Novel protecting group strategies in the synthesis of oligosaccharides

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Chapter 2

Chemoselective Cleavage of para-Methoxybenzyl and Naphthyl Ethers using a Catalytic Amount of HCl in Hexafluoroisopropanol

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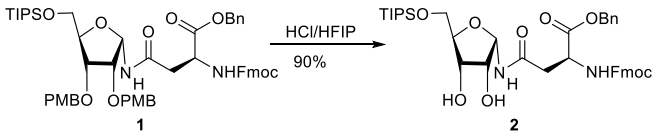
Introduction

Protecting groups play a pivotal role in synthetic organic chemistry.[1–4] In oligosaccharide synthesis protecting groups are used to (temporarily) mask hydroxyl and amino groups to allow for selective modification of other functionalities on the carbohydrate ring. Besides blocking specific functionalities that otherwise would partake in a glycosylation event, the protective group pattern of carbohydrate building blocks also has a profound effect on the outcome of a glycosylation reaction in terms of yield and stereoselectivity. Various types of protecting groups are available to mask carbohydrate hydroxyls, and amongst the most commonly used groups are the benzyl-type ethers. Besides being robust to a wide variety of reaction conditions, the sterically minimally intrusive benzyl-type ethers stand out because of their non-participating nature. Therefore benzyl-type ethers are often the group of choice to protect the C-2-OH when 1,2-*cis* linkages are to be installed. Substituted benzyl ethers, such as the *p*-methoxybenzyl (PMB) and 2-naphthylmethyl (Nap) ether are attractive, electron rich benzyl ethers, as they can be removed en route to the oligosaccharide using oxidative or acidic cleavage conditions.[2] For their removal, generally strong oxidizing agents, such as ceric ammonium nitrate or 1,2-dichloro-3,4-dicyano-quinone (DDQ), in combination with biphasic reaction media, are used. These conditions can be disadvantageous when dealing with sensitive compounds or solid phase reactions.[5–10] Alternatively, the PMB and Nap groups can be split off under acidic conditions, using a large molar excess of rather strong Brønsted or Lewis acids such as TFA[11,12] or HF.pyridine[13], the use of which can jeopardize the integrity of acid labile functionalities in the molecule (acetals, silyl ethers etc.). Recently introduced methods to cleave PMB ethers include the use of $FeCl_3$[14] and $AgSbF_6$/trimethoxybenzene.[15] Exotic conditions to remove PMB ethers are described,[16] however the applicability remains questionable, since the reagents and conditions require thorough chemical experience. These methods[14–16] require relatively long reaction times and have not been employed to remove the more stable Nap ethers. The invention of mild, homogeneous and fast reaction conditions to selectively remove PMB or Nap ethers will make these groups even more useful in (carbohydrate) synthesis and open up routine application in both solution and solid phase settings.

Such a reagent can be found in the work of Palladino and Stetsenko, who recently described the use of hydrochloric acid in a fluorinated alcohol, such as hexafluoro-*iso*-propanol (HFIP),[17] to unmask *tert*-butyl protected hydroxyl and carboxylic acid functions in solid phase peptide synthesis.[18–20] The reactivity of this deprotection system arises from the effective hydrogen bonding of the fluorinated alcohol to the chloride leading to the generation of “naked” protons. In the synthesis of poly adenoside diphosphate ribosylated (poly-ADPR) peptides mild conditions to transform ribosyl glutamine **1** into building block **2** were required, suitable for solid phase synthesis (Scheme 1).

Scheme 1. Deprotection of PMB groups with catalytic HCl.



To this end both PMB ethers at the C2 and C3 positions, installed to allow for the stereoselective construction of the 1,2-*cis* ribosyl linkage, had to be removed. It was found that the use of TFA in DCM rapidly cleaved both ethers but also led to substantial epimerization at the anomeric center. The use of oxidative conditions (DDQ in DCM/H_2O) led to the formation of several side products. In contrast, the use of a catalytic amount of HCl in HFIP prevented these side reactions and resulted in the clean removal of the PMB ethers. Encouraged by this profitable outcome the scope and limitations of the latter cleavage method was explored, the result of which are presented in this chapter. It was found that a catalytic amount of HCl can be sufficient to cleave both PMB and Nap ethers, while chemoselectivity between these two ethers can also be attained. The applicability of the use of Nap-ethers and their HCl/HFIP mediated removal in the synthesis of a sulfated mannuronic acid di- and tetrasaccharide is demonstrated in Chapter 5. The non-participating nature of the Nap-ethers in the building blocks used in this synthesis is crucial for the stereoselective formation of the β-mannuronic acid linkage.[21–23]

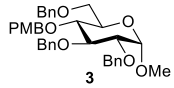
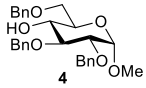
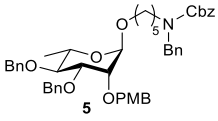
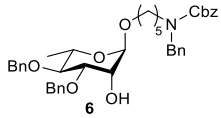
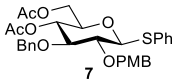
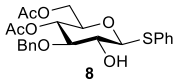
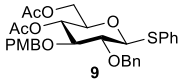
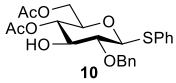
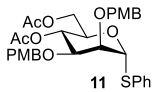
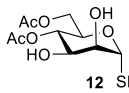
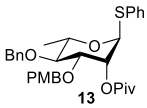
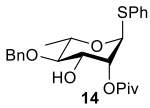
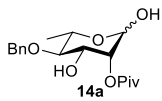
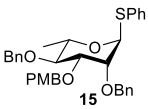
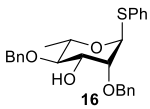
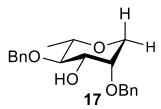
Results and Discussion

A series of substrates varying in protection pattern was tested with the new method. The first substrate that was subjected to a catalytic amount of HCl (0.1 equiv) in DCM/HFIP was O-glycoside **3**, carrying a PMB group at C-4 (Table 1, entry 1). Upon addition of a preformed HCl/HFIP mixture to a solution of **3** in DCM/HFIP, the reaction mixture turned dark purple within seconds, indicative for the formation of p-methoxybenzyl cationic species. Within minutes all substrate had been consumed and transformed into a single product (**4**). Besides the formation of the desired alcohol, TLC analysis showed the formation of a lipophilic side product. LC-MS analysis of this side product indicated this to be a PMB derived polymer, indicating that the PMB cations, released during the reaction, are not scavenged by HFIP but instead react with another PMB ether in a Friedel−Crafts manner, resulting in the formation of the polymer, for which a putative mechanism is provided in Scheme 2.[14,24]

The same conditions (0.1 equiv HCl DCM/HFIP 1:1) also cleanly cleaved the PMB group from the C2-OH in rhamnoside **5** (entry 2), carrying an aminopentanol spacer. The anomeric acetal was completely stable under the conditions used. Next, various thioglycosides were explored. Glucoside **7**, carrying a single PMB group at C2-OH, was subjected to the deprotection mixture to uneventfully afford alcohol **8**. Likewise, the C3-OPMB ether was cleanly removed from glucoside **9** to give compound **10**. Mannoside **11**, carrying two PMB ethers, was deprotected equally efficient leading to diol **12** in 80% yield

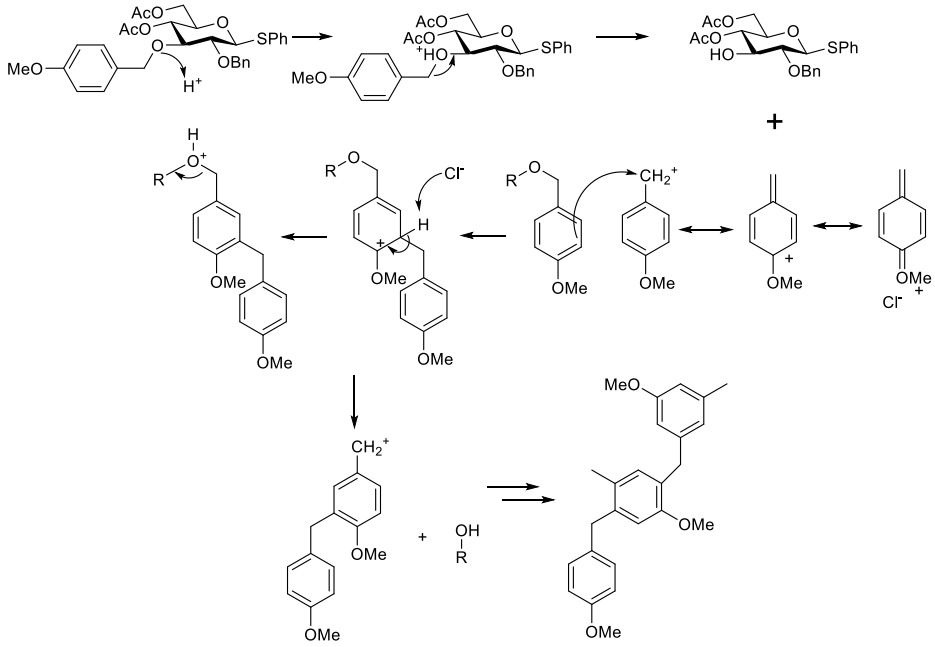
(entry 5). When rhamnoside **13** was subjected to the deprotection conditions (0.1 equiv HCl DCM/HFIP 1:1), a complex mixture resulted. Notably, the characteristic purple color was absent, and the reaction required hours to reach completion. Besides the desired product **14**,

Table 1. Deprotection of PMB protected carbohydrates

Entry	Substrate	Conditions	Product	Yield
1	 **3**	0.1 eq. HCl/HFIP	 **4**	96%
2	 **5**	0.1 eq. HCl/HFIP	 **6**	82%
3	 **7**	0.1 eq. HCl/HFIP	 **8**	90%
4	 **9**	0.1 eq. HCl/HFIP	 **10**	81%
5	 **11**	0.1 eq. HCl/HFIP	 **12**	80%
6	 **13**	1.0 eq. HCl/HFIP 3.0 eq. TES, 0°C	 **14**  **14a**	**14**: SPh, 85% **14a**: OH, n.d.
7	 **15**	1.0 eq. HCl/HFIP 3.0 eq. TES, 0°C	 **16**  **17**	**16:** SPh, 75% **17:** H, 14%.

