Supporting Information for

Enantioselective Synthesis and Profiling of Potent, Non-linear Analogues of Antimalarial Tetraoxanes E209 and N205

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1. Computational Details

All calculations were carried out at ground state in the gas phase using density functional theory as implemented in Gaussian16. All geometry optimisations were performed with the M062X functional and using the 6-31G* basis set for C, H, O and P atoms, and LANL2DZ for Rh atoms. Vibrational frequencies were calculated at the same level to ensure each transition states possessed only one negative frequency.

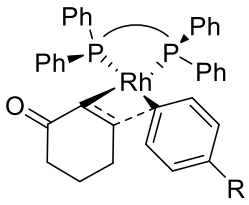
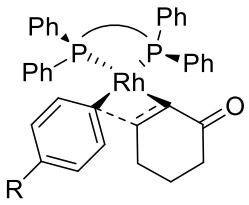
	TS	G (au)	ΔG(kcal/mol)
	Favoured	-3026.738580	-4.4797
	Disfavoured	-3026.731441	

Table S1: Table summarising transition state energies for favoured and disfavoured transition states (TS) of Rhodium (I) catalysed conjugate addition of phenylboronic acid with 2-cyclohexen-1-one

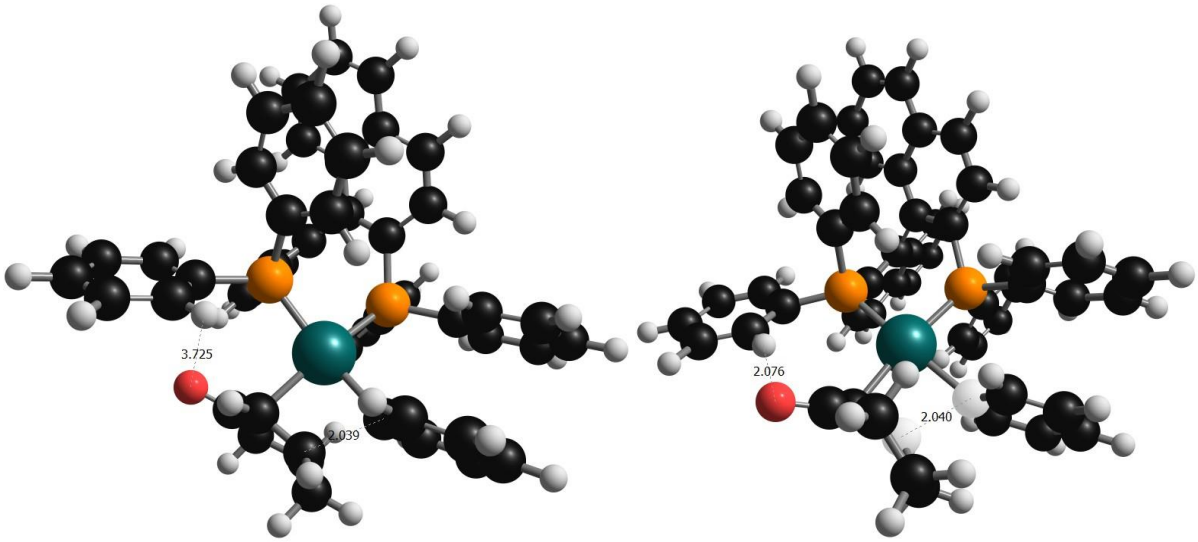


Figure S1: Transition states for favoured and disfavoured products

2. Antimalarial Data

Compounds	*D10* IC_{50} (nM)	*W2* IC_{50} (nM)
9a	17.46 ± 4.86	19.20 ± 5.70
9b	20.77 ± 7.66	22.46 ± 8.45
9c	12.92 ± 4.43	12.80 ± 3.55
10a	17.38 ± 0.49	15.98 ± 5.34
10b	15.96 ± 5.50	15.82 ± 6.16
10c	16.39 ± 4.15	17.68 ± 7.13
14a	12.49 ± 4.64	11.25 ± 1.15
14b	15.22 ± 3.34	15.20 ± 5.53
14c	58.79 ± 17.27	53.59 ± 14.19
15a	10.58 ± 4.54	10.28 ± 2.42
15b	16.46 ± 4.17	14.88 ± 3.05
15c	15.68 ± 5.39	14.44 ± 2.15
CQ	31.92 ± 2.77	462.02 ± 97.57
DHA	2.59 ± 0.67	1.02 ± 0.28

Table S2: IC_{50} of nonlinear tetraoxane containing antimalarials, chloroquine (CQ) and dihydroartemisinin (DHA) against P. falciparum strains, D10 (CQ sensitive) and W2 (CQ resistant)

P. falciparum cultures were prepared according to Trager and Jensen with slight modifications.[1] For the chemosensitivity assays, compounds were dissolved in DMSO and serial dilutions made with complete medium constituted by RPMI 1640 (EuroClone, Celbio) with the addition of 1% AlbuMax (Invitrogen, Milan, Italy), 0.01% hypoxanthine, 20 mM Hepes, and 2 mM glutamine. Asynchronous cultures with parasitaemia of 1-1.5 % and final hematocrit of 1 % were added and the plates were incubated for 72 h at 37 °C. Parasite growth was determined spectrophotometrically by measuring pLDH activity according to Makler with modifications.[2,3] 50 % inhibitory (IC_{50}) values are expressed as mean ± standard deviation (SD) of three different experiments, each performed in duplicate.

3. FaSSIF Solubility Data

Approximately 5mg of each sample was weighed into a glass test tube which was subsequently charged with 3 mL of FaSSIF media or 0.1 N HCl as well as a FaSSIF blank. Samples were mixed at 50rpm by a rotator (Intilli Mixer RM-2M) at 37°C for 1 hour. Mixtures were filtered using 13 mm disk filter (Millipore Millex-HEMF PES 0.45 μm, Merck Millipore) and the filtrate analysed by HPLC. Final pH values were measured using a pH meter (F-53, HORIBA)

4. Pharmacokinetic Properties Assays

The DMPK data showed in the Table 3 were assessed through a high through-put platform kindly provided by AstraZeneca U.K. The methods of the three assays, including aqueous solubility in pH 7.4 PBS buffer, microsome and hepatocyte clearance measurements have been reported previously.[4]

The *in vivo* PK data showed in the Table 6 were obtained in PK studies carried out by a CRO (ChemPartner, Shanghai, China) on behalf of the project team through outsourcing. All *in vivo* PK studies conformed to AAALAC International and NIH guidelines as reported in the Guide for the Care and Use of Laboratory Animals, National Research Council (2011); People's Republic of China, Ministry of Science & Technology, "Regulations for the Administration of Affairs Concerning Experimental Animals," 1988. Full data is included in Tables S3-S6.

Table S3 Individual and mean plasma concentration-time data of TDD-N205 after an IV dose of 2 mg/kg in male SD rats[1]								
Dose	Dose	Sampling	Concentration			**Mean**	SD	CV(%)
(mg/kg)	route	time	(ng/mL)			**(ng/mL)**		
		(hr)	Rat#1	Rat#2	Rat#3			
2	IV	0.083	397	441	407	**415**	23.1	5.56
		0.25	136	211	216	**188**	44.8	23.9
		0.5	102	149	132	**128**	23.8	18.6
		1	53.3	76.5	68.1	**66.0**	11.7	17.8
		2	26.7	27.7	23.1	**25.8**	2.42	9.37
		4	7.68	12.5	6.68	**8.95**	3.11	34.8
		6	1.89	2.88	2.33	**2.37**	0.496	21.0
		8	1.65	3.32	2.94	**2.64**	0.875	33.2
		12	0.905	1.01	1.14	**1.02**	0.118	11.6
		24	0.408	BQL[2]	BQL	**0.408**	NA	NA
PK parameters[3]		Unit	Rat#1	Rat#2	Rat#3	**Mean**	SD	CV(%)
CL		L/hr/kg	7.60	6.09	6.85	**6.85**	0.756	11.0
V_{ss}		L/kg	17.3	9.52	11.8	**12.9**	4.00	31.1
AUC_{last}		hr*ng/mL	258	323	283	**288**	32.7	11.4
AUC_{INF}		hr*ng/mL	263	328	292	**294**	32.7	11.1
Terminal $t_{1/2}$		hr	8.40	3.61	5.10	**5.70**	2.45	43.0
Regression points		hr	8,12,24	6,8,12	6,8,12	**NA**	NA	NA
MRT_{INF}		hr	2.27	1.56	1.72	**1.85**	0.374	20.2

1) No abnormal clinical symptom was observed

2) BQL = Below quantifiable limit of 1.00 ng/mL for IV and PO group in male SD rat plasma.

3) PK parameters were estimated by non-compartmental model using WinNonlin 8.2

Table S4 Individual and mean plasma concentration-time data of TDD-N205 after a PO dose of 10 mg/kg in male SD rats[1]

Dose[2] (mg/kg)	Dose route	Sampling time (hr)	Concentration (ng/mL)			**Mean (ng/mL)**	SD	CV(%)
			Rat#4	Rat#5	Rat#6			
10	PO	0.5	28.5	14.7	26.2	**23.1**	7.39	32.0
		1	24.2	23.1	34.5	**27.3**	6.29	23.1
		2	27.1	16.4	50.8	**31.4**	17.6	56.0
		3	97.6	27.6	68.3	**64.5**	35.2	54.5
		4	89.5	45.7	91.0	**75.4**	25.7	34.1
		5	75.3	183	127	**128**	53.9	41.9
		6	47.4	102	49.5	**66.3**	30.9	46.7
		7	24.8	37.2	33.1	**31.7**	6.32	19.9
		12	8.71	16.7	9.90	**11.8**	4.31	36.6
		24	1.61	1.25	0.917	**1.26**	0.347	27.5
PK parameters		Unit	Rat#4	Rat#5	Rat#6	**Mean**	SD	CV(%)
T_{max}		hr	3.00	5.00	5.00	**4.33**	1.15	26.6
C_{max}		ng/mL	97.6	183	127	**136**	43.4	31.9
AUC_{last}		hr*ng/mL	527	660	615	**601**	67.6	11.2
AUC_{INF}		hr*ng/mL	538	667	619	**608**	65.2	10.7
Terminal $t_{1/2}$		hr	4.41	3.42	3.32	**3.72**	0.602	16.2
Regression points		hr	7,12,24	7,12,24	7,12,24	**NA[4]**	NA	NA
F[5]		%	36.5	45.3	42.0	**41.3**	4.43	10.7

1. No abnormal clinical symptom was observed during entire in-life study.

2. The IV dosing solution was prepared in 10%DMSO and 90% 5%Tween80 in 20 mM phosphate buffer (pH 3.0). The PO dosing solution was prepared in 52 mM citric acid.

3. Concentrations within 75%-100% of the LLOQ were considered within LC/MS-MS normal instrumental variation and included in data presentation and PK parameter estimation.

4. NA: Not available.

5. F value was determined by the following equation:

If AUClast/AUCINF＞80%: F=(AUCINF-EX×DOSEIV)/(AUCINF-IV×DOSEEX)*100%

If AUClast/AUCINF＜80%: F=(AUClast-EX×DOSEIV)/(AUClast-IV×DOSEEX)*100%

Table S5 Individual and mean plasma concentration-time data of 14a after an IV dose at 2 mg/kg in SD rats[1]								
Dose (mg/kg)	Dose route	Sampling time (hr)	Concentration (ng/mL)			**Mean (ng/mL)**	SD	CV(%)
			Rat #1	Rat #2	Rat #3			
2	IV	0.083	788	568	447	**601**	173	28.8
		0.25	360	314	279	**318**	40.6	12.8
		0.5	180	168	192	**180**	12.0	6.67
		1	110	96.6	113	**107**	8.73	8.20
		2	30.1	26.2	31.1	**29.1**	2.59	8.89
		4	2.35	2.07	3.44	**2.62**	0.724	27.6
		6	1.66	1.88	2.26	**1.93**	0.304	15.7
		8	BQL[2]	BQL	BQL	**BQL**	NA	NA
		24	BQL	BQL	BQL	**BQL**	NA	NA
PK parameters[3]		Unit	Rat #1	Rat #2	Rat #3	**Mean**	SD	CV(%)
CL		L/hr/kg	4.71	5.70	5.67	**5.36**	0.567	10.6
V_{ss}		L/kg	3.04	4.00	4.69	**3.91**	0.832	21.3
Regression time		hr	0.25~6	0.083~6	0.083~6	**NA**	NA	NA
Terminal $T_{1/2}$		hr	0.714	0.696	0.748	**0.719**	0.0264	0.0261
AUC_{last}		hr*ng/mL	423	349	350	**374**	42.7	11.4
AUC_{INF}		hr*ng/mL	425	351	352	**376**	42.4	11.3
MRT_{INF}		hr	0.645	0.701	0.827	**0.724**	0.0932	12.9

1) No abnormal clinical symptom was observed

2) BQL = Below quantifiable limit of 1.00 ng/mL for IV and PO group in male SD rat plasma.

