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SYNTHESIS OF A POLYMER-SUPPORTED SIALIC ACID GLYCOSYL DONOR

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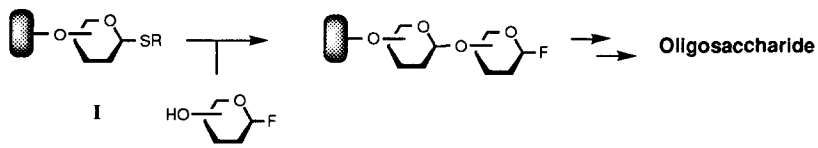
Abstract: A sialic acid glycosyl donor **9** immobilized on polyethyleneglycol monomethyl ether (MPEG) was prepared. Glycosylation of galactose derivatives **10** or **15** with **9** led to α-linked disaccharides **13** and **16**, respectively.© 1997 Elsevier Science Ltd. All rights reserved.

Since biomedical potential of oligosaccharides and related glycoconjugates has been well recognized[1], development of methodologies effective for rapid assembly of oligosaccharide is attracting current attention. In this context, polymer support approach is particularly promising in principle[2]. Recently, we have reported a novel strategy of polymer support oligosaccharide synthesis[3], based on the concept of orthogonal glycosylation strategy[4]. This approach most typically starts from polymer supported thioglycoside **I**. Reaction with glycosyl acceptor **II** carrying a glycosyl fluoride functionality gives diglycosyl fluoride which can then be used as a glycosyl donor for the second coupling. Elongation of glycan chain can be performed by iterative glycosylation with alteranative use of thioglycoside and glycosyl fluoride as acceptors. Since silalic acid (NeuAc) most frequently exists as a non-reducing end terminal residue, polymer supported NeuAc thioglycoside is required in order to extend the approach into NeuAc containing oligosaccharide.



I **II**

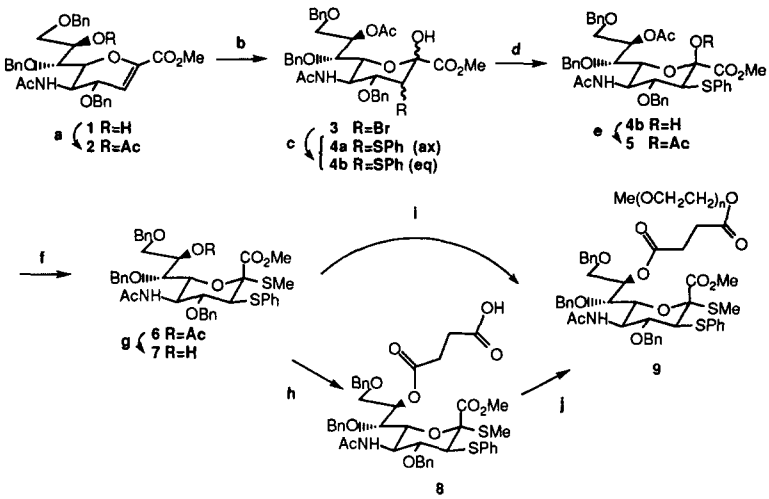
NeuAc donor **9** was designed based on the considerations that follow. Firstly, polyethylene glycol monomethyl ether (MPEG) was chosen as a polymer sector[2c]. By doing so, glycosylation can be performed in a solution phase manner, thereby avoiding the pseudo-high dilution problem inherent to solid phase systems. In addition, the quality check of products can be easily performed spectroscopically in a conventional manner. Secondly, stereocontrolling auxiliary (SPh) approach[5] was adopted for the initial attempt of polymer support NeuAc glycosylation, because this approach should guarantee the nearly complete stereochemical control irrespective of the reactivity of acceptor and reaction conditions (solvent, promoter, etc.[6]).

Synthesis of **9** (**Scheme 1**) started from known 8-OH derivative **1**[7], which was first converted into acetate **2**. Stereoselective incorporation of the SPh substituent at C-3 position was performed in the same manner as described previously for the perbenzylated cognate[5a,7]. Thus, sequential treatments with NBS

and PhSK afforded **4** as a mixture of diastereomers (**4a**:**4b**=6:1) which was epimerized into **4b**. Subsequent acetylation into **5** and treatment with Me_3SiSMe-TMSOTf[8] afforded **6**[9] that was deacetylated into **7**.

