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Highly Alpha-Selective Sialyl Phosphate Donors for Efficient Preparation of Natural Sialosides

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N-Acetyl neuraminic acid (Neu5Ac) is most frequently found at the terminal end of glycoconjugates on the cell surface. This terminally exposed position allows Neu5Ac-containing conjugates to be exploited as receptors for viruses and bacteria, in addition to governing a wide variety of biological processes, such as tumor metastasis, cell differentiation, and cell–cell interactions.[1] In naturally occurring sialosides, Neu5Ac is found linked to galactosides through the α-(2→3) or α(2→6) linkage in N- and O-linked glycoproteins, and also to *N*-acetylgalactosamine through the α(2→6) linkage in O-linked glycoproteins. In addition, polysialosides formed by the α(2→8) or α(2→9) linkages are constituents of glycoproteins and glycolipids.[2] The biological significance of sialoside receptors has driven research for their efficient synthesis. This has included significant efforts directed toward the development of sialic acid donors for efficient α-sialylation,[3] including the use of anomeric leaving groups, such as halides,[4] phosphites,[5] sulfides,[6] xanthates,[7] and phenyltrifluoroacetimidates,[8] the introduction of an auxiliary group at C-1[9] and C-3,[10] the modification of the *N*-acetyl functional group at C-5,[11] or the optimized combinations of the leaving group with positional modification.[12] However, high yielding α-selective sialylation is still problematic owing to the presence of the C-1 electron-withdrawing carboxyl group at the tertiary anomeric center and the lack of a participating group at C-3 to direct the stereochemical outcome of glycosylation.

The development of new strategies for the convergent synthesis of saccharides is a major focus in carbohydrate chemistry. Approaches such as armed–disarmed;[13] one-pot;[14] reactivity-based, programmable one-pot;[6b,15] solid-phase;[16] orthogonal;[17] and pre-activation[18] methods have been developed to improve efficiency, with the ultimate goal of developing an automated method for oligosaccharide synthesis.[14–16] The basic concept of these strategies involves the selective activation of one donor in the presence of an acceptor with the same or different leaving groups, so the newly formed product can be directly elongated without further aglycon leaving group adjustment. However, these approaches are not applicable to all glycosides. For example, sialic acid thioglycosides have limitations in our programmable reactivity-based, one-pot strategy due to their poor and narrow range of anomeric reactivity values (RRVs).[12a,19] To resolve the problem, sialylated disaccharides have been used as building blocks.[20] However, application of this strategy is limited by the lack of an efficient and α-selective sialic acid donor that possesses a leaving group orthogonal to the thioglycoside.[20] Herein, we report a new sialylation reagent **1** that employs an *N*-acetyl-5-*N*,4-*O*-carbonyl protection with dibutyl phosphate as the leaving group. Furthermore, the new donor was applied to develop efficient strategies to use to create natural sialosides.

Many researchers have focused on the modification of the *N*-acetyl functional group of sialic acid for highly efficient α-sialylation. However, there is no general donor for different acceptors. The choice of C-5 modification to be used is highly dependent on protecting groups and the nature of glycosyl acceptors. There is an excellent review on C-5 modification by De Meo.[11] Crich and co-workers have shown that the *N*-acetyl-5-*N*,4-*O*-carbonyl thiosialoside can

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provide high α-selectivity and excellent yield in sialylation reactions, and importantly, that the oxazolidinone group can be readily cleaved under mild conditions leaving the acetamide intact.[12f] Building on this method for its applicability to one-pot procedures, we designed a donor that combines the *N*-acetyl-5-*N*,4-*O*-carbonyl protection and phosphite derivatives as the leaving group. Unfortunately, attempts to transform the *N*-acetyl-5-*N*,4-*O*-carbonyl-protected thiosialoside donor to the corresponding phosphite donor were not successful. The ring-opening product was obtained as the major product in the hydrolytic step. Thus, we turned to the phosphate approach.

