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Note

A concise synthesis of methyl 2,6-dideoxy-2-fluoro-β-L-talopyranoside☆

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Abstract

The 4,6-benzylidene acetal of methyl 2-deoxy-2-fluoro-α,β-D-glucopyranoside underwent inversion at C-3 via an oxidation–reduction sequence, and treatment of the derived 3-acetate with *N*-bromosuccinimide in carbon tetrachloride gave methyl 3-*O*-acetyl-4-*O*-benzoyl-6-bromo-2,6-dideoxy-2-fluoro-α-D-allopyranoside (**6**). Dehydrobromination of **6** and reduction of the resultant 5,6-ene gave the 5-epimer of **6**, which after removal of the ester substituents, afforded the title compound in good overall yield.

Keywords: Fluoro sugars; 2,6-Dideoxy-2-fluoro-L-talose; Configurational inversion; Anthracycline glycons

1. Introduction

Semisynthetic anthracycline glycosides based on the 3′-deamino-3′-hydroxydoxorubicin structure [2] and having an axial halogen atom at the C-2′ position have shown [3] promise as antitumor agents. The 2′-iodo structures are readily generated [3] by alkoxyhalogenation from appropriate glycal precursors, and the 2′-bromo and 2′-chloro analogs can be conveniently produced [4] via halogenation of glycals and subsequent glycosidic coupling. The corresponding 2′-fluoro structures are not similarly accessible from glycals, and alternative procedures are necessary [5] to construct the required 2,6-dideoxy-2-fluoro-L-talopyranose precursor sugar.

Here we present a concise synthesis of this fluoro sugar, as its methyl β-glycoside **9**, utilizing as precursor 2-deoxy-2-fluoro-α-D-glucopyranose tetraacetate, itself accessible [6] in two steps from D-mannose. The sequence is closely modeled after the methodology successfully utilized in this laboratory [7] for synthesis of daunosamine from D-mannose, and affords **9** in 27% net yield on all steps.

2. Results and discussion

The synthesis begins from 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucopyranose, which was prepared by treating β-D-mannopyranose-1,3,4,6-tetraacetate with diethylaminosulfur trifluoride by the method of Kováč [6]. Glycosidation and deacetylation of this compound was accomplished in a single step with

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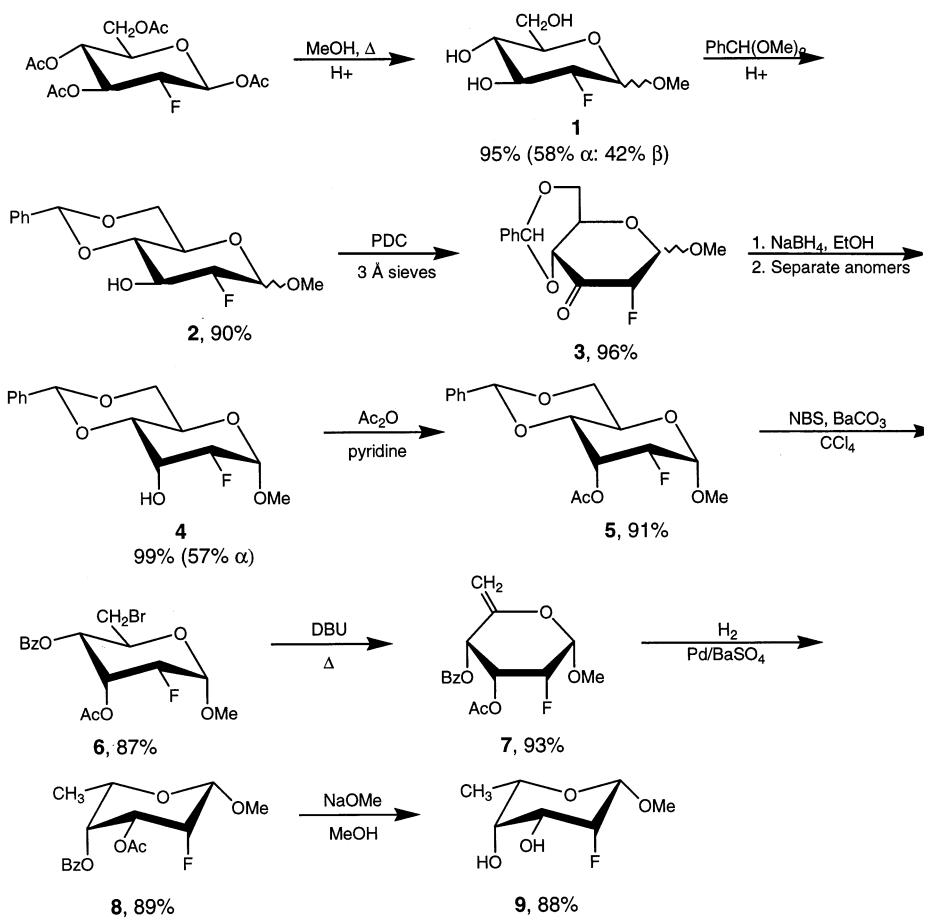
Dowex-50W (H^+) resin in refluxing methanol. The products of the reaction proved to be an inseparable mixture (**1**) of the methyl α- and β-glycosides, with an anomeric composition of 58% α and 42% β as determined by ^1H NMR spectroscopy. Benzylidenation of this anomeric mixture was carried out using a modification of the procedure of Evans [8]. The anomers could be separated at this point by careful chromatography; however, in view of the difficulty involved in the chromatography and the resulting decrease in yield, the anomeric mixture **2** was used in the next step without further purification (Scheme 1).

