# Synthesis of 2′,3′-Dideoxy-2′-trifluoromethylnucleosides from α-Trifluoromethyl-α,*β*-unsaturated Ester

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The treatment of α-bromo-α,*β*-unsaturated esters **2** with $FSO_2CF_2CO_2Me$ and CuI in DMF/HMPA constitutes a new synthetic scheme for the preparation of α-trifluoromethyl-α,*β*-unsaturated esters **3**. The trifluoromethylation of (*Z*)/(*E*)-ethyl 3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-bromo-2-propenoate (**2e**), which is derived from 1-(*R*)-glyceraldehyde acetonide, yields the key intermediate α-trifluoromethyl-α,*β*-unsaturated esters **3e**. This is transformed into anomeric acetates **8a** and **8b** and is used for the synthesis of a number of 2′,3′-dideoxy-2′-trifluoromethylnucleosides.

## Introduction

The need for new antiviral and anticancer agents has led to the discovery of a class of modified nucleosides.[1] Fluorinated nucleosides are attractive compounds, with the fluorine incorporated either into the base or sugar moiety. The introduction of a fluorine atom into the sugar moiety of some nucleosides resulted in compounds with a broad spectrum of antiviral and anticancer activity.[2] Since fluorine and trifluoromethyl groups have similar inductive effects, $\sigma = 0.5$ and 0.45, respectively, we were interested in incorporation a trifluoromethyl group at the 2′ position of the sugar ring for several reasons. First, the electronegativity of trifluoromethyl group should stabilize the anomeric bond and suppress a significant pathway of in vivo decomposition,[3] thereby improving the acid stability of the nucleoside. Second, hydroxyl groups often serve as "handles" for the first step in oxidative degradation of biomolecules in vivo.[4] By replacing OH with $CF_3$, it cannot undergo oxidative catabolism. Third, the lipophilicity of the trifluoromethyl group should improve the transport characteristics of the nucleoside.

Although monofluorinated[5] and *gem*-difluorinated[6] sugar nucleosides have been widely studied, only a few trifluoromethylated sugar nucleosides have been reported, which is probably due to the shortcomings of existing synthetic methods. These methods are based on the condensation of appropriate carbohydrate precursors, bearing 2- or 3-trifluoromethyl groups, with bases. The carbohydrate precursors were prepared via the addition of trifluoromethyltrimethylsilane to suitably protected 2- or 3-oxo sugars.[7] This requires several synthetic steps, including the difficult and low-yielding Barton-type deoxygenation of the unreactive tertiary hydroxyl function. Recently, a new method for the preparation of 2′-trifluoromethyl-2′,3′-dideoxyuridine derivatives was reported via the nucleophilic substitution at the unsaturated carbon of the difluoromethylene group with a fluoride anion.[8] In this paper, we describe a novel and general route to α-trifluoromethyl-α,*β*-unsaturated ester and its use as a key intermediate in the synthesis of 2′,3′-dideoxy-2′-trifluoromethylnucleosides.

## Results and Discussion

**A New Route to α-Trifluoromethyl-α,*β* -Unsaturated Esters 3.** α-Trifluoromethyl-α,*β*-unsaturated esters **3** have served as building blocks for the preparation of trifluoromethylated biologically active compounds.[9] Several years ago, Lang et al.[10] reported that the Reformatskii reaction of methyl 2,2-dichloro-3,3,3-trifluoropropionate with aldehydes followed by acylation and

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**Scheme 1**

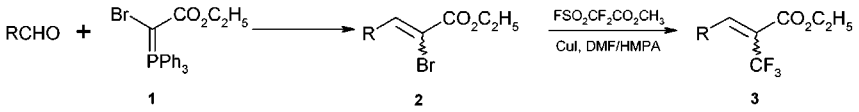
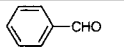
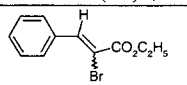
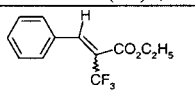
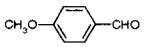
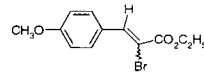
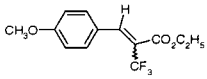
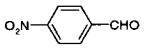
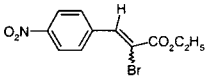
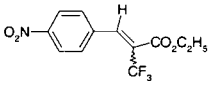
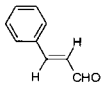
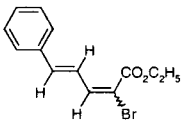
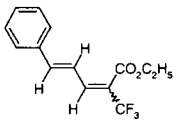
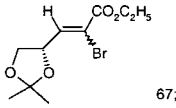
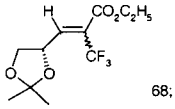
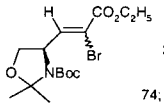
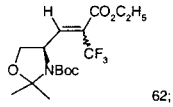


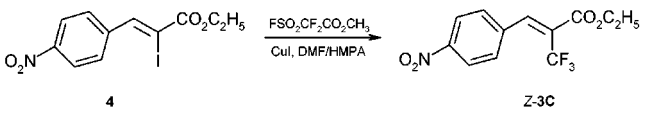

**Table 1. Synthesis of α-Trifluoromethyl-α,β-unsaturated Esters 3**

| Entry | Aldehyde | Intermediate **2** Yield (%)[a], *Z*:*E*[b] | Product **3** Yield (%)[c], *Z*:*E*[d] |
|---|---|---|---|
| 1 |  |  **2a** 67; 83:17 |  **3a** 90; 61:39 |
| 2 |  |  **2b** 89; 92:8 |  **3b** 93; 76:24 |
| 3 |  |  **2c** 98; 86:14 |  **3c**[e] 87; 89:11 |
| 4 |  |  **2d** 87, 79:21 |  **3d**[e] 42, 80:20 |
| 5 |  |  **2e** 67; 92:8 |  **3e** 68; 89:11 |
| 6 |  |  **2f** 74; 95:5 |  **3f** 62; 76:24 |

[a] Yields were based on aldehydes. [b] This ratio was determined by $^1$H NMR. [c] Yields were based on **2**. [d] This ratio was determined by $^{19}$F NMR. [e] These compounds were prepared from the *Z*-**3**.

reductive elimination gave compound **3**, formed as nearly a 1:1 mixture of *E* and *Z* isomers. We have developed a new method for the predominant preparation of (*Z*)-α-trifluoromethyl-α,β-unsaturated esters **3**. The new route to **3** was based on the trifluoromethylation of α-bromo-α,β-unsaturated esters **2** (Scheme 1). Ylide **1** was prepared from triphenylphosphine and ethyl bromoacetate in four steps in 50% overall yield.[11] The Wittig reaction of aldehydes with ylide **1** provided the *Z* isomer of α-bromo-α,β-unsaturated esters **2** as the major product in high yield (Table 1). The *Z* and *E* isomer of compounds **2c** and **2d** can be separated by column chromatography. However, other *Z* and *E* isomers of α-bromo-α,β-unsaturated esters could not be separated and the mixture was directly used in the next reaction. Although the reaction of the in-situ generated trifluoromethylcopper reagent ($CF_3Cu$) with alkenyl and aryl halides is useful for direct introduction of the trifluoromethyl group into a molecule,[12] the coupling of in-situ generated $CF_3Cu$ with α-halo-α,β-unsaturated esters has not been reported. We were delighted to observe that the treatment of a 92:8 mixture of *Z*-and *E*-**2e** with $FSO_2CF_2CO_2Me$ and CuI in DMF/HMPA [13] at 75 °C gave a 89:11 mixture of *Z*- and *E*-**3e** in 68% isolated yield. Various kinds of α-bromo-α,β-unsaturated esters **2** were used for the preparation of α-trifluoromethyl-α,β-unsaturated esters **3** under the same reaction conditions (Table 1). The configuration of the double bond in **3** was determined by the chemical shifts of the alkenyl proton. The alkenyl proton in the *Z* isomer appeared at lower field than in the *E* isomer.[10] The following observations of the trifluoromethylation are noteworthy: (1) The slow addition via syringe and an excess of $FSO_2CF_2CO_2Me$ (2.0 equiv) were necessary for the total conversion of α-bromo-α,β-unsaturated esters **2**. Otherwise, the pure compound **3** was not obtained, because **3** and **2** could not be separated by column chromatography. Use of 1.0 or 2.5 equiv of CuI offered no advantage over 0.2 equiv of CuI. (2) The *Z* isomer of compound **3** was produced as the major product. Some isomerization occurred when the pure *Z* isomers of **2c** and **2d** reacted to form mixtures of *Z* and *E* isomers of **3c** and **3d**, respectively (entries 3 and 4). When a mixture of *Z* and *E* isomers of compound **2** was used for the trifluoromethylation, the *Z*:*E* ratio of compound **3** decreased (entries 1, 2, 3, and 6). Whereas α-iodo-α,β-unsaturated ester **4** was subjected to the same trifluoromethylation conditions, the configuration of the double bond remained intact (Scheme 2). However, the preparation of **4** proved to be quite problematical.[14] (3) In the case of compound **2d** (entry 4), the isolated yield was low (42%) because fluoro-containing byproducts were produced and detected by $^{19}$F NMR of the reaction mixture.[15]

**Scheme 2**




**Synthesis of 2′,3′-Dideoxy-2′-trifluoromethylnu-**

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(12) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555.
(13) (a) Chen, Q. Y.; Wu, S. W. *J. Chem. Soc. Chem. Commun.* **1989**, 705. (b) Qing, F. L.; Fan, J.; Sun, H.; Yue, X. J. *J. Chem. Soc., Perkin Trans 1* **1997**, 3053. (c) Fei, X. X.; Tian, W. S.; Chen, Q. Y. *J. Chem. Soc., Perkin Trans 1* **1998**, 1139.

