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O-Sialylation with *N*-Acetyl-5-*N*,4-*O*-Carbonyl Protected Thiosialoside Donors in Dichloromethane; Facile and Selective Cleavage of the Oxazolidinone Ring

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Abstract

An *N*-acetyl-5-*N*,4-*O*-carbonyl protected thiosialoside donor, the structure of which has been defined through X-ray crystallography, was prepared and tested in couplings to a wide range of acceptors. This donor gives excellent yields and α -selectivities in linking with various primary alkyl and carbohydrate acceptors under the *N*-iodosuccinimide and trifluoromethanesulfonic acid in situ activation method at $-40\text{ }^{\circ}\text{C}$ in dichloromethane. The favorable affect of the oxazolidinone substructure for α -sialylation is illustrated by a comparison study with a *N,N*-diacetylsialyl donor, which exhibited inferior yields and α -selectivities. The sialylation selectivity is independent of the anomeric configuration of the donor, but is highly related to the reaction temperature under the NIS/TfOH activation method. In contrast to the NIS/TfOH method, the $\text{Ph}_2\text{SO}/\text{Tf}_2\text{O}$ promotion gives β -selective couplings in dichloromethane. The oxazolidinone of the *N*-acetyl-5-*N*,4-*O*-carbonyl protected sialosides, both α - and β -anomers, could be cleaved cleanly by treatment with sodium methoxide under mild conditions without removal of the acetamide.

Introduction

Sialic acids have been known for more than half a century as important residues incorporated in a wide spread of oligosaccharides and glycoconjugates with important functional roles in mammalian biology.¹ Among the more than 30 naturally occurring derivatives of sialic acids, *N*-acetylneuraminic acid (Neu5Ac) is the most common one and is present in a variety of glycosidic linkages, most typically α -(2,3) and α -(2,6) linkages to galactose (or lactose), as well as α -(2,8) and/or α -(2,9) linkages in polysialic acids. Over the years considerable efforts have been spent on the development of methodologies and strategies for efficient α -sialoside installation allowing for the chemical, enzymatic, or chemoenzymatic synthesis of complex sialoconjugates.² However, α -sialylation remains a formidable challenge owing to the inherent obstacles in sialic acid's unique structure: the hindered C-2-ketal carbon and the methylene C-3 ring carbon, prone to 2,3-elimination.

Progress in sialylation methodologies can be characterized into several categories: the application of various leaving groups, such as halides,³ sulfides,⁴ xanthates,⁵ phosphates,⁶ hydroxyl groups,⁷ and *N*-phenyltrifluoroacetimidates;⁸ introduction of auxiliary participating

groups at the C-3 position, including halogen,⁹ sulfide,¹⁰ selenide,^{10b} or oxygen substituents;^{10c, 11} the use of C-1 neighboring group participations;¹² modification of the amino protective groups at the C-5 position;¹³ and the development of new promoters, such as NIS/TfOH,¹⁴ NIS/TMSOTf,¹⁵ DMTST,¹⁶ NBS/Bu₄NOTf,¹⁷ and Ph₂SO/Tf₂O.^{7, 18}

We directed our efforts in the α -sialylation field to the investigation of a new thiosialoside donor **1** featuring *N*-acetyl-5-*N*,4-*O*-carbonyl protection based on the knowledge that fused structures like 2-*N*,3-*O*-carbamates in glucosamine,¹⁹ 2,3-*O*-carbonates in glucose,²⁰ and 3,4-*O*-carbonates in rhamnopyranose²¹ can have dramatic affects on glycosylations, whether present in donors or acceptors. During the course of our investigation, Takahashi and coworkers described a related study on the use of 5-*N*,4-*O*-oxazolidinones as sialic acid donors (**2**) and acceptors (**3,4**), and achieved an elegant synthesis of α -(2 $\rightarrow$ 8)-oligosialosides by this means.²² Our donor **1** differs from **2** by the presence of the *N*-acetamido group, which we included because of the known beneficial effects of double nitrogen protection,¹³ and to facilitate deprotection.

