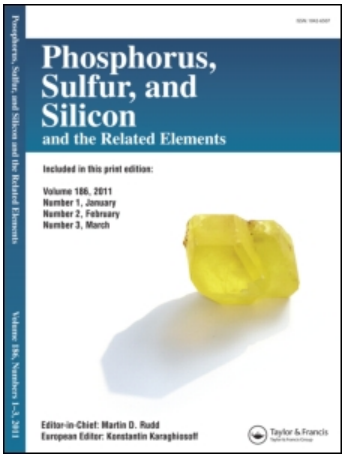

Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Carbovir-Related Compounds and Phosphonate Analogues

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To cite this Article Pham, Phuong -T. and Vince, Robert(2007) 'Carbovir-Related Compounds and Phosphonate Analogues', Phosphorus, Sulfur, and Silicon and the Related Elements, 182: 4, 779 — 791
To link to this Article: DOI: 10.1080/10426500601047578
URL: http://dx.doi.org/10.1080/10426500601047578

Phosphorus, Sulfur, and Silicon, 182:779–791, 2007

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500601047578

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Carbovir-Related Compounds and Phosphonate Analogues

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Detailed syntheses of carbovir-related cis-[2-(9H-Purin-9-yl)-3-cyclopentene]-1-methanols and phosphonates of selected analogues are presented. Our interest in this chemistry stems from antiviral activity shown by closely related compounds. Access to the key β-lactam was achieved by the reaction of monocyclopentadiene with chlorosulfonyl isocyanate at −78°C rather than at the reported[1] ambient temperature, where only the less ring-strained and more stable γ-lactam is formed.

Keywords Carbocyclic nucleosides; carbovir triphosphate; HIV reverse transcriptase; lactam

INTRODUCTION

Although many nucleoside derivatives designed to target viral reverse transcriptase have been synthesized, only a handful have been marketed for use in combinational therapeutic treatment of AIDS.[2,3] A series of carbocyclic nucleosides originated from our laboratory has led to the development of a clinically useful drug. These carbocyclic 2′,3′-didehydro-2′,3′-dideoxy-2-amino-6-substituted purines were termed carbovirs.[4,5] The parent compound, carbocyclic 2′,3′-didehydro-2′,3′-dideoxyguanosine (carbovir **1a**), is enzymatically converted to the active form, carbovir triphosphate, which inhibits HIV reverse transcriptase. All other active derivatives in this series are ultimately converted to the same active metabolite. Thus, the anti-HIV drug derived

Received July 12, 2006; accepted August 29, 2006.
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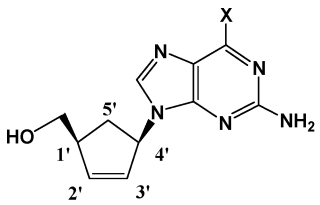
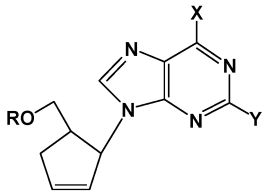


1a, carbovir, X = OH
1b, abacavir, X = HN-◁



2a, R = H
2b, R = $(HO)_2P(O)CH_2$-

SCHEME 1

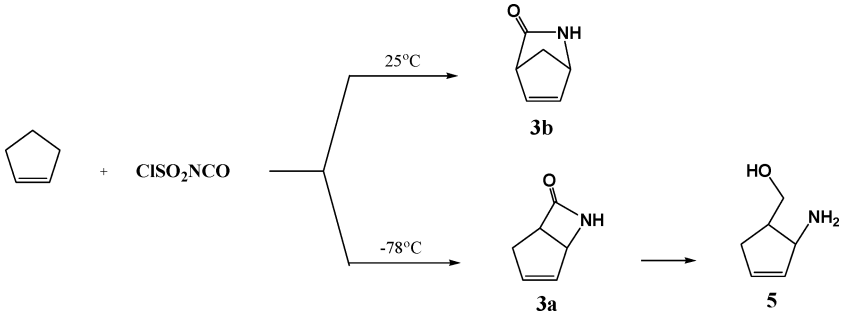
from this series, abacavir **1b** (Ziagen™), derives its activity via conversion to carbovir triphosphate (Scheme 1).

Nevertheless, the continuous need for new anti-HIV agents arises from the development of drug resistance as well as toxicity after prolonged use of the nucleosides.[6,7] We report herein the syntheses of a series of novel carbovir-related carbocyclic nucleosides (**2a**), in which the 4'hydroxymethyl group was replaced by a 5′ hydroxymethyl. Phosphonates of selected analogs (**2b**) were also prepared as the introduction of phosphonate in the design of more useful antiviral agents have been well documented.[8–10]

DISCUSSION

The key in preparing our title compounds **2a** and derivatives was to obtain 2-azabicyclo[3.2.0]hept-3-en-7-one, β-lactam (**3a**).

