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6'-Oxa Analogs of S-Adenosylhomocysteine

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Abstract

S-Adenosylmethionine (AdoMet) is a ubiquitous cofactor in biomethylations and, in that role, becomes S-adenosylhomocysteine (AdoHcy), which serves as a biofeedback inhibitor of the methylation process. In seeking to avail unexplored structural variations of AdoHcy for biological studies, its 6'-oxa analog and two corresponding carbocyclic nucleosides (based on aristeromycin and neplanocin) have been prepared via common convergent syntheses.

Keywords

S-adenosylhomocysteine; aristeromycin; neplanocin; Schöllkopf auxiliary

Introduction

Biological methylation is a prominent feature for the successful metabolism of numerous small molecules and those that fall into the oligomer and polymer categories.¹ It is not surprising, then, that one approach to chemotherapeutic agent design is to prevent this methylation from occurring in pathogen driven circumstances.² A fruitful outcome in this direction has been to interfere with the methyl donating capabilities of S-adenosylmethionine (AdoMet, **1**, Figure 1), a ubiquitous cofactor in the aforementioned biomethylations.³ One approach has been to exploit the feedback inhibitory effects⁴ of S-adenosylhomocysteine (AdoHcy, **2**), which arises from the AdoMet donation reaction. Numerous laboratories have focused on this consequence by inhibiting the hydrolase that converts AdoHcy into adenosine and homocysteine, thereby increasing the presence of AdoHcy for feedback control.⁵ On the other hand, less⁶ attention has considered analogs of AdoHcy itself, particularly at its side chain sulfur center,⁷ as a more direct means of

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inhibiting the demands cast upon AdoMet. For this purpose, this report describes the synthesis of the 6'-oxa analog of AdoHcy (**3**) and its carbocyclic partners based on aristeromycin (**4**) and nplanocin (**5**).

Results

A convergent approach to targets **3–5** was envisioned that would begin with a *bis*-homologated ribofuranose derivative (**6** for the preparation of target compound **3**) and a cyclopentyl/cyclopentenyl frame (**7a** and **7b** for **4** and **5**, respectively) (Figure 1). These units would then be suitably functionalized for introducing (1) the Schöllkopf auxiliary as the protected amino acid at the arrow-designated carbon in Figure 2 and (2) the requisite adenine unit at the C-1 center. The initial objective thus became the preparation of the 5-membered ring participants **6**, **7a** and **7b** for this purpose (Schemes 1 and 2).

The synthesis of **6** (Scheme 1) began with allylation of the primary hydroxyl substituent of the protected ribose derivative **9** (obtained from 2,3-*isopropylidene* ribose **8**⁸) to afford **10**. Glycolization followed by oxidative cleavage and subsequent reduction converted **10** into **11**, which was, then, tosylated to **12**. To avoid any future difficulties in removing the PMB group under oxidative circumstances, it was removed at this time to give **13**. Protection of the resultant anomeric hydroxyl of **13** as a TBS silyl ether gave **6**.

Achieving **7a/7b** (Scheme 2) began (for **7a**) with a vinylic Michael addition to enone **14**⁹ that was followed by a Luche reduction¹⁰ and subsequent silylation of the newly formed secondary alcohol to produce **15**. Oxidative cleavage of the olefinic center of **15** followed by reduction afforded **16a**.¹¹ Preparation of the relevant cyclopentenyl unit **7b** commenced with, first, silylation of allylic alcohol **17** (available from ribose via enone **18**, Scheme 2)^{12,13} and removal of the primary *t*-butyldimethylsilyl group to provide **16b**. Both **16a** and **16b** were allylated at their primary hydroxyl center to result in **19a/19b**. Glycolization of these products followed by periodate oxidative cleavage and sodium borohydride reduction resulted in **20a** and **20b** (as in the **15** to **16a** procedure), which were transformed into the requisite derivatives **7a** and **7b** by tosylation.

Coupling of **6** with the Schöllkopf reagent^{7d,14} gave **21** (Scheme 3). Removal of the silyl protection of **21** gave **22**. Installation of the adenine component was achieved by converting **22** to its C-1 chloro derivative (HMPT/CCl₄) followed by a nucleophilic substitution reaction involving the anion of N⁶, N⁶-*bis*-(*t*-butoxycarbonyl) protected adenine to yield **23**. Deprotection of **23** resulted in the desired target compound **3**.

Similarly, **7a** and **7b** were converted to **4** and **5** (Scheme 3) through **24–26**.

Experimental Section

¹H and ¹³C NMR spectra were recorded on either a Bruker AC 250 spectrometer (250 MHz for proton and 62.5 MHz for carbon) or a Bruker AV 400 spectrometer (400 MHz for proton and 100 MHz for carbon), referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The mass spectral data were obtained using a Waters Micromass QTOF Premier mass spectrometer. The reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Diamond silica gel 60-F254 precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Column chromatography was performed on Whatman silica, 230–400 mesh, and 60 Å using elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (¹H and ¹³C NMR) homogeneous materials.

((3a*R*,4*R*,6*R*,6a*R*)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl)methanol (9)

Compound **8**⁶ (2.98 g, 16.6 mmol) was dissolved in DMF. The solution was cooled to 0 °C and NaH (0.68 g, 60% in mineral oil, 17 mmol) was added portionwise. The mixture was stirred at this same temperature for 1 h; *p*-methoxybenzyl chloride (2.76 mL, 20.4 mmol) was then added. The solution was warmed to room temperature and stirred overnight. The solvent was removed under reduced pressure and the residue partitioned between H₂O and EtOAc. The aqueous phase was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc=2:1) to give **9** as a colorless oil (3.38 g, 65.6%). ¹H NMR (400 MHz, CDCl₃) δ 7.26 (m, 2H), 6.89 (m, 2H), 5.16 (s, 1H), 4.83 (d, J=6.0 Hz, 1H), 4.69 (d, J=11.2 Hz, 1H), 4.62 (m, 2H), 4.50 (d, J=11.2 Hz, 1H), 4.43 (m, 1H), 3.80 (s, 3H), 3.68 (m, 2H), 1.47 (s, 3H), 1.30 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 159.7, 130.0, 128.6, 114.1, 112.1, 107.7, 88.4, 86.0, 81.5, 69.9, 55.3, 26.4, 24.7. Calcd HRMS for C₁₆H₂₂O₆: 310.1416; Found: 310.1409.

