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Synthesis of EFdA via a Diastereoselective Aldol Reaction of a Protected 3-Keto Furanose

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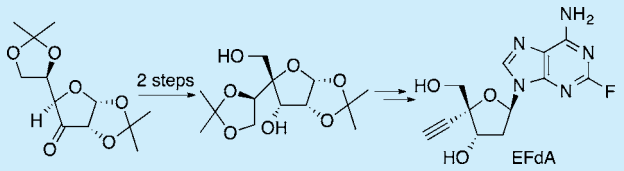
Supporting Information

ABSTRACT: An efficient enantioselective total synthesis of EFdA, a remarkably potent anti-HIV nucleoside analogue with various favorable pharmacological profiles, has been achieved in 37% overall yield from diacetone-D-glucose by a 14-step sequence that features a highly diastereoselective installation of the tetrasubstituted stereogenic center at the C4′ position, direct oxidative cleavage of an acetonide-protected diol derivative to an aldehyde, and one-pot 2′-deoxygenation of a ribonucleoside intermediate.



4′-Ethynyl-2-fluoro-2′-deoxyadenosine (EFdA, **1**) is a nucleoside reverse transcriptase inhibitor (NRTI) created by collaborative studies among the Ohrui group, Mitsuya group, and Yamasa Corp. (Figure 1).[1] The structure of **1** differs

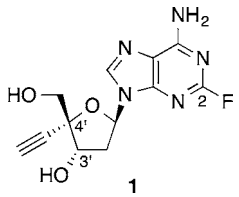


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Figure 1. Structure of EFdA.

substantially from other NRTIs clinically approved for the treatment of human immunodeficiency virus (HIV) infection, since it retains the 3′-OH functionality of 2′-deoxyadenosine as well as the presence of the 2-fluoro substituent.[2] The installation of an ethynyl group and a fluoro substituent at the C4′ and C2 positions of the parent natural nucleoside, respectively, while maintaining the 3′-hydroxy group, endowed **1** with highly promising pharmacological profiles as an anti-HIV agent including (1) exceptionally potent antiviral activity against both wild-type and multidrug-resistant HIV-1 strains (ED_{50}, low nM to pM level),[3] (2) no acute toxicity in ICR mice at a dose of 100 mg/kg,[1a,4] and (3) longer intracellular half-life ($t_{1/2}$, 17.2 h) of its active form (EFdA-5′-triphosphate) than that of zidovudine triphosphate (AZT-5′-triphosphate, $t_{1/2}$, 2.8 h),[3a] which may enable a once- or twice-daily regimen and thereby improve the quality of life (QOL) of people suffering from AIDS. Because of these favorable characteristics of **1** in terms of potency, safety, and pharmacokinetics, detailed mechanistic as well as clinical studies have been carried out on **1**. There is particular interest in establishing why resistance to **1** occurs less frequently,[5] and these investigations are actively in progress aimed at developing **1** as a therapeutic agent for HIV infection.[6]

As for the synthesis of **1**, there have been only two methods developed: one by Ohrui and co-workers and the other by us. The first synthesis of **1** reported by Ohrui et al.,[1a,b] which led to the discovery of **1** as a potent NRTI, required a lengthy 18-step sequence from the expensive starting material 2-amino-2′-deoxyadenosine, which resulted in a modest overall yield of 2.5%. The second synthesis accomplished by our group succeeded in reducing the number of steps and enhancing the overall yield [18% over 12 steps from (*R*)-glyceraldehyde acetonide], but unfortunately, it necessitated careful chromatographic separation of diastereomeric intermediates at an early and a late stage of the synthesis.[7] The problems posed in the two previous syntheses prompted our efforts at developing a more efficient synthesis of **1** that could supply **1** more easily. We describe herein a new practical synthesis of **1** in 37% overall yield from diacetone-D-glucose by a 14-step sequence which requires only four chromatographic purifications and involves an exclusively diastereoselective construction of the tetrasubstituted asymmetric center at the C4′ position.

