Tetrachlorophthalimido- and Pent-4-enoyl-Protected Glucosamines as Precursors for Preparation of 2-Azido-2-deoxyglucopyranosyl Building Blocks

Lars Olsson, Zhaozhong J. Jia, and Bert Fraser-Reid*

Natural Products and Glycotechnology Research Institute Inc., 4118 Swarthmore Road, Durham, North Carolina 27707

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Introduction

Hexosamines are components of many naturally occurring, and biologically active, carbohydrate structures. For efforts to evaluate and explore their function, synthetic compounds related to the native structures are of great value. Therefore, improvement of synthetic methods used to produce hexosamine building blocks is of continuing interest.

Generally, synthesis of α-linked glucosamines involves the use of a 2-azido-2-deoxy-protected glycosyl donor[1] as the precursor. Several methods for introducing the azido group at C-2 have been developed over the last two decades, including the following: azidonitration[2] or azidophenylselenylation[3] of glycals, azide ion displacement of C-2 triflates,[4] and azide ion opening of 2,3-anhydro derivatives.[5] Although these methods have been proven useful, some problems can also be expected. The procedures involved are in many cases time consuming, and furthermore, anomeric α/*β*-mixtures and/or substantial amounts of the undesired 2-epimer may be produced.

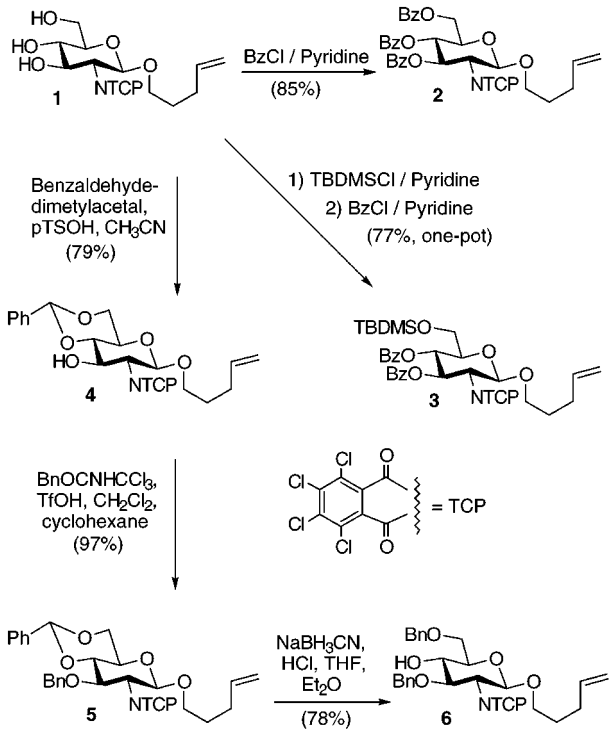
In recent years, the diazotransfer reaction[6,7] has been introduced to carbohydrate chemistry,[8−10] where a free amine is treated with trifluoromethanesulfonyl azide (TfN_3) to produce an azido sugar. This procedure allows the 2-azido-2-deoxy product to be obtained from the desired hexosamine without tampering with the original C-2 configuration. Anomeric protecting groups can be introduced stereospecifically, utilizing *N*-acetyl as guiding group prior to the diazotransfer,[9] a feature of great practical significance when contemplating a multistep synthesis.

Results and Discussion

For our program of synthesizing hexosamine-containing natural products, two new and mildly removable amino-protecting groups, tetrachlorophthalimido[11] (TCP) and pent-4-enoyl,[12,13] have been developed and used.[14,15] In this report, we will further demonstrate the usefulness of these protecting groups in preparation of 2-azido-2-deoxy building blocks.

Since selectively protected TCP-derivatives can be prepared on a large scale and in good yields using simple methods,[11] we desired to examine these derivatives as precursors for 2-azido-2-deoxyproducts. Substrates were readily prepared from the *n*-pentenyl glycoside **1** as outlined in Scheme 1. The tri- and dibenzoates (**2** and **3**) as well as the benzylidene derivative **4** were prepared under standard conditions. However, an acid-catalyzed benzylation procedure[16] was required for the conversion of **4** into **5** because of the base-lability of TCP.[11] Notably Garegg's stereoselective reductive benzylidene opening[17] works well to produce the 4-OH derivative **6**.

