Pergamon

Tetrahedron 58 (2002) 6019–6026

TETRAHEDRON

Expeditious synthesis of aziridine-based cofactor mimics

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Received 3 May 2002; accepted 6 June 2002

Abstract—*S*-Adenosyl-L-methionine mimics were synthesized in a linear fashion highlighting methodology that bypasses the need for adenine base protection. These aziridine-based cofactor mimics are envisioned as useful biochemical tools and potential therapeutic agents whose mechanism of action hinges upon aberrant methyltransferase enzymes. Aziridination of the 5′ position of adenosine was effected by convergence of suitably protected 5′-aminoadenosine with various dibromopropionates. The economy and high yields for this route to said aziridine-based cofactors is highly amenable to large-scale chemistry which no doubt will be vital to their development as therapeutics and biochemical tools. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

DNA interstrand cross-linking is one of the most potent and useful forms of DNA modification used in chemotherapies. Cross-linking selectivity often results due to drug activation processes attributed to oxidizing or reducing environments characteristic of diseased cells.[1] Indeed, gene therapy has been exploited as an effective means of attenuating drug action based upon overexpression of certain enzymes associated with these environmental conditions.[2] In addition, many DNA sequence-selective targeting methods have been developed resulting in impressive selectivities and affinities.[3] Surprisingly, the exploitation of enzymatic DNA modification mechanisms has received considerably less attention. Such an approach has advantages over traditional methods. First, the sequence specificity of DNA alkylation results not from a small molecule:DNA interaction, but rather a protein:DNA interaction. Second, the association of drug with the DNA modifying enzyme affords a drug trafficking mechanism potentially capable of shielding the drug from inactivating species such as cytosolic nucleophiles or oxidants.

Perhaps the most well studied of the DNA modification enzymes are those involved in DNA methylation.[4] Methylations at cytosine C5 and N4 and at adenosine N6 play an integral role in prokaryotic defense mechanisms. In eukaryotes, a large body of data has revealed excellent correlation between DNA methylation and gene repression.[5] Silenced genes are generally methylated in their regulatory regions, whereas their expressed counterparts are unmethylated. Genes differentially expressed in different tissues are differentially methylated.[6] Not surprisingly, aberrant DNA methylation is inherent in a number of oncogenic processes and is thought, in some cases, to be a leading contributor to carcinogenesis.[7] This suggests that agents capable of taking part in or deterring Mtase-dependent transcriptional errors would be of significant clinical importance. For instance, regions of the genome that might be improperly repressed due to aberrant methylation of CpG units (a signature of numerous cancers) might be de-repressed by the replacement of DNA bound methyl groups with non-natural moieties. Indeed the concept of 'cofactor mimicry' offers abundant chemotherapeutic opportunity through alterations of transcriptionally relevant molecular recognition processes, as well as from the simple standpoint of sequence specific DNA damaging moieties.

This rationale underscores the importance of recent work by Weinhold and co-workers.[8] The C5′ aziridine **3** affords a substitute for SAM in the M.*Taq*I catalyzed *alkylation* of adenine within the recognition sequence 5′TCGA3′ (Scheme 1).[8] Instead of generating the N6 methylated dA residue, substrate adenylation is accomplished via ring-opening of the aziridine. Importantly, the regiochemistry of DNA substrate modification is identical to the *S*-adenosyl-L-methionine (SAM, **2**) dependent methylation. Notably, a fluorescent analog of **3** has also been shown to substitute for SAM in the C5 cytosine alkylation by M.*Hha*I DNA methyltransferase.[9]

The stability of the free base **3** suggests that such a cofactor structure may be amenable to conjugation with other DNA-reactive functionalities thus affording access to synthetic agents which derive biological activity (as a function of DNA sequence selectivity) from selected

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Keywords: *S*-adenosyl-L-methionine; aziridine-based cofactor mimics; 5′-aminoadenosine; Gabriel–Cromwell.

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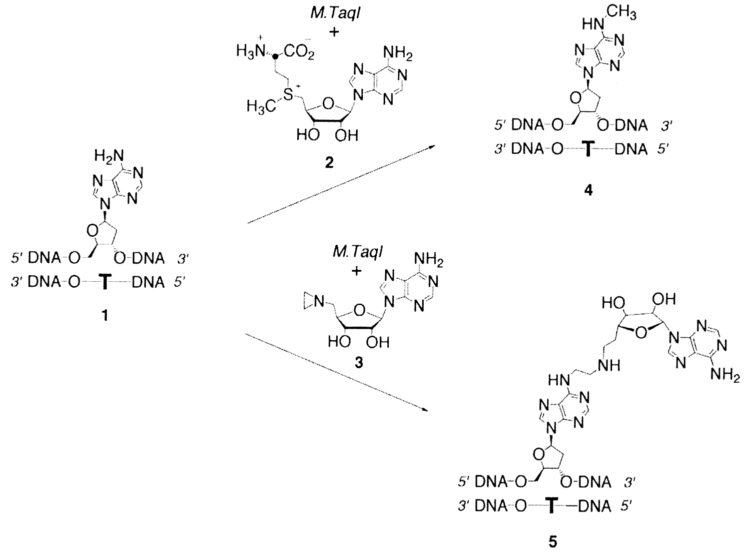
PII: S0040-4020(02)00590-2

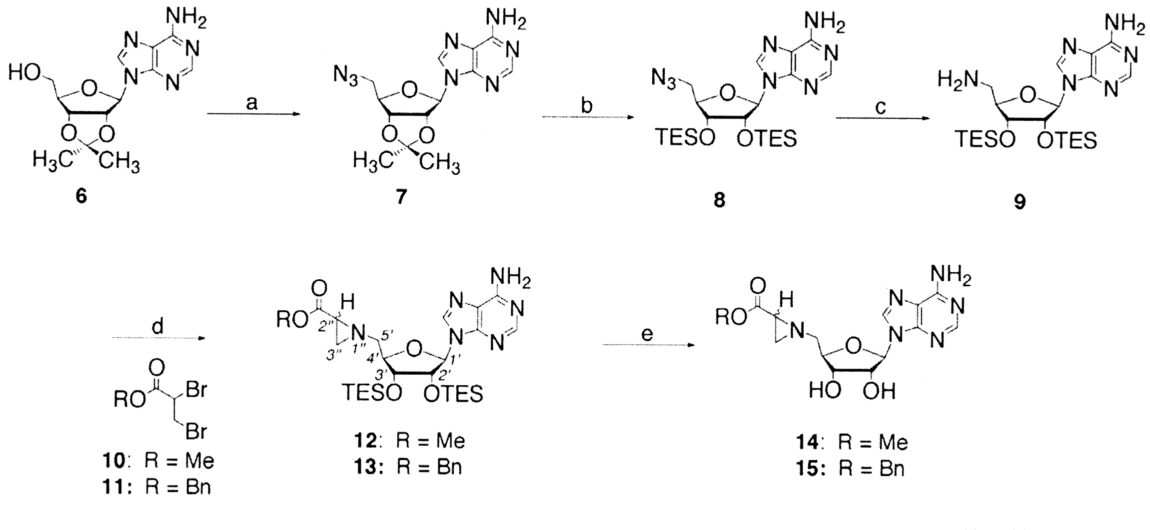


Scheme 1.

