SYNTHESIS OF 2′,3′-DIDEOXY-2′-TRIFLUOROMETHYL-*N*-AZANUCLEOSIDES

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Dedicated to the memory of Professor Miloš Hudlický.

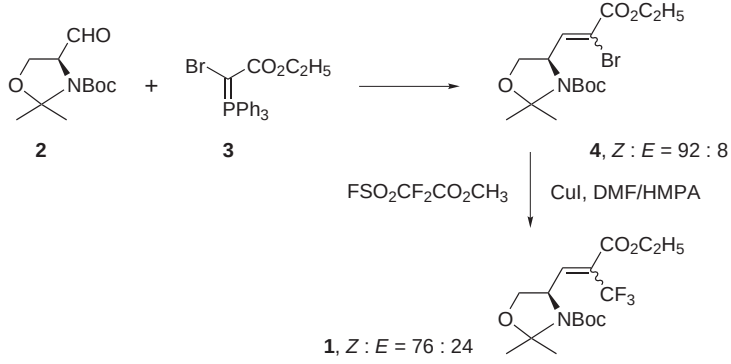
The trifluoromethylation of (*Z*)/(*E*)-*tert*-butyl (4*S*)-4-(2′-ethoxycarbonyl-2′-bromoprop-1′-enyl)-2,2-dimethyloxazolidine-3-carboxylate (**4**), which is derived from chiral serine aldehyde, yields α-trifluoromethyl-α,β-unsaturated ester **1**. Compound **1** is used as a key intermediate for the synthesis of a number of 2′,3′-dideoxy-2′-trifluoromethyl-*N*-azanucleosides.

Keywords: Trifluoromethylation; α-Trifluoromethyl-α,β-unsaturated ester; Nucleosides; Azanucleosides; Aminosugars; Antivirals; Fluorinated compounds.

The need for new antiviral and anticancer agents has led to the discovery of a class of modified nucleosides[1]. In particular, sugar-modified derivatives have proved to be of current interest for the use of cancer and viral chemotherapy[2]. Azanucleosides, in which the pyranose or furanose ring oxygen is replaced by nitrogen, are an important class of modified nucleosides[3]. 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[4]. 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. 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. To our knowledge, there is no report on the fluorinated azanucleoside. In this article, we describe a novel and general route to 2′,3′-dideoxy-2′-trifluoromethyl-*N*-azanucleosides.

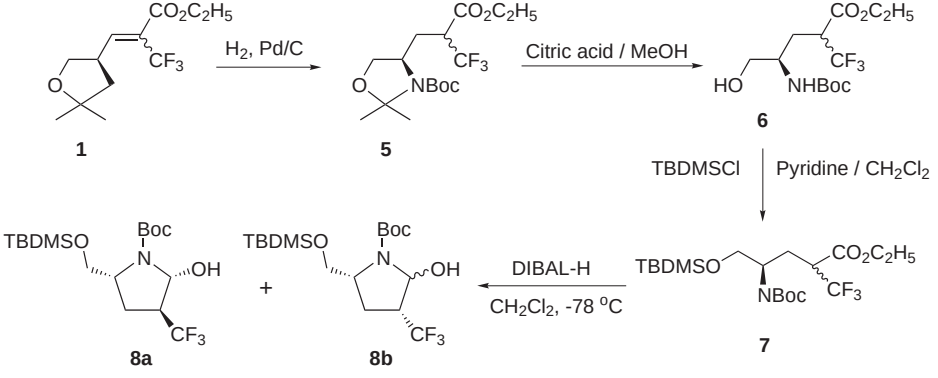
RESULTS AND DISCUSSION

α-Trifluoromethyl-α,β-unsaturated ester **1**, prepared from chiral serine aldehyde[7] **2** (Scheme 1), was used as the key intermediate for the preparation of 2′,3′-dideoxy-2′-trifluoromethyl-*N*-azanucleosides. The Wittig reaction of aldehyde **2** with ylide **3** provided the *Z* isomer of α-bromo-α,β-unsaturated ester **4** as the major product (*Z* : *E* = 92 : 8) in 93% yield. The treatment of **4** with $FSO_2CF_2CO_2Me$ and CuI in DMF/HMPA gave a 76 : 24 mixture of *Z*- and *E*-**1** in 62% isolated yield[8].



