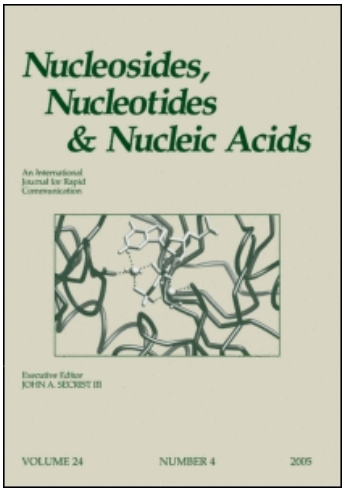

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NEW SYNTHESIS OF L-FMAU FROM L-ARABINOSE

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NEW SYNTHESIS OF L-FMAU FROM L-ARABINOSE

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ABSTRACT

A new synthesis of 2′-deoxy-2′-fluoro-5-methyl-β-L-arabinofuranosyl uracil (**13**, L-FMAU) was achieved in 10 steps from L-arabinose.

INTRODUCTION

Hepatitis B virus (HBV) is estimated to chronically infect approximately 300 million people worldwide[1]. These individuals are at risk for the development of liver failure, cirrhosis, and hepatocellular carcinoma. In addition, it is estimated that of those chronically infected, approximately 1 million die annually from HBV-induced liver disease. At present, interferon (IFN)[2] and lamivudine (3TC)[3a] are the only available treatments for chronic hepatitis B in the United States. IFN efficacy is partial and of limited duration, with less than 30% of the chronic carriers being treated with IFN responding to the treatment[2]. In clinical trials, lamivudine, has proven to be effective in decreasing the levels of HBV DNA in the serum of chronically infected patients[3b]. However, many patients relapsed shortly after cessation of therapy[3b]. In addition, there are now reports of the isolation of 3TC-resistant variants of HBV from the serum of patients undergoing 3TC therapy[3b]. Several other nucleoside analogs are currently undergoing investigation as potential anti-HBV agents; emtricitabine, entecavir, famciclovir[4], DAPD[5] and L-FMAU[6a].

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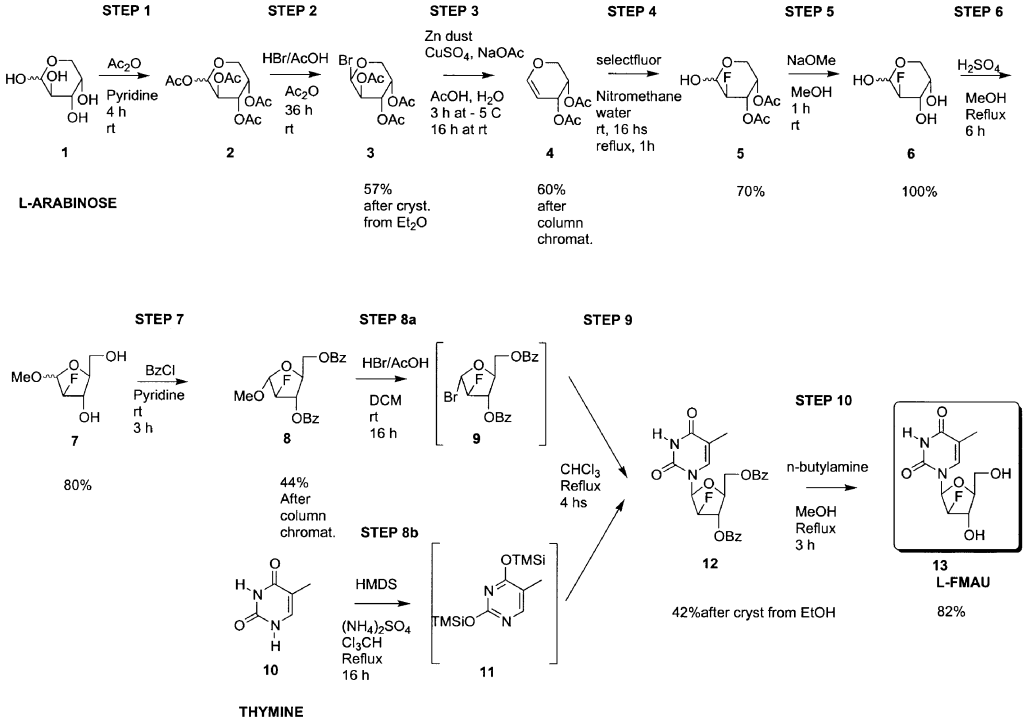
L-FMAU, originally reported by Chu and coworkers[6a] based on a previous synthesis of D-FMAU[6b], is one of the most promising agents against HBV. L-FMAU showed low toxicity in rats and woodchucks[7], potent in vivo antiviral activity against chronically infected woodchuck (WHV), respectable bioavailability in rats[8] and woodchucks[9], and showed no significant virus rebound up to 36 weeks after cessation of the drug treatment[10]. For these reasons an extensive effort was recently devoted to identifying an efficient and inexpensive synthesis of L-FMAU[6a,11–12].

