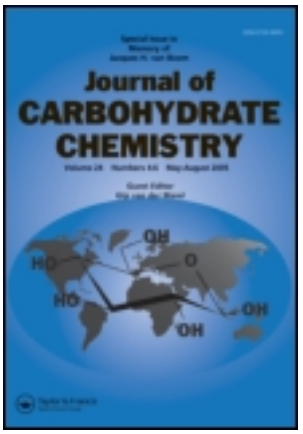

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An Alternative Method for Regioselective, Anomeric Deacylation of Fully Acylated Carbohydrates

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AN ALTERNATIVE METHOD FOR REGIOSELECTIVE, ANOMERIC DEACYLATION OF FULLY ACYLATED CARBOHYDRATES

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ABSTRACT

Ethylenediamine in admixture with acetic acid has been found useful to selectively effect the title conversion and can be of general utility. Reaction rates anomeric deacylations effected with this reagent are slower than with reagents introduced earlier, resulting in easier control and greater selectivity of deprotection.

INTRODUCTION

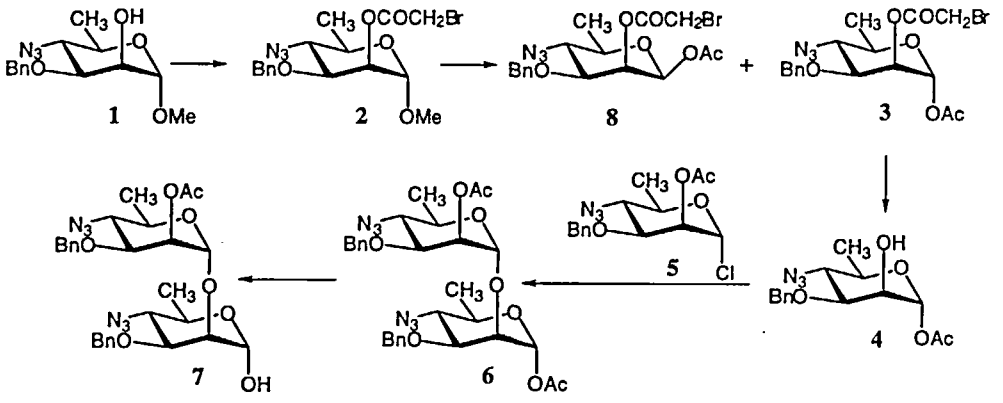
Per-*O*-acylated carbohydrates which have the anomeric position unsubstituted are important intermediates in carbohydrate chemistry.[1] Except for hydrolysis of scarce glycosyl halides,[2] this class of compounds is usually prepared by anomeric deacylation of fully acylated derivatives with basic reagents, such as hydrazine hydrate,[3] hydrazine acetate,[4] 2-aminoethanol,[5] stannic tetrachloride,[6] piperidine,[7] ammonia,[8,9] organotin reagents,[1] potassium cyanide,[1] butylamine,[10] dimethylamine,[10] or potassium hydroxide.[1] The rate of the anomeric deacylation varies depending both on the anomeric configuration of the starting sugar and the nature of substituents present. It is therefore useful to have a large choice of reagents applicable for this purpose in various situations.

Our work on neoglycoconjugates from large, synthetic fragments of the O-polysaccharide of *Vibrio cholerae* O:1 (for the background of this work, see ref. 11,12) required compound **7** as the intermediate for the preparation of the corresponding trichloroacetimidate. The conversion **6**→**7** was not quite satisfactory using some of the quoted reagents. In search for an alternative way for anomeric deprotection, we have found that ethylenediamine in admixture with acetic acid is capable of effecting the title conversion very selectively and can be of general utility. Of several organic solvents tried, tetrahydrofuran was found most suitable. Reaction rates of 1-deacylations effected with this reagent are slower than with reagents introduced earlier, resulting in easier control and greater selectivity of deprotection. This is particularly advantageous when working with very precious oligosaccharides, such as **7**.

