Synthesis of 8-(ω-Hydroxyalkyl)-, 8-(ω-Hydroxyalk-1-enyl)-, and 8-(ω-Hydroxyalk-1-ynyl)adenines Using the *tert*-Butyldimethylsilyloxymethyl Group, a New and Versatile Protecting Group of Adenine

Pascal Lang, Géraldine Magnin, Gérald Mathis, Alain Burger,* and Jean-François Biellmann

Laboratoire de Chimie Organique Biologique, UMR 7509, Faculté de Chimie, Université Louis Pasteur, 1 rue Blaise Pascal, 67008 Strasbourg Cedex, France

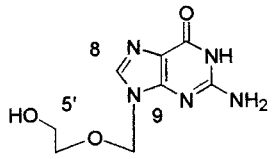
aburger@chimie.u-strasbg.fr

Received May 31, 2000

The synthesis of 12 analogues of adenine substituted at C-8 by an ω-hydroxyalkyl, ω-hydroxyalk-1-enyl, or ω-hydroxyalk-1-ynyl chain of various length has been carried out in five or six steps starting from adenine. The analogues were obtained using a new protecting group of adenine, the *tert*-butyldimethylsilyloxymethyl group. 9-*tert*-Butyldimethylsilyloxymethyl-adenine is more soluble than adenine in organic solvents. It was prepared regiospecificaly in two steps from adenine and was amenable to C-8 iodination under basic conditions and to subsequent introduction of the various carbon chains at C-8 by palladium-catalyzed cross-coupling reactions (Stille or Sonogashira). The protecting group was removed under acidic conditions, thus demonstrating its versatility.

Introduction

Acyclonucleosides represent a class of nucleoside analogues with promising antitumoral activities and with strong antiviral activities against herpes virus, hepatitis virus, retroviruses including HIV, and other viruses. The lead compounds are acyclovir **1**, 9-(2-hydroxyethoxymethyl)guanine, and **2** (PMEA, adefovir), 9-(phosphonomethoxyethyl)adenine.[1]



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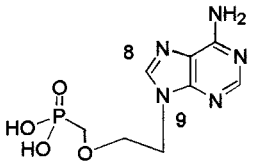

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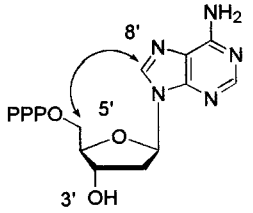

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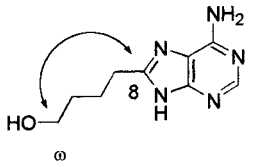

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After cellular phosphorylation, these molecules, lacking the 3′ hydroxyl group of the natural substrate, lead to chain termination or inhibition of DNA elongation and illustrate that cyclic carbohydrate is not necessarily required in order to mimic nucleoside binding to enzyme. In the fight against AIDS and other viral infections, it is important to find new molecules that are more active and more specific. For example, the development of drug resistance remains a major problem in the treatment of HIV disease and AIDS, even in the context of the multidrug combination therapy now widely in use. Thus, the important therapeutic value of acyclonucleosides has attracted the attention of nucleoside chemists. Whereas a large variety of N-9 modified purine analogues have been prepared,[2] only a few examples of C-8 modified purines are known. Modification at C-8 is another attractive position[3] to be explored for the preparation of new adenine analogues. In support of this idea, a recent X-ray crystal structure of 2′-deoxythymidine triphosphate and a DNA duplex bound to HIV-1 reverse transcriptase showed that the base of the nucleotide substrate adopts an *anti* conformation for complementary base pairing with the template.[4] For a productive binding to the active site, 2′-deoxyadenosine triphosphate **3** should adopt a comparable *anti* conformation, thereby pointing the C-8 hydrogen of the base in the direction of the 5′ triphosphate of the deoxyribose counterpart. As part of a project directed toward the synthesis of novel antiviral and antineoplastic agents, we have prepared adenine linked at C-8 by a flexible alkyl or a more rigid alkenyl or alkynyl chain[2] to an ω-hydroxyl group where the suitably oriented terminal hydroxyl group may mimic the 5′ hydroxyl group of 2′-deoxyadenosine (for an example see analogue **4**).

* Ph: +33-3-88-41-68-33.

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(2) For a recent review, see: El Ashry, E. S. H.; El Kilany, Y. *Adv. Heterocycl. Chem.* **1998**, *69*, 129−215.

(3) A number of 8-substituted derivatives of acyclovir have been prepared and evaluated for their antiviral, antimetabolic, and cytotoxic properties. Interestingly, several of them have higher in vitro antiviral specificity than the parent molecule. Robins, M. J.; Hatfield, P. W.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1984**, *27*, 1486−1492.

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10.1021/jo000841o CCC: $19.00
Published on Web 10/21/2000

The preparation of C-8 substituted adenines could be envisioned by two main routes. Both routes involve the completion of the base by ring closure of an imidazole or a pyrimidine precursor[5] but suffer several disadvantages. For instance, the imidazole method involves the introduction of the substituent at an earlier step than in the pyrimidine method. However in the latter approach, ring closure is often difficult to achieve and therefore requires harsh conditions. A more straightforward route is the introduction of the C-8 substituent onto the purine base. The direct introduction of the alkyl substituent is based on alkyl radical addition[6] and C-8 lithiation.[7] Alternative methods involved nucleophilic substitution[8] of an electrophilic base or palladium-catalyzed cross-coupling reactions. Among these methods, protocols using palladium are the most satisfactory with respect to yield, regioselectivity and the scope of the reaction. Although the preparation of C-8 substituted purine nucleosides by palladium-catalyzed coupling procedures is well precedented,[9] the synthesis of 8-alkynyl-adenine analogues is reported in only two publications.[10] Koyama et al.[10a] described the cross-coupling of 8-bromoadenine or 8-bromoadenosine with alkynes in DMSO. In contrast to adenosine, they observed that preparation of the 8-alkynyladenine analogues was difficult by direct coupling and suggested that a N-9-substituent is required for efficient coupling. One major concern in the field of adenine chemistry is its low solubility in most organic solvents. Thus, to prepare the adenine analogues, we needed a protecting group of adenine stable under the conditions required for the chemical modifications and increasing its solubility in organic solvents. Allyl,[11] benzyl,[12] cyanoethyl,[13] and pivaloyloxymethyl[14] groups have been used as protecting groups of adenine; however, none of them fulfilled all the criteria required.[15] The potential application of C-8 substituted-ω-hydroxyl adenines led us to investigate their preparation. In this paper, we described the syntheses of 8-(ω-hydroxyalkyl)-, 8-(ω-hydroxyalk-1-enyl)-, and 8-(ω-hydroxyalk-1-ynyl)adenines of various chain length employing a new protecting group of adenine, the *tert*-butyldimethylsilyloxymethyl group.[16]

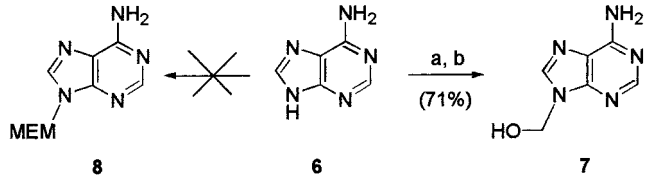
Results and Discussion

Our strategy involves the preparation of an 8-iodoadenine derivative as the key intermediate for the palladium-catalyzed cross-coupling reactions. We initially chose to protect adenine with the trimethylsilylethoxymethyl group (SEM[17]) for the preparation of the C-8 iodo intermediate **5**.

