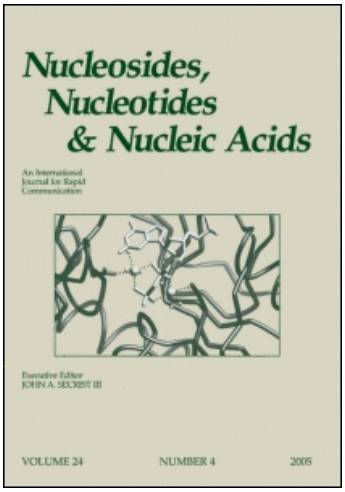

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Synthesis of the Optically Active Carbocyclic Analogs of the Four 2'-Deoxyribonucleoside Monophosphates

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SYNTHESIS OF THE OPTICALLY ACTIVE CARBOCYCLIC ANALOGS OF THE FOUR 2'-DEOXYRIBONUCLEOSIDE MONOPHOSPHATES

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Abstract. The (+)-enantiomer of the carbocyclic analogs of the four 2'-deoxyribonucleoside monophosphate constituents of DNA, C-dAMP[2] (**1: A**), C-dGMP (**1: G**), C-dCMP (**1: C**), and C-TMP (**1: T**) have been synthesized *via* the Mitsunobu coupling reaction. Two new N^3-protected thymines were developed en route.

Carbocyclic analogs of ribonucleosides and deoxyribonucleosides, in which the furanose oxygen of the sugar moiety is replaced by a methylene group, have generated considerable interest due to their anti-tumor and anti-viral activities[3]. In addition, carbocyclic ribonucleotide analogs have proven useful in mechanistic and substrate-specificity studies on the enzymes involved in the biosynthesis of the purine nucleotides[4-10]. Moreover, these analogs exhibit properties, relative to their natural counterparts, which are useful in biological systems. These include: (i) increased stability toward loss of base in acidic media; (ii) a slightly higher lipophilicity; and (iii) better metabolic stability toward the enzymes which cleave the glycosidic linkage of natural nucleosides[11].

As part of our program to explore the enzymology of carbocyclic nucleotides, we now report the synthesis of the optically active carbocyclic analogs of the four 2'-deoxyribonucleotide constituents of DNA: (+)-C-dAMP (**1: A**), (+)-C-dGMP (**1: G**), (+)-C-dCMP (**1: C**), and (+)-C-TMP (**1: T**). Future

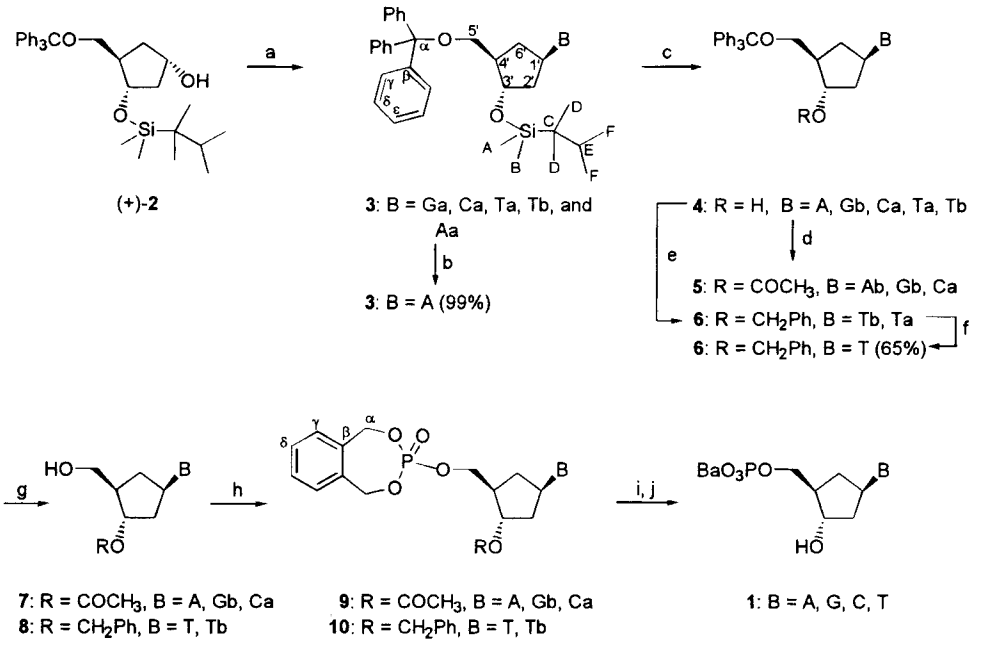
studies will involve their evaluation, as the triphosphates, with DNA and other polymerases.

RESULTS AND DISCUSSION

Several approaches toward the synthesis of carbocyclic analogs of 2'-deoxyribonucleosides have been reported[11]. We have opted for a convergent strategy, starting from the optically active alcohol (+)-**2** (SCHEME 1), described by Borthwick *et al.*[12]. Our initial attempts involved converting (+)-**2** to the 1,3-diol, with subsequent conversion to the 1,3-cyclic sulfate[13]. The cyclic sulfate is activated for direct nucleophilic displacement, by the appropriate base, selectively at position 1[13]. We abandoned this route because, unfortunately, the 3'-sulfate displacement product was extremely difficult to purify. Moreover, the 3',5'-diol intermediate resulting from de-sulfation is not designed to be selectively phosphorylated at the 5' position.

Mitsunobu coupling of (+)-**2**[12] with the appropriately protected bases appeared to be an attractive alternative since the differential lability of the protecting groups of (+)-**2** would permit selective 5'-phosphorylation. Thus, (+)-**2** was subjected to Mitsunobu coupling (SCHEME 1) with the protected bases **Aa**, **Ga**[14], **Ca**[15], **Ta** and **Tb** (FIG. 1) under conditions similar to those reported by Jenny *et al.*[16], providing **3** in good yields (70-90%, TABLE 1). In the purine series (**Aa, Ga**), N^9 coupling (versus N^7) was exclusively observed[16,17].

As noted previously[11], Mitsunobu coupling of pyrimidines is more problematic, both in terms of protecting group strategies and N *versus* O alkylation. For example, although N^3-benzoyl thymine[18] can be prepared in good yield and this protection is compatible with Mitsunobu coupling, only moderate yields of the protected coupling product are obtained due to loss of the benzoyl group either during the reaction or during purification[19]. In order to avoid this lability problem, thymine was N^3-protected as the benzyl, crotyl (**Ta**), and benzyloxymethyl (BOM, **Tb**) derivatives. While benzyl protection afforded good yields of **3**, we were unable to remove this group at the end, despite numerous



Reagents: a. Ph_3P, DEAD, THF; b. NH_3 (liq); c. TBAF, THF; d. acetic anhydride, pyridine, DMAP; e. benzyl bromide, NaH, DMF; f. NaOH, DMSO, 50 °C; g. for **5**, 0.2 M glycine•HCl, pH 2.2, MeOH, reflux; for **6**, 1 N HCl, MeOH, reflux; h. 1. o-xylene-N,N-diethylphosphoramidite, 1H-tetrazole, THF, 2. *m*CPBA, CH_2Cl_2; i. for **9**, NH_4OH, MeOH; j. 1. H_2, 10% Pd/C, 2. $BaBr_2$.

SCHEME 1

attempts. We then turned our attention to crotyl and BOM protection. **Ta** and **Tb** were prepared by treating thymine with crotyl chloride or benzyloxymethyl chloride (BOM-Cl) in DMSO and NaOH at 50 °C. Good N^3 selectivity (69%) was achieved with crotyl chloride, but BOM-Cl afforded the desired N^3 derivative in only 11.8% yield; the remainder consisted of the N^1 and N^1,N^3 derivatives. Nevertheless, BOM protection was preferred due to its stability to the reaction conditions and its high deprotection yield.

As observed previously[20], the reaction temperature during Mitsunobu coupling is a critical factor for regioselectivity. With **Ca**, we observed exclusive N^1-alkylation at 0 °C. In contrast, with **Ta** and **Tb** significant O^2-alkylation (50%)

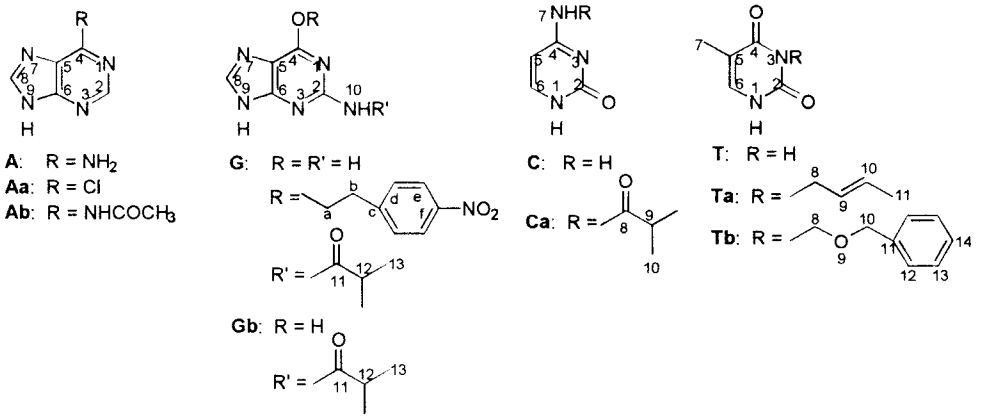


FIGURE 1. Structures of the bases used. Guanine (**G**) is shown in tautomeric form for simplicity.

TABLE 1: Summary of observed yields (%).

3	4	5 or 6	7 or 8	9 or 10	1	Overall
Aa (92)	**A** (92)	**Ab** (79)	**A** (92)	**A** (70)	**A** (68)	29
Ga (80)	**Gb** (47)	**Gb** (98)	**Gb** (75)	**Gb** (71)	**G** (69)	13
Ca (90)	**Ca** (93)	**Ca** (91)	**Ca** (83)	**Ca** (97)	**C** (100)	61
Ta (71)	**Ta** (92)	**Ta** (97)	**T** (47)	**T** (99)	**T** (100)	19
Tb (77)	**Tb** (86)	**Tb** (90)	**Tb** (90)	**Tb** (89)	**T** (74)	35

occurred at 0°C. By decreasing the temperature to -78°C, the yield of the desired N^1-alkylated product was increased to 70-80%.

From **3**, we intended to remove the trityl group, phosphorylate the 5'-hydroxyl, and complete the deprotection sequence to provide **1**. De-tritylation with formic acid-ether[21] provided the 5'-hydroxyl analogs in good yields (60-90%), allowing a direct 5'-phosphorylation. This way had to be abandoned due to phosphate decomposition under de-silylations conditions (TBAF, THF, 25 °C).

Our alternate route (SCHEME 1) involved replacing the silyl protecting group with protecting groups whose deprotection conditions are more compatible with the protected phosphate functionality. Thus **3** were converted to **4**. We found that the guanine O^6-[2-(p-nitrophenyl)ethyl] protecting group was removed during the de-silylation which affords a new method for removing this protecting group. This property of the nitrated aromatic ring has been recently observed with the p-nitrobenzyloxymethylene group[22]. The free 3'-OH of **4** was re-protected with groups which are stable toward trityl hydrolysis conditions. Benzyl ether was chosen for **4: Ta,** and **Tb** providing **6: Ta** and **Tb**. **6: Ta** was then converted, under strong alkaline conditions, to **6: T** in only moderate yield (65%). This result prompted us to develop the BOM protecting strategy. The base protecting groups of **4: A, Gb,** and **Ca** were labile toward benzylation conditions (NaH), so acetylation was carried out instead to generate **5: Ab, Gb,** and **Ca**. In the case of **4: Gb** and **Ca**, DMAP activation had to be avoided because of the unexpected replacement of the *iso*-butyryl group with an acetyl group. It appears that a catalytic amount of DMAP (0.1 eq) is sufficient to catalyze removal of the *iso*-butyryl protecting group to generate the free amine which is then acetylated.

5 and **6** were subjected to de-tritylation conditions to generate **7** and **8**, respectively. The acid labile ester of **5** required the use of a buffer to maintain the pH around 2, although the N-acetyl group of **5: Ab** was hydrolyzed during this conversion. Subsequent phosphorylation of **7** and **8** with o-xylene-N,N-diethylphosphoramidite[23], followed by *in-situ* oxidation of the resulting phosphite with *m*CPBA, gave **9** and **10**. Moderate yields were obtained when B was a purine (**9: Ab** and **Gb**), and excellent yields were obtained with the pyrimidines (**9: Ca, 10: T,** and **Tb**) (TABLE 1). Removal of the protecting groups gave the final products **(+)-1: A, G, C,** and **T**, which were isolated as their barium salts[24]. ^1H, ^{13}C and ^{31}P NMR and negative ion electrospray mass spectra were in agreement with the proposed structures.