(3a*R*,4*R*,6*R*,6a*R*)-4-(Allyloxymethyl)-6-(4-methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxole (10)

The just described **9** (10.02 g, 32.32 mmol) was dissolved in DMF (50 mL) and NaH (1.54 g, 38.5 mmol, 60% in mineral oil) added in portions. Allyl bromide (5.50 mL, 64.1 mmol) was then added dropwise *via* a syringe. The mixture was stirred at room temperature (12 h) followed by the addition of H₂O (10 mL) to quench the reaction. The mixture was extracted with Et₂O (3×100 mL). The combined organic layers were washed with H₂O (3×20 mL), brine (50 mL), dried (Na₂SO₄), and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc=20:1) to give **10** as a colorless oil (8.97 g, 79.5%). ¹H NMR (CDCl₃, 250 MHz) δ 7.22 (m, 2H), 6.89 (m, 2H), 5.85–5.92 (m, 1H), 5.13–5.31 (m, 3H), 4.61–4.68 (m, 3H), 4.37–4.46 (m, 2H), 4.02 (m, 2H), 3.82 (s, 3H), 3.50 (m, 2H), 1.48 (s, 3H), 1.30 (s, 3H); ¹³C NMR (CDCl₃, 62 MHz) δ 159.4, 134.6, 129.8, 129.2, 117.3, 113.8, 112.3, 106.9, 85.3, 85.2, 82.2, 72.2, 71.0, 68.8, 55.3, 26.4, 24.9; Calcd HRMS for C₁₉H₂₆O₆ (M-CH₃): 335.1495; Found: 335.1499.

2-(((3a*R*,4*R*,6*R*,6a*R*)-6-(4-Methoxybenzyloxy)-2,2-dimethyltetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl)methoxy)ethanol (11)

Compound **10** (7.11 g, 20.31 mmol) was dissolved in THF (50 mL) and to this NMO (7.20 mL, 50% in H₂O, 31.2 mmol) was added followed by OsO₄ (20 mg, 0.078 mmol). The reaction mixture was stirred at room temperature overnight. Sodium thiosulfate (10 g) was added. The mixture was stirred for another 2 h. The mixture was filtered through a short silica gel column (5 cm) and the column rinsed with EtOAc. The combined organic liquids were concentrated. The residue was dissolved in CH₂Cl₂/H₂O (1:1, 30 mL) and NaIO₄ (6.40 g, 30.0 mmol) added at room temperature. The mixture was stirred 3 h. The organic layer was diluted with CH₂Cl₂ (100 mL), separated, washed with H₂O (20 mL), dried (Na₂SO₄), and concentrated. The residue was dissolved in MeOH (30 mL) at 0 °C and NaBH₄ (1.80 g, 48.6 mmol) added portionwise. The mixture was stirred at the same temperature for 30 min. Saturated NH₄Cl solution (30 mL) was added and the mixture filtered through celite. The filtrate was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexanes/EtOAc=3:1 to 1:1) to give **11** as a colorless oil (5.41 g, 75.2%). ¹H NMR (CDCl₃, 400 MHz) δ 7.25 (m, 2H), 6.88 (m, 2H), 5.14 (s, 1H), 4.69 (d, J=6.0 Hz, 1H), 4.62–4.65 (m, 2H), 4.36–4.40 (m, 2H), 3.80 (s, 3H), 3.72 (m, 2H), 3.54–3.60 (m, 4H), 2.38 (m, 1H), 1.47 (s, 3H), 1.31 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 159.6, 129.9, 129.3, 114.1, 112.6, 107.5, 85.7, 85.5, 82.3, 72.6, 72.4, 69.2, 61.9, 55.5, 26.7, 25.2; Calcd HRMS for C₁₈H₂₆O₇ (M-CH₃): 339.1444; Found: 339.1444.

2-(((3a*R*,4*R*,6*R*,6a*R*)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl)methoxy)ethyl 4-Methylbenzenesulfonate (12)

Compound **11** (6.05 g, 17.0 mmol), TEA (20 mL), TsCl (3.90 g, 20.5 mmol), and DABCO (50 mg) were mixed in CH₂Cl₂ (100 mL) and this mixture stirred at room temperature 30 min. Water (10 mL) was added and the organic layer separated, washed with brine (20 mL), dried (Na₂SO₄), and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc=5:1) to give **12** as an orange oil (7.15 g, 82.3%). ¹H NMR (CDCl₃, 400 MHz) δ 7.80 (m, 2H), 7.31 (m, 2H), 7.22 (m, 2H), 6.87 (m, 2H), 5.10 (s, 1H), 4.55–4.60 (m, 3H), 4.37 (d, J=11.6 Hz, 1H), 4.24 (m, 1H), 4.09–4.16 (m, 2H), 3.80 (s, 3H), 3.67 (m, 2H), 3.43 (m, 2H), 2.43 (s, 3H), 1.47 (s, 3H), 1.30 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 159.6, 145.0, 133.2, 130.0, 129.9, 129.4, 128.2, 114.1, 112.6, 107.2, 85.5, 85.1, 82.3, 72.4, 69.3, 68.9, 55.5, 26.6, 25.1, 21.8; Calcd HRMS for C₂₅H₃₂O₉S: 508.1767; Found: 508.1774.

2-(((3a*R*,4*R*,6*R*,6a*R*)-6-Hydroxy-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)ethyl 4-Methylbenzenesulfonate (13)

Derivative **12** (4.87 g, 9.59 mmol) was dissolved in CH₂Cl₂/H₂O (20:1, 30 mL) and to this DDQ (1.10 g, 4.85 mmol) was added. The mixture was stirred vigorously at room temperature for 3 h. The resulting precipitate was removed by filtration. The filtrate was diluted with CH₂Cl₂ (100 mL) and washed with saturated NaHCO₃ solution (3×30 mL). The organic layer was dried (Na₂SO₄), and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc=3:1) to give **13** as an orange oil (β:α=6:1, 2.88 g, 77.4%). ¹H NMR (CDCl₃, 400 MHz) for the β isomer δ 7.82 (m, 2H), 7.37 (m, 2H), 5.27 (d, J=10.8 Hz, 1H), 4.71 (m, 1H), 4.45 (d, J=5.6 Hz, 1H), 4.32 (m, 1H), 4.11–4.20 (m, 3H), 3.72–3.78 (m, 2H), 3.55–3.65 (m, 2H), 2.45 (s, 3H), 1.48 (s, 3H), 1.31 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) for the β isomer δ 145.2, 132.6, 129.9, 128.0, 112.1, 103.9, 87.2, 85.3, 81.8, 72.6, 69.1, 68.2, 26.4, 24.8, 21.7; Calcd HRMS for C₁₇H₂₄O₈S (M+NH₄): 406.1537; Found: 406.1536.

