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Highly efficient α-*C*-sialylation promoted by $(p\text{-Tol})_2SO/Tf_2O$ with *N*-acetyl-5-*N*,4-*O*-oxazolidione protected thiosialoside as donor†

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Based on a preactivation protocol with $(p\text{-Tol})_2SO/Tf_2O$, a practical, straightforward, and high-yielding synthesis of α-sialyl *C*-glycosides was accomplished by coupling *N*-acetyl-5-*N*,4-*O*-oxazolidione protected thiosialoside with various trimethylsilyl enol ethers and allyltrimethylsilanes. High yields and excellent α-selectivities were obtained for the strong π-nucleophiles with large nucleophilicity values (N = 4.4–9.0), irrespective of whether silyl enol ethers, silyl ketene acetals or allyltrimethylsilanes were used for the electrophilic *C*-sialylation.

Introduction

N-Acetylneuraminic acids (Neu5Ac), mostly located at the terminal end of oligosaccharides and glycoconjugates, have vital biological functions in higher animals and human beings.[1] Among the types of sialosides, *C*-glycosides, whose interglycosidic oxygen atoms are substituted by carbon atoms, possess exclusive resistance to chemical and enzymatic degradation and display potential applications in the development of Neu5Ac-containing antiviral drugs and vaccines.[2]

Due to the requirement of C–C bond formation at a new tertiary carbon atom center, it is more challenging to synthesize *C*-sialosides than other *C*-glycosides. In 1991, three groups of investigators[3] independently reported the formation of simple allyl and hydroxymethyl *C*-glycosides of Neu5Ac, but with poor α-selectivity or low reaction yield. Over the years, a few glycosylation strategies, especially the SmI_2-mediated reductive coupling reactions with appropriate Neu5Ac donors such as sialyl sulfones,[4a] chlorides,[4b] sulfides[5a] and acetates,[5b] have been developed for efficient α-*C*-sialylation to provide novel series of catabolically stable *C*-sialoside analogues of glycoconjugates.[4–6] It is reported that *C*-glycosides can be obtained from silyl enol ethers with high stereoselectivity in Sakurai/Mukayiama-type reactions.[7] For electrophilic α-*C*-sialylation with silyl enol ethers, very recently, *N*-acetyl-5-*N*,4-*O*-oxazolidione-protected sialyl phosphate (**2**) was found to be an efficient sialyl donor for the construction of α-*C*-sialosides in the presence of trimethylsilyl trifluoromethanesulfonate.[8a] It is noted that donor **2** is, in fact, derived from the corresponding *N*-acetyloxazolidinone protected thiosialoside **1**[8b] (Fig. 1), which was first prepared by our laboratory and has proven to be an excellent *O*-sialylation donor to couple with various alcohol receptors.[9a] In an effort to simplify the synthetic sequence of *C*-sialosides and avoid the preparation of complex samarium(III) organometallic species, herein we report that donor **1** is truly a practical *C*-sialyl donor. The reaction, promoted by a $(p\text{-Tol})_2SO/Tf_2O$ system, occurs with a wide variety of silyl enol ethers as acceptors in high α-selectivity and good isolated yield.

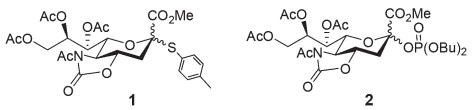

Fig. 1 Structures of *N*-acetyloxazolidinone protected sialyl donors.

Results and discussion

In previous reports,[9] we have established that both diphenyl sulfoxide/trifluoromethanesulfonic anhydride (Ph_2SO/Tf_2O)[9d] and *N*-iodosuccinimide/trifluoromethanesulfonic acid (NIS/TfOH)[9a] promotion systems can efficiently activate thiosialoside **1α** to afford the desired α-*O*-sialylation products. The stereoselectivity and yield of the sialylation can be modulated by carefully changing the added amount of Ph_2SO. In the current study, inspired by above results, we initially attempted the *C*-sialylation between **1α** and acetophenone trimethylsilyl enol ether (**3**) under Ph_2SO/Tf_2O preactivation conditions in dichloromethane. To our surprise, the expected *C*-sialyl derivative **4** was successfully obtained in 71% yield with exclusive α-stereoselectivity (Table 1, entry 1). When $(p\text{-Tol})_2SO$ was used

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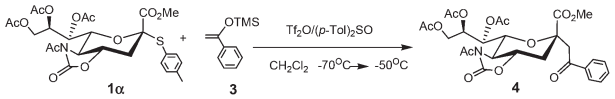
Table 1 Effects of different promoters and amount of $(p\text{-Tol})_2SO$ on the *C*-sialylation



