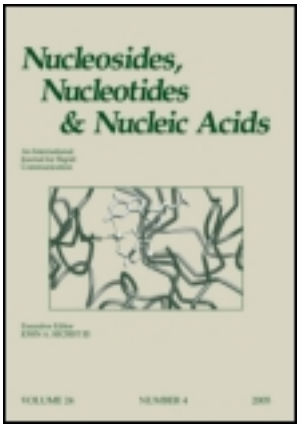

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A PRACTICAL SYNTHESIS OF L-FMAU FROM L-ARABINOSE

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ABSTRACT: A practical synthesis of 2'-deoxy-2'-fluoro-5-methyl-β-L-arabinofuranosyl uracil (**14**, L-FMAU) was developed from L-arabinose. L-Arabinose was converted to L-ribose **5**, which was used for the synthesis of bromosugar **12** *via* 2,3,5-*O*-tribenzoyl-1-*O*-acetyl-β-L-ribofuranose **8**, which was subjected to condensation with silylated thymine and the resulting protected L-FMAU **13** was deprotected to afford L-FMAU in 14 steps in 8 % overall yield.

INTRODUCTION

As hepatitis B virus (HBV) is known to be a major cause of chronic liver disease, leading to cirrhosis and hepatocellular carcinoma,[1] for the past several years significant efforts have been focused on the development of chemotherapeutic agents. Although safe and effective vaccines are available for prevention of HBV infection, over 350 million people worldwide are chronically infected with HBV. Currently, only interferon α-2b was approved by the Food and Drug Administration for the treatment of chronic HBV infection. The usefulness of interferon α-2b was, however, limited due to side effects and marginal efficacy.[2] In the search for safe and clinically effective agents for the treatment of HBV infection, a number of nucleosides have been recently reported as potent and promising anti-HBV agents, such as lamivudine (3TC),[3] famciclovir,[4] DAPD,[5] L-FMAU,[6] and BMS200475.[7]

L-FMAU was reported by Chu *et al.* as a potent antiviral agent against HBV (EC_{50} 0.1 μM in 2.2.15 cells).[6] In contrast to its D-enantiomers, L-FMAU did not interfere with the mitochondrial functions and showed no bone marrow toxicity up to 100 μM *in vitro*. In preliminary *in vivo* toxicity studies in mice for 30 days (50 mg/kg/day) as well as in

woodchucks for 3 months (10 mg/kg/day), L-FMAU did not show any apparent toxicities as well as no significant abnormalities of clinical chemistry were observed.[8] Furthermore, L-FMAU exhibited potent *in vivo* antiviral activity against chronically infected woodchuck hepatitis virus (WHV) and showed respectable bioavailability in rats[9] and in woodchucks.[10] Additionally, L-FMAU did show no significant virus rebound up to 36 weeks after cessation of the drug treatment.[11] These outstanding features of L-FMAU make it one of the promising clinical candidates for the treatment of chronic HBV infections.

Originally, L-FMAU has been synthesized from L-ribose adapting a synthetic method for D-FMAU.[11] In order to prepare L-ribose, Chu and his coworkers developed a procedure for the synthesis of L-ribose from L-xylose.[13] However, the commercial cost of L-ribose and L-xylose hampered the synthesis of a large quantity of L-FMAU for preclinical studies. Therefore, it was necessary to develop a more efficient method for additional biological evaluations. Furthermore, the emergence of L-nucleosides in medicinal applications has demanded readily available intermediates, such as 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose, which is not commercially available.[14] Herein, we wish to report a practical synthesis of L-FMAU from L-arabinose, in which we describe the preparation of L-ribose derivative from L-arabinose in a large scale.

The key strategy for the synthesis of L-FMAU was centered on the inversion of the 2-hydroxy group of L-arabinose to obtain the requisite ribo-configuration. Although several group reported the synthesis of L-ribose derivative by the inversion of 2-hydroxy group of L-arabinose,[15] it was not satisfactory for a large scale synthesis. Ballou reported the synthesis of D-erythrose from D-arabinose *via* benzyl 3,4-*O*-isopropylidene-β-D-arabinoside.[16] This benzyl isopropylidene protection was found to be suitable for a stereoselective hydride transfer during the reduction of **3** with $NaBH_4$.