The disaccharide **6** was prepared by silver trifluoromethanesulfonate (triflate)-mediated condensation of the known[13,14]glycosyl chloride **5** with the nucleophile **4**. The latter was obtained from the methyl glycoside **1**[13-15] applying standard chemistry shown in the Scheme. The critical step was the selective de-*O*-bromoacetylation of **3** with thiourea, which was a single product reaction (→**4**) when performed in the presence of a weak organic base.[16] Treatment of **6** as described in the general procedure for deacetylation (See Experimental) yielded the desired product in 96% yield as a mixture of anomers, from which the α-anomer **7** crystallized. Anomeric deprotection of per-*O*-acetylated gentiobiose worked also very well (see Experimental). Results with some other carbohydrates, including some 1-*O*-benzoyl derivatives, are summarized in the Table.

EXPERIMENTAL

General methods. Unless stated otherwise, optical rotations were measured at 25 °C for solutions in $CHCl_3$ (*c* 1) with a Perkin Elmer automatic polarimeter, Model 341. All reactions were monitored by thin-layer chromatography (TLC) on silica gel-coated glass slides (Whatman or Analtech). Detection was effected by charring with 5% sulfuric

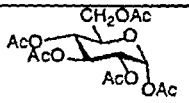
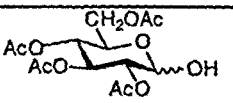
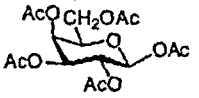
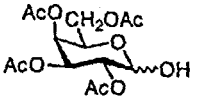
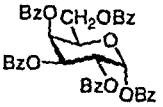
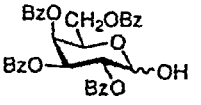
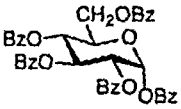
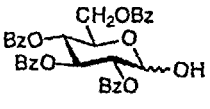
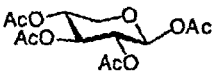
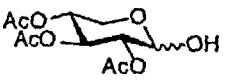
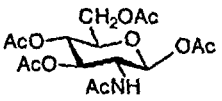
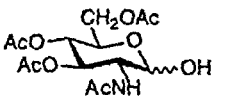
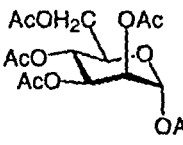
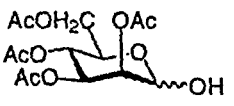
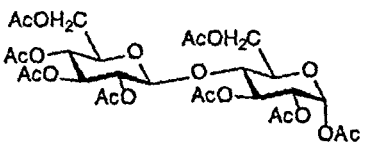
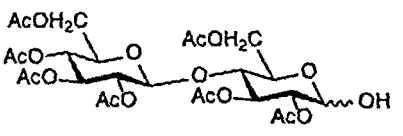


Scheme

acid in ethanol and, when applicable, by UV light. Preparative chromatography was performed by gradient elution from columns of Silica Gel 60 (Merck, particle size 0.035-0.070 mm) using at the onset of development a solvent mixture slightly less polar than that used for TLC. Assignments of NMR signals, obtained at 300 MHz for ^{1}H and 75 MHz for ^{13}C at 25 °C, were made by first-order analysis of spectra and, when feasible, the assignments were supported by APT and/or DEPT experiments, homonuclear decoupling and/or homo- and heteronuclear 2-dimensional correlation spectroscopy. Solutions in organic solvents were dried with anhydrous sodium sulfate, and concentrated at 40 °C/2 kPa.

General procedures for anomeric deacetylation. Glacial acetic acid (1.4 mmol) was added dropwise and with stirring to a solution of ethylenediamine (1.2 mmol) in THF (25 mL), resulting in immediate formation of a precipitate which remained present until aqueous work-up. The starting peracetate (1 mmol) was added and the mixture was stirred 16–24 h. TLC (3:2 hexane–acetone) then showed absence of the starting material and presence of a product which, in most cases, appeared as two poorly separated spots representing a mixture of anomers (NMR). Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic phase was washed sequentially with dilute HCl, aq. $NaHCO_3$ and water, dried and concentrated. Crystallization and/or chromatography then gave the desired products.

