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# Fast Access to Robust *C*-Sialoside Multimers

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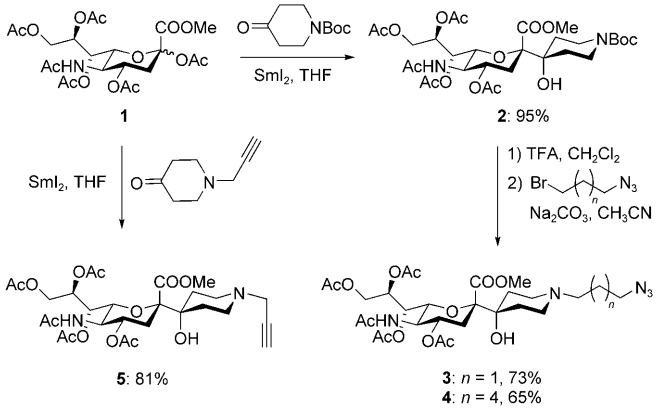
Interactions between cell-surface glycoconjugates and receptors play a crucial role in a wide range of biological events with a presentation of glycans at cell surfaces as an ensemble of many different arrangements. This explains in part why most glycan-based interactions necessitate multivalency to achieve a biologically significant interaction.[1] *N*-Acetylneuraminic acid (Neu5Ac), the major member of the sialic acid family,[2–4] is commonly located as an α-ketosidically linked terminal sugar on cell surface glycoconjugates. As a result of this external position within glycoconjugates, it is involved in numerous biological phenomena,[3,4] including pathological interactions of human cells with bacteria and viruses.[5] This has led to intense research interest in sialic acid chemistry,[6] comprising the design of potent chemotherapeutic agents against the influenza virus[7] or the elaboration of diagnostic tools that could facilitate fast and accurate virus detection.[8] The stability of the diagnostic constructs to external conditions and to enzymatic activities of the target is often a serious and under-evaluated problem.[9]

In this context, we have developed a collection of new oligovalent *C*-sialosides attached to different scaffolds able to provide diverse combinations of valency and geometry that could effectively interact with various biological targets. The well-defined oligomeric *C*-sialoside structures were prepared by using a very short synthetic pathway combining two high-yielding key steps: our recently reported samarium-mediated Reformatsky-coupling reaction by using anomeric acetates **1**[10] (Scheme 1) and the copper(I)-catalyzed Huisgen cycloaddition of azide and alkyne,[11] a model reaction of the "click" chemistry.[12] This highly regioselective reaction introduces 1,4-disubstituted 1,2,3-triazole units[13] linking, efficiently, sialic acid derivative monomers to various multivalent core compounds.[14]




Scheme 1. Synthesis of the *C*-sialoside monomers **3**–**5** by reductive samariation.

With the intended cycloaddition reactions we envisioned two possible approaches for the construction of the multivalent species. The central multivalent core can present either alkyne or azide functionalities to react with *C*-sialoside monomers bearing the complementary functional group. Hence, the monomeric azide or alkyne *C*-sialosides required were promptly prepared from anomeric acetates **1**. We previously showed that reductive samariation of **1** with cyclic ketones under Barbier conditions was a straightforward α-selective and high yielding reaction.[10] For the purpose of this study, the choice of a substituted piperidin-4-one, a symmetrical cyclic ketone, was essential to provide high-coupling efficiency without adding a new stereogenic center. Thus, treatment of an α/β diastereomeric mixture of pentaacetylated *N*-acetyl neuraminic acid methyl ester **1**[10] and commercial NBoc protected piperidin-4-one (2 equiv) with a freshly prepared 0.1 M $SmI_2$ THF solution (3 equiv), furnished, after the usual aqueous work-up and flash chromatography, the intermediate α-*C*-glycoside **2** in 95% yield (Scheme 1). This reaction conducted on a gram scale exemplifies well the efficiency of this procedure with a cyclic ketone as an electrophile. Trifluoroacetic acid-mediated de-

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protection followed by alkylation of the corresponding amine using $BrCH_2(CH_2)_nCH_2N_3$[15] in the presence of $Na_2CO_3$ afforded the two *C*-sialosides **3** ($n=1$) and **4** ($n=4$), which were fully characterized (see Supporting Information).

