***N*-(2-Pyridyl)glycine hydrochloride**: mp 200–205 °C dec (lit.[19] mp 190 °C).

***N*-(2-Pyridyl)glycine**: mp 170–174 °C (lit.[19] mp 175 °C).

***N*-(2-Pyridyl)-α-alanine hydrochloride**: mp 198–210 °C dec; ^{1}H-NMR (DMSO-d_6, 60 MHz) δ 1.5 (d, 3 H, J = 7.8 Hz, Me), 4.8 (q, 1 H, J = 7.8 Hz, CH), 7.4 (m, 2 H), 7.7–8.1 (m, 2 H), 8.8–9.6 (m, 1 H); IR (KBr) ν 1730, 1650 (CO) cm^{-1}. Anal. Calcd for $C_8H_{11}N_2O_2Cl$: C, 47.40; H, 5.43; N, 13.83, Cl, 17.53. Found: C, 47.12; H, 5.67; N, 13.96; Cl, 17.79.

***N*-(2-Pyrimidinyl)-α-alanine**: mp 180–183 °C (H_2O); ^{1}H NMR (DMSO-d_6, 60 MHz) δ 1.3 (d, 3 H, J = 7.0 Hz, Me), 4.2 (qt, 1 H, $J_1 = J_2$ = 7.0 Hz, CH), 6.3 (t, 1 H), 7.0 (d, 1 H, NH), 7.9 (d, 2 H); IR (KBr) ν 1695 (CO) cm^{-1}. Anal. Calcd for $C_7H_9N_3O_2$: C, 50.30; H, 5.38; N, 25.10. Found: C, 49.98; H, 5.65; N, 25.04. The corresponding hydrochloride salt was a viscous yellow oil.

***N*-(2-Thiazolyl)-α-alanine hydrochloride**: mp 170–190 °C dec; ^{1}H NMR (DMSO-d_6, 60 MHz) δ 1.5 (d, 3 H, J = 7.2 Hz, Me), 4.7 (q, 1 H, J = 7.2 Hz, CH), 7.0 (d, 1 H), 7.3 (d, 1 H); IR (KBr) ν 1740 (CO) cm^{-1}. Anal. Calcd for $C_6H_9N_2O_2SCl$: C, 34.53; H, 4.31; N, 13.43; S, 15.34; Cl, 17.02. Found: C, 34.34; H, 4.36; N, 13.58; S, 15.32; Cl, 17.29.

***N*-(2-Pyrimidinyl)phenylglycine hydrochloride**: mp 185–190 °C; ^{1}H NMR (DMSO-d_6, 60 MHz) δ 5.7 (s, 1 H, CH), 7.0 (t, 1 H), 7.2–8.0 (m, 5 H), 8.6 (d, 2 H); IR (KBr) ν 1730, 1640 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_3O_2Cl$: C, 54.23; H, 4.52; N, 15.82; Cl, 13.37. Found: C, 54.51; H, 4.43; N, 15.52; Cl, 13.12.

***N*-(2-Thiazolyl)phenylglycine hydrochloride**: mp 86–92 °C; ^{1}H NMR (DMSO-d_6, 60 MHz) δ 5.8 (s, 1 H, CH), 6.9 (d, 1 H), 7.1–7.7 (m, 6 H); IR (KBr) ν 1730 (CO) cm^{-1}. Anal. Calcd for $C_{11}H_{11}N_2O_2SCl$: C, 48.79; H, 4.06; N, 10.35; S, 11.83; Cl, 13.12. Found: C, 48.52; H, 4.37; N, 10.32; S, 11.90; Cl, 12.87.

Hydrolysis of α-Amino Ester 4g. Following the general procedure for the hydrolysis of α-amino esters **4**, 0.2 g of compound **4g** in 5 N hydrochloric acid (2 mL) were heated under reflux for 3 h. After this time the solvent was removed under vacuo and the white crystalline solid thus obtained was treated with saturated sodium carbonate solution (4 mL). In this way 0.19 g of a yellow powdered solid was obtained. This compound was identical with an authentic sample of 2-phenyl-1*H*-imidazo[1,2-*a*]pyridinium-3-olate (**2**, X = CH).[13]

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Registry No. **2** X = CH, Ar = Ph, 106492-20-0; **3** R = Me·$HClO_4$, 126190-30-5; **4a**, 100377-28-4; **4b**, 53051-79-9; **4c**, 126190-19-0; **4d**, 126190-20-3; **4e**, 28036-34-2; **4f**, 126190-21-4; **4g**, 126190-22-5; **4h**, 126190-23-6; **4i**, 126190-24-7; **4j**, 126190-25-8; **4k**, 126190-26-9; **4l**, 126190-27-0; **4m**, 126190-28-1; **4n**, 126190-29-2; **5a**, 52946-88-0; **5a**·HCl, 112656-88-9; **5d**·HCl, 122886-09-3; **5k**, 126190-31-6; **5l**·HCl, 126190-33-8; **5m**·HCl, 126190-32-7; **5n**·HCl, 126190-34-9; glyoxal, 107-22-2; pyruvaldehyde, 78-98-8; phenylglyoxal, 1074-12-0; 2-aminopyridine, 504-29-0; 4-methyl-2-aminopyridine, 695-34-1; 5-chloro-2-aminopyridine, 1072-98-6; 2-aminopyrimidine, 109-12-6; 2-aminothiazole, 96-50-4; 2-aminopyrazine, 5049-61-6.

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Synthesis of Complex 6′-Alkynyl-6′-dethia Nucleoside Analogues of *S*-Adenosylhomocysteine as Potential Inhibitors of Methyltransferases

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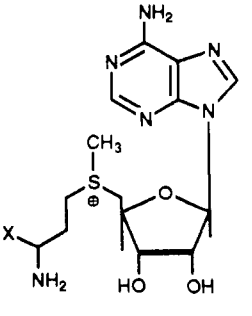
The synthesis of complex acetylenic nucleosides containing a 5′,6′ carbon–carbon bond has been investigated. Two synthetic routes were studied, both starting with an α-substituted butyrolactone. The lactone could be converted to an β-keto sulfone and then to the corresponding enol phosphate diphenyl ester. Reductive elimination to yield the desired aryl acetylene could not be effected without some overreduction to the substituted olefin. Alternatively, the lactone could be converted to an appropriately protected γ-hydroxy aldehyde which was then homologated to a terminal acetylene. The successful synthesis of a prototypic member of the target class of compounds involved a Pd-mediated coupling of an aryl iodide to the appropriately functionalized terminal acetylene. The resulting aryl acetylene was then further elaborated to the target amino acid derivative; viz, a 6′-alkynyl-6′-dethia analogue of *S*-adenosylhomocysteine.

Introduction

The reaction of a variety of cellular nucleophiles with electrophilic biochemical alkylating agents such as *S*-adenosylmethionine (AdoMet, **1**) or its decarboxylated derivtive, dcAdoMet, **2**, is extremely important in cellular metabolism. AdoMet acts as a methyl donor in the methylation of molecules as diverse as catecholamines and nucleic acids.[1] Similarly dcAdoMet acts as an aminopropyl donor in the biosynthesis of the cationic polyamines, spermidine and spermine, which are known to interact with anionic nucleic acids[2] and otherwise affect cell growth and differentiation.



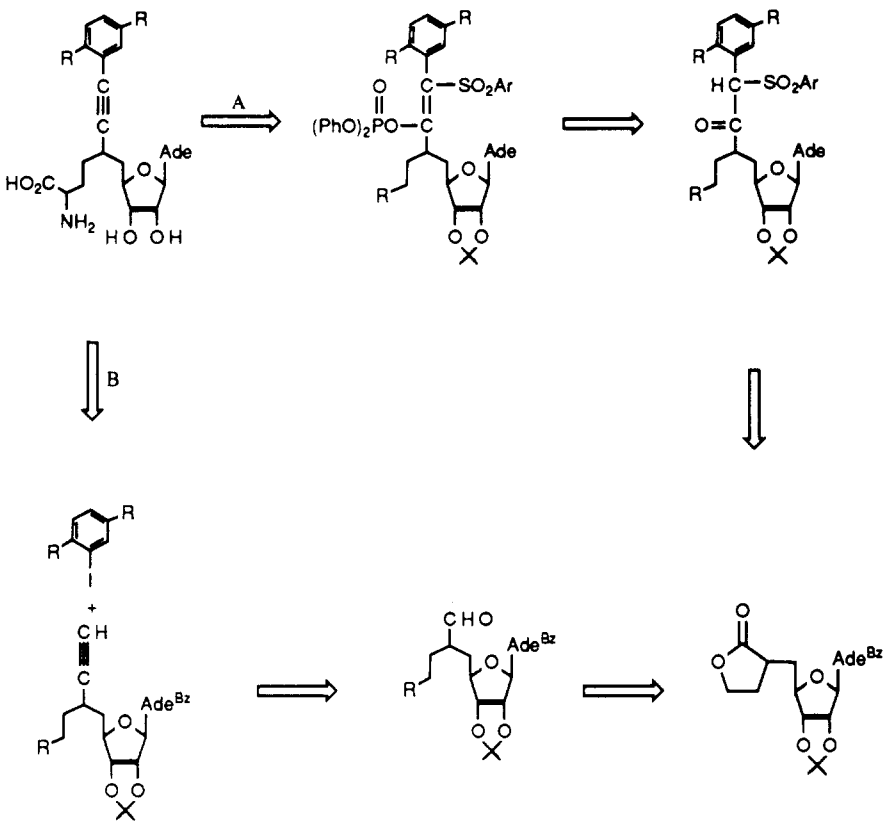
1, X=CO_2H
2, X=H

Stereochemical studies of the reactions catalyzed by methyltransferases, e.g., catechol *O*-methyltransferase (COMT),[3] and aminopropyltransferases, e.g., spermidine

(1) *Biological Methylation and Drug Design*, Borchardt, R. T., Creveling, C. R., Ueland, P. M., Eds.; Humana Press: Clifton, NJ, 1986.
(2) Tabor, C. W.; Tabor, H. *Ann. Rev. Biochem.* **1984**, *53*, 749.

0022-3263/90/1955-3147$02.50/0

Scheme I



synthase,[4] have led to the conclusion that these alkyl-transfer reactions involve a direct S_N2 attack of the nucleophilic substrate on the electrophilic substrate. It is not yet clear whether general base catalysis of intramolecular alkyl-transfer reactions, observed in several model reactions,[5] is operative in the case of the enzyme-catalyzed reactions. Kinetic studies have shown that both COMT and spermidine synthase are severely inhibited by accumulation of the thioether products, *S*-adenosylhomocysteine (AdoHcy) and 5′-deoxy-5′-(methylthio)adenosine, respectively.[6] A large number of laboratories have been involved in the synthesis and biological evaluation of a wide variety of structural analogues of these naturally occurring product inhibitors.[6] Although many of these compounds have been of considerable utility in the study of intracellular alkyl-transfer reactions, it is unlikely that one can obtain specific inhibition of a particular alkyl-transfer reaction of interest by using a structural analogue of a product which is common to all such reactions. As a result, we have undertaken the synthesis of a series of "multisubstrate adduct" inhibitors of methyltransferases[7] and aminopropyltransferases.[8,9] In the case of the aminopropyltransferases, the multisubstrate adduct inhibitors have proven to be extremely potent inhibitors and exquisitely specific for the target enzyme, spermidine synthase[10] or spermine synthase.[11] These compounds have been used extensively in the study of the regulation of polyamine biosynthesis in vitro.[12]

There is considerable interest in the development of selective COMT inhibitors as adjuncts to the dopamine precursor, L-DOPA, in the treatment of Parkinson's disease.[13] Unfortunately, our initial attempts to design synthetic multisubstrate adduct inhibitors for a methyltransferase such as COMT have not met with as much success.[7] Encouraged by the results with aminopropyltransferases briefly summarized above, we have undertaken the synthesis of a new class of compounds designed to be specific inhibitors of individual methyltransferases of interest. Considering the mechanistic data obtained by ourselves (loc. cit.) and others,[14] we have proposed a transition state **3** for the COMT-catalyzed reaction in which the 3-hydroxyl group attacks the electrophilic methyl group in a classic S_N2 mechanism. A reasonable mimic of this array is represented by **5** or **6**, incorporating surrogates for the COMT nucleophilic substrates, 3,4-dihydroxybenzoic acid or epinephrine, respectively, and the electrophilic methyl donor, AdoMet, connected via an acetylenic moiety. In this paper, we describe the synthesis of **4**, a prototypic member of this new class of compounds, viz, 6′-alkynyl-6′-dethia analogues of AdoHcy. In principle, it should be possible, using the synthetic methods described in this paper, to place a variety of substituents on

