Tetrahedron Letters 49 (2008) 5111–5114

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Thioester-assisted α-sialylation reaction

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ARTICLE INFO

Article history:
Received 7 April 2008
Revised 22 May 2008
Accepted 26 May 2008
Available online 12 June 2008

Keywords:
Sialic acid
Glycosylation
Thioester
Auxiliary
Galactal

ABSTRACT

α-Selective sialylation reactions were carried out using novel sialic acid building blocks that possess a thioester auxiliary. In contrast to other arylthio- and benzylthioester derivatives, sialyl phosphite **1a** (with the phenylthioester moiety) was employed as the α-selective building block, and was reacted with various primary alcohols, including the C6–OH group of galactose and glucose, with moderate to excellent α-selectivities. For C3–OH of the galactose, 4,6-di-*O*-benzylgalactal afforded desired α-linkage with excellent selectivity.

Sialic acids have been found on the non-reducing terminus of various glycans on cell surfaces. Sialylated glycolipids and glycoproteins on cell membranes are closely associated with physiological processes involving cell adhesion, signal transduction, and fertilization.[1] Some kinds of sialylated glycans are known as cancer antigens and play a significant role in malignant transformation and metastasis.[2] Several infectious bacteria and viruses also interact with these glycans in their entry stage.[3]

Chemical synthesis of sialic acid-terminated glycans requires investigations of α-selective sialic acid building blocks.[4] Upon an activation of the leaving group at the C2-position, the resulting oxocarbenium ion is destabilized by the electron-withdrawing ester group on the anomeric center. As a consequence, the less reactive tertiary anomeric center becomes susceptible to elimination to give a C2,3-dehydro sialic acid derivative. Furthermore, the C3-deoxy structure can cause difficulty in controlling the stereoselectivity in the sialylation reactions.

To address these issues, recent advances in sialic acid building blocks have provided two solutions: first, the use of C5-amino protecting groups,[5] such as *N*-TFA,[5b] carbamate,[5d–f] and C4,5-oxazolidinone[5g–i] groups, have been shown to improve the reactivity as well as the stereoselectivity of α-sialylation reactions. Second, the use of C3-participating groups, such as OH,[6a] Br,[6b] SR,[6c–e] and (O–(C=S)R)[6f] was shown to assist in the stereoselective formation of α-sialoside through a three- or five-membered ring intermediate.

The use of such building blocks, however, would require an additional step to remove the participating group in order to generate the deoxy moiety, and therefore, the participating functionalities were introduced on the carboxylic acid moiety at the C1-position through an alternate approach.[7] Specifically, building blocks that possess $-(CH_2)_2CN$[7b] or $-CH_2CONMe_2$[7c,d] have favored the formation of the α-sialoside, presumably through intermediates that coordinate with the auxiliaries. Furthermore, such ester functionalities can be deprotected via mild hydrolysis during the final global deprotection step. To date, however, satisfactory yield and stereoselectivity have yet to be achieved in the formation of a naturally occurring sialyl-α(2-3)-galactose unit.

To improve the stereoselectivity in C1-participation strategy, novel sialic acid building blocks **1a–e**, which possess a thioester moiety at the C1-position, were employed. Presumably, the auxiliary group would augment the 'nitrile effect',[8] in which, upon activation of the building block, the thioester moiety would stabilize the proposed five-membered intermediate in the presence of the nitrile solvent (Fig. 1). In this Letter, we initially described tuning of thioester auxiliaries from the points of stability, yield, and stereoselectivity in the glycosylation with C6–OH of the galactoside **6**. Furthermore, the applicability of building block **1a** in sialylation reactions was investigated using several acceptor alcohols.

