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Synthesis of haptens for the development of immunoassays for the monitoring of intracellular anti-HIV nucleosides and nucleotides

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Abstract—A series of nine modified dideoxynucleosides and dideoxynucleotides has been synthesized for preparing antigenic conjugates with keyhole lympet haemocyanin in order to produce specific antibodies, and develop immunoassays. Derivatives of ddI, ddA, d4T, 3TC, and the corresponding 5′-*O*-monophosphates were designed incorporating an amino spacer at the base for conjugation with the proteinic antigenic carrier.

1. Introduction

The first compounds to demonstrate anti-HIV (Human Immunodeficiency Virus) activity were dideoxynucleosides (ddNs). At present, five ddNs are approved by the US Food and Drug Administration and are currently used for treating HIV-infected patients (AZT, ddI, ddC, d4T, and 3TC). They will be followed by a number of new nucleoside compounds that are currently under clinical evaluation. It has been well established that these compounds do not have intrinsic antiviral activity.[1] They penetrate cells through a passive process and are successively metabolized into their monophosphate, diphosphate, and triphosphate by intracellular kinases and nucleotidases. The resulting triphosphates can then inhibit competitively the ADN polymerase of the virus, called reverse transcriptase (RT), because they all lack a 3′-hydroxyl group and work as chain terminators.

Due to the poor fidelity of RT, a large number of mutations spontaneously occur during the replication process.[2,3] That hypervariability of the virus acts in favor of the emergence of variants that are resistant to the antiviral compound used and severely limits the long-term effectiveness of the drug.[4,5] Whatever the antiviral drug administered, in the framework of monotherapies, resistance phenomena are observed within a few weeks or months. The combination of anti-HIV agents has shown to prevent or delay the appearance of these resistances as evidenced by the lowering or even disappearance of the viral load for months or years.[6–9] In these conditions however, the emergence of other causes leading to therapy failure are observed.[10–12] They are essentially related to the complex metabolism of the drugs interfering with the general metabolic pathway of nucleosides and nucleotides. For example it has been shown that long-term exposure to AZT affects in vitro and in vivo the efficiency of phosphorylation of thymidine kinase,[13–15] or that intracellular accumulation of AZT monophosphate (AZTMP) may decrease the conversion of the host cell thymidine monophosphate to thymidine diphosphate and thus lead to cellular toxicity.[16,17] More recently, results were reported suggesting that a combined use of AZT and d4T could interfere with the intracellular formation of d4T triphosphate leading to a decrease in the treatment efficacy.[18,19] These results and others highlight the importance of the intracellular metabolism for the activity of nucleoside inhibitors of HIV RT.[20–24] In addition, a number of reports in the literature describe a great variability in the production of the phosphorylated metabolites of antiviral nucleosides in treated patients.[25–28] That interindividual variability considerably complicates the interpretation of clinical data on treated patients in such a manner that treatments and posologies cannot be efficiently optimized from one patient to the other. This prompted us to develop competitive enzyme immunoassays (EIA) to monitor the intracellular concentration of anti-HIV nucleosides and their phosphorylated metabolites.[29–32] The EIA technique is fast and efficient, and is perfectly adapted to monitoring of intracellular nucleotides as it may allow specific detec-

Keywords: dideoxynucleoside; HIV; enzyme immunoassay; monophosphate; ddI; d4T; 3TC.

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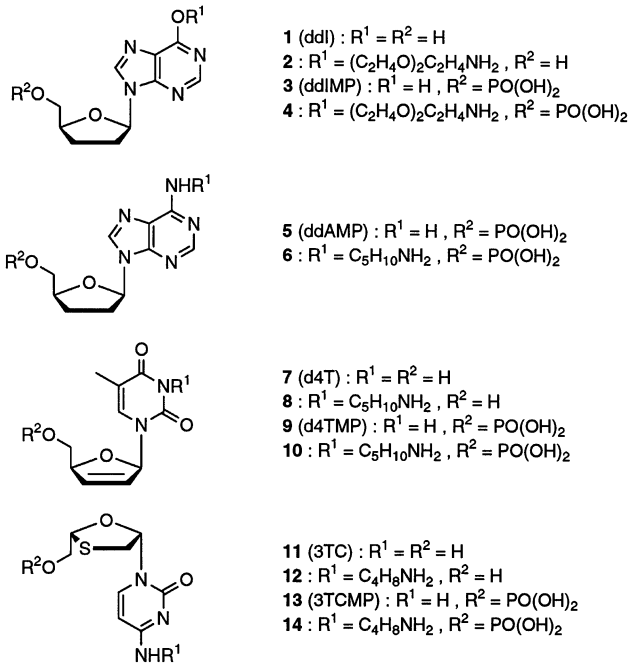


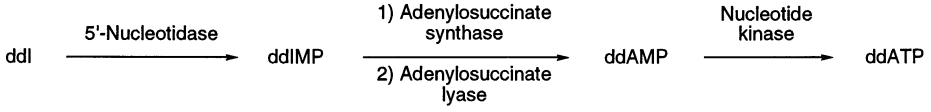
Figure 1.

tion of haptens in the picomolar–nanomolar concentration range. The assay is based on the use of specific antibodies raised against the substance to monitor and of a hapten/acetylcholinesterase conjugate as tracer.[31]

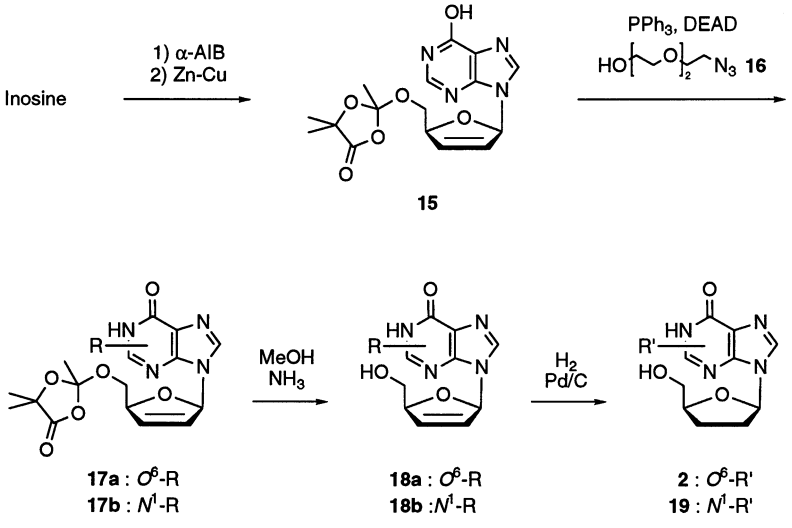
Herein, we describe the synthesis of a series of haptens designed for the production of specific antibodies against ddI, d4T, 3TC, and their monophosphate (MP) metabolites.

2. Results and discussion

The specific antibodies needed to build up an immunoassay are produced in animal hosts injected with the hapten or a derivative. In order to trigger off an immune response in a recipient animal, low molecular weight antigens (such as the nucleosides and nucleotides we are interested in) have to be covalently coupled to a macromolecular carrier, i.e. a protein (bovine serum albumin, keyhole limpet hemocyanin), a liposome, 'a polymer'. The coupling reaction generally requires a prior chemical modification of the antigen in order to introduce a functionalized spacer arm able to react with the carrier. Furthermore the antigen modification should not hamper the recognition specificity of the hapten by the elicited antibodies. In the case of the non-natural nucleoside and nucleotide antigens we are concerned with, we opted for anchoring the spacer at the nucleobase to point out the ribose moiety and the phosphate group, when present, as major antigenic determinant(s) (Fig. 1). Compounds **2**, **8**, and **12** were designed to immunize rabbits against ddI **1**, d4T **7**, and 3TC **11**, respectively. An amino spacer was introduced in the O^6-position in ddI, at N^3 in d4T, and at N^4 in 3TC. This will allow the further preparation of conjugates by anchoring the compounds onto the antigenic carrier by direct cross-linking with glutaraldehyde. Compounds **4** and **6** were prepared to elicit antibodies against ddIMP **3** and ddAMP **5**, respectively, in order to take into account the particular metabolic pathway for ddI[24] (Scheme 1). Compounds **10** and **14** were



Scheme 1.



Scheme 2.

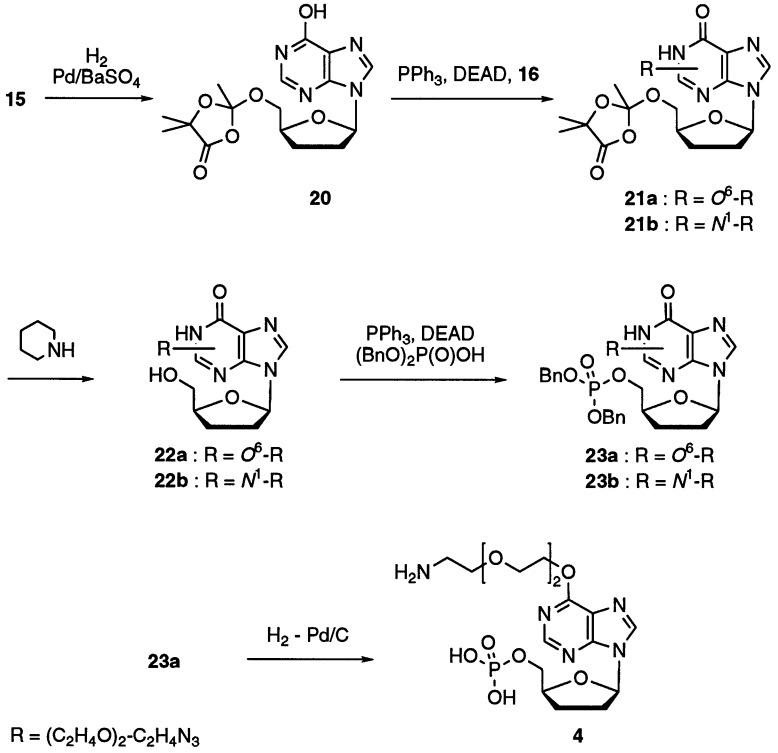
synthesized to raise antibodies against d4TMP **9** and 3TCMP **13**.

2.1. Synthesis of the ddI and ddA derivatives

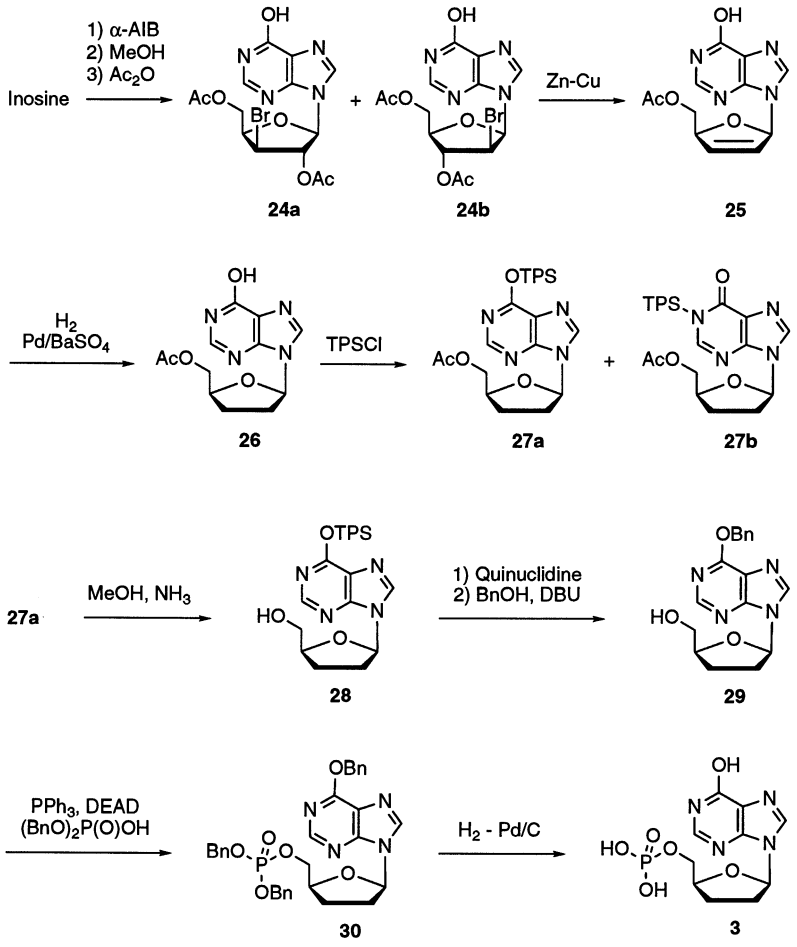
The ddI derivative **2** bearing a linker in the O^6-position was prepared in 5 steps, starting from inosine (Scheme 2). The first 2 steps were realized according to Bhat et al..[33] Inosine was reacted with 2-acetoxy-2-methylpropanoyl bromide (α-AIB, Mattock's bromide).[34,35] Reductive elimination of the bromoacetate mixture obtained was readily accomplished with zinc–copper couple in acetic acid. The resulting compound **15** was then treated with azido alcohol **16**[36] under Mitsunobu conditions[37] to yield a mixture of the O^6- and N^1-alkylated products. The compounds were separated by chromatography over silica gel and regioisomers **17a** and **17b** were obtained as mixtures of two diastereomers. A further treatment of **17a** (resp. **17b**) with methanolic ammonia yielded compound **18a** (resp. **18b**) that was then hydrogenolyzed over Pd/C. The double bond and the azido group were reduced simultaneously and compound **2** (resp. **19**) was obtained quantitatively.

