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Synthesis of Guanine α -Carboxy Nucleoside Phosphonate (G- α -CNP), a direct inhibitor of multiple viral DNA polymerases

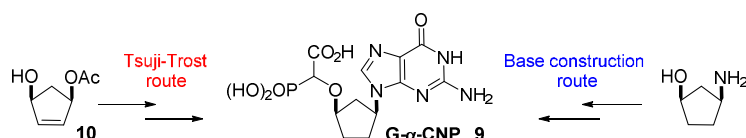
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Abstract: The synthesis of guanine α -carboxy nucleoside phosphonate (G- α -CNP) is described. Two routes provide access to racemic G- α -CNP **9**, one via base construction and the other utilizing Tsuji–Trost allylic substitution. The latter methodology was also applied to the enantiopure synthesis of both antipodes of G- α -CNP, each of which shows interesting antiviral DNA polymerase activity. Additionally, we report an improved multi-gram scale preparation of the cyclopentene building block **10**, starting material for the preferred Tsuji–Trost route to **9**.

Carbocyclic nucleosides have been of interest to medicinal chemists for several decades,^{1–3} due to their broad spectrum of biological activity and therapeutic importance in the treatment of conditions such as cancer,⁴ hepatitis and HIV infections.⁵ Current clinical examples include the anti-HIV drug abacavir **1** and entecavir **2**, for the treatment of hepatitis B virus (HBV) (Figure 1), and interest in the design and synthesis of new carbanucleosides continues unabated. We recently reported the synthesis of a new class of nucleoside phosphonate analogues, α -carboxy nucleoside phosphonates (α -CNPs), which show potent inhibitory activity against HIV-1 reverse transcriptase (RT) without the need for prior (metabolic) activation.⁶ This feature of α -CNPs sets them apart from all current nucleoside and nucleotide analogue drugs (e.g. tenofovir **3**) which require phosphorylation by viral and/or cellular kinases in order to become active.⁷

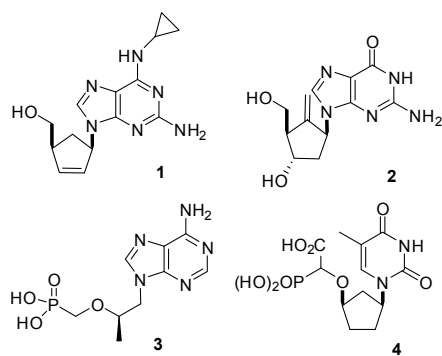


Figure 1. Some nucleoside analogue antivirals (**1-3**) and T- α -CNP (**4**)

The key structural feature of α -CNPs is a carboxyl group at the alpha position of the carbocyclic nucleoside phosphonate, as exemplified by thymine CNP (T- α -CNP) **4**. Crystallographic studies of the interaction between the prototype thymine T- α -CNP and HIV-1 reverse transcriptase reveal that the carboxylate oxygen and both phosphonate oxygens of the CNP chelate to a Mg^{2+} ion (B) at the enzyme active site, in a manner analogous to the chelation by α -, β - and γ -phosphate oxygens of the natural dTTP (Figure 2).⁸ Retention of Watson-Crick base-pairing leads to specificity not seen with other nucleotide-competing reverse transcriptase inhibitors (NcRTIs). With an α -CNP bound at the substrate binding site, hydrolysis and incorporation of an incoming dNTP by RT can no longer take place and RT inhibition thereby occurs. In this way, α -CNPs act as nucleoside triphosphate mimics and behave as NcRTIs.

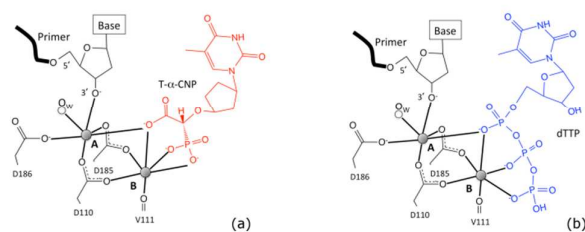


Figure 2. Binding of T- α -CNP (**a**) and dTTP (**b**) at the polymerase active site of HIV-1 RT

Our original report described the synthesis of α -CNPs containing the nucleobases thymine **4**, adenine **5**, cytosine **6**, uracil **7** and 5-fluorouracil **8**.⁶ However, initial attempts to prepare the

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3 guanine α -CNP **9** using the same methodology had proved unsuccessful. As guanine is a key
4 functionality in many drugs we were keen to obtain and evaluate G- α -CNP. Herein we extend
5 the series of α -CNPs to include the synthesis of the guanine analogue **9** (Figure 3).
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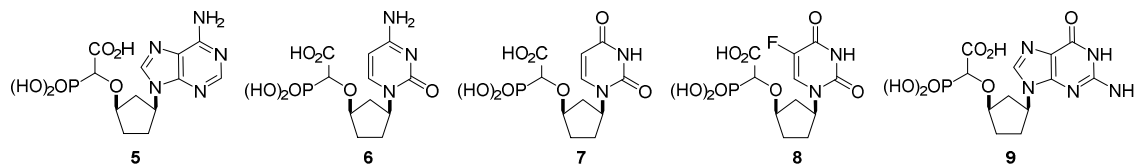


Figure 3. α -Carboxy nucleoside phosphonates (α -CNPs)

We recently reported the biological activity of G- α -CNP.⁹ The guanine analogue (IC_{50} : 0.62 μ M) proved to be an equally potent inhibitor of HIV-1 RT as the prototype T- α -CNP (IC_{50} : 0.41 μ M) with activity residing only in the L-isomer as previously reported for the original series of α -CNPs.⁸ However, when herpes virus DNA polymerases (i.e. HSV-1, HCMV) were investigated, interestingly both (D)-G- α -CNP and (L)-G- α -CNP were found to inhibit herpes DNA polymerases in a non-competitive manner with respect to the natural dNTPs, a result indicative of interaction at a location other than the polymerase substrate active site of the herpes-encoded enzymes. This variation in inhibition profile across a range of viral polymerases is unprecedented and identifies G- α -CNP as an inhibitor of multiple viral DNA polymerases, with a different molecular mechanism of inhibition depending on the nature of the enzyme.

Our original strategy for α -CNP synthesis involved O-H insertion of trimethyl phosphonodiazooacetate with the widely-used cyclopentene building block **10** followed by incorporation of the desired nucleobase using Tsuji-Trost^{10,11} methodology (Figure 4, Route I) and was successfully applied to the synthesis of pyrimidine (**4,6-8**) and adenine (**5**) α -CNPs. The convergent approach with late-stage attachment of the nucleobase is attractive because base protection is not required. However, Tsuji-Trost allylic substitution proved to be capricious: yields were only moderate in general and in the case of purine bases quite poor, due to competition between N9- and N7-insertion.¹² Therefore, when this strategy was unsuccessful for the guanine analogue we explored other options.