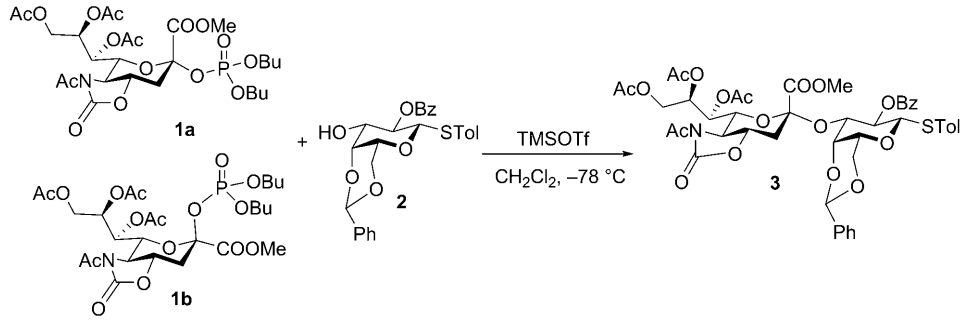
Less attention has been given to phosphate methods because of reported low yields and poor α-selectivity in glycosylation reactions.[5a,d] To our surprise, dibutyl sialyl phosphate **1** can be synthesized by the treatment of *N*-acetyl-5-*N*,4-*O*-carbonyl-protected thiosialoside and commercially available dibutyl phosphate in the presence of *N*-iodosuccinimide (NIS), catalytic triflic acid, and 4 Å molecular sieve at 0 °C in CH_2Cl_2. Under these conditions, the α- and β-phosphate sialoside isomers were obtained as a 3/1 mixture in 96% yield (Scheme 1).

The configurations of the glycosyl phosphates have profound effects on reactivity and stereoselectivity.[21] For example, pure α- and β-anomeric isomers **1a** and **1b** were reacted with acceptor **2** (Table 1), in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (1 equiv) in CH_2Cl_2, α-phosphate **1a** was completely activated at −78 °C within 5 min, while the β-phosphate **1b** was only partially activated over a short time. On the other hand, phosphate **1b** could be fully activated by TMSOTf at higher temperature (−50 °C) in only 5 min. Both anomeric donors afforded the products in similar yields, albeit in slightly different α/β ratios. The difference in reactivity between **1a** and **1b** is smaller when compared with the galactosyl phosphate donor.[21]

Encouraged by these preliminary results, we investigated the glycosyl donor properties of **1a** in producing naturally occurring sialoside linkages (Table 2). Regioselective sialylation of galactopyranoside 4,6-diols **4** (Table 2, entry 2) under TMSOTf activation in CH_2Cl_2 at −78 °C, gave sialylated (2→6)disaccharides **5** with complete α selectivity and high yields. Moreover, sialylation of one equivalent of diol **6** (Table 2, entry 3) with **1a**, gave Neu5Acα(2→6)GalNAc sialylated disaccharide product **7** as a single α isomer in 71% yield, along with a disialylated trisaccharide in 13% yield, and 2,3-glycal in 9% yield. For another sialylation of **8**, an anomer of **6**, disaccharide **9** was synthesized in 70% yield (Table 2, entry 4). Compound **7** possesses the framework of sialyl-T_N-antigen (Neu5Acα(2→6)GalNAcα(1→1)Ser/Thr) and can be easily modified to O-linked sialylated antigens, such as sialyl-TF antigen (Galβ(1→3)(NeuAcα(2→6)GalNAcα(1→1)Ser/Thr).[22] Glycosylation with sialic acid C-8 (Table 2, entry 5) and C-9 (entry 6) acceptors was also investigated. Good α selectivity is still retained because single α-anomeric products **11** and **13** were obtained in 67 and 82% yield, respectively. The α configuration was assigned by the ^3J(C-1,H-3_{ax}) coupling constants (Table 2).[23] This method is a general protocol for the efficient and α-selective synthesis of major naturally occurring α(2,6)-, α(2,3)-, α(2,8)-, and α(2,9)-sialosides, with special note that the sialyl disaccharides can be directly applied to subsequent glycosylation without aglycon adjustment.

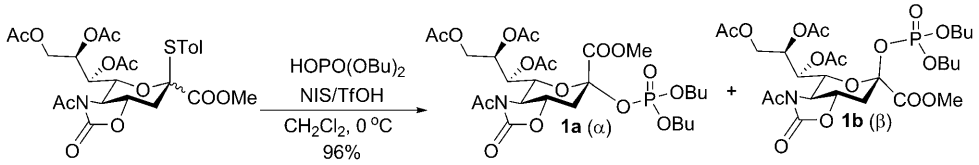
To extend the synthetic method into the programmable one-pot strategy, the RRVs of the sialylated disaccharides **3**, **5**, and **14**, were measured (Scheme 2).[6b] Disaccharide **3** showed the highest reactivity among the three building blocks. Compound **14**, containing the extra C-4 *O*-benzylation, is 1.7-fold more reactive than **5**. In general, the sialyla-

Table 1. Comparison of reactivities between sialyl α-phosphate **1a** and sialyl β-phosphate **1b**.