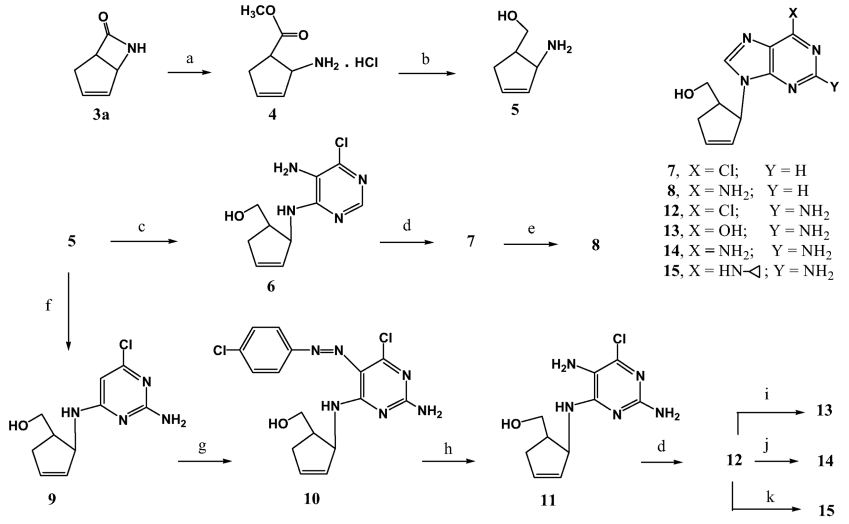
The reaction of chlorosulfonyl isocyanate and cyclopentadiene at ambient temperature was found to give 2-azabicyclo[2.2.1]hept-5-en-3-one, γ- or Vince Lactam (**3b**), rather than the reported[1] β-lactam (**3a**). To obtain the desired β-lactam, the reaction temperature had to be lowered significantly. When the reaction temperature was lowered between -5 and -10°C, β-lactam began to form resulting in a mixture of lactams. At -78°C the reaction proceeded to give selectively β-lactam, following treatment with sodium sulfite (Scheme 2). ^{1}H NMR spectra for both lactams agreed well with reported literature values.[1,11] While δ values for the methylene hydrogens of γ-lactam were found between 2.39–2.18 ppm, the reported shifts were 2.38–2.20 ppm. The δ values for the allylic methylene hydrogens of β-lactam were found to be slightly more downfield between 2.67–2.33 ppm. These values are again comparable with the reported chemical shifts of 2.68–2.38 ppm. This downfield



SCHEME 2 Reaction conditions yielding β- and γ-lactams.

shift reflects the proximity of the two hydrogens to the double bond in β-lactam.

Synthetic routes for the preparations of compounds **8** and **12–14** starting from cis ($\pm$) mixture of β-lactam isomers are outlined in Scheme 3. Thus, hydrolysis of (**3a**) with methanolic HCl followed by reduction with calcium borohydride provided the amino alcohol **5** (63%). Coupling of **5** with 5-amino-4,6-dichloropyrimidine and



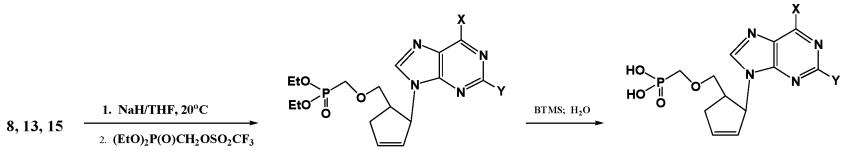
SCHEME 3 (a) 1N HCl/MeOH, reflux; (b) $Ca(BH_4)_2$, THF; (c) 5-amino-4,6-dichloropyrimidine, Et_3N, BuOH, reflux; (d) $(EtO)_3CH$, HCl, aq. 0.5 N HCl; (e) liquid NH_3, 65°; (f) 2-amino-4,6-dichloropyrimidine, Et_3N, BuOH, reflux; (g) 4-$ClC_6H_4N_2^+Cl^-$, HOAc, aq. NaOAc; (h) Zn, aq. HOAC, EtOH/H_2O, reflux; (i) 1 N HCl; (j) liquid NH_3, 80°C; (k) cyclopropylamine/EtOH, reflux.

2-amino-4,6-dichloropyrimidine in the presence of triethylamine furnished intermediates **6** and **9**, respectively. Diazotization of **9** was carried out with 4-chlorophenyldiazonium chloride at 65°C rather than 25°C due to the insolubility of the starting material at lower temperature. A mixture of **9** and NaOAc in H_2O/acetic acid was heated to 65°C for 20 minutes before the diazonium reagent was added. Compound **10** was obtained in good yield (89%). Reduction of **10** with zinc-acetic acid afforded the 2,5-diamino-6-chloro-4-pyrimidinyl product **11**.

Compounds **6** and **11** were converted to the corresponding 9-substituted-6-chloropurine **7** and 2-amino-6-chloro-9-purin-9-yl **12** by ring closure with triethylorthoformate under acidic conditions followed by mild acid hydrolysis. Compounds **8** and **14** were obtained by reaction of the corresponding 6-chloro intermediates with liquid ammonia under pressure.

Treatment of **12** with 1N HCl at 65°C for 5 h gave **13** in a moderate yield of 67%. The 6-cyclopropylamine analogue **15** was obtained by the reaction of **12** with excess cyclopropylamine in ethanol under pressure at 65–70°C.[12]

Phosphonate analogues of 6-aminopurine (**16**), 6-hydroxy-2-aminopurine (**17**), and 6-cyclopropylamine-2-aminopurine (**18**) were obtained by reaction of the corresponding alcohols with diethyl phosphonomethyltriflate in the presence of NaH. The yields of these reactions were rather poor (20%). Hydrolysis of the phosphonate esters were carried out using Bromotrimethyl Silane (BTMS) followed by treatment with H_2O (Scheme 4). ^{31}P NMR showed that while these phosphonate esters resonate around 22 ppm, their corresponding acids shifted upfield by about 2.7 ppm. Proton-phosphorus coupling of 2 Hz was observed in ^1H NMR spectra of esters **17a** and **18a**. This long-range coupling ($^4J_{PH}$) has been previously reported in the literature[13] with values of 2.4 to 3.2 Hz.



