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Formation of Ethyl 1-Thiomannopyranosides from 2-*O*-Chloroacetylated and 2-*O*-Levulinoylated Synthons

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With the aim to prepare key glycosyl donors for the synthesis of fragments of the O-specific polysaccharides of *Vibrio cholerae* O:1, 1-*O*-acetyl derivatives of perosamine bearing participating 2-*O*-chloroacetyl or 2-*O*-levulinoyl groups were treated with EtSH and $BF_3{\cdot}Et_2O$. While poor stereoselectivity of the formation of ethyl 1-thioglycosides (α:β = 3:2) was observed with 2-*O*-chloroacetylated intermediates, the same products can be obtained with good stereoselectivity (α:β = 7:1) from 2-*O*-levulinoylated intermediates. Selective regeneration of the carbonyl group from dithioketals in the presence of S,O-acetals by treatment with $AgNO_3$ and Ag_2O in $MeCN/H_2O$ is also described. The conversion allows direct preparation of 1-thioglycosides from carbohydrates protected with the levulinic ester group.

Introduction

Thioglycosides are useful synthons in carbohydrate chemistry.[1,2] While they themselves are important glycosyl donors for the synthesis of glycosides and oligosaccharides, they can be converted into other glycosyl donors.[3–5] Thioglycosides containing free hydroxy groups can be used as glycosyl acceptors, either in combination with other classes of glycosyl donors or with 1-thioglycosides by applying the "armed-disarmed" concept.[6] The importance of haloacetyl and levulinoyl (levulinoyl ester, Lev)[7–10] protecting groups in carbohydrate chemistry lies in the fact that they can be selectively removed in the presence of other acyl groups. Thus, thioglycosides protected in such way have become popular tools in synthetic carbohydrate chemistry. Within our attempts to improve existing syntheses of oligosaccharides related to the O-specific polysaccharide of *Vibrio cholerae* O:1, we have examined and here report the stereoselectivity of conversion of some 1-*O*-acetyl-2-*O*-chloroacetyl and 1-*O*-acetyl-2-*O*-levulinoyl derivatives of perosamine to the corresponding ethyl 1-thioglycosides. Preparation of 1-thioglycosides from chloroacetylated intermediates was uneventful. To the best of our knowledge, the conversion of Lev-protected sugars to 1-thioglycosides has not been described. Instead, the conventional synthetic route to Lev-protected 1-thioglycosides[11–14] starts with a commercially available carbohydrate, which is converted to a 1-thioglycoside and functionalized before the Lev group is introduced at the desired position. The sequence normally takes several synthetic steps, and requires preparation of, and working with a large amount of the 1-thioglycoside. In addition, the reaction sequence often involves replacement of a temporary protecting group with the Lev group, which increases the number of synthetic steps. This roundabout way is normally practiced lest the treatment of Lev-protected substances with reagents leading to 1-thioglycosides might be accompanied by transformation of the oxo function in the Lev group to form the corresponding dithioketal. Indeed, when we attempted the preparation of the thioglycosides **11** and **14** from the Lev-protected acetates **6** and **8** the keto group of the Lev-protecting group became functionalized, and the major products were the dithioketals **10** and **13**. Here we report a simple protocol to regenerate the keto group, allowing direct preparation of 1-thioglycosides from Lev-protected sugars in high yield.

Results and Discussion

Within our work aimed at a glycoconjugate vaccine against *Vibrio cholerae* O1, we are interested in the synthesis of oligosaccharides composed of α-(1→2)-linked 3-deoxy-L-*glycero*-tetronamido-D-perosamine (Scheme 1). Such substances mimic the O-antigenic region (O-PS) of the bacterium lipopolysaccharide. Oligosaccharides composed of *N*-acylated amino sugars can be built up by two strategies. According to the most common one,[15–17] the sequence is built up from azido sugars, and the azido groups in the oligosaccharide thus obtained are then further transformed, eventually to their *N*-acylamido counterparts. In the second approach, the oligosaccharide is constructed from intermediates having the acylamido side chain already in place.[17,18] The latter strategy has the advantage that it often minimizes the number of chemical manipulations with the intermediate, higher oligosaccharides. For that approach we needed a thioglycoside synthon derived from perosamine whose 4-amino group was protected with 2,4-di-*O*-acetyl-3-deoxy-L-

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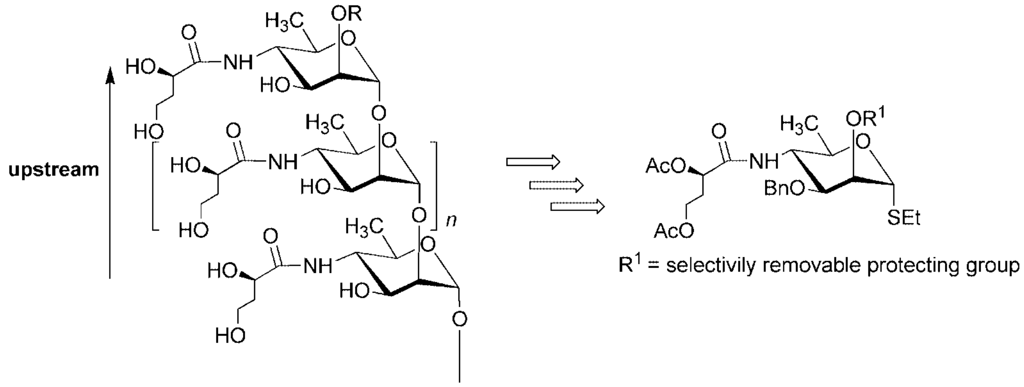


Scheme 1.

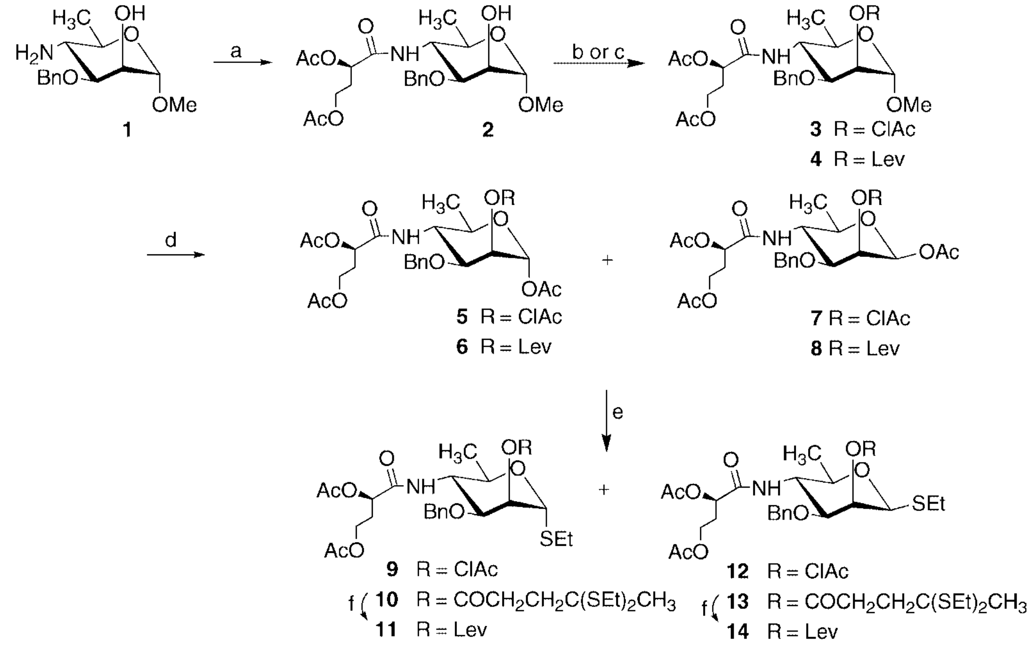
glycero-tetronic acid,[19] and with a temporary and permanent blocking groups at position 2 and 3, respectively. Based on precedents,[15,16] positioning a benzyl ether group as a permanent protecting group for position 3 in the desired synthon was an easy task. The temporary protecting group had to be selectively removable in the presence of acetyl groups, *and* be capable of providing anchimeric assistance in the formation of the 1,2-α-mannopyranosyl linkage. Our extensive experience with introduction and cleavage of haloacetyl groups[20,21] prompted us to first explore the utility of the chloroacetyl group for that purpose. The chloroacetyl group can be introduced under mild basic conditions using chloroacetyl chloride and, preferably, tetramethylurea[22] (TMU) in dichloromethane, and several reagents[23–25] that leave other acyl groups intact are available for its removal. The influence of haloacetyl groups on the reactivity at the anomeric center of carbohydrates is not clear. Decreased reactivity of such synthons has been reported[26–29] but, contrary to Lemieux and co-workers' finding[28] that the chloroacetyl group is a less efficient participating group than the simple acetyl group, Oscarson and Svahnberg[30] reported 83% yield of the 1,2-*trans*-linked product using a 2-*O*-chloroacetylated ethyl 1-thio-xylopyranoside. Encouraged by Oscarson and Svahnberg's[30] observation, we expected ample anchimeric assistance in the formation of the 1,2-*trans*-glycosidic linkage, especially because, in the *manno* series, the anomeric effect favors the formation of such linkage.[31]