Entry	Conditions[a]	Yield[b] (%)	$\alpha:\beta$[c]
1	Tf_2O/Ph_2SO (2.0 equiv.)	71	α
2	$Tf_2O/(p\text{-Tol})_2SO$ (0.6 equiv.)	61	α
3	$Tf_2O/(p\text{-Tol})_2SO$ (1.2 equiv.)	68	α
4	$Tf_2O/(p\text{-Tol})_2SO$ (2.0 equiv.)	82	α
5	$Tf_2O/(p\text{-Tol})_2SO$ (3.0 equiv.)	84	α
6	$Tf_2O/(p\text{-Tol})_2SO$ (4.0 equiv.)	15	α

[a] 1.2 equiv. Tf_2O was used for the reactions. [b] Isolated yields after column chromatography. [c] Determined by ^1H NMR spectroscopy; α indicates that no β product was detected.

as additive instead of Ph_2SO for the *C*-sialylation, the reaction yield was improved from 71% to 82% (Table 1, entry 4), indicating that $(p\text{-Tol})_2SO$ is more closely matched with sialyl donor **1** (containing *p*-tolyl sulfide as leaving group) than Ph_2SO. The results are also comparable with our previous observations,[9e] wherein the $(p\text{-Tol})_2SO$ was a superior additive for *O*-sialylation with *N*-acetyl-5-*N*,4-*O*-oxazolidione protected sialyl sulfoxide as donor.

Next, we further probed the influence of different added amounts of $(p\text{-Tol})_2SO$ on the *C*-sialylation. As shown in Table 1, when the amount of $(p\text{-Tol})_2SO$ was increased from 0.6 equiv. to 4.0 equiv., the optimum amount of $(p\text{-Tol})_2SO$ additive was 2.0–3.0 equiv., with the highest *C*-sialylation yield reaching 82–84%. Meanwhile, only the α-*C*-sialyl product was obtained in the reaction with different amounts of $(p\text{-Tol})_2SO$. In addition, the effect of reaction temperature on the model *C*-sialylation was also examined. The reaction yields were closely related to the temperature (Table 2). Ranging the temperature from −70 °C to −20 °C, the yield decreased gradually from 82% to 68%, suggesting that lower reaction temperature was more appropriate for the *C*-glycosylations. Finally, we used the sialylation conditions described in entry 1 of Table 2 for the following *C*-sialylations with silyl enol ethers as acceptors.

With regard to the mechanism of the *C*-glycosylation (Scheme 1), the *N*-acetyl-5-*N*,4-*O*-oxazolidione protected oxacarbenium cation **6** is believed to be the first crucial intermediate, resulting from the activation of thiosialoside **1** by di-*p*-tolyl sulfoxide bis(triflate) **5** which is generated *in situ* from the promoter pair $(p\text{-Tol})_2SO$ and Tf_2O. As proposed by Crich for the *N*,*N*-diacetyl counterpart[10] and our previous studies,[9d,e] **6** would either rapidly decompose to the 2,3-glycal **7**, or be efficiently trapped by excess $(p\text{-Tol})_2SO$ (1–2 equiv.)[11] to provide the *N*-acetyloxazolidinone protected C2-sialyloxosulfonium salt **8a**/**8b**, which is considered as the second crucial intermediate for the sialylation and should be more stable from −70 °C to −50 °C (Table 2). The more reactive β-C2-sialyloxosulfonium intermediate **8b** could be quickly attacked by a nucleophile such as trimethylsilyl enol ether, allyltrimethylsilane or alcohol to obtain the α-*C*- or *O*-sialyl product. It is noteworthy that more excess $(p\text{-Tol})_2SO$ (3 equiv.) additive led to a very low *C*-sialylation yield (Table 1, entry 6) with excellent α-selectivity. In sharp contrast, the reaction yield of *O*-sialylation under similar reaction conditions was extraordinarily high (96%), but with declined α-selectivity (α/β = 2.7 : 1).[9d] Similarly, as described in our previous work, the larger of excess $(p\text{-Tol})_2SO$ (3 equiv.) may produce C2-sialyloxosulfonium supramer **9a**/**9b**,[9d] the third crucial intermediate, which accounts for the above experimental results. It is suggested that the sialyloxosulfonium species have following relative electrophilicity ranking: **8b** > **8a** > **9a** ≅ **9b**. In addition, the *C*- and *O*-nucleophiles should fit the relative nucleophilicity order: alcohol > trimethylsilyl enol ether or allyltrimethylsilane.[12] Therefore, alcohol reacts with **9a**/**9b** to give high reaction yield and low α-selectivity; with **8a**/**8b** to afford low reaction yield and high α-selectivity.[9d] The nucleophilicity of trimethylsilyl enol ether is too weak to attack **9a**/**9b** which could be the major intermediate with 4 equiv. of $(p\text{-Tol})_2SO$ used for the sialylation (Table 1, entry 6), and consequently the yield of the *C*-sialylation is poor. Noticeably, with 2–3 equiv. of $(p\text{-Tol})_2SO$ (Table 1, entries 4 and 5) trimethylsilyl enol ether mainly attacks **8a**/**8b**, especially the more reactive **8b**, to provide higher product yield and excellent α-selectivity.

