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HIGHLY STEREOSELECTIVE GLYCOSYLATION OF SIALIC ACID AIDED BY STEREOCONTROLLING AUXILIARIES

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Abstract: α-Selective glycosylation of sialic acid was achieved by using a sialic acid donor which carries a stereocontrolling auxiliary such as selenide or sulfide group at *C*-3 position.

INTRODUCTION

Sialic acid-containing glycoconjugates, especially gangliosides, were revealed to play critical roles in numerous biological phenomena such as cellular recognition, oncogenesis etc.[1] Glycosylation using sialic acid-derived donors has been recognized as a most challenging task in carbohydrate chemistry for the following reasons. First, the *C*-2 carbon, on which sugar residues are to be connected, is quarternary and carries an electron withdrawing carboxylate group. Consequently, substitution reactions at that position are inevitably disfavoured sterically as well as electronically. Second, sialic acid possesses a *C*-3 deoxy structure and exists solely as a 2α (equatorial) glycoside which is less favoured in a stereoelectronic sence. Therefore, classical stereocontrolling tactics in glycoside synthesis, such as in situ anomerization or neighbouring acyloxy group participation,[2] can not be applied for this particular type of glycoside. In spite of such difficulties, reasonable success has been achieved by use of the chloride **1**[3] or the bromide **2**[4] and total syntheses of relatively simple gangliosides were reported.[5] Furthermore, recent investigation by Goto and coworkers revealed that the introduction of a hydroxy group at *C*-3, i.e. **3**, substantially improves the yield and succeeded, for the first time, in the synthesis of α-NeuAc(2→8)NeuAc derivatives.[6] However, in general, these previous methods suffer from unsatisfactory yield and, more seriously, the lack of stereoselectivity.

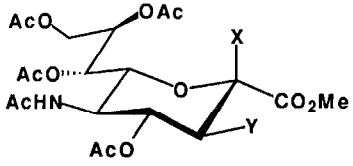
In recent years, a variety of gangliosides with multiple sialic acid residues have been identified and the biochemical importance of these molecules attracts much attention.[1c,7] Obviously, in order to pursue a synthetic approach toward such challenging structures, much improvement in this crucial operation is prerequisite. Recently we reported an efficient approach to the highly stereoselective synthesis of 2α-glycosides of sialic acid by taking advantage of the stereocontrolling nature of phenylselenyl or phenylthio substituents, which we believe to provide a general and reliable tool in ganglioside synthesis.[8] Described herein is a full account of these results.

RESULTS AND DISCUSSION

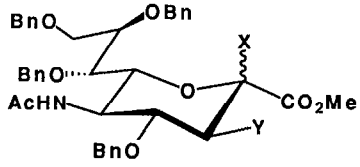
At the outset of our investigation, we presupposed the necessity to make a reasonable choice in installing a rational stereochemical bias which is supported by precedents. From this point of view we decided to investigate the methodology based on the neighbouring group participation, and our attention was focused on the stereodirecting property of a vicinal selenide or sulfide substituent, which was exemplified in recent reports on stereoselective syntheses of α- and β-2-deoxyglycosides.[9] Thus, if glycosylation is performed by using a sialic acid donor such as **4** or **5**, we would expect the reaction to give the corresponding α-glycoside in a high and predictable stereoselectivity, through the intermediacy of the episelenonium or the episulfonium ion **8**. Absolutely essential for this scenario is the stereoselective introduction of the *C*-3β substituent. This problem, although seemingly difficult, could be simplified by choosing the corresponding hemiketal as an intermediate whose *C*-3 position should be epimerizable under basic condition. Thus, thermodynamically favoured β(equatorial) isomer **6** or **7** is expected to be obtained as a major product after equilibration.

Following these considerations, we first looked into the synthesis of the fluoride **4** which carries a phenylselenyl group as a stereocontrolling auxiliary. The synthesis was started from the 2,3-dehydro derivative **9a** which in turn was synthesized from the known tetraacetate **10**[6d] via carboxylic acid **9b**. In order to functionalize the *C*-2 and *C*-3 positions properly, phenylselenyl acetate ($PhSeOCOCH_3$)[10] was chosen as an electrophile, which was generated *in situ* from phenylselenyl chloride and silver acetate. The reaction proceeded smoothly in the presence of catalytic trimethylsilyl triflate[11] to afford a mixture of products **11**, **12**, and **6**, in which axial adducts far predominates over equatorial one (**11**+**12**:**6**=11:1). Treatment of these, as a mixture, with sodium methoxide caused deacetylation as well as epimerization at *C*-3 to afford a 2:1 mixture of **6** and **12** which was readily separated by silica gel chromatography. After recycling of recovered **12** twice, the key intermediate **6**, with the desired configuration and functionality, was obtained in an 83% overall yield from **9a**. Subsequent conversion to the fluoride **4** (α:β≥20:1) was easily achieved by the action of DAST (diethylaminosulfur trifluoride)[12] at -40°C.

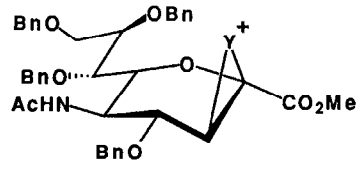
Glycosylation was carried out in the presence of silver triflate and tin(II)chloride[13], with primary and secondary alcohols **17**[14], **18**[15] and **19**[16] as glycosyl acceptors, to afford the corresponding α-glycosides **21**, **25**, **29a** and **29b** stereoselectively (Table 1). The yield turned out to be quite dependent on the polarity of the media and, as far as we examined, carbon tetrachloride gave the most favourable result (entry 1-4). The only isolable by-product was the 2,3-dehydro derivative **9a** which can be recycled. Besides the aforementioned Ag(I)-Sn(II) combination, tin(II)triflate[17] and tri-n-butyltin triflate[18] were also found to be effective as promoters, although the formation of a minor amount of the β-glycoside **32** was observed (entry 5,6). This complication presumably originates from a sequential elimination-addition process of cationic selenium species such as phenylselenyl triflate[19]. The phenylselenyl group of the products was removed smoothly by tin hydride reduction to afford **22**, **26** and **33**. These were further converted to **23**[4], **27** and **30**[16b], respectively, which gave the unambiguous confirmation of the stereochemistry. On the other hand, the diastereomeric fluoride **13** derived



	X	Y
1	Cl	H
2	Br	H
3	Br	OH



	X	Y
4	F	SePh
5a	F	SPh
b	Cl	SPh
c	Br	SPh
6	OH	SePh
7	OH	SPh



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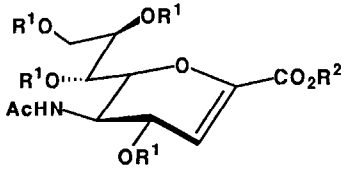
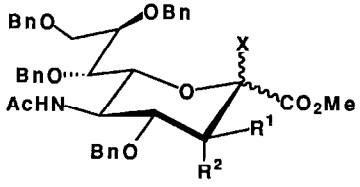
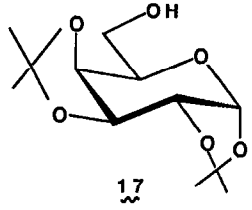
Y = SePh, SPh



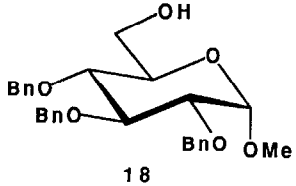
	R^1	R^2
9a	Bn	Me
b	Bn	H
10	Ac	Me



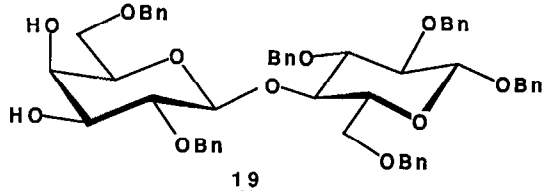
	R^1	R^2	X
11	H	SePh	OAc
12	H	SePh	OH
13	H	SePh	F
14	H	Br	OH
15	Br	H	OH
16	H	SPh	OH



17



18



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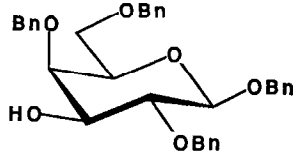

20

21 Bn SePh
22 Bn H
23 Ac H
24 Bn SPh
25 Bn SePh
26 Bn H
27 Ac H
28 Bn SPh
29a Bn Me SePh
30 H H H
31a Bn Me SPh
32
34 Bn Me SPh
35 Bn Me H
36 H H H
29b Y = SePh
31b Y = SPh
33

from **12** was subjected to glycosylation with **17** and the β-glycoside **32** was obtained stereoselectively in a high yield (entry 7).

