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Note

An alternative high yielding and highly stereoselective method for preparing an α-Neu5NAc-(2,6)-D-GalN$_3$ building block suitable for further glycosylation

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Abstract—This paper deals with new approaches to α-Neu5NAc-(2,6)-D-GalN$_3$ building blocks, suitable as glycosylation donors. The major improvement, by comparison with the results of the literature, lies in the glycosylation step of a new D-galactosamine acceptor (*tert*-butyldimethylsilyl 3-*O*-acetyl-2-azido-2-deoxy-β-D-galactopyranoside) with *O*-methyl-*S*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)onate] dithiocarbonate as the *N*-acetylneuraminic acid donor. The reaction affords the expected disaccharide in high yield (85%) and a complete α-Neu5NAc stereoselectivity. A subsequent oxidation step, eliminating the glycal by-product allows an easier purification. Afterwards, the *tert*-butyldimethylsilyl disaccharide can be transformed into a donor, after cleavage of the anomeric group in smooth conditions.

Keywords: D-Galactosamine; *N*-Acetylneuraminic acid; α-Glycosylation; Glycal oxidation

Sialic acids are endowed with fundamental biological properties. They can be found either as glycoproteins or glycolipids lying, most often, at the outer part of cell membranes. They fulfil several biological functions, either resulting in molecular recognition (e.g., cell adhesion and proliferation, immunological defence, protein survival), or induced by their negative charge (e.g., conformation, viscosity or solubility of glycoproteins, total negative charge at the surface of cells).[1,2] Sialic acids constitute a family of about 40 constituents, amongst which *N*-acetylneuraminic acid (Neu5Ac) **1** is the most representative. The synthesis of Neu5Ac containing oligosaccharides has been extensively studied, mostly since they were discovered as antigenic determinants of the Thomson–Friendenrich family, over-expressed at the surface of cancer cells.

The glycosylation with sialic acid donors is one of the most challenging in the field for several reasons: (a) the anomeric centre is a hindered quaternary centre, (b) it is deactivated by the presence of the carboxylate residue, (c) no stereo-orientation can be expected from the nature of a substituent at C-3, (d) the nucleophilic substitution at the anomeric position is in competition with a favoured elimination reaction giving rise to a glycal.[3,4]

In a seek for preparing amphiphilic derivatives of Neu5Ac(α2-6)GalNAcα, in a view to embed into liposome bilayers or phospholipid monolayers,[5,6] we have investigated several methods described in the literature. Thus, donors **2** and **3** were reacted, in various conditions, with α-D-GalNAc acceptors carrying hydrophobic aglycons. None of them afforded the expected glycosides in good yields (best yield 24%) and/or good stereocontrols (α/β ~ 1:1).[7] The discordance with the results of the literature reported for shorter aglycons,[8] was attributed to phase separation and/or possible disfavourable

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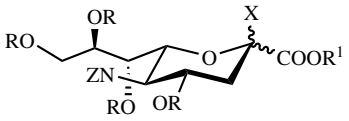
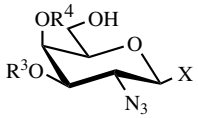
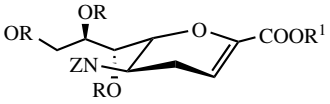


	R	R^1	NZ	X
1	H	H	NHAc	OH
2	Ac	Me	NHAc	β-Cl
3	Ac	Me	NHAc	α-S(C=S)OEt
4	Ac	Me	NHAc	α/β-SMe
5	Bn	Bn	N_3	α-STol
6	Ac	Me	N_3	α-STol



	X	R^3	R^4
7	OAll	β-D-Gal	H
8	OAll	H	H
9	OTBDMS	H	H
10	OTBDPS	Bn	H
11	OTBDPS	H	H
12	OTBDPS	-CMe_2-	
13	SEt	Ac	H
14	OTBDMS	Ac	H



	R	R^1	NZ
15a	Ac	Me	NHAc
15b	Ac	Me	N_3
15c	Bn	Bn	NHAc

Figure 1.

conformations in the highly hydrophobic acceptor alcohols, mainly at low temperatures. Therefore, we decided to attempt the glycosylation with a galactosamine acceptor that could allow a subsequent activation at the anomeric centre for a further glycosylation step (Fig. 1).

The results of the literature concerning glycosylations with neuraminic acid donors and 2-azido galactosamine acceptors that could be reactivated easily at the anomeric position are reported in Table 1.

As can be seen from Table 1 (entries 1–7), either the glycosylation yields or the α/β stereoselectivities are unsatisfactory for preparing the expected disaccharides. The best glycosylation yield (entry 1) is obtained with a low stereoselectivity, whereas the best stereoselectivities (entries 5–7) are observed for glycosylations in modest yields.

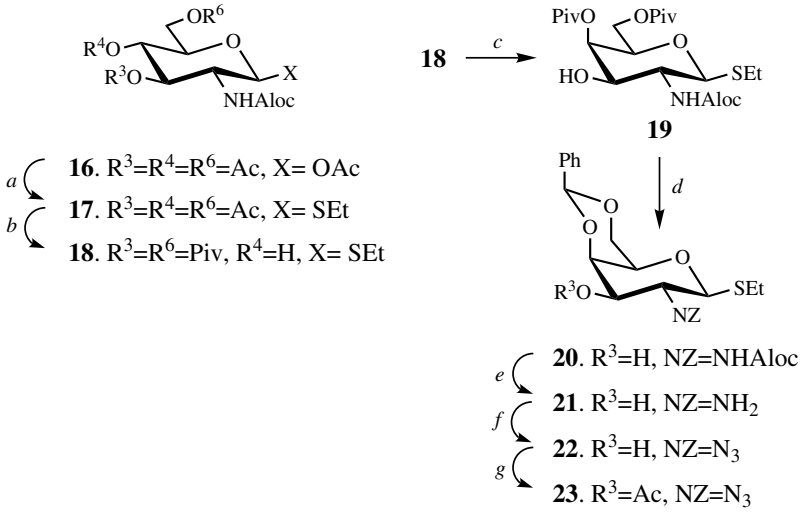
Table 1. Glycosylation of 2-azido-2-deoxy-D-galactopyranoside acceptors (**7**–**14**) with neuraminic acid donors (**2**–**6**)