2-(((3a*R*,4*R*,6*S*,6a*R*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydrofuro-[3,4-*d*][1,3]dioxol-4-yl)methoxy)ethyl 4-Methylbenzenesulfonate (6)

To **13** (1.54 g, 3.97 mmol) dissolved in dry CH₂Cl₂ (60 mL) was added DMAP (20 mg). The solution was treated with imidazole (0.68 g, 10.4 mmol) and TBSCl (1.21 g, 8.07 mmol) at 0 °C. The solution was then warmed to room temperature and stirred for 2 h. Water (20 mL) was added to quench the reaction. The organic layer was separated, washed with brine, dried (Na₂SO₄), and concentrated under reduce pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc=5:1) to give **6** as a colorless oil (1.32 g, 66.2%). ¹H NMR (CDCl₃, 400 MHz) δ 7.79 (m, 2H), 7.35 (m, 2H), 5.34 (s, 1H), 4.65 (dd, J=6.0, 0.4 Hz, 1H), 4.49 (d, J=6.0 Hz, 1H), 4.13 (m, 3H), 3.66 (m, 2H), 3.43 (m, 2H), 2.45 (s, 3H), 1.47 (s, 3H), 1.32 (s, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 144.8, 132.9, 129.9, 128.0, 112.3, 103.3, 87.2, 84.9, 82.5, 72.6, 69.1, 68.7, 26.5, 25.7, 25.1, 21.7, 17.9, -4.3, -5.4; Calcd HRMS for C₂₃H₃₈O₈SSi (M+NH₄): 520.2406; Found: 520.2400.

***tert*-Butyl((3a*R*,4*S*,6*R*,6a*R*)-2,2-dimethyl-6-vinyl-tetrahydro-3a*H*-cyclopenta-[*d*]-[1,3]dioxol-4-yloxy)dimethylsilane (15)**

Vinylmagnesium bromide (25 mL, 1.0 M in THF, 25 mmol) was added to a suspension of CuBr•SMe₂ (0.41 g, 2.0 mmol) in THF (30 mL) at -78 °C. The mixture was stirred at this temperature for 1 h. To this was added, dropwise, enone **14**⁸ (3.0 g, 19 mmol), HMPA (10 mL) and TMSCl (3.2 mL, 25 mmol) at -78 °C. The resulting mixture was warmed to room temperature and stirred overnight. Saturated NH₄Cl solution (30 mL) was then added to

quench the reaction. The mixture was extracted with Et₂O (3×100 mL). The combined organic phases were washed with brine (100 mL), dried (Na₂SO₄), and concentrated. The residue was dissolved in MeOH (100 mL) and CeCl₃•7H₂O (7.4 g, 20 mmol) added at 0 °C. This was followed by the portionwise addition of NaBH₄ (0.74 g, 20 mmol). The resulting mixture was stirred at this temperature for 1 h. Saturated NH₄Cl solution (20 mL) was added to quench the reaction. The mixture was filtered through celite and the filtrate concentrated. The residue was extracted with Et₂O (3×100 mL) and the combined organic phases dried over (Na₂SO₄), and filtered through a short silica gel column (10 cm). The filtrate was concentrated and the residue dissolved in CH₂Cl₂ (100 mL). TBSCl (3.0 g, 20 mmol) and imidazole (2.0 g, 31 mmol) were then added to this solution at room temperature. The mixture was stirred 3 h and H₂O (10 mL) added to quench the reaction. The organic layer was separated, washed with H₂O (20 mL), dried (Na₂SO₄), and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc=20:1) to give **15** as a colorless oil (2.5 g, 43% in 3 steps). ¹H NMR (CDCl₃, 400 MHz) δ 5.76 (m, 1H), 5.02–5.08 (m, 2H), 4.37 (m, 2H), 4.07 (m, 1H), 2.66 (m, 1H), 2.03 (m, 1H), 1.73 (m, 1H), 1.49 (s, 3H), 1.31 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 139.1, 114.7, 111.3, 84.1, 80.1, 72.5, 44.3, 35.6, 26.3, 25.7, 24.7 18.4, –4.4, –4.7. Calcd HRMS for C₁₆H₃₀O₃Si (M+H): 299.2042; Found: 299.2043.

((3*aR*,4*R*,6*S*,6*aR*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)methanol (16a)

To compound **15** (2.5 g, 8.4 mmol) dissolved in THF (50 mL) was added NMO (3.6 mL, 50% in H₂O, 16 mmol) followed by OsO₄ (20 mg, 0.078 mmol). The resulting mixture was stirred at room temperature overnight. Sodium thiosulfate (5 g) was then added and the mixture stirred for an additional 2 h. This mixture was filtered through a short silica gel column followed by rinsing the column with EtOAc. The combined organic phases were concentrated. The residue was dissolved in CH₂Cl₂/H₂O (1:1, 30 mL) and NaIO₄ (2.1 g, 9.9 mmol) then added at room temperature. The mixture was stirred 3 h. The organic layer was diluted with CH₂Cl₂ (90 mL), separated, washed with H₂O (20 mL), dried (Na₂SO₄), and concentrated. The residue was dissolved in MeOH (30 mL) at 0 °C and to this NaBH₄ (0.30 g, 6.4 mmol) was added, portionwise. This mixture was stirred at the same temperature for 30 min. Saturated NH₄Cl solution (30 mL) was added and the mixture was filtered through celite. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (hexanes/EtOAc=3:1 to 1:1) to give **16a** as a colorless oil (2.1 g, 84%). The NMR spectrum was consistent with the literature.¹¹

((3*aR*,6*S*,6*aR*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-6,6*a*-dihydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)methanol (16b)

