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Synthesis and Potent Anti-leukemic Activity of Novel 5'-Norcarbocyclic *C*-nucleoside Phosphonic Acids

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The first synthetic route to 5'-norcarbocyclic *C*-nucleoside [7-oxa-7,9-dideazadenosine (furo[3,2-*d*]pyrimidine) and 9-deazaadenosine (pyrrolo[3,2-*d*]pyrimidine)] phosphonic acids from commercially available 1,3-dihydroxy cyclopentane was described. The key C-C bond formation from sugar to base precursor was performed using Knoevenagel-type condensation from a ketone derivative. Synthesized *C*-nucleoside phosphonic acids were tested for anti-HIV activity as well as anti-leukemic activity. Compound **26** showed significant anti-leukemic activity.

Key Words : Antiviral agent, Anti-leukemic agent, *C*-nucleoside, Knoevenagel reaction

Introduction

C-Nucleosides[1] such as pseudoisocytidine,[2] tiazofurin,[3] selenazofurin,[4] 9-deazaadenosine (**1**),[5] and 4-amino-8-β-D-ribofuranosylpyrazolo[1,5-*a*]-1,3,5-triazine (**2**, D-APTR)[6] have received considerable attention because of their chemical stability and anti-leukemic activity. The carbocyclic *C*-nucleoside[7] is a unique class of nucleosides in which the heterocycle is connected to a sugar moiety by a C-C bond instead of the C-N bond of the natural nucleosides. Recently, Schneller *et al*. reported a novel synthetic route of carbocyclic 4'-*epi*-formycin (**3**) *via* a procedure based on an asymmetric aldol/ring-closing metathesis strategy.[8]

Carbocyclic nucleosides[9] are a group of compounds that are structurally similar to natural nucleosides in which the furanose oxygen is replaced by a methylene group. Replacement of the furanose ring oxygen by carbon is of particular interest because the resulting carbocyclic nucleosides possess greater metabolic stability to phosphorylase,[10] which cleaves the glycosidic bond of nucleosides. The recent discovery of cpAP (**4**)[11] as an anti-HIV agent gives strong impetus to the search for novel nucleosides in this class of compounds (Figure 1).

A nucleoside 5'-phosphate is essentially a nucleoside monophosphate analogue.[12] However, the phosphonate has certain advantages over its phosphate counterpart because it is metabolically stable owing to its phosphorus-carbon bond, which is not susceptible to hydrolytic cleavage.[13] The spatial location of the oxygen atom, particularly the β-position, with regard to the phosphorus atom in the nucleoside analogue plays a critical role in its antiviral activity. Increased antiviral activity conferred by this oxygen atom may be attributed to increased binding capacity of the phosphonate analogs to target enzymes.[14] More importantly, the presence of a 5'-phosphonate allows the first phosphorylation step required for nucleoside activation to be skipped, thereby bypassing this inefficient and often rate-limiting step in the conversion to 5'-triphosphate. This is frequently a limiting step in the phosphorylation sequence that ultimately leads to triphosphates.[15] Like a nucleoside monophosphate, a nucleoside phosphonate can be further phosphorylated by cellular nucleotide kinases.[16] The concept of nucleoside phosphonate has been applied to design chain terminators for anti-HIV chemotherapy and proved to be valid.

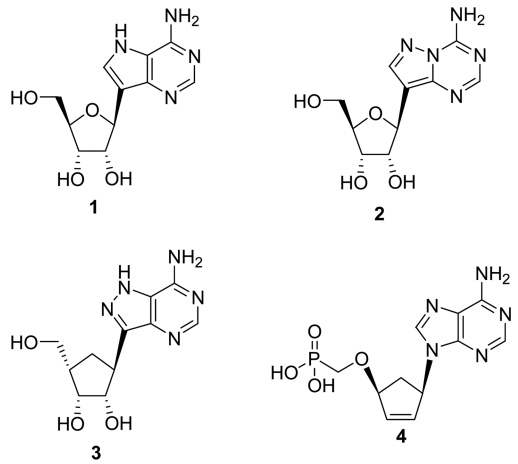
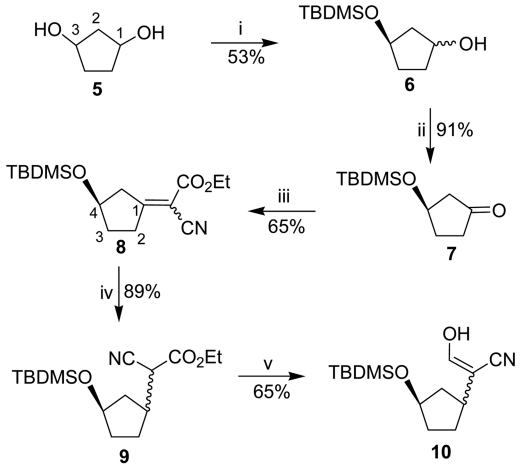


Figure 1. Design rationale of 5'-norcarbocyclic *C*-nucleoside phosphonic acid analogs

On the basis of the advantageous chemical stability and clinically significant biological properties of *C*-nucleosides and carbocyclic nucleoside phosphonic acids, we aimed to synthesize hybrid nucleosides in the form of 5'-norcarbocyclic *C*-nucleoside phosphonic acids. Herein, we report the synthesis of novel 5'-norcarbocyclic furo and pyrrolo[3,2-*d*]pyrimidine nucleoside phosphonic acids and their biological evaluation.



Reagents: i) TBDMSCl, imidazole, CH_2Cl_2; ii) Dess-Martin periodinane, CH_2Cl_2; iii) $NCCH_2CO_2Et$, KO*t*-Bu, EtOH; iv) H_2, 10% Pd/C, MeOH; v) Dibal-H, ether.