Therefore, L-arabinose was treated with benzyl alcohol and HCl gas to give benzyl-β-L-arabinoside (**1**) in 94 % yield and 3- and 4-hydroxy groups were protected with dimethoxy propane (DMP) in the presence of *p*-TsOH to yield benzyl 3,4-*O*-isopropylidene-β-L-arabinoside (**2**). The benzyl arabinoside **2** was subjected to oxidation with pyridnium dichromate (PDC) in refluxing CH_2Cl_2 followed by reduction with $NaBH_4$ in MeOH at 0 °C to give the key intermediate **4** in 53 % yield in three steps. Compound **4** was deprotected by 4% CF_3CO_2H to afford L-ribose (**5**), which, without isolation, was treated successively with 1% HCl-MeOH, BzCl-pyridine and then Ac_2O-AcOH-H_2SO_4 to give 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (**8**) as a crystalline product in 40 % yield in four steps.[17]

The ribose derivative **8** was treated with saturated hydrogen chloride in CH_2Cl_2 at 0 °C followed by hydrolysis/migration to give 1,3,5-tri-*O*-benzoyl-α-L-ribofuranose (**9**) in 64 % yield, which was treated with SO_2Cl_2 and imidazole in DMF-CH_2Cl_2 to give the

imidazoyl sulfonate **10**. Without further purification, the imidazole derivative **10** was used in fluorination with HF·3TEA to yield 1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro-α-L-arabinofuranose (**11**).[18] Bromination of the key intermediate **11** with HBr-AcOH gave a bromosugar derivative **12**, which was condensed with silylated thymine in $CHCl_3$ under refluxing conditions to give the protected L-FMAU **13** in 69.5 % yield from **9**. Deprotection of **13** with methanolic ammonia afforded the final product **14** in 88.2 % yield (SCHEME 1).

In summary, we have developed an efficient and practical procedure for L-ribose derivative and L-FMAU in 8% overall yield from L-arabinose, which can be readily adaptable for the synthesis of other L-nucleosides.