The enzymology of these carbocyclic nucleotides will be reported elsewhere.

EXPERIMENTAL SECTION

General

NMR spectra were recorded on a Bruker AC-300 spectrometer. Optical rotations were measured with a Rudolph Autopol III polarimeter at the sodium D line in a 10 cm pathlength cell at 25 °C and concentrations are reported in g/100 mL. TLC was performed with either silica gel plates (Eastman 13181) or, for the phosphomonoesters, cellulose plates (Eastman 13254). Column chromatography was performed on silica gel 60 (70-230 mesh). Solvents were reagent grade and dried using standard procedures[25]. Reactions, unless otherwise noted, were run under anhydrous conditions under nitrogen.

I. (+)-C-dAMP ((+)-1: A):

(-)-β-D-Carbocyclic-1'-(6-chloro-9*H*-purin-9-yl)-3'-O-(dimethylthexylsilyl)-5'-O-trityl-2'-deoxyribonucleoside, or (-)-(1S, 2R, 4R)-4-(6-chloro-9*H*-purin-9-yl)-1-O-(dimethylthexylsilyl)-2-(trityloxymethyl)-cyclopentan-1-ol (3: Aa) : To a cold (0 °C), stirred solution of Ph_3P (1.59 g, 6 mmol, 2.3 eq.) in THF (12 mL), was added DEAD (1.0 mL, 6 mmol, 2.3 eq.) slowly, and this solution was maintained at 0 °C for 20 min. This cold solution was then added slowly to a cold (0 °C), stirred suspension of alcohol **(+)-2** (1.34 g, 2.59 mmol, 1 eq.) and 6-chloropurine (0.63 g, 4 mmol, 1.6 eq.) in dry THF (12 mL). The resulting mixture was kept at 0 °C for 30 min, and then allowed to warm 25 °C. The orange mixture became clear after 1.25 h. After 16 h at 25 °C, the mixture was evaporated to dryness and the residue was purified on silica gel (ether-hexanes, 1:4 to 1:2), to give 1.55 g (2.38 mmol, 92%) of **3: Aa** as an oil. TLC (silica, ether-hexanes, 1:1) R_f 0.51; $[\alpha]_D$ -3.8 (c=1.38, CH_3OH); ^1H NMR (COSY 90, $CDCl_3$, TMS) δ 8.68 (s, 1 H, H-2), 8.08 (s, 1 H, H-8), 7.5-7.2 (2 m, 15 H, Ph), 5.15 (q, 1H, J=8.1 Hz, H-1'), 4.4-4.3 (m, 1 H, H-3'), 3.24 (ABX, 2 H, Δδ=0.11 ppm, J_{AB}=9.2 Hz, J_{AX}=6.2 Hz, J_{BX}=5.8 Hz, H-5'), 2.7-2.55 (m, 1 H, H-6'), 2.4-2.2 (m, 2 H, H-4', H-2'), 2.2-2.1 (m, 1 H, H-2'), 2.0-1.85 (m, 1 H, H-6'), 1.59 (sept., 1 H, J=6.8 Hz, H-E), 0.87, 0.85, 0.80 (3 s, 12 H, H-D, H-F), 0.05, 0.02 (2 s, 6 H, H-

A, H-B)); ^{13}C NMR ($CDCl_3$) δ 151.8 (C-4), 151.5 (C-2), 151.0 (C-6), 144.0 (C-8, C-β), 132.3 (C-5), 128.7 (C-γ), 127.8 (C-δ), 127.0 (C-ε), 86.7 (C-α), 73.7 (C-3'), 64.3 (C-6'), 54.9 (C-1'), 48.2 (C-4'), 40.5 (C-2'), 34.2 (C-5'), 33.9 (C-E), 24.7 (C-C), 20.3 (C-F), 18.6 (C-D), -2.6,-2.8 (C-A, C-B).

(-)-β-D-Carbocyclic-1'-(9*H*-adenin-9-yl)-3'-O-(dimethylthexylsilyl)-5'-O-trityl-2'-deoxyribonucleoside, or (-)-(1S, 2R, 4R)-4-(9*H*-adenin-9-yl)-1-O-(dimethylthexylsilyl)-2-(trityloxymethyl)-cyclopentan-1-ol (3: A): To a -78 °C solution of **3: Aa** (1.5 g, 2.31 mmol) in CH_3OH-acetone (1:1, 6 mL), in a bomb, was added liquid ammonia (5 mL). The cylinder was sealed, and the solution was stirred at 70 °C for 24 h. The bomb was cooled to -78 °C, opened and left in the hood overnight to allow the NH_3 to evaporate. Evaporation of solvent left a residue that was purified on silica gel (CH_3OH in CH_2Cl_2, 0→2%) to yield 1.53 g (2.3 mmol, 99%) of **3: A** as an oil. TLC (silica, CH_2Cl_2-CH_3OH, 97:3) R_f 0.40; $[\alpha]_D$ +1.08 (c=1.3, CH_3OH); $[\alpha]_D$ -8.3 (c=1.28, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 8.32 (s, 1 H, H-2), 7.77 (s, 1 H, H-8), 7.45-7.2 (2 m, 15 H, Ph), 5.68 (s, 2 H, NH_2), 5.09 (q, 1 H, J=8.7 Hz, H-1'), 4.3-4.25 (m, 1 H, H-3'), 3.22 (ABX, 2 H, Δδ=0.13 ppm, J_{AB}=9.1 Hz, J_{AX}=6.3 Hz, J_{BX}=5.6 Hz, H-5'), 2.7-2.55 (m, 1 H, H-6'), 2.35-2.2 (m, 2 H, H-4', H-2'), 2.2-2.1 (m, 1 H, H-2'), 1.9-1.75 (m, 1 H, H-6'), 1.57 (sept., 1 H, J=6.9 Hz, H-E), 0.84 (d, 6 H, J=6.8 Hz, H-F), 0.79, 0.78 (2 s, 6 H, H-D), 0.03, -0.01 (2 s, 6 H, H-A, H-B); ^{13}C NMR ($CDCl_3$) δ 155.4 (C-4), 152.6 (C-6), 150.2 (C-2), 144.0 (C-β), 139.0 (C-8), 128.7 (C-δ), 127.8 (C-γ), 127.0 (Cε), 120.3 (C-5), 86.6 (C-α), 73.7 (C-3'), 64.5 (C-5'), 54.1 (C-1'), 48.3 (C-4'), 40.7 (C-2'), 34.2 (C-6'), 32.0 (C-E), 24.7 (C-C), 20.3 (C-F), 18.6 (C-D), -2.6, -2.9 (C-A, C-B).

(-)-β-D-Carbocyclic-1'-(9*H*-adenin-9-yl)- 5'-O-trityl-2'-deoxyribo-nucleoside, or (-)-(1S, 2R, 4R)-4-(9*H*-adenin-9-yl)-2-(trityloxymethyl)-cyclopentan-1-ol (4: A): To a solution of **3: A** (1.1 g, 1.73 mmol) in THF (10 mL) was added TBAF (1 M in THF) (3.5 mL, 2 eq.). The resulting solution was stirred at 25 °C for 20 h, evaporated to dryness and the residue was purified on silica gel (ether-hexanes, 1:4 → 1:0, then ethyl acetate-CH_3OH, 1:0 → 19:1), to yield 790 mg (1.61 mmol, 92.9%) of **4: A**. TLC (silica, CH_2Cl_2-CH_3OH, 95:5) R_f

0.2; $[\alpha]_D$ -15.7 (c=0.95, $CHCl_3$); ^1H NMR (CD_3OD, TMS) δ 8.15 (s, 1 H, H-2), 8.10 (s, 1 H, H-8), 7.5-7.15 (2 m, 15 H, Ph), 5.08 (q, 1 H, J=8.8 Hz, H-1'), 4.34 (dd, 1 H, J=6.8 Hz, J=4.4 Hz, H-3'), 3.3-3.2 (m, 2 H, H-5'), 2.6-2.1 (m, 4 H, H-6', H-4', 2 H-2'), 2.0-1.9 (m, 1 H, H-6'); ^{13}C NMR (CD_3OD) δ 154.1 (C-6), 153.4 (C-4), 150.7 (C-2), 145.6 (C-β), 141.2 (C-8), 129.9 (C-δ), 128.8 (C-γ), 128.1 (C-ε), 120.6 (C-5), 87.9 (C-α), 74.0 (C-3'), 65.8 (C-5'), 55.2 (C-1'), 48.2 (C-4'), 41.3 (C-2'), 35.5 (C-6').

(+)-β-D-Carbocyclic-3'-O-acetyl-1'-[(N^6-acetyl)-9*H*-adenin-9-yl]-5'-O-trityl-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-1-O-acetyl-4-[(N^6-acetyl)-9*H*-adenin-9-yl]-2-(trityloxymethyl)-cyclopentan-1-ol (5: Ab): To a solution of **4: A** (0.74 g, 1.5 mmol) in dry pyridine (50 eq, 6.1 mL) was added DMAP (0.37 g, 3 mmol, 2 eq.). This solution was cooled to 0 °C, and acetic anhydride (0.71mL, 7.5 mmol, 5 eq.) was slowly added. The resulting solution was stirred for 40 h at 25 °, solvent was evaporated, and the residue was purified on silica gel (ether-hexanes, 1:4 → 1:0, then ethyl acetate-CH_3OH, 1:0 → 19:1), to give 0.68 g (1.18 mmol, 78.8%) of product after crystallization from CH_3OH. TLC (silica, ethyl acetate-CH_3OH, 9:1) R_f 0.42; $[\alpha]_D$ +7.4 (c=1.09, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 8.86 (s, 1 H, NHAc), 8.66 (s, 1 H, H-2), 8.00 (s, 1 H, H-8), 7.5-7.2 (2 m, 15 H, Ph), 5.3-5.25 (m, 1 H, H-3'), 5.15-5.05 (m, 1 H, H-1'), 3.30 (ABX, 2 H, Δδ=0.06 ppm, J_{AB}=9.3 Hz, J_{AX}=5.2 Hz, J_{BX}=5.5 Hz, H-5'), 2.63 (s, 3 H, NH-CO-CH_3), 2.65-2.3 (m, 4 H, H-6', H-4', 2 H-2'), 2.1-2.0 (m, 1 H, H-6'), 2.06 (s, 3 H, O-CO-CH_3); ^{13}C NMR ($CDCl_3$) δ 170.7 (NH-CO-CH_3), 170.4 (O-CO-CH_3), 152.0 (C-6), 151.5 (C-4), 149.3 (C-2), 143.8 (C-β), 141.3 (C-8), 128.6 (C-δ), 127.8 (C-γ), 127.1 (C-ε), 122.2 (C-5), 86.7 (C-α), 75.6 (C-3'), 63.7 (C-5'), 54.0 (C-1'), 44.8 (C-4'), 38.3 (C-2'), 34.0 (C-6'), 25.6 (NH-CO-CH_3), 21.1 (O-CO-CH_3).

(+)-β-D-Carbocyclic-3'-O-acetyl-1'-(9*H*-adenin-9-yl)-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-1-O-Acetyl-4-(9*H*-adenin-9-yl)-2-(hydroxymethyl)-cyclopentan-1-ol (7: A): To a solution of **5: Ab** (459 mg, 0.797 mmol) in THF (4 mL) and CH_3OH (2 mL) was added 0.2 M glycine•HCl, pH 2.2 (9 mL) and 1 N HCl (0.3 mL). The mixture was refluxed for 4 h, cooled, evaporated to dryness, and the residue was purified on silica gel (CH_3OH in CH_2Cl_2, 0→10%),

affording 246 mg (0.738 mmol, 92.6%) of product. TLC (silica, ethyl acetate-CH_3OH, 9:1) R_f 0.18; $[\alpha]_D$ +13.0 (c=1.09, CH_3OH); ^1H NMR (CD_3OD, TMS) δ 8.43 (s, 1 H, H-2), 8.37 (s, 1 H, H-8), 5.25-5.1 (m, 2 H, H-3', H-1'), 3.71 (d, 2 H, J=5.6 Hz, H-5'), 2.6-2.5 (m, 2 H, H-6', H-4'), 2.45-2.35 (m, 2 H, 2 H-2'), 2.1-2.0 (m, 1 H, H-6'), 2.04 (s, 3 H, O-CO-C$\underline{H}_3$); ^{13}C NMR (CD_3OD) δ 172.5 (O-$\underline{C}$O-CH_3), 152.5 (C-6), 150.4 (C-4), 146.0 (C-2), 143.8 (C-8), 120.3 (C-5), 77.0 (C-3'), 63.7 (C-5'), 55.9 (C-1'), 48.0 (C-4'), 39.3 (C-2'), 34.6 (C-6'), 21.0 (O-CO-$\underline{C}H_3$).