Scheme 1. Synthesis of cyclopentyl enol intermediate **10**.

Results and Discussion

For the synthesis of target carbocyclic *C*-nucleoside phosphonic acids, we utilized commercially available 1,3-dihydroxy cyclopropane **5** as a starting material (Scheme 1). Selective monosilylation of diol **5** produced cyclopentanol **6**, which was oxidized to the ketone **7** using Dess–Martin conditions.[17] The cyclopentanone **7** was subjected to Knoevenagel-type condensation[18] with ethyl cyanoacetate and potassium *tert*-butoxide in EtOH to give cyclopentylidene intermediate **8** with a 65% yield. The selective catalytic hydrogenation of **8** using 10% Pd/C under hydrogen produced compound **9** as a stereoisomeric mixture.

The intermediate **9** was reduced to the enol **10** by diisobutylaluminium hydride, which was *O*-alkylated with chloroacetonitrile using cesium carbonate to smoothly produce the enol ether **11** with a 52% two-step yield. Nitrile anion cyclization of **11** was performed with a 4-fold excess of LDA in anhydrous tetrahydrofuran at −70 °C to produce furan analogs **12α** (19%) and **12β** (21%).[19] A complete nuclear Overhauser effect (NOE) NMR study enabled clear determination of the relative stereochemistry of **12α** and **12β** (Figure 2). For compound **12β**, the spectrum showed a strong NOE (1.5%) corresponding to H-1' ↔ H-4' coupling. On the basis of this finding, we concluded that the 4'-OTBDMS and the 1'-furan base of **12β** were located on the b face. In contrast, the spectra of **12α** showed only a weak H-1' ↔ H-4' NOE (1.0%); hence, it was defined as the 1,4'-*trans* isomer. The

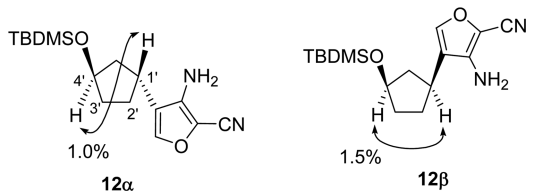
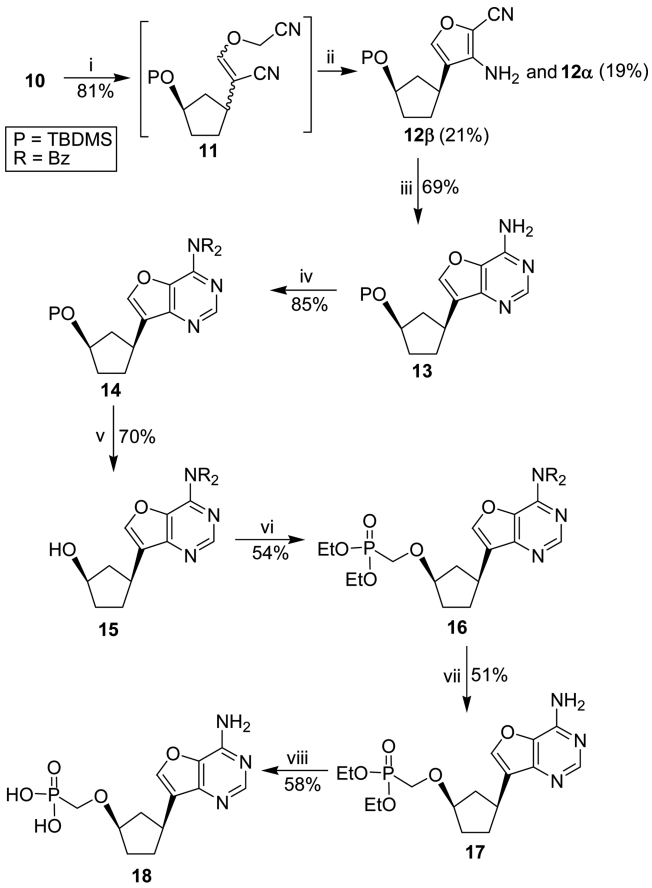


Figure 2. NOE differences between the proximal hydrogens of **12α** and **12β**.