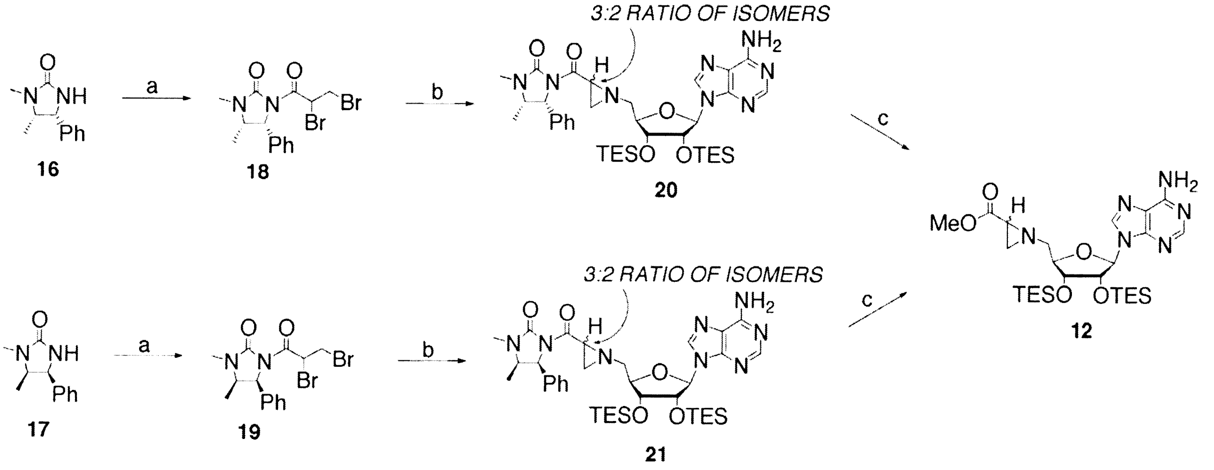
methyltransferases. Our interest in the design and synthesis of such agents necessitated the development of a highly efficient route to 'tetherable' analogs of **3**. Gabriel–Cromwell aziridination affords rapid access to the desired agents.

2. Results and discussion

There are few examples of efficient *N*-alkylation of aziridines with alkyl halides and sulfonates; condensations with yields >90% typically involve benzyl halides.[10] This, coupled with the anticipated limitations on possible coupling components facilitated the development of alternative methodologies by which functionalized aziridines could be appended to adenosine at the 5′ position. Critical to these other methodologies was an efficient means of obtaining on large scale, 5′-aminoadenosine or related congeners bearing suitable protection of the 2′,3′-diol. Using a Mitsunobu variation of chemistry recently reported by Austin and co-workers, we found that the desired OH→NH_2 interconversion coupled with silylation of both the 2′ and 3′ alcohols could be most expeditiously effected by treatment of commercially available **6** with diphenylphosphoryl azide (DPPA), triphenylphosphine (PPh_3), diethylazodicarboxylate (DEAD) as shown in Scheme 2.[11,12] Azide installation in this manner proceeded in 73% yield. The azide **7** was highly amenable to acetonide cleavage with trifluoroacetic acid[13] and subsequent 2′,3′ reprotection as the 2′,3′ bis(triethylsilyl ether).[14] Disilylation permitted not only improved solubility traits throughout the remainder of the synthesis, but also allowed for a high degree of aziridine survival upon final diol deprotection. Staudinger reduction of the azide **8** ultimately afforded the highly versatile 5′ amine **9** in 74% yield over three steps from azide **7**.[15]



Scheme 2. (a) DPPA, PPh_3, DEAD, THF; (b) 1. TFA/H_2O, 2. chlorotriethylsilane, imidazole, DMF; (c) PPh_3, THF, H_2O; (d) **10** or **11**, TEA, THF; (e) nBu$_4$NF, dioxane.



Scheme 3. (a) Dibromopropionyl chloride, CH_3CN; (b) TEA, THF, **4**; (c) TEA, MeOH.

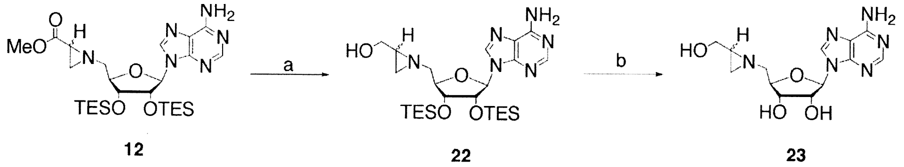
Although a host of chemistries have been used in our laboratories to prepare such compounds, by far the most efficient hinges upon the reaction of **9** with α,β-unsaturated α-bromo carbonyl compounds.[16,17] Our particular interests rested on the reaction of **9** with dibromopropionic methyl and benzyl esters **10** and **11**. The reasons for this are twofold. First, we envisioned that such aziridine carboxylates might serve as more potent or effective cofactor mimics than the analogous unsubstituted aziridines such as **3**. Secondly, the anticipated products would present two potential avenues by which to conjugate DNA damaging moieties or perhaps drug delivery tools.

Treatment of amine **9** with dibromopropionates **10** or **11** in the presence of triethylamine in refluxing THF afforded diastereomeric mixtures of 5′ aziridines in good (80–87%) yields. Perhaps most remarkable is that no protection of the adenine base is necessary. Coupled with the potential for introduction of molecular diversity via the use of different dibromopropionates, this condensation represents a powerful addition to the repertoire of nucleoside modification chemistry. Following 5′ aziridine construction, simple cleavage of the silyl ethers with TBAF[18] affords a diastereomeric mixture of each SAM mimic.

In addition to the rapid construction of potentially diverse nucleoside aziridines this chemistry holds promise for generating stereodiverse populations of cofactor mimics. Diastereomeric mixtures of aziridine-based cofactors were initially envisioned to be readily separable by HPLC. Although this was true in the case of the carbobenyloxy aziridines this was not the case for diastereomeric mixture **14** or its precursor **12**. Efforts to remedy this entailed the exploitation of asymmetrically disposed dibromopropionate **18** and its antipode **19**.

Cardillo and co-workers successfully employed a related system in their synthesis of chiral benzyl aziridine-2-carboxylates.[17a] It must be noted, however, that an important difference in the two systems exists. Unlike the Cardillo system, the aziridines of interest here do not bear substituents at both aziridine carbons. We rationalized on the basis of a chiral protonation step immediately following initial Michael-type addition to the transient bromoacrylate that auxiliaries **16** and **17** might afford asymmetric induction at the brominated α carbonyl center. Such rationale is reminiscent of synthetic strategies applied to β-sheet mimetic construction.[16c] This would presumably set aziridine stereochemistry due to SN_2 displacement of bromide with concomitant aziridine ring closure. This, in fact was found not to be the case. Rather, we determined that, regardless of dibromopropionate stereochemistry a 3:2 ratio of aziridine stereoisomers was consistently obtained. That a ratio of 1:1 is typically observed using non-chiral bromopropionates clearly indicates a stereochemical bias in the auxiliary-based system yet a mechanistic rationale for asymmetric induction *regardless of auxiliary stereochemistry* is not yet apparent. It is clear that the asymmetric environment of the adenosine ribose framework exerts influence upon the stereochemical outcome. However, this influence relies upon the ureadiyl moieties of **18** and **19**. Although efforts are still underway to explain this interesting phenomenon, what was found was that the dibromopropionate auxiliaries ultimately afforded aziridines highly amenable to separation by conventional chromatography. Thus, although the ureadiyl moieties **18** and **19** serve partly as chiral auxiliaries for aziridination (in combination with the adenosine ribose) they serve, most importantly in our hands, as separatory auxiliaries.