First, building blocks **1a–e**, which possess benzylthio and arylthio moieties, were synthesized from phenylthioglycoside **2**[9] (Scheme 1).[10] Prior to the introduction of the thioester moieties, the methyl ester group of **2** was selectively removed using LiCl in pyridine,[11] then treatment with acid provided carboxylic acid **3** in 91% yield. Liberated carboxyl group of **3** was activated by using chloroformic chloride, and succeeding addition of thiols to give the corresponding thioester building blocks **4a–e** in moderate yields.[12] Although sialylation reactions using thioglycoside **4a** were performed by the treatment with NIS and TfOH, the reactions did not proceed due to the sluggish activation rate of **4a**. From this

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0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.154

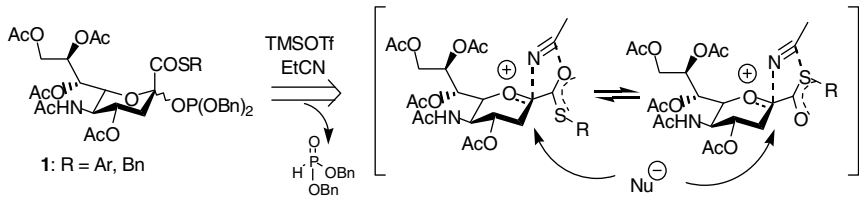
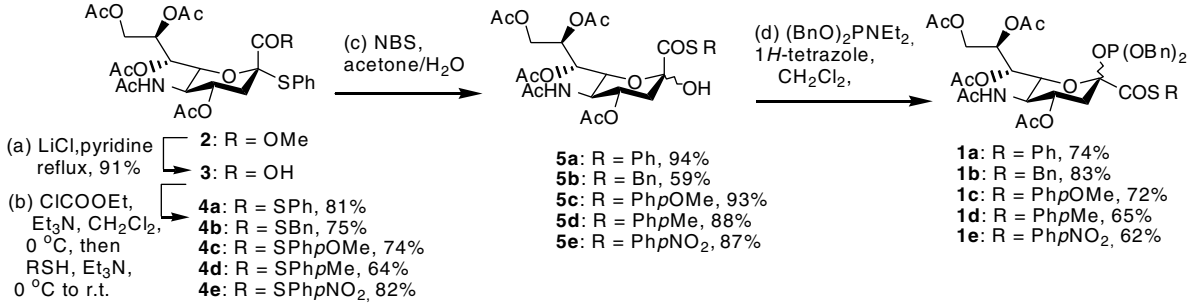


Figure 1. Structure of novel sialic acid building block **1** and plausible reaction mechanism.



Scheme 1. Reagents and conditions for the synthesis of **1a–e**.

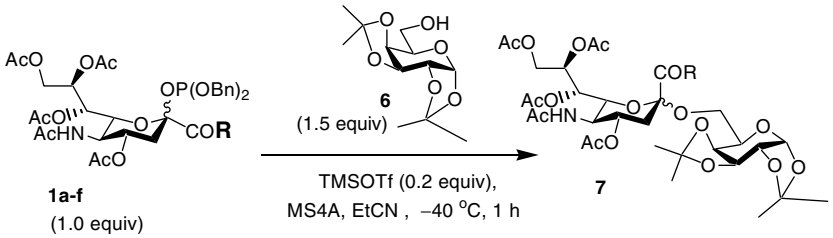
result, the anomeric phenylthio moiety was substituted with a more reactive phosphite group.[13] Hydrolysis for the phenylthio group of **4a–e** was achieved using NBS under acetone/H_2O conditions to afford **5a–e**.[14] Subsequently, the phosphite leaving group was introduced using *N*,*N*-diethyldibenzylphosphoramidite with 1*H*-tetrazole[13b] to afford desired **1a–e**.

To investigate the effects of the thioester moieties, sialylation reactions between building blocks **1a–f** (1.0 equiv) and the C6–OH of galactoside **6** (1.5 equiv) were carried out (Table 1).[15] In all cases, phosphites **1a–f** were readily activated using catalytic amounts of TMSOTf at −40 °C in propionitrile (EtCN).[16] According to our results, phenylthioester **1a** (entry 2) and benzylthioester **1b** (entry 3) gave good yields as well as better selectivities, in comparison to the corresponding methyl ester **1f** (entry 1). Based on this result, further investigations were demonstrated to study the electron-donating/withdrawing substituents on the thiophenyl aromatic system. Sialylation reactions involving building blocks **1c**, **1d**, and **1e** (entries 4–6, respectively) proceeded smoothly to afford the corresponding disaccharides in moderate to good yields. With respect to the stereoselectivity, *p*-methoxyphenylthioester **1c** (entry 4) and *p*-tolylthioester **1d** (entry 5) exhibited moderate α-selectivities (α/β = 4.5–4.7:1). In contrast, thioester **1e** (entry 6), which possesses an electron-withdrawing nitro function, resulted in low selectivity (α/β = 2.5:1). Among these entries, phenylthioester **1a** demonstrated good α-selectivity and yield, and was selected as the optimal building block for further sialylation reactions with various acceptor alcohols. Furthermore, **1a** exhibited the best conversion along the preparation scheme from **3** to **1a**.

