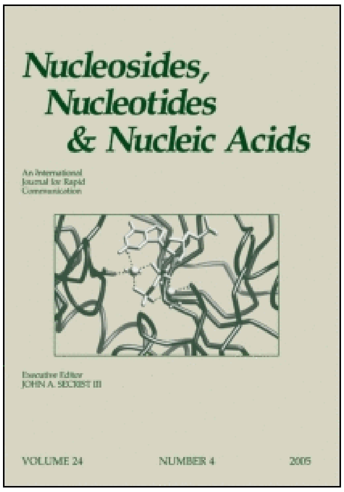

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Synthesis of Chiral Carbocyclic Ribonucleotides

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SYNTHESIS OF CHIRAL CARBOCYCLIC RIBONUCLEOTIDES

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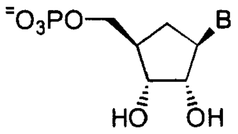
ABSTRACT: The carbocyclic analogs of CMP, UMP, GMP, IMP, and ribo-TMP, of the same absolute configuration as the naturally occurring β-D-ribofuranose-based ribonucleoside monophosphates, have been synthesized. The synthetic route employed Mitsunobu coupling of the heterocycles, appropriately protected where necessary, with a differentially protected, chiral carbocyclic core.

Chiral carbocyclic nucleosides and nucleotides are distinguished from their natural, ribofuranose-based counterparts, by a methylene group replacing the ribose ring oxygen. This replacement imparts properties to these analogs which are useful in a biological context. These include increased stability toward chemical and enzymatic glycosidic bond cleavage and increased lipophilicity[2]. Many carbocyclic nucleosides have shown valuable biological activity, including anti-tumor and anti-viral activities[3]. Several carbocyclic ribonucleotides have proven very useful in mechanistic and substrate-specificity studies with enzymes involved in purine nucleotide biosynthesis[4-10].

As part of our continuing efforts to explore and characterize the enzymology of carbocyclic nucleotides, we report herein the synthesis of the optically active carbocyclic analogs of CMP (C-CMP[11], **1**: **C**), UMP (C-UMP, **1**: **U**), GMP (C-GMP, **1**: **G**), IMP (C-IMP, **1**: **H**), and ribo-TMP (C-rTMP, **1**: **T**). Future studies will be directed toward enzymological evaluation of these analogs.



1: B = C, T, U, G, H

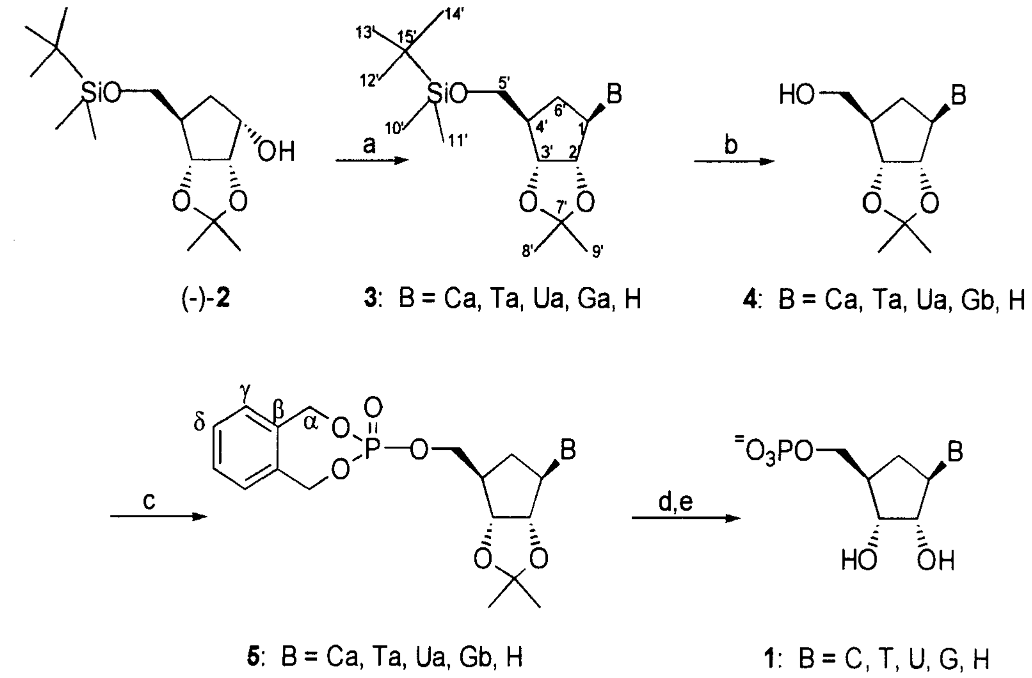
RESULTS AND DISCUSSION

A number of approaches have been devised for the synthesis of chiral carbocyclic ribonucleosides and ribonucleotides[12]. We have opted for a convergent route employing Mitsunobu coupling[13] of the heterocycles, appropriately protected where required, with the differentially protected, chiral cyclopentanol[14], **(−)-2**, as outlined in SCHEME 1. **(−)-2** was chosen as the chiral core since it provides an appropriate precursor for selective 5'-phosphorylation.

Therefore, **(−)-2** was coupled with the bases **Ga**[15], **Ca**[16], **Ta**[17], **Ua**, and **H** (FIG. 1), under conditions similar to those previously reported[17,18], providing **3** in acceptable yields (31-96%, TABLE 1). The choice of benzyloxymethyl as the protecting group for the N^3-position of uracil and thymine resulted from our previous synthesis of the carbocyclic 2'-deoxy pyrimidine nucleotides[17]. The lower yields obtained with **Ca** (56%) and **H** (31%) resulted from competing O-alkylation even though the Mitsunobu coupling was conducted at −78 °C to minimize this competing reaction[17,19]. The desired products were readily separated from their regioisomers by silica gel chromatography.

The conversion of **3** to **4** was accomplished through the use of tetrabutylammonium fluoride (TBAF) in THF. With **3: Ta** and **Ua**, an unidentified by-product, which was not un-reacted starting material, accounted for approximately 30% of the crude product. Treatment of **3: Ga** with TBAF in THF effected simultaneous removal of the *p*-nitrophenylethyl protecting group to afford **4: Gb**, as observed previously[17].

Phosphorylation of the 5'-hydroxyl of **4** was achieved through the use of *o*-xylylene-N,N-diethylphosphoramidite and 1H-tetrazole[20], followed by *in situ* oxidation of the phosphite intermediate with *m*CPBA to give **5** in 47-99% yield after purification. Hydrogenolysis under acidic conditions effected removal of the protecting groups from **5:**



(-)-**2**

3: B = Ca, Ta, Ua, Ga, H

4: B = Ca, Ta, Ua, Gb, H

5: B = Ca, Ta, Ua, Gb, H

1: B = C, T, U, G, H

Reagents: a. Ph_3P, DEAD, THF; b. TBAF, THF; c. 1, *o*-xylylene-N,N-diethylphosphoramidite, 1H-tetrazole, THF, 2, *m*CPBA; d. NH_4OH, CH_3OH for **5: Ca** and **Gb**; e. 1, H_2, 10% Pd/C, TFA, EtOH, 2, $BaBr_2$, pH 8.5.

