Tetrahedron 65 (2009) 6039–6046

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Developing an efficient route to the synthesis of nucleoside 1-alkynylphosphonates

Maïa Meurillon, Franck Gallier, Suzanne Peyrottes *, Christian Périgaud

IBMM, UMR 5247 CNRS-UM1-UM2, Equipe Nucléosides & Effecteurs Phosphorylés, Université Montpellier 2, cc 1705, place E. Bataillon, 34095 Montpellier Cedex 05, France

ARTICLE INFO

Article history:
Received 3 April 2009
Received in revised form 19 May 2009
Accepted 26 May 2009
Available online 29 May 2009

Keywords:
Nucleotide analogue
1-Alkynylphosphonate
Sugar phosphonate

ABSTRACT

A series of ribonucleoside 1-alkynylphosphonates have been synthesized using a palladium-catalyzed phosphonylation of terminal 1,1-dibromo-1-alkene nucleosidic derivatives and high selectivity for product distribution was observed during this step. Both nucleosidic and osidic pathways were explored and the corresponding optimization study is reported herein.

1. Introduction

Alkynylphosphonate derivatives belong to an interesting family as they permit among other transformations,[1] the direct preparation of vinyl-phosphonate with *Z*-stereochemistry by a simple reduction step.[2] Besides classical methods,[1] only a few pathways have emerged for their efficient preparation.[3–5] As example, synthesis of such compounds may involve two key reactions: an aldehyde homologation leading to a 1,1-dibromo-1-alkene as intermediate,[6] followed by a Pd catalyzed phosphonylation originally reported by Hayes et al.[4] The first step is comparable to a Wittig reaction and leads to a 1,1-dibromo-1-alkene that also allows the preparation of terminal alkynes following the well-known Corey–Fuchs reaction.[7] During the course of our ongoing work studying 5′-mononucleotide analogues bearing a stable P–C bond,[8,9] we were interested in the optimization of the overall procedure for the synthesis of a variety of ribonucleoside 1-alkynylphosphonates. Basically, two synthetic routes may be envisaged to reach the targeted compounds: an osidic (involving the synthesis of an alkynylphosphonate sugar derivative and further condensation with various heterocycles) or a nucleosidic strategy (Fig. 1). Both routes have been explored and results are reported herein.

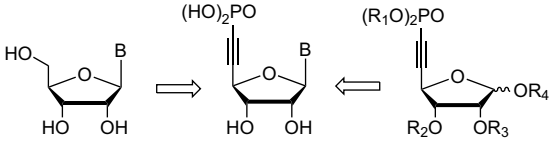


Figure 1. Synthetic routes to nucleoside 1-alkynylphosphonates.

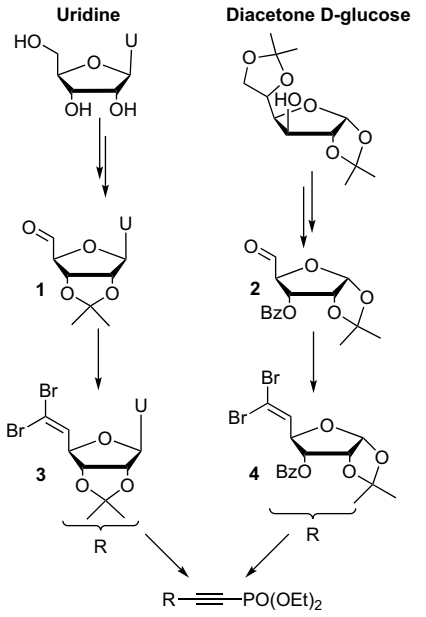
2. Probing aldehyde's homologation for osidic and nucleosidic substrates

As the literature concerning experimental conditions for the preparation of 1,1-dibromo-1-alkenes (one-carbon homologation of an aldehyde) was abundant and somewhat puzzling,[6,7,10] we initially focused on the preparation of 1,1-dibromo-1-alkene derivatives **3** and **4** (Scheme 1). Starting materials **1** and **2**, corresponding to the nucleosidic and osidic aldehydes, were obtained using previously published procedures[11–13,9] from commercially available uridine and diacetone D-glucose.

Selected experimental conditions corresponding to the literature data were applied to aldehydes **1** and **2**, and are presented in Table 1. Briefly, we studied the effect of the purity of the starting material, the sequential addition of the reagents, the order of addition and the additive effects on the yield of desired derivatives obtained after column chromatography. In the case of the nucleosidic starting material **1**, the purity of the aldehyde appeared as a key factor for the reaction to proceed and the use of crude material from the oxidation step was detrimental. Furthermore, the poor results obtained for the nucleosidic substrate were mainly due

* Corresponding author. Tel.: +33 4 67 14 49 64; fax: +33 4 67 54 96 10.
E-mail address: peyrottes@univ-montp2.fr (S. Peyrottes).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.05.064



Scheme 1. Reactions studied for the optimization.

Table 1
Optimization of the reaction conditions for the aldehyde homologation

Entry	Substrate	Addition order	Stoechiometry (equiv)	Yield[a] (%)
1	**1**	Aldehyde	1	12
	2	CBr_4 then PPh_3	2 and 4	58
2	**1**	Aldehyde	1	14
	2	CBr_4 then PPh_3	2 and 4×1	61
3	**1**	Aldehyde (repurified) 1 equiv		40
		CBr_4 then PPh_3	2 and 4×1	
4	**1**	Aldehyde (repurified)	1	39
	2	CBr_4 then PPh_3, MW	2 and 4	41
5	**1**	PPh_3 then CBr_4	5 and 2.5	24
	2	Aldehyde	1	61
6	**1**	PPh_3 then CBr_4	5 and 2.5	29
		Aldehyde (repurified)	1	
7	**1**	PPh_3, Zn, then CBr_4	1.97 and 2.05	4
	2	Aldehyde	1	48
8	**1**	Aldehyde	1	6
	2	PPh_3 supported then CBr_4	4 and 2	42

[a] Isolated after column chromatography.

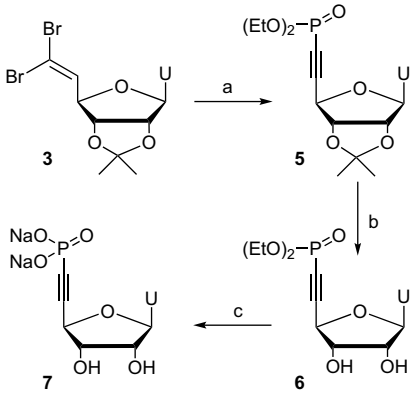
to the difficulty in isolating pure batch of **1** (entries 2 and 3) and its low stability.

Contrary to the data reported, the sequential addition of PPh_3 (entries 1–2),[14] the reagent addition order (entries 1 and 5), as well as the presence of Zn powder[7,15] (which allows the use of less triphenylphosphine, entry 7) have minor effects on the yield. As expected, the reaction time was shortened when using microwave irradiations (MW, entries 1 and 4). Supported PPh_3 was used in order to easily isolate the reaction products (entry 8) but did not lead to a real enhancement of the yield.[16] Thus, the osidic substrate **2** led to better results than the nucleosidic one **1**.

3. Synthesis of ribonucleoside 1-alkynylphosphonates

3.1. Nucleosidic route

The transformation of intermediate **3** to alkynylphosphonate **5** was achieved using the Pd catalyzed phosphonylation procedure (i.e., $Pd(OAc)_2$, 1,1′-bis(diphenylphosphinoferrocene) (dppf), diethyl phosphite, propylene oxide in *N*,*N*-dimethylformamide (DMF)) in 61% yield (Scheme 2) previously reported for a 2′-deoxythymidine derivative as sole nucleosidic substrate.[4] Then, treatment of **5** with aqueous trifluoroacetic acid solution at room temperature removed the 2′,3′-*O*-isopropylidene group and provided compound **6** in modest yield.