(-)-β-D-Carbocyclic-3'-O-acetyl-1'-(9*H*-adenin-9-yl)-5'-O-(o-xylene-phosphate)-2'-deoxyribonucleoside, or (-)-(1S, 2R, 4R)-1-O-acetyl-4-(9*H*-adenin-9-yl)-2-[(o-xylenephosphoryloxy)methyl]-cyclopentan-1-ol (9: A): To a dried mixture of **7: A** (165 mg, 0.57 mmol), o-xylene-N,N-diethylphosphor-amidite (203 mg, 0.86 mmol, 1.5 eq.), and 1-H tetrazole (119 mg, 1.71 mmol, 3 eq.) was added at dry THF (10 mL). The mixture was stirred at 25 °C for 6 h, and then cooled to - 40 °C. A solution of *m*CPBA (60%, 327 mg, 1.14 mmol, 2 eq.) in CH_2Cl_2 (2 mL) was added and stirring was continued at 4°C for 15 h. A 10% $Na_2S_2O_5$ solution (2 mL) was added and the mixture was evaporated to dryness. The residue was dissolved in ethyl acetate (30 mL), and washed successively with 10% $Na_2S_2O_5$ (5 mL), 5% $NaHCO_3$ (2 x 20 mL), and brine (5 mL) and dried over $MgSO_4$. Purification on silica gel (CH_3OH in CH_2Cl_2, 0→5%) gave 188 mg (0.4 mmol, 70%) of product. TLC (silica, CH_2Cl_2-CH_3OH, 9:1) R_f 0.45; $[\alpha]_D$ -6.5 (c=1.07, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 8.26 (s, 1 H, H-2), 7.92 (s, 1 H, H-8), 7.4-7.25 (2 m, 4 H, o-xylene), 6.28 (s, 2 H, N$\underline{H}_2$), 5.35-5.15 (m, 5 H, 4 H-α, H-3'), 5.1-5.0 (m, 1 H, H-1'), 4.45-4.3 (m, 2 H, H-5'), 2.65-2.5 (m, 3 H, H-6', H-4', H-2'), 2.45-2.3 (m, 1 H, H-2'), 2.2-2.1 (m, 1 H, H-6'), 2.08 (s, 3 H, O-CO-C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 170.4 (O-$\underline{C}$O-CH_3), 155.6 (C-6), 152.6 (C-4), 149.9 (C-2), 138.7 (C-8), 135.3 (C-β), 129.2 (C-γ),129.0 (C-δ), 120.1 (C-5), 74.9 (C-3'), 68.5 (C-5'), 68.4 (C-α), 53.6 (C-1'), 45.0 (C-4'), 38.2 (C-2'), 33.3 (C-6'), 21.1 (O-CO-$\underline{C}H_3$); ^{31}P NMR ($CDCl_3$, H_3PO_4(ext.)) δ 0.18.

(+)-C-dAMP or (+)-(1S, 2R, 4R)-4-(9*H*-adenin-9-yl)-2-[(phosphoryloxy)-methyl]-cyclopentan-1-ol (1: A): To a stirred solution of **9: A** (50 mg, 0.106 mmol) in CH_3OH (2 mL) was added concentrated NH_4OH (3 mL) and stirring was

continued for 15 h at 25 °C. TLC (silica, CH_2Cl_2-CH_3OH, 9:1) R_f 0.39 indicated complete reaction. After evaporation of solvent, the oil was dissolved in CH_3OH (1 mL), 95% ethanol (2 mL) and H_2O (0.5 mL), and hydrogenated (1 atm.) over 10% Pd/C (20 mg) for 16 h. The suspension was filtered through Celite and solvent was evaporated. The residue was dissolved in water (2 mL). 1 M $BaBr_2$ (0.21 mL, 0.21 mmol, 2 eq.) was added and the pH was adjusted to pH 8.4. Inorganic phosphate precipitated and was removed by centrifugation. The supernatant (2 mL) was treated with ethanol (10 mL, 5 vol.) and the resulting suspension was kept at –20 °C for 1 h. The precipitate was collected by centrifugation, washed with ethanol and ether, and dried *in vacuo* to afford **(+)-1: A** (31.2 mg, 0.072 mmol, 68%) as a white powder. TLC (cellulose, ethanol-water-acetic acid, 7:3:1) R_f 0.38; TLC (cellulose, n-butanol-acetic acid-water, 5:2:3) R_f 0.53; $[\alpha]_D$ +10.3 (c=0.35, H_2O, pH 5); ^1H NMR (D_2O, HOD, pH2) δ 8.41 (s, 1 H, H-2), 8.28 (s, 1 H, H-8), 5.15-5.0 (m, 1 H, H-1'), 4.34 (dd, 1 H, J= 6.6 Hz, J=5.0 Hz, H-3'), 4.05-4.0 (m, 2 H, H-5'), 2.6-2.5 (m, 1 H, H-6'), 2.45-2.1 (m, 3 H, H-4', 2 H-2'), 2.0-1.8 (m, 1 H, H-6'); ^{13}C NMR (D_2O, HOD, pH2) δ 148.9 (C-6), 148.0 (C-4), 143.5 (C-2), 142.7 (C-8), 128.1 (C-5), 71.6 (C-3'), 66.6 (C-5'), 53.6 (C-1'), 46.1 (C-4'), 39.1 (C-2'), 32.6 (C-6'); ^{31}P NMR (D_2O, HOD, pH2, H_3PO_4 (ext.)) δ 2.90; MS (esi) MH^- 328.1, calcd. for $C_{11}H_{16}N_5O_5P$, M 329.2.

II. (+)-C-dGMP ((+)-1: G):

(+)-β-D-Carbocyclic-1'-(9*H*-{N^2-isobutyryl-O^6-[2-(p-nitrophenyl)ethyl]-guanin-9-yl})-3'-O-(dimethylthexylsilyl)-5'-O-trityl-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-4-(9*H*-{N^2-isobutyryl-O^6-[2-(p-nitrophenyl)ethyl]-guanin-9-yl})-1-O-(dimethylthexylsilyl)-2-(trityloxymethyl)-cyclopentan-1-ol (3: Ga): To a stirred suspension of **Ga**[14] (372 mg, 1 mmol, 2eq.) in dry dioxane (15 mL) was added a solution of Ph_3P (400 mg, 1.5 mmol, 3 eq.) and **(+)-2** (260 mg, 0.5 mmol) in dry THF (10 mL). DEAD (0.245 mL, 1.5 mmol, 3 eq.) was then added slowly over 5 min and stirring was continued at 25 °C for 20 h. The mixture was filtered, the filtrate was evaporated to dryness, and the residue was purified on silica gel (ether-hexanes, 1:1 → 2:1) to provide 344 mg (0.4 mmol, 80%) of **3:**

Ga. TLC (silica, ether-hexanes, 1:2) R_f 0.27; $[\alpha]_D$ +5.7 (c=0.56, CH_3OH); ^1H NMR ($CDCl_3$, TMS, COSY 90) δ 8.16 (d, 2 H, J=8.7 Hz, H-e), 7.77 (s, 1 H, H-8), 7.68 (s, 1 H, H-g), 7.52 (d, 2 H, J=8.7 Hz, H-d), 7.5-7.2 (2 m, 15 H, Ph), 5.03 (quint., 1 H, J=8.8 Hz, H-1'), 4.81 (t, 2 H, J=6.7 Hz, H-a), 4.25-4.2 (m, 1 H, H-3'), 3.32 (t, 2 H, J=6.7 Hz, H-b), 3.18 (ABX, 2 H, Δδ=0.15 ppm, J_{AB}=9.1 Hz, J_{AX}=6.2 Hz, J_{BX}=5.3 Hz, H-5'), 2.65-2.55 (m, 1 H, H-6'), 2.3-2.1 (m, 3 H, H-4', 2 H-2'), 1.95-1.85 (m, 1 H, H-6'), 1.63 (m, 1 H, H-12), 1.57 (sept., 1 H, J=6.8 Hz, H-E), 1.19 (d, 3 H, J=6.7 Hz, H-13), 1.17 (d, 3 H, J=6.9 Hz, H-13), 0.85 (d, 6 H, J=6.8 Hz, H-F), 0.79, 0.78 (2 s, 6 H, H-D), 0.03, -0.01 (2 s, 6 H, H-A, H-B); ^{13}C NMR ($CDCl_3$) δ 176.2 (C-11), 160.6 (C-4), 153.2 (C-6), 151.6 (C-2), 146.9 (C-8), 145.8 (C-f), 144.0 (C-β), 140.2 (C-c), 130.0 (C-d), 128.7 (C-δ), 127.9 (C-γ), 127.1 (C-ε), 123.7 (C-e), 118.5 (C-5), 86.7 (C-α), 73.7 (C-3'), 66.7 (C-a), 64.6 (C-5'), 54.1 (C-1'), 48.2 (C-4'), 40.9 (C-2'), 35.3 (C-12), 35.2 (C-b), 34.2 (C-E, C-6'), 24.8 (C-c), 20.3 (C-F), 19.2 (C-13), 18.6 (C-D), -2.6,-2.8 (C-A, C-B).

(-)-β-D-Carbocyclic-1'-(9*H*-[N^2-isobutyryl]-guanin-9-yl)-5'-O-trityl-2'-deoxyribonucleoside, or (-)-(1S, 2R, 4R)-4-(9*H*-[N^2-isobutyryl]-guanin-9-yl)-2-(trityloxymethyl)-cyclopentan-1-ol (4: Gb): To a stirred solution of **3: Ga** (2.32 g, 2.67 mmol) in THF (5 mL) was added acetic acid (0.16 mL, 2.67 mmol, 1 eq.) and TBAF (1 M in THF) (8 mL, 8 mmol, 3 eq.). After 5 days at 25 °C, solvent was evaporated and the residue was purified on silica gel (ether-hexanes, 1:9 → 1:0, then ether-ethyl acetate, 1:1, then ethyl acetate-CH_3OH, 1:0 → 19:1) to give 722 mg (1.25 mmol, 47%) of **4: Gb**. TLC (silica, CH_2Cl_2-CH_3OH, 19:1) R_f 0.23; $[\alpha]_D$ -3.8 (c=1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 12.09 (s, 1 H, H-1), 8.97 (s, 1 H, H-10), 7.64 (s, 1 H, H-8), 7.45-7.4 and 7.35-7.2 (2 m, 15 H, Ph), 5.0-4.85 (m, 1 H, H-1'), 4.40 (dd, 1 H, J=10.4 Hz, J=4.4 Hz, H-3'), 3.26 (ABX, 2 H, Δδ=0.1 ppm, J_{AB}=9.1 Hz, J_{AX}=6.2 Hz, J_{BX}=4.9 Hz, H-5'), 2.45-2.3 (m, 2 H, H-6', H-4'), 2.3-2.2 (m, 2 H, H-2'), 2.03 (dd, 1 H, J=22.2 Hz, J=10.3 Hz, H-6'), 1.65 (s, 2 H, H-12, O<u>H</u>), 1.12 (d, 3 H, J=6.9 Hz, H-13), 1.07 (d, 3 H, J=6.9 Hz, H-13); ^{13}C NMR ($CDCl_3$) δ 178.4 (C-11), 155.6 (C-6), 148.2 (C-2), 146.8 (C-4), 143.9 (C-β), 137.6 (C-5), 128.6 (C-δ), 128.0 (C-γ), 127.2 (C-ε), 121.9 (C-8),

86.9 (C-α), 74.4 (C-3'), 65.2 (C-5'), 53.9 (C-1'), 47.5 (C-4'), 40.8 (C-2'), 36.3 (C-12), 34.0 (C-6'), 18.8 (C-13).

