the same conditions as the assay except without vitamin K_1 epoxide. At various time intervals (0, 1, 2, 3, 4, 5 h) aliquots (40 μL) were withdrawn from the incubation mixtures, diluted into an assay mixture containing 40 μM vitamin K_1 epoxide, 3 mM DTT, and 0.02% Emulgen 911 (total volume 500 μL), and assayed for vitamin K_1 epoxide reductase activity as described above.

Competitive Inhibition of Vitamin K_1 Epoxide Reductase by Substrate Analogues. Vitamin K_1 epoxide reductase activity (0.8 mg of microsomes) was measured by varying concentrations (10, 12.5, 16.5, 25, and 40 μM) of vitamin K_1 epoxide and 5 mM DTT in the absence and presence of the analogues (0, 20, 40, and 60 μM). Enzyme assays were the same as described above. Double-reciprocal plots of enzyme activity versus vitamin K_1 epoxide concentration at various concentrations of the substrate analogues were constructed. Inhibition constants (K_i) were determined from replots of $K_{m,app}$ versus the concentration of the substrate analogues.

The experiment also was carried out at varying DTT concentrations (0.33, 0.50, 0.67, 1.0, 2.0 mM) and 40 μM vitamin K_1 epoxide in the presence of 1 (R = CH_2F) (0, 20, 40, 60 μM). Assays were done as described above.

Substrate Activity of 1 (R = CH_2OH), 7, 11, 13, and 16. The assay (minus vitamin K_1 epoxide) was carried out as above with the alternative substrates (1 (R = CH_2OH), 7, 11, 13, and 16) at 100, 66.7, 50, 40, 33, 25, 20, 16.5, 14.5, 12.5, 11, and 10 μM. The corresponding quinone products generated (2-hydroxyvitamin K_1,[17] 6, 10, 18, 15) were used as standards to quantitate the amount of enzyme-generated product. No epoxide reduction occurred under the same conditions when either microsomes or DTT was omitted.

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Synthesis and Antiviral Activity of (*S*)-9-[4-Hydroxy-3-(phosphonomethoxy)butyl]guanine

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The synthesis of (*S*)-9-[4-hydroxy-3-(phosphonomethoxy)butyl]guanine (**3**), starting from (*S*)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (**4**), is described. Alkylation of trityl derivative **7** with (diethylphosphono)methyl triflate provided phosphonate **8**, which was readily converted to mesylate **12** in three steps. Nucleophilic substitution of the mesylate group of **12** by 2-amino-6-chloropurine sodium salt led to (*S*)-2-amino-6-chloro-9-[3-[(diethylphosphono)methoxy]-4-(tetrahydro-2*H*-pyran-2-yloxy)butyl]purine (**13**). Sequential treatment of **13** with trimethylsilyl bromide and then with 2 N HCl furnished **3**. Preliminary in vitro screening indicated that **3** exhibited a potent activity against human cytomegalovirus (HCMV) but was not active against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). The adenine and cytosine derivatives (**14** and **15**) did not exhibit activity against HSV-1 and -2 and HCMV.

The discovery of the potent selective antiherpes agents 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir)[1] and 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, ganciclovir, **1**)[2-4] has led to an extensive search for novel nucleoside analogues with improved properties. DHPG is an exceptionally potent agent against a broad range of herpesviruses including herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2),[2-4] human cytomegalovirus (HCMV),[3,4] varicella-zoster virus,[3] and Epstein–Barr virus.[3] Although the clinical use of DHPG for the treatment of cytomegalovirus retinitis has been approved, some adverse toxicological effects of DHPG in humans[5] prompted further search for a more effective agent against HCMV. Recently, HCMV has also been recognized as one of the most important pathogens in immunocompromised and aquired immune deficiency syndrome (AIDS) patients.[6] As the essential feature of the biochemical mechanism, DHPG is known to be converted to its monophosphate **2** by HSV thymidine kinases (TKs) or host kinases and then to the triphosphate by host cell kinases.[3] This triphosphate, in turn, acts as a viral DNA polymerase inhibitor.[7] Since HCMV is not known to code for a viral TK, a phosphonate