16a, X = NH_2; Y = H
17a, X = OH; Y = NH_2
18a, X = HN◁; Y = NH_2

16b, X = NH_2; Y = H
17b, X = OH; Y = NH_2
18b, X = HN◁ ; Y = NH_2

SCHEME 4

CONCLUSION

In conclusion, the synthesis of a series of novel carbovir-related compounds was achieved from the key β-lactam, 2-azabicyclo[3.2.0]hept-3-en-7-one, to give a racemic mixture of the desired carbocyclic nucleosides and selected phosphonate analogues. The key step in the described synthetic strategy is based on a newly modified method to selectively access the key intermediate β-lactam.

EXPERIMENTAL

General

All reagents and anhydrous solvents were obtained from Sigma-Aldrich. BTMS was distilled before use. Diethyl phosphonomethyltriflate was prepared by the reaction of trifluoromethane sulfonyl chloride with diethylhydroxymethyl phosphonate following the procedure described by Phillion and Andrew.[14] Diethylhydroxymethyl phosphonate was prepared by the reaction of diethylphosphite with paraformaldehyde in the presence of triethylamine under reflux condition.[10]

^{1}H and ^{31}P NMR spectra were recorded on a Varian 300 instrument. Chemical shifts are reported relative to external Me_4Si, internal $CDCl_3$, or external 85% H_3PO_4 (^{31}P). TLC was done on E. Merck (Darmstadt, Germany) silica gel (0.25 mm thickness) 60F-254 glass plates. Plates were visualized using 5% phosphomolybdic acid in EtOH. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

2-Azabicyclo[2.2.1]hept-5-en-3-one (3b)

A solution of freshly distilled cyclopentadiene (4.50 g, 68.1 mmol) in anhydrous CH_2Cl_2 (10 mL) was added to a solution of chlorosulfonyl isocyanate (5.25 mL, 8.50 g, 60.3 mmol) in CH_2Cl_2 (90 mL) over a period of 20 min at ambient temperature. After the complete addition, the reaction was continued stirring for 10 min and then quenched with a solution of sodium sulfite (20 g/80 mL H_2O). The CH_2Cl_2 layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×150 mL). Combined organic layers were dried and concentrated to give a crude brown oil (1.80 g, 32.0%). ^{1}H NMR identified the product as **3b**. NMR values obtained were identical with those reported for γ-lactam. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.82–6.73 (m, 1H, C6H=C), 6.68–6.62 (m, 1H, C=C5H), 6.3 (broad s, 1H, NH), 4.33 (s, 1H, C1-H), 3.20 (s, 1H, C4-H), 2.39–2.18 (m, 2H, C7-H2).

6-Azabicyclo[3.2.0] hept-3-en-7-one (3a)

A solution of freshly distilled cyclopentadiene (9.3 g, 140.8 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise (15 min) to a solution of chlorosulfonyl isocyanate (14.6 g, 9.0 mL, 103.4 mmol) in CH_2Cl_2 (300 mL) at −78°C. The reaction mixture was continued stirring for 4 h with cooling and was then added in portion to an aqueous solution of Na_2SO_3 (60 g/200 mL H_2O). After 30 min of stirring at ambient temperature, the organic layer was separated and taken up in MeOH (200 mL) and dried over $MgSO_4$. Removal of the solvent gave crude yellow oil ($R_f = 0.65$, $CHCl_3$:MeOH, 5:1), which was further purified by flash chromatography (CH_2Cl_2:MeOH, 300:5) to give 6.70 g of **3a** (59%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.92 (broad s, 1H, NH), 5.98–5.95 (m, 1H, C4H=C), 5.94–5.88 (m, 1H, C=C3H), 4.43 (broad s, 1H, C5-H), 3.76–3.73 (m, 1H, C1-H), 2.67–2.33 (m, 2H, C2-H_2).

Cis-(+)-Methyl-(2-aminocyclopent-3-ene)1-carboxylate Hydrochloride (4)

6-azabicyclo[3.2.0]hept-3-en-7-one **3a** (6.42 g, 58.8 mmol) was dissolved in 1N methanolic HCl (150 mL) and refluxed for 3 h. The solvent was then removed in vacuo and the residue chromatographed (ETOAc: MeOH) on a silica gel column to give **4** as an off-white solid, m.p. 181–182°C: 5.59 g (68%). MS (FAB): m/e 142 ($M^+ + 1$). ^{1}H NMR [$(CD_3)_2SO$, 300 MHz]: δ 8.19 (broad s, 2H, NH_2), 6.16–6.14 (m, 1H, C3H=C), 5.60–5.77 (m, 1H, C=C4H), 4.27 (d, 1H, C2H, $J = 8$ Hz), 3.66 (s, 3H, CH_3O), 3.49–3.40 (m, 1H, C1H), 2.82–2.53 (m, 2H, C5H_2). Anal. calcd. ($C_7H_{11}NO_2$.HCl.1/8 CH_3OH): C, 47.12; H, 7.22; N, 7.72; found: C, 47.46; H, 7.46; N 7.73.

