Approaches to intramolecular sialylation
1. Synthesis of pseudodisaccharide Neu5Ac-(1-2)-Gal with ester-linked monosaccharide residues

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An efficient approach was developed for ester-linking the sterically hindered carboxy group of *N*-acetylneuraminic acid with the secondary hydroxy group at C(2) of galactose. Putative precursors of the glycosidically linked disaccharide Neu5Ac-(2-3)-Gal were prepared.

Key words: sialic acids, *N*-acetylneuraminic acid, sialooligosaccharides, galactose, esters, regioselectivity, acylation, glycosylation, NMR spectroscopy.

The development of efficient procedures for the synthesis of complex oligosaccharides and conjugates containing sialic acid residues, in particular, *N*-acetylneuraminic acid (Neu5Ac), is an important problem of the synthetic carbohydrate chemistry because these structures are responsible for various immunological, neurobiological, oncological, and other biological processes.[1]

In recent years, considerable progress has been observed in the chemical synthesis of Neu5Ac glycosides (see the review[2]). However, the efficiency and stereoselectivity of sialylation are often far from the desired ideal and are sometimes unpredictable. Small (at first glance) changes in the structures of a glycosyl donor or a glycosyl acceptor as well as variations in the reaction temperature, solvent, or promoter can substantially influence the results of glycosylation. This is typical of the oligosaccharide synthesis as a whole.[3] In the case of sialylation, the process is additionally complicated by elimination as a side reaction giving rise to glycal. Presently, this reaction is considered as the main reason for a decrease in the yield of sialosides.[2] For this reason, sialylation products are isolated in highest yields where the undesirable formation of glycal is suppressed in one way or another. It should be noted that even the use of a substantial excess of an expensive sialyl donor does not necessarily lead to an increase in the preparative yield of the desired glycosylation product. One of the possible approaches to the synthesis of Neu5Ac glycosides involves intramolecular sialylation (Scheme 1). In this case, glycosylation proceeds as a monomolecular reaction due to which the target formation of the glycosidic bond is expected to more efficiently compete with the side formation of Neu5Ac-derived glycal.

Intramolecular glycosylation, which has become popular in recent years, involves linking of a glycosyl donor with a glycosyl acceptor by a chemical bond (often through a bridge), subsequent intramolecular delivery of the glycosyl acceptor to the anomeric center of the glycosyl donor upon activation of the latter (glycosylation proper), and cleavage of the temporary bond to give the target oligosaccharides in which the monosaccharide residues are linked through the newly formed glycosidic bond (see Scheme 1 and the review[4]). In many cases,[4] intramolecular glycosylation has advantages over traditional intermolecular glycosylation, allows one to prepare products in higher yields, and makes it possible to control the configuration of the newly formed glycosidic bond. Generally, intramolecular glycosylation occurs *via* 5—13-membered cyclic products. Numerous studies demonstrated that the size of the ring that formed can play a decisive role in both the efficiency and stereoselectivity of intramolecular glycosylation. However, no conclusions still can be made as to the optimum size of the ring, and the solution of this question is to be found in each particular case. It should be noted that an attempt (unsuccessful) to use this approach for performing sialylation was made only in one investigation[5] out of dozens of studies on intramolecular glycosylation. Intermolecular dimerization appeared to be the main direction of this reaction, whereas no intramolecular sialylation products were detected. In this connection, it is of particular importance to study in detail the reasons why the above-mentioned attempt to

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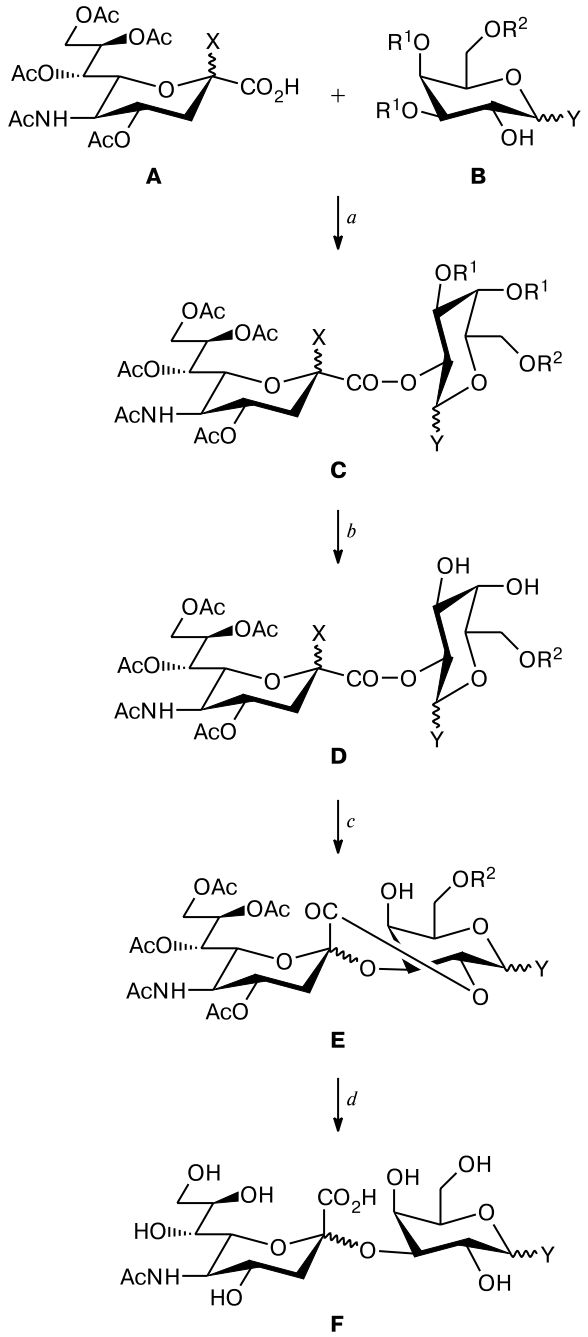
Scheme 1



