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Monoglycosyl, diglycosyl, and dinucleoside methylenediphosphonates: direct synthesis and antiviral activity

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Abstract—A direct and general access to D-glycosyl 3-, 5-, or 6-methylenediphosphonates, di-D-glycosyl 1,5-, 3,5-, 3,6-, 5,5-, or 6,6-methylenediphosphonates and dithymidine 3′,5′-methylenediphosphonate is described. The method involves the one-pot alkylidenediphosphorylation of glycosyl or thymidine derivatives. No antiviral activity was detected against a panel of RNA and DNA viruses.

Keywords: Pyrophosphate analogues; Glycosyl methylenediphosphonate; Diglycosyl methylenediphosphonate; Dithymidine methylenediphosphonate; Lithiated carbanions; Antiviral activity

1. Introduction

Many investigations have shown that the methylenediphosphonate group is a metabolically stable bioisosteric replacement for the pyrophosphate moiety.[1] The glycosyl methylenediphosphonates and their derivatives have found broad applications as stable analogues of natural products and as potential candidates for therapeutics. For example, the synthesis of methylenediphosphono and nucleoside methylenediphosphono sugars as potential inhibitors of glycosyltransferases has been described.[2] A number of nucleoside methylenediphosphonates have also been reported.[1,3] Thus, uridine 5′-[(α-D-galactopyranosyl hydroxy phosphinyl)-methyl]phosphonate inhibits competitively a specific glycoprotein galactosyltransferase.[2] The synthesis, structural features, and biological activity of nucleoside methylenediphosphonate analogues of ADP or GDP have been studied.[4] A NAD+ analogue incorporating a methylenediphosphonate linkage in place of the natural pyrophosphate has been reported to act as an inhibitor of ADP ribosyl cyclase and to resist phosphatase degradation.[5] Recently, methylenediphosphonate analogues of mycophenolic acid adenine dinucleotide (MAD),[6] thiazole-4-carboxamide adenine dinucleotide (TAD),[7] and benzamide adenine dinucleotide (BAD)[7a,8] have been described as potential inosine monophosphate dehydrogenase (IMPDH) inhibitors. The synthesis of a possible mechanism-based bis-substrate inhibitor of the elongating α-D-mannosyl phosphate transferase in *Leishmania*, comprising a guanosine subunit bound to the synthetic acceptor substrate through the methylenediphosphonate linker has also been reported.[9]

However, the synthesis and biological investigations of di-D-glycosyl methylenediphosphonates and dinucleoside 3′,5′-methylenediphosphonates seemed unknown. To the best of our knowledge, only the syntheses of diglycosyl or dinucleoside methylphosphonates are documented.[10] We describe here a general carbanionic access to monoglycosyl and mononucleoside

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methylenediphosphonates; di-D-glycosyl and dinucleoside methylenediphosphonates. These compounds represent stable potential mechanism-based transition state inhibitors of D-glycosyl phosphate transferase or DNA-polymerase, respectively.

2. Results and discussion

Our first goal was the preparation of the model triethyl methylenediphosphonate monosubstituted by a glycosyl or a nucleoside moiety based on our previous synthetic strategy of one-pot alkylidene diphosphorylation of nucleophiles.[11]

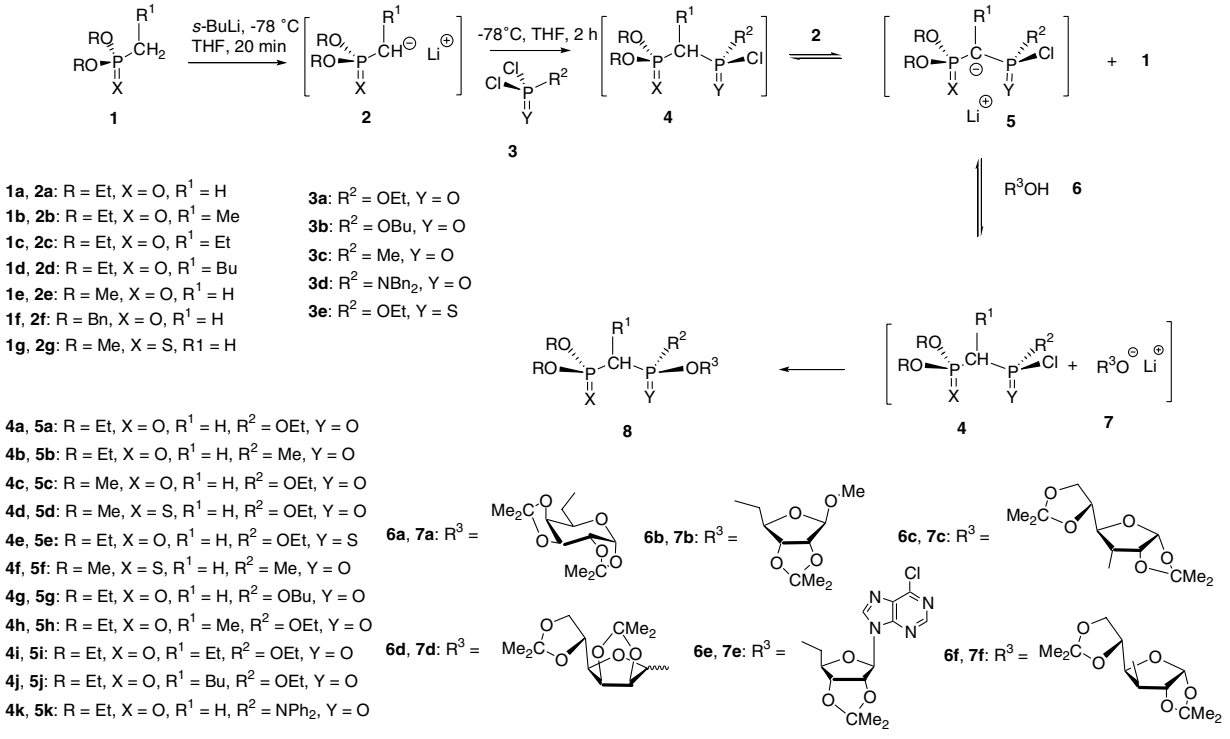
2.1. Synthesis of triethyl glycosyl alkylidenediphosphonates and triethyl nucleoside methylenediphosphonates 8

The approach involved a one-pot five-step sequence. The key step of the synthesis proceeded by a direct introduction of the diphosphonate moiety on a suitably protected carbohydrate **6** by way of the chloride intermediate **4** (Scheme 1).

The first step was the phosphorylation of the α-lithio alkylphosphonate **2** by the dichloride phosphorus reagent **3**. The difference of reactivity between the two chloride atoms in **3** was sufficient at low temperature to control the monosubstitution and to obtain **4**. The latter compound was immediately deprotonated to **5** as a result of a rapid acid–base exchange between **4** and the lithiated carbanion **2**. Therefore, two equivalents of **2** were required to get **5** in optimum yield. Further treatment of carbanion **5** with one equivalent of a suitably protected sugar **6** led to a novel acid–base exchange involving the reprotonation of **5** into **4** with the simultaneous formation of the lithium alcoholate **7**. This derivative reacted with **4** to give the desired crude P-monoglycosyl methylenediphosphonate or P-mononucleoside methylenediphosphonate **8.**

The evolution of the reaction was monitored by ^{31}P NMR spectroscopy. Assignment of ^{31}P, ^{1}H, and ^{13}C NMR signals of pure products was deduced from two-dimensional ^{31}P–^{1}H correlation and direct two-dimensional ^{13}C–^{1}H correlation experiments, respectively. By the use of this 'one-pot' sequence, various monoglycosyl methylenediphosphonates **8** were prepared (Chart 1).

It was noted that our initial study described the formation of a low amount of tetraethyl methylenediphosphonate as a side product always present in a range 0–5% in all crude products.[11b] We now found that the choice of the lithiated base was the factor that controlled the formation of this side product. The use of *s*-BuLi instead of *n*-BuLi suppressed completely the formation of tetraethyl methylenediphosphonate. Consequently, with this reagent, the methylenediphosphonate **8** was the sole diphosphorylated product obtained without any side product. The dialkyl alkylphosphonate **1** in excess was easily removed under diminished pressure (**1a**, **1e**, **1g**) or by chromatography (**1b–d**, **f**). Neutral aluminum oxide was preferred to silica gel to



Scheme 1. Synthesis of monoglycosyl and mononucleoside alkylidenediphosphonates **8**.

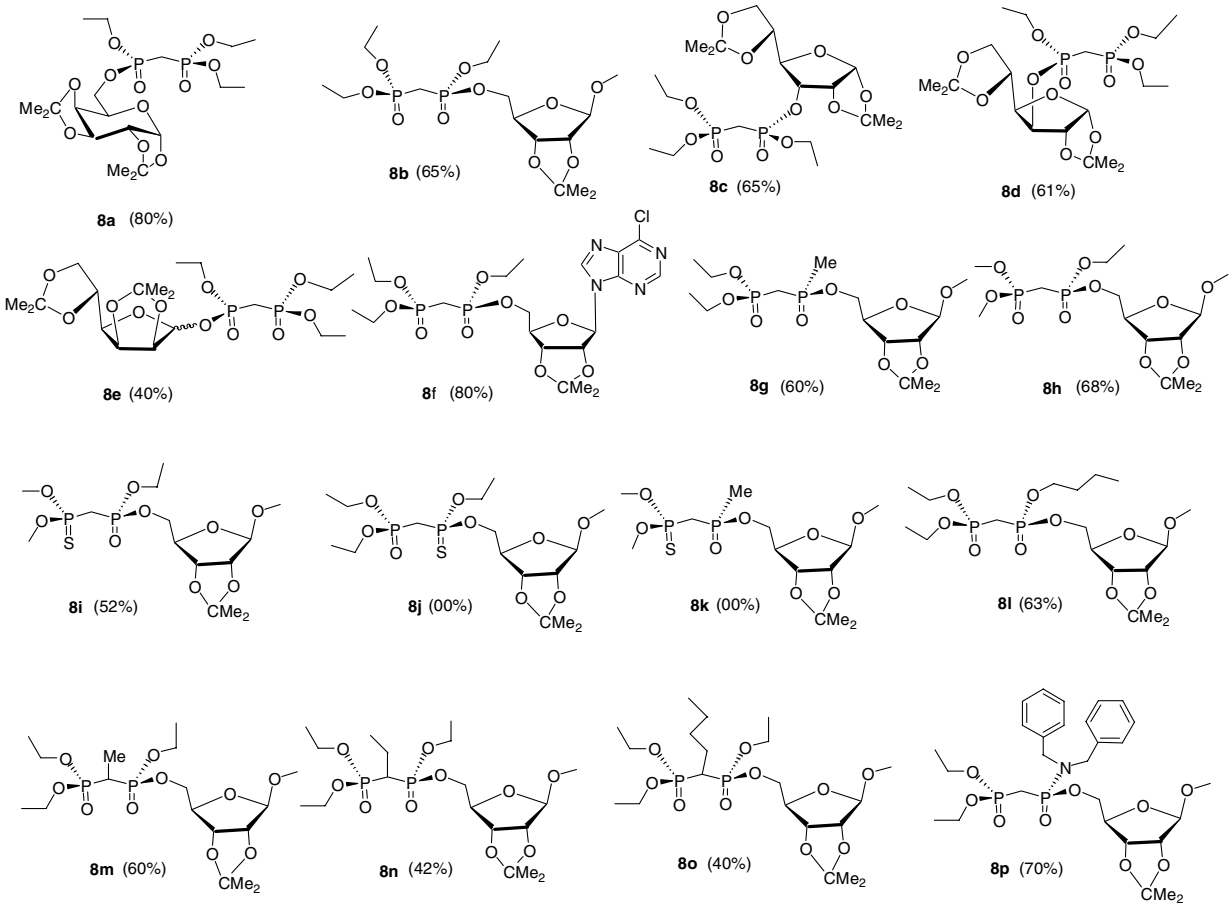


Chart 1. Monoglycosyl alkylidenediphosphonates **8** synthesized by the one-pot carbohydrate alkylidenediphosphorylation method.

avoid the partial decomposition of the diphosphorylated compound **8**. The reaction involved the creation of the second phosphorus atom as a chiral center but was not stereoselective. D-Glycosyl diphosphonates **8** were obtained as a mixture of two epimers in a ratio 1:1 as judged by ^{31}P NMR analysis of the crude product in the cases where the diastereomers could be distinguished, which was not always possible. Moreover, it was not possible to obtain the pure stereomers by chromatography.

