Sulfonium salt activation in oligosaccharide synthesis

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Chapter 2

A Novel Route Towards the Stereoselective Synthesis of 2-Azido-2-Deoxy-β-D-Mannosides

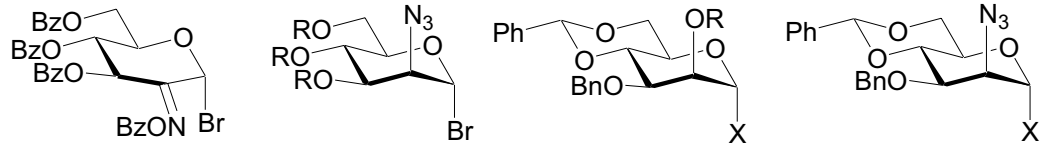
R. E. J. N. Litjens, M. A. Leeuwenburgh, G. A. van der Marel, J. H. van Boom, Tetrahedron Lett. **2001**, *42,* 8693.

Abstract: Low temperature mannosylation of glycosyl acceptors under the agency of *S*-(4-methoxyphenyl) benzenethiosulfinate (MPBT) and trifluoromethanesulfonic anhydride (Tf_2O) with *p*-methoxyphenyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside, readily available from D-mannosamine hydrochloride, affords 2-azido-2-deoxy-D-mannosides with high β-selectivity in good yields.

Introduction

The structure and the immunological properties of a multitude of polysaccharides of bacterial origin have been established. These findings, together with progress in the construction of these polymers have been implemented in the development of synthetic vaccines.[1-3] The structure of a number of bacterial polysaccharides and lipopolysaccharides is characterized by the presence of β-linked mannosamine residues. The stereoselective introduction of β-mannosamine linkages is severely hampered by stereo-electronic effects and over the years several approaches to tackle this problem have been reported. Of the methods thus far explored for the introduction of the β-mannosamine motif, the use of the 2-(benzoyloxyimino)-2-deoxy-α-D-*arabino*-hexapyranosyl bromide **1** (See Figure 1) as a glycosyl donor[4,5] proved to be superior, in terms of easy accessibility and β-selectivity, to the originally proposed 2-azido-2-deoxy-α-D-mannopyranosyl bromides **2a,b**.[6]On the other hand, the methodology involving the *a posteriori* introduction of the azido function *via* S_N2-substitution at C-2 in β-linked glucosides[7] was very rewarding in the elaboration of the β-ManNAc element in the repeating unit of *Streptococcus pneumoniae* 19F capsular polysaccharide.[8,9]

Figure 1



1

2a: R = Bn
b: R = Ac

3a: X = SEt, R = TBS
b: X = SPh, R = Bn

4a: X = SPh
b: X = SEt
c: X = SMP

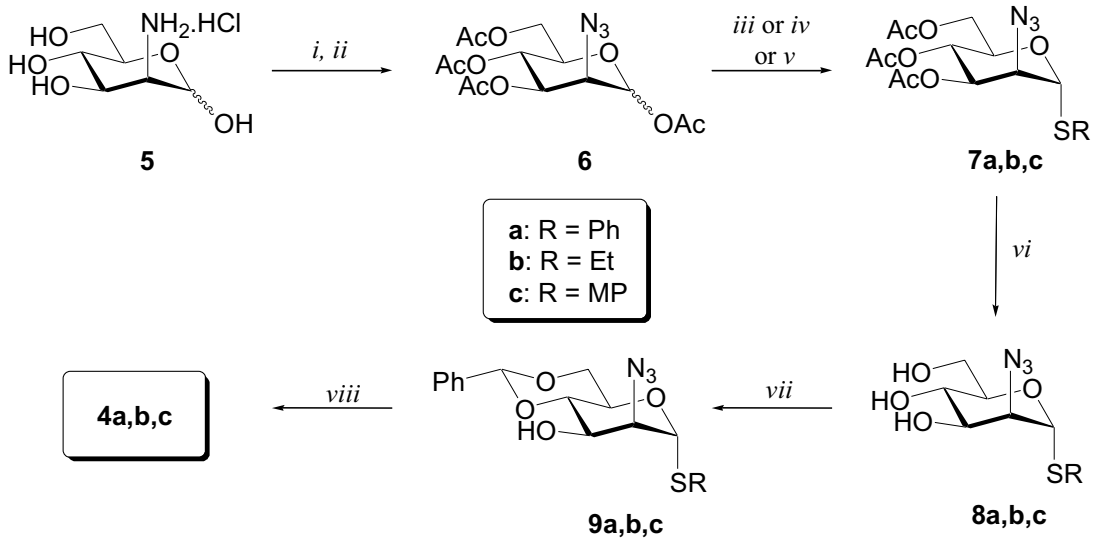
Recently, Crich and Sun[10] attained a high β:α ratio and good yield of D-mannosides by activation of 2,3-di-*O*-alkyl-4,6-*O*-benzylidene-1-thio-α-D-mannosides **3a,b** at low temperature with *in situ* generated phenylsulfenyl triflate (PhSOTf) and subsequent addition of glycosyl acceptors. The mannosidation protocol could be improved substantially[11] from a practical point of view by using the combination of crystalline and stable *S*-(4-methoxyphenyl) benzenethiosulfinate (MPBT) and trifluoromethanesulfonic anhydride (Tf_2O), instead of PhSOTf, in the

transformation of donors **3a,b** into the α-mannosyl triflates, which are proposed[10,11,12] to play a decisive role[13] in β-product formation. In this chapter, the efforts in the condensation of the similarly protected ethyl(phenyl) 2-azido-2-deoxy-1-thio-mannosides **4a,b,c** with glycosyl acceptors by the latter glycosidation protocol are described as a novel approach towards 2-azido-2-deoxy-β-D-mannosides.

