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Note

Variant synthetic pathway to glucuronic acid-containing di- and trisaccharide thioglycoside building blocks for continued synthesis of *Cryptococcus neoformans* capsular polysaccharide structures

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Abstract—An alternative pathway to glucuronic acid-containing di- and trisaccharide thioglycoside building blocks, suitable for the synthesis of *Cryptococcus neoformans* capsular polysaccharide structures, has been developed. As opposed to our earlier synthesis, this approach features the introduction of the glucuronic acid motif at the di- and trisaccharide level through oxidation of a glucose residue. This approach circumvents problems encountered in glycosylations with glucuronic acid donors and benzylation of glucuronic acid-containing derivatives. Selective protection of primary alcohols was obtained at the di- and trisaccharide stage using TBDMS or trityl protecting groups, respectively. After benzylation of the secondary hydroxyl groups and subsequent removal of the TBDMS or trityl group, oxidation of the free primary alcohols to carboxylic acids was performed in high yield using the TEMPO–BAIB reagent mixture, which does not tend to oxidize thioglycosides. The new approach requires a number of extra steps, but has proven to be more reliable and easily reproducible.

Keywords: Oligosaccharide synthesis; Thioglycosides; Oxidation

We had earlier published synthetic pathways to donor building blocks suitable for the synthesis of *Cryptococcus neoformans* CPS structures, including those corresponding to Xyl*p*-(1→2)-Man*p* and Xyl*p*-(1→2)-[Xyl*p*-(1→4)]-Man*p* di- and trisaccharides[1] as well as Glc*p*A-(1→2)-Man*p* and Glc*p*A-(1→2)-[Xyl*p*-(1→4)]-Man*p* di- and trisaccharides.[2] These compounds were subsequently used in the synthesis of larger structures (up to heptasaccharides) with variant acetylation patterns, which have been used in antibody binding- and immunizing experiments.[3]

Although the synthesis of Xyl*p*-(1→2)-Man*p* di- and trisaccharide building blocks is practical, the synthesis of the glucuronic acid-containing building blocks is not always reliable and is difficult to perform on a large scale. This is due to a number of reasons: the low stereoselectivity in couplings with Glc*p*A-donors with non-participating groups, the low reactivity and yields in couplings with Glc*p*A-donors with participating groups and difficulties in benzylating glucuronic acid derivatives in reproducibly high yield. These are all known problems frequently experienced in the synthesis of uronic acid-containing oligosaccharides.[4] An often used solution to these problems is to instead start with a suitably protected aldose donor and to perform glycosylations and alkylations prior to oxidation to the 6-carboxylic acid function present in uronic acids.[4] This approach has earlier been applied to the synthesis of a *Cryptococcus* pentasaccharide O-glycosidic structure by van Boom and co-workers.[5] We herein report on our

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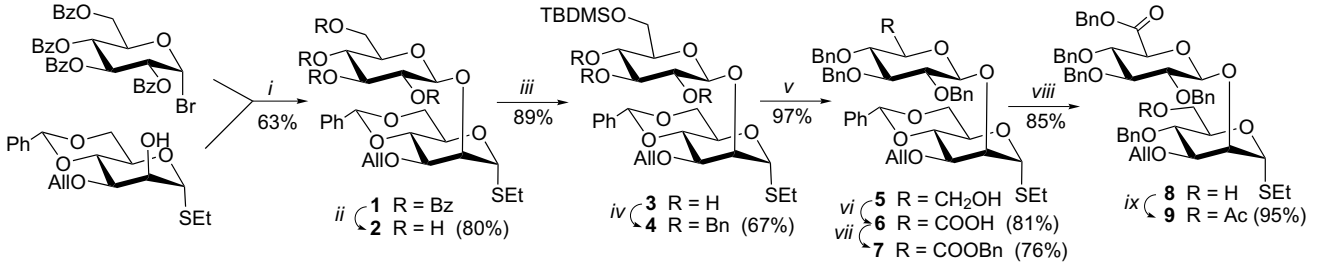
experiences in employing this approach in the synthesis of the di- and trisaccharide thioglycoside building blocks **9** and **17**.

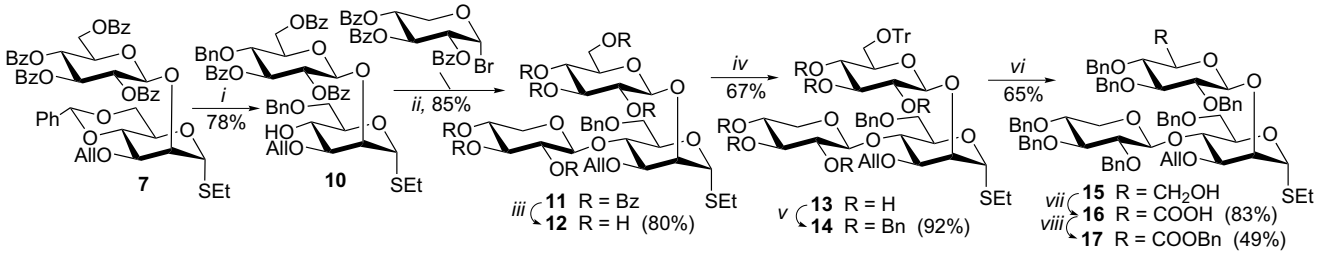
The same acceptor used in our earlier building block syntheses, ethyl 2-*O*-allyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside,[1] was employed in these studies. Glycosylation of this alcohol with 2,3,4,6-tetra-*O*-benzyl-D-glucopyransosyl bromide promoted by silver triflate gave a good yield (63%) of the (1→2)-β-linked disaccharide **1** (Scheme 1). Deacylation by treatment with sodium methoxide yielded the tetraol **2** in 80% yield. Regioselective protection of the primary position, to allow later deprotection and oxidation at C-6′, was performed using two different protecting groups, either a TBDMS group or a trityl group. The former gave a better yield in the selective protection and deprotection whereas the latter gave a better yield in the intermediate benzylation (no migration observed). Thus, silylation using TBDMSCl and DMAP in pyridine gave an 89% yield of the 6′-*O*-silyl compound **3**, which was benzylated (BnBr, NaH, DMF) to afford compound **4** in 67% yield together with 13% of the 4-*O*-TBDMS isomer. Attempts to change conditions to avoid silyl migration during the alkylation reaction were not successful. Desilylation with TBAF afforded the 6′-OH derivative **5** almost quantitatively (97%).

Thioglycosides are stable to almost any protecting and functional group manipulation and interconversions.[6] More or less only two types of reactions constitute a problem: oxidation and catalytic hydrogenolysis. With regard to oxidations, DMSO-based oxidations do not oxidize the sulfur, whereas with other reagents (e.g., PDC) oxidation often occurs. However, it has been shown that oxidations with TEMPO–BAIB[7] generally do not affect thioglycosides.[8] Other features of this reagent are that it is most selective for primary positions and that the carboxylic acid is obtained. Oxidation of **5** using this reagent mixture gave the desired uronic acid derivative **6** in high yield (80%). Treatment with $PhCHN_2$ then gave the known benzyl ester **7** in 76% yield. We were primarily interested in the 6-O-acetylated disaccharide building block **9**, and this was obtained from **7** using an improved pathway. Regioselective opening of the benzylidene acetal with Et_3SiH–$PhBCl_2$[9] gave the primary alcohol **8**, which was acetylated to afford **9** in an overall 81% yield. As compared to the earlier synthesis of this building block, this route is longer (9 steps as compared to 5 steps), but more reliable and reproducible. The overall yields of both routes are comparable (∼15%).

In the synthesis of the trisaccharide, the fact that xylopyranosides have no primary hydroxyl group could be utilized (Scheme 2). First, the benzylidene acetal of disaccharide **7** was again regioselectively opened, but now to yield the 4-hydroxy derivative **10** by the use of the $NaCNBH_3$–HCl reagent system.[10] Silver triflate-promoted glycosylation of this acceptor with 2,3,4-tri-*O*-benzyl-xylopyranosyl bromide afforded the β-(1→4)-linked trisaccharide **11** in 85% yield. Deacylation (NaOMe–MeOH, →**12**, 80%) followed by regioselective protection of the primary alcohol, this time using trityl chloride, gave the 6′-*O*-trityl derivative **13** (65%), which was benzylated to afford **14** (92%). Detritylation using *p*-TsOH in $CHCl_3$–MeOH gave the 6′-hydroxy derivative



Scheme 1. Reagents: (i) AgOTf, DTBP, CH_2Cl_2; (ii) NaOMe, MeOH; (iii) TBDMSCl, DMAP, pyridine; (iv) BnBr, NaH, DMF; (v) TBAF, $CHCl_3$/MeOH, (vi) TEMPO, BAIB, CH_2Cl_2/H_2O; (vii) $PhCHN_2$, EtOAc; (viii) Et_3SiH, $PhBCl_2$, CH_2Cl_2; (ix) Ac_2O, pyridine.



