# Synthesis of Enantiomerically Pure 5′-Aza Noraristeromycin Analogs

Arun Ghosh, Allen R. Ritter, and Marvin J. Miller*

*Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556*

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The synthesis of a novel class of enantiomerically pure azanoraristeromycins is described. An asymmetric hetero Diels–Alder reaction using amino acid-derived chiral acylnitroso dienophiles **2** was used to prepare optically pure allylic acetate substrate **10**. The palladium(0)-catalyzed addition of the sodium salt of adenine to optically pure acetate **10** was achieved to give $N^9$-alkylated adenine adduct **11** in good yield. Catalytic osmium tetraoxide dihydroxylation of the didehydro analog provided both diol products **17** and **18**, corresponding to common natural and unnatural nucleosides, respectively.

## Introduction

Due to the ongoing need for effective anticancer agents and the impending epidemic nature of acquired immunodeficiency syndrome (AIDS), the extent of research directed at finding good therapeutic agents useful for the treatment of cancers and viral infections has increased significantly.[1] The search for anticancer agents has led to the discovery of a number of antiviral nucleoside analogs that have been approved for the treatment of viral infections. However, due to their inherent toxicity, most of these nucleoside anitiviral agents have found limited clinical application.[2] Replacement of the furanosyl oxygen of a nucleoside by a methylene group provides carbocyclic nucleosides.[3] Three-, four-, and six-membered ring carbocyclic nucleoside analogs have also been studied.[4,5] The absence of the heteroatom in the carbocyclic ring prevents chemical or enzymatic processes that degrade normal, ribose-containing nucleosides.[6]

The first naturally-occurring carbocyclic nucleosides, aristeromycin and neplanocin A (Figure 1), have displayed significant biological activity.[7] The therapeutic potential of aristeromycin is, however, limited by its cytotoxicity. More recently, noraristeromycin was found to have improved antiviral activity with no cytoxicity.[8] Replacement of the hydroxymethyl group of aristeromycin or the 4′-hydroxyl of noraristeromycin with an amino functionality would help determine the structure–activity relationships of the carbocyclic nucleosides. We report here the convergent synthesis of a novel class of enantiomerically pure carbocyclic nucleoside analogs, *N*-acylated 5′-aza carbocyclic nucleosides **1**, related to noraristeromycin.

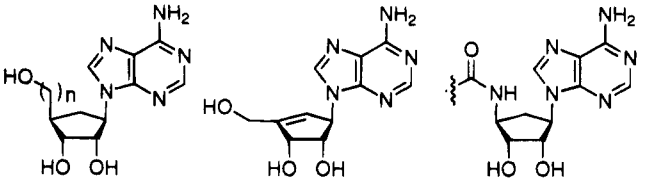


**Figure 1.** Natural carbocyclic nucleosides and novel synthetic analog **1**.

## Carbocyclic Nucleoside Analogs

Concurrent with the search for novel, potent antiviral agents has been the development of new methods for the sythesis of carbocyclic nucleosides. A convergent synthesis of nucleoside analogs involves the coupling of the carbocyclic ring with the nucleoside base or some derivative of the base. This method is efficient in that a variety of nucleoside base analogs can be added to a given carbocyclic precursor. Benneche and co-workers[9] recently reported the palladium (tetrakis)triphenylphosphine-catalyzed addition of the sodium salt of $O^6$-protected guanine analogs to allylic acetates.[10] Alkylation of adenine has been reported to occur solely on $N^9$ under some conditions, but also at $N^7$, $N^3$, and $N^1$. Other routes to optically active carbocyclic nucleosides have included nucleophilic additions to epoxides[11] and mesylates or tosylates.[10,12] Bestmann and Roth[13] have used Mitsunobu conditions to couple purine derivatives to allylic alcohols with subsequent amination and debenzylation to form neplanocin A analogs. The Michael addition of a purine base to an optically pure D-glucose derived nitrocyclo-

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(1) For a discussion of inhibitors of enzymes involved with purine and pyrimidine metabolism see: Hobbs, J. B. In *Comprehensive Medicinal Chemistry*; Hansch, C., Ed.; Pergamon: New York, 1990; Vol. 2, p 306.

(2) The mode of action of nucleosides and their importance in chemotherapy was recently reviewed. Perigaud, C.; Gosselin, G.; Imbach, J.-L. *Nucleosides and Nucleotides* **1992**, *11*, 903.

(3) By definition, a C-nucleoside is a nucleoside in which the base is attached to the furanoside *via* a glycosidic C–C bond. The carbocyclic nucleoside analogs do not contain a glycosidic linkage.

(4) Chen, X.; Siddiqi, S. M.; Schneller, S. W. *Tetrahedron Lett.* **1992**, *33*, 2249, and references therein.

(5) Bolitt, V.; Chaguir, B.; Sinou, D. *Tetrahedron Lett.* **1992**, *33*, 2481.

(6) Marquez, V. E.; Lim, M.-I. *Med. Res. Rev.* **1986**, *6*, 1.

(7) Goodchild, J. In *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Wiley: New York, **1982**; Vol. 6B, p 99.

(8) Patil, S. D.; Schneller, S. W.; Hosoya, M.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1992**, *35*, 3372.

(9) Gunderson, L.-L., Benneche, T.; Undheim, K. *Tetrahedron Lett.* **1992**, *33*, 1085.

(10) Several reviews describe $\pi$-allyl palladium chemistry: (a) Hegedus, L. S. In *The Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Patai, S., Eds.; Wiley: New York, 1985; Vol. 2, p 401. (b) Tsuji, J. *Ibid*, Vol. 3, p 163. (c) Pearson, A. J. *Ibid.* Vol. 4, p 889.

(11) Borthwick, A.; Evans, D. N.; Kirk, B. E.; Biggadike, K.; Exall, A. M.; Youds, P.; Roberts, S. M.; Knight, D. J.; Coates, J. A. V. *J. Med. Chem.* **1990**, *33*, 179.

(12) Biggadike, K.; Borthwick, A. D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Youds, P. *J. Chem. Soc., Chem. Commun.* **1987**, 1083.

(13) Bestmann, H. J.; Roth, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 99.

