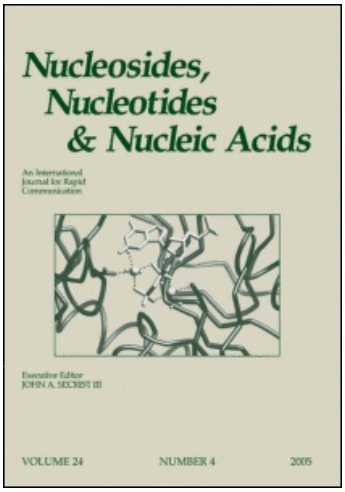

Nucleosides, Nucleotides and Nucleic Acids

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Asymmetric Synthesis of 4'-Methyl-2',3'-dideoxynucleosides

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ASYMMETRIC SYNTHESIS OF 4'-METHYL-2',3'-DIDEOXYNUCLEOSIDES[1]

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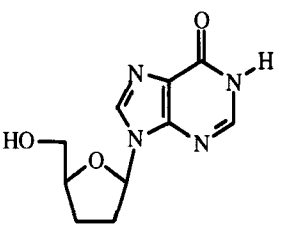
Abstract: The stereoselective preparation of a 4-methyl-2,3-dideoxyribose derivative is described which utilizes (–)-menthyl pyruvate as a chiral template and an organocerium addition as the key carbon-carbon bond-forming step. The 4-methyl-2,3-dideoxyribose derivative was used as a substrate for a Vorbrüggen pyrimidine glycosylation giving an α,β-mixture of 4'-methyl-2',3'-dideoxynucleosides.

Among the leading compounds used for antiviral therapy, dideoxynucleosides and their derivatives remain at the forefront.[2a-d] Nucleosides such as ddI (**1**), ddC (**2**) and 3TC (**3**), which have been approved for clinical use,[2e] interfere with replication of the viral genome by chain termination. The generation of new classes of nucleosidic antivirals based on the 2,3-dideoxyribose component may involve skeletal modifications of the ribose ring. Such modifications may require the incorporation of alkyl groups so as to alter the conformation of the ribose moiety or adjust the lipophilicity of the entire nucleoside. There have been recent reports of the synthesis and evaluation of 4'-alkyl-2',3'-dideoxynucleosides,[3a] 4'-acyl-2'- and 4'-alkyl-2'-deoxynucleosides[3b,d] as potential antiviral agents.[4] These reports have prompted us to disclose our results in connection with the synthesis of 4'-methyl-2',3'-dideoxynucleoside **4**.



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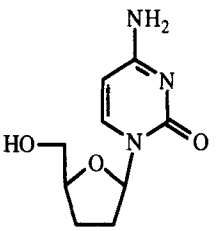

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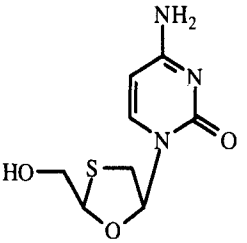

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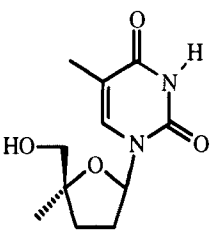
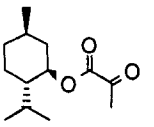


