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Stereoselective Synthesis of *S*-Linked $\alpha(2\rightarrow8)$ and $\alpha(2\rightarrow8)/\alpha(2\rightarrow9)$ Hexasialic Acids

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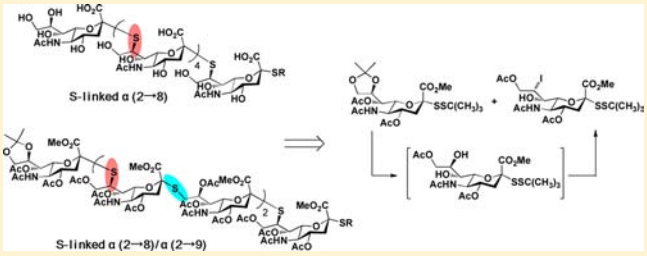
Supporting Information

ABSTRACT: A new approach for the synthesis of *S*-linked $\alpha(2\rightarrow8)$ and alternating $\alpha(2\rightarrow8)/\alpha(2\rightarrow9)$ oligosialic acids by *S*-alkylation has been developed, using chemo- and stereoselective alkylation of a C2-thiolated sialoside donor (nucleophile) with either a C8- or C9-iodide-activated sialoside acceptor (electrophile). An efficient intramolecular acetyl group migration from the C7 to C9-position of the sialoside under mild basic conditions was used to generate the C8-iodide, the key sialyl acceptor (electrophile). Using this strategy, the syntheses of *S*-linked $\alpha(2\rightarrow8)$ and $\alpha(2\rightarrow8)/\alpha(2\rightarrow9)$ hexasialic acids were achieved.



1. INTRODUCTION

Sialic acids are implicated in a multitude of biological processes including cellular adhesion, the inflammatory response, cell signaling, and cell differentiation.[1a,b] Sialic acid (Neu5Ac, *N*-acetylneuraminic acid) is typically located at the nonreducing terminus of glycoconjugates such as the glycoproteins and glycolipids of vertebrates, and is a component of the capsular polysaccharides of pathogenic bacteria.[2a,b] Three kinds of linear homopolymers of polysialic acids have been identified on mammalian or bacterial cell surfaces, including $\alpha(2\rightarrow9)$ (**1a**), $\alpha(2\rightarrow8)$ (**2a**), or the alternating $\alpha(2\rightarrow8)/\alpha(2\rightarrow9)$ (**3a**) Neu5Ac unit, as shown in Figure 1.[3] Recent advances in glycobiology suggest that $\alpha(2\rightarrow8)$ and $\alpha(2\rightarrow9)$ di/oligosialic acid and polysialic acids play critical roles in the biological events that occur on the cell surface.[4a−c] For example, polysialic acids isolated from the causative agent of meningitis, *Neisseria meningitides* serogroup B and C strains, differ in their chemical and immunological properties.[5] In addition, $\alpha(2\rightarrow8)$-linked di/trisialic acid residues are common structural units of gangliosides, and an $\alpha(2\rightarrow9)$-linked disialosyl structure was identified at the terminals of longer poly lactosaminyl glycans isolated from PA1 human embryonal carcinoma cells.[6] Moreover, the $\alpha(2\rightarrow9)$-linked polysialic acids were found on C-1300 mouse neurobrastoma cells (NB41A3),[7] and in sea urchin sperm flagella.[8] Due to their presence on bacterial and cancer cell surfaces, oligosialic acids are considered good targets for the development of vaccines.[9]

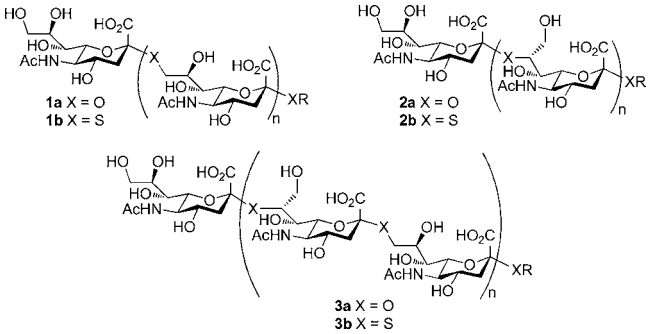


Figure 1. Structures of *O*- and *S*-linked $\alpha(2\rightarrow9)$, $\alpha(2\rightarrow8)$ and alternating $\alpha(2\rightarrow8)/\alpha(2\rightarrow9)$ sialosides.

