Pergamon

Tetrahedron 56 (2000) 1423–1428

TETRAHEDRON

Facile Preparation of Divalent Sialoside Derivatives by Olefin Metathesis Reaction

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Received 22 October 1999; revised 6 January 2000; accepted 7 January 2000

Abstract—Olefin metathesis catalyzed by $RuCl_2(CHPh)(PCy_3)_2$ (**1**) has been used to synthesize homodimers of O- and S-alkenyl α-sialoside derivatives. The reactions afforded reasonable to good yields under mild reaction conditions. *Trans*-geometrical isomers were preferred in all cases.

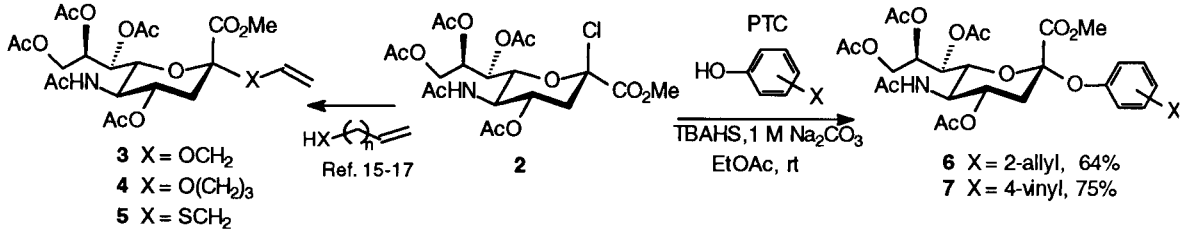
Introduction

N-Acetylneuraminic acid (NeuAc) represents the most ubiquitous member of the sialic acid family of derivatives present on cell surface glycoproteins and glycolipids.[1] It plays important roles in many biological processes, such as regulation of biofluids and mucins viscosity[2] and disaggregation of cells by repulsive effects.[3] Moreover, as terminal substituents, sialic acids are ideally suited to participate in protein–carbohydrate interactions that mediate cell surface recognition phenomena. Indeed, cell surface sialosides are known to serve as ligands for microbial toxins,[4] bacterial and viral adhesins,[5,6] and for mammalian lectins responsible for cell–cell adhesion.[7,8]

Olefin metathesis catalyzed by transition metal has recently emerged as a powerful tool for the formation of C–C bonds in organic syntheses.[9] Grubbs' ruthenium carbene complex **1**[10] is specially useful in this area because of its high reactivity, stability to air, and tolerance to many functional groups. However, only few examples have been reported in carbohydrate-related ring-closing metathesis,[11] cross-metathesis,[12] and ring-opening metathesis[13] reactions. It seemed appealing to apply the olefin metathesis reaction toward the synthesis of carbohydrate homodimers. Recently, we reported an efficient method to synthesize alkenyl O- and C-carbohydrate homodimers using Grubbs' ruthenium carbene complex **1**.[14] To further explore the scope and generality of this method, we describe herein the facile synthesis of divalent sialoside derivatives by olefin metathesis reaction.

Results and Discussion

The requisite allyl **3**[15] and *n*-pentenyl O-α-sialoside **4**[16] were readily accessible from the corresponding alcohols using β-acetochloroneuraminic acid **2** in the presence of silver salicylate. Allyl thiosialoside **5** was also prepared from **2** using phase transfer catalysis (PTC) as previously reported.[17] Following improved phase transfer catalyzed conditions developed in our laboratory,[18] the synthesis of aryl α-sialosyl derivatives **6** and **7** was achieved at room temperature in a two phase system using ethyl acetate, 1 M sodium carbonate and tetrabutylammonium hydrogen sulfate as phase transfer catalyst. The reactions were entirely stereospecific and provided crystalline **6** and **7** in 64 and 75% yield, respectively (Scheme 1).



Scheme 1.

Keywords: olefin metathesis; divalent sialoside; allyl O-α-sialoside.

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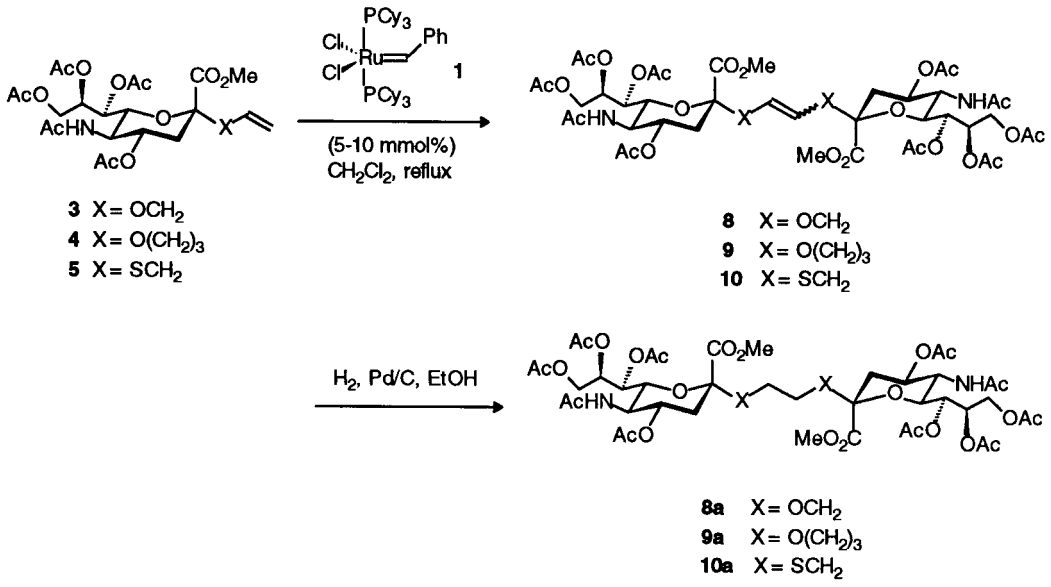