3) PK parameters were estimated by non-compartmental model using WinNonlin 8.2

Table S6 Individual and mean plasma concentration-time data of 14a after a PO dose at 10 mg/kg in SD rats[1]								
Dose[2]	Dose	Sampling	Concentration			**Mean**	SD	CV(%)
(mg/kg)	route	time	(ng/mL)			**(ng/mL)**		
		(hr)	Rat #4	Rat #5	Rat #6			
10	PO	0.083	9.40	14.6	3.32	**9.11**	5.65	62.0
		0.25	78.0	76.0	35.0	**63.0**	24.3	38.5
		0.5	241	202	110	**184**	67.3	36.5
		1	364	296	260	**307**	52.8	17.2
		2	406	426	397	**410**	14.8	3.62
		4	221	146	74.7	**147**	73.2	49.7
		6	60.3	53.4	17.9	**43.9**	22.8	51.9
		8	18.8	14.9	6.83	**13.5**	6.10	45.2
		24	2.56	1.73	BQL	**2.15**	NA	NA
PK parameters[3]		Unit	Rat #4	Rat #5	Rat #6	**Mean**	SD	CV(%)
T_{max}		hr	2.00	2.00	2.00	**2.00**	0.00	0.00
C_{max}		ng/mL	406	426	397	**410**	14.8	3.62
Regression time		hr	6~24	6~24	4~8	**NA**	NA	NA
Terminal $T_{1/2}$		hr	4.44	4.10	1.16	**3.23**	1.81	55.8
AUC_{last}		hr*ng/mL	1742	1501	1031	**1425**	361	25.4
AUC_{INF}		hr*ng/mL	1759	1511	1043	**1438**	363	25.3
F[4]		%	93.5	80.4	55.5	**76.4**	19.3	25.3

1) No abnormal clinical symptom was observed

2) The IV and PO dosing solution was prepared in 10%DMSO +90%(5%Tween80 in 20 mM phosphate buffer (pH 3.0)).

3) PK parameters were estimated by non-compartmental model using WinNonlin 8.2

4) The bioavailability (F%) was calculated as following:

AUClast-PO/AUCINF-PO > 80%: F=(AUCINF-PO*DoseIV)/(mean AUCINF-IV*DosePO)

AUClast-PO/AUCINF-PO ≤ 80% or AUCINF was not available: F=(AUClast-PO*DoseIV)/(mean AUClast-IV*DosePO)"

5. Experimental Procedures

Unless stated, all materials were purchased from commercial sources (Sigma Aldrich, Fluorochem, STREM, Alfa Aesar or Apollo) and used without any further treatment. Flash column chromatography (FCC) was performed using silica gel (Aldrich 40-63 μm, 230-400 mesh). Thin layer chromatography (TLC) was performed using aluminium backed 60F254 silica plates. Visualization was achieved by UV fluorescence, $KMnO_4$ solution and heat, 4 wt. % ninhydrin solution in ethanol and heat, or *p*-anisaldehyde solution in ethanol and heat. Proton nuclear magnetic resonance spectra (NMR) were recorded at 400 MHz or 500 MHz. ^{13}C NMR spectra were recorded at 100 MHz or 125 MHz. Chemical shifts (δ) are given in parts per million (ppm) and are listed downfield with tetramethylsilane as a reference. Peaks are described as singlets (s), doublets (d), triplets (t), quartets (q), quintets (quint) multiplets (m) and broad (br.). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. All assignments of NMR spectra were based on 1D NMR data.

Mass spectra were recorded on Agilent QTOF 7200 and Micromass LCT mass spectrometers. For chemical and electrospray ionisation modes ammonia or methanol were used as solvent systems respectively. Microanalyses (%C, %H, %N) were carried out in the University of Liverpool Microanalysis laboratory. Melting points were determined on a Gallenkamp melting point apparatus in degrees Celsius. Chiral HPLC was performed on an Agilent Technologies 1200 series with chiral columns (Chiralpak AD-H, OD, OD-H columns 4.6 × 250 mm, (Daicel Chemical Ind., Ltd.)).

General Procedure A: Rhodium catalysed 1,4-conjugate addition of a boronic acid or ester into cyclohexanone

A round bottomed flask charged with Acetylacetonatobis(ethylene)rhodium(I) and dioxane (0.2M) was degassed and flushed with nitrogen. BINAP (0.1 eq.), $KOH_{(aq)}$ (1:10 ratio to dioxane, 0.1M) and boronic acid were added sequentially before degassing with sonication under vacuum. The cloudy orange mixture was stirred under nitrogen for 10 minutes before adding cyclohexanone (1 eq.). The mixture was degassed and flushed with nitrogen for a final time before heating overnight at 100°C. Upon completion, the dark red mixture was filtered through a plug of silica (eluent Et_2O) and concentrated *in vacuo* to yield the crude product as a dark brown oil.

General Procedure B: Benzyl Deprotection by Palladium Catalysed Hydrogenation

To a colourless solution of benzyl protected phenol in ethyl acetate (0.06 M) was added Pd/C (10% w/w, 5 mol% Pd). The atmosphere was immediately replaced with hydrogen and allowed to stir at room temperature. Upon completion, as determined by TLC, the reaction mixture was filtered through celite and concentrated *in vacuo*, affording the product as a white solid.

General Procedure C: Acetylation of a Phenol with Acetic Anhydride

To a solution of phenol in DCM (0.5 M) was added triethylamine (2 eq.) before the mixture was cooled to 0°C. Acetic anhydride (3 eq.) was added dropwise over 5 minutes. The mixture was allowed to reach room temperature and stirred for 45 minutes before completion was determined by TLC. The mixture was washed with distilled water (3 x 30 ml), saturated sodium bicarbonate (2 x 30 ml) and brine (30 ml). The organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to yield the product as a white solid.

General Procedure D: Rhenium catalysed tetraoxane formation with a cyclohexanone and adamantanone

To a clear solution of cyclohexanone (1 eq.) in MeCN (0.8 M) and formic acid (0.8 M) was added 50 % hydrogen peroxide solution (0.8 M) dropwise at 0°C and allowed to reach room temperature. The mixture was stirred at room temperature for 30 minutes before being diluted with distilled water (10 ml) and extracted with DCM (3 x 30 ml). The combined organic extracts were dried over anhydrous MgSO4 and concentrated *in vacuo* to a volume of approximately 10 ml. The solution of crude dihydroperoxide was diluted with anhydrous DCM (10 ml). To the mixture 2-adamantanone (1.2 eq.) was added and the mixture was cooled to 0°C. Re_2O_7 (0.02 eq.) was added and the mixture was allowed to reach room temperature. The pale-yellow solution was stirred

overnight at room temperature before being filtered through a plug of silica (eluent DCM). The mixture was concentrated *in vacuo* to yield the crude product as a pale-yellow oil.

General Procedure E: Hydrolysis of an Acetyl Group with LiOH

To a solution of phenyl acetate in THF and water (5:2 ratio) was added LiOH (3 eq). The mixture was stirred at room temperature for 2 hours then neutralised with dilute HCl. The THF was removed under reduced pressure and the aqueous phase was extracted with DCM (2 x 20 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to yield the product as a white solid

General Procedure F: S_N2 of an alcohol into an alkyl chloride containing hydrochloride salt

To a clear solution of alcohol (1 eq.) in MeCN was added K_2CO_3 (3 eq.). The mixture was stirred for 1 hour before the addition of alkyl chloride hydrochloride salt (1.1 eq.). The turbid solution was stirred under reflux for 24 hours. The mixture was filtered and concentrated *in vacuo* to yield the crude product.

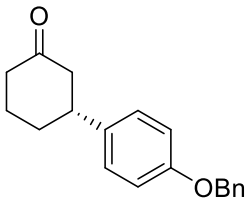
General Procedure G: Reduction of an Ester with $LiAlH_4$

A solution of $LiAlH_4$ in THF (2 eq, 1M) was added dropwise to a solution of ester (1eq) in THF (0.5 M) at 0°C and allowed to stir. Reaction was monitored for completion by TLC and upon completion, approximately 30 minutes, was quenched with HCl solution (1 M) and extracted with ethyl acetate (3 x 30 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to yield the product as a white foam.

General Procedure H: Benzyl Mesylate formation from a Benzyl Alcohol and SN2 of an amine or amine hydrochloride

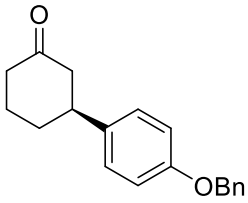
To a solution of benzyl alcohol (1 eq) and triethylamine (2 eq) in DCM (50 ml) was added methane sulfonyl chloride (2 eq) at 0ºC and under N_2. The mixture was allowed to stir at 0ºC for 1 hour before washing with 5% aqueous sodium bicarbonate (50 ml) and water (50 ml). The organic phase was dried over $MgSO_4$ and concentrated in vacuo to yield the crude product as a white foam used without further purification. Crude product was divided for use in multiple reactions. Amine or amine hydrochloride (2 eq) was added to a solution of benzyl mesylate (1 eq) and triethylamine (2 – 4 eq) in anhydrous DCM (0.05 M) under N_2 atmosphere and allowed to stir for 12 hours at room temperature. Upon completion determined by TLC the mixture was diluted with DCM (50 ml) and washed with distilled water (2 x 20 ml) and brine (20 ml). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product as a clear oil.

Preparation of (*R*)-3-(4-benzyloxyphenyl)cyclohexan-1-one (3a)



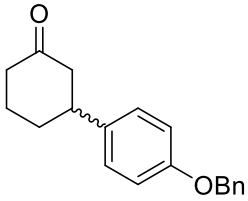
General procedure A was implemented with acetylacetonatobis(ethylene)rhodium(I) (4 mol% Rh), R-BINAP (389 mg, 0.624 mmol), 4-benzyloxyphenylboronic acid (8.90 g, 39.0 mmol) and 2-cyclohexenone (1g, 10.4 mmol) affording the crude product as a dark red oil. The crude product was purified by FCC eluting in 10 % EtOAc in hexane. Product containing fractions were combined and concentrated *in vacuo* affording the product as a white solid (1.65 g, 57 %): ^{1}H NMR (500 MHz, CDCl3) δ 7.51 – 7.32 (m, 5H), 7.17 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 5.09 (s, 2H), 3.04 – 2.95 (m, 1H), 2.65 – 2.34 (m, 4H), 2.22 – 2.04 (m, 2H), 1.90 – 1.73 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 210.78, 157.63, 137.18, 136.96, 128.58, 127.93, 127.53, 127.43, 115.10, 70.17, 49.17, 43.97, 41.15, 33.02, 25.44. HRMS: [ESI+] Calculated for $C_{19}H_{21}O_2$: 281.1536. Found [M+H]+: 281.1530 Diff: 1.05 ppm; The ee of the *R*-enantiomer was determined to be >99% [determined by HPLC, Chiralpak OD-H, n-hexane/isopropanol = 95:5, λ = 225 nm, t (major) = 15.603 min].

Preparation of (S)-3-(4-benzyloxyphenyl)cyclohexan-1-one (3b)



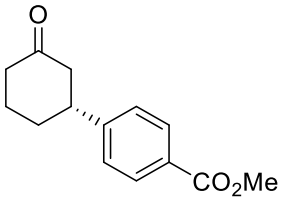
General procedure A was implemented with Acetylacetonatobis(ethylene)rhodium(I) (7 mol% Rh), S-BINAP (647 mg, 1.04 mmol), 4-benzyloxyphenylboronic acid (8.89 g, 39.0 mmol) and 2-cyclohexenone (1g, 10.4 mmol) affording the crude product as a dark red oil. The crude product was purified by FCC eluting in 10 % EtOAc in hexane. Product containing fractions were combined and concentrated *in vacuo* affording the product as a white solid (1.51 g, 52 %): ^{1}H NMR (400 MHz, CDCl3), δ 7.47 – 7.28 (m, 5H), 7.13 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 5.03 (s, 2H), 2.95 (m, 1H), 2.63 – 2.24 (m, 4H), 2.19 – 1.97 (m, 2H), 1.85 – 1.68 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 211.16, 157.56, 137.08, 136.90, 128.62, 127.99, 127.56, 127.49, 115.00, 70.09, 49.24, 44.01, 41.21, 33.02, 25.51. HRMS: [CI+] Calculated for $C_{19}H_{24}NO_2$: 298.1802. Found [M+NH4]+: 298.1805 Diff: 1.01 ppm; The ee of the *S*-enantiomer was determined to be >99% [determined by HPLC, Chiralpak OD-H, n-hexane/isopropanol = 95:5, λ = 225 nm, t (S) = 17.526 min].

Preparation of 3-(4-benzyloxyphenyl)cyclohexan-1-one (3c)



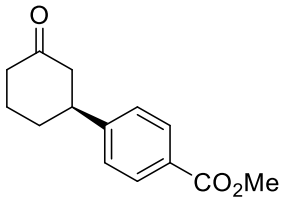
General procedure A was implemented with Acetylacetonatobis(ethylene)rhodium(I) (8 mol% Rh), rac-BINAP (0.12 eq.), 4-benzyloxyphenylboronic acid (4 eq) and 2-cyclohexenone (1 eq) affording the crude product as a dark red oil. The crude product was purified by FCC eluting in 10 % EtOAc in hexane. Product containing fractions were combined and concentrated *in vacuo* affording the product as a white solid (49-59 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.29 (m, 5H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 5.04 (s, 2H), 3.04 – 2.87 (m, 1H), 2.61 – 2.25 (m, 4H), 2.17 – 1.96 (m, 2H), 1.88 – 1.69 (m, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.21, 157.54, 137.06, 136.88, 128.62, 128.00, 127.56, 127.50, 114.97, 70.08, 49.25, 44.01, 41.21, 33.01, 25.51.; HRMS: [ESI+] Calculated for $C_{19}H_{21}O_2$: 281.1536. Found [M+H]+: 281.1538 Diff: -0.84 ppm.

