77705-59-0; 17, 80271-17-6; 18, 69764-19-8; 19, 35771-74-5; 20, 80271-20-1; 21a, 115582-72-4; 21a·HCl, 119971-35-6; 22a, 115582-73-5; 22a·HCl, 119971-36-7; 23a, 119971-37-8; 23a·HCl, 119971-38-9; 1,2,3,4-tetrahydroacridin-9-ol, 56717-04-5; 3-(N,N-dimethylamino)propylamine, 109-55-7; tetrahydrothiopyran-4-one, 1072-72-6; 4-[(methylsulfonyl)amino]-2-methoxyaniline, 57165-06-7; 11-methyl-4a,10,10a,11-tetrahydro-5H-indeno[1,2-b]-quinolin-10-one, 119971-39-0; 3-methyl-1-indanone, 6072-57-5.

Synthesis and Biological Evaluation of *S*-Adenosyl-1,12-diamino-3-thio-9-azadodecane, a Multisubstrate Adduct Inhibitor of Spermine Synthase

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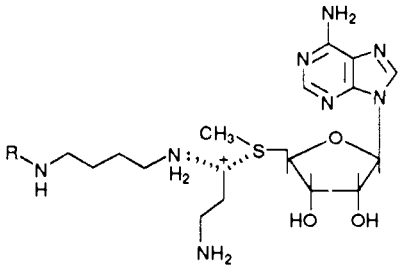
As part of a continuing search for specific inhibitors of the enzymes involved in polyamine biosynthesis, we have designed and synthesized a multisubstrate adduct inhibitor, *S*-adenosyl-1,12-diamino-3-thio-9-azadodecane (AdoDATAD), in which critical portions of the nucleophilic aminopropyl acceptor are covalently linked to critical portions of the electrophilic aminopropyl donor to form a potent and specific inhibitor of spermine synthase. In addition, the corresponding desamino analogue which was designed to lack activity against spermine synthase on the basis of substrate structure–activity data has been synthesized as a control. Preliminary biological results demonstrate that AdoDATAD is a potent and specific inhibitor of mammalian spermine synthase in vitro, while being almost completely devoid of inhibitory activity toward the closely related aminopropyltransferase spermidine synthase. The desamino analogue, as predicted, showed no inhibitory activity against either enzyme. AdoDATAD represents an important addition to the arsenal of specific enzyme inhibitors available for blockade of the polyamine biosynthetic pathway at specific sites.

The polyamines spermidine and spermine are synthesized in vivo by a pair of closely related aminopropyltransferases (APT), spermidine synthase (putrescine aminopropyltransferase, PAPT, EC 2.5.1.16) and spermine synthase (spermidine aminopropyltransferase, SAPT, EC 2.5.1.22).[1] In these reactions, nucleophilic attack by putrescine or spermidine at the electrophilic methylene carbon of decarboxylated *S*-adenosylmethionine (dcAdoMet) leads to transfer of an aminopropyl group to the incoming nucleophile to form spermidine or spermine, respectively. We have recently demonstrated that, in the case of spermidine synthase from *Escherichia coli*, transfer of the aminopropyl group occurs via a ternary complex involving direct nucleophilic attack (single displacement) rather than through an aminopropylated enzyme intermediate (double displacement).[2] Thus, the transition state for the APT-mediated transfer of an aminopropyl group should resemble the structure:



In a previous report, the synthesis and biological evaluation of *S*-adenosyl-1,8-diamino-3-thiooctane (AdoDATO) were described.[3] This compound is to date the most potent inhibitor known for spermidine synthase, while showing virtually no inhibitory activity against spermine synthase.[4] The high degree of potency and specificity exhibited by multisubstrate adduct inhibitors such as AdoDATO is, in theory, due to their resemblance to the substrate portion of the ternary complex.[5] As part of a research program involving the rational design and synthesis of APT inhibitors exhibiting a high degree of specificity, we now report the synthesis and preliminary biological evaluation of *S*-adenosyl-1,12-diamino-3-thio-9-azadodecane (AdoDATAD, **1**), the corresponding multisubstrate adduct inhibitor for the spermine synthase reaction. The synthesis and evaluation of the desamino analogue, **2**, predicted to be a very poor inhibitor of spermine synthase on the basis of the known structural requirements for substrate binding to the APT active site,[6] is also described. Preliminary studies using purified mammalian spermine synthase have shown that **1** is a potent and specific inhibitor of this enzyme and offers great potential, especially in combination with AdoDATO and other specific inhibitors of polyamine biosynthesis, for studies of this pathway in mammalian cells.[7]

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[†] Rensselaer Polytechnic Institute.
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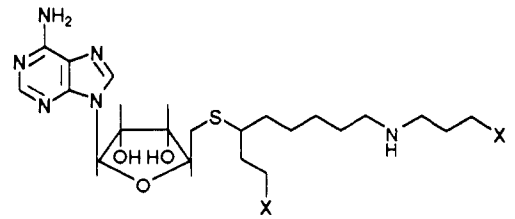

1, X = NH_2
2, X = H

Chemistry

The synthetic routes employed in the synthesis of **2** and **1** are shown in Schemes I and II, respectively. The synthesis of the bis-desamino compound, **2**, was studied first and provided a model for evaluating various synthetic strategies for both **1** and **2**. The original strategy called for the synthesis of a suitably *N*-protected *N*-propyl 6-thioacetyloctane, such as the *tert*-butyloxycarbonyl- (Boc-) protected synthon **8**, as a key intermediate. Generation of the thiolate anion of **8** in situ ($NaOCH_3$) in the presence of 5′-deoxy-5′-chloroadenosine (5′Cl-Ado) would afford the coupled precursor to the control molecule, **2**. Removal of the Boc group would then provide the desired analogue, **2**. Thus, 2-ethylcyclohexanone was treated with *m*-chloroperbenzoic acid to produce ϵ-caprylolactone (**3**),[8] which was subsequently converted to the open-chain derivative 6-chlorooctanoyl chloride (**4**) by using $ZnCl_2$ and $SOCl_2$.[9] Coupling of the acid chloride **4** to *n*-propylamine afforded the expected substituted amide **5** in good yield. The amide was then reduced with $NaBH_4$·CF_3COOH[10] to the corresponding amine **6**, isolated as the hydrochloride salt. Protection of the secondary amine was accomplished by reacting **6** with di-*tert*-butyl dicarbonate[11] to produce **7**, which was then converted to the desired 6-thioacetyl derivative **8** by using KSAc in DMSO.[12] Although coupling of the thiolate derived from **8** to chloroadenosine could be effected, the yields were generally low and byproducts complicated the isolation of a pure sample of either **2** or its *N*-Boc precursor.

An alternate approach to the desired control analogue **2** involved the synthesis of the N-protected mesylate **12**. Treatment of the lactone **3** with trimethylaluminum and *n*-propylamine[13] afforded *N*-propyl-6-hydroxyoctanamide (**9**), which was reduced with B_2H_6·THF[14] to yield the corresponding secondary amine **10**. Completion of the synthesis was investigated by using four different amine-portecting groups. The [(*p*-toluenesulfonyl)amino]-carbonyl (Tac) group, which is formed by reacting the secondary amine with *p*-toluenesulfonyl isocyanate and readily removed in refluxing 95% alcohol,[15] was found to be unsuitable for our purposes since it lacked selectivity for nitrogen and formed a derivative in which both the 6-hydroxyl and the secondary nitrogen had been acylated. In the case of the control synthon **12**, where the terminal carbons are nonfunctionalized, both the Boc and carbobenzyloxy (Cbz) protecting groups were satisfactory in the synthesis of the desired end product. Ultimately, deblocking of the Boc- and Cbz-protected precursors, **14a** and **14b**, to yield **2** proceeded in 92 and 76% yield, respectively. However, hydrogenolysis of the Cbz group took place sluggishly, requiring 3 days at 50 psi and fresh catalyst every 24 h for complete removal. The slow reaction rate was most likely due to poisoning of the catalyst by the thioether linkage in the Cbz-protected precursor, **14b**.[16] Since a deblocking methodology involving hydrogenolysis proved to be required when this chemistry was extended to the synthesis of the proposed inhibitor **1** (see below), a more labile alternative to Cbz was necessary. The *p*-nitrocarbobenzyloxy (*p*-NO_2Cbz) protecting group has been shown to be readily removable by hydrogenolysis, even in the presence of a thioether.[17] Thus, the free amine **10** was converted to the *p*-NO_2Cbz analogue **11c** and then mesylated to afford the desired synthon **12c**.

