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Synthesis of Optically Pure "Open-chain" Nucleotide Derivatives of Asymmetrized *Tris*(hydroxymethyl)methane

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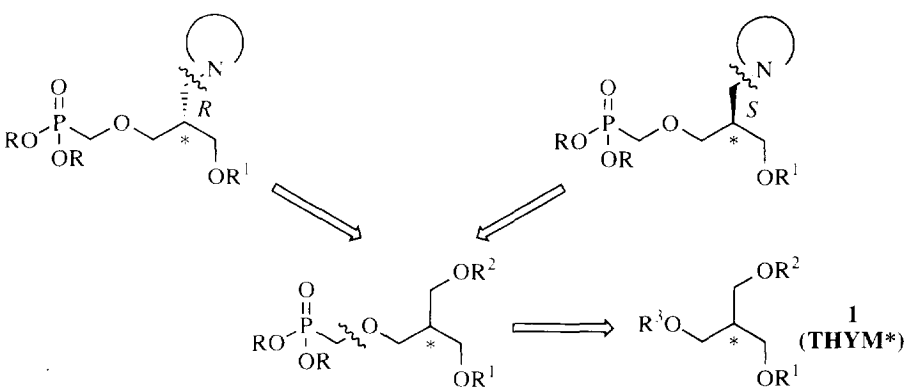
Abstract: Both enantiomers of an "open-chain" phosphonomethoxy analogue of cytidine 5'-monophosphate containing the *tris*(hydroxymethyl)methane moiety have been synthesised, in high enantiomeric excess, starting from (*E*)-2-(acetoxymethyl)-5-metylhex-3-en-1-ol of *R* configuration.

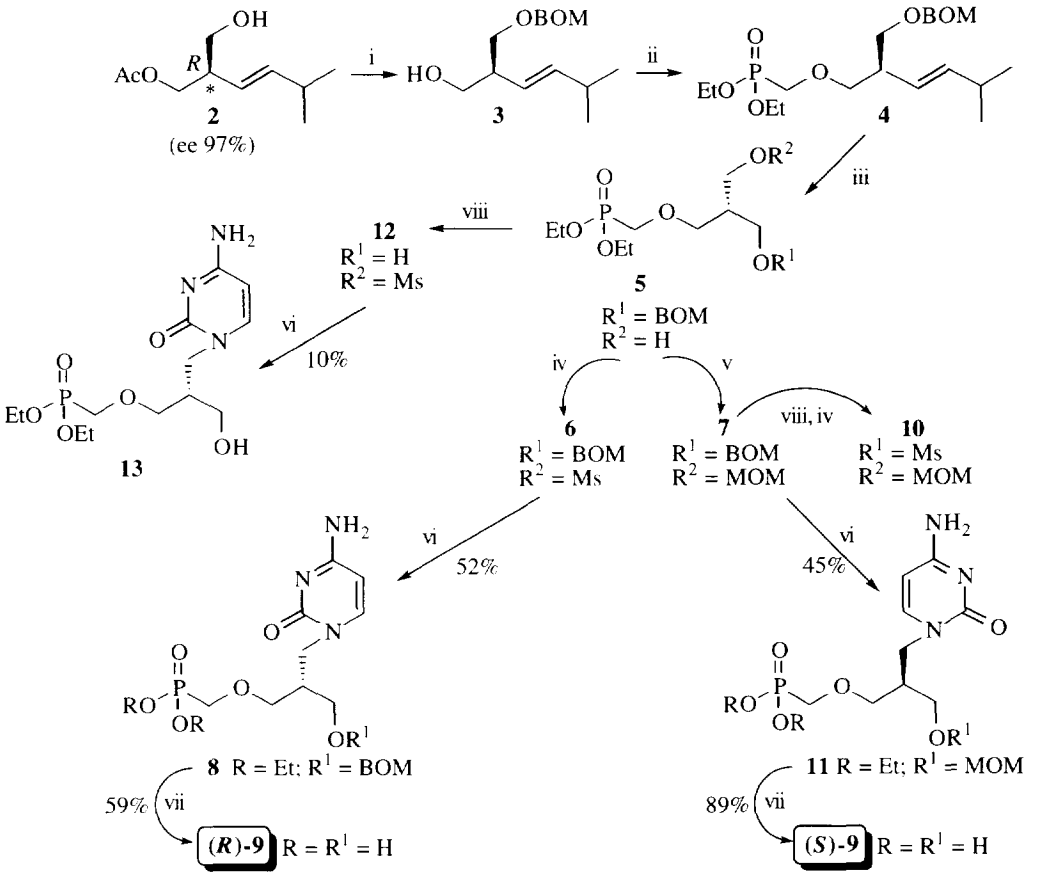
Nucleoside analogues have gained great importance because of their biological activity, particularly as antiviral and antitumoral compounds.[1] Among them, carboacyclic derivatives in which the furanose ring has been replaced by an "open-chain" fragment have stimulated increasing interest since the discovery of the potent and selective anti-herpesvirus activity of 9-(2'-hydroxyethoxymethyl)guanine (Acyclovir, **ACV**).[2] As for all nucleoside and nucleotide analogues, the "acyclic" compounds most likely exert their biological activity following sequential activation to the corresponding triphosphates. Since the first phosphorylation is often the rate-limiting step in the activation process, analogues of nucleoside 5'-monophosphates (nucleotides) have recently been investigated because of their potential for greater potency and a broader spectrum of activity.

In this area, phosphonate esters, in which the P-O-C bond of nucleotides is exchanged for a P-C-O bond, have been proposed as metabolically stable, isosteric and isoelectronic analogues of nucleoside 5'-monophosphates. Interestingly, some carbocyclic phosphonate nucleosides proved to be biologically active[3] and the broad spectrum antiviral activity of some "open-chain" (phosphonomethoxy)alkyl purine and pyrimidine derivatives, even against thymidine kinase (TK) deficient DNA and retroviruses, has recently been quoted.[4]

Scheme 1



Scheme 2



Ac: CH_3CO; BOM: $PhCH_2OCH_2$; Tf: CF_3SO_2; Ms: CH_3SO_2; MOM: CH_3OCH_2; TMS: $(CH_3)_3Si$.

i) BOMCl, $EtN(i\text{-}Pr)_2$, CH_2Cl_2 rt; KOH, MeOH, rt; 92%. ii) *n*-BuLi, $(EtO)_2P(O)CH_2OTf$, THF, -30°C, 62% (93% if referred to unrecovered substrate). iii) O_3, CH_2Cl_2 / MeOH, then $NaBH_4$, -78°C → 0°C, 74%. iv) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0°C → rt, 98%. v) MOMCl, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, rt, 69% (81% if referred to unrecovered substrate). vi) cytosine, $CsCO_3$ DMF, 90°C. vii) TMSCl, NaI, CH_3CN, rt. viii) 10% Pd / C, EtOH, rt, > 90%.

