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Novel 1,6-Anhydro-β-lactose Derivatives for Rapid and Efficient Syntheses of Oligosaccharide Sequences Containing N-Acetyllactosamine

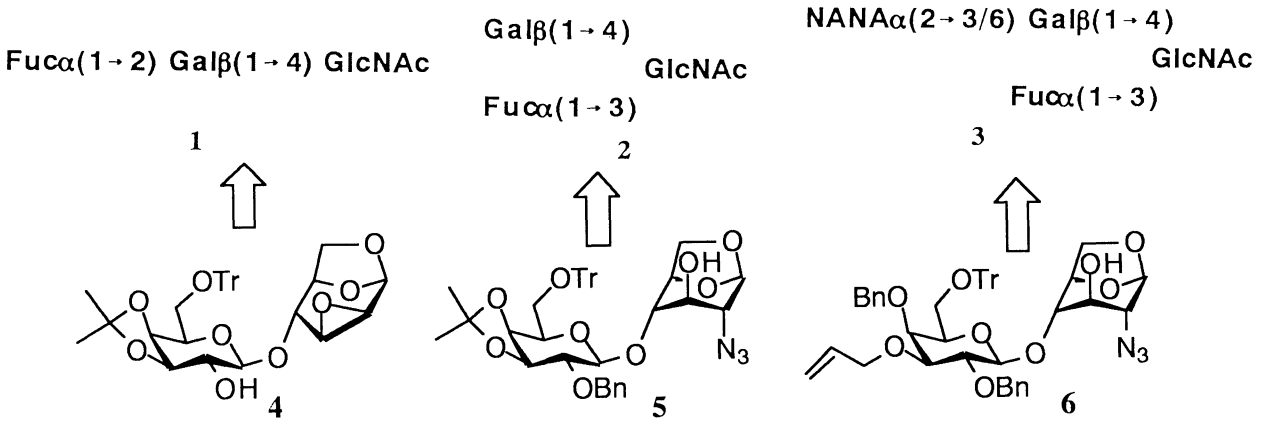
Shin-Ichiro NISHIMURA,* Sadao MURAYAMA,† Keisuke KURITA,† and Hiroyoshi KUZUHARA††
Department of Polymer Science, Faculty of Science, Hokkaido University, Sapporo 060
†Department of Industrial Chemistry, Faculty of Engineering, Seikei University, Musashino, Tokyo 180
†† RIKEN (The Institute of Physical and Chemical Research), Wako, Saitama 351-01

Fully functionalized glycosyl acceptors for the efficient syntheses of cell-surface carbohydrate determinants containing N-acetyllactosamine have been systematically prepared by the regioselective manipulations of a readily available 1,6-anhydro-6'-O-trityl-β-lactose as a key starting material. Versatility of the standardized intermediates having an unprotected hydroxyl group C-3 or C-2' position are also preliminarily demonstrated by the glycoside formation with the known fucose derivatives.

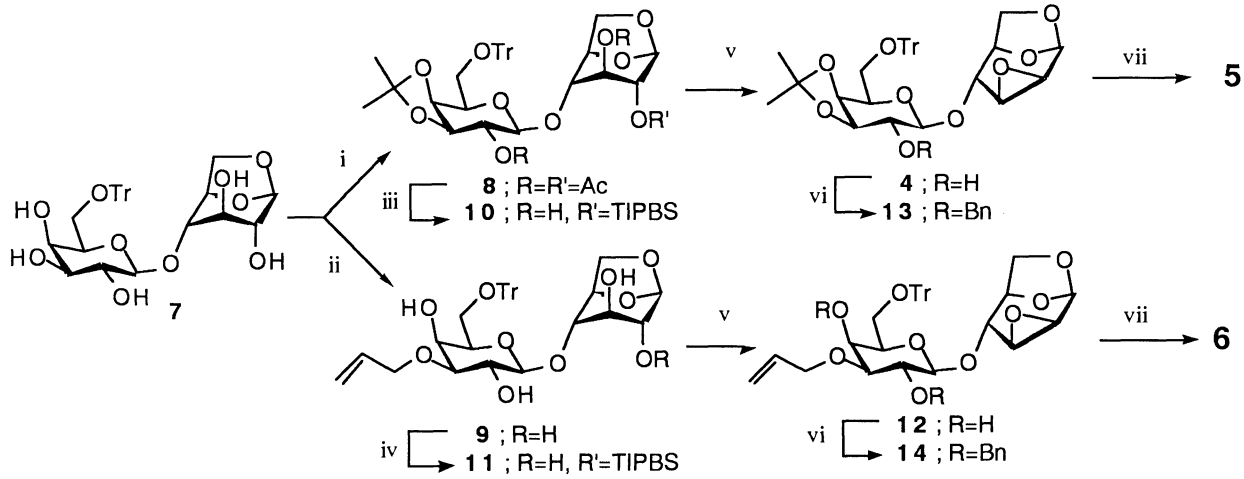
One crucial and indispensable function of oligosaccharide chains at the cell surface is as recognition sites for determining specificity of cell-cell interactions. Recent topics in glycobiology have been focused on the dramatic changes and roles of oligosaccharide structures in association with differentiation, development, and oncogenesis. [1] Especially, our attention has been directed toward the biological importance of the oligosaccharide sequences containing N-acetyllactosamine [Galpβ(1→4)GlcpNAc] as an invariable "core" structure. Scheme 1 illustrates typical examples of the N-acetyllactosamine-containing structures such as blood type determinant (**1**, H type epitope)[2] and oligosaccharide sequences which are highly or specifically expressed during mammalian cell adhesion [**2** (Lewis x) and **3** (sialyl Lewis x)].[3]