anomeric lactol **14a** was formed in this reaction, indicating that alkylation of the anomeric thiofunction by the PMB cation occurred as a side reaction. Expulsion of the activated aglycon then leads to hydrolysis of the thioglycoside.[25] To circumvent this side reaction, triethylsilane (TES) was added to the reaction mixture to scavenge the released PMB cations. Because it was reasoned that the addition of a scavenger would necessitate the use of at least an equimolar amount of HCl, 1 equiv of HCl and 3 equiv of scavenger were used. These conditions resulted in clean removal of the PMB group from rhamnoside **13** and the isolation of alcohol **14** in 85% yield (entry 6). When the same conditions were used to cleave the PMB group from rhamnoside **15**, the desired alcohol **16** was obtained in 75%

Scheme 2. Mechanism for the formation of PMB polymer



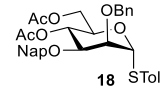
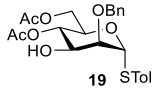
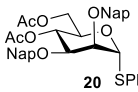
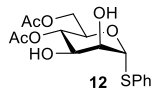
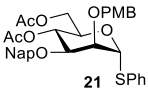
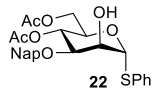
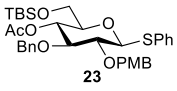
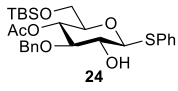
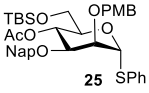
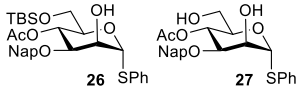
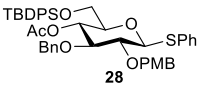
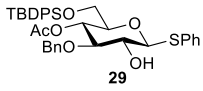
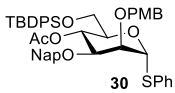
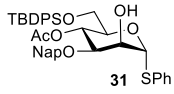
alongside desulfurized compound **17** (entry 7). Here, activation of the thiofunction in **15** or **16** could not be completely suppressed because of the high reactivity of the rhamnoside, being a 6-deoxy glycoside featuring solely "arming" benzyl ether protecting groups. Of note, the anomeric linkage in O-rhamnoside **5**/**6** (entry 2) is completely stable under the acidic conditions.

Since Nap ethers can be removed under acidic conditions, it was investigated whether Nap ethers can also be cleaved using the HCl/HFIP cocktail. Mannoside **18** (Table 2) was subjected to the catalytic cleavage conditions described above (0.1 equiv. HCl DCM/HFIP 1 : 1). These conditions proved not forceful enough to cleave the Nap ether and the reaction progressed very slow and led to a low yield of the desired alcohol. The amount of acid was raised to an equimolar amount. The addition of triethyl silane as a scavenger led to the clean and controllable formation of alcohol **19** (entry 1, Table 2). Similarly, deprotection of bis-Nap ether **20** proceeded uneventfully to give diol **12** (entry 2).

Based on these results it was reasoned that the difference in reactivity of the PMB and Nap ethers towards the HCl/HFIP combination should allow for the selective removal of a PMB ether in the presence of a Nap ether. The addition of a catalytic amount of HCl to mannoside **21** proved this hypothesis and the PMB ether in **21** was selectively cleaved to give alcohol **22** in good yield (entry 3, Table 2). The orthogonality of the PMB ether with respect to commonly used silyl ethers was explored next.[1,26] Removal of the PMB ether in **23** and **25** was accompanied by partial cleavage of *tert*-butyldimethylsilyl (TBS) groups at the primary hydroxyl function (entries 4 and 5). Although conditions that left the TBS

ethers untouched could not be identified, it was found during the optimization of these reactions that a catalytic amount of HCl could be used in combination with a stoichiometric amount of scavenger (TES). Besides, the more acid stable *tert*-butyldiphenylsilyl (TBDPS) was stable to this catalytic cleavage cocktail and selective deprotection of the PMB ether in **28** in the presence of a TBDPS ether gave glucosyl alcohol **29** in 89% yield (entry 6). Similarly, the PMB ether in mannoside **30** was selectively deblocked, leaving both the primary TBDPS ether and the secondary napthyl ether unaffected (entry 7). When mannoside **30** was subjected to 5% trifluoroacetic acid in DCM,[1] compound **31** was obtained in 77% yield, where oxidative removal of the C-2-O-PMB using DDQ,[1] resulted in a complex mixture.

Table 2. Nap deprotection and selectivity

Entry	Substrate	conditions	Product	Yield
1	 **18**	1.0 eq. HCl/HFIP 3.0 eq. TES	 **19**	86%
2	 **20**	2.0 eq. HCl/HFIP 5.0 eq. TES	 **12**	67%
3	 **21**	0.1 eq. HCl/HFIP 3.0 eq. TES	 **22**	80%
4	 **23**	0.1 eq. HCl/HFIP 1.0 eq. TES	 **24**	48%
5	 **25**	0.1 eq. HCl/HFIP 1.0 eq. TES	 **26** **27**	**26**: OTBS, 63% **27**: OH, 24%
6	 **28**	0.1 eq. HCl/HFIP 1.0 eq. TES	 **29**	89%
7	 **30**	0.1 eq. HCl/HFIP 1.0 eq. TES	 **31**	88%

Conclusion

In summary, a new, fast, and homogeneous deprotection method for electron-rich benzyl-type ethers is described employing HCl in HFIP. PMB and Nap ethers can be removed with a catalytic amount of acid in a selective manner without affecting other groups. PMB ethers can also be selectively cleaved with respect to Nap ethers by limiting the amount of HCl. The ease of cleavage of these groups under the established conditions is a valuable asset for the utility of the PMB and Nap ethers in synthetic (carbohydrate) chemistry. The

latter is illustrated by the succesfull application of the HCl/HFIP method in the synthesis of complex fucosazide donors[27] as well as its use in constructing *E. faecium* wall teichoic acid fragments.[28] The mild, fast, and homogeneous reactions conditions should allow for their use in a solid-phase reaction setting. Also in stereoselective glycosylation reactions that are mediated through external nucleophiles ("moderators"), the use of a protecting group scheme that builds on all-benzyl ether-type protecting groups that can be selectively removed will be very valuable.[29]

Experimental Section

General experimental procedures. All chemicals were used as received unless stated otherwise. ^{1}H and ^{13}C NMR spectra were recorded on a 400/100 MHz, 500/125 MHz, 600/150 MHz or a 850/214 MHz spectrometer. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard. Coupling constants are given in Hz. All individual signals were assigned using 2D-NMR spectroscopy, HH-COSY, HSQC and HMBC. IR spectra are reported in cm^{-1}. Flash chromatography was performed on silica gel 60 (0.04 – 0.063 mm). TLC-analysis was followed by detection by UV-absorption (254 nm) where applicable and by spraying with 20% sulfuric acid in ethanol followed by charring at ~150 °C or by spraying with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}H_2O$ (25 g/l) and $(NH_4)_4Ce(SO_4)_4{\cdot}{}_2H_2O$ (10 g/l) in 10% sulfuric acid in water followed by charring at 50 °C. LC-MS standard eluents used were A: 100% H_2O, B: 100% acetonitrile, C: 1% TFA in H_2O. The column used was a C18 column (4.6 mmD × 50 mmL, 3µ particle size). All analyses were 13 min, with a flow-rate of 1 ml/min. High-resolution mass spectra were recorded on a LTQ-Orbitrap equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 275ºC) with resolution R=60.000 at m/z=400 (mass range = 150-4000) and dioctylphtalate (m/z=391.28428) as "lock mass". HCl/HFIP solution were freshly prepared prior to use.

Methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (4) Compound **3**[30] (0.117 g, 0.200 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.1 mL 0.2M HCl/HFIP was added. After 150 seconds the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **4** in 96% yield (0.0891 g, 0.19 mmol). TLC R_f 0.35 (Tol/EtOAc, 9/1, v/v); ^{1}H NMR($CDCl_3$, 500 MHz): δ 7.39 – 7.20 (m, 15H, CHarom), 4.99 (d, 1H, *J* = 11.5 Hz, CH*H* OBn), 4.78 – 4.70 (m, 2H, CH*H* OBn, CHH OBn), 4.68 – 4.61 (m, 2H, C*H*H OBn, H-1), 4.55 (q, 2H, *J* = 12.1, 12.1, 12.1 Hz, CH_2 OBn), 3.78 (t, 1H, *J* = 9.2, 9.2 Hz, H-3), 3.74 – 3.64 (m, 3H, H-5, H-6), 3.59 (t, 1H, *J* = 9.2, 9.2 Hz, H-4), 3.52 (dd, 1H, *J* = 9.6, 3.5 Hz, H-2), 3.37 (s, 3H, OMe), 2.37 (s, 1H, 4-OH); ^{13}C NMR(CDCl3, 126 MHz): δ 138.9, 138.2, 138.1 (Cq), 128.6, 128.5, 128.4, 128.2, 128.0, 128.0, 127.9, 127.7, 127.7 (CHarom), 98.3 (C-1), 81.6 (C-3), 79.7 (C-2), 75.5 (CH_2Bn), 73.7 (CH_2Bn), 73.2 (CH_2Bn), 70.9 (C-4), 70.0 (C-5), 69.6 (C-6), 55.3 (CH_3OMe).

