Synthesis of 3-*O*-sialyl and 6-*O*-sulfo derivatives of dimeric *N*-acetyl lactosamine as specific acceptors for α-l-fucosyltransferases

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The stereoselective syntheses of 3-*O*-sialyl and 6-*O*-sulfo dimeric lactosamine derivatives 1–4 are accomplished through the use of key glycosyl donors 13 and 15.

In continuation of our efforts towards the synthesis of biologically important oligosaccharides, we have developed an elegant synthesis of 3-*O*- and 6-*O*-substituted dimeric lactosamine derivatives. **1**–**4**[1] (Fig. 1), which were prepared from the key intermediates **5**–**13** (Fig. 2) by stereoselective transformation, as described in Schemes 1–3. Our approach is based upon the observation that an *O*-acetyl group can be selectively removed in the presence of a 6-*O*-pivaloyl substituent to give 6-*O*-pivaloyl β-d-galactopyranosyl linked compounds. Glycosylation of **5** with **9** under Mukaiyama's conditions ($SnCl_2$–AgOTf)[2] followed by acetylation with pyridine–acetic anhydride afforded the β(1→3) linked disaccharide **14** in 8% yield and the β(1→4) linked disaccharide **15** in 48% yield. The ^{1}H NMR spectrum of **15** displayed characteristic signals for H-3, H-1 (δ 5.71–5.67), H-1′ (δ 4.50, d, J = 8.0 Hz), 4 × OAc (δ 2.08, 2.04, 1.93 and 0.86) and 2 × CMe_3 (δ 1.25 and 1.17). Isopropylidenation of **11**, using Catelani's procedure,[3] followed by acetylation with pyridine–acetic anhydride and deacetonation provided the acceptor **16** in 66% yield. The ^{1}H NMR spectrum gave characteristic signals at δ 5.70 (dd, H-3), 2.10 and 1.09 (2 × OAc) and 1.27 and 1.23 (2 × CMe_3). Condensation of the donor **15** with **16** under NIS–triflic acid conditions at −30 °C gave **17** in 76% yield. The ^{1}H NMR spectrum of **17** displayed characteristic signals at δ 5.71–5.59 (2 × dd and d, H-3, H-3″ and H-4″), 5.46 (d, J = 8.3 Hz, H-1″), 5.24 (d, J = 8.5 Hz, H-1), 5.09 (dd, H-2‴), 4.97 (dd, H-2′), 4.53 (d, J = 7.9 Hz, H-1‴), 4.43 (d, J = 7.6 Hz, H-1′), 2.10–1.49 (cluster of singlets, 6 × OAc) and 1.25, 1.23 and 1.94 (4 × CMe_3) which confirmed a β(1→3) conformation of the newly incorporated glycosidic linkage. De-*O*-acetylation of **17** in MeOH–CH_2Cl_2 (1 : 1, *v*/*v*) with MeOH–MeONa (pH 10) at 0 °C provided the acceptor **18** in 95% yield. The ^{1}H NMR spectrum gave characteristic signals at δ 5.58–5.69 (2 × dd, H-3″ and H-3), 5.34 (d, H-1″, J = 8.2 Hz), 5.24 (d, H-1, J = 8.4 Hz), 4.82 (dd, H-2′), 4.73 (d, J = 7.8 Hz, H-1‴), 4.35 (d, J = 7.7 Hz, H-1′), 1.84, 1.75 and 1.49 (each s, 3 × OAc) and 1.25, 1.23, 1.22 and 0.97 (each s, 4 × CMe_3) confirming the assigned structure.