Cis-(+) -[2-(5-Amino-6-chloro-4-pyrimidinyl)-amino-cyclopent-3-ene]1-methanol (6)

A suspension of finely grounded $CaCl_2$ (7.16 g. 64.5 mmol) and $NaBH_4$ (4.88 g, 129 mmol) in anhydrous THF (400 mL) was stirred at r.t. for 1.5 h. To the suspension was added a solution of **4** (5.0 g, 28 mmol) in anhydrous THF (200 mL), and the reaction mixture was stirred for 20 h at r.t. The reaction was quenched by adding H_2O until bubbling ceased. The resulting salt was filtered off and washed with ethanol. The filtrate was concentrated and azeotroped several times with absolute EtOH to give a brown syrup, identified by ^{1}H NMR as the amino alcohol **5** (2.0 g, 63%), and was used in the following reaction without further purification. ^{1}H NMR ($CDCl_3$, 300 NHz): δ 6.12–6.11 (m, 1H, C3H=C), 5.88–5.86 (m, 1H, C=C4H), 5.67 (broad s, 2H, NH_2),

4.33 (d, 1H, C2H, J = 2Hz), 3.90–3.78 (m, 2H, CH_2OH), 3.41–3.25 (m, 1H, C1H), 2.50–2.48 (m, 2H, $C5H_2$).

A solution of **5** (3.0 g, 26.50 mmol), triethylamine (11 mL), and 5-amino-4,6-dichloropyrimidine (4.16 g, 25.4 mmol) in n-butanol (150 mL) was refluxed at 110°C for 24 h. Excess solvent was removed in vacuo, and the residue was chromatographed on a silica gel column (EtOAc:hexane). Product **6** was obtained as an off-white solid: (4.1 g, 64%), m.p. 120–124°C. MS (FAB): m/e 241 (M^+ +1), 239 (M^+ -1). ^1H NMR [$(CD_3)_2SO$, 300 MHz]: δ 7.72 (s, 1H, C2'H), 6.50 (d, 1H, NH, *J*= 8 Hz), 5.98–5.96 (m, 1H, C3H=C), 5.72–5.71 (m, 1H, C=C4H), 5.28–5.24 (m, 1H, C2H), 5.08 (broad s, 2H, NH_2), 4.31–4.27 (m, 1H, OH), 3.64–3.20 (m, 3H, CH_2OH and C1H), 2.48–2.25 (m, 2H, $C5H_2$). Anal. calcd. ($C_{10}H_{13}N_4OCl$): C, 49.90; H, 5.44; N, 23.28; found: C, 50.12; H, 5.57; N, 23.35.

Cis-(+)-[2-(6-Chloro-9H-purin-9-yl)cyclopent-3-ene]1-methanol (7)

A solution of **6** (3.0 g, 13 mmol) in triethyl orthoformate (75 mL) and conc. HCl (0.75 mL) was stirred overnight at r.t. The reaction mixture was then concentrated under pressure, and the residue was stirred in 0.5 N HCl (20 mL) for 3 h. The resulting aqueous solution was neutralized to pH ~ 7–8 with 1N NaOH, concentrated in vacuo, and azeotroped with absolute EtOH. The residue was chromatographed (EtOAc:MeOH) on a silical gel column to a give white solid **7** (1.08 g, 35%), m.p. 158–160°C. MS (FAB): m/e 251 (M^++1). ^1H NMR [$(CD_3)_2SO$, 300 MHz]: δ 8.76, 8.41 (each s, each 1H, C2'H and C8'H), 6.33–6.32 (m, 1H, C3H=C), 5.09–5.90 (m, 1H, C=C4H), 5.81–5.78 (m, 1H, C2H), 4.25 (broad s, 1H, OH), 3.15–2.70 (m, 2H, CH_2OH and 1H, C1H), 2.60–2.42 (m, 2H, $C5H_2$). Anal. calcd. ($C_{11}H_{11}N_4$ ClO): C, 52.91; H, 4.42; N, 22.35; found: C, 52.91; H, 4.22; N, 22.69.

Cis-(+)-[2-(6-amino-9H-purin-9-yl)cyclopent-3-ene]-1-methanol (8)

A solution of **7** (850 mg, 3.4 mmol) in absolute MeOH (20 mL) was transferred to a stainless-steel bomb, and excess liquid NH_3 was added. The bomb was sealed and heated in an oil bath at 65°C for 20 h. Volatiles were removed, and the residue was purified by flash chromatography ($CHCl_3$/MeOH) to give the desired product as an off-white solid (714 mg, 91%), m.p. 184–186°C. ^1H NMR [$(CD_3)_2SO$, 300 MHz]: δ 8.11, 7.81 (each s, each 1H, C2′H and C8′H), 7.19 (broad s, 2H, NH_2), 6.29–6.27 (m, 1H, C3H=C), 5.90–5.88 (m, 1H, C=C4H), 5.60 (d, 1H, C2H, $J = 7$ Hz), 4.35 (broad s, 1H, OH), 3.33–2.89 (m, 2H, CH_2OH), 2.63–2.75 (m,

1H, C1H), 2.60–2.40 (m, 2H, C5H_2). Anal. calcd. ($C_{11}H_{13}N_5O$): C, 57.13; H, 5.67; N, 30.28; found: C, 57. 31; H, 5.59; N, 30.35.

