# A Flexible, Efficient Synthesis of (±)-Carbocyclic Phosphonic Acid Nucleoside Derivatives

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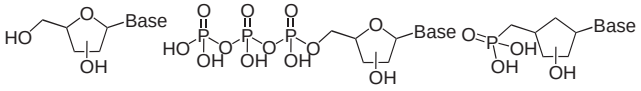
**Abstract:** An efficient and flexible synthesis of cyclopentane and hydroxylated cyclopentane phosphonic acid analogues is described. The key step involves the opening of an epoxide with either a nucleoside base or a selenyl anion to access the target molecules.

**Key words:** phosphonic acids, ribose analogues, nucleosides, epoxide

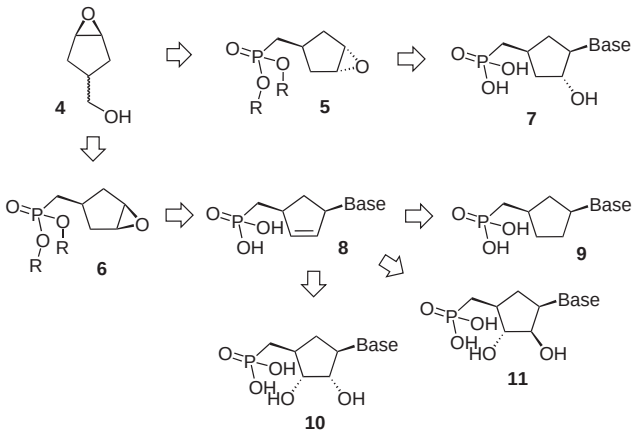
Chemotherapies based on the administration of analogues of nucleosides and deoxynucleosides **1** have proved successful against a range of cancers and viral infections such as HIV, cytomegalovirus, and herpes virus.[1] In each case, intracellular processing of the nucleoside to its triphosphate **2** generates the active form of the nucleoside.[2] This phosphorylation sequence is often stepwise, and performed by more than one cellular kinase, and the initial formation of the nucleoside monophosphate is often the most difficult step in the sequence. Strategies to facilitate or bypass this first phosphorylation step have included the use of prodrugs of the pre-formed monophosphate.[3] Phosphonic acids **3** are rather more chemically stable analogues of the monophosphate which in some cases can still undergo phosphorylation and generate effective mimics of a nucleoside triphosphate (Figure 1).[4]




1 2 3

**Figure 1** Nucleosides, nucleoside triphosphates, and carbocyclic phosphonic acid nucleoside mimics.

We have been investigating synthetic procedures which would allow us to access a range of phosphonic acid analogues of carbocyclic nucleosides.[5] Herein, we wish to report a flexible synthesis of hydroxy, dihydroxy and dideoxy versions using an efficient epoxide-opening strategy outlined in Scheme 1. Carbocyclic ribose analogues have been synthesised in a variety of ways, usually starting with ribose itself or a substituted cyclopentane derivative.[6] Such routes could be adapted to access phosphonic acids, however, we wished to maximise the flexibility of our route, and chose to synthesise all targets via the readily prepared epoxy-alcohol **4**. In this strategy, nucleoside bases can be added to the *meso*-*trans*-epoxy-phosphonylmethyl cyclopentane **5** to generate directly 3′-deoxycarbocyclic nucleosides **7**. Conversely, the *cis*-epoxyphosphonylmethyl cyclopentane **6** could be converted to an allyl species onto which bases could be appended using Pd-π-allylation chemistry,[7] providing access to a range of ribose **10**, arabinose **11**, cyclopentane **9** and cyclopentene **8** analogues. This article describes how this strategy was put into practice.




**Scheme 1** An epoxide-opening strategy to access cyclopentene **8**, cyclopentane **9**, hydroxycyclopentane **7**, *cis*-dihydroxycyclopentane **10** and *trans*-dihydroxycyclopentane **11** phosphonic acid nucleoside mimics.