SCHEME 1

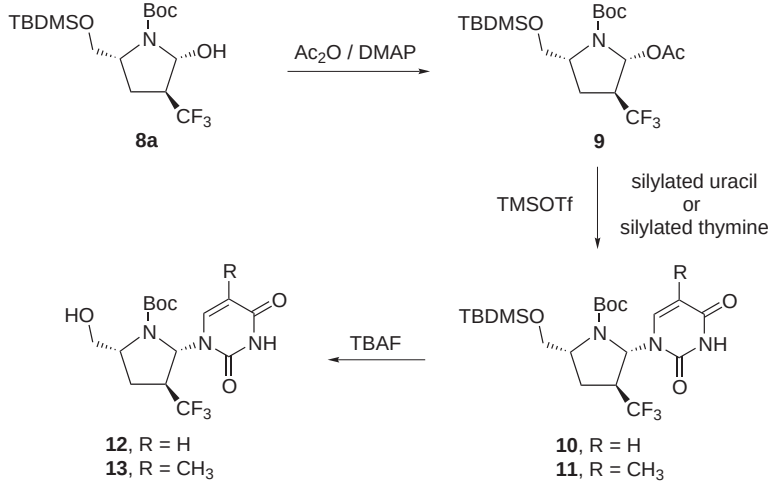
Due to difficulties in separation of (*Z*)-**1** and (*E*)-**1** isomers, the mixture was directly used in the next reaction (Scheme 2). Hydrogenation of **1** in the presence of 10% Pd/C afforded **5** as a mixture of the C-2 epimers (*syn* : *anti* = 3.9 : 1, determined by ^{19}F NMR spectrum) in 95% yield. Treatment of **5** with citric acid in methanol at 60 °C provided alcohol **6** in 58% yield. Protection of the hydroxyl group with *tert*-butyldimethylsilyl chloride (TBDMSCl)



SCHEME 2

gave **7** in 92% yield. The cyclized acetal **8a** and **8b** were obtained *via* intramolecular nucleophilic addition by reduction of compound **7** with diisobutylaluminum hydride (DIBAL-H) in anhydrous CH_2Cl_2 at –78 °C. Compounds **8a** and **8b** were separated in a ratio of 4.6 : 1 by column chromatography on silica gel. **8a** was the single α anomer and used for the synthesis of 2′,3′-dideoxy-2′-trifluoromethyl-*N*-azanucleosides, whereas **8b** was a mixture of α and β anomers.

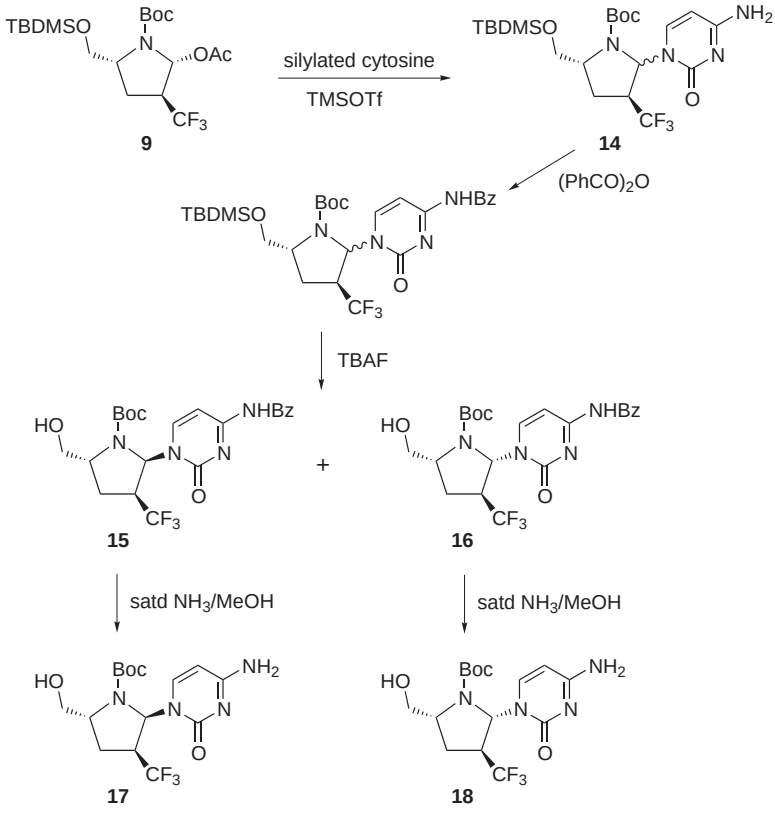
The acetylation of **8a** with acetic anhydride in CH_2Cl_2 yielded the single α anomeric acetate **9**. Coupling of **9** with silylated uracil and thymine under Vorbruggen conditions[9] (glycosylation reaction) provided exclusively the α anomers **10** and **11**, respectively (Scheme 3). The removal of the silyl group with TBAF gave 2′,3′-dideoxy-2′-trifluoromethyl-*N*-azanucleosides **12**