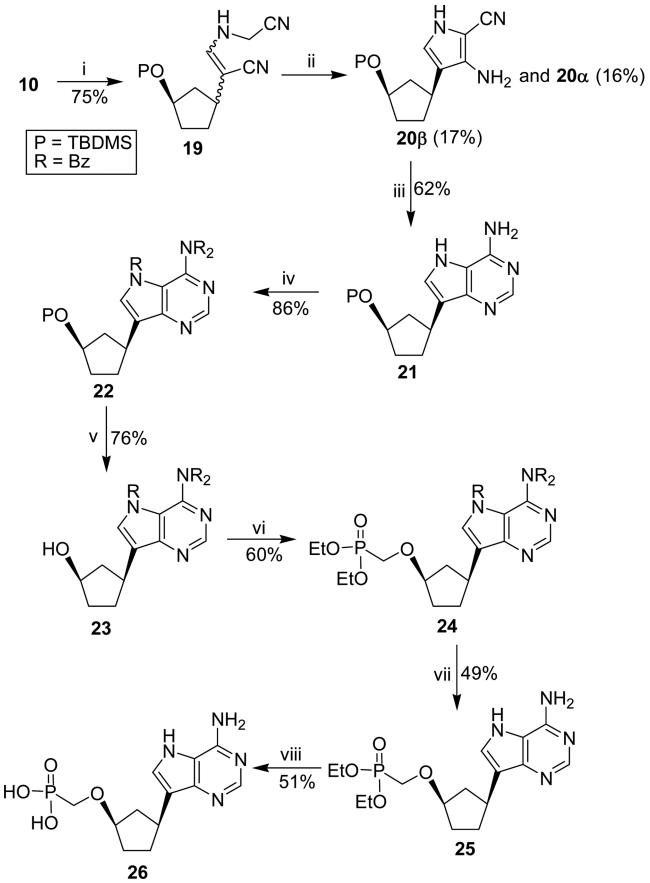


Reagents: i) $ClCH_2CN$, Cs_2CO_3, DMF; ii) LDA, -70 °C, THF; iii) formamidine acetate, EtOH; iv) BzCl, pyridine; v) TBAF, THF; vi) $(EtO)_2POCH_2OTf$, LiO-*t*-Bu, THF; vii) NH_3, MeOH, rt; viii) TMSBr, 2,6-lutidine, CH_3CN.

Scheme 2. Synthesis of 5'-norcarbocyclic 7-oxa-7,9-dideazaadenosine phosphonic acid.

aminonitrile **12β** is a versatile intermediate for the synthesis of a number of furo[3,2-*d*]pyrimidine *C*-nucleosides. Treatment of **12β** with formamidine acetate ($HN{=}CHNH_2{\cdot}HOAc$) in refluxing ethanol provided **13** with a 69% yield. For the synthesis of desired nucleoside phosphonic acid, benzoylation of **13** with benzoyl chloride in dry pyridine yielded the di-*N*-benzoyl derivative **14** in an 85% yield.[20] The removal of the silyl protecting group of compound **14** by using tetra-*n*-butylammonium fluoride (TBAF) afforded the 5'-nornucleoside analogue **15**, which was treated with diethylphosphonomethyl triflate[21] using lithium *t*-butoxide to yield the nucleoside phosphonate analogue **16**. The selective deprotection of the base moiety of **16** was achieved by using saturated methanolic ammonia at 25 °C to afford the corresponding 5'-nornucleoside phosphonate derivative **17**. Hydrolysis of **17** by treatment with bromotrimethylsilane in CH_3CN in the presence of 2,6-lutidine gave a desired 5'-norcarbocyclic furo[3,2-*d*]pyrimidine nucleoside phosphonic acid **18** (Scheme 2).[22]

For the synthesis of 5'-norcarbocyclic pyrrolo[3,2-*d*]pyrimidine nucleoside phosphonic acid, the common enol intermediate **10** was treated with aminoacetonitrile monosulfate ($H_2NCH_2CN{\cdot}H_2SO_4$) in MeOH to produce enamine inter-



Reagents: i) aminoacetonitrile monosulfate, NaOAc, MeOH; ii) (a) ethyl chloroformate, DBU, CH_2Cl_2; (b) DBU, CH_2Cl_2; (c) K_2CO_3, EtOH; iii) formamidine acetate, EtOH; iv) BzCl, pyridine; v) TBAF, THF; vi) $(EtO)_2POCH_2OTf$, LiO-*t*-Bu, THF; vii) NH_3, MeOH, rt; viii) TMSBr, 2,6-lutidine, CH_3CN.

Scheme 3. Synthesis of 5'-norcarbocyclic 9-deazaadenosine phosphonic acid.

mediate **19** with a 75% yield. Sequentially, *N*-protection of **19** with ethyl chloroformate, DBU-induced cyclization[23] and deformylation gave the pyrrolo derivatives **20α** and **20β**, respectively.[24] Their relative stereochemistries were also unambiguously determined by NOE studies. Treatment of **20β** with formamidine acetate gave the protected 5'-norcarbocyclic-9-deazaadenosine analog **21** with a 62% yield. For the synthesis of 5'-norcarbocyclic-9-deazaadenosine nucleoside phosphonic acid, perbenzoylation of **21** with benzoyl chloride in dry pyridine yielded the tri-*N*-benzoyl derivative **22** in an 86% yield by using a procedure similar[20] to that described for **14**, which was desilylated using TBAF to give 5'-norcarbocyclic nucleoside analog **23**, which was phosphonated to produce **24** by the same conditions as those used to prepare **16**. The debenzoylation of **24** was achieved by using saturated methanolic ammonia at 25 °C to afford the corresponding 5'-norcarbocyclic 9-deazaadenosine phosphonate **25**. From this intermediate, the targeted 5'-norcarbocyclic pyrrolo[3,2-*d*]pyrimidine nucleoside phosphonic acid **26** was prepared using a hydrolysis procedure similar to that described for the preparation of **19** (Scheme 3).

It should be noted that the synthesized 5'-norcarbocyclic nucleoside phosphonic acids **18** and **26** were novel compounds that were not previously reported in the literature. The antiviral activity of nucleoside phosphonic acids is mostly explained by their intracellular metabolism to their diphosphates, which is followed by incorporation into the viral genome and chain termination.[25] As shown in Table 1, the synthesized compounds **18** and **26** were tested against HIV-1 and showed moderate antiviral activity, as well as cytotoxicity, at concentrations up to 100 μM. This result indicates that their antiviral activity might be a result of cytotoxicity. Anti-HIV activity was determined in human peripheral blood mononuclear (PBM) cells infected with HIV-1 strain *LAI*. The cytotoxicity of the compounds was evaluated in parallel with their antiviral activity based on the viability of mock-infected cells.[26]