Synthesis of N^6-formyl-2′,3′-isopropylidene-5′-thioacetyladenosine (**13**) was accomplished by starting with 2′,3′-isopropylideneadenosine. Tosylation at the 5′-position followed by N^6 formylation provided the 5′-*O*-tosyladenosine species, which was then converted to the corresponding 5′-thioacetyl derivative **13** by treatment with KSAc in DMF.[12] Coupling of the thionucleoside moiety to the mesylate, **12**, was accomplished by generation of the thiolate anion derived from **13** in situ ($NaOCH_3$) in the presence of **12**. Rigorous exclusion of oxygen during this reaction is crucial, since oxidative conversion of the thiolate to the disulfide results in drastic lowering of the yield of the desired product, **14**.[2] Prior to addition of $NaOCH_3$, the reaction mixture was frozen and thawed five times with liquid nitrogen under a dynamic argon atmosphere in order to ensure complete removal of oxygen from the solution.

Deblocking of the *p*-NO_2Cbz-protected precursor, **14c**, was carried out in a Parr hydrogenator at 50 psi over a 2-day period. After the first 12 h, the IR peak at 1528 cm^{-1} had disappeared, and the benzylic peak in the NMR (5.23) shifted upfield 0.2 ppm, indicating that reduction of the aromatic NO_2 group had occurred prior to removal of the protecting group from **14c**. (This apparent reduction of the *p*-NO_2 functionality was observed even after hydrogenolysis for 2 h at ambient pressure.) A second 12-h period was then sufficient to completely remove the *p*-NO_2Cbz group, and subsequent removal of the isopropylidene group (88% formic acid) afforded crude **2** as the formate salt. Final purification could be effected by plug filtration on a silica column eluted with $CHCl_3$/CH_3OH/NH_4OH (2:2:1), which readily removed the aromatic byproducts from the desired compound, **2**.

A similar synthetic strategy was employed for the synthesis of the potential inhibitor **1** (Scheme II). Conversion of adipic acid monomethyl ester to the acid chloride, followed by Friedel–Crafts-type coupling with ethylene gas and immediate reduction of the resulting β-chloro ketone, provided the 6-hydroxy-8-chlorooctanoic acid methyl ester.[18] The ester was then cleaved (LiOH) and the free acid, **16**, was coupled to 3-chloropropylamine by using DCC/HOBt to afford the dichlorohydroxyamide **19**. Reduction of the amide to the corresponding secondary amine derivative **20** was then effected by using diborane as pre-

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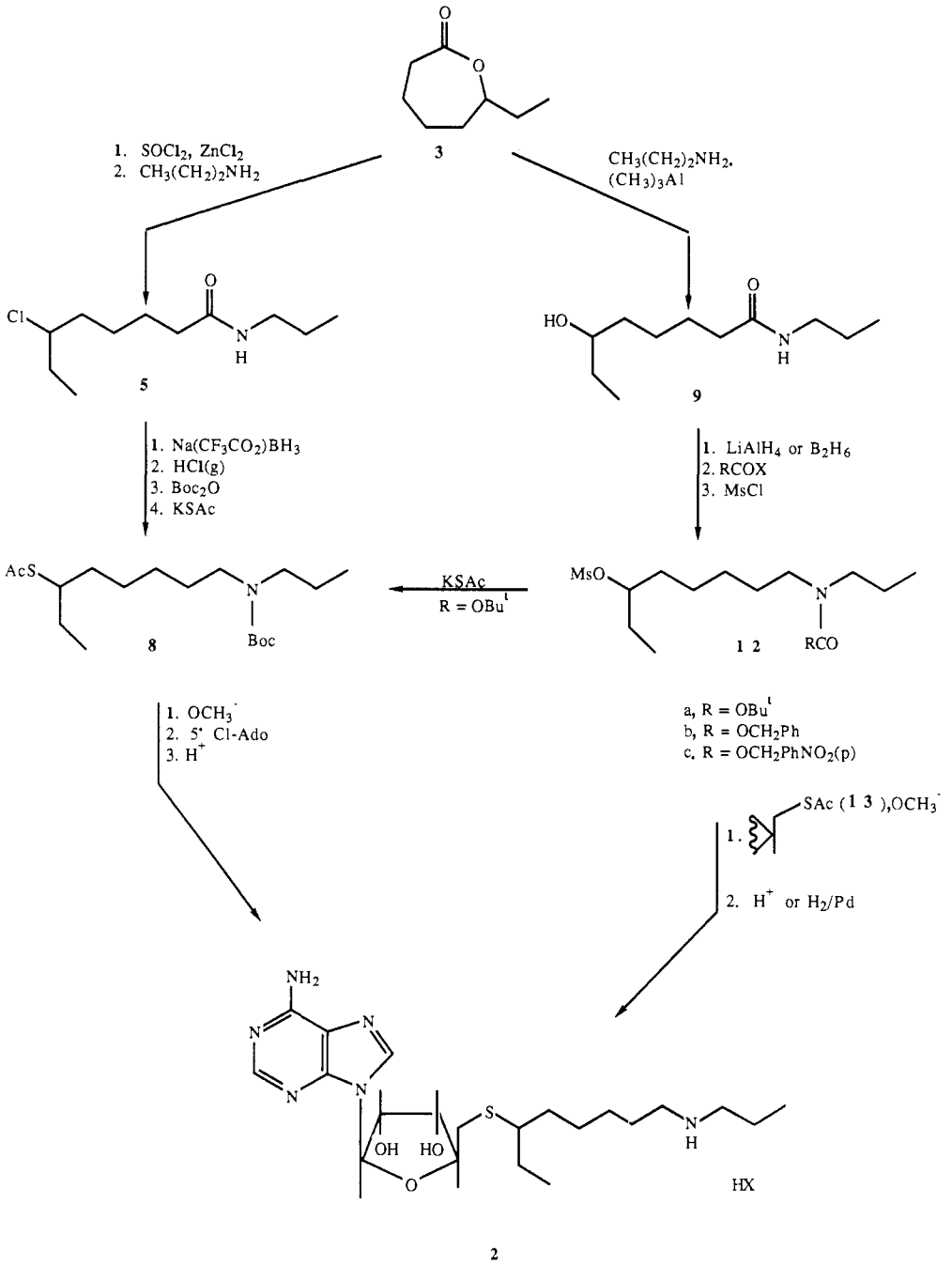
Scheme I



viously described. Me_3Al-mediated aminolysis of 7-(2-chloroethyl)oxepanone (**15**) with 3-chloropropylamine also led to **19** but in lower yields than for the route described above.

As in the case of the synthesis of the desamino analogue **2**, the choice of a nitrogen-protecting group was crucial to the outcome of the synthesis of **1**. The synthesis could not be accomplished in acceptable yield with the Boc protecting group, because the Boc-protected mesylate **23a** proved to be somewhat unstable. This instability is presumably due to facile intramolecular cyclization as previously demonstrated with other carbamates under neutral conditions.[19] The Cbz protecting group was also found to be unsuitable for the synthesis of **1**. This group could not be removed from the Cbz-protected precursor **24b**, even after several days of hydrogenolysis at 50 psi with fresh catalyst every 24 h. Conversely, as described above for the synthesis of **2**, the p-NO_2Cbz group was readily removed from precursor **14c**. Thus, protection of the secondary amine **20** with p-NO_2CbzCl afforded **21c**. Conversion of **21c** to the diazido analogue **22c** and mesylation of the alcohol function afforded the desired synthon **23c**. Coupling of the mesylate to the thiolate derived from **13** was then carried out as described above to produce the fully protected precursor **24c**. This derivative was subjected to hydrogenolysis and treated with formic acid as described to yield the crude inhibitor **1** as the formate salt. The crude preparation was then purified on silica in a manner analogous to that described for the desamino analogue.