(3) Woodard, R. W.; Tsai, M.-D.; Floss, H. G.; Crooks, P. A.; Coward, J. K. *J. Biol. Chem.* **1980**, *255*, 9124.
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(8) Tang, K.-C.; Mariuzza, R.; Coward, J. K. *J. Med. Chem.* **1981**, *24*, 1277.
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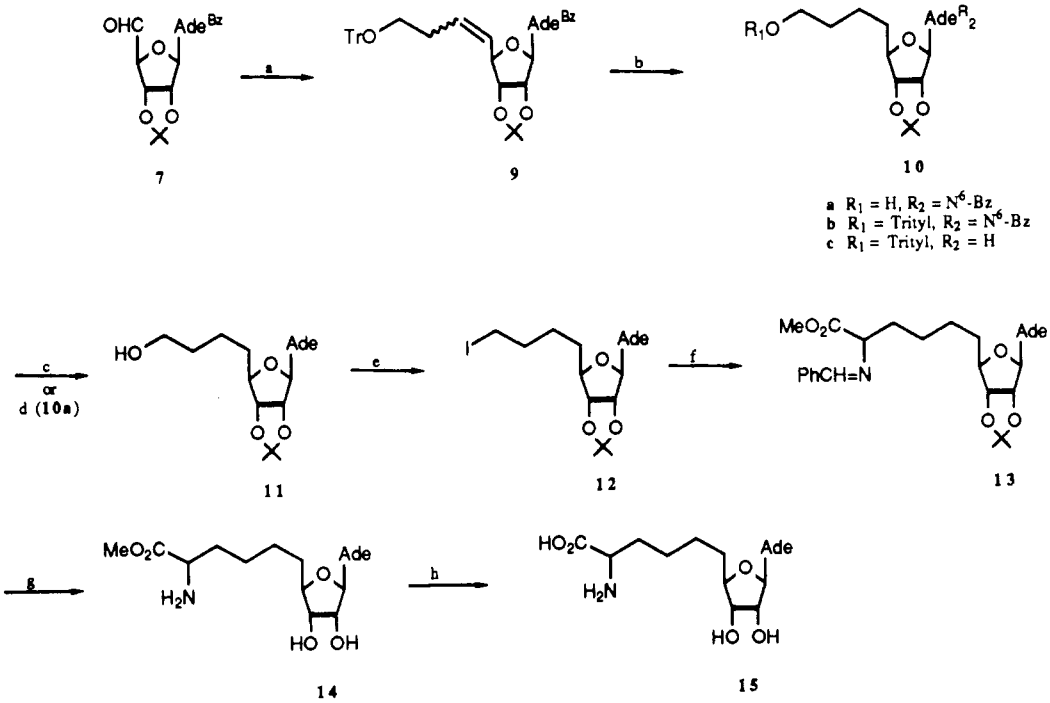
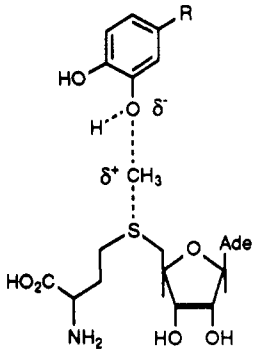
Scheme II[a]

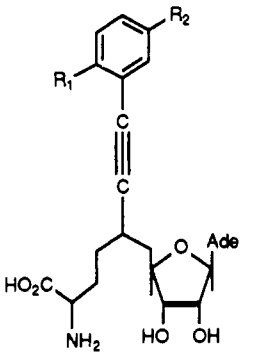


[a] Reagents: (a) $TrO(CH_2)_3P^+Ph_3Br^-$ (8), *n*-BuLi, THF; (b) H_2/PtO_2, EtOH, 60 psi; (c) Li/NH_3; (d) NH_4OH, aqueous MeOH; (e) $(PhO)_3P^+CH_3I^-$, CH_2Cl_2; (f) $PhCH{=}NCH_2CO_2Me$/LDA, THF/HMPA; (g) 80% HCO_2H; (h) K_2CO_3, MeOH/H_2O.

the alkyne which mimic the nucleophilic component of the ternary complex for any one of the multitude of AdoMet-dependent specific methyltransferases.



3



4, $R_1{=}R_2{=}H$
5, $R_1{=}OH$, $R_2{=}CO_2H$
6, $R_1{=}OH$
$R_2{=}CH(OH)CH_2NHCH_3$

Results and Discussion

Synthetic Strategy (Scheme I). The two routes which were investigated to develop a general synthesis of **4–6** are outlined retrosynthetically in Scheme I. The synthesis of the target compounds via route A involves the reductive elimination of a phosphoenol arylsulfonyl nucleoside. This nucleoside could be derived from the corresponding β-ketosulfonyl nucleoside, and this β-ketosulfonyl nucleoside could be synthesized by the coupling of an aryl sulfonyldianion to a lactone nucleoside or its equivalents. Via route B, **4–6** could be obtained by the arylation of a terminal acetylenic nucleoside with an aryl iodide. The terminal acetylenic nucleoside could be derived from the corresponding aldehyde nucleoside, and the aldehyde nucleoside could be synthesized from the same lactone nucleoside. It was envisioned that the amino acid portion of the target compounds could be elaborated by addition of an amino acid equivalent to an electrophilic carbon, e.g., alkyl halide or sulfonate on the side chain. Therefore, the synthesis of the 6′-dethia analogue of AdoHcy (**15**) was investigated as a model for this type of synthetic elaboration. In addition to the synthetic purpose, 6′-dethia AdoHcy is of use as a less complex compound, lacking the catecholamine portion of **6**, in the enzyme inhibition studies.

Synthesis of the 6′-Dethia Analogue of AdoHcy (Scheme II). The synthesis of the 6′-dethia analogue of AdoHcy **15** is shown in Scheme II. The phosphonium bromide **8** used in the first step was prepared by tritylation of 3-hydroxypropyl bromide with trityl bromide, DMAP, and Et_3N in DMF,[15] followed by the triphenylphosphine treatment of the resulting O-tritylated intermediate in refluxing benzene. Condensation of **8** with the anhydrous 5′-aldehyde nucleoside **7**[16] in the presence of *n*-BuLi in THF from −78 °C to 0 °C smoothly produced the bond-extended cis and trans olefinic nucleoside **9** (about 2:1 ratio of cis:trans) in 89–95% yield. Detritylation and reduction of the double bond of **9** by catalytic hydrogenation was not straightforward. Several attempts to effect these two reactions either simultaneously or stepwise using catalytic hydrogenation and/or treatment with Li/NH_3 or Na/NH_3 failed to give the desired alcohol, **11**, in acceptable yields.[17–19] Hydrogenation of **9** with Adams catalyst (PtO_2) at 60 psi of hydrogen pressure for 3 days afforded only a 24% yield of the desired N^6-benzoyl hydroxypropyl nucleoside **10a** along with 68% of the N^6-benzoyl O-trityl-protected nucleoside **10b** and 7% of the debenzoylated O-trityl-protected nucleoside **10c**. It is known that palladium hydroxide on carbon[20] is an effective catalyst for

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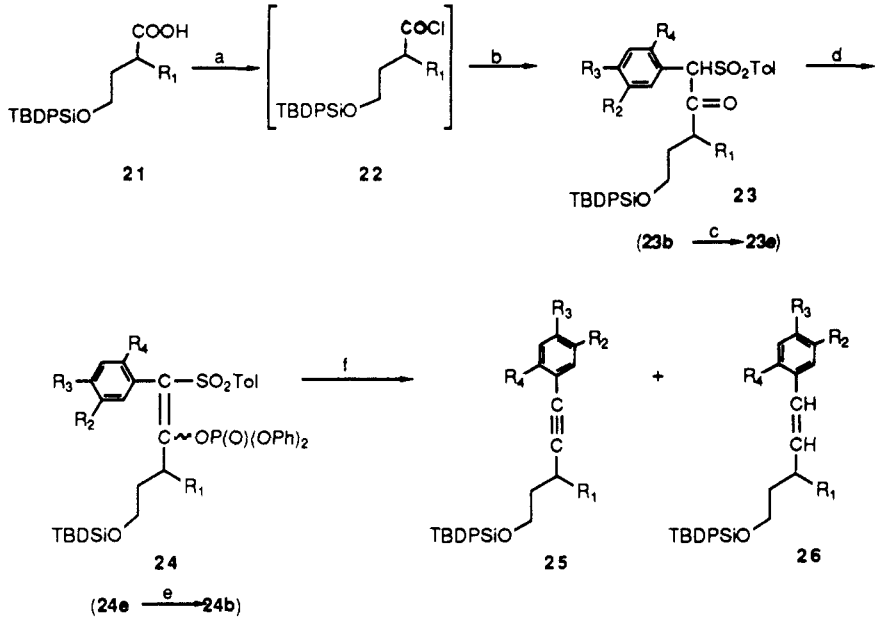
Scheme III[a]



	R1	R2	R3	R4
a	CH_3	H	OCH_3	H
b	2',3'-ipAdo	H	OCH_3	H
c	CH_3	CH_3	H	OCH_3
d	2',3'-ipAdo	CH_3	H	OCH_3
e	N^6-DMF-2',3'-ipAdo	H	OCH_3	H

[a] Reagents: (a) $SOCl_2$; (b) 5-R_2-4-R_3-2-R_4-C_6H_2-CH_2SO_2Tol(16 or 17)/BuLi, THF; (c) $(MeO)_2CHN(Me)_2$, DMF; (d) $ClP(O)(OPh)_2$, DMAP, Et_3N, CH_3CN; (e) HOAc/EtOH/H_2O (v/v, 3/2/1); (f) 5.65% Na-Hg, THF/DMSO.

debenzylation, and Hanessian et al.[21] have used this catalyst to achieve a successful detritylation in their studies. Using this catalyst (32% by weight) for the detritylation of the mixture of **10b** (major) and **10c** (minor) in EtOH under 50 psi of hydrogen pressure for 3 days gave 31% of **10a** and 24% of **11**. Debenzoylation of the isolated **10a** with ammonium hydroxide in methanol[22] at room temperature for 18 h produced **11** in 89% yield. Ultimately, the conditions described in the Experimental Section were found to be optimal for the conversion of **9** to **11** without purification of the intermediates **10a–c**. The hydroxypropyl nucleoside **11** was converted to the iodopropyl nucleoside **12** in 75–77% yield by reacting **11** with methyltriphenoxyphosphonium iodide in methylene chloride.[23] Treatment of the benzylidene-derived methyl glycinate[24] with 1 equiv of lithium diisopropylamide (LDA) followed by 1 equiv of **12** in THF and HMPA from −78 °C to room temperature provided the desired adduct **13** in 95% crude yield. ^1H NMR and TLC studies of the crude **13** indicated that the conversion of **12** to **13** was completed. Purification of **13** was not attempted due to its instability toward silica gel chromatography. Acid hydrolysis of the crude **13** with 90% trifluoroacetic acid at room temperature for 20 min[22] in order to cleave both the isopropylidene and the benzylidene groups also caused a great deal of depurination. Better results were achieved by using 80% formic acid[25] at room temperature for 5–6 h which gave a much cleaner formate salt of **14**. Pure **14** (free of the formate salt) could be obtained by the purification of crude **14** on preparative reverse-phase (C-18) HPLC. However, it is more convenient to convert the crude **14** directly to the final product **15**. Thus, base hydrolysis of the methyl ester group of **14** with 5 equiv of K_2CO_3 in aqueous MeOH[25] at room temperature overnight produced the crude 6′-dethia AdoHcy, **15**. A portion of crude **15** was purified on preparative reverse-phase (C-18) HPLC to give pure **15** in 22% overall yield from **12**.

These results, especially those involving the conversion of the hydroxypropyl nucleoside **11** to the 6′-dethia analogue of AdoHcy **15**, and the experience obtained from the preparative reverse-phase HPLC separations of polar molecules provided an experimental basis for the synthesis and purification of the prototype **4** in the route B approach described below.

Route A Approach (Scheme III). The methodology used in this approach for the construction of the carbon–carbon triple bond was developed independently by Bartlett's[26] and Lythgoe's[27] groups in 1978. They reported

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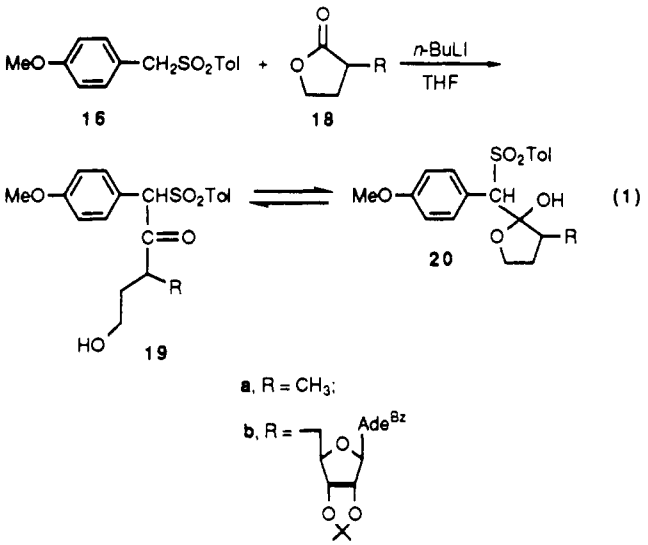
the synthesis of acetylenes in good yields from carboxylic acid derivatives (esters, acid chlorides, and lactone) and alkyl phenyl sulfones. However, similar chemistry with benzyl phenyl sulfones was not explored. For the synthesis of the proposed inhibitors **5** and **6** via this approach, one needs a disubstituted benzylphenylsulfone to couple with a lactone nucleoside. In order to investigate the feasibility of using a benzyl phenyl sulfone in this approach, several model reactions were first carried out (eq 1). When re-

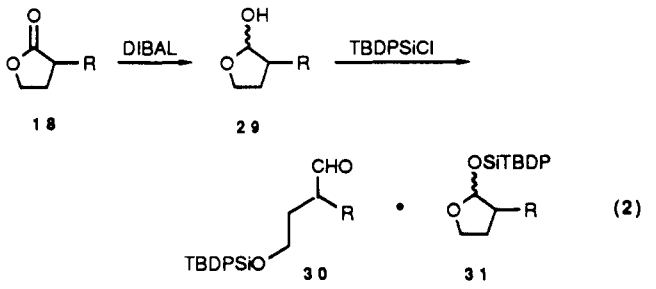


action of α-methyl-γ-butyrolactone, **18a**, with benzyl phenyl sulfone gave only poor yields of the desired β-keto sulfone, even under forcing conditions,[28] the more electron-rich *p*-methoxybenzyl phenyl sulfone, **16**, was investigated. More satisfactory yields were obtained in the reaction of **16** and **18a**, leading to an equilibrium mixture of the desired β-keto sulfone **19a** and the hemiketal **20a**. Unfortunately, when the lactone nucleoside **18b**[29] was allowed to react with the α,α-dilithio derivative of **16** in THF (−78 °C to room temperature) only about 3% of the desired β-ketosulfonyl nucleoside **19b** was isolated.