SCHEME 3

and **13**. Similarly, **9** was condensed with silylated cytosine afforded a 2 : 1 mixture of α and β anomer of **14** (Scheme 4). The α and β anomer of **14** could not be separated. Benzoylation of the amino group of **14**, followed by removal of the silyl group gave **15** and **16**, which were readily separated by column chromatography on silica gel. Treatment of **15** and **16** with a saturated solution of ammonium in methanol afforded 2′,3′-dideoxy-2′-trifluoromethyl-*N*-azanucleosides **17** and **18**, respectively.

The configuration assignments of the anomeric center were made on the basis of 1D and 2D NMR spectroscopy. The configuration of the CF_3 was assigned mainly by ^{19}F NMR spectrum, in which the CF_3 at lower field was assigned as the α-trifluoromethyl isomer and the one at higher field were



SCHEME 4

assigned as the β isomer. This assignment was further confirmed by the NOESY experiment of **17** and **18** (Fig. 1). Compounds **12**, **13**, **17**, and **18** are a class of "reverse nucleosides" [10], enantiomers of normal nucleosides.

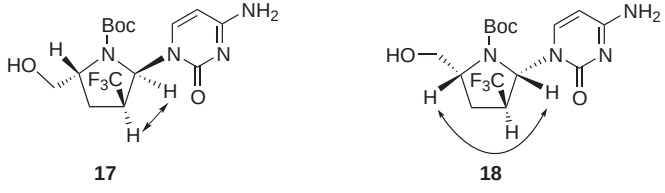


FIG. 1
NOE correlation from NOESY spectra of **17** and **18**

EXPERIMENTAL

^{1}H NMR spectra were recorded on either a Bruker AM300 (300 MHz) or a Bruker AM400 (400 MHz) spectrometer, with TMS as internal standard. ^{19}F NMR spectra were recorded on either an EM-360L (56.4 MHz) or a Bruker AM300 (282 MHz) spectrometer, with CF_3COOH as the external standard and upfield is positive. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. IR spectra (wavenumbers in cm^{-1}) were recorded on a Shimadzu IR-440 Spectrometer. The mass spectra were recorded on a Finnigan-MAT-8430 mass spectrometer using EI ionization at 70 eV.

Ethyl (*Z*)/(*E*)-2-Bromo-3-[(*S*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl]-acrylate (**4**)

A solution of triphenylcarbethoxybromomethylenephosphorane (**3**; 37.5 g, 87.7 mmol) and (*S*)-Garner's aldehyde **2** (20.0 g, 87.7 mmol) in dichloromethane (350 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 procedure was repeated three times, the combined extracts were filtered, and the filtrate was concentrated to yield a yellow oil. The oil was purified by column chromatography on silica gel (hexane– ethyl acetate 20 : 1) to give 30.9 g (93%) of (*Z*)/(*E*)-**4** (92 : 8, by ^{1}H NMR) as a light amber oil. ^{1}H NMR (300 MHz,CD_3COCD_3): 7.26 (d, *J* = 7.8, 0.93 H); 6.77 (d, *J* = 7.8, 0.07 H); 5.11–4.76 (m, 1 H); 4.71–4.29 (m, 3 H); 3.87–3.80 (m, 1 H); 1.59–1.30 (m, 18 H). IR (thin film): 2 982, 1 705, 1 616. MS, *m/z*: 380 (M^+ + 1, 1), 57 (100). For $C_{15}H_{24}BrNO_5$ (378.3) calculated: 47.63% C, 6.40% H, 3.70% N; found: 47.44% C, 6.505% H, 3.78% N.