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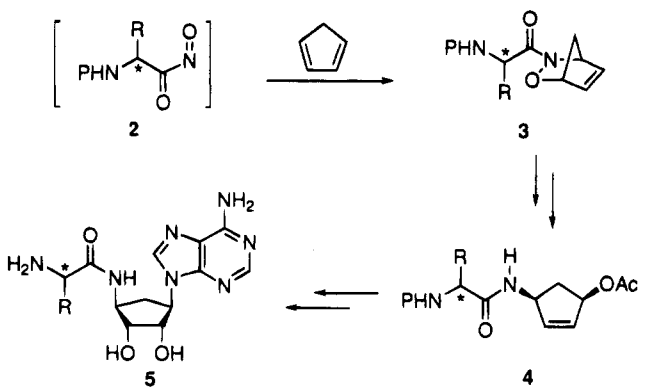
**Scheme 1**



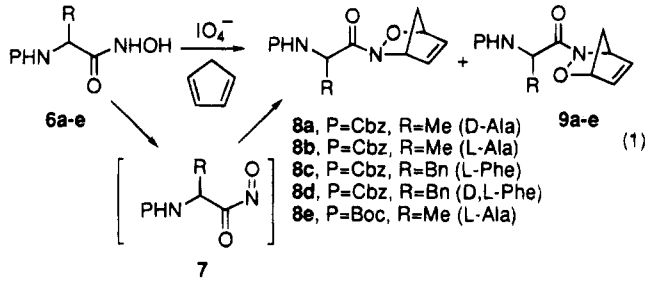
pentene gave optically pure aristeromycin precursors.[14] Variations on these asymmetric convergent approaches to carbocyclic nucleosides are described in recent reviews.[15]

Linear approaches to carbocyclic nucleoside analogs involve construction of the nucleoside base on chiral cyclopentylamines that have typically been elaborated from the chiral pool or a symmetrical Diels–Alder reaction followed by resolution. Both chemical[16] and enzymatic resolution[17] techniques have been used to prepare optically pure carbocyclic nucleoside precursors from the symmetrical Diels–Alder reaction approach to the nucleosides. Several approaches from amino acids and carbohydrates have also been developed.[18] An asymmetric Diels–Alder approach has been applied to the synthesis of chiral substituted cyclopentenylamines.[11,19]

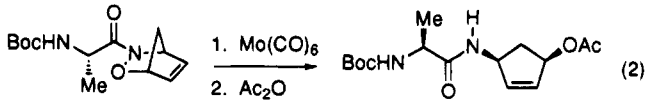
As summarized in Scheme 1, key features of our new route to aza noraristeromycines include a Diels–Alder reaction with an amino acid-derived acylnitroso compound **2**,[20] N–O reduction to form the carbocycle **4**, direct incorporation of the required base (adenine) with retention of configuration, and subsequent diastereoselective dihydroxylation. Details of each aspect of this overall sequence are provided.

## 5′-Aza Noraristeromycins

As described previously,[20] amino acid-based hydroxamic acids **6a–e** were obtained by hydroxaminolysis of the corresponding *N*-protected amino acid methyl esters. Thus, L- and D-alanine, and L- and D,L-phenylalanine were *N*-protected and esterified under standard conditions. Hydroxaminolysis of each ester gave the desired hydroxamic acid.[21] Periodate-mediated oxidation of hydroxamic acids **6a–e** to acylnitroso dienophiles **7a–e** in the presence of 5 equiv of freshly distilled cyclopentadiene afforded a mixture of chromatographically separable optically pure diastereomers **8a–e** and **9a–e** in 65–90% yield.[22] The ratio of diastereomers (i.e., **8a**:**9a**, 3:1; **8b**:**9b**, 1:3; **8c**:**9c**, 1:1.5)[20] was determined by HPLC analysis.[23] The structure of the major diastereomer formed using D-alanine as a chiral auxiliary was determined by X-ray crystal structure analysis.



Molybdenum hexacarbonyl[24,25] efficiently (90–95%) cleaved the hydroxamate N–O bond of cycloadducts **8** and **9** (eq 2). Acetylation of the resulting alcohol derived from **9e** produced allylic acetate **10** in 87% yield (eq 2). This substrate allows for a convergent preparation of carbocyclic nucleosides[26] and an efficient approach to a novel class of 5′-aza carbocyclic nucleosides.



The palladium(0)-catalyzed addition of the sodium salt of adenine to acetate **10** initially afforded three products: the novel 5′-aza analogs of carbocyclic nucleosides **11** and **12** and an intramolecular adduct subsequently confirmed to be oxazolidine **13**[27] (eq 3). The three products and residual starting material were separable by silica gel chromatography. Alternatively, when precisely 1 equiv of the sodium salt of adenine was formed by the addition of 1 equiv of sodium hydride to adenine in DMF, followed by the addition of a mixture of 1 equiv of allylic acetate **10** and tetrakis(triphenylphosphine)-palladium(0) (5–10 mol % relative to allylic acetate) in DMF, only nucleoside analogs **11** and **12** (4:1) were obtained in up to 92% yield (after a second chromatography) with none of the undesired oxazolidine. Addition of sodium hydride to a mixture of acetate **10** and Pd(0) catalyst in DMF provided only the intramolecular adduct **13**.[27]

(14) Yoshikawa, M.; Okaichi, Y.; Cha, B. C.; Kitagawa, I. *Tetrahedron* **1990**, *46*, 7459.

(15) (a) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. (b) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611.

(16) (a) Madhavan, G. V. B.; Martin, J. C. *J. Org. Chem.* **1986**, *51*, 1287. (b) Chen, J.; Grim, M.; Rock, C.; Chan, K. *Tetrahedron Lett.* **1989**, *30*, 5543. For alternatives routes to chiral cyclopentylamines.

(17) (a) Sicsic, S.; Ikbal, M.; Le Goffic, F. *Tetrahedron Lett.* **1987**, *28*, 1887. (b) Balzarini, J.; Baumgartner, H.; Bodenteich, M.; De Clerq, E.; Griengl, H. *J. Med. Chem.* **1989**, *32*, 1861. (c) Taylor, S. J. C.; Sutherland, A. G.; Lee, C.; Wisdom, R.; Thomas, S.; Roberts, S. M.; Evans, C. *J. Chem. Soc., Chem. Commun.* **1990**, 1120.