The increasing needs for the rapid and sophisticated syntheses of the carbohydrate determinants prompted us to undertake a convergent approach to the syntheses of these oligosaccharides based on chemospecific manipulations of a key disaccharide material,[4] a conformationally restricted 1,6-anhydro-β-lactose. In this paper we describe a novel method for the large-scale preparation of the versatile glycosyl acceptors which would greatly facilitate the synthetic procedures of the longer and complicated oligosaccharide sequences containing N-acetyllactosamine. Three suitable candidates **4**, **5**, and **6** were designed as "standardized intermediates" by retrosynthetic analyses of the three oligosaccharide determinants **1**, **2**, and **3**, respectively (see Scheme 1).

With respect to the reactivities of hydroxyl groups of 1,6-anhydro-4',6'-O-benzylidene-β-lactose, Tejima and his coworkers reported in the pioneering papers[5] that the order of reactivities of the secondary hydroxyl groups were 3' > 2 > 3 > 2' (Benzoylation) and 2 > 3' > 3 > 2' (tosylation). Moreover, Morikawa and Kuzuhara also found that much higher reactivity of the equatorial hydroxyl group at C-3' position made further chemospecific modifications of this disaccharide difficult.[6] Scheme 2 summarizes the systematic conversions of 1,6-anhydro-6'-O-trityl-β-lactose **7**[7] into the building blocks **4**, **5**, and **6**. The scheme planned here contains



