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Synthesis of Complex δ-Acetylenic Amino Acids as Potential Multisubstrate Adduct Inhibitors of Methyltransferases

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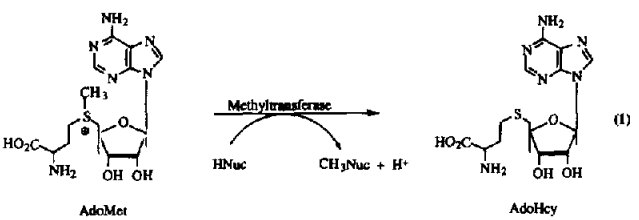
Abstract—The synthesis of two types of δ-acetylenic amino acids is described. Key intermediates were derived from terminal acetylenes via two different routes: (1) palladium-mediated, Heck-type arylation, and (2) Simmons–Smith homologation followed by reaction of the resulting propargylic organometallic with a benzoyltrimethylsilane. Further elaboration to the desired amino acids involved the coupling of carbanions derived from *N*-benzylidene glycine esters to complex alkyl halides. The synthesis of nonnucleoside δ-acetylenic amino acids was successfully effected using this chemistry. In the case of the nucleoside-containing amino acids, a potential multisubstrate adduct inhibitor of catechol *O*-methyltransferase was synthesized via this route. Unfortunately, the sensitivity to acid of 5′-deoxy, 5′-carbanucleosides prevented successful completion of the synthesis of a second nucleoside-containing δ-amino acid as a possible inhibitor of phenethanolamine *N*-methyltransferase. Copyright © 1996 Elsevier Science Ltd

Introduction

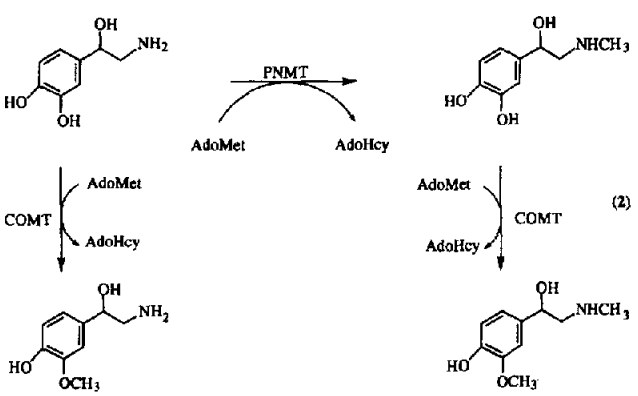
There are many enzyme-catalyzed reactions that use *S*-adenosylmethionine (AdoMet) or decarboxylated AdoMet (dcAdoMet) as substrates for the methylation [equation (1)] or aminopropylation of numerous cellular nucleophiles. Two methyltransferases, catechol *O*-methyltransferase (COMT, EC 2.1.1.6) and phenethanolamine *N*-methyltransferase [PNMT, EC 2.1.1.28, equation (2)], are involved in catecholamine metabolism. Spermidine synthase (EC 2.5.1.16), and spermine synthase (EC 2.5.1.22) are two aminopropyltransferases involved in polyamine biosynthesis. Our research on these two groups of enzymes reactions has used a wide variety of approaches, including nonenzymic model reactions,[1] steady-state enzyme kinetics,[2,3] and stereochemistry.[4,5] Earlier work on the design and synthesis of inhibitors of these enzymes involved a series of metabolically stable analogues of the inhibitory nucleoside products of each reaction.[6] In the course of subsequent research, we were successful in identifying extremely potent and specific inhibitors of three enzymes involved in the biosynthesis of the polyamines, putrescine, spermidine, and spermine. These inhibitors of ornithinine decarboxylase[7] spermidine synthase[8,9] and spermine synthase[10] were all designed based on mechanistic considerations incorporated in the so-called 'multisubstrate analogue' approach.[11] Efforts to use this same approach with the methyltransferases have not been as successful. Thus, we[12] and others[13–16] have failed to obtain potent and specific multisubstrate analogue inhibitors of a variety of AdoMet-dependent methyltransferases.

Key words: methyltransferase, multisubstrate inhibitor, acetylenic amino acid, organometallic chemistry, enzyme inhibitor.

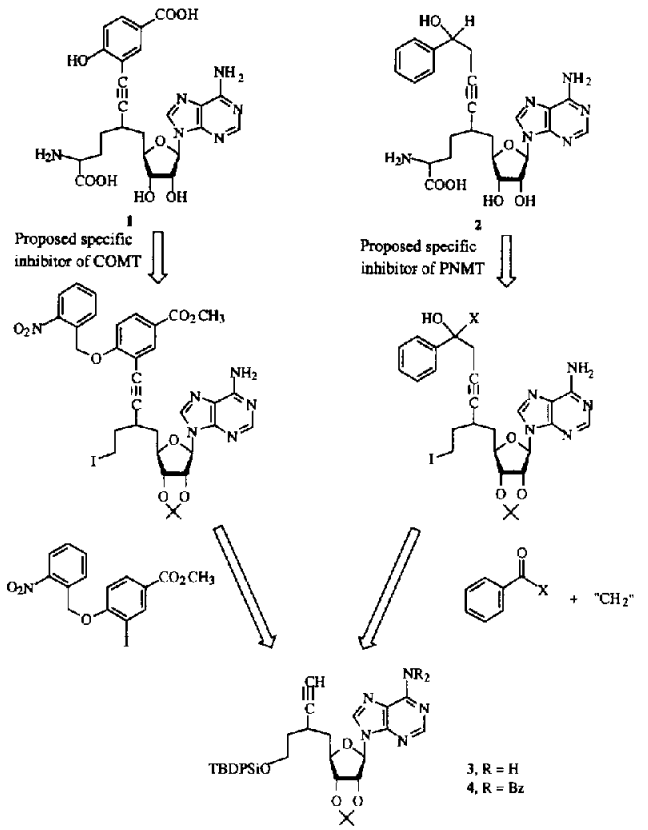


(1)

In the present work, we have focused our attention on the synthesis of **1** and **2**, two complex δ-acetylenic amino acids containing a second δ-substituent, the nucleoside 5′-deoxyadenosine, as potential multisubstrate analogue inhibitors of COMT and PNMT, respectively. By retrosynthetic analysis (Scheme 1), a proposed synthesis of these two compounds was designed. Both retrosyntheses converge on similar starting materials, **3** or **4**, each derived from the



(2)



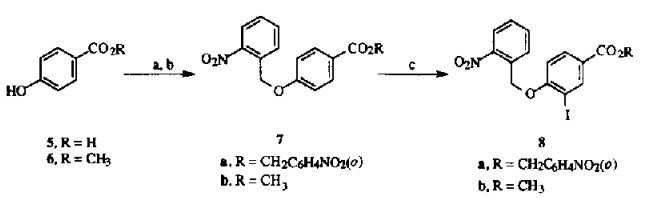
Scheme 1.

N^6-benzoyl derivative previously synthesized in our laboratory.[17]

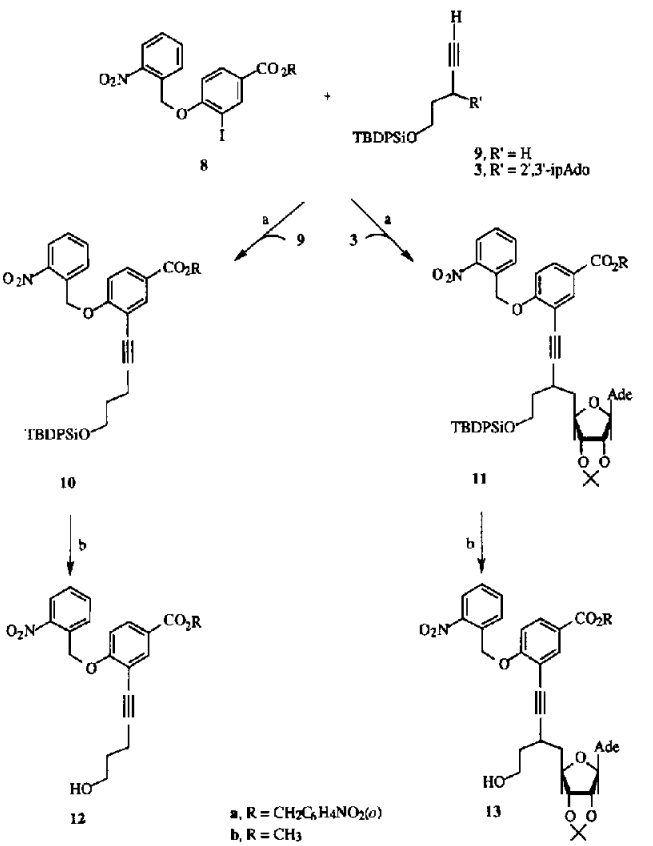
Results and Discussion

Synthesis

As shown in Scheme 1, a key step in the synthesis of acetylenic nucleosides such as **1** involves the Pd^0-mediated coupling of a terminal acetylene and an aryl iodide.[17] The synthesis of two suitably functionalized aryl iodides was readily accomplished (Scheme 2) and subsequent Heck-type coupling of the functionalized aryl iodides (**8**) with terminal acetylenes **3** or **9** proceeded in moderate to excellent yields (Scheme 3). Introduction of the amino acid moiety via alkylation of *N*-benzylidene glycinate methyl (**16**), *t*-butyl (**17**), or trimethylsilylethyl (**18**) esters with **14** or **15** led to the desired carboxyl-protected amino acids (**19** and **20**) in fair to excellent yields (Scheme 4). Attempts to remove the *t*-butyl ester of **20a** by a variety of acid-catalysed reactions (e.g., TFA, H_2SO_4/MeOH, HCl/MeOH) led to cleavage of the glycosidic bond.[18] The sensitivity of 5′-deoxy, 5′-carba analogues of adenosine to acid has been reported previously,[19–21] but stability of this class of molecules under acidic conditions has also been reported.[19,22–24] Electron-withdrawing groups at C-5′ apparently stabilize the distal glycosidic bond, presumably by destabilizing the proposed oxocarbocation intermediate or transition state of the hydrolysis reaction. In an attempt to circumvent problems due to the use of acid in the final deprotection step, the trimethylsilylethyl (TMSE) ester was explored. The alkylation of **18** by **15** provided the TMSE corresponding amino acid, **20b**, in high yield.[25] Unfortunately, subsequent deprotection steps resulted in complex mixtures of products, including **1**, which could be separated only by extensive chromatography, ultimately involving preparative HPLC. The difficulties experienced in the deprotection of *t*-butyl (**20a**) and TMSE (**20b**) ester precursors of **1** led us to synthesize the methyl ester (**20c**) and explore its hydrolysis under basic conditions. As shown in equation (3), stepwise removal of the 2′,3′-isopropylidene group (80% HCOOH), the methyl ester (1 N LiOH, MeOH/H_2O), and nitrobenzyl ether (photolysis) successfully completed the synthesis of the desired target compound, **1**.

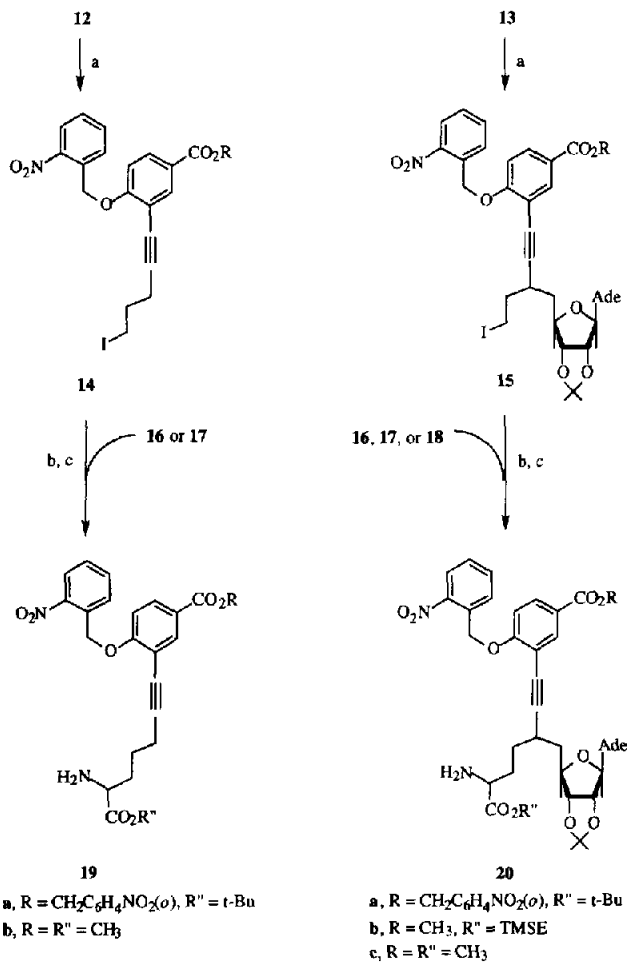


Scheme 2. Reagents: (a) $NaOCH_3$ (2.4 equiv, **5**→**7a**; 1.2 equiv, **6**→**7b**; (b) *o*-nitrobenzylbromide (2.4 equiv, **5**→**7a**; 1.2 equiv, **6**→**7b**), DMF; 66% (**7a**), 85% (**7b**); (c) AgTFA, CH_2Cl_2, I_2, 49% (**8a**), 92% (**8b**).



Scheme 3. Reagents: (a) $PdCl_2(PPh_3)_2$, Et_3N, CuI, DMF, 60% (**10a**), 85% (**10b**), 44% (**11a**), 75% (**11b**); (b) TBAF, THF/HOAc (99:1), 80% (**12a**), 65% (**12b**), 92% (**13a**), 99% (**13b**).

The synthesis of **2**, a homopropargylic and benzylic alcohol, from the acetylenic nucleoside **3** could be envisioned as resulting from the reaction of an organometallic acetylenic carbanion and a suitable electrophile such as a phenacyl halide, a styrene oxide, or a benzoyl equivalent. Several model reactions were carried out in an attempt to explore these alternatives.[25] A review of the Heck reaction[26] indicates that the use of phenacyl halides is precluded, but no details are provided. In our hands, attempted coupling of acetylene **9** with phenacyl bromide under standard Heck reaction conditions, but replacing Et_3N with the nonnucleophilic base, 1,8-bis(dimethylamino)naphthalene,[27] was unsuccessful. Similarly, attempts to use 1-alkynylstannanes[28] in this type of chemistry also failed. Success was achieved by use of Simmons–Smith chemistry to homologate the terminal acetylene and subsequent regioselective reaction of the resulting organometallic species with an acyl silane, e.g., equation (4), **9**→**21a**.[29] In the present work, we sought to extend this chemistry to the synthesis of a homopropargylic alcohol also containing the nucleoside moiety required for the synthesis of **2** from **4**; i.e., equation (4), **4**→**21b**.



Scheme 4. Reagents: (a) $(PhO)_3P^+CH_3I^-$, CH_2Cl_2, 79% (**14a**), 70% (**15a**), 84% (**15b**); (b) $PhCH{=}NCH_2CO_2R''$ (**16**, R"=CH_3; **17**, R"=*t*-Bu; **18**, R"=TMSE), LDA, THF/HMPA (9:1); (c) 80% HCO_2H, **19a**, or HOAc/CH_2Cl_2 (<1%), **20a,c**, 33% (**19a**), 68% (**20a**), 56% (**20c**).

