Stereoselective Syntheses of β-L-FD4C and β-L-FddC

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Stereocontrolled syntheses of two potent antiviral agents, β-L-FD4C and β-L-FddC, were accomplished both in 10-step sequences, with an overall yield of 27% and 25%, respectively. It is worthwhile to mention that the introduction of a phenylseleno moiety to the C-2α position of the lactone **4** can now be performed in a stereocontrolled fashion, providing the key intermediate **5**α in 75% yield.

Introduction

Since the approval of 3′-deoxy-3′-azidothymidine (AZT)[1] as a first-line therapeutic agent for the treatment of human immunodeficiency virus (HIV), considerable effort has been devoted to design and synthesis of nucleoside analogs that would inhibit the replication of this and related viruses. Out of this effort came the discovery of a series of novel nucleoside analogs possessing potent antiviral activity, including 2′,3′-dideoxycytidine (D-ddC),[2] 2′,3′-dideoxyinosine (D-ddI),[3] and 2′,3′-dideoxy-2′,3′-didehydrothymidine (D-D4T).[4]

More recently, a number of L-configuration nucleoside analogs, the enantiomers of the natural D-nucleosides, have emerged as potent antiviral agents against HIV and HBV.[5] The interest in L-nucleosides was spurred in recent years by the fact that L-nucleosides would be recognized by virus-encoded or bacterial enzymes but not by normal mammalian enzymes.[6a] For example, Spadari et al. reported that L-thymidine is not recognized by human thymidine kinase but functions as a specific substrate for the herpes simplex virus type 1 (HSV-1) viral enzyme and reduces HSV-1 multiplication in HeLa cells.[6b] Thus, L-nucleosides are generally endowed with minimal host toxicity while maintaining good antiviral/antibacterial activity.

To date, β-L-SddC (3TC, **1**) is the first and only L-nucleoside derivative that has been approved by the FDA for use in combination therapy against HIV and HBV.[7] In light of this encouraging finding, a large number of 2′,3′-dideoxy (dd)- and 2′,3′-didehydro-2′,3′-dideoxy (D4)-L-nucleoside analogs have been synthesized and evaluated as potential antiviral agents. 2′,3′-Dideoxy-2′,3′-didehydro-β-L-fluorocytidine (β-L-FD4C, **2**)[8] and 2′,3′-dideoxy-β-L-fluorocytidine (β-L-FddC, **3**)[9] were found to be promising new leads. When evaluated *in vitro* against HIV, both of these agents were found to be more potent than 3TC (**1**). Thus, the design of a convergent synthesis for these highly potent antiviral agents is an important endeavor. In this paper, we wish to report a highly stereoselective and high-yielding synthesis for both **2** and **3**.

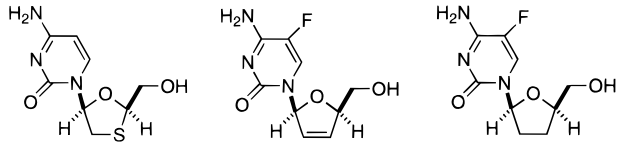

Figure 1. Structures of representative L-nucleosides.

Discussion

The first synthesis and the antiviral activity assessment of β-L-FD4C (**2**) was reported recently by Lin and Cheng at Yale.[8] Prompted by the impressive anti-HIV and anti-HBV activity displayed by this novel L-nucleoside, we launched a synthetic program with the aim of designing a high-yielding and practical synthesis of β-L-FD4C (**2**).

As depicted in Scheme 1, the logic of our approach is based on the recent findings from Chu,[11] Liotta,[12] and others.[13] These authors have shown that a bulky substituent (e.g. R = SePh, SAr) bonded to the C-2α position of lactol **7** can exert a remarkable directing effect in the N-glycosylation reaction at C-1, ensuring the formation

