Stereoselective Synthesis of 3′-Deoxy-3′-fluoroadenosine

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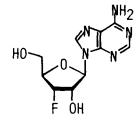
Synopsis. A new fluorinated nucleoside, 3′-deoxy-3′-fluoroadenosine(**1**), has been synthesized by a six-step synthesis from methyl 2-*O*-benzyl-5-*O*-*t*-butyldimethylsilyl-β-D-xylofuranoside (**2a**). Activation of O-3 by formation of a triflate followed by nucleophilic displacement allowed introduction of fluoride ion in a stereospecific manner at C-3.

Nucleoside derivatives with a fluorine atom on the sugar moiety are potential antitumor and/or antiviral agents. Extensive studies on the synthesis and biological activity of nucleosides possessing *trans*-fluorohydrin moiety at the C-2′ and C-3′ positions have been reported. Thus, 2′-deoxy-2′-fluoro-β-D-arabinofuranosyl pyrimidines have been found to exhibit selective inhibitory activity against herpes simplex viruses.[1] The synthesis of 3′-fluorinated derivatives, such as 3′-deoxy-3′-fluoro-β-D-xylofuranosyl purines/pyrimidines[2] and 3′-deoxy-3′-fluoro-β-D-arabinofuranosyl purines/pyrimidines have also been reported.[3]

However, there have been only limited reports on the synthesis of nucleosides with a *cis*-fluorohydrin moiety at the C-2′ and C-3′ positions; e.g. 2′-deoxy-2′-fluoroadenosine[4] and -thymidine.[5]



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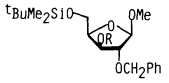
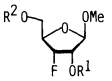


2a : R = H
2b : R = SO_2CF_3



3a : R^1=R^2=H
3b : R^1=CH_2Ph, R^2=H
3c : R^1=R^2=COPh

We describe here the novel synthesis of 3′-deoxy-3′-fluoroadenosine, a new class of fluorinated nucleoside. The synthetic plan to reach the fluorinated nucleoside **1** required access to the 3-deoxy-3-fluororibofuranoside **3a**. The latter would be readily available via an appropriately blocked 3-deoxy-3-fluoroarabinofuranoside.[6] However, inversion of configuration at C-2 to give the desired ribo type product did not occur. For example, methyl 3-deoxy-3-fluoro-2-*O*-(methylsulfonyl)arabinofuranoside failed to react with CsOAc[7] and the Mitsunobu reaction[8] (EtO_2CN=NCO_2Et-Ph_3P-HCOOH) of methyl 3-deoxy-3-fluoroarabinofuranoside resulted only in recovery of the starting material.[9] Synthesis of the desired deoxyfluoro sugar was finally accomplished by the displacement of the trifluoromethanesulfonate at C-3 of xyloside **2b** with fluoride ion.

The C-2 hydroxyl group of methyl 3,5-*O*-isopropylidene-β-D-xylofuranoside[10] was protected with a benzyl group (100% yield). Hydrolysis of the isopropylidene group with acetic acid-H_2O (8:3) at 50 °C followed by selective protection of the primary hydroxyl group with *t*-butyldimethylsilyl chloride gave methyl 2-*O*-benzyl-5-*O*-*t*-butyldimethylsilyl-β-D-xylofuranoside (**2a**) in 87% yield. Conversion of the free 3-hydroxyl group into the trifluoromethanesulfonate (**2b**) followed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at room temperature gave the desired fluorinated compound **3b** in 58% yield (from **2a**). The stereoisomer, 3-deoxy-3-fluoroxylofuranoside,[2a] could not be detected in the reaction mixture by the examination of the ^{19}F NMR spectra. By contrast, the direct fluorination of the alcohol **2a** with piperidinosulfur trifluoride[11] gave the fluorinated sugar in low yield.

Removal of the benzyl protecting group in compound **3b**, followed by protection of the resulting diol with benzoyl chloride gave the dibenzoate (**3c**) (50% yield). The methyl glycoside was converted into the glycosyl bromide with 30%-HBr-acetic acid and coupled with adenine monobenzoate in the presence of mercury(II) cyanide to give the protected adenosine in 63% yield. Deprotection of the benzoyl group with methanolic sodium methoxide afforded 3′-deoxy-3′-fluoroadenosine **1** in 90% yield.