Having failed to assign stereochemical configuration to aziridines derived from Gabriel–Cromwell reactions with **9**, we sought the independent synthesis of each stereoisomer of hydroxymethyl aziridines. Importantly, the conversion of methyl ester **12** to the hydroxymethyl analog was desirable for conjugation to other biologically relevant moieties. This, coupled with the ability to separate auxiliary modified aziridine stereoisomers **20** and **21** on large scale led to an important realization. As shown in Scheme 3, carboxyaziridines **20** and **21** are readily converted to methyl ester **12** upon exposure to methanolic triethylamine with **16** and **17** easily recovered intact.[19] Exposure of each stereoisomer of **12** to $LiAlH_4$ at low temperature affords the corresponding primary alcohol **22**[20] in 76% yield (Scheme 4). Notably, introduction of the hydroxymethyl functionality at this point allows for selective modification of **22** with DNA modifying



Scheme 4. (a) $LiAlH_4$, THF, −20°C; (b) *n*Bu_4NF, dioxane.

agents of choice, while leaving other potentially nucleophilic sites masked. Desilylation of **22** with TBAF affords **23** in 75% yield.

Finally, with a facile means by which to derive 'tetherable' cofactor mimics in diastereomerically pure form, we endeavored to assign aziridine stereochemistry. Very simply, we synthesized each stereoisomer of **22** via aminolysis of *R*-(+) and *S*-(−) *O*-benzyl glycidol, respectively. Conversion of the resulting amino alcohols to their respective stereoisomerically pure aziridines was accomplished using Mitsunobu conditions and ^1H NMR chemical shifts compared with those of previously obtained Gabriel–Cromwell adducts.[21] The synthesis of similarly substituted aziridines had been noted to be very difficult and our efforts substantiated this observation. Subjection of *O*-benzyl glycidol-derived amino alcohols to triphenylphosphine, and DEAD in refluxing THF afforded aziridines in ~40% yield after very careful chromatographic separation.

We had noted earlier, a remarkable difference in ^1H chemical shifts of the C5′ hydrogens based upon the aziridine stereochemistry and this was again evident in the *O*-benzyl-derived aziridines. Spectral analysis revealed the R aziridine to possess chemical shifts of 2.57 and 2.76 ppm for C5′ Ha and Hb, respectively. Alternatively, S aziridines demonstrate chemical shifts of 2.42 and 2.96 ppm for Ha and Hb, respectively. Using these observations, we have thus assigned stereochemical configuration to all carboxy and hydroxymethyl-functionalized aziridines. We also note that the 3:2 ratio of Cromwell adducts obtained for compounds **20** and **21** indicates the preferred formation in both cases of the S aziridine over the R isomer.

3. Conclusions

Described herein is the highly efficient synthesis of SAM mimics bearing differentially tetherable functionalities. Synthesis of the 5′ amine core, followed by Gabriel–Cromwell aziridination affords carboxyaziridines capable of facile reduction to the hydroxymethyl analogs. Silyl ether cleavage from both 2′ and 3′ alcohols using TBAF affords aziridine-based cofactor mimics of interest. Stereochemical assignment of the resulting SAM mimics has been achieved through independent stereocontrolled synthesis of each stereoisomer of *O*-benzyl **22**. Cofactor mimics thus obtained are currently being evaluated for compatibility with a host of DNA and protein methyltransferases. Progress on the application of these molecules as potential chemotherapeutics and biochemical tools will be reported shortly.

4. Experimental

4.1. General

All reactions were carried out under an inert atmosphere of argon unless indicated otherwise. All reagents were obtained from available commercial sources and used without additional purification. Anhydrous THF was from a J.T. Baker Cycle-Tainer product number 9446-Q1. Melting points were determined using a Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on Varian ui400 and ui500 spectrometers using solvent as the internal reference; the chemical shifts are reported in ppm, in δ units. Mass spectra were obtained from Colorado State University on a Fisions VG Autospec spectrometer.

4.1.1. 5′-Azido-5′-deoxy-2′,3′-isopropylidene adenosine 7. To 450 mL, dry THF at 0°C was added PPh_3 (21.5 g, 82.0 mmol). The solution was allowed to stir for 10 min and DEAD (14.2 g, 81.3 mmol) was added and the resulting mixture stirred for an additional 10 min. The ice bath was removed and to the warming solution was added DPPA (22.6 g, 82.1 mmol) over a period of 5 min, followed by addition of **6** (25.0 g, 81.5 mmol). The reaction was allowed to stir for 36 h sheltered from light. The resulting white precipitate was filtered and washed with petroleum ether. The solvent was evaporated in vacuo to reveal a thick orange oil. Column chromatography on silica gel (3:1:0.1 $EtOAc/CH_2Cl_2/MeOH$) afforded **7** as a gummy white solid (19.8 g, 73.1%). Mp 126–130°C. ^1H NMR ($CDCl_3$) δ 8.40 (s, 1H), 7.95 (s, 1H), 6.12 (d, J=2.4 Hz, 1H), 5.62 (bs, 2H), 5.45 (dd, J=6.4, 2.4 Hz, 1H), 5.05 (dd, J=6.4, 3.6 Hz, 1H), 4.39 (m, 1H), 3.61 (dd, J=12.8, 6.0 Hz, 1H), 3.56 (dd, J=13.2, 6.0 Hz, 1H), 1.61 (s, 3H), 1.42 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.0, 153.8, 149.7, 140.0, 120.5, 114.8, 91.1, 86.1, 84.2, 82.0, 52.3, 27.6, 25.8. FAB-LRMS: calcd for $C_{13}H_{16}N_8O_3$ $(M+H^+)$ 333.32; obsd 333.2.

4.1.2. 5′-Azido-5′-deoxy-2′,3′-bis-(*O*-triethylsilyl)adenosine 8. To 100 mL, 10:1 TFA/H_2O at 0°C was added **7** (15.3 g, 45.9 mmol). After 5 min, the reaction was allowed to warm to room temperature and stirred for an additional 20 min. The solution was evaporated in vacuo and co-evaporated repetitively with ethanol to render a gummy white foam. To the crude 5′-azidoadenylate (20.7 g, 70.8 mmol) in 100 mL dry DMF at 0°C, was added imidazole (38.6 g, 566.8 mmol) and chlorotriethylsilane (19.8 g, 131.1 mol). The reaction was stirred for 2 h at room temperature. An aqueous workup was performed (NH_4Cl, EtOAc, brine), the combined organic layers dried over Na_2SO_4 and evaporated in vacuo. A crude light yellow solid, **8**, was obtained which was taken directly forward.