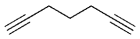
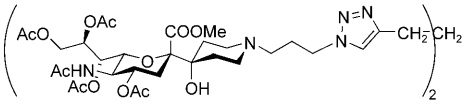
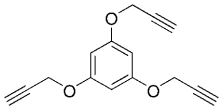
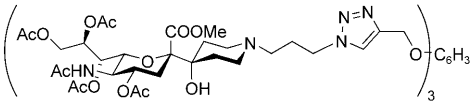
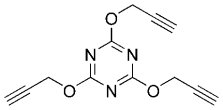
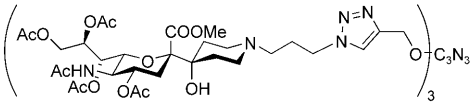
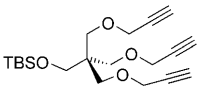
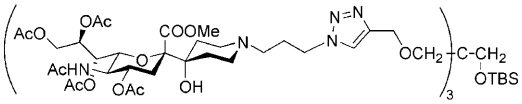
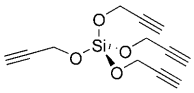
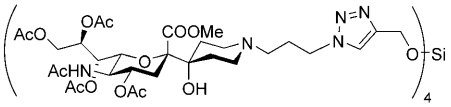
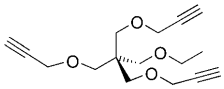
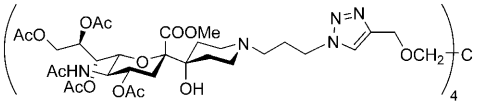
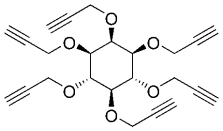
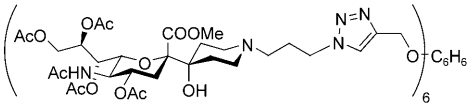
For the other route, a *C*-sialoside bearing a primary alkyne group was prepared using the same methodology. Reduction with $SmI_2$ of **1** in the presence of *N*-propargylated piperidin-4-one[16] in the conditions described above directly provided *C*-sialoside **5** in 81% yield (Scheme 1).

The multivalent cycloadducts, obtained in the first approach from reaction of *C*-sialoside **3** with various oligoalkyne core structures, are presented in Table 1. They were derived from heptadiyne and propargylated phloroglucinol,[17] triazyne,[18] tetrachlorosilane,[19] pentaerythritol,[20] or *myo*-inositol,[17] producing di-, tri-, tetra- or hexavalent structures, respectively (Table 1). Two different copper-catalyzed reaction conditions were experimentally used: conditions A [sodium ascorbate (0.1 equiv) and $CuSO_4{\cdot}5H_2O$ (0.01 equiv) in water/isopropanol 1:1],[21] and conditions B [diisopropylethylamine (DIPEA, 0.5 equiv) and $[Cu(PPh_3)_3Br]$ (0.03 equiv) in THF].[22] In most cases the multivalently linked products were obtained in moderate to excellent yields (39–100%; Table 1) after flash chromatography purification.

Experimentally, a 10% excess of the sialylated monomers was used to ensure, after two days at room temperature, a total conversion of all alkyne functionalities. Nevertheless, the isolated yields were modulated by the structure of the core substrates and the conditions (A/B) used, without any rational explanation. For instance, dimer **6** and trimer **8** were isolated in very capricious yields depending on the cycloaddition conditions (entries 1 and 3, Table 1) whereas these conditions had no impact on the efficiency in producing oligomers **9** and **10** (entries 4 and 5, Table 1). Conditions B were, however, more wide-ranging and convenient to use. Hexavalent structure **12** derived from *myo*-inositol was obtained in excellent yields under these experimental conditions. Trimeric structure **9** with an *O*-silyl protected primary alcohol, which was obtained in 69–72% yield (conditions A or B, entry 4, Table 1), is a potentially useful modular component for further incorporation in more complex structures.

