Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Protecting-Group-Free Synthesis of Clevudine (L-FMAU), a Treatment of Hepatitis B Virus

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I. Experimental Section

General Methods

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Methylene chloride (CH_2Cl_2) was purified using a Vacuum Atmospheres Inc. Solvent Purification System. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality available and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and charring with a solution of 3 g of PhOH and 5 mL of H_2SO_4 in 100 mL of EtOH, followed by heating with a heatgun. SiliaFlash® P60 40-63 µm (230-400 mesh) was used for flash column chromatography. NMR spectra were recorded with an Agilent DD2 500 MHz spectrometer and calibrated using residual undeuterated solvent ($CDCl_3$:^{1}H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm; acetone-d_6: ^{1}H δ = 2.05 ppm, ^{13}C δ = 29.84 ppm; methanol-d_4: ^{1}H δ = 3.31 ppm, ^{13}C δ = 49.00 ppm) as an internal reference. Coupling constants (*J*) are reported in Hertz (Hz), and the following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q= quartet, p = quintet, m = multiplet, br = broad. Assignments of NMR signals were made by homonuclear (COSY) and heteronuclear (HSQC, HMBC, HOESY, ^{19}F) two-dimensional correlation spectroscopy. Infrared spectra were recorded using an ABB Bomem MB-Series Arid Zone FT-IR MB-155 Spectrometer. High resolution mass spectra (HRMS) were measured with an Agilent 6210 LC Time of Flight mass spectrometer in electrospray mode. Either protonated molecular ions $[M + nH]^{n+}$, sodium adducts $[M + Na]^+$ or ammonium adducts $[M + NH_4]^+$ were used for empirical formula confirmation. Optical rotations were measured with a JASCO DIP-360 digital polarimeter, and are reported in units of 10^{-1} (deg cm^2 g^{-1}).

General Procedures

General Procedure I: Bromination of anomeric position

To a stirred solution of carbohydrate (1 equiv.) at 0 °C in CH_2Cl_2 (0.16 M) was added HBr/AcOH 33 wt% (0.32 M). The mixture was warmed to room temperature and stirred for the indicated amount of time. Then, the solution was poured in an ice-cold saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted 3 times with CH_2Cl_2. The organic phase was finally washed with a saturated aqueous NaCl solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give anomeric bromine.

General Procedure II: Glycosylation with bis(trimethylsilyl)thymine

Solution A : To a solution of thymine (3 equiv.) and ammonium sulfate (0.3 equiv.) in anhydrous $CHCl_3$ was added HMDS (9 equiv.). The solution was heated at 125 °C in a sealed tube for 16 hours.

Solution B : The glycosyl bromide (1 equiv.) was dissolved in anhydrous $CHCl_3$ under N_2 atmosphere. The solution **A** was added to the solution **B** and the resulting solution was heated at 80 °C for 24 hours.

Workup for protected compound: The mixture was cooled to room temperature and ice was added to the solution. $CHCl_3$ and cold water were added and the aqueous phase was extracted 3 times with $CHCl_3$. The organic phase was washed with a cold saturated $NaHCO_3$ solution, cold saturated NaCl solution, dried over Na_2SO_4 and concentrated.

Workup for protected-group free compound: The mixture was cooled to room temperature then methanol was added and the resulting mixture was stirred for 1 h at this temperature. The solution was filtered under Celite® and washed with methanol. The solvents were evaporated under reduce pressure.

General Procedure III: Deprotection of ester protecting group

Protected carbohydrate was solubilized in a solution of 7 N NH_3/MeOH (0.09 M). The resulting solution was stirred 24 h at room temperature. The solution was evaporated to dryness, coevaporated 3 times with EtOAc and finally triturated with EtOAc (3 times), CH_2Cl_2 (3 times) and dried.

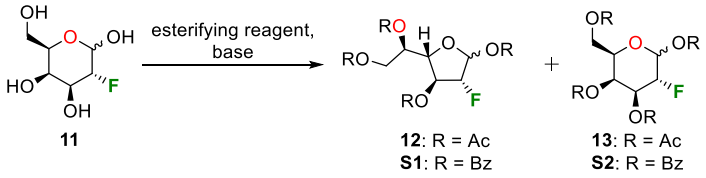
General Procedure IV: Oxidative cleavage and aldehyde reduction

To a stirred solution of diol (1 equiv.) in methanol/water (0.013 M, 1:1) was added $NaIO_4$ (1.5 equiv.) at room temperature. The mixture was stirred for 2 h in the dark. After this time, $NaBH_4$ (1.75 equiv.) was added and the mixture was stirred another 2 h in the dark and then neutralized to pH ≈ 7 with an acidic resin (Amberlite IR-120). The mixture was filtered and concentrated under reduced pressure.

Optimisation of the pyranose-to-furanose isomerization

Using Liu's protocol (Ac_2O, pyridine at 110 °C for 3.5 hours),[1] we were constrained with a low 25% yield (entry 1). Consequently, we increased the temperature in an attempt to obtain the thermodynamically less favored furanose derivatives (entry 2 and 3). Unfortunately, this change only resulted in slightly lower yields. Next, we evaluated using a base with a higher boiling point (2-methylpyridine, entry 4), however this resulted also in a lower yield. Finally, we explored other acylating reagents with the optimized temperature of 110 °C (entry 5 and 6). Benzoic anhydride furnished a slightly higher yield providing compound **S1** in 32% yield.

Table S1. Optimisation of the synthesis of 2-deoxy-2-fluoro-galactofuranose **12** and **22** from 2-deoxy-2-fluoro-glactopyranose **11**.



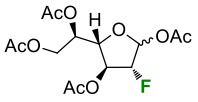
11

12: R = Ac
S1: R = Bz

13: R = Ac
S2: R = Bz

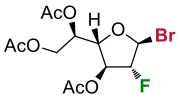
Entry	Reagent	Base	Temperature (°C)	Product (Yield (%))	
1	Ac_2O	Pyridine	110	**12** (25)	**13** (73)
2[b]	Ac_2O	Pyridine	150	**12** (23)	**13** (34)
3[b]	Ac_2O	Pyridine	180	**12** (20)	**13** (29)
4[b]	Ac_2O	2-methylpyridine	180	**12** (17)	**13** (15)
5	BzCl	Pyridine	110	**S1** (22)	**S2** (45)
6	Bz_2O	Pyridine	110	**S1** (32)	**S2** (52)

[a] Yields were determined with the ^{19}F NMR (470 MHz, $CDCl_3$) using 2-fluoro-4-nitrotoluene as internal standard.
[b] Reaction performed in a sealed tube.



1,3,5,6-Tetra-*O*-acetyl-2-deoxy-2-fluoro-α/β-D-galactofuranose (12).

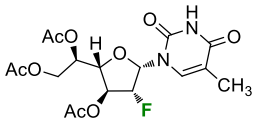
2-deoxy-2-fluoro-D-galactopyranose **11** (1.56 g, 4.44 mmol) was solubilized in pyridine (11.70 mL) and heated at 110 °C for 2 h. Then, acetic anhydride (7.55 mL, 79.92 mmol, 18 equiv.) was added dropwise at this temperature. The mixture was stirred an additional 1.5 h at 110 °C. After this time, the mixture was cooled to room temperature, concentrated under reduced pressure and coevaporated 3 times with toluene. The residue was purified using flash column chromatography (silica gel, EtOAc/Hexanes, 3:14 to 1:1) to give an anomeric mixture (α/β = 1:3) of **12** as a colorless oil (381.2 mg, 1.09 mmol, 25 % yield). The spectroscopic data derived from compound **12** match those reported in the literature.[1]



3,5,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-galactofuranosyl bromide (17).