In order to investigate the reactions of better electrophiles, the acid chlorides **22a** and **22b** were prepared from the corresponding carboxylic acids **21a**[30] and **21b**,[29] respectively, by thionyl chloride treatment (see Scheme III). Condensation of the acid chloride **22a** with the dianion of **16** in THF (−78 °C to −20 °C) gave the β-keto sulfone **23a** in up to 67% yield. In a similar manner, the β-ketosulfonyl nucleoside **23b** was obtained in up to 76% yield from **22b** and **16**. Condensation of **22a** with the dianion of the 2-methoxy-5-methylbenzyl tolyl sulfone **17** furnished the β-keto sulfone **23c** in up to 56% yield. However, when **22b** was reacted with the dianion of **17**, the yields for the desired **23d** ranged only from 19 to 52%. In most of the cases, the yields were in the range of only 30%. Reaction of the dianion derived from **17** with 2-ethylhexanoyl chloride gave the corresponding β-keto sulfone in 80% yield, thus establishing the efficacy of this anion in the synthesis of less complex β-keto sulfones. The *p*-methoxybenzyl keto sulfones, **23a** and **23b**, were further converted to their corresponding enol phosphates. Thus, enol phosphorylation of **23a** with diphenyl phosphorochloridate, 4-(dimethylamino)pyridine (DMAP), and triethylamine in CH_3CN at 70 °C for 30 min produced the enol phosphate **24a** in 78% yield. Reductive elimination of **24a** with 5.65% Na–Hg in THF and DMSO furnished the disubstituted alkyne **25a** in 68% yield. The alkyne **25a** so obtained was contaminated with a trace amount (<5%) of the overreduced olefin **26a**, which was inseparable from **25a**.

In order to convert **23b** to **24b**, one first had to protect the N^6-amino group of the adenosyl moiety of **23b**.[31] Treatment of **23b** with *N,N*-dimethylformamide dimethyl acetal in DMF[32] produced the N^6-imino-protected β-ketosulfonyl nucleoside **23e**. Due to the instability of **23e** toward silica gel chromatography, it was used immediately without purification in the next step. Enol phosphorylation of the crude **23e** with diphenyl phosphorochloridate afforded the N^6-imino-protected enol phosphate nucleoside **24e**. Again without purification, **24e** was deprotected at its N^6-imino group selectively with acetic acid in aqueous ethanol to achieve the desired enol phosphate nucleoside **24b** in 38% overall yield from **23b**. Unfortunately, reductive elimination of **24b** (0.1 mmol) with 5.6% Na–Hg in THF and DMSO produced a 42% yield of an unseparated mixture of the desired alkyne nucleoside **25b** and the overreduced olefin nucleoside **26b**. The ratio of **25b** to **26b** could not be determined using ^1H NMR because of the complexity of the spectrum.[33] Our investigation of the route A approach has revealed several drawbacks as described above. However, this route is effective in affording nonnucleoside aryl acetylenes such as **25a** in good yield (41% overall from **21a**).

Route B Approach (Scheme IV). One of the two key steps in the route B approach is the conversion of an aldehyde to a terminal acetylene. Corey and Fuchs reported in 1972[34] the synthesis of terminal acetylenes from the corresponding aldehydes via dibromo olefins. This method was adopted by Jones et al.[35] in the synthesis of the chain-extended acetylenic nucleoside from the corresponding N^6-benzoyl-2′,3′-isopropylidene-adenosine 5′-aldehyde. Based on the compatibility of a nucleoside with the Corey and Fuchs chemistry, as demonstrated by Jones et al., this method was investigated. Reduction of the lactone **18a** with 1.2 equiv of DIBAL in toluene and THF gave the lactol **29a** (eq 2). Without isolation, **29a** was

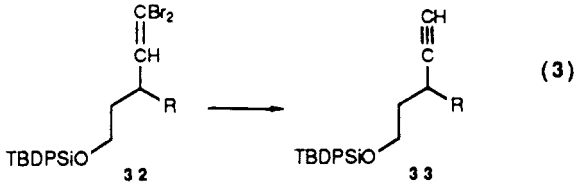


immediately treated with TBDPSiCl to afford the desired *O*-silyl-protected aldehyde **30a** in 26% overall yield from **18a**. The undesired **31a** was not observed. Similarly, reduction of **18b** with 2.5–3.5 equiv of DIBAL in toluene

(28) Kaiser, E. M.; Solter, L. E.; Schwarz, R. A.; Beard, R. D.; Hauser, C. R. *J. Am. Chem. Soc.* **1971**, *93*, 4237.
(29) Lyga, J. W.; Secrist, J. A. III *J. Org. Chem.* **1983**, *48*, 1982.
(30) The acid **21a** was prepared in three steps from **18a** in a similar manner to that described[29] for the synthesis of **21b** from **18b**.
(31) Initial attempts to phosphorylate **23b** directly with diphenyl phosphorochloridate resulted in the formation of N^6-phosphorylated β-ketosulfonyl nucleoside.
(32) Holy, A. In *Synthetic Procedures in Nucleic Acid Chemistry* Zorbach, W. W., Tipson, R. S., Eds.; Wiley: New York, 1968; Vol. I, p 172.
(33) The mass spectrum of the mixture gave a ratio of 45:55 for the molecular ions of **25b** (717 amu) vs **26b** (719 amu).
(34) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(35) Jones, G. H.; Moffatt, J. G.; Rudinskas, A. J.; Simpson, R. Abstract, 172nd National Meeting of the American Chemical Society, 1976, CARB 96.

and THF smoothly afforded the lactol nucleoside **29b** in 62–86% yield. Silylation of **29b** with TBDPSiCl under various conditions frequently gave an inseparable mixture of the desired O-silylated aldehyde nucleoside **30b** and the undesired O-silylated lactol nucleoside **31b**. Among the many reaction conditions studied,[36] the best result obtained was 88% total yield with a ratio of **30b**:**31b** equal to 73:27. A similar problem was also observed by Nicolaou and Magolda[37] in their silylation of a six-membered ring lactol.

Treatment of the mixture of **30b** and **31b** with CBr_4 (2 equiv), PPh_3 (2 equiv), and Zn dust (2 equiv) in CH_2Cl_2 resulted in quantitiative recovery of the unreacted starting mixture. The consumption of the in situ generated phosphorus ylide, $Ph_3P{=}CBr_2$, by the deprotonation of N^6-amide proton of the purine base might be the cause of this failure. Therefore, treatment of the same mixture of **30b** and **31b** with 6 equiv of CBr_4, 6 equiv of PPh_3, and 6 equiv of Zn in CH_2Cl_2 smoothly gave the desired dibromo olefinic nucleoside **32b** in 66% yield, corrected for the recovery of the inert silylated lactol **31b**. The conversion of **32b** to the corresponding terminal acetylenic nucleoside, **33b** (eq 3), was first attempted with 4 equiv of *n*-butyl-



(3)

lithium (2 of the 4 equiv of *n*-BuLi were used to prevent the interference arising from the deprotonation of the N^6-amide and possibly the C-8[38] protons of the adenine ring) in THF (−78 °C to 0 °C). These reaction conditions produced a very complex crude mixture as indicated by its TLC analysis. After extensive efforts to effect a chromatographic separation of this mixture, less than 22% yield of the debenzoylated terminal acetylenic nucleoside **33c** and a 3% yield of the α-isomer of the N^6-benzoylated terminal acetylenic nucleoside were isolated.[39] Corey and Fuchs also used 1.5% lithium amalgam in THF as an alternative method to convert those dibromo olefins which are sensitive to alkyllithium to the desired terminal acetylenes. However, numerous attempts to employ 1.5% Li–Hg in the conversion of **32b** to **33b** gave only a complex mixture of products.[36] In conclusion, the results obtained from both methods (i.e. *n*-BuLi and 1.5% Li–Hg), indicate that routine synthesis of the terminal acetylenic nucleoside is not practical using the method of Corey and Fuchs.

Better results were obtained when the dimethyl (diazomethyl)phosphonate **34**[40] was used for the one-step conversion of **30b** to **33b**. Treatment of the mixture of **30b** and **31b** with **34** in the presence of potassium *tert*-butoxide in THF from −78 °C to room temperature smoothly produced the desired N^6-benzoylated terminal acetylenic nucleoside **33b** in 56–77% yield, corrected for the recovery of the inert **31b** (Scheme IV). The characteristic ^1H NMR identification of **33b** is the unique two sets of doublets due to the acetylenic CH (ca. 2:1 ratio of diastereomers) at ca. 2.05 ppm with an allylic coupling constant of 2.4 Hz. The arylation of terminal acetylenes with aryl iodides or bromides using palladium(II)[41] or palladium(0)[42] and copper iodide resulting in the formation of disubstituted alkynes are well-documented. Initial attempts to arylate the terminal acetylenic group of **33b** with 1 equiv of iodobenzene, 0.02 equiv of $(PPh_3)_2PdCl_2$, and 0.005 or 0.02 equiv of CuI in Et_3N (nondeoxygenated) under N_2 at room temperature according to Hagihara's procedure,[41a] resulted in the formation of greenish-blue reaction solutions without the expected precipitate, $Et_3N{\cdot}HI$. At the end of the reactions, only unreacted **33b** was isolated. The arylation was further investigated with the model terminal acetylene **33a** by using the same reaction conditions as above (0.02 equiv of CuI) with nondeoxygenated solvent. This time the reaction solution was brown in color, and the expected precipitate was observed. At the end of the reaction, a 92% crude yield of the desired arylated product was obtained. The presence of the greenish-blue color might indicate oxidation of the active copper(I) to the inactive copper(II) in the nondeoxygenated solvent. Without the active copper(I) catalyst, the arylation will not occur. For the model arylation reaction, on the contrary, the color of the reaction and the high yield of the desired product suggest that the oxidation of copper(I) to copper(II) did not occur. One possible explanation for the difference between the nucleoside **33b** and the model compound **33a** toward the arylation reaction is that the heterocyclic adenine moiety of **33b** might catalyze the oxidation of copper(I) to copper(II) in the oxygen-containing solvent. When **33b** was treated with 1.07 equiv of iodobenzene, 0.04 equiv of $(PPh_3)_2PdCl_2$, and 1.01 equiv of CuI in fully deoxygenated Et_3N at 50 °C under argon for 3 h, followed by overnight at room temperature, the disubstituted arylalkyne nucleoside **35** was smoothly produced in 78% yield. The use of noncatalytic amounts of CuI is due to the concern of any possible interactions between the copper catalyst and the carbonyl oxygen of the N^6-benzoyladenine moiety of **33b**.[43]

Proceeding further along in Scheme IV, debenzoylation of **35** with methanolic ammonium hydroxide at room temperature for 18 h gave the debenzoylated nucleoside **36** in 94% yield. Desilylation of **36** with tetrabutylammonium fluoride in THF with 1% HOAc produced the hydroxy nucleoside **37** in 82–97% yield. The addition of 1% HOAc to the reaction solution serves to prevent the possible formation of ring closure products, such as **40** and **41**.[44] Treatment of **37** with methyltriphenoxyphosphonium iodide in CH_2Cl_2 furnished the iodo nucleoside **38** in 77–86% yield. Displacement of the iodo group of **38** proceeded smoothly with the carbanion of the

(36) Yau, E. K.; Ph.D. Thesis, Rensselaer Polytechnic Institute, Troy, NY, 1987.

(37) Nicolaou, K. C.; Magolda, R. L. *J. Org. Chem.* **1981**, *46*, 1506 and references therein.

(38) Maki, Y.; Suzuki, M.; Kameyama, K.; Sako, M. *J. Chem. Soc., Chem. Commun.* **1981**, 658.

(39) Treatment of **30a** with CBr_4 (2 equiv), PPh_3 (2 equiv), and Zn dust (2 equiv) in CH_2Cl_2 according to the Corey and Fuchs procedure produced the expected dibromo olefin **32a** in 95% yield. The transformation of the dibromo olefin into the corresponding terminal acetylene **33a** (eq 3) using 2 equiv of *n*-BuLi in THF was achieved in 99% yield. Details on the conversion of **30a** to **33a** are found in the supplementary material.

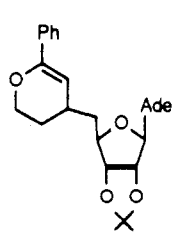
(40) (a) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837. (c) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379.

(41) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627. (c) Robins, M. J.; Barr, P. J. *Tetrahedron Lett.* **1981**, 421. (d) Schroeder, A. C.; Bloch, A.; Perman, J. L.; Bobek, M. *J. Med. Chem.* **1982**, *25*, 1255. (e) Sharma, R. A.; Kavai, I.; Hughes, R. G.; Bobek, M. *J. Med. Chem.* **1984**, *27*, 410. (f) Shealy, Y. F.; O'Dell, C. A.; Arnett, G.; Shannon, W. M. *J. Med. Chem.* **1986**, *29*, 79.

(42) Hobbs, F. W., Jr. *J. Org. Chem.* **1989**, *54*, 3420.