Based on the above, we first prepared the 2-*O*-chloroacetyl mannoside **3**, starting from **2**, which was obtained from the known[32] amine **1** and 2,4-di-*O*-acetyl-3-deoxy-L-*glycero*-tetronic acid (Scheme 2).[19] Acetolysis of **3** gave anomeric α- and β-1-*O*-acetyl derivatives **5** and **7**, respectively, in a ratio of 5.8:1 (89%, combined yield), from which the pure α-derivative **5** could be isolated by chromatography in 76% yield.

Treatment of compound **5** with EtSH in the presence of $BF_3{\cdot}Et_2O$ gave the thioglycosides **9** and **12** with poor stereoselectivity in a ratio of 3:2 (NMR). This contrasted sharply with related reactions[18] carried out under the same conditions with 2-*O*-acetylated 1-thioglycoside as the glycosyl donor, which gave 1,2-*trans* products with high stereoselectivity. Various solvents tried (Table 1, Entries 1–4) as a reaction medium in the conversion of **5** had no effect on the product distribution but formation of minor byproducts, resulting from partial deacetylation in the tetronic acid residue (NMR), was virtually eliminated only when a mixture of toluene/dioxane[33] was used (Table 1, Entries 5–7). The poor stereoselectivity of formation of thioglycosides **9** and **12** prompted us to look for a different protecting group at *O*-2, a group that could provide more efficient anchimeric assistance during formation of the 1,2-*trans*-glycosidic linkage. We turned our attention to the levulinoyl group,[34] which can be selectively cleaved in the presence of acyl groups, and whose utility as a temporary protecting group at position 2 in glycosyl donors targeting 1,2-*trans* glycosides has been documented.[9,12,13]

At the onset of this work we aimed to explore the extent of dithioketal formation in the levulinoyl group under conditions commonly used for preparation of 1-thioglycosides.[35,36] Thus, we prepared 2-*O*-levulinoyl derivative **4** from **2** (Scheme 1) in virtually theoretical yield, employing 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDAC) to activate levulinic acid, instead of the commonly used,[7,37] toxic DCC. Acetolysis of **4** afforded α- and β-acetyl derivatives **6** and **8** in a ratio of 6.7:1 (NMR). When pure **6** was treated with EtSH in the presence of $BF_3{\cdot}Et_2O$ four products were formed (TLC). Resolution of the mixture by chromatography gave the dithioketals **10** and **13** (49 and 12%, respectively), and the desired 1-thioglycosides **11** and **14** (23 and 5%, respectively). The favored formation of α-thioglycoside clearly showed that the levulinoyl group has a much stronger α-directing effect in the formation of mannosides than the chloroacetyl group. In that regard it would meet our requirements for the protecting group at position 2 in the glycosyl donor, provided we managed to deal successfully with the formation of the dithioketal during 1-thioglycosidation.

Corey and co-workers[38] and others[39,40] have shown that carbonyl groups can be regenerated from their respective dithioacetals or -ketals, but these authors did not investigate selective cleavage in the presence of S,O-acetals. The reagent described by Crich and Picione[41] (1-benzenesulfonyl piperidine/triflic anhydride) does not differentiate between S,O-acetals and S,S-acetals or -ketals. When compound **10** was treated with $AgNO_3/Ag_2O$ in MeCN (Corey



Scheme 2. a. 2,4-Di-*O*-acetyl-3-deoxy-L-*glycero*-tetronic acid, EDAC, CH_2Cl_2, room temp.; b. R = ClAc: $ClCH_2COCl$, TMU, CH_2Cl_2, room temp.; c. R = Lev: $CH_3COCH_2CH_2CO$, EDAC, DMAP, CH_2Cl_2, room temp.; d. Ac_2O, AcOH, H_2SO_4, room temp.; e. EtSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, room temp.; f. $AgNO_3$, Ag_2O, CH_3CN/H_2O, room temp.

Table 1. Effect of solvent and the ClAc and Lev protection at position 2 on the stereoselectivity of thioglycoside formation.[a]

Entry	Compound	Solvent	$BF_3{\cdot}Et_2O$ [equiv.]	EtSH [equiv.]	*t* [h]	Products	α/β	Yield [%]
1	**5**	DCM	1.5	2.5	5	**9**, **12**	3:2	50
2	**5**	DCM	3	3	4	**9**, **12**	3:2	56
3	**5**	MeCN	3	10	56	**9**, **12**	3:2	73
4	**5**	DME	4	10	336	**9**, **12**	3:2	69
5	**5**	toluene/1,4-dioxane	4	10	144	**9**, **12**	3:2	85
6	**5**	1:4 toluene/1,4-dioxane	6	10	48	**9**, **12**	3:2	97
7	**5**+**7**[b]	1:4 toluene/1,4-dioxane	6	10	48	**9**, **12**	3:2	97
8	**6**	DCM	3	3.5	5	**11**, **14**	7:1	85[c]
9	**6**	1:4 toluene/1,4-dioxane	6	10	192	**11**, **14**	4:1	95[c]
10	**8**	DCM	3	3.5	5	**11**, **14**	3:2	81[c]
11	**6**+**8**[d]	DCM	3	3.5	5	**11**, **14**	6:1	79[c]

[a] All reactions were performed at room temperature in a 0.15 M solution of the compound in the quoted solvent. [b] A purified but unresolved mixture of acetates (ratio 3:1) was used. [c] The yield was calculated after cleavage of the dithioketals. [d] A crude mixture of acetates resulting directly from acetolysis of **4** was used to prepare the thioglycosides.

and coworkers' conditions),[38] it was converted virtually exclusively to the thioglycoside **11** (TLC, NMR). Having found that S,O-acetals are stable under these conditions, we have developed a simple procedure for conversion of dithioketals to ketones in the presence of S,O-acetals. Such transformation is important in carbohydrate chemistry, as it allows high-yielding preparation of 1-thioglycosides directly from Lev ester protected sugars. The procedures described in the Exp. Sect. can be applied both to the purified substances and the isolated, but unresolved products of treatment of levulinoyl-protected 1-*O*-acetyl derivatives with a thiol and $BF_3{\cdot}Et_2O$ as a catalyst.