Preparation of Methyl (R)-4-(3-oxocyclohexyl)benzoate (4a)



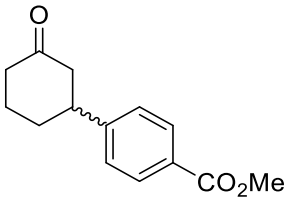
General procedure A was implemented with Acetylacetonatobis(ethylene)rhodium(I) (7 mol% Rh), R-BINAP (648 mg, 0.73 mmol), (4-(methoxycarbonyl)phenyl)boronic acid (7.02 g, 39.0 mmol) and 2-cyclohexenone (1g, 10.4 mmol) affording the crude product as a dark red oil. The crude product was purified by FCC eluting in 10 % EtOAc in hexane. Product containing fractions were combined and concentrated *in vacuo* affording the product as a white solid (2.21 g, 91 %): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 3.91 (s, 3H), 3.08 (tt, J = 11.7, 3.9 Hz, 1H), 2.63 – 2.35 (m, 4H), 2.20 – 2.06 (m, 2H), 1.93 – 1.72 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 209.93, 166.77, 149.43, 130.04, 128.77, 126.61, 51.94, 48.40, 44.61, 41.04, 32.46, 25.36. HRMS: [ESI+] Calculated for $C_{14}H_{17}O_3$: 233.1172. Found [M+H]+: 233.1170 Diff: -0.37 ppm; The ee of the R-enantiomer was determined to be >99% [determined by HPLC, Chiralpak AD-H, n-hexane/isopropanol = 97:3, λ = 225 nm, t (R) = 15.619 min].

Preparation of Methyl (S)-4-(3-oxocyclohexyl)benzoate (4b)



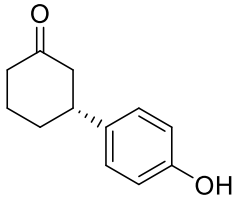
General procedure A was implemented with Acetylacetonatobis(ethylene)rhodium(I) (4 mol% Rh), R-BINAP (194 mg, 0.31 mmol), (4-(methoxycarbonyl)phenyl)boronic acid (3.51 g, 19.5 mmol) and 2-cyclohexenone (500 mg, 4.2 mmol) affording the crude product as a dark red oil. The crude product was purified by FCC eluting in 10 % EtOAc in hexane. Product containing fractions were combined and concentrated *in vacuo* affording the product as a white solid (450 mg, 79 %): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 3.91 (s, 3H), 3.08 (tt, J = 11.8, 3.9 Hz, 1H), 2.63 – 2.34 (m, 4H), 2.22 – 2.04 (m, 2H), 1.92 – 1.73 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 210.25, 166.83, 149.45, 130.05, 128.69, 126.66, 52.06, 48.45, 44.65, 41.10, 32.46, 25.42; HRMS: [ESI+] Calculated for $C_{14}H_{17}O_3$: 233.1172. Found [M+H]+: 233.1172 Diff: 0.28 ppm; The ee of the *S*-enantiomer was determined to be 98 % [determined by HPLC, Chiralpak AD-H, n-hexane/isopropanol = 97:3, λ = 225 nm, t (S) = 19.527 min, t(R) = 15.834 min].

Preparation of Methyl 4-(3-oxocyclohexyl)benzoate (4c)



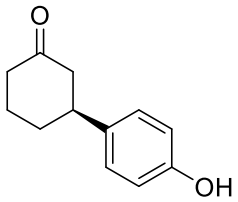
General procedure A was implemented with Acetylacetonatobis(ethylene)rhodium(I) (7 mol% Rh), R-BINAP (648 mg, 1.04 mmol), (4-(methoxycarbonyl)phenyl)boronic acid (7.49 g, 41.6 mmol) and 2-cyclohexenone (1g, 10.4 mmol) affording the crude product as a dark red oil. The crude product was purified by FCC eluting in 10 % EtOAc in hexane. Product containing fractions were combined and concentrated *in vacuo* affording the product as a white solid (70 - 88 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 3.91 (s, 3H), 3.08 (tt, J = 11.7, 4.3 Hz, 1H), 2.66 – 2.29 (m, 4H), 2.23 – 2.01 (m, 2H), 1.96 – 1.71 (m, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.28, 166.85, 149.43, 130.07, 128.71, 126.66, 52.07, 48.47, 44.66, 41.12, 32.47, 25.43.; HRMS: [ESI+] Calculated for $C_{14}H_{17}O_3$: 233.1172. Found [M+H]+: 233.1179 Diff: -4.35 ppm

Preparation of (R)-3-(4-hydroxyphenyl)cyclohexan-1-one (5a)



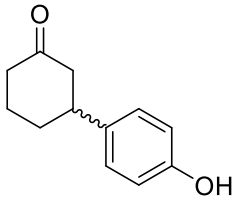
General procedure B was implemented with (R)-3-(4-benzyloxyphenyl)cyclohexan-1-one) (1.4 g, 4.99 mmol) affording the product as a white solid (quantitative). ^{1}H NMR (500 MHz, CDCl3) δ 7.13 – 7.07 (m, 2H), 6.85 – 6.80 (m, 2H), 5.25 (s, 1H), 2.98 (tt, J = 11.8, 3.8 Hz, 1H), 2.64 – 2.35 (m, 4H), 2.20 – 2.05 (m, 2H), 1.88 – 1.73 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.79, 154.34, 136.56, 127.68, 115.47, 49.24, 43.99, 41.18, 32.98, 25.47. HRMS: [ESI-] Calculated for $C_{12}H_{13}O_2$: 189.0921. Found [M-H]-: 189.0921 Diff: 0.21 ppm.

Preparation of (S)-3-(4-hydroxyphenyl)cyclohexan-1-one (5b)



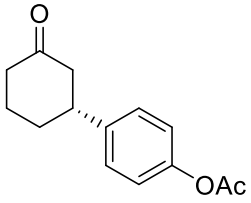
General procedure B was implemented with (S)-3-(4-benzyloxyphenyl)cyclohexan-1-one) (1.29 g, 4.60 mmol) affording the product as a white solid (quantitative). ^{1}H NMR (400 MHz, CDCl3) δ 7.06 (d, J = 8.5 Hz, 2H), 6.84 – 6.79 (m, 2H), 6.29 (s, 1H), 2.94 (tt, J = 11.9, 3.8 Hz, 1H), 2.63 – 2.32 (m, 4H), 2.09 (m, 2H), 1.86 – 1.67 (m, 2H). ^{13}C NMR (101 MHz, CDCl3) δ 212.84, 154.64, 136.21, 127.65, 115.56, 49.23, 44.01, 41.17, 32.94, 25.47. HRMS: [ESI+] Calculated for $C_{12}H_{15}O_2$: 191.1067. Found [M+H]+: 191.1071 Diff: -2.1 ppm.

Preparation of 3-(4-hydroxyphenyl)cyclohexan-1-one (5c)



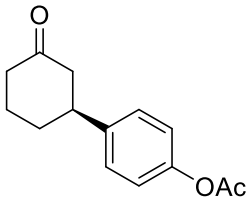
General procedure B was implemented with 3-(4-benzyloxyphenyl)cyclohexan-1-one) affording the product as a white solid (quantitative). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.05 (s, 1H), 3.07 – 2.89 (m, 1H), 2.84 – 1.50 (m, 8H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 212.60, 154.59, 136.29, 127.66, 115.54, 49.24, 44.01, 41.18, 32.95, 25.48.; HRMS: [ESI+] Calculated for $C_{12}H_{15}O_2$: 191.1067. Found [M+H]+: 191.1071 Diff: -2.43 ppm.

Preparation of (R)-3-(4-acetoxyphenyl)cyclohexan-1-one (6a)



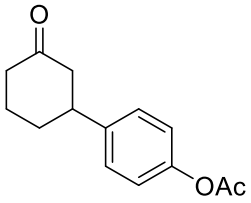
General procedure C was implemented with (R)-3-(4-hydroxyphenyl)cyclohexan-1-one (940 mg, 4.99 mmol) affording the product as a white solid (quantitative): ^{1}H NMR (500 MHz, CDCl3) δ 7.26 – 7.22 (m, 2H), 7.09 – 7.04 (m, 2H), 3.03 (tt, J = 11.9, 3.8 Hz, 1H), 2.64 – 2.34 (m, 4H), 2.31 (s, 3H), 2.20 – 2.06 (m, 2H), 1.91 – 1.73 (m, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 210.71, 169.58, 149.27, 141.86, 127.57, 121.72, 48.95, 44.17, 41.15, 32.79, 25.45, 21.12. HRMS: [ESI+] Calculated for $C_{14}H_{16}NaO_3$: 255.0992. Found [M+Na]+: 255.0989 Diff: 0.95 ppm.

Preparation of (S)-3-(4-acetoxyphenyl)cyclohexan-1-one (6b)



General procedure C was implemented with (S)-3-(4-hydroxyphenyl)cyclohexan-1-one (875 mg, 4.6 mmol) affording the product as a white solid (quantitative): ^{1}H NMR (400 MHz, CDCl3) δ 7.22 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 8.5 Hz, 2H), 3.09 – 2.92 (m, 1H), 2.65 – 2.31 (m, 4H), 2.29 (s, 3H), 2.20 – 2.01 (m, 2H), 1.91 – 1.63 (m, 2H). ^{13}C NMR (101 MHz, CDCl3) δ 210.69, 169.55, 149.26, 141.85, 127.55, 121.70, 48.93, 44.16, 41.13, 32.78, 25.44, 21.10. HRMS: [CI+] Calculated for $C_{14}H_{20}NO_3$: 250.1438. Found [M+NH_4]+: 250.1439 Diff: -0.52 ppm.

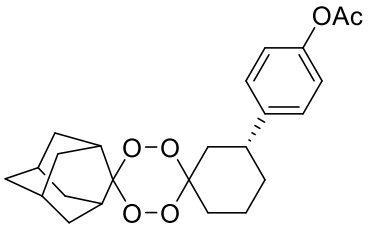
Preparation of 3-(4-acetoxyphenyl)cyclohexan-1-one (6c)



General procedure C was implemented with 3-(4-hydroxyphenyl)cyclohexan-1-one affording the product as a white solid (quantitative): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 3.02 (tt, J = 11.8, 3.9 Hz, 1H), 2.65 – 2.31 (m, 4H), 2.30 (s, 3H), 2.20 – 2.05 (m, 2H), 1.91 – 1.73 (m, 2H).; ^{13}C NMR

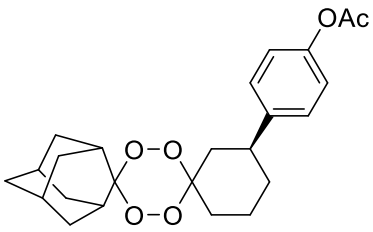
(101 MHz, $CDCl_3$) δ 210.73, 169.59, 149.27, 141.85, 127.56, 121.72, 48.95, 44.17, 41.15, 32.80, 25.45, 21.12.; HRMS: [ESI+] Calculated for $C_{14}H_{17}O_3$: 233.1172. Found [M+H]+: 233.1181 Diff: -3.96 ppm.

Preparation of 4-((1R,3R,3''R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5] tetraoxane-6',1''-cyclohexan]-3''-yl)phenyl acetate (7a)



General procedure D was implemented with (R)-3-(4-acetoxyphenyl)cyclohexan-1-one (1.18 g, 5.1 mmol), MeCN (6 ml), HCO_2H (6 ml), and H_2O_2 (6 ml) then 2-adamantanone (913mg, 6.1 mmol) and Re_2O_7 (50 mg, 0.1 mmol) affording the crude product as a yellow oil. Product was purified by FCC eluting in 5 % ethyl acetate in hexane. Product containing fractions were combined and concentrated *in vacuo* affording the product as a white solid (484 mg, 23 %): ^{1}H NMR (500 MHz, CDCl3) δ 7.26 (s, br, 2H), 7.03 (d, J = 8.3 Hz, 2H), 2.88 (s, 1H), 2.30 (s, 3H), 2.14 – 1.37 (m, 22H); ^{13}C NMR (126 MHz, CDCl3) δ 169.60, 149.05, 149.01, 127.83, 121.47, 110.51, 108.26, 39.38 (br), 36.97, 33.74 (br), 33.19, 33.16, 33.11, 30.22 (br), 27.07, 21.78 (br), 21.12; HRMS: [ESI+] Calculated for $C_{24}H_{30}NaO_6$: 437.1935. Found [M+Na]+: 437.1940 Diff: 1.14 ppm.

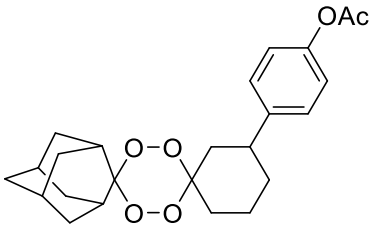
Preparation of 4-((1R,3R,3''S,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5] tetraoxane-6',1''-cyclohexan]-3''-yl)phenyl acetate (7b)



General procedure D was implemented with (S)-3-(4-acetoxyphenyl)cyclohexan-1-one (0.96 g, 4.1 mmol), MeCN (5 ml), HCO_2H (5 ml), and H_2O_2 (5 ml) then 2-adamantanone (726 mg, 4.8 mmol) and Re_2O_7 (39 mg, 0.08 mmol) affording the crude product as a yellow oil. Product was purified by FCC eluting in 5 % ethyl acetate in hexane. Product containing fractions were combined and concentrated *in vacuo* affording the product as a white solid (500 mg, 29 %): ^{1}H NMR (500 MHz, CDCl3) δ 7.26 (s, br, 2H), 7.04 (d, J = 8.2 Hz, 2H), 2.89 (s, br, 1H), 2.31 (s, 3H), 2.13 – 1.03 (m, 22H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.63, 127.86 (br), 121.47, 110.53, 108.27,

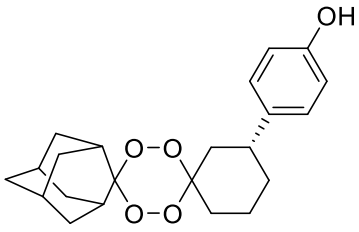
39.43 (br), 36.97, 33.77 (br), 33.19, 33.17, 33.12, 30.10 (br), 27.07 (br), 21.81 (br), 21.13; HRMS: [ESI+] Calculated for $C_{24}H_{30}NaO_6$: 437.1935. Found [M+Na]+: 437.1935 Diff: -1.92 ppm.