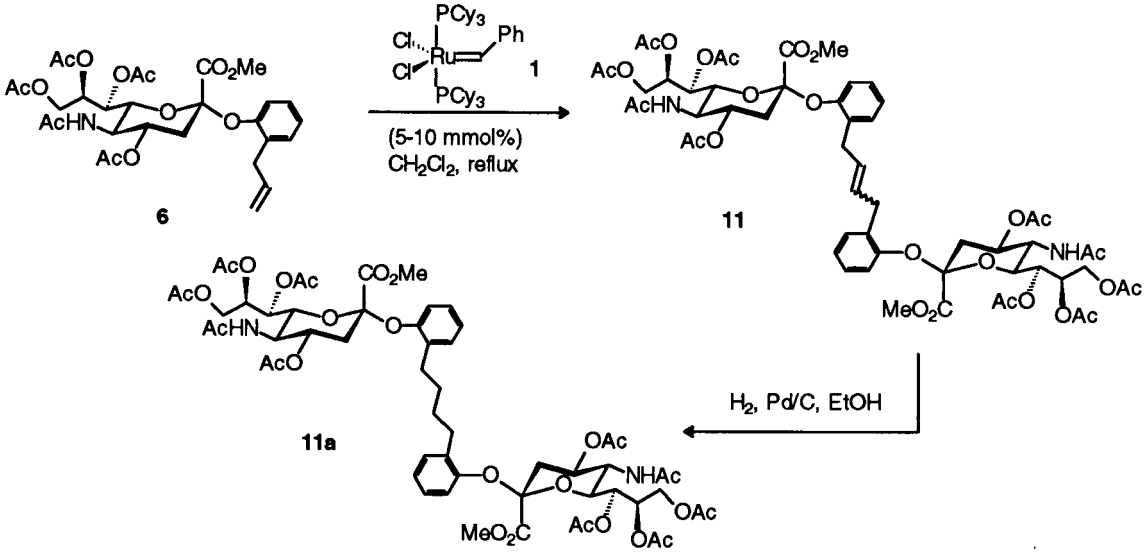
Scheme 2.

Treatment of allyl O-α-sialoside **3** with 5 mol% of Grubbs' catalyst **1** in refluxing CH_2Cl_2 under nitrogen afforded homodimer **8** in 82% yield as a mixture of 7:1 *E* and *Z* isomers (Scheme 2). Some starting material together with trace amount of cross-metathesis product from the initially released styrene was also obtained.

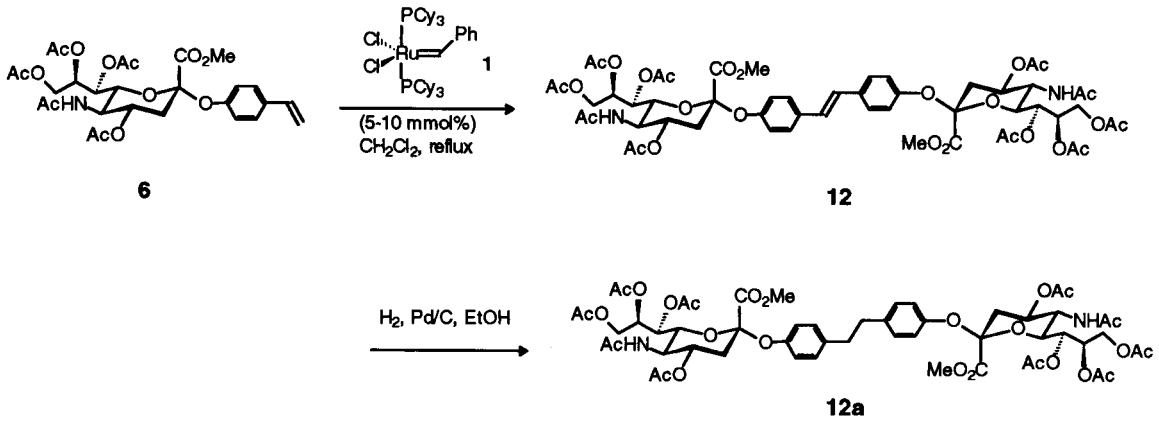
The ratio of the inseparable *E* and *Z* isomers could not be determined from the ^{1}H NMR spectrum of the dimer **8** because of overlapping signals. However, it could be assigned after compound **8** was deacetylated under trans-esterification conditions (NaOMe, MeOH). The ^{13}C NMR spectrum was more informative to confirm the identity of the *E* and *Z* isomers. It is generally accepted that the carbon α to the double bond in the *Z* isomer is more shielded than that in the *E* isomer due to the γ effect.[19] The empirical relationship $\delta_{\alpha(Z)}<\delta_{\alpha(E)}$ allowed us to assign the relative configuration of the *E* and *Z* isomers. For instance, the ^{13}C NMR spectrum of **8** showed a downfield shift for C-2′ in the *E* isomer (δ 64.6 ppm, $\Delta\delta$ 3.7 ppm) compared to δ 60.9 ppm for that of the *Z* isomer.