To better understand the interactions between polysaccharides and their receptors, it is necessary to use chemically pure oligosaccharides as biochemical probes. However, the interglycosidic bonds of polysaccharides, especially in polysialic acid, are very labile under even mildly acidic or basic conditions, and are susceptible to degradation by glycosyl hydrolases. Thus, carbohydrate mimics resistant to hydrolysis are required for glycobiology studies instead.[10] Replacement of the glycosidic oxygen atom by another heteroatom such as sulfur has been shown to enhance the stability of the glycosidic linkage toward hydrolysis by either chemical or enzymatic means[11] while maintaining the parent oligosaccharides biochemical activities. Recently, both Bundle et al.[12] and Schmidt et al.[13] have synthesized sialic acid-containing tumor antigens, in which the sialic acid at the nonreducing end was linked to reducing end saccharides via a *S*-glycosidic bond. Furthermore, when the *S*-linked ganglioside analogues were conjugated with tetanus toxoid, the antibodies produced in mice by the above vaccines showed specific recognition of the parent *O*-linked antigens[12b,c] as well as a longer half-life of *S*-linked vaccines. This work strongly suggests that the synthesis of chemically pure *S*-linked oligosialic acid antigens for the development of carbohydrate-

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based vaccines would be of great value. However, *S*-linked oligosialosides such **1b** and **2b**, as shown in Figure 1, are challenging synthetic targets due to the difficulty in controlling the anomeric stereochemistry.

Various methods have been reported for the synthesis of *S*-linked oligosaccharides,[14] the most common approach being the use of either a nonanomeric or an anomeric thiol as the nucleophile to react with an electrophilic glycosides, including S_N2 displacement of a leaving group by thiolated sugar derivatives; Michael-type additions of thiolates to enones; Lewis-acid-catalyzed glycosylations between a glycosyl acceptor with a SH group and a glycosyl donor; and use of thiirane intermediates as alkylating reagents.[14] Unfortunately, epimerization of the anomeric thiol during thiol deprotection was a near ubiquitous problem.[14] In addition, disulfide bond formation was found to be the main competing reaction[15] as well as thiol-oxidation[16] and elimination.[15,17a,b] All of these complicate desired product isolation and decrease yield. Furthermore, although many methods have been reported for the synthesis of *S*-linked glycoconjugates that bear sialic acid at the terminal position,[10b,14] these methods are unsuitable for the synthesis of oligosialic acids.[18] In addition, the thiol protecting groups upon which these methods depend are intolerant of the conditions under which the functional group is transformed during the synthesis of sialic donor/acceptor.

Recently, we developed an effective "*S*-alkylation" method for α-selective sialylation using an anomeric *tert*-butyl disulfide protected acceptor (electrophile), and exemplified its utility in the synthesis of *S*-linked $\alpha(2\rightarrow9)$ octasialic acid.[18] We concluded that because the anomeric thiol group in the donor (nucleophile) is fixed, nucleophilic displacement of an iodide leaving group at the C9 position of the sialyl acceptor (electrophile) would deliver only the α-anomer during sialylation.

Three major advantages accompany the use of this "*S*-alkylation" method. First, disulfide bond formation is significantly reduced, by inhibition of thiol−thiol exchange, a common problem usually encountered during a thiol nucleophilic substitution reactions.[19] Second, the impervious nature of the unsymmetrical *tert*-butyl disulfide protecting group at the anomeric thiol group enables varied functional group transformation during the synthesis of the sialic acid building blocks. Lastly, the disulfide bond can be easily cleaved using sodium 2-mercaptomethane sulfonate, without changing the anomeric stereochemistry. Herein, we seek to extend this principle of "*S*-alkylation" for the synthesis of homo-oligosialic acids by focusing on the intriguing case of a hitherto unknown iodide leaving group at the C8-position of sialyl acceptor for construction of $\alpha(2\rightarrow8)$ glycosidic bond.