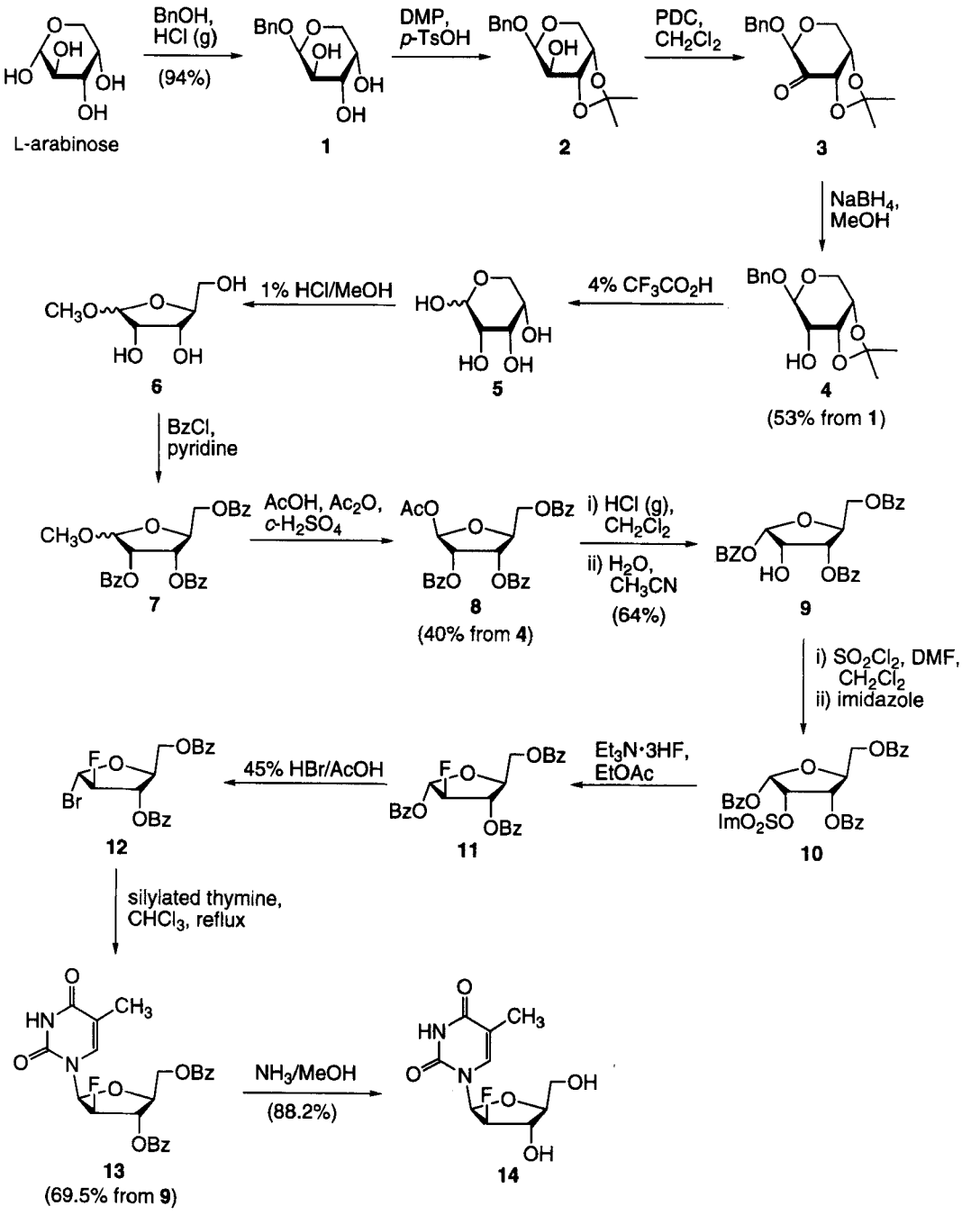
EXPERIMENTAL

Melting points were determined on a Mel-temp II and are uncorrected. ^1H NMR spectra were recorded on a Bruker 400 MHz spectrometer with Me_4Si as internal standard; chemical shifts are reported in parts per millon (δ), and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). UV spectra were obtained on a Beckman DU-7 spectrometer. Optical rotations were measured on a Jasco DIP-370 Digital Polarimeter. TLC was performed on Uniplates (Silica gel) purchased from Analtech Co. Column chromatography was performed using MN-Kieselgel G (TLC grade, 2-20 μm) for vacuum flash chromatography and Baker silica gel (40 μm) for flash chromatography. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

1-*O*-Benzyl-β-L-arabinoside (1). Benzyl alcohol (1000 mL) was saturated with hydrogen chloride for 40 min at 0 °C and to which L-arabinose (200 g, 1.33 mol) was added and the mixture was stirred at room temperature for 10 h. During these periods compound **1** precipitated. EtOAc (1.5 L) was slowly added with stirring for an additional precipitation. Filteration of the resulting solid, washing with EtOAc and drying in air gave compound **1** as a white solid (300 g, 94%), which was used in next step without further treatment.

1-*O*-Benzyl-3,4-*O*-isopropylidene-β-L-riboside (4). A mixture of 1-*O*-benzyl-β-L-arabinoside (**1**) (200 g, 0.83 mol), 2,2-dimethoxypropane (240 mL, 1.95 mol) and *p*-TsOH·H_2O (4 g, 0.02 mol) in acetone (2000 mL) was stirred at room temperature for 2 h. The reaction mixture was then neutralized with triethylamine and evaporated under reduced pressure to give compound **2** as a yellowish syrup, which was used for the next reaction without further purification.