Scheme 1 outlines our retrosynthetic analysis of **1**. To install the nucleobase unit of **1** in a stereoselective manner, we chose a 2′-acetoxyfuranose derivative **3** as a key intermediate; its N-glycosidation with 2-fluoroadenine should proceed in a highly *β*-selective manner based on the neighboring group participation of the 2′-acetoxy substituent,[8] and subsequent 2′-deacetylation of the resulting product would lead to ribonucleoside derivative **2**. Deoxygenation at the C2′ position of **2** followed by deprotection would then furnish the target molecule **1**. The acetylenic intermediate **3** would be derived from aldehyde **4** by an appropriate alkyne-forming reaction.

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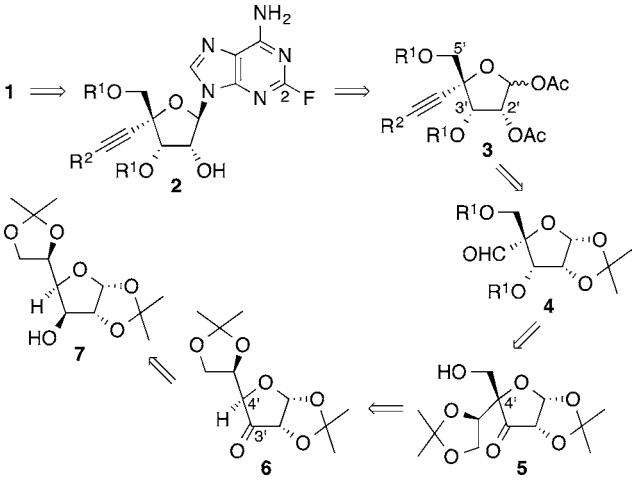
Scheme 1. Retrosynthetic Analysis of 1

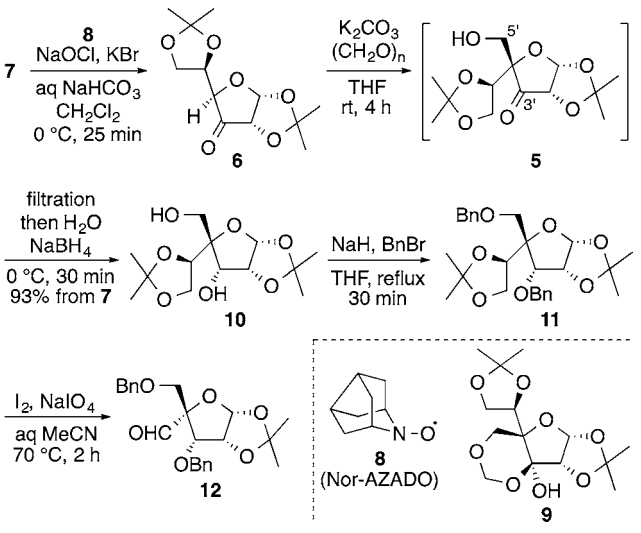


The aldehyde **4** would be obtainable by diastereoselective reduction of ketone **5** from the convex face of the bicyclic fused ring system and subsequent chemoselective deprotection of the terminal acetonide followed by oxidative cleavage of the vicinal diol intermediate produced. For the diastereoselective formation of **5** bearing a tetrasubstituted asymmetric center at the C4′ position, we envisaged the use of the aldol reaction of protected 3-keto furanose **6** with formaldehyde. Based on a literature precedent,[9] treatment of **6** under suitable basic conditions was anticipated to produce an enolate intermediate with a double bond at the C3′−C4′ position. The electrophilic approach of formaldehyde to the enolate from the less hindered *β*-face would then give **5** in a diastereoselective manner. Compound **6** is commercially available or can be readily prepared by oxidation of the cheap starting material diacetone-D-glucose (**7**).