Coupling with the polymer was performed by reacting with succinylated PEG monomethyl ether[10] (MPEGSu) by the action of 1-(2-mesitylenesulfonyl)-3-nitro-1,2,4-triazole (MSNT)[11]. Alternatively, **7** was converted into 8-O-succinate **8** and then coupled with MPEG. In either route, NeuAc-PEG conjugate **9**[12] of nearly identical quality was obtained[13].

Scheme 1



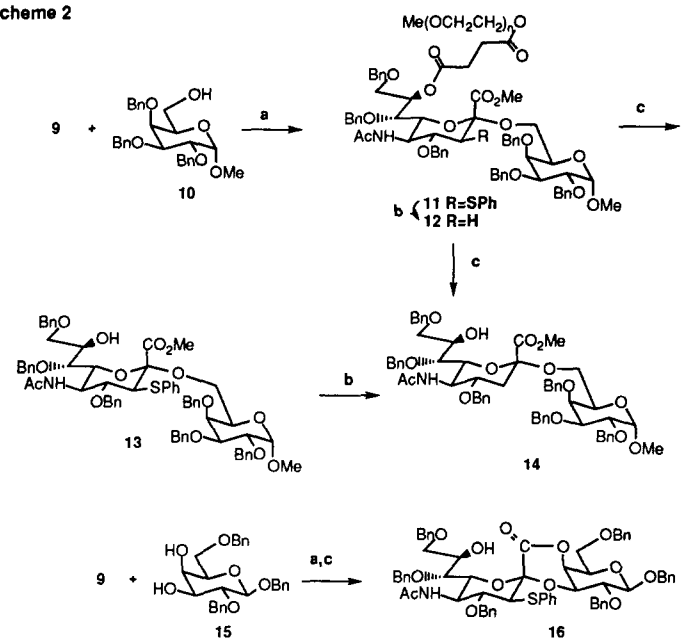
a, Ac_2O/Py, 22°C, 10 h, 99%; b, NBS, H_2O–MeCN (1:8), 26°C, 2.5h; c, PhSK, t-BuOH–THF, 4°C, 2.5h, 88% over all from **1**; d, 0.005M DBU, toluene, 4°C, 8h, 78%; e, Ac_2O, Py, DMAP, CH_2Cl_2, 4°C, 14h, then r.t., 4h, 93%; f, $MeSSiMe_3$, Me_3SiOTf, $Cl(CH_2)_2Cl$, molecular sieves 4A, 50°C, 2h, 91%; g, 0.05M MeONa, MeOH, r.t., 13h, 92%; h, succinic anhydride, Py, DMAP, 75°C, 17h, 63%; i: MPEGSu, MSNT, N-methylimidazole, CH_2Cl_2, r.t., 91 h, 50-55%; j, 1. MPEG, MSNT, N-methylimidazole, CH_2Cl_2, 28°C, 38 h, 55-65%; 2. Ac_2O, Py, CH_2Cl_2, r.t., 14 h

Galactose derivative **10** with a free primary hydroxyl group was chosen as a model glycoside acceptor (**Scheme 2**). Thioglycoside function of **9** could be effectively activated with $MeSSMe_2$·OTf (DMTST)[14] to afford a quite reasonable yield (65–70%) of disaccharide **13**[9], after cleavage from polymeric product **11**[12]. Ample precedents[5] strongly support the anomeric configuration of NeuAc to be α that was confirmed by $^3J_{C\text{-}H}$ value between C-1 and H-3_{ax} of NeuAc. Auxiliary phenylthio substituent was reductively removed by treatment with Ph_3SnH/AIBN to afford **14**[9] in 75% yield[15]. Removal of the SPh group was also effective at the polymer bound stage. Thus, standard desulfurization of **11** (Ph_3SnH/AIBN) led to polymer **12** , treatment of which with 0.1M MeONa in MeOH gave **14** in 70% overall yield.

Less reactive **15** was also glycosylated successfully to give the 2→3 linked product[12] which was isolated as a lactone **16**[9] in 50–60% yield ($^3J_{C1^2\text{-}H3^2ax}$ 7.3 Hz).

In summary, a sialic acid glycosyl donor **9** supported on a soluble polymer (MPEG) was synthesized and demonstrated to be effective for stereoselective glycosylation.