Olefin metathesis of the longer spacer *n*-pentenyl O-α-sialoside **4** under similar reaction conditions afforded homodimer **9** in 88% yield as a 3:1 mixture of *E* and *Z* isomers. Monomer **4** was more reactive than **3** because of less steric hindrance around the quaternary anomeric center, as a consequence, the *E* and *Z* stereoselectivity decreased from 7:1 to 3:1.

Sulfur-containing compounds have long been known to act as poisons for transition metal catalysts because of their strong coordinating properties, which cause them to block the reactive sites of the metals.[20] So, as expected, allyl thiosialoside **5** showed less reactivity toward Grubbs' catalyst **1** when compared to the



Scheme 3.



Scheme 4.

Table 1. Olefin self metathesis of alkenyl sialic acids

Entry	Substrate	Product	Catalyst amount (mol %)	Time (h)	Yield (%)[a]	(*E*/*Z*) Ratio[b]
1	**3**	**8**	5	6	82	7/1[c]
2	**4**	**9**	5	2	88	3/1[c]
3	**5**	**10**	10	24	26	2.5/1
4	**6**	**11**	5	2	78	1.7/1
5	**7**	**12**	10	24	37	1/0

[a] After purification by column chromatography.
[b] Determined by ^{1}H NMR.
[c] The ratio was determined from its deacetylated derivatives.

corresponding O-glycoside analogs (**3**, **4**). However, the expected homodimer **10** could be obtained in 26% yield together with recovered starting material **5** by using more catalyst and prolonged heating.

To further explore the scope of this method, the more rigid 2-allylphenyl sialoside **6** and 4-vinylphenyl sialoside **7** were treated with Grubbs' catalyst under similar reaction conditions to give compounds **11** and **12** in 78 and 37% yields, respectively (Schemes 3 and 4). Interestingly, compound **12** was obtained as a single *E* isomer. The results and conditions are summarized in Table 1.

Each of the α-sialodimers **8**–**12** were transformed into single compound by hydrogenation at atmospheric pressure (10% Pd/C, 1–12 h) to give their corresponding saturated α-sialodimers **8a**–**12a**, respectively, in quantitative yields.

In summary, olefin metathesis reaction provides a facile approach toward the synthesis of divalent sialoside derivatives. The reactions afforded reasonable yields under mild reaction conditions. Vinyl substituted aryl sialosides provided only the *trans* isomer as previously expected on the basis of analogous results.[14c]

Experimental

General methods

Melting points were determined on a Gallenkamp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 500 instrument. Proton chemical shifts (δ) were given relative to internal $CHCl_3$ (7.24 ppm) for $CDCl_3$ solutions. Carbon chemical shifts were given relative to $CDCl_3$ (77.0 ppm). Assignments were based on COSY, HMQC and DEPT experiments. Mass spectra were obtained using a Kratos II H instrument (FAB-glycerol). Optical rotations were measured on a Perkin–Elmer 241 polarimeter and were run at 23°C. Thin layer chromatography (TLC) was performed on silica gel 60 F-254, and column chromatography was carried out on silica gel 60.

General procedure for the preparation of aryl sialosides by PTC reaction

To a solution of freshly prepared β-acetochloroneuraminic acid **2** (0.4 g, 0.78 mmol) in ethyl acetate (10 mL) was added a solution of phenol derivatives (2-allyl phenol or 4-vinyl phenol) (2 equiv.) and tetrabutylammonium hydrogen sulfate (265 mg, 0.78 mmol) in 1 M sodium carbonate (10 mL). The reaction mixture was vigorously stirred at room temperature until TLC indicated complete transformation of the starting material (1 h). The reaction was diluted with ethyl acetate (20 mL). The organic layer was separated and washed with saturated sodium chloride solution (20 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using dichloromethane–methanol (30:1) as eluant to obtain pure product.