Ethyl (*Z*)/(*E*)-3-[(*S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl]-2-(trifluoromethyl)-acrylate (**1**)

To a solution of **4** (24.9 g, 66.1 mmol) in anhydrous DMF (210 ml) and HMPA (35 ml) was added CuI (3.16 g, 16.5 mmol). Then the mixture was heated to 75 °C, and a solution of $FSO_2CF_2CO_2Me$ (26.4 ml, 231.5 mmol) in DMF (35 ml) was added *via* syringe over a period of 12 h. After stirring at 75 °C for 30 h, the reaction mixture was treated with saturated aqueous NH_4Cl 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 column chromatography on silica gel (hexane–ethyl acetate 25 : 1) to give a mixture of 14.1 g (62%) of (*Z*)/(*E*)-**1** (76 : 24, by ^{19}F NMR) as an amber oil. ^{1}H NMR (300 MHz, CD_3COCD_3): 7.21 (d, *J* = 8.7, 0.67 H); 6.94 (d, *J* = 8.4, 0.33 H); 5.19–4.97 (m, 1 H); 4.36–4.26 (m, 3 H); 3.91–3.85 (m, 1 H); 1.61–1.20 (m, 18 H). ^{19}F NMR (56.4 MHz, $CDCl_3$): –18.0 (s, 2.27 F); –12.5 (s, 0.73 F). IR (thin film): 2 984, 1 735, 1 710. MS, *m/z*: 380 (M^+ + 1, 2), 57 (100). For $C_{16}H_{24}F_3NO_5$ (367.4) calculated: 52.31% C, 6.59% H, 3.81% N; found: 52.42% C, 6.58% H, 4.07% N.

Ethyl 3-[(*S*)-3-(*tert*-Butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl]-2-(trifluoromethyl)-propanoate (**5**)

10% of Pd/C (1.46 g, 1.37 mmol) was added to a solution of (*Z*)/(*E*)-**1** (7.20 g, 19.62 mmol) in ethyl acetate (150 ml) at room temperature under 1 atm of hydrogen. After stirring for 5 h, the reaction mixture was filtered, and the solvent was removed to give the crude oil. This oil

was purified by column chromatography on silica gel (hexane–ethyl acetate 10 : 1) to afford 6.88 g (95%) of **5** as a colorless oil. ^{1}H NMR (300 MHz, CD_3COCD_3): 4.24–4.28 (m, 2 H); 4.02–4.06 (m, 2 H); 3.77 (m, 1 H); 3.44 (m, 1 H); 2.19 (m, 2 H); 1.28–1.55 (m, 18 H). ^{19}F NMR (282 MHz, CD_3COCD_3): –13.7 (d, *J* = 8.2); –12.9 (d, *J* = 8.4). IR (thin film): 2 984, 2 941, 2 881, 1 749, 1 702. MS, *m/z*: 370 (M^+ + 1, 2); 254 (60), 57 (100). For $C_{16}H_{26}F_3NO_5$ (369.4) calculated: 52.02% C, 7.10% H, 3.79% N; found: 52.22% C, 7.14% H, 3.88% N.

Ethyl 4-[(*tert*-Butoxycarbonyl)amino]-5-hydroxy-2-(trifluoromethyl)pentanoate (**6**)

A mixture of **5** (6.93 g, 18.8 mmol), 5% aqueous citric acid solution (50 ml) and methanol (100 ml) was stirred at 60 °C for 4 h. Then the solvent and water were removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–ethyl acetate 3 : 1) to give 3.58 g (58%) of the alcohol **6** as a colorless oil. ^{1}H NMR (300 MHz, CD_3COCD_3): 4.19–4.34 (m, 2 H); 3.39–3.63 (m, 4 H); 2.23 (m, 1 H); 1.88 (m, 1 H); 1.24–1.41 (m, 12 H). ^{19}F NMR (282 MHz, CD_3COCD_3): –13.3 (d, *J* = 8.4); –13.0 (d, *J* = 8.2). IR (thin film): 3 385, 2 983, 2 940, 1 748, 1 691. MS, *m/z*: 330 (M^+ + 1, 5), 230 (56), 57 (100). For $C_{13}H_{22}F_3NO_5$ (329.3): 47.41% C, 6.73% H, 4.25% N; found: 47.46% C, 6.76% H, 4.20% N.