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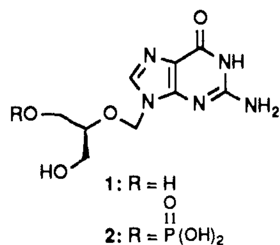
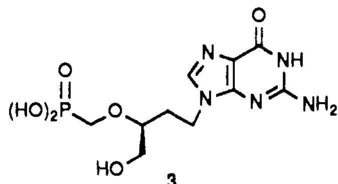


analogue such as 3 which mimics monophosphate 2, thus

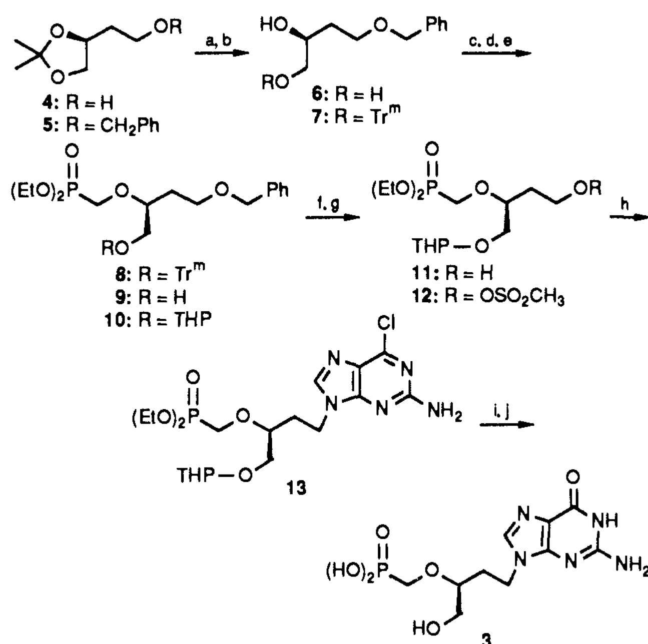


bypassing the initial enzymatic phosphorylation, would be promising as a potential chemotherapeutic agent against HCMV. Furthermore, the initial phosphorylation of DHPG by HSV-TK has been demonstrated to generate stereospecifically the *S* isomer of 2,[8] therefore, we have set our goal to synthesize 3 with the *S* chirality.

Recently, new [(phosphonomethoxy)alkyl]purine and -pyrimidine derivatives have emerged as potent antiviral agents.[9] These analogues effectively inhibited a wide array of DNA viruses and retroviruses.[9] The characteristic phosphonomethyl ether functionality present in [(phosphonomethoxy)alkyl]purine and -pyrimidine derivatives is expected to be chemically and metabolically stable.[10] Moreover, the β-oxygen atom in the phosphonomethyl ether functionality enhances the acidity of the phosphonate and brings its second pK_a closer to that of the phosphate ester.[11] In addition to this isoelectronic nature, the oxygen atom in the immediate vicinity of phosphorus has been demonstrated to play a critical role for the enzymatic phosphorylation and thus for antiviral activity.[11]

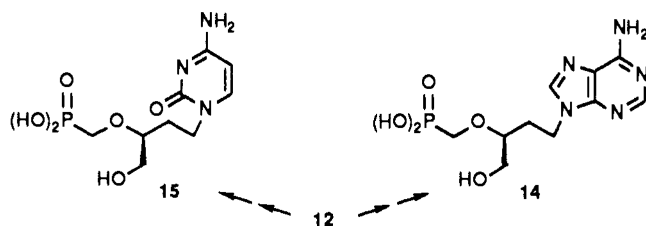
Although 3 was designed as a mimic of DHPG monophosphate 2, it may also be regarded as a one carbon homologated analogue of 9-[(3-hydroxy-2-(phosphonomethoxy)propyl]guanine (HPMPG), which is reported[9f] to exhibit broad-spectrum antiviral activity. In the present paper, we report on the synthesis and in vitro antiviral activity of 3 and the related adenine and cytosine analogues (14, 15).