a. Formation of a temporary bond between a glycosyl donor and a glycosyl acceptor. *b*. Removal of temporary protective groups. *c*. Activation of the anomeric center, formation of the glycosidic bond. *d*. Cleavage of the temporary bond, removal of protective groups.

perform "intramolecular" sialylation was unsuccessful, to reveal the factors responsible for either an intramolecular or intermolecular reaction direction in these systems, and, finally, to develop new more efficient approaches to intramolecular glycosylation. The present study is the first in a series of publications devoted to these problems.

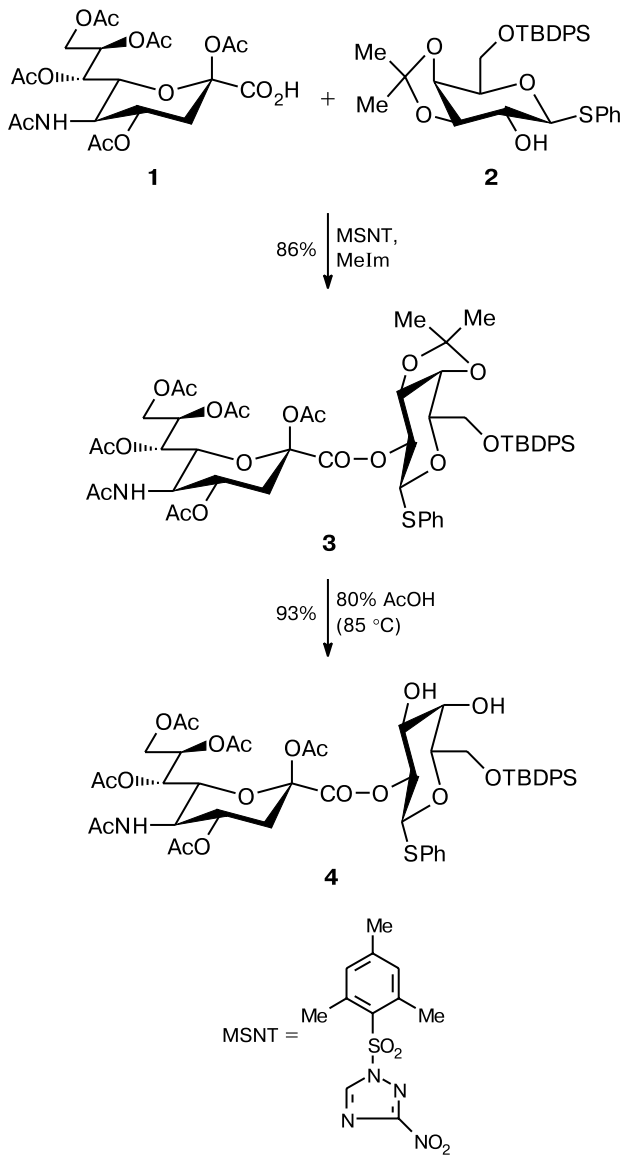
In the initial step of the study, we chose the disaccharide Neu5Ac-(α2-3)-Gal as the target product. According to the concept of intramolecular sialylation (see Scheme 1), its first step involves linking of glycosyl donor **A** to glycosyl acceptor **B** by a temporary bond (step *a*). It is known[6] that (α2′-3)-sialooligosaccharides are prone to generate (1′-2)-lactones (for example, compound **E** in Scheme 1). Hence, compounds in which the residue of a protected Neu5Ac derivative is ester-linked directly through its carboxy group to the not-to-be-glycosylated hydroxy group at C(2) of the galactose residue would be appropriate to consider as first non-glycosidically linked "disaccharide" precursors. The remaining hydroxy groups in the galactose residue should be differently protected so that the OH groups at C(3) and C(4) could be deprotected selectively. It is reasonable to use the 3,4-*O*-isopropylidene group as such an orthogonal group. This group can be removed in a weakly acidic medium in which ester groups remain intact.[7]

For this approach to be employed successfully, it is necessary first of all to elucidate whether it is possible to bind the carboxy group of the Neu5Ac residue to the secondary OH group at C(2) of the galactose residue through the ester bond and then to selectively deprotect the OH groups at C(3) and C(4) (which is necessary for the subsequent successful sialylation at O(3) of the galactose residue) with the retention of the protective group at O(6) and prevention of migration of the acyl residue (Neu5Ac). The stability of the temporary intersaccharide bond under typical glycosylation conditions is also of importance.