Table 1. The antiviral activity of the synthesized nucleoside analog compounds

Compound No.	Anti-HIV-1 (PBM) EC_{50} (μM)	Cytotoxicity (PBM) IC_{50} (μM)	Cytotoxicity (Vero) IC_{50} (μM)
18	21.6	42	25
26	9.7	20	8.4
AZT	0.007	>100	40
PMEA	0.42	>100	25

AZT: azidothymidine. PMEA: 9-[2-(phosphonomethoxy)ethyl]adenine. EC_{50} (μM): concentration (μM) required to inhibit the replication of HIV-1 by 50%. IC_{50} (μM): concentration (μM) required to inhibit the cell growth of unaffected cells by 50%

Table 2. *In vitro* inhibitory activity for tumor growth of the synthesized nucleoside analog compounds

Compound No.	L-1210 ID_{50} (μg/mL)	P-815 ID_{50} (μg/mL)
18	7.6	8.3
26	1.7	0.8
9-deazaadenosine (**1**)	< 0.01	< 0.01

ID_{50} (μg/mL): dose (μg/mL) required to inhibit the *in vitro* tumor growth by 50%. in murine leukemic cell lines

In addition, the final *C*-nucleosides **18** and **26** were screened *in vitro* inhibitory activity for tumor growth against mouse leukemia cell lines (L-1210, P-815), according to the technique described by Fischer,[27] with some modifications.[28] The results summarized in Table 2 indicate that pyrrolo[3,2-*d*]pyrimidine analog **26** was more active than **18**, but was much less active than 9-deazaadenosine (**1**) itself.

Conclusions

Based on the potent biological activity of *C*-nucleosides and 5'-norcarbocyclic nucleoside phosphonic acids, we have designed and successfully synthesized novel 5'-norcarbocyclic *C*-nucleoside phosphonic acids starting from 1,3-dihydroxy-cyclopentane. The data presented herein indicate that synthesized nucleoside phosphonic acid analogs showed moderate cytotoxicity-derived anti-HIV activity and anti-

leukemic activity. Further studies evaluating the anti-leukemic activity of these systems are in progress.

Experiments

Melting points were determined using a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded using a JEOL 300 Fourier transform spectrometer (JEOL, Tokyo, Japan). Chemical shifts are reported in parts per million (δ), and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublets). UV spectra were recorded using a Beckman DU-7 spectrophotometer (Beckman, South Pasadena, CA, USA). Mass (MS) spectra were recorded in electrospray ionization (ESI) mode. Elemental analyses were performed using a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA). Thin-layer chromatography (TLC) was performed using Uniplates (silica gel) purchased from Analtech Co. (7558, Newark, DE, USA). All reactions were carried out under nitrogen atmosphere unless otherwise specified. Anhydrous dichloromethane, benzene, and pyridine were obtained by distillation from CaH_2. Anhydrous THF was obtained by distillation from Na and benzophenone, immediately prior to use.

(*rel*)-(1*S* and 1*R*,3*S*)-3-(*t*-Butyldimethylsilanyloxy) cyclopentanol (6). TBDMSCl (2.29 g, 15.25 mmol) was added slowly to a solution of **5** (1.41 g, 13.87 mmol) and imidazole (1.41 g, 20.80 mmol) in CH_2Cl_2 (100 mL) at −10 °C and stirred for 7 h at the same temperature. Saturated $NaHCO_3$ solution (10 mL) was poured into the mixture and stirred for 1 h at room temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in water (200 mL) and extracted with diethyl ether (200 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to produce compound **6** (1.58 g, 53%) as an isomeric mixture: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.27-3.20 (m, 2H), 1.98-1.52 (m, 6H), 0.89 (m, 9H), 0.02 (m, 6H).

(±)-3-(*t*-Butyldimethylsilanyloxy) cyclopentanone (7). Compound **6** (2.43 g, 11.25 mmol) was added to a solution of Dess–Martin periodinane (10.38 g, 24.5 mmol) in CH_2Cl_2 (100 mL) at 0 °C, and stirred for 24 h at room temperature under argon gas. The solvent was removed and the residue was triturated with diethyl ether (150 mL). Following filtration through a pad of silica gel, the organic solution was washed with a solution of sodium thiosulfate pentahydrate (13 g) in water (100 mL), ice-cold saturated $NaHCO_3$ (80 mL), and brine (80 mL) and dried over $MgSO_4$. The solvent was filtered, concentrated *in vacuo*, and purified by silica gel column chromatography (EtOAc/hexane, 1:10) to produce compound **7** (2.19 g, 91%) as a colorless syrup. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76-3.74 (m, 1H), 2.34-2.02 (m, 6H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.6, 63.5, 52.6, 37.1, 31.5, 25.7, 18.4, −4.7. Anal. calcd. for $C_{11}H_{22}O_2Si$: C, 61.63; H, 10.34; found: C, 61.72; H, 10.26; MS *m/z* 215 $(M+H)^+$.

(±)-(*E*&*Z*)-Ethyl 2-cyano-2-[4-(*t*-butyldimethylsilanyloxy) cyclopentylidene] acetate (8). Potassium *tert*-butoxide (6.73 g, 60.0 mmol) was added to a solution of **7** (2.57 g, 12.0 mmol) and ethyl cyanoacetate (6.78 g, 60.0 mmol) in ethanol (80 mL) at 0 °C. The mixture was stirred for 5 h at room temperature and concentrated under reduced pressure. The mixture was quenched by water (12 mL) and further diluted with 150 mL of water. The mixture was then extracted with EtOAc (200 m) 2 times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:15) to give crude ester derivative **8** (7.8 g, 65%) as a colorless oil. Without further purification, compound **8** was subjected to the next reaction.