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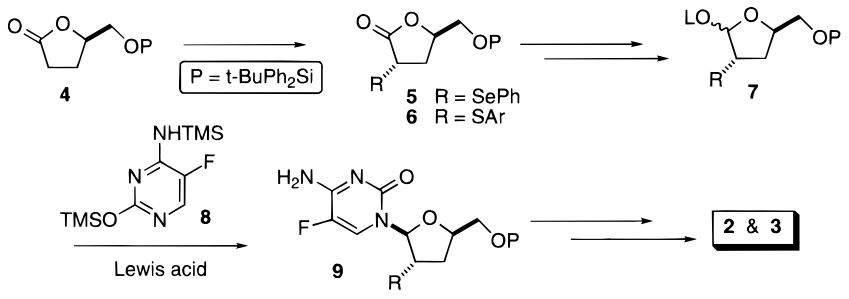
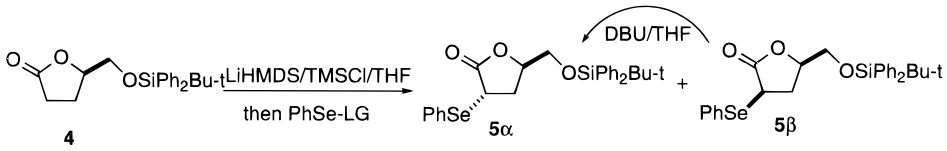
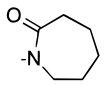
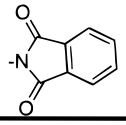
Scheme 1. Proposed Synthetic Plan



Scheme 2



LG	Temp. (0°C)	Y (5α%)	Y (5β%)	Ratio (5α/5β)
-Br	-78	60	24	2.5:1
	-78	40	13.5	3.0:1
	-78	70-75	<1.7	**>40:1**

of the desired *cis*-nucleosides (e.g. **9**). On the basis of observations made by the above investigators, we envisioned that high stereoselectivity in the N-glycosylation step (**7** to **9**) may be achieved *via* a similar Lewis acid-catalyzed coupling between lactol **7** and the bis-TMS-fluorocytosine (**8**). Successful incorporation of 5-fluorocytosine directly can shorten the synthesis of **2** and **3** by two steps (in comparison with ref 8), thereby contributing to the overall efficiency of the synthesis. Furthermore, since oxidative removal of the arylsulfenyl group in compound **9** (R = SAr) requires elevated temperature, we decided to use the phenylseleno moiety at C-2 as the handle for stereoselectivity. Thus, at the end of the sequence, oxidative removal of the phenylseleno group in **9** should provide the β-L-FD4C (**2**). On the other hand, reductive removal of the 2α-phenylseleno moiety from **9** should produce the β-L-FddC (**3**).

As shown in Scheme 2, we began our synthetic effort with C-2 phenylselenation of the lactone **4**,[11a] a known intermediate prepared in four steps from readily available D-glutamic acid. In agreement with the report from Chu,[11b,c] C-2 phenylselenation of the lactone **4** with phenylseleno bromide provided a mixture of products (**5**α and **5**β) with a ratio of 2.5:1 favoring the desired 2α-phenylseleno lactone **5**α. As expected, chromatographic separation of **5**α from its diastereomer **5**β proved to be a rather difficult undertaking. Although compound **5**β can be converted partially to the desired diastereomer **5**α by refluxing a THF solution of **5**β with DBU, the tedious labor required and the overall cost associated with this process precluded its utility as a choice for scale-up. In view of this problem, we felt that the use of *bulkier* phenylseleno reagents could in principle lead to higher level of facial selectivity in the C-2 phenylselenation reaction. Indeed, reaction of the trimethylsilylenol ether (generated *in situ* from **4**) with (phenylseleno)caprolactam yielded a slightly higher ratio of **5**α/**5**β (3:1).[14] Following the same logic, we then decided to use another bulky *N*-(phenylseleno)phthalimide[15] as our phenylselenation reagent. To our satisfaction, attempted C-2 phenylselenation at −78 °C gave an excellent level of selectivity (**5**α/**5**β > 40:1), affording the desired diastereomer **5**α in 70−75% yield. Thus, a stereospecific method for the C-2α phenylselenation of lactone **4** has been firmly established.

Having solved the problem encountered in the stereoselective synthesis of the C-2α phenylseleno lactone **5**α, our next goal was to explore the reaction conditions that will allow the stereospecific N-glycosylation at C-1. As shown in Scheme 3, C-2α phenylseleno lactone **5**α was first reduced with DIBAL-H in toluene at −78 °C to afford the lactol **10** in 87−98% yield. Acetylation of lactol **10** yielded the corresponding C-1 acetyl-lactol **11** in nearly quantitative yield. Coupling of the bis-TMS-5-fluorocytosine **8** (prepared *in situ* from 5-fluorocytosine) with **11** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) provided, to our satisfaction, the desired 1,4-*cis*-nucleoside **12** in greater than 95% yield.[11b−d]

