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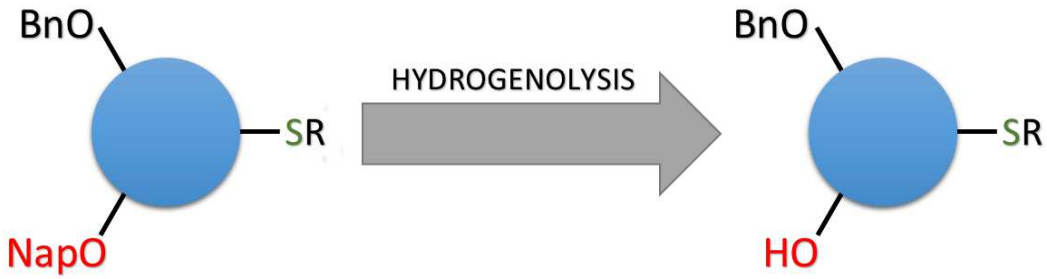

Hydrogenolytic Cleavage of Naphthylmethyl Ethers in the Presence of Sulfides

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Abstract. With the aid of a series of model thioether or thioglycoside containing polyols protected with combinations of benzyl ethers and 2-naphthylmethyl ethers it is demonstrated that the latter are readily cleaved selectively under hydrogenolytic conditions in the presence of the frequently catalyst-poisoning sulfides. These results suggest the possibility of employing 2-naphthylmethyl ethers in place of benzyl ethers in synthetic schemes when hydrogenolytic deprotection is anticipated in the presence of thioether type functionality.

Keywords: Naphthylmethyl ethers, benzyl ethers, hydrogenolysis, thioethers, thioglycosides

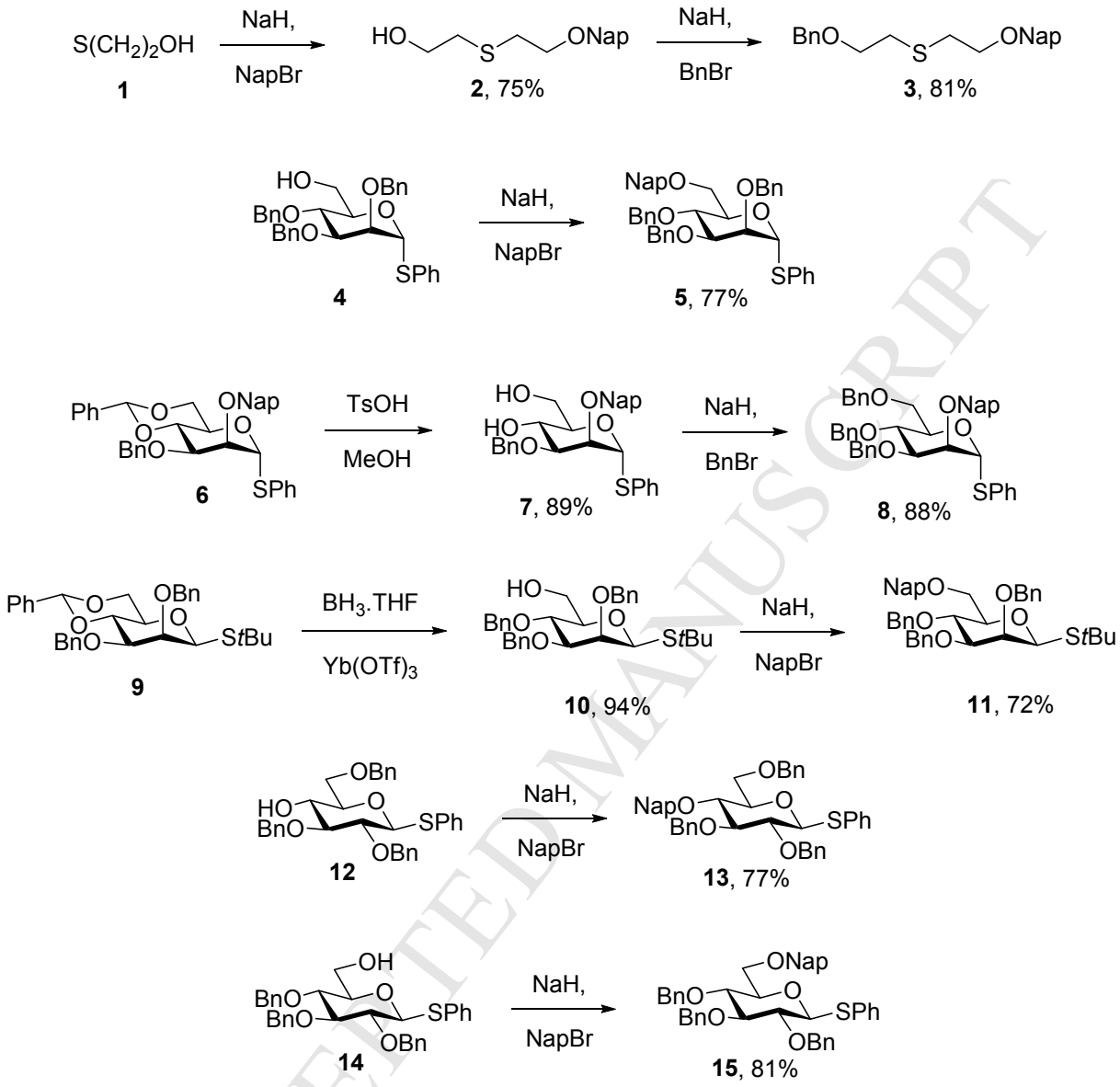
1. Introduction.