The *trans*-epoxy-alcohol **4a**[8] was synthesised in six straightforward steps (Scheme 2) from dimethyl malonate, by a sequence of allylation, RCM,[8a] saponification, reduction, alcohol silyl-protection and a *trans*-selective epoxidation.[9] The latter process afforded a 3:1 mixture of *trans*:*cis* epoxides from which the *trans*-isomer was isolated in 40% yield following silica gel column chromatography. Compound **4a** was converted to the corresponding iodide[10] and then to the diisopropyl phosphonate ester in a standard Arbuzov reaction. We have found throughout this work that diisopropyl phosphonates give generally cleaner reactions than the corresponding ethyl or methyl

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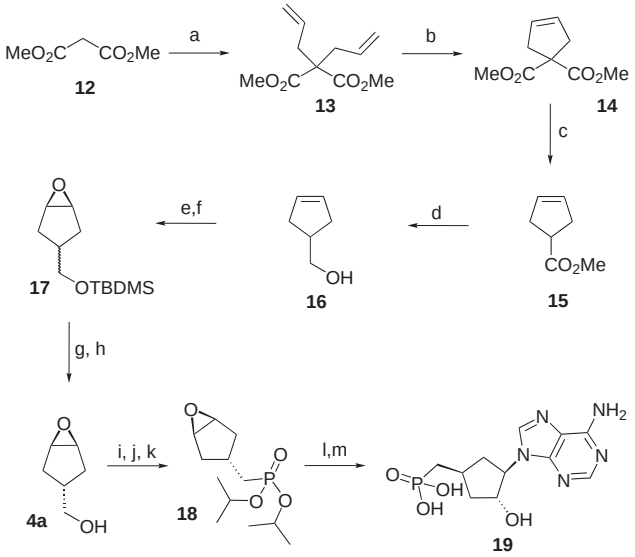
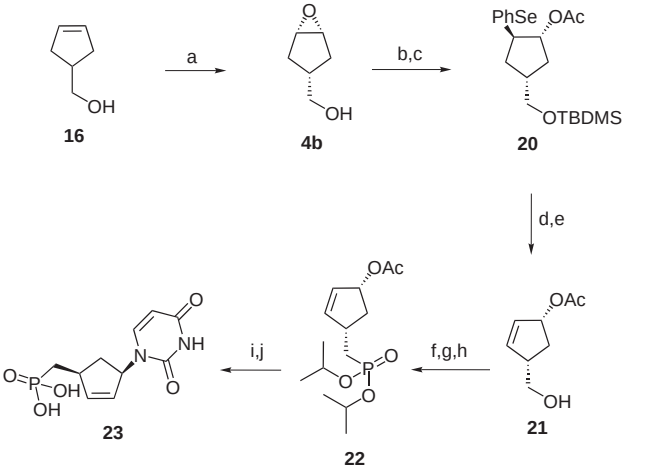
phosphonate esters. Reaction of this epoxide with adenine and $Cs_2CO_3$ gave a 41% yield of the racemic carbocyclic nucleoside mimic. The epoxide-opening reaction did prove to be quite sluggish and required extended reaction times in hot DMF to give the desired alcohol product. Standard TMSBr-mediated deprotection of the phosphonate ester provided the corresponding phosphonic acid **19**[15] in 40% yield.




**Scheme 2** a. NaOMe, allyl bromide, MeOH, 3 h, 0 °C to r.t., 87%; b. Grubbs' catalyst, $CH_2Cl_2$, 72 h, reflux, 93%; c. LiCl, DMSO, 150 °C, 3 h, 78%; d. $LiAlH_4$, THF, 1 h, 0 °C to r.t., 72%; e. TBDMSCl, imidazole, DMF, 16 h, r.t., 96%; f. MCPBA, $CH_2Cl_2$, 1 h, 0 °C to r.t., 97%; g and h. TBAF, THF, 1 h, r.t., then silica gel chromatography, 40% (for *trans*-isomer); i. TsCl, $Et_3N$, DMAP, $CH_2Cl_2$, 16 h, 0 °C, 93%; j. NaI, butanone, 5 h, reflux, 91%; k. P(O*i*-Pr)$_3$, 30 h, 120 °C, 58%; l. adenine, $Cs_2CO_3$, DMF, Kryptofix, 9 d, 120 °C, 41%; m. TMSBr, MeCN, 16 h, r.t., 40%.