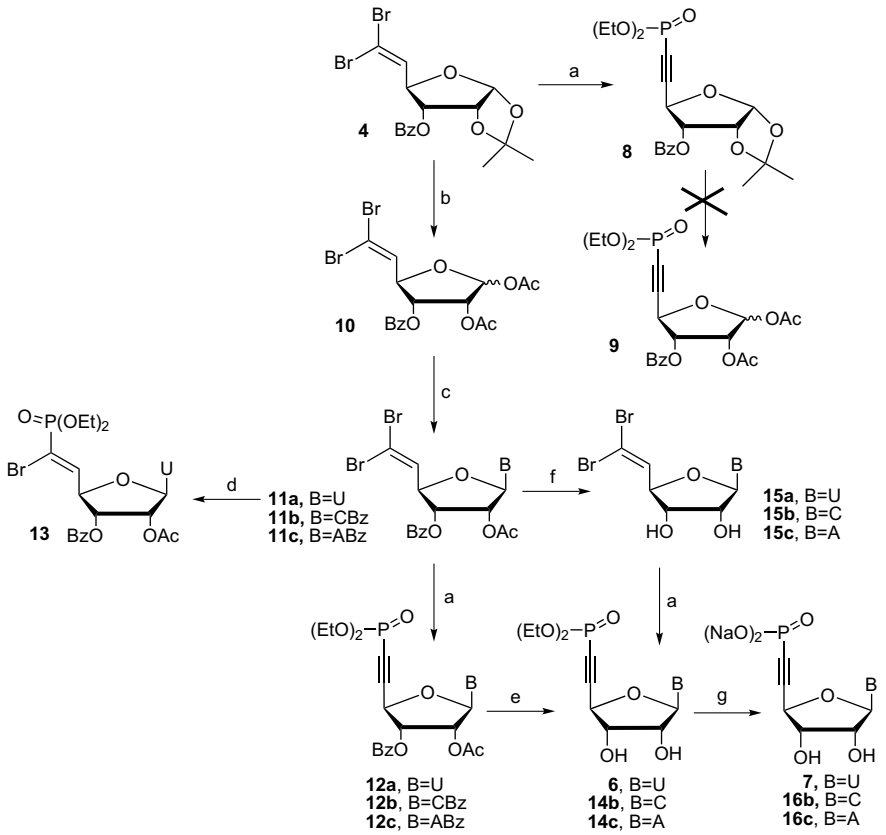
Scheme 2. Reagents and conditions: (a) $(EtO)_2P(O)H$, $Pd(OAc)_2$, dppf, propylene oxide, DMF, 90 °C, overnight, 61%; (b) trifluoroacetic acid/H_2O (7:3), rt, 24 h, 60%; (c) (i) TMSBr, DMF, rt, 6 days (ii) TEAB, pH7, (iii) DOWEX Na^+, 96%.

Finally, the ethyl phosphonate protecting groups were eliminated by using bromotrimethylsilane (TMSBr) in DMF and after purification by reverse-phase chromatography, and ionic exchange the desired alkynylphosphonate analogue of uridine **7** was obtained as its sodium salt. As foreseen from the results of the optimization study, derivative **7** was obtained in six steps from uridine but in only 4% overall yield.

3.2. Osidic route

We first envisaged to reach the key intermediate **9** (Scheme 3) and then introduced variability through nucleobase condensations. In this respect, the osidic alkynylphosphonate **8** was obtained in 44% yield from the osidic substrate **4** using the same conditions as those used for the synthesis of **5** from **3**. However, despite several attempts (Ac_2O/AcOH/H_2SO_4;[17] TFA 80% then Ac_2O, DMAP, pyridine;[18] and AcOH aq then Ac_2O, DMAP, and pyridine[19]), we were unable to isolate the per-acylated derivative **9** required for further glycosylation. Back to the 1,1-dibromo-1-alkene **4**, we decided to perform per-acetylation and glycosylation steps prior to phosphonylation. Thus, key sugar intermediate **10** was isolated in 59% yield using the classical procedure[17] and glycosylation was performed in standard Vorbrüggen conditions,[20] leading to the corresponding nucleoside analogues **11a–c** in good yields (69–88%). Thus, the following two steps, consisting of the removal of base-labile protecting groups and phosphonylation, may be performed in interchangeable order and both routes were explored.

In the first pathway, protected nucleoside alkynylphosphonates **12a–c** were obtained from corresponding 1,1-dibromo-1-alkenyl nucleoside analogues using a slightly modified procedure compared to substrate **3**. Indeed, heating overnight at 90 °C had a deteriorating effect on the reaction mixture corresponding to the phosphonylation step, which led to the desired compounds in low yields (<15%). Investigations towards optimum reaction conditions were carried out. Based on the literature data,[4,15] several parameters were studied including different solvents, temperature, and the nature of the scavenger. When DMF was replaced by toluene, a new and unique product corresponding to the bromo-alkenylphosphonate **13** was isolated in good yield (52%). Formation of this derivative may be due to an early coupling of the diethylphosphite during the catalytic cycle (vide infra). Replacement of propylene oxide (scavenger) by triethylamine was ineffective and the reaction did not proceed at all. Finally, using DMF but decreasing the



Scheme 3. Osidic pathway to nucleoside alkynylphosphonates. (a) $(EtO)_2P(O)H$, $Pd(OAc)_2$, dppf, propylene oxide, DMF, 80 or 90 °C, overnight, 44–76%; (b) AcOH, Ac_2O, H_2SO_{4cat}, 59%; (c) sylilated base, ACN, TMSOTf, 69–88%; (d) $(EtO)_2P(O)H$, $Pd(OAc)_2$, dppf, propylene oxide, toluene, 80 °C, overnight, 52%; (e) NEt_3, H_2O, MeOH (1:1:5), rt, 3 h, 17–53%; (f) NaOMe, MeOH, rt, 90–96%; (g) (i) TMSBr, DMF, rt, then TEAB (pH 7, 1 M), (ii) DOWEX Na^+.

temperature from 90 to 80 °C was conclusive and the isolated yield of the desired compounds **12a–c** was substantially increased (64–76%) when the reaction mixture was first filtrated through a Celite cake before removing the solvent in vacuum and performing the silica gel chromatography of the resulting crude material.

We next turned our attention to the removal of the base-labile protecting groups, thus treatment of derivatives **12a–c** in standard conditions (i.e., methanolic ammonia, sodium methanolate, etc.) yielded complex mixtures. The expected compounds **6** and **14b,c** were only obtained in modest to low yields using aqueous triethylamine in methanol.

Thus, the second pathway that involved the removal of the protecting groups before performing the phosphonylation was tested. Derivatives **11a–c** were treated in the presence of sodium methoxide and afforded intermediates **15a–c** in good yields (~90%). These last products were then converted into the desired alkynylphosphonates **6** and **14b,c** using the previously reported conditions.[4]

Starting from the 1,1-dibromo-1-alkenyl nucleoside analogues **11a–c**, the second route appeared more attractive in term of yields (45% compared to 30% over the two steps) and experimental procedures.

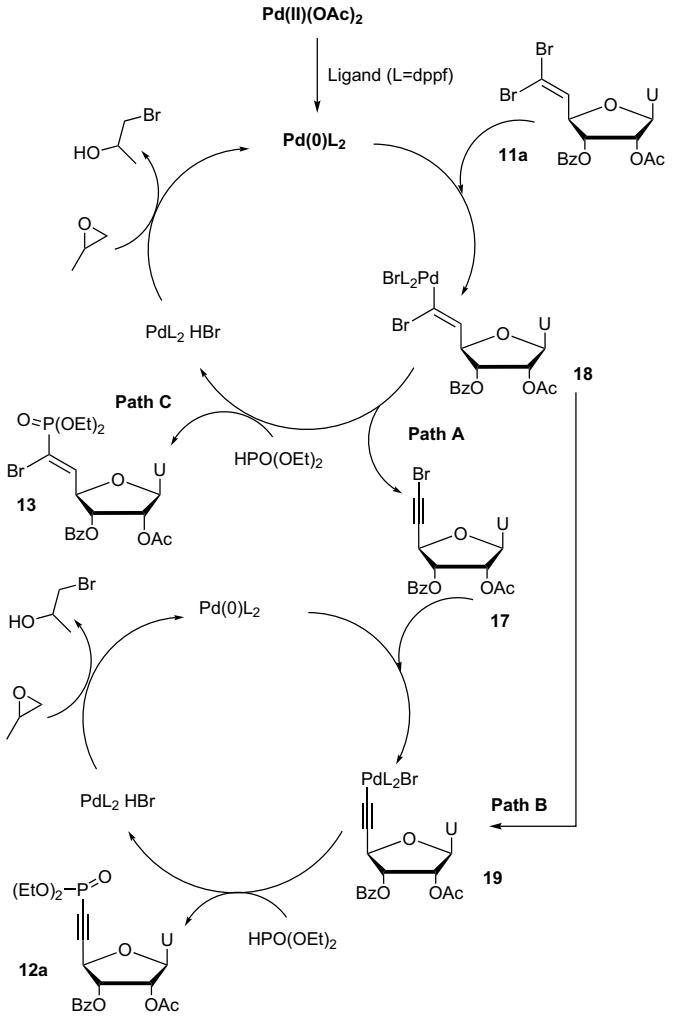
Finally, the phosphonic acid protecting groups were eliminated using TMSBr in DMF. The desired 1-alkynylphosphonate nucleoside analogues **7** and **16b,c** were obtained as their sodium salts after purification by reverse-phase (RP-C18) chromatography and ionic exchange on a DOWEX-resin.

3.3. Mechanistic considerations

A possible mechanism, which accounts for the formation of both alkynyl- and bromo-alkenylphosphonate derivatives, is proposed in Scheme 4. Our hypothesis is based on the work of Shen et al.[14] who reported a ligand effect on the product distribution (i.e., alkyne formation versus monocoupling) whereas we observed a solvent effect. The nature of the solvent appeared as a key parameter of the reaction course. Thus, formation of the alkynylphosphonate **12a** may result from two consecutive oxidative Pd(0) insertions. During the first catalytic cycle, the formation of the alkynyl bromide derivative **17** (path A) is due to a cis-β-hydrogen elimination from the bromoalkene palladium complex **18**. Then, a second Pd(0) insertion lead to the alkynyl palladium complex **19** that undergoes coupling with diethylphosphite to afford the desired alkynylphosphonate derivative **12a**. A working hypothesis is that in highly dipolar and coordinating solvents such as DMF, the intermediate **17** is efficiently formed (path A), or alternatively an elimination of HBr from complex **18** is favoured and leads directly to the formation of complex **19** (path B). When a non-polar and aprotic solvent such as toluene was used path C was preponderant and gave rise to the formation of the bromo-alkenylphosphonate **13**. Additional experiments carried out in toluene, with a postponed addition of the diethylphosphite (47%) or increasing amount of the Pd catalyst (48%), had no effect on the yield of the reaction and did not show the formation of other derivatives than **13**.