Initial attempts to prepare the ddIMP derivative **4** by phosphorylation of **18a** with **16** followed by hydrogenolysis failed. Under the Mitsunobu reaction conditions **18a** rapidly decomposes and deglycosylation products are obtained quantitatively. The poor stability of **18a** is likely due to the presence of the double bond in the sugar ring and our further strategy required its saturation prior to phosphorylation (Scheme 3). Thus starting from the earlier precursor **15**, the 2′,3′-double bond was first reduced by hydrogenolysis[33] and compound **20** was alkylated with azido alcohol **16** under the Mitsunobu conditions[37] to yield 54% of the O^6-alkylated product **21a** and 44% of the N^1-regioisomer **21b**. These two compounds were separated by chromatography and isomer **21a** was treated with piperidine to provide the 5′-hydroxy compound **22a**. Phosphorylation of **22a** afforded **23a** in 86% yield and further hydrogenolysis led to the target compound **4**. The same reaction sequence involving isomer **21b** has been investigated. Removal of the 5′-protecting group and subsequent phosphorylation were achieved in 82 and 81% yield, respectively. The resulting compound **23b** is less stable than **23a**, presumably due to the lowered aromaticity of the purine base. Consequently final hydrogenolysis and animal immunizations were not further considered. It is likely that our attempts to phosphorylate the N^1-alkylated compound **18b** failed for similar reasons as only deglycosylation products were isolated.

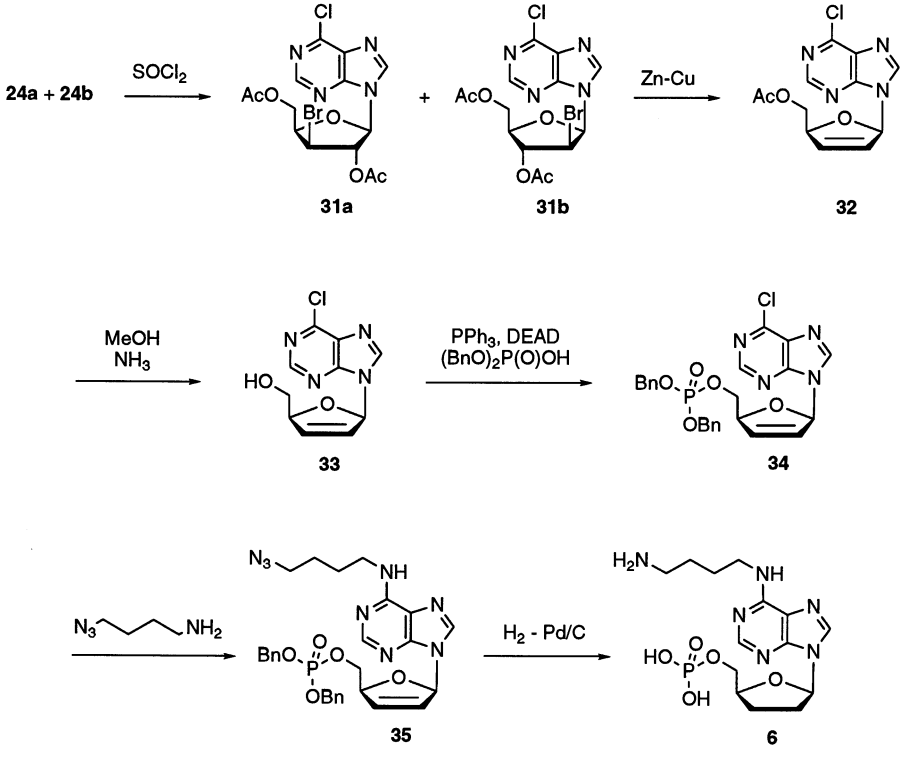
ddIMP **3** was synthesized using a slightly different pathway and introducing a variation adapted from a previous work by Townsend[38] (Scheme 4). Inosine was treated with an excess of Mattock's bromide. At the end of the reaction methyl alcohol was added to decompose the intermediate *ortho*-acetate. The crude material was dried and directly acylated with acetic anhydride. Purification over silica gel afforded a mixture of regioisomers **24a** and **24b**. Treatment with Zn–Cu couple led to the formation of the unsaturated nucleoside **25** that was hydrogenated over poisoned $Pd/BaSO_4$. In that case the use of poisoned catalyst revealed necessary to avoid partial deglycosylation of the substrate as previously reported by Manchand in similar cases.[39] The resulting compound **26** was sulfonylated with 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl) under the conditions described by Hata,[40] Jones,[41] and Noyori.[42] Under these conditions however the N^1-sulfonylated



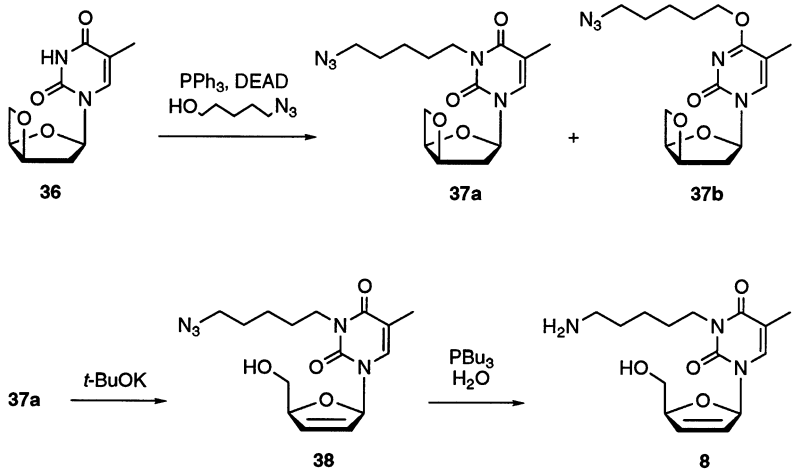
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

compound **27b** was preferentially obtained whereas the expected O^6-derivative **27a** was isolated in only 12% yield. Treatment of the latter compound with methanolic ammonia at 0°C allowed removal of the 5′-protecting group. The sulfonyl moiety in compound **28** was then displaced by benzyl alcohol using the conditions developed by Hata and Noyori.[40,42] The resulting compound **29** was phosphorylated with phosphoric acid dibenzyl ester under the Mitsunobu conditions[37] to yield phosphotriester **30** which was finally deprotected by hydrogenolysis to afford ddIMP **3**. Very surprisingly there is no other report on the chemical synthesis of ddIMP in the literature to our knowledge.[43]

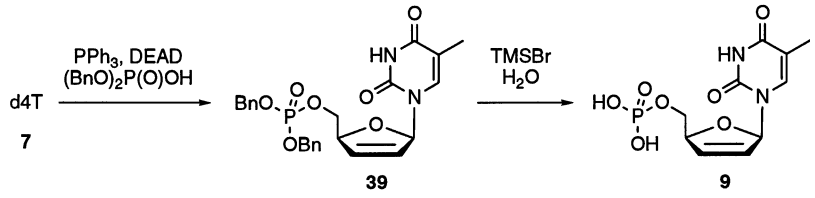
Though ddAMP hapten **6** could be elaborated from **28**, the poor yield obtained in the preparation of the latter compound led us to look for a more efficient route. So we went a few steps back and prepared compound **6** starting from the mixture of the earlier intermediates **24a** and **24b** (Scheme 5). Chlorination under conditions described by Robins and Basom[44] led to the 6-chloropurines **31a** and **31b** that were further transformed into compound **32** upon treatment with Zn–Cu couple. The acetyl protecting group was removed in methanolic ammonia at 0°C and **33** was phosphorylated in the same way as **29**. The resulting phosphotriester **34** was then reacted with 4-azido-1-butylamine to yield compound **35** that was finally deprotected by hydrogenolysis and transformed into the target compound **6**. Finally it is worth noting that all our attempts to synthesize **6** starting from **25** or **26** failed as chlorination led to complete depurination of the compounds.

2.2. Synthesis of d4T derivatives

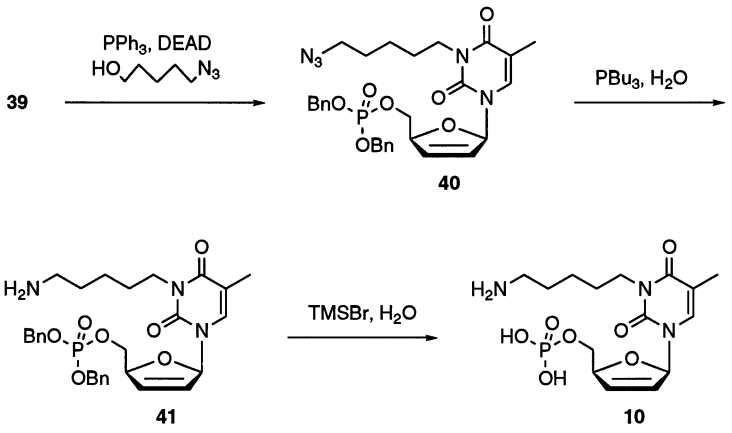
The d4T derivatives were prepared from thymidine (Scheme 6). The nucleoside was readily transformed into cyclonucleoside **36** according to Horwitz.[45,46] That compound was then alkylated under the Mitsunobu conditions[47] with 5-azido-1-pentanol. The reaction was quantitative and regioisomer **37a** was obtained in 94% yield (**37b**:5%). The major regioisomer was treated with potassium *tert*-butoxide and opening of the oxetane led to the d4T derivative **38**. A final reduction of the azide group using a Staudinger reaction[48] produced the target compound **8**.

The treatment of **36** under basic conditions furnished d4T **7** as described by Horwitz.[45,46] The synthesis of d4TMP **9** has been already described.[49] Mansuri et al. obtained the nucleotide in 33% yield using phosphorus oxychloride as phosphorylating agent. In order to avoid purification problems we proceeded in a different manner (Scheme 7). The phosphorylation of **7** with phosphoric acid dibenzyl ester under Mitsunobu conditions yielded compound **39** that was easily purified over silica gel. Subsequent removal of the phosphate protecting groups using trimethylsilyl bromide led to pure d4TMP **9** after simple aqueous work up. The yield over these two steps was 75%.

The functionalized d4TMP derivative **10** was prepared from **39** according to a procedure that was previously established for the synthesis of AZT derivatives[30,50] (Scheme 8). Alkylation with 5-azido-1-pentanol under the Mitsunobu conditions[47] led exclusively to the N^3-alkylated product



Scheme 7.



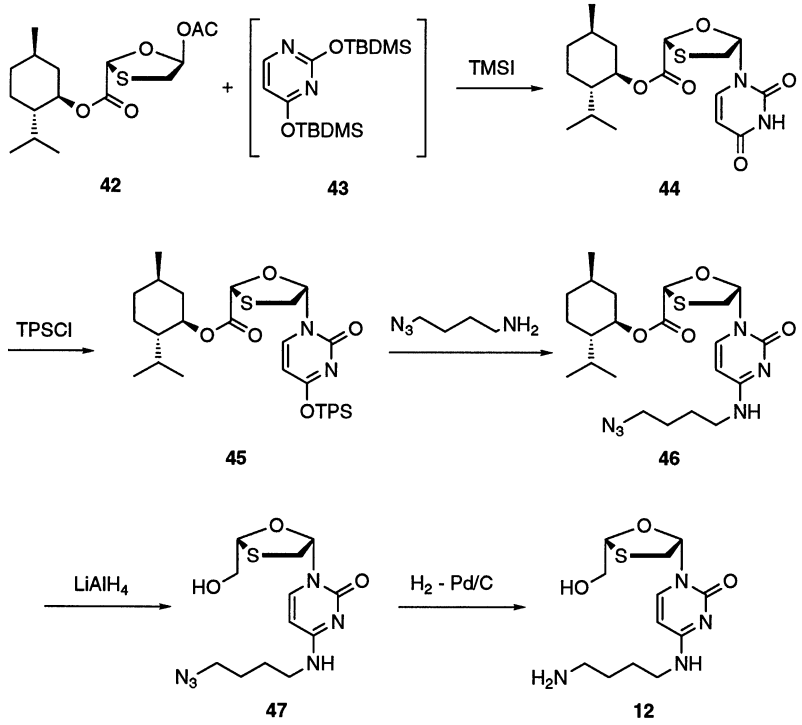
Scheme 8.

40. This result is slightly different from the one obtained during alkylation of cyclonucleoside **36** and in agreement with the total regioselectivity generaly observed with other thymidine derivatives.[30,47,51] Reduction of compound **40** with tri-*n*-butylphosphine in the presence of water led to **41** that was finally deprotected with trimethylsilyl bromide to yield **10**.

