An Efficient Synthesis of Phosphonate Derivatives of 1,2-Disubstituted Carbocyclic Purine Nucleosides with a Cyclopentane Ring

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Abstract: The synthesis of phosphonate 1,2-disubstituted carbocyclic nucleosides with a cyclopentane ring is described following two different strategies: inclusion of the phosphonomethyl group before or after coupling of the carbocyclic moiety with the heterocyclic base. The diethyl [(trifluoromethanesulfonyl)oxy]methanephosphonate is the key phosphonylating agent for both the strategies.

Key words: nucleosides, phosphonates, carbocycles, Mitsunobu reaction

Nucleoside analogues are regarded as a very interesting group of chemotherapeutic agents because their administration against a range of cancers and viral infections has been successful.[1] Mostly nucleosides, natural and synthetic, need to be metabolized by intracellular enzymes to their respective 5′-triphosphate derivatives to generate the active form. The initial formation of the nucleoside monophosphate is normally the limiting step in the enzymatic phosphorylation sequence.[2] In addition, phosphate derivatives of nucleoside analogues cannot be used directly as therapeutic agents because they rapidly undergo cleavage in vivo.[2a] For these reasons, there have been numerous attempts to accomplish structural approaches that mimic the phosphate moiety. In this area, phosphonate analogues, containing the enzyme stable ether P–C–O moiety, have been proposed as an interesting alternative and have emerged as promising candidates.[3]

Acyclic nucleoside phosphonates such as cidofovir (**1**), adefovir (**2**) and tenofovir (**3**) are becoming widely useful for treatment of viral diseases.[1c,4] On the other hand, chemotherapeutic properties were found in several phosphonate derivatives of furanose, for example, in compounds **4a** and **5a**;[5] their carbocyclic analogues **4b** and **5b** were also described (Figure 1).[6]

In recent years, we became interested in exploring the therapeutic potential of 1,2-disubstituted carbonucleosides (OTCs) in which the usual 1,3-substitution pattern of the carbocycle is replaced by a 1,2-pattern. We have developed a series of *cis* and *trans* purine-based OTCs in which the pseudosugar is a cyclopentane, a cyclopentene, or a cyclohexane ring.[7] Some of these compounds, in particular with *cis*-stereochemistry, have shown an interesting antitumoral activity[8] and also an antiviral activity against certain viruses such as varicella-zoster virus[9] and respiratory syncytial virus.[7c]

At this point, and because of the few examples found in the literature on the synthesis of carbocyclic phosphonate nucleosides, we considered it very interesting to explore and establish a synthetic route to prepare phosphonate derivatives of OTCs. Previously we have used two different methods to synthesize carbonucleosides: construction of the heterocyclic base on the primary amino group of an appropriate amino alcohol,[7a,b] and a convergent approach based on Mitsunobu coupling.[7c] In this study, we were in-

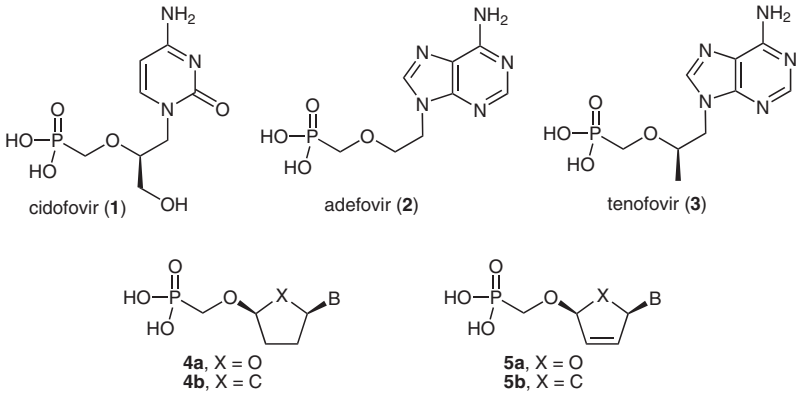

Figure 1 Nucleoside phosphonates with therapeutic properties

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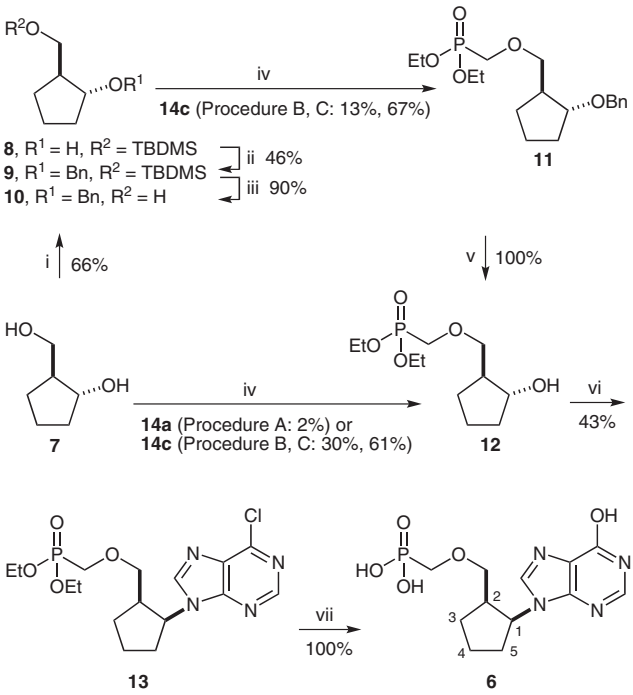
terested in developing a more possible straightforward synthetic route, and the convergent strategy seems to be the more adequate.

