Synthesis of a Useful Lauryl Thioglycoside of Sialic Acid and its Application[†]

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Abstract

An efficient synthesis of a useful thioglycosyl donor **2** was accomplished directly from known peracetylated sialic acid methyl ester and 1-dodecanethiol (lauryl mercaptan) in the presence of BF_3—OEt_2. The reactivities of the lauryl glycosides for glycosidation by means of TMSOTf as a convenient promoter were investigated, and the lauryl thioglycoside showed satisfactory activities. Further transformation of the lauryl glycoside was also attempted to give a 5-azide analogue **14** of the sialic acid, which was also reacted with a secondary alcohol in the presence of TMSOTf to give known glycoside **15** in high yield.

Keywords: thioglycosides; lauryl mercaptan; sialic acid; glycosidation; carbohydrates

Oligosaccharide chains of glycoconjugates take important biological events such as fertilization, differentiation, aging, malignant alteration, and so on.[1] Sialylated oligosaccharides have various oligosaccharide structures and play roles in cell recognition and signaling.[2] Since sialic acid usually exists at the nonreducing ends of oligosaccharide chains of glycoconjugates on the cell surface, it seems that there are many

opportunities for interaction between carbohydrate and receptor protein. In order to investigate the significance and mechanisms of those ligand—receptor interactions, a method for synthesizing sialooligosaccharide is needed.[3] Glycosidation to form sialoside by using various glycosyl donors derived from sialic acid has been extensively investigated.[4] Although those donors are useful for assembly of sialic acid moiety into oligosaccharide chains, an improvement of the preparation of sialyl donors is ongoing. In the chemical syntheses of sialooligosaccharides, the thioglycoside methodology is frequently used for such objective, despite the fact that a large number of sialyl donors have been prepared.[4] For making thioglycoside donors of sialic acid, a variety of volatile thiols or those stinking TMS derivatives are generally utilized.[5] Recently, Sakairi *et al.* reported thioglycosides having a lauryl moiety in order to avoid such undesired factors, and the lauryl thioglycosides showed efficient ability for the glycoside syntheses.[6] In this paper, we describe an efficient synthesis of novel thioglycoside **2** of sialic acid having a lauryl moiety from known fully protected sialic acid derivative **1** and its applications, including possible utilization as a glycosyl donor and further transformation of **2** into its 5-azide analogue **14**.

For preparation of methyl 5-acetamido-2,4,7,8,9-penta-*O*-acetyl-3,5-dideoxy-D-glycero-D-galacto-2-nonulopyranosonate **1** as a starting material, we selected Sinaÿ's protocol[7] to obtain anomeric mixtures of **1** in high yield. Although preparation of a thioglycoside of sialic acid is usually carried out using a TMS derivative of the thiol in the presence of Lewis acid as a catalyst, direct conversion of **1** into its thioglycoside was tested, since a TMS derivative of l-dodecanthiol is not available. Acetate **1** was treated with 1-dodecanthiol (4 molar excess) in the presence of BF_3—OEt_2[8] (3 molar excess) at 0 °C and then at rt, and the reaction was monitored by TLC until disappearance of **1**. The usual work-up of the reactant gave an anomeric mixture of **2**, which was separated by means of silica gel chromatography into anomers¶, **2α** (26.2%), $[\alpha]_D^{28}$ +26° (*c* 1.09, $CHCl_3$) and **2β** (59.2%), $[\alpha]_D^{28}$ -67°(*c* 0.91, $CHCl_3$). The total yield of **2** was 85.4% after isolation. The structure of each anomer was confirmed by the results of ^{1}H NMR[9] and the results are summarized in Table 1.