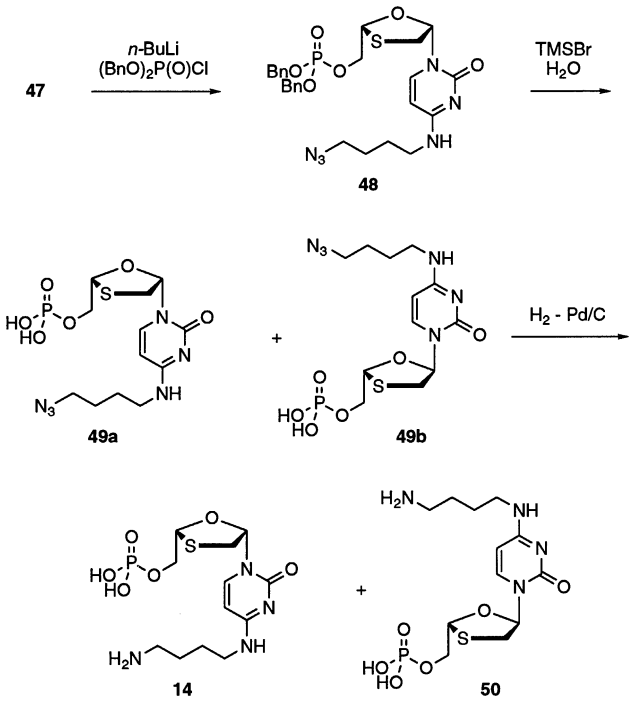
2.3. Synthesis of 3TC derivatives

The 3TC derivatives were synthesized starting from compound **42** previously described by Tse[52] (Scheme 9). Bis-*tert*-butyldimethylsilyl-uracil **43** prepared in situ was reacted with compound **42** in the presence of trimethylsilyl iodide to form compound **44**. Treatment with TPSCl quantitatively led to the O-sulfonylated regioisomer **45**. Nucleophilic displacement of the sulfonate moiety with 4-azido-1-butylamine yielded azido ester **46** that was further quantitatively reduced with $LiAlH_4$ into **47**. An exact control of the operating conditions was necessary to avoid reduction of the azide group and straightforward transformation of **46** into **12**. The final reduction of the azide moiety was achieved by hydrogenolysis and compound **12** was obtained in 84% yield. During our attempts to directly reduce **46** into **12** with $LiAlH_4$ the final purification step revealed tedious and led to a lower yield when compared to the two-step procedure.

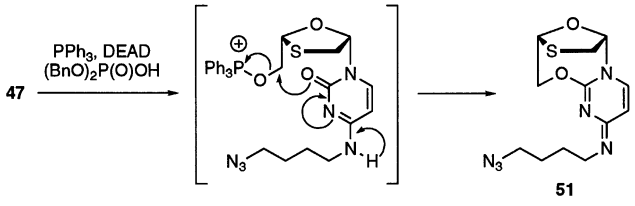
Compound **14** was prepared starting from intermediate **47** (Scheme 10). Phosphorylation of the primary hydroxyl group happened to be unexpectedly difficult. Reactions proceeding through an activation of the 5′-hydroxyl group invariably failed and led exclusively to the formation of cyclonucleoside **51** (Scheme 11). Different activated



Scheme 9.



Scheme 10.



Scheme 11.

phosphorus species were used in standard conditions but with little success. The best conditions we could find out involve a double deprotonation of **47** with *n*-butyllithium and subsequent reaction with dibenzyl chlorophosphate. Following that procedure, compound **48** was prepared in 80% yield. The removal of the two benzyl phosphate protecting groups was carried out using trimethylsilyl bromide and water. The reaction was quantitative but proceeded with partial inversion of configuration at the anomeric position. That phenomenon has been previously reported with other nucleotide derivatives.[30] The two isomers **49a** and **49b** were not separated and final reduction of the azide groups by hydrogenolysis led to a mixture of compounds **14** and **50**. These two compounds were separated by HPLC and **14** was obtained in 76% yield.

3. Conclusion

The different haptens described herein have been coupled to the carrier protein KLH (keyhole lympet hemocyanin) using glutaraldehyde and the conjugates have been injected into rabbits. The production and selection of monoclonal antibodies were realized using an enzymatic tracer prepared by anchoring acetylcholinesterase to the different haptens. Detailed procedures and immunological results will be reported elsewhere.

4. Experimental

4.1. General

Unless otherwise stated, all chemicals used were of commercial sources. THF, Et_2O and dioxane were distilled over Na/benzophenone and CH_2Cl_2 over CaH_2, just before use. Methanol and DMF were dried over 3 Å molecular sieves previously heated for 12 h at 180°C under reduced pressure (0.1 mmHg). Triethylamine was dried over Na and pyridine over KOH. Reactions were monitored by TLC (Merck precoated plates 0.25 mm, silica gel 60 F_{254}, 0.040–0.060 mm, 230–400 mesh ASTM). Liquid chromatography was performed on silica gel 60 (Merck, 0.040–0.060 mm, 230–400 mesh ASTM). Melting points were measured with a Reichert–Jung Thermo-Galen instrument coupled to an optical microscope. ^{1}H-, ^{13}C-, and ^{31}P NMR spectra were recorded on Brucker-WP-200-Sy and Brucker–Avance-DPX-300 spectrometers, and chemical shifts δ are in ppm relative to an internal reference resulting from incomplete deuteration of the NMR solvent (^{1}H: $CHCl_3$ at 7.27 ppm or CD_2HOD at 3.31 ppm, the latter for $CDCl_3/CD_3OD$ solutions, HDO at 4.63 ppm; ^{13}C: $CDCl_3$ at 77.0 ppm or CD_3OD at 49.0 ppm, the latter for $CDCl_3/CD_3OD$ solutions; ^{31}P: H_3PO_4 at 0.00 ppm). ^{13}C NMR spectra in D_2O were calibrated at 3.31 ppm by addition of a drop of CD_2HOD. ^{31}P NMR spectra were recorded in the proton-decoupled mode. IR spectra were recorded on Perkin–Elmer-1600-FTIR or Perkin–Elmer-Spectrum2000-FTIR spectrometers, and absorption values ν are in cm^{-1}. Mass Spectra (MS) were recorded on a Finnigan-4600 quadrupole instrument at chemical ionization. Mass data are reported in mass units (*m/z*). Abbreviations: s, singlet; d, doublet; t, triplet; h, heptuplet; q, quintuplet; m, multiplet; b, broad. Analytical HPLC studies were carried out in the gradient mode (A: 0.1% TFA in H_2O; B: 0.04% TFA in CH_3CN; $t_{0\ min}$ A/B 10:0, $t_{60\ min}$ A/B 8:2) using a reversed phase column (Nucleosil $5C_{18}$, 250×4.6 mm, 0.1 μm; flow rate 1 ml/min at 25°C) and a photodiode array detector (LKB 2410, detection at 267 nm).

4.1.1. 2′,3′-Dideoxy-*O*^{6}-[1-(8-amino-3,6-dioxaoctyl)]inosine (2). Compound **18a** (92 mg, 0.23 mmol) and Pd/C 10% (10 mg) in methanol (5 ml) are vigorously stirred under hydrogen atmosphere for 4 h. The catalyst is filtered off and washed with methanol (5 ml). The filtrate is reduced under vacuum to yield **2** as a white hygroscopic powder (86 mg, 99%). Anal. HPLC t_R 52 min. ^{1}H NMR ($CDCl_3/CD_3OD$ 1/1, 300 MHz) δ 8.57 (s, 1H); 8.47 (s, 1H); 6.33 (t, J=5.3 Hz, 1H); 4.73 (m, 2H); 4.47 (m, 1H); 3.95–3.89 (m, 3H); 3.77–3.65 (m, 7H); 3.16 (m, 2H); 2.56–2.49 (m, 2H); 2.23–2.08 (m, 2H). ^{13}C NMR ($CDCl_3/CD_3OD$ 1/1, 75 MHz) δ 160.6; 152.4; 151.4; 142.6; 121.9; 87.1; 82.9; 70.8; 70.4; 69.4; 67.2; 66.4; 63.7; 40.1; 33.4; 25.7. MS (CI/NH_3) *m/z* 368 $[M+H]^+$. IR (film) ν 3369; 2930; 1666; 1605; 1472; 1340; 1110.

4.1.2. 2′,3′-Dideoxy-5′-*O*-dihydroxyphosphoryl inosine (3). To compound **30** (9 mg, 0.017 mmol) in methanol

(4 ml) are added 4 drops of water and Pd/C 10% (4 mg). The mixture is vigorously stirred under hydrogen atmosphere for 2 h. The catalyst is filtered off, washed with methanol (5 ml) and water (5 ml). The filtrate is reduced in vacuo to yield **3** as a white hygroscopic powder (4 mg, 82%). Anal. HPLC t_R 6 min. ^{1}H NMR (D_2O/CD_3OD 1/1, 300 MHz) δ 8.28 (s, 1H); 8.01 (s, 1H); 6.19 (dd, J=3.4, 6.8 Hz, 1H); 4.32–4.25 (m, 1H); 3.93–3.72 (m, 2H); 2.52–2.28 (m, 2H); 2.12–1.74 (m, 2H). ^{13}C NMR (D_2O/CD_3OD 1/1, 50 MHz) δ 159.6; 150.3; 146.8; 141.3; 124.7; 86.3; 82.5 (d, J=8.7 Hz); 66.7 (d, J=4.3 Hz); 33.0; 26.2. ^{31}P NMR (D_2O/CD_3OD 1/1, 121.5 MHz) δ 3.07. MS (CI/NH_3) m/z 220 $[M-H_2PO_4+H]^+$. IR (film) ν 3396; 2949; 1603; 1470; 1058.

4.1.3. 2′,3′-Dideoxy-5′-*O*-dihydroxyphosphoryl-O^6-[1-(8-azido-3,6-dioxaoctyl)]inosine (4). Compound **4** (24 mg, 51%) is obtained as a white hygroscopic powder from compound **23a** following the same procedure as described for **3**. Anal. HPLC t_R 43 min. ^{1}H NMR (D_2O, 300 MHz) δ 8.53 (s, 1H); 8.26 (s, 1H); 6.23 (d, J=4.1 Hz, 1H); 4.53 (m, 2H); 4.30 (m, 1H); 3.86–3.52 (m, 10H); 2.96 (t, J=5.3 Hz, 2H); 2.54–2.31 (m, 2H); 2.08–1.92 (m, 2H). ^{13}C NMR (D_2O/CD_3OD 1/1, 50 MHz) δ 161.0; 152.6; 151.7; 143.3; 121.7; 86.2; 82.8; 70.9; 70.4; 67.5; 66.1; 40.0; 33.0; 26.1. ^{31}P NMR (D_2O/CD_3OD 1/1, 121.5 MHz) δ 4.79. MS (CI/NH_3) m/z 351 $[M-H_2PO_4+H]^+$. IR (Kbr) ν 3397; 3119; 2931; 1601; 1096.

4.1.4. 2′,3′-Dideoxy-5′-*O*-dihydroxyphosphoryl-N^6-[1-(4-aminobutyl)]adenosine (6). Compound **6** (6 mg, 51%) is obtained as a white hygroscopic powder from compound **35** following the same procedure as described for **3**. RP-18 TLC (H_2O/CH_3CN 1/1) R_f O.55. Anal. HPLC t_R 20 min. ^{1}H NMR (D_2O, 300 MHz) δ 8.29 (s, 1H); 8.07 (s, 1H); 6.20 (dd, J=7.2, 3.6 Hz, 1H); 4.32 (m, 1H); 4.02–2.93 (m, 2H); 3.49 (m, 2H); 2.90 (m, 2H); 2.54–2.30 (m, 2H); 2.14–1.72 (m, 2H); 1.68–1.53 (m, 4H). ^{13}C NMR (D_2O, 75 MHz) δ 149.6; 149.5; 147.5; 134.5; 116.0; 79.4; 76.5; 60.7; 34.2; 27.0; 22.0; 20.7; 20.2; 19.2. ^{31}P NMR (D_2O, 121.5 MHz) δ 3.42. MS (CI/NH_3) m/z 290 $[M-H_2PO_4+H]^+$. IR (film) ν 3401; 2938; 1623; 1083.

4.1.5. 3′-Deoxy-2′,3′-didehydro-N^3-[1-(5-aminopentyl)]-thymidine (8). Compound **38** (16 mg, 0.048 mmol) is stirred in THF (2 ml) with tri-*n*-butylphosphine (26 μl, 0.106 mmol) and water (3 μl, 0.144 mmol) at room temperature. The reaction is monitored by TLC. When at completion, the solvents are removed under vacuo and the crude residue is purified by chromatography (AcOEt/EtOH: 100/0–0/100) to yield **8** as a white powder (9 mg, 61%). Anal. HPLC t_R 45 min. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.46 (s, 1H); 7.03 (s, 1H); 6.35 (ddd, J=5.9, 1.9, 1.5 Hz, 1H); 5.87 (ddd, J=5.9, 1.9, 1.5 Hz, 1H); 4.93 (m, 1H); 3.95 (t, J=6.6 Hz, 2H); 3.98–3.75 (m, 2H); 3.16 (dt, J=6.2, 6.1 Hz, 2H); 1.89 (s, 3H); 1.79–1.37 (m, 6H). ^{13}C NMR ($CDCl_3$/CD_3OD 1/1, 50 MHz) δ 163.8; 151.6; 134.9; 134.5; 126.3; 109.9; 90.7; 87.2; 63.2; 41.0; 39.9; 26.7; 24.2; 23.6; 13.1. MS (CI/NH_3) m/z 310 $[M+H]^+$. IR (film) ν 3322; 2944; 2855; 1700; 1666; 1639; 1467; 1239; 1089.