Entry	Acceptor	Donor (equiv)	Yield (%)	α/β Ratio	Ref.
1	**7**	**2** (5)	85	1.1/1	9
2	**8**	**2** (1)	49	5/1	10
3	**9**	**3** (2)	61	6.7/1	11
4	**9**	**4** (nd)	50	3.6/1	11
5	**10**	**5** (2)	61	9/1	12
6	**11**	**5** (2)	43	α Only	12
7	**12**	**6** (nd)	53	10/1	13
8	**13**	**2** (2)	45	3/1	This work
9	**14**	**3** (2)	85	α Only	This work

Concerning the donors, it can be mentioned that: (a) lengthy multistep preparations of azido sialic acid derivatives (entries 5–7) do not result in drastic yield increases, though they afford excellent α-stereoselectivities, (b) whatever the leaving group is, the glycosylation yields stay in the range of 40–60% with one exception (entry 1) that could be explained by the use of a large excess of donor (5 equiv) with regard to the acceptor, (c) a competitive elimination reaction most often affords glycals **15a**–**c**, whatever the donor is.[7,14]

Concerning the acceptors, it can be pointed out that: (a) protection at C-4 is not necessary since this position is very unreactive (the yield reported in entry 7 is in same the range as others), (b) protection at C-3 is of interest, affording better yields without affecting the stereoselectivity to a great extent (compare the results of entries 5 and 6), furthermore diglycosylation at C-3 and C-6 was reported for unprotected acceptors,[8a] (c) the azido function at C-2 affords better results than the 2-acetamido counterpart.[15] Also, it should be pointed out that a non-participating group at C-2 is necessary in a view to performing an α-glycosylation, after reactivation at the anomeric position. It is aforementioned that most of these comments are also valid for other galactosamine acceptors, not dealt with, in the present paper.

As a result of the above observations, we decided to attempt the glycosylation of acceptors **13** and **14**, which have not been reported previously to our knowledge. Both are *O*-acetylated at OH-3, unprotected at OH-6



Scheme 1. Reagents and conditions: (a) EtSH, $BF_3{\cdot}Et_2O$–CH_2Cl_2, 0 °C; (b) MeONa, MeOH, rt, then $(CH_3)_3CCOCl$, pyridine–CH_2Cl_2, rt; (c) Tf_2O, CH_2Cl_2–pyridine, −15 °C, then H_2O, 80 °C; (d) MeONa, MeOH, rt, then PhCH–$(OMe)_2$, TsOH, rt; (e) 2.5 M NaOH, reflux; (f) TfN_3, DMAP, CH_3CN, rt; (g) Ac_2O, pyridine.

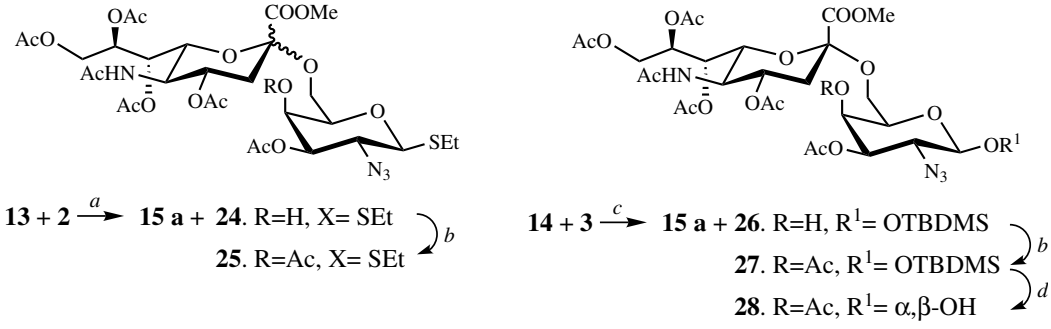
and OH-4; they carry an azido function at C-2 and a group at anomeric position that can be either directly used for a further glycosylation (**13**), or selectively cleaved in smooth conditions (**14**) for a subsequent activation.

Acceptor **13** was prepared following the reaction pathway depicted in Scheme 1. The *N*-allyloxycarbonyl derivative **16**[16] was treated with ethanethiol and boron-trifluoride etherate to afford **17** (80% yield). Zemplén de-*O*-acetylation and treatment with pivaloyl chloride in CH_2Cl_2/pyridine gave rise to 3,6-di-*O*-pivaloyl compound **18** in 88% overall yield. The latter was treated with triflic anhydride and the C-4 position was inverted by hydrolysis at 80 °C to afford compound **19** (90% overall yield) resulting in a concomitant migration of pivaloyl ester from C-3 to C-4, as already reported by Lay et al.[17]

After cleavage of the pivaloyl esters and re-protection as a 4,6-*O*-benzylidene derivative **20** in usual conditions (78% overall yield), the *N*-allyloxycarbonyl group was hydrolyzed with 2.5 M, NaOH at reflux since Pd(0) complexes reported earlier[16] were shown to be less satisfactory, in this instance. Thus, the free amino compound **21** was obtained in 96% yield. The latter was treated with triflyl azide[18] (in situ formed by reaction of triflic anhydride and sodium azide) to afford compound **22** (96% yield). This reaction pathway to **22** (40% overall yield from compound **16**) could constitute an interesting alternative to the usual azidonitration of D-galactal.[19] Compound **22** was finally acetylated at OH-3 to afford **23** (95% yield) and the benzylidene group was cleaved in usual conditions (69% yield) to afford the acceptor diol **13**.