Concerning the formation of 1-thioglycosides from 1-*O*-acetyl-2-*O*-levulinyl- and 1-*O*-acetyl-2-*O*-(chloroacetyl)-mannopyranoses we can conclude that the latter are not suitable starting materials when the α anomer is the desired product. The 1,2-*trans*-1-thioglycoside **11**, can be obtained with higher stereoselectivity from the α-1-*O*-acetate **6** than from its β counterpart **8** (Table 1, Entries 8–10). A comparable combined yield of **11** and **14** in about the same α:β ratio can be obtained (Table 1, Entry 11) from the crude mixture of acetates **6** and **8** resulting from acetolysis of **4**. The β-acetate **8** is converted to thioglycosides **11** and **14** with no better stereoselectivity than are the corresponding α- or β-chloroacetyl derivatives (Table 1, Entry 10). The solvent plays an important role in this conversion. The reaction in dichloromethane is faster, and allows the use of a smaller amount of reagents compared to a toluene/dioxane mixture (Table 1, Entry 8, 9). On the other hand, when DCM is the solvent, formation of small amounts of by products due to deacetylation in the tetronic acid side chain and debenzylation takes place, which accounts for the slightly decreased yield (Table 1, Entry 8). The reaction in toluene/dioxane mixture (Table 1, Entry 9) is much slower than that in DCM but practically no side products are formed. The use of larger amounts of reagents is required under these conditions, to maintain a reasonable rate of the conversion. While higher combined yield of the thioglycosides can be obtained at those conditions, they are obtained with poorer stereoselectivity. The reaction conditions reported in the Experimental represent a compromise, taking into account the variables discussed above.

Experimental Section

General Methods: Unless stated otherwise, optical rotations were measured at ambient temperature for solutions in chloroform, with a Perkin–Elmer automatic polarimeter, Model 341. All reactions were monitored by thin-layer chromatography (TLC) on glass slides coated with Silica gel 60. Column chromatography was performed by elution from columns of silica gel with the CombiFlash Companion Chromatograph (Isco, Inc.). Solvent mixtures less polar than those used for TLC were used at the onset of separation. Nuclear Magnetic Resonance (NMR) spectra were measured at 300 MHz (^{1}H) and 75 MHz (^{13}C) with a Varian Gemini or Varian Mercury spectrometer, or at 600 MHz (^{1}H) and 150 MHz (^{13}C) with a Bruker Avance 600 spectrometer. Assignments of NMR signals were made by homonuclear and heteronuclear 2-dimensional correlation spectroscopy, run with the software supplied with the spectrometers. When reporting assignment of NMR signals, nuclei associated with the N-amido side chain are denoted with a prime. Liquid Chromatography/Electron-Spray Ionization Mass Spectrometry (LC-ESI-MS) was performed with a Hewlett–Packard 1100 MSD spectrometer. Gas chromatography/Electron-Impact Mass Spectrometry (GC-EI-MS) was performed with a Hewlett–Packard 5898A spectrometer. Attempts have been made to obtain correct combustion analysis data for all new compounds. However, some compounds tenaciously retained traces of solvents, despite exhaustive drying, and analytical figures for carbon could not be obtain within ±0.4%. Structures of these compounds follow unequivocally from the mode of synthesis, NMR spectroscopic data, and *m*/*z* values found in their mass spectra, and their purity was verified by TLC and NMR spectroscopy. Solutions in organic solvents were dried with anhydrous Na_2SO_4, and concentrated at 40 °C/2 kPa.

Methyl 3-*O*-Benzyl-4-(2,4-di-*O*-acetyl-3-deoxy-L-*glycero*-tetronamido)-4,6-dideoxy-α-D-mannopyranoside (2): A suspension of EDAC (6.86 g, 35.75 mmol) in dichloromethane (100 mL) was added dropwise at room temperature to a stirred solution of the amino sugar **1**[32] (8 g, 29.8 mmol) and 2,4-*O*-acetyl-3-deoxy-L-*glycero*-tetronic acid[19] (7.3 g, 35.75 mmol) in dichloromethane (200 mL). Stirring was continued for 1 h, when TLC (CH_2Cl_2/MeOH, 10:1) showed the conversion was complete. The mixture was filtered, the filtrate concentrated and chromatography of the residue (CH_2Cl_2/MeOH, 50:1 → 10:1) gave the desired product **2** (12.47 g, 92%), m.p. 118–119 °C (from Et_2O containing a few drops of EtOH). $[\alpha]_D$ = +24.6 (*c* = 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.92 (d, $J_{NH,4}$ = 8.8 Hz, 1 H, NH), 5.17 (dd, $J_{2',3a'}$ = 7.9, $J_{2',3b'}$ = 3.2 Hz, 1 H, 2′-H), 4.75 (d, $J_{1,2}$ = 1.5 Hz, 1 H, 1-H), 4.66, 4.47 (2 d, ^2J = 12.0 Hz, 2 H, CH_2Ph), 4.21–4.03 (m, 3 H, 4′-H, incl. dd, 4.03, $J_{2,3}$ = 3.2, $J_{3,4}$ 10.3 Hz, 2-H), 3.96 (q, *J* = 10.3 Hz, 1 H, 4-H), 3.82–3.72 (m, 2 H, 3-H, 5-H), 3.37 (s, 3 H, OCH_3), 2.55 (br. s, 1 H, OH), 2.26–1.97 (m, 8 H, 3′-H, incl. 2 s, 2.07, 2.03, 2 CH_3CO), 1.21 (d, $J_{5,6}$ = 6.2 Hz, 3 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.62 (NHCO), 169.35 (2 CH_3CO), 100.17 (C-1), 75.76 (C-3), 71.06 (C-2′), 70.86 (CH$_2$Ph), 66.79 (C-5), 66.68 (C-2), 59.95 (C-4′), 54.96 (OCH_3), 52.09 (C-4), 30.81 (C-3′), 20.78, 20.69 (2 CH$_3$CO), 17.80 (C-6) ppm. ESI-MS: *m*/*z* = 476.1897 ([M + Na]$^+$; calcd. 476.1902). $C_{22}H_{31}NO_9$ (453.2): calcd. C 58.27, H 6.89, N 3.09; found C 58.27, H 6.90, N 3.21.

Methyl 3-*O*-Benzyl-2-*O*-chloroacetyl-4-(2,4-di-*O*-acetyl-3-deoxy-L-*glycero*-tetronamido)-4,6-dideoxy-α-D-mannopyranoside (3): Tetramethylurea (1.2 mL, 15 mmol), followed by a solution of **2** (2.2 g, 5 mmol) in dichloromethane (20 mL), was added at 0 °C to a solution of chloroacetyl chloride (1.2 mL, 15 mmol) in dichloromethane (20 mL), and the mixture was stirred overnight at room temperature. When the reaction was complete (TLC, toluene/acetone, 4:1), ice-cold aq. $NaHCO_3$ was added, and the stirring was continued for 30 min. The mixture was partitioned between dichloromethane and water, and the combined organic layers were dried and concentrated. The residue was chromatographed (toluene/acetone, 95:5 → 85:15), to give **3** (2.45 g, 95%.), m.p. 124–125 °C (from EtOH). $[\alpha]_D$ = –2.8 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.80 (d, $J_{NH,4}$ = 6.6 Hz, 1 H, NH), 5.43 (dd, $J_{1,2}$ = 1.9, $J_{2,3}$ = 2.7 Hz, 1 H, 2-H), 5.16 (dd, $J_{2',3a'}$ = 8.1, $J_{2',3b'}$ = 4.2 Hz, 1 H, 2′-H), 4.70 (d, 1 H, 1-H), 4.65, 4.36 (2 d, ^2J = 11.6 Hz, 2 H, CH_2Ph), 4.24–4.02 (m, 4 H, H-4′, incl. s, 4.17, $ClCH_2CO$), 3.94–3.76 (m, 3 H, 3-H, 4-H, 5-H), 3.37 (s, 3 H, OCH_3), 2.27–1.97 (m, 8 H, 3′-H, incl. 2 s, 2.06, 2.04, 2 CH_3CO), 1.21 (d, $J_{5,6}$ = 6.3 Hz, 3 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.89 (NHCO), 169.59, 169.40 (2 CH$_3$$C$O), 166.88 (ClCH$_2$$C$O), 98.39 (C-1), 73.33 (C-3), 71.08 (C-2′), 71.00 (CH$_2$Ph), 68.98 (C-2), 67.38 (C-5), 59.91 (C-4′), 55.19 (OCH_3), 52.71 (C-4), 40.85 ($ClCH_2$), 30.89 (C-3′), 20.83, 20.77 (2 CH$_3$CO), 17.90 (C-6) ppm. ESI-MS: *m*/*z* = 530.1793 ([M + 1]$^+$; calcd. 530.1772). $C_{22}H_{31}NO_9$ (529.2): calcd. C 54.39, H 6.09, N 2.64; found C 54.46, H 6.07, N 2.64.

