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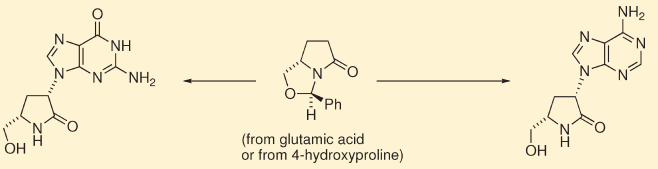
Synthesis of 3-Guaninyl- and 3-Adeninyl-5-hydroxymethyl-2-pyrrolidinone Nucleosides

Abdullah Saleh,[‡] John G. D'Angelo,[§] Martha D. Morton, Jesse Quinn, Kendra Redden,[∥] Rafal W. Mielguz,[†] Christopher Pavlik, and Michael B. Smith*

Department of Chemistry, 55 N. Eagleville Road, University of Connecticut, Storrs, Connecticut 06269-3060, United States

Supporting Information

ABSTRACT: L- And D-glutamic acids, as well as *trans*-4-hydroxy-L-proline, are converted to the corresponding 3-guaninyl-5-hydroxymethyl-2-pyrrolidinone (**4**) or 3-adeninyl-5-hydroxymethyl-2-pyrrolidinone (**5**) nucleoside analog. The protecting group used to block the lactam nitrogen in key intermediates has a significant effect on the diastereoselectivity of the coupling reaction with adenine or guanine.



INTRODUCTION

Human immune-deficiency virus type 1 (HIV-1) is the causative organism for acquired immune-deficiency syndrome (AIDS),[1] and despite great progress in chemotherapeutic treatment and prevention,[2] millions have lost their lives. The World Health Organization estimates that as of 2009 33.3 million people were living with AIDS, and 1.8 million died in 2009.[3] Several forms of chemotherapy are based on key events in the life cycle of HIV-1, including interception of the viral enzyme, reverse transcriptase (RT).[4] The HIV-RT enzyme converts the viral RNA to proviral DNA, and there are two general classes of RT inhibitors: nucleoside-based reverse transcriptase inhibitors (NRTI's)[5] and non-nucleoside reverse transcriptase inhibitors (NNRTI's).[6] Significant toxicity is associated with many NRTIs, and there is evidence that much of this toxicity results from the inhibition of mitochondrial DNA replication. AZT (**1**), for example, is known to cause bone marrow suppression, but the delay of disease progression often outweighs the complications caused by treatment with AZT.[7] One FDA-approved anti-HIV NRTI treatment is abacavir (**2**),[8] which after the intracellular monophosphorylation, is converted to carbovir monophosphate, which is further phosphorylated to the biologically active carbovir triphosphate. Carbovir (**3**),[8] an anti-HIV drug marketed by GlaxoSmithKline, was first identified as a potent anti-HIV agent in 1990. It has comparable activity to the clinically used AZT and lower toxicity. There have been several syntheses of carbovir, with the first in 1990 by Vince and co-workers,[9a,d] the discoverers of carbovir. In the scheme reported by Vince and co-workers, a guanine derivative was structurally modified to incorporate the cyclopentene unit, rather than begin with a cyclopentene and then attach a guanine unit.

Analyses of **1**−**3** (see Scheme 1), as well as other related antiviral drugs, show that a nucleobase and a hydroxymethyl unit are attached to a relatively flat five-membered ring. The synthesis of such compounds remains an area of interest with respect to synthesis and biological studies.[9,8c,d] Our interest in this area began with our previous work that used enantiopure lactams as chiral templates for synthesis. We published several papers that converted L-glutamic acid to chiral 2-pyrrolidinone derivatives via pyroglutamate esters.[10] The planarity of the lactam ring in 5-substituted-2-pyrrolidinone derivatives is well-established.[10] We speculated that 2-pyrrolidinone could be used as a replacement for the cyclopentene ring in **3** or similar compounds. Such a target required the attachment of a purine or pyrimidine base to C3 of a 5-hydroxymethyl-2-pyrrolidinone derivative. We therefore examined synthetic routes to establish the efficacy of using pyroglutamate and 3-hydroxyproline as chiral templates in a proof-of-principle study to prepare the two compounds shown in Scheme 1: 3-guaninyl-5-hydroxymethyl-2-pyrrolidinone (**4**) and the 3-adeninyl-5-hydroxymethyl-2-pyrrolidinone (**5**). We have completed synthetic routes to both compounds and report their total synthesis.

RESULTS AND DISCUSSION

L-Glutamic acid is an attractive starting material due to its commercial availability, low cost, and widespread use. In a study that is highly relevant to our targeted compounds, Nielsen and co-workers reported a synthesis of conformationally restricted peptide nucleic acid (PNA) derivatives from D-glutamic acid (**6**).[11] As shown in Scheme 2, formation of 2-pyrrolidinone-5-carboxylic acid (pyroglutamic acid) was followed by reduction to the hydroxymethyl derivative and protection of the alcohol and nitrogen to give the *O*-TBDPS, *N*-Boc derivative **7**. α-Hydroxylation with MoOPH, via the lactam enolate anion, gave **8** as a key intermediate. The PNA monomer was prepared by conversion of **8** to **9** in several steps, followed by a Mitsunobu coupling that incorporated adenine, with clean inversion of configuration

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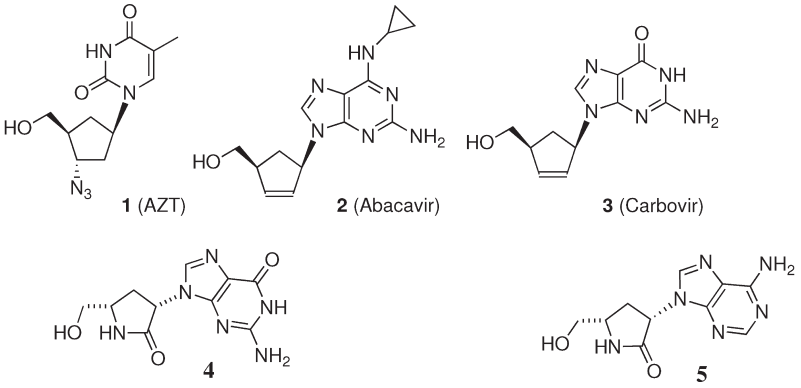
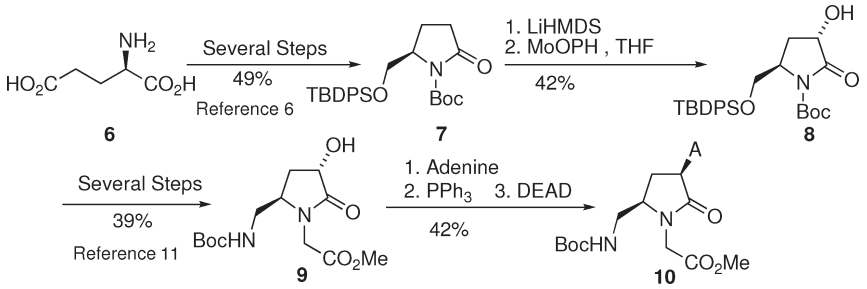
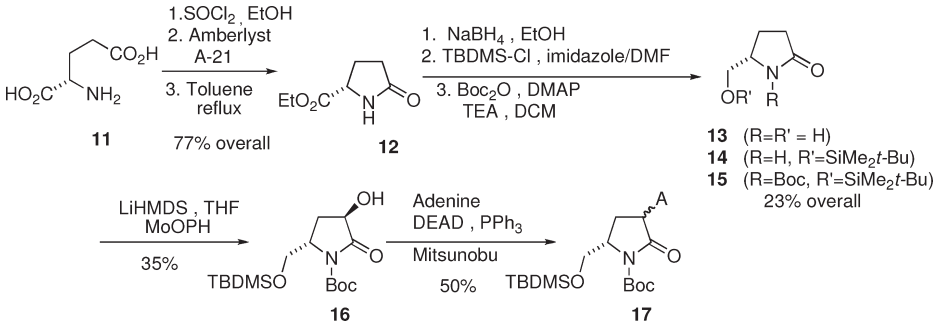
Scheme 1. AZT (1), Abacavir (2), and Carbovir (3) and the 3-Guaninyl-5-hydroxymethyl-2-pyrrolidinone (4) and 3-Adeninyl-5-hydroxymethyl-2-pyrrolidinone (5) Targets