4

Our route to the 4-alkyl-2,3-dideoxyribose system employed (–)-menthyl pyruvate **5**[5] as a chiral template through which the stereochemistry at C-4 is developed. The Büchi-Wüest Grignard **6**,[6,7] derived from the corresponding bromide under ultrasonic conditions (THF/0°C), was treated with an ultrasonically-prepared suspension of dry cerium trichloride (–78°C/THF).[8] Chemoselective addition of the resultant organocerium reagent (–78°C) to ketoester **5** furnished (–)-menthyl hydroxyester **7** (81%) after quenching with aqueous ammonium chloride, extractive workup and flash-column chromatography. Mosher ester[9] derivative **9** was prepared by reductive hydrolysis of **7** ($LiAlH_4/Et_2O$) followed by direct treatment of the resultant diol **8** with (+)-MTPA-Cl (CH_2Cl_2/DMAP). The ^{19}F NMR of the derived MTPA ester **9** showed a single enantiomer as characterized by an ^{19}F peak at 4.52 ppm. The acid-catalyzed transacetalization of the menthyl hydroxyester **7** to produce the menthyl ester glycoside **10a** proved to be somewhat problematic. Exposure of **7** to aqueous acetic acid (80%) followed by removal of the volatile components and direct treatment with fresh saturated methanolic HCl (rt/1h) provided the expected α,β anomeric mixture of methyl glycosides **10a** accompanied by **10b**, a product of appreciable racemization at C-4.[10] Reduction of **10a/10b** with lithium aluminum hydride (ether/rt) followed by a silica gel quench and Mosher ester derivatization with (+)-MTPA-Cl (CH_2Cl_2/DMAP) to produce **11** confirmed complete racemization as evidenced by ^{19}F NMR. An improved procedure for the transacetalization involved treatment of **7** with BF_3 etherate in ether/methanol (1:1) at 0°C and gave the α,β anomeric mixture of methyl dideoxyribosides **10a/10b** (2:1) in 76% chemical yield. Reduction of the ribosides ($LiAlH_4$/ether/rt) followed by direct treatment with benzoyl chloride/DMAP (CH_2Cl_2/rt) furnished the α,β mixture of methyl (5-O-benzoyl)-2,3-dideoxyribosides **12** (92%). Vorbrüggen reaction of **12** with freshly prepared 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine in the presence of freshly distilled *tert*-butyldimethylsilyl triflate (CH_3CN/0°-25°C/2h) provided the anomeric mixture of 5'-O-benzoyl thymidines **13** (81%)



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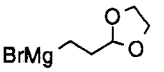

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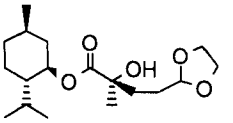

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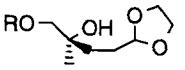
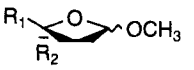
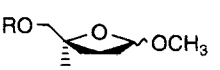


8, R=H
9, R=(+)-MTPA



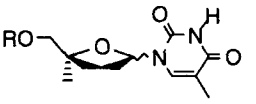
10a, R_1=COO-menthyl
R_2=CH_3
10b, R_1=CH_3
R_2=COO-menthyl



11, R=(+)-MTPA
12, R=benzoyl

after basic quench (aqueous $NaHCO_3$), extraction and silica gel column chromatography. Removal of the benzoyl ester function of **13** was facilitated by treatment with methanolic sodium hydroxide (2h/rt) and thus afforded the chromatographically-separable (silica gel, CH_2Cl_2/acetone, 2:1) α-

(39%) and β-(55%) nucleosides **4**.[12] Derivatization [(+)-MTPA-Cl/CH_2Cl_2/DMAP/30min/rt] of **4**-β and ^{19}F NMR of the resultant Mosher ester derivative **14** revealed a 2:1 mixture of enantiomeric nucleosides (^{19}F δ 4.60/4.97 ppm).



13, R=benzoyl
14, R=(+)-MTPA
4, R=H

In conclusion, we have detailed a stereoselective route to 4'-methyl-2',3'-dideoxythymidine **4** which is based on both chiral auxiliary methodology and the chemoselectivity provided by the addition of organocerium reagents to α-ketoesters. By varying the nature of the chiral auxiliary, either antipode of the 4-methyl-2,3-dideoxyribose system should become available. Based on Whitesell's[13] model involving diastereoselective Grignard additions to 8-phenylmenthyl glyoxalate esters, we expected an organocerium addition to operate in a similar mode with (–)-menthyl substrate to give *S*-**7**. The mode of addition was confirmed by conversion to **4**β. Although one would expect lower de's with Grignard additions to menthyl pyruvates as opposed to the 8-phenylmenthyl analogues, a more comparable selective addition in the case of the menthyl analogue may be the result of reagent control[8a,14] promoted by the coordination sphere of the organocerium reagent. Although the formation of anomers during the Vorbrüggen reaction is a result of the absence of a 2-directing group, work is currently underway to incorporate a directing group in a Büchi-Wüest type fragment.

EXPERIMENTAL

General. ^1H NMR spectra were recorded on a Bruker AMX-500 instrument. ^{13}C and ^{19}F NMR spectra were recorded on a Varian XL-300 instrument. All NMR experiments employed $CDCl_3$ as solvent and internal standard except ^{19}F NMR experiments where TFA was used as an external standard. Infrared spectra were recorded with a Mattson Galaxy Series 5000 FT instrument (KBr) and are expressed in cm^{-1}. THF and ether were distilled from Na/benzophenone ketyl. CH_3CN, xylenes and CH_2Cl_2 were distilled from CaH_2. All other solvents were ACS reagent grade and used as commercially available. Flash chromatography was carried out using silica gel (E. Merck 9385, 230-400 mesh). Thin-layer chromatography was performed on silica gel plates (E. Merck 5715) and was visualized with UV light and anisaldehyde stain. Celite filtrations were performed with Johns Manville Celite 521. Filtrates and chromatographic fractions were concentrated under vacuum using a standard rotary evaporator. Optical rotations were recorded with a Jasco DIP 370. Ultrasonic experiments employed a Sonics and Materials Vibra-Cell 300W system with a 1/4" titanium probe (20 kHz).