1-*O*-Acetyl 3-*O*-Benzyl-2-*O*-chloroacetyl-4-(2,4-di-*O*-acetyl-3-deoxy-L-*glycero*-tetronamido)-4,6-dideoxy-α- (5) and -β-D-mannopyranoside (7): A solution of the methyl glycoside **3** (500 mg, 0.6 mmol) in a mixture of 50:20:0.25 Ac_2O/AcOH/H_2SO_4 (10 mL) was stirred for 11 h at room temperature, when TLC (hexane/acetone, 2:1) showed that the reaction was complete. NaOAc–trihydrate was added, to neutralize sulfuric acid, followed by cold aq. $NaHCO_3$ to hydrolyze excess of Ac_2O and neutralize the AcOH formed. After partitioning between water and dichloromethane, the organic phase was dried, concentrated, and the residue was chromatographed (CH_2Cl_2/acetone, 99:1 → 10:1). Eluted first was **5** (400 mg, 76%). **5:** $[\alpha]_D$ = –1.6 (*c* = 2.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.08 (d, $J_{1,2}$ = 1.9 Hz, 1 H, 1-H), 6.03 (d, $J_{NH,4}$ = 7.9 Hz, 1 H, NH), 5.43 (dd, $J_{2,3}$ = 3.2 Hz, 1 H, 2-H), 5.13 (dd, $J_{2',3a'}$ = 7.7, $J_{2',3b'}$ = 5.1 Hz, 1 H, 2′-H), 4.68, 4.38 (2 d, ^2J = 11.5 Hz, 2 H, CH_2Ph), 4.18–4.03 (m, 6 H, 3-H, 4′-H, 5-H, incl. s, 4.16, $ClCH_2CO$), 3.76 (q, *J* = 10.5 Hz, 1 H, 4-H), 2.28–1.97 (m, 11 H, 3′-H, incl. s, 2.16, CH_3CO-1 and 2 s, 2.10, 2.06, 2 CH_3CO-2′,4′), 1.23 (d, $J_{5,6}$ = 6.0 Hz, 3 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.87 (NHCO), 169.61, 169.51 (2 CH$_3$$C$O-2′,4′), 168.30 (CH$_3$$C$O-1), 166.51 (ClCH$_2$$C$O), 90.71 ($J_{C,H}$ = 176.6 Hz, C-1), 72.56 (C-3), 71.38 (C-2′), 71.00 (CH$_2$Ph), 69.21 (C-5), 68.22 (C-2), 59.81 (C-4′), 53.21 (C-4), 40.62 ($ClCH_2$), 30.82 (C-3′), 20.84, 20.77, 20.68 (3 CH$_3$CO), 17.88 (C-6) ppm. ESI-MS: *m*/*z* = 580.1562 ([M + Na]$^+$; calcd. 580.1562). $C_{25}H_{32}ClNO_{11}$ (557.2): calcd. C 53.81, H 5.78, N 2.51; found C 53.38, H 5.73, N 2.48. Eluted next was **7** (70 mg. 13%). **7:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.98 (d, $J_{NH,4}$ = 7.5 Hz, 1 H, NH), 5.80 (d, $J_{1,2}$ = 0.9 Hz, 1 H, 1-H), 5.67 (dd, $J_{2,3}$ = 2.8 Hz, 1 H, 2-H), 5.14 (dd, $J_{2',3a'}$ = 7.9, $J_{2',3b'}$ = 4.9 Hz, 1 H, 2′-H), 4.68, 4.36 (2 d, ^2J = 11.3 Hz, 2 H, CH_2Ph), 4.24–4.03 (m, 4 H, 4′-H, incl. s, 4.24, $ClCH_2CO$), 3.98–3.85 (m, 2 H, H-5, incl. 3.95, dd, $J_{3,4}$ = 10.4 Hz, 3-H), 3.66 (q, *J* = 10.4 Hz, 1 H, 4-H), 2.28–2.00 (m. 11 H, 3′-H, incl. s, 2.17, CH_3CO-1, and 2 s, 2.11, 2.05, 2 CH_3CO-2′,4′), 1.25 (d, $J_{5,6}$ = 5.8 Hz, 3 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.69 (NHCO), 169.65, 168.61 (2 $CH_3\mathit{C}O$-2′,4′), 167.14 ($CH_3\mathit{C}O$-1), 161.14 ($ClCH_2\mathit{C}O$), 90.71 ($J_{C,H}$ = 161.8 Hz, C-1), 74.41 (C-3), 71.64 (C-5), 71.28 ($\mathit{C}H_2Ph$), 71.08 (C-2′), 68.51 (C-2), 59.87 (C-4′), 53.49 (C-4), 40.80 ($ClCH_2$), 30.90 (C-3′), 20.87 ($\mathit{C}H_3CO$), 20.76 (2 C, 2 $\mathit{C}H_3CO$), 17.88 (C-6) ppm. ESI-MS: *m/z* = 558.1755 ([M + 1]$^+$; calcd. 558.1755). Combined yield, 470 mg (89%; α:β = 5.8:1).

Ethyl 3-*O*-Benzyl-2-*O*-chloroacetyl-4-(2,4-di-*O*-acetyl-3-deoxy-L-*glycero*-tetronamido)-4,6-dideoxy-1-thio-α- (9) and -β-D-mannopyranoside (12)

