EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201301543

Synthesis of Unnatural Phosphonosugar Analogues

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Keywords: Medicinal chemistry / Glycomimetics / Bioisosteres / Carbohydrates / Phosphorus heterocycles

The first synthesis of new cyclic phosphonates (phostones), analogues of pentafuranoses containing a phosphorus atom in place of the anomeric carbon in the deoxyribose and deoxyxylose series, is described. Two methods, of respectively six and seven steps, were developed in parallel, and each gave the racemic phosphonosugars in good yields. Compounds analogous to the alpha and beta anomers were isolated and fully characterized by NMR spectroscopy.

Introduction

The search for new bioisosteric groups that will be able to modulate the metabolic and/or the drug pharmacokinetic properties is a critical issue for innovation in drug discovery. Changes in pharmacological activity or bioavailability, or even adverse effects of a drug can result from minor changes of the original lead compound. Bioisosterism represents a fruitful approach that medicinal chemists can use to elicit biological activity.[1] Recent studies in our group demonstrated that the phosphinolactone group (O–P=O) can be considered to be a bioisostere of a hemiacetal functionality (O–C–OH).[2] This idea has been successfully used in the development of two families of cyclic phosphorus heterocycles with completely different biological activities (Figure 1). Considering oxazaphosphinane **1**, there is an analogy between the phosphinolactone and the lactol group of hydroxybupropion, and these two structures have a close correspondence in terms of both polarity and biological activity. When 1,4,2-oxazaphosphinane **1** was screened for biological activity in the forced-swimming test with mice, it was found firstly to have the ability to diffuse through the blood–brain barrier, and secondly to induce a biological response higher than the reference compound, racemic hydroxybupropion. This result highlights the fact that strategic replacement of a carbon atom by phosphorus could be really useful for enhancing the biological response, and more particularly in this case, for the treatment of depression and attention-deficit hyperactivity disorder (ADHD).[2a] Phostines **2**, specifically designed as a combination of glycopyranosides and *C*-arylglycosides represent a new family of glycomimetics designed to target CNS (central nervous system) cancer without affecting normal astrocytes. They showed the ability to induce cytotoxicity in C6 glial strain cells at micromolar concentrations.[2b]

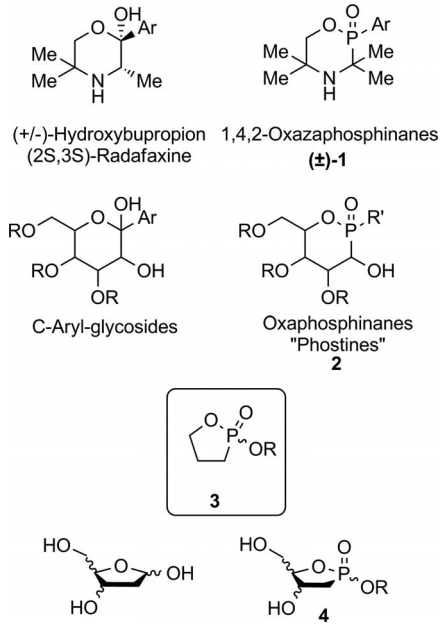

Figure 1. Analogy between the lactol and phosphinolactone groups, and phosphonate analogue **4** of 2-deoxy ribose or 2-deoxy xylose.

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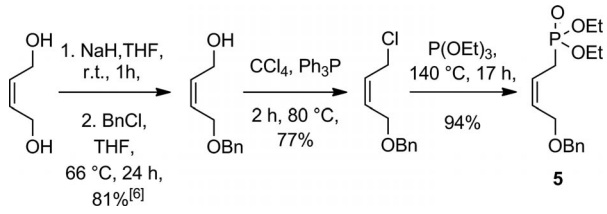
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301543

Phostones **3**, cyclic phosphonic acids based on a five-membered ring have gained considerable attention due to their diverse biological profiles. They have been considered as candidate inhibitors for purine nucleotide phosphorylase (PNP) and also for various isomerase enzymes.[3]

In this paper, we describe the synthesis of new unnatural phospha-analogues **4** of 2-deoxy ribose and the 2-deoxy xylose that are unknown to date.[4] Recently, modified pentoses have been shown to act as substrates of aldolases.[5]

