (3.43 g, 10.63 mmol) were added to a vigorously stirred mixture of **12** (1.0 g, 1.06 mmol) in CH_2Cl_2/H_2O (2:1, 60 mL) and the two-phase reaction mixture was stirred at 20 °C for 5 h. The progress of the reaction was followed by TLC (toluene/EtOAc/AcOH, 16:3:1). The reaction was quenched by the addition of an aqueous solution of $Na_2S_2O_3$ (10% aq). The mixture was extracted with EtOAc and the organic layer was dried over $MgSO_4$ and concentrated. Purification by silica gel flash column chromatography (toluene → toluene–EtOAc, 95:5 → 90:10 → 85:15 → toluene–EtOAc–AcOH, 16:3:1) gave **13** (0.97 g, 97%); R_f 0.39 (toluene–EtOAc–AcOH, 16:3:1); $[\alpha]_D$ +23 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79–7.73 (m, 4H, ArH), 7.49–7.44 (m, 3H, ArH), 7.35–7.24 (m, 20H, ArH), 5.36 (br s, 1H, H-1), 5.01 (d, 1H, J_{gem} = 10 Hz, PhCH_2), 4.94 (d, 1H, J_{gem} = 10.5 Hz, PhCH_2), 4.87 (m, 2H, PhCH_2, NAPCH_2), 4.76 (d, 1H, J_{gem} = 11 Hz, PhCH_2), 4.71 (d, 1H, J_{gem} = 11.5 Hz, PhCH_2), 4.67–4.63 (m, 3H, H-1′, PhCH_2), 4.60 (d, 1H, J_{gem} = 11 Hz, NAPCH_2), 4.56 (d, 1H, J_{gem} = 11.5 Hz, PhCH_2), 4.35–4.26 (m, 3H, H-2, H-6a, H-6b), 4.22–4.19 (m, 1H, H-5), 4.07 (d, 1H, $J_{4',5'}$ = 7.5 Hz, H-5′), 4.01 (dd ≈ t, 1H, H-4′), 3.95 (m, 2H, H-3, H-4), 3.69 (dd ≈ t, 1H, H-3′), 3.63 (dd ≈ t, 1H, H-2′), 2.63–2.52 (m, 2H, SCH_2CH$_3$), 1.75 (s, 3H, COCH_3), 1.25 (t, 3H, SCH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6 (CO), 170.0 (COOH), 138.2, 138.1, 137.8, 137.3, 134.6, 133.3, 133.1 (ArC), 128.8–126.1 (ArCH), 103.0 (C-1′), 82.9 (C-3′), 82.3 (C-1), 80.3 (C-2′), 79.4 (C-4′), 79.0 (C-3), 77.3 (C-2), 75.3, 75.2, 75.1 (3 × PhCH$_2$), 74.6 (C-5′), 74.3 (PhCH$_2$), 74.1 (C-4), 71.8 (NAPCH$_2$), 70.0 (C-5), 63.2 (C-6), 25.7 (SCH$_2$CH$_3$), 20.5 (COCH$_3$), 14.9 (SCH$_2$-CH$_3$); HRMS (ESI): [M+Na]$^+$ Calcd for $C_{55}H_{58}O_{12}NaS$, 965.3547; found, 965.3520. Anal. Calcd for $C_{55}H_{58}O_{12}S$: C, 70.04; H, 6.20; S, 3.40. Found: C, 69.49; H, 6.03; S, 3.56.

1.11. Ethyl [benzyl (2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl)uronate]-(1 → 2)-6-*O*-acetyl-4-*O*-benzyl-3-*O*-(2-methylnaphthalenyl)-1-thio-α-D-mannopyranoside (14)

Cesium carbonate (95 mg, 1.54 mmol) was added to a solution of **13** (0.97 g, 1.03 mmol) in dry DMF (35 mL) at 20 °C. After