Preparation of 4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenyl acetate (7c)



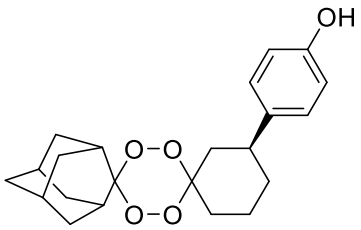
General procedure D was implemented with 3-(4-acetoxyphenyl)cyclohexan-1-one (1 g, 4.3 mmol), MeCN (5 ml), HCO_2H (5 ml), and H_2O_2 (5 ml) then 2-adamantanone (779mg, 5.2 mmol) and Re_2O_7 (42 mg, 0.08 mmol) affording the crude product as a yellow oil. Product was purified by FCC eluting in 5 % ethyl acetate in hexane. Product containing fractions were combined and concentrated *in vacuo* affording the product as a white solid (637 mg, 36 %): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (s, br, 2H), 7.00 (d, J = 8.3 Hz, 2H), 2.85 (s, 1H), 2.27 (s, 3H), 2.11 – 1.34 (m, 22H).; 13C NMR (126 MHz, CDCl3) δ 169.50, 135.46, 127.78 (br), 121.45, 110.44, 108.21, 39.33 (br), 36.94, 33.71 (br), 33.15, 33.13, 33.08, 30.15 (br), 27.07, 21.79 (br), 21.08; HRMS: [ESI+] Calculated for $C_{24}H_{30}NaO_6$: 437.1935. Found [M+Na]+: 437.1947 Diff: -2.79 ppm.

Preparation of 4-((1R,3R,3''R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5] tetraoxane-6',1''-cyclohexan]-3''-yl)phenol (8a)



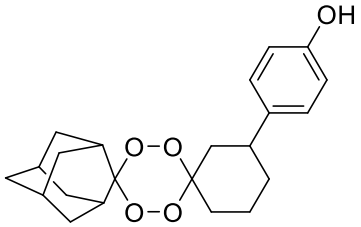
General procedure E was implemented with 4-((1R,3R,3"R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenyl acetate (484 mg, 1.17 mmol) and LiOH (84 mg, 3.50 mmol) in THF and water (7 ml) affording the product as a white solid (quantitative): ^{1}H NMR (500 MHz, CDCl3) δ 7.12 (s, br, 2H), 6.80 (d, J = 7.7 Hz, 2H), 4.95 (s, 1H), 2.82 (s, br, 1H), 2.18 – 1.11 (m, 22H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.99, 127.94 (br), 115.27, 110.53, 108.45, 38.76 (br), 36.97, 33.94 (br), 33.19, 33.17, 33.12, 30.18 (br), 27.07 (br), 21.79 (br); HRMS: [ESI+] Calculated for $C_{22}H_{28}NaO_5$: 395.1829. Found [M+Na]+: 395.1825 Diff: 0.91 ppm.

Preparation of 4-((1S,3S,3''S,5S,7S)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenol (8b)



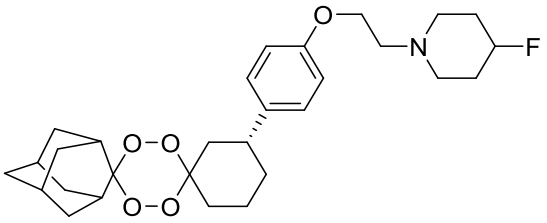
General procedure E was implemented with 4-((1S,3S,3"S,5S,7S)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenyl acetate (500 mg, 1.21 mmol) and LiOH (87 mg, 3.62 mmol) in THF and water (7 ml) affording the product as a white solid (quantitative): ^{1}H NMR (500 MHz, CDCl3) δ 7.12 (s, br, 2H), 6.79 (d, J = 7.4 Hz, 2H), 4.95 (s, 1H), 2.82 (s, 1H), 2.16 – 1.17 (m, 22H); ^{13}C NMR (126 MHz, CDCl3) δ 154.01, 127.93 (br), 115.26, 110.52, 108.44, 38.89 (br), 36.98, 33.96 (br), 33.19, 33.17, 33.12, 30.17 (br), 27.07 (br), 21.89 (br); HRMS: [ESI+] Calculated for $C_{22}H_{28}NaO_5$: 395.1829. Found [M+Na]+: 395.1829 Diff: 0.12 ppm.

Preparation of 4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenol (8c)



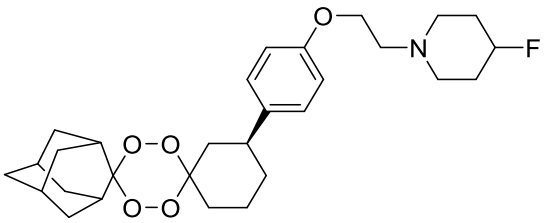
General procedure E was implemented with 4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenyl acetate (600 mg, 1.45 mmol) and LiOH (104 mg, 4.35 mmol) in THF and water (7 ml) affording the product as a white solid (quantitative): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (s, 2H), 6.80 (d, J = 7.7 Hz, 2H), 4.95 (s, 1H), 2.82 (s, 1H), 2.19 – 1.19 (m, 22H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.00, 127.94 (br), 115.25, 110.50, 108.42, 38.92 (br), 36.30, 33.92 (br), 33.19, 33.17, 33.12, 30.19 (br), 27.06 (br), 21.99 (br); HRMS: [ESI+] Calculated for C22H28NaO5: 395.1829. Found [M+Na]+: 395.1825 Diff: 1.07 ppm.

Preparation of 1-(2-(4-((1R,3R,3''R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenoxy)ethyl)-4-fluoropiperidine (9a)



General procedure F was implemented with 4-((1R,3R,3"R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenol (98 mg, 0.26 mmol), MeCN (10 ml), K_2CO_3 (145 mg, 1.05 mmol) and 1-(2-chloroethyl)-4-fluoropiperidine hydrochloride (48 mg, 0.29 mmol) to yield the crude product as a yellow oil. The crude product was purified by FCC eluting in 15 % ethyl acetate in hexane. The product containing fractions were combined and concentrated *in vacuo* to yield product as a light-yellow foam. (81 mg, 62 %): mp 68-71°C; 1H NMR (500 MHz, CDCl3) δ 7.16 (s, J = 8.7 Hz, 2H), 6.87 (d, J = 7.3 Hz, 2H), 4.70 (dm, J = 48.7 Hz, 1H), 4.10 (t, J = 5.7 Hz, 2H), 2.90 – 2.77 (m, 3H), 2.77 – 2.65 (m, 2H), 2.59 – 2.47 (m, 2H), 2.12 – 1.19 (m, 26H); ^{13}C NMR (126 MHz, CDCl3) δ 157.22, 127.74 (br), 114.56, 110.48, 108.41, 88.28 (d, J = 168.8 Hz), 66.02, 57.15, 49.97 (d, J = 5.9 Hz), 38.82 (br), 36.98, 33.94 (br), 33.19, 33.17, 33.12, 31.41 (d, J = 19.5 Hz), 29.71 (br), 27.08 (br), 21.89 (br); HRMS: [ESI+] Calculated for $C_{29}H_{41}FNO_5$: 502.2963. Found [M+H]+: 502.2966 Diff -0.47 ppm. The ee of the *R*-enantiomer was determined to be >99% [determined by HPLC, Chiralpak AD-H, n-hexane/isopropanol = 99:1, λ = 225 nm, t (R) = 29.118 min] ; purity 98.25% (UV225 nm).

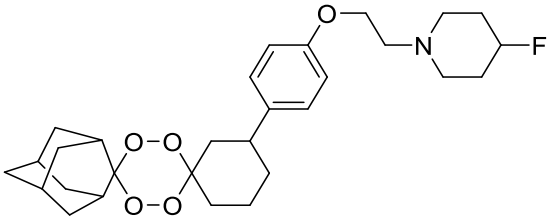
Preparation of 1-(2-(4-((1S,3S,3''S,5S,7S)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenoxy)ethyl)-4-fluoropiperidine (9b)



General procedure F was implemented with 4-((1S,3S,3"S,5S,7S)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenol (118 mg, 0.32 mmol), MeCN (10 ml), K_2CO_3 (175 mg, 1.27 mmol) and 1-(2-chloroethyl)-4-fluoropiperidine hydrochloride (70 mg, 0.35 mmol) to yield the crude product as a yellow oil. The crude product was purified by FCC eluting in 20 % ethyl acetate in hexane. The product containing fractions were combined and concentrated *in vacuo* to yield product as a light-yellow foam. (49 mg, 31 %): mp 65-69ºC; Elemental Analysis: Found: C, 69.1; H, 8.2; N,2.7. $C_{28}H_{39}NO_6$ requires C, 69.25; H, 8.09; N,2.88%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (s, 2H), 6.87 (d, J = 7.0 Hz, 2H), 4.70 (dm, J = 48.6 Hz, 1H), 4.10 (t, J = 5.6 Hz, 2H), 2.90 – 2.78 (m, 3H), 2.77 – 2.66 (m, 2H), 2.59 – 2.46 (m, 2H), 2.13 – 1.18 (m, 26H); ^{13}C NMR (126 MHz,

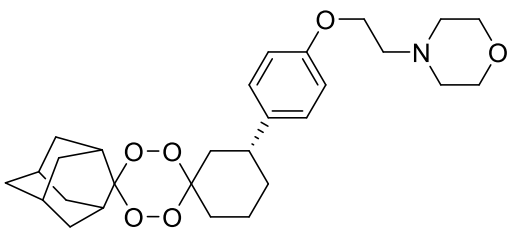
CDCl3) δ 157.24, 127.73 (br), 114.57, 108.41, 88.33 (d, J = 168.5 Hz), 66.07, 57.17, 50.00 (d, J = 5.7 Hz), 38.79 (br), 36.98, 33.92 (br), 33.19, 33.17, 33.12, 31.46 (d, J = 19.5 Hz), 30.11 (br), 27.08 (br), 21.82 (br); HRMS: [ESI+] Calculated for $C_{29}H_{41}FNO_5$: 502.2963. Found [M+H]+: 502.2973 Diff -1.9 ppm. The ee of the S-enantiomer was determined to be >99% [determined by HPLC, Chiralpak AD-H, n-hexane/isopropanol = 99:1, λ = 225 nm, t (S) = 25.205 min]; purity 98.78% (UV225 nm).

Preparation of 1-(2-(4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenoxy)ethyl)-4-fluoropiperidine (9c)



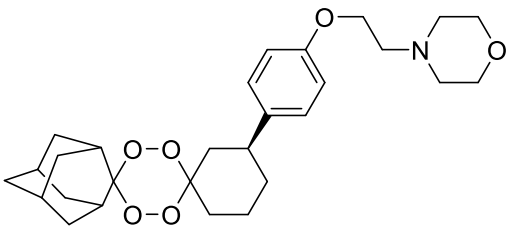
General procedure F was implemented with 4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenol (288 mg, 0.77 mmol), MeCN (20 ml), K_2CO_3 (321 mg, 2.32 mmol) and 1-(2-chloroethyl)-4-fluoropiperidine hydrochloride (50 mg, 0.85 mmol) to yield the crude product as a yellow oil. The crude product was purified by FCC eluting in 15 % ethyl acetate in hexane. The product containing fractions were combined and concentrated *in vacuo* to yield product as a light yellow foam. (227 mg, 59 %): mp 58-61^{o}C; Elemental Analysis: Found: C, 69.1; H, 8.2; N,2.7. $C_{28}H_{39}NO_6$ requires C, C, 69.25; H, 8.09; N,2.88%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (s, 2H), 6.87 (d, J = 7.1 Hz, 2H), 4.69 (dm, J = 48.7 Hz, 1H), 4.09 (t, J = 5.7 Hz, 2H), 2.92 – 2.77 (m, 3H), 2.77 – 2.66 (m, 2H), 2.58 – 2.46 (m, 2H), 2.13 – 1.19 (m, 26H); ^{13}C NMR (126 MHz, CDCl3) δ 157.26, 127.75 (br), 114.57, 110.44, 108.39, 88.31 (d, J = 170.5 Hz), 66.08, 57.17, 50.02 (d, J = 5.6 Hz), 38.79 (br), 36.98 (b), 33.95 (br), 33.18, 33.17, 33.12, 31.50 (d, J = 19.4 Hz), 30.14 (br), 27.09 (br), 21.86 (br); HRMS: [ESI+] Calculated for $C_{29}H_{41}FNO_5$: 502.2963. Found [M+H]+: 502.2971 Diff -1.53 ppm; purity 98.75% (UV225 nm).