(18) (a) Park, K. H.; Rapoport, H. *J. Org.Chem.* **1994**, *59*, 394. (b) Bergmeier, S. C.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 5019. (c) Bergmeier, S. C.; Cobas, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369. (d) Arita, M.; Adachi, K.; Ito, Y.; Sawai, H.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 4049. (e) Tadano, K.; Kimura, H.; Ogawa, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1355.

(19) Arai, Y.; Hayashi, K.; Koizumi, T. *Tetrahedron Lett.* **1988**, *29*, 6143.

(20) For a preliminary presentation of Diels–Alder reactions of amino acid derived acylnitroso compounds, see: Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4602.

(21) Miller, M. J.; Biswas, A.; Krook, M. A. *Tetrahedron* **1983**, *39*, 2571.

(22) The cyclopentadiene adducts were separable by simple column chromatography. Boc protected amino acid-derived hydroxamic acids reacted with the same diastereoselectivity as Cbz protected hydroxamic acids.

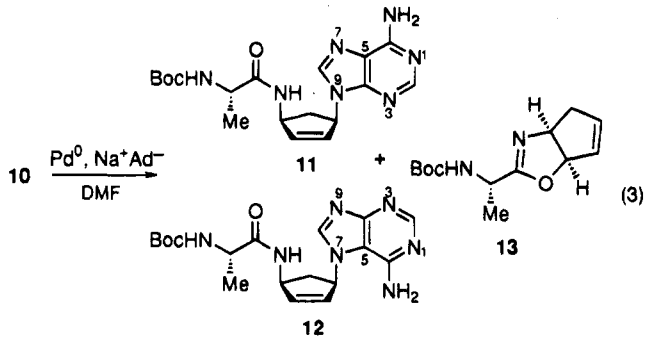
(23) Normal phase HPLC was performed on a 25.4 cm × 4.6 mm 5 μm Econosil silica gel column with 20% 2-propanol in hexanes as eluent and 254 nm detection. The difference in retention time of the two diastereomers was greater than 3 min.

(24) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; DeSarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351.

(25) For a discussion about the mechanism of metal-carbonyl-induced reduction of isoxazoles, see: Nitta, M.; Kobayashi, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1401.

(26) Miller, A.; Procter, G. *Tetrahedron Lett.* **1990**, *30*, 1043.

(27) Hansel, J.-G.; O'Hogan, S.; Lensky, S.; Ritter, A. R.; Miller, M. J. *Tetrahedron Lett.* **1995**, *36*, 2913.

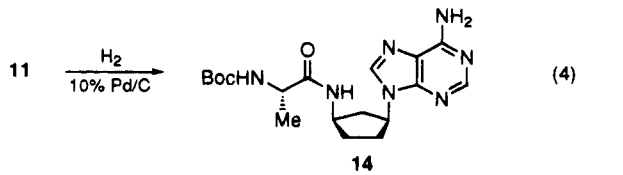



Apparently, no reports of 5′-aza noraristeromycin derivatives such as **11** have appeared in the literature. While a mixture of $N^9$ and $N^7$ adenine alkylated carbocyclic nucleosides (**11** and **12**, respectively) was formed, the overall process of forming nucleosides from the acylnitroso hetero Diels–Alder reaction cycloadducts (**9** → **11**) was very effective.

By $^1$H and $^{13}$C NMR, and mass spectrometric analysis, two isomeric adenine-containing compounds were isolated from the palladium-catalyzed addition reaction. Literature precedent suggested that nucleophilic addition of adenine could result in the formation of both $N^9$ and $N^7$ alkylation products.[28] While the structures of these two products ($N^9$ and $N^7$) can be assigned from the analysis of the relative trends of chemical shifts of specific purine $^1$H and $^{13}$C NMR signals,[15,29] more concrete evidence for the assignment of the structures was made using gated decoupling NMR spectroscopy.[30] As expected, in the major diastereomer **11** (eq 3), $C^4$ was coupled to three protons long range, $H^2$, $H^8$, and $H^{1'}$ (ddd), and $C^5$ was coupled to one proton long range, $H^8$ (d), evidence in support of the structure assigned to the major product. Although, in the minor isomer **12**, the coupling pattern was not as clearly visible, the broadened dd patterns for $C^4$ coupling to two proton long range ($H^2$ and $H^8$), and a dd for $C^5$ coupling ($H^8$ and $H^{1'}$) was consistent with the structural assignment.

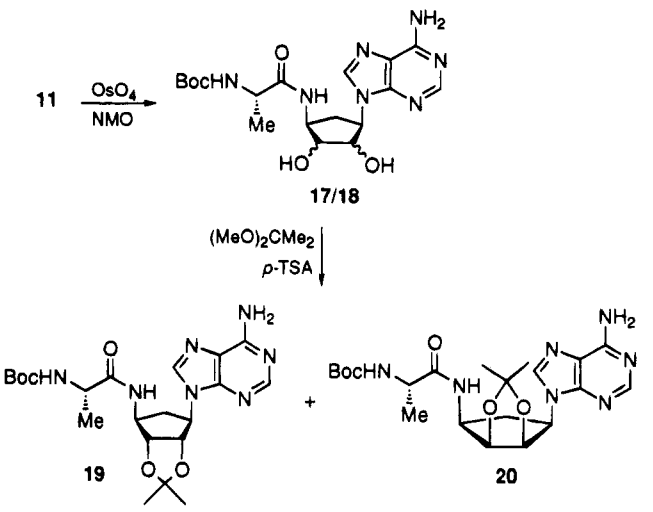
Fortunately, a derivative of the major product from the Pd(0)-catalyzed reaction, acetonide **19** (synthesis described below), was crystallized. A single crystal X-ray analysis of acetonide **19** confirmed that the structure assigned to the major isomer was in fact the $N^9$ alkylated adenine derivative **11**.

In order to eventually survey the biological activity of 5′-aza nucleoside analogs, besides **11** itself, the olefin of 5′-aza nucleoside **11** was reduced to give saturated analog **14** using hydrogen with 10% Pd on carbon as the catalyst (eq 4).