**Scheme 3**

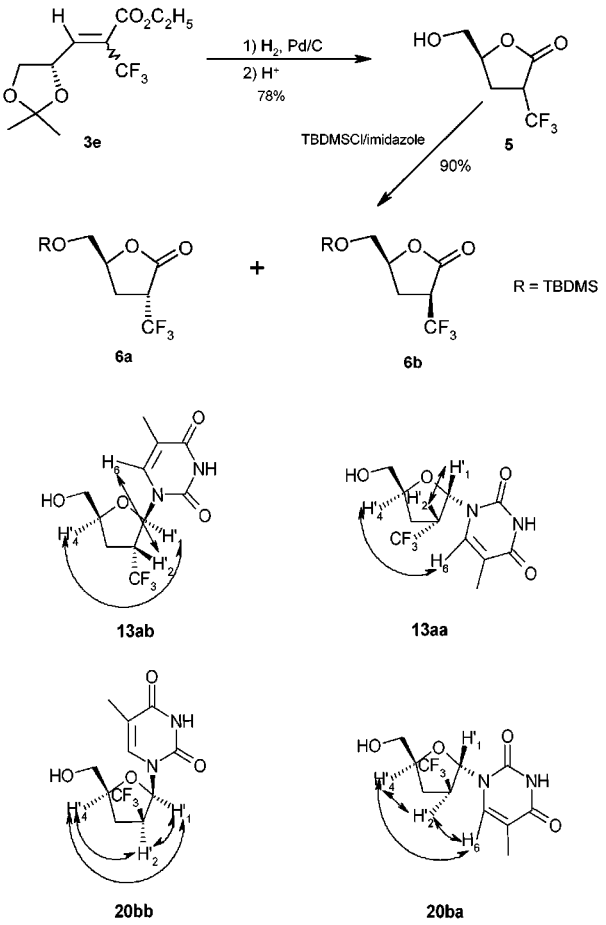



**Figure 1.** NOE correlations from NOESY spectra of **13ab**, **13aa**, **20bb**, and **20ba**.

**cleosides.** With the α-trifluoromethyl-α,*β*-unsaturated esters **3e** in hand (entry 5 in Table 1), we turned our attention to the application of this trifluoromethyl-containing building block to the preparation of 2′,3′-dideoxy-2′-trifluoromethylnucleosides. Due to difficulties in separation of (*Z*)-**3e**/(*E*)-**3e** isomers (*Z*:*E* = 89:11), the mixture was directly used in next reaction (Scheme 3). Hydrogenation of **3e** in the presence of palladium on activated carbon (10% Pd), followed by deprotection and closure in the presence of 2.0 mol % of 1 N HCl under reduced pressure, afforded lactone **5** as a mixture of the C-2 epimers (syn:anti = 1.67:1, determined by $^{19}$F NMR) in 78% yield. Protection of the hydroxyl group of **5** with TBDMSCl gave **6a** and **6b**, which were readily separated by silica gel column chromatography. Identification of trifluoromethyllactone **6a** and **6b** as the α-trifluoromethyl isomer ("down") and *β*-trifluoromethyl isomer ("up"), respectively, was accomplished by X-ray crystal structure determination of 2′,3′-dideoxy-2′-trifluoromethylnucleoside **13ab** (Figure 2) and the NOESY experiments of **13ab**, **13aa**, **20bb**, and **20ba** (Figure 1).

The α-trifluoromethylated lactone **6a** was reduced by DIBAL-H in anhydrous THF to provide exclusively *β* anomeric lactol **7a**, which was then treated with acetic anhydride to afford the single *β* anomeric acetate **8a**

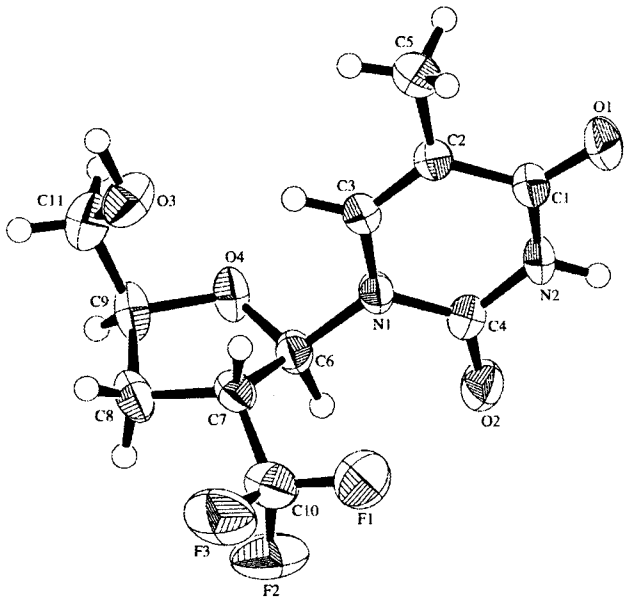



**Figure 2.** ORTEP drawing of the X-ray crystallographic structure of **13ab**.

(Scheme 4). Similarly, the *β*-trifluoromethylated lactone **6b** was transformed predominantly, but not exclusively, into α anomeric acetate **8b** under the same reaction conditions (Scheme 5). The reduction of **6b** with DIBAL-H gave a higher yield of lactol than **6a**. It is of interest to note that when the lactol **7b** (α/*β* = 2.3:1 determined by $^{1}$H NMR) was treated with acetic anhydride, the *β* anomer was converted into the α anomer (**8b** α/*β* =11.2:1 determined by $^{19}$F NMR). This difference was presumably due to the steric interaction of trifluoromethyl group and acetyl group. Coupling of **8a** with silylated uracil, thymine, and *N*$^4$-benzoylcytosine under Vorbruggen conditions (glycosylation reactions)[16] gave mainly the *β* anomers in high yields (Scheme 4 and Table 2). The silyl-protected nucleosides could be resolved by column chromatography into the separate anomers, except compounds **16ba** and **16bb**. This is different from other silyl-protected nucleosides in that the α and *β* anomers could not be separated by column chromatography.[5e] The removal of the 5′-silyl group and the *N*$^4$-benzoyl group with TBAF and a saturated solution of ammonia in methanol respectively gave 2′,3′-dideoxy-2′α-trifluoromethylnucleosides **12**, **13**, and **15**. The 2′*β* trifluoromethylated acetate **8b** was condensed with silylated pyrimidine bases, as described for **8a**, to afford the mainly α anomers of 2′,3′-dideoxy-2′*β*-trifluoromethylnucleosides **19**, **20**, and **22** (Scheme 5 and Table 2).

Stereochemical assignments of the final compounds were made on the basis of 1D and 2D NMR spectroscopy and X-ray crystallography. The configuration of the anomeric center was assigned mainly by $^{1}$H NMR, in which the anomers with H4′ at lower field were assigned as the α anomers and the ones at higher field were assigned as the *β* anomers on the basis of the deshielding effect of the base moiety[17] (Table 3). This assignment was further confirmed by the NOESY experiment of **13ab**,

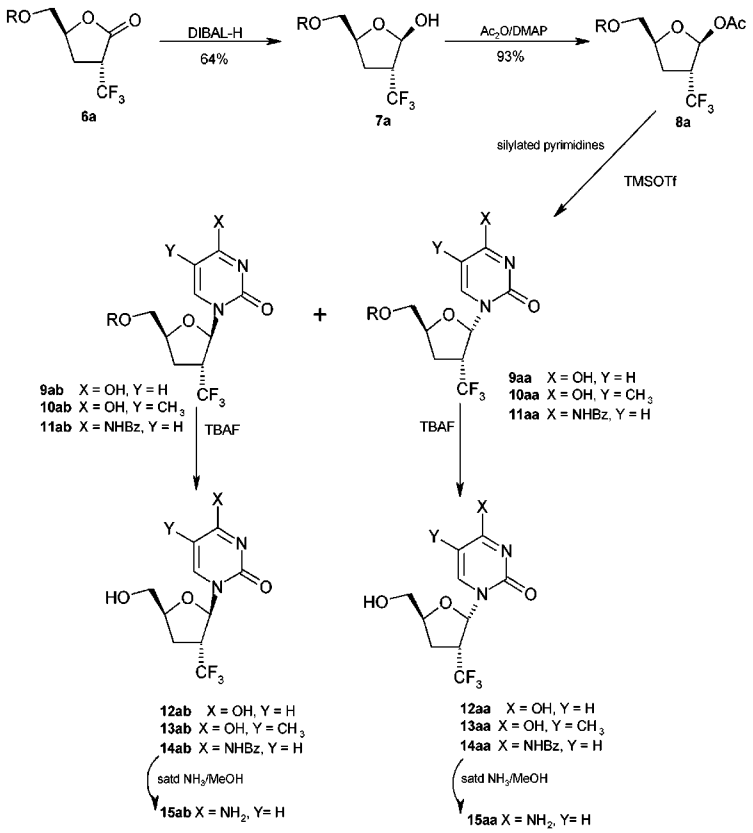
(14) Chenault, J. Dupin, J. E. *Synthesis* **1987**, 498.