As seen in Chart 1, the products **8** were obtained in moderate to good yields (40–80%). The strategy allowed the preparation of monoglycosyl methylenediphosphonates **8** with a wide range of sugars **6** (protected D-galactose, D-ribose, D-allose, D-altrose, D-mannose derivatives). It was possible to introduce the sugar **6** via the 5-OH, or 6-OH, 3-OH, 1-OH. The 6-chloro-9-β-D-(2′,3′-*O*-isopropylidene)-ribofuranosyl-purine was of particular interest for the preparation of the corresponding P-nucleoside methylenediphosphonate **8f**. This indicated that the bulkiness of the nucleophile **6** did not affect the efficiency of the process. The process was also influenced by the nature of the starting phosphonate **1**: the reaction with the methylthiophosphonate **1g** was less efficient than that with the oxygenated analogue **1e** (compare **8h**, **8i**). In the same way, the reaction between α-lithio methylthiophosphonate **2g** and **3c** did not allow for the formation of the ribosyl diphosphonate **8k**. Substitution of the methylene position with an alkyl group (**1b**–**d**) increased the steric hindrance, and yields decreased with a bulky R^1 substituent (compare **8m**, **8n**, **8o**). The electron-withdrawing groups in **3a**–**b** promoted a fast reaction with the carbanion **2**. On the contrary, with a sulfur atom in **3e**, the reaction failed (**8j**). Indeed, monitoring of the reaction by ^{31}P NMR spectroscopy showed that substitution of the first chlorine in the dichlorothiophosphate **3e** was not achieved even at room temperature.

Encouraged by these preliminary results, the synthesis of di-D-glycosyl methylenediphosphonates and dinucleoside 3′,5′-methylenediphosphonates was explored according to the same procedure of one-pot alkylidene diphosphorylation of sugars.

2.2. Synthesis of diglycosyl methylenediphosphonates 10

The procedure required as a preliminary step the preparation of glycosyl phosphorodichloridates **3f**–**j** (Chart 2).

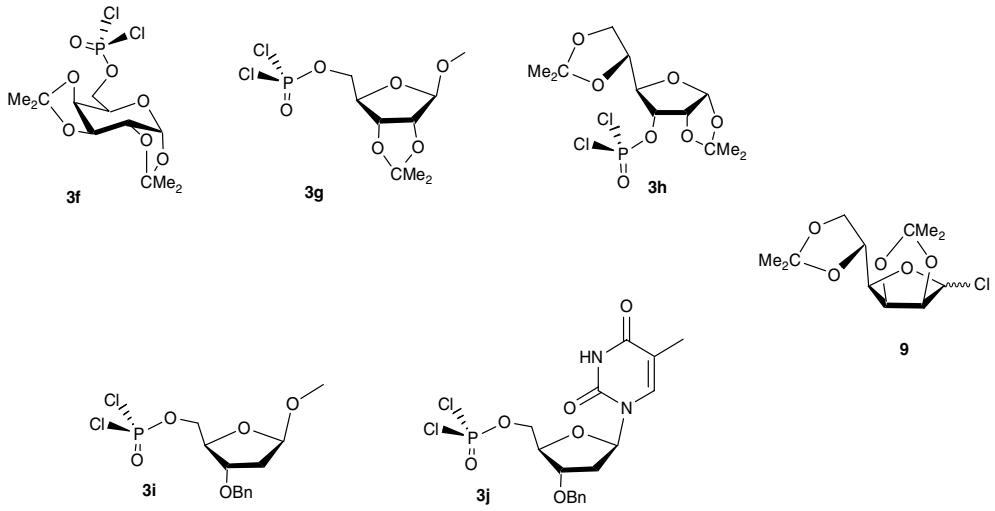


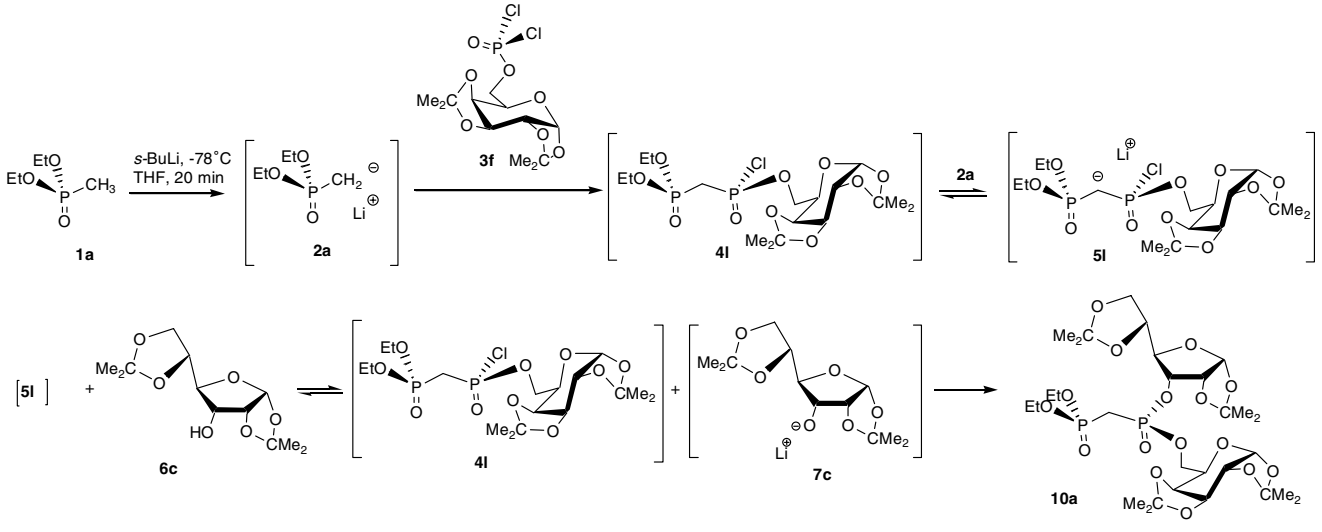
Chart 2. Products of the reaction between $POCl_3$ and protected sugar derivatives **6**.

These compounds were obtained from the reaction between the free OH of a suitably protected sugar **6** and $POCl_3$ in the presence of Et_3N at 0 °C in diethyl ether. Subsequent filtration of the triethylammonium chloride led to the expected products **3f–j** quantitatively. However, the reaction failed with 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose. In this case, the high reactivity of the anomeric hydroxyl was not compatible with the acidic reaction medium and chlorination occurred with the formation of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranosyl chloride **9** as the major product in agreement with the results of Freudenberg and Wolf.[13]

Then, we set up the reaction sequence, exemplified by the preparation of **10a** in Scheme 2, with diethyl methylphosphonate **1a** as a model reagent using galactosyl phosphorodichloridate **3f** as the first electrophilic substrate leading to **4l** followed by the nucleophilic attack of a second carbohydrate **6c** onto **5l** to afford diglycosyl methylenediphosphonate **10a**. Different diglycosyl methylenediphosphonates **10** were thus synthesized (Chart 3).

The spectroscopic data of the crude material showed the formation of two diastereomers **10** in a 1:1 ratio, which were partially separated by chromatography. Obviously, the reaction was not stereoselective.

The introduction in the same molecule of two glycosyl residues linked to the same phosphorus atom did not affect the efficiency of the process. The method afforded diglycosyl methylenediphosphonates in a 66–80% yield range. It should be noted that a variety of nucleophilic carbohydrates **6** could react with the anionic intermediates **5** via a primary OH, a secondary OH or an ano-



Scheme 2. One-pot preparation of diglycosyl methylenediphosphonates **10** exemplified in the case of the synthesis of **10a**.

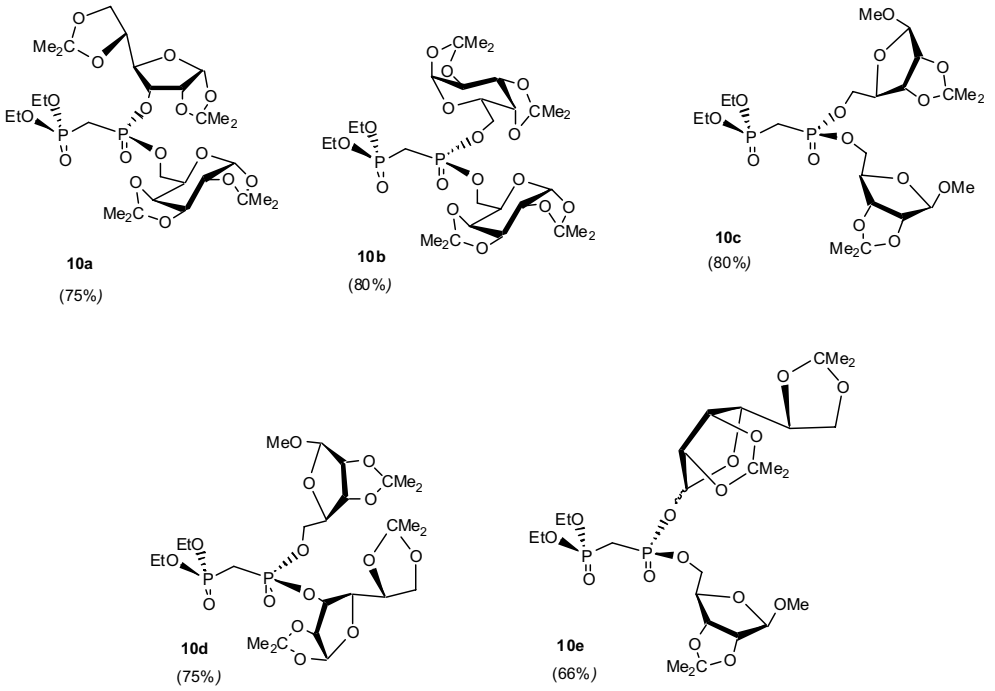


Chart 3. The different diglycosyl methylenediphosphonates **10** synthesized by the one-pot carbohydrate alkylidene diphosphorylation method.

meric OH. It was noted that the latter result indicated an interesting alternative to overcome the difficulty encountered above in the preparation of D-mannosyl phosphorodichloridate that failed.