Originally, L-FMAU (**13**, Scheme 1) was synthesized from L-ribose by Chu and coworkers[6a] adapting a synthetic method already published by Tann and coworkers[6b] for D-FMAU. Since L-ribose is an expensive and not readily available material, Chu and his coworkers developed a procedure for the synthesis of L-FMAU from L-xylose[11]. Finally the same group developed a synthesis from L-arabinose[12]. These processes either start from an expensive sugar (L-ribose or L-xylose) and/or involve very long synthetic routes (14 steps from L-arabinose and 14 steps from L-xylose). In addition they involve the use of a nucleophilic form of fluoride, like KHF_2 or Et_3N-3HF, which is difficult to handle and requires the activation of the hydroxyl group to be displaced. The instability of DAST prevents the use of this reagent on large



Scheme 1.

scale. The conversion of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-L-ribofuranose (TBAR) to 1,3,5-tri-O-benzoyl-β-L-ribofuranose also generates 2,3,5-tri-O-benzoyl-β-L-ribofuranose that has to be separated and reconverted to TBAR.

In pursuit of a better route we envisioned a synthetic procedure that involved two key steps (Scheme 1):

1 electophilic addition of a fluorine to the double bond of L-arabinal (easily accessible from commercially available L-arabinose) to afford compound **5**. There are several precedents in the literature for the addition of these electrophilic reagents to D-arabinal:

a Trifluoromethyl hypofluorite (CF_3OF)[13]. The inconvenience of this reagent is that the reaction must be run at $-78°C$ and gives a mixture of compounds that require separation by column chromatography.
b Acetyl Hypoflurite (CH_3COOF)[14]. This reagent is hard to handle. At $-78°C$ gives good stereoselectivity, but at room temperature the selectivity is poor.
c Selectfluor^{TM} (F-TEDA-BF_4)[15]. Selectfluor^{TM} is an easy to handle and inexpensive reagent that gives relatively good yield (68%) and selectivity (7:1) at room temperature.

Other reagents known to add to glycals are:

d Xenon difluoride (XeF_2)[16a-c], and
e Elemental fluorine (F_2)[17].

The last two reagents give poor yields and 1,2-difluoro products are difficult to hydrolyze.

2 Another key step of this synthesis is the conversion of the pyranose **6** to the methyl-furanoside **7** for which there is no precedent in the literature for either enantiomer.