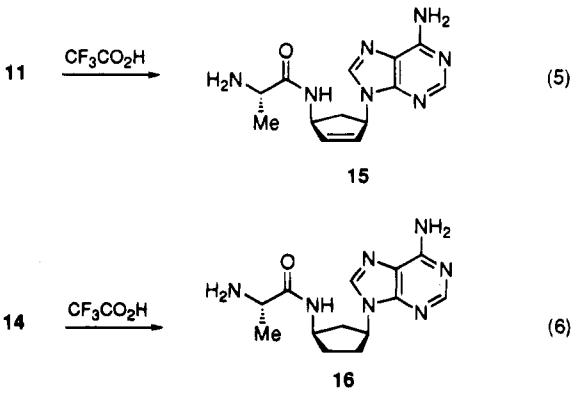



Subsequent removal of the Boc protecting group from unsaturated nucleoside **11** and saturated nucleoside **14** using trifluoroacetic acid gave the corresponding trifluoroacetate salts of **15** and **16** (eqs 5 and 6). Both products were successfully crystallized as HCl salts using HCl-saturated ether. The HCl salts were, however, very hygroscopic and on filtration the flocculent white solids

**Scheme 2**




became viscous oils.[31] Both samples were freeze-dried following ion-exchange chromatography. The free bases were isolated and were less hygroscopic than the ammonium salts.




Further derivatization of **11** was accomplished by *cis*-dihydroxylation of unsaturated nucleoside **11** with catalytic osmium tetraoxide to provide a 90% yield of diols **17** and **18** (Scheme 2). While regular chromatographic purification provided partially separated **17** (32%) and **18** (26%), the stereochemistry of the diastereomeric diols was discerned from the $^1$H NMR spectrum of rather easily separable acetonides **19** and **20** (quantitative yield from diols **17** and **18**, Scheme 2). The major diastereomer formed had the diol functionality *anti* to the two nitrogen ring substituents. Based on mass recovery from the chromatographic separation of the diastereomeric diols, a 3:2 mixture of diols **17** and **18** was obtained in the *cis*-dihydroxylation. While the formation of diastereomeric

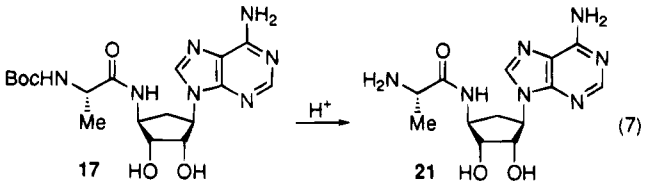
(28) (a) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1988**, *53*, 1294. (b) Jones, J. W.; Robins, R. K. *J. Am. Chem. Soc.* **1962**, *84*, 1914. (c) Kline, P. C.; Serianni, A. S. *J. Org. Chem.* **1992**, *57*, 1772. Alkylation at $N^3$ of adenine also has been reported and was used to prepare the natural product triacanthine: Leonard, N. J.; Deyrup, J. A. *J. Am. Chem. Soc.* **1962**, *84*, 2148 and 3-β-D-ribofuranosyladenine: (a) Leonard, N. J.; Laursen, R. A.; *J. Am. Chem. Soc.* **1963**, *85*, 2026. (b) Leonard, N. J.; Laursen, R. A. *Biochemistry* **1965**, *4*, 354.

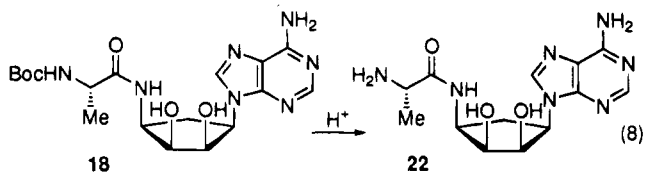
(29) (a) Kjellberg, J.; Johansson, N. G. *Tetrahedron*, **1986**, *42*, 6541. (b) Chenon, M.-T.; Pugmire, R. J.; Grant, D. M.; Panzica, R. P.; Townsend, L. B. *J. Am. Chem. Soc.* **1975**, *97*, 4636.

(30) A proton coupled $^{13}$C NMR with NOE, see: Derome, A. E. In *Modern NMR Techniques for Chemistry Research*; Baldwin, J. E., Ed.; Pergamon: New York, 1987; Chapter 5.

(31) Analysis of the oil revealed that no decomposition of the substrate had occurred.

diols was expected to be more selective,[32] diols **17** and **18** were separated and deprotected with trifluoroacetic acid (eqs 7 and 8). The resulting free base diols **21** and **22** were purified by ion exchange chromatography. *N*-Boc protected diols **17** and **18** were also deprotected with 1:1 THF:1.0 N HCl in quantitative yield.




In summary, the efficient preparation of a novel group of 5′-aza carbocyclic noraristeromycin derivatives was achieved. The palladium(0)-catalyzed addition of adenine to an allylic acetate derived from the asymmetric acylnitroso hetero Diels–Alder reaction gave a mixture of two isomeric nucleosides. The major product was shown to be the desired $N^9$ alkylated adenine. The preparations of optically pure forms of the 2′,3′-dihydroxy-, 2′,3′-dideoxy-, and 2′,3′-dideoxy-2′,3′-didehydroanalogs of the novel 5′-aza nucleosides were efficient.

## Experimental Section

General methods and instruments used have been described previously.[33] Normal phase, achiral HPLC analyses were performed on a Beckmann Model 332 liquid chromatography system using an Alltech Econosil column (5 μm, 25 cm × 4.6 mm) and a UV detector set at 254 nm. Chiral HPLC was performed using the same instrument fitted with a Regis Pirkle Covalent Naphthyl-D-alanine column (5 μm, 25 cm × 4.6 mm) also with UV detection at 254 nm.

**Compounds 6–10.** The details of the syntheses and optical purity determinations for these compounds has been reported.[20] However, a modification in the workup procedure provided an improved yield of **10**.