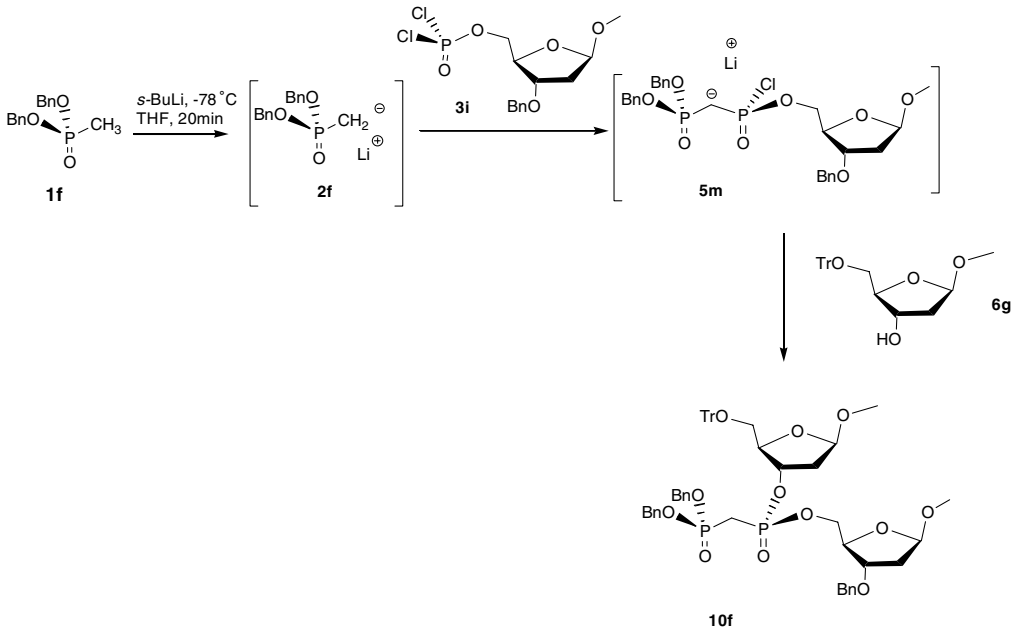
2.3. Syntheses of 10f as a model of dinucleoside methylenediphosphonate and dinucleoside methylenediphosphonate 10g

To demonstrate the utility of the process, the access to dinucleotide analogues was then tested. The strategy consisted of preparing a diphosphonate **10** that could be regioselectively functionalized with *O*-benzyl protections compatible with the nucleotide chemistry and with a view to further deprotect **10** in one step. In a first attempt, we faced the synthesis of di-deoxyribosyl methylenediphosphonate **10f** as a model. Consequently, dibenzyl methylphosphonate **1f**, methyl 2-deoxy-5-*O*-trityl-β-D-ribofuranoside **6g** and methyl 3-*O*-benzyl-2-deoxy-β-D-ribofuranoside **6h** were prepared as starting materials.[14] Considering the high sensitivity of the *O*-trityl group of methyl 2-deoxy-5-*O*-trityl-2-deoxy-β-D-ribofuranoside **6g** toward acidic conditions, we preferred to prepare methyl 3-*O*-benzyl-2-deoxy-β-D-ribofuranosyl phosphorodichloridate **3i** instead of the tritylated analogue possibly prepared from **6g**. The procedure for obtaining **10f**, in a one-pot sequence, by treating the α-lithio dibenzyl methylphosphonate **2f** with phosphoro dichloridate **3i** was then studied (Scheme 3).

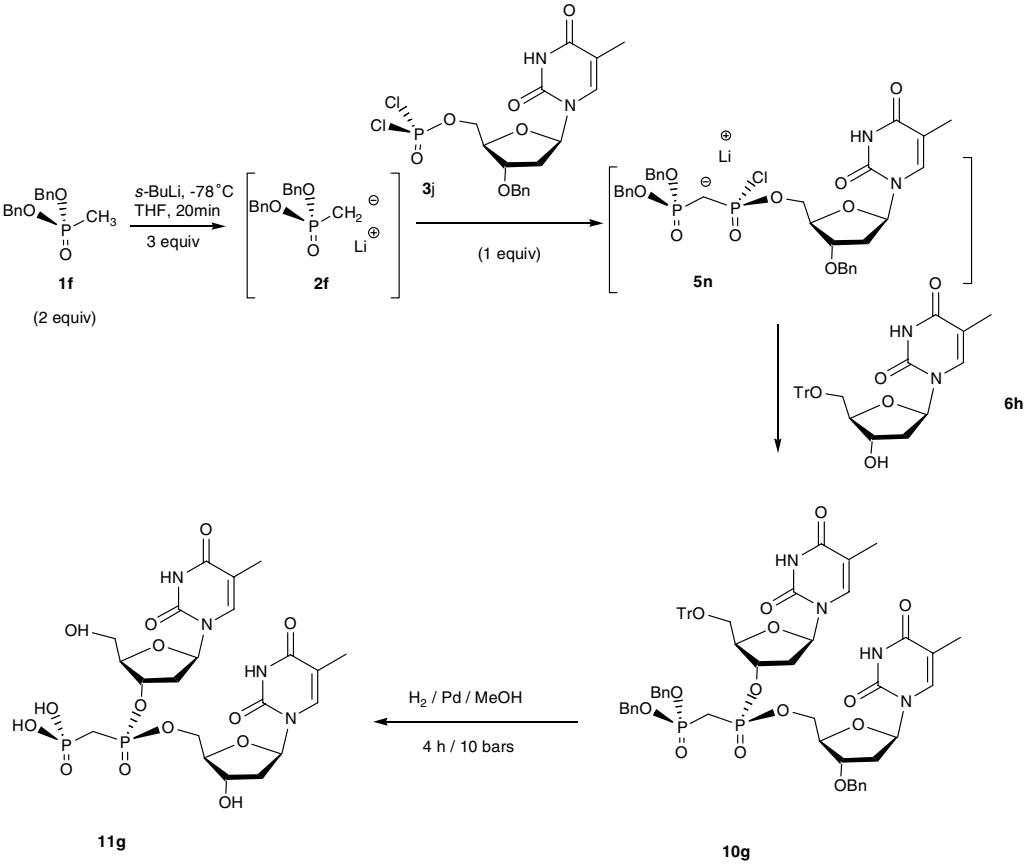
The α-lithio dibenzyl methylphosphonate **2f** reacted slowly with **3i** compared with the reactions of α-lithio diethyl methylphosphonate **2a** with **3** leading to **8a**–**e**,**g**,**l**,**p**. Whereas the formation of the intermediate **5** was complete after 2 h at −78 °C with α-lithio diethyl methylphosphonate **2a**, the ^{31}P NMR monitoring of the reaction in the present case showed the slow appearance of two ^{31}P NMR doublets at δ +20.2 ppm and δ +39.1 ppm ($^{2}J_{PP}$ 65 Hz) for the anion **5m**, only formed in 50% yield in time. Moreover, the anion **5m** reacted relatively slowly with methyl 2-deoxy-5-*O*-trityl-β- D-ribofuranoside **6g** in THF. After 4 h stirring from −78 to 20 °C, the integration of the ^{31}P NMR doublets at δ +18 ppm and δ +15 ppm that appeared for the product **10f** showed that its formation in the reaction medium did not exceed 35% yield. These difficulties were likely the result of the steric hindrance of both carbanion **5m** and methyl 2-deoxy-5-*O*-trityl-β-D-ribofuranoside **6g**. Compound **10f** was isolated after chromatography on neutral aluminum oxide in a moderate yield (30%).

We then focused our attention on the synthesis of a new dinucleotide methylenediphosphonate analogue **10g** of the natural dithymidine pyrophosphate with the same *O*-benzyl strategy (Scheme 4).

α-Lithio dibenzyl methylphosphonate **2f** (2 equiv) reacted with thymidine phosphoro dichloridate **3j** in the presence of an excess of *s*-BuLi (3 equiv) to compensate for lithiation of thymine moiety. The examination of the reaction mixture by ^{31}P NMR analysis revealed the presence of the expected intermediate **5a** (two doublets at δ +20 ppm and δ +39.2 ppm, $^{2}J_{P\text{-}P}$ 70 Hz). After 2 h, the 5-*O*-trityl-thymidine **6h** was added (1 equiv).[15] As a result of the increase in the steric hindrance of



Scheme 3. Synthesis of dideoxyribosyl methylenediphosphonate **10f**.



Scheme 4. Synthesis of dithymidine methylenediphosphonate **10g** and dithymidine methylenediphosphonic acid **11g**.

the reagents, a period of 15 h was required to yield 30% of the desired product **10g**. It was noted that the efficiency of the process was also closely related to the nature of the protecting groups. The use of a *O*-benzyl

protection which was justified by the necessity of a facile further deprotection suffered nevertheless from the drawback of a carbanionic strategy.[16] Moreover, the nitrogen metallation of the heterocycle was also a difficulty. Finally, the dinucleotide analog **10g** was hydrogenolyzed selectively and quantitatively with H_2/Pd/C in MeOH to provide the expected methylenediphosphonic acid **11g** (30% overall yield from **1f**).

2.4. Antiviral activity

Compounds **8f**, **10c**, and **11g** were evaluated against DNA viruses (herpes simplex viruses HSV-1, HSV-2, vaccinia virus, in E_6SM cell cultures), and RNA viruses (vesicular stomatitis virus, Coxsackie B4, respiratory syncytial virus in Hela cell cultures; parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie B4 and Punta Toro virus in Vero cell cultures). Antiviral Assays were performed according to previously established procedures.[17]

No specific antiviral activity (i.e., minimal antiviral effective concentration >5-fold lower than minimal cytotoxic concentration) was noted for any of the compounds tested against any of the viruses evaluated at concentration up to 100 μg/mL.

3. Conclusion

The application oı the one-pot alkylidene phosphorylation of nucleophiles to a general preparation of 3-, 5-, or 6-monoglycosyl methylenediphosphonates; diglycosyl 1,5-, 3,5-, 3,6-, 5,5-, or 6,6-methylenediphosphonates; 3′,5′-dinucleoside methylenediphosphonates, analogues of natural various pyrophosphates is described. The one-pot five-step reaction sequence gives a direct, fast, and efficient access to crude glycosyl or nucleoside methylenediphosphonates **8** in a short time with different substitutents on the α-carbon (R^1) or on the phosphorus atom (R^2). These results compare favorably with the methods described.[1,3a,6a,7b,12] Moreover, the method allowed a double substitution on one phosphorus atom of the alkylidenediphosphonate with two glycosyl moieties identical or different, or two nucleosides, leading to the new stable species **10** closely related to the possible transition state of D-glycosyl phosphate transferase or DNA-polymerase, respectively. However, these compounds did not exhibit antiviral activity toward DNA and RNA viruses. Consequently, their supposed resemblance with such mechanism-based transition states of D-glycosyl phosphate transferase or DNA-polymerase appears as insufficient to make them valuable inhibitors. The adaptation of the method to the synthesis of triphosphonate analogues of dinucleoside 3′,5′-triphosphate is under investigation.

4. Experimental

4.1. General

^{1}H NMR, ^{13}C NMR, and ^{31}P NMR were run at 250, 62.9, and 101.6 MHz, respectively. NMR spectra were obtained in $CDCl_3$. Chemicals shifts were given as δ ppm values and J values were given in Hertz (Hz). Data for ^{1}H NMR spectra are reported in δ units downfield from internal Me_4Si. ^{13}C NMR spectra were referenced to $CDCl_3$ peak at 77 ppm relatively to Me_4Si. Orthophosphoric acid (85%) was used as an external standard for ^{31}P NMR. Infrared spectra were obtained using a Nicolet 205 spectrometer and are given in cm^{-1}. Mass spectra were obtained on an Autospec Fited Cesium Gun (Micromass, Manchester). Et_2O was distilled over P_2O_5 and stored over Na. THF was freshly distilled over Na/benzophenone prior to use. Non aqueous reactions were performed in an oven-dried glassware under nitrogen atmosphere. Reactions were monitored by TLC on aluminum-backed silica gel-coated 60 F254 plates with detection by charring with H_2SO_4. Column chromatography was carried out on Silica Gel 60 (70–230 mesh) with the indicated eluent, dried and distilled shortly before use.