Results and discussion

The synthesis of the requisite thiomannosides **4a**,**b** *via* a six-step sequence from commercially available D-mannosamine hydrochloride **5** is presented in Scheme 1.

Scheme 1



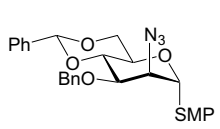
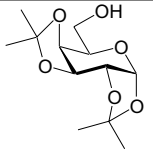
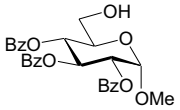
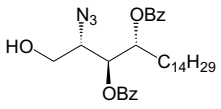
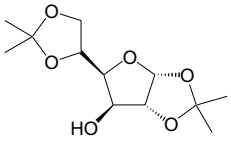
Reagents and conditions: *i*. TfN_3, K_2CO_3, $CuSO_4$ (cat.), H_2O, MeOH, CH_2Cl_2; *ii*. Ac_2O, DMAP (cat.), pyridine, **6**: 88% (2 steps); *iii*. PhSH, $BF_3.OEt_2$, CH_2Cl_2, 35 °C, **7a**: 55%; *iv*. EtSH, $BF_3.OEt_2$, CH_2Cl_2, 35 °C, **7b**: 70%; *v*. MPSH, $BF_3.OEt_2$, CH_2Cl_2, 35 °C, **7c**: 59%; *vi*. KO*t*Bu, MeOH, **8a,b,c**: quant.; *vii*. $PhCH(OMe)_2$, $HBF_4.OMe_2$, DMF, **9a**: 88%, **9b**: 91%, **9c**: 88%; *viii* BnBr, NaH, DMF, **4a**: 96%, **4b**: 90%, **4c**: 97%. MP = *p*-OMePh.

Subjection of **5** to diazo transfer reaction[14] and subsequent acetylation led to fully acetylated derivative **6** as a mixture of anomers. Treatment of **6** with for example ethanethiol in the presence of $BF_3.OEt_2$ followed by deacetylation gave ethyl 1-thio-α-D-mannopyranoside **8b**. Acetalisation of **8b** with benzaldehyde dimethylacetal under the agency of $HBF_4.OMe_2$ followed by benzylation afforded ethylthio donor **4b** in an overall yield of 50% based on **5**.

In the first instance, phenylthio donor **4a** in dry CH_2Cl_2 was activated for 5 min at -60 °C with MPBT/Tf_2O in the presence of 2,6-di-*tert*-butylpyridine (DTBMP). Addition of diacetone-D-galactose **10** and analysis of the mixture, after additional stirring for 10 min at –60°C, revealed the presence of starting materials and no trace of the expected coupling products. Moreover, executing the activation step at higher temperature (-60°C→-20°C) or prolonged reaction times were also not successful. In addition, glycosidation at temperatures above -20°C led to intractable mixtures of products. Similar results were also obtained in subjecting the ethylthiodonor **4b** to the same glycosidation conditions.

The failure of activating donors **4a,b** at low temperature can be explained[15] by taking into consideration that the nucleophilicity of the sulfur atom at the anomeric center will be decreased due to the electron withdrawing effect of the 2-azido group.[16] Consequently, replacement of the anomeric functions in **4a,b** by the more electron donating *p*-methoxyphenylthio group could have a beneficial effect on the activation step.

Table 1: MPBT promoted glycosidation of thiomannoside **4c**.

Entry	Donor	Acceptor	Product	Yield (%)[a,b]	α:β ratio
1	 **4c**	 **10**	**14**	83	1:2.1
2[c]	**4c**	 **11**	**15**	87	1:4
3	**4c**	 **12**	**16**	59	β
4	**4c**	 **13**	**17**	61	β

[a]Total yield and α:β ratio were assigned after separation of the anomers.[b]Yield based on **4c**.[c]α:β ratio determined by ^{1}H-NMR spectroscopy.