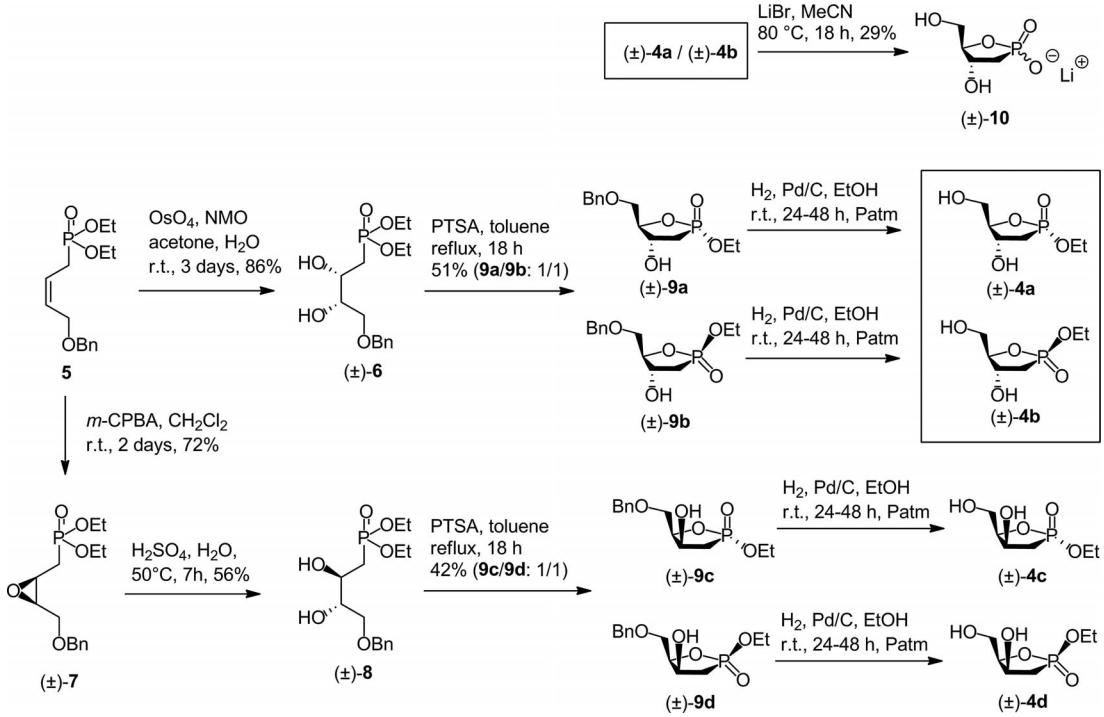


Scheme 1. Synthesis of diethyl (*Z*)-4-benzyloxy-but-2-enylphosphonate (**5**).

Results and Discussion

All the target structures were synthesized starting from diethyl (*Z*)-4-benzyloxy-but-2-enylphosphonate (**5**). The synthesis of **5** itself (Scheme 1) began with the mono-benzylation of *cis*-buten-1,4-diol with sodium hydride and benzyl chloride, which occurred in 81% yield.[6] In an Appel reaction using triphenylphosphine and carbon tetrachloride,[7] the hydroxy compound was converted in 77% yield into the alkyl chloride, which was used as an electrophile in the next step. The synthesis of the P–C linkage using a Michaelis–Arbuzov reaction was carried out without solvent at 140 °C for 17 h with 2 equiv. of triethyl phosphite, and the desired phosphonate (i.e., **5**) was formed in high yield (94%).[8]

Then, the first goal was to develop the appropriate conditions for the phospha-lactonization. The *like* diol (i.e., **6**) was obtained, using conditions described in the literature, in 86% yield from **5** by the reaction of *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant and osmium tetraoxide (9% solution in water; Scheme 2).[9] From alkene **5**, *unlike* diol **8** was also obtained by a two-step sequence involving epoxidation with *m*-chloroperbenzoic acid in 72% yield, followed by the epoxide-ring opening under aqueous acidic conditions in 56% yield.[10] This ring opening reaction was completely stereospecific, which can be explained by protonation of the epoxide without formation of a carbocation. Then, under acidic conditions [4-toluenesulfonic acid (PTSA) in toluene], open-chain intermediates **6** or **8** cyclized in an intramolecular transesterification process to give mixtures of diastereomers **9a** and **9b** (1:1) or diastereomers **9c** and **9d** (1:1), all as racemates, in 51 and 42% yields, respectively. Purification of the mixtures **9a/9b** and **9c/9d** by silica gel column chromatography allowed the separation of each diastereomer of phospha deoxyribose (i.e., **9a** and **9b**) and phospha deoxyxylose (i.e., **9c** and **9d**). Deprotection of the benzyl group of each diastereomer of **9** by catalytic hydrogenolysis (H_2/Pd/C) gave the free 5′-hydroxy analogues (i.e., **4a**–**4d**). Finally, the lithium salt of the free acid (i.e., **10**) was obtained by heating the diastereomeric mixture of **4a** and **4b** in acetonitrile with anhydrous lithium bromide. The formation of only one diastereomer confirmed that **4a** and **4b** were epimeric only at the phosphorus atom.



Scheme 2. Synthesis of the unnatural phospha-sugar analogues **4a**–**4d**.

The relative configurations of the carbon chiral centres in compounds **9a**–**9d** were determined by evaluating proton–proton coupling constants and by NOE spectroscopy (Figure 2).

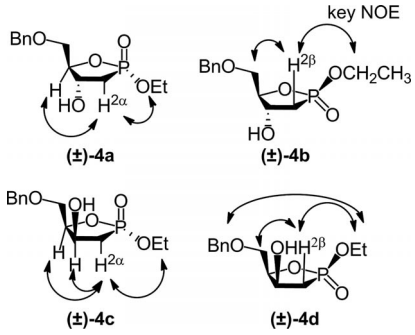


Figure 2. Key NOE correlations for **4a**–**4d**.

For compound **9a**, NOEs were observed between 2α-H and OEt and between 2α-H and 4-H, which suggests that the ethoxy and benzyloxymethyl groups were on opposite faces of the ring. In contrast, for diastereomer **9b**, NOEs were observed between 2β-H, OEt, and the benzyloxymethyl substituents, consistent with a *cis* relationship. Furthermore, the difference between the NOEs observed for **9c** and **9d** and those observed for diastereomers **9a** and **9b** clearly demonstrated that **9c** and **9d** belonged to the deoxyxylose series.