Results and Discussion

Donor **1** was prepared from **5**²³ on a gram scale following the protocol employed for the introduction of *N*-acetyl-2-*N*,3-*O*-carbamates to the glucosamine series (Scheme 1).^{19g,h} The anomer **9** was prepared analogously from **7**²³ (Scheme 1). Both **1** and **9** are crystalline solids and showed excellent shelf-stability.

First, the coupling of **1** with two alkyl alcohols, 1-octanol and 1-adamantanol, was surveyed under the diphenyl sulfoxide and triflic anhydride activation conditions in the presence of the hindered base 2,4,6-tri-*tert*-butylpyrimidine (TTBP) developed for other thiosialoside donors.¹⁸ In both cases, β sialosides were obtained predominantly (Table 1, entries 1 and 2). Couplings to carbohydrate acceptors also showed unfavorable α -selectivities (Table 1, entries 3 and 4). The anomeric stereochemistry of all coupling products is assigned on the basis of the chemical shifts of the sialic acid *H*-3eq²⁴ and the ³*J*_{C1, H-3ax} coupling constants.²⁵ The fused oxazolidinone structure does not affect the distinct difference of the ³*J*_{C1, H-3ax} coupling constants between α - and β -anomers.

Under the same Ph₂SO/Tf₂O preactivation conditions, the *N,N*-diacetyl protected sialoside donor **14** provided higher α -selectivities (Table 2, entries 1–3) than **1** in couplings to the same acceptors, indicating that the oxazolidinone group is detrimental to α -sialylation under the Ph₂SO/Tf₂O activation conditions.

When the NIS/TfOH activation method was applied to sialylations with **1** in CH₂Cl₂ at –40 °C, we found that excellent yields and α -selectivities were obtained with 1-octanol (Table 3, entry 1), benzyl alcohol (Table 3, entry 2), and 3 β -cholestanol (Table 3, entry 3). With the

tertiary alcohol 1-adamantanol the α -selectivity dropped somewhat but the yield was still excellent (Table 3, entry 4).

The influence of temperature on the sialylation of **1** under NIS/TfOH activation method in dichloromethane was studied with 1-adamantanol as the acceptor. The results show that higher α -selectivity could be achieved at lower temperature (Table 4, entry 1 and 2), but at the expense of reduced reaction rate. At $-78\text{ }^{\circ}\text{C}$, no activation was observed over a period of several hours (Table 4, entry 3).

A series of carbohydrate acceptors were then coupled with **1** by the standard NIS/TfOH promotion method in dichloromethane at $-40\text{ }^{\circ}\text{C}$. Sialylation of methyl 2,3,4-tri-*O*-benzyl- α -D-glucopyranoside afforded the corresponding disaccharide **20** cleanly as a single α anomer (Table 5, entry 1). Excellent yields and α -selectivities were also obtained with methyl 1,2;3,4-di-*O*-isopropylidene- α -D-galactopyranoside and methyl 2,3,4-tri-*O*-benzyl- α -D-galactopyranoside (Table 5, entries 2 and 3) both affording important linkage types. With the secondary sugar acceptors, methyl 2,3-*O*-isopropylidene- α -L-rhamnopyranoside and methyl 2,4,6-tri-*O*-benzyl- β -D-galactopyranoside, good yields were obtained but the reactions gave predominantly β -sialosides (Table 5, entries 4 and 5). In the regioselective 3-*O*-sialylation of methyl 2,6-di-*O*-benzyl- β -D-galactopyranoside, a greater population of α -anomer was obtained, but there still remains room for improvement (Table 5, entry 6).

The favorable affects of the 5-*N*,4-*O*-carbonyl protecting system under the NIS/TfOH conditions are illustrated by comparison of Table 3, entry 1 and Table 5, entry 2 with corresponding couplings to the *N,N*-diacetyl protected donor **14** presented in Table 6. It is also noteworthy that couplings with **1** generally proceed faster under the NIS/TfOH conditions than those to **14**, and typically afford higher yields owing to a reduced propensity for glycal formation.