Scheme 1



The pentenyl glycoside **6** was treated with ethylenediamine (4.0 equiv) for smooth removal of the TCP group (Scheme 2). It was found that removal of the side

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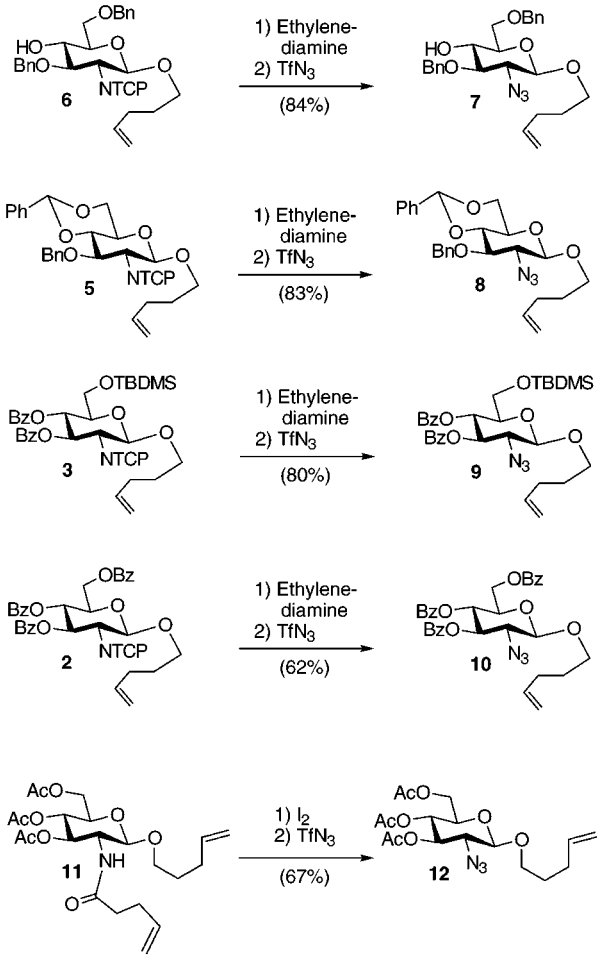
Scheme 2



products from the TCP-deprotecting step was necessary for formation of the final product in acceptable and reproducible overall yields. And so, rough purification of the intermediate amine followed. Overnight reaction with TfN_3 (CAUTION!)[18] in acetonitrile then gave the 2-azido derivative **7**. The results with substrates **3**, **5** and **6** indicate that commonly applied protecting groups such as benzylidene acetals and benzyl and *tert*-butyldimethylsilyl ethers survive the conversion well. Overnight treatment with ethylenediamine was allowed routinely for substrates **5** and **6**, and clean deprotection was achieved with no breakdown detected.

Ester protecting groups required special consideration. Yields were lower when benzoates were present (**2** and **3**) owing to some ester cleavage during the ethylenediamine treatment. The primary 6-*O*-benzoate was especially labile, as a comparison of the obtained yields of **9** and **10** shows. In these cases, careful monitoring by TLC, allowing as short reaction time as possible, was important to obtain best yields.

Acetate groups are not as sturdy,[11] but for such cases use of the pent-4-enoyl group seemed advantageous, since its deprotection by iodine occurs under nonbasic conditions. Indeed, transformation of substrate **11** into to 2-azido product **12** shows that this is a promising approach.

The diazotransfer step caused no concern. Reactions proceeded excellently in all cases in a spot-to-spot fashion.

In summary, by use of mildly removable TCP or pent-4-enoyl amino-protecting groups, followed by diazotransfer, 2-azido-2-deoxy derivatives could be prepared in good yields. Common carbohydrate protecting groups are compatible with the methods, allowing advanced differentially protected derivatives to be transformed into their azido analogues. The late introduction of the azido group is of special preparative value, allowing relatively large amounts of building blocks to be synthesized conveniently.[19] Further exploration of this methodology and use of the 2-azido-2-deoxy building blocks in the synthesis of α-linked glucosamine glycosides is currently under way.

Experimental Section

General Remarks. Solvents of commercial anhydrous grade have been used without further purification. TLC plates (Riedel-de Haen, coated with silica gel 60 F 254) were detected by UV and by charring with 8% sulfuric acid. Silica gel (Spectrum SIL 58, 230−400 mesh, grade 60) was used for column chromatography. All NMR spectra were recorded at 25 °C at 400 MHz (^{1}H) or 100 MHz (^{13}C), and chemical shifts are reported relative to internal TMS. Accurate mass measurements were made using FAB at 10K resolution, and elemental analyses were conducted by Atlantic Microlab, Norcross, GA. Procedures for preparation of compounds **1**, **2**, **4**, and **5** can be found in ref 11.