RESULTS AND DISCUSSION

Peracetylated bromosugar **3** (Steps 1 and 2) was obtained as a solid, following a literature procedure[18], in 57% yield after crystallization from ether. The material was very unstable at room temperature and was used immediately or stored in a freezer. L-Arabinal (**4**, Step 3) was obtained as a syrup, according to a literature procedure[19], in 60% yield after column chromatography. Initial attempts to run the reaction under aprotic[20] conditions or in one-pot from L-arabinose[21] gave poor yields. Addition of Selectfluor^{TM} to L-arabinal (**4**, Step **4**) was done by a modification of a literature procedure[15] to afford compound **5** as a syrup in 70% yield. Traces of what could possibly be the L-ribo isomer were detected by ^{19}F-NMR (ratio L-arabino:L-ribo 30:1). The D-isomer of **5** was made by a similar

procedure[15]. Deacetylation (Step 5) was achieved with NaOMe in methanol in one hour at room temperature. The desired unprotected sugar **6** was obtained as an oil in 100% yield. ^{1}H-NMR and ^{13}C-NMR were in agreement with the ones described in the literature for the D-isomer[22a]. The D-isomer of **6** was previously made by three different groups, but in less efficient ways[13,22a,b]. Treatment of **6** (Step 6) with one equivalent of either sulfuric or hydrochloric acid at room temperature failed to give the desired furanoside. Only unreacted starting material was detected. Using nine equivalents of hydrochloric acid gave the desired product **7**, which was contaminated with starting material. The best result, so far, was achieved by refluxing **6** with **1** equivalent of sulfuric acid in dry methanol. After 6 hours, all of the starting material had disappeared affording **7** as an oil in 80% yield. ^{1}H-, ^{13}C- and ^{19}F-NMR indicated a 3:1 α:β mixture of anomers, with some minor impurities. The α-D[22b] and β-D[23] isomers of **7** were previously made by two different groups, but in less efficient ways. Benzoylation of crude **7** (Step 7) gave a mixture that was resolved by flash column chromatography to afford the α furanoside form of **8** as an oil in 44% yield. Other fractions were isolated and are being characterized. The same reaction was described[24] for the D-isomer. Wright et al.[24] partially describe the D-isomer of **8**: optical rotation and CHF, but no spectroscopic data was provided. The absolute value for the optical rotation was similar to the one described for the D-isomer: $[\alpha]_D^{20} = -98$ (c 1.0 EtOH) (lit.[24] $[\alpha]_D^{20} = +108$ (c 1.8 EtOH for the D-isomer).

Coupling of the methyl glycoside **8** with thymine (**10**) (Steps 8 and 9) under standard conditions[12] afforded the known di-O-benzoyl-L-FMAU (**12**) in 42% yield after crystallization from EtOH. The ^{1}H-NMR was identical to spectra described in the literature for the L[11,12]- and D-isomers[6b], and to a reference sample. The melting point (160°C) was identical to the reference sample but differed with the values published in the literature: 120–122°C for the D-isomer[6b] and 118–120°C for the L-isomer[11]. Debenzoylation of **12** (Step 10) was achieved with n-butylamine in refluxing methanol, reducing the reaction time to 3 hs in comparison to the 24 or 48 hs required when ammonia was used at room temperature[11,12]. Yield of L-FMAU (**13**) was 82%. Melting point: 188°C (lit.[12] mp 185–187°C, lit[11] 184–185°C, lit.[6b] 187–188°C) for the D-isomer; $[\alpha]_D^{20} = -93$ (c 0.25 MeOH) (lit.[11] $[\alpha]_D^{20} = -111$ (c 0.23 MeOH), lit.[12] $[\alpha]_D^{20} = -112$ (c 0.23 MeOH)); ^{1}H-NMR was identical to the ones described in the literature[6b,11,12] and to a reference sample.

Conclusions

In summary, we have achieved the first "true" synthesis of L-FMAU from L-arabinose in 10 steps. All the reagents and starting materials are inexpensive and no special equipment was required.