SCHEME 1

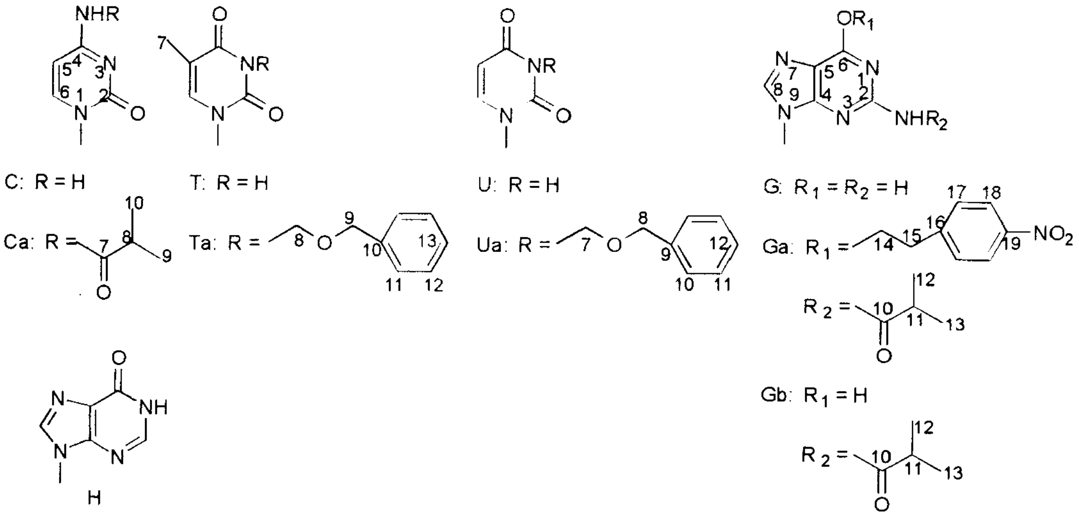


FIGURE 1. Structures of the bases employed. Guanine (G) is drawn in tautomeric form for simplicity.

TABLE 1: Summary of isolated yields (%).

3	4	5	1
Ca (56)	Ca (86)	Ca (99)	C (67)
Ta (96)	Ta (42)	Ta (99)	T (60)
Ua (85)	Ua (46)	Ua (74)	U (79)
Ga (70)	Gb (44)	Gb (47)	G (42)
H (31)	H (75)	H (80)	H (33)

Ta, **Ua**, and **H** to generate **1**: **T**, **U**, and **H**, isolated as the barium salts, in 60, 79, and 33% yield, respectively. Treatment of **5**: **Ca** and **Gb** with ammonium hydroxide in methanol, prior to hydrogenolysis, resulted in removal of the isobutyryl protecting group. The base de-protected intermediates from **5**: **Ca** and **Gb** were carried through the acidic hydrogenolysis to afford **1**: **C** and **G**, as the barium salts, in 67 and 42% yield, respectively.

This constitutes the first convergent syntheses of the chiral carbocyclic analogs of guanylate (GMP), cytidylate (CMP), uridylate (UMP), inosinate (IMP) and ribothymidylate (rTMP).

EXPERIMENTAL SECTION

General. DEAD, Ph_3P, mCPBA, 10% Pd/C, Celite, 1H-tetrazole, uracil, guanine, cytosine, and $BaBr_2$ were purchased from Aldrich. Silica gel 60 (70-230 mesh), thymine, hypoxanthine, TBAF (1M in THF), reagent grade salts and solvents, TFA and Eastman silica gel and cellulose TLC plates were procured from Fisher. The absolute EtOH was obtained from Quantum Chemicals. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a Bruker AC-300 spectrometer at 300.13, 75.44, and 121.49 MHz, respectively. 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. Solvents were reagent grade and dried using standard procedures.[21] Reactions were run under anhydrous conditions and nitrogen, unless otherwise noted.

Synthesis of Chiral Carbocyclic Ribothymidylate (1: T)

(+)-β-D-Carbocyclic-1'-(1H-[N^3-benzyloxymethyl]-thymin-1-yl)-2',3'-O-isopropylidene-5'-O-(*tert*-butyldimethylsilyl) ribonucleoside (3: Ta): To a cold (-78 °C), stirred solution of (–)-**2**[14] (890 mg, 2.95 mmol., 1.0 eq.) and N^3-BOM-thymine[17] (800 mg, 3.25 mmol., 1.1 eq.) in anhydrous THF (5 ml) was added a cold (0 °C) solution of DEAD (0.928 ml, 5.9 mmol., 2 eq.) and Ph$_3$P (1.54 g, 5.9 mmol., 2 eq.) in THF (10 ml). The resulting mixture was stirred at -78 °C for one hour followed by stirring at 25 °C for twelve hours. The clear amber solution was evaporated and the residue was purified on silica gel (ether-hexanes, 1:9) to afford **3: Ta** (1.5 g, 2.83 mmol, 96.2%): TLC (silica, ether-hexanes, 1:2) R_f 0.28; ^{1}H NMR (CDCl$_3$, TMS) δ 7.51-7.43 (m, 5H, H-11-H-13), 7.20 (s, 1H, H-6), 5.56-5.53 (m, 1H, H-1'), 5.35 (s, 2H, H-8), 5.19-5.16 (m, 1H, H-3'), 4.76 (s, 2H, H-9), 4.68-4.61 (m, 1H, H-2'), 4.01 (ABX, 2H, $\Delta\delta$ = 0.15 ppm, J_{AB} = 10.1 Hz, J_{AX} = 2.7 Hz, J_{BX} = 3.78 Hz, H-5'), 2.41-2.35 (m, 2H, H-6',H-4'), 2.28-2.26 (m, 1H, H-6'), 2.02 (s, 3H, H-7), 1.67 (s, 3H, H-8'), 1.43 (s, 3H, H-9'), 1.06-1.04 (3s, 9H, H-12'-H-14'), 0.19 (s, 6H, H-10', H-11'); ^{13}C NMR (CDCl$_3$) δ 163.3 (C-4), 151.3 (C-2), 136.9 (C-6), 136.7 (C-10), 127.9-127.6 (C-11-C-13), 112.3 (C-7'), 110.7 (C-5), 82.3 (C-2'), 81.1 (C-3'), 76.9 (C-8), 71.7 (C-9), 64.0 (C-5'), 57.1 (C-1'), 47.6 (C-4'), 31.2 (C-6'), 27.8 (C-8'), 25.7 (C-12'-C-14'), 25.4 (C-9'), 13.9 (C-15'), 12.8 (C-7), -5.5 (C-10', C-11'); $[\alpha]_D$ +13.46 (c = 0.78, CHCl$_3$).

(+)-β-D-Carbocyclic-1'-(1H-[N^3-benzyloxymethyl]-thymin-1-yl)-2',3'-O-isopropylidene ribonucleoside (4: Ta): To a cold (0 °C), stirred solution of **3: Ta** (1.50 g, 2.83 mmol., 1.0 eq.) was added TBAF (1M in THF) (4.24 ml, 4.24 mmol, 1.5 eq.). After twelve hours at 25 °C, the solvent was evaporated and the residue was purified on silica gel (ether-hexanes, 1:9 to 1:0) to afford 500 mg (1.20 mmol., 42.5%) of **4: Ta**: TLC (silica, 5% MeOH in CH$_2$Cl$_2$) R_f 0.12; ^{1}H NMR (CDCl$_3$, TMS) δ 7.33-7.27 (m, 5H, H-11-H-13), 7.1 (s, 1H, H-6), 5.47-5.40 (m, 1H, H-1'), 5.22 (s, 2H, H-8), 5.04-5.00 (m, 1H, H-3'), 4.75-4.71 (m, 1H, H-2'), 4.62 (s, 2H, H-9), 3.78-3.76 (d, 2H, J = 5.9 Hz, H-5'), 2.36-2.29 (m, 1H, H-4'), 2.19-2.03 (m, 2H, H-6'), 1.89 (s, 3H, H-7), 1.54 (s, 3H, H-8'), 1.29 (s, 3H, H-9'); ^{13}C NMR (CDCl$_3$) δ 163.3 (C-4), 151.3 (C-2), 136.9 (C-6), 136.8 (C-10), 129.0-127.6 (C-11-C-13), 112.4 (C-7'), 110.7 (C-5), 82.6 (C-3'), 82.2

(C-2'), 76.8 (C-8), 71.7 (C-9), 64.4 (C-5'), 57.1 (C-1'), 47.2 (C-4'), 30.5 (C-6'), 29.4 (C-8'), 25.3 (C-9'), 12.7 (C-7); $[\alpha]_D$ +13.5 (c = 0.69, $CHCl_3$).