To a mixture of compound **2** and pyridinium dichromate (240 g, 0.63 mol) in CH_2Cl_2 (2000 mL), Ac_2O (240 ml, 2.54 mol) was added at 0 °C and then the mixture was refluxed



SCHEME 1

until the starting material disappeared (ca. 4 h). The solvents were removed under reduced pressure to an 1/3 of the original volume and the residue poured into EtOAc (1500 mL) with vigorous stirring using mechanical stirrer, which was then filtered through a Celite pad. The filter cake was thoroughly washed with EtOAc. The blackish combined filterate was filtered again through a silica gel (2-20 micron) column (20 cm height, 10 cm in diameter). The silica gel was washed with EtOAc until no more compound **3** was detected on TLC. The combined clear filterate was evaporated to give compound **3** as a syrup, which was coevaporated twice with toluene. The syrup was dissolved in 2000 mL of methanol and cooled to -20 °C. To the resulting solution, $NaBH_4$ (40 g, 1.06 mol) was very slowly added over 3 h at -20 °C. After completion of the reaction, the solution was neutralized with acetic acid and evaporated under reduced pressure to give a white solid, which was partitioned between EtOAc (1000 mL) and water (200 mL). The aqueous layer was extracted with EtOAc (100 mL). The combined organic layer was washed with brine (200 mL), dried ($MgSO_4$), and then evaporated to yield a white solid, which was recrystallized from hot hexane (700 mL) to give compound **4** (123g, 50% from **1**) as white crystals: mp 79-80 °C; $[\alpha]^{27}_D$+126.5° (c 0.87, EtOH); ^{1}H NMR δ (ppm) 7.26-7.36 (m, 5H, Ar), 4.85 (d, 1H, J = 7.99 Hz, H-1), 4.82 (d, 1H, J = 12.1, $PhCH_2$-), 4.56 (d, 1H, J = 12.1 Hz, $PhCH_2$-), 4.50 (dd, 1H, J = 8.10 Hz, H-2), 4.27 (m, 1H, H-3), 3.86 (dd, 1H, J = 3.44, 12.9 Hz, H-5), 3.74 (dd, 1H, J = 3.31, 12.9 Hz, H-5), 3.73 (m, 1H, H-4), 1.55 (s, 3H, $-CH_3$), 1.37 (s, 3H, $-CH_3$); Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27, H, 7.12. Calcd for $C_{15}H_{20}O_5$: C, 64.16, H, 7.12.

1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (8). Compound **4** (201 g, 0.717 mol) in 4% CF_3CO_2H (1000 mL) was refluxed until the starting material (ca. 1 h) and the intermediate (1-*O*-benzyl derivative) were disappeared (ca. 4-8 h). The reaction mixture was cooled to rt and washed with CH_2Cl_2 (4 x 500 mL) to remove benzyl alcohol. The aqueous layer was evaporated *in vacuo* and coevaporated with toluene (2 x 200 mL) to give compound **5** as a yellowish syrup, which was completely dried under high vacuum to remove trace amounts of water.

Compound **5** was treated with 1% HCl in methanol (2000 mL) and then stirred at rt for 2 h. The mixture was neutralized with pyridine (183 mL) and concentrated *in vacuo* at 30-35 °C to give a yellowish syrup, which was coevaporated with pyridine to yield compound **6** as a yellowish syrup. Compound **6** was dissolved in pyridine (800 mL) and benzoyl chloride (212 mL) was added dropwise at 0 °C, which was stirred at rt for 8 h. After the reaction was almost completed, the mixture was heated at 45 °C and for 1.5 h and the mixture was cooled to rt. Excess of pyridine was removed *in vacuo* at 35-40 °C and the residue was dissolved in EtOAc (1500 mL), which was successively washed with cold H_2O (500 mL), cold 3 N H_2SO_4 (576 mL), sat. $NaHCO_3$ (2 x 500 mL), and then brine

(500mL). The organic layer was dried ($MgSO_4$ and activated carbon), filtered through a silica gel (2-20μ) pad and evaporated to afford compound **7** as a yellowish syrup.