We investigated the synthesis of a representative phosphonate derivative of OTCs, a (±)-*cis*-hypoxanthine analogue **6** with a cyclopentane ring. As the Mitsunobu reaction normally proceeds with inversion of configuration, the 1,2-*trans*-diol **7** was required as the starting material (Scheme 1).[7a]



Scheme 1 *Reagents and conditions*: (i) TBDMSCl, imidazole, DMF, r.t.; (ii) NaH, BnBr, Bu_4NI, THF, r.t.; (iii) TBAF, THF; (iv) Procedure A or B: **14a** or **14c**, NaH, THF, 0 °C; Procedure C: **14c**, *n*-BuLi, THF, –30 °C; (v) Procedure D: H_2, 10% Pd/C, MeOH, 2413 mbar, r.t.; (vi) 6-chloropurine, DEAD, Ph_3P, THF, r.t.; (vii) (1) TMS-Br, CH_2Cl_2, r.t., (2) H_2O, acetone, 80 °C.

In order to develop a shorter and more versatile methodology, we preferred to introduce the phosphonomethyl moiety into the diol prior to the Mitsunobu coupling. The diethyl [(*p*-toluenesulfonyl)oxy]methanephosphonate (**14a**) (Figure 2) is the most common intermediate used in the literature to introduce phosphonate groups.[10–12] Attempts to introduce directly the phosphonomethyl group into the diol **7** by generation of the alkoxide with NaH, followed by treatment with the tosylphosphonate **14a** in anhydrous THF,[10] gave compound **12** in a very poor yield (2%). Therefore, the secondary hydroxyl group of the diol **7** was protected as the benzyl ether **10**. Compound **10** was obtained in three steps: selective protection of primary hydroxyl group as *tert*-butyldimethylsilyl ether, followed by benzylation of secondary hydroxyl group and selective deprotection of the previously obtained silyl ether (Scheme 1). However, worse results were obtained when **10** was treated with the tosylphosphonate derivative under the above-mentioned conditions, since mostly unreacted compound **10** was recovered, no traces of phosphonate **11** were detected and surprisingly a transesterification product **15a** was isolated in a small amount (6% yield) (Figure 2). Similar results were obtained (compound **15b**, 9% yield) when the tosylphosphonate derivative **14a** was replaced by diethyl [(methanesulfonyl)oxy]methanephosphonate (**14b**) (Figure 2), that to our knowledge has not been used previously.

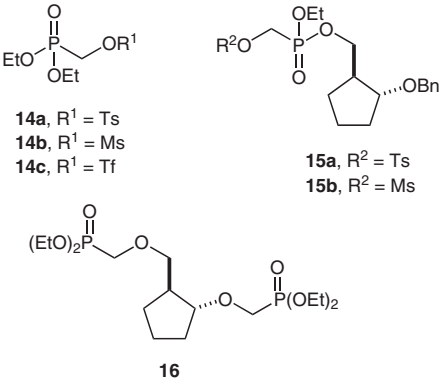
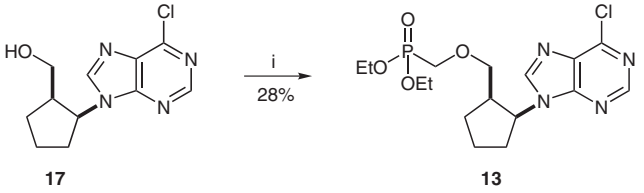


Figure 2 Phosphonylating agents **14**, transesterification products **15** and dialkylated compound **16**

The use of a more reactive sulfonylphosphonate, like the diethyl [(trifluoromethanesulfonyl)oxy]methanephosphonate (**14c**),[13] was necessary to avoid the formation of transesterification products. The treatment of the benzyl ether **10** with the triflate **14c** under mild conditions (24 hours at 0 °C) led to the formation of the corresponding phosphonate derivative **11** in poor yield (13%), a high proportion of compound **10** was recovered, but no traces of the transesterification product were detected. This result was highly improved when the reaction was carried out with *n*-BuLi at –30 °C and **11** was obtained in 67% yield. Hydrogenolysis of benzyl ether **11** afforded the desired alcohol **12** in quantitative yield.

The effectiveness of the reaction with the triflate **14c** encouraged us to try the inclusion of the phosphonate moiety into the diol **7**. Direct transformation of **7** into the phosphonate derivative **12** was possible using **14c** and NaH at 0 °C (30% yield). This result was improved when *n*-BuLi at –30 °C was used and **12** was obtained in 60% yield. It was possible in both cases to control the selectivity of the phosphonylating reaction through the primary alcohol and only traces of the dialkylated compound **16** were isolated (Figure 2).