Experimental

Melting points were determined on a Mettler FP80, the IR spectra on a JASCO IR-810 spectrophotometer, and the NMR spectra on a JEOL JNM-FX-90Q spectrometer. Chemical shifts are given in δ with tetramethylsilane as an internal standard. Ultraviolet spectra were recorded with a Shimadzu MPS-2000 spectrophotometer. Rotatory power at sodium D line was measured with a JASCO DIP-140 polarimeter. Elemental analyses were performed by the microanalytical group of Asahi Glass Co., Ltd. Research Center. Purification of products were carried out with column chromatography on silica gel (Merck, 0.063—0.200 mm or 0.040—0.063 mm).

Methyl 2-*O*-Benzyl-5-*O*-*t*-butyldimethylsilyl-β-D-xylofuranoside (2a). Benzyl bromide (108.7 g, 0.64 mol) was added to a suspension of methyl 3,5-*O*-isopropylidene-β-D-xylofuranoside[10] (63 g, 0.31 mol) and silver oxide (76 g, 0.31 mol) in *N*,*N*-dimethylformamide (DMF) (200 ml) at room temperature over a period of 20 min. After 24 h, the mixture was filtrated on Celite 545 and the solvent was evaporated. Purification by column chromatography (toluene-ethyl acetate=5:1) gave 92 g (100% yield) of benzyl ether: ^1H NMR ($CDCl_3$) δ=1.37 (6H, s), 3.41 (3H, s), 3.9—4.4 (5H, m), 4.59 (2H, s), 4.98 (1H, s), 7.32 (5H, s).

This compound was dissolved in 164 ml of acetic acid and 66 ml of water and the solution was heated in a bath at 50 °C for 1 h. Evaporation to dryness in vacuo and short column chromatography gave crude diol (65.1 g, 92% yield).

To a solution of the diol (53.8 g, 0.21 mol) in DMF (200 ml) was added imidazole (43.4 g, 0.63 mol) and *t*-butyldimethylsilyl chloride (31.9 g, 0.21 mol) at 0 °C. After 3 h, the mixture

was poured into sat. aq. sodium hydrogencarbonate (1000 ml) and the solution was extracted with chloroform. The combined extracts, dried with magnesium sulfate, were evaporated to dryness in vacuo. Purification by column chromatography (toluene-ethyl acetate=5 : 1) gave **2a** (74.4 g, 95% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ=0.10 (6H, s), 0.91 (9H, s), 3.37 (3H, s), 3.9—4.1 (3H, m), 5.2—4.4 (2H, m), 4.61 (2H, s), 4.93 (1H, s), 7.32 (5H, s).

Methyl 2-*O*-Benzyl-3-deoxy-3-fluoro-β-D-ribofuranoside (3b). To a solution of **2a** (74.4 g, 0.20 mol) and 2,6-lutidine (64.6 g, 0.60 mol) in dichloromethane (250 ml) was added trifluoromethanesulfonic anhydride (113.0 g, 0.40 mol) at 0 °C over a period of 1 h. After 2 h, the mixture was washed with sat. aq. copper sulfate (200 ml×3) and purified by short column chromatography to give 106.8 g of a crude triflate (**2b**).

Tetrabutylammonium fluoride (1 M† tetrahydrofuran (THF) solution, 370 ml, 0.37 mol) was added to the solution of the crude triflate in THF (250 ml) at 0 °C. After 7 h, the solvent was evaporated under reduced pressure and the residue was purified by silica-gel column to give **3b** (30.2 g, 58% yield (2 steps)): ^{1}H NMR ($CDCl_3$) δ=3.47 (3H, s), 4.0—4.2 (2H, m), 4.55 (2H, s), 4.5—5.1 (4H, m), 5.27 (1H, s), 7.33 (5H, s); ^{19}F NMR ($CDCl_3$, relative to CCl_3F) −207.1 ppm (ddd, J=13.4, 22.0, 53.7 Hz).

Methyl 2,5-Di-*O*-benzoyl-3-deoxy-3-fluoro-β-D-ribofuranoside (3c). The benzyl ether (**3b**) (30 g, 0.12 mol) dissolved in ethanol (100 ml) was stirred in the presence of 5% palladium on charcoal (20 g) under a hydrogen atmosphere for 24 h. Removal of the catalyst by filtration and concentration gave a diol **3a**.

