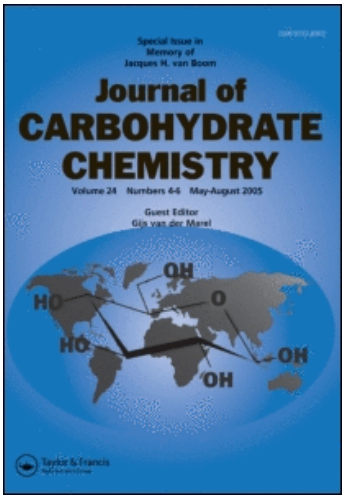


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# Synthesis of Selectively Protected Chitobiose and Chitotriose Derivatives from one Precursor. Versatile Building Blocks for Oligosaccharide Synthesis

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*COMMUNICATION*

# SYNTHESIS OF SELECTIVELY PROTECTED CHITOBIOSE AND CHITOTRIOSE DERIVATIVES FROM ONE PRECURSOR. VERSATILE BUILDING BLOCKS FOR OLIGOSACCHARIDE SYNTHESIS

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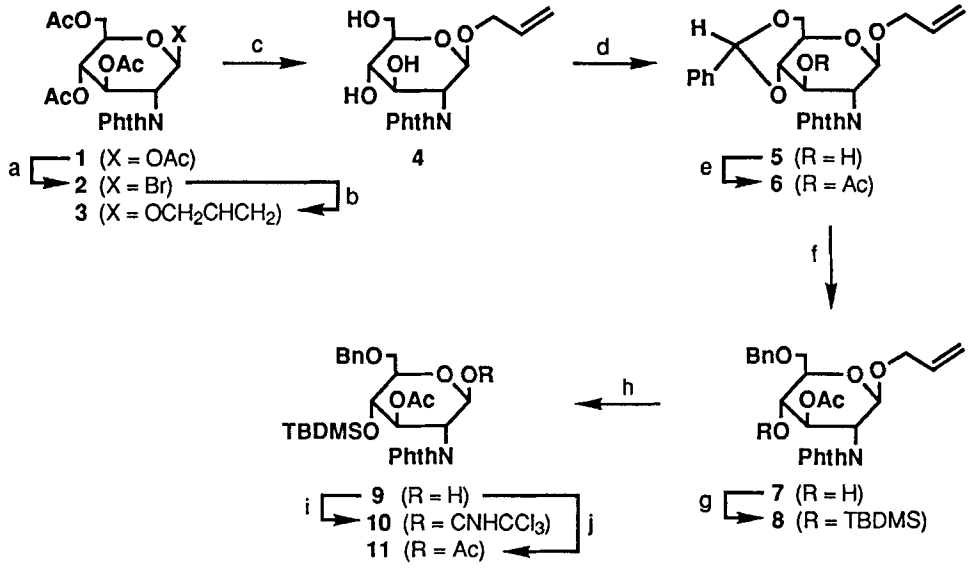
The inner core region of cell surface *N*-glycoproteins consists of a chitobiose substructure[2], containing β-(1,4)-linked disaccharides of glucosamine. Such carbohydrate structures are also found as repeating units of the bacterial cell wall peptidoglycan[3] and in novel tetra- and pentasaccharide plant hormones, which are nodulation factors on legume roots.[4] Since the first synthesis of a chitobiose derivative in 1966 by Paulsen,[5] approaches to these compounds have relied mainly on the oxazoline method.[6] The coupling reactions of aminosugar chlorides,[7] bromides,[8] acetates[9] and trichloroacetimidates[10] to suitable glycosyl acceptors have also been described. Most of these syntheses[11] require two completely different coupling partners; only in very few examples could the glycosyl donor and acceptor be obtained from the same starting material.[12] During our investigations into the stereocontrolled synthesis of glucosamine oligosaccharides, we required an economical synthetic route to protected derivatives of chitotriose. For the purpose of easy oligomerization, the anomeric protecting group of every building block had to be exchangeable selectively with the activating group for the next glycosylation. In this paper, we report an efficient approach to chitobiose and chitotriose from a single precursor. Furthermore, the hydroxyl groups at C-1, C-3, C-4, C-6 of these oligosaccharides are

differentially protected. This protecting group scenario allows a specific access to any of these functionalities by regioselective deblocking. The *N*-phthalimide group was chosen out of several possible amino protecting groups to ensure β-selectivity and simultaneous activation in the coupling.[13]