Several other carbocyclic phosphonic acids were synthesised according to Scheme 3 and Scheme 4. The *cis*-epoxy-alcohol **4b** was produced exclusively from the hydroxymethyl cyclopentene **16** using vanadyl(acac) promoted epoxidation[11] and then reacted with NaSePh, generated in situ with diphenyldiselenide and $NaBH_4$,[12] and the intermediate seleno-alcohol protected as its acetate ester.

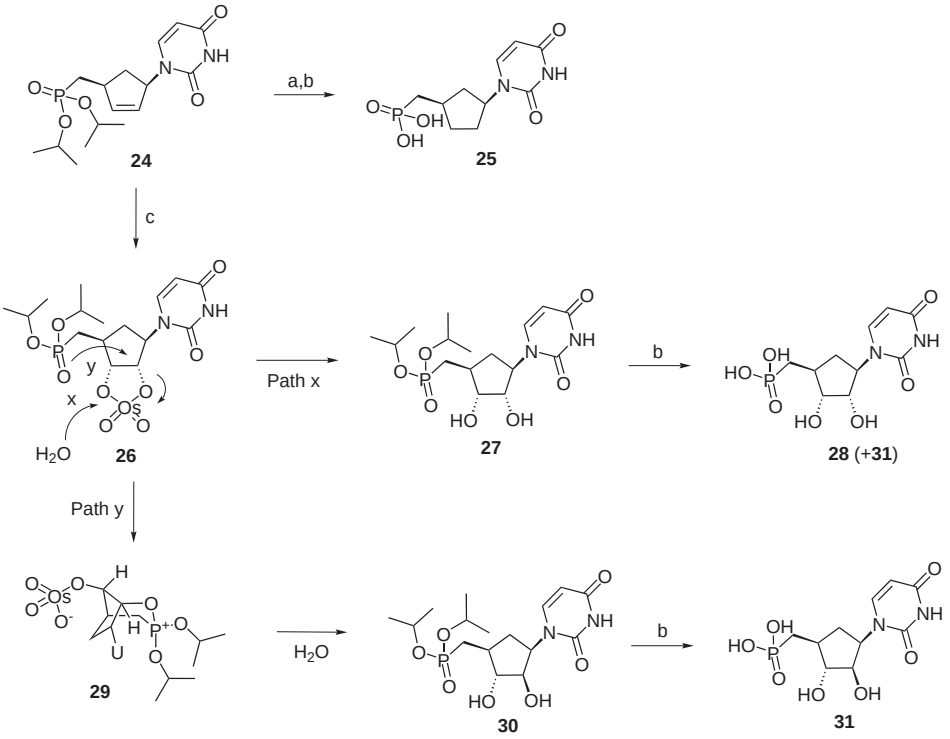
Hydrogen peroxide-mediated selenide oxidation and elimination provided the allyl acetate **21**[16] in excellent yield. Deprotection of the silyl ether and conversion of the resulting alcohol to its phosphonate ester **22** was carried out according to the sequence described above. The allyl acetate was activated with *tetrakis*-triphenylphosphine palladium, and the resulting π-allyl palladium species alkylated with uracil.[7] This resulted in a single regioisomer of a diastereoisomerically pure product,[13] which when deprotected under standard TMSBr conditions gave the cyclopentene phosphonic acid **23**.




**Scheme 3** a. VO(acac)$_2$, TBHP, $CH_2Cl_2$, 48 h, r.t., 89%; b. TBDMSCl, imidazole, $CH_2Cl_2$, 2 h, r.t., 100%; c. $(PhSe)_2$, $NaBH_4$, EtOH, 1 h, 0 °C to r.t., then 1 h, reflux, then $Ac_2O$, $Et_3N$, DMAP, $CH_2Cl_2$, 16 h, 0 °C to r.t., 100%; d. $H_2O_2$, Hünigs base, 1-butanol, $CH_2Cl_2$, 1 h, 50 °C, 79%; e. TBAF, THF, 1 h, r.t., 40%; f. TsCl, $Et_3N$, DMAP, 48 h, 0 °C, 98%; g and h. NaI, butanone, 5 h, reflux, then P(O*i*-Pr)$_3$, 65 h, 120 °C, 36%; i. uracil, Pd(PPh$_3$)$_4$, THF, DMSO, LiH, 0.5 h, 50 °C, 47%; j. TMSBr, MeCN, 16 h, r.t., 54%.

