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A novel strategy towards the synthesis of orthogonally functionalised 4-aminoglycosides

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A tethered nucleophilic substitution strategy for the stereoselective introduction of axially oriented amino functions on suitably protected gluco- and mannopyranosides is presented. The obtained oxazine is a versatile building block, which after some manipulation, could be used in the construction of highly functionalised oligosaccharides.

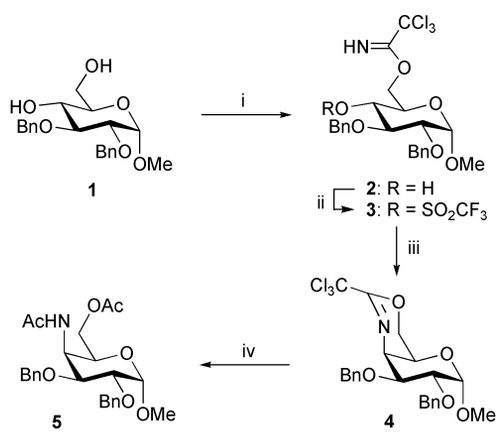
Introduction

The broad variety of naturally occurring carbohydrate structures originates, apart from the large number of possible interglycosidic linkages, from the wide diversity encountered in their monosaccharide constituents. Aminosugars,[1] hexapyranoses bearing diversely functionalised amino groups at different positions, represent an important category of carbohydrate units, found in numerous oligosaccharides and glycoconjugates. For instance, aminosugars are not only important as essential components of bacterial capsular polysaccharides,[2] but also as structural elements of aminoglycoside antibiotics.[3] The biological importance of natural products containing aminosugars demands the development of efficient synthetic routes to these monosaccharides. Our focus in this field is directed towards the stereoselective introduction of C-4 amino functions *cis* relative to the neighbouring C-5 hydroxymethyl group of hexapyranosides.[4]

A convenient route to the regio- and stereoselective introduction of nitrogen substituents entails the use of tethered nitrogen nucleophiles.[5] In this respect, allylic trichloroacetimidates have been employed in an Overman rearrangement to provide the corresponding allylic trichloroacetamides.[6] Alternatively, IBX[7] or NIS-mediated[8] cyclisation of allylic trichloroacetimidates gives the corresponding *trans*-disposed iodo-oxazolines. In line with these studies, we here report a novel, straightforward synthesis of orthogonally protected 4-amino glycosides. A key element of our strategy is the selective introduction of a trichloroacetimidate moiety at OH-6 of partially protected gluco- and mannopyranosides. The hydroxyl at C-4 is transformed into a suitable leaving group amenable to base-induced substitution by the tethered imidate moiety to provide the corresponding oxazine. We further demonstrate that, after hydrolysis and suitable protection, the thus obtained aminoglycosides can be readily applied as building blocks in oligosaccharide synthesis.

Results and discussion

As a first example, the transformation of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **1**[9] into methyl 4-acetamido-6-*O*-acetyl-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranoside **5** was undertaken (Scheme 1). Treatment of **1** with trichloroacetonitrile (Cl_3CCN) in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to the selective formation of 6-*O*-acetimidate **2** in 89% yield. Installation of the 4-*O*-triflate (Tf_2O, pyridine) followed by base-mediated cyclisation of resulting **3** gave oxazine **4** (80% yield, 2 steps), the structural integrity of which was fully established by spectroscopic analysis. Transformation of **1** *via* a three-step one pot procedure afforded oxazine **4** in slightly improved yield (89% over 3 steps). Acidic hydrolysis of **4** and acetylation of the intermediate aminoalcohol gave methyl 4-acetamido-6-*O*-acetyl-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranoside **5**.



Scheme 1 *Reagents and conditions*: i, Cl_3CCN, DBU, DCM, 0 °C, 89%. ii, Tf_2O, pyr, DCM, 0 °C. iii, DiPEA, 80%. iv, 80% AcOH in H_2O, then Ac_2O, pyr, 89%.

Next, diversely functionalised manno- and glucopyranosides were employed in the tethered nucleophilic substitution sequence (Table 1). Subjection of methyl 2,3-di-*O*-benzyl-α-D-mannopyranoside **6**[10] to the three-step one pot procedure afforded oxazine **7**, albeit in a moderate yield (entry 1). Closer inspection of the sequence of reactions revealed that the first two steps, which entailed installation of the 6-*O*-imidate and 4-*O*-triflate functions, proceeded with equal efficiency as observed for the synthesis of its glucopyranose congener **3** (Scheme 1). Arguably, the axial oriented 2-*O*-benzyl group in mannopyranoside **6** may cause 1,3-diaxial strain in the transition state hampering the formation of oxazine **7**. Hydrolysis and acetylation of **7** gave fully protected 4-deoxy-4-aminotaloside **8**.

At this stage, we were interested in finding out whether our approach could be applied to protected thioglycosides, representing useful building blocks in the assembly of oligosaccharides (entries 2–4).[11] To our satisfaction, ethyl 2,3-*O*-isopropylidene-1-thio-α-D-mannopyranoside **9**[12] was readily transformed into oxazine **10** (entry 2). Unmasking of the oxazine ring in **10** proceeded with concomitant partial hydrolysis of the isopropylidene protecting group, leading, after acetylation, to the mixture of 4-deoxy-4-aminotalosides **11** and **12** in

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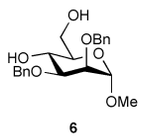
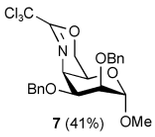
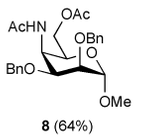
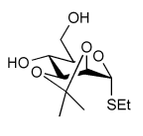
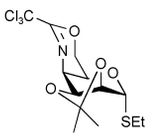
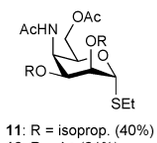
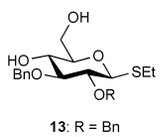
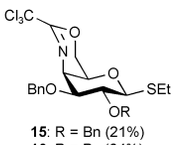
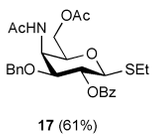
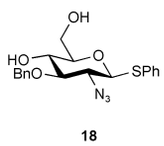
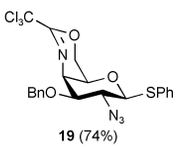
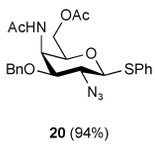
Table 1 Different examples of tethered nucleophilic inversion