Pent-4-enyl 3,4-Di-*O*-benzoyl-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (3). Pent-4-enyl 2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (**1**) (951 mg, 1.84 mmol), *tert*-butyldimethylsilyl chloride (305 mg, 2.03 mmol), and a catalytic amount of DMAP were dissolved in pyridine (15 mL) and stirred overnight at room temperature. TLC indicated that silylation was complete, and benzoyl chloride (534 μL, 4.60 mmol) was added to the reaction mixture. Stirring continued, and further additions of benzoyl chloride were made 2 and 4 h after the first (200 μL, 1.72 mmol, each time). After 6 h of benzoylation, the reaction was completed, and water (2 mL) was added. Five minutes later, the reaction mixture was partitioned between 5% HCl (aqueous) and toluene. The organic phase was washed with 5% HCl (aqueous) and $NaHCO_3$ (saturated, aqueous), dried ($MgSO_4$), and evaporated. Flash chromatography (petroleum ether/EtOAc 12:1) gave product **3** as a white crispy foam in 77% yield (1168 mg, 1.41 mmol). NMR data: ^{13}C δ −5.4 (two signals), 18.3, 25.8, 28.5, 29.9, 55.8, 62.8, 69.0, 70.0, 71.7, 75.2, 97.7, 114.9, 128.3−129.8 (several signals), 133.3, 133.4, 137.7, 165.1, 166.1; ^{1}H (selected data) δ 5.47 (d, 1H, J = 8.4 Hz), 5.53 (t, 1H, J = 9.2 Hz), 5.68 (m, 1H), 6.12 (t, 1H, J = 9.0 Hz). Anal. Calcd for $C_{39}H_{41}NO_9SiCl_4$: C, 55.92; H, 4.93; N, 1.67. Found: C, 56.03; H, 4.95; N, 1.61.

Pent-4-enyl 3,6-Di-*O*-benzyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (6). Pent-4-enyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (**5**) (1133 mg, 1.63 mmol) was dissolved in a mixture of THF/diethyl ether (2:1, 75 mL). $NaBH_3CN$ (1000 mg, 15.9 mmol) was added in one portion and the mixture stirred for 5 min. HCl (g) was bubbled into the mixture for 2 min, and 15 min later, all starting material was consumed. Water (25 mL) and toluene (100 mL) were added, and the resulting phases were separated. The organic layer was washed with brine, $NaHCO_3$ (saturated aqueous) twice, dried ($MgSO_4$), and evaporated. Gradient flash chromatography (petroleum ether/EtOAc 8:1−4:1) gave product **6** (890 mg, 1.28 mmol, 78%). NMR data: ^{13}C δ 28.4, 29.8, 56.0, 68.8, 70.6, 73.4, 73.8, 74.7, 75.0, 79.4, 97.8, 114.8, 126.9, 127.8−128.5 (several signals), 137.4, 137.7, 138.6; ^{1}H (selected data) δ 5.09 (d, 1H, J = 8.0 Hz), 5.61 (m, 1H). This compound (**6**) has previously been synthesized and fully characterized using a different procedure and starting material. See ref 11.

Preparation of compounds **7**−**10** followed the general procedure: The TCP-protected compound (1 equiv) was dissolved in

(18) Considering the hazardous nature of TfN_3, it should be prepared in situ and used in solution only according to refs 6 and 8.

(19) Gram amount single preparations of advanced compound **7** have been carried out.

THF/CH_3CN/EtOH 2:1:1 (50 mg/mL) and heated to 65 °C. Ethylenediamine (4.0 equiv) was added and the mixture stirred for appropriate time (2−16 h) as judged by TLC. When all starting material was consumed, the mixture was evaporated, and the intermediate amine was purified by flash chromatography (petroleum ether/EtOAc, appropriate mixture) and dried in a vacuum. The dried residue was dissolved in CH_3CN (40 mg/mL). DMAP (1 equiv) and TfN_3 (CAUTION!,[18] 2.5 equiv from a 0.4 M CH_2Cl_2 solution, prepared as described in ref 8) were added, and the mixture was stirred overnight at room temperature. The reaction mixture was then evaporated until 20% of solvent remained and applied directly to flash chromatography (petroleum ether/EtOAc, appropriate mixture), which gave pure azido product. Characterization data for **7**−**10** are given below.

