Spiropentane Mimics of Nucleosides: Analogues of 2′-Deoxyadenosine and 2′-Deoxyguanosine. Synthesis of All Stereoisomers, Isomeric Assignment, and Biological Activity

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Synthesis of spirocyclic analogues of 2′-deoxyadenosine and 2′-deoxyguanosine (**12a**−**15a** and **12b**−**15b**) is described. Rhodium-catalyzed reaction of ethyl diazoacetate with methylenecyclopropane **19**, obtained from 2-bromo-2-bromomethylcyclopropane **17** via debromination (**16**), reduction (**18**), and acetylation (**19**), gave a mixture of all four isomeric spiropentanes **20a**−**20d**. Hydrolysis afforded hydroxy carboxylic acids **21a**−**21d**. Acetylation of separated *proximal* + *medial-syn* isomers **21a** + **21b** and *medial anti* + *distal* isomers **21c** + **21d** furnished acetates **22a** + **22b** and **22c** + **22d**. Curtius rearrangement effected by diphenylphosphoryl azide in *tert*-butyl alcohol performed separately with mixtures **22a** + **22b** and **22c** + **22d** led to BOC-amino spiropentanes **23a** + **23b** and **23c** + **23d**. After deacetylation all isomers **24a**−**24d** were separated and deprotected to give aminospiropentane hydrochlorides **25a**−**25d**. Free bases were of limited stability. The heterocyclic moieties were introduced into individual isomers **25a**−**25d** via 6-chloropurine derivatives **26a**−**26d** or **30a**−**30d**. Ammonolysis of **26a**−**26d** furnished the adenine isomeric series **12a**−**15a**, whereas guanine derivatives **12b**−**15b** were obtained by hydrolysis of **30a**−**30d** with formic acid. The isomeric assignments followed from IR spectra of BOC-aminospiropentanes **24a**−**24d** and NMR spectra of **12a**−**15a** including NOE and (H,H) COSY. The *proximal* and *medial-syn* isomers **12a** and **12b** were modest inhibitors of human cytomegalovirus (HCMV) and Epstein−Barr virus (EBV) in culture, whereas the *medial-anti* isomer **12c** was a substrate for adenosine deaminase. The distal isomer **15b** was an anti-EBV agent. The *medial-syn* phosphoralaninate **34** was an effective inhibitor of HCMV replication in vitro. It was also active against herpes simplex virus type 1 (HSV-1), varicella zoster virus (VZV), human immunodeficiency virus (HIV-1), hepatitis B virus (HBV), and EBV with a varying degree of cytotoxicity.

Introduction

Nucleoside analogues are in the focus of current interest as antiviral and antitumor agents.[1] Structures which include analogues having carbohydrate (furanose) or various modifications thereof (e.g., cyclopentane and dioxa- and oxathiacyclopentane) exhibit diverse biological effects. The relevant examples are anti-AIDS drugs AZT (zidovudine, **1**, Chart 1) or 3TC (lamivudine, **2**). Removal of part or parts of nucleoside furanose moiety resulting in a substantial simplification of the structure led in many cases to new antiviral agents of significant therapeutic potency. Thus, acyclic nucleoside analogues acyclovir (**3**) and ganciclovir (**4**) are established antiherpetic drugs. 2′,3′-Dideoxyribonucleosides (**5**) are potent anti-HIV agents. The tetrahydrofuran moiety of the latter analogues can be viewed as a relatively rigid "spacer" between the groups important for antiviral activity—heterocyclic base and the hydroxymethyl group.

Replacement of the tetrahydrofuran moiety with other rigid groups of similar size also provided new antiviral agents. Allene derivatives adenallene (**6a**) and cytallene (**6b**) are potent anti-HIV agents,[2−4] and the latter also inhibits replication of hepatitis B virus (HBV).[5] More recently, we have described a new class of nucleoside analogues, (*Z*)- and (*E*)-methylenecyclopropanes **7** and **8**. The purine derivatives of (*Z*)-isomers **7** were found to exhibit a particularly strong and broad-spectrum antiviral activity.[6−8] By contrast, compounds with a transposed heterocyclic and hydroxymethyl moiety **9** and **10**

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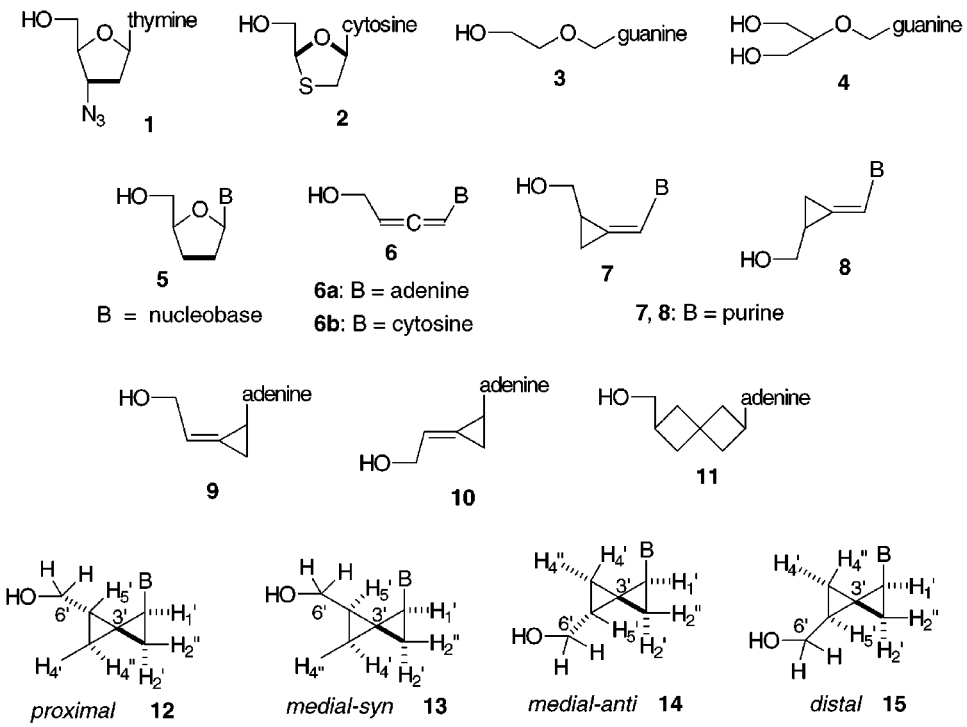
Chart 1



12 - 15, series a: B = adenine, series b: B = guanine

were devoid of antiviral effect, but the (*E*)-isomer **10** was a substrate of moderate efficacy for adenosine deaminase.[9] Interestingly, the spiro[3.3]heptane analogue of adenosine **11** displayed some potency against human cytomegalovirus (HCMV) in vitro, but it was resistant to adenosine deaminase.[10] For a further investigation of structure−activity relationships in this series, spiro[2.2]-pentanes **12**−**15** are considered crucial because their structures[11] are related to all aforementioned analogues **6**−**11**. They are derived by replacement of double bonds with a cyclopropane ring system in structures **6**−**10**, and also, they can be considered as ring-contracted mimics of spiro[3,3]heptane **11**.

Spiropentanes are currently not in the center of attention of synthetic organic chemistry.[12] Possible reasons for this neglect may include the fact that natural products comprising such a spirocyclic system have not been found. Nevertheless, biologically active agents based on a spiropentane structure have been reported. Thus, spiropentylacetic acid is capable of inhibiting acyl-CoA dehydrogenases.[13] Very recently, it was shown that spiropentylacetyl-CoA is a mechanism-based inactivator of acyl-CoA dehydrogenases.[14] Interestingly, these studies have also indicated a biological relationship of spiropentane and methylenecyclopropane analogues. Nevertheless, it must be stressed that biological effects of stereochemically more complex 1,4(5)-disubstituted spiropentanes have not been described to the best of our knowledge.

A seminal publication of Gajewski and Burka[11] outlined the problems of stereoisomerism of 1,4(5)-disubstituted spiropentanes and also procedures for synthesis of these isomers. Their separation relied heavily on vapor-phase chromatography, a method poorly suitable for obtaining starting materials for further syntheses. Later, a mixture of four stereoisomeric 1,2,4(5)-trisubstituted spiropentanes was obtained by reaction of methylcyclopropanediphenylsulfonium ylide with chalcone, and their isomeric structure was determined by ^{1}H NMR spectroscopy after derivatization with europium(III) shift reagent,[15] but the isomers were not separated. More recently, a 2:1 mixture of 1-bromo-4(5)-ethoxycarbonylspiropentanes of an unspecified isomeric composition was prepared[16] and used in a futile attempt to alkylate adenine. In this paper, we describe synthesis and biological investigation of two complete isomeric sets of spiropentane nucleoside analogues comprising adenine and guanine moieties, compounds **12a**−**15a** and **12b**−**15b**.

Synthesis

In the absence of stereoselective procedures[17] for synthesis of distinct (*proximal*, *medial-syn*, *medial-anti*,

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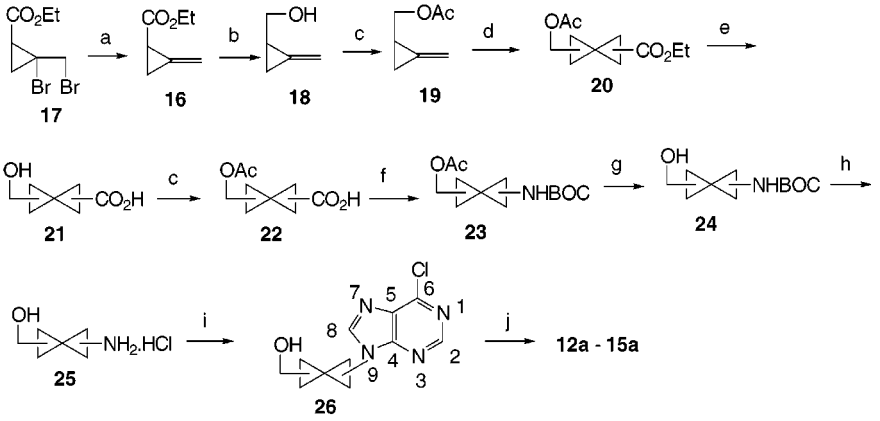
(17) Previous work[11] indicated that addition of diazomethane to *syn*-2-ethylene-1-carbethoxycyclopropane catalyzed by $CuSO_4$ in pentane led to a mixture of *proximal* and *medial-anti* spiropentanes (2:1) whereas reaction with an *anti*- isomer afforded *medial-syn* and *distal* spiropentanes (2:1).

Scheme 1[a]



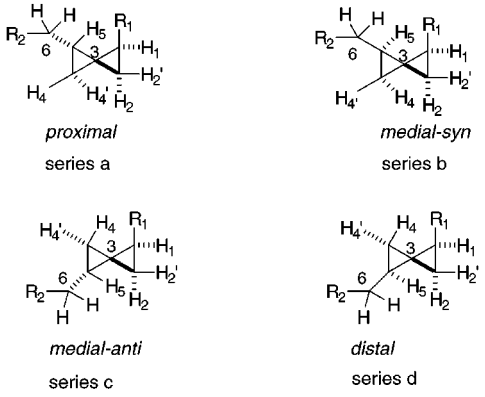
[a] Conditions: (a) Zn, AcOH−Et_2O. (b) $LiAlH_4$, Et_2O. (c) Ac_2O, pyridine. (d) N_2CHCO_2Et, $Rh_2(OAc)_4$, CH_2Cl_2. (e) (1) NaOH, aqueous MeOH. (2) Separation of **21a** + **21b** and **21c** + **21d**. (3) c. (f) $(PhO)_2P(O)N_3$, NEt_3, tBuOH Δ. (g) (1) K_2CO_3, aqueous MeOH. (2) Separation of **24a**−**24d**. (h) HCl, MeOH. (i) (1) 4,6-Dichloro-5-nitropyrimidine, NEt_3, EtOH. (2) $SnCl_2$, $CH(OEt)_3$. (j) NH_3, MeOH, Δ.

or *distal*) isomers of 1,4(5)-disubstituted spiropentanes, a "combinatorial" approach seemed advantageous. Thus, synthesis of a mixture of common intermediates was contemplated from which all four possible isomers **12a**−**15a** and **12b**−**15b** needed for biological evaluation could be generated. Ethyl methylenecyclopropanecarboxylate (**16**), which was used previously for the synthesis of several 1,4-disubstituted spiropentanes,[11] was a convenient starting material (Scheme 1). Although other procedures for the preparation of **16** have been described,[11,18] we have conveniently used zinc-catalyzed debromination of ethyl 2-bromo-2-bromomethylcyclopropane-1-carboxylate[6] (**17**). Compound **16**, obtained in 80% yield, was reduced with $LiAlH_4$ to give methylenecyclopropylmethanol (**18**, 85%). The latter was converted to acetate **19** (87.5%).