The results described above, which present the first complete stereochemical control in sialic acid glycosylation, demonstrate that our initial proposal is principally adequate. However, the yield was not always satisfactory, especially when the secondary alcohol **19** was used as a glycosyl acceptor. This is largely caused by the predominant formation of **9a**, as a result of the elimination of phenylselenyl cation. This unpleasant tendency was attenuated by changing the *C*-3 substituent to a sulfide group, which was expected to be less prone to leave as a cationic species based on consideration of the relative polarizability.

Table 1 Reactions of fluorides **4** and **13** with alcohols

entry[a]	fluoride	alcohol(equiv)	promoter[b]	solvent	temp,time	products yield(%)		
						21	**32**	**9a**
1	4	**17** (1.5)	A	$(ClCH_2)_2$	r.t., 5h	18	_	69
2	4	**17** (1.5)	A	toluene	r.t., 18h	34	_	60
3	4	**17** (1.5)	A	CCl_4	r.t., 18h	46	_	33
4	4	**17** (1.5)	A	Et_2O	r.t., 18h	5	_	82
5	4	**17** (1.6)	B	CCl_4	r.t., 4h	45	5	43
6	4	**17** (1.6)	C	CCl_4	r.t., 16h	42	21	20
7	**13**	**17** (1.2)	A	$(ClCH_2)_2$	r.t., 1h	-	82	-
						25		**9a**
8	**4**	**18** (2.0)	A	CCl_4	r.t., 3h	72		19
						29a	**29b**	**9a**
9	4	**19**(2.1)	A	CCl_4	r.t., 18h	20	5	68

a) All reactions were carried out under an atmosphere of dry nitrogen in the presence of molecular sieves 4A. b) A: AgOTf-$SnCl_2$, B: $Sn(OTf)_2$, C: n-Bu_3SnOTf.

Following this analysis, we decided to investigate the 2-halo-3β-phenylthio derivative **5** as a sialic acid donor. The immediate precursor **7** was synthesized as described below, again starting from compound **9a**. At first, **9a** was treated with *N*-bromosuccinimide[6d] to afford a mixture of bromohydrins **14** and **15** (97%, **14**:**15**=4.1:1). The modest stereoselectivity was proved to be of little consequence, since both diastereomeres could be converted into **7** as follows. The diaxial isomer **14** was treated with thiophenol in the presence of base and the resultant 3α-sulfide **16** was immediately treated with DBU. The epimerization proceeded with remarkable ease and **7** was obtained in an 83% yield from **14**. On the other hand, the equatorial isomer **15** directly afforded **8** on treatment with thiophenol. As a result, **9a** could be transformed into the key intermediate **7** in a 73% overall yield. Hemiketal **7** was further converted to the fluoride **5a** [DAST; 96%, α:β=2:1], the chloride **5b** [$(Me_2N)_3P$, CCl_4; 99%] and the bromide **5c** [$(Me_2N)_3P$, CBr_4; 97%], all of which were reasonably stable to endure chromatographic purification on silica gel.

These halides were then subjected to glycosylation under typical reaction conditions, namely $AgOSO_2CF_3$-$SnCl_2$ for **5a**, $AgOSO_2CF_3$ for **5b** and $Hg(CN)_2$-$HgBr_2$ for **5b** and **5c**. As glycosyl acceptors, compounds **17**, **18**, **19** and **20**[20] were examined and the results are summarized in Table 2. All reactions proceeded stereoselectively, giving α-glycosides **24**, **28**, **31a** and **34** as the major products. In accordance with our expectation, substantially higher yields were obtained by adopting a phenylthio group as a *C*-3 auxiliary. The bromide **5c** served best in terms of both

yield and selectivity. The most gratifying was the reaction with the lactose derivative **19** (entry 10). The product **31a**, which represents the common trisaccharide unit of various gangliosides[5a)5b)], was obtained in a yield as high as 78% under almost complete stereo- and regiochemical control. Also remarkable is that even the severely congested galactose derivative **20** could be attached stereoselectively, albeit in a modest yield (entry 11).

Table 2 Reactions of **5a**, **5b** and **5c** with alcohols

entry[a)]	halide[b)]	alcohol[b)]	promoter[e)]	solvent	temp(°C)	time(h)	product	yield[f)]	α : β[h)]
1	**5a**[c)]	**17**	A	Et_2O	20	18	**24**	56%[g)]	7 : 1
2	**5a**[c)]	**17**	A	$(ClCH_2)_2$	20	18	**24**	58%[g)]	20 : 1
3	**5a**[c)]	**17**	A	CCl_4	20	18	**24**	72%[g)]	20 : 1
4	**5a**[d)]	**19**	A	CCl_4	20	18	**31a**	45%	3.5: 1
							31b	5%	i)
5	**5b**	**17**	B	CCl_4	20	18	**24**	52%	i)
6	**5b**	**17**	C	CCl_4	30	72	**24**	46%	i)
7	**5b**	**18**	C	CCl_4	40	40	**28**	71%	i)
8	**5b**	**19**	C	CCl_4	40	40	**31a**	64%	30 : 1
							31b	2%	i)
9	**5c**	**17**	C	CCl_4	20	18	**24**	72%	i)
10	**5c**	**19**	C	CCl_4	20	18	**31a**	78%	i)
							31b	2%	i)
11	**5c**	**20**	C	CCl_4	20	18	**34**	24%	i)

a) All reactions were carried out under an atmosphere of dry nitrogen in the presence of molecular sieves 4A. b) Molar ratio of halide: acceptor was 1:1.6. c) An anomeric mixture (α:β=2:1) was used. d) Pure α-anomer was used. e) A: AgOTf (2.0 equiv)-$SnCl_2$ (2.0 equiv). B: AgOTf (2.0 equiv). C: $Hg(CN)_2$(1.6 equiv)-$HgBr_2$(0.5 equiv). f) Based on used halides except in entry 1~3. g) Yields were based on consumed **3**. h) Determined by individual isomer separation. i) Corresponding β-isomers could not be detected.

The sulfide groups of the products were removed reductively (Ph_3SnH, AIBN) to afford **22**, **26**, **33** and **35**. The stereochemistry of compounds **22**, **26** and **33** was confirmed already (*vide supra*) while compound **35** was fully deprotected to **36** which was reported previously[5c)].

The results described here clearly demonstrate the practicality of the strategy based on stereocontrolling auxiliaries. The versatility of the present method in ganglioside synthesis is obvious and the synthetic study along this line is under current investigations.

EXPERIMENTAL

General. — Melting points were determined with a Büchi 510 melting point apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer Model 241 MC polarimeter, for solutions in $CHCl_3$ at 20±3°C. Column chromatography was performed on columns of Silica Gel (Merck, 70-230 mesh). Flash chromatography was performed on columns of Wako Gel C-300 (200-300 mesh). Analytical TLC was performed on Silica Gel $60F_{254}$ (Merck, Darmstadt). Preparative TLC was performed on 20cm x 20cm plates coated with 0.5mm thickness of Silica Gel $60F_{254}$ (Merck, Darmstadt). ^1H NMR spectra were measured on a JNM-GX400 (400 MHz), a JNM-GX500 (500 MHz), or a JNM-FX90Q (90 MHz) spectrometer, in solutions of $CDCl_3$, unless noted otherwise. The values of δ are expressed in ppm downfield from the signal for internal Me_4Si. All reactions except hydrogenation were carried out under an atmosphere of nitrogen. 1,2-Dichloroethane, carbon tetrachloride and *t*-butanol were distilled from CaH_2. DMSO was distilled under reduced pressure in the presence of CaH_2. Toluene and THF were distilled from sodium benzophenone ketyl. Ether was distilled from $LiAlH_4$. Methanol was distilled from $Mg(OMe)_2$. Carbon tetrabromide was recrystallized from n-hexane. All other solvents and reagents were used as received.

