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Note

The methyl ether as a protective group: synthesis of aminocyclitols

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Although the conversion of methyl ethers into the corresponding formates, using chromium trioxide in glacial acetic acid, is a mild and easy procedure that does not attack *O*-acyl, acetamido, azido, bromo, trichloroacetamido, and phthalimido groups, few examples are known[1–3], probably due to the poor yields.

The *O*-methyl (protective) group proved to be advantageous in a stereoselective synthesis of inosamines[4] and inosdiamines[5], but the final complete removal remained a major challenge. The moderate yield of the chromium trioxide method applied in the synthesis of 1L-1-azido-1-deoxy-*myo*-inositol[3] prompted an investigation of possible improvements in the procedure.

The modified work-up that was developed avoided the usual treatment with active carbon by reduction of all remaining Cr(VI) with sodium oxalate and neutralisation of the mixture with sodium carbonate prior to extraction with chloroform. The yields achieved in this way now justify the choice of the *O*-methyl protective group in multi-step syntheses.

The following two examples demonstrate the applicability of oxidative cleavage of methyl ethers in aminocyclitol chemistry. The stereoselective preparation[4] of racemic 2-amino-4-bromo-2,4-dideoxy-*myo*-inositol (**9**) started with the methylation of 4,5-dibromocyclohexane-*trans*-1,2-diol (**1**) to give **2**. After elimination of 2 mol of hydrogen bromide from **2**, the resulting *trans*-5,6-dimethoxy-1,3-cyclohexadiene (**3**) was subjected to a Diels–Alder reaction with 1-chloro-1-nitrosocyclohexane to give the bicyclic dihydro-1,2-oxazine derivative **4**, which was reduced to the aminoalcohol and then acetylated to yield **5**. Bromination of the double bond in **5** produced stereoselectively the bromohydrin **6** via neighboring-group participation[6] of the amido function. Acetylation of **6** gave **7**, which was demethylated with chromium trioxide to afford the diformate **8** that was hydrolysed to give **9** (44% from **1**).

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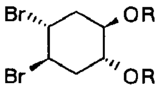
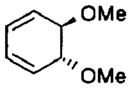
Although requiring one step less, the analogous sequence[7] starting with the diacetate **10** gave an overall yield of **9** from **1** of 27–28%.

Application of the chromium trioxide method gave 4-*O*-acetyl-1,5,6-trideoxy-2,3-di-*O*-formyl-1-phthalimido-5-trichloroacetamido-*muco*-inositol (**12**) accessible in a yield of 83% from the 2,3-di-*O*-methyl precursor **11** (ref. 5), which was *O*-demethylated as described above within 14 h.



1 R = H
2 R = Me
10 R = Ac



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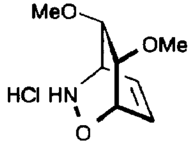

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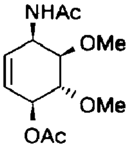

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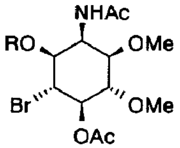
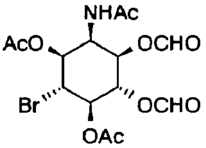


6 R = H
7 R = Ac



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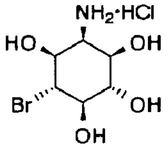

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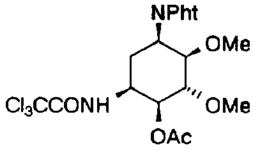

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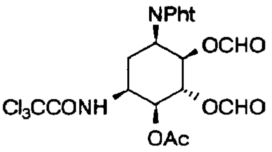
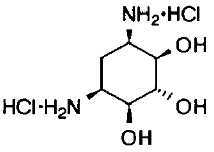
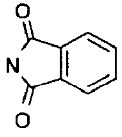


12



13

NPht =



Treatment of **12** with 10 equiv. of hydrazine in ethanol–chloroform (5:2) at 80° yielded the new 2-deoxystreptamine isomer, 1,5-diamino-1,5,6-trideoxy-*muco*-inositol (**13**).