Phosphonate ester **24** could be simply hydrogenated under Pd catalysis and deprotected to give the analogous cyclopentane **25** (Scheme 4). Phosphonate ester **24** also served as an ideal material to introduce a *cis*-dihydroxyl functionality through simple *cis*-hydroxylation. When **24** was treated with $OsO_4$ and NMO in a mixture of acetone and water, two major products were formed. When these were isolated by silica gel chromatography, we were surprised to discover that both the *cis*- (**27**) and *trans*-dihydroxy (**30**) cyclopentanes had formed in the osmylation reaction.[14] We rationalised this finding through the intermediate cyclic osmate **26** undergoing competitive hydrolysis by water to give the *cis* isomer **27** (path x), or being captured by the phosphonyl group through an intermediate such as **29**, followed by hydrolysis (path y) leading to the *trans*-isomer **30**. Deprotection of each isomer separately gave the final phosphonic acids. The *cis* to *trans* ratio of the osmylation step always favoured the *trans*-isomer by an approximately 3:1 ratio. It was found that during the TMSBr-mediated deprotection step, the separated *cis*-dihydroxy phosphonate **27** underwent further 2′-isomerisation to give a 2:1 ratio of diol phosphonic acids in favour of the *trans*-isomer. This latter isomerisation presumably proceeds by activation of the 2′-OH by either a proton or TMS, followed by $S_N2$ displacement by the phosphonate ester, similar to path y described in Scheme 4.[17]

Above is described a flexible synthesis of a range of cyclopentane phosphonic acid analogues, all based on an epoxide ring-opening strategy. Application of this chemistry to further examples of racemic nucleoside mimics, and asymmetric versions thereof, will be reported in due course.




**Scheme 4** a. $H_2$ (1 atm.), Pd/C (20%), EtOH, 18 h, r.t., 100%; b. TMSBr, MeCN, 16 h, r.t., 20% for compound **25**; 12% for compound **31**, 29% for compound **28**; c. $OsO_4$, NMO, acetone, $H_2O$, 16 h, 50 °C, 66% overall (22% of **27**, 44% of **30**).

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(13) Assumed to be the diastereoisomer shown by direct analogy to literature reports for such π-allyl Pd-mediated base attachments.[7].

(14) Assignment of facial selectivity for the initial osmylation, and *cis*- and *trans*-diols was made by proton NMR methods (Figure 2), by firstly rigorously assigning each proton using COSY, followed by NOE experiments (vide infra).


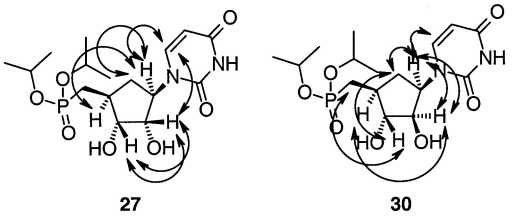


**Figure 2** NOE assignments for the *cis*-diol **27** and the *trans*-diol **30**.


(15) **Experimental Procedure, Preparation of 19.**
To a solution of 6-amino-purine (1 g, 7.4 mmol) in *N*,*N*-dimethylformamide (160 mL) was added $Cs_2CO_3$ (4.82 g, 14.8 mmol, 2 equiv), Kryptofix 2.2.2 (279 mg, 0.74 mmol, 0.1 equiv) and **4a** (4.27 g, 16.3 mmol, 2.2 equiv). The reaction mixture was stirred under argon at 120 °C for 4 d. After this time, HPLC analysis indicated that the reaction was 20% complete, therefore a further 1.94 g (1 equiv) **4a** were added and stirring continued at 120 °C for a further 5 d. The reaction mixture was then cooled, concentrated in vacuo purified by flash chromatography (silica, 5–20% MeOH in $CH_2Cl_2$) to give 1.2 g (41%) of the phosphonate ester as a yellow solid; mp 157–159 °C. $^1$H NMR ($CD_3OD$): δ = 1.31 (d, 12 H), 1.90–2.20 (m, 5 H), 2.60–2.80 (m, 2 H), 4.65 (m, 2 H), 8.16 (2 × s, 2 H); LRMS ($ES^+$): *m/z* (rel. int.) = 398.24 $[M + H]^+$. Chemical purity by HPLC, Synergy