Results of the sialylation reactions of **1a** (α/β = 1:4) with various acceptor alcohols are shown in Table 2. First, to examine the conversion rate of **1a**, sialylation reactions were carried out using excess amounts of *n*-octanol, cyclohexanol, and 1-adamantanol. As shown in entry 1, the use of *n*-octanol **8** provided glycoside **15** in 91% yield with moderate α-selectivity (α/β = 6:1). Similarly, the use of cyclohexanol **9**, which was chosen as a simple secondary alcohol, readily provided glycoside **16** in 87% yield (α/β = 4.2:1). In contrast, 1-adamantanol **10** afforded glycoside **17** in low yield (entry 5), presumably due to the steric hindrance.

Next, sialylation reactions between **1a** and the C6–OH group of galactoside and glucoside were investigated. In the case of galacto-

Table 1
The sialylation reactions using novel sialic acid building blocks **1a–f**



Entry	R	Yield (%)	α/β Ratio[a]
1	OMe (**1f**)	**7f**, 90	3.8:1
2	SPh (**1a**)	**7a**, 89	5.8:1
3	SBn (**1b**)	**7b**, 92	5.2:1
4	SPh*p*OMe (**1c**)	**7c**, 77	4.5:1
5	SPh*p*Me (**1d**)	**7d**, 87	4.7:1
6	SPh*p*NO_2 (**1e**)	**7e**, 74	2.5:1

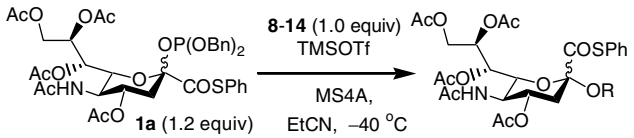
[a] α/β Ratio was determined by ^{1}H NMR spectra.

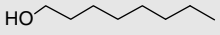
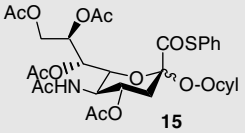
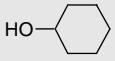
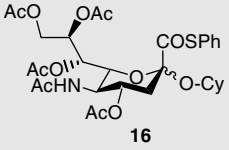
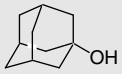
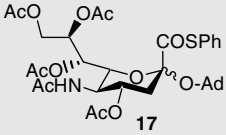
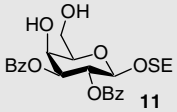
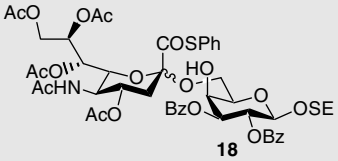
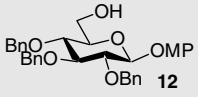
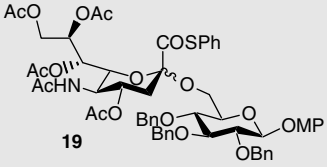
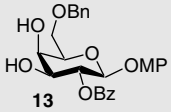
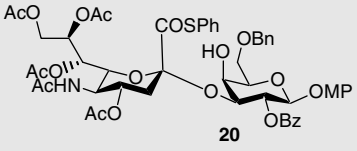
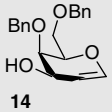
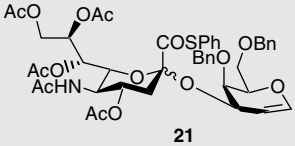
side **11**, which features a 4,6-diol, the reaction readily proceeded to provide **18** in 87% yield with excellent α-selectivity (α/β = 9:1, entry 2).[17] The use of glucose acceptor **12** provided desired sialoside **19** in 57% yield with moderate selectivity (α/β = 5:1, entry 3).