Entry	Substrate	Oxazine[a] (yield)[c]	Product[b] (yield)[c]
1	 **6**	 **7** (41%)	 **8** (64%)
2	 **9**	 **10** (54%)	 **11**: R = isoprop. (40%) **12**: R = Ac (21%)
3	 **13**: R = Bn **14**: R = Bz	 **15**: R = Bn (21%) **16**: R = Bz (64%)	 **17** (61%)
4	 **18**	 **19** (74%)	 **20** (94%)

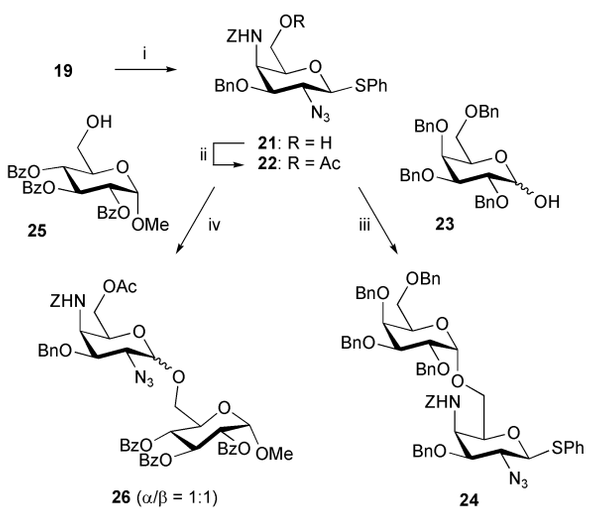
[a] Cl_3CCN, DBU, DCM, 0 °C, then Tf_2O, pyr, DCM, 0 °C, then D*i*PEA. [b] 80% AcOH in H_2O, then Ac_2O, pyr. [c] Isolated yields.

good overall yield. An unexpected difference in efficiency in the outcome of the three-step oxazine synthesis was observed in the case of ethyl thioglucosides **13**[13] and **14**[14] (entry 3). In both cases, selective installation of the primary trichloroacetimidate proceeded uneventfully. However, treatment of the intermediate 6-*O*-acetimidate in **13** with triflic anhydride and pyridine followed by DiPEA mediated cyclisation afforded oxazine **15** in a rather poor yield. The latter may be ascribed to the high nucleophilic nature of the anomeric thioacetal. A decrease in nucleophilicity[15] of the thioacetal by installation of an electron withdrawing 2-*O*-benzoyl, as in **14**, led after the triflation–substitution sequence to formation of oxazine **16** in satisfactory yield. Analogously, application of the sequence of reactions to phenyl 2-azido-3-*O*-benzyl-2-deoxy-1-thio-α-D-glycoside **18**,[16] bearing an electron withdrawing azide at C-2, provided the 2,4-diamino derivative **19** in a good yield (entry 4). Both oxazines **16** and **19** were readily hydrolysed and acetylated leading to the 4- acetamidogalactosides **17** and **20** in 61% and 94% yield, respectively.

Orthogonally protected oxazine **19** was selected as a model compound to be used both as donor and acceptor in ensuing glycosylation reactions. Diaminogalactosides possessing differently functionalised amino functions are frequently encountered in natural products, for instance as 2-acetamido-4-amino-2,4,6-trideoxy-galactopyranosides present in the capsular polysaccharides of *Bacteroides fragilis*.[2] Furthermore, we recently demonstrated[17] that partially protected thioglycosides can be effectively employed as acceptor glycosides in the dehydrative condensation procedure developed by Gin *et al.*[18] Aglycon **21** was readily obtained after acidic hydrolysis of oxazine **19** and subsequent selective reaction of the amine with *N*-(benzyloxycarbonyloxy)succinimide (ZOSu). Dehydrative condensation was accomplished by activating 2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranose **23**[19] under the influence of diphenylsulfide bis(triflate) prepared *in situ*, followed by addition of acceptor **21** to afford the α-linked thiodisaccharide **24** in 65% yield. Next, the fully orthogonally protected thiodonor **22** was prepared by acetylation of compound **21**. Activation of this highly "disarmed"[15] donor was accomplished by treatment with diphenylsulfoxide (DPS)–triflic anhydride (Tf_2O)[20] which was shown to be a more potent thiophilic promoter system than the analogous benzenesulfinyl piperidine (BSP)–Tf_2O[21] combination recently developed by the Crich laboratory. Addition of methyl glucoside **25**,[22] to the activated donor, smoothly afforded disaccharide **26** as an anomeric mixture in excellent yield (Scheme 2).[23]

Conclusion

In summary, a new, straightforward synthetic procedure for the construction of 4-amino-4-deoxyglycosides, and their application as donors and acceptors in condensation reactions towards disaccharides, is presented. Future research will be devoted to implementation of this strategy in the synthesis of complex oligosaccharides containing aminoglycoside moieties.



Scheme 2 *Reagents and conditions*: i, 80% AcOH in H_2O, then ZOSu, pyr, rt, 95%. ii, Ac_2O, pyr, quant. iii, **23**, DPS, Tf_2O, TTBP, DCM, −60 °C, then **21**, 65%. iv, **22**, DPS, Tf_2O, DCM, −60 °C, then **25**, 95%.

Experimental

General

^1H and ^{13}C NMR spectra were recorded on a Jeol JNM-FX-200 (200/50.1 MHz) and a Bruker AV-400 (400/100 MHz) spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard. Coupling constants are given in Hz. All given ^{13}C spectra are proton decoupled. Mass spectra were recorded with PE/SCIEX API 165 with electronspray interface and Q-Star Applied Biosystems Q-TOF (TOF-section). Optical rotations were measured on a Propol automatic polarimeter. Traces of water in the donor and acceptor glycosides, diphenylsulfoxide and TTBP were removed by co-evaporation with toluene. TTBP was synthesised as described by Crich *et al.*[24] Dichloromethane (DCM, Baker) was boiled under reflux over P_2O_5 for 2 h and was distilled immediately prior to use. Solvents used for flash chromatography and TLC were of technical grade and distilled before use. Flash chromatography was performed on Baker silica gel (0.063–0.200 mm). TLC-analysis was conducted on DC-fertigfolien (Schleicher & Schuell, F1500, LS254) with detection by UV-absorption (254 nm) were applicable and by spraying with 20% sulfuric acid in ethanol followed by charring at ~150 °C or by spraying with a solution of $(NH_4)_6Mo_7O_{24}\cdot H_2O$ (25 g l^{-1}) in 10% sulfuric acid followed by charring at ~150 °C. Free amine functions were detected by spraying with a ninhydrin solution in EtOH followed by charring at ~150 °C.