15 min, BnBr (243 μL, 2.05 mmol) was added dropwise at 0 °C. The temperature was then allowed to rise to 20 °C over 2 h (TLC, toluene–EtOAc–AcOH, 16:3:1). After complete consumption of the starting material, water (100 mL) was added, and the resulting mixture was extracted once with EtOAc (200 mL), the layers were separated, and the organic layer was washed with brine (2 × 100 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by silica gel flash column chromatography (toluene–EtOAc, 100:0 → 87:13) gave **14** (853 mg, 81%). R_f 0.74 (toluene/EtOAc 5:1); $[\alpha]_D$ +20 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81–7.76 (m, 4H, ArH), 7.51–7.45 (m, 3H, ArH), 7.39 (m, 2H, ArH), 7.33–7.12 (m, 23H, ArH), 5.42 (d ≈ s, 1H, H-1), 5.14 (d, 1H, J_{gem} = 10.0 Hz, PhC*H*$_2$), 5.08 (d ≈ s, 2H, PhC*H*$_2$OC(=O)), 4.97–4.93 (m, 2H, PhC*H*$_2$), 4.89–4.87 (d, 1H, J_{gem} = 11.0 Hz, NAPC*H*$_2$), 4.80–4.76 (m, 2H, PhC*H*$_2$), 4.63–4.61 (d, 1H, J_{gem} = 10.0 Hz, PhC*H*$_2$), 4.57–4.51 (m, 4H, H-1′, PhC*H*$_2$, NAPC*H*$_2$), 4.37–4.34 (m, 2H, $J_{5,6a}$ = 4.5 Hz, H-2, H-6a), 4.28–4.25 (dd, 1H, $J_{5,6b}$ = 2.0 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6b), 4.20 (m, 1H, H-5), 4.00–3.94 (m, 3H, H-4, H-4′, H-5′), 3.92 (dd, 1H, $J_{2,3}$ = 3.3 Hz, $J_{3,4}$ = 9.3 Hz, H-3), 3.72 (m, 1H, H-2′), 3.68 (m, 1H, H-3′), 2.62–2.57 (m, 2H, SC*H*$_2$CH$_3$), 1.68 (s, 3H, COC*H*$_3$), 1.26 (t, 3H, SCH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6 (C=O), 167.9 (*C*OOBn), 138.5, 138.3, 138.0, 137.9, 135.1, 134.9, 133.4, 133.2 (Ar*C*), 129.1–125.9 (Ar*CH*), 103.0 (C-1′), 84.0 (C-3′), 82.3 (C-1), 81.3 (C-2′), 78.9 (C-4′), 78.3 (C-3), 76.2 (C-2), 75.8, 75.2, 75.1 (3 × PhC*H*$_2$), 74.9 (C-5′), 74.0 (C-4), 70.8 (NAPCH$_2$), 69.9 (C-5), 67.4 (PhCH$_2$), 63.3 (C-6), 25.8 (SCH$_2$CH$_3$), 20.5 (COCH$_3$), 15.0 (SCH$_2$*C*H$_3$); HRMS (ESI): $[M+Na]^+$ Calcd for $C_{62}H_{64}O_{12}S$, 1055.4016; found, 1055.4011. Anal. Calcd for $C_{62}H_{64}O_{12}S$: C, 72.07; H, 6.24; S, 3.10. Found: C, 71.58; H, 6.22; S, 3.36.

1.12. [Benzyl (2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl) uronate]-(1 → 2)-1,6-anhydro-4-*O*-benzyl-3-*O*-(2-naphthalenylmethyl)-β-D-mannopyranose (18β) and [Benzyl (2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)uronate]-(1 → 2)-1,6-anhydro-4-*O*-benzyl-3-*O*-(2-naphthalenylmethyl)-β-D-mannopyranose (18α)

Method A—TMSOTf (4 μL, 0.02 mmol) was added at 0 °C to a solution of methyl (2,3,4-tri-*O*-acetyl-D-glucopyranosyl)uronate trichloroacetimidate (192 mg, 0.40 mmol) and **17** (95 mg, 0.24 mmol) in dry CH_2Cl_2 (7 mL) containing 4 Å acid washed molecular sieves. The reaction was stirred a 0 °C for 1 h and then quenched by the addition of Et_3N (0.5 mL). The solvents were removed under reduced pressure and the residue was purified by silica gel flash chromatography (cyclohexane/EtOAc 65:35) to give methyl (2,3,4-tri-*O*-acetyl-β-D-glucopyranosyl)uronate-(1 → 2)-1,6-anhydro-4-*O*-benzyl-3-*O*-(2-naphthalenylmethyl)-β-D-mannopyranose (130 mg, 0.18 mmol, 76%); R_f 0.26 (cyclohexane/EtOAc 3:2); $[\alpha]_D$ −54 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88–7.00 (m, 12H, ArH), 5.45 (s, 1H, H-1), 5.28 (m, 2H, H-3′, H-4′), 5.10 (t, 1H, $J_{2',3'}$ = 8.4 Hz, H-2′), 4.98 (d, 1H, J_{gem} = 12.2 Hz, PhC*H*$_2$), 4.86 (d, 1H, $J_{1',2'}$ = 8.4 Hz, H-1′), 4.66 (d, 1H, J_{gem} = 12.2 Hz, PhC*H*$_2$), 4.43 (d, 1H, $J_{5,6b}$ = 5.4 Hz, H-5), 4.32 (d, 1H, J_{gem} = 12.4 Hz, PhC*H*$_2$), 4.26 (d, 1H, $J_{6a,6b}$ = 7.2 Hz, H-6a), 4.16 (d, 1H, J_{gem} = 12.2 Hz, PhC*H*$_2$), 4.06 (d, 1H, $J_{4',5'}$ = 9.5 Hz, H-5′), 4.02–3.98 (m, 1H, H-3), 3.87 (dd, 1H, $J_{1,2}$ = 1.2 Hz, $J_{2,3}$ = 5.1 Hz, H-2), 3.73 (s, 3H, OC*H*$_3$), 3.70-3.67 (m, 1H, H-6b), 3.33 (s, 1H, H-4), 2.04, 2.04, 2.02 (3s, 9H, 3 × COC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 169.5, 169.3 (3 × *C*OCH$_3$), 167.1 (*C*OOCH$_3$), 137.6, 136.0, 133.4, 133.2 (Ar*C*), 128.5-126.1 (Ar*CH*), 100.9 (C-1′), 100.1 (C-1), 78.0 (C-4), 76.1 (C-2 and C-3), 74.6 (PhCH$_2$), 74.5 (C-5), 72.6 (C-5′), 72.4 (C-3′ or C-4′), 71.6 (C-2′), 71.3 (PhCH$_2$), 69.5 (C-3′ or C-4′), 65.1 (C-6), 52.9 (OCH$_3$), 20.7, 20.7, 20.6 (3 × COCH$_3$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{37}H_{40}O_{14}Na$, 731.2316; found, 731.2349.