As also shown in Scheme 3, the syntheses of both β-L-FD4C (**2**) and β-L-FddC (**3**) were completed in two steps from **12**. Treatment of **12** with hydrogen peroxide in the presence of pyridine afforded up to 95% yield of the D4 nucleoside **13**, thereby the final β-L-FD4C **2**, upon triethylamine trihydrofluoride-mediated desilylation.[16] On

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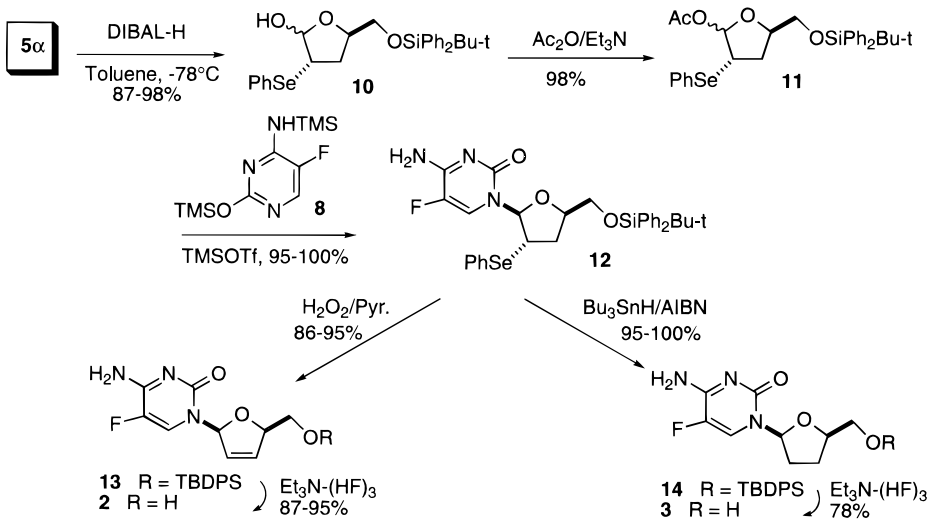
(15) Crystalline *N*-(phenylseleno)phthalimide can be purchased from Beta Chemicals, Inc. Fax: (203)786-5437.

Scheme 3



the other hand, reductive removal of the phenylseleno moiety in **12** was accomplished using tributyltin hydride as the reductant[11b,c] and afforded the 2′,3′-dideoxy nucleoside **14** in almost quantitative yield. After final desilylation, the desired β-L-FddC **3** was isolated in 78% yield.

Both β-L-FD4C (**2**) and β-L-FddC (**3**) synthesized in our laboratory as well as 3TC (**1**) were evaluated for their anti-HBV activity using a slightly modified literature procedure.[17] The EC_{50} (extracellular) values of these L-nucleosides were found to be 7.5 nM for **2**, 74 nM for **3** and 45 nM for **1**. Thus, β-L-FD4C is six-fold more potent than 3-TC in this assay, whereas, β-L-FddC is 1.6-fold less potent than 3-TC in the same assay. Given the variability of this assay, the result obtained in our laboratory is in good agreement with that reported by Lin and Cheng.[8]

In summary, we have reported herein a convergent synthetic route that allows large scale synthesis of potent antiviral agents β-L-FD4C (**2**) and β-L-FddC (**3**) in a stereocontrolled fashion. These two L-nucleosides were constructed in 10 steps from commercial available D-glutamic acid. It is important to note that simply switching the staring material to L-glutamic acid, the same reaction sequence described herein also allows the synthesis of the enantiomers of **2** and **3**.

Experimental Section

C-2′ Phenylseleno Lactones (5α and 5β). A THF solution (106 mL) of the lactone **4** (12.50 g, 35.27 mmol) ($[\alpha]^{23}_D$ = −25.42° (*c* = 1.06, $CHCl_3$)) was treated at −78 °C with LiHMDS (35.30 mL, 1 M in THF) for 15 min, and neat TMSCl (4.48 mL, 35.27 mmol) was then added over 2 min. The resulting reaction mixture was stirred at −78 °C for 1 h. A THF solution (40 mL) of PhSeBr (8.34 g, 35.27 mmol) was added slowly over 20 min. The reaction mixture was stirred at −78 °C for 30 min and then at rt for 2 h. The reaction was then quenched with saturated NH_4Cl solution. The reaction solvent was partially removed *in vacuo*. The resulting mixture was extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. Upon evaporation, the resulting residue was purified by silica gel column chromatography (10−20% EtOAc/hexanes) to afford 10.80 g (60%) of the 2′α-phenylselenide **5**α along with 4.40 g (24%) of its isomer **5**β.