Scheme 1

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Table 1

Given the success of the preparation of a thioglycoside of sialic acid having a lauryl moiety, we next turned our attention to the potency of **2** as a glycosyl donor for application to sialoside synthesis. A large number of methods for activation of thioglycosides have been developed and are summarized in review papers.[5] Since the activation of thioglycoside is similar to that of the *n*-pentenyl glycoside, initially introduced by Fraser-Raid *et al.*,[10] Schmidt *et al.*[11] reported a convenient system for activation of a thioglycosyl donor by using NIS—TMSOTf as mediators instead of NIS—TfOH, IDCP, NIS—TESOTf, as well as DMTST. Because of the low cost, easy handling, and availability of TMSOTf, we investigated the usefulness of a TMSOTf—NIS system for activating the lauryl thioglycoside **2**, and the results are summarized in Scheme 2 and Table1. In the preliminary glycosidation, the thioglycoside **2α** and secondary alcohol **3** as a typical control were condensed by using NIS—TMSOTf in acetonitrile at -35 °C for 3 h. When TLC showed complete disappearance of **2α**, the reaction mixture was filtered on a pad of Celite. The usual work-up gave **8α**[12] in 46.0% yield and **8β** in 32.9% yield (α:β = 58:42) after chromatographic separation, **8α**, $[\alpha]_D^{24}$ -20° (*c* 0.60, $CHCl_3$). In the case of **2β**, the same treatment with alcohol **3** in the presence of TMSOTf gave **8α** in 52.6% yield and **8β** in 39.5% yield (α:β = 57:43) after isolation. Glycosidation of **2** with primary alcohols, **4** and **5**, was performed in same manner as that described for alcohol **3** to afford known **9**[13] and **10** in high yields with similar stereoselectivity, **10**, $[\alpha]_D^{37}$ -13° (*c* 0.21, $CHCl_3$). As for secondary alcohols, **6**[14] and **7**[15], the glycosidation also proceeded smoothly to give known **11**[14] and **12**, respectively, in high yields, **12**, $[\alpha]_D^{34}$ -6.3° (*c* 1.00, $CHCl_3$). These results suggested that the lauryl glycoside **2** underwent TMSOTf-promoted glycosidation with various alcohols, the anomeric ratio of the newly formed glycosidic bonds was dependent on the anomeric configuration of the donor, and the α-selectivity of **2α** in the glycosidation reaction was slightly higher than that of **2β**. However, using β-lauryl thioglycoside **2β** as a donor for the glycosidation gives a higher yield than that of **2α** even though α-selectivity is lower.

Scheme 2

Table 2

[¶]All new compounds with specific rotation data gave satisfactory results of elemental analyses or high resolution mass spectra.

In our ongoing synthetic study of sialyl oligosaccharides, we previously reported the synthesis and reactivity of a 5-azido analogue of sialic acid.[16] 5-Azido analogues have been prepared by several groups,[17] and 5-azido analogues of sialic acid are therefore of great importance for developing *N*-substituted sialooligosaccharide. Therefore, conversion of **2β** into its 5-azido analogue **14** was attempted by the previously reported method shown in Scheme 3. In brief, de-*O*-acetylation of **2β** followed by acid hydrolysis of the acetamide[18] gave corresponding ammonium salt **13**, which was treated with TfN_3 followed by usual acetylation to give pure **14** in 89.6% yield after silica gel chromatographic purification, $[\alpha]_D^{31}$ -90° (*c* 1.31, $CHCl_3$), IR (KBr) 2114 ($\nu_{N=N=N}$) and 1748 ($\nu_{C=O}$) cm^{-1}, ^1H NMR ($CDCl_3$) δ 3.21 (t, 1 H, $J_{4,5} = J_{5,6}$ 10.2 Hz, H-5). The azide **14** was quantitatively condensed with an alcohol **3** by TMSOTf-mediated glycosidation as described above to yield known **15α** (48.9%) and **15β** (51.1%) (α:β = 49:51) after isolation. The reaction also gave glycal product **16** in 43.4% yield based on **14**. In contrast to our previous study of 5-azido sialic acid,[16] the yield of α glycoside from **14** was unfortunately lower than that from phenyl thioglycoside (60.7%).