Compound **17**^{12,13} (0.85 g, 2.8 mmol) was dissolved in CH₂Cl₂ (30 mL) and to this was added TBSCl (0.85 g, 5.6 mmol) and imidazole (0.36 g, 5.6 mmol) at room temperature. The mixture was stirred at this temperature for 5 h. Water (10 mL) was added to quench the reaction. The organic layer was separated, dried (Na₂SO₄), and filtered through a short silica gel column. The filtrate was concentrated under reduced pressure (H₂O bath temperature: 80 °C). The resulting colorless oil was dissolved in THF and cooled to –78 °C. To this TBAF (2.8 mL, 1.0 M in THF, 2.8 mmol) was added. The solution was slowly warmed to room temperature. Saturated NH₄Cl solution (10 mL) was added. The resulting mixture was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (3×20 mL), dried (Na₂SO₄), and concentrated. The residue was purified with silica gel column chromatography (hexanes/EtOAc=2:1) to give **16b** as a colorless oil (0.54 g, 63%). ¹H NMR (CDCl₃, 400 MHz) δ 5.67 (m, 1H), 4.89 (m, 1H), 4.64–4.67 (m, 2H), 4.30–4.38 (m, 2H), 2.05 (br, 1H), 1.42 (s, 3H), 1.37 (s, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.12 (s,

3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 143.7, 130.5, 112.4, 83.2, 79.1, 74.5, 60.2, 27.4, 26.7, 25.9, 18.5, -4.4, -4.7. Calcd HRMS for $\text{C}_{15}\text{H}_{28}\text{O}_4\text{Si}$ (M+H): 301.1835; Found: 301.1825.

((3*aR*,4*S*,6*R*,6*aR*)-6-(Allyloxymethyl)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta-[*d*][1,3]dioxol-4-yloxy)(*tert*-butyl)dimethylsilane (19a)

To compound **16a** (1.6 g, 5.3 mmol) dissolved in DMF (50 mL) was added NaH (0.25 g, 6.3 mmol, 60% in mineral oil) in portions. Allyl bromide (1.1 mL, 12 mmol) was then added to this mixture, dropwise, *via* a syringe. The mixture was stirred at room temperature for 12 h. Water (10 mL) was added to quench the reaction. The mixture was extracted with Et_2O (3 $\times$ 100 mL). The combined organic phases were washed with H_2O (3 $\times$ 20 mL), brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (hexanes/ EtOAc =20:1) to give **19a** as a colorless oil (1.6 g, 83%). ^1H NMR (CDCl_3 , 400 MHz) δ 5.89 (m, 1H), 5.14–5.26 (m, 2H), 4.38 (m, 2H), 4.19 (m, 1H), 3.94 (m, 2H), 3.37 (m, 1H), 3.30 (m, 1H), 2.24 (m, 1H), 2.05 (m, 1H), 1.68 (m, 1H), 1.48 (s, 3H), 1.31 (s, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 134.8, 116.7, 111.3, 82.5, 80.9, 77.3, 72.9, 72.0, 42.3, 34.8, 26.6, 26.1, 24.9, 18.5, -4.4, -4.7. Calcd HRMS for $\text{C}_{18}\text{H}_{34}\text{O}_4\text{Si}$ (M+H): 343.2305; Found: 343.2312.

((3*aR*,4*S*,6*aR*)-6-(Allyloxymethyl)-2,2-dimethyl-4,6*a*-dihydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yloxy)(*tert*-butyl)dimethylsilane (19b)

Following the same procedure given for **19a**, **16b** (0.50 g, 1.7 mmol) resulted in **19b** as colorless oil (0.48 g, 85%). ^1H NMR (CDCl_3 , 400 MHz) δ 5.85–5.95 (m, 1H), 5.70 (m, 1H), 5.26 (m, J =17.2 Hz, 1H), 5.19 (m, J =10.4 Hz, 1H), 4.88 (d, J =4.8 Hz, 1H), 4.65 (m, 2H), 4.13 (m, 2H), 4.03 (m, 2H), 1.39 (s, 3H), 1.37 (s, 3H), 0.91 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 141.8, 134.6, 131.6, 117.2, 112.2, 82.8, 78.9, 74.6, 71.9, 66.5, 27.5, 26.8, 25.9, 18.5, -4.4, -4.7.

2-(((3*aR*,4*R*,6*S*,6*aR*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)methoxy)ethanol (20a)

Allyl derivative **19a** (0.80 g, 2.3 mmol) was dissolved in THF (50 mL) and to this NMO (0.90 mL, 50% in H_2O , 4.0 mmol) was added, which was followed by OsO_4 (10 mg, 0.039 mmol) addition. The mixture was stirred at room temperature overnight at which time $\text{Na}_2\text{S}_2\text{O}_3$ (2 g) was added. This new mixture was stirred for another 2 h. The mixture was then filtered through a short silica gel column. The column was rinsed with EtOAc/MeOH (5:1, 100 mL) and the combined organic phases concentrated. The residue was dissolved in $\text{MeOH/H}_2\text{O}$ (1:1, 30 mL) and to this solution NaIO_4 (0.73 g, 3.4 mmol) was added at room temperature. The mixture was stirred for 3 h at this temperature following which time the mixture was cooled to 0 $^\circ\text{C}$ and NaBH_4 (0.30 g, 6.4 mmol) added portionwise. The mixture was stirred at the same temperature for 30 min. Saturated NH_4Cl solution (30 mL) was added and the mixture was filtered through celite. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (hexanes/ EtOAc =3:1 to 1:1) to give **20a** as a colorless oil (0.60 g, 86%). ^1H NMR (CDCl_3 , 400 MHz) δ 4.38 (m, 2H), 4.14 (m, 1H), 3.72 (m, 2H), 3.55 (m, 2H), 3.42 (m, 1H), 3.35 (m, 1H), 2.29 (br, 1H), 2.03 (m, 2H), 1.62 (m, 1H), 1.49 (s, 3H), 1.31 (s, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 111.6, 82.3, 80.9, 73.0, 72.9, 72.2, 61.8, 42.4, 34.6, 26.5, 26.0, 24.9, 18.5, -4.4, -4.8. Calcd HRMS for $\text{C}_{17}\text{H}_{34}\text{O}_5\text{Si}$ (M+H): 347.2254; Found: 347.2249.