Inversion of the stereochemistry at C-3 of **2** was accomplished via a stereospecific oxidation–reduction procedure. The oxidation was carried out using the methodology developed by Herscovici and Antonakis [9] for the molecular sieve-assisted oxidation of carbohydrates. Pyridinium dichromate (PDC) was freshly prepared according to the procedure of Corey and Suggs [10], and the molecular sieves (3 Å) were dried overnight at 160 °C in vacuo. The product was only slightly soluble in dichloromethane, the reaction solvent, and it precipitated out as a fluffy white solid upon cooling or partial evaporation of the solvent. Again, the anomers could be separated by careful chromatography, but the product was used without further purification in the next step. Reduction of the resulting ketone **3** was accomplished with sodium borohydride in ethanol. Because of the large difference in R_f values ($\Delta R_f = 0.1$) of the reduction products of the α and β anomers, the desired α product **4** was easily separated from the product mixture. In a separate experiment using the pure α anomer of **3**, the reduction was shown to be stereospecific, that is, the reaction product was the desired D-*allo* isomer with no trace of the D-*gluco* isomer being detected. This fact was established by comparing the ^1H NMR spec-



Scheme 1.

tra of **2** and **4**, which show $J_{2,3} = 8.9$ Hz for **2**, as would be expected for the *trans*-diaxial relationship of these protons in a D-glucose derivative and $J_{2,3} = 3.5$ Hz for **4**, as would be expected for the axial–equatorial relationship of these protons in a D-allose derivative.

Compound **4** was acetylated at OH-3 using acetic anhydride and pyridine to give **5** in 91% yield. Opening of the benzylidene acetal ring of **5** was performed with *N*-bromosuccinimide (NBS) using standard Hanessian–Hullar [11] conditions for this type of reaction, to give **6** as colorless needles from ethanol. The dehydrobromination of **6** was accomplished with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene to give the 5,6-unsaturated derivative **7** as a low-melting solid that was unstable at room temperature, but which could be stored at −20 °C for short periods.

Inversion of the stereocenter at C-5 in **6** was completed by hydrogenation of the alkene product **7** in dry ethyl acetate over 10% palladium–barium sulfate. Previous studies in this laboratory [7] indicated that hydrogenation of a 5,6-unsaturated sugar derivative with a stereochemistry comparable with **7** would lead to stereospecific addition of hydrogen from above the sugar ring to yield the desired L-*talo* product **8**. This was confirmed by ^{1}H NMR spectroscopy, which demonstrated a $J_{1,F}$ value of 18.5 Hz characteristic of a *trans*-diaxial relationship between fluorine and the C-1 proton, and indicative of the $^1C_4$ conformation of this compound, which is to be expected for this L sugar derivative. The synthesis was completed by deacylation of **8** with methanolic sodium methoxide to yield **9** as a crystalline solid, in 27% overall yield from 2-deoxy-2-fluoro-β-D-glucopyranose tetraacetate.

