Stereoselective C-Sialylation

Synthesis of a Carbon-Linked Mimic of the Disaccharide Component of the Tumor-Related SialylTn Antigen**

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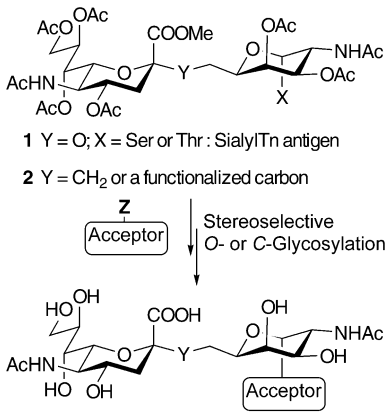
Among the large number of known tumor-associated carbohydrate motifs, Tn (GalNAcα1→*O*-Ser/Thr) and sialylTn (Neu5Acα2→6GalNAcα1→*O*-Ser/Thr) are the most specific to human epithelial tumor cells (breast, colon, ovarian, lung, and pancreatic cancers).[1] The sialylTn antigen, which is expressed on membrane-bound mucin-type glycoproteins, appears in transformed cells by premature sialylation of *N*-acetylgalactosamine, the first sugar moiety of the nascent *O*-glycane side chains in glycoproteins.[2] Integration of these antigens into synthetic vaccine constructs induces an anticancer immune response in which the carbohydrate domain plays a decisive role in determining immunogenicity.[1,3] The glycosylated antigen is, however, partially deglycosylated during the priming period.[4] It is therefore important to evaluate compounds in which the carbohydrate moiety cannot be detached from the peptide. We previously reported a mimic of the Tn antigen that could be incorporated into immunogenic glycopeptides.[5] We now describe the easy access to a carbon-linked mimic **2** of the Neu5Acα2→6GalNAcα1→OR disaccharidic component of the sialylTn antigen (Scheme 1).[6,7]



Scheme 1. SialylTn tumor antigen **1** and a stable analogue of the sialyl-*N*-acetylgalactosaminyl donor **2** for "block" synthesis.

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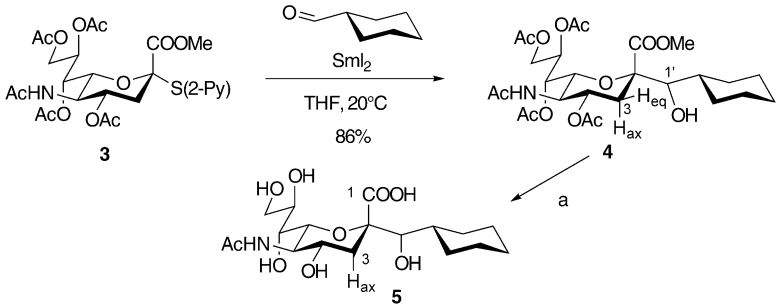
The synthesis was designed in such a way that an activated disaccharidic block would be available for modular attachment to a wide variety of acceptors.[8] Integrated in a vaccine, this segment would not be sensitive to enzymatic cleavage of the sialyl and the galactosaminyl moieties. This stable mimic may also be useful for the immunodiagnosis of different tumors or for the affinity purification of specific receptors.

We previously established that a samarium diiodide (SmI_2) promoted Barbier reaction with glycosyl 2-pyridyl sulfones is a rapid approach for the stereoselective assembly of C-glycosides.[9–11] In an interesting extension to this work, Linhardt and co-workers showed that the procedure worked equally well with anomeric pyridyl sulfones of 2-ulosonic esters.[12] They later reported that anomeric chlorides or phenyl sulfones could also be used in this procedure without the need of activation by hexamethyl phosphoramide (HMPA).[13] These results were expected since reduction of a functional group α to both an ester group and an oxygen atom (Reformatsky-type reaction) is much more facile than the same operation on a functional group α to an oxygen atom alone. This observation suggests that functional groups other than halides, sulfones, or phosphates would also be appropriate anomeric anion precursors for Neu5Ac or related ulosonic acid derivatives. We report here a synthesis which relies on the unprecedented use of a stable and crystalline 2-pyridyl sulfide of the *N*-acetylneuraminic acid derivative **3** as the anionic precursor in a samarium–Reformatsky procedure.[14]