Scheme 1. Retrosynthetic analyses

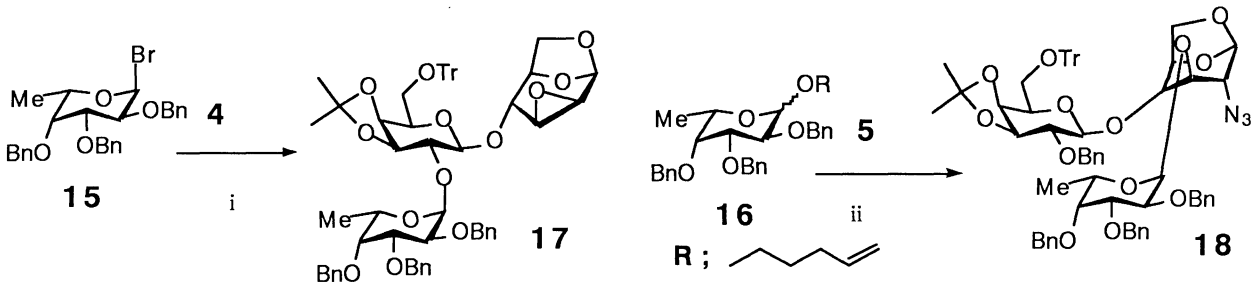


Scheme 2. Reagents and conditions : (i) 1.5 equiv. $Mc_2C(OMe)_2$, 10-camphorsulfonic acid cat., DMF, 60 ℃, 20 mmHg, 6 h; then Ac_2O, pyridine, 25 ℃, 16 h, 57%; (ii) 1.1 equiv. $Bu_2Sn=O$, toluene, 125 ℃, 20 mmHg, 4 h; then 10 equiv. $CH_2=CHCH_2Br$, 0.5 equiv. Bu_4NI, 95 ℃, 20 h, 62%; (iii) NaOMe cat., MeOH; 4.5 equiv. TIPBSCl, 1.5 equiv. dimethylaminopyridine (DMAP), pyridine, 25 ℃, 18 h, 81%; (iv) 3.0 equiv. TIPBSCl, 1.0 equiv. DMAP, pyridine, 25 ℃, 16 h, 66%; (v) 3 equiv. 1 M NaOH aq., THF-MeOH, 25 ℃, 15 h, 87% for **4** and 78% for **12**; (vi) BnBr, BaO, $Ba(OH)_2 \cdot 8H_2O$, DMF, 89% for **13** and 78% for **14**; (vii) 10 equiv. NaN_3, 10 equiv. CsF, DMF, 110 ℃, 48 h, 65% for **5** and 92% for **6**.

1,6-anhydro-6'-O-trityl-β-lactose **7**[7] into the building blocks **4**, **5**, and **6**. The scheme planned here contains two important steps for the selective modifications of a key starting material **7**; (a) protections of highly reactive 3'-OH group prior to the introduction of a suitable leaving group at C-2 position, and (b) selective introduction of a sterically hindered leaving group, 2,4,6-triisopropylbenzenesulfonyl group.

As anticipated, protections of 3'-OH group of **7** accelerated the further regioselective modifications and conversions. Indeed, ketalization of **7** proceeded smoothly and gave the 3',4'-O-isopropylidene derivative as peracetate **8**[8] {$[\alpha]_D^{23}$-22° (c 0.23, $CHCl_3$)} in 57% yield from **7**. Alternatively, selective allylation of **7** through the specific activation of cis 1,2-diol group with dibutyltin oxide[9] afforded 3'-O-allylated derivative **9**{62% from **7**;$[\alpha]_D^{23}$-48° (c 0.26, $CHCl_3$)}. Next, the intermediates **8** and **9** were converted into 2-O-

triisopropylbenzenesulfonyl (TIPBS-) derivatives **10** {81%; $[\alpha]_D^{23}$ 2.6° (c 0.25, $CHCl_3$)} and **11** {66%; $[\alpha]_D^{23}$-2.0° (c 1.71, $CHCl_3$)} with position specificity.[10] Treatment of diol **10** with aqueous sodium hydroxide solution yielded epoxide **4** as a convenient glycosyl acceptor for the blood type H antigen {87%; $[\alpha]_D^{23}$-27° (c 0.21, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): 7.48-7.25 (m, 15 H, aromatic), 5.70 (d, 1 H, J 2.9 Hz, H-1), 3.62 (ddd, 1 H, J 3.0, 7.1 and 8.3 Hz, H-2'), 2.71 (d, 1 H, J 2.7 Hz, 2'-OH), 1.50 and 1.35 (each s, each 3 H, Me_2C)}. Similarly, the triol **11** was converted into epoxide **12** {90%; $[\alpha]_D^{23}$-17° (c 0.24, $CHCl_3$)}. Benzylation of the epoxides **4** and **12** gave 2'-O-benzyl derivative **13** {89%; m. p. 158-160 °C; $[\alpha]_D^{23}$ 2.4° (c 0.52, $CHCl_3$)} and 2',4'-di-O-benzyl derivative **14** {78%; $[\alpha]_D^{23}$-22° (c 0.31, $CHCl_3$)}, respectively. Finally, azidolyses of the epoxides **13** and **14** occurred stereospecifically to afford the key synthons **5** (65%) and **6** (78%) having an unprotected hydroxyl group at C-3 position.[11]



Scheme 3. Reagents and conditions: (i) 1.0 equiv. of **4**, 3 equiv. Et_4NBr, 4 A MS, $ClCH_2CH_2Cl$-DMF, 25 °C, 20 h, 55%; (ii) 1.0 equiv. of **5**, 1.0 equiv. $I(collidine)_2ClO_4$, 4 A MS, CH_2Cl_2-Et_2O, 25 °C, 14 h, 50%.