Indeed, it turned out that activation of donor **4c**, prepared in a similar fashion as **4a,b** (Scheme 1), for 15 min at -35°C followed by the addition at -60°C of diacetone-D-galactose **10**, led to the expected disaccharide **14** (entry 1 in Table 1) as a mixture of anomers in good yield within 10 min. The stereochemistry of the

mannosidic bond in the resulting individual anomers was firmly ascertained[17] on the basis of the C1-H1 heteronuclear one-bond coupling constants ($^1J_{C1,H1}$). An increase of β-selectivity was observed (entry 2) in the glycosylation of methyl 2,3,4-*O*-benzoyl-glucopyranoside **11** with **4c**. On the other hand, condensation of **4c** (entry 3) with the relatively less reactive primary alcohol function in phytosphingosine derivative **12** led to the exclusive formation, although in moderate yield, of the 2-azido-2-deoxy-β-mannoside **16**. A similar result was observed (entry 4) in the glycosidation of **4c** with the secondary hydroxyl group in acceptor **13**. At this stage, it is also of interest to note that the stereochemistry and yield of the mannosidations summarized in Table 1 do not deviate substantially from those observed earlier by Crich and Smith using the corresponding α-D-thiomannosides **3b** as donor. However, the β-selectivity of the condensation of **4c** with acceptor **11** (entry 2) is less pronounced in comparison with the nearly exclusive formation of the β-mannoside resulting from the coupling of the corresponding partially acetylated glucose acceptor with phenyl α-D-thiomannoside **3b**.

Conclusion

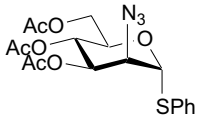
In conclusion, the results described in this chapter indicate that the readily accessible and orthogonally protected *p*-methoxyphenyl 2-azido-2-deoxy-α-D-mannoside **4c** shows promise in the construction of β-ManNHAc disaccharides.

Experimental Section

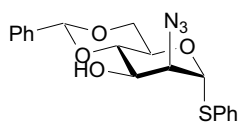
General methods: Dichloromethane was refluxed with P_2O_5 and distilled before use. MPBT was synthesized as described by Crich *et al.*[11] Trifluoromethanesulfonic anhydride was stirred for 3 hours on P_2O_5 and subsequently distilled. All chemicals (Fluka, Acros, Merck, Aldrich, Sigma) were used as received. Reactions were performed under an inert atmosphere under strictly anhydrous conditions. Traces of water from reagents used in reactions that require anhydrous conditions were removed by coevaporation with toluene or dichloroethane. Molecular sieves (3Å) were flame dried before use. Column chromatography was performed on Merck silica gel 60 (0.040-0.063 mm). TLC analysis was conducted on DC-fertigfolien (Schleicher & Schuell, F1500, LS254) or HPTLC aluminum sheets (Merck, silica gel 60, F254). Compounds were visualized by UV absorption (254 nm), by spraying with 20% H_2SO_4 in ethanol or with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ 25g/L, followed by charring at ± 140ºC. ^1H and ^{13}C NMR spectra were recorded with a Jeol JNM-FX-200 (200 and 50 MHz), a Bruker DPX 300 (300 and 75 MHz) or a Bruker AV 400 (400 and 100 MHz). NMR spectra were recorded in

$CDCl_3$ with chemical shifts (δ) relative to tetramethylsilane unless stated otherwise. Mass spectra were recorded on a PE/SCIEX API 165 equipped with an Electrospray Interface (Perkin-Elmer).

General procedure for glycosylations with MPBT: To a stirred mixture of *p*-methoxyphenyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside **4c** (101 mg, 0.2 mmol), MPBT (66 mg, 0.25 mmol), DTBMP (102 mg, 0.5 mmol) and 3Å Ms in DCM (2.5 mL) at -35ºC was added Tf_2O (70 μL, 0.4 mmol). After 15 min, the reaction mixture was cooled to -60ºC and subsequently a solution of the acceptor (0.4 mmol) in DCM (1 mL) was added dropwise. The mixture was stirred for 10 min at -60ºC followed by additon of MeOH, warmed to room temperature, filtered, washed with sat. aq. $NaHCO_3$ followed by brine and the organics were dried (Na_2SO_4) and concentrated under reduced pressure. The glycosides were isolated by column chromatography. Yields are based on **4c**.

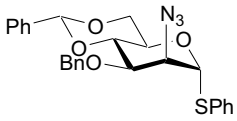


Phenyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-thio-α-D-mannopyranoside (7a): To a solution of per-acetate manazide **6** (1.8 g, 5.0 mmol) in DCE (25 mL) were added PhSH (565 μL, 5.5 mmol) and $BF_3.OEt_2$ (1.27 mL, 10.0 mmol). The mixture was warmed to 35ºC and stirred for 5h after which TLC analysis (ethyl acetate/toluene 1/3 v/v) showed complete conversion of the starting material. Ethyl acetate was added and the mixture was washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (ethyl acetate/light petroleum 1/20 →1/4 v/v) to give thioglycoside **7a** (1.17 g, 2.76 mmol, 55%) as a colorless oil. ^{1}H-NMR: δ (ppm) 7.45 (m, 2H, H arom.), 7.30 (m, 3H, H arom.), 5.53 (d, 1H, H-1, J = 0.8 Hz), 5.48 (m, 2H, 2x H-6), 4.47 (m, 1H, H-5), 4.28 (d, 1H, H-2, J = 3.2 Hz), 4.25 (t, 1H, H-4, J = 5.1 Hz), 4.06 (dd, 1H, H-3, J = 11.7, 2.2 Hz), 2.11 (s, 3H, -O(CO)CH_3), 2.07 (s, 3H, -O(CO)CH_3), 2.04 (s, 3H, -O(CO)CH_3). ^{13}C-NMR: δ (ppm) 170.2, 169.6, 169.3, 132.2, 131.7, 129.0, 127.9, 85.4, 70.8, 69.3, 65.8, 62.4, 61.9, 20.4, 20.2. ESI-MS (M+Na): 446.2.