Reaction of compound **19** with ethyl diazoacetate catalyzed[19] by $Rh_2(OAc)_4$ in CH_2Cl_2 gave a mixture of all four possible stereoisomeric spiropentanes **20a**−**20d**. The mixture was partially resolved by column chromatography on silica gel to give less polar *proximal* and *medial-syn* isomers **20a** + **20b** (46%) followed by more polar *medial-anti* and *distal* isomers **20c** + **20d** (38%).

The unresolved mixture of **20a**−**20d** was hydrolyzed with NaOH in aqueous ethanol to give after chromatographic separation *proximal* and *medial-syn* isomers **21a** + **21b** and *medial-anti* and *distal* isomers **21c** + **21d** in 52% and 45% yields, respectively. Acetylation of **21a** + **21b** gave acetates **22a** + **22b** (96%), and **21c** + **21d** afforded **22c** + **22d** (97%). Thus, it was possible to resolve the original mixture into two pairs of isomers early in the synthetic sequence.

Isomers **22a** + **22b** were subjected to a Curtius rearrangement after activation with diphenylphosphoryl azide[20] and triethylamine in tert-butyl alcohol to give the BOC-aminospiropentanes **23a** + **23b** (78%). Compounds **23a** + **23b** were deacetylated using K_2CO_3 in aqueous methanol to give, after column chromatography on silica gel, *proximal* and *medial-syn* isomers **24a** and **24b** in 17% and 80% yields, respectively. Acetates **22c** + **22d**



20a - 20d: R_1 = CO_2Et, R_2 = OAc
21a - 21d: R_1 = CO_2H, R_2 = OH
22a - 22d: R_1 = CO_2H, R_2 = OAc
23a - 23d: R_1 = NHBOC, R_2 = OAc,
24a - 24d: R_1 = NHBOC, R_2 = OH,
25a - 25d: R_1 = NH_2.HCl, R_2 = OH,
26a - 26d: R_1 = 6-chloropurin-9-yl, R_2 = OH
30a - 30d: R_1 = 2-acetamino-6-chloropurin-9-yl, R_2 = OH
Atom numbering for **26a - 26d** and **30a - 30d**:
1' through 6' (see formulas **12a - 15a**)

were also transformed to a mixture of the BOC-amino derivatives, which were partially separated by chromatography to afford *medial-anti* and *distal* isomers **23c** and **23d** in a total yield of 76%. Deacetylation then furnished compounds **24c** and **24d**, which were readily resolved by chromatography in 43% and 53% yields, respectively. Removal of the BOC group from separated isomers **24a**−**24d** was accomplished with HCl in methanol to give the corresponding amine hydrochlorides **25a**−**25d** in quantitative yields.

The introduction of heterocyclic bases, adenine and guanine, into spiropentane systems of **25a**−**25d** was performed as follows. A new one-pot procedure led to a considerable simplification of the current methods.[21] In the case of spiropentyladenines **12a**−**15a**, amines **25a**−**25d** were first alkylated with 4,6-dichloro-5-nitropyrimidine[22] in the presence of triethylamine in ethanol at room

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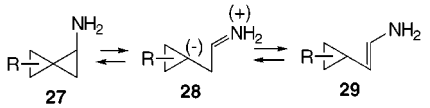
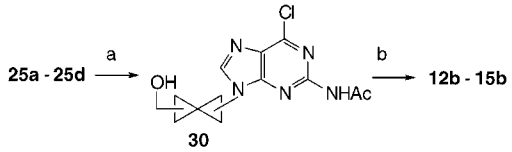
Scheme 2



Scheme 3[a]



[a] Conditions: (a) (1) 2-Acetamino-4,6-dichloro-5-nitropyrimidine, NEt_3, EtOH−DMF (1:1). (2) $SnCl_2$, $CH(OEt)_3$. (b) (1) 80% HCO_2H, Δ. (2) NH_3, MeOH.

temperature for 2 h. The solvents were then evaporated, and the crude product was treated with $SnCl_2$ and triethyl orthoformate for 16 h. Chromatography then furnished 6-chloropurine derivatives **26a**−**26d** in yields ranging from 45% to 57%. Ammonolysis with NH_3 in methanol (autoclave at 100 °C for 15 h) gave the desired adenine analogues **12a**−**15a** in 75−91% yield.

It is interesting to note that alkylation of **25a**−**25d** with 4,6-dichloro-5-aminopyrimidine, which is commonly used in nucleoside analogue synthesis[21] and requires a higher temperature, led only to destruction of the spiropentane moiety. Further investigation indicated that free bases **25a**−**25d** have a limited stability. Thus, the free base of *medial-syn* isomer **25b** was obtained in approximately 70−80% purity by TLC after treatment of the hydrochloride with 10% KOH in aqueous methanol and subsequent chromatography. It was completely decomposed after standing in $CDCl_3$ overnight. Additional experiments performed with isomers **25a**, **25c**, and **25d** in 10% KOH in D_2O indicated stability at room temperature (9 h), approximately 20−30% decomposition at 50 °C (16 h), and complete degradation at 80−90 °C (5 h). These results are in line with a previous report indicating a limited stability of aminospiropentane itself.[23] In this respect, aminospiropentanes resemble another class of strained amines, aminocubanes, which also lack a sufficient stability.[24] It is not clear whether this behavior may reflect a partial enamine (aldimine) character of such amines (see structures **27**, **28**, and **29** in Scheme 2).

A similar approach was employed for synthesis of spiropentylguanines **12b**−**15b**. In this case, the alkylation of amines **25a**−**25d** was performed with 2-acetamino-4,6-dichloro-5-nitropyrimidine[25,26] (Scheme 3). The respective intermediates were then cyclized using the $SnCl_2$−triethyl orthoformate reagent as described above to give 2-acetamino-6-chloropurines **30a**−**30d** in yields ranging from 41% to 58%. Hydrolysis and deacetylation were performed using 80% formic acid followed by

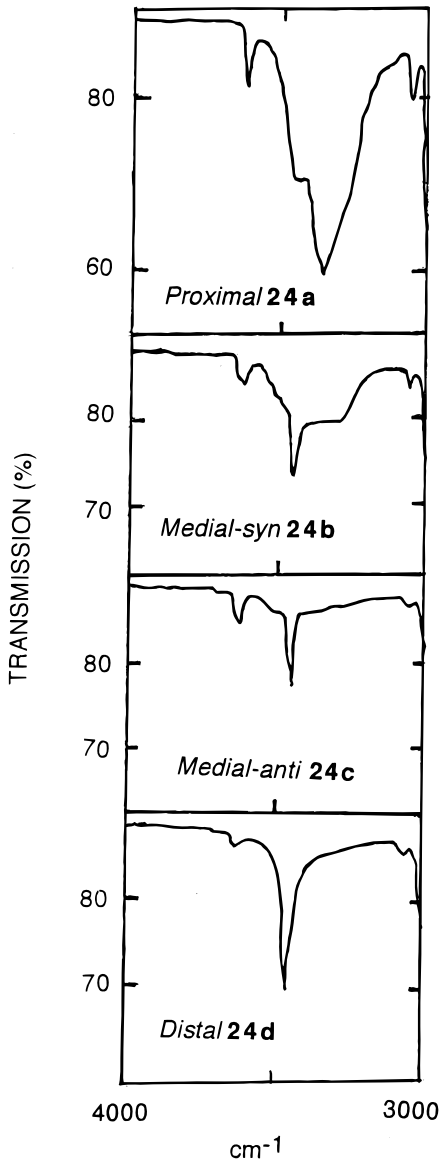


Figure 1. IR spectra (3000−4000 cm^{-1} region) of stereoisomeric BOC derivatives **24a**−**24d** in CCl_4.

treatment with NH_3/methanol to give guanine analogues **12b**−**15b** in 75−85% yield.

NMR Spectra and Isomeric Assignment. Preliminary data revealed that the polarity of isomeric spiropentanes (mobility on TLC) followed the order *proximal* > *medial-syn* > *medial-anti* > *distal* irrespective of the 1,4(5)-substituents involved. In addition, IR spectra of 4-hydroxymethyl-1-BOC-amino derivatives **24a**−**24d** (0.03−0.04 M in CCl_4) revealed a significant intramolecular hydrogen bonding in *proximal* and *medial-syn* isomers **24a** and **24b** (broad bands at 3300−3500 cm^{-1}), whereas these bands were absent in the *medial-anti* and *distal* isomers **24c** and **24d** (Figure 1). As expected, this absorption was especially strong in the *proximal* isomer **24a**. Small peaks found in all these isomers at 3620−3640 cm^{-1} can possibly be attributed to hydrogen bonding of OH to the "edge" of the adjacent cyclopropane ring.[11] It is worthwhile to note that O−H−O hydrogen bonding was observed in the *proximal* 1,4-bis(hydroxymethyl)-spiropentane but not in the *medial* isomer.[11] However, in this case the hydrogen-bonded structure **31** comprised

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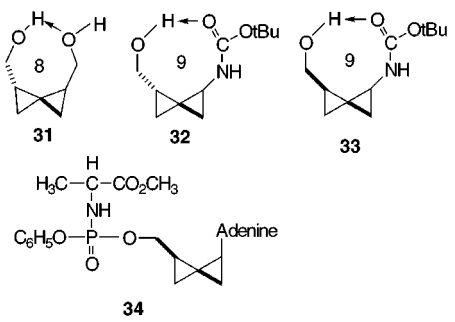
an eight-membered ring, whereas in the *proximal* and *medial-syn* isomers **24a** and **24b** (structures **32** and **33**)



31 **32** **33**

34

nine-membered rings are involved. Although the IR spectra provided information for differentiation between *proximal* and *medial-syn* isomers **24a** and **24b**, additional data were necessary for confirmation and assignment of *medial-anti* and *distal* isomers **24c** and **24d**. This information has followed from the detailed NMR investigation of one set of the final products, spiropentyladenines **12a**−**15a**. The *cis* and *trans* coupling constants of cyclopropane protons, $J_{2'(2'')},_{1'}$ and $J_{4'(4'')},_{5'}$, of analogues **12a**−**15a** and **12b**−**15b** fall within the range of similar values found for simple cyclopropane systems[27] (J_{cis} = 6−10 Hz, typically 8 Hz; J_{trans} = 3−6 Hz, typically 5 Hz). Assignments of all protons were corroborated with the aid of NOE (Tables 1−4), DEPT, and (H,C) and (H,H) COSY NMR spectra. The H_2 and H_8 signals of analogues **12a**−**15a** were unresolved or very close ($\Delta\delta_{max} < 0.02$), and they resembled similar signals in adenallene[2] (**6a**). In the absence of significant chemical shift differences of the H_8 protons and in view of the fact that the $H_{6'}(H_{6''})$ signals were magnetically nonequivalent in all four isomers, a preliminary assignment of the isomeric structures successfully used in case of (*Z*)- and (*E*)-methylenecyclopropane analogues[6] **7** and **8** could not be perfomed.

The NOE experiments were crucial for distinguishing all isomers. Thus, *proximal* isomer **12a** showed NOE enhancement of the $H_8(H_2)$ signal of 1.7% and 2%, respectively, after irradiation of $H_{6'}$ and $H_{6''}$ (Table 1). Conversely, irradiation of $H_8(H_2)$ led to 0.2% and 0.4% enhancement of $H_{6'}$ and $H_{6''}$. It is assumed that purine bases in all isomers are in an *anti*-like conformation,[28] with the C_8 facing $C_{5'}$ or $C_{4'}$, and the H_8 is then responsible for this effect.[29] Somewhat surprisingly, no NOE was seen between the $H_{6'}$, $H_{6''}$, or OH and $H_8(H_2)$ of **13a** (Table 2), although an intramolecular hydrogen bonding was present in the corresponding precursor, compound **24b** (Figure 1). According to expectation, in the *medial-anti* and *distal* isomeric pair **14a** and **15a** only the former exhibited an NOE enhancement of $H_8(H_2)$ after irradiation of $H_{6'}$ and $H_{6''}$ (Table 3, 1%). The NOE was also observed between protons located on the same face of the spiropentane system, $H_{4''}$ and $H_8(H_2)$ of the *medial-anti* isomer **14a** (5.2 and 0.8%) as well as $H_{4'}$ and $H_8(H_2)$ of the distal isomer **15a** (5.1 and 1%). Similar effects were absent in compounds **12a** and **13a**.