(-)-Menthyl-4-(1,3-dioxolane-2-yl)-2-hydroxy-2-methylbutanoate (7): $CeCl_3x7H_2O$ (1.0 g, 2.69 mmol) was ground to a powder and gradually heated to 140°C under vacuum

(0.025 torr). Heating at this temperature was continued for 3 h. The resulting gray powder was suspended in THF (20 mL) under argon atmosphere and subjected to ultrasonic irradiation for 30 min. Grignard reagent **6** was generated by ultrasound-promoted reaction of 2-(2-bromoethyl)-1,3-dioxolane (0.3 mL, 2.56 mmol) with Mg (0.094 g, 3.87 mmol) in THF (5 mL) at 0°C under argon. The generated Grignard reagent was added to the cooled (–78°C) suspension of $CeCl_3$ via cannula. The mixture was stirred at –78°C (15 min) and then added by cannula to a solution of **5** (0.141 g, 0.624 mmol) in THF (10 mL) at –78°C. Stirring was continued (30 min). The reaction was quenched with 10% NH_4Cl solution (5 mL) and allowed to warm to room temperature. The mixture was filtered through celite and extracted with ether (3x20 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to an oil. The residue was flash-chromatographed (hexane/ethylacetate 5:1) to remove the bulk of impurities. ^1H NMR analysis of the resulting impure colorless oil (0.23 g) showed a 3:2 mixture of the desired adduct **7** (170 mg, 81%) and the product of Wurtz coupling. The crude oil was used for further transformations without further purification. A small sample of pure **7** (6 mg) was obtained for NMR analysis. R_f 0.27 (hexane/EtOAc, 3:1); IR (KBr/cm^{-1}) 1720. ^1H NMR: δ 4.85 (dd, J=4.6, 5.1, 1H, 2H of dioxolane), 4.69 (m, 1H, menthyl), 3.92 (m, 2H, dioxolane), 3.82 (m, 2H, dioxolane), 3.36 (d, J=13.4, 1H, OH), 1.95-1.65 (m, 7H, menthyl + 3,4), 1.58-1.37 (m, 6H, menthyl + 2-CH_3), 0.99 (m, 2H, menthyl), 0.88 (m, 7H, menthyl), 0.72 (d, J=6.9, 3H, menthyl). ^{13}C NMR: δ 176.6, 104.2, 76.2, 76.1, 74.1, 73.9, 64.9, 46.9, 46.8, 40.5, 34.1, 34.0, 31.4, 31.3, 28.5, 28.2, 26.3, 26.1, 26.0, 25.9, 23.1, 22.9, 22.0, 20.8, 15.9, 15.8.

(-)-Menthyl(methyl-2,3-dideoxy-4-methylpentafuran) uronate (10a/10b): Crude ester **7** (0.15 g, 0.46 mmol) was dissolved in 1:1 mixture of anhydrous ether and methanol (20 mL) under nitrogen atmosphere. The solution was cooled to 0°C and $BF_3{\cdot}Et_2O$ (500 μL, 4.07 mmol) was added by syringe. The mixture was allowed to warm to room temperature and stirring was continued (18 h). After the reaction was complete as observed by TLC, triethylamine (0.5 mL) was added and the volatile components were removed under vacuum. The syrupy residue was diluted with ether (10 mL) and filtered through Celite. The filtrate was concentrated to an oil and purified by flash chromatography (hexane/ethylacetate 10:1) which afforded the mixture of **10a** and **10b** (0.106 g) as a colorless oil in 76% yield. R_f 0.60 (hexane/ethylacetate 3:1); IR (KBr/cm^{-1}) 1726; ^1H NMR (**10a**): δ 5.10-5.03 (m, 1H, 1), 4.67 (m, 1H, menthyl), 3.35 (m, 3H, OCH_3), 2.59-2.24 (m, 1H, menthyl), 2.03-1.89 (m, 4H, 2, 3), 1.81 (m, 1H, menthyl), 1.66 (m, 2H, menthyl), 1.55-1.42 (m, 6H, menthyl + 4-CH_3), 1.10-0.91 (m, 2H, menthyl), 0.88 (m, 7H, menthyl), 0.73 (m, 3H, menthyl); ^{13}C NMR: δ 174.2, 106.0, 84.5, 83.6, 74.8, 54.8, 50.1, 47.0, 40.6, 34.5, 33.3, 32.6, 32.1, 31.4, 23.1, 22.1, 20.8, 15.9.

