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Practical synthesis of 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (FddA) via a purine 3′-deoxynucleoside

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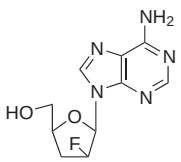
Abstract—A practical synthesis of 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**1**, FddA) via a 6-chloro-9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-9*H*-purine (**6**) is described. Fluorination at the C2′-β position of the purine 3′-deoxynucleoside was improved by the introduction of 6-chloro group, and proceeded in moderate yield. The total yield of FddA from readily available starting material **6** was 35%. © 2001 Elsevier Science Ltd. All rights reserved.

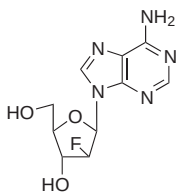
9-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)-adenine (**1**, FddA, lodenosine) is an anti-HIV agent,[1] and its synthesis has attracted considerable attention. FddA has significant advantages over a non-fluorinated dideoxynucleoside such as dideoxyinosine (**3**, ddI, didanosine) and dideoxyadenosine (**4**, ddA) because of its stability under acidic conditions,[1a,b] its activity against dideoxynucleoside-resistant strains of HIV,[2] and its ability to permeate the blood–brain barrier (BBB).[3] Compound **1** is currently being tested in clinical trials for the treatment of AIDS.[1d,4]

Although **1** has been synthesized by several different methods,[1,4a,5] the introduction of fluorine at C2′-β of the sugar moiety is still a critical point. The yield of fluorination at the C-2 (*arabino*) position of sugar derivatives has gradually improved,[6] but the synthesis requires many steps and still remains subject to α-anomer formation during condensation with a nucleic base.[1b,7] Consequently, the total yield of **1** was limited.

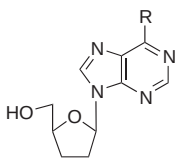
Watanabe, Pankiewicz and their co-workers reported[8] an excellent method for fluorination of riboside at the C2′-β position by conformation control to synthesize F-ara-A (**2**). They found that a C2′-β fluorinated compound was obtained from $O^{2'},O^{5'},N^6$-tritrityladenosine in 30% yield, but an unexpected isonucleoside was obtained in 51% yield as a side product. Recently, Maruyama et al. also reported[9] an F-ara-A synthesis with 6-chloropurine riboside derivatives with an excellent fluorination yield. They found that 3′,5′-di-*O*-trityl-6-chloropurine riboside gave the C2′-β fluorinated compound in 87% yield. We improved this method in FddA synthesis.[10] However, this riboside route requires deoxygenation of the 3′-hydroxyl group after the critical fluorination step, and this results in the loss of



1: FddA



2: F-ara-A



3: R=OH (ddI)
4: R=NH_2 (ddA)

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precious fluorinated compound. The method also requires a multi-step synthesis and an expensive reagent for the deoxygenation.

Accordingly, direct fluorination at the C2′-β position of a purine 3′-deoxynucleoside might be a more attractive approach. Marquez studied[1a] the fluorination of protected 3′-deoxy adenosine with tetrabutylammonium fluoride, however, a fluorinated compound was not obtained. Herdewijn et al.[11] and Shiragami et al.[12] reported the fluorination of 5′-*O*-tritylated and 5′-*O*-acetylated 3′-deoxy adenosine, respectively, with diethylaminosulfur trifluoride (DAST), but the yields of the fluorinated compounds were only 10% in both cases.

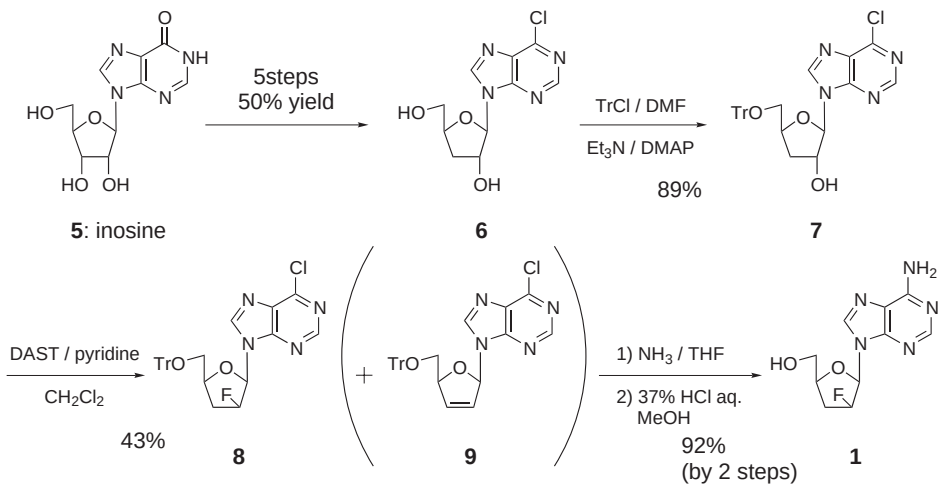
We report here a practical synthesis of FddA through 6-chlorinated purine 3′-deoxynucleoside, which was obtained from inosine (**5**) in short steps. The method does not require deoxygenation after fluorination. This is also the first report regarding the C2′-β fluorination of purine 3′-deoxynucleoside in moderate yield.