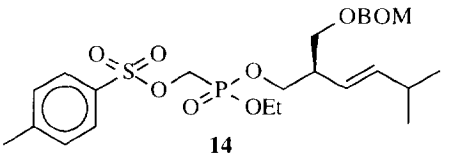
Among this class of nucleotide analogues, (*S*)-1-[3'-hydroxy-2'-(phosphonomethoxy)propyl]cytosine [(*S*)-**HPMPC**][5] showed a very high antiviral activity against a wide range of DNA viruses, superior in some respects to that of acyclovir.

Since marked differences in the biological activity of the two enantiomeric forms of a compound are usually found also in acyclic nucleosides,[4a, 6] it is of primary importance to synthesise new potential antiviral drugs in both enantiomeric forms, in order to evaluate their single specific biological activity.

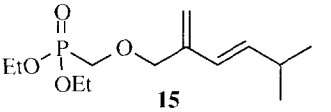
In connection with the extensive research interest into the preparation and evaluation of novel carbocyclic analogues of nucleosides and nucleotides,[7] we now report the stereodivergent and enantiospecific synthesis of (*R*)- and (*S*)-1-[3'-hydroxy-2'-(phosphonomethoxymethyl)propyl]cytosine **9**, starting from the same chiral precursor, that is the optically active monoacetate **2** (e.e. > 97%). Monoacetate **2** is synthetically

equivalent to asymmetrized *tris*(hydroxymethyl)methane (THYM*) **1** that is a new versatile chiral building block, accessible in high enantiomeric excess through a chemoenzymatic route.[8]

The retrosynthetic analysis (Scheme 1) of both (*R*)- and (*S*)-**9**, shows that no reaction at the chiral centre of THYM* is involved in the synthetic strategy, but only enantiospecific chemical manipulations of the three hydroxymethyl branches are required. Nevertheless, thanks to the *enantiodivergency*[8] of our chiral building block, both enantiomer of the final product could be obtained from the same chiral precursor.



14

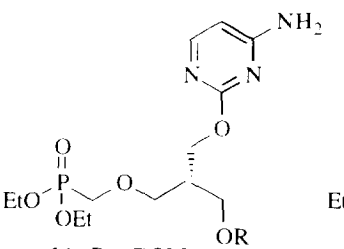


15

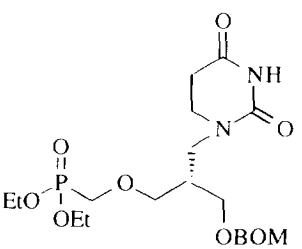
Preparation of **3** (Scheme 2) was carried out as already described.[8] Attempts to transform **3** into **4** by treatment with diethyl phosphonomethyltosylate through a known procedure[9] were unsuccessful, since only traces of a product **14** of transesterification at phosphorus were isolated. Thus phosphonate ester **4** was synthesised, in high yield, using diethyl phosphonomethyltriflate as phosphonylating reagent,[10] under carefully controlled conditions (see Experimental); when more drastic reaction conditions (temperature, reaction time, reagent excess) were applied, a substantial amount of diethyl phosphonate **15**, resulting from an elimination reaction to give a conjugated alkene, was formed as a by-product. Ozonolysis, followed by $NaBH_4$ reduction of the resulting aldehyde, gave the key intermediate **5** (ee > 95%), the optical purity of which was confirmed by NMR analysis of the corresponding Mosher's esters.

In order to get to the (*R*) enantiomer of the target molecule **9** the hydroxyl group of **5** was converted into mesylate **6** through standard methodologies. Nucleophilic displacement of the mesylate by cytosine using cesium carbonate[5b] as a base afforded the desired *N*-alkylated product **8**, in moderate yield, along with a substantial amount of the *O*-alkylated isomer **16** (ratio of *N*-alkykated *vs.* *O*-alkylated product was approximately 3 : 1). Attempts to reductively remove the benzyloxymethyl protecting group under various reaction conditions resulted in no reaction at all, or in complicated reaction mixtures, or, when catalytic hydrogenation was run in methanol in the presence of 10% palladium on carbon and calcium carbonate, in the isolation of (*R*)-1-[2'-(benzyloxymethoxymethyl)-3'-(diethylphosphonomethoxy)propyl]dihydrouracil **19**, that is only the cytosine ring was affected.[5b] On the other hand, when the acetal function in the mesylate **5** was removed before performing the coupling with cytosine, only a poor amount (10%) of the desired *N*-alkylated product **13** were detected after the reaction of alcohol **12** with the nucleic base. Finally, we succeeded in removing the acetal group in **8** using iodotrimethylsilane,[11] generated *in situ* from chlorotrimethylsilane and sodium iodide, which simultaneously deprotected also the phosphonate ester to give the expected target (*R*)-**9** in a straightforward manner.

The synthesis of the enantiomeric (*S*)-**9** required, starting from **5**, two additional steps, in order to "invert" the configuration at the chiral carbon. This goal was easily achieved using a protecting group interchange "trick", *i. e.* simply varying the type and position of protecting groups. Thus, using again standard methodologies, the hydroxyl in **5** was protected as methoxymethyl ether, benzyloxymethyl protecting group was selectively removed, and the resulting free hydroxyl was converted into a mesylate ester. Once again, coupling with cytosine in the presence of cesium carbonate and simultaneous deprotection of primary alcohol and phosphonate ester proved to be the protocol of choice, affording (*S*)-**9** in total



16 R = BOM
17 R = H
18 R = MOM



19

chemical and optical yields comparable to (*R*)-**9**.

In conclusion, we have demonstrated that the highly versatile and enantiodivergent THYM* can be a valuable chiral building block for the synthesis of "open chain" nucleoside and nucleotide analogues.

Assays to evaluate the biological activity of compounds (*R*)-**9** and (*S*)-**9** are in progress and they will be readily published. Extension to more functionalized intermediates of these classes is in progress in our laboratory.

We wish to thank MURST (40% and 60%) and CNR for financial support and for a fellowship (to V. M.).

EXPERIMENTAL

General - UV spectra were recorded on a Perkin-Elmer 554 spectrometer and IR spectra were recorded on a Perkin-Elmer 881 spectrometer. NMR spectra (^1H and ^{13}C) were recorded as $CDCl_3$, [$^2H_6$]-DMSO or D_2O solutions on a Varian Gemini 200 spectrometer at 200 MHz (H) and 50 MHz (C) using tetramethylsilane (TMS), sodium 3-trimethylsilylpropionate or dioxane as internal standards; chemical shifts (δ) are in ppm, coupling constants (J) are in Hertz (Hz); a * means that the value was obtained through double resonance experiments. Attribution of ^{13}C signals was made also with the aid of DEPT and HETCOR experiments. Optical rotatory powers ($[\alpha]_D$) were measured with JASCO DIP 181 polarimeter as 1 - 2% solutions in the indicated solvent. Melting points (mp) were determined on a Büchi 535 digital apparatus.

'Usual workup' means that the given reaction mixture was extracted (Et_2O or AcOEt), the organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure.