2. RESULTS AND DISCUSSION

Our strategy for the synthesis of *S*-linked $\alpha(2\rightarrow8)$ oligosialic acid (**4**) is based on an S_N2-substitution reaction between a sialyl electrophile **6** and nucleophile **7**, as shown in Figure 2. Sialyl electrophile **6** can be obtained by a selective inversion of configuration at C8-hydroxyl group of **8**, and the sugar chain elongated from the nonreducing to reducing end. Both building blocks **7** and **8** are readily accessibly from known compound **9**.[18]

A literature survey revealed that acetyl group migration from C7 to the C9-hydroxyl group in Neu5Ac could be achieved under acidic[20a] or neutral[20b] conditions. Thus, building block **8** was expected to be obtained by acetyl group migration from C7

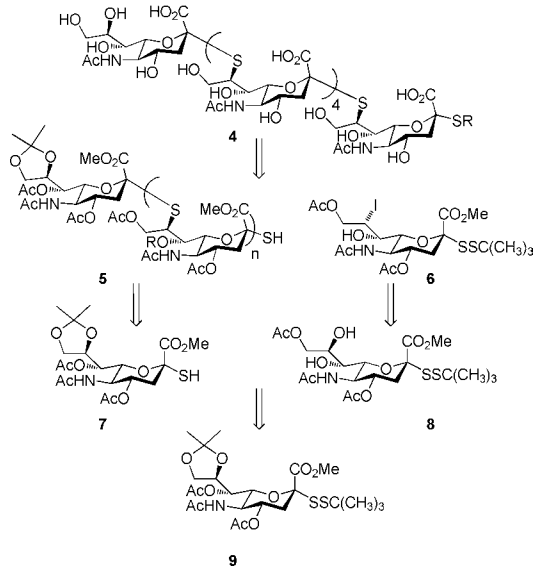
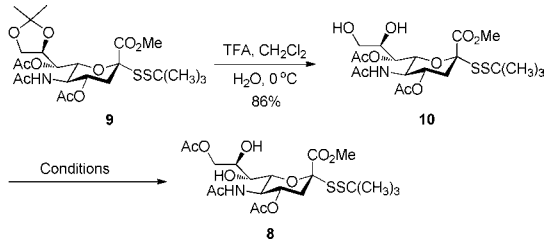


Figure 2. Strategy for the synthesis of *S*-linked α-(2→8) hexasialic acid **4**.

to the C9-hydroxyl group of the disulfide **10**, itself synthesized from **9** by acid-catalyzed (TFA) de-*O*-isopropylidenation in wet dichloromethane (Table 1). Introduction of the iodide leaving

Table 1. Investigation of Acetyl Group Migration To Yield Building Block 8



entry	acid or base sources	conditions	product (%)
1	TFA	CH_2Cl_2, H_2O, 0 °C to rt, 20 h	<30
2	IR-120 resin (H^+)	CH_3CN, H_2O, rt, 15 h	22
3	IR-120 resin (H^+)	THF, H_2O, rt, 15 h	25−30
4	DOWEX-50 (H^+) resin	THF, H_2O, rt, 15 h	∼30
5		MeOH, reflux, 24 h	SM
6	NEt_3	MeOH, EA, 10 h	42
7	DOWEX 550 (OH^-) resin	EA, 50 °C, 20 h	77

group at C8 in **8** is by an S_N2-type substitution, which first requires selective protection of the most reactive C9-hydroxyl group in **10**, as shown in Table 1. To our surprise, the migration of C7-acetyl group in **10** to the C9-position was sluggish under the acidic conditions tested and the desired compound **8** was obtained only in disappointing yields of 22−30% (Table 1, entries 1−4). Under the neutral conditions (refluxing methanol), only starting material was recovered (entry 5). However, the migration yield could be improved to 42% in the presence of triethylamine (entry 6), and to 77% using the mildly basic resin (Dowex 550 OH^-)[21] and ethyl acetate at 50 °C (entry 7). The position of the C9−Ac group in **8** was unambiguously confirmed by 2D NMR spectroscopy: $^1H-^1H$ COSY spectra revealed that the chemical shifts of the

