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Concise Synthesis of the Anti-HIV Nucleoside EFdA

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EFdA (4′-ethynyl-2-fluoro-2′-deoxyadenosine), a nucleoside reverse transcriptase inhibitor with extremely potent anti-HIV activity, was concisely synthesized from (*R*)-glyceraldehyde acetonide in an 18% overall yield by a 12-step sequence involving highly diastereoselective ethynylation of an α-alkoxy ketone intermediate. The present synthesis is superior, both in overall yield and in the number of steps, to the previous one which required 18 steps from an expensive starting material and resulted in a modest overall yield of 2.5%.

Key words: EFdA; anti-HIV; AIDS; nucleoside; *N*-glycosidation

Since the first approval of zidovudine (also called azidothymidine, AZT) for clinical use in 1987, seven additional nucleoside reverse transcriptase inhibitors (NRTIs), including abacavir (ABC) and tenofovir (TNF), have been approved and prescribed for people infected by human immunodeficiency virus (HIV) or patients suffering from acquired immunodeficiency syndrome (AIDS) caused by HIV infection (Fig. 1).[1,2] All of the furanose or pseudofuranose portions in the eight NRTIs are structurally devoid of the 3′-hydroxyl (3′-OH) group which is present in natural nucleosides and is indispensable for DNA chain elongation by viral reverse transcriptases (RTs). Therefore, once incorporated as their 6′-monophosphate into the 3′-terminus of a viral DNA primer, the nucleoside analogs without the 3′-OH functionality block further nucleotide addition by RTs, and thereby serve as obligate DNA chain elongation terminators.[3,4] The absence of the 3′-OH group has long been considered to be a prerequisite for NRTIs to exert anti-HIV activity, probably due to the reasonable and readily understandable mode of action.[5]

In recent years, however, it has been revealed that nucleoside derivatives bearing the 3′-OH group also exhibited significant anti-HIV activity by inhibiting viral reverse transcriptases through several mechanisms of action.[3] Among the NRTIs with the 3′-OH group, EFdA [4′-ethynyl-2-fluoro-2′-deoxyadenosine (**1**), also abbreviated as 4′Ed2FA], designed by Ohrui and co-workers stands out as a promising anti-HIV agent.[6–11] Their modification made at two positions (2 and 4′) of the parent natural nucleoside 2′-deoxyadensine endowed **1** with the following remarkable pharmacological profiles: (i) exceptionally potent inhibitory activity against HIV-1 replication [*e.g.*, EC_{50} for HIV-1_{NL4-3} = 50 pM in phytohemagglutinin-activated peripheral blood mononuclear cells (PBMCs), which is several orders of magnitude more effective than that of any currently prescribed NRTIs such as AZT (22 nM) and TNF (3300 nM)];[5] (ii) excellent *in vitro* selectivity indices ($SI = CC_{50}/EC_{50}$; *e.g.*, >200,000 for HIV-1_{NL4-3} in PBMCs, and 134,000 for HIV-1_{IIIB} in MT-4 cells), which are superior to that of AZT (SI = 10,800 for HIV-1_{IIIB} in MT-4 cells);[5,12,13] (iii) no acute toxicity toward ICR mice at a dose of 100 mg/kg;[6,14] (iv) retention of efficacy even against a wide spectrum of drug-resistant HIV-1 variants including multidrug-resistant clinical isolates;[12–14] and (v) longer intracellular half-life value ($t_{1/2}$, 17.2 h) in 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.[13] From these favorable properties, EFDA (**1**), which is currently under preclinical evaluation, is attracting rising attention as a potential therapeutic agent for HIV-infected patients.[3,4]

In contrast to the various biological and medicinal studies on **1** that have been progressively reported, there has been only one way to supply EFdA (**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%.[6,7] The limited availability of **1** as well as its promising pharmacological profiles just described prompted our synthetic efforts to supply a sufficient amount of **1** to further promote its biological and clinical research. These efforts have recently culminated in an enantioselective 12-step total synthesis of **1** in an 18% overall yield from the simple starting material, (*R*)-glyceraldehyde acetonide.[15] We describe in this article a full account of our total synthesis of **1**, including some unsuccessful attempts.

Results and Discussion

Our synthetic plan for EFdA (**1**) is shown in Scheme 1. We considered that the target molecule (**1**) would be obtained *via* *N*-glycosidation of activated 2′-deoxyfuranose derivative **2** with 2-fluoroadenine **3**,

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Abbreviations: BSA, *N*,*O*-bis(trimethylsilyl)acetamide; DMAP, 4-(dimethylamino)pyridine; DMP, Dess-Martin's periodinane; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; MOM, methoxymethyl; MTPA, α-methoxy-α-(trifluoromethyl)phenylacetyl; PPTS, pyridinium *p*-toluenesulfonate; TBDPS, *tert*-butyldiphenylsilyl; Tf, trifluoromethanesulfonyl; TIPS, triisopropylsilyl; TMS, trimethylsilyl

which in turn is commercially available or readily obtainable from 2,6-diaminopurine in a single step.[16,17] Glycosyl donor **2** could be prepared by oxidative cleavage of the terminal double bond of **4**, followed by spontaneous hemiacetal ring formation and subsequent activation of the resulting anomeric hydroxy group. To appropriately install the stereochemistry at the C4′ position of **4**, we planned to use diastereoselective addition of an acetylene derivative to suitably protected hydroxy ketone **5** which could be obtained from the well-known chiral building block, (*R*)-glyceraldehyde acetonide (**6**), by diastereoselective allylation coupled with some functional group manipulations.

To achieve high diastereoselectivity in the ethynylation step of our synthetic plan (**5** → **4** in Scheme 1), we chose known MOM-protected acetal **7**[18–20] as the starting point (Scheme 2), since our literature search revealed that the addition of acetylide anions to α-hydroxy ketones would proceed with high diastereoselectivity when the hydroxy group was protected as its MOM ether.[21,22] Compound **7** was readily obtained from **6** in two steps, comprising highly diastereoselective allylation of **6** with allylzinc bromide and MOM-protection of the resulting alcohol according to the literature.[18–20] Selective deprotection of the acetonide group of **7** was conducted by its treatment with PPTS in aqueous methanol to form **8**, the primary hydroxy group of which was then protected as its TBDPS ether **9**. Swern oxidation of **9** gave MOM-protected ketone **10**, which was then subjected to an addition reaction with (triisopropylsilyl)ethynylmagnesium bromide to afford acetylenic alcohol **11** as a single diastereomer. The stereochemistry of **11** was determined later at the stage of **2a** by observing a diagnostic NOE correlation between the C3′ proton and the C5′ protons (see structure **2a** in Scheme 2). This complete stereoselectivity in the formation of **11** would be explained by assuming chelation-controlled transition state **10′** depicted in Scheme 2; the acetylenic nucleophile would approach the C4′ carbonyl from its less-hindered *si*-face.[21] Ozonolysis of **11** and subsequent spontaneous cyclization proceeded uneventfully to give furanose derivative **12**, the anomeric hydroxy group of which was then activated by acetylation to furnish glycosyl donor **2a**. *N*-Glycosidation of **2a** with 2-fluoroadenine **3** was implemented under the silyl-Hilbert–Johnson reaction conditions.[23–25] Fluorinated nucleobase **3** (1.6 eq.) was thus treated for 4 h with a silylating agent [BSA (**13**), 1.9 eq.] and Lewis acid (TMSOTf, 1.8 eq.) in refluxing MeCN to generate the corresponding silylated nucleobase, which was then allowed to react with **2a** at refluxing temperature for 2 h to give a mixture of **14α**