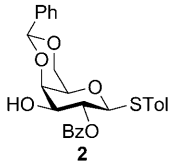
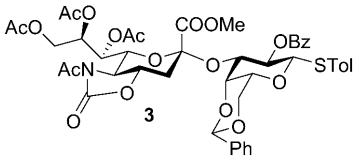
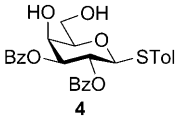
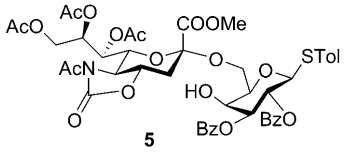
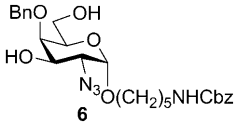
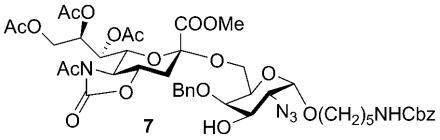
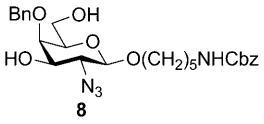
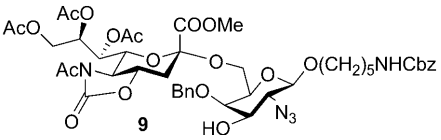
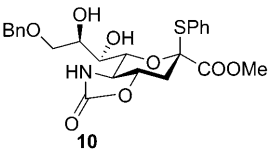
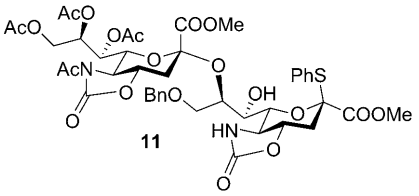
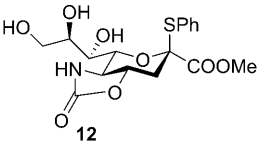
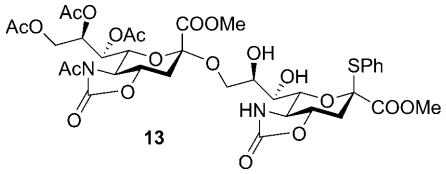
Donor	Acceptor	Reaction time [min]	*T* [°C]	Yield[a] [%]	α/β[b]
1a	**2**	5	−78 °C	83	α only
1b	**2**	5	−50 °C	82	10:1

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.



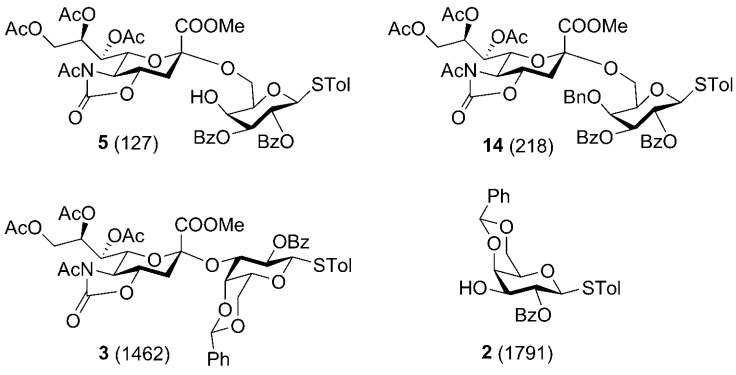
Scheme 1. Synthesis of *N*-acetyl-5-*N*,4-*O*-carbonyl-protected sialyl phosphate donor **1**. Tol = *p*-tolyl.

Table 2. Results of sialylation by using the *N*-acetyl-5-*N*,4-*O*-carbonyl-protected sialyl phosphate **1a**.