Methyl 5-O-benzoyl-2,3-dideoxy-4-methyl-α and β-D-ribofuranoside (12): To a slurry of lithium aluminum hydride (71 mg, 0.2 mmol) in ether (1 mL) was added an ethereal solution of **10** (42 mg, 0.14 mmol) and the resulting suspension was stirred at room temperature (10 min). Upon completion of the reaction as indicated by TLC, portionwise addition of some

flash silica gel quenched the remaining $LiAlH_4$. The mixture was diluted with ether, filtered through a short flash column and concentrated. The residue was dissolved in CH_2Cl_2 (1 mL) and to the stirred solution DMAP (69 mg, 0.56 mmol) and benzoyl chloride (50 μL, 0.43 mmol) were added. Stirring was continued for 1 h. Purification of the anomeric mixture was accomplished by concentration followed by column chromatography (pentane/ether, 20:1) to yield **12** (32 mg, 92%) as a colorless oil. A small sample of β-anomer (3 mg) was isolated for NMR analysis. R_f 0.41 (hexane/ethylacetate 3:1); IR (KBr/cm^{-1}) 1732; ^1H NMR: δ 8.02 (d, J=7.4, 2H, o-H of Ph), 7.55 (t, 1H, p-H of Ph), 7.43 (t, 2H, m-H of Ph), 5.02 (d, J=4.6, 1H, 1), 4.17 (dd, J=11.1, 17.3, 2H, 5), 3.34 (s, 3H, OCH_3), 1.98 (m, 4H, 2, 3), 1.44 (s, 3H, 4-CH_3); ^{13}C NMR: δ 165.9, 133.0, 130.1, 129.6, 128.4, 105.7, 82.8, 70.2, 54.4, 33.3, 32.4, 26.0.

1-(5-O-Benzoyl-2,3-dideoxy-4-methyl-α and β-D-*glycero*-pentofuranosyl)thymine (13): 2,4-Bis(trimethylsilyloxy)-5-methylpyrimidine was prepared by addition of chlorotrimethylsilane (460 μL, 3.62 mmol) to a solution of thymine (0.152 g, 1.2 mmol) in hexamethyldisilazane (2.0 mL) and brought to reflux (4 h) under argon atmosphere. The volatile components of the resulting homogeneous mixture were removed under vacuum. The oily residue was rubbed twice with xylene (1 mL) and placed under high vacuum to remove any traces of HMDS. The carbohydrate precursor **12** (86 mg, 0.34 mmol) was dissolved in CH_3CN (5 mL) and added to the crude persilylated thymine under nitrogen. The mixture was cooled to 0°C and TBDMS triflate was added (190 μL, 0.827 mmol) and the mixture was stirred at room temperature (2 h). The reaction mixture was quenched with a few drops of saturated $NaHCO_3$ and concentrated. The white residue was flash-chromatographed (hexane/ethylacetate, 2:1) giving the mixture of anomers **13** as a syrup (96 mg, 81%). R_f 0.15 (hexane/ethylacetate 1:1); IR (KBr/cm^{-1}) 1714, 1699, 1668; ^1H NMR: δ 8.48-8.06 (br s, 1H, NH) 8.03 (t, 2H, o-H of Ph), 7.57 (m, 1H, p-H of Ph), 7.45 (t, 2H, m-H of Ph), 7.23 (m, 1H, H-6 of thymine), 6.14 (m, 1H, 1'), 4.40 (m, 1H, 5'), 4.27 (m, 1H, 5'), 2.55 (m, 1H, 2'), 2.22 (m, 1H, 2'), 2.04 (m, 1H, 3') 1.94 (m, 1H, 3'), 1.56 (m, 3H, 5-CH_3 of thymine), 1.40 (s, 3H, 4'-CH_3); ^{13}C NMR: δ 166.6, 166.4, 133.1, 130.1, 129.7, 129.6, 128.4, 128.3, 99.3, 99.2, 83.1, 70.9, 70.0, 33.8, 33.2, 32.3, 31.7, 26.2, 24.3.

