Pergamon

Tetrahedron Letters 39 (1998) 1657–1660

TETRAHEDRON LETTERS

# A New Synthetic Approach to the Clinically Useful, Anti-HIV-Active Nucleoside, 9-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (β–FddA). Introduction of a 2'-β-Fluoro Substituent via Inversion of a Readily Obtainable 2'-α-Fluoro Isomer.

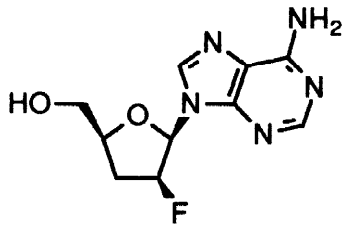
Maqbool A. Siddiqui, John S. Driscoll and Victor E. Marquez*

*Laboratory of Medicinal Chemistry, Division of Basic Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892*

Received 7 November 1997; accepted 16 December 1997

**Abstract.** A convenient route to the anti-HIV active compound, 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**1**, β-FddA) started with the facile introduction of fluorine at C2' from the α-side of protected 9-(β-D-arabinofuranosyl)adenine (ara-A). Inversion of the stereochemistry at C2' was accomplished via a stable vinyl intermediate (**6**), which underwent stereoselective reduction of the double bond to give the desired 2'-F-*threo* isomer with the opposite β-fluoro stereochemistry. Published by Elsevier Science Ltd.

9-(2,3,-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**1**, β–FddA) is a new anti-HIV drug, currently in clinical trial, that has shown potent in vitro and in vivo activity against HIV in experimental models.[1,2] One of the most promising aspects of β–FddA is its effectiveness against HIV strains resistant to zidovudine (AZT), zalcitabine (dideoxycytine, ddC), and even didanosine (dideoxyinosine, ddI).[3] Several




**1** (β-FddA)

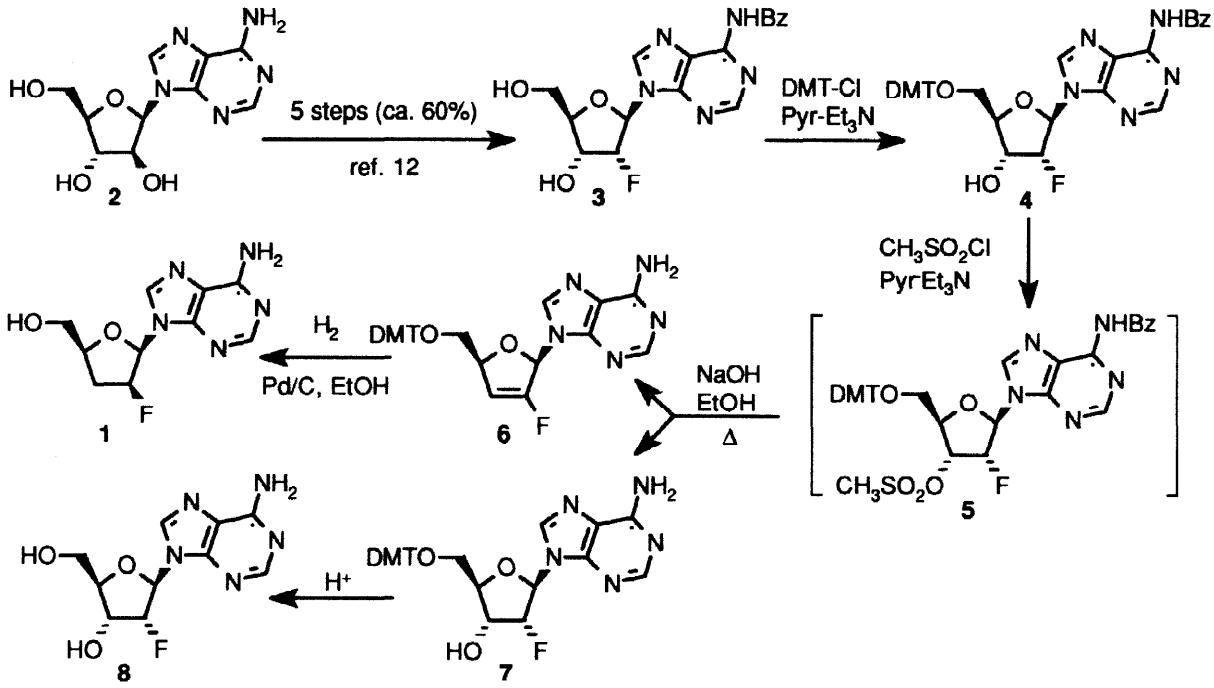
methods of synthesis of β-FddA have been reported, and, in each case, the effective introduction of the fluorine atom at the "up", or β-position of the aglycone has proven to be a challenge. The convergent approaches consisting of coupling a fluorinated sugar with a purine base have progressively improved the yield of the β-fluorosugar precursor, but have failed to optimize the coupling step.[1,4,5] This low efficiency purine coupling stands in sharp contrast to the more efficient glycosylation of pyrimidines employing the same fluorosugar.[4] The more attractive linear approaches, where one introduces the fluorine directly onto the β-position of a purine nucleoside, also give poor yields.[6,7] A clever, but lengthy modification of a linear approach employing bulky 3',5 '-di-*O*-trityl groups which changed the sugar conformation and reduced the preponderance of elimination products gave better yields.[8-10] However, this procedure appears to be impractical for a large scale synthesis.