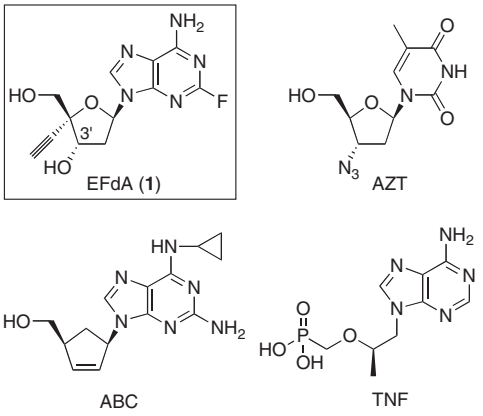
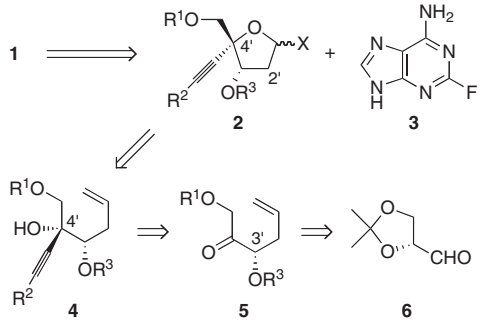
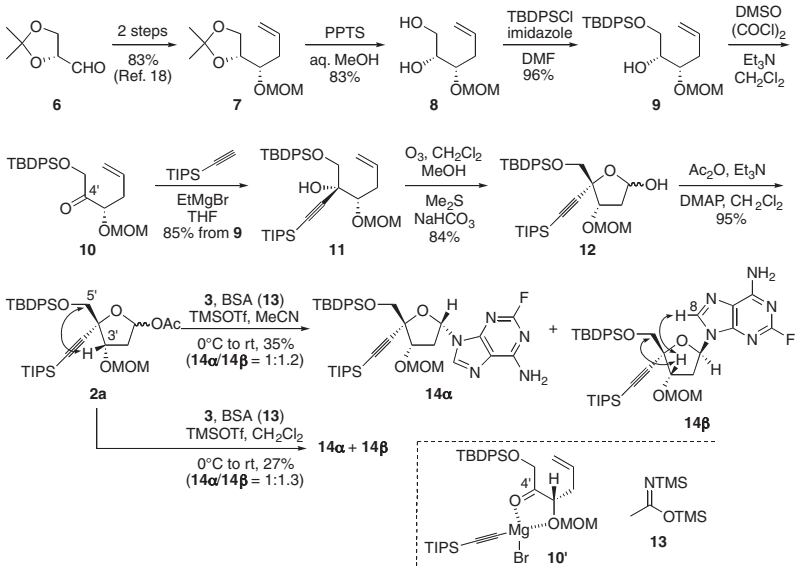


Fig. 1. Structures of EFdA (**1**) and Related Nucleoside Reverse Transcriptase Inhibitors.



Scheme 1. Synthetic Plan for EFdA (**1**).



Scheme 2. Preparation of Glycosyl Donor **2a** and Its Glycosidation with 2-Fluoroadenine (**3**).

and **14β** in a 35% yield with a poor diastereoselectivity of 1:1.2, favoring the desired β-anomer **14β**. The stereochemistry of the products was assigned on the basis of NOE correlations observed between the C3′ proton and the protons at the C8 and C5′ positions in **14β**. Changing the solvent from MeCN to CH_2Cl_2 did not improve either the stereoselectivity or the chemical yield, resulting in the formation of a 1:1.3 anomeric mixture of **14α** and **14β** in only a 27% yield.

To improve the diastereoselectivity of the *N*-glycosidation process, we next attempted a highly stereoselective method for preparing 2′-deoxy-β-ribonucleosides that has recently been reported by Zhang and co-workers.[26] As shown in Fig. 2, this method takes advantage of the *N*-acetylglycinate residue at the C3′ position of 2′-deoxyfuranose derivative **A** as a stereo-directing group, giving β-*N*-glycoside **C** with high diastereoselectivity (up to 98%) *via* the formation of oxocarbenium ion intermediate **B** stabilized intramolecularly by the *N*-acetylglycinate residue. Scheme 3 outlines the preparation of glycosyl donor **2b** bearing the stereo-directing group. The MOM protecting group of **11** was selectively removed by treating with $ZnBr_2$ and 1-dodecanethiol in CH_2Cl_2[27,28] to give diol **15**. The esterification of **15** with *N*-acetylglycine in the presence of EDCI and DMAP proceeded considerably sluggishly, affording **16** in a 67% yield [94% based on the recovered starting material (brsm)] after reacting at room temperature for 13 h. Ozonolysis of **16** and subsequent acetylation of lactol intermediate **17** afforded **2b** which was then subjected to *N*-glycosidation with **3**. As shown in Table 1, the *N*-glycosidation of **2b** with a silylated nucleobase generated from **3** in dichloroethane, which had been used as the solvent in the reported protocol,[26] exhibited no stereoselectivity, giving a mixture of **18α** and **18β** in a ratio of *ca.* 1:1 with an unsatisfactory yield of 21% (entry 1). The use of CH_3CN, a solvent often used for this type of *N*-glycosidation,[25,29,30] or toluene, a typical solvent for Lewis acid-mediated reactions, did not improve the diastereoselectivity at all, affording a *ca.* 1:1 mixture of **18α** and **18β** in both cases (entries 2 and 3). The poor diastereoselectivity in the *N*-glycosidation of **2b** might be ascribable, in part, to the difficulty in the formation of transition state **B′** (Fig. 3), in which the α-oriented acetylenic substituent at the C4′ position is located on the sterically congested concave side of the pseudo-bicyclic ring system.

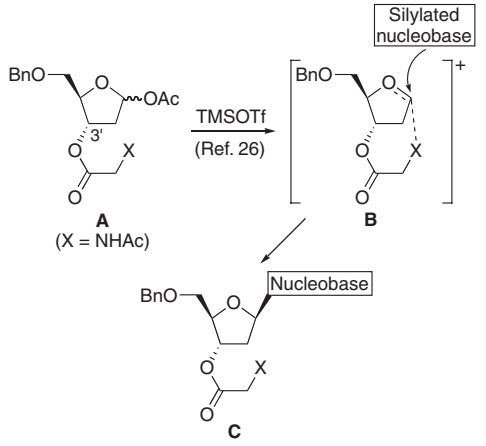
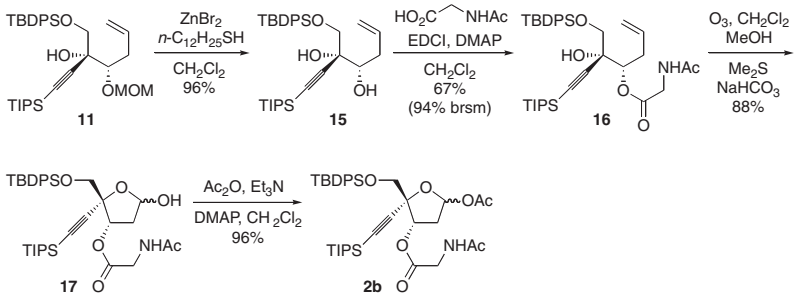
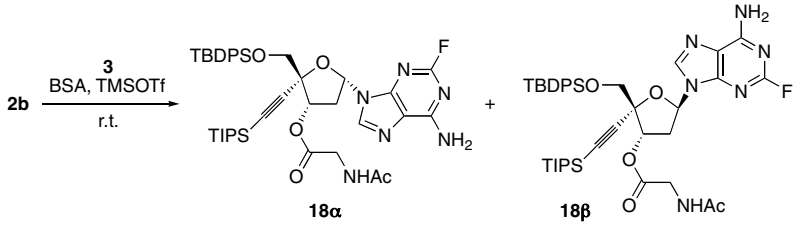