Preparation of 4-(2-(4-((1R,3R,3''R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenoxy)ethyl)morpholine (10a)



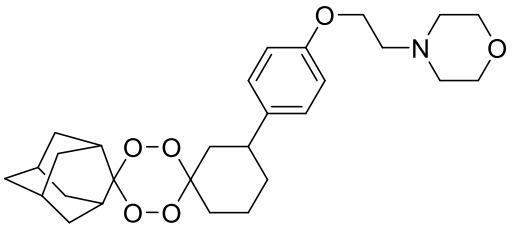
General procedure F was implemented with 4-((1R,3R,3"R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenol (125 mg, 0.34 mmol), MeCN (10 ml), K_2CO_3 (186 mg, 1.34 mmol) and 4-(2-chloroethyl)-morpholine hydrochloride (50 mg, 0.27 mmol) to yield the crude product as a clear oil. The crude product was purified by FCC eluting in 40% EtOAc in hexane. The product containing fractions were combined and concentrated *in vacuo* to yield product as a white foam. (88 mg, 54 %): mp 61-65ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (br, s, 2H), 6.87 (d, J = 6.6 Hz, 2H), 4.11 (t, J = 5.2 Hz, 2H), 3.80 – 3.71 (m, 4H), 2.90 – 2.75 (m, 3H), 2.66 – 2.55 (m, 4H), 2.21 – 1.04 (m, 22H); ^{13}C NMR (126 MHz, CDCl3) δ 157.20, 127.78, 114.57, 110.47, 108.39, 66.94, 65.81, 57.69, 54.09, 38.77 (br), 36.97, 33.97 (br), 33.19, 33.17, 33.12, 30.16 (br), 27.07 (br), 21.86 (br); HRMS: [ESI+] Calculated for $C_{28}H_{40}NO_6$: 486.2850. Found [M+H]+: 486.2857 Diff -1.38 ppm. The ee of the *R*-enantiomer was determined to be 98.91% [determined by HPLC, Chiralpak OD, n-hexane/isopropanol = 95:5, λ = 225 nm, t (R) = 11.879 min, t (S) = 14.851 min]; purity 98.87% (UV225 nm).

Preparation of 4-(2-(4-((1R,3R,3''S,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenoxy)ethyl)morpholine (10b)



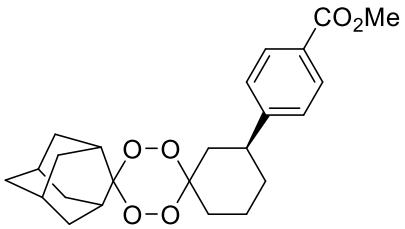
General procedure F was implemented with 4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenol (118 mg, 0.0.32 mmol), MeCN (10 ml), K_2CO_3 (175 mg, 1.27 mmol) and 4-(2-chloroethyl)-morpholine hydrochloride (52.14, 0.35 mmol) to yield the crude product as a clear oil. The crude product was purified by FCC eluting in 40% EtOAc in hexane. The product containing fractions were combined and concentrated *in vacuo* to yield product as a white foam. (90 mg, 60 %): mp 56-62ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 2H), 6.85 (d, J = 8.0 Hz, 2H), 4.09 (t, J = 5.7 Hz, 2H), 3.75 – 3.71 (m, 4H), 2.88 – 2.71 (m, 3H), 2.60 – 2.54 (m, 4H), 2.18 – 1.18 (m, 22H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.19, 127.75 (br), 114.56, 110.47, 108.39, 66.92, 65.78, 57.68, 54.08, 38.90 (br), 36.97, 33.92 (br), 33.18, 33.16, 33.11, 30.15 (br), 27.07 (br), 21.94 (br); HRMS: [ESI+] Calculated for $C_{28}H_{40}NO_6$: 486.2850. Found [M+H]+: 486.2862 Diff -2.43 ppm. The ee of the *S*-enantiomer was determined to be 97.89% [determined by HPLC, Chiralpak OD, n-hexane/isopropanol = 95:5, λ = 225 nm, t (S) = 14.357 min, t (R) = 12.447 min]; purity 98.25% (UV225 nm).

Preparation of 4-(2-(4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenoxy)ethyl)morpholine (10c)



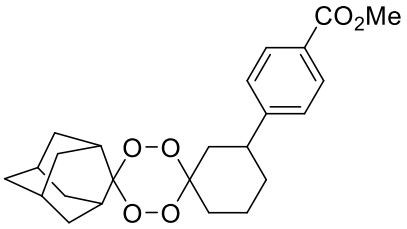
General procedure F was implemented with 4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenol (90 mg, 0.24 mmol), MeCN (10 ml), K_2CO_3 (100 mg, 0.72 mmol) and 4-(2-chloroethyl)-morpholine hydrochloride (50 mg, 0.27 mmol) to yield the crude product as a clear oil. The crude product was purified by FCC eluting in 40% EtOAc in hexane. The product containing fractions were combined and concentrated *in vacuo* to yield product as a white foam. (65 mg, 56 %): mp 56-58^{o}C; Elemental Analysis: Found: C, 69.5; H, 7.8; N,2.8. $C_{28}H_{39}NO_6$ requires C, 69.3; H, 8.1; N,2.9%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (br, s, 2H), 6.87 (d, J = 7.4 Hz, 2H), 4.12 (t, J = 5.6 Hz, 2H), 3.75 (t, J = 4.6 Hz, 4H), 2.89 – 2.79 (m, 3H), 2.60 (br, t, J = 4.4 Hz, 4H), 2.13 – 1.21 (m, 22H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.21, 127.79, 127.73, 114.57, 110.49, 108.40, 66.95, 65.82, 57.70, 54.10, 38.95 (br), 36.97, 33.95 (br), 33.19, 33.17, 33.12, 30.19 (br), 27.08 (br), 22.27 (br) ; HRMS: [ESI+] Calculated for $C_{28}H_{40}NO_6$: 486.2850. Found [M+H]+: 486.2852 Diff -0.38 ppm; purity 99.62% (UV225 nm).

Preparation of 4-((1r,3r,3”S,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzoate (11b)



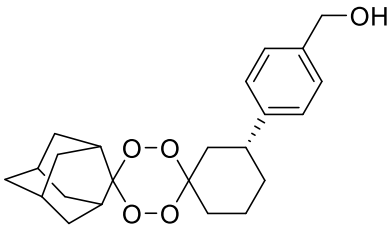
General procedure D was implemented with methyl S-4-(3-oxocyclohexyl)benzoate (940 mg, 4.03 mmol), MeCN (5 ml), HCO_2H (5 ml), and H_2O_2 (5 ml) affording the crude product as a yellow oil. Product was purified by FCC eluting in 5 % ethyl acetate in hexane. Product containing fractions were combined and concentrated *in vacuo* affording the product as a white solid (657 mg, 39 %):^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 7.9 Hz, 2H), 7.33 (s, 2H), 3.92 (s, 3H), 3.01 – 2.88 (m, 1H), 2.12 – 1.41 (m, 22H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.90, 150.73, 129.85, 128.43, 126.88, 110.52, 108.07, 51.87, 39.92 (br), 36.99, 33.40 (br), 33.19, 33.17, 33.12, 30.33 (br), 27.11 (br), 21.93 (br); HRMS: [ESI+] Calculated for $C_{24}H_{30}NaO_6$: 437.1935. Found [M+Na]+: 437.1943 Diff: -1.93 ppm.

Preparation of 4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzoate (11c)



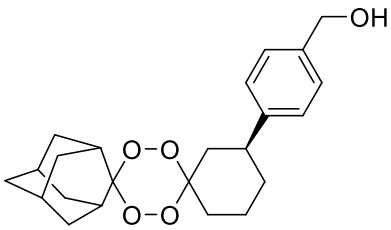
General procedure D was implemented with methyl 4-(3-oxocyclohexyl)benzoate (1.5 g, 6.5 mmol), MeCN (7 ml), HCO_2H (7 ml), and H_2O_2 (7 ml) affording the crude product as a yellow oil. Product was purified by FCC eluting in 5 % ethyl acetate in hexane. Product containing fractions were combined and concentrated *in vacuo* affording the product as a white solid (937 mg, 35 %): ^{1}H NMR (500 MHz, CDCl3) δ 8.00 (d, *J* = 7.9 Hz, 2H), 7.41 – 7.21 (m, 2H), 3.92 (s, J = 24.0 Hz, 3H), 3.03 – 2.85 (m, 1H), 2.16 – 1.40 (m, 22H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.03, 150.79, 129.89, 126.95, 110.61, 108.13, 52.02, 39.84 (br), 36.96, 33.43 (br), 33.19, 33.17, 33.12, 30.14 (br), 27.07 (br), 21.79 (br); HRMS: [ESI+] Calculated for $C_{24}H_{30}NaO_6$: 437.1935. Found [M+Na]+: 437.1953 Diff: -4.15 ppm.

Preparation of (4-((1S,3S,3''S,5S,7S)-dispiro[adamantane-2,3'-[1,2,4,5] tetraoxane-6',1''-cyclohexan]-3''-yl)phenyl)methanol (12a)



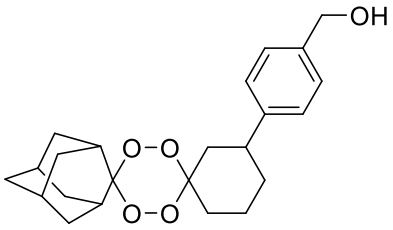
General procedure G was implemented with 1M $LiAlH_4$ in THF (2.1 ml) and methyl 4-((1R,3R,3''R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzoate (435 mg, 1.05 mmol). (quantitative): 1H NMR (500 MHz, CDCl3) δ 7.33 (d, J = 6.6 Hz, 2H), 7.27 (s, 2H), 5.10 (s, 2H), 3.21 (s, br, 1H), 2.90 (s, 1H), 2.10 – 1.37 (m, 22H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.96, 128.60, 127.13 (br), 110.50, 108.27, 66.15, 39.73 (br), 36.96, 33.67 (br), 33.19, 33.16, 33.11, 30.22 (br), 27.07 (br), 21.82 (br); HRMS: [ESI+] Calculated for C23H30NaO5: 409.1985. Found [M+Na]+: 409.1987. Diff: 0.49 ppm.

Preparation of (4-((1S,3S,3''S,5S,7S)-dispiro[adamantane-2,3'-[1,2,4,5] tetraoxane-6',1''-cyclohexan]-3''-yl)phenyl)methanol (12b)



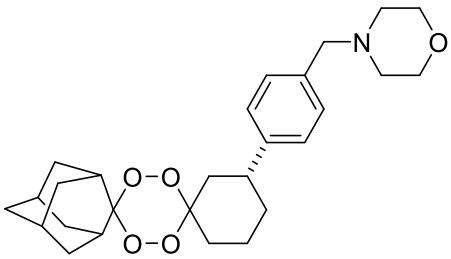
General procedure G was implemented with 1M $LiAlH_4$ in THF (3.2 ml) and methyl (4-((1S,3S,3"S,5S,7S)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenyl)methanol (656 mg, 1.58 mmol). (quantitative): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 6.7 Hz, 2H), 7.26 (s, br, 2H), 4.66 (s, 2H), 3.21 (s, br, 1H), 2.98 – 2.75 (m, 1H), 2.14 – 1.36 (m, 22H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.72, 127.28, 127.09 (br), 110.52, 108.34, 65.09, 39.73(br), 36.97, 33.73(br), 33.19, 33.18, 33.12, 30.19(br), 27.08(br), 21.85 (br).; HRMS: [ESI+] Calculated for C23H30NaO5: 409.1985. Found [M+Na]+: 409.1982. Diff: 0.85 ppm.

Preparation of (4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenyl)methanol (12c)



General procedure G was implemented with 1M $LiAlH_4$ in THF (4.5 ml) and methyl 4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)benzoate (920 mg, 2.22 mmol). (841 mg, 98 %): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 6.9 Hz, 2H), 7.31 – 7.15 (br, s, 2H), 4.69 (s, 2H), 3.21 (s, 1H), 2.97 – 2.82 (m, 1H), 2.24 – 1.36 (m, 22H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.98, 127.30, 127.10, 110.53, 65.21, 39.49 (br), 36.97, 33.74 (br), 33.19, 33.17, 33.12, 30.20 (br), 27.08 (br), 21.94 (br); Calculated for C23H30NaO5: 409.1985. Found [M+Na]+: 409.1986 Diff: 0.24 ppm.

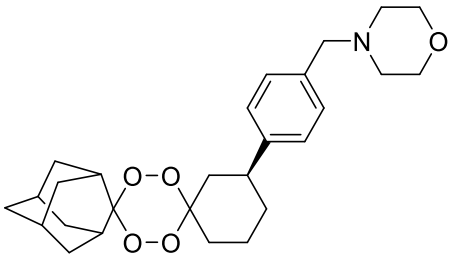
Preparation of 4-(4-((1r,3r,3”R,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzyl)morpholine (14a)



General procedure H was implemented with (4-((1R,3R,3"R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenyl)methanol (720 mg, 1.86 mmol), triethylamine (0.52 ml, 3.72 mmol) and methane sulfonyl chloride (0.29 ml, 3.72 mmol) then 4-((1R,3R,3"R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)benzyl methanesulfonate (**13a**, 257 mg, 0.55 mmol), triethylamine (0.15 ml, 1.1 mmol) and morpholine (0.10 ml, 1.11 mmol). Crude product was

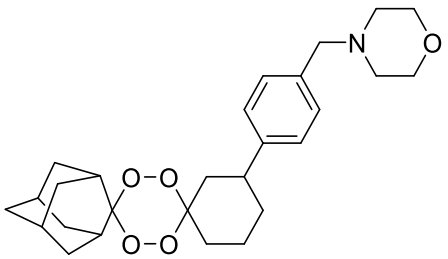
purified by FCC eluting in 40 % ethyl acetate in hexane. Product containing fractions were combined and concentrated *in vacuo* to yield the product as a white foam (181 mg, 72 %): Mp 93-95°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 6.7 Hz, 2H), 7.22 (br, s, 2H), 3.79 – 3.66 (m, 4H), 3.49 (br, s, 2H), 2.96 – 2.79 (m, 1H), 2.46 (br, s, 4H), 2.23 – 1.18 (m, 22H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.75, 129.36, 126.77, 110.50, 108.37, 67.04, 63.16, 53.62, 39.61, 36.97, 33.71, 33.19, 33.17, 33.12, 30.12, 27.07, 22.09. ;HRMS: [ESI+] Calculated for $C_{27}H_{38}NO_5$: 456.2744. Found [M+H]+: 456.2749. Diff: -1.06 ppm. The ee of the *R*-enantiomer was determined to be 97.50% [determined by HPLC, Chiralpak OD, n-hexane/isopropanol = 90:10, λ = 225 nm, t (R) = 5.353 min, t (S) = 6.183 min]; purity 97.81% (UV225 nm).