Although the p-NO_2Cbz moiety proved to be the most suitable nitrogen-protecting group for the synthesis of **1**, some problems were encountered during the deprotection step. The byproduct of p-NO_2Cbz hydrogenolysis is p-toluidine, which, although unremovable by simple ex-

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Scheme II

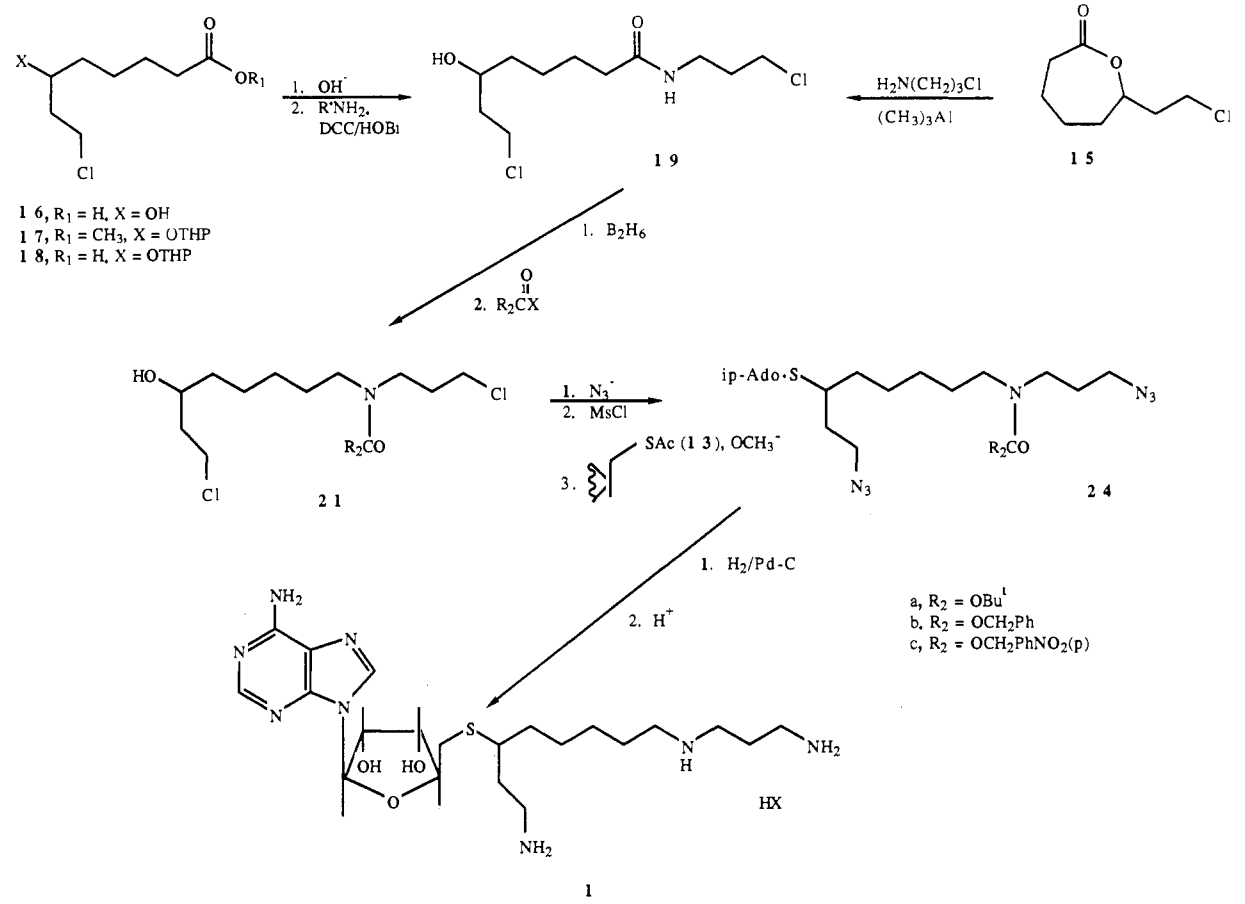
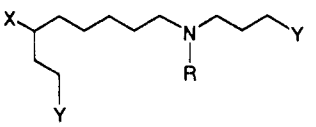


Table I. 1,3,12-Trisubstituted 9-Azododecanes: Preparation and Physicochemical Properties

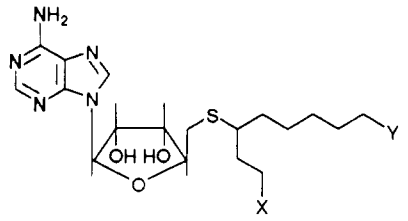


no.	X	Y	R	method	physical form	yield, %	formula	anal.[a]
11a	OH	H	Boc	A	liquid	91	$C_{16}H_{33}NO_3$	C, H, N
11b	OH	H	Cbz	B	oil	75	$C_{19}H_{31}NO_3$	HRMS[b]
11c	OH	H	*p*-NO_2Cbz	B	oil	97		nd[c]
12a	OMs	H	Boc	C	oil	76	$C_{17}H_{35}NO_5S$	C, H, N, S
12b	OMs	H	Cbz	C	oil	64		nd
12c	OMs	H	*p*-NO_2Cbz	C	oil	99	$C_{20}H_{32}N_2O_7S$	HRMS
14a	ipAdo-5′-S	H	Boc	D	amorphous solid	76	$C_{29}H_{48}N_6O_5S$	C, H, N, S
14b	ipAdo-5′-S	H	Cbz	D	oil	76	$C_{32}H_{46}N_6O_5S$	C, H, N, S
14c	ipAdo-5′-S	H	*p*-NO_2Cbz	D	oil	42	$C_{32}H_{45}N_7O_7S$	HRMS
21a	OH	Cl	Boc	A	oil	77	$C_{16}H_{31}NO_3Cl_2$	C, H, N, Cl[d]
21b	OH	Cl	Cbz	B	oil	84	$C_{19}H_{29}NO_3Cl_2$	C, H, N, Cl[e]
21c	OH	Cl	*p*-NO_2Cbz	B	oil	70		nd
22a	OH	N_3	Boc	E	oil	93	$C_{16}H_{31}N_7O_3$	C, H, N[f]
22b	OH	N_3	Cbz	E	oil	65	$C_{19}H_{29}N_7O_3$	C, H, N
22c	OH	N_3	*p*-NO_2Cbz	E	oil	88		nd
23a	OMs	N_3	Boc	C	oil	92	$C_{17}H_{33}N_7O_5S$	C, H, N, S[g]
23b	OMs	N_3	Cbz	C	oil	88	$C_{20}H_{31}N_7O_5S$	C, H, N, S
23c	OMs	N_3	*p*-NO_2Cbz	C	oil	99	$C_{20}H_{30}N_8O_7S$	HRMS
24a	ipAdo-5′-S	N_3	Boc	D	oil	28		nd
24b	ipAdo-5′-S	N_3	Cbz	D	oil	80	$C_{32}H_{44}N_{12}O_5S$	C, H, N, S[h]
24c	ipAdo-5′-S	N_3	*p*-NO_2Cbz	D	amorphous gum	43	$C_{32}H_{43}N_{13}O_7S$	HRMS

[a] Indicated analyses were within 0.4% of calculated values unless otherwise noted. ^{1}H NMR, IR, and UV spectra were consistent with assigned structures. [b] HRMS: (**11b**) calcd M^+ 321.2304, found M^+ 321.2293; (**12c**) calcd MH^+ 445.2008, found MH^+ 445.2014; (**14c**) calcd MH^+ 672.3179, found MH^+ 672.3181; (**23c**) calcd MH^+ 527.2036, found MH^+ 527.2046; (**24c**) calcd MH^+ 754.3207, found MH^+ 754.3193. [c] nd = not determined. [d] Cl: calcd, 19.90; found, 19.06. [e] C: calcd, 58.45; found, 58.98. Cl: calcd, 18.16; found, 17.06. [f] N: calcd, 26.54; found, 25.96. [g] N: calcd, 21.91; found 21.49. S: calcd, 7.16; found, 6.50. [h] N: calcd, 23.71; found, 23.17.

traction, could easily be separated from the desired product via plug filtration on silica gel. An unexpected finding was that during hydrogenolysis of **24c** to remove the *p*-NO_2Cbz moiety, the isopropylidene protecting group was simultaneously cleaved to yield **1** directly, rather than the expected isopropylidene-protected material.[20] The mechanism

Table II. Inhibition of Aminopropyltransferases by Multisubstrate Adducts[a]



compd	X	Y	I_{50}, nM spermidine synthase	I_{50}, nM spermine synthase
	H	H	$>5 \times 10^5$	$>2 \times 10^5$
AdoDATO	NH_2	NH_2	50	$>2 \times 10^5$
2	H	$NHCH_2CH_2CH_3$	$>5 \times 10^5$	$>5 \times 10^5$
1 (AdoDATAD)	NH_2	$NHCH_2CH_2CH_2NH_2$	1.3×10^4	20

[a] Assays run at [dcAdoMet] = 5 μM.