Pent-4-enyl 2-Azido-3,6-di-*O*-benzyl-2-deoxy-*β*-D-glucopyranoside (7). NMR data: ^{13}C δ 28.7, 30.0, 65.8, 69.6, 70.0, 71.8, 73.8, 73.9, 75.0, 82.4, 102.2, 115.0, 127.8−128.6 (several signals), 137.6, 137.9, 138.0; ^1H (selected data) δ 4.27 (d, 1H, J = 8.0 Hz), 4.52−5.08 (m, 6H), 5.76 (m, 1H). Anal. Calcd for $C_{25}H_{31}N_3O_5$: C, 66.21; H, 6.89; N, 9.27. Found: C, 66.33; H, 6.92; N, 9.29.

Pent-4-enyl 2-Azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-*β*-D-glucopyranoside (8). NMR data: ^{13}C δ 28.7, 30.0, 66.1, 66.2, 68.6, 69.9, 74.9, 78.9, 81.5, 101.3, 102.6, 115.1, 125.7, 127.9−129.0 (several signals), 137.1, 137.8; ^1H (selected data) δ 4.34 (2 overlapping signals, d, 1H, J = 8.0 Hz and 1H, q), 4.76−5.08 (m, 4H), 5.57 (s, 1H), 5.81 (m, 1H). Anal. Calcd for $C_{25}H_{29}N_3O_5$: C, 66.50; H, 6.47; N, 9.31. Found: C, 66.65; H, 6.50; N, 9.30.

Pent-4-enyl 2-Azido-3,4-di-*O*-benzoyl-6-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-*β*-D-glucopyranoside (9). NMR data: ^{13}C δ −5.4 (two signals), 18.3, 25.8, 28.8, 30.0, 62.7, 64.3, 69.5, 69.6, 72.8, 75.1, 102.1, 115.2, 128.4−129.8 (several signals), 133.3 (two signals), 137.8, 165.2, 166.6; ^1H (selected data) δ 4.54 (d, 1H, J = 7.9 Hz), 4.97−5.10 (m, 2H), 5.37 (t, 1H, J = 9.2 Hz), 5.43 (t, 1H, J = 9.7 Hz), 5.68 (m, 1H). Anal. Calcd for $C_{31}H_{41}N_3O_7Si$: C, 62.50; H, 6.94; N, 7.05. Found: C, 62.61; H, 7.01; N, 7.11.

Pent-4-enyl 2-Azido-3,4,6-tri-*O*-benzoyl-2-deoxy-*β*-D-glucopyranoside (10). NMR -data: ^{13}C δ 28.7, 30.0, 63.2, 64.2, 69.7, 69.8, 72.0, 72.5, 102.3, 115.2, 128.4−129.8 (several signals), 133.1, 133.4, 133.5, 165.3, 165.6, 166.1; ^1H (selected data) δ 4.58 (2 overlapping signals, d, 1H, J = 8.0 Hz and q, 1H), 4.97−5.10 (m, 2H), 5.47−5.56 (m, 2H), 5.80 (m, 1H). HRMS: calcd for $C_{32}H_{31}N_3O_8$ $(M - H)^+$ 584.2032, found 584.2043.

Pent-4-enyl 3,4,6-Tri-*O*-acetyl-2-azido-2-deoxy-*β*-D-glucopyranoside (12). Compound **11**[12] (102 mg, 0.22 mmol) was dissolved in THF (1 mL), an equal amount of water was added, and a cloudy mixture was obtained. Additional THF was added until a clear solution formed, whereafter iodine (171 mg, 0.67 mmol) was added. After 20 min, all starting material was consumed. NaS_2O_3 (s) was added to decolorize the brown mixture, which then was evaporated, and the amine purified by flash chromatography (toluene/EtOAc 1:2). Diazotransfer was achieved as described above for compounds **7**−**10** to give **12** (60 mg, 0.150 mmol, 67%). NMR data: ^{13}C δ 20.5, 20.6, 20.7, 28.8, 30.2, 61.9, 63.7, 68.4, 69.8, 71.6, 72.4, 102.0, 115.2, 137.7, 169.8, 170.2, 170.9; ^1H (selected data) δ 4.39 (d, 1H, J = 8.1 Hz), 4.98 (m, 4H), 5.80 (m, 1H). MS (FAB): m/z 400.2, MH^+.

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