Acceptor **14** was prepared in 59% yield by acidic cleavage (60% trifluoroacetic acid) of the known *tert*-butyldimethylsilyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-galactopyranoside.[20]

The glycosylations of acceptors **13** and **14** were attempted with the easily accessible donors **2** and **3** in various conditions (Scheme 2). The best results are



Scheme 2. Reagents and conditions: (a) AgOTf, THF, −15 °C to rt; (b) Ac_2O, pyridine, rt; (c) MeSOTf, CH_2Cl_2–CH_3CN, −63 °C; (d) TBAF, THF–AcOH, rt.

reported in Table 1 (entries 8 and 9). When **13** was used as the acceptor and **3** as the donor in glycosylation reactions with usual promoters,[21] only the degradation of the acceptor was observed. Nevertheless, glycosylation of **13** with donor **2**, promoted by silver triflate, afforded the expected glycoside **24**, although in low yield (45%) and with a low stereoselectivity (α/β, 3/1) to our disappointment. On the contrary, when compound **14** was used as the acceptor and xanthate **3** as the donor, the expected disaccharide **26** was obtained with an excellent yield using 2 equiv of donors only. The best stereoselectivity (α-anomer only) and yield (85%) were achieved in conditions very close to that reported by Halkes et al. (CH_2Cl_2–CH_3CN as solvent and MeSOTf as the promoter).[21]

As already pointed out, one of the difficulties encountered in glycosylation reactions with neuraminic acid is the competitive elimination leading to glycal **15a**. Besides the consumption of donor, the formation of the latter requires a separation that is often difficult. This drawback was overcome by a smooth oxidation of the glycosylation mixture with a catalytic amount of ruthenium tetraoxide in $CCl_4/CH_3CN/H_2O$, as reported for the oxidation of olefins.[22] This oxidation (impossible in the case of the thioethylglycoside **24**) afforded highly polar species that could be removed easily from the reaction mixture.

Finally, disaccharides **24** and **26** could be O-acetylated at C-4 to **25** and **27**, respectively. The latter was deprotected in the usual conditions at C-1 to afford **28** that can be, in turn, reactivated as a trichloroacetimidate for a further glycosylation, if necessary.[7,10] The use of disaccharide **28** as a glycosylation precursor for the synthesis of amphiphilic compounds is now under investigation in our laboratory.

1. Experimental

1.1. General methods

Pyridine was dried by boiling with CaH_2 prior to distillation. Dichloromethane was washed twice with water, dried with $CaCl_2$ and distilled from CaH_2. Tetrahydrofurane was distilled from sodium-benzophenone. Methanol was distilled from magnesium. Acetonitrile was distilled from CaH_2. Pyridine, THF and CH_2Cl_2 were stored over 4 Å molecular sieves; CH_3CN and MeOH over 3 Å molecular sieves. Melting points were determined on a Büchi apparatus and were uncorrected. Thin layer chromatography was performed on aluminium sheets coated with Silica gel 60 F_{254} (E. Merck). Compounds were visualized by spraying the TLC plates with dilute 15% aq H_2SO_4, followed by charring at 150 °C for a few minutes. Column chromatography was performed on silica gel Geduran Si 60 (E. Merck). Optical rotations were recorded on a Perkin–Elmer 241 polarimeter in a 1 dm cell at 21 °C. ^1H and ^{13}C NMR spectra were recorded with a Bruker AM-300 (working at 300 and 75 MHz, respectively) and a Bruker AM-500 (working at 500 and 125 MHz, respectively) spectrometers with Me_4Si as internal standard. Elemental analyses were performed by the 'Laboratoire Central d'Analyses du CNRS' (Vernaison, France). Mass spectra were recorded on a Finnigan Mat 95 XL apparatus in FAB mode.

1.2. Ethyl 3-*O*-acetyl-2-azido-2-deoxy-1-thio-β-D-galactopyranoside (13)

Compound **22**[19] (1.50 g, 4.45 mmol) was stirred overnight in a 2:1 pyridine–Ac_2O mixture (30 mL). After evaporation and co-evaporation with toluene twice, the mixture was purified by column chromatography (1:1 EtOAc–petroleum ether). Compound **23** (1.60 g, 95%) was obtained as white crystals identical with that already described in the literature.[19] This derivative (200 mg, 0.527 mmol) was dissolved in dry CH_2Cl_2 (6.6 mL) and treated at 0 °C with $BF_3{\cdot}Et_2O$ (20 μL, 0.3 equiv) and EtSH (250 μL, 3.3 mmol) for 1 h. The mixture was then treated with satd aq $NaHCO_3$ (3 mL), diluted with CH_2Cl_2 and washed with water. After evaporation, the mixture was purified by column chromatography (3:1 EtOAc–petroleum ether). Compound **13** was obtained as white crystals (106 mg, 69%): mp 107 °C; $[\alpha]_D$ −22 (*c* 1.0, $CHCl_3$); R_f 0.27 (2:1 EtOAc–petroleum ether); ^1H NMR ($CDCl_3$): δ 4.80 (dd, 1H, $J_{3,4}$ 2.8 Hz, $J_{3,2}$ 10.0 Hz, H-3), 4.39 (d, 1H, $J_{1,2}$ 10.2 Hz, H-1), 4.23 (dd, 1H, $J_{4,5}$ 0.8 Hz, H-4), 3.93 (m, 2H, H-6a,6b), 3.86 (t, 1H, H-2), 3.53 (m, 1H, H-5), 2.81 (m, 2H, CH_2S), 2.21 (s, 3H, CH_3CO), 1.38 (t, 3H, *J* 7.6 Hz, CH_3CH$_2$S). ^{13}C NMR ($CDCl_3$): δ 170.3 (CH$_3$*C*O), 84.8 (C-1), 77.4, 75.5, 67.7 (C-3,4,5), 62.8 (C-6), 60.2 (C-2), 25.3 (SCH_2), 21.1 (*C*H$_3$CO), 15.1 (*C*H$_3$CH$_2$S). Anal. Calcd for $C_{10}H_{17}N_3O_5S$ (291.33): C, 41.23; H, 5.88; N, 14.42. Found: C, 41.06; H, 5.90; N, 14.22.

1.3. *tert*-Butyldimethylsilyl 3-*O*-acetyl-2-azido-2-deoxy-β-D-galactopyranoside (14)

A soln of *tert*-butyldimethylsilyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-β-D-galactopyranoside[20] (380 mg, 0.869 mmol) in CH_2Cl_2 (20 mL) was treated for 18 h at rt, with 60% aq CF_3CO_2H (0.7 mL). After neutralization with satd aq $NaHCO_3$, the mixture was extracted with CH_2Cl_2 and the organic layer was dried over $MgSO_4$, before evaporation and purification by column chromatography (1:1 EtOAc–petroleum ether).