Procedure A (from pure 5): Activated molecular sieves (4 Å, 35 mg) were added at 0 °C to a stirred solution of **5** (374 mg, 0.67 mmol) in toluene/1,4-dioxane (1:4, 5 mL). After 30 min, EtSH (0.56 mL, 6.7 mmol) and $BF_3{\cdot}Et_2O$ (0.51 mL, 4.02 mmol) were added, and the reaction mixture was stirred at room temperature for 48 h, when TLC (toluene/acetone, 5:1) showed that the reaction was complete. The mixture was neutralized with solid $NaHCO_3$, filtered, concentrated, and the residue was chromatographed. Eluted first was the *α*-D-mannopyranoside **9** (200 mg, 53%). **9:** M.p. 81–82 °C (from *i*Pr_2O containing a few drops of EtOAc). $[\alpha]_D$ = +21.7 (*c* = 1.8; $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 5.82 (d, $J_{NH,4}$ = 8.3 Hz, 1 H, NH), 5.53 (dd, $J_{1,2}$ = 1.7, $J_{2,3}$ = 3.1 Hz, 1 H, 2-H), 5.27 (d, 1 H, 1-H), 5.17 (dd, $J_{2',3a'}$ = 8.1, $J_{2',3b'}$ = 4.7 Hz, 1 H, 2′-H), 4.64, 4.36 (2 d, ^2J = 11.7 Hz, 2 H, $C\mathit{H_2}Ph$), 4.22–4.11 (m, 4 H, 4′a-H, 5-H, incl. 2 d, 4.22, 4.16, ^2J = 15.3 Hz, $ClCH_2CO$), 4.08–4.05 (m, 1 H, 4′b-H), 3.93 (q, *J* = 10.4 Hz, 1 H, 4-H), 3.82 (dd, $J_{3,4}$ = 10.6 Hz, 1 H, 3-H), 2.67–2.58 (m, 2 H, $SC\mathit{H_2}CH_3$), 2.36–2.15 (m, 1 H, 3′a-H), 2.09–2.03 (m, 7 H, 3′b-H, incl. 2 s, 2.07, 2.06, 2 CH_3CO), 1.29 (t, *J* = 7.4 Hz, 3 H, $SCH_2C\mathit{H_3}$), 1.21 (d, $J_{5,6}$ = 6.2 Hz, 3 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.84 (NHCO), 169.56, 169.38 (2 $CH_3\mathit{C}O$), 166.76 ($ClCH_2\mathit{C}O$), 81.84 ($J_{C,H}$ = 166.1 Hz, C-1), 73.60 (C-3), 71.02 (C-2′), 70.98 ($\mathit{C}H_2Ph$), 70.91 (C-2), 68.12 (C-5), 59.88 (C-4′), 52.84 (C-4), 40.83 ($ClCH_2$), 30.86 (C-3′), 25.65 ($S\mathit{C}H_2CH_3$), 20.79, 20.76 (2 $\mathit{C}H_3CO$), 17.76 (C-6), 14.81 ($SCH_2\mathit{C}H_3$) ppm. ESI-MS: *m/z* = 582.1542 ([M + Na]$^+$; calcd. 582.1541). $C_{25}H_{34}ClNO_9S$ (559.2): calcd. C 53.61, H 6.12, N 2.50; found C 53.64, H 6.21, N 2.48. Eluted next was the β-D-mannopyranoside **12** (115 mg, 31%). **12:** M.p. 150.5–151.5 °C (from EtOH), $[\alpha]_D$ = –101.4 (*c* = 0.8; $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 6.11 (d, $J_{NH,4}$ = 7.9 Hz, 1 H, NH), 5.72 (d, $J_{2,3}$ = 3.3 Hz, 1 H, 2-H), 5.11 (dd, $J_{2',3a'}$ = 8.0, $J_{2',3b'}$ = 4.7 Hz, 1 H, 2′-H), 4.75 (s, 1 H, 1-H), 4.72, 4.34 (2 d, ^2J = 11.1 Hz, 2 H, $C\mathit{H_2}Ph$), 4.26, 4.21 (2 d, ^2J = 15.4 Hz, 2 H, $ClCH_2CO$), 4.16–4.12 (m, 1 H, 4′a-H), 4.09–4.05 (m, 1 H, 4′b-H), 4.02 (dd, $J_{3,4}$ = 10.7 Hz, 1 H, 3-H), 3.95–3.92 (m, 1 H, 5-H), 3.53 (q, *J* = 10.1 Hz, 1 H, 4-H), 2.76–2.70 (m, 2 H, $SC\mathit{H_2}CH_3$), 2.20–2.14 (m. 1 H, 3′a-H), 2.08–2.03 (m, 7 H, 3′b-H, incl. 2 s, 2.07, 2.05, 2 CH_3CO), 1.29 (t, *J* = 7.4 Hz, 3 H, $SCH_2C\mathit{H_3}$), 1.23 (d, $J_{5,6}$ = 6.2 Hz, 3 H, 6-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.91 (NHCO), 169.57, 169.48 (2 $CH_3\mathit{C}O$), 166.95 ($ClCH_2\mathit{C}O$), 81.44 ($J_{C,H}$ = 143.8 Hz, C-1), 75.37 (C-3), 74.47 (C-5), 71.43 ($\mathit{C}H_2Ph$), 71.00 (C-2), 70.92 (C-2′), 59.84 (C-4′), 54.37 (C-4), 40.75 ($ClCH_2$), 30.91 (C-3′), 25.53 ($S\mathit{C}H_2CH_3$), 20.82, 20.69 (2 $\mathit{C}H_3CO$), 18.19 (C-6), 14.85 ($SCH_2\mathit{C}H_3$) ppm. ESI-MS: *m/z* = 582.1542 ([M + Na]$^+$; calcd. 582.1541). $C_{25}H_{34}ClNO_9S$ (559.2): calcd. C 53.61, H 6.12, N 2.50; found C 53.60, H 6.01, N 2.41.

Procedure B (from a mixture of 5 and 7): Activated molecular sieves (4 Å, 150 mg) were added at 0 °C to a stirred 3:1 mixture of **5** and **7** (374 mg, 1.56 mmol) in toluene/1,4-dioxane (1:4, 12 mL). After 30 min, EtSH (1.17 mL, 15.6 mmol) and $BF_3{\cdot}Et_2O$ (1.19 mL, 9.36 mmol) were added, and the reaction mixture was stirred at room temperature. After 48 h, when TLC (toluene/acetone, 5:1) showed that the reaction was complete, the mixture was neutralized with solid $NaHCO_3$, filtered and concentrated. Chromatography of the residue (toluene/acetone, 5 → 10%) afforded the α-thiomannoside **9** (195 mg, 52%) and the β-thiomannoside **12** (168 mg, 45%).

Methyl 3-*O*-Benzyl-4-(2,4-di-*O*-acetyl-3-deoxy-L-*glycero*-tetronamido)-4,6-dideoxy-2-*O*-levulinoyl-α-D-mannopyranoside (4): EDAC (11.02 g, 42.9 mmol) and DMAP (5.24 g, 42.9 mmol) were added to a stirred solution of **2** (6.5 g, 14.3 mmol) and levulinic acid (4.98 g, 42.9 mmol) in dichloromethane (25 mL). After stirring overnight at room temperature, TLC (hexane/acetone, 2:1) showed that the reaction was complete. The mixture was washed with 0.2 M HCl (50 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were washed with aq. $NaHCO_3$, dried, and concentrated. The residue was chromatographed (hexane/acetone, 4:1 → 2:1) to give **4** (7.67 g, 98%), m.p. 75–76 °C (from Et_2O). $[\alpha]_D$ = –3.1 (*c* = 0.9; $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 5.79 (d, $J_{NH,4}$ = 8.8 Hz, 1 H, NH), 5.37 (dd, $J_{1,2}$ = 1.9, $J_{2,3}$ = 3.1 Hz, 1 H, 2-H), 5.17 (dd, $J_{2',3a'}$ = 8.0, $J_{2',3b'}$ = 4.6 Hz, 1 H, 2′-H), 4.67 (d, 1 H, 1-H), 4.63, 4.33 (2 d, ^2J = 11.8 Hz, 2 H, $C\mathit{H_2}Ph$), 4.16–4.13 (m, 1 H, 4′a-H), 4.07–4.03 (m, 1 H, 4′b-H), 3.91 (q, *J* = 10.4 Hz, 1 H, 4-H), 3.82 (dd, $J_{3,4}$ = 10.6 Hz, 1 H, 3-H), 3.79–3.74 (m, 1 H, 5-H), 3.36 (s, 3 H, OCH_3), 2.74–2.66 (m, 4 H, CH_2CH_2), 2.22–2.17 (m, 4 H, 3′a-H, incl. s, 2.17, CH_3), 2.07–2.02 (m, 7 H, 3′b-H, incl. 2 s, 2.06, 2.03, 2 CH_3CO), 1.22 (d, $J_{5,6}$ = 6.3 Hz, 3 H, 6-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 206.35 ($CH_2\mathit{C}O$), 171.89 ($CH_2\mathit{C}OO$), 170.89 (NHCO), 169.56, 169.36 (2 $CH_3\mathit{C}O$), 98.69 (C-1), 73.43 (C-3), 71.09 (C-2′), 70.56 ($\mathit{C}H_2Ph$), 67.35 (C-5), 67.21 (C-2), 59.92 (C-4′), 55.09 (OCH_3), 52.70 (C-4), 37.95 ($\mathit{C}H_2CO$), 30.88 (C-3′), 29.76 (CH_3), 28.11 ($\mathit{C}H_2COO$), 20.84, 20.78, (2 $\mathit{C}H_3CO$), 17.97 (C-6) ppm. ESI-MS: *m/z* = 574.2264 ([M + Na]$^+$; calcd. 574.2268). $C_{27}H_{37}NO_{11}$ (551.2): calcd. C 58.79, H 6.76, N 2.54; found C 58.80, H 6.97, N 2.46.