We used readily accessible peracetate **1** containing the free carboxy group[8] as the carboxy-containing Neu5Ac derivative (Scheme 2). Its condensation with the known[9] alcohol **2** in the presence of 1-mesitylenesulfonyl-3-nitro-1,2,4-triazole (MSNT)[10] and *N*-methylimidazole (MeIm) proceeded surprisingly efficiently. The corresponding "disaccharide" **3** consisting of ester-linked monosaccharide residues was isolated in 86% yield. Its deacetonation with 80% AcOH (85 °C) proceeded smoothly and was not accompanied by migration of the Neu5Ac residue (migration of the acetyl groups is well known[11]) as evidenced by a low-field position of the signal for H(2) of the galactose residue in the ^{1}H NMR spectrum of diol **4** prepared in 93% yield. Thus, we demonstrated that the neuraminic acid residue can be efficiently and regioselectively bound to the secondary OH group of the galactose residue.

Preliminary experiments on activation of the anomeric position of the neuraminic acid residue in compound **4** by different Lewis acids ($FeCl_3$, $BF_3 \cdot Et_2O$, or TMSOTf in CH_2Cl_2) demonstrated that the silyl protective group is unstable under these conditions. In all cases, mixtures of

Scheme 2



MeIm is *N*-methylimidazole

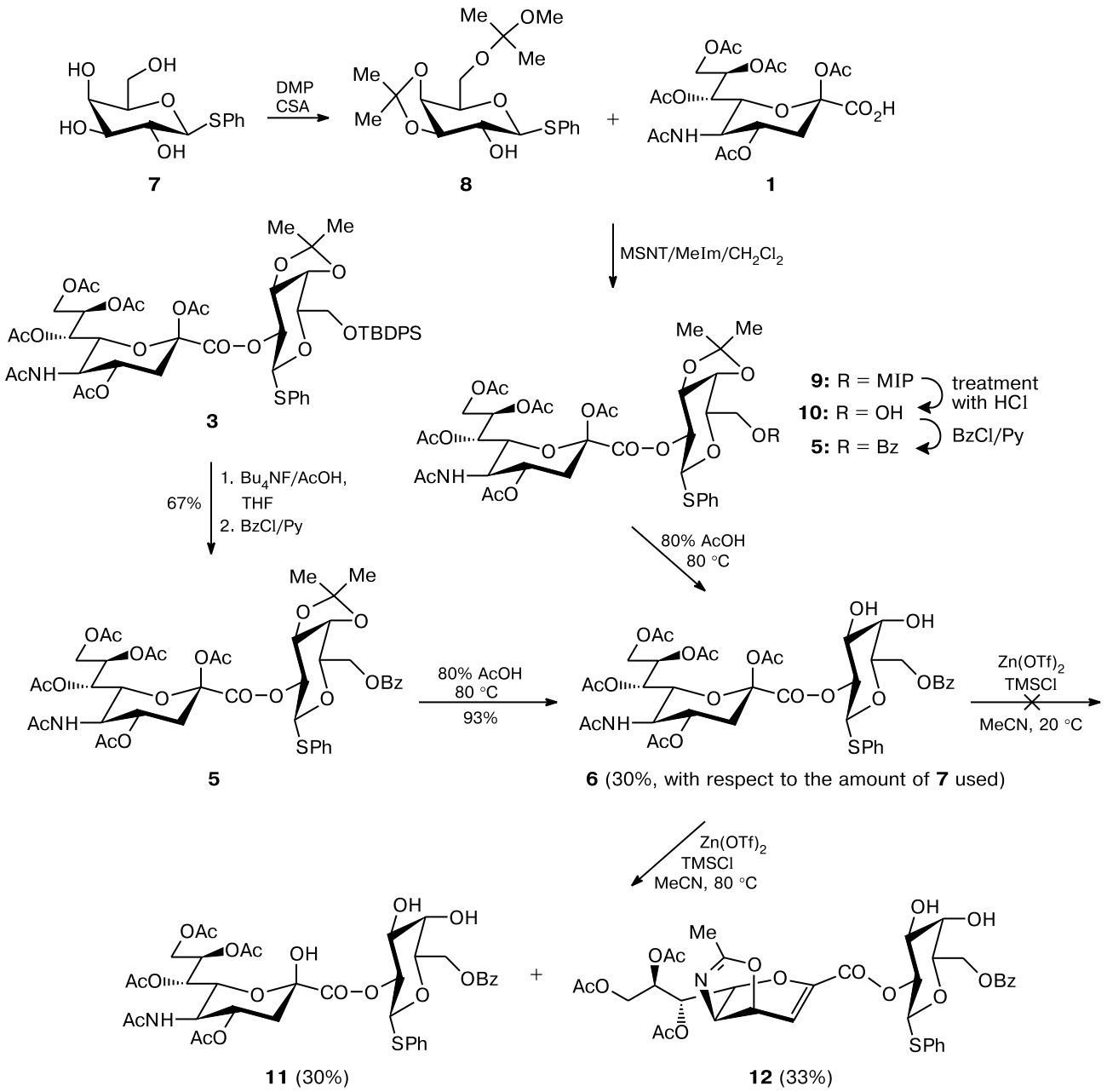
products were obtained. Their ^{1}H NMR spectra have no signals of the *tert*-butyldiphenylsilyl group. The main conclusion drawn from these experiments is that the successful use of non-glycosidically linked "disaccharides" for intramolecular sialylation requires that the protective group at O(6) be more stable under acidic conditions. We chose the benzoyl group as such a protective group (Scheme 3).