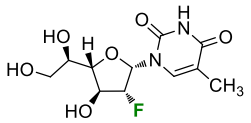
Synthesized according to general procedure I, starting from **12** (46.0 mg, 0.1313 mmol) to give **17** (α/β = >1:20) as a yellowish oil; R_f = 0.42 (silica, EtOAc/Hexanes, 1:2); $[\alpha]_D^{25}$ = –117.3 (c 0.4, $CHCl_3$); IR (ATR, NaCl) ν 2920, 2854, 1727, 1372, 1214, 1091, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.50 (dd, $^3J_{H1\text{-}F2}$ = 12.4 Hz, $^3J_{H1\text{-}H2}$ = 0.9 Hz, 1H, H1), 5.52 (ddd, $^3J_{H5\text{-}H6b}$ = 6.9 Hz, $^3J_{H5\text{-}H6a}$ = 4.8 Hz, $^3J_{H5\text{-}H4}$ = 3.3 Hz, 1H, H5), 5.34 (ddd, $^2J_{H2\text{-}F2}$ = 50.2 Hz, $^3J_{H2\text{-}H3}$ = 1.2 Hz, $^3J_{H2\text{-}H1}$ = 0.9 Hz, 1H, H2), 5.05 (ddd, $^3J_{H3\text{-}F2}$ = 22.5 Hz, $^3J_{H3\text{-}H4}$ = 4.9 Hz, $^3J_{H3\text{-}H2}$ = 1.2 Hz, 1H, H3), 4.54 (ddd, $^3J_{H4\text{-}H3}$ = 4.9 Hz, $^3J_{H4\text{-}H5}$ = 3.3 Hz, $^4J_{H4\text{-}F2}$ = 0.9 Hz, 1H, H4), 4.30 (dd, $^2J_{H6a\text{-}H6b}$ = 11.8 Hz, $^3J_{H6a\text{-}H5}$ = 4.8 Hz, 1H, H6a), 4.20 (dd, $^2J_{H6b\text{-}H6a}$ = 11.8 Hz, $^3J_{H6b\text{-}H5}$ = 7.0 Hz, 1H, H6b), 2.16 (s, 3H, COCH_3), 2.10 (s, 3H, COCH_3), 2.06 (s, 3H, COCH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 170.2, 170.0 (3C, 3 × *C*O), 100.5 (d, $^1J_{C2\text{-}F2}$ = 192.7 Hz, 1C, C2), 87.3 (d, $^2J_{C1\text{-}F2}$ = 32.3 Hz, 1C, C1), 84.1 (d, $^3J_{C4\text{-}F2}$ = 1.0 Hz, C1, C4), 75.9 (d, $^2J_{C3\text{-}F2}$ = 31.1 Hz, 1C, C3), 68.6 (1C, C5), 62.4 (1C, C6), 20.82, 20.78, 20.76 (3C, 3 × CO*C*H_3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –166.18 (ddd, $^2J_{F2\text{-}H2}$ = 50.2

Hz, $^{3}J_{F2\text{-}H3}$ = 22.3 Hz, $^{3}J_{F2\text{-}H1}$ = 12.4 Hz, 1F, F2) ppm; HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{12}H_{20}BrFNO_7^+$ 388.0402, found 388.0390.



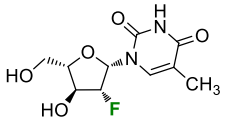
1-(3',5',6'-Tri-*O*-acetyl-2'-deoxy-2'-fluoro-α-D-galactofuranosyl)thymine (19).

Synthesized according to general procedures I and II, starting from **12** (40.0 mg, 0.114 mmol). Purified by flash column chromatography (silica gel, EtOAc/Hexanes, 1:2 to 4:1) to give **19** (α/β = >20:1) as an amorphous white foam (34.6 mg, 0.083 mmol, 73% yield over two steps). R_f = 0.44 (silica, EtOAc/Hexanes, 3:1); $[\alpha]_D^{25}$ = –10.5 (c 0.5, $CHCl_3$); IR (ATR, Diamond) ν 3046, 2360, 1740, 1693, 1367, 1213, 1037 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H, N*H*), 7.44 (q, $^{4}J_{CH\text{=}C\text{-}CH3a}$ = $^{4}J_{CH\text{=}C\text{-}CH3b}$ = $^{4}J_{CH\text{=}C\text{-}CH3c}$ = 1.2 Hz, 1H, C*H*=C), 6.26 (dd, $^{3}J_{H1'\text{-}F2'}$ = 22.4 Hz, $^{3}J_{H1'\text{-}H2'}$ = 2.6 Hz, 1H, H1'), 5.51 (dt, $^{3}J_{H5'\text{-}H6b'}$ = 6.6 Hz, $^{3}J_{H5'\text{-}H6a'}$ = $^{3}J_{H5'\text{-}H4'}$ = 4.6 Hz, 1H, H5'), 5.25 (ddd, $^{3}J_{H3'\text{-}F2'}$ = 16.5 Hz, $^{3}J_{H3'\text{-}H4'}$ = 2.6 Hz, $^{3}J_{H3\text{-}H2}$ = 0.9 Hz 1H, H3'), 5.04 (ddd, $^{2}J_{H2'\text{-}F2'}$ = 50.4 Hz, $^{3}J_{H2'\text{-}H1'}$ = 2.6 Hz, $^{3}J_{H2'\text{-}H3'}$ = 0.9 Hz, 1H, H2'), 4.35 (dd, $^{2}J_{H6a'\text{-}H6b'}$ = 11.9 Hz, $^{3}J_{H6a'\text{-}H5'}$ = 4.6 Hz, 1H, H6a'), 4.28 (dd, $^{2}J_{H6b'\text{-}H6a'}$ = 11.9 Hz, $^{3}J_{H6b'\text{-}H5'}$ = 6.7 Hz, 1H, H6b'), 4.18 (ddd, $^{3}J_{H4'\text{-}H5'}$ = 4.6 Hz, $^{3}J_{H4'\text{-}H3'}$ = 2.6 Hz, $^{4}J_{H4'\text{-}F2'}$ = 0.7 Hz 1H, H4'), 2.15 (s, 3H, COC*H*$_3$), 2.12 (s, 3H, COC*H*$_3$), 2.08 (s, 3H, COC*H*$_3$), 1.95 (d, $^{4}J_{CH3\text{-}CH=C}$ = 1.2 Hz, 3H, C*H*$_3$) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 170.1, 169.5, 163.5, 150.3 (5C, 5 × *C*O), 136.7 (d, *J* = 4.2 Hz, 1C, *C*H=C), 110.8 (1C, CH=*C*), 92.2 (d, $^{1}J_{C2'\text{-}F2'}$ = 192.8 Hz, 1C, C2'), 84.4 (d, $^{2}J_{C1'\text{-}F2'}$ = 16.1 Hz, 1C, C1'), 81.8 (1C, C4'), 76.3 (d, $^{2}J_{C3'\text{-}F2'}$ = 30.5 Hz, 1C, C3'), 69.8 (1C, C5'), 62.6 (1C, C6'), 20.9, 20.8, 20.7 (3C, 3 × CO*C*H$_3$), 12.7 (1C, *C*H$_3$) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –201.98 (dddd, $^{2}J_{F2'\text{-}H2'}$ = 50.4 Hz, $^{3}J_{F2'\text{-}H1'}$ = 22.4 Hz, $^{3}J_{F2'\text{-}H3'}$ = 16.5 Hz, $^{4}J_{F2'\text{-}H4'}$ = 0.7 Hz, 1F, F2') ppm; HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{17}H_{22}FN_2O_9^+$ 417.1304, found 417.1318.



1-(2'-Deoxy-2'-fluoro-α-D-galactofuranosyl)thymine (20).

Synthesized according to general procedure III, starting from **19** (9.3 mg, 0.022 mmol) to give **20** (α/β = >20:1) as an amorphous white solid (5.2 mg, 0.018 mmol, 82% yield). R_f = 0.29 (silica, MeOH/CH_2Cl_2, 1:9); $[\alpha]_D^{25}$ = –18.5 (c 0.1, $CHCl_3$); IR (ATR, NaCl) ν 3348, 2924, 1693, 1468, 1283, 1028, 785 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.85 (q, $^4J_{CH=C\text{-}CH3a} = {}^4J_{CH=C\text{-}CH3b} = {}^4J_{CH=C\text{-}CH3c}$ = 1.3 Hz, 1H, C*H*=C), 6.16 (dd, $^3J_{H1'\text{-}F2'}$ = 14.3 Hz, $^3J_{H1'\text{-}H2'}$ = 4.6 Hz, 1H, H1'), 5.03 (ddd, $^2J_{H2'\text{-}F2'}$ = 53.1 Hz, $^3J_{H2'\text{-}H1'}$ = 4.6 Hz, $^3J_{H2'\text{-}H3'}$ = 3.4 Hz, 1H, H2'), 4.45 (ddd, $^3J_{H3'\text{-}F2'}$ = 22.5 Hz, $^3J_{H3'\text{-}H4'}$ = 6.3 Hz, $^3J_{H3'\text{-}H2'}$ = 3.4 Hz, 1H, H3'), 3.87 – 3.81 (m, 2H, H4', H5'), 3.68 (s, 1H, H6a'), 3.67 (s, 1H, H6b'), 1.88 (d, $^4J_{CH3\text{-}CH=C}$ = 1.2 Hz, 3H, C*H*$_3$) ppm; ^{13}C NMR (126 MHz, CD_3OD) δ 166.3, 152.1 (2C, 2 × *C*O), 139.2 (d, *J* = 2.8 Hz, 1C, *C*H=C), 110.6 (1C, CH=*C*), 97.4 (d, $^1J_{C2'\text{-}F2'}$ = 192.9 Hz, 1C, C2'), 84.2 (d, $^2J_{C1'\text{-}F2'}$ = 17.4 Hz, 1C, C1'), 83.3 (d, $^3J_{C4'\text{-}F2'}$ = 5.8 Hz, 1C, C4'), 75.1 (d, $^2J_{C3'\text{-}F2'}$ = 25.2 Hz, 1C, C3'), 71.4 (1C, C5'), 64.2 (1C, C6'), 12.3 (1C, *C*H$_3$) ppm; ^{19}F NMR (470 MHz, CD_3OD) δ –200.49 (ddd, $^2J_{F2'\text{-}H2'}$ = 53.2 Hz, $^3J_{F2'\text{-}H3'}$ = 22.6 Hz, $^3J_{F2'\text{-}H1'}$ = 14.3 Hz, 1F, F2') ppm; HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{11}H_{16}FN_2O_6^+$ 291.0987, found 291.0988.

