Organic & Biomolecular Chemistry

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ARTICLE

A synthetic strategy to xylose-containing thioglycoside tri- and tetrasaccharide building blocks corresponding to *Cryptococcus neoformans* capsular polysaccharide structures

Cite this: DOI: 10.1039/x0xx00000x

Received 00th December 2014,
Accepted 00th January 2015

DOI: 10.1039/x0xx00000x

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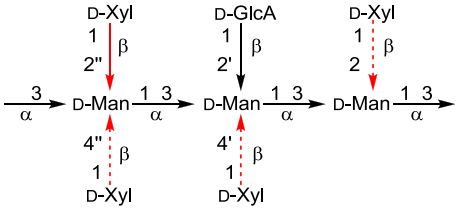
As part of an ongoing project aimed at developing vaccine candidates against *Cryptococcus neoformans* the preparation of tri- and tetrasaccharide thioglycoside building blocks, to be used in construction of structurally defined part structures of *C. neoformans* GXM capsular polysaccharide, was investigated. Using a naphtalenylmethyl (NAP) ether as a temporary protecting group and trichloracetimidate donors in optimized glycosylations the target building blocks, ethyl 6-*O*-acetyl-2,4-di-*O*-benzyl-3-*O*-(2-naphtalenylmethyl)-α-D-mannopyranosyl-(1→3)-[2,3,4-tri-O-benzyl-β-D-xylopyranosyl-(1→2)]-4,6-di-*O*-benzyl-1-thio-α-D-mannopyranoside (**16**) and ethyl 2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)-4,6-di-*O*-benzyl-3-*O*-(2-naphtalenylmethyl)-α-D-mannopyranosyl-(1→3)-[2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)]-6-*O*-acetyl-4-*O*-benzyl-1-thio-α-D-mannopyranoside (**21**), were efficiently prepared. These synthesized thiosaccharide building blocks were then used as donors in high-yielding (~90%) DMTST promoted glycosylations to a spacer-containing acceptor to, after deprotection, afford GXM polysaccharide part structures ready for protein conjugation to give vaccine candidates. Also, the NAP groups in the building blocks were removed to obtain tri- and tetrasaccharide acceptors suitable for further elongation towards larger thiosaccharide building blocks.

Introduction

Cryptococcus neoformans is a fungal pathogen causing severe infections in immunocompromised individuals, e.g., it is now the most prevalent infection in AIDS-patients in Africa.[1] The discovery that monoclonal antibodies (mAbs) can protect against cryptococcal infections in mice encouraged the development of vaccines against the infection.[2-5] *Cryptococcus neoformans* is surrounded by capsular polysaccharides, of which the major one is the GXM-polysaccharide containing glucuronic acid, xylose and mannose residues, and vaccines candidates have been preferentially based on these structures. The polysaccharides themselves, in contrast to most bacterial polysaccharides, are not immunogenic, but glycoconjugate vaccines composed of the polysaccharide linked to a carrier protein have been tested and proven promising.[6,7] However, the discovery that the polysaccharide contained epitopes that could elicit both protective, non-protective and even disease-enhancing antibodies[2,3] raised serious concerns about employing whole polysaccharide in such conjugate vaccines. Consequently, a new approach of using synthetic oligosaccharides is attractive since it includes the possibility to focus the antibody response on epitopes that elicit protective immunity.[4,5] Such synthetic structures would provide unique tools to investigate the structure-activity relationship (SAR) between the immune response and specific GXM structures and to investigate the epitope specificity of protective and non-protective mAbs. Structural analysis indicates that GXM are heteropolymers comprised of different triads linked together (Fig. 1),[8] why the GXM polysaccharide is highly variable and heterogeneous and can't be used in SAR studies. Given this complexity of the GXM and that there are no enzymes available to regioselectively cleave GXM, synthetic structures provide the only means for the planned studies. The aim is to explore the hypothesis that it is possible to focus an immune response to make only protective antibodies. We have already established the converse, that certain oligosaccharides can focus the response to non-protective antibodies.[9,10,11] There is evidence that some protective epitopes are conformational.[12] Hence, synthesizing longer oligosaccharides that can attain conformations like those found in the native polysaccharide is a major target. To efficiently perform these syntheses, larger building blocks than the disaccharides we have so far been using are desired. Herein we describe the development of a strategy that allows construction of larger donor structures and its application to the synthesis of xylose-containing tri- and tetrasaccharide thioglycoside building blocks and their subsequent transformation into acceptors as well as their use as donors in synthesis of spacer-containing tetra-and pentasaccharide GXM part structures.



Xylose substitution

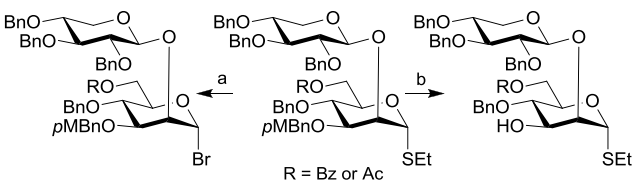
Serotype	2	2"	4'	4"
A	X	X		
B	X	X	X	
C	X	X	X	X
D		X		

Figure 1. Suggested structures of *C. neoformans* GXM serotype triads

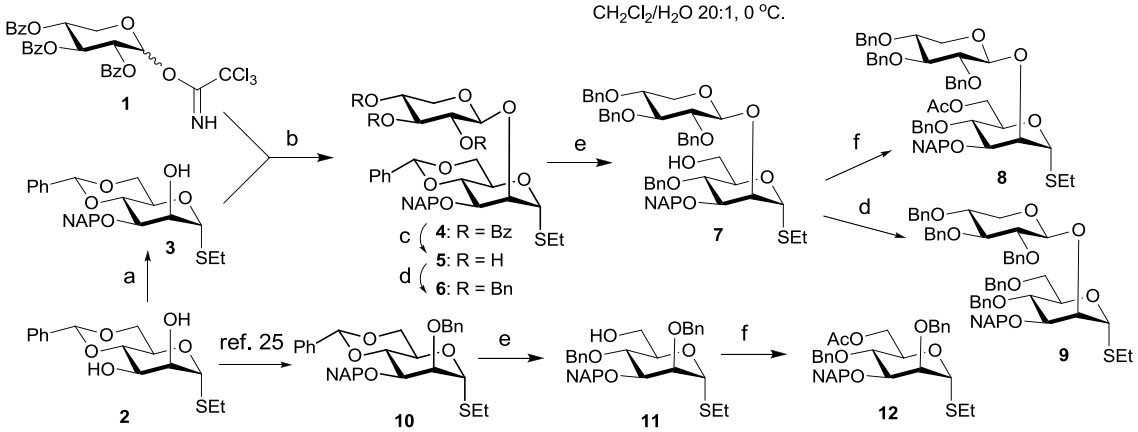
Results and discussion

As mentioned in the introduction the structure of the GXM is believed to be built up of triads, i.e., substituted trisaccharide mannans, as depicted in Fig 1, and the serotyping depending on the amount of xylose substituents. GXM is also heterogeneously acetylated. The acetylation is crucial for virulence, knock-out mutants that can't introduce the acetates are not virulent.[13] The acetates are positioned at the 6-OH of the mannose backbone but not present in the residues carrying 4-*O*-xylose substitutions and in serotype A and D there are about 2 acetates per mannose triad. Serotype A and D are the most prevalent in humans and these structures (both without 4-*O*-xylose substitutions) are therefore our primary targets. The A/D donor building blocks, synthesized and used in vaccine candidate syntheses, so far have been ethyl thioglycosides with benzyl ethers and esters as permanent protecting groups, and a 3-*O*-allyl group as a temporary protecting group.[14-16] This approach has worked well and allowed efficient synthesis of up to heptasaccharide structures with variant acetylation patterns.[9] However, when these blocks were to be combined to yield larger thioglycoside structures through orthogonal glycosylations, issues were encountered with the allyl protecting group. The unsaturated allyl function precluded the transformation of the thioglycoside into a bromo sugar donor using bromine and, more unexpectedly, problems were experienced in the removal of the allyl group to create a thioglycoside acceptor. Many deallylation methods were tested, but the yields in the rearrangement reaction to give the enol ether were poor. Various catalysts, e.g. $PdCl_2$ and Wilkinson's catalyst, that had been successful with O-glycoside substrates, failed with the thioglycoside. Our own methodology using SmI_2,[17] which earlier had worked well on thioglycosides, also proved unsuccessful. Performing the rearrangement with a strong base finally afforded the 3-OH acceptor but only in a moderate yield (~40%). These experiences forced us to develop a new strategy including a more suitable temporary protecting group. Before the selection of the allyl group, other protecting groups had been tested, mainly a TBDMS group and a *p*-methoxybenzyl (*p*MBn) group, but both these were found to be inferior to the allyl group, the TBDMS group due to problems with migration as well as low yields in glycosylation and benzylidene opening reactions and the *p*MBn groups due to its acid lability.[18] However, since there is not that many good temporary protecting groups and most acyl protecting groups are not compatible with the presence of acetates in the target structures, routes using the TBDMS and the *p*MBn groups were revisited. Again the TBDMS group was found to give low yields in a number of reactions but the problem with the acid lability of the *p*MBn group could be overcome, at least in most reactions.

Hence, 3-*O*-*p*MBn protected disaccharide building blocks could be prepared in a five-step synthesis starting from benzobromoxylose and ethyl 4,6-*O*-benzylidene-3-*O*-(4-methoxybenzyl)-1-thio-α-D-mannopyranoside[19] in around an overall yield of 35%.[20] These could then be effectively converted to bromosugar donors or 3-OH acceptors through treatment with Br_2 or DDQ, respectively (Scheme 1).[20]



Scheme 1. Reagents and conditions: (a) Br_2, CH_2Cl_2, 0 °C; (b) DDQ, CH_2Cl_2/H_2O 20:1, 0 °C.



Scheme 2. Reagents and conditions: (a) Bu_2SnO, Bu_4NI, NAPBr, toluene, reflux 88%; (b) TBDMSOTf, CH_2Cl_2, AW-300 MS ,-78 °C to 20 °C, overnight, 86%; (c) NaOMe, MeOH, 20 °C, 88%; (d) NaH, BnBr, DMF, 0 °C to 20 °C, 88% for **6**, 99% for **9**; (e) Bu_2BOTf, BH_3 (1 M in THF), 94% for **7**, 84% for **11**; (f) Ac_2O, pyridine, 20 °C, 98% for **8**, 96% for **12**.

