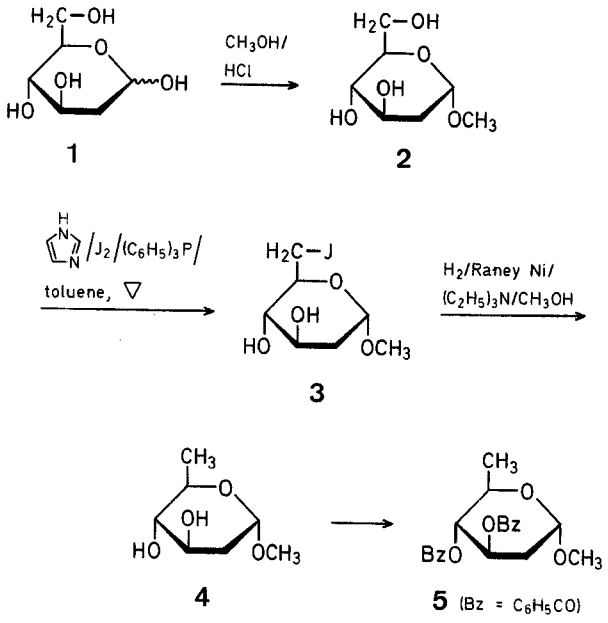

An Expeditious Synthesis of Methyl 2,6-Dideoxy-α-D-*arabino*-hexopyranoside

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Methyl 2,6-dideoxy-α-D-*arabino*-hexopyranoside (**4**), a glycoside isolated from the methanolysis products of a number of antibiotics, *inter alia*, chlorothricin[1], chromomycin A_3[2], curamycin[3], olivomycin[4], and venturicidin B[5], and the methyl glycoside of the deoxy sugar obtained from the leaves of *Digitalis canariensis* L[6], is a potentially useful intermediate for practical alternative syntheses of amino sugar constituents of various antibiotics [e.g., 3-amino-2,3,6-trideoxy-D-*arabino*-hexose (D-acosamine) from sporaviridin[7] and its *N,N*-dimethyl derivative (D-angolosamine) from the macrolide angolamycin[8]] and of the enantiomorph of daunosamine (and analogs or derivatives thereof), the carbohydrate constituent of the anthracycline antitumour antibiotics, daunorubicin[8], and adriamycin[10].

Although a multi-step synthesis of **4** has been reported[11], a more efficient process was desired for studies on the total synthesis of natural products, employing **4** as a chiral synthetic intermediate. The approach taken involved the selective replacement of the C-6 primary hydroxy group in methyl 2-deoxy-α-D-glucopyranoside (**2**)[12] by halogen and subsequent reductive dehalogenation. Compound **2** was readily prepared via 2-deoxy-D-glucose (**1**) in a five-step sequence from D-glucose[12,13].

Initially, introduction of the bromo group at C-6 of **2** was attempted by the triphenylphosphine/*N*-bromosuccinimide method[14]. Although the desired methyl 6-bromo-2,6-dideoxy-α-D-*arabino*-hexopyranoside was obtained from the reaction, ease of isolation required conversion to its 3,4-diacetate, and, on a large scale (0.1 mol), the work-up proved to be unwieldy and yields found to decrease with the size of the reaction.

Consequently, this method was abandoned in favor of the reagent systems developed by Garegg and Samuelsson[15] for converting a hydroxy into an iodo group in carbohydrates: (a) triphenylphosphine, iodine, and imidazole in toluene, and (b) triphenylphosphine and 2,4,5-triiodoimidazole in toluene. With substrate **2**, the operationally simpler reagent system (a) also proved to be the more efficient.

Thus, heating a mixture of **2** (the crude product from the methyl glycosidation of 2-deoxy-D-glucose[12] was used), triphenylphosphine, iodine, and imidazole in molar proportions of 1:1.5:1.4:3 in toluene for 5 h afforded, after purification by preparative H.P.L.C. on silica gel, syrupy methyl 2,6-dideoxy-6-iodo-α-D-*arabino*-hexopyranoside (**3**) in 76% yield. Reductive deiodination was readily achieved by catalytic hydrogenation in methanol in the presence of Raney nickel and triethylamine. Chromatographically homogeneous methyl 2,6-dideoxy-α-D-*arabino*-hexopyranoside (**4**) was obtained in 88% yield, which was characterized by conversion in quantitative yield into the known[11] crystalline 3,4-dibenzoate (**5**).