Entry	Acceptor	Product	Yield [%]	α/β ratio[c]	δ_{C1} [ppm]	^3J(C-1,H-3$_{eq}$) [Hz]
1	 **2**	 **3**	83	α only	168.7	5.5
2	 **4**	 **5**	85	α only	168.2	5.7
3	 **6**	 **7**	71	α only	168.4	6.2
4	 **8**	 **9**	70	α only	168.3	6.0
5	 **10**	 **11**	67[a]	α only	168.7	6.0
6	 **12**	 **13**	82[b]	α only	168.5	6.0

[a] Better yield was obtained when a mild base, such as $NaHCO_3$, was chosen to quench the reaction. [b] Some product decomposed into other uncharacterized side products after silica gel chromatography, and thus reduced the yield. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

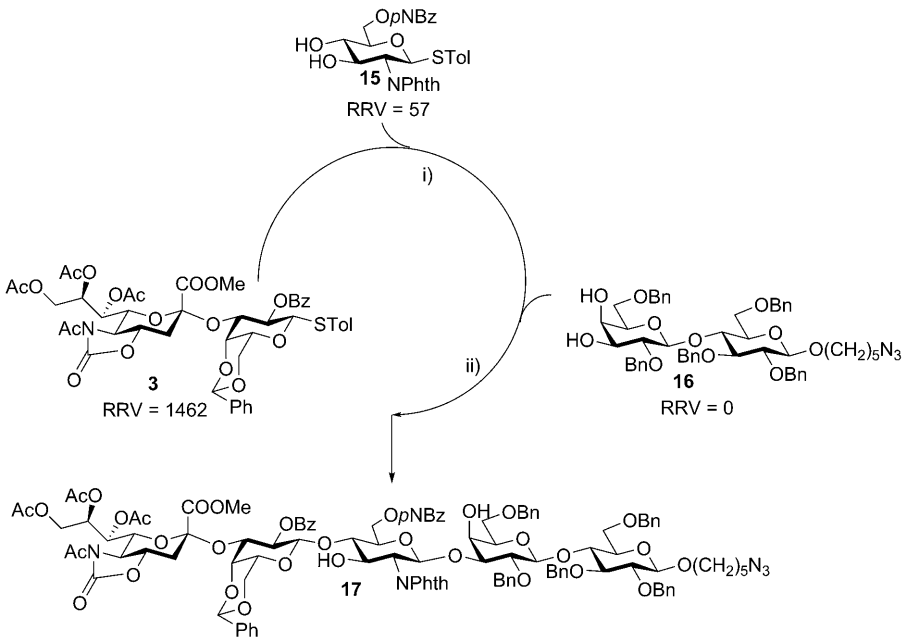
tion of a thioglycoside results in a modest deactivation of the anomeric reactivity of the acceptor, as exemplified by **3**.



Scheme 2. Relative reactivity values (in parentheses) of sialylated disaccharides. Bn = benzyl, Bz = benzoyl.