To probe the effect of anomeric configuration of the donor on sialylation, we tested the sialylations of α -anomeric isomer **9** under these NIS/TfOH promotion conditions in CH_2Cl_2 . Comparable yields and selectivities were obtained in couplings with the same alcohols as for donor **1** (Table 7). Clearly these sialylation reactions proceed through a common intermediate whose constitution is independent of the original anomeric configuration of the donors.

The hydrolysis of oxazolidinones typically requires harsh conditions often involving treatment with barium or lithium hydroxide in hot aqueous ethanol which results in the concomitant removal of the acetamide group for *N*-acetyloxazolidinones.²⁶ Exceptions have been described but these appear to be limited to the β -series of glucosamine-based *N*-acetyloxazolidinones.^{19c,e,h} We found that the oxazolidinone of the *N*-acetyl-5-*N*,4-*O*-carbonyl protected sialosides could be removed selectively by treatment with sodium methoxide in methanol at room temperature, affording the desired *N*-acetamido products easily and cleanly (Table 8). This result parallels Oscarson's report on the deprotection of glycosides of *N*-acetyl-2-*N*,3-*O*-oxazolidinone protected 4,6-di-*O*-benzyl-D-glucosamine, which gives the *N*-acetyl-glycosides directly.^{19e} This deprotection method does not depend on the anomeric configuration of substrates, and renders application of the *N*-acetyl-5-*N*,4-*O*-carbonyl system especially attractive for the synthesis of complex sialoconjugates and oligosialosides by eliminating harsh conditions for oxazolidinone cleavage and the extra steps for reinstalling acetamido group.

Further studies on the properties of *N*-acetyl-5-*N*,4-*O*-carbonyl protected thiosialosides and their applications in synthesis of various sialosides are underway in our laboratory.

Experimental Section

Methyl (phenyl 5-amino-5-*N*,4-*O*-carbonyl-3,5-dideoxy-2-thio- β -D-galacto-non-2-ulopyranoside)onate (6)

A stirred solution of methyl (phenyl 5-acetamideo-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio- β -D-glycero-D-galacto-2-nonulo pyranosid)onate (**5**)²³ (5.00 g, 8.57 mmol, 1.00 eq) in methanol (80 mL) was treated with methanesulfonic acid (1.68 mL, 25.7 mmol, 3.0 eq) at room temperature, and then refluxed under Ar for 24 h. After cooling down to room temperature, the reaction mixture was quenched with excess triethylamine, and then concentrated under reduced pressure. The concentrate and NaHCO₃ (3.60 g, 42.8 mmol, 5.0 eq) were dissolved in CH₃CN (30 mL) and H₂O (60 mL) and cooled to 0 °C. To the vigorously stirred mixture, 4-nitrophenyl chloroformate (4.32 g, 21.4 mmol, 2.5 eq) in CH₃CN (30 mL) was added slowly through a dropping funnel, after which stirring was continued for 3 h at 0 °C. The resulting mixture was extracted with ethyl acetate (100 mL $\times$ 3) and the combined extracts were washed with brine, and then dried over Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography, eluting with EtOAc then EtOAc/MeOH from 10/1 to 5/1 to give the title compound (**6**) as white foam (2.67 g, 6.68 mmol, 78% after two steps). $[\alpha]_D^{14} = -186.0$ ($c = 3.2$, MeOH). ¹H NMR (500 MHz, CD₃OD) δ : 7.61-7.59 (m, 2H), 7.39-7.35 (m, 3H), 4.69 (dd, $J = 1.5$, 10.0 Hz, 1H), 4.62 (dt, $J = 4.0$, 12.5 Hz, 1H), 3.83 (dd, $J = 2.5$, 11.0 Hz, 1H), 3.75-3.69 (m, 2H), 3.60 (s, 3H), 3.62-3.57 (m, 2H), 2.88 (dd, $J = 4.0$, 13.0 Hz, 1H), 2.42 (dd, $J = 13.5$, 15.0 Hz, 1H); ¹³C NMR (125 MHz, CD₃OD) δ : 169.1, 161.1, 136.3, 129.6, 129.3, 128.7, 89.6, 77.8, 74.4, 70.7, 69.8, 63.5, 58.0, 52.1, 37.0. ESIHRMS Calcd. for C₁₇H₂₁N₁O₈SNa ([M + Na]⁺): 422.08804; found: 422.08939.