EXPERIMENTAL SECTION

General Methods

Melting points were determined in open glass capillaries by use of a Thomas-Hoover apparatus and were uncorrected. ^{1}H-NMR spectra were recorded at 400 MHz with a Varian XL-400 spectrometer. Hexafluorobenzene (δ: −163 ppm) was used as an internal standard for ^{19}F-NMR. Evaporations were performed under diminished pressure using a Buchi rotatory evaporator at 40°C unless otherwise indicated. Solutions were dried over anhydrous Na_2SO_4. TLC was performed on precoated glass plates (0.25 mm) with Silica Gel $60F_{254}$ (E. Merck, Darmstad). Flash column chromatography was performed with Silica Gel 60 (230–400 mesh, E. Merck, Darmstad). Elemental analyses were performed by Atlantic Microlab (Atlanta, GA).

1,2,3,4-Tetra-O-acetyl-L-arabinopyranose[18] (2). Acetic anhydride (360 mL, 388 g, 2.8 mol) was added slowly over a period of 30 min to a well stirred suspension of L-arabinose (**1**) (100 g, 0.67 mol) in dry pyridine (270 mL) at 0°C. The suspension was then stirred at room temperature for 4 hs after which it became a light brown colored solution. Excess pyridine and acetic anydride were removed by azeotropic evaporation with toluene. Crude **2** was obtained as a clear oil and was used in the next step without any further purification.

1-α-Bromo-2,3,4-tri-O-acetyl-L-arabinopyranose[18] (3). Crude tetra-O-acetyl-L-arabinopyranose (**2**) was dissolved in a mixture of 30% wt HBr in AcOH (400 mL, 2.0 mol) and acetic anhydride (8.0 mL). The solution was stirred at room temperature for 36 h. The reaction mixture was diluted with methylene chloride (400 mL) and successively washed with: water (3×600 mL), sat. $NaHCO_3$ (2×500 mL) and water (3×600 mL), dried, filtered and evaporated to a syrup that was crystallized from ethyl ether to afford **3** (129 g, 0.380 mol, 57% from **1**) as a white solid; ^{1}H-NMR ($CDCl_3$) δ: 6.67 (1H, d, J = 3.8, H-1), 5.37 (2H, m) and 5.06 (1H, m) (H-2, H-3 and H-4), 4.18 (1H, d, J = 13.3, H-5), 3.91 (1H, dd, J = 13.3 and J = 1.7, H-5′), 2.13 (3H, s, CH_3COO), 2.09 (3H, s, CH_3COO), 2.01 (3H, s, CH_3COO).

3,4-di-O-Acetyl-L-arabinal[18,19] (4). To a well stirred solution of NaOAc (35 g, 0.43 mol) and AcOH (115 mL) in water (200 mL) at −5°C, was slowly added a solution of $CuSO_4 \cdot 5H_2O$ (7 g, 28 mmol) in water (23 mL), and then Zn dust (70 g, 0.11 mol) in portions, maintaining the temperature at or below −5°C. Bromosugar **3** (34 g, 0.10 mol), was added to this suspension in portions and the mixture stirred vigorously for 3 hs at −5°C and then overnight at room temperature. The mixture was filtered and washed with water (250 mL) and methylene chloride (250 mL). The phases were separated,

and the aqueous layer washed with methylene chloride (2×125 mL). The combined organic layers were successively washed with: water (2×250 mL), sat. $NaHCO_3$ (2×1250 mL) and water (2×250 mL), dried, filtered, and evaporated to a colorless syrup (~ 20 g). The syrup was purified by flash column chromatography (300 g silica gel, hexane:EtOAc 4:1) to afford **4** (12.0 g, 60 mmol, 60%) as a colorless syrup; ^{1}H-NMR ($CDCL_3$) δ: 6.48 (1H, d, J = 6.0, H-1), 5.44 (1H, m, H-3), 5.19 (1H, dt, J = 4.0, J = 4.0, J = 9, H-4), 4.83 (1H, dd, J = 5.0, J = 6.0, H-4), 4.00 (2H, m, H-5 and H-5′), 2.08 (3H, s, CH_3COO), 2.07 (3H, s, CH_3COO).