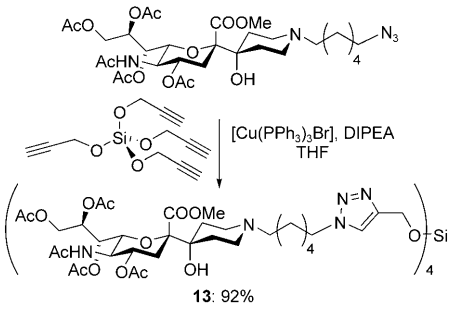
Construction of sialoclusters possessing a longer methylene spacer with increased flexibility that connects the carbohydrate moiety with the multivalent core was equally efficient. This is illustrated by the efficacy of the cycloaddition between azide bearing *C*-sialoside **4** and tetrapropargyloxysilane, which furnished the tetravalent product **13** in 92% yield (Scheme 2).

Table 1. Cycloaddition of *C*-sialoside **3** with oligoalkyne core structures.

| Entry | Multivalent core | Product | | Yield [%][a] (condition A)[b] | Yield [%][a] (condition B)[c] |
|---|---|---|---|---|---|
| 1 |  |  | **6** | 39 | 74 |
| 2 |  |  | **7** | nt[d] | 74 |
| 3 |  |  | **8** | 100 | 58 |
| 4 |  |  | **9** | 69 | 72 |
| 5 |  |  | **10** | 69 | 74 |
| 6 |  |  | **11** | 69 | 43 |
| 7 |  |  | **12** | nt[d] | 90 |

[a] Yields for isolated products after chromatography on silica gel. [b] Condition A: sodium ascorbate (0.1 equiv), $CuSO_4{\cdot}5H_2O$ (0.01 equiv) in water/isopropanol 1:1, 48 h at RT. [c] Condition B: $iPr_2NEt$ (0.5 equiv), $[Cu(PPh_3)_3Br]$ (0.03 equiv) in THF, 48 h at RT. [d] Not tested.



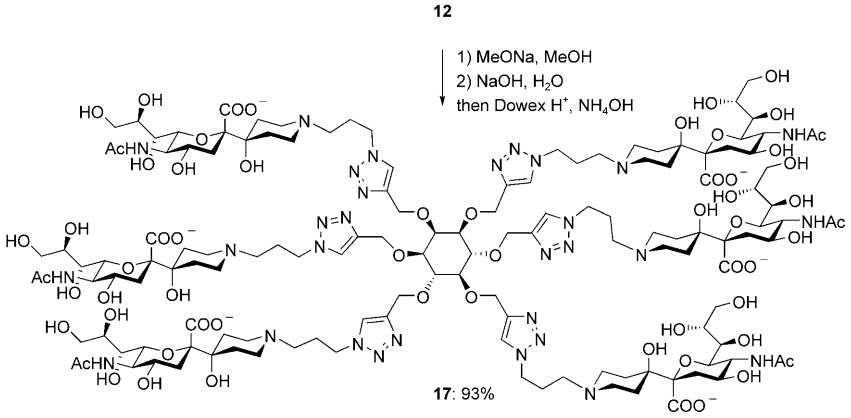

Scheme 2. Synthesis of tetrameric *C*-sialoside **13**.

NMR and MS analyses confirmed the symmetric structures of all multivalent compounds with $^{1}H$ and $^{13}C$ NMR first-order spectra. Reactions were fully regioselective with the exclusive formation of 1,4-disubstituted triazole rings.