Benzyl ethers are very widely employed as semi-permanent protecting groups in organic chemistry and carbohydrate chemistry and are typically removed by hydrogenolysis at the end of a synthetic sequence.[1,2] However, quoting Kocienski “A typical cause of vexation in the catalytic

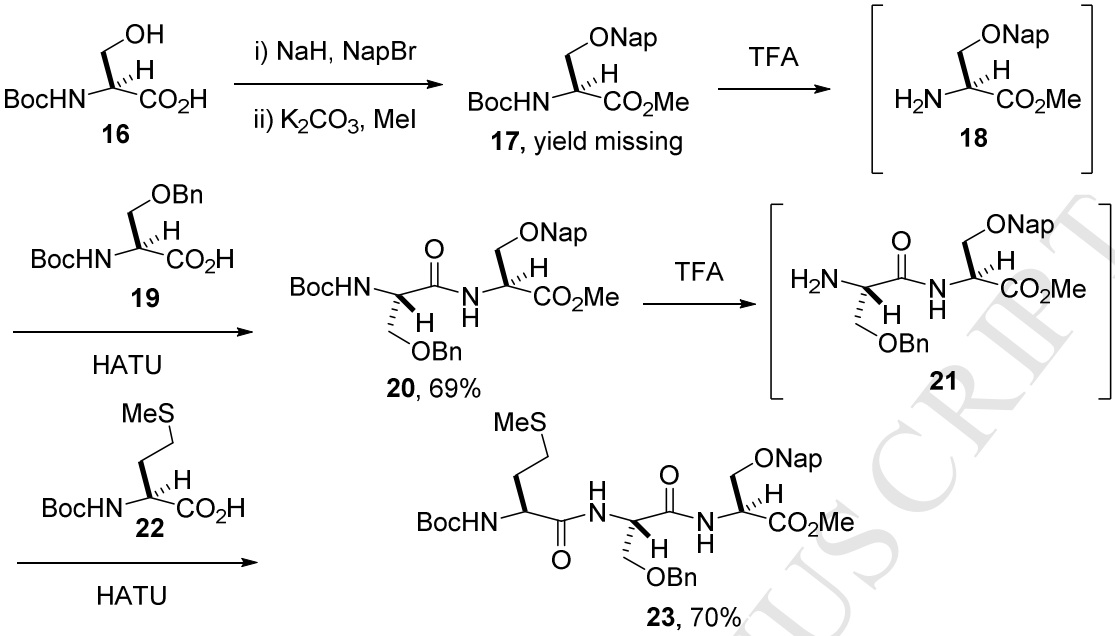
hydrogenolysis of benzyl ethers is catalyst poisoning which can occur when the substrate contains thioethers".[2] Such problems, which often go unreported, are widespread, can sometimes be solved by recourse to large amounts of catalyst,[3,4] and are frequently circumvented by recourse to the far less convenient reductive cleavage of benzyl ethers with sodium in liquid ammonia or related protocols.[4-8] Confronted with such problems in our laboratory we were intrigued by the possibility of employing 2-naphthylmethyl (Nap) ethers in place of benzyl ethers. 2-Naphthylmethyl ethers have enjoyed widespread use and continuous refinement in carbohydrate chemistry as surrogates for *p*-methoxybenzyl ethers since their introduction to the field by Matta,[9-14] because of their greater stability to Brønsted acids but comparable ease of removal under oxidative condition with dichlorodicyanoquinone. However, it was the selective hydrogenolytic removal of Nap ethers in presence of benzyl ethers initially reported by Spencer[15] that suggested the possibility of their use as a possible remedy to the problem in hand. Here, we report the synthesis of a series of compounds containing benzyl and Nap together with either thioethers or thioglycosides and demonstrate that indeed the Nap ethers are removed selectively under these conditions.

2. Results and discussion

An initial test substrate and a series of carbohydrate-based model compounds characterized by the presence of a thioether or thioglycoside, multiple benzyl ethers and a 2-naphthylmethyl ether were synthesized by standard means (Scheme 1). A peptide-based substrate was prepared as described in Scheme 2.



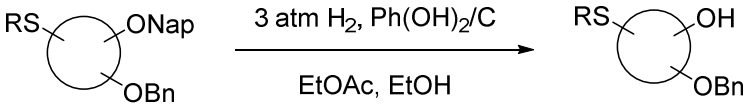
Scheme 1. Synthesis of Substrates for Hydrogenolysis.

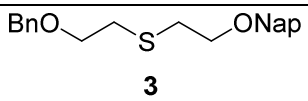
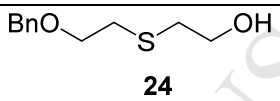
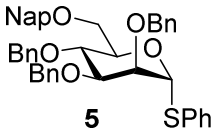
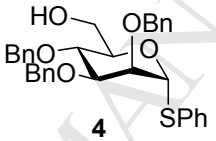
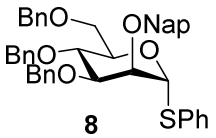
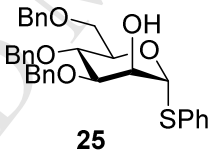
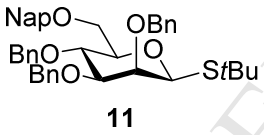
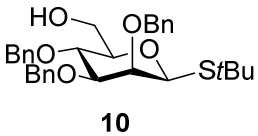
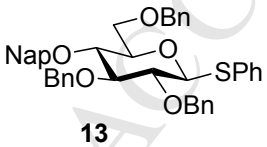
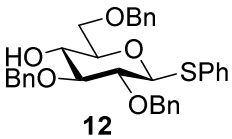
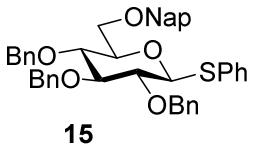
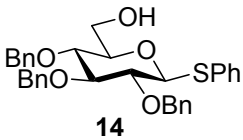