Compound **14** (186 mg, 59%) was obtained as an amorphous solid: $[\alpha]_D$ +6 (*c* 1.0, $CHCl_3$); R_f 0.38 (1:1 EtOAc–petroleum ether); ^1H NMR ($CDCl_3$): δ 4.51 (dd, 1H, $J_{3,4}$ 3.2 Hz, $J_{3,2}$ 10.9 Hz, H-3), 4.42 (d, 1H,

$J_{1,2}$ 7.5 Hz, H-1), 3.93 (d, 1H, $J_{4,5}$ 0.8Hz, H-4), 3.75 (dd, 1H, $J_{6a,5}$ 5.5 Hz, $J_{6a,6b}$ 11.9 Hz, H-6a), 3.68 (dd, 1H, $J_{6b,5}$ 4.5 Hz, H-6b), 3.53 (ddd, 1H, H-2), 3.35 (ddd, 1H, $J_{4,5}$ 0.7 Hz, H-5), 2.20 (s, 3H, CH_3CO), 0.96 (s, 9H, SiC(CH_3)$_3$), 0.18 (s, 6H, Si(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): δ 170.5 (CH_3*C*O), 97.5 (C-1), 73.8, 73.4, 67.2, 63.33 (C-2, 3, 4, 5), 62.1 (C-6), 25.6 (Si*C*(CH$_3$)$_3$), 21.0 (*C*H$_3$CO), 18.0 (SiC(*C*H$_3$)$_3$), −4.2, −5.1 (Si(*C*H$_3$)$_2$). Anal. Calcd for $C_{14}H_{27}N_3O_6Si$ (361.46): C, 46.52; H, 7.53; N, 11.62. Found: C, 46.24; H, 7.62; N, 11.60.

1.4. Ethyl 3,4,6-tri-*O*-acetyl-2-allyloxycarbonylamino-2-deoxy-1-thio-β-D-glucopyranoside (17)

A soln of compound **16**[16] (7.50 g, 16.92 mmol) in CH_2Cl_2 (75 mL) was treated at 0 °C with EtSH (2.5 mL) and BF_3·Et_2O (4 mL) for 3 h under argon. The mixture was then washed with satd aq $NaHCO_3$ and dried over Na_2SO_4. After evaporation, the mixture was purified by column chromatography (1:1 EtOAc–petroleum ether). Compound **17** (6.0 g, 80%) was obtained as white crystals: mp 133–134 °C (EtOH); $[\alpha]_D$ −18 (*c* 1.0, $CHCl_3$); R_f 0.66 (1:1 EtOAc–petroleum ether); ^{1}H NMR ($CDCl_3$): δ 5.91 (m, 1H, CH_2=C*H*–), 5.34–5.15 (m, 3H, CH_2=CH–, H-3), 5.08 (dd, 1H, $J_{3,4}$ 9.5 Hz, $J_{4,5}$ 9.5 Hz, H-4), 4.86 (m, 1H, $J_{NH,H\text{-}2}$ 8.8 Hz, NH), 4.62 (d, 1H, $J_{1,2}$ 10.2 Hz, H-1), 4.58 (m, 2H, CH_2=CH–CH_2–), 4.26 (dd, 1H, $J_{5,6a}$ 5.0 Hz, $J_{6a,6b}$ 12.3 Hz, H-6a), 4.13 (dd, 1H, $J_{5,6b}$ 2.3 Hz, H-6b), 3.75 (ddd, 1H, $J_{2,3}$ 9.5 Hz, H-2), 3.70 (m, 1H, H-5), 2.74 (m, 2H, CH_2S), 2.08, 2.04, 2.03 (3 s, 9H, 3 CH_3CO), 1.26 (t, 3H, *J* 7.4 Hz, CH_3CH$_2$S). ^{13}C NMR ($CDCl_3$): δ 170.7, 169.5 (CH_3*C*O), 155.7 (NH*C*OO), 132.6 (CH_2=*C*H–), 117.5 (*C*H_2=CH–), 84.6 (C-1), 75.7 (C-3), 73.7 (C-5), 68.8 (C-4), 65.8 (CH_2=CH–*C*H_2–), 62.5 (C-6), 55.0 (C-2), 24.3 (*C*H$_2$S), 20.8, 20.7, 20.6 (*C*H$_3$CO), 14.8 (*C*H$_3$CH$_2$S). Anal. Calcd for $C_{18}H_{27}NO_9S$ (433.47): C, 49.87; H, 6.28; N, 3.23. Found: C, 49.66; H, 6.35; N, 3.28.