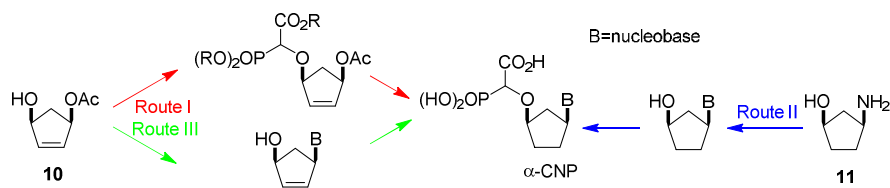
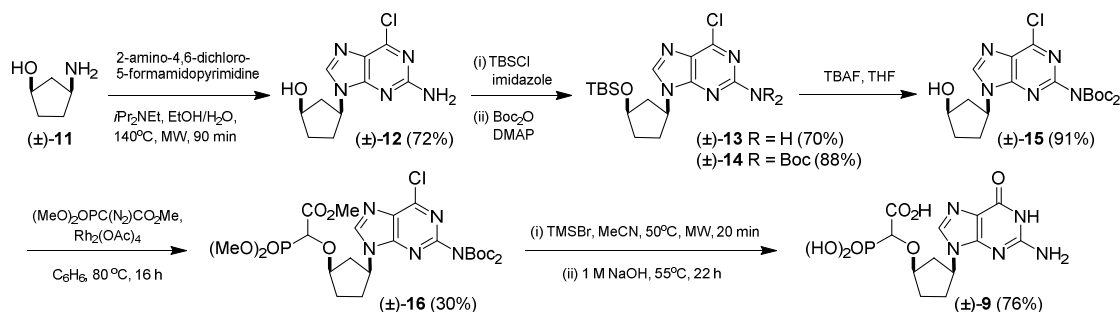


Figure 4. Routes to α -CNPs from **10** and **11**

Several synthetic methodologies can be applied to carbocyclic nucleosides, among them base construction from cyclopentyl amines (Figure 4, Route II).^{1,2} In this instance, base construction proved effective and a convenient one-pot microwave procedure¹³ was employed in the synthesis of racemic guanine α -CNP **9** (Scheme 1). Reaction of *cis*-3-aminocyclopentanol **11** with 2-amino-4,6-dichloro-5-formamidopyrimidine afforded the hydroxycyclopentylpurine **12** in 72% yield. Temporary TBS protection of the alcohol gave **13** then Boc protection of the amine afforded **14**, which was treated with TBAF to provide alcohol **15** required for the O–H insertion step. Reaction of **15** with trimethyl phosphondiazoacetate in the presence of rhodium acetate as catalyst for 16 h at reflux in benzene afforded the protected nucleoside phosphonate **16** in 30% yield following careful chromatography. As with previous CNPs, **16** was formed as an equimolar mixture of diastereomers at the position alpha to the phosphonate. Reaction of **16** with TMSBr in the microwave¹⁴ followed by treatment with aqueous sodium hydroxide removed all protecting groups and converted the chloropurine to guanine, thereby providing racemic guanine α -CNP **9** in 76% yield following charcoal chromatography.

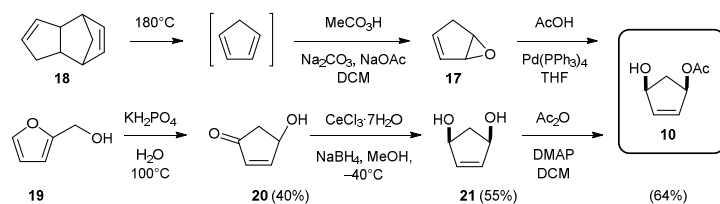
Scheme 1. Synthesis of (\pm)-G- α -CNP **9** via base construction



This strategy of initial purine base construction followed by late-stage introduction of the phosphonate moiety provided access to the racemic guanine α -CNP. As we had expected, preliminary biological evaluation was promising and, as a result, we directed our synthetic efforts towards enantiopure material. The commercial availability of both enantiomers of allylic acetate **10** now encouraged us to revisit routes from this starting material, and literature precedent for coupling of **10** with 2-amino-6-chloropurine¹⁵ offered a means of introducing the base at the first step (Figure 4, Route III), in line with the racemic synthesis. We chose to develop this route first using racemic **10**.

In the past we have used a well-established route to the acetate **10** which involves the palladium catalyzed ring-opening of cyclopentadiene mono-epoxide **17** with acetic acid (Scheme 2).^{16,17} Now we desired to use an alternative route to avoid both the tedious process of cracking cyclopentadiene **18** and the time-consuming distillation of the epoxide **17**. The acid-promoted rearrangement of furfuryl alcohol **19** to the hydroxyenone has been described several times by means of batch- or flow-based processes.¹⁸⁻²¹ In a batch reaction at a 0.3 mol scale, we found that the hydroxyenone **20** can easily be isolated in 40% yield (11 g per batch) following trivial workup.

Scheme 2. Synthesis of acetate **10**

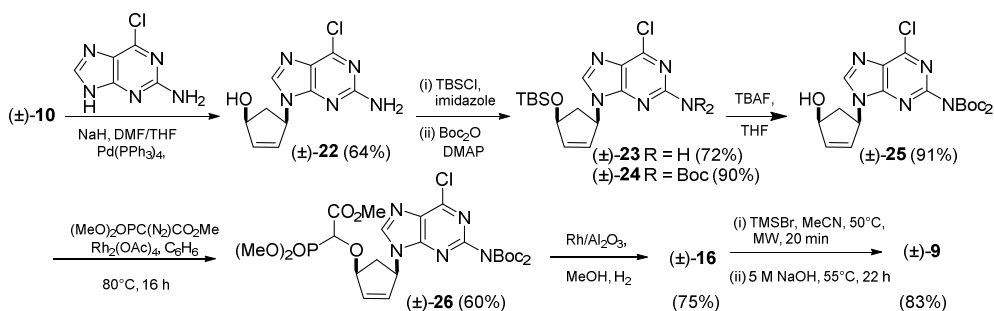


The *cis*-selective reduction of protected derivatives of **20** has also been described,¹⁸ and in fact the reduction of the unprotected enone, using modified Luche conditions, has been reported to afford 9:1 *cis/trans* selectivity;²² importantly, crude **20** can be used without any purification, and the *cis* and *trans* diastereomers of **21** can be separated by chromatography. The very high water solubility of the diol means that aqueous workup is impractical and thus purification is hampered by the presence of the excess CeCl_3 required for the best selectivity. On a small scale, the reported procedure works well (quench the reaction with silica gel and column the residue directly) but on a scale of a few grams, this proves difficult due to the relatively large volume of silica required, and the very large volumes of solvents

