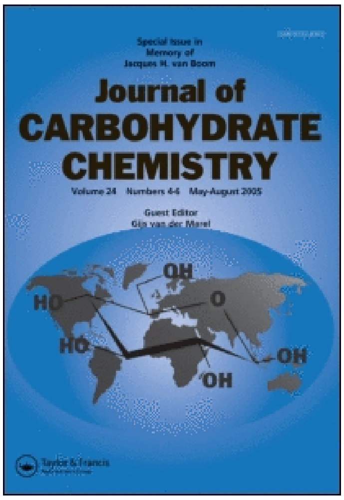


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# EFFICIENT SYNTHESES OF METHYL 2-AMINO-2-DEOXY-3,4,6-TRI-*O*-BENZYL-α-D-GLUCOPYRANOSIDE AND ITS 2-*tert*-BUTOXYCARBONYLAMINO- AND 2-METHYLAMINO DERIVATIVES FROM *N*-ACETYL-D-GLUCOSAMINE

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## ABSTRACT

The synthesis of the title compounds started with *N*-acetylglucosamine which was converted into the corresponding methyl glycoside and *O*-protected with benzyl groups. Subsequent *N*-protection as its *N*-BOC-*N*-acetyl derivative and sequential removal of the *N*-acetyl group and of the BOC group led in good yield to the target compounds in multigram amounts.

## INTRODUCTION

While the preparation of protected derivatives of 2-acetamido-2-deoxy sugars is well documented, the direct protection of the hydroxyl groups of 2-amino sugars leaving the amino group free is mostly restricted to acetyl protecting groups.[1] The absence of an

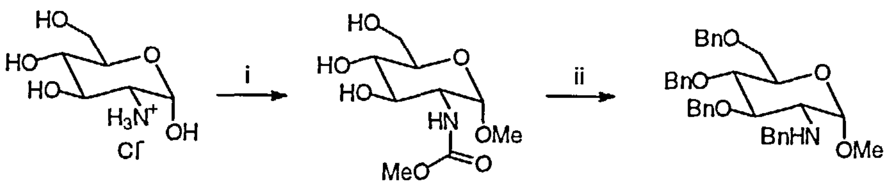
*N*-acyl group which strongly deactivates the amino group toward *N*-alkylation, complicates the introduction of protecting groups by alkylation of alcohols. Thus benzyl ethers cannot be efficiently introduced on 2-amino-2-deoxy sugars. To circumvent this problem several protecting groups of the nitrogen function have been proposed over the years.[2-7] The drawback of these derivatives is the low availability of these protected forms of amino sugars. The use of *N*-acetyl derivatives of 2-amino sugars is attractive but the removal of the 2-acetamido group is cumbersome.[8]

In connection with a synthetic programme aiming at the synthesis of *O*-benzyl protected 2-amino-2-deoxy sugars, we turned our attention to the preparation of the title compounds from D-glucosamine.



## RESULTS AND DISCUSSION

In our first experiments, D-glucosamine hydrochloride **1** was treated with methyl chloroformate to provide in one step the known methyl 2-deoxy-2-methoxycarbonylamino derivative **2** in 80% yield on a 20 g scale.[3,4] Attempts to benzylate this compound under standard conditions (NaH, BnBr, DMF) gave the expected benzylated compound in very poor yield. The same result was observed upon treatment of compound **2** with benzyl bromide in the presence of barium oxide/barium hydroxide mixture. Mostly decomposition of the carbamate derivative followed by benzylation of the amino group to give **3** was observed in both cases.