Preparation of 4-(4-((1r,3r,3”S,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzyl)morpholine (14b)



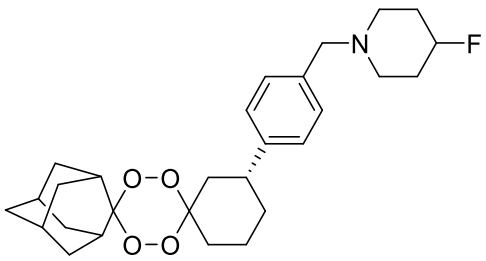
General procedure H was implemented with (4-((1S,3S,3"S,5S,7S)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenyl)methanol (612 mg, 1.58 mmol), triethylamine (0.44 ml, 3.17 mmol) and methane sulfonyl chloride (0.26 ml, 3.17 mmol) then 4-((1S,3S,3"S,5S,7S)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)benzyl methanesulfonate (**13b**, 238 mg, 0.51 mmol), triethylamine (0.14 ml, 1.02 mmol) and morpholine (0.09 ml, 1.02 mmol). Crude product was purified by FCC eluting in 40 % ethyl acetate in hexane. Product containing fractions were combined and concentrated *in vacuo* to yield the product as a white foam (27 mg, 31 %): Mp 93-95°C; ^{1}H NMR (400 MHz, CDCl3) δ 7.25 (d, J = 6.9 Hz, 2H), 7.18 (br, s, 2H), 3.78 – 3.61 (m, 4H), 3.47 (br, s, 2H), 2.92 – 2.73 (m, 1H), 2.43 (br, s, 4H), 2.11 – 1.32 (m, 22H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.70, 129.36, 126.76 (br), 110.50, 108.36, 67.02, 63.15, 53.61, 39.65 (br), 36.97, 33.73 (br), 33.18, 33.16, 33.11, 30.12 (br), 27.06, 21.93 (br); HRMS: [ESI+] Calculated for $C_{27}H_{38}NO_5$: 456.2744. Found [M+H]+: 456.2747 Diff: -0.59 ppm. The ee of the *S*-enantiomer was determined to be 98.51% [determined by HPLC, Chiralpak OD, n-hexane/isopropanol = 90:10, λ = 225 nm, t (S) = 6.037 min, t (R) = 5.423 min]; purity 97.94% (UV225 nm).

Preparation of 4-(4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzyl)morpholine (14c)



General procedure H was implemented with (4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenyl)methanol (820 mg, 2.12 mmol), triethylamine (0.6 ml, 4.25 mmol) and methane sulfonyl chloride (0.35 ml, 4.25 mmol) then 4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzyl methanesulfonate (**13c**, 500 mg, 1.08 mmol), triethylamine (0.3 ml, 2.15 mmol) and morpholine (0.18 ml, 2.15 mmol.) Crude product was purified by FCC eluting in 40 % ethyl acetate in hexane. Product containing fractions were combined and concentrated *in vacuo* to yield the product as a white foam (399 mg, 81 %): Mp 73-75°C; ^{1}H NMR (400 MHz, CDCl3) δ 7.25 (d, J = 6.3 Hz, 2H), 7.18 (br, s, 2H), 3.77 – 3.63 (m, 4H), 3.47 (br, s, 2H), 2.92 – 2.73 (m, 1H), 2.48 – 2.38 (m, 4H), 2.11 – 1.19 (m, 22H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.74, 129.35, 126.75 (br), 110.49, 108.36, 67.03, 63.16, 53.62, 39.58 (br), 36.97, 33.72 (br), 33.19, 33.16, 33.11, 30.17 (br), 27.06 (br), 21.95 (br); HRMS: [ESI+] Calculated for $C_{27}H_{38}NO_5$: 456.2744. Found [M+H]+: 456.2751. Diff: -1.48 ppm; purity 99.81% (UV225 nm).

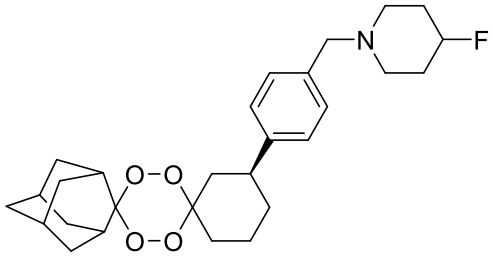
Preparation of 1-(4-((1R,3R,3''R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzyl)-4-fluoropiperidine (15a)



General procedure H was implemented with (4-((1R,3R,3"R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenyl)methanol (720 mg, 1.86 mmol), triethylamine (0.52 ml, 3.72 mmol) and methane sulfonyl chloride (0.29 ml, 3.72 mmol) then 4-((1R,3R,3"R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)benzyl methanesulfonate (**13a**, 244 mg, 0.53 mmol), triethylamine (0.29 ml, 2.1 mmol) and 4-fluoropiperidine hydrochloride (146 mg, 1.05 mmol). Crude product was purified by FCC eluting in 5 % methanol in DCM. Product containing fractions were combined and concentrated *in vacuo* to afford the product as a faintly yellow foam (158 mg, 64 %): mp 89-92°C; ^{1}H NMR (500 MHz, CDCl3) δ 7.28 – 7.07 (m, 4H), 4.69 (dm, J = 48.8 Hz, 1H), 3.49 (s, 2H), 2.95 – 2.78 (s, br, 1H), 2.60 (s, 2H), 2.37 (s, 2H), 2.09 – 1.40 (m, 26H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.40, 129.20 (br), 126.73, 110.50, 108.38, 88.82 (d, J = 171.6 Hz), 62.66, 49.52 (d, *J* = 5.2 Hz), 39.34 (br), 36.98, 33.75 (br),

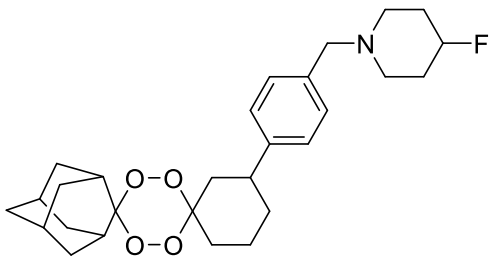
33.19, 33.17, 33.12, 31.56 (d, J = 19.5 Hz), 30.22 (br), 27.07 (br), 21.82 (br); HRMS: [ESI+] Calculated for $C_{28}H_{39}FNO_4$: 472.2858. Found [M+H]+: 472.2862 Diff: -0.95 ppm. The ee of the *R*-enantiomer was determined to be >99% [determined by HPLC, Chiralpak OD, n-hexane/isopropanol = 95:5, λ = 225 nm, t (R) = 8.320 min]; purity 98.42% (UV225 nm).

Preparation of 1-(4-((1R,3R,3''S,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzyl)-4-fluoropiperidine (15c)



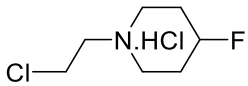
General procedure H was implemented with (4-((1S,3S,3"S,5S,7S)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenyl)methanol (612 mg, 1.58 mmol), triethylamine (0.44 ml, 3.17 mmol) and methane sulfonyl chloride (0.26 ml, 3.17 mmol) then 4-((1S,3S,3"S,5S,7S)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)benzyl methanesulfonate (**13b**, 210 mg, 0.45 mmol), triethylamine (0.25 ml, 1.8 mmol) and 4-fluoropiperidine hydrochloride (126 mg, 0.90 mmol). Crude product was purified by FCC eluting in 5 % methanol in DCM. Product containing fractions were combined and concentrated *in vacuo* to afford the product as a faintly yellow foam (142 mg, 67 %): mp 83-86ºC; ^{1}H NMR (500 MHz, CDCl3) δ 7.28 – 7.08 (m, 4H), 4.69 (d, J = 48.8 Hz, 1H), 3.49 (s, 2H), 2.88 (s, br, 1H), 2.60 (s, 2H), 2.37 (s, 2H), 2.13 – 1.36 (m, 26H).; 13C NMR (126 MHz, CDCl3) δ 144.32, 129.21, 126.74, 110.50, 108.42, 108.39, 80.92, 62.67, 49.56, 49.52, 49.51, 36.97, 33.19, 33.17, 33.12, 31.63, 31.47, 27.08, 27.07.; HRMS: [ESI+] Calculated for $C_{28}H_{39}FNO_4$: 472.2858. Found [M+H]+: 472.2857 Diff: 0.16 ppm. The ee of the *S*-enantiomer was determined to be 98% [determined by HPLC, Chiralpak OD, n-hexane/isopropanol = 95:5, λ = 225 nm, t (S) = 9.764 min, t (R) = 8.043 min]; purity 97.53% (UV225 nm).

Preparation of 13c – 1-(4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzyl)-4-fluoropiperidine



General procedure H was implemented with (4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)phenyl)methanol (820 mg, 2.12 mmol), triethylamine (0.6 ml, 4.25 mmol) and methane sulfonyl chloride (0.35 ml, 4.25 mmol) then 4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1"-cyclohexan]-3"-yl)benzyl methanesulfonate (**13c**, 200 mg, 0.43 mmol), triethylamine (0.24 ml, 1.72 mmol) and 4-fluoropiperidine hydrochloride (120 mg, 0.86 mmol). Crude product was purified by FCC eluting in 5 % methanol in DCM. Product containing fractions were combined and concentrated *in vacuo* to afford the product as a faintly yellow foam (77 mg, 37 %): mp 74-76°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 6.8 Hz, 2H), 7.22 (br, s, 2H), 4.69 (dm, J = 48.8 Hz, 1H), 3.50 (s, 2H), 2.88 (s, 1H), 2.60 (br, s, 2H), 2.38 (br, s, 2H), 2.15 – 1.38 (m, 26H).; ^{13}C NMR (126 MHz, CDCl3) δ 136.39, 129.22, 126.72 (br), 110.50, 108.38, 88.80 (d, J = 168.9 Hz), 62.65, 49.50 (d, J = 4.6 Hz), 39.58 (br), 36.98, 33.76 (br), 33.19, 33.17, 33.12, 31.54 (d, J = 19.4 Hz), 30.19 (br), 27.07 (br), 21.88 (br); HRMS: [ESI+] Calculated for $C_{28}H_{39}FNO_4$: 472.2858. Found [M+H]+: 472.2861 Diff: -0.69 ppm; purity 98.42% (UV225 nm).

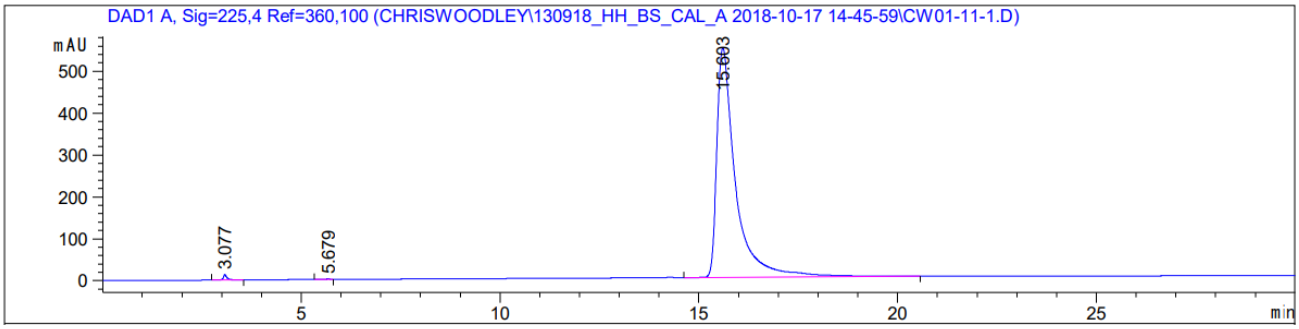
Preparation of 1-(2-chloroethyl)-4-fluoropiperidine hydrochloride



To a solution of 4-fluoropiperidine hydrochloride (500 mg, 3.58 mmol) and K_2CO_3 (2.48 g, 17.9 mmol) in MeCN (25 ml) was added 2-bromoethanol (0.5 ml, 7.16 mmol. The mixture was stirred under reflux for 2 h before. The solution was filtered and concentrated *in vacuo* to yield crude 2-(4-fluoropiperidin-1-yl)ethan-1-ol as a yellow oil; this was carried through to the next step without further purification. The residue was dissolved in DCE (5 ml) and thionyl chloride (1.6 ml, 21.4 mmol) was added. The cloudy yellow mixture was stirred under reflux overnight and was allowed to cool to room temperature. Diethyl ether was added resulting in a white precipitate forming, this was collected by suction filtration and washed with diethyl ether affording the product as a yellow-white solid (557 mg, 77 %). ^{1}H NMR (500 MHz, MeOD) δ 3.45 (m, 1H), 2.46 (t, J = 6.3 Hz, 2H), 2.05 (t, J = 6.3 Hz, 2H), 2.02 – 1.64 (m, 4H), 0.82 – 0.46 (m, 4H); ^{13}C NMR (126 MHz, MeOD) δ 86.87 (d, J = 171.0 Hz), 61.52, 40.81, 40.33, 31.39 (d, J = 21.0 Hz). Characterisation data consistent with literature.[5]