Methyl (phenyl 5-amino-5-*N*,4-*O*-carbonyl-3,5-dideoxy-2-thio- α -D-galacto-non-2-ulopyranoside)onate (8)

8 was prepared from **7**²³ following the same procedure as **6**. $[\alpha]_D^{15} = +23.1$ ($c = 3.1$, MeOH). ¹H NMR (500 MHz, CD₃OD) δ : 7.58-7.56 (m, 2H), 7.44-7.41 (m, 1H), 7.38-7.35 (m, 2H), 4.06-4.01 (m, 1H), 3.85-3.79 (m, 3H), 3.69-3.60 (m, 2H), 3.59 (s, 3H), 3.56 (dd, $J = 2.0$, 9.0 Hz, 1H), 3.12 (dd, $J = 4.0$, 12.0 Hz, 1H), 2.23 (t, $J = 12.5$ Hz, 1H); ¹³C NMR (125 MHz, CD₃OD) δ : 169.1, 160.9, 136.4, 130.0, 128.6, 87.9, 78.31, 78.28, 71.6, 70.0, 63.2, 57.0, 52.3, 36.7. ESIHRMS Calcd. for C₁₇H₂₁N₁O₈SNa ([M + Na]⁺): 422.08804; found: 422.08929.

Methyl (phenyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-2-thio- β -D-galacto-non-2-ulopyranoside)onate (donor 1)

A solution of compound **6** (2.67 g, 6.68 mmol) in pyridine (20 mL) was treated with Ac₂O (24 mL) and stirred at room temperature overnight, and concentrated under reduced pressure. The residue was dissolved in anhydrous CH₂Cl₂, treated with EtN(*i*-Pr)₂ (11.6 mL, 66.8 mmol, 10 eq), then cooled to 0 °C before acetyl chloride (3.87 mL, 53.4 mmol, 8 eq) was added dropwise, and the mixture stirred at 0 °C for 1 h. After warming to room temperature, the resulting solution was poured into saturated aqueous NaHCO₃ solution, the organic layer was separated, the aqueous layer was extracted twice with CH₂Cl₂ and the combined organic phase was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc/Hex (1:1) to give donor **1** as yellowish solid (3.49g, 92%), which can be further purified by recrystallization from EtOAc/Et₂O/Hex to afford white needle crystals. mp 152–153 °C (EtOAc/Et₂O/Hexanes). $[\alpha]_D^{14} = -117$ ($c = 0.8$, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ : 7.47-7.31 (m, 5H), 5.52 (t, $J = 2.0$ Hz, 1H), 4.96 (td, $J = 1.5$, 8.5 Hz, 1H), 4.86 (dd, $J = 2.5$, 9.0 Hz, 1H), 4.76 (dt, $J = 4.0$, 13.0 Hz, 1H), 4.34 (dd, $J = 2.5$, 12.0 Hz, 1H), 3.86 (dd, $J = 8.0$, 11.5 Hz, 1H), 3.73 (dd, $J = 9.0$, 11.5 Hz, 1H), 3.60 (s, 3H), 2.88 (dd, $J = 3.5$, 13.0 Hz, 1H), 2.49 (s, 3H), 2.32 (t, $J = 12.5$ Hz, 1H), 2.12 (s, 3H), 2.05 (s, 3H), 1.93 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ : 172.5, 171.3, 170.4, 169.8, 167.8 (C-1, ³J_{C-1, H-3ax} = 2.50 Hz), 153.6, 136.8, 130.2, 129.2, 128.2, 88.3, 75.7,

75.1, 73.9, 72.7, 62.9, 59.6, 52.8, 36.0, 24.8, 21.2, 20.85, 20.76. Anal. Calcd for $C_{25}H_{29}NO_{12}S$: C, 52.90; H, 5.15; N, 2.47. Found: C, 53.01; H, 5.15; N, 2.45.

