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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7431–7435

Synthesis of *N*,*N*-Ac,Boc laurylthio sialoside and its application to O-sialylation

Kiyoshi Ikeda,* Keisuke Miyamoto and Masayuki Sato

Department of Organic Chemistry, School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka-shi 422-8526, Japan

Received 23 July 2007; revised 23 August 2007; accepted 24 August 2007
Available online 29 August 2007

Abstract—The combination of the 5-*N*-*tert*-butoxycarbonyl (Boc) group of laurylthio sialoside and cyclopentyl methyl ether (CPME) as a solvent enhanced the reactivity and α-selectivity of the sialyl donor during sialylation. Selective deprotection of the *N*-Boc group of sialoside, including an acid-sensitive isopropylidene function, was successfully achieved by $Yb(OTf)_3$–SiO_2. Transformation of *N*,*N*-Ac,Boc into an *N*-acetylglycolyl group of sialoglycoside was easily performed via selective N-deacylation of the mixed Ac-*N*-Boc carbamate, subsequent Boc group removal, and acylation.
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1. Introduction

N-Acetylneuraminic acid (sialic acid, Neu5Ac) and its various analogues are critical components of many glycoconjugates involved in biologically important ligand–receptor interactions.[1] The development of an efficient method of O-sialylation has been a challenging task in the field of sialic acid chemistry.[2] One important trend focuses on the utilization of the thioglycoside of sialic acids for milder and stereoselective O-glycosylation,[3] however, one drawback is the extremely unpleasant odor of thiols employed for thioglycoside formation.[4] Recently, Matsuoka and co-workers reported thioglycoside of sialic acids with a lauryl moiety to avoid this disadvantage, and its application to stereoselective O-sialylation.[5] Modifications of NHAc of sialic acid donors have been reported to influence the reactivity and α-selectivity of sialylation. It is well recognized that the replacement of the *N*-acetyl functional group at C-5 with *N*,*N*-diacetyl (NAc_2),[6] *N*-trifluoroacetyl (NTFA),[7] *N*-2,2,2-trichloroethoxycarbonyl (NTroc),[8] *N*-fluorenylmethoxycarbonyl (Fmoc),[9] *N*-phthaloyl (Npht),[10] azido,[11] or *N*,*N*-Ac,Boc[12] in the sialyl donor results in higher yields and, in some cases, better α-selectivity during sialylation. Temporary *N*-Boc protected the sialyl donor, allowing varying acyl moiety at the nitrogen atom of neuraminic acid residue after assembling the oligosaccharide backbone.[13]

As a part of our program aimed at the development of new O-sialylation,[14] we report the preparation of novel *N*,*N*-diacyl analogues of sialic acid **2** with a laurylthio moiety as the residual group during sialylation and their application to stereoselective O-sialylation.

2. Results and discussion

As shown in Scheme 1, three laurylthio glycosides with NHAc, NAc_2, and *N*,*N*-Boc,Ac at the C-5 position (**2a**, **2b**, and **2c**, respectively), and a *N*,*N*-Boc,Ac phenylthio glycoside **2d** were tested for their reactivity and α-selectivity in sialylation with acceptors. Initially, we investigated the preparation of **2** to evaluate their potential for undergoing efficient glycosylation (Scheme 1). Acetate **1** was treated with 1-dodecanethiol in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 to give anomeric mixtures of thioglycoside **2a**[5] in 84% yield. *N*,*N*-Diacylated donors **2b**[15] and **2c**[16] were successfully prepared by the treatment of **2a** with isopropenyl acetate and PTSA or with Boc_2O and pyridine in 89% or 99% yield. *N*,*N*-Ac,Boc phenylthio glycoside **2d**[12] was prepared from **1** in 80% yield over two steps.

Initial glycosylation experiments were carried out with the reaction of glycosyl donor **2b** with *p*-nitrobenzyl alcohol **3a**[17] as an acceptor, and the results are shown

Keywords: *N*,*N*-Ac,Boc laurylthio sialoside; O-sialylation; CPME, *N*-Acetylglycolyl sialoglycoside.
* Corresponding author. Tel./fax: +81 54 264 5108; e-mail: ikeda@ys2.u-shizuoka-ken.ac.jp