Table 1. NOE Enhancements of the *proximal* Isomer 12a

	obsd H (% NOE)								
irr (δ, H)	$H_{4''}$	$H_{4'}$	$H_{2'}$, $H_{5'}$	$H_{2''}$	$H_{6'}$	$H_{6''}$	$H_{1'}$	H_8, H_2	OH
0.90, $H_{4''}$		14.7			2.3	0.7	2.5		1.4
1.00, $H_{4'}$	14.5		7.5						
1.48, 1.51, $H_{2'}$, $H_{5'}$		1.7		9.3		1.3	4.2		1.1
2.01, $H_{2''}$			22.8					12.1	
2.82, $H_{6'}$	1.9		2.8		19	0.6	1.7	8.7	
2.95, $H_{6''}$			5.2	19.5			2	6.2	
4.01, $H_{1'}$	0.8		3.6				2.6		
4.35, OH									
8.11, H_8, H_2				1.9	0.2	0.4	1.2		0.3

Table 2. NOE Enhancements of the *medial-syn* Isomer 13a

	obsd H (% NOE)								
irr (δ, H)	$H_{4''}$	$H_{4'}$	$H_{2'}$, $H_{5'}$	$H_{2''}$	$H_{6'}$	$H_{6''}$	$H_{1'}$	H_8, H_2	OH
0.75, $H_{4''}$		20.4	1		1.9	1.2			
1.23, $H_{4'}$	19.5		2.5				2.2		
1.49, $H_{2'}$, $H_{5'}$		2.2		8.5	1.4	1	5.4	2.8	
1.65, $H_{2''}$			21					7.3	
3.20, $H_{6'}$	2.3		3	1.0		22.5			
3.50, $H_{6''}$	1		3.5		21				−17.5
3.86, $H_{1'}$		0.8	4.8					2.5	2
4.60, OH									
8.10, 8.12, H_8, H_2			1.2	1.3					

Table 3. NOE Enhancements of the *medial-anti* Isomer 14a

	obsd H (% NOE)								
irr (δ, H)	$H_{4''}$	$H_{4'}$	$H_{5'}$	$H_{2'}$	$H_{2''}$	$H_{6'}$, $H_{6''}$	$H_{1'}$	H_8, H_2	OH
0.75, $H_{4''}$		20				3	0.6	5.2	
0.95, $H_{4'}$	21		6.5		0.7				
1.47, $H_{5'}$		3.6				3	1.4		1
1.55, $H_{2'}$					15.7		10.6		
1.69, $H_{2''}$		1		17.5			1	9.4	
3.67, 3.72, $H_{6'}$, $H_{6''}$	2−3		4.7				2	1	3
3.86, $H_{1'}$			0.8	3				2.8	
4.60, OH									
8.09, 8.10, H_8, H_2	0.8				1.5		1.2		

Table 4. NOE Enhancements of the *distal* Isomer 15a

	obsd H (% NOE)								
irr (δ, H)	$H_{4''}$	$H_{4'}$	$H_{2'}$, $H_{5'}$	$H_{2''}$	$H_{6'}$	$H_{6''}$	$H_{1'}$	H_8, H_2	OH
0.66, $H_{4''}$		23		1	1.5	1.7			
1.10, $H_{4'}$	23		7					5.1	
1.54, $H_{2''}$	0.7		16					6.6	
1.64, $H_{2'}$, $H_{5'}$		2.1		8.1	1.2	1.3	6.9		0.7
3.32, $H_{6'}$	1.3		4.2			9.2			−24
3.44, $H_{6''}$	1		4.2		9				−24
3.74, $H_{1'}$			6					2.4	
4.57, OH									
8.09, 8.10, H_8, H_2		1		1			1.5		

The NOE between $H_{1'}$ and $H_{4''}$ (0.8% and 2.5%, Table 1, $H_{1'}\cdots H_{4''}$ = 3.15 Å) was characteristic of the *proximal* isomer **12a**, whereas no effect was seen between the $H_{1'}$ and $H_{4'}$ ($H_{1'}\cdots H_{4'}$ = 3.87 Å). As expected, this trend was reversed in *medial-syn* isomer **13a** with the observed interaction between $H_{1'}$ and $H_{4'}$ (0.8% and 2.2%, Table 2, $H_{1'}\cdots H_{4'}$ = 3.14 Å) and none between $H_{1'}$ and $H_{4''}$ ($H_{1'}\cdots H_{4''}$ = 3.82 Å). In *medial-anti* and *distal* isomers **14a** and **15a** the only $H_{1'}$ and $H_{4'}(H_{4''})$ interaction was noted in the former (0.6%, Tables 3 and 4). A strong NOE enhancement found between H_8 and $H_{4''}$ of the *medial-anti* isomer **14a** and H_8 and $H_{4'}$ of the *distal* isomer **15a** (5.2 and 5.1 Hz, respectively) is also characteristic. These effects were absent in the *proximal* and *medial-syn* isomers **12a** and **13a**. All these data established the isomeric structures of **12a**−**15a** and the respective precursors **24a**−**24d**.

(27) Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*; VCH Publishers: New York, 1991; p 77.

(28) Saenger, W. *Principles of Nucleic Acid Structure;* Springer-Verlag: New York, 1984; p 69.

(29) Difficulty in pinpointing the "right" signal (presumably H_8) from poorly resolved singlets of H_8 and H_2 may account for lower NOE effects.

Table 5. Antiviral Activity of Spiropentane Nucleoside Analogues[a]

compd	HCMV[b] HFF[c]	HSV-1 BSC-1[d]	HSV-1 Vero[c]	HSV-2 Vero[c,e]	VZV HFF[c,f]	EBV Daudi[g]	HIV-1 CEM-SS[e,h]	HBV 2.2.15[e]
12a	28/>100	>100/>100	>50/89	>50	>86.5	4.8/15(0.95)[i]	>100	>10
13a	20/>100[j]	70/>100	>50/>100	>50	245	22/>202(0.61)[i]	>100	>10
14a	>100/>100	>100/>100	>50/>100	>50	242	153/202	>100	>10
15a	>100/>100	>100/>100	>50/>100	>50	>433	>216/>216	>100	>10
12b	>100/>100	>100/>100	>50/>100	>50	>399[k]	>199/>199	>100	>10
13b	>100/>100	>100/>100	>50/>100	>50	>399[k]	>199/>199	>100	>10
14b	>100/>100	>50/>100	>100/>100	>50	>399[k]	>199/>199	>100	>10
15b	>100/>100	>100/>100	>50/>100	>50	>399[k]	6.0/>199 (12)[i]	>100	>10
34	0.38/100	7.0/70	20/27	31	>8.5(1.4)[k]	2.8/7.6	3.5	3.1
control	2.9/>100[l]	2.0/>100[m]	13.5/>200[m]	32.3[m]	9.3/>444[m]	8.4/>222[m]	0.5/>10[n]	2.3/6[o]

[a] Inhibition of viral replication (EC_{50}, μM) and cytotoxicity (IC_{50}, μM) in the host cells. The data are listed as EC_{50}/IC_{50}. For a description of antiviral assays see refs 6 and 7. [b] Towne strain. [c] Plaque reduction assay. [d] Enzyme-linked immunosorbent assay (ELISA). The cytotoxicities were determined in KB cells. [e] The cytotoxicities were determined in CEM cells; see HSV-1/Vero. [f] For cytotoxicities in HFF cells see HCMV/HFF. [g] Viral capsid antigen (VCA) immunofluorescence (IF) or ELISA assay. [h] Supernatant reverse transcriptase assay. [i] Inhibition of EBV DNA synthesis. [j] EC_{50}/IC_{50} 40/>404 in the AD 169 strain and 10.5/>404 in MCMV/MEF assay. [k] Cytopathic effect (CPE) inhibition assay. [l] Ganciclovir. [m] Acyclovir. [n] Zidovudine (AZT). [o] Zalcitabine (ddC).

Long-range coupling across the spiropentane ring system was observed in the (H,H) COSY NMR spectra of *medial-anti* and *distal* isomers **14a** and **15a**, but it was absent in *proximal* and *medial-syn* isomers **12a** and **13a**. It is especially extensive in *medial-anti* isomer **14a**, where all spiropentane protons with the exception of $H_{2''}$ are involved. A long-range interaction between $H_{1'}$ and $H_{6',6''}$ was also seen. By contrast, a similar coupling takes place only between the $H_{1'}$ and $H_{4''}$ of the *distal* isomer **15a**. It is recognized that the rigidity of a spiropentane system offers a good opportunity for this type of coupling, but the reasons for the observed isomer selectivity are not entirely clear.

Biological Activity

Among analogues **12a**−**15a** and **12b**−**15b**, adenine *proximal* and *medial-syn* isomers **12a** and **13a** as well as guanine *distal* isomer **15b** exhibited antiviral activity in several assays (Table 5). Compounds **12a** and **13a** were moderately active against HCMV in human foreskin fibroblast (HFF) culture as determined by a plaque reduction assay (EC_{50} 28 and 20 μM, respectively). The *medial-syn* isomer **13a** was also potent against murine cytomegalovirus (MCMV; EC_{50} 10.5 μM) in mouse embryonic fibroblast (MEF) cells. Little or no cytotoxicity was observed. The *proximal* isomer **12a** was the most effective against Epstein−Barr virus (EBV) in Daudi cells with EC_{50} 4.8 μM, but it was cytotoxic (IC_{50} 15 μM). The guanine *distal* isomer **15b** was virtually equipotent (EC_{50} 6.0 μM), but it was noncytotoxic (IC_{50} > 199 μM). Compound **13a** was less active (EC_{50} 22 μM), and it was also noncytotoxic (IC_{50} > 202 μM). Antiviral activity of *medial syn* and *proximal* isomers **13a** and **12a** is in line with the findings that antiviral activity of the cisoid analogues (e.g., **7**) is usually superior to that of transoid analogues[6] (e.g., **8**), but the anti-EBV efficacy of the *distal* isomer **15b** is an exception. A different activity trend was found in deamination of **12a**−**15a** catalyzed by adenosine deaminase. Only *medial-anti* isomer **14a** was a substrate, though with a very low reaction rate ($t_{1/2}$ >120 h). Analogues **12a**, **13a**, and **15a** were not deaminated. In summary, biological activity was found among all four isomeric types, although the distances between the heterocyclic base (adenine) and hydroxymethyl group ($N^9 \cdots C_{6'}$) vary significantly between 3.54 (**12a**) and 5.01 (**15a**) Å. At this point, it is difficult to rationalize the antiviral results, but roughly, the trend follows that of methylenecyclopropane analogues:[6−8] little activity against HIV-1, herpes simplex virus type 1 (HSV-1), and HSV-2 and more potency against CMV and EBV.

Inactive nucleoside analogues including allenic[30,31] and methylenecyclopropane derivatives[32] can be activated by conversion to lipophilic pronucleotides, thus bypassing the first phosphorylation step in their mechanism of action.[33] Therefore, the *medial-syn* isomer **13a**, which exhibited the most potent anti-HCMV effect at noncytotoxic levels from all analogues investigated in the present study, was transformed to phenyl phosphoralaninate **34**. Indeed, the activity of the latter prodrug against HCMV (EC_{50} 0.38 μM) was increased over 50-fold compared to that of **13a**, whereas the cytotoxicity remained low (IC_{50} 100 μM). There was a similar increase of activity against HBV (EC_{50} 3.1 μM) and HIV-1 (EC_{50} 3.5 μM). Antiviral activity was also seen against HSV-1 (EC_{50} 7 μM), and cytotoxicity in T-lymphoblastoid cell line CEM and epidermoid oral carcinoma KB cells was 27 and 70 μM, respectively. Phosphoralaninate **34** was also active against EBV with EC_{50} 2.8 μM, albeit it was cytotoxic to uninfected cells with an IC_{50} of 7.8 μM. It was also effective against varicella zoster virus (VZV; EC_{50} 1.4 μM, IC_{50} 95 μM) in a cytopathic effect inhibition assay. Compound **34** is a substrate for pig liver esterase (PLE), a current model of intracellular esterases,[30,34] which also indicates that the mechanism of its antiviral activity may be related to that of similar prodrugs of nucleoside analogues.[30,31,33] All these results indicated that (i) design of antiviral nucleoside analogues where the 2′-deoxyribofuranose moiety is replaced by a spiropentane system is possible and (ii) the biological activity of such analogues can be increased by conversion to lipophilic phosphates capable of generating the phosphorylated species inside the virus-infected cells. These results are also in agreement with a hypothesis that phosphorylation is indispensable for the mechanism of antiviral activity of **13a**.