Methyl (2-allylphenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-d-*glycero*-α-d-*galacto*-2-nonulopyranosid) onate (6). White solid (64%); mp 86–88°C; $[\alpha]_D$=+0.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.09–6.40 (m, 4H, aromatic H), 5.88–5.81 (m, 1H, –C*H*═), 5.79 (d, 1H,

$J_{5,NH}$=10.1 Hz, NH), 5.31–5.30 (m, 2H, H-7, H-8), 4.99–4.94 (m, 2H, =CH_2), 4.87 (m, 1H, H-4), 4.38 (d, 1H, $J_{5,6}$=10.9 Hz, H-6), 4.23 (dd, 1H, $J_{8,9a}$=2.0 Hz, $J_{9a,9b}$=12.4 Hz, H-9a), 4.12–4.09 (m, 2H, H-9b, H-5), 3.53 (s, 3H, OCH_3), 3.03–3.28 (m, 2H, –CH_2CH=), 2.63 (dd, 1H, $J_{3e,4}$=4.7 Hz, $J_{3a,3e}$=12.9 Hz, H-3e), 2.16 (dd, 1H, $J_{3a,4}$=12.4 Hz, H-3a), 2.06, 2.05, 1.96, 1.95, 1.82 (5s, 15H, NAc, OAc). ^{13}C NMR ($CDCl_3$) δ 170.7–169.9 (C=O), 168.1 (C-1), 150.2, 131.1, 129.9, 127.2, 123.8 (aromatic C), 136.5 (C-2′), 115.5 (C-1′), 100.1 (C-2), 73.4 (C-6), 69.5 (C-8), 68.9 (C-4), 68.0 (C-7), 62.0 (C-9), 52.7 (CH_3O), 49.1 (C-5), 37.9 (C-3), 34.4 (C-3′), 23.0, 20.9, 20.7, 20.6 (NAc, OAc); FAB-MS: 608.3 ([M+1]$^+$, 41.1%); Anal. Calcd for $C_{29}H_{37}NO_{13}$: C, 57.33; H, 6.14; N: 2.31. Found: C, 57.03; H, 5.99; N, 2.37.

Methyl (4-vinylphenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosid) onate (7). White solid (75%); mp 81–82°C; $[\alpha]_D$=+14.8 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 2H, *J*=8.8 Hz, aromatic H), 6.93 (d, 2H, aromatic H), 6.57 (dd, 1H, –C*H*=), 5.77 (d, 1H, $J_{5,NH}$=11.1 Hz, NH), 5.58 (d, 1H, J_{trans}=17.6 Hz, CH_2=), 5.30 (m, 2H, H-7, H-8), 5.10 (d, 1H, J_{cis}=11.0 Hz, CH_2=), 4.87 (ddd, 1H, H-4), 4.36 (dd, 1H, $J_{5,6}$=10.7 Hz, $J_{6,7}$<1 Hz, H-6), 4.25 (dd, 1H, $J_{8,9a}$=1.5 Hz, $J_{9a,9b}$=12.7 Hz, H-9a), 4.10 (dd, 1H, $J_{8,9b}$=2.6 Hz, H-9b), 4.04 (ddd, 1H, $J_{4,5}$=10.4 Hz, H-5), 3.57 (s, 3H, OCH_3), 2.62 (dd, 1H, $J_{3e,4}$=4.7 Hz, $J_{3a,3e}$=13 Hz, H-3e), 2.14 (dd, 1H, $J_{3a,4}$=12.7 Hz, H-3a), 2.07, 2.05, 1.96, 1.95, 1.82 (5s, 15H, NAc, OAc); ^{13}C NMR ($CDCl_3$) 170.8–169.9 (C=O), 168.1 (C-1), 153.3, 133.4, 127.1, 119.8 (aromatic C), 135.9 (C-2′), 113.0 (C-1′), 99.9 (C-2), 76.8 (C-6), 69.5 (C-8), 68.8 (C-4), 67.4 (C-7), 62.0 (C-9), 52.8 (CH_3O), 49.1 (C-5), 38.0 (C-3), 23.0, 20.9, 20.7, 20.6 (NAc, OAc); FAB-MS: 594.3 ([M+1]$^+$, 28.7%); Anal. Calcd for $C_{28}H_{35}NO_{13}$: C, 56.66; H, 5.94; N: 2.36. Found: C, 56.42; H, 5.86; N, 2.48.

Typical procedure for the preparation of divalent sialoside derivatives 8–12 by olefin metathesis reaction

To a solution of alkenyl glycoside (100 mg) in dry dichloromethane (2 mL) was added ruthenium catalyst (5–10 mol%). The reaction mixture was refluxed under nitrogen for 2–24 h. The reaction was monitored by TLC. The reaction mixture was concentrated and purified by silica gel column chromatography using dichloromethane–methanol (20:1) as eluant to obtain pure product.