Conclusions

In conclusion, a six–seven-step synthesis in the racemic series was developed to give new unnatural analogues of deoxyribo- and deoxyxylose in good yields. Further work directed towards the synthesis of nucleoside-bearing unnatural sugar analogues and their biological applications is currently underway, and the results will be reported in due course.

Experimental Section

General Remarks: Unless otherwise stated, commercially available chemicals were used as received without further purification. Before use, solvents were heated at reflux over the appropriate drying agent and distilled under a nitrogen atmosphere. All moisture sensitive reactions were performed in flame-dried septum-sealed glassware under a nitrogen atmosphere. ^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded with a Bruker DRX 400 MHz spectrometer in [D_6]DMSO, $CDCl_3$, or D_2O as solvent, operating at frequencies of 400.13 MHz (^{1}H), 100.62 MHz (^{13}C), and 161.97 MHz (^{31}P). The ^{31}P NMR spectra are decoupled. HRMS measurements were carried out with a Micromass Q-TOF instrument (ESI^+ ionization mode).

(*Z*)-4-(Benzyloxy)but-2-en-1-ol:[6] At 0 °C under a nitrogen atmosphere, *cis*-butene-1,4-diol (30 g, 340 mmol) was carefully added to a suspension of sodium hydride (4.8 g, 120 mmol) in THF (140 mL). The mixture was stirred at room temperature for 1 h, then benzyl chloride (14.4 mg, 110 mmol) was added, and the resulting mixture was stirred overnight at 75 °C. The reaction was quenched at ambient temperature with NH_4Cl (saturated aq.), and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2 70–200 μm; heptane/ethyl acetate, 100:0 to 80:20) to give the monoprotected diol (14 g, 81%) as a colourless oil. b.p. 110–112 °C/0.07 Torr. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 3.01 (s, 1 H), 4.08–4.12 (m, 2 H), 4.13–4.17 (m, 2 H), 4.54 (s, 2 H), 5.70–5.77 (m, 1 H), 5.78–5.86 (m, 1 H), 7.27–7.44 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 58.55, 65.65, 72.49, 127.86, 127.91, 128.02, 128.51, 132.52, 137.87 ppm.

(*Z*)-[(4-Chlorobut-2-enyloxy)methyl]benzene:[11] Under nitrogen, triphenylphosphine (19.60 g, 75 mmol, 1.2 equiv.) was added to a solution of (*Z*)-4-(benzyloxy)but-2-en-1-ol (11.48 g, 64 mmol, 1.0 equiv.) in CCl_4 (46 mL). The mixture was stirred at 80 °C for 2 h, then pentane (60 mL) was added at ambient temperature, and part of the triphenylphosphine oxide was removed by filtration. The combined organic phases were dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2 35–70 μm; heptane/CH_2Cl_2, 100:0 to 20:80) to give the chloro-compound (9.69 g, 77%) as a colourless oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 4.12–4.16 (m, 2 H), 4.17–4.20 (m, 2 H), 4.58 (s, 2 H), 5.80–5.92 (m, 2 H), 7.31–7.49 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 59.25, 65.18, 72.48, 127.84, 127.86, 128.49, 128.52, 130.82, 137.99 ppm.

Diethyl (*Z*)-4-(Benzyloxy)but-2-enylphosphonate (5): In a round-bottomed flask equipped with a Dean–Stark trap and a condenser, under nitrogen, triethyl phosphite (14.2 mL, 83 mmol, 2.0 equiv.) and (*Z*)-[(4-chlorobut-2-enyloxy)methyl]benzene (8.13 g, 41 mmol, 1.0 equiv.) were mixed, and the mixture was heated at 140 °C for 17 h. The mixture was then concentrated, and the residue was purified by flash chromatography (SiO_2 70–200 μm; heptane/EtOAc, 100:0 to 50:80) to give phosphonate **5** (11.67 g, 94%) as a colourless oil. ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 27.04 ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.22 (t, $^{3}J_{H,H}$ = 7.1 Hz, 6 H), 2.55 (dd, $^{2}J_{P,H}$ = 22.4, $^{3}J_{H,H}$ = 8.0 Hz, 2 H), 3.88–4.11 (m, 6 H), 4.44 (s, 2 H), 5.46–5.64 (m, 1 H), 5.67–5.84 (m, 1 H), 7.12–7.32 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.42 (d, $^{3}J_{C,P}$ = 6.0 Hz), 26.33 (d, $^{1}J_{C,P}$ = 140.2 Hz), 61.92 (d, $^{2}J_{C,P}$ = 6.7 Hz), 65.61 (d, $^{4}J_{C,P}$ = 2.3 Hz), 72.38, 121.47 (d, $^{2}J_{C,P}$ = 11.3 Hz), 127.67, 127.77, 128.39, 130.81 (d, $^{3}J_{C,P}$ = 13.7 Hz), 138.09 ppm. HRMS (ESI): calcd. for $C_{15}H_{24}O_4P$ 299.1412; found 299.1419.