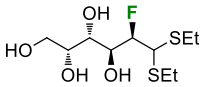


1-(2'-Deoxy-2'-fluoro-β-L-arabinofuranosyl)thymine (1).

From compound **20**: Synthesized according to general procedure IV, starting from **20** (20.3 mg, 0.070 mmol). Purified by flash column chromatography (silica gel, MeOH/DCM, 1:19 to 1:9) to give **1** (α/β = >1:20) as an amorphous white solid (16.7 mg, 0.0642 mmol, 92% yield over two steps). The spectroscopic data derived from compound **1** match those reported in the literature.[2]

From compound **26**: Synthesized according to general procedure III, starting from **26** (23.2 mg, 0.067 mmol) to give **1** (α/β = >1:20) as an amorphous white solid (13.5 mg, 0.052 mmol, 77% yield).

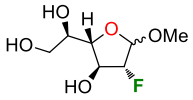
From compound **9**: Synthesized according to general procedures I and II, starting from **9** (10.1 mg, 0.061 mmol). Purified by flash column chromatography (silica gel, MeOH/DCM, 1:19 to 1:9) to give an anomeric mixture (α/β, 1:4) of **1** as an amorphous white solid (4.1 mg, 0.0158 mmol, 26% yield over two steps).



2-Deoxy-2-fluoro-D-galactopyranose diethyl dithioacetal (22).

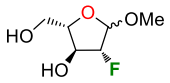
2-deoxy-2-fluoro-D-galactopyranose **11** (1.03 g, 5.65 mmol) was solubilized in HCl 37% (2.74 mL). The solution was cooled to 0 °C and ethanethiol (1.22 mL, 16.95 mmol, 3 equiv) was added. The mixture was stirred 1 h at 0 °C. The acid was neutralized to pH ≈ 7 with the addition of 1M NaOH solution dropwise at 0 °C. The solvents were concentrated under an air flow. Acetone (50 mL) was added to the crude material. The solution was filtered to remove NaCl salt and concentrated to offer **22** as an amorphous white solid (1.59 g, 5.51 mmol, 98% yield). R_f = 0.66 (silica, MeOH/CH_2Cl_2, 1:9); $[\alpha]_D^{25}$ = –10.6 (c 0.2, Acetone); IR (ATR, Diamond) ν 3288, 2955, 1294, 1105, 1043, 758 cm^{-1}; ^{1}H NMR (500 MHz, Acetone-d_6) δ 4.76 (ddd, $^2J_{H2\text{-}F2}$ = 46.4 Hz, $^3J_{H2\text{-}H1}$ = 9.9 Hz, $^3J_{H2\text{-}H3}$ = 1.2 Hz, 1H, H2), 4.35 (dd, $^3J_{H1\text{-}H2}$ = 9.9 Hz, $^3J_{H1\text{-}F2}$ = 7.4 Hz, 1H, H1), 4.23 – 4.12 (m, 2H, H3, O*H*3), 3.96 (qd, $^3J_{H5\text{-}H4}$ = $^3J_{H5\text{-}H6a}$ = $^3J_{H5\text{-}H6b}$ = 6.1 Hz, $^3J_{H5\text{-}OH5}$ = 1.5 Hz, 1H, H5), 3.86 (t, $^3J_{OH6\text{-}H6a}$ = $^3J_{OH6\text{-}H6b}$ = 5.6 Hz, 1H, O*H*6), 3.78 (d, $^3J_{OH5\text{-}H5}$ = 1.4 Hz, 1H, O*H*5), 3.77 (s, 1H, O*H*4), 3.70 – 3.64 (m, 3H, H4, H6a, H6b), 2.80 – 2.66 (m, 4H, 2 × SCH_2), 1.24 (t, $^3J_{CH3\text{-}SCH2a}$ = $^3J_{CH3\text{-}SCH2b}$ = 7.5 Hz, 6H, 2 × CH_3) ppm; ^{13}C NMR (126 MHz, Acetone-d_6) δ 94.4 (d, $^1J_{C2\text{-}F2}$ = 182.9 Hz, 1C, C2), 71.0 (d, $^3J_{C4\text{-}F2}$ = 3.9 Hz, 1C, C4), 70.9 (1C, C5), 70.3 (d, $^2J_{C3\text{-}F2}$ = 19.1 Hz, 1C, C3), 64.9 (1C, C6), 51.6 (d, $^2J_{C1\text{-}F2}$ = 21.9 Hz, 1C, C1), 25.6, 24.9 (2C, 2 × S*C*H_2), 14.84, 14.79 (2C, 2 × *C*H_3) ppm; ^{19}F NMR (470 MHz, Acetone-d_6) δ –195.82 (dddd, $^2J_{F2\text{-}}$

$_{H2}$ = 46.4 Hz, $^{3}J_{F2-H3}$ = 26.5 Hz, 11.9, $^{3}J_{F2-H1}$ = 7.4 Hz, 1F, F2) ppm; HRMS (ESI) m/z : [M + H]$^{+}$ calcd for $C_{10}H_{21}FO_4Na^{+}$ 311.0763, found 311.0766.



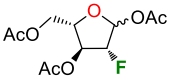
Methyl 2-deoxy-2-fluoro-α/β-D-galactofuranoside (10).

To a stirred solution of compound **22** (1.59 g, 5.51 mmol) in methanol (46 mL) was added iodine (5.87 g, 23.14 mmol, 4.2 equiv). After stirred 2 h at room temperature, solid $NaHCO_3$ (56.77 g) was added and the reaction was stirred 5 minutes. Then, solid $Na_2S_2O_3$ (45.54 g) was added to quench the excess of iodine. The mixture was stirred 10 minutes before the addition of $AgNO_3$ (15.75 g). The resulting mixture was stirred for another 1 hour, filtrated under Celite® and concentrated under reduce pressure. The crude solid was purified by flash column chromatography (silica gel, MeOH/CH_2Cl_2, 1:49 to 1:9) to give an anomeric mixture (α/β = 1:12) of **10** as a colorless oil (853.8 mg, 4.35 mmol, 79 % yield). R_f = 0.51 (silica, MeOH/CH_2Cl_2, 1:9); $[\alpha]_D^{25}$ = –131.3 (c 0.5, MeOH); IR (ATR, Diamond) ν 3375, 2937, 1194, 1101, 1028, 982, 947 cm^{-1}; Spectral data for the β anomer (**10β**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (dd, $^{3}J_{H1-F2}$ = 10.1 Hz, $^{3}J_{H1-H2}$ = 0.6 Hz, 1H, H1), 4.86 (ddd, $^{2}J_{H2-F2}$ = 50.8 Hz, $^{3}J_{H2-H3}$ = 1.4 Hz, $^{3}J_{H2-H1}$ = 0.6 Hz, 1H, H2), 4.27 (dddd, $^{3}J_{H3-F2}$ = 22.4 Hz, $^{3}J_{H3-OH3}$ = 7.5 Hz, $^{3}J_{H3-H4}$ = 5.1 Hz, $^{3}J_{H3-H2}$ = 1.4 Hz, 1H, H3), 4.04 (t, $^{3}J_{H4-H3}$ = $^{3}J_{H4-H5}$ = 5.0 Hz, 1H, H4), 3.85 (dq, $^{3}J_{H5-H4}$ = 5.0 Hz, $^{3}J_{H5-OH5}$ = $^{3}J_{H5-H6a}$ = $^{3}J_{H5-H6b}$ = 4.9 Hz, 1H, H5), 3.82 – 3.74 (m, 2H, 1H, H6a, H6b), 3.42 (s, 3H, OC*H*$_3$), 2.71 (d, *J* = 7.5 Hz, 1H, O*H*3), 2.55 (d, $^{3}J_{OH6-H6}$ = 4.9 Hz, 1H, O*H*5), 2.26 (s, 1H, O*H*6) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 106.2 (d, $^{2}J_{C1-F2}$ = 34.5 Hz, 1C, C1), 99.5 (d, $^{1}J_{C2-F2}$ = 182.2 Hz, 1C, C2), 85.8 (d, $^{3}J_{C4-F2}$ = 2.8 Hz, 1C, C4), 76.3 (d, $^{2}J_{C3-F2}$ = 26.2 Hz, 1C, C3), 71.4 (1C, C5), 64.2 (1C, C6), 55.2 (1C, *C*H$_3$) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –191.11 (ddd, $^{2}J_{F2-H2}$ = 50.8 Hz, $^{3}J_{F2-H3}$ = 22.3 Hz, $^{3}J_{F2-H1}$ = 10.1 Hz, 1F, F2) ppm; HRMS (ESI) m/z : [M + H]$^{+}$ calcd for $C_7H_{13}FO_5Na^{+}$ 219.0645, found 219.0652.