2-(((3a*R*,6*S*,6a*R*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-6,6a-dihydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)methoxy)ethanol (20b)

Compound **19b** (0.35 g, 1.0 mmol) was dissolved in *tert*-BuOH/H₂O (1:1, 10 mL) and to this AD-mix-β (1.4 g) was added. The mixture was stirred at room temperature for 24 h. Sodium thiosulfate (2.0 g) was added to quench the reaction. The mixture was extracted with EtOAc (3×50 mL) and the combined organic layers washed with brine (30 mL), dried (Na₂SO₄), and concentrated. The residue was dissolved in MeOH/H₂O (1:1, 10 mL) and then NaIO₄ (0.26 g, 1.2 mmol) was added. The mixture was stirred at room temperature for 3 h followed by the portionwise addition of NaBH₄ (0.24 g, 5.1 mmol). The mixture was stirred at room temperature for 30 min. Saturated NH₄Cl solution (10 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×100 mL) and the combined organic layers washed with brine (30 mL), dried (Na₂SO₄), and concentrated. The residue was purified by a silica gel column chromatography (hexanes/EtOAc=2:1) to produce **20b** as colorless oil (0.34 g, 96%). ¹H NMR (CDCl₃, 400 MHz) δ 5.69 (m, 1H), 4.89 (d, J=5.2 Hz, 1H), 4.65 (m, 2H), 4.19 (m, 2H), 3.75 (m, 2H), 3.59 (m, 2H), 1.41 (s, 3H), 1.37 (s, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 141.6, 131.9, 112.3, 82.9, 78.9, 74.5, 71.9, 67.5, 61.8, 27.4, 26.7, 25.9, 18.5, -4.4, -4.7. Calcd HRMS for C₁₇H₃₂O₅Si (M+H): 345.2097; Found: 345.2095.

2-(((3a*R*,4*R*,6*S*,6a*R*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)methoxy)ethyl 4-Methylbenzenesulfonate (7a)

Compound **20a** (0.20 g, 0.58 mmol), TEA (2 mL), TsCl (0.20 g, 1.1 mmol) and DABCO (5 mg) were mixed in CH₂Cl₂ (20 mL) and stirred at room temperature 30 min. Water (5 mL) was added and the organic layer separated, washed with brine (20 mL), dried (Na₂SO₄), and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc=5:1) to give **7** as an orange oil (0.24 g, 83%). ¹H NMR (CDCl₃, 400 MHz) δ 7.80 (m, 2H), 7.33 (m, 2H), 4.31 (m, 2H), 4.13 (m, 3H), 3.62 (m, 2H), 3.37 (m, 1H), 3.28 (m, 1H), 2.45 (s, 3H), 2.18 (m, 1H), 2.05 (m, 1H), 1.53 (m, 1H), 1.47 (s, 3H), 1.30 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 144.9, 133.0, 129.9, 127.9, 111.4, 82.2, 80.9, 77.2, 73.2, 72.9, 69.1, 68.5, 68.0, 42.2, 34.6, 26.6, 25.6, 24.9, 21.7, 18.5, -4.4, -4.7. Calcd HRMS for C₂₄H₄₀O₇SSi (M+H): 501.2342; Found: 501.2338.

2-(((3a*R*,6*S*,6a*R*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-6,6a-dihydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl)methoxy)ethyl 4-Methylbenzenesulfonate (7b)

Following the same process for obtaining **7a**, derivative **20b** (0.24 g, 0.70 mmol) provided **7b** as an orange oil (0.33 g, 95%). ¹H NMR (CDCl₃, 400 MHz) δ 7.80 (m, J=8.4 Hz, 2H), 7.34 (m, J=8.4 Hz, 2H), 5.64 (d, J=1.2 Hz, 1H), 4.80 (d, J=4.0 Hz, 1H), 4.63 (m, 2H), 4.08–4.18 (m, 4H), 3.64–3.67 (m, 2H), 2.44 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 144.8, 141.2, 133.0, 132.0, 129.9, 128.0, 112.2, 82.7, 78.9, 74.5, 69.1, 68.2, 67.6, 27.4, 26.8, 25.9, 21.7, 18.2, -4.4, -4.7. Calcd HRMS for C₂₄H₃₈O₇SSi (M-CH₃): 483.1873; Found: 483.1865.

(2*S*,5*R*)-2-(2-(((3a*R*,4*R*,6*S*,6a*R*)-6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)ethyl)-3,6-diethoxy-5-*isopropyl*-2,5-dihydropyrazine (21)

(*R*)-3,6-Diethoxy-2-*isopropyl*-2,5-dihydropyrazine (1.50 mL, 7.04 mmol) was dissolved in THF (3 mL) and this solution cooled to -78 °C. *n*-BuLi (3.00 mL, 2.5 M in hexanes, 7.50 mmol) was then added in dropwise. The mixture was stirred at -78 °C for 1 h. To this was added **6** (2.76 g, 5.49 mmol) dissolved in THF (5 mL) in a dropwise manner using a syringe. The mixture was slowly warmed to -30 °C and kept 2 h at this temperature followed by warming to room temperature and then stirring overnight. Water (10 mL) was added to

quench the reaction. The mixture was extracted with Et₂O (3×50 mL) and the combined organic layers washed with brine (30 mL), dried (Na₂SO₄), and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc=10:1) to give **21** as an orange oil, which was contaminated with (*R*)-3,6-diethoxy-2-*isopropyl*-2,5-dihydropyrazine (2.03 g). This product was used directly in next step without further purification. ¹H NMR (CDCl₃, 400 MHz) δ 5.35 (s, 1H), 4.72 (m, 1H), 4.51 (m, 1H), 3.85–4.25 (m, 6H), 3.42–3.65 (m, 4H), 2.25 (m, 2H), 2.15 (m, 1H), 1.85 (m, 1H), 1.47 (s, 3H), 1.25 (m, 9H), 1.03 (d, J= 6.8 Hz, 3H), 0.89 (s, 9H), 0.77 (d, J= 6.8 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H). Calcd HRMS for C₂₇H₅₀N₂O₇Si: 542.3387; Found: 542.3379.