Scheme 2. Reagents: (i) $NaCNBH_3$, HCl/Et_2O, THF; (ii) AgOTf, DTBP, CH_2Cl_2; (iii) NaOMe, MeOH; (iv) TrCl, DMAP, pyridine; (v) BnBr, NaH, DMF; (vi) pTsOH, $CHCl_3$/MeOH, (vii) TEMPO, BAIB, CH_2Cl_2/H_2O; (viii) $PhCHN_2$, EtOAc.

15 (67%), which was oxidized, again using TEMPO–BAIB, to yield the glucuronic acid **16**, once more in a high yield (83%). Transformation into the benzyl ester using phenyl diazomethane then gave the known trisaccharide building block **17**. For the synthesis of the trisaccharide block, this new approach is better. The disadvantage of the three extra steps needed (protection, deprotection and oxidation of the primary alcohol) is more than compensated by the higher yields in and the reproducibility of the glycosylation and the benzylation reactions performed.

In conclusion, efficient and reproducible pathways to glucuronic acid-containing derivatives **9** and **17** have been developed. These thioglycosides are important building blocks in the synthesis of *C. neoformans* CPS structures.

1. Experimental

1.1. General methods

TLC was carried out on Merck precoated 60 F_{254} plates using AMC (ammonium molybdate–cerium(IV) sulfate–10% sulfuric acid 100 g:2 g:2 L) or 8% H_2SO_4 for visualization. Column chromatography was performed on silica gel (0.040–0.063 mm, Amicon) or reversed phase gel (C18 60A 40–63 μm). NMR spectra were recorded in $CDCl_3$ (Me_4Si, δ 0.00 ppm) or D_2O (acetone ^{13}C δ 30.89 ppm, $^1H = 2.22$ ppm) at 25 °C on a Varian 300 MHz or 400 MHz instrument. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Organic solutions were dried over Na_2SO_4 before concentration, which was performed under reduced pressure.

1.2. Ethyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→2)-3-*O*-allyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (1)

Silver triflate (2.33 g, 9.08 mmol) dissolved in dry toluene was added at −50 °C to a stirred mixture of 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl bromide (5.99 g, 9.08 mmol), ethyl 3-*O*-allyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (1.60 g, 4.54 mmol) and 2,6-di-*tert*-butylpyridine (510 μL, 2.27 mmol) in distilled CH_2Cl_2 (150 mL) containing crushed 4 Å molecular sieves (1.5 g). The reaction mixture was allowed to attain room temperature overnight. The progress of the reaction was followed by TLC (toluene–EtOAc, 6:1). After 18 h, Et_3N (1.5 mL) was added, the mixture was diluted with CH_2Cl_2 (150 mL), filtered through Celite, concentrated and purified by silica gel chromatography (toluene–EtOAc, 20:1) to give **1** (2.7 g, 63%); $[\alpha]_D$ +32.8 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.10 (3H, br t, $J = 7.6$ Hz, SCH_2CH_3), 2.40 (2H, dq, $J = 7.0$, $J = 7.2$ Hz, SCH_2CH_3), 3.46 (1H, t, $J = 10.0$ Hz, H-6_I), 3.77 (1H, dd, $J = 3.2$, $J = 9.6$ Hz, H-3_I), 3.83 (1H, dd, $J = 4.4$, $J = 10.0$ Hz, H-$6'_I$), 3.97 (1H, m, H-5_I), 4.01 (1H, t, $J = 9.6$ Hz, H-4_I), 4.13 (2H, dd, $J = 1.6$, $J = 5.6$ Hz, $OCH_2CH{=}CH_2$), 4.18 (1H, ddd, $J = 3.2$, 5. $J = 6$, 9.6 Hz, H-5_{II}), 4.24 (1H, dd, $J = 1.2$, $J = 3.2$ Hz, H-2_I), 4.51 (1H, dd, $J = 6.0$, $J = 12.0$ Hz, H-6_{II}), 4.65 (1H, dd, $J = 2.8$, $J = 12.0$ Hz, H-$6'_{II}$), 4.96 (1H, d, $J = 7.6$ Hz, H-1_{II}), 5.02 (1H, dq, $J = 1.6$, $J = 10.8$ Hz, $OCH_2CH{=}CH_2$), 5.18 (1H, d, $J = 0.8$ Hz, H-1_I), 5.22 (1H, dq, $J = 1.6$, $J = 17.2$ Hz, $OCH_2CH{=}CH_2$), 5.47 (1H, s, CHC_6H_5), 5.65 (1H, dd, $J = 7.6$, $J = 10.0$ Hz, H-2_{II}), 5.68 (1H, t, $J = 10.0$ Hz, H-3_{II}), 5.81 (1H, dddt, $J = 1.6$, $J = 5.6$, $J = 10.8$, $J = 17.2$ Hz, $OCH_2CH{=}CH_2$), 5.93 (1H, t, $J = 9.6$ Hz, H-4_{II}), 7.11–8.01 (25H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.9 (q, SCH_2CH_3), 25.6 (t, SCH_2CH_3), 63.5 (t, C-6_{II}), 64.6 (d, C-5_I), 68.5 (t, C-6), 69.9 (d, C-3_{II}), 71.0 (t, $OCH_2CH{=}CH_2$), 71.8 (d, C-2_{II}), 72.7 (d, C-4_{II}), 72.8 (d, C-5_{II}), 74.2 (d, C-3_I), 78.3 (d, C-2_I), 78.6 (d, C-4_I), 82.7 (d, C-1), 100.2 (d, C-1_{II}), 101.7 (d, CHC_6H_5), 117.2 (t, $OCH_2CH{=}CH_2$), 126.2–129.9 (24C) (Ar-C), 131.7 (d, CHC_6H_5), 133.2, 133.3, 133.4, 133.6 (4 × s, 4 × COC_6H_5), 134.7 (d, OCH_2CHCH_2), 137.7 (s, CHC_6H_5), 164.9, 165.3, 166.0, 166.2 (4 × s, 4 × COC_6H_5); HRMS (ESI): $[M+Na]^+$ calcd for $C_{52}H_{50}O_{14}S$, 953.2813; found, 953.2793.

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

Compound **1** (1.8 g, 1.93 mmol) was dissolved in dry MeOH (80 mL), 1 M methanolic NaOMe (1.5 mL) was added and the mixture was stirred overnight at room temperature. The progress of the reaction was followed by TLC (CH_2Cl_2–MeOH, 9:1). Acetic acid (15 drops) was added, the stirring was continued for 30 min, then the mixture was concentrated and purified by silica gel chromatography (CH_2Cl_2–MeOH, 15:1) to yield **2** (0.8 g, 80%); $[\alpha]_D$ +9.8 (*c* 0.2, DMSO-d_6); ^1H NMR (400 MHz, DMSO): δ 1.28 (3H, dt, $J = 0.8$, $J = 7.6$ Hz, SCH_2CH_3), 2.40 (2H, dq, $J = 7.0$, $J = 7.2$ Hz, SCH_2CH_3), 3.07 (1H, br s, OH), 3.38–3.42 (1H, m, H-5_{II}), 3.50–3.66 (3H, m, H-2_{II}, H-3_{II}, H-4_{II}), 3.82–3.91 (4H, H-6_I, H-6_{II}, H-$6'_{II}$, H-3_I), 4.11–4.26 (5H, m, H-2_I, H-4_I, H-5_I, H-$6'_I$, $OCH_2CH{=}CH_2$), 4.31 (1H, dd, $J = 6.0$ Hz, $J = 12.8$ Hz, $OCH_2CH{=}CH_2$), 4.48 (1H, br s, OH), 4.53 (1H, d, $J = 8.0$ Hz, H-1_{II}), 5.21 (1H, br d, $J = 10.4$ Hz, $OCH_2CH{=}CH_2$), 5.31 (1H, br d, $J = 18.4$ Hz, $OCH_2CH{=}CH_2$), 5.35 (1H, s, H-1_I), 5.60 (1H, s, CHC_6H_5), 5.90 (1H, ddt, $J = 6.0$, $J = 10.4$, $J = 16.8$ Hz, $OCH_2CH{=}CH_2$), 7.33–7.39 (3H, m, Ar-H), 7.46–7.50 (2H, m, Ar-H); ^{13}C NMR (100.6 MHz, DMSO): δ 15.2 (q, SCH_2CH_3), 25.7 (t, SCH_2CH_3), 62.2 (t, C-6_{II}), 64.7 (d, C-5_I), 68.8 (t, C-6_I), 70.0 (d, C-4_{II}), 71.5 (d, C-2_{II}), 72.6 (t, $OCH_2CH{=}CH_2$), 74.7 (d, C-3_I), 75.8 (d, C-4_I), 76.1 (d, C-3_{II}), 76.4 (d,