3,4-di-O-Acetyl-2-deoxy-2-fluro-L-arabinopyranose (5). To a well stirred solution of glycal **4** (12.0 g, 60 mmol) in nitromethane:water (4:2, 120 mL) was added Selectfluor^{TM} (26 g, 73 mmol). The solution was stirred overnight at room temperature. The solution was then heated at reflux for 1 h to complete the reaction. After cooling to room temperature, the nitromethane was removed in vacuo. Water (150 mL) was added and extracted with EtOAc (3×150 mL). The combined organic fractions were successively washed with: 1N HCl (2×200 mL), and water (2×200 mL), dried, filtered, and evaporated to afford crude **5** (9.9 g, 42 mmol, 70%) as a syrup; ^{13}C-NMR ($CDCl_3$) δ: 170.35 (CH_3COO), 170.27 (CH_3COO), 95.01 (C-1α, d, $J_{C\text{-}1,F} = 24.5$), 90.81 (C-1β, d, $J_{C\text{-}1,F} = 21.5$), 89.10 (C-2α, d, $J_{C\text{-}2,F} = 184.3$), 85.85 (C-2β, d, $J_{C\text{-}2,F} = 188.0$), 70.61 (C-3α, d, $J_{C\text{-}3,F} = 19.5$), 69.57 (C-4β, d, $J_{C\text{-}4,F} = 7.7$), 68.66 (C-4α, d, $J_{C\text{-}4,F} = 8.3$), 67.53 (C-3β, d, $J_{C\text{-}3,F} = 17.8$), 63.90 (C-5α), 60.26 (C-5β), 20.73 (CH_3COO), 20.67 (CH_3COO), 20.62 (CH_3COO), 20.56 (CH_3COO). ^{19}F-NMR ($CDCl_3$) δ -205.61 (dd, J = 11.0 and J = 51.8, F-2α-anomer), -207.02 (dd, J = 9.0 and J = 49.0, F-2β-anomer).

Anal. Calcd. For $C_9H_{13}O_6F$: C, 45.77; H, 5.55. Found: C, 45.64; H, 5.51.

2-Deoxy-2-fluoro-L-arabinopyranose (6). A solution of **5** (5.7 g, 24.1 mmol) in dry methanol (220 mL) was treated with 0.1 N NaOMe in methanol (114 mL, 11.4 mmol) and stirred for 1 h at room temperature. The solution was then neutralized with DOWEX 50W X8-100, filtered and evaporated to afford crude **6** (3.7 g, 24 mmol, 100%) as a yellow syrup; ^{13}C-NMR (D_2O) δ: 94.19 (C-1α, d, $J_{C\text{-}1,F} = 23.0$), 92.24(C-2α, d, $J_{C\text{-}2,F} = 179.6$), 90.10 (C-1β, d, $J_{C\text{-}1,F} = 20.3$), 88.60 (C-2β, d, $J_{C\text{-}2,F} = 182.3$), 70.77 (C-3α, d, $J_{C\text{-}3,F} = 18.2$), 69.03 (C-4β, d, $J_{C\text{-}4,F} = 8.0$), 68.90 (C-4α, d, $J_{C\text{-}4,F} = 10.2$), 66.85 (C-3β, d, $J_{C\text{-}3,F} = 18.2$), 66.32 (C-5α), 62.21 (C-5β). ^{19}F-NMR (CD_3OD) δ -204.11 (dd, J = 12.6 and J = 51.7, F-2α-anomer), -206.45 (d, J = 47.3, F-2β-anomer).