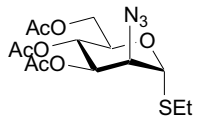


Phenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside (9a): To a solution of triacetate **7a** (1.17 g, 2.76 mmol) in MeOH (15 mL) was added KO*t*Bu (65 mg). After 30 min, TLC analysis (ethyl acetate) showed full consumption of the starting compound and the mixture was neutralized with DOWEX-H^+ to pH ~ 7, filtered and concentrated *in vacuo*. The resulting product was dissolved in DMF (15 mL) and benzaldehyde dimethylacetal (460 μL, 3.0 mmol) and $HBF_4.OMe_2$ (360 μL, 3.0 mmol) were added. After 16h, the reaction was quenched with Et_3N (500 μL) and the mixture was concentrated. The resulting product was purified by column chromatography (ethyl acetate/light

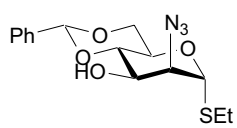
petroleum 1/20 → 1/5 v/v) to yield title compound **9a** (932 mg, 2.42 mmol, 88%) as a white foam. ^{1}H-NMR: δ (ppm) 7.33 (m, 10H, H arom.), 5.59 (s, 1H, C*H*-benzylidene), 5.48 (s, 1H, H-1), 4.35 (m, 4H, H-2, 2x H-6, H-5), 4.00 (dd, 1H, H-3, *J* = 11.6, 2.3 Hz), 3.82 (t, 1H, H-4, *J* = 10.2 Hz). ^{13}C-NMR: δ (ppm) 136.9, 133.0, 131.7, 129.2, 128.5, 126.5, 102.3, 86.8, 79.04, 68.8, 68.1, 65.0, 64.5. ESI-MS (M+Na): 408.1.



Phenyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside (4a): To a solution of alcohol **9a** (763 mg, 1.98 mmol) in DMF was added BnBr (280 μL, 2.38 mmol) and the mixture was chilled to 0ºC. NaH (94 mg, 2.38 mmol) was added. After 1h, TLC analysis (ethyl acetate/light petroleum 1/4 v/v) showed full conversion of the starting material. MeOH (200 μL) was added and the mixture was concentrated *in vacuo*. The residue was purified over a silica gel column (ethyl acetate/light petroleum 1/40 → 1/10 v/v) to give the desired product (908 mg, 1.92 mmol, 96%) as a white solid. mp = 96ºC. ^{1}H-NMR: δ (ppm) 7.46 (m, 15H, H arom.), 5.66 (s, 1H, C*H*-benzylidene), 5.46 (s, 1H, H-1), 4.96 (d, 1H, -C*H*Ph, *J* = 12.0 Hz), 4.78 (d, 1H, -C*H*Ph, *J* = 12.0 Hz), 4.46 (m, 1H, H-5), 4.21 (m, 4H, H-2, H-3, 2x H-6), 3.87 (t, 1H, H-4, *J* = 9.9 Hz). ^{13}C-NMR: δ (ppm) 137.9, 137.5, 132.9, 131.8, 129.3, 129.0, 128.5, 128.2, 128.0, 127.9, 127.6, 126.2, 101.6, 87.0, 79.1, 75.9, 73.3, 68.2, 65.1, 64.0. ESI-MS (M+Na): 498.4.

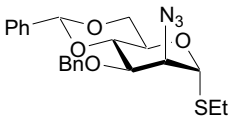


Ethyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-thio-α-D-mannopyranoside (7b): To a solution of per-acetate manazide **6** (2.0 g, 5.4 mmol) in DCE (25 mL) were added EtSH (500 μL, 6.5 mmol) and $BF_3.OEt_2$ (1.4 mL, 10.8 mmol). The mixture was heated to 35ºC and stirred for 3.5 h after which TLC analysis (ethyl acetate/light petroleum 1/1 v/v) showed full consumption of the starting material. Ethyl acetate was added and the mixture was washed with sat. aq. $NaHCO_3$. The organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification over a silicagel column (ethyl acetate/light petroleum 1/7 →1/4 v/v) gave the title compound (1.42 g, 3.8 mmol, 70%) as a colorless oil. ^{13}C-NMR: δ (ppm) 170.3, 169.6, 169.3, 82.1, 71.1, 68.6, 65.9, 62.5, 61.9, 25.2, 20.4, 20.2, 14.5. ESI-MS (M+Na): 398.2.