1-(2,3-Dideoxy-4-methyl-α-D-*glycero*-pentafuranosyl)thymine (4α) and 1-(2,3-Dideoxy-4-methyl-β-D-*glycero*-pentafuranosyl)thymine (4β): The anomeric mixture of **13** (22 mg, 65 μmol) was dissolved in methanol (1 mL). NaOH (19 mg, 0.48 mmol) was added. The solution was allowed to stir for 2 h. After the reaction was complete as observed by TLC, the solvent was removed under vacuum. The white residue was dissolved in dichloromethane/acetone (1:1) and filtered through a short silica gel column. The filtrate was concentrated and purified by flash chromatography (dichloromethane/acetone, 2:1) yielding the α-anomer **4α** (6 mg, 39%) and the β-anomer **4β** (9 mg, 55%).

4α: R_f 0.15 dichloromethane/acetone (3:1); IR (KBr/cm^{-1}) 1696, 1687; ^1H NMR: δ 8.52 (br s, 1H, NH), 7.20 (s, 1H, H-6 of thymine), 6.11 (t, 1H, 1'), 3.53 (dd, J=5.32, 6.24, 1H, 5'), 3.47

(dd, J=5.09, 6.47, 1H, 5'), 2.45 (m, 1H, 2'), 2.23 (m, 1H, 2'), 1.96-1.92 (m, 4H, 5-CH_3 of thymine + 3'), 1.83 (m, 1H, 3'), 1.23-1.19 (m, 4H, 4-CH_3 + OH); ^{13}C NMR: δ 163.6, 150.4, 135.0, 111.0, 86.2, 85.7, 68.6, 34.7, 32.2, 32.0, 29.6, 23.8, 22.7, 12.7.

4β: $[\alpha]_D^{25}$ + 4.2 (c 0.4, MeOH); R_f 0.23 dichloromethane/acetone (3:1); IR (KBr/cm^{-1}) 1688; ^1H NMR: δ 8.78 (br s, 1H, NH), 7.50 (s, 1H, H-6 of thymine), 6.10 (t, 1H, 1'), 3.73 (dd, J=4.6, 6.9, 1H, 5'), 3.57 (dd, J=5.32, 6.24, 1H, 5'), 2.45 (m, 1H, 2'), 2.41 (br m, 1H, OH), 2.28 (m, 1H, 2'), 2.17 (m, 1H, 3'), 1.88 (s, 3H, 5-CH_3 of thymine), 1.71 (m, 1H, 3'), 1.22-1.20 (s, 3H, 4'-CH_3); ^{13}C NMR: δ 163.7, 150.4, 136.6, 110.8, 85.9, 85.7, 68.1, 31.9, 31.4, 29.6, 23.6, 12.6.

4-(1,3-Dioxolane-2-yl)-2-hydroxy-2-methylbutyl-3,3,3-trifluoro-2-methoxy-2-phenyl propanoate (9). (+)-Mosher Ester of 8: Crude **7** (58 mg) containing 41 mg (13 μmol) of pure **7** was dissolved in anhydrous ether (5 mL). A slurry of $LiAlH_4$ (16 mg, 0.43 mmol) in ether (1 mL) was added under argon atmosphere. The mixture was stirred (10 min) and quenched with silica gel. The resulting gray suspension was diluted with ether (10 mL) and filtered through a short silica gel column. The filtrate was concentrated to an oil and flash-chromatographed (pentane/ether, 1:2). The resulting clear oil (11 mg, 51%) was dissolved in CH_2Cl_2 (1 mL) and cooled to 0°C. DMAP (34 mg, 0.27 mmol) was added followed by (+)-MTPA chloride (25 μL), 0.13 mmol). The solution was allowed to stir for 5 min. Evaporation of the solvent and chromatography (pentane/ether, 2:1) gave pure **9** (12 mg, 49%). R_f 0.12 hexane/ethylacetate (3:1); IR (KBr/cm^{-1}) 1752, 1187, 1032; ^1H NMR: δ 7.51 (m, 2H, o-H of Ph), 7.39 (m, 3H, m- and p-H of Ph), 4.84 (m, 1H, 2-H of dioxolane), 4.16 (ddd, J=10.6, 10.9, 11.1, 2H, 1), 3.95-3.80 (m, 4H, dioxolane), 3.54 (s, 3H, OCH_3), 2.40 (s, 1H, OH), 1.81-1.53 (m, 4H, 3, 4), 1.17 (s, 3H, 2-CH_3); ^{13}C NMR: δ 166.4, 132.2, 129.7, 128.5, 104.1, 72.4, 70.8, 65.0, 55.5, 32.1, 32.0, 27.5, 23.9; ^{19}F NMR: δ 4.52.