Ethyl 4-[(*tert*-Butoxycarbonyl)amino]-5-(*tert*-butyldimethylsilyloxy)-2-(trifluoromethyl)-pentanoate (**7**)

To a solution of the alcohol **6** (3.54 g, 10.76 mmol) in CH_2Cl_2 (40 ml) was added *tert*-butyldimethylsilyl chloride (3.23 g, 21.52 mmol) and imidazole (2.19 g, 32.28 mmol). After being stirred for 2 h at room temperature, the reaction mixture was poured onto water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give a yellowish oil. The oil was purified by column chromatography on silica gel (hexane–ethyl acetate 8 : 1) to give 4.37 g (92%) of compound **7**. ^{1}H NMR (300 MHz, CD_3COCD_3): 4.24 (q, *J* = 7.1, 2 H); 3.59–3.69 (m, 3 H); 3.44 (m, 1 H); 2.20 (m,1 H); 1.90 (m, 1 H); 1.41 (s, 9 H); 1.28 (t, *J* = 7.1, 3 H); 0.91 (s, 9 H); 0.09 (s, 6 H). ^{19}F NMR (282 MHz, CD_3COCD_3): –13.2 (s); –13.9 (s). IR (thin film): 3 448, 3 382, 2 980, 2 959, 2 933, 2 861, 1 750, 1 720. MS, *m/z*: 444 (M^+ + 1, 3), 344 (82), 57 (100). For $C_{19}H_{36}F_3NO_5Si$: (443.6) calculated: 51.44% C, 8.18% H, 3.16% N; found: 51.23% C, 8.15% H, 3.10% N.

tert-Butyl (2*R*,3*S*,5*R*)-2-Hydroxy-5-[(*tert*-butyldimethylsilyloxy)methyl]-3-(trifluoromethyl)-pyrrolidine-1-carboxylate (**8a**) and
tert-Butyl (2*R*,3*R*,5*R*)-2-Hydroxy-5-[(*tert*-butyldimethylsilyloxy)methyl]-3-(trifluoromethyl)-pyrrolidine-1-carboxylate (**8b**)

A solution of **7** (4.35 g, 9.19 mmol) in anhydrous dichloromethane (100 ml) was cooled to –78 °C, and a 1.0 M solution of DIBAL-H in cyclohexane (29.46 ml, 29.46 mmol) was added dropwise over a period of 1 h. The reaction mixture was stirred at –78 °C for 3 h. Then the reaction was quenched by the slow addition of methanol below –70 °C, until no more gas elution occurred. The mixture was then allowed to warm to room temperature, 1 M HCl (100 ml) was added, and the mixture was stirred for 1 h. The aqueous layer was extracted with ether. The organic layers were combined, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give a yellowish oil. The oil was purified by column chromatography on silica gel (hexane–ethyl acetate 10 : 1) to give 2.56 g (64%) of **8a** as an amber oil and 0.60 g (15%) of **8b** as an amber oil.

8a: ^{1}H NMR (300 MHz, CD_3COCD_3): 5.59 (d, *J* = 3.0, 1 H); 4.02 (br, 1 H); 3.83 (dd, *J* = 9.3, 4.3, 1 H); 3.68 (br, 1 H); 3.02 (m, 1 H); 2.76–2.27 (m, 1 H); 2.20–2.10 (m, 1 H); 1.47 (s, 9 H); 0.92 (s, 9 H); 0.11 (s, 6 H). ^{19}F NMR (282 MHz, CD_3OD): –10.5 (s).

8b: ^{1}H NMR (300 MHz, CD_3COCD_3): 5.61 (br, 0.93 H); 5.51 (d, *J* = 3.3, 0.07 H); 3.97–4.04 (m, 1 H); 3.85 (m, 1 H); 3.74 (m, 1 H); 2.97 (m, 1 H); 2.20–2.34 (m, 2 H); 1.49 (s, 0.63 H); 1.46 (s, 8.37 H); 0.92 (s, 8.37 H); 0.91 (s, 0.63 H); 0.11 (s, 5.58 H); 0.08 (s, 0.42 H). ^{19}F NMR (282 MHz, CD_3OD): –15.7 (s). IR (thin film): 3 443, 2 959, 2 933, 2 861, 1 688. MS, *m/z*: 402 (M^+ + 3, 5), 57 (91), 282 (100). For $C_{17}H_{32}F_3NO_4Si$ (399.5) calculated: 51.10% C, 8.07% H, 3.51% N; found: 51.21% C, 8.18% H, 3.54% N.