Scheme I[a]



[a](a) 3 N HCl, MeOH; (b) (4-methoxyphenyl)diphenylmethyl chloride, TEA; (c) NaH, (diethylphosphono)methyl triflate; (d) Amberlyst 15, MeOH; (e) 3,4-dihydro-2*H*-pyran, *p*-TSA; (f) Pd/C, H_2; (g) CH_3SO_2Cl, TEA; (h) 2-amino-6-chloropurine, NaH; (i) TMSBr, DMF; (j) 2 N HCl.

Scheme II



Chemistry

As shown in Scheme I, the synthesis of 3 commenced with (*S*)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (4), which was obtained by acid-catalyzed cyclization of (*S*)-1,2,4-butanetriol 2-(1-methyl-1-methoxyethyl ether) according to the procedure of Meyers and his co-workers.[12] The hydroxyl functionality of 4 was protected first as the benzyl ether by alkylation with benzyl bromide. Diol 6, generated by acid-catalyzed hydrolysis of 5, reacted smoothly with 4-methoxytrityl chloride in CH_2Cl_2 to give monotrityl derivative 7 in 84% yield. This site-selective tritylation was crucial to distinguish the primary and the secondary hydroxyl groups in diol 6. At this stage, the sodium salt of 7 was alkylated with (diethyl phosphono)methyl triflate[13] in THF to give the desired phosphonate 8 in 58% yield. The use of the triflate was necessary in this case, because (diethylphosphono)methyl *p*-toluenesulfonate[14] was found to be ineffective for this alkylation. Since catalytic hydrogenolysis of 8 removed both benzyl and trityl protecting groups, conversion of the trityl group

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Table I. Antiherpes and Anticellular Activities of Acyclic Phosphonates in Tissue Culture

	ID_{50},[a] μg/mL			
virus or cell	3	14	15	DHPG
HSV-1 (BWS)[b]	>100	>100	>100	0.2
HSV-2 (G)	97	>100	>100	1.6
HCMV (AD-169)	1.0	>100	>100	5.0
vero cells	>100	>100	>100	>100
MRS-5 cells	10	>100	>100	>100

[a] Determined by plaque-reduction assays in vero (HSV) or MRC-5 cells (HCMV) or cell-proliferation assays in uninfected cell. [b] The strain is given in parentheses.

to the hydrogenolysis-stable protecting group was necessary. Selective removal of the trityl group was achieved under mild acidic conditions to give alcohol **9**, which was then converted to tetrahydropyranyl ether **10** in almost quantitative yield. Catalytic hydrogenolysis of **10** removed the benzyl protecting group, and the resulting alcohol **11** was converted to mesylate **12** by treatment with methanesulfonyl chloride and triethylamine. The coupling between the mesylate **12** and 2-amino-6-chloropurine sodium salt in DMF provided the N-9 purine derivative **13** in 52% yield with no observable N-7 isomer after silica gel chromatography. Final deprotection of **13** was effected in 47% yield by treatment with bromotrimethylsilane in DMF followed by acidic hydrolysis of the 6-chloropurine. The side-chain attachment at the N-9 position in **3** was ascertained by its ^{13}C NMR (δ 117.816 for the C-5 signal)[15] and UV (λ_{max} 252 and 274 nm)[16] spectra which were consistent with the published data of N-9 alkylated isomers. In a similar manner to that described above, the adenine and the cytosine analogues (**14** and **15**) were also prepared from mesylate **12** (Scheme II).