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3 (CH₂Cl₂/MeOH) required to fully elute the product. Care must be taken to avoid using too
4 much methanol in the eluent as this carries through significant amounts of cerium chloride.
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6 The problem was conveniently solved by using deactivated alumina to adsorb the crude
7 product, followed by a preliminary plug column on deactivated alumina prior to
8 chromatography on silica gel. Following this work-up the desired cis diol **21** can be isolated
9 in >50% yield on a 5 g scale. With convenient access to the diol, the monoacetate is readily
10 prepared in 50–65% yield following a literature procedure.²³ In practice this route provides
11 straightforward access to multi-gram quantities of the monoacetate **10**; the overall yield
12 starting from furfuryl alcohol is typically 14%. The diacetate side-product formed in the
13 acetylation reaction can be recycled to the diol, or used as a substrate for enzymatic
14 hydrolysis to provide enantioenriched **10**, thereby enabling full product utilization.
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23 Coupling of **10** with 2-amino-6-chloropurine in the presence of
24 tetrakis(triphenylphosphine)palladium(0), following literature protocol for exclusive N9-
25 insertion,¹⁵ afforded the N9-product **22** in 64% yield (Scheme 3). Sequential TBS and Boc
26 protection of hydroxycyclopentenylpurine **22** provided **23** and **24** in yields of 72% and 90%,
27 respectively, then treatment of **24** with TBAF released the allylic alcohol **25** (91%) required
28 for the key O–H insertion reaction. Reaction of **25** with trimethyl phosphonodiazacetate in
29 refluxing benzene, in the presence of rhodium acetate dimer, afforded the unsaturated
30 nucleoside phosphonate **26** in 60% yield. Catalytic hydrogenation of the cyclopentenyl
31 double bond proved problematic with this substrate using palladium on carbon, but was
32 readily achieved with rhodium on alumina to provide the protected nucleoside phosphonate
33 **16**, which confirmed the regioselectivity of the Tsuji–Trost reaction.²⁴ Finally, reaction of **16**
34 with TMSBr in the microwave followed by treatment with aqueous sodium hydroxide, as
35 before, conveniently removed all protecting groups and converted the chloropurine to
36 guanine to give the racemic guanine α -CNP **9**, as an equimolar mixture of diastereomers, in
37 83% yield following charcoal chromatography.
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49 **Scheme 3.** Synthesis of (\pm)-G- α -CNP via allylic substitution
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The strategy of introducing the base before the phosphonate moiety, this time starting from the allylic acetate **10** (Figure 4, Route III), once again proved successful. As anticipated, carrying out the key O–H insertion reaction with the allylic alcohol **25** was more efficient (60%) than when the cyclopentyl alcohol **15** was employed (30%), facilitating good yields for the introduction of both the base and the phosphonate moiety, and allowing preparation of gram quantities of racemic guanine α -CNP **9**. This methodology offers an effective route to the previously elusive guanine α -CNP which is applicable to both racemic and enantiopure syntheses, making it the route of choice to G- α -CNP.

Having optimised the synthesis of racemic guanine α -CNP we turned our attention to enantiopure material. The commercial availability of both enantiomers of allylic acetate **10** allowed parallel syntheses of both antipodes of **9** (each as a pair of diastereomers); accordingly, the L-isomer of G- α -CNP (–)-**9** was prepared from (–)-**10** via the above route and the D-isomer (+)-**9** was obtained from the enantiomeric acetate (+)-**10** (Figure 5). Yields, in each case, were similar to those obtained for the racemate, and optical rotation values for the D- and the L-series were mutually opposite in sign throughout the synthetic sequences. Our original report assigned (D)- and (L)-G- α -CNP as (–) and (+) respectively,⁹ based on optical rotations recorded in aqueous THF. We now find that more reproducible optical rotation values for **9** can be obtained in aqueous sodium hydroxide solution and, therefore, in this solvent (D)-G- α -CNP is assigned as (+)-**9** and (L)-G- α -CNP is assigned as (–)-**9**. Access to both antipodes of G- α -CNP enabled biological evaluation of each pair of diastereomers. Interestingly, the L-isomer showed potent activity against HIV-1 RT whereas both the D- and the L-isomer were active against herpes virus DNA polymerases, identifying G- α -CNP as a direct inhibitor of multiple viral DNA polymerases.⁹

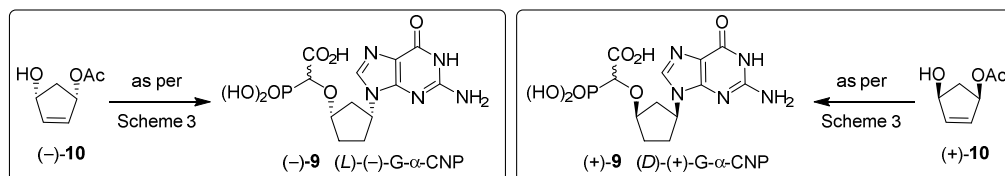


Figure 5. Diastereomers of G- α -CNP obtained from enantiopure synthesis

In conclusion, we have developed a convenient, multi-gram scale preparation of the widely used cyclopentene building block, allylic acetate **10**. By reversing the order of key steps in our original route to α -CNPs we have now synthesised the biologically active guanine analogue G- α -CNP **9** in good yield, in racemic and both enantiopure forms from **10**. Base construction was also shown to be a viable route to racemic **9**. These complementary methodologies (Figure 4, Route I, II and III) offer scope for further diversification and access to modified α -CNPs.

Experimental Section.

General information. Solvents were distilled prior to use as follows: dichloromethane was distilled from phosphorus pentoxide; ethyl acetate was distilled from potassium carbonate; tetrahydrofuran was distilled from sodium benzophenone. Solvents were degassed, as required, by purging with nitrogen. Organic phases were dried using anhydrous magnesium sulfate. Microwave reactions were carried out using a CEM Discover S-Class in conjunction with Synergy software. Sealed vials (10 mL or 35 mL) were used and temperature was measured externally using an IR sensor. Unless otherwise stated, reactions were heated using a heating block. ^1H , ^{13}C and ^{31}P NMR spectra were recorded at 20 °C on 300, 400, 500 or 600 MHz spectrometers. Chemical shifts are given in ppm relative to TMS as an internal standard. ^{31}P chemical shifts are referenced to H_3PO_4 (external standard). Coupling constants (J) are given in hertz (Hz). The integration of ^1H NMR spectra was used to determine the diastereomer ratios of α -CNP compounds. In some cases the signal for the PCH was not observed in the ^{13}C NMR spectrum. Optical rotations were measured at 20 °C at 589 nm in a 10 cm cell; concentrations (c) are expressed in g/100 mL and $[\alpha]$ is expressed in units of 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$. High resolution mass spectra (HRMS) were recorded on a Time of Flight spectrometer in electrospray ionization (ESI) mode. Column chromatography was carried out

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3 using silica gel 60 unless otherwise stated. Thin layer chromatography (TLC) was carried out
4 on pre-coated silica gel plates (Merck 60 PF254); visualisation was achieved by UV (254 nm)
5 detection and/or staining with vanillin, ceric ammonium molybdate, or potassium
6 permanganate. Charcoal chromatography was carried out using activated carbon Darco G-60,
7 according to the procedure described previously.²⁵ Tetrakis(triphenylphosphine)palladium(0)
8 was prepared as described in the literature.²⁶

14 **Synthesis of Racemic G- α -CNP 9 from amino alcohol 11**

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18 *Cis*-3-Aminocyclopentanol (**11**). 3-Cbz-Aminocyclopentanol was prepared according to
19 published procedures.²⁷ Flash chromatography of the *cis*/*trans* mixture, eluting with 95:5,
20 DCM:MeOH afforded *cis*-3-Cbz-aminocyclopentanol as a white solid; δ_{H} (400.1 MHz,
21 CDCl₃) 1.52–1.89 (4H, m), 1.90–2.28 (3H, m), 4.04–4.23 (1H, m), 4.30–4.45 (1H, m), 5.08
22 (2H, s), 5.45 (1H, s), 7.24–7.44 (5H, m); δ_{C} {¹H} (100.6 MHz, CDCl₃) 31.7, 34.3, 42.3, 51.5,
23 66.5, 73.1, 128.0, 128.5, 136.7, 155.8; HRMS (ES+) *m/z*: [M+H]⁺ Calcd for C₁₃H₁₈NO₃
24 236.1287; Found 236.1284. To a solution of *cis*-3-Cbz-aminocyclopentanol (377 mg, 1.6
25 mmol) in methanol (20 mL) was added 5% palladium on carbon (110 mg, 5.5 mg, 3 mol %) and the mixture was stirred under a balloon of hydrogen overnight. After filtration through
26 Celite and washing with MeOH (20 mL) then DCM (10 mL), concn of the filtrate under
27 reduced pressure afforded the title compound **11** as an oil in 88% yield (143 mg); δ_{H} (400.1
28 MHz, CDCl₃) 1.53–2.00 (6H, m), 2.02–2.84 (3H, m), 3.59–3.72 (1H, m), 4.20–4.32 (1H, m);
29 δ_{C} {¹H} (100.6 MHz, CDCl₃) 33.0, 34.8, 43.8, 52.2, 74.4; HRMS (ES+) *m/z*: [M+H]⁺ Calcd
30 for C₅H₁₂NO 102.0919; Found 102.0916.