(43) In more recent studies, when the debenzoylated acetylenic nucleoside **33c** was treated with 2,5-disubstituted iodobenzenes, only 0.08 equiv of CuI was needed to achieve 95–99% yields of the desired products (E. K. Yau and J. K. Coward, unpublished results).

(44) (a) Ronald, R. C.; Lansinger, J. M.; Lillie, T. S.; Wheeler, C. J. *J. Org. Chem.* **1982**, *47*, 2541. (b) Garcia, H.; Iborra, S.; Primo, J.; Miranda, M. A. *J. Org. Chem.* **1986**, *51*, 4432.



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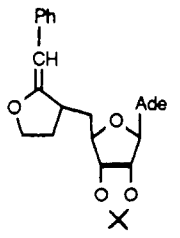

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benzylidene-derived methyl glycinate in THF/HMPA using conditions similar to those described previously for the synthesis of **13**. Acid hydrolysis of crude **39** with 80% formic acid followed by base saponification with K_2CO_3 in aqueous MeOH afforded crude **4**. Purification was achieved on preparative reverse-phase (C-18) HPLC, which gave pure **4** as a white solid in 70% overall yield from **38**. The structure of **4** was confirmed by spectral characterization including ^1H NMR, ^{13}C NMR, FAB, and high-resolution desorption CI mass spectra.

In preliminary studies, the inhibition of COMT by **4** and **15** has been compared with the known potent product inhibitor, AdoHcy. At saturating concentrations of both substrates used, 3,4-dihydrobenzoic acid (2 mM) and AdoMet (100 μM), 94% inhibition was observed at 90 μM AdoHcy whereas 83 μM of the carbon analogue, **15**, produced only 23% inhibition. Similarly, at a concentration of 175 μM of **4**, only 10% inhibition of the COMT-catalyzed reaction was observed. Based on our previous experience with multisubstrate adduct inhibitors of aminopropyltransferases,[8-11] we expected that molecules such as **4** and **15**, lacking the key recognition elements for forming the enzyme–substrate complex, would be poor inhibitors. More complex molecules such as **5** and **6**, which contain these elements, should be more potent inhibitors of this important enzyme.

Conclusion

Of the two routes, A and B, which were investigated for the synthesis of **4**, only route B is satisfacotry for our purposes. Route A is less efficient than route B in terms of the total steps (13 vs 10), yields, and also the formation of the overreduced olefin, most notably in the nucleoside series. The synthesis of **4** has been effected in 10 steps from the starting lactone nucleoside **18b** with an overall yield as high as 18% using route B. The methods developed in this approach for the synthesis of **4** have proven to be practical and efficient for the synthesis of more highly substituted intermediates enroute to **5** and **6** (M. Burns, E. K. Yau, and J. K. Coward, unpublished results). Efforts are currently underway in our laboratory to use these new methods for the synthesis of other members of this class of compounds containing surrogates for the nucleophilic substrates of other *S*-adenosylmethionine dependent methyltransferases which are closely linked in cellular metabolism, e.g., phenethanolamine *N*-methyltransferase in catecholamine biosynthesis. Finally, the use of a linear acetylenic bond linking two substrates together as synthesized in this study, can also be applied to the possible synthesis of multisubstrate analogue inhibitors for other methyltransferases, such as bacterial protein methyltransferase or viral mRNA (guanine-7)-methyltransferase.

Experimental Section

Materials and Methods. Bis(triphenylphosphine)palladium(II) dichloride and sodium *p*-toluenesulfinate were purchased from Alfa Chemical Co. Dimethyl (phthalimidomethyl)-phosphonate was purchased from Lancaster Synthesis Ltd. All reaction solvents were purified by known methods.[45] The phrase "worked up in the usual manner" refers to washing the organic layer with water and saturated brine, drying it over $MgSO_4$, filtering, and evaporating to dryness. Solvent deoxygenation was accomplished by bubbling a stream of argon through the solvent during two freeze–thaw cycles using liquid nitrogen. Melting points were determined in open capillary tubes on a Thomas-Hoover Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on Varian T-60, Perkin-Elmer FTR-600, Varian XL-200, and Bruker (WP-100, WP-270, WM-300, and WM-360) instruments. Proton and carbon resonances are reported as parts per million versus internal standards: tetramethylsilane for organic solvents and 3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt hydrate for D_2O. Phosphorus resonances are reported relative to phosphoric acid. IR spectra were recorded on a Perkin-Elmer 298 spectrometer. UV spectra were recorded on a Perkin-Elmer 552 spectrometer. Low- and high-resolution mass spectra were recorded on a Hewlett-Packard 5987A and a VG Analytical 70-250-S instrument, respectively. Analytical thin-layer chromatography was carried out on silica gel (EM reagents, catalog no. 5775) and reverse phase (Analtech, 250 μm). Semipreparative and preparative silica gel chromatography was performed on precoated plates (Analtech 1000, 1500, and 2000 μm thickness), a Harrison Research Model 7924 chromatotron (Analtech 1-, 2-, and 4-mm rotor plates), flash column,[46] and filtering-column chromatography.[47] Analytical HPLC was performed on an Altex 110A pump with a Whatman Partisil PXS ODS-2 column, a Waters 6000A solvent delivery system with a Z-module C18 cartridge, and a Rainin HXP gradient system with a Dynamax C18 column. Semipreparative and preparative HPLC were done on a Rainin HXP gradient system with Dynamax C18 columns (10 mm × 250 mm and 21.4 mm × 250 mm). α-Methyl-γ-butyrolactone (**18a**) was obtained from Aldrich, and the nucleoside lactone **18b** was prepared as described by Lyga and Secrist.[29] Benzylidine-derived methyglycinate was prepared as previously described.[24]

(3-(Trityloxy)propanyl)triphenylphosphonium Bromide (8). A solution of 695 mg (0.45 mL, 5 mmol) of 3-hydroxypropyl bromide, 1.86 g (5.75 mmol) of trityl bromide, 30.5 mg (0.25 mmol) of DMAP, and 607 mg (0.84 mL, 6 mmol) of Et_3N in 15 mL of dry DMF was stirred at room temperature under N_2 for 1 day. This solution was poured into an ice–water bath with stirring, and the resulting mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was worked up in the usual manner to give 2.23 g of a crude oily product. This crude product was purified by filtering-column chromatography on silica gel ($CHCl_3$; R_f = 0.85) to give 1.88 g (99%) of pure crystalline 3-*O*-tritylpropyl bromide, mp 78–80 °C. ^1H NMR ($CDCl_3$): δ 7.41, 7.26 (2 m, 15 H, ArH), 3.57 (t, J = 6.7 Hz, 2 H, OCH_2), 3.21 (t, J = 5.8 Hz, 2 H, CH_2Br), 2.12 (m, 2 H, CH_2). Mass spectrum (rel intensity): m/e 303 ($M^+ - C_6H_5$, 15).

A solution of the 3-(trityloxy)propyl bromide (6.82 g, 17.9 mmol) and 4.72 g (18 mmol) of PPh_3 in 30 mL of dry benzene was heated at reflux temperature for 10–20 h. The desired product **8** precipitated from solution, was removed from the reaction mixture by filtration, and was washed twice with dry benzene. The combined filtrate was heated at reflux for another 10–20 h. This procedure was repeated five times, and a total of six crops of the desired **8** (7.59 g, 66%) was obtained, mp 235–238 °C dec. ^1H NMR ($CDCl_3$): δ 7.76, 7.27 (2 m, 30 H, ArH), 3.70 (m, 2 H, CH_2P), 3.46 (t, J = 5.7 Hz, 2 H, OCH_2), 1.88 (m, 2 H, CH_2). ^{31}P NMR ($CDCl_3$, ppm): 24.79. Anal. Calcd for $C_{40}H_{36}BrOP$: C, 74.65; H, 5.64; Br, 12.42. Found: C, 74.79; H, 5.85; Br, 12.20.

N^6-Benzoyl-2′,3′-isopropylidene-5′-(3-(trityloxy)-1-propen-1-yl)-5′-deoxyadenosine (9). A suspension of 1.53 g (3.59 mmol) of hydrated **7**[16] in 268 mL of dry benzene was heated at reflux temperature for 60–70 min with a Dean–Stark trap. At the end of the reflux period, the reaction mixture became clear. Benzene was removed under reduced pressure, and anhydrous **7** was obtained as a white foam. ^1H NMR (DMSO-d_6) showed it was 100% free aldehyde: δ 11.27 (br s, 1 H, NH), 9.34 (s, 1 H,

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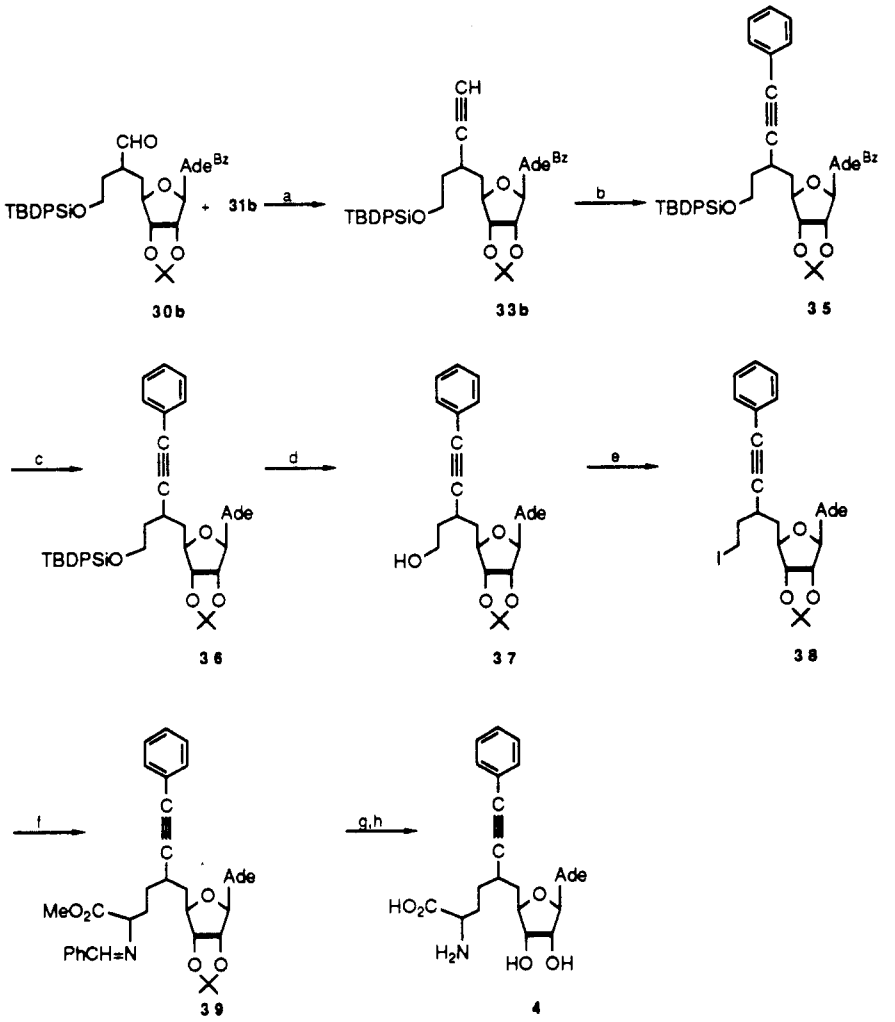
(46) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(47) Yau, E. K.; Coward, J. K. *Aldrichimica Acta* **1988**, *21*, 106–107. For a similar procedure developed independently, see: Pelletier, S. W.; Chokshi, H. P.; Desai, H. K. *J. Nat. Prod.* **1986**, *49*, 892.

Scheme IV[a]



[a] Reagents: (a) $N_2CHP(O)(OMe)_2$ (**34**), KOBu^t, THF; (b) PhI, $(PPh_3)_2PdCl_2$, CuI, Et_3N; (c) NH_4OH, MeOH; (d) $Bu_4N^+F^-$, THF/HOAc (v/v, 99/1); (e) $(PhO)_3P^+CH_3I^-$, CH_2Cl_2; (f) PhCH=NCH_2CO_2Me/LDA, THF/HMPA; (g) 80% HCO_2H; (h) K_2CO_3, $MeOH/H_2O$.

CHO), 8.65, 8.64 (2 s, 2 H, H_8, H_2), 8.07, 7.60 (2 m, 5 H, ArH), 6.59 (s, 1 H, H_1'), 5.54 (dd, J = 1.7, 6.3 Hz, 1 H, H_3'), 5.44 (d, J = 6.3 Hz, 1 H, H_2'), 4.82 (d, J = 1.7 Hz, 1 H, H_4'), 1.55, 1.37 (2 s, 6 H, $C(CH_3)_2$). To a stirred solution of 4.42 g (6.88 mmol) of **8** in 11.5 mL of dry THF was added dropwise 4.98 mL (7.22 mmol) of 1.45 M *n*-BuLi in hexane at −78 °C under nitrogen. This solution was warmed to 0 °C for 10 min and then cooled back to −78 °C. To this solution was added dropwise a solution of 3.58 mmol of the freshly prepared free aldehyde **7** in 5 mL of dry THF. The reaction mixture was stirred at −78 °C for 5 h, −20 °C for 1 h, and 0 °C for 2 h. Aqueous HOAc (50%) was added to quench the reaction. The workup procedure was done in $CHCl_3$ in the usual manner. The crude material was purified by filtering-column chromatography on silica gel (96:4 CH_2Cl_2/MeOH; R_f = 0.51) to give 2.38 g (96%) of *cis*- and *trans*-**9** as a white foam. IR (film, cm^{-1}): 3400, 3200, 3060, 2996, 2920, 1700, 1606, 1585, 1485, 1450, 1250, 1210, 1080, 910. ^1H NMR ($CDCl_3$): δ 9.06 (br s, 1 H, NH), 8.85, 8.83 (2 s, 2:1 ratio, 1 H, H_8), 8.09, 8.08 (2 s, 2:1 ratio, 1 H, H_2), 8.05, 7.43 (2 m, 20 H, ArH), 6.15 (overlapping two sets of d, J = 2 Hz, 1 H, H_1'), 5.92–5.50 (m, 3 H, HC=CH, H_2'), 5.14, 4.70 (two sets of dd, 2:1 ratio, 1 H, H_3'), 4.98 (dd, 1 H, H_4'), 3.13 (m, 2 H, OCH_2), 2.50, 2.31 (2 m, 2 H, CH_2), 1.65, 1.40 (2 s, 6 H, $C(CH_3)_2$). HR mass spectrum calcd for $C_{42}H_{40}N_5O_5$ (MH^+) m/e 694.3029, obsd m/e 694.3032.

