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

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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,7 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 lifecycle 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 (NRTIs)5 and non-nucleoside reverse transcriptase inhibitors (NNRTIs).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 phosphorylation, 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-pyrolidinone derivatives via pyroglutamate esters.10 The planarity of the lactam ring in 5-substituted-2-pyrolidinone derivatives is well-established.10 We speculated that 2-pyrolidinone 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-pyrolidinone 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-pyrolidinone-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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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 Nielsen’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: $^{\text{S}}$-[\{\text{tert-butyldimethylsilyloxy} \} \text{methyl}]$^{\text{3R}}$-adenin-9-yl-2-pyrrolidinone-N-tert-butylicarbamate + $^{\text{S}}$-[\{\text{tert-butyldimethylsilyloxy} \} \text{methyl}]$^{\text{3S}}$-adenin-9-yl-2-pyrrolidinone-N-tert-butylicarbamate. 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...
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 (79% yield) was followed by protection of the alcohol moiety to give (71% yield). Oxidation used the protocol of Zhang et al. (ruthenium oxide and periodate) to give lactam (76% yield), and deprotection of the alcohol moiety with TBAF gave (63% yield). Two routes were used to prepare the targeted . The first used a Mitsunobu coupling of with unprotected adenine that gave (46% yield, as a 1:1 mixture of diastereomers at C3: methyl N-tert-butoxycarbonyl-3R-adeninylpyroglutamate and methyl N-tert-butoxycarbonyl-3S-adeninylpyroglutamate. The second route was the less efficient conversion of to tosylate (75% yield). Isolation of confirmed that this compound was enantiopure and configurationally stable. Subsequent reaction with adenine in DMF with potassium carbonate gave , but as observed in the Mitsunobu coupling with , the use of enantiopure led to as a 1:1 mixture of diastereomers at C3. Interestingly, we recovered unreacted and found that the C3 stereocenter had epimerized. In other words, the enantiopure starting material, , 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, and work reported by others, 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, and we also prepared it in an earlier work. Conversion of glutamic acid to 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 and of D-glutamic acid.
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/C0 required the opposite stereochemistry for the C3 hydroxyl group (see Scheme 1), but Mitsunobu inversion17 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

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

Scheme 7. Synthesis of 4
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. However, gave a satisfactory 76% yield of 35. The reaction of 35 with benzaldehyde and terephthalic acid gave the expected hydroxymethyl lactam unit. It is well-known that the free hydroxy group was protected as a nitrophenylethanol moiety to give 38 in 70% yield, and subsequent reaction with adenine under Mitsunobu conditions gave the expected N-tert-butoxycarbonyl-trans-4-hydroxy-L-proline methyl ester (18). Deprotection by catalytic hydrogenation gave 39 in 65% yield. Deprotection by catalytic hydrogenation gave 38 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 isobutyryl amide in 70% yield, and subsequent reaction with adenine under Mitsunobu conditions gave 27 in 25% yield. Deprotection by catalytic hydrogenation gave 40 in quantitative yield.

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 purine base to the C3 position of 5-hydroxymethyl-2-pyrrolidinone can be prepared with equal facility using the glutamic acid route, from L-glutamic acid and D-glutamic acid, respectively.

**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 benzenophene; methylene chloride, toluene, and benzene were distilled from CaH2 and DMF was stirred with CaH2 for several hours, filtered, and then vacuum distilled. n-Butyllithium was standardized before use, using diphenylacetic acid. 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. 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-pyrrolidinone-SS-carboxylate (12), ethyl 2-pyrrolidinone-SR-carboxylate, trans-4-hydroxy-L-proline methyl ester hydrochloride salt, SS-(hydroxymethyl)-2-pyrrolidinone (13), N-tert-butoxycarbonyl-trans-4-hydroxy-L-proline methyl ester (18), SR-(hydroxymethyl)-2-pyrrolidinone (28), N-tert-butoxycarbonyl-trans-3-trans-3-butylidene-2-pyrrolidinone methyl ester (29), methyl-SN-N-tert-butoxycarbonyl-3R-tert-butyldimethylsiloxypyrglotamate (20), methyl SS-N-tert-butoxycarbonyl-3R-tert-butyldimethylsiloxypyrglotamate (21), SS,S,SR-phenyltetrahydropyrrolo[1,2-O]oxazol-2-one (24), 3S-hydroxy-SS,S,SR-phenyltetrahydropyrrolo[1,2-O]oxazol-2-one (25), 3S-hydroxy-SS,S,SR-phenyltetrahydropyrrolo[1,2-O]oxazol-2-one (26), N2-isobutylguanin monohydroxide (37), 9-acetyl-N2-isobutylguanin (38), and N2-isobutyl-O6-2-[p-(nitrophenyl)ethyl]guanin (39).