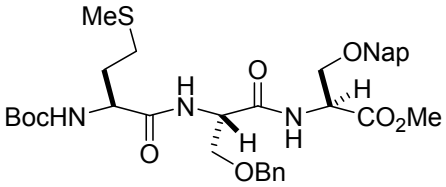
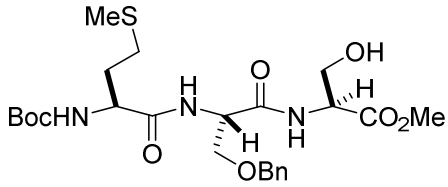
Scheme 2. Synthesis of a Peptide-Based Substrate.

After a brief survey of catalysts and conditions, hydrogenolysis over palladium hydroxide on carbon in ethanolic ethyl acetate under the 3 atmospheres of hydrogen were found to be suitable for cleavage of the naphthylmethyl ethers in good yield, with the solvent chosen so as to dissolve the widest range of substrates and products. As reported in Table 1 under these conditions naphthylmethyl ethers in variety of diverse steric environments could be removed in good to excellent yield in the presence of one or more benzyl ethers and thioethers or thioglycosides. Thus, the naphthylmethyl ether is cleanly removed in the presence of alkyl thioethers and thioglycosides (Table 1, entries 1, 4, and 7) and in the presence of aryl thioglycosides, whether axial or equatorial (Table 1, entries 2, 3, 5, and 6) always in the presence of one or more benzyl ethers. Additionally, as demonstrated by the example of entry 7 (Table 1) the selective hydrogenolysis may be affected in the presence of amide and carbamate groups.

Table 1. Selective Hydrogenolysis of Naphthylmethyl Ethers in the Presence of Benzyl Ethers and Thioethers or Thioglycosides.



Entry	Substrate	Product	Time (h)	% Yield
1	 **3**	 **24**	12	72
2	 **5**	 **4**	2	92
3	 **8**	 **25**	16	65
4	 **11**	 **10**	3	89
5	 **13**	 **12**	6	70
6	 **15**	 **14**	2	88

7	 **23**	 **26**	7	88

3. Conclusion.

Nap ethers are cleaved by hydrogenolysis in the presence of benzyl ethers in compounds carrying thioether or thioglycoside groups, thereby extending the possible uses of the Nap group. The results also suggest that Nap ethers be considered as replacements for benzyl ethers in synthetic schemes when global deprotection by hydrogenolysis is anticipated in the presence of thioethers and thioglycosides, although we have yet to test this possibility.

4. Experimental section

4.1. ***General***

All reactions were conducted under an atmosphere of nitrogen or argon. Extracts were dried over sodium sulfate and chromatography was carried out over silica gel. Sephadex chromatography was carried out over Sephadex C25**.** Specific rotations were measured on an automatic polarimeter with a path length of 10 cm in chloroform solution unless otherwise stated. High-resolution (HRMS) mass spectra were recorded in the electrospray mode using a time of flight mass analyzer (ESI-TOF).

4.2.1 2-((2-(Naphthalen-2-ylmethoxy)ethyl)thio)ethanol (2).

To a suspension of sodium hydride (0.43 g, 10.9 mmol, 60% in mineral oil) in dry THF (30 mL), under argon, cooled to 0 °C, was slowly added 2,2-thiodiethanol **1** (3.3 g, 27.15 mmol). The

reaction mixture was stirred for 1 h before 2–(bromomethyl)naphthalene (2.0 g, 9.05 mmol) in dry THF (20 mL) was added dropwise, and stirring continued for 5 h. The reaction mixture was diluted with water (50 mL) and extracted diethyl ether (50 mL x 2). The organic layer was washed with water and brine and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. Chromatographic purification (hexane ethyl acetate 6:1-2:1) gave the title compound **2** (1.78 g, 75%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.76 (m, 4H), 7.53 – 7.43 (m, 3H), 4.71 (s, 2H), 3.71 (t, *J* = 6.0 Hz, 2H), 3.69 (t, *J* = 6.4 Hz, 2H), 2.78 (t, *J* = 6.4 Hz, 2H). 2.76 (t, *J* = 6.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3, 133.2, 133.0, 128.3, 127.9, 127.7, 126.6, 126.2, 126.0, 125.7, 73.3, 69.9, 60.8, 35.9, 31.6. ESIHRMS calcd for $C_{22}H_{24}O_2SNa$ $[M + Na]^+$, 385.0925; found; 385.0921.