2′,3′-Isopropylidene-5′-(3-hydroxyprop-1-yl)-5′-deoxyadenosine (11). A solution of 350 mg (0.5 mmol) of **9**, 100 mg of 5% Pd/C, and 30 mg of PtO_2 in 12 mL of absolute EtOH and two drops of glacial HOAc was shaken in a hydrogenator at 55 psi for 2 days, at which time another fresh 30 mg of PtO_2 and six drops of HOAc were added to this mixture. The hydrogenation was continued at 60 psi for 2 days. After the removal of the catalyst and solvent, a crude mixture of **10a** (minor), **10b** (major), and **10c** (minor) was obtained. This crude mixture was dissolved in 5 mL of dry THF, and to this solution at −78 °C was added 8 mL of liquid NH_3 (freshly distilled over sodium). To this solution was added 34 mg of lithium. The reaction mixture was stirred at −78 °C for 3 h under argon and then quenched with MeOH. The mixture was worked up in $CHCl_3$ in the usual manner. The crude product obtained was purified by filtering-column chromatography on silica gel (step gradient elution with 97:3, 95:5, and finally 90:10 CH_2Cl_2/MeOH) to give 53 mg (30%) of the desired **11**. IR (film, cm^{-1}): 3345, 3185 (very strong, OH, NH_2), 2984, 2920, 2864, 1640, 1595, 1472, 1420, 1375, 1325, 1210, 1075, 910, 865, 730. UV (MeOH): λ_{max} = 258 nm. ^1H NMR ($CDCl_3$): δ 8.35, 7.91 (2 s, 2 H, H_8, H_2), 6.29 (br s, 2 H, NH_2), 6.05 (d, J = 2.3 Hz, 1 H, H_1'), 5.51 (dd, J = 2.3, 6.4 Hz, 1 H, H_2'), 4.83 (dd, J = 3.7, 6.4 Hz, 1 H, H_3'), 4.19 (m, 1 H, H_4'), 3.61 (t, J = 6 Hz, 2 H, OCH_2), 2.80 (br s, 1 H, OH), 1.75–1.39, 1.61, 1.39 (m, 2 s, 12 H, H_5', CH_2, $C(CH_3)_2$). ^{13}C NMR ($CDCl_3$, ppm): 156.07 (C_4), 153.10 (C_2), 149.36 (C_6), 139.69 (C_8), 120.06 (C_5), 114.55 ($C(CH_3)_2$), 90.40, 86.98, 84.29, 84.13 (C_1', C_2', C_3', C_4'), 61.92 (OCH_2), 33.17 (CH_2), 32.36 (C_5'), 27.22, 25.48 ($C(CH_3)_2$), 22.00 (CH_2). HR mass spectrum calcd for $C_{16}H_{24}N_5O_4$ (MH^+) m/e 350.1828, obsd m/e 350.1824.

2′,3′-Isopropylidene-5′-(3-iodoprop-1-yl)-5′-deoxyadenosine (12). Methyltriphenoxyphosphonium iodide (427 mg, 0.95 mmol) was weighed in a glovebag under nitrogen into a two-neck round-bottom flask. To this flask at −78 °C was added dropwise a solution of 220 mg (0.63 mmol) of **11** in 12 mL of dry CH_2Cl_2 (precooled to −70 °C) under nitrogen. The reaction mixture was

stirred while warming from −78 °C to room temperature over 30 min, and then stirred at room temperature for 2 h. The reaction mixture was diluted with $CHCl_3$ and then washed with aqueous $Na_2S_2O_3$. The organic layer was worked up in the usual manner to give 561 mg of a crude product. This crude product was immediately purified by flash column chromatography on silica gel (70:25:5 EtOAc/hexane/EtOH; R_f = 0.24) to give 218 mg (75%) of the desired **12** as a pale yellow foam. IR (film, cm^{-1}): 3320, 3168, 2982, 2940, 1640, 1595, 1472, 1420, 1370, 1325, 1292, 1210, 1155, 1080, 910, 868, 730. UV (MeOH): λ_{max} = 258 nm. ^1H NMR ($CDCl_3$): δ 8.37, 7.91 (2 s, 2 H, H_8, H_2), 6.33 (br s, 2 H, NH_2), 6.05 (d, J = 2.3 Hz, 1 H, H_1'), 5.52 (dd, J = 2.3, 6.4 Hz, 1 H, H_2'), 4.86 (dd, J = 3.7, 6.4 Hz, 1 H, H_3'), 4.16 (m, J = 3.2, 3.7 Hz, 1 H, H_4'), 3.13 (t, J = 7 Hz, 2 H, ICH_2), 1.80–1.30, 1.62, 1.40 (m, 2 s, 12 H, H_5', CH_2, $C(CH_3)_2$). ^{13}C NMR ($CDCl_3$, ppm): 155.94 (C_4), 153.14 (C_2), 149.47 (C_6), 139.92 (C_8), 120.38 (C_5), 114.60 ($C(CH_3)_2$), 90.39, 86.77, 84.30, 84.09 (C_1', C_2', C_3', C_4'), 33.05 (CH_2), 32.25 (C_5'), 27.25, 26.51 ($C(CH_3)_2$), 25.50 (CH_2), 5.97 (ICH_2). HR mass spectrum calcd for $C_{16}H_{23}IN_5O_3$ (MH^+) m/e 460.0846, obsd m/e 460.0855.

5′-(4-Amino-4-carboxybut-1-yl)-5′-deoxyadenosine (15). To 1 equiv of LDA (generated from 1 equiv of diisopropylamine in 17.7 mL of dry THF and 1.4 mL of dry HMPA with 1.05 equiv of n-BuLi at −78 °C) was added dropwise 157 mg (0.89 mmol) of benzylidene-derived methylglycinate[24] at −78 °C under nitrogen. This solution was stirred at −78 °C for 30 min, at which time a solution of 388 mg (0.84 mmol) of **12** in 0.8 mL dry THF was added dropwise at the same temperature. The reaction mixture was stirred at −78 °C for 3 h, −78 °C to 0 °C over 1 h, 0 °C for 1 h, and then room temperature for 2 h. The reaction mixture was diluted with Et_2O, and the Et_2O layer was washed with ice-cold aqueous NH_4Cl. The separated organic layer was worked up in the usual manner to give 420 mg (93%) of a crude yellow foam **13**. IR (film, cm^{-1}): 3212, 3180 (NH_2), 1732 (C=O). ^1H NMR ($CDCl_3$): δ 8.34, 7.92 (2 s, H_8, H_2), 8.26 (s, N=CH), 7.76, 7.43 (2 m, ArH), 6.39 (br s, NH_2), 6.03 (d, H_1'), 5.46 (dd, H_2'), 4.80 (dd, H_3'), 4.14 (m, H_4'), 3.96 (m, CH), 3.73 (s, OCH_3), 2.00–1.30, 1.59, 1.37 (m, 2 s, H_5', CH_2, $C(CH_3)_2$). Mass spectrum (rel intensity): m/e 509 (MH^+, 3.2), 477 ($M^+ - OCH_3$, 0.02), 449 ($M^+ - CO_2Me$, 1.5). A solution of 370 mg (0.73 mmol) of crude **13** in 7.4 mL of 80% HCOOH was stirred at room temperature for 5 h, and the completion of the reaction was checked by TLC (reverse phase, 6:4 MeOH/H_2O). Formic acid was removed in vacuo at room temperature to give the crude methyl ester **14**. The crude **14** could be purified by reverse-phase HPLC with gradient elution of 10–60% solvent A (6:4 CH_3CN/H_2O) in solvent B (0.1 M NH_4HCO_3). Pure **14** could be collected from those fractions with k' = 2.53. UV (MeOH): λ_{max} = 258 nm. ^1H NMR (CD_3OD): δ 8.22, 8.20 (2 s, 2 H, H_8, H_2), 5.94 (d, J = 4.5 Hz, 1 H, H_1'), 4.72 (overlapping two sets of dd, J = 4.5, 5 Hz, 1 H, H_2'), 4.14 (overlapping dd, J = 5 Hz, 1 H, H_3'), 3.98 (m, J = 5, 5.2 Hz, 1 H, H_4'), 3.67 (s, 3 H, OCH_3), 3.43 (t, J = 6 Hz, 1 H, CH), 1.78–1.40 (m, 8 H, CH_2). ^{13}C NMR ($CDCl_3$, ppm): 177.21 (C=O), 157.39 (C_4), 153.93 (C_2), 150.70 (C_6), 141.41 (C_8), 120.65 (C_5), 90.12 (C_1'), 85.64 (C_4'), 75.08 (CH), 54.98, 52.41 (C_2', C_3'), 34.38, 35.44, 26.67, 26.37 (CH_2). FAB mass spectrum (rel intensity): m/e 381 (MH^+, 12).

Routinely, the crude methyl ester **14** was used directly in the following base hydrolysis reaction without further purification. Crude **14** obtained as described above was dissolved in 6.7 mL of 50% aqueous MeOH. Powered K_2CO_3 (436 mg, 5 equiv) was added to the stirred solution. The reaction mixture was stirred overnight at room temperature and then neutralized with 1 N HCl. After solvent removal, the crude residue was extracted with MeOH (5 × 1 mL). The MeOH extract was concentrated in vacuo to give 405 mg of a crude yellow foam. Part of this foam (100 mg) was purified by preparative reverse-phase HPLC with gradient elution of 0–50% solvent A (6:4 CH_3CN/H_2O) in solvent B (0.1 M NH_4HCO_3) to give 14.7 mg of pure **15** (22%) obtained from those fractions with k' = 2.59, and 6.5 mg of the methyl ester **14** (9.5%) recovered from those fractions with k' = 6.59. For the desired **15**, a colorless solid after removal of all NH_4HCO_3. UV (MeOH): λ_{max} = 258 nm. ^1H NMR (CD_3OD): δ 8.22, 8.21, 8.20 (3 s, 2 H, H_8, H_2), 5.94 (d, J = 4.8 Hz, 1 H, H_1'), 4.71 (overlapping dd, 1 H, H_2'), 4.15 (overlapping dd, 1 H, H_3'), 4.01 (m, 1 H, H_4'), 3.52 (m, 1 H, CH), 1.81, 1.50 (2 m, 8 H, $(CH_2)_4$). ^{13}C NMR (CD_3OD–H_2O, ppm): 175.13 (C=O), 156.93 (C_4), 153.83 (C_2), 150.20 (C_6), 141.08 (C_8), 120.11 (C_5), 89.00 (C_1'), 85.52, 85.47 (C_4'), 74.94 (CH), 74.61 (C_3'), 56.10 (C_2'), 33.89, 33.84, 31.80, 31.77, 26.01, 25.96, 25.62, 25.52 (CH_2). FAB mass spectrum (rel intensity): m/e 367 (MH^+, 8.9). HR mass spectrum calcd for $C_{14}H_{23}N_6O_3$ ($MH - CO_2$)$^+$ m/e 323.1832, obsd m/e 323.1827.

***p*-Methoxybenzyl Tolyl Sulfone (16).** To a solution of 6.06 g (38.8 mmol) of *p*-methoxybenzyl chloride in 58 mL of dry DMF was added 7.28 g (40.9 mmol) of sodium *p*-toluenesulfinate at one portion. The reaction mixture was heated at 70 °C for 3 h, at which time DMF was removed in vacuo. The residue was dissolved in CH_3Cl and worked up in the usual manner to give 10.6 g of a white solid. This solid was recrystallized from MeOH to give 9.20 g (86%) of crystalline **16**, mp 121–124 °C. ^1H NMR ($CDCl_3$): δ 7.54–6.77 (four sets of d, 8 H, ArH), 4.23 (s, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 2.42 (s, 3 H, CH_3). Anal. Calcd for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.84. Found: C, 65.11; H, 5.78.

2-Methoxy-5-methylbenzyl Tolyl Sulfone (17). Use of the procedure described for **16** provided 5.59 g (82%) of crystalline **17**, mp 128–129.5 °C. ^1H NMR ($CDCl_3$): δ 7.53–6.54 (m, 7 H, ArH), 4.39 (s, 2 H, CH_2), 3.33 (s, 3 H, OCH_3), 2.40, 2.27 (2 s, 6 H, CH_3). Anal. Calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25; S, 11.04. Found: C, 66.74; H, 6.27; S, 11.34.