Treatment of the readily available tetraacetate **1**[14] with hydrogen bromide in acetic acid leads almost quantitatively to the glucosyl bromide **2**[14,15] which can be easily glycosylated under Helferich conditions[16] to give the allyl glycoside **3**[17]. Acidic deacetylation[15b,18] of **3** affords **4** which is converted to benzylidene acetal **5**. Acetylation of **5** followed by the sodium cyanoborohydride reductive ring opening[19] of the benzylidene acetal in **6** leads to the partially unprotected sugar **7** which serves as glycosyl acceptor in the coupling reaction to chitobiose. Only three more steps are necessary to obtain the corresponding glycosyl donor. Silylation of **7** with TBDMS chloride and imidazole protects the free 4-position. The anomeric deprotection proceeds easily using the new deallylation method developed in this laboratory.[20] Finally, addition of **9** to trichloroacetonitrile[21] gives the trichloroacetimidate **10** as the required glycosyl donor (Scheme 1).



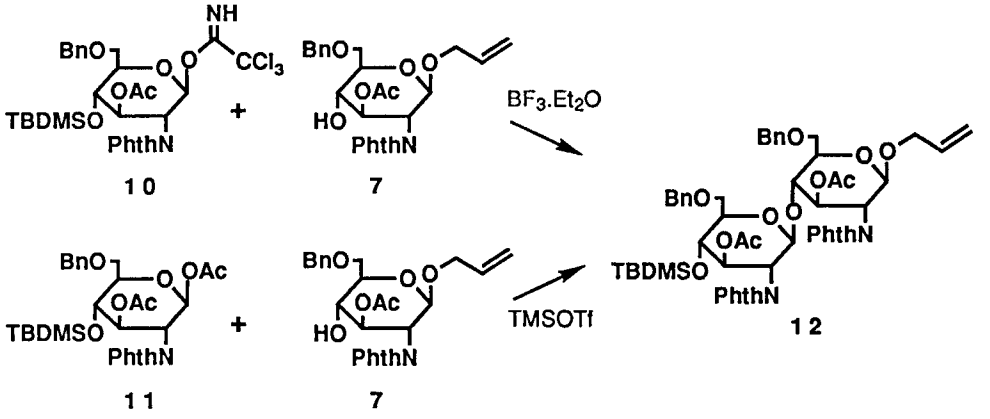
**Scheme 1**




a) HBr/HOAc, 96 %; b) Allyl alcohol, $Hg(CN)_2$, 74 %; c) HCl, $H_2O$, Acetone, 53 %; d) $PhCH(OMe)_2$, TsOH, 82 %; e) $Ac_2O$, Pyridine, 91 %; f) $NaBH_3CN$, HCl, 80 %; g) TBDMSCl, Imidazole, 77 %; h) 1. $CODIr^+(PMePh_2)_2\ PF_6^-$, 2. $OsO_4$, $Me_3NO$, 75 %; i) $Cl_3CCN$, NaH, 56 %; j) $Ac_2O$, Pyridine, 73 %.