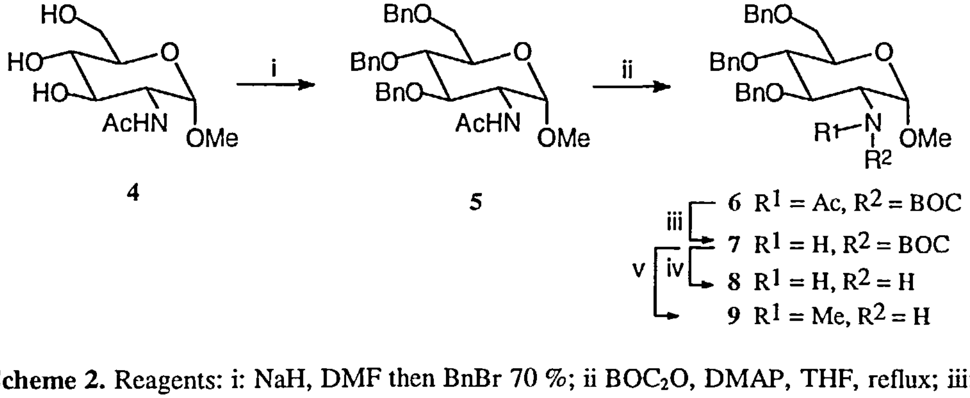
**1** **2** **3**

**Scheme 1.** Reagents and conditions: i: MeOH, Na, $Na_2CO_3$ then MeOCOCl, 80%; ii: NaH, DMF then BnBr or BaO, $Ba(OH)_2$, BnBr.

While this work was in progress a paper by Burk and Allen attracted our attention.[9] These authors took advantage of the facile hydrolysis of imide derivatives in basic medium[10-12] to achieve the *N*-deacetylation of *N*-BOC-*N*-acetyl derivatives of amino-acids and of glucosamine under mild conditions. We tried to apply this methodology to our problem. Thus the known compound **4**[13] was benzylated under standard conditions to give compound **5** [14, 15] in 70% yield on 70 g scale. This compound was then treated with 4.3 equivalents of $BOC_2O$ in dry tetrahydrofuran at reflux in the presence of a catalytic amount of DMAP, to provide the corresponding *N*-acetyl-*N*-BOC derivative **6** which was not isolated but was submitted immediately to *N*-deacetylation. To our delight this reaction worked very well and upon treatment of **6** with hydrazine hydrate (4 equiv) in the presence of methanol. Compound **7** was obtained in 85% yield for the two steps on a 70 g scale.

The BOC group of the previously unknown compound **7** was treated in trifluoroacetic acid to give the free amine **8** in 90 % yield. On the other hand, we prepared by the same route the corresponding *N*-methyl derivative **9** by simple treatment of compound **7** with lithium aluminium hydride. Compound **9** was obtained in good yield (77%).

We have proposed an efficient method for the preparation, on a large scale, of the previously unknown 2-amino-2-deoxy sugars derivatives **7**-**9** starting from *N*-acetyl glucosamine. The key feature of this sequence is a one pot *N*-alkoxycarbonylation-*N*-




**Scheme 2.** Reagents: i: NaH, DMF then BnBr 70 %; ii $BOC_2O$, DMAP, THF, reflux; iii: $NH_2NH_2$-$H_2O$, MeOH, rt, 85 % for the two steps; iv: TFA, rt, 90 %; v: $LiAlH_4$, THF reflux, 77 %.

deacetylation of *N*-acetyl derivatives under mild conditions. The reaction conditions are likely compatible with a number of protecting groups and should find useful applications in the synthesis of amino sugars.

## EXPERIMENTAL

$^1$H NMR spectra were recorded with a Bruker AC 250 operating at 250 MHz and 63 MHz for the $^{13}$C, using deuteriochloroform as solvent. Assignments were confirmed by double irradiation or two dimensional spectroscopy. Chemical shifts are reported relative to internal $SiMe_4$. IR spectra were recorded on a Perkin-Elmer Spectrum 1000 spectrometer. TLC was performed on silica gel plates (Merck 60F $_{254}$). Column chromatography used silica gel (Merck 60 70-23 mesh). Preparative high pressure liquid chromatography was performed using a 40mm diameter stainless steel column (Prochrom, Champigneulles, France) containing silica gel (Merck 60 40-60 μ). Optical rotations were measured on a Perkin-Elmer 141 polarimeter at 20 °C. Melting points were measured in capillary tubes and are uncorrected. The elementary analyses were performed by the Service Central de Microanalyses du CNRS at Vernaison, France. Mass spectra were obtained on a Nermag R10-10C in the EI mode.



