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Enantioselective Total Synthesis of the Potent Anti-HIV Nucleoside EFdA

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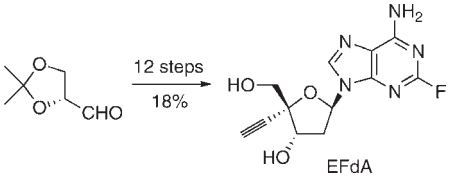
ABSTRACT



A concise enantioselective total synthesis of 4′-ethynyl-2-fluoro-2′-deoxyadenosine (EFdA), an extremely potent anti-HIV agent, has been accomplished from (*R*)-glyceraldehyde acetonide in 18% overall yield by a 12-step sequence involving a highly diastereoselective ethynylation of an α-alkoxy ketone intermediate.

EFdA [4′-ethynyl-2-fluoro-2′-deoxyadenosine (**1**), also abbreviated as 4′Ed2FA] is a nucleoside analog designed by Ohrui and co-workers as a nucleoside reverse transcriptase inhibitor (NRTI) for the treatment of human immunodeficiency virus (HIV) infection (Figure 1).[1] The 2′-deoxyadenosine analog **1**, modified at the 2- and 4′-positions of the parent natural nucleoside, forms a stark structural contrast to eight existing NRTIs clinically approved for AIDS treatment in its retention of the 3′-hydroxyl group; any of the currently prescribed drugs such as zidovudine (AZT) and stavudine lack the 3′-hydroxyl function requisite for DNA chain elongation by viral reverse transcriptases and thereby serve as chain elongation terminators.[2] The modifications at the two positions (2 and 4′) of 2′-deoxyadenosine while retaining its 3′-hydroxyl endowed **1** with promising properties as an anti-HIV drug as follows: (1) exceptionally potent inhibitory activity against HIV-1 replication [e.g., EC_{50} (HIV-1_{NL4-3}), 50 pM in phytohemagglutinin-activated peripheral blood mononuclear cells, which is several orders of magnitude better than those of any currently prescribed NRTIs such as AZT (22 nM) and tenofovir (3300 nM)];[3] (2) excellent in vitro selectivity indices (SI = CC_{50}/EC_{50}) (e.g., 200,000 for HIV-1_{NL4-3}, 134,000 for HIV-1_{IIIB});[3−5] (3) no acute toxicity in ICR mice at a dose of 100 mg/kg;[1a,6] (4) retention of efficacy even against a wide spectrum of

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drug-resistant HIV-1 variants including multidrug-resistant clinical isolates;[4–6] and (5) a longer intracellular half-life value ($t_{1/2}$, 17.2 h) of its active form (EFdA-5′-triphosphate) than that of AZT-5′-triphosphate (2.8 h), which may enable a once-daily or twice-daily regimen.[5] From these favorable pharmacological profiles, EFdA (**1**) is increasingly coming under the spotlight as a potential therapeutic agent for AIDS.

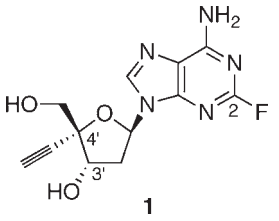
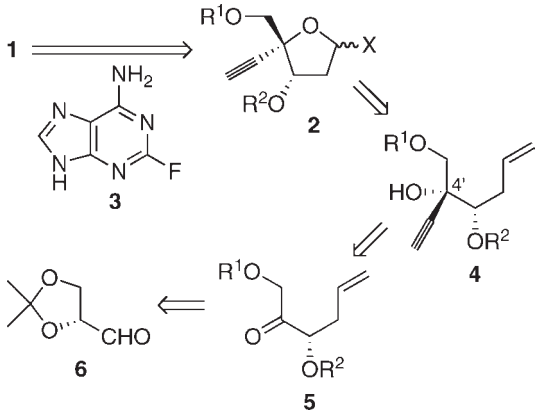


Figure 1. Structure of the anti-HIV nucleoside EFdA (**1**).

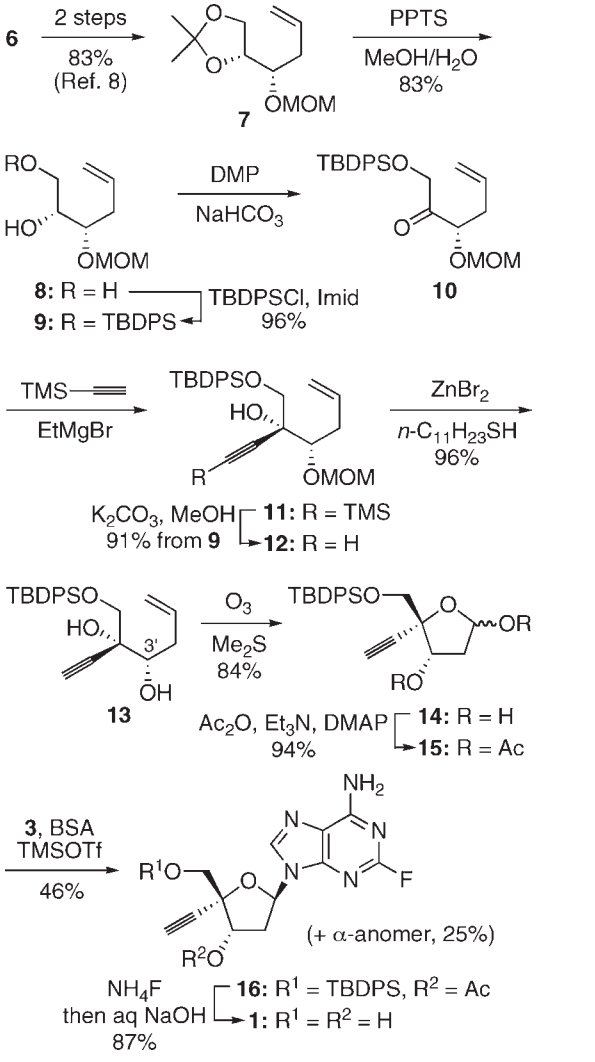
Despite the remarkable physiological properties of **1** reported one after another, there has been only one way to supply **1**, the synthesis by Kohgo and co-workers which required a considerably lengthy 18-step sequence from the expensive starting material 2-amino-2′-deoxyadenosine, resulting in a modest overall yield of 2.5%.[1a,b] The limited availability of **1** as well as its striking antiviral potency and low toxicity in mice prompted our synthetic efforts to supply a sufficient amount of **1** to further promote its biological and clinical research. We describe herein a new efficient 12-step synthesis of **1** in 18% overall yield from (*R*)-glyceraldehyde acetonide.