1-*O*-Acetyl-3-*O*-benzyl-4-(2,4-di-*O*-acetyl-3-deoxy-L-*glycero*-tetronamido)-4,6-dideoxy-2-*O*-levulinoyl-α- (6) and -β-D-mannopyranose (8): A solution of methyl glycoside **4** (4.2 g, 7.6 mmol) in a mixture of 50:20:0.25 $Ac_2O/AcOH/H_2SO_4$ (120 mL) was stirred for 1 h at room temperature, when TLC (hexane/acetone, 2:1) showed that the reaction was complete. After processing, as described above for the preparation of **5** and **7**, the mixture of **6** and **7** (6.7:1, NMR) was chromatographed (CH_2Cl_2/acetone, 99:1 → 90:10). Eluted first was the α-D-mannopyranose **6** (3.57 g, 81%). **6:** $[\alpha]_D$ = –25.2 (*c* = 1.7; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.17 (d, $J_{NH,4}$ = 8.5 Hz, 1 H, NH), 6.04 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 5.36 (dd, $J_{2,3}$ = 2.9 Hz, 1 H, 2-H), 5.13 (dd, $J_{2',3a'}$ = 7.8, $J_{2',3b'}$ = 4.9 Hz, 1 H, 2′-H), 4.65, 4.36 (2 d, ^2J = 11.4 Hz, 2 H, $C\mathit{H_2}Ph$), 4.19–4.02 (m, 4 H, 5-H, 4′-H, 3-H), 3.83 (q, *J* = 10.4 Hz, 1 H, 4-H), 2.76–2.64 (m, 4 H, CH_2CH_2), 2.28–1.98 (m, 13 H, 3′-H, incl. 4 s, 2.15, 2.10, 2.06, 2.03, 3 CH_3CO, CH_3), 1.22 (d, $J_{5,6}$ = 6.2 Hz, 3 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.99 ($CH_2\mathit{C}O$), 171.46 ($CH_2\mathit{C}OO$), 170.68 (NHCO), 169.45, 169.39 (2 $CH_3\mathit{C}O$-2′,4′), 168.24 ($CH_3\mathit{C}O$-1), 90.89 ($J_{C,H}$ = 176.4 Hz, C-1), 72.54 (C-3), 70.85 (C-2′), 70.78 ($\mathit{C}H_2Ph$), 69.06 (C-5), 69.41 (C-2), 59.71 (C-4′), 52.91 (C-4), 37.65 ($\mathit{C}H_2CO$), 30.67 (C-3′), 29.51 (CH_3), 27.77 ($\mathit{C}H_2COO$), 20.69, 20.61, 20.51 (3 $\mathit{C}H_3CO$), 17.77 (C-6) ppm. ESI-MS *m/z*: 602.2221 ([M + Na]$^+$; calcd. 602.2213). $C_{28}H_{37}NO_{12}$ (579.2): C 58.02, H 6.43, N 2.42; found: C 57.92, H 6.29, N 2.39.

Eluted next was β-D-mannopyranose (**8**, 0.44 g, 10%). **8:** M.p. 157–159 °C (from EtOAc/*i*Pr_2O, 1:1). $[\alpha]_D$ = –71 (*c* = 0.3; $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.01 (d, $J_{NH,4}$ = 7.8 Hz, 1 H, NH), 5.76 (br. s, 1 H, 1-H), 5.67 (br. d, $J_{2,3}$ = 2.9 Hz, 1 H, 2-H), 5.14 (dd, $J_{2',3a'}$ = 7.2, $J_{2',3b'}$ = 4.6 Hz, 1 H, 2′-H), 4.66, 4.32 (2 d, ^2J =

11.4 Hz, 2 H, $\mathrm{C}H_2\mathrm{Ph}$), 4.20–4.02 (m, 2 H, 4′-H), 3.89–3.82 (m, 2 H, 5-H, incl. 3.88, dd, $J_{3,4}$ = 10.1 Hz, 3-H), 3.70 (q, J = 9.5 Hz, 1 H, 4-H), 2.81–2.67 (m, 4 H, $\mathrm{CH_2CH_2}$), 2.18–2.04 (m. 13 H, 3′-H, incl. 4 s, 2.18, 2.12, 2.07, 2.04, 3 $\mathrm{CH_3CO}$, $\mathrm{CH_3}$), 1.29 (d, $J_{5,6}$ = 5.9 Hz, 3 H, 6-H) ppm. ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ = 205.97 ($\mathrm{CH_2}C\mathrm{O}$), 172.16 ($\mathrm{CH_2}C\mathrm{OO}$), 170.91 (NHCO), 169.56, 169.52 (2 $\mathrm{CH_3}C\mathrm{O}$-2′,4′), 168.82 ($\mathrm{CH_3}C\mathrm{O}$-1), 90.89 ($J_{\mathrm{C,H}}$ = 161.8 Hz, C-1), 74.46 (C-3), 71.63 (C-5), 71.04 (C-2′), 70.78 ($C\mathrm{H_2Ph}$), 66.50 (C-2), 59.85 (C-4′), 53.37 (C-4), 37.88 ($C\mathrm{H_2CO}$), 30.89 (C-3′), 29.77 ($\mathrm{CH_3}$), 27.98 ($C\mathrm{H_2COO}$), 20.83, 20.73, 20.72 (3 $C\mathrm{H_3CO}$), 17.86 (C-6) ppm. ESI-MS: m/z = 602.2192 ($[\mathrm{M+Na}]^+$; calcd. 602.2213). $\mathrm{C_{28}H_{37}NO_{12}}$ (579.2): calcd. C 58.02, H 6.43, N 2.42; found C 57.94, H 6.36; N 2.48.

Ethyl 3-*O*-Benzyl-4-(2,4-di-*O*-acetyl-3-deoxy-L-*glycero*-tetronamido)-4,6-dideoxy-2-*O*-levulinoyl-1-thio-α- (11) and -β-D-mannopyranoside (14)