(15) $^{19}$F NMR spectra were obtained on either 56.4 or 282 MHz spectrometer using $CF_3CO_2H$ as external standard, downfield shifts being designated as negative.

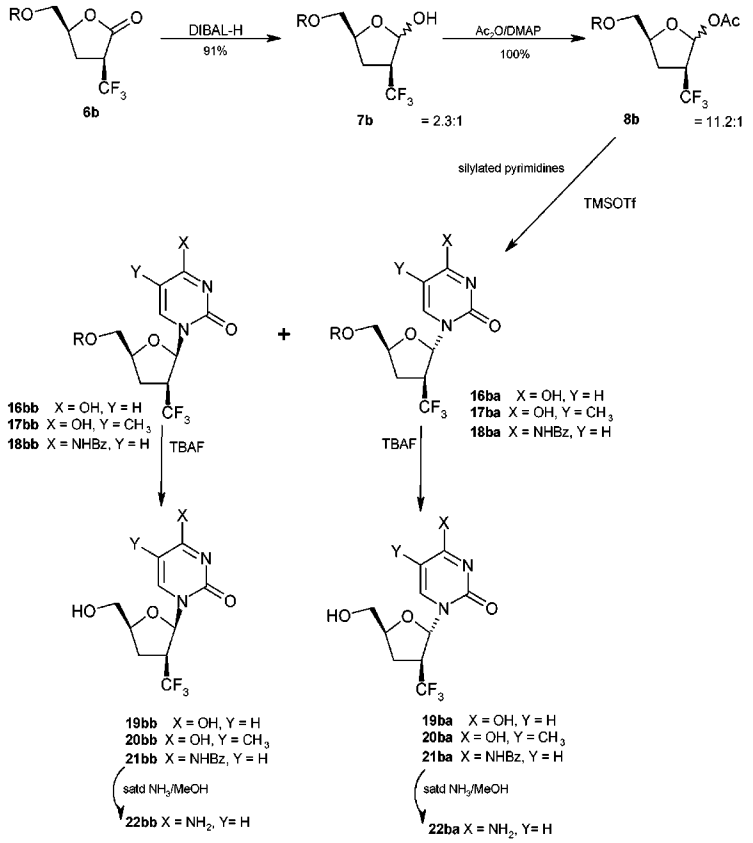
(16) (a) Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234. (b) Vorbrüggen, H.; Hofle, G. *Chem. Ber.* **1981**, *114*, 1256.

(17) Chun, B. K.; Olegen, S.; Hong, J. H.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **2000**, *65*, 685.

**Scheme 4**




**Scheme 5**




**13aa**, **20bb**, and **20ba** (Figure 1) as well as X-ray crystallography of **13ab** (Figure 2). An additional key to the assignment of configuration of the anomeric center was the polarity of the nucleosides as observed by thin-layer chromatography. When the 2′-trifluoromethyl group was at the α-position ("down") of the nucleosides, the α anomer is more polar than the $\beta$ anomer. In contrast, the $\beta$ anomer is more polar than the α anomer in the

**Table 2. The Glycosylation Reactions of 8a and 8b**

| bases | sugar | β/α | yield(%)[a] | product |
|---|---|---|---|---|
| uracil | **8a** | 1.43/1[b] | 75 | **9ab** + **9aa** |
| thymine | **8a** | 2.42/1[c] | 90 | **10ab** + **10aa** |
| $N^4$-Bz-cytosi ne | **8a** | 1.67/1[b] | 85 | **11ab** + **11aa** |
| uracil | **8b** | 1/2.33[c] | 77 | **16bb** + **16ba** |
| thymine | **8b** | 1/2.88[d] | 85 | **17bb** + **17ba** |
| $N^4$-Bz-cytosi ne | **8b** | 1/2.77[b] | 73 | **18bb** + **18ba** |

[a] Isolated yields. [b] Determined by isolated products. [c] Determined by $^1$H NMR. [d] Determined by $^{19}$F NMR.

**Table 3. Some Selected $^1$H NMR Data of the Synthesized Nucleosides**

| compd | H4 δ (ppm) | compd | H4 δ (ppm) |
|---|---|---|---|
| **12ab** | 4.23 | 12aa | 4.59 |
| **13ab** | 4.44 | 13aa | 4.85 |
| **15ab** | 4.46 | 15aa | 4.78 |
| | | 19ba | 4.78 |
| **20bb** | 4.37 | 20ba | 4.79 |
| **22bb** | 4.35 | 22ba | 4.81 |

"up" (β-position) 2′-trifluoromethylated nucleosides. This is due to the dipole−dipole interaction between the dipole of the C−$CF_3$ bond and the dipole of the C−N bond.[5e] In the "down" 2′-trifluoromethyl nucleosides, the strong dipole of the C−$CF_3$ bond opposes the C−N anomeric bond dipole in the β anomer and reduces the overall molecular dipole. Conversely, the α anomer has a geometry that allows reinforcement of the molecular dipole through the addition of the C−$CF_3$ and C−N bond dipoles. Thus, the α anomer is more polar than the β anomer in α- 2′-trifluoromethyl nucleosides.

Of the 11 nucleosides listed in Table 3, only **12ab** and **12aa**[8] have been synthesized from natural precursors. The 2′-trifluoromethyl group was introduced by the nucleophilic addition of fluoride on the unsaturated carbon of the difluoromethylene group.[18,19] The advantage of our methodology is that no carbonyl is needed for trifluoromethyl introduction. Thus, we are not limited to natural nucleosides as starting materials, and it is easy to access the unnatural 2′-trifluoromethyl nucleosides.

In conclusion, a new and efficient preparation of α-trifluoromethyl-α,β-unsaturated esters has been developed. The key step in this new route involves the trifluoromethylation of α-bromo-α,β-unsaturated esters. We have used α-trifluoromethyl-α,β-unsaturated ester **3e** as the key intermediate to synthesize 2′,3′-dideoxy-2′-trifluoromethylnucleosides. Currently, these nucleosides are undergoing biological evalution for activity against viruses and as potential anticancer agents.

## Experimental Section

**Representative Procedure for the Synthesis of α -Trifluoromethyl-α,β-unsaturated Esters 3. (*Z*)/(*E*)-Ethyl 3-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-trifluoromethyl-2-propenoate (3e).** A solution of triphenylcarbethoxybromomethylenephosphorane **1** (26.26 g, 61.5 mmol) and 1-(*R*)-glyceraldehyde acetonide (8.00 g, 61.5 mmol) in $CH_2Cl_2$ (300 mL) was heated under reflux with stirring for 24 h. After the solvent was removed, the residue was refluxed for 30 min with a mixture of hexane/ethyl acetate (6:1,100 mL). The process was repeated three times, the combined extracts were filtered, and the filtrate was concentrated to yield a yellow oil. The oil was purified by silica gel column chromatography (hexane: ethyl acetate = 15:1) to give 12.29 g (72% yield) of (*Z*)/(*E*)-ethyl 3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-bromo-2-propenoate (**2e**) (92:8 by $^1$H NMR) as a clear colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.0 Hz, 1H), 4.88 (m, 1H), 4.22 (m, 3H), 3.66 (m, 1H), 1.42−1.25 (m, 9H); IR (thin film) 2988, 1733, 1259, 1063, 1031 cm$^{-1}$; MS *m*/*z* 281 ($M^+$+1, 4), 279 ($M^+$ −1, 4), 43 (100). Anal. Calcd for $C_{10}H_{15}O_4Br$: C, 43.01; H, 5.38. Found: C, 43.25; H, 5.54. To a solution of **2e** (11.00 g, 39.4 mmol) in anhydrous DMF (138 mL) and HMPA (20 mL) was added CuI (1.51 g, 7.89 mmol). Then the mixture was heated to 75 °C, and a solution of $FSO_2CF_2CO_2Me$ (10.01 mL, 78.86 mmol) in DMF (20 mL) was added via syringe over a period of 15 h. After the mixture was stirred for 14 h at 75 °C, the reaction mixture was treated with saturated aqueous $NH_4$-Cl and was filtered. The filtrate was extracted with diethyl ether. Then organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 40:1) to give a mixture of 7.29 g (68% yield) of (*Z*)/(*E*)-**3e** (89:11, by $^1$H NMR) as a yellowish oil:$^1$H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.0 Hz, 0.11H), 7.26 (d, *J* = 7.0 Hz, 0.89H), 5.10 (m, 1H), 4.27 (m, 3H), 3.72 (m, 1H), 1.48−1.26 (m, 9H); $^{19}$F NMR (56.4 MHz, $CDCl_3$) δ −11.9 (s, 0.33F), −17.6 (s, 2.67F); IR (thin film) 2991, 1737, 1375, 1264, 1149 cm$^{-1}$; MS *m*/*z* 269 (M + 1,10), 43 (100). Anal. Calcd for $C_{11}H_{15}O_4F_3$: C, 49.25; H, 5.60. Found: C, 49.22; H, 5.79.