4.1.6. 3′-Deoxy-2′,3′-didehydro-5′-*O*-dihydroxyphosphoryl thymidine (9). Compound **39** (12 mg, 0.026 mmol) in anhydrous dichloromethane (1.5 ml) is treated dropwise with trimethylsilyl bromide (17 μl, 0.130 mmol) at room temperature. The mixture is stirred for 10 h before 5% ammonia (250 μl) is added. The solvent is removed in vacuo and the residue is solubilized in water (1 ml), washed twice with ethyl acetate and the aqueous phase is lyophilized to yield the ammonium salt of **9** (8 mg, 99%) as a white hygroscopic powder. RP-18 TLC (H_2O/CH_3CN 8/2) R_f 0.8. ^{1}H NMR (D_2O, 200 MHz) δ 7.52 (s, 1H); 6.86 (m, 1H); 6.39 (ddd, J=6.2, 1.5, 1.5 Hz, 1H); 5.85 (ddd, J=6.2, 2.2, 2.2 Hz, 1H); 5.00 (m, 1H); 3.92 (m, 2H); 1.82 (s, 3H). ^{13}C NMR (D_2O, 75 MHz) δ 166.1; 152.6; 136.1; 134.0; 125.2; 110.4; 90.8; 85.9 (d, J=8.7 Hz); 65.4; 12.1. ^{31}P NMR (D_2O, 121.5 MHz) δ 1.60. MS (CI/NH_3) m/z 208 $[M-H_2PO_4+H]^+$. IR (KBr) ν 3425; 3201; 3072; 1696; 1678; 1090.

4.1.7. 3′-Deoxy-2′,3′-didehydro-5′-*O*-dihydroxyphosphoryl-N^3-[1-(5-aminopentyl)]thymidine (10). Compound **10** is obtained as its ammonium salt starting from **41** (15 mg, 0.027 mmol) and following the procedure described for the preparation of compound **9**. The crude material is purified by preparative RP-18 TLC (H_2O/CH_3CN 70/30) to yield **10** (8 mg, 67%) as a white powder. RP-18 TLC (H_2O/CH_3CN 7/3) R_f 0.7. Mp >230°C. Anal. HPLC t_R 35 min. ^{1}H NMR (D_2O, 200 MHz) δ 7.51 (s, 1H); 6.90 (d, J=2.9 Hz, 1H); 6.38 (dd, J=6.0, 2.9 Hz, 1H); 5.84 (dd, J=3.7, 2.1 Hz, 1H); 4.99 (m, 1H); 3.94 (m, 2H); 3.82 (t, J=6.6 Hz, 2H); 3.00 (t, J=6.6 Hz, 2H); 1.80 (s, 3H); 1.54–1.49 (m, 2H); 1.44–1.39 (m, 2H); 1.23–1.19 (m, 2H). ^{13}C NMR (D_2O, 75 MHz) δ 165.7; 152.3; 136.1; 133.9; 125.2; 110.5; 90.8; 85.8 (d, J=8.7 Hz); 65.4 (d, J=4.4 Hz); 41.4; 39.1; 28.3; 26.1; 23.0; 12.1. ^{31}P NMR (D_2O, 121.5 MHz) δ 1.51. MS (CI/NH_3) m/z 293 $[M-H_2PO_4+H]^+$. IR (KBr) ν 3131; 2284; 1696; 1396; 1243.

4.1.8. 5′-(*S*)-{N^4-[1-(4-Aminobutyl)]cytosin-1-yl}-2′(*R*)-hydroxymethyl-1′,3′-oxathiolane (12). Compound **12** (19 mg, 84%) is prepared from **47** following the procedure previously described for **2**. Anal. HPLC t_R 22 min. ^{1}H NMR (CD_3OD, 200 MHz) δ 7.94 (d, J=7.6 Hz, 1H); 6.29 (t, J=5.0 Hz, 1H); 5.86 (d, J=7.6 Hz, 1H); 5.27 (t, J=4.0 Hz, 1H); 3.93–3.86 (m, 2H); 3.42–3.34 (m, 2H); 3.30 (AB part of ABX syst., J_{AB}=12.0, J_{AX}=5.5, J_{BX}=4.7 Hz, ν_A=3.30, ν_B=3.30, 2H); 2.76 (t, J=6.8 Hz, 2H); 1.67–1.54 (m, 4H). ^{13}C NMR (CD_3OD, 50 MHz) δ 165.5; 158.3; 141.0; 96.9; 88.8; 87.6; 64.2; 41.4; 41.0; 38.1; 29.4; 27.2. MS (CI/NH_3) m/z 301 $[M+H]^+$. IR (film) ν 3279; 2922; 1643; 1574; 1510; 1050.

4.1.9. (−)-2′-Deoxy-5′-*O*-dihydroxyphosphoryl-N^3-[1-(5-aminopentyl)]-3′-thiacytidine (14). A mixture of compounds **14** and **50** is obtained from **49a** and **49b** following the procedure previously described for **3**. Stereoisomer **14** (13 mg, 76%) is purified by preparative HPLC (Zorbax SB C18, 250×20 mm, 5 μm; flow rate 1 ml/min at 25°C; isocratic mode 0.25 M $(NH_4)_2CO_3$/CH_3CN 98:2 at pH 7; t_R 7 min). Anal. HPLC t_R 7 min. ^{1}H NMR (D_2O, 300 MHz) δ 8.23 (d, J=8.3 Hz, 1H); 6.20 (dd, J=5.3, 3.1 Hz, 1H); 6.03 (d, J=8.3 Hz, 1H); 5.36 (m, 1H); 4.27–4.17 (m, 1H); 4.08–3.98 (m, 1H); 3.51–3.44 (m, 1H); 3.42–3.30 (m, 2H); 3.26–3.16 (m, 1H); 2.97–2.85 (m, 2H); 1.70–1.55 (m, 4H). ^{13}C NMR (D_2O/CD_3OD 1/1,

50 MHz) δ 158.2; 149.6; 143.4; 96.2; 88.1; 87.3; 65.9; 43.5; 42.9; 38.2; 25.0; 24.8. ^{31}P NMR (D_2O, 121.5 MHz) δ 1.13. MS (CI/NH_3) *m/z* 284 $[M-H_2PO_4+H]^+$. IR (KBr) ν 3413; 3107; 2943; 1725; 1660; 1190; 1064.

4.1.10. 2′,3′-Didehydro-2′,3′-dideoxy-5′-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-*O*^{6}-[1-(8-azido-3,6-dioxaoctyl)]inosine (17a). Triphenylphosphine (1.50 g, 5.72 mmol) in anhydrous THF (5 ml) is added dropwise to a mixture of nucleoside **15** (1.95 g, 3.17 mmol), azido alcohol **16**[36] (0.78 g, 4.46 mmol), and DEAD (0.90 ml, 5.71 mmol). The solution is stirred for 45 min and the solvent is removed under reduced pressure. The crude residue is chromatographed over silica gel (AcOEt/EtOH 95/5–0/100) to yield the O^6-alkylated product **17a** (1/1 mixture of the two diastereomers) (0.87 g, 52%) as a glassy solid. TLC (AcOEt/EtOH 85/15) R_f 0.8. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.46 (s, 1H); 8.09 (s, 1H); 8.06 (s, 1H); 7.08 (dd, *J*=3.0, 1.5 Hz, 1H); 6.38–6.31 (m, 1H); 6.04 (d, *J*=3.8 Hz, 1H); 5.06 (m, 1H); 4.70 (t, *J*=4.9 Hz, 2H); 3.89 (t, *J*=4.9 Hz, 2H); 3.81–3.75 (m, 8H); 3.30 (t, *J*=5.0 Hz, 2H); 1.65 and 1.64 (2s, 3H); 1.47–1.35 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.2 and 172.2; 160.4; 152.0; 151.7; 140.6 and 140.2; 133.8 and 133.6; 125.9 and 125.7; 125.6 and 125.5; 121.3 and 120.1; 88.2 and 88.1; 84.9 and 84.6; 78.7 and 77.9; 70.6; 70.4; 69.8; 69.0; 66.0 and 65.3; 63.1 and 62.6; 50.4; 25.4 and 25.1; 24.8 and 24.6; 24.4 and 24.1. MS (CI/NH_3) *m/z* 537 $[M+NH_4]^+$. IR (film) ν 2936; 2876; 2103; 1801; 1599.

4.1.11. 2′,3′-Didehydro-2′,3′-dideoxy-5′-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-*N*^{1}-[1-(8-azido-3,6-dioxaoctyl)]inosine (17b). Compound **17b** (0.77 g, 47%) is obtained as a mixture of two diastereomers during the preparation of **17a**. TLC (AcOEt/EtOH: 85/15) R_f 0.5. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.08 (s, 1H); 7.91 and 7.89 (2s, 1H); 6.97 (m, 1H); 6.39 (d, *J*=5.9 Hz, 1H); 6.06 (d, *J*=5.9 Hz, 1H); 5.08 (m, 1H); 4.24 (t, *J*=4.4 Hz, 2H); 3.83–3.75 (m, 1H); 3.75 (t, *J*=4.4 Hz, 2H); 3.69–3.55 (m, 7H); 3.33 (t, *J*=4.8 Hz, 2H); 1.69 and 1.68 (2s, 3H); 1.51–1.43 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.4 and 172.4; 156.5; 148.5; 147.4; 138.3 and 137.8; 134.1 and 133.9; 125.6 and 125.4; 124.2; 120.3; 88.1; 85.1 and 84.7; 78.8 and 78.0; 70.4; 70.3; 69.4; 68.6; 63.1 and 62.6; 50.5; 46.3; 25.6 and 25.2; 25.1 and 24.7; 24.6 and 24.5. MS (CI/NH_3) *m/z* 537 $[M+NH_4]^+$. IR (film) ν 3448; 2872; 2108; 1801; 1696.

4.1.12. 2′,3′-Didehydro-2′,3′-dideoxy-*O*^{6}-[1-(8-azido-3,6-dioxaoctyl)]inosine (18a). Compound **17a** (115 mg, 0.221 mmol) is stirred with methanolic ammonia (10 ml) at room temperature for 8 h. The solvent is removed under reduced pressure and the crude residue is purified by chromatography over silica gel (AcOEt/EtOH 1/0–9/1) to yield compound **18a** as a colorless and viscous oil (86 mg, 99%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (s, 1H); 8.12 (s, 1H); 6.98 (m, 1H); 6.47 (m, 1H); 6.02 (m, 1H); 5.11 (m, 1H); 4.77 (dd, *J*=5.3, 3.1 Hz, 2H); 4.01 (td, *J*=10.6, 1.9 Hz, 1H); 3.95 (t, *J*=5.0 Hz, 2H); 3.90 (td, *J*=12.8, 2.8 Hz, 1H); 3.75–3.64 (m, 6H); 3.36 (t, *J*=5.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.8; 151.9; 151.4; 141.4; 134.7; 125.8; 122.4; 90.6; 88.7; 70.8; 70.6; 70.0; 69.2; 66.3; 63.8; 50.7. MS (CI/NH_3) *m/z* 392 $[M+H]^+$; 409 $[M+NH_4]^+$. IR (film) ν 3347; 2873; 2110; 1669; 1601.

4.1.13. 2′,3′-Didehydro-2′,3′-dideoxy-*N*^{1}-[1-(8-azido-3,6-dioxaoctyl)]inosine (18b). Compound **17b** (56 mg, 0.10 mmol) is stirred with methanolic ammonia (10 ml) at 60°C in a sealed vessel for 2 h. The solvent is removed under reduced pressure and the crude residue is purified by chromatography over silica gel ($CHCl_3$/EtOH 95/5–85/15) to yield compound **18b** as a colorless and viscous oil (43 mg, 99%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.17 (s, 1H), 8.06 (s, 1H); 6.93 (m, 1H); 6.44 (ddd, *J*=5.8, 1.7, 1.6 Hz, 1H); 5.99 (ddd, *J*=5.8, 1.8, 1.6 Hz, 1H); 5.05 (m, 1H); 4.22 (t, *J*=4.8 Hz, 2H); 4.10–4.03 (m, 1H); 3.87–3.75(m, 1H); 3.74 (t, *J*=4.8 Hz, 2H); 3.60–3.57 (m, 6H), 2.32 (t, *J*=5.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.8; 148.3; 147.1; 139.3; 134.7; 125.4; 121.0; 88.5; 87.9; 70.4; 70.3; 69.9; 68.5; 63.1; 50.4; 46.3. MS (CI/NH_3) *m/z* 392 $[M+H]^+$. IR (film) ν 3337; 2107; 1693; 1350; 1080.