4.1.3. 5′-Amino-5′-deoxy-2′,3′-bis-(*O*-triethylsilyl)adenosine 9. To crude **8** (25.0 g, 48.0 mmol) in 300 mL dry THF, was added triphenylphosphine (18.9 g, 72.0 mmol) and the solution was stirred for 15 min. Water (11.2 g, 624 mmol) was added and the solution was heated at reflux for 1.5 h. The solvent was removed in vacuo. Column chromatography on silica pre-treated with 1% TEA (4:2:1 EtOAc/CH_2Cl_2/MeOH) gave **9** as white solid (16.8 g, 74.0%). Mp 164–167°C. ^1H NMR ($CDCl_3$) δ 8.35 (s, 1H), 7.95 (s, 1H), 6.48 (bs, 2H), 5.86 (d, *J*=6.1 Hz, 1H), 5.15 (dd, *J*=5.9, 4.6 Hz, 1H), 4.28 (dd, *J*=4.4, 2.8 Hz, 1H), 4.09 (m, 1H), 3.08 (dd, *J*=13.5, 3.6 Hz, 1H), 3.02 (dd, *J*=13.3, 5.6 Hz, 1H), 2.25 (bs, 2H), 0.95 (t, *J*=8.0 Hz, 9H), 0.78 (t, *J*=8.1 Hz, 9H), 0.64 (q, *J*=8.0 Hz, 6H), 0.38 (qq, *J*=16.0, 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 156.2, 153.6, 150.1, 141.1, 121.0, 90.0, 87.6, 74.0, 73.8, 44.0, 7.2, 6.9, 5.8, 5.5. FAB-LRMS: calcd for $C_{22}H_{42}N_6O_3Si_2$ (M+H$^+$) 495.78; obsd 495.2.

4.1.4. Methyl 2,3-dibromopropionate 10. Dibromopropionyl chloride (13.1 g, 52.3 mmol) in 25 mL dry THF was added to a suspension of methanol (3.35 g, 104.6 mmol) and potassium hydrogen carbonate (12.6 g, 125.5 mmol) in 25 mL dry THF at 0°C over 10 min. The reaction was warmed to room temperature and stirred for 2 h. The reaction was then chilled to 0°C and filtered. An aqueous workup was performed (H_2O, EtOAc, brine), dried over Na_2SO_4 and evaporated in vacuo. Column chromatography on silica (1:1:1 Pet Et/EtOAc/MeOH) rendered **10** as a clear oil (10.23 g, 79.5%). ^1H NMR ($CDCl_3$) δ 4.46 (dd, *J*=11.2, 4.5 Hz, 1H), 3.94 (dd, *J*=11.2, 9.9 Hz, 1H), 3.85 (s, 3H), 3.68 (dd, *J*=9.9, 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 168.2, 53.6, 40.9, 29.8.

4.1.5. Benzyl 2,3-dibromopropionate 11. Dibromopropionyl chloride (8.72 g, 34.9 mmol) in 18 mL dry THF was added to a suspension of benzyl alcohol (3.15 g, 29.1 mmol) and potassium hydrogen carbonate (6.99 g, 69.8 mmol) in 22 mL dry THF at 0°C over 10 min. The reaction was warmed to room temperature and stirred for 2 h. The reaction was then chilled to 0°C and filtered. An aqueous workup was performed (H_2O, EtOAc, brine), dried over Na_2SO_4 and evaporated in vacuo. Column chromatography on silica (2:1 Pet Et/EtOAc) gave **11** as a clear oil (6.89 g, 73.6%). ^1H NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.25 (s, 2H), 4.47 (dd, *J*=11.2, 3.6 Hz, 1H), 3.93 (dd, *J*=10.8, 10.0 Hz, 1H), 3.66 (dd, *J*=10.0, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 167.6, 134.9, 128.88, 128.86, 128.53, 68.3, 41.3, 29.9.

4.1.6. 5′-Aziridino-5′-deoxy-(2″-carboxylmethyl)-2′,3′-bis-(*O*-triethylsilyl)adenosine 12. To **20a** (0.600 g, 0.814 mmol) in 11 mL dry MeOH was added triethylamine (0.494 g, 4.885 mmol). The solution was heated at reflux for 2 h. The reaction was cooled and an aqueous workup was performed (EtOAc, H_2O, brine), dried over Na_2SO_4 and evaporated in vacuo. The crude was taken directly forward due to co-migration of the auxiliary. The signals due to **12a** (*S aziridine*) could be discerned: ^1H NMR ($CDCl_3$) δ 8.26 (s, 1H), 7.97 (s, 1H), 6.29 (s, 2H), 5.91 (d, *J*=5.6 Hz, 1H), 5.04 (dd, *J*=5.6, 4.4 Hz, 1H), 4.30 (m, 2H), 3.73 (s, 3H), 3.04 (dd, *J*=12.8, 3.6 Hz, 1H), 2.47 (dd, *J*=12.8, 6.4 Hz, 1H), 2.16 (dd, *J*=6.4, 3.2 Hz, 1H), 2.12 (dd, *J*=3.2, 1.2 Hz, 1H), 1.74 (dd, *J*=6.4, 1.2 Hz, 1H), 0.98 (t, *J*=8.0 Hz, 9H), 0.78 (t, *J*=8.0 Hz, 9H), 0.65 (q, *J*=8.0 Hz, 6H), 0.35 (qq, *J*=16.0, 8.0 Hz, 6H); ^{13}C ($CDCl_3$) δ 170.21, 154.80, 151.77, 148.72, 119.47, 87.91, 83.81, 72.90, 72.87, 60.33, 51.25, 36.08, 33.61, 5.84, 5.53, 3.92, 3.50; FAB-HRMS: calcd for $C_{26}H_{46}N_6O_5Si_2$ (M+H$^+$) 579.31; obsd 579.314.

A similar procedure was performed with **20b**. The signals due to **12b** (*R aziridine*) could be discerned: ^1H NMR ($CDCl_3$) δ 8.28 (s, 1H), 7.98 (s, 1H), 6.29 (s, 2H), 5.91 (d, *J*=5.6 Hz, 1H), 5.05 (dd, *J*=5.2, 4.4 Hz, 1H), 4.41 (dd, *J*=4.4, 2.4 Hz, 1H), 4.25 (m, 1H), 3.67 (s, 3H), 2.96 (dd, *J*=12.8, 5.2 Hz, 1H), 2.51 (dd, *J*=12.8, 6.0 Hz, 1H), 2.23 (dd, *J*=6.4, 3.2 Hz, 1H), 2.18 (dd, *J*=3.2, 1.2 Hz, 1H), 1.65 (dd, *J*=6.4, 1.2 Hz, 1H), 1.00 (t, *J*=8.0 Hz, 9H), 0.80 (t, *J*=8.0 Hz, 9H), 0.67 (q, *J*=8.0 Hz, 6 H), 0.37 (qq, *J*=16.0, 8.0 Hz, 6H); ^{13}C ($CDCl_3$) δ 170.04, 154.81, 151.76, 148.62, 110.49, 88.21, 83.35, 72.68, 72.65, 60.18, 51.11, 36.05, 33.50, 5.82, 5.55, 3.89, 3.45; FAB-HRMS: calcd for $C_{26}H_{46}N_6O_5Si_2$ (M+H$^+$) 579.31; obsd 579.314.