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Experimental Section

General Methods. See ref 6. TLC and column chromatography were performed as described previously.[35]

Ethyl Methylenecyclopropanecarbonate (16). To a solution of ethyl 2-bromo-2-bromomethylcyclopropanecarbonate[6] (**17**; 36.0 g, 0.126 mol) in ether (150 mL) and acetic acid (20 mL) was added zinc powder (40 g, 0.63 mol) in portions with stirring at room temperature. The stirring was continued for 16 h. The solids were filtered off and washed with ether (3 × 30 mL). The filtrate was washed successively with 5% HCl, water, aqueous $NaHCO_3$, and brine and dried (Na_2SO_4). Evaporation of the solvent at atmospheric pressure furnished the crude product, which was distilled to give compound **16**, bp 60 °C, 5 Torr (12.8 g, 80%). The ^{1}H NMR spectrum was identical to that reported.[17]

(Methylenecyclopropyl)methyl Acetate (19). A solution of compound **16** (30.0 g, 0.23 mol) in ether (40 mL) was added to a stirred mixture of $LiAlH_4$ (4.1 g, 0.12 mol) in ether (180 mL) at such a rate to maintain a gentle reflux. The resultant mixture was refluxed for 10 h. It was then quenched carefully with H_2O (8 mL) and 20% aqueous NaOH (16 mL). The ether phase was separated and the remaining white precipitate extracted with ether (5 × 20 mL). The combined ether phase was distilled using a Vigreux column to give (methylenecyclopropane)methanol (**18**), bp 50−55 °C, 5 Torr (16.9 g, 85%). The ^{1}H NMR spectrum was identical to that described.[17] To the solution of **18** (16.0 g, 0.2 mol) in pyridine (25 mL) was added acetic anhydride (25 mL) dropwise with stirring, which was continued at room temperature overnight. The reaction was quenched with water and the product extracted with pentane (4 × 70 mL). The combined organic phase was washed successively with saturated $CuSO_4$, 5% HCl, aqueous $NaHCO_3$, and brine and dried (Na_2SO_4). Pentane was removed at atmospheric pressure using a Vigreux column, and the product **19** was distilled: bp 60−65 °C, 5 Torr (21.0 g, 87.5%); ^{1}H NMR ($CDCl_3$) δ 5.45 (m, 1H) and 5.41 (m, 1H), 4.04 (dd, 1H, ^3J = 6.3 Hz, ^2J = 11.2 Hz) and 3.86 (dd, 1H, ^3J = 8.1 Hz, ^2J = 11.2 Hz), 2.04 (s, 3H), 1.77 (m, 1H), 1.34 (tt, 1H, $^2J = {}^3J$ = 9.0 Hz, ^4J = 2.2 Hz) and 0.98 (m, 1H); ^{13}C NMR δ 171.06, 132.04, 104.78, 66.98, 20.94, 14.24, 8.67; EI-MS *m*/*z* 125 (M − H, 17.0), 111 (M − CH_3, 7.3), 96 (M − CH_2O, 32.0), 84 (M − $COCH_2$, 100.0), 67 (M − CH_3CO_2, 59.1). Anal. Calcd for $C_7H_{10}O_2$: C, 66.67; H, 7.94. Found: C, 66.82; H, 8.18.

1-Carbethoxy-5-acetoxymethylspiropentanes 20a−20d. The method for preparation of dibromo derivative[6] **17** was followed. Ethyl diazoacetate (90%, 10.0 mL, 85 mmol) in CH_2Cl_2 (10 mL) was added to a stirred mixture of $Rh_2(OAc)_4$ (200 mg, 0.45 mmol) and (methylenecyclopropyl)methyl acetate (**19**; 8.25 g, 65.4 mmol) in CH_2Cl_2 (20 mL) by a syringe pump over a period of 24 h. The reaction mixture was diluted with ethyl acetate (50 mL) and water (50 mL). The unsaturated byproducts (diethyl fumarate and maleate) were removed by a slow addition of solid $KMnO_4$ (8 g) with stirring. Solid $NaHSO_3$ was then added at 0−5 °C to remove excess $KMnO_4$; MnO_2 was filtered off and washed with ethyl acetate (5 × 80 mL) using a sonicator. The combined organic phase was washed with aqueous $NaHSO_3$ and brine and dried (Na_2SO_4). Evaporation of solvent afforded the crude product as a mixture of diastereoisomers **20a−20d** (11.5 g, 84%). Chromatography on a silica gel column in hexanes−ethyl acetate (30:1 → 20:1) gave the faster moving fraction of *proximal* and *medial-syn* isomers **20a** + **20b** (6.1 g, 44%) followed by a slower moving fraction containing the *medial-anti* and *distal* isomers **20c** + **20d** (5.0 g, 36%).

Data for compounds 20a + 20b: ^{1}H NMR ($CDCl_3$) δ 4.22−3.63 (m, 4H), 2.0, 1.97 (2s, 3H, ratio 4:1), 1.89 (m, 1H), 1.7−1.4 (m) and 1.2 (m), 0.98 and 0.78 (2m, ratio 1:4, total 8H); ^{13}C NMR δ 173.06, 171.07, 170.90, 67.06, 66.15, 60.43, 60.21, 20.89, 22.34, 19.67, 19.34, 16.35, 15.59, 14.24, 14.11, 12.60, 12.53, 11.77, 10.31; EI-MS *m*/*z* 213 (M + H, 13.4), 169 (M − CH_3CO, 4.9), 153 (M − CH_3CO_2, 65.4), 139 (M − CO_2Et, 26.7), 125 (100.0); HRMS calcd for $C_9H_{12}O_2$ (M − CH_3CO_2H) 152.0837, found 152.0830. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.26; H, 7.55. Found: C, 62.03; H, 7.48.

Data for compounds 20c + 20d: ^{1}H NMR ($CDCl_3$) δ 4.09−3.82 (m, 4H), 2.0, 1.97 (s, 3H), 1.90 (m, 1H), 1.17 (2t, 3H), 1.58−1.28 (m), 1.06 (m), 0.85 (t) and 0.72 (t, ratio 2:1, total 5H); ^{13}C NMR δ 173.52, 173.11, 170.92, 67.20, 67.03, 60.27, 22.71, 20.81, 19.72, 17.96, 16.70, 16.58, 14.21, 14.15, 12.52, 10.11, 10.02; EI-MS *m*/*z* 213 (M + H, 0.1), 169 (M − CH_3CO, 1.2), 152 (M − CH_3CO_2H, 59.0), 139 (M − CO_2Et, 15.9), 79 (100.0); HRMS calcd for $C_9H_{12}O_2$ (M − CH_3CO_2H) 152.0837, found 152.0832. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.26; H, 7.55. Found: C, 62.10; H, 7.51.

1-Carboxy-5-hydroxymethylspiropentanes 21a−21d. A solution of 1-carbethoxy-4-acetoxymethylspiropentanes **20a−20d** (5.36 g, 25.3 mmol) in ethanol−water (4:1, 100 mL) was added dropwise into 50% aqueous NaOH (10 mL) with stirring and ice-cooling. The stirring was continued for 16 h at room temperature. The volume of the mixture was reduced by evaporation in vacuo, and the pH was adjusted to 3 with 4 M HCl. The remaining solvent was evaporated, and the solid residue was extracted with CH_2Cl_2−MeOH (10:1, 4 × 30 mL). Evaporation of the extract gave a product which showed three spots on TLC (CH_2Cl_2−MeOH, 6:1), **21a** (R_f 0.65), **21b** (R_f 0.62), partly overlapped and clearly separated from **21c** + **21d** (R_f 0.45). Column chromatography on silica gel in CH_2Cl_2−MeOH (10:1) afforded partially separated isomers **21a** + **21b** (1.88 g, 52.3%) and unseparated compounds **21c** + **21d** (1.61 g, 44.8%) as syrups.

Data for *proximal*-1-carboxy-5-hydroxymethylspiropentane (21a): ^{1}H NMR (D_2O) δ 3.73 (dd, 1H, ^3J = 5.4 Hz, ^2J = 11.0 Hz) and 3.06 (t, 1H, $^2J = {}^3J$ = 11.0 Hz), 1.93 (m, 1H), 1.59 (m, 1H), 1.38 (m, 2H), 0.98 (t, J = 6.1 Hz) and 0.75 (1H, m, 2H).

Data for *medial-syn*-1-carboxy-5-hydroxymethylspiropentane (21b). ^{1}H NMR (D_2O) δ 3.56 (dd, 1H, ^3J = 6.0 Hz, ^2J = 11.4 Hz) and 3.06 (dd, 1H, ^3J = 8.0 Hz, ^2J = 11.4 Hz), 1.88 (dd, 1H, $^3J_{trans}$ = 3.5 Hz, $^3J_{cis}$ = 5.0 Hz), 1.20 (m, 3H), 1.01 (dd, 1H, ^2J = 4.0 Hz, $^3J_{cis}$ = 6.5 Hz) and 0.70 (t, 1H, $^2J = {}^3J_{trans}$ = 4.0 Hz); ^{13}C NMR δ 174.82, 64.06, 22.54, 19.71, 19.40, 12.44, 11.73; EI-MS *m*/*z* 143 (M + H, 1.7), 125 (M − OH, 4.1), 43 (100.0); HRMS calcd for $C_9H_{12}O_2$ (M + H) 143.0708, found 143.0707.

Data for *medial-anti*- and *distal*-1-carboxy-5-hydroxymethylspiropentane (21c + 21d): ^{1}H NMR (D_2O) δ 3.34 and 3.24 (m, 2H), 1.88 and 1.74 (2m, 1H), 1.34 (2m, 2H), 1.24 and 1.15 (2m, 2H), 0.98, 0.86, 0.70 and 0.67 (4m, 2H); ^{13}C NMR δ 175.45, 175.06, 64.13, 64.86, 23.27, 22.87, 20.83, 20.24, 17.82, 14.16, 12.47, 9.76; EI-MS *m*/*z* 143 (M + H, 6.4), 125 (M − OH, 30.9), 107 (13.6), 97 (47.7), 79 (92.3), 39 (100.0); HRMS calcd for $C_9H_{12}O_2$ (M + H) 143.0708, found 143.0705.

1-Carboxy-5-acetoxymethylspiropentanes 22a−22d. Each of the mixtures of isomers **21a** + **21b** (1.88 g, 13.2 mmol) and **21c** + **21d** (1.61 g, 11.3 mmol) was dissolved in acetic anhydride−pyridine (1:2, 12 mL), and the solution was allowed to stand at room temperature for 16 h. The volatile components were evaporated, and the residue was dissolved in water (10 mL) and lyophilized. The crude product was chromatographed on a silica gel column in CH_2Cl_2−MeOH−AcOH (100:2:0.3) to give 1-carboxy-4-acetoxymethylspiropentanes **22a** + **22b** (2.34 g, 96%) and **22c** + **22d** (2.02 g, 97%), respectively, as syrups.

Data for *proximal*- and *medial-syn*-1-carboxy-5-acetoxymethylspiropentane (22a + 22b, Ratio 1:4): ^{1}H NMR ($CDCl_3$) δ 3.98 (dd, 1H, ^3J = 7.2 Hz, ^2J = 11.5 Hz) and 3.72 (dd, 1H, ^3J = 7.0 Hz, ^2J = 11.5), 1.92 (3H, s), 1.85 (dd, 1H, $^3J_{trans}$ = 4.1 Hz, $^3J_{cis}$ = 7.5 Hz), 1.65 and 1.53 (m, 1H), 1.44 (t, 1H, $^2J = {}^3J_{trans}$ = 3.5 Hz) and 1.28 (dd, 1H, ^2J = 4.0 Hz, $^3J_{cis}$ = 7.4 Hz, ratio 1:4), 1.12 (dd, 1H, ^2J = 4.8 Hz, $^3J_{cis}$ = 8.0 Hz) and 0.95, 0.77 (t, 1H, $^2J = {}^3J_{trans}$ = 4.8 Hz); ^{13}C NMR δ 179.67, 171.24, 66.84, 66.03, 23.25, 23.02, 20.72, 19.53, 19.21, 16.37, 15.73, 15.04, 13.49, 11.66.

Data for *medial-anti*- and *distal*-1-carboxy-5-acetoxymethylspiropentane (22c + 22d, Ratio 1:1.2): ^{1}H NMR ($CDCl_3$) δ 3.98 (m, 1H) and 3.80 (2dd, overlaped, 1H, J = 7.4,

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11.0 Hz and 7.2, 10.3 Hz), 1.91 (s, 3H), 1.88 (m, 1H), 1.59−1.29 (m), 1.09 (m) and 0.81−0.74 (2t, total 5H). ^{13}C NMR δ 179. 93, 179.14, 171.27, 66.05, 23.62, 23.13, 20.71, 19.58, 17.85, 16.78, 16.65, 14.84, 13.30, 10.12.

***proximal*- and *medial-syn*-5-Acetoxymethyl-1-(*tert*-butoxycarbonylamino)spiropentanes (23a and 23b).** Diphenylphosphoryl azide (0.964 mL, 4.5 mmol) was added dropwise with stirring into the solution of compounds **22a** + **22b** (550 mg, 3.0 mmol) in *tert*-butyl alcohol (10 mL) containing Et_3N (0.753 mL, 5.4 mmol). The resulting mixture was refluxed for 4 h. After evaporation of *tert*-butyl alcohol, the residue was dissolved in ethyl acetate (100 mL). The resulting solution was washed with aqueous NH_4Cl and brine, dried (Na_2SO_4), and evaporated. The crude product was chromatographed on a silica gel column in hexanes−ethyl acetate (9:1 → 8:1) to give a mixture of spiropentanes **23a** and **23b** (598 mg, 78%). Partial separation of isomers was achieved in hexanes−ethyl acetate (10:1), and uniform isomers **23a** and **23b** were used for characterization.