(+)-β-D-Carbocyclic-1'-(1H-[N^3-benzyloxymethyl]-thymin-1-yl)-2',3'-O-isopropylidene-5'-O-(*o*-xylylenephosphate) ribonucleoside (5: Ta): To a solution of **4: Ta** (500 mg, 1.2 mmol., 1.0 eq.) in anhydrous THF (5 ml) were added 1H-tetrazole (101 mg, 1.44 mmol, 1.2 eq.) and *o*-xylylene-N,N-diethylphosphoramidite (396 mg, 1.5 mmol, 1.25 eq.). After fourteen hours, the solution was cooled to -78 °C and *m*CPBA (434 mg, 1.8 mmol, 1.5 eq.) was added. The reaction was stirred at -78 °C for an hour, then at 25 °C for three hours. The solvent was evaporated and the residue was purified on silica gel (1.5% MeOH in CH_2Cl_2) to yield **5: Ta** (707 mg, 1.18 mmol., 99.8%) as a white solid: TLC (silica, 3% MeOH in CH_2Cl_2) R_f 0.13; ^1H NMR ($CDCl_3$, TMS) δ 7.37-7.27 (m, 9H, H-11-H-13, H-γ, H-δ), 7.06 (s, 1H, H-6), 5.44-5.39 (m, 1H, H-1'), 5.30-5.23 (m, 6H, H-3', H-2', H-α), 5.21 (s, 2H, H-8), 4.60 (s, 2H, H-9), 4.37-4.27 (m, 2H, H-5'), 2.49-2.44 (m, 1H, H-4'), 2.26-2.19 (m, 2H, H-6'), 1.86 (s, 3H, H-7), 1.51 (s, 3H, H-8'), 1.27 (s, 3H, H-9'); ^{13}C NMR ($CDCl_3$) δ 163.3 (C-4), 151.3 (C-2), 137.2 (C-6), 135.4 (C-10), 129.1-127.7 (C-11-C-13, C-β-C-γ), 112.7 (C-7'), 110.7 (C-5), 82.9 (C-2'), 82.6 (C-3'), 76.6 (C-8), 71.8 (C-9), 68.8 (C-α), 68.3 (C-5'), 66.8 (C-α), 56.6 (C-1'), 46.0 (C-4'), 30.9 (C-6'), 27.8 (C-8'), 25.4 (C-9'), 12.8 (C-7); ^{31}P NMR ($CDCl_3$, H_3PO_4 (ext.)) -0.31; $[\alpha]_D$ +7.02 (c = 0.28, $CHCl_3$).

(+)-β-D-Carbocyclic-1'-(1H-thymin-1-yl) ribonucleoside monophosphate or Carbocyclic Ribothymidylate, C-rTMP (1: T): A degassed solution of **4** (700 mg, 1.17 mmol., 1.0 eq.) in 95% EtOH (25 ml) and TFA (10 drops) was hydrogenated (50 psi.) over 10% Pd/C (150 mg) for twelve hours. The suspension was filtered through Celite and then evaporated and co-evaporated with ether (4 x 10 ml). The residue was dissolved in water (5 ml) and 1 M $BaBr_2$ (3.51 ml, 3.51 mmol, 3 eq.) was added. The pH was adjusted to pH 8.5 and the resulting suspension was stirred at 0 °C for two hours. Inorganic phosphate was removed by centrifugation and the supernatant was treated with EtOH (100 ml, 5 vol.). The resulting suspension was kept at -20 °C for twelve hours. The precipitate was collected by centrifugation, and washed with EtOH (2 x 5 ml) and ether (5 ml) and dried to afford **1: T** (330 mg, 0.7 mmol., 60%): TLC (cellulose, *n*-

BuOH: H_2O: HOAc, 5:3:2) R_f 0.13; ^{1}H NMR (D_2O, DCl, pH 2.5) δ 7.09 (s, 1H, H-6), 4.92 (m, 1H, H-1'), 4.34 (m, 1H, H-3'), 4.01 (m, 1H, H-2'), 3.7-3.68 (m, 2H, H-5'), 3.42 (d, 1H, J = 7.0 Hz, H-4'), 2.1 (m, 1H, H-6'), 1.80-1.78 (d, 1H, J = 7.7 Hz, H-6'), 1.61 (s, 3H, H-7); ^{13}C NMR (D_2O, DCl, pH 2.5) δ 167.6 (C-4), 153.8 (C-2), 137.9 (C-6), 110.8 (C-5), 73.6 (C-2'), 72.8 (C-3'), 68.4 (C-5'), 56.7 (C-1'), 44.3 (C-4'), 25.9 (C-6'), 12.9 (C-7); ^{31}P NMR (D_2O, DCl, pH 2.5, H_3PO_4 (ext.)) δ 3.13; $[\alpha]_D$ +1.67 (c = 0.77, H_2O); MS (ESI): $[M-H]^-$ 335, Calculated for $C_{11}H_{17}N_2O_8P$, M 336.

Synthesis of Chiral Carbocyclic Uridylate (1: U)

N^3-Benzyloxymethyluracil (BOM-uracil, Ua): Dried uracil (2.5 g, 22 mmol) was dissolved in dry DMSO (20 ml) and DMF (7 ml). After stirring for 10 min. at room temperature, NaH (0.92 g, 27.5 mmol, 1.25 eq.) was added and the resulting mixture was stirred for 5 h at 25 °C. Benzyloxymethyl chloride (4.33 g, 27.5 mmol, 1.25 eq.) was added and the resulting mixture was stirred overnight at 25 °C. Evaporation of solvent left a residue that was purified by silica gel chromatography (N^1,N^3-bisbenzyloxymethyluracil and N^1-benzyloxymethyluracil eluted with ether-hexanes, 1:4; N^3-benzyloxymethyluracil eluted with ether-hexanes, 1:1) to afford Ua (0.73 g, 3.1 mmol, 14.6%): TLC (silica, ether) R_f 0.50; ^{1}H NMR ($CDCl_3$, TMS) δ 9.72 (s, 1H, N-H), 7.35-7.26 (m, 5H, H-10-H-12), 7.12 (d, J = 6.7 Hz, 1H, H-6), 5.78-5.75 (d, J = 6.7 Hz, 1H, H-5), 5.29-5.22 (s, 2H, H-8), 4.71-4.61 (s, 2H, H-7); ^{13}C NMR ($CDCl_3$) δ 163.5 (C-4), 151 (C-2), 143 (C-6), 136.5 (C-9), 128.5-127.8 (C-10-C-12), 103.2 (C-5), 76.1 (C-8), 71.6 (C-7).

(+)-β-D-Carbocyclic-1'-(1H-[N^3-benzyloxymethyl]-uracil-1-yl)-2',3'-O-isopropylidene-5'-O-(*tert*-butyldimethylsilyl) ribonucleoside (3: Ua): N^3-BOM-uracil (0.73 g, 3.14 mmol, 1.5 eq.) and alcohol (−)-2[14] (0.632 g, 2.09 mmol., 1.0 eq.) were dried for three hours at 60 °C. Anhydrous THF (5 ml) was added and the solution was stirred at -78 °C for ten minutes while DEAD (0.83 ml, 5.23 mmol, 2.5 eq.) was added dropwise to Ph_3P (1.37 g, 5.23 mmol, 2.5 eq.) in THF (10 ml) at 0 °C. The DEAD/ PPh_3 complex was stirred for ten minutes before being added to the BOM-uracil/cyclopentanol mixture. The reaction was stirred at -78 °C for one hour before being brought to room temperature to stir for twelve hours. The clear amber solution was evaporated and the crude product was purified (silica gel, ether-hexanes, 1:9 to 1:0) to yield **3: Ua** (0.92 g, 1.78 mmol., 85%): TLC (silica, ether) R_f 0.78; ^{1}H NMR ($CDCl_3$, TMS) δ 7.32-7.24 (m, 5H, H-10-H-12), 7.21 (d, 1H, J = 7.9 Hz, H-6), 5.73-5.71 (d, 1H, J = 7.9 Hz, H-5), 5.43 (m, 1H, H-1'), 5.25 (s, 2H, H-7), 5.02-4.95 (m, 1H, H-3'), 4.63 (s, 2H, H-8), 4.52-4.50 (m, 1H, H-2'), 3.76-3.74 (d, 2H, J = 6.0 Hz, H-5'), 2.35-2.30 (m, 2H, H-4', H-6'), 2.17-2.09 (m, 1H, H-6'), 1.52 (s, 3H, H-8'), 1.31 (s, 3H, H-9'), 0.89 (s, 9H, H-12'-H-14'), 0.05 (s, 6H, H-10', H-11'); ^{13}C NMR ($CDCl_3$) δ 162.3 (C-4), 151.1 (C-2), 140.6 (C-6), 136.4 (C-9), 128.3-127.5 (C-10-C-12), 112.2 (C-7'), 102.5 (C-5), 82.0 (C-2'), 80.1 (C-3'), 76.7 (C-7), 71.6 (C-8), 63.7 (C-5'), 56.7 (C-1'), 47.2 (C-4'), 30.9 (C-6'), 27.6 (C-8'), 25.6 (C-12'-C-14'), 25.3 (C-9'), 14.0 (C-15'), -5.6 (C-10', C-11');.$[\alpha]_D$ +8.94 (c = 0.10, $CHCl_3$).