Reaction of **12** with 6-chloropurine (3 equiv) in the presence of diethyl azodicarboxylate (DEAD, 2 equiv) and Ph_3P (2 equiv) in THF at room temperature gave the N-9 isomer, *cis*-6-chloropurine derivative **13**, in 43% yield. The relative configuration of compound **13** was determined by ^1H NMR spectroscopy, NOE effects are present between H-1 and H-2. On the other hand, compound **13** was also prepared from the corresponding (±)-*cis*-nucleoside analogue **17**[8] using the triflate **14c** as phosphonylating reagent in the presence of sodium hydride at 0 °C



17 13

Scheme 2 *Reagents and conditions*: (i) Procedure B: **14c**, NaH, THF, 0 °C

(Scheme 2). This last transformation has allowed us to confirm the N-9 substitution and the *cis*-stereochemistry of compound **13** obtained previously by Mitsunobu coupling.

Finally, the diethyl ester group of the phosphonate **13** was hydrolyzed in quantitative yield by treatment with bromotrimethylsilane (TMSBr) followed by heating at 80 °C with a mixture of acetone–water (1.5:2).[14] Under these conditions the chloro atom of C-6 was replaced by an hydroxyl group, affording the phosphonate derivative of hypoxanthine **6**.

In conclusion, we have developed two possible strategies to obtain phosphonates of 1,2-disubstituted carbocyclic purine nucleosides when the carbocycle is a cyclopentane ring: inclusion of the phosphonomethyl group in an appropriate nucleoside precursor prior to the coupling with the heterocyclic base and inclusion of this moiety into the nucleoside analogue in the final step. The first strategy is more direct and interesting in order to synthesize different phosphonates of 1,2-disubstituted carbocyclic nucleosides from a common synthon. Furthermore, the selectivity of the phosphonylating reaction of the diol **7** through the primary alcohol allows us to obtain nucleoside analogue phosphonates in three steps. In both strategies we have established that the diethyl [(trifluoromethanesulfonyl)oxy]methanephosphonate (**14c**) is the key phosphonylating reagent.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-400 instrument, using TMS as internal standard [chemical shifts (δ) in ppm, *J* in Hz]. Assignment of the signals was performed by NOE, DEPT, HMQC, or HMBC experiments. Mass spectra were recorded using a Hewlett-Packard 5988A spectrometer. Microanalyses were performed using a PerkinElmer 240B elemental analyzer. Silica gel (Merck 60, 230–400 mesh) was used for flash chromatography (FC). Analytical TLC was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm).

Phosphonates **14a**[10–12] and **14c**[13] were prepared according to the literature.

Diethyl Methanesulfonyloxymethanephosphonate (14b)

To a solution of diethyl hydroxymethylphosphonate[15] (100 mg, 0.60 mmol) in CH_2Cl_2 (3 mL) was added dropwise MsCl (74 mg, 50 μL, 0.65 mmol) and Et_3N (0.13 mL) at 0 °C. The mixture was stirred and the temperature was allowed to reach r.t. gradually and then the stirring was continued for an additional 4 h. After adding H_2O (3 mL), the product was extracted with CH_2Cl_2 (2 × 3 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (9 mL), brine (9 mL), and dried (Na_2SO_4). The solvent was removed in vacuo to obtain **14b** (117 mg, 80%) as a colorless oil, which was used directly for reactions in Procedure A without further purification; R_f = 0.41 (CH_2Cl_2–MeOH, 95:5).

^{1}H NMR ($CDCl_3$): δ = 4.42 (d, *J* = 8.9 Hz, 2 H, CH_2P), 4.22 (m, 4 H, 2 × CH_2CH_3), 3.13 (s, 3 H, CH_3), 1.38 (t, *J* = 7.1 Hz, 3 H, 2 × CH_2CH_3).

^{13}C NMR ($CDCl_3$): δ = 63.8 (d, *J* = 6.4 Hz, CH_2CH_3), 61.5 (d, *J* = 169.7 Hz, CH_2P), 38.4 (CH_3), 16.8 (d, *J* = 5.7 Hz, CH_2CH_3).

MS (EI): *m*/*z* (%) = 247 ([M + 1]$^+$, 6), 219 (M$^+$ – C_2H_3, 32), 201 (M$^+$ – C_2H_5O, 10), 191 (M$^+$ – C_4H_7, 18), 188 (17), 173 (21), 167 (M$^+$ – CH_3SO_2, 18), 160 (34), 137 (M$^+$ – $C_2H_5SO_3$, 63), 109 (M$^+$ – $C_4H_9SO_3$, 100), 81 (23), 79 (25), 65 (14).