6. HPLC Traces

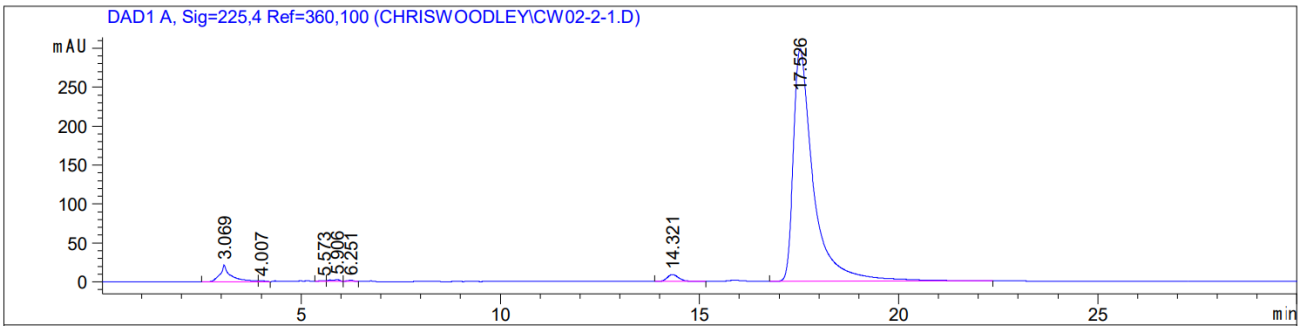
Compound 3a – (R)-3-(4-benzyloxyphenyl)cyclohexan-1-one



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.077	BB	0.0914	85.50282	13.23137	0.4723
2	5.679	BB	0.1028	8.00371	1.18454	0.0442
3	15.603	BB	0.4755	1.80094e4	547.80420	99.4835
Totals :				1.81029e4	562.22011	

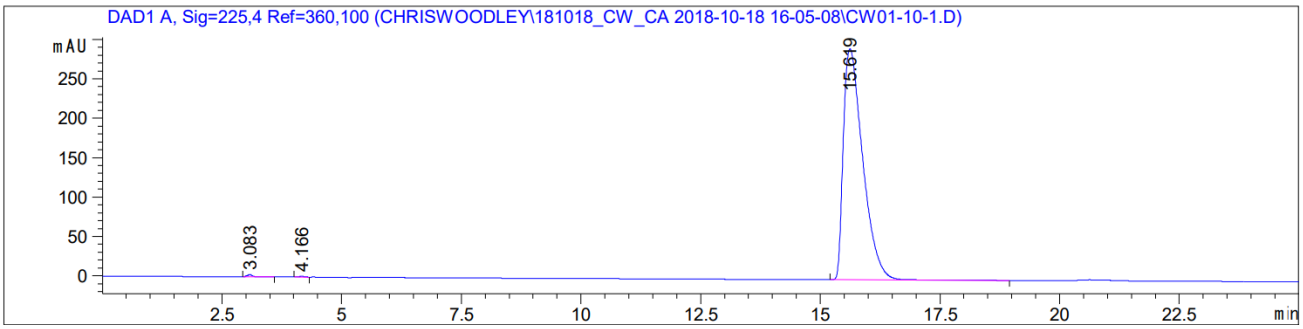
Compound 3b – (S)-3-(4-benzyloxyphenyl)cyclohexan-1-one



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.069	BV	0.2368	409.25650	21.43253	3.6658
2	4.007	VB	0.1446	15.70401	1.44686	0.1407
3	5.573	BV	0.1484	13.86686	1.27991	0.1242
4	5.906	VV	0.2252	41.70144	2.46708	0.3735
5	6.251	VB	0.1557	19.72846	1.86140	0.1767
6	14.321	BB	0.3067	178.85628	8.96721	1.6021
7	17.526	BB	0.5138	1.04849e4	298.53259	93.9170
Totals :				1.11640e4	335.98758	

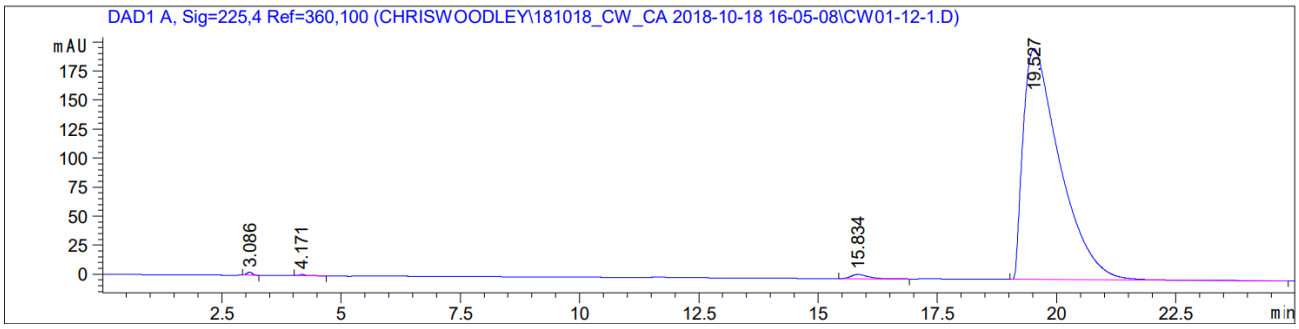
Compound 4a – Methyl (R)-4-(3-oxocyclohexyl)benzoate



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.083	BB	0.1093	21.15536	2.82716	0.2553
2	4.166	BB	0.0908	7.06406	1.16351	0.0853
3	15.619	BB	0.4306	8257.12695	293.20563	99.6594
Totals :				8285.34637	297.19629	

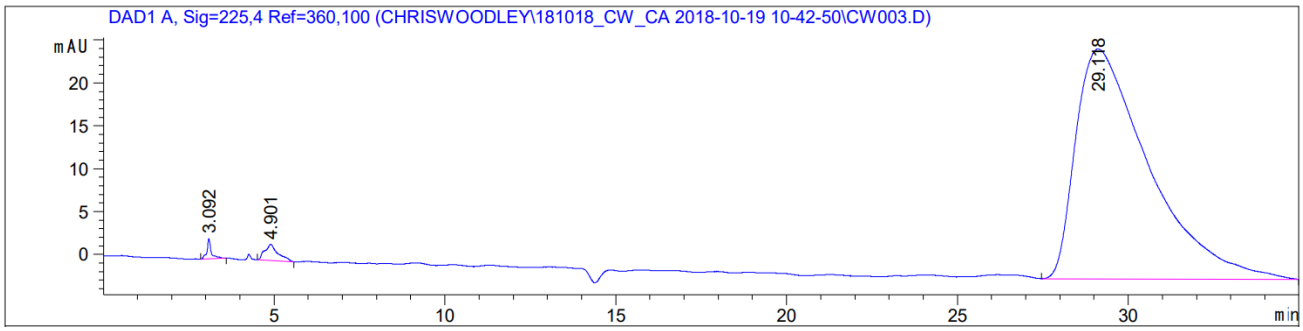
Compound 4b – Methyl (S)-4-(3-oxocyclohexyl)benzoate



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.086	BB	0.1076	19.34566	2.69911	0.1801
2	4.171	BB	0.0966	7.56454	1.15190	0.0704
3	15.834	BB	0.3638	88.81503	3.62568	0.8268
4	19.527	BBA	0.8031	1.06266e4	198.95992	98.9227
Totals :				1.07423e4	206.43660	

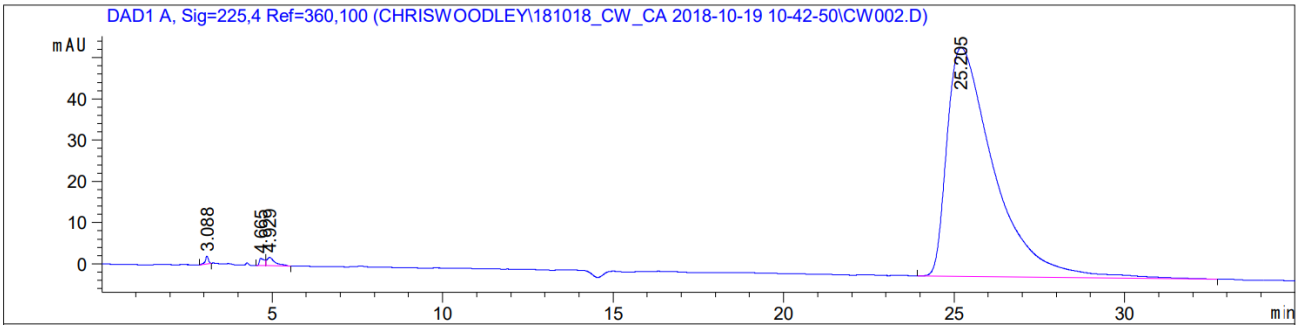
Compound 9a 1-(2-(4-((1R,3R,3''R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenoxy)ethyl)-4-fluoropiperidine



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.092	BB	0.1222	20.60752	2.35202	0.5070
2	4.901	BB	0.3540	50.48227	1.87585	1.2420
3	29.118	BBA	1.9634	3993.60693	26.78693	98.2510
Totals :				4064.69673	31.01480	

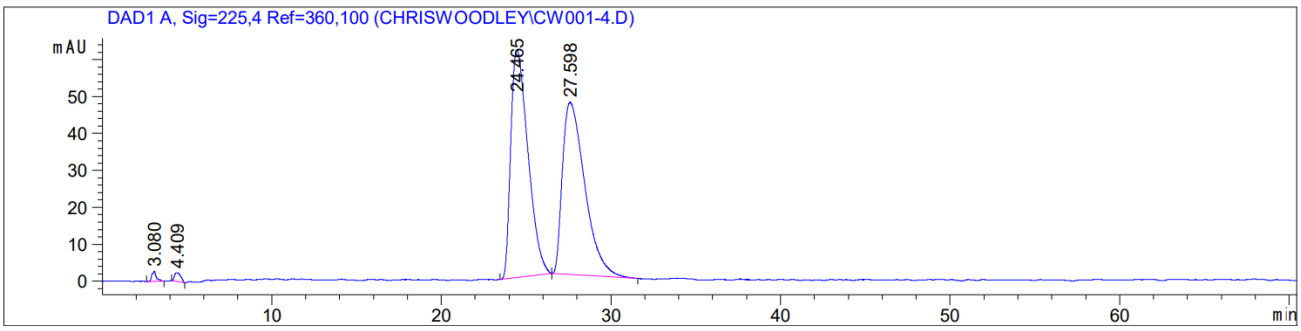
Compound 9b 1-(2-(4-((1S,3S,3''S,5S,7S)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenoxy)ethyl)-4-fluoropiperidine



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.088	BB	0.0950	12.37847	1.92474	0.2298
2	4.665	BV	0.1355	18.01052	1.78816	0.3343
3	4.929	VB	0.2446	35.09722	2.02125	0.6515
4	25.205	BB	1.3792	5321.58301	55.47506	98.7844
Totals :				5387.06922	61.20921	

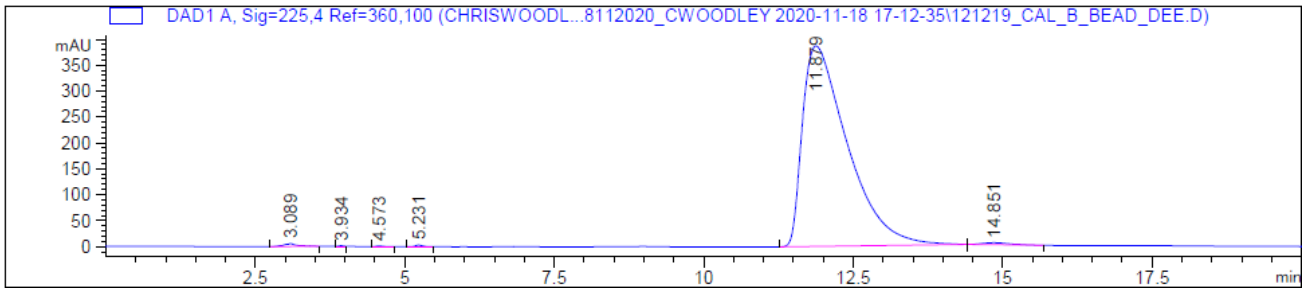
Compound 9c 1-(2-(4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenoxy)ethyl)-4-fluoropiperidine



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.080	BB	0.2407	48.69857	2.69672	0.5572
2	4.409	BB	0.3830	60.45036	2.32752	0.6917
3	24.465	BB	1.0778	4345.43750	61.69215	49.7240
4	27.598	BB	1.3855	4284.52930	46.65203	49.0270
Totals :				8739.11573	113.36843	

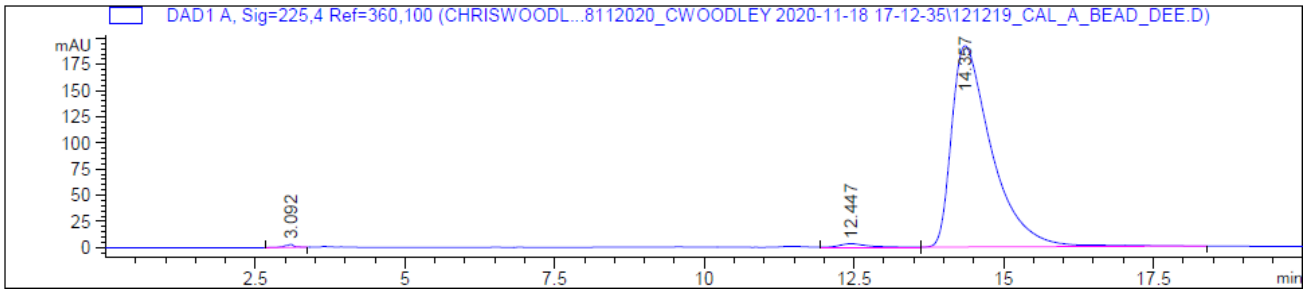
Compound 10a 4-(2-(4-((1R,3R,3''R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenoxy)ethyl)morpholine



