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Note

The preparation and attempted alkylation of some 6-cyano-carbohydrates

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As part of a project involving the enantiospecific synthesis of natural products from carbohydrate precursors, a method was required for the extension of hexoses from C-6 which at the same time allowed further reaction at the site of extension. A promising approach to this problem appeared to involve the synthesis and subsequent base-promoted alkylation of such nitrile derivatives as **7** and **8**. The ready availability of 6-bromo-6-deoxy derivatives from 4,6-*O*-benzylidene derivatives[1] led us to an examination of methods for displacing bromide with cyanide ion. We now report a new high-yielding method for achieving this end, based on the *in situ* preparation of tetrabutylammonium cyanide.

The C-6 nitrile **3** was prepared as follows. Treatment[1] of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside[2] (**1**) with *N*-bromosuccinimide gave methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside (**2**) in high yield. Reaction of **2** with tetrabutylammonium cyanide[3] in refluxing acetonitrile gave the nitrile **3** isolated in poor yield after extensive chromatography. *O*-Debenzoylation of **3** gave an alcohol which could not be benzylated or methoxymethylated. Presumably, formation of an anion from HO-4 led to an intramolecular reaction with the cyano group. The bromide **2** was therefore converted *via* methyl 6-bromo-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside (**4**) into the 4-*O*-methoxyethoxymethyl (**5**) and 4-*O*-benzyl (**6**) derivatives under standard conditions (see Experimental), and a method for converting these compounds into the desired nitriles was sought.

As tetrabutylammonium cyanide is extremely deliquescent, an attempt was made to prepare the reagent *in situ* from the corresponding tetrafluoroborate and sodium cyanide. Thus, treatment of bromides **5** or **6** with tetrabutylammonium tetrafluoroborate and sodium cyanide in 1:1 *N*,*N*-dimethylformamide–acetonitrile at room temperature for 7 days gave the nitriles **7** (83%) and **8** (78%), respectively.

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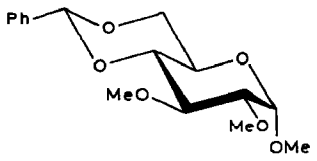

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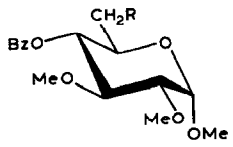
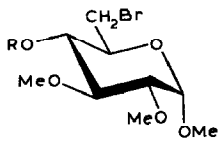
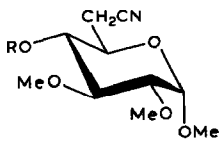


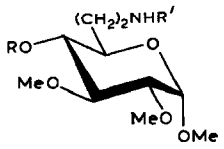
2 R = Br
3 R = CN



4 R = H
5 R = $MeOCH_2CH_2OCH_2$
6 R = Bzl



7 R = $MeOCH_2CH_2OCH_2$
8 R = Bzl
11 R = H



9 R = Bzl, R′ = H
10 R = Bzl, R′ = Ac

Heating of the reaction mixtures caused decomposition. The structure of **8** was confirmed by reduction ($LiAlH_4$ in ether at 0°) to the amine **9**, which was acetylated (pyridine/acetic anhydride) to give 7-acetamido-4-*O*-benzyl-6,7-dideoxy-2,3-di-*O*-methyl-α-D-*gluco*-heptopyranoside (**10**).

Attempted alkylation of the nitriles **7** and **8** was unsuccessful. Treatment with a variety of strong bases (lithium di-isopropylamide, potassium hexamethyldisilazide, sodium hydride, lithium diethylamide, and *tert*-butyl-lithium) either in the presence of, or followed by addition of, methyl iodide gave only recovered starting material. Attempted deuteration also failed and it is apparent that no α-carbanion was formed.

EXPERIMENTAL

^{1}H-N.m.r. spectra were recorded at 250 MHz with a Bruker WM250 instrument, and ^{13}C-n.m.r. spectra at 22.6 MHz with a Bruker HFX90 instrument, for solutions in $CDCl_3$ (internal Me_4Si). I.r. spectra were recorded with a Perkin–Elmer 297 instrument, with polystyrene (1601 cm^{-1}) as standard. Mass spectra were recorded with an A.E.I. MS30 instrument. Melting points were measured with a Gallenkamp heated-block apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 141 automatic polarimeter, using a 10-cm cell. Column chromatography was carried out on silica gel 60 (Merck, 230–400 mesh). Preparative and analytical t.l.c. was performed on Merck silica gel 60 GF-254 and F-254 (Merck), respectively, with detection by u.v. light or by charring with H_2SO_4. Ether was distilled from lithium aluminium hydride before use. Tetrahydrofuran was dried over potassium hydroxide and distilled from lithium aluminium hydride. Light petroleum refers to the fraction b.p. 40–60°.