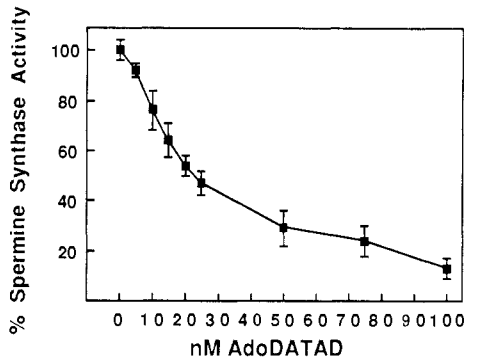


Figure 1. Concentration dependence of the inhibition of spermine synthase by AdoDATAD (1). Assays were done in the presence of 5 μM dcAdoMet.

underlying the cleavage of the acetonide and/or the glycosidic bond of **24c** during hydrogenolysis of the *p*-NO_2Cbz group remains to be elucidated.

Biological Results and Discussion

Compounds **1** and **2** were studied as inhibitors of partially purified spermine synthase isolated from rat ventral prostate.[21] Enzyme assays were carried out as previously described.[22] As shown in Table II, **1** is a potent and specific inhibitor of spermine synthase, while the bis-desamino compound **2** is essentially inactive as anticipated in our design considerations. The data obtained in a typical assay of spermine synthase inhibition by **1** are shown in Figure 1. Under identical conditions, 100 μM **2** showed <20% inhibition of spermine synthase activity. These data can be compared with previously published data on the spermidine synthase inhibitor, AdoDATO, and its bis-desamino analogue (Table II). This comparison shows that the design and synthesis of mechanism-based multisubstrate adduct inhibitors of aminopropyltransferases lead to two highly specific compounds which may be used to probe the regulation of polyamine biosynthesis in mammalian cells. Such studies, previously reported for AdoDATO[4] and currently in progress with **1** (A. E. Pegg and J. K. Coward, unpublished results), show that compounds of this type are effective in modulating intracellular polyamine biosynthesis.

Experimental Section

Melting points were determined on a Mel-temp capillary melting point apparatus and are uncorrected. Sonication was carried out with a Branson Model 12 sonicator. Hydrogenations were performed by using a Parr apparatus. All chemicals were of reagent quality and were used without further purification with the exception of several solvents noted below. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-200, a Bruker WP-100, or a Bruker WP-270-SP instrument. Chemical shifts are reported as δ values (ppm) and are referenced to tetramethylsilane. Ultraviolet (UV) spectra were obtained on a Perkin-Elmer 552 spectrophotometer. Infrared (IR) spectra were measured on a Perkin-Elmer 237-B spectrometer or a Nicolet 5DXB FT-IR spectrometer and are referenced to polystyrene. High-resolution mass spectra were determined on a VG Analytical Model 70-250-S mass spectrometer. Microanalyses were performed by Atlantic Microlab, Atlanta, GA. Silica gel 60 PF_{254} plates (E. Merck No. 5735) were used for analytical thin-layer chromatography (TLC). All preparative-scale chromatographies were performed on E. Merck silica gel 60 (No. 9385), 230–400 mesh.

All solvents used in reactions were dry distilled under nitrogen atmosphere prior to use, unless noted otherwise. Tetrahydrofuran (THF), toluene, and diethyl ether (Et_2O) were distilled over sodium benzophenone ketyl, while benzene was distilled over sodium. Carbon tetrachloride (CCl_4) was distilled over calcium chloride ($CaCl_2$), and methylene chloride (CH_2Cl_2) and chloroform ($CHCl_3$) were distilled over calcium sulfate ($CaSO_4$). Pyridine and triethylamine were distilled over potassium hydroxide. Dimethylformamide (DMF) was distilled over barium oxide or magnesium sulfate ($MgSO_4$), and ethyl formate, over phosphorus pentoxide. Methanol was distilled from magnesium and iodine under an argon atmosphere and stored over activated (280 °C) 3-Å molecular sieves. Trimethylaluminum was obtained from Alfa as a 25% solution in hexane. Lithium iodide, lithium azide, and aluminum trichloride were also purchased from Alfa. Potassium thioacetate, obtained from Kodak, was triturated with 2-butanone and vacuum-dried prior to use. 2-Ethylcyclohexanone was purchased from Wiley Organics. All other organic reagents were purchased from Aldrich.

7-Ethyloxepanone (ε-Caprylolactone) (3). *m*-Chloroperbenzoic acid (22.0 g, 0.130 mol) was added to a stirred solution of 2-ethylcyclohexanone (12.0 g, 0.090 mol) in 200 mL of CH_2Cl_2, and the reaction mixture was allowed to continue stirring at room temperature for 24 h under a $CaCl_2$ drying tube. The resulting white suspension was filtered and the filter cake washed with CH_2Cl_2. The filtrate was washed with two 100-mL portions each of 1.0 N $NaHSO_3$, 1.0 N Na_2SO_3, 1.0 N $NaHCO_3$, water, and saturated aqueous NaCl. The organic phase was dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed in vacuo to yield a pale yellow oil, which was distilled (bp 54–57 °C/0.2 mmHg) to yield **3** as a clear, colorless liquid (12 g, 93% yield): ^1H NMR ($CDCl_3$) δ 0.95 (3 H, t, CH_3), 1.70 (8 H, m, CH_2), 2.60 (2 H, t, CH_2CO), 4.20 (1 H, q, CH); IR 1725 cm^{-1} (lactone C=O). Anal. ($C_8H_{14}O_2$) C, H.

6-Chlorooctanoyl Chloride (4). To ε-caprylolactone **3** (4.80 g, 33.8 mmol) was added $ZnCl_2$ (92 mg, 0.68 mmol), and the mixture was cooled in an ice bath. Thionyl chloride (4.52 g, 38 mmol) was added dropwise with stirring, and the resulting pale yellow solution was heated at 50–60 °C overnight. The excess $SOCl_2$ was removed in vacuo, and the crude product was distilled (bp 58–62 °C/0.05 mmHg) and redistilled (bp 49–52 °C/0.035 mmHg) to yield 3.59 g (54%) of **4** as a clear colorless liquid: ^1H NMR ($CDCl_3$) 1.00 (3 H, t, CH_3), 1.65 (8 H, m, CH_2), 2.95 (2 H, t, CH_2COCl), 3.80 (1 H, m, CH); IR 1818 cm^{-1} (COCl).

***N*-Propyl-6-chlorooctanamide (5).** To a solution of **4** (2.23 g, 11.3 mmol) in 30 mL of anhydrous ether was added *n*-propylamine (1.34 g, 22.6 mmol), and the resulting suspension was allowed to stir overnight. The precipitate was removed by filtration, and the ether was removed in vacuo to afford a viscous oily product. The crude product was vacuum-distilled (bp 104–108 °C/0.025 mmHg) to yield **5** as a clear colorless liquid (1.96 g, 79%): ^1H NMR ($CDCl_3$) δ 1.00 (6 H, t, CH_3), 1.65 (10 H, m, CH_2), 2.40

(20) Subjecting a 1:1 mixture of *p*-nitrotoluene and 2′,3′-isopropylideneadenosine to identical hydrogenation conditions resulted in the formation of *p*-toluidine but did not result in the cleavage of either the acetonide or the glycosidic bond as determined by NMR and UV spectroscopy.