Oxazine 4

A solution of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **1** (0.5 g; 1 mmol) in 5 ml DCM was cooled to 0 °C under an Ar

atmosphere. Subsequently trichloroacetonitrile (0.10 mL; 1.05 mmol; 1.05 eq.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3 μL; 0.01 mmol; 0.01 eq.) were added to the solution. According to TLC analysis, all starting material was consumed after 5 min. Subsequent treatment of the reaction mixture with pyridine (0.4 mL; 5 mmol; 5 eq.) and trifluoromethanesulfonic anhydride (0.24 mL; 1.5 mmol; 1.5 eq.) afforded the triflated product in 5 min at 0 °C. Base induced cyclisation was accomplished by addition of diisopropylethylamine (1.0 mL; 5 mmol; 5 eq.) and stirring was continued for 3½ h. The reaction mixture was purified by flash chromatography (20% EtOAc–PE). Removal of the eluent gave 0.40 g (0.80 mmol; 80%) of the title compound **4** as a yellow oil. TLC: 35% EtOAc in PE. $[\alpha]_D^{22}$: +63.4 (c = 1, $CHCl_3$). IR (cm^{-1}): 1718, 1679, 1510, 1496, 1454, 1352, 1220, 1195, 1089, 1043, 1028, 1001 ^{1}H NMR (400 MHz, $CHCl_3$): δ = 3.37 (s, 3H, CH_3(OMe)), 3.62 (dd, 1H, J = 3.5 Hz, J = 10.1 Hz, H-2), 3.94 (m, 1H, H-4), 4.04 (br d, 1H, J = 2.0 Hz, H-5), 4.13 (dd, 1H, J = 10.1 Hz, J = 4.4 Hz, H-3), 4.29 (d, 1H, J = 11.8 Hz, H-6), 4.42 (dd, 1H, J = 11.8, J = 1.3 Hz, H-6), 4.60 (d, 1H, J = 3.5 Hz, H-1), 4.65 (d, 1H, J = 11.8 Hz, C*H*HPh); 4.77–4.88 (m, 3H, C*H*HPh, CH_2Ph), 7.25–7.47 (m, 10H, H(Ar)); ^{13}C NMR (100.8 MHz, $CHCl_3$): δ = 54.1 (C-4), 55.7 (Me), 60.4 (C-5), 69.2 (C-6), 71.8 (CH_2(Bn)), 73.8 (CH_2(Bn)), 75.2 (C-3), 75.6 (C-2), 99.5 (C-1), 127.4–128.3 (CH(Ar)), 138.3 (C_q(Bn)), 138.9 (C_q(Bn)), 153.0 (C=NH); MS (m/z, ESI): 500 ($M + H^+$).

Methyl 4-acetamido-6-*O*-acetyl-2,3-di-*O*-benzyl-4-deoxy-α-D-galactopyranose 5

A solution of oxazine **4** (0.44 g; 0.89 mmol) in 5 mL 80% AcOH–H_2O was stirred for 30 min at ambient temperature. After removal of the solvent under reduced pressure, the residue was co-evaporated several times with toluene. The crude product was subsequently dissolved in 4 mL pyridine and treated with 1 mL Ac_2O. Stirring was continued for 8 h before the solvent was removed *in vacuo*. After co-evaporation with toluene the crude mixture was purified by flash chromatography (30% EtOAc–PE). Removal of the eluent gave 0.49 g (0.79 mmol, 89%) of the title compound **5** as a yellow oil. TLC: 35% EtOAc–PE. $[\alpha]_D^{22}$: + 2.8 (c = 1, $CHCl_3$). IR: 1739, 1651, 1369, 1232, 1195, 1155, 1099, 1028; ^{1}H NMR (400 MHz, $CHCl_3$): δ = 2.04 (s, 3H, CH_3(Ac)), 2.06 (s, 3H, CH_3(Ac)), 3.38 (s, 3H, CH_3(OMe)), 3.45–3.49 (dd, 1H, J = 4.0 Hz, J = 10.1 Hz, H-2), 3.96–4.00 (dd, 1H, J = 10.7 Hz, J = 4.7 Hz, H-3), 4.08–4.15 (m, 3H, H-5, H-6, H-6), 4.52 (d, 1H, J = 11.1 Hz, C*H*HPh), 4.64 (d, 1H, J = 4.0 Hz, H-1), 4.65 (d, 1H, J = 12.2 Hz, C*H*HPh), 4.77 (t, 1H, J = 4.4 Hz, H-4), 4.78 (d, 1H, J = 11.1 Hz, C*H*HPh), 4.86 (d, 1H, J = 12.2 Hz, C*H*HPh), 5.60 (d, 1H, J = 10.1 Hz, NH), 7.26–7.39 (m, 10H, H(Ar)); ^{13}C NMR (100.8 MHz, $CHCl_3$): δ = 20.8 CH_3(Ac)), 23.5 (CH_3(Ac)), 47.6 (C-4), 55.4 (CH_3-(OMe)), 63.2 (C-6), 66.7 (C-5), 71.7 (CH_2(Bn)), 73.6 (CH_2(Bn)), 75.3 (C-2), 76.0 (C-3), 98.6 (C-1), 127.7–128.4 (Ar), 137.9 (C_q(Bn)), 138.2 (C_q(Bn)), 170.5 (C=O) HRMS: (M + H) calcd for $C_{15}H_{33}NO_7$ 458.2101, found 458.2097.