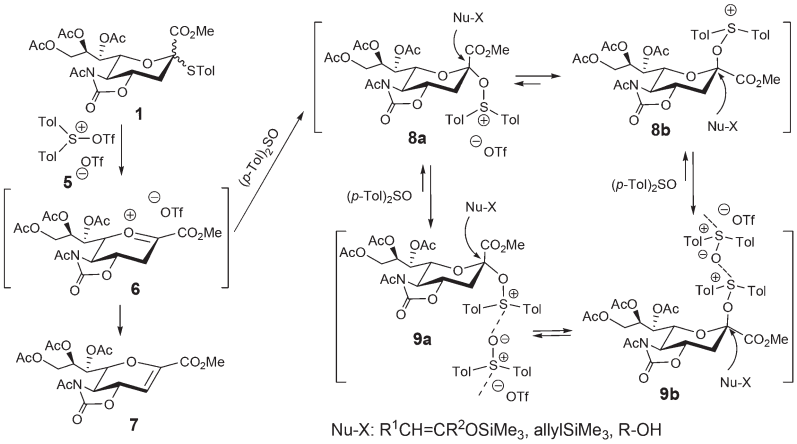
To further verify the effectiveness of $(p\text{-Tol})_2SO/Tf_2O$ as a promoting system for *C*-sialylation, a series of trimethylsilyl enol ethers and allyltrimethylsilanes were applied to the *C*-glycosylation with thiosialoside **1** as donor under identical conditions (Table 3). All these neutral π-nucleophiles have varying nucleophilicity values (N = 1.8–9.0) as defined by Mayr and co-workers.[13]

The nucleophilicity of silyl enol ethers plays an important role in the *C*-sialylation. Both high reaction yield and exquisite α-selectivity were obtained in the *C*-sialylation of donor **1** with enoxy silane nucleophiles **3**, **10**, **12**, **14** (N = 5.2–8.2, Table 3, entries 1, 4–6).[13,14] When a weak nucleophile **16** (N = 3.8) was employed for the electrophilic substitution, the ketone **17** was obtained in moderate yield, but with low stereoselectivity (α/β = 2.6 : 1, Table 3, entry 7). Similar results were also reported during the *C*-sialylation of *N*-acetyloxazolidinone protected sialyl phosphate (**2**) with **16**.[8a] With strong nucleophiles **18** and **20** (N = 8.2 and 9.0, respectively) derived from esters, only single α isomers were obtained in 72–84% yields. Application of this method to the preparation of sialyl aldehyde **23** from trimethylsiloxyethene (**22**) gave exclusive α-selectivity and 43%

Table 2 Effect of temperature on the *C*-sialylation[a]

Entry	Conditions[b]	Yield[c] (%)	$\alpha:\beta$[d]
1	−70 °C 2.0 h then −50 °C 2.0 h	82	α
2	−50 °C 4.0 h	79	α
3	−40 °C 4.0 h	75	α
4	−30 °C 4.0 h	77	α
5	−20 °C 4.0 h	68	α

[a] See Table 1 for reaction scheme. [b] 1.2 equiv. Tf_2O and 2.0 equiv. $(p\text{-Tol})_2SO$ were used for the reactions. [c] Isolated yields after column chromatography. [d] Determined by ^1H NMR spectroscopy.



Scheme 1 Three proposed crucial intermediates in the sialylation of thiosialoside **1** with $(p\text{-Tol})_2SO/Tf_2O$.

yield. Comparing the glycosylations with **16** and **22** as nucleophiles, the yields are comparative, but glycal **7** was obtained in lower yield in the case of **22** than that of **16**, suggesting that aldehyde **23** was partially decomposed during flash chromatography due to its instability to silica gel.

With allyltrimethylsilane **24** as a sialyl acceptor with a poor *N* value (N = 1.8), the coupling reaction provided **25** in 50% yield and very low stereoselectivity (α/β = 1 : 1.2, Table 3, entry 12). However, in the case of **26** with a higher *N* value (N = 4.4), the *C*-sialylation yield jumped to 86%, and the stereoselectivity was also significantly improved from α/β = 1 : 1.2 to α only (Table 3, entry 14). The results further illustrated that the *C*-sialylation is sensitive to the nucleophilicity values, and strong nucleophiles (either trimethylsilyl enol ethers or allyltrimethylsilane) give both higher yields and α-selectivities.

