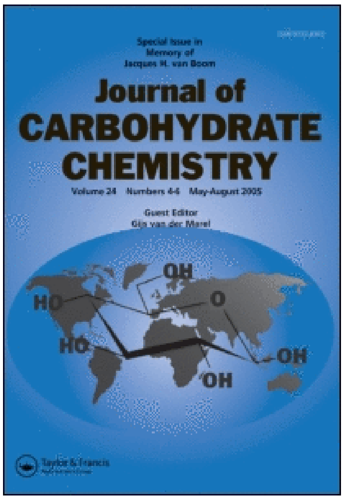

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THE TMSOTf-PROMOTED "ONE POT" β-GLYCOSIDATIONS OF PERACETYLATED CHITOBIOSE

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ABSTRACT

β-Glycosidations of peracetylated chitobiose with such alcohols as methyl, allyl, benzyl, isopropyl, *tert*-butyl alcohol and 1,2:3,4-*O*-diisopropylidene-1-*O*-α-D-galactoside were carried out in good yields by employing TMSOTf as a promoter. The reaction proceeded through the oxazoline intermidiate.

INTRODUCTION

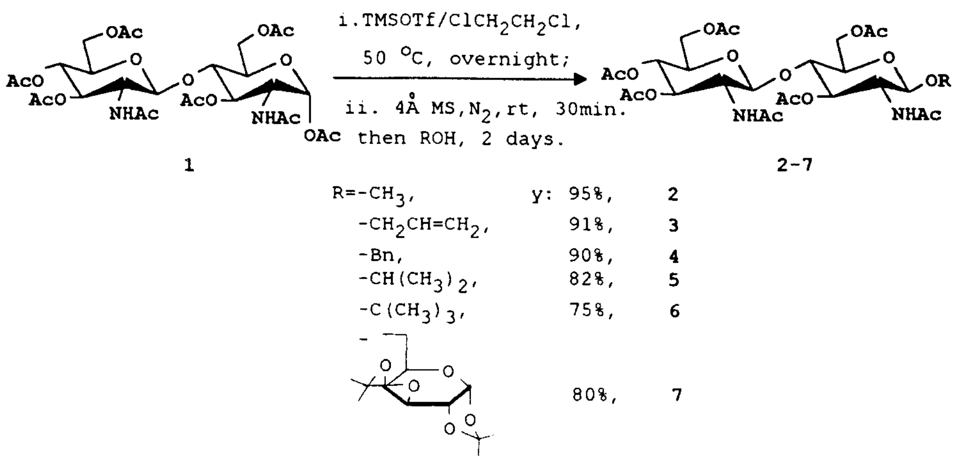
The β-(1→4) linked *N*-acetylglucosamine chitooligosaccharide fragments are widely distributed in many biologically important compounds. The inner core region of cell surface *N*-glycoproteins consists of a chitobiose substructure.[1] Chitobiose is also found as repeating units of the bacterial cell wall peptidoglycan.[2] On the other hand, chitooligosacchrides play significant roles in eliciting defense related responses in various plants.[3] The tetra- and pentachitosaccharides are the backbone of the nodulation factors on legume roots.[4] Furthermore, some chitooligosaccharides and their derivatives possess immunostimulating and antitumor activities.[5]

The synthetic approaches to these compounds have relied mainly on a variety of coupling reactions of glucosamine derivatives.[6] A facile way to achieve these biologically interesting compounds is to employ peracetylated chitobiose as a starting material,[7,8] which is readily accessible from chemical or enzymatic degradation of chitin.[8,9] Only based on an efficient glycosidation reaction, can the peracetylated chitobiose be changed into proper acceptors and donors. The glycosidation of 2-acetamido-2-deoxy sugars mainly rely on the oxazoline method.[10] By treatment with TMSOTf (trimethylsilyl triflate), the peracetylated chitobiose was easily changed to its oxazoline in high yield, the glycosidation reactions of this oxazoline with such simple alcohols as methanol, 2-propen-1-ol, and 2,2,2-trichloroethanol in the presence of trifluoromethanesulfonic acid as catalyst gave the corresponding β-glycosides in 76%, 53%, and 40% yield, respectively.[8] On the other hand, the glycosidations of 2-methyl (3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyranose [2,1-d]-2-oxazoline[11] and 2-methyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactosyl)-3,6-di-*O*-acetyl-1,2-dideoxy-α-D-glucopyranose [2,1-d]-2-oxazoline[12] can be promoted by TMSOTf.

We report here facile TMSOTf-promoted "one pot" β-glycosidation reactions of peracetylated chitobiose **1**.

RESULTS AND DISCUSSION

Peracetylated chitobiose was transformed completely into its oxazoline derivative by treatment with TMSOTf (1.1 equiv) at 50 °C overnight. After the mixture was cooled to room temperature, it was stirred under dry 4Å molecular sieve for a period before the alcohol was added, otherwise, the yield of glycoside was drastically lowered. The results are summarized in the Scheme. The yields of glycosides were good with all alcohol glycosyl acceptors we employed, including isopropyl and *tert*-butyl alcohols. Only the β-anomers were found in their ^{1}H NMR spectra. On the other hand, the intermediate oxazoline can be separated and purifided by silica gel chromatography,[13] which can be also converted into corresponding glycosides in good yield by employing TMSOTf (0.2 equiv) as catalyst. By employing $FeCl_3$[14] or BF_3OEt_2[15] as catalyst, the yields of the glycosides were less than 35% with ally and benzyl alcohol as the glycosyl acceptors, and no glycoside product was observed with isopropyl alcohol as the glycosyl acceptor.