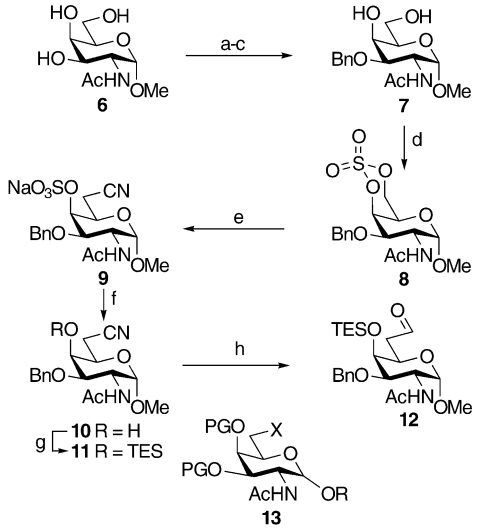
The feasibility of this approach was first assessed with a simple aldehyde and 2-pyridyl sulfide **3**, which is available from the corresponding 2-*O*-acetate (AcCl, AcOH, HCl[15a] then 2-sulfanylpyridine (1.2 equiv), K_2CO_3 (1.3 equiv), toluene/acetone;[15b] 60% yield over the two steps). Treatment of a solution of sulfide **3** and cyclohexanecarbaldehyde (1.5 equiv) in THF at 20°C with a freshly prepared solution of SmI_2[16] in THF led to a very fast consumption of the one-electron reducing agent.[17] After a standard workup, the C-glycosyl derivatives **4** were obtained in an approximately 1:1 diastereomeric ratio and separated by chromatography (86% yield; Scheme 2).

Both compounds displayed a standard $_5C^2$-chair conformation as determined by ^1H NMR analysis ($J_{3ax,4}$, $J_{4,5}$, and $J_{5,6}$ values of 10.2, 11.8, and 10.5 Hz, respectively, for one isomer and of 12.0, 10.5, and 10.5 Hz for the other). The expected equatorial orientation of the newly formed C–C bond at the quaternary center was determined by NOE measurements on both isomers of **4** (NOE contacts between $H_{1'}$ and H_{3eq}/H_{3ax} and not H_4/H_6). This stereochemical assignment was further confirmed by the large values of the C_1-H_{3ax} heteronuclear coupling constants observed in the deprotected C-glycosyl compounds **5** ($^3J = 8.0$ Hz for one isomer and 7.3 Hz for the other); these values are typical of a *trans* diaxial orientation of the C_1–C_2 and C_3–H_{3ax} bonds.[18]



Scheme 2. SmI_2-induced coupling of pyridyl sulfide **3** with cyclohexanecarbaldehyde. 2-Py = 2-pyridyl. a) MeONa, MeOH, 20°C, overnight; NaOH, MeOH-H_2O, 20°C, 2 h, then Dowex 50W-X8-H^+ form, 90%.

Preparation of the required aldehyde **12** (Scheme 3) started from methyl α-D-*N*-acetylgalactosamine (**6**), which was obtained by Fischer glycosylation[19] (MeOH, Dowex