(*like*)-(±) Diethyl (2*R*,3*R*)-4-(Benzyloxy)-2,3-dihydroxybutylphosphonate (6): At room temperature under nitrogen, phosphonate **5** (3.0 g, 10 mmol), *N*-methylmorpholine *N*-oxide (2.7 g, 20 mmol), and osmium tetraoxide (25 mg, 0.01 mmol) were sequentially added to a mixture of acetone and water (8:2; 315 mL). After 3 d, the reaction mixture was diluted with CH_2Cl_2, and the resulting mixture was washed with Na_2SO_3 (10% aq.) and brine. The organic phase was dried with $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (SiO_2 35–70 μm; CH_2Cl_2/EtOAc, 100:0 to 0:100) to give dihydroxy butylphosphonate **6** (2.59 g, 86%) as a colourless oil. ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 31.27 ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.25 (t, $^{3}J_{H,H}$ = 7.1 Hz, 6 H), 1.91 (ddd, $^{2}J_{P,H}$ = 15.8, $^{2}J_{H,H}$ = 15.5, $^{3}J_{H,H}$ = 9.5 Hz, 1 H), 2.12 (ddd, $^{2}J_{P,H}$ = 19.2, $^{2}J_{H,H}$ = 15.5, $^{3}J_{H,H}$ = 2.8 Hz, 1 H), 3.04 (d, $^{3}J_{H,H}$ = 4.9 Hz, 1 H), 3.54 (dd, $^{2}J_{H,H}$ = 9.7, $^{3}J_{H,H}$ = 6.1 Hz, 1 H), 3.58 (dd, $^{2}J_{H,H}$ = 9.7, $^{3}J_{H,H}$ = 4.2 Hz, 1 H), 3.64–3.71 (m, 1 H), 3.87 (d, $^{3}J_{H,H}$ = 3.6 Hz, 1 H), 3.89–3.98 (m, 1 H), 3.98–4.15 (m, 4 H), 4.47 and 4.49 (2 d, $^{2}J_{H,H}$ = –11.9 Hz, 2 H), 6.96–7.57 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.38 and 16.40 (2 d, $^{3}J_{C,P}$ = 6.1 Hz), 29.13 (d, $^{1}J_{C,P}$ = 139.8 Hz), 62.03 and 62.05 (2 d, $^{2}J_{C,P}$ = 6.5 Hz), 67.81 (d, $^{2}J_{C,P}$ = 5.4 Hz), 71.00, 72.91 (d, $^{3}J_{C,P}$ = 14.9 Hz), 73.50, 127.80, 127.85, 128.47, 137.79 ppm. HRMS (ESI): calcd. for $C_{15}H_{26}O_6P$ 333.1467; found 333.1461.

(±)-Diethyl (2*S*,3*S*)-[4-(Benzyloxymethyl)oxiran-2-yl]methylphosphonate (7): Compound **5** (2.0 g, 6.7 mmol) was dissolved in CH_2Cl_2 (10 mL) in a Pyrex tube with a screw cap. A solution of dry *m*-CPBA (3.31 g, 15 mmol) in CH_2Cl_2 (10 mL) in the presence of $MgSO_4$ was added. The reaction mixture was stirred at room temperature for 40 h, then it was washed with Na_2CO_3 (saturated aq.; 12 mL) and water. The organic phase was dried with $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (SiO_2 35–70 μm; CH_2Cl_2/EtOAc, 100:0 to 50:50) to gve compound **7** (1.51 g, 72%) as a colourless oil. ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 26.63 ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.25 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H), 1.91 (ddd, $^3J_{H,H}$ = 6.4, $^2J_{H,H}$ = 15.4, $^2J_{P,H}$ = 19.8 Hz, 1 H), 2.07 (ddd, $^2J_{P,H}$ = 19.2, $^2J_{H,H}$ = 15.4, $^3J_{H,H}$ = 6.2 Hz, 1 H), 3.12–3.27 (m, 2 H), 3.44 (dd, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 6.3 Hz, 1 H), 3.74 (dd, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 3.8 Hz, 1 H), 3.97–4.15 (m, 4 H), 4.47 and 4.56 ($^2J_{H,H}$ = 11.9 Hz, 2 H), 7.19–7.30 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.43 (d, $^3J_{C,P}$ = 5.9 Hz), 26.19 (d, $^1J_{C,P}$ = 139.8 Hz), 50.36 (d, $^2J_{C,P}$ = 1.5 Hz), 55.14 (d, $^3J_{C,P}$ = 7.3 Hz), 62.02 (d, $^2J_{C,P}$ = 5.9 Hz), 62.06 (d, $^2J_{C,P}$ = 6.6 Hz), 68.00, 73.38, 127.30, 127.87, 128.47, 137.67 ppm. HRMS (ESI): calcd. for $C_{15}H_{23}O_5P$ 315.1361; found 315.1350.