A solution of the compound above (109 mg, 0.15 mmol) in dry methanol (4 mL) was treated with MeONa (6 μL, 1 M in methanol). After stirring at rt for 1 h, H_2O (0.6 mL), and NaOH (0.1 mL, 2 M) were added. After additional 30 min, the mixture was neutralised with Dowex 50 (H^+) ion exchange resin, filtered, and concentrated. To a solution of the crude residue in dry DMSO (3 mL), BnBr (0.18 mL, 1.5 mmol, 2.5 equiv/OH) and NaH (60 mg, 60%, 2.5 equiv/OH) were added at 15 °C (water bath temperature). The water bath was changed to 20 °C after the reaction mixture had turned solid (ca. 15 min) and left for 25 min, when the reaction was quenched by the addition of EtOAc (7 mL) and water (3 mL). The organic layer was separated, washed with acetic acid (5%, aq) and brine, dried (Na_2SO_4), filtered, concentrated, and purified by silica gel flash column chromatography (cyclohexane/EtOAc 85:15) to give pure **18β** (49 mg, 34%); R_f 0.13 (cyclohexane/EtOAc 85:15); $[\alpha]_D$ +28.0 (*c*1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85–6.94 (m, 32H, ArH), 5.49 (s, 1H, H-1), 5.16 (s, 2H, *CH*$_2$Ph), 5.08 (d, 1H, J_{gem} = 10.7 Hz, PhC*H*$_2$), 4.98 (d, 1H, J_{gem} = 12.4 Hz, PhC*H*$_2$), 4.91 (d, 1H, J_{gem} = 11.0 Hz, PhC*H*$_2$), 4.79-4.67 (m, 4H, PhC*H*$_2$), 4.64 (d, 1H, $J_{1',2'}$ = 7.6 Hz, H-1′), 4.50 (d, 1H, J_{gem} = 11.0 Hz, PhC*H*$_2$), 4.45 (d, 1H, $J_{5,6b}$ = 5.3 Hz, H-5), 4.33 (d, 1H, $J_{6a,6b}$ = 6.5 Hz, H-6a), 4.28 (d, 1H, J_{gem} = 12.4 Hz, PhC*H*$_2$), 4.07 (d, 1H, J_{gem} = 12.4 - Hz, PhC*H*$_2$), 4.01–3.98 (m, 2H, H-3, H-5′), 3.90–3.83 (m, 2H, H-2, H-4′), 3.74 (t, 1H, H-6b), 3.68 (t, 1H, $J_{2',3'} = J_{3',4'}$ = 9.0 Hz, H-3′), 3.61–3.56 (m, 1H, H-2′), 3.31 (s, 1H, H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6 (*C*OOBn), 138.5, 138.3, 138.0, 137.6, 136.3, 135.1, 133.4, 133.2 (Ar*C*), 128.7-126.1 (Ar*CH*), 105.0 (C-1′), 100.5 (C-1), 83.9 (C-3′), 81.9 (C-2′), 79.5 (C-4′), 78.1 (C-4), 77.0 (C-2), 76.5 (C-3 or C-5′), 75.9, 75.4, 75.2 (3 × PhC*H*$_2$), 74.7 (C-3 or C-5′), 74.6 (PhC*H*$_2$), 74.6 (C-5), 71.3, 67.5 (2 × PhC*H*$_2$), 65.1 (C-6); HRMS (ESI): $[M+Na]^+$ calcd for $C_{58}H_{56}O_{11}Na$, 951.3720; found, 951.3704.