Methyl 2,3-di-*O*-benzyl-6-trichloroacetimidate-α-D-glucopyranoside 2

To a stirred solution of methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **1** (1.79 g; 5 mmol) in 25 ml DCM at 0 °C was added trichloroacetonitrile (0.5 mL; 5 mmol, 1 eq.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (5 μL; 0.05 mmol; 0.05 eq.). Stirring was allowed for 45 min after which the reaction mixture was concentrated (waterbath ~ 30 °C). Flash chromatography (20% EtOAc–PE) and removal of the eluent gave 2.23 g. (4.31 mmol, 89%) of the title compound **2** as a colourless oil. TLC: 50% EtOAc–PE. ^{1}H NMR (400 MHz, $CHCl_3$): δ = 3.39 (s, 3H, CH_3(OMe)), 3.46 (dd, 1H, J = 9.0 Hz, H-4), 3.50 (dd, 1H, J = 9.6 Hz, J = 3.6 Hz, H-2), 3.82 (t, 1H, J = 9.2 Hz, H-3), 3.87 (m, 1H, J = 10.1 Hz, J = 5.0 Hz, H-5), 4.48 (d, 1H, J = 11.8 Hz, H-6), 4.60 (d, 1H, J = 3.4 Hz, H-1), 4.61 (dd, 1H, J = 11.9 Hz, J = 5.0 Hz, H-6), 4.64 (d, 1H, J = 11.9 Hz, C*H*HPh), 4.76 (d, 2H, J = 11.6 Hz, 2 × C*H*HPh), 4.97 (d, 1H, J = 11.3 Hz, C*H*HPh), 7.29–7.37 (m, 10H, CH(Ar)), 8.23 (br s, 1H, NH); ^{13}C NMR (100.8 MHz, $CHCl_3$): δ = 55.1 (CH_3(OMe)), 68.5 (C-6), 69.6 (C-5), 70.0 (C-4), 73.2 (CH_2(Bn)), 75.6 (CH_2(Bn)), 79.6 (C-2), 81.0 (C-3), 98.1 (C-1), 127.8–128.5 (Ar), 137.9 (C_q(Bn)), 138.6 (C_q(Bn)); MS (m/z, ESI): 518.1 ($M + H^+$), 540.0 ($M + Na^+$).

Oxazine 7

Oxazine **7** was obtained from methyl 2,3-di-*O*-benzyl-α-D-mannopyranoside **6** *via* the same procedure as described for the conversion of compound **1** to **4**. The reaction mixture was purified by flash chromatography (15% EtOAc–PE). Removal of the eluent gave 75 mg (0.15 mmol, 41%) of the title compound **7** as a yellow oil. ^{1}H NMR (400 MHz, $CHCl_3$): δ = 3.38 (s, 3H, CH_3(OMe)), 3.66 (t, 1H, J = 2.6 Hz, H-2), 4.01 (m, 2H, J = 2.6 Hz, J = 4.7 Hz, H-4, H-5), 4.06 (dd, 1H, J = 4.6 Hz, J = 2.6 Hz, H-3), 4.28 (d, 1H, J = 11.2 Hz, H-6), 4.54 (dd, 1H, J = 11.5 Hz, J = 2.6 Hz, H-6), 4.66 (d, 2H, J = 12.3 Hz, 2 × C*H*HPh), 4.78 (d, 1H, J = 12.0 Hz, C*H*HPh), 4.85 (d, 1H, J = 2.7 Hz, H-1), 4.86 (d, 1H, J = 12.5 Hz, C*H*HPh), 7.31 (m, 10H, H(Ar)); ^{13}C NMR (100.8 MHz, $CHCl_3$): δ = 52.4 (C-4), 55.4 (CH_3(OMe)), 61.4 (C-5), 68.7 (C-6), 70.9 (CH_2(Bn)), 72.7 (CH_2(Bn)), 74.1 (C-2, C-3), 101.0 (C-1), 127.6–128.4 (Ar), 138.3 (C_q(Bn)), 138.9 (C_q(Bn)), 151.8 (C=N); MS (m/z, ESI): 500.0 ($M + H^+$), 522.1 ($M + Na^+$).

Methyl 4-acetamido-6-*O*-acetyl-2,3-di-*O*-benzyl-4-deoxy-α-D-talopyranoside 8

Compound **8** was prepared from oxazine **7** *via* the same procedure as described for the conversion of compound **4** into **5**. The reaction mixture was purified by flash chromatography (20% EtOAc–PE). Removal of the eluent gave 43 mg (0.096 mmol, 64%) of the title compound **4** as a yellow oil. TLC: 40% EtOAc–PE. $[\alpha]_D^{22}$: +36.8 (c = 0.66, $CHCl_3$). IR (cm^{-1}): 1739, 1670, 1515, 1454, 1369, 1230, 1114, 1041. ^{1}H NMR (400 MHz, $CHCl_3$): δ = 1.81 (s, 3H, NHAc), 2.06 (s, 3H, CH_3(Ac)), 3.34 (s, 3H, CH_3(OMe)), 3.76 (m, 1H, J = 1.6 Hz, H-2), 3.81 (dd, 1H, J = 4.2 Hz, J = 3.1 Hz, H-3), 3.97 (m, 1H, H-5), 4.12 (dd, 1H, J = 8.0 Hz, J = 3.6 Hz, H-6), 4.24 (dd, 1H, J = 11.7 Hz, J = 4.2 Hz, H-6), 4.43 (d, 1H, J = 11.6 Hz, C*H*HPh), 4.66 (m, 1H, H-4), 4.68 (d, 2H, J = 11.2 Hz, 2 × C*H*HPh), 4.76 (d, 1H, J = 11.0 Hz, C*H*HPh), 4.81 (d, 1H, J = 1.2 Hz, H-1), 6.95 (d, 1H, J = 9.3 Hz, NH), 7.30 (m, 10H, H(Ar)); ^{13}C NMR (100.8 MHz, $CHCl_3$): δ = 20.8 (CH_3(Ac)), 23.2 (CH_3(Ac)), 46.5 (C-4), 54.8 (CH_3(OMe)), 64.0 (C-6), 68.2 (C-5), 69.9 (CH_2(Bn)), 72.1 (C-3), 74.1 (CH_2(Bn)), 76.2 (C-2), 99.9 (C-1), 127.5–128.4 (Ar), 137.6 (C_q(Bn)), 137.8 (C_q(Bn)), 170.7 (C=O); HRMS: (M + H) calcd for $C_{15}H_{33}NO_7$ 458.2101, found 458.2174.

Oxazine 10

Oxazine **10** was obtained from ethyl 2,3-*O*-isopropylidene-1-thio-α-D-mannopyranoside **9** *via* the same procedure as described for the conversion of compound **1** into **4**. The reaction mixture was purified by flash chromatography (10% EtOAc–PE). Removal of the eluent gave 216 mg (0.55 mmol, 54%) of the title compound **10** as a yellow oil. ^{1}H NMR (400 MHz, $CHCl_3$): δ = 1.23 (t, 3H, J = 7.4 Hz, CH_3(SEt)), 1.27 (s, 3H, CH_3(isoprop.)), 1.47 (s, 3H, CH_3(isoprop.)), 2.62 (m, 2H, CH_2(SEt), 4.19 (d, 1H, J = 7.2 Hz, H-2), 4.23 (m, 1H, H-4), 4.27 (s, 1H, H-5), 4.28 (m, 1H, H-6), 4.35 (m, 1H, H-6), 4.67 (dd, 1H, J = 7.2 Hz, J = 3.7 Hz, H-3), 5.07 (s, 1H, H-1); ^{13}C NMR (100.8 MHz, $CHCl_3$): δ = 14.7 (CH_3(SEt)), 24.9 (CH_3-(isoprop.)), 25.4 (CH_2(SEt)), 26.1 (CH_3(isoprop.)), 49.5 (C-4), 61.1 (C-5), 67.2 (C-6), 72.0 (C-2), 76.0 (C-3), 81.4 (C-1), 110.4 (C_q(isoprop.), 154.1 (C=N); MS (m/z, ESI): 390 ($M + H^+$), 412 ($M + Na^+$).