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(2 H, br t, CH_2CO), 3.2 (2 H, q, CH_2N), 3.85 (1 H, m, CH), 7.55 (1 H, br s, NH); IR 1650 (amide I), 1550 cm^{-1} (amide II). Anal. ($C_{11}H_{22}NOCl$) C, H, N, Cl.

N-Propyl-6-chlorooctylamine Hydrochloride (6). Sodium borohydride (4.26 g, 0.113 mol) in 30 mL of dry THF was placed in a dry 100-mL round-bottom flask, and 12.83 g (0.113 mol) of trifluoroacetic acid in 10 mL of dry THF was added via syringe over a period of 10 min. A 2.32-g portion of *N*-propyl-6-chlorooctanamide (**5**, 11 mmol) in 5 mL of dry THF was added via syringe, and the solution was stirred at room temperature for 48 h. The solvent was evaporated and the residue was dissolved in chloroform. The chloroform solution was washed with water and saturated NaCl and dried over anhydrous $MgSO_4$. This solution was filtered and the solvent removed in vacuo to yield the crude amine, which was dissolved in dry ether. Dry HCl gas was passed through the ether solution to afford 0.803 g of **6** (31%) as the hydrochloride salt (white solid, mp 194–195 °C): ^1H NMR ($CDCl_3$) δ 1.00 (6 H, t, CH_3), 1.60 (12 H, m, CH_2), 2.90 (4 H, t, CH_2N), 3.80 (1 H, m, CH), 9.10 (2 H, br s, NH_2^+). Anal. ($C_{11}H_{25}NCl_2$) C, H, N, Cl.

N-Propyl-N-(*tert*-butyloxycarbonyl)-6-chlorooctylamine (7). A 0.956-g (4.0-mmol) portion of **6** was dissolved in 10 mL of 1.0 N NaOH, followed by 1.659 g (2.0 mmol) of $NaHCO_3$, and the mixture was stirred for 10 min. A 0.862-g portion (3.8-mmol) of di-*tert*-butyl dicarbonate was then added, and the stirring was continued for 48 h at room temperature. The crude product was distilled (bp 80–95 °C/0.05 mmHg) and redistilled (bp 95–99 °C/0.05 mmHg) to give 0.625 g (52%) of pure **7**: ^1H NMR ($CDCl_3$) δ 1.00 (6 H, pair of t, CH_3), 1.50 (21 H, m CH_2 and *tert*-butyl), 3.15 (4 H, t, CH_2N), 3.80 (1 H, m, CH); IR 1690 cm^{-1} (COO). Anal. ($C_{16}H_{32}NO_2Cl$) C, H, N, Cl.

N-Propyl-N-(*tert*-butyloxycarbonyl)-6-(acetylthio)-octylamine (8). To a solution of **7** (0.712 g, 2.3 mmol) in 5 mL of dry DMSO was added 0.525 g (4.6 mmol) of potassium thioacetate, and the solution was allowed to stir overnight at room temperature followed by heating at 55–60 °C for 48 h. The DMSO was removed in vacuo and the residue was dissolved in 100 mL of $CHCl_3$. The chloroform layer was washed with 100 mL of water and 100 mL of saturated aqueous NaCl and dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent afforded a dark-colored crude product, which was distilled (bp 120–123 °C/0.05 mmHg) to yield 0.451 g of pure **8** (57% yield): ^1H NMR ($CDCl_3$) δ 0.95 (6 H, pair of t, CH_3), 1.35 (21 H, m, CH_2 and *tert*-butyl), 2.35 (3 H, s, $COCH_3$), 3.15 (5 H, m, CH_2N and CH); IR 1690 cm^{-1} (C=O). Anal. ($C_{18}H_{35}NO_3S$) C, H, N, S.

N-Propyl-6-hydroxyoctanamide (9). A 500-mL round-bottom flask (flame-dried) was equipped with an overhead mechanical stirrer, a reflux condenser fitted with a nitrogen inlet, and a rubber septum. Benzene (150 mL) and 36 mL of a 25% solution of trimethylaluminum in hexane were then added to the flask via syringe. The solution was cooled to −10 to −15 °C, and propylamine (10 mL, 0.122 mol) was slowly injected into the flask with stirring. After 20 min, the cooling bath was removed, and the solution was allowed to warm to room temperature. A solution of ε-caprylolactone (**3**) (13.0 g, 91.4 mmol) in 8 mL of benzene was added dropwise via syringe. The resulting mixture was refluxed under nitrogen for 4 days, or until analytical TLC indicated that the starting lactone was entirely consumed. The mixture was cooled to 0 °C and the reaction was quenched by the cautious addition of water. The mixture was stirred an additional 30 min to ensure complete hydrolysis, and the resulting oxides were removed by filtration and washed with ethyl acetate. The filtrate was transferred to a separatory funnel, and the aqueous layer was washed with three 150-mL portions of ethyl acetate. The organic layers were pooled, washed with four 100-mL portions of water and 100 mL of saturated aqueous NaCl, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent in vacuo afforded **9** as an amber oil. The product was crystallized from ethyl ether/pentane to yield pure **9** as a white crystalline solid (13.0 g, 70% yield): mp 54–55 °C; ^1H NMR ($CDCl_3$) δ 0.90 (6 H, t, CH_3), 1.46 (10 H, m, CH_2), 2.18 (2 H, t, CH_2C=O), 2.94 (1 H, s, OH), 3.16 (2 H, q, N–CH_2), 3.50 (1 H, m, CH), 6.44 (1 H, m, NH). Anal. ($C_{11}H_{23}NO_2$) C, H, N.

N-Propyl-6-hydroxyoctylamine (10). A 3.0-g portion of **9** (15 mmol) was placed in a 100-mL flame-dried round-bottom flask equipped with a reflux condenser and a rubber septum under a continuous stream of nitrogen. The mixture was cooled to 0 °C, and 54 mL (54 mmol) of a 1.0 N solution of B_2H_6·THF was added via syringe with stirring. The solution was refluxed for 2 h and then allowed to stir at room temperature overnight under nitrogen. The reaction was quenched by the cautious addition of 15 mL of 6.0 N HCl, and the THF was removed in vacuo. The aqueous layer was basified (pH 12) with powdered KOH and extracted with three 25-mL portions of chloroform. The organic layers were combined and dried over anhydrous $MgSO_4$. Filtration and removal of the chloroform in vacuo afforded 2.89 g of **10**, as a white solid in quantitative yield. The crude product was sufficiently pure to be used in subsequent reactions without further purification: ^1H NMR ($CDCl_3$) δ 0.89 (6 H, t, CH_3), 1.43 (13 H, br m, CH_2 and NH), 2.60 (4 H, m, CH_2–NH), 2.89 (1 H, s, OH), 3.46 (1 H, m, CH); IR 3540–3000 cm^{-1} (br, NH and OH).

N-(*tert*-Butyloxycarbonyl)-N-propyl-6-hydroxyoctylamine (11a). To a solution of *N*-propyl-6-hydroxyoctylamine (**10**) (8.5 g, 33.2 mmol) dissolved in reagent grade $CHCl_3$ (60 mL) were added $NaHCO_3$ (2.8 g, 33.2 mmol), dissolved in H_2O (30 mL), and solid NaCl (83 mmol). The resulting mixture was cooled to 0 °C, and di-*tert*-butyl dicarbonate (7.25 g, 33.2 mmol) was added, with stirring. The reaction was heated at reflux for 2 h. After the reaction was cooled to room temperature, the $CHCl_3$ was removed in vacuo and the residual aqueous solution extracted with EtOAc (3 × 150 mL). The combined organic phases were washed with 5% $KHSO_4$ (3 × 100 mL), H_2O (150 mL), saturated NaCl (150 mL), and dried ($MgSO_4$). Filtration and removal of the solvent in vacuo at the rotary evaporator gave a light yellow oil. Distillation at reduced pressure provided **11a** as a clear, colorless liquid (8.6 g, 91% yield), bp 113 °C/0.005 mmHg. Chromatography on silica (CH_3Cl/CH_3OH, 9:0.5) was carried out on a portion of the material to afford an analytical sample: ^1H NMR ($CDCl_3$) δ 3.5 (quintet, 1 H), 3.2 (t, 4 H), 2.6 (br s, 1 H), 1.8–1.2 (m, 21 H), 1.0–0.8 (sextet, 6 H); IR 3300 (–OH), 1675 cm^{-1} (C=O). Anal. ($C_{16}H_{33}NO_3$) C, H, N. Other Boc-protected amines synthesized by this procedure (method A) are listed in Table I.