Data for *proximal* isomer 23a: ^{1}H NMR ($CDCl_3$) δ 5.21 (br s, 1H), 4.60 (dd, 1H, ^3J = 5.7 Hz, ^2J = 11.7 Hz) and 3.60 (dd, 1H, ^3J = 9.0 Hz, ^2J = 11.4 Hz,), 3.08 (br s, 1H), 2.07 (s, 3H), 1.66 (1H, m), 1.43 (s, 9H), 1.18 (t, 1H, $^2J = {}^3J_{trans}$ = 5.5 Hz) and 1.04 (dd, 1H, ^2J = 4.5 Hz, $^3J_{cis}$ = 7.5 Hz), 0.86 (t, 1H, $^2J = {}^3J$ = 4.2 Hz) and 0.80 (t, 1H, $^2J = {}^3J$ = 4.2 Hz); ^{13}C NMR δ 171.32, 156.37, 79.28, 67.82, 20.98, 28.88, 28.32, 18.76, 16.10, 14.67, 11.55; CI-MS *m*/*z* 256 (M + H, 2.2), 200 (M + H − 2-methylpropene, 100.0); HRMS calcd for $C_9H_{13}NO_4$ (M + H − tBu) 199.0845, found 199.0840. Anal. Calcd for $C_{13}H_{21}O_4N$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.33; H, 8.30; N, 5.35.

Data for *medial-syn* isomer 23b: ^{1}H NMR ($CDCl_3$) δ 4.94 (br s, 1H), 3.88 (d, 2H), 2.76 (br s, 1H), 1.94 (s, 3H), 1.46 (m, 1H), 1.34 (s, 9H), 1.08 (m, 1H) and 1.00 (t, 1H, $^2J = {}^3J$ = 4.5 Hz, H_2), 0.75 (t, 1H, $^2J = {}^3J$ = 4.2 Hz) and 0.66 (t, 1H, $^2J = {}^3J$ = 4.2 Hz); ^{13}C NMR δ 170.94, 156.36, 79.09, 67.64, 20.78, 28.16, 27.94, 19.88, 13.64, 11.81, 11.48; CI-MS *m*/*z* 256 (M + H, 6.5), 200 (M + H − 2-methylpropene, 100.0); HRMS calcd for $C_9H_{13}NO_4$ (M + H − tBu) 199.0845, found 199.0847. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.18; H, 8.18; N, 5.69.

***medial-anti*- and *distal*-5-Acetoxymethyl-1-(*tert*-butoxycarbonyl)aminospiropentanes (23c and 23d).** Both isomers were prepared as described above for spiropentanes **23a** and **23b** from a mixture of *medial-anti* and *distal*-1-carboxy-4-acetoxymethylspiropentanes (**22c** + **22d**; 550 mg, 3.0 mmol). Chromatography in petroleum ether−ethyl acetate (8:1 → 7:1) afforded partially separated spiropentanes **23c** and **23d** (586 mg, 76%). Uniform isomers **23c** and **23d** were used for characterization.

Data for *medial-anti* isomer 23c: ^{1}H NMR ($CDCl_3$) δ 4.85 (br s, 1H), 4.15 (br s, 1H) and 4.00 (dd, 1H, *J* = 7.3 and 11.3 Hz), 2.91 (br s, 1H), 2.00 (s, 3H), 1.51 (t, 1H, *J* = 6.0 Hz), 1.40 (s, 9H), 1.17 (t, 1H, *J* = 6.0 Hz) and 1.00 (dd, 1H, ^2J = 4.5 Hz, $^3J_{cis}$ = 7.5 Hz), 0.83 (t, 1H, *J* = 4.2 Hz) and 0.78 (t, 1H, *J* = 4.6 Hz); ^{13}C NMR δ 171.12, 156.31, 79.26, 67.39, 28.27, 26.94, 20.94, 20.45, 17.11, 13.56, 8.67; CI-MS *m*/*z* 256 (M + H, 44.2), 200 (100.0); HRMS calcd for $C_9H_{13}NO_4$ (M + H − tBu) 199.0845, found 199.0848. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.03; H, 8.25; N, 5.43.

Data for *distal* isomer 23d: ^{1}H NMR ($CDCl_3$) δ 4.76 (br, 1H), 4.00 (dd, 1H, *J* = 7.0 and 11.4 Hz) and 3.90 (dd, 1H, *J* = 7.3 and 11.4 Hz), 2.86 (br s, 1H, H_1), 2.02 (s, 3H), 1.60 (m, 1H, H_5), 1.39 (s, 9H), 1.19 (t, 1H, ^2J = 5.0 Hz) and 1.12 (dd, 1H, ^2J = 4.5 Hz, $^3J_{cis}$ = 7.9 Hz), 0.78 (t, 1H, *J* = 4.2 Hz) and 0.70 (t, 1H, *J* = 4.5 Hz); ^{13}C NMR δ 171.11, 156.18, 79.41, 67.26, 28.26, 20.92, 20.00, 16.53, 11.79, 8.68; CI-MS *m*/*z* 256 (M + H, 2.9), 200 (80.0), 156 (9.3), 140 (100.0), 96 (80.4); HRMS calcd for $C_9H_{13}NO_4$ (M + H − tBu) 199.0845, found 199.0840. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 60.93; H, 8.24; N, 5.48.

***proximal*- and *medial-syn*-5-Hydroxymethyl-1-(*tert*-butoxycarbonyl)aminospiropentanes (24a and 24b).** A mixture of isomers **23a** and **23b** (1.42 g, 5.57 mmol) and K_2CO_3 (845 mg, 6.13 mmol) in MeOH−H_2O (5:1, 30 mL) was stirred at room temperature for 16 h. Solvents were evaporated, and the residue was extracted with ethyl acetate (4 × 30 mL). Evaporation afforded spiropentanes **24a** + **24b**, which were readily separated by TLC (hexanes−ethyl acetate, 2:1, R_f 0.6 and 0.3, respectively). Column chromatography on silica gel in hexanes−ethyl acetate (6:1 → 4:1) gave the *proximal* isomer **24a** (200 mg, 17%) and *medial-syn* isomer **24b** (950 mg, 80%).

Data for *proximal* isomer 24a: IR (0.044 M solution in CCl_4) 3620, 3460 (sh) and 3360 (br, OH and NH), 2980 (C−H), 1710 and 1690 (C=O), 1545 (NH, amide II) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.33 (br s, 1H), 4.11 (dd, 1H, ^3J = 4.2 Hz, ^2J = 11.0 Hz) and 3.81 (br s, 1H), 3.09 (t, 1H, $^3J_{cis} = {}^3J_{trans}$ = 8.8 Hz), 2.94 (br s, 1H), 1.56 (m 1H), 1.36 (s, 9H), 1.10 (m, 1H) and 0.87 (dd, 1H, $^3J_{cis}$ = 8.8 Hz, ^2J = 4.5 Hz), 0.77 (t, 1H, $^2J = {}^3J$ = 3.9 Hz) and 0.68 (m, 1H); ^{13}C NMR δ 157.39, 79.13, 64.81, 28.90, 28.34, 19.14, 18.28, 15.25, 10.77; CI-MS *m*/*z* 214 (M + H, 18.5), 180 (2.2), 158 (M + H − 2-methylpropene, 100.0); HRMS calcd for $C_7H_{11}NO_3$ (M + H − tBu) 157.0740, found 157.0740.

Data for *medial-syn* isomer 24b: IR (0.046 M solution in CCl_4) 3620, 3450 and 3450−3400 (br, OH and NH), 2980 (C−H), 1720 and 1700 (sh, C=O), 1545 (NH, amide II) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.48 (br s, 1H), 3.86 (br s, 1H), 3.56 (dd, 1H, ^3J = 6.0 Hz, ^2J = 10.5 Hz) and 3.30 (dd, 1H, ^3J = 7.5 Hz, ^2J = 10.5 Hz), 2.84 (m, 1H), 1.36 (m, 1H), 1.32 (s, 9H), 0.95 (t, 2H, *J* = 5.7 Hz), 0.81 (t, 1H, *J* = 4.2 Hz) and 0.54 (t, 1H, *J* = 4.5 Hz); ^{13}C NMR δ 156.78, 79.05, 65.38, 28.53, 28.30, 19.38, 18.99, 16.96, 11.11; CI-MS *m*/*z* 214 (M + H, 4.9), 158 (M + H − 2-methylpropene, 100.0); HRMS calcd for $C_7H_{11}NO_3$ (M + H − tBu) 157.0740, found 157.0741.

***medial-anti*- and *distal*-5-Hydroxymethyl-1-(*tert*-butoxycarbonyl)aminospiropentanes (24c and 24d).** Hydrolysis of the isomeric mixture **23c** + **23d** (925 mg, 3.6 mmol) was performed according to the procedure described above for **23a** + **23b**. Isomers **24c** and **24d** were resolved by TLC (petroleum ether−ether, 1:1), R_f 0.6 and 0.52, respectively. Column chromatography on silica gel in petroleum ether (5:1 → 4:1) gave *medial-anti* isomer **24c** (334 mg, 43%) and *distal* isomer **24d** (413 mg, 53%).

Data for *medial-anti* isomer 24c: IR (0.034 M solution in CCl_4): 3630, 3460 (OH and NH), 2990 (C−H), 1730 (C=O), 1550 (NH, amide II) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.91 (br s, 1H), 3.79 (br s, 2H, H_6), 2.92 (br s, 1H), 2.75 (br s, 1H), 1.43 (s, 10H), 1.10 (t, 1H, *J* = 5.4 Hz) and 0.99 (br s, 1H), 0.94 (m, 1H) and 0.86 (br s, 1H); ^{13}C NMR δ 157.24, 79.74, 62.16, 28.24, 26.75, 20.16, 19.23, 12.93, 6.70; CI-MS *m*/*z* 214 (M + H, 15.1), 158 (100.0); HRMS calcd for $C_7H_{11}NO_3$ (M + H − tBu) 157.0740, found 157.0734.

Data for *distal* isomer 24d: IR (0.031 M solution in CCl_4): 3640, 3460 (OH and NH), 2990 (C−H), 1730 (sh), 1710 (C=O), 1545 (NH, amide II) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.95 (br s, 1H,), 3.44 and 3.41 (2m, 2H), 3.16 (br s, 1H), 2.78 (br s, 1H), 1.46 (br s, 1H), 1.32 (s, 9H), 1.15 (t, 1H, $^2J = {}^3J_{trans}$ = 6.0 Hz) and 0.96 (dd, 1H, ^2J = 5.0 Hz, $^3J_{cis}$ = 7.8 Hz), 0.68 (t, 1H, *J* = 4.2 Hz) and 0.55 (t, 1H, *J* = 4.5 Hz); ^{13}C NMR δ 156.62, 79.32, 65.00, 28.48, 28.23, 19.77, 14.06, 11.70, 8.09; CI-MS *m*/*z* 214 (M + H, 31.0), 158 (100.0); HRMS calcd for $C_7H_{11}NO_3$ (M + H − tBu) 157.0740, found 157.0740.

1-Amino-5-hydroxymethylspiropentane Hydrochlorides 25a−25d. A solution of a single isomer of BOC-aminospiropentane **24a**, **24b**, **24c**, or **24d** (1−2 mmol) was stirred in 2 M HCl in MeOH (10−20 mL) at room temperature for 16 h, whereupon it was evaporated to give 1-amino-4-hydroxymethylspiropentane hydrochloride **25a**, **25b**, **25c**, or **25d** in quantitative yield.

Data for *proximal* isomer 25a: ^{1}H NMR (D_2O) δ 3.59 (dd, 1H, ^3J = 7.4 Hz, ^2J = 11.0 Hz) and 3.53 (dd, 1H, ^3J = 7.0 Hz, ^2J = 11.0 Hz), 2.94 (m, 1H), 1.68 (m, 1H), 1.24 (t, 1H, *J* = 6.6 Hz) and 1.13 (m, 1H), 1.03 (dd, 1H, ^2J = 4.5 Hz, ^3J = 7.6 Hz) and 0.83 (t, 1H, *J* = 4.5 Hz); ^{13}C NMR δ 63.75, 28.14, 19.37, 17.00, 10.94, 10.14; EI-MS *m*/*z* 114 (M − Cl, 29.6), 55 (100.0); HRMS calcd for C_6H_8N (M − H − H_2O − HCl) 94.0657, found 94.0654.