Methyl (phenyl 5-acetamido-7,8,9-tri-O-acetyl-5-N,4-O-carbonyl-3,5-dideoxy-2-thio-D-glycero- α -D-galacto-non-2-ulopyranoside)onate (donor 9)

9 was prepared from **8** following the same procedure as **1**. mp 148–149 °C (EtOAc/Et₂O/Hexanes). $[\alpha]_D^{14} = +13.4$ ($c = 1.1$, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ : 7.56–7.26 (m, 5H), 5.54 (dd, $J = 1.5, 6.0$ Hz, 1H), 5.34 (dt, $J = 3.0, 7.0$ Hz, 1H), 4.42 (dd, $J = 3.0, 12.5$ Hz, 1H), 4.34 (dd, $J = 1.5, 9.5$ Hz, 1H), 4.19 (dd, $J = 7.0, 12.0$ Hz, 1H), 3.98–3.92 (m, 1H), 3.59 (dd, $J = 9.0, 11.0$ Hz, 1H), 3.58 (s, 3H), 3.10 (dd, $J = 3.5, 12.0$ Hz, 1H), 2.45 (s, 3H), 2.16 (s, 3H), 2.11 (t, $J = 13.0$ Hz, 1H), 2.07 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ : 171.9, 170.7, 170.2, 170.1, 168.1 (C-1, $^3J_{C-1, H-3ax} = 7.50$ Hz), 153.4, 136.6, 130.2, 129.0, 128.3, 87.7, 75.7, 72.5, 70.5, 62.6, 59.1, 53.1, 36.7, 24.7, 21.1, 21.0, 20.9. Anal. Calcd for $C_{25}H_{29}NO_{12}S$: C, 52.90; H, 5.15; N, 2.47. Found: C, 53.13; H, 5.11; N, 2.47.

Coupling Protocol with Ph₂SO/TfOH/TTBP in Dichloromethane—A solution of donor **1** (0.11 mmol, 1eq.), diphenyl sulfoxide (0.32 mmol, 3eq.), TTBP (0.22 mmol, 2eq.), and activated 4 Å powdered sieves in anhydrous dichloromethane (2 mL) was stirred for 1 h at room temperature under an argon atmosphere, and then cooled to –78 °C, followed by addition of Tf₂O (0.12 mmol, 1.1eq.). After 10 min, a solution of the acceptor (0.22 mmol, 2eq.) in dichloromethane (1 mL) was added. The reaction mixture was stirred for 1–6 h at –78 °C and then warmed up to room temperature, diluted with dichloromethane, filtered through Celite, washed with saturated aqueous NaHCO₃, dried over Na₂SO₄, and concentrated under reduced pressure. The glycosides were isolated by column chromatography on silica gel eluting with THF/Hex systems to afford the sialosides.

Coupling Protocol with NIS/TfOH in Dichloromethane—A solution of donor **1** (61.3 mg, 0.11 mmol, 1.0 eq), acceptor (0.16 mmol, 1.5 eq) and activated 5 Å powdered molecular sieves (216 mg, 2.0 g/mmol) in anhydrous dichloromethane (2 mL) was stirred overnight under an argon atmosphere, and then cooled to –40 °C followed by addition of NIS (58.3 mg, 0.26 mmol, 2.4 eq) and TfOH (9.5 μ L, 0.11 mmol, 1.0 eq). The reaction mixture was stirred at –40 °C for 20 min to 2 h until the disappearance of the donor on TLC, then quenched with triethylamine (22.6 μ L, 0.16 mmol, 1.5 eq) and then warmed to room temperature. The mixture was diluted with dichloromethane, filtered through Celite, washed with 20% aqueous Na₂S₂O₃ solution, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with THF/Hex system to afford the sialosides.