Scheme

EXPERIMENTAL

General Methods. Solvents were purified in the usual way. Melting points are uncorrected. Optical rotations given in units of 10^{-1}deg cm^{2}g^{-1}, were determined with a Perkin-Elmer Model 241 MC polarimeter at 22 °C. IR spectra were measured with IR-440 spectrometer. ^{1}H NMR spectra were recorded on Bruker AM-300 spectrometers using TMS as internal standard. Mass spectra were taken on HP5989A, and VG Quattro MS/MS spectrometers. TLC was performed using silica gel plates F254 (Merk). Column chromatography was performed using silica gel, partical size 10-40μm, purchased from Qindao Ocean Chemical Factory.

Typical Procedure. To a suspension of peracetylated chitobiose **1** (2.0 g, 2.96 mmol) in dry $ClCH_2CH_2Cl$ (40 mL), was added TMSOTf (0.63 mL, 3.26 mmol). After the mixture was stirred at 50 °C overnight, the resulting solution was cooled to room temperature under N_2 and dry 4Å MS (1 g) was added. The mixture was stirred for 30 min at room temperature and then alcohol (3.0 equiv) was added. After the mixture was stirred for another 2 days, it was neutralized with Et_3N, then filtered. The solid was washed with CH_2Cl_2-MeOH (10:1) several times. The filtrate and washings were combined, and concentrated. The residue was chromatographed on silica gel with CH_2Cl_2/MeOH (50:1 v/v) as the eluent to give the product (75%-95%).

Methyl 2-Acetamido-3,6-di-*O*-acetyl-2-deoxy-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-β-D-glucopyranoside (2). R_f 0.36 (10:1 CH_2Cl_2/MeOH); mp 282-284 °C (from MeOH); $[\alpha]_D^{22}$ -55.9° (*c* 0.30, $CHCl_3$) [Lit.[8] mp 284 °C (from MeOH), $[\alpha]_D^{22}$ -44° (*c* 0.55, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 5.99 (d, 1H, J=9.0 Hz, N'-H), 5.74 (d, 1H, J=9.5 Hz, N-H), 5.19 (t, 1H, J=9.5 Hz, H-3'), 5.11 (t, 1H, J=8.3 Hz, H-3), 5.06(t, 1H, J=9.6 Hz, H-4'), 4.56 (d, 1H, J=8.4 Hz, H-1'), 4.40-4.35 (m, 3H), 4.06 (m, 3H), 3.90 (dd, 1H, J=8.7,9.4 Hz, H-2'), 3.74 (t, 1H, J=8.5 Hz, H-4), 3.64 (m, 2H), 3.47 (s, 3H, -OMe), 2.14-1.95 (m, 21H, 7×Ac); EI-MS: *m/z* 649 (0.8, M^+), 617 (0.5, M^+-OMe), 330 (51), 288 (12).

Allyl 2-Acetamido-3,6-di-*O*-acetyl-2-deoxy-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-β-D-glucopyranoside (3). R_f 0.40 (10:1 CH_2Cl_2/MeOH); mp 253-254 °C (from EtOH); $[\alpha]_D^{22}$ -56.3° (*c* 0.38 $CHCl_3$) [Lit.[8] mp 254 °C (from EtOH), $[\alpha]_D^{22}$ -42° (*c* 0.43, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 6.04 (d, 1H, J=9.0 Hz, N'-H), 5.85 (m, 1H, $-CH_2\underline{CH}=CH_2$), 5.78 (d, 1H, J=9.2 Hz, N-H), 5.26 (m, 2H, $-CH_2CH=\underline{CH_2}$), 5.19 (t, 1H, J=9.5 Hz, H-3'), 5.16 (t, 1H, J=9.1 Hz, H-3), 5.06 (t, 1H, J=9.8 Hz, H-4'), 4.57 (d, 1H, J=8.3 Hz, H-1'), 4.51 (d, 1H, J=7.6 Hz, H-1), 4.40-4.22 (m, 4H), 4.05 (m, 3H), 3.89 (dd, 1H, J=8.7,9.3 Hz, H-2'), 3.74 (t, 1H, J=8.2 Hz, H-4), 3.65 (m, 2H), 2.14-1.95 (m, 21H, 7×Ac); EI-MS: *m/z* 675 (1.6, M^+), 617 (1.2, M^+-$OCH_2CH=CH_2$), 330 (65), 288 (3).