(+)-β-D-Carbocyclic-3'-O-acetyl-1'-(9*H*-[N^2-isobutyryl]-guanin-9-yl)-5'-O-trityl-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-1-O-acetyl-4-(9*H*-[N^2-isobutyryl]-guanin-9-yl)-2-(trityloxymethyl)-cyclopentan-1-ol (5: Gb): To a solution of **4: Gb** (0.71 g, 1.23 mmol) in dry CH_2Cl_2 (15 mL) and pyridine (1.2 mL, 14.7 mmol, 12 eq.) was added acetic anhydride (0.6 mL, 6.15 mmol, 5 eq). The solution was stirred at 25 °C for 3 days, then evaporated to dryness and the residue was purified on silica gel (CH_3OH in CH_2Cl_2, 0 →10%) to yield 745 mg (1.2 mmol, 98%) of **4: Gb**. TLC (silica, CH_2Cl_2-CH_3OH, 19:1) R_f 0.27; $[\alpha]_D$ +14.6 (c=1.06, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS, COSY 90) δ 12.1 (s, 1 H, H-1), 8.64 (s, 1 H, H-10), 7.68 (s, 1 H, H-8), 7.5-7.4 and 7.35-7.2 (2 m, 15 H, Ph), 5.35-5.3 (m, 1 H, H-3'), 4.9-4.8 (m, 1 H, H-1'), 3.25 (m, 2 H, H-5'), 2.7-2.55 (m, 1 H, H-6'), 2.45-2.2 (m, 4 H, H-4', H-6', 2 H-2'), 2.13 (s, 3 H, $COCH_3$), 2.2-2.1 (m, 1 H, H-12), 1.03 (d, 3 H, J=6.8 Hz, H-13), 0.96 (d, 3 H, J=6.9 Hz, H-13); ^{13}C NMR ($CDCl_3$) δ 178.4 (C-11), 170.5 ($COCH_3$), 155.4 (C-6), 149.1 (C-2), 147.0 (C-4), 144.0 (C-β), 137.8 (C-5), 128.5 (C-δ), 127.9 (C-γ), 127.2 (C-ε), 122.0 (C-8), 86.6 (C-α), 75.9 (C-3'), 63.5 (C-5'), 54.5 (C-1'), 44.6 (C-4'), 38.4 (C-2'), 36.2 (C-12), 33.6 (C-6'), 18.6 (C-13).

(+)-β-D-Carbocyclic-3'-O-acetyl-1'-(9*H*-[N^2-isobutyryl]-guanin-9-yl)-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-1-O-acetyl-4-(9*H*-[N^2-isobutyryl]-guanin-9-yl)-2-(hydroxymethyl)-cyclopentan-1-ol (7: Gb): A solution of **5: Gb** (0.7 g, 1.13 mmol) in THF (4 mL), CH_3OH (4 mL), 0.2 M glycine•HCl, pH 2.2 (12 mL) and 1 N HCl (0.6 mL) was refluxed for 6 h. Solvent was evaporated and the residue was purified on silica gel (CH_3OH in CH_2Cl_2, 0 →10%) to provide 235 mg (0.62 mmol, 55%, corrected for recovered **5: Gb**, 75.8%) of product and 0.19 g (0.3 mmol, 27%) of starting material. TLC (silica, CH_2Cl_2-CH_3OH, 9:1) R_f 0.41; $[\alpha]_D$ +12.5 (c=1.16, CH_3OH); ^1H NMR (CD_3OD, TMS) δ 9.03 (s, 1 H, H-8), 5.2-5.05 (m, 2 H, H-3', H-1'), 3.6-3.75 (m, 2 H, H-5'), 2.8-2.7 (m, 1 H, H-6'), 2.65-2.2 (m, 4 H, H-4', H-6', 2 H-2'), 2.06 (s, 3 H, $COCH_3$), 2.15-1.95 (m, 1 H, H-12), 1.22 (d, 6 H, J=6.7 Hz, H-13); ^{13}C NMR (CD_3OD) δ 182.1 (C-11), 172.4 ($COCH_3$),

154.6 (C-6), 151.2 (C-2), 148.5 (C-4), 139.4 (C-5), 115.7 (C-8), 76.8 (C-3'), 63.4 (C-5'), 56.9 (C-1'), 40.9 (C-4'), 39.2 (C-2'), 37.0 (C-12), 34.2 (C-6'), 21.1 ($CO\underline{C}H_3$), 19.3 (C-13).

(-)-β-D-Carbocyclic-3'-O-acetyl-1'-(9*H*-[N^2-isobutyryl]-guanin-9-yl)-5'-O-(o-xylenephosphate)-2'-deoxyribonucleoside, or (-)-(1S, 2R, 4R)-1-O-acetyl-4-(9*H*-[N^2-isobutyryl]-guanin-9-yl)-2-[(o-xylenephosphoryloxy)methyl] cyclopentan-1-ol (9: Gb): To a dried mixture of **7: Gb** (0.198 g, 0.522 mmol), o-xylene-N,N-diethylphosphoramidite (251mg, 1.04 mmol, 2 eq.), and 1-H tetrazole (75 mg, 1.04 mmol, 2 eq.) was added dry THF (5 mL). After 21 h at 25 °C, TLC (silica, CH_2Cl_2-CH_3OH, 19:1) R_f 0.4 showed consumption of all the starting material. The solution was cooled to -78 °C, and a solution of *m*CPBA (60%, 378 mg, 1.3 mmol, 2.5 eq.) in CH_2Cl_2 (3 mL) was added. After 7 h stirring at 25 °C, 10% $Na_2S_2O_5$ (1 mL) was added. Solvent was evaporated and the residue was dissolved in ethyl acetate (20 mL). The ethyl acetate solution was washed successively with 10% $Na_2S_2O_5$ (5 mL), 5% $NaHCO_3$ (2 x 5 mL), and brine (5 mL), and dried over $MgSO_4$. Purification of the residue on silica gel (CH_3OH in CH_2Cl_2, 0→10%) gave 208 mg (0.37 mmol, 71%) of product. TLC (silica, CH_2Cl_2-CH_3OH, 9:1) R_f 0.54; $[\alpha]_D$ -8.0 (c=0.95, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS, COSY 90) δ 12.26 (s, 1 H, H-1), 10.83 (s, 1 H, H-10), 7.64 (s, 1 H, H-8), 7.5-7.2 (m, 4 H, Ph), 5.4-5.1 (m, 5 H, 4 H-α, H-3'), 5.0-4.8 (m, 1 H, H-1'), 4.55-4.4 (m, 2 H, H-5'), 2.95-2.8 (m, 1 H, H-6'), 2.78 (sept., 1 H, J=6.8 Hz, H-12), 2.7-2.6 (m, 1 H, H-4'), 2.55-2.35 (m, 2 H, 2 H-2'), 2.09 (s, 3 H, $COC\underline{H}_3$), 2.25-2.05 (m, 1 H, H-6'), 1.27 (d, 6 H, J=6.4 Hz, H-13); ^{13}C NMR ($CDCl_3$) δ 180.1 (C-11), 170.4 ($\underline{C}OCH_3$), 155.7 (C-6), 148.1 (C-2), 147.6 (C-4), 139.3 (C-5), 135.1 (C-β), 129.6 (C-γ), 129.3 (C-δ), 122.7 (C-8), 77.1 (C-3'), 69.3 (C-α), 68.7 (C-5'), 56.9 (C-1'), 44.7 (C-4'), 37.0 (C-2'), 35.6 (C-12), 30.0 (C-6'), 21.1 ($CO\underline{C}H_3$), 19.0 (C-13); ^{31}P NMR ($CDCl_3$, H_3PO_4(ext.)) δ -0.6.

(+)-C-dGMP or (+)-(1S, 2R, 4R)-4-(9*H*-guanin-9-yl)-2-[(phosphoryloxy)-methyl]-cyclopentan-1-ol (1: G): A solution **9: Gb** (45 mg, 84.7 μmol) in CH_3OH (4 mL) concentrated NH_4OH (1 mL) was stirred at 25 °C for 24 h. After evaporation of solvent, the residual oil was dissolved 95% ethanol (3 mL) and

H_2O (0.5 mL) and hydrogenated (1 atm.) over 10% Pd/C (10 mg) for 15 h. The suspension was filtered through Celite and solvent was evaporated. The residue was dissolved in water (2 mL). 1 M $BaBr_2$ (0.17 mL, 0.17 mmol, 2 eq.) was added and the pH was adjusted to pH 8.4. Inorganic phosphate precipitated and was removed by centrifugation. The supernatant (2 mL) was treated with ethanol (10 mL, 5 vol.) and the resulting suspension was kept at –20 °C for 1 h. The precipitate was collected by centrifugation, washed with ethanol and ether, and dried *in vacuo* to afford **(+)-1: G** (28.1 mg, 58.4 μmol, 69%) as a white powder. TLC (cellulose, n-butanol-acetic acid-water, 5:2:3) R_f 0.38; $[\alpha]_D$ +13.2 (c=0.42, H_2O, pH 5); ^1H NMR (D_2O, HOD, pH2) δ 9.02 (s, 1 H, H-8), 5.14 (quint., 1 H, J=8.4 Hz, H-1'), 4.47 (dd, 1 H, J=11.2 Hz, J=4.8 Hz, H-3'), 4.06 (ABX, 2 H, Δδ=0.07 ppm, J_{AB}=10.4 Hz, J_{AX}=5.1 Hz, J_{BX}=5.2 Hz, H-5'), 2.8-2.6 (m, 1 H, H-6'), 2.55-2.3 (m, 3 H, H-4', 2 H-2'), 2.15-1.95 (m, 1 H, H-6'); ^{13}C NMR (D_2O, HOD, pH2) δ 155.0 (C-6), 154.5 (C-2), 149.7 (C-4), 135.8 (C-8), 108.1 (C-5), 71.7 (C-3'), 65.3 (C-5'), 54.4 (C-1'), 46.3 (C-4'), 38.9 (C-2'), 32.0 (C-6'); ^{31}P NMR (D_2O, HOD, pH2, H_3PO_4(ext.)) δ 3.47; MS (esi) MH^- 344.1, calcd. for $C_{11}H_{16}N_5O_6P$, M 345.2.

III. (+)-C-dCMP ((+)-1: C)

(+)-β-D-Carbocyclic-3'-O-(dimethylthexylsilyl)-1'-(1*H*-[N^6-isobutyryl]-cytosin-1-yl)-5'-O-trityl-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-1-O-(dimethylthexylsilyl)-4-(1*H*-[N^6-isobutyryl]-cytosin-1-yl)-2-(trityloxymethyl) cyclopentan-1-ol (3: Ca): To a cold (0 °C), stirred solution of Ph_3P (1.49 g, 5.69 mmol, 3 eq.) THF (15 mL), was slowly added DEAD (0.93 mL, 5.69 mmol, 3 eq.). This solution was stirred at 0 °C for 20 min and then added slowly to a cold (0 °C), stirred suspension of dry alcohol **(+)-2** (0.98 g, 1.9 mmol, 1 eq.) and **Ca**[19] (0.69 g, 3.79 mmol, 2 eq.) in THF (15 mL). The resulting mixture was stirred at 0 °C for 30 min, and then allowed to warm to 25 °C and became clear. After 18 h at 25 °C, solvent was evaporated and the residue was purified on silica gel (ether-hexanes, 1:9 → 1:3), to give 1.2 g (0.88 mmol, 90%) of **3: Ca** as an oil. TLC (silica, ether-hexanes, 1:3) R_f 0.32; $[\alpha]_D$ -0.15° (c=1.3, CH_3OH); $[\alpha]_D$ +2.3°

(c=1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS, COSY 90) δ 8.46 (d, 1 H, J=5.6 Hz, H-6), 8.09 (s, 1 H, H-7), 7.87 (d, 1 H, J=5.7 Hz, H-5), 7.5-7.25 (2 m, 15 H, Ph), 5.50 (quint., 1 H, J=6.7 Hz, H-1'), 4.17 (q, 1 H, J=7.7 Hz, H-3'), 3.20 (AB, 2 H, Δδ = 0.25 ppm, J_{AB}=8.8 Hz, H-5'), 2.8-2.55 (m, 1 H, H-6'), 2.63 (sept., 1 H, J=6.9 Hz, H-9), 2.3-2.15 (m, 1 H, H-4'), 2.07 (t, 2 H, J=6.1 Hz, H-2'), 1.8-1.65 (m, 1 H, H-6'), 1.58 (sept., 1 H, J=6.8 Hz, H-E), 1.26 (d, 6 H, J=6.9 Hz, H-10), 0.88 (d, 6 H, J=7 Hz, H-F), 0.82, 0.80 (2 s, 6 H, H-D), 0.07, -0.02 (2 s, 6 H, H-A, H-B); ^{13}C NMR ($CDCl_3$) δ 176.0 (C-8), 164.2 (C-4), 160.4 (C-2), 158.9 (C-6), 144.1 (C-β), 128.6 (C-δ), 127.6 (C-γ), 126.8 (C-ε), 103.6 (C-5), 86.3 (C-α), 76.2 (C-1'), 73.4 (C-3'), 65.1 (C-5'), 47.4 (C-4'), 41.3 (C-2'), 36.7 (C-6'), 34.4 (C-9), 34.1 (C-E), 24.6 (C-C), 20.2 (C-F), 19.1 (C-10), 18.5 (C-D), -2.6, -3.1 (C-A, C-B).