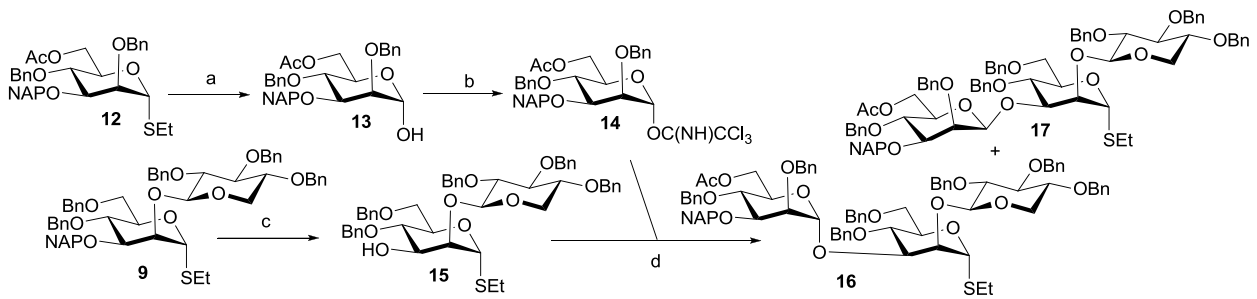
However, when these acceptors and donors were tested in orthogonal glycosylation reactions the yields were again low. Not only hydrolysis of the *p*MBn ether was again a problem but also hydrolysis of the glycosyl bromide was observed. With these reoccurring problems with the *p*-methoxybenzyl group, our attention was turned to the 2-naphtalenylmethyl (NAP) group, which is removed like the *p*-methoxybenzyl group by DDQ or CAN treatment but considered to be more acid stable.[21] We recently used this protecting group in the synthesis of glucuronic acid containing disaccharide GXM building blocks.[22] The NAP group was introduced regioselectively on **2**[23] by known tin activation methodology[24] in an 88% yield (Scheme 2). The coupling of **1**[25] and **3** was then carried out using TBDMSOTf in the presence of commercial acid-washed molecular sieves to prevent orthoester formation. Compound **4** was obtained in an 86% yield. At this stage benzoyl groups, which ensured the stereoselective course of the glycosylation, were exchanged for benzyl groups affording **6** in a 77% yield over two steps. The regioselective opening of the benzylidene ring using Bu_2BOTf/BH_3[25] afforded compound **7** (94%), which was either acetylated (→**8**, 98%) or benzylated (→**9**, 99%). The monosaccharide building block **12,** required for the construction of serotype D structures, was prepared from **10**[27] by opening of the benzylidene ring, employing the same conditions used for **7** (→**11**, 84%) followed by acetylation (→**12**, 96%).

From this set of mono- and disaccharide building blocks the synthesis of the target tri- and tetrasaccharide building blocks, **16** (serotype D) and **21** (serotype A), respectively, was now attempted. The same strategy was used for both serotypes (reported in Scheme 3 and 4) and involves two steps prior to the glycosylation reaction: 1) preparation of the thioglycoside acceptor by removing the orthogonal protecting group; and 2) conversion of the thioglycoside donor into a suitable one for the orthogonal glycosylation.

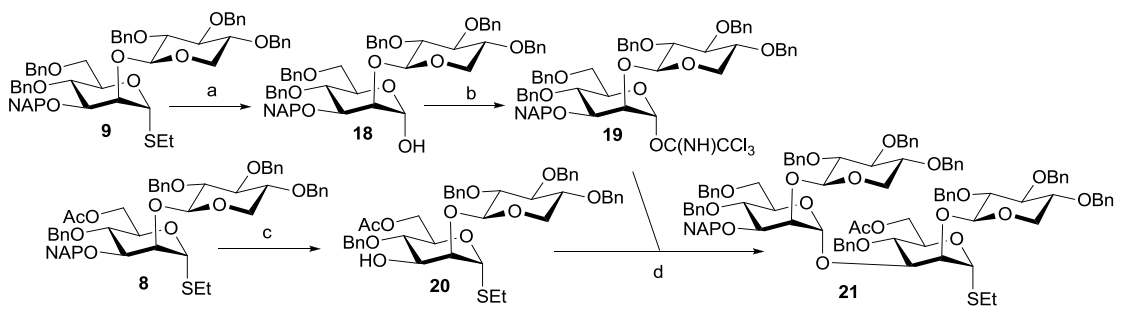
Acceptors **15** and **20** were obtained by removing the NAP group with DDQ in a mixture of CH_2Cl_2/H_2O or CH_2Cl_2/*t*-BuOH. This second solvent system gave slightly better yields (75% and 70% respectively) and reduced the benzyl removal side reaction which has been reported by Crich and Yao.[28]

Considering our earlier experiences with the orthogonal silver triflate-promoted glycosylations using the *p*MBn-protected bromo sugar donors, where major side products were due to hydrolysis of the glycosyl bromide in addition to the *p*MBn group, we decided to try trichloroacetimidates as glycosyl donors instead. The imidate donors were obtained from **9** and **12** after hydrolysis of the thioethyl glycoside with NIS and trifluoroacetic acid in a vigorously stirred CH_2Cl_2/H_2O mixture and subsequent activation of the anomeric position (DBU, Cl_3CCN in CH_2Cl_2).

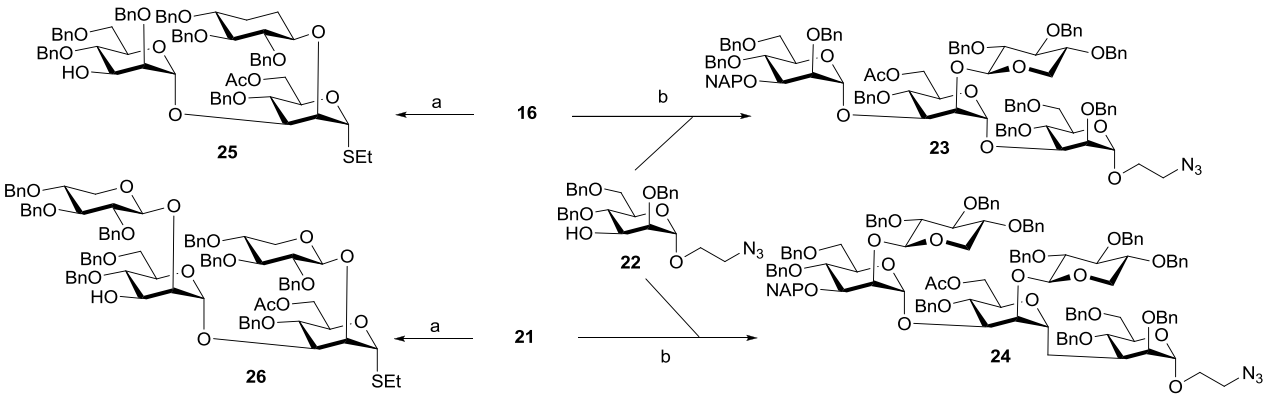
Initially, couplings with the new trichloroacetimidate donors **14** and **19** proceeded in very low yields (Schemes 2 and 3). Optimizing the conditions for tetrasaccharide **21**, catalysts TMSOTf and TBDMSOTf were found to be the best, but in CH_2Cl_2 they still produced **21** in a maximum yield of only 25%. Changing the solvent to either diethyl ether or acetonitrile gave no product at all, but when toluene was tried (at -20 ºC) a better yield was obtained (~50%). Further optimization established that employing the inverse glycosylation procedure[29] to these couplings, i.e., adding the donor to a premix of the acceptor and the promoter, was a most high-yielding and reliable methodology to the target structures. Tetrasaccharide **21** was reproducibly obtained in over 90% yield from acceptor **20** and donor **19** (1.2 equiv.). In the synthesis of the trisaccharide **16** a



Scheme 3. Reagents and conditions: (a) NIS, TFA, CH_2Cl_2/H_2O (20:1), 0 °C, 1 h, 86% (α/β = 9:1); (b) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 90 min, 90%; (c) DDQ, CH_2Cl_2/H_2O (10:1), 3.5 h min, 65% or DDQ, CH_2Cl_2/t-BuOH (10:1), 90 min, 75%; (d) TMSOTf, toluene, AW-300 MS, -20 °C, **16**:**17** = 65%:18% or TMSOTf, toluene, AW-300 MS, rt, **16**:**17** = 75%:9%.



Scheme 4. Reagents and conditions: (a) NIS, TFA, CH_2Cl_2/H_2O (20:1), 0 °C, 90 min, 85% (α/β = 5:1); (b) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 90 min, quant.; (c) DDQ, CH_2Cl_2/H_2O (20:1), 90 min, 70%; (d) TBDMSOTf, toluene, AW-300 MS ,-40 °C, 95%.

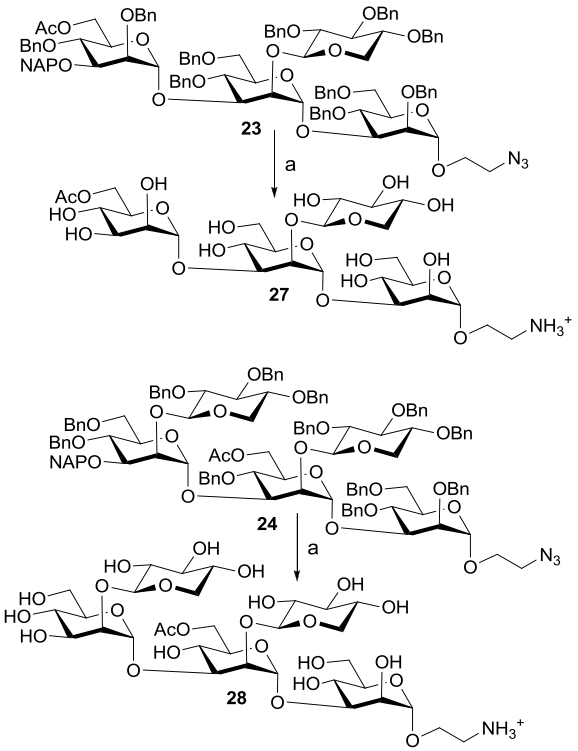


Scheme 5. Reagents and conditions: (a) DDQ, CH_2Cl_2/H_2O or t-BuOH (10:1), 72% for **25**, 68% for **26;** (b) DMTST, Et_2O, MS 4 Å, 0 °C to 20 °C, 89% for **23**, 92% for **24**..

3.5:1 α/β-mixture was obtained in an 83% yield using the same conditions. The anomeric configurations were unambiguously confirmed by the ^{1}H-^{13}C ^1J coupling constant value (**16**, $J_{C1'\text{-}H1'}$ = 175 Hz; **17**, $J_{C1'\text{-}H1'}$ = 155 Hz). Higher α-selectivity, 8:1 (84% yield), was obtained running the glycosylation reaction at room temperature instead of at -20 °C. Similar temperature effects on the stereoselectivity of glycosylations have been reported.[30]

The new thiosaccharide building blocks **16** and **21** were then tested as donors in dimethyl(methylthio)sulfonium triflate (DMTST)[31] promoted glycosylations with acceptor **22**[14] (Scheme 5). Both glycosylations proceeded with complete α-stereoselectivity and derivatives **23** and **24** were obtained in 89% and 92% yield respectively.

Also, compounds **16** and **21** were converted, through DDQ-based removal of the NAP group, to two new 3-OH acceptors (Scheme 5), the trisaccharide **25** (72%) and the tetrasaccharide **26** (68%), to allow continued synthesis of even larger thioglycoside building blocks. Compounds **23** and **24** were completely deprotected by means of hydrogenolysis to afford spacer-equipped GXM part structures **27** and **28** in a 72% and a 69% yield respectively (Scheme 6).



Scheme 6. Reagents and conditions: (a) H_2/Pd-C (30 bar), EtOAC, H_2O, AcOH, 72% for **27**, 69% for **28**.

Conclusions

In conclusion, an efficient and reliable strategy to tri- and tetrasaccharide thioglycoside building blocks corresponding to *Cryptococcus neoformans* GXM oligosaccharide structures has been developed. The introduction of a 2-naphtalenylmethyl ether as a temporary protecting group allowed efficient transformation of synthesized thioglycoside mono- and disaccharides into both 3-OH acceptors and other types of glycosyl donors. Use of trichloroacetimidate donors in couplings employing the inverse glycosylation protocol with TBDMOTf or TMSOTf as promoters in toluene was found to be an efficient methodology to construct tri- and tetrasaccharide thioglycoside building blocks, which can be converted into even larger building blocks by reiteration of the developed approach. The synthesized thioglycoside building blocks were shown to be excellent donors in model glycosylation reactions proceeding with complete α-selectivity in ~90% yield and were also effectively transformed into acceptor structures.