(3*aR*,4*R*,6*R*,6*aR*)-6-((2-((2*S*,5*R*)-3,6-Diethoxy-5-*isopropyl*-2,5-dihydropyrazin-2-yl)ethoxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (22)

Compound **21** (1.72 g mixture from the previous step) was dissolved in THF (5 mL) and to this was added TBAF (10.0 mL, 1M in THF). This mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (hexanes/EtOAc=3:1) to give **22** as a colorless oil (0.81 g, 60%). ¹H NMR (CDCl₃, 250 MHz) δ 5.28 (d, J=11.0 Hz, 1H), 4.95 (d, J=11.0 Hz, 1H), 4.75 (d, J=6.0 Hz, 1H), 4.37 (m, 1H), 4.00–4.22 (m, 5H), 3.85–3.95 (m, 1H), 3.55–3.72 (m, 4H), 2.35–2.45 (m, 1H), 2.15–2.30 (m, 2H), 1.78–1.90 (m, 1H), 1.48 (s, 3H), 1.28 (m, 9H), 1.03 (d, J=6.8 Hz, 3H), 0.71 (d, J=6.8 Hz, 3H); ¹³C NMR (CDCl₃, 60 MHz) δ 163.6, 162.9, 111.9, 103.8, 87.5, 85.6, 81.9, 71.9, 68.8, 60.8, 53.9, 52.3, 33.6, 29.2, 26.4, 24.8, 20.8, 19.1, 16.8, 14.4, 14.3; Calcd HRMS for C₂₁H₃₆N₂O₇: 428.2523; Found: 428.2518.

9-((3*aR*,4*R*,6*R*,6*aR*)-6-((2-((2*S*,5*R*)-3,6-Diethoxy-5-*isopropyl*-2,5-dihydropyrazin-2-yl)ethoxy)methyl)-2,2-dimethyl-tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-6-*bis*(*tert*-butoxycarbonyl)aminopurine (23)

Compound **22** (0.61 g, 1.4 mmol) was dissolved in THF (10 mL) and then CCl₄ (0.20 mL, 2.0 mmol) was added. At –78 °C, HMPT (0.35 mL, 2.0 mmol) was introduced dropwise. The mixture was stirred at the same temperature for 1 h then warmed to 0 °C followed by additional stirring for 1 h. The solution was again re-cooled to –78 °C and the sodium salt of Ad(Boc)₂ in DMF (10 mL) (prepared by addition of 260 mg 60% NaH in mineral oil to 1.80 g Ad(Boc)₂ in 10 mL DMF) added dropwise. The mixture was warmed to room temperature and stirred overnight. Water (20 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×50 mL) and the combined organic fractions washed with brine (3×30 mL), dried (Na₂SO₄), and concentrated. The residue was purified by silica gel column chromatography (hexanes/EtOAc=3:1) to give **23** as a yellow oil (0.23 g, 25%). ¹H NMR (CDCl₃, 400 MHz) δ 8.88 (s, 1H), 8.38 (s, 1H), 6.28 (d, J=2.8 Hz, 1H), 5.23 (m, 1H), 4.95 (m, 1H), 4.52 (m, 1H), 3.95–4.23 (m, 6H), 3.55–3.65 (m, 4H), 2.25 (m, 1H), 2.28 (m, 1H), 1.82 (m, 1H), 1.65 (s, 3H), 1.38–1.48 (m, 27H), 1.02 (d, J=7.2 Hz, 3H), 0.70 (d, J=7.2 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 163.3, 163.0, 152.9, 152.3, 150.4, 150.3, 143.4, 133.6, 137.0, 129.3, 114.2, 91.4, 85.8, 85.1, 83.7, 81.8, 70.9, 68.4, 60.75, 60.71, 60.62, 60.56, 52.6, 33.8, 31.9, 27.8, 27.3, 25.3, 19.1, 14.4, 14.3; Calcd HRMS for C₃₆H₅₅N₇O₁₀: 745.4010; Found: 745.3993.

(*S*)-2-Amino-4-(((2*R*,3*S*,4*R*,5*R*)-5-(6-amino-9*H*-purin-9-yl)-3,4-dihydroxy-tetrahydrofuran-2-yl)methoxy)butanoic Acid (3)

The purine derivative **23** (0.10 g, 0.92 mmol) was dissolved in TFA/H₂O (2:1, 2 mL) at –20 °C. This solution was stirred at 0 °C for 6 h. IRA-67 ion exchange resin was added to neutralize the mixture. The resin was removed by filtration and the solvent concentrated at reduced pressure. The residue was dissolved in MeOH/H₂O (2:1, 2 mL) and K₂CO₃ (0.20 g, 1.4 mmol) was added. The mixture was stirred at room temperature for 5 h and the solvent removed under reduced pressure. The residue was purified by silica gel column

chromatography (EtOAc/MeOH/NH₄OH (29.6%) =1:1:1) to give **3** as a white foam (0.03 g, 61%). mp >210 °C (decomposed). ¹H NMR (D₂O, 250 MHz) δ 8.35 (s, 1H), 8.22 (s, 1H), 6.07 (d, J=5.0 Hz, 1H), 4.78 (m, 2H), 4.43 (m, 1H), 4.32 (m, 1H), 3.65–3.85 (m, 4H), 2.15–2.25 (m, 2H). ¹³C NMR (D₂O, 62 MHz) δ 175.3, 155.8, 152.8, 149.1, 140.7, 118.7, 88.3, 83.7, 74.2, 71.0, 70.8, 68.8, 54.0, 30.6. Calcd HRMS for C₁₄H₂₀N₆O₆ (M+H): 369.1522; Found: 369.1525.

(2S,5R)-2-(2-(((3aR,4R,6S,6aR)-6-(tert-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)methoxy)ethyl)-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazine (24a)

Following a procedure similar to that for obtaining **21**, (*R*)-3,6-Diethoxy-2-isopropyl-2,5-dihydropyrazine (0.43 mL, 2.0 mmol) and **7a** (0.52 g, 1.0 mmol) resulted **24a** as orange oil (0.50 g, 89%). ¹H NMR (CDCl₃, 400 MHz) δ 4.28–4.38 (m, 3H), 4.15 (m, 2H), 4.10 (m, 2H), 4.05 (m, 1H), 3.87 (m, 1H), 3.55 (m, 1H), 3.45 (m, 1H), 3.25–3.35 (m, 2H), 2.25 (m, 1H), 2.17 (m, 2H), 2.05 (m, 1H), 1.77 (m, 1H), 1.62 (m, 1H), 1.48 (s, 3H), 1.25–1.32 (m, 9H), 1.03 (d, J=6.8 Hz, 3H), 0.91 (s, 9H), 0.72 (d, J=6.8 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 163.4, 163.0, 111.1, 82.5, 81.1, 73.1, 72.7, 67.7, 61.9, 61.8, 60.6, 60.5, 52.6, 42.3, 31.9, 29.2, 26.6, 26.1, 24.8, 19.1, 18.5, 16.7, 14.7, 14.4, –4.4, –4.7. Calcd HRMS for C₂₈H₅₂N₂O₆Si: 540.3595; Found: 540.3584.