Methylphosphonic dichloride was easily available from Lancaster Synthesis. Alkyl phosphorodichloridates **3a**–**e** and α-lithio dibenzyl methylphosphonate **2f** were easily prepared according to our previous works.[18]

4.2. Preparation of glycosyl methylenediphosphonates 8

In a typical procedure, THF (8 mL) was added under N_2, at −30 °C, to *s*-BuLi 1.6 M in hexane (2.1 mmol, 1.35 mL). The soln was cooled to −78 °C and the dialkyl methylphosphonate or dialkyl methylthiophosphonate **1** (2 mmol) in THF (8 mL) was added. The resulting mixture was stirred for 20 min. Then alkylphosphorodichloridate or methylphosphonic dichloride **3** (1 mmol) in THF (10 mL) was added at −78 °C. The resulting mixture was stirred for 2 h. Protected sugar **6** was added at −78 °C and the reaction mixture was allowed slowly to warm to room temperature. The soln was hydrolyzed at this temperature. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), the organic layer was dried (Na_2SO_4), and the solvents were evaporated under diminished pressure. The crude product was purified on a neutral aluminum oxide gel chromatographic column with EtOAc to give **8**.

4.2.1. *O*′-Ethyl *O*′-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosyl)[(diethoxyphosphinyl)methyl]phosphonate 8a. From **1a** (304 mg), colorless oil, 402 mg (80%) diastereomeric mixture: ^{31}P NMR.

R_f (EtOAc) 0.27; IR (KBr): ν 1255, 1030; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.47 (d, 1H, $J_{1,2}$ 5 Hz, H-1), 4.56 (dd, 1H, $J_{2,3}$ 2 Hz, $J_{3,4}$ 8 Hz, H-3), 4.31 (dd, 1H, H-2),

4.30–4.00 (m, 10H, H-4, H-5, H-6, OCH_2CH$_3$), 2.50 (app-t, 2H, J_{HP} 21 Hz, PCH_2P), 1.52 (s, 3H, Me$_2$C), 1.45 (s, 3H, Me$_2$C), 1.39 (s, 3H, Me$_2$C), 1.33 (s, 3H, Me$_2$C), 1.32 (t, 9H, J 6 Hz, OCH$_2$CH_3); ^{13}C NMR (62.9 MHz, CDCl$_3$): δ 108.3 (s, C), 107.5 (s, C), 95.2 (s, C-1), 69.7 (s, C-3), 69.4 (s, C-2), 66.3 (d, $^3J_{CP}$ 5 Hz, C-5), 66.0 (d, J_{CP} 5 Hz, C-4), 61.4 (d, $^2J_{CP}$ 5 Hz, OCH$_2$CH$_3$), 60.2 (d, J_{CP} 5 Hz, C-6), 24.9 (s, Me$_2$C), 24.3 (app-2t, J_{CP} 137 Hz, PCH$_2$P), 23.9 (s, Me$_2$C), 23.4 (s, Me$_2$C), 15.3 (d, J_{CP} 5 Hz, OCH$_2$CH$_3$); ^{31}P NMR (101.6 MHz, CDCl$_3$): δ 18.0 (d, 1P, J_{PP} 6 Hz), 17.5 (d, 1P, J_{PP} 6 Hz), 16.9 (br s, 2P); FABMS: m/z 503 [M+H]$^+$, 100%; Anal. Calcd for $C_{19}H_{36}O_{11}P_2$: C, 45.42; H, 7.22; O, 35.03; P, 12.33. Found: C, 45.01; H, 7.47; O, 34.66; P, 12.86.

4.2.2. *O*′-Ethyl *O*′-(methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)[(diethoxyphosphinyl)methyl]phosphonate 8b. From **1a** (289 mg), colorless oil, 267 mg (65%) diastereomeric mixture: ^{13}C NMR.

R_f (EtOAc) 0.21; IR (KBr): ν 1580, 1550, 1260, 1020; ^{1}H NMR (400 MHz, CDCl$_3$): δ 4.97 (br s, 1H, H-1); 4.76 (dd, 1H, $J_{2,3}$ 4 Hz, $J_{3,4}$ 5 Hz, H-3), 4.60 (d br, 1H, H-2), 4.34–4.39 (m, 1H, H-4), 4.20–4.10 (m, 6H, OCH_2CH$_3$), 4.00–4.10 (m, 2H, H-5), 3.32 (s, 3H, OCH_3), 2.49 (app-t, 2H, J_{HP} 21 Hz, PCH_2P), 1.44 (s, 3H, Me$_2$C), 1.36 (t, 9H, J 7 Hz, OCH$_2$CH_3), 1.32 (s, 3H, Me$_2$C), ^{31}P NMR (170 MHz, CDCl$_3$): δ 17.6 (d, 1P, J_{PP} 6 Hz), 15.3 (d, 1P, J_{PP} 6 Hz); ^{13}C NMR (100.62 MHz, CDCl$_3$): δ 111.3 (s, C), 108.4 (s, C-1), 84.0 (s, C-2), 83.9 (d, J_{CP} 6 Hz, C-4), 80.5 (s, C-3), 65.1 (d, J_{CP} 6 Hz, C-5), 64.9 (d, J_{CP} 6 Hz, C-5), 61.5 (d, J_{CP} 6 Hz, OCH$_2$CH$_3$), 53.8 (s, OCH$_3$), 25.4 (s, Me$_2$C), 24.2 (app-t, J_{CP} 137 Hz, PCH$_2$P), 23.9 (s, Me$_2$C), 15.3 (d, J_{CP} 6 Hz, OCH$_2$CH$_3$); FABMS: m/z 447 [M+H]$^+$, 100%.

4.2.3. *O*′-Ethyl *O*′-(1,2:5,6-di-*O*-isopropylidene-α-D-allofuranosyl)[(diethoxyphosphinyl)methyl]phosphonate 8c. From **1a** (303 mg), colorless oil, 325 mg (65%) diastereomeric mixture: ^{1}H, ^{31}P, and ^{13}C NMR.

R_f (EtOAc) 0.21; IR (KBr): ν 1580, 1550, 1260, 1025; ^{1}H NMR (250 MHz, CDCl$_3$): δ 5.77 (d, 1H, $J_{1,2}$ 4 Hz, H-1), 5.72 (d, 1H, $J_{1,2}$ 4 Hz, H-1), 4.83 (app-t, 1H, H-2), 4.57 (app-t, 1H, $J_{2,3}$ 4 Hz, H-2), 4.31–3.87 (m, 11H, H-3, H-4, H-5, H-6, OCH_2CH$_3$), 2.57 (app-t, 2H, J_{HP} 21 Hz, PCH_2P), 2.54 (app-t, 2H, J_{HP} 21 Hz, PCH_2P), 1.56 (s, 3H, Me$_2$C), 1.51 (s, 3H, Me$_2$C), 1.47 (s, 3H, Me$_2$C), 1.44 (s, 3H, Me$_2$C), 1.35 (t, 9H, J 6 Hz, OCH$_2$CH_3); ^{13}C NMR (62.9 MHz, CDCl$_3$): δ 112.8 (s), 109.5 (s), 103.5 (s, C-1), 103.4 (s, C-1), 78.9 (s, C-2), 77.8 (s, C-2), 78.6 (s, C-4), 77.6 (s, C-4), 74.9 (d, J_{CP} 5 Hz, C-3), 74.5 (d, J_{CP} 5 Hz, C-3), 71.5 (s, C-5), 65.0 (s, C-6), 62.0 (d, J_{CP} 7 Hz, OCH$_2$CH$_3$), 61.9 (d, J_{CP} 7 Hz, OCH$_2$CH$_3$), 26.4 (s, Me$_2$C), 26.3 (s, Me$_2$C), 25.9 (s, Me$_2$C), 25.7 (app-t, J_{CP} 137 Hz, PCH$_2$P), 25.4 (app-t, J_{CP} 137 Hz, PCH$_2$P), 16.0 (d, J_{CP} 6 Hz, OCH$_2$CH$_3$); ^{31}P NMR (101.6 MHz, CDCl$_3$): δ 18.3 (br s, 1P), 18.3 (d, 1P, J_{PP} 5 Hz), 17.7 (d, 1P, J_{PP} 5 Hz), 16.7 (br s, 2P); ^{31}P NMR (101.6 MHz, C$_6$D$_6$): δ 17.9 (br s, 1P), 17.4 (br s, 1P), 16.8 (br s, 1P); Anal. Calcd for $C_{19}H_{36}O_{11}P_2$: C, 45.42; H, 7.22; O, 35.03; P, 12.33. Found: C, 45.23; H, 7.44; O, 35.26; P, 12.07.

4.2.4. *O*′-Ethyl *O*′-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)(diethoxyphosphinyl)methyl]phosphonate 8d. From **1a** (335 mg), colorless oil, 348 mg (61%).

R_f (EtOAc) 0.50; IR (KBr): ν 1580, 1550, 1260, 1025; ^{1}H NMR (250 MHz, CDCl$_3$): δ 5.94 (d, 1H, $J_{1,2}$ 4 Hz, H-1), 4.88 (d, 1H, H-2), 4.31–3.97 (m, 11H, H-3, H-4, H-5, H-6, OCH_2CH$_3$), 2.48 (app-t, 2H, J_{HP} 21 Hz, PCH_2P), 1.48 (s, 3H, Me$_2$C), 1.41 (s, 3H, Me$_2$C), 1.36 (s, 3H, Me$_2$C), 1.33 (t, 9H, J 5 Hz, OCH$_2$CH_3), 1.29 (s, 3H, Me$_2$C); ^{13}C NMR (62.9 MHz, CDCl$_3$): δ 111.3 (s), 108.8 (s), 104.8 (s, C-1), 83.8 (s, C-2), 83.4 (s, C-4), 80.1 (d, J_{CP} 6 Hz, C-3), 71.8 (s, C-5), 67.0 (s, C-6), 62.3 (d, J_{CP} 6 Hz, OCH$_2$CH$_3$), 26.6 (s, Me$_2$C), 26.5 (s, Me$_2$C), 25.9 (s, Me$_2$C), 25.6 (app-t, J_{CP} 135 Hz, PCH$_2$P), 25.0 (s, Me$_2$C) 16.0 (d, J_{CP} 5 Hz, OCH$_2$CH$_3$); ^{31}P NMR (101.6 MHz, CDCl$_3$): δ 17,1 (d, 1P, J_{PP} 6 Hz), 16.3 (d, 1P, J_{PP} 6 Hz); Anal. Calcd for $C_{19}H_{36}O_{11}P_2$: C, 45.42; H, 7.22; O, 35.03; P, 12.33. Found: C, 45.21; H, 7.47; O, 34.88; P, 12.44.

4.2.5. *O*′-Ethyl *O*′-(2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)[(diethoxyphosphinyl)methyl]phosphonate] 8e. From **1a** (304 mg), yellow oil, 195 mg (40%) diastereomeric mixture: ^{13}C NMR.