4. Conclusion

The synthesis of novel 5′-mononucleotide analogues bearing a 5′-alkynylphosphonate moiety (in the pyrimidine and purine series) has been achieved. Nucleosidic and osidic synthetic strategies have been explored. The latter appeared more convenient in terms of overall yield and also allowed the coupling of various nucleobases to an appropriate sugar derivative prior to phosphonylation. Interestingly, high selectivity for product distribution was



Scheme 4. Proposed mechanism for the formation of alkynyl- and bromo-alkenyl-phosphonate derivatives **12a** and **13**, respectively.

observed during the palladium-catalyzed phosphonylation step. Usefulness of this synthetic approach for the preparation of structurally related nucleoside phosphonate analogues of biological interest is currently being explored.

5. Experimental section

5.1. General

Unless otherwise stated, ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz with proton decoupling at 25 °C using a Bruker 300 Avance or DRX 400. Chemical shifts are given in δ values referenced to the residual solvent peak ($CDCl_3$ at 7.26 and 77 ppm or DMSO-d_6 at 2.49 and 39.5 ppm) relative to TMS. Deuterium exchange, decoupling and COSY experiments were performed in order to confirm proton assignments. Coupling constants, *J*, are reported in hertz. 2D ^{1}H–^{13}C heteronuclear COSY were recorded for the attribution of ^{13}C signals. Unless otherwise stated, ^{31}P NMR spectra were recorded at ambient temperature at 121 MHz with proton decoupling. Chemical shifts are reported relative to external H_3PO_4. FAB mass spectra were recorded in the positive-ion or negative-ion mode on a JEOL JMS-DX 300, using thioglycerol/glycerol (1:1, v/v, GT) as matrix. Specific rotations were measured with a Perkin–Elmer Model 341 spectropolarimeter (path length 1 cm) and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were carried out by the Service de Microanalyses du CNRS, Division de Vernaison (France). TLC was performed on precoated aluminium sheets of silica gel 60 F_{254} (Merck, Art. 9385), visualization of products being accomplished by UV absorbance followed by charring with 5% ethanolic sulfuric acid with heating for carbohydrates and nucleotides. Flash chromatography was carried out using 63–100 μm silica gel (Merck Art. No. 115101) otherwise 40–63 μm silica gel (Merck Art. No. 109385) was used. Thin layer chromatography was carried out using aluminium supported silica gel 60 plates (Merck Art. No. 105554). MW experiments were carried out using a single mode cavity synthesizer to ensure reproducibility and safety and were performed in a sealed Pyrex glass vessel (2–5 mL content) under argon atmosphere, using a microwave synthesizer Initiator 2.0 from Biotage (Biotage AB, Sweden) set at 300 W (frequency 2.45 GHz) with a 10 s premixing time. The temperature was monitored with an internal infrared probe. Solvents were reagent grade or purified by distillation prior to use, and solids were dried over P_2O_5 under reduced pressure at rt. Moisture sensitive reactions were performed under argon atmosphere using oven-dried glassware. All aqueous (aq) solutions were saturated with the specified salt unless otherwise indicated. Organic solutions were dried over Na_2SO_4 after workup and solvents were removed by evaporation at reduced pressure. Starting material such as diacetone-D-glucose was purchased from Acros Organics and uridine was from Carbosynth.

5.2. Chemistry

5.2.1. 1-(2′,3′-O-Isopropylidene-5′,6′-dideoxy-6′,6′-dibromo-β-D-ribo-5′-hexenofuranosyl)uracil, ***3***

Chromium(VI) oxide (17.0 g, 170 mmol) was suspended in anhydrous dichloromethane (170 mL) and DMF (40 mL). After 15 min stirring, acetic anhydride (16 mL) and pyridine (28 mL) were added dropwise, at 0 °C. A solution of 2′,3′-isopropylideneuridine[11] (12.1 g, 43 mmol) in dichloromethane (170 mL) and DMF (40 mL) was added at 0 °C over 30 min. The reaction mixture was stirred for 1 h, the chromium salts were precipitated in cold ethyl acetate (2 L) and the resulting suspension was filtered over silica gel. The crude solution was concentrated under reduced pressure, co-evaporated with toluene and dried over P_2O_5.

The crude aldehyde (6.1 g, 21.6 mmol) was dissolved in dichloromethane (180 mL) and carbon tetrabromide (14.3 g, 43.2 mmol) and triphenylphosphine (22.6 g, 86.4 mmol) were added. The mixture was stirred at room temperature for 22 h. The mixture was diluted with dichloromethane and washed with water. The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. Two column chromatography of the crude materials on silica gel (toluene/EtOAc, 7:3, v/v) gave compound **3** as a white solid (2.25 g, 12%).

R_f (toluene/EtOAc, 1:1, v/v) 0.3. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.48 (br s, 1H exchangeable, NH), 7.75 (d, J=8.0 Hz, 1H, H-6), 6.83 (d, J=8.2 Hz, 1H, H-5′), 5.77 (d, J=1.1 Hz, 1H, H-1′), 5.64 (dd, J=2.1–8.0 Hz, 1H, H-5), 5.14 (dd, J=1.3–6.3 Hz, 1H, H-2′), 4.87 (dd, J=3.5–6.3 Hz, 1H, H-3′), 4.61 (dd, J=3.5–8.1 Hz, 1H, H-4′), 1.50, 1.29 (2s, 6H, $C(CH_3)_2$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.3 (C-4), 150.4 (C-2), 143.8 (C-6), 137.0 (C-5′), 113.2 ($C(CH_3)_2$), 101.7 (C-5), 94.0 (C-1′), 93.1 (C-6′), 87.3 (C-4′), 84.0, 83.9 (C-2′,C-3′), 26.8, 25.0 ($C(CH_3)_2$). SM FAB>0 m/z 441, 439, 437 $(M+H)^+$. Relative intensity 1:2:1; FAB<0 m/z 439, 437, 435 $(M-H)^-$. Relative intensity 1:2:1. UV λ_{max}=255 nm (ε_{max}=11,500), λ_{min}=230 nm (ε_{min}=4200) (EtOH 95). $[\alpha]_D^{20}$ +76 (*c* 0.5, CH_2Cl_2). Anal. Calcd for $C_{13}H_{14}Br_2N_2O_5$: C, 35.64; H, 3.22; N, 6.39. Found: C, 35.76; H, 3.34; N, 6.13.

5.2.2. 3-O-Benzoyl-6,6-dibromo-5,6-dideoxy-1,2-O-isopropylidene-D-allofuranose, ***4***

The aldehyde **2** (0.144 g, 0.49 mmol) was dissolved in dry dichloromethane (8 mL) and the solution was cooled to 0 °C.

Carbon tetrabromide (0.328 g, 0.99 mmol) and triphenylphosphine (0.518 g, 1.98 mmol, in four parts) were added. The mixture was stirred at room temperature for 1 h and then diluted with dichloromethane. The resulting organic layer was washed with water, dried over $MgSO_4$, filtered and evaporated under reduced pressure. A column chromatography of the crude materials on silica gel (CH_2Cl_2 to CH_2Cl_2/EtOAc 9:1, v/v) afforded compound **4** as a white powder (0.134 g, 61%).

R_f (toluene/EtOAc, 9:1, v/v) 0.6. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (m, 2H, H-Ar), 7.73 (m, 1H, H-Ar), 7.59 (m, 2H, H-Ar), 6.81 (d, J=8.4 Hz, 1H, H-5), 5.94 (d, J=3.6 Hz, 1H, H-1), 4.98 (m, 2H, H-2, H-3), 4.84 (m, 1H, H-4), 1.49, 1.30 (2s, 6H, $C(CH_3)_2$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8 (C=O), 134.8 (C-5), 133.9, 129.3, 129.0, 128.6 (C-Ar), 112.5 ($C(CH_3)_2$), 104.1 (C-1), 95.2 (C-6), 77.2 (C-4), 76.6, 75.6 (C-2, C-3), 26.5, 26.4 ($C(CH_3)_2$). MS ESI>0 m/z 447, 449, 451 $(M+H)^+$. Relative intensity 1:2:1. HRMS calcd for $C_{16}H_{17}Br_2O_5$: 446.9443; found: 446.9455. UV λ_{max}=272 nm (ε_{max}=10,100), λ_{min}=249 nm (ε_{min}=7000) (EtOH 95). $[\alpha]_D^{20}$ +97.6 (c 1.04, MeOH). Anal. Calcd for $C_{16}H_{16}Br_2O_5$: C, 42.89; H, 3.60. Found: C, 43.28; H, 4.37.