Methyl 2-deoxy-2-fluoro-α/β-L-arabinofuranoside (9).

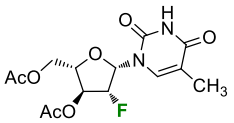
Synthesized according to general procedure IV, starting from **10** (832.4 mg, 4.24 mmol). Purified by flash column chromatography (silica gel, MeOH/DCM, 1:49 to 3:47) to give an anomeric mixture (α/β = 10:1) of **9** as a colorless oil (669.2 mg, 4.03 mmol, 95% yield). $R_{f\alpha}$ = 0.48 (silica, MeOH/CH_2Cl_2, 1:19); $R_{f\beta}$ = 0.42 (silica, MeOH/CH_2Cl_2, 1:19); $[\alpha]_D^{25}$ = –109.5 (c 0.6, $CHCl_3$); IR (ATR, Diamond) ν 3369, 2934, 1194, 1086, 1036, 982 cm^{-1}; Spectral data for the α isomer (**9*α***):^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (dd, $^3J_{H1\text{-}F2}$ = 10.2 Hz, $^3J_{H1\text{-}H2}$ = 1.3 Hz, 1H, H1), 4.84 (dt, $^2J_{H2\text{-}F2}$ = 50.5 Hz, $^3J_{H2\text{-}H1}$ = $^3J_{H2\text{-}H3}$ = 1.3 Hz, 1H, H2), 4.19 (dddd, $^3J_{H3\text{-}F2}$ = 22.2 Hz, $^3J_{H3\text{-}OH3}$ = 7.7 Hz, $^3J_{H3\text{-}H4}$ = 4.8 Hz, $^3J_{H3\text{-}H2}$ = 1.3 Hz, 1H, H3), 4.06 (qd, $^3J_{H4\text{-}H5a}$ = $^3J_{H4\text{-}H5b}$ = $^3J_{H4\text{-}H3}$ = 4.7 Hz, $^4J_{H4\text{-}F2}$ = 1.9 Hz, 1H, H4), 3.83 (ddd, $^2J_{H5a\text{-}H5b}$ = 11.9 Hz, $^3J_{H5a\text{-}OH5}$ = 6.4 Hz, $^3J_{H5a\text{-}H4}$ = 4.6 Hz, 1H, H5a), 3.74 (ddd, $^2J_{H5b\text{-}H5a}$ = 11.9 Hz, $^3J_{H5b\text{-}OH5}$ = 6.4 Hz, $^3J_{H5b\text{-}H4}$ = 4.8 Hz, 1H, H5b), 3.41 (s, 3H, OCH_3), 3.32 (dd, $^3J_{OH3\text{-}H3}$ = 7.7 Hz, $^4J_{OH3\text{-}F2}$ = 2.1 Hz, 1H, O*H*3), 2.67 (t, $^3J_{OH5\text{-}H5a}$ = $^3J_{OH5\text{-}H5b}$ = 6.4 Hz, 1H, O*H*5) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 106.2 (d, $^2J_{C1\text{-}F2}$ = 34.4 Hz, 1C, C1), 99.6 (d, $^1J_{C2\text{-}F2}$ = 181.8 Hz, 1C, C2), 85.2 (d, $^3J_{C4\text{-}F2}$ = 2.6 Hz, 1C, C4), 75.5 (d, $^2J_{C3\text{-}F2}$ = 25.9 Hz, 1C, C3), 62.1 (1C, C5), 55.1 (1C, OCH_3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –191.10 (ddd, $^2J_{F2\text{-}H2}$ = 50.5 Hz, $^3J_{F2\text{-}H3}$ = 22.1 Hz, $^3J_{F2\text{-}H1}$ = 10.1 Hz, 1F, F2) ppm; HRMS (ESI) m/z : [M + H]$^+$ calcd for $C_6H_{11}FO_4Na^+$ 189.0539, found 189.0536.



1,3,5-Tri-*O*-acetyl-2-deoxy-2-fluoro-α/β-L-arabinofuranose (24).

Compound **9** (103.6 mg, 0.624 mmol) was solubilized in a mixture of Ac_2O and AcOH (1.93 mL, 20:1) and the resulting solution was heated at 100 °C for 2 h. After cooling to room temperature, H_2SO_4 (20 µL, 0.3732 mmol, 0.60 equiv.) was added and the mixture was stirred at room temperature for 2 h. The mixture was dropped in a saturated aqueous $NaHCO_3$ solution (10 mL). This aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL),

washed with a saturated aqueous $NaHCO_3$ solution (30 mL) and a saturated aqueous NaCl solution (30 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained crude was purified by flash column chromatography (silica gel, EtOAc/hexanes, 1:4 → 1:2) to give an anomeric mixture (α/β = 8:1) of **24** as a colorless oil (157.9 mg, 0.5674 mmol, 91 %). $R_{f\alpha}$ = 0.59 (EtOAc/hexanes, 1:2); $R_{f\beta}$ = 0.49 (EtOAc/hexanes, 1:2); A pure fraction of the α anomer was used for characterization. $[\alpha]_D^{25}$ = –61.5 (c 0.7, $CHCl_3$); IR (ATR, Diamond) ν 2924, 2853, 1740, 1371, 1213, 1117, 962 cm^{-1}; Spectral data for the α anomer (**24α**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (dd, $^3J_{H1\text{-}F2}$ = 10.5 Hz, $^3J_{H1\text{-}H2}$ = 1.0 Hz, 1H, H1), 5.15 (ddd, $^3J_{H3\text{-}F2}$ = 21.5 Hz, $^3J_{H3\text{-}H4}$ = 4.3 Hz, $^3J_{H3\text{-}H2}$ = 1.0 Hz, 1H, H3), 5.01 (dt, $^2J_{H2\text{-}F2}$ = 48.8 Hz, $^3J_{H2\text{-}H1}$ = $^3J_{H2\text{-}H3}$ = 1.0 Hz, 1H, H2), 4.42 (dd, $^2J_{H5a\text{-}H5b}$ = 11.8 Hz, $^3J_{H5a\text{-}H4}$ = 3.7 Hz, 1H, H5a), 4.37 (ddd, $^3J_{H4\text{-}H5b}$ = 5.1 Hz, $^3J_{H4\text{-}H3}$ = 4.3 Hz, $^3J_{H4\text{-}H5a}$ = 3.7 Hz, 1H, H4), 4.25 (dd, $^2J_{H5b\text{-}H5a}$ = 11.8 Hz, $^3J_{H5b\text{-}H4}$ = 5.1 Hz, 1H, H5b), 2.14 (s, 3H, COCH_3), 2.11 (s, 3H, COCH_3), 2.09 (s, 3H, COCH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 170.0, 169.2 (3C, 3 × *C*OCH$_3$), 99.1 (d, $^2J_{C1\text{-}F2}$ = 37.5 Hz, 1C, C1), 97.6 (d, $^1J_{C2\text{-}F2}$ = 184.5 Hz, 1C, C2), 83.1 (d, $^3J_{C4\text{-}F2}$ = 1.4 Hz, 1C, C4), 76.5 (d, $^2J_{C3\text{-}F2}$ = 30.7 Hz, 1C, C3), 63.0 (1C, C5), 21.1, 20.84, 20.77 (3C, 3 × CO*C*H$_3$) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –190.30 (ddd, $^2J_{F2\text{-}H2}$ = 48.9 Hz, $^3J_{F2\text{-}H3}$ = 21.4 Hz, $^3J_{F2\text{-}H1}$ = 10.5 Hz, 1F, F2) ppm; HRMS (ESI) m/z : $[M + NH_4]^+$ calcd for $C_{11}H_{19}FNO_7^+$ 296.1140, found 296.1144.



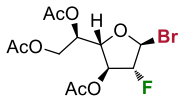
1-(3',5'-Di-*O*-acetyl-2'-deoxy-2'-fluoro-β-L-arabinofuranosyl)thymine (26).