An analog of diol **4** containing the benzoyl group at O(6) (**6**) was readily prepared from silyl ether **3**. Desilylation (Bu_4NF) followed by benzoylation (BzCl/Py) afforded benzoate **5** in 67% yield. Deacetonation of the latter with 80% AcOH (80 °C) gave rise to the target diol **6** in 93% yield. The ^{1}H NMR spectrum of **6** has low-field signals for H(2) and H(6), which indicates that acyl substituents are bound only to O(2) and O(6) of the galactose residue. Diol **6** was also prepared according to an alternative procedure from commercial thiogalactoside **7** and sialic acid acetate **1** without purification of intermediates. Treatment of **7** with an excess of 2,2-dimethoxypropane in the presence of camphorsulfonic acid (CSA) rapidly afforded alcohol **8** in virtually quantitative yield. This compound was identified by TLC by comparing it with an authentic sample.[9] Condensation of crude alcohol **8** with acid **1** in the presence of MSNT gave "disaccharide" **9** whose treatment with dilute HCl (work-up of the reaction mixture in a separating funnel) led to removal of the 2-methoxyisopropyl (MIP) protective group from O(6) to give alcohol **10**. Subsequent benzoylation of **10** produced the known benzoate **5** (identified by TLC by comparing it with an authentic sample) whose deacetonation afforded the target diol **6** isolated in a total yield of 30%, which corresponds, on the average, to ~67% yield in each of steps **8** + **1** → **9** → **10** → **5**.

An attempt to activate the anomeric position in acetate **6** by the $Zn(OTf)_2$—TMSCl system[12] in MeCN at 20 °C did not lead to a noticeable reaction. Refluxing of the reaction mixture resulted in the virtually complete disappearance of the starting acetate **6**. The hydrolysis product of anomeric acetate (**11**, 30%) and the bicyclic elimination product (**12**, 34%) containing the dihydrooxazole ring were isolated from the reaction mixture. The structure of hemiacetal **11** was confirmed by the disappearance of one of the signals of the acetyl groups from the ^{1}H NMR spectrum as well as by upfield shifts of the signals for $H(3)_{eq}$ (δ_H 2.57 → 2.29) and C(2) (δ_C 97.2 → 95.3) of the Neu5Ac residue. The remaining signals in the NMR spectra of hemiacetal **11** did not undergo substantial changes as compared to those observed in the spectrum of the starting acetate **6**. The presence of the C(2)=C(3) double bond in compound **12** is indicated by the positions of the NMR signals for H(3), C(2), and C(3) of the Neu5Ac residue characteristic[13] of sialic acid glycals (Tables 1—3). The formation of the dihydrooxazole ring[14] fused with the pyranose ring at positions 4 and 5 of the glycal is confirmed by the absence of the signal of the AcNH group (δ_C ~23) and the appearance of the signal of the methyl group (MeC) at δ_C 14.2 in the ^{13}C NMR spectrum of compound **12** as well as by a downfield shift of the signal for C(5) of the Neu5Ac residue (δ_C 49.1 → 61.9) and an upfield shift of the signal for H(6) of the Neu5Ac residue (δ_H 4.03 → 3.30).

To summarize, we developed an efficient procedure for binding the sterically hindered carboxy group of the Neu5Ac residue to the secondary OH group at C(2) of the galactose residue by an ester bond. This intersaccharide ester bond is stable in an acidic medium under different conditions typical of glycosylation, which holds promise for successful intramolecular sialylation. This approach

Scheme 3



DMP is dimethoxypropane, CSA is camphorsulfonic acid; MIP = CMe_2OMe

can also be used for the preparation of other non-glycosidically linked "disaccharide" precursors of the glycosidically linked disaccharide Neu5Ac-(α2-3)-Gal with different "bridges". It is also evident that further experiments should be performed with Neu5Ac derivatives in which the anomeric position can be activated under much milder conditions than those used in the present study for the anomeric acetate.