Biological Results and Discussion

Results of antiviral activity testing by the plaque-reduction assay against herpesviruses are listed in Table I. Since the DHPG triphosphate and the diphosphoryl derivative of (*R*,*S*)-HPMPG have been demonstrated to be selective inhibitors of viral DNA polymerase,[7,9f] a prerequisite for **3** to have antiherpetic activity is assumed to be that it be phosphorylated further to its diphosphate. Despite poor activity against HSV-1 and HSV-2, compound **3** exhibited a very potent activity against HCMV, comparable to that of DHPG. This result appears to suggest a significant level of phosphorylation of **3** by host enzymes; however, its diphosphate may be a poor inhibitor of HSV-1 and HSV-2 DNA polymerase, but an effective inhibitor of the HCMV DNA polymerase. A similar trend of antiviral activity against herpesviruses was also reported for 9-[[1-(dihydroxyphosphinyl)-4-hydroxy-3-butoxy]methyl]guanine,[17] an isosteric isomer of **3**. The cytotoxic effect of **3** is somewhat dependent on the cell line used in the assay. Thus, **3** exhibited ID_{50}'s of >100 μg/mL in vero cells and 10 μg/mL in MRC-5 cells (human lung fibroblast).

Compounds **14** and **15** had no antiviral activity at concentrations up to 100 μg/mL. The inactivity of **15** against HCMV is somewhat surprising because 9-[(1,3-dihydroxy-2-propoxy)methyl]cytosine,[18] a cytosine analogue of DHPG, has potent activity against HCMV that is comparable to the activity of DHPG.

Experimental Section

General Methods. Nuclear magnetic resonance (^1H, ^{13}C NMR) spectra were run on a Varian Gemini-300 300-MHz spectrometer with trimethylsilane as the internal reference. The chemical shift values are expressed in δ values (parts per million). Ultraviolet spectra were recorded on a Perkin-Elmer 552 spectrophotometer. Analytical results for compounds indicated by the molecular formula were within ±0.4% of the calculated values.

(*S*)-4-[2-(Benzyloxy)ethyl]-2,2-dimethyl-1,3-dioxolane (5). To a suspension of 57% sodium hydride in mineral oil (6.6 g, 0.16 M) in THF (250 mL) at 25 °C was added (*S*)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (**4**) (21.3 g, 0.15 M) and the mixture was heated at reflux for 2 h under nitrogen. To this solution at 10 °C was added benzyl bromide (25.2 g, 0.15 M). After stirring at 25 °C for 2 h, the mixture was heated at reflux for 1 h. Insoluble material was removed by filtration, and the filtrate was concentrated to dryness. The residual oil was chromatographed on silica gel using CH_2Cl_2–hexane as eluent to give **5** (25.0 g, 72.6%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.402 (s, 3 H), 1.9 (m, 2 H), 3.55 (q, J = 2.7, 5.4 Hz, 1 H), 3.58 (q, J = 5.1, 7.5 Hz, 2 H), 4.06 (q, J = 5.4, 8.1 Hz, 1 H), 4.22 (m, 1 H), 4.5 (s, 2 H), 7.33 (s, 5 H). Anal. ($C_{14}N_{20}O_3$) C, H.

(*S*)-3-(Benzyloxy)-1-[[diphenyl(4-methoxyphenyl)methoxy]methyl]propanol (7). To a solution of **5** (25 g, 0.11 M) in methanol (200 mL) was added 3 N HCl (4 mL). After stirring for 4 h at 25 °C, the solution was evaporated in vacuo, taken up in CH_2Cl_2, and washed with aqueous $NaHCO_3$. The CH_2Cl_2 was dried over $MgSO_4$ and evaporated to give diol **6** as a colorless oil. This material was used for the next step without further purification. Thus, to a solution of diol **6** (20 g, 0.1 M) in CH_2Cl_2 (300 mL) and [(4-methoxyphenyl)diphenyl]methyl chloride (31 g, 0.1 M) in CH_2Cl_2 (300 mL) was added at 0 °C triethylamine (13 g, 0.13 M) over 5 min. After stirring at 0 °C for 90 min, the mixture was stirred for 16 h and filtered through Celite. The filtrate was washed with 10% H_3PO_4, aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated in vacuo. The residual oil was chromatographed on silica gel using CH_2Cl_2 as eluent to give **7** (42 g, 84%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.78 (m, 2 H), 3.58 (m, 2 H), 3.76 (s, 3 H), 3.84 (m, 2 H), 3.99 (m, 1 H), 4.45 (s, 2 H), 6.8–7.2 (m, 14 H).

