Fluorinated Intermediates in the Synthesis of β–2-Fluorodideoxynucleosides

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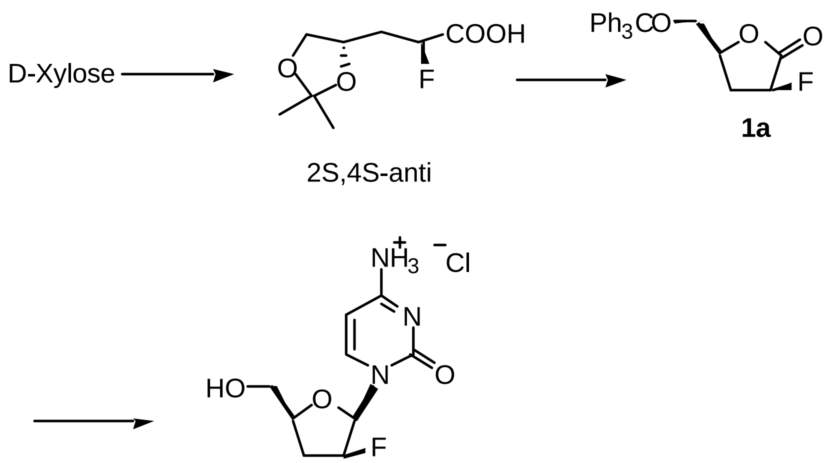
The need for fluorinated materials that can be used as building blocks for the synthesis of complex molecules, especially fluorinated compounds with biomedicinal use, is extremely high [1,2]. Fluorinated nucleosides represent an extremely vigorous area of study because of the potent anti-viral and anti-cancer properties observed. Several reviews are available on this subject [3-9].

A highly promising anti-HIV nucleoside, 1-(2,3-dideoxy-2-fluoro-β–D-*threo*-pentofuranosylcytosine (β-2-F-ddC, **2**), has been prepared by Okabe,*et.al.* [9]. Their synthesis involved cyclization of an enzymaticlly resolved fluoroacid to produce the novel 3S-*cis* fluorinated tetrahydrofuranone **1a.** The nucleoside **2** was formed in 7.9% overall yield. (Scheme 1).

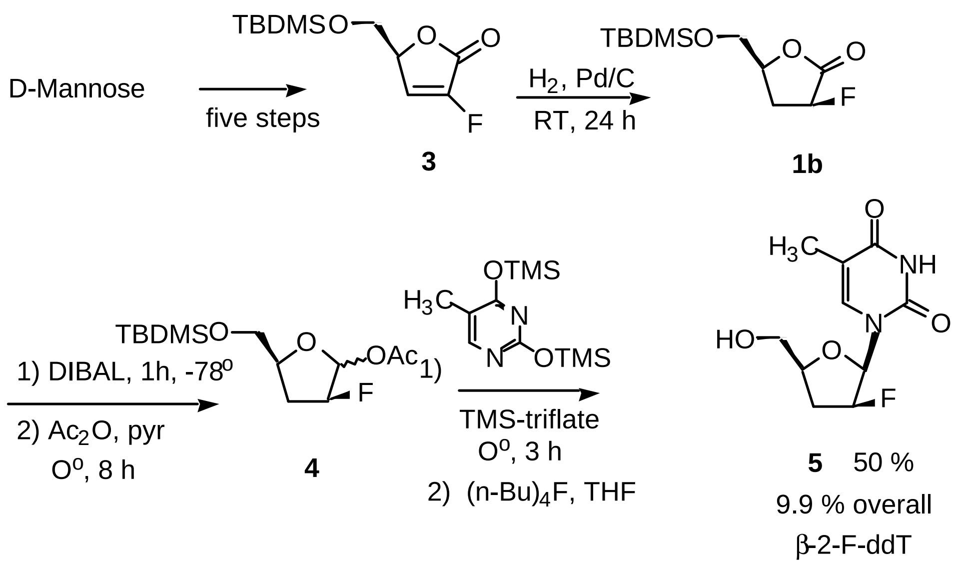
Scheme 1



2 β-2-F-ddC · HCl

Several years ago we prepared an unsaturated fluorinated lactone (**3**) from D-mannose for use as a template in building fluorinated molecules [10]. We previously utilized **3** in the synthesis of a fluorinated pyrethrin [11]. Now, we show the synthetic utility of **3** in the preparation of the Okabe lactone, **1b**, (TBDMS protected) by stereoselective catalytic hydrogenation. In addition we used **1b** in the synthesis of 1-(2,3-dideoxy-2-fluoro-β–D-*threo* -pentafuranosylthymine (β-2-F-ddT), another promising anti-HIV substance [6]. The results are shown in Scheme 2.