Table. Anomeric Deacylation of Selected Carbohydrate Derivatives

Starting Material	Product[a]	Yield [%]
		92[b]
		95–100[c]
		85[b]
		86[b]
		95–100[c]
		90[c]
		95–100[c]
		95–100[c]

a. Products gave CI mass and NMR spectra consistent with the expected structures. b. Isolated by column chromatography as a mixture of anomers. c. Estimated by TLC.

General procedures for anomeric debenzoylation. Debenzoylation is carried out as described for deacetylation, except using 2:1:1 ethylenediamine–acetic acid–1-*O*-benzoyl derivative (molar ratios), and the reaction time is extended to ~3 d.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-acetyl-α,β-D-glucopyranose (2,2′3′3′4,4′6′-Hepta-*O*-acetyl-α,β-gentiobiose). This compound was

prepared from the corresponding peracetate[17] (500 mg), following the general procedure. Chromatography gave the title compound (428 mg, 91%) as a mixture of anomers, mp 177-178 °C (from acetone–hexane). ^{1}H NMR ($CDCl_3$ + D_2O) for the predominating α-anomer: δ 5.44 (bt, 1 H, J ~10 Hz, H-3), 5.34 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.14 (t, 1 H, J 9.4 Hz, H-3'), 5.00 (t, 1 H, J 9.7 Hz, H-4'), 4.90 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.3 Hz, H-2'), 4.84 (bt, 1 H, J ~9.7 Hz, H-4), 4.76 (dd, 1 H, $J_{2,3}$ 10.3 Hz, H-2), 4.49 (d 1 H, $J_{1,2}$ 8.0 Hz, H-1'), 4.21–4.11 (m, 3 H, H-5,6'a,b), 3.83 (dd, 1 H, $J_{5,6a}$ 2.0, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.64 (ddd, 1 H, $J_{4,5}$ 10.0, $J_{5,6a}$ 2.6, $J_{5,6b}$ 4.0 Hz, H-5'), 3.50 (dd, 1 H, $J_{5,6b}$ 6.3 Hz, H-6b), 2.02, 1.97, 1.96, 1.94, 1.93 (5 s, 3 H each), 2.00 (s, 6 H, 7 $COCH_3$); ^{13}C NMR ($CDCl_3$ + D_2O) for the predominating α-anomer: δ 100.91 (C-1'), 89.53 (C-1), 72.39 (C-3'), 71.70 (C-5'), 70.92 (2 C, C-2,2'), 69.83 (C-3), 68.99 (C-4), 68.43 (C-6), 68.04 (C-4'), 67.60 (C-5), 61.58 (C-6'); CIMS: *m/z* 654 ([M + 18]$^+$).

Anal. Calcd. for $C_{26}H_{36}O_{18}$: C, 49.06; H, 5.70. Found: C, 49.00; H, 5.79.

Methyl 4-Azido-3-*O*-benzyl-2-*O*-bromoacetyl-4,6-dideoxy-α-D-mannopyranoside (2). Tetramethylurea (0.44 mL) followed by a solution of methyl 4-azido-3-*O*-benzyl-4,6-dideoxy-α-D-mannopyranoside[13-15] (**1**, 1 g, 3.4 mmol) in CH_2Cl_2 (5 mL), was added at 0 °C to a solution of bromoacetyl bromide (0.85 mL, 10 mmol) in dichloromethane (5 mL), and the mixture was stirred at room temperature overnight. Ice was added to decompose the excess of the reagent, the mixture was partitioned between water and dichloromethane, the organic solvent was washed with aq $NaHCO_3$, concentrated, and the residue was chromatographed (10:1 hexane–EtOAc) to give amorphous **2** (1.4 g, ~100%), $[\alpha]_D$ +74° (*c* 0.9). ^{1}H NMR ($CDCl_3$): δ 5.34 (dd, 1 H, $J_{1,2}$ 1.9, $J_{2,3}$ 3.3 Hz, H-2), 4.68, 4.52 (2 d, 1 H each, ^2J 11.1 Hz, CH_2Ph), 4.66 (s, 1 H, H-1), 3.89 (s, 2 H, CH_2Br), 3.81 (dd, 1 H, $J_{3,4}$ 9,8 Hz, H-3), 3.53 (m, 1 H, H-5), 3.38 (t, J 9.8 Hz, H-4), 3.35 (s, 3 H, OCH_3), 1.34 (d, 3 H, $J_{5,6}$ 6.2 H, H-6); ^{13}C NMR ($CDCl_3$): δ 98.26 (C-1), 76.00 (C-3), 71.80 (CH_2Ph), 69.13 (C-2), 66.81 (C-5), 63.91 (C-4), 55.12 (OCH_3), 25.64 (CH_2Br), 18.45 (C-6).