(*S*)-Diethyl [[3-(Benzyloxy)-1-[[diphenyl(4-methoxyphenyl)methoxy]methyl]propoxy]methyl]phosphonate (8). To a suspension of 57% sodium hydride in mineral oil (2.8 g, 70 mmol) in dry THF (300 mL) was added 28 g (59.6 mmol) of **6** and the mixture was heated at 60 °C for 3 h under nitrogen. To this solution was added at 5 °C a solution of (diethylphosphono)methyl triflate (20 g, 66.7 mmol) in THF (20 mL). After stirring at 25 °C for 16 h, the mixture was evaporated in vacuo, taken up in CH_2Cl_2 (600 mL), washed with water, 10% H_3PO_4, aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated in vacuo. The residual oil was chromatographed on silica gel using CH_2Cl_2–3% MeOH as eluent to give **8** (21.2 g, 58%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.20–1.35 (m, 6 H), 1.82 (m, 2 H), 3.17 (m, 2 H), 3.5–3.7 (m, 4 H), 3.78 (s, 3 H), 4.45 (s, 2 H), 6.8–7.5 (m, 19 H).

(*S*)-Diethyl [[3-(Benzyloxy)-1-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]propoxy]methyl]phosphonate (10). To a solution of **8** (26.3 g, 43 mmol) in MeOH (120 mL) was added Amberlyst 15 ion-exchange resin (6.0 g). After stirring at 25 °C for 4 h, the mixture was filtered through Celite, and the filtrate was evaporated in vacuo. The residual oil was chromatographed on silica gel using CH_2Cl_2 as eluent to give **9** (13.9 g, 93%) as a colorless oil. To a solution of **9** (11.5 g, 33.3 mmol) and 3,4-dihydro-2*H*-pyran (3.4 g, 40 mmol) in CH_2Cl_2 (200 mL) was added a solution of *p*-toluenesulfonic acid monohydrate (100 mg, 0.5 mmol) in ether (10 mL) at 25 °C. After stirring at 25 °C for 2 h, the solution was washed with aqueous $NaHCO_3$, dried over

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$MgSO_4$, and concentrated in vacuo. The oily residue was chromatographed on silica gel using CH_2Cl_2 as eluent to give **10** (13.6 g, 95%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.27 (m, 6 H), 1.4–1.9 (m, 8 H), 3.3–3.9 (m, 13 H), 4.45 (s, 2 H), 4.55 (br s, 1 H), 7.28 (m, 5 H). Anal. ($C_{21}H_{35}O_7P$) C, H.

(*S*)-Diethyl [[3-[(Methylsulfonyl)oxy]-1-[(tetrahydro-2*H*-pyran-2-yloxy)methyl]propoxy]methyl]phosphonate (12). A mixture of **10** (11.3 g, 26.3 mmol) and 10% palladium on activated carbon (5.6 g) in EtOH (200 mL) was hydrogenated in a Parr hydrogenator at 50 psi for 16 h. The catalyst was filtered through Celite and washed with MeOH, and the combined solvents were evaporated to give **11** (8.4 g, 93%) as a colorless oil. This material was used for the next step without purification. Thus, a solution of **11** (3.8 g, 11.2 mmol) and methanesulfonyl chloride (1.6 g, 13.6 mmol) in CH_2Cl_2 (60 mL) was added at 0 °C to a solution of triethylamine (2.35 g, 23 mmol) in CH_2Cl_2 (5 mL). After stirring at 0 °C for 2 h, the CH_2Cl_2 was washed with 30% H_3PO_4 and brine, dried over $MgSO_4$, and evaporated in vacuo. The crude oil was chromatographed on silica gel using CH_2Cl_2 as eluent to give **12** (4.0 g, 85%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.25 (m, 6 H), 1.4–2.0 (m, 8 H), 2.95 (s, 3 H), 3.40 (m, 2 H), 3.6–4.4 (m, 11 H), 4.55 (br s, 1 H).