General Procedure for the Synthesis of 23a–d (Scheme III). Thionyl chloride (2.22 mL, 30 mmol) was added to 1.5 mmol of the carboxylic acids, **21a**[30] or **21b**[29] at 0 °C under N_2. The mixture was stirred at room temperature for 1 h. The excess of thionyl chloride was removed by a stream of nitrogen. The resulting residue was further evaporated in vacuo for 2 h to give the acid chlorides **22a** or **22b**, which were used directly in the following procedure. To a mechanically stirred 0.67 M solution of **16** or **17** in dry THF was added dropwise a solution of 2.09 equiv of n-BuLi in hexane under nitrogen from −10 to −60 °C. The suspension was stirred at −60 °C for 1 h and then cooled to −78 °C. A solution of the acid chloride, **22a** (0.87 equiv) or **22b** (0.5 equiv), in a minimum amount of THF was added dropwise to this orange suspension. The mixture was stirred at −78 °C for 1–3 h and −20 °C for 30 min and then quenched with aqueous HOAc. The resulting solution was adjusted to pH 7 and then partitioned between water and EtOAc. The organic layer was washed with saturated $NaHCO_3$ and worked up in the usual manner to give the crude products, which were purified as described below. Details on the purification and properties of **23a** and **23c**, both derived from **21a**, are found in the supplementary material.

2′,3′-Isopropylidene-5′-(1-*p*-anisoyl-1-(tolylsulfonyl)-2-oxo-5-((*tert*-butyldiphenylsilyl)oxy)pent-3-yl)-5′-deoxyadenosine (23b). The crude product obtained was purified by filtering-column chromatography on silica gel (95:5 CH_2Cl_2/MeOH; R_f = 0.25) to give 203 mg (76%) pure **23b** as a colorless foam. IR (film, cm^{-1}): 3310, 3175 (br s, NH_2), 1714 (C=O), 1320, 1150 (SO_2). ^1H NMR ($CDCl_3$): δ 8.48–7.92 (m, 2 H, H_8, H_2), 7.66–6.68 (m, 18 H, ArH), 6.06 (m, 3 H, H_1', NH_2), 5.52, 5.50, 5.19 (three sets of dd, J = 2.6, 6.6 Hz, 1 H, H_2'), 5.42, 5.37, 5.33 (3 s, 1 H, *R* and *S* SO_2CH), 5.26, 4.95, 4.62 (dd, 2 m, J = 2.9, 6.6 Hz, 1 H, H_3'), 4.62, 4.32 (2 m, 1 H, H_4'), 3.73 (m, 3 H, OCH_3), 3.80–3.10 (m, 3 H, OCH_2, *R* and *S* CH), 2.38 (m, 3 H, CH_3), 2.38–1.44 (m, 4 H, H_5', CH_2), 1.66–0.88 (br m, 15 H, $C(CH_3)_2$, *tert*-butyl). Anal. Calcd for $C_{48}H_{55}N_5O_8SSi$: C, 64.77; H, 6.23; N, 7.87; S, 3.60. Found: C, 64.69; H, 6.28; N, 7.83; S, 3.55.

2′,3′-Isopropylidene-5′-(1-(2-methoxy-5-methylphenyl)-1-(tolylsulfonyl)-2-oxo-5-((*tert*-butyldiphenylsilyl)oxy)-pent-3-yl)-5′-deoxyadenosine (23d). THF and HMPA (9:1) was used as the reaction solvent. The crude product obtained was purified by filtering-column chromatography on silica gel (70:25:5 EtOAc/hexane/EtOH; R_f = 0.23) to give 435 mg (48%) of **23d** as a foam. IR (film, cm^{-1}): 3330, 3180 (NH_2), 1716 (C=O), 1323, 1150 (SO_2). UV (MeOH): λ_{max} = 258 nm. ^1H NMR ($CDCl_3$): δ 8.38, 8.27, 8.22, 8.01, 7.92 (5 s, 2 H, H_8, H_2), 7.70–7.00, 6.60 (2 m, 17 H, ArH), 6.10, 5.86 (m, d, J = 2 Hz, 4 H, NH_2, $CHSO_2$, H_1'), 5.44, 5.37, 5.14 (dd, d, dd, J = 2, 6.7 Hz, 1 H, H_2'), 5.22, 4.90, 4.54 (dd, 2 m, J = 2.5, 6.7 Hz, 1 H, H_3'), 4.54, 4.18 (2 m, 1 H, H_4'), 3.64 (m, 2 H, OCH_2), 3.34, 3.30, 3.26 (3 s, 3 H, OCH_3), 3.07 (m, 1 H, CH), 2.35, 2.26, 2.14 (3 s, 3 H, CH_3), 2.20–1.25 (m, 10 H, H_5', CH_2, $C(CH_3)_2$), 0.93, 0.89, 0.87 (3 s, 9 H, *tert*-butyl). ^{13}C NMR ($CDCl_3$, ppm): 203.08, 202.85, 202.70 (C=O), 155.68, 155.53, 149.29, 144.36, 144.29, 135.45, 135.38, 135.31, 133.60, 133.48, 131.27, 129.77, 129.67, 129.58, 129.51, 128.80, 128.68, 128.63, 127.72, 127.64, 127.59, 127.55,

110.63 (Ar), 155.19, 155.13 (C_4), 153.14, 153.02 (C_2), 140.07, 139.47 (C_8), 135.15, 135.13 (C_6), 120.17, 120.15 (C_5), 115.81, 115.06, 114.82 ($C(CH_3)_2$), 90.08, 90.02, 89.43 (C_1'), 84.28, 84.25, 84.07, 83.84, 83.68, 83.09 (C_2', C_3', C_4'), 70.05, 69.93 ($CHSO_2$), 60.72 (OCH_2), 55.52, 55.39 (OCH_3), 46.38, 46.06, 45.63 (CH), 33.08, 33.01, 32.33, 31.94, 31.34 (C_5', CH_2), 25.44, 25.38 (*tert*-butyl, $C(CH_3)_2$), 21.54, 20.41 ($ArCH_3$), 19.07, 18.98 (*tert*-butyl). FAB mass spectrum (rel intensity): *m/e* 904 (M^+, 33), 614 (M^+-289, 6).

2',3'-Isopropylidene-5'-(1-*p*-anisoyl-1-(tolylsulfonyl)-2-((diphenoxyphosphinyl)oxy)-5-((*tert*-butyldiphenylsilyl)oxy)-2-penten-3-yl)-5'-deoxyadenosine (24b). A solution of 589 mg (0.66 mmol) of **23b** and 237 mg (0.26 mL; 1.99 mmol) of *N,N*-dimethylformamide dimethyl acetal in 1.33 mL of dry DMF was stirred at room temperature under nitrogen for 10 h. DMF was removed in vacuo, and the resulting residue was coevaporated twice with toluene to give 588 mg of crude **23e**. This crude **23e**, 235 mg (0.18 mL, 0.88 mmol) of diphenyl phosphochloridate, and 18.2 mg (0.14 mmol) of DMAP were dissolved in 1.1 mL of dry CH_3CN. To this solution was added 0.144 mL (1.03 mmol) of Et_3N at room temperature under nitrogen. The reaction mixture was heated at 64 °C for 20 min. The cooled solution was diluted with $CHCl_3$ and worked up in the usual manner to give 627 mg of crude **24e**. This crude product was dissolved in a solution of 23.6 mL of HOAc/EtOH/H_2O (2:3:1, v:v:v). This mixture was stirred at room temperature for 5–6 h. After the removal of solvent in vacuo, the resulting residue was purified by filtering-column chromatography on silica gel (65:30:5 EtOAc/hexane/EtOH; R_f = 0.4) to give 286 mg (38%) of the desired **24b** and 83 mg (11% recovery) of the N^6-protected **24e**. For **24b**. IR (film, cm^{-1}): 3320, 3175 (br s, NH_2), 1320, 1150 (SO_2). ^1H NMR ($CDCl_3$): δ 8.34, 8.32, 8.23, 8.21, 7.99, 7.79 (ms, 2 H, H_8, H_2), 7.70–6.36 (m, 28 H, ArH), 6.11–5.84 (m, 3 H, H_1', NH_2), 5.48–5.29 (three sets of dd, 1 H, H_2'), 5.50, 4.84, 4.55 (2 m, 1 H, H_3'), 4.55, 4.44, 4.16 (m, 1 H, H_4'), 4.04, 2.70 (2 m, 1 H, *R* and *S* CH), 3.82–3.36 (m, 5 H, OCH_3, OCH_2), 2.38, 2.34, 2.32, 2.29 (4 s, 3 H, $ArCH_3$), 2.20–1.36 (m, 10 H, H_5', CH_2, $C(CH_3)_2$), 1.06, 1.04, 0.89, 0.83 (4 s, 9 H, *tert*-butyl). ^{31}P NMR ($CDCl_3$, ppm): −19.65, −19.94, −20.15, −20.37. FAB mass spectrum (rel intensity): *m/e* 1122 (MH^+, 71). HR mass spectrum calcd for $C_{60}H_{65}N_{50}O_{11}PSSi$ (MH^+) *m/e* 1122.3908, obsd *m/e* 1122.3943.

N^6-Benzoyl-2',3'-isopropylidene-5'-(2-hydroxytetrahydrofuran-3-yl)-5'-deoxyadenosine (29b). To a solution of 1.42 g (3 mmol) of **18b**[29] in 40 mL of dry toluene and 30 mL of dry THF was added dropwise 10.1 mL of 1 M DIBAL in toluene at −78 °C under nitrogen. The reaction mixture was stirred at −78 °C for 3 h. A solution of 3 mL of MeOH and 2 mL of aqueous NH_4Cl was added to quench the reaction. The mixture was extracted with EtOAc, and the EtOAc extract was worked up in the usual manner to give 1.35 g of a crude foam. This crude foam was purified by filtering-column chromatography on silica gel (98:2 CH_2Cl_2/MeOH) to give 1.06 g (74%) of foamy **29b** (100% lactol form). IR (film, cm^{-1}): 3265 (OH), 2980, 2930, 1700, 1610, 1570, 1510, 1453, 1250, 1210, 1080. ^1H NMR ($CDCl_3$): δ 9.04 (br s, 1 H, NH), 8.83, 8.11 (2 s, 2 H, H_8, H_2), 8.04, 7.57 (2 m, 5 H, ArH), 6.11 (m, 1 H, H_1'), 5.52 (m, 1 H, H_2'), 5.37, 5.21, 5.07 (3 s, 1 H, OCH), 4.92 (m, 1 H, H_3'), 4.30 (m, 1 H, H_4'), 4.08–3.66 (m, 2 H, OCH_2), 3.09, 2.54 (2 m, 1 H, *R* and *S* CH), 2.18–1.92 (m, 4 H, H_5', CH_2), 1.62, 1.40 (2 s, 6 H, $C(CH_3)_2$). ^{13}C NMR ($CDCl_3$, ppm): 164.78 (N—C=O), 152.66 (C_2), 151.40 (C_4), 149.96 (C_6), 142.28 (C_8), 133.86, 132.63, 128.75, 127.97 (Ar), 123.83 (C_5), 114.97 ($C(CH_3)_2$), 102.87, 97.81 (OCH), 90.59 (C_1'), 85.80 (C_4'), 84.49 (C_2'), 84.17 (C_3'), 66.87, 66.61 (OCH_2), 43.46, 41.14 (CH), 35.65, 32.58 (CH_2), 30.89, 29.19 (C_5'), 27.22, 25.44 ($C(CH_3)_2$). FAB mass spectrum (rel intensity): *m/e* 482 (MH^+ 2.53), 464 ($MH^+ - H_2O$, 3.21). HR mass spectrum calcd for $C_{24}H_{28}N_5O_6$ (MH^+) *m/e* 482.2040, obsd *m/e* 482.2023.

N^6-Benzoyl-2',3'-isopropylidene-5'-(1-formyl-3-((*tert*-butyldiphenylsilyl)oxy)-1-propyl)-5'-deoxyadenosine (30b). To a solution of 481 mg (1 mmol) of **29b** and 68.1 mg (1.01 mmol) of imidazole in 2.81 mL of dry DMF was added dropwise 0.26 mL (*d* = 1.06, 1 mmol) of *tert*-butyldiphenylchlorosilane at room temperature under nitrogen. The solution was stirred at 50 °C for 40 min, at which time 34 mg of imidazole (0.5 mmol) was added in one portion and then immediately followed by dropwise addition of 0.13 mL of *tert*-butyldiphenylchlorosilane (0.5 mmol). The resulting mixture was allowed to continue to stir at 50 °C for 40 min. The above additions and stirring procedure were repeated again. At the end of the reaction, DMF was removed in vacuo, and the resulting residue was worked up in $CHCl_3$ in the usual manner to give 751 mg of crude syrup. This syrup was purified by filtering-column chromatography on silica gel (8:1:1 $CHCl_3$/acetone/EtOAc; R_f = 0.29) to give 636 mg (88%) of a ca. 3:1 mixture of the desired **30b** and the O-silylated lactol **31b**, isolated as a foam. This material is suitable for use in further transformations.