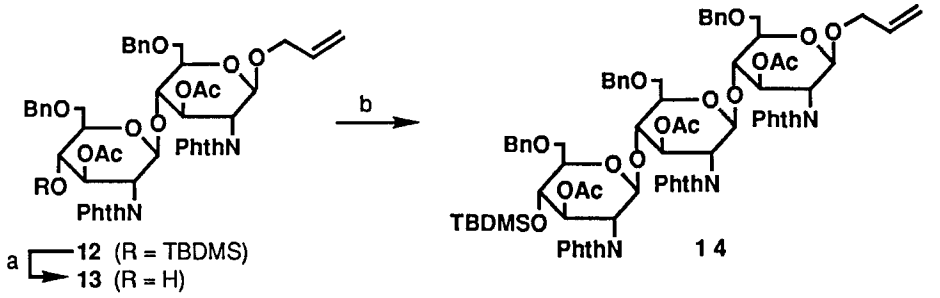
The coupling of **7** and **10** to afford the disaccharide **12** proceeds in 44 % using the trichloroacetimidate method.[22] The application of trimethylsilyl triflate activation,[17b] which is advantageous in the case of glycosyl acceptors with low reactivity,[23] was found to increase the yield of this coupling. Thus the β-acetate **11**, easily available from the hemiacetal **9**, can be linked to glycosyl acceptor **7** in 65 % yield (Scheme 2).

**Scheme 2**




Standard desilylation of the protected chitobiose derivative **12** and Schmidt coupling of the disaccharide **13** with glycosyl donor **10** led to the desired trisaccharide **14**[24] (Scheme 3).

**Scheme 3**




a) 40 % aq. HF, $CH_3CN$, 76 %; b) **10**, $BF_3.Et_2O$, 61 %.

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24. All new compounds were characterized by $^{1}$H-NMR, $^{13}$C-NMR and high-resolution mass spectrometry. Spectroscopical and analytical data are given for compounds **7**, **10 - 14**.

**7** : $^{1}$H NMR (500 MHz, $CDCl_3$, coupling constants in Hz) 7.84 - 7.82 (m, 2 H), 7.72 - 7.69 (m, 2 H), 7.36 - 7.34 (m, 2 H), 7.30 - 7.27 (m, 3 H), 5.73 - 5.68 (m, 1 H), 5.64 (dd, 1 H, J = 8.6, 10.6), 5.39 (d, 1 H, J = 8.5), 5.10 (bd, 1 H, J = 17.2), 5.00 (bd, 1 H, J = 10.4), 4.61 (q, 2 H, J = 12.0), 4.28 - 4.24 (m, 2 H), 4.02 (bdd, 1 H, J = 6.2, 13.0), 3.83 - 3.78 (m, 3 H), 3.74 - 3.71 (dd, 1 H, J = 4.5, 9.4), 3.05 (d, 1 H, J = 3.9), 1.91 (s, 3 H).

HR-MS (FAB$^+$) calcd for $C_{26}H_{27}NO_8$ $(MH)^+$ 482.5062, found 482.5053.

**10** : $^{1}$H NMR (500 MHz, $CDCl_3$, coupling constants in Hz) 8.63 (s, 1 H), 7.82 - 7.80 (m, 2 H), 7.70 - 7.68 (m, 2 H), 7.36 - 7.25 (m, 5 H), 6.68 (d, 1 H, J = 8.8), 5.66 (dd, 1 H, J = 8.5, 10.5), 4.65 (d, 1 H, J = 12.2), 4.58 (d, 1 H, J = 12.2), 4.80 (dd, 1 H, J = 8.9, 10.5), 4.05 (t, 1 H, J = 9.0), 3.90 - 3.80 (m, 3 H), 1.88 (s, 3 H), 0.80 (s, 9 H), 0.06 (s, 3 H), 0.02 (s, 3 H).

HR-MS (FAB$^+$) calcd for $C_{31}H_{37}Cl_3N_2O_8Si$ $(MH)^+$ 701.0922, found 701.0925.

**11** : $^1$H NMR (500 MHz, $CDCl_3$, coupling constants in Hz) 7.83 (bm, 2 H), 7.72 - 7.70 (m, 2 H), 7.36 - 7.26 (m, 5 H), 6.55 (d, 1 H, J = 8.8), 5.62 (dd, 1 H, J = 8.5, 10.5), 4.60 (d, 1 H, J = 12.0), 4.56 (d, 1 H, J = 12.0), 4.32 (dd, 1 H, J = 8.8, 10.4), 4.00 (dd, 1 H, J = 0.8, 8.6), 3.80 - 3.70 (m, 3 H), 1.96 (s, 3 H), 1.85 (s, 3 H), 0.77 (s, 9 H), 0.03 (s, 3 H), -0.02 (s, 3 H).