Experimental Section

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) sulphate, 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 d = 0.00 ppm) or D_2O (standardized against the residual solvent peak, d = 4.79) at 25 °C on a Varian instrument (500 MHz for ^{1}H and 125 MHz for ^{13}C or 600 MHz for ^{1}H and 150 MHz for ^{13}C). Coupling constants are given in Hertz (Hz). HRMS spectra were recorded on a micromass LCT

instrument using electrospray ionisation (ESI) in either the positive or negative modes. Optical rotations were measured with a Perkin-Elmer 343 polarimeter at the sodium D-line (589 nm) at 20 °C using a 1 dm cell. All reactions containing air- and moisture-sensitive reagents were carried out under an argon atmosphere. Organic phases were dried over $MgSO_4$ before evaporation, which was performed under reduced pressure at temperatures not exceeding 40 °C.

Ethyl 4,6-*O*-benzylidene-3-*O*-(2-naphtalenylmethyl)-1-thio-α-D-mannopyranoside (3)

A solution of compound **2** (13.00 g, 41.62 mmol) and $(Bu)_2SnO$ (13.98 g, 56.18 mmol) in anhydrous toluene (420 mL) was heated under reflux with continuous removal of water (Dean-Stark trap). After 3 h, the mixture was concentrated to half-volume, $(Bu)_4NI$ (20.75 g, 56.18 mmol) and NAPBr (10.12 g, 45.77 mmol) were added, and the reaction mixture was refluxed for another 3 h (TLC, toluene/EtOAc, 1:3). The reaction mixture was diluted with EtOAc (400 mL), and the organic layer was washed sequentially with H_2O (3 × 300 mL), 10% aq. KF-solution (3 × 300 mL) and brine (1 × 300 mL), dried over $MgSO_4$, and concentrated *in vacuo* to an orange oily residue. Purification by flash column chromatography (SiO_2, 350 mL, 7.5 cm, pentane → pentane-Et_2O, 3:1→2:1→1:1→1:2→1:3) gave **3** (16.66 g, 88%) as a pale yellow syrup; R_f 0.50 (toluene/EtOAc 3:1); $[\alpha]^{20}_D$ +143.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82-7.71 (m, 4H, Ar-H), 7.51-7.36 (m, 8H, Ar-H), 5.62 (s, 1H), 5.37 (s, 1H), 4.98 (benzylic d, 1H, J_{gem} = 11.5 Hz), 4.87 (benzylic d, 1H, J_{gem} = 11.5 H), 4.25-4.21 (m, 2H), 4.19-4.15 (m, 2H), 3.96-3.93 (dd, 1H, *J* = 3.5 Hz, *J* = 9.5 Hz), 3.88 (m, 1H), 2.87 (s, 1H), 2.66-2.53 (m, 2H,), 1.27 (t, 3H, SCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.5, 135.2, 133.2, 133.1, 128.9, 128.3, 128.2, 127.9, 127.7, 126.6, 126.1, 126.0, 125.6, 101.7, 84.2, 79.1, 75.9, 73.0, 71.4, 68.7, 63.8, 24.9, 14.8. HRMS (ESI): $[M+Na]^+$ Calcd for $C_{26}H_{28}O_5NaS$, 475.1555. Found: 475.1534; Anal. Calcd for $C_{26}H_{28}O_5S$: C, 69.00; H, 6.24; S, 7.09. Found: C, 68.93; H, 6.06; S, 7.34 %.

Ethyl 2,3,4-tri-*O*-benzoyl-β-D-xylopyranosyl-(1→2)-4,6-*O*-benzylidene-3-*O*-(2-naphtalenylmethyl)-1-thio-α-D-mannopyranoside (4)

A catalytic amount of TBDMSOTf (450 μL, 1.96 mmol) was added to a solution of donor **1** (11.90 g, 19.62 mmol) and acceptor **3** (8.88 g, 19.62 mmol) in dry CH_2Cl_2 (250 mL) containing crushed acid-washed molecular sieves (Aldrich AW-300) kept at -78 °C in an atmosphere of nitrogen. The temperature was allowed to rise to 20 °C overnight (TLC, toluene/EtOAc 6:1). The reaction mixture was neutralised with Et_3N (1.64 mL, 11.77 mmol), the solids were removed by filtration, and the filtrate was concentrated *in vacuo* to a yellowish foam. Purification by flash column chromatography (SiO_2, 400 mL, 7.5cm, toluene/EtOAc, 98:2→96:4→94:6→92:8→90:10→88:12→ 86:14) gave **4** (15.09 g, 86%) as a colourless amorphous solid; R_f 0.58 (toluene/EtOAc 9:1); $[\alpha]^{20}_D$ −0.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (m, 2H), 8.07 (m, 2H, Ar-H), 7.98 (m, 2H, Ar-H), 7.86 (m, 1H, Ar-H), 7.81-7.79 (m, 2H, Ar-H), 7.71-7.70 (m, 1H, Ar-H), 7.58-7.36 (m, 15H, Ar-H), 7.28-7.25 (m, 2H, Ar-H), 5.63 (t, 1H, *J* = 4.0 Hz), 5.36 (t, 1H, *J* = 3.0 Hz), 5.32 (s, 1H), 5.15 (d, 1H, *J* = 1.5 Hz), 5.10 (m, 2H), 5.04 (benzylic d, 1H, J_{gem} = 12.4 Hz), 4.98 (benzylic d, 1H, J_{gem} = 12.4 Hz), 4.91 (dd, 1H, *J* = 2.5 Hz, *J* = 12.5 Hz), 4.36 (s, 1H), 4.12-4.07 (m, 1H), 4.03-4.00 (m, 3H), 3.78 (dd, 1H, *J* = 3.0 Hz, *J* = 13.0 Hz), 3.51 (t, 1H, *J* = 10.0 Hz), 2.61-2.49 (m, 2H), 1.21 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.6, 165.2, 164.9, 137.7, 135.8, 133.4, 133.3, 133.0, 130.3, 130.0, 129.9, 129.6, 129.3, 128.9, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 126.3, 126.2, 126.1, 125.8, 125.6, 101.4, 95.9, 82.3, 78.9, 76.1, 75.4, 73.1, 68.5, 68.3, 67.9, 67.4, 64.5, 59.4, 25.5, 14.9; HRMS (ESI): $[M+Na]^+$ Calcd for $C_{52}H_{48}O_{12}NaS$, 919.2764; found, 919.2803; Anal. Calcd for $C_{52}H_{48}O_{12}S$: C, 69.63; H, 5.39; S, 3.57. Found: C, 69.09; H, 5.20; S, 3.64 %.

Ethyl β-D-xylopyranosyl-(1→2)-4,6-*O*-benzylidene-3-*O*-(2-naphtalenylmethyl)-1-thio-α-D-mannopyranoside (5)

A catalytic amount of NaOMe (7 mg, 0.12 mmol) was added to a solution of **4** (1.12 g, 1.25 mmol) in dry MeOH (20 mL). The mixture was stirred at 20 °C 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 *in vacuo*. Purification by flash column chromatography on silica gel (SiO_2, 200 mL, 4.5 cm, CH_2Cl_2/MeOH, 99:1→98:2→97:3→96:4→95:5) gave **5** (0.64 g, 88%) as a colourless, amorphous solid; R_f 0.39 (CH_2Cl_2/MeOH 9:1); $[\alpha]^{20}_D$ +37.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81-7.73 (m, 4H, Ar-H), 7.52-7.50 (m, 2H, Ar-H), 7.47-7.43 (m, 3H, Ar-H), 7.39-7.37 (m, 3H, Ar-H), 5.65 (s, 1H), 5.29 (d, *J* = 1.1 Hz, 1H), 5.03 (benzylic d, 1H, J_{gem} = 12.0 Hz), 4.86 (benzylic d, 1H, J_{gem} = 12.0 Hz), 4.58 (d, 1H, *J* = 6.0 Hz), 4.24-4.20 (m, 4H), 4.05 (dd, 1H, *J* = 4.5 Hz, *J* = 12.0 Hz), 4.01 (dd, 1H, *J* = 9.5 Hz, *J* = 3.4 Hz), 3.93 (d, 1H, *J* = 3.5 Hz), 3.90-3.86 (m, 1H), 3.62-3.61 (m, 1H), 3.53-3.48 (m, 2H), 3.31 (d, 1H, *J* = 2.5 Hz), 3.26 (dd, 1H, *J* = 8.5 Hz, *J* = 12.0 Hz), 2.79 (d, 1H, *J* = 3.5 Hz), 2.67-2.55 (m, 2H), 1.26 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.5, 134.7, 133.2, 133.1, 129.0, 128.3, 128.28, 128.0, 127.7, 127.3, 126.2, 126.1, 126.0, 101.7, 100.7, 84.3, 79.7, 75.0, 74.2 (2C), 73.8, 69.9, 69.4, 68.6, 64.9, 64.4, 25.6, 15.0. HRMS (ESI): $[M+H]^+$ Calcd for $C_{31}H_{37}O_9S$, 585.2158; found, 585.2150; Anal. Calcd for $C_{31}H_{36}O_9S$: C, 63.68; H, 6.21; S, 5.48. Found: C, 60.97; H, 5.96; S, 5.00 %.

Ethyl 2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)-4,6-*O*-benzylidene-3-*O*-(2-naphtalenylmethyl)-1-thio-α-D-mannopyranoside (6)

NaH (2.83 g, 70.81 mmol, 60% oil dispersion) was washed with pentane (3 × 80 mL) prior to use. NaH was added portionwise to a solution of **5** (9.20 g, 15.74 mmol) in dry DMF (100 mL) at 0 °C in an atmosphere of nitrogen. After 15 min, BnBr (7.48 mL, 62.96 mmol) was added dropwise at 0 °C under vigorous stirring. The temperature was then allowed to rise 20 °C over 2 h (TLC, toluene/EtOA 6:1). After complete consumption of the starting material, residual NaH was quenched with MeOH, and then with H_2O (300 mL). The resulting mixture was extracted once with EtOAc (400 mL), the layers were separated, and the organic layer was washed with brine (1 × 300 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 600 mL, 7.5 cm, toluene→toluene/EtOAc, 98:2→96:4→94:6→92:8→90:10→88:12) gave **6** (11.80 g, 88%) as a colourless, amorphous solid; R_f 0.58 (toluene/EtOAc 5:1); $[\alpha]^{20}_D$ −1.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (m, 1H, Ar-H), 7.81-7.79 (m, 1H, Ar-H), 7.76-7.75 (m, 1H, Ar-H), 7.68-7.66 (m, 1H, Ar-H), 7.52-7.26 (m, 23H, Ar-H), 5.60 (s, 1H), 5.41 (d, *J* = 0.8 Hz, 1H), 5.01 (benzylic d, 1H, J_{gem} = 10.0 Hz), 4.92-4.84 (m, 4H), 4.72 (benzylic d, 1H, J_{gem} = 10.0 Hz), 4.71 (benzylic d, 1H, J_{gem} = 12.0 Hz), 4.61 (benzylic d, 1H, J_{gem} =

12.0 Hz), 4.45 (d, 1H, *J* = 7.0 Hz), 4.28 (dd, 1H, *J* = 2.5 Hz, *J* = 1.0 Hz), 4.26-4.19 (m, 3H), 4.00 (dd, 1H, *J* = 5.0 Hz, *J* = 12.0 Hz), 3.97-3.94 (m, 1H), 3.84-3.80 (m, 1H), 3.69-3.65 (m, 1H), 3.60 (t, 1H, *J* = 8.7 Hz), 3.58-3.54 (m, 1H), 3.25 (dd, 1H, *J* = 11.6 Hz, *J* = 9.7 Hz), 2.62-2.51 (m, 2H), 1.22 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.7, 138.4, 138.1, 137.7, 135.8, 133.3, 132.9, 128.8, 128.5, 128.4, 128.3, 128.2, 127.9, 127.9, 127.9, 127.8, 127.8, 127.6, 127.6, 126.3, 126.1, 125.9, 125.7, 125.6, 103.2, 101.6, 83.8, 83.3, 81.4, 78.8, 77.8, 75.5, 75.1, 74.7, 73.3, 71.8, 68.8, 64.6, 64.1, 25.6, 15.0; HRMS (ESI): $[M+Na]^+$ Calcd for $C_{52}H_{54}O_9NaS$, 877.3386; found, 877.3403; Anal. Calcd for $C_{52}H_{54}O_9S$: C, 73.04; H, 6.37; S, 3.75. Found: C, 73.11; H, 6.33; S, 3.91 %.