**(*Z*)/(*E*)-Ethyl 3-Phenyl-2-trifluoromethyl-2-propenoate (3a).** $^1$H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 0.61H), 7.35(s, 0.39H), 7.34 (s, 5H), 4.31 (q, *J* = 7.1 Hz, 1.22H), 4.21 (q, *J* = 7.1 Hz, 0.78H), 1.32 (t, *J* = 7.1 Hz, 1.83H), 1.14 (t, *J* = 7.1 Hz, 1.17H); $^{19}$F NMR (56.4 MHz, $CDCl_3$) δ −19.7 (s, 1.83F), −13.7 (s, 1.17F); IR (thin film) 1733, 1641, 1400, 1279 cm$^{-1}$; MS *m*/*z* 245 ($M^+$ + 1, 12), 244 ($M^+$ , 65), 199 (100).

**(*Z*)/(*E*)-Ethyl 3-(4-Methoxyphenyl)-2-bromo-2-propenoate (2b).**$^1$H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.93 (d, *J* = 8.1 Hz, 2H), 6.97 (d, *J* = 8.1 Hz, 2H), 4.36 (q, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 1.40 (t, *J* = 7.0 Hz, 3H); IR (thin film) 1720, 1602, 1512, 1255, 1176 cm$^{-1}$; MS *m*/*z* 286 ($M^+$ + 1,100), 285 ($M^+$ , 81), 284 ($M^+$ −1, 100). Anal. Calcd for $C_{12}H_{13}O_3Br$: C, 50.55; H, 4.59. Found: C, 50.36; H, 4.59.

**(*Z*)/(*E*)-Ethyl 3-(4-Methoxyphenyl)-2-trifluoromethyl-2-propenoate (3b).**$^1$H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.41 (d, *J* = 9.5 Hz, 1.52H), 7.30 (d, *J* = 9.5 Hz, 0.48H), 6.91 (m, 2H), 4.34 (m, 2H), 3.83 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 2.28H), 1.26 (t, *J* = 7.1 Hz, 0.72H); $^{19}$F NMR (56.4 MHz, $CDCl_3$) δ −15.2 (s, 0.72F), −20.6 (s, 2.28F); IR (thin film) 1726, 1606, 1514, 1265, 1178 cm$^{-1}$; MS *m*/*z* 275 ($M^+$ + 1, 18), 274 ($M^+$, 100). Anal. Calcd for $C_{13}H_{13}O_3F_3$: C, 56.94; H, 4.78. Found: C, 56.88; H, 4.74.

**(*Z*)-Ethyl 3-(4-Nitrophenyl)-2-bromo-2-propenoate (2c).** $^1$H NMR (300 MHz, $CDCl_3$) δ 8.28 (t, *J* = 9.0 Hz, 3H), 7.96 (d, *J* = 9.0 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); IR (KBr) 1710, 1610, 1511, 1349, 1261 cm$^{-1}$; MS *m*/*z* 301 ($M^+$ + 1, 12), 299 ($M^+$ − 1, 12), 192 (100). Anal. Calcd for $C_{11}H_{10}NO_4Br$: C, 44.00; H, 3.33; N, 4.67. Found: C, 44.09; H, 3.24; N, 4.58.

**(*E*)-Ethyl 3-(4-Nitrophenyl)-2-bromo-2-propenoate (2c).** $^1$H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.0 Hz, 2H), 7.44 (t, *J* = 9.0 Hz, 3H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H); IR (KBr) 3109, 1728, 1598, 1521, 1347, 1220 cm$^{-1}$; MS *m*/*z* 301 ($M^+$ + 1, 13), 299 ($M^+$ − 1, 12), 192 (100).

**(*Z*)-Ethyl 3-(4-Nitrophenyl)-2-trifluoromethyl-2-propenoate (3c).** $^1$H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.0 Hz, 2H), 8.11 (s, 1H), 7.54 (d, *J* = 9.0 Hz, 2H), 4.26 (q, *J* = 7.0 Hz, 2H), 1.39 (t, *J* = 7.0 Hz, 3H); $^{19}$F NMR (56.4 MHz, $CDCl_3$) δ −19.0 (s); IR (KBr) 1772, 1639, 1603, 1521 cm$^{-1}$; MS *m*/*z* 290 ($M^+$ + 1, 12), 289($M^+$, 26), 244 (100). Anal. Calcd for $C_{12}H_{10}NO_4F_3$: C, 49.83; H, 3.49; N, 4.84. Found: C, 49.80; H, 3.59; N, 4.84.

**(*E*)-Ethyl 3-(4-Nitrophenyl)-2-trifluoromethyl-2-propenoate (3c).** $^1$H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.0 Hz, 2H), 7.53 (d, *J* = 9.0 Hz, 2H), 7.51 (s, 1H), 4.39 (q, *J* = 7.0 Hz, 2H), 1.39 (t, *J* = 7.0 Hz, 3H); $^{19}$F NMR (56.4 MHz, $CDCl_3$) δ −12.6 (s); IR (KBr) 1727, 1656, 1600, 1519 cm$^{-1}$; MS *m*/*z* 289 ($M^+$, 27), 244 (100). Anal. Calcd for $C_{12}H_{10}NO_4F_3$: C, 49.83; H, 3.49; N, 4.84. Found: C, 49.86; H, 3.65; N,4.78.

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(19) Serafinowski, P. J.; Barnes, C. L. *Synthesis* **1997**, 225

**(2*Z*)-Ethyl 5-Phenyl-2-bromopenta-2,4-dienoate (2d).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.84 (d, $J$ = 8.9 Hz, 1H), 7.54 (m, 2H), 7.37 (m, 3H), 7.17 (m, 2H), 4.41 (q, $J$ = 7.1 Hz, 2H), 1.37 (t, $J$ = 7.1 Hz, 3H); IR (thin film) 1720, 1616, 1585, 1263 cm$^{-1}$; MS $m/z$ 282 ($M^+ + 1$, 16), 281 ($M^+$, 10), 280 ($M^+ - 1$, 16), 128 (100).

**(2*E*)-Ethyl 5-Phenyl-2-bromopenta-2,4-dienoate (2d).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.82 (m, 1H), 7.50 (m, 2H), 7.34 (m, 4H), 6.81 (d, $J$ = 15.5 Hz, 1H), 4.34 (q, $J$ = 7.1 Hz, 2H), 1.41 (t, $J$ = 7.1 Hz, 3H); IR (thin film) 2983, 1720, 1616, 1585, 1263, 1220 cm$^{-1}$; MS $m/z$ 282 ($M^+ + 1$, 12), 280 ($M^+ - 1$, 13), 128 (100).

**(2*Z*)-Ethyl 5-Phenyl-2-trifluoromethylpenta-2,4-dienoate (3d).** $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.72 (d, $J$ = 11.9 Hz, 1H), 7.53 (m, 2H), 7.41 (m, H), 7.11 (d, $J$ = 15.2 Hz, 1H), 4.33 (q, $J$ = 7.1 Hz, 2H), 1.36 (t, $J$ = 7.1 Hz, 3H); $^{19}$F NMR (56.4 MHz, $CDCl_3$) $\delta$ −20.7 (s). IR (thin film) 1724, 1623, 1290, 1257, 1140 cm$^{-1}$; MS $m/z$ 271 ($M^+ + 1$, 49), 270 ($M^+$, 100).

**(*Z*)/(*E*)-*tert*-Butyl (4S)-4-(3′-Ethoxycarbonyl-2′-bromoprop-1′-enyl)-2,2-dimethyloxazolidine-3-c arboxylate (2f).** $^1$H NMR (300 MHz, $CD_3COCD_3$) $\delta$ 7.26 (d, $J$ = 7.8 Hz, 0.93H), 6,77 (d, $J$ = 7.8 Hz, 0.07H), 5.11−4.76 (m, 1H), 4.71−4.29 (m, 3H), 3.87−3.80 (m, 1H), 1.59−1.30 (m, 18H); IR (thin film) 2982, 1705, 1616 cm$^{-1}$; MS $m/z$ 380 ($M^+ + 1$, 1), 57 (100); Anal. Calcd for $C_{15}H_{24}BrNO_5$: C, 47.63; H, 6.40; N, 3.70. Found: C, 47.44; H, 6.50; N, 3.78.