Scheme 2. The Nielsen Synthesis of Peptide Nucleic Acid 10



Scheme 3. Conversion of L-Glutamic Acid to Adeninyl Derivative 17 via the Nielsen Approach



to give **10**.[11] We anticipated a straightforward preparation of **4** or **5** by simply modifying Nielsen's synthetic route to obtain the free lactam rather than **10**. We chose to target the adenine derivative first because of the extensive protecting group manipulation that is required for coupling guanine. Initially, we converted L-glutamic acid (**11**) to ethyl pyroglutamate, **12**. We chose **11** for the development work due to its greater availability and lower price relative to D-glutamic acid, **6**. Following Nielsen's protocol,[11] the ester group was reduced with sodium borohydride to give **13** and the alcohol moiety was protected as the TBDMS derivative (**14**) as shown in Scheme 3. Our target was the free lactam, so the lactam nitrogen required a protecting group, which is a structural difference when compared to Nielsens's synthesis that required the preparation of **9**. We chose the *N*-Boc group, and **15** was generated in 23% overall yield from **12**. Subsequent generation of the enolate anion and reaction with MoOPH gave **16** in 35% yield. Coupling with adenine proceeded smoothly under Nielsen's Mitsunobu conditions to give **17**, but there was a problem. We obtained **17** as a 1:1 mixture of diastereomers at C3: *S*-[(*tert*-butyldimethylsilyloxy)methyl]-3*R*-adenin-9-yl-2-pyrrolidinone-*N*-*tert*-butylcarbamate + *S*-[(*tert*-butyldimethylsilyloxy)methyl]-3*S*-adenin-9-yl-2-pyrrolidinone-*N*-*tert*-butylcarbamate. It was clear that the stereochemical integrity of C3 had been compromised. For that reason, we did not deprotect **17** to give the final target. It was not clear why this product should be configurationally unstable when Nielsen prepared **10** without a problem. The main structural difference between **10** and **17** was the presence of the *N*-Boc group, and we speculated that the presence of this group allowed epimerization to occur. While the cause of this effect is not proven, we

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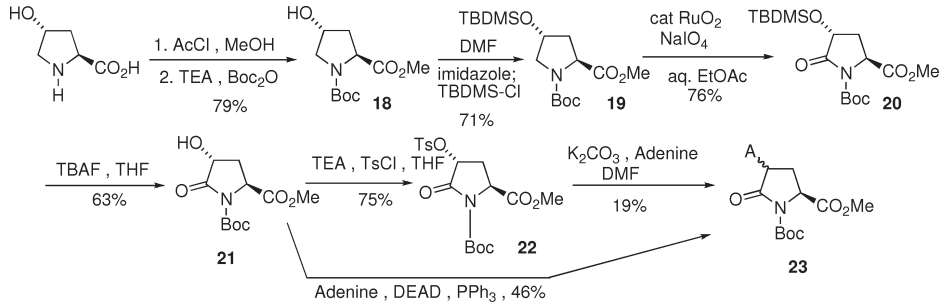
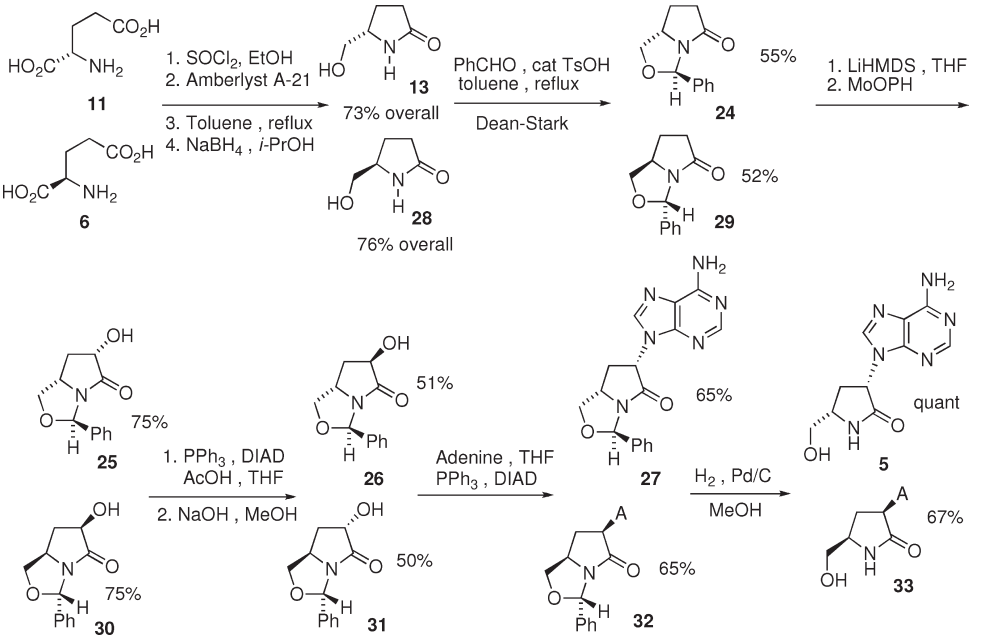
Scheme 4. Synthesis of 23 from 4-Hydroxy-L-proline



Scheme 5. Enantioselective Synthesis of 5 from L-Glutamic Acid and of 33 from D-Glutamic Acid



speculate that the Boc group enhances the acidity of the C3 proton, which would make it subject to epimerization.

In order to probe this issue, we prepared the 3-adeninyl lactam by an alternative route that allowed two different coupling procedures, as outlined in Scheme 4. We modified the synthetic sequence to use commercially available *trans*-4-hydroxy-L-proline as a starting material. Conversion to the *N*-Boc methyl ester **18** (79% yield) was followed by protection of the alcohol moiety to give **19** in 71% yield. Oxidation used the protocol of Zhang et al.[12] (ruthenium oxide and periodate)[13] to give lactam **20** in 76% yield, and deprotection of the alcohol moiety with TBAF gave **21** in 63% yield. Two routes were used to prepare the targeted **23.** The first used a Mitsunobu coupling of **21** with unprotected adenine that gave **23** directly, in 46% yield, as a 1:1 mixture of diastereomers at C3: methyl *N*-*tert*-butoxycarbonyl-3*R*-adeninylpyroglutamate and methyl *N*-*tert*-butoxycarbonyl-3*S*-adeninylpyroglutamate. The second route was the less efficient conversion of **21** to tosylate **22** (75% yield). Isolation of **22** confirmed that this compound was enantiopure and configurationally stable. Subsequent reaction with adenine in DMF with potassium carbonate gave **23**, but as observed in the Mitsunobu coupling with **21**, the use of enantiopure **22** led to **23** as a 1:1 mixture of diastereomers at C3. Interestingly, we recovered unreacted **22** and found that the C3 stereocenter had epimerized. In other words, the enantiopure starting material, **22**, was recovered as a mixture of diastereomers at C3 after the reaction. Unfortunately, these experiments did not provide a suitable solution to preparing a configurationally stable adeninyl lactam.

From previous work in our laboratory,[10a] and work reported by others,[14] we were aware of the influence of the nitrogen protecting group on the reactivity of chiral 2-pyrrolidinone derivatives. Once again, we speculate that the presence of the *N*-Boc group leads to enhanced acidity of the proton at C3, which in turn leads to configurational instability. It was clear that Nielsen's route led to an adenine derivative without loss of stereochemical integrity. Proceeding on the assumption that the presence of the *N*-Boc group was responsible for the configurational instability, the synthetic sequence was changed to modify the protecting group on nitrogen.

Frydman and co-workers reported the synthesis of bicyclic derivative **24**,[15] and we also prepared it in an earlier work.[10a] Conversion of glutamic acid to **24** provides protection of both the hydroxymethyl group as well as the lactam nitrogen. The reactions in Scheme 5 show the conversion of L-glutamic acid **11**