(*unlike*)-(±)-Diethyl (2*S*,3*R*)-4-(Benzyloxy)-2,3-dihydroxybutylphosphonate (8): H_2SO_4 (1 M aq.; 1 mL) was added to a solution of **7** (1.51 g, 4.8 mmol) in THF (30 mL). The mixture was stirred at 50 °C for 7 h. After the starting material had been completely consumed (^{31}P NMR), NaOH (1 M aq.; 1.8 mL) was added. The solution was concentrated to dryness, and CH_2Cl_2 was added to the residue. The mixture was filtered, then the filtrate was dried with $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (SiO_2 35–70 μm; CH_2Cl_2/EtOAc, 100:0 to 50:50) to give compound **8** (0.93 g, 58%) as a colourless oil. ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 30.47 ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.33 (t, $^3J_{H,H}$ = 7.1 Hz, 6 H), 1.97 (ddd, $^2J_{P,H}$ = 19.4, $^2J_{H,H}$ = 15.3, $^3J_{H,H}$ = 3.9 Hz, 1 H), 2.04 (ddd, $^2J_{P,H}$ = 16.5, $^2J_{H,H}$ = 15.3, $^3J_{H,H}$ = 9.0 Hz, 1 H), 3.18 (d, $^3J_{H,H}$ = 6.3 Hz, 1 H), 3.52 (dd, $^2J_{H,H}$ = 9.6, $^3J_{H,H}$ = 5.8 Hz, 1 H), 3.55 (dd, $^2J_{H,H}$ = 9.6, $^3J_{H,H}$ = 4.5 Hz, 1 H), 3.61–3.68 (m, 1 H), 3.74 (d, $^3J_{H,H}$ = 4.3 Hz, 1 H), 3.97–4.15 (m, 5 H), 4.47 and 4.49 (dd, $^2J_{H,H}$ = 11.9 Hz, 2 H), 7.36–7.66 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.36 and 16.42 (2 d, $^3J_{C,P}$ = 6.2 Hz), 30.12 (d, $^1J_{C,P}$ = 139.7 Hz), 61.94 and 62.02 (2 d, $^2J_{C,P}$ = 6.3 Hz), 67.13 (d, $^2J_{C,P}$ = 4.4 Hz), 71.70, 72.61 (d, $^3J_{C,P}$ = 14.4 Hz), 73.55, 127.77, 127.80, 128.44, 137.83 ppm. HRMS (ESI): calcd. for $C_{16}H_{26}O_6P$ 333.1467; found 333.1464.

(*like*)-(±)-(4*R*,5*R*)-5-Benzyloxymethyl-2-ethoxy-4-hydroxy-2-oxo-2-phosphatetrahydrofurans (9a–9b): Under nitrogen, PTSA (149 mg, 0.9 mmol) was added to a solution of **6** (1.21 g, 3.6 mmol) in toluene (49 mL). The mixture was heated at reflux for 18 h, then it was concentrated to dryness. The residue was purified by flash chromatography (SiO_2 35–70 μm; EtOAc/EtOH, 100:0 to 95:5) to give diastereomer **9a** (±)-P(*R*),^{3}C(*R*),^{4}C(*R*) (0.10 g, 10%), diastereomer **9b** (±)-P(*S*),^{3}C(*R*),^{4}C(*R*) (0.21 g, 21%), and a mixture of **9a** and **9b** (0.22 g, 21%). HRMS (ESI): calcd. for the mixture (**9a** and **9b**) $C_{13}H_{20}O_5P$ 287.1048; found 287.1055.

Data for **9a**: P(*R*),^{3}C(*R*),^{4}C(*R*). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 44.47 ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.34 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.94 (ddd, $^2J_{P,H}$ = $^2J_{H,H}$ = 15.2, $^3J_{H,H}$ = 5.9 Hz, 1 H), 2.35 (ddd, $^2J_{H,H}$ = 15.2, $^2J_{P,H}$ = 13.8, $^3J_{H,H}$ = 7.4 Hz, 1 H), 3.68 (d, $^3J_{H,H}$ = 4.6 Hz, 2 H), 4.01 (d, $^3J_{H,H}$ = 4.6 Hz, 1 H), 4.11–4.30 (m, 3 H), 4.35–4.47 (m, 1 H), 4.54 and 4.60 (2 d, $^2J_{H,H}$ = –12.0 Hz, 2 H), 7.23–7.44 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.46 (d, $^3J_{C,P}$ = 5.8 Hz), 28.98 (d, $^1J_{C,P}$ = 120.1 Hz), 62.72 (d, $^2J_{C,P}$ = 6.7 Hz), 69.97 (d, $^3J_{C,P}$ = 7.3 Hz), 70.11 (d, $^2J_{C,P}$ = 6.1 Hz), 73.71, 83.85 (d, $^2J_{C,P}$ = 6.3 Hz), 127.76, 127.90, 128.51, 137.55 ppm.

Data for **9b**: P(*S*),^{3}C(*R*),^{4}C(*R*). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 44.36 ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.19 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 2.03 (ddd, $^2J_{P,H}$ = 15.4, $^2J_{H,H}$ = 15.1, $^3J_{H,H}$ = 6.8 Hz, 1 H), 2.24 (ddd, $^2J_{H,H}$ = 15.1, $^2J_{P,H}$ = 13.3, $^3J_{H,H}$ = 6.8 Hz, 1 H), 3.54–3.70 (m, 2 H), 3.92–4.13 (m, 2 H), 4.25–4.33 (m, 1 H), 4.33–4.41 (m, 1 H), 4.47 and 4.49 ($^2J_{H,H}$ = 12.0 Hz, 2 H), 7.13–7.32 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.37 (d, $^3J_{C,P}$ = 5.9 Hz), 29.21 (d, $^1J_{C,P}$ = 119.0 Hz), 62.81 (d, $^2J_{C,P}$ = 6.6 Hz), 69.54 (d, $^3J_{C,P}$ = 7.9 Hz), 69.72 (d, $^2J_{C,P}$ = 4.3 Hz), 73.53, 84.13 (d, $^2J_{C,P}$ = 5.8 Hz), 127.62, 127.82, 128.43, 137.69 ppm.