Hydro RP18 4.6 × 150 mm, 0–40% MeCN over 20 min then held for 5 min, aq phase 20 mM $NaH_2PO_4$, pH 2, 93.7% (260 nm). Bromotrimethylsilane (4.9 mL, 3.7 mmol, 3.3 equiv) was added to a portion of this ester (450 mg, 1.13 mmol) in MeCN (10 mL) and then stirred overnight at r.t. The reaction mixture was concentrated in vacuo, added to $H_2O$ (10 mL) and adjusted to pH 4.5 with 1 M NaOH solution. After removing the solvent in vacuo the residue was added to $H_2O$ (3 mL). Then, 5 drops of TFA were added and the resultant solution purified by preparative HPLC. Freeze drying gave 260 mg (74%) of **19** as a white solid. $^1$H NMR (18% DCl in $D_2O$): δ = 0.15–0.40 (m, 5 H), 0.75–0.90 (m, 2 H), 2.90 (m, 1 H), 3.25 (m, 1 H), 6.85 (s, 1 H), 7.85 (s, 1 H). $R_f$ = 0.6 (1:1:1:1:1 toluene–acetone–BuOH–$H_2O$–HOAc). LRMS ($ES^+$): *m/z* (rel. int.) = 314.10 $[M + H]^+$. Chemical purity by HPLC, Synergy Hydro RP18 4.6 × 150 mm, 0–20% MeCN over 20 min then held for 5 min, aq phase 20 mM $NaH_2PO_4$, pH 7, 96.97% (261 nm).

(16) **Experimental Procedure, Preparation of 21.**
To a stirred solution of diphenyl diselenide (180 g, 0.58 mol, 1 equiv) in EtOH (8 L) at 0 °C was slowly added in small portions $NaBH_4$ over 70 min. Compound **4b** (262 g, 1.15 mol, 2 equiv) was then added dropwise to the reaction mixture over 15min and the solution was allowed to warm to r.t. The reaction mixture was subsequently heated at reflux for 1 h, air was blown over the cooled solution, and the solvent was removed in vacuo. The residue was dissolved in $CH_2Cl_2$ (2 L), the organic fraction was washed with $H_2O$ (2 × 300 mL) and brine (300 mL), dried over $MgSO_4$, and the solvent was removed in vacuo. The crude hydroxyselenide (39 g, 88.7 mmol, 1 equiv) was subsequently dissolved in $CH_2Cl_2$ (400 mL) and $Et_3N$ (12.7 mL, 90.9 mmol, 1 equiv) and 4-(dimethylamino)pyridine (4 mg, 0.033 mmol) were added. The reaction mixture was then cooled to 0 °C and acetic anhydride (8.5 mL, 90.1 mmol, 1 equiv) was added dropwise over 15 min. The reaction mixture was then stirred at r.t. overnight. Then, $CH_2Cl_2$ (1 L) and $H_2O$ (1 L) were added, the organic layer was separated, washed with $H_2O$ and brine, and the solvent was removed in vacuo to give crude **20** (450 g, 100%) as an oil. $^1$H NMR ($CDCl_3$): δ = 0.02 (s, 6 H), 0.87 (s, 9 H), 1.43 (m, 1 H), 1.83 (m, 1 H), 1.92 (s, 3 H), 2.02 (m, 1 H), 2.26–2.39 (m, 2 H), 3.51 (d, 2 H), 3.64 (m, 1 H), 5.11 (m, 1 H), 7.22–7.29 (m, 3 H), 7.51–7.62 (m, 2 H). A portion of crude **20** (20 g, 48.2 mmol, 1 equiv) was taken up and stirred in $CH_2Cl_2$ (150 mL) at 0 °C and to this was added 35% aq $H_2O_2$ (50 mL) and *N*,*N*-diisopropylethylamine (18.5 mL, 106 mmol, 2.2 equiv). After stirring for 15 min, 1-BuOH (75 mL) was added and the reaction mixture was heated at 50 °C for 40 min. The reaction mixture was then allowed to cool to r.t. and 1 M citric acid (200 mL) was added. The organic layer was washed with sat. $NaHCO_3$ (200 mL) and brine (200 mL), and was then concentrated in vacuo. The residue was dissolved in hexane (500 mL) and washed with $H_2O$ (2 × 500 mL). The organic phase was filtered and concentrated under vacuum to give **21** (10 g, 79%) as a brown oil. $^1$H NMR ($CDCl_3$): δ = 0.06 (s, 6 H), 0.85 (s, 9 H), 1.49 (dt, 1 H), 2.02 (s, 3 H), 2.39 (dt, 1 H), 2.80 (m, 1 H), 3.52 (d, 2 H), 5.62 (m, 1 H), 5.84 (m, 1 H), 6.02 (m, 1 H).

