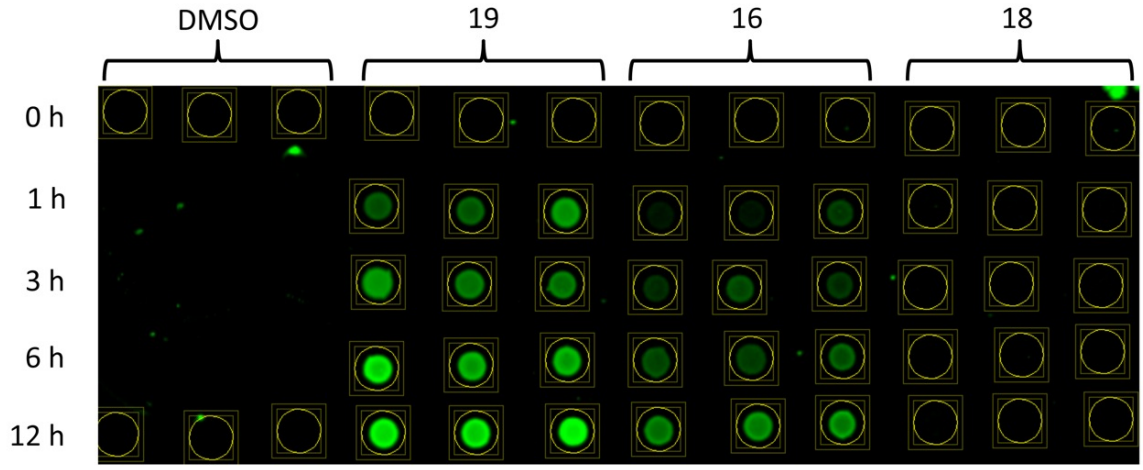
Table of Contents

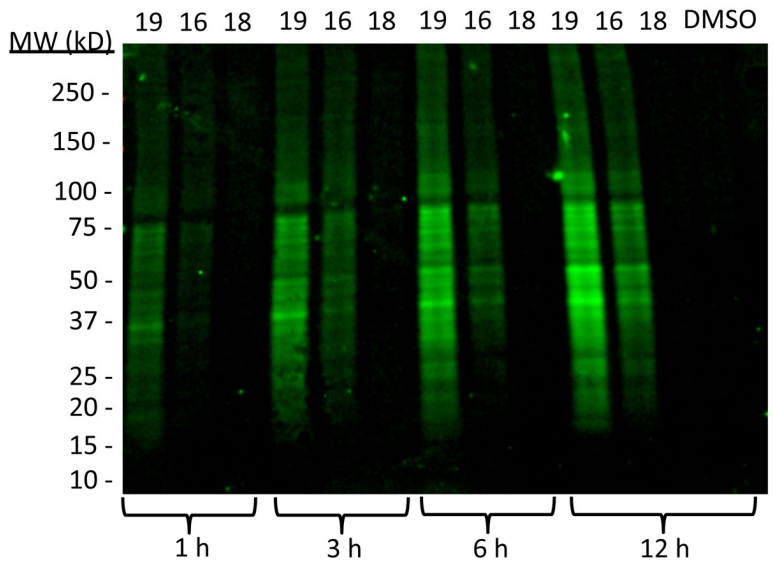
1) Supplementary Figures and Tables

Supplementary Table S1. In vitro solubility and stability data for **1**, **11** and **13**.

Compound	MW	Solubility pH 7.4	Stability $t_{1/2}$ (h) or % remaining at 120 min		
			human plasma	CD-1 mouse plasma	simulated gastric fluid
1	392.53	104 μM	91%	100%	8 h
11	507.62	>200 μM	90%	2 h	18 h
13	351.44	>200 μM	83%	86%	2 h



Supplementary Figure S1 α-Puromycin dot blot from parasite lysates treated with **16**, **18**, or **19** for 0, 1, 3, 6, or 12 h in triplicate. Lysates were standardized for total protein content using the Thermo Scientific Pierce BCA Protein Assay (BCA); 1 μg of total protein was spotted per sample. A time dependent increase in fluorescence signal was observed for free puromycin (**19**) and the trioxolane-puromycin conjugate **16**. The non-peroxidic dioxolane-puromycin control **18** showed negligible fluorescence signal at all time points, as expected. Quantification of the dot blot signal intensity data is presented in Figure 3 of the main text.



Supplementary Figure S2. α-Puromycin western blot of parasite lysates treated with **16**, **18**, or **19** for 1, 3, 6, or 12 h. Lysates were standardized for total protein content using BCA and 9 μg of total protein was loaded per sample. Puromycin incorporation was observed across a broad range of proteins consistent with its mechanism of action and previous reports (Ueki et al. 2013). A time dependent increase in fluorescence signal was observed for free puromycin (**19**) and the trioxolane-puromycin conjugate **16**. Dioxolane-puromycin control **18** showed negligible fluorescence signal at all time points, as expected.

Experimental Procedures

2) General Procedures and Materials

^{1}H NMR spectra were recorded on a Varian INOVA-400 400 MHz spectrometer. Chemical shifts are reported in δ units (ppm). NMR spectra were referenced relative to residual NMR solvent peaks. Coupling constants (*J*) are reported in hertz (Hz). Unless otherwise noted all chemical reagents and solvents used were purchased from Sigma-Aldrich. Dichloromethane was purchased from Fisher Scientific. Alcohol **10** was prepared as described previously (Mahajan et. al. *ChemMedChem* **2011**, *6*, 415-419). 3-Hydroxycyclohexan-1-one was synthesized as described previously (Karmee, S. K. et al *Tetrahedron: Asymm.* **2011,** *22,* 1736-1739). *O*-Methyl 2-adamantanone oxime was prepared as described (U.S. Pat. Appl., 20040186168, 23 September 2004). Air and/or moisture sensitive reactions were carried out under an argon atmosphere in oven-dried glassware using anhydrous solvents from commercial suppliers. Air and/or moisture sensitive reagents were transferred via syringe or cannula

and were introduced into reaction vessels through rubber septa. Solvent removal was accomplished with a rotary evaporator at ca. 10-50 Torr. Column chromatography was carried out using a Biotage SP1 flash chromatography system and silica gel cartridges from Biotage. Analytical TLC plates from EM Science (Silica Gel 60 F254) were employed for TLC analyses. LC/MS data were acquired on a Waters Micromass ZQTM mass spectrometer equipped with Waters 2795 Separation Module and Waters 2996 Photodiode Array Detector. Separations were carried out with an XTerra® MS C18, 5μm, 4.6 x 50 mm column, at ambient temperature (unregulated) using a mobile phase of water-methanol containing a constant 0.10 % formic acid.

DMEM/FBS: Dulbecco's Modified Eagle Medium (DMEM) purchased from HyClone was supplemented with 10% fetal bovine serum (FBS, Gibco), Penicillin/Streptomycin (1x final concentration, Gemini Bio-Products), Sodium Pyruvate (1mM, HyClone), and non-essential amino acids (UCSF Cell Culture Facility).