Fig. 2. β-Selective *N*-Glycosidation of 2′-Deoxyfuranose Derivative (**A**) by Zhang *et al.*



Scheme 3. Preparation of Glycosyl Donor **2b**.

Table 1. *N*-Glycosidation of **2b**



Entry[a]	Solvent	**3** (eq.)	BSA (eq.)	TMSOTf (eq.)	Time (h)	Product (ratio, yield)
1	$(CH_2Cl)_2$	1.7	2.0	1.9	12	**18α**/**18β** (*ca.* 1:1, 21%)
2	CH_3CN	1.8	2.0	1.9	6	**18α**/**18β** (*ca.* 1:1, 33%)
3	toluene	1.7	2.0	1.9	13.5	**18α**/**18β** (*ca.* 1:1, 36%)

[a] A mixture of **3**, BSA, and TMSOTf in the solvent indicated was refluxed for 4 h. To the resulting mixture was added a solution of **2b** in the same solvent at 0 °C, and the mixture was stirred at room temperature for the time indicated.

Aiming to reduce the steric bulkiness of the C4′ acetylenic substituent, we next planned to subject sterically less demanding glycosyl donor **2c** (Scheme 4), which is devoid of the bulky triisopropyllsilyl moiety, to the *N*-glycosidation reaction. An outline of the preparation of **2c** is shown in Scheme 4. Dess–Martin oxidation of compound **9** and subsequent addition of (trimethylsilyl)ethynylmagnesium bromide to resulting ketone **10** gave **19** as a single diastereomer. Methanolytic removal of the TMS group of **19** afforded **20**. Its MOM group was then deprotected to give diol **21**, whose enantiomeric excess was evaluated to be >95% by a ^{1}H-NMR analysis of corresponding (*R*)- and (*S*)-3′-mono-MTPA esters **22**. Acylation of the secondary hydroxy group of **21** with *N*-acetylglycine went to completion by stirring the reaction mixture for 12 h at room temperature, and provided **23** in an 89% yield which contrasts with the sluggishness in the acylation of corresponding TIPS-protected diol **15** (see Scheme 3). Finally, ozonolysis of **23** and subsequent acetylation of resulting lactol **24** provided **2c** which was subjected to an *N*-glycosidation reaction with **3** (Table 2). All of the reactions in Table 2 were conducted by using CH_3CN as a solvent, since preliminary experiments indicated that lesser amounts of undesired impurities were produced in CH_3CN than in other solvents. Table 2 shows that the *N*-glycosidation of **2c** with **3**, under analogous conditions to those employed in entry 2 of Table 1, gave a mixture of **25α** and **25β** with somewhat improved diastereoselectivity (**25α**/**25β** = *ca.* 1:2), albeit in less than a 10% yield (not optimized, entry 1). Interestingly, when a mixture of **3**, **2c** and BSA (5.6 eq.) in MeCN was heated at reflux for about 2 h before adding TMSOTf and subsequent refluxing of the resulting mixture,[31,32] a mixture of N^6-trimethylsilylated glycosidation products (**26α** and **26β**) was obtained in a better yield of 46% with no change in diastereoselectivity (**26α**/**26β** = *ca.* 1:2, entry 2). In addition, the reaction led to a complex mixture when too great an excess of TMSOTf (5.0 eq.) was used (entry 3).

The experiments conducted so far revealed the poor diastereoselectivity in the *N*-glycosidation of the glycosyl donors (**2a**, **2b** and **2c**), exhibiting an α/β selectivity of 1:2 at best as shown in Table 2. We therefore finally decided to prioritize the conciseness of the synthetic route over the diastereoselectivity of the *N*-glycosidation step. The modified synthetic route is shown in Scheme 5. Compound **21** was exposed to ozonolysis conditions to give cyclic hemiacetal **27** as an anomeric mixture. The ratio of the α-anomer to β-anomer was 2.8:1 as judged by

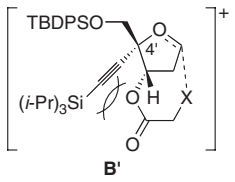
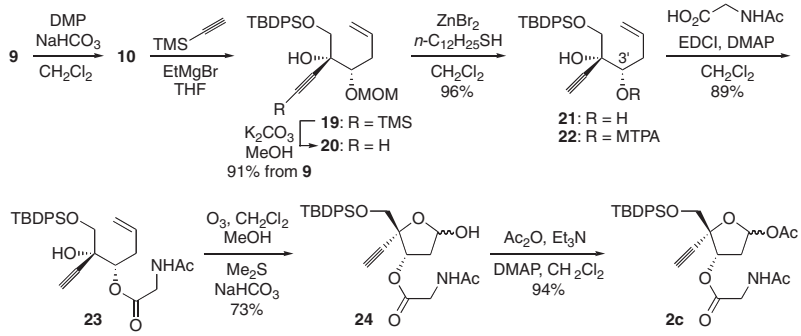
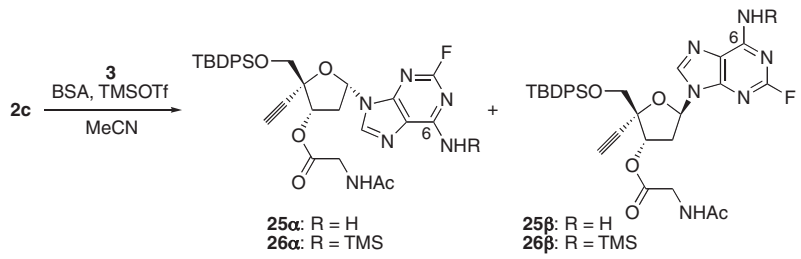


Fig. 3. Unfavorable Steric Interaction in the Transition State Leading to **18β**.



Scheme 4. Preparation of Glycosyl Donor **2c**.