R_f (EtOAc) 0.32; IR (KBr): ν 1580, 1550, 1250, 1025; ^{1}H NMR (250 MHz, CDCl$_3$): δ 5.88 (dd, 1H, $J_{1,2}$ 3 Hz, J_{HP} 5 Hz, H-1), 4.71 (m, 1H, H-3), 4.60 (dd, 1H, $J_{2,3}$ 5 Hz, H-2), 4.30–4.43 (m, 1H, H-5), 4.30–3.80 (m, 9H, H-4, H-6, OCH_2CH$_3$), 2.46 (app-t, 2H, J_{HP} 21 Hz, PCH_2P), 1.46 (s, 3H, Me$_2$C), 1.44 (s, 3H, Me$_2$C), 1.43 (s, 3H, Me$_2$C), 1.37 (s, 3H, Me$_2$C), 1.32 (t, 9H, J 6 Hz, OCH$_2$CH_3); ^{13}C NMR (62.9 MHz, CDCl$_3$): δ 112.3 (s), 109.0 (s), 108.9 (d, J_{CP} 6.5 Hz, C-1), 85.6 (s, C-4), 81.7 (s, C-3), 81.6 (s, C-3), 79.5 (d, J_{CP} 7 Hz, C-2), 78.7 (d, J_{CP} = 7 Hz, C-2), 73.0 (s, C-5), 72.5 (s, C-5), 66.5 (s, C-6), 66.2 (s, C-6), 62.4 (d, J_{CP} 5 Hz, OCH$_2$CH$_3$), 61.1 (d, J_{CP} 5 Hz, OCH$_2$CH$_3$), 26.5 (s, Me$_2$C), 25.5 (s, Me$_2$C), 24.9 (s, Me$_2$C), 24.9 (app-t, J_{CP} 137 Hz, PCH$_2$P), 24.2 (s, Me$_2$C), 16.0 (d, J_{CP} 5 Hz, OCH$_2$CH$_3$); ^{31}P NMR (101.6 MHz, CDCl$_3$): δ 16.4 (d, 1P, J_{PP} 6 Hz), 16.2 (d, 1P, J_{PP} 6 Hz); FABMS: m/z 503 [M+H]$^+$, 100%.

4.2.6. *O*′-Ethyl *O*′-[2′,3′-*O*-isopropylidene-1′-(6-chloropurin-9-yl)-β-D-ribofuranosyl][(diethoxyphosphinyl)methyl]-phosphonate 8f. From **1a** (380 mg), colorless syrup, 568 mg (80%) diastereomeric mixture: ^{1}H, ^{31}P, and ^{13}C NMR.

R_f (EtOAc) 0.25; IR (KBr): ν 1580, 1550, 1250, 1030; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.79 (s, 1H, H-8), 8.57 (s, 1H, H_2), 8.51 (s, 1H, H-2), 6.28 (d, 1H, $J_{1',2'}$ 3 Hz, H-1′), 6.25 (d, 1H, $J_{1',2'}$ 3 Hz, H-1′), 5.48 (dd, 1H, $J_{3',2'}$ 3 Hz, $J_{3',4'}$ 6 Hz, H-3′), 5.42 (dd, 1H, $J_{3',2'}$ 3 Hz, $J_{3',4'}$ 6 Hz, H-3′), 5.19 (dd, 1H, H-2′), 5.12 (dd, 1H, H-2′), 4.60–4.52 (m, 1H, H-4′), 4.45–3.95 (m, 8H, H-5′, OCH_2CH$_3$), 2.40 (app-t, 2H, J_{HP} 21 Hz, PCH_2P), 2.39 (app-t, 2H, J_{HP} 21 Hz, PCH_2P), 1.64 (s, 3H, Me$_2$C), 1.41 (s, 3H, Me$_2$C), 1.33 (t, 9H, J 7 Hz, OCH$_2$CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 151.5 (s, C-8), 150.8 (s, C-5), 150.7 (s, C-5), 150.6 (s, C-4), 150.5 (s, C-4), 144.3 (s, C-2), 132.5 (s, C-6), 113.9 (s), 90.3 (s, C-1′), 90.2 (s, C-1′), 84.7 (d, J_{CP} 6 Hz, C-4′), 83.5 (s, C-2′), 80.5 (s, C-3′), 66.1 (d, J_{CP} 5 Hz, C-5′), 64.9 (d, J_{CP} 5 Hz, C-5′), 62.1 (d, J_{CP} 6 Hz, OCH$_2$CH$_3$), 60.9 (d, J_{CP} 6 Hz, OCH$_2$CH$_3$), 26.4 (s, Me$_2$C), 24.6 (app-t, J_{CP} 137 Hz, PCH$_2$P), 24.6 (s, Me$_2$C), 15.7 (br s, OCH$_2$CH_3); ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 18.4 (d, 1P, J_{PP} 5 Hz), 18.1 (d, 1P, J_{PP} 5 Hz), 16.3 (d, 1P, J_{PP} 5 Hz), 16.1 (d, 1P, J_{PP} 5 Hz); Anal. Calcd for $C_{20}H_{31}ClN_4O_{11}P_2$: C, 42.23; H, 5.49; N, 9.85; P, 10.89. Found: C, 41.95; H, 5.70; O, 9.52; P, 10.83.

4.2.7. *O*′-Methyl *O*′-(methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)[(diethoxyphosphinyl)methyl]phosphonate] 8g.

From **1a** (304 mg), colorless syrup, 250 mg (60%).

R_f (EtOAc) 0.15; IR (KBr): ν 1580, 1550, 1250, 1030; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.98 (s, 1H, H-1); 4.75 (app-t, 1H, $J_{3,2} = J_{3,4}$ 6 Hz, H-3), 4.60 (d, 1H, H-2), 4.35 (t, 1H, $J_{3,4}$ 6 Hz, H-4), 4.23–3.93 (m, 6H, H-5, OCH_2CH$_3$), 3.32 (s, 3H, OCH_3), 2.45 (dd, 2H, J_{HP} 18 Hz, J_{HP} 20 Hz, PCH_2P), 1.73 (d, 3H, J_{HP} 15 Hz, PCH_3), 1.45 (s, 3H, Me$_2$C), 1.37 (t, 6H, J 6 Hz, OCH$_2$CH_3), 1.33 (s, 3H, Me$_2$C); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 111.4 (s); 108.5 (s, C-1), 86.8 (d, J_{CP} 5 Hz, C-4), 84.1 (s, C-2), 80.7 (s, C-3), 64.2 (d, J_{CP} 6 Hz, C-5), 63.4 (d, J_{CP} 6 Hz, C-5), 61.7 (d, J_{CP} 6 Hz, OCH$_2$CH$_3$), 61.4 (d, J_{CP} 6 Hz, OCH$_2$CH$_3$), 54.0 (s, OCH$_3$), 27.8 (dd, J_{CP} 137 Hz, J_{CP} 134 Hz, PCH$_2$P), 25.5 (s, Me$_2$C), 24.0 (s, Me$_2$C), 15.9 (d, J_{CP} 5 Hz, OCH$_2$CH_3), 10.2 (d, J_{CP} 82.0 Hz, PCH$_3$); ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 43.7 (d, 1P, J_{PP} 5 Hz), 17,1 (d, 1P, J_{PP} 5 Hz); FABMS: m/z 417 $[M+H]^+$, 100%.

4.2.8. *O*′-Ethyl *O*′-(methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)[(dimethoxyphosphinyl)methyl]phosphonate 8h.

From **1e** (290 mg), colorless syrup, 332 mg (68%).

R_f (EtOAc) 0.21; IR (KBr): ν 1580, 1550, 1260, 1030; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.92 (s, 1H, H-1), 4.70 (app-t, 1H, $J_{3,2} = J_{3,4}$ 6 Hz, H-3), 4.54 (d, 1H, H-2), 4.36–4.27 (m, 1H, H-4), 4.22–4.10 (m, 2H, OCH_2CH$_3$), 4.10–3.97 (m, 2H, H-5), 3.77 (d, 6H, J_{HP} 12 Hz, POCH_3), 3.28 (s, 3H, OCH_3), 2.45 (app-t, 2H, J_{HP} 21 Hz, PCH_2P), 1.42 (s, 3H, Me$_2$C), 1.31 (t, 3H, J_{HH} 5 Hz, OCH$_2$CH_3), 1.27 (s, 3H, Me$_2$C); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 110.5 (s), 107.7 (s, C-1), 83.7 (d, J_{CP} 5 Hz, C-4), 83.4 (s, C-2), 79.9 (s, C-3), 64.5 (d, J_{CP} 5 Hz, C-5), 61.2 (d, J_{CP} 7 Hz, OCH$_2$CH$_3$), 53.0 (s, COCH$_3$), 51.4 (d, J_{CP} 6 Hz, POCH$_3$), 24.7 (s, Me$_2$C), 23.2 (s, Me$_2$C), 22.2 (app-t, J_{CP} 137 Hz, PCH$_2$P), 14.6 (s, OCH$_2$CH_3), ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 19.5 (d, 1P, J_{PP} 5 Hz), 17.3 (d, 1P, J_{PP} 5 Hz); FABMS: m/z 419 $[M+H]^+$, 100%.

4.2.9. *O*′-Ethyl *O*′-(methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)[(dimethoxythiophosphinyl)methyl]phosphonate 8i.

From **1f** (310 mg), colorless oil, 250 mg (52%).

R_f (EtOAc) 0.20; IR (KBr): ν 1580, 1550, 1260, 1030, 830; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.98 (s, 1H, H-1), 4.85 (app-t, 1H, $J_{32} = J_{34}$ 6 Hz, H-3), 4.60 (d, 1H, H-2), 4.37–4.20 (m, 1H, H-4), 4.20–4.10 (m, 2H, H-5), 4.10–3.98 (m, 2H, OCH_2CH$_3$), 3.80 (d, 6H, J_{HP} 14 Hz, POCH_3), 3.45 (s, 3H, COCH_3), 2.79 (dd, 2H, J_{HP} 18.5 Hz, J_{HP} 20.5 Hz, PCH_2P), 1.50 (s, 3H, Me$_2$C), 1.37 (t, 3H, J 7 Hz, OCH$_2$CH_3), 1.33 (s, 3H, Me$_2$C); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 112.0 (s), 108.1 (s, C-1), 84.6 (s, C-4), 84.4 (s, C-3), 81.2 (s, C-2), 65.6 (d, J_{CP} 6 Hz, C-5), 65.4 (d, J_{CP} 6 Hz, C-5), 63.3 (d, J_{CP} 7 Hz, OCH$_2$CH$_3$), 54.6 (d, J_{CP} 6 Hz, POCH$_3$), 53.1 (s, COCH$_3$), 32.9 (dd, J_{CP} 105 Hz, J_{CP} 133 Hz, PCH$_2$P), 26.0 (s, Me$_2$C), 24.5 (s, Me$_2$C), 15.9 (d, J_{CP} 6 Hz, OCH$_2$CH_3), ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 58.2 (d, 1P, J_{PP} 6 Hz), 16.2 (d, 1P, J_{PP} 6 Hz); FABMS: m/z 435 $[M+H]^+$, 100%.

4.2.10. *O*′-Butyl *O*′-(methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)[(diethoxyphosphinyl)methyl]phosphonate 8l.

From **1a** (304 mg), colorless syrup, 299 mg (63%).