The unique stability of the *O*-methyl protective group recommends its application in multi-step syntheses, since the conversion of hydroxyl groups into methyl ethers, a formerly unrewarding strategy for protection, is no longer limited by low yields on deprotection.

EXPERIMENTAL

Melting points were determined with Büchi SMP-20 and Gallenkamp instruments, and are uncorrected. I.r. spectra were recorded with a Perkin–Elmer IR 397 spectrometer, and ^{1}H- and ^{13}C-n.m.r. spectra with Bruker WM 250 (250 MHz/63 MHz) and WM 300 (300 MHz/75.5 MHz) spectrometers. Microanalysis was performed with a Perkin–Elmer 240 B instrument. Mass spectra were obtained with a Varian MAT 311 instrument at the mass spectroscopy laboratory of the Technische Hochschule Darmstadt. T.l.c. was performed on Silica Gel 60 F_{254} (Merck), using mixtures of ethyl acetate–hexane. Column chromatography was performed on Silica Gel 60 (Merck, 0.063–0.2 mm/70–230 mesh). All solvents were distilled and dried over appropriate molecular sieves before use.

(±)-*2-Acetamido-3,5-di-O-acetyl-4-bromo-2,4-dideoxy-1,6-di-O-methyl*-myo-*inositol* (**7**). — Bromine (419 mg, 2.62 mmol) was added during 45 min to a solution of **5**[4] (677 mg, 2.61 mmol) in dichloromethane (10 mL) at 0°. The mixture was stored at room temperature for 1 h, and the excess of bromine was then removed by the addition of acetone (1 mL). The solvents were removed under reduced pressure, the residue was stirred for 30 min with water (~5 mL), and the pH of the solution was adjusted to 8 with sodium carbonate. The mixture was evaporated and the residue (**6**) was acetylated with acetic anhydride–pyridine (10:1, 11 mL) overnight. The mixture was concentrated *in vacuo*, and a solution of the residue in dichloromethane (100 mL) was washed with 0.01 M HCl (30 mL), saturated aqueous sodium hydrogen carbonate (30 mL), and water (30 mL), then concentrated to give **7** (352 mg, 89%), m.p. 227° (from ethyl acetate–hexane); $\nu_{\max}^{\mathrm{KBr}}$ 3340 (NH), 1750 (acetate C=O), 1645 (amide C=O), 1545 (amide C–N), and 1370 cm^{-1} (acetate C–H). N.m.r. data: ^{1}H (CDCl$_3$, internal Me$_4$Si), δ 5.30 (1 H, $J_{\mathrm{NH},2}$ 8.1 Hz, N–H), 5.10 (1 H, $J_{5,4}$ 10.7, $J_{5,6}$ 9.6 Hz, H-5), 4.92 (2 H, $J_{2,1}$ 4.6, $J_{2,\mathrm{NH}}$ 8.1, $J_{3,4}$ 11 Hz, H-2,3), 4.01 (1 H, $J_{4,3}$ 11, $J_{4,5}$ 10.7 Hz, H-4), 3.47 1 H, $J_{1,2}$ 4.6, $J_{1,6}$ 9.8 Hz, H-1), 3.22 (1 H, $J_{6,5}$ 9.6, $J_{6,1}$ 9.8 Hz, H-6), 3.51 and 3.37 (2 s, each 3 H, 2 OMe), 2.16, 2.08, and 2.06 (3 s, each 3 H, 3 Ac); ^{13}C (CDCl$_3$), δ 170.97, 169.79, 169.39 (3 C=O), 81.1 (C-1), 78.02 (C-6), 73.85 (C-3), 71.33 (C-5), 60.57, 57.47 (2 OMe), 48.25 (C-2), 47.30 (C-4), 23.36, 20.81, 20.64 (3 CH$_3$CO). Mass spectrum (field desorption): *m/z* 398 (88%, $M^{+\cdot}$), 396 (100%, $M^{+\cdot}$), 316 (51%, $M^{+}-$Br).

Anal. Calc. for $C_{14}H_{22}BrNO_7$ (396.238): C, 42.44; H, 5.59; N, 3.53. Found: C, 42.32; H, 5.51; N, 3.47.