Ethyl 4-acetamido-6-*O*-acetyl-2,3-*O*-isopropylidene-1-thio-α-D-talopyranoside 11

Compound **11** was prepared from oxazine **10** *via* the same procedure as described for the conversion of compound **4** into **5**. The reaction mixture was purified by column chromatography (EtOAc). Removal of the eluent gave 77 mg (0.22 mmol, 40%) of the title compound **11** as a yellow oil, together with 50 mg (0.13 mmol, 21%) ethyl 4-acetamido-2,3,6-tri-*O*-acetyl-1-thio-α-D-talopyranoside **12**. TLC: 40% EtOAc–PE. $[\alpha]_D^{22}$: +142.0 (c = 1, $CHCl_3$). IR (cm^{-1}): 1739, 1666, 1519, 1373, 1235, 1211, 1083, 1037, 1002; ^{1}H NMR (400 MHz, $CHCl_3$): δ = 1.32 (t, 3H, J = 7.4 Hz, CH_3(SEt), 1.34 (s, 3H, CH_3(isoprop.)), 1.50 (s, 3H, CH_3(isoprop.)), 2.04 (s, 3H, CH_3(Ac)), 2.06 (s, 3H, CH_3(Ac)), 2.57 (m, 1H, C*H*H(SEt)), 2.74 (m, 1H, C*H*H(SEt)), 4.05 (dd, 1H, J = 5.9 Hz, J = 1.0 Hz, H-2), 4.10 (dd, 1H, J = 11.8 Hz, J = 4.1 Hz, H-6), 4.23 (d, 1H, J = 11.8 Hz, H-6), 4.34 (t, 1H, J = 5.9 Hz, H-3), 4.38 (m, 1H, H-5), 4.47 (m, 1H, H-4), 5.52 (s, 1H, H-1), 5.86 (d, 1H, J = 9.9 Hz, NH) ^{13}C NMR (100.8 MHz, $CHCl_3$): δ = 15.1 (CH_3(SEt)), 21.6 (CH_3(Ac)), 24.3 (CH_3(Ac)), 24.8 (CH_2(SEt)), 26.2 (CH_3(isoprop.)), 27.1 (CH_3(isoprop.)), 46.5 (C-4), 64.1 (C-6), 67.5 (C-5), 72.2 (C-3), 74.6 (C-2), 80.1 (C-1), 110.0 (C_q(isoprop.), 170.5 (C=O), 171.3 (C=O); HRMS: (M + H) calcd for $C_{15}H_{26}NO_6S$ 348.1403, found 348.1434.

Ethyl 4-acetamido-2,3,6-tri-*O*-acetyl-1-thio-α-D-tallopyranoside 12

TLC: 40% EtOAc–PE. ^{1}H NMR (400 MHz, $CHCl_3$): δ = 1.30 (t, 3H, J = 7.4 Hz, CH_3(SEt)), 2.00 (s, 3H, CH_3(Ac)), 2.04 (s, 3H, CH_3(Ac)), 2.07 (s, 3H, CH_3(Ac)), 2.20 (s, 3H, CH_3(Ac)), 2.66 (m, 2H, CH_2(SEt)), 4.12 (dd, 1H, J = 11.8 Hz, J = 4.6 Hz, H-6), 4.22 (dd, 1H, J = 11.7 Hz, J = 7.7 Hz, H-6), 4.59 (dd, 1H, J = 10.3 Hz, J = 3.6 Hz, H-4), 4.65, (m, 1H, H-5), 5.17 (t, 1H, J = 3.6 Hz, H-3), 5.21 (m, 1H, J = 3.5 Hz, H-2), 5.31 (s, 1H, H-1), 6.19 (d, 1H, J = 10.1 Hz, NH); ^{13}C NMR (100.8 MHz, $CHCl_3$): δ = 14.5 (CH_3(SEt)), 20.5 (CH_3(Ac)), 20.6 (CH_3(Ac)), 21.0 (CH_3(Ac)), 23.2 (CH_3(Ac)), 24.9 (CH_2(SEt)), 46.9 (C-4), 62.8 (C-6), 65.7 (C-2), 68.2 (C-5), 70.6 (C-3), 82.5 (C-1), 168.7 (C=O), 169.3 (C=O), 169.9 (C=O), 170.3 (C=O); MS (m/z, ESI): 414 (M + Na^+).

Oxazine 15

Oxazine **15** was obtained from ethyl 2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside **13** *via* the same procedure as described for the conversion of compound **1** into **4**. The reaction mixture was purified by flash chromatography (20% EtOAc–PE). Removal of the eluent gave 63 mg (0.12 mmol, 21%) of the title compound **15** as a yellow oil. ^{1}H NMR (400 MHz, $CHCl_3$): δ = 1.23 (t, 3H, J = 7.6 Hz, CH_3(SEt)), 2.60–2.70 (m, 2H, J = 7.5 Hz, CH_2(SEt)), 3.55 (t, 1H, J = 9.2 Hz, H-2), 3.75 (dd, 1H, J = 8.9 Hz, J = 4.3 Hz, H-3), 3.83 (br s, 1H, H-5), 3.93 (br s, 1H, H-4), 4.32 (d, 1H, J = 11.7 Hz, H-6), 4.39 (d, 1H, J = 9.4 Hz, H-1), 4.55 (d, 1H, J = 10.2 Hz, H-6), 4.78–4.89 (m, 4H, 2 × CH_2Ph), 7.25–7.44 (m, 10H, CH(Ar)); ^{13}C NMR (100.8 MHz, $CHCl_3$): δ = 15.0 (CH_3(SEt)), 22.9 (CH_2(SEt)), 53.3 (C-4), 67.4 (C-5), 67.4 (C-6), 69.4 (CH_2(Bn)), 71.6 (CH_2(Bn)), 76.6 (C-2), 80.3 (C-3), 83.9 (C-1), 127.6–133.0 (Ar), 138.1 (C_q(Bn)), 138.2 (C_q(Bn)), 154.4 (C=N); MS (m/z, ESI): 532.1 (M + H^+), 554.1 (M + Na^+).