Experimental

The reactions were performed with the use of anhydrous solvents purified according to standard procedures and commercial reagents (Aldrich and Fluka). Thin-layer chromatography was carried out on plates with silica gel on aluminum foil (Merck). Column chromatography was performed on silica gel 60 (40—63 μm, Merck). The ^1H and ^{13}C NMR spectra were

Table 1. ^{13}C NMR spectra (δ_C, $CDCl_3$) of the compounds synthesized

Compound	R[a]	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	Ar	MeCN	MeCOO	C=O
1	Neu	168.4	97.3	36.2	68.7	49.2	72.4	67.8	71.2	62.0	—	22.95	20.77, 20.86, 20.92	170.3, 170.4, 170.8, 171.08, 171.15
3[b] (HETCOR)	Neu	164.6	97.4	36.0	68.4	49.2	72.9	68.1	71.6	62.2		23.2	20.67, 20.77, 20.82, 20.88, 20.97	167.8, 170.2, 170.3, 170.4, 170.8, 171.1
	Gal	84.8	73.7	76.7	73.4	76.9	63.0	—	—	—	125.3, 127.6, 127.67, 127.71, 128.2, 128.9, 129.0, 129.1, 129.7, 131.7, 133.3, 133.34, 135.6, 137.8			
4[c]	Neu	165.7	97.3	36.4	68.2[d]	49.1	72.8	67.9[d]	71.8	62.5		23.2	20.8 (2C), 20.9 (2C), 21.1	169.0, 170.1, 170.4, 170.8, 171.0, 171.3
	Gal	85.4	73.2	73.2	69.1	78.9	63.3	—	—	—	125.3, 127.6, 127.8, 127.9, 128.2, 128.9, 129.0, 129.65, 129.76, 131.6, 133.1, 133.6, 134.8, 135.6, 137.9			
5[e] (HETCOR)	Neu	164.7	97.3	36.0	68.3[d]	49.2	73.0	68.0[d]	71.5	62.2		23.2	20.6, 20.7, 20.80, 20.86, 20.93	166.3, 167.9, 170.1, 170.3 (2C), 170.8, 171.0
	Gal	84.8	74.3	76.3	73.5 (2 C)	73.5 (2 C)	64.2	—	—	—	125.3, 127.6, 128.4, 128.8, 129.7, 129.9, 131.6, 133.2, 133.5, 142.7			
6[f]	Neu	165.8	97.2	36.5	68.2[d]	49.1	72.9	67.9[d]	71.9	62.5		23.1	20.76, 20.79, 20.84 (2C), 21.0	166.4, 169.2, 170.1, 170.4, 170.8, 171.0, 171.4
	Gal	85.5	73.3	72.4	69.1	76.3	63.9	—	—	—	127.7, 128.4, 128.9, 129.8, 129.9, 131.7, 133.2, 133.3			
11	Neu	166.5	95.3	36.9	69.0[d]	49.0	72.6	68.8[d]	72.2	62.8		23.1	20.81, 20.87, 20.89, 21.2	168.5, 170.2, 170.5, 170.8, 172.2
	Gal	85.6	72.3	77.9	69.3[d]	76.3	63.7	—	—	—	127.7, 128.2, 128.5, 128.90, 128.96, 129.04, 129.7, 131.4, 132.0, 133.3			
12[g]	Neu	161.1	109.1	147.2	69.4	61.9	76.2	67.7	72.2	62.1		14.2	20.7, 20.8, 21.1	166.5, 167.5, 169.5, 170.7
	Gal	86.1	72.5	72.3	69.4	76.4	63.6	—	—	—	127.5, 128.2, 128.5, 128.8, 129.0, 129.7, 129.8, 131.4, 133.3, 133.8			

[a] R is a monosaccharide residue. [b] Other signals (δ): 77.3 ($\underline{C}Me_3$); 26.8 ($C\underline{Me}_3$); 110.4 ($\underline{C}Me_2$); 26.4, 27.6 ($C\underline{Me}_2$). [c] Other signals (δ): 77.2 ($\underline{C}Me_3$); 26.8 ($C\underline{Me}_3$).
[d] The assignments can be interchanged. [e] Other signals (δ): 110.9 ($\underline{C}Me_2$); 26.3, 27.5 ($C\underline{Me}_2$). [f] Other signals (δ): 110.9 ($\underline{C}Me_2$); 26.3, 27.5 ($C\underline{Me}_2$).
[g] Other signals (δ): 77.2 (Me$\underline{C}$=N).

Table 2. ^{1}H NMR spectra (δ_H, $CDCl_3$) of the compounds synthesized[a]