GC–MS spectra were obtained with an HP-1 column gas chromatogram—mass spectrometer. H1 and 13C 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, CDCl3 was used as a solvent unless otherwise stated; chemical shifts are in δ 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.

(55)-[(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 DMPF was treated with 4.7 g (31.3 mmol) of chloro-tert-butylmethylsilane. The reaction mixture was stirred for 24 h at ambient temperature. At this time, 75 mL of Et2O was added and the crude product was washed with water and brine and dried over anhydrous Na2SO4, and the solvents were removed in vacuo. Purification by flash chromatography (100% EtOAc) gave 4.45 g of (55)-[(tert-butyl)dimethylsilyloxy]methyl]-2-pyrrolidinone, 14, 11 as a yellow oil (19.40 mmol, 75%). H1 NMR: δ 0.00 (s, 6H), 0.87 (s, 9H), 1.60–2.50 (m, 4H), 3.35–3.80 (m, 3H), 6.65 (bs, NHH+) 13C 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). HR-TOF MS: 3225 (2%, 3224 (50%), 75 (53), 74 (23), 59 (23), 58 (18). (15). HR-TOF MS: found m/z 230.2576, m/z 230.1576; calcd for C11H23NO2SiNa (M + H+) m/z 230.2576, m/z 230.1576; calcd for C11H23NO2SiNa m/z 252.1396 (M + Na+), found m/z 252.1388.

(25)-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 CH2Cl2 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 Et3N respectively. The reaction mixture was stirred at ambient temperature for 24 h, and 25 mL of Et2O was added. The ether was washed with 10% citric acid, satd NaHCO3, and brine. The organic layer was dried over anhydrous Na2SO4, and the solvents were evaporated in vacuo. Purification by flash chromatography (CH2Cl2–EtOAc, 15:1) gave 1.9 g of (25)-S-5-[(tert-butyl)dimethylsilyloxy]methyl]-2-pyrrolidinone-1-N-tert-butylcarbamate, 15, 11 as a yellow oil (5.5 mmol, 93%). H1 NMR: δ 0.00 (s, 6H), 0.85 (s, 9H), 1.30 (s, 9H), 1.70–2.60 (m, 4H), 15 (10), 116 (24), 116 (24), 116 (24), 116 (24), 75 (53), 74 (23), 59 (23), 58 (18). (15). HR-TOF MS: found m/z 230.2576, m/z 230.1569; calcd for C11H23NO2SiNa m/z 252.1396 (M + Na+), found m/z 252.1388.
55-S-[tert-Butyldimethylsilyloxy)methyl]-3R-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 NH₄Cl was added to quench the reaction, and THF was removed in vacuo. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine and dried (anhdydrous Na₂SO₄), 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%). H NMR: δ 0.00 (s, 6H), 0.85 (s, 9H), 1.50 (s, 9H), 2.00−2.05 (m, 2H), 3.50−4.00 (m, 2H), 4.10−4.20 (m, 1H), 4.55−6.65 74 (m, 1H). C NMR: δ 1.4, 18.6, 26.6, 32.0, 56.6, 64.2, 70.4, 83.8, 150.1, 175.1. MS: 272 (4), 232 (33), 189 (13), 188 (100), B, 110 (21), 74 (27), 59 (13), 57 (51), 56 (11). HR-TOF MS: calc'd for C₁₇H₃₄NO₇Si m/z 346.2050, found m/z 346.2047; calc'd for C₁₇H₃₄NO₇SinNa m/z 368.1869 (M + Na⁺), found m/z 368.1862.

55-S-[tert-Butyldimethylsilyloxy)methyl]-3R-adenin-9-yl-2-pyrrolidinone-N-tert-butylcarbamate, 17. Slow addition of 0.665 g (2.5 mmol) of PPh₃ 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 21, 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 C₂₁H₃₄N₆O₄Si, found m/z 463.2496; calc'd for C₂₁H₃₄N₆O₄SiNa m/z 485.2308 (M + Na⁺), found m/z 485.2399.