Finally, reactions involving naturally occurring α(2-3)-linkages of galactose derivatives were carried out. Although galactose diol acceptor **13** possesses a relatively reactive C3–OH group, desired disaccharide **20** was produced in merely 31% yield (entry 6).[18] In contrast, the use of galactal **14**,[19] which possesses an exposed nucleophilic C3-OH, as the acceptor substrate,[20] proceeded smoothly to afford disaccharide **21** in 81% yield with excellent selectivity (entry 7, α/β = 9:1), which were better than those of **1f** and **14** (56%, α/β = 3.5:1).

In summary, sialic acid thioester building blocks **1a–e** were synthesized from **2** in three steps involving thioesterification, hydrolysis, and introduction of the phosphite group. The resulting

Table 2
Glycosylation reaction of **1a** with various acceptor alcohols



Entry	Acceptor	Products	Time	Yield (%)	α/β Ratio
1	 **8**	 **15**	30 min	91[a]	6:1
2	 **9**	 **16**	1 h	87[a]	4.2:1
3	 **10**	 **17**	1 h	27[a]	8:1
4	 **11**	 **18**	1 h	87	9:1
5	 **12**	 **19**	1 h	57[b]	5:1
6	 **13**	 **20**	3 h	31[b]	α[d]
7	 **14**	 **21**	1 h 1 h	81 56[c]	9:1 3.5:1[c]

[a] 3.0 equiv of acceptor was used to determine conversions.
[b] CH_3CN/CH_2Cl_2 = 1:2 was used for solvent due to solubility of the MP glycosides.
[c] Donor **1f** (methyl ester) was used.
[d] α-Anomer was isolated as a major product. SE: 2-trimethylsilylethyl, MP: *p*-methoxyphenyl.

thioester building blocks were subjected to sialylation reactions (Table 1), in which phenylthioester **1a** exhibited the best α-selectivity in EtCN, and was chosen for the subsequent sialylation reactions with various acceptor alcohols. For primary acceptor alcohols, **1a** afforded α-sialosides in good yield. In the case of secondary acceptors, galactal **14** was reacted with **1a** to give desired sialoside **21** with good α-selectivity. As to the presumable reaction mechanism, sialic acid building block **1a** was activated by TMSOTf, then stable five-membered intermediate was immediately formed with nitrile solvent that approaches from β-face by the 'nitrile effect' (Fig. 1). Finally, the acceptor alcohol attacks from the α-face to form resulting α-sialoside dominantly.

Acknowledgments

This work was supported by the 'Science Frontier Project of Kanagawa University' from the Ministry of Education, Science, Sports and Culture, Japan, and by Grants-in-Aid for Scientific Research for Young Scientists B (No. 20710171 to S.H.) from Japan Society for the Promotion Science (JSPS). We thank Ms. A. Masuda (Kanagawa University) for technical assistance.

Supplementary data

Synthetic procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra of compounds **1a**, **1b**, **1c**, **1d**, **1e**, **3**, **4a**, **4b**, **4c**, **4d**, **4e**, **7a**, **7b**, **7c**, **7d**, **7e**, **16**, **17**, **18**, **19**, **20**, and **21**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.154.

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10. Ethylthio ester was also synthesized, but the production yields through the preparation steps were low because of the labile ethylthio moiety.
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14. For the synthesis of **5b** carrying benzylthioester, partial decomposition was confirmed in this conditions.
15. The phosphite **1f**[13] carrying methyl ester was also prepared to compare the effect of ester moiety.
16. The reaction was also carried out in CH_2Cl_2, but undesirable β-anomer was dominantly provided (α/β ratio = 0.5–0.8/1; data were not shown).
17. Produced inseparable mixture of **18α**/**18β** was capable for separation after acetylation.
18. The resulting mixture of this reaction was accompanied by several side products. MALDI-TOF mass spectra suggested that intralactonized byproducts between C1-carboxylic acid of sialic acid residue and C4–OH of galactose residue were observed.
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