All Western Blot and Dot Blot images were analyzed with Licor Image Studio Software to determine signal intensity. Graphing and analysis of data was done using GraphPad Prism 6 Software.

3) In vitro Fragmentation Studies

Solutions of trioxolane conjugate **12** or **14** (0.6 mM) in 1 mL of 1:1 water-acetonitrile (or DMEM/FBS with 10% DMSO) were treated with 1 mL of $FeBr_2$ (60 mM) in deionized H_2O (or DMEM) and stirred at 37 °C. Aliquots were taken at various time points and analyzed by LC/MS. The chromatography method involved gradient elution from 0-95% MeOH in water (constant 0.1% formic acid) over 15 min. The trioxolane fragmentation reactions were followed by observing the decreasing absorbance (λ = 240 nM) of the peaks corresponding to the parent compounds **12** and **14.** The subsequent β-elimination processes were followed by observing the increasing absorbance (λ = 240 nM) of the peak corresponding to liberated 2,5-dichloroanaline (Scheme 1). These signals were integrated at various time points using Mass Lynx software. GraphPad Prism Software was used to fit the data to one-phase exponential decay and one-phase exponential association equations for the trioxolane fragmentation and β-elimination reactions respectively.

4) *Plasmodium falciparum* EC_{50} determinations

The growth inhibition assay for *P. falciparum* was conducted as described previously (Sijwali et al. PNAS, **2004**, *101*, 8721) with minor modifications. Briefly, *Plasmodium falciparum* strain W2 synchronized ring-stage parasites were cultured in human red blood cells in 96-well flat bottom culture plates at 37 ºC, adjusted to 1% parasitemia and 2% hematocrit under an atmosphere of 3% O_2, 5% CO_2, 91% N_2 in a final volume of 0.1 mL per well in RPMI-1640 media supplemented with 0.5% Albumax, 2 mM L-glutamine and 100 μM hypoxanthine in the presence of various concentrations of inhibitors. Tested compounds were serially diluted 1:3 in the range 10,000 – 4.6 nM (or 1,000-0.006 nM for more potent analogs), with a maximum DMSO concentration of 0.1%. Following 48 hours of incubation, the cells were fixed by adding 0.1 ml of 2% formaldehyde in phosphate buffered saline, pH = 7.4 (PBS). Parasite growth was evaluated by flow cytometry on a FACsort (Becton Dickinson) equipped with AMS-1 loader (Cytek Development) after staining with 1 nM of the DNA dye YOYO-1 (Molecular Probes) in 100 mM NH_4Cl, 0.1% Triton x-100 in 0.8% NaCl. Parasitemias were determined from dot plots (forward scatter vs. fluorescence) using CELLQUEST software (Becton Dickinson). EC_{50} values for growth inhibition were determined from plots of percentage control parasitemia over inhibitor concentration using GraphPad Prism software.

5) Puromycin incorporation studies

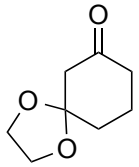
Plasmodium falciparum strain W2 synchronized trophozoites at 2% hematocrit, grown under 3% O_2, 6% CO_2, 91% N_2 in medium RPMI-1640 supplemented with 0.5% Albumax, 2 mM L-glutamine and 100 μM hypoxanthine, were incubated for 1, 3, 6 and 12 hours with 400 nM tested compounds in triplicate and maximum DMSO concentration of 0.04%. Cells were centrifuged (3000xG/ 5 min), supernatant removed and the red blood cells were lysed with 0.01% saponin in PBS. Released parasites were centrifuged (3000xG/ 5 min), washed in PBS and the pellet frozen at -80^{o}C. Samples were thawed in RIPA lysis buffer supplemented with sigma protease inhibitor cocktail (P8340, 1:100) and standardized for total protein concentration via BCA then diluted to a concentration of 1000ng/μL of total protein in lysis buffer.

Dot blot procedure: 1μL of each standardized lysate was spotted on Immobilon PVDF membrane, blocked with 5% non-fat milk in tris-buffered saline with 0.1% Tween-20 (TBS-T) for 1 h at rt, and then incubated for 16 h with 1:2000 α-puromycin in 2.5% non-fat milk in TBS-T at 4 °C. The blot was washed 3

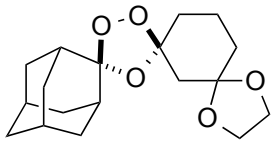
times with TBS-T for 5 min and once with phosphate-buffered saline with 0.1% Tween-20 (PBS-T) then incubated at rt for 1 h with 1:10,000 Li-cor IRDye Goat anti-Mouse 2° antibody (926-32210) in Odyssey blocking buffer (#927-40000) + 0.2% Tween-20 and 0.01% sodium dodecyl sulfate (SDS). The blot was washed 3 times with PBS-T for 5 min and once with PBS then imaged for fluorescent signal on an Odessey Classic Infrared Imaging System.

Western blot procedure**:** Lysates were denatured at 95°C for 10 min in 1x laemmli loading buffer with 0.05 M dithiothreitol (DTT) and 9 µg of total protein lysate per sample was loaded onto a 4–20% Mini-PROTEAN® TGX™ Gel and run for 40 min at 185 V. The blots were transferred to Immobilon PVDF membrane at 35 V for 1 h and then blocked, stained and imaged as in the dot blot experiments.

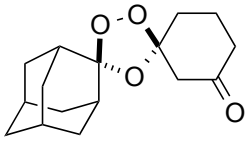
6) Synthetic Procedures



Synthesis of 1,4-dioxaspiro[4.5]decan-7-one (6). A 250-mL, 2-necked flask equipped with a stirbar, glass stopper, and a Dean-Stark trap charged with 4 Å molecular sieves and topped with a reflux condenser and argon inlet adapter was charged with 1,3-cycohexadione (10 g, 89 mmol, 1 equiv) and 100 mL of anhydrous acetonitrile. The mixture was brought to reflux. Ethylene glycol (4.49 mL, 80.3 mmol, 0.9 equiv) and camphor sulfonic acid (1.0 g, 4.46 mmol, 0.05 equiv) were added in single portions sequentially. The reaction mixture was refluxed for 18 h (draining the dean stark trap occasionally) and allowed to cool to rt. Sodium bicarbonate (ca. 5 g) was added as a solid and the reaction mixture was stirred vigorously at rt for 15 min and concentrated to afford a reddish orange residue. The resulting residue was suspended in 200 mL of EtOAc and 50 mL satd aq $NaHCO_3$ solution. The organic phase was washed with 3, 30-mL portions of satd aq $NaHCO_3$ solution, washed with 40 mL of satd aq NaCl solution, dried over Na_2SO_4 with stirring, filtered, and concentrated to afford an orange oil. Purification via column chromatograhpy on 120 g of silica gel (elution with 0-25% EtOAc/Hex) afforded 4.43 g of **6** as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz); δ 3.90 - 4.02 (m, 4H), 2.59 (s, 2H), 2.33 (t, *J* = 6.23 Hz, 2H), 1.82 - 1.95 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.7, 110.2, 64.9, 51.9, 40.5, 34.4, 20.4; LRMS (ESI) *m/z* $[2M+78]^+$ calcd for $C_8H_{12}O_3$:390.2; found: 390.2 (2M+DMSO).