Methyl 4-O-benzoyl-6-cyano-6-deoxy-2,3-di-O-methyl-α-D-glucopyranoside

(**3**). — To a solution of methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside (0.8 g, 2.0 mmol) in acetonitrile (50 mL) was added tetrabutylammonium cyanide (2.0 g, 7.5 mmol). The mixture was stirred at 70° for 2.5 h and then concentrated under reduced pressure, and the residue was partitioned between dichloromethane and water. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (2:1 light petroleum–ethyl acetate) of the residue gave **3** (0.5 g, 75%) as a light-brown oil, $[\alpha]_D^{20}$ +44° (*c* 11, chloroform); ν_{max}^{film} 2250 (C≡N) and 1729 cm^{-1} (C=O). Mass spectrum: *m/z* 335 (M^+), 304 (M^+ − OMe) (Found: 335.1386. $C_{17}H_{21}NO_6$ requires 335.1369). N.m.r. data: ^1H, δ 8.07 (m, 2 H, aromatic), 7.62 (m, 1 H, aromatic), 7.48 (m, 2 H, aromatic), 5.01 (dd, 1 H, *J* 10.0 and 9.0 Hz, H-4), 4.93 (d, 1 H, *J* 3.5 Hz, H-1), 4.09 (m, 2 H, H-5,6*e*), 3.73 (t, 1 H, *J* 9.5 Hz, H-6*a*), 3.57, 3.54, and 3.49 (3 s, each 3 H, MeO-1,2,3), 3.51 (t, 1 H, *J* 9.0 Hz, H-3), 3.39 (dd, 1 H, *J* 3.6 and 9.0 Hz, H-2); ^{13}C, δ 185.3 (C=O), 133–128 (aromatics), 116.4 (CN), 97.5 (C-1), 81.0 and 80.3 (C-2,3), 73.6 (C-4), 65.5 (C-5), 60.8 and 59.0 (MeO-2,3), 55.4 (MeO-1), 20.9 (C-6).

Methyl 6-bromo-6-deoxy-2,3-di-O-methyl-α-D-*glucopyranoside* (**4**). — To a solution of methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2,3-di-*O*-methyl-α-D-glucopyranoside[3] (**2**; 1.0 g, 2.57 mmol) in methanol (75 mL) was added methanolic M sodium methoxide (2 mL). When the reaction was complete, as determined by t.l.c. (1:1 light petroleum–ethyl acetate), the mixture was neutralised with Zeocarb 225 (H^+) resin, filtered, and concentrated under reduced pressure. Flash chromatography (1:1 light petroleum–ethyl acetate) of the residue gave **4** (0.67 g, 92%), $[\alpha]_D^{20}$ +110.5° (*c* 0.3, chloroform); ν_{max}^{film} 3490 (OH), 2920 and 2838 cm^{-1} (CH). Mass spectrum: *m/z* 253/255 (M^+ − OMe), 221/223 (M^+ − OMe − MeOH), 173 (M^+ − HBr − MeOH). N.m.r. data: ^1H, δ 4.89 (d, 1 H, *J* 3.7 Hz, H-1), 3.75 (m, 2 H, H-6,6), 3.64 (s, 3 H, MeO-1), 3.50 and 3.47 (2 s, each 3 H, MeO-2,3), 3.4-3.7 (m, 3 H, H-3,4,5), 3.27 (dd, 1 H, *J* 3.7 and 9.5 Hz, H-2), 3.71 (d, 1 H, *J* 2.6 Hz, OH); ^{13}C, δ 97.5 (C-1), 82.8 and 81.9 (C-2,3), 71.8 (C-4), 70.0 (C-5), 61.2 and 58.5 (MeO-2,3), 55.4 (MeO-1), 33.4 (C-6).

Anal. Calc. for $C_9H_{17}BrO_5$: C, 37.90; H, 6.05. Found: C, 37.64; H, 5.72.

