Supporting Information for

Synthesis and in vivo Profiling of Desymmetrized Antimalarial Trioxolanes with Diverse Carbamate Side Chains

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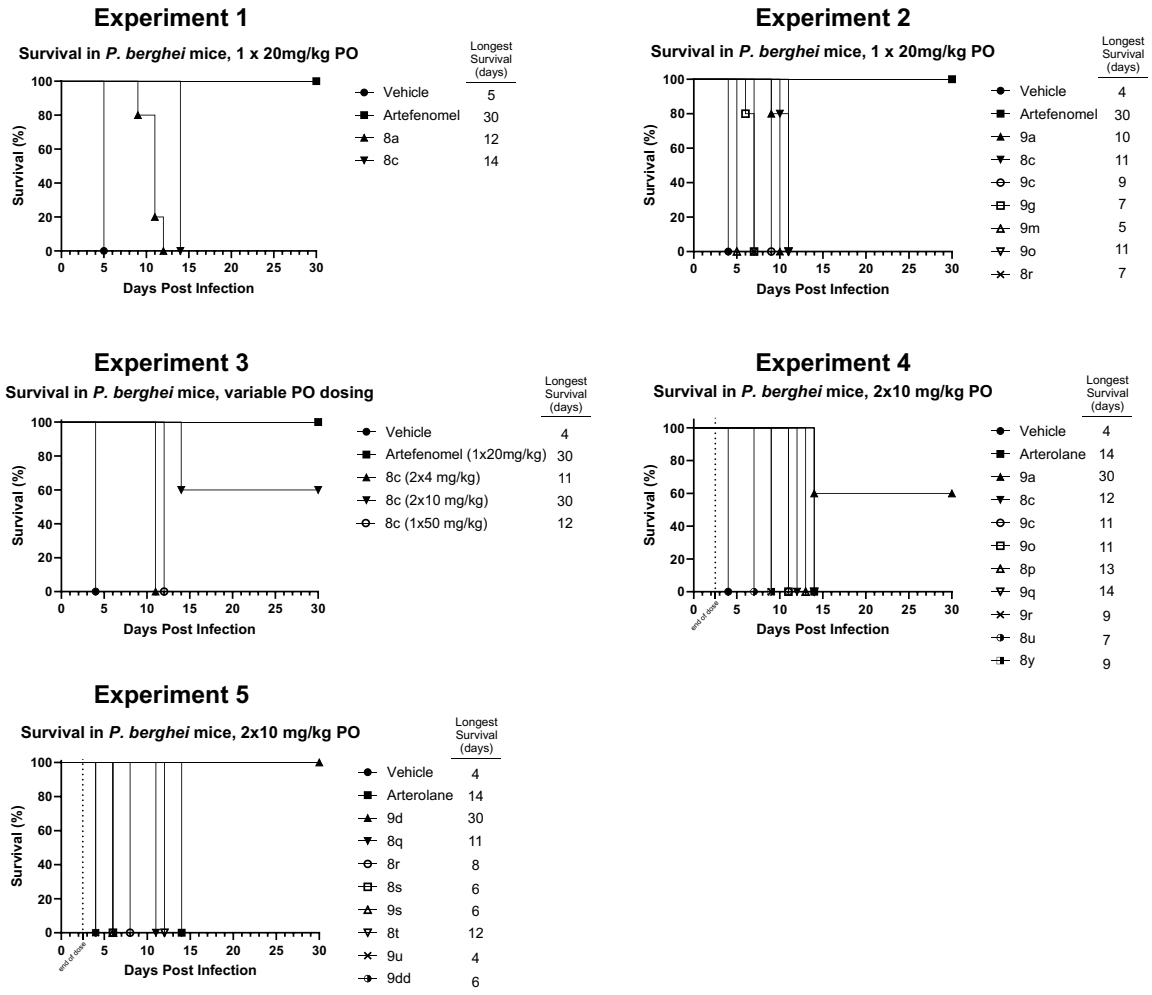


Supplemental Figure S1. Kaplan-Meier survival curves for in vivo pharmacodynamic studies in female Swiss-Webster mice infected intraperitoneally on day 0 with *P. berghei*-infected murine erythrocytes. All dosing schedules (as noted above) were started on day 1. Subjects were continuously monitored for parasitemia via daily giemsa-stained blood smears, terminated according to humane endpoint conditions described in methods, and considered cured if no parasitemia could be detected at day 30. n=5 per treatment group.

Supplementary Tables

Table S1. Pharmacokinetic parameters for **8a**, **9a**, and **9d** following IV (3 mg/kg) and PO (10 mg/kg) doses in female CD-1 mice (n = 3 per group).

8a (4776)					
IV			PO		
Parameter	units	estimated value	Parameter	units	estimated value
CL	L/hr/kg	6.51	T_{max}	hr	1.00
Vss	L/kg	2.79	C_{max}	ng/mL	147
$T_{1/2}$	hr	0.724	$T_{1/2}$	hr	2.09
AUC_{last}	ng/mL*hr	458	AUC_{last}	ng/mL*hr	555
AUC_{INF}	ng/mL*hr	461	AUC_{INF}	ng/mL*hr	604
MRT_{INF}	hr	0.428	F	%	39.3

9a (4767)					
IV			PO		
Parameter	units	estimated value	Parameter	units	estimated value
CL	L/hr/kg	4.62	T_{max}	hr	2.00
Vss	L/kg	2.50	C_{max}	ng/mL	191
$T_{1/2}$	hr	1.21	$T_{1/2}$	hr	1.44
AUC_{last}	ng/mL*hr	648	AUC_{last}	ng/mL*hr	818
AUC_{INF}	ng/mL*hr	650	AUC_{INF}	ng/mL*hr	841
MRT_{INF}	hr	0.541	F	%	38.9

9d (5489)					
IV			PO		
Parameter	units	estimated value	Parameter	units	estimated value
CL	L/hr/kg	3.96	T_{max}	hr	2.00
Vss	L/kg	2.33	C_{max}	ng/mL	240
$T_{1/2}$	hr	1.66	$T_{1/2}$	hr	1.66
AUC_{last}	ng/mL*hr	752	AUC_{last}	ng/mL*hr	1038
AUC_{INF}	ng/mL*hr	757	AUC_{INF}	ng/mL*hr	1087
MRT_{INF}	hr	0.587	F	%	43.1

For comparison, liver blood flow in mouse = 7.2 L/hr/kg

Synthetic Procedures

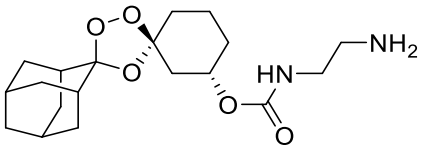
Materials

All chemical reagents were obtained commercially and used without further purification unless otherwise stated. Anhydrous solvents were purchased from Sigma-Aldrich and were used without further purification. Solvents used for flash column chromatography and workup procedures were purchased from either Sigma-Aldrich or Fisher Scientific. Column chromatography was performed on Silicycle Sili-prep cartridges using a Biotage Isolera Four automated flash chromatography system.

Instrumentation

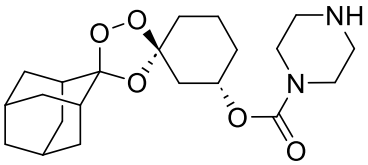
NMR spectra were recorded on a Bruker Avance III HD 400 MHz (with 5 mm BBFO Z-gradient Smart Probe), calibrated to $CH(D)Cl_3$ as an internal reference (7.26 and 77.00 ppm for ^{1}H and ^{13}C NMR spectra, respectively). Data for ^{1}H NMR spectra are reported in terms of chemical shift (δ, ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ, ppm), with multiplicity and coupling constants in the case of C-F coupling. The following abbreviations are used to denote these multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent, or combinations of these. LC-MS and compound purity were determined using a Waters Micromass ZQ 4000, equipped with a Waters 2795 Separation Module, a Waters 2996 Photodiode Array Detector, and a Waters 2424 ELSD. Separations were carried out with an XBridge BEH C18, 3.5 µm, 4.6 mm × 20 mm column, at ambient temperature (unregulated) using a mobile phase of water-methanol containing a constant 0.10% formic acid.

Synthetic procedures for final compounds and Boc-protected intermediates



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (2-aminoethyl)carbamate (9d).

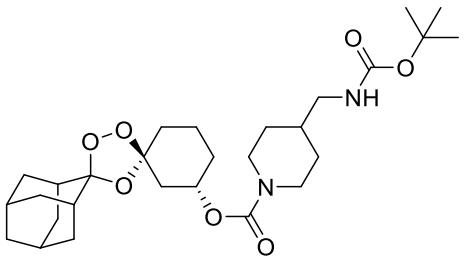
To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.225 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (94.1 µL, 0.675 mmol, 3.0 equiv.), followed by ethylenediamine (75 µL, 1.12 mmol, 5.0 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 4 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) / CH_2Cl_2 with the desired product eluting at 15% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (2-aminoethyl)carbamate (62.0 mg, 0.169 mmol, 75%) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 4.6-4.8 (m, 1H), 3.22 (t, 2H, J = 6.2 Hz), 2.80 (t, 2H, J = 6.2 Hz), 2.1-2.3 (m, 1H), 2.04 (br d, 2H, J = 11.9 Hz), 1.9-2.0 (m, 5H), 1.7-1.9 (m, 11H), 1.65 (dt, 1H, J = 3.7, 12.7 Hz), 1.3-1.6 (m, 3H) ^{13}C NMR (MeOD, 100 MHz) δ 157.2, 111.2, 108.6, 70.9, 41.6, 40.6, 39.9, 36.4, 36.4, 36.4, 34.4, 34.4, 33.3, 30.3, 27.0, 26.6, 19.4, 0.7; MS (ESI) calc for $C_{19}H_{31}N_2O_5$ $[M+H]^+$: m/z 367.22 found 367.29



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl piperazine-1-carboxylate (9e).

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (25 mg, 0.056 mmol, 1.0 equiv.) in dichloromethane (1.5 mL) was added

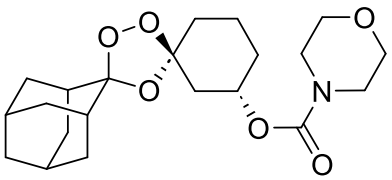
triethylamine (31 µL, 0.22 mmol, 4.0 equiv.), followed by piperazine (4.8 mg, 0.056 mmol, 1.0 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 18 h. The reaction was then quenched with DCM, washed with water, and the organic layer was extracted 3 times with 1N NaOH until the aqueous layer was colorless (indicating that *p*-nitrophenol had been depleted). The collected organic fractions were dried over $MgSO_4$, concentrated under reduced pressure. The crude residue was purified using flash column chromatography chromatography (12 g silica gel cartridge, 0-100% EtOAc:Hexanes). The fractions containing the product were combined and concentrated to yield (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl piperazine-1-carboxylate (20.6 mg, 0.053 mmol, 93.9%) as a white solid. HNMR indicated the presence of grease (long-chain linear aliphatic hydrocarbon) which was carried through as an impurity. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.84 (tt, 1H, J = 4.5, 9.3 Hz), 3.4-3.6 (m, 4H), 2.89 (br s, 4H), 2.2-2.3 (m, 1H), 1.9-2.1 (m, 7H), 1.7-1.9 (m, 7H), 1.5-1.6 (m, 2H), 1.4-1.5 (m, 2H), 1.0-1.2 (m, 6H). MS (ESI) calc for $C_{21}H_{33}N_2O_5$ $[M+H]^+$: m/z 393.24 found 393.39



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 4-(((tert-butoxycarbonyl)amino)methyl)piperidine-1-carboxylate.

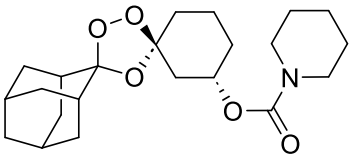
To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (62.6 µL, 0.449 mmol, 2 equiv.), followed by tert-butyl (piperidin-4-ylmethyl)carbamate (96.2 mg, 0.449 mmol, 2 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 4.5 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-50% EtOAc:Hexanes) with the desired product eluting at 35% EtOAc. The fractions containing the product were combined and

lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 4-(((tert-butoxycarbonyl)amino)methyl)piperidine-1-carboxylate (117 mg, 0.224 mmol, 100%) as a white solid. MS (ESI) calc for $C_{28}H_{44}N_2O_7Na$ $[M+Na]^+$: m/z 543.30 found 543.19



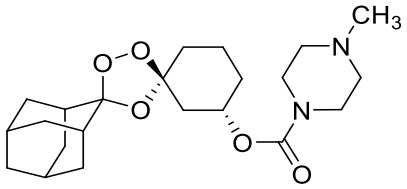
(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl morpholine-4-carboxylate (9f).

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (25 mg, 0.056 mmol, 1.0 equiv.) in dichloromethane (1.5 mL) was added triethylamine (31 µL, 0.22 mmol, 4.0 equiv.), followed by morpholine (7.3 mg, 0.084 mmol, 1.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 18 h. The reaction was then quenched with DCM, washed with water, and the organic layer was extracted 3 times with 1N NaOH until the aqueous layer was colorless (indicating that *p*-nitrophenol had been depleted). The collected organic fractions were dried over $MgSO_4$, concentrated under reduced pressure. The crude residue was purified using flash column chromatography chromatography (12 g silica gel cartridge, 0-100% EtOAc:Hexanes). The fractions containing the product were combined and concentrated to yield (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl morpholine-4-carboxylate (19.5 mg, 0.049 mmol, 88.4%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.8-4.9 (m, 1H), 3.66 (br s, 4H), 3.4-3.5 (m, 4H), 2.2-2.3 (m, 1H), 1.9-2.0 (m, 7H), 1.7-1.9 (m, 7H), 1.5-1.7 (m, 3H), 1.2-1.5 (m, 2H) MS (ESI) calc for $C_{21}H_{31}NO_6Na$ $[M+Na]^+$: m/z 416.20 found 416.20



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-ylpiperidine-1-carboxylate (9g).