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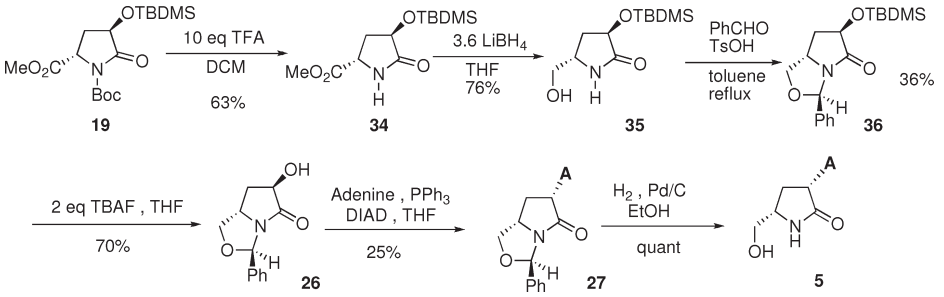
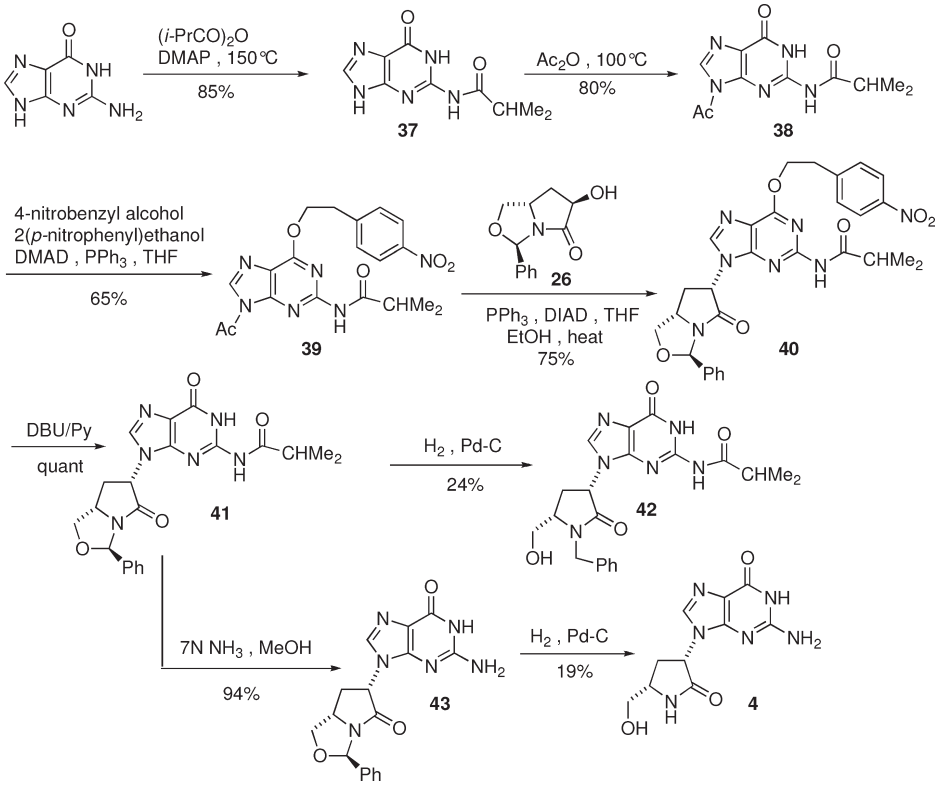
Scheme 6. Enantioselective Synthesis of 5 from *trans*-4-Hydroxy-L-proline



Scheme 7. Synthesis of 4



to ethyl pyroglutamate, followed by reduction to give **13** in 73% overall yield. We prepared enantiopure **24** from **13** in 55% isolated yield using Frydman's procedure. Hara et al previously reported the MoOPH hydroxylation of **24** to give **25** via the enolate anion.[16] Interestingly, **25** was obtained in 75% yield as a single diastereomer, where *syn*-hydroxylation resulted from coordination of the MoOPH reagent with the enolate anion derived from **24**.[16] Unfortunately, the targeted stereochemistry based on **1**−**3** required the opposite stereochemistry for the C3 hydroxyl group (see Scheme 1), but Mitsunobu inversion[17] provided **26** in 51% yield. A second Mitsunobu reaction incorporated the adenine moiety to give **27** in 65% yield as a single stereoisomer. We were gratified to find that **27** was configurationally stable, and catalytic hydrogenation provided a quantitative yield of the targeted **5**, as a completely stable compound. These results clearly suggest that the *N*-Boc group in **16** and in **22** was responsible for the configurational instability at C3 of the lactam, whereas **26** provided a configurationally stable vehicle to the targeted nucleobase lactam.

Given our previous problems with configurational stability, and in order to provide further proof of stereocontrol in the synthesis, we targeted the antipode of **5**, using D-glutamic acid (**6**) as the starting material. The synthetic sequence is identical and shown for comparative purposes in Scheme 5. Initial conversion to the hydroxymethyl lactam **28** was followed by conversion to **29** by reaction with benzaldehyde and tosic acid. Hydroxylation via MoOPH gave **30** and Mitsunobu inversion led to **31**. Mitsunobu coupling with adenine gave **32**, and catalytic hydrogenation gave the expected **33**. As shown in Scheme 5, the isolated yields are virtually identical to those obtained with L-glutamic acid, except for the conversion of **32** to **33**. The diminished yield of **33** relative to the conversion of **27** to **28**

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represents a single experiment and is not optimized. It is clear that antipodes **5** and **33** can be prepared with equal facility using the glutamic acid route, from L-glutamic acid and D-glutamic acid, respectively

We next targeted **5** using *trans*-4-hydroxy-L-proline as the chiral template for comparative purposes, but we modified the previous sequence in Scheme 4 to prepare **26** as the key intermediate. Using the methodology described in Scheme 4 we prepared **19**, and standard deprotection at nitrogen gave **34** in 63% yield, as shown in Scheme 6. In this case, **34** gave poor yields of **35** when reduced with sodium borohydride. Reduction of the ester moiety with lithium borohydride,[18] however, gave a satisfactory 76% yield of **35**. The reaction of **35** with benzaldehyde and tosic acid gave the expected **36**, but in only 36% yield. This reaction is the result of a single experiment and was not optimized. Deprotection of the 3-hydroxy unit gave **26** in 70% yield, and subsequent reaction with adenine under Mitsunobu conditions gave **27** in 25% yield. Deprotection by catalytic hydrogenation gave **5** in quantitative yield.

We next applied this methodology to the synthesis of the guanine derivative, which is the formal analog of **2** or **3** from Scheme 1, using **26** as the key intermediate for introduction of the hydroxymethyl lactam unit. It is well-known that the free amine group in guanine requires protection prior to coupling at N9. Guanine was therefore converted to isobutryl amide **37** and then acetylated to give **38** in 85% and 80% yield, respectively (see Scheme 7). The lactam moiety of **38** was protected as a nitrophenylethanol moiety to give **39** in 65% yield. This elaborate protection strategy allowed **39** to undergo a Mitsunobu coupling reaction at N9 with **26** to give **40** in 75% yield, with the expected inversion of configuration at the α-carbon of the 2-pyrrolidinone unit. Deprotection of the nitrophenylethanol unit gave **41**, but attempts to reduce the oxazolidine ring by catalytic hydrogenation gave the *N*-benzyl lactam **42** rather than the unsubstituted lactam. However, the reaction of **41** with 7 N ammonia-in-methanol[19] gave **43** in 94% yield, and subsequent hydrogenation gave the targeted **4**, but in only 19% yield. The regiochemistry at N9 was established by HMBC, which clearly showed the correlation between H3′ and C4.

In conclusion, we have shown that it is possible to attach a purine base to the C3 position of 5-hydroxymethyl-2-pyrrolidinone. The choice of protecting groups is quite important, as the use of *N*-Boc derivatives for coupling with the nucleobase led to configurational instability, which may be due to enhanced acidity of the proton at C3. The bicyclic derivative **26** is prepared from L-glutamic acid or from *trans*-4-hydroxy-L-proline, and **31** can be prepared from D-glutamic acid. Both the 3-adeninyl derivative **5** and 3-guaninyl derivative **4** can be prepared by these methods. Incorporation of other nucleobases via similar methodology may be feasible, although we anticipate protecting group issues in the synthesis of other derivatives. This work constitutes a successful proof-of-principle for the preparation of 3-nucleobase analogs of the antiviral compounds **1**−**3**.

EXPERIMENTAL SECTION

All chemicals and reagents were used as received unless otherwise stated. All solvents were dried according to standard procedures. THF was distilled from sodium benzophenone; methylene chloride, toluene, and benzene were distilled from CaH_2; and DMF was stirred with CaH_2 for several hours, filtered, and then vacuum distilled. *n*-Butyllithium was standardized before use, using diphenylacetic acid.[20] Water-sensitive and air-sensitive reactions were carried out under a nitrogen blanket. Flash chromatography was performed using silica gel (60 Å, 32−63 μm).