The second approach to sialoclusters was also possible with the cycloaddition of alkyne *C*-sialoside **5** with various oligo-azide[23,24] core compounds. This approach is, however, potentially less attractive due to the hazardous manipulation of multi-azido compounds. Di- and trivalent cycloadducts **14–16** were obtained in good yields (71–79%; Table 2) under reaction conditions B {DIPEA, [Cu(PPh$_3$)$_3$Br]}. Once again the cycloadditions were fully regioselective in favor of 1,4-disubstituted triazole formation. Optimized conditions are described here that provide completion of the multiple cycloadditions with the oligo-propargylated (or azido) scaffolds. Generally, stopping the cycloaddition reaction at shorter times afforded a mixture of lower oligomers, which was difficult to separate.[25]

Final deprotection of these multivalent *C*-sialosides was easily accomplished, as with the transformation of hexavalent structure **12** into the corresponding deprotected product **17** by a two-step procedure of deacetylation and saponification providing hexamer **17** in 93% isolated yield (Scheme 3).

In summary, we have shown that multiple azide–alkyne cycloaddition with *C*-sialoside substrates and complementary functionalized multivalent scaffolds provide efficiently a variety of well-defined architectures presenting *C*-sialoside motifs in diverse geometrical arrangements. We believe that the structural diversity of these constructs will be useful in exploring their differential avidity properties towards sialo-binding proteins on cell surfaces.



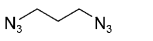
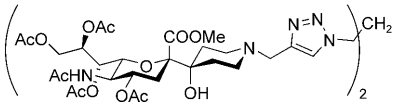
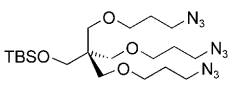
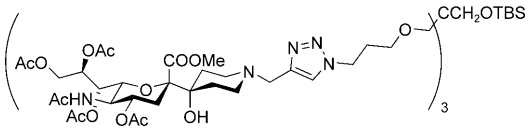
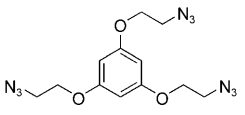
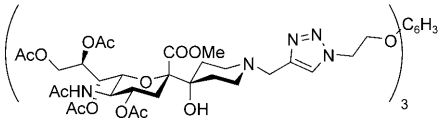

Scheme 3. Total deprotection of hexavalent compound **12**.

## Experimental Section

Detailed experimental procedures have been provided in the Supporting Information. Representative procedures for the $SmI_2$ Reformatsky coupling reaction and the cycloaddition reaction are reported below.

**4-*C*-[Methyl(5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-non-2-ulopyranosyl)onate]-*N*-(*tert*-butoxycarbonyl)-4-piperidinol (2)**: To a stirred solution of the peracetylated derivative **1** (1.00 g, 1.89 mmol) and *N*-Boc-piperidin-4-one (0.75 g, 3.76 mmol) in THF (4 mL) was added a freshly prepared 0.1 M solution of $SmI_2$ in THF (56 mL, 5.60 mmol). After stirring at room temperature for 3.5 h, saturated aqueous $NH_4Cl$ solution and $CH_2Cl_2$ were added to the reaction mixture. The organic phase was separated and the aqueous phase was extracted twice with $CH_2Cl_2$. The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution, dried over $Na_2SO_4$, filtered and evaporated. The residue was purified by flash chromatography (toluene/acetone

Table 2. Cycloaddition of *C*-sialoside **5** with oligoazide core structures.

| Entry | Multivalent core | Product[a] | | Yield [%][b] |
|---|---|---|---|---|
| 1 |  |  | **14** | 75 |
| 2 |  |  | **15** | 79 |
| 3 |  |  | **16** | 71 |

[a] Condition B: *i*Pr$_2$NEt (0.5 equiv), [Cu(PPh$_3$)$_3$Br] (0.03 equiv) in THF, 48 h at RT. [b] Yields for isolated products after chromatography on silica gel.