R_f (EtOAc) 0.25; IR (KBr): ν 1580, 1550, 1260, 1025; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.98 (s, 1H, H-1), 4.77 (app-t, 1H, $J_{3,2} = J_{3,4}$ 6 Hz, H-3), 4.60 (d, 1H, H-2), 4.40–4.32 (m, 1H, H-4), 4.26–4.00 (m, 8H, H-5, OCH_2CH$_3$, OCH_2CH$_2$), 3.33 (s, 3H, OCH_3), 2.49 (app-t, 2H, J_{HP} 21 Hz, PCH_2P), 1.60 (m, 2H, CH_2CH$_2$O), 1.45 (s, 3H, Me$_2$C), 1.41–1.31 (m, 8H, CH$_2$CH_2CH$_3$, OCH$_2$CH_3), 1.34 (s, 3H, Me$_2$C), 0.95 (t, 3H, J 7 Hz, CH$_2$CH$_2$CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 111.9 (s), 108.8 (s, C-1), 84.5 (s, C-2), 84.4 (br s, C-4), 81.0 (s, C-3), 65.5 (d, $J_{CP} = 6$ Hz, C-5), 65.3 (d, J_{CP} 6 Hz, C-5), 62.0 (d, J_{CP} 6 Hz, OCH$_2$CH$_3$), 60.8 (d, J_{CP} 6 Hz, OCH$_2$CH$_2$), 54.4 (s, OCH$_3$), 31.9 (d, J_{CP} 6 Hz, CH$_2$CH$_2$O), 24.8 (app-t, J_{CP} 137 Hz, PCH$_2$P), 24.4 (s, Me$_2$C), 18.1 (s, CH$_2$CH_2CH$_3$), 15.8 (d, J_{CP} 6 Hz, OCH$_2$CH_3), 13.0 (s, CH$_2$CH$_2$CH_3); ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 17.6 (d, 1P, J_{PP} 6 Hz), 16.7 (d, 1P, J_{PP} 6 Hz); FABMS: m/z 475 $[M+H]^+$, 100%.

4.2.11. *O*′-Ethyl *O*′-(methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)[(diethoxyphosphinyl)-1-ethyl]phosphonate 8m.

From **1b** (320 mg), colorless oil, 266 mg (60%).

R_f (EtOAc) 0.15; IR (KBr): *v* 1580, 1550, 1260, 1020; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.98 (s, 1H, H-1), 4.75 (dd, 1H, $J_{2,3}$ 6 Hz, $J_{3,4}$ 5 Hz, H-3), 4.59 (d, 1H, H-2), 4.41–4.29 (m, 1H, H-4), 4.28–4.00 (m, 8H, H_5, OCH_2CH_3), 3.33 (s, 3H, OCH_3), 2.62–2.28 (m, 1H, PC*H*P), 1.48 (s, 3H, Me_2C), 1.38 (s, 3H, Me_2C), 1.36–1.30 (m, 12H, $CHCH_3$, OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 111.7 (s), 108.9 (s, C-1), 84.7 (br s, C-3, C-4), 81.2 (s, C-2), 65.5 (d, J_{CP} 7 Hz, C-5), 62.0 (d, J_{CP} 6 Hz, OCH_2CH_2), 53.6 (s, OCH_3), 33.2 (d, J_{CP} 137 Hz, J_{CP} 107 Hz, PCHP), 26.0 (s, Me_2C), 24.5 (s, Me_2C), 16.0 (d, J_{CP} 5 Hz, OCH_2CH_3), 9.1 (s, $CHCH_3$); ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 22.2 (d, 1P, J_{PP} 5 Hz), 21.3 (d, 1P, J_{PP} 5 Hz); FABMS: *m*/*z* 461 $[M+H]^+$, 100%.

4.2.12. *O*′-Ethyl *O*′-(methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)[(diethoxyphosphinyl)-1-propyl]phosphonate 8n. From **1c** (314 mg), colorless oil, 174 mg (42%).

R_f (EtOAc) 0.20; IR (KBr): *v* 1580, 1550, 1255, 1030; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.95 (s, 1H, H-1), 4.73 (d, 1H, $J_{3,2}$ 6 Hz, H-3), 4.58 (d, 1H, H-2), 4.41–4.29 (m, 1H, H-4), 4.22–3.97 (m, 8H, H-5, OCH_2CH_3), 3.31 (s, 3H, OCH_3), 2.25 (app-tt, 1H, J_{HP} 24 Hz, J_{HH} 6 Hz, PC*H*P), 1.80–1.60 (m, 2H, $CHCH_2CH_3$), 1.47 (s, 3H, Me_2C), 1.36 (s, 3H, Me_2C), 1.32 (t, 9H, *J* 7 Hz, OCH_2CH_3), 1.31 (t, 3H, *J* 7 Hz, $CHCH_2CH_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 111.1 (s), 108.2 (s, C-1), 84.3 (s, C-3), 83.9 (s, C-4), 80.4 (s, C-2), 61.3 (d, J_{CP} 5 Hz, C-5), 60.0 (d, J_{CP} 6 Hz, OCH_2CH_2), 53.6 (s, OCH_3), 37.3 (app-t, J_{CP} 133 Hz, PCHP), 31.8 (d, J_{CP} 6 Hz, $CHCH_2CH_3$), 25.2 (s, Me_2C), 23.7 (s, Me_2C), 16.0 (d, J_{CP} 5 Hz, $CHCH_2CH_3$), 15.8 (d, J_{CP} 5 Hz, OCH_2CH_3), ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 22.1 (d, 1P, J_{PP} 6 Hz), 21.2 (d, 1P, J_{PP} 6 Hz); FABMS: *m*/*z* 475 $[M+H]^+$, 100%.

4.2.13. *O*′-Ethyl *O*′-(methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)[(diethoxyphosphinyl)-1-pentyl]phosphonate 8o. From **1d** (295 mg), colorless syrup, 142 mg (40%).

R_f (EtOAc) 0.20; IR (KBr): *v* 1580, 1550, 1250, 1030; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.97 (s, 1H, H-1), 4.75 (d, 1H, $J_{2,3}$ 6 Hz, H-3), 4.59 (d, 1H, H-2), 4.40–4.31 (m, 1H, H-4), 4.25–4.03 (m, 8H, H-5, OCH_2CH_3), 3.33 (s, 3H, OCH_3), 2.31 (app-tt, 1H, J_{HP} 24 Hz, J_{HH} 6 Hz, PC*H*P), 1.80–1.50 (m, 8H, $CH_2CH_2CH_2CH_2CH_3$), 1.48 (s, 3H, Me_2C), 1.38 (s, 3H, Me_2C), 1.32 (t, 12H, *J* 7 Hz, CH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 111.5 (s), 108.5 (s, C-1), 84.7 (s, C-3), 84.2 (s, C-4), 80.7 (s, C-2), 66.7 (d, J_{CP} 6 Hz, C-5), 66.2 (d, $^2J_{CP}$ 6 Hz, C-5), 60.5 (d, J_{CP} 6 Hz, OCH_2CH_2), 54.0 (s, OCH_3), 36.0 (app-t, J_{CP} 134 Hz, PCHP), 30.5 (s, $CHCH_2CH_2$), 29.4 (d, $J_{CP} = 17$ Hz, $CHCH_2$), 25.6 (s, Me_2C), 24.0 (s, Me_2C), 21.6 (s, $CH_2CH_2CH_3$), 15.6 (d, J_{CP} 6 Hz, OCH_2CH_3), 13.1 (s, $CH_2CH_2CH_3$); ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 22.3 (d, 1P, J_{PP} 6 Hz), 21.4 (d, 1P, J_{PP} 6 Hz); FABMS: *m*/*z* 503 $[M+H]^+$, 100%.

4.2.14. *O*′-Ethyl *O*′-(methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)[(dibenzylaminophosphinyl)methyl]phosphonate 8p. From **1a** (300 mg), yellow syrup, 412 mg (70%) diastereomeric mixture: ^{1}H, ^{31}P, and ^{13}C NMR.

IR (KBr): *v* 960, 1025, 1100, 1250; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.25–7.40 (m, 10H, Ph), 4.94 (s, 1H, H-1), 4.93 (s, 1H, H-1), 4.85 (d, 1H, $J_{2,3}$ 6 Hz, H-3), 4.60 (d, 1H, H-2), 4.54 (d, 1H, H-3), 4.48 (d, 1H, H-2), 4.37–4.00 (m, 20H, NCH_2, OCH_2CH_3, H-4), 3.80–3.62 (m, 2H, H-5), 3.28 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3), 2.51 (app-t, 2H, J_{HP} 20 Hz, PCH_2P), 2.47 (app-t, 2H, J_{HP} 20 Hz, PCH_2P), 1.50–1.25 (m, 24H, Me_2C, CH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 136.7 (Ph), 128.7–128.3 (m, Ph), 112.1 (s), 109.1 (s, C-1), 84.7 (s, C-2), 84.5 (d, J_{CP} 7 Hz, C-4), 81.4 (s, C-3), 64.0 (d, J_{CP} 6 Hz, C-5), 63.8 (d, J_{CP} 6 Hz, C-5), 62.3–62.2 (m, OCH_2CH_3), 54.7 (s, 3H, OCH_3), 54.6 (s, 3H, OCH_3), 48.1 (s, NCH_2), 26.4 (dd, J_{CP} 125 Hz, J_{CP} 158 Hz, PCH_2P), 26.1 (s, Me_2C), 24.7 (s, Me_2C), 16.1 (d, J_{CP} 6 Hz, CH_2CH_3); ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 24.7 (d, 1P, J_{PP} 7 Hz; 1P), 24.6 (d, 1P, J_{PP} 7 Hz), 20.2–20.3 (m, 2P); FABMS: *m*/*z* 598 $[M+H]^+$, 100%.

4.3. Preparation of glycosyl phosphorodichloridates 3

A mixture of **6** (10 mmol) and Et_3N (10 mmol, 1.01 g) in anhyd Et_2O (20 mL) was added to $POCl_3$ (10 mmol, 1.53 g) in anhyd Et_2O (20 mL) at 0 °C under nitrogen. The mixture was stirred for 4 h before it was slowly allowed to warm to 25 °C. The soln was filtered and the solvents were evaporated under reduced pressure. The crude product **3** was used without purification.

4.3.1. *O*-(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranosyl)-6-phosphorodichloridate 3f. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.54 (d, 1H, $J_{1,2} = 5$ Hz, H-1), 4.66 (dd, 1H, $J_{2,3} = 2.5$ Hz, $J_{3,4}$ 8 Hz, H-3), 4.55–4.40 (m, 2H, H-6), 4.36 (dd, 1H, H-2), 4.27 (dd, 1H, $J_{4,5}$ 1.5 Hz, H-4), 4.12 (dt, 1H, $J_{5,6}$ 6 Hz, H-5), 1.54 (s, 3H, Me_2C), 1.46 (s, 3H, Me_2C), 1.35 (s, 6H, Me_2C); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 109.6 (s), 108.7 (s), 95.9 (s, C-1), 70.3 (s, C-3), 70.1 (s, C-4), 70.0 (s, C-2), 69.9 (d, J_{CP} 8.5 Hz, C-6), 66.0 (d, J_{CP} 9.5 Hz, C-5), 25.7 (s, Me_2C), 25.6 (s, Me_2C), 24.6 (s, Me_2C), 24.1 (s, Me_2C); ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 5.4 (s, 1P).