The β-anomer **1β**[15] was also examined for the *C*-sialylation with trimethylsilyl enol ethers **3** and **22**, and allyltrimethylsilane **24** as nucleophiles (Table 3, entries 3, 11 and 13). Similar reaction yields and stereoselectivities were obtained compared with the corresponding reactions with **1α** as donor (Table 3, entries 1, 10 and 12). The results are different from the *C*-sialylation reported by Crich and co-workers,[8a] wherein the reaction yield or α-selectivity was highly dependent on the anomer configuration of sialyl phosphate donor **2**, and **2α** was more favorable for *C*-sialylation than **2β**. Because the preactivation protocol was utilized for the glycosylation in this study, with anomer **1α** as donor the crucial intermediates **6**, **8a**/**8b** and **9a**/**9b** and their equilibrium concentrations should be nearly the same as those with anomer **1β** as donor (Scheme 1). As a result, donors **1α** and **1β** have no distinguishable effects on the *C*-sialylation. In addition, to demonstrate the practicality of the current *C*-sialylation strategy, the model *C*-sialylation was successfully scaled up from the preparation of ~35 mg of ketone **4** (Table 3, entry 1) to ~140 mg (Table 3, entry 2) in high yields (82–88%). The anomeric stereochemistry of all new coupling products was assigned on the basis of $^3J_{C1,H3ax}$ coupling constants.[5c,16] Generally, the α isomers of the *C*-sialylations have higher $^3J_{C1,H3ax}$ coupling constants varying from 6.6 to 7.6, which are consistent with the data described in literature.[5c]

Conclusion

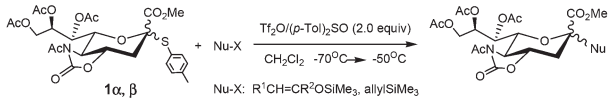
In summary, in spite of the development of a few *C*-sialylation strategies in sialic acid chemistry, herein is described the first direct *C*-sialylation of *N*-acetyloxazolidinone[17] protected thiosialoside based on a preactivation protocol with $(p\text{-Tol})_2SO/Tf_2O$. The efficiency of the *C*-sialylation is not only regulated by the reaction conditions, especially the added amount of $(p\text{-Tol})_2SO$, but also dependent on the reactivity of the nucleophiles. High reaction yield and excellent α-selectivity were obtained for strong π-nucleophiles with large nucleophilicity values (N = 4.4–9.0), irrespective of whether silyl enol ethers, silyl ketene acetals or allyltrimethylsilane were used for the electrophilic *C*-sialylation. The *C*-sialylation methodology developed in this study simplifies the existing synthetic route to build sialyl *C*-glycosides and affords a powerful tool to explore the syntheses of complex *C*-sialylconjugates and glycomimetics.

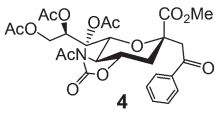
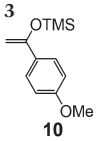
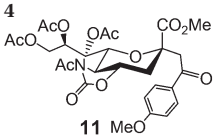
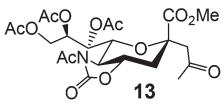
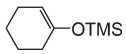
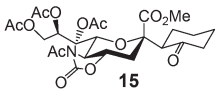
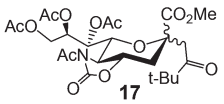
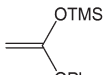
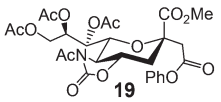
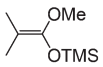
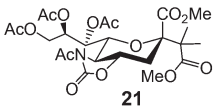
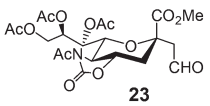
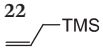
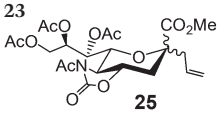
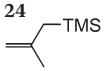
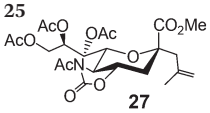
Experimental

General

All chemicals were purchased as reagent grade and used without further purification. Dichloromethane was distilled over calcium hydride (CaH_2). The reactions between donor **1** and different acceptors were carried out under anhydrous conditions (argon atmosphere) with anhydrous solvent. Reactions were monitored by analytical thin-layer chromatography on silica gel F_{254} glass plates. Spots were detected under UV (254 nm) or by staining with a solution of acidic ceric ammonium molybdate and EtOH–H_2SO_4 (3%). Flash column chromatography was performed on silica gel (200–300 mesh). ^{1}H NMR spectra were recorded with a 400 MHz NMR spectrometer at 20 °C. Chemical shifts (in ppm) were referenced to tetramethylsilane (δ = 0 ppm) in deuterated chloroform. ^{13}C NMR spectra were recorded with a 400 MHz NMR spectrometer (100 MHz) and calibrated with $CDCl_3$ (δ = 77.23 ppm). High-resolution mass spectra were recorded using electrospray ionization (ESI).