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42 2-Amino-6-chloro-9-(*cis*-3'-hydroxycyclopentyl)purine (**12**). Freshly prepared amino alcohol
43 **11** (143 mg, 1.4 mmol) was dissolved in 1:1 EtOH:H₂O (8 mL) in a 35 mL microwave vial
44 and 2-amino-4,6-dichloro-5-formamidopyrimidine (351 mg, 1.7 mmol, 1.2 eq) then Hünig's
45 base (472 μ L, 350 mg, 2.7 mmol, 1.9 eq) was added. The resulting cream suspension was
46 subjected to microwave irradiation at 140 °C for 90 min. Removal of the solvent afforded a
47 crude red oil which was purified by flash chromatography, eluting with 2:98 to 5:98
48 MeOH:EtOAc, to provide 257 mg (72%) of the title compound **12** as a white foam; δ_{H} (300.1
49 MHz, CDCl₃) 1.67–1.87 (1H, m), 1.96–2.15 (2H, m), 2.24–2.39 (2H, m), 2.52 (1H, ddd, *J* =
50 15.5, 10.7, 5.5), 4.40–4.53 (1H, m), 4.78–4.93 (1H, m), 5.27 (1H, d, *J* = 6.4), 5.58 (2H, s),
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7.98 (1H, s); δ_C $\{^1H\}$ (75.5 MHz, $CDCl_3$) 30.6, 35.4, 41.2, 54.7, 72.2, 125.8, 142.6, 151.6, 152.5, 158.4; HRMS (ES+) m/z: $[M+H]^+$ Calcd for $C_{10}H_{13}N_5OCl$ 254.0809; Found 254.0798.

2-Amino-6-chloro-9-(*cis*-3'-*tert*-butyldimethylsilyloxycyclopentyl)purine (**13**). Alcohol **12** (314 mg, 1.2 mmol), *tert*-butyldimethylchlorosilane (280 mg, 1.9 mmol, 1.5 eq) and imidazole (211 mg, 3.1 mmol, 2.5 eq) were dissolved in anhydrous DMF (1.5 mL) under nitrogen and the solution was stirred at rt for 18 h. It was poured into brine (80 mL) and extracted with EtOAc (3 \times 35 mL). The combined organic layers were washed with brine (80 mL), dried over $MgSO_4$ and concd under reduced pressure to afford the crude product, which was subjected to flash chromatography, eluting with 1:1, hexane: EtOAc, to provide 320 mg (70%) of the title compound **13** as a white solid; δ_H (400.1 MHz, $CDCl_3$) 0.107 (3H, s), 0.113 (3H, s), 0.93 (9H, s), 1.76–1.98 (3H, m), 2.01–2.16 (1H, m), 2.27–2.51 (2H, m), 4.42–4.51 (1H, m), 4.93–5.13 (3H, m), 8.22 (1H, s); δ_C $\{^1H\}$ (100.6 MHz, $CDCl_3$) –4.8, –4.7, 18.1, 25.9, 32.3, 35.5, 42.9, 52.8, 72.9, 125.3, 142.1, 151.0, 153.7, 158.8; HRMS (ES+) m/z: $[M+H]^+$ Calcd for $C_{16}H_{27}N_5OClSi$ 368.1673; found 368.1662.

2-*bis*-Boc-Amino-6-chloro-9-(*cis*-3'-*tert*-butyldimethylsilyloxycyclopentyl)purine (**14**). Aminopurine **13** (120 mg, 0.3 mmol) and DMAP (3 mg, 7.5 mol %) were dissolved in anhydrous THF (5 mL) and Boc_2O (209 mg, 220 μ L, 0.9 mmol) was added. The solution was stirred under nitrogen for 18 h then concd under reduced pressure and the residue subjected to flash chromatography, eluting with 6:4, hexane: EtOAc, to provide 163 mg (88%) of the title compound **14** as a sticky white solid; δ_H (400.1 MHz, $CDCl_3$) 0.12 (3H, s), 0.13 (3H, s), 0.94 (9H, s), 1.45 (18H, s), 1.79–2.03 (3H, m), 2.04–2.18 (1H, m), 2.36–2.56 (2H, m), 4.46–4.57 (1H, m), 5.15–5.28 (1H, m), 8.63(1H, s); δ_C $\{^1H\}$ (100.6 MHz, $CDCl_3$) –4.85, –4.72, 18.1, 25.9, 27.9, 32.6, 35.5, 43.0, 53.6, 73.0, 83.5, 130.0, 145.9, 150.7, 150.8, 151.6, 152.6; HRMS (ES+) m/z: $[M+H]^+$ Calcd for $C_{26}H_{43}N_5O_5ClSi$ 568.2722; Found 568.2726.

2-*bis*-Boc-Amino-6-chloro-9-(*cis*-3'-hydroxycyclopentyl)purine (**15**). Purine **14** (425 mg, 0.7 mmol) was dissolved in anhydrous THF (10 mL) under nitrogen and ice-cooled. A solution of TBAF in THF (1 M, 820 μ L, 0.8 mmol) was added and the reaction was stirred in ice for 40 min and then for 50 min with cooling removed. The solvent was removed under reduced pressure and the residue subjected to flash chromatography, eluting with 5:95, MeOH: DCM, to provide 310 mg (91%) of the title compound **15** as a white solid; δ_H (300.1 MHz, $CDCl_3$)

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3 1.46 (18H, s), 1.78–1.96 (1H, m), 1.97–2.16 (2H, m), 2.18–2.48 (2H, m), 2.49–2.64 (1H, m),
4 3.04 (1H, d, $J = 4.0$), 4.54 (1H, s), 5.03–5.19 (1H, m), 8.48 (1H, s); $\delta_{\text{C}} \{^1\text{H}\}$ (100.6 MHz,
5 CDCl_3) 27.9, 31.7, 35.4, 41.7, 54.7, 72.2, 83.7, 130.4, 146.0, 150.6, 151.1, 151.4, 152.1;
6 HRMS (ES+) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{29}\text{N}_5\text{O}_5\text{Cl}$ 454.1857; Found 454.1862.
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11 *2-bis-Boc-Amino-6-chloro-9-(cis-3'-*