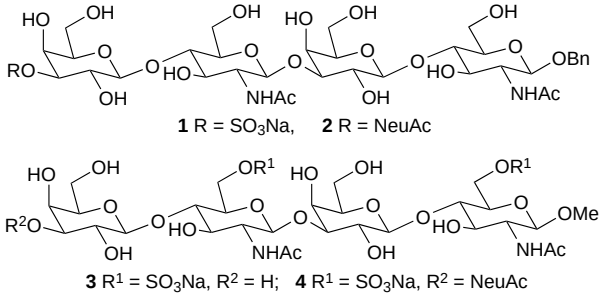


Fig. 1 Target molecules sialyl and sulfated dimeric lactosamine **1**–**4**

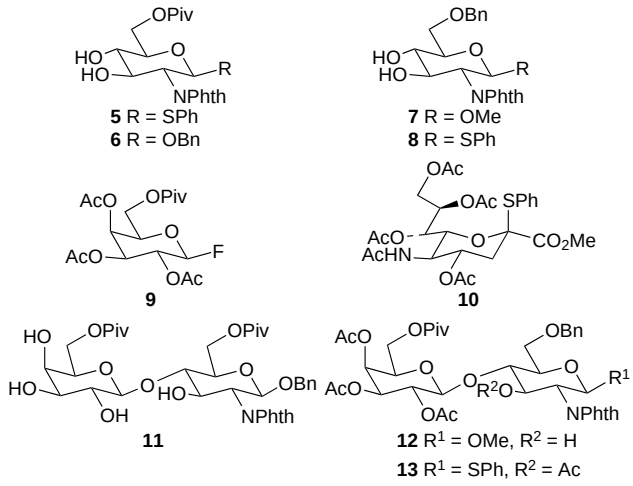
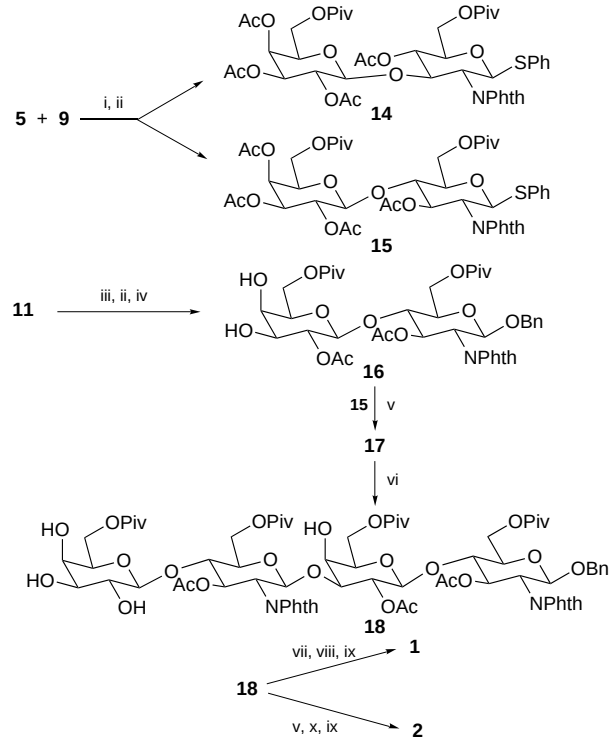
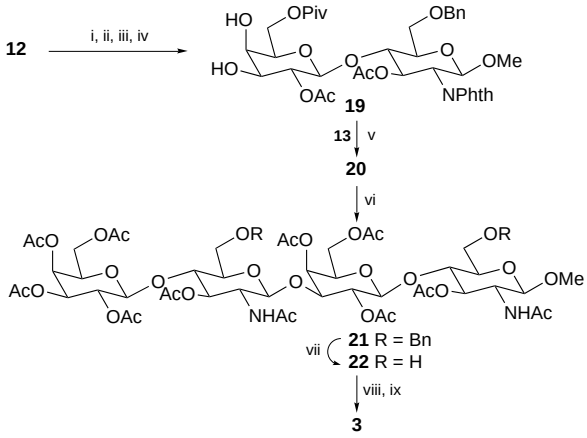


Fig. 2 Key intermediates **5**–**13** involved in the synthesis of target molecules **1**–**4**



Scheme 1 *Reactions and conditions*: i, **5** (1.0 equiv.), **9** (1.5 equiv.), AgOTf (1.20 equiv.), 4 Å molecular sieves, CH_2Cl_2–toluene (5 : 1, v/v), −15 °C to room temp., 5 h; ii, pyridine–Ac_2O (2 : 1, v/v); iii, 0.15% CSA, DMP, 24 h, MeOH–H_2O (10 : 1, v/v), 100 °C, 6 h; iv, 70% aq. AcOH, 70 °C, 2 h; v, **15** (1.05 equiv.), or **10** (3.0 equiv.), NIS (3.0 equiv.)–triflic acid, −30 °C, 2 h; vi, MeOH–CH_2Cl_2 (1 : 1, v/v), MeONa (pH 10), 2 h; vii, SO_3–pyridine complex in pyridine (6.0 equiv.), 5 °C, 16 h; viii, MeOH–hydrazine hydrate (4 : 1, v/v), 100 °C, 16 h, Ac_2O (excess), MeOH–CH_2Cl_2 (1 : 1, v/v), 0 °C, 1 h; ix, MeOH–MeONa, 24 h; x, LiI (10 equiv.), pyridine, 120 °C, 3 h