Tetrahydrofuran (THF) was always freshly distilled from K / Ph_2CO; CH_2Cl_2, Et_2O, and *N,N*-dimethylformamide (DMF) were purchased as dry solvents from Aldrich and stored over 4 Å molecular sieves. Petroleum ether (PE) refers to the fraction boiling in the range 40 - 60°C.

All reactions requiring dry conditions were run under an inert atmosphere (N_2).

TLC analyses were carried out on silica gel plates, which were developed by spraying a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1 g) in H_2SO_4 (31 ml) and H_2O (469 ml) or an aqueous solution of potassium permanganate and warming. R_f were measured after an elution of 7 - 9 cm. Column chromatographies were run following the method of 'flash chromatography',[12] using 230 - 400 mesh silica gel (Merck). Ion-exchange chromatography was performed on Amberlite CG-120-II (H^+ form, 200-400 mesh), with the specified eluent.

All compounds gave satisfactory spectroscopic and analytical data.

Synthesis of optically active (*R*) monoacetate **2** through enzymatic acetylation of the corresponding diol has been already reported,[13] as well as the synthesis of (*R*) alcohol **3**.[8a]

Diethyl (R)-(E)-[4-(benzyloxymethoxymethyl)-7-methyl-2-oxaoct-5-ene]phosphonate 4 - Alcohol **3** (2.09 g, 7.90 mmol) was dissolved in dry THF (50 ml) and the solution was cooled to -30°C. *n*-BuLi (1.6 M solution in hexane, 5.4 ml, 8.70 mmol) was added dropwise and, after 30 minutes, a solution of (diethylphosphonometyl)triflate[10] (4.75 g, 15.81 mmol) in dry THF (20 ml) was added. The reaction mixture was stirred at -30°C for 24 h. The solution was treated with a saturated aqueous solution of $NaHCO_3$ and sub-

jected to usual work-up (Et_2O) to give, after chromatography (PE / AcOEt 70 : 30 → 40 : 60), pure **4** as a colourless oil (62%, 93% if referred to unrecovered starting material). R_f = 0.27 (PE / AcOEt 40 : 60); $[\alpha]_D$ = +0.4° (*c* 1.69, $CHCl_3$); IR ($CHCl_3$): 2870-3120 (CH), 1455 (C=C), 1260 (P=O), 1022 (P-O-C); ^1H NMR ($CDCl_3$): 0.97 (d, *J* 6.7 Hz, 6 H, Me_2CH), 1.33 (t, *J* 7.1 Hz, 6 H, 2 x $MeCH_2OP$), 2.26 (app octet, *J* 6.6 Hz, 1 H, Me_2CH), 2.50-2.67 (m, 1 H, $CHCH_2OR$), 3.52-3.64 (m, 4 H, 2 x CH_2OR), 3.79 (d, *J* 8.4 Hz, 2 H, CH_2P), 4.16 (app d of quartet, *J* 7.1 & 7.9 Hz, J^*_{gem} 8.0 Hz, 4 H, 2 x $MeCH_2OP$), 4.59 (s, 2 H, CH_2Ph), 4.74 (s, 2 H, OCH_2O), 5.32 (ddd, *J* 1.0, 7.5, 15.8 Hz, 1 H, CH=CHPr^i), 5.55 (dd, *J* 6.6, 15.8 Hz, 1 H, Pr^{i}CH=CH), 7.25-7.40 (m, 5 H, Ph*H*). ^{13}C NMR ($CDCl_3$): 16.50 (d, *J* 5.7 Hz, CH_3CH_2OP), 22.45 [$(CH_3)_2CH$], 31.13 [$(CH_3)_2CH$], 42.79 [$CH(CH_2OR)_2$], 62.38 (d, *J* 6.4 Hz, CH_3CH_2OP), 65.34 (d, *J* 164.7 Hz, PCH_2), 68.58 (CH_2OBOM), 69.23 (CH_2Ph), 74.39 (d, *J* 11.5 Hz, CH_2OCH_2P), 94.67 (OCH_2O), 124.68 (CH=CH), 127.60 (Ar*C* para), 127.78 & 128.34 (Ar*C* ortho and meta), 137.82 (Ar*C* ipso), 140.19 (*C*H=CH).

When more drastic reaction conditions (temperature, reaction time, reagent excess) were applied, compound **15** was isolated as a by-product (20%). ^1H NMR ($CDCl_3$): 1.01 (d, *J* 6.7 Hz, 6 H, Me_2CH), 1.28-1.42 (m, 6 H, 2 x $MeCH_2OP$), 2.16-2.40 (m, 1 H, Me_2CH), 3.51-3.64 (m, 2 H, CH_2OCH_2P), 3.72-3.84 (m, 2 H, CH_2P), 4.07-4.28 (m, 4 H, 2 x $MeCH_2OP$), 5.11 (s, 2 H, CH_2=), 5.80 (dd, *J* 6.5, 16.0 Hz, 1 H, Pr^{i}CH=CH), 6.01 (d, *J* 16.5 Hz, 1 H, Pr^{i}CH=C*H*).

When (diethylphosphonomethyl)-*p*-toluensulfonate[9] (1.2 eq) instead of the corresponding triflate and various bases (NaH, KH or *n*-BuLi, 1.1 eq) in dry DMF or THF were used, compound **14** was isolated as the only product (10%) together with some unreacted starting material (30 ÷ 50%). R_f = 0.21 (PE / AcOEt 60 : 40); ^1H NMR ($CDCl_3$): 0.96 (d, *J* 6.8 Hz, 6 H, Me_2CH), 1.30 (t, *J* 7.2 Hz, 3 H, $MeCH_2OP$), 2.26 (app octet, *J* 6.9 Hz, 1 H, Me_2CH), 2.44 (s, 3 H, *Me*-Ph), 2.50-2.70 (m, 1 H, $CHCH_2OR$), 3.50-3.65 (m, 2 H, CH_2OBOM), 4.18 (d, *J* 10.0 Hz, 2 H, CH_2P), 4.05-4.19 (m, 4 H, $MeCH_2OP$ & CH_2OCH_2P), 4.58 (s, 2 H, CH_2Ph), 4.73 (s, 2 H, OCH_2O), 5.27 (ddd, *J* 1.0, 7.9, 15.7 Hz, 1 H, CH=CHPr^i), 5.57 (ddd, *J* 1.8, 6.6, 15.5 Hz, 1 H, Pr^{i}CH=CH), 7.25-7.45 (m, 7 H, Ar*H*), 7.79 (app d, *J* 8.3 Hz, 2 H, Me-Ph*H*).