5-Acetamido-4,7,8,9-tetra-*O*-benzyl-2,3-dehydro-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonic acid 9b. A mixture of compound **10** (1.649 g, 3.49 mmol) and 0.1 M methanolic sodium methoxide (5 ml, 0.5 mmol) in methanol (50 ml) was stirred at room temperature for 3 h. The resulting mixture was neutralized with Amberlyst A-15 resin and diluted with water (50 ml). The resin was filtered off and the filtrate was concentrated *in vacuo* to afford the tetraol (1.05 g) as a white powder, which was dissolved in DMSO (20 ml). To the solution, with stirring, were added successively benzyl bromide (4.8 ml, 40 mmol), barium oxide (3.05 g, 19.9 mmol), tetra-n-butylammonium iodide (70 mg, 0.19 mmol) and potassium hydroxide (2.23 g, 39.7 mmol). After stirring at room temperature for 18 h, methanol (4 ml) was added and the mixture was stirred for additional 30 min. The resulting mixture was diluted with ether (100 ml) and water (100 ml) and acidified with 2N hydrochloric acid. Layers were separated and the aqueous layer was extracted with ether (150 ml x 2). The combined organic layers were washed successively with water (200 ml) and brine (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography on silica gel in 15:10:1 n-hexane-ethyl acetate-acetic acid to afford compound **9b** (1.770 g, 79%); m.p. 126-128°C, $[\alpha]_D$ -7.7° (c 1.0), Rf 0.42 in 10:10:1 n-hexane-ethyl acetate-acetic acid; ^1H NMR (90 MHz) δ 6.19 (d, 1 H, 3.5 Hz, H-3), 5.24 (d, 1 H, 7.2 Hz, NH), 1.72 (s, 3 H, NH).

Anal. Calc. for $C_{39}H_{41}NO_8$: C, 71.87; H, 6.34; N, 2.15. Found: C, 71.58; H, 6.31; N, 2.14.

Methyl 5-acetamido-4,7,8,9-tetra-*O*-benzyl-2,3-dehydro-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonate 9a. Compound **9b** (3.272 g, 5.02 mmol) was treated at 0°C with ethereal diazomethane in ether-methanol (3:1, 40 ml). Excess diazomethane was destroyed with acetic acid and the mixture was concentrated *in vacuo*. Chromatography of the residue on silica gel in 3:2 n-hexane-ethyl acetate afforded compound **9a** (3.198 g, 96%); $[\alpha]_D$ -3.3° (c 1.0); Rf 0.27 in 3:2 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 6.135 (d, 1 H, 4.2 Hz, H-3), 5.164 (d, 1 H, 7.6 Hz, NH), 4.152 (dd, 1 H, 5.6, 4.6 Hz, H-7), 3.979 (ddd, 1 H, 5.4, 4.6, 4.4 Hz, H-8), 3.905 (dd, 1 H, 10.0, 5.4 Hz, H-9), 3.770 (s, 3 H, CO_2Me), 3.705 (dd, 1 H, 10.0, 4.4 Hz, H-9'), 1.736 (s, 3 H, Ac).

Anal. Calc. for $C_{40}H_{43}NO_8$: C, 72.16; H, 6.51; N, 2.10. Found: C, 71.91; H, 6.52; N, 2.05.

Methyl 5-Acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-phenylseleno-D-*erythro*-β-L-*gluco*-2-nonulopyranosonate 6 and its diastereomer 12. To a stirred solution of PhSeCl (48 mg, 0.25 mmol) in 1,2-dichloroethane (0.5 ml) was added $AgOCOCH_3$ (42 mg, 0.25 mmol) at 0°C. The mixture was stirred at room temperature for 15 min and cooled down to 0°C again. To the suspension were added successively a solution of compound **9a** (60.5 mg, 0.0906 mmol) in 1,2-dichloroethane (1.5 ml) and trimethylsilyl triflate (3 μl, 0.02 mmol). The mixture was stirred at 0°C for 30 min and diluted with ethyl acetate (20 ml). Aq $NaHCO_3$ (20 ml) was added and the mixture was filtered through Celite. The filtrate was extracted with ethyl acetate (20 ml x 2) and the combined organic layers were washed with brine (20 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography of the residue on silica gel in 2:1 n-hexane-ethyl acetate afforded compound **11** (63.1 mg, 79%); Rf 0.34 in 3:2 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 3.884 (d, 1 H, 4.2 Hz, H-3), 3.785 (s, 3 H, CO_2Me), 1.742 (s, 3 H, Ac), 1.685 (s, 3 H, Ac); together with hemiketals **12** (8.6 mg, 11%) and **6** (6.5 mg, 9%).

In a separate run of the reaction, 670.5 mg (1.01 mmol) of compound **9a** afforded a mixture of products **11**, **12** and **6** (849.5 mg) which was, without separation, treated with 0.1 M methanolic sodium methoxide (4 ml, 0.4 mmol) in methanol (10 ml) at room temperature for 20 h. Acetic acid (0.1 ml) was added and the mixture was concentrated *in vacuo*. The residue was separated by chromatography on silica gel in 3:2 n-hexane-ethyl acetate to afford **6** (522.5 mg, 62%) and **12** (272.5 mg, 32%).

6: m.p. 103-105°C; $[\alpha]_D$ -0.5° (c 1.0); Rf 0.41 in 3:2 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 4.883 (d, 1 H, 9.5 Hz, NH), 4.425 (dd, 1 H, 9.8, 1.5 Hz, H-6), 4.172 (ddd, 1 H, J 9.8, 9.5 Hz, H-5), 4.129 (d, 1 H, 1.5 Hz, OH), 4.035 (dd, 1 H, 10.7, 9.8 Hz, H-4), 3.769 (dd, 1 H, 9.3, 1.5 Hz, H-7), 3.759 (dd, 1 H, 10.5, 2.2 Hz, H-9), 3.697 (ddd, 1 H, 9.3, 3.2, 2.2 Hz, H-8), 3.629 (s, 3 H, CO_2Me), 3.628 (dd, 1 H, 10.5, 3.2 Hz, H-9'), 3.590 (dd, 1 H, 10.7, 1.5 Hz, H-3), 1.723 (s, 3 H, Ac).

Anal. Calc. for $C_{46}H_{49}NO_9Se$: C, 65.86; H, 5.89; N, 1.67. Found: C, 65.74; H, 5.96; N, 1.69.

12: Rf 0.19 in 3:2 n-hexane-ethylacetate; ^1H NMR (400 MHz) δ 4.347 (dd, 1 H, 9.6, 3.9 Hz, H-4), 4.259 (dd, 1 H, 10.5, 1.7 Hz, H-6), 4.087 (ddd, 1 H, 10.5, 9.6, 8.5 Hz, H-5), 3.966 (ddd, 1 H, 8.5, 3.7, 2.2 Hz, H-8), 3.928 (dd, 1 H, 10.5, 2.2 Hz, H-9), 3.883 (d, 1 H, 3.9 Hz, H-3), 3.762 (s, 3 H, CO_2Me), 3.718 (dd, 1 H, 10.5, 3.7 Hz, H-9'), 1.744 (s, 3 H, Ac).

Anal. Calc. for $C_{46}H_{49}NO_9Se$: C, 65.86; H, 5.89; N, 1.67. Found: C, 65.69; H, 6.19; N, 1.53.

Compound **12** was equilibrated twice with sodium methoxide under the same condition as above to afford additional **6**. Total yield of **6** was 703.6 mg (83%).

Methyl 5-acetamido-4,7,8,9-tetra-*O*-benzyl-2,3,5-trideoxy-2-fluoro-3-phenylseleno-D-*erythro*-α-L-*gluco*-2-nonulopyranosoate 4. To a stirred solution of compound **6** (289.3 mg, 0.345 mmol) in 2:1 toluene-1,2-dichloroethane (3 ml) was added diethylaminosulfur trifluoride (0.42 ml, 3.4 mmol) at -40°C. The mixture was stirred at -40°C for 3 h and at room temperature for 1 h. Aq $NaHCO_3$ (5 ml) was added carefully and the mixture was diluted with ethyl acetate (30 ml) and washed with water (20 ml). The aqueous layer was extracted with ethyl acetate (30 ml) and the combined organic layers were washed with brine (30 ml) dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography of the residue on silica gel in 3:2 n-hexane-ethyl acetate afforded the fluoride **4** (254.6 mg, 88%) with more than 95% anomeric purity; Rf 0.43 in 3:2 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 4.458 (d, 1 H, 10.7 Hz, NH), 4.436 (dd, 1 H, 9.8, 9.2 Hz, H-4), 3.868 (ddd, 1 H, 10.7, 10.4, 9.2 Hz, H-5), 3.830 (ddd, 1 H, 8.3, 2.9, 2.7 Hz, H-8), 3.770 (dd, 1 H, 10.4, 1.7 Hz, H-6), 3.643 (s, 3 H, CO_2Me), 3.337 (dd, 1 H, 13.4, 9.8 Hz, H-3), 1.642 (s, 3 H, Ac).