*Methyl 6-bromo-6-deoxy-4-*O*-(methoxyethoxymethyl)-2,3-di-*O*-methyl-α-D-glucopyranoside* (**5**). — A solution of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside[3] (**1**; 6.5 g, 0.02 mol) in carbon tetrachloride was boiled under reflux for 1 h with *N*-bromosuccinimide (4.5 g, 25 mmol) and barium carbonate (4.5 g, 38 mmol), then cooled, filtered, and concentrated under reduced pressure. A solution of the residual brown oil in methanol (150 mL) was stirred with methanolic M sodium methoxide (5 mL) for 12 h, then neutralised with (H^+) resin, and concentrated. A solution of the residual dark oil in dichloromethane was treated with activated charcoal, filtered through Celite, and concentrated under reduced pressure. A solution of the oily residue in dry tetrahydrofuran (150 mL) was boiled under reflux for 12 h with sodium hydride (60% dispersion in oil; 1.6 g, 0.04 mol) and methoxyethoxymethyl chloride (5.0 g, 0.04 mol). The reaction was

then quenched with methanol and concentrated under reduced pressure. The resulting oil was partitioned between dichloromethane and water, and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (light petroleum–ethyl acetate gradient) of the residue gave **5** (3.4 g, 44%), $[\alpha]_D^{25}$ +138° (*c* 0.3, chloroform); ν_{max}^{film} 2916, 2920, 2900, and 2812 cm^{-1} (CH). Mass spectrum: *m/z* 374/372 (M^+), 343/341 (M^+ – OMe). N.m.r. data: ^1H, δ 3.23 (dd, 1 H, *J* 3.7 and 9.1 Hz, H-2), 3.4–3.5 (m, 10 H, H-3,4,5,6,6 and OCH_2CH_2O), 3.40, 3.46, 3.51, and 3.58 (4 s, each 3 H, MeO-1,2,3 and MEM-OMe), 4.86 (d, 1 H, *J* 3.7 Hz, H-1), 4.87 and 4.98 (AB, 2 H, *J* 6.6 Hz, OCH_2O); ^{13}C, δ 33.5 (C-6), 55.3 (MeO-1), 58.8 (MEM-OMe), 59.0 and 60.9 (MeO-2,3), 68.1 (OCH_2CH_2OMe), 69.6 and 71.8 (C-4,5), 71.8 (OCH_2CH_2OMe), 81.9 and 82.9 (C-2,3), 97.0 (C-1), 97.3 (OCH_2O).

Anal. Calc. for $C_{13}H_{25}BrO_7$: C, 41.83; H, 6.75. Found: C, 41.92; H, 6.74.

*Methyl 4-O-benzyl-6-bromo-6-deoxy-2,3-di-O-methyl-α-*D*-glucopyranoside* (**6**). — To a solution of **4** (5.6 g, 20 mmol) in dry tetrahydrofuran (125 mL) was added sodium hydride (60% dispersion in oil; 0.91 g, 23 mmol) and benzyl chloride (2.9 g, 0.23 mol). The mixture was boiled under reflux until the reaction was complete, as determined by t.l.c. (2:1 light petroleum–ethyl acetate). The reaction mixture was quenched with a little methanol and diluted with water, the product was extracted into dichloromethane, and the extract was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Flash column chromatography (5:2 light petroleum–ethyl acetate) of the product yielded **6** (3.9 g, 55%), $[\alpha]_D^{20}$ +94° (*c* 5.5, chloroform). N.m.r. data: ^1H, δ 3.26 (dd, 1 H, *J* 3.7 and 9.5 Hz, H-2), 3.38–3.81 (m, 5 H, H-3,4,5,6,6), 3.44, 3.54, and 3.65 (3 s, each 3 H, MeO-1,2,3), 4.68 and 4.91 (AB, 2 H, *J* 10.9 Hz, $PhCH_2$), 4.86 (d, 1 H, *J* 3.3 Hz, H-1), 7.35 (m, 5 H, aromatics); ^{13}C, δ 33.5 (C-6), 55.2 (MeO-1), 58.8 and 60.8 (MeO-2,3), 69.2 (C-5), 75.0 (C-4), 79.4 ($PhCH_2$), 81.9 and 83.4 (C-2,3), 97.4 (C-1), 127.8–137.9 (aromatics).

Anal. Calc. for $C_{16}H_{23}BrO_5$: C, 51.21; H, 6.18. Found: C, 51.41; H, 6.15.