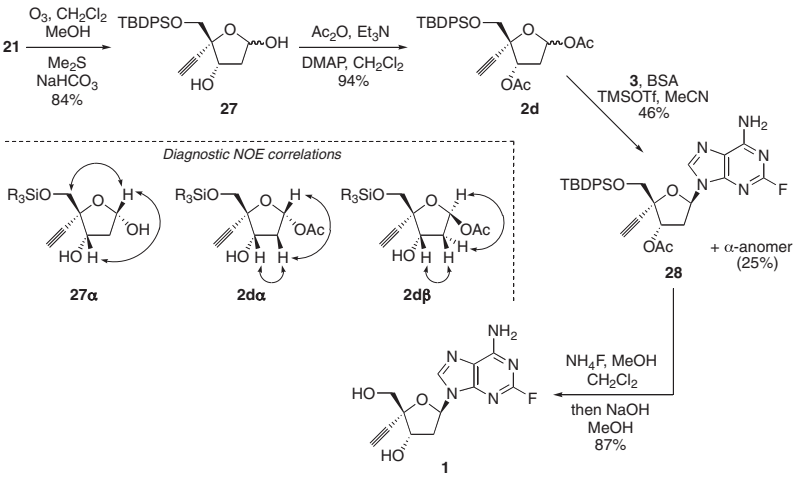
Table 2. *N*-Glycosylation of **2c**



Entry	**3** (eq.)	BSA (eq.)	TMSOTf (eq.)	Temperature	Time (h)	Product (ratio, yield)
1[a]	1.5	1.9	1.9	r.t.	16	**25α**/**25β** (*ca.* 1:2, <10%)
2[b]	1.7	5.6	2.1	reflux	22	**26α**/**26β** (*ca.* 1:2, 46%)
3[b]	1.5	5.5	5.0	reflux	23	decomposition

[a] A mixture of **3**, BSA, and TMSOTf in CH_3CN was refluxed for 4 h. To the mixture was added a solution of **2c** in CH_3CN at 0 °C, and the mixture was stirred at room temperature for 16 h.

[b] A mixture of **3**, BSA, and **2c** in CH_3CN was refluxed for *ca.* 2 h. To the mixture was added TMSOTf at 0 °C, and the mixture was refluxed for the time indicated.



Scheme 5. Completion of the Synthesis of EFdA (**1**).

the ^{1}H-NMR analysis; the stereochemistry of each anomer was determined from the NOEs indicated in Scheme 5 for α-anomer **27*α***. The two hydroxy groups of **27** were acetylated to afford glycosyl donor **2d** as a 1:1.4 anomeric mixture, favoring the β-anomer in this case; the stereochemistry of the anomers (**2d*α*** and **2d*β***) was determined by observing the NOEs indicated in Scheme 5. *N*-Glycosidation of **2d** with **3** under analogous conditions to those employed in entry 2 of Table 2 proceeded considerably cleanly, furnishing a 1.6:1 mixture of β-anomer **28** and the corresponding α-anomer; in this case, no corresponding N^6-silylated products were obtained (*cf.* **26*β***in Table 2). Chromatographic purification of the mixture gave **28** in a 46% isolated yield together with the α-anomer (25%). Finally, the two protecting groups of **27** were easily removed by successively treating with NH_4F[33,34] and a methanolic solution of NaOH in one pot, providing EFdA (**1**) as a white crystalline solid [mp 220.0–221.4 °C (dec.)] in a good yield of 87%. The ^{1}H-NMR spectrum of **1** was identical with that of an authentic sample of EFdA.

In conclusion, the enantioselective total synthesis of EFdA (**1**) was accomplished in an 18% overall yield from commercially available protected aldehyde **6** *via* 12 steps, this being much better both in overall yield and in the number of steps than the previous synthesis by Kohgo and co-workers (2.5% overall yield in 18 steps from 2-amino-2′-deoxyadenosine). Attempts to improve the diastereoselectivity of the *N*-glycosidation step as well as to convert the undesired α-anomer of **28** into desired anomer **28** in the presence of various Lewis acids are currently underway and will be reported in due course.

Experimental

IR spectra were recorded by a Jasco FT/IR-4100 spectrometer, using an ATR (ZnSe) attachment, and are reported in cm^{-1}. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian MR-400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) or a Varian 600TT spectrometer (600 MHz for ^{1}H and 125 MHz for ^{13}C) unless otherwise stated. Optical rotation values were measured with a Jasco DIP-371 polarimeter or a Horiba Septa-300 polarimeter, and the mass spectra were obtained with a Jeol JMS-700 spectrometer operated in the FAB mode. Melting point (mp) data were determined with Yanaco MP-J3 apparatus and are uncorrected. Merck silica gel 60 (7–230 mesh) was used for column chromatography unless otherwise stated. All solvents for the reactions were distilled prior to use: THF from Na and benzophenone; MeOH from Mg and I_2; and CH_2Cl_2, MeCN and DMF from CaH_2.

*(*R*)-4-[(*S*)-1-Methoxymethoxy-3-butenyl]-2,2-dimethyl-1,3-dioxolane (**7**).* Compound **7** was obtained by diastereoselective allylation of **6**, with subsequent MOM-protection and chromatographic purification according to the procedure reported in Refs. 18–20. $[\alpha]^{21}_D$ +23.5 (*c* 1.10, $CHCl_3$); IR ν_{max}: 3080 (w), 1643 (w), 1213 (s), 1153 (s); ^{1}H-NMR (400 MHz) δ: 1.35 (3H, s), 1.41 (3H, s), 2.28–2.42 (2H, m), 3.38 (3H, s), 3.74 (1H, ddd, J = 5.5, 5.5, 5.5 Hz), 3.89 (1H, dd, J = 8.0, 6.4 Hz), 4.04 (1H, dd, J = 8.0, 6.4 Hz), 4.10 (1H, ddd, J = 6.4, 6.4, 5.5 Hz), 4.70 (1H, d, J = 7.2 Hz), 4.72 (1H, d, J = 7.2 Hz), 5.10 (1H, dm, J = 10.0 Hz), 5.13 (1H, dm, J = 17.1 Hz), 5.87 (1H, dddd, J = 17.1, 10.0, 7.1, 7.1 Hz); ^{13}C-NMR (100 MHz) δ: 25.3, 26.4, 36.0, 55.7, 66.0, 76.8, 77.1, 96.3, 109.0, 117.6, 134.1; HRMS (FAB) m/z: calcd. for $C_{11}H_{21}O_4$, 217.1440; found, 217.1444 ($[M+H]^+$).

*(2*R*,3*S*)-3-Methoxymethoxy-5-hexene-1,2-diol (**8**).* To a stirred solution of **7** (3.87 g, 17.9 mmol) in MeOH/H_2O (100:1, 182 mL) was added PPTS (227 mg, 0.903 mmol) at room temperature. After 1.5 h, the mixture was stirred at 55 °C for 1.5 h and then at 60 °C for an additional 2 h. The mixture was quenched with solid $NaHCO_3$ and concentrated *in vacuo*. The residue was diluted with ether, and the resulting ethereal solution was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 20:1) to give 2.62 g (83%) of **8**. $[\alpha]^{23}_D$ +60.9 (*c* 1.13, $CHCl_3$); IR ν_{max}: 3400 (br s), 3077 (w), 1641 (w), 1098 (s); ^{1}H-NMR (400 MHz) δ: 2.30–2.45 (3H, m), 3.04 (1H, d, J = 7.4 Hz), 3.42 (3H, s), 3.62–3.82 (4H, m), 4.66 (1H, d, J = 6.6 Hz), 4.70 (1H, d, J = 6.6 Hz), 5.10 (1H, dm, J = 10.2 Hz), 5.14 (1H, dm, J = 17.2 Hz), 5.83 (1H, dddd, J = 17.2, 10.2, 7.0, 7.0 Hz); ^{13}C-NMR (100 MHz) δ: 36.1, 55.9, 62.9, 72.7, 81.0, 97.3, 117.8, 134.1; HRMS (FAB) m/z: calcd. for $C_8H_{17}O_4$, 177.1127; found, 177.1133 ($[M+H]^+$).