5

We wished to take advantage of both the iodide and SEM protecting group in our initial investigation. Compared to bromo derivatives, higher reactivity of iodo derivatives in palladium-catalyzed cross-coupling reaction is well-known. The SEM protecting group has proven to be useful in ortho metalation of pyrroles and imidazoles[18] and subsequent iodination.[18d] Adenine was successively treated with sodium hydride in DMF and SEMCl to afford the N-9 protected adenine in 50% yield. Iodination was carried out by a procedure similar to that employed for 8-iodo-cordycepin[7e] to give compound **5** in 34% yield. Although the key intermediate **5** can be used for C-8 functionalization, we focused our attention on its preparation in order to improve the low overall yield. We investigated adenine protection in the presence of the methoxyethoxymethyl chloride reagent (MEMCl[19]) instead of the expensive SEMCl (Scheme 1). Since adenine

Scheme 1[a]



[a] (a) 1.2 equiv NaOH, H_2O; (b) MEMCl

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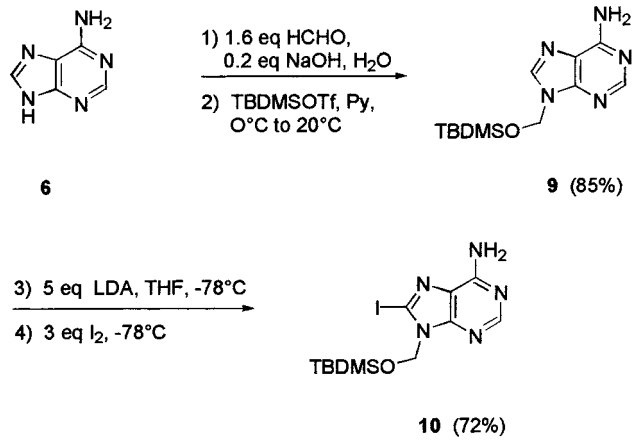
is soluble in water at basic pH and the reactivity of the base at the N-9 position is enhanced under basic conditions,[5] we decided to study the reaction of adenine and MEMCl in alkaline water.

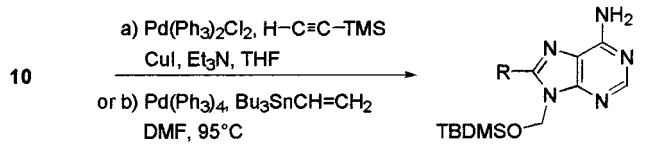
Addition of MEMCl to an alkaline aqueous solution of adenine **6** afforded a precipitate, which was collected by filtration. Unexpectedly, ^{1}H and ^{13}C NMR (DMSO-d_6) and MS analysis showed that the new compound corresponded to the 9-hydroxymethyladenine **7** rather than to the MEM product **8**. For instance, in the ^{1}H NMR spectrum, a singlet at 5.49 ppm integrating for two protons was compatible with the hydroxymethylene. It is unlikely that the formation of the hemiaminal resulted from the decomposition of MEM-adenine. The MEM protecting group is known to be stable in basic media and removable under acid conditions. More likely, the MEMCl reagent hydrolyzed to generate formaldehyde faster than it reacted with adenine. The liberated formaldehyde was then trapped by adenine. Reactions of heterocyclic NH with formaldehyde have precedence in the literature. Katritzky and Akutagawa[20] used formaldehyde as a transient protecting group of benzimidazole. This fortuitous observation led us to develop a new protecting group of adenine, the *tert*-butyldimethylsilyloxymethyl group (Scheme 2).

Scheme 2



The TBDMSO-methyl group was introduced on adenine **6** in two steps. The reaction of adenine with formaldehyde in water was studied under various conditions of reagent concentration and reaction time. The best yield was obtained when a suspension of adenine **6** in water was treated with 0.2 equiv of NaOH followed by addition of 1.6 equiv of formaldehyde for 2 h. A mixture of 9-hydroxymethyl adenine **7** and unreacted adenine **6** was isolated quantitatively in a 86:14 ratio. The ratio of products was determined from the ^{1}H NMR spectrum (DMSO-d_6) of the crude product. The reaction was highly regioselective and none of the other N-3, N-6, and N-7 regioisomers could be observed. The hydroxyl group of the sensitive hemiaminal **7** was then blocked with a TBDMS group. The mixture of compounds was suspended in pyridine at O°C and reacted with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf[21]). The remaining adenine was readily removed at this stage in the aqueous phase during extraction. After washing of the crude extract with hexane, the silyl ether **9** was isolated as a pure compound in 85% overall yield. The N-9 regioselectivity of adenine protection was unambiguously determined by means of UV and NMR.[16] The ^{1}H NMR of **9** showed without any ambiguity that the 6-NH_2 was not substituted as the integration of its signal corresponds to two protons. The absorption spectrum (λ_{max} 262 nm) and the chemical shifts of C-4 (149.1 ppm) and C-5 (118.6) in the ^{13}C NMR spectrum of silyl ether **9** were in agreement with the substitution at N-9. In addition, long-range heteronuclear coupling constants between the methylene protons and the carbons C-2, C-4, and C-8 confirmed this assignment. In the next step, the 8-iodo derivative **10** was prepared in 72% yield after C-8 lithiation of the silyl ether of adenine with excess LDA in THF at −78 °C followed by quenching with iodine. The regiochemical assignment of C-8 iodination was determined by comparison of the ^{13}C spectral data of known adenosine,[22] 2-iodo-,[23] and 8-iodoadenosine[15a] derivatives. Substitution of C-2 or C-8 by iodide affects the chemical shift of these carbons and is characterized by a large upfield shift, whereas the chemical shifts of the other purine carbons are barely affected. An upfield shift varies from 152.2 to 120 ppm for C-2 iodination of adenosine and from 139.8 to 101.4 ppm for C-8 iodination. The spectrum of the iodo compound **10** showed chemical shifts comparable to the signals assigned for the purine carbons of the 8-iodoadenosine derivative. In particular, a characteristic chemical shift of 99.2 ppm was observed as expected for C-8 on iodination in this position.

Having the 8-iodo protected adenine **10** in hand, the utility of this intermediate in palladium-catalyzed cross-coupling reaction was explored in two model reactions with trimethylsilylacetylene and tributylvinylstannane by procedures developed previously for adenosine.[9a,f]



11 (54%) : R = C≡C−TMS
12 (77%) : R = CH=CH$_2$

The reaction of iodo compound **10** with trimethylsilylacetylene in the presence of a catalytic amount of $(Ph_3)_2$-$PdCl_2$, CuI, and Et_3N in THF proceeded smoothly at 20 °C to give the coupling compound **9** in 54% yield (unoptimized). On the other hand, the vinyl group was introduced on adenine in good yield when the reaction was carried out with tributylvinyltin and a catalytic amount of $Pd(Ph_3)_4$ in DMF at 95 °C. Therefore, the 8-iodo intermediate **10** is amenable to conversion to the desired adenine derivatives by a palladium-catalyzed coupling reaction with a suitable source of alkynyl or alkenyl reagents.