(+)-β-D-Carbocyclic-1'-(1H-[N^3-benzyloxymethyl]-uracil-1-yl)-2',3'-O-isopropylidene ribonucleoside (4: Ua): Compound **3: Ua** (1.08 g, 2.09 mmol., 1.0 eq.) was dissolved in THF (15 ml) and stirred at 25 °C for ten minutes before the dropwise addition of TBAF (1M in THF) (3.13 ml, 3.13 mmol, 1.5 eq.) and stirring was continued for twelve hours. The crude product was purified on silica gel (ether-hexanes, 1:3 to 1:0) to provide **4: Ua** (388 mg, 0.96 mmol., 46.2%) as an oil: TLC (silica, 3% MeOH in CH_2Cl_2) R_f 0.03; ^{1}H NMR ($CDCl_3$, TMS) δ 7.33-7.28 (m, 5H, H-10-H-12), 7.20 (d, 1H, J = 7.8 Hz, H-6), 5.74-5.72 (d, 1H, J = 7.8 Hz, H-5), 5.30 (m, 1H, H-1'), 5.23 (s, 2H, H-7), 5.04-5.02 (m, 1H, H-3'), 4.68-4.64 (m, 1H, H-2'), 4.62 (s, 2H, H-8), 3.82 (m, 2H, H-5'), 2.23-2.2 (m, 2H, H-4', H-6'), 2.13-2.1 (m, 1H, H-6'), 1.53 (s, 3H, H-8'), 1.26 (s, 3H, H-9'); ^{13}C NMR ($CDCl_3$) δ 162.6 (C-4), 151.4 (C-2), 141.0 (C-6), 136.6 (C-9), 128.6-127.8 (C-10-C-12), 112.6 (C-7'), 102.8 (C-5), 82.8 (C-2'), 82.7 (C-3'), 76.6 (C-7), 71.9 (C-8), 64.5 (C-5'), 57.0 (C-1'), 47.4 (C-4'), 30.7 (C-6'), 27.8 (C-8'), 25.5 (C-9'); $[\alpha]_D$ +15.83 (c = 0.36, $CHCl_3$).

(+)-β-D-Carbocyclic-1'-(1H-[N^3-benzyloxymethyl]-uracil-1-yl)-2',3'-O-isopropylidene-5'-O-(*o*-xylylenephosphate) ribonucleoside (5: Ua): To the alcohol **4: Ua** (388 mg, 0.96 mmol., 1.0 eq.) in anhydrous THF (10 ml) at 0 °C were added 1H-tetrazole (102 mg, 1.45 mmol, 1.5 eq.) and *o*-xylylene-N,N-diethylphosphoramidite (510 mg, 1.93 mmol, 2.0 eq.). The mixture was stirred at 25 °C. After fourteen hours the starting material was consumed. The solution was cooled to -78 °C, and *m*CPBA (466 mg, 1.93 mmol, 2 eq.) was added. The reaction was stirred at -78 °C for an hour and then at 25 °C for three hours. Evaporation of solvent left a residue that was purified on silica gel (2% MeOH in CH_2Cl_2) to leave **5: Ua** (422 mg, 0.72 mmol., 74.8%) as a white solid: TLC (silica, 3% MeOH in CH_2Cl_2) R_f 0.08; ^{1}H NMR ($CDCl_3$, TMS) δ 7.35-7.22 (m, 9H, H-10-H-12, H-γ, H-δ), 7.20 (d, 1H, J = 7.8 Hz, H-6), 5.70-5.69 (d, 1H, J = 7.8 Hz, H-5), 5.37-5.33 (m, 1H, H-1'), 5.28 (s, 2H, H-7), 5.23-5.20 (m, 4H, H-α), 4.97-4.95 (m, 1H, H-3'), 4.65-4.63 (m, 1H, H-2'), 4.59 (s, 2H, H-8), 4.40-4.22 (m, 2H, H-5'), 2.45-2.40 (m, 1H, H-4'), 2.25-2.16 (m, 2H, H-6'), 1.46 (s, 3H, H-8'), 1.24 (s, 3H, H-9'); ^{13}C NMR ($CDCl_3$) δ 163.3 (C-4), 151.4 (C-2), 141.0 (C-6), 135.5 (C-9), 129.1-127.8 (C-10-C-12, C-β), 112.8 (C-7'), 102.8 (C-5), 82.9 (C-2'), 81.6 (C-3'), 76.6 (C-7), 71.9 (C-8), 68.9 (C-α), 68.5 (C-α), 64.5 (C-5'), 56.5 (C-1'), 46.1 (C-4'), 30.9 (C-6'), 27.9 (C-8'), 25.5 (C-9'); ^{31}P NMR ($CDCl_3$, H_3PO_4 (ext.)) δ - 0.29; $[\alpha]_D$ +9.3 (c = 0.43, $CHCl_3$).

(-)-β-D-Carbocyclic-1'-(1H-uracil-1-yl)-ribonucleoside monophosphate or Carbocyclic Uridylate, C-UMP (1: U): A degassed solution of **5: Ua** (422 mg, 0.72 mmol., 1.0 eq.) in 95% EtOH (5 ml) and TFA (5 drops) was hydrogenated (50 psi.) over 10% Pd/C (100 mg) for twelve hours. The semi-solid remaining after filtration and evaporation was dissolved in water (5 ml) and 1M $BaBr_2$ (0.85 ml, 0.85 mmol, 2.5 eq.) was added. The pH was adjusted to pH 8.5 and the mixture was stirred at 0 °C for two hours. The suspension was centrifuged at 7500 rpm for fifteen minutes, the supernatant was collected, and five volumes (100 ml) of 95% EtOH were added. The suspension was kept at -20 °C for twelve hours. The barium salt was collected by centrifugation at 7500 rpm for fifteen minutes. The salt was washed with EtOH (2 x 5 ml) and then ether (5 ml). The white salt was dried to give 263 mg (0.571 mmol., 79.0% yield) of **1: U**: TLC (cellulose, *n*-BuOH: H_2O: HOAc, 5:3:2) R_f 0.41; ^{1}H NMR (D_2O, DCl, pH 2.5) δ 7.08-7.05 (d, 1H, J = 7.5 Hz, H-6), 5.44-5.42 (d, 1H, J = 7.5 Hz, H-5), 4.76-4.73 (m, 1H, H-1'), 4.17 (m, 1H, H-3'), 4.17-4.14 (m, 1H, H-2'), 3.84-3.71 (m, 2H, H-5'), 1.94 (m, 1H, H-4'), 1.67-1.52 (m, 2H, H-6'); ^{13}C NMR (D_2O, DCl, pH 2.5) δ 168.3 (C-4), 150.0 (C-2), 143 (C-6), 103.0 (C-5), 74.9 (C-2'), 73.6 (C-3'), 69.4 (C-5'), 59.6 (C-1'), 45.3 (C-4'), 26.8 (C-6'); ^{31}P NMR (D_2O, DCl, pH 2.5, H_3PO_4 (ext.)) δ 2.89; $[\alpha]_D$ -2.56 (c = 0.19, H_2O); MS (ESI): $[M-H]^-$ 321, Calculated for $C_{10}H_{15}N_2O_8P$, M 322.