Method B (CH$_2$Cl$_2$, −40 °C)—A solution of **15** (131 mg, 0.19 mmol) and **17** (49 mg, 0.12 mmol) in dry CH_2Cl_2 (3 mL) containing 4 Å molecular sieves was cooled to −40 °C under a N_2 atmosphere before the addition of a $BF_3{\cdot}Et_2O$ solution in dry CH_2Cl_2 (0.02 M, 1.0 mL, 0.16 equiv). After 2 h the reaction was quenched by the addition of Et_3N (0.4 mL). The mixture was allowed to attain rt, then filtered through a Celite pad, and concentrated. Purification of the residue by silica gel flash chromatography (cyclohexane/EtOAc 85:15 → 8:2) gave **18α/18β** (63.8 mg, 0.069 mmol, 55%) as a 1:1.7 mixture.

Method C (CH$_2$Cl$_2$, −78 °C)—As Method B but the glycosylation was performed at −78 °C to give **18α/18β** in the same yield but as a 1:2.2 mixture.

Method D (CH$_2$Cl$_2$/(CH$_3$)$_3$CCN, −78 °C)—As Method C but the glycosylation was performed in a dry solvent mixture of CH_2Cl_2 and $(CH_3)_3CCN$ (3:1, 24 mL) to give **18α/18β** in the same yield but as a 1:9 mixture.

^{1}H NMR-**18α** (500 MHz, $CDCl_3$): δ 5.63 (s, 1H, H-1), 5.49 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1′); ^{13}C NMR-**18α** (125 MHz, $CDCl_3$): δ 169.6 (*C*OOBn), 138.6, 138.4, 138.3, 137.7, 136.4, 135.4, 133.4, 133.1 (Ar*C*), 128.7-126.1 (Ar*CH*), 101.2 (C-1), 100.0 (C-1′), 81.1 (C-3′), 79.9 (C-2′), 79.7 (C-4′), 78.5 (C-2), 78.5 (C-4), 75.6 (PhCH$_2$), 74.9 (C-5′), 74.9 (PhCH$_2$), 74.8 (C-3), 74.0, 73.6, 71.4 (3 × PhCH$_2$), 70.9 (C-5), 67.2 (PhCH$_2$), 65.1 (C-6).

1.13. 1,6-Anhydro-4-*O*-benzyl-3-*O*-(2-naphthalenylmethyl)-2-*O*-[*N*-[benzyl (2,3,4-tri-*O*-benzyl-D-glucopyranosyl)uronate]-ethanimidyl]-β-D-mannopyranose (19)

A solution of **15** (102 mg, 0.26 mmol) and **17** (273 mg, 0.39 mmol) in a mixture of dry CH_2Cl_2 CH_3CN (3:1, 4 mL) containing 4 Å molecular sieves was cooled under N_2 to −78 °C before adding a $BF_3{\cdot}Et_2O$ solution in dry CH_2Cl_2 (0.02 M, 2.2 mL, 0.16 equiv). After 1.5 h the reaction was quenched by addition of Et_3N (0.4 mL). The mixture was allowed to attain room temperature, filtered through Celite, and concentrated. Purification by silica gel flash chromatography (cyclohexane/EtOAc 7:3) gave **19**

(131 mg, 0.135 mmol, 52%) as a 9:1 α:β mixture. R_f 0.24 (cyclohexane/EtOAc 7:3); ^{1}H NMR **19α** (500 MHz, $CDCl_3$): δ 7.83–6.94 (m, 32H, ArH), 5.63 (s, 1H, H-1), 5.11 (d, 1H, $J_{1',2'}$ = 4.2 Hz, H-1′), 5.03 (m, 3H, H-2, PhCH_2), 4.85–4.68 (m, 6H, H-5′, PhCH_2), 4.62 (d, 1H, J_{gem} = 11.8 Hz, PhCH_2), 4.55-4.42 (m, 4H, H-5, PhCH_2), 4.39–4.37 (m, 1H, H-3), 4.24 (d, 1H, $J_{6a,\ 6b}$ = 7.1 Hz, H-6a), 4.11 (d, 1H, J_{gem} = 12.6 Hz, PhCH_2), 4.02 (t, 1H, $J_{2',3'} = J_{3',4'}$ = 9.2 Hz, H-3′), 3.84 (t, 1H, $J_{4',5'}$ = 9.2 Hz, H-4′), 3.77–3.70 (m, 2H, H-2′, H6b), 3.35 (s, 1H, H-4), 1.90 (s, 3H, CH_3C); ^{13}C NMR **19α** (125 MHz, $CDCl_3$): δ 170.1(*C*OOBn), 162.9 (C=N), 138.7, 138.3, 138.2, 137.6, 135.5, 135.0, 133.4, 133.2 (Ar*C*), 128.6-126.2 (Ar*CH*), 99.9 (C-1), 84.5 (C-1′), 82.2 (C-3′), 80.6 (C-4′), 80.5 (C-2′), 76.3 (C-4), 75.8 (PhCH_2), 75.5 (C-5), 75.0, 74.4, 74.3 (3 × PhCH_2), 73.9 (C-3), 72.3 (C-5′), 71.2 (PhCH_2), 70.5 (C-2), 67.4 (PhCH_2), 65.1 (C-6), 16.0 (CH_3C); HRMS (ESI): $[M+Na]^+$ calcd for $C_{60}H_{59}NO_{11}Na$, 992.3986; found, 992.4008.