4.1.14. 2′,3′-Dideoxy-*N*^{1}-[1-(8-amino-3,6-dioxaoctyl)]-inosine (19). Compound **19** (186 mg, 98%) is obtained from **18b** following the same procedure as described for **3**. For analytical purposes, the compound is purified by preparative TLC (EtOH/MeOH 95/5). Anal. HPLC t_R 39 min. ^{1}H NMR ($CDCl_3$/CD_3OD 1/1, 300 MHz) δ 8.06 (s, 1H); 8.03 (s, 1H); 6.06 (dd, *J*=5.6, 4.6 Hz, 1H); 4.06–4.00 (m, 3H); 3.73–3.61 (m, 3H); 3.47–3.41 (m, 7H); 2.92–2.88 (m, 2H); 2.35–2.48 (m, 2H); 2.02–1.95 (m, 2H). ^{13}C NMR ($CDCl_3$/CD_3OD 1/1, 75 MHz) δ 156.6; 148.2; 146.7; 138.8; 123.9; 85.6; 82.0; 70.0; 69.6; 68.1; 67.0; 63.2; 45.7; 39.4; 32.4; 25.1. MS (CI/NH_3) *m/z* 368 $[M+H]^+$. IR (film) ν 3368; 2919; 2496; 1684; 1349; 1108.

4.1.15. 2′,3′-Dideoxy-5′-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)inosine (20). Compound **15** (3.58 g, 9.88 mmol) and Pd (5%) on $BaSO_4$ (2.70 g) are stirred in a mixture of methanol (30 ml) and methoxyethanol (40 ml) under hydrogen atmosphere for 2 h. The catalyst is filtered off and the solvent is removed under reduced pressure. The crude residue is purified by chromatography over silica gel (AcOEt/EtOH 9/1–5/5) to yield **20** (1/1 mixture of two diastereomers) (1.50 g, 42%) as a colorless and glassy solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 and 8.28 (2s, 1H); 8.13 and 8.09 (2s, 1H); 6.26 (dd, *J*=4.2, 4.1 Hz, 1H); 4.35 (m, 1H); 3.78 (AB part of an ABXX′ syst., J_{AB}=29.6, J_{AX}=10.2, $J_{AX'}$=3.4, J_{BX}=10.4, $J_{BX'}$=4.2 Hz, ν_A=3.86, ν_B=3.70, 2H); 2.56–2.48 (m, 2H); 2.06–2.17 (m, 2H); 1.73 (s, 3H); 1.53 and 1.51 (2s, 3H); 1.50 and 1.47 (2s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.6 and 174.5; 159.1; 148.2; 145.1; 138.5 and 138.2; 125.0; 120.4; 85.8 and 85.7; 79.7; 79.2 and 79.0; 65.8 and 65.6; 33.0 and 32.9; 25.9 and 25.8; 25.7 and 25.6; 25.5 and 25.3; 24.7 and 24.6. MS (CI/NH_3) *m/z* 365 $[M+H]^+$. IR (film) ν 2984; 1800; 1700; 1207; 1174.

4.1.16. 2′,3′-Dideoxy-5′-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-*O*^{6}-[1-(8-azido-3,6-dioxaoctyl)]inosine (21a). Compound **21a** (0.94 g, 55%) is prepared (1/1 mixture of two diastereomers) from **20** following the same procedure as for **17a**. Purification is achieved over silica gel (Et_2O/CH_3CN/AcOEt/EtOH 60/20/20/0–0/0/25/75). TLC (AcOEt/EtOH 8/2) R_f 0.8. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.49 and 8.48 (2s, 1H); 8.27 and 8.26 (2s, 1H); 6.34 (dd, *J*=5.8, 1.7 Hz, 1H); 4.75 (t, *J*=4.9 Hz, 2H); 4.39 (m, 1H);

3.96 (t, J=4.9 Hz, 2H); 3.84–3.59 (m, 8H); 3.39 and 3.36 (2t, J=5.1 Hz, 2H); 2.60–2.50 (m, 2H); 2.26–2.08 (m, 2H); 1.76 (s, 3H); 1.53 and 1.52 (2s, 3H); 1.49 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.5; 160.5; 151.8 and 151.7; 151.2; 140.6 and 140.2; 121.9; 120.3; 85.8 and 85.7; 79.6 and 79.0; 78.0; 70.8; 70.6; 70.0; 69.2; 66.1; 63.2 and 62.9; 50.6; 32.9 and 32.8; 30.2 and 29.6; 26.0 and 25.6; 25.5 and 25.3; 24.6 and 24.4. MS (CI/NH_3) m/z 522 $[M+H]^+$. IR (film) ν 3408; 2939; 2105; 1799; 1741; 1604; 1303.

4.1.17. 2′,3′-Dideoxy-5′-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-*N*^{1}-[1-(8-azido-3,6-dioxaoctyl)]inosine (21b). That compound (0.77 g, 44%) is obtained as a side product during the preparation of **21a**. TLC (AcOEt/EtOH 8/2) R_f 0.5. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 (s, 1H); 7.98 (s, 1H); 6.20 (m, 1H); 4.33 (m, 1H); 4.22 (m, 2H); 3.74 (t, J=4.7 Hz, 2H); 3.67–3.50 (m, 8H); 3.31 (t, J=4.9 Hz, 2H); 2.54–2.45 (m, 2H); 2.17–2.04 (m, 2H); 1.71 (s, 3H); 1.56 and 1.54 (2s, 3H); 1.53 and 1.50 (2s, 3H). MS (CI/NH_3) m/z 522 $[M+H]^+$.

4.1.18. 2′,3′-Didehydro-2′,3′-dideoxy-*O*^{6}-[1-(8-azido-3,6-dioxaoctyl)]inosine (22a). Piperidine (890 μl, 9.00 mmol) is added to compound **21a** (938 mg, 1.80 mmol) in anhydrous methanol (25 ml). The reaction mixture is refluxed for 5 h and a second portion of piperidine (890 μl, 9.00 mmol) is added. After an additional 5 h refluxing period the reaction is at completion. The solvent is removed in vacuo and the residue is purified over silica gel (AcOEt/EtOH 9/1) to yield **22a** (591 mg, 84%) as a glassy solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49 (s, 1H); 8.09 (s, 1H); 6.17 (t, J=6.3 Hz, 1H); 4.76 (t, J=5.0 Hz, 2H); 4.37–4.33 (m, 1H); 4.04–3.93 (m, 3H); 3.74–3.59 (m, 7H); 3.36 (t, J=5.1 Hz, 2H); 2.75–2.66 (m, 1H); 2.46–2.35 (m, 2H); 2.24–2.14 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.9; 151.6; 150.9; 141.5; 122.8; 87.8; 81.7; 70.8; 70.6; 70.3; 70.0; 66.3; 64.7; 50.6; 32.4; 25.9. MS (CI/NH_3) m/z 394 $[M+H]^+$. IR (film) ν 3360; 2921; 2101; 1596; 1308.

4.1.19. 2′,3′-Didehydro-2′,3′-dideoxy-*N*^{1}-[1-(8-azido-3,6-dioxaoctyl)]inosine (22b). Compound **22b** (0.78 g, 82%) is prepared from **21b** following the same procedure as for **22a**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.04 (s, 1H); 7.97 (s, 1H); 7.35–7.29 (m, 10H); 6.20 (dd, J=6.2, 4.8 Hz, 1H); 5.02 (d, J=9.1 Hz, 4H); 4.23–4.09 (m, 5H); 3.76 (t, J=4.6 Hz, 2H); 3.70–3.57 (m, 6H); 3.35 (t, J=5.1 Hz, 2H); 2.54–2.02 (m, 4H). MS (CI/NH_3) m/z 654 $[M+H]^+$.

4.1.20. 2′,3′-Dideoxy-5′-*O*-dibenzyloxyphosphoryl-*O*^{6}-[1-(8-azido-3,6-dioxaoctyl)]inosine (23a). PPh_3 (240 mg, 0.92 mmol) in anhydrous THF (4 ml) is added dropwise to nucleoside **22a** (50 mg, 0.13 mmol), phosphoric acid dibenzyl ester (39 mg, 0.14 mmol), and DEAD (144 μl, 0.92 mmol) in THF (8 ml). After 2 h the solvent is removed under reduced pressure and the residue is purified by chromatography (Et_2O/AcOEt/EtOH 1/0/0–0/6/4) to yield **23a** (71 mg, 86%) as a glassy solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.46 (s, 1H); 8.13 (s, 1H); 7.35–7.30 (m, 10H); 6.28 (t, J=5.1 Hz, 1H); 5.00 (d, J=8.8 Hz, 4H); 4.74 (t, J=4.9 Hz, 2H); 4.30–4.03 (m, 3H); 3.95 (t, J=4.9 Hz, 2H); 3.75–3.62 (m, 6H); 3.35 (t, J=5.1 Hz, 2H); 2.54–2.44 (m, 2H); 2.11–2.03 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.5; 151.8; 151.3; 140.3; 135.4 (d, J=7.1 Hz); 128.6; 128.5; 127.8; 121.8; 85.5; 79.4 (d, J=8.7 Hz); 70.6; 69.9; 69.4; 69.1; 68.0 (d, J=5.8 Hz); 66.1; 50.5; 32.1; 25.8. ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ −0.04. MS (CI/NH_3) m/z 654 $[M+H]^+$. IR (film) ν 2950; 2105; 1736; 1597; 1469; 1275; 1036.

4.1.21. 2′,3′-Dideoxy-5′-*O*-dibenzyloxyphosphoryl-*N*^{1}-[1-(8-azido-3,6-dioxaoctyl)]inosine (23b). Compound **23b** (0.34 g, 81%) is prepared from **22b** following the same procedure as for **23a**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.46 (s, 1H); 8.13 (s, 1H); 7.35–7.30 (m, 10H); 6.28 (t, J=5.1 Hz, 1H); 5.00 (d, J=8.8 Hz, 4H); 4.74 (t, J=4.9 Hz, 2H); 4.30–4.03 (m, 3H); 3.95 (t, J=4.9 Hz, 2H); 3.75–3.62 (m, 6H); 3.35 (t, J=5.1 Hz, 2H); 2.54–2.44 (m, 2H); 2.11–2.03 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.5; 151.8; 151.3; 140.3; 135.4 (d, J=7.1 Hz); 128.6; 128.5; 127.8; 121.8; 85.5; 79.4 (d, J=8.7 Hz); 70.6; 69.9; 69.4; 69.1; 68.0 (d, J=5.8 Hz); 66.1; 50.5; 32.1; 25.8. ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ −0.04. MS (CI/NH_3) m/z 654 $[M+H]^+$. IR (film) ν 2950; 2105; 1736; 1597; 1469; 1275; 1036.

4.1.22. 9-(2′,5′-Di-*O*-acetyl-3′-bromo-3′-deoxy-β-D-xylofuranosyl)hypoxanthine and 9-(3′,5′-di-*O*-acetyl-2′-bromo-3′-deoxy-β-D-xylofuranosyl)hypoxanthine (24a and 24b). A suspension of inosine (5.0 g, 18.6 mmol) in dry acetonitrile is treated dropwise at 0°C with 2-acetoxyisobutyryl bromide (8.2 ml, 56.1 mmol). Material dissolves after 2 h and the mixture is stirred at room temperature for 10 h. Anhydrous methanol (5 ml) is added and after 15 min the solvents are removed in vacuo. The crude residue is dissolved in anhydrous pyridine (120 ml) and acetic anhydride (11.4 ml, 120.8 mmol) is added dropwise at room temperature. The reaction mixture is stirred for 30 min before evaporation and the residue is purified by chromatography (AcOEt/EtOH 100/0–95/5) to yield a mixture of the two regioisomers **24a** and **24b** (7.74 g, 99%, **24a/24b** 76/24) as a white foam. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.36 (s, 1Ha); 8.35 (s, 1Hb); 8.25 (s, 1Ha); 8.13 (s, 1Hb); 6.35 (d, J=4.2 Hz, 1Hb); 6.18 (d, J=3.0 Hz, 1Ha); 5.68–5.65 (m, 1Ha); 5.50 (t, J=2.3 Hz, 1Hb); 4.68 (dd, J=4.2, 2.3 Hz, 1Hb); 4.39–4.53 (m, 4Ha and 2Hb); 4.30 (m, 1Hb); 2.18–1.97 (m, 6Ha and 6Hb). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.0 (b); 170.2 (a); 169.0 (a,b); 158.7 (a,b); 148.4 (a); 147.7 (b); 146.0 (a,b); 138.2 (a,b); 124.7 (a,b); 87.8 (a); 85.0 (b); 83.0 (a); 80.6 (b); 78.5 (b); 77.9 (a); 64.7 (a); 64.0 (b); 49.2 (a); 48.8 (b); 24.4 (b); 24.2 (a); 20.5 (b); 20.4 (a). MS (CI/NH_3) m/z 415 and 417 $[M+H]^+$. IR (film) ν 2982; 1744; 1700; 1371; 1221.