4.3.2. *O*-(Methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-5-phosphorodichloridate 3g. ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.94 (s, 1H, H-1), 4.65 (d, 1H, $J_{2,3}$ 6 Hz, H-2), 4.55 (dd, 1H, $J_{3,4}$ 4 Hz, H-3), 4.39 (dd, 1H, $J_{4,5}$ 8 Hz, H-4), 4.27–4.20 (m, 2H, H-5), 3.30 (s, 3H, OCH_3), 1.42 (s, 3H, Me_2C), 1.27 (s, 3H, Me_2C); ^{13}C NMR ($CDCl_3$): δ 113.0 (s), 109.7 (s, C-1), 85.0 (s, C-2), 84.0 (d, J_{CP} 11 Hz, C-4), 81.3 (s, C-3), 70.8 (d, J_{CP} 9.5 Hz, C-5), 55.4 (s, OCH_3), 26.5 (s, Me_2C), 25.0 (s, Me_2C); ^{31}P NMR ($CDCl_3$): δ 5.0 (s, 1P).

4.3.3. *O*-(1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranosyl)-3-phosphorodichloridate 3h. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.83 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.89–4.78 (m, 1H, H-2), 4.47–3.70 (m, 4H, H-3, H-5, H-6), 3.92 (dd, 1H, *J* 5.5 Hz, *J* 8.5 Hz, H-4), 1.59 (s, 3H, Me_2C), 1.48 (s, 3H, Me_2C), 1.38 (s, 3H, Me_2C), 1.36 (s, 3H, Me_2C), ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 114.0 (s), 110.2 (s), 103.0 (s, C-1), 78.3 (d, J_{CP} 9 Hz, C-4), 77.9–77.6 (m, C-2, C-3), 74.7 (s, C-5), 65.7 (s, C-6), 26.8 (s, Me_2C), 26.6 (s, Me_2C), 26.3 (s, Me_2C), 24.9 (s, Me_2C); ^{31}P NMR (101.6 MHz,$CDCl_3$): δ 6.1 (s, 1P).

4.3.4. *O*-(Methyl-3-*O*-benzyl-2-deoxy-β-D-ribofuranosyl)-5-phosphorodichloridate 3i. ^{31}P NMR (101.6 MHz, THF): δ 5.9 (s, 1P).

4.3.5. (5′-*O*-Trityl-thymidine)-3′-phosphorodichloridate 3j. ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 6.2 (s, 1P).

4.4. Synthesis of diglycosyl methylenediphosphonates 10

The same procedure as for **8** was used. The crude products were purified on a aluminum oxide gel chromatographic column to give **10**.

4.4.1. *O*′-(1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranosyl) *O*′-(1,2:5,6-di-*O*-isopropylidene-α-D-allofuranosyl)-[(diethoxyphosphinyl)methyl]phosphonate 10a. From **1a** (290 mg), colorless syrup, 512 mg (75%) diastereomeric mixture: ^{1}H, ^{31}P, and ^{13}C NMR.

R_f (acetone) 0.70; IR (KBr): *v* 1580, 1550, 1260, 1020; ^{1}H NMR (250 MHz,$CDCl_3$): δ 5.77 (d, 1H, $J_{1',2'}$ 4 Hz, H-1′), 5.76 (d, 1H, $J_{1,2}$ 4 Hz, H-1), 5.52 (d, 1H, $J_{1',2'}$ 5 Hz, H-1′), 4.87 (app-t, 1H, $J_{1,2} = J_{2,3}$ 4 Hz, H-2), 4.77 (dd, 1H, $J_{23} = 5$ Hz, H-2), 4.64–4.59 (m, 1H, H-3′), 4.32 (dd, 1H, $J_{2',3'}$ 5 Hz, H-2′), 4.39–3.92 (m, 13H, H-3, H-4, H-5, H-6, H-4′, H-5′, H-6′, OCH_2CH_3), 2.66 (app-t, 2H, J_{HP} 21 Hz, PCH_2P), 2.62 (dd, 2H, J_{HP} 22 Hz, J_{HP} 20 Hz, PCH_2P), 1.57 (s, 3H, Me_2C), 1.54 (s, 3H, Me_2C), 1.51 (s, 3H, Me_2C), 1.48 (s, 3H, Me_2C), 1.43 (s, 3H, Me_2C), 1.36 (s, 3H, Me_2C), 1.35 (s, 3H, Me_2C), 1.32 (s, 3H, Me_2C), 1.26 (t, 6H, *J* 7 Hz, OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 113.1 (s); 113.0 (s), 112.6 (s), 109.7 (s), 109.3 (s), 108.5 (s), 103.7 (s, C-1), 96.1 (s, C-1′), 79.5 (s, C-2), 78.9 (s, C-2), 77.2 (d, J_{CP} 7 Hz, C-4), 75.4 (s, C-5), 74.7 (d, J_{CP} 6 Hz, C-3), 74.2 (d, J_{CP} 6 Hz, C-3), 70.5 (s, C-4′), 70.3 (s, C-2′), 70.2 (s, C-3′), 67.2 (d, J_{CP} 6 Hz, C-5′), 66.7 (d, J_{CP} 6 Hz, C-5′), 65.6 (s, C-6), 65.0 (d, J_{CP} 6 Hz, C-6′), 62.6 (d, J_{CP} 6 Hz, OCH_2CH_3), 26.5 (s, Me_2C), 26.4 (s, Me_2C), 25.9 (s, Me_2C), 25.8 (app-t, J_{CP} 137 Hz, PCH_2P), 25.8 (s, Me_2C), 25.1 (s, Me_2C), 24.9 (s, Me_2C), 24.8 (s, Me_2C), 24.3 (s, Me_2C), 16.2 (d, J_{CP} 6 Hz, OCH_2CH_3); ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 18.7 (d, 1P, J_{PP} 6 Hz), 18.5 (d, 1P, J_{PP} 6 Hz), 16.6 (d, 1P, J_{PP} 6 Hz), 16.5 (d, 1P, J_{PP} 6 Hz); FABMS: *m*/*z* 739.3 $[M+Na]^+$.

4.4.2. Bis-*O*′,*O*′-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosyl)[(diethoxyphosphinyl)methyl]phosphonate 10b. From **1a** (300 mg), colorless syrup, 541 mg (80%).

R_f (1:1 EtOAc/hexane) 0.42; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.47 (d, 2H, $J_{1,2}$ 5 Hz, H-1), 4.55 (dd, 2H, $J_{2,3}$ 2 Hz, $J_{3,4}$ 7 Hz, H-3), 4.26 (dd, 2H, H-2), 4.26–3.98 (m, 12H, H-4, H-5, H-6, CH_2CH_3), 2.53 (app-t, 2H, J_{HP} 21 Hz, PCH_2P), 1.48 (s, 6H, Me_2C), 1.38 (s, 6H, Me_2C), 1.29 (t, 6H, *J* 7 Hz, CH_2CH_3), 1.27 (br s, 12H, Me_2C); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 109.3 (s), 108.6 (s), 96.0 (s, C-1), 70.5 (s, C-3), 70.4 (s, C-4), 70.3 (s, C-2), 66.9 (d, J_{CP} 6 Hz, C-5), 65.1 (d, J_{CP} 6 Hz, C-6), 65.0 (d, J_{CP} 6 Hz, C-6), 62.5 (d, J_{CP} 6 Hz, CH_2CH_3), 25.9 (s, Me_2C), 25.8 (s, Me_2C), 24.8 (s, Me_2C), 25.3 (app-t, J_{CP} 137 Hz, PCH_2P), 24.3 (s, Me_2C), 16.2 (d, J_{CP} 6 Hz, CH_2CH_3), ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 18.5 (d, 1P, J_{PP} 6 Hz), 16.8 (d, 1P, J_{PP} 6 Hz); FABMS: *m*/*z* 739.3 $[M+Na]^+$.

4.4.3. Bis-*O*′,*O*′-(1-*O*-methyl-2,3-*O*-isopropylidene β-D-ribofuranosyl)[(diethoxyphosphinyl)methyl]phosphonate 10c. From **1a** (322 mg), colorless syrup, 512 mg (80%).

R_f (1:1 EtOAc/hexane) 0.55; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.90 (d, 2H, $J_{1,2}$ 1.5 Hz, H-1), 4.69 (app-t, 2H, $J_{2,3} = J_{3,4}$ 6 Hz, H-3), 4.53 (dd, 2H, H-2), 4.33–4.27 (m, 2H, H-4), 4.19–4.05 (m, 4H, CH_2CH_3), 4.10–3.98 (m, 4H, H-5), 3.26 (s, 6H, OCH_3), 2.47 (app-t, 2H, J_{HP} 21.0 Hz, PCH_2P), 1.40 (s, 6H, Me_2C), 1.30 (t, 6H, *J* 7.0 Hz, CH_2CH_3), 1.25 (s, 6H, Me_2C); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 112.4 (s), 109.2 (s, 1), 84.9 (s, 2), 84.8 (d, J_{CP} 6.5 Hz, C-4), 81.4 (s, C-3), 66.1 (d, J_{CP} 6 Hz, C-5), 62.6 (d, J_{CP} 6 Hz, CH_2CH_3), 54.9 (s, OCH_3), 25.3 (app-t, *J* 137 Hz, PCH_2P), 24.8 (s, Me_2C), 16.2 (d, J_{CP} 5.5 Hz, CH_2CH_3); ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 18.1 (d, 1P, J_{PP} 5 Hz), 16.3 (d, 1P, *J* 5 Hz); FABMS: *m*/*z* 627.2 $[M+Na]^+$.

4.4.4. *O*′-(1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranosyl) *O*′-(1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)-[(diethoxyphosphinyl)methyl]phosphonate 10d. From **1a** (290 mg), colorless syrup, 472 mg (75%) diastereomeric mixture: ^{1}H, ^{31}P, and ^{13}C NMR.

R_f (1:1 EtOAc/hexane) 0.40; IR (KBr): *v* 1580, 1550, 1260, 1020; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.70 (d, 1H, $J_{1,2}$ 2.5 Hz, H-1), 4.88 (d, 1H, $J_{1',2'}$ 3 Hz, H-1′), 4.74–4.62 (m, 2H, H-2, H-3′), 4.52 (d, 1H, H-2′), 4.36–4.25 (m, 2H, H-4′, H-3), 4.19–4.06 (m, 4H, OCH_2CH_3), 4.06–3.98 (m, 3H, H-6, H-4), 3.97–3.87 (m, 2H, H-5′), 3.22 (s, 3H, OCH_3), 2.76–2.44 (m, 2H, PCH_2P), 1.49 (s, 3H, Me_2C), 1.42 (s, 3H, Me_2C), 1.41 (s, 3H, Me_2C), 1.39 (s, 3H, Me_2C), 1.28 (t, 6H, *J* 6 Hz, OCH_2CH_3), 1.27 (s, 3H, Me_2C), 1.24 (s, 3H, Me_2C); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 113.4 (s, C), 112.5

(s, C), 110.1 (s, C), 109.5 (s, C-1), 103.8 (s, C-1′), 85.2 (s, C-2′), 85.0 (d, J_{CP} 7 Hz, C-4′), 81.8 (s, C-3′), 79.0 (s, C-2), 78.1 (d, J_{CP} 7 Hz, C-4), 75.2 (d, J_{CP} 6 Hz, C-3), 75.0 (s, C-5), 74.8 (d, J_{CP} 6 Hz, C-3), 65.6 (s, C-6), 65.4 (d, J_{CP} 7 Hz, C-5′), 26.9 (s, Me_2C), 26.8 (s, Me_2C), 26.6 (s, Me_2C), 26.4 (s, Me_2C), 25.8 (app-t, J_{CP} 137 Hz, P*C*H$_2$P), 25.1 (s, Me_2C), 24.9 (s, Me_2C), 16.5 (d, J_{CP} 6 Hz, OCH$_2$*C*H$_3$); ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 18.8 (d, 1P, J_{PP} 5 Hz), 17.0 (d, 1P, J_{PP} 7 Hz), 16.2 (app-d, br, 2P); FABMS : m/z 661 $[M+H]^+$, $m/z = 683.3$ $[M+Na]^+$.