Cis-(+)-Methyl-[2-(6-amino-9H-purin-9-yl)cyclopent-3-ene]-1-diethylphosphonate (16a)

A suspension of **8** (700 mg, 3 mmol) and NaH (83 mg, 3.5 mmol) in anhydrous THF (150 mL) was stirred overnight at r.t. under a N_2 atmosphere. The reaction flask was cooled to -20°C, and 1.4 eq. of diethyl phosphonomethyl triflate (1.23 g, 4.10 mmol) in THF (50 mL) was added dropwise over 2 h. Stirring was continued for another 2 h and the reaction was quenched with MeOH. The solvent was removed in vacuo, and the residue was chromatographed to give light yellow oil (200 mg, 17%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.29, 7.65 (each s, each 1H, C2'H and C8'H), 6.52 (s, 2H, NH_2), 6.28–6.27 (m, 1H, C3H=C), 5.83–5.81 (m, 1H, C=C4H), 5.72 (d, 1H, C2H, $J = 7$Hz), 4.07–3.93 (m, 4H, OC H_2CH_3), 3.38–3.05 (m, 4H, CH_2OC and P[O]C H_2), 3.00–2.90 (m, 1H, C1H), 2.70–2.80 (m, 2H, C5H_2), 1.24–1.18 (m, 6H, OCH_2C H_3). ^{31}P NMR, proton coupled ($CDCl_3$, 300 MHz): δ 21. 99 (m). Anal. calcd. ($C_{16}H_{24}N_5O_4$P.1/2 H_2O): C, 49.23; H, 6.46; N, 17.94; found: C, 49.40; H, 6.44; N, 17.83.

Cis-(+)-Methyl-[2-(6-amino-9H-purin-9-yl)cyclopent-3-ene]-1-phosphonic Acid (16b)

Diethyl phosphonate ester **16a** (100 mg, 0.3 mmol) was dissolved in anhydrous acetonitrile (20 mL), and freshly distilled bromotrimethyl silane (1.0 mL) was added. The reaction mixture was stirred under N_2 at r.t. for 24 h. Excess BTMS and solvent were removed under reduced pressure. The grayish residue was dissolved in cold H_2O (1 mL), and acetone was added dropwise until a white precipitate was formed. Recrystallization with H_2O:acetone ($\sim$1:4) gave a white solid (45 mg, 52%), m.p. 218–220°C. MS (FAB): m/e 326 (M^+ +1), 324 (M^+ -1). ^{1}H NMR [$(CD_3)_2$SO, 300 MHz]: δ 8.16, 7.90 (each s, each 1H, C2'H and C8'H), 7.39 (broad s, 2H, NH_2), 6.31 (broad s, 1H, C3H=C), 5.82 (broad s, 1H, C=C4H), 5.61 (broad s, 1H, C2H), 3.20–2.89 (m, 4H, C H_2OC and P[O]C H_2), 2.90–2.80 (m, 1H, C1H), 2.40–2.20 (m, 2H, C5H_2). ^{31}P {1H} NMR [$(CD_3)_2$SO, 300 MHz]:δ 19.12 ppm. Anal. calcd. ($C_{12}H_{16}N_5O_4$.1/2H_2O): C, 43.11; H, 5.13; N, 20.95; found: C, 43.08; H, 4.48; N, 21.05.

Cis-(±)-2-[(2,5-Diamino-6-chloropyrimidin-4-yl)-amino] cyclopent-3-enyl Methanol (9)

A mixture of **5** (3.15 g, 27.8 mmol), 2-amino 4,6-dichloropyrimidine (4.80 g, 29.0 mmol), and triethylamine (7.5 mL) in n-butanol (250 mL) was refluxed for 48 h. The solvent was evaporated in vacuo, and the

residue was chromatographed (ETOAc:MeOH) to give the desired product **9** as an off-white solid (1.0 g, 14%), m.p. 210–212°C. MS(FAB): m/e 241 ($M^+ +1$). ^{1}H NMR [$(CD_3)_2SO$, 300 MHz]: δ 6.20 (d, 1H, NH, $J = 8$ Hz), 5.96–5.94 (m, 1H, C3H=C), 5.72–5.89 (m, 1H, C=C4H), 5.66 (broad s, 2H, NH_2), 5.13 (broad s, 1H, C2H), 4.36 (broad s, 1H, OH), 3.94 (broad s, 2H, NH_2), 3.42–3.33 (m, 2H, CH_2OH), 3.32–3.23 (m, 1H, C1H), 2.48–2.25 (m, 2H, C5H_2). Anal. calcd. ($C_{10}H_{13}N_4OCl$): C, 49.90; H, 5.44; N, 23.28; found: C, 49.77; H, 5.19; N, 23.10.