(*S*)-2-Amino-6-chloro-9-[3-[(diethylphosphono)methoxy]-4-(tetrahydro-2*H*-pyran-2-yloxy)butyl]purine (13). To a suspension of 57% sodium hydride in mineral oil (200 mg, 14.6 mmol) in dry DMF (30 mL) was added 2-amino-6-chloropurine (1.35 g, 8 mmol) under nitrogen. After stirring at 25 °C for 45 min, the mixture was heated at 55 °C for 2 h. To this solution was added at 25 °C a solution of **12** (3.28 g, 8 mmol) in DMF (8 mL) and the mixture was heated at 65 °C for 5 h. The solution was then concentrated in vacuo, taken up in CH_2Cl_2, washed with water, 30% H_3PO_4, aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was chromatographed on silica gel using CH_2Cl_2–5% MeOH as eluent to give **13** (2.1 g, 52%) as a slightly yellow, hard oil: ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 6 H), 1.3–2.1 (m, 8 H), 3.40 (m, 2 H), 3.6–4.4 (m, 13 H), 4.65 (br s, 1 H), 5.51 (s, 2 H), 7.86 (s, 1 H). Anal. ($C_{19}H_{31}N_5O_6PCl$) C, H, N.

(*S*)-9-[4-Hydroxy-3-(phosphonomethoxy)butyl]guanine Disodium Salt (3). To a solution of **13** (2.5 g, 5.1 mmol) in CH_3CN (40 mL) was added at 0 °C bromotrimethylsilane (3 mL) under nitrogen. After stirring at 0 °C for 3 h, the volatiles were removed in vacuo, the residual oil was dissolved in 2 N HCl (10 mL), and the solution was heated at 110 °C. Water was then evaporated in vacuo and the residue was adjusted to pH 8 with aqueous $NaHCO_3$. Evaporation of water gave an amorphous solid which was purified by C-18 reverse phase column under 8 psi of pressure using water as eluent to give **3** (800 mg, 47%) as a white solid: ^1H NMR (D_2O) δ 1.95 (m, 2 H), 3.36 (m, 1 H), 3.435 (dd, J = 3.8, 12.3 Hz, 1 H), 3.54 (d, J = 9.4 Hz, 2 H), 3.7 (dd, J = 3.8, 12.3 Hz, 1 H), 4.12 (t, J = 7.2 Hz, 2 H), 7.88 (s, 1 H); ^{13}C NMR (D_2O) δ 32.570, 42.340, 64.005, 67.833, 69.854, 80.793, 80.947, 117.816, 142.079, 153.300, 155.502, 160.889; UV max (H_2O) 252 nm (ε 12 159), 274 nm (ε 8882). Anal. Calcd for $C_{10}H_{14}N_5O_6PNa_2 \cdot 2.5H_2O$: C, 28.42; H, 4.55; N, 16.65. Found: C, 28.36; H, 5.14; N, 16.15.

In a manner similar to that described for the synthesis of **3**, compounds **14** and **15** were prepared by coupling of **12** and adenine and cytosine. The spectroscopic data are as follows.