4.2.2 2-(2-Naphthalen-2-ylmethoxy)ethyl 2-(benzyloxy)ethyl) sulfide (3)

A solution of **2** (1.2 g, 4.58 mmol) in dry DMF (22 mL) under argon, was cooled to 0 ˚C and treated with NaH (0.27 g, 60% dispersion in mineral oil). The reaction mixture was stirred for 10 min before benzyl bromide (0.61 ml, 5.04 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 2 h before it was cooled to 0 ˚C and quenched with MeOH (1 mL), and concentrated in *vacuo*. The concentrate was dissolved in ethyl acetate, washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (hexane-ethyl acetate (9:1)) to give the title compound (1.3 g, 81%) as a colorless oil. ;^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 – 7.81 (m, 3H), 7.80 – 7.76 (m, 1H), 7.51 – 7.43 (m, 3H), 7.36 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 4.69 (s, 2H), 4.51 (s, 2H), 3.69 (t, *J* = 6.7 Hz, 2H), 3.65 (t, *J* = 6.7 Hz, 2H), 2.82 (t, *J* = 6.1 Hz, 2H), 2.80 (t, *J* = 6.1 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.1, 135.6, 133.2, 133.0, 128.4, 128.2, 127.9, 127.8, 127.7, 127.6,

126.4, 126.1, 125.9, 126.0, 73.1, 73.0, 70.0, 32.1, 32.1. ESIHRMS calcd for $C_{22}H_{24}O_2SNa$ [M + Na]$^+$, 375.1395; found; 375.1396.

4.2.3 Phenyl 2,3,4-tri-*O*-benzyl-6-*O*-(2-naphthyl)methyl-1-thio-α-D-mannopyranoside (5).

A solution of **4**[16] (0.30 g, 0.57 mmol) in anhydrous DMF (6 mL), was cooled to 0 ˚C, treated with NaH (60% dispersion in mineral oil, 33 mg,) under argon, and stirred for 20 min. A solution 2–(bromomethyl) naphthalene (0.33 mg, 1.5 mmol,) in DMF (2 mL) was added slowly followed by TBAI (40 mg, 0.11 mmol). The reaction mixture was stirred for 12 h, after which it was quenched with methanol (0.2 mL) and water (10 mL). The mixture was extracted with ethyl acetate, and the combined organic phase was washed with HCl (1 M), saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The resulting brown oil was purified by silica chromatography, eluting with hexane-ethyl acetate (9:1) to give **5** (0.29 g, 74%) as a colorless oil. $[\alpha]^{RT}_{D=}$ +44 (*c* 0.24, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 – 7.80 (m, 1H), 7.78 – 7.75 (m, 3H), 7.49 – 7.44 (m, 5H), 7.40 – 7.27 (m, 10H), 7.25 – 7.15 (m, 6H), 7.14 – 7.09 (m, 2H), 5.64 (d, *J* = 1.7 Hz, 1H), 4.91 (d, *J* = 10.7 Hz, 1H), 4.82 (d, *J* = 12.4 Hz, 1H), 4.75 (d, *J* = 12.4 Hz, 1H), 4.66 (d, *J* = 12.4 Hz, 1H), 4.64 (d, *J* = 12.4 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, z1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 10.7 Hz, 1H), 4.32 (ddd, *J* = 9.9, 5.1, 1.9 Hz, 1H), 4.10 (t, *J* = 9.6 Hz, 1H), 4.02 (dd, *J* = 3.2, 1.7 Hz, 1H), 3.91 – 3.87 (m, 2H), 3.80 (dd, *J* = 10.9, 1.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.3, 138.2, 137.9, 135.8, 134.4, 133.2, 132.9, 131.6, 129.0, 128.4, 128.4, 128.3, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.4 126.4, 126.0, 125.9, 125.7, 85.8, 80.2, 76.3, 75.2, 75.0, 73.4, 72.8, 72.1, 71.9, 69.1. ESIHRMS calcd for $C_{44}H_{42}O_5SNa$ [M + Na]$^+$,705.2651; found; 705.2654.

4.2.4 Phenyl 3-*O*-benzyl-2-*O*-(2-naphthyl)methyl-1-thio-α-D-mannopyranoside (7).

A solution of **6**[17] (0.6 g, 1.02 mmol) in $CHCl_3$-MeOH (4:1, 16 mL) was treated with *p*-TsOH monohydrate (0.2 g, 1.02 mmol) and stirred under argon at room temperature for 2 h, after which, it was quenched with triethylamine (0.2 mL) and concentrated. The residue was purified by flash column chromatography over silica gel (hexane/ethyl acetate 1:1) to give **7** (0.44 g, 89%) as a colorless oil. $[\alpha]^{RT}_{D=}$ +0.4 (*c* 0.55, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 – 7.79 (m, 1H), 7.78 – 7.75 (m, 2H), 7.74 – 7.71 (m, 1H), 7.50 – 7.44 (m, 3H), 7.38 – 7.35 (m, 2H), 7.34 – 7.28 (m, 5H), 7.27 – 7.23 (m, 3H), 5.55 (d, *J* = 1.5 Hz, 1H), 4.82 (d, *J* = 12.3 Hz, 1H), 4.72 (d, *J* = 12.3 Hz, 1H), 4.57 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.16 (t, *J* = 9.1Hz 1H), 4.14 – 4.10 (m, 1H), 4.05 (dd, *J* = 3.0, 1.5 Hz, 1H), 3.92 – 3.80 (m, 2H), 3.71 (dd, *J* = 9.1, 3.0 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.7, 135.1, 133.8, 133.2, 133.1, 131.9, 129.1, 128.6 128.3, 128.0, 127.9, 127.9, 127.7, 127.7, 126.8, 126.2, 126.1, 125.9, 86.2, 79.6, 75.5, 73.3, 72.33, 71.8, 67.3, 62.7. ESIHRMS calcd for $C_{30}H_{30}O_5SNa$ $[M + Na]^+$, 525.1712; found; 525.1719.