N-(Carbobenzyloxy)-N-propyl-6-hydroxyoctylamine (11b). A solution of *N*-propyl-6-hydroxyoctylamine (**10**) (468 mg, 2.5 mmol), 1 M KOH (8 mL), benzyl chloroformate (461 mg, 2.7 mmol), and Et_2O (8 mL) was allowed to stir at room temperature overnight. The biphasic mixture was then transferred to a separatory funnel, the aqueous phase was extracted with Et_2O (3 × 30 mL), and the organic phases were combined and dried ($MgSO_4$). Filtration and solvent removal in vacuo at the rotary evaporator (20 °C) gave a pale yellow oil. Chromatography on silica ($CHCl_3/CH_3OH$, 15:0.5) provided **11b** as a clear, pale yellow oil (600 mg, 75% yield): ^1H NMR ($CDCl_3$) δ 7.4 (s, 5 H), 5.1 (s, 2 H), 3.4 (br s, 1 H), 3.3–3.0 (br m, 4 H), 1.7–1.3 (m, 13 H), 1.0–0.9 (m, 6 H); IR 3480 (OH), 1680 cm^{-1} (C=O). HRMS: calcd for $C_{19}H_{31}NO_3$, M^+ 321.2304; found, M^+ 321.2293. Other Cbz- and *p*-NO_2Cbz-protected amines synthesized by this procedure (method B) are listed in Table I.

N-(*tert*-Butyloxycarbonyl)-N-propyl-6-[(methylsulfonyl)oxy]octylamine (12a). To a solution of *N*-(*tert*-butyloxycarbonyl)-*N*-propyl-6-hydroxyoctylamine (**11a**) (8.6 g, 30 mmol) in CH_2Cl_2 (45 mL) at 0 °C were added triethylamine (5 mL, 36 mmol) and methanesulfonyl chloride (3 mL, 39 mmol). A white precipitate (triethylamine hydrochloride) began forming immediately, and the reaction was allowed to stir at room temperature overnight under N_2. The mixture was then transferred to a separatory funnel with the aid of CH_2Cl_2, and the organic layer was washed with 10% HCl (6 × 50 mL), H_2O (30 mL) and saturated NaCl (60 mL) and dried ($MgSO_4$). Filtration and removal of the solvent in vacuo at the rotary evaporator (20 °C) provided a light yellow oil. Chromatography on silica (C_6H_6/CH_3OH, 98:2) gave **12a** as a clear, colorless liquid (8.4 g, 76% yield): ^1H NMR ($CDCl_3$) δ 4.7 (quintet, 1 H), 3.2–3.0 (m, 4 H), 3.0 (s, 3 H), 1.8–1.2 (m, 21 H), 1.2–0.8 (sextet, 6 H); IR 1675 (cm^{-1} (C=O). Anal. ($C_{17}H_{35}NO_5S$) C, H, N, S. Other mesylates synthesized by this procedure (method C) are listed in Table I.

S-(5′-Deoxy-2′,3′-O-isopropylidene-5′-adenosyl)-N-(*tert*-butyloxycarbonyl)-N-propyl-6-thiooctylamine (14a). A 15-mL, two-neck, round-bottom flask equipped with rubber septa with gas inlet and outlet needles inserted was flame-dried and then cooled to room temperature, under argon. 5′-Deoxy-N^6-formyl-2′,3′-*O*-isopropylidene-5′-thioacetyladenosine (**13**) (1.5 g,

3.8 mmol) was quickly added to the flask, followed by a solution of *N*-(*tert*-butyloxycarbonyl)-*N*-propyl-6-[(methylsulfonyl)oxy]-octylamine (**12a**) (790 mg, 2.16 mmol) in methanol (8 mL). The resulting suspension was shielded from light and frozen with liquid nitrogen and then thawed and frozen five times in succession under a continuous stream of argon. Finally, sodium methoxide (410 mg, 7.6 mmol) was quickly added to the thawed mixture, which became clear and homogeneous within 5 min. The reaction was stirred at room temperature under argon, shielded from light for 48 h (a suspension had reformed after 14 h), and then sonicated (25 °C) for 12 h, or until analytical TLC showed that the starting materials had been consumed. The solvent was removed in vacuo (25 °C) and the residue transferred to a separatory funnel with the aid of $CHCl_3$ and saturated NaCl. The aqueous phase was extracted with $CHCl_3$ (3 × 50 mL), and the organic phases were combined, washed with saturated NaCl (50 mL), and dried ($MgSO_4$). Filtration and removal of the solvent at the rotary evaporator (20 °C) gave a pale yellow glassy foam. Chromatography on silica (EtOAc/i-PrOH, 10:1) provided **14a** as a clear, colorless, viscous oil which became a white solid upon trituration in pentane (900 mg, 76% yield): ^1H NMR ($CDCl_3$) δ 8.4 (s, 1 H, H-2), 8.0 (s, 1 H, H-8), 6.1 (d, 1 H, H-1′), 5.9 (br s, 2 H, NH_2), 5.6–5.5 (m, 1 H, H-2′), 5.1–5.0 (m, 1 H, H-3′), 4.5–4.4 (m, 1 H, H-4′), 3.2–3.0 (br m, 4 H), 2.9–2.6 (m, 2 H, H-5′), 2.6–2.4 (br m, 1 H), 1.8–1.0 (m, 21 H), 0.95–0.8 (m, 6 H). Anal. ($C_{29}H_{48}N_6O_5S$) C, H, N, S. Other protected 5′-alkylthioadenosines synthesized by this procedure (method D) are listed in Table I.

***S*-(5′-Deoxy-5′-adenosyl)-*N*-propyl-6-thiooctylamine (2).** A suspension of *S*-(5′-deoxy-2′,3′-*O*-isopropylidene-5′-adenosyl)-*N*-(carbobenzyloxy)-*N*-propyl-6-thiooctylamine (**14b**) (75 mg, 0.12 mmol) and 10% Pd/C (65 mg) in MeOH (4 mL) was hydrogenated at 55 psi, and at room temperature for 24 h. Following catalyst filtration and evaporation of the filtrate in vacuo, the resulting residue was again subjected to hydrogenation under the same conditions. The product so obtained, a colorless, slightly turbid, oily residue, was shown to be completely devoid of the Cbz protecting group by ^1H NMR. Finally, the acetonide protecting group was removed by dissolving the hydrogenation product in 91.5% formic acid (3 mL) and allowing the resulting solution to stir at room temperature for 3 h. Evaporation of the acid at reduced pressure (25 °C, 5 mmHg) provided a colorless, translucent oily residue, which was dissolved in water and washed with EtOAc. The aqueous phase was lyophilized to give **2** as a flocculent, off-white, very hygroscopic material (45 mg, 76% yield): ^1H NMR (CD_3OD) δ 8.3 (s, 1 H, H-2), 8.2 (s, 1 H, H-8), 6.0 (d, 1 H, H-1′), 4.4–4.3 (quartet, 1 H, H-3′), 4.3–4.1 (m, 1 H, H-4′), 3.3 (d, 2 H, H-5′), 3.0–2.8 (m, 4 H), 2.7–2.5 (br m, 1 H), 1.8–1.1 (m, 12 H), 1.1–0.8 (m, 6 H); HPLC (Waters system with Z-module C_{18} μBondapak column) t_R = 12.5 min (CH_3OH/H_2O, 4:1). HRMS: calcd for $C_{21}H_{36}N_6O_3S$, MH^+ 453.2648; found, 453.2657.