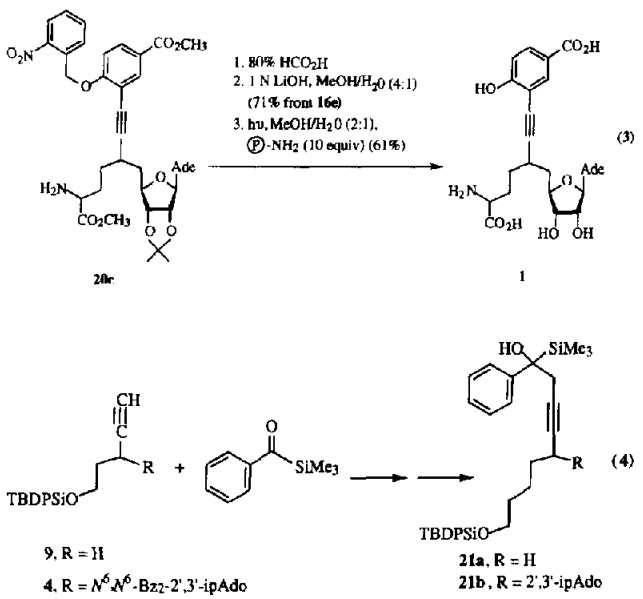
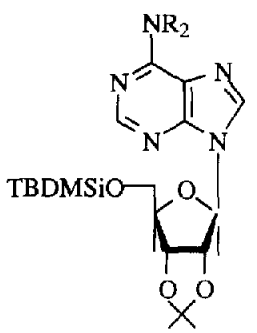


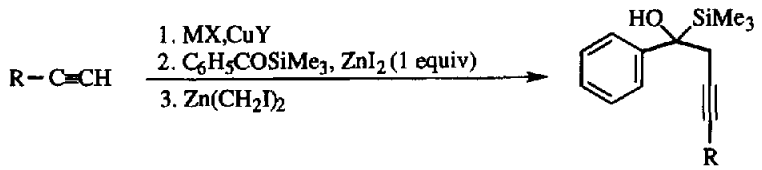
Table 1 shows the results of a series of experiments using **9** (or phenylacetylene in one case) and benzoyltrimethylsilane under a variety of reaction conditions. In most cases, the reactions were carried out in the presence of 5'-*O*(TBDMSi)-2',3'-isopropylideneadenosine derivatives, **22** and **23** in order to ascertain the stability of the nucleoside under the reaction conditions. In the cases where a direct comparison was made, the presence of the protected nucleoside had a deleterious effect on the yield of the desired C-silylated



22, R = H
23, R = Bz

homopropargylic alcohol. From these experiments, it was concluded that the coupling reaction using an acetylenic nucleoside would not be as clean as in the simpler systems [Table 1,(a)][29] and that yields of the desired nucleoside-containing homopropargylic alcohol would be modest at best. The reaction conditions that led to highest yields of the desired product and also demonstrated the stability of the model nucleoside [Table 1, (f) and (h)] were selected for use in coupling of **4** to benzoyltrimethylsilane in the presence of the Simmons–Smith reagent, $Zn(CH_2I)_2$. The reaction conditions are summarized in Table 2 and demonstrate that, while both sets of conditions led to poor yields of the desired product (**24**), the use of reaction sequence

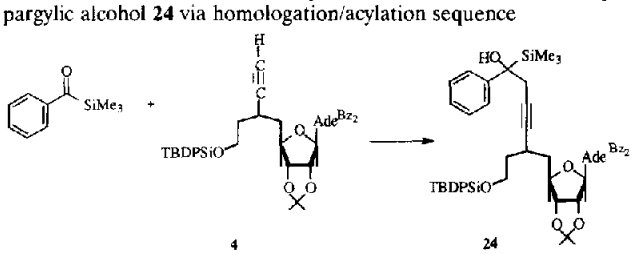
Table 1. Survey of homologation reaction conditions in the absence or presence of protected adenosine derivatives



	R	MX	CuY	$Zn(CH_2I)_2$	Add'n	Yield, %
(a)	TBDPSi—O—$(CH_2)_3$— (**9**)	*n*-BuLi (1.1 equiv) THF, −78 °C→0 °C	CuCN (1.5 equiv) LiCl (3.0 equiv) −78 °C→0 °C	3.6 equiv −10 °C	None	64[a]
(b)	TBDPSi—O—$(CH_2)_3$— (**9**)	*n*-BuLi (1.1 equiv) THF, −78 °C→0 °C	CuCN (1.5 equiv) LiCl (3.0 equiv) −78 °C→0 °C	3.6 equiv −10 °C	**23**	0[b]
(c)	TBDPSi—O—$(CH_2)_3$— (**9**)	None	CuOBut (5 equiv) DME, 0 °C	6 equiv −10 °C	None	32[c]
(d)	TBDPSi—O—$(CH_2)_3$— (**9**)	None	CuOBut (5 equiv) DME, 0 °C	6 equiv −10 °C	**22**	23[d]
(e)	C_6H_5	—[e]	CuI (1.1 equiv) THF, rt	5 equiv −10 °C	None	49[f]
(f)	TBDPSi—O—$(CH_2)_3$— (**9**)	—[e]	CuI (2.5 equiv) THF, rt	8 equiv −10 °C	**23**	39[g]
(g)	TBDPSi—O—$(CH_2)_3$— (**9**)	LDA (1.1 equiv) THF, −78 °C→0 °C	CuCN (1.5 equiv) LiCl (3.0 equiv) −78 °C→0 °C	3.3 equiv −10 °C	**22**	24[h]
(h)	TBDPSi—O—$(CH_2)_3$— (**9**)	LDA (1.5 equiv) THF, −78 °C	CuI (2.5 equiv) LiCl (5.0 equiv) −78 °C	5 equiv −10 °C	**23**	54[i]

[a]See ref 29.
[b]Nucleoside **23** unstable under reaction conditions; none recovered.
[c]Isolated 21% of desilylated product of Brook rearrangement.
[d]Isolated trace amount of desilylated product of Brook rearrangement; recovered 94% of nucleoside **22**, stable under reaction conditions.
[e]DBU (1.1 and 2.5 equiv) used in reaction (e) and (f), respectively.
[f]Use of *n*-BuLi resulted in 79% yield of desired product.[29]
[g]Nucleoside **23** stable under reaction conditions; recovered 93% of **23** and 47% of RC≡CH.
[h]Recovered 41% **22** and 52% RC≡CH.
[i]Recovered 97% **23** and 12% RC≡CH.

Table 2. Conversion of 6′-acetylenic nucleoside **4** to homopropargylic alcohol **24** via homologation/acylation sequence



4 **24**

Reaction sequence	Yield, %
1. (a) **4**, DBU (2.5 equiv), CuI (2.5 equiv), THF, rt, 8 h (b) $C_6H_5COSiMe_3$ (1.0 equiv), ZnI_2 (1 equiv), −10 °C (c) $Zn(CH_2I)_2$ (8 equiv), −10 °C	9[a]
2. (a) **4**, LDA (1.5 equiv), THF, −78 °C, 0.5 h (b) CuCN (2.5 equiv), LiCl (5.0 equiv), −78 °C (c) $C_6H_5COSiMe_3$ (1.0 equiv), ZnI_2 (1 equiv), −10 °C (d) $Zn(CH_2I)_2$ (9 equiv), −10 °C	26[b]

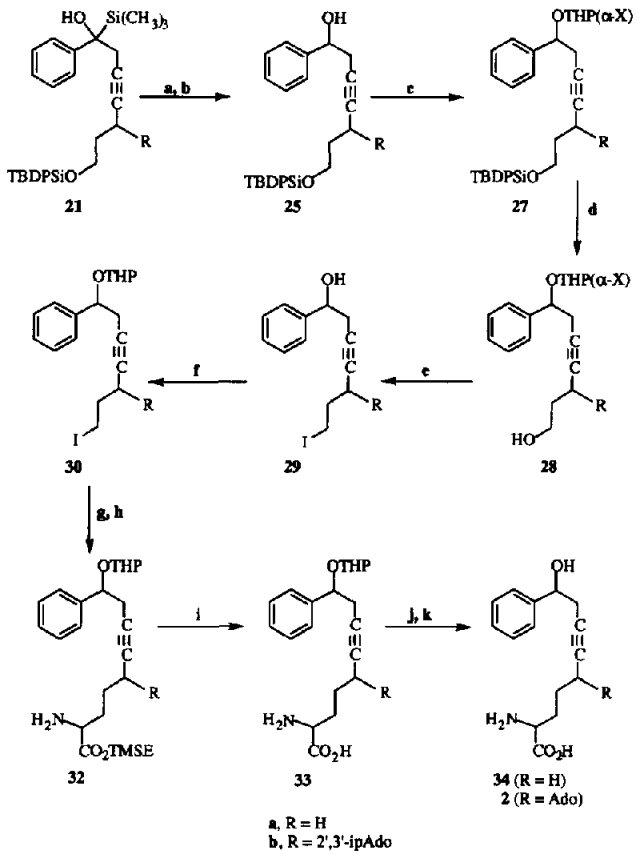
[a]Recovered 86% unreacted **4**.
[b]Recovered 19% unreacted **4**; isolated 8% debenzoylated **24**.

"2" was clearly superior to sequence "1". These results were then applied to a larger scale synthesis of **24**, in anticipation of completing the synthesis of **2**. Subsequent removal of the N^6-benzoyl protecting groups led to **21b** [equation (4)] in 81% yield.

Conversion of **21b** to **25b** via the Brook rearrangement[30] (Scheme 5) resulted in the formation of **25b** in as high as 82% yield.[31] Further elaboration of the Brook rearrangement product (**25**) is outlined in Scheme 5. In the case of the nonnucleoside series (**25a–34**), the sequence provided the desired final product (**34**), a phenyl-substituted homopropargylic alcohol incorporated within a δ-acetylenic amino acid. A deficiency of this synthetic route in the "a" series is the lability of the benzylic alcohol protecting groups, resulting in the sequential protection, removal, and reprotection of the alcohol. Nonetheless, this route was effective in establishing the feasibility of the synthesis of this type of substituted amino acid.

Similar chemistry was applied to the nucleoside homopropargylic alcohol **25b**. Conversion of **25b** to the desired amino acid ester (**32b**) was accomplished via a

truncated route that avoided the protection–deprotection sequence used in the nonnucleoside series, **25a→30a**. Use of the less acid-sensitive unsubstituted THP group allowed for the direct conversion of **28b** (X = H) to **30b**. However, final deprotection to provide the final target compound, **2**, was unsuccessful due to difficulty in removing the protecting groups at the benzylic alcohol (THP), and the ribose hydroxyl groups (isopropylidene) from the extremely acid-sensitive 5′-carbanucleoside.

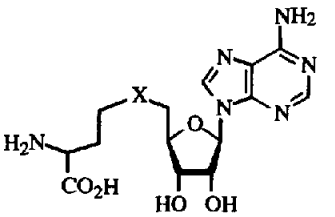


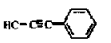
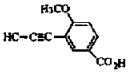
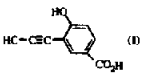
Scheme 5. Reagents: (a) KOBut, THF 0 °C; (b) HOAc in CH_2Cl_2,[29] 82% (**25b**); (c) 5,6-dihydro-4-methoxy-2*H*-pyran (X = OCH_3) or 5,6-dihydropyran (X = H), PPTS, CH_2Cl_2, 69% (**27a**), 45% (**27b**); (d) TBAF in THF, 91% (**28a**), 35% (**28b**); (e) PPh_3, imidazole, I_2 in THF, 79% (**29a**), 63% (**30b**); (f) 5,6-dihydropyran, PPTS, CH_2Cl_2, 92% (**30a**); (g) PhCH=NCH_2CO_2 TMSE (**18**), LDA, THF/HMPA −78 °C; (h) HOAc in CH_2Cl_2, 56% (**32a**), 49% (**32b**) overall yields for two steps; (i) TBAF in THF; (j) HOAc:THF:H_2O (4:2:1) 50 °C, 9 h; (k) anion exchange chromatography.

Biochemical evaluation

Compound **1** and related analogues of *S*-adenosylhomocysteine (AdoHcy) were assayed as inhibitors of COMT using 3,4-dihydroxybenzoic acid (2 mM) as the acceptor substrate[32] in the presence of 100 μM AdoMet. As shown in Table 3, neither **1** nor the OCH_3 analogue[33] were potent inhibitors of this enzyme. In addition, as previously reported,[17] both the phenylacetylene and unsubstituted 5′-carba analogue of *S*-adenosylhomocysteine show only very weak activity as COMT inhibitors. None of the target compounds were inhibitors of PNMT in assays using β-phenethanolamine and AdoMet as substrates.[34]

Table 3. COMT inhibition data



X =	Inhibitor concentration (μM)	COMT activity (% of control)
—S—	21	50
NCH_3	77	100
CH_2	83	74
	175	90
	73	93
	93	74

Assays run with saturating concentrations of AdoMet (100 μM) and 3,4-dihydroxybenzoic acid (2 mM).

It could be argued that replacement of the sulfur atom in AdoHcy by carbon in the compounds synthesized in this research leads to poor inhibitory activity because of a loss of a hydrogen-bond acceptor in the inhibitor. However, we have previously shown that the 5′-aza analogue of AdoHcy, with NH in place of S, is a very poor inhibitor of COMT and two other methyltransferases.[35] In addition, the 5′-NCH_3 analogue of AdoHcy has been synthesized[36,37] and, as shown in Table 1, it is inactive as an inhibitor of COMT at concentration three times the IC_{50} of AdoHcy. In contrast, we have recently synthesized a 5′-deoxy, 5′-carba inhibitor of spermidine synthase and it is the most potent inhibitor of that enzyme yet described (IC_{50} ca. 5 nM).[9] Thus, while it is not clear why the 5′-deoxy, 5′-carba compounds in Table 1 are such poor inhibitors of COMT and PNMT, the use of this type of nucleoside amino acid is not ruled out in all AdoMet- or dcAdoMet-dependent alkyltransferases.

Experimental

General procedures

All reagents and starting materials were from commercial sources and were used without further purification. Tetrahydrofuran was distilled from sodium/benzophenone ketyl immediately before use. CH_2Cl_2, pyridine, toluene, and triethylamine were distilled from CaH_2. All reactions involving air- or moisture-sensitive reactions were run under a blanket of dry argon. Solvent deoxygenation was performed by bubbling argon through the solvent while freezing with liquid N_2

and allowing to thaw twice. Melting points were obtained on a Thomas–Hoover Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs at Norcross, Georgia, or at the Elemental Analysis Laboratory at the University of Michigan Chemistry Department. HRMS were run on a VG-Analytical 70–250 high-resolution mass spectrometer. Other MS were obtained with a Finnigan 4500 GC/MS-EICI system. ^{1}H NMR spectra were recorded at 300 (Bruker WM-300) or 360 MHz (Bruker WM-360) using internal tetramethylsilane as a standard with organic solvents. Spectra obtained in D_2O used TSP as the internal standard. ^{13}C NMR were obtained at 90 or 75 MHz. FT-IR spectra were obtained using a Nicolet 5-DX instrument. Analytical TLC was performed using aluminum backed silica gel 60-F254 plates (EM reagents, cat. #5775). Preparative TLC was performed on 2000 micron Analtech plates. Short filtering column chromatography was performed as previously described.[38] Analytical HPLC was performed with an Altex 110A pump and a Whatman Partisil PXS ODS-2 reverse-phase column (4 × 250 mm). Preparative HPLC was performed on a Rainin HXP gradient system with Dynamax C18 columns (10 × 250 and 21.4 × 250 mm).

The syntheses described below result in several compounds containing multiple chiral centers. Spectral data obtained for these compounds confirm the presence of diastereomeric mixtures. Where clearly distinguishable, resonances due to multiple diastereomers are grouped together; e.g., ^{1}H NMR for **11a**: 1.00 and 0.95 (2s, 9H, *t*-butyl); ^{13}C NMR for **11a**: 114.58 and 114.42. Due to the structural complexity of the molecules synthesized in this research, an unambiguous numbering and lettering system[39] has been used to assign observed resonances in the NMR spectral data to specific nuclei in each new compound.