3. Experimental

General methods.—Solvents were purified and dried as recommended [12] and were evaporated under diminished pressure below 50 °C. TLC was performed on precoated glass plates (0.25 mm) of Silica Gel 60 F254 (E. Merck); detection was performed by spraying with H_2SO_4 and subsequent heating. Flash chromatography was performed as recommended [13] with Silica Gel 60 (230–400 mesh, E. Merck). Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter at ~25 °C. ^{1}H and ^{13}C NMR spectra at 500 and 125 MHz, respectively, were recorded by Dr C.E. Cottrell with a Bruker AM 500 instrument (unless otherwise noted). The ^{19}F spectra at 235 MHz were recorded by C. Engelman with a Bruker AM 250 instrument. Chemical shifts are in ppm from Me_4Si, measured from the $CHCl_3$ lock signal at δ 7.26. Mass spectra were obtained with a VG 70-250S mass spectrometer in the FAB mode in a 'magic bullet' matrix and were recorded by D. Chang. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Methyl 2-deoxy-2-fluoro-α,β-D-glucopyranoside (**1**).—To a solution of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucopyranose [6] (4.28 g, 12.2 mmol) in 60 mL of dry MeOH, Dowex-50W (H^+) resin (12.8 g), which had been exhaustively washed with dry MeOH and dried overnight in vacuo at 50 °C, was added. The resulting mixture was boiled under reflux for 48 h at 75–78 °C, at which time TLC (4:1 $CHCl_3$–MeOH) revealed a single spot, R_f 0.57. The mixture was diluted with $CHCl_3$ (240 mL) and filtered through a sintered glass funnel containing a small pad of silica gel with 10% $MgSO_4$. Removal of the solvent gave a colorless oil, which by NMR spectroscopy, was a mixture of anomers (58% α, 42% β); yield 2.27 g (95%). This oil was used in the next step without further purification. An analytical sample of the anomeric mixture was obtained by flash chromatography with 4:1 $CHCl_3$–MeOH; $[\alpha]_D$ +76.6° (*c* 1.1, H_2O); MS: *m/z* 197 (M + 1), 165 (M + 1 − MeOH), 177 (M + 1 − HF); ^{1}H NMR (500 MHz, Me_2SO-d_6): δ 4.83 (d, $J_{1,2} = 3.8$ Hz, H-1α), 4.41 (dd, $J_{1,2} = 7.7$ Hz, $J_{1,F} = 2.2$ Hz, H-1β). Anal. Calcd for $C_7H_{13}FO_5$ (196.19): C, 42.85; H, 6.69. Found: C, 42.70; H, 6.70.

Methyl 4,6-O-benzylidene-2-deoxy-2-fluoro-α,β-glucopyranoside (**2**).—To a suspension of **1** (2.27 g, 11.6 mmol) in dry MeCN (50 mL), α,α-dimethoxytoluene (2.78 mL, 18.5 mmol) and *p*-toluenesulfonic acid (26 mg) were added. After 2 h, TLC (1:1 hexane–EtOAc)

indicated only a trace of **1** remaining. The solvent was removed at 40 °C to yield a slightly opaque oil that showed no **1** by TLC. The oil was dissolved in boiling ether, and the resulting solution was cooled to −20 °C. This gave a white solid, which by TLC was an anomeric mixture. The total yield of product after processing of mother liquors was 2.96 g (90%). This solid was used in the next step without further purification. An analytical sample of the α anomer was obtained by flash chromatography with 2:1 hexane–EtOAc; mp 155–156 °C, $[\alpha]_D$ +106° (*c* 1, $CHCl_3$), (lit. [14] mp 163–164 °C, $[\alpha]_D$ +116.3°); MS: *m/z* 285 (M + 1), 253 (M + 1 − MeOH), 207 (M + 1 − Ph), 179 (M + 1 − PhCHO). Anal. Calcd for $C_{14}H_{17}FO_5$ (284.30): C, 59.14; H, 6.04. Found: C, 59.06; H, 6.06.

*Methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-α,β-*D*-ribo-hexopyranosid-3-ulose* (**3**).—To a solution of **2** (1.16 g, 4.08 mmol) in dry CH_2Cl_2 (50 mL), pyridinium dichromate (2.30 g, 6.12 mmol) and crushed 3 Å molecular sieves (4.0 g, dried overnight at 160 °C in vacuo) were added. After 4 h, TLC (2:1 hexane–EtOAc) indicated no starting material. The mixture was diluted with ether (250 mL) and filtered through a sintered glass funnel containing a small pad of silica gel with 10% $MgSO_4$. Evaporation of the solvent gave the product as a white solid; yield 1.10 g (96%). This solid was used in the next step without further purification. An analytical sample of the α anomer was obtained by flash chromatography with 1:1 hexane–EtOAc; mp 216–217 °C (dec.), $[\alpha]_D$ +114° (*c* 1, $CHCl_3$), ν_{max} 1754 cm^{-1} (CO); MS: *m/z* 283 (M + 1), 251 (M + 1 − MeOH), 177 (M + 1 − PhCHO). Anal. Calcd for $C_{14}H_{15}FO_5$ (282.28): C, 59.56; H, 5.37. Found: C, 59.34; H, 5.42.

*Methyl 4,6-*O*-benzylidene-2-deoxy-2-fluoro-α-*D*-allopyranoside* (**4**).—A solution of **3** (0.90 g, 3.17 mmol) in EtOH (50 mL) was cooled to −20 °C and $NaBH_4$ (0.362 g, 9.57 mmol) was added. The mixture was allowed to warm slowly to room temperature, at which point it became homogeneous. The excess borohydride was decomposed by dropwise addition of 1.0 M HOAc until effervescence ceased. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2 (50 mL). The resulting solution was washed with satd aq $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), and the solvent was evaporated to yield an oil, which was adsorbed onto a small amount of silica gel and purified by flash chromatography with 3:2 hexane–EtOAc to furnish first a solid (0.38 g, 42%) that was shown by NMR spectroscopy to be a 2:1 mixture of the β anomer of **4** and its 3-epimer. Continued elution of the column gave **4** (0.52 g, 57%) as a white, crystalline solid; mp 109–110 °C, $[\alpha]_D$ +126° (*c* 1, $CHCl_3$); MS: *m/z* 285 (M + 1), 253 (M + 1 − MeOH), 179 (M + 1 − PhCHO). Anal. Calcd for $C_{14}H_{17}FO_5$ (284.3): C, 59.14; H, 6.04. Found: C, 59.22; H, 6.08.

*Methyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-fluoro-α-*D*-allopyranoside* (**5**).—To a solution of **4** (0.52 g, 1.83 mmol) in dry pyridine (20 mL) at 0 °C, Ac_2O (10 mL) and a catalytic amount of 4-dimethylaminopyridine were added and the solution was left overnight to warm to room temperature. Removal of the solvent using toluene for azeotropic removal of pyridine gave a yellow oil that was filtered through a short column of silica gel with 2:1 hexane–EtOAc to yield **5** (0.544 g, 91%) as a crystalline solid after drying in vacuo at 50 °C; mp 79–80 °C, $[\alpha]_D$ +91° (*c* 1.4, $CHCl_3$); MS: *m/z* 327 (M + 1), 295 (M + 1 − MeOH), 267 (M + 1 − HOAc), 221 (M + 1 − PhCHO). Anal. Calcd for $C_{16}H_{19}FO_6$ (326.34): C, 58.88; H, 5.88. Found: C, 58.94; H, 5.91.