12 (carbomethoxy(dimethylphosphono)methoxy)cyclopentyl)purine (**16**). Alcohol **15** (310 mg,
13 0.68 mmol) was dissolved in degassed benzene (5 mL) then trimethyl phosphonodiazacetate
14 (156 mg, 0.75 mmol, 1.1 eq) and activated sieves were added and the mixture was stirred
15 under nitrogen for 30 min. Rhodium(II) acetate (3 mg, 1 mol %) was added and the reaction
16 mixture was heated under reflux for 16 h then filtered and concd under reduced pressure.
17 Flash chromatography of the residue (2:98 to 5:95, MeOH:EtOAc) afforded the title
18 phosphonate **16** in 30% yield (131 mg, dr 1:1); δ_{H} (400.1 MHz, CDCl_3) 1.45 (18H, s), 1.74–
19 2.33 (4H, m), 2.37–2.65 (2H, m), 3.82–3.95 (9H, m), 4.27–4.41 (1H, m), 4.42 (0.5H, d,
20 $J_{\text{PH}}=19.2$), 4.49 (0.5H, d, $J_{\text{PH}}=20.2$), 5.17–5.35 (1H, m), 8.74 (0.5H, s), 8.90 (0.5H, s); δ_{C}
21 $\{^1\text{H}\}$ (75.5 MHz, CDCl_3) 27.9, 30.8, 31.6, 31.96, 32.02, 40.22, 40.32, 53.1, 54.0–54.4, 73.7
22 (d, $J_{\text{PC}} = 160.4$), 74.5 (d, $J_{\text{PC}} = 159.5$), 82.0 (d, $J_{\text{PC}} = 11.6$), 83.0 (d, $J_{\text{PC}} = 8.7$), 83.6, 129.95,
23 129.99, 145.9, 146.2, 150.68, 150.69, 150.8, 151.5, 152.7, 167.6 (d, $J_{\text{PC}} = 2.1$), 167.9 (d, J_{PC}
24 = 2.8); δ_{P} (121.5 MHz, CDCl_3) 16.57, 16.78; HRMS (ES+) m/z : $[\text{M}+\text{H}]^+$ Calcd for
25 $\text{C}_{25}\text{H}_{38}\text{N}_5\text{O}_{10}\text{ClP}$ 634.2045; Found 634.2030.
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37 9-(*cis-3'-(Carboxy(phosphono)methoxy)cyclopentyl)guanine* (**9**). Phosphonopurine **16** (57
38 mg, 0.09 mmol) was suspended in acetonitrile (2 mL) in a 10 mL microwave vial, TMSBr
39 (119 μL , 138 mg, 0.9 mmol) was added and the reaction mixture was subjected to microwave
40 irradiation at 50 °C for 20 min. MeOH (2 mL), containing 3 drops of water, was added and
41 the orange solution was stirred for 30 min. After removal of the solvent under reduced
42 pressure, 1 M sodium hydroxide (1.4 mL, 1.4 mmol) was added and the resulting solution
43 was stirred at 55 °C for 22 h. Removal of the solvent under reduced pressure afforded a
44 residue which was subjected to charcoal column chromatography eluting with ammonia (30%
45 aq.) to provide 29 mg of **9** as a cream solid (76% as the ammonium salt, dr 1:1); δ_{H} (400.1
46 MHz, D_2O) 1.08–2.00 (4H, m), 2.00–2.14 (1H, m), 1H 2.40–2.50 (1H, m), 3.93 (0.5H, d, $J =$
47 18.2), 3.99 (0.5H, d, $J = 18.3$) 4.03–4.10 (1H, m), 4.51–4.62 (1H, m), 8.03 (0.5H, s), 8.04
48 (0.5H, s); $\delta_{\text{C}} \{^1\text{H}\}$ (125.8 MHz, D_2O) 29.4, 30.5, 30.6 ($2 \times \text{CH}_2$), 37.8, 38.8 (CH_2), 53.3, 53.5
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(CH-1'), 80.0, 80.5 (CH-3'), 115.8 (C-5), 138.8 (CH-8), 151.2 (C-4), 153.4 (C-6), 158.8, 158.9 (C-2), 177.6 (CO₂H); δ_P (162.0 MHz, D₂O) 12.36, 12.48; HRMS (ES+) m/z: [M+H]⁺ Calcd for C₁₂H₁₇N₅O₇P 374.0866; Found 374.0861.

Synthesis of Racemic G- α -CNP **9** from acetate **10**

4-Hydroxy-2-cyclopenten-1-one (**20**). A solution of furfuryl alcohol (26 mL, 0.3 mol) and KH₂PO₄ (2g, 14.7 mmol) in water (500 mL) was purged with nitrogen gas for 2 h before being placed in a pre-equilibrated 125 °C heating block and stirred for 48 h. After being cooled to rt the mixture was washed with DCM (3 × 50 mL). The washings were back-extracted once with water (50 mL) and the combined aqueous phases were evaporated under reduced pressure. The residue was taken with DCM (100 mL), dried with MgSO₄, filtered and concd to afford the hydroxy enone **20** as an amber colored oil (11.3 g, 40%) which could be used without purification; δ_H (400.1 MHz, CDCl₃) 2.29 (1H, dd, J = 18.5, 1.8), 2.79 (1H, dd, H = 18.5, 6.1), 5.03–5.12 (1H, m), 6.20–6.29 (1H, m), 7.55–7.65 (1H, m).

cis-1,4-Dihydroxy-2-cyclopentene (**21**). A solution of the enone **20** (5.0 g, 51 mmol) and CeCl₃·7H₂O (40 g, 107 mmol) in MeOH (150 mL) was cooled to an internal temperature of –40 °C and stirred while powdered NaBH₄ (2.0 g, 53 mmol) was added in small portions during about 30 min. After the addition the solution was allowed to warm slowly to rt overnight. Deactivated alumina (10% v/v H₂O, 90 g) was added and the mixture was evaporated to dryness under reduced pressure. The residue was eluted over a plug of deactivated alumina (10% v/v H₂O, 150 g) using 5% MeOH/DCM to afford the crude product which was purified by flash chromatography on silica gel, eluting with 5% MeOH/DCM to afford the *cis*-diol **21** as a colorless, fern-like solid (2.8 g, 55%); δ_H (400.1 MHz, MeOD) 1.44 (1H, dt, J = 13.5, 5.4), 2.75 (1H, dt, J = 13.5, 7.3), 4.60 (2H, m), 5.92 (2H, br s).

cis-4-Acetoxy-2-cyclopenten-1-ol (**10**). A solution of the *cis*-diol **21** (2.8 g, 28 mmol), DMAP (0.34 g, 0.28 mmol) and acetic anhydride (3.0 mL, 3.24 g, 31.7 mmol) in DCM (75 mL) was stirred overnight at ambient temperature. The mixture was concd under reduced pressure and the residue was purified by flash chromatography (SiO₂, 1:1 EtOAc/Hexanes) to afford the desired mono acetate **10** as a white solid (2.5 g, 64%); δ_H (400.1 MHz, CDCl₃)