N-benzyl-N--3,4-di-O-benzyl-2-O-p-methoxybenzyl-α-L-rhamno-pyranoside (5) *N*-benzyl-*N*-benzyloxycarbonyl-5-aminopentanyl-3,4-di-*O*-benzyl-α-L-rhamno-pyranoside[31] (0.908 g, 1.39 mmol) was coevaporated twice with anhydrous toluene before being dissolved in DMF (4 mL). The mixture was cooled to 0°C, after which sodium hydride (60% dispersion in mineral oil, 0.08 g, 2.08 mmol) was added. The mixture was stirred for 10 minutes followed by addition of *para*-methoxybenzylchloride (0.28 mL, 2.08 mmol). After 115 minutes, the reaction was quenched with sat. aq. $NaHCO_3$, diluted with Et_2O and washed with water. The organic layer was dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **5** in 75% yield (0.802 g, 1.03 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30 (m, 22H, CH_{arom}), 7.17 (s, 1H, CH_{arom}), 6.83 (d, 2H, *J* = 8.6 Hz, CH_{arom}), 5.17 (d, 2H, *J* = 9.4 Hz, CH_2 Cbz), 4.93 (d, 1H, *J* = 10.8 Hz, CH*H* OBn), 4.72 – 4.54 (m, 6H, C*H*H OBn, CH_2 OBn, CH_2 OPMB, H-1), 4.48 (s, 2H, CH_2 Bn), 3.82 – 3.73 (m, 5H, CH_3 OMe, H-2, H-3), 3.66 – 3.50 (m, 3H, H-5, CH_2), 3.33 – 3.10 (m, 1H, H-4, CH_2), 1.66 – 1.37 (m, 5H, CH_2), 1.34 – 1.07 (m, 6H, CH_3 H-6, CH_2); ^{13}C-NMR (CDCl3, 101 MHz): δ 159.3, 138.8, 138.0, 130.6 (C_q), 129.6, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 113.9 (CH_{arom}), 98.1 (C-1), 80.7 (C-3), 80.4 (C-4), 75.6 (CH_2Bn), 74.6 (C-2), 72.5, 72.2 (CH_2 PMB/Bn), 68.1 (C-5), 67.3 (CH_2Bn), 55.4 (CH_3 OMe), 50.7, 50.3 (CH_2), 29.3 (CH_2), 23.5 (CH_2), 18.2 (CH_3 C-6); HRMS: $[M+NH_4]^+$ calculated for $C_{48}H_{59}N_2O_8$ 791.42659, found 791.42758.

N-benzyl-N-benzyloxycarbonyl-5-aminopentanyl-3,4-di-O-benzyl-α-L-rhamno-pyranoside (6) Compound **5** (0.157 g, 0.200 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.1 mL 0.2M HCl/HFIP was added. After 150 seconds the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **6** in 82% yield (0.108 g, 0.165 mmol). TLC R_f 0.15 (Tol/EtOAc, 9/1, v/v); IR (neat, cm^{-1}): 694, 731, 910, 984, 1028, 1051, 1069, 1096, 1227, 1304, 1362, 1421,

1452, 1472, 1497, 1695, 1728, 2930; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 – 7.17 (m, 20H, CH_{arom}), 5.17 (d, 2H, *J* = 11.1 Hz, CH_2 Cbz), 4.87 (d, 1H, *J* = 10.9 Hz, CH*H* OBn), 4.75 (s, 1H, H-1), 4.69 – 4.60 (m, 3H, CH_2 OBn), 4,49 (s, 2H, CH_2 OBn), 3.99 (s, 1H, H-2), 3.81 (d, 1H, *J* = 7.0 Hz, H-3), 3.68 (m, 1H, H-5), 3.58 (m, 1H, CH_2) 3.44 (t, 1H, *J* = 9.3, 9.3 Hz, H-4), 3.26 – 3.19 (m, 3H, CH_2), 2.41 (bs, 1H, 2-OH), 1.53 – 1.47 (m, 4H, 2 x CH_2), 1.30 – 1.26 (m, 5H, CH_3-6, CH_2); ^{13}C-NMR (CDCl3, 126 MHz): δ 138.5, 138.1, (C_q), 128.6, 128.6, 128.5, 128.5, 128.1, 128.0, 127.9, 127.9, 127.8, 127.4 (CH_{arom}), 99.0 (C-1), 80.3 (C-3), 80.1 (C-4), 75.5 (CH_2Bn), 72.1 (CH_2), 68.7 (C-2), 67.4 (CH_2), 67.4 (C-5), 67.3 (CH_2 Cbz), 50.6, 50.3 (CH_2Bn), 47.2, 46.2 (CH_2), 29.2 (CH_2), 23.5 (CH_2), 18.0 (CH_3-6). Analytical data are identical to literature precendence.

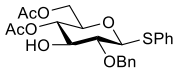
Phenyl 4,6-di-*O*-acetyl-3-*O*-benzyl-2-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (7) Phenyl 4,6-*O*-benzylidene-3-*O*-benzyl-2-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside[32] (1.76 g, 3.00 mmol) was dissolved in DCM/MeOH (15 mL/ 15 mL) and p-toluenesulfonic acid monohydrate (0.06 g, 0.30 mmol) was added. When TLC analysis showed complete consumption of the starting material, the reaction was neutralized with Et_3N. The crude was dissolved in pyridine (12 mL), cooled to 0°C, followed by addition of 1.3 mL Ac_2O. The reaction was stirred overnight after which it was quenched with EtOH and concentrated. The crude mixture was diluted with EtOAc, washed with 1M HCl, sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Column purification (hexanes/EtOAc) gave compound **7** in 84% yield (1.428 g, 2.52 mmol). ^{1}H NMR($CDCl_3$, 500 MHz): δ 7.57 (dd, 2H, *J* = 7.6, 1.9 Hz, CH_{arom}), 7.36 – 7.19 (m, 10H, CH_{arom}), 6.86 (d, 2H, *J* = 8.6 Hz, CH_{arom}), 5.03 (t, 1H, *J* = 9.7, 9.7 Hz, H-4), 4.82 (m, 2H, 2x CH*H* OBn/OPMB), 4.67 – 4.57 (m, 3H, H-1, 2x C*H*H OBn/OPMB), 4.20 (dd, 1H, *J* = 12.2, 5.7 Hz, H-6), 4.10 (dd, 1H, *J* = 12.2, 2.2 Hz, H-6), 3.77 (s, 3H, OMe), 3.64 (t, 1H, *J* = 9.1, 9.1 Hz, H-3), 3.60 – 3.49 (m, 2H, H-2, H-5), 2.06 (s, 3H, CH_3 Ac), 1.90 (s, 3H, CH_3 Ac); ^{13}C NMR($CDCl_3$, 126 MHz): δ 170.6, 169.6 (C=O Ac), 159.4, 138.0, 133.2 (C_q), 132.1, 130.0 (CH_{arom}), 129.8 (C_q), 128.9, 128.4, 127.8, 127.7, 113.8 (CH_{arom}), 87.5 (C-1), 83.7 (C-3), 80.2 (C-2), 75.8 (C-5), 75.4, 75.2 (CH_2Bn/PMB), 69.6 (C-4), 62.6 (C-6), 55.2 (CH_3 OMe), 20.7, 20.7 (CH_3 Ac); HRMS: $[M+NH_4]^+$ calculated for $C_{31}H_{38}NO_8$ 584.23126, found 584.23151.

Phenyl 4,6-di-*O*-acetyl-3-*O*-benzyl-1-thio-β-D-glucopyranoside (8) Compound **7** (0.134 g, 0.236 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.12 mL 0.2M HCl/HFIP was added. After 15 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **8** in 88% yield (0.093 g, 0.207 mmol). TLC R_f 0.50 (PE/EtOAc, 2/1, v/v); $[\alpha]_D^{20}$ -6.8 (*c* 1, DCM); IR (neat, cm^{-1}): 692, 740, 1026, 1220, 1365, 1739, 2885, 2953, 3375; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.58 – 7.52 (m, 3H, CH_{arom}), 7.36 – 7.24 (m, 13H, CH_{arom}), 4.98 (t, 1H, *J* = 9.8 Hz, H-4), 4.83 (d, 1H, *J* = 11.8 Hz, CH*H* Bn), 4.69 (d, 1H, *J* = 11.8 Hz, C*H*H Bn), 4.51 (d, 1H, *J* = 9.3 Hz, H-1), 4.21 – 4.10 (m, 2H, H-6), 3.62 – 3.51 (m, 3H, H-2, H-3, H-5), 2.65 (s, 1H, 2-OH), 2.07 (s, 3H, CH_3 Ac); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.8, 169.7 (C=O Ac), 138.2 (C_q), 133.3 (CH_{arom}), 131.3 (C_q), 129.1, 128.5, 128.5, 127.9, 127.9 (CH_{arom}), 88.1 (C-1), 82.9 (C-3), 76.2 (C-5), 74.8 (CH_2Bn), 72.5 (C-2), 69.5 (C-4), 62.7 (C-6), 29.8, 20.9 (CH_3 Ac); HRMS: $[M+Na]^+$ calculated for $C_{23}H_{26}O_7SNa$ 469.12915, found 469.12830.

Phenyl 4,6-di-*O*-acetyl-2-*O*-benzyl-3-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (9) Phenyl 4,6-*O*-benzylidene-3-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside[33] (0.443 g, 0.92 mmol) was coevaporated twice with anhydrous toluene before being dissolved in DMF (5 mL). The mixture was cooled to 0°C, after which sodium hydride (60% dispersion in mineral oil, 0.07 g, 1.84 mmol) was added. The mixture was stirred for 10 minutes followed by addition of benzylbromide (0.21 mL, 1.84 mmol). When TLC analysis showed complete consumption of the starting material, the reaction was quenched with sat. aq. $NaHCO_3$. The mixture was diluted with Et_2O, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. The crude was dissolved in DCM/MeOH (15 mL/ 15 mL), followed by addition of p-toluenesulfonic acid monohydrate until the pH was acidic. The reaction was stirred for 95 minutes after which it was neutralized with Et_3N and concentrated. The diol was dissolved in 5 mL pyridine, cooled to 0°C and 0.35 mL Ac_2O was added. After overnight stirring, the reaction was quenched with MeOH and concentrated. Column purification (Pent/EtOAc) gave compound **9** in 58% yield (0.301 g, 0.53 mmol). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59 – 7.53 (m, 2H, CH_{arom}), 7.43 – 7.20 (m, 8H, CH_{arom}), 7.15 (d, 2H, *J* = 8.6 Hz, CH_{arom}), 6.84 (d, 2H, *J* = 8.6 Hz, CH_{arom}), 5.02 (t, 1H, *J* = 9.7, 9.7 Hz, H-4), 4.87 (d, 1H, *J* = 10.2 Hz, CH*H* OBn), 4.72 (m, 2H, CH_2

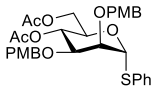
OBn/OPMB), 4.65 (d, 1H, *J* = 9.8 Hz, H-1), 4.58 (d, 1H, *J* = 11.0 Hz, C*H*H OBn/OPMB), 4.21 (dd, 1H, *J* = 12.2, 5.7 Hz, H-6), 4.11 (dd, 1H, *J* = 12.2, 2.1 Hz, H-6), 3.77 (s, 3H, CH_3 OMe), 3.65 (t, 1H, *J* = 9.1, 9.1 Hz, H-3), 3.62 – 3.48 (m, 3H, H-2, H-5), 2.07 (s, 3H, CH_3 Ac), 1.95 (s, 3H, CH_3 Ac); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.7, 169.6 (C=O Ac), 159.3, 137.8, 133.2 (C_q), 132.3 (CH_{arom}), 130.1 (C_q), 129.5, 129.0, 128.5, 128.3, 128.0, 127.9, 113.9 (CH_{arom}), 87.5 (C-1), 83.4 (C-3), 80.6 (C-2), 76.9 (C-5), 75.6, 75.1 (CH_2 OBn/OPMB), 69.8 (C-4), 62.7 (C-6), 55.3 (CH_3 OMe), 20.9, 20.9 (CH_3 Ac); HRMS: $[M+NH_4]^+$ calculated for $C_{31}H_{38}NO_8$ 584.23126, found 584.23143.