Pure **30b** (free of **31b**) could be obtained in 32–39% yield when DMF/HMPA (1:2 or 1:1; v:v) was used as the reaction solvent in the procedure described above. IR (film, cm^{-1}): 3240 (NH), 3060, 2923, 2844, 1700 (C=O), 1605, 1580, 1505, 1450, 1296, 1210, 1090, 700. ^1H NMR ($CDCl_3$): δ 9.57, 9.53 (two sets of d, *J* = 1.2 Hz, 1 H, *R* and *S* CHO), 9.00 (br s, 1 H, NH), 8.89, 8.06 (2 s, 2 H, H_8, H_2), 8.04, 7.64, 7.44 (2 m, 15 H, ArH), 6.07 (d, *J* = 2 Hz, 1 H, H_1'), 5.46 (dd, *J* = 2, 6 Hz, 1 H, H_2'), 4.90 (dd, 1 H, H_3'), 4.30 (m, 1 H, H_4'), 3.65 (m, 2 H, OCH_2), 2.67 (m, 1 H, CH), 2.20, 1.84 (2 m, 4 H, H_5', CH_2), 1.62, 1.39 (2 s, 6 H, $C(CH_3)_2$), 1.02, 0.99 (2 s, 9 H, *tert*-butyl). ^{13}C NMR ($CDCl_3$, ppm): 203.38, 203.30 (*R* and *S* CHO), 164.65 (C=O), 153.77 (C_2), 151.17 (C_4), 149.80 (C_6), 142.34 (C_8), 135.52, 133.31, 133.26, 132.78, 129.75, 129.64, 129.03 (Ar), 123.70 (C_5), 115.01 ($C(CH_3)_2$), 90.34, 90.25 (C_1'), 85.70–83.90 (ms, C_2', C_3', C_4'), 61.15 (OCH_2), 45.75 (CH), 32.00 (C_5'), 27.02, 25.43 ($C(CH_3)_2$), 26.74, 19.07 (*tert*-butyl). Anal. Calcd for $C_{40}H_{45}N_5O_6Si$: C, 66.74; H, 6.30; N, 9.73. Found: C, 66.70; H, 6.41; N, 9.65.

N^6-Benzoyl-2',3'-isopropylidene-5'-(1,1-dibromo-5-((*tert*-butyldiphenylsilyl)oxy)-1-penten-3-yl)-5'-deoxyadenosine (32b). A suspension of 635 mg (2.42 mmol) of PPh_3, 803 mg (2.42 mmol) of CBr_4, and 158 mg (2.42 mmol) of Zn dust in 19.5 mL of dry CH_2Cl_2 was stirred at room temperature under nitrogen for 1 day, at which time a solution of 290 mg (0.40 mmol) of **30b** and **31b** (3:1) in 1 mL of CH_2Cl_2 was added. The reaction mixture was stirred at room temperature for 7 h. Solvent was removed under reduced pressure, and the resulting residue was purified by filtering-column chromatography on silica gel (65:30:5 EtOAc/hexane/EtOH) to give 86 mg of pure **32b** (R_f = 0.6), in addition to a mixture of 128 mg of **32b** and silylated lactol (**31b**) from the starting material (R_f = 0.52). This mixture was further purified by preparative TLC (eluted three times with 97:3 $CHCl_3$/MeOH) to give 65 mg of pure **32b** and 48 mg of a 1:1 mixture of **32b** and of **31b**. The total yield of the desired **32b** was 175 mg (50%). The yield of **32b**, corrected for the amount of unreactive **31b** in the starting material, is 66% (49.6 ÷ 0.75). IR (film, cm^{-1}): 3240, 3065, 2938, 2858, 1700, 1605, 1580, 1450, 1250, 1210, 1155, 1100, 867, 755, 700. ^1H NMR ($CDCl_3$): δ 9.24 (br s, 1 H, NH), 8.82, 8.79 (2 s, 1 H, H_8), 8.09 (s, 1 H, H_2), 8.02, 7.40 (2 m, 15 H, ArH), 6.13 (two sets of d, *J* = 10 Hz, 1 H, HC=), 6.10 (d, *J* = 2 Hz, 1 H, H_1'), 5.54 (m, 1 H, H_2'), 4.87 (m, 1 H, H_3'), 4.26 (m, 1 H, H_4'), 3.59 (m, 2 H, OCH_2), 2.80 (m, 1 H, CH), 1.96–1.44 (m, 4 H, H_5', CH_2), 1.63, 1.39 (2 s, 6 H, $C(CH_3)_2$), 1.04, 1.00 (2 s, 9 H, *tert*-butyl). Anal. Calcd for $C_{41}H_{45}Br_2N_5O_5Si$: C, 56.23; H, 5.18; Br, 18.25; N, 8.00. Found: C, 56.16; H, 5.22; Br, 18.22; N, 7.94.

Dimethyl (Diazomethyl)phosphonate (34).[40] A solution of 13.2 g (49.1 mmol) of dimethyl (phthalimidomethyl)phosphonate and 1.66 g (1.64 mL; 51.8 mmol) of anhydrous hydrazine in 84.7 mL of dry MeOH was stirred at room temperature under nitrogen for 3 days. A white precipitate was removed by filtration and washed twice with dry MeOH. The combined filtrate was evaporated at 0 °C in vacuo, and the resulting residue was immediately dissolved in 13.6 mL of cold glacial HOAc. While the mixture was mechanically stirred at −17 °C in a round-bottom flask equipped with an inner thermometer, a solution of 4.96 g (71.2 mmol) of $NaNO_2$ in 11.3 mL of ice-cold H_2O was added dropwise. The reaction temperature was kept below −10 °C during the addition of $NaNO_2$. The reaction mixture was stirred at −10 °C for 30 min, 0 °C for 15 min, and then cooled back to −10 °C. To this cold mixture was added slowly, in small portions, 19.6 g of $NaHCO_3$. The mixture was warmed to room temperature, and another 9.82 g of $NaHCO_3$ was added in small portions with vigorous stirring. After the resulting foaming subsided, the mixture was filtered. The filter was washed twice with CH_2Cl_2, and the combined filtrate was diluted with 200 mL of CH_2Cl_2. The CH_2Cl_2 layer was washed with saturated $NaHCO_3$ and NaCl,

dried over with $MgSO_4$, filtered, and concentrated in vacuo. A crude yellow liquid (5.48 g) was obtained. This liquid was subjected to vacuum distillation (short-path) and 3.2 mL (d = 1.27; 4.06 g; 55%) or pure **34** was collected at 45–56 °C (0.15–0.3 Torr) (lit.[40] bp 59 °C (0.42 Torr)). IR (film, cm^{-1}): 2110 (C=N=N), 1250 (P=O), 1030 (P—O—C). ^1H NMR ($CDCl_3$): δ 3.81 (d, J = 0.6 Hz, 1 H, CH), 3.79 (d, J = 11.8 Hz, 3 H, OCH_3). ^1H NMR (neat): δ 4.42 (d, J = 10.5 Hz, 1 H, CH), 3.68 (d, J = 11.8 Hz, 3 H, OCH_3). ^{13}C NMR ($CDCl_3$, ppm, P–C coupled): 54.07 (d, J = 5.4 Hz, OCH_3), 29.64 (d, J = 230.9 Hz, CH). ^{31}P NMR ($CDCl_3$, ppm): 22.52. Mass spectrum (rel intensity): m/e 150 (M^+, 40).

N^6-Benzoyl-2′,3′-isopropylidene-5′-(5-((*tert*-butyldiphenylsilyl)oxy)-1-pentyn-3-yl)-5′-deoxyadenosine (33b). To a magnetically stirred solution of 64.1 mg (0.57 mmol) of potassium *tert*-butoxide in 1.07 mL of dry THF was added dropwise 85.7 mg (0.57 mmol) of **34** in 1.42 mL of dry THF at −78 °C under nitrogen. This solution was stirred at the same temperature for 15 min, and to this solution was added dropwise 360 mg (0.5 mmol) of a ca. 1:1 mixture of **30b** and **31b** in 1.42 mL of THF. The reaction mixture was stirred at −78 °C for 5 h and then quenched with aqueous HOAc. The mixture was worked up in CH_2Cl_2 in the usual manner to give 381 mg of a crude foam. This foam was purified by filtering-column chromatography on silica gel (82:10:8 $Et_2O/CHCl_3$/EtOAc; R_f = 0.4) to give 111 mg (31%) of pure **33b**. The corrected yield of **33b** from **30b** is 56.4% (31 ÷ 0.55). IR (film, cm^{-1}): 3308 (HC≡), 2119 (C≡C). ^1H NMR ($CDCl_3$): δ 9.04 (br s, 1 H, NH), 8.84, 8.83 (2 s, 1 H, H_8), 8.11, 8.08 (2 s, 1 H, H_2), 8.04, 7.64, 7.38 (2 m, 15 H, ArH), 6.12 (d, J = 2.5 Hz, 1 H, H_1'), 5.54 (overlapping two sets of dd, J = 2.5, 6.8 Hz, 1 H, H_2'), 4.94 (m, 1 H, H_3'), 4.56 (m, 1 H, H_4'), 3.76 (m, 2 H, OCH_2), 2.80 (m, 1 H, CH), 2.07, 2.05 (2 d, J = 2.4 Hz, 1 H, R and S HC≡), 1.90 (m, 2 H, H_5'), 1.64 (m, 2 H, CH_2), 1.64, 1.40 (2 s, 6 H, $C(CH_3)_2$), 1.03, 0.95 (2 s, 9 H, *tert*-butyl). ^{13}C NMR ($CDCl_3$, ppm): 165.30, 165.24 (C=O), 153.37 (C_2), 151.86, 151.74 (C_4), 150.37 (C_6), 143.07, 142.89 (C_8), 136.19, 134.25, 133.42, 130.23, 130.17, 129.46, 128.53, 128.28, 128.22, 128.19 (Ar), 124.24 (C_5), 115.42, 115.30 ($C(CH_3)_2$), 104.77 (HC≡), 91.48, 91.32 (C_1'), 86.56, 86.17 (R and S ≡C), 85.73, 85.60, 84.99, 84.94, 84.68, 84.50 (C_2', C_3', C_4'), 61.82, 61.75 (OCH_2), 39.35, 38.71, 38.46, 37.95 (C_5', CH_2), 27.84, 27.82, 27.45, 27.36, 26.06, 25.83, 25.17, 19.83, 19.73 ($C(CH_3)_2$, CH, *tert*-butyl). Mass spectrum (rel intensity): m/e 715 (M^+, 0.12), 658 ($M^+ - C_4H_9$, 10.0). Anal. Calcd for $C_{41}H_{45}N_5O_5Si$: C, 68.79; H, 6.34; N, 9.78. Found: C, 68.73; H, 6.44; N, 9.37.

N^6-Benzoyl-2′,3′-isopropylidene-5′-(5-((*tert*-butyldiphenylsilyl)oxy)-1-phenyl-1-pentyn-3-yl)-5′-deoxyadenosine (35). To a 15-mL two-neck round-bottom flask containing 8.11 mg (0.04 equiv) of $PdCl_2(PPh_3)_2$ and 55.9 mg (1.01 equiv) of CuI was added at room temperature under argon a solution of 208 mg (0.29 mmol) of **33b** in 3.5 mL of fully deoxygenated Et_3N, followed by 35 μL (d = 1.82; 0.31 mmol) of iodobenzene. The reaction mixture was heated at 50 °C with stirring for 3 h (white precipitate was formed) and then at room temperature overnight. Solvent was removed in vacuo, and the resulting residue was dissolved in $CHCl_3$ and washed twice with a 2.5% EGTA suspension. The $CHCl_3$ layer was then worked up in the usual manner to give 235 mg of a crude foam. This foam was purified by filtering-column chromatography on silica gel (9:1 $Et_2O/CHCl_3$; R_f = 0.23) to give 178 mg (78%) of a pale yellow foam **35**. IR (film, cm^{-1}): 2214 (very weak, C≡C). ^1H NMR ($CDCl_3$): δ 9.27 (br s, 1 H, NH), 8.83 (br, s, 1 H, H_8), 8.11, 8.09 (2 s, 1 H, H_2), 8.04–7.26 (2 m, 20 H, ArH), 6.13 (d, J = 2.4 Hz, 1 H, H_1'), 5.55 (overlapping two sets of dd, J = 2.4, 6.7 Hz, 1 H, H_2'), 5.01 (overlapping two sets of dd, J = 3.5, 6.7 Hz, 1 H, H_3'), 4.63 (m, 1 H, H_4'), 3.85 (m, 2 H, OCH_2), 2.99 (m, 1 H, CH), 1.96 (m, 2 H, H_5'), 1.80 (m, 2 H, CH_2), 1.64, 1.40 (2 s, 6 H, $C(CH_3)_2$), 1.05, 0.98 (2 s, 9 H, *tert*-butyl). ^{13}C NMR ($CDCl_3$, ppm): 164.51 (C=O), 152.79 (C_2), 151.50 (C_4), 149.71 (C_6), 142.40, 142.19 (C_8), 135.54-127.61 (Ar), 123.66, 123.56, 123.53 (C_5, *Ar*-C≡), 114.78, 114.61 ($C(CH_3)_2$), 91.41, 91.04 (R and S Ar-*C*≡), 90.92, 90.65 (C_1'), 85.47, 85.04, 84.48, 84.33, 84.07, 83.89 (C_2', C_3', C_4'), 83.14, 82.71 (R and S ≡C), 61.42 (OCH_2), 39.11, 38.14 (C_5', CH_2), 27.26, 26.77, 26.13, 25.46, 19.23, 19.14 ($C(CH_3)_2$, CH, *tert*-butyl). Mass spectrum (rel intensity): m/e 792 (M^+, 1.71), 735 ($M^+ - C_4H_9$, 2.0).