1.14. Ethyl 4-*O*-benzyl-3-*O*-(2-naphthalenylmethyl)-1-thio-α-D-mannopyranoside (20)

Compound **2** (1.20 g, 2.64 mmol) was dissolved in dry THF (20 mL) under N_2 and the solution was cooled to 0 °C before the dropwise addition of BH_3 in THF (1 M, 26 mL, 26 mmol) and, after an additional 5 min, 1 M Bu_2BOTf in CH_2Cl_2 (2.64 mL, 2.64 mmol). After 2 h, Et_3N was carefully added followed by dropwise addition of MeOH until gas evolution ceased. The solution was co-evaporated three times with MeOH and the residue was purified by silica gel flash chromatography (cyclohexane/EtOAc 7:3 → 1:1) to afford **20** (1.08 g, 2.38 mmol, 90%); R_f 0.42 (toluene/EtOAc 7:3); $[\alpha]_D$ +116 (*c* 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82–7.22 (m, 12H, ArH), 5.34 (br s, 1H, H-1), 4.89 (d, 1H, J_{gem} = 11.0 Hz, PhCH_2), 4.85–4.77 (m, 2H, CH_2Ph), 4.69 (d, 1H, J_{gem} = 11.0 Hz, PhCH_2), 4.13 (br s, 1H, H-2), 4.03 (dt, 1H, $J_{4,5}$ = 9.3 Hz, $J_{5,6a} = J_{5,6b}$ = 2.8 Hz H-5), 3.97 (t, 1H, $J_{3,4}$ = 9.3 Hz, H-4), 3.90 (dd, 1H, $J_{2,3}$ = 3.1 Hz, H-3), 3.84–3.80 (m, 2H, H-6a, H6b), 3.32–3.25 (m, 1H, OH-2), 2.63–2.46 (m, 3H, SCH_2CH$_3$, OH-6), 1.21 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4, 135.2, 133.4, 133.2 (Ar*C*), 128.5–125.9 (Ar*CH*), 83.7 (C-1), 80.4 (C-3), 75.3 (PhCH_2), 74.3 (C-4), 72.3, 72.2 (PhCH_2, C-5), 70.2 (C-2), 62.0 (C-6), 25.1 (SCH_2CH_3), 14.9 (SCH_2CH_3); HRMS (ESI): $[M+Na]^+$ Calcd for $C_{26}H_{306}O_5$ SNa, 477.1712; found, 477.1700.

1.15. Ethyl 6-*O*-acetyl-4-*O*-benzyl-3-*O*-(2-naphthalenylmethyl)-1-thio-α-D-mannopyranoside (21)

Compound **20** (131 mg, 0.29 mmol) was dissolved in dry CH_2Cl_2 (4 mL) under N_2 and the solution was cooled to −78 °C before adding collidine (76 μL, 0.58 mmol) and AcCl (20.5 μL, 0.29 mmol). After 1 h, the reaction was quenched by the addition of H_2O (5 mL). The mixture was allowed to attain room temperature and the organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by silica gel flash column chromatography (cyclohexane/EtOAc 8:2) to give **21** (135 mg, 2.38 mmol, 94%) as a syrup; R_f 0.61 (cyclohexane/EtOAc 8:2); $[\alpha]_D$ +116 (*c*1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85–7.25 (m, 12H, ArH), 5.36 (br s, 1H, H-1), 4.89 (d, 1H, J_{gem} = 10.9 Hz, PhCH_2), 4.86–4.80 (m, 2H, PhCH_2), 4.60 (d, 1H, J_{gem} = 10.9 Hz, PhCH_2), 4.34–4.28 (m, 2H, H-6a, H-6b), 4.23 (ddd, 1H, $J_{4,5}$ = 9.4 Hz, $J_{5,6a}$ = 4.7 Hz, $J_{5,6b}$ = 2.5 Hz, H-5), 4.14 (br s, 1H, H-2), 3.92 (dd, 1H, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.4 Hz, H-3), 3.82 (t, 1H, H-4), 2.68–2.52 (m, 3H, SCH_2CH$_3$, OH), 2.03 (s, 3H, COCH_3), 1.28 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9 ($COCH_3$), 138.1, 135.3, 133.4, 133.3 (Ar*C*), 128.6–125.9 (Ar*CH*), 83.6 (C-1), 80.7 (C-3), 75.3 (PhCH_2), 74.4 (C-4), 72.3 (PhCH_2), 70.0, 69.9 (C-2, C-5), 63.5 (C-6), 25.1 (SCH_2CH_3), 21.0 ($COCH_3$), 15.0 (SCH_2CH_3); HRMS (ESI): $[M+Na]^+$ calcd for $C_{283}H_{32}O_6$ SNa, 519.1817; found, 519.1799.