MoOPH was prepared according to literature methods.[21] The following compounds used for the preparation of key compounds were prepared using literature procedures. Details for the synthesis of each compound listed here are provided in the cited reference, and in the Supporting Information: ethyl 2-pyrrolidone-5*S*-carboxylate (**12**),[11a,d,e] ethyl 2-pyrrolidinone-5*R*-carboxylate,[22] *trans*-4-hydroxy-L-proline methyl ester hydrochloride salt,[23] 5*S*-(hydroxymethyl)-2-pyrrolidinone (**13**),[24] *N*-*tert*-butoxycarbonyl-*trans*-4-hydroxy-L-proline methyl ester (**18**),[25] 5*R*-(hydroxymethyl)-2-pyrrolidinone (**28**),[11d−f,h] *N*-*tert*-butoxycarbonyl-*trans*-3-*tert*-butyldimethylsilyl ether L-proline methyl ester (**19**),[26] methyl 5*S*-*N*-*tert*-butoxycarbonyl-3*R*-*tert*-butyldimethylsilyloxypyroglutamate (**20**),[27] methyl 5*S*-*N*-*tert*-butoxycarbonyl-3*R*-hydroxypyroglutamate (**21**),[28] 5*S*,8*R*-phenyltetrahydropyrrolo[1,2-*O*]oxazol-2-one (**24**),[29] 3*S*-hydroxy-5*S*,8*R*-phenyltetrahydropyrrolo[1,2-*O*]oxazol-2-one (**25**),[29] 3*S*-hydroxy-5*S*,8*S*-phenyltetrahydropyrrolo[1,2-*O*]oxazol-2-one (**26**),[30,31] *N*2-isobutyrylguanine monohydrate (**37**),[33a,b] 9-acetyl-*N*2-isobutyrylguanine (**38**),[33] and *N*2-isobutyryl-*O*6-[2-(*p*-nitrophenyl)ethyl]guanine (**39**).[33]

GC−MS spectra were obtained with an HP-1 column gas chromatogram−mass spectrometer. ^1H and ^{13}C NMR were respectively collected at 300.13 MHz for proton and at 75.48 MHz for carbon and at 400.144 MHz for proton and 100.65 MHz for carbon. In all cases, $CDCl_3$ was used as a solvent unless otherwise stated; chemical shifts are in ppm (δ) relative to TMS as an internal standard. All IR spectra are reported in cm^{-1}. Mass spectra (MS) [displayed as m/z (% base peak)] were recorded via GC−MS or via LC−MS.

(5*S*)-{[(*tert*-Butyl)dimethylsilyloxy]methyl}-2-pyrrolidinone, 14. A mixture of 3.0 g of **13** (26.0 mmol) and 4.4 g (65.0 mmol) of imidazole dissolved in 15 mL of DMF was treated with 4.7 g (31.3 mmol) of chloro-*tert*-butyldimethylsilane. The reaction mixture was stirred for 24 h at ambient temperature. At this time, 75 mL of Et_2O was added and the crude product was washed with water and brine and dried over anhydrous Na_2SO_4, and the solvents were removed in vacuo. Purification by flash chromatography (100% EtOAc) gave 4.45 g of (5*S*)-{[(*tert*-butyl)dimethylsilyloxy]methyl}-2-pyrrolidinone, **14**,[11] as a yellow oil (19.40 mmol, 75%). ^1H NMR: δ 0.00 (s, 6H), 0.87 (s, 9H), 1.60−2.50 (m, 4H), 3.35−3.80 (m, 3H), 6.65 (br s, NH). ^{13}C NMR: δ 0.4, 18.5, 23.3, 25.2, 30.3, 56.2, 67.0; 178.8. IR (film): 3225 (NH); 1700 (C═O) cm^{-1}. MS: 229 (1, M), 200 (4), 172 (100, B), 158 (54), 155 (10), 128 (22), 116 (24), 84 (50), 75 (53), 74 (24), 73 (51), 59 (23), 58 (18), 55 (17). HR-TOF MS: calcd for $C_{11}H_{24}NO_2Si$ ($M + H^+$) m/z 230.2576, found m/z 230.1569; calcd for $C_{11}H_{23}NO_2SiNa$ m/z 252.1396 ($M + Na^+$), found m/z 252.1388.

(2*S*)-5{[(*tert*-Butyl)dimethylsilyloxy]methyl}-2-pyrrolidinone-1-*N*-*tert*-butylcarbamate, 15. A solution of 1.34 g (6.0 mmol) of **14** in 25 mL of CH_2Cl_2 was treated with 2.61 g (11.6 mmol) of $(Boc)_2O$, 0.71 g (6.0 mmol) of DMAP, and 0.81 mL (6.0 mmol) of Et_3N, respectively. The reaction mixture was stirred at ambient temperature for 24 h, and 25 mL of Et_2O was added. The ether was washed with 10% citric acid, satd $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, and the solvents were evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2−EtOAc, 15:1) gave 1.9 g of (2*S*)-5{[(*tert*-butyl)dimethylsilyloxy]methyl}-2-pyrrolidinone-1-*N*-*tert*-butylcarbamate, **15**,[11] as a yellow oil (5.5 mmol, 93%). ^1H NMR: δ 0.00 (s, 6H), 0.85 (s, 9H), 1.30 (s, 9H), 1.70−2.60 (m, 4H), 3.40−4.00 (m, 3H); ^{13}C NMR: δ 1.2, 18.4, 21.4, 25.9, 28.3, 32.6, 59.1, 64.6, 82.6, 150.2, 174.9. MS: 257 (2). 256 (9), 216 (41), 172 (100, B), 156 (51), 100 (13), 84 (21), 75 (20), 73 (33), 59 (11), 58 911), 57 (68), 55 (13). HR-TOF MS: calcd for $C_{16}H_{32}NO_4Si$ m/z 330.2101, found m/z 330.2094; calcd for $C_{16}H_{32}NO_4SiNa$ m/z 352.1920 ($M + Na^+$), found m/z 352.1902.

5*S*-[(*tert*-Butyldimethylsilyloxy)methyl]-3*R*-hydroxy-2-pyrrolidinone-*N*-*tert*-butylcarbamate, 16. Dropwise addition of 9.0 mL (9.0 mmol, 1.0 M in hexane) of *n*-butyllithium to a solution of 1.9 mL (9.0 mmol) of hexamethyldisilazane dissolved in 20 mL of THF was followed by cooling to −78 °C and stirring at −78 °C for 30 min. At this time, 1.36 g (3.0 mmol) of **15**, dissolved in 20 mL of THF and cooled to −78 °C, was added in 10 portions. The reaction mixture was stirred at −78 °C for 30 min and then warmed to −40 °C over a period of 40 min. A total of 2.61 g (6.0 mmol) of MoOPH was added in two portions, and the reaction mixture assumed a greenish color. After stirring for 1 h at −40 °C, half-saturated NH_4Cl was added to quench the reaction, and THF was removed in vacuo. The aqueous phase was extracted with EtOAc, the combined organic phases were washed with brine and dried (anhydrous Na_2SO_4), and the solvents were evaporated in vacuo. The crude materials were combined and purified by flash chromatography (gradient solvent system: EtOAc in hexane from 2:3 to 2:1) to give 0.49 g of **16** (1.4 mmol, 47%).[34] ^{1}H NMR: δ 0.00 (s, 6H), 0.85 (s, 9H), 1.50 (s, 9H), 2.00−2.50 (m, 2H), 3.50−4.00 (m, 2H), 4.10−4.20 (m, 1H), 4.55−4.65 74 (m, 1H). ^{13}C NMR: δ 1.4, 18.6, 26.2, 28.6, 32.0, 56.5, 64.2, 70.4, 83.8, 150.1, 175.9. MS: 272 (4), 232 (33), 189 (13), 188 (100, B), 140 (17), 116 (43), 100 (21), 75 (24), 73 (27), 59 (13), 57 (51), 56 (11). HR-TOF MS: calcd for $C_{16}H_{32}NO_5Si$ *m*/*z* 346.2050, found *m*/*z* 346.2047; calcd for $C_{16}H_{31}NO_5SiNa$ *m*/*z* 368.1869 (M + Na^+), found *m*/*z* 368.1862.

5*S*-[(*tert*-Butyldimethylsilyloxy)methyl]-3*R*-adenin-9-yl-2-pyrrolidinone-*N*-*tert*-butylcarbamate, 17. Slow addition of 0.656 g (2.5 mmol) of PPh_3 followed by 0.675 g (5.0 mmol) of adenine and 0.404 g (2.0 mmol) of diisopropyldiazodicarboxylate (DIAD) to a solution of 0.345 g (1.0 mmol) of **16** dissolved in 10 mL of dry THF was followed by stirring for 48 h. Solvents were evaporated in vacuo, and purification by flash chromatography (100% EtOAc then 5% MeOH in EtOAc and 10% MeOH in EtOAc) afforded 0.218 g of **17** (0.5 mmol, 50%). ^{1}H NMR: δ 0.00 (s, 6H), 0.85 (s, 9H), 1.55 (s, 9H), 2.60−2.90 (m, 2H), 3.7−4.2 (m, 2H), 4.38−4.43 (m, 1H), 5.78−5.88 (m, 1H), 7.80 (s, 1H), 8.30 (s, 1H). ^{13}C NMR: δ 1.5, 18.7, 26.4, 28.5, 30.1, 56.5, 56.9, 64.7, 84.4, 120.2, 140.4, 150.1, 150.6, 153.5, 155.9, 169.4. HR-TOF MS: calcd for $C_{21}H_{35}N_6O4Si$ *m*/*z* 463.2489 (M + H^+), found *m*/*z* 463.2496; calcd for $C_{21}H_{34}N_6O4SiNa$ *m*/*z* 485.2308 (M + Na), found *m*/*z* 485.2299.