1.5. Ethyl 2-allyloxycarbonylamino-2-deoxy-3,6-di-*O*-pivaloyl-1-thio-β-D-glucopyranoside (18)

The thioethylglucoside **17** (4.50 g, 10.38 mmol) was treated overnight with a chip of sodium in MeOH (100 mL) at rt. After neutralization with Amberlite IR 120 H^+, filtration and evaporation, the crude product was solubilized in a mixture of pyridine (31 mL) and CH_2Cl_2 (15 mL). After cooling to 0 °C, pivaloyl chloride (4.1 mL, 33.3 mmol) was added dropwise for 1 h. After 2 h at 0 °C, the reaction was quenched with MeOH (4 mL). The mixture was diluted with CH_2Cl_2 and washed successively at 0 °C with 10% aq HCl, satd aq $NaHCO_3$ and water. After drying over Na_2SO_4 and evaporation, the mixture was purified by column chromatography (1:2 EtOAc–petroleum ether). Compound **18** (4.35 g, 88%) was obtained as white crystals: mp 105 °C; $[\alpha]_D$ −37 (*c* 1.0, $CHCl_3$); R_f 0.64 (1:2 EtOAc–petroleum ether); ^{1}H NMR (CD_3COCD_3): δ 6.34 (d, 1H, $J_{NH,H\text{-}2}$ 9.9 Hz, NH), 5.93 (m, 1H, CH_2=C*H*–), 5.32–5.11 (m, 2H, CH_2=CH–), 5.04 (dd, 1H, $J_{2,3}$ 10.1 Hz, $J_{3,4}$ 9.0 Hz, H-3), 4.76 (d, 1H, $J_{1,2}$ 10.4 Hz, H-1), 4.69 (d, 1H, $J_{OH,H\text{-}4}$ 3.0 Hz, OH), 4.48 (m, 2H, CH_2=CH–CH_2–), 4.48 (dd, 1H, $J_{5,6a}$ 1.3 Hz, $J_{6a,6b}$ 11.8 Hz, H-6a), 4.18 (dd, 1H, $J_{5,6b}$ 5.8 Hz, H-6b), 3.74 (ddd, 1H, H-2), 3.63 (m, 2H, H-4,5), 2.71 (m, 2H, CH_2S), 1.28 (t, 3H, *J* 7.4 Hz, CH_3CH$_2$S), 1.21, 1.16 (m, 18H, 2 (CH_3)$_3$CO). ^{13}C NMR ($CDCl_3$): δ 179.8, 179.1 (*C*O(CH$_3$)$_3$), 155.9 (NH*C*OO), 132.7 (CH_2=*C*H–), 117.6 (*C*H_2=CH–), 84.3 (C-1), 77.3, 76.3 (C-3,5), 69.6 (C-4), 65.6 (CH_2=CH–*C*H_2–), 63.8 (C-6), 54.7 (C-2), 39.0, 38.9 (*C*(CH$_3$)$_3$), 27.2, 27.0 (C(*C*H$_3$)$_3$), 24.1 (S*C*H$_2$), 15.0 (*C*H$_3$CH$_2$S). Anal. Calcd for $C_{22}H_{37}NO_8S$ (475.59): C, 55.56; H, 7.84; N, 2.95. Found: C, 55.22; H, 7.80; N, 2.98.

1.6. Ethyl 2-allyloxycarbonylamino-2-deoxy-4,6-di-*O*-pivaloyl-1-thio-β-D-galactopyranoside (19)

Tf_2O (2 mL, 11.8 mmol) was added dropwise to a soln of **18** (4.28 g, 9.00 mmol) in 1,2-dichloroethane (70 mL) and pyridine (4.7 mL), cooled at −15 °C. After 4 h stirring at −15 °C, water (4.3 mL) was added and the mixture was heated to 80 °C for 2 h. After cooling, the mixture was diluted with CH_2Cl_2 and successively washed with 5% aq HCl, satd aq $NaHCO_3$ and water. After drying over Na_2SO_4 and evaporation, the mixture was purified by column chromatography (1:1 EtOAc–petroleum ether). Compound **19** (3.85 g, 90%) was obtained as a colourless oil: $[\alpha]_D$ −21 (*c* 1.0, $CHCl_3$); R_f 0.50 (1:1 EtOAc–petroleum ether); ^{1}H NMR ($CDCl_3$): δ 5.92 (m, 1H, CH_2=C*H*–), 5.37–5.20 (m, 2H, CH_2=CH–), 5.37 (dd, 1H, $J_{3,4}$ 3.2 Hz, $J_{4,5}$ 0.7 Hz, H-4), 5.01 (br d, 1H, $J_{NH,\ H\text{-}2}$ 7.3 Hz, NH), 4.61–4.58 (m, 3H, H-1, CH_2=CH–*C*H_2–), 4.16 (dd, 1H, $J_{5,6a}$ 7.2 Hz, $J_{6a,6b}$ 11.2 Hz, H-6a), 4.07 (dd, 1H, $J_{5,6b}$ 6.2 Hz, H-6b), 3.95 (m, 1H, H-3), 3.90 (m, 1H, H-5), 3.68 (ddd, 1H, $J_{1,2}$ 9.4 Hz, $J_{2,3}$ 10.4 Hz, H-2), 2.72 (m, 2H, SCH_2), 1.30 (t, 3H, *J* 7.4 Hz, CH_3CH$_2$S). ^{13}C NMR ($CDCl_3$): δ 178.3, 178.0 (*C*O(CH$_3$)$_3$), 157.0 (NH*C*OO), 132.5 (CH_2=*C*H–), 117.8 (*C*H_2=CH–), 83.9 (C-1), 74.8 (C-5), 72.1 (C-3), 68.9 (C-4), 66.0 (CH_2=CH–*C*H_2–), 62.1 (C-6), 53.9 (C-2), 39.3, 38.7 (*C*(CH$_3$)$_3$), 27.2, 27.1 (C(*C*H$_3$)$_3$), 24.0 (S*C*H$_2$), 14.9 (*C*H$_3$CH$_2$S). Anal. Calcd for $C_{22}H_{37}NO_8S$ (463.58): C, 55.56; H, 7.84; N, 2.95. Found: C, 55.57; H, 8.09; N, 2.85.

1.7. Ethyl 2-allyloxycarbonylamino-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-galactopyranoside (20)

Compound **19** (3.60 g, 7.57 mmol) was O-deacetylated as already described for **17** and then solubilized in