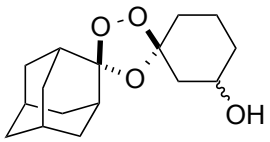


Synthesis of trispiro[adamantane-2,2'-[1,3,5]trioxolane-4',1''-cyclohexane-3'',2'''-[1,3]dioxolane] (7). A 200-mL recover flask equipped with a stirbar was charged with ketone **6** (1.0 g, 6.4 mmol, 1 equiv), carbon tetrachloride (100 mL), and *O*-methyl 2-adamantaone oxime (2.3 g, 13 mmol, 2 equiv). The reaction mixture was cooled at 0 °C while ozone was bubbled through the solution (0.6 L/min, 30% power) for 1.5 h. Additional oxime (0.500 g, 2.78 mmol, 0.4 equiv) was added and the bubbling of ozone was continued at 0 °C for an additional 1 h. After 2.5 h total reaction time, the reaction mixture was sparged with oxygen for 5 min at 0 °C and sparged with argon for 5 min while warming to rt. The mixture was then concentrated to afford a colorless oil. Purification via column chromatography on 120 g of silica gel (elution with 5% EtOAc/hexanes) afforded 2.01 g (97%) of trioxolane **7** as a colorless oil: IR (neat): 2914, 2858, 1471, 1452, 1420, 1382, 1361, 1342, 1314, 1221, 1180, 1116, 1086, 1066, 1044, 1022, 968, 946, 918, 817, 817 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 3.99 - 4.06 (m, 1 H), 3.89 - 3.97 (m, 3 H), 1.45 - 2.11 (m, 22 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 111.4, 109.1, 108.9, 64.9, 64.5, 43.2, 37.0, 36.54, 36.52, 35.3, 35.1, 34.9, 34.7, 34.3, 34.2, 27.1, 26.7, 19.8; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{26}O_5$:323.1853; found: 323.1853.

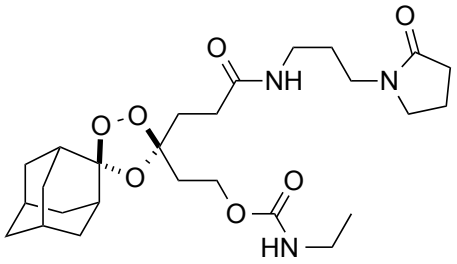


Synthesis of dispiro[adamantane-2,2'-[1,3,5]trioxolane-4',1''-cyclohexane]-3''-one (8). A 200-mL recovery flask equipped with a stirbar was charged with the acetal **7** (2.01 g, 6.24 mmol, 1 equiv), CH_2Cl_2 (100 mL) and acetone (20 mL). The mixture was cooled at 0 °C and powdered iron trichloride hexahydrate (5.1 g, 19 mmol, 3 equiv) was added in a single portion. The reaction mixture was allowed to warm to rt over 10 min, and was stirred at rt for 1.5 h. The reaction mixture was diluted with 200 mL of EtOAc and 100 mL H_2O. The aqueous phase was separated and extracted with three 40-mL portions of EtOAc. The combined organic phases were washed with 50 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil. This material was dissolved in 25 mL of CH_2Cl_2

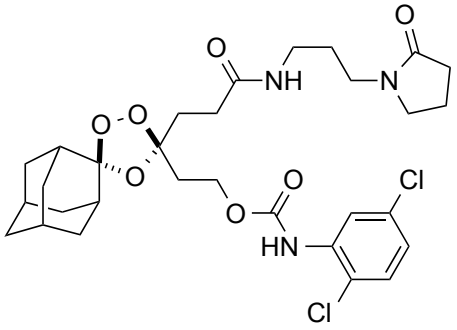
and deposited onto 10 g of silica gel. The resulting free flowing powder was transferred to the top of a 120 g column of silica gel. Gradient elution (0-20% EtOAc/hexanes) afforded 1.66 g (96%) of ketone **8** as a colorless oil: IR (neat): 2914, 2858, 2360, 1721, 1471, 1453, 1421, 1383, 1351, 1315, 1296, 1253, 1217, 1111, 1086, 1068, 1042, 1018, 933 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.70 (s, 2 H), 2.33 (t, *J* = 6.8 Hz, 2 H), 2.07 - 1.99 (m, 2 H), 1.99 - 1.63 (m, 18 H); 13C NMR ($CDCl_3$, 100 MHz) 206.4, 112.8, 109.4, 50.9, 40.3, 36.8, 36.4, 36.3, 34.91, 34.86, 34.8, 33.6, 26.9, 26.5, 20.0; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{22}O_4$: 279.1591; found: 279.1593



Synthesis of dispiro[adamantane-2,2'-[1,3,5]trioxolane-4',1''-cyclohexane]-3''-ol (9). A 50-mL, two-necked, recovery flask equipped with a stirbar, argon inlet adapter, and rubber septum was charged with a solution of ketone **8** (0.236 g, 0.8 mmol, 1.0 equiv.) in tetrahydrofuran (4.5 mL). The solution was cooled at -78 °C while a solution of sodium borohydride (0.030 g, 0.8 mmol, 0.9 equiv) in ethanol (9.5 mL; with 0.05 mL of 1 M aq NaOH) was added dropwise via syringe at a rate such that the internal temperature did not exceed -65 °C. The reaction mixture was stirred at -78 °C for 2 h and allowed to warm slowly to 0 °C over 3 h. The reaction was diluted with 10 mL of EtOAc, allowed to warm to rt, and further diluted with 20 mL of EtOAc and 20 mL H_2O. The aqueous layer was separated and extracted with three 20-mL portions of EtOAc. The combined organic phases were washed with 20 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a white semi solid. Purification via column chromatography on 40 g of silica gel (elution with 20% EtOAc/hexanes) afforded 0.173 g (67%) of alcohol **9** (59:41 mixture of diastereomers)[1] as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.97 (s, 1 H), 1.52-2.11 (m, 22 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 112.0, 109.3, 109.2, 68.5, 68.2, 42.8, 41.9, 37.0, 36.9, 36.6, 36.5, 36.4, 35.2, 35.11, 35.07, 35.04, 34.97, 34.96, 34.1, 34.0, 33.7, 33.3, 27.1, 26.7, 26.6, 19.6, 19.3.