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3 1.66 (2H, dt, $J = 14.7, 3.7$), 1.88 (1H, br s), 2.06 (3H, s), 2.81 (1H, dt, $J = 14.7, 7.4$) 4.67–
4 4.77 (1H, m), 5.46–5.55 (1H, dd, $J = 7.4, 3.7$), 5.96–6.03 (1H, m), 6.09–6.15 (1H, m). Earlier
5 fractions from the column afforded the diacetate as a colorless oil (1.1 g, 21%); δ_{H} (400.1
6 MHz, CDCl_3) 1.75 (1H, dt, $J = 15.0, 3.8$), 2.07 (6H, s), 2.89 (1H, dt, $J = 15.0, 7.6$), 5.55 (2H,
7 dd, $J = 7.6, 3.8$), 6.10 (2H, s).
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13 2-Amino-6-chloro-9-(*cis*-4'-hydroxycyclopent-2'-enyl)purine (**22**). To a suspension of 2-
14 amino-6-chloropurine (1.31 g, 7.7 mmol) in anhydrous DMF (18 mL) under nitrogen was
15 added sodium hydride (60% dispersion in mineral oil, 0.31 g, 7.7 mmol) to afford a clear
16 solution, which was stirred at 60 °C for 1 h. A solution of *cis*-4-acetoxy-2-cyclopenten-1-ol
17 **10** (1.0 g, 7.0 mmol), tetrakis(triphenylphosphine)palladium(0) (0.41 g, 5 mol %) and
18 triphenylphosphine (0.28 g, 15 mol %) in anhydrous THF (15 mL) was stirred in the dark for
19 15 min then added to the DMF solution. Thereafter, the reaction mixture was stirred in the
20 dark at 60 °C for 18 h then concd under reduced pressure and the residue slurried in DCM
21 and filtered through Celite. The filtrate was concd under reduced pressure and the residue
22 subjected to flash chromatography, eluting firstly with 1:1, hexane: EtOAc then EtOAc and
23 finally 5:95, MeOH:EtOAc, to afford alcohol **22** as a white solid (1.13 g, 64%); δ_{H} (400.1
24 MHz, $\text{DMSO}-d_6$) 1.67 (1H, dt, $J = 14.0, 4.3$), 2.85 (1H, dt, $J = 14.0, 7.7$), 4.67–4.76 (1H, m),
25 5.27–5.34 (1H, m), 5.35 (1H, d, $J = 6.1$), 5.96–6.02 (1H, m), 6.15–6.23 (1H, m), 6.86 (2H, s),
26 8.02 (1H, s); δ_{C} { ^1H } (100.6 MHz, $\text{DMSO}-d_6$) 41.0, 56.9, 73.6, 123.5, 130.4, 139.6, 141.3,
27 149.4, 153.4, 159.6; HRMS (ES⁺) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{10}\text{H}_{11}\text{N}_5\text{OCl}$ $[\text{M}+\text{H}]^+$ 252.0652;
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41 2-Amino-6-chloro-9-(*cis*-4'-*tert*-butyldimethylsilyloxycyclopent-2'-enyl)purine (**23**). Alcohol
42 **22** (1.13 g, 4.5 mmol), imidazole (0.76 g, 11.2 mmol) and *tert*-butyldimethylsilyl chloride
43 (1.02 g, 6.8 mmol) were dissolved under nitrogen in anhydrous DMF (4.5 mL) and the
44 resulting solution was stirred for 17 h. Thereafter, it was poured into brine (200 mL) and
45 extracted with EtOAc (3 × 120 mL). The combined organic extracts were washed with brine
46 (300 mL), dried over MgSO_4 and concd under reduced pressure to afford the crude product.
47 Purification by flash chromatography (1:1, hexane: EtOAc) provided 1.18 g (72%) of the title
48 compound **23** as a white solid; δ_{H} (400.1 MHz, CDCl_3) 0.10 (3H, s), 0.13 (3H, s), 0.91 (9H,
49 s), 1.81 (1H, dt, $J = 14.4, 3.0$), 2.87 (1H, dt, $J = 14.4, 7.3$), 4.84–4.92 (1H, m), 5.19 (2H, s),
50 5.41–5.50 (1H, m), 5.90–5.98 (1H, m), 6.15–6.23 (1H, m), 8.02 (1H, s); δ_{C} { ^1H } (100.6 MHz,
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CDCl₃) -4.78, -4.66, 18.1, 25.8, 41.9, 56.7, 75.2, 125.4, 130.9, 139.4, 141.7, 151.1, 153.3, 158.9; HRMS (ES⁺) m/z: [M+H]⁺ Calcd for C₁₆H₂₅N₅OClSi 366.1517; Found 366.1516.

2-bis-Boc-Amino-6-chloro-9-(cis-4'-tert-butyltrimethylsilyloxycyclopent-2'-enyl)purine (24). Aminopurine **23** (1.18 g, 3.2 mmol) and DMAP (39 mg, 0.3 mmol, 10 mol %) were dissolved in anhydrous THF (15 mL) under nitrogen and Boc₂O (2.1 g, 2.2 mL, 9.6 mmol) was added. The solution was stirred at RT for 4.5 days then concd under reduced pressure. Flash chromatography of the residue (6:4, hexane: EtOAc) afforded 1.65 g (90%) of the title compound **24** as a white foam; δ_H (300.1 MHz, CDCl₃) 0.11 (3H, s), 0.14 (3H, s), 0.91 (9H, s), 1.47 (18H, s), 1.85 (1H, dt, *J* = 14.6, 2.5), 2.87 (1H, ddd, *J* = 14.8, 8.2, 6.8), 4.87–4.96 (1H, m), 5.60–5.70 (1H, m), 5.96–6.03 (1H, m), 6.21–6.29 (1H, m), 8.40 (1H, s); δ_C {¹H} (75.5 MHz, CDCl₃) -4.83, -4.67, 18.0, 25.8, 27.9, 41.9, 57.5, 75.1, 83.6, 130.1, 130.6, 139.9, 145.5, 150.7, 151.0, 151.8, 152.2; HRMS (ES⁺) m/z: [M+H]⁺ Calcd for C₂₆H₄₁N₅O₅ClSi 566.2566; Found 566.2551.

2-bis-Boc-Amino-6-chloro-9-(cis-4'-hydroxycyclopent-2'-enyl)purine (25). Unsaturated purine **24** (1.62 g, 2.9 mmol) was dissolved in anhydrous THF (20 mL) under nitrogen and ice-cooled. TBAF (1 M soln in THF, 3.1 mL, 3.1 mmol) was added and the solution was stirred in ice for 30 min then cooling was removed and stirring was continued for a further 90 min. After brief removal of the solvent under reduced pressure the residue was diluted with water (300 mL) and extracted with EtOAc (3 × 300 mL). The combined organic extracts were dried and concd to give the crude product which was subjected to flash chromatography (EtOAc) to afford alcohol **25** as a white foam (1.18 g, 91%); δ_H (400.1 MHz, CDCl₃) 1.47 (18H, s), 2.05–2.15 (1H, m), 3.05 (1H, overlapping dt, *J* = 15.8, 7.9), 3.72–3.82 (1H, m), 4.87–4.97 (1H, m), 5.43–5.52 (1H, m), 5.88–5.95 (1H, m), 6.32–6.39 (1H, m), 8.24 (1H, s); δ_C {¹H} (100.6 MHz, CDCl₃) 27.9, 40.2, 59.8, 75.2, 83.9, 129.9, 131.0, 140.2, 145.6, 150.4, 151.3, 151.5, 151.8; HRMS (ES⁺) m/z: [M+H]⁺ Calcd for C₂₀H₂₇N₅O₅Cl 452.1701; Found 452.1706.