C-5_{II}), 79.1 (d, C-2_I), 84.9 (d, C-1), 101.6 (d, *C*HC$_6$H$_5$), 102.0 (d, C-1_{II}), 118.7 (t, OCH$_2$CH=*C*H$_2$), 126.1 (d, 2C), 128.4 (d, 2C), 129.1 (d) (Ar-C), 134.2 (d, OCH$_2$*C*H=CH$_2$), 137.6 (s) (Ar-C); MALDI-TOF MS: $[M+Na]^+$ calcd for $C_{24}H_{34}O_{10}S$, 514.59; found, 537.58.

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

tert-Butyldimethylchlorosilane (282 mg, 1.03 mmol) was added to a solution of **2** (440 mg, 0.86 mmol) in pyridine (11 mL) at room temperature 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 chromatography (toluene–EtOAc, 1:2) to afford **3** (480 mg, 89%); $[\alpha]_D$ +12.1 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CHCl_3$): δ 0.09 (3H, (CH$_3$)$_3$C(C*H*$_3$)$_2$Si), 0.10 (3H, (CH$_3$)$_3$C(C*H*$_3$)$_2$Si), 0.91 (9H, (C*H*$_3$)$_3$C(CH$_3$)$_2$Si), 1.28 (3H, dt, $J = 0.8$, $J = 7.2$ Hz, SCH$_2$C*H*$_3$), 2.55–2.69 (2H, m, SC*H*$_2$CH$_3$), 2.86 (1H, br s, OH), 3.19 (1H, br s, OH), 3.38–3.43 (1H, m, H-5_{II}), 3.46–3.51 (1H, m, H-2_{II}), 3.58–3.64 (2H, m, H-3_I, H-3_{II}), 3.81 (1H, dd, $J = 5.2$, $J = 10.8$ Hz, H-6_{II}), 3.85–3.89 (2H, m, H-4_{II}, H-6_I), 3.92 (1H, dd, $J = 4.4$, $J = 10.8$ Hz, H-$6'_{II}$), 4.12–4.26 (5H, m, H-2_I, H-4_I, H-5_I, H-$6'_I$, OC*H*$_2$CH=CH$_2$), 4.39 (1H, ddt, $J = 1.2$, $J = 5.6$, $J = 12.4$ Hz, OC*H*$_2$CH=CH$_2$), 4.58 (1H, d, $J = 8.0$ Hz, H-1_{II}), 5.23 (1H, dq, $J = 1.6$, $J = 10.4$ Hz, OCH$_2$CH=C*H*$_2$), 5.28 (1H, s, H-1_I), 5.29 (1H, dq, $J = 1.6$, $J = 17.2$ Hz, OCH$_2$CH=C*H*$_2$), 5.60 (1H, s, C*H*C$_6$H$_5$), 5.86–5.96 (1H, m, OCH$_2$C*H*=CH$_2$), 7.34–7.40 (3H, m, Ar-H), 7.46–7.50 (2H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −5.3 (q, 2C, (CH$_3$)$_3$C(*C*H$_3$)$_2$Si), 15.2 (q, SCH$_2$*C*H$_3$), 18.4 (s, (CH$_3$)$_3$*C*(CH$_3$)$_2$Si), 25.7 (t, S*C*H$_2$CH$_3$), 26.0 (q, 3C, (*C*H$_3$)$_3$C(CH$_3$)$_2$Si), 64.3 (t, C-6_{II}), 64.5 (d, C-5_I), 68.8 (t, C-6_I), 70.1 (d, C-2_{II}), 72.4 (d, C-3_I), 73.5 (t, O*C*H$_2$CH=CH$_2$), 73.7 (d, C-2_I), 74.9 (d, C-4_{II}), 75.5 (d, C-5_{II}), 75.9 (d, C-3_{II}), 79.9 (d, C-4_I), 85.8 (d, C-1), 101.5 (d, C-1_{II}), 101.7 (d, *C*HC$_6$H$_5$), 119.1 (t, OCH$_2$CH=*C*H$_2$), 126.1 (d, 2C), 128.4 (d, 2C), 129.1 (d) (Ar-C), 133.8 (d, OCH$_2$*C*H=CH$_2$), 137.6 (s) (Ar-C); HRMS (ESI): $[M+Na]^+$ calcd for $C_{30}H_{48}O_{10}SSi$, 651.2630; found, 651.2608.

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

A 60% oil dispersion of sodium hydride (132 mg, 3.29 mmol) was added to a solution of **3** (460 mg, 0.73 mmol) and benzyl bromide (350 μL, 2.94 mmol) in DMF (30 mL) at room temperature and the reaction mixture was stirred overnight. The progress of the reaction was followed by TLC (toluene–EtOAc, 6:1). MeOH (1 mL) was carefully added and the mixture was diluted with toluene (100 mL), washed with water (2 × 50 mL), dried and concentrated. Purification on a silica gel column (toluene–EtOAc, 30:1) gave **4** (440 mg, 67%). 13% of the migrated product ethyl 2,3,6-tri-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-β-D-glucopyranosyl-(1→2)-3-*O*-allyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside was also isolated. **4**: $[\alpha]_D$ +38.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CHCl_3$): δ 0.09 (3H, (CH$_3$)$_3$C(C*H*$_3$)$_2$Si), 0.11 (3H, (CH$_3$)$_3$C(C*H*$_3$)$_2$Si), 0.93 (9H, (C*H*$_3$)$_3$C(CH$_3$)$_2$Si), 1.32 (3H, dt, $J = 1.2$, $J = 7.2$ Hz, SCH$_2$C*H*$_3$), 2.59–2.74 (2H, m, SC*H*$_2$CH$_3$), 3.33–3.38 (1H, m, H-5_{II}), 3.59–3.72 (3H, m, H-2_{II}, H-3_{II}, H-4_{II}), 3.76–3.92 (3H, m, H-6_I, H-$6'_I$, H-6_{II}), 3.96 (1H, dd, $J = 3.2$, $J = 10.0$ Hz, H-3_I), 4.17–4.34 (5H, m, H-4_I, H-5_I, H-$6'_{II}$, OC*H*$_2$CH=CH$_2$), 4.37 (1H, d, $J = 3.6$ Hz, H-2_I), 4.52 (1H, d, $J = 7.6$ Hz, H-1_{II}), 4.70 (1H, d, $J = 10.8$ Hz), 4.73 (1H, d, $J = 10.4$ Hz), 4.84 (1H, d, $J = 11.2$ Hz), 4.89 (1H, d, $J = 10.8$ Hz), 4.97 (1H, d, $J = 11.2$ Hz), 5.14 (1H, d, $J = 10.4$ Hz) (OC*H*$_2$Ph), 5.21 (1H, dq, $J = 1.2$, $J = 11.6$ Hz, OCH$_2$CH=C*H*$_2$), 5.38 (1H, dq, $J = 1.2$, $J = 17.2$ Hz, OCH$_2$CH=C*H*$_2$), 5.52 (1H, s, H-1_I), 5.58 (1H, s, C*H*C$_6$H$_5$), 5.91–6.01 (1H, m, OCH$_2$C*H*=CH$_2$), 7.29–7.40 (16H, m), 7.44–7.46 (2H, m), 7.51–7.55 (2H, m) (Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ −5.1 (q, (CH$_3$)$_3$C(*C*H$_3$)$_2$Si), −5.3 (q, (CH$_3$)$_3$C(*C*H$_3$)$_2$Si), 15.1 (q, SCH$_2$*C*H$_3$), 18.4 (s, (CH$_3$)$_3$*C*(CH$_3$)$_2$Si), 25.7 (t, S*C*H$_2$CH$_3$), 26.1 (q, 3C, (*C*H$_3$)$_3$C(CH$_3$)$_2$Si), 62.5 (t, C-6_{II}), 64.6 (d, C-5_I), 68.8 (t, C-6_I), 70.5 (t, O*C*H$_2$CH=CH$_2$), 73.7 (d, C-3_I), 75.1 (t, *C*H$_2$Ph), 75.3 (t, *C*H$_2$Ph), 75.8 (t, *C*H$_2$Ph), 76.5 (d, 2C, C-2_I, C-5_{II}), 77.5 (d, C-4_{II}), 78.9 (d, C-4_I), 82.2 (d, C-2_{II}), 82.9 (d, C-1_I), 84.9 (d, C-3_{II}), 101.6 (d, C-1_{II}), 101.7 (d, *C*HC$_6$H$_5$), 117.6 (t, OCH$_2$CH=*C*H$_2$), 126.1 (d, 2C), 127.7 (d), 127.9 (d, 2C), 128.0 (d, 4C), 128.2 (d, 2C), 128.5 (d, 2C), 128.5 (d, 4C), 128.6 (d, 2C), 128.9 (d) (Ar-C), 134.8 (d, OCH$_2$*C*H=CH$_2$), 137.7, 138.4, 138.5, 138.7 (4 × s) (Ar-C); HRMS (ESI): $[M+Na]^+$ calcd for $C_{51}H_{66}O_{10}SSi$, 921.4038; found, 921.4080.