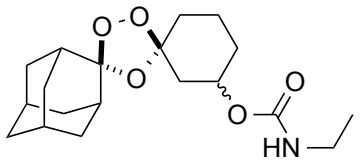


Synthesis of 2-[3-[3-oxo-3-[3-(2-oxopyrrolidin-1-yl)propylamino]propyl]spiro[1,2,4-trioxolane-5,2'-adamantane]-3-yl]ethyl N-ethylcarbamate (11). A 20-mL scintillation vial equipped with a stirbar and screw cap was charged alcohol **10** (0.084 g, 0.2 mmol, 1.0 equiv.), pyridine (0.023 ml, 0.3 mmol, 1.5 equiv.), toluene (1 mL), and ethyl isocyanate (0.076 ml, 1.0 mmol, 5.0 equiv.). The resulting mixture was stirred at 50 °C for 42 h and then diluted with 50 mL of CH_2Cl_2 and 20 mL of H_2O. The aqueous layer was separated and extracted with three 20-mL portions of CH_2Cl_2. The combined organic phases were washed with 30 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a colorless oil. Purification via column chromatography on 12 g of silica gel (elution with 7% MeOH/CH_2Cl_2) and purification of mixed fractions on 12 g of silica gel (elution with 5% MeOH/EtOAc) afforded 0.069 g (71%) of carbamate **11** as a viscous, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (br s, 1 H), 5.64 (br s, 1 H), 4.18 (t, *J* = 5.6 Hz, 2 H), 3.32-3.41 (m, 4 H), 3.15-3.19 (m, 4 H), 2.41 (t, *J* = 8.0 Hz, 2 H), 2.33 (t, *J* = 8.0 Hz, 2 H), 1.66-2.23 (m, 22 H), 1.11 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 172.5, 156.6, 112.3, 109.8, 60.5, 47.5, 39.6, 36.8, 36.5, 36.3, 35.9, 35.6, 35.5, 35.2, 35.0, 34.9, 34.7, 31.8, 31.4, 31.1, 26.9, 26.6, 26.5, 18.1, 15.5; LRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{41}N_3O_7$: 508.3; found: 508.3.



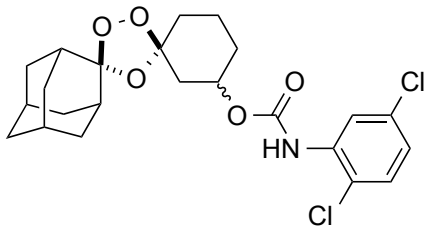
Synthesis of 2-[3-[3-oxo-3-[3-(2-oxopyrrolidin-1-yl)propylamino]propyl]spiro[1,2,4-trioxolane-5,2'-adamantane]-3-yl]ethyl N-(2,5-dichlorophenyl)carbamate (12)

A 20-mL scintillation vial was charged with alcohol **10** (0.030 g, 0.1 mmol, 1.0 equiv.) and toluene (1.000 ml). Pyridine (0.011 ml, 0.1 mmol, 2.0 equiv.) was added via microliter pipettor and 2,5-dichlorophenyl isocyanate (0.070 g, 0.4 mmol, 5.4 equiv.) was added as a solid in a single portion. The reaction mixture was stirred at rt for 24 h. The reaction mixture was filtered through a pad of Celite with the aid of 40 mL Et_2O, 20 mL CH_2Cl_2 , and 20 mL H_2O. The aqueous layer was separated and extracted with three, 20 mL portions of Et_2O. The combined organic phases were washed with 30 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a white solid which was further purified via column chromatography (12 g SiO_2, loaded as suspension in CH_2Cl_2) eluting with 5% MeOH/CH_2Cl_2 to afford the desired product which was further purified via column chromatography (25 g SiO_2) eluting with 5% MeOH/CH_2Cl_2 to afford 27 mg (63%) of carbamate **12** as a complex mixture of diastereomers. For the mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 1.83 Hz, 1H), 7.49 (br. s., 1H), 6.98 (ddd, *J* = 1.28, 2.47, 8.52 Hz, 1H), 6.81 (t, *J* = 5.59 Hz, 1H), 4.34 (t, *J* = 6.59 Hz, 2H), 3.31 - 3.44 (m, 4H), 3.15 - 3.24 (m, 2H), 2.33 - 2.43 (m, 4H), 2.12 - 2.29 (m, 4H), 1.63 - 2.10 (m, 18H), 1.25 (br. s., 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 172.2, 153.1, 136.0, 133.6, 129.9, 124.0, 120.9, 120.8, 117.4, 112.6, 109.6, 61.7, 47.5, 39.6, 36.8, 36.6, 36.4, 35.6, 35.2, 35.2, 35.0, 34.9, 34.8, 31.6, 31.2, 31.1, 29.9, 26.9, 26.6, 26.6, 18.1, 9.5 LRMS (ESI) m/z $[M+H]^+$ calcd for $C_{30}H_{39}Cl_2N_3O_7$: 624.2; found 624.2.

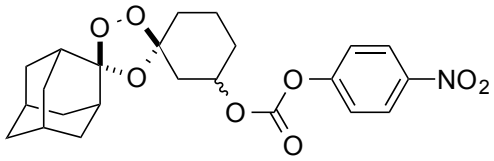


Synthesis of dispiro[adamantane-2,2'-[1,3,5]trioxolane-4',1''-cyclohexane]-3''-yl N-ethylcarbamate (13). A 20-mL, scintillation vial equipped with a stirbar and screw cap was charged with alcohol **9**, toluene (1 mL), and pyridine (50 µL, 0.62 mmol, 1.5 equiv). Ethyl isocyanate (70 µL, 0.83 mmol, 2.1 equiv) was added via syringe and the resulting mixture was stirred at rt for 17 h. Additional ethyl isocyanate (0.100 mL, 1.26 mmol, 3 equiv) was added and the resulting mixture was heated at 50 °C for 72 h. After 89 h total reaction time, the reaction mixture was diluted with 20 mL of CH_2Cl_2 and 20 mL of H_2O. The aqueous layer was separated and extracted with three 20-mL portions of CH_2Cl_2. The combined organic phases were washed with 30 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a pale yellow oil. Purification via column chromatography on 25 g of silica gel (gradient elution with 20-25% EtOAc/hexanes) afforded 0.107 g (74%) of carbamate **13** as a colorless

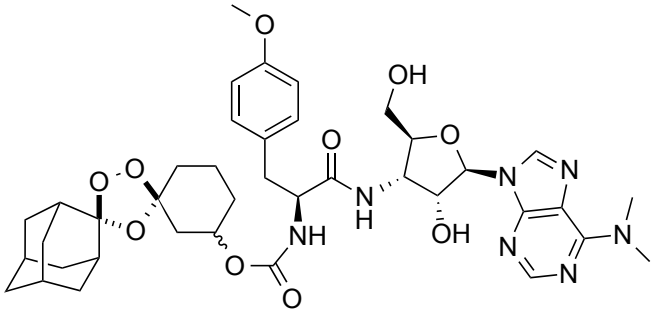
oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83-4.89 (m, 1 H), 4.71 (m, 1 H), 4.64 (m, 1 H), 3.18-3.22 (m, 4 H), 2.15-2.24 (m, 2 H), 1.85-2.03 (m, 18 H), 1.44-1.81 (m, 22 H), 1.09-1.13 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 155.8, 111.9, 111.7, 108.9, 108.7, 71.0 70.8, 40.4, 40.2, 36.9, 36.5, 36.42, 36.37, 35.9, 35.01, 34.99, 34.9, 34.88, 34.86, 30.90, 30.86, 27.04, 27.00, 26.64, 26.61, 19.9, 19.8, 15.4; LRMS (ESI) *m/z* [2M+H]+ calcd for $C_{19}H_{29}NO_5$: 703.40; found: 703.3.