Phenyl 4,6-di-*O*-acetyl-2-*O*-benzyl-β-D-glucopyranoside (10) Compound **9** (0.107 g, 0.188 mmol) was



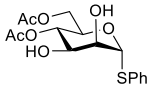
dissolved in 1:1 DCM/HFIP (2 mL) and 0.1 mL 0.2M HCl/HFIP was added. After 20 min the reaction was quenched by addition of pyridine and the mixture was concentrated. Purification by column chromatography (Tol/EtOAc) gave **10** in 81% yield (0.068 g, 0.152 mmol). TLC: R_f 0.38 (PE/EtOAc, 2/1, v/v); $[\alpha]_D^{20}$ -45.6 (*c* 1, DCM); IR (neat, cm^{-1}): 700, 744, 1028, 1043, 1228, 1371, 1739, 2922, 3477; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.58 – 7.54 (m, 2H, CH_{arom}), 7.37 – 7.26 (m, 8H, CH_{arom}), 4.95 (d, 1H, *J* = 10.9 Hz, H-1), 4.90 (t, 1H, *J* = 9.7, 9.7 Hz, H-4), 4.71 (d, 1H, *J* = 10.9 Hz, CH*H* Bn), 4.64 (d, 1H, *J* = 9.8 Hz, C*H*H Bn), 4.22 (dd, 1H, *J* = 12.2, 5.7 Hz, H-6), 4.14 (dd, 1H, *J* = 12.2, 2.3 Hz, H-6), 3.73 (t, 1H, *J* = 9.0, 9.0 Hz, H-3), 3.60 (ddd, 1H, *J* = 10.0, 5.7, 2.3 Hz, H-5), 3.43 – 3.39 (t, 1H, *J* = 10 Hz, 8.5 Hz, H-2), 2.68 (s, 1H, 3-OH), 2.08 (s, 3H), 2.07 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.8, 170.6 (C=O Ac), 137.9 (C_q), 133.3 (C_q), 132.2, 129.1, 128.7, 128.4, 128.3, 127.9 (CH_{arom}), 87.3 (C-1), 80.7 (C-2), 76.5 (C-3), 75.7 (C-5), 75.5 (CH_2Bn), 70.4 (C-4), 62.8 (C-6), 20.9, 20.9 (CH_3 Ac); HRMS: $[M+Na]^+$ calculated for $C_{23}H_{26}O_7SNa$ 469.12915, found 469.12861.

Phenyl 4,6-di-*O*-acetyl-2,3-di-*O*-*p*-methoxybenzyl-1-thio-α-D-mannopyranoside (11) Phenyl 4,6-*O*-



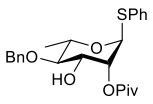
benzylidene-1-thio-α-D-mannopyranoside[34] (1.85 g, 5.13 mmol) was coevaporated twice with anhydrous toluene before being dissolved in DMF (13 mL). The mixture was cooled to 0°C, after which sodium hydride (60% dispersion in mineral oil, 0.62 g, 15 mmol) was added. The mixture was stirred for 10 minutes followed by addition of *para*-methoxybenzylchloride (2.16 mL, 15 mmol). When TLC analysis showed complete consumption of the starting material, the reaction was quenched with sat. aq. $NaHCO_3$. The mixture was diluted with EtOAc, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. The crude was dissolved in MeOH (50 mL), followed by addition of p-toluenesulfonic acid monohydrate (0.09 g, 0.45 mmol). The reaction was stirred for 95 minutes after which it was neutralized with Et_3N and concentrated. The compound was purified by column chromatography (Pent/EtOAc). The diol was dissolved in 20 mL pyridine, cooled to 0°C and 2.17 mL Ac_2O was added. After overnight stirring, the reaction was quenched with EtOH and concentrated. Column purification (Pent/EtOAc) gave compound **11** in 64% yield (1.95 g, 3.26 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 – 7.38 (m, 2H, CH_{arom}), 7.33 – 7.17 (m, 7H, CH_{arom}), 6.85 (m, 4H, CH_{arom}), 5.52 (d, 1H, *J* = 1.6 Hz, H-1), 5.39 (t, 1H, *J* = 9.7, 9.7 Hz, H-4), 4.66 – 4.54 (m, 2H, CH_2PMB), 4.51 – 4.36 (m, 2H, CH_2PMB), 4.31 (ddd, 1H, *J* = 9.6, 6.1, 2.1 Hz, H-6), 4.23 (dd, 1H, *J* = 12.0, 6.1 Hz, H-5), 4.11 (dd, 1H, *J* = 12.0, 2.2 Hz, H-6), 3.97 – 3.91 (m, 1H, H-2), 3.83 – 3.68 (m, 7H, 2x CH_3 OMe, H-3), 2.04 (s, 3H, CH_3 Ac), 2.01 (s, 3H, CH_3 Ac); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 169.7 (C=O Ac), 159.4, 133.8 (C_q), 131.6 (CH_{arom}), 129.9, 129.8 (C_q), 129.6, 129.3, 129.1, 127.7, 113.9, 113.8 (CH_{arom}), 85.9 (C-1), 76.5 (C-3), 75.2 (C-2), 71.9, 71.5 (CH_2PMB), 70.0 (C-5), 68.2 (C-4), 63.0 (C-6), 55.3 (CH_3 OMe), 21.0, 20.8 (CH_3 Ac); HRMS: $[M+NH_4]^+$ calculated for $C_{32}H_{40}NO_9S$ 614.24183, found 614.24212.

Phenyl 4,6-di-*O*-acetyl-1-thio-α-D-mannopyranoside (12) Compound **11** (0.112 g, 0.188 mmol) was dissolved

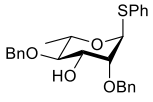


in 1:1 DCM/HFIP (2 mL) and 0.12 mL 0.2M HCl/HFIP was added. After 3 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Pent/EtOAc) gave **12** in 79% yield (0.053 g, 0.148 mmol). TLC: R_f 0.21 (PE/EtOAc, 1/1, v/v); $[\alpha]_D^{20}$ +169.0 (*c* 1, DCM); IR (neat, cm^{-1}): 744, 1051, 1232, 1735, 2933, 3300; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 – 7.39 (m, 2H, CH_{arom}), 7.39 – 7.19 (m, 3H, CH_{arom}), 5.60 (d, 1H, *J* = 1.4 Hz, H-1), 5.11 (t, 1H, *J* = 9.7 Hz, H-4), 4.46 (ddd, 1H, *J* = 10.0, 5.8, 2.2 Hz, H-5), 4.34 (dd, 1H, *J* = 12.1, 5.9 Hz, H-6), 4.23 (dd, 1H, *J* = 3.5, 1.6 Hz, H-2), 4.08 (dd, 1H, *J* = 12.1, 2.2 Hz, H-6), 3.94 (dd, 1H, *J* = 9.4, 3.4 Hz, H-3), 3.29 (s, 2H, 2-OH, 3-OH), 2.15 (s, 3H, CH_3 Ac), 2.03 (s, 3H, CH_3 Ac); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 171.0

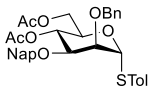
(C=O Ac), 133.3 (C_q SPh), 131.7, 129.2, 127.9 (CH_{arom}), 87.6 (C-1), 72.2 (C-2), 70.8 (C-3), 70.2 C-4), 69.1 (C-5), 62.7 (C-6), 21.1, 20.9 (CH_3 Ac); HRMS: $[M+Na]^+$ calculated for $C_{16}H_{20}O_7SNa$ 379.08219, found 379.08213.