Thus, 6-chloro-9-(3-deoxy-β-D-*erythro*-pentofuranosyl)-9*H*-purine (**6**)[13] was readily synthesized from **5** by a modification of the method described by Norman and Reese[14] (Scheme 1), without using expensive reagent. The process was already confirmed with large-scale production in 3,000 liter scale. The details of this synthesis will be reported elsewhere. The 5′-hydroxyl group in **6** was selectively protected with 3.3 equivalents of trityl chloride (TrCl) in the presence of triethylamine (Et_3N) and 4-dimethylaminopyridine (DMAP) in DMF at 50°C. After conventional work-up and purification by silica gel chromatography, pure **7**[15] was obtained as an oil in 89% yield.

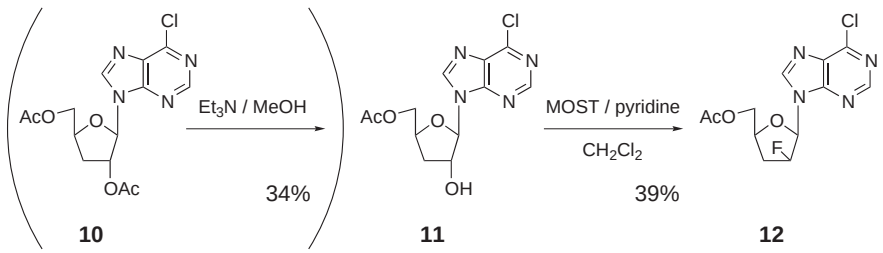
Treatment of the tritylated compound **7** with 2.6 equivalents of diethylaminosulfur trifluoride (DAST) in the presence of pyridine in dichloromethane under reflux conditions gave a C2′-β fluorinated compound (**8**) in 43% yield after purification by preparative silica gel plate. Almost the same amount of side product was also formed. This side product was separated and shown to be an elimination product (**9**), but was not an isonucleoside as reported by Watanabe.[8a] The ^1H NMR spectrum of **8**[16] shows a C2′ proton at $\delta = 5.25$ with a large geminal coupling constant ($J_{2',F} = 53.7$ Hz), indicating that a fluorine atom is attached to C2′. This is also supported by vicinal coupling constants of H1′-F ($J_{1',F} = 19.1$ Hz) and H3′-F ($J_{3',F} = 35.0$, 27.5 Hz). Since the ^1H NMR spectrum shows long-range coupling between H-8 and the C2′ fluorine ($J_{8,F} = 2.8$ Hz), the fluorine should be in the β configuration.[11] Therefore, **8** was confirmed to have a C2′-β fluorinated structure.

After separation and purification, compound **8** was treated with ammonia in tetrahydrofuran (THF) followed by acidic hydrolysis to give FddA (**1**). Its spectroscopic properties were identical in all respects to the published data.[1,10]

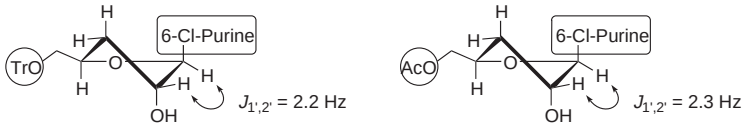
The 5′-*O*-acetylated compound (**11**)[17] was also synthesized by selective deprotection of the di-protected compound **10** (Scheme 2), to investigate if the size of



Scheme 1.



Scheme 2.



7: C3'-endo **11**: C3'-endo

Figure 1.

5′-hydroxyl protecting group changed the sugar conformation[8] and affected the yield of fluorination. Although a risk of undesired deprotection during the fluorination is present, fluorination of **11** was performed by morpholinosulfur trifluoride (MOST), which is an alternative reagent of DAST and it reacted more mildly. Thus, treatment of the acetylated compound **11** with MOST in the presence of pyridine in dichloromethane under reflux conditions gave a C2′-β fluorinated compound (**12**)[18] in 39% yield after purification by silica gel column chromatography. In this study, it was revealed that the size of 5′-hydroxyl protecting group did not influence the sugar conformation and gave a similar yield of the fluorination.