tert-Butyl (2*R*,3*S*,5*R*)-2-(Acetyloxy)-5-[(*tert*-butyldimethylsilyloxy)methyl]-3-(trifluoromethyl)-pyrrolidine-1-carboxylate (**9**)

To a solution of **8a** (2.54 g, 6.37 mmol) in anhydrous CH_2Cl_2 (60 ml), DMAP (80 mg, 0.64 mmol) and acetic anhydride (4.0 ml, 38.2 mmol) were added, and the resulting solution was stirred at room temperature overnight. The reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution and stirred for 25 min. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a light amber oil. The oil was purified by column chromatography on silica gel (hexane–ethyl acetate 8 : 1) to give compound **9** (93%) as an amber oil. ^{1}H NMR (300 MHz, CD_3COCD_3): 6.66 (d, *J* = 1.2, 1 H); 4.02–4.00 (m, 1 H); 3.80 (br, 2 H); 3.21 (m, 1 H); 2.36 (m, 1 H); 2.22 (m, 1 H); 2.01 (s, 3 H); 1.42 (s, 9 H); 0.91 (s, 9 H); 0.09 (s, 6 H). ^{19}F NMR (282 MHz, CD_3OD): –10.4 (s). IR (thin film): 2 960, 2 933, 2 860, 1 759, 1 715. MS, *m/z*: 442 (M^+ + 1, 6), 441 (M^+, 13), 73 (38), 57 (100). For $C_{19}H_{34}F_3NO_5Si$ (441.6) calculated: 51.68% C, 7.76% H, 3.20% N; found: 51.46% C, 7.86% H, 3.20% N.

tert-Butyl (2*S*,3*S*,5*R*)-5-[(*tert*-Butyldimethylsilyloxy)methyl]-2-[5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]-3-(trifluoromethyl)pyrrolidine-1-carboxylate (**11**)

To a stirred solution of compound **9** (0.31 g, 0.705 mmol) and thymine (0.25 g, 1.97 mmol) in anhydrous acetonitrile (20 ml) was added *N*,*O*-bis(trimethylsilyl)acetamide (1.35 ml, 4.09 mmol). The reaction mixture was stirred under reflux for 30 min. After cooling to 0 °C, trimethylsilyl triflate (0.35 ml, 1.68 mmol) was added dropwise and the solution was stirred at room temperature for 16 h. The reaction mixture was quenched with cold saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with dichloromethane. The combined extract was washed with brine, dried over Na_2SO_4, and concentrated to give a yellow oil. The oil was purified by column chromatography on silica gel (hexane–ethyl acetate 3.5 : 1) to give 0.27 g (69%) of **11** as a white foam. ^{1}H NMR (300 MHz, CD_3COCD_3): 7.34 (s, 1 H); 6.33 (d, *J* = 7.5, 1 H); 4.16–4.12 (m, 2 H); 3.92 (dd, *J* = 11.9, 4.3, 1 H); 3.48 (m, 1 H); 2.42–2.30 (m, 2 H); 1.88 (s, 3 H); 1.37 (s, 9 H); 0.97 (s, 9 H); 0.20 (s, 6 H). ^{19}F NMR (282 MHz, CD_3OD): –11.2 (d, *J* = 8.0). IR (KBr): 3 207, 3 065, 2 959, 2 860, 1 696. MS, *m/z*: 224 (100), 57 (82). For $C_{22}H_{36}F_3N_3O_5Si$ (507.6) calculated: 52.05% C, 7.15% H, 8.28% N; found: 52.19% C, 7.23% H, 8.23% N.

tert-Butyl (2*S*,3*S*,5*R*)-5-[(*tert*-Butyldimethylsilyloxy)methyl]-2-[2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]-3-(trifluoromethyl)pyrrolidine-1-carboxylate (**10**)

Compound **10** (0.38 g, 76%) was prepared as a white foam from compound **9** (0.50 g, 1.125 mmol) using the same conditions as for **11**. ^{1}H NMR (300 MHz, CD_3COCD_3): 7.92 (d, *J* =