***O*-[Methyl(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-phenylseleno-D-*erythro*-α-L-*gluco*-2-nonulopyranosyl)onate]-(2→6)-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose 21.**

Method A: To a stirred mixture of $AgOSO_2CF_3$ (30 mg, 0.12 mmol), $SnCl_2$ (22 mg, 0.12 mmol) and molecular sieves 4A (0.12 g) in carbon tetrachloride (0.5 ml) was added dropwise a solution of compounds **4** (61.9 mg, 0.0736 mmol) and **17** (31 mg, 0.12 mmol) in carbon tetrachloride (4 ml) at -20°C. The mixture was stirred at -20°C for 30 min, at 0°C for 30 min and at room temperature for 2 h and diluted with ethyl acetate (30 ml). Aq $NaHCO_3$ (5 ml) was added and the suspension was stirred for 10 min and filtered through Celite. The filtrate was washed with water (30 ml) and the aqueous layer was extracted with ethyl acetate (30 ml). The combined organic layers were washed with brine (30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography of the residue on silica gel in 3:2 n-hexane-ethyl acetate afforded the disaccharide **21** (37.0 mg, 46%) together with **9a** (16.1 mg, 33%).

21: $[\alpha]_D$ -2.6° (c 1.1); Rf 0.35 in 3:2 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 5.480 (d, 1 H, 4.9 Hz, H-1a), 4.493 (d, 1 H, 7.8, 2.4 Hz, H-3a), 4.146 (dd, 1 H, 7.9, 1.8 Hz, H-4a), 3.632 (s, 3 H, CO_2Me), 3.209 (d, 1 H, 10.7 Hz, H-3b), 1.593 (s, 3 H, Ac).

Anal. Calc. for $C_{58}H_{67}NO_{14}Se$: C, 64.44; H, 6.25; N, 1.30. Found: C, 64.47; H, 6.36; N, 1.26.

Method B: To a stirred mixture of $Sn(OSO_2CF_3)_2$ (20 mg, 0.048 mmol) and molecular sieves 4A (80 mg) in carbon tetrachloride (0.2 ml) was added a solution of compounds **4** (22.5 mg, 0.0268 mmol) and **17** (11 mg, 0.042 mmol) in carbon tetrachloride (0.8 ml) at 0°C. The mixture was stirred at 0°C for 4 h and at room temperature for 18 h. Work-up and chromatographic separation as described in **Method A** afforded a 10:1 mixture of compounds **21** and **32** (14.5 mg, 50%) together with **9a** (7.6 mg, 43%).

Method C: To a stirred mixture of compounds **4** (24.3 mg, 0.0289 mmol) and **17** (12 mg, 0.046 mmol) and molecular sieves 4A (80 mg) in carbon tetrachloride (2 ml) was added a solution of n-$Bu_3SnOSO_2CF_3$ (18 mg, 0.040 mmol) in carbon tetrachloride (0.2 ml) at 0°C. After stirring at room temperature for 16 h, work-up and chromatographic separation afforded a 2:1 mixture of compounds **21** and **32** (19.6 mg, 63%) together with **9a** (3.8 mg, 20%).

Methyl *O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-phenylseleno-D-*erythro*-α-L-*gluco*-2-nonulopyranosyl)onate]-(2→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 25. Compound **4** (50.2 mg, 0.0597 mmol) was reacted with **18** (59 mg, 0.13 mmol) in a same manner as described for the preparation of compound **21** (**Method A**). Chromatographic separation on silica gel in 3:2 n-hexane-ethyl acetate afforded the disaccharide **25** (55.3 mg, 72%) together with **9a** (7.7 mg, 19%).

25: $[\alpha]_D$ +21.1° (c 0.9); Rf 0.35 in 3:2 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 4.577 (d, 1 H, 3.7 Hz, H-1a), 4.313 (dd, 1 H, 9.5, 9.5 Hz, H-3a), 4.230 (dd, 1 H, 11.0, 2.0 Hz, H-6b), 4.051 (dd, 1 H, 10.5, 2.0 Hz, H-6a), 3.997 (dd, 1 H, 10.5, 4.6 Hz, H-6a'), 3.884 (t, 1 H, 9.3 Hz, H-4b), 3.817 (ddd, 1 H, 7.6, 4.0, 2.0 Hz, H-8b), 3.703 (dd, 1 H, 10.7, 2.0 Hz, H-9b), 3.662 (dd, 1 H, 7.6, 2.0 Hz, H-7b), 3.605 (s, 3 H, CO_2Me), 3.447 (dd, 1 H, 10.7, 4.0 Hz, H-9b'), 3.347 (dd, 1 H, 9.5, 3.4 Hz, H-2a), 3.340 (dd, 1 H, 9.5, 9.3 Hz, H-4a), 3.281 (s, 3 H, OMe), 3.231 (d, 1 H, 9.3 Hz, H-3b), 1.556 (s, 3 H, Ac).

Anal. Calc. for $C_{74}H_{79}NO_{14}Se$: C, 69.15; H, 6.19; N, 1.09. Found: C, 68.81; H, 6.21; N, 1.12.

Benzyl *O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-phenylseleno-D-*erythro*-α-L-*gluco*-2-nonulopyranosyl)onate]-(2→3)-*O*-(2,6-di-*O*-benzyl-β-D-

galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside 29a and its regioisomer 29b. To a stirred mixture of $AgOSO_2CF_3$ (47 mg, 0.18 mmol), $SnCl_2$ (35 mg, 0.18 mmol) and molecular sieves 4A (150 mg) in carbon tetrachloride (1 ml) was added a solution of compounds **4** (95.9 mg, 0.114 mmol) and **19** (201 mg, 0.228 mmol) in carbon tetrachloride (4 ml) at 0°C. The mixture was stirred at 0°C for 30 min and at room temperature for 18 h. After work-up as described for the preparation of compound **21**, chromatographic separation on silica gel in 3:1 toluene-ethyl acetate and repurification on preparative TLC in 1:1 n-hexane-ethyl acetate afforded regioisomeric trisaccharides **29a** (39.4 mg, 20%) and **29b** (9.9 mg, 5%) together with **9a** (51.8 mg, 68%).

29a: $[\alpha]_D$ +7.1° (c 0.8); Rf 0.29 in 3:2 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 3.579 (s, 3 H, CO_2Me), 3.281 (d, 1 H, 10.3 Hz, H-3c), 1.646 (s, 3 H, Ac).

Anal. Calc. for $C_{100}H_{105}NO_{19}Se$: C, 70.49; H, 6.21; N, 0.82. Found: C, 70.41; H, 6.24; N, 0.85.

29b: Rf 0.25 in 3:2 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 3.472(s, 3 H, CO_2Me), 3.211 (d, 1 H, 11.2 Hz, H-3c), 1.627 (s, 3 H, Ac).

Compound **29b** was fully characterized as corresponding C-3b acetate; $[\alpha]_D$ +17.3° (c 0.4); Rf 0.32 in 3:2 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 4.462 (dd, 1 H, 10.4, 3.7 Hz, H-3b), 4.001 (dd, 1 H, 10.4, 1.5 Hz, H-6c), 3.428 (s, 3 H, CO_2Me), 1.854 (s, 3 H, Ac), 1.540 (s, 3 H, Ac).

Anal. Calc. for $C_{102}H_{107}NO_{20}Se$: C, 70.17; H, 6.18; N, 0.80. Found: C, 69.86; H, 6.33; N, 0.78.