The acetylenic nucleoside **3** was obtained from the N^6-benzoyl derivative[17] by ammonolysis with NH_4OH/MeOH. Several intermediates in the synthesis of the N^6-benzoyl derivative from 2′,3′-isopropylideneadenosine were prepared by modified procedures.[25] Synthesis of the methyl (**16**)[40] and *t*-butyl (**17**)[41] esters of *N*-benzylidene glycine was carried out as previously described.

N^6,N^6-Dibenzoyl-5′-deoxy-5′-[5-(*t*-butyldiphenylsilyloxy)-1-pentyn-3-yl]-2′,3′-*O*-isopropylideneadenosine (4). To the clear solution of 500 mg (0.698 mmol) of acetylene **3** in 6 mL of pyridine (freshly distilled from NaOH) was added dropwise at 0 °C 0.196 g (1.4 mmol, 0.16 mL.) of benzoyl chloride. The reaction was allowed to reach room temperature and stirred for 7 h. The reaction was quenched by pouring onto ice and extracted with CH_2Cl_2 (2 × 50 mL). The organic layer was washed with satd $NaHCO_3$, H_2O, brine, then dried and evaporated to give 0.56 g (98%) of crude off-white foam. Column chromatography (hexanes:EtOAc, 65:35) gave 0.48 g (84%) of pure white product. ^{1}H NMR ($CDCl_3$): δ 8.64 (d, 1H, H_8), 8.15 (m, 1H, H_2), 7.86–7.26 (m, 20ArH), 6.09 (d, 1H, $H_{1'}$), 5.43 (m, 1H, $H_{2'}$), 4.87 (m, 1H, $H_{3'}$), 4.50 (m, 1H, $H_{4'}$), 3.80 (m, 2H, $H_{8'}$), 2.75 (m, 1H, $H_{6'}$), 2.03 (dd, 1H, C≡CH), 1.86–1.60 (m, 4H, $H_{5'}$ and $H_{7'}$), 1.63 and 1.38 (2s, 6H, 2 CH_3), 1.03 and 1.00 (2s, 9H, *t*-butyl); ^{13}C NMR ($CDCl_3$): 173.10, 152.34, 152.23, 152.08, 143.93, 135.54, 135.49, 134.12, 133.76, 133.70 132.88, 129.53, 129.40 128.64, 128.64, 127.56, 114.87 and 114.81, 90.52, 85.49, 84.87, 84.17, 84.13, 84.03, 83.89, 70.68 and 70.32, 61.32 and 61.14, 38.71 and 38.07, 37.73 and 37.44, 27.18, 26.81, 25.40 and 24.52, 19.12.

***o*-Nitrobenzyl 4-(*o*-nitrobenzyloxy)benzoate (7a).** Into a dry flask was added 1.0 g (7.24 mmol) of 4-hydroxybenzoic acid (**5**), 0.94 g (17.4 mmol) of sodium methoxide and 20 mL of dry MeOH. The slightly yellow solution was stirred at room temperature for 1 h when the MeOH was removed under high vacuum (3 mm Hg). To the resulting yellow solid was added 10 mL of dry DMF producing a yellow suspension. To this mixture was added 3.75 g (17.4 mmol) of *o*-nitrobenzyl bromide in 5 mL of DMF dropwise at room temperature. The reaction mixture was stirred at room temperature for 2 h when it was worked up by evaporation of the DMF under high vacuum. The resulting yellow solid was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was separated and the H_2O layer was washed again with CH_2Cl_2. The CH_2Cl_2 layers were combined and washed with H_2O, brine, dried, filtered, and evaporated giving 2.94 g (100%) crude yellow solid. Crystallization from EtOAc gave 1.96 g (66%) of pure, slightly yellow **7a**; mp 127–128 °C. ^{1}H NMR ($CDCl_3$): δ 8.25–7.05 (m, 12H, ArH), 5.76 (s, 2H, benzyl ester), 5.57 (s, 2H, benzyl ether).

Methyl 4-(*o*-nitrobenzyloxy)benzoate (7b). Into a dry flask was added 1.0 g (6.6 mmol) of methyl 4-hydroxybenzoate (**6**), 0.432 g (8 mmol) of sodium methoxide and 30 mL of dry MeOH. The slightly yellow solution was stirred at room temperature for 20 min. The MeOH was evaporated in vacuo and 10 mL of DMF was added to dissolve the white residue. The DMF was evaporated in vacuo, leaving a heterogeneous white solid/oil. To this residue was added 12 mL of dry DMF which dissolved most of the white solid. Into this flask was then added 1.86 g (8.6 mmol) of *o*-nitrobenzyl bromide in 8 mL of dry DMF at room temperature. A slight precipitate in the yellow mixture was noted. After a total of 30 min the DMF was evaporated in vacuo giving a yellow solid. This solid was dissolved in EtOAc and washed twice with water, brine, then dried and evaporated giving 2.28 g (120%) of a pale-yellow solid. This material was crystallized from MeOH giving 1.61 g (85%) of **7b**; mp 112–113 °C. ^{1}H NMR ($CDCl_3$): δ 8.21 (dd, 1H, J=8.2 and 1.3 Hz, H_7), 8.01 (d, 2H, J=8.2 Hz, H_2 and H_6), 7.86 (d, 1H, J=8.0 Hz, H_{10}), 7.70 (td, 1H, J=8.0 Hz and 1.4 Hz, H_9), 7.52 (t, 1H, J=8.2 Hz, H_8), 7.01 (d, 2H, J=8.2 Hz, H_5 and H_3), 5.56 (s, 2H, benzylic), 3.90 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 166.59, 161.71, 146.50, 133.99, 133.04, 131.70, 128.52, 128.42, 125.05, 123.49, 114.45, 66.81, 51.85.

***o*-Nitrobenzyl 3-(iodo)-4-(*o*-nitrobenzyloxy)benzoate (8a).** Into a dry flask was added 803 mg (3.6 mmol) of AgO_2CCF_3 that was flame dried with a propane torch under argon. Into a separate dry flask was placed 1.06 g (2.6 mmol) of **7a** which was then dissolved in 50 mL of dry CH_2Cl_2. This solution was added to the above flask containing dry AgO_2CCF_3. A solution of 758 mg (2.99 mmol) of I_2 in 50 mL of CH_2Cl_2 was next added dropwise over a 1 h period. The reaction was stirred at room temperature for 18 h when large amounts of white precipitate were noted. This precipitate, AgI, was filtered off and washed repeatedly with CH_2Cl_2. The filtrate was washed with H_2O, 5% $Na_2S_2O_3$ and brine, dried and evaporated to give 1.22 g (88%) crude yellow solid. This material was crystallized from EtOAc: MeOH (9:1) to give 682 mg (49%) of pure-white solid; mp 205–210 °C. ^1H NMR ($CDCl_3$): δ 8.56–6.96 (m, 11H, ArH), 5.76 (s, 2H, benzyl ester), 5.63 (s, 2H, benzyl ether); HRMS (FAB^+): calcd for $C_{21}H_{15}N_2O_7IH$ (MH^+) *m/e* 533.9924, obsd: 533.9911 (4.8% bp). Anal. calcd for $C_{21}H_{15}H_2O_7I$: C, 47.21; H, 2.83; N, 5.24. Found: C, 46.99; H, 2.85; N, 5.16%.

Methyl 3-iodo-4-(*o*-nitrobenzyloxy)benzoate (8b). To a suspension of 1.0 g (3.5 mmol) of methyl 4-(*o*-nitrobenzyloxy)benzoate (**7b**) and 1.54 g (7.0 mmol) of silver trifluoroacetate (flame dried in the flask prior to use) in 14 mL dry CH_2Cl_2, was added dropwise a solution of 1.24 g (4.87 mmol) of finely powdered I_2 in 20 mL of dry CH_2Cl_2 at room temperature under N_2. The reaction underwent an immediate decolorization and a white precipitate was noticed. TLC analysis ($CHCl_3$:hexane, 7:3) after 19 h showed only trace amounts of reactants. AgI was filtered off and the filtrate was diluted with $CHCl_3$ and washed with $NaHCO_3$, H_2O, and brine followed by treatment with activated charcoal. The organic layer was dried then evaporated to give 1.36 g (95%) crude off-white product. Column chromatography ($CHCl_3$:hexane, 7:3; R_f 0.40) gave 1.32 (92%) of the pure product **8b**. ^1H NMR ($CDCl_3$): δ 8.52 (d, 1H, $J=2.0$ Hz, H_2), 8.20 (m, 2H, H_7 and H_{10}), 8.03 (dd, 1H, $J=8.5$ Hz and 2.0 Hz, H_6), 7.77 (t, 1H, $J=7.4$ Hz, H_9), 7.54 (t, 1H, $J=7.4$ Hz, H_8), 6.94 (d, 1H, $J=8.5$ Hz, H_5), 5.62 (s, 2H, benzylic), 3.91 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 165.32, 160.00, 146.00, 141.14, 134.43, 132.62, 131.69, 128.77, 128.60, 125.10, 115.00, 111.44, 85.70, 67.95, 52.16; HRMS calcd for $C_{15}H_{12}NO_5IH$ (MH^+) *m/e* 412.9760, obsd: *m/e* 412.9751.

5-(*t*-Butyldiphenylsiloxy)pent-1-yne (9). Into a dry flask was added 0.44 g (6.5 mmol) of imidazole, 0.46 mL (0.42 g, 5 mmol) of 4-pentyn-1-ol (Farchan Laboratories) and 20 mL of dry DMF. This clear solution was stirred at 0 °C when 1.43 mL (1.51 g, 5.5 mmol) of *t*-butyldiphenylsilyl chloride was added dropwise. The resulting clear solution was stirred at room temperature for 16 h when it was checked by TLC analysis (cyclohexane:CH_3CN, 98:2; R_f 0.43). This showed the reaction was complete. The reaction was stopped by the addition of satd $NaHCO_3$. The resulting suspension was diluted with Et_2O and washed with $NaHCO_3$, water, and brine. The Et_2O layer was dried, and evaporated leaving 2.157 g of crude yellow oil. Vacuum distillation through a short-path apparatus gave 1.028 g (64% yield) clear oil (bp 125–127 °C, 0.5 mm Hg). IR (neat, cm^{-1}) 3300, 2450, 2360, 2118 (weak, C≡C), 1430, 1110, 820, 700. ^1H NMR ($CDCl_3$): δ 7.68–7.23 (m, 10H, ArH), 3.74 (t, 2H, $J=6.0$ Hz, H_e), 2.34 (td, 2H, $J=6.5$ and 2.6 Hz, H_c), 1.91 (t, 1H, $J=2.6$ Hz, HC≡), 1.77 (q, 2H, $J=6.0$ and 6.5 Hz, H_g), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR ($CDCl_3$): δ 135.59, 133.85, 129.61, 127.66, 84.16, 68.37, 62.29, 31.46, 26.88, 19.25, 14.99.

***o*-Nitrobenzyl 3-(5-*t*-butyldiphenylsiloxy-4-pentynyl-1)-4-(*o*-nitrobenzyloxy)benzoate (10a).** Into a dry flask was added 133 mg (0.41 mmol) of acetylene **9**, 11 mg (0.015 mmol) of $PdCl_2(PPh_3)_2$, 11 mg (0.058 mmol) of CuI and 5 mL of dry, degassed Et_3N. Into another flask was dissolved 180 mg (0.34 mmol) of **8a** in 15 mL of Et_3N and 30 mL CH_2Cl_2 with slight heating. The large amounts of solvents and heating were necessary to form this solution. This solution was added dropwise to the other flask. After several hours at room temperature much white precipitate was noted. The brown suspension was stirred at room temperature for 24 h when it was worked up by evaporation of the solvents, dilution with CH_2Cl_2, washing with 5% EGTA suspension, H_2O and brine, dried, and evaporated giving 275 mg (100%) crude yellow solid. This material was purified by column chromatography (hexane:EtOAc, 85:15; R_f 0.13) giving 190 mg (60%) pure white solid **10a**. ^1H NMR ($CDCl_3$): δ 8.20–6.98 (m, 21H, ArH), 5.77 (s, 2H, benzyl ester), 5.57 (s, 2H, benzyl ether), 3.82 (t, 2H, H_e), 2.68 (t, 2H, H_c), 1.93 (quint, 2H, H_d), 1.03 (s, 9H, *t*-butyl); ^{13}C NMR ($CDCl_3$): δ 165.05, 162.25, 147.67, 146.63, 135.58, 135.24, 134.17, 133.81, 133.14, 132.48, 131.15, 129.62, 128.92, 128.92, 128.78, 128.47, 128.39, 127.67, 125.11, 125.02, 122.66, 114.33, 111.78, 95.69, 75.80, 67.27, 63.24, 62.50, 31.77, 26.83, 19.23, 16.29.

Methyl 4-(*o*-nitrobenzyloxy)-3-(5-*t*-butyldiphenylsiloxy-1-pentyn-1-yl)benzoate (10b). To a dry flask containing 18 mg (0.09 mmol) of CuI, 32 mg of $PdCl_2(PPh_3)_2$ (0.045 mmol) and 400 mg (1.24 mmol) of 5-(*t*-butyldiphenylsiloxy)pent-1-yne (**9**) was added 15 mL of dry Et_3N and 8 mL of dry CH_2Cl_2 (both solvents had been deoxygenated). To the resulting dark brown suspension was added dropwise a solution of 466 mg (1.13 mmol) of aryl iodide **8b** in 10 mL of the same deoxygenated Et_3N and dried CH_2Cl_2 (1:1). Due to the limited solubility of **8b** in Et_3N, CH_2Cl_2 was added as a co-solvent. A white precipitate was noted. The resulting dark brown solution was stirred in the dark under argon for 16 h, after which a large amount of white precipitate was seen. TLC analysis (cyclohexane:CH_2Cl_2:EtOAc, 80:15:5; R_f 0.40) showed the reaction was nearly complete. The solvents were removed in vacuo and the residue was dissolved in CH_2Cl_2, washed with 2% EGTA suspension twice, once with water then with brine. It was then dried and evaporated giving 730 mg (97%) of crude brown oil.

Column chromatography (cyclohexane:CH_2Cl_2:EtOAc, 80:15:5) gave 637 mg (85% yield) of the pure product **10b**. ^1H NMR ($CDCl_3$): δ 8.18 (d, 1H, J=8.2 Hz, H_7), 8.09 (d, 1H, J=2.2 Hz, H_2), 8.03 (d, 1H, J=8.0 Hz, H_{10}), 7.95 (dd, 1H, J=8.7 and 2.2 Hz, H_6), 7.66 (m, 4H, ArH), 7.59 (t, 1H, J=8.0 Hz, H_9), 7.44 (t, 1H, J=8.2 Hz, H_8), 6.95 (d, 1H, J=8.7 Hz, H_5), 5.56 (s, 2H, benzylic), 3.90 (s, 3H, CH_3), 3.83 (t, 2H, J=6.0 Hz, H_c), 2.67 (t, 2H, J=6.5 Hz, H_c), 1.92 (q, 2H, J=6.0 Hz and 6.5 Hz, H_d), 1.05 (s, 9H, *t*-butyl); ^{13}C NMR ($CDCl_3$): δ 166.14, 161.78, 146.50, 135.53, 135.09, 134.09, 133.76, 133.25, 130.83 129.55, 128.32, 127.60, 124.93, 123.26, 114.00, 111.55, 95.29, 75.89, 67.17, 62.45, 51.97, 31.77, 26.89, 26.82, 22.87, 19.22, 16.25. HRMS: calcd for $C_{36}H_{37}NO_6SiH$ (MH^+) *m/e* 608.2468, obsd: *m/e* 608.2430 (7.3% bp).