**Methyl 2-Deoxy-3,4,6-tri-*O*-benzyl-2-(tert-butyloxycarbonylamino)-α-D-gluco-pyranoside (7).** A solution of the known compound **5**[14, 15] (70 g, 138.5 mmol), $BOC_2O$ (100 g, 457 mmol, 3.3 equiv) and DMAP (3.4 g, 27.6 mmol, 0.2 equiv) in dry tetrahydrofuran (400 mL) was refluxed for 5 h. An additional amount of $BOC_2O$ (30 g, 1 equiv) was again added, and the mixture was left for 36 h at room temperature. The solution was diluted with methanol (400 mL), and hydrazine (17.5 mL, 152.3 mmol, 4 equiv) was added. After stirring for 1 h the solvents were removed in vacuo and the residue was dissolved in dichloromethane (400 mL). The organic layer was washed with aqueous hydrochloric acid, water, aqueous sodium bicarbonate, and then water. The organic layer was dried over magnesium sulfate and concentrated after filtration. The product was then purified on a silica gel column (hexane/ethyl acetate 3:1) to give pure **7**

(66.1 g, 85%) as white crystals. mp 91 °C (hexane/$CH_2Cl_2$); $R_f$ 0.5 (hexane/ethyl acetate 3:1); $[\alpha]_D$ +63.7° (c 0.6, $CHCl_3$); IR ($cm^{-1}$) : 3362, 1698. $^1$H NMR ($CDCl_3$): δ 1.46 (s, 9H, $(CH_3)_3C$), 3.38 (s, 3H, $OCH_3$), 3.74 (m, 5H, *H*-3, *H*-4, *H*-5, *H*-6, *H*-6'), 4.02 (m, 1H, *H*-2), 4.55 (2d, 2H, *J* 11 Hz, $CH_2Ph$), 4.65 (d, 1H, *J* 11 Hz,$CH_2Ph$), 4.70 (m, 2H, N*H*, *H*-1), 4.75 (d, 1H, *J* 11 Hz, $CH_2Ph$), 4.82 (2d, 2H, *J* 11 Hz, $CH_2Ph$), 7.28 (m, 15H, *H* aromatics); $^{13}$C NMR ($CDCl_3$): δ 28.41, 28.74 (2C), ($(CH_3)_3C$), 54.62 ($OCH_3$), 55.23 (*C*-2), 69.03 (*C*-6), 71.18 (*C*-5), 73.65 ($CH_2Ph$), 75.11 ($CH_2Ph$), 75.22 ($CH_2Ph$), 78.71 (*C*-4), 79.54 ($(CH_3)_3C$), 81.41 (*C*-3), 99.62 (*C*-1), 127.46-128.60 (*C* aromatics), 138.46, 138.60, 138.93 (*C* aromatics), 155.58 (CONH). EIMS: *m/z*: 564 (2) $[M+1]^+$, 476 (29), 91 (100).

Anal. Calcd for $C_{33}H_{41}NO_7$: C,70.25; H, 7.58, N, 2.62. Found: C, 70.3; H, 7.4; N, 2.5.



**Methyl 2-Amino-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-glucopyranoside (8).** A solution of compound **7** (800 mg, 1.42 mmol) in trifluoroacetic acid (10 mL) was stirred for 15 min and then concentrated to dryness under vacuum. The residue was dissolved in dichloromethane and the organic phase was washed with 3N aqueous sodium hydroxide and water. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by preparative high pressure column chromatography (dichloromethane/ethyl acetate/methanol 10:10:1) gave pure **8** (580 mg, 90 %) as a gum which crystallized slowly: mp 37 °C ($CH_2Cl_2$). $R_f$ 0.4 (methanol/dichloromethane 19.5:0.5); $[\alpha]_D$ +105.2° (c = 1.0, $CHCl_3$); IR ($cm^{-1}$): 3387 (broad). $^1$H NMR ($CDCl_3$): δ 1.76 (s, 2H, $NH_2$); 2.84 (dd, 1H, $J_{1,2}$ 3,5 $J_{2,3}$ 10 Hz, *H*-2); 3.38 (s, 1H, $OCH_3$); 3.70 (m, 5H, *H*-3, *H*-4, *H*-5, *H*-6, *H*-6'); 4.55 (2d, 2H, $CH_2Ph$); 4.68 (d, 1H, *J* 11 Hz, $CH_2Ph$); 4.72 (d, 1H, $CH_2Ph$); 4.77 (d, 1H, *H*-1); 4.81 (d, 1H, *J* 11 Hz, $CH_2Ph$) 4.97 (d, 1H, $CH_2Ph$); 7.25 (m, 15H, *H* aromatics). $^{13}$C NMR, $CDCl_3$: δ 55.39 (OCH3); 56.34 (*C*-2); 68.70 (*C*-6); 71.01 (*C*-5); 73.73 ($CH_2Ph$); 74.95 ($CH_2Ph$); 75.77 ($CH_2Ph$); 79.03 (*C*-4); 83.92 (*C*-3); 100.76 (*C*-1); 127.9-128.8 (tertiary aromatics *C*); 138.24, 138.40, 138.80 (quaternary aromatics *C*). EIMS: *m/z*: 464 (19) $[M+1]^+$, 476 (9), 91 (100).