***O*-[Methyl(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl)onate]-(2→6)-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose 22.** A solution of compound **21** (22.8 mg, 0.0211 mmol), n-Bu_3SnH (12 μl, 0.045 mmol) and AIBN (1 mg, 6 μmol) in toluene (1 ml) was heated under reflux for 15 min. The mixture was concentrated *in vacuo* and the residue was purified by chromatography on silica gel in 3:2 n-hexane-ethyl acetate to afford compound **22** (15.9 mg, 82%); $[\alpha]_D$ -29.8° (c 1.2); Rf 0.32 in 2:1 toluene-ethyl acetate; ^1H NMR (400 MHz) δ 5.479 (d, 1 H, 4.9 Hz, H-1a), 4.560 (dd, 1 H, 7.8, 2.4 Hz, H-3a), 4.273 (dd, 1 H, 4.9, 2.4 Hz, H-2a), 4.239 (dd, 1 H, 7.8, 1.5 Hz, H-4a), 4.122 (dd, 1 H, 10.7, 1.7 Hz, H-6b), 3.955 (ddd, 1 H, 7.0, 4.3, 1.7 Hz, H-8b), 3.803 (ddd, 1 H, 10.5, 10.0, 8.8 Hz, H-5b), 3.642 (s, 3 H, CO_2Me), 2.790 (dd, 1 H, 12.5, 4.3 Hz, H-3beq), 1.760 (s, 3 H, Ac), 1.745 (dd, 1 H, 12.5, 11.9 Hz, H-3bax).

Anal. Calc. for $C_{52}H_{63}NO_{14}$: C, 67.44; H, 6.86; N, 1.51. Found: C, 67.50; H, 7.06; N, 1.46.

Methyl *O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl)onate]-(2→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 26. Compound **25** (23.0 mg, 0.0179 mmol) was treated with n-Bu_3SnH (11 μl, 0.041 mmol) and AIBN (1 mg, 6 μmol) in toluene (1 ml) under reflux for 2 h. The mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel in 3:2 n-hexane-ethyl acetate to afford **26** (14.3 mg, 71%); $[\alpha]_D$ +2.2° (c 1.0); Rf 0.19 in 3:2 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 4.565 (d, 1 H, 3.7 Hz, H-1a), 4.074 (dd, 1 H, 10.5, 1.5 Hz, H-6b), 3.642 (s, 3 H, CO_2Me), 3.500 (dd, 1 H, 9.3, 3.7 Hz, H-2a), 3.336 (s, 3 H, OMe), 2.835 (dd, 1 H, 12.5, 4.2 Hz, H-3beq), 1.771 (s, 3 H, Ac), 1.758 (dd, 1 H, 12.5, 12.0 Hz, H-3bax).

Anal. Calc. for $C_{68}H_{75}NO_{14}$: C, 72.26; H, 6.69; N, 1.24. Found: C, 72.11; H, 6.79; N, 1.24.

Benzyl *O*-(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→3)-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside-(1c→4b)-lactone 33. A solution of compound **29a** (19.8 mg, 0.0116 mmol), Ph_3SnH (10 mg, 0.208 mmol) and AIBN (1 mg, 6 μmol) in toluene (1 ml) was heated under reflux for 1 h and concentrated *in vacuo*. Chromatography of the residue on silica gel in 4:1 toluene-ethyl acetate afforded **33** (17.0 mg, 96%); $[\alpha]_D$ +2.3° (c 0.7); Rf 0.44 in 3:1 toluene-ethyl acetate; ^1H NMR (400 MHz) δ 5.139 (d, 1 H, 3.9 Hz, H-4b), 4.804 (d, 1 H, 9.8 Hz, NH), 4.492 (d, 1 H, 7.8 Hz, H-1b or 1a), 4.353 (d, 1 H, 7.8 Hz, H-1a or 1b), 2.285 (dd, 1 H, 13.4, 5.4 Hz, H-3beq), 1.780 (dd, 1 H, 13.4, 10.9 Hz, H-3bax), 1.771 (s, 3 H, Ac).

Anal. Calc. for $C_{93}H_{97}NO_{18}\cdot H_2O$: C, 72.78; H, 6.37; N, 0.91. Found: C, 72.74; H, 6.46; N, 0.91.

***O*-[Methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl)onate]-(2→6)-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose 23.** Compound **22** (11.2 mg, 0.0121 mmol) in methanol (1 ml) was hydrogenated under atmospheric pressure at 50°C in the presence of 10% Pd/C (18 mg). After 4 h, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in pyridine-acetic anhydride (3:1, 0.4 ml) containing 4-DMAP (1 mg) and the mixture was stirred at room temperature for 3 h and concentrated *in vacuo*. Chromatography of the residue on silica gel in

2:1 toluene-acetone afforded **23** (8.0 mg, 92%); Rf 0.29 in 2:1 toluene-acetone. ^{1}H NMR (400 MHz, C_6D_6) of compound **23** was in good agreement with the data reported by Paulsen et al[4].

Methyl *O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosyl)onate]-(2→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside 27. Compound **26** (19.5 mg, 0.0173 mmol) was debenzylated and acetylated as described for the preparation of **23**. Chromatographic purification on silica gel in 1:1 toluene-acetone afforded **27** (13.4 mg, 98%); Rf 0.51 in 1:1 toluene-acetone; ^{1}H NMR (400 MHz) δ 5.436 (dd, 1 H, 10.0, 9.8 Hz, H-3a), 5.346 (ddd, 1 H, 9.0, 5.6, 2.4 Hz, H-8b), 5.297 (dd, 1 H, 9.0, 1.7 Hz, H-7b), 5.166 (t, 1 H, 9.8 Hz, H-4a), 4.937 (d, 1 H, 3.7 Hz, H-1a), 4.882 (dd, 1 H, 10.0, 3.7 Hz, H-2a), 4.876 (ddd, 1 H, 12.2, 10.0, 4.8 Hz, H-4b), 4.260 (dd, 1 H, 12.5, 2.4 Hz, H-9b), 4.049 (dd, 1 H, 12.5, 5.6 Hz, H-9b'), 3.807 (s, 3 H, CO_2Me), 3.384 (s, 3 H, OMe), 2.624 (dd, 1 H, 12.8, 4.8 Hz, H-3beq), 1.978 (dd, 1 H, 12.8, 12.2 Hz, H-3bax).

***O*-(5-acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→3)-*O*-(β-D-galactopyranosyl)-(1→4)-D-glucopyranose 30.** To a solution of compound **33** (14.5 mg, 0.00956 mmol) in dioxane (1 ml) and water (0.3 ml) was added 1.25 N aq LiOH (0.3 ml). The mixture was stirred at room temperature for 20 h, diluted with water (10 ml), acidified with 0.5 N HCl and extracted with ethyl acetate (20 ml x 2). The combined organic layers were washed with brine (20 ml x 2), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in methanol (1 ml) and hydrogenated in the presence of 10% Pd/C (12 mg) under atmospheric pressure at 50°C for 5 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in 0.03 N NaOH (0.5 ml) and chromatographed on Cephadex G-25 in water to afford **30** (6.0 mg, 98%) as a sodium salt, whose ^{1}H NMR data was identical with the one reported before.

Methyl 5-acetamido-4,7,8,9-tetra-*O*-benzyl-2,3,5-trideoxy-2-fluoro-3-(phenylseleno)-D-*erythro*-β-L-*manno*-2-nonulopyranosonate 13. To a stirred solution of **12** (12.9 mg, 0.0154 mmol) in THF (0.5 ml) was added diethylaminosulfur trifluoride (20 μl, 0.16 mmol) at -20°C and the mixture was stirred at -20°C for 30 min. After work-up as described for the preparation of **4**, purification on preparative TLC in 2:1 n-hexane-ethyl acetate afforded **13** (9.0 mg, 70%); Rf 0.38 in 1:1 n-hexane-ethyl acetate; ^{1}H NMR (400 MHz) δ 4.450 (dd, 1 H, 10.5, 1.5 Hz, H-6), 4.356 (dd, 1 H, 10.3, 4.2 Hz, H-4), 3.946 (ddd, 1 H, 8.6, 3.7, 2.6 Hz, H-8), 3.812 (s, 3 H, CO_2Me), 3.809 (dd, 1 H, 8.6, 1.5 Hz, H-7), 3.800 (dd, 1 H, 10.7, 2.6 Hz, H-9), 3.682 (dd, 1 H, 10.7, 3.7 Hz, H-9'), 1.772 (s, 3 H, Ac).