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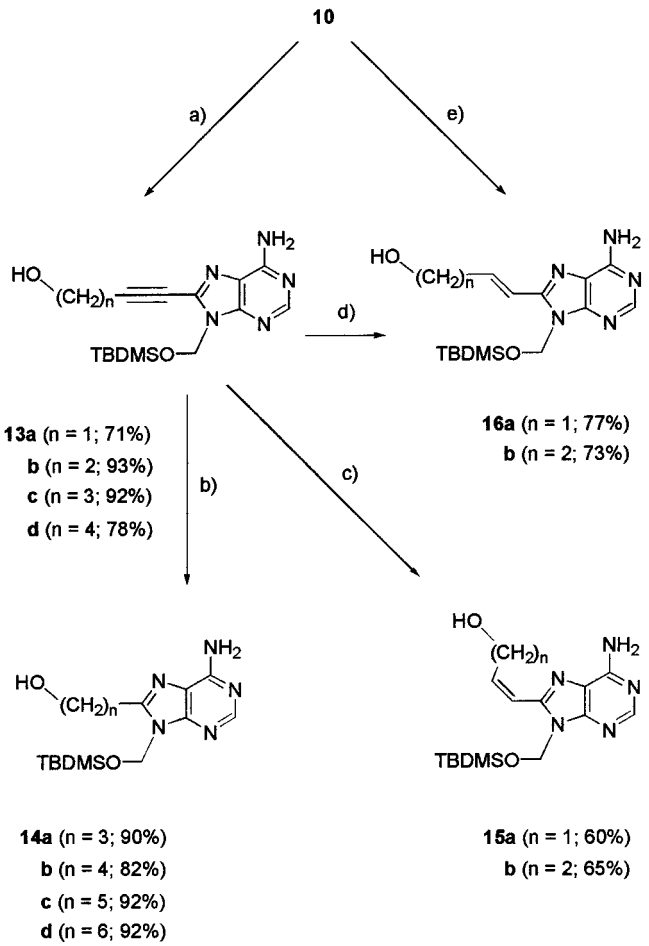
Scheme 3[a]

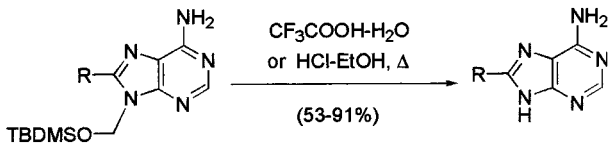


[a] (a) $Pd(Ph_3)_2Cl_2$, CuI, *i*-Pr_2NH, THF, H−C≡C−$(CH_2)_n$OH; (b) Pd/C (10%), H_2, AcOEt/MeOH; (c) for **15a**, Lindlar catalyst, quinoline, H_2, AcOEt/MeOH; for **15b**, Pd/$BaSO_4$, H_2, Py/MeOH; (d) for **16a**, $LiAlH_4$, THF, 0 °C; (e) for **16b**, $Pd(Ph_3)_4$, DMF, 90 °C, (*E*)-Bu_3SnCH=CH-$(CH_2)_2$OH.

The present approach was extended to the preparation of the desired 8-(ω-hydroxyalkyl)-, 8-(ω-hydroxyalkenyl)-, and 8-(ω-hydroxyalkynyl)adenine analogues of various chain length (Scheme 3).

Introduction of the 3−6 carbon chains on C-8 of the purine was achieved in good to excellent yield under Sonogashira and Stille conditions in the presence of the corresponding commercial alkynols and of (*E*)-vinylstannane, respectively. The alkynyl analogues **13a**−**d** are synthetically useful for further transformation, for instance, for the preparation of alkenyl or alkyl derivatives. Indeed, catalytic hydrogenation over palladium under an atmospheric pressure of hydrogen afforded in high yields the corresponding ω-hydroxyalkyl derivatives **14a**−**d**. Partial hydrogenation was illustrated by the reduction of alkynols **13a,b**. Partial reduction of compound **13a** was carried out over Lindlar catalyst in the presence of quinoline[24] and afforded a mixture of (*Z*) alkenyl compound **15a** (69%), (*E*) isomer **16a** (9%), and fully reduced alkyl compound **14a** (22%). The product ratio was deduced from the ^{1}H NMR spectrum ($CDCl_3$) of the crude extract by comparison of the integrations of the H-2 signals. A similar mixture of products was observed on partial reduction over Lindlar catalyst of 8-alkynyladenosine analogues.[9e] The (*Z*) compound **13a** was isolated in 60% yield. Surprisingly, compound **13b** was unaffected when treated under the same conditions but was reduced to the (*Z*) compound **15b** in 65% yield when reacted with another source of poisoned catalyst (Pd/$BaSO_4$[25]). The (*E*) isomers **16a,b** were obtained in good yields by hydride reduction of the propargylic alcohol **13a** with $LiAlH_4$ in THF[26] and, alternatively, for the homologous compound **16b**, under Stille conditions with the readily available (*E*) vinylstannane.[27]

NMR, UV, IR, MS, and combustion analysis of the new compounds furnished physical data in harmony with the assigned structures. For example, on the UV spectra, a significant bathochromic shift of about 30 nm was observed upon conjugaison of a double or a triple bound with the purine base as expected from the Woodward−Fieser rules.[28] Absorption maxima were measured near 265 nm for protected adenine **9** and C-8 alkyl analogues **14a**−**d** and near 295 nm for C-8 alk-1-ynyl and alk-1-enyl derivatives **13a**−**d**, **15a,b**, and **16a,b**. The triple bond of the alkynyl analogues **13a**−**d** was identified in IR by an absorption band near 2240 cm^{-1} and in ^{13}C NMR by two signals at about 70 and 97 ppm. From the ^{1}H NMR spectra, the chemical shifts and the coupling constants of the olefinic protons unambiguously characterized the (*E*) and (*Z*) isomers **15a,b** and **16a,b**, respectively. In $CDCl_3$, (*Z*) olefinic protons appeared at about 6.5 and 6.8 ppm with a vicinal coupling constant of 11.9 Hz, whereas (*E*) olefinic protons appeared at about 6.9 and 7.2 ppm with a vicinal coupling constant of 15.8 Hz.



13a-d : R = −C≡C−$(CH_2)_n$−OH **17a-d**

14a-d : R = −$(CH_2)_{n+2}$−OH **18a-d**

15a,b : R = (*Z*)−CH=CH-$(CH_2)_n$−OH **19a,b**

16a,b : R = (*E*)−CH=CH-$(CH_2)_n$−OH **20a,b**

a : n = 1, **b** : n = 2, **c** : n = 3, **d** : n = 3

The N-9 protecting group of the adenine analogues **13a**, **14a**, **15a,b**, and **16a** was removed under acidic conditions with trifluoroacetic acid in water**.** It should be pointed out that under these conditions, the (*Z*) stereochemistry of the double bound of compounds **15a,b** remained unchanged since no (*E*) isomer was detected on the ^{1}H NMR spectrum of the crude product. For compounds **13b**−**d**, **14b**−**d,** and **16b**, deprotection in CF_3COOH−H_2O was too sluggish but was efficiently conducted with hydrochloric acid in refluxing ethanol. Under these conditions, the product was easily isolated by precipitation of the purine hydrochloride analogue after addition of AcOEt to the reaction medium.

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Conclusion

The synthesis of 12 analogues of adenine, **17**−**20**, substituted at C-8 by an *ω*-hydroxyalkyl, *ω*-hydroxyalkenyl, or *ω*-hydroxyalkynyl chain of various length has been carried out in five or six steps starting from adenine. The analogues were obtained using a new protecting group of adenine, the *tert*-butyldimethylsilyloxymethyl group. This protecting group rendered adenine more soluble in organic solvents facilitating the purification of the adenine derivatives. Furthermore, it was compatible under the different conditions required for the synthesis of the target compounds (LDA, $LiAlH_4$, and Pd-catalyzed reactions) and was removed under acidic conditions, thus demonstrating its versatility. Evaluation of the biological activity of these and other compounds is currently in progress.