Anal. Calcd for $C_{16}H_{20}N_3O_5$: C, 46.39; H, 4.86; Br, 19.29; N, 10.14. Found: C, 46.48; H, 4.84; Br, 19.19; N, 10.20.

1-*O*-Acetyl-4-azido-3-*O*-benzyl-2-*O*-bromoacetyl-4,6-dideoxy-α- (3) and β-D-mannopyranose (8). The methyl glycoside **2** (1.1 g) was treated with a mixture of 25:10:0.25 Ac_2O–AcOH–H_2SO_4 (22 mL) for 2 h at room temperature. TLC (4:1 hexane–EtOAc) showed that two products were formed, the faster moving largely predominating. NaOAc trihydrate was added, to neutralize sulfuric acid, and the reaction mixture was poured into a stirred mixture of ice and $NaHCO_3$ solution, to destroy excess Ac_2O. After partitioning between water and CH_2Cl_2, the organic phase was dried, concentrated, and the residue was chromatographed.

Eluted first was the α-acetyl derivative **3** (0.9 g, 77%), $[\alpha]_D$ +85° (*c* 1.4). ^1H NMR ($CDCl_3$): δ δ 6.04 (d, 1 H, $J_{1,2}$ 1.9 Hz, H-1), 5.34 (dd, 1 H, $J_{2,3}$ 3.2 Hz, H-2), 4,72, 4.56 (2 d, 1 H each, ^2J 11.0 Hz, CH_2Ph), 3.91 (s, 2 H, CH_2Br), 3.82 (dd, 1 H, $J_{3,4}$ 9.9 Hz, H-3), 3.59 (m, 1 H, H-5), 3.46 (t, 1 H, *J* 10.0 Hz, H-4), 2.10 (s, 3 H, $COCH_3$), 1.34 (d, 3 H, $J_{5,6}$ 6.1 Hz, H-6). ^{13}C NMR ($CDCl_3$): δ 90.56 ($J_{C,H}$ 176.6 Hz, C-1), 75.68 (C-3), 71.97 (CH_2Ph), 69.31 (C-5), 68.10 (C-2), 63.49 (C-4), 25.20 (CH_2Br), 20.75 (COCH_3), 18.44 (C-6); CIMS: *m/z* 461 ($[M + 18]^+$).

Anal. Calcd for $C_{17}H_{20}BrN_3O_6$: C, 46.16; H, 4.56; Br, 18.06; N, 9.50. Found: C, 46.37; H, 4.57; Br, 17.84; N, 9.55.

Eluted next was the β-acetyl derivative **8** (0.1 g, 8.5 %). ^1H NMR ($CDCl_3$): δ 5.62 (d, 1H, $J_{1,2}$ 2.1 Hz, H-1), 5.50 (dd, 1 H, $J_{2,3}$ 3.1 Hz, H-2), 4.64, 4.45 (2 d, 1 H each, ^2J 11 Hz, CH_2Ph), 3.89 (s, 2 H, CH_2Br), 3.53 (dd, 1 H, $J_{3,4}$ 9.4 Hz, H-3), 3.34 (t, partially overlapped, *J* 9.8 Hz, H-4), 3.25 (m, partially overlapped, H-5), 2.01 (s, 3 H, $COCH_3$), 1.31 (d, 3 H, $J_{5,6}$ 5.9 Hz, H-6). ^{13}C NMR ($CDCl_3$): δ 90.65 ($J_{C,H}$ 162.3 Hz, C-1), 77.93 (C-3), 72.05 (C-5), 71.72 (CH_2Ph), 68.31 (C-2), 63.28 (C-4), 25.39 (CH_2Br), 20.62 (COCH_3), 18.31 (C-6). CIMS: *m/z* 461 ($[M + 18]^+$).