*(2*R*,3*S*)-1-(*tert*-Butyldiphenylsilyloxy)-3-methoxymethoxy-5-hexen-2-ol (**9**).* To a stirred solution of **8** (4.03 g, 22.9 mmol) in DMF (110 mL) were successively added imidazole (3.89 g, 57.2 mmol) and TBDPSCl (6.2 mL, 23.8 mmol) at room temperature in a nitrogen atmosphere. After 2 h, the mixture was diluted with brine and extracted with ether. The extract was successively washed with water and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to give 9.12 g (96%) of **9**. $[\alpha]^{22}_D$ +8.9 (*c* 1.18, $CHCl_3$); IR ν_{max}: 3459 (w), 1641 (w), 1105 (vs), 1033 (vs), 770 (vs); ^{1}H-NMR (400 MHz) δ: 1.07 (9H, s), 2.26–2.42 (2H, m), 2.70 (1H, d, J = 4.3 Hz), 3.26 (3H, s), 3.62–3.82 (4H, m), 4.59 (1H, d, J = 6.9 Hz), 4.62 (1H, d, J = 6.9 Hz), 5.05 (1H, dm, J = 10.1 Hz), 5.08 (1H, dm, J = 17.2 Hz), 5.83 (1H, dddd, J = 17.2, 10.1, 7.1, 7.1 Hz), 7.34–7.48 (6H, m), 7.60–7.70 (4H, m); ^{13}C-NMR (100 MHz) δ: 19.2, 26.8 (3C), 35.3, 55.7, 64.6, 72.7, 78.6, 96.5, 117.3, 127.8 (4C), 129.8 (2C), 133.05, 133.08, 134.6, 135.5

(2C), 135.6 (2C); HRMS (FAB) *m/z*: calcd. for $C_{24}H_{35}O_4Si$, 415.2305; found, 415.2310 ($[M+H]^+$).

*(3*R*,4*S*)-3-[(*tert*-Butyldiphenylsilyloxy)methyl]-4-methoxymethoxy-6-hepten-1-yn-3-ol (**20**).* To a stirred solution of **9** (4.42 g, 10.4 mmol) in CH_2Cl_2 (100 mL) were successively added solid $NaHCO_3$ (4.38 g, 52.2 mmol) and DMP (5.74 g, 13.5 mmol) at room temperature in a nitrogen atmosphere. After 25 min, additional $NaHCO_3$ (5.35 g, 63.6 mmol) and DMP (1.37 g, 3.23 mmol) were added, and the resulting mixture was stirred for 20 min. The mixture was quenched with a mixture of satd. aq. $NaHCO_3$, satd. aq. $Na_2S_2O_3$ and water (1:1:1), and then extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9:1) to give **10** which was then taken up in THF (88 mL). A solution of bromo(trimethylsilylethynyl)magnesium was prepared by adding EtMgBr (1.0 M in THF, 14.0 mL, 14.0 mmol) to a solution of ethynyltrimethylsilane (2.00 mL, 1.36 mmol) in THF (14 mL) at 0 °C and subsequently stirring the resulting mixture at room temperature for 1 h. To the Grignard reagent was added the solution of **10** in THF just obtained at −78 °C in a nitrogen atmosphere, and the mixture was gradually warmed to 0 °C over 3 h and stirred for an additional 13 h. To the mixture containing **19** were successively added MeOH (100 mL) and K_2CO_3 (2.88 g, 20.8 mmol), and the mixture was stirred at reflux for 2 h. Since the desilylation was sluggish with the THF/MeOH solvent, these solvents (THF and MeOH) were evaporated, and the residue was diluted with MeOH (100 mL) and mixed with additional K_2CO_3 (2.71 g, 19.6 mmol). The mixture was stirred at room temperature for 20 min, quenched with satd. aq. NH_4Cl, and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to give 4.17 g (91%) of **20**. $[\alpha]^{23}_D$ −5.0 (*c* 1.04, $CHCl_3$); IR ν_{max}: 3462 (w), 3302 (m), 1641 (w), 1040 (vs), 701 (vs); ^{1}H-NMR (400 MHz) δ: 1.09 (9H, s), 2.43 (1H, dddm, J = 14.7, 8.8, 7.7 Hz), 2.49 (1H, s), 2.69 (1H, ddddd, J = 14.7, 6.5, 3.3, 1.6, 1.6), 3.22 (3H, s), 3.32 (1H, s), 3.73 (1H, dd, J = 8.8, 3.3 Hz), 3.80 (1H, d, J = 9.8 Hz), 3.85 (1H, d, J = 9.8 Hz), 4.62 (1H, d, J = 6.8 Hz), 4.69 (1H, d, J = 6.8 Hz), 5.05 (1H, dm, J = 10.2 Hz), 5.13 (1H, dddd, J = 17.0, 1.7, 1.7, 1.6 Hz), 5.91 (1H, dddd, J = 17.0, 10.2, 7.7, 6.5 Hz), 7.34–7.48 (6H, m), 7.64–7.76 (4H, m); ^{13}C-NMR (100 MHz) δ: 19.3, 26.8 (3C), 35.7, 56.0, 67.8, 73.4, 73.7, 80.9, 83.7, 97.6, 117.1, 127.76 (2C), 127.78 (2C), 129.9 (2C), 132.6, 132.7, 135.5, 135.6 (2C), 135.7 (2C); HRMS (FAB) *m/z*: calcd. for $C_{26}H_{35}O_4Si$, 439.2304; found, 439.2302 ($[M+H]^+$).

*(3*R*,4*S*)-3-[(*tert*-Butyldiphenylsilyloxy)methyl]-6-hepten-1-yne-3,4-diol (**21**).* To a stirred solution of **20** (1.23 g, 2.80 mmol) in CH_2Cl_2 (28 mL) were successively added $ZnBr_2$ (805 mg, 3.58 mmol) and 1-dodecanethiol (1.3 mL, 5.43 mmol) at room temperature. After 30 min, the mixture was quenched with satd. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6:1) to give 1.06 g (96%) of **21**. $[\alpha]^{24}_D$ −2.4 (*c* 1.05, $CHCl_3$); IR ν_{max}: 3512 (m), 3303 (m), 1643 (w), 1111 (vs), 700 (vs); ^{1}H-NMR (400 MHz) δ: 1.09 (9H, s), 2.17 (1H, d, J = 5.7 Hz), 2.23 (1H, ddddd, J = 14.5, 10.3, 7.8, 1.0, 1.0 Hz), 2.48 (1H, s), 2.65 (1H, ddddd, J = 14.5, 6.2, 2.5, 1.3, 1.3 Hz), 3.30 (1H, s), 3.77 (1H, ddd, J = 10.3, 5.7, 2.5 Hz), 3.85 (1H, d, J = 10.0 Hz), 3.92 (1H, d, J = 10.0 Hz), 5.14 (1H, dm, J = 10.2 Hz), 5.17 (1H, dm, J = 17.2 Hz), 5.90 (1H, dddd, J = 17.2, 10.2, 7.8, 6.2 Hz), 7.36–7.48 (6H, m), 7.64–7.74 (4H, m); ^{13}C-NMR (100 MHz) δ: 19.3, 26.8 (3C), 36.1, 67.7, 73.2, 73.7, 74.3, 82.9, 117.8, 127.8 (2C), 127.9 (2C), 130.00, 130.01, 132.4, 132.5, 135.0, 135.56 (2C), 135.63 (2C); HRMS (FAB) *m/z*: calcd. for $C_{24}H_{31}O_3Si$, 395.2043; found, 395.2045 ($[M+H]^+$).