(*E*, *Z*) 1,4-Di-*O*-(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-but-2-ene (8). ^{1}H NMR ($CDCl_3$) 5.66 (m, 2H, H-1′ *trans*, H-1′ *cis*), 5.51–5.23 (m, 6H, NH, H-8, H-7), 4.76 (m, 2H, H-4), 4.23–4.18 (m, 4H, H-9a, –CH_2C=), 4.04–3.96 (m, 6H, H-9b, H-6, H-5), 3.77–3.71 (m, 2H, –CH_2C=), 3.70 (s, 6H, OCH_3), 2.52 (dd, 2H, $J_{3e,4}$=4.5 Hz, $J_{3a,3e}$=12.8 Hz, H-3e), 1.87 (dd, 2H, $J_{3a,4}$=12.6 Hz, H-3a), 2.06, 1.96, 1.95, 1.79 (5s, 30H, NHAc, OAc); ^{13}C NMR ($CDCl_3$) 170.85–169.97 (C=O), 168.26 (C-1 *cis*), 168.18 (C-1 *trans*), 128.18 (C-1′ *cis*), 128.14 (C-1′ *trans*), 98.56 (C-2 *cis*), 98.28 (C-2 *trans*), 72.46 (C-6 *cis*), 72.39 (C-6 *trans*), 69.14 (C-4 *cis*), 69.02 (C-4 *trans*), 68.55 (C-8), 67.25 (C-7), 64.58 (C-2′ *trans*), 62.30 (C-9 *trans*), 62.19 (C-9 *cis*), 60.92 (C-2′ *cis*), 52.59 (OCH_3), 49.22 (C-5), 37.94 (C-3 *trans*), 37.85 (C-3 *cis*); FAB-MS: 1035.4 ([M+1]$^+$, 5.3%); Anal. Calcd for $C_{44}H_{62}N_2O_{26}$: C, 51.06; H, 6.04; N: 2.71. Found: C, 50.67; H, 5.97; N, 2.72.

(*E*, *Z*) 1,8-Di-*O*-(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-oct-4-ene (9). ^{1}H NMR ($CDCl_3$) δ 5.53 (d, 2H, $J_{5,NH}$=9.5 Hz, NH), 5.36–5.24 (m, 6H, H-1′ *trans*, H-1′ *cis*, H-8, H-7), 4.77 (m, 2H, H-4), 4.25 (dd, 2H, $J_{8,9a}$=2.6 Hz, $J_{9a,9b}$=12.4 Hz, H-9a), 4.08–3.86 (m, 6H, H-9b, H-6, H-5), 3.71 (s, 6H, OCH_3), 3.69 (m, 2H, –OCH_2–), 3.15 (m, 2H, –OCH_2–), 2.51 (dd, 2H, $J_{3e,4}$=4.6 Hz, $J_{3a,\ 3e}$=12.8 Hz, H-3e), 1.87 (dd, 2H, $J_{3a,4}$=12.5 Hz, H-3a), 2.07, 2.06, 1.97, 1.96, 1.81 (5s, 30H, NHAc, OAc), 1.98 (m, 4H, –CH_2CH=), 1.52 (m, 4H, –OCH$_2$CH_2–); ^{13}C NMR ($CDCl_3$) δ 170.88–169.97 (C=O), 168.45 (C-1), 129.78 (C-1′ *trans*), 129.32 (C-1′ *cis*), 98.68 (C-2), 72.41 (C-6), 69.15 (C-4), 68.86 (C-8), 67.38 (C-7), 64.35 (C-4′ *trans*), 64.29 (C-4′ *cis*), 62.28 (C-9), 52.51 (OCH_3), 37.98 (C-3), 29.51 (C-3′ *cis*), 29.43 (C-3′ *trans*), 28.70 (C-2′ *trans*), 23.32 (C-2′ *cis*); FAB-MS: 1091.5 ([M+1]$^+$, 4.3%); Anal. Calcd for $C_{48}H_{70}N_2O_{26}$: C, 52.84; H, 6.47; N: 2.57. Found: C, 52.49; H, 6.46; N, 2.59.

Compound (10). ^{1}H NMR ($CDCl_3$) δ 5.54 (t, 1.14H, *J*=3.9 Hz, H-1′ *trans*), 5.48 (t, 0.86H, *J*=5.2 Hz, H-1′ *cis*), 5.36–5.18 (m, 6H, H-8, H-7, NH), 4.83 (m, 2H, H-4), 4.28–4.25 (m, 2H, H-9a *cis*, H-9a *trans*), 4.08–4.06 (m, 2H, H-9b *cis*, H-9b *trans*), 4.00 (ddd, 2H, *J*=10.4 Hz, H-5), 3.71–3.76 (m, 2H, H-6), 3.78 (s, 1.71H, OCH_3 *cis*), 3.76 (s, 4.29H, OCH_3 *trans*), 3.34–3.18 (m, 2H, H-2′ *cis*, H-2′ *trans*), 2.69–2.65 (m, 2H, H-3e *cis*, H-3e *trans*), 1.93 (m, 2H, H-3a), 2.12, 2.10, 1.99, 1.98, 1.83 (5s, 30H, NHAc, OAc); ^{13}C NMR ($CDCl_3$) δ 170.84–169.97 (C=O), 168.46 (C-1 *cis*), 168.22 (C-1 *trans*), 128.39 (C-1′ *trans*), 127.89 (C-1′ *cis*), 83.25 (C-2 *cis*), 82.87 (C-2 *trans*), 74.20 (C-6 *cis*), 74.02 (C-6 *trans*), 69.53 (C-4), 68.70 (C-8 *cis*), 68.44 (C-8 *trans*), 67.34 (C-7 *cis*), 67.25 (C-7 *trans*), 62.16 (C-9), 53.01 (OCH_3 *trans*), 52.99 (OCH_3 *cis*), 49.36 (C-5), 37.82 (C-3), 30.41 (C-2′ *trans*), 25.40 (C-2′ *cis*); FAB-MS: 1067.4 ([M+1]$^+$, 3.9%); Anal. Calcd for $C_{44}H_{62}N_2O_{24}S_2$: C, 49.52; H, 5.86; N: 2.63. Found: C, 49.41; H, 5.97; N, 2.63.