Scheme 2



The high diastereoselectivity (>99 %) observed in the hydrogenation of **3** is the major factor in the success of the synthesis. Proof for the 3S-*cis* structure of **1b** comes from comparison of the ^{1}H NMR spectra of **1b** with spectra obtained from Dr. Okabe for **1a**. Both the 3S-*cis* and 3R-*trans* isomers have resonances that overlap, but the 5-methine proton is very distinct. In the 3S-*cis* isomer the 5-methine is found as a multiplet at δ 4.53 whereas in the 3R-*trans* isomer the 5-methine proton occurs as a doublet at δ 4.75 [12]. Compound **1b** obtained in the catalytic hydrogenation of the unsaturated lactone **3** shows only the 5-methine resonance for the 3S-*cis* isomer without a trace of the 3R-*trans* isomer.

Further proof of the stereochemistry of **1b** comes from its conversion to 1-(2,3-dideoxy-2-fluoro-β-D-*threo*--pentofuranosyl)thymine (β–2-F-ddT, **5**), a known nucleoside prepared by Sterzycki, *et. al.* [6]. As shown in Scheme 2, reduction of the lactone followed by acetylation gives the acetate **4**. Vorbrüggen coupling [13] with protected thymine provides the TBDMS-β–2-F-ddT. Removal of the TBDMS function occurs readily with tetra-butyl ammonium fluoride to provide the unprotected β–2-F-ddT (**5**).

The anti-HIV activity of both **2** [9] and **5** [6] has been published.

Experimental Details

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian UNITY plus 300 MHz Spectrometer system. The proton (^{1}H) NMR were recorded at 300.05 MHz with external tetramethylsilane (TMS, δ =0.00 ppm) as a reference. Carbon (^{13}C) NMR were recorded at 75.46 MHz with internal deuterated chloroform (δ =77.00 ppm) as a reference. Fluorine (^{19}F) NMR were recorded at 282.3 MHz with external trifluoroacetic acid (TFA, δ =0.00 ppm) as a reference. TFA is a singlet at δ–76.5 relative to $CFCl_3$, the common fluorine NMR standard.

*(3S-cis)-3-Fluoro-5-[(t-butyldimethylsiloxy)methyl]-2-tetrahydrofuranone (**1b**)*

To a solution of 0.14 g (0.57 mmol) of **3** dissolved in 25 mL of 100% ethanol in a hydrogenation bottle was added 10 mg of 5 % palladium on activated carbon. The reaction bottle was placed on the Parr apparatus and the pressure of the hydrogen gas gauge was set at 30 psi. Hydrogenation was conducted for 8 hours at rt. The mixture was filtered through a CHEMWARE fluorocarbon membrane (75 mm) and the solvent was removed on an evaporator to give 0.14 g (99 %) of clear pure liquid product **1b.** ^{1}H-NMR: ($CDCl_3$) δ 0.05 (s, CH_3Si), 0.88 (s, t-Bu), 2.56 (m, H4), 3.85 (d of d, J_{gem} = 11.4 Hz, $J_{H4\text{-}CH2}$ = 3.5 Hz, CH_2OSi), 4.53 (m, H5), 5.23 (d of t, J_{gemHF} = 51 Hz); ^{13}C-NMR: ($CDCl_3$) δ -5.4 (CH_3Si), 18.2 (quat C of t-Bu), 25.7 (t-Bu), 36.0 (d, J_{CF} = 21.1 Hz, C4), 67.1(CH_2OSi), 76.5 (C5), 86.1 (d, J_{gemCF} = 182.6 Hz, C3), 170.0 (d, J_{CF} = 23.3 Hz, C=O); ^{19}F-NMR: ($CDCl_3$) δ -117.49 (m). Anal. Calcd for $C_{11}H_{21}FO_3Si$: C, 53.20; H, 8.93; F, 7.65. Found: C, 53.22; H, 8.77, F, 7.80.