Table 3 *C*-Sialylation of thiosialoside donor **1** with various trimethylsilyl enol ethers and allyltrimethylsilanes



Entry	Donor	Nucleophile	*N* value[a]	Product	Yield[b]	$\alpha:\beta$[c]
1[d]	**1α**	 **3**	6.2	 **4**	82%	α
2[e]	**1α**	**3**	6.2	**4**	88%	α
3	**1β**	**3**	6.2	**4**	86%	α
4	**1α**	 **10**	6.2–8.2	 **11**	95%	α
5	**1α**	 **12**	5.4	 **13**	96%	α
6[d]	**1α**	 **14**	5.2	 **15**	71%	α
7[d]	**1α**	 **16**	3.8	 **17**	37% + 54% **7**	2.6 : 1
8	**1α**	 **18**	8.2	 **19**	72%	α
9	**1α**	 **20**	9.0	 **21**	84%	α
10[d,f]	**1α**	 **22**	—	 **23**	43% + 26% **7**	α
11[f]	**1β**	**22**	—	**23**	40% + 24% **7**	α
12[d,f]	**1α**	 **24**	1.8	 **25**	50% + 50% **7**	1 : 1.2
13[f]	**1β**	**24**	1.8	**25**	45% + 49% **7**	1 : 1
14	**1α**	 **26**	4.4	 **27**	86%	α

[a] See ref. 13 and 14. [b] Yield of isolated products. [c] Determined by ^{1}H NMR spectroscopy. [d] The ^{1}H NMR spectroscopic data are consistent with those reported in ref. 8*a*. [e] A large-scale sialylation was carried out with 160 mg of donor **1α** used for the reaction. [f] 10.0 equiv. of acceptor was used in the reaction.

General coupling protocol for the *C*-salylation

A solution of sialyl donor (0.069 mmol, 1 equiv.), $(Tol)_2SO$ (0.138 mmol, 2 equiv.) and activated 4 Å powdered sieves in anhydrous dichloromethane (2 mL) was stirred for 15 min at −70 °C under argon, followed by addition of Tf_2O (13.4 μL, 1.2 equiv.). After stirring the mixture for 30 min, a solution of acceptor (5 equiv.) in anhydrous dichloromethane (1 mL) was added. The resulting mixture was then stirred for 2.0 hours at −70 °C then warmed to −50 °C for another 2.0 hours. After quenching with Et_3N (0.1 mL), the mixture was diluted with dichloromethane (50 mL), filtered through Celite®, washed with saturated brine (10 mL × 3), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was

purified by silica gel column chromatography eluting with a petroleum ether–EtOAc system to give the coupling products.

Methyl (2-*C*-(2-oxa-2-*p*-methoxylphenylethyl)-5-*N*-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranitol)onate (11). This compound was prepared according to the general procedure for *C*-sialylation with a sialyl donor **1α** (40.1 mg, 0.069 mmol) and **10** (76.7 mg, 0.345 mmol). Purification by column chromatography over silica gel (hexanes–AcOEt = 1 : 1) gave the desired product (39.8 mg, 95%) as colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 5.45 (d, J = 6.7 Hz, 1H), 5.17 (dt, J = 2.6, 6.7 Hz, 1H), 4.62 (d, J = 9.4 Hz, 1H), 4.25 (dd, J = 2.6, 12.2 Hz, 1H), 4.19 (dt, J = 3.3, 12.5 Hz, 1H), 3.88 (s, 3H), 3.86 (dd, J = 6.8, 12.2 Hz, 1H), 3.77 (s, 3H, $COOCH_3$), 3.57 (d, J = 14.8 Hz, 1H), 3.56 (t, J = 9.5 Hz, 1H), 3.30 (d, J = 14.8 Hz, 1H), 2.87 (dd, J = 3.5, 12.4 Hz, 1H, H-3eq), 2.47 (s, 3H), 2.31 (t, J = 12.7 Hz, 1H, H-3ax), 2.13 (s, 3H), 2.03 (s, 3H), 1.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.9, 172.1, 171.5 (C1, $^3J_{C1,H3ax}$ = 7.1 Hz), 170.6, 170.4, 169.8, 164.0, 153.7, 131.1, 130.1, 113.7, 78.5, 75.8, 75.6, 72.2, 70.1, 62.7, 59.4, 55.6, 52.9, 46.1, 35.1, 24.7, 21.1, 20.8, 20.7 ppm; HRMS (ESI-TOF): m/z calcd for $C_{28}H_{33}NO_{14}Na$ $[M + Na]^+$ 630.1799, found: 630.1771.