**1(*R*)-*O*-Acetyl-4(*S*)-[*N*-(*N*-Boc-L-alanyl)amino]cyclopent-2-ene (10).**[20] To a solution of Diels–Alder adduct **9e** (1.0 g, 3.7 mmol) in $CH_3CN$–water (80 mL, 15:1) was added $Mo(CO)_6$ (0.8, 3.0 mmol). The mixture was refluxed for 2 h at which time TLC analysis indicated that the reaction was complete. The cooled reaction mixture was concentrated and partitioned between 1 N citric acid and EtOAc (50 mL, 1:1). To the above was added solid $NaIO_4$ portionwise until the aqueous layer was colorless. The aqueous phase was extracted repeatedly with EtOAc, washed successively with saturated sodium sulfite and brine, dried, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel using EtOAc as eluent afforded 950 mg (95%) of the desired allylic alcohol.

To a solution of the above alcohol (392 mg, 1.46 mmol) in 12 mL of pyridine–$CH_2Cl_2$ (2:1) was added acetic anhydride (0.30 mL, 2.92 mmol). After stirring overnight at 25 °C, the reaction mixture was diluted with EtOAc, washed repeatedly with 1 N HCl to remove any remaining pyridine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel yielded 392 mg (87%) of **10** as a white solid with identical spectral features reported earlier.[20]

**1(*R*)-(*N*$^9$-Adenyl)-4(*S*)-[*N*-(*N*-Boc-L-alanyl)amino]cyclopent-2-ene (11).** In a typical procedure, a magnetically stirred slurry of adenine (674 mg, 4.99 mmol) in anhydrous DMF (30 mL) was treated with 200 mg (4.16 mmol) of 50% NaH suspended in oil at rt under argon. The solution became nearly homogeneous within the next 5 to 10 min, and a white precipitate began to appear. After an additional 10 min at rt, the reaction mixture was placed in an oil bath preheated to 35–40 °C. The warmed solution was then charged with a slightly yellow DMF suspension containing the colorless allylic acetate **10** (1.29 g, 4.16 mmol) and the yellow tetrakis(triphenylphosphine)palladium(0) catalyst (5 mol %). The mixture became nearly homogeneous within 15 min. An additional portion (5 mol %) of catalyst was added if the starting material was not consumed within 1 h. The reaction mixture was cooled to rt and was poured into water. The aqueous phase was then extracted repeatedly with $CH_2Cl_2$ until no additional product was being removed from the aqueous layer (monitored by TLC). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under vacuum to give a viscous oil. Purification by flash chromatography (using as the eluent a gradient of EtOAc to 10% MeOH–EtOAc) yielded, after rechromatography of the mixed fractions, 1.3 g (81%) of diastereomerically pure material and a mixed fraction (165 mg). The total mass recovery (1.47 g) accounted for 92% of the starting allylic acetate. The early fractions (less polar) provided the desired $N^9$-alkylated nucleoside **11** as amorphous solids (1.04 g, 66%): mp 101–105 °C; $R_f$ = 0.31 (10% MeOH in EtOAc, eluted twice); $[\alpha]^{20}_D$ 81.3° ($c$ = 0.21, $CH_2Cl_2$); HPLC analysis 25 cm × 4.6 mm, 5 μm Econosil $SiO_2$ column; flow rate, 2.1 mL/min; eluent, 10:10:80 IPA–$CHCl_3$–hexanes; UV detection at 254 nm ($t_R$ = 54 min); IR (neat) 3300, 3200, 2975, 1700, 1645, 1595, 1370, 1170 cm$^{-1}$; $^1$H NMR (9:1, $CDCl_3$–DMSO-$d_6$) δ 1.40 (s, 12 H), 2.04 (bd, $J$ = 15.0 Hz, 1 H), 3.08 (dt, $J$ = 15.0, 9.0 Hz, 1 H), 4.23 (m, 1 H), 5.22 (bs, 1 H), 5.45 (d, $J$ = 8.1 Hz, 1 H), 5.86 (d, $J$ = 5.2 Hz, 1 H), 6.04 (bs, 1 H), 6.11 (d, $J$ = 5.2 Hz, 1 H), 7.00 (bs, 1 H), 7.90 (s, 1 H), 8.37 (s, 1 H), 8.76 (d, $J$ = 8.7 Hz, 1 H); $^{13}$C NMR (9:1, $CDCl_3$–DMSO-$d_6$) δ 18.59, 28.07, 37.00, 50.29, 53.17, 59.71, 79.56, 120.13, 130.22, 136.85, 139.76, 148.68, 152.37, 155.27, 155.33, 155.93, 172.11. Anal. Calcd for $C_{18}H_{25}N_7O_3$: C, 55.80; H, 6.50; N, 25.31. Found: C, 56.03; H, 6.39; N, 25.10.

**1(*R*)-(*N*$^7$-Adenyl)-4(*S*)-[*N*-(*N*-Boc-L-alanyl)amino]cyclopent-2-ene (12).** The minor nucleoside product **12** (260 mg, 16%), presumed to be $N^7$-alkylated adenine, was isolated from the later fractions (more polar) after chromatography of the reaction product as described in the previous experimental: $R_f$ = 0.14 (10% MeOH in EtOAc, eluted twice); HPLC analysis 25 cm × 4.6 mm, 5 μm Econosil $SiO_2$ column; flow rate, 2.1 mL/min; eluent, 10:10:80 IPA–$CHCl_3$–hexanes; UV detection at 254 nm ($t_R$ = 74.5 min); IR (thin film) 3310, 3200, 2980, 2930, 1700, 1650, 1450, 1365, 1170 cm$^{-1}$; $^1$H NMR (9:1, $CDCl_3$–DMSO-$d_6$) δ 1.34 (d, $J$ = 6.9 Hz, 3 H), 1.40 (s, 9 H), 2.10 (bd, $J$ = 15.3 Hz, 1 H), 3.12 (dt, $J$ = 15.0, 9.0 Hz, 1 H), 4.18 (m, 1 H), 5.17 (m, 1 H), 5.67 (bd, $J$ = 7.8 Hz, 1 H), 5.91 (dt, $J$ = 5.4, 1.5 Hz, 1 H), 6.11 (dt, $J$ = 5.4, 2.1 Hz, 1 H), 6.51 (d, $J$ = 7.2 Hz, 1 H), 8.03 (bs, 2 H), 8.31 (s, 1 H), 9.37 (d, $J$ = 8.4 Hz, 1 H); $^{13}$C NMR (9:1, $CDCl_3$–DMSO-$d_6$) δ 17.33, 27.01, 35.21, 49.27, 52.13, 64.32, 77.59, 119.58, 128.24, 136.95, 141.13, 147.54, 151.34, 153.90, 170.87; HRMS (EI) $m/e$ calcd for $C_{18}H_{25}N_7O_3$: 387.2019, found 387.2008.