Synthesized according to general procedures I and II, starting from **24** (146.6 mg, 0.527 mmol). Purified by flash column chromatography (silica gel, EtOAc/Hexanes, 2:3 to 3:2) to give **26** (α/β = >1:20) as an amorphous white solid (110.6 mg, 0.321 mmol, 61% yield over two steps). R_f = 0.36 (silica, EtOAc/Hexanes, 4:1); $[\alpha]_D^{25}$ = –32.0 (c 0.5, $CHCl_3$); IR (ATR, NaCl) ν 2360, 1746, 1693, 1368, 1289, 1225 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 1H, N*H*), 7.33 (dt, $^4J_{CH\text{=}C\text{-}CH3a}$ = 2.3 Hz, $^4J_{CH\text{=}C\text{-}CH3b}$ = $^4J_{CH\text{=}C\text{-}CH3c}$ = 1.0 Hz, 1H,

C*H*=C), 6.20 (dd, $^{3}J_{H1'\text{-}F2'}$ = 22.3 Hz, $^{3}J_{H1'\text{-}H2'}$ = 2.8 Hz, 1H, H1'), 5.22 (ddd, $^{3}J_{H3'\text{-}F2'}$ = 16.6 Hz, $^{3}J_{H3'\text{-}H4'}$ = 2.8 Hz, $^{3}J_{H3'\text{-}H2'}$ = 0.8 Hz, 1H, H3'), 5.09 (ddd, $^{2}J_{H2'\text{-}F2'}$ = 50.2 Hz, $^{3}J_{H2'\text{-}H1'}$ = 2.8 Hz, $^{3}J_{H2'\text{-}H3'}$ = 0.8 Hz, 1H, H2'), 4.47 (dd, $^{2}J_{H5b'\text{-}H5a'}$ = 12.0 Hz, $^{3}J_{H5b'\text{-}H4'}$ = 5.9 Hz, 1H, H5b'), 4.41 (dd, $^{2}J_{H5a'\text{-}H5b'}$ = 12.0 Hz, $^{3}J_{H5a'\text{-}H4'}$ = 3.9 Hz, 1H, H5a'), 4.22 (ddd, $^{3}J_{H4'\text{-}H5b'}$ = 5.9 Hz, $^{3}J_{H4'\text{-}H5a'}$ = 4.0 Hz, $^{3}J_{H4'\text{-}H3'}$ = 2.8 Hz, 1H, H4'), 2.16 (s, 1H, COCH_3), 2.12 (s, 1H, COCH_3), 1.94 (d, $^{4}J_{CH3\text{-}CH=C}$ = 1.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 169.4, 163.4, 150.2 (4C, 4 × *C*O), 136.3 (d, *J* = 4.2 Hz, *C*H=C), 110.6 (1C, CH=*C*), 92.3 (d, $^{1}J_{C2'\text{-}F2'}$ = 191.7 Hz, 1C, C2'), 84.5 (d, $^{2}J_{C1'\text{-}F2'}$ = 16.3 Hz, 1C, C1'), 81.1 (1C, C4'), 75.9 (d, $^{2}J_{C3'\text{-}F2'}$ = 30.4 Hz, 1C, C3'), 62.6 (1C, C5'), 20.8, 20.6 (2C, 2 × CO*C*H_3), 12.6 (1C, *C*H_3) ppm; ^{19}F NMR (470 MHz, $CDCl_3$) δ –202.08 (ddd, $^{2}J_{F2'\text{-}H2'}$ = 50.3 Hz, $^{3}J_{F2'\text{-}H1'}$ = 22.4 Hz, $^{3}J_{F2'\text{-}H3'}$ = 16.7 Hz, 1F, F2') ppm; HRMS (ESI) m/z : $[M + NH_4]^+$ calcd for $C_{14}H_{18}FN_2O_7^+$ 345.1093, found 345.1109.

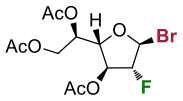
II. NMR spectra of compounds

^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)



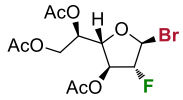
17

^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)



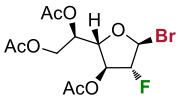
17

^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)



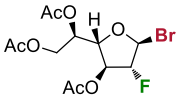
17

COSY NMR Spectrum



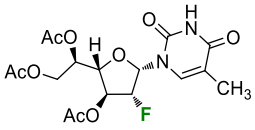
17

HSQC NMR Spectrum



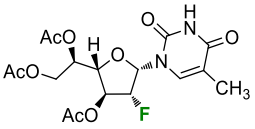
17

^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)



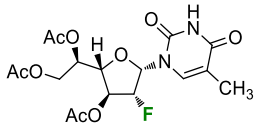
19

^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)

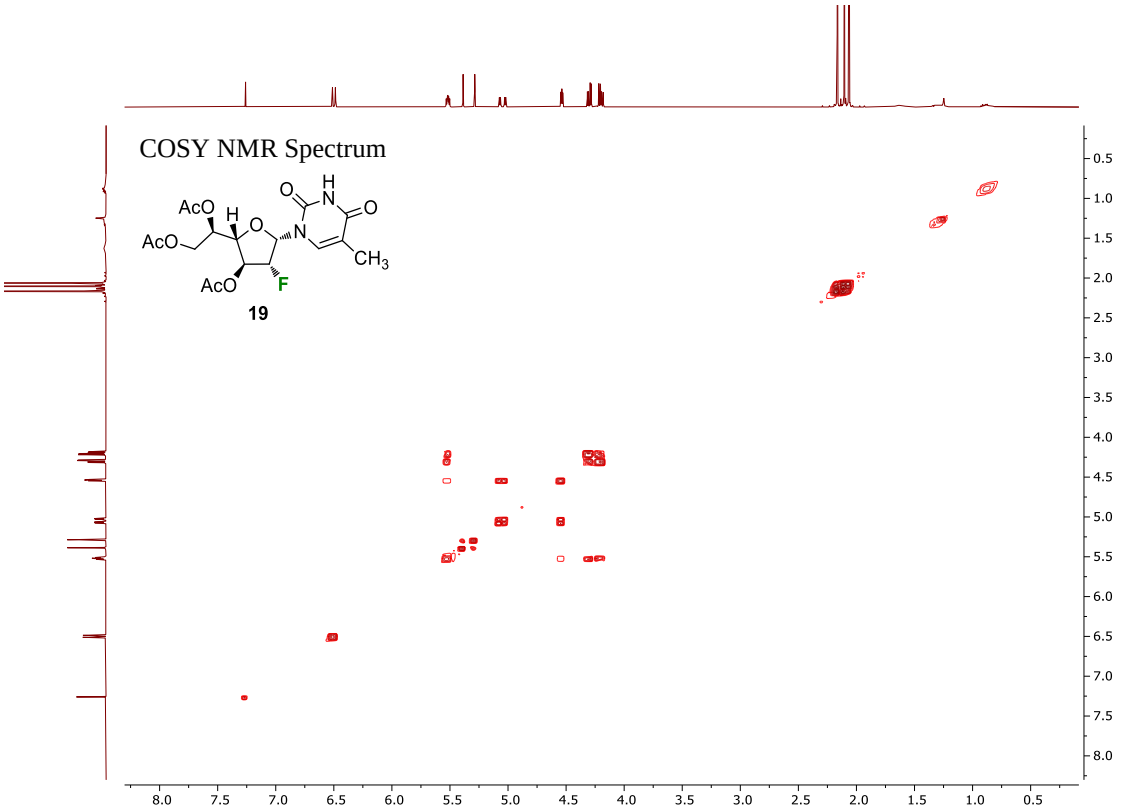


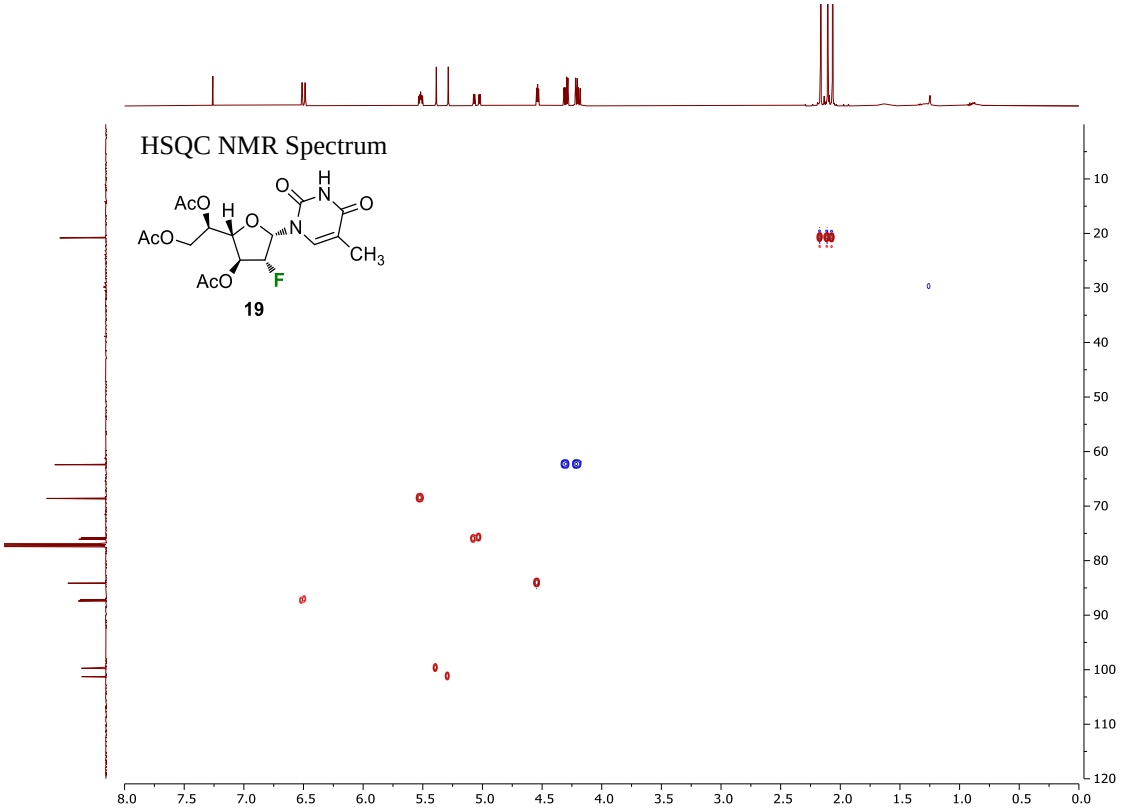
19

^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)