(3S,5S)-3-Fluoro-5-[(t-butyldimethylsilyl)methyl]-2-tetrahydrofuranol Acetate ***(4).***

a) Reduction of the Ester.

A 50 mL round bottom flask equipped with a magnetic stirrer, under nitrogen atmosphere was charged with 100 mg (0.40 mmol) of **1b** and 5 mL of methylene chloride. The temperature of the flask was lowered to -78 ^{o}C and 1.1 mL of 1.0 M diisobutylaluminum hydride in methylene chloride was added and the solution was stirred for 1 hour. While still cold the mixture was worked up in dilute nitric acid and washed with water and dried over anhydrous sodium sulfate. After the solvent was evaporated, 85.3 mg (85%) of alcohol was obtained as a clear liquid. ^{1}H-NMR: ($CDCl_3$) δ 0.11 (s, CH_3Si), 1.01 (s, t-Bu), 1.92 (b, OH), 2.40 (m, broad, H4), 4.59 (m, H5), 4.97 (m, J_{gemHF} = 52 Hz), 5.58 (d, J_{HF} = 15 Hz, H1); ^{13}C-NMR: ($CDCl_3$) δ -5.3 (CH_3Si), 18.2 (quat C of t-Bu), 25.5 (t-Bu), 34.6 (d, J_{CF} = 21.1 Hz, C4), 60.8 (CH_2OSi), 74.5 (C5), 91.8 (d, J_{gemCF} = 168 Hz, C3), 106.6 (d, J_{CF} = 18 Hz, C2); ^{19}F-NMR: ($CDCl_3$) δ -113.25 (m).

b) Acylation of the Alcohol.

A mixture of the alcohol prepared above (500 mg, 2 mmol) and 2.5 g of acetic anhydride was added to a 50 mL round bottom flask. To this mixture was added 0.1 g of pyridine. The resulting mixture was placed in a refrigerator and allowed to stand overnight. The mixture was then dissolved in 25 mL of methylene chloride, washed with several portions of sodium bicarbonate and water, then dried over anhydrous sodium sulfate. The solvent was then evaporated to yield 0.53 g of **4** (91%) as a light brown liquid**.** ^{1}H-NMR: ($CDCl_3$) δ 0.021 (s, CH_3Si), 1.06 (s, t-Bu), 2.0 (s, $CH_3C{=}O$), 2.37 (m, H4), 3.55 (m, CH_2OSi), 4.50 (m, H5), 4.97 (m, J_{gemHF} = 51 Hz, H3), 6.27 (d, J_{HF} = 15 Hz, H2); ^{13}C-NMR: ($CDCl_3$) δ -5.4 (CH_3Si), 18.2 (*quat* C of t-Bu), 20.6 ($CH_3C{=}O$), 25.7 (t-Bu), 31.1 (d, J_{CF} = 21 Hz, C4), 61.4 (CH_2OSi), 73.9 (C5), 94.8 (d, J_{gemHF} = 180 Hz, C3), 100.9 (d, J_{CF} = 17 Hz, C2), 169 (C=O); ^{19}F-NMR: ($CDCl_3$) δ -113.8 (m). Anal. Calcd for $C_{13}H_{25}FO_4Si$: C, 53.40; H, 8.63. Found: C, 53.61; H, 8.64.

1-[2'-Fluoro-2',3'-dideoxy-5-O-(t-butyldimethylsilyl)-b-*D-threo-pentafuranosyl] thymine (TBDMS*-b-*2-F-ddT).*

To 1.0 g (8 mmol) of dried finely powered thymine was added 8 mL of hexamethyldisilazane and 1 mL of trimethylsilyl chloride. The resulting suspension was refluxed at 140 ºC, with exclusion of moisture, until complete dissolution of the thymine had occurred. Removal of the silylating agents under high vacuum afforded the silylated base as an oil which was used immediately without further purification.