Experimental Section

Material and Methods. Melting points are uncorrected. NMR spectra were recorded on either 200 or 400 MHz spectrometers. MS were measured by electronic impact (EI, 70 eV), by chemical ionization (CI, NH_3), or by fast atom bombardment (FAB, matrix nitrobenzyl alcohol). Microanalyses were performed by the Service de Microanalyses de Strasbourg. Unless otherwise indicated, all reagents were obtained from commercial suppliers and were used without purification. All experiments sensitive to air or/and to moisture were carried out under an argon atmosphere in oven dried (120 °C) glassware assembled under a stream of argon. Anhydrous solvents were freshly distilled before use: tetrahydrofuran from sodium benzophenone ketyl, pyridine from CaH_2, and DMF from P_2O_5 (distilled under reduced pressure). Analytical thin-layer chromatography was performed on silica gel precoated TLC plates (Merck, 60, F254). Flash chromatography was performed on silica gel (Merck, 60, 230−400 mesh).

9-Trimethylsilylethoxymethyl-adenine. Adenine (1 g, 7.4 mmol) was added to a suspension of sodium hydride (0.428 g) in anhydrous DMF (18 mL). After 20 h of stirring at 20 °C, trimethylsilylethoxymethyl chloride (1.43 mL, 8 mmol) was added. The mixture was stirred further for 12 h prior to the evaporation of DMF. The residue was dissolved in $CHCl_3$, washed with a saturated $NaHCO_3$ solution and water, and dried (Na_2SO_4), and volatiles were evaporated. Chromatography on silica gel ($CHCl_3$/EtOH, 95:5) afforded SEM-adenine in 50% yield: ^{1}H NMR ($CDCl_3$) δ −0.04 (6H, s), 0.92 (2H, t, J = 8.2 Hz), 3.61 (2H, t, J = 8.2 Hz), 5.58 (2H, s), 5.65 (1H, ls), 7.95 (1H, s), 8.40 (1H, s); ^{13}C NMR (DMSO-d_6) δ −1.49 (p), 17.0 (s), 65.8 (s), 71.3 (s), 118.4 (q), 141.3 (t), 149.7 (q), 152.8 (t), 155.9 (q).

8-Iodo-9-trimethylsilylethoxymethyl-adenine (5). To a suspension of SEM-adenine (0.5 g, 1.9 mmol) in anhydrous THF (12 mL) at −78 °C was added dropwise a solution of LDA (5 equiv) in THF (12 mL) followed by addition of dry HMPA (5 mL). After 6 h of stirring, the reaction solution was treated at −78 °C by dropwise addition of iodine (2.4 g, 9.5 mmol) in dry THF (12 mL). After 30 min, the solution was quenched with acetic acid (0.55 mL); warmed to room temperature; diluted with $CHCl_3$; washed with a 5% sodium metabisulfite solution, a saturated $NaHCO_3$ solution, and water; and dried (Na_2SO_4), and volatiles were evaporated. Chromatography on silica gel ($CHCl_3$/EtOH, 95:5) gave compound **5** in 34% yield: ^{1}H NMR ($CDCl_3$) δ −0.03 (9H, s), 0.94 (2H, t, J = 8.2 Hz), 3.63 (2H, t, J = 8.2 Hz), 5.53 (2H, s), 5.62 (2H, s), 8.30 (1H, s); ^{13}C NMR (DMSO-d_6) δ −1.42 (p), 17.0 (s), 66.1 (s), 72.8 (s), 102.3 (q), 120.5 (q), 151.5 (q), 152.9 (t), 154.6 (q).

9-*tert*-Butyldimethylsilyloxymethyl-adenine (9). A suspension of adenine (8 g, 59.2 mmol) in water (118 mL) was treated with a 0.1 N NaOH solution (29.6 mL, 3.0 mmol) and an aqueous solution of formaldehyde (2.6 mL, 94.7 mmol) (the pH of the 40% aqueous solution of formaldehyde was checked before use and adjusted to neutrality with a 1 N aqueous solution of NaOH). After 2 h of stirring at 20 °C, the suspension, consisting of a mixture of adenine (14%) and hemiaminal **7** (86%), was filtered. The mother liquors were neutralized with 1 N HCl, and an additional amount of products was precipitated out and collected by filtration. The combined solids were dried over P_2O_5 in vacuo. Drying was repeated until P_2O_5 remained a powder. The finely ground intermediate products were suspended in dry pyridine at 4 °C (120 mL) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (17.8 mL, 77.6 mmol) was added. The reaction was allowed to reach room temperature and stirred further for 3 h prior to the evaporation of pyridine. $CHCl_3$ and water were added to the residue. Compound **9** was extracted with $CHCl_3$, and the unreacted adenine was eliminated in the aqueous phase. After evaporation of volatiles, the crude extract was washed with hexane to afford the pure silyl ether **9** in 85% overall yield: mp 228−230 °C; UV(EtOH); λ_{max} 262 nm (ϵ 15700); ^{1}H NMR ($CDCl_3$) δ 0.10 (6H, s); 0.88 (9H, s), 5.62 (2H, ls), 5.75 (2H, s), 7.97 (1H, s), 8.38 (1H, s); ^{13}C NMR (DMSO-d_6) δ −5.3 (p), 17.6 (q), 25.4 (p), 66.3 (s), 118.5 (q), 140.6 (t), 149.1 (q), 153.3 (t), 155.4 (q); MS, CI (NH_4^+), (m/z) 280.2 (MH^+, 100), 222.0 (26), 135.9 (8). Anal. Calcd for $C_{12}H_{21}N_5OSi$: C 51.58, H 7.57, N 25.06. Found: C 51.51, H 7.72, N 25.18.

8-Iodo-9-*tert*-butyldimethylsilyloxymethyl-adenine (10). To a stirred suspension at −78 °C of compound **9** (2.2 g, 7.9 mmol) in anhydrous THF (20 mL) was added dropwise LDA (39.5 mmol) in anhydrous THF (20 mL). After 5 h of stirring, to the solution at −78 °C was added iodine (6 g, 23.7 mmol) in anhydrous THF (20 mL) dropwise in order that the reaction temperature did not exceed −60 °C. The reaction mixture was stirred further for 30 min, quenched with acetic acid (2.25 mL, 39.4 mmol), allowed to reach room temperature and diluted with $CHCl_3$. The mixture was washed with an aqueous solution of sodium metabisulfite, neutralized with a $NaHCO_3$ solution, and washed with water. Evaporation of volatiles, chromatography over silica gel ($CHCl_3$/EtOH, 95:5), and recrystallization in chloroform/hexane afforded **10** in 72% yield: mp >235 °C (dec); UV (CH_3OH) λ_{max} 270 nm (ϵ 15300); ^{1}H NMR ($CDCl_3$) δ 0.12 (6H, s), 0.88 (9H, s), 5.59 (2H, s), 5.68 (2H, s), 8.31 (1H, s); ^{13}C NMR (DMSO-d_6) δ −5.1 (p), 18.1 (q), 25.5 (p), 68.3 (s), 99.2 (q), 122.2 (q), 151.4 (q), 153.1 (t), 153.8 (q); MS (CI, NH_4^+) (m/z) 406.2 (MH^+, 36), 280.2 (100), 135.9 (13). Anal. Calcd for $C_{12}H_{20}IN_5OSi$: C 35.56, H 4.97, N 17.28. Found: C 35.57, H 4.92, N 17.34.

9-*tert*-Butyldimethylsilyloxymethyl-8-trimethylsilylethynyl-adenine (11). To a degassed solution under Ar of compound **10** (200 mg, 0.49 mmol) in THF (4 mL) was added Et_3N (0.14 mL, 0.98 mmol). The solution was degassed once more. CuI (20%, 40 mg), $Pd(PPh_3)_2Cl_2$ (10%, 20 mg), and trimethylsilylacetylene (0.27 mL, 1.97 mmol) were introduced successively. The slurry was stirred for 4 h at 20 °C, volatiles were evaporated, and the crude product was purified by chromatography on silica gel ($CHCl_3$/EtOH, 95:5) to give **11** in 54% yield: ^{1}H NMR ($CDCl_3$) δ 0.12 (6H, s), 0.31 (9H, s), 0.87 (9H, s), 5.74 (2H, s), 5.78 (2H, s), 8.39 (1H, s).