Scheme 3

In conclusion, an efficient synthesis of thiolauryl glycoside **2** was accomplished using nonstinking thiol, and TMSOTf-mediated glycosidation of both anomers was tested and showed excellent reactivities. Further transformation of thioglycoside **2β** into corresponding azido analogue **14** was performed, and **14** also underwent TMSOTf-mediated glycosidation to give a known glycoside in high yield. This methodology is applicable for our synthetic studies[19] of "Glyco-Silicon Functional Materials", including assembly of sialyl lactose[19c] and sialyl lactosamine,[19d] and the results will be reported in the near future.

Acknowledgments

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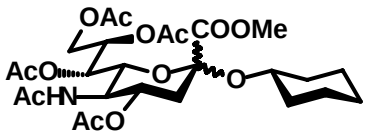
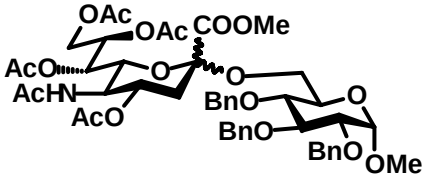
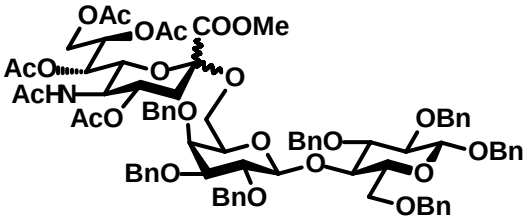
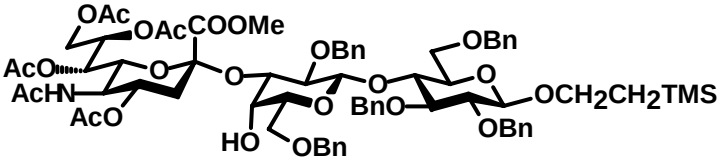
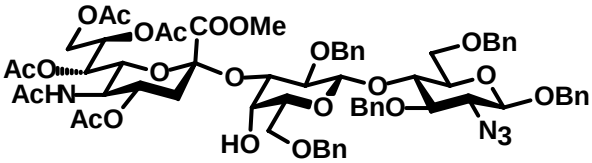
Table 1. Selected chemical shifts and *J* values related to sialic acid moieties.

Compound	H-3eq (ppm)	H-4 (ppm)	$J_{7,8}$ (Hz)	Δδ|H-9a-H-9b| (ppm)
2α	2.71	4.86	8.1	0.20
2β	2.52	5.27	2.68	0.63
8α[a]	2.60	4.83	8.0	0.20
8β[a]	2.44	5.18	2.4	0.81
9α[b]	2.65	4.86	9.1	0.28
9β[b]	2.48	5.17	ND[e]	0.97
10α	2.53	4.84	ND[e]	0.25
10β	2.33	4.82	ND[e]	0.60
11[c]	2.50	4.85	7.9	0.36
12	2.51	4.86	8.0	0.33
14	2.66	5.29	1.6	0.55
15α[d]	2.66	5.28	5.8	0.48
16	5.97[f]	5.56	6.1	0.34

[a]Lit. Ref #12. [b]Lit. Ref #13. [c]Lit. Ref #14. [d]Lit. Ref #16. [e]ND means not determined due to overlapping of other protons [f]H-3 proton of the glycal.

Table 2. Results of glycosidation of **2** with alcohols.

Donor	Acceptor R-OH	Product	Yield[a] (%)	Ratio[b] (α:β)
2α	**3**	 **8**	79	58:42
2β			92	57:43
2α	**4**	 **9**	87	71:29
2β			93	65:35
2α	**5**	 **10**	70	63:37
2β			83	57:43
2α	**6**	 **11**	48	1:0[c]
2β			55	1:0[c]
2α&2β	**6**	**11**	50	1:0[c]
2α&2β	**7**	 **12**	66	1:0[c]

[a]Isolated yield based on alcohol. [b]Mol/mol ratio after isolation. [c]Isolation of β-anomer was not conducted.

