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Nucleosides. CXLIX. Novel and Practical Synthesis of α-Monofluoro- and α,α-Difluorothymidine (F-TDR and F_2-TDR)

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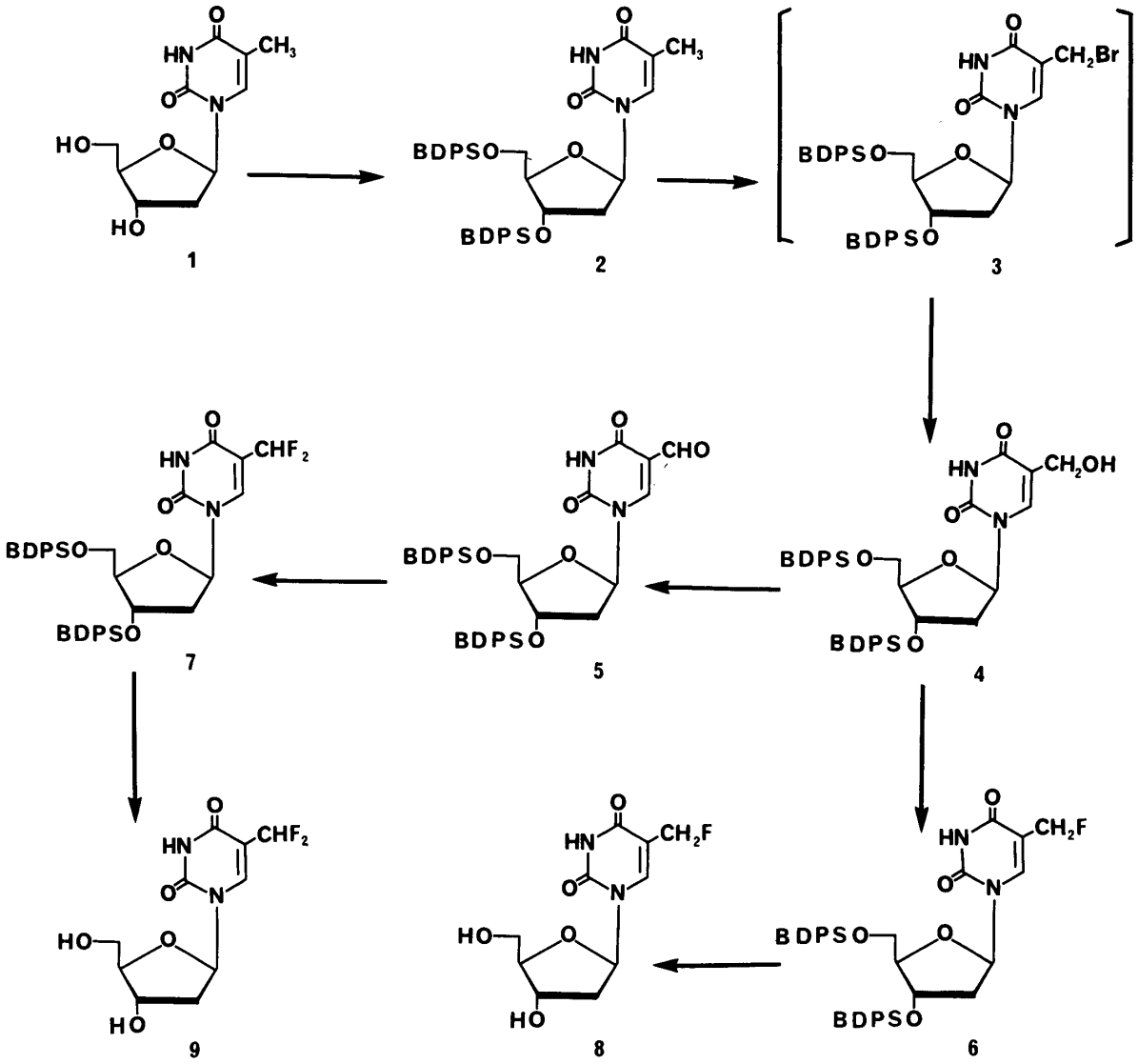
Di-*O*-*tert*-butyldiphenylsilyl (BDPS)-thymidine (**2**) was converted to α-bromo-3′,5′-di-*O*-BDPS-thymidine (**3**) by photobromination. Crude **3** was hydrolyzed to the α-hydroxythymidine derivative **4** which was oxidized with MnO_2 to the 5-formyluracil nucleoside **5**. Fluorination of **4** with diethylamino-sulfur trifluoride afforded the protected α-fluorothymidine **6**. Similarly, **5** was converted into the α,α-difluorothymine nucleoside **7**. These protected fluorothymidines (**6** and **7**) were deblocked by treatment with tetra-*n*-butylammonium fluoride to give α-fluorothymidine (**8**, F-TDR) and α,α-difluorothymidine (**9**, F_2-TDR).