4.1.23. 5′-*O*-Acetyl-2′,3′-didehydro-2′,3′-dideoxyinosine (25). The previous white foam (500 mg, 1.20 mmol) is dissolved in anhydrous THF (14 ml) and to the clear solution is added Zn–Cu couple (0.5 g) and 2 drops of glacial acetic acid. The reaction mixture is vigorously stirred at room temperature for 12 h. The resulting suspension is filtered over a celite pad. The filtrate is reduced under vacuum and the residue is purified by chromatography ($CHCl_3$/MeOH 10/0–8/2) to yield **25** (146 mg, 44%) as a white crystalline powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (s, 1H); 8.09 (s, 1H); 7.06 (m, 1H); 6.41 (d, J=6.0 Hz, 1H); 6.13 (d, J=6.0 Hz, 1H); 6.13 (d, J=6.0 Hz, 1H); 5.18 (m, 1H); 4.35 (AB part of ABX syst.,

J_{AB}=12.1, J_{AX}=4.1, J_{BX}=3.4 Hz, ν_A=4.42, ν_B=4.28, 2H); 2.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.3; 148.8; 145.4; 138.3; 133.7; 127.3; 125.9; 88.6; 84.9; 65.4; 21.2. MS (CI/NH_3) *m/z* 277 $[M+H]^+$. IR (film) ν 3062; 1743; 1698.

4.1.24. 5′-*O*-Acetyl-2′,3′-dideoxyinosine (26). Compound **26** (104 mg, 72%) is obtained as a white powder starting from **25** and following the same procedure as described for **19**. Purification is achieved by chromatography over silica gel (AcOEt/EtOH 9/1–6/4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.18 (s, 1H); 8.16 (s, 1H); 6.27 (dd, *J*=5.3, 4.5 Hz, 1H); 4.44–4.21 (m, 3H); 2.59–2.55 (m, 2H); 2.24–2.07 (m, 2H); 2.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3; 159.2; 148.2; 144.7; 138.3; 119.9; 85.7; 79.2; 65.6; 29.7; 24.5; 21.1. MS (CI/NH_3) *m/z* 279 $[M+H]^+$. IR (film) ν 2919; 1737; 1696.

4.1.25. 5′-*O*-Acetyl-2′,3′-dideoxy-*O*^{6}-(2,4,6-triisopropylbenzenesulfonyl)inosine (27a). 2,4,6-Triisopropylbenzenesulfonyl chloride (2.88 g, 9.52 mmol) in dichloromethane (18 ml) is added dropwise to a mixture of nucleoside **26** (1.32 g, 4.75 mmol), 4-DMAP (27 mg, 0.24 mmol), and anhydrous triethylamine (2.65 ml, 19.0 mmol) in dichloromethane (30 ml) at room temperature. The reaction mixture is stirred for 4 h and saturated aqueous $NaHCO_3$ and NaCl solutions (15 and 5 ml, respectively) are added. The mixture is extracted with dichloromethane (5×20 ml). The organic layer is dried over Na_2SO_4, reduced in vacuo, and purified over silica gel (Et_2O/AcOEt 7/3). The O^6-sulfonylated product **27a** (307 mg, 12%) is obtained as a white powder. TLC (AcOEt/Et_2O 7/3) R_f 0.75. Mp 113°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (s, 1H); 8.35 (s, 1H); 7.22 (s, 2H); 6.36 (dd, *J*=6.2, 3.0 Hz, 1H); 4.45–4.25 (m, 5H); 2.92 (h, *J*=6.8 Hz, 1H); 2.65–2.60 (m, 2H); 2.19–2.08 (m, 4H); 1.33 (d, *J*=6.6 Hz, 6H); 1.32 (d, *J*=6.6 Hz, 6H); 1.31 (s, *J*=6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5; 154.7; 154.3; 153.2; 151.1; 151.0; 143.0; 131.1; 123.8; 123.2; 86.1; 79.5; 64.6; 34.2; 32.5; 29.7; 25.7; 24.5; 23.4; 20.7. IR (film) ν 2955; 1739; 1600; 1561; 1233. MS (CI/NH_3) *m/z* 545 $[M+H]^+$.

4.1.26. 5′-*O*-Acetyl-2′,3′-dideoxy-*N*^{1}-(2,4,6-triisopropylbenzenesulfonyl)inosine (27b). The N^1-sulfonylated compound **27b** (620 mg, 36%) is obtained as the major reaction product during the preparation of **27a**. TLC (AcOEt/Et_2O 7/3) R_f 0.65. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.85 (s, 1H); 8.01 (s, 1H); 7.19 (s, 2H); 6.28 (dd, *J*=6.4, 2.6 Hz, 1H); 4.44–4.22 (m, 3H); 4.41 (h, *J*=6.8 Hz, 1H); 2.90 (h, *J*=6.8 Hz, 1H); 2.51 (m, 2H); 2.28–2.09 (m, 1H); 2.06 (s, 3H); 1.23 (d, *J*=6.3 Hz, 6H); 1.21 (d, *J*=6.3 Hz, 6H); 1.20 (d, *J*=6.3 Hz, 6H). MS (CI/NH_3) *m/z* 545 $[M+H]^+$.

4.1.27. 2′,3′-Dideoxy-*O*^{6}-(2,4,6-triisopropylbenzenesulfonyl)inosine (28). Compound **28** is obtained starting from **27** and following the procedure previously described for **18a**, unless the reaction is carried out at 0°C for 5 h. Purification over silica gel (hexane/AcOEt 1/1) yields **28** as a white powder (51 mg, 54%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.55 (s, 1H); 8.47 (s, 1H); 7.22 (s, 2H); 6.27 (dd, *J*=6.0, 5.7 Hz, 1H); 4.38–4.29 (m, 3H); 4.05–3.99 (m, 1H); 3.70–3.63 (m, 1H); 2.92 (h, *J*=6.8 Hz, 1H); 2.64–2.13 (m, 4H); 1.32 (d, *J*=6.6 Hz, 6H); 1.31 (d, *J*=6.6 Hz, 6H); 1.30 (d, *J*=6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.0; 154.4; 153.0; 151.1; 151.0; 144.0; 131.1; 123.9; 123.6; 87.3; 82.2; 63.8; 34.3; 32.9; 29.7; 25.4; 24.5; 23.5. MS (CI/NH_3) *m/z* 503 $[M+H]^+$. IR (film) ν 3360; 2962; 1606; 1589; 1386.

4.1.28. *O*^{6}-Benzyl-2′,3′-dideoxyinosine (29). Benzyl alcohol (47 μl, 0.45 mmol) and quinuclidine (6 mg, 0.05 mmol) are added to nucleoside **28** (25 mg, 0.05 mmol) in anhydrous dichloromethane (2.5 ml). The solution is stirred for 10 min at 0°C then DBU (11 μl, 0.08 mmol) is added and the reaction mixture is allowed to slowly warm to room temperature for 12 h. The solvent is removed under reduced pressure and the crude residue is chromatographed over silica gel (hexane/AcOEt 1/5–0/1) to yield **29** (10 mg, 62%) as a white crystalline powder. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.54 (s, 1H); 8.07 (s, 1H); 6.16 (dd, *J*=6.9, 5.9 Hz, 1H); 5.68 (s, 2H); 4.39–4.33 (m, 1H); 4.03 (dd, *J*=12.8, 1.8 Hz, 1H); 3.71–3.59 (m, 1H); 2.81–2.67 (m, 1H); 2.51–2.33 (m, 2H); 2.31–2.15 (m, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.8; 151.6; 150.9; 141.5; 135.9; 128.4; 128.3; 128.2; 123.0; 87.9; 81.7; 68.5; 64.7; 32.4; 25.9. MS (CI/NH_3) *m/z* 327 $[M+H]^+$; 344 $[M+NH_4]^+$. IR (film) ν 3311; 2922; 1600; 1461; 1344; 1222.

4.1.29. *O*^{6}-Benzyl-5′-*O*-dibenzyloxyphosphoryl-2′,3′-dideoxyinosine (30). Compound **30** (94 mg, 56%) is prepared starting from nucleoside **29** and following the same procedure as described for **23a**. The compound is purified by chromatography over silica gel (Et_2O/AcOEt/EtOH 1/1/0–0/9/1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.51 (s, 1H); 8.15 (s, 1H); 7.40–7.28 (m, 15H); 6.30 (dd, *J*=4.9, 5.7 Hz, 1H); 5.68 (s, 2H); 5.01 (AB part of ABX syst., J_{AB}=8.7, J_{AX}=12.4, J_{BX}=12.1 Hz, ν_A=5.04, ν_B=4.99, 4H); 4.31 (m, 1H); 4.22–4.07 (m, 2H); 2.55–2.47 (m, 2H); 2.14–2.01 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.5; 151.9; 151.4; 140.4; 136.1; 128.8; 128.6; 128.4; 128.3; 128.1; 128.0; 122.0; 85.6; 79.5 (d, *J*=8.7 Hz); 69.5 (d, *J*=5.8 Hz); 68.4; 68.1 (d, *J*=5.8 Hz); 29.7; 25.9. ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 0.58. MS (CI/NH_3) *m/z* 588 $[M+H]^+$. IR (film) ν 2922; 1739; 1600; 1455; 1005.

4.1.30. 6-Chloro-9-(2′,5′-di-*O*-acetyl-3′-bromo-3′-deoxy-β-D-xylo-furanosyl)purine (31a) and 6-chloro-9-(3′,5′-di-*O*-acetyl-2′-bromo-3′-deoxy-β-D-xylofuranosyl)purine (31b). A solution of thionyl chloride (1.98 ml, 27.3 mmol) and DMF (0.96 ml, 12.4 mmol) in dichloromethane (24 ml) is added dropwise over 3 h to a mixture of the two regioisomers **24a** and **24b** (1.0 g, 2.4 mmol) in refluxing dichloromethane (60 ml). The reaction mixture is refluxed for 12 h more, cooled down to room temperature and stirred for 30 min with saturated aqueous $NaHCO_3$. The solution is extracted with dichloromethane and the organic layer is dried over Na_2SO_4 and reduced in vacuo. The crude residue is purified by chromatography over silica gel (Et_2O) to yield the two regioisomers **31a** (0.71 g, 68%) and **31b** (0.23 g, 22%) as white crystalline powders. **31a**: TLC (Et_2O) R_f 0.55. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H); 8.62 (s, 1H); 6.31 (d, *J*=2.3 Hz, 1H); 5.78 (dd, *J*=1.9, 1.5 Hz, 1H); 4.62–4.48 (m, 4H); 2.19 (s, 3H); 2.13 (s, 3H). ^{13}C NMR

($CDCl_3$, 50 MHz) δ 170.0; 168.7; 152.0; 150.9; 150.8; 143.0; 131.5; 88.1; 82.5; 78.8; 64.5; 48.6; 20.5; 20.3. IR (film) ν 2986; 1751; 1561; 1216; 1043. MS (CI/NH_3) *m/z* 435 $[M+H]^+$. **31b**: TLC (Et_2O) R_f 0.4. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.77 (s, 1H); 8.48 (s, 1H); 6.49 (d, J=2.6 Hz, 1H); 5.63 (dd, J=3.1, 2.9 Hz, 1H); 4.78 (dd, J=4.1, 2.6 Hz, 1H); 4.62–4.48 (m, 3H); 2.18 (s, 3H); 2.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.1; 169.2; 151.9; 150.4; 150.3; 143.4; 131.7; 85.2; 81.1; 78.8; 64.1; 50.8; 20.9; 20.4. MS (CI/NH_3) *m/z* 435 $[M+H]^+$. IR (film) ν 2986; 1751; 1561; 1216; 1043.

4.1.31. 6-Chloro-9-(5′-*O*-acetyl-2′,3′-dideoxy-β-D-*glycero*-pent-2′-enofuranosyl)purine (32). Compound **32** is prepared starting from the mixture of regioisomers **31a** and **31b** and following the same procedure as described for **25**. Chromatography over silica gel (Et_2O/AcOEt 1/0–1/1) yields **32** (104 mg, 49%) as a glassy solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.75 (s, 1H); 8.31 (s, 1H); 7.16 (ddd, J=3.0, 1.5, 1.5 Hz, 1H); 6.43 (ddd, J=6.0, 1.9, 1.5 Hz, 1H); 6.17 (ddd, J=6.0, 1.9, 1.9 Hz, 1H); 5.19 (m, 1H); 4.29 (AB part of ABX syst., J_{AB}=12.4, J_{AX}=3.8, J_{BX}=3.0 Hz, ν_A=4.35, ν_B=4.22, 2H); 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8; 151.6; 151.0; 150.2; 143.1; 133.6; 131.3; 125.2; 88.2; 84.8; 63.9; 20.3. MS (CI/NH_3) *m/z* 295 $[M+H]^+$; 312 $[M+NH_4]^+$. IR (film) ν 3506; 3404; 2943; 2813; 2355; 1572; 1237.

4.1.32. 6-Chloro-9-(2′,3′-dideoxy-β-D-*glycero*-pent-2′-enofuranosyl)purine (33). The compound is prepared from **32** and following the same procedure as described for **28**. The crude material is purified by chromatography (Et_2O/AcOEt 9/1–0/1) to yield **33** (221 mg, 96%) as a white crystalline powder. Mp 190°C. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H); 8.54 (s, 1H); 7.12 (broad s, 1H); 6.50 (broad d, J=6.0 Hz, 1H); 6.07 (broad d, J=6.0 Hz, 1H); 3.95 (AB part of ABX syst., J_{AB}=12.4, J_{AX}=2.3, J_{BX}=2.6 Hz, ν_A=4.01, ν_B=3.88, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.9; 151.1; 151.0; 144.7; 135.2; 131.8; 125.1; 89.6; 88.6; 63.2. MS (CI/NH_3) *m/z* 253 $[M+H]^+$; 270 $[M+NH_4]^+$.