Compound (11). ^{1}H NMR ($CDCl_3$) δ 7.24–6.93 (m, 8H, aromatic H), 5.60 (t, 0.74H, *J*=5.2 Hz, H-1′ *cis*), 5.56 (t, 1.26H, *J*=3.7 Hz, H-1′ *trans*), 5.50 (d, 2H, $J_{5,NH}$=10.1 Hz, NH), 5.35–5.31 (m, 4H, H-7, H-8), 4.92–4.87 (m, 2H, H-4), 4.48–4.37 (m, 2H, H-6 *cis*, H-6 *trans*), 4.26 (dd, 2H, $J_{8,9a}$=2.3 Hz, $J_{9a,9b}$=12.8 Hz, H-9a), 4.12 (dd, 2H, $J_{8,9b}$=4.7 Hz, H-9b), 4.09–4.05 (m, 2H, H-5 *cis*, H-5 *trans*), 3.55 (s, 2.22H, OCH_3 *cis*), 3.53 (s, 3.78H, OCH_3 *trans*), 3.41 (t, 1.48H, H-2′ *cis*), 3.29 (t, 2.52H, H-2′ *trans*), 2.65 (dd, 0.74H, H-3e *cis*), 2.68 (dd, 1.26H, $J_{3e,4}$=4.7 Hz, $J_{3a,3e}$=13.0 Hz, H-3e *trans*), 2.20–2.11 (m, 2H, H-3a *cis*, H-3a *trans*), 2.06, 2.05, 1.96, 1.95, 1.82 (5s, 30H, NHAc, OAc). ^{13}C NMR ($CDCl_3$) δ 170.73–169.87 (C=O), 168.06 (C-1 *cis*), 168.02 (C-1 *trans*), 129.74 (C-1′ *trans*), 128.34 (C-1′ *cis*), 100.23 (C-2), 73.34 (C-6 *cis*), 73.31 (C-6 *trans*), 69.40 (C-8 *trans*), 69.36 (C-8 *cis*), 68.80 (C-4 *trans*), 68.76 (C-4 *cis*), 67.42 (C-7), 61.96 (C-9), 52.80 (CH_3O *cis*), 52.75 (CH_3O *trans*), 49.25 (C-5), 37.94

(C-3 *cis*), 37.80 (C-3 *trans*), 32.99 (C-2′ *trans*), 27.67 (C-2′ *cis*); FAB-MS: 1187.5 ($[M+1]^+$, 11.1%); Anal. Calcd for $C_{56}H_{70}N_2O_{26}$: C, 55.64; H, 5.95; N: 2.36. Found: C, 55.38; H, 5.98; N, 2.30.

Compound (12). White solid (CH_2Cl_2–Hexane); mp 110–111°C; $[\alpha]_D$=+201° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36 (d, 4H, *J*=8.8 Hz, aromatic H), 7.01 (d, 4H, aromatic H), 6.93 (s, 2H, –C*H*═), 5.37–5.33 (m, 6H, NH, H-7, H-8), 4.94 (ddd, 2H, H-4), 4.40 (dd, 2H, $J_{5,6}$=10.8 Hz, $J_{6,7}$=1.7 Hz, H-6), 4.30 (dd, 2H, $J_{8,9a}$=2.4 Hz, $J_{9a,9b}$=12.5 Hz, H-9a), 4.15 (dd, 2H, $J_{8,9b}$=4.7 Hz, H-9b), 4.07 (ddd, 2H, $J_{4,5}$=10.4 Hz, $J_{5,NH}$=11.1 Hz, H-5), 3.63 (s, 6H, OCH_3), 2.68 (dd, 2H, $J_{3e,4}$=4.6 Hz, $J_{3a,\ 3e}$=12.9 Hz, H-3e), 2.20 (dd, 2H, $J_{3a,4}$=12.5 Hz, H-3a), 2.13, 2.11, 2.02, 2.01, 1.89 (5s, 30H, NAc, OAc); ^{13}C NMR ($CDCl_3$) δ 170.9–170.0 (C═O), 168.1 (C-1), 153.2, 133.2, 127.3, 120.0 (aromatic C), 127.1 (–H*C*═), 100.0 (C-2), 73.3 (C-6), 69.2 (C-8), 68.7 (C-4), 67.3 (C-7), 62.0 (C-9), 52.9 (CH_3O), 49.4 (C-5), 38.1 (C-3); FAB-MS: 1159.3 ($[M+1]^+$, 0.4%); Anal. Calcd for $C_{54}H_{66}N_2O_{26}$: C, 56.86; H, 5.74; N: 2.42. Found: C, 56.04; H, 5.66; N, 2.42.

Preparation of divalent sialoside derivatives 8a–12a by reduction reaction—typical procedure

To α-sialodimer **8** (20 mg,) in ethanol (2 mL) was added 10% Pd/C (2 mg). The mixture was stirred at room temperature for 1 h under hydrogen atmosphere. The reaction mixture was filtered and concentrated to yield compound **8a** as a white solid (20 mg, 100%).