Methyl 5*S*-*N*-*tert*-Butoxycarbonylpyroglutamate 3*R*-*p*-Toluenesulfonate, 22. A solution of **21** (2.5 g, 9.6 mmol) in dry THF (25 mL) was immersed in a dry ice/acetone bath. Triethylamine (3.1 mL, 22.2 mmol) was added dropwise via a plastic syringe. Tosyl chloride (1.8 g, 9.4 mmol) in 15 mL of THF was added by addition funnel and the dry ice/acetone bath was allowed to warm to ambient temperature. The reaction was subsequently stirred under nitrogen for 4 days. The resulting mixture was partitioned between 100 mL of $CHCl_3$ and 100 mL of water, and the organic layer was washed with 1 M HCl and then water (3 × 30 mL each). The combined organic phases were washed with brine and dried over $MgSO_4$. Filtration was followed by evaporation of the solvent in vacuo to give a solid that was crystallized from diethyl ether, to give 2.62 g of **22** (6.34 mmol, 66%) as a white solid. Mp: 144−147 °C. ^{1}H NMR: δ 1.45 (s, 9H), 2.4−2.48 (m, 1H), 2.42 (s, 3H), 2.57−2.63 (m, 1H), 3.77 (s, 3H), 4.58−4.61 (m, 1H), 5.03−5.07 (m, 1H), 7.31−7.33 (m, 2H), 7.82−7.84 (m, 2H). ^{13}C NMR: δ 21.7, 27.8, 29.6, 53.0, 55.2, 74.1, 84.8, 128.2, 129.0, 132.7, 145.5, 148.7, 166.1, 170.9. IR (KBr): 3008, 1773, 1752, 1722, 1309 cm^{-1}. HR-TOF MS: calcd for $C_{18}H_{23}NO_8NaS$ *m*/*z* 436.1042, found *m*/*z* 436.1009.

Methyl *N*-*tert*-Butoxycarbonyl-3-adeninylpyroglutamate, 23. *Method A.* A mixture of **21** (0.150 g, 1.9 mmol), adenine (1.28 g, 9.5 mmol), and triphenylphosphine (1.74 g, 6.65 mmol) in 20 mL of THF was stirred for several minutes, and diisopropylazadicarboxylate (0.77 mL, 3.9 mmol) was added dropwise via plastic syringe, over a period of 80 min. The resultant reaction mixture was a creamy orange suspension, which was stirred for a total of 4 days, during which time a pink color was observed. The THF was evaporated in vacuo and the residue taken up in $CHCl_3$ and filtered to remove adenine and other chloroform-insoluble byproducts. Evaporation gave a rust-colored oil that was purified by flash chromatography (silica gel, EtOAc, then 10% MeOH/EtOAc) to give 0.32 g of **23** (0.85 mmol, 45%) as a 1:1 mixture of C3 diastereomers (designated A and B) as determined by NMR. ^{1}H NMR: δ 1.48 (s, 9H), 2.65−2.70 (m, 1H), 2.99−3.08 (m, 1H), 3.77 (B), 3.82 (A) (d, 3H, *J* = 7.5 Hz), 4.63−4.67 (B, t), 4.82−4.85 (A, d, *J* = 9 Hz) (1H), 5.35−5.38 (A, t, *J* = 11 Hz), 5.42−5.47 (B, t) (1H), 6.15 (A), 6.18 (B) (m, 2H), 7.82 (A), 7.91 (B) (2s, 1H), 8.25, 8.27 (2s, 1H). ^{13}C NMR: δ 28.25, 28.29, 28.8, 30.3, 31.3, 53.4, 53.51, 55.52, 56.1, 77.7, 85.1, 85.6, 140.2, 149.3, 150.3, 153.5, 156.1, 168.0, 171.5, 180.1. IR (KBr): 3327, 3165, 2963, 1792, 1759 cm^{-1}. HR-TOF MS: calcd for $C_{16}H_{20}N_6O_5Na$ *m*/*z* 399.1393 (M + Na), found *m*/*z* 399.1413.

Method B. Adenine (0.108 g, 0.8 mmol) was added to 20 mL of DMF under a N_2 purge. Sodium hydride (60% dispersion in oil, 0.032 g, 0.8 mmol) was added and the suspension became a solution after a few minutes, at which time a solution of 0.3 g (0.7 mmol) of **22** in DMF was added via an addition funnel. After stirring overnight, the solution was an orange color, and stirring continued at ambient temperature for a total of 3 days. The solvent was evaporated in vacuo and purification by flash chromatography (silica gel, 5% MeOH/ethyl acetate) gave 56 mg of **23** (150 mmol, 21%) as a 1:1 mixture of C3 diastereomers.

3*S*-*N*9-Adeninyl-5*S*,8*R*-phenyltetrahydropyrrolo[1,2-*O*]oxazol-2-one, 27. A solution of 177.5 mg (0.81 mmol) of **26** in dioxane was treated with 0.524 g (2.0 mmol) of PPh_3, followed by 0.546 g (4.04 mmol) of adenine. Addition of 0.39 mL (0.40 g, 2.0 mmol) of DIAD to this suspension, in two portions at ambient temperature, was followed by stirring at ambient temperature for 24 h. The solvents were evaporated in vacuo, and the residue was purified by column chromatography (EtOAc then 15% MeOH in CH_2Cl_2) to give 0.177 g of **27** as a white solid (0.53 mmol, 65%). Mp: >300 °C. ^{1}H NMR: δ 2.35−2.45 (m, 1H) and 2.90−3.10 (m, 1H), 3.85−3.90 (m, 1H), 4.10−4.15 (m, 1H), 4.28−4.35 (m, 1H), 5.50−5.55 (m, 1H), 6.41 (s, 1H), 7.25−7.45 (m, 5H), 7.84 (s, 1H), 8.27 (s, 1H). ^{13}C NMR: δ 33.0, 55.3, 58.3, 72.3, 87.7, 120.0, 128.8, 129.2, 133.5, 133.6, 137.9, 140.1, 153.3, 170.5. HR-TF MS: calcd for $C_{17}H_{17}N_6O_2$ *m*/*z* 337.1413 (M + H^+), found *m*/*z* 337.1407; calcd for $C_{17}H_{16}N_6O_2Na$ *m*/*z* 359.1232 (M + Na^+), found *m*/*z* 359.1236.

3*S*-Adenin-9-yl-5*S*-(hydroxymethyl)-2-pyrrolidinone, 5. A suspension of 26 mg of 10% Pd-on-C in MeOH was purged at least five times by evacuation of the reaction flask and then filling with hydrogen, while the solution was stirred vigorously. A solution of 0.021 g (0.06 mmol) of **27** in 10 mL of MeOH was added, followed by the addition of 0.1 mL of concd HCl. The reaction was stirred for 13 h under a hydrogen atmosphere (a hydrogen-filled balloon). At this time, 0.2 g of solid $NaHCO_3$ was added, the suspension was filtered through a Celite mat, and the solids were washed with MeOH. The solvents were removed in vacuo and the crude product was purified by flash chromatography (20% MeOH in CH_2Cl_2) to give 0.0154 g of **5** as a white solid (0.06 mmol, 100%). Mp: >300 °C. ^{1}H NMR (D_2O): δ 2.30−2.40 (m, 1H) and 2.82−2.98 (m, 1H), 3.70−3.80 (m, 1H) and 3.90−3.98 (m, 1H), 4.10−4.20 (m, 1H), 5.60−5.70 (m, 1H), 8.29 (s, 1H), 8.30 (s, 1H). ^{13}C NMR: δ 32.7, 56.0, 58.7, 65.9, 144.7, 152.5, 155.5, 158.0, 167.9, 177.9. HR-TOF MS: calcd for $C_{10}H_{13}N_6O_2 + H^+$ *m*/*z* 249.1081, found *m*/*z* 249.1100; calcd for $C_{10}H_{12}N_6O_2Na^+$ *m*/*z* 271.0900, found *m*/*z* 271.0919.