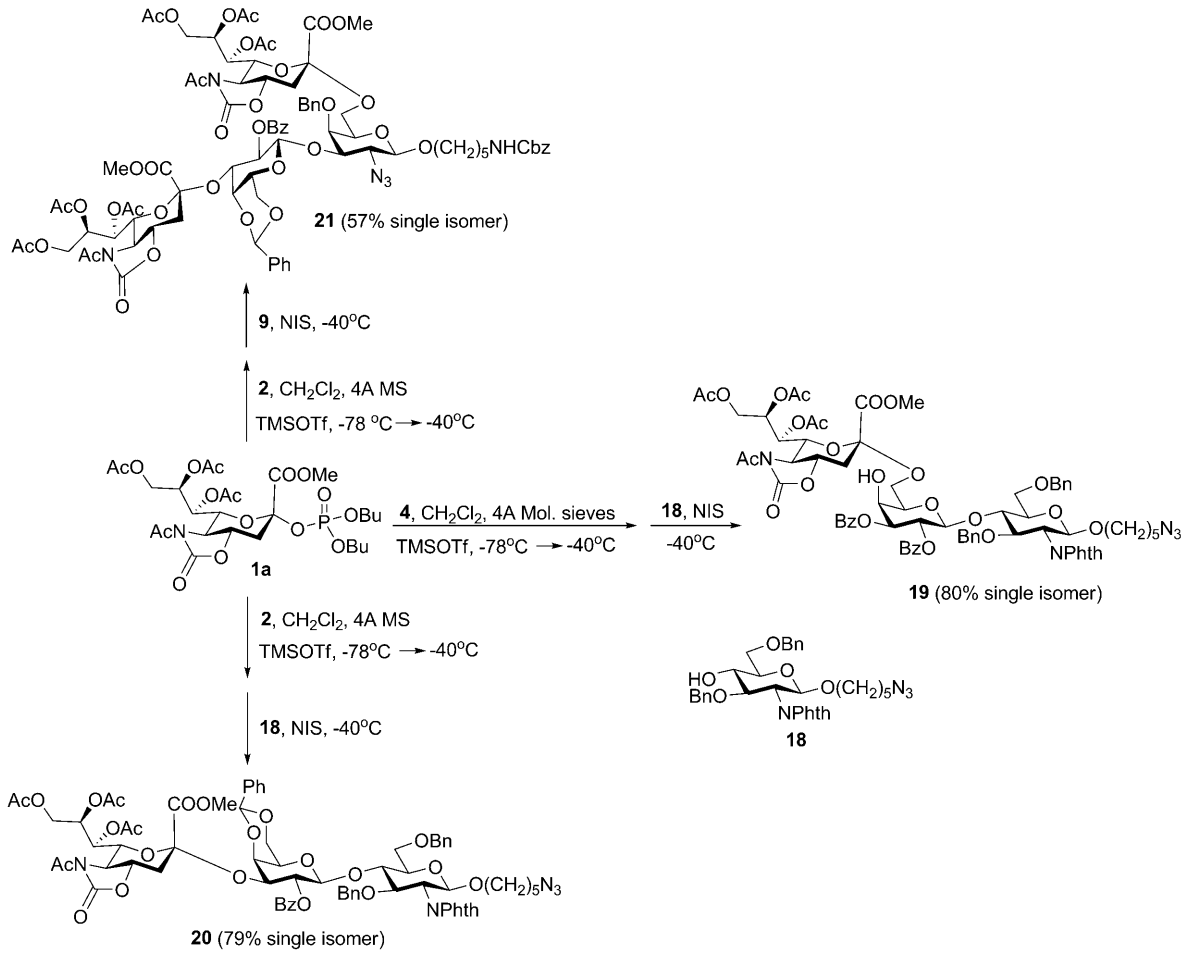
To demonstrate the synthetic application of sialylated disaccharides as building blocks, we conducted a representative reactivity-based, one-pot synthesis of the α(2→3)-linked sialylated pentasaccharide **17**. The RRVs of all three building units, **3** (RRV = 1462), **15** (RRV = 57), and **16** (RRV = 0), presented an appropriate reactivity profile for one-pot synthesis. The one-pot synthetic operation was performed in the presence of NIS/trifluoromethanesulfonic acid (TfOH) promoter system (Scheme 3). The second glycosylation between **15** and **16** required higher temperatures (−20 °C to room temperature). Obtaining the high-yielding, one-pot glycosylation product (48 %) indicated that the sialylated disaccharides with Neu5Ac as the terminal residue can be used as building blocks for the programmable one-pot synthesis of oligosaccharides.

We next turned our attention to using the sialyl phosphate donor **1a** in an orthogonal one-pot synthesis of sialosides. Two trisaccharides **19** (NeuAcα(2→6)Galβ(1→4)GlcNAc), **20** (NeuAcα(2→3)Galβ(1→4)GlcNAc), and tetrasaccharide



Scheme 3. Reactivity-based one-pot glycosylation of pentasaccharide **17**. i) NIS, TfOH, 4 Å molecular sieves, CH_2Cl_2, −78 °C; ii) NIS, TfOH, −20 °C to RT. Phth = phthaloyl.

21 with disialosylgalactosylglobo-side (DSGG) epitope[24] (NeuAcα(2→3)Galβ(1→4)-(NeuAcα(2→6)GalNAc) were used as one-pot targets (Scheme 4). Treatment of the first acceptor **4** (1.0 equiv) with **1a** (1.5 equiv) under the activation of TMSOTf gave disaccharide **5**. Next, the second coupling proceeded, without added TfOH, within 30 min with the addition of NIS (1.2 equiv). The trisaccharide **19** was produced in excellent yield as only α product (80% based on second acceptor, crude result). Parallel studies were done by the assembly of α(2→3)-linked trisaccharide **20** and tetrasaccharide **21** (Scheme 4).[25] The α configuration was assigned by the ^3J(C-1,H-3$_{ax}$) coupling constants

