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A Rapid and Efficient Synthesis of a Trisaccharide Sequence Related to the Core Structure of the Asparagine-linked Type Glycoproteins by Using a Chitobiose Derivative as a Key Starting Material

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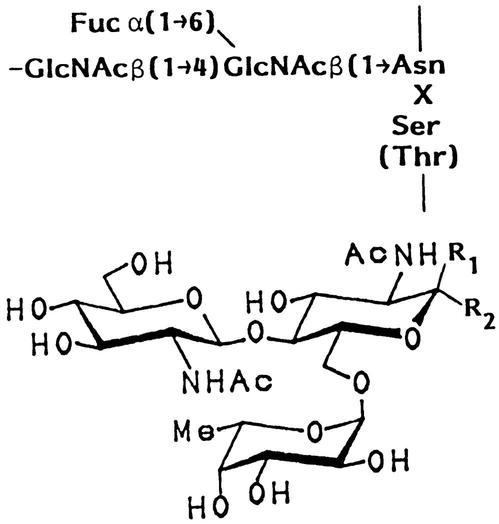
Allyl 2-acetamido-3-O-benzyl-4-O-(2-acetamido-3-O-benzyl-4,6-O-benzylidene-2-deoxy-β-D-glucopyranosyl)-2-deoxy-β-D-glucopyranoside (**5**) was efficiently prepared from chitobiose octaacetate in high yield. Coupling of **5** with 2,3,4-tri-O-benzyl-α-L-fucopyranosyl bromide by the halide ion-catalyzed glycosidation reaction afforded the protected trisaccharide intermediate in 58% yield. Deallylation followed by catalytic hydrogenolysis gave 2-acetamido-4-O-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-2-deoxy-6-O-(α-L-fucopyranosyl)-D-glucopyranose.

Asparagine-linked type sugar chains of glycoproteins contain a core structure which is invariably attached through the N,N'-diacetylchitobiose linkage to L-asparagine residue of the polypeptide main chain, and in some cases this chitobiose moiety is glycosylated with L-fucopyranose residue. The syntheses of α-L-fucosylated N,N'-diacetylchitobiose **1** and its β-methyl glycoside **2** have already been completed in fairly complicated procedures by the stepwise condensation reactions of three monosaccharide components.[1,2] However, the formation of the 1,4-linkage of chitobiose moiety seems to be extremely time-consuming and complicated process in both synthetic sequences. In spite of the increasing needs for such synthetic oligosaccharides and related derivatives in biochemical or medical fields, the rather complicated synthetic procedures of these oligosaccharide derivatives have often made their effective applications difficult.

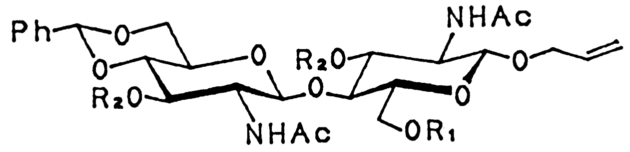


1: R_1, R_2=H, OH
2: R_1=H, R_2=OMe

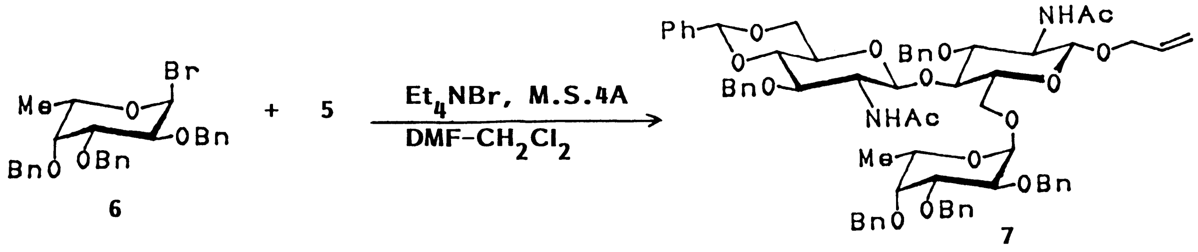
Recently, we have reported a facile preparation of chitobiose octaacetate by regiospecific degradation of chitin, derivatization for protection against later manipuration,[3] and the use as a key starting material for the synthesis of a peripheral trisaccharide sequence of a pituitary glycoprotein hormone.[4] This communication deals with a shorter and efficient synthetic route of a trisaccharide structure **1** using a chitobiose derivative as a convenient building block.