To a solution of **7** in acetic acid (144 mL, 2.52 mol) and acetic anhydride (334 mL, 3.54 mol), *c*-H_2SO_4 (48 mL, 0.9mol) was slowly added dropwise at 0 °C, during which crystals precipitated. In order to induce additional crystallization, the mixture was kept in a refrigerator overnight. The resulting mixture was poured into an ice-water (700 mL) mixture, filtered and the filter cake was twice washed with cold water. The solid was dissolved in EtOAc (2000 mL), which was washed with water (500 mL), sat. $NaHCO_3$ (500 mL) and brine (500 mL). The organic layer was dried ($MgSO_4$ and activated carbon) and filtered through a silica gel (2-20μ) pad. Removal of the solvent and recrystallization of the residue from methanol gave compound **8** as a crystal (144.7 g, 40% from compound **4**): mp 124-125 °C (lit.[13] mp 124-125 °C); $[\alpha]^{25}_D$ -22.1° (*c* 1.0, pyridine) [lit.[13] $[\alpha]_D$-45.6 (*c* 1.0, $CHCl_3$); D-enantiomer $[\alpha]_D$ +24.3 (*c* 1.0, pyridine)]; ^1H NMR ($CDCl_3$) δ (ppm) 8.09-7.32 (m, 15H, Ar-H), 6.43 (s, 1H, H-1), 5.91 (dd, 1H, J = 4 Hz, H-3), 5.79 (d, 1H, J = 8 Hz, H-2), 4.81-4.76 (m, 2H, H-4 and H-5), 4.54-4.49 (m, 1H, H-5), 2.00 (s, 3H, CH_3COO).

1,3,5-Tri-*O*-benzoyl-α-L-ribofuranose (9). HCl (gas) was bubbled into a solution of compound **8** (50 g, 99.16 mmol) in anhydrous CH_2Cl_2 (460 mL) and AcCl (7.5 mL) at 0 °C for 1.5 h. The resulting solution was kept in a refrigerator for 12 h and then evaporatored in vacuo. The residue was coevaporated with toluene (3 x 150 mL) at 45 °C and redissolved in CH_3CN (105 mL). To the stirred solution, water (13 mL) was added dropwise at 0 °C. After 30 min., white solids precipitated, which was kept in a refrigerator for 2 h to induce additional precipitation. After filtration of the resulting solid, the filter cake was carefully washed with cold diethyl ether. The white solid obtained was dissolved in EtOAc. The solution was washed with sat. $NaHCO_3$ to remove remaining HCl and then dried ($MgSO_4$). Filtration and removal of the solvent gave compound **9** as a white solid (29.2 g, 63.7%): mp 137-139 °C; $[\alpha]^{20}_D$ –82.01° (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm) 7.31, 8.19 (m, 15H, Ar-H), 6.69 (d, 1H, J = 4.6 Hz, H-1). 5.59 (dd, 1H, J = 6.7, 1.8 Hz, H-3), 4.64, 4.80 (m, 4H, H-2, H-4, and H-5), 2.30 (br s, D_2O exchangable, OH).

1,3,5-Tri-*O*-benzoyl-2-*O*-imidazolylsulfonyl-α-L-ribofuranose (10). Compound **9** (107.0 g, 0.232 mol) was dissolved in CH_2Cl_2 (1070 mL) and DMF (214 mL). To the solution, SO_2Cl_2 (0.463 mol, 62.5 g, 37.2 mL) was added dropwise at low temperature (-10 to -78 °C). The resulting solution was stirred at rt for 3 h, which was then cooled in ice-bath. To the solution with efficient stirring, imidazole (2.32 mol, 157.8 g) was added portionwise at the rate keeping the temperature of reaction mixture under 5 °C. The resulting mixture was stirred at rt for 20 h and ice-water (400 mL) was added.

Aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic solution was washed with brine (200 mL) and dried ($MgSO_4$). Solvent was removed under reduced pressure and DMF under high vaccum. The residue (syrup) was coevaporated with 2-propanol (100 mL) under reduced pressure to give white solid **10**, which was used for the next reaction without further purification.