ε-(2-Chloroethyl)-ε-caprolactone (15). *m*-Chloroperoxybenzoic acid (17.4 g, 101 mmol) was added to a stirred solution of 2-(2-chloroethyl)cyclohexanone[23] (11.6 g, 72.3 mmol) in CH_2Cl_2 (300 mL). After the addition was completed, the reaction was allowed to continue stirring at room temperature for 5 days under a $CaCl_2$ drying tube. The resulting white suspension (*m*-chlorobenzoic acid) was then filtered and the filter cake washed with CH_2Cl_2. The filtrate was transferred to a separatory funnel and washed with 1 M $NaHSO_3$ (200 mL), saturated $NaHCO_3$ (3 × 150 mL), and saturated NaCl (2 × 150 mL) and dried ($MgSO_4$). Filtration and solvent removal at the rotary evaporator gave a light yellow oil. The material was subjected to chromatography on silica (hexanes/EtOAc, 5:3), which provided **15** as a clear, colorless liquid (10.5 g, 83% yield): ^1H NMR ($CDCl_3$) δ 4.5–4.4 (m, 1 H), 3.7–3.5 (m, 2 H), 2.7–2.5 (m, 2 H), 2.2–1.4 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 175.0 (*C*=O), 76.4 (*O*CH), 40.8 (CH_2CO), 38.7 (CH_2CH_2Cl), 34.7 (CH_2CHO), 34.4 (CH_2Cl), 27.9 (CH_2CH_2CO), 22.8 ($CH_2CH_2CH_2CO$); IR 1725 cm^{-1} (C=O). Anal. ($C_8H_{13}ClO_2$) C, H, Cl.

6-Hydroxy-8-chlorooctanoic Acid (16). Ethyl 6-hydroxy-8-chlorooctanoate[18] (12.0 g, 54 mmol) and 3.40 g of $LiOH·H_2O$ (81 mmol) were dissolved in 40 mL of 75% ethanol and allowed to stir at room temperature overnight. The solvent was then removed under reduced pressure and the residue partitioned between 75 mL of water and 75 mL of ethyl acetate. The organic layer was discarded, and the aqueous layer was acidified to pH 2 with 10% HCl and extracted with three 50-mL portions of ethyl acetate. The combined organic layers were washed with 50 mL of saturated NaCl solution and subsequently dried over anhydrous $MgSO_4$. Filtration and evaporation of the solvent yielded 10.80 g of **16** as a clear colorless oil in quantitative yield. This preparation was sufficiently pure to be used in the next reaction without further manipulation: ^1H NMR ($CDCl_3$) δ 1.06–1.97 (9 H, m, CH_2 and OH), 2.32 (2 H, t, CH_2Cl), 3.67 (2 H, t, CH_2COO), 3.82 (1 H, m, CH), 7.36 (1 H, s, COOH); IR 1700 cm^{-1} (COOH). Anal. ($C_8H_{15}ClO_3$) C, H, Cl.

6-(Tetrahydropyranyloxy)-8-chlorooctanoic Acid Methyl Ester (17). Methyl 8-chloro-6-hydroxyoctanoate[18] (3.303 g, 16 mmol), dihydropyran (1.487 g, 17.7 mmol), and 1 drop of 12 N HCl were stirred at 0 °C for 10 min and then stirred at ambient temperature overnight. A small amount of powdered KOH was added and the mixture was stirred until a pH = ca. 8 was obtained. Ether (40 mL) was added and the mixture was filtered. The ether was removed by rotary evaporation, and the residue was dried under vacuum, leaving 4.0 g (ca. 85%) of a clear liquid. The crude material distilled at 121–122 °C/0.100 mmHg to give 3.31 g (71%) of clear, colorless methyl ester **17**: ^1H NMR ($CDCl_3$) δ 1.60 (14 H, m, CH_2), 2.30 (2 H, t, CH_2COO), 3.65 (8 H, m, OCH_3, CH, CH_2, and CH_2Cl), 4.65 (1 H, s, HC(–O)–O); IR 1700 (COO), absence of 3200–3600 cm^{-1} (OH). Anal. ($C_{14}H_{25}ClO_4$) C, H, Cl.

The free acid **18** was prepared by reacting the methyl ester (2.0 g, 6.83 mmol) in 20 mL of MeOH with *powdered* KOH (0.431 g, 7.68 mmol), and the solution was stirred at ambient temperature for $1^1/_2$ days. The solvent was removed, and the residue was dissolved in 55 mL of H_2O, giving a milky white solution. The mixture was washed with $CHCl_3$ (2 × 40 mL), and the aqueous layer was acidified (pH = 2) with concentrated HCl and immediately extracted with $CHCl_3$ (2 × 40 mL). The $CHCl_3$ extracts were combined, washed with saturated NaCl (40 mL), and dried over anhydrous Na_2SO_4. The solvent was removed, yielding 1.845 g (97%) of the crude compound **18**: ^1H NMR ($CDCl_3$) δ 1.60 (14 H, m, CH_2), 2.30 (2 H, t, CH_2COO), 3.65 (5 H, m, CH_2O, CH_2Cl, and CH), 4.65 (1 H, s, HC(–O)–O), 10.55 (1 H, s, COOH); IR 1700 (COO), 2500–3700 cm^{-1} (COOH). A portion of the acid **18** was converted to its dicyclohexylamine (DCHA) salt, mp 90–91 °C, for analysis. Anal. ($C_{25}H_{46}NO_4Cl$) C, H, N, Cl.

***N*-(3-Chloropropyl)-8-chloro-6-hydroxyoctanamide (19).**
(a) From 15. A 250-mL, three-necked, round-bottom flask was equipped with an overhead mechanical stirrer, a reflux condenser fitted with an argon inlet at its top, and a rubber septum. The entire apparatus was flame-dried and then allowed to cool to room temperature under argon. 3-Chloropropylamine hydrochloride (1.8 g, 14 mmol) was added quickly to the flask and then suspended in toluene (20 mL). The mixture was cooled to –10 to –15 °C with stirring, and 4.3 mL (15 mmol) of a 25% solution of trimethylaluminum in hexane was injected slowly into the flask. After the addition was completed, the suspension had dissolved, and the resulting clear, light yellow solution was stirred for 20 min before being allowed to warm to room temperature. Finally, a solution of ε-(2-chloroethyl)-ε-caprolactone (**15**) (1.9 g, 11 mmol) in toluene (25 mL) was added dropwise, whereupon the reaction mixture became turbid and darker yellow. The reaction was heated (130 °C) for 4 days, during which time it turned orange and markedly nonhomogeneous. After the reaction was cooled to room temperature, it was quenched by the slow, cautious addition of H_2O and allowed to stir for 30 min to ensure complete hydrolysis. Once all of the solid residue had dissolved, the mixture was transferred to a separatory funnel. The aqueous phase was saturated with NaCl and extracted with $CHCl_3$ (3 × 40 mL), and the organic phases were pooled, washed with saturated NaCl (40 mL), and dried ($MgSO_4$). Filtration and solvent removal at the rotary evaporator gave a dark orange oil. Chromatography on silica (CH_3Cl/CH_3OH, 9:1) provided **19** as a light yellow oil (912 mg, 39% yield). Although all attempts at recrystallization failed, a clean, off-white solid (540 mg, 25% yield) was obtained by trituration in pentane: ^1H NMR ($CDCl_3$) δ 5.9 (br s, 1 H), 4.0–3.2 (m, 7 H), 2.6–1.0 (m, 13 H); IR 3300 (OH), 3100 (NH), 1650 (amide

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I), 1550 cm^{-1} (amide II). Anal. ($C_{11}H_{21}NO_2Cl_2$) C, H, N, Cl.

(b) From 16. A 4.0-g portion of **16** (20.4 mmol) was placed in a 200-mL round-bottom flask along with 2.24 mL (2.07 g, 20.4 mmol) of *N*-methylmorpholine, 2.80 g (20.4 mmol) of 1-*N*-hydroxybenzotriazole, 2.66 g (20.4 mmol) of 3-chloropropylamine hydrochloride, and 60 mL of previously dried DMF. The flask was cooled to 0 °C, and 4.6 g (22.4 mmol) of dicyclohexylcarbodiimide was added in one portion with stirring. The yellow solution was allowed to stir at room temperature for 4 days, at which time the DMF was evaporated (35 °C, 2 mmHg) and the residue taken up in 30 mL of ethyl acetate. The ethyl acetate layer was filtered through a 0.45-μm Zetapore filter, washed with three 25-mL portions of 10% HCl, three 25-mL portions of 1.0 M $NaHCO_3$, and 30 mL of saturated aqueous NaCl, and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent in vacuo yielded a pale yellow oil, which was purified by plug filtration (silica gel 60, 7 × 10 cm column) eluted with $CHCl_3$/CH_3OH (9:1) to yield 4.91 g (89%) of **19** (R_f = 0.41) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.44 (3 H, m, CH_2 and OH), 1.7–2.3 (8 H, m, CH_2), 3.1–3.9 (8 H, m, CH_2Cl, CH_2CO, and CH_2N), 4.10 (1 H, m, CH), 7.08 (1 H, m, NH); IR 1635 (amide I), 1535 cm^{-1} (amide II).