*Determination of the enantiomeric excess of **21**.* (*R*)- and (*S*)-Mono-MTPA esters **22** were prepared by respectively treating **21** with 4.8 equiv of (*S*)- and (*R*)-MTPACl in pyridine overnight at room temperature; the disappearance of starting material **21** was checked by TLC. The TBDPSO-bearing methylene protons of the (*R*)-MTPA ester were observed as a singlet at δ 3.65 (2H, s) in ^{1}H-NMR (600 MHz, $CDCl_3$), while those of the (*S*)-MTPA ester were detected at δ 3.73 (1H, d, J = 10.3 Hz) and d 3.75 (1H, d, J = 10.3 Hz). A comparison of the two spectra indicated the enantiomeric excess of **21** to be more than 95%.

*(2*R/S*,4*S*,5*R*)-5-[(*tert*-Butyldiphenylsilyloxy)methyl]-5-ethynyltetrahydrofuran-2,4-diol (**27**).* Ozone was bubbled into a solution of **21** (3.21 g, 8.13 mmol) in CH_2Cl_2/MeOH (4:1, 100 mL) at −78 °C for 25 min. After removing excess ozone by a stream of O_2 (for about 10 min), $NaHCO_3$ (3.33 g, 39.6 mmol) and Me_2S (6.0 mL, 81.7 mmol) were successively added, and the resulting mixture was gradually warmed to room temperature. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2:1–3:2) to give 2.71 g (84%) of **27** as an anomeric mixture (α-anomer/β-anomer = 2.8:1). $[\alpha]^{24}_D$ +5.7 (*c* 0.99, $CHCl_3$); IR ν_{max}: 3411 (br s), 3291 (s), 1084 (vs), 701 (vs); ^{1}H-NMR (400 MHz) δ: 1.05 (0.74 × 9H, s), 1.09 (0.26 × 9H, s), 2.10 (0.26H, d, J = 6.9 Hz), 2.16 (0.74H, ddd, J = 13.6, 1.4, 0.8 Hz), 2.16–2.24 (0.26H, m), 2.31 (0.26H, ddd, J = 13.5, 6.5, 2.2 Hz), 2.36 (0.74H, ddd, J = 13.6, 5.3, 5.3 Hz), 2.65 (0.26H, s), 2.70 (0.74H, s), 2.80 (0.74H, d, J = 5.5 Hz), 3.00 (0.26H, d, J = 6.1 Hz), 3.57 (0.74H, d, J = 7.2 Hz), 3.63 (0.74H, d, J = 10.6 Hz), 3.76 (0.74H, d, J = 10.6 Hz), 3.81 (0.26H, d, J = 10.5 Hz), 3.85 (0.26H, d, J = 10.5 Hz), 4.42 (0.74H, ddd, J = 5.5, 5.3, 1.4 Hz), 4.62 (0.26H, br q, J = 6.9 Hz), 5.51 (0.74H, br dd, J = 7.2, 5.0 Hz), 5.58 (0.26H, ddd, J = 6.1, 5.5, 5.2 Hz), 7.34–7.50 (6H, m), 7.60–7.74 (4H, m); ^{13}C-NMR (100 MHz) δ: 19.2, 26.7/26.8 (3C), 41.2/41.8, 67.1/67.5, 72.3/74.0, 77.7, 80.7, 84.3/85.9, 97.9/100.2, 127.8/127.9 (4C), 129.88/129.92/129.96/130.03 (2C), 132.61/132.64 (2C), 135.6/135.7 (4C); HRMS (FAB) *m/z*: calcd. for $C_{23}H_{28}O_4SiNa$, 419.1655; found, 419.1656 ($[M+Na]^+$).

*(2*R*,3*S*,5*R*/S)-5-Acetoxy-2-[(*tert*-butyldiphenylsilyloxy)methyl]-2-ethynyltetra-hydrofuran-3-yl acetate (**2d**).* To a stirred solution of **27** (135 mg, 0.340 mmol) and DMAP (25.8 mg, 0.211 mmol) in CH_2Cl_2 (3.5 mL) were successively added Et_3N (210 mL, 1.51 mmol) and Ac_2O (130 mL, 1.38 mmol) at room temperature. After 1.5 h, the mixture was quenched with satd. aq. NH_4Cl and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to give 153 mg (94%) of **2d** as an anomeric mixture (α-anomer/β-anomer = 1:1.4). $[\alpha]^{24}_D$ −11.4 (*c* 0.97, $CHCl_3$); IR ν_{max}: 3281 (w), 1744 (vs), 1227 (s), 702 (s); ^{1}H-NMR (400 MHz) δ: 1.05 (0.42 × 9H, s), 1.09 (0.58 × 9H, s), 1.86 (0.58 × 3H, s), 2.11 (0.42 × 3H, s), 2.12 (0.58 × 3H, s), 2.15 (0.42 × 3H, s), 2.24 (0.42H, dm, J = 14.5 Hz), 2.44 (0.58H, ddd, J = 13.7, 7.0, 5.6 Hz), 2.508 (0.58H, ddd, J = 13.7, 7.0, 2.5 Hz), 2.509 (0.42H, s), 2.53 (0.58H, s), 2.70 (0.42H, ddd, J = 14.5, 7.8, 5.4 Hz), 3.82 (0.58H, d, J = 10.8 Hz), 3.83 (0.42H, d, J = 10.8 Hz), 3.86 (0.58H, d, J = 10.8 Hz), 3.90 (0.42H, d, J = 10.8 Hz), 5.65 (0.42H, dd, J = 7.8, 1.6 Hz), 5.73 (0.58H, t, J = 7.0 Hz), 6.41 (0.42H, d, J = 5.4 Hz), 6.43 (0.58H, dd, J = 5.6, 2.5 Hz), 7.34–7.48 (6H, m), 7.64–7.74 (4H, m); ^{13}C-NMR (100 MHz) δ: 19.2/19.3, 21.0, 21.2/21.3, 26.68/26.71 (3C), 37.3/38.9, 66.5/67.9, 72.0/73.5, 76.40/76.43, 79.0/79.2, 84.1/85.9, 96.5/98.6, 127.72/127.76 (2C), 127.82/127.83 (2C), 129.7/129.8/129.9 (2C), 132.4/132.6, 132.7/132.9, 135.5 (2C), 135.6/135.7 (2C), 169.96/169.97, 170.35/170.38; HRMS (FAB) *m/z*: calcd. for $C_{27}H_{32}O_6SiNa$, 503.1866; found, 503.1864 ($[M+Na]^+$).