1-O-Methyl-2-deoxy-2-fluoro-L-arabinofuranoside (7). A solution of **6** (790 mg, 5.2 mmol) and H_2SO_4 (60.1 μL, 1.1 mmol) in dry methanol (12.2 mL) was heated at reflux for 6 hs. The reaction was cooled to room temperature, neutralized with DOWEX SBR, filtered and evaporated to

afford crude **7** (700 mg, 4.21 mmol, 80%) as a syrup; ^{13}C-NMR (CD_3OD) δ: 107.48 (C-1α, d, $J_{C\text{-}1,F} = 35.6$), 103.20 (C-2α, d, $J_{C\text{-}2,F} = 178.8$), 101.98 (C-1β, d, $J_{C\text{-}1,F} = 16.8$), 96.80 (C-2β, d, $J_{C\text{-}2,F} = 199.3$), 85.15 (C-4α, d, $J_{C\text{-}3,F} = 5.0$), 83.69 (C-4β, d, $J_{C\text{-}4,F} = 10.7$), 76.70 (C-3α, d, $J_{C\text{-}4,F} = 27.0$), 74.54 (C-3β, d, $J_{C\text{-}3,F} = 21.5$), 65.00 (C-5β), 62.52 (C-5α). 55.58 (OCH_3 β), 54.94 (OCH_3 α). ^{19}F-NMR (CD_3OD) δ -189.97 (ddd, J = 12.0, J = 26.0 and J = 51.0, F-2α-anomer), -207.83 (dd, J = 19.0 and J = 50.0, F-2β-anomer).

1-O-Methyl-2-deoxy-2-fluro-3,5-di-O-benzoyl-L-arabinofuranoside (8). To a well stirred solution of **7** (664 mg, 4 mmol) in dry pyridine (10 mL) at 0°C, benzoyl chloride (2.5 mL, 3.0 g, 21.5 mmol) was added slowly. After stirring for 30 min at 0°C, it was left at room temperature for 3 hs. The reaction was quenched with water (10 mL) and sat. $NaHCO_3$ (30 mL) and stirred for 30 min. It was then diluted with methylene chloride (50 mL) and more sat. $NaHCO_3$ (30 mL). The organic layer was separated and successively washed with: sat. $NaHCO_3$ (50 mL), water (2 × 50 mL), 1N HCl (2 × 50 mL), water (50 mL), sat. $NaHCO_3$ (50 mL) and water (2 × 50 mL), dried, filtered and evaporated to a brown syrup (1.9 g), that was purified by flash column chromatography (50 g silica gel, hexane:EtOAc 95:5). A major fraction was isolated as a syrup and characterized as **8** (α anomer, 670 mg, 1.79 mmol, 44%); $[\alpha]_D^{20} = -98$ (c 1.0 EtOH) (lit.[24] $[\alpha]_D^{20} = +108$ (c 1.8 EtOH for the D-isomer); ^{1}H-NMR ($CDCl_3$) δ:8.20–7.40 (15 H, m, ArH), 5.48 (1H, dd, J = 5.0, J = 23.1, H-3), 5.21 (1H, d, J = 10.6, H-1), 5.11 (1H, d, J = 49.2, H-2), 4.76 (1H, dd, J = 3.6 and J = 12.0, H-5), 4.63 (1H, dd, J = 4.4 and J = 12.0, H-5′), 3.45 (3H, s, OCH_3); ^{13}C-NMR ($CDCl_3$) δ 166.20 (C=O), 165.67 (C=O), 133.57 (Ar), 133.07 (Ar), 129.87 (Ar), 129.76 (Ar), 128.49 (Ar), 128.31 (Ar) 106.22 (C-1, d, $J_{C\text{-}1,F} = 35.1$), 98.20 (C-2, d, $J_{C\text{-}2,F} = 182.7$), 80.85 (C-4), 77.58 (C-3, D, $J_{C\text{-}3,F} = 30.4$), 63.62 (C-5), 54.86 (OCH_3); ^{19}F-NMR ($CDCl_3$) δ -191.70 (ddd, J = 10.0, J = 23.0 and J = 50.0, F-2α-anomer).

Anal. Calcd. For $C_{20}H_{19}O_6F$: C, 64.17; H, 5.12. Found: C, 64.14; H, 5.08.