Scheme 1. Retrosynthetic Analysis of EFdA (**1**)



Our retrosynthetic analysis of **1** is shown Scheme 1. We planned to obtain the target molecule **1** via *N*-glycosylation of activated cyclic hemiacetal **2** with 2-fluoroadenine **3**. The glycosyl donor **2** would be prepared through oxidative cleavage of the terminal double bond of **4** followed by spontaneous hemiacetal ring formation. The stereochemistry at the 4′-position of **4** was considered to be installable by diastereoselective addition of an acetylide anion to alkoxy ketone **5**, which in turn could be readily prepared from (*R*)-glyceraldehyde acetonide **6** via diastereoselective allylation and subsequent functional group manipulations.

Scheme 2. Synthesis of EEdA (**1**)



Taking into account the diastereoselective ethynylation step in the retrosynthetic plan (**5** → **4**, Scheme 1), we chose MOM-protected acetal **7** as the starting point,[7] a known compound readily obtainable from **6** in 83% overall yield through two steps consisting of diastereoselective allylation of **6** with allylzinc bromide and MOM protection of the resulting secondary alcohol (Scheme 2).[8] Deprotection of the acetonide group of **7** under acidic conditions followed by selective TBDPS protection of the primary hydroxyl group of the resulting diol **8** afforded **9**.

(7) For examples of diastereoselective addition of acetylide anions to MOM-protected α-hydroxy ketones, see: (a) Maddaford, A.; Wainwright, P.; Glen, R.; Fisher, R.; Dragovich, P. S.; Gonzalez, J.; Kung, P.-P.; Middleton, D. S.; Pryde, D. C.; Stephenson, P. S.; Sutton, S. C. *Synthesis* **2007**, 1378–1384. (b) Druais, V.; Hall, M. J.; Corsi, C.; Wendeborn, S. V.; Meyer, C.; Cossy, J. *Tetrahedron* **2010**, *66*, 6358–6375.

Oxidation of the alcohol **9** with the Dess–Martin periodinane gave ketone **10**, which was then subjected to the addition of the acetylide anion prepared by treating (trimethylsilyl)acetylene with EtMgBr. Expectedly, this reaction proceeded highly diastereoselectively, providing **12** as a single stereoisomer in 91% overall yield from **9** after removal of the TMS protecting group of the resulting adduct **11** followed by chromatographic purification. Deprotection of the MOM group of **12** was effected efficiently with $ZnBr_2$ and 1-dodecanethiol in CH_2Cl_2 to give diol **13** in nearly quantitative yield,[9] the enantiomeric excess of which was determined to be >95% by ^{1}H NMR analyses of the corresponding (*R*)- and (*S*)-3′-mono-MTPA esters. Ozonolysis of the terminal double bond of **13** accompanied by spontaneous hemiacetal ring formation afforded **14** as an anomeric mixture (α/β = 2.8:1 as judged by ^{1}H NMR analyses including NOE experiments).[10] After acetylation of the anomeric and 3′-hydroxyl groups to form **15** (α/β = 1:1.4),[10] the resulting anomeric mixture was subjected to the silyl-Hilbert–Johnson reaction using 2-fluoroadenine (**3**) as a nucleophilic base to afford **16** in an isolated yield of 46% along with the corresponding α-anomer (25%).[11] Finally, desilylation of **16** with NH_4F and subsequent one-pot hydrolysis of the acetate function gave the target molecule EFdA (**1**) as a white microcrystalline solid,[12] the ^{1}H NMR of which was identical with that of an authentic sample of EFdA.

In conclusion, the enantioselective total synthesis of EFdA (**1**) was accomplished in 18% overall yield from the commercially available protected aldehyde **6** via 12 steps (or 22% overall yield from the known compound **7** through 10 steps) using the chelation-controlled diastereoseletive ethynylation of α-alkoxy ketone **10** as the key transformation. Attempts to improve the stereoselectivity of the *N*-glycosylation step as well as to convert the undesired α-anomer of **16** into the corresponding β-anomer are now underway.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For the use of $ZnBr_2$/*n*-BuSH and $ZnBr_2$/*n*-PrSH to deprotect MOM ethers, see: (a) Sohn, J.-H.; Waizumi, N.; Zhong, H. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 7290–7291. (b) Han, J. H.; Kwon, Y. E.; Sohn, J.-H.; Ryu, D. H. *Tetrahedron* **2010**, *66*, 1673–1677.

(10) For diagnostic NOE correlations in the anomers of **14** and **15**, see the Supporting Information.

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