*(2*R*,3*S*,5*R*)-5-(6-Amino-2-fluoropurin-9-yl)-2-[(*tert*-butyldiphenylsilyloxy)-methyl]-2-ethynyltetrahydrofuran-3-yl acetate (**28**).* To compound **3** (188 mg, 1.23 mmol) were added a solution of **2d** (387 mg, 0.805 mmol) in CH_3CN (8.0 mL) and BSA (1.10 mL, 4.50 mmol) at room temperature. The mixture was stirred at reflux for 2.5 h and then cooled to 0 °C. To the resulting solution was added TMSOTf (0.300 mL, 1.66 mmol), before the mixture was stirred at room temperature for 15 min and then at reflux for an additional 17 h. The mixture was quenched with satd. aq. $NaHCO_3$ and filtered through a pad of Celite. The filtrate was diluted with water and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 100:1) to give 213 mg (46%) of **28** and 115 mg (25%) of the corresponding α-anomer. *Compound **28**.* Mp 182.6–183.3 °C; $[\alpha]^{26}_D$ +24.3 (*c* 1.13, $CHCl_3$); IR ν_{max}: 1747 (m),

1635 (s), 1362 (s), 702 (vs); ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 0.96 (9H, s), 2.13 (3H, s), 2.61 (1H, ddd, J = 14.0, 6.8, 4.7 Hz), 3.20 (1H, ddd, J = 14.0, 6.8, 6.8 Hz), 3.74 (1H, s), 3.78 (1H, d, J = 10.6 Hz), 3.95 (1H, d, J = 10.6 Hz), 5.82 (1H, dd, J = 6.8, 4.7 Hz), 6.37 (1H, dd, J = 6.8, 6.8 Hz), 7.32–7.38 (4H, m), 7.42–7.48 (2H, m), 7.54–7.64 (4H, m), 7.78–7.85 (1H, br s), 7.85–8.04 (1H, br s), 8.27 (1H, s); ^{13}C-NMR (150 MHz) δ: 19.1, 21.1, 26.7 (3C), 34.6, 66.7, 72.9, 79.6, 79.8, 83.0, 83.3, 118.0, 128.03 (2C), 128.05 (2C), 130.16, 130.18, 132.5, 132.7, 135.3 (2C), 135.4 (2C), 140.3, 150.5 (d, J_{CF} = 20.2 Hz), 157.9 (d, J_{CF} = 21.3 Hz), 158.7 (d, J_{CF} = 204.4 Hz), 169.6; HRMS (FAB) m/z: calcd. for $C_{30}H_{33}FN_5O_4Si$, 574.2286; found, 574.2290 ([M + H]$^+$). *α-Anomer of* ***28***. Mp 221.0–221.7 °C; $[\alpha]^{25}_D$ +16.7 (c 1.03, $CHCl_3$); IR ν_{max}: 3330 (w), 3276 (w), 1759 (m), 1372 (s), 700 (vs); ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 1.05 (9H, s), 2.08 (3H, s), 2.81 (1H, ddd, J = 14.4, 3.8, 3.5 Hz), 3.05 (1H, ddd, J = 14.4, 7.3, 7.3 Hz), 3.75 (1H, d, J = 10.6 Hz), 3.77 (1H, s), 3.79 (1H, d, J = 10.6 Hz), 5.71 (1H, dd, J = 7.3, 3.5 Hz), 6.37 (1H, dd, J = 7.3, 3.8 Hz), 7.44–7.54 (6H, m), 7.66–7.74 (4H, m), 7.80–7.98 (2H, br m), 8.29 (1H, s); ^{13}C-NMR (150 MHz) δ: 19.1, 21.1, 26.8 (3C), 36.6, 67.5, 73.3, 79.2, 80.5, 83.4, 84.8, 117.4, 128.26 (2C), 128.27 (2C), 130.3, 130.4, 132.3, 132.4, 135.4 (2C), 135.5 (2C), 139.1, 150.9 (d, J_{CF} = 20.2 Hz), 157.9 (d, J_{CF} = 21.3 Hz), 159.0 (d, J_{CF} = 203.6 Hz), 169.5; HRMS (FAB) m/z: calcd. for $C_{30}H_{33}FN_5O_4Si$, 574.2286; found, 574.2285 ([M + H]$^+$).

*(2R,3S,5R)-5-(6-Amino-2-fluoropurin-9-yl)-2-ethynyl-2-(hydroxymethyl)-tetrahydrofuran-3-ol (**1**).* To a stirred solution of **28** (66.2 mg, 0.115 mmol) in MeOH/CH_2Cl_2 (2:1, 1.5 mL) was added NH_4F (85.1 mg, 2.30 mmol) at room temperature. After 16 h, MeOH (0.5 mL) was added, and the resulting mixture was stirred for an additional 27 h. To the mixture was added 10% (w/v) methanolic NaOH (1.5 mL) to adjust the pH value of the mixture to *ca.* 10. After 10 min, Dowex 50W×8 (200–400 mesh (H)) was added until the pH value of the mixture reached *ca.* 4. To the resulting mixture was added $CaCO_3$ (259 mg, 2.59 mmol), and the mixture was stirred for 30 min. The mixture was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to give 29.3 mg (87%) of **1**. Mp 220.0–221.4 °C (dec.); $[\alpha]^{25}_D$ +12.4 (c 0.97, MeOH); IR ν_{max}: 3315 (br m), 3179 (br m), 1690 (vs), 1356 (vs); ^{1}H-NMR (600 MHz, DMSO-d_6) δ: 2.43 (1H, ddd, J = 13.2, 7.3, 7.3 Hz), 2.70 (1H, ddd, J = 13.2, 6.8, 5.1 Hz), 3.52 (1H, s), 3.54 (1H, dd, J = 11.7, 6.4 Hz), 3.65 (1H, dd, J = 11.7, 5.0 Hz), 4.57 (1H, m), 5.32 (1H, m), 5.60 (1H, m), 6.24 (1H, dd, J = 7.2, 5.1 Hz), 7.82 (1H, br s), 7.92 (1H, br s), 8.31 (1H, s); ^{13}C-NMR (150 MHz) δ: 38.3, 64.4, 70.3, 79.2, 81.7, 82.2, 85.4, 117.6, 140.0, 150.4 (d, J_{CF} = 20.7 Hz), 157.8 (d, J_{CF} = 21.2 Hz), 158.8 (d, J_{CF} = 203.4 Hz); HRMS (FAB) m/z: calcd. for $C_{12}H_{13}FN_5O_3$, 294.1002; found, 294.1000 ([M + H]$^+$).