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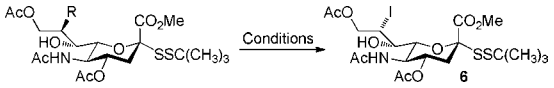
methylene protons at C9 of **10** at 3.46 and 3.66 ppm are shifted to 4.13 and 4.39 ppm in **8**, consistent with reported Neu5Ac analogues.[20a]

We next focused our attention on the installation of the iodide functionality at the less hindered C8-hydroxyl group of **8** (Table 2). Initial attempts to displace a C8-sulfonic ester (such as -OTs, and -OMs) using sodium iodide were unsuccessful (entries 1–2).

Table 2. Synthesis of C8-I Leaving Group of Sialyl Acceptor 6



entry	R	conditions	yield (%)
1	OMs	A[a]	–[e]
2	OTs	A[a]	–[e]
3	OTf	A[a]	<20
4	OH	B[b]	28
5	OH	C[c]	45
6	OH	D[d]	69

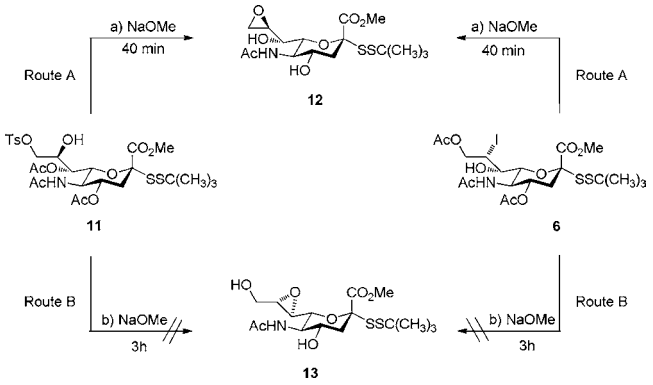
[a]NaI, acetone, reflux, 12 h. [b]I_2, PPh_3-polymer bound, imidazole, toluene, 80 °C, 4 h. [c]TMSCl, NaI, CH_3CN, 0 °C, 4 h. [d]$Cl_2Si(CH_3)_2$, NaI, CH_3CN, 0 °C, 4 h. [e]Recovered starting material.

Even the use of the highly activated C8-triflate ester gave unsatisfying yield (entry 3). However, subjecting **8** to Mitsunobu condition (iodine with polymer bound triphenylphosphine)[22] aforded **6** in 28% yield (entry 4), and when chlorotrimethylsilane and sodium iodide in acetonitrile were used,[23a] compound **6** was obtained in a much better yield of 45% (entry 5). Surprisingly, substituting chlorotrimethylsilane to the more reactive dichlorodimethylsilane under the same reaction conditions gave the desired compound **6** in an acceptable yield of 69% (entry 6). It is possible that the reaction mechanism may be similar to chlorotrimethylsilane-sodium iodide reagent which forms iodotrimethylsilane *in situ*, proposed by Olah and co-workers.[23b]

To determine the stereochemistry of C8 in compound **6**, we first compared the chemical shift and coupling constants of C8 proton with reported C8-I sialoside analogues.[24a,b] The epoxide **12**[25] produced from building block **6** was found to be identical with that from compound **11** in which the orientation of C8-hydroxyl group is known (Scheme 1). Under basic conditions, both compounds **6** and **11** underwent an S_N2 type displacement to give the same epoxide **12** (Route A). Notably, $^1H-^1H$ COSY NMR showed the chemical shifts of the C9 protons to be 2.7–2.8 ppm, indicating that the Payne rearrangement product, an epoxide **13**, is not formed—even under harsh reaction conditions (Route B). This observation clearly indicates the stereochemistry of C8 in compound **6** to have inverted (to *S* configuration).