(-)-β-D-Carbocyclic-1'-(1*H*-[N^6-isobutyryl]-cytosin-1-yl)-5'-O-trityl-2'-deoxyribonucleoside, or (-)-(1S, 2R, 4R)-4-(1*H*-[N^6-isobutyryl]-cytosin-1-yl)-2-(trityloxymethyl)-cyclopentan-1-ol (4: Ca): To a stirred solution of **3: Ca** (0.957 g, 1.41 mmol) in THF (1 mL) was added TBAF (1 M in THF) (4.3 mL, 4.3 mmol, 3 eq.), and the resulting solution was stirred at 25 °C for 14 h. Solvent was evaporated and the residue was purified on silica gel (ether-hexanes, 1:2 → 1:0) to afford 0.71 g (1.31 mmol, 93%) of product. TLC (silica, ether-hexanes, 2:1) R_f 0.17; $[\alpha]_D$ -15.7 (c=1.16, $CHCl_3$), ^1H NMR ($CDCl_3$, TMS) δ 8.35 (d, 1 H, J=5.6 Hz, H-6), 8.29 (s, 1 H, H-7), 7.77 (d, 1 H, J=5.6 Hz, H-5), 7.5-7.2 (2 m, 15 H, Ph), 5.45-5.35 (m, 1 H, H-1'), 4.3-4.1 (m, 1 H, H-3'), 4.0-3.6 (ls, 1 H, OH), 3.37 (dd, 1 H, J=9 Hz, J=5.3 Hz, H-5'), 3.12 (dd (=t), 1 H, J=8.7 Hz, H-5'), 2.57 (sept., 1 H, J=6.7 Hz, H-9), 2.5-2.4 (m, 1 H, H-6'), 2.3-2.1 (m, 3 H, H-4', 2 H-2'), 1.5-1.35 (m, 1 H, H-6'), 1.22 (d, 6 H, J=6.9 Hz, H-10); ^{13}C NMR ($CDCl_3$) δ 176.3 (C-8), 163.9 (C-4), 160.3 (C-2), 159.0 (C-6), 143.8 (C-β), 128.5 (C-δ), 127.8 (C-γ), 127.0 (C-ε), 103.8 (C-5), 86.9 (C-α), 75.7 (C-3'), 75.4 (C-1'), 66.6 (C-5'), 46.3 (C-4'), 40.6 (C-2'), 36.6 (C-6'), 33.9 (C-9), 19.1 (C-10).

(+)-β-D-Carbocyclic-3'-O-acetyl-1'-(1*H*-[N^6-isobutyryl]-cytosin-1-yl)-5'-O-trityl-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-1-O-acetyl-4-(1*H*-[N^6-isobutyryl]-cytosin-1-yl)-2-(trityloxymethyl)-cyclopentan-1-ol (5: Ca): Acetic anhydride (0.28 mL, 2.94 mmol, 2 eq.) was added slowly to a cold (0 °C), stirred

solution of **4: Ca** (0.79 g, 1.47 mmol) in dry CH_2Cl_2 (1 mL) and pyridine (3.6 mL, 44.1 mmol, 30 eq.). The solution was stirred at 25 °C for 3 days. The residue, after solvent evaporation, was purified on silica gel (ether-hexanes, 1:9 → 1:1), to provide 0.89 g (1.34 mmol, 91%) of **5: Ca** as an oil. TLC (silica, ether-hexanes, 2:1) R_f 0.47; $[\alpha]_D$ +9.5 (c=1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, COSY 90) δ 8.37 (d, 1 H, J=5.6 Hz, H-6), 8.22 (s, 1 H, H-7), 7.80 (d, 1 H, J=5.6 Hz, H-5), 7.5-7.2 (2 m, 15 H, Ph), 5.40 (quint., 1 H, J=6.8 Hz, H-1'), 5.17 (dd, 1 H, J=12.3 Hz, J=5.5 Hz, H-3'), 3.18 (AB, 2 H, Δδ=0.06 ppm, J_{AB}=9.8 Hz, H-5'), 2.65-2.45 (m, 2 H, H-6', H-9), 2.45-2.1 (m, 3 H, H-4', 2 H-2'), 2.02 (s, 3 H, $COC\underline{H}_3$), 1.69 (ddd, 1 H, J=13.7 Hz, J=8.9 Hz, J=6.8 Hz, H-6'), 1.24 (d, 6 H, J=6.9 Hz, H-10); ^{13}C NMR ($CDCl_3$) δ 176.0 (C-8), 170.4 ($\underline{C}OCH_3$), 164.2 (C-4), 160.4 (C-2), 159.0 (C-6), 144.1 (C-β), 128.7 (C-δ), 127.7 (C-γ), 126.9 (C-ε), 103.9 (C-5), 86.5 (C-α), 76.6 (C-3'), 75.9 (C-1'), 64.3 (C-5'), 44.0 (C-4'), 38.6 (C-2'), 36.8 (C-6'), 33.8 (C-9), 21.2 ($CO\underline{C}H_3$), 19.1 (C-10).

(-)-β-D-Carbocyclic-3'-O-acetyl-1'-(1*H*-[N^6-isobutyryl]-cytosin-1-yl)-2'-deoxyribonucleoside, or (-)-(1R, 2S, 4R)-1-O-acetyl-4-(1*H*-[N^6-isobutyryl]-cytosin-1-yl)-2-(hydroxymethyl)-cyclopentan-1-ol (7: Ca): A solution of **5: Ca** (0.88 g, 1.5 mmol) in acetone (5 mL), CH_3OH (10 mL) and 0.2 M glycine•HCl, pH2.2 (10 mL) was refluxed for 12 h. Solvent was evaporated, the residue was dissolved in ethyl acetate (20 mL), and washed with H_2O (10 mL), and brine (10 mL), and dried over $MgSO_4$. After solvent evaporation, the residue was purified on silica gel (ether-hexanes, 1:1 → 1:0, then ethyl acetate-CH_3OH, 1:0 → 9:1) to give 427 mg (1.25 mmol, 83.4%) of product. TLC (silica, ether) R_f 0.26; $[\alpha]_D$ -16.0 (c=1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS) δ 8.38 (d, 1 H, J=5.6 Hz, H-6), 7.90 (s, 1 H, H-7), 7.81 (d, 1 H, J=5.6 Hz, H-5), 5.45 (quint., 1 H, J=5.9 Hz, H-1'), 5.18 (dd, 1 H, J=11.7 Hz, J=5.5 Hz, H-3'), 3.75-3.65 (m, 2 H, H-5'), 2.7 (s, 1 H, $O\underline{H}$), 2.65-2.45 (m, 2 H, H-6', H-9), 2.35-2.2 (m, 3 H, H-4', 2 H-2'), 2.07 (s, 3 H, $COC\underline{H}_3$), 1.64 (ddd, 1 H, J=13.4 Hz, J=7.4 Hz, J=5.6 Hz, H-6'), 1.25 (d, 6 H, J=6.9 Hz, H-10); ^{13}C NMR ($CDCl_3$) δ 176.1 (C-8), 171.5 ($\underline{C}OCH_3$), 164.0 (C-4), 160.4 (C-2), 159.1 (C-6), 104.0 (C-5), 76.4 (C-3'), 76.1 (C-1'), 64.2 (C-5'), 47.0 (C-4'), 38.5 (C-2'), 36.8 (C-6'), 33.8 (C-9), 21.2 ($CO\underline{C}H_3$), 19.1 (C-10).

(+)-β-D-Carbocyclic-3'-O-acetyl-1'-(1*H*-[N^6-isobutyryl]-cytosin-1-yl)-5'-O-(o-xylenephosphate)-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-1-O-acetyl-4-(1*H*-[N^6-isobutyryl]-cytosin-1-yl)-2-[(o-xylenephosphoryloxy)-methyl]-cyclopentan-1-ol (9: Ca): To a dried mixture of **7: Ca** (0.377 g, 1.12 mmol), o-xylene-N,N-diethylphosphoramidite (0.4 g, 1.68 mmol, 1.5 eq.), and 1-H tetrazole (0.16 g, 2.24 mmol, 2 eq.), was added dry THF (15 mL). After stirring for 3 h at 25 °C, the mixture was cooled to - 78 °C, and treated with a solution of *m*CPBA (60%, 0.64 g, 2.24 mmol, 2 eq.) in CH_2Cl_2 (4 mL). This was stirred at 25 °C for 2 h, followed by addition of 10% $Na_2S_2O_5$ (2 mL). The residue, after evaporation of solvent, was dissolved in ethyl acetate (30 mL), and washed successively with 10% $Na_2S_2O_5$ (10 mL), 5% $NaHCO_3$ (2 x 10 mL), and brine (10 mL), and dried over $MgSO_4$. Purification of the residue on silica gel (ether-hexanes, 1:4 → 1:0, then ethyl acetate-ether, 1:1), gave 564 mg (1.09 mmol, 97%) of product. TLC (silica, ethyl acetate-ether, 1:1) R_f 0.26; $[\alpha]_D$ +3.5 (c=1.07, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 8.36 (d, 1 H, J=5.6 Hz, H-6), 7.79 (d, 1 H, J=5.7 Hz, H-5), 7.77 (s, 1 H, H-7), 7.4-7.2 (2 m, 4 H, Ph), 5.45 (quint., 1 H, J=6.5 Hz, H-1'), 5.25-5.1 (2 m, 5 H, 4 H-α, H-3'), 4.3-4.2 (m, 2 H, H-5'), 2.6-2.45 (m, 3 H, H-4', H-6', H-9), 2.4-2.3 (m, 1 H, H-2'), 2.25-2.1 (m, 1 H, H-2'), 2.0 (s, 3 H, $COCH_3$), 1.85-1.75 (m, 1 H, H-6'), 1.25 (d, 6 H, J=6.9 Hz, H-10); ^{13}C NMR ($CDCl_3$) δ 176.0 (C-8), 170.5 ($\underline{C}OCH_3$), 163.9 (C-4), 160.4 (C-2), 159.0 (C-6), 135.4 (C-β), 129.1 (C-γ), 129.0 (C-δ), 104.0 (C-5), 76.0 (C-3'), 75.2 (C-1'), 68.6 (C-5'), 68.4 (C-α), 44.3 (C-4'), 37.8 (C-2'), 36.8 (C-6'), 33.3 (C-9), 21.0 ($CO\underline{C}H_3$), 19.1 (C-10) ; ^{31}P NMR ($CDCl_3$, H_3PO_4(ext.)) δ -0.25.

(+)-C-dCMP or (+)-(1S, 2R, 4R)-4-(1*H*-cytosin-1-yl)-2-[(phosphoryl-oxy)methyl]-cyclopentan-1-ol (1: C): A solution of **9: Ca** (521 mg, 1 mmol) in THF (3 mL), CH_3OH (10 mL), and concentrated NH_4OH (20 mL) was stirred at 25 °C for 9 days. TLC (silica, ethyl acetate-CH_3OH, 1:1) R_f 0.13, showed complete deprotection of both ester and amide. The residual oil was dissolved in CH_3OH (10 mL), 95% ethanol (10 mL) and H_2O (0.5 mL), and hydrogenated (1 atm.) over 10% Pd/C (40 mg) for 14 h. The suspension was filtered through Celite and solvent was evaporated. The residue was dissolved in water (5 mL).