Diethyl (R)-[4-(benzyloxymethoxymethyl)-5-hydroxy-2-oxapentane]phosphonate 5 - Ozonolysis of alkene **4** (1.82 g, 4.39 mmol) was carried out as already described[8a] in dry MeOH (28 ml) and CH_2Cl_2 (50 ml). After adding Me_2S (6.2 ml), $NaBH_4$ (831 mg, 21.96 mmol) was added. The reaction mixture was warmed slowly to 0°C and stirred for 2.5 h. The solution was treated with a saturated aqueous solution of NH_4Cl (40 ml), evaporated under reduced pressure and subjected to usual work-up (AcOEt) to give, after chromatography (AcOEt / MeOH 95 : 5), pure **5** as a colourless oil (74%). R_f = 0.34 (AcOEt / MeOH 95 : 5); $[\alpha]_D$ = -4.4° (*c* 1.78, $CHCl_3$); IR ($CHCl_3$): 3400 (OH), 2800-3100 (CH), 1602 (C=C), 1193 (P=O), 1019 (P-O-C); ^1H NMR ($CDCl_3$): 1.34 (t, *J* 7.2 Hz, 6 H, 2 x $MeCH_2OP$), 2.06-2.20 (m, 1 H, $CHCH_2OR$), 3.60-3.82 (m, 4 H, CH_2OBOM & CH_2OCH_2P), 3.66 (d, *J* 6.2 Hz, 2 H, CH_2OH), 3.78 (d, *J* 7.4 Hz, 2 H, CH_2P), 4.16 (app d of quartet, *J* 7.1 & 7.6 Hz, J^*_{gem} 7.7 Hz, 4 H, 2 x $MeCH_2OP$), 4.60 (s, 2 H, CH_2Ph), 4.75 (s, 2 H, OCH_2O), 7.25-7.40 (m, 5 H, Ph*H*). ^{13}C NMR: 16.50 (d, *J* 5.6 Hz, CH_3CH_2OP), 41.64 [$CH(CH_2OR)_2$], 62.10 (CH_2OH), 62.47 (d, *J* 6.8 Hz, CH_3CH_2OP), 65.26 (d, *J* 163.0 Hz, PCH_2), 66.89 (CH_2OBOM), 69.52 (CH_2Ph), 72.35 (d, *J* 9.0 Hz, CH_2OCH_2P), 94.84 (OCH_2O), 127.70 (Ar*C* para), 127.80 & 128.40 (Ar*C* ortho and meta), 137.70 (Ar*C* ipso).

(R)-[2'-(Benzyloxymethoxymethyl)-3'-(diethylphosphonomethoxy)propyl] methanesulfonate 6 - A solution of alcohol **5** (60 mg, 0.16 mmol) in dry CH_2Cl_2 (3.6 ml) was cooled to 0°C. Methanesulfonyl chloride (18 µl, 0.24 mmol) was added rapidly via syringe followed after 10 min by triethylamine (60 µl, 0.40 mmol). The reaction mixture was allowed to warm to room temperature and then poured into water. Usual work-up (Et_2O) followed by chromatography (AcOEt / PE 90 : 10) gave pure **6** as a colourless oil (quantitative yield). R_f = 0.47 (AcOEt / PE 90 : 10); ^1H NMR ($CDCl_3$): 1.34 (t, *J* 7.0 Hz, 6 H, 2 x $MeCH_2OP$), 2.37 (app septet, *J*

5.7 Hz, 1 H, C*H*CH$_2$OR), 3.00 (s, 1 H, CH_3SO$_2$), 3.56-3.72 (m, 4 H, CH_2OBOM & CH_2OCH$_2$P), 3.78 (d, *J* 8.3 Hz, 2 H, CH_2P), 4.10-4.26 (m, J^{*}_{gem} 8.1 Hz, 4 H, 2 x MeCH_2OP), 4.33 (d, *J* 5.7 Hz, 2 H, CH_2OMs), 4.59 (s, 2 H, CH_2Ph), 4.74 (s, 2 H, OCH_2O), 7.27-7.40 (m, 5 H, Ph*H*). ^{13}C NMR (CDCl$_3$): 16.56 (d, *J* 5.7 Hz, *C*H$_3$CH$_2$OP), 37.10 (*C*H$_3$SO$_2$), 39.64 [*C*H(CH$_2$OR)$_3$], 62.44 (d, *J* 6.5 Hz, CH$_3$*C*H$_2$OP), 64.93 (*C*H$_2$OBOM), 65.46 (d, *J* 165.7 Hz, P*C*H$_2$), 67.62 (*C*H$_2$OMs), 69.63 (*C*H$_2$Ph), 70.61 (d, *J* 11.5 Hz, *C*H$_2$OCH$_2$P), 94.90 (O*C*H$_2$O), 127.80 & 128.44 (Ar*C* ortho, meta and para), 137.62 (Ar*C* ipso).

(R)-1-[2'-(Benzyloxymethoxymethyl)-3'-(diethylphosphonomethoxy)propyl]cytosine 8 - A solution of mesylate **6** (1.04 g, 2.29 mmol) in dry DMF (30 ml) was vigorously stirred and heated to 90°C. Cytosine (306 mg, 2.75 mmol) was added followed by addition of cesium carbonate (1.49 g, 4.58 mmol). The reaction mixture was stirred at 90°C for 3 h, allowed to cool to room temperature, and then filtered to remove insoluble material. The filtrate was concentrated to give a yellow gum which was purified by flash chromatography (CH$_2$Cl$_2$ / MeOH 10 : 1 → 9 : 1) and the desired *N*-alkylated product **8** was isolated as a yellowish solid (52%) along with the *O*-alkylated isomer **16** (22%) as a yellow gum. Compound **8** was recrystallized (AcOEt / PE) to give a white crystalline solid.