Data for *medial-syn* isomer 25b: ^{1}H NMR (D_2O) δ 3.51 (dd, 1H, ^3J = 6.7 Hz, ^2J = 11.0 Hz), 3.38 (dd, 1H, ^3J = 7.2 Hz,

^2J = 11.0 Hz), 2.83 (dd, 1H, $^3J_{trans}$ = 3.3 Hz, $^3J_{cis}$ = 6.6 Hz), 1.54 (m, 1H), 1.17 (t, 1H, J = 6.4 Hz), 1.09 (m, 2H) and 0.69 (t, 1H, J = 4.2 Hz); ^{13}C NMR δ 64.19, 27.49, 16.91, 16.49, 10.42, 8.14; EI-MS m/z 114 (M − Cl, 4.9), 55 (100.0); HRMS calcd for C_6H_8N (M − H − H_2O − HCl) 94.0657, found 94.0655. Anal. Calcd for $C_6H_{12}ClNO$: C, 48.16; H, 8.03; N, 9.36. Found: C, 47.93; H, 7.97; N, 9.16.

Data for *medial-anti* isomer 25c: ^{1}H NMR (D_2O) δ 3.50 (2H, dd, J = 3.6 and 9.6 Hz), 2.98 (1H, d, J = 4.2 Hz), 1.56 (m, 1H), 1.32 (1H, t, J = 6.7 Hz), 1.16 (2H, m), and 0.83 (1H, t, J = 4.2 Hz); ^{13}C NMR δ 64.24, 26.29, 19.46, 17.27, 10.04, 8.22; EI-MS m/z 114 (M − Cl, 14.1), 55 (100.0); HRMS calcd for $C_6H_{12}NO$ (M − Cl) 114.0919, found 114.0918.

Data for *distal* isomer 25d: ^{1}H NMR (D_2O) δ 3.45 (2H, m), 2.86 (1H, dd, $^3J_{trans}$ = 2.5 Hz, $^3J_{cis}$ = 6.7), 1.56 (m, 1H), 1.32 (1H, t, $^2J = {}^3J_{trans}$ = 6.5 Hz) and 1.13 (1H, dd, ^2J = 4.8 Hz, $^3J_{trans}$ = 8.4 Hz), 1.07 (1H, dd, ^2J = 3.3 Hz, $^3J_{cis}$ = 6.3 Hz) and 0.79 (1H, t, J = 4.8 Hz); ^{13}C NMR δ 63.84, 27.51, 18.84, 17.03, 8.15, 7.94; EI-MS m/z 114 (M − Cl, 3.4), 55 (100.0); HRMS calcd for $C_6H_{12}NO$ (M − Cl) 114.0919, found 114.0916; HRMS calcd for C_6H_8N (M − H − H_2O − HCl) 94.0657, found 94.0659.

6-Chloro-9-(5-hydroxymethylspiropent-1-yl)purines 26a − 26d. A mixture of aminospiropentane **25a**, **25b**, **25c**, or **25d**, 4,6-dichloro-5-nitropyrimidine (1.2 molar equiv), and Et_3N (2.5 molar equiv) in ethanol was stirred at room temperature for 2 h. The solvents were evaporated, and a solid residue was stirred with an excess of triethyl orthoformate and $SnCl_2{\cdot}H_2O$ (6.0 molar equiv) at room temperature for 16 h. After evaporation of solvents, water (20 mL) was added, and the pH was adjusted to 8.0 with saturated aqueous K_2CO_3. The solution was evaporated, the residue was washed with CH_2Cl_2−MeOH (10:1, 5 × 30 mL), and evaporation of the solvents gave the crude product, which was purified by column chromatography on silica gel to furnish compound **26a**, **26b**, **26c**, or **26d**).

Data for *proximal* isomer 26a: yield 156 mg (47%) from **25a** (198 mg, 1.28 mmol), 4,6-dichloro-5-nitropyrimidine (312 mg, 1.60 mmol), Et_3N (0.465 mL, 3.3 mmol), EtOH (10.0 mL), $CH(OEt)_3$ (15 mL), and $SnCl_2{\cdot}H_2O$ (1.82 g, 8.0 mmol); solvent for chromatography CH_2Cl_2−MeOH (40:1 → 30:1); UV max (EtOH) 265, 217 nm; ^{1}H NMR ($CDCl_3$) δ 8.59 and 8.22 (2H, 2s), 4.07 (1H, dd, $^3J_{trans}$ = 3.3 Hz, $^3J_{cis}$ = 7.2 Hz), 3.52 (1H, dd, ^3J = 5.0 Hz, ^2J = 11.0 Hz) and 3.17 (1H, dd, ^3J = 7.0 Hz, ^2J = 11.0 Hz), 3.37 (1H, br s), 1.79 (1H, dd, J = 3.8 and 6.0 Hz), 1.63 (2H, m), 1.06 (2H, m); ^{13}C NMR δ 153.00, 151.40, 150.40, 144.91, 131.63, 62.27, 32.70, 20.47, 19.79, 12.13, 10.40; EI-MS m/z 253 (4.8) and 251 (M + H, 19.0), 252 (2.9) and 250 (M, 4.6), 235 (17.5) and 233 (M − OH, 58.2), 221 (70.5) and 219 (M − CH_2OH, 100.0); HRMS calcd for $C_{11}H_{11}{}^{35}ClN_4O$ 250.0621, found 250.0620.

Data for *medial-syn* isomer 26b: yield 181 mg (56%) from **25b** (190 mg, 1.28 mmol), 4,6-dichloro-5-nitropyrimidine (300 mg, 1.54 mmol), Et_3N (0.446 mL, 3.2 mmol), EtOH (10.0 mL), $CH(OEt)_3$ (15 mL), and $SnCl_2{\cdot}H_2O$ (1.75 g, 7.68 mmol); solvent for chromatography CH_2Cl_2−MeOH (30:1 → 25:1); UV max (EtOH) 265 (ϵ 10 800), 215 (ϵ 16 500) nm; ^{1}H NMR ($CDCl_3$) δ 8.58 and 8.41 (2H, 2s), 4.07 (1H, dd, $^3J_{trans}$ = 3.5 Hz, $^3J_{cis}$ = 7.0 Hz), 3.94 (1H, dd, ^3J = 5.1 Hz, ^2J = 10.2 Hz) and 3.27 (1H, dd, J = 9.0 Hz, J = 10.8 Hz), 2.80 (1H, br s, OH), 1.73 (1H, dd, J = 3.5 and 5.6 Hz), 1.60 (1H, t, J = 6.5 Hz) and 1.58 (3H, m), 1.33 (1H, dd, ^2J = 4.8 Hz, $^3J_{cis}$ = 8.4 Hz) and 0.85 (1H, t, $^2J = {}^3J_{trans}$ = 4.8 Hz); ^{13}C NMR δ 152.50, 151.64, 150.45, 144.44, 131.21, 65.06, 32.13, 20.29, 18.85, 11.93, 11.52; EI-MS m/z 253 (5.2) and 251 (M + H, 20.2), 252 (3.0) and 250 (M, 4.8), 235 (18.4) and 233 (M − OH, 42.8), 221 (64.1) and 219 (M − CH_2OH, 100.0); HRMS calcd for $C_{11}H_{11}{}^{35}ClN_4O$ 250.0621, found 250.0618.

Data for *medial-anti* isomer 26c: yield 203 mg (45%) from **25c** (270 mg, 1.82 mmol), 4,6-dichloro-5-nitropyrimidine (423 mg, 2.18 mmol), Et_3N (0.634 mL, 4.55 mmol), EtOH (16.0 mL), $CH(OEt)_3$ (25 mL), and $SnCl_2{\cdot}H_2O$ (2.46 g, 6.0 mmol); solvent for chromatography CH_2Cl_2−MeOH (25:1 → 20:1); UV max (EtOH) 265, 217 nm; ^{1}H NMR ($CDCl_3$) δ 8.60 and 8.21 (2H, 2s), 3.98 (1H, dd, ^3J = 5.0 Hz, ^2J = 11.3 Hz) and 3.90 (3H, m), 1.69 (1H, t, J = 6.4 Hz), 1.61 (1H, dd, J = 3.3 and 5.7 Hz) and 1.59 (1H, m), 1.00 (1H, dd, ^2J = 4.8 Hz, $^3J_{cis}$ = 8.1 Hz) and 0.90 (1H, t, $^2J = {}^3J_{trans}$ = 4.9 Hz); ^{13}C NMR δ 152.70, 151.63, 150.79, 145.55, 131.80, 62.68, 30.03, 20.51, 19.74, 12.63, 8.66; EI-MS m/z 253 (6.8) and 251 (M + H, 24.5), 252 (4.4) and 250 (M, 5.0), 235 (17.8) and 233 (M − OH, 50.3), 221 (76.0) and 219 (M − CH_2OH, 100.0), 206 (18.7), 181 (25.2), 155 (97.0); HRMS calcd $C_{11}H_{11}{}^{35}ClN_4O$ 250.0621, found 250.0624.

Data for *distal* isomer 26d: yield 291 mg (57%) from **25d** (300 mg, 2.03 mmol), 4,6-dichloro-5-nitropyrimidine (472 mg, 2.43 mmol), Et_3N (0.707 mL, 5.07 mmol), EtOH (16.0 mL), $CH(OEt)_3$ (25 mL), and $SnCl_2{\cdot}H_2O$ (2.75 g, 12.2 mmol); solvent for chromatography CH_2Cl_2−MeOH (25:1 → 20:1); UV max (EtOH) 265, 215 nm; ^{1}H NMR ($CDCl_3$) δ 8.61 and 8.20 (2H, 2s), 3.84 (1H, dd, $^3J_{trans}$ = 3.0 Hz, $^3J_{cis}$ = 6.9 Hz), 3.76 (1H, br s), 3.66 (1H, dd, ^3J = 6.3 Hz, ^2J = 11.3 Hz) and 3.50 (1H, dd, ^3J = 7.3 Hz, ^2J = 11.3 Hz), 1.84 (1H, dt, J = 6.3 Hz), 1.76 (1H, t, J = 6.4 Hz) and 1.50 (1H, dd, J = 3.3 and 5.7 Hz), 1.26 (1H, dd, ^2J = 4.8 Hz, $^3J_{cis}$ = 8.4 Hz) and 0.76 (1H, t, $^2J = {}^3J_{trans}$ = 4.8 Hz); ^{13}C NMR δ 152.78, 151.86, 150.57, 145.00, 131.24, 64.39, 31.25, 20.19, 11.32, 9.62; EI-MS 253 (3.9) and 251 (M + H, 13.2), 252 (3.0) and 250 (M, 4.7), 235 (13.8) and 233 (M − OH, 43.6), 221 (67.5) and 219 (M − CH_2OH, 100.0); EI-MS calcd for $C_{11}H_{11}{}^{35}ClN_4O$ 250.0621, found 250.0618.

9-(5-Hydroxymethylspiropentyl-1-yl)adenines 12a, 13a, 14a, and 15a. A mixture of 6-chloro-9-(5-hydroxymethylspiropentyl-1-yl)purine **26a**, **26b**, **26c**, or **26d** in 25% NH_3 in methanol (50 mL) was heated in an autoclave at 100 °C (oil bath) for 15 h. After cooling, the volatile components were evaporated, and the crude product was chromatographed on a silica gel column in CH_2Cl_2−methanol (100:5 → 100:10) to give compound **12a**, **13a**, **14a**, or **15a**.

Data for *proximal* isomer 12a: yield 126 mg (80%) from **26a** (172 mg, 0.69 mmol); mp 235−237 °C; UV max (EtOH) 261 (ϵ 14 000), 209 (ϵ 19 000) nm; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.11 (2H, 2 overlapped s, H_2 and H_8), 7.19 (2H, s, NH_2), 4.35 (1H, t, J = 5.4 Hz, OH), 4.01 (1H, dd, $^3J_{trans}$ = 3.5 Hz, $^3J_{cis}$ = 7.5 Hz, $H_{1'}$), 2.95 (1H, dt, ^3J = 5.5 Hz, ^2J = 11.0 Hz) and 2.82 (1H, ddd, ^3J = 4.5 and 7.5 Hz, ^2J = 12.0 Hz, $H_{6''}$ and $H_{6'}$), 2.01 (1H, dd, J = 4.0 and 5.5 Hz, $H_{2''}$), 1.49 (2H, m, $H_{2'}$ and $H_{5'}$), 1.00 (1H, dd, ^2J = 4.5 Hz, $^3J_{cis}$ = 7.5 Hz, $H_{4'}$), 0.89 (1H, d, J = 4.0 and 4.5 Hz, $H_{4''}$); ^{13}C NMR (125.7 MHz) δ 156.37, 152.74, 151.15, 139.53, 119.51 (purine), 62.29 ($C_{6'}$), 32.07 ($C_{1'}$), 20.72 ($C_{5'}$), 19.96 ($C_{3'}$), 11.93 ($C_{2'}$), 10.70 ($C_{4'}$); EI-MS m/z 232 (M + H, 15.2), 231 (M, 9.1), 214 (M − OH, 79.6), 200 (M − CH_2OH, 100.0), 135 (adenine, 53.9); HRMS calcd for $C_{11}H_{13}N_5O$ 231.1120, found 231.1116. Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.12; H, 5.67; N, 30.29. Found: C, 57.21; H, 5.77; N, 30.14.