5.2.3. 1-(2′,3′-O-Isopropylidene-5′,6′-dideoxy-6′-diethyl phosphono-β-D-ribo-5′-hexynofuranosyl)uracil, **5**

Palladium(II) acetate (78 mg, 0.35 mmol) and dppf (383 mg, 0.7 mmol) were dissolved in DMF (9 mL). The mixture was stirred at room temperature for 20 min. A solution of 1-(2′,3′-*O*-isopropylidene-5′,6′-dideoxy-6′,6′-dibromo-β-D-*ribo*-5′-hexenofuranosyl)uracil (**3**) (760 mg, 1.7 mmol), diethylphosphite (0.45 mL, 3.5 mmol) and propylene oxide (0.22 mL, 5.2 mmol) in DMF (24 mL) was added dropwise at room temperature. The solution was stirred for 16 h at 90 °C. The solution was evaporated under high reduce pressure and co-evaporated with absolute ethanol. Column chromatography of crude materials on silica gel (EtOAc/cyclohexane, 3:1, v/v) gave the desired compound as a yellow-orange foam (450 mg, 61%).

R_f (EtOAc) 0.2. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.48 (br s, 1H exchangeable, NH), 7.73 (d, J=8.0 Hz, 1H, H-6), 5.84 (s, 1H, H-1′), 5.62 (d, J=8.0 Hz, 1H, H-5), 5.28 (d, J=6.1 Hz, 1H, H-2′), 5.18 (dd, J=2.9–6.0 Hz, 1H, H-3′), 5.06 (t, J=3.2 Hz, 1H, H-4′), 4.1–4.0 (m, 4H, OCH_2CH_3), 1.48, 1.31 (2s, 6H, $C(CH_3)_2$), 1.26 (2t, J=7.0 Hz, 6H, OCH_2CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.3 (C-4), 150.2 (C-2), 143.6 (C-6), 113.19 ($C(CH_3)_2$), 101.5 (C-5), 96.8 (C-5′, d, J=48.0 Hz), 93.9 (C-1′), 84.3 (C-4′, d, J=70.4 Hz), 76.5 (C-6′, d, J=286.3 Hz), 76.6 (C-2′), 76.5 (C-3′), 63.2–63.1 (OCH_2CH_3), 26.4, 24.8 ($C(CH_3)_2$), 15.8, 15.7 (OCH_2CH_3). ^{31}P NMR (100 MHz, DMSO-d_6) δ −8.4. SM FAB>0 m/z 829 $(2M+H)^+$, 415 $(M+H)^+$; FAB<0 m/z 827 $(2M-H)^-$, 413 $(M-H)^-$, 111 $(B)^-$. UV λ_{max}=256 nm (ε_{max}=9500), λ_{min}=225 nm (ε_{min}=1500) (EtOH 95). $[\alpha]_D^{20}$ +18.8 (c 0.85, MeOH). Anal. Calcd for $C_{17}H_{23}N_2O_8P$: C, 49.28; H, 5.59; N, 6.76; P, 7.48. Found: C, 49.38; H, 5.62; N, 6.61; P, 7.54.

5.2.4. 1-(5′,6′-Dideoxy-6′-diethylphosphono-β-D-ribo-5′-hexynofuranosyl)uracil, **6**

Compound **5** (430 mg, 1.04 mmol) was dissolved in an aqueous solution of trifluoroacetic acid (70%, v/v, 8 mL/mmol) at room temperature. After 4 h and additional trifluoroacetic acid (3 mL), the reaction was still incomplete after 24 h. Thus, the solution was evaporated under reduced pressure and co-evaporated with absolute ethanol. Column chromatography of the crude materials on reverse phase (H_2O/CH_3CN, 20–50%) gave the title compound as a white solid (225 mg, 60%) after freeze-drying and the recovered initial substrate (130 mg, 30%).

Derivative **6** (24 mg, 42%) could also be prepared by treatment of **12a** (80 mg, 0.15 mmol) with a mixture of MeOH/water/triethylamine (5:1:1, v/v/v) for 3 h at room temperature.

R_f (CH_2Cl_2/MeOH, 9:1, v/v) 0.3. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.45 (br s, 1H exchangeable, NH), 7.54 (d, J=8.1 Hz, 1H, H-6), 5.89 (sl, 1H exchangeable, OH), 5.78 (d, J=2.4 Hz, 1H, H-1′), 5.76 (br s, 1H exchangeable, OH), 5.70 (d, J=8.0 Hz, 1H, H-5), 4.68 (t, J=3.9 Hz, 1H, H-4′), 4.20 (m, 2H, H-2′, H-3′), 4.10 (m, 4H, OCH_2CH_3), 1.29 (t, J=7.1 Hz, 6H, OCH_2CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.0 (C-4), 150.5 (C-2), 140.5 (C-6), 102.4 (C-5), 96.8 (C-5′, d, J=48.2 Hz), 89.8 (C-1′), 77.2 (C-6′, d, J=286.8 Hz), 74.5, 72.6 (C-2′, C-3′), 72.4 (C-4′, d, J=4.2 Hz), 63.2, 63.1 (OCH_2CH_3), 15.9, 15.8 (OCH_2CH_3). ^{31}P NMR (100 MHz, DMSO-d_6) δ −8.4. SM FAB>0 m/z 749 $(2M+H)^+$, 375 $(M+H)^+$, 263 $(M-B)^+$; FAB<0 m/z 747 $(2M-H)^-$, 373 $(M-H)^-$, 111 $(B)^-$. UV λ_{max}=259 nm (ε_{max}=9600), λ_{min}=228 nm (ε_{min}=2300) (EtOH 95). $[\alpha]_D^{20}$ +5.8 (c 0.86, MeOH). Anal. Calcd for $C_{14}H_{19}N_2O_8P\cdot 0.1H_2O$: C, 44.71; H, 5.15; N, 7.45; P, 8.24. Found: C, 44.36; H, 5.34; N, 7.33; P, 8.29.

5.2.5. 1-(5′,6′-Dideoxy-6′-phosphono-β-D-ribo-5′-hexynofuranosyl)uracil (disodium salt), **7**

Derivative **6** (145 mg, 0.39 mmol) was dissolved in anhydrous DMF (20 mL/mmol), and then TMSBr (10 equiv) was added at 0 °C. The mixture was stirred at room temperature until completion of the reaction was indicated by TLC. The reaction mixture was neutralized with 1 M aqueous TEAB and concentrated under high vacuum. Column chromatography of the crude materials on reverse phase (H_2O) gave the corresponding phosphonic acid and the title compound **7** was obtained as a white solid (135 mg, 96%) after ion exchange on DOWEX Na^+ and freeze-drying.

R_f (*i*PrOH/NH_4OH 30%/H_2O, 7:1:2, v/v/v) 0.14. ^{1}H NMR (300 MHz, D_2O) δ 7.65 (d, J=8.1 Hz, 1H, H-6), 5.81 (d, J=6.1 Hz, 1H, H-1′), 5.79 (d, J=8.4 Hz, 1H, H-5), 4.61 (t, J=3.1 Hz, H-4′), 4.38 (t, J=5.0 Hz, H-2′), 4.22 (t, J=4.0 Hz, H-3′). ^{13}C NMR (75 MHz, D_2O) δ 166.2 (C-4), 151.8 (C-2), 141.75 (C-6), 103.0 (C-5), 89.3 (C-1′), 88.5 (C6′, d, J=237.7 Hz), 87.0 (C-5′, d, J=40.1 Hz), 74.9 (C-4′), 74.1 (C-2′, C-3′). ^{31}P NMR (100 MHz, D_2O) δ −10.8. SM FAB>0 m/z 363 $(M+H)^+$, 341 $(M+2H-Na)^+$; FAB<0 m/z 339 $(M-Na)^-$, 317 $(M-2Na+H)^-$. UV λ_{max}=260 nm (ε_{max}=10,200), λ_{min}=229 nm (ε_{min}=2200) (H_2O). $[\alpha]_D^{20}$ −6.6 (c 0.91, H_2O). Anal. Calcd for $C_{10}H_9N_2Na_2O_8P\cdot 2H_2O$: C, 30.16; H, 3.29; N, 7.04; P, 7.78. Found: C, 30.13; H, 3.40; N, 6.71; P, 8.10.

5.2.6. 3-O-Benzoyl-5,6-dideoxy-6-diethylphosphono-1,2-O-isopropylidene-β-D-allo-5-hexynofuranose, **8**

Similar procedure as for derivative **5** was applied to 1, 1-dibromo-1-alkene **4** (90 mg, 0.20 mmol). The desired alkynylphosphonate **8** (37 mg, 44%) was isolated as a yellow oil after purification by silica gel column chromatography using dichloromethane/EtOAc (1:0 to 0:1, v/v) as eluent.