(±)-*trans*-2-(*tert*-Butyldimethylsilyloxymethyl)cyclopentanol (8)

To a solution of compound **7**[7a] (829 mg, 7.15 mmol) and imidazole (1.17 g, 17.2 mmol) in DMF (8 mL) was added a solution of TBDMSCl (1.62 g, 10.7 mmol) in DMF (6.5 mL). The mixture was stirred at r.t. for 3 h and diluted with Et_2O (20 mL). The Et_2O layer was washed with H_2O (3 × 20 mL) and dried (Na_2SO_4). The residue obtained by evaporation of Et_2O was purified by column chromatography on silica gel (hexane–EtOAc, 95:5) to afford **8** (1.092 g, 66%) as a colorless oil; R_f = 0.20 (hexane–EtOAc, 9:1).

^{1}H NMR ($CDCl_3$): δ = 3.98 (q, *J* = 7.1 Hz, 1 H, H-1), 3.80 (dd, *J* = 9.6, 5.1 Hz, 1 H, *H*CHO), 3.48 (t, *J* = 9.6 Hz, 1 H, HC*H*O), 2.63 (s, 1 H, OH), 1.95 (m, 2 H, H-2, 1H-5), 1.74 (m, 2 H, 1H-3, 1H-4), 1.58 (m, 2 H, 1H-4, 1H-5), 1.16 (m, 1 H, 1H-3), 0.90 [s, 9 H, $(CH_3)_3C$], 0.08 and 0.07 [2 s, 6 H, $(CH_3)_2Si$].

^{13}C NMR ($CDCl_3$): δ = 78.5 (C-1), 67.0 (CH_2O), 49.2 (C-2), 33.8 (C-5), 25.9 [$(CH_3)_3C$], 25.8 (C-3), 21.6 (C-4), 18.2 [$(CH_3)_3C$], –5.5 and –5.6 [$(CH_3)_2Si$].

MS (EI): *m*/*z* (%) = 213 (M$^+$ – OH, 2), 173 (M$^+$ – C_4H_9, 27), 155 (M$^+$ – $C_4H_{11}O$, 7), 105 (44), 81 (56), 74 (100).

Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.55; H, 11.37. Found: C, 62.83; H, 11.12.

(±)-*trans*-1-Benzyloxy-2-(*tert*-butyldimethylsilyloxymethyl)cyclopentane (9)

A solution of compound **8** (820 mg, 3.57 mmol) in THF (25 mL) was added dropwise to a suspension of NaH (285 mg, 7.13 mmol, 60% dispersion in mineral oil) in THF (13 mL) at 0 °C. After stirring at r.t. for 1 h, BnBr (934 mg, 649 μL, 5.35 mmol) and Bu_4NI (133 mg, 0.36 mmol) were added. The mixture was stirred at r.t. for 68 h, followed by quenching with sat. aq NH_4Cl (33 mL). The product was extracted with Et_2O (4 × 30 mL). The combined organic layers were washed with H_2O (100 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 99.5:0.5) to afford **9** (527 mg, 46%) as a colorless oil, and to recover compound **8** (358 mg); R_f = 0.61 (hexane–EtOAc, 9:1).

^{1}H NMR ($CDCl_3$): δ = 7.32 (m, 4 H_{arom}), 7.25 (m, 1 H_{arom}), 4.50 (s, 2 H, CH_2Ph), 3.80 (m, 1 H, H-1), 3.54 (dd, *J* = 10.0, 5.9 Hz, 1 H, *H*CHO), 3.48 (dd, *J* = 10.0, 5.6 Hz, 1 H, HC*H*O), 2.16 (m, 1 H, H-2), 1.84 (m, 1 H, 1H-5), 1.74 (m, 3 H, 1H-3, 1H-4, 1H-5), 1.58 (m, 1 H, 1H-4), 1.30 (m, 1 H, 1H-3), 0.89 [s, 9 H, $(CH_3)_3C$], 0.03 [s, 6 H, $(CH_3)_2Si$].

^{13}C NMR ($CDCl_3$): δ = 139.1, 128.3, 127.6, 127.3, 82.7 (C-1), 70.8, 64.7, 48.1 (C-2), 32.1 (C-5), 27.2 (C-3), 25.9 [$(CH_3)_3C$], 23.3 (C-4), 18.3 [$(CH_3)_3C$], –5.4 [$(CH_3)_2Si$].

MS (EI): *m*/*z* (%) = 320 (M$^+$, 0.12), 263 (M$^+$ – C_4H_9, 0.96), 171 (7), 92 (30), 91 (100), 73 (6).

Anal. Calcd for $C_{19}H_{32}O_2Si$: C, 71.19; H, 10.06. Found: C, 71.25; H, 10.19.

(±)-*trans*-2-Benzyloxycyclopentylmethanol (10)

To a solution of compound **9** (527 mg, 1.65 mmol) in THF (25 mL) was added 1 M solution of TBAF in THF (1.8 mL). The mixture was stirred at r.t. for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 99.5:0.5) to give **10** (306 mg, 90%) as a colorless oil; R_f = 0.55 (hexane–EtOAc, 1:1).