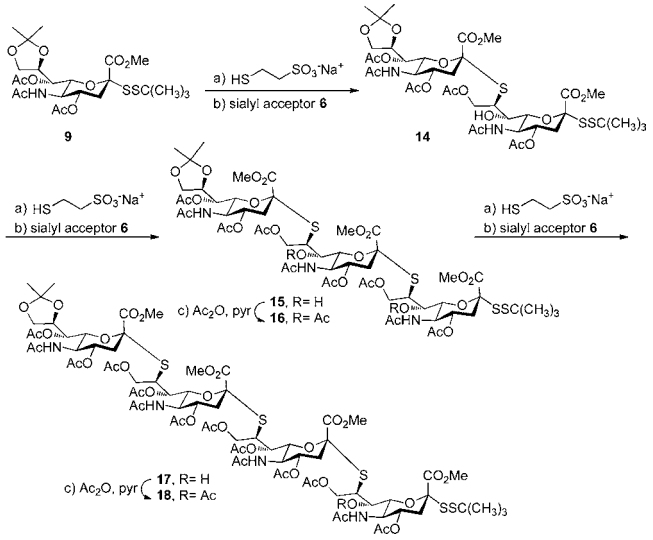
The reactivity at C8 of sialyl electrophile **6** was next investigated. Treatment of **6** with potassium thioacetate in DMF for 20 h resulted in inversion of C8 configuration to give the corresponding thioacetate in 76% yield.[26] Having established a model S_N2 type substitution reaction at C8-iodide (C8-I) in **6**, we next conducted the synthesis of *S*-linked $\alpha(2\rightarrow8)$ oligosialosides from precursor **9**, as shown in Scheme 2. The unsymmetrical disulfide bond of **9** was cleaved using sodium 2-mercaptoethanesulfonate[27] to generate the corresponding thiol nucleophile, which was immediately reacted

Scheme 1. Synthesis of 8,9-Epoxide 12[a]



[a]Reagents and conditions: a) NaOMe, MeOH, 0 °C, 40 min, 89% for **11**; 88% for **6**; b) NaOMe, MeOH, 0 °C to rt, 3 h.

Scheme 2. Synthesis of $\alpha(2\rightarrow8)$ Tetrasialic Acid[a]



[a]Reagents and conditions: a) Sodium 2-mercaptoethanesulfonate, DMF, H_2O, DIPEA, −15 °C to rt. b) Et_2NH, **6**, DMF, rt; 62% (two steps) for **14**; 46% (two steps) for **15**; 38% for **17** (two steps). c) Ac_2O, Pyr, rt, 87% for **16**; 89% for **18**.

with sialyl electrophile **6** to afford $\alpha(2\rightarrow8)$ disialoside **14** (62% yield for two steps). The configuration of newly formed glycosidic bond was assigned by NMR spectroscopy. In a selective proton decoupling ^{13}C NMR experiment,[28a,b] the coupling pattern of disialoside **14** gave two doublet signals of C1 with characteristic coupling constants of 7.38 and 7.46 Hz, respectively, unequivocally confirming two α-glycosidic bonds. By repeating these procedures, *S*-linked $\alpha(2\rightarrow8)$ trisialoside **15** and tetrasialoside **17** were successfully synthesized in yields 46% and 38% over two steps, respectively. When the substitution reaction was performed in the synthesis of oligosaccharide, the yield of thiol–thiol exchange side product was found to gradually increase, and compounds **14** (26% yield) and **16** (35% yield) were recovered in the synthesis of tri- and tetrasialosides, respectively.[29] Notably, no β-anomer was observed in the substitution reactions. To facilitate characterization, the hydroxyl groups on compounds **15** and **17** were acylated (Ac_2O, Py), and fully protected sialosides **16** and **18** were isolated in 87% and 89% yield, respectively. However, when the corresponding thiol nucleophile was used

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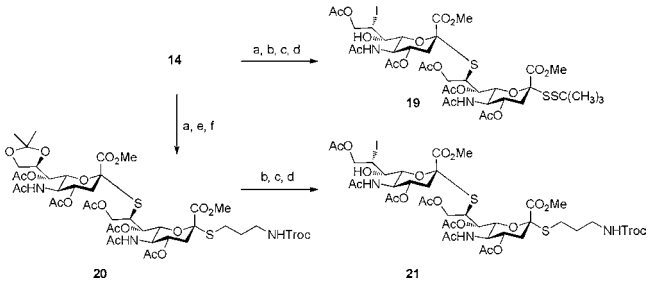
in the synthesis of pentasialoside, only **18**, in which the disulfide bond was cleaved before substitution, was recovered under standard reaction conditions, indicating that thiol−thiol exchange became the major reaction