4.2.5 Phenyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-naphthyl)methyl-1-thio-α-D-mannopyranoside (8).

To a solution of **7** (0.27 g, 0.54 mmol) in anhydrous DMF (2.6 mL) was added NaH (86 mg, 60% dispersion in mineral oil) at -15 °C. After stirring for 5 min BnBr (0.15 mL, 1.23 mmol) was added, and the mixture was warmed to room temperature and stirred for 6 h. The reaction mixture was quenched with MeOH (0.4 mL, at 0 °C) and diluted with ethyl acetate, washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (hexane: ethyl acetate 9:1) to afford **8** as a colorless oil (0.32 g, 88%). $[\alpha]^{RT}_{D=}$ +33 (*c* 0.42, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 – 7.81 (m, 1H), 7.80 – 7.71 (m, 3H), 7.52 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.44 – 7.41 (m, 2H), 7.37 – 7.27 (m, 12H), 7.23 (dt, *J* = 9.3, 7.3 Hz, 5H), 5.65 (d, *J* = 1.7 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.91 (d, *J* = 12.5 Hz, 1H), 4.81 (d, *J* = 12.5 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.65 (d,

J = 11.7 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.58 (d, *J* = 10.8 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.31 (ddd, *J* = 9.9.6, 5.1, 1.9 Hz, 1H), 4.13 (t, *J* = 9.6 Hz, 1H), 4.07 (dd, *J* = 3.1, 1.7 Hz, 1H), 3.92 – 3.85 (m, 2H), 3.78 (dd, *J* = 9.6, 3.1 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.4, 138.4, 138.2, 135.4, 134.4, 133.2, 133.0, 131.7, 129.0, 128.4, 128.4, 128.3, 128.2, 128.0, 128.0, 127.8, 127.8, 127.7, 127.6, 127.5, 127.4, 126.8, 126.1, 126.0, 126.0, 85.9, 80.2, 76.2, 75.2, 75.0, 73.3, 72.8, 72.2, 72.0, 69.2. ESIHRMS calcd for $C_{44}H_{42}O_5SNa$ $[M + Na]^+$, 705.2651; found; 705.2654.

4.2.6 *tert*-Butyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-mannopyranoside (10).

To a solution of **9**[4] (130 mg, 0.25 mmol) in dry DCM (3 mL) was added BH_3.THF (1.0 M in THF, 1.3 mL, 1.25 mmol) under argon with stirring. After 10 mins yttrium (III) trifluoromethanesulfonate (15.5mg, 0.025 mmol) was added and the reaction mixture was stirred under argon at room temperature for 2 h. The reaction mixture was cooled to 0 ˚C, then triethylamine (50 µL, 0.04 mmol) was added dropwise followed by slow addition of methanol (100 µL). The solvent was removed under reduced pressure and the residue was taken up methanol and then concentrated to give a residue, which was purified by flash column chromatography on silica gel using hexane-ethyl acetate (4:1) as eluent. The product was obtained as a light yellow oil (117 mg, 90 %). $[\alpha]^{RT}_{D}$ = -23 (*c* 1.78, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 – 7.04 (m, 15H), 4.94 (d, *J* = 11.3 Hz, 1H), 4.91 (d, *J* = 11.3 Hz, 1H), 4.79 (d, *J* = 10.9 Hz, 1H), 4.72 (d, *J* = 11.8 Hz, 1H), 4.67 (d, *J* = 11.8 Hz, 2H), 4.66 (d, *J* = 1.0 Hz, 1H), 4.64 (d, *J* = 10.9 Hz, 1H), 4.00 (dd, *J* = 3.0, 1.0 Hz, 1H), 3.90 (t, *J* = 9.5 Hz, 1H), 3.84 (dd, *J* = 11.9, 3.0 Hz, 1H), 3.40 – 3.33 (m, 1H), 1.36 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.3, 138.1, 128.4, 128.4, 128.2, 128.1, 128.1, 127.8, 127.7, 127.5, 127.4, 84.5, 82.3, 79.9, 78.5, 77.2, 77.0, 76.9, 75.3, 75.2, 74.9, 72.3, 62.7, 43.3, 31.6. ESIHRMS calcd for $C_{31}H_{38}O_5SNa$ $[M + Na]^+$, 545.2338; found; 545.2341.

4.2.7 *tert*-Butyl 2,3,4-tri-*O*-benzyl-6-*O*-(2-naphthyl)methyl-1-thio-β-D-mannopyranoside (11).