Ethyl 2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)-3-*O*-(2-naphtalenylmethyl)-4-*O*-benzyl-1-thio-α-D-mannopyranoside (7)

A 1 M solution of BH_3 in THF (138.0 mL, 138.0 mmol) was added to a solution of **6** (11.80 g, 13.80 mmol) in dry CH_2Cl_2 (200 mL) kept at 0 °C in an atmosphere of nitrogen. After 5 min, a 1 M solution of Bu_2BOTf (13.80 mL, 13.80 mmol) was added dropwise at 0 °C, and the reaction mixture was stirred for 90 min (TLC, toluene/EtOAc 6:1). After complete consumption of the starting material, the reaction was quenched with Et_3N, followed by dropwise addition of MeOH at 0 °C. The mixture was concentrated *in vacuo*, and the residue was re-dissolved and co-concentrated with MeOH (3 × 200 mL). The syrupy residue was re-dissolved in MeOH, the solution was filtered through a short pad of Celite, and the filtrate was concentrated *in vacuo* to a yellow oil. Purification by flash column chromatography (SiO_2, 500 mL, 7.5 cm, toluene→toluene/EtOAc, 97:3→96:4→91:9→88:12→85:15→82:18→79:21) gave **7** (10.98 g, 94%) as a colourless foam; R_f 0.38 (toluene/EtOAc 6:1); $[\alpha]^{20}_D$ +42.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83-7.81 (m, 2H, Ar-H), 7.77-7.75 (m, 1H, Ar-H), 7.72-7.70 (m, 1H, Ar-H), 7.50 (dd, 1H, *J* = 2.0 Hz, *J* = 9.0 Hz, Ar-H), 7.48-7.44 (m, 2H, Ar-H), 7.38-7.27 (m, 20H, Ar-H), 5.39 (d, 1H, *J* = 1.5 Hz), 5.02 (benzylic d, 1H, J_{gem} = 10.5 Hz), 4.99 (benzylic d, 1H, J_{gem} = 11.0 Hz), 4.92 (benzylic d, 1H, J_{gem} = 12.0 Hz), 4.86 (benzylic ABq, 2H, *J* = 13.2 Hz), 4.74-4.71 (m, 2H), 4.62 (benzylic d, 1H, J_{gem} = 11.7 Hz), 4.60 (benzylic d, 1H, J_{gem} = 10.9 Hz), 4.42 (d, 1H, *J* = 7.5 Hz), 4.22 (s, 1H), 4.00-3.94 (m, 2H), 3.92-3.91 (m, 2H), 3.77-3.65 (m, 3H), 3.59 (t, 1H, *J* = 8.8 Hz), 3.56-3.52 (m, 1H), 3.23 (dd, 1H, *J* = 11.4 Hz, *J* = 10.2 Hz), 2.60-2.49 (m, 2H), 1.23 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.7, 138.6, 138.5, 138.2, 135.4, 133.3, 133.1, 128.5, 128.4, 128.4, 128.3, 128.0, 128.0, 127.9, 127.9, 127.9, 127.7, 127. 7, 127.6, 127.5, 127.2, 126.4, 126.0, 125.8, 103.2, 83.9, 82.2, 81.2, 78.7, 77.5, 76.5, 75.5, 75.2, 74.8, 73.4, 72.2, 71.4, 64.2, 62.5, 25.5, 14.9; HRMS (ESI): $[M+Na]^+$ Calcd for $C_{52}H_{56}O_9NaS$, 879.3543; found, 879.3524; Anal. Calcd for $C_{52}H_{56}O_9S$: C, 72.87; H, 6.59; S, 3.74. Found: C, 72.71; H, 6.57; S, 3.83 %.

Ethyl 2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)-6-*O*-acetyl-4-*O*-benzyl-3-*O*-(2-naphtalenylmethyl)-1-thio-α-D-mannopyranoside (8)

Ac_2O (5.71 mL, 60.29 mmol) was added to a solution of **7** (6.46 g, 7.54 mmol) in dry pyridine (100 mL), and the mixture was stirred at 20 °C for 5 h (TLC, toluene/EtOAc, 9:1). The reaction mixture was concentrated *in vacuo*, and then re-dissolved and co-evaporated with toluene (3 × 100 mL). Purification by flash column chromatography (SiO_2, 200 mL, 4.5 cm, toluene →toluene/EtOAc, 97:3→96:4→91:9→88:12→85:15) gave **8** (6.64 g, 98%) as a colourless oil; R_f 0.59 (toluene/EtOAc 6:1); $[\alpha]^{20}_D$ +46.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83-7.81 (m, 2H, Ar-H), 7.77 (benzylic d, 1H, *J* = 8.5 Hz, Ar-H), 7.72-7.70 (m, 1H, Ar-H), 7.51 (benzylic dd, 1H, *J* = 1.0 Hz, *J* = 8.5 Hz, Ar-H), 7.48-7.45 (m, 2H, Ar-H), 7.40-7.25 (m, 20H, Ar-H), 5.38 (s, 1H), 5.10 (benzylic d, 1H, J_{gem} = 10.0 Hz), 4.98 (benzylic d, 1H, J_{gem} = 10.5 Hz), 4.94-4.85 (m, 3H), 4.75-4.71 (m, 2H), 4.64-4.61 (m, 2H), 4.55 (benzylic d, 1H, J_{gem} = 10.5 Hz), 4.40 (d, 1H, *J* = 7.5 Hz), 4.34 (dd, 1H, *J* = 4.3 Hz, *J* = 11.9 Hz), 4.27 (dd, 1H, *J* = 1.9 Hz, *J* = 11.9 Hz), 4.22 (m, 1H), 4.20-4.17 (m, 1H), 4.00-3.95 (m, 2H), 3.91 (dd, 1H, *J* = 3.5 Hz, *J* = 9.5 Hz), 3.71-3.66 (m, 1H), 3.60-3.54 (m, 2H), 3.23 (t, 1H, *J* = 10.5 Hz), 2.60-2.55 (m, 2H), 1.73 (s, 3H), 1.23 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 138.8, 138.3, 138.2, 138.1, 135.3, 133.3, 133.1, 128.9, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 126.5, 126.0, 125.9, 103.5, 84.0, 82.5, 81.3, 78.8, 77.4, 76.7, 75.6, 75.2, 75.1, 74.2, 73.4, 71.4, 70.0, 64.2, 63.4, 25.7, 20.5, 15.0. HRMS (ESI): $[M+Na]^+$ Calcd for $C_{54}H_{58}O_{10}NaS$, 921.3648; found, 921.3619; Anal. Calcd for $C_{54}H_{58}O_{10}S$: C, 72.14; H, 6.50; S, 3.57. Found: C, 71.99; H, 6.45; S, 3.43 %.

Ethyl 2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)-4,6-di-*O*-benzyl-3-*O*-(2-naphtalenylmethyl)-1-thio-α-D-mannopyranoside (9)

NaH (734 mg, 18.34 mmol, 60% oil dispersion) was washed with pentane (3 × 30 mL) prior to use. NaH was added portionwise to a solution of **7** (4.49 g, 5.24 mmol) in dry DMF (100 mL) at 0 °C in an atmosphere of nitrogen. After 15 min, BnBr (1.87 mL, 15.72 mmol) was added dropwise at 0 °C under vigorous stirring. The temperature was then allowed to rise 20 °C over 4 h (TLC, toluene/EtOA 9:1). After complete consumption of the starting material, residual NaH was quenched with MeOH, and then with H_2O (200 mL). The resulting mixture was extracted once with EtOAc (400 mL), the layers were separated, and the organic layer was washed with brine (1 × 200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 200 mL, 4.5 cm, toluene→toluene/EtOAc, 98:2→96:4→94:6→92:8 →90:10) gave **9** (5.02 g, > 99%) as a colourless syrup. R_f 0.59 (toluene/EtOAc 9:1); $[\alpha]^{20}_D$ +44.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82-7.81 (m, 2H, Ar-H), 7.76-7.74 (m, 1H, Ar-H), 7.70-7.68 (m, 1H, Ar-H), 7.51-7.12 (m, 28H, Ar-H), 5.41 (d, 1H, *J* = 1.0 Hz), 5.10 (benzylic d, 1H, J_{gem} = 11.0 Hz), 4.97 (benzylic d, 1H, J_{gem} = 10.5 Hz), 4.92 (benzylic d, 1H, J_{gem} = 11.5 Hz), 4.90 (benzylic d, 1H, J_{gem} = 11.5 Hz), 4.83 (benzylic d, 1H, J_{gem} = 11.5 Hz), 4.74-4.71 (m, 2H), 4.61 (benzylic d, 1H, J_{gem} = 12.0 Hz), 4.54 (benzylic d, 1H, J_{gem} = 10.5 Hz), 4.53 (benzylic d, 1H, J_{gem} = 10.0 Hz), 4.41 (d, 1H, *J* = 7.5 Hz), 4.39 (m, 2H), 4.21 (m, 1H), 4.13 (dd, 1H, *J* = 3.0 Hz, *J* = 9.5 Hz), 4.05 (t, 1H, *J* = 9.5 Hz), 3.96 (dd, 1H, *J* = 5.0 Hz, *J* = 12.0 Hz), 3.92 (dd, 1H, *J* = 3.0 Hz, *J* = 9.0 Hz), 3.78 (dd, 1H, *J* = 4.0 Hz, *J* = 10.5 Hz), 3.69-3.64 (m, 2H), 3.58-3.51 (m, 2H), 3.22 (m, 1H), 2.64-2.52 (m, 2H), 1.23 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.9, 138.7, 138.6, 138.3, 138.2, 135.5, 133.3, 133.1, 129.0, 128.5, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 126.5, 125.9, 125.8, 103.5, 84.0, 82.3, 81.1, 78.9, 77.4, 76.9, 75.5, 75.2, 75.0, 74.7, 73.4, 73.2, 72.0, 71.4, 69.5, 64.2, 25.5, 15.0; HRMS (ESI): $[M+Na]^+$ Calcd for $C_{59}H_{62}O_9NaS$, 969.4012; found, 969.4032; Anal. Calcd for $C_{59}H_{62}O_9S$: C, 74.81; H, 6.60; S, 3.39. Found: C, 74.70; H, 6.56; S, 3.28 %.