(2S,5R)-2-(2-(((3aR,6S,6aR)-6-(tert-Butyldimethylsilyloxy)-2,2-dimethyl-6,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)methoxy)ethyl)-3,6-diethoxy-5-isopropyl-2,5-dihydropyrazine (24b)

As with **24a**, the procedure used for obtaining **21** was followed with (*R*)-3,6-Diethoxy-2-isopropyl-2,5-dihydropyrazine (0.32 mL, 1.5 mmol) and **7b** (0.25 g, 0.50 mmol) gave **24b** as an orange oil (0.22 g, 81%). ¹H NMR (CDCl₃, 400 MHz) δ 5.68 (m, 1H), 4.85 (m, 1H), 4.64 (m, 2H), 4.05–4.16 (m, 7H), 3.89 (m, 1H), 3.63 (m, 1H), 3.55 (m, 1H), 2.15–2.25 (m, 2H), 1.85 (m, 1H), 1.39 (s, 3H), 1.36 (s, 3H), 1.25 (m, 6H), 1.00 (d, J=6.8 Hz, 3H), 0.92 (s, 9H), 0.72 (d, J=6.8 Hz, 3H), 0.13 (s, 3H), 0.12 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 163.5, 163.3, 142.3, 131.5, 112.3, 83.0, 79.1, 74.8, 67.8, 67.4, 60.9, 60.8, 60.7, 52.8, 34.4, 32.1, 27.6, 27.1, 26.1, 19.3, 18.7, 16.9, 14.5, –4.2, –4.6. Calcd HRMS for C₂₈H₅₀N₂O₆Si (M+H): 539.3516; Found: 539.3506.

(3aS,4S,6R,6aR)-6-((2-((2S,5R)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)ethoxy)methyl)-2,2-dimethyl-tetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (25a)

The tosylated **24a** (0.50 g, 0.92 mmol) was dissolved in THF (10 mL). To this was added, with the assistance of a syringe, TBAF (2.0 mL, 1M in THF, 2.0 mmol). The mixture was heated to 60 °C and kept at this temperature for 30 min. The solvent was removed under reduced pressure, and the residue purified by silica gel column chromatography (hexanes/EtOAc=3:1) to afford **25a** as orange oil (0.16 g, 43%). ¹H NMR (CDCl₃, 400 MHz) δ 4.49 (m, 1H), 4.45 (m, 1H), 4.08–4.21 (m, 5H), 3.96 (m, 1H), 3.87 (m, 1H), 3.53 (m, 1H), 3.45 (m, 1H), 3.35 (m, 1H), 3.25 (m, 1H), 2.40 (d, J=8.4 Hz, 1H), 2.25 (m, 2H), 2.12 (m, 1H), 1.82 (m, 3H), 1.49 (s, 3H), 1.34 (s, 3H), 1.25–1.28 (m, 6H), 1.03 (d, J=6.8 Hz, 3H), 0.72 (d, J=6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 163.2, 163.1, 111.2, 83.1, 79.6, 76.3, 72.2, 67.8, 60.69, 60.65, 60.57, 60.51, 52.7, 42.0, 35.5, 34.2, 31.9, 26.2, 26.1, 14.4, 14.3. Calcd HRMS for C₂₂H₃₈N₂O₆: 426.2730; Found: 426.2733.

(3aS,4S,6aR)-6-((2-((2S,5R)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)ethoxy)methyl)-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (25b)

Undertaking the same process that resulted in **25a**, product **24b** (0.20 g, 0.37 mmol) afforded **25b** as a colorless oil (0.14 g, 90%). ¹H NMR (CDCl₃, 400 MHz) δ 5.75 (m, 1H), 4.95 (m,

1H), 4.75 (m, 1H), 4.55 (m, 1H), 4.05–4.15 (m, 7H), 3.88 (m, 1H), 3.63 (m, 1H), 3.55 (m, 1H), 2.71 (br, 1H), 2.15–2.25 (m, 2H), 1.85 (m, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 1.35 (m, 6H), 1.00 (d, J=6.8 Hz, 3H), 0.72 (d, J=6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 163.5, 163.3, 143.0, 131.2, 112.6, 83.1, 77.9, 73.5, 67.8, 67.1, 60.9, 60.8, 60.7, 52.8, 34.8, 32.0, 27.8, 26.7, 19.2, 16.8, 14.6, 14.5. Calcd HRMS for C₂₂H₃₆N₂O₆ (M+H): 425.2651; Found: 425.2661.

9-((3*aS*,4*R*,6*R*,6*aR*)-6-((2-((2*S*,5*R*)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)ethoxy)methyl)-2,2-dimethyl-tetrahydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)-9*H*-purin-6-di(*tert*-butoxycarbonyl)amine (26a)

Compound **25a** (0.14 g, 0.33 mmol) was dissolved in THF and to this was added Ph₃P (0.17 g, 0.66 mmol) and Ad(Boc)₂ (0.22 g, 0.66 mmol). DIAD (0.13 mL, 0.66 mmol) was then added, portionwise, *via* a syringe at 0 °C. The mixture was warmed to room temperature and stirred overnight. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc=3:1) to give **26a** as an orange oil (0.14 g, 57%). ¹H NMR (CDCl₃, 400 MHz) δ 8.85 (s, 1H), 8.21 (s, 1H), 5.09 (m, 1H), 4.95 (m, 1H), 4.85 (m, 1H), 4.63 (m, 1H), 4.05–4.21 (m, 6H), 3.85 (m, 1H), 3.55 (m, 3H), 2.45 (m, 2H), 2.25 (m, 1H), 2.15 (m, 1H), 1.90 (m, 1H), 1.55 (s, 3H), 1.47 (s, 18H), 1.35 (s, 3H), 1.27 (m, 6H), 1.03 (d, J=6.8 Hz, 3H), 0.70 (d, J=6.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 163.4, 163.2, 153.5, 151.8, 150.6, 150.4, 143.9, 129.4, 113.7, 83.7, 71.8, 67.9, 61.9, 60.6, 60.5, 59.6, 52.7, 43.8, 33.9, 33.7, 31.9, 27.9, 27.8, 27.7, 25.1, 21.9, 21.8, 19.2, 16.8, 14.4, 14.2. Calcd HRMS for C₃₇H₅₇N₇O₉: 743.4218; Found: 743.4208.