5′-Deoxy-5′-[5-(*t*-butyldiphenylsiloxy)-1-[2-(*o*-nitrobenzyloxy)-5-[*o*-nitrobenzyloxy)carbonyl]phenyl]-1-pentyn-3-yl]2′,3′-*O*-isopropylideneadenosine (11a). This reaction was run twice using 492 and 173 mg of (1.08 mmol total) acetylenic nucleoside **3** in the same manner as described for **10a** (except for the inclusion of deoxygenated DMF as cosolvent). The reactions were stirred at room temperature for 52 h. Purification of the combined crude products was by column chromatography (hexane:EtOAc:MeOH, 60:35:5; R_f 0.18) to give 480 mg (44%) of the pure product **11a** as a slightly brown solid. ^1H NMR ($CDCl_3$): δ 8.34 and 8.33 (2s, 1H, H_8 of adenine), 8.13 (m, 4H, ArH), 8.02 (m, 1H, ArH), 7.92 (d, 1H, ArH), 7.86 (d, 1H, H_2 of adenine), 7.65–7.20 (m, 14H, ArH), 6.98 (d, 1H, ArH), 6.02 (d, 1H, $H_{1'}$), 5.77 (s, 2H, benzyl ester), 5.67 (d, 2H, NH_2), 5.52 (br s, benzyl ether and $H_{2'}$), 4.95 (m, 1H, $H_{3'}$), 4.62 (m, 1H, $H_{4'}$), 3.83 (m, 2H, $H_{8'}$), 3.07 (m, 1H, $H_{6'}$), 2.07–1.75 (m, 4H, $H_{5'}$ and $H_{7'}$), 1.57, 1.52 and 1.36, 1.34 [4s, 6H, $C(CH_3)_2$], 1.00 and 0.95 (2s, 9H, *t*-butyl); ^{13}C NMR ($CDCl_3$): δ 164.96, 162.29, 162.22, 155.62, 153.09, 149.47, 146.62, 140.01 and 139.86, 135.49, 135.30, 135.26, 134.09, 133.80 and 133.75, 133.04, 132.38, 131.23, 129.50, 128.96, 128.74, 128.31, 127.55 125.03, 124.88, 122.69, 120.3, 114.58 and 114.42, 114.11, 111.78, 97.51 and 97.21, 90.73 and 90.48, 65.20, 84.99, 84.63, 84.53, 84.05, 83.87, 77.94 and 77.55, 67.24, 63.22, 61.51, 39.13 and 38.45, 38.21 and 37.69, 27.20 and 27.15, 25.44 and 25.38, 26.84 and 26.74, 26.47 and 25.81, 19.09. HRMS (FAB^+): calcd for $C_{55}H_{55}N_7O_{11}SiH$ (MH^+) *m/e* 1018.3807, obsd: 1018.3806 (1.3% bp). Anal. calcd for $C_{55}H_{55}N_7O_{11}Si \cdot 2H_2O$: C, 62.60; H, 5.64; N, 9.30. Found: C, 62.53; H, 5.28; N, 9.24%.

5′-Deoxy-5′-[5-(*t*-butyldiphenylsiloxy)-1-[2-(*o*-nitrobenzyloxy)-5-[(methoxy)carbonyl]phenyl]-1-pentyn-3-yl]-2′,3′-*O*-isopropylideneadenosine (11b). Into a dry flask containing 710 mg (1.16 mmol) of the acetylenic nucleoside **3**, 18 mg (0.097 mmol) of CuI and 34 mg (0.048 mmol) of $PdCl_2(PPh_3)_2$ was added 9 mL of fully deoxygenated Et_3N. At first this solution had an orange color, but on stirring for 5 min it took on a dark brown color. To a 35 mL flask containing 500 mg (1.21 mmol) of the aryl iodide **8b** was added 6 mL of the same deoxygenated Et_3N and 8 mL of deoxygenated CH_2Cl_2. The resulting solution was added dropwise to the above flask and after 1.5 h a white precipitate formed. TLC analysis (100% EtOAc) after 20 h showed that the reaction was complete. The solvents were removed in vacuo and the residue was dissolved in CH_2Cl_2 and washed twice with 2% EGTA suspension, once with H_2O, and once with brine. Drying followed by evaporation gave 1.20 g (115%) off-white crude product. Silica gel chromatography (100% EtOAc; R_f 0.18) gave 784 mg (75% yield) of pure-white compound **11b**. IR (KBr, cm^{-1}): 3400 (broad, NH_2), 1715. ^1H NMR ($CDCl_3$): δ 8.33 (d, 1H, H_8 (adenine ring)), 8.10 (d, 1H, H_7), 8.07 (dd, 1H, H_{10}), 7.98–7.86 (m, 3H, H_6, H_2 (adenine ring), ArH), 7.60 (m, 4H, ArH and H_9), 7.47 (t, 1H, H_8), 7.37–7.21 (m, 6H, ArH), 6.94 (d, 1H, H_5), 6.02 (s, 1H, $H_{1'}$), 5.60 (bs, 2H, exchg with D_2O, NH_2), 5.51 (m, 3H, $H_{2'}$ and benzylic), 4.95 (m, 1H, $H_{3'}$), 4.64 (m, 1H, $H_{4'}$), 3.91 (s, 3H, CH_3), 3.86–3.76 (m, 2H, $H_{8'}$), 3.08 (m, 1H, $H_{6'}$), 2.05–1.94 (m, 2H, $H_{5'}$), 1.86–1.74 (m, 2H, $H_{7'}$), 1.55 and 1.35 [2s, 6H, $C(CH_3)_2$], 1.01 and 0.93 [2s, 9H, $C(CH_3)_3$]; ^{13}C NMR ($CDCl_3$): δ 165.94, 161.72, 155.72, 152.95, 146.41, 141.10, 135.40, 135.36, 135.04, 133.95 133.03, 130.90, 129.44, 128.15, 127.45, 124.71, 123.17, 114.42, 114.26, 113.65, 111.48, 97.02 and 96.73, 90.59 and 90.36, 85.13, 84.88, 84.51, 84.78, 83.94, 83.76, 77.62 and 77.31, 67.03, 61.37, 51.81, 39.03 and 38.33, 38.10 and 37.58, 27.07, 27.02, 26.72, 26.61, 26.35, 25.65, 25.32, 25.26, 19.06 and 18.95. HRMS (FAB^+): calcd for $C_{49}H_{52}N_6O_9SiH$ (MH^+) *m/e* 897.3643, obsd: 897.3613 (100% bp). Anal. calcd for $C_{49}H_{52}N_6O_9Si$: C, 65.61; N, 5.84; H, 9.37. Found: C, 65.24; N, 5.85; H, 9.29%.

5-Hydroxy-1-[2-(*o*-nitrobenzyloxy)-5-[(*o*-nitrobenzyloxy)-carbonyl]phenyl]-1-pentyne (12a). Into a dry flask was dissolved 166 mg (0.23 mmol) of **11a** in 3 mL dry THF containing 2 drops of HOAc. To this light-brown colored solution was added 0.57 mL (0.57 mmol) of 1 M TBAF in THF dropwise at room temperature. This brown solution was stirred at room temperature for 5 h when it was diluted with CH_2Cl_2 and H_2O. The organic layer was separated and washed with brine, dried, and evaporated giving 160 mg (>100%) of off-white solid. This material was purified by column chromatography (hexane:$CHCl_3$:MeOH, 6:3:1; R_f 0.26) to give 90 mg (80%) of **12a** as a white grainy solid. ^1H NMR ($CDCl_3$): δ 8.22–6.97 (m, 11H, ArH), 5.76 (s, 2H, benzyl ester), 5.62 (s, 2H, benzyl ether), 3.84 (t, 2H, H_e), 2.65 (t, 2H, H_c), 1.92 (quint, 2H, H_d); ^{13}C NMR ($CDCl_3$): δ 164.92, 162.22, 147.82, 146.91, 135.36, 135.18, 134.77, 134.02, 133.60, 132.87, 132.24, 131.12, 129.53, 129.07, 128.74, 128.57, 127.63, 124.98, 122.78, 114.17, 111.91, 95.16, 76.14, 67.45, 63.20, 61.70, 31.38, 16.29.

5-Hydroxy-1-[2-(*o*-nitrobenzyloxy)-5-[(methoxy)carbonyl]-phenyl]-1-pentyne (12b). To a brown-colored solution of 595 mg (0.98 mmol) of **11b** in 12 mL of dry THF and 0.12 mL of glacial acetic acid was added dropwise 2.5 mL of 1 M TBAF in THF (2.5 mmol) under argon at room temperature. The reaction was followed by TLC ($CHCl_3$:EtOAc, 8:2; R_f 0.33) and after 20 h it was complete. The reaction solution was diluted with

CH_2Cl_2, washed with H_2O, satd $NaHCO_3$, and satd NaCl. The organic layer was dried followed by evaporation to give 537 mg (>100%) of a light-brown solid. Silica gel chromatography ($CHCl_3$:EtOAc, 8:2) gave 234 mg (65% yield) of **12b**. IR (KBr, cm^{-1}): 3400 (broad, —OH), 1700 (C=O), 1320, 1140, 1030, 730. ^1H NMR ($CDCl_3$): δ 8.20 (d, 1H, H_7), 8.09 (s, 1H, H_2), 8.03 (m, 1H, H_{10}), 7.93 (d, 1H, H_6), 7.72 (t, 1H, H_9), 7.51 (t, 1H, H_8), 6.94 (d, 1H, H_5), 5.58 (s, 2H, benzylic), 3.88 (s, 3H, CH_3), 3.84 (t, 2H, H_c), 2.64 (t, 2H, H_c), 1.91 (quint, 2H, H_d), 1.80 (bs, 1H, exchange with D_2O, —OH); ^{13}C NMR ($CDCl_3$): δ 165.99, 161.58, 146.40, 134.80, 134.01, 132.89, 130.74, 128.32, 124.83, 122.98, 113.56, 111.37, 94.81, 75.98, 67.07, 61.38, 51.86, 31.29, 16.09. HRMS (CI with methane) calcd for $C_{20}H_{19}NO_6H$ (MH^+) *m/e* 370.1291, obsd: *m/e* 370.1300 (100% bp). Anal. calcd for $C_{20}H_{19}NO_6$: C, 65.03: N, 3.79: H, 5.18. Found: C, 64.60: N, 3.69: H, 5.10%.

5′-Deoxy-5′-[5-hydroxy-1-[2-(*o*-nitrobenzyloxy)-5-[(*o*-nitrobenzyloxy)carbonyl]phenyl]-1-pentyn-3-yl]2′,3′-*O*-isopropylideneadenosine (13a). The reaction was run at room temperature for 21 h with 470 mg (0.46 mmol) of **11a** in the same manner as described for the synthesis of **12a**. Column chromatography (EtOAc:MeOH, 93:7; R_f 0.26) gave 336 mg (92%) of compound **13a** as an off-white solid. IR (KBr pellet, cm^{-1}): 3360 (broad, —OH), 2230 (weak, —C≡C—), 1719, 1646, 1600, 1576, 1527, 1421, 1374, 1216, 1004. ^1H NMR ($CDCl_3$): δ 8.30 (d, 1H, H_8 of adenine), 8.19–8.10 (m, 3H, H_7, H_{11} and H_2), 8.00 (m, 2H, H_{14} and H_{10}), 7.93 (d, 1H, H_6), 7.89 and 7.80 (s, 1H, H_2 of adenine), 7.69–7.33 (m, 4H, H_9, H_{13}, H_{12} and H_8), 6.98 (dd, 1H, H_5), 6.11 and 5.99 (s, 2H, NH_2), 6.02 and 5.90 (d, 1H, $H_{1'}$), 5.76 (d, 2H, benzyl ester), 5.58 (d, 2H, benzyl ether), 5.53 (m, 1H, $H_{2'}$), 5.00 and 4.90 (m, 1H, $H_{3'}$), 4.72 and 4.56 (m, 1H, $H_{4'}$), 3.70 (m, 2H, $H_{8'}$), 3.02 (m, 1H, $H_{6'}$), 2.5 (br m, 1H, exchange w/D_2O, —OH), 2.24–1.71 (m, 4H, $H_{5'}$ and $H_{7'}$), 1.56 and 1.51, 1.36 and 1.35 [s, 6H, $(CH_3)_2$—C); ^{13}C NMR ($CDCl_3$): δ 164.82, 162.10, 162.03, 155.63, 153.00 and 152.91, 149.15 and 148.90, 147.54, 146.51 and 146.43, 140.11 and 139.70, 135.18, 134.09, 133.66, 132.75 and 132.71, 132.23, 131.26, 128.81, 128.68, 128.42, 128.31, 128.22, 128.14, 124.96, 124.81, 122.51, 120.02 and 119.91, 114.45 and 114.10, 113.60, 111.61, 97.08 and 96.82, 91.36 and 90.33, 84.84, 84.66, 84.22, 83.86, 83.27, 78.06 and 77.79, 67.25 and 67.20, 63.19, 60.25 and 60.20, 38.77 and 38.35, 38.18 and 37.42, 27.05 and 27.00, 26.27 and 25.94, 25.32 and 25.13. A sample sent for HRMS and elemental analysis was crystallized from MeOH. HRMS (FAB^+): calcd for $C_{39}H_{37}N_7O_{11}H$ (MH^+) 780.2629, obsd: 780.2634 (29% bp). Anal. calcd for $C_{39}H_{37}N_7O_{11}\cdot 0.5H_2O$: C, 59.39; H, 4.86; N, 12.43. Found: C, 59.44; H, 4.73; N, 12.46%.

5′-Deoxy-5′-[5-hydroxy-1-[2-(*o*-nitrobenzyloxy)-5-[(methoxy)carbonyl]phenyl]-1-pentyn-3-yl]2′,3′-*O*-isopropylideneadenosine (13b). This reaction was run with 985 mg (1.10 mmol) of **12b** in the same fashion as described for the synthesis of **12a**. After 17 h TLC analysis (EtOAc:MeOH, 95:5; R_f 0.24) showed the reaction was complete. Work up in an analogous fashion gave 1.11 g (>100%) crude brown foam. Silica gel chromatography (EtOAc:MeOH, 95:5) gave 716 mg (99% yield) off-white **13b**. IR (KBr, cm^{-1}): 3400, 1710, 1630, 1216, 1080, 728. ^1H NMR ($CDCl_3$): δ 8.31 (d, 1H, H_8, adenine ring), 8.16 and 8.11 (two sets of dd, 1H, H_7), 8.10 and 8.09 (two sets of d, 1H, H_2), 7.95 (m, 2H, H_{10} and H_6), 7.89 and 7.79 (2s, 1H, H_2, adenine ring), 7.66 and 7.54 (two sets of t, 1H, H_9), 7.46 and 7.33 (two sets of t, 1H, H_8), 6.95 (two sets of d, 1H, H_5), 6.05 (bs, 2H, NH_2), 6.02 and 5.89 (two sets of d, 1H, $H_{1'}$), 5.54 (m, 3H, benzylic and $H_{2'}$), 5.00 and 4.91 (2m, 1H, $H_{3'}$), 4.71 and 4.57 (2m, 1H, $H_{4'}$), 3.90 (s, 3H, CH_3), 3.89–3.70 (m, 2H, $H_{8'}$), 3.00 (m, 1H, $H_{6'}$), 2.45 (bs, 1H, exchange w/D_2O, —OH), 2.21–1.70 (m, 4H, $H_{7'}$ and $H_{5'}$), 1.58, 1.53 and 1.37 [m, 6H, $C(CH_3)_2$]; ^{13}C NMR ($CDCl_3$): δ 165.70, 161.44, 155.63, 152.66, 148.57, 145.99, 139.82, 134.75, 133.86, 132.69, 130.83, 128.01, 124.59, 122.80, 119.57, 114.17, 113.81, 113.02, 111.18, 96.60 and 96.37, 91.09 and 90.05, 84.71, 84.45, 83.99, 83.66, 83.10, 77.98 and 77.71, 66.83, 59.48, 51.71, 38.62 and 38.07, 37.33, 26.78, 26.05, 25.67, 25.11, 24.93. HRMS (FAB^+): calcd for $C_{33}H_{34}N_6O_9H$ (MH^+): 659.2466, obsd: 659.2441 (100% bp).

