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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.

1. 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**, Fig. 1), a ubiquitous cofactor in the aforementioned biomethylations.[3] One approach has been to exploit the feedback inhibitory effects[4] 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, less[6] attention has considered analogs of AdoHcy itself, particularly at its side chain sulfur center,[7] as a more direct means of 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 neplanocin (**5**).

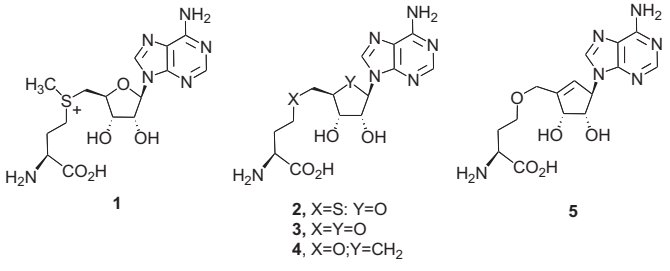

Fig. 1. *S*-Adenosylmethionine, *S*-adenosylhomocysteine, and targer analogs.

2. 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) (Fig. 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 Fig. 2 and (2) the requisite adenine unit at the C-1 center. The initial objective thus became the preparation of the five-membered ring participants **6**, **7a**, and **7b** for this purpose (Schemes 1 and 2).

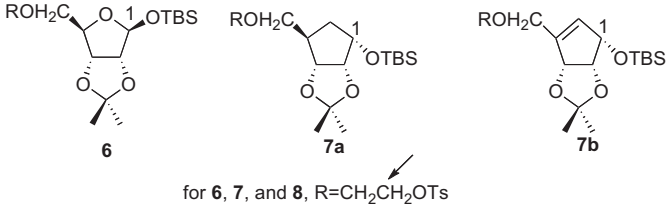

Fig. 2. Requisite five-membered ring partners in target syntheses.

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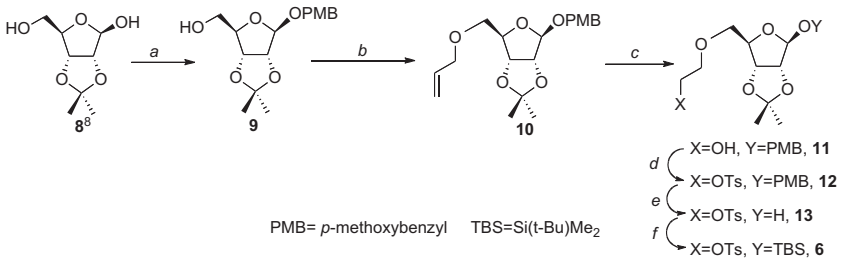
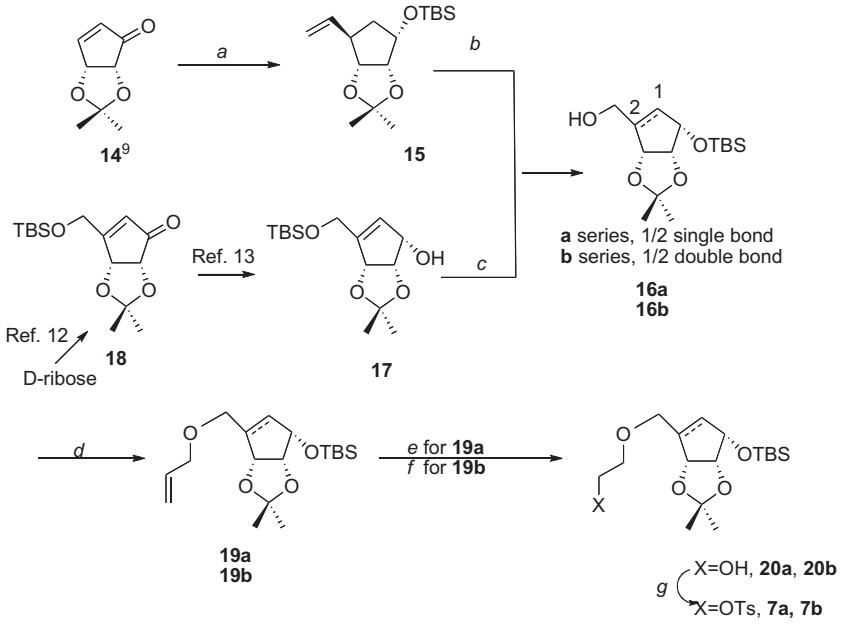