To suppress this undesired thiol−thiol exchange, the synthetic strategy was modified to a more convergent approach using disaccharide building blocks (Scheme 3). The disulfide

Scheme 3. Synthesis of C8-Iodide (C8-I)-Activated Disialoside 19 and 21[a]



[a]Reagents and conditions: a) Ac_2O, pyr, rt, 92%; b) TFA, CH_2Cl_2, H_2O, 0 °C; c) DOWEX 550 (OH^-) resin, ethyl acetate, 50 °C; d) $Cl_2Si(CH_3)_2$, NaI, CH_3CN, 0 °C, 48% for **19**, 50% for**21** (three steps); e) sodium 2-mercaptoethanesulfonate, DMF, H_2O, DIPEA, −15 °C to rt; f) Et_2NH, 2,2,2-trichloroethyl-(3-iodopropyl)carbamate, DMF, rt, 72% (three steps).

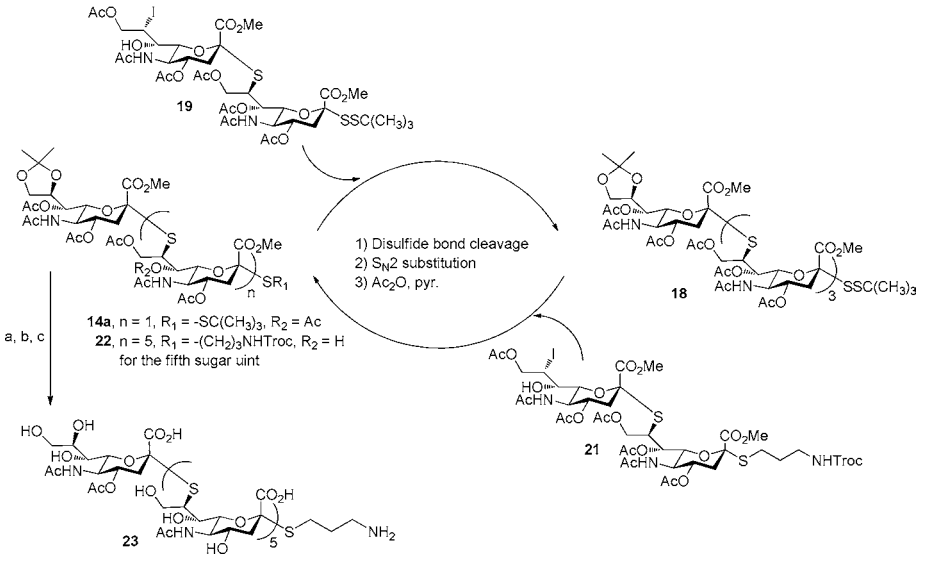
functionality at the reducing-end of the disaccharide **14** was replaced by a sulfide substituent containing a protected amino group for future conjugation. Compounds **19** and **21** were synthesized from disialoside **14**, and the synthesis of hexasialoside was pursued. Acetylation (Ac_2O, Pyr) of **14** followed by de-*O*-isopropylidenation (TFA, H_2O−CH_2Cl_2), base-catalyzed (DOWEX 550 (OH^-)) migration of the acetyl group from C7 to the C9-hydroxyl group, and installation of iodide at the C8-position using $Cl_2Si(CH_3)_2$/NaI gave **19** in a yield of 48% over four steps. Disialyl electrophile **21** was synthesized from intermediate **20** following procedures similar to those described above (50% overall yield for three steps). Compound **20** was obtained from precursor **14** by acetylation (Ac_2O, Pyr), cleavage of the disulfide bond (sodium 2-mercaptoethane sulfonate in DMF), and base-promoted *S*-alkylation with 2,2,2-trichloroethyl-(3-iodopropyl)carbamate. The yield over these three steps was 72%.