This compound was synthesized from **10** by alkylation with sodium hydride and 2-naphthylmethyl bromide, as described for compound **5**, in 72% yield as a pale yellow oil. $[\alpha]^{RT}_{D}$ = -19.7 (*c* 0.62, $CHCl_3$) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 – 7.68 (m, 4H), 7.54 – 7.38 (m, 5H), 7.33 – 7.12 (m, 13H), 4.93 (d, *J* = 11.5 Hz, 1H), 4.86 (d, *J* = 10.9 Hz, 1H) 4.84 (d, *J* = 11.5 Hz, 1H), 4.73 (d, *J* = 12.1 Hz, 1H), 4.71 (d, *J* = 12.1 Hz, 1H) 4.69 (d, *J* = 11.8 Hz, 1H), 4.66 (d, *J* = 1.0 Hz, 1H) 4.63 (d, *J* = 11.8 Hz, 1H), 4.55 (d, *J* = 10.9 Hz, 1H), 3.99 (dd, *J* = 3.1, 1.0 Hz, 1H), 3.88 (t, *J* = 9.5 Hz, 1H), 3.80 (dd, *J* = 10.8, 1.8 Hz, 1H), 3.72 (dd, *J* = 10.8, 6.5 Hz, 1H), 3.64 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.54 – 3.50 (m, 1H), 1.39 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.2, 138.2, 136.0, 132.9, 128.4, 128.2, 128.1, 128.0, 128.0, 127.9, 127.6, 127.6, 127.5, 127.4, 126.3, 125.9, 125.9, 125.6, 84.7, 82.1, 79.8, 78.2, 75.1, 75.0, 74.9, 73.4, 72.2, 69.9, 43.4, 31.7. ESIHRMS calcd for $C_{31}H_{38}O_5SNa$ $[M + Na]^+$, 685.2964; found; 685.2969.

4.2.8 Phenyl 2,3,6-tri-*O*-benzyl-4-*O*-(2-naphthyl)methyl-1-thio-β-D-glucopyranoside (13).

This compound was prepared in 77% yield by alkylation of **12** with sodium hydride and benzyl bromide, as described for compound **5**, and had spectral data consistent with the literature.[18]

4.2.9 Phenyl 2,3,4-tri-*O*-benzyl-6-*O*-(2-naphthyl)methyl-1-thio-β-D-glucopyranoside (15).

This compound was synthesized from **14,** by alkylation with sodium hydride and 2-naphthylmethyl bromide, as described for compound **5**, in 81% yield as a colorless oil. $[\alpha]^{RT}_{D}$ = +3 (*c* 1.78, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 4H), 7.63 – 7.58 (m, 2H), 7.49 – 7.45 (m, 3H), 7.41 – 7.37 (m, 2H), 7.36 – 7.26 (m, 8H), 7.26 – 7.18 (m, 6H), 7.15 – 7.10 (m, 2H), 4.90 (d, *J* = 10.3 Hz, 2H), 4.85 (d, *J* = 10.9 Hz, 1H), 4.82 (d, *J* = 10.9 Hz, 1H), 4.77 (d, *J* =

12.2 Hz, 1H), 4.74 (d, *J* = 10.2 Hz, 1H), 4.71 (d, *J* = 9.9 Hz, 1H), 4.69 (d, *J* = 7.7 Hz, 1H), 4.58 (d, *J* = 10.8 Hz, 1H), 3.83 (dd, *J* = 10.9, 1.9 Hz, 1H), 3.77 (d, *J* = 4.7 Hz, 1H), 3.72 (t, *J* = 8.9 Hz, 1H), 3.67 (t, *J* = 9.4 Hz, 1H), 3.57 – 3.50 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.4, 138.0, 137.9, 135.7, 133.8, 133.3, 133.0, 131.9, 128.9, 128.4, 128.4, 128.4, 128.2, 128.1, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 127.4, 126.4, 126.1, 125.8, 125.8, 87.5, 86.7, 80.8, 79.1, 77.8, 75.8, 75.4, 75.0, 73.5, 69.0. ESIHRMS calcd for $C_{44}H_{42}O_5SNa$ $[M + Na]^+$, 705.2651; found; 705.2651.

4.2.10 *N*-(*tert*-Butoxycarbonyl)-*O*-(2-naphthyl)methyl-L-serine Methyl Ester (17).

A solution of *N*-Boc-L-serine **16** (2.1 g, 10.2 mmol) in anhydrous DMF (20 mL) was cooled to -15 ˚C, treated with NaH (0.6 g, 10.5 mmol, 60% dispersion in mineral oil) under argon and stirred for 30 min. A solution 2–(bromomethyl)naphthalene (2.26 mg, 10.24 mmol,) in DMF (5 mL) was slowly added followed by TBAI (0.36 g, 0.1 mmol). The reaction mixture was stirred for 12 h, after which it was diluted with ethyl acetate (20 mL), poured into water, and extracted with ethyl acetate. The organic layer was washed with HCl (0.5M), and water, dried ($MgSO_4$) and concentrated in *vacuo*. The residue (2.0 g) was dissolved in acetone (40 mL), cooled to 0 ˚C and treated with K_2CO_3 (1.1 g, 8.6 mmol) followed by MeI (0.8 mL, 5.7 mmol). The reaction mixture was warmed to room temperature and stirred for 10 h, then was filtered and diluted with ethyl acetate, washed with $Na_2S_2O_5$, water, brine and dried over Na_2SO_4, and concentrated in *vacuo*. Purification by silica gel chromatography (hexane:ethyl acetate 85:15) gave the title compound (2.2 g, 60%) as a colorless oil. $[\alpha]^{RT}_{D\,=}$ +12 (*c* 2.80, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 3H), 7.71 (s, 1H), 7.51 – 7.44 (m, 2H), 7.38 (dd, *J* = 8.5, 1.7 Hz, 1H), 5.42 (d, *J* = 8.8 Hz, 0H), 4.70 (d, *J* = 12.3 Hz, 1H), 4.63 (d, *J* = 12.3 Hz, 1H), 4.50 – 4.37 (m, 1H), 3.89 (dd, *J* = 9.4, 3.3 Hz, 1H), 3.73 (s, 3H), 3.71 (dd, *J* = 9.7, 3.7 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 155.4, 135.0, 133.2, 133.0, 128.2, 127.8, 127.7, 126.4, 126.2,

126.0, 125.5, 80.0, 73.3, 70.0, 54.0, 52.4, 28.3. ESIHRMS calcd for $C_{20}H_{25}NO_5Na$ $[M + Na]^+$, 382.1630; found; 382.1632.