Melting points were determined with a Thomas-Hoover "Unimelt" apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. N.M.R. spectra were recorded at 300 MHz with a Varian SC-300 N.M.R. spectrometer; chemical shifts are given on the δ scale with tetramethylsilane (δ = 0.00) as the internal standard. H.P.L.C. was performed on dual Prep-PAK™ 500 silica columns using a Waters Associates Prep LC/System 500.

Methyl 2,6-Dideoxy-6-iodo-α-D-*arabino*-hexopyranoside (3):
A mixture of crude methyl 2-deoxy-α-D-glucopyranoside[12] (**2**; 6.0 g, 33.7 mmol), imidazole (6.88 g, 101 mmol), iodine (11.96 g, 47.1 mmol), and triphenylphosphine (13.25 g, 50.5 mmol) in toluene (450 ml) is stirred for 5 h at 75 °C, cooled, and filtered through Celite. The gummy residue in the reaction vessel is triturated with chloroform and the resulting solid filtered. The combined filtrates are evaporated and the syrup subjected to preparative H.P.L.C. on silica gel with 2:1 chloroform/ethyl acetate as eluent to remove T.L.C. more-mobile impurities and a small amount of the less-mobile β-anomer of **3**. Evaporation of the appropriate fractions gave pure syrupy **3**; yield: 7.4 g (76%); $[\alpha]_D^{27}$: +97° (*c* 0.9, chloroform).

$C_7H_{13}JO_4$	calc.	C 29.18	H 4.55	J 44.05
(288.1)	found	29.12	4.72	43.88

^{1}H-N.M.R. (D_2O): δ = 1.76 (m, H-2ax, $J_{H\text{-}1,H\text{-}2ax}$ = 3.7 Hz, $J_{H\text{-}2ax,H\text{-}2eq}$ = 13.4 Hz, $J_{H\text{-}2ax,H\text{-}3}$ = 11.8 Hz); 2.18 (broad dd, H-2eq, $J_{H\text{-}2eq,H\text{-}3}$ = 5.0 Hz); 3.43 (s, OCH_3); 3.91 (oct, H-5); 4.92 ppm (broad d, H-1).

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Methyl 2,6-Dideoxy-α-D-*arabino*-hexopyranoside (4):
A mixture of **3** (6.45 g, 22.4 mmol), triethylamine (2 ml), and Raney nickel (~10 g) in methanol (150 ml) is hydrogenated at a pressure of 2.7 atm for 48 h at room temperature. The catalyst is then removed by filtration through Celite and the filtrate evaporated. The resulting syrup is dissolved in a small volume of methanol (~5 ml) and the solution passed through a short column of AG501-X8 mixed bed resin to remove triethylamine hydroiodide. The effluent is evaporated, the syrup dissolved in a small volume of chloroform (~5 ml), and the solution passed through a short column of silica gel (Merck # 7734), with 25:1 chloroform/methanol as eluent, to remove nickel salts. Pure **4** is obtained as a chromatographically homogeneous syrup (T.L.C. on silica gel, 9:1 chloroform/methanol); yield: 3.2 g (88%).

$C_7H_{14}O_4$	calc.	C 51.84	H 8.70
(162.2)	found	51.55	8.63

^{1}H-N.M.R. (D_2O): $\delta = 1.29$ (d, C—CH_3); 1.74 (m, H-2ax, $J_{H\text{-}1,H\text{-}2ax} = 3.6$ Hz, $J_{H\text{-}2ax,H\text{-}2eq} = 13.5$ Hz); 2.16 (broad dd, H-2eq, $J_{H\text{-}2eq,H\text{-}3} = 5.0$ Hz); 3.13 (t, H-4, $J_{H\text{-}3,H\text{-}4} = J_{H\text{-}4,H\text{-}5} = 9.5$ Hz); 3.36 (s, OCH_3); 3.72 (m, H-5); 3.85 (m, H-3); 4.87 ppm (broad d, H-1).

Treatment of **4** with benzoyl chloride in pyridine affords crystalline methyl 3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (**5**); yield: 100%; m.p. 80–83 °C; $[\alpha]_D^{27}$: 0° (*c* 0.9, chloroform); Lit.[11], m.p. 93–94 °C; $[\alpha]_D$: −0.5° (*c* 1.0, chloroform).

The ^{1}H-N.M.R. spectral data for **5** in $CDCl_3$ were in excellent agreement with reported values[11].

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