Ethyl 2,4-di-*O*-benzyl-3-*O*-(2-naphtalenylmethyl)-1-thio-α-D-mannopyranoside (11)

Compound **10** (1.30 g, 2.40 mmol) was dissolved in 1M BH_3 in THF (24 mL, 24 mmol) and the mixture was stirred at 0 °C for 5 min before adding drop wise 1M Bu_2BOTf in CH_2Cl_2 (2.4 mL, 2.4 mmol). After 2 h, Et_3N was carefully added followed by drop wise addition of MeOH until gas evolution ceased. The solution was co-concentrated three times with MeOH and the crude was purified by flash column chromatography on silica gel (toluene/EtOAc 7:3) to give pure **11** (1.10 g, 2.02 mmol, 84%) as a syrup; R_f 0.44 (toluene/EtOAc 7:3); $[\alpha]^{20}_D$ +65.3 (*c* 1.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83-771 (m, 4H, Ar-H), 7.48-7.22 (m, 13H, Ar-H), 5.31 (d, 1H, *J* = 1.3 Hz), 4.97 (benzylic d, 1H, J_{gem} = 11.0 Hz), 4.75-4.70 (m, 4H), 4.68 (benzylic d, 1H, J_{gem} = 11.0 Hz), 4.06-3.98 (m, 2H), 3.92 (dd, 1H, *J* = 3.0, *J* = 8.7 Hz), 3.88 (dd, 1H, *J* = 1.3, *J* = 3.0 Hz), 3.85-3.77 (m, 2H), 2.61-2.48 (m, 2H), 1.98 (t, 1 H, *J* = 6.5 Hz), 1.21 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.6, 138.2, 135.8, 133.4, 133.1, 128.5, 128.5, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 126.5, 126.2, 126.0, 125.9, 82.4, 80.6, 76.8, 75.3, 75.1, 72.6, 72.5, 72.3, 62.5, 25.5, 15.0; HRMS (ESI): $[M+Na]^+$ calcd for $C_{33}H_{36}NaO_5S$, 567.2181; found, 567.2162.

Ethyl 6-*O*-acetyl-2,4-di-*O*-benzyl-3-*O*-(2-naphtalenylmethyl) -1-thio-α-D-mannopyranoside (12)

Ac_2O (10 mL) was added to a solution of **11** (1.02 g, 1.87 mmol) in pyridine (20 mL). The mixture was stirred at room temperature overnight and then co-evaporated with toluene (3 × 40 mL). The crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 9:1) to give pure **12** (1.05 g, 1.80 mmol, 96%) as a white foam; R_f 0.17 (9:1 cyclohexane/EtOAc); $[\alpha]^{20}_D$ +61.2 (*c* 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84-7.70 (m, 4H, Ar-H), 7.48-7.21 (m, 13H, Ar-H), 5.37 (d, 1H, *J* = 1.1 Hz), 4.96 (benzylic d, 1H, J_{gem} = 10.9 Hz), 4.74-4.65 (m, 4H), 4.60 (benzylic d, 1H, J_{gem} = 10.9 Hz), 4.39 (dd, 1H, *J* = 11.9 Hz, *J* = 5.0 Hz), 4.32 (dd, 1H, *J* = 2.2, 11.9 Hz), 4.18 (ddd, 1H, *J* = 2.2, 5.0, 9.4 Hz), 3.97 (t, 1H, *J* = 9.3 Hz), 3.91 (dd, 1H, *J* = 3.0, 9.3 Hz), 3.89 (dd, 1H, *J* = 1.1, 3.0 Hz), 2.64-2.50 (m, 2H), 2.04 (s, 3H), 1.24 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 138.3, 138.1, 135.6, 133.4, 133.1, 128.5, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.8, 126.6, 126.2, 126.0, 125.9, 82.1, 80.5, 76.4, 75.2, 74.8, 72.2, 72.1, 70.4, 63.6, 25.6, 20.9, 15.1; HRMS (ESI): $[M+Na]^+$ calcd for $C_{35}H_{38}NaO_6S$, 609.2287; found, 609.2303.

6-*O*-acetyl-2,4-di-*O*-benzyl-3-*O*-(2-naphtalenylmethyl)-1-thio-D-mannopyranose (13)

NIS (702,6 mg, 3.12 mmol) and TFA (0.24 mL, 3.12 mmol) were added to a vigorously stirred solution of **12** (1.83 g, 3.12 mmol) in CH_2Cl_2 (26 mL) and H_2O (2.6 mL) at 0 °C. After 1h, the reaction was quenched by adding 10% aq $Na_2S_2O_3$ solution (10 mL). The reaction mixture was extracted with CH_2Cl_2 (20 mL), the layers were separated, and the organic layer was washed with sat. $NaHCO_3$ (aq., 20 mL), then dried over $MgSO_4$, filtered and concentrated. The crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 3:2) to give pure **13** (1.45 g, 2.68 mmol, 86%) as 9:1 α:β mixture; R_f 0.25 (cyclohexane/EtOAc 3:2); ^{1}H NMR (500 MHz, $CDCl_3$ α-compound): δ = 7.84-7.70 (m, 4H, Ar-H), 7.48-7.42 (m, 3H, Ar-H), 7.38-7.22 (m, 10H, Ar-H), 5.23 (dd, 1H, *J* = 1.2, 3.2 Hz), 4.96 (benzylic d, 1H, J_{gem} = 10.9 Hz), 4.79-4.68 (m, 4H), 4.62 (benzylic d, 1H, J_{gem} = 10.9 Hz), 4.38 (dd, 1H, *J* = 1.8, 11.8 Hz), 4.25 (dd, 1H, *J* = 5.2, 11.8 Hz), 4.06-4.00 (m, 2H), 3.97-3.93 (m, 1H), 3.84-3.82 (m, 1H), 3.14 (d, 1 H, *J* = 3.2 Hz), 2.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 138.4, 138.3, 135.9, 133.4, 133.1, 128.5, 128.5, 128.2, 128.2, 128.0, 127.9, 127.8, 127.8, 126.4, 126.2, 126.0, 125.9, 92.8, 79.9, 75.3, 74.9, 74.8, 72.8, 72.4, 70.4, 63.9, 21.0; HRMS (ESI): $[M+Na]^+$ calcd for $C_{33}H_{34}NaO_7$, 565.2202; found, 565.2230.

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

Method A - To a solution of **9** (640 mg, 0.68 mmol) in CH_2Cl_2/H_2O 10:1 (12 mL) DDQ (463 mg, 2.04 mmol) was added. The reaction mixture was stirred at room temperature for 3.5h and then quenched by addition of sat. $Na_2S_2O_3$ (aq.,20 mL). The organic layer was diluted with CH_2Cl_2 (20 mL), washed three times with sat. $NaHCO_3$ (aq., 3 × 20 mL), dried ($MgSO_4$), filtered and concentrated. The crude was purified by flash column chromatography on silica gel (cyclohexane/ EtOAc 9:1) to give pure **15** (355 mg, 0.44 mmol, 65%) as a white foam.

Method B - To a solution of **9** (136 mg, 0.14 mmol) in CH_2Cl_2/t-BuOH 10:1 (2.2 mL) DDQ (65 mg, 0.28 mmol) was added. The reaction mixture was stirred at room temperature for 1.5 h and then quenched by addition of sat. $Na_2S_2O_3$ (aq., 5 mL). The organic layer was diluted with CH_2Cl_2 (8 mL), washed three times with sat. $NaHCO_3$ (aq., 3 × 8 mL), dried ($MgSO_4$), filtered and concentrated. The crude was purified by flash column chromatography on silica gel (cyclohexane/EtOAc 9:1) to give pure **15** (87 mg, 0.11 mmol, 75%); R_f 0.12 (cyclohexane/EtOAc 3:2); $[\alpha]^{20}_D$ +60.4 (*c* 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47-7.13 (m, 25H, Ar-H), 5.37 (bs, 1H, H-1), 4.99 (benzylic d, 1H, J_{gem} = 10.5 Hz), 4.94 (benzylic d, 1H, J_{gem} = 10.5 Hz), 4.90 (benzylic d, 1H, J_{gem} = 11.1 Hz), 4.85 (benzylic d, 1H, J_{gem} = 11.1 Hz), 4.72 (benzylic d, 1H, J_{gem} = 11.2 Hz), 4.65 (benzylic d, 1H, J_{gem} = 11.2 Hz), 4.60 (benzylic d, 1H, J_{gem} = 11.0 Hz), 4.59 (benzylic d, 1H, J_{gem} = 11.0 Hz), 4.53 (benzylic d, 1H, J_{gem} = 12.1 Hz), 4.46 (benzylic d, 1H, J_{gem} = 12.1 Hz), 4.35 (d, 1H, *J*= 7.7 Hz), 4.13 (ddd, 1H, *J* = 9.8 Hz, *J* = 4.5 Hz, *J* = 1.4 Hz), 4.03 (dd, 1H, *J*= 1.3 Hz, *J* = 3.4 Hz), 3.99-3.91 (m, 2H), 3.80 (dd, 1H, *J* = 10.9 Hz), 3.76-3.69 (m, 2H), 3.64-3.58 (m, 1H), 3.56 (t, 1H, *J* = 8.9 Hz), 3.42-3.38 (m, 1H), 3.20 (dd, 1H, *J* = 10.3, 11.5 Hz), 3.08 (d, 1H, *J* = 9.2 Hz), 2.64-2.50 (m, 2H), 1.23 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.8, 138.8, 138.6, 138.4, 138.2, 128.7, 128.6, 128.4, 128.4, 128.4, 128.3, 128.1, 128.0, 128.0, 128.0, 127.9, 127.7, 127.7, 127.6, 127.5, 104.1, 83.8, 82.7, 82.3, 81.2, 77.5, 77.2, 75.8, 75.1, 75.0, 73.6, 73.4, 71.7, 71.7, 69.5, 64.3, 25.3, 15.0; HRMS (ESI): $[M+Na]^+$ calcd for $C_{48}H_{54}O_9NaS$, 829.3386; found, 829.3346.

Ethyl 6-*O*-acetyl-2,4-di-*O*-benzyl-3-*O*-(2-naphtalenylmethyl) -α-D-mannopyranosyl-(1→3)-[2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)]-4,6-di-*O*-benzyl-1-thio-α-D-mannopyranoside (16) and **Ethyl 6-*O*-acetyl-2,4-di-*O*-benzyl-3-*O*-(2-naphtalenylmethyl)-β-D-mannopyranosyl-(1→3)-[2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)]-4,6-di-*O*-benzyl-1-thio-α-D-mannopyranoside (17)**

General procedure for **14**:

To a solution of **13** (266 mg, 0.5 mmol) in dry CH_2Cl_2 (5 mL), trichloroacetonitrile (0.295 mL, 2.99 mmol) and DBU (1.5 µL, 0.01 mmol) were added at 0 °C under nitrogen atmosphere. After 1.5 h, the mixture was concentrated *in vacuo* and filtered

through a short column of silica gel (cyclohexane/EtOAc 1:1) affording **14** (315 mg) which was used in the subsequent glycosylation reaction without any characterisation.

Method A – To a solution of **15** (180 mg, 0.22 mmol) in dry toluene (5 mL) powdered molecular sieves 4 Å (50 mg) and TMSOTf (4 μL, 0.022 mmol) were added at -20 °C under N_2 atmosphere. After stirring for 10 min, a solution of **14** (230 mg, 0.33 mmol) in dry toluene (2 mL) was added drop wise. After 1 h, the reaction was quenched by addition of Et_3N (1 mL). The reaction mixture was filtered through a pad of Celite, concentrated *in vacuo* and the crude was purified by flash column chromatography on silica gel (toluene/EtOAc 9.5:5 → 9:1) to give pure **16** (194 mg, 0.15 mmol, 65%) and pure **17** (53 mg, 0.04 mmol, 18%).

Method B - To a solution of **15** (150 mg, 0.19 mmol) in dry toluene (4 mL) powdered molecular sieves 4 Å (40 mg) and TMSOTf (3.5 μL, 0.019 mmol) were added at room temperature under N_2 atmosphere. After stirring for 10 min, a solution of **14** (191 mg, 0.27 mmol) in dry toluene (1.5 mL) was added drop wise. After 1 h, the reaction was quenched by addition of Et_3N (0.8 mL). The reaction mixture was filtered through a pad of Celite, concentrated and the crude was purified by flash column chromatography on silica gel (toluene/EtOAc 9.5:5 → 9:1) to give pure **16** (186 mg, 0.14 mmol, 75%) and pure **17** (22 mg, 0.02 mmol, 9%).