Phenyl 4-*O*-benzyl-2-*O*-Pivaloyl-1-thio-α-L-rhamnopyranoside (14) Compound **13**[7] (0.156 g, 0.276 mmol) was dissolved in a 1:1 DCM/HFIP mixture (2.8 mL) and TES (0.13 mL, 0.84 mmol) was added. The mixture was cooled to 0°C and 1.4 mL of a 0.2M HCl/HFIP solution was added. After TLC and TLC/MS analysis showed complete conversion of the starting material in a lower running spot, the reaction was quenched with sat. aq. $NaHCO_3$ and diluted with DCM. The aqueous layer was washed with DCM and the combined organic layers were washed with a sat. aq. NaCl solution, dried over $MgSO_4$ and concentrated. Silica gel column purification afforded compound **14** in 85% yield (0.102 g, 0.23 mmol). TLC: R_f 0.55 (PE/EtOAc, 9/1, v/v); $[\alpha]_D^{20}$ -123.0 (*c* 1, DCM); IR (neat, cm^{-1}): 690, 738, 1097, 1151, 1280, 1479, 1730, 2972, 3469; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 – 7.42 (m, 2H, CH_{arom}), 7.40 – 7.21 (m, 8H, CH_{arom}), 5.36 (d, 1H, *J* = 1.2 Hz, H-1), 5.33 (dd, 1H, *J* = 3.3, 1.5 Hz, H-2), 4.81 (d, 1H, *J* = 11.2 Hz, CH*H* Bn), 4.74 (d, 1H, *J* = 11.2 Hz, C*H*H Bn), 4.24 (dq, 1H, *J* = 9.5, 6.2, 6.2, 6.2 Hz, H-5), 4.09 (d, 1H, *J* = 10.4 Hz, H-3), 3.38 (t, 1H, *J* = 9.4, 9.4 Hz, H-4), 2.21 (s, 1H, 3-OH), 1.35 (d, 3H, *J* = 6.2 Hz, CH_3-6), 1.23 (s, 9H, CH_3-Piv); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.1 (C=O Piv), 138.1 (C_q), 133.9 (C_q), 132.1, 129.2, 128.7, 128.3, 128.2, 127.8 (CH_{arom}), 86.0 (C-1), 81.7 (C-4), 75.2 (CH_2 Bn), 74.0 (C-2), 71.1 (C-3), 68.7 (C-5), 39.2 (C_q Piv), 27.2 (CH_3 Piv), 18.1 (CH_3-6); HRMS: $[M+Na]^+$ calculated for $C_{24}H_{30}O_5SNa$ 453.17062, found 453.17055.

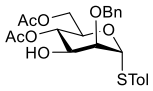


Phenyl 2,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside (16) Compound **15**[7] (0.108 g, 0.194 mmol) was dissolved in a 1:1 DCM/HFIP mixture (2 mL) and TES (0.09 mL, 0.58 mmol) was added. The mixture was cooled to 0°C and 0.97 mL of a 0.2M HCl/HFIP solution was added. After TLC and TLC/MS analysis showed complete conversion of the starting material in a lower running spot, the reaction was quenched with sat. aq. $NaHCO_3$ and diluted with DCM. The aqueous layer was washed with DCM and the combined organic layers were washed with a sat. aq. NaCl solution, dried over $MgSO_4$ and concentrated. Silica gel column purification afforded compound **16** in 76% yield (0.064 g, 0.147 mmol). TLC: R_f 0.78 (PE/EtOAc, 2/1, v/v); $[\alpha]_D^{20}$ -116.0 (*c* 1, DCM); IR (neat, cm^{-1}): 694, 736, 1026, 1066, 1082, 1583, 2873, 3030, 3061; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36 – 7.23 (m, 15H, CH_{arom}), 5.56 (s, 1H, H-1), 4.91 (d, 1H, *J* = 11.1 Hz, CH*H* Bn), 4.74 (d, 1H, *J* = 11.7 Hz, CH*H* Bn), 4.67 (d, 1H, *J* = 11.1 Hz, C*H*H Bn), 4.53 (d, 1H, *J* = 11.7 Hz, C*H*H Bn), 4.16 (dq, 1H, *J* = 9.4, 6.2, 6.2, 6.2 Hz, H-5), 4.00 – 3.95 (m, 2H, H-2, H-3), 3.40 (t, 1H, *J* = 9.1, 9.1 Hz, H-4), 2.37 (bs, 1H, 3-OH), 1.34 (d, 3H, *J* = 6.2 Hz, CH_3-6); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.5, 137.5, 134.5 (C_q), 131.6, 129.2, 128.7, 128.6, 128.3, 128.2, 128.1, 127.9, 127.5 (CH_{arom}), 85.1 (C-1), 82.5 (C-4), 80.1 (C-2), 75.3 (CH_2Bn), 72.5 (CH_2Bn), 72.2 (C-3), 68.7 (C-5), 18.1 (CH_3-6); HRMS: $[M+Na]^+$ calculated for $C_{26}H_{28}O_4SNa$ 459.16005, found 459.15943.



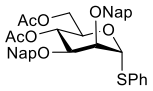
Tolyl 4,6-di-*O*-acetyl-2-*O*-benzyl-3-*O*-(2-naphthylmethyl)-1-thio-α-D-mannopyranoside (18) Tolyl 4,6-*O*-benzylidene-2-*O*-benzyl-3-*O*-(2-naphthylmethyl)-1-thio-α-D-mannopyranoside[35] (1.37 g, 2.28 mmol) was dissolved in DCM/MeOH (3 mL/ 12 mL) and p-toluenesulfonic acid monohydrate (0.043 g, 0.228 mmol) was added. The reaction was stirred for 5 days after which it was neutralized with Et_3N. The crude was dissolved in pyridine (12 mL), cooled to 0°C, followed by addition of 1.3 mL Ac_2O. The reaction was stirred overnight after which it was quenched with EtOH and concentrated. The crude mixture was diluted with EtOAc, washed with 1M HCl, sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Column purification (PE/EtOAc) gave compound **18** in 70% yield (0.969 g, 1.61 mmol). ^{1}H NMR($CDCl_3$, 400 MHz): δ 7.87 – 7.79 (m, 3H, CH_{arom}), 7.74 (s, 1H CH_{arom}), 7.53 – 7.48 (m, 1H CH_{arom}), 7.48 – 7.37 (m, 2H CH_{arom}), 7.37 – 7.21 (m, 7H CH_{arom}), 7.12 – 7.05 (m, 2H CH_{arom}), 5.54 – 5.43 (m, 2H, H-1, H-4), 4.84 – 4.51 (m, 4H, CH_2 Bn/Nap), 4.39 – 4.30 (m, 1H, H-5), 4.25 (dd, 1H, *J* = 12.1, 6.0 Hz, H-6), 4.17 – 4.06 (m, 1H, H-6), 4.05 – 3.98 (m, 1H, H-2), 3.84 (dd, 1H, *J* = 9.6, 2.9 Hz, H-3), 2.32 (s, 3H, CH_3 Tol), 2.07 – 2.01 (m, 6H, 2x CH_3 Ac); ^{13}C NMR($CDCl_3$, 101 MHz): δ 170.8, 169.8 (C=O Ac), 138.0, 137.7, 135.3, 133.3, 133.1 (C_q), 132.2, 129.9 (CH_{arom}), 129.9 (C_q), 128.4, 128.3, 128.0, 127.8, 127.8, 126.5, 126.3, 126.1, 125.7, 118.8 (CH_{arom}), 86.1 (C-1), 77.0 (C-3), 75.5 (C-2), 72.2, 71.8 (CH_2 OBn/ONap), 69.9 (C-5), 68.1 (C-4), 63.0 (C-6), 21.2, 21.0, 20.9 (CH_3 Tol, Ac); HRMS: $[M+NH_4]^+$ calculated for $C_{35}H_{40}NO_7S$ 618.25200, found 618.25193.

Tolyl 4,6-di-*O*-acetyl-2-*O*-benzyl-1-thio-*α*-D-mannopyranoside (19) Compound **18** (0.117 g, 0.195 mmol) was



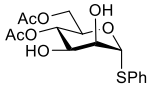
dissolved in 1:1 DCM/HFIP (2 mL) and 0.09 mL TES was added. The solution was treated with 0.97 mL 0.2M HCl/HFIP. After 33 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (hexanes/EtOAc) gave **19** in 86% yield (0.077 g, 0.168 mmol). TLC: R_f 0.56 (PE/EtOAc, 2/1, v/v); $[\alpha]_D^{20}$ +61.6 (*c* 1, DCM); IR (neat, cm^{-1}): 781, 1051, 1101, 1226, 1739, 2924, 3477; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 – 7.27 (m, 6H, CH_{arom}), 7.12 (d, 2H, *J* = 8.0 Hz, CH_{arom}), 5.57 (s, 1H, H-1), 5.14 (t, 1H, *J* = 9.9, 9.9 Hz, H-4), 4.74 (d, 1H, *J* = 11.6 Hz, C*H*H Bn), 4.53 (d, 1H, *J* = 11.6 Hz, CH*H* Bn), 4.42 (ddd, 1H, *J* = 9.9, 5.8, 2.0 Hz, H-5), 4.27 (dd, 1H, *J* = 12.1, 5.9 Hz, H-6), 4.12 (dd, 1H, *J* = 12.1, 2.1 Hz, H-6), 4.01 (dd, 1H, *J* = 3.5, 1.1 Hz, H-2), 3.90 (s, 1H, H-3), 2.39 (s, 1H, 3-OH), 2.33 (s, 3H, CH_3 STol), 2.12 (s, 3H, CH_3 Ac), 2.05 (s, 3H, CH_3 Ac); ^{13}C-NMR(CDCl3, 100 MHz): δ ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8 (C=O Ac), 138.2 (C_q), 137.1 (C_q), 132.5, 130.0 (CH_{arom}), 129.6 (C_q), 128.7, 128.3, 128.1 (CH_{arom}), 85.3 (C-1), 79.3 (C-2), 72.4 (CH_2 Bn), 70.3 (C-3), 69.9 (C-4), 69.2 (C-5), 62.9 (C-6), 21.2 (CH_3 STol), 21.1, 20.9 (CH_3 Ac); HRMS: $[M+Na]^+$ calculated for $C_{24}H_{28}O_7SNa$ 483.14480, found 483.14387.