**Oxazolidine (13)** has been described.[27] In an experiment otherwise identical with that described for **11** and **12**, the allylic acetate **10** (50 mg) was treated with Pd(0) catalyst and 100 mol % of NaH. The product was isolated as described above to afford **13** as the only product in 80% yield.[27]

**1(*R*)-(*N*$^9$-Adenyl)-4(*S*)-[*N*-(*N*-Boc-L-alanyl)amino]cyclopentane (14).** To a solution of unsaturated nucleoside **11** (30 mg, 0.078 mmol) in MeOH (5 mL) was added approximately 10 mg of 10% Pd on carbon. The suspension was stirred under 1 atm of hydrogen. The reaction was complete in 1 h (TLC analysis). The reaction mixture was filtered through a short pad of Celite and the filtrate concentrated to afford **14** as a

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(33) Teng, M.; Miller, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 548.

white solid in near quantitative yield. An analytical sample was recrystallized from EtOAc and hexanes: mp 110–114 °C; $R_f$ = 0.31 (10% MeOH in EtOAc); $^1$H NMR $\delta$ 1.42 (s, 9 H), 1.45 (d, $J$ = 6.9 Hz, 3 H), 1.82 (m, 1 H), 2.00 (m, 1 H), 2.14 (m, 1 H), 2.26 (m, 1 H), 2.32 (m, 1 H), 2.63 (m, 1 H), 4.30 (m, 1 H), 4.54 (m, 1 H), 4.86 (m, 1 H), 5.52 (m, 1 H), 6.28 (s, 2 H), 7.81 (s, 1 H), 8.43 (s, 1 H), 9.37 (d, $J$ = 6.9 Hz, 1 H); $^{13}$C NMR $\delta$ 19.42, 28.29, 30.79, 33.35, 36.61, 50.07, 50.34, 56.14, 79.68, 120.97, 140.97, 148.35, 152.22, 155.30, 155.95, 171.90. Anal. Calcd for $C_{18}H_{27}N_7O_3$: C, 55.51; H, 6.99; N, 25.18. Found: C, 55.31; H, 7.19; N, 24.98.

**1(*R*)-(*N*$^9$-Adenyl)-4(*S*)-[*N*-(L-alanyl)amino]cyclopent-2-ene, Free Base (15).** A solution of *N*-Boc protected unsaturated nucleoside **11** (151 mg, 0.39 mmol) in $CH_2Cl_2$ (3 mL) was treated with anhydrous trifluoroacetic acid (1.5 mL) at rt and stirred under argon. After completion of the reaction (10–15 min), the volatile components were removed to give a viscous oil which became a glassy solid upon standing under vacuum. All attempts to make ammonium salts to obtain a crystalline sample were unsuccessful. The HCl salt was hygroscopic and could not be isolated. However, the free base, obtained in near quantitative yield after ion-exchange chromatography (BIO-RAD AG 50W-X8, 200–400 mesh, prewashed sequentially with MeOH, acetone, dilute $NH_4OH$, water, and then dilute HCl) using 1 M $NH_4OH$ as the eluent, was found to be not hygroscopic and afforded a foamy solid upon lyophilization: $R_f$ = 0.20 (20% MeOH–EtOAc, 3% $NH_4OH$); $[\alpha]^{20}_D$ 62.8° ($c$ = 0.47, MeOH); IR (neat) 3325, 3200, 1650, 1600, 1570, 1475 cm$^{-1}$; $^1$H NMR ($CD_3OD$) $\delta$ 1.32 (d, $J$ = 6.9 Hz, 3 H), 1.88 (dt, $J$ = 14.1, 5.1 Hz, 1 H), 3.13 (dt, $J$ = 14.1, 8.7 Hz, 1 H), 3.49 (q, $J$ = 6.9 Hz, 1 H), 5.03 (m, 1 H), 5.60 (m, 1 H), 6.05 (dt, $J$ = 5.4, 1.8 Hz, 1 H), 6.13 (dt, $J$ = 5.4, 2.1 Hz, 1 H), 8.12 (s, 1H), 8.22 (s, 1H); $^{13}$C NMR ($CD_3OD$) $\delta$ 20.93, 39.40, 51.45, 55.09, 60.41, 120.53, 132.31, 137.72, 141.31, 150.19, 153.61, 157.34, 174.47; HRMS (FAB) calcd for $C_{13}H_{18}N_7O$ ($MH^+$) 288.1573, found 288.1582.

**1(*R*)-(*N*$^9$-Adenyl)-4(*S*)-[*N*-(L-alanyl)amino]cyclopentane (16).** A solution of saturated *N*-Boc-L-Ala-adenine-containing nucleoside **14** (45 mg, 0.12 mmol) in $CH_2Cl_2$ (3 mL) was charged with 2 mL of anhydrous trifluoroacetic acid at rt under argon. TLC analysis indicated completion of the reaction within 20 min. The mixture was concentrated under vacuum to give the trifluoroacetic acid salt of **16** as a light colored oil in near quantitative yield. As for **15**, the flocculent white solid HCl salt proved to be very hygroscopic and was not isolable. The free base, obtained after ion-exchange chromatography as described in the previous experiment, was dissolved in water and was freeze-dried, resulting in the formation of a less hygroscopic glassy solid: $R_f$ = 0.07 (15% MeOH–EtOAc); $[\alpha]^{20}_D$ −8.4° ($c$ = 0.13, MeOH); reverse phase HPLC analysis using the OPA derivatization technique;[34] $t_R$ = 24.83 min; $^1$H NMR ($CD_3OD$) $\delta$ 1.36 (d, $J$ = 6.9 Hz, 3 H), 1.85–2.15 (m, 3 H), 2.28 (m, 1 H), 2.67 (ddd, $J$ = 16.5, 9.3, 7.5 Hz, 1 H), 3.59 (q, $J$ = 6.9 Hz, 1 H), 4.36 (m, 1 H), 4.98 (m, 1 H), 8.16 (s, 1 H), 8.23 (s, 1 H); $^{13}$C NMR ($CD_3OD$) $\delta$ 20.67, 31.35, 32.75, 38.45, 51.00, 51.34, 56.51, 120.87, 142.00, 150.07, 153.29, 157.42, 175.95; HRMS (FAB) calcd for $C_{13}H_{20}N_7O$ ($MH^+$) 290.1729, found 290.1717.