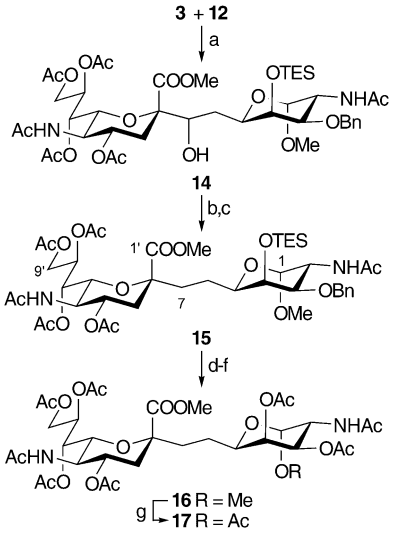


Scheme 3. Preparation of aldehyde **12**. Reagents and conditions: a) $PhCH(OMe)_2$, CSA, DMF, 40°C, 2 h, 60%; b) BnBr (3.5 equiv), $Ba(OH)_2 \cdot 8H_2O$, BaO, DMF, 25°C, 77%; c) AcOH/H_2O (70/30), 70°C, 1 h, 88%; d) $SOCl_2$, Et_3N, CH_2Cl_2, 0°C, 1 h; cat. $RuCl_3 \cdot 3H_2O$, $NaIO_4$, $CH_3CN/CH_2Cl_2/H_2O$ (2/2/3), 25°C, 1 h, 65%; e) NaCN, DMF, 25°C, 3 h, 97%; f) cat. H_2SO_4, moist THF, 25°C, 1 h, 86%; g) TESOTf (3 equiv), pyridine, DMAP, CH_2Cl_2, 0°C, 0.5 h, 80%; h) DIBAL-H (3.3 equiv in 3 portions every 20 min), CH_2Cl_2, −78°C, 1 h, 60%. CSA = camphorsulfuric acid, Bn = benzyl, TES = triethylsilyl, DMAP = 4-dimethylaminopyridine, DIBAL-H = diisobutylaluminum hydride.

50W-X8, H^+ form, reflux, 24 h) of *N*-acetyl-D-galactosamine or, more conveniently for large-scale preparations, by transformation of the inexpensive *N*-acetyl-D-glucosamine.[20]

A standard three-step sequence provided diol **7** which was converted into 4,6-cyclic sulfate **8** by using the procedure of Gao and Sharpless.[22] Regioselective ring opening of cyclic sulfate **8** at C-6[23] by sodium cyanide provided cyanide sulfate **9** in high yield which, after hydrolytic removal of the intermediate sulfate, gave alcohol **10**. This high-yielding one-carbon extension of the sugar chain at position 6 is in stark contrast to all attempts at nucleophilic displacement of iodides or sulfonates by cyanide ions in the more conventional 6-iodo (or 6-*O*-sulfonates) derivatives of *N*-acetyl-D-galactosamine **13** with a variety of protecting groups at positions 3 and 4 (OPG in **13**, including OH groups).[24] These attempts all failed and yielded only elimination

products.[25] Triethylsilylation at position 4 furnished **11**, and careful reduction of the nitrile with diisobutylaluminum hydride at −78 °C provided the aldehyde **12**, which was used immediately after purification in the next step.[26] The samarium–Reformatsky coupling procedure, as described above, with sulfide **3** (1.5 equiv) and aldehyde **12** afforded the carbon-linked dimer **14** in high yield (93 %) as a 1:1 diastereomeric mixture (Scheme 4).[27]



Scheme 4. Preparation of the carbon-linked sialyl-*N*-acetylgalactosaminyl donor **17**. Reagents and conditions: a) SmI_2 (2.5 equiv), THF, 25 °C, 93 %; b) $(Imid)_2CS$ (10 equiv), CH_3CN, reflux, 4 h; c) Ph_3SnH (2.5 equiv), C_6F_5OH (1 equiv), cat. AIBN, toluene, reflux, 2 h, 65 % over two steps; d) $MeOH/HCl_{aq}$, 25 °C, 2 h, 95 %; e) H_2, Pd/C, EtOH, cat. HCl_{aq}, 94 %; f) Ac_2O, pyridine, 94 %; g) $Ac_2O/AcOH/H_2SO_4$ (8/2/0.1), 25 °C, 6 h, 70 %. Imid = imidazole, AIBN = azobisisobutyronitrile.

Alcohols **14** were converted into thiocarbonates by treatment with a large excess of *N,N′*-thiocarbonyldiimidazole in refluxing acetonitrile and deoxygenated by employing triphenyltin hydride, catalytic AIBN, and pentafluorophenol,[28] which yielded the required C-disaccharide **15** as a single compound (65 % for the two steps). Desilylation, hydrogenolysis, and acetylation provided the peracetylated C-dimer **16**.[29] The high stability of the linkage between the *N*-acetylneuraminyl and the *N*-acetylgalactosaminyl residues now allows for modifications under conditions that are unacceptable with a native O linkage. Thus, acetolysis of the methyl glycoside in dimer **16** provided anomeric acetate **17**, which can be easily converted into other anomeric substituents usable in "block" synthesis.