Scheme 2



a, DMTST, CH_2Cl_2, molecular sieves 4A, –40°C~ 27°C, 22 h; b, Ph_3SnH, AIBN, toluene, 80°C, 2; h; c, 0.1M MeONa, MeOH, r.t., 14 h.

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References and Notes

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1. Kobata, A. *Acc. Chem. Res.* **1993**, *26*, 319; Varki, A. *Glycobiology* **1993**, *3*, 97; Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683.

2. Leading references: (a) Danishefsky, S. J.; McClure, K. F.; Randolph, J. T.; Ruggeri, R. B. *Science* **1993**, *260*, 1307. (b) Schuster, M.; Wang, P.; Paulson, J. C.; Wong, C.-H. *J. Am. Chem. Soc.* **1994** *116*, 1135. (c) Douglas, S. P.; Whitfield, D.; Krepinsky, J. J. *J. Am. Chem. Soc.* **1994** *117*, 2116. (d) Yan, L.; Taylor, C. M.; Goodnow, Jr., R.; Kahne, D. *J. Am. Chem. Soc.* **1994**, *116*, 6953. (e) Randolph, J. T.; McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5712. (f) Rademann J.; Schmidt, R. R. *Tetrahedron Lett.* **1996**, *37*, 3989. (g) Hunt, J. A.; Roush, W. R. *J. Am. Chem. Soc.* **1996**, *118*, 9998.