1.6. Ethyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→2)-3-*O*-allyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (5)

TBAF (180 mg, 0.570 mmol) was added to a solution of **4** (379 mg, 0.421 mmol) in THF (30 mL) and the mixture was stirred at room temperature for 1 h. The progress of the reaction was followed by TLC (toluene–EtOAc, 6:1). The reaction mixture was then concentrated and purified by silica gel chromatography (toluene–EtOAc, 10:1) to yield **5** (320 mg, 97%); $[\alpha]_D$ +46.4 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CHCl_3$): δ 1.25 (3H, t, $J = 7.6$ Hz, SCH$_2$C*H*$_3$), 2.06 (1H, br s, OH), 2.55–2.64 (2H, m, SC*H*$_2$CH$_3$), 3.35–3.39 (1H, m,

H-5$_{II}$), 3.54–3.61 (2H, m, H-2$_{II}$, H-4$_{II}$), 3.62–3.72 (2H, m, H-3$_{II}$, H-6$_{II}$), 3.76–3.84 (2H, m, H-6$_I$, H-6$'_{II}$), 3.86 (1H, dd, $J = 3.2$, $J = 9.6$ Hz, H-3$_I$), 4.14 (1H, t, $J = 9.6$ Hz, H-4$_I$), 4.18–4.29 (5H, m, H-2$_I$, H-6$'_I$, H-5$_I$, OCH_2CH=CH$_2$), 4.49 (1H, d, $J = 8.0$ Hz, H-1$_{II}$), 4.62 (1H, d, $J = 10.8$ Hz), 4.70 (1H, d, $J = 10.0$ Hz), 4.82 (1H, d, $J = 11.2$ Hz), 4.84 (1H, d, $J = 10.8$ Hz), 4.94 (1H, d, $J = 11.2$ Hz), 5.02 (1H, d, $J = 10.0$ Hz) (OCH_2Ph), 5.18 (1H, dq, $J = 1.2$, $J = 10.4$ Hz, OCH$_2$CH=CH_2), 5.33 (1H, dq, $J = 1.2$, $J = 17.2$ Hz, OCH$_2$CH=CH_2), 5.40 (1H, s, H-1$_I$), 5.56 (1H, s, CHC$_6$H$_5$), 5.86–5.96 (1H, m, OCH$_2$CH=CH$_2$), 7.23–7.48 (20H, m, Ar-H); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ 15.2 (q, SCH$_2$$CH_3$), 25.8 (t, SC$H_2CH_3$), 62.3 (t, C-6$_{II}$), 64.7 (d, C-5$_I$), 68.9 (t, C-6$_I$), 71.6 (t, OC$H_2$CH=CH$_2$), 74.7 (d, C-3$_I$), 75.2 (t, CH$_2$Ph), 75.3 (t, CH$_2$Ph), 75.9 (t, CH$_2$Ph), 76.5 (d, C-5$_{II}$), 77.7 (d, C-4$_{II}$), 79.2 (d, 2C, C-2$_I$,C-4$_I$), 81.0 (d, C-2$_{II}$), 83.7 (d, C-1$_I$), 84.6 (d, C-3$_{II}$), 101.8 (d, CHC$_6H_5$), 103.2 (d, C-1$_{II}$), 117.2 (t, OCH$_2$CH=CH$_2$), 126.2 (d, 2C), 127.8 (d), 128.0 (d, 2C), 128.1 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 128.6 (d, 6C), 128.7 (d, 2C), 129.0 (d) (Ar-C), 134.9 (d, OCH$_2$$C$H=CH$_2$), 137.6, 138.0, 138.3, 138.7 (4 × s) (Ar-C); HRMS (ESI): [M+Na]$^+$ calcd for C$_{45}$H$_{52}$O$_{10}$S, 807.3173; found, 807.3208.

1.7. Ethyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranosyluronic acid-(1→2)-3-*O*-allyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (6)

To a vigorously stirred mixture of **5** (314 mg, 0.40 mmol) in CH$_2$Cl$_2$ (20 mL) and H$_2$O (10 mL), TEMPO (250 mg, 1.60 mmol) and BAIB (1.29 g, 4.0 mmol) were added at room temperature for 2 h. The progress of the reaction was followed by TLC (hexane–EtOAc–HOAc, 16:3:1). The reaction was quenched by the addition of 10% solution of Na$_2$S$_2$O$_3$ (25 mL). The mixture was extracted with EtOAc (2 × 80 mL), the combined organic layers were dried and concentrated. Purification of the residue on a silica gel column (hexane–EtOAc–HOAc, 16:3:1) gave **6** (260 mg, 81%); [α]$_D$ +9.1 (*c* 0.5, CHCl$_3$); ^{1}H NMR (400 MHz, CHCl$_3$): δ 1.23 (3H, t, $J = 7.6$ Hz, SCH$_2$CH_3), 2.52–2.62 (2H, m, SCH_2CH$_3$), 3.57 (1H, t, $J = 8.0$ Hz, H-2$_{II}$), 3.66 (1H, t, H-3$_{II}$), 3.80 (1H, t, $J = 11.6$ Hz, H-6$_I$), 3.88 (1H, dd, $J = 3.2$, $J = 10.0$ Hz, H-3$_I$), 4.11 (1H, t, $J = 7.2$ Hz, H-4$_{II}$), 4.11 (1H, t, $J = 9.6$ Hz, H-4$_I$), 4.14 (1H, d, $J = 7.2$ Hz, H-5$_{II}$), 4.19–4.26 (5H, m, H-2$_I$, H-5$_I$, H-6$'_I$, OCH_2CH=CH$_2$), 4.65 (1H, d, $J = 7.6$ Hz, H-1$_{II}$), 4.69 (2H, s), 4.70 (1H, d, $J = 10.0$ Hz), 4.75 (1H, d, $J = 11.2$ Hz), 4.82 (1H, d, $J = 11.2$ Hz), 4.88 (1H, d, $J = 10.0$ Hz) (OCH_2Ph), 5.15 (1H, br d, $J = 10.4$ Hz, OCH$_2$CH=CH_2), 5.29 (1H, br d, $J = 17.2$ Hz, OCH$_2$CH=CH_2), 5.33 (1H, s, H-1$_I$), 5.57 (1H, s, CHC$_6$H$_5$), 5.83–5.92 (1H, m, OCH$_2$CH=CH$_2$), 7.26–7.48 (20H, m, Ar-H); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ 15.1 (q, SCH$_2$$CH_3$), 25.8 (t, SC$H_2CH_3$), 64.7 (d, C-5$_I$), 68.8 (t, C-6$_I$), 72.0 (t, OC$H_2$CH=CH$_2$), 74.3 (t, CH$_2$Ph), 74.6 (d, C-3$_I$), 75.1 (d, C-5$_{II}$), 75.2 (t, CH$_2$Ph), 75.3 (t, CH$_2$Ph), 79.2 (d, C-4$_I$), 79.4 (d, C-2$_I$), 79.8 (d, C-4$_{II}$), 80.2 (d, C-2$_{II}$), 82.8 (d, C-3$_{II}$), 83.6 (d, C-1$_I$), 101.8 (d, CHC$_6H_5$), 102.9 (d, C-1$_{II}$), 118.2 (t, OCH$_2$CH=CH$_2$), 126.2 (d, 2C), 127.9 (d, 3C), 128.1 (d), 128.2 (d), 128.4 (d, 4C), 128.6 (d, 8C), 129.1 (d) (Ar-C), 134.2 (d, OCH$_2$$C$H=CH$_2$), 137.5 (2C), 138.0, 138.3, (4 × s) (Ar-C); HRMS (ESI): [M+Na]$^+$ calcd for C$_{45}$H$_{50}$O$_{11}$S, 821.2966; found, 821.2977.