Scheme 1. Reagents and conditions: a, PMBCl, NaH, 67%, b, NaH, allylBr, 79%; c, (i) NMO, OsO_4; (ii) $NaIO_4$; (iii) $NaBH_4$, 75% after three steps; d, TsCl, TEA, DABCO (cat.), 82%; e, DDQ, 77%; f, TBSCl, imidazole, 66%.



Scheme 2. Reagents and conditions: a (i) vinylMgBr, $CuBr \cdot SMe_2$, TMSCl; (ii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$; (iii) TBSCl, imadazole, 42% after three steps; b, (i) NMO, OsO_4; (ii) $NaIO_4$; (iii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, 84% after three steps; c, (i) same as step a (iii); (ii) TBAF, −40 °C, 63% after two 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, DABCO (cat.), 83% for **7a**, 83% for **7b**.

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 reduction[10] 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 *tert*-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 ($HMPT/CCl_4$) followed by a nucleophilic substitution reaction involving the anion of N^6,N^6-bis-(*tert*-butoxylcarbonyl) protected adenine to yield **23**. Deprotection of **23** resulted in the desired target compound **3**.

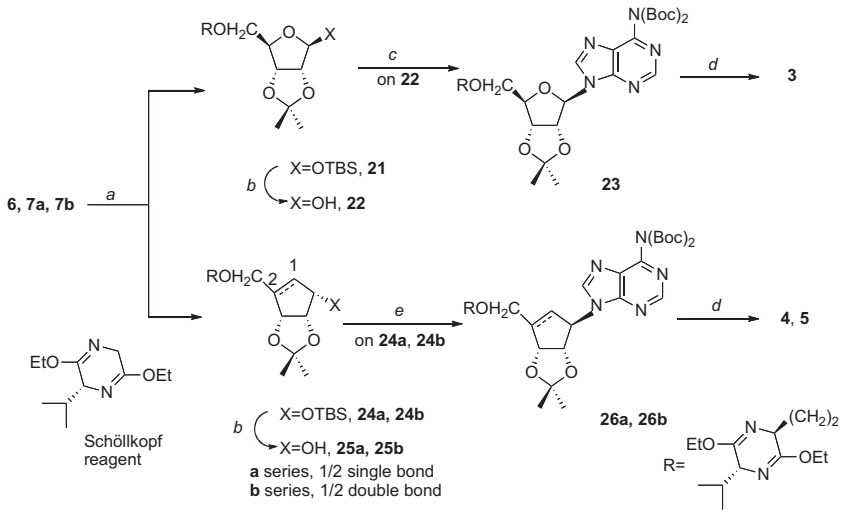
Similarly, **7a** and **7b** were converted to **4** and **5** (Scheme 3) through **24**–**26**.

3. Experimental section

3.1. General

^1H and ^{13}C 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 ^{13}C NMR) homogeneous materials.

*3.1.1. ((3aR,4R,6R,6aR)-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



Scheme 3. Reagents and conditions: a, Schöllkopf reagent, *n*-BuLi, 68% for **21**, 89% for **24a**, 81% for **24b**; b, TBAF, 60% for **22**, 60% for **25a**, 90% for **25b**, c, (i) HMPT, CCl_4, (ii) NaH, $Ad(Boc)_2$, 25% for two steps; d, (i) TFA/H_2O; (ii) K_2CO_3, yields for two steps, 61% for **3**, 46% for **4**, 71% for **5**; e, Ph_3P, DIAD, $Ad(Boc)_2$, 57% for **26a**, 73% for **26b**.