We first designed the chitobiosyl acceptor **5** which should be glycosylated with the readily available donor **6**. This key intermediate **5** having an unprotected hydroxyl group at the C-6 position was prepared by regioselective protections of N,N'-diacetylchitobiose. Since the protective group of the 6-OH group should be removable in the presence of other blocking groups, 4,4'-dimethoxytriphenylmethyl (DMTr-) group, easily removable by treatment with weak acids, was selected as a temporary protective group of C-6 position distinguishable from benzylidene of 4',6'-hydroxyl groups and benzyl protections of 3- and 3'-hydroxyl groups.

Allyl 2-acetamido-4-O-(2-acetamido-2-deoxy- β-D-glucopyranosyl)-2-



3: R_1=DMTr, R_2=Ac
4: R_1=DMTr, R_2=Bn
5: R_1=H, R_2=Bn



deoxy-β-D-glucopyranoside,$^{3)}$ readily obtainable from chitobiose octaacetate, was converted to the 6-O-dimethoxytrityl derivative **3** (R_f 0.50 in 5:4:1 $CHCl_3$-EtOAc-MeOH) by 3 step-reactions in 60% overall yields; (i) α,α'-dimethoxytoluene-camphorsulfonic acid in DMF, (ii) 4,4'-dimethoxytriphenylmethyl chloride-pyridine and (iii) acetic anhydride-pyridine. Compound **3**: $[\alpha]_D^{25}$-33.9°(c 1.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 1.97, 2.00 and 2.05 (s, four 3 H, -$COCH_3$), 3.80 (s, two 3 H, OCH_3), and 5.46 (s, 1 H, benzylidene).$^{5)}$ After O-deacetylation of 3 by sodium methoxide in methanol, 3,3'-hydroxyl groups were benzylated with benzyl bromide, BaO, and $Ba(OH)_2$ $8H_2O$ in DMF to give **4** (R_f 0.64 in 9:1 $CHCl_3$-EtOH) in 95% yield; $[\alpha]_D^{23}$-19.9° (c 1.17, $CHCl_3$); ^{1}H-NMR ($CDCl_3$):δ 1.62 and 1.65 (s, two 3 H, $COCH_3$), 3.70 (s, two 3 H, OCH_3), 4.63-4.84 (dd, two 2 H, $PhCH_2$), and 5.49 (s, 1 H, benzylidene). Selective removal of dimethoxytrityl group at the C-6 position of **4** was successfully performed by the treatment with pyridinium p-toluenesulfonic acid in ethanol-chloroform system for 30 min at room temperature, giving the key chitobiosyl acceptor **5** (R_f 0.40 in 9:1 $CHCl_3$-EtOH) in 79% yield; mp 285-287 °C (dec.); $[\alpha]_D^{23}$-42.8° (c 0.115, DMSO); ^{1}H-NMR (DMSO-d_6): δ 1.77 and 1.83 (s, two 3 H, $COCH_3$), 5.65 (s, 1 H, benzylidene), and 7.27-7.43 (m, 15 H, aromatic).

The properly protected chitobiosyl acceptor **5** was successively fucosylated in 58% yield (based on the quantity of **5** used) with 1.3 equivalents of the known 2,3,4-tri-O-benzyl-α-L-fucopyranosyl bromide

6⁽⁶⁾ using the halide ion-catalyzed procedure,[7] i. e., tetraethylammonium bromide and 4A molecular sieves in dichloroethane/DMF to give an amorphous trisaccharide **7** (R_f 0.56 in 9:1 $CHCl_3$-EtOH); $[\alpha]_D^{23}$ -39.9 °(c 2.26, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 1.04 (d, 3 H, J=6.6 Hz, H-6"), 1.85 and 1.92 (s, two 3 H, $COCH_3$), 4.53 (br s, 1 H, J<1 Hz, H-1"), 4.63 and 4.70 (d, two 1 H, J=8.0 Hz, H-1 and 1'), 5.50 (s, 1 H, benzylidene), and 7.22-7.44 (m, 30 H, aromatic). Deallylation of trisaccharide **7** with $PdCl_2$ in aq. AcOH-AcONa[8] followed by catalytic hydrogenolysis yielded the free trisaccharide **1** in 49% overall yield from **7**; $[\alpha]_D^{23}$ -30.4 °(c 0.56, H_2O);[9] ^{13}C-NMR (D_2O): δ 16.5 (C-6"),91.7 (C-1α), 96.1 (C-1β), 100.8 (C-1"), 102.4 (C-1'), and 175.8 (C=O).

In conclusion, an efficient synthetic procedure of trisaccharide **1** was established by using a properly protected chitobiose derivative **5**. This may enable us to prepare a new class of pseudo-glycoprotein[10] having pendant trisaccharide sequence **1** related to the core structure of the asparagine-linked type glycoproteins. The results will be reported in the near future.

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