(17) **Experimental Procedure, Preparation of 31.**
The cyclopentene **24** (1.63 g, 4.60 mmol) was dissolved in acetone (5 mL) and to this NMO (539 mg, 9.2 mmol) was added followed by 1% $OsO_4$ in $H_2O$ (2.5 mL). This mixture was heated at 50 °C overnight. More NMO (50 mg, 0.85 mmol) was added and stirred for a further 2 h at 50 °C. The solution was then concentrated by evaporation and purified by flash chromatography (85:15 $CH_2Cl_2$–MeOH) to give **27** (220 mg, 0.56 mmol, 12%) and **30** (530 mg, 1.36 mmol, 29%). Analytical data for **27**: $R_f$ = 0.3 (10% MeOH in $CH_2Cl_2$). $^1$H NMR ($CD_3OD$): δ = 1.30 (d, 12 H), 1.70 (m, 1 H), 1.90 (m, 1 H), 2.15 (m, 2 H), 2.30 (m, 1 H), 4.05 (t, 1 H), 4.20 (dd, 1 H), 4.65 (m, 2 H), 5.10 (m, 1 H), 5.65 (d, 1 H), 7.90 (d, 1 H). Analytical data for **30**: $R_f$ = 0.2 (10% MeOH in $CH_2Cl_2$). $^1$H NMR ($CD_3OD$): δ = 1.30 (d, 12 H), 1.60 (m, 1 H), 1.80 (m, 1 H), 2.15 (m, 2 H), 2.35 (m, 1 H), 3.80 (t, 1 H), 4.20 (t, 1 H), 4.45 (m, 1 H), 4.65 (m, 2 H), 5.65 (d, 1 H), 7.60 (d, 1 H). Trimethylsilylbromide (1.8 mL, 13.6 mmol) was added to a stirred solution of **30** (530 mg, 1.36 mmol) in MeCN (20 mL) under an atmosphere of nitrogen, the reaction mixture was stirred overnight at r.t. The reaction was not complete and therefore more trimethylsilylbromide (2 mL) was added. This mixture was left at r.t. for a further 2 d. The solvent was then removed under vacuum. Then, $H_2O$ (10 mL) was added to the reaction mixture, which was basified with 1 M aq NaOH and subsequently acidified with TFA. The solvent was removed under reduced pressure and $H_2O$ (10 mL) was added. The crude product was purified by HPLC (0.1% TFA in $H_2O$ 10 min, then 10% MeCN, Atlantis) and freeze dried to give **31** (245 mg, 0.80 mmol, 59%). $R_f$ = 0.30 (1:1:1:1:1 toluene–acetone–butan-1-ol–$H_2O$–HOAc). $^1$H NMR ($D_2O$): δ = 1.30–1.60 (m, 2 H), 1.70–2.00 (m, 2 H), 2.15 (m, 1 H), 3.80 (m, 1 H), 4.00 (dd, 1 H), 4.90 (q, 1 H), 5.50 (d, 1 H), 7.80 (d, 1 H), 11.10 (s, 1 H). LRMS ($ES^+$): *m/z* (rel. int.) = 307.12 $[M + H]^+$. Chemical purity by HPLC, Synergy Hydro 4.6 × 150 mm, 1.0 mL/min, 0– 40% MeCN over 20 min then to 70% over 5 min, held at 70% for 5 min, aq phase 20 mM $NaH_2PO_4$, pH 2.5, 97.82% (270 nm).