1-(3′,5′-di-O-Benzoyl-2′-deoxy-2′-fluoro-β-L-arabinofuranosyl)thymine[11] (12). To a well stirred solution of **8** (1.31 g, 3.5 mmol) in dry methylene chloride (2.6 mL) at 0°C, was slowly added 30% wt HBr in AcOH (3.7 mL, 5.1 g, 1.5 g of HBr, 18.6 mmol). The solution was then stirred at room temperature overnight. The brown-red solution was evaporated under vacuum at or below 40°C. It was then coevaporated with dry benzene (3 × 3 mL) and then once with dry chloroform (3 mL). Bromosugar **9** was obtained as a syrup, which was redissolved in dry chloroform (4 mL): solution A.

At the same time a mixture of thymine (**10**, 971 mg, 7.7 mmol), ammonium sulfate (89 mg), and 1,1,1,3,3,3-hexamethyldisilazane (3.7 g, 4.9 mL, 23.0 mmol) in dry chloroform (33.0 mL) was heated at reflux overnight. The resulting clear solution, (an indication that all the thymine

was silylated to form compound **11**) was cooled to room temperature: solution B.

Solution A was added to solution B and heated at reflux for 4 hs. The reaction was quenched with MeOH (2 mL). A precipitate appeared and the suspension was further stirred for 1 h at room temperature. The solids were filtered through celite and washed with chloroform. The organic phase ($\sim$100 mL) was washed with water (100 mL), $NaHCO_3$ (100 mL) and water (2×100 mL), dried, filtered and evaporated to a solid. It was crystallized from EtOH to afford pure **12** (700 mg, 1.5 mmol, 42%) as a white solid; mp 160°C was identical to an original sample of **12** (lit[6b] 120–122 C for the D-isomer and 118–120°C for the L-isomer[11]); ^{1}H-NMR ($CDCl_3$) δ: 8.52 (1H, bs, N-H), 8.13–7.43 (10H, m, ArH), 7.36 (1H, q, J = 1, C-H thymine), 6.35 (1H, dd, J = 3.0 and J = 22.2, H-1), 5.64 (1H, dd, J = 3.0 and J = 18.0, H-3), 5.32 (1H, dd, J = 3.0 and J = 50.0, H-2), 4.86–4.77 (2H, m, H-5 and H-s′), 4.49 (1H, q, H-4), 1.76 (3H, d, J = 1.0, Thymine CH_3).

1-(2′-Deoxy-2′-fluoro-β-L-arabinofuranosyl)thymine[11,12] (13). A solution of **12** (700 mg, 1.5 mmol) and n-butylamine (55 g, 7.5 mL, 75 mmol) in methanol (15 mL) was heated at reflux for 3 hs. The solution was evaporated to dryness, coevaporated three times with EtOAc and finally suspended in EtOAc, filtered and dried to afford **13** (320 mg, 1.23 mmol, 82%) as a white solid; mp: 188°C (lit.[12] mp 185–187°C, lit[11] 184–185°C, lit.[6b] 187–188°C for the D-isomer); $[\alpha]_D^{20} = -93$ (c 0.25 MeOH) (lit.[11] $[\alpha]_D^{20} = -111$ (C 0.23 MeOH), lit.[12] $[\alpha]_D^{20} = -112$ (c 0.23 MeOH)); ^{1}H-NMR (DMSO-d_6) δ 11.0 (1H, bs, N-H), 7.58 (1H, s, C-H thymine), 6.09 (1H, dd, J = 4.2 and J = 15.6, H-1), 5.85 (1H, bs, OH), 5.10 (1H, bs, OH), 5.02 (1H, dt, J = 4.0, J = 3.8 and J = 52.8, H-2), 4.22 (1H, dt, J = 3.8, J = 4.0 and J = 20.3, H-3), 3.76 (1H, q, J = 4.0 and J = 9.5, H-4), 3.69–3.57 (2H, m, H-5 and H-5′), 1.77 (3H, s, Thymine CH_3).

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