Anal. Calcd for $C_{28}H_{33}NO_5$: C, 72.54; H, 7.17, N, 3.02. Found: C, 71.9; H, 7.3; N, 3.1.

**Methyl 2-Deoxy-3,4,6-tri-*O*-benzyl-2-(*N*-methylamino)-α-D-glucopyranoside (9).** To a solution of 7 (63 g, 111 mmol) in anhydrous tetrahydrofuran (250 mL) was added dropwise at 0 °C a suspension of $LiAlH_4$ (15.3 g, 400 mmol, 3.6 equiv) in 200 mL of anhydrous tetrahydrofuran. The mixture was refluxed for 3 h then cooled to 0 °C and water (15 mL), 30% aqueous sodium hydroxide (15 mL) and water (45 mL) were added successively. After stirring for 30 min the solids were filtered off. These solids were suspended in tetrahydrofuran (100 mL) and the suspension heated around 45 °C for 15 min. The combined organic phases were concentrated, and the residue was taken up in dichloromethane (400 mL). The organic phase was washed with water and dried over magnesium sulfate. Filtration and concentration gave a residue which was purified on a silica gel column (hexane / ethyl acetate1:1) to give pure compound 9 (41g, 77 %) as a gum. $R_f$ 0.3 ($CH_2Cl_2$/MeOH 9:1); $[\alpha]_D$ +76.1° (c 1.0, $CHCl_3$); IR ($cm^{-1}$) : 3340 (broad). $^1H$ NMR. $CDCl_3$: δ 1.76 (s, 1H, N*H*); 2.45 (s, 3H, NC*H*$_3$); 2.72 (dd, 1H, $J_{1,2}$ 3.7, $J_{2,3}$ 11 Hz, *H*-2); 3.40 (s, 1H, OC*H*$_3$); 3.74 (m, 5H, *H*-3, *H*-4, *H*-5, *H*-6, *H*6'); 4.52 (2d, 2H, 2C*H*$_2$Ph); 4.66 (d, 1H, *J* 11 Hz, C*H*$_2$Ph); 4.76 (d, 1H, C*H*$_2$Ph); 4.80 (d, 1H, C*H*$_2$Ph); 4.84 (d, 1H, *H*-1); 4.91 (d, 1H, C*H*$_2$Ph); 7.25 (m, 15H, *H* aromatics). $^{13}C$ NMR, $CDCl_3$: δ 35.15 (N*C*H$_3$); 55.35 (CO*C*H$_3$); 63.96 (*C*-2); 68.95 (*C*-6); 70.82 (*C*-5); 73.77 (*C*H$_2$Ph); 75.03 (*C*H$_2$Ph); 75.80 (*C*H$_2$Ph); 79.01 (*C*-4); 82.17 (*C*-3); 98.41 (*C*-1); 127.90-128.70 (tertiary aromatics *C*); 138.20, 138.42, 138.84 (quaternary aromatics *C*). EIMS: *m/z*: 478 (12) $[M+1]^+$, 445 (2), 91 (100).

Anal. Calcd for $C_{29}H_{35}NO_5$: C, 72.93; H, 7.38, N, 2.93. Found: C, 73.3; H, 7.6; N, 3.1.



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