(*rel*)-(1*S* and 1*R*,4*R*)-Ethyl-2-[4-(*t*-butyldimethylsilanyloxy)cyclopentyl]-2-isocyanoacetate (9). To a solution of **8** (1.2 g, 3.88 mmol) in methanol (10 mL), 10% Pd/C (120 mg) was added. The mixture was thoroughly deoxygenated, then saturated with hydrogen and stirred for 24 h. The charcoal was removed by filtration through a short Celite® pad, which was thoroughly washed with methanol. Evaporation of the solvent gave a crude product which was purified by column chromatography (EtOAc/hexane, 1:10) to yield 1.07 g (89%) of **9** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.16 (q, J = 7.0 Hz, 2H), 3.41 (m, 1H), 3.26-3.28 (m, 1H), 2.24-2.25 (m, 1H), 1.75-1.35 (m, 6H), 1.31 (t, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H); Anal. calcd. for $C_{16}H_{29}NO_3Si$: C, 61.69; H, 9.38; N, 4.50; found: C, 61.82; H, 9.34; N, 4.54; MS *m/z* 312 $(M+H)^+$.

(*rel*)-(1*S* and 1*R*,4*R*)-2-[4-(*t*-Butyldimethylsilanyloxy) cyclopentyl]-3-hydroxyacrylonitrile (10). Diisobutylaluminium hydride (3.98 mL, 1 M in hexane) was added to a solution of **9** (1.24 g, 3.98 mmol) in anhydrous ether (8 mL) at −78 °C over 10 min. The resulting mixture was stirred for 10 min and quenched with MeOH (8 mL). The resulting white solid was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give enol **10** (691 mg, 65%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.45 (s, 1H), 3.58-3.56 (m, 1H), 2.47-2.44 (m, 1H), 1.75-1.34 (m, 6H), 0.87-0.88 (m, 9H), 0.02-0.03 (m, 6H); Anal. calcd. for $C_{14}H_{25}NO_2Si$: C, 62.87; H, 9.42; N, 5.24; found: C, 62.74; H, 9.50, N, 5.19.

(*rel*)-(*E*&*Z*)-3-(Cyanomethoxy)-2-[(1*S* and 1*R*,4*R*)-4-(*t*-butyldimethylsilanyloxy) cyclopentyl] acrylonitrile (11). To a solution of compound **10** (1.10 g, 4.14 mmol), cesium carbonate 5.39 g, 16.56 mmol) in anhydrous DMF (30 mL) was added chloroacetonitrile (2.48 g, 33.12 mmol), and the solution was stirred at room temperature for 24 h. The reaction mixture was poured water (150 mL) and extracted with *t*-butyl methyl ether (150 mL) three times. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (EtOAc/Benzene, 1:10) to give **11** (1.02 g, 81%) as an isomeric mixture. The mixture was subjected directly to

the next step.

(*rel*)-3-Amino-4-[(1'*R*,4'*R*)-4'-(*t*-butyldimethylsilanyloxy) cyclopentyl] furan-2-carbonitrile (12a) and (*rel*)-3-amino-4-[(1'*S*,4'*R*)-4'-(*t*-butyldimethylsilanyloxy) cyclopentyl] furan-2-carbonitrile (12β). To the solution of the carbonitrile **11** (1.6 g, 5.22 mmol) in anhydrous THF (20 mL), a solution of LDA (2.24 g, 21 mmol) in anhydrous THF (15 mL) was added dropwise at −70 °C and stirred for 2 h. The mixture was quenched with a saturated solution of ammonium chloride (150 mL) and stirred for 1 h at room temperature. The mixture was extracted with EtOAc (150 mL) 3 times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/Hexane, 3:1) to give **12α** (303 mg, 19%) and **12β** (335 mg, 21%). Spectroscopic data for **12α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (s, 1H), 4.28 (br s, 2H, D_2O exchangeable), 3.31-3.29 (m, 1H), 2.82-2.83 (m, 1H), 2.02-1.37 (m, 6H), 0.88-0.89 (m, 9H), 0.02 (s, 6H); Anal. calcd. for $C_{16}H_{26}N_2O_2Si$: C, 62.70; H, 8.55; N, 9.14; found: C, 62.56; H, 8.50; N, 9.29; MS *m/z* 307 $(M+H)^+$. Spectroscopic data for **12β**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (s, 1H), 4.30 (br, 2H, D_2O exchangeable), 3.34-3.31 (m, 1H), 2.81-2.79 (m, 1H), 2.00-1.35 (m, 6H), 0.88-0.89 (m, 9H), 0.03 (s, 6H); Anal. calcd. for $C_{16}H_{26}N_2O_2Si$: C, 62.70; H, 8.55; N, 9.14; found: C, 62.85; H, 8.63; N, 9.08; MS *m/z* 307 $(M+H)^+$.

(*rel*)-[(1*S*,4'*R*)-9-[4'-(*t*-Butyldimethylsilanyloxy) cyclopentyl] 7-oxa-7,9-dideazaadenosine (13). To a solution of **12β** (650 mg, 2.12 mmol) in EtOH (20 mL), formamidine acetate (2.20 g, 21.2 mmol) was added and the reaction mixture was refluxed for 48 h. The solvent was concentrated under reduced pressure, and the residue was partitioned between dichloromethane and water. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 10:1) to give **13** (487 mg, 69%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.28 (br s, 2H, D_2O exchangeable), 8.63 (s, 1H), 8.51 (s, 1H), 3.29-3.30 (m, 1H), 2.82-2.83 (m, 1H), 2.07-2.08 (m, 1H), 1.94-1.47 (m, 5H), 0.88-0.89 (m, 9H), 0.03-0.04 (m, 6H); Anal. calcd. for $C_{17}H_{27}N_3O_2Si$ (+1.0 MeOH): C, 59.19; H, 8.55, N, 11.50; found: C, 59.28; H, 8.48; N, 11.58; MS *m/z* 334 $(M+H)^+$.