9-((3*aS*,4*R*,6*aR*)-6-((2-((2*S*,5*R*)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)ethoxy)methyl)-2,2-dimethyl-4,6*a*-dihydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)-9*H*-purin-6-bis(*tert*-butoxycarbonyl)amine (26b)

Pursuing the same procedure that gave **26a**, **25b** (0.12 g, 0.28 mmol) was converted to **26b** as an orange oil (0.15 g, 73%). ¹H NMR (CDCl₃, 250 MHz) δ 8.90 (s, 1H), 7.99 (s, 1H), 5.83 (m, 1H), 5.66 (m, 1H), 5.35 (m, J=8.0 Hz, 1H), 4.73 (m, J=9.2 Hz, 1H), 4.05–4.15 (m, 7H), 3.90 (m, 1H), 3.65 (m, 2H), 2.25 (m, 2H), 1.90 (m, 1H), 1.50 (s, 6H), 1.46 (s, 18H), 1.35 (m, 6H), 1.03 (d, J=6.8 Hz, 3H), 0.70 (d, J=6.8 Hz, 3H); ¹³C NMR (CDCl₃, 62.9 MHz) δ 163.2, 153.6, 153.0, 152.3, 150.6, 150.4, 142.8, 129.3, 121.8, 112.8, 84.4, 83.8, 71.9, 67.9, 67.3, 65.0, 60.7, 60.6, 60.5, 52.6, 34.2, 31.9, 27.8, 27.4, 25.9, 19.1, 16.7, 14.4, 14.3. Calcd HRMS for C₃₇H₅₅N₇O₉ (M+H): 742.4139; Found: 742.4133.

(*S*)-2-Amino-4-(((1*R*,2*R*,3*S*,4*R*)-4-(6-amino-9*H*-purin-9-yl)-2,3-dihydroxycyclopentyl)methoxy)butanoic Acid (4)

The protected material **26a** (0.13 g, 0.17 mmol) was treated with TFA/H₂O (3:1, 3 mL) at room temperature overnight. The solvent was removed under reduced pressure. The residue was dissolved in MeOH/H₂O (3:1, 10 mL), K₂CO₃ (0.20 mg, 1.4 mmol) was added. The mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (EtOAc/MeOH/NH₄OH) (29.6%:1:1:1) to give **4** as white foam (30 mg, 46%). mp >200 °C (decomposed). ¹H NMR (D₂O/MeOD, 400 MHz) δ 8.24 (s, 1H), 8.17 (s, 1H), 4.75 (m, 1H), 4.50 (m, 1H), 4.09 (m, 2H), 3.85 (m, 1H), 3.65 (m, 2H), 3.55 (m, 2H), 2.40 (m, 2H), 2.25 (m, 1H), 2.15 (m, 1H); ¹³C NMR (D₂O/MeOD, 100 MHz) δ 173.4, 155.4, 152.0, 149.1, 140.5, 118.7, 74.7, 72.5, 72.2, 67.9, 59.6, 53.7, 42.8, 29.9, 28.9. Calcd HRMS for C₁₅H₂₂N₆O₅ (M+H): 367.1730; Found: 367.1740.

(S)-2-Amino-4-(((3R,4S,5R)-3-(6-amino-9H-purin-9-yl)-4,5-dihydroxycyclopent-1-en-1-yl)methoxy)butanoic Acid (5)

Analogous to the route that provided **4**, compound **26b** (0.12 g, 0.16 mmol) gave **5** as a white foam (40 mg, 71%), mp >180 °C (decomposed). ¹H NMR (D₂O, 400 MHz) δ 8.17 (s, 1H), 8.14 (s, 1H), 6.10 (m, 1H), 5.54 (m, 1H), 4.75 (d, J=5.2 Hz, 1H), 4.48 (t, J=5.8 Hz, 1H), 4.35 (m, 2H), 3.95 (m, 1H), 3.82 (m, 2H), 2.30 (m, 1H), 2.23 (m, 1H); ¹³C NMR (D₂O, 100 MHz) δ 174.0, 155.1, 151.9, 148.8, 145.2, 140.8, 127.8, 127.5, 118.6, 77.1, 73.0, 67.7, 64.4, 53.7, 29.9. Calcd HRMS for C₁₅H₂₀N₆O₅ (M+H): 365.1573; Found: 365.1577.

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Figure 1.
S-Adenosylmethionine, S-Adenosylhomocysteine and Target Analogs.

Figure 2.
Requisite 5-Membered Ring Partners in Target Syntheses

Scheme 1.

Reagents and conditions: *a*, PMBCl, NaH, 67%; *b*, NaH, allylBr, 79%; *c*, (i) NMO, OsO₄; (ii) NaIO₄; (iii) NaBH₄, 75% after 3 steps; *d*, TsCl, TEA, DABCO (cat.), 82%; *e*, DDQ, 77%; *f*, TBSCl, imidazole, 66%.

Scheme 2.

Reagents and conditions: *a*, (i) vinylMgBr, CuBr•SMe₂, TMSCl; (ii) NaBH₄, CeCl₃•7H₂O; (iii) TBSCl, imidazole, 43% after 3 steps; *b*, (i) NMO, OsO₄; (ii) NaIO₄; (iii) NaBH₄, CeCl₃•7H₂O, 84% after 3 steps; *c*, (i) same as step *a* (iii); (ii) TBAF, -40 °C, 63% after 2 steps; *d*, NaH, allylBr, 83% for **19a**, 85% for **19b**; *e*, same as step *b*, 86%; *f*, (i) AD-mix-β; same as steps (ii) and (iii) within step *b*, 96%; *g*, TsCl, TEA, DABCO (cat.), 83% for **7a**, 83% for **7b**.

Scheme 3.

Reagents and conditions: *a*, Schöllkopf reagent, *n*-BuLi, 68% for **21**, 89% for **24a**, 81% for **24b**; TBAF, 60% for **22**, 60% for **25a**, 90% for **25b**; *c*, (i) HMPT, CCl₄, (ii) NaH, Ad(Boc)₂, 25% for 2 steps; *d*, (i) TFA/H₂O; (ii) K₂CO₃, yields for two steps, 61% for **3**, 46% for **4**, 71% for **5**; *e*, Ph₃P, DIAD, Ad(Boc)₂, 57% for **26a**, 73% for **26b**.