*Methyl 3-*O*-acetyl-4-*O*-benzoyl-6-bromo-2,6-dideoxy-2-fluoro-α-*D*-allopyranoside* (**6**).—Dry CCl_4 (50 mL) was filtered over alumina into a round-bottom flask containing a mixture of **5** (0.888 g, 2.72 mmol), NBS (0.533 g, 2.99 mmol), and $BaCO_3$ (0.537 g, 2.72 mmol). (Note: The NBS and $BaCO_3$ had been dried in vacuo for 3 h at 80 °C.) The resulting mixture was stirred vigorously at 75–80 °C under reflux until the usual color changes were complete (ca. 20 min), at which time TLC (2:1 hexane–EtOAc) indicated that no starting material was present. The mixture was filtered through Celite, and the filter cake was washed with hot CCl_4 (200 mL). The solvent was removed, and the residue was dissolved in CH_2Cl_2 (100 mL). The resulting solution was washed with satd aq $NaHCO_3$

and brine, dried (Na_2SO_4), and the solvent removed to yield a light-yellow solid. This solid was recrystallized from 95% EtOH to yield **6** (0.961 g, 87%) as colorless needles; mp 149–150 °C, $[\alpha]_D$ +105° (*c* 1, $CHCl_3$); MS: *m/z* 405 (M^+), 373 ($M^+ - MeOH$), 327 ($M + 1 - HBr$). Anal. Calcd for $C_{16}H_{18}BrFO_6$ (405.23): C, 47.42; H, 4.49; Br, 19.72. Found: C, 47.49; H, 4.52, Br, 19.66.

Methyl 3-O-acetyl-4-O-benzoyl-2,6-dideoxy-2-fluoro-α-D-ribo-hex-5-enopyranoside (**7**).—A solution of **6** (0.101 g, 0.249 mmol) in 5 mL of dry benzene was heated to reflux, and DBU (0.075 mL, 0.499 mmol) was added to the hot solution under argon. After 2 h, TLC (2:1 hexane–EtOAc) indicated incomplete reaction. An additional 0.038 mL of DBU was added, and the reaction was allowed to continue for 30 min, at the end of which time TLC indicated that all of the starting material had been consumed. The mixture was diluted with benzene, washed with 5% HCl (2 × 15 mL), satd aq $NaHCO_3$ (2 × 15 mL) and H_2O (1 × 15 mL), dried (Na_2SO_4), and the solvent was removed in vacuo to yield **7** (0.075 g, 93%) as a chromatographically homogeneous, very low melting solid; $[\alpha]_D$ +91° (*c* 1, $CHCl_3$); MS: *m/z* 325 (M + 1), 293 (M + 1 − MeOH), 265 (M + 1 − HOAc). Anal. Calcd for $C_{16}H_{17}FO_6$ (324.32): C, 59.25; H, 5.29. Found: C, 59.18; H, 5.33.

Methyl 3-O-acetyl-4-O-benzoyl-2,6-dideoxy-2-fluoro-β-L-talopyranoside (**8**).—To a solution of **7** (0.643 g, 1.98 mmol) in dry EtOAc (10 mL), 10% $Pd/BaSO_4$ (0.090 g) was added and hydrogen was gently bubbled into the mixture. The reaction was complete in 30 min by TLC (2:1 hexane–EtOAc). The mixture was filtered through Celite, and the solvent evaporated. The residue was filtered through a short column of silica gel with 2:1 hexane–EtOAc to yield **8** (0.573 g, 89%) as a thick colorless oil; $[\alpha]_D$ −1.3° (*c* 1.88, $CHCl_3$); MS: *m/z* 327 (M + 1), 307 (M + 1 − HF), 295 (M + 1 − MeOH). Anal. Calcd for $C_{16}H_{19}FO_6$ (326.34): C, 58.88; H, 5.88. Found: C, 58.96; H, 5.94.

Methyl 2,6-dideoxy-2-fluoro-β-L-talopyranoside (**9**).—To a solution of **8** (0.455 g, 1.39 mmol) in dry MeOH (20 mL), a 25% methanolic NaOMe solution (0.160 mL) was added. The reaction was complete in 10 min by TLC (1:1 hexane–EtOAc). An excess of solid CO_2 was added, and the solvent was removed. The residue was taken up in EtOAc and filtered through a short column of silica gel with EtOAc to yield **9** (0.220 g, 88%) as a white solid; mp 136–137 °C, $[\alpha]_D$ +63.7° (*c* 1.45, $CHCl_3$); MS: *m/z* 181 (M + 1), 161 (M + 1 − HF), 149 (M + 1 − MeOH). Anal. Calcd for $C_7H_{13}FO_4$ (180.19): C, 46.66; H, 7.29. Found: C, 46.40; H, 7.24.

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