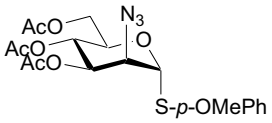


Ethyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside (9b): To a solution of triacetate **7b** (1.18 g, 3.8 mmol) in MeOH (15 mL) was added KO*t*Bu (70 mg, 0.6 mmol). After 40 min, TLC analysis (ethyl acetate/light petroleum 1/1 v/v) showed full conversion of the starting compound. The mixture was neutralized with DOWEX-H^+ to pH ~ 7, filtered and concentrated. The resulting oil was dissolved in DMF (15 mL) and benzaldehyde dimethylacetal (630 μL, 4.18 mmol) and $HBF_4.OMe_2$ (485 μL, 3.99

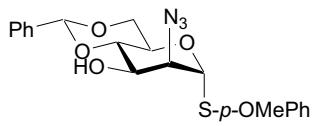
mmol) were added. After overnight reaction, Et_3N was added, the reaction mixture concentrated *in vacuo* and the resulting oil applied on a silicagel column (ethyl acetate/light petroleum 1/20 → 1/4 v/v) to give the title compound (1.12 g, 3.3 mmol, 87%) as a colorless oil. ^{1}H-NMR: δ (ppm) 7.41 (m, 2H, H arom.), 7.37 (m, 3H, H arom.), 5.58 (s, 1H, C*H*-benzylidene), 5.29 (s, 1H, H-1), 4.20 (m, 3H, H-3, H-4, H-6), 4.05 (d, 1H, H-2, *J* = 3.7 Hz), 3.87 (m, 2H, H-6, H-5), 2.61 (m, 2H, S-CH_2-), 1.28 (t, 3H, CH_3, *J* = 7.3 Hz). ^{13}C-NMR: δ (ppm) 136.9, 129.2, 128.3, 126.3, 102.2, 83.2, 79.1, 68.8, 68.2, 65.1, 63.8, 25.3, 14.7. ESI-MS (M+Na): 360.1.



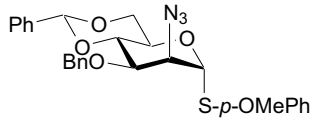
Ethyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside (4b): Alcohol **9b** (1.12 g, 3.3 mmol) was dissolved in DMF and BnBr (470 μL, 3.6 mmol) was added. The mixture was chilled to 0ºC and NaH (160 mg, 3.96 mmol) was added portionwise. After overnight reaction, MeOH (200 μL) was added and the solution was concentrated under reduced pressure. Purification of the resulting oil by silica gel chromatography (light petroleum → ethyl acetate/light petroleum 1/10 v/v) afforded the desired compound (1.28 g, 2.98 mmol, 90%) as a colorless oil. ^{1}H-NMR: δ (ppm) 7.36 (m, 10H, H arom.), 5.63 (s, 1H, C*H*-benzylidene), 5.25 (s, 1H, H-1), 4.90 (d, 1H, -C*H*Ph, *J* = 11.7 Hz), 4.71 (d, 1H, -C*H*Ph, *J* = 11.7 Hz), 4.20 (m, 4H, H-3, H-4, 2x H-6), 4.03 (d, 1H, H-2, *J* = 3.3 Hz), 3.86 (m, 1H, H-5), 2.62 (m, 2H, S-CH_2-), 1.29 (t, 3H, 7.3 Hz). ^{13}C-NMR: δ (ppm) 137.8, 137.7, 128.1, 127.7, 127.5, 126.0, 101.5, 83.4, 79.2, 75.9, 73.3, 68.4, 64.3, 64.1, 25.3, 14.8. ESI-MS (M+Na): 450.2.



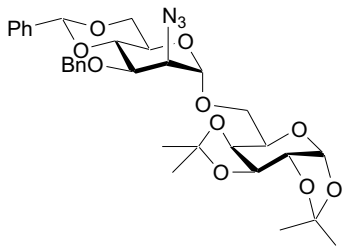
***p*-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-1-thio-α-D-mannopyranoside (7c):** To a solution of per-acetate manazide **6** (13.72 g, 10.0 mmol) in DCE (50 mL) were added MPSH (1.48 mL, 12.0 mmol) and BF_3.OEt_2 (2.5 mL, 20.0 mmol). The mixture was warmed to 35ºC and stirred for 10h after which TLC analysis (ethyl acetate/toluene 1/3 v/v) showed complete conversion of the starting material. Ethyl acetate was added and the mixture was washed with sat. aq. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered and the volatiles were removed under reduced pressure. The residue was purified by column chromatography (ethyl acetate/light petroleum 1/20 →1/4 v/v) gave thioglycoside **7c** (2.66 g, 5.87 mmol, 59%) as a slightly yellow solid. ^{1}H-NMR: δ (ppm) 7.39 (d, 2H, *J* = 8.8 Hz, H arom.), 6.84 (d, 2H, *J* = 8.8 Hz, H arom.), 5.35 (s, 1H, H-1), 5.32 (m, 2H, 2x H-6), 4.51 (m, 1H, H-5), 4.24 (m, 2H, H-2, H-4), 4.05 (dd, 1H, H-4, *J* = 12.4, 2.2 Hz), 3.78 (s, 3H, OMe), 2.09 (s, 3H, -O(CO)CH_3), 2.07 (s, 3H, -O(CO)CH_3), 2.05 (s, 3H, -O(CO)CH_3). ^{13}C-NMR: δ (ppm):170.1, 169.5, 169.2, 160.0, 134.8, 122.1, 114.6, 86.2, 70.8, 69.2, 65.9, 62.1, 54.9, 20.3, 20.1. ESI-MS (M+Na): 476.3.



