Discovery and Optimization of Potent GPR40 Full Agonists Containing Tricyclic Spirocycles

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Supporting Information

List of Contents:

Abbreviations of the solvents and reagents: CDCl3, deuterochloroform; DMSO-d6, hexadeuterodimethyl sulfoxide; EtOAc, ethyl acetate; MeOH, methanol; EtOH, ethanol; iPrOH (IPA), 2-propanol; DMF, N,N-dimethylformamide; DMSO, dimethyl sulfoxide; THF, tetrahydrofuran; Et_2O, diethyl ether; DME, 1,2-dimethoxyethane; ACN or CH_3CN, acetonitrile; DCM or CH_2Cl_2, dichloromethane; LiOH, Lithium hydroxide; NH_4Cl, ammonium chloride; $NaHCO_3$, sodium hydrogen carbonate; $MgSO_4$, magnesium sulfate; Na_2SO_4, sodium sulfate; K_2CO_3, potassium carbonate; Cs_2CO_3, cesium carbonate; TBAF, tetrabutylammonium fluoride; Pd/C, palladium on carbon; Et_3N or TEA, triethylamine; HCl, hydrochloric acid; AcOH, acetic acid; NBS, N-bromosuccinimide; S-phos, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl; DBU, 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine; TBDPSCl, *tert*-Butylchlorodiphenylsilane

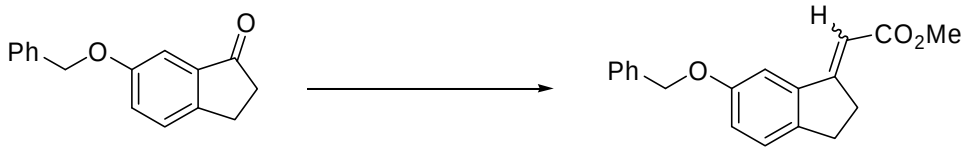
General chemistry: All reactions were conducted under an inert gas atmosphere (nitrogen or argon) using a Teflon-coated magnetic stir bar at the temperature indicated. Commercial reagents and anhydrous solvents were used without further purification. Analytical thin layer chromatography (TLC) and flash chromatography were performed on Merck silica gel 60 (230-400 mesh). Removal of solvents was conducted by using a rotary evaporator, and residual solvent was removed from nonvolatile compounds using a vacuum manifold maintained at approximately 1 Torr. All yields reported are isolated yields. Product purification by flash chromatography was performed using Teledyne-ISCO Redisep normal phase silica gel columns on a Teledyne-ISCO Companion; or by preparative reversed-phase high pressure liquid chromatography (RP-HPLC) using an Agilent 1100 Series HPLC and Phenomenex Gemini C18 column (5 micron, 100 mm × 30 mm i.d.), eluting with a binary solvent system A and B using a gradient elusion [A: H_2O with 0.1% trifluoroacetic acid (TFA); B: CH_3CN with 0.1% TFA; standard method 10-95% A:B] with UV detection at 220 nm. Low-resolution mass spectral (MS) data were determined on Agilent 1200 series LC connected to an Agilent 6140 quadrupole MS analyzer (ESI). High-resolution mass spectra (HRMS) were obtained on an Agilent 6510 Q-TOF MS with an Agilent 1200 LC on the front end. ^1H NMR spectra were obtained on a Bruker Avance III 500 (500 MHz) or Bruker Avance II 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = single; d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad. Optical rotations ($[\alpha]_D$) were measured on a JASCO P-1020 polarimeter. Specific rotations are given as deg/dm, and the concentrations are reported as g/100mL of the specific solvent and were recorded at the temperature indicated.

Synthesis of head groups:

Head group H1

H1.1 **H1.2**

6-(Benzyloxy)-2,3-dihydroinden-1-one (H1.2). A mixture of 6-hydroxy-2,3-dihydroinden-1-one (5.0 g, 34 mmol), 1-(bromomethyl) benzene (4.4 mL, 37 mmol) and cesium carbonate (25 g, 78 mmol) in DMF were stirred at room temperature for 23 hours. The reaction mixture was diluted with EtOAc (400 mL). The mixture was washed with brine and dried over anhydrous sodium sulfate. After removing solvent by rotary evaporation, the residue was purified by flash chromatography (1:4 EtOAc/hexanes). Product **H1.2** was obtained in 67% yield as a white solid.

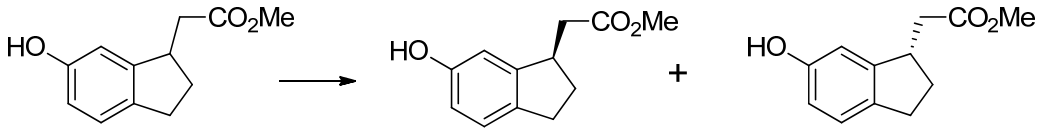


H1.2 **H1.3**

(E)-Methyl 2-(6-(benzyloxy)-2,3-dihydroinden-1-ylidene)acetate (H1.3). At -78^{o}C, lithium bis(trimethylsilyl)amide (1.0 M in hexanes) (4 mL, 26 mmol) was added slowly to a solution of methyl 2-(trimethylsilyl)acetate (4 g, 26 mmol) in THF (20 mL). The reaction mixture was maintained at -78^{o}C for 22 minutes. **H1.2** (3.5 g, 15 mmol) in THF (20 mL) was then added slowly to the mixture. The mixture was stirred at -78^{o}C and allowed to warm to room temperature overnight. The reaction mixture was then poured into water (30 mL) and extracted with EtOAc (300 mL). The organic layers were washed with brine and dried over anhydrous sodium sulfate. After removing solvent by rotary evaporation, the residue was purified by flash chromatography (1:4 EtOAc/hexanes). The Product **H1.3** was obtained in 38% yield as a white solid.