Cis-(±)-[2-[2-amino-6chloro-5-[(4-chlorophenyl)azol]-4-pyrimidyl]-amino]-cyclopent-3-enyl Methanol (10)

p-Chlorobenzenediazonium chloride was prepared by adding dropwise a solution of sodium nitrite (325 mg, 4.75 mmol) in H_2O (2.5 mL) to a solution of p-chloroaniline (575 mg, 4.50 mmol) in 3N HCl (10 mL) at 0°C. Freshly prepared p-chlorobenzenediazonium chloride was added dropwise to a the reaction mixture containing **9** (3.17 g, 13.2 mmol) and sodium acetate (25 g) in HOAc (25 mL)/H_2O (25 mL) at 65–70°C. Heating was removed following the complete addition, and the reaction mixture was stirred overnight at r.t. A yellow precipitate was obtained after suction filtration and washing of the solid with H_2O (1.4 g, 89%), R_f= 0.76 ($CHCl_3$:MeOH, 5:1), m.p. > 300°C. MS (FAB): m/e 379 (M+). ^{1}H NMR [$(CD_3)_2SO$, 300 MHz]: δ 10.39 (d, 1H, NH,$J = 9$ Hz), 7.68–7.53 (m, 4H, C6H4), 7.58 (broad s, 2H, NH_2), 6.00–5.97 (m, 1H, C3H=C), 5.80–5.77 (m, 1H, C=C4H), 5.35 (t, 1H, C2H, $J = 9$ Hz), 4.66 (t, 1H, OH $J = 5$ Hz), 3.52–3.37 (m, 2H, CH_2OH), 2.60–2.40 (m, 2H, C5H_2). Anal. calcd. ($C_{16}H_{16}N_6Cl$): C, 50.67; H, 4.25; N, 22.16; found: C, 50.52; H, 4.15; N, 21.96.

Cis-(±)-2-(2,5-diamino-6-Chloro-9H-purin-9-yl)cyclopent-3-enyl Methanol (11)

A mixture containing **10** (1.0 g, 2.6 mmol), acetic acid (4 mL), and zinc (1.80 g, 27.5 mmol) in EtOH (200 mL)/H_2O (100 mL) was refluxed for 2 to 3 h, and concentrated under reduced pressure. The residue was taken up in saturated $NaHCO_3$ (50 mL) and extracted with $CHCl_3$ (3 × 50 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to give a brown oil, which was further purified by flash chromatography (CH_2Cl_2: MeOH) on a silica gel column. The analytically pure product was obtained as an off-white solid (600 mg, 89%), $R_f = 0.54$ ($CHCl_3$:MeOH, 5:1), m.p. 158–160°C. MS (CI, 150°C): 256 ($M^+ +1$), 243 ($M^+ -12$), 241 ($M^+ -14$). ^{1}H NMR [$(CD_3)_2SO$, 300 MHz]: δ 6.19 (d, 1H, NH, $J = 8$ Hz), 5.96–5.94 (m, 1H, C3H=C), 5.72–5.69 (m, 1H, C=C4H), 5.66 (broad s, 2H, NH_2), 5.13 (t, 1H, C2H, $J = 7$ Hz), 4.34 (broad s, 1H,

C1H), 2.48–2.22 (m, 2H, C5H_2). Anal. calcd. ($C_{10}H_{14}N_4ClO$): C, 46.97; H, 5.52; N, 27.39; found: C, 47.17; H, 5.55; N, 27.46.

Cis-(±)-2-(2-Amino-6-chloro-1-9H-dihydropurin-9-yl)cyclopent-3-enyl Methanol (12)

To a solution of **11** (800 mg, 3.13 mmol) in anhydrous DMF (10 mL) was added triethylorthoformate (50 mL) and conc. HCl (0.5 mL). The reaction mixture was stirred overnight at r.t. Excess solvent was removed under pressure. The residue was taken up in 0.5N HCl (30 mL) and stirred for 4 h. The solution was adjusted to pH ~ 8 with 1N NaOH and then extracted with $CHCl_3$ (3 × 50 mL). Combined $CHCl_3$layers were dried over $MgSO_4$ and evaporated in vacuo. Further purification was carried out by flash chromatography (CH_2Cl_2:MeOH) to give an off-white glassy solid (682 mg, 82%), $R_f = 0.51$ ($CHCl_3$:MeOH, 5:1); m.p. 138–142°C. MS (EI, 150°C): m/e 266 (M^+ +1), 267 (M^+ +2), 268 (M^+ +3), 232 (M^+ −33). ^{1}H NMR [$(CD_3)_2SO$, 300 MHz]: δ 7.80 (s, 1H, C8'H), 6.89 (broad s, 2H, NH_2), 6.27–6.26 (m, 1H, C3H=C), 5.87–5.84 (m, 1H, C=C4H), 5.49 (broad d, 1H, C2H, J= 7 Hz), 4.35 (t, 1H, OH, $J = 4$ Hz), 3.06–3.02 (m, 2H, CH_2OH), 2.70–2.52 (m, 1H, C1H), 2.55–2.38 (m, 2H, C5H_2). Anal. calc'd. ($C_{11}H_{12}N_5ClO.1/2\ H_2O$): C, 48.10; H, 4.77; N, 25.49; found: C, 48.14; H, 5.04;N, 25.66.

Cis-(±)-2-(2-Amino-1-9H-dihydropurin-6-9-yl)cyclopent-3-enyl Methanol (13)

A solution of **12** (280 mg, 1.1 mmol) in 1N HCl was heated to 65°C for 5 h and neutralized with 1N NaOH. The reaction mixture was concentrated, and the residue was applied through a silica gel column (EtOAc:MeOH) to give an off-white solid (175 mg, 67%), $R_f = 0.11$ ($CHCl_3$:MeOH, 5:1); m.p. 185°C began to dec w/o melt. MS (FAB): m/e 248 (M^+ +1), 246 (M^+ −1). ^{1}H NMR [$(CD_3)_2SO$, 300 MHz]: δ 10.77 (broad s, 1H, C=C4H), 5.31 (d, 1H, C2H, $J = 7$ Hz), 4.41 (t, 1H, OH, $J = 7$ Hz), 3.08–2.82 (m, 2H, CH_2OH), 2.61–2.52 (m, 1H, C1H), 2.40–2.22 (m, 2H, C5H_2). Anal. calcd. ($C_{11}H_{13}N_5O_2$): C, 53.44; H, 5.30; N, 28.33; found: C, 53.60; H, 5.52; N, 28.15.