In conclusion, the reductive samariation of a pyridyl sulfide of methyl *N*-acetylneuraminate is a useful and high-yielding approach for stereoselective α-C-sialylation. One may notice here that anomeric sulfides of Neu5Ac are also good glycosyl donors in stereoselective α-O-sialylation.[30] C-Disaccharidic building block **17** can be readily transformed into a variety of glycosyl donors for β-selective O-glycosylation by standard procedures, for α-selective O-glycosylation by a modification of Koganti's procedure,[31] and α-[10] or β-[32]selective C-glycosylations on a wide range of adapted acceptors for different biological applications.

Experimental Section

14: A 0.1 M solution of SmI_2 in THF (6.5 mL, 0.65 mmol of SmI_2) was added to a stirred mixture of pyridyl sulfide **3** (151 mg, 0.26 mmol) and freshly prepared aldehyde **12** (78 mg, 0.17 mmol) at 20 °C under Ar. After stirring the mixture for 10 min, saturated aqueous NH_4Cl was added and the reaction mixture was extracted three times with CH_2Cl_2. The combined organic phases were washed twice with water, dried with Na_2SO_4, and evaporated to dryness. Flash chromatography (toluene/acetone, 2/1) gave **14** (148 mg, 93 %). Isomers of **14** were separated at this stage (isomer ratio of 1:1). The following steps of the synthesis are, however, carried on with the mixture. Selected data for one of the isomers of **14**: ^{1}H NMR ($CDCl_3$, 250 MHz, atom numbering of the natural dimer): $\delta = 7.36$–7.25 (m, 5H, Ph), 5.41 (ddd, $J_{7',8'} = 7.6$, $J_{8',9'a} = 6.9$, $J_{8',9'b} = 2.2$ Hz, 1H, H-8′), 5.25 (dd, $J_{7',8'} = 7.6$, $J_{6',7'} = 2.2$ Hz, 1H, H-7′), 5.26 (d, $J_{NH,5'} = 10.0$ Hz, 1H, NH Neu5Ac), 5.17 (d, $J_{NH,2} = 9.6$ Hz, 1H, NH Gal), 4.82 (ddd, $J_{4',3'ax} = 11.8$, $J_{4',5'} = 10.1$, $J_{4',3'eq} = 4.4$ Hz, 1H, H-4′), 4.71 and 4.39 (2 × d, $J = 12$ Hz, 2H, CH_2Ph), 4.61 (d, $J_{1,2} = 3.7$ Hz, 1H, H-1), 4.50 (ddd, $J_{2,3} = 10.6$, $J_{2,NH} = 9.6$, $J_{1,2} = 3.7$ Hz, 1H, H-2), 4.34 (dd, $J_{9'a,9'b} = 12.2$, $J_{8',9'b} = 2.2$ Hz, 1H, H-9′b), 4.11 (d, $J_{3,4} = 2.8$ Hz, 1H, H-4), 4.01 (ddd, $J_{5',6'} = 10.2$, $J_{4',5'} = 10.1$, $J_{5',NH} = 10$ Hz, 1H, H-5′), 3.99 (dd, $J_{9'a,9'b} = 12.2$, $J_{8',9'a} = 6.9$ Hz, 1H, H-9′a), 3.92–3.82 (m, 2H, H-5,7), 3.89 (dd, $J_{5',6'} = 10.2$, $J_{6',7'} = 2.3$ Hz, 1H, H-6′), 3.76 (s, 3H, $COOCH_3$), 3.42 (dd, $J_{2,3} = 10.6$, $J_{3,4} = 2.8$ Hz, 1H, H-3), 3.26 (s, 3H, OCH_3), 2.71 (d, $J_{7,OH} = 11.2$ Hz, 1H, OH), 2.47 (dd, $J_{3'eq,3'ax} = 12$, $J_{3'eq,4'} = 4.4$ Hz, 1H, H-3′eq), 2.15, 2.09, 2.02, and 2.00 (4 × s, 12H, $OCOCH_3$), 1.84 (s, 3H, $NCOCH_3$) 1.70 (dd, $J_{3'eq,3'ax} = 12$, $J_{3'ax,4} = 11.8$ Hz, 1H, H-3′ax), 1.51–1.41 (m, 2H, H-6a,b), 0.95 (t, $J = 7.9$ Hz, 9H, CH_3CH_2Si), 0.65 ppm (q, $J = 7.9$ Hz, 6H, CH_2Si); MS (ES): $m/z = 949$ $[M+Na]^+$; HR-MS (ES) for $C_{43}H_{66}NaN_2O_{18}Si$; calcd: 949.3977; found: 949.3989.