Scheme 2 *Reagents and conditions*: i, MeOH–CH_2Cl_2 (1 : 1, v/v), MeONa, 0 °C, 2 h, 85%; ii, DMP, PTS, room temp., 1.5 h, 89%; iii, pyridine–Ac_2O (2 : 1, v/v), room temp., 12 h, 89%; iv, 70% aq. AcOH, 65 °C, 2.5 h, 66%; v, **13** (0.95 equiv.), NIS (3.0 equiv.)–triflic acid, −20 °C, 1 h, 54%; vi, EtOH–hydrazine hydrate (4 : 1, v/v), 100 °C, 16 h, pyridine–Ac_2O (2 : 1, v/v), room temp., 12 h, 84%; vii, 10% Pd–C, H_2, MeOH, 16 h; 50%; viii, SO_3–pyridine complex in DMF (10 equiv.), 0 °C, 16 h; ix, MeOH–MeONa, 16 h; Na^+ resin, 35% from **22**

Removal of both the phthalimido and acetate groups from **20** was accomplished by treatment with hydrazine hydrate in ethanol (1 : 9, v/v) at 80 °C followed by N-acetylation to give **23** in 65% yield. Condensation of sialic acid donor **10** with **23** at −40 °C followed by *O*-acetylation gave **24** in 35% yield (based on **23** consumed). The synthesis of **4** from **24** was achieved by a sequence of reactions similar to those described for the preparation of **3** from **21**. The structures of **1**–**4** were confirmed by ^1H and ^{13}C NMR spectroscopy.†

Our preliminary examination of Galβ1,4(6-sulfo) GlcNAcβ1,3 Galβ1,4(6-sulfo) GlcNAcβ-O-Me (**3**) and Neu-Acα2,3Galβ1,4(6-sulfo)GlcNAcβ1,3Galβ1,4(6-sulfo) GlcNAcβ-O-Me (**4**) indicated that both of these compounds were equally active as acceptors for human colon tumour α1,3-l-fucosyltransferase.

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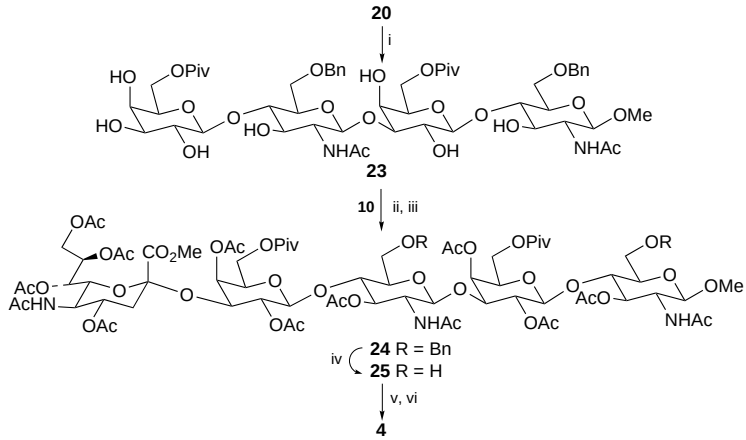
Footnote

† *Selected data* for **1**: $[\alpha]_D$ 7 (*c* 1.5, H_2O) [lit.,[12] −12.2 (*c* 0.5, H_2O)]; ^{13}C NMR (D_2O, 100.6 MHz): δ 101.86 (C-1‴), 101.72 (C-1′), 101.45 (C-1″), 98.81 (C-1), 81.04 (C-3′), 77.49 (C-3‴), 73.89 (C-4″), 73.85 (C-4), 59.90 (C-6‴ and C-6′), 59.09 (C-6″), 58.85 (C-6), 54.19 (C-2″), 53.99 (C-2). For **2**: $[\alpha]_D$ +186 (*c* 0.2, H_2O); ^1H NMR (D_2O, 400 MHz): δ 4.84 (d, *J* = 12 Hz,