(±)-*2-Acetamido-3,5-di-O-acetyl-4-bromo-2,4-dideoxy-1,6-di-O-formyl*-myo-*inositol* (**8**). — To chromium trioxide (1.99 g, 20 mmol) in acetic acid (40 mL) was added **7** (0.793 g, 2 mmol). The mixture was stirred for 5–6 h at room temperature and then diluted with water (60 mL), sodium oxalate (2.25 g, 21 mmol) was added, and the pH was adjusted to 7–8 by addition of sodium carbonate. The mixture was extracted with chloroform (>2 × 200 mL), and the combined extracts were dried (Na$_2$SO$_4$) and concentrated to afford solid **8** (652 mg, 77%), m.p. 222° (from dichloromethane–methanol); $\nu_{\max}^{\mathrm{KBr}}$ 3330 (NH), 2980, 2960 (CHO), 1735 (acetyl C=O), 1650 (amide C=O), and 1550 cm^{-1} (amide C–N). N.m.r. data: ^{1}H (CDCl$_3$, internal Me$_4$Si), δ 8.16 (s, 1 H, CHO), 8.07 (s, 1 H, CHO), 5.63 (1 H, $J_{1,2}$ 4, $J_{1,6}$ 9.0 Hz, H-1), 5.60 (1 H, $J_{NH,2}$ 8.0 Hz, N–H), 5.61 (1 H, $J_{6,1}$ 9, $J_{6,5}$ 11 Hz, H-6), 5.52 (1 H, $J_{5,4}$ 10, $J_{5,6}$ 11 Hz, H-5), 5.41 (1 H, $J_{3,2}$ 4.2, $J_{3,4}$ 12 Hz, H-3), 5.07 (1 H, $J_{2,3}$ 4.2, $J_{2,1}$ 4 Hz, H-2), 4.45 (1 H, $J_{4,5}$ 10, $J_{4,3}$ 12 Hz, H-4), 2.03, 2.01, and 1.99 (3 s, each 3 H, 3 Ac); ^{13}C ($CDCl_3$), δ 170.93, 169.91, 169.09 (3 C=O, Ac), 160.55, 160.26 (2 CHO), 72.36, 70.94, 69.93, 68.22 (C-1,3,5,6), 49.45, 48.53 (C-2,4), 22.48, 20.37, 20.22 (3 CH_3CO); Mass spectrum (field desorption): *m/z* 424 (100%, $M^{+\cdot}$), 426 (83%, $M^{+\cdot}$), 412 (37%), 410 (42%), 408 (39%), 406 (39%).

Anal. Calc. for $C_{14}H_{18}BrNO_9$ (424.20): C, 39.64; H, 4.27; N, 3.30. Found: C, 39.56; H, 4.29; N, 3.26.

(±)-*2-Amino-4-bromo-2,4-dideoxy*-myo-*inositol* (**9**). — A mixture of **8** (424 mg, 1 mmol) and conc. HCl–methanol (1:3, 10 mL) was boiled under reflux for 3 h, then concentrated under reduced pressure. The residue was crystallised from methanol (1 mL) and acetone, to give **9** (269 mg, 96%), m.p. 208°; lit.[7] m.p. 210–213°.

(±)-*4*-O-*Acetyl-1,5,6-trideoxy-2,3-di*-O-*methyl-1-phthalimido-5-trichloroacetamido*-muco-*inositol* (**11**). — The literature procedure[5] was modified. Instead of reaction for 6 h to afford the acetamido derivative of **11**, the dehalogenation was stopped after 2 h to give **11** as the major product, m.p. 183°.