**(*Z*)/(*E*)-*tert*-Butyl (4S)-4-(3′-Ethoxycarbonyl-2′-trifluoromethylprop-1′-enyl)-2,2-dimethyloxazoli dine-3-carboxylate (3f).** $^1$H NMR (300 MHz, $CD_3COCD_3$) $\delta$ 7.21 (d, $J$ = 8.7 Hz, 0.67H), 6,94 (d, $J$ = 8.4 Hz, 0.33H), 5.19−4.97 (m, 1H), 4.36−4.26 (m, 3H), 3.91−3.85 (m, 1H), 1.61−1.20 (m, 18H); $^9$F NMR (56.4 MHz, $CDCl_3$) $\delta$ −18.0 (s, 2.27F), −12.5 (s, 0.73F); IR (thin film) 2984, 1735, 1710 cm$^{-1}$; MS $m/z$ 380 ($M^+ + 1$, 2), 57 (100); Anal. Calcd for $C_{16}H_{24}F_3NO_5$: C, 52.32; H, 6.54; N, 3.81. Found: C, 52.42; H, 6.58; N, 4.07.

**(2*R*,4*S*/2*S*,4*S*)-5-Hydroxy-2-trifluoromethylpentan-4-olide (5).** 10% of Pd/C (2.00 g, 1.88 mmol) was added to a solution of (*Z*)/(*E*)-**3e** (7.10 g, 26.49 mmol) in ethanol (150 mL) at room temperature under 1 atm of hydrogen. After stirring for 24 h, the reaction mixture was filtered, and the solvent was removed to give a colorless oil that was used in the next step. The oil and 1 N HCl (2 mL) were stirred at 50−55 °C under atmospheric pressure for 2 h and then under a reduced pressure at 60 mmHg overnight. The excess water was removed by stirring at that temperature under high vacuum for 3 h. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to give 3.80 g (78% yield, two steps) of a mixture of (2*R*/2*S*)-trifluoromethyl lactone **5**:$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.70−4.62 (m, 1H), 3.95 (m, 1H), 3.65−3.60 (m, 2H), 3.27 (s, 1H), 2.53 (m, 1H), 2.32 (m, 1H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −7.78 (d, $J$ = 8.7 Hz, 1.88F), −8.10 (d, $J$ = 8.7 Hz, 1.12F); IR(thin film) 3422, 2959, 1779, 1374, 1124 cm$^{-1}$; MS $m/z$ 185 ($M^+ + 1$, 29), 77 (100). Anal. Calcd for $C_6H_7O_3F_3$: C, 39.14; H, 3.83. Found: C, 39.49; H, 3.77.

**(2*R*,4*S*/2*S*,4*S*)-5-(*tert*-Butyldimethylsiloxy)-2-trifluoromethylpentan-4-olide (6a and 6b).** To a solution of lactone **5** (3.73 g, 20.29 mmol) in $CH_2Cl_2$ (50 mL) were added *tert*-bytyldimethylsilyl chloride (8.84 g, 40.57 mmol) and imidazole (4.14 g, 60.86 mmol) in $CH_2Cl_2$ (30 mL) with stirring. After being stirred for 50 min at room temperature, the reaction mixture was poured onto water. The organic layer was washed with brine, dried over $Na_2SO_4$, and concentrated to give a yellowish oil. The oil was purified by silica gel column chromatography (hexane:ethyl acetate = 8:1) to give 3.21 g (53% yield)of compound **6a** as a white solid and 2.23 g (37% yield) of compound **6b** as a white solid. **6a:**$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.68 (m, 1H), 3.93 (dd, $J$ = 11.5 Hz, 2.2 Hz, 1H), 3.69 (dd, $J$ = 11.5 Hz, 2.0 Hz, 1H), 3.55 (m, 1H), 2.50 (m, 1H), 0.90 (s, 9H), 0.09 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −7.80 (d, $J$ = 8.8 Hz); IR (KBr) 2962, 1775, 1369, 1294, 1258, 1129 cm$^{-1}$; MS $m/z$ 299 ($M^+ + 1$, 18), 298 ($M^+$, 2), 77(100). Anal. Calcd for $C_{12}H_{21}O_3F_3Si$: C, 48.30; H,7.03. Found: C,48.15; H, 7.16. **6b**:$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.54 (m, 1H), 3.93 (dd, $J$ =11.6 Hz, 3.4 Hz, 1H), 3.75 (dd, $J$ = 11.6 Hz, 3.4 Hz, 1H), 3.46 (m,1H), 2.49 (m,2H), 0.89 (s, 9H), 0.09 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −8.34 (d, $J$ = 8.39); IR (KBr) 2935, 1760, 1263, 1127 cm$^{-1}$; MS $m/z$ 241 (2), 77 (100).

**(2*R*,4*S*)-5-*O*-(*tert*-Butyldimethylsilyl)-2,3-dideoxy-2-trifluoromethylpentof uranose (7a).** To a flask were added lactone **6a** (2.74 g, 9.19 mmol) and anhydrous THF (90 mL). The solution was cooled to −78 °C, and a 1.0 M solution of DIBAL-H in cyclohexane (5.52 mL, 55.2 mmol) was added dropwise over a period of 50 min. This was allowed to stir at −78 °C for 5 h, then the reaction mixture was quenched by the slow addition of methanol at −20 °C, until no more gas elution occurred. The mixture was then allowed to warm slowly to ambient temperature, and 50 mL of 1 N HCl was added to the mixture. This was stirred for 30 min.The aqueous layer was extracted with diethyl ether. The organic layers were combined, washed with saturated aqueous $NaHCO_3$ and brine, dried over $Na_2SO_4$, and concentrated to give a oil. The oil was purified by silica gel column chromatography (hexane:ethyl acetate = 8:1) to give 1.772 g (64% yield) of lactol **7a** as a yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.47 (d, 1H), 4.48 (m, 1H), 3.84 (dd, $J$ = 11.0 Hz, 2.0 Hz, 1H), 3.54 (dd, $J$ = 11.0 Hz, 2.0 Hz,1H), 2.90 (m, 1H), 2.19 (m, 2H), 0.96 (s, 9H), 0.14 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −5.95 (d, $J$ = 10.1 Hz); IR (thin film) 3418, 2958, 1273, 1166, 1134 cm$^{-1}$; MS $m/z$ 283 ($M^+$ −OH, 1), 75 (100). Anal. Calcd for $C_{12}H_{23}O_3F_3Si$: C, 47.98; H, 7.72. Found: C, 47.91; H, 7.96.

**(2*S*,4*S*)-5-*O*-(*tert*-Butyldimethylsiyl)-2,3-dideoxy-2-trifluoromethylpentofu ranose (7b).** Compound **7b** (2.046 g, 91%) was prepared as a light yellow oil from compound **6b** (2.228 g, 7.48 mmol) using the same procedure as for **7a**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.63 (d, $J$ = 2.10 Hz, 0.7H), 5.39 (d, $J$ = 4.27 Hz, 0.3H), 4.37 (m, 1H), 3.71 (m, 2H), 2.91 (m, 1H), 2.24 (m, 2H), 0.94 (s, 6.3H), 0.90 (s, 2.7H), 0.14 (s, 4.2H), 0.07 (s, 1.8H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −6.86 (d, $J$ = 9.6 Hz, 2.26F), −11.31 (d, $J$ = 8.2 Hz, 0.74F); IR (thin film) 3420, 2958, 1261, 1170, 1141 cm$^{-1}$; MS (EI) 300 ($M^+$, 3), 43 (100). Anal. Calcd for $C_{12}H_{23}O_3F_3Si$: C, 47.98; H, 7.72. Found: C, 47.77; H, 7.74.

**(2*R*,4*S*)-1-*O*-Acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-2-trifluoromethylpentofuranose (8a).** To a flask were added lactol **7a** (1.77 g, 5.9 mmol) and anhydrous $CH_2Cl_2$ (70 mL). Then DMAP (0.070 g, 0.59 mmol) and acetic anhydride (3.4 mL, 35.4 mmol) were added, and the solution was stirred at room-temperature overnight. Upon completion, the reaction was poured into a saturated $NaHCO_3$ solution and stirred for 15 min. The organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated to give light yellow oil. The oil was purified by silica gel column chromatograph (hexane:ethyl acetate = 10:1) to give compound **8a** (93% yield) as a clear colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.52 (d, $J$ = 1.4 Hz, 1H), 4.52 (m, 1H), 3.80 (m, 2H), 3.18 (m, 1H), 2.35 (m, 2H), 2.19 (s, 3H), 1.03 (s, 9H), 0.20 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −6.64 (d, $J$ = 9.5 Hz); IR (thin film) 2938, 1763, 1228, 1135 cm$^{-1}$; MS $m/z$ 283 ($M^+$ −OAc, 6), 43 (100). Anal. Calcd for $C_{14}H_{25}O_4F_3Si$: C, 49.10; H, 7.36. Found: C, 49.07; H, 7.30.