1 M $BaBr_2$ (2 mL, 2 mmol, 2 eq.) was added and the pH was adjusted to pH 8.4. Inorganic phosphate precipitated and was removed by centrifugation. The supernatant (7 mL) was treated with ethanol (35 mL, 5 vol.) and the resulting suspension was kept at –20 °C for 1 h. The precipitate was collected by centrifugation, washed with ethanol and ether, and dried *in vacuo* to afford **(+)-1: C** (467 mg, 1 mmol, 100%) as a white powder. TLC (cellulose, ethanol-water-acetic acid, 7:3:1) R_f 0.64; $[\alpha]_D$ +9.6 (c=0.52, H_2O, pH 5); ^1H NMR (D_2O, HOD, COSY 90, pH1) δ 7.85 (d, 1 H, J=6.0 Hz, H-6), 6.47 (d, 1 H, J=6.0 Hz, H-5), 5.65-5.55 (m, 1 H, H-1'), 4.36 (dd, 1 H, J=13.5 Hz, J=6.8 Hz, H-3'), 4.10 (d, 2 H, J=6.3 Hz, H-5'), 2.6-2.5 (m, 1 H, H-6'), 2.4-2.25 (m, 2 H, H-4', H-2'), 2.2-2.1 (m, 1 H, H-2'), 1.9-1.75 (m, 1 H, H-6'); ^{13}C NMR (D_2O, HOD, pH1) δ 166.1 (C-4), 156.8 (C-2), 142.5 (C-6), 99.2 (C-5), 79.7 (C-3'), 72.1 (C-1'), 67.2 (C-5'), 45.2 (C-4'), 39.5 (C-2'), 32.0 (C-6'); ^{31}P NMR (D_2O, HOD, H_3PO_4(ext.)) δ 2.78 (pH 1), 6.95 (pH 8); MS (esi) MH^- 304.1, calcd. for $C_{10}H_{16}N_3O_6P$, M 305.2.

IV. (+)-C-dTMP ((+)-1: T):

A. N^3-BOM thymine pathway :

N^3-benzyloxymethylthymine (Tb): To dry thymine **T** (1 g, 7.9 mmol) in dry DMSO (15 mL) was added finely powdered NaOH (0.38 g, 9.48 mmol, 1.2 eq.). Benzyloxymethyl chloride (2.0 g, 8.69 mmol, 1.1 eq.) was slowly added (exothermic), and the resulting solution was stirred at 50 °C for 16 h. Solvent was evaporated, the residue was dissolved in ethyl acetate-CH_2Cl_2 (4:1, 50 mL), and washed with water (2 x 20 mL), and brine (20 mL), and dried ($MgSO_4$). Purification on silica gel (ether-hexanes, 1:9 → 1:0) gave 0.23 g (0.93 mmol, 11.8%) of product. TLC (silica, ether) R_f 0.42; ^1H NMR ($CDCl_3$, TMS) δ 9.5 (s, 1 H, H-1), 7.35-7.25 (m, 5 H, Ph), 7.11 (s, 1 H, H-6), 5.22 (s, 2 H, H-10), 4.62 (s, 2 H, H-8), 1.91 (s, 3 H, $C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 164.1 (C-4), 151.3 (C-2), 138.9 (C-6), 136.7 (C-11), 128.5, 128.1 (C-12, C-13), 111.6 (C-5), 76.0 (C-8), 71.6 (C-10), 12.2 ($\underline{C}H_3$).

(+)-β-D-Carbocyclic-1'-(1*H*-[N^3-benzyloxymethyl]-thymin-1-yl)-3'-O-(dimethylthexylsilyl)-5'-O-trityl-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-

4-(1*H*-[N^3-benzyloxymethyl]-thymin-1-yl)-1-O-(dimethylthexylsilyl)-2-(trityl-oxymethyl)-cyclopentan-1-ol (3: Tb): To a cold (0 °C), stirred solution of Ph_3P (0.85 g, 3.18 mmol, 3 eq.) in THF (11 mL), was slowly added DEAD (0.575 mL, 3.18 mmol, 3 eq.). After 15 min at 0 °C, this cold solution was slowly added to a stirred solution of **(+)-2** (0.55 g, 1.06 mmol) and **Tb** (0.39 g, 1.59 mmol, 1.5 eq.) in THF (6 mL) at -78 °C. The reaction was kept at -78 °C for 2 h, and then at 25 °C for 18 h. After solvent evaporation, the residue was purified on silica gel (ether-hexanes, 0:1 → 1:1), to give 0.681 g (0.82 mmol, 77%) of pure product as an oil. TLC (silica, ether-hexanes, 1:1) R_f 0.51; $[\alpha]_D$ +10.2 (c=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 7.7-7.2 (2 m, 20 H, Ph), 7.06 (s, 1 H, H-6), 5.65-5.45 (m, 1 H, H-1'), 5.24 (s, 2 H, H-8), 4.28 (dd, 1 H, J=14.9 Hz, J=7.5 Hz, H-3'), 3.39 (dd, 1 H, J=8.6 Hz, J=3.9 Hz, H-5'), 3.03 (t, 1 H, J=8.2 Hz, H-5'), 2.4-2.0 (m, 4 H, H-6', H-4', 2 H-2'), 1.92 (s, 3 H, C$\underline{H}_3$), 1.80 (ddd, 1 H, J=11.5 Hz, J=6.8 Hz, J=6.7 Hz, H-6'), 1.53 (sept., 1 H, J=6.9 Hz, H-E), 0.80 (d, 6 H, J=6.8 Hz, H-F), 0.74, 0.72 (2 s, 6 H, H-D), 0.01, -0.11 (2 s, 6 H, H-A, H-B); ^{13}C NMR ($CDCl_3$) δ 163.7 (C-4), 151.4 (C-2), 144.5 (C-β), 137.0 (C-6), 136.7 (C-11), 128.8, 128.5, 128.1, 127.8, 127.6, 126.7 (C-12, C-13, C-14, C-δ, C-γ, C-ε), 110.9 (C-5), 86.3 (C-α), 76.6 (C-8), 73.8 (C-3'), 71.7 (C-10), 65.4 (C-5'), 49.9 (C-1'), 48.8 (C-4'), 37.1 (C-2'), 34.2 (C-E), 30.7 (C-6'), 24.7 (C-C), 20.3 (C-F), 18.6 (C-D), 13.1 ($\underline{C}H_3$), -2.4, -3.0 (C-B, C-A).

(-)-β-D-Carbocyclic-1'-(1*H*-[N^3-benzyloxymethyl]-thymin-1-yl)-5'-O-trityl-2'-deoxyribonucleoside, or (-)-(1S, 2R, 4R)-4-(1*H*-[N^3-benzyloxy-methyl]-thymin-1-yl)-2-(trityloxymethyl)-cyclopentan-1-ol (4: Tb): To a solution of **3: Tb** (0.68 g, 0.91 mmol) in THF (2 mL) was added TBAF (1 M in THF) (5.5 mL, 5.5 mmol, 6 eq.), and the solution was stirred at 25 °C for 3 days. The residue after evaporation of solvent was purified on silica gel (ether-hexanes, 0:1 → 1:0), to give 0.473 g (0.78 mmol, 86%) of product. TLC (silica, ether-hexanes, 2:1) R_f 0.2; $[\alpha]_D$ -16.7 (c=0.97, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 7.5-7.2 (2 m, 20 H, Ph), 6.99 (s, 1 H, H-6), 5.6-5.5 (m, 1 H, H-1'), 5.16 (s, 2 H, H-10), 4.58 (s, 2 H, H-8), 4.50 (q, 1 H, J=8.3 Hz, H-3'), 3.40 (dd, 1 H, J=8.9 Hz, J=5.1 Hz, H-5'), 3.21 (t, 1 H, J=8.6 Hz, H-5'), 2.8-2.5 (ls, 1 H, O$\underline{H}$), 2.5-2.4 (m, 1

H, H-6'), 2.3-2.1 (m, 1 H, H-4'), 2.0-1.8 (m, 3 H, 2 H-2', H-6'), 1.85 (s, 3 H, C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 163.6 (C-4), 151.3 (C-2), 144.0 (C-β), 136.9 (C-6), 136.8 (C-11), 128.8, 128.7, 128.5, 128.1, 127.9, 127.7, 127.0 (C-12, C-13, C-14, C-δ, C-γ, C-ε), 110.8 (C-5), 87.1 (C-α), 77.1 (C-8), 76.1 (C-3'), 71.8 (C-10), 66.6 (C-5'), 49.5 (C-1'), 47.8 (C-4'), 36.6 (C-2'), 30.0 (C-6'), 13.0 ($\underline{C}H_3$).

(+)-β-D-Carbocyclic-3'-O-benzyl-1'-(1*H*-[N^3-benzyloxymethyl]-thymin-1-yl)-5'-O-trityl-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-1-O-(benzyl)-4-(1*H*-[N^3-benzyloxymethyl]-thymin-1-yl)-2-(trityloxymethyl)-cyclopentan-1-ol (6: Tb): To a cold (0 °C), stirred solution of **4: Tb** (415 mg, 0.69 mmol) in dry DMF (3 mL), was added NaH (60% dispersion, 83 mg, 2.1 mmol, 3 eq.) and benzyl bromide (0.25 mL, 2.1 mmol, 3 eq.). This suspension was stirred at 25 °C for 3 days. Ethanol (3 drops) was added, then H_2O (2 mL), and the resulting solution was extracted with ether (3 x 10 mL). The ether extract was washed with brine (10 mL), dried ($MgSO_4$), and evaporated to leave a residue that was purified on silica gel (ether-hexanes, 0:1 → 1:0) to afford 428 mg (0.62 mmol, 90%) of product. TLC (silica, ether-hexanes, 2:1) R_f 0.47; $[\alpha]_D$ +10.2 (c=0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS) δ 7.5-7.1 (2 m, 25 H, Ph), 6.97 (d, 1 H, J=1.1 Hz, H-6), 5.6-5.5 (m, 1 H, H-1'), 5.20 (s, 2 H, H-8), 4.61 (s, 2 H, H-10), 4.44 (AB, 2 H, Δδ=0.07 ppm, J_{AB}=11.7 Hz, C$\underline{H}_2$Ph), 4.25 (dd, 1 H, J=7.3 Hz; J=6.4 Hz, H-3'), 3.32 (dd, 1 H, J=8.9 Hz, 4.8 Hz, H-5'), 3.19 (dd, 1 H, J=8.8 Hz, J=5.7 Hz, H-5'), 2.6-2.45 (m, 1 H, H-6'), 2.35-2.05 (m, 3 H, H-4', 2 H-2'), 1.95-1.8 (m, 1 H, H-6'), 1.88 (s, 3 H, C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 163.7 (C-4), 151.4 (C-2), 144.4 (C-β), 138.9 (CH$_2\underline{Ph}$), 137.0 (C-6), 136.7 (C-11), 128.8, 128.5, 128.2, 128.1, 127.8, 127.7, 127.3, 126.8 (C-12, C-13, C-14, C-δ, C-γ, C-ε, CH$_2\underline{Ph}$), 110.8 (C-5), 86.3 (C-α), 81.0 (C-3'), 77.1 (C-8), 71.8 ($\underline{C}H_2$Ph, C-10), 64.3 (C-5'), 50.3 (C-1'), 46.3 (C-4'), 34.0 (C-2'), 30.1 (C-6'), 13.1 ($\underline{C}H_3$).

(+)-β-D-Carbocyclic-3'-O-benzyl-1'-(1*H*-[N^3-benzyloxymethyl]-thymin-1-yl)-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-1-O-(benzyl)-4-(1*H*-[N^3-benzyloxymethyl]-thymin-1-yl)-2-(hydroxymethyl)-cyclopentan-1-ol (8: Tb): A solution of **6: Tb** (0.443 g, 0.64 mmol) in THF (3 mL), CH_3OH (8 mL) and 1 N HCl (1 mL) was refluxed for 2 h. The solvent was evaporated, and the residue

was purified on silica gel (ether-hexanes, 1:6 → 1:0) to provide 260 mg (0.576 mmol, 90%) of product. TLC (silica, ether-hexanes, 2:1) R_f 0.1; $[\alpha]_D$ +38.1 (c=0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 7.4-7.2 (m, 10 H, Ph), 7.04 (s, 1 H, H-6), 5.65-5.55 (m, 1 H, H-1'), 5.20 (s, 2 H, H-8), 4.61 (s, 2 H, H-10), 4.52 (AB, 2 H, Δδ=0.06 ppm, J_{AB}=11.6 Hz, C$\underline{H}_2$Ph), 4.29 (dd, 1 H, J=6.7 Hz; J=6.2 Hz, H-3'), 3.85-3.7 (m, 2 H, H-5'), 2.55-2.4 (m, 1 H, H-6'), 2.3-2.1 (m, 2 H, H-4', H-2'), 2.05-1.9 (m, 3 H, H-2', H-6', O$\underline{H}$), 1.88 (s, 3 H, C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 163.7 (C-4), 151.4 (C-2), 138.5 ($CH_2\underline{Ph}$), 136.9 (C-6, C-11), 128.5, 128.3, 128.1, 127.7, 127.6, 127.5 (C-12, C-13, C-14, $CH_2\underline{Ph}$), 110.9 (C-5), 83.0 (C-3'), 77.1 (C-8), 71.8 ($\underline{C}H_2$Ph), 71.6 (C-10), 65.4 (C-5'), 50.3 (C-1'), 47.4 (C-4'), 34.3 (C-2'), 28.7 (C-6'), 13.0 ($\underline{C}H_3$).