Selected data for **16**; ^{1}H NMR ($CDCl_3$, 250 MHz, atom numbering of the natural dimer): $\delta = 5.8$ (d, $J_{NH,5} = 9.5$ Hz, 1H, NH Gal), 5.55–5.28 (m, 3H, H-7′,8′,NH Neu5Ac), 5.19 (d, $J_{3,4} = 2.9$ Hz, 1H, H-4), 5.08 (dd, $J_{2,3} = 10.9$, $J_{3,4} = 2.9$ Hz, 1H, H-3), 4.76 (ddd, $J_{4',3'ax} = 12.5$, $J_{4',5'} = 10.0$, $J_{4',3'eq} = 4.4$ Hz, 1H, H-4′), 4.7 (d, $J_{1,2} = 3.7$ Hz, 1H, H-1), 4.51 (ddd, $J_{2,3} = 10.9$, $J_{2,NH} = 10.2$, $J_{1,2} = 3.7$ Hz, 1H, H-2), 4.29 (dd, $J_{9'a,9'b} = 12.3$, $J_{9'a,8'} = 2.0$ Hz, 1H, H-9′a), 4.05 (dd, $J_{9'a,9'b} = 12.3$, $J_{8',9'b} = 4.9$ Hz, 1H, H-9′b), 3.97 (m, 1H, H-5′), 3.75 (m, 2H, H-5,6′), 3.71 (s, 3H, $COOCH_3$), 3.35 (s, 3H, OCH_3), 2.43 (dd, $J_{3'eq,3'ax} = 12.5$, $J_{3'eq,4'} = 4.4$ Hz, 1H, H-3′eq), 2.17, 2.09, 2.07, 2.00, 1.98, 1.95, and 1.93 (7 × s, 21H, $OCOCH_3$), 1.92 (m, 1H, H-6b), 1.84 (s, 3H, $NCOCH_3$), 1.78–1.70 (m, 2H, H-6a,7b), 1.72 (dd, $J_{3'ax,3'eq} = 12.5$, $J_{3'ax,4'} = 12.5$ Hz, 1H, H-3′ax), 1.16 ppm (m, 1H, H-7a); MS (ES): $m/z = 813$ $[M+Na]^+$; HR-MS (ES) for $C_{34}H_{50}NaN_2O_{19}$; calcd: 813.2905; found: 813.2905.

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[27] It is interesting to note that the same samarium–Reformatsky coupling reaction conducted with the corresponding anomeric chloride failed,[13a] and provided only the reduction products of both the chloride and the aldehyde **12** in high yield. Since this aldehyde is unusually sensitive to reduction by SmI_2, a much faster transfer rate of the first electron in the pyridyl sulfide **3** (inner-sphere transfer) compared to that of the chloride (outer-sphere transfer) most certainly explains this dramatic difference.

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[29] Besides NOE measurements and $^3J_{C1,H3ax}$ values as determined in isomers **4**, the stereochemical assignment of the quaternary center in **16** (C-2′) may also be based on empirical data extracted from simple 1D ^{1}H NMR spectra: the chemical shift of H4′ (4.76 ppm in **16**) and the $\Delta\delta$ value of H9a-H9b (0.24 ppm in **16**). For the empirical rules with C-glycosides see refs. [12, 13] and with O-glycosides, see H. Paulsen, H. Tietz, *Angew. Chem.* **1982**, *94*, 934; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 927; K. Okamoto, T. Kondo, T. Kondo, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 637.

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