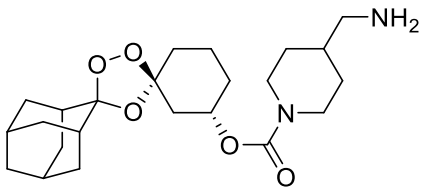
To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (25 mg, 0.056 mmol, 1.0 equiv.) in dichloromethane (1.5 mL) was added triethylamine (31 µL, 0.22 mmol, 4.0 equiv.), followed by piperidine (7.2 mg, 0.084 mmol, 1.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 18 h. The reaction was then quenched with DCM, washed with water, and the organic layer was extracted 3 times with 1N NaOH until the aqueous layer was colorless (indicating that *p*-nitrophenol had been depleted). The collected organic fractions were dried over $MgSO_4$, concentrated under reduced pressure. The crude residue was purified using flash column chromatography chromatography (12 g silica gel cartridge, 0-100% EtOAc:Hexanes). The fractions containing the product were combined and concentrated to yield (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-ylpiperidine-1-carboxylate (20.6 mg, 0.053 mmol, 93.9%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.8-4.9 (m, 1H), 3.42 (br d, 4H, J = 5.4 Hz), 2.1-2.3 (m, 1H), 1.9-2.1 (m, 7H), 1.7-1.9 (m, 11H), 1.5-1.6 (m, 5H), 1.2-1.5 (m, 2H). MS (ESI) calc for $C_{22}H_{33}NO_5Na$ [M+Na]$^+$: m/z 414.23 found 414.25



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 4-methylpiperazine-1-carboxylate (9h).

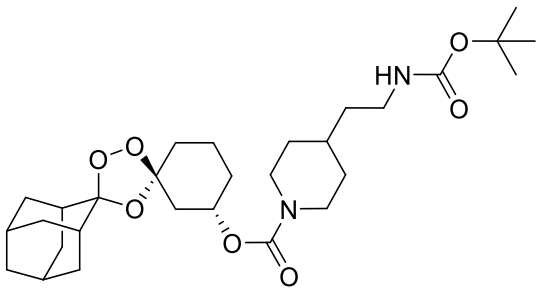
To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.225 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (78.2 µL, 0.561 mmol, 2.5 equiv.), followed by 1-methylpiperazine (78.2 µL, 0.561 mmol, 2.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) / CH_2Cl_2) with the desired product eluting at 5% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the

product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 4-methylpiperazine-1-carboxylate (62.0 mg, 0.169 mmol, 75%) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 4.8-4.9 (m, 1H), 3.4-3.6 (m, 4H), 2.2-2.4 (m, 6H), 1.9-2.0 (m, 8H), 1.7-1.9 (m, 12H), 1.5-1.6 (m, 1H), 1.2-1.5 (m, 2H); ^{13}C NMR (MeOD, 100 MHz) δ 154.6, 111.7, 108.6, 71.2, 54.7, 46.2, 39.8, 36.8, 36.3, 36.2, 35.0, 34.8, 34.7, 34.6, 34.2, 30.6, 26.9, 26.5, 19.5; MS (ESI) calc for $C_{22}H_{35}N_2O_5$ $[M+H]^+$: m/z 407.25 found 407.38



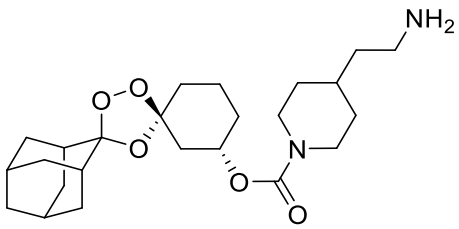
(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 4-(aminomethyl)piperidine-1-carboxylate (9j).

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 4-({[(tert-butoxy)carbonyl]amino}methyl)piperidine-1-carboxylate (117 mg, 0.224 mmol, 1 equiv.) in MeOH (5 mL) cooled to 0 ºC was added acetyl chloride (160 , 2.24 mmol, 10 equiv) dropwise via microsyringe. The reaction was stirred at 0 ºC for 5 minutes before being allowed to return to room temperature. After 4.5 h, the reaction was quenched with 10 mL 1 M Na_2CO_3 (10 mL) and diluted with DCM (15 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (2 x 10 mL), followed by brine (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) / CH_2Cl_2) with the desired product eluting at 15% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 4-(aminomethyl)piperidine-1-carboxylate (35 mg, 0.083 mmol, 37%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.8-4.9 (m, 1H), 4.1-4.3 (m, 2H), 2.6-2.8 (m, 4H), 2.2-2.3 (m, 1H), 1.9-2.1 (m, 7H), 1.5-1.9 (m, 16H), 1.39 (br d, 1H, J = 9.0 Hz), 1.27 (s, 2H), 1.1-1.2 (m, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 154.7, 111.6, 108.7, 71.1, 43.7, 39.8, 36.8, 36.3, 36.3, 35.0, 34.8, 34.7, 34.6, 34.1, 30.7, 29.7, 26.9, 26.5, 19.6; MS (ESI) calc for $C_{23}H_{37}N_2O_5$ $[M+H]^+$: m/z 421.27 found 421.20



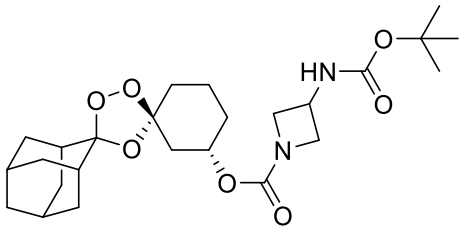
(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 4-(2-{[(tert-butoxy)carbonyl]amino}ethyl)piperidine-1-carboxylate.

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (62.6 µL, 0.449 mmol, 2 equiv.), followed by tert-butyl N-[2-(piperidin-4-yl)ethyl]carbamate (103 mg, 0.449 mmol, 2 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 4.5hr. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-50% EtOAc:Hexanes) with the desired product eluting at 35% EtOAc. The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 4-(2-{[(tert-butoxy)carbonyl]amino}ethyl)piperidine-1-carboxylate (74.5 mg, 0.139 mmol, 62%) as a white solid. MS (ESI) calc for $C_{29}H_{46}N_2O_7Na$ $[M+Na]^+$: m/z 557.32 found 557.70



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 4-(2-aminoethyl)piperidine-1-carboxylate (9k).

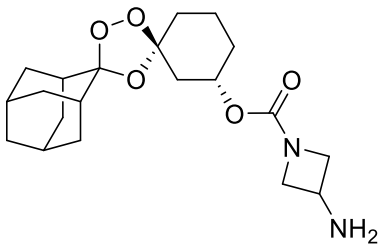
To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 4-(2-{[(tert-butoxy)carbonyl]amino}ethyl)piperidine-1-carboxylate (74.5 mg, 0.139 mmol, 1 equiv) in MeOH (5 mL) cooled to 0 ºC was added acetyl chloride (99.1 µL, 1.39 mmol, 10 equiv) dropwise via microsyringe. The reaction was stirred at 0 ºC for 5 minutes before being allowed to return to room temperature. After 16 h, the reaction was quenched with 10 mL 1 M Na_2CO_3 (10 mL) and diluted with DCM (15 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (2 x 10 mL), followed by brine (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) / CH_2Cl_2 with the desired product eluting at 15% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 4-(2-aminoethyl)piperidine-1-carboxylate (27.3 mg, 0.062 mmol, 45%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 4.7-4.9 (m, 1H), 4.0-4.2 (m, 2H), 2.8-3.0 (m, 4H), 2.74 (br t, 4H, *J* = 11.9 Hz), 2.1-2.3 (m, 1H), 2.02 (br s, 2H), 1.9-2.0 (m, 5H), 1.7-1.9 (m, 6H), 1.7-2.1 (m, 4H), 1.3-1.6 (m, 5H), 1.28 (s, 1H), 1.14 (br d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 154.7, 111.6, 108.7, 77.2, 71.1, 43.9, 39.9, 38.6, 37.7, 36.8, 36.3, 36.3, 35.0, 34.8, 34.7, 34.6, 34.1, 33.4, 31.9, 30.7, 26.9, 26.5, 19.6; MS (ESI) calc for $C_{24}H_{39}N_2O_5$ $[M+H]^+$: m/z 435.29 found 435.64



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-{[(tert-butoxy)carbonyl]amino}azetidine-1-carboxylate.

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (78.2 µL, 0.561 mmol, 2.5 equiv.), followed by tert-butyl N-[(azetidin-3-yl)methyl]carbamate (96.7 mg, 0.561 mmol, 2.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 4.5hr. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3

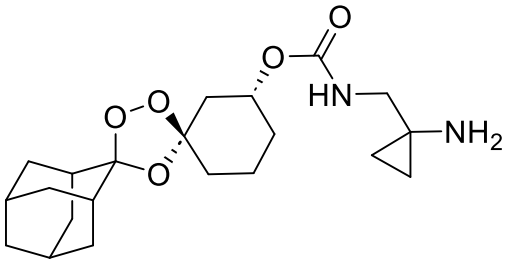
(4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-50% EtOAc:Hexanes) with the desired product eluting at 35% EtOAc. The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-{[(tert-butoxy)carbonyl]amino}azetidine-1-carboxylate (104.0 mg, 0.217 mmol, 97%) as a white solid. MS (ESI) calc for $C_{25}H_{38}N_2O_7Na$ $[M+Na]^+$: m/z 501.26 found 501.27



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-aminoazetidine-1-carboxylate (9m).

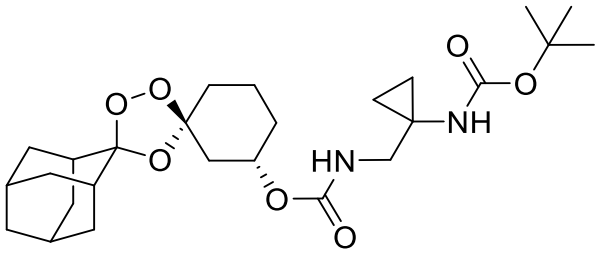
To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-{[(tert-butoxy)carbonyl]amino}azetidine-1-carboxylate (51.4 mg, 0.107 mmol, 1 equiv.) in MeOH (5 mL) cooled to 0 ºC was added acetyl chloride (76.4 µL, 2.17 mmol, 10 equiv.) dropwise via microsyringe. The reaction was stirred at 0 ºC for 5 minutes before being allowed to return to room temperature. After 16 h, the reaction was quenched with 10 mL 1 M Na_2CO_3 (10 mL) and diluted with DCM (15 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (2 x 10 mL), followed by brine (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) / CH_2Cl_2 with the desired product eluting at 15% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-aminoazetidine-1-carboxylate (15 mg, 0.040 mmol, 37%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.6-4.9 (m, 1H), 4.1-4.4 (m, 3H), 3.8-4.0 (m, 1H), 2.3-2.4 (m, 1H), 2.1-2.3 (m, 3H), 1.9-2.1 (m, 4H), 1.91 (br s, 1H), 1.7-1.9 (m, 5H), 1.6-1.7 (m, 1H), 1.5-1.6 (m, 1H), 1.3-1.5 (m, 1H), 1.3-1.3 (m, 5H), 0.9-0.9 (m, 1H) ^{13}C NMR ($CDCl_3$,

100 MHz) δ 111.6, 100.0, 77.2, 71.5, 42.4, 39.9, 36.8, 36.3, 34.7, 33.9, 33.3, 31.9, 30.6, 29.7, 29.5, 29.4, 29.3, 26.9, 26.4, 24.8, 22.7, 19.6, 14.1 MS (ESI) calc for $C_{20}H_{30}N_2O_5Na$ $[M+Na]^+$: m/z 401.21 found 401.50



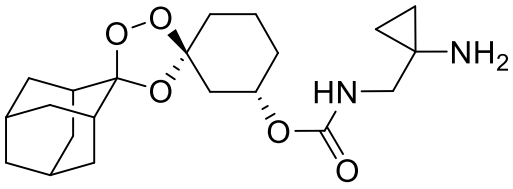
(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl ((3-aminooxetan-3-yl)methyl)carbamate (8o).

To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (50 mg, 0.11 mmol, 1.0 equiv.) in dichloromethane (1.5 mL) was added triethylamine (47 µL, 0.34 mmol, 3.0 equiv.), followed by 1-(aminomethyl)cyclopropan-1-amine, HCl (27 mg, 0.17 mmol, 1.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was then quenched with DCM, washed with water, and the organic layer was extracted 3 times with saturated NaHCO3 until the aqueous layer was colorless (indicating that *p*-nitrophenol had been depleted). The collected organic fractions were dried over $MgSO_4$, concentrated under reduced pressure. The crude residue was purified using flash column chromatography chromatography (12 g silica gel cartridge, 0-20% methanol (with 0.8 N ammonia) in DCM). The fractions containing the product were combined and concentrated to yield (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-ylpiperazine-1-carboxylate (33.9 mg, 0.086 mmol, 78.5%) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 4.6-4.8 (m, 1H), 3.15 (s, 2H), 2.1-2.3 (m, 1H), 2.0-2.1 (m, 3H), 1.7-2.0 (m, 16H), 1.65 (dt, 1H, J = 3.7, 12.7 Hz), 1.3-1.5 (m, 3H), 0.58 (br d, 4H, J = 6.3 Hz) ^{13}C NMR (100 MHz, MeOD) δ 157.4, 111.2, 108.6, 70.8, 48.9, 39.9, 36.4, 36.4, 36.4, 34.4, 33.8, 33.4, 30.3, 27.0, 26.6, 19.4, 11.2 MS (ESI) calc for $C_{21}H_{33}N_2O_5$ $[M+H]^+$: m/z 393.24 found 393.32



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclopropyl)methyl]carbamate.