5*R*,8*S*-Phenyltetrahydropyrrolo[1,2-*O*]oxazol-2-one, 29. A solution of 4.9 g of **28** (42.6 mmol), 5.94 g (56.0 mmol) of benzaldehyde, and 0.10 g (0.58 mmol) of *p*-toluenesulfonic was heated at reflux in 30 mL of toluene for 16 h with a Dean−Stark trap. The reaction was cooled and then washed with 5% $NaHCO_3$, satd sodium bisulfite, water, and brine. The toluene was evaporated in vacuo and the brown oil was

purified by Kügelrohr distillation to give 4.43 g of **29** as a colorless oil (22.0 mmol, 52%). ^{1}H NMR: δ 1.80−1.90 (m, 1H) and 2.20−2.35 (m, 1H), 2.4−2.55 (m, 1H), 2.60−2.80 (m, 1H), 3.40 (t, 1H), 4.00−4.15 (m, 1H), 4.16−4.20 (dd, 1H), 6.30 (s, 1H), 7.20−7.45 (m, 5H). ^{13}C NMR: δ 22.7, 33.4, 58.8, 71.6, 87.0, 125.9, 128.4, 129.8, 138.8, 178.1. MS (m/z): 203 (21, M^+), 202 (100, B), 173 (9), 145 (15), 144 (20), 126 (12), 119 (11), 117 (24), 105 (60), 104 (23), 97 (10), 92 (10), 91 (23), 90 (23), 89 (22), 77 (37), 69 (12), 63 (10), 55 (20), 51 (27), 50 (11); calcd for $C_{12}H_{14}NO_2$ m/z 204.1025 ($M + H^+$), found m/z 204.1033.

3*R*-Hydroxy-5*R*,8*S*-phenyltetrahydropyrrolo[1,2-*O*]oxazol-2-one, 30. LDA was prepared by mixing 0.98 mL (0.71 g, 7.0 mmol) of diisopropylamine with 9.5 mL (7.0 mmol) of *n*-butyllithium (0.74 M in hexane) in dry THF at 0 °C for 1 h. Addition of 1.02 g (5.02 mmol) of **29** in THF to the LDA solution at −78 °C was followed by stirring at this temperature for 30 min. At this time, 3.43 g (7.90 mmol) of MoOPH was added at −78 °C and the mixture was warmed to −40 °C over a period of 2 h. The reaction was quenched by addition of a satd aq solution of Na_2SO_3 the mixture extracted with EtOAc, washed with 5% HCl and brine, and then dried over Na_2SO_4. Solvents were evaporated in vacuo. The residue was purified by column chromatography (3:1 hexane−ether) to give 0.82 g of **30** as yellow oil (3.7 mmol, 75%). ^{1}H NMR: δ 1.80−1.90 (m, 1H) and 2.75−2.85 (m, 82 1H), 3.55−3.65 (m, 1H), 3.90−4.03 (m, 1H), 4.25−4.35 (m, 1H), 4.70−4.80 (m, 1H), 6.32 (s, 1H), 7.30−7.50 (m, 5H). ^{13}C NMR: δ 36, 55, 72.97, 73.02, 87.3, 126.5, 129, 129.3, 138.3, 176.9. MS (m/z): 219 (44, M^+), 218 (63), 175 (9), 132 (27), 107 (49), 106 (23), 105 (100, B), 98 (8), 91 (37), 90 (27), 89 (23), 79 (28), 77 (43), 69 (24), 51 (22); calcd for $C_{12}H_{13}NO_3Na$ m/z 242.0793 ($M + Na^+$), found m/z 242.0813.

3*S*-Hydroxy-5*R*,8*S*-phenyltetrahydropyrrolo[1,2-*O*]oxazol-2-one, 31. A solution of 0.4 g (1.8 mmol) of **30** in 10 mL of dry THF was treated with a solution of 1.10 g (9.0 mmol) of benzoic acid in 15 mL of toluene at 0 °C and stirred for 2 min. This mixture was treated with 1.8 g (8.9 mmol) of DIAD dropwise and the reaction mixture warmed to ambient temperature and stirred for 24 h. EtOAc was added and the mixture was washed with 0.5 M aq citric acid, brine, satd aq $NaHCO_3$, and brine again. The organic phase was dried over Na_2SO_4 and filtered, and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography (4:1 hexane−ether then 1:1 hexane−ether). This material (0.92 g) was dissolved in MeOH and cooled to 0 °C, and 0.18 g (3.3 mmol) of NaOMe in MeOH was added, dropwise. The mixture was stirred for 30 min and the reaction was quenched by addition of half-saturated aq NH_4Cl. The organic phase was extracted with EtOAc followed by CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and filtered, and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography (EtOAc then 9:1 CH_2Cl_2−MeOH to give 0.200 g of **31** (0.9 mmol, 50%). ^{1}H NMR: δ 2.10−2.20 (m, 1H) and 2.20−2.25 (m, 1H), 3.30−3.38 (m, 1H), 4.10−4.20 (m, 2H), 4.40−4.45 (m, 1H), 6.17 (s, 1H), 7.20−7.35 (m, 5H). ^{13}C NMR: δ 31.8, 57.21, 71.7, 74, 87.1, 126.1, 128.7, 129.0, 138.2, 177.5. MS (m/z): 219 (44, M^+), 218 (63), 15 (9), 132 (27), 107 (49), 106 (23), 105 (100, B), 98 (8), 91 (37), 90 (27), 89 (23), 79 (28), 77 (43), 69 (24), 51 (22). HR-TOF MS: calcd for $C_{12}H_{13}NO_3Na$ m/z 242.0793 ($M + Na^+$), found m/z 242.0813.

3*R*-*N*9-Adeninyl-5*R*,8*S*-phenyltetrahydropyrrolo[1,2-*O*]-oxazol-2-one, 32. A solution of 0.100 g (0.46 mmol) of **31** in anhydrous THF was treated with 0.300 g (1.14 mmol) of PPh_3, followed by 0.310 g (2.29 mmol) of adenine. Addition of 0.190 g (0.94 mmol) of DIAD in two portions to this suspension, at ambient temperature, was followed by stirring at ambient temperature for 24 h. The solvents were evaporated in vacuo, and the residue was purified by flash chromatography (EtOAc then 15% MeOH in CH_2Cl_2) to give 0.100 g of **32** as a white solid (0.3 mmol, 65%). Mp: >300 °C. ^{1}H NMR (CD_3OD): δ 2.51−2.61 (m, 1H) and 2.88−3.00 (m, 1H), 3.85−3.90 (m, 1H), 4.20−4.35 (m, 2H), 5.70−5.85 (m, 1H), 6.20 (s, 1H), 7.25−7.45 (m, 5H), 7.84 (s, 1H), 8.17 (s, 1H). ^{13}C NMR (CD_3OD): δ 33.0, 57.3, 60.3, 73.5, 88.9, 127.6, 129.7, 130.0, 130.2, 138.8, 142.6, 150.3, 157.6, 172.4. HR-TOF MS: calcd for $C_{17}H_{17}N_6O_2$ m/z 337.1413 ($M + H^+$), found m/z 337.1410; calcd for $C_{17}H_{16}N_6O_2Na$ m/z 359.1232 ($M + Na^+$), found m/z 359.1238.

3*R*-Adenin-9-yl-5*R*-(hydroxymethyl)-2-pyrrolidinone, 33. A suspension of 120 mg of 10% Pd-on-C in MeOH was purged five times by evacuation of the reaction flask and then filling with hydrogen, while the reaction was stirred vigorously. A solution of 0.080 g of **32** (0.24 mmol) in 10 mL of MeOH was added, followed by 1.0 mL of concd HCl. The reaction was stirred for 22 h under a hydrogen atmosphere (hydrogen balloon), and 0.9 g of solid $NaHCO_3$ was added. The suspension was filtered through a Celite mat that was washed with MeOH, and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography (20% MeOH in CH_2Cl_2) and the resulting yellowish solid washed several times with chloroform to give 0.040 g of **33** as a white solid (0.16 mmol, 67%). Mp: >300 °C. ^{1}H NMR (D_2O): δ 2.15−2.29 (m, 1H) and 2.67−2.80 (m, 1H), 3.52−3.77 (m, 2H) and 3.80−4.00 (m, 1H), 5.36−5.48 (m, 1H), 8.00 (s, 1H). ^{13}C NMR (CD_3OD): δ 31.5, 54.6, 57.0, 65.1, 142.4, 153.9, 157.4, 174.2. HR-TOF MS: calcd for $C_{10}H_{13}N_6O_2$ m/z 249.1100 ($M + H^+$), found m/z 249.1081; calcd for $C_{10}H_{12}N_6O_2Na$ m/z 271.0919 ($M + Na^+$), found m/z 271.0900.