5-Iodo-1-[2-(*o*-nitrobenzyloxy)-5-[(*o*-nitrobenzyloxy)carbonyl]phenyl]-1-pentyne (14a). Into a dry flask was weighed 177 mg (0.39 mmol) of $(PhO)_3P^+CH_3I^-$ in a glove bag under N_2. To this flask at −78 °C was added a solution of 120 mg (0.245 mmol) of **12a** in 10 mL of dry CH_2Cl_2. This produced a yellow suspension that was stirred at −78 °C for 0.5 h; upon warming to room temperature, the mixture turned to an orange colored solution. TLC (hexane:$CHCl_3$:MeOH, 6:3:1) showed starting material left after 5 h at room temperature. Another 75 mg (0.166 mmol) of $(PhO)_3P^+CH_3I^-$ was added at room temperature. TLC after 20 h showed no remaining starting material. The reaction was diluted with $CHCl_3$ and washed with 5% NaS_2O_3, H_2O and brine, dried, and evaporated giving 260 mg (>100%) crude off-white oil. Column chromatography (benzene:$CHCl_3$, 7:3; R_f 0.22) gave 116 mg (79%) pure **14a** as a white solid. ^1H NMR ($CDCl_3$): δ 8.23–6.99 (m, 11H, ArH), 5.76 (s, 2H, benzyl ester), 5.62 (s, 2H, benzyl ether), 3.39 (t, 2H, H_c), 2.67 (t, 2H, H_c), 2.14 (quint, 2H, H_d); ^{13}C NMR ($CDCl_3$): δ 164.91, 162.21, 147.69, 146.79, 135.28, 134.25, 133.73, 132.89, 132.32, 131.33, 128.98, 128.78, 128.62, 128.47, 125.10, 125.07, 122.70, 113.86, 111.81, 93.46, 76.73, 67.39, 63.27, 32.17, 20.73, 5.16. HRMS (EI): calcd for $C_{26}H_{21}N_2O_7I$ 600.0394; obsd: 600.0383 (23% bp).

5′-Deoxy-5′-[5-iodo-1-[2-(*o*-nitrobenzyloxy)-5-[(*o*-nitrobenzyloxy)carbonyl]phenyl]-1-pentyn-3-yl]2′,3′-*O*-isopropylideneadenosine (15a). This compound was obtained in the same way as described for the synthesis of **14a**. From 322 mg (0.41 mmol) of **13a** was obtained 259 mg (70%) of **15a** after two column chromatography steps (CH_2Cl_2:MeOH, 97:3; R_f 0.20). An aromatic impurity in this compound was observed by TLC, ^1H and ^{13}C NMR. IR (KBr pellet, cm^{-1}): 3420, 1718, 1679, 1599, 1526, 1374, 1342, 1297, 1216, 1098,

1027, 730. ^{1}H NMR ($CDCl_3$): δ 8.35 and 8.34 (2s, 1H, H_8 of adenine), 8.22–8.13 (m, 3H, H_7, H_{11} and H_2), 8.04–7.99 (m, 2H, H_{10} and H_6), 7.90 (d, 1H, H_2 of adenine), 7.75–7.64 (m, 3H, H_{14}, H_9 and H_{13}), 7.53–7.48 (m, 2H, H_{12} and H_8), 7.22 (m, < 1H, impurity), 7.00 (d, 1H, H_5), 6.87 (m, 1H, impurity), 6.04 (d, 1H, $H_{1'}$), 5.86 (s, 2H, NH_2), 5.77 (s, 2H, benzyl ester), 5.60 (d, 2H, benzyl ether), 5.54 (dd, 1H, $H_{2'}$), 5.00 (m, 1H, $H_{3'}$), 4.60 (m, 1H, $H_{4'}$), 3.29 (m, 2H, $H_{8'}$), 2.95 (m, 1H, $H_{6'}$), 2.10–1.90 (m, 4H, $H_{5'}$ and $H_{7'}$), 1.56 and 1.53, 1.37 and 1.35 [s, 6H, $(C\underline{H}_3)_2$—C]; ^{13}C NMR ($CDCl_3$): δ 164.81, 162.14, 155.62, 152.92, 149.15, 147.54, 146.58, 140.142 and 139.87, 135.19, 134.26, 133.69, 132.75 and 132.22, 131.42, 129.51, 128.82, 128.69, 128.49, 128.30, 124.99, 122.52, 120.22 and 120.10, 120.00, 115.48, 114.52 and 114.28, 113.42, 111.66, 95.48 and 95.29, 90.89 and 90.41, 84.97, 84.75, 84.52, 84.27, 83.86, 83.58, 78.60 and 78.39, 67.25, 63.21, 38.89, 38.20 and 37.62, 30.86 and 30.42, 27.05 and 26.98, 25.32 and 25.22, 3.41 and 2.97. HRMS (FAB$^+$): calcd for $C_{39}H_{36}N_7O_{10}IH$ (MH^+) *m/e* 890.1647, obsd: 890.1677 (74% bp).

5′-Deoxy-5′-[5-iodo-1-[2-(*o*-nitrobenzyloxy)-5-[(-methoxy)carbonyl]phenyl]-1-pentyn-3-yl]2′,3′-*O*-isopropylideneadenosine (15b). This reaction was run with 495 mg (0.75 mmol) of **13b** in the same fashion as described for the synthesis of **14a**. It was stirred for 2.5 h when TLC analysis (EtOAc:MeOH, 98:2) showed the reaction to be complete. The work up gave 973 mg of crude yellow oil. This material was purified by silica gel chromatography (EtOAc:MeOH, 98:2; R_f 0.28) giving 487 mg (84% yield) of pure-white foam product **15b**. IR (KBr, cm^{-1}): 3450 (broad), 1718, 1640, 1600, 1579, 1210, 1134, 767. ^{1}H NMR ($CDCl_3$): δ 8.35 (s, 1H, H_8, adenine ring), 8.20 (d, 1H, H_7), 8.10 (dd, 1H, H_2), 8.00 (d, 1H, H_{10}), 7.97 (dd, 1H, H_6), 7.88 (d, 1H, H_2, adenine ring), 7.72 (t, 1H, H_9), 7.50 (t, 1H, H_8), 6.97 (d, 1H, H_5), 6.03 (d, 1H, $H_{1'}$), 5.62–5.53 (m, 5H, NH_2, benzylic, $H_{2'}$), 4.97 (m, 1H, $H_{3'}$), 4.63 (m, 1H, $H_{4'}$), 3.90 (s, 3H, —$C\underline{H}_3$), 3.34–3.21 (m, 2H, $H_{8'}$), 3.02–2.84 (m, 1H, $H_{6'}$), 2.08–1.89 (m, 4H, $H_{7'}$, $H_{5'}$), 1.58, 1.56 and 1.37 [3s, 6H, $C(C\underline{H}_3)_2$]; ^{13}C NMR ($CDCl_3$): δ 165.85, 161.68, 155.80, 152.87, 149.08, 146.43, 140.07, 135.01, 134.19, 132.83, 131.16, 128.21, 124.90, 123.11, 120.29, 114.39, 114.15, 113.07, 111.44, 95.11 and 94.93, 90.80 and 90.34, 84.97, 84.72, 84.52, 84.24, 83.82 and 83.56, 78.72 and 78.51, 67.11, 51.90, 38.91, 38.20, 37.58, 30.83, 30.35, 26.95 and 25.30, 3.44 and 2.95. HRMS (FAB$^+$): calcd for $C_{33}H_{33}N_6O_8IH$ (MH^+) *m/e* 769.1483, obsd: 769.1508 (100% bp).

2-Trimethylsilylethyl *N*-benzylideneglycinate (18).

(a) *N*-Carboxybenzyloxy 2-trimethylsilylethyl glycinate. A solution of 7.19 g (43 mmol) of carbonyldiimidazole in 50 mL of dry THF was added to a solution of 6.0 g (28.7 mmol) of *N*-Cbz-glycine in 50 mL of dry THF at room temperature. This golden solution was stirred at room temperature for 1 h when 3.73 g (4.5 mL, 31.5 mmol) of 2-trimethylsilylethanol was added. The reaction solution was stirred for 18 h when it was diluted by H_2O and EtOAc. The EtOAc layer was washed with brine, dried, and evaporated to give 11.54 g of crude yellow oil. Purification by column chromatography (cyclohexane:EtOAc, 8:2) gave 6.33 g (71%) of the pure product as a clear oil. ^{1}H NMR ($CDCl_3$): δ 7.37–7.31 (m, 5H, ArH), 5.25 (br s, 1H, NH), 5.13 (s, 2H, benzyl CH_2), 4.25 [t, 2H, $CO_2C\underline{H}_2$], 3.95 (d, 2H, H_α), 1.00 [t, 2H, $C\underline{H}_2Si(CH_3)_3$], 0.03 [s, 9H, $Si(C\underline{H}_3)_3$]; ^{13}C NMR ($CDCl_3$): δ 169.8, 156.1, 136.2, 128.0 and 127.6, 66.5, 63.1, 42.5, 16.9, −1.9. HRMS (CI w/NH_3): calcd for $C_{15}H_{23}NO_4SiNH_4^+$ 327.1740, obsd: 327.1738 (0.41% bp). Also observed M-(CH_2CH_2) ion at 299 (1.1% bp). Anal. calcd. for $C_{15}H_{23}NO_4Si$: C, 58.22; H, 7.49; N, 4.53. Found: C, 58.53; H, 7.83; N, 4.44%.

(b) 2-Trimethylsilylethyl glycinate. A mixture of 4.21 g (13.6 mmol) of the ester from (a) and 10% Pd/C (200 mg) in 150 mL of abs EtOH was hydrogenated under 50 psi H_2 pressure in a Parr bomb hydrogenator for 20 h at room temperature. This mixture was filtered through a pad of Celite and the pad was washed twice with 50 mL of abs EtOH. The combined filtrates were evaporated to give 2.33 g (98%) of crude cloudy oil. ^{1}H NMR ($CDCl_3$): δ 4.23 [t, 2H, $CO_2C\underline{H}_2$], 3.41 (s, 2H, H_α), 1.50 (br s, 2H, NH_2), 1.00 [t, 2H, $C\underline{H}_2Si(CH_3)_3$], 0.03 (s, 9H, $Si(C\underline{H}_3)_3$]. HRMS (CI w/NH_3): calcd for $C_7H_{17}NO_2SiH$ (MH^+): 176.1107, obsd: 176.1102 (6% bp). Also obsd M-(CH_2CH_2) ion at 148 (bp).

(c) 2-Trimethylsilylethyl *N*-benzylideneglycinate (18). To the mixture produced by 2.33 g (13.3 mmol) of the product obtained in (b), 1.12 g of $MgSO_4$ (dried in an oven at 120 °C for 2 days before its use) and 1.44 g (1.38 mL, 13.6 mmol) of distilled benzaldehyde in 30 mL of dry CH_2Cl_2 was added dropwise 3.76 mL of dry Et_3N at 0 °C. The reaction was allowed to warm to room temperature and stirred for 16 h. The mixture was filtered and the filtrate was evaporated. The residue was diluted with ether and washed with H_2O, brine, dried, and evaporated to give 3.22 g (90%) of pure **15** as a slightly yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.29 (s, 1H, $C\underline{H}$=N), 7.78 and 7.44 (m, 5H, ArH), 4.39 (s, 2H, H_α), 4.28 (t, 2H, $CO_2C\underline{H}_2$), 1.04 [t, 2H, $CH_2Si(CH_3)_3$], 0.04 [s, 9H, $Si(C\underline{H}_3)_3$]; ^{13}C NMR ($CDCl_3$): δ 170.0, 165.1, 135.6, 131.0 and 128.4, 63.1, 62.1, 17.2, −1.6. HRMS (CI w/NH_3): calcd for $C_{14}H_{21}NO_2SiH$ (MH^+): 264.1420, obsd: 264.1426 (3% bp). Also observed M-(CH_2CH_2) ion at 236 (4% bp). Anal. calcd for $C_{14}H_{21}NO_2Si$: C, 63.84; H, 8.04; N, 5.32. Found: C, 63.61; H 8.03; N 5.30%.

6-Amino-6-[(*t*-butoxy)carbonyl]-1-[2-(*o*-nitrobenzyloxy)-5-[(*o*-nitrobenzyloxy)carbonyl]phenyl]-1-hexyne (19a). Into a dry flask containing 0.019 mL (14 mg, 0.14 mmol) of dry diisopropylamine in 3 mL of dry THF and 0.3 mL of dry HMPA was added 0.085 mL of 1.6 M *n*-BuLi (0.14 mmol) at −78 °C under argon. This flask was stirred at −78 °C for 30 min when 30 mg (0.13 mmol) of *t*-butyl benzylidene glycinate (**17**) in 2 mL of THF was added dropwise. After the first drop was added the reaction solution changed to a deep red color. After 30 min at this temperature 80 mg (0.133

mmol) of iodo compound **14a** in 2 mL of THF was added dropwise. The temperature was allowed to rise to 0 °C and after 3 h was diluted with ether and washed with ice-cold satd NH_4Cl solution. The organic layer was washed with H_2O, brine, dried, and evaporated giving 70 mg (76%) crude imino ester as a white foam. TLC (hexane:CH_2Cl_2:MeOH, 6:3:1), ^1H and ^{13}C NMR showed no starting iodo compound remained. Treatment of this crude product (70 mg, 0.1 mmol) with 8 mL of 80% HCOOH gave after 16 h 60 mg yellow solid upon evaporation of the solvent. Column chromatography (hexane:CH_2Cl_2:MeOH, 6:3:1; R_f 0.29) gave 20 mg (33%) *t*-butyl ester **19a**. IR (film, cm^{-1}): 2990, 2950, 2850, 2198 (weak, C≡C), 1723 (strong), 1600, 1526, 1368, 1342, 1255, 1217, 729. ^1H NMR ($CDCl_3$): δ 8.24–6.98 (m, 11H, ArH), 5.76 (s, 2H, benzyl ester), 5.62 (s, 2H, benzyl ether), 3.37 (m, 1H, H_f), 2.57 (t, 2H, H_c), 1.80 (m, 4H, H_e and H_d), 1.44 (s, 9H, *t*-butyl); ^{13}C NMR ($CDCl_3$): δ 175.23, 162.20, 135.28, 134.22, 133.74, 133.13, 131.16, 128.97, 128.77, 128.53, 128.44, 125.08, 122.71, 120.21, 114.24, 111.85, 95.43, 81.15, 76.32, 67.38, 63.25, 54.74, 34.21, 28.05, 25.00, 19.62.

5′-Deoxy-5′-[6-amino-6-[(*t*-butoxy)carbonyl]-1-[2-(*o*-nitrobenzyl-oxy)-5-[(*o*-nitrobenzyloxy)carbonyl]phenyl]-1-hexyn-3-yl]2′,3′-*O*-isopropylideneadenosine (20a). This synthesis was carried out in the same fashion as described for the synthesis of **19a**. From 244 mg (0.27 mmol) of **15a** and 61 mg (0.28 mmol) of **17** was obtained 210 mg (78%) of crude imino ester that contained ca. 10% starting material **15a** an indicated by TLC, ^1H and ^{13}C NMR. HRMS (FAB^+) calcd for $C_{52}H_{52}N_8O_{12}H$ (MH^+) *m/e* 981.3783, obsd: 981.3723 (40.3% bp).