CH_3CN (50 mL). Benzaldehyde dimethylacetal (2.20 mL, 14.66 mmol) and TsOH (150 mg) were then added and the mixture was stirred at rt for 18 h. After addition of Et_3N (1 mL), the mixture was diluted with CH_2Cl_2 and washed with satd aq $NaHCO_3$, then with water. After drying over Na_2SO_4, the solvent was evaporated to dryness and the product was recrystallized twice from EtOH. Compound **20** (2.44 g, 78%) was obtained as white crystals: mp 193–194 °C (EtOH); $[\alpha]_D$ −38 (*c* 1.0, $CHCl_3$); ^1H NMR (CD_3COCD_3): δ 7.58–7.35 (m, 5H, C_6H_5), 6.32 (d, 1H, $J_{NH,H-2}$ 8.1 Hz, NH), 5.93 (m, 1H, CH_2=C*H*–), 5.66 (s, 1H, C*H*Ph), 5.30, 5.14 (m, 2H, CH_2=CH–), 4.63 (d, 1H, $J_{1,2}$ 9.3 Hz, H-1), 4.51 (m, 2H, CH_2=CH–CH_2–), 4.32 (m, 1H, H-4), 4.20 (d, 1H, $J_{5,6a}$ 1.5 Hz, $J_{6a,6b}$ 12.3 Hz, H-6a), 4.14 (dd, 1H, $J_{5,6b}$ 1.6 Hz, H-6b), 3.94 (ddd, 1H, $J_{2,3}$ 9.0 Hz, H-2), 3.90–3.82 (m, 2H, H-3, OH), 3.63 (m, 1H, H-5), 2.80 (m, 2H, CH_2S), 1.25 (t, 3H, *J* 7.4 Hz, CH_3CH_2S). Anal. Calcd for $C_{19}H_{25}NO_6S$, H_2O (413.477): C, 55.19; H, 6.58; N, 3.38. Found: C, 55.17; H, 6.70; N, 3.37.

1.8. Ethyl 2-amino-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-galactopyranoside (21)

Compound **20** (2.20 g, 5.32 mmol), dissolved in EtOH (20 mL) was refluxed in the presence of 10% aq NaOH for 10 h. After cooling to rt, the mixture was filtrated and the filter cake was washed with water (3 × 10 mL) before drying under vacuum. Compound **21** (1.59 g, 96%) was obtained as a white amorphous solid: $[\alpha]_D$ −73 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.49–7.37 (m, 5H, C_6H_5), 5.55 (s, 1H, C*H*Ph), 4.34 (dd, 1H, $J_{5,6a}$ 1.0 Hz, $J_{6a,6b}$ 12.5 Hz, H-6a), 4.27 (d, 1H, $J_{1,2}$ 9.8 Hz, H-1), 4.18 (m, 1H, H-4), 4.03 (dd, 1H, $J_{5,6b}$ 1.3 Hz, H-6b), 3.58–3.50 (m, 2H, H-3,5), 3.14 (ddd, 1H, $J_{2,3}$ 9.0 Hz, H-2), 2.79 (m, 2H, CH_2S), 1.90 (m, 3H, OH, NH_2), 1.34 (t, 3H, *J* 7.4 Hz, CH_3CH_2S). ^{13}C NMR ($CDCl_3$): δ 137.8, 129.3, 128.3, 126.5 (C_6H_5), 101.4 (*C*HPh), 86.5 (C-1), 75.0, 74.3 (C-3,5), 70.0 (C-4), 69.6 (C-6), 52.5 (C-2), 23.5 (SCH_2), 15.3 (CH_3CH_2S). Anal. Calcd for $C_{15}H_{21}NO_4S$ (311.389): C, 57.85; H, 6.79; N, 4.49. Found: C, 57.62; H, 6.87; N, 4.46.

1.9. Ethyl 2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-galactopyranoside (22)

Trifluoromethane sulfonic anhydride (1.82 mL, 10.77 mmol) was added dropwise over 30 min to a mixture of NaN_3 (3.46 g, 53.22 mmol) in water (15 mL) and CH_2Cl_2 (15 mL), cooled at 0 °C. After 2 h stirring at 0 °C, the organic layer was separated and the aq layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were then washed with satd aq $NaHCO_3$, water and finally dried over Na_2SO_4. After filtration, the resulting TfN_3 soln was added in 1 h to a mixture of compound **21** (1.55 g, 4.98 mmol) and DMAP (669 mg, 5.48 mmol) in CH_3CN (25 mL), under argon. After 16 h stirring at rt, the mixture was concentrated to 10 mL, diluted with EtOAc (150 mL) and washed with satd aq $NaHCO_3$. After drying over Na_2SO_4 and evaporation, the mixture was purified by column chromatography (3:2 EtOAc–petroleum ether). Compound **22** (1.61 g, 96%) was obtained as a white material, crystallizing on standing: mp 105–106 °C (lit.[19] 106–109 °C); $[\alpha]_D$ − 40 (*c* 1.0, $CHCl_3$, lit.[19] −45); R_f 0.50 (1:1 EtOAc–petroleum ether); ^1H NMR ($CDCl_3$): δ 7.53–7.38 (m, 5H, C_6H_5), 5.57 (s, 1H, C*H*Ph), 4.35 (dd, 1H, $J_{5,6a}$ 1.4 Hz, $J_{6a,6b}$ 12.6 Hz, H-6a), 4.31 (d, 1H, $J_{1,2}$ 9.8 Hz, H-1), 4.23 (dd, 1H, $J_{3,4}$ 3.4 Hz, $J_{4,5}$ 0.5 Hz, H-4), 4.04 (dd, 1H, $J_{5,6b}$ 1.8 Hz, H-6b), 3.68 (dd, 1H, $J_{2,3}$ 10.3 Hz, H-2), 3.65 (dd, 1H, H-3), 3.48 (m, 1H, H-5), 2.82 (m, 2H, CH_2S), 1.36 (t, 3H, *J* 7.5 Hz, CH_3CH_2S). ^{13}C NMR ($CDCl_3$): δ 137.5, 128.4, 126.5 (C_6H_5), 101.4 (*C*HPh), 83.6 (C-1), 74.7, 73.4, 69.9 (C-3,4,5), 69.2 (C-6), 63.3 (C-2), 24.1 (SCH_2), 15.0 (CH_3CH_2S).