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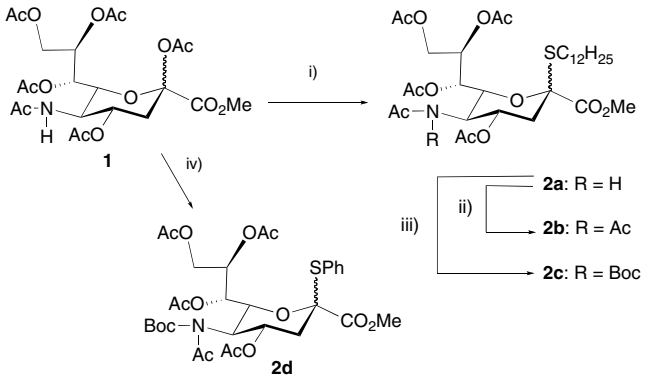
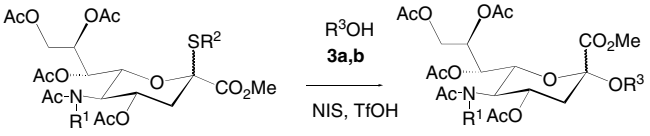
doi:10.1016/j.tetlet.2007.08.088



Scheme 1. Reagents and conditions: (i) 1-dodecanethiol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 24 h, 84%; (ii) isopropenyl acetate, PTSA, 65 °C, 17 h, 89%; (iii) Boc_2O, DMAP, THF, reflux, 4 h, 99%; (iv) (1) thiophenol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 24 h, 89%, (2) Boc_2O, DMAP, THF, reflux, 20 h, 90%.

in Table 1. The glycosylation reaction between **2b** and 1.5 M equiv of **3a** using 3.0 M equiv of NIS and 1.0 M equiv of TfOH[18] and MS 3 Å in CH_3CN as expected from the assistance of the nitrile solvent effect[19] at −40 °C gave the expected glycoside **4a** in 70% yield as an anomeric mixture with β-anomer as the major product (α:β = 1:1.8) (entry 1). Next, the donor property of **2c** having an *N*-Boc moiety was examined and a small increment of α-selectivity of **2c** glycosylation with **3a** was observed (79%, α:β = 1.3:1) (entry 2). Encouraged by these results, the solvent effect of CPME[20] was examined. High α-selectivity in the condensation of **2c** with **3a** in CPME was observed (85%, α:β = 10:1) (entry 3). In sharp contrast to this, the sialylation of **2a** with **3a** in CPME was nonselective, together with the formation of the 2,3-dehydro glycal derivative (11%) (entry 4). When Et_2O was used as a solvent, both yield and α-selectivity in sialylation were low (62%, α:β = 2.8:1) (entry 5). Interestingly, the glycosylation of **2d** with **3a**

Table 1. Glycosylation reaction with C-5 *N*-protected sialic acid derivatives **2a–d**



2a-d: R^1 = H, Ac, Boc; R^2 = Ph, $C_{12}H_{25}$

4a-f: R^1 = H, Ac, Boc

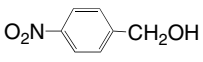
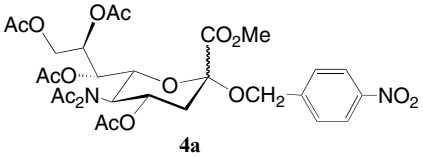
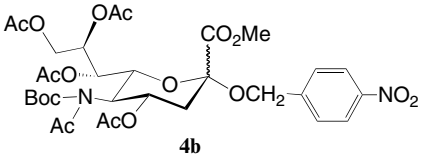
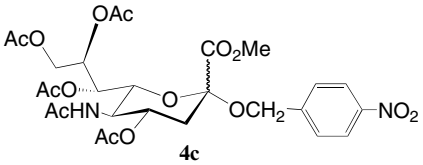
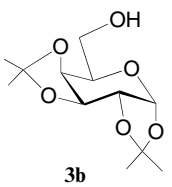
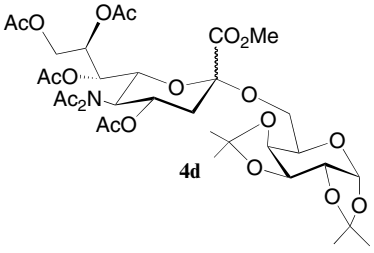
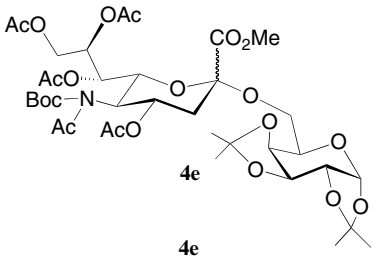
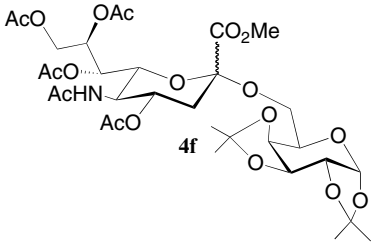
Entry	Glycosyl donor **2**	Glycosyl acceptor **3**	Condition[a]	Product **4**	Yield[b] (%) (α/β ratio)
1	**2b**	 **3a**	CH_3CN, −40 °C	 **4a**	70 (1:1.8)
2	**2c**	**3a**	CH_3CN, −40 °C	 **4b**	79 (1.3:1)
3	**2c**	**3a**	CPME, −40 °C	**4b**	85 (10:1)
4	**2a**	**3a**	CPME, −40 °C	 **4c**	77 (1:1)
5	**2c**	**3a**	Et_2O, −40 °C	**4b**	62 (2.8:1)
6	**2d**	**3a**	CPME, −40 °C	**4b**	59 (6:1)
7	**2b**	 **3b**	CH_3CN, −40 °C	 **4d**	72 (1:2)