The silylated thymine was sealed in a flask and flushed with dry nitrogen gas. A solution of **4** (100 mg, 0.34 mmol) in dichloromethane was then added to the base and the mixture was cooled to 0 ºC. To the cooled mixture, trimethylsilyl trifluoromethanesulfonate (TMS-triflate, 1.1 molar equivalent) was added dropwise with stirring. The mixture was then allowed to warm to room temperature with stirring for a further 3 hours. After this time the reaction was quenched by addition of sodium bicarbonate solution, and the mixture was extracted and washed several times with dichloromethane and brine. The combined organic extracts were then dried over magnesium sulfate to yield 60 mg of **TBDMS-5** (49% yield from **4**) as a light brown liquid. ^{1}H-NMR: ($CDCl_3$) δ 0.06 (s, CH_3Si), 1.24 (s, t-Bu), 2.11 (s, CH_3 on C5) 2.57 (m, H3'), 3.74 (m, H5'), 4.65 (m, H4'), 5.20 (d of t, J_{gemHF} = 51 Hz, H2'), 5.92 (d, J_{HF} = 15 Hz, H1'),8.07 (s, H6), 9.01 (NH); ^{13}C-NMR: ($CDCl_3$) δ -5.4 (CH_3Si), 18.3 (quat C of t-Bu), 12.9 (C6), 14.1 (CH_3 on C5), 18.3 (quat C of t-Bu), 37.2 (d, J_{CF} = 21 Hz, C3'), 64.7 (C6'), 73.9 (C5'), 85.3 (d, J_{gemHF} = 193 Hz, C2'), 87.6 (d, J_{HF} = 17

Hz, C1'), 101.2 (C5), 129.0 (C6), 141.8 (C2), 170.5 (C4); ^{19}F-NMR: ($CDCl_3$) δ -115.03 (m). Anal. Calcd for $C_{16}H_{27}FN_2O_4Si$: C, 53.61; H, 7.59; F, 5.30. Found: C, 53.44; H, 7.68; F, 5.11.

*1-(2'-Fluoro-2',3'-dideoxy-*b-*D-threo-pentofuranosyl)thymine (*b*-2-F-ddT,**5**).*

A mixture containing **TBDMS-5** (50 mg, 1.40 mmol) and 1 mL of tetra-n-butylammonium fluoride (1 M in THF) was allowed to stand overnight. The THF was removed under a stream of nitrogen and the residue was chromatographed on silica gel (ethyl acetate/ ethanol, 12:1) to give pure **5** (30 mg, 88 %), mp 160-162 ^{o}C (lit. [6] mp 162-164 ^{o}C), ^{19}F NMR (acetone d-6) δ -114.91(m). Proton and carbon NMR data were identical with published data [6].

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References

[1] R. Filler, Y. Kobayashi , L. M. Yagupolski, *Organic Fluorine Compounds in Medicinal Chemistry and Biomedical Application* Elsevier, Amsterdam,1993.

[2] M. Hudlicky, A.E Pavlath, eds., *Chemistry of Organic Fluorine Compounds. II* ACS Monograph 187, Washington, D. C. 1995.

[3] M. Nasr, J. Cradock, M. Johnston, *Aids Research and Human Retroviruses* 9 (1992) 135.

[4] D. E. Bergstrom, D. J. Swartling, in *Fluorine Containing Molecules* J. F.

Liebman, A. Greenberg, W. R.Dolbier, eds. VCH, 1988, p 259.

[5] V. E. Marquez, C. K.-h. Tseng, J. A. Kelley, H. Mitsuya, S. Broder, J. S. Roth, J. Driscoll, *Biochemical Pharmacology* , 36 (1987) 2719.

[6] R. Sterzycki, I. Ghazzouli, V. Brankovan, J. C. Martin, M. M. Mansuri, *J. Med. Chem.* 33 (1990) 2150.

[7] A. VanAerschot, J. Balzarini, R. Pauwels, L. Kerremans, E. DeClercq, P. Herdewijn, *Nucleosides and Nucleotides* 8 (1989) 1121.

[8] P. L. Coe, R. R. Telekar, R. T. Walker, *J. Fluorine Chem*. 69 (1994) 19 and references cited therein.

[9] M. Okabe, R.-C. Sun, G. B. Zenchoff, *J. Org. Chem.* 56 (1991) 4392.

[10] T. B. Patrick, M V. Lanahan, C. Yang, J. Walker, C. L. Hutchinson, B. E. Neal, *J. Org. Chem.* 59 (1994) 1210.

[11] T. B. Patrick, B. E. Neal, *Synlett* (1996) 1227.

[12] We thank Dr. Okabe for supplying these NMR data.

[13] H. Vorbrüggen, H.; K. Krolikiewicz, K.; B. Bennua, B. *Chem. Ber*. 114 (1981)1234.