**(2*S*,4*S*)-1-*O*-Acetyl-5-*O*-(*tert*-butyldimethylsilyl)-2,3-dideoxy-2-trifluoromethylpentofuranose (8b).** Compound **8b** (2.19 g, 100%) was prepared as a clear colorless oil from compound **7b** (1.921 g, 6.40 mmol) using the same procedure as for compound **8a:**$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.42 (d, $J$ = 1.7 Hz, 1H), 4.31 (m, 1H), 3.75 (m, 2H), 3.06 (m, 1H), 2.30 (m, 1H), 2.06 (s, 3H), 1.98 (m, 1H), 0.90 (s, 9H), 0.08 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −6.88 (d, $J$ = 9.1 Hz, 2.69F), −11.48 (d, $J$ = 8.3 Hz, 0.31F); IR (thin film) 2959, 1759, 1226, 1108, 839 cm$^{-1}$; MS $m/z$ 283 ($M^+$ −OAc, 7), 43 (100). Anal. Calcd for $C_{14}H_{25}O_4F_3Si$: C, 49.10; H, 7.36. Found: C, 49.26; H, 7.52.

**Representative Procedure for the Coupling of a Silylated Base with Sugar: (2′*R*)-D-5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-dideoxy-2′-trifluoromethyluridine (9ab and 9aa).** To a stirred solution of compound **8a** (0.250 g, 0.731 mmol) and uracil (0.229 g, 2.047 mmol) in anhydrous acetonitrile (35 mL) was added *N*,*O*-bis(trimethylsilyl)acetamide (1.05 mL, 4.240 mmol).The reaction mixture was stirred at reflux for 30 min. After cooling to 0 °C, trimethylsilyl triflate

(0.35 mL, 1.681 mmol) was added dropwise and the solution was stirred for 24 h at room temperature. Saturated aqueous $NaHCO_3$ was added to the reaction mixture, which was then extracted with $CH_2Cl_2$. The combined extract was washed with brine, dried over $Na_2SO_4$, and concentrated to give a yellow oil. The oil was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 1:1) to give 89 mg (30.9% yield) of α anomer **9aa** as a white foam, and 127 mg (44.1% yield) of *β* anomer **9ab** as a white solid. 9ab:$^1$H NMR (400 MHz, $CDCl_3$) *δ* 9.04 (s, 1H), 7.91 (d, *J* =8.1 Hz, 1H), 6.28 (d, *J* = 4.9 Hz, 1H), 5.72 (d, *J* = 8.1 Hz, 1H), 4.34 (m, 1H), 4.03 (dd, *J* = 11.7 Hz, 2.2 Hz, 1H), 3.69 (dd, *J* = 11.7 Hz, 2.2 Hz, 1H), 3.06 (m, 1H), 2.38 (m,1H), 2.25 (m, 1H), 0.94 (s, 9H), 0.13 (s, 6H);$^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −7.33 (d, *J* = 8.7 Hz); IR (KBr) 3195, 2950, 1683, 1462, 1380, 1259, 1126 cm$^{-1}$; MS *m*/*z* 395 ($M^+$ + 1, 2), 394 ($M^+$, 1), 169 (100). Anal. Calcd for $C_{16}H_{25}N_2O_4F_3Si$: C, 48.72; H, 6.39; N, 7.10. Found: C, 48.26; H, 6.38; N, 6.69. **9aa**:$^1$H NMR (400 MHz, $CDCl_3$) *δ* 8.49 (s, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 6.23 (d, *J* = 4.3 Hz, 1H), 5.73 (d, *J* = 8.1 Hz, 1H), 3.62 (dd, *J* = 11.2 Hz, 3.1 Hz, 1H), 2.35 (m, 2H), 0.91 (s, 9H), 0.10 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −10.13 (d, *J* = 9.5 Hz); IR (KBr) 3208, 3120, 2958, 1710, 1681, 1460, 1386, 1255, 1177 cm$^{-1}$; MS *m*/*z* 396 ($M^+$ + 2, 1), 395 ($M^+$ + 1, 4), 169 (100).

**(2′*S*)-D-5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-dideoxy-2′-trifluoromethyluridine (16bb and 16ba).** Compounds **16bb** and **16ba** (218 mg, 77%) were prepared as a white foam from compound **8b** (250 mg, 0.731 mmol) using the same procedure as for **9aa** and **9ab**: $^1$H NMR (400 MHz, $CDCl_3$) *δ* 9.21−9.08 (m, 1H), 7.92 (d, *J* = 8.1 Hz, H6), 7.20 (d, *J* = 8.0 Hz, H6), 6.42 (d, *J* = 7.2 Hz, H1′), 5.77 (m, H5 and H1′), 5.70 (d, *J* = 8.1 Hz, H5), 4.61 (m, H4′), 4.18 (m, H4′), 4.10−3.60 (m, H5′), 3.54−3.39 (m, H2′), 2.40−2.16 (m, H3′), 0.94−0.92 (m, 9H), 0.12−0.07 (m, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −11.13 (d, *J* = 7.8 Hz, 0.9F), −6.94 (d, *J* = 7.24 Hz, 2.1F); IR (KBr) 3199, 3067, 2959, 1693, 1465, 1378, 1262, 838 cm$^{-1}$; MS *m*/*z* 395 ($M^+$ + 1, 5), 169 (100). Anal. Calcd for $C_{16}H_{25}N_2O_4F_3Si$: C, 48.72; H, 6.39; N, 7.10. Found: C, 48.45; H, 6.52; N, 6.91.

**(2′*R*)-D-5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-dideoxy-2′-trifluoromethylthymidinem (10ab and 10aa).** Compounds **10ab** (151 mg, 64%) and **10aa** (63 mg, 26%) were prepared as a white solid respectively from compound **8a** (200 mg, 0.584 mmol) using the same conditions as for compounds **9ab** and **9aa. 10ab**: $^1$H NMR (400 MHz, $CDCl_3$) *δ* 8.41 (s, 1H), 7.40 (s, 1H), 6.24 (d, *J* = 6.2 Hz, 1H), 4.28 (m, 1H), 3.98 (dd, *J* = 11.5 Hz, 2.3 Hz, 1H), 3.69 (dd, *J* = 11.5 Hz, 2.6 Hz, 1H), 3.05 (m, 1H), 2.36 (m, 1H), 2.27 (m, 1H), 1.93 (s, 3H), 0.96 (s, 9H), 0.16 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −7.42 (d, *J* = 8.42 Hz); IR (KBr) 3187, 2932, 1681 cm$^{-1}$; MS (FAB) 409 ($M^+$ + 1), 407-($M^+$ − 1). Anal. Calcd for $C_{17}H_{27}N_2O_4F_3Si$: C, 49.98; H, 6.66; N, 6.86. Found: C, 49.88; H, 6.58; N, 6.75. **10aa**:$^1$H NMR (400 MHz, $CDCl_3$) *δ* 9.33 (s, 1H), 7.21 (s, 1H), 6.24 (d, *J* = 5.8 Hz, 1H), 4.56 (m, 1H), 3.80 (dd, *J* = 11.1 Hz, 3.0 Hz, 1H), 3.62 (dd, *J* = 11.1 Hz, 2.6 Hz, 1H), 3.48 (m, 1H), 2.36 (m, 2H), 1.92 (s, 3H), 0.89 (s, 9H), 0.08 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −7.20 (d, *J* = 9.4 Hz).

**(2′*S*)-D-5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-dideoxy-2′-trifluoromethylthymidinem (17bb and 17ba).** Compounds **17bb** (39 mg, 22%) and **17ba** (114 mg, 63%) were prepared as a white solid respectively from compound **8b** (150 mg, 0.439 mmol) using the same procedure as for compounds **9ab** and **9aa**. **17bb**: $^1$H NMR (400 MHz, $CDCl_3$) *δ* 8.76 (s, 1H), 7.43 (s, 1H), 6.27 (d, *J* = 7.3 Hz, 1H), 4.10 (m, 1H), 4.01 (dd, *J* = 11.5 Hz, 3.0 Hz, 1H), 3.81 (dd, *J* = 11.5 Hz, 3.4 Hz, 1H), 3.36 (m, 1H), 2.24 (m, 2H), 1.93 (s, 3H), 0.95 (s, 9H), 0.13 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −10.76 (d, *J* = 8.5 Hz); IR (KBr) 3168, 3035, 1699, 1681, 1264, 1172 cm$^{-1}$; MS *m*/*z* 409($M^+$ + 1, 5), 407($M^+$ − 1, 1), 351 (100). Anal. Calcd for $C_{17}H_{27}N_2O_4F_3Si$: C, 49.98; H, 6.66; N, 6.86. Found: C, 49.72; H, 6.99; N, 6.35. **17ba**:$^1$H NMR (400 MHz, $CDCl_3$) *δ* 9.31 (s, 1H), 7.00 (s, 1H), 5.79 (d, *J* = 6.0 Hz, 1H), 4.61(m, 1H), 3.76 (dd, *J* = 11.2 Hz, 3.8 Hz, 1H), 3.65 (dd, *J* = 11.2 Hz, 3.8 Hz, 1H), 3.58 (m, 1H), 0.90 (s, 9H), 0.09 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −6.96 (d, *J* = 8.5 Hz).