8: R$_f$ = 0.50 (CH$_2$Cl$_2$ / MeOH 3 : 1); [α]$_D$ = +12.9° (*c* 1.04, MeOH); mp = 78 - 80°C; UV (MeOH): 209, 275; IR (nujol): 3182 & 3379 (NH$_2$), 2800-3100 (CH), 1657 (C=O), 1598 (C=C, C=N), 1462 (C=C), 1024 (P-O-C); ^{1}H NMR (CDCl$_3$): 1.32 (t, *J* 7.1 Hz, 6 H, 2 x *Me*CH$_2$OP), 2.42-2.58 (m, 1 H, C*H*CH$_2$OR), 3.48-3.68 (m, 4 H, CH_2OBOM & CH_2OCH$_2$P), 3.74 (d, *J* 8.8 Hz, 2 H, CH_2P), 3.82 (app dd, *J* 2.7 & 7.0 Hz, 2 H, CH_2N), 4.14 (app d of quintet, *J* 1.9 & 7.1 Hz, 4 H, 2 x MeCH_2OP), 4.58 (s, 2 H, CH_2Ph), 4.73 (s, 2 H, OCH_2O), 5.75 (d, *J* 7.1 Hz, 1 H, C*H*=CHN), 7.36 (d, *J* 7.0 Hz, 1 H, CH=C*H*N), 7.26-7.40 (m, 5 H, Ph*H*). ^{13}C NMR (CDCl$_3$): 16.54 (d, *J* 5.7 Hz, *C*H$_3$CH$_2$OP), 38.67 [*C*H(CH$_2$OR)$_3$], 48.96 (*C*H$_2$N), 62.44 (d, *J* 6.3 Hz, CH$_3$*C*H$_2$OP), 65.22 (d, *J* 165.9 Hz, P*C*H$_2$), 66.08 (*C*H$_2$OBOM), 69.62 (*C*H$_2$Ph), 71.54 (d, *J* 11.8 Hz, *C*H$_2$OCH$_2$P), 94.03 (*C*=C-N), 94.88 (O*C*H$_2$O), 127.72 (Ar*C* para), 127.76 & 128.42 (Ar*C* ortho and meta), 137.66 (Ar*C* ipso), 146.80 (C=*C*-N), 156.67 (*C*-NH$_2$), 165.63 (*C*=O). ^{1}H NMR ([^{2}H$_6$]-DMSO): 1.21 (t, *J* 7.0 Hz, 6 H, 2 x *Me*CH$_2$OP), 2.20-2.40 (m, 1 H, C*H*CH$_2$OR), 3.44-3.56 (m, 4 H, CH_2OBOM & CH_2OCH$_2$P), 3.66 (d, *J* 6.9 Hz, 2 H, CH_2N), 3.78 (d, *J* 8.1 Hz, 2 H, CH_2P), 4.03 (app quintet, *J* 7.0 Hz, 4 H, 2 x MeCH_2OP), 4.52 (s, 2 H, CH_2Ph), 4.68 (s, 2 H, OCH_2O), 5.61 (d, *J* 6.9 Hz, 1 H, C*H*=CHN), 6.97 (bs, 2 H, NH_2), 7.26-7.38 (m, 5 H, Ph*H*), 7.47 (d, *J* 7.0 Hz, 1 H, CH=C*H*N). ^{13}C NMR ([^{2}H$_6$]-DMSO): 16.27 (d, *J* 5.3 Hz, *C*H$_3$CH$_2$OP), 38.47 [*C*H(CH$_2$OR)$_3$], 48.10 (*C*H$_2$N), 61.62 (d, *J* 6.4 Hz, CH$_3$*C*H$_2$OP), 64.10 (d, *J* 160.9 Hz, P*C*H$_2$), 65.58 (*C*H$_2$OBOM), 68.53 (*C*H$_2$Ph), 70.95 (d, *J* 11.6 Hz, *C*H$_2$OCH$_2$P), 92.98 (*C*=C-N), 94.18 (O*C*H$_2$O), 127.35 (Ar*C* para), 127.56 & 128.13 (Ar*C* ortho and meta), 137.85 (Ar*C* ipso), 146.33 (C=*C*-N), 155.76 (*C*-NH$_2$), 165.76 (*C*=O).

16: R$_f$ = 0.50 (CH$_2$Cl$_2$ / MeOH 10 : 1); [α]$_D$ = -2.8° (*c* 1.06, CHCl$_3$); IR (CHCl$_3$): 3418 (NH$_2$), 2800-3100 (CH), 1589-1618 (C=C, C=N), 1295 (P=O), 1019 (P-O-C); ^{1}H NMR (CDCl$_3$): 1.31 (t, *J* 7.2 Hz, 6 H, 2 x *Me*CH$_2$OP), 2.45 (app sextet, *J* 5.9 Hz, 1 H, C*H*CH$_2$OR), 3.66-3.85 (m, 4 H, CH_2OBOM & CH_2OCH$_2$P), 3.78 (d, *J* 8.0 Hz, 2 H, CH_2P), 4.15 (app quintet, *J* 7.3 Hz, 4 H, 2 x MeCH_2OP), 4.37 (app dd, *J* 1.1 & 5.9 Hz, 2 H, CH_2O-C=N), 4.57 (s, 2 H, CH_2Ph), 4.74 (s, 2 H, OCH_2O), 5.04 (bs, 2 H, NH_2), 6.08 (d, *J* 5.7 Hz, 1 H, C*H*=CHN), 7.26-7.40 (m, 5 H, Ph*H*), 8.00 (d, *J* 5.7 Hz, 1 H, CH=C*H*N). ^{1}H NMR ([^{2}H$_6$]-DMSO): 1.20 (t, *J* 7.0 Hz, 6 H, 2 x *Me*CH$_2$OP), 2.22-2.36 (m, 1 H, C*H*CH$_2$OR), 3.56-3.69 (m, 4 H, CH_2OBOM & CH_2OCH$_2$P), 3.81 (d, *J* 8.1 Hz, 2 H, CH_2P), 4.02 (app quintet, *J* 7.1 Hz, 4 H, 2 x MeCH_2OP), 4.19 (d, *J* 6.1 Hz, 2 H, CH_2O-C=N), 4.50 (s, 2 H, CH_2Ph), 4.70 (s, 2 H, OCH_2O), 6.07 (d, *J* 5.8 Hz, 1 H, C*H*=CHN), 6.89 (bs, 2 H, NH_2), 7.22-7.40 (m, 5 H, Ph*H*), 7.84 (d, *J* 5.9 Hz, 1 H, CH=C*H*N). ^{13}C NMR ([^{2}H$_6$]-DMSO): 16.39 (d, *J* 5.4 Hz, *C*H$_3$CH$_2$OP), 39.01 [*C*H(CH$_2$OR)$_3$], 61.78 (d, *J* 6.3 Hz, CH$_3$*C*H$_2$OP), 64.41 (d, *J* 161.3 Hz, P*C*H$_2$), 63.98 (*C*H$_2$O-C=N), 65.27 (*C*H$_2$OBOM), 68.66 (*C*H$_2$Ph), 70.95 (d, *J* 11.4 Hz, *C*H$_2$OCH$_2$P), 94.30 (O*C*H$_2$O), 99.51 (*C*=C-N), 127.49 (Ar*C* para), 127.76 & 128.27 (Ar*C* ortho and meta), 137.97 (Ar*C* ipso), 156.18 (C=*C*-N), 164.81 (N=*C*-O), 165.40 (*C*-NH$_2$).