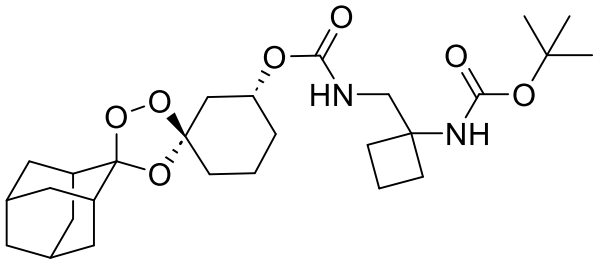
To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (62.6 µL, 0.449 mmol, 2.0 equiv.), followed by tert-butyl (1-(aminomethyl)cyclopropyl)carbamate (83.6 mg, 0.449 mmol, 2.0 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-50% EtOAc:Hexanes) with the desired product eluting at 30% EtOAc. The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclopropyl)methyl]carbamate (80.6 mg, 0.164 mmol, 72.9%) as a white solid. MS (ESI) calc for $C_{26}H_{40}N_2O_7Na$ $[M+Na]^+$: m/z 515.27 found 515.48



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-aminocyclopropyl)methyl]carbamate (9o).

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclopropyl)methyl]carbamate (80.6 mg, 0.164 mmol, 1 equiv) in

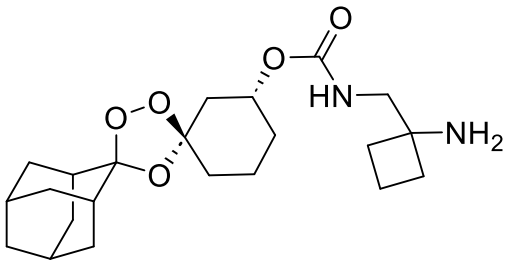
MeOH (5 mL) cooled to 0 ºC was added acetyl chloride (116 µL, 1.64 mmol, 10 equiv) dropwise via microsyringe. The reaction was stirred at 0 ºC for 5 minutes before being allowed to return to room temperature. After 16 h, the reaction was quenched with 10 mL 1 M Na_2CO_3 (10 mL) and diluted with DCM (15 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (2 x 10 mL), followed by brine (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) / CH_2Cl_2) with the desired product eluting at 10% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-aminocyclopropyl)methyl]carbamate (50.5 mg, 0.129 mmol, 78.6%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.01 (br t, 1H, J = 5.7 Hz), 4.76 (br s, 1H), 3.19 (br d, 2H, J = 5.7 Hz), 2.2-2.4 (m, 2H), 2.13 (br s, 3H), 1.9-2.1 (m, 9H), 1.7-1.9 (m, 8H), 1.4-1.7 (m, 3H), 1.2-1.4 (m, 2H), 0.5-0.7 (m, 4H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2, 111.6, 108.7, 71.1, 50.0, 40.3, 36.8, 36.3, 34.9, 34.8, 34.7, 34.7, 34.5, 33.8, 30.7, 26.9, 26.5, 19.7, 13.0, MS (ESI) calc for $C_{21}H_{33}N_2O_5$ $[M+H]^+$: m/z 393.24 found 393.37



(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclobutyl)methyl]carbamate.

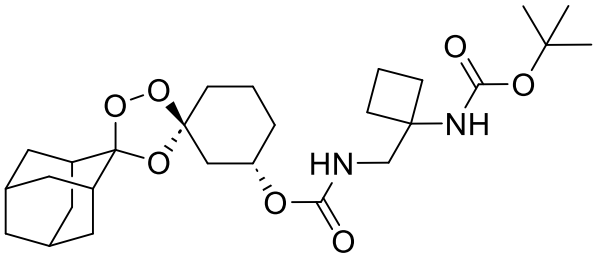
To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (78.2 µL, 0.561 mmol, 2.5 equiv.), followed by tert-butyl (*R*)-piperidin-3-ylcarbamate (112.0 mg, 0.561 mmol, 2.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL),

dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-50% EtOAc:Hexanes) with the desired product eluting at 30% EtOAc. The fractions containing the product were combined and lyophilized to (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclobutyl)methyl]carbamate (114 mg, 0.224 mmol, 100%) as a white solid. MS (ESI) calc for $C_{27}H_{42}N_2O_7Na$ $[M+Na]^+$: m/z 529.29 found 529.28



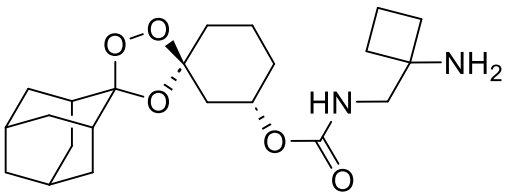
(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-amino-cyclobutyl)methyl]carbamate (8p).

To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclobutyl)methyl]carbamate (114 mg, 0.224 mmol, 1 equiv) in MeOH (5 mL) cooled to 0 ºC was added acetyl chloride (161 µL, 2.27 mmol, 10 equiv) dropwise via microsyringe. The reaction was stirred at 0 ºC for 5 minutes before being allowed to return to room temperature. After 16 h, the reaction was quenched with 10 mL 1 M Na_2CO_3 (10 mL) and diluted with DCM (15 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (2 x 10 mL), followed by brine (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) / CH_2Cl_2) with the desired product eluting at 10% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the product were combined and lyophilized to give (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-aminocyclobutyl)methyl]carbamate (84.8 mg, 0.209 mmol, 93.3%) as a white solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 5.3-5.5 (m, 1H), 4.7-4.9 (m, 1H), 3.2-3.4 (m, 2H), 2.98 (br s, 3H), 2.2-2.4 (m, 1H), 1.9-2.1 (m, 12H), 1.7-1.9 (m, 9H), 1.5-1.7 (m, 3H), 1.2-1.4 (m, 2H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1, 111.5, 108.8, 71.0, 56.0, 48.1, 40.3, 36.8, 36.3, 34.9, 34.8, 34.7, 33.8, 33.3, 30.7, 26.9, 26.5, 19.8, 12.9 MS (ESI) calc for $C_{22}H_{35}N_2O_5$ $[M+H]^+$: m/z calc 407.25 found 407.43



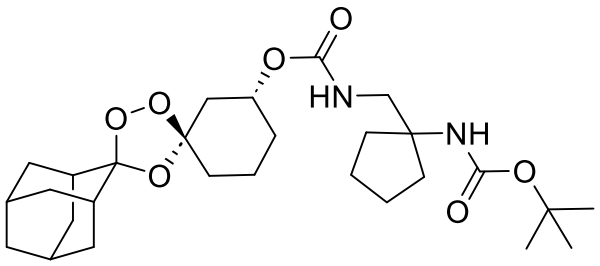
(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclobutyl)methyl]carbamate.

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (62.6 µL, 0.449 mmol, 2.0 equiv.), followed by tert-butyl (1-(aminomethyl)cyclobutyl)carbamate (83.6 mg, 0.449 mmol, 2.0 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-50% EtOAc:Hexanes) with the desired product eluting at 30% EtOAc. The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclobutyl)methyl]carbamate (84.8 mg, 0.167 mmol, 75%) as a white solid. MS (ESI) calc for $C_{27}H_{42}N_2O_7Na$ $[M+Na]^+$: m/z 529.29 found 529.18



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-amino-cyclobutyl)methyl]carbamate (9p).

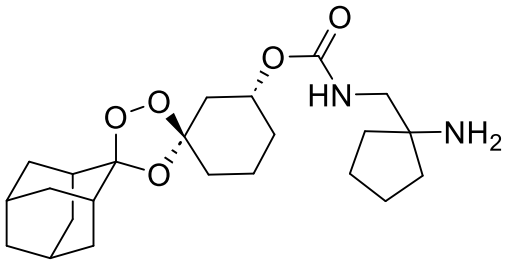
To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclobutyl)methyl]carbamate (84.8 mg, 0.167 mmol, 1 equiv) in MeOH (5 mL) cooled to 0 ºC was added acetyl chloride (119 µL, 1.67 mmol, 10 equiv) dropwise via microsyringe. The reaction was stirred at 0 ºC for 5 minutes before being allowed to return to room temperature. After 16 h, the reaction was quenched with 10 mL 1 M Na_2CO_3 (10 mL) and diluted with DCM (15 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (2 x 10 mL), followed by brine (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) / CH_2Cl_2) with the desired product eluting at 10% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-aminocyclobutyl)methyl]carbamate (46.9 mg, 0.115 mmol, 69%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.31 (br s, 1H), 4.7-4.9 (m, 1H), 3.2-3.4 (m, 2H), 2.73 (br s, 4H), 2.2-2.4 (m, 1H), 1.9-2.1 (m, 11H), 1.7-1.9 (m, 8H), 1.5-1.7 (m, 3H), 1.2-1.4 (m, 2H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.6, 111.5, 108.8, 77.2, 71.0, 56.0, 48.1, 40.3, 36.8, 36.3, 34.9, 34.8, 34.7, 33.8, 33.3, 30.7, 26.9, 26.5, 19.8, 12.9 MS (ESI) calc for $C_{22}H_{35}N_2O_5$ $[M+H]^+$: m/z 407.25 found 407.38



(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclopentyl)methyl]carbamate.

To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (78.2 µL, 0.561 mmol, 2.5 equiv.), followed by tert-butyl (1-(aminomethyl)cyclopentyl)carbamate (120.0 mg, 0.561 mmol, 2.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had

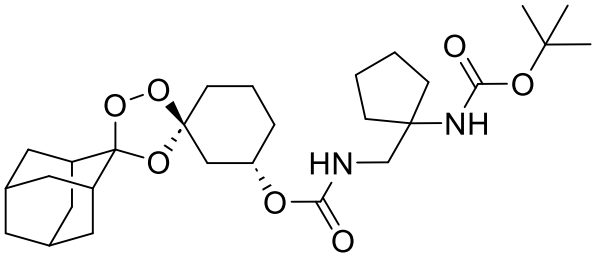
been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-50% EtOAc:Hexanes) with the desired product eluting at 30% EtOAc. The fractions containing the product were combined and lyophilized to give (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclopentyl)methyl]carbamate (117.0 mg, 0.224 mmol, 100%) as a white solid. MS (ESI) calc for $C_{28}H_{44}N_2O_7$ $[M+H]^+$: m/z 543.30 found 543.44



(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-aminocyclopentyl)methyl]carbamate (8q).

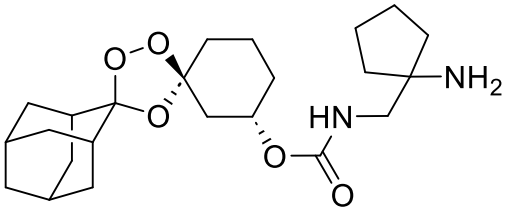
To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclopentyl)methyl]carbamate (117 mg, 0.225 mmol, 1 equiv) in MeOH (5 mL) cooled to 0 ºC was added acetyl chloride (160 µL, 2.25mmol, 10 equiv) dropwise via microsyringe. The reaction was stirred at 0 ºC for 5 minutes before being allowed to return to room temperature. After 16 h, the reaction was quenched with 10 mL 1 M Na_2CO_3 (10 mL) and diluted with DCM (15 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (2 x 10 mL), followed by brine (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) / CH_2Cl_2) with the desired product eluting at 10% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the product were combined and lyophilized to give (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-aminocyclopentyl)methyl]carbamate (86.3 mg, 0.205 mmol, 91.3%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 5.36 (br s, 1H), 4.7-4.9 (m, 1H), 3.1-3.4 (m, 2H), 2.83 (br s, 2H), 2.28 (br dd, 1H, *J* = 2.2, 12.7 Hz), 1.99 (br d, 5H, *J* = 13.9 Hz), 1.92 (br s, 2H), 1.7-1.9 (m, 8H), 1.6-1.7 (m, 3H), 1.5-1.6 (m, 4H), 1.2-1.4 (m, 2H) ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 156.5, 111.5, 108.8,

71.0, 59.0, 49.5, 40.3, 37.8, 36.8, 36.3, 34.9, 34.8, 34.7, 33.8, 30.8, 26.9, 26.5, 24.0, 19.8 MS (ESI) calc for $C_{23}H_{37}N_2O_5$ $[M+H]^+$: m/z 421.27 found 421.53



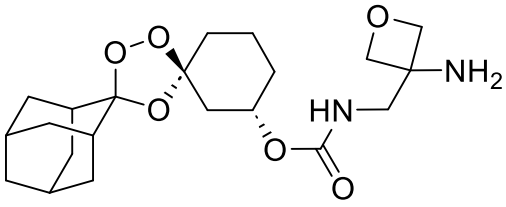
(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclopentyl)methyl]carbamate.

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (62.6 µL, 0.449 mmol, 2.0 equiv.), followed by tert-butyl N-[1-(aminomethyl)cyclopentyl]carbamate (96.2 mg, 0.449 mmol, 2.0 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-50% EtOAc:Hexanes) with the desired product eluting at 30% EtOAc. The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclopentyl)methyl]carbamate (97.3 mg, 0.186 mmol, 83%) as a white solid. Product was confirmed using TLC and used immediately in the next reaction.



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-amino-cyclopentyl)methyl]carbamate (9q).

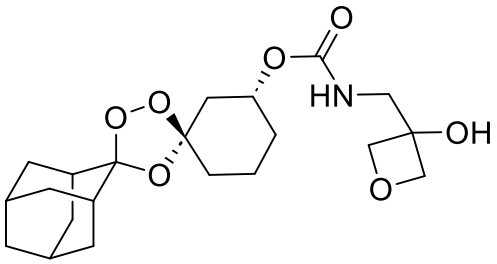
To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-{[(tert-butoxy)carbonyl]amino}cyclopentyl)methyl]carbamate (97.3 mg, 0.186 mmol, 1 equiv) in MeOH (5 mL) cooled to 0 ºC was added acetyl chloride (133 µL, 1.86 mmol, 10 equiv) dropwise via microsyringe. The reaction was stirred at 0 ºC for 5 minutes before being allowed to return to room temperature. After 16 h, the reaction was quenched with 10 mL 1 M Na_2CO_3 (10 mL) and diluted with DCM (15 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (2 x 10 mL), followed by brine (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) / CH_2Cl_2) with the desired product eluting at 10% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(1-aminocyclopentyl)methyl]carbamate (41.6 mg, 0.098 mmol, 53.2%) as a white solid. HNMR indicated the presence of some residual PNP, which was carried through as an impurity. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.6-4.8 (m, 1H), 3.51 (s, 2H), 2.2-2.4 (m, 1H), 1.9-2.1 (m, 8H), 1.76 (br s, 16H), 1.28 (s, 5H), 0.9-1.0 (m, 1H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 111.6, 77.2, 60.8, 60.8, 36.8, 36.3, 34.8, 33.8, 30.7, 29.7, 29.4, 29.3, 26.9, 26.5, 23.9, 22.9, 22.7, 19.9 MS (ESI) calc for $C_{23}H_{37}N_2O_5$ $[M+H]^+$: m/z 421.27 found 421.53



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(3-aminooxetan-3-yl)methyl]carbamate (9r).