**(2′*R*)-D-*N*$^4$-Benzoyl-5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-dideoxy-2′-trifluoromethylcytidine (11ab and 11aa).** Compounds **11ab** (194 mg, 53%) and **11aa** (116 mg, 32%) were prepared as a white solid respectively from compound **8a** (250 mg, 0.731 mmol) using the same procedure as for compounds **9ab** and **9aa**. **11ab**: $^1$H NMR (300 MHz, $CDCl_3$) *δ* 8.51 (d, *J* = 7.5 Hz, 1H), 7.93 (d, *J* = 7.4 Hz, 2H), 7.62−7.52 (m, 4H), 6.32 (d, *J* = 2.8 Hz, 1H), 4.45 (m, 1H), 4.14 (dd, *J* = 11.8 Hz, 2.2 Hz, 1H), 3.75 (dd, *J* = 11.8 Hz, 2.2 Hz, 1H), 3.17 (m, 1H), 2.40 (m, 1H), 2.20 (m, 1H), 0.96 (s, 9H), 0.16 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −7.62 (d, *J* = 9.1 Hz); IR (KBr) 3222, 1674, 1625, 1486, 1259 cm$^{-1}$; MS *m*/*z* 498 ($M^+$ + 1, 1), 497 ($M^+$, 1), 105 (100). Anal. Calcd for $C_{23}H_{30}N_3O_4F_3Si$: C, 55.52; H, 6.08; N, 8.44. Found: C, 55.36; H, 6.27; N, 8.35. **11aa**:$^1$H NMR (300 MHz, $CDCl_3$) *δ* 7.99−7.94 (m, 3H), 7.61−7.52 (m, 4H), 6.23 (d, *J* = 5.6 Hz, 1H), 4.61 (m, 1H), 3.86 (dd, *J* = 11.2 Hz, 3.3 Hz, 1H), 3.67(m, 2H), 2.45 (m, 2H), 0.92 (s, 9H), 0.09 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −10.04 (d, *J* = 9.4 Hz).

**(2′*S*)-D-*N*$^4$-Benzoyl-5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-dideoxy-2′-trifluoromethylcytidine (18bb and 18ba).** Compounds **18bb** (194 mg, 54%) and **18ba** (70 mg, 19%) were prepared as a white solid respectively from compound **8b** (250 mg, 0.731 mmol) using the same procedure as for compounds **9ab** and **9aa**. **18bb**: $^1$H NMR (300 MHz, $CDCl_3$) *δ* 8.29 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 7.3 Hz, 2H), 7.62−7.51 (m, 4H), 6.45 (d, *J* = 7.0 Hz, 1H), 4.23 (m, 1H), 4.06 (dd, *J* = 11.5 Hz, 2.9 Hz, 1H), 3.82 (dd, *J* = 11.5 Hz, 3.2 Hz, 1H), 3.55 (m, 1H), 2.30 (m, 2H), 0.97 (s, 9H), 0.20 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −10.99 (d, *J* = 8.6 Hz, 3F); IR (KBr) 3416, 1669, 1630, 1552, 1487, 1259, 838 cm$^{-1}$; MS *m*/*z* 440 ($M^+$ −57, 29), 105 (100). Anal. Calcd for $C_{23}H_{30}N_3O_4F_3Si$: C, 55.52; H, 6.08; N, 8.44. Found: C, 55.70; H, 6.18; N,8.58. **18ba**:$^1$H NMR (300 MHz, $CDCl_3$) *δ* 7.94 (d, *J* = 7.5 Hz, 2H), 7.65 (m, 2H), 7.52 (m, 3H), 5.77 (d, *J* = 5.2 Hz, 1H), 4.80 (m, 1H), 3.88 (m,1H), 3.78 (dd, *J* = 11.3 Hz, 3.9 Hz, 1H,), 3.69 (dd, *J* = 11.3 Hz,4.2 Hz,-1H), 2.43 (m, 1H), 2.24 (m, 1H), 0.92 (s, 9H), 0.08 (s, 6H); $^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −6.92 (d, *J* = 8.3 Hz).

**Representative Procedure for the Deprotection of Silyl-Protected Uracil and Thymine Nucleosides: *β*-D-(2′*R*)-2′,3′-Dideoxy-2′-trifluoromethyluridine (12ab).** A stirred solution of protected nucleoside **9ab** (0.107 g, 0.272 mmol) in anhydrous THF (10 mL) was treated with a 1.0 M solution of TBAF in THF (0.54 mL, 0.54 mmol) at room temperature. After stirring for 30 min, the solvent was removed and the residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 1:4) to give 49 mg (64% yield) of **12ab** as a white solid: mp 168−170 °C; $[\alpha]^{20}_D$ +9.8° (*c* 0.15, MeOH); $^1$H NMR (300 MHz, MeOH-*d*$_4$) *δ* 7.92 (d, *J* = 8.1 Hz, 1H), 6.18 (d, *J* = 5.4 Hz, 1H), 5.69 (d, *J* = 8.1 Hz, 1H), 4.23 (m, 1H), 3.78 (dd, *J* = 12.1 Hz, 2.6 Hz, 1H), 3.60 (dd, *J* = 12.1 Hz, 3.5 Hz, 1H), 3.34 (m, 1H), 2.32 (m, 1H), 2.23 (m, 1H);$^{19}$F NMR (282 MHz, $CDCl_3$) *δ* −9.66 (d, *J* = 9.1 Hz); IR (KBr) 3473, 3042, 1675, 1117 cm$^{-1}$; MS *m*/*z* 281 ($M^+$ + 1, 4), 113 (100). Anal. Calcd for $C_{10}H_{11}N_2O_4F_3$: C, 42.87; H, 3.96; N, 10.00. Found: C, 43.09; H, 3.93; N, 9.90.

**α-D-(2′*R*)-2′,3′-Dideoxy-2′-trifluoromethyluridine (12aa).** Compound **12aa** (25 mg, 78%) was prepared as a white solid from compound **9aa** (45 mg, 0.114 mmol) using the same conditions as for compound **12ab**: mp170−172 °C; $[\alpha]^{20}_D$ −72.3° (*c* 0.315, MeOH);$^1$H NMR (300 MHz, MeOH-*d*$_4$) *δ* 7.60 (d, *J* = 8.2 Hz, 1H), 6.29 (d, *J* = 6.4 Hz, 1H), 5.65 (d, *J* = 8.2 Hz, 1H), 4.6 (m, 1H), 3.66−3.57 (m, 2H), 3.50 (dd, *J* = 12.1 Hz, 4.0 Hz, 1H), 2.34 (m, 2H); $^{19}$F NMR (282 MHz, MeOH-*d*$_4$) *δ* −13.12 (d, *J* = 9.8 Hz).

**α-D-(2′S)-2′,3′-Dideoxy-2′-trifluoromethyluridine (19ba).** A mixture of **16ba** and **16bb** (216 mg, 0.548 mmol) was treated using the same conditions as for compound **12ab** to give a mixture of α/*β* anomers (138 mg, 90%), which was recrystallized from ethyl acetate and hexane to give compound **19ba** (86 mg, 56% yield) as a white solid: mp197−199 °C; $[\alpha]^{20}_D$ +18.0° (*c* 0.31, MeOH); $^1$H NMR (300 MHz, MeOH-*d*$_4$) *δ* 7.88 (d, *J* = 8.1 Hz, 1H), 6.32 (d, *J* = 6.6 Hz, 1H), 5.92 (d, *J* =8.1 Hz, 1H), 4.78 (m, 1H), 3.87 (m, 1H), 3.73 (dd, *J* = 12.1 Hz, 4.7 Hz, 1H), 2.63 (m, 1H), 2.30 (m, 1H); $^{19}$F NMR (282 MHz, MeOH-*d*$_4$) *δ* −9.54 (d, *J* = 8.7 Hz); IR (KBr) 3535, 3164, 1719,

1678 $cm^{-1}$; MS *m*/*z* 282 ($M^+ + 2$, 1), 281 ($M^+ + 1$, 2), 280 ($M^+$, 1), 149 (100).

***β*-D-(2′*R*)-2′,3′-Dideoxy-2′-trifluoromethylthymidine (13ab).** Compound **13ab** (80 mg, 77%) was prepared as a white solid from compound **10ab** (144 mg, 0.353 mmol) using the same conditions as for compound **12ab**: mp 213−214 °C; $[\alpha]^{20}_D$ −1.9° (*c* 0.31, MeOH); $^1$H NMR (400 MHz, MeOH-$d_4$) $\delta$ 7.99 (s, 1H), 6.43 (d, $J$ = 5.6 Hz, 1H), 4.44 (m, 1H), 4.03 (dd, $J$ = 12.2 Hz, 2.9 Hz, 1H), 3.85 (dd, $J$ =12.2 Hz, 3.6 Hz, 1H), 3.54 (m, 1H), 2.59 (m, 1H), 2.08 (s, 3H); $^{19}$F NMR (282 MHz, MeOH-$d_4$) $\delta$ −9.64 (d, $J$ = 8.9 Hz); IR (KBr) 3434, 3182, 3063, 1691, 1477, 1276 $cm^{-1}$; MS *m*/*z* 263($M^+$ −31, 9), 126 (100). Anal. Calcd for $C_{11}H_{13}N_2O_4F_3$: C, 44.90; H, 4.45; N, 9.52. Found: C, 44.97; H, 4.31; N, 9.48.