1-(3,5-Di-*O*-benzoyl-2-fluoro-β-L-arabinofuranosyl)thymine (13). A mixture of the imidazolate derivative **10** obtained above, $Et_3N{\cdot}3HF$ (224.1 g, 1.39 mol) and EtOAc (824 mL) was heated at 80 °C for 3 h. Et_3N (0.696 mol, 70.3 g, 92.5 ml) was then slowly added to the mixture and stirred for additional 1 h at the same temperature, after which the mixture was cooled to rt. The resulting solution was poured into ice-water containing $NaHCO_3$ to neutralize to pH 7. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic solution was washed with brine and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was redissolved in CH_2Cl_2 (300 mL), filtered through silica gel pad, and washed with CH_2Cl_2. The solvent was removed to give crude 2-fluoro-sugar **11** (101.0 g), which was redissolved in CH_2Cl_2 (150 mL). To the solution, HBr/AcOH (45% w/v, 1.09 mol, 88.2 g, 195.9 mL) was added at 0 °C and stirred at rt for 15 h. Evaporation of the resulting solution to dryness under reduced pressure gave a syrup which was coevaporated with toluene (3 x 100 mL) to obtain the sugar bromide **12** as a semisolid, which was redissolved in $CHCl_3$ (200 mL) for the condensation described below:

A mixture of thymine (0.44 mol, 55.44 g), $(NH_4)_2SO_4$ (5 g) and HMDS (1.32 mol, 212.5 g, 278.9 ml) in $CHCl_3$ (1900 mL) was refluxed for 24 h to give a near clear solution. To the solution, a solution of sugar bromide **12** in $CHCl_3$ was added and refluxed for additional 24 h. The resulting mixture was cooled to rt. H_2O (200 mL) was added to the reaction mixture, stirred at rt for 30 min and filtered. Organic layer was separated, dried (Na_2SO_4), and filtered through a Celite pad which was washed with EtOAc. The combined organic solution was evaporated to give a solid which was recrystallized from EtOH (100 mL) to obtain 3',5'-*O*-dibenzoyl L-FMAU **13** (78.0 g, 69.5 % from the alcohol **9**) as a crystal: UV (MeOH) λ_{max} 264.0 nm; ^1H NMR ($CDCl_3$) δ (ppm): 8.55 (s, NH), 8.12-7.37 (m, 11H, Ar), 6.35 (dd, 1H, J_{F-H} = 22.4 Hz, H-1'), 5.64 (dd, 1H, J_{F-H} = 20.4 Hz, H-3'), 5.32 (dd, J_{F-H} = 50.2 Hz, H-2'), 4.82 (m, 2H, H-5), 4.50 (m, 1H, H-4'), 1.76 (s, 3H, CH_3).

1-(2-Fluoro-β-L-arabinofuranosyl)thymine (14). To a suspension of **13** (83.0 g, 0.18 mol) in methanol (1000 ml), NH_3 gas was bubbled for 2-3 h to obtain a clear solution which was stirred at rt for additional 48 h. The solvent was removed under reduced pressure and the residue was triturated with Et_2O. The resulting solid was collected by filtration, redissolved in methanol (500 ml) and decolorized with charcoal twice. Methanol

was removed and the resulting solid was recrystallized from hot acetonitrile to give final **14** as a crystal (40.58 g, 88.2%): mp 185-187 °C (lit.[13] mp 184-185 °C); $[\alpha]^{20}_{D}$ -112.06° (*c* 0.23, MeOH) [lit.[13] $[\alpha]_{D}$ -111.77 (*c* 0.23, CH_3OH)]; UV (H_2O) λ_{max} 265.0 (ε 9695) (pH 2), 265.5 (ε 9647) (pH 7), 265.5 nm (ε 7153) (pH 11); ^{1}H NMR (DMSO-d_6) δ (ppm): 11.45 (s, NH), 7.59 (s, 1H, H-6), 6.10 (dd, 1H, J_{F-H} = 15.4 Hz, H-1'), 5.88 (d, 1H, 3'-OH), 5.13 (t, 1H, 5'-OH), 5.04 (dt, 1H, J_{F-H} = 52.8 Hz, H-2'), 4.22 (dq, 1H, J_{F-H} = 18.4, Hz, H-3'), 3.76 (m, 1H, H-4'), 3.63 (m, 2H, H-5'), 1.78 (s, 3H, CH_3).

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