4.4.5. *O*′-(2,3:5,6-Di-*O*-isopropylidene-α-D-mannopyranosyl) *O*′-(1-*O*-methyl-2,3-*O*-isopropylidene-β-D-ribofuranoside)[(diethoxyphosphinyl)methyl]phosphonate 10e. From **1** (310 mg), colorless syrup, 444 mg (66%) diastereomeric mixture: ^{1}H, ^{31}P, and ^{13}C NMR.

IR (KBr): ν 1580, 1550, 1260, 1020; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.88 (app-t, 1H, $J_{1,2}$ 6 Hz, J_{HP} 6.0 Hz, H-1), 4.97 (br s, 1H, H-1′), 4.80–4.70 (m, 2H, H-3′, H-3), 4.65–4.55 (m, 2H, H-2, H-2′), 4.43–4.30 (m, 2H, H-5, H-4′), 4.23–3.97 (m, 9H, H-4, H-6, H-5′, OC*H*$_2$CH$_3$), 3.31 (s, 3H, OC*H*$_3$), 2.60–2.38 (m, 2H, PC*H*$_2$P), 1.50–1.30 (m, 24H, Me_2C, OCH$_2$C*H*$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 113.0 (s), 112.3 (s, C-1′), 112.2 (s), 109.0 (s), 108.9 (d, J_{CP} 12 Hz, C-1), 85.6 (s, C-4), 84.8 (s, C-3′), 82.0 (s, C-3), 81.3 (s, C-2′), 79.6 (s, C-2), 78.8 (s, C-2′), 78.8 (s, C-2), 73.1 (s, C-5), 72.6 (s, C-5), 66.4 (s, C-6), 62.7–62.3 (m, C-5′), 61.3 (d, J_{CP} 6 Hz, O*C*H$_2$CH$_3$), 54.8 (s, O*C*H$_3$), 26.7 (s, Me_2C), 26.6 (s, Me_2C), 26.2 (s, Me_2C), 25.7 (s, Me_2C), 25.7 (app-t, J_{CP} 138.5 Hz, P*C*H$_2$P), 25.7 (s, Me_2C), 25.2 (app-t, J_{CP} 136.5 Hz, P*C*H$_2$P), 25.1 (s, Me_2C), 24.7 (s, Me_2C), 24.5 (s, Me_2C), 24.3 (s, Me_2C), 16.1 (d, J_{CP} 6.0 Hz, OCH$_2$*C*H$_3$); ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 18.2 (d, 1P, J_{PP} 5Hz), 17.6 (d, 1P, J_{PP} 5 Hz), 16.8 (d, 1P, J_{PP} 5 Hz), 16.4 (d, 1P, J_{PP} 5 Hz); FABMS: m/z 683.3 $[M+Na]^+$.

4.5. Synthesis of 10f and 10g

The same procedure as for **8** was used, but the stirred mixture of *s*-BuLi and dibenzyl methylphosphonate **1f** was maintained for 30 min at −78 °C. The reaction between **5m** and methyl-5-*O*-trityl-2-deoxy-β-D-ribofuranoside **6g** or **5n** with 5′-*O*-trityl-thymidine **6h** involved a stirring for 15 h at room temperature before hydrolysis.

4.5.1. *O*′-(Methyl-5′-*O*-trityl ribofuranosyl) *O*′-(methyl-3′-*O*-benzyl-ribofuranosyl)[(dibenzyloxyphosphinyl)methyl]phosphonate 10f. From **1f** (553 mg), colorless syrup, 241 mg (35%) diastereomeric mixture: ^{1}H, ^{31}P, and ^{13}C NMR.

R_f (1:1 EtOAc/hexane) 0.50; IR (KBr): ν 1260, 1020; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.60–7.20 (m, 30H, Ph); 5.30–5.00 (m, 6H, POC*H*$_2$Ph, H-1, H-1′), 4.30–4.20 (m, 2H, COC*H*$_2$Ph), 4.38–3.73 (m, 6H, H-5′, H-3, H-4, H-3′, H-4′), 3.30 (s, 3H, OC*H*$_3$), 3.26 (s, 3H, OC*H*$_3$), 3.24–3.18 (m, 2H, H-5), 2.62–2.40 (m, 2H, PC*H*$_2$P), 2.25–1.92 (m, 4H, H-2, H-2′); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 138.2–127.2 (m, Ph), 105.7 (s, C-1′), 105.5 (s, C-1), 84.9 (d, J_{CP} 7.0 Hz, C-4′), 84.0 (d, J_{CP} 7.0 Hz, C-4), 79.0 (s, C-3′), 74.6 (d, J_{CP} 6.0 Hz, C-3), 71.6 (s, CO*C*H$_2$Ph), 67.4 (d, J_{CP} 5.0 Hz, PO*C*H$_2$Ph), 65.4 (d, J_{CP} 7.0 Hz, C-5′), 65.3 (s, C-5), 55.4 (s, O*C*H$_3$), 55.3 (s, O*C*H$_3$), 40.0 (s, C-2′), 39.1 (s, C-2), 25.4 (app-t, J_{CP} 137 Hz, P*C*H$_2$P); ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 18.8 (d, 1P, J_{PP} 6.0 Hz), 17.4 (br s, 2P), 17.0 (d, 1P, J_{PP} 6.0 Hz); ESIMS m/z 970.3 $[M-H+Na]^+$.

4.5.2. *O*′-(5′-*O*-Trityl-thymidine-3′-yl) *O*′-(3′-*O*-benzyl-thymidine-5′-yl)[(dibenzyloxyphosphinyl)methyl]phosphonate 10g. From **1f** (564 mg), colorless syrup, 269 mg (30%) diastereomeric mixture: ^{1}H, ^{31}P, and ^{13}C NMR.

R_f (1:1 EtOAc/hexane) 0.42; IR (KBr): ν 1260, 1020; ^{1}H NMR ($CDCl_3$): δ 8.85 (br s, 2H, H-3, H-3′), 8.63 (s, 2H, C*H*=C, C*H*=C), 7.59–7.23 (m, 30H, Ph), 6.15–6.13 (m, 2H, H-1, H-1′), 5.30–5.00 (m, 4H, POC*H*$_2$Ph), 4.56 (2d, 2H, J 12.0 Hz, COC*H*$_2$Ph), 4.36–4.07 (m, 4H, H-3, H-4, H-3′, H-4′), 3.97–3.87 (m, 2H, H-5′), 3.50–3.30 (m, 2H, H-5), 2.76–2.44 (m, 2H, PC*H*$_2$P), 2.44–2.30 (m, 4H, H-2, H-2′), 1.70 (s, 3H, C*H*$_3$), 1.47 (s, 3H, C*H*$_3$); ^{13}C NMR ($CDCl_3$): δ 166.8 (s, C-4, C-4′), 149.0 (s, C-2, C-2′), 143.0 (s, *C*Ph$_3$), 137.0 (s, *C*H=C), 136.7 (s, Ph), 135.8 (d, J_{CP} 5.0 Hz, Ph), 135.6 (s, *C*H=C), 134.0 (s, Ph), 128.8–127.2 (m, Ph), 111.2 (s, *C*CH$_3$), 111.1 (s, *C*CH$_3$), 85.3 (s, C-1′), 84.9 (d, J_{CP} 7.0 Hz, C-4′), 84.5 (s, C-1), 84.1 (d, J_{CP} 7.0 Hz, C-4), 78.5 (s, C-3′), 74.8 (d, J_{CP} 6.0 Hz, C-3), 71.5 (s, CO*C*H$_2$Ph), 67.7 (d, J_{CP} 3.0 Hz, PO*C*H$_2$Ph), 65.4 (d, J_{CP} 7.0 Hz, C-5′), 63.6 (s, C-5), 40.9 (d, J_{CP} 2.0 Hz, C-2), 37.2 (s, C-2′), 25.6 (app-t, J_{CP} 136 Hz, P*C*H$_2$P), 12.5 (s, *C*H$_3$), 11.8 (s, *C*H$_3$); ^{31}P NMR ($CDCl_3$): δ 18.8 (d, 1P, J_{PP} 7.0 Hz), 17.6 (br s, 2P), 17.2 (d, 1P, J_{PP} 7.0 Hz); ESMS m/z 1158.4 $[M-H+Na]^+$.

4.6. Deprotection of 10g

To a soln of **10g** (0.1 mmol, 88 mg), in MeOH (10 mL), was added palladium (10% on charcoal, 500 mg). The mixture was stirred at room temperature under a 30 bar pressure of hydrogen for 4 h, then filtered through Celite, and the filtrate was evaporated under diminished pressure to yield **11g**.

4.6.1. *O*-(Thymidine-3′-yl) *O*-(thymidine-5′-yl)[(dihydrogenphosphonyl)methyl]phosphonic acid 11g. From **1f** (564 mg), colorless syrup, 191 mg (30%), diastereomeric mixture: ^{1}H, ^{31}P, and ^{13}C NMR.

IR (KBr): 3200–2500, 1260, 1020; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.52 (s, C*H*=C), 8.10 (s, C*H*=C), 6.97 (br s, O*H*), 6.42 (t, 1H, $J_{1',2'}$ 6.5 Hz, H-1′), 6.16 (t, 1H, $J_{1,2}$ 6.5 Hz, H-1), 4.64–4.58 (m, 1H, H-3′), 4.38–4.24 (m, 3H, H-4, H-3, H-4′), 4.00–3.70 (m, 4H, H-5, H-5′), 2.80–2.45 (m, 2H, PCH_2P), 2.45–2.28 (m, 4H, H-2, H-2′), 1.73 (s, 3H, CH_3), 1.52 (s, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 163.8 (s, *C*=O), 158.9 (s, *C*=O), 149.0 (s, *C*=O), 145.0 (s, *C*=O), 137.8 (s, *C*H=C), 137.2 (s, *C*H=C), 111.1 (s, *C*CH_3), 111.0 (s, *C*CH_3), 85.5 (d, J_{CP} 7.0 Hz, C-4′), 85.2 (s, C-1′), 82.8 (s, C-1), 80.5 (d, J_{CP} 7.0 Hz, C-4), 74.8 (d, J_{CP} 6.0 Hz, C-3), 72.2 (s, C-3′), 65.5 (d, J_{CP} 7.0 Hz, C-5′), 62.9 (s, C-5), 40.5 (s, C-2′), 38.4 (d, J_{CP} 3.0 Hz, C-2), 27.2 (dd, J_{CP} 137 Hz, J_{CP} 120 Hz, P*C*H_2P), 13.3 (s, *C*H_3), 12.8 (s, *C*H_3); ^{31}P NMR (101.6 MHz, $CDCl_3$): δ 18.8 (br s, 1P), 13.0 (br s, 1P).

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