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.225 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (440.0 µL, 3.16 mmol, 14.1 equiv.), followed by 3-(ammoniomethyl)oxetan-3-aminium oxalate (200 mg, 1.04 mmol, 4.64 equiv.) at rt. The bright yellow mixture was allowed

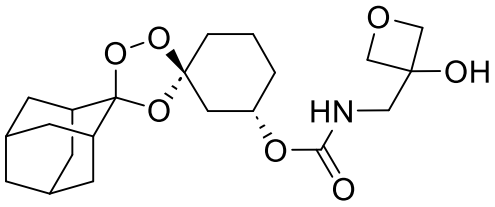
to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) / CH_2Cl_2) with the desired product eluting at 5% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(3-aminooxetan-3-yl)methyl]carbamate (84.8 mg, 0.208 mmol, 92.5%) as a white solid. NMR and UPLC/MS indicated the presence of an unknown impurity which was carried through initial compound evaluation. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.7-4.8 (m, 1H), 4.50 (br d, 2H, *J* = 6.3 Hz), 4.43 (d, 2H, *J* = 6.6 Hz), 3.52 (br s, 1H), 2.60 (br s, 1H), 2.2-2.3 (m, 1H), 1.8-2.0 (m, 14H), 1.7-1.8 (m, 7H), 1.5-1.6 (m, 3H), 1.2-1.3 (m, 9H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.4, 111.6, 108.7, 82.3, 71.3, 56.5, 40.2, 36.7, 36.3, 35.8, 34.8, 34.8, 33.8, 31.9, 30.9, 30.7, 29.7, 29.4, 26.9, 26.4, 25.8, 22.7, 19.7, 14.1 MS (ESI) calc for $C_{21}H_{33}N_2O_6S$ $[M+H]^+$: m/z 409.23 found 409.48



(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(3-hydroxyoxetan-3-yl)methyl]carbamate (8s).

To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.225 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (78.2 µL, 0.561 mmol, 2.5 equiv.), followed by 3-(aminomethyl)oxetan-3-ol (57.9 mg, 0.561 mmol, 2.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$),

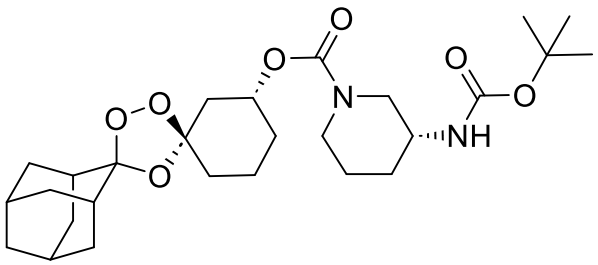
and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) / CH_2Cl_2) with the desired product eluting at 5% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the product were combined and lyophilized to give (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(3-hydroxyoxetan-3-yl)methyl]carbamate (92.1 mg, 0.225 mmol, 100%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (br s, 1H), 4.7-4.8 (m, 1H), 4.62 (d, 2H, J = 7.1 Hz), 4.44 (d, 2H, J = 6.8 Hz), 3.63 (d, 2H, J = 5.8 Hz), 2.2-2.4 (m, 1H), 1.9-2.0 (m, 7H), 1.7-1.9 (m, 8H), 1.7-1.7 (m, 1H), 1.4-1.7 (m, 2H), 1.2-1.4 (m, 2H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.2, 111.7, 108.6, 81.7, 72.1, 47.5, 40.1, 36.8, 36.3, 36.3, 34.8, 34.7, 33.7, 30.6, 26.9, 26.4, 19.7 MS (ESI) calc for $C_{21}H_{32}NO_7$ $[M+H]^+$: m/z 410.22 found 410.43



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(3-hydroxyoxetan-3-yl)methyl]carbamate (9s).

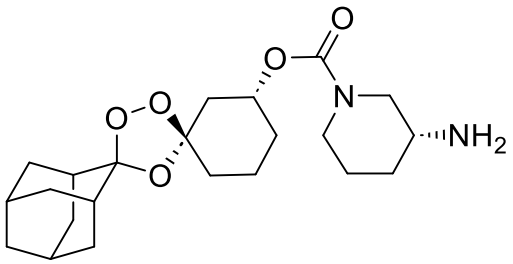
To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.225 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (78.2 µL, 0.561 mmol, 2.5 equiv.), followed by 3-(aminomethyl)oxetan-3-ol (57.9 mg, 0.561 mmol, 2.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) / CH_2Cl_2) with the desired product eluting at 5% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-[(3-hydroxyoxetan-3-yl)methyl]carbamate (51.8 mg, 0.127 mmol, 56.4%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (br s, 1H), 4.7-4.9 (m, 1H), 4.62 (d, 2H, J = 6.8 Hz), 4.44 (d, 2H, J = 7.1 Hz), 4.37 (br s, 1H), 3.62 (d, 2H, J = 5.8 Hz),

2.2-2.3 (m, 1H), 1.99 (br d, 5H, *J* = 7.8 Hz), 1.7-1.9 (m, 9H), 1.7-1.7 (m, 3H), 1.4-1.7 (m, 2H), 1.2-1.4 (m, 2H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.0, 111.7, 108.6, 81.7, 72.1, 47.5, 40.1, 36.8, 36.3, 36.3, 34.8, 34.7, 33.7, 30.6, 29.7, 26.9, 26.4, 19.7 MS (ESI) calc for $C_{21}H_{32}NO_7$ $[M+H]^+$: m/z 410.22 found 410.38



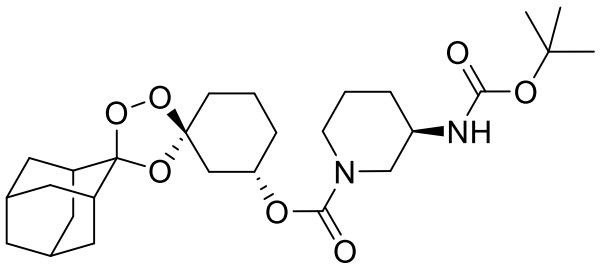
(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (*3R*)-3-{[(tert-butoxy)carbonyl]amino}piperidine-1-carboxylate.

To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (78.2 µL, 0.561 mmol, 2.5 equiv.), followed by tert-butyl (*R*)-piperidin-3-ylcarbamate (112.0 mg, 0.561 mmol, 2.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-50% EtOAc:Hexanes) with the desired product eluting at 30% EtOAc. The fractions containing the product were combined and lyophilized to (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (*3R*)-3-{[(tert-butoxy)carbonyl]amino}piperidine-1-carboxylate (114.0 mg, 0.224 mmol, 100%) as a white solid. MS (ESI) calc for $C_{27}H_{42}N_2O_7Na$ $[M+Na]^+$: m/z 529.29 found 529.08



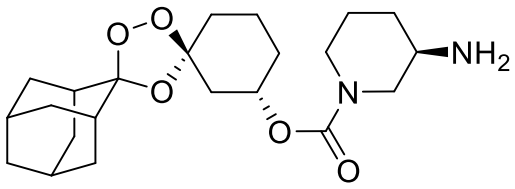
(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (*3R*)-3-aminopiperidine-1-carboxylate (8t).

To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (*3R*)-3-{[(tert-butoxy)carbonyl]amino}piperidine-1-carboxylate (114 mg, 0.225 mmol, 1 equiv) in MeOH (5 mL) cooled to 0 ºC was added acetyl chloride (160 µL, 2.25mmol, 10 equiv) dropwise via microsyringe. The reaction was stirred at 0 ºC for 5 minutes before being allowed to return to room temperature. After 16 h, the reaction was quenched with 10 mL 1 M Na_2CO_3 (10 mL) and diluted with DCM (15 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (2 x 10 mL), followed by brine (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) / CH_2Cl_2) with the desired product eluting at 10% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the product were combined and lyophilized to give (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (*3R*)-3-aminopiperidine-1-carboxylate (71.3 mg, 0.175 mmol, 77.9%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-4.9 (m, 1H), 3.97 (br d, 1H, J = 11.0 Hz), 3.77 (br s, 1H), 2.88 (br s, 2H), 2.47 (br s, 4H), 2.1-2.4 (m, 1H), 1.9-2.0 (m, 8H), 1.7-1.9 (m, 8H), 1.6-1.7 (m, 2H), 1.3-1.6 (m, 4H), 1.27 (s, 1H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.6, 111.6, 108.7, 71.4, 47.5, 43.8, 39.9, 36.8, 36.3, 36.3, 34.9, 34.8, 34.7, 34.6, 34.1, 30.6, 29.7, 26.9, 26.5, 23.3, 19.6 MS (ESI) calc for $C_{22}H_{35}N_2O_5$ $[M+H]^+$: m/z calc 407.25 found 407.43



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (*3R*)-3-{[(tert-butoxy)carbonyl]amino}piperidine-1-carboxylate.

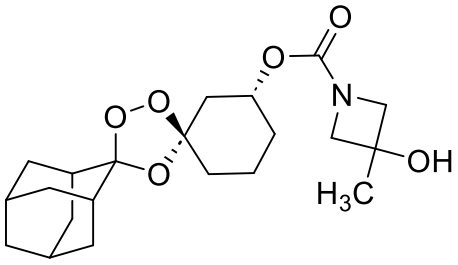
To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (78.2 µL, 0.561 mmol, 2.5 equiv.), followed by tert-butyl (R)-piperidin-3-ylcarbamate (112 mg, 0.561 mmol, 2.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-50% EtOAc:Hexanes) with the desired product eluting at 30% EtOAc. The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (3R)-3-{[(tert-butoxy)carbonyl]amino}piperidine-1-carboxylate (88.7 mg, 0.175 mmol, 78%) as a white solid. MS (ESI) calc for $C_{27}H_{42}N_2O_7$ $[M+H]^+$: m/z 529.29 found 529.24



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (*3R*)-3-aminopiperidine-1-carboxylate (9t).

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (*3R*)-3-{[(tert-butoxy)carbonyl]amino}piperidine-1-carboxylate (88.7 mg, 0.175 mmol, 1 equiv) in MeOH (5 mL) cooled to 0 ºC was added acetyl chloride (124 µL, 1.75 mmol, 10 equiv) dropwise via microsyringe. The reaction was stirred at 0 ºC for 5 minutes before being allowed to return to room temperature. After 16 h, the reaction was quenched with 10 mL 1 M Na_2CO_3 (10 mL) and diluted with DCM (15 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (2 x 10 mL), followed by brine (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% MeOH (containing 0.7 N NH_3) /

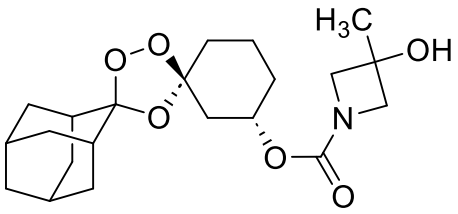
CH_2Cl_2) with the desired product eluting at 15% MeOH (containing 0.7 N NH_3) / CH_2Cl_2). The fractions containing the product were combined and lyophilized to give (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (*3R*)-3-aminopiperidine-1-carboxylate (15 mg, 0.040 mmol, 15%) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 4.7-4.8 (m, 1H), 3.98 (br d, 1H, J = 10.2 Hz), 3.83 (br s, 1H), 2.7-3.1 (m, 5H), 2.2-2.3 (m, 1H), 1.9-2.1 (m, 7H), 1.6-1.9 (m, 12H), 1.3-1.6 (m, 4H), 1.27 (s, 2H); ^{13}C NMR (MeOD, 100 MHz) δ 154.3, 111.6, 108.7, 71.4, 47.4, 43.9, 39.9, 36.8, 36.3, 34.9, 34.8, 34.7, 34.7, 34.1, 31.9, 30.7, 29.7, 26.9, 26.5, 23.4, 22.7, 19.6; MS (ESI) calc for $C_{22}H_{35}N_2O_5$ $[M+H]^+$: m/z 407.25 found 407.38



(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-methylazetidine-1-carboxylate (8u).

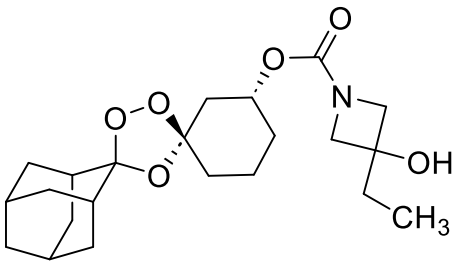
To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (78.2 µL, 0.561 mmol, 2.5 equiv.), followed by 3-methylazetidin-3-ol (48.9 mg, 0.561 mmol, 2.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 10-100% EtOAc:Hexanes) with the desired product eluting at 35% EtOAc. The fractions containing the product were combined and lyophilized to (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-methylazetidine-1-carboxylate (88.3 mg, 0.224 mmol, 100%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-4.8 (m, 1H), 3.8-4.1 (m, 4H), 2.2-2.3 (m, 1H), 1.9-2.1 (m, 7H), 1.7-1.9 (m, 5H), 1.4-1.7 (m, 9H), 1.2-1.4 (m, 3H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2, 111.6, 108.7, 71.2, 68.5,

63.4, 40.1, 36.8, 36.3, 34.9, 34.8, 34.7, 33.9, 30.7, 29.7, 26.9, 26.4, 26.2, 19.6 MS (ESI) calc for $C_{21}H_{31}NO_6Na$ $[M+Na]^+$: m/z 416.20 found 416.43



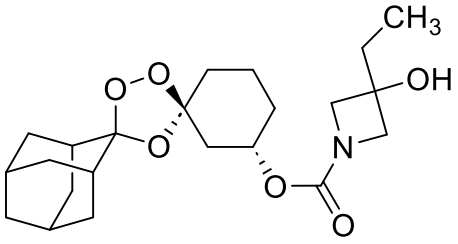
(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-methylazetidine-1-carboxylate (9u).