1:1) to furnish *C*-sialoside **2** (1.20 g, 1.78 mmol, 95%) as a white powder. M.p. 114–115 °C; $[\alpha]_D^{26} = -22.7$ ($c = 0.4$ in $CHCl_3$); $^1$H NMR (360 MHz, $CDCl_3$): $\delta = 5.48$ (d, 1H; $^3J$(NH,H-5) = 10.1 Hz, NH), 5.39 (ddd, 1H; $^3J$(H-8,H-7) = 8.3 Hz, $^3J$ (H-8,H-9b) = 6.1 Hz, $^3J$(H-8,H-9a) = 2.6 Hz, H-8), 5.27 (dd, 1H; $^3J$(H-7,H-8) = 8.3 Hz, $^3J$(H-7,H-6) = 2.2 Hz, H-7), 4.71 (ddd, 1H; $^3J$(H-4,H-3$_{ax}$) = 12.6 Hz, $^3J$(H-4,H-5) = 9.6 Hz, $^3J$(H-4,H-3$_{eq}$) = 4.4 Hz, H-4), 4.29 (dd, 1H; $^3J$(H-9a,H-9b) = 12.3 Hz, $^3J$(H-9a,H-8) = 2.6 Hz, H-9a), 4.00 (dd, 1H; $^3J$(H-9b,H-9a) = 12.3 Hz, $^3J$(H-9b,H-8) = 6.1 Hz, H-9b), 4.04–3.97 (m, 2H; H-5, H-6), 3.97–3.88 (m, 2H; $NCH_2$ of cyclohexyl), 3.76 (s, 3H; $COOCH_3$), 3.11–2.95 (m, 2H; $NCH_2$ of cyclohexyl), 2.80 (brs, 1H; OH), 2.43 (dd, 1H; $^3J$(H-3$_{eq}$,H-3$_{ax}$) = 12.6 Hz, $^3J$(H-3$_{eq}$,H-4) = 4.4 Hz, H-3$_{eq}$), 2.15, 2.11, 2.03, 2.00 (4s, 12H; 4 $OCOCH_3$), 1.86 (t, 1H; $^3J$(H-3$_{ax}$,H-3$_{eq}$) = $^3J$(H-3$_{ax}$,H-4) = 12.6 Hz, H-3$_{ax}$), 1.85 (s, 3H; $NCOCH_3$), 1.78–1.54 (m, 4H; 2$CH_2$ of cyclohexyl), 1.44 ppm (s, 9H; $C(CH_3)_3$); $^{13}$C NMR (90 MHz, $CDCl_3$): $\delta = 170.9$, 170.8, 170.6, 170.2, 169.9, 169.6 (5 *C*$OCH_3$, C-1), 154.6 (*C*$OOC(CH_3)_3$), 85.5 (C-2), 79.3 (O*C*$(CH_3)_3$), 73.7 (COH), 73.1 (C-6), 70.1 (C-4), 68.4 (C-8), 67.6 (C-7), 62.6 (C-9), 52.4 ($COOCH_3$), 49.1 (C-5), 39.3, 39.1 (2 $NCH_2$ of cyclohexyl), 32.8 (C-3), 31.4, 31.0 (2 $CH_2$ of cyclohexyl), 28.3 ($OC(CH_3)_3$), 23.0 ($NCOCH_3$), 20.8, 20.7, 20.6 ppm (4$OCOCH_3$); MS (ESI POS): *m*/*z*: 697.1 $[M+Na]^+$; HRMS: *m*/*z*: calcd for $C_{30}H_{46}N_2O_{15}Na$: 697.2790; found: 697.2794.