^{1}H NMR ($CDCl_3$): δ = 7.33 (m, 4 H_{arom}), 7.28 (m, 1 H_{arom}), 4.57 (d, *J* = 11.7 Hz, 1 H, *H*CHPh), 4.47 (d, *J* = 11.7 Hz, 1 H, HC*H*Ph), 3.77 (q, *J* = 5.9 Hz, 1 H, H-2), 3.62 (dd, *J* = 10.5, 5.9 Hz, 1 H, *H*CHOH), 3.55 (dd, *J* = 10.5, 7.8 Hz, 1 H, HC*H*OH), 2.18 (m, 1 H, H-1), 2.01 (br s, 1 H, OH), 1.87 (m, 2 H, 1H-3, 1H-5), 1.72 (m, 2 H, 1H-3, 1H-4), 1.60 (m, 1 H, 1H-4), 1.23 (m, 1 H, 1H-5).

^{13}C NMR ($CDCl_3$): δ = 138.6, 128.4, 127.6, 127.5, 84.1 (C-2), 71.2 (*C*H_2Ph), 65.9 (CH_2O), 47.8 (C-1), 31.4 (C-3), 26.4 (C-5), 22.3 (C-4).

MS (EI): *m*/*z* (%) = 206 (M^+, 2), 188 ($M^+ - H_2O$, 9), 108 ($M^+ - C_6H_{10}O$, 20), 107 ($M^+ - C_6H_{11}O$, 28), 92 (24), 91 ($M^+ - C_6H_{11}O_2$, 100), 82 (24), 79 (8), 67 (12).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.43; H, 8.95.

Phosphonate Derivatives; General Procedure

Procedure A: A solution of the corresponding alcohol (0.20–0.90 mmol) in THF (0.5 mL) was added dropwise to a suspension of NaH (1.1 equiv, 60% dispersion in mineral oil) in THF (0.5 mL). After stirring at r.t. for 1 h, the mixture was cooled to 0 °C and the phosphonylating agent **14a** or **14b** (1.1–1.5 equiv) was added. The mixture was stirred at 0 °C for 3 h and then for 24 h at r.t. After removal of the solvent, the residue was dissolved in EtOAc (8 mL) and washed with H_2O (2 × 5 mL). The organic layer was dried (Na_2SO_4), and concentrated to dryness. The residue was purified by column chromatography on silica gel to give the corresponding phosphonate.

Procedure B: A solution of the corresponding alcohol (0.15–0.20 mmol) in THF (0.5 mL) was added dropwise to a suspension of NaH (1.1 equiv, 60% dispersion in mineral oil) in THF (0.5 mL). After stirring at r.t. for 1 h, the mixture was cooled to 0 °C and a solution of **14c** (1.1–1.5 equiv) in THF (0.4 mL) was added. The mixture was stirred at 0 °C for 24 h, followed by quenching with H_2O (5 mL). The product was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), and concentrated to dryness. The residue was purified by column chromatography on silica gel to give the corresponding phosphonate.

Procedure C: To a solution of the corresponding alcohol (0.24 mmol) in THF (2 mL), at –30 °C, was added dropwise *n*-BuLi in hexanes (1.1 equiv). After stirring for 1 h, a solution of **14c** (2.1 equiv) in THF (0.8 mL) was added and stirring was continued at –30 °C for 24 h. The mixture was quenched with sat. aq $NaHCO_3$ (2 mL) and the product was extracted with Et_2O (4 × 3 mL). The combined organic layers were dried (Na_2SO_4), and concentrated to dryness. The residue was purified by column chromatography on silica gel to give the corresponding phosphonate.

(±)-*trans*-1-(Diethylphosphonomethoxymethyl)-2-benzyloxycyclopentane (11)

Procedure B: Compound **11** (7 mg, 13%) was obtained as a colorless oil from **10** (30 mg, 0.15 mmol), NaH (7 mg, 0.17 mmol, 60% dispersion in mineral oil), and **14c** (66 mg, 0.22 mmol). The reaction did not proceed to completion and the purification by column chromatography on silica gel (hexane–EtOAc, 3:1 → 1:1) gave **11** and the recovered compound **10** (20 mg).

Procedure C: Compound **11** (58 mg, 67%) was obtained as a colorless oil from **10** (50 mg, 0.24 mmol), *n*-BuLi (1.48 M in hexanes, 0.18 mL, 0.27 mmol), and **14c** (146 mg, 0.49 mmol). The reaction did not proceed to completion and the purification by column chromatography on silica gel (hexane–EtOAc, 1:4) gave **11** and the recovered compound **10** (5 mg).

11

R_f = 0.37 (hexane–EtOAc, 1:4).

^{1}H NMR ($CDCl_3$): δ = 7.33 (m, 4 H_{arom}), 7.26 (m, 1 H_{arom}), 4.52 (d, *J* = 11.9 Hz, 1 H, *H*CHPh), 4.47 (d, *J* = 11.9 Hz, 1 H, HC*H*Ph), 4.15 (m, 4 H, 2 × CH_2CH$_3$), 3.78 (d, *J* = 8.2 Hz, 2 H, CH_2P), 3.76 (m, 1 H, H-2), 3.49 (m, 2 H, CH_2O), 2.28 (m, 1 H, H-1), 1.90 (m, 1 H, 1H-5), 1.75 (m, 3 H, 1H-4, H-3), 1.59 (m, 1 H, 1H-4), 1.32 (t, *J* = 7.1 Hz, 6 H, 2 × CH_3), 1.31 (m, 1 H, 1H-5).