Keywords——α-monofluorothymidine; α,α-difluorothymidine; 5-monofluoromethyl-2′-deoxyuridine; 5-difluoromethyl-2′-deoxyuridine; practical synthesis

In previous reports from our Laboratory[2,3] we described the synthesis of α-monofluoro- and α,α-difluoro-thymine nucleosides. The synthesis of such nucleosides has been the subject of extensive studies[4] since the discovery of the antitumor and antiviral activities of 2′-deoxy-5-trifluoromethyluridine (F_3-TDR).[5] Our original synthesis involved photobromination[6] of a partially protected thymine nucleoside, *e.g.*, 5′-*O*-*tert*-butyldiphenylsilyl(BDPS)-thymidine, with bromine in carbon tetrachloride followed by nucleophilic displacement of the bromine with fluorine. Several shortcomings in this reaction sequence were apparent: (1) Incomplete solubility of the monosilylated nucleosides in CCl_4 during bromination step lowered the reproducability of yields of bromomethyl products. (2) When 1 eq of Br_2 was used in the monobromination, the formation of the undesirable α,α-dibromide was unavoidable and unreacted starting material always present in the reaction mixture. Consequently, fluorination of this mixture with AgF yielded the desired α-monofluoro nucleoside contaminated with considerable amounts of the unfluorinated and α,α-difluorinated thymine nucleosides. Very careful chromatographic separation was necessary to isolate the desired product. (3) The yields of fluorinated products very much depended on the quality of AgF and MeCN (freshly distilled over P_2O_5). Due to instability of mixed halogen silver salts,[7] large excess of AgF was always required.

In order to overcome the above disadvantages, we developed a novel method which is described below. Thymidine (**1**, Chart 1) was treated with 2 eq of *tert*-butyldiphenylsilyl chloride (BDPSCl) in DMF in the presense of imidazole to afford the 3′,5′-di-*O*-BDPS-thymidine (**2**) which was completely soluble in CCl_4. Photochemical bromination of **2** using *N*-bromosuccinimide (NBS) by the procedure reported by Shealy *et al.*[8] afforded the 5-monobromomethyl derivative **3** in high yield which, without purification, was hydrolyzed by means of $NaHCO_3$ to give 3′,5′-di-*O*-BDPS-α-hydroxythymidine (**4**). Treatment of **4** with diethylamino-sulfur trifluoride (DAST)[9] in CH_2Cl_2 afforded the desired 5-monofluoro



BDPS = *tert*-butyldiphenylsilyl

Chart 1

methyluracil nucleoside **6** in 66% yield. Alternatively, the 5-hydroxy-methyl derivative **4** was oxidized with active MnO_2 to the 5-formyluracil nucleoside **5**.[10] Treatment of **5** with DAST afforded the protected α,α-difluorothymidine **7** in 70% yield. It should be noted that no cleavage of the BDPS protecting groups was noticed in the course of these fluorination reactions. Removal of the BDPS protecting groups of **6** and **7** with tetra-*n*-butylammonium fluoride (TBAF) afforded α-fluorothymidine (**8**, F-TDR) and α,α-difluorothymidine (**9**, F_2-TDR), respectively. Attempts at fluorination with simultaneous removal of the BDPS protecting groups to prepare F-TDR (**8**) directly from **3** by treatment with TBAF[11] failed. Only very low yield of **8** was obtained.