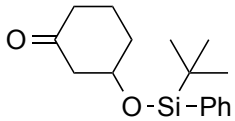
Synthesis of dispiro[adamantane-2,2'-[1,3,5]trioxolane-4',1''-cyclohexane]-3''-yl N-(2,5-dichlorophenyl)carbamate (14). A 20-mL, scintillation vial equipped with a screw cap and stirbar was charged with alcohol **9** (40:60 dr, 0.060 g, 0.210 mmol, 1.0 equiv), toluene (1 mL), pyridine (20 µL, 0.210 mmol, 1 equiv), and 2,5-dichlorophenyl isocyanate (0.080 g, 0.430 mmol, 2 equiv). The reaction mixture was stirred at rt for 18 h. The resulting cloudy reaction mixture was filtered with the aid of 50 mL of EtOAc. The filtrate was washed with 20 mL of H_2O. The aqueous layer was extracted with three 20-mL portions of EtOAc. The combined organic phases were washed with 20 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to a yellow oil. Purification via column chromatography on 50 g of silica gel (elution with 7% EtOAc/hexanes) afforded 0.077 g (79% yield) of **14** as a colorless oil: ^{1}H NMR (400MHz, $CDCl_3$) δ 8.28 (m, 1 H), 7.28 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.11 (s, 1 H), 6.97 (ddd, *J* = 8.0, 2.4, 1.6 Hz, 1 H, one diastereomer), 7.09 (s, 1 H, one diastereomer), 4.98-5.05 (m, 1 H, one diastereomer), 4.86-4.92 (m, 1 H, one diastereomer), 2.26-2.34 (m, 2 H), 1.41-2.07 (m, 20 H); 152.4, 152.2, 135.87, 135.84, 133.8, 129.9, 128.8, 123.74, 123.69, 120.2, 119.9, 119.8, 112.20, 111.98, 108.7, 108.6, 72.8, 72.4, 40.2, 40.0, 36.96, 36.94, 36.6, 36.50, 36.45, 35.2, 35.1, 35.04, 35.00, 34.99, 34.96, 34.94, 33.99, 33.87, 30.8, 30.6, 27.07, 27.05, 26.67, 26.65, 19.88, 19.85; LRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{27}Cl_2NO_5$: 468.1; found: 468.6.



Synthesis of dispiro[adamantane-2,2'-[1,3,5]trioxolane-4',1''-cyclohexane]-3''-yl 4-nitrophenyl carbonate (15). A 50-mL heat-gun dried, two-necked, round-bottomed flask equipped with a stirbar, argon inlet adapter and rubber septum was charged with the alcohol **9** (0.500 g, 1.78 mmol, 1.0 equiv), dichloromethane (7 mL), N,N-diisopropylethylamine (0.932 mL, 5.35 mmol, 3.0 equiv), and 4-dimethylaminopyridine (0.218 g, 1.78 mmol, 1 equiv). The mixture was cooled to 0 °C while 4-nitrophenyl chloroformate (0.719 g, 3.57 mmol, 2 equiv) was added as a solid in two portions (some gas evolution observed). The reaction mixture was stirred at 0 °C for 15 min, allowed to warm to rt over 10 min, and stirred at rt for 10 min. The reaction mixture was diluted with 30 mL of Et_2O, washed with 10 mL of 5% aq $KHSO_4$ solution, washed with five 10-mL portions of satd aq $NaHCO_3$ solution, washed with 25 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a yellow/orange semi-solid. This material was dissolved in 25 mL of CH_2Cl_2 and deposited onto 5 g of silica gel. The free flowing powder was loaded atop a 80 g silica gel cartridge. Gradient elution (0-20% EtOAc/hexanes) afforded 0.747 g (94%) of carbonate **15** (as a 90:10 mixture of diastereomers) as pale yellow glassy oil: IR (neat) 2915, 2859, 1765, 1615, 1594, 1526, 1493, 1452, 1348, 1259, 1215, 1168, 1114, 1140, 1087, 1067, 1045, 1020, 980, 858, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 - 8.31 (m, 2 H), 7.36 - 7.41 (m, 2 H), 4.92 - 5.00 (m, 1 H, one diastereomer), 4.81 - 4.90 (m, 1 H, one diastereomer), 2.33 - 2.36 (m, 1 H, one diastereomer), 2.40 (ddt, *J*=12.9, 4.3, 1.9 Hz, 1 H, one diastereomer), 2.07 - 2.15 (m, 1 H), 1.64 - 2.03 (m, 18 H), 1.55 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 151.8, 145.5, 125.5, 121.9, 112.2, 108.5, 76.4, 39.8, 36.9, 36.6, 36.5, 35.1, 35.0, 34.9, 33.7, 30.3, 27.0, 26.6, 19.8; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{27}NO_8$: 445.1809; found 446.1789.



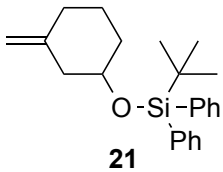
Synthesis of (4'R)-dispiro[adamantane-2,2'-[1,3,5]trioxolane-4',1''-cyclohexane]-3''-yl N-[(1S)-1-{[(2S,3S,4R,5R)-5-[6-(dimethylamino)-9H-purin-9-yl]-4-hydroxy-2-(hydroxymethyl)oxolan-3-yl]carbamoyl}-2-(4-methoxyphenyl)ethyl]carbamate (16). A 20 mL scintillation vial was charged with carbonate **15**, Puromycin dihydrochloride from Streptomyces alboniger (0.031 g, 0.1 mmol, 1.0 equiv.), and 4-dimethylaminopyridine (0.001 g, 0.0 mmol, 0.1 equiv.) and the atmosphere was replace with argon. This material was dissolved with N,N-dimethylformamide (2 ml) and N,N-diisopropylethylamine (0.108 ml, 0.6 mmol, 5.1 equiv.) was added to the resulting solution which was allowed to stir at rt under argon for 4 hours then diluted with 10mL of EtOAc and washed with three 15-mL portions of satd aq $NaHCO_3$ solution. The aqueous layer was back extracted with 20mL EtOAc and the organic layers were combined, washed with 20mL of satd aq NaCl solution, and then dried over MgSO4, filtered and concentrated to give a light yellow oil. Purification via column chromatography on 12g of silica gel (eluting with a 10-100% gradient of EtOAc/Hex) afforded a light yellow oil which was further purified by column chromatography on 12 g of silica gel (eluting with 5-10% MeOH/CH_2Cl_2) to afford 0.026 g (61%) of carbamate **16** as a white solid**.** ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (br. s, 1H), 8.30 - 8.33 (m, 1H), 8.19 (s, 1H), 7.16 (d, *J* = 8.61 Hz, 2H), 6.85 (d, *J* = 8.61 Hz, 3H), 5.92 (d, *J* = 2.75 Hz, 1H), 4.70 - 4.78 (m, 1H), 4.53 - 4.60 (m, 2H), 4.31 - 4.39 (m, 1H), 3.94 - 4.00 (m, 1H), 3.77 - 3.85 (m, 1H), 3.76 (s, 3H), 3.52 - 3.59 (m, 1H), 3.49 (br. s., 5H), 2.99 (td, *J* = 6.71, 13.51 Hz, 1H), 2.81 - 2.89 (m, 1H), 2.06 - 2.21 (m, 1H), 1.93 - 2.03 (m, 2H), 1.89 (d, *J* = 9.52 Hz, 4H), 1.63 - 1.82 (m, 12H), 1.53 - 1.62 (m, 2H), 1.25 - 1.47 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 173.2, 158.7, 156.3, 154.2, 150.9, 149.0, 138.0, 130.0, 128.8, 120.1, 113.5, 111.4, 111.2, 108.6, 108.4, 90.5, 83.4, 73.8, 73.7, 71.5, 71.2, 60.8, 56.6, 54.3, 50.6, 46.6, 46.3, 46.0, 39.7, 37.8, 37.3, 36.3, 34.3, 33.3, 33.2, 30.2, 29.4, 26.9, 26.5, 19.3; HRMS (ESI) *m/z* $[M+H]^+$ calcd $C_{39}H_{52}N_7O_{10}$: 778.3770; found: 778.3751.