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 H_2O and EtOAc. The aqueous phase was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), 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%). ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{22}O_6$: 310.1416; found: 310.1409.

*3.1.2. (3aR,4R,6R,6aR)-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 H_2O (10 mL) to quench the reaction. The mixture was extracted with Et_2O (3×100 mL). The combined organic layers were washed with H_2O (3×20 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 **10** as a colorless oil (8.97 g, 79.5%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{19}H_{26}O_6$ (M−CH_3): 335.1495; found: 335.1499.

*3.1.3. 2-(((3aR,4R,6R,6aR)-6-(4-Methoxybenzyloxy)-2,2-dimethyl-tetrahydrofuro[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 H_2O, 31.2 mmol) was added followed by OsO_4 (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 CH_2Cl_2/H_2O (1:1, 30 mL) and $NaIO_4$ (6.40 g, 30.0 mmol) added at room temperature. The mixture was stirred 3 h. The organic layer was diluted with CH_2Cl_2 (100 mL), separated, washed with H_2O (20 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in MeOH (30 mL) at 0 °C and $NaBH_4$ (1.80 g, 48.6 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 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%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{18}H_{26}O_7$ (M−CH_3): 339.1444; found: 339.1444.

*3.1.4. 2-(((3aR,4R,6R,6aR)-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 CH_2Cl_2 (100 mL) and this mixture stirred at room temperature for 30 min. Water (10 mL) was added and the organic layer separated, washed with brine (20 mL), dried (Na_2SO_4), 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%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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, 69.0, 68.9, 55.5, 26.6, 25.1, 21.8. Calcd HRMS for $C_{25}H_{32}O_9S$: 508.1767; found: 508.1774.

*3.1.5. 2-(((3aR,4R,6R,6aR)-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 CH_2Cl_2/H_2O (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 CH_2Cl_2 (100 mL) and washed with saturated $NaHCO_3$ solution (3×30 mL). The organic layer was dried (Na_2SO_4), 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%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{17}H_{24}O_8S$ (M+NH_4): 406.1537; found: 406.1536.

*3.1.6. 2-(((3aR,4R,6S,6aR)-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 CH_2Cl_2 (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 (Na_2SO_4), 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%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{23}H_{38}O_8SSi$ (M+NH_4): 520.2406; found: 520.2400.

*3.1.7. tert-Butyl((3aR,4S,6R,6aR)-2,2-dimethyl-6-vinyl-tetrahydro-3aH-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 $CuBr\cdot SMe_2$ (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 were 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 NH_4Cl solution (30 mL) was then added to quench the reaction. The mixture was extracted with Et_2O (3×100 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in MeOH (100 mL) and $CeCl_3\cdot 7H_2O$ (7.4 g, 20 mmol) added at 0 °C. This was followed by the portionwise addition of $NaBH_4$ (0.74 g, 20 mmol). The resulting mixture was stirred at this temperature for 1 h. Saturated NH_4Cl solution (20 mL) was added to quench the reaction. The mixture was filtered through Celite and the filtrate concentrated. The residue was extracted with Et_2O (3×100 mL) and the combined organic phases dried (Na_2SO_4), and filtered through a short silica gel column (10 cm). The filtrate was concentrated and the residue dissolved in CH_2Cl_2 (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 for 3 h and H_2O (10 mL) was added to quench the reaction. The organic layer was separated, washed with H_2O (20 mL), dried (Na_2SO_4), 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 three steps). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{16}H_{30}O_3Si$ (M+H): 299.2042; found: 299.2043.