Table 1 (*continued*)

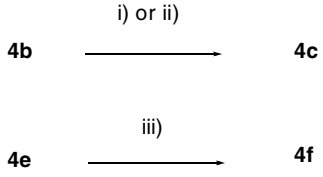
Entry	Glycosyl donor **2**	Glycosyl acceptor **3**	Condition[a]	Product **4**	Yield[b] (%) (α/β ratio)
8	**2c**	**3b**	CH_3CN, −40 °C	 **4e**	62 (2.2:1)
9	**2c**	**3b**	CPME, −40 °C	**4e**	Quant. (α only)
10	**2c**	**3b**	Et_2O, −40 °C	**4e**	75 (6:1)
11	**2c**	**3b**	CPME, −40 °C	**4e**	47 (5.7:1)[c]
12	**2a**	**3b**	CPME, −40 °C	 **4f**	77 (1.9:1)
13	**2a**	**3b**	CPME, −80 °C	**4f**	66 (3.8:1)

[a] With respect to **2**, 1.5 equiv of **3** and 2.0 equiv of NIS and 1.0 equiv of TfOH were used. Reaction time was 16 h.

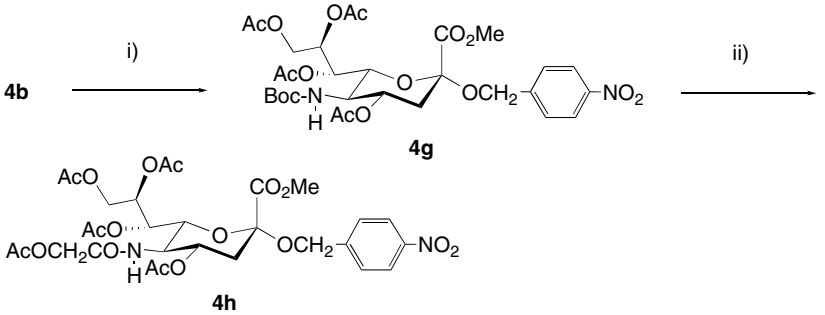
[b] Isolated yields. The stereochemistry of **4** was confirmed by ^1H NMR (500 MHz) spectral comparison of the chemical shifts of $3H_{eq}$ signals of glycosides. Anomeric ratios were determined on the basis of the integration ratios of the $3H_{eq}$ signals of glycosides in ^1H NMR spectroscopy.

[c] With respect to **2**, 1.5 equiv of **3** and 2.0 equiv of NIS and 1.0 equiv of AgOTf were used. Reaction time was 16 h at −40 °C, and 24 h at room temperature.

catalyzed by NIS/TfOH in CPME at −40 °C gave **4b** in inferior yield (59%) and α-selectivity (α:β = 6:1) (entry 6). Coupling of **2b** with 1,2:3,4-di-*O*-isopropylidene-α-D-galactose **3b** in CH_3CN afforded the resulting (2–6)sialoside **4d** in 72% yield (α:β = 1:2) (entry 7). When the reaction of **2c** with **3b** was carried out in CH_3CN at −40 °C, an increment of α-selectivity was observed (62%, α:β = 2.2:1) (entry 8). The sialylation of **2c** with **3b** in CPME at −40 °C showed remarkable improvement in both the glycosylation yield (quantitative) and α-selectivity (only α-anomer) (entry 9).[21] The reaction using NIS-AgOTf[22] as a promoter in CPME afforded **4e** with α-anomer as the major product (47%, α:β = 5.7:1) (entry 11). Coupling of **2a** with **3b** in CPME at −40 °C resulted in the formation of **4f** with 77% yield (α:β = 1.9:1) (entry 12). When the reaction of **2a** with **3b** was carried out in CPME at −80 °C, an increment of α-selectivity was observed (α:β = 3.8:1); however, the yield of **4f** decreased to 66% (entry 13). These results show that it is important to use the combination of **2c** and CPME for higher yields and α-selectivity during sialylation.