Attempted deblocking of (R)-1-[2'-(benzyloxymethoxymethyl)-3'-(diethylphosphonomethoxy)propyl]-cytosine 8 to (R)-1-[3'-(diethylphosphonomethoxy)-2'-(hydroxymethyl)propyl]cytosine 13 - A mixture of **8** (59 mg, 0.12 mmol), 10% Pd / C (18 mg) and $CaCO_3$ (18 mg) in MeOH (5 ml) was hydrogenated at room temperature for 2 h. Additional 10% Pd / C (18 mg) was added and the reaction mixture was kept at room temperature for 15 h. The catalyst was filtered off and the crude product was purified by flash chromatography (CH_2Cl_2 / MeOH 90 : 10 → 80 : 20) to give a pure product that was identified as **19** (37%, 39% if referred to unrecovered starting material). **19**: R_f = 0.25 (CH_2Cl_2 / MeOH 90 : 10); ^1H NMR ([$^2H_6$]-DMSO): 1.22 (t, *J* 7.0 Hz, 6 H, 2 x *Me*CH_2OP), 2.09-2.26 (m, 1 H, *CH*CH_2OR), 2.44 (app t, *J* 6.7 Hz, 2 H, *CH*$_2$C=O), 3.16-3.64 (m, 8 H, *CH*$_2$OBOM, *CH*$_2$OCH$_2$P, CH_2*CH*$_2$N & CH*CH*$_2$N), 3.79 (d, *J* 8.1 Hz, 2 H, *CH*$_2$P), 4.03 (app quintet, *J* 7.2 Hz, J^*_{gem} 8.4 Hz, 4 H, 2 x MeC*H*$_2$OP), 4.53 (s, 2 H, *CH*$_2$Ph), 4.69 (s, 2 H, O*CH*$_2$O), 7.25-7.40 (m, 5 H, Ph*H*). ^{13}C NMR ([$^2H_6$]-DMSO): 16.28 (d, *J* 5.4 Hz, *CH*$_3$CH$_2$OP), 26.23 (*CH*$_2$C=O), 39.01 [*CH*(CH$_2$OR)$_3$], 42.76 (CH_2*CH*$_2$N), 46.43 (CH*CH*$_2$N), 61.61 (d, *J* 6.4 Hz, CH_3*CH*$_2$OP), 64.17 (d, *J* 160.8 Hz, P*CH*$_2$), 66.14 (*CH*$_2$OBOM), 68.48 (*CH*$_2$Ph), 71.59 (d, *J* 9.6 Hz, *CH*$_2$OCH$_2$P), 94.24 (O*CH*$_2$O), 127.34 (Ar*C* para), 127.54 & 128.13 (Ar*C* ortho and meta), 137.93 (Ar*C* ipso), 158.44 (N*C*(O)N), 167.61 (CH_2*C*(O)N).

When the same reaction was performed using Pd black in EtOH / cyclohexene at reflux, no reaction was observed. Using Pd / C (10%) and hydrogen in AcOH or PhSH (2 eq) and $BF_3 \cdot Et_2O$ (4 eq) in dry CH_2Cl_2 a complicated mixture of different products was obtained.

(R)-[3'-(Diethylphosphonomethoxy)-2'-(hydroxymethyl)propyl] methanesulfonate 12 - A mixture of mesylate **6** (70 mg, 0.15 mmol) and Pd / C (10%, 23 mg) in EtOH (5 ml) was treated with hydrogen at room temperature. When the reaction was complete (tlc analysis) the catalyst was filtered off, the solvent evaporated and pure **12** was obtained (94%) as a colourless oil. R_f = 0.27 (AcOEt / MeOH 90 : 10); ^1H NMR ($CDCl_3$): 1.36 (t, *J* 7.1 Hz, 6 H, 2 x *Me*CH_2OP), 2.17-2.31 (m, 1 H, *CH*CH_2OR), 3.04 (s, 1 H, *CH*$_3$SO$_2$), 3.71-3.80 (m, 4 H, *CH*$_2$OH & *CH*$_2$OCH$_2$P), 3.80 (d, *J* 7.2 Hz, 2 H, *CH*$_2$P), 4.17 (app quintet, *J* 7.1 Hz, J^*_{gem} 8.1 Hz, 4 H, 2 x MeC*H*$_2$OP), 4.32 (d, *J* 6.5 Hz, 2 H, *CH*$_2$OMs). ^{13}C NMR ($CDCl_3$): 16.53 (d, *J* 5.6 Hz, *CH*$_3$CH$_2$OP), 37.17 (*CH*$_3$SO$_2$), 41.36 [*CH*(CH$_2$OR)$_3$], 59.82 (*CH*$_2$OH), 62.57 (d, *J* 6.6 Hz, CH_3*CH*$_2$OP), 65.23 (d, *J* 165.0 Hz, P*CH*$_2$), 67.88 (*CH*$_2$OMs), 70.63 (d, *J* 7.7 Hz, *CH*$_2$OCH$_2$P).

(R)-1-[3'-(Diethylphosphonomethoxy)-2'-(hydroxymethyl)propyl]cytosine 13 - A solution of mesylate **12** (49 mg, 0.14 mmol) in dry DMF (3.5 ml) was vigorously stirred and heated to 90°C. Cytosine (19 mg, 0.17 mmol) was added followed by addition of cesium carbonate (95 mg, 0.29 mmol). The reaction mixture was stirred at 90°C for 2.5 h, allowed to cool to room temperature, and then filtered to remove insoluble material. The filtrate was concentrated to give a yellow gum which was purified by flash chromatography (CH_2Cl_2 / MeOH 3 : 1) to give *N*-alkylated product **13** (10%) along with the *O*-alkylated isomer **17**.

13: R_f = 0.10 (CH_2Cl_2 / MeOH 3 : 1); ^1H NMR ([$^2H_6$]-DMSO): 1.25 (t, *J* 7.0 Hz, 6 H, 2 x *Me*CH_2OP), 2.20-2.40 (m, 1 H, *CH*CH_2OR), 3.20-3.54 (m, 4 H, *CH*$_2$OH & *CH*$_2$OCH$_2$P), 3.63 (d, *J* 6.9 Hz, 2 H, *CH*$_2$N), 3.79 (d, *J* 8.4 Hz, 2 H, *CH*$_2$P), 4.05 (app quintet, *J* 7.6 Hz, 4 H, 2 x MeC*H*$_2$OP), 4.66 (t, 4.52 *J* 4.9 Hz, O*H*), 5.64 (d, *J* 7.1 Hz, 1 H, C*H*=CHN), 6.81-7.14 (bs, 2 H, N*H*$_2$), 7.50 (d, *J* 7.5 Hz, 1 H, CH=C*H*N).

17: R_f = 0.30 (CH_2Cl_2 / MeOH 3 : 1); ^1H NMR ($CDCl_3$): 1.34 (t, *J* 7.1 Hz, 6 H, 2 x *Me*CH_2OP), 2.14-2.32 (m, 1 H, *CH*CH_2OR), 3.46-3.62 (m, 4 H, *CH*$_2$OH & *CH*$_2$OCH$_2$P), 3.77 (d, *J* 8.3 Hz, 2 H, *CH*$_2$P), 3.91 (d, *J* 5.9 Hz, 2 H, *CH*$_2$O-C=N), 4.16 (app d of quartet, *J* 7.2 & 8.0 Hz, *J* *8.0 Hz, 4 H, 2 x MeC*H*$_2$OP), 5.88 (d, *J* 7.1 Hz, 1 H, C*H*=CHN), 7.42 (d, *J* 7.2 Hz, 1 H, CH=C*H*N).