*3.1.8. ((3aR,4R,6S,6aR)-6-(tert-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3aH-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 H_2O, 16 mmol) followed by OsO_4 (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 CH_2Cl_2/H_2O (1:1, 30 mL) and $NaIO_4$ (2.1 g, 9.9 mmol) then added at room temperature. The mixture was stirred 3 h. The organic layer was diluted with CH_2Cl_2 (90 mL), separated, washed with H_2O (20 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in MeOH (30 mL) at 0 °C and to this $NaBH_4$ (0.30 g, 6.4 mmol) was added, portionwise. This 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 **16a** as a colorless oil (2.1 g, 84%). The NMR spectrum was consistent with the literature.[11]

*3.1.9. ((3aR,6S,6aR)-6-(tert-Butyldimethylsilyloxy)-2,2-dimethyl-6,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)methanol (**16b**).* Compound **17**[12,13] (0.85 g, 2.8 mmol) was dissolved in CH_2Cl_2 (30 mL) and to this were 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 (Na_2SO_4), and filtered through a short silica gel column. The filtrate was concentrated under reduced pressure (H_2O 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 NH_4Cl 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 (Na_2SO_4), 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%). ^{1}H NMR ($CDCl_3$, 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 $C_{15}H_{28}O_4Si$ (M+H): 301.1835; found: 301.1825.

*3.1.10. ((3aR,4S,6R,6aR)-6-(Allyloxymethyl)-2,2-dimethyl-tetrahydro-3aH-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 (3×100 mL). The combined organic phases were washed with H_2O (3×20 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%). ^{1}H 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 $C_{18}H_{34}O_4Si$ (M+H): 343.2305; found: 343.2312.

*3.1.11. ((3aR,4S,6aR)-6-(Allyloxymethyl)-2,2-dimethyl-4,6a-dihydro-3aH-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 a colorless oil (0.48 g, 85%). ^{1}H 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.

*3.1.12. 2-(((3aR,4R,6S,6aR)-6-(tert-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3aH-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 $Na_2S_2O_3$ (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 MeOH/H_2O (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 °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%). ^{1}H 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 $C_{17}H_{34}O_5Si$ (M+H): 347.2254; found: 347.2249.

*3.1.13. 2-(((3aR,6S,6aR)-6-(tert-Butyldimethylsilyloxy)-2,2-dimethyl-6,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-yl)methoxy)ethanol (**20b**).* Compound **19b** (0.35 g, 1.0 mmol) was dissolved in *t*-BuOH/H_2O (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 (Na_2SO_4), and concentrated. The residue was dissolved in MeOH/H_2O (1:1, 10 mL) and then $NaIO_4$ (0.26 g, 1.2 mmol) was added. The mixture was stirred at room temperature for 3 h followed by the portionwise addition of $NaBH_4$ (0.24 g, 5.1 mmol). The mixture was stirred at room temperature for 30 min. Saturated NH_4Cl 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 (Na_2SO_4), and concentrated. The residue was purified by a silica gel column chromatography (hexanes/EtOAc=2:1) to produce **20b** as a colorless oil (0.34 g, 96%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{17}H_{32}O_5Si$ (M+H): 345.2097; found: 345.2095.

*3.1.14. 2-(((3aR,4R,6S,6aR)-6-(tert-Butyldimethylsilyloxy)-2,2-dimethyl-tetrahydro-3aH-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 CH_2Cl_2 (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 (Na_2SO_4), 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%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{24}H_{40}O_7SSi$ (M+H): 501.2342; found: 501.2338.

*3.1.15. 2-(((3aR,6S,6aR)-6-(tert-Butyldimethylsilyloxy)-2,2-dimethyl-6,6a-dihydro-3aH-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%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{24}H_{38}O_7SSi$ (M−CH_3): 483.1873; found: 483.1865.

*3.1.16. (2S,5R)-2-(2-(((3aR,4R,6S,6aR)-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 Et_2O (3×50 mL) and the combined organic layers washed with brine (30 mL), dried (Na_2SO_4), 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. ^{1}H NMR ($CDCl_3$, 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 $C_{27}H_{50}N_2O_7Si$: 542.3387; found: 542.3379.