4.1.33. 6-Chloro-9-(5′-*O*-dibenzyloxyphosphoryl-2′,3′-dideoxy-β-D-*glycero*-pent-2′-enofuranosyl)purine (34). The compound is prepared from **33** following the same procedure as described for **30**. The crude material is purified by chromatography (AcOEt/EtOH 95/5) to yield **34** (35 mg, 36%) as a glassy solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H); 8.27 (s, 1H); 7.35–7.26 (m, 10H); 7.14 (ddd, J=3.0, 1.5, 1.5 Hz, 1H); 6.32 (ddd, J=6.0, 1.9, 1.5 Hz, 1H); 6.05 (ddd, J=6.0, 2.3, 1.5 Hz, 1H), 5.08–4.89 (m, 5H); 4.14 (AB part of ABXX′ syst., J_{AB}=11.5, J_{AX}=6.8, $J_{AX'}$=3.4, J_{BX}=6.4, $J_{BX'}$=3.4 Hz, ν_A=4.19, ν_B=4.08, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.1; 151.4; 150.9; 143.6; 135.3 (d, J=5.3 Hz); 133.6; 131.7; 128.5; 128.0; 127.9; 125.8; 88.5; 85.6 (d, J=7.3 Hz); 69.5; 67.0 (d, J=5.8 Hz). ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 0.21. MS (CI/NH_3) *m/z* 514 $[M+H]^+$. IR (film) ν 3485; 1590; 1561; 1273; 1191.

4.1.34. N^6-[1-(4-Azidobutyl)]-5′-*O*-dibenzyloxyphosphoryl-2′,3′-didehydro-2′,3′-dideoxyadenosine (35). Compound **34** (35 mg, 0.07 mmol), 4-azido-1-butylamine (8 mg, 0.07 mmol), and triethylamine (10 μl, 0.07 mmol) are stirred at room temperature for 5 h in anhydrous methanol (2.5 ml). The solvent is removed under reduced pressure and the crude residue is chromatographed over silica gel (AcOEt/EtOH 1/0–95.7/2.5) to yield **35** (17 mg, 42%) as a glassy solid. A fraction of starting material (13 mg, 37%) is recovered. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.40 (s, 1H); 7.89 (s, 1H); 7.37–7.28 (m, 10H); 7.08 (m, 1H); 6.28 (ddd, J=5.6, 1.7, 1.7 Hz, 1H); 5.03 (m, 1H); 4.98 (d, J=8.6 Hz, 4H); 4.11 (AB part of ABXX′ syst., J_{AB}=11.3, J_{AX}=6.6, $J_{AX'}$=3.4, J_{BX}=6.2, $J_{BX'}$=3.4 Hz, ν_A=4.16, ν_B=4.07, 2H); 3.67–3.73 (m, 2H); 3.34 (t, J=6.4 Hz, 2H); 1.68–1.82 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.4; 154.9; 138.1; 135.4; 132.9; 129.5; 128.9; 128.6; 128.0; 126.4; 119.6; 88.0; 85.1 (d, J=8.3 Hz); 69.4 (d, J=5.5 Hz); 67.5 (d, J=5.5 Hz); 51.1; 27.0; 26.4; 26.3. ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 0.41. MS (CI/NH_3) *m/z* 592 $[M+H]^+$. IR (film) ν 3308; 2096; 1619; 1278; 1008.

4.1.35. N^1-(3,5-Anhydro-2-deoxy-β-D-pentafuranosyl)-N^3[-1-(5-azidopentyl)]thymidine (37a). DEAD (127 μl, 0.806 mmol) is added to triphenylphosphine (211 mg, 0.806 mmol) in anhydrous THF (1 ml). The resulting solution is added dropwise to a mixture of oxetane **36**[45,46] (100 mg, 0.446 mmol) and 5-azido-1-pentanol (69 mg, 0.535 mmol) in THF (5 ml). The solution is stirred at room temperature for 90 min before the solvent is removed under vacuum. The residue is purified by chromatography over silica gel (Et_2O/AcOEt/EtOH 1/0/0–0/9/1) to yield **37a** (142 mg, 94%) as a white powder. TLC (AcOEt/EtOH 95/5) R_f 0.6. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.97 (d, J=1.5 Hz, 1H); 6.70 (dd, J=5.3, 5.2 Hz, 1H); 5.51 (dt, J=2.9, 1.8 Hz, 1H); 4.93 (dt, J=1.8, 4.0 Hz, 1H); 4.45 (AB part of ABX syst., J_{AB}=8.2, J_{AX}=3.8, J_{BX}=1.7 Hz, ν_A=4.76, ν_B=4.14, 2H); 3.92 (t, J=7.5 Hz, 2H); 3.23 (t, J=6.8 Hz, 2H); 2.47 (m, 2H); 1.91 (d, J=1.5 Hz, 3H); 1.71–1.54 (m, 4H); 1.46–1.31 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.1; 151.7; 134.2; 110.6; 89.4; 87.1; 80.4; 75.8; 51.0; 41.0; 37.9; 28.3; 26.8; 23.9; 13.2. MS (CI/NH_3) *m/z* 336 $[M+H]^+$; 353 $[M+NH_4]^+$. IR (film) ν 2942; 2097; 1666; 1461; 1267.

4.1.36. N^1-(3,5-Anhydro-2-deoxy-β-D-pentafuranosyl)-O^4-[1-(5-azidopentyl)]thymidine (37b). Compound **37b** (7 mg, 5%) is a side product isolated in the preparation of **37a**. TLC (AcOEt/EtOH 95/5) R_f 0.3. ^1H NMR ($CDCl_3$, 200 MHz) δ 8.10 (s, 1H); 6.72 (dd, J=6.6, 4.0 Hz, 1H); 5.53 (m, 1H); 5.02 (m, 1H); 4.51 (AB part of ABX syst., J_{AB}=8.2, J_{AX}=3.8, J_{BX}=1.7 Hz, ν_A=4.30, ν_B=4.22, 2H); 4.42 (t, J=6.6 Hz, 2H); 3.30 (t, J=6.6 Hz, 2H); 2.58–2.53 (m, 2H); 1.98 (s, 3H); 1.38–1.92 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.4; 156.7; 139.9; 105.2; 90.5; 87.2; 81.1; 75.6; 67.0; 51.2; 39.3; 28.5; 28.1; 23.2; 12.5. MS (CI/NH_3) *m/z* 336 $[M+H]^+$. IR (film) ν 2924; 2098; 1674.

4.1.37. N^3-[1-(5-Azidopentyl)]-3′-deoxy-2′,3′-didehydrothymidine (38). Nucleoside **37a** (33 mg, 0.1 mmol) and potassium *tert*-butoxide (12 mg, 0.1 mmol) are stirred in anhydrous DMSO (2 ml) at room temperature for 4 h. DMSO is removed in vacuo. The residue is solubilized in water (0.5 ml) and saturated aqueous NH_4Cl (3 ml) is added. The mixture is extracted with dichloromethane and ethyl acetate. The organic layer is dried over Na_2SO_4, reduced under vacuum and purified by chromatography (Et_2O/AcOEt/EtOH 6/4/0–0/9/1) to yield **38** (16 mg, 59%) as a

white crystalline powder. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.41 (d, J=1.5 Hz, 1H); 7.05 (ddd, J=3.3, 1.5, 1.5 Hz, 1H); 6.33 (ddd, J=5.8, 1.8, 1.5 Hz, 1H); 5.87 (ddd, J=5.8, 2.2, 1.5 Hz, 1H); 4.93 (m, 1H); 3.95 (t, J=6.9 Hz, 2H); 3.99–3.83 (m, 1H); 3.95 (t, J=7.3 Hz, 2H); 3.85–3.73 (m, 1H); 3.27 (t, J=6.9 Hz, 2H); 1.89 (d, J=1.5 Hz, 3H); 1.74–1.58 (m, 4H); 1.50–1.38 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.4; 152.3; 134.3; 134.1; 126.7; 110.2; 90.7; 86.9; 63.6; 51.2; 41.1; 28.5; 27.0; 24.0. MS (CI/NH_3) m/z 336 $[M+H]^+$; 353 $[M+NH_4]^+$. IR (film) ν 3467; 2933; 2100; 1694; 1667; 1633; 1467.

4.1.38. 3′-Deoxy-2′,3′-didehydro-5′-*O*-dibenzyloxyphosphoryl thymidine (39). The preparation is similar to that described for **23a**, starting from d4T.[46] The crude reaction mixture is purified by chromatography (Et_2O/AcOEt/EtOH 1/0/0–0/9/1) to yield compound **39** (313 mg, 75%) as a white powder. Mp 103°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62–7.31 (m, 11H); 6.99 (ddd, J=1.9, 1.9, 1.1 Hz, 1H); 6.17 (ddd, J=5.7, 1.9, 1.5 Hz, 1H); 5.82 (ddd, J=5.7, 1.5, 1.1 Hz, 1H); 5.04 (AB part of ABX syst., J_{AB}=16.8, J_{AX}=8.7, J_{BX}=9.0 Hz, ν_A=5.06, ν_B=5.02, 4H); 4.93–4.87 (m, 1H); 4.16 (AB part of ABXX′ syst., J_{AB}=11.7, J_{AX}=6.2, $J_{AX'}$=2.6, J_{BX}=6.2, $J_{BX'}$=2.6 Hz, ν_A=4.19, ν_B=4.13, 2H); 1.81 (d, J=0.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.5; 150.6; 135.9; 135.4; 132.9; 128.8; 128.7; 128.1; 127.4; 111.3; 89.4; 84.5 (d, J=8.7 Hz); 69.6; 69.5; 12.1. ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 0.75. MS (CI/NH_3) m/z 502 $[M+NH_4]^+$. IR (film) ν 3189; 3067; 2922; 1689; 1461; 1250; 1005.

4.1.39. N^3-[1-(5-Azidopentyl)]-3′-deoxy-2′,3′-didehydro-5′-*O*-dibenzyloxyphosphoryl thymidine (40). The preparation is similar to that described for **37a**, starting from **39**. The crude reaction mixture is purified by chromatography (Et_2O/AcOEt/EtOH 1/0/0–0/9/1) to yield compound **40** (142 mg, 47%) as a white powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.28 (m, 10H); 7.24 (d, J=1.2 Hz, 1H); 7.02 (ddd, J=1.9, 1.7, 1.5 Hz, 1H); 6.13 (ddd, J=5.7, 1.7, 1.5 Hz, 1H); 5.79 (d, J=5.7 Hz, 1H); 5.00 (AB part of ABX syst., J_{AB}=11.7, J_{AX}=8.6, J_{BX}=8.8 Hz, ν_A=5.01, ν_B=4.99, 4H); 4.87 (m, 1H); 4.12 (AB part of ABXX′ syst., J_{AB}=11.5, J_{AX}=5.8, $J_{AX'}$=3.0, J_{BX}=5.8, $J_{BX'}$=3.0 Hz, ν_A=4.15, ν_B=4.09, 2H); 3.91 (t, J=7.5 Hz, 2H); 3.21 (t, J=6.8 Hz, 2H); 1.81 (d, J=1.2 Hz, 3H); 1.67–1.55 (m, 4H); 1.44–1.34 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.2; 151.2; 133.8; 133.0; 132.6; 128.6; 128.5; 128.1; 127.4; 110.3; 90.0; 84.2 (d, J=8.7 Hz); 69.4 (d, J=5.8 Hz); 67.2 (d, J=5.8 Hz); 51.0; 40.9; 28.2; 26.8; 23.8; 12.7. ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 0.66. MS (CI/NH_3) m/z 613 $[M+NH_4]^+$. IR (film) ν 3444; 2922; 2089; 1700; 1667; 1639; 1439.

4.1.40. N^3-[1-(5-Aminopentyl)]-3′-deoxy-2′,3′-didehydro-5′-*O*-dibenzyloxyphosphoryl thymidine (41). The preparation is similar to that described for **8**, starting from **40**. The crude reaction mixture is purified by preparative TLC (AcOEt/EtOH 85/15) to yield compound **41** (35 mg, 56%) as a glassy solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.30 (m, 10H); 7.24 (s, 1H); 7.04 (ddd, J=1.9, 1.7, 1.5 Hz, 1H); 6.16 (d, J=6.0 Hz, 1H); 5.82 (m, 1H); 5.02 (AB part of ABX syst., J_{AB}=11.7, J_{AX}=8.7, J_{BX}=8.7 Hz, ν_A=5.05, ν_B=4.99, 4H); 4.90 (m, 1H); 4.17 (AB part of ABXX′ syst., J_{AB}=11.6, J_{AX}=6.0, $J_{AX'}$=3.0, J_{BX}=5.9, $J_{BX'}$=2.6 Hz, ν_A=4.19, ν_B=4.15, 2H); 3.91 (t, J=6.8 Hz, 2H); 3.16 (dt, J=6.8, 5.6 Hz, 2H); 1.81 (s, 3H); 1.63–1.51 (m, 4H); 1.41–1.29 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.4; 151.4; 135.3; 133.9 (d, J=10.1 Hz); 132.8; 128.6; 128.4; 128.0; 127.6; 110.5; 90.2; 84.4; 69.5 (d, J=5.8 Hz); 67.4; 41.0; 40.3; 29.3; 26.9; 24.2; 12.9. ^{31}P NMR ($CDCl_3$, 121.5 MHz) δ 0.71. MS (CI/NH_3) m/z 571 $[M+H]^+$; 588 $[M+NH_4]^+$. IR (film) ν 3366; 2931; 1701; 1666; 1637; 1461; 1249; 1008.