2-bis-Boc-Amino-6-chloro-9-(cis-4'-(carbomethoxy(dimethylphosphono)methoxy)cyclopent-2'-enyl)purine (26). Alcohol **25** (1.15 g, 2.5 mmol) and trimethyl phosphonodiazacetate (634 mg, 3.0 mmol) were suspended in degassed benzene (12 mL), activated sieves were added and the mixture was stirred under nitrogen for 75 min. The mixture was inserted into a heated

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3 block at 95 °C then rhodium(II) acetate (22 mg, 2 mol %) was added and the reaction mixture
4 was heated under reflux overnight. After 16 h a second portion of catalyst (11 mg, 1 mol %)
5 was added and reflux was continued for a further 4 h then the reaction mixture was filtered
6 and concd under reduced pressure. Flash chromatography of the residue (EtOAc to 5:95,
7 MeOH:EtOAc) afforded phosphonate **26** as a fawn foam in 60% yield (0.97 g, dr 1:1); δ_{H}
8 (500.1 MHz, CDCl_3) 1.47 (18H, 2 closely spaced s), 2.05–2.18 (1H, m), 2.85–2.98 (1H, m),
9 3.78–3.93 (9H, m), 4.49 (0.5H, d, $J_{\text{PH}}=25.4$), 4.53 (0.5H, d, $J_{\text{PH}}=24.9$), 4.72–4.83 (1H, m),
10 5.67–5.75 (1H, m), 6.14–6.20 (1H, m), 6.41–6.48 (1H, m), 8.44 (0.5H, s), 8.48 (0.5H, s); δ_{C}
11 $\{^1\text{H}\}$ (125.8 MHz, CDCl_3) 27.9, 38.3, 38.6, 53.07, 53.11, 54.1–54.4, 57.05, 57.13, 74.94 (d,
12 $J_{\text{PC}} = 159.6$), 74.96 (d, $J_{\text{PC}} = 159.6$), 83.69, 83.70, 84.5 (d, $J_{\text{PC}} = 10.2$), 84.7 (d, $J_{\text{PC}} = 11.4$),
13 130.1, 133.8, 134.2, 135.9, 136.4, 145.3, 145.5, 150.74, 150.76, 151.1, 151.8, 152.2, 167.5 (d,
14 $J_{\text{PC}} = 2.5$), 167.7 (d, $J_{\text{PC}} = 2.5$); δ_{P} (121.5 MHz, CDCl_3) 16.1, 16.3; HRMS (ES+) m/z:
15 $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{25}\text{H}_{36}\text{N}_5\text{O}_{10}\text{ClP}$ 632.1888; Found 632.1877.
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26 *2-bis-Boc-Amino-6-chloro-9-(cis-3'-*

27 (carbomethoxy(dimethylphosphono)methoxy)cyclopentyl)purine (**16**). Phosphonate **26** (1.25
28 g, 2.0 mmol) was dissolved in MeOH (15 mL), 5% Rh on alumina (250 mg, 12.5 mg, 6 mol
29 %) was added and the reaction mixture was stirred under a balloon of hydrogen for 5 h then
30 filtered through Celite, washing with MeOH (100 mL) and DCM (100 mL). The combined
31 filtrate was concd and the residue subjected to flash chromatography (EtOAc - 5:95,
32 MeOH:EtOAc) to provide 0.95 g (75%, dr 1:1) of phosphonate **16** as a white foam, identical
33 spectroscopically to **16** prepared above.
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40 *9-(cis-3'-(Carboxy(phosphono)methoxy)cyclopentyl)guanine (**9**). Phosphonopurine **16** (355*
41 mg, 0.6 mmol) was suspended in acetonitrile (2 mL) in a 10 mL microwave vial, TMS
42 bromide (740 μL , 857 mg, 5.6 mmol) was added and the reaction mixture was subjected to
43 microwave irradiation at 50 °C for 20 min. MeOH (2 mL), containing 200 μL water, was
44 added to give an orange solution which was stirred for 2 h. After removal of the solvent under
45 reduced pressure, 5 M sodium hydroxide (2.8 mL, 14 mmol) was added and the resulting
46 solution was stirred at 55 °C for 22 h. Removal of the solvent under reduced pressure
47 followed by charcoal column chromatography of the residue eluting with ammonia (30% aq.)
48 provided 181 mg of **9** as a cream solid (83% yield as ammonium salt, dr 1:1).
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3 **Synthesis of (L)-G- α -CNP (-)-9.** All products in the enantiopure series below were identical
4 by ^1H NMR to their racemic counterparts.
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8 (-)-(1'*S*,4'*R*)-2-Amino-6-chloro-9-(4'-hydroxycyclopent-2'-enyl)purine ((-)-**22**). This was
9 prepared following the procedure described for **22**, starting from 2-amino-6-chloropurine
10 (0.66 g, 3.9 mmol) and sodium hydride (60% dispersion in mineral oil, 0.15 g, 3.52 mmol) in
11 anhydrous DMF (12 mL), and (1*R*,4*S*)-*cis*-4-acetoxy-2-cyclopenten-1-ol (-)-**10** (0.50 g, 3.5
12 mmol), tetrakis(triphenylphosphine)palladium(0) (0.20 g, 0.17 mmol, 5 mol %) and
13 triphenylphosphine (0.14 g, 0.53 mmol, 15 mol %) in anhydrous THF (15 mL). The product
14 (-)-**22** was isolated as a white powder, yield 0.48 g (54%); $[\alpha]_D^{20} - 30$ (*c* 0.54, MeOH) [lit.²⁸
15 $[\alpha]_D^{26} - 11.5$ (*c* 0.54, MeOH)].
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23 (-)-(1'*S*,4'*R*)-2-Amino-6-chloro-9-(4'-*tert*-butyldimethylsilyloxycyclopent-2'-enyl)purine
24 ((-)-**23**). This was prepared following the procedure described for **23**, starting from (-)-**22**
25 (0.45 g, 1.8 mmol), imidazole (0.27 g, 4.0 mmol) and *tert*-butyldimethylsilyl chloride (0.33 g,
26 2.2 mmol) in anhydrous DMF (2 mL). The product (-)-**23** was isolated as a fluffy white
27 solid, yield 0.50 g (76%); $[\alpha]_D^{20} - 3.2$ (*c* 0.60, CHCl_3).
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33 (-)-(1'*S*,4'*R*)-2-*bis*-Boc-Amino-6-chloro-9-(4'-*tert*-butyldimethylsilyloxycyclopent-2'-
34 enyl)purine ((-)-**24**). This was prepared following the procedure described for **24**, starting
35 from the aminopurine (-)-**23** (0.55 g, 1.5 mmol), DMAP (18 mg, 0.15 mmol, 10 mol %) and
36 Boc_2O (1.03 mL, 0.98 g, 4.5 mmol) in anhydrous THF (7 mL). The product (-)-**24** was
37 isolated as a white foam, yield 0.73 g (86%); $[\alpha]_D^{20} - 11$ (*c* 1.11, CHCl_3).
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43 (-)-(1'*S*,4'*R*)-2-*bis*-Boc-Amino-6-chloro-9-(4'-hydroxycyclopent-2'-enyl)purine ((-)-**25**).
44 This was prepared following the procedure described for **25**, starting from the *bis*-boc-
45 aminopurine (-)-**24** (0.73 g, 1.3 mmol) and TBAF (1M in THF, 1.4 mL, 1.4 mmol) in
46 anhydrous THF (9 mL). The product (-)-**25** was isolated as a fluffy white solid, yield 0.55 g
47 (93%); $[\alpha]_D^{20} - 93$ (*c* 1.05, CHCl_3).
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53 (+)-(1'*S*,4'*R*)-2-*bis*-Boc-Amino-6-chloro-9-(4'-
54 (carbomethoxy(dimethylphosphono)methoxy)cyclopent-2'-enyl)purine ((+)-**26**). This was
55 prepared following the procedure described for **26**, starting from the alcohol (-)-**25** (0.55 g,
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3 1.2 mmol), trimethyl diazophosphonoacetate (0.30 g, 1.4 mmol) and rhodium(II) acetate (11
4 mg, 2 mol%) in benzene (10 mL). A second portion of catalyst (8 mg, 1.5 mol%) was added
5 after 16h and heating under reflux was continued for a further 90 min thereafter. The product
6 (+)-**26** was isolated as a foamy solid, yield 0.46 g (60%, dr 1:1); $[\alpha]_D^{20}$ 2.4 (*c* 0.91, CHCl₃).
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11 (+)-(1'*R*,3'*S*)-2-*bis*-Boc-Amino-6-chloro-9-(3'-
12 (carbomethoxy(dimethylphosphono)methoxy)cyclopentyl)purine ((+)-**16**). This was prepared
13 following the procedure described for **16**, starting from the phosphonate (+)-**26** (0.46 g, 0.7
14 mmol) and 5% Rh on alumina (90 mg, 4.5 mg, 6 mol %) in MeOH (6 mL). The product (+)-
15 **16** was isolated as a foamy solid, yield 0.33 g (72%, dr 1:1); $[\alpha]_D^{20}$ 15 (*c* 0.95, CHCl₃).
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21 (-)-(1'*R*,3'*S*)-9-(3'-(Carboxy(phosphono)methoxy)cyclopentyl)guanine ((-)-**9**). This was
22 prepared following the microwave procedure described for **9**, starting from the phosphonate
23 (+)-**16** (333 mg, 0.5 mmol) and TMSBr (693 μL, 804 mg, 5.2 mmol) in acetonitrile (2 mL),
24 followed by stirring in methanol (2 mL) containing water (200 μL), and finally by warming
25 in 5 M sodium hydroxide (3.1 mL, 15.7 mmol). The product (-)-**9** was obtained as a cream
26 solid after charcoal chromatography eluting with ammonia (30% aq.), yield 159 mg (77% as
27 the ammonium salt, dr 1:1); $[\alpha]_D^{20}$ -3.5 (*c* 0.51, 0.1M NaOH).
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34 **Synthesis of (D)-G- α -CNP (+)-**9****. All products in the enantiopure series below were identical
35 by ¹H NMR to their racemic counterparts.
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40 (+)-(1'*R*,4'*S*)-2-Amino-6-chloro-9-(4'-hydroxycyclopent-2'-enyl)purine ((+)-**22**). This was
41 prepared following the procedure described for **22**, starting from 2-amino-6-chloropurine
42 (0.66 g, 3.9 mmol) and sodium hydride (60% dispersion in mineral oil, 0.15 g, 3.52 mmol) in
43 anhydrous DMF (12 mL), and (1*S*,4*R*)-*cis*-4-acetoxy-2-cyclopenten-1-ol (+)-**10** (0.50 g, 3.5
44 mmol), tetrakis(triphenylphosphine)palladium(0) (0.20 g, 0.17 mmol, 5 mol %) and
45 triphenylphosphine (0.14 g, 0.53 mmol, 15 mol %) in anhydrous THF (15 mL). The product
46 (+)-**22** was isolated as a white powder, yield 0.63 g (71%); $[\alpha]_D^{20}$ 26 (*c* 0.55, MeOH).
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53 (+)-(1'*R*,4'*S*)-2-Amino-6-chloro-9-(4'-*tert*-butyldimethylsilyloxycyclopent-2'-enyl)purine
54 ((+)-**23**). This was prepared following the procedure described for **23**, starting from (+)-**22**
55 (0.62 g, 2.5 mmol), imidazole (0.37 g, 5.5 mmol) and *tert*-butyldimethylsilyl chloride (0.47 g,
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3.1 mmol) in anhydrous DMF (2.8 mL). The product (+)-**23** was isolated as a fluffy white solid, yield 0.75 g (82%); $[\alpha]_D^{20}$ 2.8 (*c* 0.6, CHCl₃).