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (78.2 µL, 0.561 mmol, 2.5 equiv.), followed by 3-methylazetidin-3-ol (48.9 mg, 0.561 mmol, 2.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 10-100% EtOAc:Hexanes) with the desired product eluting at 35% EtOAc. The fractions containing the product were combined and lyophilized to yield (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-methylazetidine-1-carboxylate (77.0 mg, 0.196 mmol, 87.2%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-4.8 (m, 1H), 3.8-4.0 (m, 4H), 2.50 (br s, 1H), 2.2-2.3 (m, 1H), 1.9-2.1 (m, 7H), 1.7-1.9 (m, 6H), 1.5-1.7 (m, 10H), 1.2-1.4 (m, 2H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2, 111.6, 108.7, 71.2, 68.5, 63.4, 40.1, 36.8, 36.3, 36.3, 34.9, 34.8, 34.7, 33.9, 30.7, 29.7, 26.9, 26.4, 26.2, 19.6 MS (ESI) calc for $C_{21}H_{31}NO_6Na$ $[M+Na]^+$: m/z 416.20 found 416.33



(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-ethyl-3-hydroxyazetidine-1-carboxylate (8v).

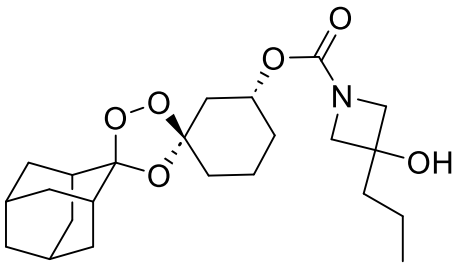
To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (110 µL, 0.786 mmol, 3.5 equiv.), followed by 3-ethylazetidin-3-ol (79.5 mg, 0.786 mmol, 3.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-60% EtOAc:Hexanes) with the desired product eluting at 30% EtOAc. The fractions containing the product were combined and lyophilized to yield (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-ethyl-3-hydroxyazetidine-1-carboxylate (67.2 mg, 0.165 mmol, 73.5%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-4.8 (m, 1H), 3.87 (q, 4H, J = 9.2 Hz), 2.2-2.3 (m, 1H), 2.08 (br d, 1H, J = 11.2 Hz), 1.9-2.0 (m, 7H), 1.7-1.9 (m, 9H), 1.4-1.7 (m, 3H), 1.2-1.4 (m, 2H), 0.99 (t, 3H, J = 7.4 Hz) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2, 111.6, 108.7, 71.4, 71.2, 61.6, 40.0, 36.8, 36.3, 34.9, 34.8, 34.7, 33.9, 31.6, 30.7, 26.9, 26.5, 19.6, 7.4 MS (ESI) calc for $C_{22}H_{33}NO_6Na$ $[M+Na]^+$: m/z 430.22 found 430.34



(*S,S*)-dispiro[adamantane-2,2'-[1,3,5]trioxolane-4',1''-cyclohexan]-3''-yl 3-ethyl-3-hydroxyazetidine-1-carboxylate (9v).

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (110 µL, 0.786 mmol, 3.5 equiv.), followed by 3-methylazetidin-3-ol (79.5 mg, 0.786 mmol, 3.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous

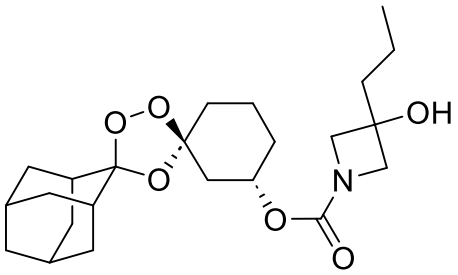
layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-60% EtOAc:Hexanes) with the desired product eluting at 30% EtOAc. The fractions containing the product were combined and lyophilized to yield (*S,S*)-dispiro[adamantane-2,2'-[1,3,5]trioxolane-4',1''-cyclohexan]-3''-yl 3-ethyl-3-hydroxyazetidine-1-carboxylate (71.4 mg, 0.175 mmol, 78.1%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-4.8 (m, 1H), 3.8-3.9 (m, 4H), 2.1-2.3 (m, 1H), 2.06 (s, 1H), 1.9-2.0 (m, 8H), 1.7-1.9 (m, 9H), 1.4-1.7 (m, 3H), 1.2-1.4 (m, 2H), 0.99 (t, 3H, J = 7.4 Hz) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1, 111.6, 108.7, 71.4, 71.1, 61.6, 40.0, 36.8, 36.3, 36.3, 34.9, 34.8, 34.7, 33.9, 31.6, 30.7, 26.9, 26.5, 19.6, 7.4 MS (ESI) calc for $C_{22}H_{33}NO_6Na$ $[M+Na]^+$: m/z 430.22 found 430.29



(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-propylazetidine-1-carboxylate (8w).

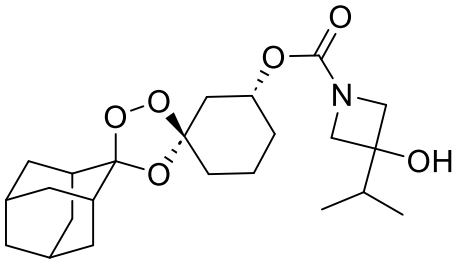
To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (93.9 µL, 0.673 mmol, 3 equiv.), followed by 3-propylazetidin-3-ol (79.5 mg, 0.673 mmol, 3 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-60% EtOAc:Hexanes) with the desired product eluting at 20% EtOAc. The fractions containing the product were combined and lyophilized to yield (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-propylazetidine-1-carboxylate (94.6 mg, 0.224 mmol, 100%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-

4.8 (m, 1H), 3.8-3.9 (m, 4H), 2.2-2.3 (m, 1H), 2.14 (br s, 1H), 1.9-2.0 (m, 7H), 1.7-1.9 (m, 12H), 1.6-1.7 (m, 1H), 1.4-1.6 (m, 3H), 1.3-1.4 (m, 1H), 0.99 (t, 3H, J = 7.4 Hz) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1, 111.6, 108.7, 71.1, 71.0, 62.1, 41.0, 40.1, 36.8, 36.3, 36.3, 34.9, 34.8, 34.7, 33.9, 30.7, 26.9, 26.5, 19.6, 16.7, 14.2 MS (ESI) calc for $C_{23}H_{35}NO_6Na$ $[M+Na]^+$: m/z 444.24 found 444.35



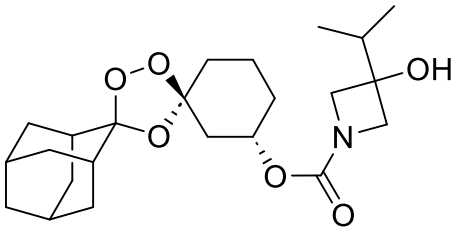
(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-propylazetidine-1-carboxylate (9w).

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (110 µL, 0.786 mmol, 3.5 equiv.), followed by 3-propylazetidin-3-ol (90.5 mg, 0.786 mmol, 3.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-60% EtOAc:Hexanes) with the desired product eluting at 20% EtOAc. The fractions containing the product were combined and lyophilized to yield (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-propylazetidine-1-carboxylate (94.6 mg, 0.224 mmol, 100%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-4.8 (m, 1H), 3.8-3.9 (m, 4H), 2.2-2.3 (m, 1H), 2.13 (br s, 1H), 1.9-2.0 (m, 7H), 1.7-1.9 (m, 12H), 1.6-1.7 (m, 1H), 1.4-1.6 (m, 3H), 1.3-1.4 (m, 1H), 0.99 (t, 3H, J = 7.3 Hz) ^{13}C NMR ($CDCl_3$, 100 MHz) δ156.1, 111.6, 108.7, 71.1, 71.0, 62.1, 41.0, 40.1, 36.8, 36.3, 36.3, 34.9, 34.8, 34.7, 33.9, 30.7, 26.9, 26.5, 19.6, 16.7, 14.2 MS (ESI) calc for $C_{23}H_{35}NO_6Na$ $[M+Na]^+$: m/z 444.24 found 444.30



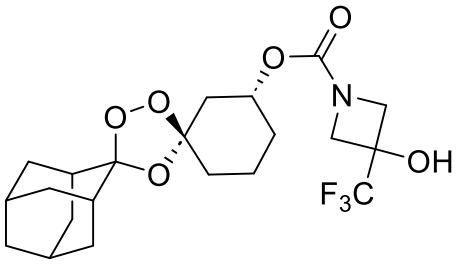
(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-(propan-2-yl)azetidine-1-carboxylate (8x).

To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (93.9 µL, 0.673 mmol, 3 equiv.), followed by 3-isopropylazetidin-3-ol (77.6 mg, 0.673 mmol, 3 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-60% EtOAc:Hexanes) with the desired product eluting at 40% EtOAc. The fractions containing the product were combined and lyophilized to yield (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-(propan-2-yl)azetidine-1-carboxylate (94.6 mg, 0.224 mmol, 100%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-4.8 (m, 1H), 3.8-4.0 (m, 4H), 2.2-2.3 (m, 1H), 2.12 (br s, 1H), 1.9-2.0 (m, 8H), 1.7-1.9 (m, 7H), 1.4-1.7 (m, 3H), 1.3-1.4 (m, 1H), 0.95 (d, 6H, J = 6.8 Hz) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1, 111.6, 108.7, 73.8, 71.1, 60.7, 40.0, 36.8, 36.3, 36.3, 34.9, 34.8, 34.8, 34.7, 33.9, 30.7, 26.9, 26.5, 19.6, 15.5 MS (ESI) calc for $C_{23}H_{35}NO_6Na$ $[M+Na]^+$: m/z 444.24 found 444.30



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-(propan-2-yl)azetidine-1-carboxylate (9x).

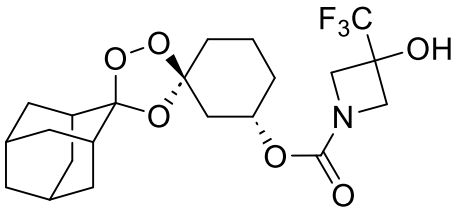
To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (110 µL, 0.786 mmol, 3.5 equiv.), followed by 3-isopropylazetidin-3-ol (90.5 mg, 0.786 mmol, 3.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-60% EtOAc:Hexanes) with the desired product eluting at 40% EtOAc. The fractions containing the product were combined and lyophilized to yield (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-(propan-2-yl)azetidine-1-carboxylate (97.8 mg, 0.232 mmol, Quant.) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-4.8 (m, 1H), 3.8-4.0 (m, 4H), 2.1-2.3 (m, 1H), 1.9-2.0 (m, 9H), 1.7-1.9 (m, 6H), 1.4-1.7 (m, 7H), 1.2-1.4 (m, 1H), 0.95 (d, 6H, J = 6.8 Hz) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1, 111.6, 108.7, 73.9, 71.1, 60.7, 40.0, 36.8, 36.3, 36.3, 34.9, 34.8, 34.7, 34.7, 33.9, 30.7, 26.9, 26.5, 19.6, 15.5 MS (ESI) calc for $C_{23}H_{35}NO_6Na$ $[M+Na]^+$: m/z 444.24 found 444.40



(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-(trifluoromethyl)azetidine-1-carboxylate (8y).

To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (78.2 µL, 0.561 mmol, 2.5 equiv.), followed by 3-(trifluoromethyl)azetidine-3-ol (79.2 mg, 0.561 mmol, 2.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried

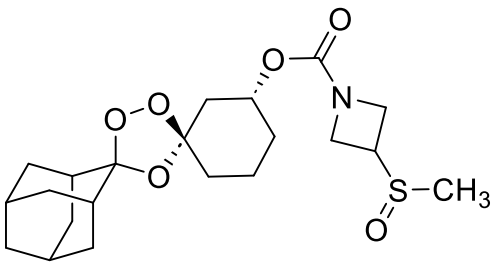
($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% Methanol (with 0.8 N NH_3):DCM) with the desired product eluting at 8% MeOH. The fractions containing the product were combined and lyophilized to yield (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-(trifluoromethyl)azetidine-1-carboxylate (56.0 mg, 0.125 mmol, 55.8%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-4.8 (m, 1H), 4.25 (d, 2H, J = 10.0 Hz), 4.00 (br d, 2H, J = 10.0 Hz), 3.67 (br s, 1H), 2.2-2.3 (m, 1H), 1.9-2.1 (m, 7H), 1.7-1.9 (m, 7H), 1.4-1.7 (m, 3H), 1.2-1.4 (m, 2H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.8, 129.7, 127.4, 125.7, 122.9, 127.2, 127.5, 111.8, 108.6, 72.0, 69.4, 57.2, 56.7, 39.9, 36.7, 36.3, 34.9, 34.8, 34.7, 33.8, 30.5, 29.7, 26.8, 26.4, 19.5 MS (ESI) calc for $C_{21}H_{27}F_3NO_6$ [M-H]- m/z 446.18 found 446.29



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-(trifluoromethyl)azetidine-1-carboxylate (9y).