Methyl (2-*C*-(2-oxa-2-methylethyl)-5-*N*-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranitol)onate (13). This compound was prepared according to the general procedure for *C*-sialylation with a sialyl donor **1α** (40.1 mg, 0.069 mmol) and **12** (45.0 mg, 0.345 mmol). Purification by column chromatography over silica gel (hexanes–AcOEt = 1 : 1) gave the desired product (34.1 mg, 96%) as colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.50 (dd, J = 1.5, 6.1 Hz, 1H), 5.30 (dt, J = 2.5, 7.4 Hz, 1H), 4.71 (dd, J = 1.4, 9.4 Hz, 1H), 4.40 (dd, J = 2.5, 12.2 Hz, 1H), 4.13 (dt, J = 3.6, 12.9 Hz, 1H), 3.95 (dd, J = 7.4, 12.2 Hz, 1H), 3.78 (s, 3H, $COOCH_3$), 3.61 (dd, J = 9.6, 10.9 Hz, 1H), 3.05 (d, J = 15.3 Hz, 1H), 2.85 (d, J = 15.3 Hz, 1H), 2.72 (dd, J = 3.6, 12.3 Hz, 1H, H-3eq), 2.48 (s, 3H), 2.22 (s, 3H), 2.19 (t, J = 12.6 Hz, 1H, H-3ax), 2.14 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.9, 172.2, 171.4 (C1, $^3J_{C1,H3ax}$ = 7.6 Hz), 170.8, 170.4, 169.9, 153.6, 77.9, 76.1, 75.3, 72.7, 70.6, 63.1, 59.3, 53.0, 51.1, 34.9, 31.7, 24.7, 21.1, 20.8 ppm; HRMS(ESI-TOF): m/z calcd for $C_{22}H_{29}NO_{13}Na$ $[M + Na]^+$ 538.1537, found: 538.1528.

Methyl (2-*C*-(2-oxa-2-phenoxylethyl)-5-*N*-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranitol)onate (19). This compound was prepared according to the general procedure for *C*-sialylation with a sialyl donor **1α** (40.1 mg, 0.069 mmol) and **18** (71.9 mg, 0.345 mmol). Purification by column chromatography over silica gel (hexanes–AcOEt = 1 : 1) gave the desired product (29.5 mg, 72%) as white solid. M.p. 62–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (t, J = 7.9 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1H), 7.12 (d, J = 7.7 Hz, 2H), 5.48 (dd, J = 1.6, 5.4 Hz, 1H), 5.40 (dt, J = 2.6, 7.6 Hz, 1H), 4.74 (dd, J = 1.6, 9.3 Hz, 1H), 4.41 (dd, J = 2.6, 12.2 Hz, 1H), 4.13 (dt, J = 3.4, 12.9 Hz, 1H), 4.04 (dd, J = 7.4, 12.1 Hz, 1H), 3.83 (s, 3H, $COOCH_3$), 3.72 (dd, J = 9.6, 10.9 Hz, 1H), 3.19 (d, J = 14.8 Hz, 1H), 3.02 (d, J = 14.8 Hz, 1H), 2.87 (dd, J = 3.5, 12.2 Hz, 1H, H-3eq), 2.49 (s, 3H), 2.40 (t, J = 12.7 Hz, 1H, H-3ax), 2.13 (s, 3H), 2.07 (s, 3H), 1.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 171.0 (C1, $^3J_{C1,H3ax}$ = 6.8 Hz), 170.6, 170.5, 170.0, 166.6, 153.4, 150.3, 129.4, 126.1, 121.4, 78.1, 76.6, 75.4, 73.0, 70.8, 62.9, 59.3, 53.2, 43.7, 35.2, 24.7, 21.1, 20.7 ppm; HRMS(ESI-TOF): m/z calcd for $C_{27}H_{31}NO_{14}Na$ $[M + Na]^+$ 616.1642, found: 616.1621.

Methyl (2-*C*-(1,1-dimethyl-2-oxa-2-methoxylethyl)-5-*N*-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3, 5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranitol)onate (21). This compound was prepared according to the general procedure for *C*-sialylation with a sialyl donor **1α** (40.1 mg, 0.069 mmol) and **20** (70.0 μL, 0.345 mmol). Purification by column chromatography over silica gel (hexanes–AcOEt = 1 : 1) gave the desired product (32.4 mg, 84%) as colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (dd, J = 1.6, 6.5 Hz, 1H), 5.40 (dt, J = 2.7, 6.8 Hz, 1H), 4.50 (dd, J = 1.5, 9.4 Hz, 1H), 4.37 (dd, J = 2.6, 12.2 Hz, 1H), 4.08 (dd, J = 6.9, 12.2 Hz, 1H), 3.85 (dt, J = 3.7, 12.7 Hz, 1H), 3.79 (s, 3H, C1OOCH$_3$), 3.73 (s, 3H), 3.57 (dd, J = 9.6, 11.1 Hz, 1H), 2.79 (dd, J = 3.8, 12.1 Hz, 1H, H-3eq), 2.68 (t, J = 12.6 Hz, 1H, H-3ax), 2.47 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 1.31 (s, 3H), 1.21 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 171.6, 170.3, 170.0, 169.9 (C1, $^3J_{C1,H3ax}$ = 6.8 Hz), 169.4, 153.3, 84.2, 76.1, 75.7, 72.5, 69.8, 62.5, 58.7, 52.3, 51.7, 49.1, 31.6, 24.3, 20.9, 20.8, 20.7, 20.4 ppm. HRMS(ESI-TOF): m/z calcd for $C_{24}H_{34}NO_{14}$ $([M + H])^+$ 560.1979, found: 560.1980.