Cis-(±)-2-(2,6-Diamino-1-9H-dihydropurin-6-9-yl)cyclopent-3-enyl Methanol (14)

Liquid ammonia was added to a solution of **12** (100 mg, 0.4 mmol) in absolute MeOH (15 mL); the bomb then was sealed and heated to 80°C for 48 h. Ammonia and methanol were evaporated, and the residue was chromatrographed on a silica gel column to give an off-white solid (53 mg, 57%), R_f= 0.22 ($CHCl_3$:MeOH, 5:1), m.p. 232–234°C. MS (FAB): m/e 247 (M^+ +1). ^{1}H NMR [$(CD_3)_2SO$, 300 MHz]: δ.37 (s, 1H, C8'H), 6.70 (s,

2H, NH_2), 6.28–6.24 (m, 1H, C3H=C), 5.91–5.85 (m, 1H, C=C4H), 5.84 (broad s, 2H, NH_2), 5.87 (d, 1H, C2H, $J = 7$ Hz), 4.48 (broad s, 1H, OH), 3.10–2.84 (m, 2H, CH_2OH), 2.68–2.59 (m, 1H, C1H), 2.42–2.25 (m, 2H, C5H_2). Anal. calc'd. ($C_{11}H_{14}N_6O$): C, 53.65; H, 5.73; N, 34.13; found: C, 53.30; H, 5.76; N, 33.91.

Cis-(±)-2-(2, 6-Cyclopropylamino-1-9H-dihydropurin-6-9-yl) cyclopent-3-enylmethanol (15)

To a solution of **12** (100 mg, 0.4 mmol) in absolute ethanol (20 mL) was added excess cyclopropylamine (1 mL). The bomb was sealed and heated to 65–70°C for 48 h. The volatiles were evaporated, and the residue was chromatographed on a silica gel column (CH_3Cl:MeOH) and recrystallized in CH_3CN to give a white solid (52 mg, 48%), R_f = 0.56 ($CHCl_3$:MeOH, 5:1), m.p. 168–170°C. MS (FAB): m/e 287 ($M^+ + 1$). ^{1}H NMR [$(CD_3)_2SO$, 300 MHz]: δ 7.36 (s, 1H, C8'H), 6.31–6.21 (m, 1H, C3H=C), 5.85 (broad s, 3H, C=C4H and NH_2), 5.40 (broad d, 1H, C2H, $J = 7$ Hz), 4.42 (broad s, 1H, OH), 3.20–2.28 (m, 2H, CH_2OH), 2.63–2.50 (m, 1H, C1H), 2.42–2.25 (m, 2H, C5H_2), 0.84–0.75 (m, 4H, CH_2CH_2). Anal. calcd. ($C_{14}H_{18}N_6O$): C, 58.73; H, 6.34; N, 29.35; found: C, 58.50; H, 6.41; N, 29.37.

Cis-(±)-Methyl-2-[(2-amino-1-9H-dihydropurin-6-on-9-yl) cyclopent-3-enylmethanol]-1-diethyl Phosphonate (17a)

A suspension of **13** (280 mg, 1.13 mmol) and NaH (81 mg, 3.4 mmol) in anhydrous THF (150 mL) was stirred at ambient temperature overnight under nitrogen. The suspension was cooled to −20°C, and diethylphosphonomethyl triflate (680 mg, 2.27 mmol) in THF (10 mL) was added dropwise. Stirring was continued for 4 h at −20°C, and 4°C overnight. Methanol was added to quench the reaction, and excess solvents were removed in vacuo. The residue was purified by flash chromatography on a silical gel column (EtOAc:MeOH) to give a white solid (95 mg, 21%), R_f = 0.26 ($CHCl_3$:MeOH, 5:1), m.p. 72–75°C. MS (FAB): m/e 398 ($M^+ + 1$), 396 ($M^+ - 1$). ^{1}H NMR ($CDCl_3$): δ 10.60 (broad s, 1H, NH), 7.37 (s, 1H, C8′H), 6.49 (broad s, 2H, NH_2), 6.24–6.22 (m, 1H, C3H=C), 5.85–5.83 (m, 1H, C=C4H), 5.38 (d, 1H, C2H, $J = 7$ Hz), 3.99–3.88 (m, 4H, OCH_2CH_3), 3.44–3.60 (m, 2H, P[O]CH_2), 3.22–3.00 (m, 2H, CH_2OC), 2.82–2.71 (m, 1H, C1H), 2.58–2.42 (m, 2H, C5H_2), 1.16 (dt, 6H, $OCH_2C\ H_3$, $^4J_{PH} = 2$ Hz, $^3J_{HH} = 7$ Hz). ^{31}P NMR, proton coupled ($CDCl_3$, 300 MHz): δ 2.30 (m). Anal. calcd. ($C_{16}H_{24}N_5O_5P.2H_2O$): C, 44.34; H, 6.61; N, 16.16; found: C, 44.28; H, 6.65; N, 15.76.