Synthesis of Chiral Carbocyclic Cytidylate (1: C)

(-)-β-D-Carbocyclic-1'-(1H-[N^4-isobutyryl]-cytosin-1-yl)-2',3'-O-isopropylidene-5'-O-(*tert*-butyldimethylsilyl) ribonucleoside (3: Ca): Isobutyramido cytosine[16] (587 mg, 3.24 mmol, 2.0 eq.) and Ph_3P (1.27 g, 4.86 mmol, 3 eq.) were dried at 40 °C for two hours before the addition of anhydrous THF (10 ml). The mixture was stirred at 0 °C for ten minutes, followed by dropwise addition of DEAD (0.76 ml, 4.86 mmol, 3 eq.). The clear orange solution was stirred at 0 °C for twenty minutes before a solution of (–)- **2**[14] (500 mg, 1.66 mmol., 1.0 eq.) in anhydrous THF (10 ml) was added via syringe. The reaction was stirred at 25 °C for six hours then brought to reflux for twelve hours. The solvent was evaporated and the brown oil was purified on silica gel (ether-hexanes, 1:9 to 1:2) to afford **3: Ca** (430 mg, 0.92 mmol., 56%) as an oil: TLC (silica, ether) R_f 0.78; ^{1}H NMR ($CDCl_3$, TMS) δ 8.45 (bs, 1H, N-H), 8.37-8.35 (d, 1H, J = 5.7 Hz, H-5), 7.79-7.77 (d, 1H, J = 5.7 Hz, H-6), 5.21 (m, 1H, H-1'), 4.59 (m, 1H, H-3'), 4.26-4.14 (dd, 1H, J = 7.1 Hz, J = 3.5 Hz, H-2'), 3.65-3.56 (ABX, 2H, Δδ = 0.20 ppm, J_{AB} = 7.7 Hz, J_{AX} = 4.5 Hz, J_{BX} = 7.6 Hz, H-5'), 2.57-2.52 (m, 1H, H-8), 2.34-2.32 (dd, 2H, J = 7.6 Hz, J = 4.5 Hz, H-6'), 1.85-1.82 (m, 1H, H-4'), 1.45 (d, 3H, J = 6.0 Hz, H-9), 1.39 (d, 3H, J = 6.1 Hz, H-10), 1.25 (s, 3H, H-8'), 1.23 (s, 3H, H-9'), 0.86 (s, 9H, H-12'-H-14'), 0.12 (s, 6H, H-10', H-11'); ^{13}C NMR ($CDCl_3$) δ 176.3 (C-7), 163.6 (C-4), 160.4 (C-2), 159.5 (C-6), 110.6 (C-7'), 104.0 (C-5), 84.8 (C-2'), 82.1 (C-3'), 71.8 (C-1'), 63.6 (C-5'), 47.7 (C-4'), 36.5 (C-8), 31.5 (C-6'), 26.7 (C-8'), 25.8 (C-12'-C-14'), 24.2 (C-9'), 19.0 (C-9, C-10), 14.3 (C-15'), -5.5 (C-10', C-11'); $[\alpha]_D$ -9.5 (c = 0.73, $CHCl_3$).

(-)-β-D-Carbocyclic-1'-(1H-[N^4-isobutyryl]-cytosin-1-yl)-2',3'-O-isopropylidene ribonucleoside (4: Ca): To a cold (0 °C) solution of **3: Ca** (430 mg, 0.92 mmol., 1.0 eq.) in THF (15 ml) was added TBAF (1M in THF) (0.97 ml, 0.97 mmol, 1.05 eq.) dropwise. The reaction was stirred at 0 °C for an hour, then at 25 °C for twelve hours. The solvent was removed under vacuum and the residue was purified on silica gel (ether-hexanes, 1:9 to 3% MeOH in CH_2Cl_2) to give **4: Ca** (280 mg, 0.79 mmol., 86.7%) as a clear oil: TLC (silica, ether) R_f 0.12; ^{1}H NMR ($CDCl_3$, TMS) δ 8.67 (s, 1H, N-H), 8.41-8.39 (d, 1H, J = 5.8 Hz, H-5), 7.84-7.83 (d, 1H, J = 5.8 Hz, H-6), 5.25 (m, 1H, H-

1'), 4.67 (m, 1H, H-3'), 4.62 (m, 1H, H-2'), 3.78- 3.65 (m, 2H, H-5'), 2.67-2.57 (m, 1 H, H-8), 2.48-2.41 (m, 2H, H-4', H-6'), 1.87 (m, 1H, H-6'), 1.48 (d, 3H, J = 6.0 Hz, H-9), 1.35 (d, 3H, J = 6.1 Hz, H-10), 1.29 (s, 3H, H-8'), 1.27 (s, 3H, H-9'); ^{13}C NMR ($CDCl_3$) δ 177 (C-7), 163 (C-4), 161 (C-2), 159.8 (C-6), 111 (C-7'), 104 (C-5), 85.0 (C-2'), 83.1 (C-3'), 71.8 (C-1'), 63.7 (C-5'), 47.8 (C-4'), 36.5 (C-8), 31.5 (C-6'), 26.4 (C-8'), 23.8 (C-9'), 19.0 (C-9, C-10); $[\alpha]_D$ -7.67 (c = 0.37, $CHCl_3$).

(-)-β-D-Carbocyclic-1'-(1H-[N^4-isobutyryl]-cytosin-1-yl)-2',3'-O-isopropylidene-5'-O-(*o*-xylylenephosphate) ribonucleoside (5: Ca): To a cold (0 °C), stirred solution of **4: Ca** (280 mg, 0.79 mmol., 1.0 eq.) in THF (15 ml) were added 1H-tetrazole (132 mg, 1.18 mmol, 15 eq.) and *o*-xylylene-N,N-diethylphosphoramidite (378 mg, 1.58 mmol, 2 eq.) and stirring was continued for four hours. Then *m*CPBA (410 mg, 1.58 mmol, 2 eq.) was added and the resulting solution was stirred at 25 °C for twelve hours. The solvent was evaporated and the crude product was purified on silica gel (ether-hexanes, 1:6 to 1:0) to provide **5: Ca** (450 mg, 0.84 mmol., >100 %) as a damp, white solid: TLC (silica, ether) R_f 0.15; ^{1}H NMR ($CDCl_3$, TMS) δ 8.59(s, 1H, N-H), 8.39-8.37 (d, 1H, J = 5.7 Hz, H-5), 7.84-7.82 (d, 1H, J = 5.7 Hz, H-6), 7.40-7.34, 7.32-7.28 (2m, 4H, H-γ, H-δ), 5.30-5.18 (m, 5H, H-1', H-α's), 4.72 (m, 1H, H-3'), 4.61 (m, 1H, H-2'), 4.28-4.24 (m, 2H, H-5'), 3.09-3.03 (m, 1H, H-8), 2.67-2.58 (m, 2H, H-4', H-6'), 2.50-2.41 (m, 1H, H-6'), 1.48 (d, 3H, J = 6.0 Hz, H-9), 1.30 (d, 3H, J = 6.1 Hz, H-10), 1.25 (s, 3H, H-8'), 1.23 (s, 3H, H-9'); ^{13}C NMR ($CDCl_3$,) δ 176.5 (C-7), 163.4 (C-4), 160.2 (C-2), 159.3 (C-6), 135.3 (C-β), 129.0-128.9 (C-γ, C-δ), 110.7 (C-7'), 104.2 (C-5), 84.5 (C-2'), 82.6 (C-3'), 81.4 (C-1'), 71.0 (C-5'), 68.4 (C-α), 46.1 (C-4'), 36.4 (C-8), 31.3 (C-6'), 26.4 (C-8'), 24.1 (C-9'), 19.0 (C-9, C-10); ^{31}P NMR ($CDCl_3$, H_3PO_4 (ext.))δ -0.26; $[\alpha]_D$ -6.21 (c = 0.45, $CHCl_3$).