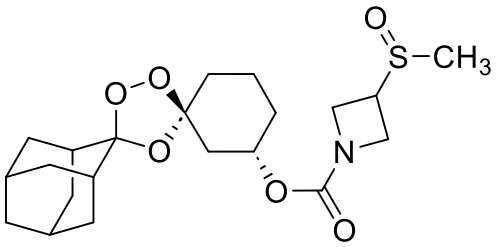
To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (78.2 µL, 0.561 mmol, 2.5 equiv.), followed by 3-(trifluoromethyl)azetidine-3-ol (79.2 mg, 0.561 mmol, 2.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% Methanol (with 0.8 N NH_3):DCM) with the desired product eluting at 8% MeOH. The fractions containing the product were combined and lyophilized to yield (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-hydroxy-3-(trifluoromethyl)azetidine-1-carboxylate (73.9 mg, 0.165 mmol, 73.6%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-4.8 (m, 1H), 4.23 (d, 2H, J = 10.0 Hz), 3.99 (br d, 2H, J = 9.7 Hz), 2.2-2.4 (m, 2H), 1.9-2.1 (m, 8H), 1.7-1.9 (m, 7H), 1.5-1.7 (m, 3H), 1.3-1.4 (m, 1H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.9, 126.4, 111.8, 108.5, 72.1, 69.3, 57.0, 56.7, 39.9, 36.7, 36.3,

34.8, 34.8, 34.7, 34.7, 33.8, 30.5, 26.8, 26.4, 19.5 MS (ESI) calc for $C_{21}H_{27}F_3NO_6$ [M-H]- m/z 446.18 found 446.39



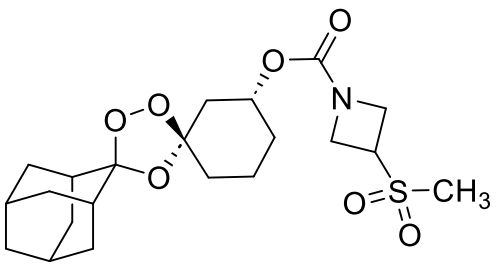
(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-methanesulfinylazetidine-1-carboxylate (8z).

To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (110 µL, 0.786 mmol, 3.5 equiv.), followed by 3-(methylsulfinyl)azetidine (93.6 mg, 0.786 mmol, 3.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% Methanol (with 0.8 N NH_3):DCM) with the desired product eluting at 8% MeOH. The fractions containing the product were combined and lyophilized to yield (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-methanesulfinylazetidine-1-carboxylate (79.3 mg, 0.186 mmol, 83%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 4.7-4.8 (m, 1H), 4.4-4.6 (m, 1H), 4.0-4.3 (m, 3H), 3.56 (tt, 1H, *J* = 5.6, 8.3 Hz), 2.48 (s, 3H), 2.2-2.4 (m, 1H), 2.08 (br s, 1H), 1.98 (br d, 5H, *J* = 13.6 Hz), 1.90 (br s, 2H), 1.7-1.9 (m, 10H), 1.4-1.6 (m, 2H), 1.2-1.4 (m, 1H) ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 155.6, 111.6, 108.6, 100.0, 71.6, 49.2, 48.5, 40.0, 36.8, 36.3, 35.7, 34.9, 34.8, 34.7, 34.7, 33.8, 30.6, 26.9, 26.4, 19.6 MS (ESI) calc for $C_{21}H_{31}NO_6SNa$ $[M+Na]^+$ m/z 448.18 found 448.25



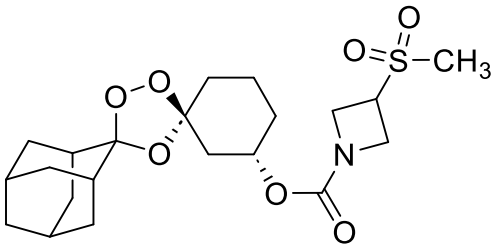
(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-methanesulfinylazetidine-1-carboxylate (9z).

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (110 µL, 0.786 mmol, 3.5 equiv.), followed by 3-(methylsulfinyl)azetidine (93.6 mg, 0.786 mmol, 3.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% Methanol (with 0.8 N NH_3):DCM) with the desired product eluting at 8% MeOH. The fractions containing the product were combined and lyophilized to yield (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-methanesulfinylazetidine-1-carboxylate (72.8 mg, 0.171 mmol, 76.2%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.73 (td, 1H, J = 5.3, 10.2 Hz), 4.4-4.5 (m, 1H), 4.2-4.3 (m, 2H), 4.0-4.1 (m, 1H), 3.56 (tt, 1H, J = 5.6, 8.2 Hz), 2.48 (s, 3H), 2.2-2.3 (m, 1H), 2.0-2.2 (m, 1H), 1.98 (br d, 6H, J = 13.4 Hz), 1.90 (br s, 2H), 1.6-1.9 (m, 12H), 1.2-1.4 (m, 2H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.6, 111.6, 108.6, 71.6, 49.1, 48.5, 40.0, 36.8, 36.3, 35.7, 34.9, 34.8, 34.7, 34.7, 33.8, 30.6, 26.9, 26.4, 19.6 MS (ESI) calc for $C_{21}H_{31}NO_6SNa$ $[M+Na]^+$ m/z 448.18 found 448.35



Synthesis of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-methanesulfonylazetidine-1-carboxylate (8aa).

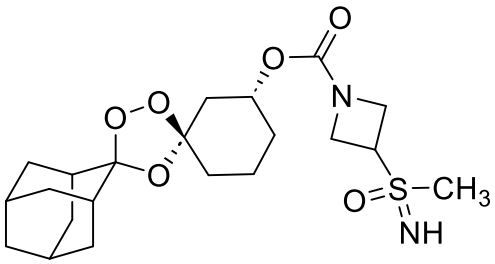
To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (110 µL, 0.786 mmol, 3.5 equiv.), followed by 3-(methylsulfonyl)azetidine (106.0 mg, 0.786 mmol, 3.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% Methanol (with 0.8 N NH_3):DCM) with the desired product eluting at 8% MeOH. The fractions containing the product were combined and lyophilized to yield (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-methanesulfonylazetidine-1-carboxylate (10.8 mg, 0.224 mmol, 10.9%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-4.8 (m, 1H), 4.2-4.4 (m, 4H), 3.8-4.1 (m, 1H), 2.9-3.0 (m, 3H), 2.2-2.3 (m, 1H), 1.9-2.1 (m, 7H), 1.91 (br s, 2H), 1.7-1.9 (m, 8H), 1.5-1.7 (m, 7H), 1.2-1.4 (m, 5H), 0.8-1.0 (m, 1H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.1, 111.7, 108.6, 71.9, 50.1, 49.5, 40.0, 38.4, 36.8, 36.3, 34.9, 34.8, 34.7, 34.7, 33.8, 31.9, 30.6, 29.7, 26.9, 26.4, 19.6 MS (ESI) calc for $C_{21}H_{31}NO_7SNa$ $[M+Na]^+$ m/z 464.17 found 464.40



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-methanesulfonylazetidine-1-carboxylate (9aa).

To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (110 µL, 0.786 mmol, 3.5 equiv.), followed by 3-(methylsulfonyl)azetidine (106.0 mg, 0.786 mmol, 3.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic

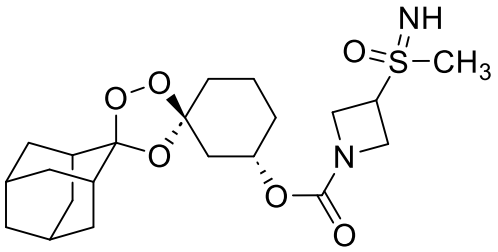
phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% Methanol (with 0.8 N NH_3):DCM) with the desired product eluting at 8% MeOH. The fractions containing the product were combined and lyophilized to yield (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-methanesulfonylazetidine-1-carboxylate (15.3 mg, 0.035 mmol, 15.4%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-4.8 (m, 1H), 4.2-4.4 (m, 4H), 3.8-4.1 (m, 1H), 2.9-3.0 (m, 3H), 2.2-2.3 (m, 1H), 1.9-2.1 (m, 7H), 1.7-1.9 (m, 10H), 1.4-1.7 (m, 3H), 1.2-1.4 (m, 4H), 0.8-1.0 (m, 1H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 111.7, 108.6, 71.9, 50.1, 49.5, 40.0, 38.4, 36.8, 36.3, 35.8, 34.9, 34.8, 34.7, 34.7, 33.8, 30.6, 29.7, 26.9, 26.4, 19.6 MS (ESI) calc for $C_{21}H_{31}NO_7SNa$ $[M+Na]^+$ m/z 464.17 found 464.35



(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-[imino(methyl)oxo-lambda6-sulfanyl]azetidine-1-carboxylate (8bb).

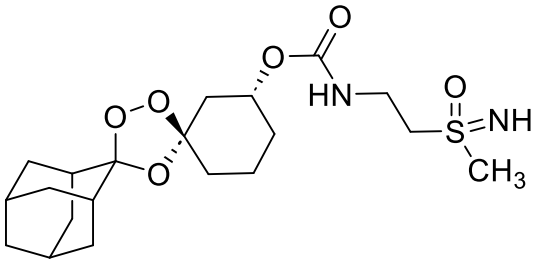
To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (110 µL, 0.786 mmol, 3.5 equiv.), followed by azetidine-3-yl(imino)(methyl)-l6-sulfanone (105 mg, 0.786 mmol, 3.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% Methanol (with 0.8 N NH_3):DCM) with the desired product eluting at 8% MeOH. The fractions containing the product were combined and lyophilized to yield (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl

3-[imino(methyl)oxo-lambda6-sulfanyl]azetidine-1-carboxylate (61.5 mg, 0.140 mmol, 62.2%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.5-4.8 (m, 1H), 4.1-4.3 (m, 4H), 3.02 (s, 2H), 2.85 (br s, 2H), 2.24 (br d, 1H, J = 11.4 Hz), 1.9-2.0 (m, 6H), 1.7-1.9 (m, 6H), 1.4-1.7 (m, 3H), 1.2-1.4 (m, 1H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.6, 111.7, 108.6, 71.9, 52.0, 40.2, 40.0, 36.7, 36.3, 34.8, 34.8, 34.7, 34.7, 33.8, 30.6, 29.7, 26.9, 26.4, 19.6 MS (ESI) calc for $C_{21}H_{33}N_2O_6S$ $[M+H]^+$ m/z 441.21 found 441.34



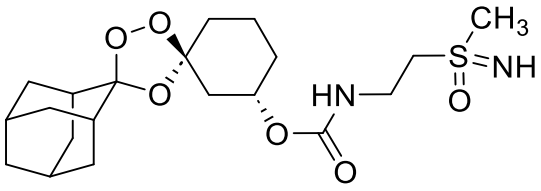
(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-[imino(methyl)oxo-lambda6-sulfanyl]azetidine-1-carboxylate (9bb).

To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (110 µL, 0.786 mmol, 3.5 equiv.), followed by azetidine-3-yl(imino)(methyl)-l6-sulfanone (105 mg, 0.786 mmol, 3.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% Methanol (with 0.8 N NH_3):DCM) with the desired product eluting at 8% MeOH. The fractions containing the product were combined and lyophilized to yield (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl 3-[imino(methyl)oxo-lambda6-sulfanyl]azetidine-1-carboxylate (22.0 mg, 0.050 mmol, 22.2%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-4.8 (m, 1H), 4.3-4.4 (m, 4H), 4.1-4.3 (m, 1H), 3.27 (br d, 2H, J = 16.1 Hz), 3.15 (br s, 2H), 2.2-2.4 (m, 1H), 1.9-2.1 (m, 8H), 1.7-1.9 (m, 7H), 1.4-1.7 (m, 2H), 1.2-1.4 (m, 3H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.6, 111.7, 108.6, 100.0, 72.0, 52.0, 40.1, 36.7, 36.3, 34.8, 34.8, 33.8, 30.6, 29.7, 26.9, 26.4, 19.6 MS (ESI) calc for $C_{21}H_{32}N_2O_6SNa$ $[M+Na]^+$ m/z 463.19 found 463.70



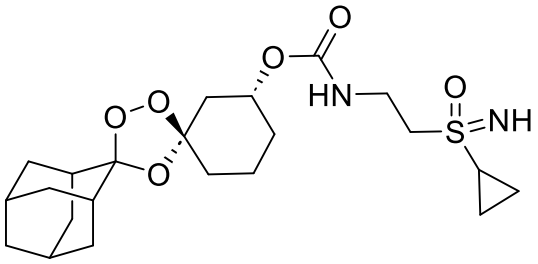
(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-{2-[imino(methyl)oxo-lambda6-sulfanyl]ethyl}carbamate (8cc).

To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (110 µL, 0.786 mmol, 3.5 equiv.), followed by (2-aminoethyl)(imino)(methyl)-l6-sulfanone (96.0 mg, 0.786 mmol, 3.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% Methanol (with 0.8 N NH_3):DCM) with the desired product eluting at 8% MeOH. The fractions containing the product were combined and lyophilized to yield (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-{2-[imino(methyl)oxo-lambda6-sulfanyl]ethyl}carbamate (22.3 mg, 0.052 mmol, 23.2%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.6-4.8 (m, 1H), 3.7-3.8 (m, 2H), 3.4-3.6 (m, 2H), 3.2-3.4 (m, 4H), 2.1-2.4 (m, 1H), 1.9-2.0 (m, 7H), 1.7-1.9 (m, 6H), 1.4-1.6 (m, 2H), 1.2-1.4 (m, 3H) ^{13}C NMR ($CDCl_3$, 100 MHz) Shift 155.9, 111.6, 108.7, 77.3, 71.6, 55.6, 43.2, 40.2, 36.8, 36.3, 36.3, 35.5, 34.8, 34.8, 33.7, 30.7, 29.7, 26.9, 26.4, 19.8 MS (ESI) calc for $C_{20}H_{33}N_2O_6S$ $[M+H]^+$ m/z 429.21 found 429.39



(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-{2-[imino(methyl)oxo-lambda6-sulfanyl]ethyl}carbamate (9cc).