20

Synthesis of 3-[(*tert*-butyldiphenylsilyl)oxy]cyclohexan-1-one (20). A 50-mL, recovery flask equipped with a stirbar, rubber septum, and argon inlet was charged with 3-hydroxycyclohexan-1-one (0.566 g, 5.0 mmol, 1.0 equiv.), N,N-dimethylformamide (18 mL), imidazole (0.675 g, 9.9 mmol, 2.0 equiv), and cooled to 0 °C. *t*-Butyl(chloro)diphenyl silane (1.547 mL, 6 mmol, 1.2 equiv) was added rapidly dropwise

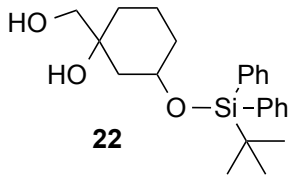
and the reaction mixture was allowed to warm to slowly warm to rt over ca 1 h and stir at rt overnight. The reaction mixture was diluted with 30 mL of EtOAc and 30 mL of H_2O. The aqueous layer was separated and extracted with three 20-mL portions of EtOAc. The combined organic phases were washed with 20 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to a pale yellow liquid. Purification via column chromatography on 120 g of silica gel (gradient elution with 0-5% EtOAc/hexanes) afforded 1.558 g (ca 90% purity) of **20** as a colorless oil which was carried forward to the next reaction without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 - 7.70 (m, 4H), 7.37 - 7.46 (m, 6H), 4.22 (quin, *J* = 4.90 Hz, 1H), 2.45 (d, *J* = 4.94 Hz, 2H), 2.33 - 2.41 (m, 1H), 2.22 - 2.31 (m, 1H), 2.09 - 2.21 (m, 1H), 1.76 - 1.82 (m, 2H), 1.61 - 1.71 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 135.9, 135.9, 134.0, 133.8, 130.0, 129.9, 127.8, 127.8, 71.2, 50.5, 41.3, 33.0, 27.1, 20.7, 19.3; LRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{28}OSi$: 353.2; found: 353.1.



21

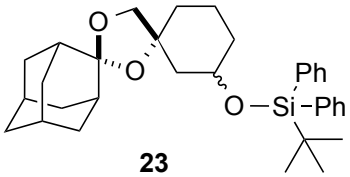
Synthesis of *tert*-butyl[(3-methylidenecyclohexyl)oxy]diphenylsilane (21). A 50-mL, 2-neck round-bottomed flask equipped with a stir bar, rubber septa, and an argon inlet was charged with methyltriphenylphosphonium iodide (0.987 g, 2.4 mmol, 1.2 equiv) and THF (20 mL) to give a light yellow, milky suspension. A solution of *n*-BuLi (1.42 M in THF) was added dropwise to this suspension until the starting material dissolved and a bright orange color persisted (ca. 1.2 mL, 3.0 mmol, 1.5 equiv). This solution was stirred at rt for 10 minutes at and then a solution of ketone **20** (0.715 mg, 2.0 mmol, 1.0 equiv) in THF (6 mL) was added dropwise to the reaction mixture. The reaction mixture was allowed to stir at rt for 90 min then diluted with CH_2Cl_2 (50mL) and washed with H_2O (50 mL). The aqueous layer was extracted twice with 25 mL portions of CH_2Cl_2 and the combined organic phases were washed with 25 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford an orange oil. Purification via column chromatography on 80 g of silica gel (elution with 10% EtOAc/hexanes) afforded 0.552 g (69% over two steps) of **21** as a white solid: ^{1}H NMR (400MHz, $CDCl_3$): δ 7.65 - 7.78 (m, 3 H), 7.30 - 7.49 (m, 5 H), 4.64 (d, *J* = 1.1 Hz, 1 H), 4.52 (d, *J*=1.1 Hz, 1 H), 3.75 (ddd, *J*=8.7, 5.0, 4.0 Hz, 1 H), 2.34 (dd, *J*=12.8, 4.2 Hz, 1 H), 2.05 - 2.19 (m, 2 H), 1.93 - 2.05 (m, 1 H), 1.71 - 1.84 (m, 2 H), 1.46 - 1.61 (m, 1 H), 1.12 - 1.33 (m, 2 H), 1.04 - 1.12 (m, 9 H); ^{13}C NMR (100MHz, $CDCl_3$): δ 146.9, 136.0, 136.0, 135.0,

134.9, 134.9, 134.1, 133.9, 129.7, 129.7, 129.0, 128.8, 127.7, 127.6, 109.1, 72.1, 44.5, 35.1, 34.5, 27.2, 24.1, 19.4.