In contrast to the difficulty of introducing a β-fluorine at C2', the direct introduction of fluorine at the

0040-4039/98/$19.00 Published by Elsevier Science Ltd.
*PII:* S0040-4039(98)00014-8

same site from the α-side is not difficult. Indeed, there are a number of useful reported syntheses of 2'-deoxy-2'-fluoronucleosides, including the 2'-F-*erythro* isomer of β-FddA [α-FddA, 9-(2,3-dideoxy-2-fluoro-β-D-*erythro*-pentofuranosyl)adenine].[1,10-12]

**Scheme 1**

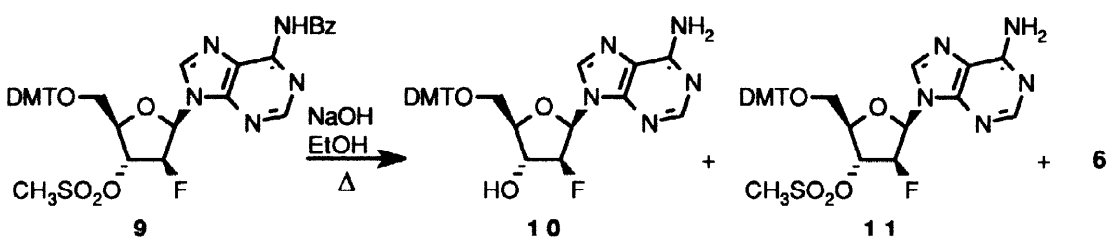



We reasoned that an efficient synthesis of β-FddA could be developed if we allowed fluorination to proceed from the preferred α-face with the subsequent inversion of the stereochemistry of the fluorine at C2' to give the desired β-configuration. This might be accomplished via a 2',3'-dideoxy-2',3'-didehydro-2'-fluoro intermediate (a vinyl fluoride), which upon hydrogenation from the less hindered α-side would yield the desired 2'-F-*threo*, β-fluoro stereochemistry. Precedent for this type of approach was found in the hydrogenolysis of acetylated aldonolactones in the presence of Pd/C and triethylamine, where the transiently formed 2,3-unsaturated lactones underwent stereospecific hydrogenation controlled by the stereochemistry at C4.[13] A similar stereospecific hydrogenation was also reported for pyrimidine nucleosides involving 2'-deoxy-2'-fluoro-β-D-arabinofuranosyl uracil, or thymine. These compounds with a suitable leaving group at C3' (i.e., methylsulfonate) formed the corresponding *O*-2,3'-anhydro intermediate, which underwent base-catalyzed ring opening, via *trans*-elimination involving the C2' hydrogen, to give the corresponding vinyl fluoride (2',3'-dideoxy-2',3'-didehydro-2'-fluoro nucleoside).[14,15] Direct hydrogenation of the vinyl fluoride intermediate in the case of the uridine analogue produced the corresponding 2'-F-*threo*, or 2'-β-fluorodideoxyuridine in good yield.[15]