1.8. Ethyl benzyl (2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl)uronate-(1→2)-3-*O*-allyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (7)

A solution of **6** (235 mg, 0.294 mmol) in EtOAc (50 mL) was titrated with PhCHN$_2$[†] (0.3 M solution in Et$_2$O, 3 mL, 0.9 mmol) at room temperature until full conversion was observed by TLC (toluene–EtOAc, 6:1). After 2 h, the reaction was concentrated and purified by silica gel chromatography (toluene–EtOAc, 20:1) to afford **7** (200 mg, 76%); [α]$_D$ +26.7 (*c* 0.8, CHCl$_3$), lit.[2] +22; ^{1}H NMR (400 MHz, CHCl$_3$): δ 1.26 (3H, t, $J = 7.6$ Hz, SCH$_2$CH_3), 2.54–2.64 (2H, m, SCH_2CH$_3$), 3.62–3.64 (2H, m, H-2$_{II}$, H-3$_{II}$), 3.77 (1H, t, $J = 11.6$ Hz, H-6$_I$), 3.83–3.92 (3H, m, H-3$_I$, H-4$_{II}$, H-5$_{II}$), 4.03–4.15 (3H, m, H-4$_I$, OCH_2CH=CH$_2$), 4.21–4.27 (3H, m, H-2$_I$, H-5$_I$, H-6$'_I$), 4.47 (1H, d, $J = 10.4$ Hz) (OCH_2Ph), 4.48 (1H, d, $J = 7.6$ Hz, H-1$_{II}$), 4.67 (1H, d, $J = 10.4$ Hz), 4.71 (1H, d, $J = 10.4$ Hz), 4.77 (1H, d, $J = 11.2$ Hz), 4.90 (1H, d, $J = 11.2$ Hz), 5.03 (1H, d, $J = 10.4$ Hz), 5.12 (2H, s), (OCH_2Ph), 5.10 (1H, dt, $J = 1.6$, $J = 10.4$ Hz, OCH$_2$CH=CH_2), 5.28 (1H, dt, $J = 1.6$, $J = 17.2$ Hz, OCH$_2$CH=CH_2), 5.40 (1H, d, $J = 1.2$ Hz, H-1$_I$), 5.53 (1H, s, CHC$_6$H$_5$), 5.78–5.88 (1H, m, OCH$_2$CH=CH$_2$), 7.07–7.47 (25H, m, Ar-H); ^{13}C NMR (100.6 MHz, CDCl$_3$): δ 15.1 (q, SCH$_2$$CH_3$), 25.9 (t, SC$H_2CH_3$), 64.7 (d, C-5$_I$), 67.5 (t, CH$_2$Ph), 68.9 (t, C-6$_I$), 70.5 (t, OCH_2CH=CH$_2$), 74.2 (d, C-3$_I$), 74.9 (d, C-4$_{II}$), 75.2 (t, CH$_2$Ph), 75.4 (t, CH$_2$Ph), 76.0 (t, CH$_2$Ph), 77.7 (d, C-2$_I$), 78.8 (d, C-4$_I$), 79.1 (d, C-5$_{II}$), 81.4 (d, C-2$_{II}$), 83.3 (d, C-1$_I$), 84.1 (d, C-3$_{II}$), 101.8 (d, CHC$_6H_5$), 102.8 (d, C-1$_{II}$), 117.3 (t, OCH$_2$CH=CH$_2$), 126.2 (d, 2C), 127.8 (d), 127.9 (d, 3C), 128.0 (d, 2C), 128.1 (d), 128.3 (d, 2C), 128.5 (d, 2C), 128.6 (d, 4C), 128.7 (d, 3C), 128.8 (d, 4C), 129.1 (d) (Ar-C), 134.7 (d, OCH$_2$$C$H=CH$_2$), 135.5, 137.7, 138.0, 138.2, 138.5, (5 × s) (Ar-C), 167.9 (s, C-6$_{II}$); HRMS (ESI): [M+Na]$^+$ calcd for C$_{52}$H$_{56}$O$_{11}$S, 911.3436; found, 911.3477.

[†] PhCHN$_2$ is potentially explosive and may burn violently when exposed to air. This compounds can be redistilled under high vacuum.[11]

1.9. Ethyl benzyl (2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl)uronate-(1→2)-3-*O*-allyl-4-*O*-benzyl-1-thio-α-D-mannopyranoside (8)

A solution of **7** (178 mg, 0.200 mmol) in CH_2Cl_2 (20 mL), containing crushed 4 Å molecular sieves (0.5 g), was cooled to −78 °C and Et_3SiH (97 μL, 0.607 mmol) and $PhBCl_2$ (100 μL, 0.762 mmol) were added. The reaction mixture was stirred at −78 °C for 2 h. Then Et_3N (0.8 mL) was added, the mixture was allowed to attain room temperature, concentrated and purified by silica gel chromatography (toluene–EtOAc, 12:1) to yield **8** (152 mg, 85%); $[\alpha]_D$ +14.9 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CHCl_3$): δ 1.28 (3H, t, 7.2 Hz, SCH_2CH_3), 2.56–2.66 (2H, m, SCH_2CH_3), 3.63–3.76 (4H, m, H-2_{II}, H-3_{II}, H-6_I, H-$6'_I$), 3.79 (1H, dd, $J = 3.2$, $J = 9.6$ Hz, H-3_I), 3.90 (1H, t, $J = 9.6$ Hz, H-4_I), 3.90–3.94 (2H, m, H-4_{II}, H-5_{II}), 3.95–4.02 (2H, m, H-5_I, $OCH_2CH{=}CH_2$), 4.14–4.18 (1H, m, $OCH_2CH{=}CH_2$), 4.23 (1H, dd, $J = 1.2$, $J = 3.2$ Hz, H-2_I), 4.51–4.53 (2H, m, H-1_{II}, OCH_2Ph), 4.59 (1H, d, $J = 11.2$ Hz), 4.70 (1H, d, $J = 10.8$ Hz), 4.74 (1H, d, $J = 10.8$ Hz), 4.78 (1H, d, $J = 10.8$ Hz), 4.90 (1H, d, $J = 10.4$ Hz), 5.06 (1H, d, $J = 10.4$ Hz), 5.15 (2H, s), (OCH_2Ph), 5.15 (1H, dt, $J = 0.8$, $J = 10.4$ Hz, $OCH_2CH{=}CH_2$), 5.27 (1H, dt, $J = 0.8$, $J = 17.2$ Hz, $OCH_2CH{=}CH_2$), 5.40 (1H, s, H-1_I), 5.84–5.94 (1H, m, $OCH_2CH{=}CH_2$), 7.11–7.39 (25H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.0 (q, SCH_2CH_3), 25.7 (t, SCH_2CH_3), 62.6 (t, C-6_I), 67.5 (t, CH_2Ph), 70.3 (t, $OCH_2CH{=}CH_2$), 72.2 (d, C-5_I), 74.7 (d, C-4_I), 74.9 (d, 2C, C-4_{II}, CH_2Ph) 75.2 (t, CH_2Ph), 75.4 (t, CH_2Ph), 75.9 (t, CH_2Ph), 76.4 (d, C-2_I), 78.3 (d, C-3_I), 78.9 (d, C-5_{II}), 81.2 (d, C-2_{II}), 82.2 (d, C-1_I), 84.1 (d, C-3_{II}), 102.6 (d, C-1_{II}), 118.0 (t, $OCH_2CH{=}CH_2$), 127.8 (d), 127.9 (d, 2C), 128.0 (d, 5C), 128.1 (d, 2C), 128.2 (d, 2C), 128.5 (d, 6C), 128.6 (d, 2C), 128.7 (d), 128.8 (d, 2C), 128.9 (d, 2C) (Ar-C), 134.8 (d, $OCH_2CH{=}CH_2$), 135.2, 138.0, 138.4, 138.5, 138.6 (5 × s) (Ar-C), 167.9 (s, C-6_{II}); HRMS (ESI): $[M+Na]^+$ calcd for $C_{52}H_{58}O_{11}S$, 913.3592; found 913.3624.