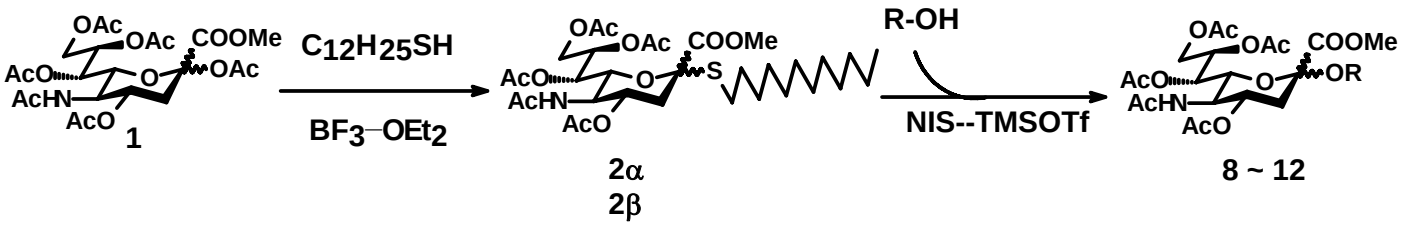
Legends to Schemes

Scheme 1. *Reagents and conditions:* i) Dodecanthiol (4 molar excess), BF_3—OEt_2 (3 molar excess), CH_2Cl_2, 0 °C→rt, 3.5 h.

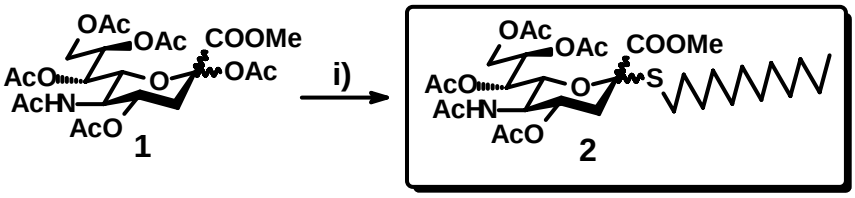
Scheme 2. *Reagents and conditions:* i) NIS (2 molar excess), TMSOTf (0.2 molar excess), R-OH (0.5 molar excess), MS3A, CH_3CN, -35 °C, 3 h.

Scheme 3. *Reagents and conditions:* i) NaOMe, MeOH, -rt, 2 h; ii) CH_3SO_3H (2 molar excess), MeOH, 60 °C, 19 h; iii) TfN_3 (4.5 molar excess), DMAP (3 molar excess), MeOH, rt, overnight, then, Ac_2O—Pyr, rt; iv) NIS (2 molar excess), TMSOTf (0.2 molar excess), **3** (0.5 molar excess), MS3A, CH_3CN, -35 °C, 3 h.

Graphical abstract



Scheme 1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O
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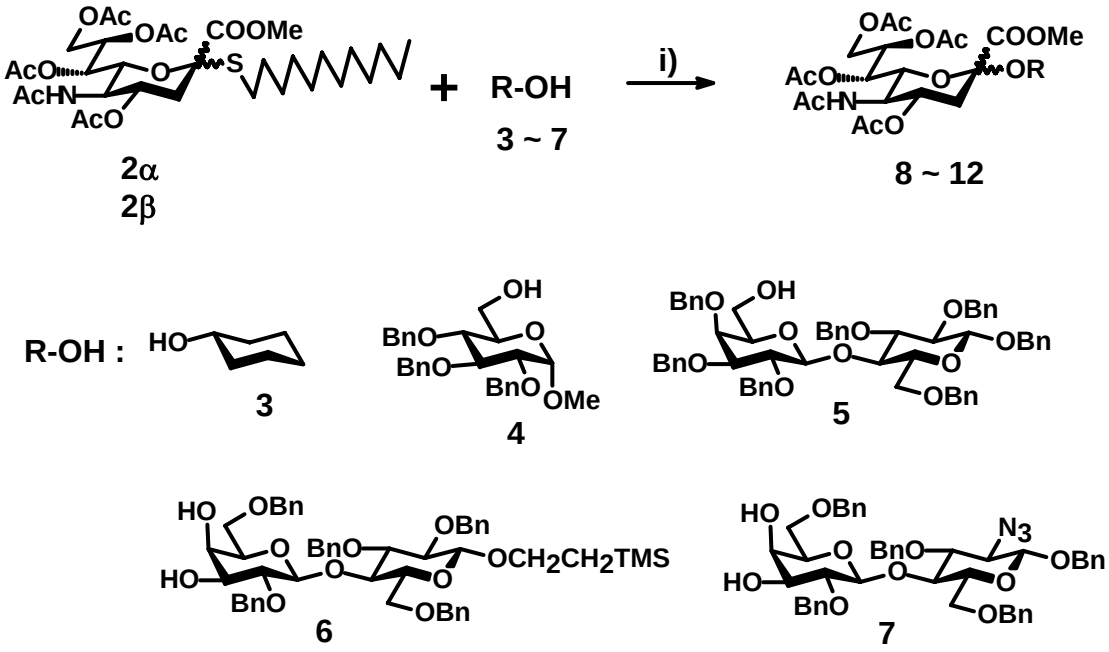
AcO
2