9-*tert*-Butyldimethylsilyloxymethyl-8-vinyl-adenine (12). A solution of compound **10** (500 mg, 1.2 mmol) in DMF (10 mL) was degassed twice. Tetrakistriphenylphosphine palladium (25 mg, 5%) was introduced, and the mixture was degassed once more. Vinyltributyltin (1.8 mL, 6.1 mmol) was added, and the reaction mixture under Ar was stirred at 95 °C for 2 h. After filtration on Celite, DMF was evaporated. Chromatography over silica gel ($CHCl_3$ and $CHCl_3$/EtOH, 98:2) afforded **12** in 77% yield: mp 199−201 °C; UV (CH_3OH) λ_{max} 234 nm (ϵ 24400), λ_{max} 296 nm (ϵ 21100); ^{1}H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.84 (9H, s), 5.73 (1H, dd, J_1= 11.2 Hz, J_2 = 1.4 Hz), 5.78 (2H, s), 5.83 (2H, ls), 6.51 (1H, dd, J_1= 17.4 Hz, J_2= 1.4 Hz), 6.91 (1H, dd, J_1=17.4 Hz, J_2= 11.2 Hz), 8.33 (1H, s); ^{13}C NMR (DMSO-d_6) δ −5.4 (p), 17.9 (q), 25.4 (p), 65.7 (s), 119.0 (q), 149.0 (q), 123.2 (s), 123.9 (t), 150.5 (q), 152.9 (t), 155.1 (q); MS (CI, NH_4^+) (m/z) 306 (MH^+, 100), 248 (50), 218 (4). Anal. Calcd for $C_{14}H_{23}N_5OSi$: C 55.05, H 7.59, N 22.93. Found: C 54.73, H 7.45, N 22.88.

General Procedure 1. Pd-Catalyzed Cross-Coupling Reaction between the Iodo Derivative 10 and the Corresponding Alkynol. To a degassed solution under Ar of compound **10** (500 mg, 1.2 mmol) in THF (10 mL) was added diisopropylamine (3.3 mL). The solution was degassed once more, then CuI (10%, 50 mg), $Pd(PPh_3)_2Cl_2$ (5%, 25 mg), and the freshly distilled alkynol (4 equiv) were introduced successively. The mixture was stirred for 3 h at 20 °C, prior to the evaporation of volatiles. The residue was diluted in a minimum of ethanol and adsorbed on silica gel. Ethanol was evaporated, and the resulting adsorbed crude product was deposed on a column for silica gel chromatography ($CHCl_3$ and $CHCl_3$/EtOH, 95:5).

8-(3-Hydroxypropynyl)-9-*tert*-butyldimethylsilyloxymethyl-adenine (13a). Compound **13a** was obtained in a 71% yield according to general procedure 1: mp 227−229 °C; UV (CH_3OH) λ_{max} 294 nm (ϵ 18850); IR (KBr) 2240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.86 (9H, s), 3.12 (2H, t, J = 6.4 Hz), 3.79 (1H, t, J = 6.4 Hz), 5.68 (2H, ls), 5.78 (2H, s), 8.36 (1H, s);^{13}C NMR (DMSO-d_6) δ −5.4 (p), 17.7 (q), 25.4 (p), 49.3 (s), 66.0 (s), 73.1 (q), 95.2 (q), 118.4 (q), 132.9 (q), 148.8 (q), 153.8 (t), 155.7 (q), MS (CI, NH_4^+) (m/z) 334 (MH^+, 15), 276 (100), 246 (13). Anal. Calcd for $C_{15}H_{23}N_5O_2Si$: C 54.03, H 6.95, N 21.00. Found: C 53.54, H 6.92, N 20.87.

8-(4-Hydroxybut-1-ynyl)-9-*tert*-butyldimethylsilyloxymethyl-adenine (13b). Compound **13b** was obtained in a 93% yield according to general procedure 1: mp 196−198 °C; UV (CH_3OH) λ_{max} 294 nm (ϵ 18300); IR (KBr) 2241 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0,11 (6H, s), 0,86 (9H, s), 2,80 (2H, t, J = 5,9 Hz), 3.92 (2H, t, J = 5.9 Hz), 5.76 (2H, s), 6.09 (2H, s), 8.39 (1H, s); ^{13}C NMR (DMSO-d_6) δ −5.4 (p), 17.7 (q), 23.2 (s); 25.4 (p), 59.1 (s), 65.9 (s), 70.8 (q), 94.9 (q), 118.1 (q), 133.4 (q), 148.8 (q), 153.7 (t), 155.6 (q); MS (CI, NH_4^+) (m/z) 348 (MH^+, 100), 290 (47). Anal. Calcd for $C_{16}H_{25}N_5O_2Si$: C 55.30, H 7.25, N 20.15. Found: C 54.80, H 7.22, N 19.89.

8-(5-Hydroxypent-1-ynyl)-9-*tert*-butyldimethylsilyloxymethyl-adenine (13c). Compound **13c** was obtained in a 92% yield according to general procedure 1: mp 181−182 °C; UV (CH_3OH) λ_{max} 291 nm (ϵ 19800); IR (KBr) 2239 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0,11 (6H, s), 0,87 (9H, s), 1.94 (2H, m), 2,07 (1H, s), 2,69 (2H, t; J = 7 Hz), 3,85 (2H, t, J = 6 Hz), 5,77 (2H, s), 5,80 (2H, s), 8,38 (1H, s); ^{13}C NMR (DMSO-d_6) δ −5.4 (p), 15.3 (s), 17.6 (q), 25.4 (p), 30.9 (s), 59,2 (s), 65.9 (s), 70.2 (q), 96.7 (q), 118.1 (q), 133.4 (q), 148.8 (q), 153.6 (t), 155.6 (q); MS (CI, NH_4^+) (m/z) 362 (MH^+, 100); 304 (42). Anal. Calcd for $C_{17}H_{27}N_5O_2Si$: C 56.48, H 7.36, N 19.37. Found: C 56.74, H 7.36, N 19.49.

8-(6-Hydroxyhex-1-ynyl)-9-*tert*-butyldimethylsilyloxymethyl-adenine (13d). Compound **13d** was obtained in a 78% yield according to general procedure 1: mp 171−172 °C; UV (CH_3OH) λ_{max} 292 nm (ϵ 19200); IR (KBr) 2238 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.11 (6H, s), 0.86 (9H, s), 1.79 (4H, m), 2.17 (1H, s), 2.59 (2H; m), 3.74 (2H, m), 5.76 (2H, s), 6.00 (2H, s), 8.37 (1H, s); ^{13}C NMR (DMSO-d_6) δ −5.4 (p), 17.6 (q), 18.4 (s), 24.2 (s), 25.4 (p,), 31.4 (s), 60.0 (s), 65.8 (s), 70.4 (q), 96.8 (q), 118.1 (q), 133.4 (q), 148.8 (q), 153.6 (t), 155.6 (q); MS (FAB$^+$) (m/z) 376 (MH^+, 100), 318 (42). Anal. Calcd for $C_{18}H_{29}N_5O_2Si$: C 57.47, H 7.78, N 18.65. Found: C 57.41, H 7.50, N 18.84.