Benzyl 2-Acetamido-3,6-di-*O*-acetyl-2-deoxy-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-β-D-glucopyranoside (4). R_f 0.44 (10:1 CH_2Cl_2/MeOH); mp 264-265 °C (from MeOH); $[\alpha]_D^{22}$ -46.3 ° (*c* 0.24, $CHCl_3$); IR (KBr) 3350, 1740 (OAc), 1660 (NAc), 1540, 1360, 1230, 1040; ^1H NMR ($CDCl_3$) δ 7.30 (m, 5H, -OBn), 6.21 (d, 1H, J=7.8 Hz, N'-H), 5.79 (d, 1H, J=7.9 Hz, N-H), 5.18 (t, 1H, J=9.5 Hz, H-3'), 5.04 (m, 2H), 4.87 (d, 1H, J=11.9 Hz, $-O\underline{CH_2}Ph$), 4.59-4.34 (m, 6H), 4.12 (m, 1H), 4.03 (d, 1H, J=12.4 Hz, $-O\underline{CH_2}Ph$), 3.90 (dd, 1H, J=8.5,9.3 Hz, H-2'), 3.75 (m, 1H, H-4), 3.64 (m, 2H), 2.16-1.93 (m, 21H, 7×Ac); EI-MS: *m/z* 726 (0.5, M^++1), 617 (0.4, M^+-OBn), 330 (57), 288 (17).

Anal. Calcd for $C_{33}H_{44}N_2O_{16}$: C, 54.68; H, 6.13; N, 3.87. Found: C, 54.35; H, 5.86; N, 3.60.

Isopropyl 2-Acetamido-3,6-di-*O*-acetyl-2-deoxy-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-β-D-glucopyranoside (5). Rf 0.41 (10:1 CH_2Cl_2/MeOH); $[\alpha]_D^{22}$ -41.4° (*c* 0.35, CH_2Cl_2); IR (KBr) 3300 (N-H), 1750 (OAc), 1680 (NAc), 1540, 1370, 1230, 1040; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 5.17 (dd, 1H, J=9.4,10.3 Hz, H-3'), 5.08 (dd, 1H, J=8.6,10.3 Hz, H-3), 5.00 (t, 1H, J=9.5 Hz, H-4'), 4.56 (d, 1H, J=8.3 Hz, H-1'), 4.54 (d, 1H, J=8.2 Hz, H-1), 4.03 (m, 2H), 4.12 (q, 1H, J=5.8 Hz), 4.03 (dd, 1H, J=2.0,12.2 Hz), 3.87 (m, 2H), 3.67 (m, 3H), 3.38 (m, 1H, -O<u>CH</u>Me$_2$), 2.11-2.00 (m, 15H, 5×OAc), 1.92,1.91 (2s, 6H, 2×NAc), 1.20 (d, 3H, J=6.2 Hz, -OCH<u>Me$_2$</u>), 1.13 (d, 3H, J=6.1 Hz, -OCH<u>Me$_2$</u>); FAB-MS: *m/z* 677 (M^++1), 618, 330, 288.

***tert*-Butyl 2-Acetamido-3,6-di-*O*-acetyl-2-deoxy-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-β-D-glucopyranoside (6).** Rf 0.42 (10:1 CH_2Cl_2/MeOH); mp 258-259 °C(dec.) (from MeOH); $[\alpha]_D^{22}$ -24.8 ° (*c* 0.5, CH_2Cl_2); IR (KBr) 3300(N-H), 1740 (OAc), 1660 (NAc), 1360, 1220, 1040; ^{1}H NMR ($CDCl_3$) δ 6.04 (d, 1H, J=7.4 Hz, N'-H), 5.66 (broad, 1H, N-H), 5.28 (m, 2H), 5.03 (t, 1H, J=9.2 Hz), 4.72 (d, 1H, J=8.8 Hz, H-1'), 4.67 (d, 1H, J=7.5 Hz, H-1), 4.37 (m, 2H), 4.22 (m, 1H), 4.05 (d, 1H, J=12.2 Hz), 3.68 (m, 5H), 2.10-2.00 (m, 15H, 5×OAc), 1.94 (s, 6H, 2×NAc), 1.21 (s, 9H, -C(CH_3)$_3$); FAB-MS: *m/z* 691 (M^++1), 618, 330, 288, 228.

6-*O*-[2-Acetamido-3,6-di-*O*-acetyl-2-deoxy-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-β-D-glucopyranosyl]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (7). R_f 0.48 (10:1 CH_2Cl_2/MeOH); $[\alpha]_D^{22}$ -63.7 ° (*c* 0.42, $CHCl_3$); IR (KBr) 3350, 1740 (OAc), 1660 (NAc), 1360, 1220, 1050; ^{1}H NMR ($CDCl_3$) δ 5.97 (d, 1H, J=8.5 Hz, N'-H), 5.76 (d, 1H, J=8.8 Hz, N-H), 5.33 (d, 1H, J=4.9 Hz, H-1), 5.10 (m, 3H), 4.61-4.35 (m, 7H), 4.15-3.97 (m, 6H), 3.68 (m, 4H), 2.13-1.95 (m, 21H, 7×Ac), 1.50,1.44,1.32,1.31 (4s, 12H, 2×isopropylidene); FAB-MS: *m/z* 877 (1.0, M^+), 617 (1.5), 330 (10), 288 (20).

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