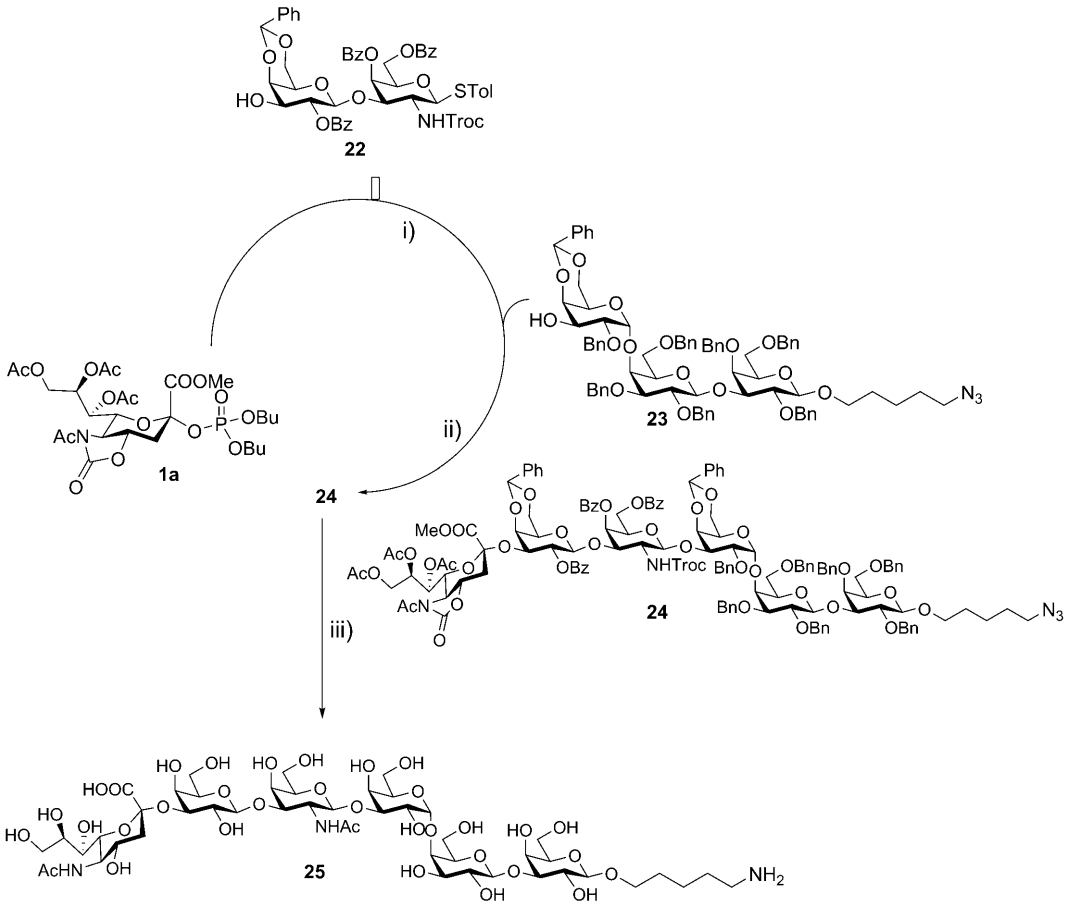


Scheme 4. Orthogonal one-pot synthesis of trisaccharides **19**, **20**, and tetrasaccharide **21**.

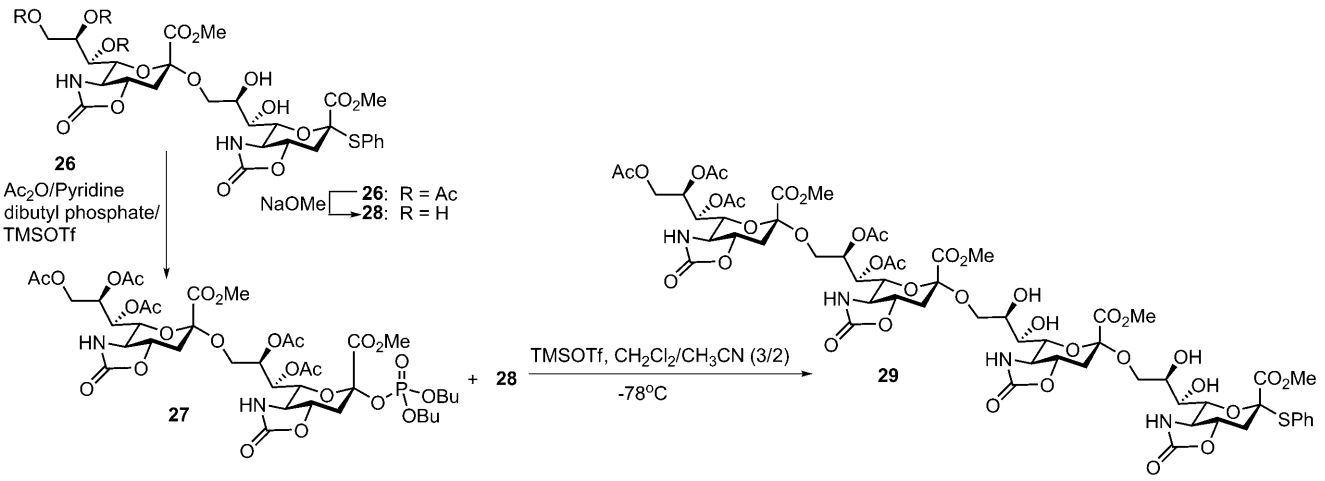
(see the Supporting Information). The power of this method was further demonstrated by the synthesis of tumor-associated antigen stage-specific embryonic antigen-4 (SSEA-4)[26] hexasaccharide, which belongs to the globo series of gangliosides. The SSEA-4 derivative **24** was synthesized in an excellent 78% yield by using the one-pot procedure outlined above. After global deprotection, the SSEA-4 hexasaccharide **25** was obtained in 30% yield (Scheme 5).