General Procedure 2. Total Hydrogenation of Alkynyl Compounds 13a−d. The alkynyl compound **13** (300 mg) was dissolved in a mixture of ethyl acetate and methanol (15 mL, 1:1). Palladium on charcoal was added (30 mg, 10%), and the mixture was degassed and placed under a hydrogen atmosphere. After 2 h, the mixture was filtered on a silica gel pad and the solvents were evaporated. The crude product was recrystallized in a mixture of ethyl acetate and hexane.

8-(3-Hydroxypropyl)-9-*tert*-butyldimethylsilyloxymethyl-adenine (14a). According to general procedure 2, compound **14a** was obtained in a 90% yield: mp 176−178 °C; UV (CH_3OH) λ_{max} 264 nm (ϵ 15450); ^1H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.86 (9H, s), 2.16 (2H, m), 3.11 (2H, t, J = 7.0 Hz), 3.78 (2H, t, J = 5.8 Hz), 5.67 (2H, ls), 5.73 (2H, s), 8.31 (1H, s); ^{13}C NMR (DMSO-d_6) δ −5.5 (p), 17.6 (q), 23.5 (s), 25.4 (p), 30.1 (s), 60.0 (s), 64.9 (s), 117.3 (q), 150.0 (q), 151.9 (q), 152.2 (t), 155.0 (q); MS (CI, NH_4^+) (m/z) 338 (MH^+, 100), 280 (9), 246 (1). Anal. Calcd for $C_{15}H_{27}N_5O_2Si$: C 53.38, H 8.06, N 20.75. Found: C 53.14, H 8.00, N 20.67.

8-(4-Hydroxybutyl)-9-*tert*-butyldimethylsilyloxymethyl-adenine (14b). According to general procedure 2, compound **14b** was obtained in a 82% yield: mp 173−175 °C; UV (CH_3OH), λ_{max} 261 nm (ϵ 13500); ^1H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.85 (9H, s), 1.74 (2H, m), 2.04 (2H, m), 3.00 (2H, t, J = 7.3 Hz), 3.15 (1H, s), 3.73 (2H, t, J = 5.8 Hz); 5.71 (4H, s), 8.31 (1H, s); ^{13}C NMR (DMSO-d_6) δ −5.5 (p), 17.5 (q), 23.4 (s), 25.4 (p), 26.6 (s), 32.0 (s), 60.3 (s), 64.9 (s), 117.4 (q), 142.6 (q), 150.0 (q), 152.2 (t), 155.0 (q); MS (FAB$^+$) (m/z), 352 (MH^+, 100); 294 (40), 264 (2). Anal. Calcd for $C_{16}H_{29}N_5O_2Si$: C 54.67, H 8.32, N 19.92. Found: C 54.90, H 8.19, N 19.56.

8-(5-Hydroxypentyl)-9-*tert*-butyldimethylsilyloxymethyl-adenine (14c). According to general procedure 2, compound **14c** was obtained in a 92% yield: mp 148−149 °C; UV (CH_3OH) λ_{max} 263 nm (ϵ 16800); ^1H NMR ($CDCl_3$) δ 0.07 (6H, s), 0.85 (9H, s), 1.65 (4H, m), 1.97 (2H, m), 2.99 (2H, t, J = 7.2 Hz), 3.35 (1H, s), 3.70 (2H, t, J = 5.9 Hz), 5.71 (2H, s), 5.81 (2H, s), 8.32 (1H, s); ^{13}C NMR (DMSO-d_6) δ −5.4 (p), 17.5 (q), 23.44 (s), 25.1 (s), 25.3 (p), 26.61 (s), 32.3 (s), 60.6 (s), 64.9 (s), 117.8 (q), 149.9 (q), 151.9 (q), 152.23 (t), 155.00 (q); MS (FAB$^+$) (m/z) 380 (MH^+, 100), 22 (41). Anal. Calcd for $C_{17}H_{31}N_5O_2Si$: C 56.03, H 8.54, N 19.15. Found: C 55.86, H 8.55, N 19.16.

8-(6-Hydroxyhexyl)-9-*tert*-butyldimethylsilyloxymethyl-adenine (14d). According to general procedure 2, compound **14d** was obtained in a 92% yield: mp 141−142 °C; UV (CH_3OH), λ_{max} 263 nm (ϵ 14000); ^1H NMR ($CDCl_3$) δ 0.07 (6H, s), 0.85 (9H, s), 1.55 (6H, m), 1.89 (2H, m); 2.99 (2H, t, J = 7.2 Hz), 3.35 (1H, s), 3.70 (2H, t, J = 5.90 Hz), 5.71 (2H, s), 5.81 (2H, s), 8.32 (1H, s); ^{13}C NMR (DMSO-d_6) δ −5.4 (p), 17.5 (q), 25.2 (s), 25.3 (p), 26.8 (s), 26.9 (s), 28.7 (s), 32.3 (s), 60.6 (s), 64.9 (s), 117.8 (q), 149.9 (q), 151.9 (q), 152.23 (t), 155.00 (q); MS (FAB$^+$) (m/z), 380 (MH^+, 100), 322 (41). Anal. Calcd for $C_{18}H_{33}N_5O_2Si$: C 56.96, H 8.76, N 18.45. Found: C 57.08, H 8.75, N 18.52.

(*Z*)-8-(3-Hydroxypropenyl)-9-*tert*-butyldimethylsilyloxymethyl-adenine (15a). Compound **13a** (100 mg, 0.3 mmol) was dissolved in a mixture of ethyl acetate and methanol (8 mL, 1:1). Lindlar's catalyst (20 mg, 20%) and quinoline (2 μL) were added. The mixture was degassed and placed in a hydrogen atmosphere. The progress of the reaction was monitored by TLC. After 4 h of stirring at 20 °C, the mixture was filtered on Celite and the solvents were evaporated. Chromatography on silica gel ($CHCl_3$/EtOH, 95:5) afforded **15a** in a 60% yield: mp 180−182 °C; UV (CH_3OH) λ_{max} 296 nm (ϵ 13900); ^1H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.84 (9H, s), 4.46 (2H, ABX_2, $J_1 \cong J_2$ = 5.8 Hz, J_3 = 1.0 Hz), 5.61 (2H, s), 5.78 (2H, s), 6.12 (1H, ls), 6.56 (1H, ABX_2, J_1 = 11.9 Hz, J_2 = 5.8 Hz), 6.78 (1H, ABX_2, J_1 = 11.9 Hz, J_2 = 1.0 Hz), 8.35 (1H, s); ^{13}C NMR (DMSO-d_6) δ −5.4 (p), 17.6 (q), 25.4 (p), 59.7 (s), 65.1 (s), 113.1 (t), 118.4 (q), 143.2 (t), 146.7 (q), 149.2 (q), 152.6 (t), 155.4 (q); MS (CI, NH_4^+) (m/z) 336 (MH^+, 100), 278 (44), 263 (32), 248 (6).