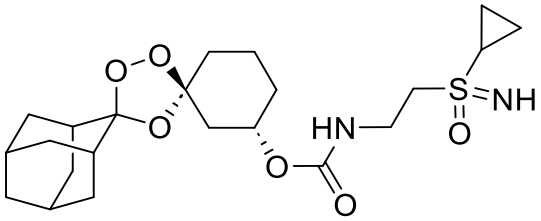
To a solution of (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (110 µL, 0.786 mmol, 3.5 equiv.), followed by (2-aminoethyl)(imino)(methyl)-l6-sulfanone (96.0 mg, 0.786 mmol, 3.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% Methanol (with 0.8 N NH_3):DCM) with the desired product eluting at 8% MeOH. The fractions containing the product were combined and lyophilized to yield (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-{2-[imino(methyl)oxo-lambda6-sulfanyl]ethyl}carbamate (8.4 mg, 0.020 mmol, 8.7%) as a white solid. NMR and UPLC/MS indicated some impurity (~10%) which was carried through downstream analysis. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.72 (br s, 1H), 3.81 (br s, 2H), 3.47 (br s, 2H), 3.2-3.4 (m, 2H), 2.2-2.4 (m, 2H), 1.9-2.1 (m, 9H), 1.85 (br s, 2H), 1.7-1.8 (m, 6H), 1.6-1.7 (m, 2H), 1.51 (br s, 1H), 1.4-1.5 (m, 1H), 1.27 (s, 9H), 1.0-1.2 (m, 1H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.9, 111.7, 108.7, 77.2, 71.7, 55.1, 42.3, 40.2, 36.8, 36.3, 35.3, 34.8, 33.7, 31.9, 30.7, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 26.9, 26.8, 26.5, 24.8, 22.7, 19.8, 14.1 MS (ESI) calc for $C_{20}H_{33}N_2O_6S$ $[M+H]^+$ m/z 429.21 found 429.34



(*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-{2-[cyclopropyl(imino)oxo-lambda6-sulfanyl]ethyl}carbamate (8dd).

To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (110 µL, 0.786 mmol, 3.5 equiv.), followed by (2-aminoethyl)(cyclopropyl)(imino)-l6-sulfanone (116.0 mg, 0.786 mmol, 3.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM

(10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% Methanol (with 0.8 N NH_3):DCM) with the desired product eluting at 8% MeOH. The fractions containing the product were combined and lyophilized to yield (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-{2-[cyclopropyl(imino)oxo-lambda6-sulfanyl]ethyl}carbamate (18.4 mg, 0.041 mmol, 18.0%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89 (br s, 1H), 4.7-4.8 (m, 1H), 3.7-3.9 (m, 2H), 3.4-3.6 (m, 2H), 3.23 (br s, 2H), 2.6-2.8 (m, 1H), 2.26 (td, 1H, *J* = 2.2, 12.9 Hz), 1.9-2.0 (m, 7H), 1.7-1.9 (m, 6H), 1.4-1.7 (m, 3H), 1.1-1.4 (m, 5H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.8, 111.6, 108.7, 71.6, 40.2, 37.1, 36.8, 36.3, 34.8, 33.7, 32.8, 31.9, 30.7, 30.0, 29.7, 26.9, 26.5, 25.9, 19.8, 14.1, 5.8, 5.2 MS (ESI) calc for $C_{22}H_{35}N_2O_6S$ $[M+H]^+$ m/z 455.22 found 455.44

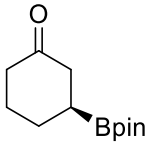


(*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl N-{2-[cyclopropyl(imino)oxo-lambda6-sulfanyl]ethyl}carbamate (9dd).

To a solution of (*R,R*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (100 mg, 0.224 mmol, 1.0 equiv.) in dichloromethane (5 mL) was added triethylamine (110 µL, 0.786 mmol, 3.5 equiv.), followed by (2-aminoethyl)(cyclopropyl)(imino)-l6-sulfanone (116.0 mg, 0.786 mmol, 3.5 equiv.) at rt. The bright yellow mixture was allowed to stir at rt for 16 h. The reaction was quenched with 1 M Na_2CO_3 (10 mL) and diluted with DCM (10 mL). The organic phase was separated and washed with additional 1 M Na_2CO_3 (4 x 10 mL) until the aqueous layer was colorless (indicating that *p*-nitrophenol had been successfully removed from the organic layer). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified using flash column chromatography (12 g silica gel cartridge, 0-20% Methanol (with 0.8 N NH_3):DCM) with the desired product eluting at 8% MeOH. The fractions containing the product were combined and lyophilized to yield (*S,S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-

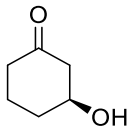
cyclohexan]-3''-yl N-{2-[cyclopropyl(imino)oxo-lambda6-sulfanyl]ethyl}carbamate (35.0 mg, 0.077 mmol, 34.3%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.7-4.8 (m, 1H), 3.8-3.9 (m, 1H), 3.74 (br d, 1H, J = 1.5 Hz), 3.55 (br d, 2H, J = 4.9 Hz), 2.2-2.4 (m, 1H), 1.9-2.0 (m, 7H), 1.86 (br s, 2H), 1.7-1.8 (m, 5H), 1.4-1.7 (m, 7H), 1.37 (br s, 2H), 1.0-1.1 (m, 4H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.8, 111.6, 108.7, 100.0, 48.1, 36.8, 36.3, 34.8, 34.7, 33.7, 30.7, 30.1, 29.7, 26.9, 26.5, 19.7, 14.1, 5.5, 4.8 MS (ESI) calc for $C_{22}H_{35}N_2O_6S$ $[M+H]^+$ m/z 455.22 found 455.49

Synthesis of (S,S) Intermediates



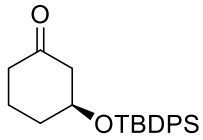
(*S*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexan-1-one (2).

A heat-gun dried, two-necked 50-mL round bottom flask equipped with an Ar(g) inlet, stirbar and rubber septum, was charged with copper(I)chloride (16.2 mg, 0.164 mmol, 0.02 equiv.), sodium tert-butoxide (23.6 mg, 0.246 mmol, 0.03 equiv.) and (*R*)-(+)-[(*R*)-2-diphenylphosphinoferrocenyl](N,N-dimethylamino)(2-diphenylphosphinophenyl)methane (*R,R*-Taniaphos) (225 mg, 0.328 mmol, 0.04 equiv.) followed by anhydrous THF (15 mL). The homogenous orange solution was stirred at rt for 30 min before a solution of bis(pinacolato)diboron (2.288 g, 9.01 mmol, 1.1 equiv.) in anhydrous THF (11 mL) was added. The reaction mixture was stirred for 10 mins at rt before 2- cyclohexen-1-one (0.793 mL, 8.192 mmol, 1.0 equiv.) was added via syringe, followed by anhydrous MeOH (663 µL, 16.383 mmol, 2.0 equiv.) and anhydrous THF (11 mL). The reaction was stirred at rt for 24 h before being judged complete by TLC (1:3, EtOAc–Hexanes with CAM staining, product Rf 0.40). The reaction mixture was then filtered through celite and the pad washed with EtOAc (100 mL), the filtrate was then concentrated under reduced pressure to a crude orange oil (3.85 g). Purification via flash column chromatography (120 g silica gel cartridge, 0-25% EtOAc–Hexanes) afforded pinacol ester (*S*)-2 (1.77 g, 7.88 mmol, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23–2.45 (m, 4H), 2.01–2.12 (m, 1H), 1.83–1.94 (m, 1H), 1.67–1.81 (m, 1H), 1.56–1.68 (m, 1H), 1.38–1.52 (m, 1H), 1.20–1.27 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 83.5, 83.4, 42.6, 41.9, 28.4, 26.5, 25.0, 24.7, 24.7; MS (ESI) calcd for $C_{12}H_{22}BO_3$ $[M+H]^+$: m/z 225.17, found: 225.06.



(*S*)-3-hydroxycyclohexan-1-one (3).

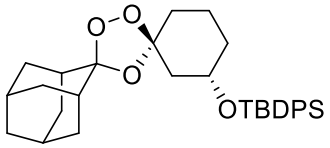
To a 150-mL round bottom flask equipped with a stirbar, rubber septum and Ar(g) inlet was added pinacol ester (*S*)-2 (1.82 g, 8.12 mmol, 1.0 equiv.) followed by THF (14 mL) and DI H_2O (5 mL). Sodium perborate (5.00 g, 32.5 mmol, 4.0 equiv.) was added to the reaction in one portion to give a colorless suspension that was stirred at rt for 3 h. TLC indicated that the reaction was complete (1:1, EtOAc–Hexanes with CAM staining, product Rf 0.31) so the mixture was filtered through a glass frit with EtOAc (100 mL) to wash the funnel. The filtrate was transferred to a separating funnel and brine (11 mL) was added, the layers were separated and the aqueous layer was back-extracted with EtOAc (3 × 30 mL) until only pinacol remained in the aqueous layer by TLC. The combined organic layers were concentrated under reduced pressure to a crude colorless oil (1.90 g). Purification via flash column chromatography (220 g silica gel cartridge, 0-80% EtOAc–Hexanes) afforded alcohol (S)-3 (794 mg, 6.96 mmol, 83%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14–4.22 (m, 1H), 2.79 (br s, 1H), 2.63 (dd, J = 14.1, 4.1 Hz, 1H), 2.40 (dd, J = 14.1, 7.5 Hz, 1H), 2.30 (t, J =6.6 Hz, 1H), 1.96–2.12 (m, 2H), 1.64–1.81 (m, 2H); MS (ESI) calcd for $C_6H_{11}O_2$ $[M+H]^+$ m/z 115.08, found 115.15.



(*S*)-3-((tert-butyldiphenylsilyl)oxy)cyclohexan-1-one (4).

To a 100-mL round bottom flask equipped with a stirbar, rubber septum and Ar(g) inlet was added alcohol (*S*)-3 (794 mg, 6.96 mmol, 1.0 equiv.), anhydrous N,N-dimethylformamide (19 mL), and imidazole (947 mg, 13.91 mmol, 2.0 equiv.). The mixture was cooled to 0 °C while tert-butyl(chloro)diphenyl silane (1.81 mL, 6.96 mmol, 1.0 equiv.) was added dropwise via syringe and the reaction was warmed gradually to rt over 16 h. The following day, the reaction mixture was diluted with EtOAc (100 mL) and DI H_2O (100 mL) and the layers were separated. The organic phase was washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered and concentrated to a

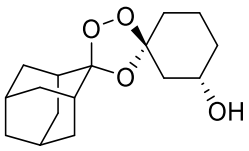
crude colorless oil (1.90 g). Purification via flash column chromatography (220 g silica gel cartridge, 0-9% EtOAc–Hexanes, product elutes during 6% EtOAc–Hexanes) afforded ketone (*S*)-4 (contaminated with 13% by weight t-BuPh2SiOH, 2.74 g, 7.77 mmol) as a colorless oil that was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.72 (m, 4H), 7.38–7.49 (m, 6H), 4.22 (app quin, J = 4.9 Hz, 1H), 2.46 (d, J = 4.9 Hz, 2H) 2.34–2.42 (m, 1H), 2.23–2.32 (m, 1H), 2.11–2.21 (m, 1H), 1.75–1.84 (m, 2H), 1.67 (dt, J = 12.5, 6.3 Hz, 1H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9, 135.8, 135.7, 134.8, 133.9, 133.6, 129.8, 129.8, 127.7, 127.7, 71.1, 50.4, 41.2, 32.9, 29.7, 26.9, 20.6, 19.2; MS (ESI) calcd for $C_{22}H_{28}O_2SiNa$ $[M+Na]^+$: m/z 375.18, found: 374.98.



(*1S,3″S*)-tert-butyl((dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl)oxy) diphenylsilane (5).

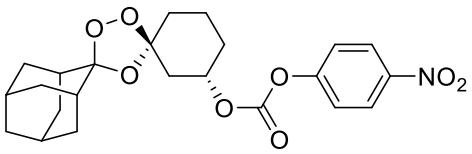
To a 200-mL recovery flask equipped with a stir bar was added ketone (*S*)-4 (2.74 g, 7.77 mmol, 1.0 equiv.), CCl_4 (114 mL), and O-methyl 2-adamantanone oxime (2.09 g, 11.66 mmol, 1.5 equiv.). The solution was cooled to 0 ˚C and sparged with O_2 for 10 minutes. The reaction was maintained at 0 ˚C while ozone was bubbled through the solution (2 L/min, 40% power). After stirring for 100 min, the reaction was deemed to be incomplete based on TLC and LCMS analysis. Additional oxime (348 mg, 1.94 mmol, 0.25 equiv.) was added in a single portion to the reaction with CCl4 (30 mL) and ozone was bubbled through the reaction for a further 2 h. Additional oxime (348 mg, 1.94 mmol, 0.25 equiv.) was added in a single portion and ozone was bubbled through the reaction for a further 40 min until TLC and LCMS showed consumption of ketone starting material. The solution was then sparged with O_2 for 10 min, sparged with Ar(g) for 10 min and concentrated under reduced pressure to a crude semi-solid (5.95 g). Purification via flash column chromatography (220 g silica gel cartridge, 0-5% EtOAc–Hexanes, product eluted during 4% EtOAc–Hexanes) afforded trioxolane (*S,S*)-5 (2.82 g, 5.44 mmol, 67% over 2-steps from 3) as a colorless solid. The diastereoselectivity of the Griesbaum co-ozonolysis was determined to be 92:8 in favor of the trans diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.72 (m, 4H), 7.35–7.46 (m, 6H), 3.88–3.97 (m, 1H), 3.74–3.87 (m, 1H), 1.91–2.11 (m, 3H), 1.63–1.80 (m, 12H), 1.45–1.62 (m, 3H), 1.15–1.44 (m, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 135.8, 135.7, 134.5 (minor diastereomer), 134.4 (minor diastereomer), 129.5, 129.5, 127.6, 127.5, 112.8, 111.2, 110.2 (minor diastereomer), 109.2, 109.0 (minor diastereomer), 77.2, 69.8, 43.8, 37.1, 37.0, 36.9, 36.8, 36.3, 36.2, 34.9, 34.9, 34.7, 34.7, 34.6, 34.4, 34.2, 34.0, 33.8, 33.6, 33.2, 31.5, 27.1, 27.1, 27.0 (app d, J = 1.5 Hz), 26.9, 26.5, 26.1 (app d, J = 1.5 Hz), 19.9, 19.2, 14.2; MS (ESI) calcd for $C_{32}H_{42}O_4Si$ $[M+Na]^+$: m/z 541.28, found: 541.08.