Data for *medial-syn* isomer 13a: yield 139 mg (88%) from **26b** (160 mg, 0.64 mmol); mp 188−190 °C; UV max (EtOH) 261 (ϵ 14 700), 208 (ϵ 20 400) nm; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.12 (1H, s, H_2), 8.11 (1H, s, H_8), 7.20 (2H, s, NH_2), 4.60 (1H, t, J = 5.5 Hz, OH), 3.86 (1H, dd, $^3J_{trans}$ = 3.5 Hz, $^3J_{cis}$ = 7.0, $H_{1'}$), 3.50 (1H, td, ^3J = 5.5 Hz, ^2J = 11.0 Hz) and 3.20 (1H, ddd, ^3J = 4.5 and 7.5 Hz, ^2J = 11.5 Hz, $H_{6''}$ and $H_{6'}$), 1.65 (1H, dd, J = 3.5 and 5.5 Hz, $H_{2''}$), 1.49 (2H, apparent t, J = 5.5 Hz, $H_{2'}$ and $H_{5'}$), 1.23 (1H, dd, ^2J = 4.5 Hz, $^3J_{cis}$ = 8.0, $H_{4'}$), 0.75 (1H, t, $^2J = {}^3J_{trans}$ = 4.5 Hz, $H_{4''}$); ^{13}C NMR (125.7 MHz) δ 156.38, 152.87, 150.95, 139.93, 119.19 (purine), 64.21 ($C_{6'}$), 30.86 ($C_{1'}$), 20.24 ($C_{5'}$), 18.77 ($C_{3'}$), 11.45, 11.21 ($C_{2'}$, $C_{4'}$); EI-MS m/z 232 (M + H, 14.0), 231 (M, 14.5), 214 (M − OH, 66.1), 200 (M − CH_2OH, 100.0), 135 (adenine, 54.8); HRMS calcd for $C_{11}H_{13}N_5O$ 231.1120, found 231.1120. Anal. Calcd for $C_{11}H_{13}N_5O{\cdot}0.9H_2O$: C, 53.39; H, 6.03; N, 28.30. Found: C, 53.16; H, 5.89; N, 28.64.

Data for *medial-anti* isomer 14a: yield 136 mg (75%) from **26c** (195 mg, 0.78 mmol); mp 185−187 °C; UV max (EtOH) 261 (ϵ 14 800), 209 (ϵ 19 700) nm; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.11 (1H, s, H_2), 8.10 (1H, s, H_8), 7.21 (2H, s, NH_2), 4.60 (1H, t, J = 5.0 Hz, OH), 3.86 (1H, dd, $^3J_{trans}$ = 3.5 Hz, $^3J_{cis}$ = 7.5 Hz, $H_{1'}$), 3.71 (1H, td, ^3J = 5.5 Hz, ^2J = 11.0 Hz) and 3.68 (1H, td, ^3J = 5.5 Hz, ^2J = 11.0 Hz, $H_{6''}$ and $H_{6'}$), 1.69 (1H, dd, J = 3.5 and 5.0 Hz, $H_{2''}$), 1.55 (1H, t, $^3J_{cis} = {}^2J$ = 6.5 Hz, $H_{2'}$), 1.47 (1H, m, $H_{5'}$), 0.95 (1H, dd, ^2J = 4.5 Hz, $^3J_{cis}$

= 8.0 Hz, $H_{4'}$), 0.75 (1H, t, $^2J = {}^3J_{trans} = 4.5$ Hz, $H_{4''}$); ^{13}C NMR (125.7 MHz) δ 156.41, 152.91, 151.08, 140.69, 119.28 (purine), 63.43 ($C_{6'}$), 29.26 ($C_{1'}$), 21.13 ($C_{5'}$), 20.61 ($C_{3'}$), 12.40 ($C_{2'}$), 9.03 ($C_{4'}$); EI-MS *m*/*z* 232 (M + H, 3.0), 231 (M, 8.2), 230 (M − H, 8.2), 214 (M − OH, 63.7), 200 (M − CH_2OH, 100.0), 135 (adenine, 62.4); HRMS calcd for $C_{11}H_{13}N_5O$ 231.1120, found 231.1117. Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.12; H, 5.67; N, 30.29. Found: C, 56.91; H, 5.68; N, 30.41.

Data for *distal* isomer 15a: yield 240 mg (91%) from **26d** (285 mg, 1.36 mmol); mp 211−214 °C; UV max (EtOH) 261 (ϵ 15 400), 209 (ϵ 20 800) nm; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.10 (1H, s, H_2), 8.09 (1H, s, H_8), 7.21 (2H, s, NH_2), 4.57 (1H, t, J = 5.5 Hz, OH), 3.74 (1H, dd, $^3J_{trans} = 3.0$ Hz, $^3J_{cis} = 7.5$ Hz, $H_{1'}$), 3.44 (1H, td, $^3J = 5.5$ Hz, $^2J = 12.0$ Hz) and 3.32 (1H, ddd, $^3J = 5.5$ and 7.0 Hz, $^2J = 12.0$ Hz, $H_{6''}$ and $H_{6'}$), 1.64 (2H, m, $H_{2'}$ and $H_{5'}$), 1.54 (1H, dd, J = 3.0 and 5.0 Hz, $H_{2''}$), 1.10 (1H, dd, $^2J = 4.0$ Hz, $^3J_{cis} = 8.0$ Hz, $H_{4'}$), 0.66 (1H, dd, J = 4.0 and 4.4 Hz, $H_{4''}$); ^{13}C NMR (125.7 MHz) δ 156.39, 152.99, 151.06, 140.62, 119.14 (purine), 63.74 ($C_{6'}$), 30.53 ($C_{1'}$), 20.53, 20.48 ($C_{5'}$, $C_{3'}$), 10.86 ($C_{2'}$), 9.34 ($C_{4'}$); EI-MS *m*/*z* 232 (M + H, 3.8), 231 (M, 13.0), 230 (6.0), 214 (M − OH, 67.7), 202 (22.6), 200 (M − CH_2OH, 100.0), 187 (16.8), 146 (17.5), 135 (adenine, 56.3); HRMS calcd for $C_{11}H_{13}N_5O$ 231.1120, found 231.1112. Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.12; H, 5.67; N, 30.29. Found: C, 56.91; H, 5.68; N, 30.41.

2-Acetamino-6-chloro-9-(5-hydroxymethylspiropent-1-yl)purines 30a, 30b, 30c, and 30d. Compounds **30a**−**30d** were prepared by a modification of the procedure employed for the synthesis of **26a**−**26d**. 2-Acetamino-4,6-dichloro-5-nitropyrimidine in DMF at 0 °C was used in reactions with aminospiropentanes **25a**−**25d**. The products **30a**−**30d** were chromatographed in CH_2Cl_2−MeOH (40:1 → 20:1).

Data for *proximal* isomer 30a: yield 212 mg (41%) from **25a** (250 mg, 1.69 mmol), 2-acetamino-4,6-dichloro-5-nitropyrimidine (470 mg, 1.86 mmol), Et_3N (0.485 mL, 3.5 mmol) in DMF (10.0 mL), $SnCl_2 \cdot H_2O$ (2.28 g, 10.2 mmol), and $CH(OEt)_3$ (15 mL); mp 200−205 °C; UV max (EtOH) 289 (ϵ 10 200), 235 (ϵ 24 800), 204 (ϵ 17 100) nm; ^{1}H NMR (DMSO-d_6) δ 10.80 (1H, s), 8.49 (1H, s), 4.16 (1H, t, J = 4.5 Hz), 4.01 (1H, dd, $^3J_{trans}$ = 3.0 Hz, $^3J_{cis}$ = 7.2 Hz), 3.09 (1H, dd, $^3J = 4.8$ Hz, $^2J = 10.0$ Hz) and 2.92 (1H, dd, $^3J = 5.5$ Hz, $^2J = 11.0$), 2.20 (3H, s), 2.15 (1H, t, J = 4.0 Hz), 1.50 (2H, m), 0.97 (1H, dd, $^2J = 4.2$ Hz, $^3J_{cis} = 7.5$ Hz), 0.85 (1H, t, $^2J = {}^3J_{trans} = 4.2$ Hz); ^{13}C NMR δ 169.21, 154.29, 152.16, 149.04, 145.59, 127.93, 62.28, 32.58, 24.99, 20.48, 20.07, 11.07, 10.74.

Data for *medial-syn* isomer 30b: yield 303 mg (58%) from **25b** (252 mg, 1.70 mmol), 2-acetamino-4,6-dichloro-5-nitropyrimidine (478 mg, 1.90 mmol), Et_3N (0.475 mL, 3.40 mmol) in DMF (10.0 mL), $SnCl_2 \cdot H_2O$ (2.30 g, 10.2 mmol), and $CH(OEt)_3$ (15 mL); mp 233−235 °C; UV max (EtOH) 288 (ϵ 10 500), 260 (ϵ 7 900), 234 (ϵ 26 400), 203 (ϵ 18 400) nm; ^{1}H NMR (DMSO-d_6) δ 10.80 (1H, s), 8.50 (1H, s), 4.49 (1H, t, J = 5.5 Hz), 3.87 (1H, dd, $^3J_{trans} = 3.0$ Hz, $^3J_{cis} = 6.9$ Hz), 3.49 (1H, td, $^3J = 5.5$ Hz, $^2J = 11.0$ Hz) and 3.13 (1H, ddd, $^3J = 4.5$ and 6.0 Hz, ^2J = 10.5 Hz), 2.20 (3H, s), 1.73 (1H, m), 1.53 (2H, m), 1.25 (1H, dd, $^2J = 4.2$ Hz, $^3J_{cis} = 8.1$ Hz), 0.76 (1H, t, $^2J = {}^3J_{trans} = 4.2$ Hz); ^{13}C NMR δ 169.76, 154.01, 152.15, 149.40, 145.97, 127.49, 64.91, 31.15, 24.88, 20.46, 18.54, 11.18, 10.98; EI-MS *m*/*z* 309 (1.1) and 307 (M, 3.9), 292 (3.0) and 290 (8.8, M − OH), 172 (8.7) and 170 (21.7, purine base − CH_2═C═O + H), 171 (15.9) and 169 (32.9, purine base − CH_2═C═O), 43 (Ac, 100.0); HRMS calcd for $C_{13}H_{14}{}^{35}ClN_5O_2$ 307.0836, found 307.0831. Anal. Calcd for $C_{13}H_{14}ClN_5O_2$: C, 50.74; H, 4.59; N, 22.76. Found: C, 50.58; H, 4.80; N, 22.69.

Data for *medial-anti* isomer 30c: yield 193 mg (50%) from **25c** (185 mg, 1.25 mmol), 2-acetamino-4,6-dichloro-5-nitropyrimidine (330 mg, 1.31 mmol), Et_3N (0.350 mL, 2.5 mmol) in DMF (10 mL), $SnCl_2 \cdot H_2O$ (1.70 g, 7.5 mmol), and $CH(OEt)_3$ (20 mL); mp 194−196 °C; UV max (EtOH) 289, 260, 234, 204 nm; ^{1}H NMR (DMSO-d_6) δ 10.80 (1H, s), 8.49 (1H, s), 4.47 (1H, t, J = 5.5 Hz, OH), 3.91 (1H, dd, $^3J_{trans} = 3.0$ Hz, $^3J_{cis} = 6.9$ Hz), 3.72 (2H, m), 2.20 (3H, s), 1.71 (1H, dd, J = 3.5 and 5.4 Hz), 1.57 (1H, dd, $^2J = 5.4$ Hz, $^3J_{cis} = 6.9$ Hz), 1.44 (1H, m), 0.93 (2H, m); ^{13}C NMR δ 169.04, 154.17, 152.27, 149.36, 146.72, 127.63, 63.36, 29.81, 24.81, 21.13, 20.76, 12.63, 8.98; EI-MS *m*/*z* 309 (1.1) and 307 (M, 5.8), 292 (7.0) and 290 (21.3, M − OH), 172 (25.2) and 170 (59.4, purine base − CH_2═C═O + H), 171 (46.5) and 169 (100.0, purine base − CH_2═C═O); HRMS calcd for $C_{13}H_{14}N_5O_2{}^{35}Cl$ 307.0836, found 307.0840.