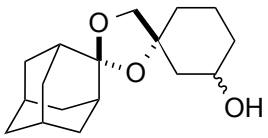
22

Synthesis of 3-[(tert-butyldiphenylsilyl)oxy]-1-(hydroxymethyl)cyclohexan-1-ol (22). A 50-mL, round-bottomed flask was charged with a solution of alkene **21** (0.552 g, 1.6 mmol, 1 equiv) in *tert*-butanol (10 mL) and H_2O (10mL). A solution of osmium tetroxide (2.5% w/v in tert-butanol, 0.124 mL, 0.2 mmol, 0.1 equiv) was then added followed by *N*-methylmorpholine oxide (0.366 g, 3.1 mmol, 2.0 equiv). This mixture was allowed to stir at rt for 27 hours then diluted with 40 mL of CH_2Cl_2 and washed with 20 mL of saturated $NaHCO_3$. The aqueous phase was extracted with three, 20-mL portions of EtOAc and the combined organic phases were washed with 20 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated. This material was deposited onto ca. 2 g of silica gel and the free flowing powder was loaded atop a 40 g silica gel cartridge. Elution (40% EtOAc/hexanes) yielded two separable sterioisomers of **22,** with a combined yield of 0.448 g (74%), which were isolated and characterized. Higher Rf isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 - 7.74 (m, 4H), 7.38 - 7.49 (m, 6H), 4.22 - 4.27 (m, 1H), 4.21 - 4.21 (m, 0H), 3.37 (dd, *J* = 11.00, 39.00 Hz, 2H), 2.04 - 2.18 (m, 2H), 1.68 - 1.75 (m, 1H), 1.57 - 1.65 (m, 1H), 1.45 - 1.54 (m, 1H), 1.39 (dd, *J* = 2.75, 14.28 Hz, 1H), 1.20 - 1.36 (m, 3H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.9, 135.9, 133.3, 133.1, 130.1, 130.1, 127.9, 127.8, 127.8, 72.7, 70.8, 70.1, 38.6, 33.9, 32.5, 27.1, 19.2, 15.9. Lower Rf isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 - 7.74 (m, 4H), 7.36 - 7.47 (m, 5H), 3.99 - 4.08 (m, 1H), 3.40 (dd, *J* = 7.14, 10.26 Hz, 2H), 2.27 (br. s., 2H), 1.73 - 1.84 (m, 2H), 1.54 - 1.62 (m, 1H), 1.43 - 1.52 (m, 2H), 1.20 - 1.43 (m, 3H), 1.09 (s, 8H); ^{13}C NMR (100 MHz, CHLOROFORM-d) δ 135.9, 134.8, 134.7, 129.7, 129.7, 127.7, 127.7, 127.7, 73.6, 71.0, 69.1, 43.0, 35.4, 33.2, 27.2, 19.4, 19.3; LRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{32}O_3Si$: 385.2; found: 385.2.



23

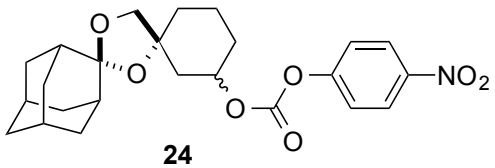
Tert-butyl({dispiro[adamantane-2,2'-[1,3]dioxolane-4',1''-cyclohexane]-3''-yloxy})diphenylsilane (23). A 100 mL round-bottomed flask equipped with a stir bar and rubber septa was charged with a solution of diol **22** (diastereomeric mixture, 0.448 g, 1.2 mmol, 1 equiv) in 10 mL of CH_2Cl_2. 2-adamantanone (0.426 g, 2.8 mmol, 2.4 equiv) and camphor sulfonic acid (0.0.075 g, 0.3 mmol, 0.3 equiv) were then added in bulk to this solution while stirring at rt. The reaction mixture was warmed to 30 °C for 17 h, allowed to cool to rt, and then diluted with ca. 20 mL of diethyl ether and washed with 20 mL of H_2O. The aqueous layer was extracted with three, 10-mL portions of CH_2Cl_2. The combined organic phases were washed with 20 mL of satd. aq. NaCl solution, dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil. Purification via column chromatography on 40 g of silica gel (elution with 5% EtOAc/hexanes) afforded 0.511 g (85-91%) of **23** as a mixture of sterioisomers: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 - 7.74 (m, 4H), 7.36 - 7.48 (m, 6H), 4.11 (tt, *J* = 4.00, 8.80 Hz, 1H, one diastereomer), 3.80 (d, *J* = 8.30 Hz, 1H, one diastereomer), 3.74 (d, *J* = 8.30 Hz, 1H, one diastereomer), 3.53 (d, *J* = 8.24 Hz, 1H, one diastereomer), 3.41 (tt, *J* = 4.30, 10.90 Hz, 1H, one diastereomer), 3.20 (dd, *J* = 1.01, 8.15 Hz, 1H, one diastereomer). 1.87 - 2.03 (m, 4H), 1.47 - 1.86 (m, 17H), 1.23 - 1.47 (m, 2H), 1.09 (d, *J* = 1.83 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 136.0, 136.0, 134.9, 134.7, 134.6, 134.6, 129.8, 129.8, 129.6, 127.8, 127.7, 127.7, 127.7, 111.7, 111.2, 80.9, 80.8, 74.3, 71.8, 70.8, 69.8, 47.0, 45.4, 38.6, 38.4, 38.0, 37.5, 37.5, 36.3, 36.1, 35.1, 35.1, 35.1, 35.1, 35.0, 34.8, 34.8, 34.6, 27.3, 27.2, 27.0, 21.1, 20.4, 19.4, 19.3; LRMS (ESI) m/z $[M+H]^+$ calcd for $C_{33}H_{44}O_3Si$: 517.3; found:517.3.



17

Synthesis of dispiro[adamantane-2,4'-[1,3]dioxolane-2',1''-cyclohexane]-3''-ol (17). A vacuum dried 35mL round-bottomed flask equipped with a stir bar, rubber septa, and an argon inlet needle was charged with a solution of dioxolane **23** (0.511 g, 1.0 mmol, 1 equiv) in THF (6 mL) and cooled to 0 °C. A solution of TBAF (1.0 M in THF, 4.9 mL, 5.0 mmol, 5 equiv) was added dropwise and the reaction mixture

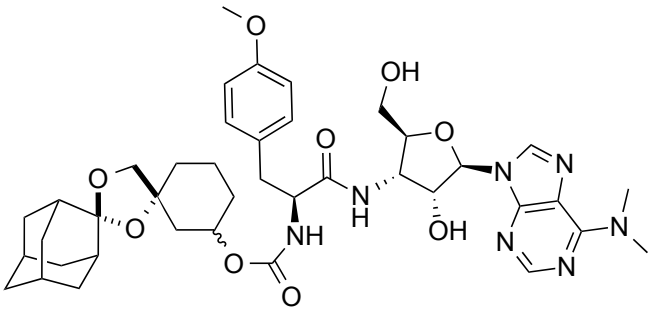
was stirred at 0 °C for 10 min, then allowed to warm to rt and stirred at rt for 17 h. The reaction mixture was diluted with 50 mL of EtOAc and washed with three, 30-mL portions of H_2O. The aqueous phase was extracted with 20 mL of EtOAc and the combined organic phases were washed with 30 mL of satd aq NaCl solution, dried over $MgSO_4$, filtered, and concentrated to a clear oil. Purification via column chromatography on 40 g of silica gel (elution with 25% EtOac/hexanes) afforded 0.273 g of **17** (91-99%) as a foamy, white oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 - 4.00 (m, 1H), 3.74 (d, *J* = 8.24 Hz, 1H, one diastereomer), 3.71 (d, *J* = 8.42 Hz, 1H, one diastereomer), 3.70 (d, *J* = 8.24 Hz, 1H, one diastereomer), 3.67 (d, *J* = 8.42 Hz, 1H, one diastereomer), 1.82 - 2.01 (m, 6H), 1.55 - 1.80 (m, 12H), 1.34 - 1.50 (m, 2H), 1.12 - 1.33 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 112.9, 112.2, 80.9, 80.7, 74.4, 74.4, 68.2, 67.9, 45.4, 41.6, 38.4, 38.1, 38.1, 37.7, 37.3, 37.2, 36.0, 35.9, 35.1, 35.1, 35.1, 35.0, 35.0, 35.0, 34.9, 32.9, 27.2, 27.0, 26.9, 26.8, 20.5, 17.5; LRMS (ESI) *m/z* $[M+H]^+$ calcd $C_{17}H_{26}O_3$: 279.2; found: 279.1.