4.2.11 *N*-(*tert*-Butoxycarbonyl)-(*O*-benzyl-L-serinyl)-*O*-(2-naphthyl)methyl)-L-serine Methyl Ester (20).

A solution of **16** (175 mg, 0.49 mmol) in dichloromethane (5 mL) was treated with trifluoroacetic acid (0.5 mL) at room temperature and stirred for 2 h. The volatiles were removed in *vacuo*, and the residue taken up in ethyl acetate, washed with saturated aqueous Na_2CO_3, followed by brine. The organic layer was dried over Na_2SO_4 and concentrated in *vacuo* to give the crude amine **18** (120 mg, 0.46 mmol) which was used without further purification. In a separate flask, a solution of *N*-Boc-*O*-benzyl-L-serine **19** (155 mg, 0.52 mmol) in DMF (3 mL) was treated with HATU (200 mg, 0.52 mmol) and DIPEA (0.3 mL) and stirred for 0.5 h at room temperature before **18** (120 mg, 0.46 mmol) was added and the resulting mixture was stirred for 3 h. The reaction mixture was cooled to 0 ˚C and quenched with trimethylamine (100 µL), diluted with H_2O (2 mL) and extracted with EtOAc (4 mL x 2). The organic layer was dried Na_2SO_4 and concentrated in *vacuo* then purified by silica gel chromatography (hexane-ethyl acetate 2:1) to give **20** as a colorless oil (77 mg, 69%). $[\alpha]^{RT}_{D=}$ +21 (*c* 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 7.83 – 7.78 (m, 3H), 7.72 (br s, 1H), 7.48 – 7.43 (m, 2H), 7.38 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.32 – 7.19 (m, 6H), 4.70 (t, *J* = 3.9 Hz, 1H), 4.64 (d, *J* = 12.2 Hz, 1H), 4.57 (d, *J* = 12.2 Hz, 1H), 4.50 (d., *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.1 Hz, 1H), 4.38 (t, *J* = 5.4 Hz, 1H), 3.88 (dd, *J* = 9.8, 4.3 Hz, 1H), 3.75 – 3.68 (m, 3H), 3.67 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.4, 170.3, 156.3, 137.8, 135.2, 133.3, 133.1, 128.0, 127.8, 127.7, 127.5, 127.4, 127.4, 127.3, 126.2, 125.8, 125.6, 125.4, 79.5, 72.8, 72.8, 72.7, 69.7, 69.1, 54.4, 52.8, 51.6, 27.3. ESIHRMS calcd for $C_{30}H_{36}N_2O_7Na$ $[M + Na]^+$, 559.2420; found; 559.2421.

4.1.2 *N*-(*tert*-Butoxycarbonyl)-L-methionyl)-(*O*-benzyl-L-serinyl)-(*O*-(2-naphthyl)methyl)-L-serine Methyl Ester (23).

A solution of **20** (70 mg, 0.13 mmol) in dichloromethane (2 mL) was treated with trifluoroacetic acid (0.2 mL) at room temperature and stirred for 2 h. The volatiles were removed in *vacuo* and the residue taken up in ethyl acetate, washed with saturated aqueous Na_2CO_3, followed by brine. The organic layer was dried over Na_2SO_4 and concentrated in *vacuo* to give the crude amine **21** (57 mg, 0.13 mmol), which was used without further purification. In a separate flask a solution of *N*-BOC-L-methionine **22** (42 mg, 0.17 mmol) in dry DMF (1 mL) was treated with HATU (65 mg, 0.17 mmol) and DIPEA (0.1 mL,) and stirred for 30 minutes at room temperature before **21** (57 mg, 0.13 mmol) was added. The reaction mixture was stirred for an additional 3 h, cooled to 0 ˚C, quenched with trimethylamine (50 µL), diluted with water (3 mL), and extracted with ethyl acetate (2 mL × 3). The organic layers were washed with brine and dried over anhydrous Na_2SO_4, then concentrated in *vacuo*. Chromatography over silica gel eluting with hexane-ethyl acetate (2:1) gave the title compound (60 mg, 70%) as a colorless oil $[\alpha]^{RT}_{D}$ = -3 (*c* 0.75, MeOH); ^{1}H NMR (600 MHz, CD_3OD) δ 7.81 – 7.75 (m, 3H), 7.70 (s, 1H), 7.47 – 7.40 (m, 2H), 7.39 – 7.34 (m, 1H), 7.30 – 7.17 (m, 5H), 4.72 – 4.66 (m, 2H), 4.65 – 4.60 (m, 1H), 4.59 – 4.53 (m, 2H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 4.41 (s, 1H), 4.25 – 4.18 (m, 1H), 2.55 – 2.39 (m, 2H), 2.09 – 1.95 (m, 4H), 1.91 – 1.78 (m, 1H), 1.38 (s, 9H). ^{13}C NMR (151 MHz, CD_3OD) δ 173.3, 170.4, 170.3, 156.5, 137.7, 135.2, 135.2, 133.3, 133.3, 133.1, 128.0, 127.8, 127.8, 127.5, 127.5, 127.4, 127.3, 126.2, 126.2, 125.8, 125.6, 125.4, 79.4, 72.9, 72.8, 72.8, 72.8, 69.4, 69.1, 69.0, 53.9, 53.7, 52.9, 52.9, 51.6, 31.4, 29.7, 3.4, 13.9. ESIHRMS calcd for $C_{35}H_{45}N_3O_8SNa$ $[M + Na]^+$, 690.2825; found; 690.2819.