8.1, 1 H); 6.19 (d, *J* = 6.2, 1 H); 5.48 (d, *J* = 8.1, 1 H); 4.07 (dd, *J* = 10.6, 2.3, 1 H); 3.98–3.94 (m, 1 H); 3.69 (dd, *J* = 10.6, 2.0, 1 H); 3.24 (m, 1 H); 2.22–2.17 (m, 2 H); 1.21 (s, 9 H); 0.78 (s, 9 H); 0.01 (s, 6 H). ^{19}F NMR (282 MHz, CD_3OD): –11.1 (d, *J* = 8.0). IR (KBr): 3 212, 3 066, 2 959, 2 934, 2 861, 1 698, 1 635. MS, *m/z*: 497 (M^+ + 4, 3), 119 (68), 91 (100). For $C_{21}H_{34}F_3N_3O_5Si$ (493.6) calculated: 51.10% C, 6.94% H, 8.51% N; found: 50.88% C, 6.855 H, 8.36% N.

tert-Butyl (2*S*,3*S*,5*R*)-5-(Hydroxymethyl)-2-[5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]-3-(trifluoromethyl)pyrrolidine-1-carboxylate (**13**)

A stirred solution of protected nucleoside **11** (0.23 g, 0.45 mmol) in anhydrous THF was treated with a 1.0 M solution of TBAF in THF (0.92 ml, 0.92 mmol) at room temperature. After stirring for 1 h, the solvent was removed and the residue was purified by column chromatography on silica gel (hexane–ethyl acetate 1 : 2.5) to give 0.18 g (97%) of **13** as a white foam. ^{1}H NMR (300 MHz, CD_3OD): 8.45 (s, 1 H); 6.52 (d, *J* = 7.0, 1 H); 4.30–4.24 (m, 2 H); 3.87 (dd, *J* = 11.9, 2.9, 1 H); 3.59 (m, 1 H); 2.49–2.42 (m, 2 H); 2.08 (s, 3 H); 1.58 (s, 9 H). ^{19}F NMR (282 MHz, CD_3OD): –8.6 (d, *J* = 8.0). IR (KBr): 3 473, 3 204, 3 064, 2 982, 1 695. MS, *m/z*: 168 (62), 57 (100). For $C_{16}H_{22}F_3N_3O_5$ (393.4) calculated: 48.85% C, 5.64% H, 10.68% N; found: 48.895 C, 5.85% H, 10.57% N.

tert-Butyl (2*S*,3*S*,5*R*)-5-(Hydroxymethyl)-2-[2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]-3-(trifluoromethyl)pyrrolidine-1-carboxylate (**12**)

Compound **12** (193 mg, 95%) was prepared as a white foam from compound **11** (254 mg, 0.51 mmol) using the same conditions as for compound **13**. ^{1}H NMR (300 MHz, CD_3OD): 8.57 (d, *J* = 8.1, 1 H); 6.53 (d, *J* = 7.0, 1 H); 5.92 (d, *J* = 8.1, 1 H); 4.20–4.14 (m, 2 H); 3.87 (dd, *J* = 10.9, 1.8, 1 H); 3.65 (m, 1 H); 2.53–2.50 (m, 2 H); 1.60 (s, 9 H). ^{19}F NMR (282 MHz, CD_3OD): –8.6 (d, *J* = 8.0). IR (KBr): 3 480, 3 063, 2 982, 1 694. MS, *m/z*: 380 (M^+ + 1, 3), 57 (88), 168 (100). For $C_{15}H_{20}F_3N_3O_5$ (379.3) calculated: 47.49% C, 5.31% H, 11.08% N; found: 47.63% C, 5.03% H, 10.82% N.

tert-Butyl (2*RS*,3*S*,5*R*)-2-[4-Amino-2-oxopyrimidin-1(2*H*)-yl]-5-[(*tert*-butyldimethylsilyloxy)-methyl]-3-(trifluoromethyl)pyrrolidine-1-carboxylate (**14**)

Compound **14** (193 mg, 95%) was prepared as a white foam from compound **9** (254 mg, 0.51 mmol) and cytosine (179 mg, 1.61 mmol) using the same conditions as for compound **11**.

tert-Butyl (2*R*,3*S*,5*R*)-2-[4-(Benzoylamino)-2-oxopyrimidin-1(2*H*)-yl]-5-(hydroxymethyl)-3-(trifluoromethyl)pyrrolidine-1-carboxylate (**15**) and
tert-Butyl (2*S*,3*S*,5*R*)-2-[4-(Benzoylamino)-2-oxopyrimidin-1(2*H*)-yl]-5-(hydroxymethyl)-3-(trifluoromethyl)pyrrolidine-1-carboxylate (**16**)