24

Synthesis of dispiro[adamantane-2,2'-[1,3]dioxolane-4',1''- cyclohexane]-3''-yl 4-nitrophenyl carbonate (24). An oven dried, 2-neck 25 mL round-bottomed flask fitted with an argon inlet and charged with a teflon stirbar was charged with a solution of alcohol **17** (38 mg, 0.1 mmol, 1.0 equiv.) in CH_2Cl_2 (4 mL) and N,N-diisopropylethylamine (0.070 ml, 0.4 mmol, 2.9 equiv.) was added to the solution. The reaction mixture was then cooled to 0 °C and 4-nitrophenyl chloroformate (90 mg, 0.4 mmol, 3.3 equiv.) and 4-dimethylaminopyridine (0.021 g, 0.2 mmol, 1.3 equiv.) were added in a single portion. The reaction mixture was stirred at 0 °C for 20 minutes, then allowed to warm to rt, and stirred at rt for 49 h. The reaction mixture was diluted with 20 mL of EtOAc and washed with five 20-mL portions of saturated aq $NaHCO_3$ solution and one 20-mL portion of satd aq NaCl solution, then dried over $MgSO_4$, filtered, and concentrated to give a pale yellow oil. Purification via column chromatography on 12 ag of silica gel (elution with 15 % EtOAc/hexanes) afforded 0.055 g (90%) of **24**. ^{1}H NMR (400Mz, $CDCl_3$): δ 8.28 - 8.30 (m, 1H), 8.25 - 8.28 (m, 1H), 7.35 - 7.41 (m, 2H), 5.07 (tt, *J* = 4.26, 10.30 Hz, 1H, one diastereomer), 4.65 (tt, *J* = 4.14, 9.68 Hz, 1H, one diastereomer), 3.76 - 3.83 (m, 2H), 2.18 - 2.24 (m, 1H), 2.09 - 2.16 (m, 1H), 1.90 - 2.04 (m, 5H), 1.82 - 1.86 (m, 1H), 1.73 - 1.82 (m, 4H), 1.57 - 1.72 (m, 8H), 1.23 - 1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.8, 152.0, 151.9, 145.5, 125.5, 122.0, 121.9, 112.8, 112.1, 80.4, 80.1,

77.6, 74.2, 72.6, 41.6, 38.4, 38.3, 38.2, 38.1, 37.3, 36.1, 35.5, 35.1, 35.0, 34.9, 30.9, 30.5, 27.2, 27.2, 26.9, 20.3, 20.0; LRMS (ESI) *m/z* $[M+H]^+$ calcd $C_{24}H_{29}NO_7$: 444.2; found: 444.3.



Synthesis of (4'S)-dispiro[adamantane-2,2'-[1,3]dioxolane-4',1''-cyclohexane]-3''-yl N-[(1S)-1-{[(2S,3S,4R,5R)-5-[6-(dimethylamino)-9H-purin-9-yl]-4-hydroxy-2-(hydroxymethyl)oxolan-3-yl]carbamoyl}-2-(4-methoxyphenyl)ethyl]carbamate (18). A 20 mL scintillation vial was charged with nitrophenyl carbonate **24** (0.054 g, 0.1 mmol, 1.0 equiv.), Puromycin dihydrochloride from Streptomyces alboniger (0.066 g, 0.1 mmol, 1.0 equiv.), and 4-dimethylaminopyridine (0.001 g, 0.0 mmol, 0.1 equiv.) and the atmosphere was replace with argon. This material was dissolved with *N*,*N*-dimethylformamide (4.320 ml, 56.0 mmol, 460.2 equiv.) and *N*,*N*-diisopropylethylamine (0.108 ml, 0.6 mmol, 5.1 equiv.) was added to the resulting solution which was allowed to stir at RT under argon for 4 hours then diluted with 15 mL of EtOAc and washed with four 20 mL portions of saturated aq $NaHCO_3$. The aqueous layer was back extracted with 30mL EtOAc and the organic layers were combined, washed with 30mL of satd aq NaCl solution, and then dried over $MgSO_4$, filtered and concentrated to give a light yellow oil. Purification via column chromatography on 12g of silica gel (eluting with a 5-10% gradient of MeOH in CH_2Cl_2) afforded the desired product contaminated with small amounts of unidentified, UV active material which was further purified by column chromatography on 40 g of silica gel (eluting with 3-5% MeOH/CH_2Cl_2) to afford 0.055 g (58 %) of **18** as an off-white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 8.30 - 8.33 (m, 1H), 8.16 (d, *J* = 3.48 Hz, 1H), 7.16 (d, *J* = 8.06 Hz, 2H), 6.84 (d, *J* = 8.24 Hz, 2H), 5.89 - 5.94 (m, 1H), 4.79 - 4.83 (m, 1H), 4.53 - 4.61 (m, 2H), 4.38 (d, *J* = 4.21 Hz, 1H), 3.98 (br. s., 1H), 3.82 (d, *J* = 12.09 Hz, 1H), 3.75 (s, 3H), 3.71 - 3.74 (m, 1H), 3.61 - 3.71 (m, 1H), 3.56 (d, *J* = 12.27 Hz, 1H), 3.47 (br. s., 6H), 2.95 - 3.04 (m, 1H), 2.81 - 2.90 (m, 1H), 1.90 - 2.05 (m, 4H), 1.79 - 1.90 (m, 2H), 1.58 - 1.78 (m, 12H), 1.39 - 1.58 (m, 2H), 1.26 - 1.35 (m, 1H), 1.14 - 1.26 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 174.7, 160.2, 158.0, 156.2, 153.1, 150.6, 139.3, 131.6, 130.4, 130.3,

121.7, 115.1, 113.2, 112.7, 92.0, 85.0, 81.8, 81.8, 75.2, 75.0, 73.3, 62.5, 58.2, 55.8, 52.1, 43.8, 39.8, 39.6, 39.2, 38.4, 37.3, 36.7, 36.0, 35.9, 32.1, 30.9, 28.7, 28.6, 28.3, 21.6, 21.3. HRMS (ESI) *m/z* $[M+H]^+$ calcd $C_{40}H_{54}N_7O_9$: 776.3978; found: 776.3954.