Oxazine 16

Oxazine **16** was obtained from ethyl 2-*O*-benzoyl-3-*O*-benzyl-1-thio-β-D-glucopyranoside **14** *via* the same procedure as described for the conversion of compound **1** into **4**. The reaction mixture was purified by flash chromatography (20% EtOAc–PE). Removal of the eluent gave 63 mg (0.12 mmol, 64%) of the title compound **16** as a yellow oil. ^{1}H NMR (400 MHz, $CHCl_3$): δ = 1.19 (t, 3H, J = 7.5 Hz, CH_3(SEt)), 2.67–2.75 (m, 2H, J = 7.5 Hz, CH_2(SEt)), 3.90–3.93 (dd, 1H, J = 9.4 Hz, J = 4.2 Hz, H-3), 3.96 (d, 1H, J = 2.1 Hz, H-5), 4.06 (br s, 1H, H-4), 4.37 (d, 1H, J = 11.7 Hz, H-6), 4.52 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 4.62 (dd, 1H, J = 11.7 Hz, J = 1.6 Hz, H-6), 4.70–4.80 (dd, 2H, J = 12.8 Hz, CH_2Ph), 5.40 (t, 1H, J = 9.5 Hz, J = 9.4 Hz, H-3), 7.18–8.03 (m, 10H, H(Ar)); ^{13}C NMR (100.8 MHz, $CHCl_3$): δ = 14.7 (CH_3(SEt)), 22.1 (CH_2(SEt)), 53.1 (C-4), 67.8 (C-5), 68.7 (C-2), 69.3 (C-6), 70.9 (CH_2(Bn)), 77.3 (C-3), 82.5 (C-1), 127.6–133.0 (Ar), 129.9 (C_q(Bz)), 137.7 (C_q(Bn)), 165.0 (C=N); MS (m/z, ESI): 544.1 (M + H^+), 568.3 (M + Na^+).

Ethyl 4-acetamido-6-*O*-acetyl-2-*O*-benzoyl-3-*O*-benzyl-4-deoxy-1-thio-β-D-galactopyranoside 17

Compound **17** was prepared from oxazine **16** *via* the same procedure as described for the conversion of compound **4** into **5**. The reaction mixture was purified by flash chromatography (45% EtOAc–PE). Removal of the eluent gave 33 mg (0.066 mmol, 61%) of the title compound **17** as a yellow oil. TLC: 35% EtOAc–PE. $[\alpha]_D^{22}$: +14.0 (c = 0.42, $CHCl_3$). IR (cm^{-1}): 1720, 1647, 1550, 1454, 1369, 1242; ^{1}H NMR (400 MHz, $CHCl_3$): δ = 1.24 (t, 3H, J = 7.4 Hz, CH_3(SEt)), 2.07 (s, 3H, CH_3(Ac)), 2.08 (s, 3H, CH_3(Ac)), 2.65–2.71 (m, 2H, J = 7.4 Hz, CH_2(SEt)), 3.74 (dd, 1H, J = 9.7 Hz, J = 4.6 Hz, H-3), 3.86 (dd, 1H, J = 6.3 Hz, J = 1.2 Hz, H-5), 4.21 (d, 2H, J = 6.3 Hz, H-6), 4.46 (d, 1H, J = 12.6 Hz, C*H*HPh), 4.56 (d, 1H, J = 10.1 Hz, H-1), 4.70 (d, 1H, J = 12.6 Hz, C*H*HPh), 4.89–4.92 (m, 1H, H-4), 5.22 (t, 1H., J = 9.9 Hz, H-2), 5.96 (d, 1H, J = 10.1 Hz, NH), 7.09–8.01 (m, 10H, H(Ar)); ^{13}C NMR (100.8 MHz, $CHCl_3$): δ = 14.9 (CH_3(SEt)), 20.8 (CH_3(Ac)), 23.3 (CH_3(Ac)), 25.2 (CH_2(SEt)), 46.6 (C-4), 63.0 (C-6), 69.9 (C-2), 70.4 (CH_2(Bn)), 76.0 (C-5), 76.6 (C-3), 84.8 (C-1), 127.6–133.2 (Ar), 129.5 (C_q(Bz)), 137.2 (C_q(Bn)), 170.4 (C=O), 170.7 (C=O) HRMS: (M + H) calcd for $C_{26}H_{32}NO_7S$ 502.1821, found 502.1828.

Oxazine 19

Oxazine **19** was obtained from phenyl 2-azido-3-*O*-benzyl-2,4-dideoxy-1-thio-β-D-glucopyranoside **18** *via* the same procedure as described for the conversion of compound **1** into **4**. The reaction mixture was purified by flash chromatography (30% EtOAc–PE). Removal of the eluent gave 4.16 g (8.2 mmol, 74%) of the title compound **19** as a yellow oil. TLC: 40% EtOAc–PE. $[\alpha]_D^{22}$: +46.2 (c = 1, $CHCl_3$). IR (cm^{-1}): 2110, 1678, 1226, 1172; ^{1}H NMR (400 MHz, $CHCl_3$): δ = 3.37 (t, 1H, J = 9.8 Hz, H-2), 3.62 (dd, 1H, J = 9.6 Hz, J = 4.4 Hz, H-3), 3.83 (dd, 1H, J = 3.7 Hz, J = 1.5 Hz, H-5), 3.88 (d, 1H, J = 4.1 Hz, H-4), 4.35 (m, 2H, J = 10.0 Hz, H-1, H-6), 4.62 (dd, 1H, J = 12.16 Hz, H-6), 4.72 (d, 1H, J = 12.1 Hz, C*H*HPh), 4.80 (d, 1H, J = 12.1 Hz, C*H*HPh), 7.26–7.55 (m, 10H, H(Ar)); ^{13}C NMR (100.8 MHz, $CHCl_3$): δ = 51.8 (C-4), 60.0 (C-5), 68.0 (C-2), 69.4 (C-6), 71.2 (CH_2(Bn)), 79.1 (C-3), 85.4 (C-1), 127.9–134.2 (Ar), 129.5 (C_q(SPh)), 137.4 (C_q(Bn)), 153.7 (C=N); MS (m/z, ESI): 513.4 (M + H^+), 535.0 (M + Na^+).