1.16. Ethyl [benzyl (2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl)uronate]-(1 → 2)-6-*O*-acetyl-4-*O*-benzyl-3-*O*-(2-naphthalenylmethyl)-1-thio-α-D-mannopyranoside (14) and Ethyl [benzyl (2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl)uronate]-(1 → 2)-6-*O*-acetyl-4-*O*-benzyl-3-*O*-(2-naphthalenylmethyl)-1-thio-α-D-mannopyranoside (14α)

A solution of **21** (389 mg, 0.78 mmol), and **15** (822 mg, 1.18 mmol) in a dry CH_2Cl_2/$(CH_3)_3CCN$ mixture (3:1, 20 mL) containing 4 Å molecular sieves was cooled under an N_2 atmosphere to −78 °C, where after $BF_3{\cdot}Et_2O$ in dry CH_2Cl_2 (0.02 M, 6.5 mL, 0.16 eq) was added drop-wise. After 1 h the reaction was quenched by the addition of Et_3N (3 mL), the mixture was allowed to attain room temperature, filtered through Celite, and concentrated. Purification on a silica gel flash column (toluene/EtOAc 97:3) gave **14** (405 mg, 0.39 mmol, 50%) and **14α** (48 mg, 0.05 mmol, 6%). For data on **14** see **1.11** above. **14α**: R_f 0.34 (toluene/EtOAc 97:3); $[\alpha]_D$ +42.4 (*c* 1.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82–7.03 (m, 32H, ArH), 5.41 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1′), 5.35 (d, 1H, $J_{1,2}$ = 1.2 Hz, H-1), 5.20 (d, 1H, J_{gem} = 12.3 Hz, PhCH_2), 5.13 (d, 1H, J_{gem} = 12.3 Hz, PhCH_2), 4.97 (d, 1H, J_{gem} = 10.9 Hz, PhCH_2), 4.84–4.68 (m, 6H, 3 × PhCH_2), 4.49–4.38 (m, 4H, 2 × PhCH_2, H-5′), 4.30–4.26 (m, 3H, H-2, H6a, H-6b), 4.15–4.11 (m, 1H, H-5), 4.05 (t, 1H, $J_{2',3'}$ = 9.3 Hz, H-3′), 3.98 (t, 1H, $J_{3,4}$ = 9.4 Hz, H-4), 3.92 (dd, 1H, $J_{2,3}$ = 2.4 Hz, H-3), 3.80–3.76 (m, 1H, H-4′), 3.58 (dd, 1H, H-2′), 2.56–2.44 (m, 2H, SCH_2CH$_3$), 1.93 (s, 3H, COCH_3), 1.18 (t, 3H, *J* = 7.4 Hz, SCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0 ($COCH_3$), 169.6 (*C*OOBn), 138.7, 138.3, 138.3, 138.1, 135.2, 135.2, 133.4, 133.2 (Ar*C*), 128.7–126.2 (Ar*CH*), 98.2 (C-1′), 83.9 (C-1), 81.0 (C-3′), 80.8 (C-3), 79.5 (C-4′), 79.4 (C-2′), 75.8 (PhCH_2), 75.7 (C-2), 75.3, 75.1 (2 × PhCH_2), 74.7 (C-4), 72.9, 71.8 (2 × PhCH_2), 71.2 (C-5), 70.7 (C-5′), 67.4 (PhCH_2), 63.3 (C-6), 25.8 (SCH_2CH_3), 20.8 ($COCH_3$), 15.1 (SCH_2CH_3); HRMS (ESI): $[M+Na]^+$ calcd for $C_{62}H_{64}O_{12}$ SNa, 1055.4016; found, 1055.4039.