^{13}C NMR ($CDCl_3$): δ = 138.9, 128.3, 127.6, 127.4, 82.9 (C-2), 75.8 (d, *J* = 11.2 Hz, CH_2O), 71.0 (*C*H_2Ph), 65.2 (d, *J* = 166.2 Hz, CH_2P), 62.4 (d, *J* = 6.5 Hz, *C*H_2CH$_3$), 45.7 (C-1), 31.9 (C-3), 27.6 (C-5), 23.1 (C-4), 16.5 (d, *J* = 5.6 Hz, CH_3).

MS (EI): *m*/*z* (%) = 357 ($[M + 1]^+$, 6), 265 ($M^+ - C_7H_7$, 11), 250 ($M^+ - C_8H_{10}$, 72), 169 ($M^+ - C_{13}H_{15}O$, 100), 167 (56), 152 (20), 141 (26), 125 (22), 96 (36), 89 (79), 82 (54), 67 (76).

Anal. Calcd for $C_{18}H_{29}O_5P$: C, 60.66; H, 8.20. Found: C, 60.35; H, 8.31.

(±)-*trans*-2-(Diethylphosphonomethoxymethyl)cyclopentanol (12)

Procedure A: Compound **12** (5 mg, 2%) was obtained as a colorless oil from **7** (100 mg, 0.86 mmol), NaH (38 mg, 0.95 mmol, 60% dispersion in mineral oil), and **14a** (305 mg, 0.95 mmol). Purification was done by column chromatography on silica gel (CH_2Cl_2–MeOH, 98:2).

Procedure B: Compound **12** (16 mg, 30%) was obtained as a colorless oil from **7** (23 mg, 0.20 mmol), NaH (10 mg, 0.25 mmol, 60% dispersion in mineral oil), and **14c** (71 mg, 0.24 mmol). The reaction did not proceed to completion and the purification was done by column chromatography on silica gel (hexane–EtOAc, 1:2 → EtOAc) gave **12** and the recovered compound **7** (7 mg).

Procedure C: Compound **12** (313 mg, 61%) was obtained as a colorless oil from **7** (224 mg, 1.93 mmol), *n*-BuLi (2.5 M in hexanes, 0.85 mL, 2.13 mmol) in THF (13 mL), and **14c** (1.154 g, 3.85 mmol) in THF (4 mL). The reaction did not proceeded to completion and the purification was done by column chromatography on silica gel (EtOAc) to give **12** and the recovered compound **7** (63 mg).

Procedure D: A solution of the compound **11** (36 mg, 0.10 mmol) in MeOH (4.8 mL) was treated with H_2 (2413 mbar) in the presence of 10% Pd/C (14 mg). The mixture was stirred at r.t. for 1 h. After separation of the catalyst by filtration, the solvent was removed in vacuo to obtain **12** (27 mg, ~100%) as a colorless oil.

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R_f = 0.21 (EtOAc).

^{1}H NMR ($CDCl_3$): δ = 4.18 (m, 4 H, 2 × CH_2CH$_3$), 4.02 (q, *J* = 6.6 Hz, 1 H, H-1), 3.80 (d, *J* = 8.0 Hz, 2 H, CH_2P), 3.67 (dd, *J* = 9.1, 5.3 Hz, 1 H, *H*CHO), 3.49 (t, *J* = 9.1 Hz, 1 H, HC*H*O), 2.73 (br s, 1 H, OH), 2.08 (m, 1 H, H-2), 1.93 (m, 1 H, 1H-5), 1.83 (m, 1 H, 1H-3), 1.74 (m, 1 H, 1H-4), 1.60 (m, 2 H, 1H-5, 1H-4), 1.35 (t, *J* = 7.0 Hz, 6 H, 2 × CH_3), 1.22 (m, 1 H, 1H-3).

^{13}C NMR ($CDCl_3$): δ = 77.4 (C-1), 76.9 (d, *J* = 11.6 Hz, CH_2O), 65.0 (d, *J* = 166.7 Hz, CH_2P), 62.5 (d, *J* = 6.5 Hz, *C*H_2CH$_3$), 62.4 (d, *J* = 6.7 Hz, *C*H_2CH$_3$), 47.3 (C-2), 34.0 (C-5), 26.4 (C-3), 21.8 (C-4), 16.4 (d, *J* = 5.7 Hz, CH_3).

MS (EI): *m*/*z* (%) = 267 ($[M + 1]^+$, 2), 238 ($M^+ - C_2H_4$, 8), 169 ($M^+ - C_6H_9O$, 72), 167 (21), 152 (74), 141 (32), 138 (42), 125 ($M^+ - C_9H_{17}O$, 100), 111 (38), 97 (35), 81 (38), 65 (34).

Anal. Calcd for $C_{11}H_{23}O_5P$: C, 49.62; H, 8.71. Found: C, 49.78; H, 8.56.