Methyl (2-*C*-(2-methylallyl)-5-*N*-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranitol)onate (27). This compound was prepared according to the general procedure for *C*-sialylation with a sialyl donor **1α** (40.1 mg, 0.069 mmol) and **26** (61.0 μL, 0.345 mmol). Purification by column chromatography over silica gel (hexanes–AcOEt = 2 : 1) gave the desired product (30.5 mg, 86%) as colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.55 (dd, J = 1.4, 6.0 Hz, 1H), 5.40 (dt, J = 2.7, 6.9 Hz, 1H), 4.96 (s, 1H), 4.79 (s, 1H), 4.50 (dd, J = 2.4, 12.2 Hz, 1H), 4.42 (dd, J = 1.4, 9.4 Hz, 1H), 4.07 (dd, J = 7.0, 12.2 Hz, 1H), 4.00 (dt, J = 3.6, 12.8 Hz, 1H), 3.77 (s, 3H, $COOCH_3$), 3.60 (dd, J = 9.5, 11.1 Hz, 1H), 2.72 (dd, J = 3.6, 12.2 Hz, 1H, H-3eq), 2.60 (d, J = 13.8 Hz, 1H), 2.48 (d, J = 13.8 Hz, 1H), 2.48 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 2.06 (t, J = 12.5 Hz, 1H, H-3ax), 2.05 (s, 3H), 1.84 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (C1, $^3J_{C1,H3ax}$ = 6.6 Hz), 170.4, 170.2, 169.6, 153.5, 139.7, 116.6, 80.9, 76.1, 75.7, 72.5, 70.6, 62.6, 59.3, 52.5, 46.5, 34.4, 24.5, 23.5, 20.9, 20.5 ppm; HRMS(ESI-TOF): m/z calcd for $C_{23}H_{32}NO_{12}$ $([M + H])^+$ 514.1925, Found 514.1917.

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Notes and references

1 (*a*) R. Schauer, *Sialic Acid: Chemistry, Metabolism and Function*, Springer, New York, 1982, vol. 10; (*b*) *Biology of the Sialic Acids*, ed. A. Rosenberg, Plenum, New York, 1995; (*c*) T. Angata and A. Varki, *Chem. Rev.*, 2002, **102**, 439.

2 (*a*) D. E. Levy and C. Tang, *The Chemistry of C-Glycosides*, Pergamon, Oxford, 1995; (*b*) X. J. Yuan and R. J. Linhardt, *Curr. Top. Med. Chem.*, 2005, **5**, 1393; (*c*) H. Ando and M. Kiso, in *Glycoscience: Chemistry and Chemical Biology*, ed. B. O. Fraser-Reid, K. Tatsuta and J. Thiem, Spring-Verlag, New York, 2nd edn, 2008, vol. 2, pp. 1313–1360; (*d*) B. Vauzeilles, D. Urban, G. Doisneau and J.-M. Beau, in *Glycoscience: Chemistry and Chemical Biology*, ed. B. O. Fraser-Reid, K. Tatsuta and J. Thiem, Spring-Verlag, New York, 2nd edn, 2008, vol. 3, pp. 2021–2078; (*e*) G.-J. Boons and A. V. Demchenko, in *Carbohydrate-Based Drug Discovery*, ed. C.-H. Wong, Wiley-VCH, Weinheim, 2003, vol. 1, pp. 55–102.

3 (*a*) H. Paulsen and P. Matschulat, *Liebigs Ann. Chem.*, 1991, 487; (*b*) K. Walliman and A. Vasella, *Helv. Chim. Acta*, 1991, **74**, 1520; (*c*) J. Nagy and M. Bednarski, *Tetrahedron Lett.*, 1991, **32**, 3953.

4 (*a*) I. R. Vlahov, P. I. Vlahova and R. J. Linhardt, *J. Am. Chem. Soc.*, 1997, **119**, 1480; (*b*) T. Polat, Y. Du and R. J. Linhardt, *Synlett*, 1998, 1195; (*c*) Y. Du, T. Polat and R. J. Linhardt, *Tetrahedron Lett.*, 1998, **39**, 5007; (*d*) H. G. Bazin, Y. Du, T. Polat and R. J. Linhardt, *J. Org. Chem.*, 1999, **64**, 7254; (*e*) B. Kuberan, S. A. Sikkander, H. Tomiyama and R. J. Linhardt, *Angew. Chem., Int. Ed.*, 2003, **42**, 2073; (*f*) K. R. Dino, S. N. Baytas, Q. Wang, E. M. Munoz, K. Tukuzoki, H. Tomiyama and R. J. Linhardt, *J. Org. Chem.*, 2005, **70**, 8197; (*g*) X. Yuan, D. K. Ress and R. J. Linhardt, *J. Org. Chem.*, 2007, **72**, 3085; (*h*) J.-H. Kim, F. Huang, M. Ly and R. J. Linhardt, *J. Org. Chem.*, 2008, **73**, 9497.