To our knowledge there is no precedent for this transformation in the purine series. However, since *trans*-elimination is normally considered to be a requisite for this type of vinyl fluoride formation, the readily obtainable 2'-deoxy-2'-fluoroadenosine analogue **4**, with the *ribo* configuration, represented the ideal test

candidate (Scheme 1). This commercially available compound had been prepared earlier from 9-(β-D-arabinofuranosyl)adenine (ara-A, **2**)[12] via $N^6$-benzoyl-9-(3,5-di-*O*-tetrahydropyran-2-yl-β-D-arabinofuranosyl)-adenine.[12] The 2'-α-fluorine was introduced by $S_N2$ displacement of a triflyl group.[12] From the 5'-dimethoxytrityl ether **4**, we synthesized the corresponding methanesulfonate ester **5** and treated it under the conditions that worked successfully for the pyrimidines (i.e., 1 N aqueous NaOH in ethanol at reflux).[15] Without optimization, the vinyl fluoride intermediate **6** was obtained in 55% yield. The other isolated product, obtained in 18% yield, was the hydrolysis product identified as 9-[5-*O*-(4,4'-dimethoxytrityl)-β-D-ribofuranosyl]adenine (**7**). We confirmed the identity of the latter product through its conversion to authentic 2'-deoxy-2'-fluoroadenosine (**8**)[12] by removal of the trityl group. The fact that this by-product was obtained is mechanistically interesting. Generally, sulfonic acid esters give C—O cleavage via a $S_N2$ mechanism, but since there was no inversion at C3', this means that either S—O cleavage occurred, or, more likely, N3 adenine intramolecular participation displaced the mesylate (C—O cleavage). Under the reaction conditions, the proposed $N^3$,3'-cyclonucleoside intermediate could be subsequently opened by hydroxide ion to give the observed hydrolysis product **7**. The desired vinyl fluoride product, **6**, was completely characterized[16] and converted to β-FddA (**1**), in one step, by hydrogenolysis, which simultaneously removed the DMT group. β-FddA was the sole product isolated from this reaction. However, due to the small scale of our experiment, the recovered yield was only 56%.[17]

**Scheme 2**




**9** **10** **11**

When a similar reaction was attempted using the isomeric 2'-deoxy-2'-fluoroarabinofuranosyladenine analogue (**9**[18], Scheme 2), the major product isolated was the completely hydrolyzed product **10** (40%), followed by the partially hydrolyzed compound **11** (21 %), and 2% of the desired vinyl fluoride (**6**), which was indistinguishable from the product obtained previously. This means that formation of the olefin mainly proceeds via a concerted *trans* elimination that begins with hydrogen abstraction at C2'.

In summary, our preliminary results indicate that the approach consisting of a direct introduction of an α-fluorine, followed by inversion of the stereochemistry via a vinyl intermediate is a viable method for the preparation of the otherwise difficult β-fluoro-substituted dideoxypurine nucleosides. A key reaction of this new approach is the hydrogenation step which proceeds with complete stereofacial selectivity. Currently, other approaches directed at optimizing the generation of the vinyl fluoride intermediate, via the use of non-nucleophilic bases, are being explored.