A THF solution (35 mL) of **5**β (4.40 g, 8.64 mmol) was treated with DBU (3.10 mL, 20.74 mmol) at rt for 24 h. The solvent was then partially removed *in vacuo*. The reaction mixture was diluted with EtOAc (150 mL) and washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried, evaporated, and purified to provide 2.3 g (52%) of **5**α along with 1.3 g (30%) of recovered **5**β.

Stereoselective Conversion of 4 to 5α Using *N*-(Phenylseleno)phthalimide. Lithium bis(trimethysilyl) amide in THF (1 M, 32.2 mL, 32.20 mmol) was added to 6 mL of THF under N_2 and cooled to −78 °C. Compound **12** (10.36 g, 29.30 mmol) dissolved in 20 mL of THF was added slowly to the above solution over 45 min at −78 °C. After 1h, TMSCl (5.0 mL, 64.46 mmol) was added dropwise over 5 min. This mixture was then stirred at −78 °C for 1 h, warmed to rt, and stirred for 2 h. The reaction mixture was then cooled to −78 °C, and *N*-(phenylseleno)phthalimide (11.0 g, 36.40 mmol) was added through a powder additional funnel over 1 h. Stirring at −78 °C was continued for 3 h, followed by warming to rt for 30 min. The reaction mixture was poured into 150 mL of $NaHCO_3$ solution and 300 mL of ether, and the organic layer was then extracted twice with $NaHCO_3$ and once with NaCl solution. The aqueous layers were back-extracted with 100 mL of ether, and the organic layers were combined, and dried over $MgSO_4$, and the solvent was removed *in vacuo*. Purification of the crude by column chromatography afforded 11.20 g of **5**α (yield 75%). Minor *cis*-isomer **5**β (200 mg) (1%) was also obtained.

^{1}H NMR of **5**α ($CDCl_3$, 300 MHz): δ 7.75−7.32 (m, 15H), 4.40 (m, 1H), 4.16 (dd, *J* = 5.4, 9.2 Hz, 1H), 3.90 (dd, *J* = 2.9, 11.5 Hz, 1H), 3.66 (dd, *J* = 3.1, 11.5 Hz, 1H), 2.75 (m, 1H), 2.33 (m, 1H), 1.10 (s, 9H); ^{13}C NMR of **5**α ($CDCl_3$, 75 MHz): δ 176.1, 135.8, 135.7, 135.6, 132.9, 132.5, 130.1, 129.5, 129.1, 128.0, 127.2, 78.8, 65.0, 37.3, 32.5, 27.0, 19.3. $[\alpha]^{23}_D$ of **5**α = −15.94° (*c* = 1.44, $CHCl_3$).

^{1}H NMR of **5**β ($CDCl_3$, 300 MHz): δ 7.70−7.26 (m, 15H), 4.54 (m, 1H), 4.07 (t, *J* = 9.5 Hz, 1H), 3.76−3.63 (m, 2H), 2.68 (m, 1H), 2.27 (m, 1H), 1.10 (s, 9H); ^{13}C NMR of **5**β ($CDCl_3$, 75 MHz): δ 175.8, 135.7, 135.5, 133.0, 132.9, 130.0, 129.4, 128.9, 127.9, 127.5, 78.8, 64.8, 37.1, 31.8, 26.9, 19.4.

Lactol 10. A toluene solution (10 mL) of the 2′α-phenylselenide lactone **5**α (1.63 g, 3.20 mmol) was treated at −78 °C with DIBAL-H (2.35 mL, 1.5 M in toluene, 3.53 mmol). After 1 h, an additional amount of DIBAL-H (0.32 mL, 1.5 M in toluene, 0.48 mmol) was added. After 30 min, the reaction was quenched at −78 °C with a saturated solution of sodium potassium tartrate (40 mL). The reaction mixture was warmed to rt and extracted with EtOAc (2 × 50 mL). The combined organic layer was further washed with saturated sodium potassium tartrate solution until a clear solution was obtained. The organic layer thus obtained was dried and evaporated *in*

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(17) Korba, B. E.; Milman, G. A cell culture assay for compounds which inhibit hepatitis B virus replication. *Antiviral Res.* **1991**, *15*, 217−228.

vacuo. The residue was chromatographed on silica gel (10−20% EtOAc/hexanes) to provide 1.60 g (98%) of **10**.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.80−7.26 (m, 15H), 5.64−5.44 (m, 1H), 4.45 (m, 1H), 4.10−3.52 (m, 4H), 2.79−2.00 (m, 2H), 1.13−1.06 (m, 9H).