Cis-(±)-Methyl-2-[(2-amino-1-9H-didehydropurin-6-on-9-yl) cyclopent-3-enylmethanol]-1-phosphonic Acid (17b)

Diethyl phosphonate ester **17a** (80 mg, 0.21 mmol) was dissolved in DMF (10 mL), and freshly distilled BTMS (2 mL) was added. The reaction mixture was stirred overnight at r.t. under nitrogen. Excess solvents were removed under reduced pressure. The residue was dissolved in cold H_2O (1.5 mL), and acetone was added dropwise until a precipitate was formed. Recrystallization was carried out in H_2O/acetone to give a white solid (45 mg, 63%). MS (FAB): m/e 342 (M^++1), 340 (M^+ −1). ^{1}H NMR (CD_3OD, 300 MHz): δ 7.38 (s, 1H, C8'H), 6.26–6.21 (m, 1H, C3H=C), 5.76–5.62 (m, 1H, C=C4H), 5.41 (d, 1H, C2H, J = 7 Hz), 3.88–3.72 (m, 2H, P[O]C H_2), 3.30–3.10 (m, 2H, C H_2OC), 2.81–2.68 (m, 1H, C1H), 2.54–2.28 (m, 2H, C5H_2). ^{31}P NMR [$(CD_3)_2SO$, 300 MHz]:δ 19.50 ppm. Anal. calcd. ($C_{12}H_{16}N_5O_5P.H_2O$): C, 40.08; H, 5.05; N, 19.50; found: C, 40.24; H, 4.73; N, 19.68.

Cis-(±)-Methyl-2-[(2-amino-6-cyclopropylamino-9H-purin-9-yl) cyclopent-3-enylmethanol]-1-diethylphosphonate (18a)]

A suspension of **15** (400 mg, 1.4 mmol) and NaH (84 mg, 3.5 mmol) in anhydrous THF (35 mL) was stirred overnight at r.t. under nitrogen. The suspension was cooled to −20°C, and diethyl phosphonomethyl triflate (800 mg, 3 mmol) in THF (10 mL) was added dropwise. Stirring was continued at −20°C for 4 h and then at 4°C overnight. MeOH was added to quench the reaction, and solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column to give slightly yellow oil (130 mg, 21%), R_f = 0.56 ($CHCl_3$:MeOH, 5:1). MS (FAB): m/e 437 (M^+ +1). ^{1}H NMR [$(CD_3)_2SO$, 300 MHz]: δ 7.26 (s, 1H, C8'H), 6.20–6.18 (m, 1H, C3H=C), 6.00 (broad s, 1H, CHN-cyclopropane), 5.77–5.75 (m, 1H, C=C4H), 5.50 (d, 1H, C2H, J = 7 Hz), 5.24 (s, 1H, NH), 5.10 (broad s, 2H, NH_2), 4.08–3.96 (m, 4H, OC H_2CH_3), 3.49–3.28 (m, 2H, P[O]C H_2), 3.22–3.03 (m, 2H, C H_2OC), 2.91–2.80 (m, 1H, C1H), 2.64–2.32 (m, 2H, C5H_2), 1.22 (dt, 6H, OCH_2C H_3, $^4J_{PH}$= 2 Hz, $^3J_{HH}$ = 7 Hz), 0.78–0.49 (m, 4H, CH_2CH_2). ^{31}P NMR, proton coupled [$(CD_3)_2SO$, 300 MHz]: δ 22.23 (m). Anal. calc'd. ($C_{19}H_{29}N_6O_4P$): C, 52.28; H, 6.70; N, 19.26; found: C, 51.89; H, 6.58; N, 19.20.

Cis-(±)-Methyl-2-[(2-amino-6-cyclopropylamino-9H-purin-9-yl) cyclopent-3-enylmethanol]-1-diethylphosphonic Acid (18b)

Diethyl phosphonate ester **18a** (120 mg, 0.28 mmol) was dissolved in CH_3CN (20 mL), and freshly distilled BTMS (1 mL) was added. The reaction mixture was stirred overnight at r.t. under nitrogen. Solvents were removed under reduced pressure, and the residue dissolved in cold H_2O (1.5 mL). Acetone was added dropwise until a precipitate was

formed. Recrystallization from H_2O/acetone gave a white solid (35 mg) in 33% yield, m.p. 232–234°C. MS (FAB): m/e 381 ($M^+ + 1$). ^1H NMR (CD_3OD, 300 MHz): δ 8.38, 8.27 (each s, each 1H, C8'H and C HN-), 6.25–6.20 (m, 1H, C3H=C), 5.70–5.68 (m, 1H, C=C4H), 5.51 (d, 1H, C2H, $J = 7$ Hz), 3.68–3.62 (m, 2H, [PO]CH_2), 3.40–3.20 (m, 2H, C$\underline{H_2}$OC), 2.91–2.78 (m, 1H, C1H), 2.50–2.25 (m, 2H, C5H_2), 0.99–0.68 (m, 4H, CH_2CH_2). ^{31}P NMR [$(CD_3)_2SO$, 300 MHz]:δ 19.48 ppm.

Anal. calc'd. ($C_{15}H_{21}N_6O_4P.H_2O$): C, 45.22; H, 5.82; N, 21.10; found: C, 45.28; H, 5.92; N, 21.29.

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