(*1S,3″S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-ol (6).

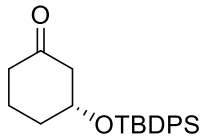
To a stirred solution of trioxolane (S,S)-5 (2.85 g, 5.49 mmol, 1.0 equiv.) in anhydrous THF (30 mL) at 0 °C was added a solution of tetrabutylammonium fluoride (1.0 M in THF, 27.5 mL, 27.5 mmol, 5.0 equiv.). The reaction mixture was allowed to warm to rt and stirred for 12 h until deemed complete by LCMS and TLC (1:9, EtOAc–Hexanes with CAM staining, product Rf 0.08). The reaction was then diluted with DI H_2O (30 mL) and extracted with EtOAc (1 × 30 mL). The aqueous layer was back-extracted with EtOAc (3 × 30 mL) and the combined organic phases were washed with brine (1 × 50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to a crude colorless oil (4.87 g). Purification via flash column chromatography (220 g silica gel cartridge, 0-29% EtOAc–Hexanes, product eluted during 20% EtOAc–Hexanes) afforded alcohol (S,S)-6 (1.37 g, 4.87 mmol, 89%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91–4.01 (m, 1H), 2.56 (br s, 1H), 1.99–2.10 (m, 3H), 1.87–1.99 (m, 5H), 1.73–1.87 (m, 6H), 1.66–1.73 (m, 6H), 1.36–1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.2, 112.0, 109.0, 68.2, 41.6, 37.2, 36.7, 36.2, 36.2, 35.0, 34.9, 34.8, 33.7, 33.7, 33.0, 31.2, 29.7, 27.1, 26.8, 26.4, 19.1; MS (ESI) calcd for $C_{16}H_{24}O_4Na$ $[M+Na]^+$: m/z 303.16, found 303.13.



(*1S,3″S*)-dispiro[adamantane-2,3'-[1,2,4]trioxolane-5',1''-cyclohexan]-3''-yl (4-nitrophenyl) carbonate (7).

To an oven-dried 250-mL round bottom flask equipped with a stirbar, Ar(g) inlet and rubber septum was added alcohol (S,S)-6 (1.30 g, 4.64 mmol, 1.0 equiv.) followed by anhydrous dichloromethane (93 mL) and N,N-diisopropylethylamine (2.63 mL, 15.1 mmol, 3.25 equiv.). 4-Dimethylaminopyridine (680 mg, 5.56 mmol, 1.2 equiv.) was added and the reaction was cooled to 0 °C before 4-nitrophenylchloroformate (3.04 g, 15.1 mmol, 3.25 equiv.) was added in two portions. The cloudy yellow solution was stirred at rt for 3 h before LCMS and TLC (1:5, EtOAc–Hexanes, product Rf 0.50) indicated that the reaction was complete. The reaction was then diluted with DI H_2O (60 mL) and extracted with dichloromethane (1 × 60 mL). The aqueous layer was back-extracted with dichloromethane (3 × 50 mL) and the combined organic phases were washed repeatedly with 1 M aq Na_2CO_3 solution until the aqueous layer was visibly less yellow (meaning that significant quantities of *p*-nitrophenol had been removed from the organic layer). The organic phase was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to a crude yellow oil (2.48 g). Purification via flash column chromatography (220 g silica gel cartridge, 0-20% EtOAc–Hexanes, product eluted during 10% EtOAc–Hexanes) afforded carbonate (S,S)-7 (1.03 g, 2.31 mmol, 50%) as a colorless solid (9:1 dr in favor of the trans diastereomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 4.93–5.01 (m, 1H, minor diastereomer), 4.82–4.90 (m, 1H), 2.41 (dt, J = 12.8, 1.9 Hz, 1H), 2.08–2.15 (m, 1H), 1.97–2.07 (m, 6H), 1.65–1.96 (m, 17H), 1.41–1.64 (m, 3H), 1.19–1.37 (m, 1H), 0.80–0.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 151.8 (minor diastereomer), 151.6, 145.3, 125.3, 121.9 (minor diastereomer), 121.7, 112.2 (minor diastereomer), 112.0, 108.3, 108.1 (minor diastereomer), 76.2, 47.0, 39.7 (minor diastereomer), 39.6, 39.3, 36.7, 36.4, 36.3 (minor diastereomer), 36.3, 35.0 (minor diastereomer), 34.9, 34.8, 34.7, 34.7, 33.5, 33.4 (minor diastereomer), 30.2 (minor diastereomer), 30.1, 29.7, 27.5, 26.8, 26.4, 19.6 (minor diastereomer), 19.6; MS (ESI) calcd for $C_{23}H_{27}NO_8Na$ [M+Na]$^+$: m/z 468.16, found 467.97.

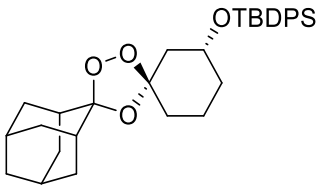
Synthesis of (*R,R*) Intermediates



(*R*)-3-((tert-Butyldiphenylsilyl)oxy)cyclohexan-1-one.

A 200 mL round-bottom flask equipped with a stirbar, rubber septum, and argon inlet was charged with (*R*)-3-hydroxycyclohexan-1-one (2.1 g, 18.4 mmol, 1.0 equiv.), N,N-

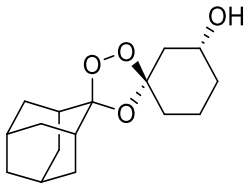
dimethylformamide (40 mL), and imidazole (2.51 g, 36.8 mmol, 2.0 equiv.). The mixture was cooled at 0 °C while tert-butyl(chloro)diphenyl silane (5.3 mL, 20.2 mmol, 1.1 equiv.) was added dropwise via syringe. The reaction mixture was allowed to slowly warm to room temperature (rt). After stirring for 16 h, the reaction was judged complete based on TLC and LC/MS analysis. The reaction mixture was then diluted with EtOAc (100 mL) and DI H_2O (100 mL). The organic phase was separated and washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated to afford a colorless oil. The crude material was purified using flash column chromatography (330 g silica gel cartridge, 0–20% EtOAc–Hexanes, product eluted during 8% EtOAc–Hex) to give the desired ketone 4 (6.01 g, 17.05 mmol, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.68–7.72 (m, 4 H), 7.39–7.49 (m, 6 H), 4.23 (t, *J* = 4.9 Hz, 1 H), 2.47 (d, *J* = 5.0 Hz, 2 H), 2.35–2.42 (m, 1 H), 2.25–2.32 (m, 1 H), 2.17 (br dd, *J* = 8.5, 5.8 Hz, 1 H), 1.78–1.83 (m, 2 H), 1.64–1.71 (m, 1 H), 1.08–1.12 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 210.0, 135.8, 135.7, 134.9, 133.9, 133.6, 129.9, 129.8, 127.7, 127.7, 71.1, 50.4, 41.2, 32.9, 26.9, 26.6, 20.6, 19.2. MS (ESI) calcd for $C_{22}H_{29}O_2Si$ $[M+H]^+$: m/z 353.19, found 353.46.



(*1R,3″R*)-tert-Butyl((dispiro[adamantane-2,3′-[1,2,4]trioxolane-5′,1″-cyclohexan]-3″-yl)oxy) diphenylsilane.

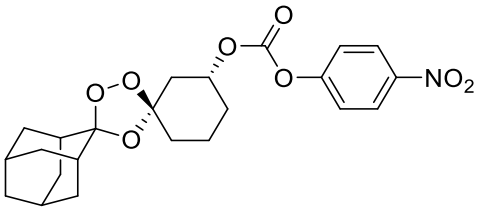
A 200 mL recovery flask was charged with ketone (*R*)-4 (1.51 g, 4.28 mmol, ca. 1 equiv), carbon tetrachloride (100 mL), and O-methyl 2-adamantanone oxime (768 mg, 4.28 mmol, 1.0 equiv). The solution was cooled to 0 °C and sparged with O2 for 10 min. The reaction was maintained at 0 °C while ozone was bubbled (2 L/min, 40% power) through the solution. After stirring for 90 min, the reaction was judged to be incomplete based on TLC and LC/MS analysis, so additional oxime (0.386 g, 2.14 mmol, 0.5 equiv) was added in a single portion to the reaction mixture followed by additional carbon tetrachloride (50 mL). Ozone was bubbled through the reaction mixture for another 45 min, after which a third portion of oxime (0.386 g, 2.14 mmol, 0.5 equiv) was added and ozone again was bubbled through the reaction for a final 45 min. The solution was then sparged with O2 for 10 min to remove any dissolved ozone, followed by sparging with argon gas for 10 min to remove any dissolved oxygen. The solution was then concentrated

under reduced pressure to provide a viscous oil. The crude material was purified using flash column chromatography (120 g silica gel cartridge, 0–20% EtOAc–Hexanes, product eluted during 5% EtOAc–Hex) to give the desired trioxolane product 5 (2.01 g, 3.87 mmol, 91%, 12:1 dr) as a colorless semisolid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (td, J = 7.7, 1.5 Hz, 4 H), 7.36–7.46 (m, 6 H), 3.89–3.96 (m, 1 H), 3.78–3.85 (m, 1 H), 1.95–2.05 (m, 3 H), 1.65–1.84 (m, 12 H), 1.46–1.65 (m, 3 H), 1.19–1.36 (m, 3 H), 1.08 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 135.8, 134.5, 134.4, 129.6, 129.5, 127.6, 127.5, 111.2, 109.2, 69.8, 43.8, 36.8, 36.3, 36.2, 34.8, 34.4, 33.8, 33.2, 27.0, 26.9, 26.5, 19.9, 19.2. MS (ESI) calcd for $C_{32}H_{42}NaO_4Si$ $[M+Na]^+$: m/z 541.28, found 541.56.



(*1R,3″R*)-Dispiro[adamantane-2,3′-[1,2,4]trioxolane-5′,1″-cyclohexan]-3″-ol.

To a stirred solution of 5 (2.0 g, 3.86 mmol, 1.0 equiv.) in THF (20 mL) was added a solution of tetrabutylammonium fluoride (1.0 M in THF, 19.2 mL, 19.3 mmol, 5.0 equiv.) dropwise while stirring at 0 °C. The reaction mixture was allowed to slowly warm to rt and was stirred for 12 h, at which point conversion was determined to be complete based on TLC and LC/MS analysis. The reaction was then diluted with brine (100 mL) and extracted with EtOAc (2 × 100 mL). The organic layer was then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a yellow oil. The crude material was purified using flash column chromatography (80 g silica gel cartridge, 0–50% EtOAc–Hexanes, product eluted during 20% EtOAc–Hex) to yield the desired product 6 (1.01 g, 3.60 mmol, 93%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.94–4.14 (m, 1 H), 2.47 (br s, 1 H), 2.07 (d, J = 4.0 Hz, 1 H), 1.90–2.05 (m, 7 H), 1.69–1.88 (m, 12 H), 1.47–1.63 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.9, 109.1, 67.9, 41.7, 36.7, 36.2, 36.2, 34.9, 34.9, 34.8, 34.7, 33.8, 33.1, 26.8, 26.4, 19.1. MS (ESI) calcd for $C_{16}H_{24}O_4$ $[M+H]^+$: m/z 281.17, found 281.51.



(*1R,3″R*)-Dispiro[adamantane-2,3′-[1,2,4]trioxolane-5′,1″-cyclohexan]-3″-yl (4-nitrophenyl) carbonate.

To an oven-dried round-bottom flask containing a magnetic stir bar under an Ar (g) atmosphere was added alcohol 6 (0.150 mg, 0.54 mmol, 1.0 equiv.), dichloromethane (10 mL), N,N-diisopropylethylamine (0.30 mL, 1.74 mmol, 3.25 equiv.), and 4-dimethylaminopyridine (0.078 g, 0.64 mmol, 1.2 equiv.). The mixture was cooled to 0 °C while 4-nitrophenyl chloroformate (0.350 g, 1.74 mmol, 3.25 equiv.) was added as a solid in two portions. The reaction mixture was allowed to warm to rt and was stirred for 3 h. The reaction was diluted with DI H_2O (100 mL) and extracted with EtOAc (1 × 100 mL). The organic layer was washed repeatedly with 1 M aq K_2CO_3 solution until the aqueous layer was colorless and no longer yellow (indicating that most of the *p*-nitrophenol had been successfully removed from the organic layer). The organic layer was then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield a viscous yellow oil. The crude material was purified using flash column chromatography (80 g silica gel cartridge, 0–25% EtOAc–Hexanes, product eluted during 10% EtOAc–Hex) to yield the desired product 7 (208 mg, 0.467 mmol, 87%) as a pale yellow oil (93:7 d.r.). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 9.1 Hz, 2 H), 7.38 (br d, J = 9.1 Hz, 2 H), 4.94 (td, J = 9.2, 4.5 Hz, 1 H, minor diastereomer), 4.79–4.88 (m, 1 H), 2.32–2.42 (m, 1 H), 2.10 (br d, J = 8.8 Hz, 1 H), 1.69–2.00 (m, 1 H), 1.64–2.01 (m, 17 H), 1.40–1.64 (m, 3 H), 1.20–1.28 (m, 1 H), 0.83–0.96 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 151.6, 145.3, 125.3, 121.9, 121.7, 111.9, 108.3, 76.2, 39.5, 36.7, 36.3, 36.3, 34.8, 34.7, 34.7, 34.7, 33.5, 30.0, 26.8, 26.4, 19.5. MS (ESI) calcd for $C_{23}H_{27}NNaO_8$ $[M+Na]^+$: m/z 468.16, found 467.99.