Lactol Acetate 11. To a dichloromethane solution (18 mL) of the lactol **10** (4.50 g, 8.80 mmol) were added triethylamine (1.59 mL, 11.44 mmol) and acetic anhydride (1.08 mL, 11.44 mmol) at 0 °C. A catalytic amount of DMAP was also added. The reaction was stirred at 0 °C for 1 h and then at rt for 12 h. The reaction was quenched with saturated $NaHCO_3$ solution (20 mL), and the resulting reaction mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layer was washed with brine, dried, and concentrated in vacuo. The residue was purified through a short silica gel column (15% ethyl acetate/hexanes) to provide 4.75 g (98%) of **11** as a thick oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74−7.20 (m, 15H), 6.44−6.22 (m, 1H), 4.44−3.52 (m, 4H), 2.58−2.08 (m, 2H), 1.86 and 1.55 (s, 1H), 1.02 and 0.92 (s, 9H). LRFAB mass calcd for $C_{29}H_{35}O_4SiSe$ (MH^+): 554, found: 554.

Compound 12. A mixture of 5-F-cytosine (1.11 g, 8.58 mmol) and ammonium sulfate (40 mg) in $(TMS)_2NH$ (10 mL) was heated to reflux for 2 h. A clear solution resulted. The reaction mixture was cooled to rt, and the solvent was removed *in vacuo*. The resulting white solids (bis-TMS-5-FC, **8**) were dried under high vacuum for 30 min.

To **8** thus prepared was added a dichloroethane solution (30 mL) of **11** (4.75 g, 8.58 mmol). To the above solution was then added at 0 °C a dichloroethane solution (10 mL) of TMSOTf (1.99 mL, 10.30 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at rt for 90 min. The reaction was then quenched with saturated NH_4Cl solution (30 mL) and extracted with dichloromethane (250 mL). The organic layer was washed with brine, dried, and concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (60−80% EtOAc/hexanes and then 10% EtOH/CH_2Cl_2) to afford 5.40 g (100%) of the desired product **12** as white foam.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, J = 5.5 Hz, 1H), 7.66−7.25 (m, 15H), 6.13 (dd, J = 1.4, 4.9 Hz, 1H), 4.32 (m, 1H), 4.11 (d, J = 11.2 Hz, 1H), 3.85 (dd, J = 6.5, 11.6 Hz, 1H), 3.69 (dd, J = 2.3, 11.8 Hz, 1H), 2.47 (m, 1H), 2.06 (m, 1H), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.2, 156.0, 151.9, 137.8, 135.8, 135.7, 135.5, 134.6, 132.6, 132.3, 130.2, 130.0, 129.4, 128.6, 128.1, 127.9, 126.9, 126.1, 125.7, 91.3, 80.5, 65.1, 44.9, 32.3, 27.1, 19.3. HRMS (FAB) calcd for $C_{31}H_{35}FN_3O_3SiSe$ (MH^+): 624.1597, found: 624.1601. $[\alpha]^{23}_D$ of **12** = −63.68° (c = 0.92, $CHCl_3$).

Compound 13. To a THF solution of phenylselenide **12** (437 mg, 0.702 mmol) was added at 0 °C 30% wt hydrogen peroxide aqueous solution (0.22 mL, 7.02 mmol). The reaction was stirred at 0 °C for 1 h and then pyridine (0.57 mL, 7.02 mmol) was added at 0 °C. The reaction was stirred at rt for 3 h. The reaction mixture was diluted with EtOAc (50 mL) and Et_2O (10 mL) and then washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and then evaporated *in vacuo* to afford a residue, which was purified by silica gel chromatography (5−10% EtOH/CH_2Cl_2) to provide 280 mg (86%) of **13**.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.95 (bs, 1H), 7.74−7.34 (m, 10H), 6.98 (d, J = 1.5 Hz, 1H), 6.10 (d, J = 5.9 Hz, 1H), 5.92 (d, J = 5.7 Hz, 1H), 5.83 (bs, 1H), 4.85 (s, 1H), 3.95 (dd, J = 3.1, 11.6 Hz, 1H), 3.77 (dd, J = 3.4, 11.7 Hz, 1H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.6, 158.4, 154.4, 138.4, 135.7, 135.2, 133.1, 132.9, 132.7, 130.1, 130.0, 127.9, 127.7, 125.4, 125.0, 91.2, 87.2, 65.3, 27.0, 19.3. HRMS (FAB) calcd for $C_{25}H_{29}FN_3O_3Si$ (MH^+): 466.1962, found: 466.1963. $[\alpha]^{23}_D$ of **13** = −24.51° (c = 3.90, $CHCl_3$).