Methyl 2,3-dideoxy-4-methyl-5-O-(3,3,3-trifluoro-2-methoxy-2-phenyl)-propanoyl-α and β-D-ribofuranoside (11): A slurry of $LiAlH_4$ (25 mg, 0.67 mmol) in ether (1 mL) was added to a solution of **10** (56 mg, 0.188 mmol) under an argon atmosphere. The mixture was stirred (10 min) and quenched with silica gel. The resulting gray suspension was diluted with ether (10 mL) and filtered through a short silica gel column. The filtrate was concentrated to an oil and flash-chromatographed (pentane/ether, 1:1). The resulting clear oil 25 mg, 99%) was dissolved in CH_2Cl_2 (1 mL) and cooled to 0°C. DMAP (83 gm, 0.68 mmol) was added followed by (+)-MTPA chloride (70 μL, 0.37 mmol). The solution was allowed to stir for 5 min. Evaporation of the solvent and chromatography (pentane/ether, 5:1) gave pure **11** (30 mg, 48%). R_f 0.39 hexane/ethylacetate (3:1); IR (KBr/cm^{-1}) 1750, 1218; ^1H NMR: δ 7.54 (m, 2H, o-H of Ph), 7.37 (m, 3H, m- and p-H of Ph), 4.97-4.78 (m, 1H, 1), 4.32-4.06 (m, 2H, 5) 3.53 (m, 3H, OCH_3), 3.27 (m, 3H, OCH_3), 2.06-1.57 (m, 4H, 2, 3), 1.32-1.19 (m, 3H, 4-CH_3); ^{13}C NMR: δ 166.4, 131.2, 129.6, 128.4, 127.5, 127.4, 122.2, 105.9, 105.8, 105.7, 82.1, 72.6, 71.4, 71.1, 55.4, 54.5, 54.4, 54.3, 32.9, 32.8, 32.6, 32.5, 32.4, 32.2, 25.8, 25.7, 24.2, 24.1; ^{19}F NMR: δ 4.21, 4.19, 4.15, 4.13.

1-[2,3-Dideoxy-4-methyl-5-O-(3,3,3-trifluoro-2-methoxy-2-phenyl)-propanoyl-β-D-*glycero*-pentafuranosyl)thymine] (14). (+)-Mosher Ester of 4β: Pure **4β** (9 mg, 36 μmol) was dissolved in CH_2Cl_2 (1 mL) and cooled to 0°C. DMAP (36 mg, 0.30 mmol) was added followed by (+)-MTPA chloride (16 μL, 88 μmol). The solution was allowed to stir for 30 min. Evaporation of the solvent and chromatography (hexane/ethylacetate, 1:1) gave pure **14** (9 mg, 53%). R_f 0.11 hexane/ethylacetate (1:1); IR (KBr/cm^{-1}) 1753, 1693, 1272; ^1H NMR: δ 8.41 (br s, 1H, NH), 7.50 (m, 2H, o-H of Ph), 7.36 (m, 3H, m- and p-H of Ph), 7.24 (m, 1H, H-6 of thymine), 6.10 (m, 1H, 1'), 4.55 (m, 1H, 5'), 4.15 (m, 1H, 5'), 3.55 (s, 2H, OCH_3), 3.51 (s, 1H, OCH_3), 2.42-1.75 (m, 6H, 5-CH_3 of thymine + 2',3'), 1.41 (m, 1H, 3'), 1.32-1.28 (m, 3H, 4'-CH_3); ^{13}C NMR: δ 166.5, 163.4, 150.3, 135.1, 132.0, 130.0, 128.6, 127.4, 127.1, 124.4, 122.1, 111.3, 84.8, 84.1, 81.9, 77.3, 77.0, 76.7, 70.5, 70.3, 55.6, 32.8, 32.5, 31.7, 31.3, 24.2, 12.1, 12.0; ^{19}F NMR: δ 4.97 (1F), 4.60 (2F).

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