*Methyl 6-cyano-6-deoxy-4-O-(methoxyethoxymethyl)-2,3-di-O-methyl-α-*D*-glucopyranoside* (**7**). — A solution of tetrabutylammonium tetrafluoroborate (7.4 g, 22.4 mmol) and sodium cyanide (1.0 g, 20.4 mmol) in *N,N*-dimethylformamide (50 mL) was stirred for 2 h. A solution of **5** (3.26 g, 8.74 mmol) in acetonitrile (50 mL) was then added. The mixture was stirred for 7 days, then diluted with water, and extracted into dichloromethane. The extract was washed with aqueous sodium chloride, dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatography (2:1 light petroleum–ethyl acetate) of the product gave **7** (2.27 g, 81%), $[\alpha]_D^{20}$ +168° (*c* 0.3, chloroform); ν_{max}^{film} 2250 cm^{-1} (CN). Mass spectrum: *m/z* 319 (M^+), 260 (M^+ – CH_2CH_2OMe), 244 (M^+ – OCH_2CH_2OMe), 228 (M^+ – CH_2CH_2OMe – MeOH), 214 (M^+ – $CH_2OCH_2CH_2OMe$), 212 (M^+ – OCH_2CH_2OMe – MeOH), 182 (M^+ – $CH_2OCH_2CH_2OMe$ – MeOH). N.m.r. data: ^1H, δ 4.97 and 4.83 (AB, 2 H, *J* 6.6 Hz, OCH_2O), 4.83 (d, 1 H, *J* 2.9 Hz, H-1), 3.57, 3.51, 3.46, and 3.40 (4 s, each 3

H, MeO-1,2,3 and MEM-OMe), 3.9–3.5 (m, 6 H, H-4,5 and OCH_2CH_2O), 3.29 (t, 1 H, *J* 9.5 Hz, H-3), 3.23 (dd, 1 H, *J* 3.7 and 9.9 Hz, H-2), 2.95 and 2.75 (ABd, 2 H, *J* 17, 7.7, and 3.3 Hz, H-6,6); ^{13}C, δ 117.4 (CN), 97.5 and 97.2 (C-1 and OCH_2O), 82.8, 81.8, 79.1, 71.7, 68.3, and 66.4 (C-2,3,4,5 and OCH_2CH_2O), 61.1, 59.1, and 59.0 (MeO-2,3 and MEM-OMe), 55.5 (MeO-1), 21.02 (C-6).

Anal. Calc. for $C_{14}H_{35}NO_7$: C, 52.65; H, 7.89; N, 4.33. Found: C, 52.41; H, 7.95; N, 4.33.

Methyl 4-O-benzyl-6-cyano-6-deoxy-2,3-di-O-methyl-α-D-glucopyranoside (**8**). — To a solution of **6** (3.28 g, 8.8 mmol) in *N,N*-dimethylformamide and acetonitrile (100 mL, 1:1) was added tetrabutylammonium tetrafluoroborate (7.4 g, 22.5 mmol) and sodium cyanide (1.0 g, 20.4 mmol). The mixture was stirred for 7 days, then diluted with aqueous sodium chloride, and extracted into dichloromethane. The extract was washed with aqueous sodium chloride, dried (Na_2SO_4), and concentrated under reduced pressure. Flash column chromatography (3:2 light petroleum–ethyl acetate) of the residue gave **8** (2.2 g, 78%), m.p. 91–93° (from light petroleum), $[\alpha]_D^{20}$ +152° (*c* 1, chloroform); ν_{max}^{film} 2250 cm^{-1} (CN). Mass spectrum: *m/z* 321 (M^+), 290 (M^+ − OMe). N.m.r. data: ^1H, δ 2.44 and 2.66 (ABd, 2 H, *J* 11.0, 6.9, and 3.7 Hz, H-6,6), 3.26 (dd, 1 H, *J* 3.6 and 10.0 Hz, H-2), 3.25 (t, 1 H, *J* 9.9 Hz, H-3), 3.44, 3.54, and 3.65 (3 s, each 3 H, MeO-1,2,3), 3.64 (t, 1 H, *J* 9.0 Hz, H-4), 3.77 (d, 1 H, *J* 3.6 Hz, H-1), 4.62 and 4.94 (AB, 2 H, *J* 11.3 Hz, $PhCH_2$), 7.35 (m, 5 H, aromatics); ^{13}C, δ 20.7 (C-6), 55.4 (MeO-1), 59.0 and 60.9 (MeO-2,3), 66.2 (C-5), 75.0 (C-4), 79.8 ($PhCH_2$), 81.9 and 83.3 (C-2,3), 97.5 (C-1), 116.9 (CN), 128–138 (aromatics).