***O*-[Methyl(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-phenylseleno-D-*erythro*-β-L-*manno*-2-nonulopyranosyl)onate]-(2→6)-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose 32.** To a stirred mixture of $AgOSO_2CF_3$ (8 mg, 0.03 mmol), $SnCl_2$ (6 mg, 0.03 mmol) and molecular sieves 4A (80 mg) in 1,2-dichloroethane was added a solution of compounds **13** (13.1 mg, 0.0156 mmol) and **17** (6.3 mg, 0.024 mmol) in 1,2-dichloroethane (0.8 ml) at -15°C. The mixture was stirred at -15°C for 30 min, at 0°C for 30 min and at room temperature for 1 h. Work-up and chromatographic separation as described for the preparation of **21** afforded the β-glycoside **32** (13.8 mg, 82%); $[\alpha]_D$ -22.4° (c 0.7); Rf 0.54 in 1:1 n-hexane-ethyl acetate; ^{1}H NMR (400 MHz) δ 5.449 (d, 1 H, 4.9 Hz, H-1a), 4.240 (dd, 1 H, 4.9, 2.2 Hz, H-2a), 4.001 (d, 1 H, 3.9 Hz, H-3b), 3.750 (s, 3 H, CO_2Me), 3.668 (dd, 1 H, 9.0, 6.8 Hz, H-6a), 3.351 (dd, 1 H, 9.0, 6.6 Hz, H-6a'), 1.721 (s, 3 H, Ac).

Anal. Calc. for $C_{58}H_{67}NO_{14}Se$: C, 64.44; H, 6.25; N, 1.30. Found: C, 64.49; H, 6.43; N, 1.30.

Methyl 5-acetamido-4,7,8,9-tetra-*O*-benzyl-3-bromo-3,5-dideoxy-D-*erythro*-L-*manno*-2-nonulopyranosonate 14 and Methyl 5-acetamido-4,7,8,9-tetra-*O*-benzyl-3-bromo-3,5-dideoxy-D-*erythro*-L-*gluco*-2-nonulopyranosonate 15. A mixture of compound **9a** (7.077 g, 10.63 mmol) and *N*-bromosuccinimide (2.27 g, 12.8 mmol) in 12:1 acetonitrile-water (130 ml) was stirred at 60°C for 30 min. After concentrated *in vacuo*, the residue was separated by chromatography on silica gel in 1:1 n-hexane-ethyl acetate to afford bromohydrins **14** (6.286 g, 78%) and **15** (1.546 g, 19%).

14: $[\alpha]_D$ +15.1° (c 0.8); Rf 0.20 in 1:1 n-hexane-ethyl acetate; ^{1}H NMR (500 MHz) δ 4.633 (d, 1 H, 3.7 Hz, H-3), 4.437 (dd, 1 H, 10.0, 3.7 Hz, H-4), 3.849 (ddd, 1 H, 10.7, 10.0, 8.3 Hz, H-5), 3.769 (s, 3 H, CO_2Me), 1.643 (s, 3 H, Ac).

Anal. Calc for $C_{40}H_{44}NO_9Br$: C, 62.99; H, 5.81; N, 1.84. Found: C, 62.65; H, 5.81; N, 1.84.

15: m.p. 148-150°C; $[\alpha]_D$ -51.8° (c 0.8); ^1H NMR (500 MHz) δ 4.497 (d, 1 H, 11.0 Hz, H-3), 3.847 (s, 3 H, CO_2Me), 1.715 (s, 3 H, Ac).

Anal. Calc. for $C_{40}H_{44}NO_9Br$: C, 62.99; H, 5.81; N, 1.84. Found: C, 62.85; H, 5.76; N, 1.87.

Methyl 5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-phenylthio-D-*erythro*-β-L-*gluco*-2-nonulopyranosonate 7.

From 14: To a stirred solution of thiophenol (1.0 ml, 9.7 mmol) in 1:1 t-butanol-THF (30 ml) was added a 0.76M solution of t-BuOK in t-butanol (10 ml, 7.6 mmol). After stirring at 0°C for 10 min, a solution of compound **14** (3.876 g, 5.082 mmol) in THF (20 ml) was added dropwise and the mixture was stirred at 0°C for 2 h and at room temperature for 1 h. The resulting mixture was diluted with ether (200 ml) and washed with water (100 ml). The aqueous layer was extracted with ether (100 ml) and the combined organic layers were washed successively with 0.2N aq NaOH (100 ml) and brine (100 ml), dried over $MgSO_4$ and concentrated *in vacuo* to afford crude **16** (4.23 g) which was dissolved in toluene (50 ml). To the solution, with stirring, was added DBU (75 μl, 0.50 mmol) at 0°C and the mixture was stirred at 0°C for 2 h and at room temperature for 30 min. The mixture was diluted with ethyl acetate (100 ml) and washed with 0.1 N aq HCl (50 ml) and the aqueous layer was extracted with ethyl acetate (50 ml). The combined organic layers were washed with brine (100 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was crystallized from ether to afford the hemiketal **7** (2.660 g). The mother liquor was concentrated *in vacuo* and purified by chromatography on silica gel in 2:1 n-hexane-ethyl acetate to give additional **7**. The total yield of **7** was 3.300 g (82%).

7: m.p. 97-99°C; $[\alpha]_D$ +9.4° (c 0.9); Rf 0.47 in 1:1 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 4.875 (d, 1 H, 9.7 Hz, NH), 4.396 (d, 1 H, 10.8 Hz, H-6), 4.205 (ddd, 1 H, 10.8, 9.7, 9.5 Hz, H-5), 3.943 (dd, 1 H, 10.8, 9.5 Hz, H-5), 3.943 (dd, 1 H, 10.8, 9.5 Hz, H-4), 3.645 (d, 1 H, 10.8 Hz, H-3), 3.559 (s, 3 H, CO_2Me), 1.772 (s, 3 H, Ac).

Anal. Calc. for $C_{46}H_{49}NO_9S$: C, 69.76; H, 6.24; N, 1.77. Found: C, 69.62; H, 6.18; N, 1.74.

From 15: Compound **15** (1.277 g, 1.674 mmol) was treated with thiophenol (0.35 ml, 3.4 mmol) and 0.76 M t-BuOK (3.3 ml, 2.5 ml) as described above. Work-up and chromatographic separation afforded **7** (593 mg, 45%).

Methyl 5-acetamido-4,7,8,9-tetra-*O*-benzyl-2,3,5-trideoxy-2-fluoro-3-phenylthio-D-*erythro*-α and β-L-*gluco*-2-nonulopyranosonate 5a. To a stirred solution of **7** (53.7 mg, 0.0678 mmol) in 2:1 toluene-1,2-dichloroethane (1.5 ml) was added diethylaminosulfur trifluoride (80 μl, 0.66 mmol) at -40°C. The mixture was stirred at -40°C for 30 min and at 0°C for 30 min and then diluted with ethyl acetate (30 ml). Aq $NaHCO_3$ (5 ml) was added and the mixture was washed with water (30 ml). The aqueous layer was extracted with ethyl acetate (30 ml) and the combined organic layers were washed with brine (30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography of the residue on silica gel in 2:1 n-hexane-ethyl acetate afforded the fluoride **5a** (51.4 mg, 96%) as a 2:1 mixture of α and β anomers.

5a: Rf 0.45 and 0.40 in 3:1 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 4.354 (dd, 2/3 H, 9.5, 9.3 Hz, H-4α), 4.005 (dd, 1/3 H, 10.3, 9.5 Hz, H-4β), 3.674 (s, 2 H, $CO_2Me\alpha$), 3.647 (dd, 2/3 H, 11.0, 3.2 Hz, H-9α), 3.586 (s, 1 H, $CO_2Me\beta$), 3.379 (dd, 2/3 H, 13.7, 9.5 Hz, H-3α), 1.695 (s, 1 H, Acβ), 1.649 (s, 2 H, Acα).

Methyl 5-acetamido-4,7,8,9-tetra-*O*-benzyl-2-chloro-2,3,5-trideoxy-3-phenylthio-D-*erythro*-β-L-*gluco*-2-nonulopyranosonate 5b. To a stirred mixture of compound **7** (469.9 mg, 0.593 mmol) and CCl_4 (0.23 ml, 2.4 mmol) in THF (10 ml) was added $(Me_2N)_3P$ (0.32 ml, 1.8 mmol) dropwise at -78°C. With stirring, the mixture was gradually warmed up to room temperature over 3 h and diluted with ether (50 ml). The mixture was washed with cold aq $NaHCO_3$ (50 ml) and the aqueous layer was extracted with ether (50 ml). The combined organic layers were washed with brine (30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography of the residue on silica gel in 3:2 n-hexane-ethyl acetate afforded the chloride **5b** (475.0 mg, 99%); Rf 0.30 in 2:1 n-hexane-ethyl acetate; ^1H NMR (400 MHz) δ 4.756 (d, 1 H, 8.1 Hz, NH), 4.635 (d, 1 H, 10.7 Hz, H-6), 4.129 (dd, 1 H, 10.0, 9.3 Hz, H-4), 3.854 (d, 1 H, 10.0 Hz, H-3), 3.792 (d, 1 H, 9.0 Hz, H-7), 3.624 (s, 3 H, CO_2Me), 1.674 (s, 3 H, Ac).