The diol **3a** was mixed with pyridine (80 ml) and benzoyl chloride (23 g, 0.16 mol), and allowed to react at room temperature for 24 h. All the volatile material was evaporated under reduced pressure and the residue was purified by column chromatography (toluene-ethyl acetate=100 : 1) to give **3c** (16.4 g, 50% yield (2 steps)). Mp 53.8 °C (hexane); ^{1}H NMR($CDCl_3$) δ=3.42 (3H, s), 3.4—4.0 (2H, m), 4.4—5.9 (4H, m), 7.2—8.3 (10H, m); ^{19}F NMR ($CDCl_3$, relative to CCl_3F) −211.6 ppm (ddd, J=4.89, 18.06, 53.22 Hz). Found: C, 63.94; H, 5.23%. Calcd for $C_{20}H_{19}O_6F$: C, 64.17; H, 5.12%.

3′-Deoxy-3′-fluoroadenosine (1). To a solution of **3c** (2.4 g, 6.4 mmol) in acetic acid (12 ml) and acetic anhydride (0.5 ml) was added 30%-hydrogen bromide-acetic acid (36 ml) at room temperature over a period of 20 min. After 4 h, all the volatile was evaporated under reduced pressure and the residue dissolved in nitromethane (20 ml) was added to the solution of 6-benzamidopurine (1.6 g, 6.7 mmol) and mercury(II) cyanide (2.4 g, 9.5 mmol) in nitromethane (80 ml) at 100 °C. The solution was refluxed for 1 h, and evaporated to dryness in vacuo at 50 °C, and the residue was suspended in chloroform (200 ml). After being washed with 30% aqueous potassium iodide (200 ml) and water (200 ml), the solution was dried with magnesium sulfate, evaporated, and purified by column chromatography (toluene-ethyl acetate=1 : 3), giving 6-benzamido-9-(2,5-di-*O*-benzoyl-3-deoxy-3-fluoro-β-D-ribofuranosyl)purine (2.16 g, 63% yield). ^{1}H NMR($CDCl_3$) δ=4.2—5.1 (3H, m), 6.0—6.6 (3H, m), 7.2—8.3 (16H, m), 8.34 (1H, s), 8.64 (1H, s); ^{19}F NMR($CDCl_3$, relative to CCl_3F) −200.0 ppm (ddd, J=18.5, 24.5, 53.0 Hz).

A solution of the protected 3′-deoxy-3′-fluoroadenosine (2.16 g, 3.73 mmol) in methanol (10 ml) and 1 M-methanolic sodium methoxide (3.73 ml, 3.73 mmol) was heated to reflux for 1 h, and then evaporated to dryness in vacuo. The residue was dissolved in water (30 ml) and neutralized with 2 M-acetic acid. Methyl benzoate was removed by washing with chloroform, and the aqueous layer was evaporated to dryness in vacuo. Purification by silica-gel column (ethyl acetate) gave the title compound: 0.91 g (90% yield); UV: λ_{max}^{pH14} 258 nm, λ_{max}^{pH7} 258 nm, λ_{max}^{pH2} 256 nm, λ_{min}^{pH14} 237 nm, λ_{min}^{pH7} 236 nm, λ_{min}^{pH2} 236 nm; mp 206.5 °C (decomp, ethanol); $[\alpha]_D^{25}$ −61.8° (H_2O, c=0.5); ^{1}H NMR (DMSO-d_6) δ=3.6—3.7 (2H, m, H-5′), 4.29 (1H, dt, J=27.6, 3.7 Hz, H-4′), 4.80—5.0 (1H, m, H-2′), 5.09 (1H, dd, J=54.4, 4.2 Hz, H-3′), 5.69 (1H, dd, J=7.3, 4.9 Hz, 5′-OH), 5.89 (1H, d, J=6.3 Hz, H-1′), 5.93 (1H, d, J=8.1 Hz, 2′-OH), 7.39 (1H, s), 8.13 (1H, s), 8.36 (1H, s); ^{19}F NMR (DMSO-d_6, relative to CCl_3F) −19.78 ppm (dt, J=54.4, 27.6 Hz); ^{13}C NMR (DMSO-d_6) δ=61.1 (d, J=12.2 Hz, C-5′), 72.0 (d, J=15.9 Hz, C-2′), 83.9 (d, J=22.0 Hz, C-4′), 86.9 (C-1′), 93.1 (d, J=181.8 Hz, C-3′), 119.4 (C-5), 141.1 (C-8), 149.1 (C-4), 152.4 (C-2), 156.2 (C-6); IR (KBr) 3300, 1650 cm^{-1}; Found: C, 44.61; H, 4.71; N, 25.99%. Calcd for $C_{10}H_{12}O_3N_5F$: C, 44.61; H, 4.49; N, 26.01%.

† 1 M=1 mol dm^{-3}.

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