Methyl 3*R*-(*O*-*tert*-Butyldimethylsilyl)-5*S*-pyroglutamate, 34. A stirred solution of **20** (1.00 g, 2.67 mmol) in dry CH_2Cl_2 (30 mL) was treated with 2.1 mL (26.7 mmol) of trifluoroacetic acid (TFA) over a period of 20 min. The resulting mixture was stirred for 5 h, diluted with CH_2Cl_2 (50 mL), and washed with satd aq $NaHCO_3$ (3 × 20 mL) and brine. The organic phase was dried over $MgSO_4$ and filtered, and solvents were evaporated in vacuo to give 0.71 g of **34** as an oil (2.6 mmol, 97%). ^{1}H NMR: δ 0.13, 0.14 (2s, 6H), 0.89 (s, 9H), 2.27−2.34 (m, 1H), 2.44−2.5 (m, 1H), 3.76 (s, 3H), 4.24−4.27 (m, 1H), 4.30−4.34 (t, 1H, J = 7 Hz), 6.54 (s, 1H). ^{13}C NMR: δ −5.2, −4.6, 18.2, 25.6, 25.7, 25.8, 35.1, 52.4, 52.6, 68.9, 172.3, and 175.9. IR (neat): 3251, 2954, 2856, 1724 cm^{-1}. HR-TOF MS: calcd for $C_{12}H_{24}NO_4Si$ m/z 274.1475, found m/z 274.1464.

5*S*-Hydroxymethyl-3*R*-(*O*-*tert*-butyldimethylsilyl)-2-pyrrolidinone, 35. The flask containing a solution of 6.99 g of **34** (25.60 mmol) in 160 mL of THF was fitted with a septum, and a N_2 purge was added. The reaction was cooled to 0 °C with stirring under N_2 and a 2 M solution of $LiBH_4$ in THF (46.1 mL, 92.2 mmol) was added over about 30 min. After stirring for 1 h at 0 °C and 1 h at ambient temperature, the reaction was cooled to 0 °C and 2.3 mL water/mmol of ester (59 mL) was slowly added, at which time a white solid separated. After addition was complete, 0.9 mL of 1:1 HCl:H_2O/mmol of ester (23 mL) was carefully added (the initial addition induced a violent reaction). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases were washed with 1 M KOH (1 × 100 mL), water (1 × 100 mL), and brine (1 × 100 mL). Drying over $MgSO_4$, filtration, and evaporation of solvents in vacuo gave 4.83 g of **35** as a foam (19.68 mmol, 77%). ^{1}H NMR: δ 0.45 (s, 6H) 0.87 (s, 9H), 2.45−2.64 (AB quartet, 2H, J = 15 Hz, 37 Hz), 3.62 (d, 2H, J = 7 H), 3.82−4.00 (m, 1H), 4.25−4.50 (m, 2H), 7.24 (s, 1H). ^{13}C NMR: δ −4.5, −4.0, 18.8, 26.3, 26.4, 34.6, 54.1, 65.8, 70.9, 178.3. HR-TOF MS: calcd for $C_{11}H_{23}NO_3SiNa$ m/z 268.1345 ($M + Na^+$), found m/z 268.1344.

3*R*-(*tert*-Butyldimethylsilyloxy)-5*S*,8*R*-phenyltetrahydropyrrolo[1,2-*O*]oxazol-2-one, 36. Benzaldehyde (2.66 mL, 25.53 mmol), **35** (4.80 g, 19.64 mmol), and *p*-toluenesulfonic acid (0.1 g, cat.) were added to 100 mL tof oluene in a flask fitted with a Dean−Stark trap, and the solution was heated at reflux for 60 h. After cooling, EtOAc (20 mL) was added and the organic layer was washed with 5% aq $NaHCO_3$ (2 × 20 mL), satd aq sodium metabisulfite (3 × 20 mL), and

finally brine (1 × 50 mL). The organic layer was dried with $MgSO_4$ and filtered, and the solvents were evaporated in vacuo. Purification by flash chromatography (120 g silica, 2:1 pentane−ether, R_f = 0.39) gave 2.33 g of **36** as an oil (7.0 mmol, 36%). ^{1}H NMR: δ 0.15. 0.16 (2s, 6H), 0.91 (s, 9H), 2.08−2.28 (m, 2H), 3.93−3.96 (m, 1H), 4.22−4.27 (m, 2H), 4.44−4.47 (m, 1H), 6.26 (s, 1H), 7.32−7.47 (m, 5H); ^{13}C NMR: δ −5.1, −4.7, 18.2, 25.7, 34.3, 56.9, 71.5, 74.9, 86.8, 126.0, 128.4, 128.6, 138.4, 176.0. IR (neat): 2930, 2857, 22.50, 1716 cm^{-1}. MS (m/z): 32, 276, 170, 129, 75. HR-TOF MS: calcd for $C_{18}H_{27}NO_3Si$ m/z 334.1838, found m/z 334.1845.

6*S*-Hydroxy-3-phenyltetrahydropyrrolo[1,2-*O*]oxazol-5-one, 26. A solution of 2.11 g of **36** (6.33 mmol) in 20 mL of dry THF was treated with 13 mL (13 mmol) of a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF via syringe. The mixture was stirred for 5 h, AcOH (0.72 mL, 12.6 mmol) was added, and the mixture was stirred for 15 min. Solvents were evaporated in vacuo directly onto silica, and flash chromatography (60 g silica, 100% ether) gave **26** contaminated with AcOH. This material was stirred in pentane overnight and filtered to give 0.97 g of **21** (4.42 mmol, 70%) as a white solid.[31] Mp: 102−104 °C. ^{1}H NMR: δ 2.18−2.33 (m, 2H), 3.39−3.45 (m, 1H), ∼4 (bs, 1H), 4.24−4.3 (m, 2H), 4.52−4.55 (m, 1H), 6.25 (s, 1H), 7.34−7.46 (m, 5H). ^{13}C NMR: δ 31.6, 57.0, 71.4, 73.7, 86.7, 125.9, 128.4, 128.6, 137.9, 177.3. IR (KBr): 3339, 1695 cm^{-1}. MS (m/z): 218, 175, 132, 105, 91, 77.

3*R*-Adeninyl-5*S*-hydroxymethyl 2-pyrrolidinone, 5. A solution of **26** (0.49 g, 2.23 mmol), PPh_3 (0.9 g, 3.4 mmol), and adenine (0.31 g, 2.23 mmol) in 12 mL of dry THF under N_2 was treated with DIAD (0.67 mL, 3.4 mmol) by slow addition. The mixture was stirred at ambient temperature overnight, diluted with $CHCl_3$ (50 mL), and filtered to remove unreacted adenine. The $CHCl_3$ was evaporated in vacuo, and the residue purified by flash chromatography (30 g silica, 10% MeOH/EtOAc) to give 0.19 g of **27** (0.56 mmol, 25%), which was taken directly to the next step without further purification. ^{1}H NMR: δ 2.53−2.6 (m, ^{1}H), 3.04−3.11 (m, 1H), 3.96−4.0 (t, 1H), 4.20−4.27 (m, 1H), 4.38−4.42 (dd, 1H), 5.61−5.66 (dd, 1H), 5.73 (bs, 1H), 6.49 (s, 1H), 7.36−7.50 (m, 5H), 7.91 (s, 1H), 8.35 (s, 1H). ^{13}C NMR: δ 32.8, 55.0, 58.1, 72.1, 87.3, 126.1, 128.6, 129, 137.7, 138.8, 153.1, 170.3.

A slurry of 10% Pd/C (120 mg) in 40 mL of MeOH was purged three times with hydrogen, and then 0.19 g of the freshly prepared **27** (0.56 mmol) in MeOH (20 mL) was added in one portion. After addition of 1 mL of concd HCl, the reaction was stirred at ambient temperature under hydrogen (H_2 balloon) for 17 h. Sodium bicarbonate (2 g) was added, the suspension was filtered through Celite, and the Celite was washed several times with MeOH. The MeOH was evaporated in vacuo to give a pale yellow solid that was purified by flash chromatography (10 g silica, 20% MeOH/CH_2Cl_2 and then 1:1 MeOH:CH_2Cl_2) to give 0.138 g of **5** as white solid (0.56 mmol, 99%). Mp: >300 °C. ^{1}H NMR (D_2O, 80 °C): δ 2.70−2.79 (m, 1H), 3.09−3.23 (m, 1H), 3.33−3.40 (m, 1H), 4.15−4.33 (m, 2H), 4.48−4.57 (m, 1H), 5.95−6.03 (m, 1H), 8.66, 8.71 (2s, 2H). ^{13}C NMR: δ 33.0, 55.3, 58.3, 72.27, 87.3, 120.0, 128.8, 129.2, 133.5, 133.6, 137.9, 140.1, 153.3. 170.5. IR (KBr): 3337, 1701, 1655 cm^{-1}.