***p*-Methoxyphenyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside (9c):** To a solution of triacetate **7c** (2.66 g, 5.87 mmol) in MeOH (25 mL) was added KO*t*Bu (140 mg). After 40 min, TLC analysis (ethyl acetate) showed full consumption of the starting compound and the mixture was neutralized with DOWEX-H^+ to pH ~ 7, filtered and concentrated *in vacuo*. The resulting product was dissolved in DMF (25 mL) and benzaldehyde dimethylacetal (1.0 mL, 7.0 mmol) and $HBF_4.OMe_2$ (700 μL, 7.0 mmol) were added. After 16h, the reaction was quenched with Et_3N (500 μL) and the mixture was concentrated. The resulting product was purified by column chromatography (ethyl acetate/light petroleum 1/20 → 1/5 v/v) to give title compound **9c** (2.00 g, 4.84 mmol, 88%) as a white foam. ^{1}H-NMR: δ (ppm) 7.51 (m, 2H, H arom.), 7.39 (m, 5H, H arom.), 6.86 (d, 2H, *J* = 8.8 Hz, H arom.), 5.56 (s, 1H, C*H*-benzylidene), 5.29 (s, 1H, H-1), 4.37 (m, 1H, H-5), 4.16 (m, 3H, H-2, 2x H-6), 3.92 (t, 1H, H-4, *J* = 9.5 Hz), 3.79 (s, 3H, OMe), 3.78 (t, 1H, H-3, *J* = 11.7), 2.94 (s, 1H, OH). ^{13}C-NMR: δ (ppm) 160.0, 137.1, 135.0, 129.4, 128.5, 126.5, 122.9, 114.8, 102.2, 87.6, 79.1, 68.8, 68.1, 65.0, 64.4, 55.2. ESI-MS (M+Na): 438.0.

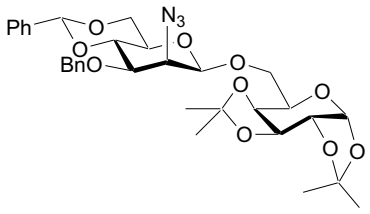


***p*-Methoxyphenyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-1-thio-α-D-mannopyranoside (4c):** Alcohol **9c** (2.01 g, 4.84 mmol) was dissolved in DMF (25 mL) and the solution was chilled to 0ºC. NaH (230 mg, 5.81 mmol) and BnBr (630 μL, 5.32 mmol) were added. After overnight reaction, TLC analysis (ethyl acetate/light petroleum 1/3 v/v) showed complete transformation of the alcohol, MeOH (500 μL) was added and the volatiles were removed under reduced pressure. Column chromatography (ethyl acetate/light petroleum 1/40 → 1/5 v/v) of the residue afforded thioglycoside **4c** (2.37 g, 4.69 mmol, 97%) as a pale yellow solid. mp = 107ºC. ^{1}H-NMR: δ (ppm) 7.50 (m, 2H), 7.34 (m, 10H, H arom.), 6.85 (d, 2H, 8.8 Hz, H arom.), 5.63 (s, 1H, C*H*-benzylidene), 5.26 (s, 1H, H-1), 4.92 (d, 1H, -C*H*Ph, *J* = 12.4 Hz), 4.74 (d, 1H, -C*H*Ph, *J* = 12.4 Hz), 4.36 (m, 1H, H-5), 4.19 (m, 4H, H-2, 2x H-6, H-3), 3.83 (t, 1H, 10.2 Hz), 3.76 (s, 3H, OMe). ^{13}C-NMR: δ (ppm) 160.1, 137.9, 137.5, 135.1, 129.0, 128.5, 128.2, 127.8, 127.6, 126.1, 122.7, 101.6, 87.8, 79.2, 75.8, 73.3, 68.3, 65.0, 63.8, 55.2. ESI-MS (M+Na): 528.2.