***N*-(3-Chloropropyl)-8-chloro-6-hydroxyoctylamine (20).** A dry 50-mL three-necked round-bottom flask equipped with a reflux condenser and rubber septa was charged with 13.3 mL (13.3 mmol) of a 1.0 M solution of diborane in THF under nitrogen, and the solution was cooled to 0 °C. A 1.0-g portion of **19** (3.7 mmol) was dissolved in 10 mL of previously dried THF and added dropwise via syringe to the diborane solution with stirring. The ice bath was removed, and the solution was allowed to stir overnight at room temperature under nitrogen. The solution was again cooled to 0 °C, and the reaction was quenched by the addition of 4 mL of 6.0 N HCl. The THF was removed in vacuo, and the aqueous layer was basified (pH 12) with powdered KOH. The aqueous layer was extracted with three 25-mL portions of chloroform, and the combined organic layers were washed over anhydrous $MgSO_4$. Filtration and removal of the chloroform in vacuo yielded 0.715 g of **20** (75.4%) as a clear oil which solidified to a white solid upon refrigeration. IR spectroscopy indicated complete reduction had occurred (disappearance of the amide bands). This preparation of **20** was used in the subsequent reactions without further purification: ^{1}H NMR ($CDCl_3$) δ 0.93 (2 H, t, CH_2), 1.43 (7 H, m, CH_2 and OH), 1.92 (4 H, pair of q, CH_2–CH–O), 2.6–2.95 (5 H, m, NH and CH_2–N), 3.60 (5 H, m, CH_2–Cl and CH); IR 3700–3020 cm^{-1} (OH and NH).

***N*-(*tert*-Butyloxycarbonyl)-*N*-(3-azidopropyl)-8-azido-6-hydroxyoctylamine (22a).** A solution of *N*-(*tert*-butyloxycarbonyl)-*N*-(3-chloropropyl)-8-chloro-6-hydroxyoctylamine (**21a**) (760 mg, 2.14 mmol), LiN_3 (421 mg, 8.6 mmol), and a catalytic quantity of LiI in DMF (2 mL) was heated at 60 °C under N_2 for 30 h. The DMF was removed at reduced pressure (25 °C, 1 mmHg) and the residue transferred to a separatory funnel with the aid of H_2O and $CHCl_3$. The aqueous phase was extracted with $CHCl_3$ (3 × 40 mL), and the organic phases were pooled, washed with saturated NaCl (50 mL), and dried ($MgSO_4$). Filtration and removal of the solvent at the rotary evaporator (25 °C) gave a yellow oil. Chromatography on silica (CH_2Cl_2/Et_2O, 10:1) provided **22a** as a clear, virtually colorless oil (1.12 g, 93% yield): ^{1}H NMR ($CDCl_3$) δ 3.8–3.6 (quintet, 1 H), 3.6–3.4 (t, 2 H), 3.4–3.0 (m, 6 H), 1.9–1.0 (m, 13 H), 1.5 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.7 (*C*=O), 79.6 ($C(CH_3)_3$), 69.0 (*C*HOH), 49.2 ($NCH_2CH_2CH_2N_3$), 48.7 ($N_3CH_2CH_2CHOH$), 47.1 (CH_2N), 44.5 ($NCH_2CH_2CH_2N_3$), 37.6 ($CHOHCH_2$), 36.1 ($N_3CH_2CH_2CHOH$), 28.5 ($C(CH_3)_3$), 28.3 ($NCH_2CH_2CH_2N_3$), 28.0 ($CHOHCH_2CH_2$), 26.4 ($CH_2CH_2CH_2N$), 25.1 (CH_2CH_2N); IR 3450 (OH), 2100 (N_3), 1680 cm^{-1} (C=O). Anal. ($C_{16}H_{31}N_7O_3$) C, H, N. Other alkyl azides synthesized by this procedure (method E) are listed in Table I.

***S*-(5′-Deoxy-5′-adenosyl)-*N*-(3-aminopropyl)-8-amino-6-thiooctylamine (1).** A 66-mg portion (0.09 mmol) of **24c** was dissolved in 3 mL of methanol and added to 50 mg of 10% Pd on carbon which had been wetted with 1 mL of ethanol. The resulting mixture was hydrogenated at 50 psi for 24 h, after which time the catalyst was filtered off (Zetapore 0.45 μm) and replaced and the mixture rehydrogenated as above. The catalyst was again replaced, the mixture hydrogenated at 50 psi overnight, and the reaction mixture filtered and concentrated in vacuo to afford 49 mg of a yellow gum. The crude product was dissolved in 1 mL of 88% formic acid and allowed to stir at room temperature for 3 h. A 5-mL portion of water was added, and the aqueous layer was washed with three 5-mL portions of ether. The water was removed by rotary evaporation (25 °C, 2 mmHg) to yield a light brown solid which was plug filtered on silica gel (2.3 × 4.2 cm), eluted with $CHCl_3$/CH_3OH/NH_4OH (2:2:1), to afford 37 mg (68.5%) of **1** (R_f = 0.36) as an off-white, fluffy hygroscopic solid: ^{1}H NMR (CD_3OD) δ 1.23–2.16 (12 H, m, CH_2), 2.82 (2 H, m, H-5′), 2.97–3.16 (9 H, m, CH_2–N, CH–S), 4.22 (1 H, m, H-4′), 4.38 (1 H, m, H-3′), 6.01 (1 H, d, H-1′), 8.24 (1 H, s, H-2), 8.34 (1 H, s, H-8); HPLC (Altex system with Whatman ODS-2 column using the ion-pairing conditions of Wagner et al.[24]) t_R = 28.9 min. HRMS: calcd for $C_{21}H_{38}N_8O_3S$, MH^+ 483.2866; found, 483.2852.

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Synthesis and Biological Properties of Purine and Pyrimidine 5′-Deoxy-5′-(dihydroxyphosphinyl)-β-D-ribofuranosyl Analogues of AMP, GMP, IMP, and CMP

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Methyl 2,3-*O*-isopropylidene-D-ribofuranoside (**1**) was converted to 1-*O*-acetyl-5-bromo-5-deoxy-2,3-di-*O*-benzoyl-D-ribofuranose (**6**) in five steps with good yield. The Arbuzov condensation of compound **6** with triethyl phosphite resulted in the synthesis of 1-*O*-acetyl-2,3-di-*O*-benzoyl-5-deoxy-5-(diethoxyphosphinyl)-D-ribofuranose (**7**). Compound **7** was used for direct glycosylation of both purine and pyrimidine bases. The glycosylation was accomplished with the dry silylated heterocyclic base in the presence of trimethylsilyl triflate. Deblocking of the glycosylation products gave exclusively the β anomer of the 5′-phosphonate analogues of 9-[5′-deoxy-5′-(dihydroxyphosphinyl)-β-D-ribofuranosyl]adenine (**13**), 9-[5′-deoxy-5′-(dihydroxyphosphinyl)-β-D-ribofuranosyl]guanosine (**16**), 9-[5′-deoxy-5′-(dihydroxyphosphinyl)-β-D-ribofuranosyl]hypoxanthine (**17**), and 9-[5′-deoxy-5′-(dihydroxyphosphinyl)-β-D-ribofuranosyl]cytosine (**15**), described here for the first time. The target compounds as well as their intermediates showed no in vitro antiviral or antitumor activity, although phosphorylation of **15** and **16** to di- and triphosphate analogues was demonstrated with use of isolated cellular enzymes.

Although a large number of natural phosphonate derivatives have been discovered in living organisms,[1] the nucleoside phosphonates have not as yet been isolated from biological sources. Analogues of nucleotides, espe-

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