(*rel*)-[(1'*S*,4'*R*)-9-[4'-(*t*-Butyldimethylsilanyloxy) cyclopentyl] 4-*N*-dibenzoyl-7-oxa-7,9-dideazaadenosine (14). Benzoyl chloride (2.12 g, 15.12 mmol) was added dropwise to a stirred solution of compound **13** (1.26 g, 3.78 mmol) in dry pyridine (10 mL) at 0 °C and stirred overnight at rt. The reaction mixture was quenched by water (10 mL) and stirred for 1 h at 0 °C. The mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was further extracted with CH_2Cl_2 2 times. The combined organic layers were washed with cold saturated $NaHCO_3$ solution, then washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/*n*-hexane, 1:8) to give **14** (1.74 g, 85%) as a form. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.58 (s, 1H), 7.84-7.45 (m, 11H), 3.34-3.35 (m, 1H), 2.78-2.79 (m, 1H), 1.91-1.48 (m, 6H), 0.89-0.90 (m, 9H), 0.02-0.03 (m, 6H); Anal. calcd. for $C_{31}H_{35}N_3O_4Si$: C, 68.73; H, 6.51, N, 7.76; found: C, 68.87; H, 6.46; N, 7.88; MS *m/z* 542 $(M+H)^+$.

(*rel*)-(1'*S*,4'*R*)-9-(4'-Cyclopentyloxy) 4-*N*-dibenzoyl-7-oxa-7,9-dideazaadenosine (15). To a solution of compound **14** (320 mg, 0.59 mmol) in THF (10 mL), tetrabutylammonium fluoride (TBAF; 0.65 mL, 1.0 M solution in THF) at 0 °C was added. The mixture was stirred for 5 h at room temperature and concentrated. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane, 1:1) to give compound **15** (176 mg, 70%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.50 (s, 1H), 7.91-7.34 (m, 11H), 3.32-3.30 (m, 1H), 2.81-2.79 (m, 1H), 2.06-2.07 (m, 1H), 1.91-1.42 (m, 5H); Anal. calcd. for $C_{25}H_{21}N_3O_4$: C, 70.25; H, 4.95, N, 9.83; found: C, 70.37; H, 4.88; N, 9.89; MS *m/z* 428 $(M+H)^+$.

(*rel*)-(1'*S*,4'*R*)-Diethyl-9-[4'-(cyclopentyloxy) 4-*N*-dibenzoyl-7-oxa-7,9-dideazaadenosine] methylphosphonate (16). Both LiO*t*-Bu (2.996 mL of 0.5 M solution in THF, 1.498 mmol) and a solution of diethyl phosphonomethyltriflate (449 mg, 1.498 mmol) in 16.0 mL of THF were slowly added to a solution of the **15** analog (320 mg, 0.749 mmol) in 8.0 mL of THF at 0 °C and stirred overnight at room temperature under anhydrous conditions. The mixture was quenched by adding saturated NH_4Cl solution (5 mL) and further diluted with additional H_2O (100 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (n-hexane/EtOAc, 1:2) to produce **16** (233 mg, 54%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (s, 1H), 7.93-7.39 (m, 11H), 4.12-4.09 (m, 4H), 3.86 (d, J = 8.0 Hz, 2H), 3.06-3.07 (m, 1H), 2.78-2.79 (m, 1H), 2.06-2.07 (m, 1H), 1.88-1.44 (m, 5H), 1.15-1.13 (m, 6H); Anal. calcd. for $C_{30}H_{32}N_3O_7P$: C, 62.39; H, 5.58; N, 7.28; found: C, 62.51; H, 5.49; N. 7.36; MS *m/z* 578 $(M+H)^+$.

(*rel*)-(1'*S*,4'*R*)-Diethyl-9-[(4'-cyclopentyloxy) 7-oxa-7,9-dideazaadenosine] methylphosphonate (17). A solution of **16** (280 mg, 0.485 mmol) in saturated methanolic ammonia (12 mL) was stirred overnight at room temperature for 6 h and the volatiles were evaporated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:8) to produce **17** (91 mg, 51%). ^{1}H (DMSO-d_6, 300 MHz) δ 9.30 (br s, 2H, D_2O exchangeable), 8.68 (s, 1H), 8.53 (s, 1H), 4.14-4.11 (m, 4H), 3.84 (d, J = 8.0 Hz, 2H), 3.12-3.13 (m, 1H), 2.78-2.79 (m, 1H), 2.01-1.43 (m, 6H), 1.12-1.13 (m, 6H); Anal. calcd. for $C_{16}H_{24}N_3O_5P$ (+1.0 MeOH): C, 50.89; H, 7.03; N, 10.47; Found: C, 50.77; H, 6.93; N, 10.32; MS *m/z* 370 $(M+H)^+$.