Phenyl 4-acetamido-6-*O*-acetyl-2-azido-3-*O*-benzyl-2,4-dideoxy-1-thio-β-D-galactopyranoside 20

Compound **20** was prepared from oxazine **19** *via* the same procedure as described for the conversion of compound **4** into **5**. The reaction mixture was purified by flash chromatography (45% EtOAc–PE). Removal of the eluent gave 1.06 g (2.27 mmol, 94%) of the title compound **20** as a yellow oil. TLC: 40% EtOAc–PE. $[\alpha]_D^{22}$: −22.2 (c = 0.24, $CHCl_3$). IR (cm^{-1}): 2110, 1739, 1654, 1535, 1438, 1365, 1230, 1103, 1037; ^{1}H NMR (400 MHz, $CHCl_3$): δ = 1.96 (s, 3H, CH_3(Ac)), 2.06 (s, 3H, CH_3(Ac)), 3.27 (1H, t, J = 10.0 Hz, H-2), 3.53 (dd, 1H, J = 9.7 Hz, J = 4.2 Hz, H-3), 3.74 (dd, 1H, J = 7.0 Hz, J = 5.0 Hz, H-5), 4.09–4.23 (m, 2H, H-6), 4.38 (d, 1H, J = 10.3 Hz, H-1), 4.50 (d, 1H, J = 10.8 Hz, C*H*HPh), 4.75 (d, 1H, J = 6.9 Hz, H-4), 4.78 (d, 1H, J = 10.8 Hz, C*H*HPh), 5.43 (d, 1H, J = 10.1 Hz, NH), 7.30–7.59 (m, 10H, H(Ar)); ^{13}C NMR (100.8 MHz, $CHCl_3$):

δ = 20.7 (CH_3(Ac)), 23.3 (CH_3(Ac)), 45.7 (C-4), 61.2 (C-2), 62.8 (C-6), 71.4 (CH_2(Bn)), 75.7 (C-5), 79.4 (C-3), 86.1 (C-1), 128.1–133.8 (Ar), 130.9 (C_q(SPh)), 136.6 (C_q(Bn)), 170.3 (C=O); HRMS: (M + H) calcd for $C_{23}H_{27}N_4O_5S$ 471.1624, found 471.1745.

Phenyl 4-(*N*-benzyloxycarbonyl)-amino-2-azido-3-*O*-benzyl-2,4-dideoxy-1-thio-β-D-galactopyranoside 21

Oxazine **19** (0.81 g, 1.58 mmol) was stirred in 5 mL 80% AcOH in H_2O at ambient temperature. After 15 min, the clear solution was diluted with toluene, concentrated and co-evaporated several times with toluene. The crude oil was dissolved in 5 mL DCM followed by addition of NEt_3 (0.26 mL; 2.0 mmol, 1.25 eq.) and ZOSu (0.40 g; 1.6 mmol, 1.01 eq.). The reaction mixture was stirred for 8 h at room temperature before EtOAc was added. The mixture was washed with 50 mL 1M HCl. The water-layer was extracted twice with 50 mL EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (50% EtOAc–PE) and removal of the eluent afforded 844 mg (1.50 mmol, 95%) of the title compound **21** as a colourless oil. TLC: 50% EtOAc–PE. $[\alpha]_D^{22}$: −6.2 (c = 1, $CHCl_3$). IR (cm^{-1}): 2110, 1705, 1512, 1257, 1215, 1056. ^{1}H NMR (200 MHz, $CHCl_3$): δ = 3.01 (br s, 1H, OH), 3.24 (t, 1H, J = 9.9 Hz, H-2), 3.57 (m, 3H, H-3, H-6), 3.72 (m, 1H, H-5), 4.36 (m, 2H, J = 10.2 Hz, H-1, H-4), 4.50 (d, 1H J = 10.9 Hz, C*H*HPh), 4.68 (d, 1H, J = 11.3 Hz, C*H*HPh), 4.83 (d, 1H, J = 7.8 Hz, NH), 5.12 (s, 2H, CH_2(Z)); ^{13}C NMR (50.4 MHz, $CHCl_3$): δ = 47.5 (C-4), 60.5 (C-6), 61.1 (C-2), 67.0 (CH_2(Z)), 70.8 (CH_2(Bn)), 77.9 (C-5), 78.8 (C-3), 86.1 (C-1), 127.6–132.6 (Ar), 131.3 (C_q(SPh)), 135.8 (C_q(Z)), 136.6 (C_q(Bn)), 157.3 (C=O); HRMS: (M + H) calcd for $C_{27}H_{29}N_4O_5S$ 521.1780, found 521.1829.

Phenyl 6-*O*-acetyl-4-(*N*-benzyloxycarbonyl)-amino-2-azido-3-*O*-benzyl-2,4-dideoxy-1-thio-β-D-galactopyranoside 22

Compound **21** (593 mg, 1.14 mmol) was dissolved in 5 mL pyridine followed by the addition of 2.5 mL Ac_2O. The reaction mixture was stirred for 2 h at room temperature. The mixture was concentrated and co-evaporated several times with toluene. After flash chromatography (30% EtOAc–PE) and removal of the eluent, 606 mg of the title compound **22** (1.14 mmol, quant.) was obtained as a colourless oil. TLC: 50% EtOAc–PE. $[\alpha]_D^{22}$: −13.4 (c = 1, $CHCl_3$). IR (cm^{-1}): 2110, 1716, 1510, 1454, 1365, 1226, 1103, 1037; ^{1}H NMR (200 MHz, $CHCl_3$): δ = 2.04 (s, 3H, CH_3(Ac)), 3.27 (t, 1H, J = 10.2 Hz, J = 9.7 Hz, H-2), 3.51 (dd, 1H, J = 9.9 Hz, J = 4.3 Hz, H-3), 3.71 (t, 1H, J = 5.8 Hz, H-5), 4.20 (m, 2H, J = 5.1 Hz, H-6), 4.34 (d, 1H, J = 10.2 Hz, C*H*HPh), 4.42 (m, 1H, H-4), 4.52 (d, 1H, J = 11.0 Hz, C*H*HPh), 4.83 (d, 2H, J = 10.6 Hz, H-1, NH), 5.08 (s, 2H, CH_2(Z)), 7.25–7.54 (m, 10H, H(Ar)); ^{13}C NMR (50.4 MHz, $CHCl_3$): δ = 20.7 (Ac), 48.0 (C-4), 61.2 (C-2), 62.9 *C-6), 67.2 (CH_2(Z)), 71.4 (CH_2(Bn)), 75.6 (C-5), 79.6 (C-3), 86.3 (C-1), 127.9–133.4 (Ar), 131.1 (C_q(SPh)), 136.0 (C_q(Z)), 136.7 (C_q(Bn)), 156.2 (C=O(Z)), 170.5 (C=O(Ac)); MS (*m*/*z*, ESI): 563.3 (M + H^+), 585 (M + Na^+).