Phenyl 4,6-di-*O*-acetyl-2,3-di-*O*-(2-naphthylmethyl)-1-thio-α-D-mannopyranoside (20) 4,6-*O*-benzylidene-1-



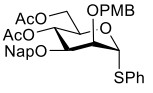
thio-α-D-mannopyranoside[34] (1.08 g, 3 mmol) was coevaporated twice with anhydrous toluene before being dissolved in DMF (15 mL). The mixture was cooled to 0°C, after which sodium hydride (60% dispersion in mineral oil, 0.48 g, 12 mmol) was added. The mixture was stirred for 10 minutes followed by addition of 2-naphthylmethylbromide (2.65 g, 12 mmol). When TLC analysis showed complete consumption of the starting material, the reaction was quenched with sat. aq. $NaHCO_3$. The mixture was diluted with EtOAc, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. The crude was dissolved in DCM/MeOH (7.5 mL/ 7.5 mL), followed by addition of p-toluenesulfonic acid monohydrate (0.057 g, 0.3 mmol). The reaction was stirred for overnight after which it was neutralized with Et_3N and concentrated. The compound was purified by column chromatography (Pent/EtOAc). The diol was dissolved in 10 mL pyridine, cooled to 0°C and 1.67 mL Ac_2O was added. After stirring for 6 days, the reaction was quenched with EtOH, diluted with EtOAc and washed with 1M HCl. Column purification (Pent/EtOAc) gave compound **20** in 57% yield (1.09 g, 1.71 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 – 7.61 (m, 8H, CH_{arom}), 7.49 – 7.41 (m, 4H, CH_{arom}), 7.41 – 7.32 (m, 4H, CH_{arom}), 7.26 – 7.17 (m, 3H, CH_{arom}), 5.59 (d, 1H, *J* = 1.6 Hz, H-1), 5.55 (t, 1H, *J* = 9.6, 9.6 Hz, H-4), 4.87 – 4.72 (m, 2H, CH_2 ONap), 4.70 – 4.54 (m, 2H, CH_2 ONap), 4.39 – 4.24 (m, 2H, H-5, H-6), 4.14 (dd, 1H, *J* = 11.8, 1.8 Hz, H-6), 4.09 – 4.01 (m, 1H, H-2), 3.86 (dd, 1H, *J* = 9.6, 3.0 Hz, H-3), 2.02 (m, 6H, 2x CH_3 Ac); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.7, 169.7 (C=O Ac), 135.2, 135.1, 133.5, 133.2, 133.1, 133.0, 133.0 (C_q), 131.5, 129.0, 128.2, 128.2, 127.9, 127.9, 127.7, 127.7, 126.8, 126.4, 126.2, 126.1, 126.0, 125.9, 125.6 (CH_{arom}), 85.8 (C-1), 77.0 (C-3), 75.4 (C-2), 72.2, 71.9 (CH_2 Nap), 70.0 (C-5), 68.0 (C-4), 62.8 (C-6), 20.9, 20.8 (CH_3 Ac); HRMS: $[M+NH_4]^+$ calculated for $C_{38}H_{40}NO_7S$ 654.25200, found 654.25266.

Phenyl 4,6-di-*O*-acetyl-1-thio-β-D-mannopyranoside (12) Compound **20** (0.127 g, 0.199 mmol) was dissolved



in 1:1 DCM/HFIP (2.0 mL) and 0.16 mL TES was added. The mixture was treated with 3.0 mL 0.2M HCl/HFIP was added. After 20 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **12** in 68% yield (0.048 g, 0.135 mmol). Spectroscopic data are in full accord with those reported previously.

Phenyl 4,6-di-*O*-acetyl-3-*O*-(2-naphthylmethyl)-2-*O*-*p*-methoxybenzyl-1-thio-α-D-mannopyranoside (21)



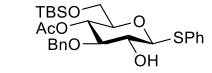
Phenyl 4,6-*O*-Benzylidene-3-*O*-(2-naphthylmethyl)-1-thio-α-D-mannopyranoside[36] (5.17 g, 10.32 mmol) was coevaporated twice with anhydrous toluene before being dissolved in DMF (25 mL). The mixture was cooled to 0°C, after which sodium hydride (60% dispersion in mineral oil, 1.2 g, 30 mmol) was added. The mixture was stirred for 10 minutes followed by addition of *para*-methoxybenzylchloride (4.1 mL, 30 mmol). When TLC analysis showed complete consumption of the starting material, the reaction was quenched with sat. aq. $NaHCO_3$. The mixture was diluted with EtOAc,

washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. After column purification (Pent/EtOAc) the compound was dissolved in DCM/MeOH (15 mL/ 15 mL), followed by addition of p-toluenesulfonic acid monohydrate (0.06 g, 0.30 mmol). The reaction was stirred overnight after which it was neutralized with Et_3N and concentrated. The compound was purified by column chromatography (Pent/EtOAc) to yield the diol in 89% yield (2.97 g, 5.57 mmol). The diol (1.425 g, 2.67 mmol) was dissolved in 15 mL pyridine, cooled to 0°C and 1.5 mL Ac_2O was added. After stirring for 3 days, the reaction was quenched with EtOH and concentrated. The crude was taken up in EtOAc, washed with 1M HCl and sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Column purification (hexanes/EtOAc) gave compound **21** in 75% yield (1.23 g, 1.99 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (m, 3H, CH_{arom}), 7.73 (s, 1H CH_{arom}), 7.48 (m, 1H, CH_{arom}), 7.47 – 7.36 (m, 4H, CH_{arom}), 7.25 (m, 6H, CH_{arom}), 6.78 (d, 2H, *J* = 8.2 Hz, CH_{arom}), 5.55 (s, 1H, H-1), 5.47 (t, 1H, *J* = 9.7, 9.7 Hz, H-4), 4.71 – 4.61 (m, 2H, CH_2 ONap/OPMB), 4.58 (m, 2H, CH_2 ONap/OPMB), 4.37 – 4.21 (m, 2H, H-5, H-6), 4.12 (d, 1H, *J* = 11.7 Hz, H-6), 4.01 (s, 1H, H-2), 3.83 (dd, 1H, *J* = 9.6, 2.9 Hz, H-3), 3.73 (s, 3H, CH_3 OMe), 2.06 – 2.00 (m, 6H, 2x CH_3 Ac); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.8, 169.8 (C=O Ac), 159.3, 135.3, 133.7, 133.3, 133.0, 131.5 (C_q), 129.7, 129.1, 128.2, 128.0, 127.8, 127.7, 126.4, 126.3, 126.1, 125.6, 113.8 (CH_{arom}), 85.8 (C-1), 77.0 (C-3), 75.0 (C-2), 71.8, 71.8 (CH_2 ONap/OPMB), 70.0 (C-5), 68.1 (C-4), 62.9 (C-6), 55.3 (CH_3 OMe), 21.0, 20.8 (CH_3 Ac); HRMS: $[M+NH_4]^+$ calculated for $C_{35}H_{40}NO_8S$ 634.24691, found 634.24718.

Phenyl 4,6-di-*O*-acetyl-3-*O*-(2-naphthylmethyl)-1-thio-α-D-mannopyranoside (22) Compound **21** (0.127 g, 0.202 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.1 mL 0.2M HCl/HFIP was added. After 5 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **22** in 80% yield (0.080 g, 0.162 mmol). TLC: R_f 0.35 (PE/EtOAc, 2/1, v/v); $[\alpha]_D^{20}$ +132.4 (*c* 1, DCM); IR (neat, cm^{-1}): 742, 1041, 1099, 1224, 1367, 1739, 2893, 3057, 3460; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88 – 7.82 (m, 3H, CH_{arom}), 7.76 (s, 1H, CH_{arom}), 7.55 – 7.47 (m, 2H, CH_{arom}), 7.50 – 7.37 (m, 3H, CH_{arom}), 7.33 – 7.23 (m, 3H, CH_{arom}), 5.63 (d, 1H, *J* = 1.4 Hz, H-1), 5.35 (t, 1H, *J* = 9.7, 9.7 Hz, H-4), 4.86 (d, 1H, *J* = 12.2 Hz, C*H*H Bn), 4.72 (d, 1H, *J* = 12.2 Hz, C*H*H Bn), 4.37 (ddd, 1H, *J* = 9.9, 5.7, 2.2 Hz, H-5), 4.30 (s, 1H, H-2), 4.24 (dd, 1H, *J* = 12.2, 5.8 Hz, H-6), 4.05 (dd, 1H, *J* = 12.2, 2.3 Hz, H-6), 3.86 (dd, 1H, *J* = 9.3, 3.2 Hz, H-3), 2.85 (s, 1H, 2-OH), 2.01 (s, 6H, 2x CH_3 Ac); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.9, 169.9 (C=O Ac), 134.7 (C_q), 133.3 (C_q), 133.3 (C_q), 133.2, 131.7, 129.2, 128.6, 128.1, 127.9, 127.8, 127.0, 126.5, 126.4, 125.7 (CH_{arom}), 86.9 (C-1), 77.1 (C-3), 72.2 (CH_2 Nap), 69.6 (C-5), 69.5 (C-2), 67.6 (C-4), 62.7 (C-6), 21.0, 20.9 (CH_3 Ac); HRMS: $[M+Na]^+$ calculated for $C_{27}H_{28}O_7SNa$ 519.14480, found 519.14406.

Phenyl 4-*O*-acetyl-3-*O*-Benzyl-2-*O*-*p*-methoxybenzyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (23) Phenyl 3-*O*-Benzyl-2-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (from synthesis compound **7**) (2.41 g, 5 mmol) was coevaporated once with anhydrous toluene. The diol was dissolved in DMF (25 mL) and cooled to 0°C. Imidazole (0.35 g, 5.2 mmol) was added followed by TBS-Cl (0.78 g, 5.2 mmol). After 100 minutes the reaction was quenched with MeOH and concentrated. The crude was dissolved in 25 mL pyridine and cooled to 0°C. Ac_2O (1.9 mL) was added and the reaction was stirred for 5 days. The reaction was quenched with EtOH and concentrated. The crude was taken up in EtOAc, washed with 1M HCl and sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Column purification (hexanes/EtOAc) gave compound **23** in 77% yield (2.45 g, 3.83 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 – 7.54 (m, 2H, CH_{arom}), 7.38 – 7.18 (m, 10H, CH_{arom}), 6.90 – 6.82 (m, 2H, CH_{arom}), 4.99 (t, 1H, *J* = 9.7, 9.7 Hz, H-4), 4.86 – 4.73 (m, 2H, C*H*H OBn/OPMB), 4.69 – 4.56 (m, 3H, H-1, C*H*H OBn/OPMB), 3.78 (s, 3H, CH_3 OMe), 3.73 – 3.59 (m, 3H, H-3, H-6), 3.52 (t, 1H, *J* = 9.6, 9.1 Hz, H-2), 3.44 (ddd, 1H, *J* = 9.9, 4.8, 3.3 Hz, H-5), 1.90 (s, 3H, CH_3 Ac), 0.90 (s, 9H, CH_3 tBu), 0.89 (s, 3H, CH_3 Me), 0.06 (s, 3H, CH_3 Me); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.6 (C=O Ac), 159.5, 138.3, 133.9 (C_q), 131.9 131.8 (CH_{arom}), 130.2 (C_q), 130.0, 129.0, 128.5, 127.9, 127.8, 127.5, 113.9 (CH_{arom}), 87.6 (C-1), 84.3 (C-3), 80.3 (C-2), 79.2 (C-5), 75.5, 75.1 (CH_2 OBn/OPMB), 70.2 (C-4), 62.9 (C-6), 55.3 (CH_3 OMe), 26.0 (CH_3 tBu), 20.9 (CH_3 Ac), 18.4 (C_q tBu), -5.2, -5.4 (CH_3 Me); $[M+NH_4]^+$ calculated for $C_{35}H_{50}O_7SSiN$ 656.30718, found 656.30769.