To a stirred solution of compound **14** (0.28 g, 0.580 mmol) in dry dichloromethane (20 ml) was added benzoic anhydride (0.17 g, 0.765 mmol). The reaction mixture was stirred at room temperature for 30 h. The solvent was removed and the residue was purified by column chromatography on silica gel (dichloromethane–MeOH 60 : 1) to afford 0.31 g (91%) of N^4-benzoylated nucleoside as an amber oil. Then treatment of this compound with TBAF under the reaction conditions for compound **11** gave separated compounds **15** and **16**.

15: ^{1}H NMR (300 MHz, CD_3COCD_3): 8.16 (d, *J* = 8.0, 1 H); 8.06 (m, 1 H); 7.70–7.36 (m, 5 H); 6.78 (d, *J* = 7.3, 1 H); 4.42 (m, 1 H); 3.96–3.86 (m, 2 H); 3.74–3.63 (m, 1 H); 2.64–2.52 (m, 1 H); 2.42–2.35 (m, 1 H); 1.29 (s, 9 H). IR (KBr): 3 341, 2 978, 2 982, 2 931, 1 706, 1 626, 1 560, 1 486, 1 371. MS, *m/z*: 482 (M^+ – 1, 1), 105 (96), 57(100).

16: ^{1}H NMR (300 MHz, CD_3COCD_3): 8.83 (d, *J* = 7.5, 1 H); 8.17–8.14 (m, 2 H); 7.70–7.36 (m, 4 H); 6.47 (br, 1 H); 4.22–4.15 (m, 2 H); 3.77 (dd, *J* = 11.0, 1.9, 1 H); 3.53 (m, 1 H); 2.48 (m, 1 H); 2.41–2.33 (m, 1 H); 1.36 (s, 9 H).

tert-Butyl (2*S*,3*S*,5*R*)-2-[4-Amino-2-oxopyrimidin-1(2*H*)-yl]-5-(hydroxymethyl)-3-(trifluoromethyl)pyrrolidine-1-carboxylate (**18**)

A solution of the protected compound **16** (91 mg, 0.188 mmol) in MeOH (10 ml) was treated with saturated methanolic ammonia (25 ml) and the reaction mixture was stirred at room temperature for 4 h. After removal of the volatile materials, the residue was purified by column chromatography on silica gel (dichloromethane–MeOH 8 : 1) to afford 65 mg (92%) of **18**. ^{1}H NMR (300 MHz, CD_3OD): 8.48 (d, *J* = 7.1, 1 H); 6.54 (br, 1 H); 6.09 (d, *J* = 7.1, 1 H); 4.28–4.25 (m, 2 H); 3.87 (dd, *J* = 11.0, 1.9, 1 H); 3.57 (m, 1 H); 2.55–2.43 (m, 2 H); 1.57 (s, 9 H). ^{19}F NMR (282 MHz, CD_3OD): –8.8 (d, *J* = 6.0). IR (KBr): 3 349, 3 212, 2 980, 1 614, 1 527, 1 493, 1 370. MS, *m/z*: 379 (M^+, 1), 377 (M^+ – 2, 0.28), 42 (66), 56 (100).

tert-Butyl (2*R*,3*S*,5*R*)-2-[4-Amino-2-oxopyrimidin-1(2*H*)-yl]-5-(hydroxymethyl)-3-(trifluoromethyl)pyrrolidine-1-carboxylate (**17**)

Compound **17** (51 mg, 90%) as a light amber foam was prepared from compound **15** (65 mg, 0.13 mmol) using the same conditions as for compound **18**. ^{1}H NMR (300 MHz, CD_3OD): 7.69 (d, *J* = 7.2, 1 H); 6.84 (d, 7.3, 1 H); 6.13 (d, *J* = 7.2, 1 H); 4.49 (m, 1 H); 4.06 (dd, *J* = 7.2, 4.2, 1 H); 3.92 (m, 1 H); 3.81 (dd, *J* = 11.4, 2.3, 1 H); 2.62 (m, 1 H); 2.48–2.43 (m, 1 H); 1.53 (s, 9 H). ^{19}F NMR (282 MHz, CD_3COCD_3): –13.2 (d, *J* = 8.0).

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