(-)-β-D-Carbocyclic-1'-(1H-cytosin-1-yl) ribonucleoside monophosphate or Carbocyclic Cytidylate, C-CMP (1: C): A solution of **5: Ca** (140 mg, 0.26 mmol., 1.0 eq.) in MeOH (1 ml) and NH_4OH (2 ml) was stirred at 0 °C for two hours then at 25 °C for two days. The solution was evaporated, then co-evaporated with ether (3 x 10 ml). The solid was dissolved in EtOH (10 ml) and TFA (5 drops) and hydrogenated over 10% Pd/C (60 mg) (>50 psi) for twenty hours. The residue, after filtration and evaporation, was dissolved in water (5 ml) and 1M $BaBr_2$ (0.78 ml, 0.78 mmol, 3 eq.) was added. The pH was adjusted to pH 8.5 with 1 N NaOH and the mixture was stirred at 0 °C for two hours. The suspension was centrifuged at 7500 rpm for fifteen minutes, the supernatant was collected, and five volumes of 95% EtOH (100 ml) were added. The suspension was kept at -20 °C for twelve hours. The barium salt was collected by centrifugation at 7500 rpm for fifteen minutes. The salt was washed with EtOH (2 x 5 ml) and ether (5 ml). The white salt was dried to give **1: C** (80 mg, 0.175 mmol, 67%); TLC (cellulose, *n*-BuOH-water-acetic acid, 5:3:2) R_f 0.27; ^{1}H NMR (D_2O, DCl, pH 6.7) 7.69 (d, 1H, J = 5.9 Hz, H-5), 6.07 (d, 1H, J = 5.9 Hz, H-6), 5.32 (m, 1H, H-1'), 4.86 (m, 1H, H-3'), 3.95 (m, 1H, H-2'), 3.26 (m, 2H, H-5'), 2.29 (m, 2H, H-4', H-6'), 2.09 (m, 1H, H-6'); ^{13}C NMR (D_2O, DCl, pH 6.7) δ 166.3 (C-2), 164.6 (C-4), 156.6 (C-6), 100.9 (C-5), 80.8 (C-1'), 76.5 (C-2'), 74.2 (C-3'), 66.3 (C-5'), 43.3 (C-4'), 30.0 (C-6'); ^{31}P NMR (D_2O, DCl, pH 6.7, H_3PO_4 (ext.)) δ 6.9; $[\alpha]_D$ -9.98 (c = 0.58, H_2O); MS (ESI): $[M-H]^-$ 320, Calculated for $C_{10}H_{16}N_3O_7P$, M 321.

Synthesis of Chiral Carbocyclic Guanylate (1: G)

(-)-β-D-Carbocyclic-1'-(9H-{N^2-isobutyryl-O^6-[p-(nitrophenyl)ethyl]-guanin-9-yl})-2',3'-O-isopropylidene-5'-O-(*tert*-butyldimethylsilyl) ribonucleoside (3: Ga): Alcohol (–)-**2**[14] (0.86 g, 2.84 mmol., 1.0 eq.) and Ph_3P (1.64g, 6.25 mmol., 2.2 eq.) were dried for two hours at 35 °C. A suspension of the protected guanine[15] (1.95 g, 5.25 mmol., 1.85 eq.) in anhydrous dioxane (20 ml) was refluxed for thirty minutes and then cooled to room temperature. The alcohol-Ph_3P mixture was dissolved in anhydrous THF (5 ml) and added to the cooled guanine suspension. The resulting mixture was stirred for fifteen minutes at 25 °C, then DEAD (0.984 ml, 6.25 mmol., 2.2 eq.) was added dropwise over ten minutes. The mixture was stirred for twelve hours at 25 °C. Solvent was evaporated and the residue was purified on silica gel (ether-hexanes, 1:9 to 1:0) to yield **3: Ga** (1.30 g, 1.99 mmol., 70%) as an oil: TLC (silica, ether-hexanes, 2:1) R_f 0.65; ^{1}H NMR ($CDCl_3$, TMS) δ 8.83 (bs, 1H, N-H), 8.22-8.19 (d, 2H, J = 8.2 Hz, H-18), 7.83 (s, 1H, H-8), 7.52 (d, 2H, J = 8.2 Hz, H-17), 5.09-5.07 (t, 2H, J =6.5 Hz, H-14), 4.89-4.84 (m, 3H, H-15, H-1'), 4.78 (m, 1H, H-3'), 3.89 (bs, 1H, H-2'), 3.81-3.76 (ABX, 2H,

$\Delta\delta$ = 0.14 ppm, J_{AB} = 9.15 Hz, J_{AX} = 3.5 Hz, J_{BX} = 6.9 Hz, H-5'), 2.55-2.48 (m, 3H, H-4', H-6'), 1.68 (s, 6H, H8', H9'), 1.52 (m, 1H, H-11), 1.42-1.39 (d, 3H, J = 6.9 Hz, H-12), 1.37-1.35 (d, 3H, J = 6.8 Hz, H-13), 1.06 (3s, 9H, H-12'-H-14'), 0.2-0.18 (2s, 6H, H-10', H-11'); ^{13}C NMR ($CDCl_3$) δ 176.0 (C-10), 160.2 (C-4), 152.1 (C-6), 151 (C-2), 146.2 (C-16), 145 (C-8), 140 (C-19), 129.6 (C-17), 123.3 (C-18), 118 (C-5), 113.1 (C-7'), 83.6 (C-2'), 80.5 (C-3'), 66.2 (C-5'), 63.3 (C-4), 57.4 (C-1'), 45.3 (C-4'), 34.9 (C-15), 33.1 (C-6'), 30.3 (C-11), 27.3 (C-8'), 25.6 (C-12'-C-14'), 24.9 (C-9'), 18.9 (C-12), 18.1 (C-13), 13.9 (C-15'), -5.7 (C-10', C-11'); $[\alpha]_D$ -5.0 (c = 0.32, $CHCl_3$).

(-)-β-D-Carbocyclic-1'-(9H-[N^2-isobutyryl]-guanin-9-yl)-2',3'-O-isopropylidene ribonucleoside (4: Gb): To a cold (0 °C), stirred solution of **3: Ga** (650 mg, 0.99 mmol., 1.0 eq.) in THF (5 ml) was added TBAF (1M in THF) (2.27 ml, 2.27 mmol, 2.25 eq.) and stirring was continued for twelve hours. Evaporation of solvent left a residue that was purified on silica gel (ether-hexanes, 2:1 to 5% MeOH in EtOAc) to afford **4: Gb** (173 mg, 0.44 mmol., 44.7%): TLC (silica, MeOH-EtOAc, 1:9) R_f 0.05; ^{1}H NMR ($CDCl_3$, TMS) δ 12.1 (bs, 1H, N^1-H), 8.75 (bs, 1H, N-H), 8.22 (s, 1H, H-8), 4.87-4.82 (t, 1H, J = 6.7 Hz, H-1'), 4.67 (m, 1H, H-3'), 4.08 (m, 1H, H-2'), 3.80-3.77 (m, 2H, H-5'), 2.63-2.61 (m, 1H, H-4'), 2.43-2.40 (m, 2H, H-6'), 1.58 (m, 1H, H-11), 1.53-1.49 (2s, 6H, H-8', H-9'), 1.24 (2d's, 6H, H-12, H-13); ^{13}C NMR ($CDCl_3$) δ 180 (C-9), 167.3 (C-6), 150.5 (C-2), 134.4 (C-8), 121.6 (C-4), 117.5 (C-5), 111.7 (C-7'), 83.5 (C-2'), 81.1 (C-3'), 61.8 (C-5'), 52.9 (C-1'), 46.6 (C-4'), 44.6 (C-11), 32.9 (C-6'), 26.9 (C-8'), 24.4 (C-9'), 18.8 (C-12, C-13); $[\alpha]_D$ -26.36, (c = 0.11, $CHCl_3$).