Data for *distal* isomer 30d: yield 278 mg (48%) from **25d** (282 mg, 1.90 mmol), 2-acetamino-4,6-dichloro-5-nitropyrimidine (510 mg, 2.03 mmol), Et_3N (0.532 mL, 3.80 mmol) in DMF (16 mL), $SnCl_2 \cdot H_2O$ (2.57 g, 11.4 mmol), and $CH(OEt)_3$ (20 mL); amorphous solid; UV max (EtOH) 289, 260, 234, 204 nm; ^{1}H NMR (DMSO-d_6) δ 10.80 (1H, s), 8.49 (1H, s), 4.55 (1H, t, $J = 5.4$ Hz), 3.78 (1H, dd, $^3J_{trans} = 3.0$ Hz, $^3J_{cis} = 6.8$ Hz), 3.44 (1H, qt, $J = 5.7$ Hz) and 3.28 (1H, qt, $J = 6.0$ Hz), 2.20 (3H, s), 1.66 (2H, m), 1.59 (1H, t, $^2J = {}^3J_{trans} = 4.2$ Hz), 1.22 (1H, dd, $^2J = 4.2$ Hz, $^3J_{cis} = 8.1$ Hz), 0.93 (1H, t, $^2J = {}^3J_{trans} = 4.2$ Hz); ^{13}C NMR δ 169.29, 154.14, 152.45, 149.33, 146.32, 127.43, 63.66, 30.98, 25.0, 20.5, 10.8, 9.3; EI-MS *m*/*z* 309 (2.8) and 307 (9.7, M), 292 (4.5) and 290 (19.2, M − OH), 172 (22.6) and 170 (64.2, purine base − CH_2═C═O + H), 171 (43.9) and 169 (100.0, purine base − CH_2═C═O).

9-(5-Hydroxymethylspiropent-1-yl)guanines 12b, 13b, 14b, and 15b. A solution of compound **30a**, **30b**, **30c**, or **30d** (150−300 mg, 0.5−1 mmol) in formic acid (80%, 10 mL) was heated at 90 °C for 16 h, whereupon it was evaporated. The solid residue was dissolved in water, and after lyophilization the crude product was stirred in NH_3/MeOH (20%, 8 mL) for 4 h at room temperature. The solvent was removed and the product recrystallized from MeOH−H_2O (15:1) to give compound **12b**, **13b**, **14b**, or **15b** as a white solid.

Data for *proximal* isomer 12b: yield 132 mg (77%) from **30a** (210 mg, 0.68 mmol); mp 235−237 °C dec; UV max (EtOH) 257 (ϵ 14 200), 206 (ϵ 15 300) nm; ^{1}H NMR (DMSO-d_6) δ 10.59 (1H, s, NH), 7.65 (1H, s, H_8), 6.46 (2H, s, NH_2), 4.39 (1H, t, J = 5.0 Hz, OH), 3.78 (1H, dd, $^3J_{trans} = 3.3$ Hz, $^3J_{cis} = 6.9$ Hz, $H_{1'}$), 3.06 (1H, m) and 2.81 (1H, m, $H_{6''}$ and $H_{6'}$), 1.84 (1H, t, $^2J = {}^3J_{trans} = 4.5$ Hz, $H_{2''}$), 1.49 (1H, m, $H_{5'}$), 1.39 (1H, t, $^3J_{cis}$ = 6.4 Hz, $H_{2'}$), 0.97 (1H, dd, $^2J = 3.9$ Hz, $^3J_{cis} = 6.6$ Hz, $H_{4'}$), 0.82 (1H, t, $^2J = {}^3J_{trans} = 4.0$ Hz, $H_{4''}$); ^{13}C NMR δ 157.26, 153.85, 152.94, 135.61, 117.28 (purine), 62.37 ($C_{6'}$), 31.74 ($C_{1'}$), 20.58, 19.86 ($C_{5'}$, $C_{3'}$), 12.0, 10.6 ($C_{2'}$, $C_{4'}$); FAB-MS *m*/*z* 249 (M, 15.6), 248 (M + H, 100.0), 215 (M − H − CH_2OH, 2.1). Anal. Calcd for $C_{11}H_{13}N_5O_2 \cdot 0.2H_2O$: C, 52.67; H, 5.38; N, 27.92. Found: C, 52.48; H, 5.57; N, 27.78.

Data for *medial-syn* isomer 13b: yield 199 mg (84%) from **30b** (290 mg, 0.94 mmol); mp 310−315 °C; UV max (EtOH) 256 (ϵ 13 800), 206 (ϵ 17 600) nm; ^{1}H NMR (DMSO-d_6) δ 10.60 (1H, s, NH), 7.65 (1H, s, H_8), 6.48 (2H, s, NH_2), 4.60 (1H, br, OH), 3.66 (1H, dd, $^3J_{trans} = 3.3$ Hz, $^3J_{cis} = 6.9$ Hz, $H_{1'}$), 3.50 (1H, dd, $^3J = 6.0$ Hz, $^2J = 11.0$ Hz) and 3.20 (1H, dd, $^3J = 7.8$ Hz, $^2J = 11.0$ Hz, $H_{6''}$ and $H_{6'}$), 1.48 (2H, m, $H_{2''}$ and $H_{5'}$), 1.39 (1H, t, $J = 6.2$ Hz, $H_{2'}$), 1.16 (1H, dd, $^2J = 4.2$ Hz, $^3J_{cis} = 8.1$ Hz, $H_{4'}$), 0.71 (1H, t, $^2J = {}^3J_{trans} = 4.2$ Hz, $H_{4''}$); ^{13}C NMR δ 157.21, 153.95, 152.70, 136.00, 116.88 (purine), 64.19 ($C_{6'}$), 30.64 ($C_{1'}$), 19.98, 18.70 ($C_{5'}$, $C_{3'}$), 11.37 ($C_{2'}$, $C_{4'}$); FAB-MS *m*/*z* 249 (M, 15.5), 248 (M + H, 100.0), 217 (M + H − CH_2OH, 16.8). Anal. Calcd for $C_{11}H_{13}N_5O_2 \cdot 0.2H_2O$: C, 52.67; H, 5.38; N, 27.92. Found: C, 52.38; H, 5.54; N, 27.83.

Data for *medial-anti* isomer 14b: yield 125 mg (80%) from **30c** (190 mg, 0.62 mmol); mp 292−295 °C dec; UV max (EtOH) 256 (ϵ 13 300), 206 (ϵ 17 000) nm; ^{1}H NMR (DMSO-d_6) δ 10.54 (1H, s), 7.66 (1H, s, H_8), 6.35 (2H, s), 4.51 (1H, t, J = 5.7 Hz, OH), 3.65 (2H, m, $H_{1'}$ + $H_{6''}$) and 3.55 (1H, td, ^3J = 6.5 Hz, $^2J = 13.0$ Hz, $H_{6'}$), 1.46 (3H, m, $H_{5'}$, $H_{2'}$ and $H_{2''}$), 0.96 (1H, dd, $^2J = 4.2$ Hz, $^3J_{cis} = 7.8$ Hz, $H_{4'}$), 0.71 (1H, t, ^2J = $^3J_{trans} = 4.5$ Hz, $H_{4''}$); ^{13}C NMR δ 157.22, 153.89, 152.80, 136.90, 116.93 (purine), 63.38 ($C_{6'}$), 29.03 ($C_{1'}$), 21.10, 20.28 ($C_{5'}$, $C_{3'}$), 12.8, 9.0 ($C_{2'}$, $C_{4'}$); FAB-MS *m*/*z* 249 (M, 15.2), 248 (M + H, 100.0), 215 (M − H − CH_2OH, 3.7). Anal. Calcd for $C_{11}H_{13}N_5O_2 \cdot 0.2H_2O$: C, 52.67; H, 5.38; N, 27.92. Found: C, 52.46; H, 5.56; N, 27.98.

Data for *distal* isomer 15b: yield 180 mg (85%) from **30d** (260 mg, 0.85 mmol); mp 305−310 °C dec; UV max (EtOH) 256 (ϵ 13 500), 206 (ϵ 16 100) nm; ^{1}H NMR (DMSO-d_6) δ 10.55 (1H, s, NH), 7.68 (1H, s, H_8), 6.40 (2H, s, NH_2), 4.52 (1H, t, J = 5.2 Hz, OH), 3.55 (1H, dd, $^3J_{trans} = 3.3$ Hz, $^3J_{cis} = 6.9$

Hz, $H_{1'}$), 3.39 (1H, td, ^3J = 5.7 Hz, ^2J = 11.4 Hz) and 3.28 (1H, td, J = 5.7 and 11.4 Hz, $H_{6''}$ and $H_{6'}$), 1.54 (2H, m, $H_{2'}$ and $H_{5'}$), 1.38 (1H, t, $^2J = {}^3J_{trans}$ = 4.3 Hz, $H_{2''}$), 1.11 (1H, dd, $^3J_{trans}$ = 4.2 Hz, $^3J_{cis}$ = 8.0 Hz, $H_{4'}$), 0.65 (1H, t, $^2J = {}^3J_{trans}$ = 4.3 Hz, $H_{4''}$); ^{13}C NMR δ 157.25, 153.89, 152.87, 136.84, 117.00 (purine), 63.7 ($C_{6'}$), 30.33 ($C_{1'}$), 20.40, 20.28 ($C_{5'}$, $C_{3'}$), 10.9, 9.3 ($C_{2'}$, $C_{4'}$); FAB-MS m/z 249 (M, 17.5), 248 (M + H, 100.0), 216 (M − CH_2OH, 19.1). Anal. Calcd for $C_{11}H_{13}N_5O_2 \cdot 0.2H_2O$: C, 52.67; H, 5.38; N, 27.92. Found: C, 52.25; H, 5.56; N, 27.58.

***medial-syn*-9-(5′-Hydroxymethylspiropentan-1′-yl)adenine (*R,S*)-4′-(methylphenylphosphoryl-(P→N)-L-alaninate (34).** A suspension of *medial-syn*-9-(5′-hydroxymethylspiropentan-1′-yl)adenine (**13a**; 200 mg, 0.866 mmol) in pyridine (15 mL) was sonicated for 10 min with external ice-cooling. A solution of phenyl chlorophosphoralaninate[32] in THF (0.161 M, 21.5 mL, 3.46 mmol) was then added with stirring followed by *N*-methylimidazole (6.93 mmol, 0.552 mL). The stirring was continued at room temperature for 4 h. The solvent was evaporated under reduced presure at 40 °C, and the residue was purified by chromatography on a silica gel column using CH_2Cl_2−CH_3OH (20:1 → 10:1) to give compound **34** (198 mg, 49%) as a colorless foam: HPLC (H_2O−MeCN, 4:1, broad peak,[36] retention time 7.72 min, purity 98.2%); UV max (EtOH) 261 (ϵ 13 100), 206 (ϵ 25 400) nm; ^{1}H NMR ($CDCl_3$) δ 8.22 (1H, s) and 7.84, 7.81, 7.74 and 7.72 (1H, 4s, H_8 and H_2), 7.10 (2H, m) and 7.03 (3H, m, Ph, 6.72 (2H, s, NH_2), 4.74 (1H, m, NH of Ala), 4.21 (1H, m, $H_{1'}$), 3.80 (3H, $H_{6'}$ and CH of Ala), 3.57 (3H, 4s, OCH_3), 1.73 (1H, m, $H_{5'}$), 1.50 (2H, m, $H_{2'}$ and $H_{2''}$), 1.44 (1H, m) and 0.90 (2H, m, $H_{4'}$ and $H_{4''}$), 1.20 (3H, m, CH_3); ^{13}C NMR δ 174.08 (CO), 155.83, 152.95, 152.77, 150.90, 150.68, 139.84, 129.51, 124.70, 120.65, 120.01, 119.33 (purine), 69.70, 52.27, 50.07, 30.74, 20.62, 20.22, 16.37, 11.52, 10.99; EI-MS m/z 473 (M + H, 1.0), 472 (M, 2.8), 94 (100.0); ^{31}P NMR 2.71, 2.70, 2.62, 2.58; HRMS calcd for $C_{21}H_{25}N_6O_5P$ 472.1624, found 472.1632. Anal. Calcd for $C_{21}H_{25}N_6O_5P$: C, 53.39; H, 5.33; N, 17.79. Found: C, 53.27; H, 5.55; N, 17.55.

(36) The product is a mixture of four diastereoisomers; see the ^{31}P NMR spectrum.

Adenosine Deaminase Assay.[6] Compounds **12a**−**15a** (0.6 mg, 2.6 μmol) and adenosine deaminase from calf intestine (0.45 unit) were incubated in 0.05 M Na_2HPO_4 (pH 7.5, 0.4 mL) at room temperature with magnetic stirring. Aliquots were periodically withdrawn and examined by TLC in CH_2Cl_2−MeOH (9:1). The spots of starting material and deamination product were eluted with ethanol, and the UV spectra were taken. Only compound **14a** was deaminated with $t_{1/2}$ > 120 h.

PLE Assay.[31] A magnetically stirred mixture of compound **34** (0.72 mg, 1.5 μM) and PLE (200 units) was incubated at 40 °C. TLC in CH_2Cl_2−MeOH (9:1) and 2-propanol−NH_4OH−H_2O (7:1:2) showed complete hydrolysis of **34** after 24 h.

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Supporting Information Available: Spectroscopic data for all new compounds. DEPT and (H,H) COSY spectra of **12a**, **13a**, **14a**, and **15a** and (H,C) COSY spectra of **14a** and **15a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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