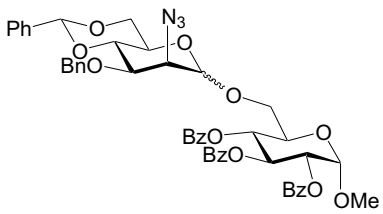


6-*O*-(2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyr-anosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (14α): Yield: 28%. R_f 0.52 (ethyl acetate/toluene 1/5 v/v). ^{1}H-NMR: δ (ppm) 7.47 (m, 2H, H arom.), 7.37 (m, 8H, H

arom.), 5.62 (s, 1H, C*H*-benzylidene), 5.53 (d, 1H, H-1, *J* = 5.0 Hz), 4.90 (d, 1H, -C*H*Ph, *J* = 12.1 Hz), 4.83 (d, 1H, H-1', *J* = 1.3 Hz), 4.72 (d, 1H, -C*H*Ph, *J* = 12.1 Hz), 4.66 (dd, 1H, H-3, *J* = 8.2, 2.8 Hz), 4.33 (dd, 1H, H-2, *J* = 5.0, 2.4 Hz), 4.16 (dd, 1H, H-6', *J* = 7.6, 1.9 Hz), 4.12 (dd, 1H, H-4, *J* = 8.0, 0.9 Hz), 4.10 (m, 3H, H-6', H-3', H-4'), 4.04 (dd, 1H, H-2', *J* = 2.8, 1.3 Hz), 3.96 (dt, 1H, H-5, *J* = 10.2, 0.9 Hz), 3.83 (m, 2H, H-5', H-6), 3.69 (dd, 1H, H-6, *J* = 10.2, 7.6 Hz), 1.54 (s, 3H, isopropylidene), 1.44 (s, 3H, isopropylidene), 1.32 (s, 3H, isopropylidene), 1.25 (s, 3H, isopropylidene). ^{13}C-NMR: δ (ppm) 137.3, 137.1, 135.3, 128.8, 128.2, 128.0, 127.5, 127.3, 126.3, 109.5, 108.6, 101.4, 98.8 ($^{1}J_{CH}$ = 169.4 Hz), 96.2, 78.3, 75.7, 73.0, 71.3, 70.5, 70.4, 69.8, 68.2, 67.9, 67.2, 63.0, 26.0, 25.8, 24.7. ESI-MS (M+H): 626.2.

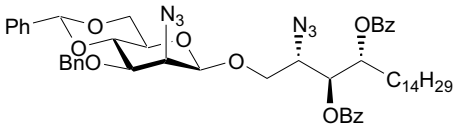


6-*O*-(2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-β-D-man-nopyranosyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (14β): Yield: 55%. R_f 0.48 (ethyl acetate/toluene 1/3 v/v). ^{1}H-NMR: δ (ppm) 7.47 (m, 2H, H arom.), 7.38 (m, 8H, H arom.), 5.58 (s, 1H, C*H*-benzylidene), 5.52 (d, 1H, H-1, *J* = 4.9 Hz), 4.84 (d, 1H, -C*H*Ph, *J* = 11.3 Hz), 4.77 (d, 1H, -C*H*Ph, *J* = 11.3 Hz), 4.69 (d, 1H, H-1', *J* = 0.9 Hz), 4.61 (dd, 1H, H-3, *J* = 8.0, 2.7 Hz), 4.36 (m, 2H, H-6', H-2), 4.18 (d, 1H, H-4, *J* = 2.1 Hz), 4.12 (m, 2H, H-2', H-6), 4.02 (m, 2H, H-4', H-5), 3.88 (t, 1H, H-6', *J* = 10.4 Hz), 3.67 (m, 2H, H-3', H-6), 3.34 (m, 1H, H-5), 1.54 (s, 3H, isopropylidene), 1.44 (s, 3H, isopropylidene), 1.34 (s, 3H, isopropylidene), 1.31 (s, 3H, isopropylidene). ^{13}C-NMR: δ (ppm) 137.4, 137.1, 135.4, 129.0, 128.3, 128.2, 127.5, 127.6, 126.3, 109.6, 108.8, 101.4, 101.0 ($^{1}J_{CH}$ = 160.2 Hz), 96.1, 78.3, 75.6, 72.5, 71.2, 70.5, 70.2, 69.9, 68.3, 68.0, 67.1, 63.0, 25.8, 24.8. ESI-MS (M+Na): 648.3.