(-)-β-D-Carbocyclic-1'-(9H-[N^2-isobutyryl]-guanin-9-yl)-2',3'-O-isopropylidene-5'-O-(*o*-xylylenephosphate) ribonucleoside (5: Gb): To cold (0 °C), stirred solution of **4: Gb** (184 mg, 0.47 mmol., 1.0 eq.) in THF (5 ml) were added 1H-tetrazole (50 mg, 0.71 mmol, 1.5 eq.) and *o*-xylylene-N,N-diethylphosphoramidite (248 mg, 0.94 mmol, 2.0 eq.) and stirring was continued for four hours. At this time, *m*CPBA (228 mg, 0.94 mmol, 2.0 eq.) was added and the resulting solution was stirred at 25 °C for twelve hours. The solvent was evaporated and the crude product was purified on silica gel (3% MeOH in CH_2Cl_2) to give **5: Gb** (130 mg, 0.22 mmol., 46.8%) as a white solid: TLC (silica, ether) R_f 0.89; ^{1}H NMR ($CDCl_3$, TMS) δ 11.1 (bs, 1H, N^1-H), 9.0 (bs, 1H, N-H), 7.80 (s, 1H, H-8), 7.4-7.2 (m, 4H, H-γ, H-δ), 5.29-5.19 (m, 4H, H-α), 5.0-4.92 (m, 1H, H-1'), 4.82-4.80 (m, 1H, H-2'), 4.63-4.59 (m, 1H, H-3'), 4.46-4.25 (ABX, 2H, Δδ = 0.16 ppm, J_{AB} = 10.4 Hz, J_{AX} = 5.9 Hz, J_{BX} = 7.4 Hz, H-5'), 2.85-2.80 (m, 1H, H-4'), 2.65-2.61 (m, 2H, H-6'), 1.85 (m, 1H, H-11), 1.55 (2s, 6H, H-8', H-9'), 1.30-1.29 (d, 3H, J = 6.0 Hz, H-12), 1.21-1.19 (d, 3H, J = 6.1 Hz, H-13); ^{13}C NMR ($CDCl_3$) δ 180.5 (C-10), 156.0 (C-6), 147.9 (C-2), 143.1 (C-8), 139.4 (C-4), 135.2 (C-β), 129.6-129.0 (C-γ, C-δ), 121.9 (C-5), 112.7 (C-7'), 84.4 (C-2'), 82.1 (C-3'), 69.0-68.7 (C-α), 63.5 (C-5'), 50.4 (C-1'), 43.6 (C-4'), 35.6 (C-11), 31.6 (C-6'), 27.7 (C-8'), 25.2 (C-9'), 19.5 (C-12), 18.9 (C-13); ^{31}P NMR ($CDCl_3$, H_3PO_4 (ext.)) δ -0.85; $[\alpha]_D$ -10.73 (c = 0.55, $CHCl_3$).

(+)-β-D-Carbocyclic-1'-(9H-guanin-9-yl) ribonucleoside monophosphate or Carbocyclic Guanylate, C-GMP (1: G): A solution of **5: Gb** (198 mg, 0.34 mmol., 1.0 eq.) in MeOH (5 ml) and concentrated NH_4OH (6 ml) was stirred for twenty hours at 25 °C. The solvent was evaporated and co-evaporated with ether (3 x 10 ml). The solid white residue was dissolved in EtOH (5 ml) and TFA (10 drops), degassed, and hydrogenated (> 50 psi) over 10% Pd/C (100 mg) for twelve hours. The semi-solid, after filtration and evaporation, was dissolved in H_2O (5 ml) and 1 M $BaBr_2$ (1.03 ml, 1.03 mmol, 3 eq.) was added. The pH of the solution was adjusted to pH 8.5 and the resulting suspension was stirred at 0 °C for two hours. The solution was centrifuged at 7500 rpm for fifteen minutes and the supernatant collected. Five volumes of 95% EtOH were added and the suspension was kept at -20 °C for twelve hours. The barium salt was collected by centrifugation at 7500 rpm, washed with EtOH (2 x 5 ml) and ether (5 ml), and dried to give **1: G** (73 mg, 0.146 mmol., 42.6 %) as a powder: TLC (cellulose, n-BuOH: H_2O: HOAc, 5:3:2) R_f 0.27; ^{1}H NMR (D_2O, DCl, pH 1.5) δ 8.8 (s, 1H, H-8), 5.2 (m, 1H, H-1'), 4.38-4.36 (m, 1H, H-3'), 4.10-4.08 (m, 1H, H-2'), 3.67 (m, 2H, H-5'), 3.20-3.19 (m, 1H, H-4'), 1.95-1.84 (m, 1H, H-6'), 1.56-1.54 (m, 1H, H-6'); ^{13}C NMR (D_2O, DCl, pH 1.5) δ 154.5 (C-6), 149.8 (C-2), 142.5 (C-4), 136.0 (C-8), 128.4 (C-5), 74.2 (C-2'), 71.2 (C-3'), 66.6 (C-5'), 61.0 (C-1'), 42.6 (C-4'), 26.9 (C-6'); ^{31}P NMR (D_2O, DCl, pH 1.5, H_3PO_4 (ext.)) δ 2.58; $[\alpha]_D$ +14.92 (c = 0.34, H_2O); MS (ESI): $[M-H]^-$ 360, Calculated for $C_{11}H_{16}N_5O_7P$, M 361.

Synthesis of Chiral Carbocyclic Inosinate (1: H)

(-)-β-D-Carbocyclic-1'-(9H-hypoxanthin-9-yl)-2',3'-O-isopropylidene-5'-O-(*tert*-butyldimethylsilyl) ribonucleoside (3: H): Alcohol (–)-**2**[14] (500 mg, 1.65 mmol., 1.0 eq.), Ph_3P (1.08g, 4.14 mmol, 2.5 eq.) and hypoxanthine (337 mg, 2.48 mmol, 1.5 eq.) were dried together for two hours at 35 °C. The dried reagents were dissolved in anhydrous THF (15 ml) and stirred at 0 °C for ten minutes before the dropwise addition of DEAD (0.652 ml, 4.14 mmol, 2.5 eq.). The reaction was stirred for an hour at 0 °C then brought to 25 °C and stirred for an additional eight hours. Solvent was evaporated and the residue was purified on silica gel using two columns. Column one used a solvent system of ether-hexanes, 1:9 to 1:0, while column two used a 1% MeOH in CH_2Cl_2 solvent system to afford **3: H** (220 mg, 0.52 mmol., 31.7%) as an oil: TLC (silica, ether) R_f 0.45; ^1H NMR ($CDCl_3$, TMS) δ 8.57 (s, 1H, H-8), 8.11 (s, 1H, H-2), 5.62 (m, 1H, H-1'), 4.75-4.71 (m, 1H, H-3'), 4.61-4.59 (m, 1H, H-2'), 3.76-3.58 (dd, 2H, J = 10.2 Hz, J = 6.5 Hz, H-5'), 2.49-2.36 (m, 2H, H-4', H-6'), 1.92-1.88 (m, 1H, H-6'), 1.48 (s, 3 H, H-8'), 1.28 (s, 3H, H-9'), 0.79 (s, 9H, H-12'-H-14'), 0.17 (s, 6H, H-10', H-11'); ^{13}C NMR ($CDCl_3$) δ 157.1 (C-6), 151.7 (C-4), 141.2 (C-2), 132.1 (C-8), 128.7 (C-5), 111.1 (C-7'), 84.8 (C-3'), 82.1 (C-2'), 63.7 (C-5'), 52.6 (C-1'), 47.5 (C-4'), 31.8 (C-6'), 26.8 (C-8'), 25.8 (C-12'-C-14'), 24.4 (C-9'), 18.4 (C-15'), -5.4 (C-10', C-11'); $[\alpha]_D$ -27.9 (c = 0.215, $CHCl_3$).