Note. **12** can be synthesized from **21a** and **22b** via the same procedure.

4.1.7. 5′-Aziridino-5′-deoxy-(2″-carboxylbenzyl)-2′,3′-bis-(*O*-triethylsilyl)adenosine 13. To **11** (1.835 g, 5.701 mmol) in 40 mL dry THF was stirred for 15 min at room temperature. **9** (2.848 g, 5.757 mmol) in 40 mL dry THF was added to the dibromide solution, followed by TEA (1.730 g, 17.099 mmol). The solution was heated at reflux for 16 h. The solution was cooled to 0°C, filtered and the residual Et_3N-HBr salts triturated with anhydrous Et_2O. The combination of organic layers was evaporated in vacuo followed by column chromatography on silica (4:2:1 EtOAc/CH_2Cl_2/MeOH) to afford **13** as a mixture of diastereomers (3.012 g, 80.7%). ^1H NMR ($CDCl_3$) δ 8.33 (s, 1H), 8.32 (s, 1H), 8.01 (s, 1H), 8.00 (s, 1H), 7.34 (m, 5H), 7.33 (m, 5H), 5.92 (d, *J*=7.5 Hz, 1H), 5.90 (d, *J*=7.5 Hz, 1H), 5.52 (bs, 2H), 5.51 (bs, 2H), 5.20 (d, *J*=5.5 Hz, 2H), 5.14 (d, *J*=5 Hz, 2H), 5.11 (dd, *J*=7, 5.5 Hz, 1H), 5.06 (dd, *J*=7, 5.5 Hz, 1H), 4.42 (dd, *J*=5.5, 4 Hz, 1H), 4.34 (dd, *J*=5, 3.5 Hz, 1H), 4.29 (m, 1H), 4.25 (m, 1H), 3.08 (dd, *J*=16, 5.5 Hz, 1H), 2.94 (dd, *J*=15.5, 7.5 Hz, 1H), 2.53 (dd, *J*=15.5, 3 Hz, 1H), 2.43 (dd, *J*=16, 8 Hz, 1H), 2.29 (dd, *J*=6.5, 3.5 Hz, 1H), 2.22 (dd, *J*=3.5, 1.5 Hz, 1H), 2.20 (dd, *J*=6.5, 3 Hz, 1H), 2.14 (dd, *J*=3, 1.5 Hz, 1H), 1.74 (dd, *J*=6.5, 1.5 Hz, 1H), 1.66 (dd, *J*=6.5, 1.5 Hz, 1H), 1.00 (t, *J*=8.0 Hz, 9H), 0.98 (t, *J*=8.0 Hz, 9H), 0.80 (t, *J*=8.0 Hz, 9H), 0.78 (t, *J*=8.0 Hz, 9H), 0.67 (q, *J*=8.0 Hz, 6 H), 0.65 (q, *J*=8.0 Hz, 6H), 0.37 (qq, *J*=16.0, 8.0 Hz, 6H), 0.35 (qq, *J*=16.0, 8.0 Hz, 6H); ^{13}C ($CDCl_3$) δ 170.83, 170.67, 156.03, 153.03, 149.98, 149.89, 140.92, 140.93, 135.74, 135.70, 128.73, 128.53, 128.52, 128.34, 120.73, 120.68, 89.44, 89.06, 84.93, 84.40, 74.24, 74.12, 74.03, 73.66, 67.14, 66.92, 61.48, 61.27, 37.41, 37.36, 35.01, 7.05, 6.76, 5.13, 4.76. FAB-HRMS: calcd for $C_{32}H_{50}N_6O_5Si_2$ (M+H$^+$) 655.34; obsd 655.347.

4.2. General procedure for 2′,3′ desilylation of 5′-aziridino-5′-deoxyadenosine analogs

To the 2′,3′-bis-(*O*-triethylsilyl)adenosine (0.1085 mmol) in 0.50 mL dry dioxane was added TBAF (0.2170 mmol) in 0.50 mL dry dioxane. The reaction was allowed to stir at room temperature for 30 min and evaporated in vacuo to reveal a yellow oil. Purification by reverse-phase HPLC (C18-100Å).

4.2.1. 5′-Aziridino-5′-deoxy-(2″-carboxylmethyl) adenosine 14.

Purification by reverse-phase HPLC on a linear gradient (5–60% CH_3CN over 20 min; retention time 15.0 min).

Compound **14a** (*S aziridine*). Yield: 34.9%. Mp 130°C (dec). ^1H NMR (D_2O) δ 8.30 (s, 1H), 8.29 (s, 1H), 6.08 (d, J=4.8 Hz, 1H), 4.59 (t, J=5.6 Hz, 1H), 4.30 (m, 1H), 3.59 (s, 3H), 3.02 (dd, J=13.6, 4.8 Hz, 1H), 2.61 (dd, J=13.6, 3.6 Hz, 1H), 2.33 (dd, J=6.8, 3.2 Hz, 1H), 2.10 (d, J=3.2 Hz, 1H), 1.88 (d, J=6.8 Hz, 1H); ^{13}C NMR (D_2O) δ 172.79, 156.53, 152.22, 149.08, 140.23, 118.91, 87.76, 82.98, 73.38, 70.83, 58.55, 52.74, 37.91, 33.41. FAB-HRMS: calcd for $C_{14}H_{18}N_6O_5$ ($M+H^+$) 351.13; obsd 351.143.

Compound **14b** (*R aziridine*). Yield: 43.3%. Mp 132°C (dec). ^1H NMR (D_2O) δ 8.36 (s, 1H), 8.25 (s, 1H), 6.08 (d, J=5.6 Hz, 1H), 4.87 (t, J=5.2 Hz, 1H), 4.38 (t, J=5.2 Hz, 1H), 4.34 (m, 1H), 3.62 (s, 3H), 3.00 (dd, J=13.2, 4.0 Hz, 1H), 2.56 (dd, J=13.2, 7.6 Hz, 1H), 2.38 (dd, J=6.8, 3.2 Hz, 1H), 2.13 (d, J=3.2 Hz, 1H), 1.89 (d, J=6.8 Hz, 1H); ^{13}C NMR (D_2O) δ 172.87, 155.07, 152.02, 149.01, 140.60, 119.06, 87.80, 83.54, 73.11, 71.44, 59.99, 52.77, 38.21, 33.05. FAB-HRMS: calcd for $C_{14}H_{18}N_6O_5$ ($M+H^+$) 351.13; obsd 351.143.

4.2.2. 5′-Aziridino-5′-deoxy-(2″-carboxylbenzyl) adenosine 15.

Purification by reverse-phase HPLC on a linear gradient of MeOH (0–50% over 4 min, 50–80% over 18 min; retention time 15.0, 16.2 min). Yield: 53.8%; mp 145°C (dec).