To a slightly yellow solution of 100 mg (0.10 mmol) of the intermediate imine in 10 mL of CH_2Cl_2 was added 3 drops of glacial acetic acid. The solution was stirred for 2.5 h when the volume was reduced to 1 mL. This solution was applied directly to a prep. TLC plate and this was developed using EtOAc:MeOH (9:1). Extraction of the lower R_f 0.18–0.10 product with CH_2Cl_2:MeOH (9:1) twice gave 77.8 mg (87%) pure **20a**. Also recovered was 10.9 mg (10.9%) of iodonucleoside **15a**. IR (KBr pellet, cm^{-1}): 3450 (broad), 1723, 1656, 1600, 1527, 1371, 1342, 1226, 1155, 1099, 731. ^1H NMR ($CDCl_3$): δ 8.29–7.46 (m, 12H, ArH), 6.98 (d, 1H, H_5), 6.20 (br s, 2H, NH_2), 6.03 (s, 1H, $H_{1'}$), 5.76 (s, 2H, benzyl ester), 5.63 and 5.60 (d, 2H, benzyl ether), 5.51 (m, 1H, $H_{2'}$), 4.94 (m, 1H, $H_{3'}$), 4.60 (m, 1H, $H_{4'}$), 3.34 (m, 1H, $H_{9'}$), 2.66 (m, 1H, $H_{6'}$), 2.07–1.56 (m, 6H, $H_{5'}$, $H_{7'}$ and $H_{8'}$), 1.50–1.23 [m, 15H, $(CH_3)_2$—C and $(CH_3)_3$—C]; ^{13}C NMR ($CDCl_3$): δ 174.50, 165.03, 162.30, 155.74, 153.04, 149.36, 146.64, 140.20, 135.32, 134.36, 133.83, 133.18 and 132.43, 131.39, 128.97, 128.83, 128.53, 128.36, 125.14, 122.66, 120.40, 114.43, 113.93, 111.82, 97.21 and 96.92, 90.85 and 90.38, 85.18, 84.97, 84.60, 84.36, 84.10 and 83.78, 81.22, 78.20 and 77.92, 67.33, 63.30, 54.67, 38.00, 32.50, 31.41, 29.60 and 29.12, 27.98, 27.07 and 25.42.

5′-Deoxy-5′-[6-amino-6-[(methoxy)carbonyl]-1-[2-(*o*-nitrobenzyloxy)-5-[(methoxy)carbonyl]phenyl]-1-hexyn-3-yl]2′,3′-*O*-isopropylideneadenosine (20c). A total of 530 mg (78%) crude foam was obtained from 640 mg (0.83 mmol) of **15b** by using a similar method to that described for the synthesis of the imine precursors of **19a** and nucleoside **20a**, except for the use of methyl benzylidene glycinate (**16**) in place of *t*-butyl benzylidene glycinate (**17**). IR (KBr, cm^{-1}): 3450 (broad), 1734, 1718, 1640, 1596. ^1H NMR ($CDCl_3$): δ 8.34 (m, 1H, H_8 of adenine), 8.21–6.93 (m, 8H, ArH), 6.00 (m, 1H, $H_{1'}$), 5.80 (bs, 2H, NH_2), 5.60 (s, 2H, benzylic), 5.45 (m, 1H, $H_{2'}$), 4.95 (m, 1H, $H_{3'}$), 4.63 (m, 1H, $H_{4'}$), 3.93 (m, 1H, $H_{9'}$), 3.89 (s, 3H, $ArCO_2CH_3$), 3.68 (m, 3H, $CHCO_2CH_3$), 2.85 (m, 1H, $H_{6'}$), 2.20–1.75 (m, 6H, $H_{5'}$, $H_{7'}$ and $H_{8'}$), 1.55 and 1.37 [m, 6H, $C(CH_3)_2$]; ^{13}C NMR ($CDCl_3$): δ 172.01, 165.94, 163.41, 161.87, 155.69, 152.90, 149.32, 146.63, 140.00, 135.69, 135.10, 134.07, 133.11, 131.16 130.97, 128.43, 125.29, 124.77, 123.38, 120.12, 114.51 and 114.35, 113.67, 111.74, 104.13, 96.87 and 95.12, 90.83, 90.69 and 90.35, 85.13, 84.91, 84.59, 84.34, 84.03 and 83.74, 78.97, 78.36 and 78.04, 72.68 and 72.46, 67.29 and 67.21, 51.79, 39.08 and 38.45, 31.58 and 31.14, 31.05 and 30.91, 29.39, 29.99, 29.45 and 28.63, 27.05 and 25.30. HRMS (FAB^+): calcd for $C_{43}H_{43}N_7O_{10}H$ (MH^+) *m/e* 818.3150, obsd: *m/e* 818.3139 (49% bp).

To the slightly yellow solution of 530 mg (0.65 mmol) of the fully protected nucleoside imino ester in 10 mL of CH_2Cl_2 was added 3 drops of glacial acetic acid. After 3 h the reaction mixture was concentrated to 2 mL and was applied directly to a prep. TLC plate and developed with EtOAc:MeOH (9:1). The product-containing zone (R_f 0.18–0.10) was scraped off the plate and extracted with EtOAc:MeOH, 9:1 to give 265 mg (56%) of pure **20c**. IR (KBr, cm^{-1}): 3325, 3180 (very strong br s, NH_2, OH), 2218 (weak, C≡C), 1719, 1642. ^1H NMR ($CDCl_3$): δ 8.32 and 8.30 (s, 1H, H_8 of adenine), 8.20 (d, 1H, H_7), 8.10 (s, 1H, H_2), 8.02 (t, 1H, H_{10}), 7.94, (d, 1H, H_6), 7.88 (d, 1H, H_2 of adenine), 7.67 (t, 1H, H_9), 7.48 (t, 1H, H_8), 6.95 (d, 1H, H_5), 6.01 (d, 1H, $H_{1'}$), 5.93 (br s, 2H, NH_2), 5.61 and 5.59 (2s, 2H, benzyl), 5.53 (dd, 1H, $H_{2'}$), 4.96 (m, 1H, $H_{3'}$), 4.61 (m, 1H, $H_{4'}$), 3.90 (s, 3H, $ArCO_2CH_3$), 3.66 (m, 3H, $CHCO_2CH_3$), 3.43 (m, 1H, $H_{9'}$), 2.72 (m, 1H, $H_{6'}$), 2.09–1.60 (m, 6H, $H_{5'}$, $H_{7'}$ and $H_{8'}$), 1.59, 1.57 and 1.37, 1.35 [dd, 6H, $C(CH_3)_2$]; ^{13}C NMR ($CDCl_3$): δ 175.63, 165.97, 161.73, 155.66, 152.83, 149.14, 146.50, 140.07, 135.07, 134.14, 133.12, 131.03, 128.31, 128.23, 124.92, 123.20, 120.00, 114.48 and 114.22, 113.48, 111.58, 96.41, 90.86 and 90.31, 85.09, 84.89, 84.56, 84.52, 83.97, 83.63, 78.29, 67.19, 54.10 and 53.86, 51.95, 38.86 and 38.36, 32.09, 31.45, 29.49, 29.26, 27.00 and 25.26. HRMS (FAB^+): calcd for $C_{36}H_{39}N_7O_{10}H$ (MH^+) *m/e* 730.2837, obsd: *m/e* 730.2849 (56% bp).

5′-Deoxy-5′-[(6-amino-6-carboxy)-1-(2-hydroxy-5-carboxyphenyl)-1-hexyn-3-yl]-adenosine (1).

(a) 5′-Deoxy-5′-[6-amino-6-[(methoxy)carbonyl]-1-[2-(*o*-nitrobenzyloxy)-5-[(methoxy)carbonyl]phenyl]-1-hexyn-3-yl] adenosine. A solution of 25 mg (0.034 mmol) of **20c** was stirred at rt in the dark in 2 mL of 80% formic acid for 3 h. The formic acid was evaporated under high vacuum to give 27 mg (>100%) of a

slightly yellow solid. IR (KBr, cm^{-1}): 3450 (broad), 1721, 1712, 1657, 1642. ^1H NMR (CD_3OD): δ 8.22 (s, 1H, H_8 of adenine), 8.17 (s, 1H, H_2, adenine), 8.13 (m, 1H, H_7), 7.97–7.90 (m, 3H, H_{10}, H_6 and H_2), 7.65 (m, 1H, H_9), 7.51 (m, 1H, H_8), 7.11 (d, 1H, H_5), 5.91 (d, 1H, $H_{1'}$), 5.59 and 5.55 (s, 2H, benzylic), 4.86 (m, 1H, $H_{2'}$), 4.41–4.19 (m, 2H, $H_{3'}$ and $H_{4'}$), 4.02 (m, 1H, $H_{9'}$), 3.86 (s, 3H, $ArCO_2CH_3$), 3.77 (s, 3H, $CHCO_2CH_3$), 2.95 (m, 1H, $H_{6'}$), 2.30–1.58 (m, 6H, $H_{5'}$, $H_{7'}$ and $H_{8'}$); ^{13}C NMR (CD_3OD): δ 171.21, 168.16, 162.90, 156.21, 152.50, 149.61, 147.43, 135.27, 133.21, 132.32, 129.91, 129.41, 125.99, 123.37, 120.32, 113.79, 112.72, 97.20, 89.43 ($C_{1'}$), 83.65, 78.43, 74.78, 68.22, 54.30 and 53.23, 53.90 and 53.75, 39.55, 31.21, 30.08, 28.83. HRMS (FAB^+): calcd for $C_{33}H_{33}N_7O_{10}H$ (MH^+) *m/e* 690.2524, obsd: *m/e* 690.2528 (58% bp).

(b) 5′-Deoxy-5′-[6-amino-6-carboxy-1-[2-(*o*-nitrobenzyloxy)-5-[carboxyphenyl]-1-hexyn-3-yl] adenosine. To a solution of 19 mg (0.026 mmol) of crude product from (a) in 2 mL of MeOH:H_2O (5:1) was added dropwise 0.105 mL of 1 N LiOH. The reaction was stirred for a total of 67 h while being monitored periodically by TLC (CH_3CN:H_2O:acetic acid, 8:1:1; R_f 0.16) and HPLC (0–100% CH_3CN in H_2O over 30 min, Altex system-Vydac C-18· analytical column: desired product diacid, t_R 10 min; monomethyl ester intermediate, t_R 15 min). After this time HPLC showed a 82:18 ratio of diacid to monomethyl ester. The reaction was quenched by the addition of roughly 1 g of Amberlite IR-120 (H^+) resin (pH 5–12), filtering and washing with MeOH and H_2O. The filtrate was evaporated at high vacuum (<40 °C) to give 16 mg crude white solid. This material was dissolved in 2.4 mL of MeOH:H_2O (1:1) by the addition of two drops of Et_3N. It was purified by preparative HPLC (Rainin Rabbit, 1.0 cm ID semi-prep Dynamax C-18 column) giving 12 mg (71% from last two reactions) diacid product as a white solid: IR (KBr, cm^{-1}): 3400 (br), 2950, 1644, 1377, 1035, 788. ^1H NMR (CD_3OD): δ 8.25 (d, 1H, H_8, adenine), 8.19 (s, 1H, H_2, adenine), 8.15 (m, 1H, H_7), 8.05 (m, 1H, H_{10}), 8.01 (d, 1H, H_2), 7.88 (dd, 1H, H_6), 7.68 (m, 1H, H_9), 7.48 (t, 1H, H_8), 6.99 (d, 1H, H_5), 5.90 (d, 1H, $H_{1'}$), 5.58 and 5.54 (2s, 2H, benzyl ether), 4.78 (m, 1H, $H_{2'}$), 4.50–4.22 (m, 2H, $H_{3'}$ and $H_{4'}$), 3.63–3.51 (m, 1H, $H_{9'}$), 2.92 (m, 1H, $H_{6'}$), 2.26–1.64 (m, 6H, $H_{5'}$, $H_{7'}$ and $H_{8'}$); ^{13}C NMR: δ 181.86, 173.78, 161.35, 156.98, 153.81, 150.40, 148.02, 141.32, 135.78, 135.53, 134.06, 133.94, 129.98, 125.84, 120.29, 113.84, 112.52, 97.58, 89.42, 84.11, 79.73, 75.07, 68.33, 55.64, 40.13, 30.59, 24.58, 19.24. HRMS (FAB^+): calcd for $C_{31}H_{31}N_7O_{10}H$ (MH^+) *m/e* 662.2211, obsd: *m/e* 662.2249 (3% bp).

Also obtained was 3 mg (18%) of monomethyl ester: ^1H NMR (CD_3OD): δ 8.25 (d, 1H, H_8, adenine), 8.19 (s, 1H, H_2, adenine), 8.15 (m, 1H, H_7), 8.05 (m, 1H, H_{10}), 8.01 (d, 1H, H_2), 7.88 (dd, 1H, H_6), 7.68 (m, 1H, H_9), 7.48 (t, 1H, H_8), 6.99 (d, 1H, H_5), 5.90 (d, 1H, $H_{1'}$), 5.58 and 5.54 (2s, 2H, benzyl ether), 4.78 (m, 1H, $H_{2'}$), 4.50–4.22 (m, 2H, $H_{3'}$ and $H_{4'}$), 3.83 (s, 3H, CH_3), 3.63–3.51 (m, 1H, $H_{9'}$), 2.92 (m, 1H, $H_{6'}$), 2.26–1.64 (m, 6H, $H_{5'}$, $H_{7'}$ and $H_{8'}$).

(c) 5′-Deoxy-5′-[(6-amino-6-carboxy)-1-(2-hydroxy-5-carboxyphenyl)-1-hexyn-3-yl]-adenosine (1). Polyacrylamide hydrazide (0.486 g) obtained from Sigma (P8885) was washed with H_2O and MeOH then placed in a 75 mL Pyrex vial with 30 mL of H_2O:MeOH (2:1). Nitrogen was bubbled through this mixture overnight. The purified nucleoside diacid from reaction (b) (12 mg, 0.0175 mmol) was transferred to this vial with MeOH and was subjected to photolysis with a 450 watt Hanovia lamp containing a Pyrex filter (>350 nm). After 2 h the now yellow reaction mixture was filtered and evaporated giving 20.1 mg crude tan solid. This crude material was decolorized with charcoal and filtrated to give 6 mg (61%) of **1** as a white solid. This material could be purified by preparative reverse-phase HPLC in low yield. ^1H NMR (CD_3OD): δ 8.29 (m, 1H, H_8, adenine), 8.21 (s, 1H, H_2, adenine), 7.91 (m, 1H, H_2), 7.76 (m, 1H, H_6), 6.74 (d, 1H, H_5), 5.98 (d, 1H, $H_{1'}$), 4.81 (m, 1H, $H_{2'}$), 4.45–4.28 (m, 2H, $H_{3'}$ and $H_{4'}$), 3.50 (m, 1H, $H_{9'}$), 2.90 (m, 1H, $H_{6'}$), 2.20–1.70 (m, 6H, $H_{5'}$, $H_{7'}$ and $H_{8'}$); ^{13}C NMR ($CDCl_3$): δ 174.75, 151.13, 159.92, 153.87, 150.31, 145.72, 135.81, 132.09, 119.50, 115.65, 100.05, 96.30, 89.59, 84.08, 74.91, 74.71, 55.99, 55.77, 39.60, 30.33, 30.04, 25.07. UV (MeOH:H_2O, 1:1): 255 and 223 nm. MS (FAB^+): 527 (3% bp). HPLC (CH_3CN:H_2O, 0→100% over 30 min: t_R 9.5 min.