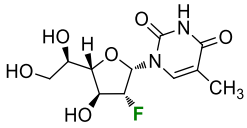


19


COSY NMR Spectrum
AcO
AcO
AcO
F
CH3
19

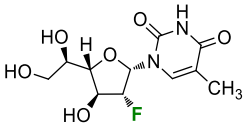

HSQC NMR Spectrum
AcO
AcO
AcO
F
CH3
19

^{1}H NMR Spectrum
(CD_3OD, 500 MHz)



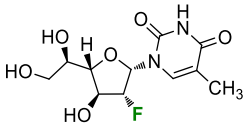
20

^{13}C NMR Spectrum
(CD_3OD, 126 MHz)



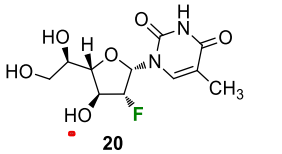
20

^{19}F NMR Spectrum
(CD_3OD, 470 MHz)

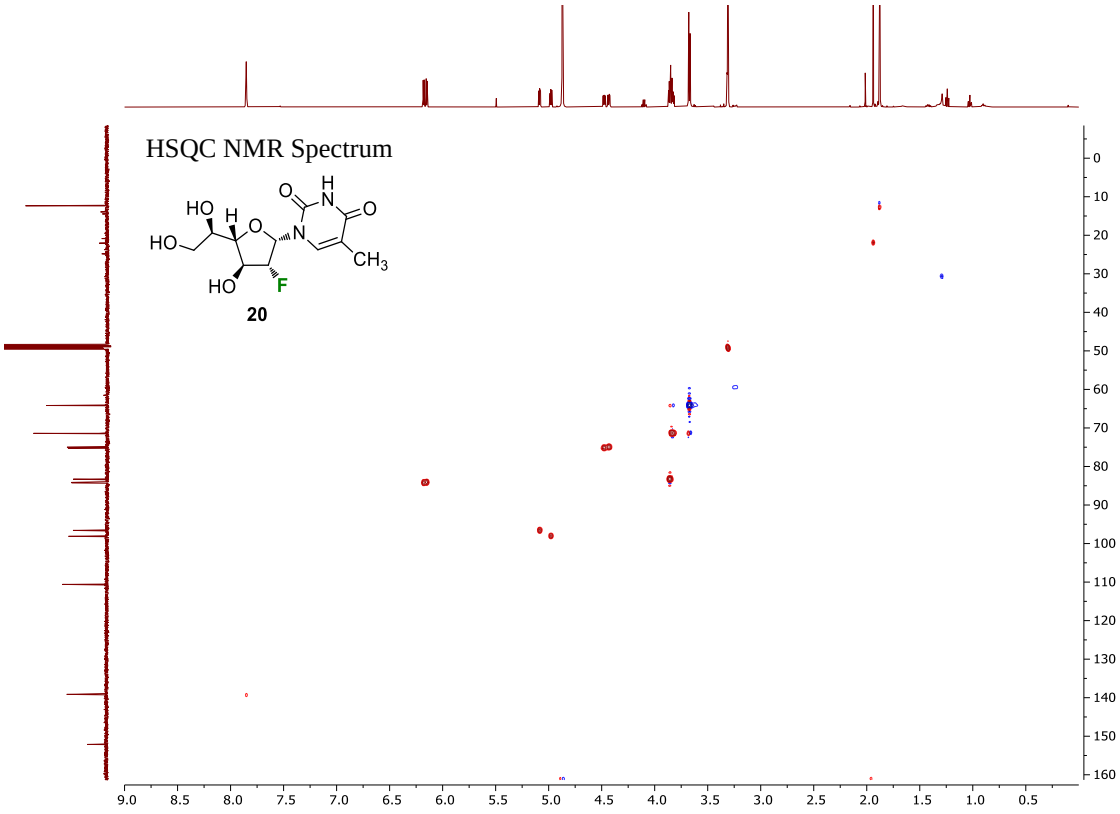


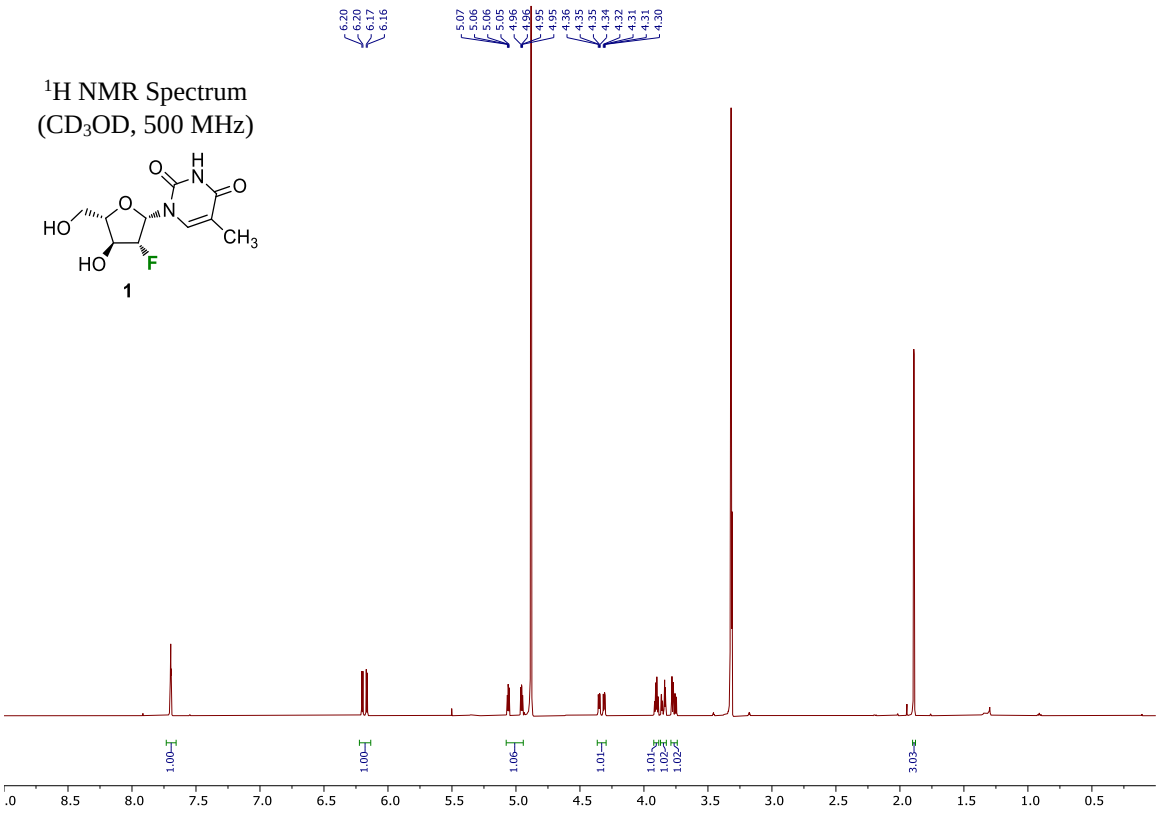
20

COSY NMR Spectrum

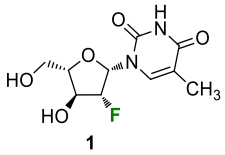


20


HSQC NMR Spectrum
HO
H
O
N
H
O
O
HO
N
CH3
HO
F
20

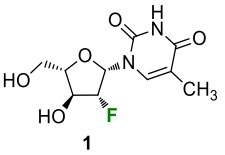

1H NMR Spectrum
(CD3OD, 500 MHz)
HO
O
N
H
O
N
CH3
HO
F
1

^{13}C NMR Spectrum
(CD_3OD, 126 MHz)



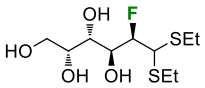
1

^{19}F NMR Spectrum
(CD_3OD, 470 MHz)



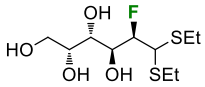
1

^{1}H NMR Spectrum
(Acetone-d_6, 500 MHz)