**1(*R*)-(*N*$^9$-Adenyl)-2(*S*),3(*R*)-dihydroxy-(4*S*)-[*N*-(*N*-Boc-L-alanyl)amino]cyclopentane (17).** A solution of nucleoside **11** (366 mg, 0.95 mmol) in THF (5 mL) was charged with *N*-methylmorpholine *N*-oxide (NMO, 149 mg, 1.1 mmol). The reaction mixture was stirred for 10 min, during which time much of the NMO dissolved. A solution of $OsO_4$ (2.5%, 0.8 mL, 10 mol%) in *tert*-butyl alcohol was then added at rt. The mixture immediately became yellow, and the reaction was complete within 3 h (monitored by TLC). Purification by flash chromatography (using as the eluent a gradient of EtOAc to 10% MeOH–EtOAc) yielded 228 mg (57%) of diastereomerically pure material along with 133 mg of a mixture of isomers. A total of 361 mg of diastereomeric diols were recovered (90% yield). The less polar diol **17** (126 mg, 32%) was obtained as a foam: mp 172–175 °C; $R_f$ = 0.18 (10% MeOH in EtOAc); $[\alpha]^{20}_D$ −109.5° ($c$ = 0.62, MeOH); IR (KBr) 3340, 2980, 1690, 1645, 1368, 1165 cm$^{-1}$; $^1$H NMR ($CD_3OD$) $\delta$ 1.23 (s, 9 H), 1.38 (d, $J$ = 6.9 Hz, 3 H), 2.24 (dd, $J$ = 15.0, 5.1 Hz, 1 H), 2.93 (m, 1 H), 3.96 (m, 2 H), 4.22 (d, $J$ = 7.8 Hz, 1 H), 4.56 (dd, $J$=3.9, 5.4 Hz, 1 H), 4.78 (m, 1 H), 8.07 (s, 1 H), 8.51 (s, 1 H); $^{13}$C NMR ($CD_3OD$) $\delta$ 18.06, 28.51, 31.81, 53.06, 55.01, 62 36, 77.09, 77.40, 80.74, 121.20, 143.47, 149.68, 154.30, 157.42, 157.78, 175.97; HRMS (EI) $m/e$ calcd for $C_{18}H_{27}N_7O_5$: 421.2073, found 421.2068.

**1(*R*)-(*N*$^9$-Adenyl)-2(*R*),3(*S*)-dihydroxy-4(*S*)-[*N*-(*N*-Boc-L-alanyl)amino]cyclopentane (18).** The more polar diastereomer, isolated from the dihydroxylation of nucleoside **11** as described in the previous experimental procedure, was obtained as a solid (102 mg, 26%): mp 169–172 °C; $R_f$ = 0.12 (10% MeOH-EtOAc); $[\alpha]^{20}_D$ +10.8° ($c$ = 0.32, MeOH); IR (KBr) 3370, 2980, 1690, 1650, 1382, 1165 cm$^{-1}$; $^1$H NMR ($CD_3OD$) $\delta$ 1.34 (d, $J$ = 7.2 Hz, 3 H), 1.44 (s, 9 H), 2.25 (dt, $J$ = 13.5, 9.0 Hz, 1 H), 2.72 (m, 1 H), 4.09 (m, 1 H), 4.14 (dd, $J$ = 5.7, 4.2 Hz, 1 H), 4.27 (m, 1 H), 4.32 (m, 1 H), 5.05 (dt, $J$ = 9.0, 6.6 Hz, 1 H), 6.96 (d, $J$ = 6.0 Hz, 1 H), 7.89 (d, $J$ = 8.1 Hz, 1 H), 8.19 (s, 1 H), 8.34 (s, 1 H); $^{13}$C NMR ($CD_3OD$) $\delta$ 18.24, 28.73, 36.33, 50.52, 51.90, 54.92, 73.04, 80.76, 119.72, 143.31, 151.04, 153.33, 157.17, 157.84, 175.62; HRMS (EI) $m/e$ calcd for $C_{18}H_{27}N_7O_5$ 421.2074, found 421.2068.

**1(*R*)-(*N*$^9$-Adenyl)-2(*S*),3(*R*)-(isopropylidenedioxy)-4(*S*)-[*N*-(*N*-Boc-L-alanyl)amino]cyclopentane (19).** A mixture of 46 mg (0.11 mmol) of diastereomeric diols **17** and **18** was charged with 5 mL of 2,2-dimethoxypropane, and several crystals of *p*-toluenesulfonic acid were added. Acetone (2 mL) was added to help dissolve the substrates. The solution became homogeneous in less than 5 min, and the reaction was complete within 15 min (monitored by TLC). The reaction was quenched by pouring into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc until no more UV active material was removed. The combined organic phases were dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel (10% MeOH–EtOAc) to afford pure diastereomeric acetonides (3:2) as an oil in near quantitative yield. The major less polar acetonide **19** crystallized from $CHCl_3$ and provided the following data: mp 283 °C dec; $R_f$ = 0.32 (10% MeOH in EtOAc); IR (KBr) 3400, 2980, 2930, 1650, 1390, 1160 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.17 (d, $J$ = 6.9 Hz, 3 H), 1.20 (s, 3 H), 1.33 (s, 9 H), 1.47 (s, 3 H), 2.39 (m, 1 H), 2.52 (m, 1 H), 3.90 (dq, $J$ = 6.9 Hz, 1 H), 4.20 (m, 1 H), 4.58 (m, 1 H), 4.83 (m, 1 H), 5.04 (m, 1 H), 6.96 (d, $J$ = 6.9 Hz, 1 H), 7.30 (s, 2 H), 8.17 (s, 1 H), 8.19 (s, 1 H), 8.42 (d, $J$ = 7.8 Hz, 1 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 18.17, 25.08, 27.27, 28.13, 35.86, 49.93, 52.97, 59.97, 78.04, 82.37, 83.95, 112.55, 119.44, 140.36, 148.98, 152.49, 155.07, 156.19, 172.52; HRMS (EI) $m/e$ calcd for $C_{21}H_{31}N_7O_5$: 461.2387, found 461.2378.