(R)-1-[2'-(Hydroxymethyl)-3'-(phosphonomethoxy)propyl]cytosine 9 - A solution of **8** (394 mg, 0.84 mmol) in dry CH_3CN (47 ml) was treated with NaI (2.52 g, 16.79 mmol) and TMSCl (2.1 ml, 16.79 mmol) at 0°C in the dark. The reaction mixture was allowed to warm up to room temperature and stirred for 15 h. After

cooling to 0°C, a 0.1 M aqueous solution of ammonium hydrogen carbonate (10 ml) was added dropwise. The resultant solution was evaporated under reduced pressure while heating in order to eliminate most of the iodine. The residue was dissolved in a 0.1 M solution of ammonium hydrogen carbonate and the mixture was evaporated. After several attempts to purify the crude material, finally the residue was dissolved in water and applied onto a column of Amberlite CG-120-II (H^+ form). The column was washed with water to remove the salts, and then with 1 M or 2 M ammonia. The desired product **9** was obtained as a white lyophiliate, after lyophilisation of appropriate fractions (59%). R_f = 0.19 (*n*-BuOH / Me_2CO / AcOH / 5 % NH_4OH / H_2O 35 : 25 : 15 : 15 : 10); $[\alpha]_D$ = +21.7° (*c* 1.00, 1 M aq HCl); mp = 123 - 126°C; UV (aq NaOH): 217, 274; UV (aq HCl): 215, 283; ^1H NMR (NaOD / D_2O): 2.06-2.24 (m, 1 H, C*H*CH_2OR), 3.34 (d, *J* 8.5 Hz, 2 H, CH_2P), 3.40-3.57 (m, 4 H, CH_2OH & CH_2OCH_2P), 3.75 (d, *J* 7.3 Hz, 2 H, CH_2N), 5.90 (d, *J* 7.3 Hz, 1 H, C*H*=CHN), 7.55 (d, *J* 7.3 Hz, 1 H, CH=C*H*N). ^1H NMR (D_2O / DCl): 2.24-2.44 (m, 1 H, C*H*CH_2OR), 3.60-3.76 (m, 4 H, CH_2OH & CH_2OCH_2P), 3.71 (d, *J* 9.1 Hz, *J* *8.9 Hz, 2 H, CH_2P), 3.93 & 4.00 (AB part of an ABX system, *J* 13.7, 7.3 & 6.0 Hz, J^*_{gem} 14.1 Hz, 2 H, CH_2N), 6.17 (d, *J* 7.6 Hz, 1 H, C*H*=CHN), 7.88 (d, *J* 7.6 Hz, 1 H, CH=C*H*N). ^{13}C NMR (D_2O / DCl): 40.57 [*C*H($CH_2OR)_3$], 50.05 (*C*H_2N), 60.93 (*C*H_2OH), 66.97 (d, *J* 159.2 Hz, P*C*H_2), 72.22 (d, *J* 12.0 Hz, *C*H_2OCH_2P), 95.11 (*C*=C-N), 150.10 (*C*-NH_2), 151.12 (C=*C*-N), 160.30 (*C*=O).

Diethyl (R)-[5-(benzyloxymethoxy)-4-(methoxymethoxymethyl)-2-oxapentane]phosphonate 7 - A solution of alcohol **5** (179 mg, 0.47 mmol) in dry CH_2Cl_2 (2.5 ml) was treated at 0°C with diisopropylethylamine (160 µl, 0.95 mmol) and a 1.5 M solution of freshly distilled methyl chloromethyl ether (490 µl, 0.71 mmol). The reaction was stirred at room temperature for 7.5 h, then diisopropylethylamine (160 µl, 0.95 mmol) and a 1.5 M solution of freshly distilled methyl chloromethyl ether (490 µl, 0.71 mmol) were added and stirring continued for 15 h at room temperature. The reaction mixture was diluted with water, extracted with AcOEt, and evaporated to give the crude product. Purification by flash chromatography (AcOEt) gave pure **7** (69%, 81% if referred to unrecovered starting material) as a colourless oil. R_f = 0.38 (AcOEt); $[\alpha]_D$ = -0.4° (*c* 1.28, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.33 (t, *J* 7.1 Hz, 6 H, 2 x *Me*CH_2OP), 2.23 (app septet, *J* 5.9 Hz, 1 H, C*H*CH_2OR), 3.34 (s, 3 H, *Me*O), 3.52-3.70 (m, 6 H, CH_2OBOM, CH_2OMOM & CH_2OCH_2P), 3.78 (d, *J* 8.4 Hz, 2 H, CH_2P), 4.16 (app d of quartet, *J* 7.1 & 7.9 Hz, J^*_{gem} 7.7 Hz, 4 H, 2 x MeCH_2OP), 4.59 (s, 2 H, CH_2Ph), 4.60 (s, 2 H, OCH_2OMe), 4.74 (s, 2 H, OCH_2OBn), 7.27-7.40 (m, 5 H, Ph*H*). ^{13}C NMR ($CDCl_3$): 16.51 (d, *J* 5.7 Hz, *C*H_3CH_2OP), 40.15 [*C*H($CH_2OR)_2$], 55.18 (O*C*H_3), 62.37 (d, *J* 6.4 Hz, CH_3*C*H_2OP), 63.77 (*C*H_2OMOM), 65.43 (d, *J* 165.4 Hz, P*C*H_2), 66.07 (*C*H_2OBOM), 69.33 (*C*H_2Ph), 71.89 (d, *J* 11.8 Hz, *C*H_2OCH_2P), 94.82 & 96.62 (O*C*H_2O), 127.64 (Ar*C* para), 127.77 & 128.36 (Ar*C* ortho and meta), 137.79 (Ar*C* ipso).

(S)-[3'-(Diethylphosphonomethoxy)-2'-(methoxymethoxymethyl)propyl] methanesulfonate 10 - A mixture of **7** (134 mg, 0.32 mmol) and 10% Pd / C (51 mg) in EtOH (11 ml) was treated with hydrogen at room temperature. After 5 h the catalyst was filtered off, the solvent evaporated and pure diethyl (*S*)-[5-hydroxy-4-(methoxymethoxymethyl)-2-oxapentane]phosphonate was obtained (97%) as a colourless oil. R_f = 0.19 (AcOEt / MeOH 90 : 10); ^1H NMR ($CDCl_3$): 1.35 (t, *J* 7.1 Hz, 6 H, 2 x *Me*CH_2OP), 2.04-2.25 (m, 1 H, C*H*CH_2OR), 3.36 (s, 3 H, CH_3O), 3.54-3.84 (m, 6 H, CH_2OMOM, CH_2OH & CH_2OCH_2P), 3.80 (d, *J* 7.6 Hz, 2 H, CH_2P), 4.17 (app d of quartet, *J* 7.1 & 8.0 Hz, J^*_{gem} 8.0 Hz, 4 H, 2 x MeCH_2OP), 4.61 (s, 2 H, OCH_2O).