3. Ito, Y. ; Kanie, O.; Ogawa, T. *Angew. Chem. Int. Ed. Engl.* **1996**, *108*, 2691.
4. Kanie, O.; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 12073.
5. (a) Ito, Y; Ogawa, T. *Tetrahedron Lett.*, **1988**, *29*, 3987; *idem. Tetrahedron*, **1990**, *46*, 89. (b) Kondo, T.; Abe, H.; Goto, T. *Chem. Lett.* **1988**, 1657. (c) Nicolaou, K. C.; Hummel, C. W.; Beckovich, N. J.; Wong, C.-H. *J. Chem. Soc., Chem. Commun.* **1991**, 870. (d) Ercegovic, T.; Magnusson, G. *J. Chem. Soc., Chem. Commun.* **1994**, 831. (e) Martichonok, V.; Whitesides, G. M. *J. Am. Chem. Soc.* **1996**, *118*, 8187.
6. For stereoselective NeuAc glycosylation using acetonitrile effect, see: Hasegawa, A.; Nagahama, T.; Ohki, H.; Hotta, K.; Ishida, H.; Kiso, M. *J. Carbohydr. Chem.* **1991**, *10*, 493; Martin, T. J.; Schmidt, R. R. *Tetrahedron Lett* . **1992**, *33*, 6123; Lönn, H.; Stanvall, K. *Tetrahedron Lett.* **1992**, *33*, 115.
7. Ito, Y.; Numata, M.; Sugimoto, M.; Ogawa, T. *J. Am. Chem. Soc.* **1989**, *111*, 8508; Ito, Y.; Nunomura, S.; Shibayama, S.; Ogawa, T. *J. Org. Chem.* **1992**, *57*, 1821.
8. Hanessian, S.; Guidon, Y. *Carbohydr. Res.* **1980**, *86*, C3; Pozsgay V.; Jennings, H. J.; *Tetrahedron Lett.* **1987**, *28*, 1375; Hasegawa, A.; Ohki, H.; Nagahama, T.; Ishida, H.; Kiso, M. *Carbohydr. Res.* **1991**, *212*, 277.
9. Selected NMR data are given. **6**: δ_H 5.23 (m, H-8), 4.32 (t, J 10 Hz, H-4), 4.07 (dd, J 10 and <1 Hz, H-6), 3.86 (s, CO_2Me), 3.26 (d, J 10.9 Hz, H-3), 3.11 (q, J 9 Hz, H-5), 2.15 (s, SMe and OAc), 1.36 (s, NAc); δ_C 170.38 and 170.10 (Ac), 167.60 ($\underline{C}O_2Me$), 86.16 (C-2), 78.31 (C-4), 75.78, 73.55, 72.42 (C-6), 72.24, 71.45 (C-7), 70.92 (C-8), 67.89 (C-9), 61.34 (C-3), 54.81 (C-5), 52.63 (OMe), 23.45 (NHCO$\underline{Me}$), 21.38 (OCO$\underline{Me}$), 12.06 (SMe). **9**: δ_H 5.25 (m, H-8), 3.27 (d, J 10.6 Hz, H-3), 2.11 (s, SMe), 1.51 (s, Ac). **13**: δ_H 4.26 (dd, J 9.9 and 9.6 Hz, H-4^2), 4.15 (dd, J 11 and <1 Hz, H-6^2), 4.01 (m, H-8^2), 3.93 (dd, J 9.9 and 3.6 Hz, H-2^1), 3.82 (dd, J 10.6 and 2.6 Hz, H-3^1), 3.73 (s, CO_2Me), 3.68 (dd, J 6 and <1 Hz, H-7^2), 3.33 (d, J 9.9 Hz, H-3^2), 3.22 (s, OMe), 1.56 (s, NHAc); δ_C 170.01 (NH$\underline{C}$OMe), 167.85 ($\underline{C}O_2Me$), 101.04 (C-2^2), 98.79 (C-1^1), 79.33, 78.87, 76.15, 75.58, 74.79, 74.64, 74.52, 73.51, 73.48, 73.03, 72.63, 71.39, 70.76, 69.83, 68.89, 62.35, 58.89, 55.31 (OMe), 53.23, 52.60 ($CO_2\underline{Me}$), 23.50 (NHCO$\underline{Me}$). **14**: δ_H 4.64 (d, J 3.3 Hz, H-1^1), 4.11 (m, H-8^2), 3.59 (s, CO_2Me), 3.45 (dd, J 9.9 and 7.9 Hz, H-6^1), 3.33 (s, OMe), 2.74 (dd, J 12.5 and 4.0 Hz, H-3^2_{eq}), 1.74 (s, Ac); δ_C 170.13 (NH$\underline{C}$OMe), 168.86 ($\underline{C}O_2Me$), 99.06 (C-2^2), 98.85 (C-1^1), 79.03, 76.33, 74.88, 74.70, 74.48, 74.70, 74.48, 73.49, 73.35, 73.19, 72.47, 70.87, 70.19, 68.79, 62.64, 55.47 (OMe), 52.85 ($CO_2\underline{Me}$), 51.70 (C-5^2), 37.34 (C-3^2), 23.65 (NHCO$\underline{Me}$). **16**: δ_H 5.25 (d, J 4.0 Hz, H-4^2), 5.17 (d, J 8.9 Hz, NH), 3.98 (dd, J 11 and <1 Hz, H-6^2), 3.85 (m, H-8^2), 3.73 (dd, J 8.9 and 7.9 Hz, H-3^2), 3.47 (d, J 10.2 Hz, H-3^2), 3.16 (d, J 5.0 Hz, OH), 1.74 (s, Ac); δ_C 169.84 (NH$\underline{C}$OMe), 164.15 ($\underline{C}O_2Me$), 102.05 (C-1^1), 98.62 (C-2^2), 82.32 (C-3^1), 78.26, 77.21, 75.83, 75.26, 74.84, 74.39, 74.36, 73.73, 73.42, 71.98, 71.48, 71.23, 71.16, 70.49, 69.54, 66.58, 57.95, 51.43, 23.65 (NHCO$\underline{Me}$).
10. Prepared from MPEG purchased from Aldrich (average M.W. 5,000). Douglas, S. P.; Whitfield, D. M.; Krepinsky, J. J. *J. Am. Chem. Soc.* **1991**, *113*, 5095.
11. Blankemeyer-Menge, B.; Nimtz, M.; Frank, R. *Tetrahedron Lett.* **1990**, *31*, 5095.
12. All MPEG-bound materials were isolated by precipitation from *t*-butyl methyl ether.
13. Coupling yields were calculated based on mass balances, assuming that all unrecovered **7** or **8** were bound to polymer. This assumption was confirmed in several runs by ^{1}H-NMR analysis of polymer samples in the known amount of *p*-nitrobenzaldehyde as an internal standard.
14. Fügedi P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, C9; Kanie, O.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1988**, *7*, 501.
15. A trace amount (< 2%) of β-linked isomer was also isolated at this stage.

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