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

**Rakesh K. Jain,† Bao-Guo Huang, E. V. Chandrasekaran and Khushi L. Matta***

*Department of Gynecologic Oncology, Rosewell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263, USA*

**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.

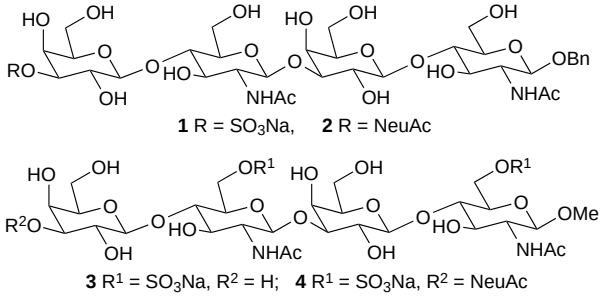



**Fig. 1** Target molecules sialyl and sulfated dimeric lactosamine **1**–**4**

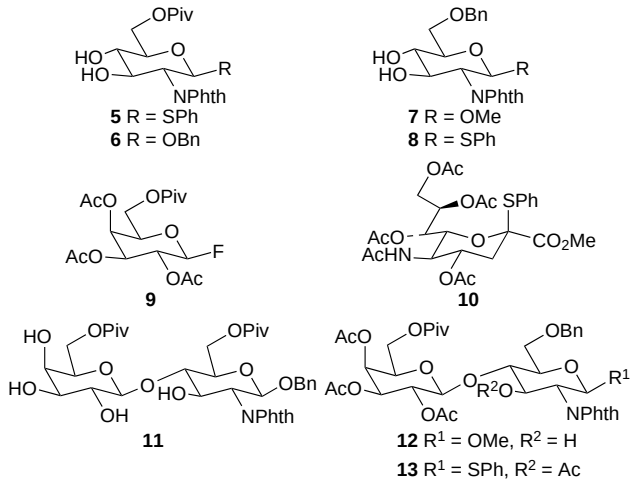
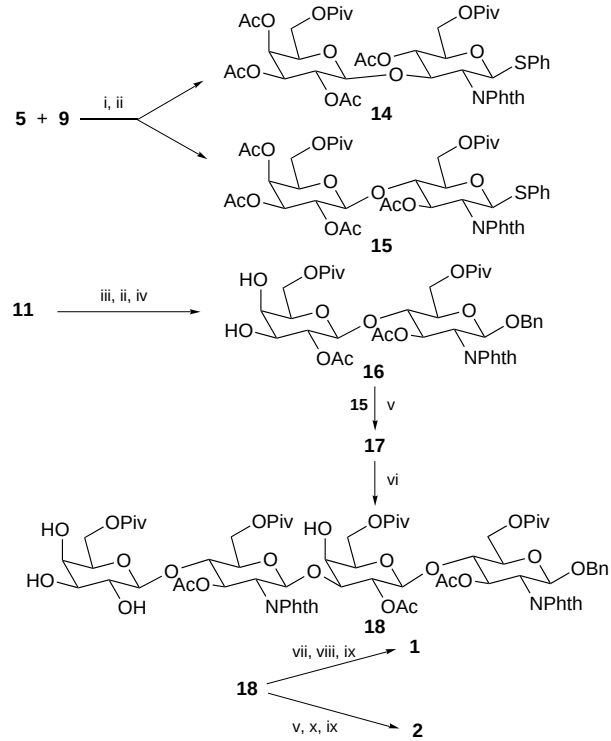
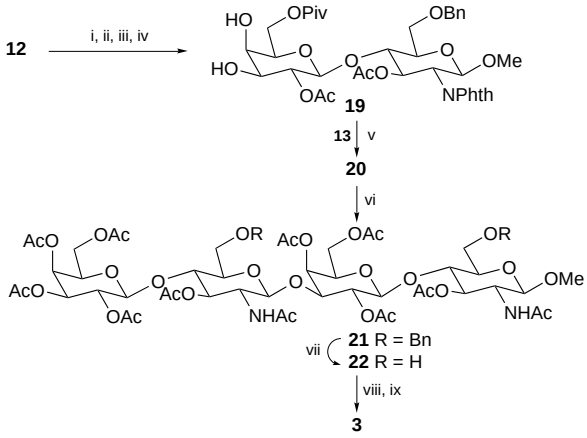



**Fig. 2** Key intermediates **5**–**13** involved in the synthesis of target molecules **1**–**4**




**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**

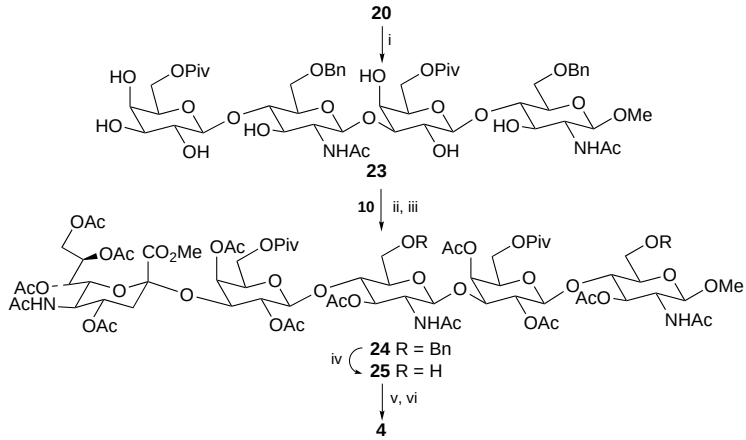
Removal of both the phthalimido and acetate groups from **20** was accomplished by treatment with hydrazine hydrate in ethanol (1 : 9, v/v) at 80 °C followed by N-acetylation to give **23** in 65% yield. Condensation of sialic acid donor **10** with **23** at −40 °C followed by *O*-acetylation gave **24** 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.

These investigations were supported by Grant No. CA 63218 awarded by the National Cancer Institute.

## 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‴).

## References

1 R. K. Jain, R. Vig, R. D. Locke, A. Mohammad and K. L. Matta, *J. Chem. Soc., Chem. Commun.*, 1996, **65**.
2 T. Mukaiyama, Y. Murai and S. Shoda, *Chem. Lett.*, 1981, 431; T. Mukaiyama, Y. Hashimoto and S. Shoda, *Chem. Lett.*, 1983, 935.
3 G. Catelani, F. Colonna and A. Marra, *Carbohydr. Res.*, 1988, **182**, 297.
4 G. V. Reddy, R. K. Jain, R. D. Locke and K. L. Matta, *Carbohydr. Res.*, 1996, **280**, 261.

*Received, 5th August 1996; Com. 6/05439K*