Although the published procedure[2,3] for the preparation of F-TDR and F_2-TDR appears to be more straightforward, the method described in this report is more practical since it is easier, more reproducible, amenable to large scale preparation, and readily applicable to the fluorination of a variety of thymine nucleosides.

Experimental

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Proton nuclear magnetic

resonance (^{1}H-NMR) spectra were recorded on a JEOL FX90Q spectrometer in $CDCl_3$ with Me_4Si as the internal standard. Chemical shifts are reported in ppm (δ) and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet), br s (broad singlet). Values given for coupling constants are first order. Elemental analyses were performed by M. H. W. Laboratories. Silica gel thin layer chromatography (TLC) was performed on Analtech Uniplates with short-wave length ultraviolet (UV) light for visualization. Column chromatography was conducted on flash grade silica gel (Merck 9385, 0.040—0.063 fm) which was packed with *n*-hexane unless specified otherwise.

3′,5′-Di-*O*-(*tert*-butyldiphenyl)silylthymidine (2)——To a solution of thymidine (**1**, 0.50 g, 2.06 mmol) and BDPSiCl (1.34 ml, 5.15 mmol) in dry *N*,*N*-dimethylformamide (DMF) (10 ml) was added imidazole (0.62 g, 9.10 mmol) and the mixture was stirred overnight at room temperature. The solvent was removed *in vacuo*, and the residue partitioned between EtOAc and H_2O (20 ml each). The aqueous layer was extracted with EtOAc (2 × 10 ml). The combined organic solutions were dried (Na_2SO_4), concentrated, and the residue chromatographed on a silica gel column (*n*-hexane–EtOAc, 4 : 1 and 3 : 1) to give **2** (1.22 g, 82%) as a foam. ^{1}H-NMR δ: 0.93 (9H, s, *tert*-Bu), 1.08 (9H, s, *tert*-Bu), 1.49 (3H, s, 5-Me), 1.81—2.45 (2H, m, H-2′,2″), 3.29 (1H, dd, H-5′, $J_{4',5'}=2.5$, $J_{5',5''}=11.5$ Hz), 3.75 (1H, dd, H-5″, $J_{4',5''}=1.9$, $J_{5',5''}=11.5$ Hz), 3.99 (1H, m, H-4′), 4.55 (1H, br d, H-3′, $J_{2',3'}=5.8$ Hz), 6.51 (1H, dd, H-1′, $J_{1',2'}=5.4$, $J_{1',2''}=8.9$ Hz), 7.19—7.81 (21H, m, H-6, Ph), 8.21 (1H, s, NH).

Anal. Calcd for $C_{42}H_{50}N_2O_5Si_2$: C, 70.15; H, 7.01; N, 3.90. Found: C, 70.32; H, 7.08; N, 3.97.

3′,5′-Di-*O*-(*tert*-butyldiphenyl)silyl-α-hydroxythymidine (4)——A mixture of **2** (2.41 g, 3.35 mmol), NBS (0.75 g, 4.21 mmol) and dry CCl_4 (170 ml) was heated under reflux in N_2 atmosphere, and irradiated with 500 W UV lamp for 2 h. The mixture was filtered, and the filtrate was concentrated *in vacuo* to give crude α-bromide **3** as a foam which was dissolved in tetrahydrofuran (THF) (7 ml). Water (7 ml) and $NaHCO_3$ (336 mg) was added to the solution, and the mixture stirred overnight at room temperature, extracted with $CHCl_3$ (2 × 50 ml). The combined organic extracts were washed (H_2O, 50 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed on a silica gel column (*n*-hexane–EtOAc, 2 : 1) to afford **4** as a white foam (1.50 g, 61%). ^{1}H-NMR δ: 0.92 (9H, s, *tert*-Bu), 1.08 (9H, s, *tert*-Bu), 1.76—2.50 (2H, m, H-2′,2″), 3.30 (1H, dd, H-5′, $J_{4',5'}=2.6$, $J_{5',5''}=11.3$ Hz), 3.59—4.07 (5H, m, H-4′,5″, 5-C<u>H</u>$_2$ O<u>H</u>), 4.53 (1H, br d, H-3′, $J_{2',3'}=5.7$ Hz), 6.48 (1H, dd, H-1′, $J_{1',2'}=5.4$, $J_{1',2''}=8.9$ Hz), 7.14—7.73 (21H, m, H-6, Ph), 8.35 (1H, s, NH).