(*rel*)-(1'*S*,4'*R*)-9-[(4'-Cyclopentyloxy) 7-oxa-7,9-dideazaadenosine] methylphosphonic acid (18). TMSBr (786 mg, 5.14 mmol) was added to a solution of phosphonate **17** (190 mg, 0.514 mmol) in anhydrous CH_3CN (12 mL) and 2,6-lutidine (1.10 g, 10.28 mmol). The mixture was heated over-

night at 69 °C under nitrogen and then concentrated *in vacuo*. The residue was co-evaporated from concentrated aqueous ammonium hydroxide (NH_4OH; 2 × 20.6 mL) and purified by triturating with acetone (10.3 mL) twice and removing the acetone by evaporation. The residue was then purified by preparative reverse-phase column chromatography using C18 silica gel. Lyophilization of the appropriate fraction produced phosphonic acid salt **18** (98 mg, 58% yield) as a white salt (ammonium salt). ^{1}H NMR (D_2O, 300 MHz) δ 8.65 (s, 1H), 8.45 (s, 1H), 3.81 (d, J = 8.2 Hz, 2H), 3.17 (m, 1H), 2.77-2.78 (m, 1H), 2.03-1.41 (m, 6H); ^{13}C NMR (D_2O, 75 MHz) δ 151.4, 147.6, 147.9, 138.1, 117.0, 85.6, 62.9 (J = 45.0 Hz), 50.2, 33.8, 31.2, 27.1; HPLC, t_R = 10.86 min; HRMS, $[M–H]^+$ calcd. 312.0765, found 312.0766.

(*rel*)-(*E*&*Z*)-3-(Cyanomethylamino)-2-[(1*S* and 1*R*,4*R*)-4-(*t*-butyldimethylsilanyloxy) cyclopentyl] acrylonitrile (19). Compound **10** (1.22 g, 4.56 mmol) was dissolved in MeOH (50 mL) followed by addition of aminoacetonitrile · monosulfate (2.81 g, 18.24 mmol) and sodium acetate (2.61 g, 31.92 mmol). The mixture was stirred for 6 h at room temperature, diluted with $CHCl_3$, and washed with water. The aqueous phase was back-washed with $CHCl_3$, the combined organic phase was dried, and the solvent was evaporated to give crude product **19** (1.04 g, 75%) as a mixture of *E/Z* diastereomers. The mixture was subjected directly to the next step.

(*rel*)-3-Amino-4-[(1'*R*,4'*R*)-4'-(*t*-butyldimethylsilanyloxy) cyclopentyl] 1H-pyrrole-2-carbonitrile (20α) and (*rel*)-3-amino-4-[(1'*S*,4'*R*)-4'-(*t*-butyldimethylsilanyloxy) cyclopentyl] 1*H*-pyrrole-2-carbonitrile (20β). To a solution of **19** (2.56 g, 8.38 mmol) in anhydrous CH_2Cl_2 (50 mL) was added 1,8-diazabicyclo[5,4,0] undec-7-ene (DBU, 2.5 mL, 16.78 mmol) and ethyl chloroformate (1.2 mL, 12.57 mmol) at 0 °C. The mixture was stirred for 2 h at room temperature. To the mixture, additional DBU (2.5 mL, 16.78 mmol) was added to induce cyclization, after which it was stirred at the same temperature for 20 h. The reaction mixture was diluted with $CHCl_3$ (150 mL) and extracted with an aqueous solution of citric acid (10%, 2 × 120 mL). The combined aqueous layer was back-washed with $CHCl_3$. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in EtOH (50 mL), treated with potassium carbonate (1.15 g, 8.38 mmol) and stirred for 1 h at rt. The reaction mixture was quenched with water and extracted with CH_2Cl_2 two times. The combined organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (EtOAc/*n*-hexane, 3:1) to give **20α** (409 mg, 16%) and **20β** (434 mg, 17%). Spectroscopic data for **20α**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87 (br s, 1H, D_2O exchangeable), 6.51 (s, 1H), 4.34 (br s, 2H, D_2O exchangeable), 3.37-3.38 (m, 1H), 2.82-2.83 (m, 1H), 2.02-1.50 (m, 6H), 0.88 (s, 9H), 0.02 (s, 6H); Anal. calcd. for $C_{16}H_{27}N_3OSi$: C, 62.91; H, 8.91; N, 13.75; found: C, 63.06; H, 8.85; N, 13.69; MS *m/z* 306 $(M+H)^+$. Spectroscopic data for **20**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91 (br s, 1H, D_2O exchangeable), 6.58 (s, 1H), 4.41 (br s, 2H, D_2O exchangeable), 3.31-3.32 (m, 1H), 2.79-2.80 (m, 1H), 1.98-1.47 (m, 6H), 0.89 (s, 9H), 0.03 (s, 6H); Anal. calcd. for $C_{16}H_{27}N_3OSi$: C, 62.91; H, 8.91; N, 13.75; found: C, 62.83; H, 8.96; N, 13.87; MS *m/z* 306 $(M+H)^+$.

(*rel*)-(1*S*,4'*R*)-9-[4'-(*t*-Butyldimethylsilanyloxy) cyclopentyl] 9-deazaadenosine (21). To a solution of **20b** (450 mg, 1.47 mmol) in EtOH (12 mL), formamidine acetate (1.53 g, 14.7 mmol) was added and the reaction mixture was refluxed for 36 h. The solvent was concentrated under reduced pressure, and the residue was diluted with dichloromethane (100 mL) and extracted with water (2 × 100 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 10:1) to give **21** (302 mg, 62%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.53 (br s, 1H, D_2O exchangeable), 9.04 (br s, 2H, D_2O exchangeable), 8.45 (s, 1H), 7.77 (d, J = 3.0 Hz, 1H, singlet with D_2O), 3.36-3.37 (m, 1H), 2.80-2.81 (m, 1H), 1.99-1.47 (m, 6H), 0.87 (s, 9H), 0.01 (s, 6H); Anal. calcd. for $C_{17}H_{28}N_4OSi$ (+1.0 MeOH): C, 59.35; H, 8.85, N, 15.38; found: C, 59.49; H, 8.78; N, 15.50; MS *m/z* 333 $(M+H)^+$.