Scheme 2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AcO
O
OR
2α
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R-OH :
HO
3
OH
BnO
BnO
BnO
O
OMe
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OH
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OBn
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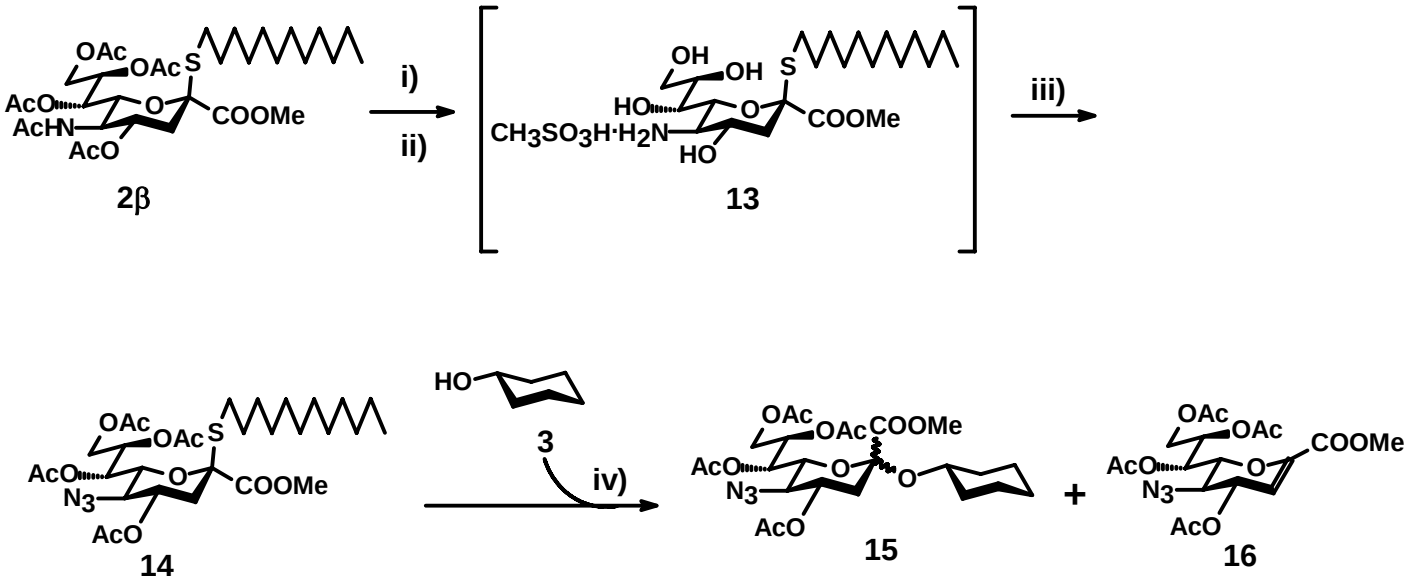
Scheme 3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AcO
14
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