Methyl 55-S-tert-Butyloxycarbonyl-3-adeninylpyroglutamate 3R-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 CHCl₃ and 100 mL of water, and the organic layer was washed with 1 M HCl and then washed with MeOH. The solvents were evaporated in vacuo, and the residue was purified by column chromatography (EtOAc then 15% MeOH in CH₂Cl₂) to give 177.5 g as a white solid (0.53 mmol, 65%). Mps: >300 °C. 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 (m, 1H), 7.25−7.45 (m, 5H), 7.84 (s, 1H), 8.27 (s, 1H). C NMR: δ 33.0, 55.5, 58.3, 72.3, 87.7, 78.0 (1H), 8.27 (s, 1H). IR (KBr): 3327, 3371, 2963, 1792, 1759 cm⁻¹. HR-TOF MS: calc'd for C₂₁H₂₃N₅O₅Na m/z 399.1393 (M + Na⁺), found m/z 399.1413.

3S-N9-Adeninyl-55,5R-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 PPh₃, followed by 0.456 (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 4 h. The solvents were evaporated in vacuo, and the residue was purified by column chromatography (EtOAc then 15% MeOH in CH₂Cl₂) to give 1.77 g of 27 as a white solid (0.53 mmol, 65%). Mps: >300 °C. 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 (m, 1H), 7.25−7.45 (m, 5H), 7.84 (s, 1H), 8.27 (s, 1H). C NMR: δ 33.0, 55.3, 58.3, 72.3, 87.7, 78.0 (1H), 8.27 (s, 1H). IR (KBr): 3327, 3371, 2963, 1792, 1759 cm⁻¹. HR-TOF MS: calc'd for C₂₁H₂₃N₅O₅Na m/z 399.1393 (M + Na⁺), found m/z 399.1413.

3S-Adeninyl-55,5S-(hydroxymethyl)-2-pyrrolidinone, 5. A suspension of 26 mg of 10% Pd-on-C in MeOH was purified at least five times by evaporation 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 1 h under a hydrogen atmosphere (a hydrogen-filled balloon). At this time, 0.2 g of solid NaHCO₃ 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 CH₂Cl₂) to give 0.0154 g of 5 as a white solid (0.06 mmol, 100%). Mps: >300 °C. H NMR (D₂O): 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). C NMR: δ 32.7, 56.0, 58.7, 65.9, 144.7, 152.5, 155.5, 158.0, 167.9, 179.7. HR-TOF MS: calc'd for C₉H₁₂NO₄Na m/z 271.0919, found m/z 271.0919.

5R,8S-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-toluenesulfonyl 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% NaHCO₃, satd sodium bisulfite, water, and brine. The toluene was evaporated in vacuo and the brown oil was...
purified by Kugelrohr distillation to give 4.43 g of 29 as a colorless oil (22.0 mmol, 52%). 1H NMR: δ 1.80−1.90 (m, 1H) and 2.20−2.35 (m, 1H), 2.40−2.55 (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). 13C 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+), 102 (100, B), 173 (99), 145 (15), 144 (20), 126 (12), 119 (11), 117 (24), 105 (60), 104 (23), 97 (10), 92 (10), 91 (20), 93 (20), 89 (22), 77 (37), 69 (12), 63 (10), 55 (20), 51 (27), 50 (11); calcd for C12H13NO3Na: m/z 204.1025 (M+Na+), found m/z 204.1033.

3R-5-tert-Butyldimethylsilyl)-25-hydroxyethyl)-2-pyrrolidone, 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 2 h under a hydrogen atmosphere (hydrogen balloon), and 0.9 g of solid NaHCO3 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 CH2Cl2) 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. 1H NMR (D2O): 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). 13C NMR (CD3OD): δ 31.5, 54.6, 57.0, 65.1, 142.4, 153.9, 157.4, 172.4. HR-TOF MS: calcd for C10H12N6O2Na: m/z 249.1100 (M+Na+), found m/z 249.1081; calcd for C10H12N6O2Na m/z 271.0919 (M+Na+), found m/z 271.0900.

Methyl 3R-(O-tert-Butyldimethylsilyl)-5S-pyrrolyl, 34. A stirred solution of 20 (1.00 g, 2.67 mmol) in dry CH2Cl2 (30 mL) was treated with 3.1 g of 2.67 mmol) of trifluoroacetic acid (TFA) over a period of 20 min. The resulting mixture was stirred for 5 h, diluted with CH2Cl2 (50 mL), and washed with satd aq NaHCO3 (5 × 20 mL) and brine. The organic phase was dried over MgSO4 and filtered, and the solvents were evaporated in vacuo to give 0.71 g of 34 as an oil (26 mmol, 97%). 1H 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 (s, 1H, J = 7 Hz), 6.54 (s, 1H). 13C NMR: δ −5.2, −4.6, 18.3, 25.6, 25.7, 25.8, 31.1, 52.4, 52.6, 68.9, 172.3, and 175.9. IR (neat): 3251, 2954, 2856, 1724 cm−1. HR-TOF MS: calcd for C15H19NO4Si: m/z 274.1475, found m/z 274.1464.