4.1.41. 5′(*S*)-(Uracil-1-yl)-1′,3′-oxathiolane-2′(*R*)-carboxylic acid (1*R*,2*S*,5*R*)-menthyl ester (44). 2,4,6-Collidine (3.47 ml, 26.23 mmol) and *tert*-butyldimethylsilyl triflate (5.51 ml, 24 mmol) are successively added dropwise to uracil (1.28 g, 11.45 mmol) in anhydrous dichloromethane (11 ml). The resulting solution is stirred at room temperature for 5 min before acetate **42**[52] (3.00 g, 9.09 mmol) in dichloromethane (11 ml) is added, followed by dropwise addition of trimethylsilyl iodide (1.42 ml, 10.00 mmol). The reaction mixture is stirred for 20 h and then decomposed by addition of saturated aqueous $Na_2S_2O_3$ (20 ml) and water (10 ml). The mixture is extracted with dichloromethane (150 ml) and the organic layer is washed with brine, and reduced in vacuo. The residue is solubilized in ether (150 ml) and saturated aqueous $NaHCO_3$ (90 ml) is carefully added under vigorous stirring, followed with *n*-hexane (35 ml) and cyclohexane (35 ml). Stirring is maintained for 20 min. The precipitate that formed is filtered, washed with *n*-hexane/cyclohexane and recrystallized in *n*-hexane/ethyl acetate/methanol to yield **44** (2.63 g, 76%) as a white powder. Mp 191°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.29 (d, J=7.9 Hz, 1H); 6.42 (dd, J=7.9, 4.9 Hz, 1H); 5.78 (d, J=7.9 Hz, 1H); 5.40 (s, 1H); 4.72 (dt, J=4.1, 10.9 Hz, 1H); 3.27 (AB part of ABX syst., J_{AB}=12.1, J_{AX}=4.9, J_{BX}=7.9 Hz, ν_A=3.41, ν_B=3.12, 2H); 2.03–1.83 (m, 2H); 1.70–1.62 (m, 2H); 1.53–1.32 (m, 2H); 1.10–0.80 (m, 3H); 0.89 (d, J=6.4 Hz, 3H); 0.87 (d, J=6.4 Hz, 3H); 0.73 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.7; 163.4; 150.4; 140.3; 102.9; 89.1; 77.6; 76.8; 47.0; 40.7; 35.1; 34.0; 31.4; 26.0; 23.1; 21.9; 20.7; 16.0. MS (CI/NH_3) m/z 383 $[M+H]^+$; 400 $[M+NH_4]^+$. IR (film) ν 3201; 2942; 1713; 1678.

4.1.42. 1′(*S*)-[O^4-(2,4,6-Triisopropylbenzenesulfonyl)-uracil-1-yl]-1′,3′-oxathiolane-2′(*R*)-carboxylic acid (1*R*,2*S*,5*R*)-menthyl ester (45). A mixture of menthyl ester **44** (704 mg, 1.84 mmol), 4-DMAP (10 mg, 0.09 mmol), and triethylamine (1.02 ml, 7.37 mmol) in anhydrous dichloromethane (10 ml) is treated with 2,4,6-triisopropylbenzenesulfonyl chloride (1.12 g, 3.69 mmol). The solution is stirred for 12 h at room temperature before the solvent is removed under vacuum. The crude residue is purified by chromatography (*n*-hexane/Et_2O 7/3) to yield **45** (1.19 g, 99%) as a white crystalline powder. Mp 134–135°C. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.82 (d, J=7.3 Hz, 1H); 7.20 (m, 2H); 6.28 (dd, J=5.1, 5.0 Hz, 1H); 6.11 (d, J=7.3 Hz, 1H); 5.50 (s, 1H); 4.75 (dt, J=4.4, 10.6 Hz, 1H); 4.26 (h, J=6.9 Hz, 2H); 3.40 (AB part of ABX syst., J_{AB}=12.4, J_{AX}=4.8, J_{BX}=5.5 Hz, ν_A=3.64, ν_B=3.17, 2H); 2.90 (h, J=6.9 Hz, 1H); 2.08–2.01 (m, 1H); 1.97–1.86 (m, 1H); 1.77–1.68 (m, 2H); 1.58–1.37 (m, 3H); 1.32 (d, J=6.8 Hz, 3H); 1.29 (d, J=6.0 Hz, 3H); 1.27 (d,

J=7.1 Hz, 3H); 1.13–0.84 (m, 3H); 0.94 (d, J=6.4 Hz, 3H); 0.91 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.3; 167.3; 154.4; 153.7; 151.2; 146.8; 130.5; 124.0; 94.9; 90.9; 79.8; 77.0; 46.9; 40.6; 37.0; 34.1; 33.9; 31.3; 29.6; 26.0; 24.5; 24.3; 23.4; 23.1; 21.8; 20.6; 16.0. MS (CI/NH_3) m/z 649 $[M+H]^+$. IR (film) ν 2954; 2928; 1737; 1682; 1545; 1189.

4.1.43. 5′(*S*)-{N^4-[1-(4-Azidobutyl)cytosin]-1-yl}-1′,3′-oxathiolane-2′(*R*)-carboxylic acid (1*R*,2*S*,5*R*)-menthyl ester (46). Compound **45** (300 mg, 0.463 mmol) and a large excess of 4-azido-1-butylamine (200 μl) in dichloromethane (0.8 ml) are stirred at 0°C for 45 min. The solvent is removed under reduced pressure and the crude residue is dissolved in dichloromethane (0.4 ml). Ether is added until precipitation occurs and the solution is kept at −10°C for 12 h. The precipitate is filtered, washed with ether and dried under vacuum to yield **46** (169 mg, 76%) as a white crystalline solid. Mp 191–192°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (d, J=7.5 Hz, 1H); 6.50 (dd, J=6.4, 6.3 Hz, 1H); 5.73 (d, J=7.5 Hz, 1H); 5.43 (s, 1H); 4.74 (dt, J=4.1, 10.7 Hz, 1H); 3.55–3.46 (m, 3H); 3.36–3.28 (m, 2H); 3.13–3.05 (m, 1H); 1.89–2.07 (m, 2H); 1.75–1.62 (m, 6H); 1.56–1.39 (m, 2H); 1.10–0.85 (m, 3H); 0.91 (d, J=6.0 Hz, 3H); 0.90 (d, J=6.0 Hz, 3H); 0.76 (d, J=6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.9; 163.8; 156.0; 140.0; 95.4; 90.2; 77.9; 76.6; 51.0; 47.0; 40.7; 40.2; 36.0; 34.0; 31.4; 26.4; 26.2; 26.0; 23.2; 21.9; 20.7; 16.0. MS (CI/NH_3) m/z 479 $[M+H]^+$. IR (film) ν 2943; 2097; 1707; 1654; 1449.

4.1.44. 5′(*S*)-{N^4-[1-(4-Azidobutyl)]cytosin-1-yl}-2′(*R*)-hydroxymethyl-1′,3′-oxathiolane (47). Lithium aluminium hydride (13 mg, 0.349 mmol) is added at 0°C to **46** (60 mg, 0.126 mmol) in anhydrous THF (3 ml). The reaction mixture is stirred for 10 min and then decomposed by addition of wet ether (2 ml), methanol (2 ml), and silica gel (1 g). The slurry is stirred for 1 h at room temperature then filtered. The filtrate is reduced under vacuum and purified by chromatography (AcOEt/EtOH 1/0–9/1) to yield **47** (41 mg, 99%) as a glassy solid. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.93 (d, J=7.5 Hz, 1H); 6.29 (dd, J=4.9, 4.8 Hz, 1H); 5.84 (d, J=7.5 Hz, 1H); 5.26 (dd, J=4.1, 3.8 Hz, 1H); 3.89 (AB part of ABX syst., J_{AB}=12.4, J_{AX}=3.8, J_{BX}=4.1 Hz, ν_A=3.92, ν_B=3.85, 2H); 3.40 (t, J=6.4 Hz, 2H); 3.33 (t, J=6.4 Hz, 2H); 3.30 (AB part of ABX syst., J_{AB}=11.9, J_{AX}=5.7, J_{BX}=4.9 Hz, ν_A=3.48, ν_B=3.11, 2H); 1.70–1.59 (m, 4H). ^{13}C NMR (CD_3OD, 50 MHz) δ 165.5; 158.3; 141.1; 96.8; 88.8; 87.6; 64.2; 52.1; 41.0; 38.2; 27.3. MS (CI/NH_3) m/z 327 $[M+H]^+$. IR (film) ν 3295; 2920; 2090; 1640.

4.1.45. 5′(*S*)-{N^4-[1-(4-Azidobutyl)]cytosin-1-yl}-2′(*R*)-dibenzyl-oxyphosphoryloxymethyl-1′,3′-oxathiolane (48). *n*-Butyl lithium (1.6 M in hexane, 190 μl, 0.304 mmol) is added dropwise at −78°C to nucleoside **47** (45 mg, 0.138 mmol) in anhydrous THF (5 ml). The solution is stirred for 30 min before dibenzyl chlorophosphate (181 mg, 0.610 mmol) in THF (1 ml) is added and then stirred for 1 h at −78°C and 12 h at room temperature. Methanol (1 ml) and 4 drops of saturated aqueous NH_4Cl are added to decompose chlorophosphate in excess. The solvent is removed in vacuo and the residue is purified by chromatography (AcOEt/EtOH 1/0–9/1) to yield **48** (65 mg, 80%) as a glassy solid. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.68 (d, J=7.5 Hz, 1H); 7.35–7.37 (m, 10H); 6,30 (t, J=5.7, 5.6 Hz, 1H); 5.76 (d, J=7.5 Hz, 1H); 5.34 (m, 1H); 5.08 (dd, J=8.7, 2.3 Hz, 4H); 4.28 (m, 2H); 3.48–3.33 (m, 4H); 3.25 (AB part of ABX syst., J_{AB}=11.7, J_{AX}=5.3, J_{BX}=6.0 Hz, ν_A=3.45, ν_B=3.06, 2H); 1.66–1.61 (m, 4H). ^{13}C NMR (CD_3OD, 50 MHz) δ 165.4; 158.1; 140.6; 137.1; 137.0; 129.8; 129.7; 129.2; 97.3; 89.1; 83.3 (d, J=7.2 Hz); 71.0 (d, J=5.8 Hz); 69.6 (d, J=5.8 Hz); 52.1; 41.0; 37.2; 27.3. ^{31}P NMR (CD_3OD, 121.5 MHz) δ −0.30. MS (CI/NH_3) m/z 588 $[M+H]^+$. IR (film) ν 3272; 2931; 2096; 1725; 1642; 1507; 1278; 1014.

4.1.46. 5′(*S*)-{N^4-[1-(4-Azidobutyl)]cytosin-1-yl}-2′(*R*)-dihydroxyphosphoryloxymethyl-1′,3′-oxathiolane (49a and 49b). The compound is prepared starting from **48** and following the same procedure as described for **9**. Compound **49** (14 mg, 99%) is obtained as a mixture of epimers (**49a/49b** 26/74) as determined by NMR. ^{1}H NMR (D_2O, 300 MHz) δ 8.32 (d, J=7.9 Hz, 1Hb); 8.09 (d, J=7.9 Hz, 1Ha); 6.27 (d, J=7.9 Hz, 1Hb); 6.20 (dd, J=5.3, 3.0 Hz, 1Ha and 1Hb); 6.04 (d, J=7.9 Hz, 1Ha); 4.27–4.17 (m, 1Ha and 1Hb); 4.08–3.99 (m, 1Ha and 1Hb); 3.53–3.45 (m, 1Ha and 1Hb); 3.38–3.30 (m, 2Ha and 2Hb); 3.28–3.17 (m, 3Ha and 3Hb); 1.72–1.48 (m, 4Ha and 4Hb). ^{13}C NMR (D_2O/CD_3OD 1/1, 50 MHz) δ 158.2 (b); 157.9 (a); 149.6 (a); 149.1 (b); 146.5 (b); 143.2 (a); 96.2 (a); 92.4 (b); 88.1 (a and b); 87.0 (d, J=8.7 Hz, b); 86.6 (d, J=7.2 Hz, a); 66.1 (d, J=4.3 Hz, a and b); 51.5 (a and b); 43.7 (b); 43.2 (a); 38.5 (b); 38.1 (a); 26.4 (b); 26.3 (a); 26.2 (b); 25.5 (a). ^{31}P NMR (D_2O, 50 MHz) δ 1.59 (b); 1.11 (a). MS (CI/NH_3) m/z 310 $[M-H_2PO_4+H]^+$. IR (film) ν 3411; 2944; 2100; 1722; 1661.

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