5 (*a*) Z. Abdallah, G. Doisneau and J. M. Beau, *Angew. Chem., Int. Ed.*, 2003, **42**, 5209; (*b*) A. Malapelle, Z. Abdallah, G. Doisneau and J. M. Beau, *Angew. Chem., Int. Ed.*, 2006, **45**, 6016; (*c*) A. Malapelle, A. Coslovi, G. Doisneau and J. M. Beau, *Eur. J. Org. Chem.*, 2007, 3145; (*d*) A. Malapelle, Z. Abdallah, G. Doisneau and J. M. Beau, *Heterocycles*, 2009, **77**, 1417.

6 (*a*) W. Notz, C. Hartel, B. Waldscheck and R. R. Schmidt, *J. Org. Chem.*, 2001, **66**, 4250; (*b*) G. Hirai, T. Watanabe, K. Yamaguchi, T. Miyagi and M. Sodeoka, *J. Am. Chem. Soc.*, 2007, **129**, 15420; (*c*) T. Watanabe, G. Hirai, M. Kato, D. Hashizume, T. Miyagi and M. Sodeoka, *Org. Lett.*, 2008, **10**, 4167.

7 (*a*) H. Kunz, J. Weiβmüller and B. Müller, *Tetrahedron Lett.*, 1984, **25**, 3571; (*b*) H. Kunz, B. Müller and J. Weissmüller, *Carbohydr. Res.*, 1987, **171**, 25.

8 (*a*) A. Noel, B. Delpech and D. Crich, *Org. Lett.*, 2012, **14**, 1342; (*b*) C.-H. Hsu, K.-C. Chu, Y.-S. Lin, J.-L. Han, Y.-S. Peng, C.-T. Ren, C.-Y. Wu and C.-H. Wong, *Chem.–Eur. J.*, 2010, **16**, 1754.

9 (*a*) F. F. Liang, L. Chen and G. W. Xing, *Synlett*, 2009, 425; (*b*) L. Chen, F. F. Liang, M. F. Xu, G. W. Xing and Z. W. Deng, *Acta Chim. Sinica*, 2009, **67**, 1355; (*c*) G. W. Xing, L. Chen and F. F. Liang, *Eur. J. Org. Chem.*, 2009, 5963; (*d*) Y. J. Wang, J. Jia, Z. Y. Gu, F. F. Liang, L. Chen, R. C. Li, M. H. Huang, C. S. Xu, J. X. Zhang, Y. Men and G. W. Xing, *Carbohydr. Res.*, 2011, **346**, 1271; (*e*) Z. Y. Gu, J. X. Zhang and G. W. Xing, *Chem.–Asian J.*, 2012, **7**, 1524; (*f*) Y. J. Wang, Z. Y. Gu and G. W. Xing, *Chem.–Asian J.*, 2012, **7**, 489.

10 D. Crich and W. Li, *Org. Lett.*, 2006, **8**, 959.

11 The second equivalent of the sulfoxide may play an analogous role to nitriles, which were used as the solvents in α-selective *O*-sialylations. See: (*a*) P. Sinäy and J. R. Pougny, *Tetrahedron Lett.*, 1976, **17**, 4073; (*b*) R. R. Schmidt and J. Michel, *J. Carbohydr. Chem.*, 1985, **4**, 141.

12 See the database of nucleophilicities and electrophilicities at http://www.cup.lmu.de/oc/mayr/DBintro.html

13 H. Mayr, B. Kempf and A. R. Ofial, *Acc. Chem. Res.*, 2003, **36**, 66.

14 J. P. Krumper, W. A. Salamant and K. A. Woerpel, *J. Org. Chem.*, 2009, **74**, 8039.

15 B. Sun and H. Jiang, *Tetrahedron Lett.*, 2011, **52**, 6035.

16 (*a*) H. Hori, T. Nakajima, Y. Nishida, H. Ohrui and H. Meguro, *Tetrahedron Lett.*, 1988, **29**, 6317; (*b*) S. Prytulla, J. Lauterwin, M. Klssinger and J. Thiem, *Carbohydr. Res.*, 1991, **215**, 345.

17 The 5-*N*,4-*O*-oxazolidinone protective group has a significant α-direction effect in sialylations, and recently Crich and co-workers conducted a deep study to explain the effect, see: P. K. Kancharla, C. Navuluri and D. Crich, *Angew. Chem., Int. Ed.*, 2012, **51**, 11105.