A solution of the alcohol (92 mg, 0.31 mmol) in dry CH_2Cl_2 (7 ml) was cooled to 0°C. Methanesulfonylchloride (36 µl, 0.46 mmol) was added rapidly *via* syringe followed after 10 min by triethylamine (110 µl, 0.77 mmol). The reaction mixture was allowed to warm to room temperature and after 3 h it was poured into water. Usual work-up (AcOEt) gave crude **10** as a colourless oil. R_f = 0.44 (AcOEt / MeOH 90 : 10); ^1H NMR ($CDCl_3$): 1.28 (t, *J* 7.1 Hz, 6 H, 2 x *Me*CH_2OP), 2.31 (app septet, *J* 5.9 Hz, 1 H,

C*H*CH_2OR), 2.97 (s, 1 H, C*H*$_3SO_2$), 3.28 (s, 3 H, C*H*$_3O$), 3.48-3.67 (m, 4 H, C*H*$_2$OMOM & C*H*$_2OCH_2P$), 3.72 (d, *J* 8.4 Hz, 2 H, C*H*$_2$P), 4.10 (app d of quartet, *J* 7.3 & 7.9 Hz, 4 H, 2 x MeC*H*$_2$OP), 4.27 (d, *J* 5.7 Hz, 2 H, C*H*$_2$OMs), 4.54 (s, 2 H, OC*H*$_2$O).

(S)-1-[3'-(Diethylphosphonomethoxy)-2'-(methoxymethoxymethyl)propyl]cytosine 11 - A solution of crude mesylate **10** (93 mg, 0.24 mmol) in dry DMF (5 ml) was vigorously stirred and heated to 90°C. Cytosine (33 mg, 0.29 mmol) was added followed by addition of cesium carbonate (160 mg, 0.49 mmol). The reaction mixture was stirred at 90°C for 3.5 h, allowed to cool to room temperature, and then filtered to remove insoluble material. The filtrate was concentrated to give a crude product which was purified by flash chromatography (CH_2Cl_2 / MeOH 15 : 1 → 10 : 1) and the desired *N*-alkylated product **11** was isolated as a colourless gum (45%) along with the *O*-alkylated isomer **18** (12%) as a very viscous colourless oil.

11: R_f = 0.15 (CH_2Cl_2 / MeOH 10 : 1); $[\alpha]_D$ = -23.2° (*c* 1.83, $CHCl_3$); $[\alpha]_D$ = -17.8° (*c* 0.73, MeOH); ^{1}H NMR ([$^2H_6$]-DMSO): 1.24 (t, *J* 7.0 Hz, 6 H, 2 x *Me*CH_2OP), 2.20-2.37 (m, 1 H, C*H*CH_2OR), 3.24 (s, 3 H, C*H*$_3$O), 3.20-3.53 (m, 4 H, C*H*$_2$OMOM & C*H*$_2OCH_2P$), 3.65 (d, *J* 6.6 Hz, 2 H, C*H*$_2$N), 3.78 (d, *J* 8.1 Hz, 2 H, C*H*$_2$P), 4.04 (app quintet, *J* 7.3 Hz, J^*_{gem} 8.1 Hz, 4 H, 2 x MeC*H*$_2$OP), 4.53 (s, 2 H, OC*H*$_2$O), 5.63 (d, *J* 7.3 Hz, 1 H, C*H*=CHN), 7.01 (bs, 2 H, N*H*$_2$), 7.48 (d, *J* 7.0 Hz, 1 H, CH=C*H*N). ^{13}C NMR ([$^2H_6$]-DMSO): 16.26 (d, *J* 5.6 Hz, *C*H_3CH_2OP), 39.01 [*C*H(CH_2OR)$_3$], 48.14 (*C*H_2N), 54.86 (*C*H_3O), 61.66 (d, *J* 5.8 Hz, CH_3*C*H_2OP), 64.14 (d, *J* 160.7 Hz, P*C*H_2), 65.36 (*C*H_2OMOM), 70.92 (d, *J* 11.3 Hz, *C*H_2OCH_2P), 93.03 (*C*=C-N), 95.84 (O*C*H_2O), 146.44 (C=*C*-N), 155.84 (*C*-NH_2), 165.84 (*C*=O).

18: R_f = 0.49 (CH_2Cl_2 / MeOH 10 : 1); $[\alpha]_D$ = +1.9° (*c* 1.14, $CHCl_3$); ^{1}H NMR ([$^2H_6$]-DMSO): 1.22 (t, *J* 7.0 Hz, 6 H, 2 x *Me*CH_2OP), 2.27 (app septet, *J* 6.0 Hz, 1 H, C*H*CH_2OR), 3.23 (s, 3 H, C*H*$_3$O), 3.49-3.67 (m, 4 H, C*H*$_2$OMOM & C*H*$_2OCH_2P$), 3.82 (d, *J* 8.1 Hz, 2 H, C*H*$_2$P), 4.04 (app d of quartet, *J* 7.1& 8.1 Hz, J^*_{gem} 8.1 Hz, 4 H, 2 x MeC*H*$_2$OP), 4.17 (d, *J* 5.9 Hz, 2 H, C*H*$_2$O-C=N), 4.55 (s, 2 H, OC*H*$_2$O), 6.07 (d, *J* 5.8 Hz, 1 H, C*H*=CHN), 6.84 (bs, 2 H, N*H*$_2$), 7.84 (d, *J* 5.9 Hz, 1 H, CH=C*H*N). ^{13}C NMR ([$^2H_6$]-DMSO): 16.21 (d, *J* 5.4 Hz, *C*H_3CH_2OP), 39.01 [*C*H(CH_2OR)$_3$], 54.50 (*C*H_3O), 61.63 (d, *J* 6.0 Hz, CH_3*C*H_2OP), 64.25 (d, *J* 161.8 Hz, P*C*H_2), 63.85 (*C*H_2O-C=N), 64.89 (*C*H_2OMOM), 70.76 (d, *J* 12.0 Hz, *C*H_2OCH_2P), 95.76 (O*C*H_2O), 99.34 (*C*=C-N), 156.11 (C=*C*-N), 164.72 (N=*C*-O), 165.30 (*C*-NH_2).

(S)-1-[2'-(Hydroxymethyl)-3'-(phosphonomethoxy)propyl]cytosine 9 - A solution of **11** (37 mg, 0.09 mmol) in dry CH_3CN (5 ml) was treated with NaI (279 mg, 1.86 mmol) and TMSCl (240 µl, 1.86 mmol) at 0°C in the dark. The reaction mixture was allowed to warm up to room temperature and stirred for 15 h. After cooling to 0°C, a 0.1 M aqueous solution of ammonium hydrogen carbonate (1 ml) was added dropwise. The resultant solution was evaporated under reduced pressure while heating in order to eliminate most of the iodine. The residue was dissolved in a 0.1 M solution of ammonium hydrogen carbonate and the mixture was evaporated. The residue was dissolved in water and directly applied onto a column of Amberlite CG-120-II (H^+ form). The column was washed with water to remove the salts, and then with 2.5-5 M ammonia. The desired product **9** was obtained as a white lyophiliate, after lyophilisation of appropriate fractions (89%). $[\alpha]_D$ = -18.1° (*c* 0.75, 1 M aq HCl).

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