Compound	R[b]	H(1)	H(2)	H(3)	H(4)	H(5)	H(6)	H(7)	H(8)	H(9)	NH	MeCN	AcO	Ar	CMe_3	CMe_2
3[c] (COSY)	Neu	—	—	2.21, 2.58 (both dd)	5.29 (ddd)	4.17 (m)	4.11 (m)	5.42 (dd)	5.04 (m)	4.06 (m), 4.46 (dd)	5.54 (d)	1.90 (s)	2.02, 2.06, 2.07, 2.12, 2.16 (all s)			
	Gal	4.82 (d)	4.88 (dd)	4.24 (t (dd))	4.31 (dd)	4.03 (m)	3.96 (m, 2 H)	—	—	—				7.10—7.80 (m)	1.06 (s)	1.31, 1.44 (both s)
4 (COSY)	Neu	—	—	2.12 (m), 2.56 (dd)	5.33 (m)	4.21 (q (ddd))	4.03 (dd)	5.42 (dd)	5.01 (m)	4.02 (m), 4.56 (dd)	5.36 (d)	1.89 (s)	2.04, 2.06 (6 H), 2.13, 2.17 (all s)			
	Gal	4.81 (d)	5.23 (t (dd))	3.92 (dd)	4.15 (d)	3.75 (br.t)	3.96 (d, 2 H)	—	—	—				7.10—7.80 (m)	1.06 (s)	—
5 (COSY)	Neu	—	—	2.18 (m), 2.58 (dd)	5.27 (ddd)	4.15 (m)	4.10 (m)	5.38 (dd)	4.97—5.17 (m)	4.03, 4.42 (both dd)	5.44 (d)	1.88 (s)	1.99, 2.04 (6 H), 2.08, 2.15 (all s)			
	Gal	4.89 (d)	4.97—5.17 (m)	4.27—4.34 (m)	4.27—4.34 (m)	4.23 (br.dd)	4.57, 4.68 (both dd)	—	—	—				7.10—8.10 (m)	—	1.34, 1.50 (both s)
6 (COSY)	Neu	—	—	2.12 (m), 2.57 (dd)	5.32 (ddd)	4.21 (ddd)	4.03 (m)	5.41 (dd)	4.99 (m)	3.96, 4.57 (both dd)	5.48 (d)	1.89 (s)	2.03, 2.04, 2.05, 2.11, 2.18 (all s)			
	Gal	4.82 (d)	5.26 (t (dd))	4.01 (m)	4.15 (d)	4.02 (m)	4.61—4.72 (m, 2 H)	—	—	—				7.10—8.10 (m)	—	—
11 (COSY)	Neu	—	—	2.10 (m), 2.29 (m)	5.18 (m)	4.18 (m)	4.32 (dd)	5.42 (m)	5.16—5.24 (m)	3.88, 4.75 (both m)	6.31 (br.d)	1.88 (s)	1.90, 1.99, 2.08, 2.13 (all s)			
	Gal	4.81 (d)	5.16—5.24 (m)	3.90 (m)	4.10 (m)	3.90 (m)	4.70 (m)	—	—	—				7.10—8.10 (m)	—	—
12 (COSY)	Neu	—	—	6.52 (d)	4.86 (dd)	3.95 (m)	3.30 (dd)	5.64 (dd)	5.55 (ddd)	4.16, 4.38 (both dd)	—	2.08 (s)	2.03, 2.06, 2.17 (all s)			
	Gal	4.84 (d)	5.25 (t (dd))	3.92 (m)	4.10 (br.d)	3.98 (m)	4.57, 4.71 (both dd)	—	—	—				7.10—8.10 (m)	—	—

[a] All spectra were recorded for samples with concentrations of 20—30 mg mL^{-1} (unless otherwise stated); in some cases, the spectral patterns depend on the concentration.
[b] R is a monosaccharide residue.
[c] The concentration is 100 mg mL^{-1}.

Table 3. Spin-spin coupling constants in the ^{1}H NMR spectra (J/Hz, $CDCl_3$) of the compounds synthesized[a]

Compound	Monosaccharide residue	$J_{1,2}$	$J_{2,3}$	$J_{3,3'}$	$J_{3',4}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$	$J_{8,9'}$	$J_{9,9'}$	$J_{5,NH}$
3	Neu	—	—	13.6	5.0	11.8	~10.7	[b]	—	—	2.2	4.5	[b]	2.4	12.6	9.3
	Gal	9.8	6.2	—	—	5.9	1.5	[b]	[b]	[b]	—	—	—	—	—	—
4	Neu	—	—	13.1	4.8	[b]	9.9	9.9	—	—	2.9	4.5	[b]	1.9	12.6	9.6
	Gal	10.2	9.4	—	—	3.4	~1.3	~5.6	~5.6	[b]	—	—	—	—	—	—
5	Neu	—	—	13.1	4.8	11.4	9.9	10.9	—	—	2.4	4.8	7.2	2.6	12.6	9.5
	Gal	9.6	[b]	—	—	3.4	~1.3	8.0	3.5	11.5	—	—	—	—	—	—
6	Neu	—	—	13.0	4.8	11.2	9.9	10.9	—	—	2.9	4.5	8.0	2.4	12.6	9.6
	Gal	10.1	8.5	—	—	3.4	[b]	[b]	[b]	[b]	—	—	—	—	—	—
11	Neu	—	—	[b]	[b]	[b]	[b]	10.9	—	—	1.9	[b]	[b]	[b]	[b]	9.2
	Gal	9.8	[b]	—	—	[b]	[b]	[b]	[b]	[b]	—	—	—	—	—	—
12	Neu	—	—	[b]	[b]	4.0	8.6	10.4	—	—	1.8	8.3	5.6	2.4	12.6	[b]
	Gal	10.0	9.9	—	—	2.9	[b]	7.4	4.9	11.7	—	—	—	—	—	—

[a] Primed digits correspond to lower-field signals for the protons of the $C(3)H_2$, $C(6)H_2$, and $C(9)H_2$ groups.
[b] Undetermined.

recorded on a Varian XL-300 instrument (300 and 75.4 MHz, respectively) in $CDCl_3$. The ^{1}H chemical shifts were measured relative to the residual signal of $CHCl_3$ (δ 7.27) and the ^{13}C chemical shifts were measured relative to the signal of $CDCl_3$ (δ 77.0). The assignment of the signals in the NMR spectra was made based on the DEPT-135 experiments and 2D correlation ^{1}H—^{1}H (COSY) and ^{13}C—^{1}H (HETCOR) spectra. The NMR spectroscopic data are given in Tables 1 and 2. The optical rotation was measured on a Perkin—Elmer 141 polarimeter. High-resolution mass spectra (FAB) were obtained on a JEOL SX-120 mass spectrometer.