The synthetic strategy reported herein is considerably shorter and simpler than those previously reported and has the potential to provide adequate amounts of functional oligosaccharides for further research such as preparation of some synthetic glycoconjugates and neoglycoproteins in the field of glycobiology. Actually, the versatility of the glycosyl acceptors prepared here was preliminarily demonstrated by the coupling reactions of the precursors **4** or **5** with the known fucosyl donors **15** or **16**, giving rise to the corresponding trisaccharide sequences **17** {55%; $[\alpha]_D^{23}$-39° (c 0.80, $CHCl_3$); ^{1}H-NMR ($CDCl_3$: 7.50-7.14 (m, 30 H, aromatic), 5.58 (d, 1 H, J 2.7 Hz, H-1), 4.44 (d, 1 H, J 8.5 Hz, H-1'), 4.32 (d, 1 H, J < 1, H-1''), 1.07 (d, 3 H, J 6.6 Hz, H-6")} and **18** (Scheme 3). Although we felt apprehension for the low reactivity of the axial hydroxyl group at C-3 position to some extent, coupling reaction of derivative **5** with **16** under Fraser-Reid condition[12] proceeded smoothly to give an important trisaccharide intermediate **18** with high stereoselectivity. {50% (47% of **5** was recovered) ; $[\alpha]_D^{23}$-24° (c 0.24, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): 7.45-7.15 (m, 35 H, aromatic), 5.50 (s, 1 H, H-1), 4.63 (s, 1 H, J<1 Hz, H-1"), 4.39 (d, 1 H, J 7.8 Hz, H-1'), 1.01 (d, 3 H, J 6.4 Hz, H-6")}. Further transformations of the trisaccharide intermediates including the applications for synthetic glycoconjugates[13] will be reported in the nearest future as a full paper.

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4) For the efficient utilization of disaccharide synthons, see, e.g. N. Sakairi and H. Kuzuhara, *Tetrahedron Lett.*, **23**, 5327 (1982); Y. Ichikawa, R. Monden, and H. Kuzuhara, *Carbohydr. Res.*, **172**, 37 (1988); S. I. Nishimura and H. Kuzuhara, *Carbohydr. Res.*, **206**, 207 (1990); L. -X. Wong, N. Sakairi, and H. Kuzuhara, *Carbohydr. Res.*, **219**, 133 (1991) and references cited therein.

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6) A. Morikawa and H. Kuzuhara, *J. Carbohydr. Chem.*, **9**, 167 (1990).

7) This compound was prepared from the 1,6-anhydro-β-lactose in ca. 83% overall yield by the following sequence: (i) 2 equiv. TrCl, pyridine, 90 ℃, 16 h; (ii) excess Ac_2O, pyridine, 25 ℃, 12 h; (iii) NaOMe cat., THF-MeOH, 25 ℃, 3 h.

8) All new compounds gave satisfactory spectral data and elemental analyses.

9) T. Ogawa and M. Matsui, *Carbohydr. Res.*, **62**, c1 (1978); S. David and S. Hanessian, *Tetrahedron*, **41**, 643 (1985).

10) The usual tosylation of monoallyl derivative **9** gave a mixture of three tosylates. The structures of **10** and **11** were elucidated by comparison of their ^{1}H-NMR spectra with those of the per-O-acetates.

11) Selected spectroscopic data for key compounds: **5**, $[\alpha]_D^{23}$-6.1° (c 0.22, $CHCl_3$); ^{1}H-NMR ($CDCl_3$), 7.46-7.23 (m, 20 H, aromatic), 5.32 (s, 1 H, H-1), 4.32 (d, 1 H, J 7.6 Hz, H-1'), 3.85 (m, 1 H, H-3), 3.20 (d, 2 H, J 6.4 Hz, H-2 and 3-OH), 1.34 and 1.28 (each s, each 3 H, Me_2C). **6**: $[\alpha]_D^{23}$-20° (c 2.23, $CHCl_3$); ^{1}H-NMR ($CDCl_3$), 7.39-7.14 (m, 25 H, aromatic), 5.28 (m, 1 H, C*H*=CH_2), 5.36-5.18 (m, 2 H, CH=CH_2), 5.28 (s, 1 H, H-1), 4.34 (d, 1 H, J 7.6 Hz, H-1'), 4.18 (br d, 1 H, J 2.9 Hz, H- 4'), 3.76 (t, 1 H, J 7.6 Hz, H-2'), 3.53 (m, 1 H, H-3), 3.34 (dd, 1 H, J 2.9 and 9.5 Hz, H-3'), 2.85 (d, 2 H, J 10.5 Hz, H-2 and 3- OH).

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