α-Sialodimers **9a**, **11a** and **12a** were obtained in the same manner from glycodimers **9**, **11** and **12** in quantitative yields. However, α-thiosialodimer **10** was treated with the same mass amount of palladium catalyst for 12 h to afford compund **10a** in 100% yield.

Compound (8a). mp 104–105°C (CH_2Cl_2–Hexane); $[\alpha]_D$=−18.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.34 (m, 2H, H-8), 5.29 (dd, 2H, $J_{6,7}$=2.1 Hz. $J_{7,8}$=8.2 Hz, H-7), 5.21 (d, 2H, $J_{NH,5}$=9.7 Hz, NH), 4.80 (m, 2H, H-4), 4.27 (dd, 2H, $J_{8,9a}$=2.7 Hz, $J_{9a,9b}$=12.4 Hz, H-9a), 4.09–3.98 (m, 6H, H-9b, H-6, H-5), 3.75 (s, 6H, OCH_3), 3.74 (m, 2H, –OC*H*$_2$–), 3.16 (m, 2H, –OC*H*$_2$–), 2.53 (dd, 2H, $J_{3e,4}$=4.6 Hz, $J_{3a,\ 3e}$=12.8 Hz, H-3e), 1.90 (dd, 2H, $J_{3a,4}$=12.6 Hz, H-3a), 2.11, 2.10, 2.00, 1.99, 1.84 (5s, 30H, NHAc, OAc), 1.55 (m, 4H, –OCH_2CH_2–); ^{13}C NMR ($CDCl_3$) 170.0–168.3 (C═O), 98.7 (C-2), 72.4 (C-6), 69.1 (C-4), 68.6 (C-8), 67.2 (C-7), 64.7 (–O*C*H_2CH_2–), 62.2 (C-9), 52.7 (OCH_3), 49.4 (C-5), 38.0 (C-3), 26.1 (–OCH_2*C*H_2–), 23.2 (NHAc), 21.0, 20.8, 20.7 (OAc); HRMS calcd for $C_{44}H_{65}N_2O_{26}$ (MH^+) *m*/*z* 1037.3826, found 1037.3836.

Compound (9a). mp 82–84°C (CH_2Cl_2–Hexane); $[\alpha]_D$=−15.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.35 (m, 2H, H-8), 5.29 (dd, 2H, $J_{6,7}$=2.0 Hz. $J_{7,8}$=8.1 Hz, H-7), 5.24 (d, 2H, $J_{NH,5}$=9.4 Hz, NH), 4.80 (m, 2H, H-4), 4.27 (dd, 2H, $J_{8,9a}$=2.7 Hz, $J_{9a,9b}$=12.4 Hz, H-9a), 4.09–3.99 (m, 6H, H-9b, H-6, H-5), 3.75 (s, 6H, OCH_3), 3.70 (m, 2H, –OC*H*$_2$–), 3.15 (m, 2H, –OC*H*$_2$–), 2.53 (dd, 2H, $J_{3e,4}$=4.7 Hz, $J_{3a,3e}$=12.8 Hz, H-3e), 1.90 (dd, 2H, $J_{3a,4}$=12.5 Hz, H-3a), 2.10, 2.09, 2.00, 1.98, 1.84 (5s, 30H, NHAc, OAc), 1.48 (m, 4H, –OCH_2CH_2–), 1.29–1.21 (m, 8H, –$O(CH_2)_2(CH_2)_2$–); ^{13}C NMR ($CDCl_3$) δ 171.0–168.5 (C═O), 98.7 (C-2), 72.4 (C-6), 69.1 (C-4), 68.7 (C-8), 67.3 (C-7), 65.0 (O*C*$H_2(CH_2)_2$), 62.3 (C-9), 52.6 (OCH_3), 49.4 (C-5), 37.7 (C-3), 29.3 (OCH_2*C*H_2CH_2), 25.8 ($O(CH_2)_2$*C*H_2), 23.1 (NHAc), 21.1, 20.8, 20.7 (OAc); HRMS calcd for $C_{48}H_{73}N_2O_{26}$ (MH^+) *m*/*z* 1093.4452, found 1093.4441.