(±)-*4*-O-*Acetyl-1,5,6-trideoxy-2,3-di*-O-*formyl-1-phthalimido-5-trichloroacetamido*-muco-*inositol* (**12**). — To a solution of **11** (400 mg, 0.787 mmol) in glacial acetic acid (20 mL) was added chromium trioxide (1 g, 10 mmol). The mixture was stirred for 14 h at room temperature and then diluted with water (80 mL), sodium oxalate (> 600 mg) was added, the pH of the solution was adjusted to 8 with sodium carbonate, and stirring was continued until the color turned dark green. The mixture was extracted with chloroform (3 × 200 mL), and the combined extracts were dried (Na_2SO_4) and concentrated to give **12** (350 mg, 83%), m.p. 259°; ν_{max}^{KBr} 3210 (NH), 3060, 2980 (CHO), 1730, 1700 (acetyl C=O), and 1660 cm^{-1} (amide C=O). N.m.r. data: ^{1}H ($CDCl_3$, internal Me_4Si), δ 8.16 (1 H, $J < 1$ Hz, CHO), 7.96 (1 H, $J < 1$ Hz, CHO), 7.81 (2 H, aromatic H), 7.75 (2 H, aromatic H), 6.84 (1 H, $J_{NH,5}$ 8.7 Hz, NH), 5.42 (1 H, $J_{4,5}$ 2.5, $J_{4,3}$ 2.8 Hz, H-4), 5.30 (1 H, $J_{3,2}$ 3.1, $J_{3,4}$ 2.8 Hz, H-3), 5.05 (1 H, $J_{2,1}$ 3.0, $J_{2,3}$ 3.1 Hz, H-2), 4.75 (1 H, $J_{1,6a}$ 12.8, $J_{1,6e}$ 3.4, $J_{1,2}$ 3.0 Hz, H-1), 4.55 (1 H, $J_{5,NH}$ 8.7, $J_{5,6a}$ 12.8, $J_{5,6e}$ 3.4, $J_{5,4}$ 2.5 Hz, H-5), 3.38 (1 H, $J_{6a,6e}$ 12.8, $J_{6a,5}$ 12.8, $J_{6a,1}$ 12.8 Hz, H-6*a*), 2.21 (s, 3 H, Ac), 1.99 (1 H, $J_{6e,5}$ 3.4, $J_{6e,6a}$ 12.8, $J_{6e,1}$ 3.4 Hz, H-6*e*); ^{13}C ($CDCl_3$), δ 169.76 (C=O, Ac), 168.06 (C=O, phthaloyl), 165.28 (C=O, amide), 159.62, 158.05 (2 C=O, CHO), 134.37, 131.3, 123.52 (3 C, aromatic), 90.12 (CCl_3), 77.20 (C-4), 68.62, 67.80 (C-3,2), 48.03 (C-1), 46.27 (C-5), 22.63 (C-6), 20.82 (CH_3CO). Mass spectrum (field desorption): *m/z* 534 (92%, $M^{+\cdot}$), 536 (100%, $M^{+\cdot}$), 538 (41%, $M^{+\cdot}$), 540 (8%, $M^{+\cdot}$).

Anal. Calc. for $C_{20}H_{17}Cl_3N_2O_9$ (535.73): C, 44.84; H, 3.20; N, 5.23. Found: C, 44.90; H, 3.26; N, 5.19.

1,5-Diamino-1,5,6-trideoxy-muco-*inositol dihydrochloride* (**13**). — A solution of **12** (500 mg, 0.92 mmol) and anhydrous hydrazine (0.2 mL, 6.5 mmol) in ethanol–chloroform (5:2, 14 mL) was stirred for 20 h at 80°, then concentrated. A solution of the residue in a small amount of water was added to a column (24 × 1.3 cm) of Dowex 50W (H^+) resin and eluted with increasing concentrations of HCl (200 mL each of 0.5, 1.0, 1.5, 2.0, 2.5, and 5M). The fraction eluted with 2M HCl contained **13** (220 mg, 87%), m.p. 264–270° (from methanol–acetone). ^{13}C-N.m.r. data (D_2O, internal 1,4-dioxane δ 67.6): δ 70.22 (C-2,4), 68.83 (C-3), 46.71 (C-1,5), 24.58 (C-6).

Anal. Calc. for $C_6H_{16}Cl_2N_2O_3$ (235.11): C, 30.65; H, 6.86; N, 11.91. Found: C, 30.67; H, 6.95; N, 11.87.

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