(-)-β-D-Carbocyclic-1'-(9H-hypoxanthin-9-yl)-2',3'-O-isopropylidene-ribonucleoside (4: H): To a cold (0 °C), stirred solution of **3: H** (400 mg, 0.952 mmol., 1.0 eq.) in THF (5 ml) was added TBAF (1M in THF) (1.24 ml, 1.24 mmol, 1.3 eq.) and stirring was continued for twelve hours. The residue, after solvent evaporation, was purified on silica gel (ether-hexanes, 1:1 to 3% MeOH in CH_2Cl_2). Product containing fractions were combined and evaporated to yield **4: H** (220 mg, 0.71 mmol., 75%): TLC (silica, 5% MeOH in CH_2Cl_2) R_f 0.2; ^1H NMR ($CDCl_3$,TMS) δ 8.57 (s, 1H, H-8), 8.26 (s, 1H, H-2), 5.59-5.57 (m, 1H, H-1'), 4.69-4.67 (m, 1H, H-3'), 4.57-4.55 (m, 1H, H-2'), 3.82-3.66 (m, 2H, H-5'), 2.56-2.38 (m, 2H, H-4', H-6'), 2.17-2.12 (m, 1H, H-6'), 1.52 (s, 3H, H-8'), 1.33 (s, 3H, H-9'); ^{13}C NMR ($CDCl_3$) δ 157.5 (C-6), 151.7 (C-4), 143.2 (C-2), 131.1 (C-8), 110.3 (C-7'), 84.9 (C-3'), 82.6 (C-2'), 62.6 (C-5'), 58.8 (C-1'), 47.7 (C-4'), 30.8 (C-6'), 26.4 (C-8'), 23.9 (C-9'); $[\alpha]_D$ -30.6 (c = 0.16, $CHCl_3$).

(-)-β-D-Carbocyclic-1'-(9H-hypoxanthin-9-yl)-2',3'-O-isopropylidene-5'-O-(*o*-xylylenephosphate) ribonucleoside (5: H): To a cold (0 °C), stirred solution of **4: H** (220 mg, 0.71 mmol., 1.0 eq.) in THF (5 ml) were added 1H-tetrazole (75.7 mg, 1.08 mmol, 1.5 eq.) and *o*-xylylene-N,N-diethylphosphoramidite (284 mg, 1.08 mmol, 1.5 eq.) and stirring was continued for four hours. Then *m*CPBA (260 mg, 1.08 mmol, 1.5 eq.) was added and stirring was continued at 25 °C for twelve hours. The solvent was removed and the crude product was purified on silica gel (3% MeOH in CH_2Cl_2) to provide **5: H** (280 mg, 0.57 mmol., 80%) as a white solid: TLC (silica, 10% MeOH in EtOAc) R_f 0.33; ^{1}H NMR (CD_3OD) δ 9.13 (s, 1H, N-H), 8.52 (s, 1H, H-8), 8.32 (s, 1H, H-2), 7.45-7.39 (m, 4H, H-γ, H-δ), 5.63 (m, 1H, H-1'), 5.37-5.29 (2m, 4H, H-α), 4.84-4.82 (m, 1H, H-3'), 4.77-4.75 (m, 1H, H-2'), 4.35-4.21 (m, 2H, H-5'), 2.68-2.50 (m, 2H, H-4', H-6'), 2.04-1.97 (m, 1H, H-6'), 1.50 (s, 3H, H-8'), 1.35 (s, 3H, H-9'); ^{13}C NMR (CD_3OD) δ 153.0 (C-6), 149.5 (C-4), 144.1 (C-2), 141.5 (C-8), 136.2 (C-β), 130.6-130.4 (C-δ, C-γ), 112.3 (C-7'), 86.0 (C-3'), 83.4 (C-2'), 70.1 (C-α), 69.9 (C-5'), 56.5 (C-1'), 47.2 (C-4'), 32.2 (C-6'), 26.9 (C-8'), 24.4 (C-9'); ^{31}P NMR (CD_3OD, H_3PO_4 (ext.)) δ 2.5; $[\alpha]_D$ -28.8 (c = 0.125, MeOH).

(-)-β-D-Carbocyclic-1'-(9H-hypoxanthin-9-yl) ribonucleotide or Carbocyclic Inosinate, C-IMP (1: H): A degassed solution of **5: H** (230 mg, 0.47 mmol., 1.0 eq.) in EtOH (15 ml) and TFA (15 drops) was hydrogenated (50 psi.) over 10% Pd/C (100 mg) for twenty hours. Filtration and evaporation left a semi-solid that was dissolved in water (5 ml) and treated with 1 M $BaBr_2$ (1.4 ml, 1.4 mmol, 3 eq.). The pH of the solution was adjusted to pH 8.5 and the suspension was stirred at 0 °C for two hours. The suspension was centrifuged at 8000 rpm for fifteen minutes and the supernatant was decanted. Five volumes of 95% EtOH were added to the supernatant and the resulting suspension was kept at -20 °C for twelve hours. The barium salt was collected by centrifugation at 8000 rpm for fifteen minutes, washed with EtOH (10 ml) and ether (2 x 10 ml) and dried to provide **1: H** (75 mg, 0.155 mmol., 33.3%) as a white powder: TLC (cellulose, *n*-BuOH: H_2O: HOAc, 5:3:2) R_f 0.48; ^{1}H NMR (D_2O, DCl, pH 2.0) δ 8.47 (s, 1H, H-8), 8.10 (s, 1H, H-2), 4.88-4.83 (m, 1H, H-1'), 3.65-3.62 (m, 1H, H-3'), 3.52-3.48 (m, 1H, H-2'), 3.39-3.36 (m, 2H, H-5'), 2.01-1.91 (m, 2H, H-6', H-4'), 1.71 (m, 1H, H-

6'); ^{13}C NMR (D_2O, DCl, pH 2.0) δ 164.18 (C-6), 159.26 (C-8), 150.20 (C-2), 145.64 (C-4), 129.92 (C-5), 78.1 (C-3'), 74.8 (C-2'), 71.5 (C-1'), 66.9 (C-5'), 41.8 (C-4'), 29.3 (C-6'); ^{31}P NMR (D_2O, DCl, pH 2.0, (H_3PO_4 (ext.)) δ 2.53; $[\alpha]_D$ -6.0 (c = 0.20, H_2O); MS (ESI): $[M-H]^-$ 345, Calculated for $C_{11}H_{15}N_4O_7P$, M 346.

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11. Abbreviations used: C-CMP, β-D-carbocyclic-1'-(1*H*-cytosin-1-yl)-ribonucleoside 5'-monophosphate; C-UMP, β-D-carbocyclic-1'-(1*H*-uracil-1-yl)-ribonucleoside 5'-monophosphate; C-GMP, β-D-carbocyclic-1'-(9*H*-guanin-9-yl) ribonucleoside 5'-monophosphate; C-IMP, β-D-carbocyclic-1'-(9*H*-hypoxanthin-9-yl) ribonucleoside 5'-monophosphate; C-rTMP, β-D-carbocyclic-1'-(1*H*-thymin-1-yl) ribonucleoside 5'-monophosphate; BOM, benzyloxymethyl; DEAD, diethyl azodicarboxylate; DMF, N, N-dimethylformamide; DMSO, dimethylsulfoxide; *m*CPBA, *meta*-chloro perbenzoic acid; TBAF, tetrabutylammonium fluoride; THF, tetrahydrofuran; TLC, thin layer chromatography; TMS, tetramethylsilane

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