1.10. Ethyl 3,4-di-*O*-acetyl-2-azido-2-deoxy-6-*O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranosyl)onate]-1-thio-β-D-galactopyranoside (25)

To a mixture of acceptor **13** (113 mg, 0.388 mmol), AgOTf (200 mg, 0.778 mmol) and 4 Å molecular sieves (320 mg) in THF (1.4 mL), cooled at −15 °C under argon and protected from light, was added a soln of donor **2**[23] (340 mg, 0.667 mmol) in THF (1 mL) over a 2 h period. After 1 h stirring at −15 °C, then 25 h at rt, the mixture was diluted with CH_2Cl_2 (25 mL) and washed with satd aq $NaHCO_3$. After drying over $MgSO_4$ and evaporation, the mixture was purified by column chromatography (EtOAc). Compound **24** (133 mg, 45%) was obtained as an α /β mixture that could be characterized by some of the signals in ^{13}C NMR ($CDCl_3$): δ 171.4–170.1 (CH_3CO), 169.1, 168.0 (CO_2CH_3), 98.9, 98.4 (C-2′), 84.5 (C-1), 62.7 (C-6, C-9′), 53.4, 52.9 (CO_2CH_3), 49.3, 49.2 (C-5′), 36.9, 36.1 (C-3′), 24.8, 24.6 (SCH_2CH_3), 14.9, 14.2 (SCH_2CH_3). A better identification could be realized after acetylation of compound **24** (131 mg, 0.171 mmol) in a mixture of pyridine (8 mL) and Ac_2O (2.5 mL), at rt, for 16 h. After evaporation under diminished pressure and coevaporation twice from toluene, the mixture was purified by column chromatography (EtOAc). Compound **25** (105 mg, 76%) was obtained as an α/β (3:1) mixture in which the ratio of anomers could be deducted from the ^1H NMR signals of H-1 (α-4.51, β-4.44) and H-3′eq (α-2.50, β-2.42). A small amount of the α-anomer could be separated by subsequent chromatographies, for identification purpose: ^1H NMR ($CDCl_3$); δ 5.42 (d, 1H, $J_{3,4}$ 2.8 Hz, H-4), 5.29 (m, 3H, N*H*Ac, H-7′, H-8′), 4.93

(dd, 1H, $J_{3,2}$ 10.1 Hz, H-3), 4.82 (m, 1H, H-4′), 4.51 (d, 1H, $J_{1,2}$ 10.4 Hz, H-1), 4.29 (dd, 1H, $J_{9a',8'}$ 2.2 Hz, $J_{9a',9b'}$ 12.2 Hz, H-9a′), 4.04 (m, 3H, H-5′, H-6′, H-9b′), 3.90 (m, 1H, H-5), 3.77 (m, 4H, CO_2CH_3, H-6a), 3.65 (t, 1H, H-2), 3.34 (dd, 1H, $J_{6b,6a}$ 10.3 Hz, $J_{6b,5}$ 7.3 Hz, H-6b), 2.79 (m, 2H, SCH_2CH_3), 2.50 (dd, 1H, $J_{3'eq,4'}$ 4.1 Hz, $J_{3'ax,3'eq}$, 12.6 Hz, H-3′eq), 2.21–2.00 (6 s, 18H, 6 CH_3CO), 1.87 (m, 4H, CH_3CO, H-3′ax), 1.34 (t, 3H, J 7.6 Hz, SCH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 171.2–171.0 (CH_3CO), 169.3 (CO_2CH_3, $J_{C\text{-}1',H\text{-}3'ax}$ 5.7 Hz), 100.0 (C-2′), 84.8 (C-1), 75.5 (C-5), 73.5 (C-3′), 73.0 (C-6′), 69.1 (C-4′), 68.4, 67.5 (C-7′, 8′), 67.1 (C-4), 63.4, 63.1 (C-6, C-9′), 61.0 (C-2), 53.3 (CO_2CH_3), 49.6 (C-5′), 38.2 (C-3′), 25.6 (SCH_2CH_3), 23.6–21.1 (CH_3CO), 15.4 (SCH_2CH_3).

1.11. *tert*-Butyldimethylsilyl 3-*O*-acetyl-2-azido-2-deoxy-6-*O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2- nonulopyranosyl)onate]-β-D-galactopyranoside (26)

A mixture of acceptor **14** (119 mg, 0.329 mmol) and donor **3**[24] (390 mg, 0.658 mmol) was carefully dried by azeotropic distillation from toluene and then kept under diminished pressure for 2 h, before solubilization in a mixture of CH_2Cl_2 (3.8 mL) and CH_3CN (9 mL). To this soln were added 4 Å molecular sieves (720 mg) and AgOTf (171 mg, 0.665 mmol); the mixture was then stirred overnight under argon. After cooling to −63 °C, a soln of MeSBr,[25] previously prepared by mixing dimethyldisulfide (1.4 mL) with bromine (0.8 mL) in CH_2Cl_2 (1.8 mL) and stirred under argon overnight (0.48 mL) was added dropwise (25 min) to the preceeding soln. After 6.5 h stirring at −63 °C, *N*,*N*-diisopropylethylamine (0.5 mL) was added to quench the reaction and after 30 min, the mixture was left reaching rt. After dissolution with CH_2Cl_2 and filtration on Celite, the organic extract was washed with water and dried over $MgSO_4$. After evaporation, the mixture was purified by column chromatography (EtOAc) to afford **26** contaminated with about 9% of glycal **15a** (total amount 314 mg). This mixture was diluted in CH_3CN (4.5 mL)–CCl_4 (4.5 mL) and water (7.5 mL) and vigorously stirred in the presence of $RuCl_3{\cdot}6H_2O$ (10 mg, 0.03 mmol) and $NaIO_4$ (435 mg, 2.03 mmol), for 30 min. After extraction with CH_2Cl_2 (75 mL), the organic soln was dried over $MgSO_4$, evaporated and purified by column chromato-graphy (EtOAc). Compound **26** (235 mg, 85%) was obtained as an amorphous solid: $[\alpha]_D$ −8 (*c* 1.0, $CHCl_3$); R_f 0.45 (EtOAc); ^1H NMR ($CDCl_3$): δ 5.38 (m, 1H, H-4), 5.34 (m, 1H, H-7′), 5.18 (m, 2H, N*H*Ac, H-8′), 4.87 (m, 1H, H-4′), 4.65 (dd, 1H, $J_{3,4}$ 3.1 Hz, $J_{3,2}$ 10.8 Hz, H-3), 4.58 (d, 1H, $J_{1,2}$ 7.6 Hz, H-1), 4.43 (dd, 1H, $J_{9a',8}$ 2.3 Hz, $J_{9a',9b'}$ 13.4 Hz, H-9a′), 4.06 (m, 4H, H-5′, 6′, 9b′, H-5), 3.82 (m, 4H, CO_2CH_3, H-6a), 3.66 (m, 2H, H-6b, H-2), 2.56 (dd, 1H, $J_{3'eq,4'}$ 4.6 Hz, $J_{3'eq,3'ax}$ 12.7 Hz, H-3′eq), 2.18, 2.15, 2.05, 2.04 (5 s, 15H, 5 CH_3CO), 1.89 (m, 4H, CH_3CO, H-3′ax), 0.95 (s, 9H, $SiC(CH_3)_3$), 0.18 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 171.0, 170.9, 170.4, 170.3, 170.2 (CH_3CO), 167.9 (CO_2CH_3), 98.8 (C-2′), 97.6 (C-1), 73.3, 73.0, 72.7, 69.5, 69.0, 67.4, 66.0, 63.3 (C-2, 3, 4, 5, C-4′, 6′, 7′, 8′), 62.6 (C-6, C-9′), 53.1 (CO_2CH_3), 49.3 (C-5′), 36.9 (C-3′), 25.7 ($SiC(CH_3)_3$), 23.2, 21.1, 21.0, 20.8 (CH_3CO), 18.0 ($SiC(CH_3)_3$), −4.1, −5.2 ($Si(CH_3)_2$); HRMS *m*/*z* calcd for $[C_{34}H_{54}N_4O_{18}Si + H]^+$: 835.3281. Found: 835.3290.