*3.1.17. (3aR,4R,6R,6aR)-6-((2-((2S,5R)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)ethoxy)methyl)-2,2-dimethyl-tetrahydrofuro [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, 1 M 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%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{21}H_{36}N_2O_7$: 428.2523; found: 428.2518.

3.1.18. 9-((3aR,4R,6R,6aR)-6-((2-((2S,5R)-3,6-Diethoxy-5-isopropyl-2,5-dihydropyrazin-2-yl)ethoxy)methyl)-2,2-dimethyl-

*tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-9H-6-bis(tert-butoxylcarboxyl)aminopurine (**23**).* Compound **22** (0.61 g, 1.4 mmol) was dissolved in THF (10 mL) and then CCl_4 (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 (Na_2SO_4), 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%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{36}H_{55}N_7O_{10}$: 745.4010; found: 745.3993.

*3.1.19. (S)-2-Amino-4-(((2R,3S,4R,5R)-5-(6-amino-9H-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/H_2O (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/H_2O (2:1, 2 mL) and K_2CO_3 (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/NH_4OH (29.6%)=1:1:1) to give **3** as a white foam (0.03 g, 61%). Mp >210 °C (decomposed). ^{1}H NMR (D_2O, 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). ^{13}C NMR (D_2O, 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 $C_{14}H_{20}N_6O_6$ (M+H): 369.1522; found: 369.1525.

*3.1.20. (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 an orange oil (0.50 g, 89%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{28}H_{52}N_2O_6Si$: 540.3595; found: 540.3584.

*3.1.21. (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%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{28}H_{50}N_2O_6Si$ (M+H): 539.3516; found: 539.3506.

*3.1.22. (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, 1 M 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 an orange oil (0.16 g, 43%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{22}H_{38}N_2O_6$: 426.2730; found: 426.2733.

*3.1.23. (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) availed **25b** as a colorless oil (0.14 g, 90%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{22}H_{36}N_2O_6$ (M+H): 425.2651; found: 425.2661.

*3.1.24. 9-((3aS,4R,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-yl)-9H-purin-6-di(tert-butoxylcarbonyl)amine (**26a**).* Compound **25a** (0.14 g, 0.33 mmol) was dissolved in THF and to this were added Ph_3P (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%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{37}H_{57}N_7O_9$: 743.4218; found: 743.4208.

*3.1.25. 9-((3aS,4R,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-yl)-9H-purin-6-bis(tert-butoxylcarbonyl)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%). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{37}H_{55}N_7O_9$ (M+H): 742.4139; found: 742.4133.

*3.1.26. (S)-2-Amino-4-(((1R,2R,3S,4R)-4-(6-amino-9H-purin-9-yl)-2,3-dihydroxycyclopentyl)methoxy)butanoic acid (**4**).* The protected material **26a** (0.13 g, 0.17 mmol) was treated with TFA/H_2O (3:1, 3 mL) at room temperature overnight. The solvent was removed under reduced pressure. The residue was dissolved in MeOH/H_2O (3:1, 10 mL), K_2CO_3 (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/NH_4OH) (29.6%)=1:1:1] to give **4** as a white foam (30 mg, 46%). Mp >200 °C (decomposed). ^{1}H NMR (D_2O/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); ^{13}C NMR (D_2O/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 $C_{15}H_{22}N_6O_5$ (M+H): 367.1730; found: 367.1740.

*3.1.27. (S)-2-Amino-4-(((3R,4S,5R)-3-(6-amino-9H-purin-9-yl)-4,5-dihydroxycyclopent-1-enyl)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). ^{1}H NMR (D_2O, 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); ^{13}C NMR (D_2O, 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 $C_{15}H_{20}N_6O_5$ (M+H): 365.1573; found: 365.1577.

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