Anal. Calc. for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.35. Found: C, 63.29; H, 7.07; N, 4.30.

Methyl 7-acetamido-4-O-benzyl-6,7-dideoxy-2,3-di-O-methyl-α-D-gluco-heptopyranoside (**10**). — Lithium aluminium hydride (17 mg, 0.63 mmol) was stirred at 0° under nitrogen in dry ether (5 mL), and a solution of **8** (0.1 g, 0.3 mmol) in dry ether (1 mL) was added; this was followed, after 5 min, by water (0.1 mL), aqueous 20% sodium hydroxide (0.075 mL), and water (0.35 mL). The solution was filtered, the insoluble material was washed with ether, and the combined filtrate and washings were dried (Na_2SO_4) and concentrated under reduced pressure. The i.r. spectrum of the resulting oil (0.086 g) showed that some **8** still remained. The procedure was repeated, allowing 15 min before quenching. The product was then dissolved in dry pyridine (5 mL), and acetic anhydride (64 mg, 0.64 mmol) was added. When acetylation was complete, as determined by t.l.c. (1:1 light petroleum–ethyl acetate), the reaction was quenched with water, and the product was extracted into dichloromethane. The extract was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The product **10** was obtained as a microcrystalline solid (23 mg, 21%) by preparative t.l.c. (1:1 light petroleum–ethyl acetate); m.p. 124–125° (from light petroleum), $[\alpha]_D^{20}$ +92.5° (*c* 3.4, chloroform); ν_{max}^{film} 3300 br (N–H) and 1655 (C=O) cm^{-1}. Mass spectrum: *m/z* 336 ($M^+ - O_2CH_3$) (Found: 336.1809. $C_{18}H_{26}NO_5$ requires 336.1811). N.m.r. data:

^{1}H, δ 1.6 and 2.1 (2 m, each 1 H, CH_2NHAc), 1.91 (s, 3 H, OAc), 3.38, 3.53, and 3.65 (3 s, each 3 H, MeO-1,2,3), 3.1–3.6 (m, 6 H, H-2,3,4,5,6,6), 4.60 and 4.93 (AB, 2 H, J 11.0 Hz, PhCH_2), 4.79 (d, 1 H, J 3.7 Hz, H-1), 5.84 (brs, 1 H, N–H), 7.35 (m, 5 H, aromatics).

*Methyl 6-cyano-6-deoxy-2,3-di-*O*-methyl-α-*D*-glucopyranoside* (**11**). — To a solution of **3** (0.49 g, 1.5 mmol) in methanol (15 mL) was added sodium methoxide (0.108 g, 2.0 mmol). After 3 h, the mixture was neutralised with Zeocarb 225 (H^+) resin, filtered, and concentrated. Flash column chromatography of the residue gave **9** (0.285 g, 1.2 mmol) as an oil, $[\alpha]_D^{20}$ +99° (c 4.6, chloroform); ν_{max}^{film} 3485 (OH) and 2225 cm^{-1} (C≡N). Mass spectrum: m/z 231 (M^+), 200 (M^+ − OMe) (Found: 200.0928. $C_{10}H_{17}NO_5$ requires 200.0923). N.m.r. data: ^{1}H, δ 4.87 (d, 1 H, J 3.6 Hz, H-1), 3.80 (m, 1 H, H-5), 3.62, 3.49, and 3.46 (3 s, each 3 H, MeO-1,2,3), 3.40 (t, 1 H, J 9.5 Hz, H-4), 3.31 (t, 1 H, J 9.5 Hz, H-3), 3.26 (dd, 1 H, J 3.6 and 9.5 Hz, H-2), 2.75 (ABd, 2 H, J 17.0, 3.5, and 7.0 Hz, H-6,6); ^{13}C, δ 116.9 (CN), 97.2 (C-1), 81.4 and 81.3 (C-2,3), 76.5 (C-4), 66.6 (C-5), 60.8 and 58.1 (MeO-2,3), 55.1 (MeO-1), 20.45 (C-6).

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