Compound 16

R_f 0.59 (toluene/EtOAc 9:1); $[\alpha]^{20}_D$ +25.7 (*c* 1.01 , $CHCl_3$);^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80-7.72 (m, 4H, Ar-H), 7.47-7.49 (m, 38H, Ar-H), 5.37 (s, 1H), 5.18 (s, 1H, H), 5.08 (benzylic d, 1H, J_{gem} = 10.2 Hz), 4.98 (benzylic d, 1H, J_{gem} = 10.2 Hz), 4.87 (benzylic d, 1H, J_{gem} = 11.1 Hz), 4.83 (benzylic d, 1H, J_{gem} = 11.1 Hz), 4.77 (benzylic d, 1H, J_{gem} = 11.8 Hz), 4.67 (benzylic d, 1H, J_{gem} = 11.8 Hz), 4.64-4.59 (m, 2H), 4.51-4.34 (m, 8H), 4.32-4.25 (m, 4H), 4.17-4.10 (m, 2H), 4.09-4.06 (m, 2H), 4.02-3.95 (m, 2H), 3.86 (t, 1H, *J* = 9.4 Hz), 3.74 (dd, 1H, *J* = 4.1, 10.7 Hz), 3.70 (dd, 1H, *J* = 1.7, 2.3 Hz), 3.63 (dd, 1H, *J* = 1.2, 10.7 Hz), 3.52 (t, 1H, *J* = 8.8 Hz), 3.48-3.41 (m, 2H), 3.11 (dd, 1H, *J* = 10.1, 11.6 Hz), 2.63-2.51 (m, 2H), 2.11 (s, 3H), 1.23 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.2, 139.0, 138.8, 138.7, 138.7, 138.4, 138.3, 138.1, 136.1, 133.4, 133.0, 129.0, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 127.5, 126.8, 126.5, 126.2, 126.0, 104.1 ($J_{C,H}$ = 155 Hz), 99.9 ($J_{C,H}$ = 170 Hz), 84.0, 82.6 ($J_{C,H}$ = 165 Hz), 81.4, 80.5, 80.1, 77.6, 77.0, 75.9, 75.7, 75.5, 75.4, 75.2, 75.1, 74.5, 73.5, 72.9, 72.6, 72.4, 72.1, 70.6, 69.4, 64.5, 63.6, 25.4, 21.2, 15.0; HRMS (ESI): $[M+Na]^+$ calcd for $C_{81}H_{86}O_{15}NaS$, 1353.5585; found, 1353.5609.

Compound 17

R_f 0.43 (toluene/EtOAc 9:1); $[\alpha]^{20}_D$ −2.8 (*c* 1.26, $CHCl_3$);^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80-7.65 (m, 4H, Ar-H), 7.45-7.16 (m, 38H, Ar-H), 5.42 (d, *J* = 2.2 Hz, 1H), 5.08 (benzylic d, 1H, J_{gem} = 10.5 Hz), 5.02-4.96 (m, 3H), 4.94-4.89 (m, 2), 4.83 (benzylic d, 1H, J_{gem} = 11.1 Hz), 4.69 (s, 1H), 4.66-4.60 (m, 4H), 4.52 (benzylic d, 1H, J_{gem} = 11.7 Hz), 4.45-4.38 (m, 5H), 4.32-4.25 (m, 2H), 4.18-4.13 (m, 2H), 4.11 (d, 1H, *J* = 2.8 Hz), 3.95-3.89 (m, 2H), 3.77-3.69 (m, 2H), 3.66 (dd, 1H, *J* = 1.8, 10.8 Hz), 3.58-3.53 (m, 2H), 3.52-3.47 (m, 2H), 3.43-3.38 (m, 1H), 3.14 (dd, 1H, *J* = 10.2, 11.4 Hz), 2.69-2.55 (m, 2H), 1.97 (s, 3H), 1.26 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 139.3, 138.9, 138.8, 138.5, 138.5, 138.3, 138.2, 135.6, 133.4, 133.1, 129.0, 128.6, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.2, 128.0, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.5, 127.3, 126.3, 126.0, 125.6, 103.2 ($J_{C,H}$ = 160 Hz), 98.8 ($J_{C,H}$ = 155 Hz), 83.9, 82.7, 81.9 ($J_{C,H}$ = 165 Hz), 81.3, 77.9, 76.8, 75.8, 75.7, 75.3, 75.0, 74.7 (2C), 74.2, 74.0, 74.0, 73.9, 73.4, 73.3, 71.5, 71.3, 69.7, 64.2, 64.0, 25.5, 21.0, 15.0 (SCH_2CH_3); HRMS (ESI): $[M+Na]^+$ calcd for $C_{81}H_{86}O_{15}NaS$, 1353.5585; found, 1353.5565.

2,3,4-Tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)-4,6-di-*O*-benzyl-3-*O*-(2-naphtalenylmethyl)-D-mannopyranose (18)

NIS (47 mg, 0.21 mmol) and TFA (16 μL, 0.21 mmol) were added to a vigorously stirred solution of **8** (200 mg, 0.21 mmol) in CH_2Cl_2/H_2O (10 mL, 20:1) at 20 °C (TLC, toluene/EtOAc 6:1). After 3 h, the reaction was quenched by adding 10% aq. $Na_2S_2O_3$-solution (10 mL). The resulting mixture was extracted once with CH_2Cl_2 (50 mL), the layers were separated, and the organic layer was washed sequentially with sat. $NaHCO_3$-solution (3 × 25 mL), and brine (1 × 25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 75 mL, 4.5 cm, toluene→toluene/EtOAc, 93:7→90:10→87:13→84:16→81:19 →75:25→70:30) gave an anomeric mixture of **18** (163 mg, 85%, α:β = 5:1) as a colourless syrup. R_f 0.16 (toluene/EtOAc 6:1). Data for the a-anomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82-7.80 (m, 2H, Ar-H), 7.76-7.74 (m, 1H, Ar-H), 7.68 (m, 1H, Ar-H), 7.51 (m, 1H, Ar-H), 7.44-7.18 (m, 22H, Ar-H), 5.31 (d, 1H), 5.05 (benzylic d, 1H, J_{gem} = 10.5 Hz), 4.97-4.89 (m, 3H), 4.83 (benzylic d, 1H, J_{gem} = 12.0 Hz), 4.75 (benzylic d, 1H, J_{gem} = 12.5 Hz), 4.70 (benzylic d, 1H, J_{gem} = 11.5 Hz), 4.59 (benzylic d, 1H, J_{gem} = 12.0 Hz), 4.54-4.48 (m, 2H), 4.45-4.37 (ABq, 2H), 4.28 (d, 1H, *J* = 7.0 Hz), 4.09 (m, 1H), 4.07-4.00 (m, 2H), 3.90 (dd, 1H, *J* = 5.5, 12.0 Hz), 3.84 (t, 1H, *J* = 9.8 Hz), 3.72-3.68 (m, 1H), 3.66-3.59 (m, 2H), 3.54 (t, 1H, *J* = 8.5 Hz), 3.50 (m, 1H), 3.07-3.01 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.9, 138.7, 138.6, 138.3, 137.8, 135.8, 133.3, 133.0. 129.3, 128.9, 128.4, 128.3, 128.3, 128.2, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 127.4, 127.0, 126.5, 125.9, 125.8, 103.4, 92.5, 83.9, 81.4, 77.8, 77.5, 75.5, 75.1, 75.0, 74.9, 74.8, 73.4, 73.3, 71.5, 71.4, 69.9, 64.0. Selected data for the β-anomer: ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 105.6, 94.6, 83.4, 81.5, 80.4, 78.7, 76.1, 75.6, 75.3, 75.2, 74.1, 73.6, 73.4, 71.6, 69.3, 64.4; HRMS (ESI): $[M+Na]^+$ Calcd for $C_{57}H_{58}O_{10}Na$, 925.3928; found, 925.3905; Anal. Calcd for $C_{57}H_{58}O_{10}$: C, 75.81; H, 6.47. Found: C, 75.76; H, 6.32 %.

1-*O*-[2,3,4-Tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)-4,6-di-*O*-benzyl-3-*O*-(2-naphtalenylmethyl)-D-mannopyranosyl] trichloroacetimidate (19)

Trichloroacetonitrile (300 μL, 3.00 mmol) and DBU (8 μL, 0.05 mmol) were added to an ice-cooled solution of **18** (455 mg, 0.50 mmol) in dry CH_2Cl_2 (20 mL) in an atmosphere of nitrogen (TLC, toluene/EtOAc 5:1). After 60 min, the mixture was concentrated *in vacuo* (water bath temperature of rotary evaporator: < 30 °C). Purification by flash column chromatography (SiO_2, neutralised with 1% Et_3N per column volumed, 20 mL, 2.3 cm, toluene→toluene/EtOAc, 98:2 →95:5→90:10→85:15) gave an anomeric mixture of **19** (527 mg) as a colourless foam; R_f 0.71 (toluene/EtOAc 5:1).

Donor **19** was prepared immediately prior to use in the subsequent inverse glycosylation with acceptor **20**.

Ethyl 2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)-6-*O*-acetyl-4-*O*-benzyl-1-thio-α-D-mannopyranoside (20)
DDQ (242 mg, 1.06 mmol) was added to a vigorously stirred mixture of **7** (600 mg, 0.67 mmol) in CH_2Cl_2/H_2O (34.1 mL, 10:1) at 20 °C. An additional amount of DDQ (182 mg, 0.80 mmol) was added after 20 min. More DDQ (182 mg, 0.80 mmol) was added after 40 min. The progress of the reaction was carefully monitored by TLC (toluene/EtOAc 6:1). After 60 min, the reaction was quenched by the adding 10% aq. $Na_2S_2O_3$-solution (100 mL). The resulting mixture was extracted once with CH_2Cl_2 (100 mL), the layers were separated, and the organic layer was washed sequentially with sat. $NaHCO_3$-solution (3 × 100 mL) and brine (1 × 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 100 mL, 4.5 cm, toluene→toluene/EtOAc, 96:4→93:7→90:10→87:13→84:16→80:20). The first fraction to appear in the eluate contained recovered starting material (60 mg). Solvent removal of the second and main fraction gave **20** (355 mg, 70%) as a colourless syrup. R_f 0.45 (toluene/EtOAc 6:1); $[\alpha]^{20}_D$ +87.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38-7.24 (m, 20H, Ar-H), 5.32 (s, 1H), 4.97 (m, 2H), 4.92-4.86 (m, 2H), 4.72 (m, 2H), 4.62 (m, 2H), 4.35-4.29 (m, 3H), 4.19-4.17 (m, 1H), 4.02 (m, 1H), 3.99-3.94 (m, 2H), 3.65-3.61 (m, 2H), 3.57 (t, 1H, *J* = 8.5 Hz), 3.41 (t, 1H, *J* = 8.3 Hz), 3.21 (t, 1H, *J* = 10.8 Hz), 3.10 (d, 1H, *J* = 9.5 Hz), 2.62-2.49 (m, 2H), 1.84 (s, 3H), 1.23 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 138.6, 138.3, 138.0, 137.9, 128.6, 128.5, 128.4, 128.4, 128.1, 128.0, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 103.9, 83.6, 82.7, 82.0, 81.3, 77.4, 76.5, 75.7, 75.1, 74.8, 73.5, 71.6, 69.6, 64.2, 63.4, 25.3, 20.6, 14.9; HRMS (ESI): $[M+Na]^+$ Calcd for $C_{43}H_{50}O_{10}NaS$, 781.3022; found, 781.3024; Anal. Calcd for $C_{43}H_{50}O_{10}S$: C, 68.05; H, 6.64; S, 4.23. Found: C, 68.09; H, 6.60; S, 4.02 %.