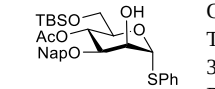
Phenyl 4-*O*-acetyl-3-*O*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (24) Compound **23**



(0.130 g, 0.203 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.033 mL TES was added. The solution was treated with 0.1 mL of a 0.2M HCl/HFIP solution. After 6 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **24** in 48% yield (0.0738 g, 0.142 mmol). TLC: R_f 0.33 (PE/EtOAc, 6/1, v/v); $[\alpha]_D^{20}$ -22.2 (*c* 1, DCM); IR (neat, cm^{-1}): 734, 1026, 1228, 1741, 2856, 2926, 3288; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.61 – 7.51 (m, 2H, CH_{arom}), 7.37 – 7.20 (m, 8H, CH_{arom}), 4.93 (t, 1H, *J* = 9.8, 9.8 Hz, H-4), 4.82 (d, 1H, *J* = 11.8 Hz, C*H*H Bn), 4.68 (d, 1H, *J* = 11.8 Hz, CH*H* Bn), 4.50 (d, 1H, *J* = 9.3 Hz, H-1), 3.74 – 3.61 (m, 2H, H-6), 3.60 – 3.43 (m, 3H, H-2, H-3, H-5), 2.46 (s, 1H, 2-OH), 1.96 (s, 3H, CH_3 Ac), 0.90 (s, 9H, CH_3 tBu), 0.07 (s, 3H, CH_3 Me), 0.05 (s, 3H, CH_3 Me); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7 (C=O), 138.4 (C_q), 133.0 (CH_{arom}), 131.6 (C_q), 129.1, 128.6, 128.3, 128.0, 127.9 (CH_{arom}), 88.1 (C-1), 83.3 (C-3), 79.6 (C-5), 74.8 (CH_2 Bn), 72.4 (C-2), 69.9 (C-4), 63.0 (C-6), 26.0 (CH_3 tBu), 21.0 (CH_3 Ac), 18.5 (C_q tBu), -5.1, -5.3 (CH_3 Me); HRMS: $[M+Na]^+$ calculated for $C_{27}H_{38}O_6SSiNa$ 541.20506, found 541.20484.

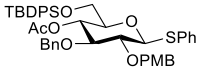
Phenyl 4-*O*-acetyl-3-*O*-(2-Naphthylmethyl)-2-*O*-*p*-methoxybenzyl-6-*O*-*tert*-butyldimethylsilyl-1-thio-α-D-mannopyranoside (25) Phenyl 3-*O*-(2-Naphthylmethyl)-2-*O*-*p*-methoxybenzyl-1-thio-α-D-mannopyranoside (from synthesis compound **21**) (0.37 g, 0.7 mmol) was coevaporated once with anhydrous toluene. The diol was dissolved in DMF (3.5 mL) and cooled to 0°C. Imidazole (0.05 g, 0.7 mmol) was added followed by TBS-Cl (0.11 g, 0.72 mmol). After 20 minutes the reaction was quenched with MeOH and concentrated. The crude was taken up in Et_2O, washed with H_2O and sat. aq. NaCl, dried over $MgSO_4$ and concentrated. The compound was dissolved in pyridine (3 mL) and cooled to 0°C, followed by addition of 1 mL Ac_2O. The reaction was stirred overnight after which it was quenched with EtOH. The mixture was concentrated, taken up in EtOAc, washed with 1M HCl, sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography gave compound **25** in 95% yield (0.457 g, 0.66 mmol). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.75 – 7.70 (m, 3H, CH_{arom}), 7.66 (s, 1H, CH_{arom}), 7.44 – 7.35 (m, 4H, CH_{arom}), 7.21 – 7.08 (m, 6H, CH_{arom}), 6.69 (d, 2H, *J* = 8.5 Hz, CH_{arom}), 5.43 (s, 1H, H-1), 5.28 (t, 1H, *J* = 9.6, 9.6 Hz, H-4), 4.60 (d, 1H, *J* = 12.4 Hz, CH*H* OPMB/OBn), 4.56 – 4.43 (m, 3H, C*H*H OPMB/OBn, CH_2 OPMB/OBn), 4.10 (bm, 1H, H-5), 3.91 (s, 1H, H-2), 3.76 – 3.67 (m, 2H, H-3, H-6), 3.63 (m, 4H, CH_3 OMe, H-6), 1.94 (s, 3H, CH_3 Ac), 0.86 – 0.77 (m, 9H, CH_3 tBu), -0.05 (s, 6H, 2x CH_3 Me); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.9 (C=O Ac), 159.3, 135.5, 134.3, 133.3, 133.0 (C_q), 131.8 (CH_{arom}), 129.9 (C_q), 129.6, 129.0, 128.2, 128.0, 127.8, 127.5, 126.5, 126.2, 126.0, 125.7, 113.8 (CH_{arom}), 85.9 (C-1), 77.2 (C-3), 75.4 (C-2), 73.3 (C-5), 71.7, 71.7 (CH_2 ONap/OPMB), 68.8 (C-4), 63.3 (C-6), 55.2 (CH_3 OMe), 26.0 (CH_3 tBu), 21.1 (CH_3 Ac), 18.4 (C_q tBu), -5.2, -5.3 (CH_3 Me); $[M+NH_4]^+$ calculated for $C_{39}H_{52}O_7SSiN$ 706.32283, found 706.32349.

Phenyl 4-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-3-*O*-(2-Naphthylmethyl)-1-thio-α-D-mannopyranoside (26)



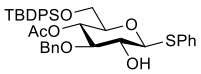
Compound **25** (0.1337 g, 0.194 mmol) was dissolved in 1:1 DCM/HFIP (2 mL) and 0.194 mL TES was added. The solution was treated with 0.095 mL of a 0.2M HCl/HFIP solution. After 3 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **26** in 61% yield (0.07 g, 0.123 mmol). TLC: R_f 0.48 (PE/EtOAc, 7/1, v/v); $[\alpha]_D^{20}$ +92.0 (*c* 1, DCM); IR (neat, cm^{-1}): 740, 777, 835, 1051, 1085, 1228, 1369, 1741, 2854, 2926, 3057, 3640; ^1H NMR ($CDCl_3$, 500 MHz): 7.83 – 7.77 (m, 3H, CH_{arom}), 7.72 (s, 1H, CH_{arom}), 7.45 – 7.42 (m, 4H, CH_{arom}), 7.38 (dd, 1H, *J* = 8.5, 1.6 Hz, CH_{arom}), 7.24 – 7.19 (m, 3H, CH_{arom}), 5.53 (d, 1H, *J* = 1.7 Hz, H-1), 5.23 (t, 1H, *J* = 9.5, 9.5 Hz, H-4), 4.81 (d, 1H, *J* = 12.2 Hz, CH*H* Nap), 4.67 (d, 1H, *J* = 12.2 Hz, C*H*H Nap), 4.27 – 4.22 (m, 1H, H-2), 4.18 (ddd, 1H, *J* = 9.3, 6.2, 2.6 Hz, H-5), 3.79 (dd, 1H, *J* = 9.2, 3.2 Hz, H-3), 3.69 (dd, 1H, *J* = 11.4, 6.2 Hz, H-6), 3.61 (dd, 1H, *J* = 11.4, 2.6 Hz, H-6), 2.74 (s, 1H, 2-OH), 1.96 (s, 3H, CH_3 Ac), 0.82 (s, 9H, CH_3 tBu), -0.03 (s, 3H, CH_3 Me), -0.04 (s, 3H, CH_3 Me); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.0 (C=O Ac), 134.9 (C_q), 133.8 (C_q), 133.3 (C_q), 133.2 (C_q), 131.8, 130.5, 129.1, 129.0, 128.6, 128.1, 128.0, 127.9, 127.6, 126.9, 126.5, 126.3, 125.8 (CH_{arom}), 87.2 (C-1), 77.3 (C-3), 72.8 (C-5), 72.0 (CH_2 Nap), 69.6 (C-2), 68.3 (C-4), 63.1 (C-6), 26.0 (CH_3 tBu), 21.1 (CH_3 Ac), 18.5 (C_q tBu), -5.2, -5.3 (CH_3 Me); HRMS: $[M+Na]^+$ calculated for $C_{31}H_{40}O_6SSiNa$ 591.22071, found 591.22003.