Compound **15a** (*R aziridine*). ^1H NMR (DMSO) δ 8.39 (s, 1H), 8.15 (s, 1H), 7.29 (m, 5H), 5.90 (d, J=5.2 Hz, 1H), 5.47 (bs, 2H), 5.06 (ABq, J=12.4 Hz, 2H), 4.60 (dd, J=5.6, 4.8 Hz, 1H), 4.18 (dd=t, J=4.4 Hz, 1H), 4.03 (m, 1H), 2.73 (dd, J=12.8, 3.6 Hz, 1H), 2.52 (dd, J=12.8, 6.4 Hz, 1H), 2.34 (dd, J=6.4, 3.2 Hz, 1H), 1.97 (dd, J=3.2, 1.6 Hz, 1H), 1.70 (dd, J=6.4, 1.6 Hz, 1H); ^{13}C (DMSO) δ 170.94, 156.77, 153.32, 150.16, 140.39, 136.60, 129.12, 128.66, 128.40, 119.81, 88.07, 84.13, 73.81, 71.92, 66.41, 61.47. FAB-HRMS: calcd for $C_{20}H_{22}N_6O_5$ ($M+H^+$) 427.43; obsd 427.1733.

Compound **15b** (*S aziridine*). ^1H NMR (DMSO) δ 8.31 (s, 1H), 8.10 (s, 1H), 7.30 (m, 5H), 7.24 (s, 2H), 5.86 (d, J=5.2 Hz, 1H), 5.52 (d, J=5.6 Hz, 1H), 5.29 (d, J=5.2 Hz, 1H), 5.05 (ABq, J=12 Hz, 2H), 4.56 (ddd=q (obsd), J=5.2 Hz, 1H), 4.17 (ddd=q (obsd), J=5.2 Hz, 1H), 3.97 (m, 1H), 2.80 (dd, J=12.8, 4.0 Hz, 1H), 2.38 (dd, J=12.8, 3.2 Hz, 1H), 2.22 (dd, J=6.4, 3.2 Hz, 1H), 1.93 (dd, J=3.2, 1.2 Hz, 1H), 1.70 (dd, J=6.4, 1.2 Hz, 1H); ^{13}C (DMSO) δ 170.98, 156.72, 153.33, 150.14, 140.19, 136.49, 129.12, 128.79, 119.66, 87.83, 84.02, 73.82, 71.87, 66.62, 61.39, 36.92, 34.89. FAB-HRMS: calcd for $C_{20}H_{22}N_6O_5$ ($M+H^+$) 427.43; obsd 427.1733.

4.2.3. (4*R*,5*S*)-1,5-Dimethyl-4-phenylimidazolidin-2-one-3-(2′,3′-dibromopropionate) 18.

To **16** (0.250 g, 1.315 mmol) in 2.5 mL dry acetonitrile was added dibromopropionyl chloride (0.395 g, 1.578 mmol) at room temperature. The solution was heated at reflux for 2 h. Upon cooling to 0°C, the reaction was diluted with 5% MeOH/CH_2Cl_2. An aqueous workup was performed (H_2O, 5% MeOH/CH_2Cl_2, brine), the resulting organic layer dried over Na_2SO_4 and solvent removed in vacuo to yield a pink oil. Column chromatography on silica gel (1:1 Pet Ether/EtOAc) yielded **18** as a mixture of diastereomers (0.436 g, 82.1%). Mp 112–114°C. ^1H NMR ($CDCl_3$) δ 7.25 (m, 10H), 6.35 (dd, J=11.5, 4 Hz, 1H), 6.24 (dd, J=11.5, 3.5 Hz, 1H), 5.39 (d, J=9.0 Hz, 1H), 5.36 (d, J=9.0 Hz, 1H), 4.00 (m, 4H), 3.66 (m, 2H), 2.89 (s, 6H), 0.83 (d, J=6.5 Hz, 6H); ^{13}C ($CDCl_3$) 166.70, 165.83, 154.73, 154.63, 135.74, 135.45, 128.77, 128.75, 128.73, 128.70, 128.60, 128.53, 60.14, 60.08, 54.00, 53.94, 40.04, 39.53, 29.84, 29.28, 28.52, 28.48, 15.31, 15.17. FAB-HRMS: calcd for $C_{14}H_{16}Br_2N_2O_2$($M+H^+$) 404.96; obsd 404.962.

4.2.4. (4*S*,5*R*)-1,5-Dimethyl-4-phenylimidazolidin-2-one-3-(2′,3′-dibromopropionate) 19.

To **17** (0.500 g, 2.639 mmol) in 5 mL dry acetonitrile was added dibromopropionyl chloride (0.790 g, 3.156 mmol) at room temperature. The solution was heated at reflux for 2 h. Upon cooling to 0°C, the reaction was diluted with 5% MeOH/CH_2Cl_2. An aqueous workup was performed (H_2O, 5% MeOH/CH_2Cl_2, brine), dried over Na_2SO_4 and evaporated in vacuo to yield a pink oil. Column chromatography on silica gel (1:1 Pet Ether/EtOAc) gave **19** as a mixture of diastereomers (0.690 g, 64.9%). Mp 113–115°C. ^1H NMR ($CDCl_3$) δ 7.25 (m, 10H), 6.34 (dd, J=11.5, 4 Hz, 1H), 6.21 (dd, J=11.5, 3.5 Hz, 1H), 5.38 (d, J=9.0 Hz, 1H), 5.35 (d, J=9.0 Hz, 1H), 4.00 (m, 4H), 3.65 (m, 2H), 2.89 (s, 6H), 0.83 (d, J=6.5 Hz, 6H); ^{13}C ($CDCl_3$) δ 166.74, 165.86, 154.76, 154.74, 135.76, 135.46, 128.81, 128.74, 128.73, 128.64, 128.57, 127.26, 60.17, 59.59, 54.03, 53.97, 40.05, 39.54, 29.86, 29.30, 28.55, 28.51, 15.35, 15.20. FAB-HRMS: calcd for $C_{14}H_{16}Br_2N_2O_2$($M+H^+$) 404.96; obsd 404.962.

4.2.5. (4‴*R*,5‴*S*)-5′-Aziridino-5′-deoxy-[2″-carboxyl-(1‴,5‴-dimethyl-4‴-phenylimidazolidin-2‴-one)]-2′,3′-bis-(*O*-triethylsilyl)adenosine 20.

To **18** (0.125 g, 0.310 mmol) in 10 mL dry THF was added **9** (0.155 g, 0.313 mmol) in 10 mL dry THF. The reaction was allowed to stir for 15 min. Upon addition of TEA (0.094 g, 0.931 mmol), the solution was heated at reflux for 16 h. The precipitate was triturated with anhydrous Et_2O and the organic removed in vacuo to yield a solid. Column chromatography on silica (5:2:1 EtOAc/CH_2Cl_2/MeOH) gave **20** as two diastereomers. Yield (0.091 g, 0.061 g, 66.5%). Mp 184°C (dec).