***N*⁶,*N*⁶-Dibenzoyl-5′-deoxy-5′-[1-phenyl-1-trimethylsilyl-1-hydroxy-7-(*t*-butyldiphenylsiloxy)-3-heptyn-5-yl]-2′,3′-*O*-isopropylideneadenosine (24)**. A solution of 875 mg (1.07 mmol) of the N^6-dibenzoylated acetylenic nucleoside **4** in 40 mL of THF was deoxygenated by the freeze–thaw method using argon. This clear solution was cooled to −78 °C and treated with 1.1 mL (1.65 mmol) of 1.5 M LDA in cyclohexane. The resulting bright red/orange colored solution was stirred at this temperature for 30 min. A solution of 246 mg (2.7 mmol) of CuCN and 233 mg (5.5 mmol) of LiCl (these salts had been dried at 150 °C for 2 h) in 30 mL of THF was added to the above solution at −78 °C. The resulting golden-yellow solution was stirred for 30 min when the temperature was raised to −10 °C. A solution of 196 mg (1.07 mmol) of benzoyltrimethylsilane and 350 mg (1.07 mmol) of ZnI_2 in 20 mL of THF was added. The preformed Simmons–Smith reagent[29] (10 mmol) was added dropwise causing a bright red color to form then disappear immediately. This red color was seen during the entire addition process. Work up after 30 min at −10 °C was carried out by quenching with satd NH_4Cl and extraction of the resulting aqueous mixture twice with ether. The ether layers were combined and washed with H_2O, brine, then dried and evaporated to give 1.5 g crude brown oil. Column chromatography (cyclohexane:EtOAc, 75:25) gave 280 mg (26%) of the desired product **24**: ^1H NMR ($CDCl_3$): δ 8.69, 8.68, 8.67 and 8.66 (s, 1H, H_8), 8.18, 8.15, 8.12, and 8.09 (s, 1H, H_2), 7.92–7.88 (m, 7H, ArH), 7.69–7.64 (m, 7H, ArH), 7.53–7.36 (m, 1H, ArH), 7.26–7.20 (m, 5H, ArH), 6.15, 6.08, 6.07 and 6.03 (d, 1H, $H_{1'}$), 5.41, 5.37, 5.29 and 5.26 (dd, 1H, $H_{2'}$), 4.90, 4.80, 4.66 and 4.56 (m, 1H, $H_{3'}$), 4.20 and 4.10 (m, 1H, $H_{4'}$), 3.83 and 3.58 (m, 2H,

$H_{8'}$), 2.96–2.54 (m, 3H, H_b and $H_{6'}$), 2.13–1.30 [m, 10H, $H_{5'}$, $H_{7'}$, $C(CH_3)_2$], 1.05 [m, 9H, $C(CH_3)_3$), 0.02 (m, 9H, $Si(CH_3)_3$]. ^1H NMR spectra clearly show the presence of the four diastereomers (ca. 1:1:2:2), with the less intense peaks usually downfield, corresponding to a 1:2 ratio of isomers at $C_{6'}$ and a 1:1 mixture at the benzylic alcohol carbon; ^{13}C NMR ($CDCl_3$): δ 172.14 , 152.31, 152.20, 151.95, 145.51, 145.44, 143.83, 135.47, 134.03, 133.77, 133.74, 132.89, 129.51, 129.38, 128.64 127.92, 127.70, 127.63, 127.55, 125.31,125.07, 124.99, 124.93, 124.85, 115.07, 114.85, 114.77, 114.69, 90.33 and 89.85, 85.57 84.91, 84.75, 84.16, 84.08, 83.89, 83.82, 85.13, 85.07, 78.48, 78.37, 78.06, 77.93, 70.69, 70.59, 70.51, 70.45, 61.33, 61.20, 61.12, 61.00, 39.34, 38.90, 38.69, 68.50, 38.25, 38.16, 37.97, 37.73, 28.57, 28.43, 28.33, 27.30, 27.12, 26.84, 26.76, 25.64, 25.38, 25.28, 25.23, 25.12, 24.82, 24.72, 19.09, −4.13. HRMS (mode FAB^+): calcd for $C_{59}H_{65}N_5O_7Si_2H$: 1012.4501, obsd: 1012.4445 (5% bp).

5′-Deoxy-5′-[1-phenyl-1-trimethylsilyl-1-hydroxy-7-(*t*-butyldiphenylsiloxy)-3-heptyn-5-yl]2′,3′-*O*-isopropylideneadenosine (21b). To the solution formed from 380 mg (0.375 mmol) of **24** in 23 mL of MeOH was added 15 mL of concentrated NH_4OH. The resulting solution was stirred for 18 h when the solvents were evaporated. Column chromatography (EtOAc:benzene, 7:3) gave 246 mg (81%) of **21b**, free of any benzamide. ^1H NMR ($CDCl_3$): δ 8.33 (m, 1H, H_8), 7.83 (m, 1H, H_2), 7.66–7.10 (m, 15H, ArH), 6.02 (m, 1H, $H_{1'}$), 5.86 (br s, 2H, NH_2), 5.45 (m, 1H, $H_{2'}$), 4.70 (m, 1H, $H_{3'}$), 4.16 (m, 1H, $H_{4'}$), 3.48 (m, 2H, $H_{8'}$), 2.92–2.70 (m, 2H, Hb), 2.60 (m, 1H, $H_{6'}$), 1.80–1.37 [m, 10H, $H_{5'}$, $H_{7'}$, $C(CH_3)_2$], 0.98 (m, 9H, Bu^t), −0.05 [m, 9H, $Si(CH_3)_3$]; ^{13}C NMR ($CDCl_3$): δ 155.66, 153.02, 149.24, 145.56, 139.67, 135.54, 133.82, 131.87, 129.46, 128.52, 128.26, 127.67, 127.28, 124.92, 120.16, 114.33, 90.44, 89.95, 85.43, 85.25, 85.07, 85.02, 84.43, 84.26, 84.04, 83.79, 78.29, 70.59, 61.26, 61.07, 60.31, 38.92, 38.75, 38.51, 38.11, 28.48, 27.28, 26.69, 25.61, 25.34, 24.88, 19.03, −4.09. HRMS (FAB^+): calcd for $C_{45}H_{57}N_5O_5Si_2H$: 804.3976, obsd: 804.3983 (22% bp).

5′-Deoxy-5′-[1-phenyl-1-hydroxy-7-(*t*-butyldiphenylsiloxy)-3-heptyn-5-yl]2′,3′-*O*-isopropylideneadenosine (25b). To a mixture of 22 mg (0.19 mmol) of KOBut in 3 mL of THF at 0 °C was added 140 mg (0.17 mmol) of **21b** in 3 mL of THF. The resulting brown solution was stirred for 1.75 h at 0 °C when it was quenched by the addition of 10 drops of glacial AcOH. The solvents were evaporated and the residue was purified by column chromatography (EtOAc:cyclohexane, 7:3) to give 98 mg (82%) of pure **25b**. ^1H NMR ($CDCl_3$): δ 8.33 (d, 1H, H_8), 7.91 and 7.66 (2d, 1H, H_2), 7.66–7.21 (m, 15H, ArH), 6.05 (m, 1H, $H_{1'}$), 5.80 (2 br s, 2H, NH_2), 5.52 (m, 1H, $H_{2'}$), 4.95 (m, 1H, $H_{3'}$), 4.70 (m, 1H, H_a), 4.44 (m, 1H, $H_{4'}$), 3.72 (m, 2H, $H_{8'}$), 2.75 (m, 1H, $H_{6'}$), 2.53 (m, 2H, H_b), 1.90–1.58 (m, 4H, $H_{5'}$ and $H_{7'}$), 1.67 and 1.40 [s, 6H, $C(CH_3)_2$], 1.00 (2s, 9H, Bu^t); ^{13}C NMR ($CDCl_3$): δ 155.62, 153.03, 149.24, 142.97, 139.94, 135.51, 133.68, 131.90, 128.27, 127.54, 127.28, 125.69, 120.25, 114.41, 90.39, 85.62, 84.57, 84.29, 83.94, 78.98, 72.42, 61.34, 38.91 and 38.30, 30.06, 27.16 and 25.46, 26.71, 19.06. HRMS (FAB^+): calcd for $C_{42}H_{49}N_5O_5SiH$: 732.3581, obsd: 732.3564 (23% bp). The dehydro side-product **26** had ^1H and ^{13}C NMR spectral properties very similar to **25b** except for the absence of the H_a proton and the C_a carbon signals. HRMS (FAB^+): calcd for $C_{42}H_{47}N_5O_4SiH$: 714.3476, obsd: 714.3477 (18% bp).

1-Phenyl-1-(4-methoxy-4-tetrahydropyranyloxy)-7-(*t*-butyl-diphenylsiloxy)-3-heptyne (27a, X=OCH$_3$). A flask containing 540 mg (1.22 mmol) of alcohol **25a**,[29] 209 mg (1.83 mmol) of 3,4-dihydro-2-methoxy-2*H*-pyran, and 15 mg (0.061 mmol) of PPTS in 5 mL of dry CH_2Cl_2 was stirred under argon at room temperature overnight. TLC analysis showed the reaction was nearly complete. Work up by dilution with CH_2Cl_2, washing with cold $NaHCO_3$, drying and evaporation gave 750 mg (>100%) crude brown oil. Column chromatography (CH_2Cl_2 first 12 fractions then 10% EtOAc added) gave 470 mg (69%) of a mixture of **27a** (X=CH_3) and its OEt analogue, **27a** (X=OEt). TLC: cyclohexane:CH_2Cl_2 (3:7): R_f 0.13 (product mixture); CH_2Cl_2:EtOAc (95:5): R_f 0.62 [**27a** (X=OCH_3)]: R_f 0.73 [**27a** (X=OEt)]. IR (neat): No —OH stretch. ^1H NMR ($CDCl_3$): δ 7.66–7.20 (m, >15H, ArH), 4.79 (t, >1H, H_a), 3.75, 3.59 and 3.45 (m, >4H, pyran OCH_2), 3.64 (t, >2H, H_g), 3.12 (s, <3H, —OCH_3), 2.67–2.40 (m, >2H, H_b), 2.21 (tt, >2H, H_e), 1.87 (m, >2H, pyran CH_2), 1.64 (quint, >2H, H_f), 1.54 (m, >2H, pyran CH_2), 1.03 (s, >9H, *t*-butyl); ^{13}C NMR [$CDCl_3$; major product (minor product)]: δ (143.6) 143.5, 135.4, 133.8, 129.4, 127.9, 127.5, 127.2, 126.5, 126.4, 99.0 (98.9), 81.7 (81.6) and 76.8 (76.7), 71.6 (71.4), 64.9, 64.8 and 64.7, 62.4, (59.8 and 55.7), 48.2, (36.0) 35.6 and (34.9) 34.31, 31.7, (29.5) 29.3, 26.8, 19.1, 15.1, (14.9 and 14.1). Subsequent reactions using EtOH-free CH_2Cl_2 resulted in exclusive formation of the methoxy derivative **23a** (X=OCH_3) in 69% yield.

5′-Deoxy-5′-[1-phenyl-1-(4-tetrahydropyranyloxy)-7-(*t*-butyl-diphenylsiloxy)-3-heptyn-5-yl]2′,3′-*O*-isopropylideneadenosine (27b, X=H). Reaction was carried out as described for the synthesis of **27a** using 70 mg (96 μmol) of **25b**, 46 mg (550 μmol) of dihydropyran, and 48 mg (191 μmol,) of PPTS in 5 mL dry CH_2Cl_2. Chromatography on silica gel (EtOAc:cyclohexane, 6:4) provided 35 mg (45%) of pure **27b** as a pair of diastereomers. TLC:EtOAc:cyclohexane (6:4): R_f 0.2. ^1H NMR ($CDCl_3$): δ 8.33 (d, 1H, H_8), 7.88 and 7.81 (2d, 1H, H_2), 7.41–7.23 (m, 15H, ArH), 6.00 (m, 1H, $H_{1'}$), 5.92 (br s, 2H, NH_2), 5.50 (m, 1H, $H_{2'}$), 4.95–4.60 (m, 3H, $H_{3'}$, H_a), 4.45 (m, 1H, $H_{4'}$), 3.80–3.30 (br m, 4H, $H_{8'}$, pyran OCH_2), 2.80–2.40 (br m, 3H, $H_{6'}$, H_b), 1.90–1.30 (br m, 4H, $H_{5'}$ and $H_{7'}$), 1.60 and 1.40 [2 pr s, 6H, $C(CH_3)_2$], 1.05 and 0.95 (2s, 9H, Bu^t).

1-Phenyl-1-(4-methoxy-4-tetrahydropyranyloxy)-7-hydroxy-3-heptyne (28a, X=OCH$_3$) and 1-phenyl-1-(4-ethoxy-4-tetrahydropyranyloxy)-7-hydroxy-3-heptyne (28a, X=OEt). To a solution of 460 mg (0.83 mmol) of silyl ether mixture **27a** (X=OCH_3:OEt=4:1) in 10

mL of dry THF was added 1 mL (1 mmol) of a 1 M solution of TBAF in THF at room temperature under argon. This solution was stirred for 2.5 h when the reaction was worked up in the usual fashion to give 440 mg (>100%) crude brown oil. Column chromatography (cyclohexane:EtOAc, 7:3) gave 186 mg (71%) pure **28a** (X=OCH_3). Also obtained was 52 mg (20%) of **28a** (X=OEt). TLC data: cyclohexane:EtOAc, 7:3; **28a** (X=OCH_3): R_f 0.15; **28a** (X=OEt): R_f 0.24. Spectral data for **28a** (X=OCH_3): ^{1}H NMR ($CDCl_3$): δ 7.41–7.22 (m, 5H, ArH), 4.83 (t, 1H, H_a), 3.83, 3.60 and 3.46 (m, 4H, 2 pyran —OCH_2), 3.63 (quart, 2H, H_g), 3.11 (s, 3H, —OCH_3), 2.60 (m, 2H, H_b), 2.22 (tt, 2H, H_c), 1.88 (m, 2H, pyran CH_2), 1.65 (quint, 2H, H_f), 1.57 (m, 2H, pyran CH_2), 1.46 (t, 1H, exchange w/D_2O, —OH); ^{13}C NMR ($CDCl_3$): δ 143.4, 128.0, 127.3 and 126.5, 99.1, 77.2 and 76.6, 71.4, 64.8 and 64.7, 61.4, 48.3, 35.5 and 34.3, 31.3, 29.2, 15.2. MS by both EI and CI w/NH_3 gave 115 as base peak. Spectral data for **28a** (X=OEt): ^{1}H NMR ($CDCl_3$): δ 7.38–7.25 (m, 5H, ArH), 4.85 (t, 1H, H_a), 3.79, 3.60 and 3.50 (m, 4H, 2 pyran —OCH_2), 3.62 (quat, 2H, C_g), 3.48 and 3.26 (m, 2H, —OCH_2), 2.55 (m, 2H, H_b), 2.20 (tt, 2H, H_c), 1.90 (m, 2H, pyran CH_2), 1.65 (quint, 2H, H_f), 1.58 (m, 2H, pyran CH_2), 1.49 (t, 1H, exchange w/D_2O, —OH), 1.01 (t, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 143.6, 128.0, 127.3 and 126.6, 99.0, 81.5 and 77.3, 71.4, 65.0 and 64.9, 61.7, 55.9, 35.9 and 35.0, 31.3, 29.5, 15.3, 15.0. MS by both EI and CI w/NH_3 gave 129 as base peak. When pure methoxy **27a** was used, a 83% yield of pure **28a** (X=OCH_3) was obtained.