1.10. Ethyl benzyl (2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl)uronate-(1→2)-6-*O*-acetyl-3-*O*-allyl-4-*O*-benzyl-1-thio-α-D-mannopyranoside (9)

Ac_2O (1 mL, 10.6 mmol) was added at room temperature to a solution of **8** (48 mg, 0.054 mmol) in pyridine (10 mL), and the mixture was stirred overnight. The progress of the reaction was observed by TLC (toluene–EtOAc, 6:1). Then toluene (40 mL) and 1 M HCl (30 mL) were added, the organic layer was separated and washed with 1 M HCl (30 mL), saturated solution of $NaHCO_3$ (30 mL) and water (40 mL), dried and concentrated. Purification of the residue by silica gel chromatography (toluene–EtOAc, 12:1) afforded **9** (48 mg, 95%); $[\alpha]_D$ +28.8 (*c* 1.0, $CHCl_3$), lit.[2] +22; ^1H NMR (400 MHz, $CHCl_3$): δ 1.29 (3H, t, $J = 7.6$ Hz, SCH_2CH_3), 1.70 (3H, s, $COCH_3$), 2.59–2.70 (2H, m, SCH_2CH_3), 3.63–3.72 (2H, m, H-2_{II}, H-3_{II}), 3.81 (1H, dd, $J = 3.2$, $J = 9.2$ Hz, H-3_I), 3.89–4.02 (4H, m, H-4_I, H-5_I, H-4_{II}, $OCH_2CH{=}CH_2$), 4.16–4.29 (4H, m, H-2_I, H-6_I, H-5_{II}, $OCH_2CH{=}CH_2$), 4.38 (1H, dd, $J = 4.0$, $J = 12.0$ Hz, H-$6'_I$), 4.50–4.55 (2H, m, H-1_{II}, OCH_2Ph), 4.56 (1H, d, $J = 10.8$ Hz), 4.63 (1H, d, $J = 10.0$ Hz), 4.75 (1H, d, $J = 10.8$ Hz), 4.79 (1H, d, $J = 11.2$ Hz), 4.94 (1H, d, $J = 11.2$ Hz), (OCH_2Ph), 5.13–5.20 (2H, m, OCH_2Ph, $OCH_2CH{=}CH_2$), 5.16 (2H, s), (OCH_2Ph), 5.30 (1H, dt, $J = 1.2$, $J = 17.2$ Hz, $OCH_2CH{=}CH_2$), 5.41 (1H, s, H-1_I), 5.91 (1H, ddt, $J = 6.0$, $J = 10.4$, $J = 17.2$ Hz, $OCH_2CH{=}CH_2$), 7.11–7.42 (25H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.1 (q, SCH_2CH_3), 20.6 (q, $COCH_3$), 25.9 (t, SCH_2CH_3), 63.5 (t, C-6_I), 67.5 (t, CH_2Ph), 70.0 (d, C-5_I), 70.1 (t, $OCH_2CH{=}CH_2$), 74.1 (d), 74.8 (d), (C-4_I, C-4_{II}), 75.2 (t, 2C, CH_2Ph), 75.4 (t, CH_2Ph), 75.9 (t, CH_2Ph), 76.5 (d, C-2_I), 78.4 (d, C-3_I), 78.9 (d, C-5_{II}), 81.2 (d, C-2_{II}), 82.5 (d, C-1_I), 84.1 (d, C-3_{II}), 102.9 (d, C-1_{II}), 118.1 (t, $OCH_2CH{=}CH_2$), 127.8 (d), 127.9 (d, 3C), 128.1 (d, 2C), 128.2 (d, 3C), 128.5 (d, 9C), 128.7 (d, 3C), 128.9 (d, 2C), 129.2 (d, 2C) (Ar-C), 134.7 (d, $OCH_2CH{=}CH_2$), 135.1, 137.9, 138.0, 138.4, 138.6 (5 × s) (Ar-C), 167.9 (s, C-6_{II}), 170.8 (s, $COCH_3$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{54}H_{60}O_{12}S$, 955.3698; found, 955.3740.

1.11. Ethyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→2)-3-*O*-allyl-6-*O*-benzyl-1-thio-α-D-mannopyranoside (10)

To a mixture of **7** (931 mg, 1.00 mmol) and $NaCNBH_3$ (380 mg, 6.05 mmol) in THF (40 mL) containing crushed 3 Å molecular sieves (0.5 g) a solution of HCl in Et_2O was added (to pH 1–2) at room temperature. The progress of the reaction was followed by TLC (toluene–EtOAc, 6:1). After 2 h, Et_3N (4 mL) was added, the mixture was diluted with CH_2Cl_2 (150 mL), filtered through Celite, concentrated and purified by silica gel chromatography (toluene–EtOAc, 7:1) to yield **10** (730 mg, 78%); $[\alpha]_D$ +22.1 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (3H, t, $J = 7.6$ Hz, SCH_2CH_3), 2.39–2.54 (2H, m, SCH_2CH_3), 3.26 (1H, dd, $J = 6.8$, $J = 10.8$ Hz, H-6_I), 3.54–3.54 (2H, m, H-3_I, H-$6'_I$), 3.74 (1H, t, $J = 9.6$ Hz, H-4_I), 3.91–3.97 (2H, m, H-5_I, $OCH_2CH{=}CH_2$), 4.15–4.22 (3H, m, H-2_I, H-5_{II}, $OCH_2CH{=}CH_2$), 4.25 (2H, s, OCH_2Ph), 4.49 (1H, dd, $J = 5.6$, $J = 12.0$ Hz, H-6_{II}), 4.64 (1H, dd, $J = 2.8$, $J = 12.0$ Hz, H-$6'_{II}$), 4.95 (1H, d, $J = 8.0$ Hz, H-1_{II}), 5.06 (1H, br d, $J = 10.0$ Hz, $OCH_2CH{=}CH_2$), 5.22 (1H, dq, $J = 1.6$, $J = 17.2$ Hz, $OCH_2CH{=}CH_2$), 5.23 (1H, s, H-1_I), 5.59 (1H, dd, $J = 8.0$, $J = 9.6$ Hz, H-2_{II}), 5.65 (1H, t, $J = 10.4$ Hz, H-4_{II}), 5.79–5.89 (1H, m, $OCH_2CH{=}CH_2$), 5.91 (1H,

t, $J = 10.0$ Hz, H-3_{II}), 7.14–8.00 (25H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.8 (q, $SCH_2\mathit{C}H_3$), 25.4 (t, $S\mathit{C}H_2CH_3$), 63.4 (t, C-6_{II}), 68.0 (d, C-4_I), 69.8 (d, C-4_{II}), 69.9 (t, $O\mathit{C}H_2CH{=}CH_2$), 70.9 (t, C-6), 71.7 (d, C-5_I), 71.8 (d, C-2_{II}), 72.6 (d, C-5_{II}), 72.9 (d, C-3_{II}), 73.4 (t, $\mathit{C}H_2Ph$), 75.6 (d, C-2_I), 77.6 (d, C-3_I), 81.3 (d, C-1), 99.8 (d, C-1_{II}), 118.1 (t, $OCH_2CH{=}\mathit{C}H_2$), 127.5–129.9 (25C) (Ar-C), 133.1, 133.3, 133.4, 133.6 (4 × s, 4 × $CO\mathit{C}_6H_5$), 134.5 (d, $OCH_2\mathit{C}HCH_2$), 138.4 (s, Ar-C), 164.9, 165.3, 165.9, 166.2 (4 × s, 4 × $\mathit{C}OC_6H_5$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{52}H_{52}O_{14}S$, 955.2970; found, 955.2949.