Ethyl 2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)-4,6-di-*O*-benzyl-3-*O*-(2-naphtalenylmethyl)-α-D-mannopyranosyl-(1→3)-[2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)]-6-*O*-acetyl-4-*O*-benzyl-1-thio-α-D-mannopyranoside (21)
A catalytic amount of TBDMSOTf (3 μL, 12 μmol) was added to a solution of acceptor **20** (874 mg, 1.15 mmol) in dry toluene (30 mL) containing crushed molecular sieves (AW-300) kept at -40 °C in an atmosphere of nitrogen. A solution of donor **19** (1.64 g, 1.56 mmol) in dry toluene (30 mL) was added dropwise over 3 h to the reaction vessel using a syringe pump (rate of addition: 10 mL per hour). After complete addition, the reaction mixture was kept at -40 °C for 1 h (TLC, toluene/EtOAc 6:1). The reaction mixture was neutralised with Et_3N (96 μL, 0.69 mmol), the solids were removed by filtration, and the filtrate was concentrated *in vacuo* to a yellowish oil. Purification by flash column chromatography (SiO_2, 200 mL, 4.5 cm, toluene→toluene/EtOAc, 96:4→93:7→90:10→87:13→84:16→81:19) gave **21** (1.80 g, 95%) as a colourless foam; R_f 0.48 (toluene/EtOAc 9:1); $[\alpha]^{20}_D$ +3.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79 (m, 1H, Ar-H), 7.76-7.74 (m, 1H, Ar-H), 7.70-7.66 (m, 2H, Ar-H), 7.49-7.14 (m, 47H, Ar-H), 5.27 (s, 1H), 5.18 (s, 1H), 5.05-4.99 (m, 3H), 4.87-4.77 (m, 6H), 4.69 (benzylic d, 1H, J_{gem} = 11.5 Hz), 4.64 (benzylic d, 1H, J_{gem} = 10.0 Hz), 4.58-4.54 (m, 3H), 4.50 (benzylic d, 1H, J_{gem} = 10.5 Hz), 4.46 (benzylic d, 1H, J_{gem} = 12.0 Hz), 4.41-4.38 (m, 2H), 4.31-4.24 (m, 6H), 4.20-4.17 (m, 2H), 4.08 (dd, 1H, *J* = 3.0, 9.0 Hz), 4.03 (dd, 1H, *J* = 3.0, 9.0 Hz), 3.95-3.87 (m, 4H), 3.83-3.78 (m, 2H), 3.75 (d, 1H, *J* = 10.0 Hz), 3.65 (dd, 1H, *J* = 6.0, 10.5 Hz), 3.58-3.53 (ddd, 1H), 3.49-3.37 (m, 4H), 3.32 (t, 1H, *J* = 8.8 Hz), 3.04 (m, 1H), 2.79 (t, 1H, *J* = 11.0 Hz), 2.56-2.45 (m, 2H), 1.82 (s, 3H), 1.20 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 139.2, 138.9, 138.8, 138.7, 138.5, 138.4, 138.1, 138.0, 135.9, 133.3, 133.0, 128.8, 128.6, 128.6, 128.4, 128.3, 128.3, 128.2, 128.2, 128.2, 127.9, 127.8, 127.8, 127.8, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 127.4, 127.3, 127.1, 126.8, 126.6, 125.9, 125.8, 103.8 ($J_{C,H}$ = 155 Hz), 103.7 ($J_{C,H}$ = 155 Hz), 100.5 ($J_{C,H}$ = 170 Hz), 83.8, 83.5, 82.7 ($J_{C,H}$ = 165 Hz), 81.5, 80.9, 80.3, 78.6, 78.3, 77.6, 77.3, 75.9, 75.6, 75.3, 75.0, 75.0, 74.93, 74.7 (2C), 74.4, 73.5, 73.2, 72.5, 72.4, 72.1, 70.1, 70.0, 63.9, 63.4, 63.2, 25.5, 20.6, 15.0; HRMS (ESI): $[M+Na]^+$ calcd for $C_{100}H_{106}O_{19}NaS$, 1665.6947; found, 1665.6919; Anal. Calcd for $C_{100}H_{106}O_{19}S$: C, 73.06; H, 6.50; S, 1.95. Found: C, 72.74; H, 6.61; S, 1.92 %.

2-Azidoethyl 6-*O*-acetyl-2,4-di-*O*-benzyl-3-*O*-(2-naphtalenyl methyl)-α-D-mannopyranosyl-(1→3)-[2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)]-4,6-di-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (23)
A solution of **16** (58 mg, 0.043 mmol), **22** (15 mg, 0.029 mmol) and 4 Å powdered molecular sieves in dry Et_2O (2.5 mL) was stirred under N_2 at 20 °C. After 30 min, the solution was cooled to 0 °C and DMTST (23 mg, 0.044 mmol) was added. The mixture was gently warmed to room temperature and stirred until the disappearance of **22**. After 2.5 h, the reaction was quenched by addition of Et_3N (0.8 mL), filtered through a pad of Celite and concentrated *in vacuo*. The crude was purified by flash column chromatography on silica gel (toluene/EtOAc 95:5 → 9:1) to give pure **23** (46 mg, 0.026 mmol, 89%) as a colourless oil; R_f 0.44 (toluene/EtOAc 9:1); $[\alpha]^{20}_D$ −2.9 (*c* 1.20, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.78-7.71 (m, 4H, Ar-H), 7.43-7.07 (m, 53H, Ar-H), 5.22 (s, 1H), 5.19 (d, *J* = 1.3 Hz, 1H), 5.04 (benzylic d, 1H, *J* = 10.7 Hz), 4.96 (benzylic d, 1H, *J* = 11.0 Hz), 4.90 (d, *J* = 1.6 Hz), 4.81-4.59 (m, 9H), 4.56-4.52 (m, 2H), 4.49 (benzylic d, 1H, *J* = 12.0 Hz), 4.44-4.34 (m, 6H), 4.29 (dd, 1H, *J* = 5.4, 11.9 Hz), 4.26-4.11 (m, 7H), 3.98 (t, 1H, *J* = 9.4 Hz), 3.94-3.80 (m, 8H), 3.79-3.72 (m, 2H), 3.67 (dd, 1H, *J* = 1.3, 10.5 Hz), 3.65-3.64 (m, 1H), 3.58-3.53 (m, 3H), 3.37-3.29 (m, 3H), 3.28-3.21 (m, 2H), 2.63 (t, 1H, *J* = 11.0 Hz), 1.98 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.1, 139.0, 139.0, 138.9, 138.8, 138.5, 138.5, 138.4, 138.3, 138.2, 138.2, 136.1, 133.4, 133.0, 128.8, 128.7, 128.6, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 127.7, 127.6, 127.5, 127.5, 127.5, 127.5, 127.4, 127.4, 126.7, 126.7, 126.6, 126.2, 126.0, 126.0, 103.9 ($J_{C,H}$ = 155 Hz), 100.3 ($J_{C,H}$ = 175 Hz), 99.8 ($J_{C,H}$ = 175 Hz), 97.9 ($J_{C,H}$ = 170 Hz), 83.4, 81.3, 80.0, 78.6, 78.5, 77.7, 77.5, 76.2, 76.0, 75.5, 75.4, 75.1 (2C), 74.9, 74.8, 74.4, 74.3, 73.6, 73.5, 72.9, 72.6, 72.5, 72.4, 72,4, 72.3, 70.4, 69.3, 69.1, 66.8, 64.0, 63.2, 50.5, 21.1; HRMS (ESI): $[M+Na]^+$ calcd for $C_{108}H_{113}N_3O_{21}Na$, 1810.7764; found, 1810.7679.

2-Azidoethyl 2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)-4,6-di-*O*-benzyl-3-*O*-(2-naphtalenylmethyl)-α-D-mannopyranosyl-(1→3)-[2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)]-6-*O*-acetyl-4-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (24)
A mixture of **21** (50 mg, 30 μmol), **22** (10 μg, 20 mmol) and crushed molecular sieves (4 Å) in dry Et_2O (3 mL) was stirred at 20 °C for 30 min. The reaction mixture was cooled to 0 °C, freshly prepared DMTST (16 mg, 62 μmol) was added, and the reaction mixture was stirred at 0 °C for 30 min. The progress of

the reaction was carefully monitored by TLC (toluene/EtOAc 9:1). The cooling bath was removed, an additional amount of DMTST was added (16 mg, 62 mmol), and stirring was continued at 20 °C for 3 h. The reaction was diluted with Et_2O, and quenched with Et_3N (28 μL, 0.20 mmol) at 0 °C. The solution was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo*. The residue was re-dissolved in CH_2Cl_2 (50 mL), and the organic layer was washed sequentially with 1 M aq. HCl-solution (3 × 25 mL), sat. $NaHCO_3$ (2 × 25 mL), and brine (1 × 25 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by flash column chromatography (SiO_2, 70 mL, 2.3 cm, toluene→toluene-EtOAc 94:6→93:7→92:8→91:9→90:10→89:11→88:12) gave **24** (59 mg, 92%) as a colourless syrup. R_f 0.39 (toluene/EtOAc 9:1); $[\alpha]^{20}_D$ + 1.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.77-7.74 (m, 2H, Ar-H), 7.68-7.66 (m, 2H, Ar-H), 7.47-7.45 (m, 1H, Ar-H), 7.42-7.06 (m, 62H, Ar-H), 5.22 (s, 1H), 5.11 (s, 1H), 5.05 (benzylic d, 1H, J_{gem} = 11.1 Hz), 4.98-4.97 (m, 3H), 4.82-4.73 (m, 7H), 4.69-4.64 (m, 3H), 4.61 (benzylic d, 1H, J_{gem} = 12.1 Hz), 4.56-4.49 (m, 5H), 4.45 (benzylic d, 1H, J_{gem} = 11.9 Hz), 4.31-4.26 (m, 4H), 4.19-4.07 (m, 7H), 4.04 (dd, 1H, *J* = 3.1, 9.5 Hz), 3.98-3.95 (m, 2H), 3.91 (d, 1H, *J* = 7.3 Hz), 3.89-3.86 (m, 2H), 3.83-3.78 (m, 5H), 3.76-3.70 (m, 3H), 3.67-3.59 (m, 3H), 3.58-3.49 (m, 3H), 3.44-3.40 (ddd, 1H, $OCH_2CH^aH^bN_3$), 3.38-3.30 (m, 3H), 3.29-3.22 (m, 3H), 2.65-2.58 (m, 2H), 1.76 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.6, 139.2, 138.9, 138.8, 138.5, 138.5, 138.3, 138.3, 138.2, 138.1, 138.1, 137.7, 135.9, 133.2, 132.9, 128.6, 128.5, 128.5, 128.5, 128.5, 128.5, 128.3, 128.2, 128.2, 128.2, 128.2, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 127.5, 127.5, 127.4, 127.4, 127.4, 127.3, 127.3, 127.3, 127.2, 126.7, 126.4, 125.9, 125.8, 103.6 ($J_{C,H}$ = 160 Hz), 103.5 ($J_{C,H}$ = 160 Hz), 100.5 ($J_{C,H}$ = 175 Hz), 99.8 ($J_{C,H}$ = 170 Hz), 97.6 ($J_{C,H}$ = 170 Hz), 83.2, 83.2, 81.5, 80.7, 79.6, 78.2, 78.2, 77.7, 77.5, 77.2, 76.1, 75.9, 75.4, 75.2, 74.9, 74.8 (2C), 74.6, 74.5, 74.5, 74.3, 74.0, 73.4, 73.2, 73.1, 72.5, 72.4, 72.3, 72.3, 72.1, 70.0, 69.5, 69.1, 66.6, 63.7, 63.2, 63.0, 50.4, 20.5; HRMS (ESI): $[M+Na]^+$ calcd for $C_{127}H_{133}N_3O_{25}Na$, 2122.9126; found, 2122.9197; Anal. Calcd for $C_{127}H_{133}N_3O_{25}$: C, 72.59; H, 6.38; N, 2.00. Found: C, 72.99; H, 6.74; N, 1.69 %.