Procedure A: EtSH (0.58 mL, 8.80 mmol) and $\mathrm{BF_3{\cdot}Et_2O}$ (0.67 mL, 5.28 mmol) were added to a stirred mixture of **6** (510 mg, 0.88 mmol) and activated molecular sieves (4 Å, 300 mg) in $\mathrm{CH_2Cl_2}$ (6 mL). After 12 h at room temperature, when TLC (hexane/acetone, 2:1) showed that all starting material had been consumed, the mixture was neutralized with solid $\mathrm{NaHCO_3}$, filtered and concentrated. The residue was chromatographed (hexane/acetone, 19:1 → 2:1) to give four products. Eluted first was ethyl 4-(2,4-di-*O*-acetyl-3-deoxy-L-*glycero*-tetronamido)-3-*O*-benzyl-4,6-dideoxy-2-*O*-(4,4-dithioethyl)pentanoyl-1-thio-α-D-mannopyranoside (**10**) (250 mg, 49%). **10:** ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 5.90 (d, $J_{\mathrm{NH},4}$ = 8.9 Hz, 1 H, NH), 5.48 (d, $J_{1,2}$ = 1.9, $J_{2,3}$ = 3.0 Hz, 1 H, 2-H), 5.25 (d, 1 H, 1-H), 5.18 (dd, $J_{2',3a'}$ = 7.4, $J_{2',3b'}$ = 4.5 Hz, 1 H, 2′-H), 4.62, 4.35 (2 d, ^2J = 11.6 Hz, 2 H, $\mathrm{C}H_2\mathrm{Ph}$), 4.21–3.90 (m, 4 H, 4′-H, 5-H, incl. q, 3.96, J = 10.1 Hz, 4-H), 3.80 (dd, $J_{3,4}$ = 10.4 Hz, 3-H), 2.70–2.53 (m, 8 H, $\mathrm{CH_2COO}$, 3 $\mathrm{SC}H_2\mathrm{CH_3}$), 2.25–1.98 [m, 10 H, 3′-H, $\mathrm{C}H_2\mathrm{C(SCH_2CH_3)_2}$, incl. 2 s, 2.06, 2.03, 2 $\mathrm{CH_3CO}$], 1.51 (s, 3 H, $\mathrm{CH_3}$), 1.29 (t, J = 7.5 Hz, 3 H, $\mathrm{SCH_2C}H_3$), 1.25–1.19 (m, 9 H, 2 $\mathrm{SCH_2C}H_3$, incl. d, 1.22, $J_{5,6}$ = 5.7 Hz, 6-H) ppm. ^{13}C NMR δ = 172.41 ($\mathrm{CH_2}C\mathrm{OO}$), 170.66 (NHCO), 169.38, 169.16 (2 $\mathrm{CH_3}C\mathrm{O}$), 82.02 ($J_{\mathrm{C,H}}$ = 164.6 Hz, C-1), 73.66 (C-3), 70.92 (C-2′), 70.52 ($C\mathrm{H_2Ph}$), 68.83 (C-2), 67.92 (C-5), 59.76 (C-4′), 58.62 ($C\mathrm{[SCH_2CH_3]_2}$), 52.82 (C-4), 35.83 ($C\mathrm{H_2C[SCH_2CH_3]_2}$), 30.70 (C-3′), 29.65 ($C\mathrm{H_2COO}$), 27.22 ($\mathrm{CH_3}$), 25.38 ($\mathrm{S}C\mathrm{H_2CH_3}$), 23.19 (2 C, 2 $\mathrm{S}C\mathrm{H_2CH_3}$), 20.69, 20.63 (2 $C\mathrm{H_3CO}$), 17.70 (C-6), 14.73 ($\mathrm{SCH_2}C\mathrm{H_3}$), 13.85 (2 C, 2 $\mathrm{SCH_2}C\mathrm{H_3}$) ppm. ESI-MS: m/z = 710.2523 ($[\mathrm{M+Na}]^+$; calcd. 710.2467).

Eluted second was amorphous ethyl 3-*O*-benzyl-4-(2,4-di-*O*-acetyl-3-deoxy-L-*glycero*-tetronamido)-4,6-dideoxy-2-*O*-(4,4-dithioethyl)-pentanoyl-1-thio-β-D-mannopyranoside (**13**) (60 mg, 12%). **13:** ^{1}H NMR (300 MHz, $\mathrm{CDCl_3}$): δ = 6.11 (d, $J_{\mathrm{NH},4}$ = 7.8 Hz, 1 H, NH), 5.68 (br. d, $J_{2,3}$ = 2.9 Hz, 1 H, 2-H), 5.12 (dd, $J_{2',3a'}$ = 8.1, $J_{2',3b'}$ = 4.8 Hz, 1 H, 2′-H), 4.73 (d, $J_{1,2}$ = 0.9 Hz, 1 H, 1-H), 4.69, 4.31 (2 d, ^2J = 11.0 Hz, 2 H, $\mathrm{C}H_2\mathrm{Ph}$), 4.19–3.90 (m, 4 H, 4′-H, 5-H, incl. dd, 3.99, $J_{3,4}$ = 10.7 Hz, 3-H), 3.52 (q, J = 10.1 Hz, 1 H, 4-H), 2.81–2.55 (m, 8 H, $\mathrm{CH_2COO}$, 3 $\mathrm{SC}H_2\mathrm{CH_3}$), 2.25–1.99 [m, 10 H, 3′-H, $\mathrm{C}H_2\mathrm{C(SCH_2CH_3)_2}$, incl. 2 s, 2.07, 2.04, 2 $\mathrm{CH_3CO}$], 1.50 (s, 3 H, $\mathrm{CH_3}$), 1.30 (t, 6 H, J = 7.5 Hz, $\mathrm{SCH_2C}H_3$, incl. d, 1.29, $J_{5.6}$ = 6.0 Hz, 6-H), 1.22, 1.21 (2 t, 6 H, J = 7.5 Hz, partially overlapped, 2 $\mathrm{SCH_2C}H_3$) ppm. ^{13}C NMR (75 MHz, $\mathrm{CDCl_3}$): δ = 172.68 ($\mathrm{CH_2}C\mathrm{OO}$), 170.85 (NHCO), 169.48, (2 C, 2 $\mathrm{CH_3}C\mathrm{O}$), 81.84 ($J_{\mathrm{C,H}}$ = 149.7 Hz, C-1), 73.59 (C-3), 74.35 (C-5), 71.15 ($C\mathrm{H_2Ph}$), 70.96 (C-2′), 68.91 (C-2), 59.84 (C-4′), 58.86 ($C\mathrm{[SCH_2CH_3]_2}$), 54.65 (C-4), 35.97 ($C\mathrm{H_2C[SCH_2CH_3]_2}$), 30.86 (C-3′), 29.56 ($C\mathrm{H_2COO}$), 27.31 ($\mathrm{CH_3}$), 25.44 ($\mathrm{S}C\mathrm{H_2CH_3}$), 23.31 (2 C, 2 $\mathrm{S}C\mathrm{H_2CH_3}$), 20.76, 20.68 (2 $C\mathrm{H_3CO}$), 18.25 (C-6), 14.86 ($\mathrm{SCH_2}C\mathrm{H_3}$), 13.99 (2 C, 2 $\mathrm{SCH_2}C\mathrm{H_3}$) ppm. ESI-MS: m/z = 710.2495 ($[\mathrm{M+Na}]^+$; calcd. 710.2467).

Eluted third was the ethyl 1-thio-α-D-mannopyranoside **11** (120 mg, 23%). **11:** M.p. 89–90 °C (from $i\mathrm{Pr_2O}$ containing a few drops of EtOH). $[\alpha]_\mathrm{D}$ = +29 (c = 0.8; $\mathrm{CHCl_3}$). ^{1}H NMR (600 MHz, $\mathrm{CDCl_3}$): δ = 5.93 (d, $J_{\mathrm{NH},4}$ = 9.0 Hz, 1 H, NH), 5.45 (dd, $J_{1,2}$ = 1.6, $J_{2,3}$ = 3.1 Hz, 1 H, 2-H), 5.24 (d, 1 H, 1-H), 5.18 (dd, $J_{2',3a'}$ = 8.0, $J_{2',3b'}$ = 4.6 Hz, 1 H, 2′-H), 4.61, 4.33 (2 d, ^2J = 11.7 Hz, 2 H, $\mathrm{C}H_2\mathrm{Ph}$), 4.18–4.04 (m, 3 H, 4′-H, 5-H), 3.97 (q, J = 10.3 Hz, 1 H, 4-H), 3.77 (dd, $J_{3,4}$ = 10.6 Hz, 1 H, 3-H), 2.74–2.56 (m, 6 H, $\mathrm{CH_2CH_2}$, $\mathrm{SC}H_2\mathrm{CH_3}$), 2.27–2.14 (m, 4 H, 3′a-H, incl. s, 2.18, $\mathrm{CH_3CO}$), 2.08–2.01 (m, 7 H, 3′b-H, incl. 2 s, 2.06, 2.03, 2 $\mathrm{CH_3CO}$), 1.28 (t, J = 7.4 Hz, 3 H, $\mathrm{SCH_2C}H_3$), 1.21 (d, $J_{5,6}$ = 6.2 Hz, 3 H, 6-H) ppm. ^{13}C NMR (150 MHz, $\mathrm{CDCl_3}$): δ = 206.29 ($\mathrm{CH_2}C\mathrm{O}$), 171.72 ($\mathrm{CH_2}C\mathrm{OO}$), 170.71 (NHCO), 169.45, 169.28 (2 $\mathrm{CH_3}C\mathrm{O}$), 82.02 ($J_{\mathrm{C,H}}$ = 167.1 Hz, C-1), 73.65 (C-3), 70.92 (C-2′), 70.44 ($C\mathrm{H_2Ph}$), 68.97 (C-2), 67.94 (C-5), 59.81 (C-4′), 52.69 (C-4), 37.78 ($C\mathrm{H_2CO}$), 30.75 (C-3′), 29.62 ($\mathrm{CH_3}$), 27.99 ($C\mathrm{H_2COO}$), 25.43 ($\mathrm{S}C\mathrm{H_2CH_3}$), 20.68, 20.64 (2 $C\mathrm{H_3CO}$), 17.70 (C-6), 14.74 ($\mathrm{SCH_2}C\mathrm{H_3}$) ppm. ESI-MS: m/z = 604.2191 ($[\mathrm{M+Na}]^+$; calcd. 604.2192). $\mathrm{C_{28}H_{39}NO_{10}S}$ (581.2): calcd. C 57.82, H 6.76, N 2.41; found C 57.91, H 6.56, N 2.37.