## References and Notes


1. Marquez, V.E.; Tseng, C. K.-H.; Mitsuya, H.; Aoki, S.; Kelley, J. A.; Ford, Jr., H.; Roth, J. S.; Broder, S.; Johns, D. G.; Driscoll, J. S. *J. Med. Chem.* **1990**, *33*, 978-985.
2. Ruxrungtham, K.; Boone, E.; Ford, Jr., H.; Driscoll, J. S.; Davey, R. T.; Lane, H. C. *Antimicrob. Ag. Chemother.* **1996**, *40* , 2369-2374.
3. Driscoll, J.S.; Mayers, D. L.; Bader, J. P.; Weislow, O. S.; Johns, D. G.; Buckheit, R. W. *Antivir. Chem. Chemother.* **1997**, *8*, 107-111.
4. Wysocki, R.J.; Siddiqui, M. A.; Barchi, Jr., J. J.; Driscoll, J. S.; Marquez, V. E. *Synthesis* **1991** 1005-1008.
5. Siddiqui, M.A.; Marquez, V. E.; Driscoll, J. S.; Barchi, Jr., J. J. *Tetrahedron Lett.* **1994**, *35*, 3263-3266.
6. Herdewijn, P.; Pauwels, R.; Baba, M.; Balzarini, J.; De Clercq, E. *J .Med. Chem.* **1987**, *30*, 2131-2137.
7. Shiragami, H.; Tanaka, Y.; Uchida, Y.; Iwagami, H.; Izawa, K.; Yukawa, T. *Nucleosides Nucleotides* **1992**, *11*, 391-400.
8. Kreminski, J.; Nawrot, B.; Pankiewicz, K. W.; Watanabe, K. A. *Nucleosides Nucleotides* **1991**, *10*, 781-798.
9. Pankiewicz, K.W.; Krzeminski, J.; Watanabe, K. A. *J. Org. Chem.* **1992**, *57*, 7315-7321.
10. Pankiewicz, K.W.; Krzeminski, J.; Ciszewski, L. A.; Ren, W. Y.; Watanabe, K. A. *J. Org. Chem.* **1992**, *57*, 553-559.
11. Olsen, D.B.; Benseler, F.; Aurup, H.; Pieken, W. A.; Eckstein, F. *Biochemistry* **1991**, *30*, 9735-9741.
12. Kawasaki, A.M.; Casper, M. D.; Freier, S. M.; Lesnik, E. A.; Zounes, M. C.; Cummins, L. L.; Gonzalez, C.; Cook, P. D. *J. Med. Chem.* **1993**, *36*, 831-841.
13. Bock, K.; Lundt, I.; Pedersen, C. *Acta Chem. Scand. B* **1981**, *35*, 155-162.
14. Martin, J.A.; Bushnell, D. J.; Duncan, I. B.; Dunsdon, S. J.; Hall, M. J.; Machin, P. J.; Merrett, J. H.; Parkes, K. E. B.; Roberts, N. A.; Thomas, G. J.; Galpin, S. A.; Kinchington, D. *J. Med. Chem.* **1990**, *33*, 2137-2145.
15. Sterzycki, R.Z.; Ghazzouli, I.; Brankovan, V.; Martin, J. C.; Mansuri, M. M. *J. Med. Chem.* **1990**, *33*, 2150-2157.
16. An analytical sample of compound **6** (foam) was obtained after silica gel column chromatography (EtOAc:hexanes, 2:1); $^1$H NMR ($CD_2Cl_2$) δ 8.30 (s, 1 H, H-8), 7.95 (s, 1 H, H-2), 7.45-7.25 (m, 9 H, Ph), 6.90 (m, 1 H, H-1'), 6.80-6.70 (m, 4 H, Ph), 5.75 (distorted t, 1 H, H-3'), 5.65 (br s, 1 H, $NH_2$), 5.05 (m, 1 H, H-4' ), 3.75 (s, 6 H, $OCH_3$), 3.40 (dd, $J$ = 10.3, 5.6 Hz, 1 H, H-5'a), 3.25 (dd, $J$ = 10.3, 3.6 Hz, H-5'b); traces of EtOAc were observed by NMR; FAB MS *m/z* (relative intensity) 554 ($MH^+$, 22), 303 ($DMT^+$, 100), 250 (M-DMT, 23). Anal. Calcd for $C_{31}H_{28}FN_5O_4$•0.5EtOAc: C, 66.31; H, 5.39; N, 11.71. Found: C, 66.59; H, 5.65; N, 11.55.
17. In our small scale reaction a significant amount of product appears to have been adsorbed to carbon, thus lowering the overall yield, since no other product could be visualized on TLC, or isolated from the reaction.
18. Compound **9** was obtained from 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine (ref. 1) following the same method used for the synthesis of **5** (Scheme 1).