Synthesis of $\alpha(2\rightarrow8)$ hexasialic acid **22** was envisioned to occur via an iterative *S*-glycosylation strategy using sialylating building blocks **14a** (obtained by acetylation of **14**), **19**, and **21**, as illustrated in Scheme 4. Starting from **14a**, iterative disulfide bond cleavage and S_N2 substitution with sialyl electrophiles **19** and **21** produced higher-order *S*-linked sialoside. Using this synthetic strategy, we achieved the synthesis of tetra- and hexa-thio-oligosialic acids. The overall yields for the tetrasialic acid (**18**) (including three steps and starting from **14a**) and hexasialic acid (**22**) (two steps without acetylation and starting from **18**) were 41% and 31%, respectively. No β-anomer product was obtained from the above substitution reactions. Methanolysis of the *O*-acetyl groups in compound **22** proceeded smoothly under Zemplén conditions (NaOMe, MeOH). The resulting mixture was further exposured to basic conditions (aqueous NaOH) at room temperature to ensure hydrolysis of the methyl esters and Troc protecting group.[30] Finally, acid-catalyzed de-*O*-isopropylidenation (TFA, MeOH/H_2O) provided $\alpha(2\rightarrow8)$ hexasialic acid **23**[31] (60% over three steps).

The above synthetic strategy was then applied to construct alternating $\alpha(2\rightarrow8)/\alpha(2\rightarrow9)$ tetra- and hexasialic acids. Synthesis of a homo-oligosialic acid with alternating glycosidic bonds has long been considered as a difficult task in carbohydrate chemistry. We anticipated that the use of our regioselective S-alkylation method in the synthesis of $\alpha(2\rightarrow8)/\alpha(2\rightarrow9)$ oligosialic acid would simplify this complicated synthetic operation.

The electrophilic (**24**) and reducing end (**25**) disaccharide building blocks were first synthesized starting from disialoside building block **14** (Scheme 5). Acetylation of **14** was followed by de-*O*-isopropylidenation, selective transformation tosylation, and substitution[18] yielded **24** in an overall yield of 50% (over three steps). Using the same strategy mentioned above to form

Scheme 4. Synthesis of $\alpha(2\rightarrow8)$ Hexasialic Acid[a]



[a]Reagents and conditions: a) NaOMe, MeOH, rt; b) 1 N NaOH, H_2O, rt; c) TFA, MeOH/H_2O, 0 °C, 60% (three steps).

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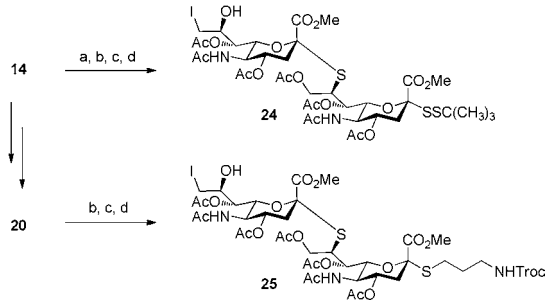
Scheme 5. Synthesis of C9 Iodide-Activated Disialosides 24 and 25[a]



[a]Reagents and conditions: a) Ac_2O, pyr, rt, 92%; b) TFA, CH_2Cl_2, H_2O, 0 °C; c) TsCl, NEt_3, DMAP, CH_3CN, rt; d) NaI, acetone, reflux, 50% for **24**, 55% for **25** (three steps).

the **20** was followed by the same transformations as described above to give **25** in 55% overall yield.

The synthesis of *S*-linked $\alpha(2\rightarrow8)/\alpha(2\rightarrow9)$ tetra- and hexasialic acids is similar to that described in the synthesis of $\alpha(2\rightarrow8)$ hexasialic acid (Scheme 4). Due to the use of a primary iodide as the electrophile, the yields of sulfur substitutions were higher than those obtained in the synthesis of $\alpha(2\rightarrow8)$ oligosialic acids (in which the more hindered electrophilic **19** and **21** were used). As shown in Scheme 6, use of building blocks **14a**, **24**, and **25**, and an iterative sequence of disulfide bond cleavage, S_N2 substitution, and acetylation, gave the higher-order *S*-sialosides. The two-step yield (S−S cleavage and substitution) for *S*-linked $\alpha(2\rightarrow8)/\alpha(2\rightarrow9)$ tetrasialic acid **26** was 58%, and the three-step yield (including acetylation) for $\alpha(2\rightarrow8)/\alpha(2\rightarrow9)$ hexasialic acid **27** was 39%. Again, no β-anomer was observed in the substitution reactions by NMR spectroscopy.