Eluted fourth was the 1-thio-β-D-mannopyranoside **14** (25 mg, 5%). **14:** M.p. 74–75 °C (from EtOAc). $[\alpha]_\mathrm{D}$ = –45.6 (c = 1.2; $\mathrm{CHCl_3}$). ^{1}H NMR (600 MHz, $\mathrm{CDCl_3}$): δ = 6.11 (d, $J_{\mathrm{NH},4}$ = 7.8 Hz, 1 H, NH), 5.65 (br. d, $J_{2,3}$ = 2.8 Hz, 1 H, 2-H), 5.11 (dd, $J_{2',3a'}$ = 8.0, $J_{2',3b'}$ = 4.7 Hz, 1 H, 2′-H), 4.72 (d, $J_{1,2}$ = 0.8 Hz, 1 H, 1-H), 4.68, 4.29 (2 d, ^2J = 11.2 Hz, 2 H, $\mathrm{C}H_2\mathrm{Ph}$), 4.16–4.11 (m, 1 H, 4′a-H), 4.08–4.05 (m, 1 H, 4′b-H), 3.98–3.93 (m, 2 H, 5-H, incl. dd, 3.97, $J_{3,4}$ = 10.9 Hz, 3-H), 3.51 (q, J = 10.1 Hz, 1 H, 4-H), 2.77–2.55 (m, 6 H, $\mathrm{CH_2CH_2}$, $\mathrm{SC}H_2\mathrm{CH_3}$), 2.20–2.13 (m, 4 H, 3′a-H, incl. s, 2.18, $\mathrm{CH_3}$), 2.08–2.02 (m, 7 H, 3′b-H, incl. 2 s, 2.06, 2.05, 2 $\mathrm{CH_3CO}$), 1.31–1.28 (m, 6 H, $\mathrm{SCH_2C}H_3$, 6-H) ppm. ^{13}C NMR (150 MHz, $\mathrm{CDCl_3}$): δ = 206.05 ($\mathrm{CH_2}C\mathrm{O}$), 172.12 ($\mathrm{CH_2}C\mathrm{OO}$), 170.94 (NHCO), 169.54, 169.51 (2 $\mathrm{CH_3}C\mathrm{O}$), 81.82 ($J_{\mathrm{C,H}}$ = 150.7 Hz, C-1), 73.39 (C-3), 74.39 (C-5), 71.09 ($C\mathrm{H_2Ph}$), 70.96 (C-2′), 69.17 (C-2), 59.61 (C-4′), 54.61 (C-4), 38.03 ($C\mathrm{H_2CO}$), 30.93 (C-3′), 29.93 ($\mathrm{CH_3}$), 27.97 ($C\mathrm{H_2COO}$), 25.50 ($\mathrm{S}C\mathrm{H_2CH_3}$), 20.86, 20.74 (2 $C\mathrm{H_3CO}$), 18.29 (C-6), 14.91 ($\mathrm{SCH_2}C\mathrm{H_3}$) ppm. ESI-MS: m/z = 604.2189 ($[\mathrm{M+Na}]^+$; calcd. 604.2192). $\mathrm{C_{28}H_{39}NO_{10}S}$ (581.2): calcd. C 57.82, H 6.76, N 2.41; found C 57.93, H 6.84, N 2.43.

Procedure B: A mixture of **6** (1.50 g, 2.58 mmol), activated molecular sieves (4 Å, 0.9 g) and EtSH (0.69 mL, 9.05 mmol) in $\mathrm{CH_2Cl_2}$ (18 mL) was stirred for 30 min. $\mathrm{BF_3{\cdot}Et_2O}$ (0.98 mL, 7.74 mmol) was added, and stirring was continued for 5 h at room temperature, when TLC (hexane/acetone, 2:1) showed that the reaction was complete. The mixture was partitioned between $\mathrm{CH_2Cl_2}$ and aq $\mathrm{NaHCO_3}$, the organic phase was dried and concentrated. $\mathrm{Ag_2O}$ (3.59 g, 15.48 mmol) and a solution of $\mathrm{AgNO_3}$ (1.31 g, 7.74 mmol) in $\mathrm{H_2O}$ (4 mL) was slowly added to a solution of the residue in $\mathrm{CH_3CN}$ (16 mL), and the mixture was stirred for 3 h, when TLC (hexane/acetone, 2:1) showed that the reaction was complete. Solid $\mathrm{NaHCO_3}$ (650 mg, 7.74 mmol) was added, the mixture was filtered through a celite pad, the filtrate was concentrated, and chromatography of the residue (hexane/acetone, 10 → 30%) gave **11** (1.10 g, 74%) and **14** (158 mg, 11%).

Procedure C: A mixture of **8** (430 mg, 0.74 mmol), EtSH (0.19 mL, 2.59 mmol) and activated molecular sieves (4 Å, 250 mg) in $\mathrm{CH_2Cl_2}$ (5 mL) was stirred at room temperature for 30 min. $\mathrm{BF_3{\cdot}Et_2O}$ (0.38 mL, 2.23 mmol) was added, and stirring was continued for 5 h when the reaction was complete, as shown by TLC (hexane/acetone, 2:1). The mixture was worked up as described above, and a solution of the crude product in CH_3CN (4 mL) was treated with Ag_2O (1.03 g, 4.46 mmol) and a solution of $AgNO_3$ (379 mg, 2.23 mmol) in H_2O (1 mL). After 3 h, when TLC (hexane/acetone, 2:1) showed that the reaction was complete, solid $NaHCO_3$ (187 mg, 2.23 mmol) was added, and the mixture was worked up as described in Procedure B. Chromatography then gave the α- (**11**, 208 mg, 48%) and the β-thioglycoside **14** (142 mg, 33%).

Procedure D: A solution of methyl glycoside **4** (410 mg, 0.74 mmol) in a mixture of 50:20:0.25 $Ac_2O/AcOH/H_2SO_4$ (8 mL) was stirred for 1 h at room temperature, when TLC (hexane/acetone, 2:1) showed that the reaction was complete. After processing, as described above for the preparation of **5** and **7**, the residue was dissolved in CH_2Cl_2 (5 mL), and activated molecular sieves (250 mg) were added followed by EtSH (0.19 mL, 2.59 mmol). Stirring was continued for 30 min, $BF_3{\cdot}Et_2O$ (0.38 mL, 2.33 mmol) was added, and the mixture was stirred at room temperature. When TLC (hexane/acetone, 2:1) showed that the reaction was complete (≈ 5 h), the mixture was worked up as in Procedure B, and a solution of the residue in CH_3CN (4 mL) was treated with Ag_2O (1.08 g, 4.66 mmol) and a solution of $AgNO_3$ (396 mg, 2.33 mmol) in H_2O (1 mL). After stirring for 3 h, when TLC (hexane/acetone, 2:1) showed the reaction to be complete, solid $NaHCO_3$ (196 mg, 2.33 mmol) was added, the mixture was filtered through a celite pad, and the filtrate was concentrated. Chromatography of the residue afforded **11** (288 mg, 67%) and **14** (50 mg, 12%).

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