Phenyl 2-*O*-(5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-non-2-ulopyranosonoyl)-6-*O*-(*tert*-butyldiphenylsilyl)-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (3). *N*-Methylimidazole (43 μL, 0.54 mmol) was added to a solution of acid **1** [8] (84 mg, 0.16 mmol) in CH_2Cl_2 (2.5 mL) under argon. The reaction mixture was transferred under argon to a flask containing MSNT (60 mg, 0.20 mmol) and the content was transferred under the same conditions to a reaction flask containing alcohol **2** [9] (74.2 mg, 0.13 mmol). The two flasks were additionally rinsed with CH_2Cl_2 (1.0 + 1.5 mL) and the resulting solutions were added to the reaction mixture, which was kept at 20 °C for 26 h (TLC demonstrated that the starting alcohol **2** was absent). The reaction mixture was diluted with CH_2Cl_2 (40 mL) and poured onto ice. The organic phase was twice washed with 0.5 *M* HCl and then with a cold saturated $NaHCO_3$ solution and ice water, each aqueous phase being reextracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were filtered through a cotton plug and concentrated to dryness. The residue was purified by column chromatography on silica gel (acetone—toluene, 3 : 7) to obtain the target "disaccharide" ester **3** (121.6 mg, 86%), $[\alpha]_D^{23}$ +0.5 (*c* 6.4, $CHCl_3$). MS (FAB, detection of positive ions): found, *m/z* 1052.3773 [M + H]. $C_{52}H_{66}NO_{18}SSi$. Calculated, *m/z* 1052.3770 [M + H].

Phenyl 2-*O*-(5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-non-2-ulopyranosonoyl)-6-*O*-(*tert*-butyldiphenylsilyl)-1-thio-β-D-galactopyranoside (4). Water (0.2 mL) was added to a solution of acetonide **3** (22.4 mg, 0.021 mmol) in AcOH (0.8 mL). The reaction solution was heated at 85 °C (bath temperature) for 30 min and concentrated to dryness. Then toluene was added to, and distilled from, the residue (×3). The residue was dried *in vacuo* to give diol **4** (20.0 mg, 93%), which was used without additional purification. MS (FAB, detection of positive ions): found, *m/z* 1012.3439 [M + H]. $C_{49}H_{62}NO_{18}SSi$. Calculated, *m/z* 1012.3457 [M + H].

Phenyl 2-*O*-(5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-non-2-ulopyranosonoyl)-6-*O*-benzoyl-3,4-*O*-isopropylidene-1-thio-β-D-galactopyranoside (5). A mixture of AcOH (41 μL, 0.72 mmol) and $Bu_4NF \cdot 3H_2O$ (90.4 mg, 0.29 mmol) was added to a solution of silyl ether **3** (75.3 mg, 0.072 mmol) in THF (1 mL). The reaction mixture was kept at 20 °C for 30 h, diluted with CH_2Cl_2 (30 mL), and poured into a cold saturated $NaHCO_3$ solution (40 mL). The aqueous layer was extracted with CH_2Cl_2 (×2). The combined organic extracts (80 mL) were washed with cold brine (2×20 mL) and water (1×10 mL), filtered through a cotton plug, and concentrated to dryness. Then toluene was added to, and distilled from, the residue. The residue was dissolved in Py (10 mL) and cooled (ice water). Then BzCl (166 μL, 1.43 mmol) was added, the reaction mixture was kept at 20 °C for 24 h, and MeOH (4 mL) was added. The reaction mixture was kept at 20 °C for 1 h and then concentrated. Toluene was added to, and distilled from, the residue, and then CH_2Cl_2 (100 mL) was added to the residue. The resulting solution was washed with 0.5 *M* HCl (2×50 mL). The aqueous phase was reextracted with CH_2Cl_2 (×2). The combined extracts (200 mL) were washed with a cold saturated $NaHCO_3$ solution (2×100 mL) and cold brine (100 mL), filtered through a cotton plug, and concentrated to dryness. The residue was purified by column chromatography on silica gel (AcOEt) to yield the target benzoate **5** (44.2 mg, 67%), $[\alpha]_D^{23}$ +0.7 (*c* 3.7, $CHCl_3$). MS (FAB, detection of positive ions): found, *m/z* 918.2863 [M + H]. $C_{43}H_{52}NO_{19}S$. Calculated, *m/z* 918.2854 [M + H].