**α-D-(2′*R*)-2′,3′-Dideoxy-2′-trifluoromethylthymidine (13aa).** Compound **13aa** (33 mg, 77%) was prepared as a white solid from compound **10aa (**60 mg, 0.147 mmol) using the same conditions as for compound **12ab:** $[\alpha]^{20}_D$ −53.9° (*c* 0.125, MeOH); $^1$H NMR (400 MHz, MeOH-$d_4$) $\delta$ 7.63 (s, 1H), 6.52 (d, 1H), 4.85 (m, 1H), 3.90 (dd, $J$ = 12.0 Hz, 3.4 Hz, 1H), 3.80 (m, 1H), 3.75 (dd, $J$ = 12.0 Hz, 4.1 Hz, 1H), 2.63 (m, 1H), 2.51 (m, 1H), 2.09 (s, 3H); $^{19}$F NMR (282 MHz, MeOH-$d_4$) $\delta$ −13.13 (d, $J$ = 9.3 Hz).

***β*-D-(2′*S*)-2′,3′-Dideoxy-2′-trifluoromethylthymidine (20bb).** Compound **20bb** (8.2 mg, 72%) was prepared as a white solid from compound **17bb** (16 mg, 0.039 mmol) using the same conditions as for compound **12ab:** mp142−144 °C; $[\alpha]^{20}_D$ +54.1° (*c* 0.085, MeOH); $^1$H NMR (400 MHz, MeOH-$d_4$) $\delta$ 8.16 (s, 1H), 6.54 (d, $J$ = 7.4 Hz, 1H), 4.37 (m, 1H), 4.15 (dd, $J$ = 12.6 Hz, 3.0 Hz, 1H), 3.92 (dd, $J$ = 12.6 Hz, 2.6 Hz, 1H), 3.81 (m, 1H), 2.44 (m, 2H), 2.06 (s, 3H); $^{19}$F NMR (282 MHz, MeOH-$d_4$) $\delta$ −13.6 (d, $J$ = 9.1 Hz).

**α-D-(2′*S*)-2′,3′-Dideoxy-2′-trifluoromethylthymidine (20ba).** Compound **20ba** (28 mg, 96%) was prepared as a white solid from compound **17ba** (41 mg, 0.100 mmol) using the same conditions as for compound **12ab:** mp 231−233 °C; $[\alpha]^{20}_D$ +20.0° (*c* 0.205, MeOH); $^1$H NMR (400 MHz, MeOH-$d_4$) $\delta$ 7.70 (s, 1H), 6.34 (d, $J$ = 6.8 Hz, 1H), 4.79 (m, 1H), 3.87 (m, 2H), 3.73 (dd, $J$ = 12.1 Hz, 4.8 Hz, 1H), 2.62 (m, 1H), 2.30 (m, 1H), 2.09 (s, 3H); $^{19}$F NMR (282 MHz, MeOH-$d_4$) $\delta$ −9.51 (d, $J$ = 8.0 Hz); IR (KBr) 3526, 3176, 1710, 1677, 1270 $cm^{-1}$; MS *m*/*z* 295 ($M^+ + 1$, 1), 126 (100). Anal. Calcd for $C_{11}H_{13}N_2O_4F_3$: C, 44.90; H, 4.45; N, 9.52. Found: C, 44.72; H, 4.50; N, 9.11.

**Representative Procedure for the Deprotection of Silyl-Protected Cytosine Nucleosides: *β*-D-(2′*R*)-2′,3′-Dideoxy-2′-trifluoromethylcytidine (15ab).** A stirred solution of protected nucleoside **11ab** (0.120 g, 0.241 mmol) in anhydrous THF(10 mL) was treated with a 1.0 M solution of TBAF in THF (0.48 mL, 0.48 mmol) at room temperature. After stirring for 30 min, the solvent was removed and the residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 1:4) to give crude desilylated cytosine derivative, which was dissolved in saturated methanolic ammonia (10 mL). The resulting reaction mixture was stirred for 12 h. After removal of the volatile materials, the residue was purified by silica gel chromatography ($CH_2Cl_2$:MeOH = 2:1) to give 46 mg (69% yield) of **15ab** as a white solid: mp 169−171 °C; $[\alpha]^{20}_D$ +28.7° (*c* 0.285, MeOH); $^1$H NMR (300 MHz, MeOH-$d_4$) $\delta$ 8.16 (d, $J$ = 7.45 Hz, 1H), 6.45 (d, $J$ = 5.1 Hz, 1H), 6.11 (d, $J$ = 7.45 Hz, 1H), 4.46 (m, 1H), 4.03 (dd, $J$ = 12.1 Hz, 2.8 Hz, 1H), 3.85 (dd, $J$ = 12.1 Hz, 3.6 Hz, 1H), 3.54 (m, 1H), 2.58 (m, 1H), 2.42 (m, 1H); $^{19}$F NMR (282 MHz, MeOH-$d_4$) $\delta$ −9.8 (d, $J$ = 9.0 Hz, 3F); IR (KBr) 3479, 3327, 3104, 1679, 1629, 1479, 1120 $cm^{-1}$; MS *m*/*z* 280 ($M^+ + 1$, 1), 279($M^+$, 3),278 ($M^+$, 2), 111 (100). HRMS Calcd for $C_{10}H_{12}N_3O_3F_3$: 279.2189. Found: 279.0821.

**α-D-(2′*R*)-2′,3′-Dideoxy-2′-trifluoromethylcytidine (15aa).** Compound **15aa** (32 mg, 73%) was prepared as a white solid from compound **11aa** (59.29 mg, 0.119 mmol) using the same conditions as for compound **15aa:** mp 214−216 °C; $[\alpha]^{20}_D$ −139.7° (*c* 0.26, MeOH); $^1$H NMR (300 MHz, MeOH-$d_4$) $\delta$ 7.88 (d, $J$ = 7.5 Hz, 1H), 6.29 (d, $J$ = 6.0 Hz, 1H), 6.10 (d, $J$ = 7.5 Hz, 1H), 4.78 (m, 1H), 3.91 (dd, $J$ = 12.0 Hz, 3.2 Hz, 1H), 3.81 (m, 2H), 2.56 (m, 2H); $^{19}$F NMR (282 MHz, MeOH-$d_4$) $\delta$ −13.01 (s).

***β*-D-(2′*S*)-2′,3′-Dideoxy-2′-trifluoromethylcytidine (22bb).** Compound **22bb** (35 mg, 90%) was prepared from **18bb** as a white solid (69 mg, 0.139 mmol) using the same conditions as for compound **15ab:** mp 113−116 °C; $[\alpha]^{20}_D$ +131.2° (*c* 0.24, MeOH);$^1$H NMR (300 MHz, MeOH-$d_4$) $\delta$ 8.19 (d, $J$ = 7.3 Hz, 1H), 6.52 (d, $J$ = 7.0 Hz, 1H), 6.07 (d, $J$ = 7.3 Hz, 1H), 4.35 (m, 1H), 4.10 (dd, $J$ = 12.4 H, 2.7 Hz, 1H), 3.91 (dd, $J$ = 12.4 Hz, 3.8 Hz, 1H), 3.78 (m, 1H), 2.40 (m, 2H); $^{19}$F NMR (282 MHz, MeOH-$d_4$) $\delta$ −13.45 (d, $J$ = 9.3 Hz).

**α-D-(2′*S*)-2′,3′-Dideoxy-2′-trifluoromethylcytidine (22ba).** Compound **22ba** (51 mg, 60%) was prepared as a white solid from **18ba** (151 mg, 0.183 mmol) using the same conditions as for compound **15ab:** mp 103−106 °C; $[\alpha]^{20}_D$ −6.1° (*c* 0.16, MeOH); $^1$H NMR (300 MHz, MeOH-$d_4$) $\delta$ 7.85 (d, $J$ = 7.4 Hz, 1H), 6.30 (d, $J$ = 6.3 Hz, 1H), 6.11 (d, $J$ = 7.4 Hz, 1H), 4.82 (m, 1H), 3.90 (m, 2H), 3.73 (dd, $J$ = 12.0 Hz, 4.6 Hz, 1H), 3.50 (m, 1H), 2.61 (m, 1H), 2.29 (m, 1H); $^{19}$F NMR (282 MHz, MeOH-$d_4$) $\delta$ −9.54 (d, $J$ = 8.7 Hz).

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