(±)-*cis*-6-Chloro-9-[2-(diethylphosphonomethoxymethyl)cyclopentyl]purine (13)

*From **12***: To a suspension of compound **12** (311 mg, 1.17 mmol), 6-chloropurine (548 mg, 3.51 mmol), and Ph_3P (620 mg, 2.34 mmol) in THF (15 mL) was added a solution of DEAD (409 mg, 370 μL, 2.35 mmol) in THF (3 mL). The mixture was stirred at r.t. for 22 h. After removal of the solvent, the residue was purified by column chromatography on silica gel (EtOAc) to give **13** (204 mg, 43%) as a colorless oil.

Procedure B: Compound **13** (18 mg, 28%) was obtained as a colorless oil from **17** (40 mg, 0.16 mmol), NaH (10 mg, 0.25 mmol, 60% dispersion in mineral oil) and **14c** (57 mg, 0.19 mmol). Reaction proceeded no completely and the purification by column chromatography on silica gel (CH_2Cl_2–MeOH, 95:5) gave **13** and the recovered compound **17** (9 mg).

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R_f = 0.32 (CH_2Cl_2–MeOH, 95:5).

^{1}H NMR ($CDCl_3$): δ = 8.73 (s, 1 H, H-2), 8.28 (s, 1 H, H-8), 5.15 (q, J = 7.7 Hz, 1 H, H-1′), 4.11 (m, 4 H, 2 × CH_2CH$_3$), 3.43 (d, J = 8.6 Hz, 2 H, CH_2P), 3.18 (m, 2 H, CH_2O), 2.67 (m, 1 H, H-2′), 2.43 (m, 1 H, 1H-5′), 2.36 (m, 1 H, 1H-5′), 2.16 (m, 1 H, 1H-4′), 2.03 (m, 1 H, 1H-3′), 1.84 (m, 2 H, 1 H-3′, 1H-4′), 1.32 (t, J = 7.0 Hz, 6 H, 2 × CH_3).

^{13}C NMR ($CDCl_3$): δ = 152.2, 151.5 (C-2), 150.7, 145.3 (C-8), 131.5 (C-5), 72.8 (d, J = 11.8 Hz, CH_2O), 64.9 (d, J = 167.2 Hz, CH_2P), 62.3 (d, J = 6.6 Hz, CH_2CH$_3$), 62.2 (d, J = 6.5 Hz, CH_2CH$_3$), 58.0 (C-1′), 42.7 (C-2′), 30.7 (C-5′), 27.3 (C-3′), 22.9 (C-4′), 16.4 (d, J = 5.4 Hz, CH_3).

MS (EI): m/z (%) = 402 (M^+, 8), 367 (11), 253 ($M^+ - C_5H_{10}PO_3$, 33), 251 ($M^+ - C_5H_{12}PO_3$, 100), 236 (17), 235 (24), 234 ($M^+ - C_5H_{13}PO_4$, 33), 152 (14), 125 (33), 78 (17).

Anal. Calcd for $C_{16}H_{24}ClN_4O_4P$: C, 47.71; H, 6.01; N, 13.91. Found: C, 47.53; H, 6.21; N, 13.75.

(±)-*trans*-2′-Benzyloxycyclopentylmethyl Ethyl *p*-Toluensulfonyloxymethylphosphonate (15a)

Procedure A: Compound **15a** (6 mg, 6%) was obtained as a colorless oil from **10** (45 mg, 0.22 mmol), NaH (10 mg, 0.25 mmol, 60% dispersion in mineral oil), and **14a** (106 mg, 0.33 mmol). The reaction did not proceeded to completion and the purification by column chromatography on silica gel (hexane–EtOAc, 1:1) gave **15a** [R_f = 0.29 (hexane–EtOAc, 1:1)] and the recovered compound **10** (26 mg).

^{1}H NMR ($CDCl_3$): δ = 7.78 (d, J = 8.3 Hz, 2 H_{arom}), 7.32 (m, 6 H_{arom}), 7.28 (m, 1 H_{arom}), 4.49 (d, J = 11.8 Hz, 1 H, *H*CHPh), 4.43 (d, J = 11.8 Hz, 1 H, HC*H*Ph), 4.18 (d, J = 9.9 Hz, 2 H, CH_2P), 4.12 (m, 2 H, OCH_2CH$_3$), 4.01 (m, 2 H, OCH$_2$), 3.75 (m, 1 H, H-2′), 2.44 (s, 3 H, CH_3), 2.28 (m, 1 H, H-1′), 1.88 (m, 1 H, 1H-5′), 1.75 (m, 3 H, H-3′, 1H-4′), 1.60 (m, 1 H, 1H-4′), 1.30 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.28 (m, 1 H, 1H-5′).

^{13}C NMR ($CDCl_3$): δ = 145.5, 138.6, 131.6, 130.0, 128.3, 128.2, 127.6, 127.5, 82.0 (C-2′), 71.1 (CH_2Ph), 68.5 (t, J = 6.0 Hz, OCH$_2$), 63.5 (d, J = 7.1 Hz, OCH_2CH$_3$), 61.1 (d, J = 170.0 Hz, CH_2P), 46.2 (C-1′), 31.7 (C-3′), 26.8 (C-5′), 22.8 (C-4′), 21.7 (CH_3), 16.3 (d, J = 5.7 Hz, CH_2CH_3).