5S-Hydroxymethyl3R-(O-tert-Butyldimethylsilyl)-2-pyrrolyl, 35. The flask containing a solution of 6.99 g of 34 (25.60 mmol) in 160 mL of THF was filled with a septum, and a N2 purge was added. The reaction was cooled to 0 °C with stirring under N2 and a 2 M solution of LiBH4 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/m/ol 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:H2O/m/ol of ester (23 mL) was carefully added (the initial addition induced a violent reaction). The aqueous layer was extracted with CH2Cl2 (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 MgSO4, filtration, and evaporation of solvents in vacuo gave 4.83 g of 35 as a foam (19.68 mmol, 77%). 1H 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 Hz), 3.82−4.00 (m, 1H), 4.25−4.50 (m, 2H), 7.24 (s, 1H). 13C 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 C15H19NO4SiNa: m/z 268.1345 (M+Na+), found m/z 268.1344.

3R-(O-tert-Butyldimethylsilyloxy)-5S,8R-hydroxyethyl)pyrrolpyrrolyl, 36. Benzaldehde (2.66 mL, 25.53 mmol), 35 (4.80 g, 19.64 mmol), and p-toluensulfonic acid (0.1 g, cat.) were added to 100 mL of oleum 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 NaHCO3 (2 × 20 mL), satd aq potassium metabisulphite (3 × 20 mL), and
finally brine (1 × 50 mL). The organic layer was dried with MgSO4 and filtered, and the solvents were evaporated in vacuo. Purification by flash chromatography (120 g silica, 2:1 pentane—ether, Rf = 0.39) gave 2.33 g of 36 as an oil (7.0 mmol, 36%). 1H 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). 13C 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, 2250, 1716 cm−1. MS (m/z): 32, 276, 170, 129, 75. HR-TOF MS: calcd for C18H20N3Si m/z 334.1838, found m/z 334.1845.

6S-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, then 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 as a white solid (0.200 g, 0.35 mmol, 76%). Mp: >300°C.

A solution of 0.100 g (0.46 mmol) of alcohol 27 (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 C3H19NO3 m/z 372.2258 (M + H)+, found m/z 372.2254; calcd for C19H20N3O m/z 394.0777 (M + Na+), found m/z 394.0773.

3S-(1-N-Isobutyrylguanin-9-yl)-5S,8R-phenyltetrahydropyrrolo[1,2-O]oxazol-5-one, 41. Dropwise addition of 1.95 g of DBU (1.8-diazabicyclo[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.

A solution of 0.12 mmol) in 30 mL of MeOH was evaporated five times by evaporation and redissolved in 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 conc HCl was added. The reaction was stirred for 48 h under a hydrogen atmosphere (H2 balloon). At this time, 1.5 g of solid NaHCO3 was added and the suspension was filtered through a Celite mat, and the solids were washed with MeOH. All solvents were evaporated in vacuo. The crude product was precipitated from CHCl3–MeOH to give 0.018 g (0.05 mmol, 24%) of 42 as an off-white solid. Mp: >300°C.

2S-(N-Isobutyrylguanin-9-yl)-5S-(hydroxymethyl)-N-benzyl-2-pyridinol, 42. A suspension of 300 mg of 10% Pd-on-C in 40 mL of MeOH was purged five times by evacuation of air, 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 conc HCl was added. The reaction was stirred for 48 h under a hydrogen atmosphere (H2 balloon). At this time, 1.0 g of solid NaHCO3 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 CHCl3–MeOH to give 0.018 g (0.05 mmol, 24%) of 42 as an off-white solid. Mp: >300°C.

3S-Guanin-9-yl-5S,8R-phenyltetrahydropyrrolo[1,2-O]oxazol-5-one, 43. A suspension of 41 (0.036 g, 0.09 mmol) and 5 mL of 7 N NH3 in MeOH was stirred in a sealed tube at ambient temperature for 60 h. The tube was open, all volatiles were evaporated in vacuo, and the residue was washed with 3 × CH2Cl2 to give 43 as a white solid (0.030 g, 0.085 mmol, 94%). Mp: >300°C.

A solution of 0.018 mmol) in 30 mL of MeOH and 1.0 mL of conc HCl was added. The reaction was stirred for 13 h under hydrogen atmosphere (H2 balloon). At this time, 2.0 g of solid NaHCO3 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 precipitated.
chromatographed. Addition to 0.5 mL of D$_2$O containing 50 nM 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$_2$O–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$_6$O$_3$ m/z 265.1049 (M + H$^+$), found m/z 265.1059.

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.

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