R_f (EtOAc) 0.49. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.01 (m, 2H, H-Ar), 7.76–7.54 (m, 3H, H-Ar), 5.97 (d, J=3.6 Hz, 1H, H-1), 5.25 (dd, J=4.6, 9.0 Hz, 1H, H-3), 5.08 (dd, J=3.1, 9.0 Hz, 1H, H-4), 4.98 (dd, J=4.1 Hz, 1H, H-2), 4.07 (m, 4H, OCH_2CH_3), 1.49, 1.28 (2s, 6H, $C(CH_3)_2$), 1.25–1.20 (t, J=7.0 Hz, 6H, OCH_2CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.6 (C=O), 134.1, 129.4, 129.2, 129.0, 128.7, 128.3 (C-Ar), 113.0 ($C(CH_3)_2$), 104.5 (C-1), 95.5 (d, J=49.0 Hz, C-5), 79.0, 74.7 (d, J=319.3 Hz, C-6), 76.7 (C-2), 75.9 (C-3), 66.9 (d, J=4.5 Hz, C-4), 63.2 (OCH_2CH_3), 26.4 ($C(CH_3)_2$), 15.7 (OCH_2CH_3). ^{31}P NMR (121 MHz, DMSO-d_6) δ −8.90. MS ESI >0 m/z 425 $(M+H)^+$. HRMS calcd for $C_{20}H_{26}O_8P$: 425.1365; found: 425.1355. UV λ_{max}=271 nm (ε_{max}=11,000), λ_{min}=248 nm (ε_{min}=6800) (EtOH 95). $[\alpha]_D^{20}$ +131.5 (c 1.0, MeOH). Anal. Calcd for $C_{20}H_{25}O_8P$: C, 56.60; H, 5.94; P, 7.30. Found: C, 56.80; H, 6.01; P, 6.80.

5.2.7. 1,2-Di-O-acetyl-3-O-benzoyl-6,6-dibromo-5,6-dideoxy-(α,β)-D-ribo-5′-hexenofuranose, **10**

A solution of dibromoalkene **4** (5.16 g, 11.52 mmol) in glacial acetic acid (43.8 mL), acetic anhydride (16.1 mL) and concentrated sulfuric acid (1.7 mL) was stirred 1 h 30 min at room temperature. The reaction mixture was diluted with dichloromethane. The resulting organic layer was successively washed with aq saturated $NaHCO_3$ solution and water, dried over $MgSO_4$, filtered and evaporated under reduced pressure. A column chromatography of the

crude materials on silica gel (toluene to toluene/ethyl acetate 8:2, v/v) gave a mixture of the two anomers (α/β in ratio 25:75) of compound **10** as white foam (2.92 g, 59%).

R_f (toluene/EtOAc, 8:2, v/v) 0.5. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (m, 2H, H-Ar), 7.73 (m, 1H, H-Ar), 7.59 (m, 2H, H-Ar), 7.00 (d, J=8.52 Hz, H-5 α-anomer), 6.92 (d, J=8.63 Hz, H-5 β-anomer), 6.43 (d, J=4.24 Hz, H-1 α-anomer), 6.13 (s, H-1 β-anomer), 5.58 (dd, J=4.89, 6.87 Hz, H-3 β-anomer), 5.50 (m, H-2 α-anomer, H-3 α-anomer), 5.46 (d, J=4.78 Hz, H-2 β-anomer), 4.90 (m, 1H, H-4), 2.16, 2.10 (2s, 6H, Ac). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.2, 168.9, 164.5 (CO), 135.9 (C-5 β-anomer), 134.5 (C-5 α-anomer), 134.0, 129.3, 129.0, 128.3 (C-Ar), 97.7 (C-1 β-anomer), 95.4 (C-6 β-anomer), 95.0 (C-6 α-anomer), 93.0 (C-1 α-anomer), 82.5 (C-4 α-anomer), 80.8 (C-4 β-anomer), 73.6, 73.5 (C-3, C-2 β-anomer), 72.0 (C-3, C-2 α-anomer), 20.8, 20.3 (Ac). MS ESI >0 m/z 491, 493, 495 $(M+H)^+$, 431, 433, 435 $(M-OAc+H)^+$. Relative intensity 1:2:1. HRMS calcd for $C_{15}H_{13}Br_2O_5$: 430.9130; found: 430.9136. UV λ_{max}=271 nm (ε_{max}=10,300), λ_{min}=249 nm (ε_{min}=6900) (EtOH 95). $[\alpha]_D^{20}$ +28.1 (c 0.99, MeOH).

5.3. Standard procedure for glycosylation, 11a–c

The nucleobase (5 equiv) was dissolved in anhydrous acetonitrile (7 mL/mmol) and *N,O*-bis(trimethylsilyl) acetamide (10 equiv) was added. The solution was refluxed for 2 h and the reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue was dissolved in anhydrous acetonitrile. Then a solution of peracetylated sugar (1 equiv) in anhydrous acetonitrile was added, followed by trimethylsilyl trifluoromethane sulfonate (4 equiv) and the resulting solution was stirred at 80 °C overnight. The reaction mixture was allowed to cool down to room temperature and diluted with dichloromethane. The resulting organic layer was successively washed with aq saturated $NaHCO_3$ solution and water, dried over $MgSO_4$, filtered and evaporated under reduced pressure.

5.3.1. *1-(2′-O-Acetyl-3′-O-benzoyl-6′,6′-dibromo-5′,6′-dideoxy-β-D-ribo-5′-hexenofuranosyl)uracil,* ***11a***

Column chromatography of the crude materials on silica gel (CH_2Cl_2 to EtOAc) gave derivative **11a** as white foam (980 mg, 88%).

R_f (toluene/EtOAc, 5:7, v/v) 0.4. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (s, 1H exchangeable, NH), 8.01 (m, 2H, H-Ar), 7.82 (d, J=8.0 Hz, 1H, H-6), 7.70 (m, 1H, H-Ar), 7.57 (m, 2H, H-Ar), 7.04 (d, J=8.8 Hz, 1H, H-5′), 5.98 (d, J=4.4 Hz, 1H, H-1′), 5.67 (m, 3H, H-5, H-2′, H-3′), 4.81 (dd, J=5.4, 8.4 Hz, 1H, H-4′), 1.95 (s, 3H, Ac). ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.3, 164.5 (C=O), 163.0 (C-4), 150.3 (C-2), 142.3 (C-6), 137.3 (C-5′), 134.0, 129.4, 129.0, 128.9, 128.4 (C-Ar), 102.4 (C-5), 95.2 (C-6′), 88.9 (C-1′), 80.9 (C-4′), 72.7, 72.0 (C-2′,C-3′), 20.2 (Ac). MS ESI>0 m/z 543, 545, 547 $(M+H)^+$. Relative intensity 1:2:1; ESI<0 m/z 541, 543, 545 $(M-H)^-$. Relative intensity 1:2:1. HRMS calcd for $C_{19}H_{17}Br_2N_2O_7$: 542.9402; found: 542.9393. UV λ_{max}=261 nm (ε_{max}=23,900), λ_{min}=244 nm (ε_{min}=18,600) (EtOH 95). $[\alpha]_D^{20}$ +20.2 (c 0.99, MeOH).

5.3.2. *N-4-Benzoyl-1-(2′-O-Acetyl-3′-O-benzoyl-6′,6′-dibromo-5′,6′-dideoxy-β-D-ribo-5′-hexenofuranosyl)cytidine,* ***11b***

Column chromatography of the crude materials on silica gel (CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1, v/v) gave derivative **11b** as white foam (183 mg, 69%).

R_f (toluene/EtOAc, 5:7, v/v) 0.35. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (s, 1H exchangeable, NH), 8.46 (d, J=6.2 Hz, 1H, H-6), 8.21 (m, 1H, H-Ar), 7.80 (m, 9H, H-Ar), 7.62 (d, J=5.4 Hz, 1H, H-5), 7.30 (d, J=8.3 Hz, 1H, H-5′), 6.23 (s, 1H, H-1′), 5.95 (m, 2H, H-2′, H-3′), 5.10 (m, 1H, H-4′), 2.21 (s, 3H, Ac). ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.6, 169.8, 168.0 (C=O), 165.0 (C-4), 154.8 (C-2), 148.1 (C-6), 135.4 (C-5′), 134.6, 133.6, 133.4, 129.9, 129.6, 129.1, 129.0 (C-Ar), 97.4 (C-5), 96.0 (C-6′), 92.3 (C-1′), 81.8 (C-4′), 73.5, 73.4 (C-2′,C-3′), 20.8 (Ac). MS ESI>0 m/z 684, 686, 688 $(M+K)^+$. Relative intensity 1:2:1; ESI<0 m/z 645, 647, 649 $(M-H)^-$. Relative intensity 1:2:1. HRMS calcd for $C_{26}H_{22}Br_2N_3O_7$: 645.9824; found: 645.9830. UV λ_{max}=263 nm (ε_{max}=35,600), λ_{min}=243 nm (ε_{min}=22,500) (EtOH 95). $[\alpha]_D^{20}$ +29.3 (c 0.99, MeOH). Anal. Calcd for $C_{26}H_{21}Br_2N_3O_7$: C, 48.25; N, 6.49. Found: C, 47.94; N, 6.78.

5.3.3. *N-6-Benzoyl-9-(2′-O-acetyl-3′-O-benzoyl-6′,6′-dibromo-5′,6′-dideoxy-β-D-ribo-5′-hexenofuranosyl)adenine,* ***11c***

Column chromatography of the crude materials on silica gel (CH_2Cl_2 to CH_2Cl_2/EtOAc 1:1, v/v) gave derivative **11c** as white foam (2.20 g, 81%).