***β*-l-FD4C (2).** To a 0 °C cooled THF solution (14 mL) of silyl ether **13** (321 mg, 0.690 mmol) was added triethylamine trihydrofluoride (0.449 mL, 2.72 mmol). After stirring at rt for 5 h, a second dose of reagent was added at 0 °C. The reaction mixture was stirred at rt for 15 h. The solvent was then removed *in vacuo*. The residue was chromatographed (5−10−20% EtOH/CH_2Cl_2) to afford 146 mg (94%) of **2**.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.01 (d, J = 7.2 Hz, 1H), 7.77 (bs, 1H), 7.52 (bs, 1H), 6.81 (d, J = 1.1 Hz, 1H), 6.30 (dd, J = 1.2, 5.9 Hz, 1H), 5.86 (dd, J = 1.3, 5.9 Hz, 1H), 5.07 (bs, 1H), 4.76 (s, 1H), 3.31−3.60 (m, 2H). The ^{1}H NMR of *β*-L-FD4C (**2**) obtained in our lab matches the spectrum reported by Lin et al. (ref 8). HRMS (FAB) calcd for $C_9H_{11}FN_3O_3$ (MH^+): 228.0784, found: 228.0784. $[\alpha]^{23}_D$ of **2** = −29.00° (c = 0.7−1.0, MeOH).

Compound 14. To a degassed benzene solution (5 mL) of **12** (323 mg, 0.519 mmol) and a catalytic amount of AIBN was added tributyltin hydride (0.279 mL, 1.038 mmol). The reaction mixture was heated to reflux for 1.5 h. The reaction mixture was cooled to rt, and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (5−10% EtOH/CH_2Cl_2) to afford 240 mg (100%) of **14**.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.17 (d, J = 4.2 Hz, 1H), 7.71−7.28 (m, 10H), 6.40 (bs, 1H), 5.98 (d, J = 6.0 Hz, 1H), 4.16−4.09 (m, 2H), 3.75−3.70 (m, 1H), 2.60−1.78 (m, 4H). CI mass calcd for $C_{25}H_{31}FN_3O_3Si$ (MH^+): 468, found: 468. $[\alpha]^{23}_D$ of **14** = −50.00° (c = 2.10, $CHCl_3$).

***β*-L-FddC (3).** To a THF solution (10 mL) of **14** (240 mg, 0.52 mmol) was added triethylamine trihydrofluoride (0.339 mL, 2.08 mmol) at 0 °C. The reaction mixture was stirred at rt for 3 h. At this point, an additional 6 equiv of the same desilylating agent was added, and the reaction mixture was stirred overnight at rt. The solvent was then removed *in vacuo*, and the resulting residue was chromatographed (10−20% EtOH/CH_2Cl_2) to provide 95 mg (78%) of the desired *β*-L-FddC (**3**) as white foam.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.26 (d, J = 7.4 Hz, 1H), 7.65 (bs, 1H), 7.43 (bs, 1H), 5.83 (m, 1H), 5.15 (bs, 1H), 4.01 (m, 1H), 3.72 (d, J = 11.7 Hz, 1H), 3.52 (d, J = 11.9 Hz, 1H), 2.27−2.20 (m, 1H), 1.91−1.75 (m, 3H). The ^{1}H NMR of *β*-L-FddC (**3**) obtained in our lab matches the spectrum reported by Lin et al. (ref 9a). HRMS (FAB) calcd for $C_9H_{13}FN_3O_3$ (MH^+): 230.0941, found: 230.0943. $[\alpha]^{23}_D$ of **3** = −84.70° (c = 1.74, MeOH).

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Supporting Information Available: ^{1}H NMR spectra of compounds **2**, **3**, **4**, **5**α, **5***β*, **10**, **11**, **12**, and **13** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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