Procedure for the Selective Cleavage of Oxazolidinones—To a solution of sialoside (0.1 mmol, 1.0 eq) in methanol (2 mL) was added a few drops of sodium methoxide solution in methanol (~70 μ L, 0.3 mmol, 3.0 eq) at room temperature. The mixture was stirred at room temperature for 30 min followed by treatment with Amberlyst® 15 ion-exchange resin for 5 min. The mixture was diluted with methanol and filtered through a sintered funnel packed with Celite and silica gel. The filter pad was rinsed with methanol (5 mL $\times$ 3) after filtration. The combined filtrates were concentrated under reduced pressure to afford the deprotected *N*-acetamido-sialosides in quantitative yield without further purification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Preparation of Donors **1** and **9**

Table 1

Ph₂SO/Tf₂O Promoted Couplings of 1

entry	acceptor	product: yield ^a (α:β)
1		10 : 97% (1:2) ^b
2		11 : 70% (1:3.7) ^b
3		12 : 93% (1:1.5) ^c
4		13 : 89% (<1:10) ^b

^a Isolated yields.^b Determined by ¹H NMR analysis of the crude reaction mixture.^c Isolated ratio.

Table 2

Ph₂SO/Tf₂O Promoted Couplings of 14

entry	acceptor	product: yield ^a (α:β) ^b
1		15 : 93% (2:1)
2		16 : 89% (3.8:1)
3		17 : 91% (1.2:1)

^a Isolated yields.^b Determined by ¹H NMR analysis of the crude reaction mixture.

Table 3
NIS/TfOH Promoted Couplings of **1** with Simple Alcohols

<p>Reaction scheme: Compound 1 (a substituted furanose with an acetate group, a phenylthio group, and a methyl ester group) reacts with an alcohol (ROH) in the presence of NIS/TfOH in CH₂Cl₂ with 5 Å MS at -40 °C to form products 10, 18, 19, and 11 (where the phenylthio group is replaced by an OR group).</p>		
entry	acceptor	product: yield ^a (α:β) ^b
1		10 : 96% (α only)
2		18 : 95% (α only)
3		19 : 89% (>10:1)
4		11 : 91% (3.3:1)

^a Isolated yields.

^b Determined by ¹H NMR analysis of the crude reaction mixture.

Table 4

The effect of Temperature on the Sialylation of 1

entry	reaction temp.	reaction time	yield ^a (α:β) ^b
1	–25 °C	20 min	90% (1.6:1)
2	–40 °C	2 h	91% (3.3:1)
3	–78 °C	—	no activation

^a Isolated yields.^b Determined by ¹H NMR analysis of the crude reaction mixture.

Table 5
NIS/TfOH Promoted Couplings of **1** with Sugar Acceptors

entry	acceptor	product: yield ^a (α:β)
1		12 : 92% (α only) ^b
2		20 : 90% (>10:1) ^b
3		21 : 85% (>10:1) ^b
4		22 : 87% (<1:10) ^b
5		23 : 85% (1:8) ^c
6		13 : 78% (1:1.3) ^{c,d}

^a Isolated yields.

^b Determined by ¹H NMR analysis of the crude reaction mixture.

^c Isolated ratio.

^d Coupled to the 3-OH.

Table 6

NIS/TfOH Promoted Couplings of 14

entry	acceptor	product: yield ^a (α:β) ^b
1		15 : 73% (1:4)
2		24 : 68% (1:1.9)

^a Isolated yields.^b Determined by ¹H NMR analysis of the crude reaction mixture.

Table 7

NIS/TfOH Promoted Couplings of 9

entry	acceptor	product: yield ^a (α:β) ^b
1		10 : 95% (α only)
2		11 : 92% (3.6:1)
3		12 : 89% (α only)

^a Isolated yields.^b Determined by ¹H NMR analysis of the crude reaction mixture.

Table 8
Selective Cleavage of the Oxazolidinones in Sialosides

entry	substrate	product
1	1	25
2	9	26
3	10a	27
4	12a	28
5	12b	29
6	20b	30
7	13a	31