1.12. Ethyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→2)-2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→4)-3-*O*-allyl-6-*O*-benzyl-1-thio-α-D-mannopyranoside (11)

Silver triflate (475 mg, 1.85 mmol) dissolved in dry toluene was added at −50 °C to a stirred mixture of 2,3,4-tri-*O*-benzoyl-D-xylopyranosyl bromide (971 mg, 1.85 mmol), **10** (690 mg, 0.74 mmol) and 2,6-di-*tert*-butylpyridine (330 μL, 1.48 mmol) in distilled CH_2Cl_2 (100 mL) containing crushed 4 Å molecular sieves (1.0 g). The temperature was allowed to go up to −20 °C. The progress of the reaction was followed by TLC (toluene–EtOAc, 3:1). After 3 h, Et_3N (1.5 mL) was added (pH 8), the mixture was diluted with CH_2Cl_2 (150 mL), filtered through Celite, concentrated and purified by silica gel chromatography (toluene–EtOAc, 22:1) to afford **11** (870 mg, 85%); $[\alpha]_D$ +22.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 4.91 (1H, d, $J = 6.5$ Hz, H-1_{III}), 4.99 (1H, d, $J = 8.0$ Hz, H-1_{II}), 5.20 (1H, d, $J = 2.4$ Hz, H-1_I); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.7 (q, $SCH_2\mathit{C}H_3$), 25.2 (t, $S\mathit{C}H_2CH_3$), 61.9 (t, C-5_{III}), 63.3 (t, C-6_{II}), 69.4 (t, C-6_I), 69.6 (d, C-4_{III}), 69.8 (d, C-4_{II}), 70.9 (t, $O\mathit{C}H_2CH{=}CH_2$), 71.3 (2C, 2 × d, C-2_{III}, C-3_{III}), 71.5 (d, C-5_I), 71.9 (d, C-2_{II}), 72.6 (d, C-5_{II}), 72.8 (t, $\mathit{C}H_2Ph$), 73.1 (d, C-3_{II}), 75.8 (d, C-4_I), 76.7 (d, C-2_I), 77.0 (d, C-3_I), 81.3 (d, C-1), 100.4 (d, C-1_{II}), 100.7 (d, C-1_{III}), 117.7 (t, $OCH_2CH{=}\mathit{C}H_2$), 127.4–130.0 (40C) (Ar-C), 133.0–133.6 (7C, 7 × s, 7 × $CO\mathit{C}_6H_5$), 134.9 (d, $OCH_2\mathit{C}HCH_2$), 138.7 (s, Ar-C), 164.9, 165.3 (2C), 165.6, 165.7, 166.0, 166.2 (7C, 7 × s, 4 × $\mathit{C}OC_6H_5$); HRMS (ESI): $[M+Na]^+$ calcd for $C_{52}H_{52}O_{14}S$, 955.2970; found, 955.2949.

1.13. Ethyl β-D-glucopyranosyl-(1→2)-β-D-xylopyranosyl-(1→4)-3-*O*-allyl-6-*O*-benzyl-1-thio-α-D-mannopyranoside (12)

Compound **11** (860 mg, 0.62 mmol) was dissolved in dry MeOH (48 mL), 1 M methanolic NaOMe (0.7 mL) was added and the mixture was stirred overnight at room temperature. The progress of the reaction was followed by TLC (CH_2Cl_2–MeOH 9:1). Next, acetic acid (20 drops) was added, the stirring was continued for 30 min, then the mixture was concentrated and purified by silica gel chromatography (CH_2Cl_2–MeOH, 9:1) to give **12** (322 mg, 80%); $[\alpha]_D$ +5.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO): δ 4.20 (1H, d, $J = 7.6$ Hz, H-1_{III}), 4.31 (1H, d, $J = 7.6$ Hz, H-1_{II}), 5.39 (1H, s, H-1_I); ^{13}C NMR (100.6 MHz, DMSO): δ 14.9 (q, $SCH_2\mathit{C}H_3$), 24.6 (t, $S\mathit{C}H_2CH_3$), 61.4 (t, C-5_{III}), 65.8 (t, C-6_{II}), 68.8 (t, C-6_I), 69.6 (d, C-5_I), 70.0 (t, $O\mathit{C}H_2CH{=}CH_2$), 70.1 (d), 71.7 (d), 72.1 (t, $\mathit{C}H_2Ph$), 72.9 (d, C-2_{III}), 73.7 (d, C-2_{II}), 74.2 (d, C-4_I), 74.7 (d, C-2_I), 76.6 (d, C-3_I), 76.6 (2C, 2 × d), 77.2 (d), 81.8 (d, C-1), 101.4 (d, C-1_{II}), 103.8 (d, C-1_{III}), 116.4 (t, $OCH_2CH{=}\mathit{C}H_2$), 127.3 (d), 127.4 (2C, 2 × d), 128.2 (2C, 2 × d) (Ar-C), 135.5 (d, $OCH_2\mathit{C}HCH_2$), 138.6 (s, Ar-C); HRMS (ESI): $[M+Na]^+$ calcd for $C_{78}H_{72}O_{21}S$, 1399.4179; found, 1399.4151.

1.14. Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-β-D-glucopyranosyl-(1→2)-2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→4)-3-*O*-allyl-6-*O*-benzyl-1-thio-α-D-mannopyranoside (14)

Compound **12** (650 mg, 1.0 mmol) was dissolved in dry pyridine (10 mL), trityl chloride (670 mg, 2.4 mmol) and *N*,*N*-dimethylaminopyridine (24 mg, 0.2 mmol) were added and the mixture was stirred at 70 °C for 4 h. The progress of the reaction was followed by TLC (CH_2Cl_2–MeOH, 9:1). Then the mixture was concentrated and purified by silica gel chromatography (CH_2Cl_2–MeOH, 10:1) to yield ethyl 6-*O*-trityl-β-D-glucopyranosyl-(1→2)-β-D-xylopyranosyl-(1→4)-3-*O*-allyl-6-*O*-benzyl-1-thio-α-D-mannopyranoside (**13**, 580 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.44 (1H, d, $J = 7.2$ Hz, H-1_{III}), 4.44 (1H, d, $J = 7.2$ Hz, H-1_{II}), 5.36 (1H, br s, H-1_I); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.2 (q, $SCH_2\mathit{C}H_3$), 25.9 (t, $S\mathit{C}H_2CH_3$), 63.9 (t, C-5_{III}), 65.6 (t, C-6_{II}), 69.1 (t, C-6_I), 69.8 (d, C-5_I), 71.4 (d), 71.8 (2C, 2 × d), 71.8 (t, $O\mathit{C}H_2CH{=}CH_2$), 73.5 (d, C-2_{III}), 73.6 (d, C-2_I), 73.8 (t, $\mathit{C}H_2Ph$), 74.2 (d), 74.8 (d), 76.1 (d), 76.3 (d), 77.3 (d, C-3_I), 83.3 (d, C-1), 87.2 (s, CPh_3), 100.7 (d, C-1_{II}), 103.4 (d, C-1_{III}), 119.2 (t, $OCH_2CH{=}\mathit{C}H_2$), 127.4 (4C, 4 × d), 128.1 (6C, 6 × d), 128.2 (2C, 2 × d), 128.6 (2C, 2 × d), 128.8 (6C, 6 × d) (Ar-C), 134.0 (d, $OCH_2\mathit{C}HCH_2$), 137.8 (s), 143.7 (s) (Ar-C).