R_f (CH_2Cl_2/EtOAc, 9:1, v/v) 0.4. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.32 (br s, 1H exchangeable, NH), 8.85, 8.78 (2s, 2H, H-2, H-8), 8.07 (m, 4H, H-Ar), 7.66 (m, 6H, H-Ar), 7.25 (d, J=8.4 Hz, 1H, H-5′), 6.54 (d, J=5.1 Hz, 1H, H-1′), 6.26 (t, J=5.4 Hz, 1H, H-2′), 5.99 (t, J=5.3 Hz, 1H, H-3′), 5.00 (dd, J=4.9, 8.4 Hz, 1H, H-4′), 2.00 (s, 3H, Ac). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.2, 165.6, 164.5 (C=O), 151.9, 151.7 (C-4, C-6), 151.9, 151.7 (2 Cq), 150.7, 143.6 (C-2, C-8), 134.7 (C-5′), 134.1, 133.2, 132.5, 129.5, 129.0, 128.5, 128.4, 125.9 (C-Ar), 95.3 (C-6′), 85.9 (C-1′), 81.4 (C-4′), 73.1 (C-3′), 72.3 (C-2′), 59.7 (C-6), 20.7 (Ac). MS ESI>0 m/z 670, 672, 674 $(M+K)^+$. Relative intensity 1:2:1; ESI<0 m/z 669, 671, 673 $(M-H)^-$. Relative intensity 1:2:1. HRMS calcd for $C_{27}H_{22}Br_2N_5O_6$: 669.9937; found: 669.9943. UV λ_{max}=279 nm (ε_{max}=26,500), λ_{min}=249 nm (ε_{min}=16,700) (EtOH 95). $[\alpha]_D^{20}$ −17.6 (c 1.02, MeOH). Anal. Calcd for $C_{27}H_{21}Br_2N_5O_6$: C, 48.31; N, 10.43. Found: C, 48.05; N, 10.03.

5.4. Standard procedure for phosphonylation, 12a–c and 14b,c

Palladium(II) acetate (0.2 equiv) and dppf (0.4 equiv) were dissolved in anhydrous DMF (25 mL/mmol of palladium complex). The mixture was stirred at room temperature for 20 min. A solution of nucleoside analogue (1 equiv), diethylphosphite (2 equiv) and propylene oxide (3 equiv) in anhydrous DMF (15 mL/mmol of nucleoside) was added dropwise at room temperature. The solution was stirred overnight at 80 °C. The solution was evaporated under high reduced pressure and co-evaporated with absolute ethanol.

5.4.1. *1-(2′-O-Acetyl-3′-O-benzoyl-5′,6′-dideoxy-6′-diethylphosphono-β-D-ribo-5′-hexynofuranosyl)uracil,* ***12a***

Column chromatography of crude materials on silica gel (dichloromethane 100% to ethyl acetate 100%) gave the desired compound **12a** (328 mg, 73%) as a yellow foam.

R_f (EtOAc) 0.5. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.62 (br s, 1H exchangeable, NH), 8.08 (m, 2H, H-Ar), 7.86 (d, J=8.1 Hz, 1H, H-6), 7.70 (m, 3H, H-Ar), 6.06 (d, J=4.6 Hz, 1H, H-1′), 5.99 (dd, J=5.9 Hz, 1H, H-3′), 5.81 (m, 2H, H-2′, H-5), 5.37 (dd, J=3.4, 5.5 Hz, 1H, H-4′), 4.21–4.11 (m, 4H, OCH_2CH_3), 2.06 (s, 3H, Ac), 1.35–1.30 (t, J=7.1 Hz, 6H, OCH_2CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.2 (C=O), 164.3 (C-4), 163.0 (C-2), 150.2 (C-6), 142.4, 134.1, 129.4, 129.0, 128.2 (C-Ar), 102.4 (C-5), 94.9, 94.2 (C-5′, d, J=48.3 Hz), 89.8 (C-1′), 79.4, 75.6 (C-6′, d, J=284.9 Hz), 73.3 (C-3′), 71.9 (C-2′), 70.4 (C-4′), 63.3, 63.2 (OCH_2CH_3), 20.2 (Ac), 15.8, 15.7 (OCH_2CH_3). ^{31}P NMR (121 MHz, DMSO-d_6) δ −8.84. MS ESI>0 m/z 521 $(M+H)^+$; ESI<0 m/z 519 $(M-H)^-$. HRMS calcd for $C_{23}H_{24}N_2O_{10}P$: 519.1169; found: 519.1182. UV λ_{max}=233 nm (ε_{max}=18,000), λ_{min}=250 nm (ε_{min}=12,000) (EtOH 95). $[\alpha]_D^{20}$ +1.6 (c 1.24, MeOH).

5.4.2. *N-4-Benzoyl-1-(2′-O-acetyl-3′-O-benzoyl-5′,6′-dideoxy-6′-diethylphosphono-β-D-ribo-5′-hexyno furanosyl)cytosine,* ***12b***

Column chromatography of crude materials on silica gel (dichloromethane 100% to ethyl acetate 100%) gave the desired compound **12b** (410 mg, 64%) as a yellow foam.

R_f (EtOAc) 0.5. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.51 (br s, 1H exchangeable, NH), 8.30–7.47 (m, 12H, H-Ar, H-6, H-5), 6.13–6.09 (m,

2H, H-1′, H-3′), 5.93 (dd, *J*=3.6, 6.2 Hz, 1H, H-2′), 5.43 (dd, *J*=3.4, 6.2 Hz, 1H, H-4′), 4.22–4.12 (m, 4H, O*CH*$_2$CH$_3$), 2.08 (s, 3H, Ac), 1.35–1.30 (t, *J*=7.0 Hz, 6H, OCH$_2$*CH*$_3$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.2 (C═O), 164.2 (C-4), 164.0 (C═O), 155.0 (C-2), 147.6 (C-6), 134.1, 132.8, 129.4, 129.0, 128.5, 128.4, 128.3 (C-Ar), 96.9 (C-5), 95.1, 94.4 (C-5′, d, *J*=48.2 Hz), 92.5 (C-1′), 79.3, 75.6 (C-6′, d, *J*=285.2 Hz), 73.6 (C-3′), 72.6 (C-2′), 70.9 (C-4′, d, *J*=4.0 Hz), 63.3, 63.2 (O*CH*$_2$CH$_3$), 20.2 (Ac), 15.8, 15.7 (OCH$_2$*CH*$_3$). ^{31}P NMR (121 MHz, DMSO-d_6) δ −8.82. MS ESI>0 *m*/*z* 624 (M+H)$^+$; ESI<0 *m*/*z* 622 (M−H)$^-$. HRMS calcd for $C_{30}H_{31}N_3O_{10}P$: 624.1747; found: 624.1741. UV λ_{max}=263 nm (ε_{max}=30,900), λ_{min}=245 nm (ε_{min}=20,800) (EtOH 95). $[\alpha]_D^{20}$ +10.0 (*c* 1.00, MeOH). Anal. Calcd for $C_{30}H_{30}N_3O_{10}P$: C, 57.79; H, 4.85; N, 6.74. Found: C, 57.29; H, 4.99; N, 6.14.

5.4.3. *N-6-Benzoyl-9-(2′-O-acetyl-3′-O-benzoyl-5′,6′-dideoxy-6′-diethylphosphono-β-D-ribo-5′-hexyno furanosyl)adenine,* ***12c***

Column chromatography of crude materials on silica gel (dichloromethane 100% to ethyl acetate 100%) gave the desired compound **12c** (550 mg, 76%) as a yellow foam.

R_f (EtOAc) 0.2. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.35 (br s, 1H exchangeable, NH), 8.88, 8.80 (2s, 2H, H-2, H-8), 8.15–7.60 (m, 10H, H-Ar), 6.66–6.58 (m, 2H, H-1′, H-2′), 6.26 (dd, *J*=4.7 Hz, 1H, H-3′), 5.59 (dd, *J*=3.7 Hz, 1H, H-4′), 4.19–4.07 (m, 4H, O*CH*$_2$CH$_3$), 2.07 (s, 3H, Ac), 1.33–1.27 (t, *J*=7.0 Hz, 6H, OCH$_2$*CH*$_3$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.2, 164.4 (Cq), 151.8, 144.0 (C-2, C-8), 150.8 (Cq), 134.2, 133.2, 132.5, 129.5, 129.0, 128.5, 128.3, 126.0 (C-Ar), 94.7, 94.1 (C-5′, d, *J*=48.2 Hz), 86.3 (C-1′), 79.7, 76.0 (C-6′, d, *J*=285.0 Hz), 74.1 (C-3′), 71.8 (C-2′), 71.0 (C-4′), 63.3, 63.2 (O*CH*$_2$CH$_3$), 20.1 (Ac), 15.8, 15.7 (OCH$_2$*CH*$_3$). ^{31}P NMR (121 MHz, DMSO-d_6) δ −8.82. MS ESI>0 *m*/*z* 648 (M+H)$^+$; ESI<0 *m*/*z* 646 (M−H)$^-$. HRMS calcd for $C_{31}H_{29}N_5O_9P$: 646.1703; found: 646.1702. UV λ_{max}=279 nm (ε_{max}=21,900), λ_{min}=253 nm (ε_{min}=13,300) (EtOH 95). $[\alpha]_D^{20}$ −14.6 (*c* 1.03, MeOH).