(*unlike*)-(±)-(4*S*,5*R*)-5-Benzyloxymethyl-2-ethoxy-4-hydroxy-2-oxo-2-phosphatetrahydrofurans (9c–9d): Under nitrogen, PTSA (114 mg, 0.6 mmol, 0.2 equiv.) was added to a solution of **8** (0.93 g, 2.8 mmol, 1 equiv.) in toluene (38 mL). The reaction mixture was stirred at reflux for 21 h, and then it was concentrated to dryness. The residue was purified by flash chromatography (SiO_2 35–70 μm; EtOAc/EtOH, 100:0 to 95:5) to give compound **9c** (±)-P(*S*),^{3}C(*S*),^{4}C(*R*) (0.25 g, 31%) and compound **9d** (±)-P(*R*),^{3}C(*S*),^{4}C(*R*) (0.09 g, 11%). HRMS (ESI): calcd. for the mixture (**9c** and **9d**) $C_{13}H_{20}O_5P$ $[M + H]^+$ 287.1048; found 287.1053.

Data for **9c**: P(*S*),^{3}C(*S*),^{4}C(*R*). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 46.02 ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.24 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 2.00 (ddd, $^2J_{H,H}$ = 15.6, $^2J_{P,H}$ = 11.7, $^3J_{H,H}$ = 2.7 Hz, 1 H), 2.08 (ddd, $^2J_{P,H}$ = 15.8, $^2J_{H,H}$ = 15.6, $^3J_{H,H}$ = 5.9 Hz, 1 H), 3.76 (d, $^3J_{H,H}$ = 5.2 Hz, 2 H), 3.84 (s, 1 H), 4.10 and 4.12 (2 dq, $^3J_{P,H}$ = 9.3, $^3J_{H,H}$ = 3.7 Hz, 2 H), 4.35 (tt, $^3J_{H,H}$ = 5.2, $^3J_{H,H}$ = $^3J_{P,H}$ = 3.7 Hz, 1 H), 4.50 and 4.52 (AB system, $^2J_{H,H}$ = 11.9 Hz, 2 H), 4.46–4.58 (m, 1 H), 7.14–7.32 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.43 (d, $^3J_{C,P}$ = 5.7 Hz), 29.87 (d, $^1J_{C,P}$ = 119.7 Hz), 63.34 (d, $^2J_{C,P}$ = 6.6 Hz), 68.74 (d, $^3J_{C,P}$ = 8.2 Hz), 69.74 (d, $^2J_{C,P}$ = 2.0 Hz), 73.71, 80.94 (d, $^2J_{C,P}$ = 9.3 Hz), 127.78, 128.00, 128.53, 137.40 ppm.

Data for **9d**: P(*R*),^{3}C(*S*),^{4}C(*R*). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 45.53 ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.26 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 2.06 (ddd, $^2J_{P,H}$ = 15.3, $^2J_{H,H}$ = 15.3, $^3J_{H,H}$ = 6.0 Hz, 1 H), 2.13 (ddd, $^2J_{H,H}$ = 15.3, $^2J_{P,H}$ = 12.7, $^3J_{H,H}$ = 3.4 Hz, 1 H), 3.79 (ddd, $^2J_{H,H}$ = 10.8, $^3J_{H,H}$ = 4.5, $^4J_{P,H}$ = 0.8 Hz, 1 H), 3.81 (ddd, $^2J_{H,H}$ = 10.8, $^3J_{H,H}$ = 5.4, $^4J_{P,H}$ = 0.2 Hz, 1 H), 4.04–4.15 (m, 2 H), 4.23 (dddd, $^3J_{H,H}$ = 5.4, $^3J_{H,H}$ = 4.5, $^3J_{H,H}$ = 3.8, $^3J_{P,H}$ = 2.8 Hz, 1 H), 4.50 (ddd, $^3J_{P,H}$ = 24.7, $^3J_{H,H}$ = 6.0, $^3J_{H,H}$ = 3.4 Hz, 1 H), 4.54 (s, 2 H), 7.20–7.37 (m, 5 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.43 (d, $^3J_{C,P}$ = 5.7 Hz), 29.87 (d, $^1J_{C,P}$ = 119.7 Hz), 63.34 (d, $^2J_{C,P}$ = 6.6 Hz), 68.74 (d, $^3J_{C,P}$ = 8.2 Hz), 69.74 (d, $^2J_{C,P}$ = 2.0 Hz), 73.71, 80.94 (d, $^2J_{C,P}$ = 9.3 Hz), 127.78, 128.00, 128.53, 137.40 ppm.

General Procedure for Deprotection of the Benzyl Group by Catalytic Hydrogenation: In a Schlenk tube, Pd (10% on C; 10–20 wt-%) was added to a solution of **9a**–**9d** (1.0 equiv.) in ethanol (0.5–0.6 mmol/mL). The mixture was degassed twice under vacuum, refilling each time with hydrogen. The reaction mixture was stirred at room temperature for 24–48 h. Then the mixture was filtered, and the filtrate was concentrated to dryness.