A 60% oil dispersion of sodium hydride (160 mg, 4.00 mmol) was added at room temperature to a solution of **13** (360 mg, 0.40 mmol) and benzyl bromide (480 μL, 4.00 mmol) in DMF (15 mL) and the reaction mixture was stirred overnight. The progress of the reaction was followed by TLC (toluene–EtOAc, 6:1). When the reaction was complete, MeOH (1 mL) was carefully added and the mixture was diluted with toluene (100 mL), washed with water (2 × 50 mL), dried and concentrated. Purification on a silica gel column (toluene–EtOAc, 25:1) gave **14** (530 mg, 92%); $[\alpha]_D$ +24.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): 4.43 (1H,

d, $J = 7.6$ Hz, H-1_{III}), 4.56 (1H, d, $J = 7.2$ Hz, H-1_{II}), 5.51 (1H, s, H-1_I); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.2 (q, SCH_2CH_3), 25.7 (t, SCH_2CH_3), 63.2 (t, C-5_{III}), 63.8 (t, C-6_{II}), 69.1 (t, C-6_I), 70.8 (t, $OCH_2CH{=}CH_2$), 72.0 (d), 73.0 (t, CH_2Ph), 73.2 (t, CH_2Ph), 74.1 (t, CH_2Ph), 75.0 (t, CH_2Ph), 75.1 (t, CH_2Ph), 75.2 (d), 75.3 (d), 75.6 (t, CH_2Ph), 75.8 (t, CH_2Ph), 75.8 (d, C-3_I), 76.0 (d, C-2_I), 78.0 (d, C-3_{III}), 78.3 (d), 81.7 (d), 81.9 (d, C-1_I), 82.5 (d, C-2_{III}), 84.3 (d), 85.1 (d), 86.7 (s, CPh_3), 101.9 (d, C-1_{II}), 103.4 (d, C-1_{III}), 117.4 (t, $OCH_2CH{=}CH_2$), 126.3–129.2 (50C, 50 × d) (Ar-C), 135.1 (d, OCH_2CHCH_2), 137.9 (s), 138.4 (s), 138.5 (s), 138.8 (2C, 2 × s), 138.9 (2C, 2 × s), 144.0 (3C, 3 × s) (Ar-C); HRMS (ESI): $[M+Na]^+$ calcd for $C_{48}H_{58}O_{14}S$, 913.3439; found, 913.3473.

1.15. Ethyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→2)-2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→4)-3-*O*-allyl-6-*O*-benzyl-1-thio-α-D-mannopyranoside (15)

Compound **14** (60 mg, 0.04 mmol) was dissolved in $CHCl_3$–MeOH (2:1, 6 mL), *p*-TsOH (2 mg, 0.01 mmol) was added and the mixture was stirred at room temperature overnight. The progress of the reaction was followed by TLC (toluene–EtOAc, 6:1). Then the mixture was diluted with $CHCl_3$ (10 mL), washed with saturated solution of $NaHCO_3$ (5 mL), water (10 mL), dried, concentrated and purified by silica gel chromatography (toluene–EtOAc, 10:1) to yield **15** (36 mg, 72%); $[\alpha]_D$ +31.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.43 (1H, d, $J = 7.6$ Hz, H-1_{III}), 4.51 (1H, d, $J = 7.6$ Hz, H-1_{II}), 5.38 (1H, s, H-1_I); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.1 (q, SCH_2CH_3), 25.6 (t, SCH_2CH_3), 62.3 (t, C-5_{III}), 63.9 (t, C-6_{II}), 69.0 (t, C-6_I), 71.8 (t, $OCH_2CH{=}CH_2$), 72.2 (d), 73.0 (d), 73.1 (t, CH_2Ph), 73.3 (t, CH_2Ph), 75.1 (t, CH_2Ph), 75.2 (2C, 2 × t, 2 × CH_2Ph), 75.5 (d, C-5_I), 75.6 (t, CH_2Ph), 75.8 (t, CH_2Ph), 77.2 (d, C-3_I), 77.6 (d), 78.0 (d, C-2_I), 78.3 (d, C-4_{III}), 81.8 (d), 82.4 (d, C-1_I), 82.4 (d, C-2_{III}), 84.3 (d, C-3_{III}), 84.7 (d), 103.2 (d, C-1_{II}), 103.8 (d, C-1_{III}), 116.7 (t, $OCH_2CH{=}CH_2$), 126.4–130.6 (35C, 35 × d) (Ar-C), 135.5 (d, OCH_2CHCH_2), 138.1 (s), 138.4 (2C, 2 × s), 138.6 (s), 138.7 (s), 138.8 (2C, 2 × s) (Ar-C); HRMS (ESI): $[M+Na]^+$, calcd for $C_{90}H_{94}O_{14}S$, 1453.6256; found 1453.6279.

1.16. Ethyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranosyluronic acid-(1→2)-2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→4)-3-*O*-allyl-6-*O*-benzyl-1-thio-α-D-mannopyranoside (16)

To a mixture of **15** (36 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) and water (1 mL), BAIB (24 mg, 0.08 mmol) and TEMPO (5 mg, 0.03 mmol) were added and the mixture was stirred at room temperature. The same amount of BAIB and TEMPO was added after 2 h, and after 4 h. The progress of the reaction was followed by TLC (toluene–EtOAc, 6:1). Then the mixture was diluted with CH_2Cl_2 (20 mL), washed with water (10 mL), dried, concentrated and purified by silica gel chromatography (hexane–EtOAc–HOAc, 14:7:1) to yield **16** (30 mg, 83%); $[\alpha]_D$ +46.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.42 (1H, d, $J = 7.6$ Hz, H-1_{III}), 4.65 (1H, d, $J = 8.0$ Hz, H-1_{II}), 5.35 (1H, s, H-1_I); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.0 (q, SCH_2CH_3), 25.5 (t, SCH_2CH_3), 63.8 (t, C-5_{III}), 68.6 (t, C-6_I), 72.3 (t, $OCH_2CH{=}CH_2$), 72.2 (d, C-5_I), 73.1 (2C, 2 × t, 2 × CH_2Ph), 74.4 (t, CH_2Ph), 75.1 (2C, 2 × t, 2 x CH_2Ph), 75.2 (t, CH_2Ph), 75.6 (t, CH_2Ph), 76.7 (d, C-4_I), 76.7 (d, C-4_{III}), 77.0 (d), 78.3 (d, C-3_I), 78.8 (d), 79.6 (d, C-4_{II}), 80.3 (d, C-2_{II}), 82.4 (d, C-1_I), 82.4 (d, C-2_{III}), 83.1 (d, C-3_{II}), 84.2 (d, C-3_{III}), 102.9 (d, C-1_{II}), 103.5 (d, C-1_{III}), 117.8 (t, $OCH_2CH{=}CH_2$), 128.8–127.5 (35C, 35 × d) (Ar-C), 134.7 (d, OCH_2CHCH_2), 137.6 (s), 138.2 (s), 138.3 (2C, 2 × s), 138.4 (s), 138.7 (s), 138.8 (s) (Ar-C), 170.2 (s, C-6_{II}); HRMS (ESI): $[M+Na]^+$ calcd for $C_{71}H_{78}O_{15}S$, 1225.4954; found, 1225.4962.

1.17. Ethyl benzyl (2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl)uronate-(1→2)-2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→4)-3-*O*-allyl-6-*O*-benzyl-1-thio-α-D-mannopyranoside (17)

A solution of **16** (30 mg, 0.025 mmol) in EtOAc (6 mL) was titrated with $PhCHN_2$[†] (0.3 M solution in Et_2O, 3 mL, 0.9 mmol) at room temperature until full conversion was observed by TLC (toluene–EtOAc, 6:1). After 2 h, the reaction was concentrated and purified by silica gel chromatography (toluene–EtOAc, 20:1) to yield **17** (16 mg, 49%); $[\alpha]_D$ +37.9 (*c* 1.0, $CHCl_3$), lit.[2] +27; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.44 (1H, d, $J = 8.0$ Hz, H-1_{III}), 4.47 (1H, d, $J = 8.8$ Hz, H-1_{II}), 5.20 (1H, d, $J = 1.6$ Hz, H-1_I); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 15.1 (q, SCH_2CH_3), 25.7 (t, SCH_2CH_3), 63.9 (t, C-5_{III}), 67.4 (t, CH_2Ph), 69.1 (t, C-6_I), 70.8 (t, $OCH_2CH{=}CH_2$), 71.9 (d), 73.0 (t, CH_2Ph), 73.2 (t, CH_2Ph), 74.6 (d, C-4_I), 74.9 (d), 75.1 (t, CH_2Ph), 75.2 (2C, 2 × t, 2 × CH_2Ph), 75.6 (t, CH_2Ph), 75.8 (t, CH_2Ph), 76.4 (d, C-3_I), 76.7 (d, C-2_I), 78.4 (d), 78.9 (d), 81.1 (d), 82.0 (d, C-1_I), 82.5 (d, C-2_{III}), 84.2 (d), 84.4 (d, C-3_{III}), 102.7 (d, C-1_{II}), 103.4 (d, C-1_{III}), 117.1 (t, $OCH_2CH{=}CH_2$), 129.3–127.4 (40C, 40 × d) (Ar-C), 135.3 (d, OCH_2CHCH_2), 137.9 (s), 138.1 (s), 138.4 (s), 138.5 (2C, 2 × s), 138.7 (s), 138.8 (s), 138.9 (s) (Ar-C), 168.0 (s, C-6_{II}).

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