Recently, Takahashi and co-workers reported the α-specific synthesis of α(2→9) trisialoside[12i] or α(2→9) tetrasialoside,[27] which have long been difficult to synthesize, by using 5*N*,4*O*-carbonyl protected thiosialosides. The sequence of assembly was from the reducing to nonreducing end. Their strategy provided the opportunity to stereoselectively elongate the sugar chain one residue at a time after selective deprotection at the C-8 or C-9 positions. Herein, we developed an alternative strategy for the synthesis of α(2→9)-tetrasialosides via the 5-*N*,4-*O*-carbonyl-protected sialyl phosphate donor. Because α(2→9)-disialoside **13** decomposed after silica gel chromatography, we synthesized disaccharides **26**, **27**, and **28** (see detailed procedures in the Supporting Information). The disaccharides of **27** (1.1 equiv) and **28** (1.0 equiv) were coupled in CH_2Cl_2/CH_3CN (3/2) co-solvent under TMSOTf (1.2 equiv) activation to give α(2,9)-tetrasialoside derivative **29** in 70% yield (Scheme 6). The α isomer is the only product in these reactions (crude result), the major side product being the unconsumed acceptor, which can be recovered and reused. The advantage of this method is that the product α(2,9)-tetrasialoside derivative can be directly subject to similar derivations to synthesize α(2,9)-octasialoside.

In conclusion, we have demonstrated the application of the sialylation reagent with the combination of C-4/C-5 modification and dibutyl phosphate leaving group for efficient and α-selective synthesis of natural sialosides that are typically difficult to make. Sialylation using a sialyl phosphate donor has several advantages. First, its heightened reactivity makes it able to react with more hindered glycosyl acceptors, such as acceptor **2**, in high yield. Second, sialylthioglycoside building units with defined stereochemistry and reactivity (RRVs), which can be used in programmable one-pot methodology, are synthesized in a facile manner by using sialyl phosphate in the presence of thioglycosyl acceptors. Third, the sialyl phosphate donor also can be used in an orthogonal one-pot glycosylation, providing an alternative choice for the rapid synthesis of sialosides, allowing the coupling of building blocks independent of their relative reactivities, such as SSEA-4. Sialyl phosphate donors are very



Scheme 5. One-pot synthesis of SSEA-4 hexasaccharide **25**. i) TMSOTf, MS 4 Å, CH_2Cl_2, −78°C, ii) NIS, overall 78%, iii) a) NaOMe, MeOH, b) Zn, AcOH, THF; c) Ac_2O, pyridine, DMAP, d) 0.1 N NaOH, e) $Pd(OH)_2$, H_2, THF/MeOH/AcOH/H_2O 10:8:1:0.7. Troc = 2,2,2-trichloroethoxycarbonyl.



Scheme 6. Synthesis of α(2→9) tetrasialic acid **29**.

efficient at creating complex natural sialosides and are being used for rapid preparation of important sialoside microarrays that would have previously been inaccessible.

Acknowledgements

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Keywords: one-pot glycosylation · sialic acids · sialyl phosphate · sialylation · synthetic methods

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