2′,3′-Isopropylidene-5′-(5-((*tert*-butyldiphenylsilyl)oxy)-1-phenyl-1-pentyn-3-yl)-5′-deoxyadenosine (36). A solution of 170 mg (0.22 mmol) of **35** in 8.7 mL of concentrated NH_4OH and 15 mL of MeOH was stirred at room temperature for 18 h. Solvent was removed in vacuo, and the resulting residue was purified by filtering-column chromatography on silica gel (initial elution with 35:65 EtOAc/$CHCl_3$, and then 35:63:2 EtOAc/$CHCl_3$/MeOH) to give 138 mg (94%) of **36** as a colorless foam. IR (film, cm^{-1}): 3338, 3189 (NH_2), 2222 (weak, C≡C). ^1H NMR ($CDCl_3$): δ 8.37 (s, 1 H, H_8), 7.92, 7.89 (2 s, 1 H, H_2), 7.66, 7.29 (2 m, 15 H, ArH), 6.07 (d, J = 2.4 Hz, 1 H, H_1'), 6.04 (br s, 2 H, NH_2), 5.54 (overlapping two sets of dd, J = 2.4, 6.3 Hz, 1 H, H_2'), 4.98 (m, 1 H, H_3'), 4.58 (m, 1 H, H_4'), 3.83 (m, 2 H, OCH_2), 2.97 (m, 1 H, CH), 2.00, 1.80 (2 m, 4 H, H_5', CH_2), 1.63, 1.39 (2 s, 6 H, $C(CH_3)_2$), 1.04, 0.97 (2 s, 9 H, *tert*-butyl). ^{13}C NMR ($CDCl_3$, ppm): 155.52 (C_4), 153.17, 153.08 (C_2), 149.49, 149.40 (C_6), 140.09, 139.82 (C_8), 135.54, 133.85, 133.74, 131.67, 129.53, 128.10, 127.60 (Ar), 123.66 (C_5), 120.43 (*Ar*-C≡), 114.64, 114.43 ($C(CH_3)_2$), 91.58, 91.23 (Ar-*C*≡), 90.75, 90.39 (C_1'), 85.29, 84.88, 84.58, 84.38, 84.09, 83.89 (C_2', C_3', C_4'), 83.03, 82.62 (R and S ≡C), 61.47 (OCH_2), 39.13, 38.19 (C_5', CH_2), 27.28, 26.86, 26.77, 26.11, 25.48, 19.14 (*tert*-butyl, CH, $C(CH_3)_2$). Mass spectrum (rel intensity): m/e 688 (M^+, 0.5), 673 ($M^+ - CH_3$, 0.7), 630.5 ($M^+ - C_4H_9$, 18.6). Anal. Calcd for $C_{40}H_{45}N_5O_4Si$: C, 69.84; H, 6.59; N, 10.18. Found: C, 69.93; H, 6.62; N, 10.14.

2′,3′-Isopropylidene-5′-(5-hydroxy-1-phenyl-1-pentyn-3-yl)-5′-deoxyadenosine (37). To a solution of 191 mg (0.28 mmol) of **36** in 3.4 mL of dry THF was added 34 μL of glacial HOAc and 0.6 mL of 1 M tetrabutylammonium fluoride in THF at room temperature under nitrogen. The progress of the reaction was monitored by TLC (95:5 $CHCl_3$/MeOH) and additional portions (2 × 0.1, 2 × 0.06, 1 × 0.03 mL) of 1 M tetrabutylammonium fluoride in THF were added at reaction intervals of 180, 270, 330, 390, and 450 min, respectively. The reaction was completed after 520 min at room temperature and the mixture was diluted with CH_2Cl_2 and water. The CH_2Cl_2 layer was worked up in the usual manner to give a crude product, which was then purified by filtering-column chromatography on silica gel (95:5 $CHCl_3$/MeOH) to give 121 mg (0.27 mmol; 97%) of pure **37**. IR (film, cm^{-1}): 3325, 3180 (very strong br s, NH_2, OH), 2218 (weak, C≡C). ^1H NMR ($CDCl_3$): δ 8.36, 8.35 (2 s, 1 H, H_8), 7.90, 7.88 (2 s, 1 H, H_2), 7.30 (m, 5 H, ArH), 6.06, 6.05 (d, J = 2.3 Hz, 1 H, H_1'), 5.92, 5.85 (2 br s, 2 H, NH_2), 5.61, 5.51 (two sets of dd, J = 2.3, 6.2 Hz, 1 H, H_2'), 4.98 (m, 1 H, H_3'), 4.63, 4.55 (2 m, 1 H, H_4'), 3.80 (m, 2 H, OCH_2), 2.87 (m, 1 H, CH), 2.05–1.64 (m, 4 H, H_5', CH_2), 1.63, 1.39 (2 s, 6 H, $C(CH_3)_2$). ^{13}C NMR ($CDCl_3$, ppm): 155.86 (C_4), 153.13, 153.05 (C_2), 149.20, 149.05 (C_6), 140.00, 139.74 (C_8), 131.61, 131.52, 128.18, 127.80, 120.03 (Ar), 123.43, 123.37 (C_5), 114.55, 114.20 ($C(CH_3)_2$), 91.35, 91.16 (Ar-*C*≡), 91.09, 90.28 (C_1'), 85.29, 85.09, 84.67, 84.19, 84.03, 83.69, 83.14, 82.93 (C_2', C_3', C_4', ≡C), 60.10, 59.94 (OCH_2), 38.98, 38.31, 37.58 (C_5', CH_2), 27.20, 26.14, 25.57, 25.40 ($C(CH_3)_2$, CH). HR mass spectrum (desorption CI) calcd for $C_{24}H_{28}N_5O_4$ (MH^+) 450.2141, found 450.2126.

2′,3′-Isopropylidene-5′-(5-iodo-1-phenyl-1-pentyn-3-yl)-5′-deoxyadenosine (38). Crude **38** (249 mg) was obtained from 0.23 mmol of **37** by using a similar method to that described for the preparation of **12**. This crude product was purified by filtering-column chromatography on silica gel (95:5 $CHCl_3$/2-propanol; R_f = 0.19) to give 111 mg (86%) of the desired **38**. IR (film, cm^{-1}): 3320, 3165, 2985, 2936, 2224 (weak, C≡C), 1700, 1600, 1590, 1580, 1425, 1330, 1210, 1085. ^1H NMR ($CDCl_3$): δ 8.38, 8.36 (2 s, 1 H, H_8), 7.92, 7.91 (2 s, 1 H, H_2), 7.30 (m, 5 H, ArH), 6.06 (d, J = 2.3 Hz, 1 H, H_1'), 6.02 (br s, 2 H, NH_2), 5.57 (two sets of dd, J = 2.3, 6.3 Hz, 1 H, H_2'), 5.01 (m, 1 H, H_3'), 4.57 (m, 1 H, H_4'), 3.26 (m, 2 H, ICH_2), 2.91, 2.80 (2 m, 1 H, R and S CH), 2.00 (m, 4 H, H_5', CH_2), 1.62, 1.39 (2 s, 6 H, $C(CH_3)_2$). ^{13}C NMR ($CDCl_3$, ppm): 155.91 (C_4), 153.10, 152.99 (C_2), 149.21, 149.14 (C_6), 140.05, 139.75 (C_8), 131.60, 131.53, 128.15, 127.91, 120.28, 120.17 (Ar), 123.16 (C_5), 114.53, 114.28 ($C(CH_3)_2$), 90.81, 90.31 (Ar-*C*≡), 89.78, 89.54 (C_1'), 85.09, 84.76, 84.53, 84.22, 83.95, 83.68, 83.48 (C_2', C_3', C_4', ≡C), 39.01, 38.27, 37.58 (C_5', CH_2), 27.14, 25.37, 25.31 ($C(CH_3)_2$, CH). HR mass spectrum (desorption CI) calcd for $C_{24}H_{27}N_5O_3I$ (MH^+) m/e 560.1159, obsd m/e 560.1180.

2′,3′-Isopropylidene-5′-(6-(methoxycarbonyl)-6-(benzylideneamino)-1-phenyl-1-hexyn-3-yl)-5′-deoxyadenosine (39). A crude foam of **39** (140 mg, >100%) was obtained from 0.22 mmol of **38** by using a similar method to that described for the preparation of **13**. ^1H NMR ($CDCl_3$): δ 8.34, 8.33 (2 s, H_8), 8.30–8.25 (5 s, N=CH), 7.88, 7.86 (2 s, H_2), 7.76, 7.42 (2 m, ArH), 6.03, 6.00

(two sets of d, J = 2.3 Hz, H_1'), 5.86 (br s, NH_2), 5.54, 5.47 (two sets of dd, J = 2.3, 6.3 Hz, H_2'), 4.95 (dd, H_3'), 4.56 (m, H_4'), 3.78 (m, CH), 2.70 (m, CH), 2.20–1.37 (m, H_5', $(CH_2)_2$), 1.60, 1.37 (2 s, $C(CH_3)_2$). Mass spectrum (desorption CI, rel intensity): m/e 609 (MH^+, 8.4).

5'-(6-Amino-6-carboxy-1-phenyl-1-hexyn-3-yl)-5'-deoxyadenosine (4). A crude sample of **4** (41.6 mg) was obtained from 140 mg of **39** by using a similar method to that described for the preparation of **15**. This crude product was purified by preparative reverse-phase HPLC with gradient elution of 0–100% solvent A (6:4 CH_3CN/H_2O) in solvent B (H_2O) to give 20.6 mg (70% yield from **38**) of the desired **4** as a foam. UV (MeOH): λ_{max} = 251 nm, λ_{min} = 240 nm. ^1H NMR (CD_3OD, δ): 8.25, 8.24, 8.21, 8.20 (4 s, 2 H, H_8, H_2), 7.30 (m, 5 H, ArH), 5.98 (two sets of d, 1 H, H_1'), 4.85 (overlapping with HOD peak, H_2'), 4.40 (m, 1 H, H_4'), 4.25 (m, 1 H, H_3'), 3.59 (m, 1 H, CH), 2.86 (m, 1 H, CH), 2.28–1.60 (m, 6 H, H_5', $(CH_2)_2$). ^{13}C NMR (CD_3OD, ppm): 174.38 (C=O), 157.37 (C_4), 153.94 (C_2), 150.62 (C_6), 141.78, 141.49 (C_8), 132.65, 132.58, 132.65, 128.94, 120.77 (Ar), 124.95 (C_5), 92.77, 92.16, 92.09 (Ar-*C*≡), 90.61, 90.55, 90.20 (C_1'), 84.44, 84.40 (C_4'), 83.86, 83.74, 83.70 (≡C), 75.42, 75.23 (*R* and *S* CH), 74.94, 74.90 (C_3'), 56.17, 56.13 (C_2'), 40.43, 40.11, 39.96 (C_5', CH_2), 32.36, 31.39, 31.20, 30.58, 30.47, 30.07 (CH_2, *R* and *S* CH). FAB mass spectrum (rel intensity): m/e 467 (MH^+, 16.8). HR mass spectrum (desorption CI) calcd for $(MH - CO_2)^+$ m/e $C_{22}H_{27}N_6O_3$ 423.2145, obsd m/e 423.2139.

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Supplementary Material Available: Procedures for the synthesis of **23a**, **23c**, **24a**, **25a**, **30a**, **32a**, and **33a** with complete spectral data (3 pages). Ordering information is given on any current masthead page.

Total Synthesis and Absolute Stereochemistry of (+)-Xestoquinone and Xestoquinol

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The first total synthesis of (+)-xestoquinone **1**, a biologically active marine natural product isolated from tropical marine sponges, was achieved. Optically pure hydroxymethyl ketone derivative (4a*R*,5*S*,8a*R*)-(+)-**8** was converted to enone (+)-**15** via the reactions of eight steps. The Diels–Alder reaction of (+)-**15** with 3,6-dimethoxybenzocyclobutene (**16**) afforded an adduct (+)-**17** of a tetracyclic system, which was converted to (12b*S*)-xestoquinone **1** via a series of five-step reactions. The CD spectrum of the synthetic sample was identical with that of the natural xestoquinone (+)-**1**. Therefore, the absolute stereochemistry of (+)-xestoquinone **1** was determined to be 12b*S*. Finally, xestoquinone (12b*S*)-(+)-**1** was converted to xestoquinol (12b*S*)-**2**, although xestoquinol **2** itself has not been isolated yet as a natural product. The absolute configuration of xestoquinone **1** was also established by the comparison of the CD spectrum of naphthalene–diene derivative **22** with the theoretically calculated CD curve of a model compound (12b*S*)-**23**.

A variety of novel quinone and hydroquinone compounds with biological activites have been isolated from tropical marine sponges (Chart I). Xestoquinone (+)-**1** was isolated from the Okinawan sponge *Xestospongia sapra* as a cardiotonic constituent by Nakamura.[2] From the same Okinawan sponge, Kitagawa[3] isolated halenaquinol (+)-**4** together with its sulfate ester, and hydroquinone (+)-**4** was easily oxidized to give halenaquinone (+)-**3**, which had been originally isolated from the sponge *Xestospongia exigua* in Western Caroline Islands by Scheuer.[4] From the view point of the instability of the hydroquinone compound, Kitagawa[3] suggested that halenaquinone **3** might be a secondary product of halenaquinol isolation. If so, xestoquinol **2** may be a genuine natural product instead of xestoquinone **1**. Recently, Schmitz[5] isolated adociaquinone A ((+)-**5**), adociaquinone B ((+)-**6**), and related compounds from sponges of the genus *Adocia* in Truk Lagoon.

We and Kitagawa have previously determined the absolute stereochemistry of halenaquinone (+)-**3** and halenaquinol (+)-**4** as shown in Chart I by the theoretical calculation of the CD spectra of pertinent derivatives.[6] Furthermore, we experimentally showed that the absolute stereostructures of (+)-**3** and (+)-**4** determined theoretically were confirmed by the total synthesis[7] of halenaquinone (+)-**3** and halenaquinol (+)-**4**. On the other hand, the absolute stereochemistry of xestoquinone has remained undetermined. Here, we report the first total synthesis of xestoquinone (+)-**1** and xestoquinol **2** and the experimental determination of their absolute stereostructures. In addition, we also describe the theoretical confirmation of the absolute configuration of the xestoquinone series on the basis of the CD spectra of naphthalene–diene derivatives with a twisted π-electron system.

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