(*S*)-9-[4-Hydroxy-3-(phosphonomethoxy)butyl]adenine disodium salt (14): ^1H NMR (D_2O) δ 1.98 (m, 2 H), 3.30 (m, 1 H), 3.43 (dd, J = 3.6, 12.3 Hz, 1 H), 3.48 (d, J = 10.0 Hz, 2 H), 3.67 (dd, J = 3.6, 12.3 Hz, 1 H), 4.2 (t, J = 7.2 Hz, 2 H), 7.92 (s, 1 H), 8.03 (s, 1 H); UV max (H_2O) 262 nm (ε 12 642). Anal. Calcd for $C_{10}H_{14}N_5O_6PNa_2 \cdot 3.5H_2O$: C, 28.12; H, 3.91; N, 16.05. Found: C, 28.30; H, 4.45; N, 16.55.

(*S*)-1-[4-Hydroxy-3-(phosphonomethoxy)butyl]cytosine (15): ^1H NMR (D_2O) δ 1.91 (m, 2 H), 3.45 (m, 1 H), 3.53 (d, J = 9.6 Hz, 2 H), 3.6–3.9 (m, 4 H), 6.03 (d, J = 7.2 Hz, 1 H), 6.72 (d, J = 7.2 Hz, 1 H); UV max (H_2O) 282 nm (ε 9486). Anal. Calcd for $C_{19}H_{16}N_3O_6P$: C, 34.74; H, 5.14; N, 13.50. Found: C, 34.64; H, 5.35; N, 13.02.

Synthesis and Dopamine Receptor Affinities of Enantiomers of 2-Substituted Apomorphines and Their *N*-*n*-Propyl Analogues

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Syntheses of (*R*)-(–)-2-methoxyapomorphine (*R*-**8**), its antipode *S*-**8**, and its (*R*)-(–)-*N*-*n*-propyl *R*-**9** derivative are described. The dopaminergic receptor affinities of these compounds and their 2-unsubstituted counterparts (*R*)-(–)-apomorphine (*R*(–)-APO, *R*-**1**), (*S*)-(+)-apomorphine (*S*(+)-APO, *S*-**1**), and (*R*)-(–)-*N*-*n*-propylnorapomorphine (*R*(–)-NPA, *R*-**2**), as well as those of (*R*)-(–)-2-chloroapomorphine (*R*(–)-2-Cl-APO, *R*-**6**), (*R*)-(–)-2-bromoapomorphine (*R*(–)-2-Br-APO, *R*-**6**), were determined with tissue membrane preparations of corpus striatum from rat brain. Contribution of both an *N*-*n*-propyl and a 2-hydroxy in (*R*)-(–)-2-hydroxy-*N*-*n*-propylnorapomorphine (*R*(–)-2-OH-NPA, *R*-**7**) or a methoxy group in (*R*)-(–)-2-methoxy-*N*-*n*-propylnorapomorphine (*R*(–)-2-OCH_3-NPA, *R*-**9**) produced the highest D_2 affinity (0.053 and 0.17 nM) and D_2 over D_1 selectivity (17 300 and 10 500 times) of the compounds evaluated. The structure–affinity relationships of these 2-substituted aporphines suggest that secondary binding sites of D_2 receptors interact with 2-substituents on the A ring of aporphines through H-bonding.

The rigid structure of aporphine alkaloids can be related to several conformations of the neurotransmitter dopamine (DA) (cis,trans-α-rotamer and trans-β-rotamer).[1,2] This unique character of aporphine derivatives has stimulated extensive study of the structure–activity relationship (SAR) of a large number of such compounds.[3] This work supports the conclusion that the α-rotamer is the biologically relevant conformation in aporphines to provide high affinity and dopaminergic activity, such as the prototype DA agonists (*R*)-(–)-apomorphine (**1**, *R*(–)-APO) and (*R*)-(–)-*N*-*n*-propylnorapomorphine (**2**, *R*(–)-NPA).

Novel 2-substituted (*R*)-(–)-apomorphines have been prepared in our laboratories.[4] These compounds, with

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