Compound **20a** (*S aziridine*). ^1H NMR ($CDCl_3$) δ 8.36 (s, 1H), 8.22 (s, 1H), 7.28 (m, 5H), 6.18 (s, 2H), 6.02 (d, J=6.4 Hz, 1H), 5.47 (d, J=8.4 Hz, 1H), 4.99 (dd, J=6, 4.4 Hz, 1H), 4.32 (dd, J=4.4, 2.4 Hz, 1H), 4.25 (m, 1H), 3.89 (dq, J=8.4, 6.8 Hz, 1H), 3.87 (dd, J=6.4, 3.2 Hz, 1H), 3.31 (dd, J=12.8, 3.6 Hz, 1H), 2.82 (s, 3H), 2.43 (dd, J=12.8, 5.6 Hz, 1H), 2.14 (dd, J=2.8, 1.2 Hz, 1H), 1.71 (dd, J=6.4, 1.2 Hz, 1H), 0.98 (t, J=8.0 Hz, 9H), 0.78 (t, *J*=8.0 Hz, 9H), 0.75 (d, *J*=6.8 Hz, 3H), 0.65 (q, *J*=8.0 Hz, 6H), 0.35 (qq, *J*=16.0, 8.0 Hz, 6H); ^{13}C (CDCl$_3$) δ 169.41, 156.17, 153.25, 150.29, 140.79, 136.63, 128.75, 128.34, 127.39, 120.15, 88.15, 85.62, 75.34, 74.19, 61.76, 59.40, 54.34, 36.89, 35.97, 28.38, 15.14, 7.13, 6.80, 5.17, 4.72. FAB-HRMS: calcd for $C_{36}H_{56}N_8O_5Si_2$ (M+H$^+$) 737.40; obsd 737.397.

Compound **20b** (*R aziridine*). ^{1}H NMR (CDCl$_3$) δ 8.35 (s, 1H), 8.25 (s, 1H), 7.24 (m, 5H), 6.10 (s, 2H), 6.01 (d, *J*=6.4 Hz, 1H), 5.35 (d, *J*=8.8 Hz, 1H), 4.77 (dd, *J*=6, 4.4 Hz, 1H), 4.41 (dd, *J*=4.4, 2.4 Hz, 1H), 4.22 (m, 1H), 3.90 (dq, *J*=8.4, 6.4 Hz, 1H), 3.84 (dd, *J*=6.4, 3.2 Hz, 1H), 2.94 (dd, *J*=12.8, 4.8 Hz, 1H), 2.82 (s, 3H), 2.63 (dd, *J*=12.8, 4.0 Hz, 1H), 2.17 (dd, *J*=2.8, 1.2 Hz, 1H), 1.68 (dd, *J*=6.4, 1.2 Hz, 1H), 1.00 (t, *J*=8.0 Hz, 9H), 0.80 (t, *J*=8.0 Hz, 9H), 0.75 (d, *J*=6.8 Hz, 3H), 0.67 (q, *J*=8.0 Hz, 6 H), 0.37 (qq, *J*=16.0, 8.0 Hz, 6H); ^{13}C (CDCl$_3$) δ 169.33, 156.17, 153.34, 149.91, 140.26, 136.61, 128.61, 128.19, 127.38, 120.07, 89.01, 83.48, 75.71, 72.76, 60.39, 59.66, 54.51, 37.19, 37.01, 28.39, 15.15, 7.02, 6.81, 5.15, 4.90. FAB-HRMS: calcd for $C_{36}H_{56}N_8O_5Si_2$ (M+H$^+$) 737.40; obsd 737.397.

4.2.6. (4‴S,5‴R)-5′-Aziridino-5′-deoxy-[2″-carboxyl-(1‴,5‴-dimethyl-4‴-phenylimidazolidin-2‴-one)]-2′,3′-bis-(*O*-triethylsilyl)adenosine 21. To **19** (0.129 g, 0.320 mmol) in 10 mL dry THF was added **9** (0.160 g, 0.323 mmol) in 10 mL dry THF. The reaction was allowed to stir for 15 min. Upon addition of TEA (0.097 g, 0.961 mmol), the solution was heated at reflux for 16 h. The precipitate was triturated with anhydrous Et$_2$O and the organic was evaporated in vacuo to yield a solid. Column chromatography on silica (5:2:1 EtOAc/CH$_2$Cl$_2$/MeOH) gave **21** as two diastereomers. Yield (0.061 g, 0.087 g, 62.8%); mp 210°C (dec).

Compound **21a** (*R aziridine*). ^{1}H NMR (CDCl$_3$) δ 8.34 (s, 1H), 8.11 (s, 1H), 7.29 (m, 5H), 6.18 (d, *J*=5.2 Hz, 1H), 5.75 (s, 2H), 5.29 (d, *J*=8.4 Hz, 1H), 4.93 (dd, *J*=6, 4.4 Hz, 1H), 4.40 (dd, *J*=4.4, 2.4 Hz, 1H), 4.25 (m, 1H), 3.88 (dq, *J*=8.4, 6.8 Hz, 1H), 3.82 (dd, *J*=6.4, 3.2 Hz, 1H), 2.89 (dd, *J*=12.8, 5.2 Hz, 1H), 2.81 (s, 3H), 2.73 (dd, *J*=12.8, 5.2 Hz, 1H), 2.23 (dd, *J*=3.2, 1.2 Hz, 1H), 1.63 (dd, *J*=6.4, 1.2 Hz, 1H), 0.98 (t, *J*=8.0 Hz, 9H), 0.80 (t, *J*=8.0 Hz, 9H), 0.79 (d, *J*=6.8 Hz, 3H), 0.66 (q, *J*=8.0 Hz, 6H), 0.41 (qq, *J*=16.0, 8.0 Hz, 6H); ^{13}C (CDCl$_3$) δ 168.99, 156.13, 153.11, 150.01, 140.48, 136.45, 128.70, 128.34, 127.30, 120.44, 89.02, 84.29, 74.88, 73.50, 61.56, 59.57, 54.31, 37.29, 35.83, 38.34, 15.15, 7.09, 6.82, 5.09, 4.81. FAB-HRMS: calcd for $C_{36}H_{56}N_8O_5Si_2$ (M+H$^+$) 737.40; obsd 737.397.

Compound **21b** (*S aziridine*). ^{1}H NMR (CDCl$_3$) δ 8.35 (s, 1H), 8.09 (s, 1H), 7.24 (m, 5H), 5.99 (s, 2H), 5.93 (d, *J*=6.4 Hz, 1H), 5.33 (d, *J*=8.4 Hz, 1H), 4.99 (dd, *J*=6, 4.4 Hz, 1H), 4.30 (m, 1H), 4.20 (dd, *J*=4.4, 2.4 Hz, 1H), 3.94 (dq, *J*=8.4, 6.4 Hz, 1H), 3.80 (dd, *J*=6.4, 2.8 Hz, 1H), 3.38 (dd, *J*=12.4, 4 Hz, 1H), 2.86 (s, 3H), 2.36 (dd, *J*=12.4, 7.2 Hz, 1H), 2.10 (dd, *J*=2.8, 1.2 Hz, 1H), 1.81 (dd, *J*=6.4, 1.2 Hz, 1H), 0.97 (t, *J*=8.0 Hz, 9H), 0.81 (d, *J*=6.8 Hz, 3H), 0.76 (t, *J*=8.0 Hz, 9H), 0.63 (q, *J*=8.0 Hz, 6 H), 0.34 (qq, *J*=16.0, 8.0 Hz, 6H); ^{13}C (CDCl$_3$) δ 169.29, 155.85, 153.05, 149.90, 141.14, 136.29, 128.60, 128.23, 127.25, 120.68, 89.07, 85.38, 74.45, 74.26, 61.61, 59.75, 54.53, 36.97, 36.11, 28.32, 15.06, 7.05, 6.73, 5.14, 4.68. FAB-HRMS: calcd for $C_{36}H_{56}N_8O_5Si_2$ (M+H$^+$) 737.40; obsd 737.397.