Scheme 3 *Reagents and conditions*: i, EtOH–hydrazine hydrate (9 : 1, v/v), 80 °C, 1 h, MeOH–Et_3N–Ac_2O (4 : 2 : 1), room temp., 2 h, 65%; ii, **10** (2.50 equiv.), NIS (3.0 equiv.)–triflic acid, MeCN, −40 °C, 1 h; iii, pyridine–Ac_2O (2 : 1, v/v), room temp., 12 h, 35% based on **23** consumed; iv, 10% Pd–C, H_2 MeOH, 24 h; v, SO_3–pyridine complex in DMF (10 equiv.), room temp., 2 h; vi, MeOH–MeONa, 48 h; H_2O, 4 h, Na^+ resin, 56% from **24**

Selective sulfation of **18** with SO_3–pyridine complex in pyridine at 5 °C provided the 3-*O*-sulfo compound which upon removal of its phthalimido group (MeOH–hydrazine hydrate, 100 °C) and *N*-acetylation followed by de-*O*-acetylation (MeOH–MeONa) gave the known compound **1** (55% from **18**).[4]

A similar NIS–triflic acid reaction of **18** with sialic acid donor **10** provided the crude pentasaccharide. The conversion of this intermediate into target compound **2** (23% from **18**) was then carried out in 4 steps: (i) LiI–pyridine (methyl ester to acid), (ii) MeOH–hydrazine hydrate (phthalimido group removal), (iii) Ac_2O–MeOH–CH_2Cl_2 (*N*-acetylation) and (iv) MeOH–MeONa (de-*O*-acetylation).

The synthesis of **3** and **4** (Schemes 2 and 3) involved the glycosylation of **8** with fluoride **9** under conditions similar to those described for the preparation of **15** (from **5**), followed by acetylation to give donor **13** along with some 1⟶3 linked disaccharide. Condensation of **13** with **19** under NIS–triflic acid conditions at −20 °C provided **20** in 54% yield. The formation of **21** from **20** was achieved by the treatment with hydrazine hydrate in ethanol (1 : 4, v/v) at 100 °C followed by acetylation with pyridine–acetic anhydride in 84% yield. The removal of *O*-benzyl (10% Pd–C) gave diol **22** which on sulfation with SO_3–pyridine complex in DMF and followed by de-*O*-acetylation gave compound **3** in 35% yield (from **22**).

H-1″), 4.69 (d, *J* = 11.0 Hz, H-1), 4.50 (d, *J* = 8.0 Hz, H-1‴), 4.41 (d, *J* = 8.0 Hz, H-1′), 2.71 (dd, J = 4.6 Hz, H-3‴e), 1.99 and 1.88 (each s, 3×NAc), 1.75 (t, *J* = 1.2 Hz, H-3‴a); ^{13}C NMR: δ 101.86 (C-1‴), 101.73 (C-1′), 101.55 (C-1″), 98.79 (C-1), 81.04 (C-3′), 77.49 (C-3‴), 74.49 (C-4″), 74.15 (C-4), 61.58 (C-9‴), 59.99 (C-6‴), 59.91 (C-6′), 59.09 (C-6″), 58.86 (C-6), 54.17 (C- 2″), 53.99 (C-2), 50.68 (C-5″), 38.63 (C-3‴); *m*/*z* 1128.5 $(M - Na)^-$. For **3**: $[\alpha]_D$ +21 (*c* 0.6, H_2O); ^{13}C NMR: δ 101.84 (C-1‴), 101.67 (C-1′), 101.56 (C-1″), 100.94 (C-1), 81.46 (C-3′), 76.88 (C-3‴), 74.33 (C-4″), 74.05 (C-4), 67.63 (C-6‴), 67.36 (C-6), 60.11 (C-6‴), 60.02 (C-6′), 56.19 (OMe), 54.15 (C-2″), 53.91 (C-2); *m*/*z* 942.9 $(M - Na)^-$. For **4**: $[\alpha]_D$ +24 (*c* 0.7, H_2O); ^{13}C NMR: δ 101.84 (C-1‴), 101.60 (C-1′), 101.15 (C-1″), 100.92 (C-1), 98.73 (C-2‴), 81.50 (C-3′), 76.79 (C-3‴), 74.29 (C-4″), 74.02 (C-4), 67.29 (C-6‴), 67.08 (C-6), 61.52 (C-9‴), 60.01 (C-6′ and C-6‴), 56.17 (OMe), 54.09 (C-2″), 53.06 (C-2), 50.60 (C-5‴), 38.57 (C-3‴).

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