(±)-2-Ethoxy-4-hydroxy-5-hydroxymethyl-2-oxo-2-phosphatetrahydrofuran (4a): From **9a** (57 mg, 0.20 mmol) with Pd (10% on C; 20 wt-%) in ethanol (1 mL) for 48 h, **4a** (28 mg, 72%) was obtained as a colourless oil. P(*R*),^{3}C(*R*),^{4}C(*R*). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 44.34 ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.27 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 2.03 (ddd, $^2J_{P,H}$ = 16.4, $^2J_{H,H}$ = 15.1, $^3J_{H,H}$

= 7.4 Hz, 1 H), 2.29 (ddd, $^2J_{H,H}$ = 15.1, $^2J_{P,H}$ = 12.7, $^3J_{H,H}$ = 7.1 Hz, 1 H), 3.67 (ddd, $^2J_{H,H}$ = 12.4, $^3J_{H,H}$ = 5.0, $^4J_{P,H}$ = 0.9 Hz, 1 H), 3.77 (dd, $^2J_{H,H}$ = 12.4, $^3J_{H,H}$ = 3.8 Hz, 1 H), 4.09 (dq, $^3J_{P,H}$ = 8.9, $^3J_{H,H}$ = 7.1 Hz, 2 H), 4.23 (dddd, $^3J_{P,H}$ = 8.7, $^3J_{H,H}$ = 5.9, $^3J_{H,H}$ = 5.0, $^3J_{H,H}$ = 3.8 Hz, 1 H), 4.36 (dddd, $^3J_{P,H}$ = 11.6, $^3J_{H,H}$ = 7.4, $^3J_{H,H}$ = 7.1, $^3J_{H,H}$ = 5.9 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.44 (d, $^3J_{C,P}$ = 5.7 Hz), 29.21 (d, $^1J_{C,P}$ = 119.2 Hz), 62.20 (d, $^3J_{C,P}$ = 4.6 Hz), 63.16 (d, $^2J_{C,P}$ = 6.5 Hz), 68.91 (d, $^2J_{C,P}$ = 8.5 Hz), 85.69 (d, $^2J_{C,P}$ = 4.9 Hz) ppm. HRMS (ESI): calcd. for $C_6H_{14}O_5P$ 197.0579; found 197.0595.

(±)-2-Ethoxy-4-hydroxy-5-hydroxymethyl-2-oxo-2-phosphatetrahydrofuran (4b): From **9b** (140 mg, 0.49 mmol) with Pd (10% on C; 20 wt-%) in ethanol (1 mL) for 48 h, **4b** (75 mg, 78%) was obtained as a colourless oil. P(*S*),^{3}C(*R*),^{4}C(*R*). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 45.36 ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.29 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 1.92 (ddd, $^2J_{P,H}$ = 16.2, $^2J_{H,H}$ = 15.1, $^3J_{H,H}$ = 6.6 Hz, 1 H), 2.35 (ddd, $^2J_{H,H}$ = 15.1, $^2J_{P,H}$ = 13.2, $^3J_{H,H}$ = 7.0 Hz, 1 H), 3.70 (ddd, $^2J_{H,H}$ = 12.7, $^3J_{H,H}$ = 3.3, $^4J_{P,H}$ = 1.9 Hz, 1 H), 3.79 (dd, $^2J_{H,H}$ = 12.7, $^3J_{H,H}$ = 3.0 Hz, 1 H), 4.03 (dddd, $^3J_{H,H}$ = 6.3, $^3J_{P,H}$ = 6.2, $^3J_{H,H}$ = 3.3, $^3J_{H,H}$ = 3.0 Hz, 1 H), 4.09 (dq, $^3J_{P,H}$ = 8.9, $^3J_{H,H}$ = 7.1 Hz, 2 H), 4.48 (dddd, $^3J_{P,H}$ = 12.9, $^3J_{H,H}$ = 7.0, $^3J_{H,H}$ = 6.6, $^3J_{H,H}$ = 6.3 Hz, 1 H), 5.13 (s, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.38 (d, $^3J_{C,P}$ = 5.9 Hz), 29.06 (d, $^1J_{C,P}$ = 119.4 Hz), 61.13 (d, $^3J_{C,P}$ = 5.8 Hz), 63.02 (d, $^2J_{C,P}$ = 6.6 Hz), 67.95 (d, $^2J_{C,P}$ = 8.2 Hz), 85.82 (d, $^2J_{C,P}$ = 5.2 Hz) ppm. HRMS (ESI): calcd. for $C_6H_{14}O_5P$ 197.0579; found 197.0589.

(±)-2-Ethoxy-4-hydroxy-5-hydroxymethyl-2-oxo-2-phosphatetrahydrofuran (4c): From **9c** (60 mg, 0.21 mmol) with Pd (10% on C; 10 wt-%) in ethanol (1 mL) for 24 h, **4c** (23 mg, 56%) was obtained as a colourless oil. P(*R*),^{3}C(*S*),^{4}C(*R*). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 46.82 ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.39 (td, $^3J_{H,H}$ = 7.1, $^4J_{P,H}$ = 0.4 Hz, 3 H), 2.06 (ddd, $^2J_{H,H}$ = 15.7, $^2J_{P,H}$ = 11.5, $^3J_{H,H}$ = 2.5 Hz, 1 H), 2.16 (ddd, $^2J_{P,H}$ = 15.9, $^2J_{H,H}$ = 15.7, $^3J_{H,H}$ = 6.0 Hz, 1 H), 3.89 (d, $^3J_{H,H}$ = 5.3 Hz, 1 H), 4.16 (dqd, $^2J_{H,H}$ = 9.1, $^3J_{H,H}$ = 7.1, $^3J_{P,H}$ = 1.2 Hz, 1 H), 4.29 (ddd, $^3J_{H,H}$ = 5.3, $^3J_{H,H}$ = 3.6, $^3J_{P,H}$ = 3.4 Hz, 1 H), 4.62 (dddd, $^3J_{P,H}$ = 28.1, $^3J_{H,H}$ = 6.0, $^3J_{H,H}$ = 3.6, $^3J_{H,H}$ = 2.5 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.37 (d, $^3J_{C,P}$ = 5.7 Hz), 29.83 (d, $^1J_{C,P}$ = 119.9 Hz), 61.08 (d, $^3J_{C,P}$ = 8.2 Hz), 63.70 (d, $^2J_{C,P}$ = 6.6 Hz), 69.81 (d, $^2J_{C,P}$ = 1.9 Hz), 81.85 (d, $^2J_{C,P}$ = 8.7 Hz) ppm. HRMS (ESI): calcd. for $C_6H_{14}O_5P$ 197.0579; found 197.0579.