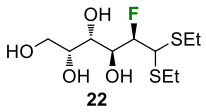
22

^{13}C NMR Spectrum
(Acetone-d_6, 126 MHz)



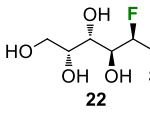
22

^{19}F NMR Spectrum
(Acetone-d_6, 470 MHz)



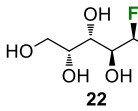
22

COSY NMR Spectrum



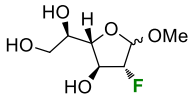
22

HSQC NMR Spectrum



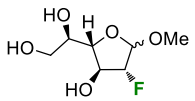
22

^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)



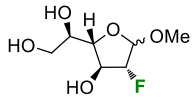
10

^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)

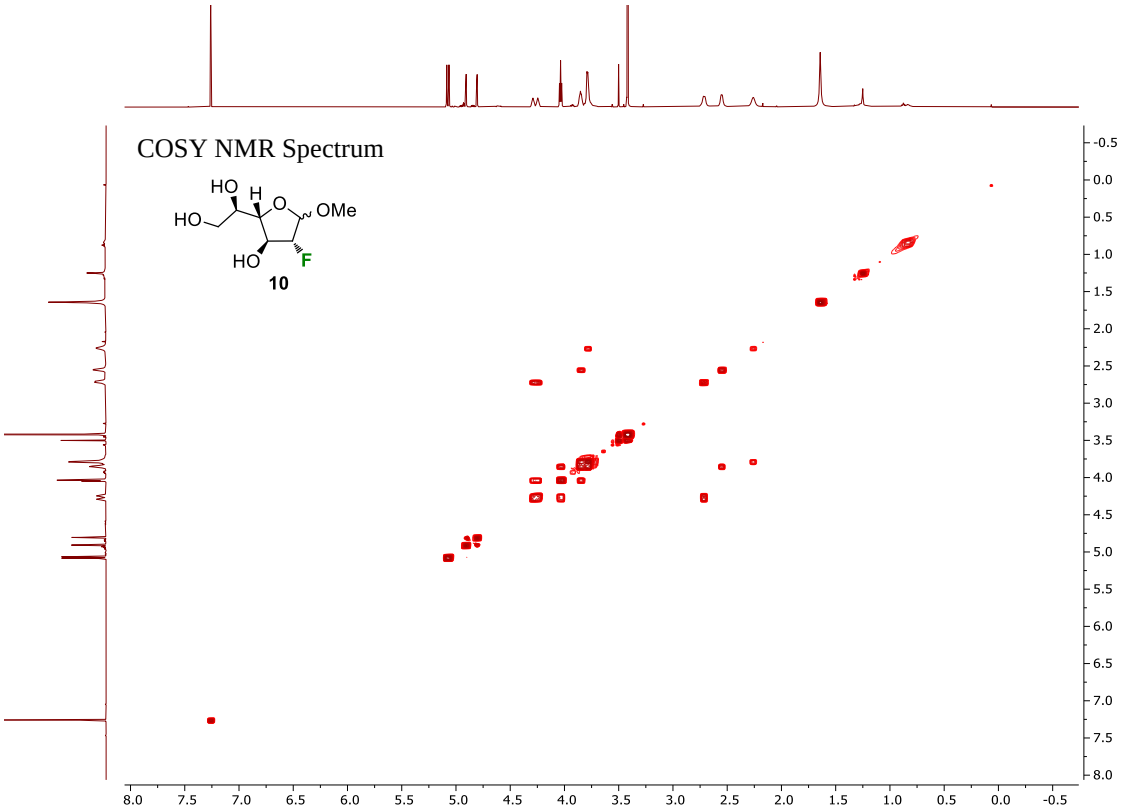


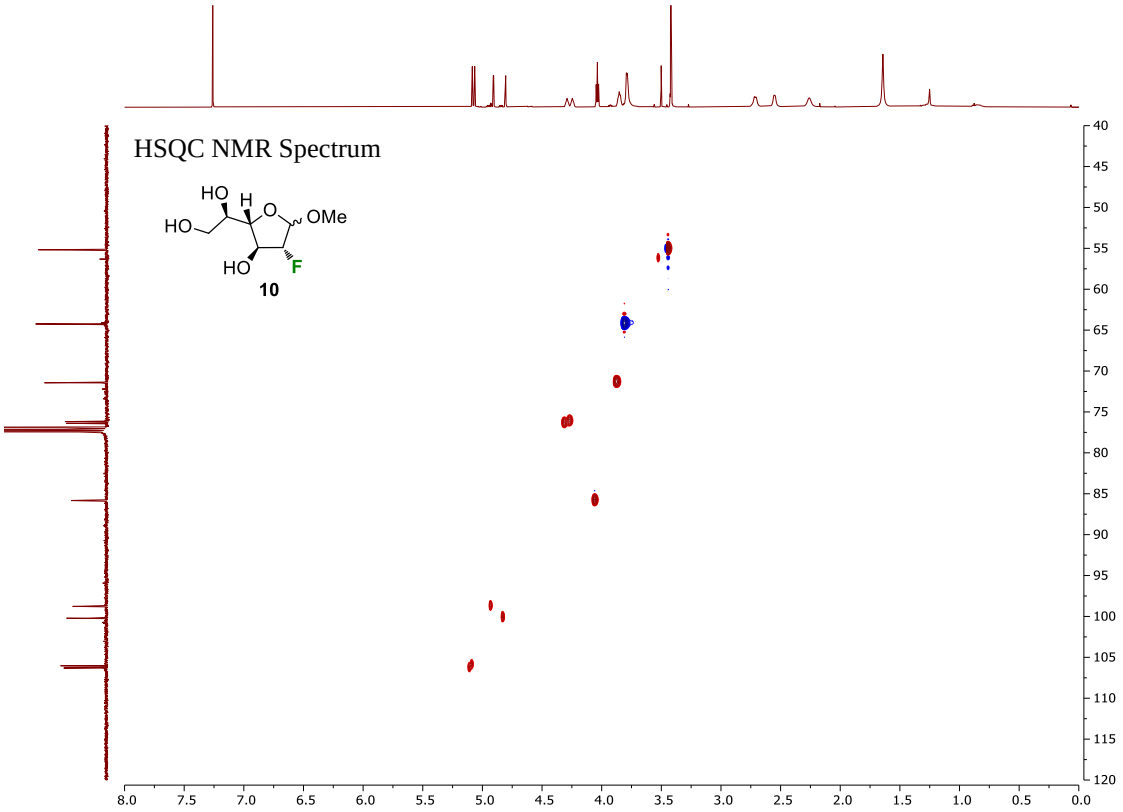
10

^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)

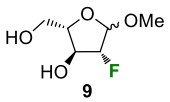


10


COSY NMR Spectrum
HO
H
O
OMe
HO
HO
F
10

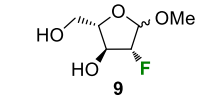

HSQC NMR Spectrum
HO
H
O
OMe
HO
HO
F
10

^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)



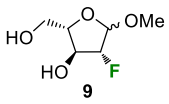
9

^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)



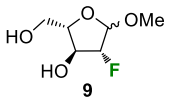
9

^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)



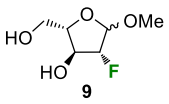
9

COSY NMR Spectrum



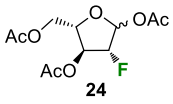
9

HSQC NMR Spectrum



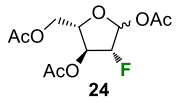
9

^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)



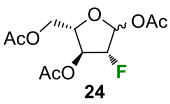
24

^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)