1-*O*-Acetyl-4-azido-3-*O*-benzyl-4,6-dideoxy-α-D-mannopyranose (4). A solution of thiourea (1.12 g, 14.7 mmol) in MeOH (10 mL) was added at 0°C to a stirred solution of **3** (2.16 g, 4.9 mmol) and the non-nucleophilic base[16] 2,4,6-trimethylpyridine

(0.98 mL, 7.35 mmol) in CH_2Cl_2 (30 mL). When TLC (4:1 toluene–EtOAc) showed that all starting material was consumed (~30 min), the mixture was concentrated and the residue was partitioned between water and CH_2Cl_2. The organic phase was dried, concentrated, and the residue was chromatographed, to give **4** (1.54 g, 98%), mp (from EtOAc–hexane), $[\alpha]_D$ +142° (*c* 1.2). ^{1}H NMR ($CDCl_3$): δ 6.01 (d, 1 H, $J_{1,2}$ 1.7 Hz, H-1), 4.73, 4.68 (2 d, 1 H each, ^2J 11.4 Hz, CH_2Ph), 3.91 (m 1 H, H-2), 3.71 (dd, 1 H, $J_{2,3}$3.2, 9.6 Hz, H-3), 3.66–3.53 (m, partially overlapped, H-5), 3.51 (m, partially overlapped, H-4), 2.65 (d, 1 H, $J_{2,OH}$ 1.6 Hz, OH), 2.10 (s, 3 H, $COCH_3$), 1.32 (d, 3 H, $J_{5,6}$ 6.0 Hz, H-6). ^{13}C NMR ($CDCl_3$): δ 92.57 (C-1), 77.70 (C-3), 72.11 (*C*H_2Ph), 69.04 (C-5), 66.31 (C-2), 63.37 (C-4), 20.87 (CO*C*H_3), 18.40 (C-6).

Anal. Calcd for $C_{15}H_{19}N_3O_5$: C, 56.06; H, 5.96; N 13.08. Found: C, 56.15; H, 5.93; N, 13.10.

2-*O*-Acetyl-4-azido-3-*O*-benzyl-4,6-dideoxy-α-D-mannopyranosyl-(1→2)-1-*O*-acetyl-4-azido-3-*O*-benzyl-4,6-dideoxy-α-D-mannopyranose (6). A mixture of the glycosyl chloride **5**[13,14] (9.3 g, 27.4 mmol), the foregoing nucleophile **4** (8.79 g, 27.4 mmol), 4 Å molecular sieves (8 g) and 1,1,3,3-tetramethylurea (3.27 mL, 27.4 mmol) in CH_2Cl_2 (170 mmol) was stirred under argon for 30 min. Silver triflate (7.74 g, 30 mmol) was added and the mixture was stirred for 1 h, when TLC (4:1 hexane–EtOAc) showed that all glycosyl donor was consumed and that one product was formed. After filtration, the filtrate was concentrated and the residue was chromatographed to give **6** (11.9 g, 70%), $[\alpha]_D$ +93° (*c* 1.2). ^{1}H NMR ($CDCl_3$): δ 5.95 (d, 1 H, $J_{1,2}$ 2.0 Hz, H-1), 5.41 (dd, 1 H, $J_{1,2}$ 1.6, $J_{2,3}$ 3.3 Hz, H-2'), 4.89 (d, 1 H, H-1'), 4.74–4.52 (4 d, partially overlapped, 4 H, 2 CH_2Ph), 3.80 (bt, partially overlapped, H-2), 3.78 (dd, partially overlapped, $J_{3,4}$ 9.8 Hz, H-3'), 3.69 (dd, 1 H, $J_{2,3}$ 3.0, $J_{3,4}$ 9.8 Hz, H-3), 3.65–3.50 (m, 2 H, H-5,5'), 3.42 (t, partially overlapped, *J* 9.8 Hz, H-4), 3.40 (t, partially overlapped, *J* 9.8 Hz, H-4'), 2.08, 2.05 (2 s, 3 H each, 2 COH_3), 1.32 (d, partially overlapped, $J_{5,6}$ 6.2 Hz, H-6), 1.30 (d, partially overlapped, $J_{5,6}$ 6.2 Hz, H-6'). ^{13}C NMR ($CDCl_3$): δ 99.27 (C-1'), 92.25 (C-1), 77.10 (C-3), 75.39 (C-3'), 72.18 (2 C, C-2, *C*H_2Ph), 71.61 (*C*H_2Ph), 69.54 (C-5'), 67.80