(±)-2-Ethoxy-4-hydroxy-5-hydroxymethyl-2-oxo-2-phosphatetrahydrofuran (4d): From **9d** (240 mg, 0.84 mmol) with Pd (10% on C; 10 wt-%) in ethanol (2 mL) for 24 h, **4d** (156 mg, 95%) was obtained as a colourless oil. P(*S*),^{3}C(*S*),^{4}C(*R*). ^{31}P NMR (161.97 MHz, $CDCl_3$): δ = 47.40 ppm. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.30 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H), 2.05 (ddd, $^2J_{H,H}$ = 15.4, $^2J_{P,H}$ = 15.2, $^3J_{H,H}$ = 6.0 Hz, 1 H), 2.11 (ddd, $^2J_{H,H}$ = 15.4, $^2J_{P,H}$ = 12.5, $^3J_{H,H}$ = 3.4 Hz, 1 H), 3.88 (dd, $^2J_{H,H}$ = 12.4, $^3J_{H,H}$ = 4.7 Hz, 1 H), 3.90 (dd, $^2J_{H,H}$ = 12.4, $^3J_{H,H}$ = 5.5 Hz, 1 H), 3.92–4.13 (m, 2 H), 4.16 (dddd, $^3J_{H,H}$ = 5.5, $^3J_{H,H}$ = 4.7, $^3J_{H,H}$ = 3.7, $^3J_{P,H}$ = 3.5 Hz, 1 H), 4.60 (dddd, $^3J_{P,H}$ = 25.3, $^3J_{H,H}$ = 6.0, $^3J_{H,H}$ = 3.7, $^3J_{H,H}$ = 3.4 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 16.44 (d, $^3J_{C,P}$ = 6.0 Hz), 29.88 (d, $^1J_{C,P}$ = 121.5 Hz), 60.77 (d, $^3J_{C,P}$ = 8.6 Hz), 62.72 (d, $^2J_{C,P}$ = 6.7 Hz), 69.12 (d, $^2J_{C,P}$ = 2.4 Hz), 82.47 (d, $^2J_{C,P}$ = 7.4 Hz) ppm. HRMS (ESI): calcd. for $C_6H_{14}O_5P$ 197.0579; found 197.0572.

(±)-4-Hydroxy-5-hydroxymethyl-2-oxo-2-phosphatetrahydrofuran Lithium Salt (10): In a Schlenk tube, anhydrous lithium bromide (18 mg, 0.025 mmol) was added to a solution of **4a** and **4b** (20 mg, 0.1 mmol) in acetonitrile (1.5 mL). The reaction mixture was stirred at 80 °C for 18 h, then the liquid was removed in vacuo and water (0.5 mL) was added to the residue. The residue was purified by flash chromatography (C_{18} 40–70 μm; water 100%) to give compound **10** (5 mg, 29%) as a colourless oil. ^{3}C(*S*),^{4}C(*R*). ^{31}P NMR (161.97 MHz, D_2O): δ = 36.56 ppm. ^{1}H NMR (400.13 MHz, D_2O): δ = 1.65 (ddd, $^2J_{P,H}$ = 17.7, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 9.1 Hz, 1 H), 2.14 (ddd, $^2J_{H,H}$ = 14.2, $^2J_{P,H}$ = 11.0, $^3J_{H,H}$ = 7.6 Hz, 1 H), 3.56 (dd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 6.2 Hz, 1 H), 3.75 (dd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 2.8 Hz, 1 H), 3.80–3.87 (m, 1 H), 4.16 (dddd, $^3J_{H,H}$ = 9.1, $^3J_{H,H}$ = $^3J_{P,H}$ = 7.6, $^3J_{H,H}$ = 5.6 Hz, 1 H) ppm. ^{13}C NMR (100.61 MHz, D_2O): δ = 29.77 (d, $^1J_{C,P}$ = 109.9 Hz), 61.68 (d, $^3J_{C,P}$ = 6.6 Hz), 68.34 (d, $^2J_{C,P}$ = 10.1 Hz), 82.34 (d, $^2J_{C,P}$ = 3.5 Hz) ppm. HRMS (ESI): calcd. for $C_4H_{10}O_5P$ 169.0266; found 169.0269.

Supporting Information (see footnote on the first page of this article): Copies of NMR spectra and HR mass spectra for all new compounds.

Acknowledgments

This research was supported in part by grants from Idenix Pharmaceuticals, Montpellier, France (IDENIX) and from the Agence Nationale de la Recherche et de la Technologie (ANRT).

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Received: October 10, 2013
Published Online: December 12, 2013