(+)-β-D-Carbocyclic-3'-O-benzyl-1'-(1*H*-[N^3-benzyloxymethyl]-thymin-1-yl)-5'-O-(o-xylenephosphate)-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-1-O-(benzyl)-4-(1*H*-[N^3-benzyloxymethyl]-thymin-1-yl)-2-[(o-xylenephosphoryloxy)methyl]-cyclopentan-1-ol (10: Tb): To a dried mixture of **8: Tb** (280 mg, 0.62 mmol), o-xylene-N,N-diethylphosphoramidite (223 mg, 0.93 mmol, 1.5 eq.), and 1-H tetrazole (89 mg, 1.24 mmol, 2 eq.) was added dry THF (6 mL). After 14 h at 25 °C, the mixture was cooled to -40 °C, and treated with a solution of *m*CPBA (60%, 358 mg, 1.24 mmol, 2 eq.) in CH_2Cl_2 (2 mL) at 25 °C for 4 h. 10% $Na_2S_2O_5$ (3 drops) was added and solvent was evaporated. The residue was dissolved in ethyl acetate (30 mL), and washed successively with 10% $Na_2S_2O_5$ (5 mL), 5% $NaHCO_3$ (2 x 10 mL), and brine (5 mL), and dried over $MgSO_4$ and evaporated. The residue was purified on silica gel (ether-hexanes, 1:4 → 1:0) to yield 350 mg (0.55 mmol, 89%) of product. TLC (silica, ether) R_f 0.24; TLC (silica, ethyl acetate) R_f 0.56; $[\alpha]_D$ +18.6 (c=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 7.4-7.2 (m, 14 H, Ph), 7.03 (d, 1 H, J=1.2 Hz, H-6), 5.65-5.5 (m, 1 H, H-1'), 5.3-5.0 (m, 6 H, 2 H-8, 4 H-α), 4.59 (s, 2 H, H-10), 4.50 (AB, 2 H, Δδ=0.08 ppm, J_{AB}=11.6 Hz, C$\underline{H}_2$Ph), 4.4-4.2 (m, 3 H, H-3', 2 H-5'), 2.6-2.4 (m, 2 H, H-6', H-4'), 2.2-2.05 (m, 2 H, H-2'), 2.05-1.9 (m, 1 H, H-6'), 1.86 (s, 3 H, C$\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 163.6 (C-4), 151.3 (C-2), 138.5 ($CH_2\underline{Ph}$), 136.9 (C-6, C-11),

135.5 (C-β), 129.0, 128.8, 128.5, 128.3, 128.1, 127.7, 127.6, 127.5 (C-12, C-13, C-14, C-γ, C-δ, CH_2Ph), 110.7 (C-5), 80.4 (C-3'), 77.1 (C-8), 71.7 (CH_2Ph, C-10), 69.0 (C-5'), 68.4, 68.3 (2 C-α), 50.0 (C-1'), 46.0 (C-4'), 33.8 (C-2'), 29.1 (C-6'), 13.0 (CH_3); ^{31}P NMR ($CDCl_3$, H_3PO_4(ext.)) δ -0.18.

(+)-C-dTMP or (+)-(1S, 2R, 4R)-2-(phosphoryloxymethyl)-4-(1*H*-thymin-1-yl)-cyclopentan-1-ol (1: T): A solution of **10: Tb** (0.28 g, 0.44 mmol) in CH_3OH (20 mL), 95% ethanol (20 mL) and CH_2Cl_2 (5 mL) was hydrogenated (50 psi) over 10% Pd/C (60 mg) for 4 days. The suspension was filtered through Celite and solvent was evaporated. TLC (cellulose, n-butanol-acetic acid-H_20, 5:2:3) R_f 0.6. The residue was dissolved in water (3 mL), 1 M $BaBr_2$ (0.9 mL, 0.9 mmol, 2 eq.) was added, and the pH was adjusted to pH 8.4. The precipitated inorganic phosphate was removed by centrifugation. The supernatant (3.8 mL) was treated with ethanol (19 mL, 5 vol.) and the resulting suspension was kept at -20 °C for 1 h. The precipitate was collected by centrifugation, washed with ethanol and ether, and dried *in vacuo* to afford **(+)-1: T** (150 mg, 0.33 mmol, 74%) as a white powder. $[\alpha]_D$ +11.1 (c=0.67, H_2O, pH 5); ^{1}H NMR (D_2O, HOD, pH 9) δ 7.49 (s, 1 H, H-6), 5.75-5.6 (m, 1 H, H-1'), 4.66 (dd, 1 H, J=7.7 Hz, J=7.2 Hz, H-3'), 4.15-3.95 (m, 2 H, H-5'), 2.7-5.55 (m, 1 H, H-6'), 2.45-2.0 (m, 4 H, H-4', 2 H-2', H-6'), 2.05 (s, 3 H, CH_3); ^{13}C NMR (D_2O, HOD, pH 9) δ 166.5 (C-4), 154.1 (C-2), 142.7 (C-6), 113.8 (C-5), 73.4 (C-3'), 64.9 (C-5'), 48.7 (C-1'), 47.3 (C-4'), 35.2 (C-2'), 28.9 (C-6'), 11.5 (CH_3); ^{31}P NMR (D_2O, HOD, pH 9, H_3PO_4(ext.)) δ 7.14; MS (esi) MH^- 319.1, calcd. for $C_{11}H_{17}N_2O_7P$, M 320.2.

B. N^3-crotyl thymine pathway :

N^3-crotyl thymine (Ta): To dry thymine (0.5 g, 3.96 mmol) in dry DMSO (5 mL) was added finely powdered NaOH (0.19 g, 4.75 mmol, 1.2 eq.). After heating at 60°C for 2 h and then cooling to 25 °C, crotyl chloride (0.66 mL, 4.75 mmol, 1.2 eq.) was added. The resulting solution was stirred at 25 °C for 12 h, then heated at 60°C for 1.5 days. Solvent was evaporated and the residue was dissolved in CH_2Cl_2 (30 mL), washed with water (20 mL) and brine (20 mL), and

dried ($MgSO_4$). Purification of the residue after solvent evaporation on silica gel (ether-hexanes, 1:4 → 1:0) gave 0.49 g (2.73 mmol, 69%) of product. TLC (silica, ether) R_f 0.31; ^1H NMR ($CDCl_3$, TMS) δ 9.67 (s, 1 H, H-1), 6.99 (s, 1 H, H-6), 5.8-5.7 (m, 1 H, H-9), 5.55-5.45 (m, 1 H, H-10), 4.26 (d, 2 H, J=6.3 Hz, H-8), 1.92 (s, 3 H, $C\underline{H}_3$), 1.75 (d, 3 H, J=6.3 Hz, H-11); ^{13}C NMR ($CDCl_3$) δ 164.4 (C-4), 151.0 (C-2), 139.6 (C-6), 131.4 (C-9), 124.6 (C-10), 110.7 (C-5), 49.2 (C-8), 17.7 (C-11), 12.3 ($\underline{C}H_3$).

(+)-β-D-Carbocyclic-1'-(1*H*-[N^3-crotyl]-thymin-1-yl)-3'-O-(dimethylthexylsilyl)-5'-O-trityl-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-4-(1*H*-[N^3-crotyl]-thymin-1-yl)-1-O-(dimethylthexylsilyl)-2-(trityloxymethyl)-cyclopentan-1-ol (3: Ta): DEAD (0.56 mL, 3.12 mmol, 3 eq.) was added slowly to a cold (0 °C), stirred solution of dry Ph_3P (0.83 g, 3.12 mmol, 3 eq.) in THF (8 mL). This was kept at 0 °C for 15 min, and then added slowly to a stirred suspension of **(+)-2** (0.54 g, 1 mmol) and **Ta** (0.3 g, 1.6 mmol, 1.6 eq.) in THF (8 mL) at -78 °C. The mixture was kept at -78 °C for 2 h, then at 25 °C for 3 days. Solvent was evaporated and the residue was purified on silica gel (ether-hexanes, 0:1 → 1:4), to give 0.484 g (0.71 mmol, 71%) of product as an oil. TLC (silica, ether-hexanes, 1:1) R_f 0.53; $[\alpha]_D$ +12.4 (c=0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 7.5-7.1 (2 m, 15 H, Ph), 6.92 (d, 1 H, J=1.05 Hz, H-6), 5.8-5.65 (m, 1 H, H-9), 5.65-5.45 (m, 2 H, H-10, H-1'), 4.3-4.15 (m, 3 H, H-3', 2 H-8), 3.34 (dd, 1 H, J=8.5 Hz, J=3.8 Hz, H-5'), 2.96 (t, 1 H, J=8.2 Hz, H-5'), 2.4-2.0 (m, 4 H, H-6', H-4', 2 H-2'), 1.9 (s, 3 H, $C\underline{H}_3$), 1.85-1.7 (m, 1 H, H-6'), 1.74 (d, 3 H, J=6.4 Hz, H-11), 1.48 (sept., 1 H, J=6.8 Hz, H-E), 0.75 (d, 6 H, J=6.8 Hz, H-F), 0.69, 0.67 (2 s, 6 H, H-D), -0.06, -0.17 (2 s, 6 H, H-A, H-B); ^{13}C NMR ($CDCl_3$) δ 163.9 (C-4), 151.1 (C-2), 144.4 (C-β), 137.4 (C-9), 131.1 (C-6), 128.8 (C-δ), 127.6 (C-γ), 124.9 (C-ε), 124.9 (C-10), 110.0 (C-5), 86.2 (C-α), 73.8 (C-3'), 65.5 (C-5'), 50.2 (C-1'), 49.8 (C-8), 48.8 (C-4'), 37.0 (C-2'), 34.1 (C-E), 30.7 (C-6'), 24.6 (C-C), 20.2 (C-F), 18.5 (C-D), 17.7 (C-11), 13.2 ($\underline{C}H_3$), -2.4, -3.1 (C-B, C-A).

(-)-β-D-Carbocyclic-1'-(1*H*-[N^3-crotyl]-thymin-1-yl)-5'-O-trityl-2'-deoxyribonucleoside, or (-)-(1S, 2R, 4R)-4-(1*H*-[N^3-crotyl]-thymin-1-yl)-2-(trityloxymethyl)-cyclopentan-1-ol (4: Ta): A solution of **3: Ta** (0.376 g, 0.554

mmol) and TBAF (1 M in THF) (1.7 mL, 1.7 mmol, 3 eq.) in THF (0.5 mL) was stirred at 25 °C for 3 days. Evaporated of solvent left a residue which was purified on silica gel (ether-hexanes; 1:4 → 4:1), to afford 0.275 g (0.51 mmol, 92.5%) of product. TLC (silica, ether-hexanes, 2:1) R_f 0.2; $[\alpha]_D$ -21.6 (c=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 7.5-7.2 (2 m, 15 H, Ph), 6.91 (d, 1 H, J=1.1 Hz, H-6), 5.8-5.4 (m, 3 H, H-9, H-10, H-1'), 4.50 (dd, 1 H, J=16.8 Hz, J=8.5 Hz, H-3'), 4.21 (d, 2 H, J=6.3 Hz, H-8), 3.41 (dd, 1 H, J=8.9 Hz, J=5.0 Hz, H-5'), 3.18 (t, 1 H, J=8.7 Hz, H-5'), 2.77 (s, 1 H, OH), 2.6-2.4 (m, 1 H, H-6'), 2.25-2.15 (m, 1 H,H-4'), 2.05-1.8 (m, 3 H, 2 H-2', H-6'), 1.88 (s, 3 H, CH_3), 1.71 (d, 3 H, J=1.1 Hz, H-11); ^{13}C NMR ($CDCl_3$) δ 163.9 (C-4), 151.1 (C-2), 143.9 (C-β), 137.6 (C-9), 131.2 (C-6), 128.6 (C-δ), 127.9 (C-γ), 127.0 (C-ε), 124.8 (C-10), 110.0 (C-5), 87.1 (C-α), 76.4 (C-3'), 66.8 (C-5'), 50.2 (C-1'), 49.4 (C-8), 47.7 (C-4'), 36.5 (C-2'), 29.9 (C-6'), 17.7 (C-11), 13.1 (CH_3).