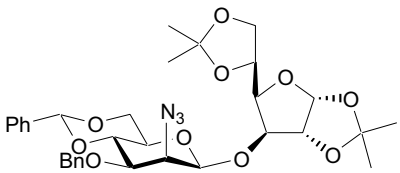


Methyl 2,3,4-tri-*O*-benzoyl-6-(2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-β-D-mannopyranosyl)-α-D-glucopyranoside and 2,3,4-tri-*O*-benzoyl-6-(2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α-D-mannopyranosyl)-α-D-glucopyranoside (15αβ): Isolated as a mixture of anomers. **15α**: Yield: 18%. R_f 0.37 (ethyl acetate/toluene 1/3 v/v). ^{13}C-NMR: δ (ppm) 165.6, 165.4, 164.9, 137.2, 136.7, 133.4, 133.0, 132.9, 129.6, 129.41, 128.8, 128.5, 128.1, 127.7, 127.7, 101.3, 99.3 ($^{1}J_{CH}$ = 171.2 Hz), 96.9, 78.6, 75.2, 73.1, 70.0, 69.5, 68.3, 67.9, 66.3, 63.8, 62.3, 55.5. ESI-MS (M+H): 872.3. **15β**: Yield: 69%. R_f 0.36 (ethyl acetate/toluene 1/3 v/v). ^{1}H-NMR: δ (ppm) 7.92 (m, 6H, H arom.), 7.29 (m, 19H, H arom.), 6.18 (t, 1H, H-3, *J* = 7.3 Hz), 5.57 (s, 1H, C*H*-benzylidene), 5.50 (t, 1H, H-4, *J* = 10.2 Hz), 5.27 (m, 2H, H-2, H-1), 4.89 (d, 1H, -C*H*Ph, *J* = 12.4 Hz), 4.75 (d, 1H, -C*H*Ph, *J* = 12.4 Hz), 4.60 (s, 1H, H-1), 4.10 (m, 5H, H-2', H-4', H-3', H-6, H-6'), 3.92 (m, 3H, H-5, H-6, H-6'), 3.48 (s, 3H, OMe). ^{13}C-NMR: δ (ppm) 165.5, 165.4, 137.1, 136.8, 133.5, 133.2, 133.0, 129.8, 129.5, 128.8, 128.5, 128.14,

127.7, 127.6, 101.4, 100.7 ($^1J_{CH}$ = 159.5 Hz), 96.6, 78.2, 75.9, 72.8, 71.9, 70.1, 69.2, 68.6, 68.1, 67.1, 65.7, 63.2, 55.4. ESI-MS (M+H): 872.4.



1-*O*-(2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-β-D-mannopyranosyl)-2(*S*)-azido-3(*S*),4(*R*)-di-*O*-benzoyl-phytosphingosine (16): Yield: 59%. R_f 0.67 (ethyl acetate/toluene 1/3 v/v). ^{1}H-NMR: δ (ppm) 8.06 (m, 4H, H arom.), 7.28 (m, 16H, H arom.), 5.62 (m, 2H, H-3, H-4), 5.55 (s, 1H, C*H*Ph), 4.83 (d, 1H, -C*H*Ph, *J* = 12.4 Hz), 4.70 (d, 1H, -C*H*Ph, *J* = 12.4 Hz), 4.56 (s, 1H, H-1'), 4.24 (d, 1H, *J* = 2.2 Hz, H-2'), 4.16 (m, 4H, 2x H-1, H-3', H-2), 3.93 (m, 3H, 2x H-6, H-4), 3.28 (m, 1H, H-5'), 1.87 (t, 2H, 2x H-5, *J* = 6.6 Hz), 1.23 (m, 22H, -CH_2-), 0.87 (t, 3H, -CH_3, *J* = 5.8 Hz). ^{13}C-NMR: δ (ppm) 165.7, 165.0, 138.2, 133.4, 133.2, 129.2, 129.0, 128.9, 128.7, 127.6, 101.4, 99.7 ($^1J_{CH}$ = 158.0 Hz), 78.2, 76.1, 72.1, 72.6, 68.9, 68.1, 67.2, 62.0, 60.9, 60.2, 55.3, 31.8, 29.5, 25.2, 22.5, 14.0. ESI-MS (M+Na): 939.6.



3-*O*-(2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-β-D-mannopyranosyl)-1,2:5,6-di-*O*-isopropylidene-α-D-gluco-furanose (17): Yield: 61%. R_f 0.47 (ethyl acetate/toluene 1/3 v/v). ^{1}H-NMR: δ (ppm) 7.50-7.33 (m, 10H, H arom.), 5.94 (d, 1H, *J* = 3.8 Hz, H-1), 5.59 (s, 1H, -C*H*Ph), 4.91 (d, 1H, -C*H*Ph, *J* = 10.2 Hz), 4.73 (d, 1H, -C*H*Ph, *J* = 10.2 Hz), 4.68 (d, 1H, H-1', *J* = 1.0 Hz), 4.50 (d, 1H, H-2, *J* = 3.8 Hz), 4,37 (m, 1H, H-5), 4.33 (m, 2H, H-4, H-3), 4.27 (dd, 1H, H-6', *J* = 10.2, 4.5 Hz), 4.18 (t, 1H, H-6, *J* = 6.4 Hz), 4.07 (m, 2H, H-4', H-6), 3,90 (d, 1H, H-2', *J* = 3.5 Hz), 3.86 (t, 1H, H-6', *J* = 10.2 Hz), 3.77 (dd, 1H, H-3', *J* = 9.5, 3.8 Hz), 3.33 (m, 1H, H-5'), 1.50 (s, 3H, -CH_3), 1.45 (s, 3H, -CH_3), 1.38 (s, 3H, -CH_3), 1.32 (s, 3H, -CH_3). ^{13}C-NMR: δ (ppm) 137.7, 137.1, 129.0, 128.5, 128.3, 127.9, 127.7, 126.0, 112.0, 108.6, 105.0, 101.5, 98.1 ($^1J_{CH}$ = 159.8 Hz), 82.6, 80.4, 80.3, 78.4, 76.4, 73.1, 73.0, 68.3, 67.5, 66.0, 63.5, 26.7, 26.5, 26.3, 25.5. ESI-MS (M+Na): 748.2.

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