4.3 General Hydrogenolysis Procedure.

20% $Pd(OH)_2/C$ was dispersed in EtOAc-EtOH (40 mL/mmol, 1:2) under argon. The mixture was degassed and stirred for 1 h under 3 atm of hydrogen before a solution of the substrate in EtOH-EtOAc (2:1, 0.05M) was added. The reaction mixture was purged with hydrogen and stirred at room temperature under a hydrogen atmosphere (3 atm) until complete by TLC. The catalyst was removed by filtration through Celite and washed with EtOAc. The filtrate was concentrated, and the resulting residue was purified by chromatography over silica gel eluting with ethyl acetate/hexane mixtures to give the products.

4.4.1 2-((2-Benzyloxyethyl)thio) ethanol (24).

Compound **3** (10 mg, 0.028 mmol) was subjected to hydrogenolysis according to the standard conditions using 20% $Pd(OH)_2$ (40 mg, 0.056 mmols). After chromatography on silica gel (hexane/ethyl acetate 2:1) the title compound was obtained as a colorless oil (4.3 mg, 72 %) with spectral data identical to the literature.[19]

4.4.2 Phenyl 2,3,4-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (4) by Selective Hydrogenolysis of 5.

Compound **5** (10 mg, 0.015 mmol) was subjected to hydrogenolysis according to the standard conditions using 20% $Pd(OH)_2$ (15 mg, 0.022 mmol). After chromatography on silica gel (hexane/ethyl acetate 4:1) the title compound was obtained as a colorless oil (7.1 mg, 92 %) with spectral data identical to the above sample and to the literature.[20]

4.4.3 Phenyl 3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (25) by Selective Hydrogenolysis of 8.

Compound **8** (11 mg, 0.016 mmol) was subjected to hydrogenolysis according to the standard conditions using 20% $Pd(OH)_2$ (22 mg, 0.032 mmol). After chromatography on silica gel

(hexane/ethyl acetate 4:1) the title compound was obtained as a colorless oil (5.7 mg, 65 %) with spectral data identical to the literature.[21]

4.4.4 *S*-*tert*-Butyl 2, 3, 4-tri-*O*-benzyl-1-thio-β-D-mannopyranoside (10) by Selective Hydrogenolysis of 11.

Compound **11** (15 mg, 0.02 mmol) was subjected to hydrogenolysis according to the standard conditions using 20% $Pd(OH)_2$ (24 mg, 0.03 mmol). Chromatographic purification (hexane/ethyl acetate 4:1) gave the title compound (10.5 mg, 89 %) as a colorless oil with spectral data identical to the above sample.

4.4.5 Phenyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (12) by Selective Hydrogenolysis of 13.

Compound **13** (10 mg, 0.015 mmol) was subjected to hydrogenolysis according to the standard conditions using 20% $Pd(OH)_2$ (15 mg, 0.022 mmol). After chromatography on silica gel (hexane/ethyl acetate 4:1) the title compound was obtained as a powder, (5.5 mg, 70 %) with spectral data identical to the literature.[22]

4.4.6 Phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (14) by Selective Hydrogenolysis of 15.

Compound **15** (10 mg, 0.015 mmol) was subjected to hydrogenolysis according to the standard conditions using 20% $Pd(OH)_2$ (15 mg, 0.022 mmol). After chromatography on silica gel (hexane/ethyl acetate 5:1) the title compound was obtained as a white powder, (7 mg, 88%) with spectral data identical to the literature.[23]

4.4.7 *N*-(*tert*-Butoxycarbonyl)-L-methionyl)-(*O*-benzyl-L-serinyl-L-serine (26).

The compound was synthesized from **23** (40 mg, 0.06 mmol) using the general hydrogenolysis protocol in the form of a colorless oil (26 mg, 82%).^{1}H NMR (600 MHz, CD_3OD) δ 7.56 – 7.02 (m, 5H), 4.63 (t, *J* = 5.3 Hz, 1H), 4.58 – 4.49 (m, 3H), 4.22 – 4.14 (m, 1H), 3.91 – 3.85 (m, 1H), 3.81 – 3.76 (m, 2H), 3.74 – 3.71 (m, 1H), 3.71 (s, 3H), 2.61 – 2.47 (m, 2H), 2.08 – 2.01 (m, 4H), 1.89 – 1.82 (m, 1H), 1.41 (s, 9H). ^{13}C NMR (151 MHz, CD_3OD) δ 173.2, 170.5, 170.4, 156.6, 137.8, 128.0, 127.5, 127.3, 79.4, 72.9, 72.8, 69.3, 61.4, 61.4, 54.9, 54.8, 54.0, 53.8, 53.0, 51.4, 31.3, 29.7, 27.3, 13.8. ESIHRMS calcd for $C_{24}H_{37}N_3O_8SNa$ $[M + Na]^+$, 550.2199; found; 550.2195.

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- Hydrogenolytic cleavage in presence of thioglycosides
- Selective hydrogenolysis
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