3*S*-*N*2-Isobutyryl-*O*6-[2-{(*p*-nitrophenyl)ethyl}guanin-9-yl)-5*S*,8*R*-phenyltetrahydropyrrolo[1,2-*O*]oxazol-5-one, 40. A solution of 0.100 g (0.46 mmol) of alcohol **26** and 300 mg of PPh_3 in anhydrous THF was treated with 450 mg of **39**. A total of 190 mg of DIAD was added to this suspension in two portions at ambient temperature, and the reaction was stirred at ambient temperature for 24 h. The solvents were evaporated in vacuo and the residue was purified by flash chromatography (EtOAc then 15% MeOH in CH_2Cl_2) to give **40** as a white solid (0.200 g, 0.35 mmol, 76%). Mp: >300 °C. ^{1}H NMR (CD_3OD): δ 1.10 (d, 6H, J = 9 H), 1.90 (s, 2H), 2.52−2.65 (m, 1H), 2.65−2.79 (m, 1H), 2.80−2.90 (m, 1H), 3.20 (bd s, 1H), 3.85−4.00 (m, 2H), 4.22−4.35 (m, 1H), 4.75 (m, 2H), 5.80−5.90 (t, 1H, J = 13.5 H), 6.20 (s, 1H), 7.20−7.60 (m, 9H), 8.15 (s, 1H). ^{13}C NMR: δ 19.9, 33.1, 36.1, 37, 57.3, 60.3, 61.7, 68.2, 73.6, 88.8, 124, 6, 127.6, 129.7, 131.5, 132.2, 133.6, 138.8, 144, 147.8, 148.3, 153.7, 163.9, 172.4, 178.5. HR-TOF MS: calcd for $C_{29}H_{30}N_7O_6$ m/z 572.2258 (M + H$^+$), found m/z 572.2254; calcd for $C_{29}H_{29}N_7O_6Na$ m/z 594.2077 (M + Na$^+$), found m/z 594.2073.

3*S*-(*N*2-Isobutyrylguanin-9-yl)-5*S*,8*R*-phenyltetrahydropyrrolo[1,2-*O*]oxazol-5-one, 41. Dropwise addition of 1.95 g of DBU (1,8-diazobicyclo[5.4.0]undec-7-ene) (12.83 mmol) to a solution of **40** (1.36 g, 12.83 mmol) in pyridine at 0 °C was followed by warming to ambient temperature and stirring for 24 h. Glacial acetic acid (1 mL, 7.4 mmol) was added, and all solvents were evaporated in vacuo. At this time, 1 mL of toluene was added to the resulting solid, which was purged with a stream of nitrogen to dryness. The yellow product was washed with EtOAc to give **41** as a white solid (0.361 g, 0.85 mmol, 36%). Mp: >300 °C. ^{1}H NMR (CD_3OD−$CDCl_3$): δ 1.13 (d, 6H, J = 10 Hz), 2.40−2.65 (m, 1H), 2.65−2.79 (m, 1H), 2.80−3.00 (m, 1H), 3.29 (d, 1H, J = 15 Hz), 3.85−3.90 (m, 1H), 4.15−4.20 (m, 1H), 4.20−4.28 (m, 1H), 5.50−5.65 (t, 1H, J = 12 Hz), 6.40 (s, 1H), 7.20−7.40 (m, 5H), 7.75 (s, 1H). ^{13}C NMR: δ 18.9, 33.1, 35.9, 54.8, 58.4, 71.7, 87.4, 126.0, 128.7, 129.2, 137.9, 139.3, 148.0, 149.0, 156.0, 158.0, 170.9, 180.0. IR (film): 1167, 1604, 1553 (3 C=O) cm^{-1}. HR-TOF MS: calcd for $C_{21}H_{23}N_6O_4$ m/z 423.1781 (M + H$^+$), found m/z 423.1777; calcd for $C_{21}H_{22}N_6O_4Na$ m/z 445.1600 (M + Na$^+$), found m/z 445.1591.

3*S*-(2-(*N*-Isobutyrylguanin-9-yl))-5*S*-(hydroxymethyl)-*N*-benzyl-2-pyrrolidinone, 42. A suspension of 300 mg of 10% Pd-on-C in 40 mL of MeOH was purged five times by evacuation and filling with hydrogen, while the mixture was vigorously stirred. A solution of 0.090 g of **41** (0.21 mmol) in 10.0 mL of MeOH and 1.0 mL of concd HCl was added. The reaction was stirred for 48 h under a hydrogen atmosphere (H_2 balloon). At this time, 1.0 g of solid $NaHCO_3$ was added and the suspension was filtered through a Celite mat, which was washed with MeOH. All solvents were evaporated in vacuo. The crude product was precipitated from $CHCl_3$−MeOH to give 0.018 g (0.05 mmol, 24%) of **42** as an off-white solid. Mp: >300 °C. ^{1}H NMR: δ 1.25 (d, 6H, J = 10 Hz), 2.40−2.55 (m 1H), 2.60−2.75 (m, 1H), 3.32 (s, 2H), 3.54−3.73 (m), 4.03 (d, 1H, J = 15 Hz), 4.15 and 5.21 (AB q, 2H, J = 10 Hz, 320 Hz[35]), 5.25−5.38 (m), 7.24−7.40 (m, 5H), 7.50 (s), 7.96 (s). HR-TOF MS: calcd for $C_{21}H_{25}N_6O_4$ m/z 425.1941 (M + H$^+$), found m/z 425.1973; calcd for $C_{21}H_{24}N_6O_4$-Na m/z 447.1752 (M + Na$^+$), found m/z 447.1757.

3*S*-Guanin-9-yl-5*S*,8*R*-phenyltetrahydropyrrolo[1,2-*O*]-oxazol-5-one, 43. A suspension of **41** (0.036 g, 0.09 mmol) and 5 mL of 7 N NH_3 in MeOH was stirred in a sealed tube at ambient temperature for 60 h. The tube was opened, all volatiles were evaporated in vacuo, and the residue was washed with 3 × CH_2Cl_2 to give **43** as a white solid (0.030 g, 0.085 mmol, 94%). Mp >300 °C. ^{1}H NMR (DMSO-d_6): δ 2.46−2.54 (m, 1H), 2.80−2.90 (m, 1H), 3.84−3.89 (m, 1H), 4.24−4.26 (m, 1H), 4.29−4.38 (m, 1H), 5.60−5.67 (m, 1H), 6.15 (s, 1H), 7.37−7.48 (m, 5H), 7.78 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 31.3, 55.7, 58, 72.5, 117.1, 126.9, 128.9, 129.3, 137.6, 139.2, 151.6, 153.8, 157.2, 171.1. HR-TOF MS: calcd for $C_{17}H_{17}N_6O_3$ m/z 353.1362 (M + H$^+$), found m/z 353.1366; calcd for $C_{17}H_{16}N_6O_3Na$ m/z 375.1182 (M + Na$^+$), found m/z 375.1191.

3*S*-Guanin-9-yl-5*S*-(hydroxymethyl)-2-pyrrolidinone, 4. A suspension of 100 mg of 10% Pd-on-C in MeOH was purged seven times by evacuation and then filled with hydrogen while the mixture was vigorously stirred. A solution of 0.043 g of **43** (0.12 mmol) in 30 mL of MeOH and 1.0 mL of concd HCl was added, and the reaction was stirred for 13 h under hydrogen atmosphere (H_2 balloon). At this time, 2.0 g of solid $NaHCO_3$ was added and the suspension was filtered through a Celite mat, and the solids were washed with MeOH. All solvents were evaporated in vacuo to give an amorphous, off-white solid. This solid was insoluble in most solvents and could not be crystallized or

chromatographed. Addition to 0.5 mL of D_2O containing two flakes of KOH allowed dissolution of the solid in order to obtain a proton NMR that was consistent with that of **4** (0.006 g, 0.02 mmol, 19%). Mp: > 300 °C. ^{1}H NMR (D_2O−KOH): 2.30−2.40 (m, 1H) and 2.85−2.92 (m, 1H), 3.62 (t, 1H), 3.70−3.80 (m, 1H), 3.92−4.12 (m, 1H), 4.50 and 5.02 (AB quartet, 2H), 5.35 (m, 1H), 7.40−7.55 (m, 2H), 7.80 (s, 1H). HR-TOF MS: calcd for $C_{10}H_{13}N_6O_3$ *m*/*z* 265.1049 ($M + H^+$), found *m*/*z* 265.1059.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: michael.smith@uconn.edu

Present Addresses

‡Department of Chemistry, The Hashemite University, Zarqa 13115, Jordan.

§Department of Chemistry, Alfred University, College of Liberal Arts & Sciences, 1 Saxon Drive, Alfred, NY 14802.

DISCLOSURE

‖NSF R.E.U. Summer Scholar, 2002.

Notes

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