Phenyl 4-(*N*-benzyloxycarbonyl)-amino-2-azido-3-*O*-benzyl-6-(2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranosyl)-2-deoxy-1-thio-β-D-galactopyranoside 24

A solution of 2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranose **23** (54 mg; 0.1 mmol), diphenylsulfoxide (40 mg; 0.2 mmol, 2 eq.) and tri-*tert*-butylpyrimidine (74 mg; 0.3 mmol, 3 eq.) in 4 ml DCM was stirred over 100 mg 4 Å activated molecular sieves for 30 min. The mixture was cooled to −78 °C before triflic acid anhydride (26 μL; 0.15 mmol, 1.5 eq.) was added. The mixture was allowed to warm to −40 °C in 1 h followed by addition of phenyl 4-(*N*-benzyloxycarbonyl)-amino-2-azido-3-*O*-benzyl-2-deoxy-1-thio-α-D-galactopyranoside **21** (52 mg; 0.1 mmol, 1 eq.) in 1 ml DCM. Stirring was continued and the reaction mixture was allowed to warm to 0 °C. Subsequently the reaction was quenched by addition of triethylamine (0.16 mL; 2 mmol, 20 eq.). Flash chromatography (20% EtOAc–PE) and removal of the eluent afforded 66 mg of the title compound **24** (65 μmol, 65%) as a yellow oil. TLC: 50% EtOAc–PE. $[\alpha]_D^{22}$: +13.2 (c = 1, $CHCl_3$). IR (cm^{-1}): 2110, 1716, 1496, 1454, 1215, 1096, 1030 ^{1}H NMR (400 MHz, $CHCl_3$): δ = 3.18 (t, 1H, J = 10.0 Hz, H-2′), 3.45 (m, 2H, J = 6.7 Hz, J = 9.7 Hz, H-3, H-6), 3.53 (dd, 1H, J = 9.3 Hz, J = 6.4 Hz, H-6), 3.59 (q, 1H, J = 5.9 Hz, H-6′), 3.75 (m, 2H, H-5′, H-6′), 3.83 (dd, 1H, J = 10.0 Hz, J = 2.7 Hz, H-3), 3.89 (s, 1H, H-4), 3.95 (t, 1H, J = 6.3 Hz, H-5), 4.02 (dd, 1H, J = 10.1 Hz, J = 3.6 Hz, H-2), 4.32 (d, 1H, J = 10.0 Hz, H-1′), 4.38 (s, 1H, H-4′), 4.40 (m 2H, CH_2Ph)), 4.56 (d, 1H, J = 11.4 Hz, C*H*HPh), 4.69 (t, 2H, J = 13.0 Hz, CH_2Ph), 4.80 (m, 3H, C*H*HPh, CH_2Ph), 4.81 (d, 1H, J = 3.2 Hz, H-1′), 4.92 (d, 1H, J = 11.4 Hz, C*H*HPh), 5.06 (dd, 2H, J = 12.2 Hz, CH_2(Z)), 7.20–7.37 (m, 35H, H(Ar)); ^{13}C NMR (100.8 MHz, $CHCl_3$): δ = 48.5 (C-4′), 61.2 (C-3′), 67.0 (CH_2(Z)), 67.6 (C-6′), 69.1 (C-6), 69.4 (C-5′), 71.3 (CH_2(Bn)), 73.1 (CH_2(Bn)), 73.4 (CH_2-(Bn)), 73.5 (CH_2(Bn)), 74.7 (CH_2(Bn)), 74.9 (C-4), 76.5 (C-2), 76.7 (C-5), 78.9 (C-3), 79.8 (C-2′), 86.2 (C-1′), 98.2 (C-1), 124.7–133.2 (Ar), 131.5 (C_q(SPh)), 136.1–138.7 (C_q(Bn)), 156.3 (C=O); HRMS: (M + H) calcd for $C_{61}H_{63}N_4O_{10}S$ 1043.4259, found 1043, 4280.

Methyl 2,3,4-tri-*O*-benzoyl-6-*O*-(6-*O*-acetyl-4-(*N*-benzyloxycarbonyl)-amino-2-azido-3-*O*-benzyl-2,4-dideoxy-α/β-D-galactopyranosyl)-α-D-glucopyranoside 26

A solution of phenyl 6-*O*-acetyl-4-(*N*-benzyloxycarbonyl)-amino-2-azido-3-*O*-benzyl-2,4-dideoxy-1-thio-β-D-galacto-pyranoside **22** (53 mg; 0.1 mmol) and diphenylsulfoxide (25 mg; 0.12 mmol, 1.2 eq.) in 3 ml DCM was stirred over 100 mg activated 4 Å molecular sieves for 30 min. The mixture was cooled to −78 °C before triflic acid anhydride (22 μL; 0.13 mmol, 1.3 eq.) was added. The mixture was stirred for 5 min followed by addition of methyl 2,3,4-tri-*O*-benzoyl-α-D-gluco-pyranoside **25** (75 mg; 0.1 mmol, 1 eq.) in 1 ml DCM. The mixture was allowed to warm to 0 °C. Subsequently the reaction was quenched by addition of triethylamine (0.16 mL; 2 mmol, 20 eq.). Flash chromatography (30% EtOAc–PE) and removal of the eluent afforded 92 mg of the title compound **26** (95 μmol, 95%) as a colourless oil. TLC: 50% EtOAc–PE. IR (cm^{-1}): 2110, 1724, 1519, 1450, 1245, 1091, 1026; ^{1}H NMR (400 MHz, $CHCl_3$): δ = 4.27 (d, 0.5H, J = 8.0 Hz, H-1′(β-anomer)), 4.90 (d, 0.5H, J = 3.4 Hz, H-1′(α-anomer)), 4.27 (d, 1H, J = 3.5 Hz, H-1); ^{13}C NMR (100,8 MHz, $CHCl_3$): δ = 96.8 (C-1), 97.9 (C-1′(α-anomer)), 102.5 (C-1′(β-anomer)); HRMS: (M + H) calcd for $C_{51}H_{51}N_4O_{15}$ 959.3345, found 959.3394.

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