**Hexamer 12** (condition B): A solution of hexa-*O*-propargylated *myo*-inositol (5.0 mg, 0.012 mmol), **3** (49 mg, 0.074 mmol), diisopropylethylamine (6 μL, 0.034 mmol) and $[Cu(PPh_3)_3Br]$ (2.3 mg, 0.002 mmol) in THF (0.2 mL) was stirred at room temperature for 48 h. After evaporation, the residue was purified by flash chromatography (dichloromethane/methanol: 8/1 with 0.5% $Et_3N$) to afford **12** (48 mg, 0.011 mmol, 90%). $[\alpha]_D^{18} = -0.4$ ($c = 0.47$ in $CHCl_3$); $^1$H NMR (360 MHz, $CDCl_3$): $\delta = 8.16$, 8.14, 8.11, 7.89 (4s, 6H; CH of triazoles), 5.39 (ddd, 6H; $^3J$(H-8,H-7) = 8.3 Hz, $^3J$(H-8,H-9b) = 6.1 Hz, $^3J$(H-8,H-9a) = 2.6 Hz, H-8), 5.28 (dd, 6H; $^3J$(H-7,H-8) = 8.3 Hz, $^3J$(H-7,H-6) = 2.2 Hz, H-7), 5.41–5.35 (m, 6H; NH), 5.02–4.61 (m, 18H; H-4 and $OCH_2$-triazole), 4.57–4.37 (m, 12H; $CH_2$N-triazole), 4.30 (dd, 6H; $^3J$(H-9a,H-9b) = 12.3 Hz, $^3J$(H-9a,H-8) = 2.6 Hz, H-9a), 4.15 (brs, 1H; H-1′), 4.07–3.92 (m, 18H; H-5, H-6 and H-9b), 3.86 (t, 2H; $^3J$ = 9.6 Hz, H-4' and H-6′), 3.78 (s, 18H; $COOCH_3$), 3.37–3.23 (m, 3H; H-1′, H-3' and H-5′), 2.98–2.66 (m, 18H; OH and $NCH_2$ of cyclohexyl), 2.62–2.31 (m, 24H; $NCH_2$ of cyclohexyl and N*C*$H_2(CH_2)_2$N-triazole), 2.44 (dd, 6H; $^3J$(H-3$_{eq}$,H-3$_{ax}$) = 12.7 Hz, $J$(H-3$_{eq}$,H-4) = 4.8 Hz, H-3$_{eq}$), 2.22–2.05 (m, 12H; $NCH_2CH_2CH_2$N-triazole), 2.14, 2.11, 2.02, 2.00 (4s, 72H; $OCOCH_3$), 1.92 (t, 6H; $^3J$(H-3$_{ax}$,H-3$_{eq}$) = $^3J$(H-3$_{ax}$,H-4) = 12.7 Hz, H-3$_{ax}$), 1.85 (s, 18H; $NCOCH_3$), 1.98–1.87, 1.79–1.59 ppm (m, 24H; $CH_2$ of cyclohexyl); $^{13}$C NMR (62,5 MHz, $CDCl_3$): $\delta = 171.0$, 170.9, 170.7, 170.1, 170.0, 169.8 (5 *C*$OCH_3$ and C-1), 145.1, 145.0, 144.7 (C of triazoles), 124.3, 124.2, 124.1 (CH of triazoles), 85.2 (C-2), 82.7 (C5′), 81.0 (C4′, C6′), 80.2 (C1′, C3′), 73.2 (C-6), 77.2 (COH), 71.7 (C2′), 70.1 (C-4), 68.4 (C-8), 67.7 (C-7), 62.7 (C-9), 54.7 (N*C*$H_2(CH_2)_2$N-triazole), 52.6 ($COOCH_3$), 49.3 (C-5), 48.8, 48.7, 48.3 ($CH_2$N-triazole and $NCH_2$-cy), 32.8 (C-3), 31.4, 31.0 ($CH_2$ of cyclohexyl), 29.6 23.1 ($NCOCH_3$), 21.3, 20.9, 20.8, 20.7 (4 $OCOCH_3$) ppm; MS (MALDI-TOF): *m*/*z*: 4354.81 $[M+H]^+$; HRMS: *m*/*z*: calcd for $C_{192}H_{283}N_{30}O_{84}$: 4352.8790; found: 4352.8810.

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