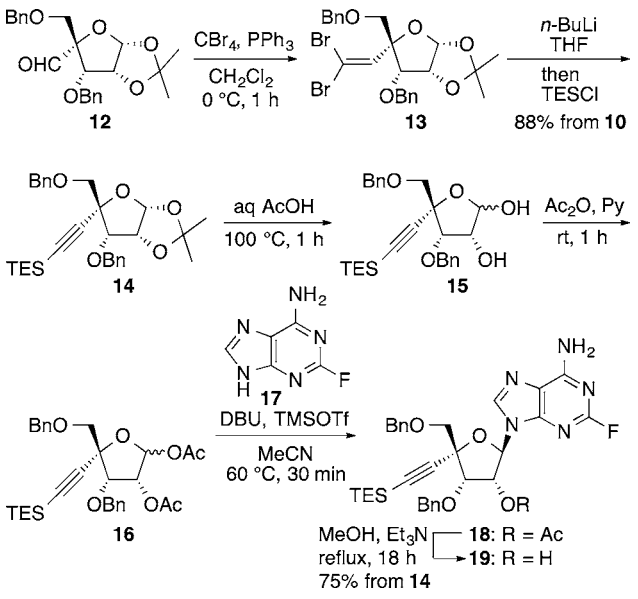
Our synthesis of **1** commenced with the oxidation of **7** to ketone **6** (Scheme 2). This transformation has previously been effected by the Dess−Martin oxidation,[10] the Swern oxidation,[11] or by reagent systems such as PDC/Ac_2O,[12] PDC/AcOH,[13] and TEMPO (0.5 mol %)/NaOCl/KBr.[14] After examination of various oxidation conditions, we found that the conversion could be best performed by treating **7** with NaOCl and KBr in CH_2Cl_2/aq $NaHCO_3$ in the presence of a surprisingly small amount (0.005 mol %) of Nor-AZADO (**8**).[15] This reaction went to completion within 30 min at 0 °C and could be successfully conducted on a multigram scale (at least up to 100 g). The new oxidation system for the conversion of **7** into **6** seems to be superior to previous ones in terms of scalability, operational easiness, and also greenness.[16] The 4′-hydroxymethylation of **6**, one of the key steps in our synthesis, proceeded as expected by simply treating **6** with paraformaldehyde and K_2CO_3 in THF, affording a mixture of aldol **5** and cyclic hemiacetal **9** (ca. 3:1), the latter of which must have been formed by 5′-*O*-hydroxymethylation of **5** with excess formaldehyde followed by cyclic hemiacetal formation between the newly formed hydroxyl group and the 3′-keto functionality. The structure of **9**, which could be isolated as a white powder from the mixture of **5** and **9**, was fully characterized by spectroscopic analyses including COSY, DEPT, and HMBC experiments.[17,18] To the best of our knowledge, this type of hydroxymethylation at the C4 position of 3-keto furanose derivatives has no precedent in the literature; a one-pot aldol−Cannizzaro reaction of a protected 5-oxo pentofuranose with formaldehyde has been known to hydroxymethylate the C4 position of the furanose derivative,[19] but the formation of two primary hydroxyl groups in the product brought about a bothersome problem regarding the selective protection of the 1,3-diol.[19b,d] The raw reaction mixture of **5** and **9**, obtained after the aldol reaction, was filtered, diluted with water, and treated directly with $NaBH_4$ to give **10** as a white solid in an excellent overall yield of 93% from **7** after purification by simple trituration. Protection of the 5′-hydroxy group of **10** as its benzyl ether **11** was then followed by chemoselective deprotection of the terminal acetonide group (I_2 in MeCN)[20] and concomitant oxidative cleavage of the resulting diol intermediate ($NaIO_4$) in one pot to give known aldehyde **12** (nearly quantitatively).[21]

The aldehyde **12** was then converted into glycosyl acetate **16** (Scheme 3) via acetylenic derivative **14** according to our

Scheme 2. Preparation of Aldehyde Intermediate 12 Bearing a 4′-Tetrasubstituted Stereocenter