HR-MS (FAB$^+$) calcd for $C_{31}H_{39}NO_9Si$ $(MH)^+$ 598.7410, found 598.7416.

**12** : $^1$H NMR (500 MHz, $CDCl_3$, coupling constants in Hz) 7.81 (m, 4 H), 7.80 - 7.67 (m, 4 H), 7.36 - 7.23 (m, 10 H), 5.70 - 5.64 (m, 2 H), 5.45 (t, 2 H, J = 9.1), 5.26 (d, 1 H, J = 8.5), 5.05 (dd, 1 H, J = 1.5, 17.2), 4.98 (dd, 1 H, J = 1.2, 10.4), 4.55 (d, 1 H, J = 12.1), 4.50 (d, 1 H, J = 12.1), 4.49 (d, 1 H, J = 12.0), 4.44 (d, 1 H, J = 12.0), 4.25 - 4.12 (m, 3 H), 4.05 (dd, 1 H, J = 8.4, 10.5), 3.98 - 3.93 (m, 2 H), 3.64 (d, 2 H, J = 2.0), 3.59 - 3.53 (m, 3 H), 3.29 (bd, 1 H, J = 9.6), 1.82 (s, 3 H), 1.80 (s, 3 H), 0.78 (s, 9 H), 0.01 (s, 3 H), -0.03 (s, 3 H).

HR-MS (FAB$^+$) calcd for $C_{55}H_{62}N_2O_{15}Si$ $(MH)^+$ 1020.1877, found 1020.1868.

**13** : $^1$H NMR (500 MHz, $CDCl_3$, coupling constants in Hz) 7.81 (m, 4 H), 7.80 - 7.67 (m, 4 H), 7.37 - 7.20 (m, 10 H), 5.70 - 5.50 (m, 3 H), 5.45 (d, 1 H, J = 8.3), 5.27 (d, 1 H; J = 8.5), 5.04 (dd, 1 H, J = 1.5, 17.1), 4.97 (dd, 1 H, J = 1.2, 10.4), 4.56 (d, 1 H, J = 12.0), 4.50 (d, 1 H, J = 12.0), 4.39 (d, 1 H, J = 12.0), 4.34 (d, 1 H, J = 12.0), 4.22 - 4.05 (m, 4 H), 3.98 - 3.90 (m, 1 H), 3.81 - 3.64 (m, 4 H), 3.55 - 3.42 (m, 3 H), 3.30 (m, 1 H), 1.83 (s, 3 H), 1.82 (s, 3 H).

HR-MS (FAB$^+$) calcd for $C_{49}H_{48}N_2O_{15}$ $(MH)^+$ 905.9251, found 905.9240.

**14** : $^1$H NMR (500 MHz, $CDCl_3$, coupling constants in Hz) 7.87 - 7.67 (m, 12 H), 7.34 - 7.22 (m, 15 H), 5.65 - 5.59 (m, 2 H), 5.52 (dd, 1 H, J = 8.9, 10.6), 5.42 - 5.37 (m, 2 H), 5.26 (d, 1 H, J = 8.4), 5.21 (d, 1 H, J = 8.5), 5.03 (dd, 1 H, J = 1.6, 17.3), 4.96 (dd, 1 H, J = 1.3, 10.4), 4.53 - 4.41 (m, 5 H), 4.19 - 4.14 (m, 3 H), 4.05 (dd, 2 H, J = 8.6, 10.7), 4.00 - 3.90 (m, 3 H), 3.58 - 3.35 (m, 8 H), 3.04 (dd, 2 H, J = 7.1, 9.6), 1.81 (s, 3 H), 1.75 (s, 3 H), 1.71 (s, 3 H), 0.78 (s, 9 H), -0.01 (s, 3 H), -0.05 (s, 3 H).

HR-MS (FAB$^+$) calcd for $C_{78}H_{83}N_3O_{22}Si$ $(MH)^+$ 1443.6066, found 1443.6068.