In fact, the ^{1}H NMR spectrum shows that both **7**[15] and **11**[17] have a C3′-*endo* conformation (Fig. 1), as indicated by the rather small vicinal coupling constant between the C1′ and C2′ protons ($J_{1',2'}$ = 2.2 Hz and 2.3 Hz). Watanabe, Pankiewicz and their co-workers reported[8a] that the C3′-*endo* conformation favors β-elimination by virtue of a trans diaxial configuration between the axial hydrogen on C3′ and the activated C2′-hydroxyl group. This argument is supported by many examples; e.g. the fluorination of N^1,$O^{3'}$,$O^{5'}$-tribenzylinosine ($J_{1',2'}$ = 2.5 Hz with 2′-*O*-triflate)[8a] and 5′-*O*-trityl-3′-deoxyadenosine ($J_{1',2'}$ = 1.1 Hz)[11] with DAST gave a poor yield.

Our 3′-deoxy-6-chloropurine nucleosides gave a moderate yield of fluorination despite the C3′-*endo* conformation. The electron-withdrawing 6-chloropurine group may have affected the yield in our case.

In conclusion, FddA (**1**) was synthesized from readily available 6-chlorinated purine 3′-deoxynucleoside **6** by fluorination of the C2′-β position. The electron-withdrawing 6-chloropurine group suppresses the formation of elimination product and isonucleoside. Consequently, the yield of fluorination at the C2′-β position of purine 3′-deoxynucleoside proceeded in moderate yield (43%). The total yield of FddA from readily available starting material **6** was 35%. The details of the reaction are now under investigation in our laboratories.

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15. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (1H, s, H-2), 8.40 (1H, s, H-8), 7.41–7.21 (15H, m, 5′O-Tr), 6.04 (1H, d, J=2.2 Hz, H-1′), 4.87 (1H, m, H-2′), 4.73 (1H, m, H-4′), 3.44 (1H, dd, J=10.6, 3.1 Hz, H_a-5′), 3.33 (1H, dd, J=10.6, 4.6 Hz, H_b-5′), 2.30 (1H, ddd, J=13.3, 7.7, 5.6 Hz, H_a-3′), 2.17 (1H, ddd, J=13.3, 6.5, 3.9 Hz, H_b-3′); UV (MeOH) λ_{max} 207 nm (logε 2.27), 265 nm (logε 0.31); HRMS (FAB+) calcd for $C_{29}H_{26}ClN_4O_3$ $(M+H)^+$ 513.1693, found 513.1717.
16. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.73 (1H, s, H-2), 8.34 (1H, d, J=2.8 Hz, H-8), 7.52–7.22 (15H, m, 5′O-Tr), 6.41 (1H, dd, J=19.1, 3.1 Hz, H-1′), 5.25 (1H, dddd, J=53.7, 5.2, 3.1, 2.0 Hz, H-2′), 4.46 (1H, m, H-4′), 3.48 (1H, dd, J=9.9, 6.6 Hz, H_a-5′), 3.30 (1H, dd, J=9.9, 3.8 Hz, H_b-5′), 2.57 (1H, dddd, J=35.0, 14.8, 9.0, 5.6 Hz, H_a-3′), 2.36 (1H, dddd, J=27.5, 15.1, 5.1, 1.7 Hz, H_b-3′); UV (MeOH) λ_{max}: 206 nm (logε 2.24), 264 nm (logε 0.37); HRMS (FAB+) calcd for $C_{29}H_{25}ClFN_4O_2$ $(M+H)^+$ 515.1650, found 515.1658.
17. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.75 (1H, s, H-2), 8.43 (1H, s, H-8), 6.04 (1H, d, J=2.3 Hz, H-1′), 4.84–4.90 (1H, m, H-2′), 4.77–4.84 (1H, m, H-4′), 4.42 (1H, dd, J=12.4, 3.0 Hz, H-5′a), 4.31 (1H, dd, J=12.4, 4.4 Hz, H-5′b), 2.18–2.31 (2H, m, H-3′ab), 2.07 (3H, s, 5′O-Ac); HRMS (FAB+) calcd for $C_{12}H_{14}ClN_4O_4$ $(M+H)^+$ 313.0704, found 313.0690.
18. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.74 (1H, s, H-2), 8.45 (1H, d, J=2.7 Hz, H-8), 6.43 (1H, dd, J=18.9, 3.1 Hz, H-1′), 5.32 (1H, dddd, J=53.4, 5.1, 3.1, 1.8 Hz, H-2′), 4.50–4.59 (1H, m, H-4′), 4.43 (1H, dd, J=11.9, 6.4 Hz, H-5′a), 4.32 (1H, dd, J=11.9, 3.7 Hz, H-5′b), 2.68 (1H, dddd, J=36.0, 15.2, 8.8, 5.2 Hz, H-3′a), 2.43 (1H, dddd, J=25.7, 15.2, 4.5, 1.7 Hz, H-3′b); HRMS (FAB+) calcd for $C_{12}H_{13}ClFN_4O_3$ $(M+H)^+$ 315.0660, found 315.0651.