Compound (10a). Mp 88–90°C (CH_2Cl_2–Hexane); $[\alpha]_D$=+27.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.34–5.28 (m, 4H, H-8, H-7), 5.20 (d, 2H, $J_{NH,5}$=10.1 Hz, NH), 4.84 (m, 2H, H-4), 4.27 (dd, 2H, $J_{8,9a}$=2.4 Hz, $J_{9a,9b}$=12.4 Hz, H-9a), 4.08 (dd, 2H, $J_{8,9b}$=4.7 Hz, H-9b), 4.00 (ddd, 2H, *J*=10.4 Hz, H-5), 3.82–3.80 (m, 2H, H-6), 3.78 (s, 6H, OCH_3), 2.70 (m, 2H, –SC*H*$_2$–), 2.68 (dd, 2H, $J_{3e,4}$=4.7 Hz, $J_{3a,3e}$=12.7 Hz, H-3e), 2.54 (m, 2H, –SC*H*$_2$–), 1.94 (dd, 2H, $J_{3a,4}$=12.4 Hz, H-3a), 2.13, 2.11, 2.01, 2.00, 1.85 (5s, 30H, NHAc, OAc), 1.57 (m, 4H, –SCH_2CH_2–); ^{13}C NMR ($CDCl_3$) δ 171.0–170.0 (C═O), 83.0 (C-2), 74.0 (C-6), 69.6 (C-4), 68.5 (C-8), 67.2 (C-7), 62.1 (C-9), 53.0 (OCH_3), 49.4 (C-5), 38.0 (C-3), 28.4 (–S*C*H_2–), 28.3 (–SCH_2*C*H_2–), 23.2 (NHAc), 21.2, 20.9, 20.8 (OAc); HRMS calcd for $C_{54}H_{65}N_2O_{24}S_2$ (MH^+) *m*/*z* 1069.3369, found 1069.3352.

Compound (11a). Mp 93–94°C (CH_2Cl_2–hexane); $[\alpha]_D$=−3.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 7.14–6.93 (m, 8H, aromatic H), 5.39–5.30 (m, 4H, H-7, H-8), 5.27 (d, 2H, $J_{5,NH}$=10.1 Hz, NH), 4.91 (m, 2H, H-4), 4.41 (dd, 2H, $J_{6,7}$=1.8 Hz, $J_{5,6}$=10.8 Hz, H-6), 4.27 (dd, 2H, $J_{8,9a}$=2.6 Hz, $J_{9a,9b}$=12.5 Hz, H-9a), 4.14 (dd, 2H, $J_{8,9b}$=4.9 Hz, H-9b), 4.07 (ddd, 2H, $J_{4,5}$=10.4 Hz, H-5), 3.55 (s, 6H, OCH_3), 2.62 (dd, 2H, $J_{3e,4}$=4.7 Hz, $J_{3a,3e}$=12.9 Hz, H-3e), 2.57 (m, 4H, –Ph–C*H*$_2$–), 2.18 (dd, 2H, $J_{3a,4}$=12.6 Hz, H-3a), 2.12, 2.10, 2.01, 2.00, 1.88 (5s, 30H, NHAc, OAc), 1.57 (m, 4H, –Ph–CH_2CH_2–); ^{13}C NMR ($CDCl_3$) δ 170.9–168.1 (C═O), 151.9, 133.4, 126.8, 124.7, 118.9 (6C, aromatic), 100.2 (C-2), 73.3 (C-6), 69.3 (C-8), 68.8 (C-4), 67.4 (C-7), 62.0 (C-9), 52.80 (CH_3O), 49.3 (C-5), 37.8 (C-3), 30.2, 29.6 (–CH_2CH_2–), 23.1 (NHAc), 21.0, 20.8, 20.7 (OAc); HRMS calcd for $C_{54}H_{73}N_2O_{26}$ (MH^+) *m*/*z* 1189.4452, found 1189.4432.

Compound (12a). Mp 102–103°C (CH_2Cl_2–Hexane); $[\alpha]_D$=+3.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.98 (d, 4H, *J*=8.6 Hz, aromatic H), 6.92 (d, 4H, aromatic H), 5.37 (m, 2H, H-8), 5.34 (dd, 2H, $J_{6,7}$=1.8 Hz. $J_{7,8}$=8.2 Hz, H-7), 5.31 (d, 2H, $J_{5,NH}$=10.1 Hz, NH), 4.90 (m, 2H, H-4), 4.34 (dd, 2H, $J_{6,7}$=1.8 Hz, $J_{5,6}$=10.8 Hz, H-6), 4.30 (dd, 2H, $J_{8,9a}$=2.5 Hz, $J_{9a,9b}$=12.5 Hz, H-9a), 4.16 (dd, 2H, $J_{8,9b}$=4.7 Hz, H-9b), 4.05 (ddd, 2H, $J_{4,5}$=10.4 Hz, H-5), 3.58 (s, 6H, OCH_3), 2.80 (m, 4H, –Ph–C*H*$_2$–), 2.66 (dd, 2H, $J_{3e,4}$=4.7 Hz, $J_{3a,3e}$=12.9 Hz, H-3e), 2.16 (dd, 2H, $J_{3a,4}$=12.6 Hz, H-3a), 2.12, 2.10, 2.03, 2.00, 1.88 (5s, 30H, NHAc, OAc); ^{13}C NMR ($CDCl_3$) δ 170.9–168.0 (C═O), 151.8, 137.3, 129.3, 120.0 (aromatic C), 100.2 (C-2), 73.2 (C-6), 69.2 (C-8), 68.9 (C-4), 67.3 (C-7), 62.0 (C-9), 52.9 (CH_3O), 49.3 (C-5), 38.0 (C-3), 37.0 (*C*H_2), 23.2 (NHAc), 21.0, 20.8, 21.7 (OAc); HRMS calcd for $C_{54}H_{69}N_2O_{26}$ (MH^+) *m*/*z* 1161.4139, found 1161.4138.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support.

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