5.4.4. *1-(2′-O-Acetyl-3′-O-benzoyl-5′,6′-dideoxy-6′-diethylphosphono-β-D-ribo-5′-hexynofuranosyl)uracil,* ***13***

When phosphonylation reaction was performed in toluene instead of DMF, compound **13** was observed as a unique product. Column chromatography of crude materials on silica gel (dichloromethane 100% to ethyl acetate 100%) gave the desired compound as yellow foam (86 mg, 52%).

R_f (EtOAc) 0.29. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.60 (br s, 1H exchangeable, NH), 8.08–7.57 (m, 5H, H-Ar), 7.95 (d, *J*=8.1 Hz, 1H, H-6), 7.40 (dd, *J*=7.8, 14.4 Hz, 1H, H-5′) 6.08 (d, *J*=4.2 Hz, 1H, H-1′), 5.87–5.76 (m, 3H, H-2′, H-3′, H-5), 5.14 (m, 1H, H-4′), 4.11 (m, 4H, O*CH*$_2$CH$_3$), 2.07 (s, 3H, Ac), 1.29 (m, 6H, OCH$_2$*CH*$_3$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.3, 164.4 (C═O), 163.0 (C-4), 150.3 (C-2), 144.3 (C-5′, d, *J*=14.9 Hz), 142.7 (C-6), 134.0, 129.3, 129.0, 128.8, 128.6, 128.3 (C-Ar), 117.9, 115.3 (C-6′, d, *J*=199.3 Hz), 102.3 (C-5), 89.9 (C-1′), 79.7 (C-4′, d, *J*=16.1 Hz), 72.5, 72.3 (C-2′, C-3′), 63.0 (O*CH*$_2$CH$_3$), 20.2 (C(*CH*$_3$)$_2$), 15.8, 15.7 (OCH$_2$*CH*$_3$). ^{31}P NMR (100 MHz, DMSO-d_6) δ −7 .9. MS ESI>0 *m*/*z* 601, 603 (M+H)$^+$. Relative intensity 1:1; ESI<0 *m*/*z* 599, 601 (M−H)$^-$. Relative intensity 1:1. HRMS calcd for $C_{23}H_{25}BrN_2O_{10}P$: 599.0430; found: 599.0436. UV λ_{max}=227 nm (ε_{max}=21,900), λ_{min}=250 nm (ε_{min}=12,200) (EtOH 95). $[\alpha]_D^{20}$ +0.9 (*c* 1.09, MeOH).

5.4.5. *1-(5′,6′-Dideoxy-6′-diethylphosphono-β-D-ribo-5′-hexynofuranosyl)cytosine,* ***14b***

Column chromatography of the crude materials on reverse phase (H$_2$O/MeOH, 0–100%) gave the titled compound as a white solid (163 mg, 45%) after freeze-drying.

Derivative **14b** (32 mg, 53%) could also be prepared by treatment of **12b** (100 mg, 0.16 mmol) with a mixture of MeOH/water/triethylamine (5:1:1, v/v/v) for 2 h 30 min, at room temperature.

R_f (EtOAc/MeOH, 3:1, v/v) 0.17. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.48 (d, *J*=7.4 Hz, 1H, H-6), 7.32–7.24 (br s, 2H exchangeable, NH$_2$), 5.85–5.73 (m, 4H, H-5, H-1′, OH), 4.63 (dd, *J*=3.4, 5.3 Hz, 1H, H-3′), 4.22 (m, 1H, H-2′), 4.14–4.04 (m, 5H, H-4′, O*CH*$_2$CH$_3$), 1.30–1.25 (t, *J*=7.1 Hz, 6H, OCH$_2$*CH*$_3$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.6 (C-4), 155.0 (C-2), 141.0 (C-6), 97.8, 97.1 (C-5′, d, *J*=48.3 Hz), 94.2 (C-5), 91.0 (C-1′), 78.6, 75.0 (C-6′, d, *J*=287.6 Hz), 74.6 (C-2′), 73.2 (C-3′), 72.0, 71.9 (C-4′, d, *J*=4.1 Hz), 63.2, 63.1 (O*CH*$_2$CH$_3$), 15.9, 15.8 (OCH$_2$*CH*$_3$). ^{31}P NMR (100 MHz, DMSO-d_6) δ −8.36. MS ESI>0 *m*/*z*, 374 (M+H)$^+$, 396 (M+Na)$^+$; ESI<0 *m*/*z* 372 (M−H)$^-$. HRMS calcd for $C_{14}H_{21}N_3O_7P$: 374.1117; found: 374.1118. UV λ_{max}=271 nm (ε_{max}=10,900), λ_{min}=232 nm (ε_{min}=7900) (EtOH 95). $[\alpha]_D^{20}$ +46.9 (*c* 0.97, MeOH). Anal. Calcd for $C_{14}H_{20}N_3O_7P$: C, 45.04. Found: C, 44.98.

5.4.6. *1-(5′,6′-Dideoxy-6′-diethylphosphono-β-D-ribo-5′-hexynofuranosyl)adenine,* ***14c***

Column chromatography of the crude materials on reverse phase (H$_2$O/MeOH, 0–100%) gave the titled compound as a yellow solid (194 mg, 59%) after freeze-drying.

Derivative **14c** (36 mg, 17%) could also be prepared by treatment of **12c** (340 mg, 0.53 mmol) with a mixture of MeOH/water/triethylamine (5:1:1, v/v/v) for 2 h 30 min at room temperature.

R_f (EtOAc/MeOH, 7:3, v/v) 0.6. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.29, 8.16 (2s, 2H, H-2, H-8), 7.35 (br s, 2H exchangeable, NH$_2$), 5.96 (d, *J*=5.1 Hz, 1H, H-1′), 4.93 (dd, *J*=4.9 Hz, 1H, H-2′), 4.77 (dd, *J*=3.9 Hz, 1H, H-4′), 4.58 (dd, *J*=4.5 Hz, 1H, H-3′), 4.13–4.02 (m, 4H, O*CH*$_2$CH$_3$), 1.29–1.24 (m, 6H, OCH$_2$*CH*$_3$). ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.1, 149.3 (Cq), 152.7, 139.7 (C-2, C-8), 119.2 (C-4), 97.5, 96.9 (C-5′, d, *J*=48.3 Hz), 88.0 (C-1′), 78.7 (C-6′), 74.9 (C-3′), 72.7 (C-2′), 72.6 (C-4′, d, *J*=4.5 Hz), 63.0 (O*CH*$_2$CH$_3$), 15.8 (OCH$_2$*CH*$_3$). ^{31}P NMR (100 MHz, DMSO-d_6) δ −8.27. MS ESI>0 *m*/*z* 398 (M+H)$^+$; ESI<0 *m*/*z* 510 (M+TFA)$^-$. HRMS calcd for $C_{15}H_{21}N_5O_6P$: 398.1229; found: 398.1239. UV λ_{max}=259 nm (ε_{max}=13,300), λ_{min}=228 nm (ε_{min}=6200) (EtOH 95). $[\alpha]_D^{20}$ +27.4 (*c* 0.95, MeOH). Anal. Calcd for $C_{15}H_{20}N_5O_6P\cdot H_2O$: C, 43.38; H, 6.34; N, 16.86. Found: C, 43.86; H, 6.28; N, 16.58.

5.5. Standard procedure for removal of basolabile protecting groups from 1,1-dibromo-1-alkene nucleosides, 15a–c

The per-acylated nucleoside (**11a**–**c**) was dissolved in anhydrous methanol (25 mL/mmol), then sodium methanolate (4 equiv) was added and the mixture was stirred at room temperature until completion of the reaction was indicated by TLC. The reaction was quenched by the addition of DOWEX 50WX2 under H$^+$ form, the resin was filtered off and the filtrate was concentrated under reduce pressure. Crude material was used with out further purification.

5.5.1. *1-(6′,6′-Dibromo-5′,6′-dideoxy-β-D-ribo-5′-hexenofuranosyl)uracil,* ***15a***

Derivative **15a** was obtained as white foam (99 mg, 90%). R_f (EtOAc) 0.3. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.44 (br s, 1H exchangeable, NH), 7.77 (d, *J*=8.1 Hz, 1H, H-6), 7.06 (d, *J*=8.8 Hz, 1H, H-5′), 5.82 (d, *J*=5.4 Hz, 1H, H-1′), 5.71 (d, 1H, H-5), 5.59 (m, 2H, OH), 4.46 (dd, *J*=4.2, 8.8 Hz, 1H, H-4′), 4.24 (m, 1H, H-2′), 4.02 (m, 1H, H-3′). ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.0 (C-4), 150.6 (C-2), 141.3 (C-6), 136.7 (C-5′), 102.0 (C-5), 93.5 (C-6′), 88.7 (C-1′), 83.3 (C-4′), 73.1 (C-3′), 72.4 (C-2′). MS ESI<0 *m*/*z* 395, 397, 399 (M−H)$^-$. Relative intensity 1:2:1. HRMS calcd for $C_{10}H_9Br_2N_2O_5$: 394.8878; found: 394.8875. UV λ_{max}=260 nm (ε_{max}=10,300), λ_{min}=233 nm (ε_{min}=3300) (EtOH 95). $[\alpha]_D^{20}$ +30.6 (*c* 0.98, MeOH).