Anal. Calcd for $C_{42}H_{50}N_2O_6Si_2$: C, 68.63; H, 6.86; N, 3.81. Found: C, 68.62; H, 6.75; N, 3.77.

3′,5′-Di-*O*-(*tert*-butyldiphenyl)silyl-2′-deoxy-5-formyluridine (5)——To a solution of **4** (1.10 g, 1.50 mmol) in MePh (60 ml) was added active MnO_2[10] (3 g), and the mixture was heated at reflux while stirring for 5 h, then filtered through a Celite pad while hot, and MnO_2 was washed well with $CHCl_3$. The combined filtrate and washings were concentrated *in vacuo*, and the residue chromatographed (*n*-hexane–EtOAc, 3 : 1 and 2 : 1) to afford a colorless foam (0.80 g, 73%). ^{1}H-NMR δ: 0.89 (9H, s, *tert*-Bu), 1.06 (9H, s, *tert*-Bu), 1.98 (1H, ddd, H-2′, $J_{1',2'}=8.4$, $J_{2',3'}=5.2$, $J_{2',2''}=12.8$ Hz), 2.59 (1H, dd, H-2″, $J_{1',2''}=5.4$, $J_{2',2''}=12.8$ Hz), 3.27 (1H, dd, H-5′, $J_{4',5'}=2.7$, $J_{5',5''}=11.7$ Hz), 3.70 (1H, dd, H-5″, $J_{4',5''}=2.5$, $J_{5',5''}=11.7$ Hz), 4.03 (1H, m, H-4′), 4.43 (1H, d, H-3′, $J_{2',3'}=5.2$ Hz), 6.29 (1H, dd, H-1′, $J_{1',2'}=8.4$, $J_{1',2''}=5.4$ Hz), 7.10—7.66 (20H, m, Ph), 8.50 (1H, s, H-6), 8.54 (1H, s, NH), 9.79 (1H, s, C<u>H</u>O).

Anal. Calcd for $C_{42}H_{48}N_2O_6Si_2$: C, 68.82; H, 6.60; N, 38.2. Found: C, 68.69; H, 6.60; N, 38.4.

3′,5′-Di-*O*-(*tert*-butyldiphenyl)silyl-α-fluorothymidine (6)——To a solution of DAST (0.035 ml, 0.29 mmol) in dry CH_2Cl_2 (1 ml) was added a solution of **4** (210 mg, 0.29 mmol) in dry CH_2Cl_2 (1 ml) at −15 °C under argon atmosphere. The mixture was stirred for 30 min at −15 °C, and the reaction quenched by addition of cold H_2O (1 ml). The organic layer was separated, washed (H_2O, 1 ml), dried (Na_2SO_4), concentrated *in vacuo*, and the residue chromatographed (*n*-hexane–EtOAc, 3 : 1) to give **6** as a colorless foam (145 mg, 66%). ^{1}H-NMR δ: 0.93 (9H, s, *tert*-Bu), 1.09 (9H, s, *tert*-Bu), 1.72—2.55 (2H, m, H-2′,2″), 3.32 (1H, dd, H-5′, $J_{4',5'}=2.7$, $J_{5',5''}=11.5$ Hz), 3.75 (1H, dd, H-5″, $J_{4',5''}=2.2$, $J_{5',5''}=11.5$ Hz), 4.01 (1H, m, H-4′), 4.53 (1H, d, H-3′, $J_{2',3'}=5.7$ Hz), 4.65 (2H, d, C<u>H</u>$_2$F, $J_{H,F}=48.0$ Hz), 6.48 (1H, dd, H-1′, $J_{1',2'}=8.8$, $J_{1',2''}=5.2$ Hz), 7.15—7.71 (20H, m, Ph), 7.78 (1H, d, H-6, $J_{6,F}=3.6$ Hz), 8.91 (1H, br s, NH).