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.089	BB	0.1874	81.23083	5.59430	0.3973
2	3.934	BB	0.0781	5.04836	1.01294	0.0247
3	4.573	BB	0.1182	9.30519	1.17727	0.0455
4	5.231	BB	0.1196	24.99027	3.18364	0.1222
5	11.879	BB	0.7858	2.02131e4	386.70657	98.8688
6	14.851	BB	0.4848	110.68507	3.37365	0.5414
Totals :				2.04443e4	401.04837	

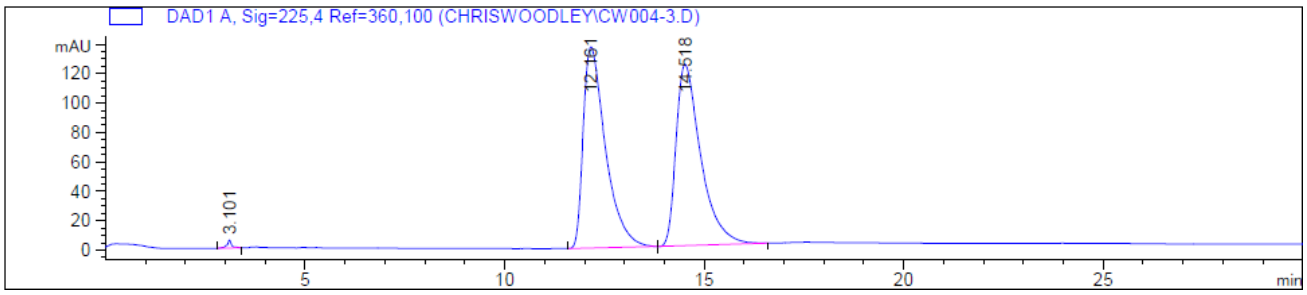
Compound 10b 4-(2-(4-((1R,3R,3''S,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenoxy)ethyl)morpholine



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.092	BB	0.1278	27.88906	2.96420	0.3081
2	12.447	BB	0.4258	95.14904	3.24793	1.0513
3	14.357	BB	0.6958	8927.99805	192.24339	98.6406
Totals :				9051.03615	198.45553	

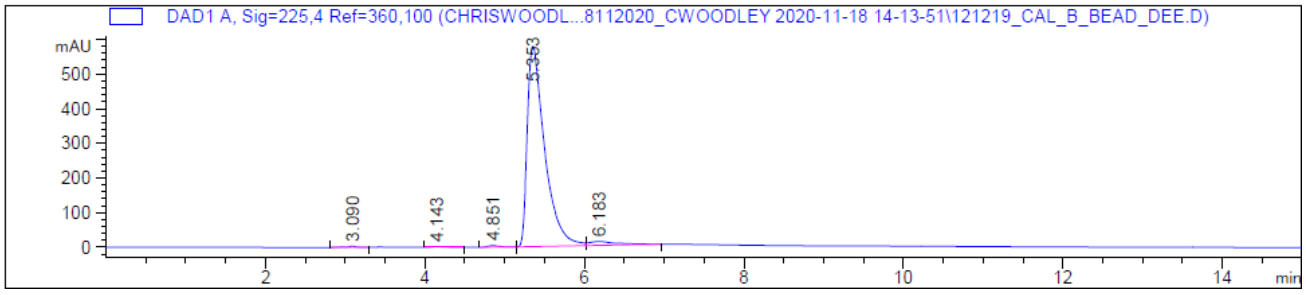
Compound 10c 4-(2-(4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)phenoxy)ethyl)morpholine



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.101	BB	0.1081	40.91174	5.29786	0.3840
2	12.161	BB	0.5873	5309.85107	136.65213	49.8338
3	14.518	BB	0.6438	5304.35449	123.33230	49.7822
Totals :				1.06551e4	265.28229	

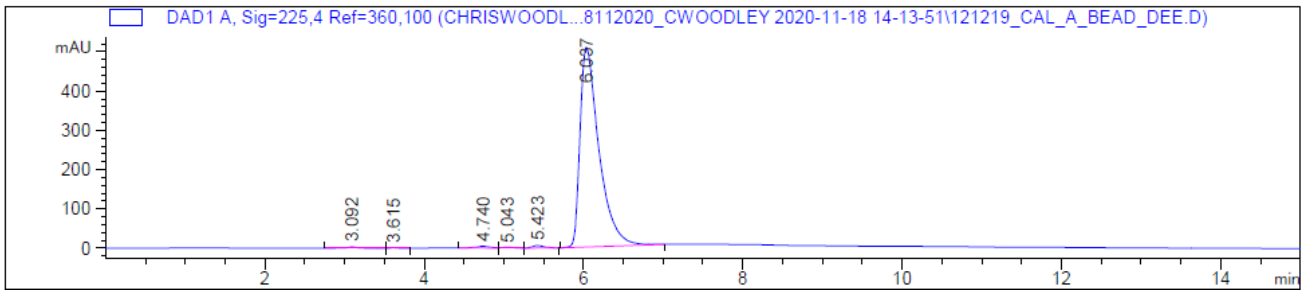
Compound 14a 4-(4-((1r,3r,3”R,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzyl)morpholine



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.090	BB	0.1133	22.57137	2.76186	0.2511
2	4.143	BB	0.1476	20.68187	2.01689	0.2301
3	4.851	BB	0.1379	42.61554	4.69594	0.4741
4	5.353	MM	0.2522	8792.20898	581.06396	97.8075
5	6.183	MM	0.2563	111.22433	7.23367	1.2373
Totals :				8989.30210	597.77234	

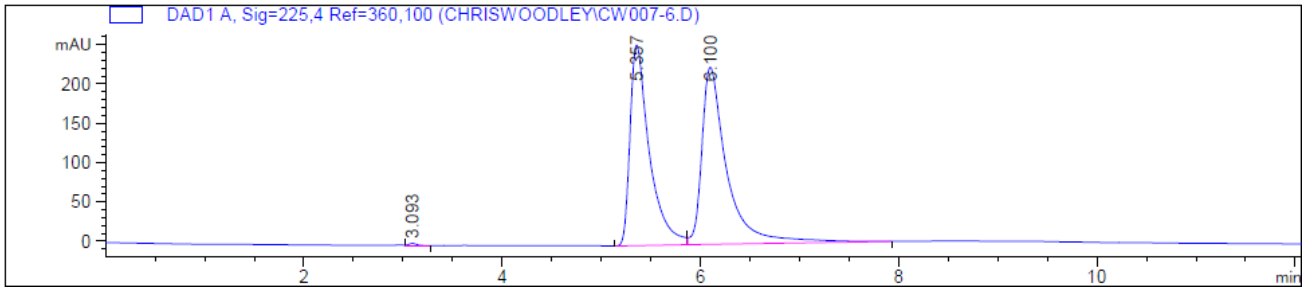
Compound 14b 4-(4-((1r,3r,3”S,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzyl)morpholine



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.092	BV	0.1217	31.15272	3.50460	0.3636
2	3.615	VB	0.0812	5.87583	1.08455	0.0686
3	4.740	BV	0.1738	57.04065	4.75878	0.6658
4	5.043	VB	0.1529	19.17785	1.91338	0.2238
5	5.423	BB	0.1609	63.08707	5.99050	0.7364
6	6.037	BB	0.2464	8391.08496	508.74527	97.9418
Totals :				8567.41907	525.99708	

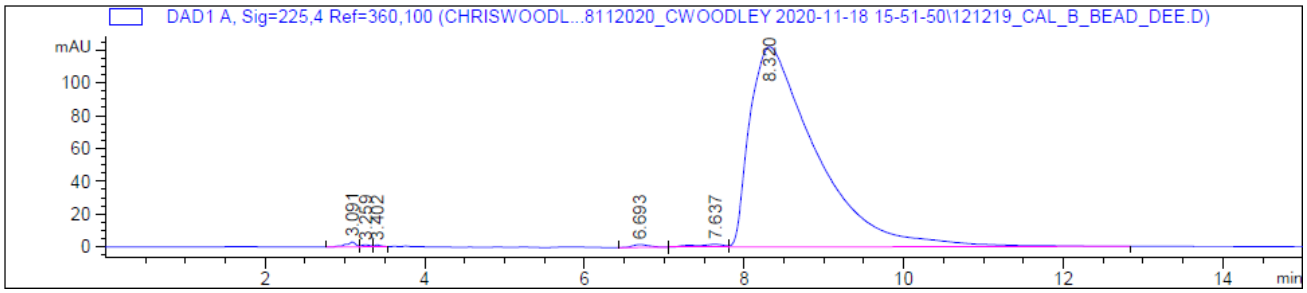
Compound 14c – 4-(4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzyl)morpholine



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.093	VB	0.0811	14.42586	2.66719	0.1934
2	5.357	BV	0.1989	3474.94434	255.08147	46.5819
3	6.100	VB	0.2555	3970.49634	225.39986	53.2248
Totals :				7459.86654	483.14852	

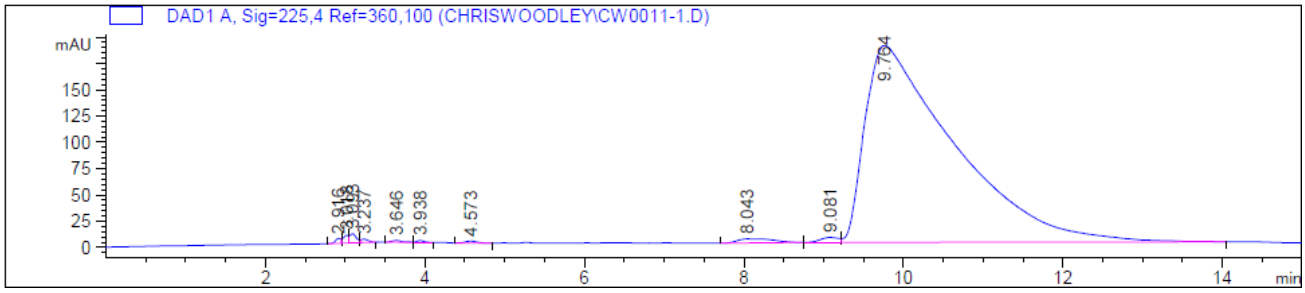
Compound 15a – 1-(4-((1R,3R,3''R,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzyl)-4-fluoropiperidine



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.091	BV	0.1182	26.17813	2.98761	0.3650
2	3.259	VV	0.1265	8.78937	1.08528	0.1226
3	3.402	VB	0.0802	5.75543	1.04581	0.0803
4	6.693	BB	0.2195	25.86897	1.76001	0.3607
5	7.637	BV	0.3752	46.48867	1.68861	0.6482
6	8.320	VB	0.8416	7058.65088	122.25112	98.4232
Totals :				7171.73145	130.81845	

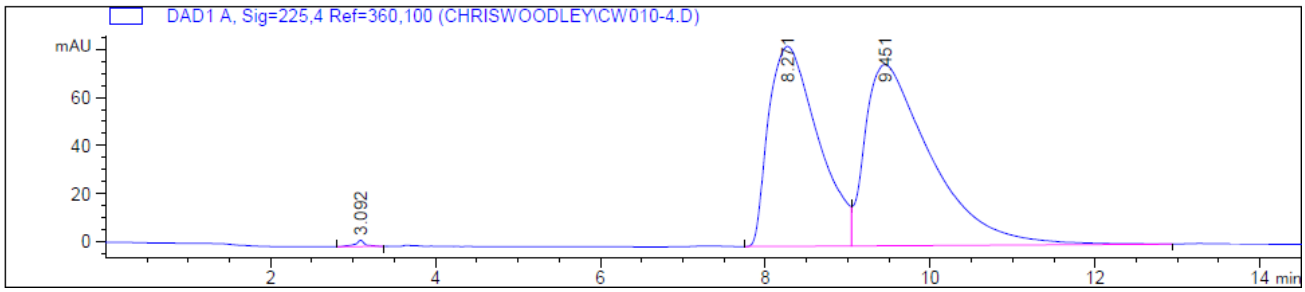
Compound 15b – 1-(4-((1R,3R,3''S,5R,7R)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzyl)-4-fluoropiperidine



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.916	BV	0.0697	21.92353	4.76170	0.1466
2	3.018	VV	0.0663	34.26775	7.36749	0.2291
3	3.093	VV	0.0837	50.83634	8.76217	0.3399
4	3.237	VB	0.0946	21.06533	3.29596	0.1408
5	3.646	BV	0.1343	15.20974	1.76938	0.1017
6	3.938	VB	0.0926	10.72343	1.72296	0.0717
7	4.573	BB	0.1473	18.25018	1.87991	0.1220
8	8.043	BB	0.4244	119.56734	3.76655	0.7994
9	9.081	BV	0.2552	78.06756	4.76327	0.5219
10	9.764	VB	1.0725	1.45872e4	187.32912	97.5269
Totals :				1.49572e4	225.41850	

Compound 15c – 1-(4-((1r,3r,5r,7r)-dispiro[adamantane-2,3'-[1,2,4,5]tetraoxane-6',1''-cyclohexan]-3''-yl)benzyl)-4-fluoropiperidine



Signal 1: DAD1 A, Sig=225,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.092	BB	0.1144	21.52324	2.60558	0.2804
2	8.271	BV	0.6432	3453.02637	83.02754	44.9888
3	9.451	VB	0.8068	4200.75977	75.30125	54.7308
Totals :				7675.30937	160.93438	

7. References

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