5.5.2. *1-(6′,6′-Dibromo-5′,6′-dideoxy-β-D-ribo-5′-hexenofuranosyl)cytosine,* ***15b***

Derivative **15b** was obtained as light yellow foam (385 mg, 91%). R_f (EtOAc) 0.1. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.67 (d, *J*=7.5 Hz, 1H,

H-6), 7.27 (br s, 1H exchangeable, NH_2), 7.04 (d, J=8.7 Hz, 1H, H-5′), 5.81 (m, 2H, H-1′, H-5), 5.50 (br s, 2H, OH), 4.45 (dd, J=5.4, 8.7 Hz, 1H, H-4′), 4.13 (dd, J=4.6 Hz, 1H, H-2′), 4.00 (dd, J=5.2 Hz, 1H, H-3′). ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.6 (C-4), 155.1 (C-2), 142.0 (C-6), 137.0 (C-5′), 94.2 (C-6′), 93.4, 90.5 (C-5, C-1′), 82.6 (C-4′), 73.3, 73.1 (C-3′, C-2′). MS ESI>0 m/z 396, 398, 400 $(M+H)^+$. Relative intensity 1:2:1. ESI<0 m/z 394, 396, 398 $(M-H)^-$. Relative intensity 1:2:1. HRMS calcd for $C_{10}H_{12}Br_2N_3O_4$: 395.9195; found: 395.9203. UV λ_{max}=271 nm (ε_{max}=11,500), λ_{min}=235 nm (ε_{min}=8600) (EtOH 95). $[\alpha]_D^{20}$ +55.3 (c 1.01, MeOH).

5.5.3. 9-(6′,6′-Dibromo-5′,6′-dideoxy-β-D-ribo-5′-hexenofuranosyl)adenine, **15c**

Derivative **15c** was obtained as light yellow foam (121 mg, 96%). R_f (EtOAc/MeOH, 8:2, v/v) 0.4. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.39, 8.16 (2s, 2H, H-2, H-8), 7.34 (br s, 1H exchangeable, NH_2), 7.16 (d, J=8.6 Hz, 1H, H-5′), 5.92 (d, J=5.7 Hz, 1H, H-1′), 4.78 (t, J=5.2 Hz, 1H, H-2′), 4.52 (dd, J=3.5, 8.6 Hz, 1H, H-4′), 4.22 (t, J=4.1 Hz, 1H, H-3′). ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.1 (C-4), 152.5, 140.1 (C-2, C-8), 149.2 (C-6), 137.2 (C-5′), 119.3 (C-6′), 92.6 (C-5), 87.6 (C-1′), 84.0 (C-4′), 73.7 (C-3′), 72.8 (C-2′). MS ESI>0 m/z 420, 422, 424 $(M+H)^+$. Relative intensity 1:2:1. ESI<0 m/z 418, 420, 422 $(M-H)^-$. Relative intensity 1:2:1. HRMS calcd for $C_{11}H_{12}Br_2N_5O_3$: 419.9307; found: 419.9308. UV λ_{max}=260 nm (ε_{max}=15,400), λ_{min}=231 nm (ε_{min}=4300) (EtOH 95). $[\alpha]_D^{20}$ +5.06 (c 0.99, MeOH).

5.6. Standard procedure for removal of phosphonate protecting groups, 16b,c

The nucleoside diethylphosphonate derivative was dissolved in anhydrous DMF (20 mL/mmol), then TMSBr (15 equiv) was added at 0 °C and the mixture was stirred at room temperature until completion of the reaction was indicated by TLC. The reaction mixture was neutralized with aqueous TEAB 1 M and concentrated under high vacuum.

5.6.1. 1-(5′,6′-Dideoxy-6′-phosphono-β-D-ribo-5′-hexynofuranosyl)cytosine (disodium salt), **16b**

Column chromatography of the crude materials on reverse phase (H_2O) gave the corresponding phosphonic acid and the titled compound was obtained as a white solid (72 mg, 72%) after ion exchange on DOWEX Na^+, dialysis with cellulose membrane and freeze-drying.

R_f (*i*PrOH/NH_4OH 30%/H_2O, 7:1:2, v/v/v) 0.08. ^{1}H NMR (300 MHz, D_2O) δ 7.79 (d, J=7.15 Hz, 1H, H-6), 6.10 (d, J=7.27 Hz, 1H, H-5), 5.96 (d, J=3.9 Hz, 1H, H-1′), 4.74 (dd, J=2.6 Hz, H-4′), 4.44 (d, J=4.0 Hz, H-2′), 4.35 (d, J=3.8 Hz, H-3′). ^{13}C NMR (75 MHz, D_2O) δ 165.8 (C-4), 157.3 (C-2), 141.7 (C-6), 96.9 (C-5), 90.3 (C-1′), 91.0–88.0 (C6′, d, J=230.2 Hz), 86.7–86.2 (C-5′, d, J=39.5 Hz), 74.9 (C-2′), 74.5 (C-3′), 73.8 (C-4′, d, J=3.3 Hz). ^{31}P NMR (121 MHz, D_2O) δ −10.2. MS ESI<0 m/z 316 $(M-H)^-$. HRMS calcd for $C_{10}H_{11}N_3O_7P$: 316.0335; found: 316.0327. UV λ_{max}=269 nm (ε_{max}=10,700), λ_{min}=226 nm (ε_{min}=6500) (H_2O). $[\alpha]_D^{20}$ +17.77 (c 1.01, H_2O).

5.6.2. 1-(5′,6′-Dideoxy-6′-phosphono-β-D-ribo-5′-hexynofuranosyl)adenine (disodium salt), **16c**

Column chromatography of the crude materials on reverse phase (H_2O) gave the corresponding phosphonic acid. The titled compound was obtained after HPLC purification, ion exchange on DOWEX Na^+ and freeze-drying as a white solid (5 mg, 3.5%).

R_f (*i*PrOH/NH_4OH 30%/H_2O, 7:1:2, v/v/v) 0.13. ^{1}H NMR (300 MHz, D_2O) δ 8.47, 8.19 (2s, 2H, H-2, H-8) 6.10 (d, J=6.02 Hz, 1H, H-1′), 4.98 (dd, J=5.23 Hz, 1H, H-2′), 4.84 (d, J=2.71 Hz, 1H, H-4′), 4.53 (d, J=3.59 Hz, 1H, H-3′). ^{13}C NMR (75 MHz, D_2O) δ 152.9, 140.2 (C-2, C-8), 86.9 (C-1′), 74.9, 74.8 (C-2′, C-3′). ^{31}P NMR (121 MHz, D_2O) δ −10.0. SM ESI<0 m/z 340 $(M-H)^-$. HRMS calcd for $C_{11}H_{11}N_5O_6P$: 340.0447; found: 340.0473.

Acknowledgements

This work was supported by Association pour la Recherche contre le Cancer (ARC). M.M. and F.G. are grateful to the CNRS & Région Languedoc-Roussillon for their doctoral fellowships.

References and notes

1. Iorga, B.; Eymery, F.; Carmichael, D.; Savignac, P. *Eur. J. Org. Chem.* **2000**, 3103.
2. Lindlar, J.; Dubuis, R. *Org. Synth.* **1966**, *46*, 89.
3. Leclerclé, D.; Mothes, C.; Taran, F. *Synth. Commun.* **2007**, *37*, 1301.
4. Lera, M.; Hayes, C. J. *Org. Lett.* **2000**, *2*, 3873.
5. Chattha, M. S.; Aguiar, A. M. *J. Org. Chem.* **1971**, *36*, 2719.
6. Desai, N. B.; McKelvie, N.; Ramirez, F. *J. Am. Chem. Soc.* **1962**, *84*, 1745.
7. Corey, E.; Fusch, P. *Tetrahedron Lett.* **1972**, *13*, 3769.
8. Peyrottes, S.; Gallier, F.; Béjaud, J.; Périgaud, C. *Tetrahedron Lett.* **2006**, *47*, 7719.
9. Gallier, F.; Peyrottes, S.; Périgaud, C. *Eur. J. Org. Chem.* **2007**, 925.
10. Sharma, R. A.; Bobek, M. *J. Org. Chem.* **1978**, *43*, 367.
11. Hampton, A. *J. Am. Chem. Soc.* **1961**, *83*, 3640.
12. More, J. D.; Finney, N. *Org. Lett.* **2002**, *4*, 3001.
13. Kralikova, S.; Budesinsky, M.; Tomeckova, I.; Rosenberg, I. *Tetrahedron* **2006**, *62*, 9742.
14. Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873.
15. Thielges, S.; Meddah, E.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2004**, *45*, 907.
16. Hodge, P.; Khoshdel, E. *React. Polym.* **1985**, *3*, 143.
17. Rosowsky, A.; Lazarus, H.; Yamashita, A. *J. Med. Chem.* **1976**, *19*, 1265.
18. Lavaire, S.; Plantier-Royon, R.; Portella, C.; DeMonte, M.; Kirn, A.; Aubertin, A. M. *Nucleosides Nucleotides* **1998**, *17*, 2267.
19. Magnani, A.; Mikuriya, Y. *Carbohydr. Res.* **1973**, *28*, 158.
20. Vorbrüggen, H.; Krolokiewicz, K.; Bennua, B. *Chem. Ber.* **1981**, *114*, 1234.