5′-Deoxy-5′-[1-phenyl-1-(4-tetrahydropyranyloxy)-7-hydroxy-3-heptyn-5-yl]2′,3′-*O*-isopropylideneadenosine (28b, X=H). Reaction was carried out as described for the synthesis of **28a** using 97 mg (119 μmol) of **27b** (X=H) and 0.3 mL 1 M TBAF in THF (300 μmol) in 6 mL CH_2Cl_2 containing ca. 100 μL glacial HOAc. Column chromatography on silica gel (EtOAc:CHOH, step gradient of 96:4 to 9:1) gave the desired product. **28b** (X=H); 25 mg (35%) as a white foam. TLC (EtOAc:MeOH, 96:4): R_f 0.13. Spectral data for **28b** (X=H): ^{1}H NMR ($CDCl_3$): δ 8.34 (d, 1H, H_8), 7.83 and 7.88 (2d, 1H, H_2), 7.41–7.23 (m, 15H, ArH), 6.00 (d, 1H, $H_{1'}$), 5.90 (2 br s, NH_2), 5.59 and 5.49 (2m, 1H, $H_{2'}$), 5.00 (br s, 1H, OH), 4.86–4.75 (m, 2H, $H_{3'}$, H_a), 4.50 and 4.43 (2m, 1H, $H_{4'}$), 3.56–3.47 (br m, 2H, $H_{8'}$), 2.72–2.55 (br m, 2H, $H_{6'}$, H_b), 1.86–1.60 (br m, 4H, $H_{5'}$, $H_{7'}$), 1.67 and 1.40 [2s, 6H, $C(CH_3)_2$]; ^{13}C NMR ($CDCl_3$): δ 155.5, 153.1, 149.3, 142.2, 140.9, 140.0, 128.3, 128.1, 127.9 and 127.4, 127.0, 126.4, 120.3, 114.4, 97.8 and 95.6, 91.1 and 90.4, 85.1, 84.8, 84.6, 84.2, 84.0, 83.7, 83.4 and 83.1, 79.7 and 79.5, 75.8, 61.8, 60.4, 39.2 and 38.7, 38.2 and 37.5, 30.5, 28.3, 27.3, 27.2, 25.6, 25.5, 25.4, 25.3, 25.1, 19.5, 19.0. HRMS (FAB$^+$): calcd for $C_{31}H_{39}O_6H$: 578.2979 $(MH)^+$, obsd: 578.2952 (54% bp).

1-Phenyl-1-hydroxy-7-iodo-3-heptyne (29a). To the brown mixture produced by stirring 435 mg (1.65 mmol) of PPh_3, 113 mg (1.65 mmol) of imidazole, and 350 mg (1.38 mmol) of I_2 in 14 mL of dry THF for 10 min was added 176 mg (0.55 mmol) of alcohol **28a** (X=OCH_3) in 5 mL of THF. After 1 h the solvent was evaporated and the resulting residue was dissolved in CH_2Cl_2 and washed with H_2O and brine. Drying and evaporation gave the crude product. Column chromatography (cyclohexane:EtOAc, 9:1) gave 136 mg (79%) of the unexpected iodo alcohol **29a**. ^{1}H NMR ($CDCl_3$): δ 7.38–7.26 (m, 5H, ArH), 4.82 (m, 1H, H_a), 3.21 (m, 2H, H_g), 2.61 (m, 2H, H_b), 2.37 (d, 1H, —OH), 2.30 (m, 2H, H_c), 1.93 (m, 2H, H_d); ^{13}C NMR ($CDCl_3$): δ 142.66, 129.29, 127.73, 125.68, 80.81, 77.34, 72.50, 32.06, 29.69, 19.68, 5.48.

1-Phenyl-1-(4-tetrahydropyranyloxy)-7-iodo-3-heptyne (30a). To a solution of 136 mg (0.43 mmol) of iodo alcohol **29a** and 5 mg (5 mol %) of PPTS in 2 mL of CH_2Cl_2 was added 73 mg (80 mL, 0.87 mmol) of freshly dried dihydropyran at room temperature. This slightly yellow solution was stirred for 5 h when it was worked up by dilution with CH_2Cl_2, then washed with H_2O and brine. Drying and evaporation giving 160 mg (92%) clear oil. As judged by TLC, ^{1}H NMR, and ^{13}C NMR this material looked pure enough to be used directly in the next alkylation reaction. IR (neat, cm^{-1}): 2950, 1480 and 1050. ^{1}H NMR ($CDCl_3$): δ 7.42–7.25 (m, 5H, ArH), 5.00 and 4.46 [t, 1H, $(RO)_2CH$], 4.81 and 4.76 (t, 1H, H_a), 4.05, 3.54 and 3.33 (m, 2H, OCH_2), 3.21 (t, 2H, H_g), 2.58 (m, 2H, H_b), 2.23 (m, 2H, H_c), 1.92–1.46 (m, 8H, 4 CH_2); ^{13}C NMR ($CDCl_3$): δ 142.12 and 140.80, 128.21, 128.01, 127.79, 127.29, 126.85, 126.32, 97.84 and 95.11, 78.61 and 78.56, 76.08 and 77.92, 76.59 and 75.57, 32.32 and 32.24, 30.50 and 30.45, 28.26 and 27.36, 25.50 and 25.33, 19.12 and 18.98, 19.64, 5.58 and 5.50. HRMS (CI w/NH_3): calcd for $C_{18}H_{23}O_2IH$: 399.0821, obsd: 399.0803 (2% bp).

5′-Deoxy-5′-[1-phenyl-1-(4-tetrahydropyranyloxy)-7-iodo-3-heptyn-5-yl]2′,3′-*O*-isopropylideneadenosine (30b, X=H). Reaction was carried out as described for the synthesis of **29a** using 25 mg (43 μmol) **28b**, 34 mg (130 μmol) PPh_3, 9 mg (130 μmol) imidazole, and 27 mg (110 μmol) of I_2 in 10 mL dry THF. The reaction was monitored by TLC and after 3 h the solvent was removed by rotary evaporation. The resulting residue was dissolved in EtOAc (1 mL), placed directly on a silica gel column, and eluted with EtOAc to provide 19 mg (63%) of **30b** as a white foam. TLC (EtOAc:MeOH, 96:4): R_f 0.33. Spectral data for **30b**: ^{1}H NMR ($CDCl_3$) very similar to spectrum described for **28b** except for resonance at δ 5.19–4.95 (br m, CH_2I) in place of resonance at δ 3.56–3.47 (br m, CH_2OH) in **28b**; also some residual Ph_3P=O impurity; ^{13}C NMR ($CDCl_3$) very similar to the spectrum described for **28b** except for resonance at δ 3.94–3.29 (CH_2I) in place of resonance at δ 61.8 (CH_2OH) in **28b**. HRMS (FAB$^+$): calcd for $C_{31}H_{38}N_5O_5IH$: 688.1996; obsd: 688.2008 (15% bp).

1-Phenyl-1-(4-tetrahydropyranyloxy)-8-amino-8-[(trimethylsilylethoxy)carbonyl] 3-octyne (32a). To a solution of 99 mg (0.38 mmol) of glycinate **18** in 4 mL of THF and 0.4 mL of HMPA at −78 °C was added 0.310 mL (0.47 mmol) of 1.5 M LDA in cyclohexane.

This brown solution was stirred at −78 °C for 30 min when 150 mg (0.38 mmol) of alkyl iodide **30a** was added dropwise in 3 mL of THF. The resulting bright-orange solution was stirred at −78 °C for 1 h and 0 °C for 1 h when it was worked up by dilution with ether, quenching with satd NH_4Cl, washing with H_2O, brine, then drying and evaporation to give 200 mg (98%) crude brown product. ^1H and ^{13}C NMR showed no starting alkyl iodide remained in this crude product. HRMS (CI w/NH_3): calcd for $C_{32}H_{43}NO_4SiH$: 534.3040, obsd: 534.3024 (100% bp). This crude material was used directly in the next step.

A solution of the imino ester intermediate **31a** (130 mg, 0.24 mmol) in 2 mL of CH_2Cl_2 and 1 mL of glacial HOAc was stirred for 1 h and then placed directly on a silica gel column. Elution with 4% MeOH in EtOAc gave 60 mg (56%) of product **32a**. IR (neat, cm^{-1}): 2900 (br s), 1728 (C=O). ^1H NMR ($CDCl_3$): δ 7.42–7.25 (m, 5H, ArH), 5.01 and 4.46 [t, 1H, $(RO)_2CH$], 4.77 (m, 1H, H_a), 4.20 (t, 2H, O_2CH_2), 4.06, 3.51 and 3.35 (m, 2H, OCH_2), 2.56 (m, 2H, H_b), 2.15 (m, 2H, H_e), 1.80–1.48 [m, 12H, $(CH_2)_3$, H_f, H_g and NH_2], 1.01 (CH_2Si), 0.05 [s, 9H, $Si(CH_3)_3$]; ^{13}C NMR ($CDCl_3$): δ 176.06, 143.00 and 140.99, 128.19, 128.01, 127.75, 127.25, 127.03 and 126.38, 98.00 and 95.03, 81.14 and 77.20, 76.84 and 75.71, 63.08, 61.78, 54.27, 34.04, 30.51, 28.35 and 27.55, 25.55 and 25.38, 19.00, 25.07, 18.57, 17.41, −1.54. HRMS (FAB^+): calcd for $C_{25}H_{39}NO_4SiH$: 446.2727, obsd: 446.2726 (90% bp).

5′-Deoxy-5′-[1-phenyl-1-(4-tetrahydropyranyloxy)-8-amino-8-[{(trimethylsilylethoxy)carbonyl}3-octyn-5-yl]-2′,3′-*O*-isopropylideneadenosine (32b). Reaction was carried out as described for the synthesis of **32a** using 13 mg (50 μmol) glycinate **18** in 2 mL THF and 0.2 mL HMPA cooled to −78 °C, to which was added 50 mL (50 μmol) of 1 M LDA in cyclohexane. The resulting yellow-green solution was stirred at −78 °C for 30 min as the color turned to a light brown at which time a solution of **30b** (13 mg, 50 μmol) in THF was added dropwise. The reaction was monitored by TLC over a period of 6 h as the temperature was maintained at −78 °C for the first 2 h and then between −10 °C and 0 °C for the remaining 4 h. Work up as described for **31a** provided 25 mg (>100%) of crude **31b** as indicated by ^1H NMR, ^{13}C NMR, and HRMS. This material was used directly in the next step.

A solution of **31b** in CH_2Cl_2 (2 mL) and glacial HOAc (ca. 100 μL) was stirred for 1.5 h at room temperature, at which time additional HOAc (ca. 100 μL) was added and stirring continued for a total of 3 h. The reaction solution was concentrated to a volume of ca. 0.5 mL by rotary evaporation and applied directly to a small silica gel column. Elution with EtOAc:CH_3OH:HOAc (8:1:1), provided 9 mg **32b** (49% overall from **30b**). TLC: CH_3CN:H_2O:HOAc (8:1:1), R_f 0.7. ^1H NMR ($CDCl_3$): δ 8.31 (d, 1H, H_8), 7.95 and 7.90 (2d, 1H, H_2), 7.35 (m, 5H, ArH), 6.20 (2 br s, NH_2), 6.05 (d, 1H, $H_{1'}$), 5.53 (m, 1H, $H_{2'}$), 5.00–4.75 [m, 3H, H_a, $H_{3'}$, $(RO)_2CH$], 4.44 (m, 1H, $H_{4'}$), 4.20 (m, 2H, O_2CH_2), 2.70–2.50 (br m, 2H, $H_{6'}$, H_b), 1.90–1.60 [m, 12H, $(CH_2)_3$, $H_{7'}$, $H_{8'}$ and NH_2], 1.01 (CH_2Si), 0.05 [s, 9H, $Si(CH_3)_3$]. Due to the small amount of sample, some peaks were obscured by residual solvent. HPLC (CH_3CN in H_2O (1% TFA), 0→100% over 30 min): t_R 17 min; HRMS (FAB^+) calcd for $C_{38}H_{54}N_6O_7SiH$: 735.3902; obsd. 735.3936 (36% bp)

1-Phenyl-1-hydroxy-8-amino-8-carboxy-3-octyne (34). To the solution of 60 mg (0.135 mmol) of amino ester **32a** in 5 mL of THF was added 0.140 mL of 1 M TBAF in THF at room temperature. TLC analysis after 8 h showed starting material remained. An additional 0.02 mL of 1 M TBAF solution was added. The reaction was worked up by evaporation of the solvent to give 100 mg of crude TBA acid salt, **33**. This material was stirred at 50 °C in 7 mL of glacial acetic acid:H_2O:THF (4:1:2) for 10 h when the solvents were evaporated giving 100 mg crude product. A 10 mg portion of this crude product was purified by anion exchange chromatography as described below. Amberlite IRA-400 (form OH) polystyrene resin was conditioned by washing with ethanol, H_2O then 1 M NH_4OH (pH 12). About 1 g was placed into a Pasteur pipette and washed repeatedly with the same pH 12 solution as above. The sample dissolved in 2 mL of this solution was applied to the top of the resin and washed with 50 mL of pH 12 solution. The eluting solution was changed to pH 3 HOAc for 25 mL and then pH 2 HOAc for 25 mL and finally with pH 1 HOAc for 25 mL. The majority of the desired product came off the column with the pH 3 and pH 2 washings. The product-containing fractions were combined and lyophilized to give 7 mg (99%) of **34** as a solid HOAc salt. TLC showed >95% purity. ^1H NMR (CD_3OD): δ 7.38–7.24 (m, 5H, ArH), 4.72 (t, 1H, H_a), 3.50 (m, 1H, H_b), 2.52 (m, 2H, H_b), 2.18 (m, 2H, H_e), 1.97–1.83 (m, 5H, H_g and O_2CCH_3), 1.57 (pent, 2H, H_f); HRMS (EI): calcd for $C_{15}H_{19}NO_3H$: 261.1365, obsd: 261.1349 (7% bp).

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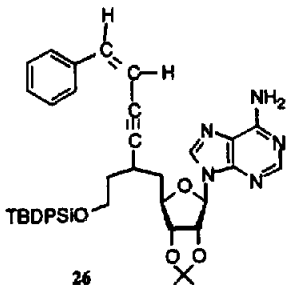

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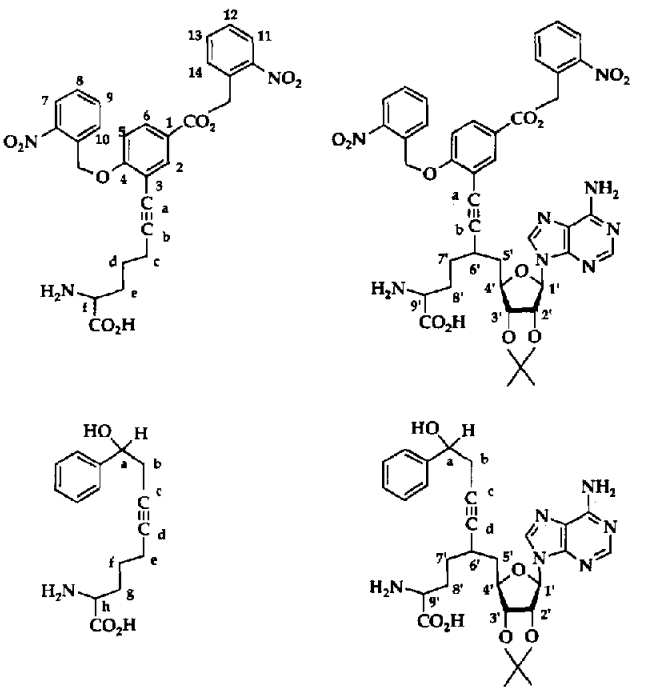

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