Anal. Calcd for $C_{42}H_{49}FN_2O_5Si_2$: C, 68.44; H, 6.70; F, 2.58; N, 3.80. Found: C, 68.21, H, 6.79; F, 2.71; N, 3.79.

3′,5′-Di-(tert-butyldiphenyl)silyl-α,α-difluorothymidine (7)——A solution of **5** (176 mg, 0.24 mmol) in dry CH_2Cl_2 (1 ml) was slowly added under argon atmosphere to a solution of DAST (0.035 ml, 0.29 mmol) in dry CH_2Cl_2 (1 ml). The mixture was stirred overnight at room temperature and then cold H_2O (1 ml) was added. The organic layer was separated, washed (H_2O), dried (Na_2SO_4), concentrated *in vacuo*, and the residue chromatographed (*n*-hexane–EtOAc, 3 : 1) to give **7** (127 mg, 70%) as a colorless foam. ^{1}H-NMR δ: 0.91 (9H, s, *tert*-Bu), 1.07 (9H, s, *tert*-Bu), 1.91 (1H, ddd, H-2′, $J_{1',2'}=9.1$, $J_{2',3'}=5.21$, $J_{2',2''}=12.8$ Hz), 2.45 (1H, dd, H-2″, $J_{1',2''}=4.9$, $J_{2',2''}=12.8$ Hz), 3.29 (1H, dd, H-5′, $J_{4',5'}=3.2$, $J_{5',5''}=11.7$ Hz), 3.69 (1H, dd, H-5″, $J_{4',5''}=2.7$, $J_{5',5''}=11.7$ Hz), 4.00 (1H, m, H-4′), 4.46 (1H, d, H-3′, $J_{2',3'}=5.2$ Hz), 6.36 (1H, dd, H-1′, $J_{1',2'}=9.1$, $J_{1'2''}=4.9$ Hz), 6.40 (1H, t, C<u>H</u>F$_2$, $J_{H,F}=54.6$ Hz), 7.08—7.68 (20H, m, Ph), 7.99 (1H, t, H-6, $J_{H,6}=0.5$ Hz), 8.32 (1H, br s, NH).

Anal. Calcd for $C_{42}H_{48}F_2N_2O_6Si_2$: C, 66.81; H, 6.41; F, 5.03; N, 3.71. Found: C, 66.72; H, 6.44; F, 5.17; N, 3.75.

α-Fluorothymidine (8, F-TDR)——To a solution of **6** (200 mg, 0.27 mmol) in dry THF (1 ml) was added a 1 M solution of TBAF in THF (0.59 ml), and the mixture was stirred for 40 min at room temperature, and then directly

chromatographed on a silica gel column (packed with CH_2Cl_2) using CH_2Cl_2–THF (1 : 2, v/v) as the eluent. After concentration of the combined UV absorbing fractions, the residue was crystallized from Me_2CO to give **8** (39 mg, 55%), mp 140 °C (dec.), undepressed upon admixture with an authentic sample.[2,3] The ^{1}H-NMR spectrum of this sample was identical with that of an authentic specimen.[2,3]

α,α-Difluorothymidine (9, F_2-TDR)——Compound **7** (150 mg, 0.20 mmol) was dissolved in dry THF (1 ml), and 0.82 M TBAF in THF (0.53 ml, 0.43 mmol) was added. The mixture was stirred at room temperature for 40 min, and then placed on a silica gel column (packed with CH_2Cl_2) and eluted with CH_2Cl_2–THF (1 : 2, v/v). The product **9** was crystallized from Me_2CO (32 mg, 58%), mp 159—160 °C, unchanged on admixture with an authentic sample.[2,3] The ^{1}H-NMR spectrum of this sample was identical with that reported previously.[3]

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References and Notes

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