(+)-β-D-Carbocyclic-3'-O-benzyl-1'-(1*H*-[N^3-crotyl]-thymin-1-yl)-5'-O-trityl-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-1-O-(benzyl)-4-(1*H*-[N^3-crotyl]-thymin-1-yl)-2-(trityloxymethyl)-cyclopentan-1-ol (6: Ta): Benzyl bromide (0.149 mL, 1.23 mmol, 3 eq.) was added to a cold (0 °C), stirred suspension of **4: Ta** (219 mg, 0.41 mmol) and NaH (60% dispersion, 49 mg, 1.23 mmol, 3 eq.) in THF (1 mL). The mixture was stirred at 25 °C for 16 h. Ethanol (0.5 mL) and H_2O (1 mL) were added and the mixture was extracted with ether (30 mL). The ether extract was washed with brine (20 mL) and dried ($MgSO_4$). Evaporation of solvent left a residue. This was purified on silica gel (ether-hexanes, 0:1 → 1:1) to provide 248 mg (0.4 mmol, 97%) of product. TLC (silica, ether-hexanes, 2:1) R_f 0.47; $[\alpha]_D$ +14.7 (c=1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 7.5-7.15 (2 m, 20 H, Ph), 6.93 (d, 1 H, J=1.1 Hz, H-6), 5.8-5.45 (m, 3 H, H-9, H-10, H-1'), 4.8-4.5 (m, 5 H, 2 H-8, H-3', CH_2Ph), 4.44 (ABX, 2 H, Δδ=0.07 ppm, J_{AB}=11.6 Hz, J_{AX}=5.5 Hz, J_{BX}=4.5 Hz, H-5'), 2.6-2.5 (m, 1 H, H-6'), 2.4-2.05 (m, 3 H, H-4', 2 H-2'), 2.05-1.9 (m, 1 H, H-6'), 1.91 (s, 3 H, CH_3), 1.74 (d, 3 H, J=6.4 Hz, H-11); ^{13}C NMR ($CDCl_3$) δ 163.9 (C-4), 151.0 (C-2), 144.3 (C-β), 138.8 (CH_2Ph), 137.4 (C-9), 130.9 (C-6), 128.1 (CH_2Ph), 127.6 (C-δ), 127.3 (C-γ), 127.1 (CH_2Ph), 126.7 (C-ε), 124.8 (C-10), 109.8 (C-5), 86.1 (C-α), 80.9 (C-3'),

71.6 ($\underline{C}H_2Ph$), 64.2 (C-5'), 50.1 (C-1'), 50.0 (C-8), 46.3 (C-4'), 34.0 (C-2'), 30.0 (C-6'), 17.6 (C-11), 13.0 ($\underline{C}H_3$).

(+)-β-D-Carbocyclic-3'-O-benzyl-1'-(1*H*-thymin-1-yl)-5'-O-trityl-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-1-O-(benzyl)-4-(1*H*-thymin-1-yl)-2-(trityloxymethyl)-cyclopentan-1-ol (6: T): Finely powdered NaOH (0.12g, 3 mmol, 10 eq.) was heated at 80°C in dry DMSO (3.5 mL) for 10 min. After cooling to 25 °C, **6: Ta** (183 mg, 0.29 mmol) was added, and the mixture was stirred at 50 °C for 4.5 h. The brown mixture was cooled to 25 °C, poured into 0.6 M potassium phosphate, pH 6.8 (10mL), and extracted into ethyl acetate (20 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$), and evaporated. Purification of the residue on silica gel (ether-hexanes, 0:1 → 2:1) gave 108 mg (0.189 mmol, 65%) of product. TLC (silica, ether-hexanes, 2:1) R_f 0.23; $[\alpha]_D$ +15.05 (c=1.01, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 9.7 (s, 1 H, H-3), 7.5-7.1 (2 m, 20 H, Ph), 6.65 (d, 1 H, J=5.3 Hz, H-6), 5.7-5.5 (m, 1 H, H-1'), 4.5-4.35 (m, 2 H, $C\underline{H}_2Ph$), 4.3-4.15 (m, 1 H, H-3'), 3.35-3.1 (2 m, 2 H, H-5'), 2.6-2.5 (m, 1 H, H-6'), 2.4-2.2 (m, 2 H, H-4', H-2'), 2.15-2.0 (m, 1 H, H-2'), 2.0-1.9 (m, 1 H, H-6'), 1.80 (s, 3 H, $C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 164.3 (C-4), 153.1 (C-2), 144.3 (C-β), 138.8 ($CH_2\underline{Ph}$), 134.4 (C-6), 128.7-126.8 ($CH_2\underline{Ph}$), 110.0 (C-5), 86.2 (C-α), 80.8 (C-3'), 71.1 ($\underline{C}H_2Ph$), 64.3 (C-5'), 49.8 (C-1'), 42.4 (C-4'), 33.9 (C-2'), 29.9 (C-6'), 12.9 ($\underline{C}H_3$).

(+)-β-D-Carbocyclic-3'-O-benzyl-1'-(1*H*-thymin-1-yl)-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-1-O-(benzyl)-4-(1*H*-thymin-1-yl)-2-(hydroxymethyl)-cyclopentan-1-ol (8: T): A stirred solution of **6: T** (85 mg, 0.148 mmol) THF (2 mL), CH_3OH (1 mL) and 1 N HCl (1 mL) was refluxed for 2 h. Solvent was evaporated and the residue was purified on silica gel (ether-hexanes-ethyl acetate-CH_3OH, 1:2:0:0 → 0:0:9:1) to provide 23 mg (0.07 mmol, 47%) of product. TLC (silica, ether) R_f 0.13; $[\alpha]_D$ +50.0 (c=1.02, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 9.9 (s, 1 H, H-3), 7.5-7.2 (m, 5 H, Ph), 6.95 (s, 1 H, H-6), 5.7-5.5 (m, 1 H, H-1'), 4.7-4.4 (m, 2 H, $C\underline{H}_2Ph$), 4.4-4.2 (m, 1 H, H-3'), 3.9-3.7 (m, 2 H, H-5'), 2.6-2.5 (m, 1 H, H-6'), 2.4-2.2 (m, 1 H, H-4'), 2.2-1.6 (m, 6 H, 2 H-2', H-5', $C\underline{H}_3$, $O\underline{H}$); ^{13}C NMR ($CDCl_3$) δ 164.2 (C-4), 152.8 (C-2), 138.4 ($CH_2\underline{Ph}$), 135.5

(C-6), 128.4 ($CH_2\underline{Ph}$), 127.6 ($CH_2\underline{Ph}$), 110.5 (C-5), 82.7 (C-3'), 71.5 ($\underline{C}H_2Ph$), 65.3 (C-5'), 49.9 (C-1'), 47.3 (C-4'), 34.3 (C-2'), 28.8 (C-6'), 13.0 ($\underline{C}H_3$).

(+)-β-D-Carbocyclic-3'-O-benzyl-1'-(1*H*-thymin-1-yl)-5'-O-(o-xylene-phosphate)-2'-deoxyribonucleoside, or (+)-(1S, 2R, 4R)-1-O-(benzyl)-4-(1*H*-thymin-1-yl)-2-[(o-xylenephosphoryloxy)methyl]-cyclopentan-1-ol (10: T): To a dried mixture of **8: T** (22 mg, 66.6 μmol), o-xylene-N,N-diethylphosphor-amidite (26 mg, 106.6 μmol, 1.6 eq.), and 1-H tetrazole (11.6 mg, 166.5 μmol, 2.5 eq.) was added dry THF (0.4 mL). After 4 h at 25 °C, the mixture was cooled to -40 °C, and treated with a solution of *m*CPBA (60%, 38 mg, 133.2 μmol, 2 eq.) in CH_2Cl_2 (0.5 mL). This was stirred at 25 °C for 14 h. 10% $Na_2S_2O_5$ (1 drop) was added and the solvent was evaporated. The residue was dissolved in ethyl acetate (20 mL), and the organic solution was washed successively with 10% $Na_2S_2O_5$ (5 mL), 5% $NaHCO_3$ (5 mL), and brine (5 mL), and dried over $MgSO_4$, Purification of the residue on silica gel (CH_2Cl_2-CH_3OH, 1:0 → 19:1), gave 33 mg (66 μmol, 99%) of product. TLC (silica, CH_2Cl_2-CH_3OH, 19:1) R_f 0.26; $[\alpha]_D$ +17.1 (c=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS) δ 9.9 (s, 1 H, H-3), 7.4-7.1 (m, 9 H, Ph), 7.01 (d, 1 H, J=5.7 Hz, H-6), 5.7-5.5 (m, 1 H, H-1'), 5.2-5.0 (m, 4 H, 4 H-α), 4.6-4.4 (m, 2 H, $C\underline{H}_2Ph$), 4.4-4.1 (m, 3 H, H-3', 2 H-5'), 2.7-2.5 (m, 1 H, H-6'), 2.5-2.3 (m, 1 H, H-4'), 2.13 (t, 2 H, J=9.2 Hz, 2 H-2'), 2.05-1.95 (m, 1 H, H-6'), 1.87 (s, 3 H, $C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 164.3 (C-4), 152.6 (C-2), 138.4 ($CH_2\underline{Ph}$), 135.4 (C-β), 134.8 (C-6), 129.1,128.9, 128.3, 127.6, 127.5 (C-γ, C-δ, $CH_2\underline{Ph}$), 109.9 (C-5), 80.3 (C-3'), 71.5 ($\underline{C}H_2Ph$), 69.2 (C-5'), 68.4 (C-α), 49.3 (C-1'), 46.0 (C-4'), 33.7 (C-2'), 28.9 (C-6'), 12.9 ($\underline{C}H_3$); ^{31}P NMR ($CDCl_3$, H_3PO_4(ext.)) δ -0.29.

(+)-C-dTMP (1: T): 10: T (29 mg, 56.6 μmol) was hydrogenated (1 atm.) in 95% ethanol (2 mL) over 10% Pd/C (10 mg) at RT for 16 h. The suspension was filtered through Celite and solvent was evaporated. The residue was dissolved in H_2O (2 mL), treated with 1 M $BaBr_2$ (0.113 mL, 113 μmol, 2 eq.), and the pH was adjusted to pH 8.4. The inorganic phosphate precipitate was removed by centrifugation. The supernatant (2.1 mL) was treated with ethanol 10.5 mL, 5 vol.) and the resulting suspension was kept at -20 °C for 1 h. The

precipitate was collected by centrifugation, washed with ethanol and ether, and dried *in vacuo* to afford 25 mg (66.6 μmol, 100%) of **1: T** as a white powder. The analytical data were identical to **1: T** obtained above.

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REFERENCES AND NOTES

1. Present address: Faculte de Pharmacie, University of Strasbourg, 74 route du Rhin, F-67401 Illkirch, France.
2. Abbreviations used: C-dAMP, β-D-Carbocyclic-1'-(9*H*-adenin-9-yl)-2'-deoxyribonucleoside 5'-monophosphate, or (1S, 2R, 4R)-4-(9*H*-adenin-9-yl)-2-[(phosphoryloxy)methyl]-cyclopentan-1-ol; C-dGMP, β-D-Carbocyclic-1'-(9*H*-guanin-9-yl)-2'-deoxyribonucleoside 5'-monophosphate, or (1S, 2R, 4R)-4-(9*H*-guanin-9-yl)-2-[(phosphoryloxy)methyl]-cyclopentan-1-ol; C-dCMP, β-D-Carbocyclic-1'-(1*H*-cytosin-1-yl)-2'-deoxyribonucleoside 5'-monophosphate or (1S, 2R, 4R)-4-(1*H*-cytosin-1-yl)-2-[(phosphoryloxy)-methyl]-cyclopentan-1-ol; C-dTMP, β-D-Carbocyclic-1'-(1*H*-thymin-1-yl)-2'-deoxyribonucleoside 5'-monophosphate or (1S, 2R, 4R)-2-(phosphoryloxy-methyl)-4-(1*H*-thymin-1-yl) cyclopentan-1-ol; BOM, benzyloxymethyl; DEAD, diethyl azodicarboxylate; DMAP, 4-dimethylaminopyridine; DMF, N,N-dimethylformamide; DMSO, dimethyl sulfoxide; *m*CPBA, *meta*-chloro-perbenzoic acid; TBAF, tetrabutylammonium fluoride; THF, tetrahydro-furan; TLC, thin layer chromatography; TMS, tetramethylsilane.
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