(+)-(1'*R*,4'*S*)-2-*bis*-Boc-Amino-6-chloro-9-(4'-*tert*-butyldimethylsilyloxycyclopent-2'-enyl)purine ((+)-**24**). This was prepared following the procedure described for **24**, starting from the aminopurine (+)-**23** (0.73 g, 2.0 mmol), DMAP (24 mg, 0.2 mmol, 10 mol%) and Boc₂O (1.38 mL, 1.3 g, 6.0 mmol) in anhydrous THF (9 mL). The product (+)-**24** was isolated as a white foam, yield 1.04 g (92%); $[\alpha]_D^{20}$ 8.6 (*c* 1.14, CHCl₃).

(+)-(1'*R*,4'*S*)-2-*bis*-Boc-Amino-6-chloro-9-(4'-hydroxycyclopent-2'-enyl)purine ((+)-**25**). This was prepared following the procedure described for **25**, starting from the *bis*-boc-aminopurine (+)-**24** (1.00 g, 1.8 mmol) and TBAF (1M in THF, 1.9 mL, 1.9 mmol) in anhydrous THF (13 mL). The product (+)-**25** was isolated as a fluffy white solid, yield 0.68 g (84%); $[\alpha]_D^{20}$ 93 (*c* 1.03, CHCl₃).

(-)-(1'*R*,4'*S*)-2-*bis*-Boc-Amino-6-chloro-9-(4'-(*tert*-butyl(methylphosphono)methoxy)cyclopent-2'-enyl)purine ((-)-**26**). This was prepared following the procedure described for **26**, starting from the alcohol (+)-**25** (0.65 g, 1.4 mmol), trimethyl diazophosphonoacetate (0.30 g, 1.4 mmol) and rhodium(II) acetate (16 mg, 2.5 mol%) in benzene (12 mL). A second portion of catalyst (9 mg, 1.4 mol%) was added after 16h and heating under reflux was continued for a further 6 h thereafter. The product (-)-**26** was isolated as a crispy foam, yield 0.54 g (59%, dr 1:1); $[\alpha]_D^{20}$ -0.7 (*c* 1.01, CHCl₃).

(-)-(1'*S*,3'*R*)-2-*bis*-Boc-Amino-6-chloro-9-(3'-(*tert*-butyl(methylphosphono)methoxy)cyclopentyl)purine ((-)-**16**). This was prepared following the procedure described for **16**, starting from the phosphonate (-)-**26** (0.54 g, 0.8 mmol) and 5% Rh on alumina (105 mg, 5.2 mg, 6 mol%) in MeOH (7 mL). The product (-)-**16** was isolated as a white solid, yield 0.35 g (65%, dr 1:1); $[\alpha]_D^{20}$ -14 (*c* 0.96, CHCl₃).

(+)-(1'*S*,3'*R*)-9-(3'-(*tert*-butyl(methylphosphono)methoxy)cyclopentyl)guanine ((+)-**9**). This was prepared following the microwave procedure described for **9**, starting from the phosphonate (-)-**16** (312 mg, 0.5 mmol) and TMSBr (650 μL, 754 mg, 4.9 mmol) in acetonitrile (2 mL),

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3 followed by stirring in methanol (2 mL) containing water (200 μ L), and finally by warming
4 in 5 M sodium hydroxide (3mL, 15 mmol). The product (+)-**9** was obtained as a cream solid
5 after charcoal chromatography eluting with ammonia (30% aq.), yield 170 mg (88% as the
6 ammonium salt, dr 1:1); $[\alpha]_D^{20}$ 2.9 (*c* 0.51, 0.1M NaOH).
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10 11 **Associated Content**

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14 Copies of ^1H and ^{13}C NMR spectra of all synthetic compounds described in the Experimental
15 Section. Supporting information is available free of charge on the ACS Publications website
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