*Diagnostic NOE correlations in compounds **2a**, **14β**, **27α**, **2dα**, and **2dβ**.* **2a** (400 MHz, $CDCl_3$): between the C3′ proton (δ: 4.69, 1H, dd, J = 9.4, 6.7 Hz) and the C5′ protons (δ: 3.82, 1H, s). **14β** (400 MHz, acetone-d_6): between the C8 proton (δ: 8.16, 1H, s) and the protons at the C3′ (δ: 5.00, 1H, t, J = 7.3 Hz) and C5′ (δ: 3.95, 1H, d, J = 11.0 Hz and δ: 4.02, 1H, d, J = 11.0 Hz) positions. **27α** (400 MHz, $CDCl_3$): between the C3′ proton (δ: 4.42, 0.74H, ddd, J = 5.5, 5.3, 1.4 Hz) and the protons at the C1′ (δ: 5.51, 0.74H, br dd, J = 7.2, 5.0 Hz) and C5′ (δ: 3.63, 0.74H, d, J = 10.6 Hz) positions. **2dα** (400 MHz, $CDCl_3$): between the C2′-β proton (δ: 2.70, 0.42H, ddd, J = 14.5, 7.8, 5.4 Hz) and the protons at the C1′ (δ: 6.41, 0.42H, d, J = 5.4 Hz) and C3′ (δ: 5.65, 0.42H, dd, J = 7.8, 1.6 Hz) positions. **2dβ** (400 MHz, $CDCl_3$): between the C1′ proton (δ: 6.43, 0.58H, dd, J = 5.6, 2.5 Hz) and the C2′-α proton (δ: 2.44, 0.58H, ddd, J = 13.7, 7.0, 5.6 Hz), and between the C2′-β proton (δ: 2.508, 0.58H, ddd, J = 13.7, 7.0, 2.5 Hz) and the C3′ proton (δ: 5.73, 0.58H, t, J = 7.0 Hz).

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References

1) Nikolenko GN, Kotelkin AT, Oreshkova SF, and Ilyichev AA, *Mol. Biol.*, **45**, 93–109 (2011).
2) Sharma B, *Neurobehav. HIV Med.*, **2**, 27–40 (2011).
3) Deval J, *Drugs*, **69**, 151–166 (2009).
4) Sarafianos SG, Marchand B, Das K, Himmel DM, Parniak MA, Hughes SH, and Arnold E, *J. Mol. Biol.*, **385**, 693–713 (2009).
5) Michailidis E, Marchand B, Kodama EN, Singh K, Matsuoka M, Kirby KA, Ryan EM, Sawani AM, Nagy E, Ashida N, Mitsuya H, Parniak MA, and Sarafianos SG, *J. Biol. Chem.*, **284**, 35681–35691 (2009).
6) Kohgo S, Ohrui H, Kodama E, Matsuoka M, and Mitsuya H, Can. Patent Appl., CA 2502109 (Mar. 22, 2005).
7) Kohgo S, Yamada K, Kitano K, Iwai Y, Sakata S, Ashida N, Hayakawa H, Nameki D, Kodama E, Matsuoka M, Mitsuya H, and Ohrui H, *Nucleosides Nucleotides Nucleic Acids*, **23**, 671–690 (2004).
8) Ohrui H, *Chem. Rec.*, **6**, 133–143 (2006).
9) Ohrui H, Hayakawa H, Kohgo S, Matsuoka M, Kodama E, and Mitsuya H, *J. Synth. Org. Chem. Jpn.*, **64**, 716–723 (2006).
10) Ohrui H, Kohgo S, Hayakawa H, Kodama E, Matsuoka M, Nakata T, and Mitsuya H, *Nucleosides Nucleotides Nucleic Acids*, **26**, 1543–1546 (2007).
11) Ohrui H, *Proc. Jpn. Acad. B*, **87**, 53–65 (2011).
12) Kawamoto A, Kodama E, Sarafianos SG, Sakagami Y, Kohgo S, Kitano K, Ashida N, Iwai Y, Hayakawa H, Nakata H, Mitsuya H, Arnold E, and Matsuoka M, *Int. J. Biochem. Cell Biol.*, **40**, 2410–2420 (2008).
13) Nakata H, Amano M, Koh Y, Kodama E, Yang G, Bailey CM, Kohgo S, Hayakawa H, Matsuoka M, Anderson KS, Cheng Y-C, and Mitsuya H, *Antimicrob. Agents Chemother.*, **51**, 2701–2708 (2007).
14) Hattori S, Ide K, Nakata H, Harada H, Suzu S, Ashida N, Kohgo S, Hayakawa H, Mitsuya H, and Okada S, *Antimicrob. Agents Chemother.*, **53**, 3887–3893 (2009).
15) Kageyama M, Nagasawa T, Yoshida M, Ohrui H, and Kuwahara S, *Org. Lett.*, **13**, 5264–5266 (2011).
16) Eaton CN and Denny Jr GH, *J. Org. Chem.*, **34**, 747–748 (1969).
17) Saischek G, Austrian Patent Appl., 505606 (Feb. 15, 2009).
18) Reddy BVS, Reddy BP, Pandurangam T, and Yadav JS, *Tetrahedron Lett.*, **52**, 2306–2308 (2011).
19) Nagaiah K, Sreenu D, Purnima KV, Rao RS, and Yadav JS, *Synthesis*, 1386–1392 (2009).
20) Einhorn C and Luche J-L, *J. Organomet. Chem.*, **322**, 177–183 (1987).
21) Maddaford A, Wainwright P, Glen R, Fisher R, Dragovich PS, Gonzalez J, Kung P-P, Middleton DS, Pryde DC, Stephenson PS, and Sutton SC, *Synthesis*, 1378–1384 (2007).
22) Druais V, Hall MJ, Corsi C, Wendeborn SV, Meyer C, and Cossy J, *Tetrahedron*, **66**, 6358–6375 (2010).
23) Wright GE and Dudycz LW, *J. Med. Chem.*, **27**, 175–181 (1984).
24) Vorbrüggen H and Ruh-Pohlenz C, *Org. React.*, **55**, 1–630 (2000).
25) Caddell JM, Chapman AM, Cooley BE, Downey BP, LeBlanc MP, Jackson MM, O'Connell TM, Phung H-M, Roper TD, and Xie S, *J. Org. Chem.*, **69**, 3212–3215 (2004).
26) Liu Z, Li D, Yin B, and Zhang J, *Tetrahedron Lett.*, **51**, 240–243 (2010).
27) Sohn J-H, Waizumi N, Zhong HM, and Rawal VH, *J. Am. Chem. Soc.*, **127**, 7290–7291 (2005).
28) Han JH, Kwon YE, Sohn J-H, and Ryu DH, *Tetrahedron*, **66**, 1673–1677 (2010).
29) Harry-O'kura RE, Smith JM, and Wolfe MS, *J. Org. Chem.*, **62**, 1754–1759 (1997).
30) Imazawa M and Eckstein F, *J. Org. Chem.*, **44**, 2039–2041 (1979).
31) Augustyns K, Rozenski J, Van Aerschot A, Janssen G, and Herdewijn P, *J. Org. Chem.*, **58**, 2977–2982 (1993).
32) Foitzik RC, Devine SM, Hausler NE, and Scammells PJ, *Tetrahedron*, **65**, 8851–8857 (2009).
33) Zhang W and Robins MJ, *Tetrahedron Lett.*, **33**, 1177–1180 (1992).
34) Kaburagi Y and Kishi Y, *Org. Lett.*, **9**, 723–826 (2007).