Methyl 5-acetamido-4,7,8,9-tetra-*O*-benzyl-2-bromo-2,3,5-trideoxy-3-phenylthio-D-*erythro*-β-L-*gluco*-2-nonulopyranosonate 5c. To a stirred mixture of **7** (60.9 mg, 0.0769 mmol) and CBr_4 (79 mg, 0.24 mmol) in THF (2 ml) was added dropwise $(Me_2N)_3P$ (43 μl, 0.24 mmol) at -78°C. With stirring, the mixture was gradually warmed up to room temperature over 3 h.

Work-up as described for the preparation of compound **5b** followed by flash chromatography on silica gel in 2:1 n-hexane-ethyl acetate afforded the bromide **5c** (63.6 mg, 97%); Rf 0.30 in 2:1 n-hexane-ethyl acetate; ^{1}H NMR (500 MHz) δ 4.585 (dd, 1 H, 10.5, 1.5 Hz, H-6), 4.157 (dd, 1 H, 9.8, 9.5 Hz, H-4), 4.103 (ddd, 1 H, 10.5, 9.8, 9.0 Hz, H-5), 3.811 (dd, 1 H, 8.0, 1.5 Hz, H-7), 3.713 (d, 1 H, 9.8 Hz, H-3), 3.669 (s, 3 H, CO_2Me), 1.675 (s, 3 H, Ac).

***O*-[Methyl(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-phenylthio-D-*erythro*-α-L-*gluco*-2-nonulopyranosyl)onate]-(2→6)-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose 24.**

Method A: To a stirred mixture of $AgOSO_2CF_3$ (20 mg, 0.078 mmol), $SnCl_2$ (15 mg, 0.079 mmol) and molecular sieves 4A (0.25 g) in carbon tetrachloride (1 ml) was added a solution of the fluoride **5a** (31.5 mg, 0.0397 mmol) and compound **17** (17 mg, 0.065 mmol) in carbon tetrachloride (2 ml) at 0°C. After stirring at room temperature for 18 h, aq $NaHCO_3$ (5 ml) was added and the mixture was stirred for 10 min, diluted with ethyl acetate (30 ml) and filtered through Celite. The filtrate was washed with water (30 ml) and the aqueous layer was extracted with ethyl acetate (30 ml). The combined organic layers were washed with brine (30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography of the residue on silica gel in 2:1 n-hexane-ethyl acetate and further separation on preparative TLC in 2:3 n-hexane-ether afforded **24** (19.7 mg, 48%, 72% based on consumed **5a**) and β-isomer (1.0 mg, 2%) together with recovered **5a** (10.4 mg, 33%).

24: $[\alpha]_D$ -4.5° (c 1.0), Rf 0.10 in 2:3 n-hexane-ether; ^{1}H NMR (500 MHz) δ 5.460 (d, 1 H, 4.9 Hz, H-1a), 4.466 (dd, 1 H, 7.9, 2.1 Hz, H-3a), 4.337 (dd, 1 H, 10.7, 1.5 Hz, H-6b), 4.256 (t, 1 H, 10.1 Hz, H-4b), 4.229 (dd, 1 H, 4.9, 2.4 Hz, H-2a), 4.059 (dd, 1 H, 7.9, 1.8 Hz, H-4a), 4.975 (dd, 1 H, 9.5, 6.7 Hz, H-6a), 3.658 (s, 3 H, CO_2Me), 3.274 (d, 1 H, 10.1 Hz, H-3b), 1.639 (s, 3 H, Ac).

Anal. Calc. for $C_{58}H_{67}NO_{14}S$: C, 67.36; H, 6.53; N, 1.35. Found: C, 67.29; H, 6.53; N, 1.30.

β-isomer: Rf 0.18 in 2:3 n-hexane-ether; ^{1}H NMR (500 MHz) δ 5.510 (d, 1 H, 4.9 Hz, H-1a), 4.976 (d, 1 H, 9.8 Hz, NH), 3.995 (dd, 1 H, 10.7, 9.5 Hz, H-4b), 3.567 (s, 3 H, CO_2Me), 3.545 (d, 1 H, 10.7 Hz, H-3b), 1.688 (s, 3 H, Ac).

Method B: To a stirred mixture of $AgOSO_2CF_3$ (34 mg, 0.13 mmol) and molecular sieves 4A (0.2 g) in carbon tetrachloride (1 ml) was added a solution of the chloride **5b** (53.5 mg, 0.0660 mmol) and compound **13** (27 mg, 0.10 mmol) in carbon tetrachloride (2 ml) at -20°C. After stirring at -20°C to room temperature for 18 h, work-up and chromatographic separation as described in **Method A** afforded **31** (35.8 mg, 52%).

Method C: To a stirred mixture of $Hg(CN)_2$ (25 mg, 0.10 mmol), $HgBr_2$ (12 mg, 0.030 mmol) and molecular sieves 4A (0.2 g) in carbon tetrachloride (1 ml) was added a solution of the chloride **5b** (53.0 mg, 0.0654 mmol) and compound **17** (27 mg, 0.10 mmol) in carbon tetrachloride (2 ml) at 0°C. The mixture was stirred at 30°C for 72 h, diluted with chloroform (30 ml) and filtered through Celite. The filtrate was washed with 10% aq KI (20 ml) and the aqueous layer was extracted with chloroform (30 ml) and the combined organic layers were washed with brine (30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Chromatographic separation of the residue afforded **24** (31.2 mg, 46%).

Method D: To a stirred mixture of $Hg(CN)_2$ (30 mg, 0.12 mmol), $HgBr_2$ (13 mg, 0.036 mmol) and molecular sieves 4A (1 ml) was added a solution of the bromide **5c** (62.5 mg, 0.0731 mmol) and compound **17** (30 mg, 0.12 mmol) in CCl_4 (2 ml) at 0°C and the mixture was stirred at 0°C to room temperature for 18 h. Work-up as described in **Method C** and chromatographic separation afforded **24** (54.7 mg, 72%).

Methyl *O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-phenylthio-D-*erythro*-α-L-*gluco*-2-nonulopyranosyl)onate]-(2→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 28. The chloride **5b** (107.9 mg, 0.133 mmol) was reacted with compound **18** (99 mg, 0.21 mmol) in the presence of $Hg(CN)_2$ (54 mg, 0.21 mmol) and $HgBr_2$ (24 mg, 0.067 mmol), in a similar manner as described for the preparation of compound **24** (**Method C**). After stirring at 40°C for 40 h, work-up followed by chromatography on silica gel in 4:1 toluene-ethyl acetate afforded compound **28** (117.0 mg, 71%).

28: $[\alpha]_D$ +19.5° (c 0.9); Rf 0.49 in 2:1 toluene-ethyl acetate; ^{1}H NMR (500 MHz) δ 4.307 (dd, 1 H, 11.3, 1.0 Hz, H-6b), 4.196 (dd, 1 H, 9.2, 8.2 Hz, H-4b), 4.027 (dd, 1 H, 10.7, 2.0 Hz, H-6a), 3.986 (dd, 1 H, 10.7, 4.9 Hz, H-6a'), 3.623 (s, 3 H, CO_2Me), 3.329 (d, 1 H, 8.2 Hz, H-3b), 3.270 (s, 3 H, OMe), 1.613 (3 H, s, Ac).

Benzyl *O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-phenylthio-D-*erythro*-α-L-*gluco*-2-nonulopyranosyl)onate]-(2→3)-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside 31a.

Method A: The fluoride **5a** (78.3 mg, 0.0986 mmol) was reacted with diol **19** (139 mg, 0.157 mmol) in the presence of $AgOSO_2CF_3$ (40 mg, 0.16 mmol), $SnCl_2$ (30 mg, 0.16 mmol) and molecular sieves 4A (0.3 g), in a similar manner as described for the preparation of compound **24** (**Method A**). After stirring at room temperature for 18 h, work-up and chromatography on silica gel in 3:1 toluene-ethyl acetate followed by repurification on preparative TLC in 1:2 n-hexane-ethyl acetate afforded compound **31a** (56.6 mg, 35%), the corresponding β-isomer (16.5 mg, 10%) and the regioisomer **31b** (8.0 mg, 5%).