1.12. *tert*-Butyldimethylsilyl 3,4-di-*O*-acetyl-2-azido-2-deoxy-6-*O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl)onate]-β-D-galactopyranoside (27)

To a soln of compound **26** (235 mg, 0.281 mmol) in pyridine (13 mL) cooled at 0 °C, was added dropwise Ac_2O (4.5 mL). The mixture was left reaching rt and stirring was continued for 18 h. After evaporation and co-evaporation from toluene under diminished pressure, the mixture was diluted with CH_2Cl_2 (25 mL) and the organic soln was washed with water and satd aq NaCl before drying over $MgSO_4$, evaporation and purification was done by column chromatography (EtOAc). Compound **27** (204 mg, 83%) was obtained as an amorphous solid: $[\alpha]_D$ −22 (*c* 1.0, $CHCl_3$); R_f 0.48 (EtOAc); ^1H NMR ($CDCl_3$): δ 5.34 (m, 3H, H-4, H-7′,8′), 5.20 (d, 1H, $J_{NH,H\text{-}5'}$ 9.5 Hz, N*H*Ac), 4.86 (ddd, 1H, $J_{3'eq,4'}$ 4.4 Hz, $J_{3'ax,4'}$ 9.8 Hz, $J_{4',5'}$ 12.3 Hz, H-4′), 4.78 (dd, 1H, $J_{3,4}$ 3.5 Hz, $J_{3,2}$ 11.1 Hz, H-3), 4.65 (d, 1H, $J_{1,2}$ 7.6 Hz, H-1), 4.29 (dd, 1H, $J_{9a',8'}$ 2.5 Hz, $J_{9a',9b'}$ 12.6 Hz, H-9a′), 4.06 (m, 3H, H-5′,6′,9b′), 3.81 (m, 5H, H-5,6a, CO_2CH_3), 3.59 (dd, 1H, H-2), 3.30 (dd, 1H, $J_{6b,5}$ 9.1 Hz, $J_{6a,6b}$ 13.9 Hz, H-6b), 2.53 (dd, 1H, $J_{3'ax,3'eq}$ 12.9 Hz, H-3′eq), 2.17–2.03 (m, 21H, 7 CH_3CO), 1.89 (m, 1H, H-3′ax), 0.97 (s, 9H, $SiC(CH_3)_3$), 0.21 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 170.9, 170.6, 170.3, 170.2, 169.8, 169.5 (CH_3CO), 167.8 (CO_2CH_3, $J_{C\text{-}1',H\text{-}3'ax}$ 6.5 Hz), 98.8 (C-2′), 97.2 (C-1), 72.5, 71.9, 71.0, 68.9, 67.9, 67.1, 66.9, 63.3 (C-2,3,4,5, C-4′,6′,7′,8′), 63.2 (C-6), 62.4 (C-9′), 52.9 (CO_2CH_3), 49.4 (C-5′), 37.9 (C-3′), 25.7 ($SiC(CH_3)_3$), 23.2, 21.0, 20.9, 20.8, 20.7 (CH_3CO), 18.1 ($SiC(CH_3)_3$), −4.2, −5.2 ($Si(CH_3)_2$); HRMS *m*/*z* calcd for $[C_{36}H_{56}N_4O_{19}Si + H]^+$: 877.3386. Found: 877.3373.

1.13. 3,4-Di-*O*-acetyl-2-azido-2-deoxy-6-*O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl)onate]-D-galacto-pyranose (28)

To a soln of compound **27** (188 mg, 0.214 mmol) in THF (2.8 mL) cooled at 0 °C were added 1M Bu_4NF in THF (0.25 mL, 4.0 equiv) and AcOH (0.12 mL).

The mixture was left reaching rt and then stirred for a further 8 h. The mixture was diluted with CH_2Cl_2 (30 mL) and successively washed with water and satd aq $NaHCO_3$ before evaporation and purification by column chromatography (EtOAc). Compound **28** (115 mg, 71%) was obtained as a colourless oil: $[\alpha]_D$ −9 (*c* 1.0, $CHCl_3$, lit.[10] −14.1); R_f 0.56 (EtOAc); ^{13}C NMR ($CDCl_3$): δ 171.5–169.8 (CH_3CO), 168.2 (CO_2CH_3), 98.8 (C-2′), 96.4 (C-1β), 92.5 (C-1α), 72.6–66.8 (C-2,3,4,5, C-4′,6′,7′,8′), 63.2, 62.9 (C-6, C-9′), 52.9 (CO_2CH_3), 49.4 (C-5′), 37.7 (C-3′), 24.7–20.7 (CH_3CO).

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