1.17. Benzyl (phenyl 3-*O*-benzyl-1-thio-β-D-glucopyranoside)uronate (23)

To a solution of **22** (600 mg, 1.66 mmol) in CH_2Cl_2 (12 mL) and H_2O (6 mL), bis(acetoxy) iodobenzene (BAIB) (1.33 g, 4.14 mmol) and 2,2,6,6,-tetramethyl piperidinoxy free radical (TEMPO) (52 mg, 0.33 mmol) were added. After 2 h, the reaction was quenched by the addition of 50% $Na_2S_2O_3$ aq solution (1.5 mL). The resulting mixture was concentrated and then co-evaporated with toluene. The residue was dissolved in dry DMF (12 mL) and BnBr (0.6 mL, 5 mmol) and Cs_2CO_3 (1.14 g, 8.3 mmol) were added. The solution was stirred at rt overnight, H_2O was then added, and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by silica gel flash column chromatography (toluene/EtOAc 9:1 → 3:2) to give **23** (348 mg, 45%); R_f 0.73 (toluene/EtOAc 1:1); $[\alpha]_D$ −41.7 (*c* 1.18, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53–7.17 (m, 15H), 5.24 (s, 2H, PhCH_2), 4.88 (s, 2H, PhCH_2), 4.53 (d, 1H, $J_{1,2}$ = 9.4 Hz, H-1), 3.90–3.84 (m, 2H, H-3, H-4), 3.49–3.43 (m, 2H, H-2, H-5), 2.95 (d, 1H, $J_{4,OH}$ = 2.3 Hz, OH-4), 2.52 (d, 1H, $J_{2,OH}$ = 1.7 Hz, OH-2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8 (*C*O), 138.4, 135.1, 131.3 (Ar*C*), 133.5–128.1 (Ar*CH*), 88.6 (C-1), 84.3 (C-3), 78.0 (C-5), 75.2 (PhCH_2), 71.7 (C-2), 71.5 (C-4), 67.6 (PhCH_2); HRMS (ESI): $[M+Na]^+$ calcd for $C_{26}H_{26}O_6$SNa, 489.1348; found, 489.1355.

1.18. Benzyl (phenyl 3-*O*-benzyl-2,4-*O*-di-*tert*-butylsilylene-1-thio-β-D-glucopyranoside) uronate (24)

To a solution of **23** (318 mg, 0.68 mmol) in dry 1,2-dichloroethane (7 mL) and 2,6-lutidine (0.41 mL, 3.55 mmol), di-*tert*butylsilyl-

bis(trifluoromethanesulfonate) (0.29 mL, 0.89 mmol) was added under N_2. The reaction mixture was stirred at rt for 3 days, then concentrated, diluted with EtOAc, washed with H_2O, 1 N HCl, sat. $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated. The crude residue was purified by silica gel flash column chromatography (toluene/EtOAc 99:1 → 8:2) to give **24** (187 mg, 45%); R_f 0.87 (toluene/EtOAc 9:1); $[\alpha]_D$ −145 (*c* 1.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57–7.13 (m, 15H), 5.55 (s, 1H, H-1), 5.04 (d, 1H, J_{gem} = 12.1 Hz, PhCH_2), 4.96 (d, 1H, J_{gem} = 12.1 Hz, PhCH_2), 4.91–4.88 (m, 1H, H-4), 4.65 (m, 3H, H-5, PhCH_2), 4.47 (d, 1H, $J_{2,3}$ = 4.0 Hz, H-2), 4.09 (t, 1H, $J_{3,4}$ = 4.0 Hz, H-3), 1.04, 0.95 (2s, 18H, 2 × (CH_3)$_3$C); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6 (*C*O), 138.8, 137.4, 135.4 (Ar*C*), 130.4–126.5 (Ar*C*H), 87.3 (C-1), 75.0 (C-5), 72.2 (PhCH_2), 70.7 (C-2), 69.6 (C-3), 67.4 (C-4), 67.1 (PhCH_2), 28.1, 28.0 (2 × (CH_3)$_3$C), 21.5, 21.2 (2 × (CH_3)$_3$*C*); HRMS (ESI): $[M+Na]^+$ calcd for $C_{34}H_{42}O_6$ SiSNa, 629.2369; found, 629.2363.

1.19. Ethyl [benzyl (3-*O*-benzyl-2,4-*O*-di-*tert*-butylsilylene-β-D-glucopyranosyl)uronate]-(1 → 2)-6-*O*-acetyl-4-*O*-benzyl-3-*O*-(2-naphthalenylmethyl)-1-thio-α-D-mannopyranoside (25)