Phenyl 2-*O*-(5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-non-2-ulopyranosonoyl)-6-*O*-benzoyl-1-thio-β-D-galactopyranoside (6). *A.* Water (1 mL) was added to a solution of ester **5** (45.1 mg, 0.049 mmol) in AcOH

(4 mL). The reaction solution was heated at 80 °C (bath temperature) for 1 h and concentrated to dryness. Then toluene was added to, and distilled from, the residue (×3). The residue was purified by column chromatography on silica gel (acetone—toluene, 1 : 1) to yield the target diol **6** as a white powder (39.2 mg, 93%), m.p. 131—132 °C, $[\alpha]_D^{23}$ –2.9 (*c* 3.2, $CHCl_3$). MS (FAB, detection of negative ions): found, *m/z* 876 [M – H], 834 [M – H – CH_2=C=O]. MS (FAB, detection of positive ions): found, *m/z* 878 [M + H], 818 [M + H – AcOH], 758 [M + H – 2 AcOH]. $C_{40}H_{48}NO_{19}S$. Calculated, *m/z* 878.2541 [M + H].

B. 2,2-Dimethoxypropane (30 mL) and then a catalytic amount of (±)-camphor-10-sulfonic acid (5 mg) were added to phenyl thiogalactoside **7** (273 mg, 1 mmol) under argon. The resulting suspension was stirred at 20 °C for 24 h and then the reaction was quenched by adding Et_3N (2 mL). The reaction mixture was concentrated, toluene was added to, and distilled from, the residue (×3) to obtain alcohol **8** (~100% yield, TLC data), which was used in the next step without additional purification.

N-Methylimidazole (320 μL, 4 mmol) was added to a solution of acid **1** (673.4 mg, 1.3 mmol) in CH_2Cl_2 (5 mL) under argon. The reaction mixture was transferred under argon to a flask containing MSNT (447.3 mg, 1.5 mmol) and the content was transferred to a reaction flask containing alcohol **8** (which was synthesized in the previous step). The two flasks were additionally rinsed with CH_2Cl_2 (2×2.5 mL) and the resulting solutions were added to the reaction mixture, which was kept under argon at 20 °C for 4 h. Then the reaction mixture was diluted with CH_2Cl_2 (100 mL) and poured onto ice. The organic phase was washed with 0.5 *M* HCl (2×300 mL) (in this step, the primary reaction product **9** disappeared and alcohol **10** formed, TLC data) and a cold saturated $NaHCO_3$ solution (300 mL), each aqueous phase being reextracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were filtered through a cotton plug and concentrated to dryness. Then toluene was added to, and distilled from, the residue. The resulting alcohol **10** was used in the next step without additional purification.

Benzoyl chloride (1.16 mL, 10 mmol) was added to a cooled (ice water) solution of alcohol **10** in Py (10 mL). The reaction mixture was kept at 20 °C for 18 h. Then finely crushed ice was added to the reaction mixture. After 30 min, the mixture was diluted with CH_2Cl_2 (200 mL). The organic layer was washed with 0.5 *M* HCl (200 mL) and a cold saturated $NaHCO_3$ solution (2×200 mL), each aqueous phase was reextracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were filtered through a cotton plug and concentrated to dryness to give benzoate **5** as a yellow syrup (according to the TLC data, it was identical with the sample synthesized as described above).

Water (2 mL) was added to a solution of acetonide **5** in AcOH (8 mL). The reaction solution was heated at 80 °C (bath temperature) for 2.5 h and concentrated to dryness. Then toluene was added to, and distilled from, the residue (×3). The residue was purified by column chromatography on silica gel (acetone—toluene, 3 : 7) to yield the target diol **6** (263 mg, 30% with respect to the amount of the starting thiogalactoside **7**) identical with the sample synthesized according to method ***A***.

Phenyl 2-*O*-(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-β-D-*glycero*-D-*galacto*-non-2-ulopyranosonoyl)-6-*O*-benzoyl-1-thio-β-D-galactopyranoside (11) and phenyl 2-*O*-{2-methyl-4,5-dihydrooxazolo[4,5:5´4´](2,6-anhydro-7,8,9-tri-*O*-acetyl-3,5-dideoxy-D-*glycero*-D-*talo*-non-2-enonoyl)}-6-*O*-benzoyl-1-thio-β-D-galactopyranoside (12). Acetonitrile (2 mL) was added to a mixture of diol **6** (28 mg, 0.032 mmol) and $Zn(OTf)_2$ (20.4 mg, 0.056 mmol) under argon. After dissolution of all components, TMSCl (6 mL) was added and the reaction mixture was heated at 80 °C (bath temperature). After 3 h, the starting diol **6** disappeared and two new products were formed (TLC data). The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with a cold saturated $NaHCO_3$ solution (30 mL). The aqueous phase was extracted with CH_2Cl_2 (5×10 mL). The combined organic extracts were filtered through a cotton plug and concentrated to dryness. The residue was purified by column chromatography on silica gel to yield compounds **11** (8.1 mg, 30%) and **12** (8.1 mg, 33%). MS (FAB, detection of positive ions): for compound **11** found, *m/z* 836.2432 (29.5%) [M + H], 818.2355 (16%) [M + H – H_2O]. $C_{38}H_{46}NO_{18}S$. Calculated, *m/z* 836.2436 [M + H]. $C_{38}H_{44}NO_{17}S$. Calculated, *m/z* 818.2330 [M + H – H_2O]. For compound **12** found, *m/z* 758.2110 [M + H]. $C_{36}H_{40}NO_{15}S$. Calculated, *m/z* 758.2119 [M + H].

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