**1(*R*)-(*N*$^9$-Adenyl)-2(*R*),3(*S*)-(isopropylidenedioxy)-4(*S*)-[*N*(*N*-Boc-L-alanyl)aminocyclopentane (20).** The minor more polar acetonide **20** was isolated as a white solid by column chromatography, as described in the previous experimental and provided the following data: mp 238 °C dec; $R_f$ = 0.21 (10% MeOH in EtOAc); IR (KBr) 3360, 3200, 2984, 2940, 1705, 1645, 1595, 1250, 1165 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.17 (d, $J$ = 6.9 Hz, 3 H), 1.17 (s, 3 H), 1.38 (s, 9 H), 1.42 (s, 3 H), 2.17 (m, 1 H), 2.35 (m, 1 H), 4.01 (m, 1 H), 4.18 (m, 1 H), 4.55 (dd, $J$ = 5.1 Hz, 1 H), 4.69 (dd, $J$ = 5.1 Hz, 1 H), 4.78 (m, 1 H), 7.09 (d, $J$ = 7.5 Hz, 1 H), 7.21 (s, 2 H), 7.47 (d, $J$ = 8.1 Hz, 1 H), 8.08 (s, 1 H), 8.13 (s, 1 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 17.96, 23.96, 25.45, 28.18, 30.38, 48.00, 49.62, 52.44, 77.28, 78.17, 78.28, 110.13, 118.50, 139.90, 149.63, 152.31, 155.11, 155.90, 172.56; HRMS (FAB) calcd for $C_{21}H_{32}N_7O_5$ ($MH^+$) 462.2464, found 462.2461.

**1(*R*)-(*N*$^9$-Adenyl)-2(*S*),3(*R*)-dihydroxy-(4*S*)-[*N*-(L-alanyl)amino]cyclopentane (21).** A suspension of the *N*-Boc protected adenine containing diol **17** (36 mg, 0.09 mmol) in $CH_2Cl_2$ (3 mL) was stirred with anhydrous trifluoroacetic acid (1 mL) at 0 °C to rt. The reaction was complete within 30 min (TLC). The volatile components were removed under vacuum, and the residue was chromatographed on an ion-exchange resin (BIO-RAD AG 50W-X8, 200–400 mesh) that

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was prewashed sequentially with MeOH, acetone, dilute $NH_4OH$, water and then dilute HCl. A total of 27 mg (98%) of white amorphous solid was isolated from the chromatography (1 M $NH_4OH$): $R_f$ = 0.12 (30% MeOH in EtOAc with $NH_4OH$); IR (KBr) 3345, 3165, 2955, 2900, 1670, 1640, 1620, 1420, 1340, 1120 $cm^{-1}$; $^1H$ NMR ($D_2O$) $\delta$ 1.13 (d, $J$ = 6.9 Hz, 3 H), 1.86 (m, 1 H), 2.62 (m, 1 H), 3.31 (m, 1 H), 3.69 (m, 1 H), 3.98 (m, 1 H), 4.43 (dd, $J$ = 4.2, 8.1 Hz, 1 H), 4.64 (m, 1 H), 5.10 (bs, 2 H), 7.25 (s, 2 H), 8.12 (s, 1 H), 8.14 (s, 1 H), 8.91 (d, $J$ = 7.8 Hz, 1 H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 21.45, 32.31, 50.18, 52.59, 59.21, 74.66, 75.29, 119.65, 141.00, 148.82, 152.07, 156.10, 156.16, 174.60; HRMS (FAB) $m/e$ calcd for $C_{13}H_{19}N_7O_3$ 321.1549, found 321.1547.

**1(*R*)-(*N*$^9$-Adenyl)-2(*R*),3(*S*)-dihydroxy-4(*S*)-[*N*-(L-alanyl)amino]cyclopentane, Free Base (22).** Following the procedure described for the synthesis of **21**, the free amine **22** was generated by the brief treatment of **18** with trifluoroacetic acid−$CH_2Cl_2$ (1:3) and was isolated as a foamy solid in near quantitative yield: $R_f$ = 0.17 (50% MeOH in EtOAc); IR (KBr) 3340, 2920, 1655, 1640, 1605, 1480, 1420, 1120, 998 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 1.13 (d, $J$ = 6.9 Hz, 3 H), 2.01 (dt, $J$ = 12.9, 9.3 Hz, 1 H), 2.50 (m, 1 H), 3.27 (q, $J$ = 6.9 Hz, 1 H), 3.93 (m, 1 H), 4.15 (m, 2 H), 4.96 (m, 1 H), 5.21 (bs, 1 H), 5.50 (bs, 1 H), 7.19 (s, 2 H), 7.93 (d, $J$ = 8.7 Hz, 1 H), 8.11 (s, 1 H), 8.20 (s, 1 H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 21.50, 36.12, 47.80, 50.24, 52.35, 70.97, 71.48, 118.35, 141.34, 149.79, 151.93, 155.87, 175.21; HRMS (FAB) calcd for $C_{13}H_{20}N_7O_3$ ($MH^+$) 322.1628, found 322.1643.

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**Supporting Information Available:** $^1H$ and $^{13}C$ NMR of compounds **12**−**22**; gated decoupled $^{13}C$ NMR of compounds **11** and **12** (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal and can be ordered from ACS; see any current masthead page for ordering information. Atomic coordinates, bond lengths and angles, thermal parameters and structure factors for compound **19** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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