(*rel*)-(1'*S*,4'*R*)-9-[4'-(*t*-Butyldimethylsilanyloxy) cyclopentyl] 7-*N*-benzoyl-4-*N*-dibenzoyl-9-deazaadenosine (22). Benzoyl chloride (3.55 g, 25.26 mmol) was added dropwise to a stirred solution of compound **21** (1.40 g, 4.21 mmol) in dry pyridine (20 mL) at 0 °C and stirred overnight at room temperature. The reaction mixture was quenched by water (20 mL) and stirred for 1 h at 0 °C. The mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (150 mL) and CH_2Cl_2 (150 mL). The aqueous layer was further extracted with CH_2Cl_2 2 times. The combined organic layers were washed with cold saturated $NaHCO_3$ solution, then washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/*n*-hexane, 1:8) to give **22** (2.33 g, 86%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (s, 1H), 7.97-7.29 (m, 16H), 3.32-3.33 (m, 1H), 2.80-2.81 (m, 1H), 1.97-1.43 (m, 6H), 0.89 (s, 9H), 0.02 (s, 6H); Anal. calcd. for $C_{38}H_{40}N_4O_4Si$: C, 70.78; H, 6.25, N, 8.69; found: C, 70.64; H, 6.36; N, 8.57; MS *m/z* 645 $(M+H)^+$.

(*rel*)-(1'*S*,4'*R*)-9-[(4'-Cyclopentyloxy) 7-*N*-benzoyl-4-*N*-dibenzoyl-9-deazaadenosine (23). To a solution of compound **22** (860 mg, 1.33 mmol) in THF (12 mL), tetrabutylammonium fluoride (TBAF, 1.59 mL, 1.0 M solution in THF) at 0 °C was added. The mixture was stirred for 6 h at room temperature and concentrated. The residue was purified by silica gel column chromatography (EtOAc/n-hexane, 1:1) to give compound **23** (535 mg, 76%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.76 (s, 1H), 8.08-7.34 (m, 16H), 3.35-3.36 (m, 1H), 2.81-2.82 (m, 1H), 2.01-2.02 (m, 1H), 1.97-1.46 (m, 5H); Anal. calcd. for $C_{32}H_{26}N_4O_4$: C, 72.44; H, 4.94, N, 10.56; found: C, 72.56; H, 4.85; N, 10.69; MS *m/z* 531 $(M+H)^+$.

(*rel*)-(1'*S*,4'*R*)-Diethyl-9-[(4'-cyclopentyloxy]) 7-*N*-benzoyl-4-*N*-dibenzoyl-9-deazaadenosine] methylphosphonate (24). Phosphonation of the alcohol **23** was accomplished by similar reaction procedures as were used for **16** to produce

24 with a 60% yield; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.78 (s, 1H), 8.08-7.34 (m, 16H), 4.10-4.08 (m, 4H), 3.79 (d, J = 8.0 Hz, 2H), 3.24-3.25 (m, 1H), 2.79-2.80 (m, 1H), 2.02-1.40 (m, 6H), 1.15-1.13 (m, 6H); Anal. calcd. for $C_{37}H_{37}N_4O_7P$: C, 65.29; H, 5.48; N, 8.23; found: C, 65.44; H, 5.41; N. 8.15; MS *m/z* 681 $(M+H)^+$.

(*rel*)-(1'*S*,4'*R*)-Diethyl-9-[(4'-cyclopentyloxy) 9-deaza-adenosine] methylphosphonate (25). Ammonolysis of the tri-*N*-benzoyl protection groups of **24** was performed by similar reaction conditions as those used for **17** to produce **25** with a 49% yield; ^{1}H (DMSO-d_6, 300 MHz) δ 12.18 (br s, 1H, D_2O exchangeable), 9.01 (br s, 2H, D_2O exchangeable), 8.52 (s, 1H), 7.89 (d, J = 2.9 Hz, 1H, singlet with D_2O), 4.11-4.09 (m, 4H), 3.81 (d, J = 8.2 Hz, 2H), 3.31-3.32 (m, 1H), 2.84-2.85 (m, 1H), 2.03-1.46 (m, 6H), 1.13-1.10 (m, 6H); Anal. calcd. for $C_{16}H_{25}N_4O_4P$ (+1.0 MeOH): C, 51.02; H, 7.30; N, 13.99; Found: C, 50.91; H, 7.23; N, 13.85; MS *m/z* 369 $(M+H)^+$.

(*rel*)-(1'*S*,4'*R*)-9-(4'-Cyclopentyloxy) 9-deazaadenosine] methylphosphonic acid (26). Deprotection of diethyl-phosphonate **25** to phosphonic acid **26** was performed by similar reaction conditions as were used for **18** with a 51% yield (ammonium salt). UV (H_2O) λ_{max} 268.0 nm; ^{1}H NMR (D_2O, 300 MHz) δ 8.55 (s, 1H), 7.82 (s, 1H), 3.76 (d, J = 8.1 Hz, 2H), 2.86-2.87 (m, 1H), 2.79-2.80 (m, 1H), 2.01-1.45 (m, 6H); ^{13}C NMR (D_2O, 75 MHz) δ 154.6, 145.3, 134.7, 129.4, 118.7, 84.8, 62.7 (J = 40.0 Hz), 48.5, 36.7, 32.6, 26.9; HPLC, t_R = 10.71 min; HRMS, $[M-H]^+$ calcd.: 311.0657; found: 311.0658.

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