(C-5), 67.02 (C-2'), 63.62 (C-4'), 63.5 (C-4), 20.90, 20.85 (2 $COCH_3$), 18.54 (C-6), 18.31 (C-6'). CIMS: *m/z* 642 ($[M + 18]^+$).

Anal. Calcd for $C_{30}H_{36}N_6O_9$: C, 57.68; H, 5.81; N 13.45. Found: C, 57.84; H, 5.84; N, 13.55.

2-*O*-Acetyl-4-azido-3-*O*-benzyl-4,6-dideoxy-α-D-mannopyranosyl-(1→2)-4-azido-3-*O*-benzyl-4,6-dideoxy-α-D-mannopyranose (7). This compound was prepared from **6**, applying the general procedure for deacetylation. Chromatography gave the title product as a mixture of anomers in 96% yield. The pure α-form showed mp 114.5–116° (from EtOAc–hexane), $[\alpha]_D$ +63° (*c* 0.9). ^1H NMR ($CDCl_3 + D_2O$): δ 5.42 (dd, 1 H, $J_{1,2}$ 1.9, $J_{2,3}$ 3.0 Hz, H-2'), 5.09 (d, 1 H, $J_{1,2}$ 1.9, H-1), 4.86 (d, 1 H, H-1'), 4.74–4.45 (m, 4 H, 2 CH_2Ph), 3.88 (bt, 1 H, H-2), 3.83–3.77 (m, 2 H, H-3,3'), 3.75–3.67 (m, 1 H, H-5'), 3.62–3.53 (m, 1 H, H-5), 3.38 (t, partially overlapped, *J* 10.2 Hz, H-4), 3.34 (t, *J* 9.9 Hz, H-4'), 2.08 (s, 3 H, $COCH_3$), 1.28 (d, partially overlapped, $J_{5,6}$ 6.3 Hz, H-6), 1.27 (d, partially overlapped, *J* 6.3 Hz, H-6'); before deuteration, the signal for H-1 appears at δ 5.12 as a doublet of doublets. $J_{1,OH}$ 3.5 Hz, and the signal for OH appears at δ 2.49 as a doublet. ^{13}C NMR ($CDCl_3 + D_2O$): δ 169.94 (CO), 99.30 ($J_{C\text{-}1,H\text{-}1}$ 171.5 Hz, C-1'), 93.17 ($J_{C\text{-}1,H\text{-}1}$ 171 Hz, H-1), 77.18 (C-3), 75.30 (C-3'), 73.90 (C-2), 72.03, 71.51 (2 CH_2Ph), 67.49 (C-5), 67.08 (C-2'), 67.01 (C-5'), 64.08 (C-4), 63.71 (C-4'), 20.84 ($COCH_3$), 18.52 (C-6'), 18.36 (C-6). CIMS: *m/z* 583 ($[M + 1]^+$).

Anal. Calcd for $C_{28}H_{34}N_6O_8$: C, 57.72; H, 5.88; N 14.42. Found: C, 58.01; H, 5.99; N, 14.30.

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