4.2.7. 5′-Aziridino-5′-deoxy-(2″-hydroxymethyl)-2′,3′-bis-(*O*-triethylsilyl)adenosine 22. To **12a** (0.499 g, 0.862 mmol) in 10 mL dry THF at −10°C was added to a 1 M solution of LiAlH$_4$ in THF (0.948 mL, 0.948 mmol) dropwise. The reaction was warmed slowly and stirred for an additional 10 min. The reaction was quenched with NaHCO$_3$ and extracted into EtOAc. The organic layer was washed with water and brine, dried over Na$_2$SO$_4$, and evaporated in vacuo. Silica gel chromatography (5:2:1 EtOAc/CH$_2$Cl$_2$/MeOH) afforded **22a** (*R aziridine*) (0.296 g, 66.0%). Mp 129–132°C. ^{1}H NMR (CDCl$_3$) δ 8.24 (s, 1H), 8.02 (s, 1H), 6.82 (s, 2H), 5.83 (d, *J*=6.0 Hz, 1H), 5.06 (dd, *J*=5.5, 4.5 Hz, 1H), 4.51 (s, 1H), 4.28 (dd, *J*=4.0, 3.5 Hz, 1H), 4.19 (m, 1H), 3.74 (dd, *J*=11.5, 2.5 Hz, 1H), 3.34 (dd, *J*=11.5, 6.0 Hz, 1H), 2.85 (dd, *J*=13.0, 3.5 Hz, 1H), 2.47 (dd, *J*=13.0, 7.0 Hz, 1H), 1.72 (m, 1H), 1.67 (d, *J*=3.5 Hz, 1H), 1.39 (d, *J*=6.5 Hz, 1H), 0.92 (t, *J*=8.0 Hz, 9H), 0.72 (t, *J*=8.0 Hz, 9H), 0.59 (q, *J*=8.0 Hz, 6H), 0.34 (qq, *J*=16.0, 8.0 Hz, 6H); ^{13}C NMR (CDCl$_3$) δ 156.25, 153.00, 149.77, 141.08, 120.58, 89.45, 85.29, 74.12, 74.06, 63.13, 62.11, 40.28, 32.04, 7.03, 6.74, 5.14, 4.74. FAB-HRMS: calcd for $C_{25}H_{46}N_6O_4Si_2$ (M+H$^+$) 551.31; obsd 551.319.

A similar procedure was performed with **12b** to obtain **22b** (*S aziridine*). Yield: 0.231 g, 66.0%. Mp 130–132°C. ^{1}H NMR (CDCl$_3$) δ 8.09 (s, 1H), 7.81 (s, 1H), 6.10 (s, 1H), 5.82 (d, *J*=7.0 Hz, 1H), 5.62 (dd, *J*=7.0, 4.0 Hz, 1H), 4.15 (d, *J*=10.5 Hz, 1H), 4.08 (d, *J*=4.0 Hz, 1H), 4.03 (t, *J*=11.0 Hz, 1H), 3.86 (d, *J*=12.0 Hz, 1H), 3.17 (dd, *J*=12.5, 9.0 Hz, 1H), 1.92 (m, 1H), 1.81 (d, *J*=12.5, 2.0 Hz, 1H), 1.69 (d, *J*=3.5 Hz, 1H), 1.32 (d, *J*=6.5 Hz, 1H), 1.02 (t, *J*=8.0 Hz, 9H), 0.72 (t, *J*=8.0 Hz, 9H), 0.68 (q, *J*=8.0 Hz, 6H), 0.28 (qq, *J*=16.0, 8.0 Hz, 6H); ^{13}C NMR (CDCl$_3$) δ 155.38, 152.46, 148.95, 141.39, 120.56, 90.28, 85.85, 75.18, 72.60, 53.38, 62.66, 41.91, 30.94, 7.08, 6.66, 5.17, 4.60. FAB-HRMS: calcd for $C_{25}H_{46}N_6O_4Si_2$ (M+H$^+$) 551.31; obsd 551.319.

4.2.8. 5′-Aziridino-5′-deoxy-(2″-hydroxymethyl) adenosine 23. Purification by reverse-phase HPLC on a linear gradient of CH$_3$CN (5–100% over 11 min; retention time 5.7 min). Yield: 39.5%; mp 140°C (dec).

Compound **23a** (*R aziridine*). ^{1}H NMR (D$_2$O) δ 8.23 (s, 1H), 8.07 (s, 1H), 5.98 (d, *J*=4.8 Hz, 1H), 4.71 (dd=t (obsd), *J*=5.2 Hz, 1H), 4.32 (dd=t (obsd), *J*=5.2 Hz, 1H), 4.28 (m, 1H), 3.58 (dd, *J*=12.0, 4.8 Hz, 1H), 3.40 (dd, *J*=12.0, 2.8 Hz, 1H), 2.77 (dd, *J*=13.2, 4.0 Hz, 1H), 2.66 (dd, *J*=13.2, 7.2 Hz, 1H), 1.91 (m, 1H), 1.72 (d, *J*=4.0 Hz, 1H), 1.61 (d, *J*=6.4 Hz, 1H); ^{13}C NMR (D$_2$O) δ 155.53, 152.90, 148.81, 140.11, 118.82, 87.86, 83.72, 73.59, 71.52, 63.47, 60.89, 39.89, 31.82. FAB-HRMS: calcd for $C_{13}H_{18}N_6O_4$ (M+H$^+$) 323.14; obsd 323.147.

Compound **23b** (*S aziridine*). ^{1}H NMR (D$_2$O) δ 8.31 (s, 1H), 8.22 (s, 1H), 6.07 (d, *J*=5.2 Hz, 1H), 4.40 (dd=t (obsd), *J*=5.2 Hz, 1H), 4.29 (m, 1H), 3.58 (dd, *J*=12.0, 4.8 Hz, 1H), 3.39 (dd, *J*=12.0, 6.8 Hz, 1H), 2.77 (dd, *J*=13.2, 3.6 Hz, 1H), 2.67 (dd, J=13.2, 6.8 Hz, 1H), 1.93 (m, 1H), 1.69 (d, J=4.0 Hz, 1H), 1.60 (d, J=6.8 Hz, 1H); ^{13}C NMR (D_2O) δ 155.68, 152.99, 148.98, 140.13, 118.95, 87.80, 83.60, 73.61, 71.50, 63.49, 60.71, 40.65, 31.00. FAB-HRMS: calcd for $C_{13}H_{18}N_6O_4$ ($M+H^+$) 323.14; obsd 323.147.

Acknowledgements

The authors gratefully acknowledge financial support provided by American Association of Colleges of Pharmacy, an NIH starter grant (ES09090-04) administered through University of Wisconsin Environmental Health Sciences Center for Developmental and Molecular Toxicology and generous startup funds provided by University of Wisconsin.

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