(*Z*)-8-(4-Hydroxybut-1-enyl)-9-*tert*-butyldimethylsilyloxymethyl-adenine (15b). Compound **13b** (500 mg, 1.43 mmol) was dissolved in a mixture of pyridine and methanol (10 mL, 1:1) and palladium on $BaSO_4$ (100 mg, 20%) was added. The slurry was degassed and was placed under a hydrogen atmosphere. The progress of the reaction was followed by TLC. After 3 h of stirring at 20 °C, the medium was filtered on Celite and the solvents were evaporated. Chromatography on silica gel ($CHCl_3$/EtOH, 95:5) afforded **15b** in a 65% yield: mp 183−184 °C; UV (CH_3OH) λ_{max} 298 nm (ϵ 17700); ^1H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.83 (9H, s), 2.88 (2H, m), 3.93 (2H, t, J = 5.7 Hz), 5.25 (1H, s), 5.59 (2H, s), 5.73 (2H, s), 6.39 (1H, m), 6.76 (1H, d, J = 11.6 Hz), 8.34 (1H, s); ^{13}C NMR (DMSO-d_6) δ −5.2 (p), 17.4 (q), 25.3 (p), 33.0 (s), 60.15 (s), 64.9 (s), 115.6 (t), 118.3 (q), 138.9 (t), 147.0 (q), 149.1 (q), 152.4 (t), 155.3 (q); MS (CI, NH_4^+) (m/z) 350 (MH^+, 5), 334 (30), 319 (55), 292 (100). Anal. Calcd for $C_{16}H_{27}N_5O_2Si$: C 54.98, H 7.79, N 20.04. Found: C 54.98, H 7.68, N 19.74.

(*E*)-8-(3-Hydroxypropenyl)-9-*tert*-butyldimethylsilyloxymethyl-adenine (16a). Compound **13a** (200 mg, 0.6 mmol) was dissolved in anhydrous THF (10 mL). To the cooled solution at 4 °C under Ar, a 1.0 M solution of lithium aluminum hydride in THF (0.6 mL, 0.6 mmol) was added dropwise. The reaction was stirred further for 2 h at 4 °C and then 1 h at room temperature and returned to 4 °C prior to quenching under vigorous stirring by portionwise addition of $Na_2SO_4 \cdot 10H_2O$ (270 mg, 0.8 mmol). After addition, the temperature was gradually warmed to reflux. Refluxing was continued until a white precipitate and a clear solution were obtained. After filtration and solvent evaporation, chromatography on silica gel ($CHCl_3$/EtOH, 95:5) afforded **16a** in a 77% yield: mp 194−196 °C; UV (CH_3OH) λ_{max} 296 nm (ϵ 14700); ^{1}H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.83 (9H, s), 4.46 (2H, m), 5.70 (2H, s), 5.76 (2H, s), 6.87 (1H, ABX_2, J = 15.8 Hz, J = 1.9 Hz), 7.16 (1H, ABX_2, J = 15.8 Hz, J = 4.6 Hz), 8.33 (1H, s); ^{13}C NMR (DMSO-d_6) δ −5.4 (p), 17.6 (q), 25.4 (p), 60.8 (s), 65.0 (s), 114.6 (t), 118.2 (q), 139.7 (t), 147.6 (q), 149.8 (q), 152.2 (t), 155.2 (q); MS (CI, NH_4^+) (m/z) 336 (MH^+, 100), 278 (25), 248 (2). Anal. Calcd for $C_{15}H_{25}N_5O_2Si$: C 53.70, H 7.51, N 20.87. Found: C 53.47, H 7.48, N 20.94.

(*E*)-8-(4-Hydroxybut-1-enyl)-9-*tert*-butyldimethylsilyloxymethyl-adenine (16b). Compound **13b** (500 mg, 1.43 mmol) was dissolved in anhydrous DMF (10 mL), the solution was degassed, $Pd(PPh_3)_4$ (10%, 50 mg) was added, and the mixture was degassed once more. The temperature was raised to 90 °C, and (*E*)-(4-hydroxybut-1-enyl)tributyltin[27] (3 equiv, 4.29 mmol) was added to the mixture under Ar. After 1 h of heating, the solution was diluted with chloroform, washed with water and brine, and dried (Na_2SO_4). Chromatography on silica gel ($CHCl_3$/EtOH, 95:5) and recrystallization (dichloromethane/hexane) gave the pure compound **16b** in a 73% yield: mp 205 °C; UV (CH_3OH) λ_{max} 302 nm (ϵ 19200); ^{1}H NMR ($CDCl_3$) δ 0.05 (6H, s), 0.85 (9H, s); 2.61 (2H, m), 3.85 (2H, t, J = 6.2 Hz), 5.71 (2H, s), 5.76 (2H, s), 6.87 (1H, ABX_2, J_1 = 15.8 Hz, J_2 = 1.9 Hz), 7.16 (1H, ABX_2, J_1 = 15.8 Hz, J_2 = 4.6 Hz), 8.33 (1H, s); ^{13}C NMR (DMSO-d_6) δ −5.4 (p), 17.5 (q), 25.3 (p), 36.2 (s), 60.1 (s), 65.0 (s), 117.9 (t), 118.1 (q), 137.1 (t), 147.6 (q), 149.7 (q), 152.2 (t), 155,2 (q); MS (CI, NH_4^+) (m/z) 351 (MH^+, 2), 334 (3), 292 (100). Anal. Calcd for $C_{16}H_{27}N_5O_2Si$: C 53.70, H 7.51, N 20.87. Found: C 53.47, H 7.48, N 20.94.

General Procedure 3. Removal of the Protecting Group. Method A. The silyl ether (0.6 mmol) was dissolved in a mixture of trifluoroacetic acid and water (5 mL, 9:1). The progress of the reaction was monitored by TLC. When hydrolysis was completed, volatiles were evaporated by azeotropic distillation with cyclohexane. The crude product was triturated with ethanol or alternatively dissolved in water and precipitated by adjusting the pH to 7 with NaOH. The hygroscopic precipitate was collected by filtration.

Method B. The silyl ether was suspended in a mixture of ethanol and hydrochloric acid (98:2) and refluxed for 1 h. To the hot solution was added ethyl acetate, and after cooling to room temperature the hygroscopic solid product was collected by filtration.

8-(3-Hydroxypropynyl)adenine (17a). According to method 3A, acidic hydrolysis of silyl ether **13a** afforded compound **17a** in a 84% yield: mp >160 °C (dec); IR (KBr) 2232 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 4.37 (2H, d, J = 6.0 Hz), 5.57 (1H, t, J = 6.0 Hz), 7.31 (2H, s), 8.11 (1H, s); ^{13}C NMR (DMSO-d_6) δ 49.1 (s), 75.0 (q), 98.1 (q), 118.8, (q), 131.7 (q), 150.3 (q), 153.3 (t), 155.2 (q); MS (IE, 70 eV, after trimethylsilylation) (m/z) 261 (M^+ + TMS, 26), 246 (14), 216 (16), 189 (M^+, 2).

8-(4-Hydroxybut-1-ynyl)adenine, hydrochloride (17b). Silyl ether **13b** was treated according to method 3B to afford compound **17b** in a 84% yield: mp >160 °C (dec); UV (CH_3OH) λ_{max} 292 nm (ϵ 23300); IR (KBr) 2242 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.69 (2H, t, J = 6.5 Hz), 3.63 (2H, t, J = 6.5 Hz), 8.50 (1H, s); ^{13}C NMR (DMSO-d_6) δ 23.0 (s), 58.9 (s), 71.1 (q), 94.5 (q), 115.5 (q), 134.3 (q), 145.7 (q), 149.7 (s), 150.4 (q); HRMS (FAB^+, MH^+) calcd 204.0885, found 204.0882.

8-(5-Hydroxypent-1-ynyl)adenine, hydrochloride (17c). Silyl ether **13c** was treated according to method 3B to afford compound **17c** in a 85% yield: mp >200 °C (dec); UV (CH_3OH) λ_{max} 286 nm (ϵ 20000); IR (KBr) 2238 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.72 (2H, m), 2.59 (2H, t, J = 7.1 Hz), 3.51 (2H, t, J = 6.3 Hz), 8.50 (1H, s), 9.25 (2H, bs); ^{13}C NMR (DMSO-d_6) δ 15.2 (s), 30.7 (s), 59.1 (s), 70.6 (q), 96.2 (q), 135.6 (q), 145.5 (q), 148.9 (s), 150.4 (q); HRMS (FAB^+, MH^+) calcd 218.1042, found 218.1041.