Ethyl 6-*O*-acetyl-2,4-di-*O*-benzyl-α-D-mannopyranosyl-(1→3)-[2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)]-4,6-di-*O*-benzyl-1-thio-α-D-mannopyranoside (25)

DDQ (52 mg, 0.23 mmol) was added to a vigorously stirred solution of compound **16** (158 mg, 0.12 mmol) in CH_2Cl_2/*t*-BuOH (20 mL, 10:1) at 20°C. The progress of the reaction was carefully monitored by TLC (toluene-EtOAc, 85:15). After 1.5 h, the reaction was quenched by adding 10% aq. $Na_2S_2O_3$-solution (10 mL). The resulting mixture was extracted once with CH_2Cl_2 (20 mL), the layers were separated, and the organic layer was washed sequentially with sat. $NaHCO_3$-solution (3 × 20 mL), and brine (1 × 20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a pale yellow oil. The residue was purified by flash column chromatography on silica gel (toluene-EtOAc, 96:4→70:30) and afforded **25** (104 mg, 72%) as a colourless foam. R_f 0.59 (toluene/EtOAc 85:15); $[\alpha]^{20}_D$ +36.0 (*c* 1.00, $CHCl_3$);^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43-7.11 (m, 35H), 5.39 (s, 1H), 5.25 (s, 1H), 5.07 (d, *J* 10.1 Hz, 1H), 4.93 (d, *J* 11.2 Hz, 1H), 4.87-4.78 (m, 3H), 4.68 (d, *J* 11.8 Hz, 1H), 4.60-4.55 (m, 2H), 4.47-4.38 (m, 3H), 4.36-4.22 (m, 6H), 4.20-4.17 (bs, 1H), 4.12-4.03 (m, 5H), 4.00 (dd, *J* 4.8 Hz, *J* 11.7 Hz, 1H), 3.79 (dd, *J* 4.1 Hz, *J* 10.8 Hz, 1H), 3.73 (dd, *J* 1.1 Hz, *J* 3.6 Hz, 1H), 3.68 (dd, *J* 1.3 Hz, *J* 10.7 Hz, 1H), 3.57-3.47 (m, 3H), 3.44 (t, *J* 8.2 Hz, 1H), 3.09 (dd, *J* 9.8 Hz, *J* 11.5 Hz, 1H), 2.63-2.51 (m, 2H), 2.28 (d, *J* 10.0 Hz, 1H), 2.11 (s, 3H), 1.23 (t, *J* 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 138.9, 138.8, 138.6, 138.6, 138.2, 138.1, 137.7, 128.9, 128.5, 128.4, 128.3, 128.3, 128.3, 127.9, 127.9, 127.7, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 126.6, 104.1, 99.0, 83.9, 82.5, 81.1, 80.6, 78.9, 77.9, 77.7, 77.1, 75.6, 75.4, 75.1, 74.7, 74.5, 73.4, 72.7, 72.3, 72.1, 71.7, 69.4, 69.4, 64.5, 63.6, 25.3, 21.2, 15.0. HRMS (ESI): $[M+Na]^+$ calcd for $C_{70}H_{78}O_{15}NaS$, 1213.4959; found, 1213.4962.

Ethyl 2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)-4,6-di-*O*-benzyl-α-D-mannopyranosyl-(1→3)-[2,3,4-tri-*O*-benzyl-β-D-xylopyranosyl-(1→2)]-6-*O*-acetyl-4-*O*-benzyl-1-thio-α-D-mannopyranoside (26)

DDQ (142 mg, 0.62 mmol) was added to a vigorously stirred solution of compound **21** (640 mg, 0.38 mmol) in CH_2Cl_2/H_2O (33 mL, 10:1) at 20°C. Additional amounts of DDQ (106 mg, 0.46 mmol) were added after 20 min. More DDQ (106 mg, 0.46 mmol) was added after 40 min. The progress of the reaction was carefully monitored by TLC (toluene-EtOAc, 6:1). After 60 min, the reaction was quenched by adding 10% aq. $Na_2S_2O_3$-solution (100 mL). The resulting mixture was extracted once with CH_2Cl_2 (200 mL), the layers were separated, and the organic layer was washed sequentially with sat. $NaHCO_3$-solution (3 × 150 mL), and brine (1 × 150 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a pale yellow oil. The residue was purified by flash column chromatography (toluene→toluene/EtOAc,96:4→93:7→90:10→87:13→84:16 →81:19 →78:22). The first fraction to appear in the eluate contained recovered starting material (67 mg). Solvent removal of the second and main fraction gave **26** (396 mg, 68%) as a colourless foam. R_f 0.15 (toluene-EtOAc, 9/1); $[\alpha]^{20}_D$ +38.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.13 (m, 45H), 5.27 (s, 1H), 5.16 (s, 1H), 5.02 (d, *J* 10.0 Hz, 1H), 4.97 (d, *J* 11.3 Hz, 1H), 4.92 (d, *J* 10.8 Hz, 1H), 4.89-4.80 (m, 5H), 4.70 (d, *J* 11.8 Hz, 1H), 4.65 (d, *J* 10.0 Hz, 1H), 4.62-4.48 (m, 6H), 4.35 (d, *J* 11.5 Hz, 1H), 4.33-4.26 (m, 5H), 4.23-4.17 (m, 2H), 4.07-4.01 (m, 2H), 3.97-3.90 (m, 2H), 3.82-3.74 (m, 4H), 3.66 (dd, *J* 5.8 Hz, *J* 10.6 Hz, 1H), 3.58-3.35 (m, 6H), 3.29-3.25 (m, 1H), 3.06-2.97 (m, 2H), 2.86 (t, *J* 11.0 Hz, 1H), 2.55-2.44 (m, 2H), 1.83 (s, 3H), 1.20 (t, *J* 7.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 139.3, 139.0, 138.8, 138.7, 138.5, 138.3 (2C), 138.2 (2C), 128.8, 128.8, 128.7, 128.6, 128.4, 128.4, 128.4, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 127.5, 126.9, 104.3, 104.0, 101.1, 83.9, 83.4, 82.9, 81.5, 80.9, 80.8, 80.7, 78.9, 77.8, 77.4, 77.3, 75.6 (2C), 75.1, 74.9, 74.9, 74.7 (2C), 73.6, 73.5, 72.8, 71.9, 70.9, 70.3, 69.9, 64.1, 63.6, 63.3, 25.7, 20.7, 15.1. HRMS (ESI): $[M+Na]^+$ calcd for $C_{89}H_{98}O_{19}NaS$, 1525.6321; found, 1525.6383.

2-Aminoethyl 6-*O*-acetyl-α-D-mannopyranosyl-(1→3)-[β-D-xylopyranosyl-(1→2)]-α-D-mannopyranosyl-(1→3)-α-D-mannopyranoside (27)

10% w Pd/C (13 mg, 12.3 mmol) was added to a solution of compound **23** (20 mg, 11.2 mmol) in AcOEt/H_2O/AcOH (4:2:1, 1.75 mL). The mixture was hydrogenolysed in a high-pressure reactor (Berghof) at 20 °C (*p* = 30 bar). After 60 h, the solids were removed by filtration using a 'sandwich filter' (3 frits stacked on top of each other in the following order: 20 μm, 10 μm, 5 μm), rinsed with H_2O (3 × 2 mL) and EtOH (3 × 2 mL), and the filtrate was concentrated *in vacuo*. Purification by reversed-phase chromatography (C-18, H_2O-MeOH,

9:1→8:2→7:3→6:4→2:8→0:10), followed by freeze-drying gave **27** (5.8 mg, 72%) as a colourless, amorphous solid. $[\alpha]^{20}_D$ +26.2 (*c* 0.45, H_2O); ^1H NMR (600 MHz, D_2O): δ = 5.12 (s, 1H), 4.95 (s, 1H), 4.74 (s, 1H), 4.33 (d, *J* 11 Hz, 1H), 4.22 (d, *J* 8 Hz, 1H), 4.11 (dd, *J* 6 Hz, 12 Hz, 1H), 4.08-4.02 (m, 1H), 3.99 (s, 2H), 3.93 (1H, s), 3.88 (dd, *J* 3 Hz, 9 Hz, 1H), 3.86-3.81 (m, 3H), 3.76-3.71 (m, 2H), 3.71-3.54 (m, 8H), 3.54-3.45 (m, 2H), 3.26 (t, *J* 9 Hz, 1H), 3.18-3.04 (m, 4H), 2.02 (s, 3H); ^{13}C anomeric signals taken from HSQC: 103.2, 103.0, 100.0, 99.8. HRMS (ESI): $[M+Na]^+$ calcd for $C_{27}H_{47}NO_{21}Na$, 744.2538; found, 744.2559.

2-Aminoethyl β-D-xylopyranosyl-(1→2)-α-D-mannopyranosyl-(1→3)-[β-D-xylopyranosyl-(1→2)]-6-*O*-acetyl-α-D-mannopyranosyl-(1→3)-α-D-mannopyranoside (**28**)
10% w Pd/C (17 mg, 16.1 mmol) was added to a solution of compound **24** (26 mg, 12.4 mmol) in AcOEt/H_2O/AcOH (4:2:1, 1.75 mL). The mixture was hydrogenolysed in a high-pressure reactor (Berghof) at 20 °C (*p* = 30 bar). After 60 h, the solids were removed by filtration using a 'sandwich filter' (3 frits stacked on top of each other in the following order: 20 μm, 10 μm, 5 μm), rinsed with H_2O (3 × 2 mL) and EtOH (3 × 2 mL), and the filtrate was concentrated *in vacuo*. Purification by reversed-phase chromatography (C-18, H_2O-MeOH, 9:1→8:2→7:3→6:4→2:8→0:10), followed by freeze-drying gave **28** (7.3 mg, 69%) as a colourless, amorphous solid. $[\alpha]^{20}_D$ +17.6 (*c* 0.40, H_2O); ^1H NMR (600 MHz, D_2O): δ = 5.09 (s, 1H), 5.04 (s, 1H), 4.76 (s, 1H), 4.32-4.21 (m, 4H), 4.11 (1H, s), 4.01 (1H, s), 3.99-3.96 (m, 2H), 3.93-3.87 (m, 1H), 3.87-3.56 (m, 13H), 3.55-3.45 (m, 4H), 3.32-3.22 (m, 2H), 3.21-3.07 (m, 6H), 1.99 (s, 3H); ^{13}C anomeric signals taken from HSQC: 102.9, 102.3, 100.5, 99.9, 99.4. HRMS (ESI): $[M+Na]^+$ calcd for $C_{32}H_{55}NO_{25}Na$, 876.2961; found, 876.2949.

Acknowledgements

We thank Science Foundation Ireland (Grants 08/IN.1/B2067 and 13/IA/1959) and Marie Curie-Intra-European Fellowships (FP7-PEOPLE-2011-IEF, project number 299710) for financial support.

Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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