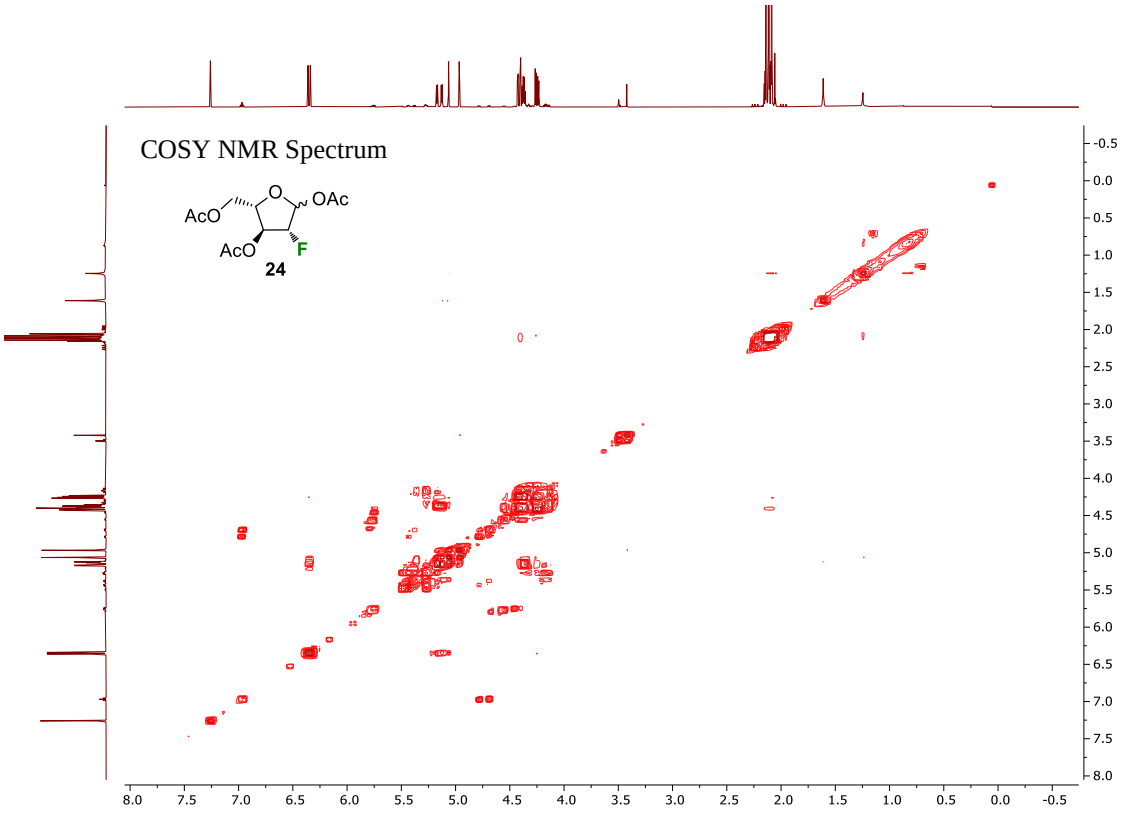


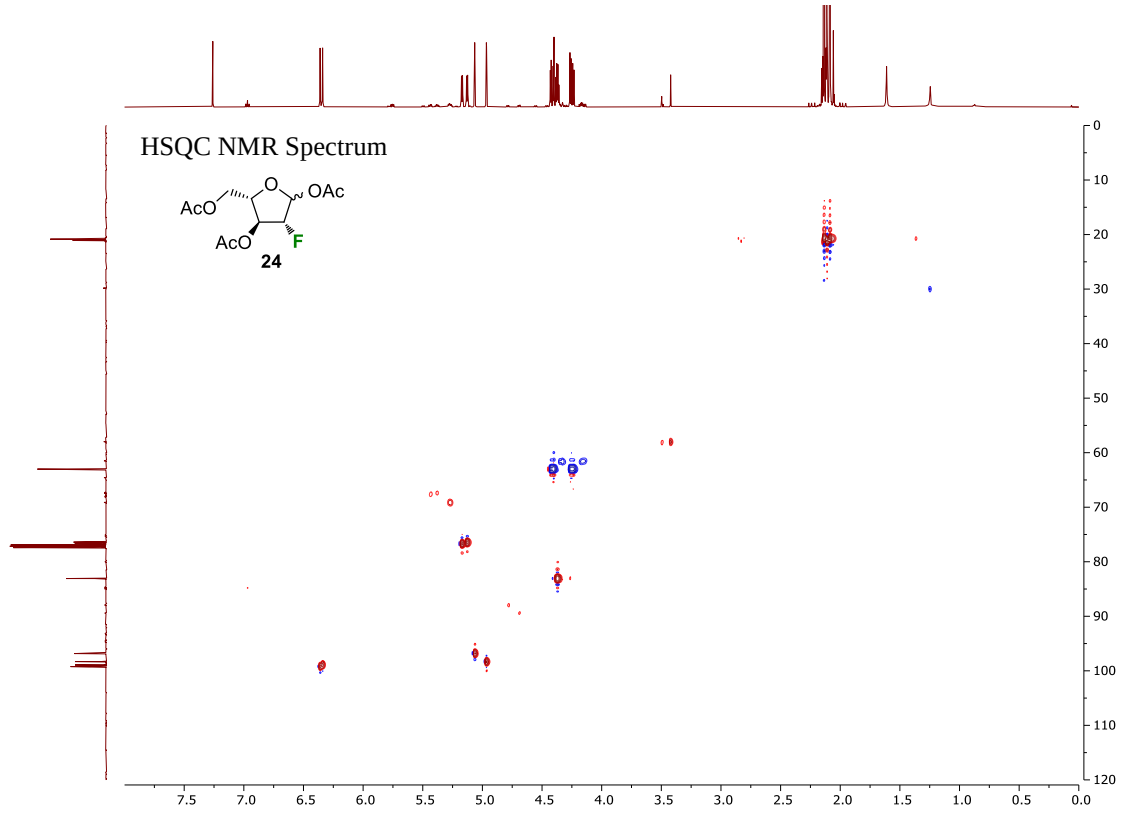
24

^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)

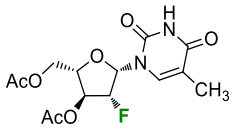


24


COSY NMR Spectrum
AcO
OAc
AcO
F
24

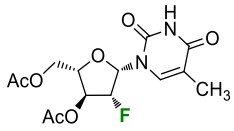

HSQC NMR Spectrum
AcO
OAc
AcO
F
24

^{1}H NMR Spectrum
($CDCl_3$, 500 MHz)



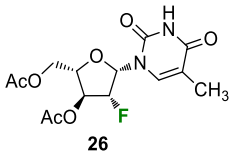
26

^{13}C NMR Spectrum
($CDCl_3$, 126 MHz)



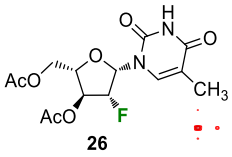
26

^{19}F NMR Spectrum
($CDCl_3$, 470 MHz)

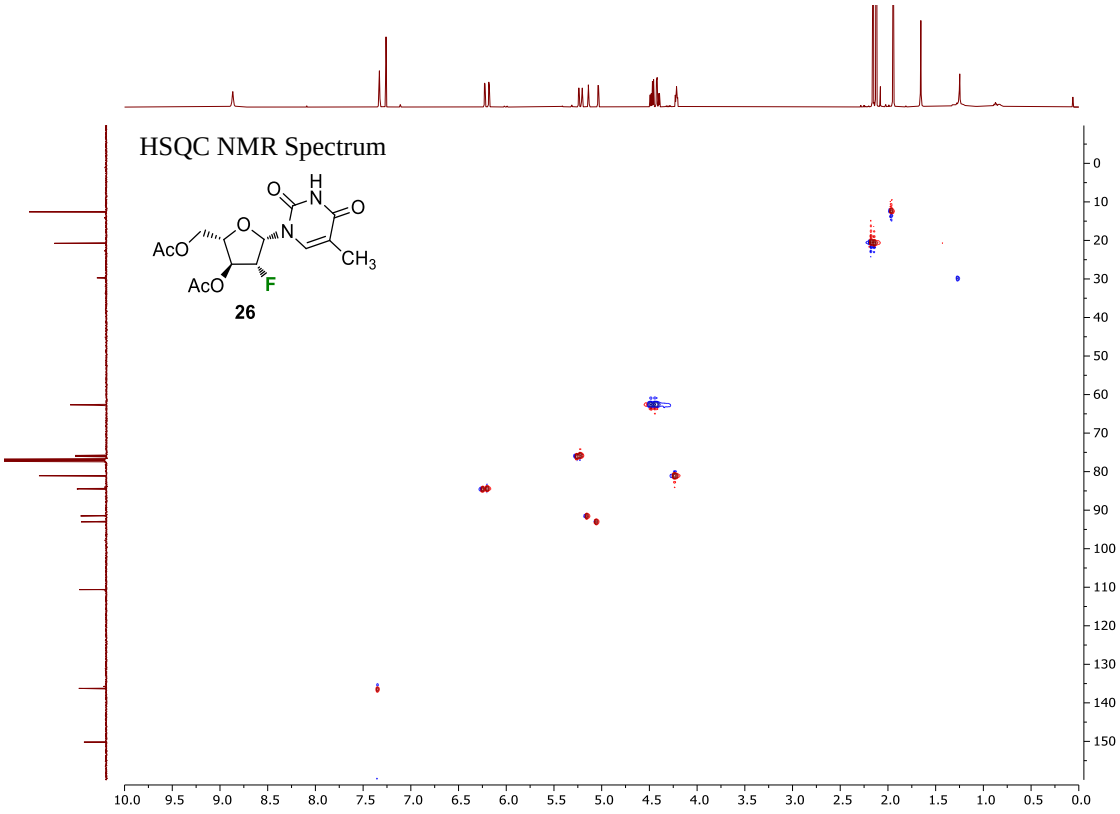


26

COSY NMR Spectrum



26


HSQC NMR Spectrum
AcO
AcO
F
CH3
26
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150

III. References

[1] Q. Zhang and H.-w. Liu, *J. Am. Chem. Soc*. 2001, **123**, 6756–6766.

[2] G. G. Sivets, *Tetrahedron* 2018, **74**, 920–931.