MS (EI): m/z (%) = 483 ([M + 1]$^+$, 0.04), 295 ($M^+ - C_8H_{11}O_3S$, 14), 155 (14), 91 (100).

Anal. Calcd for $C_{23}H_{31}O_6PS$: C, 59.21; H, 6.70. Found: C, 59.40; H, 6.53.

(±)-*trans*-2′-Benzyloxycyclopentylmethyl Ethyl Methanesulfonyloxymethylphosphonate (15b)

Procedure A: Compound **15b** (10 mg, 9%) was obtained as a colorless oil from **10** (59 mg, 0.29 mmol), NaH (14 mg, 0.35 mmol, 60% dispersion in mineral oil), and **14b** (106 mg, 0.43 mmol). The reaction did not proceeded to completion and the purification was done by column chromatography on silica gel (hexane–EtOAc, 1:1) to give **15b** [R_f = 0.26 (hexane–EtOAc, 1:1)] and the recovered compound **10** (19 mg).

^{1}H NMR ($CDCl_3$): δ = 7.33 (m, 4 H_{arom}), 7.28 (m, 1 H_{arom}), 4.54 (d, J = 11.8 Hz, 1 H, *H*CHPh), 4.45 (d, J = 11.8 Hz, 1 H, HC*H*Ph), 4.39 (d, J = 8.9 Hz, 2 H, CH_2P), 4.19 (m, 2 H, OCH_2CH$_3$), 4.08 (m, 2 H, OCH$_2$), 3.78 (m, 1 H, H-2′), 3.08 (s, 3 H, CH_3), 2.33 (m, 1 H, H-1′), 1.93 (m, 1 H, 1H-5′), 1.79 (m, 3 H, H-3′, 1H-4′), 1.62 (m, 1 H, 1H-4′), 1.35 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 1.31 (m, 1 H, 1H-5′).

^{13}C NMR ($CDCl_3$): δ = 138.5, 128.4, 127.6, 127.5, 82.0 (C-2′), 71.1 (CH_2Ph), 68.6 (t, J = 6.2 Hz, OCH$_2$), 63.5 (d, J = 6.2 Hz, OCH_2CH$_3$), 60.9 (d, J = 169.9 Hz, CH_2P), 46.3 (C-1′), 37.9 (CH_3), 31.6 (C-3′), 26.9 (C-5′), 22.8 (C-4′), 16.4 (d, J = 5.6 Hz, CH_2CH_3).

MS (EI): m/z (%) = 407 ([M + 1]$^+$, 0.03), 219 ($M^+ - C_{13}H_{15}O$, 16), 191 ($M^+ - C_4H_8O_6PS$, 9), 91 (100), 79 (17).

Anal. Calcd for $C_{17}H_{27}O_6PS$: C, 52.30; H, 6.97. Found: C, 52.42; H, 6.75.

(±)-*cis*-9-[2-(Dihydroxyphosphonomethoxymethyl)cyclopentyl]hypoxanthine (6)

To a solution of compound **13** (41 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was added dropwise TMSBr (162 mg, 140 μL, 1.03 mmol). The mixture was stirred at r.t. for 24 h. After removal of the solvent, the residue was dissolved in a mixture 1.5:2 of acetone–H_2O (3.5 mL) and heated overnight at 80 °C. The solvent was removed in vacuo to obtain **6** (33 mg, ~100%) as a colorless oil; R_f = 0.15 (*n*-BuOH–H_2O–AcOH, 10:3:2).

^{1}H NMR (DMSO-d_6): δ = 12.90 (br s, 1 H, OH aromatic), 9.05 (s, 1 H, H-2), 8.24 (s, 1 H, H-8), 5.07 (q, J = 7.8 Hz, 1 H, H-1′), 4.81 [br s, 2 H, P(OH)$_2$], 3.18 (m, 4 H, CH_2P, CH_2O), 2.58 (m, 1H, H-2′), 2.26 (m, 2 H, H-5′), 1.96 (m, 1 H, 1H-4′), 1.89 (m, 1 H, 1H-3′), 1.66 (m, 2 H, 1H-3′, 1H-4′).

^{13}C NMR (DMSO-d_6): δ = 154.4 (C-6), 147.7 (C-2), 139.1 (C-8), 118.3 (C-5), 71.8 (d, J = 11.1 Hz, CH_2O), 66.3 (d, J = 160.5 Hz, CH_2P), 58.1 (C-1′), 41.6 (C-2′), 30.1 (C-5′), 27.1 (C-3′), 22.2 (C-4′).

MS (FAB): m/z (%) = 329 ([M + 1]$^+$, 100).

Anal. Calcd for $C_{12}H_{17}N_4O_5P$: C, 43.91; H, 5.22; N, 17.07. Found: C, 43.76; H, 5.12; N, 16.87.

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