Compound **24** (53.2 mg, 87.8 μmol), Ph_2SO (21.3 mg, 0.105 mmol), and 2,4,6-tri(*tert*butyl)pyrimidine (TTBP) (53.6 mg, 0.219 mmol) were co-evaporated with toluene three times, then dissolved in dry CH_2Cl_2 (1.6 mL). After adding 4 Å molecular sieves, the solution was cooled to −60 °C. After 20 min, Tf_2O (16.3 μL, 96.6 μmol) was added and the mixture was allowed to reach −45 °C. The mixture was cooled again to −60 °C, then **21** (65.3 mg, 0.132 mmol), previously co-evaporated with toluene three times, was added dropwise as a solution in dry CH_2Cl_2 (0.6 mL). The reaction mixture was stirred for 10 min at −60 °C, then slowly warmed to 0 °C for 2 h. Et_3N was added, the mixture was diluted with EtOAc, filtered through Celite, and washed with sat. $NaHCO_3$ and brine, then dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by silica gel flash column chromatography (toluene/EtOAc 99:1 → 8:2) to give **25** (58 mg, 67%); R_f 0.56 (cyclohexane/EtOAc 4:1); $[\alpha]_D$ −22.9 (*c* 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79–7.14 (m, 22H), 5.69 (s, 1H, H-1), 5.43 (s, 1H, H-1′), 5.10 (br s, H-2), 5.05 (d, 1H, J_{gem} = 12.3 Hz, PhCH_2), 4.99 (d, 1H, J_{gem} = 12.1 Hz, PhCH_2), 4.92–4.85 (m, 2H, PhCH_2), 4.79 (d, 1H, $J_{3',4'}$ = 4.0 Hz, H-4′), 4.73–4.67 (m, 2H, PhCH_2), 4.60 (s, 1H, H-5′), 4.51–4.43 (m, 2H, PhCH_2), 4.35 (br d, 1H, $J_{5,6a}$ = 9.8 Hz, H-6a), 4.23–4.17 (m, 3H, H-5, H6b, H-2′), 4.11 (br d, 1H, H-3), 4.08 (t, 1H, $J_{2',3'}$ = 3.8 Hz, H-3′), 3.82 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 8.6 Hz, H-4), 2.73–2.60 (m, 2H, SCH_2CH$_3$), 2.02 (s, 3H, COCH_3), 1.29 (t, *J* = 7.4, SCH_2CH_3), 1.06, 0.93 (2s, 18H, 2 × (CH_3)$_3$C); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 169.1 (2 × *C*O), 138.4, 137.9, 136.7, 135.8, 133.4, 133.0 (Ar*C*), 129.2–125.7 (Ar*CH*), 95.6 (C-1′), 80.6 (C-1), 79.4 (C-3), 75.0 (C-5′), 74.6 (C-4), 74.5 (PhCH_2), 72.1 (C-2), 71.2, 71.0 (2 × PhCH_2), 70.6 (C-5), 69.3 (C-3′), 68.7 (C-4′), 67.2 (C-2′), 66.5 (PhCH_2), 64.0 (C-6), 28.1, 28.0 (2 × (CH_3)$_3$C), 26.1 (SCH_2CH$_3$), 21.4, 21.2 (2 × (CH_3)$_3$*C*), 20.8 (COCH_3), 15.1 (SCH_2CH_3); HRMS (ESI): $[M+Na]^+$ calcd for $C_{56}H_{68}O_{12}$SiSNa, 1015.4098; found, 1015.4061.

Acknowledgement

We are thankful to Science Foundation Ireland (Grant 08/IN.1/B2067) for financial support.

References

1. Oscarson, S.; Alpe, M.; Svahnberg, P.; Nakouzi, A.; Casadevall, A. *Vaccine* **2005**, *23*, 3961–3972.
2. Astronomo, R. D.; Burton, D. R. *Nat. Rev. Drug Disc.* **2010**, *9*, 308–324.
3. Alpe, M.; Svahnberg, P.; Oscarson, S. *J. Carbohydr. Chem.* **2003**, *22*, 565–577.
4. Alpe, M.; Svahnberg, P.; Oscarson, S. *J. Carbohydr. Chem.* **2004**, *23*, 403–416.
5. Vesely, J.; Rydner, L.; Oscarson, S. *Carbohydr. Res.* **2008**, *343*, 2200–2208.
6. Lahmann, M.; Andresen-Bergström, M.; Turek, D.; Oscarson, S. *J. Carbohydr. Chem.* **2004**, *23*, 123–132.
7. Schmidt, R. R.; Grundler, G. *Synthesis* **1981**, *11*, 885–887.
8. Alpe, M., Doctoral Dissertation, Stockholm University, 2003.
9. Kloosterman, M.; de Nijs, M. P.; van Boom, J. H. *J. Carbohydr. Chem.* **1986**, *5*, 215–233.
10. Borbas, A.; Szabo, Z. B.; Szilagyi, L.; Benyei, A.; Liptak, A. *Carbohydr. Res.* **2002**, *337*, 1941–1951.
11. Rydner, L., Doctoral Dissertation, Stockholm University, 2010.
12. Braccini, I.; Deorouet, C.; Esnault, J.; Herve du Penhoat, C.; Mallet, J. M.; Michon, V.; Sinay, P. *Carbohydr. Res.* **1993**, *246*, 23–41.
13. Schmidt, R. R.; Rucker, E. *Tetrahedron Lett.* **1980**, *21*, 1421–1424.
14. Brimer, K.; Vasella, A. *Helv. Chim. Acta* **1992**, *75*, 621–636.
15. Nitz, M.; Purse, B. W.; Bundle, D. R. *Org. Lett.* **2000**, *2*, 2939–2942.
16. Smoot, J. T.; Pornsuriyasak, P.; Demchenko, A. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 7123–7126.
17. Smoot, J. T.; Demchenko, A. V. *J. Org. Chem.* **2008**, *73*, 8838–8850.
18. Tiwari, P.; Oscarson, S. Unpublished results.
19. Furukawa, T.; Hinou, H.; Nishimura, S.-I. *Org. Lett.* **2012**, *14*, 2102–2105.