31a: $[\alpha]_D$ +12.3° (c 1.8); Rf 0.46 in 2:1 toluene-ethyl acetate; ^1H NMR (500 MHz) δ 4.760 (d, 1 H, 9.2 Hz, NH), 4.161 (d, 1 H, 7.6 Hz, H-1a), 3.865 (dd, 1 H, 9.5, 3.1 Hz, H-3b), 3.831 (d, 1 H, 3.1 Hz, H-4b), 3.619 (s, 3 H, CO_2Me), 3.390 (d, 1 H, 9.5 Hz, H-3c), 1.668 (s, 3 H, Ac).

Anal. Calc. for $C_{100}H_{105}NO_{19}S$: C, 72.49; H, 6.39; N, 0.85. Found: C, 72.24; H, 6.42; N, 0.88.

β-Isomer: Rf 0.60 in 2:1 toluene-ethyl acetate; ^1H NMR (500 MHz) δ 5.036 (d, 1 H, 10.7 Hz, NH), 3.408 (s, 3 H, CO_2Me), 1.400 (s, 3 H, Ac).

31b: Rf 0.43 in 2:1 toluene-ethyl acetate; ^1H NMR (400 MHz) δ 3.519(s, 3 H, CO_2Me), 3.383 (d, 1 H, 10.8 Hz, H-3c), 1.626 (s, 3 H, Ac).

The β-isomer and **31b** were converted to the corresponding *C*-4b and *C*-3b acetates, whose ^1H NMR showed the characteristic signals, δ 6.015 (d, 1 H, 9.2 Hz, NH), 5.530 (d, 1 H, 3.1 Hz, H-4b), 3.293 (s, 3 H, CO_2Me), 2.112 (s, 3 H, Ac), 1.692 (s, 3 H, Ac) and δ 3.576 (d, 1 H, H-3c), 3.455 (s, 3 H, Ac), 1.866 (s, 3 H, Ac),1.582 (s, 3 H, Ac), respectively.

Method B: The chloride **5b** (57.1 mg, 0.0705 mmol) was reacted with diol **19** (100 mg, 0.113 mmol) in the presence of $Hg(CN)_2$ (28 mg, 0.11 mmol), $HgBr_2$ (20 mg, 0.055 mmol) and molecular sieves 4A (0.2 g) in a similar manner as described for the preparation of compound **24** (**Method C**). After stirring at 40°C for 40 h, work-up and chromatographic separation afforded **31a** (72.4 mg, 62%), β-isomer (2.5 mg, 2%) and **31b** (2.4 mg, 2%).

Method C: The bromide **5c** (74.3 mg, 0.0869 mmol) was reacted with diol **19** (122 mg, 0.138 mmol) in the presence of $Hg(CN)_2$ (16 mg, 0.14 mmol), $HgBr_2$ (16 mg, 0.044 mmol) and molecular sieves 4A (0.2 g) as described for the preparation of compound **24** (**Method D**). Work-up and chromatography on silica gel in 5:1 toluene-ethyl acetate afforded anomerically pure **31a** (115.7 mg, 80%) which was revealed to be of about 98% regioisomeric purity (^1H NMR).

Benzyl *O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-3-phenylthio-D-*erythro*-α-L-*gluco*-2-nonulopyranosyl)onate]-(2→3)-2,4,6-tri-*O*-benzyl-β-D-glucopyranoside 34. The bromide **5c** (60.3 mg, 0.0705 mmol) was reacted with compound **20** (61 mg, 0.11 mmol) in the presence of $Hg(CN)_2$ (30 mg, 0.12 mmol), $HgBr_2$ (14 mg, 0.039 mmol) and molecular sieves 4A (0.2 g) as described for the preparation of compound **24** (**Method D**). Work-up, chromatography on silica gel in 5:1 toluene-ethyl acetate and repurification on preparative TLC in 3:1 toluene-ethyl acetate afforded compound **34** (22.2 mg, 24%) as a single isomer.

34: $[\alpha]_D$ -9.2° (c 1.0); Rf 0.31 in 3:1 toluene-ethyl acetate; ^1H NMR (500 MHz) δ 4.184 (d, 1 H, 7.3 Hz, H-1a), 3.728 (dd, 1 H, 9.8, 7.3 Hz, H-2a), 3.696 (dd, 1 H, 5.5, 1.8 Hz, H-7b), 3.626 (s, 3 H, CO_2Me), 3.381 (d, 1 H, 10.7 Hz, H-3b), 1.522 (s, 3 H, Ac).

Anal. Calc. for $C_{80}H_{83}NO_{14}S \cdot H_2O$: C, 72.10; H, 6.43; N, 1.05. Found: C, 72.13; H, 6.40; N, 1.02.

Desulfurization of 24 to 22. A solution of compound **24** (27.2 mg, 0.0263 mmol), Ph_3SnH (54 mg, 0.15 mmol) and AIBN (1 mg, 0.006 mmol) in toluene (1 ml) was heated under reflux for 2 h. The mixture was concentrated *in vacuo* and the residue was purified by chromatography on silica gel in 2:1 toluene-ethyl acetate to afford compound **22** (18.9 mg, 77%, 97% based on consumed **24**) together with recoverd **24** (5.6 mg, 21%).

Desulfurization of 28 to 26. Compound **28** (60.3 mg, 0.0487 mmol) was treated with Ph_3SnH (70 mg, 0.20 mmol) and AIBN (1 mg) as described for the desulfurization of compound **24**. Chromatographic purification on silica gel in 3:2 n-hexane-ethyl acetate afforded compound **26** (48.4 mg, 88%).

Desulfurization of 31a to 33. Trisaccharide **31a** (41.6 mg, 0.0251 mmol) was treated with Ph_3SnH (46 mg, 0.13 mmol) and AIBN (1 mg, 0.006 mmol) as described for the desulfurization of compound **24**. Chromatographic purification on silica gel in 1:4 n-hexane-ether afforded the lactone **33** (25.8 mg, 68%).

Benzyl *O*-[methyl(5-acetamido-4,7,8,9-tetra-*O*-benzyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-nonulopyranosyl)onate]-(2→3)-2,4,6-tri-*O*-benzyl-β-D-galactopyranoside

35. Compound **34** (16.2 mg, 0.0123 mmol) was treated with Ph_3SnH (25 mg, 0.072 mmol) and AIBN as described for the desulfurization of compound **24**. Separation on preparative TLC in 2:1 toluene-ethyl acetate afforded compound **35** (8.3 mg, 56%, 88% based on consumed **34**) and recovered **34** (5.8 mg, 36%).

35: Rf 0.41 in 2:1 toluene-ethyl acetate; ^1H NMR (500 MHz) δ 4.768 (d, 1 H, 9.8 Hz, NH), 4.185 (d, 1 H, 7.6 Hz, H-1a), 4.138 (ddd, 1 H, 10.4, 9.8, 9.4 Hz, H-5b), 3.896 (dd, 1 H, 9.8, 3.1 Hz, H-3a), 3.817 (d, 1 H, 3.1 Hz, H-4a), 3.657 (dd, 1 H, 10.1, 7.6 Hz, H-2a), 3.596 (s, 3 H, CO_2Me), 3.379 (ddd, 1 H, 11.9, 9.4, 4.6 Hz, H-4b), 2.507 (dd, 1 H, 13.4, 4.6 Hz, H-3beq), 2.011 (dd, 1 H, 13.4, 11.9 Hz, H-3bax), 1.902 (s, 3 H, Ac).

***O*-(5-Acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→3)-D-galactopyranose 36**. To a stirred solution of compound **35** (8.3 mg, 0.0069 mmol) in 10:1 1,2-dimethoxyethane-water (1.1 ml) was added 0.4 N aq LiOH (100 μl, 0.04 mmol) at 0°C and the mixture was stirred at room temperature for 18 h. The mixture was diluted with water (20 ml), acidified with 2N HCl and extracted with ethyl acetate (20 ml x 2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in methanol (1 ml) and hydrogenated under atmospheric pressure in the presence of 10% Pd/C (12 mg) at 40°C. After 48 h, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. Chromatography of the residue on Sephadex G-25 in water afforded **36** (3.0 mg, 94%).

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