Scheme 3. Conversion of Aldehyde 12 into Ribonucleoside Derivative 19



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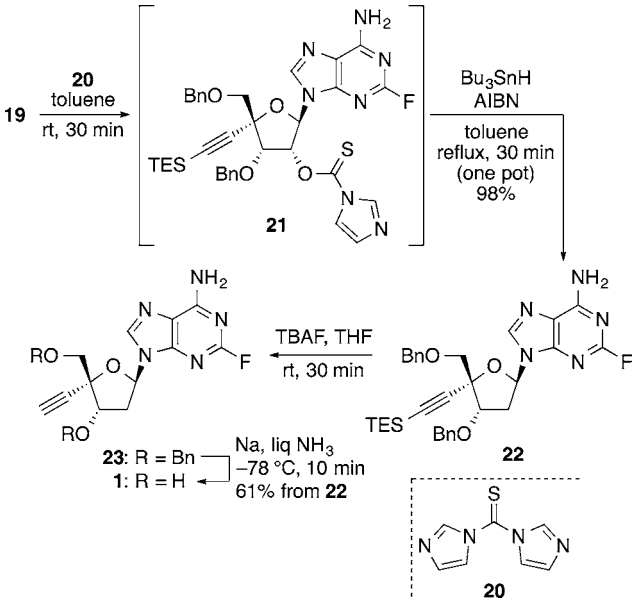
previously reported procedures except that the transformation of dibromoolefin **13** to acetylenic intermediate **14** was effected in a single operation by directly trapping an acetylide intermediate with TESCl.[21,22] Removal of the acetonide group of **14** under acidic conditions followed by bis-acetylation of the resulting hydroxyl hemiacetal **15** furnished **16**. The N-glycosylation of **16** with 2-fluoroadenine (**17**) was best performed by treating **16** with TMSOTf and DBU in MeCN to give **18**,[23] the deacetylation of which then afforded **19** as a single diastereomer. Each step of the reaction sequence from **10** to **19** proceeded in a good-to-excellent yield, providing **14** in 88% overall yield from **10** and **19** in 75% overall yield from **14**.

The final stage of our synthesis of EFdA (**1**) is shown in Scheme 4. The adenosine derivative **19** was subjected to a one-

Scheme 4. Completion of the Synthesis of EFdA (1)



pot process comprising its derivatization into **21** with 1,1′-(thiocarbonyl)diimidazole **20** and subsequent reduction of **21** under Barton–McCombie conditions,[24] providing **22** in an excellent yield of 98%. Although 2′-deoxygenation of ribonucleosides has previously been carried out in two separate steps,[25] we found that the two-step sequence could be effected in one pot by using toluene as the same solvent for both reactions.[26] Finally, the 2′-deoxyadenosine derivative **22** was exposed to TBAF in THF and then to Na in liquid ammonia to remove the TES and benzyl protecting groups, respectively, furnishing EFdA (**1**) in 61% yield for the two steps. The ^{1}H and ^{13}C NMR spectra of **1** were identical with those of an authentic material, and the specific rotation of **1** [$[\alpha]^{27}_{D}$ +12.9 (*c* 1.00, MeOH)] showed good agreement with a reported value [$[\alpha]^{25}_{D}$ +12.4 (*c* 0.97, MeOH)].[7]

In conclusion, an enantioselective total synthesis of EFdA (**1**) has been accomplished in an excellent overall yield of 37% from diacetone-D-glucose **7** by a 14-step sequence that features the diastereoselective installation of the tetrasubstituted stereocenter at the C4′ position (**6** → **5**), chemoselective acetonide hydrolysis of **11**, and concomitant oxidative cleavage of the resulting diol to form aldehyde **12**. A one-pot 2′-deoxygenation of **19** provided **22**. Of value is the fact that the present synthesis requires only four chromatographic purifications, mainly because every reaction that could potentially produce diastereomers (**6** → **5**, **5** → **10**, and **16** → **18**) proceeded with virtually perfect stereoselection. From these favorable features, as well as the use of **7** as an inexpensive starting material, the new synthesis described herein is considered to be more efficient and practical than previous syntheses.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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