Scheme 2. Reagents and conditions: (i) $Yb(OTf)_3$–SiO_2, rt, 48 h, 84%; (ii) TFA–CH_2Cl_2 (1:4), rt, 1 h, 96%; (iii) $Yb(OTf)_3$–SiO_2, rt, 48 h, 81%.



Scheme 3. Reagents and conditions: (i) (1) NaOMe, MeOH, rt, 2 h, (2) Ac_2O, pyridine, rt, 24 h, 75% over two steps; (ii) (1) TFA–CH_2Cl_2 (1:4), rt, 1 h; (2) $AcOCH_2COCl$, pyridine, rt, 24 h, 90% over two steps.

Removal of the *N*-Boc group of **4b** with TFA–CH_2Cl_2 (1:4) or $Yb(OTf)_3$–SiO_2[23] gave **4c** in 96% or 84% yield. Mild and selective deprotection of the *N*-Boc group of **4e**, including an acid-sensitive isopropylidene function with a catalytic amount of $Yb(OTf)_3$–SiO_2, proceeded smoothly to give **4f** in 81% yield (Scheme 2).

N,*N*-Boc,Ac analogues of sialic acid are of great importance for synthesizing N-substituted sialosides.[12] Thus, selective *N*,*O*-deacetylation of **4b** with sodium methoxide and successive acetylation with Ac_2O and pyridine gave *N*-Boc derivative **4g** in 75% yield over two steps, which was deprotected by TFA and subsequently submitted to N-acylation of the resulting free amino group with acetyl glycoloyl chloride and pyridine to give the corresponding *N*-acetylglycolyl glycoside **4h** in 90% yield over two steps (see Scheme 3).

3. Conclusion

In summary, we have developed an efficient method to synthesize α-sialoglycosides by using sialyl donor **2c** in CPME. It should be noted that the combination of both the long-range assistance[20] of the bulky 5-*N*-Boc group of **2c** and the solvent effect of CPME is critical for efficient α-sialylation. *N*,*N*-Boc,Ac glycoside **4b** was successfully transformed into the corresponding *N*-acetyl glycolyl sialoglycoside **4h**.

We are currently applying this methodology to the synthesis of other oligosaccharides.

Acknowledgments

This work was financially supported in part by a Grant-in-Aid for Scientific Research No. 19590103 from the Ministry of Education, Science, Sports, and Culture of Japan. The authors also thank MARUKIN BIO, INC. (Kyoto, Japan) for the generous gift of Neu5Ac. CPME used in this work was a generous gift from ZEON Corporation, R&D Center.