Phenyl 4-*O*-acetyl-3-*O*-Benzyl-2-*O*-*p*-methoxybenzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-glucopyranoside



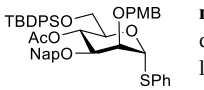
(28) Phenyl 3-*O*-Benzyl-2-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (from synthesis compound **7**) (1.23 g, 2.55 mmol) was coevaporated twice with anhydrous toluene. The diol was dissolved in DMF (13 mL) and cooled to 0°C. Imidazole (0.17 g, 2.55 mmol) was added followed by TBDPS-Cl (0.69 mL, 2.66 mmol). After 15 minutes the icebath was removed and the reaction was stirred overnight. The reaction was quenched with MeOH, concentrated, dissolved in Et_2O and washed twice with H_2O. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. The crude was dissolved in 15 mL pyridine and cooled to 0°C. Ac_2O (1.2 mL) was added and the reaction was stirred until all starting material was converted in a higher running spot. The reaction was quenched with EtOH and concentrated. The crude was taken up in EtOAc, washed with 1M HCl and sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Column purification (hexanes/EtOAc) gave compound **27** in 78% yield (1.53 g, 2.00 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 – 7.64 (m, 5H, CH_{arom}), 7.64 – 7.57 (m, 2H, CH_{arom}), 7.46 – 7.17 (m, 16H, CH_{arom}), 6.92 – 6.83 (m, 2H, CH_{arom}), 5.08 (t, 1H, *J* = 9.6, 9.5 Hz, H-4), 4.80 (m, 2H, CH*H* OBn/OPMB), 4.70 – 4.57 (m, 3H, H-1, C*H*H OBn/OPMB), 3.80 (s, 3H, CH_3 OMe), 3.70 (d, 2H, *J* = 3.7 Hz, H-6), 3.65 – 3.50 (m, 2H, H-2, H-3), 3.46 (dt, 1H, *J* = 10.0, 3.7, 3.7 Hz, H-5) 1.75 (s, 3H, CH_3 Ac), 1.06 (s, 9H, CH_3 tBu); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.5 (C=O Ac), 159.6, 138.3 (C_q), 135.8, 135.8, 134.9 (CH_{arom}), 133.9, 133.3, 133.2 (C_q), 132.0 (CH_{arom}), 130.3 (C_q), 130.1, 129.8, 129.7, 129.1, 128.6, 128.0, 127.9, 127.8, 127.8, 127.6, 114.0 (CH_{arom}), 87.7 (C-1), 84.4 (C-3), 80.5 (C-5), 79.2 (C-2), 75.5, 75.2 (CH_2 Bn/PMB), 69.8 (C-4), 63.1 (C-6), 55.4 (CH_3 OMe), 26.9 (CH_3 tBu), 20.8 (CH_3 Ac), 19.3 (C_q tBu); $[M+NH_4]^+$ calculated for $C_{45}H_{54}O_7SSiN$ 780.33848, found 780.33936.

Phenyl 4-*O*-acetyl-3-O-Benzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio-β-D-glucopyranoside (29) Compound **28**



(0.0798 g, 0.104 mmol) was dissolved in 1:1 DCM/HFIP (1 mL) and 0.017 mL TES was added. The solution was treated with 0.05 mL of a 0.2M HCl/HFIP solution. After 18 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **28** in 90% yield (0.06 g, 0.093 mmol). TLC: R_f 0.37 (PE/EtOAc, 6/1, v/v); $[\alpha]_D^{20}$ -17.2 (*c* 1, DCM); IR (neat, cm^{-1}): 740, 1028, 1112, 1228, 1747, 2929, 2954, 3028, 3496; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73 – 7.65 (m, 4H, CH_{arom}), 7.62 – 7.56 (m, 2H, CH_{arom}), 7.44 – 7.20 (m, 15H, CH_{arom}), 5.03 (t, 1H, *J* = 9.5, 9.5 Hz, H-4), 4.81 (d, 1H, *J* = 11.8 Hz, C*H*H Bn), 4.67 (d, 1H, *J* = 11.8 Hz, CH*H* Bn), 4.52 (d, 1H, *J* = 9.2 Hz, H-1), 3.73 – 3.68 (m, 2H, H-6), 3.59 – 3.47 (m, 3H, H-2, H-3, H-5), 2.47 (d, 1H, *J* = 1.4 Hz, 2-OH), 1.81 (CH_3 Ac) 1.05 (s, 9H, CH_3 tBu); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.5 (C=O Ac), 138.3 (C_q), 135.8, 135.8, 134.9 (CH_{arom}), 133.3 (C_q), 133.2 (CH_{arom}), 133.0 (C_q), 131.7, 129.8, 129.8, 129.2, 128.6, 128.3, 128.0, 127.9, 127.8, 127.8, 127.8 (CH_{arom}), 88.2 (C-1), 83.3 (C-3), 79.5 (C-5), 74.7 (CH_2 Bn), 72.5 (C-2), 69.4 (C-4), 63.0 (C-6), 26.8 (CH_3 tBu), 20.9 (CH_3 Ac), 19.3 (C_q tBu); HRMS: $[M+Na]^+$ calculated for $C_{37}H_{42}O_6SSiNa$ 665.23636, found 665.23572.

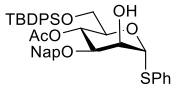
Phenyl 4-*O*-acetyl-3-*O*-(2-Naphthylmethyl)-2-*O*-*p*-methoxybenzyl-6-*O*-*tert*-butyldiphenylsilyl-1-thio-α-D-



mannopyranoside (30) Compound **21** (0.416 g, 0.6 mmol) was dissolved in MeOH and a catalytic amount of NaOMe was added. After consumption of the starting material in a lower running spot the mixture was neutralized with Amberlite-H^+ resin, filtered and concentrated. The diol was coevaporated once with anhydrous toluene, dissolved in DMF (5 mL) and cooled to 0°C. Imidazole (0.04 g, 0.6 mmol) was added followed by TBDPS-Cl (0.16 mL, 0.62 mmol). After overnight stirring the reaction was quenched with MeOH and concentrated. The compound was dissolved in pyridine (4 mL) and cooled to 0°C, followed by addition of 2 mL Ac_2O. The reaction was stirred overnight after which it was quenched with EtOH. The mixture was concentrated, taken up in Et_2O, washed with 1M HCl, sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography gave compound **25** in 50% yield (0.25 g, 0.30 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 – 7.77 (m, 3H, CH_{arom}), 7.74 (s, 1H, CH_{arom}), 7.66 (m, 4H, CH_{arom}), 7.52 – 7.16 (m, 17H, CH_{arom}), 6.80 – 6.73 (m, 2H, CH_{arom}), 5.57 (d, 1H, *J* = 1.8 Hz, H-1), 5.44 (t, 1H, *J* = 9.7, 9.7 Hz, H-4), 4.73 – 4.53 (m, 4H, 2x CH_2 ONap/OPMB), 4.29 – 4.20 (m, 1H, H-5), 4.05 – 3.99 (m, 1H, H-2), 3.85 (dd, 1H, *J* = 11.4, 6.2 Hz, H-6), 3.79 (dd, 1H, *J* = 9.4, 3.0 Hz, H-3), 3.75 – 3.64 (m, 4H, CH_3 OMe, H-6), 1.86 (s, 3H, CH_3 Ac), 1.03 (s, 9H, CH_3 tBu); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.7 (C=O), 159.3 (C_q), 135.8, 135.7 (CH_{arom}), 135.5, 134.7, 133.5, 133.4, 133.3,

133.1 (C_q), 131.3 (CH_{arom}), 129.9 (C_q), 129.7, 129.6, 129.6, 129.1, 128.2, 128.0, 127.8, 127.7, 127.6, 127.4, 126.5, 126.2, 126.0, 125.8, 113.8 (CH_{arom}), 86.0 (C-1), 77.2 (C-3), 75.4 (C-2), 73.3 (C-5), 71.8, 71.6 (CH_2 ONap/OPMB), 68.3 (C-4), 63.5 (C-6), 55.3 (CH_3 OMe), 26.8 (CH_3 tBu), 21.0 (CH_3 Ac), 19.3 (C_q tBu); $[M+NH_4]^+$ calculated for $C_{49}H_{56}O_7SSiN$ 830.35413, found 830.35472.

Phenyl 4-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl-3-*O*-(2-Naphthylmethyl)-1-thio-α-D-mannopyranoside (31)



Compound **30** (0.0825 g, 0.101 mmol) was dissolved in 1:1 DCM/HFIP (1 mL) and 0.016 mL TES was added. The solution was treated with 0.05 mL of a 0.2M HCl/HFIP solution. After 11 min the reaction was quenched by addition of sat. aq. $NaHCO_3$. The mixture was diluted DCM and the organic layer is washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated. Purification by column chromatography (Tol/EtOAc) gave **30** in 88% yield (0.0614 g, 0.0886 mmol). TLC: R_f 0.23 (PE/EtOAc, 6/1, v/v); $[\alpha]_D^{20}$ +71.8 (*c* 1, DCM); IR (neat, cm^{-1}): 740, 821, 1053, 1083, 1228, 1743, 2854, 2927, 3051, 3448; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.84 (d, 3H, *J* = 7.8 Hz), 7.76 (s, 1H), 7.67 – 7.61 (m, 4H), 7.54 – 7.46 (m, 4H), 7.45 – 7.27 (m, 7H), 7.27 – 7.19 (m, 4H), 5.62 (d, 1H, *J* = 1.6 Hz, H-1), 5.34 (t, 1H, *J* = 9.5, 9.5 Hz, H-4), 4.85 (d, 1H, *J* = 12.2 Hz, CH*H* Nap), 4.71 (d, 1H, *J* = 12.2 Hz, C*H*H Nap), 4.31 (s, 1H, H-2), 4.29 – 4.23 (m, 1H, H-5), 3.84 – 3.75 (m, 2H, H-3, H-6), 3.64 (dd, 1H, *J* = 11.5, 2.1 Hz, H-6), 2.74 (s, 1H, 2-OH), 1.85 (s, 3H, CH_3 Ac), 1.01 (s, 9H, CH_3 tBu); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.8 (C=O Ac), 135.9, 135.7, 134.8 (C_q), 134.1 (C_q), 133.5 (C_q), 133.3 (C_q), 133.3 (C_q), 133.3 (C_q), 131.4, 129.7, 129.7, 129.2, 128.6, 128.1, 127.9, 127.8, 127.7, 127.5, 127.0, 126.5, 126.3, 125.8 (CH_{arom}), 87.2 (C-1), 77.3 (C-3), 72.8 (C-5), 71.9 (CH_2 Nap), 69.7 (C-2), 67.8 (C-4), 63.3 (C-6), 26.8 (CH_3 tBu), 21.0 (CH_3 Ac), 19.3 (C_q tBu); HRMS: $[M+Na]^+$ calculated for HRMS: $[M+Na]^+$ calculated for $C_{41}H_{44}O_6SSiNa$ 715.25201, found 715.25149.

References and footnotes

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