3. CONCLUSIONS

In conclusion, an efficient method for the synthesis of *S*-linked $\alpha(2\rightarrow8)$ and $\alpha(2\rightarrow8)/\alpha(2\rightarrow9)$ hexasialic acids has been developed. The use of the *tert*-butyl-disulfide protecting group at the anomeric position allows the functional group transformations to take place and mitigates disulfide formation during the *S*-alkylation. Using DOWEX 550 (OH^-) anion-exchange resin, an effective acetyl migration from C7- to the C9-hydroxyl group of the sialoside was achieved. The combination of dichlorodimethylsilane and sodium iodide was successfully used to generate various C8-I-activated sialosides. The amino functional group tether at the reducing end of synthesized *S*-linked oligosialic acids can be used to conjugate with other molecules for biological applications. This method makes the construction of $\alpha(2\rightarrow8)$ and $\alpha(2\rightarrow9)$ glycosidic bonds feasible for the first time. It is also expected to be applicable to the synthesis of the various *S*-linked sialic acid-containing carbohydrates, which can serve as effective biochemical probes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and NMR spectral characterization of the synthesized *S*-linked $\alpha(2\rightarrow8)$ and $\alpha(2\rightarrow8)/\alpha(2\rightarrow9)$ oligosialosides. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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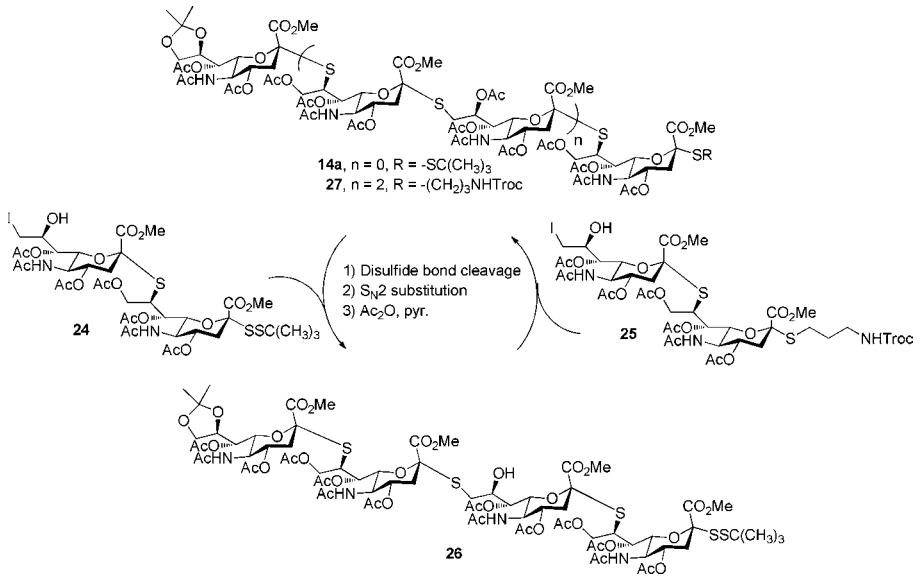
Scheme 6. Synthesis of $\alpha(2\rightarrow8)/\alpha(2\rightarrow9)$ Tetra- and Hexasialic Acids



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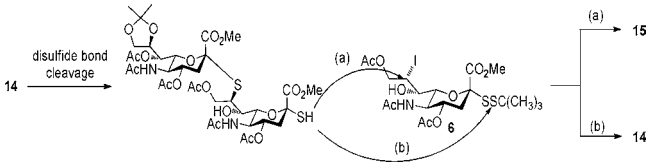

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