8-(6-Hydroxyhex-1-ynyl)adenine, hydrochloride (17d). Silyl ether **13d** was treated according to method 3B to afford compound **17d** in a 58% yield: mp >180 °C (dec); UV (CH_3OH), λ_{max} 286 nm (ϵ 21600); IR (KBr) 2237 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.62 (4H; m), 2.57 (2H; m), 3.46 (2H; t, J = 5.9 Hz), 8.51 (1H, s), 9.25 (2H; bs); ^{13}C NMR (DMSO-d_6) δ 18.22 (s), 24.0 (s), 31.4 (s), 59.9 (s), 70.8 (s), 96.2 (q), 135.6 (q), 145.6 (q), 148.8 (s), 150.4 (q); HRMS (FAB^+, MH^+) calcd 232.1198, found 232.1200.

8-(3-Hydroxypropyl)-adenine (18a). According to method 3A, acidic hydrolysis of silyl ether **14a** afforded compound **18a** in a 90% yield: IR (KBr) 3400, 3209, 2956, 2933, 2897, 2861, 1618 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.87 (2H; tt, J_1 = 7.5 Hz, J_2 = 6.2 Hz), 2.79 (2H; t, J = 7.5 Hz), 3.47 (2H; t, J = 6.2 Hz), 6.65 (2H, s), 7.98 (1H, s), 8.35 (1H, s).

8-(4-Hydroxybutyl)-adenine, hydrochloride (18b). Silyl ether **14b** was treated according to method 3B to afford compound **18b** in a 80% yield: mp >160 °C (dec); UV (CH_3OH) λ_{max} 266 nm (ϵ 11200); ^{1}H NMR (DMSO-d_6) δ 1.45 (2H, m), 1.81 (2H, m), 2.89 (2H, t, J = 7.5 Hz), 3.40 (2H, t, J = 6.4 Hz), 8.48 (1H, s), 9.04 (2H, bs); ^{13}C NMR (DMSO-d_6) δ 23.6 (s), 28.2 (s), 31.7 (s), 60.11 (s), 113.1 (q), 145.3 (q), 149.4 (q), 150.5 (t), 157.1 (q); HRMS (FAB^+, MH^+) calcd 208.1198, found 208.1205.

8-(5-Hydroxypentyl)-adenine, hydrochloride (18c). Silyl ether **14c** was treated according to method 3B to afford compound **18c** in a 84% yield: mp 167−169 °C; UV (CH_3OH) λ_{max} 266 nm (ϵ 12900); ^{1}H NMR (DMSO-d_6) δ 1.35 (6H, m), 1.81 (2H, m), 2.87 (2H, m), 3.36 (2H, m), 8.49 (1H, s), 9.05 (2H, bs); ^{13}C NMR (DMSO-d_6) δ 24.9 (s), 26.6 (s), 28.3 (s), 31.9 (s), 60.3 (s), 112.8 (q), 145.2 (q), 149.2 (q), 150.5 (t), 157.0 (q); HRMS (FAB^+, MH^+) calcd 222.1355, found 222.1358. Anal. Calcd for $C_{10}H_{16}ClN_5O$: C 46.60 H 6.26 N 27.12. Found: C 46.22 H 6.19 N 27.33.

8-(6-Hydroxyhexyl)-adenine, hydrochloride (18d). Silyl ether **14d** was treated according to method 3B to afford compound **18d** in a 81% yield: mp 166−168 °C; UV (CH_3OH) λ_{max} 266 nm (ϵ 13400); ^{1}H NMR (DMSO-d_6) δ 1.35 (6H, m), 1.77 (2H, m), 2.85 (2H, t, J = 7.5 Hz), 3.34 (2H, t, J = 6.15 Hz), 8.43 (1H, s), 8.93 (2H, bs); ^{13}C NMR (DMSO-d_6) δ 25.1 (s), 23.44 (s), 26.61 (s), 32.3 (s), 60.6 (s), 113.7 (q), 145.3 (q), 149.7 (q), 150.5 (t), 157.5 (q); HRMS (FAB^+, MH^+) calcd 236.1511, found 236.1520.

(*Z*)-8-(3-Hydroxypropenyl)adenine (19a). According to method 3A, acidic hydrolysis of silyl ether **15a** afforded compound **19a** in 91% yield: mp 196−198 °C; UV (CH_3OH) λ_{max} 296 nm (ϵ 9350); ^{1}H NMR (DMSO-d_6) δ 4.38 (2H, bs), 4.76 (1H, bs), 6.15 (1H, m), 6.31 (1H, d, J = 11.9 Hz), 7.06 (2H, bs), 8.08 (1H, s), 12.8 (1H, bs); MS (CI, NH_4^+) (m/z), 192 (MH^+, 46).

(*Z*)-8-(4-Hydroxybut-1-enyl)adenine (19b). According to method 3A, acidic hydrolysis of silyl ether **15b** afforded compound **19b** in a 53% yield: mp 188−190 °C; UV (CH_3OH) λ_{max} 292 nm (ϵ 11400); ^{1}H NMR (CD_3OD) δ 2.96 (2H, m), 3.76 (2H, t, J = 6.3 Hz), 6.19 (1H, m), 6.46 (1H, d, J = 11.8 Hz), 8.14 (1H, s); ^{13}C NMR (CD_3OD) δ 33.8 (s), 62.2 (s), 119.2 (t), 139.5 (t), 150.1 (q), 152.1 (q), 152.9 (q), 156.0 (q); HRMS (FAB^+, MH^+) calcd 206.1043, found 206.1048.

(*E*)-8-(3-Hydroxypropenyl)adenine (20a). According to method 3A, acidic hydrolysis of silyl ether **16a** afforded compound **20a** in a 89% yield: UV (CH_3OH) λ_{max} 294 nm (ϵ 12200); ^{1}H NMR (DMSO-d_6) δ 4.24 (2H, m), 6.62 (1H, ABX_2, J_1 = 16.0 Hz, J_2 = 2.0 Hz), 7.00 (1H, ABX_2, J_1 = 16.0 Hz, J_2 = 4.0 Hz), 8.38 (1H, s), 8.63 (2H, bs); ^{13}C NMR (DMSO-d_6) δ 60.5 (s), 116.2 (t), 141.2 (t), 146.2 (t), 150.3 (q), 151.0 (q), 158.6 (q), 159.3 (q); MS (CI, NH_4^+) (m/z), 192 (MH^+, 15).

(*E*)-8-(4-Hydroxybut-1-enyl)adenine, hydrochloride (20b). Silyl ether **16b** was treated according to method 3B to afford compound **20b** in a 87% yield: mp >160 °C(dec); UV (CH_3OH) λ_{max} 291 nm (ϵ 19900); ^{1}H NMR (DMSO-d_6) δ 2.50 (2H,m), 4.24 (2H, t, J = 6.4 Hz), 6.91 (1H, ABX_2, J = 16.0 Hz), 7.00 (1H, m), 8.49 (1H, s), 9.00 (2H, bs); ^{13}C NMR (DMSO-d_6) δ (ppm): 36.0 (s), 59.5 (s), 119.2 (t), 140.25 (t), 145.2 (t), 149.6 (C-8); 150.7 (C-4); 152.0 (C-6); HRMS (FAB$^+$, MH$^+$) calcd 206.1043, found 206.1042.

Acknowledgment. The Agence Nationale de la Recherche sur le Sida (ANRS) is gratefully acknowledged for financial support.

JO000841O