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15. Synthesis and characterization of **2b**: A mono-*N*-acetylated derivative **2a** (130 mg, 0.188 mmol) was dissolved in isopropenyl acetate (4 mL) and TsOH monohydrate (7.5 mg, 0.05 mmol) was added. The reaction mixture was stirred at 65 °C for 17 h, then neutralized with Et_3N and evaporated to dryness. The crude product purified by silica gel column chromatography using AcOEt–*n*-hexane (1:2) gave **2b** (123 mg, 89%). ^1H NMR (500 MHz, $CDCl_3$) δ: 0.87 (t, 3H, $J = 7.0$ Hz, $-CH_3$), 1.26–1.31 (m, 18H, $-(CH_2)_9-$), 1.50–1.54 (m, 2H, $-SCH_2CH_2-$), 1.97, 2.02, 2.05, 2.11 (s, each 3H, OAc), 2.28, 2.40 (each 3H, s, NAc_2), 2.49–2.54 (m, 2H, $-SCH_2CH_2-$), 2.67 (dd, 1H, $J_{3eq,4} = 5.2$, $J_{3ax,3eq} = 13.7$ Hz, H-3eq), 3.79 (s, 3H, OCH_3), 4.14–4.22 (m, 2H, H-5, H-9a), 4.66 (dd, 1H, $J_{9b,8} = 2.3$, $J_{9a,9b} = 12.6$ Hz, H-9b), 5.10–5.15 (m, 1H, H-8), 5.24 (dd, 1H, $J_{7,6} = 1.7$, $J_{7,8} = 4.0$ Hz, H-7), 5.40 (dd, 1H, $J_{6,5} = 10.0$, $J_{6,7} = 2.0$ Hz, H-6), 5.79 (ddd, 1H, $J_{4,5} = J_{4,3ax} = 10.9$ Hz, H-4). Positive FAB MS *m*/*z* 718 $[M+H]^+$.
16. Synthesis and characterization of **2c**: A solution of **2a** (514 mg, 0.76 mmol), Boc_2O (498 mg, 2.28 mmol), and 4-dimethylaminopyridine (DMAP) (47 mg, 0.38 mmol) in dry THF (15 mL) was refluxed for 4 h under Ar. The resulting mixture was concentrated in vacuo. The crude product purified by silica gel column chromatography using AcOEt–*n*-hexane (1:2) gave **2c** (583 mg, 99%). ^1H NMR (500 MHz, $CDCl_3$) δ: 0.88 (t, 3H, $J = 7.0$ Hz, $-CH_3$), 1.24–1.26 (m, 18H, $-(CH_2)_9-$), 1.48–1.52 (m, 2H, $-SCH_2CH_2-$), 1.66 (s, 9H, NBoc), 1.95, 2.03, 2.05, 2.07 (s, each 3H, OAc), 2.35 (s, 3H, NAc), 2.51–2.58 (m, 3H, $-SCH_2CH_2-$, H-3eq), 3.81 (s, 3H, OCH_3), 4.19 (dd, 1H, $J_{9a,8} = 7.9$, $J_{9a,9b} = 12.8$ Hz, H-9a), 4.81 (m, 2H, H-5, H-9b), 5.10–5.13 (m, 1H, H-6, H-8), 5.30 (dd, 1H, $J_{7,6} = J_{7,8} = 2.4$ Hz, H-7), 5.66 (ddd, 1H, $J_{4,5} = J_{4,3ax} = 10.9$ Hz, $J_{4,3eq} = 2.5$ Hz, H-4). Positive FAB MS *m*/*z* 798 $[M+Na]^+$.
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21. *Representative procedure for glycosylation* (Table 1, entry 9): A mixture of the glycosyl donor **2c** (39 mg, 0.050 mmol), glycosyl acceptor **3b** (20 mg, 0.075 mmol), and 4 Å molecular sieves (0.10 g) in CPME (2.0 mL) was stirred under argon for 6 h at room temperature. NIS (34 mg, 0.15 mmol) and TfOH (7.5 mg, 0.05 mmol) were added to the reaction mixture at −40 °C. The reaction mixture was stirred for 16 h at the same temperature in the dark. Upon completion, the reaction solution was diluted

with CH_2Cl_2 and the suspension was filtered off and the filtrate was washed with aqueous 10% $Na_2S_2O_3$ solution and brine and dried over anhydrous $MgSO_4$, and evaporated. Column chromatography on silica gel using AcOEt–*n*-hexane (1:1) gave **4d** (42 mg, quant.) as only an α-anomer. ^{1}H NMR ($CDCl_3$) δ: 1.31, 1.32, 1.40, 1.45 (s, each 3H, isopropylidene), 1.56 (s, 9H, NBoc), 1.96, 2.03, 2.06, 2.13 (s, each 3H, OAc), 2.36 (s, 3H, NAc), 2.73 (dd, 1H, $J_{3eq,4} = 4.9$, $J_{3ax,3eq} = 12.9$ Hz, H-3eq), 3.78 (s, 3H, OCH_3), 3.80–3.89 (m, 3H, Gal-H-5, 6a, 6b), 4.11–4.37 (m, 3H, H-9a, Gal-H-2,4), 4.59–4.63 (m, 2H, H-5, Gal-H-3), 4.69 (dd, 1H, $J_{9b,8} = 1.7$, $J_{9a,b} = 10.3$ Hz, H-9b), 5.18 (dd, 1H, $J_{6,5} = 7.7$, $J_{6,7} = 2.0$ Hz, H-6), 5.36–5.40 (m, 2H, H-7, H-8), 5.51 (d, 1H, $J_{Gal\text{-}H\text{-}1,H\text{-}2} = 4.6$ Hz, Gal-H-1), 5.70 (ddd, 1H, $J_{4,5} = 5.2$, $J_{4,3ax} = 10.4$ Hz, H-4). Positive FAB MS *m*/*z* 834 $[M+H]^+$, 856 $[M+Na]^+$.

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