H1.3 **H1.4**

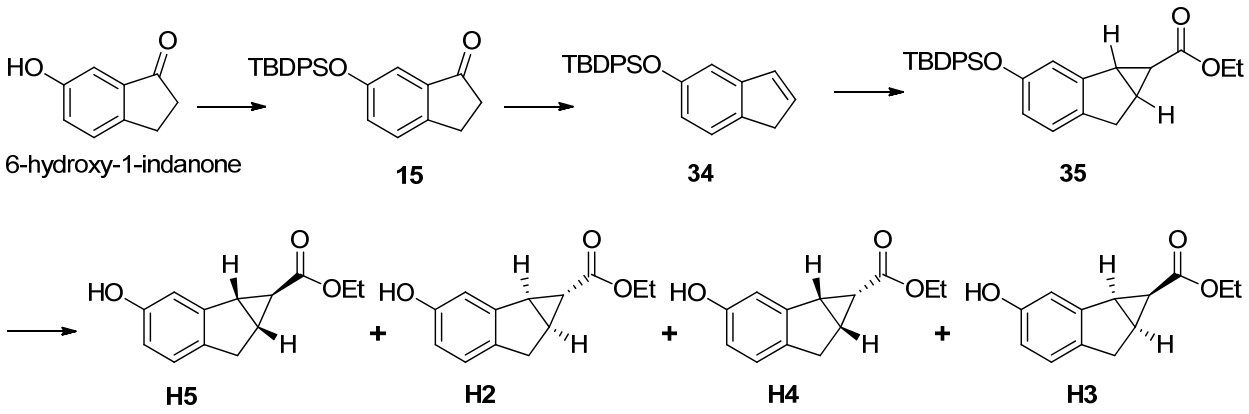
Methyl 2-(6-hydroxy-2,3-dihydro-1H-inden-1-yl)acetate(H1.4). Under hydrogen, a mixture of (E)-methyl 2-(6-(benzyloxy)-2,3-dihydroinden-1-ylidene)acetate (**H1.3**)(1.64 g, 5.57 mmol), palladium on carbon (10%) (0.462 g, 0.43 mmol) in MeOH (30 mL) were stirred for 24 hours. The mixture was then filtered through silica gel to remove the Pd/C, eluting with EtOAc. After removing solvent by rotary evaporation, the residue was purified using flash chromatography (1:1 EtOAc/hexanes). Product **H1.4** was obtained in 68% yield (0.78g) as a colorless oil.



H1.4 **H1** **H1.5**

(R)-Methyl 2-(6-hydroxy-2,3-dihydro-1H-inden-1-yl)acetate or (S)-methyl 2-(6-hydroxy-2,3-dihydro-1H-inden-1-yl)acetate (H1). Chiral separation of **H1.4** (0.78 g) was achieved using a chiral separation column: OJ; solvent: 14% IPA:hexanes. **H1** and **H1.5** were obtained in optical purity >99%. **H1**: 0.36g, first peak, retention time 13.4 min. **H1.5**: 0.36g, second peak, retention time 22.4 min.

Head groups H2~H5



6-hydroxy-1-indanone **15** **34** **35**

H5 **H2** **H4** **H3**

6-(*tert*-Butyldiphenylsilyloxy)-2,3-dihydroinden-1-one (15). A mixture of 6-hydroxy-1-indanone (250 g, 1687 mmol), t-butyldiphenylchlorosilane (487 g, 1772 mmol) and imidazole (138 g, 2025 mmol) in degassed DMF (900 mL) was heated at 60 ºC for 16 hours. The mixture was then concentrated to remove most of DMF, diluted with ether (3000 mL), filtered, and concentrated to give the initial product **15** (674 g, 100% yield) which was used in the next step reaction without further purification. MS ESI (pos.) M/E: 409 (M+Na).

(1H-inden-5-yloxy)(*tert*-butyl)diphenylsilane (34). To a solution of **15** (36.88g, 95.41 mmol) in MeOH (1L) was added $NaBH_4$ (9.39 g, 248 mmol) portion-wise, over 60 minutes. The resulting mixture was stirred at r.t. for 1 hour and quenched at 0C carefully with 2N HCl to adjust pH ~4-5. After removal of MeOH under vacuum, the residue was partitioned between saturated $NaHCO_3$ and EtOAc, washed organic layer with brine, dried over MgSO4, concentrated to give 6-(*tert*-butyldiphenylsilyloxy)-2,3-dihydro-1H-inden-1-ol (36.0 g, 97.1% yield), which was re-dissolved in DCM, cooled to 0°C, added methanesulfonyl chloride (8.858 mL, 114.5 mmol) and triethylamine (33.18 mL, 238.5 mmol). Warmed to r.t. and stirred for 16 hours. Flash chromatography purification (10% EtOAc in hexanes) gave **34** (28.3 g, 80% yield). MS ESI (pos.) M/E: 371 (M+H).

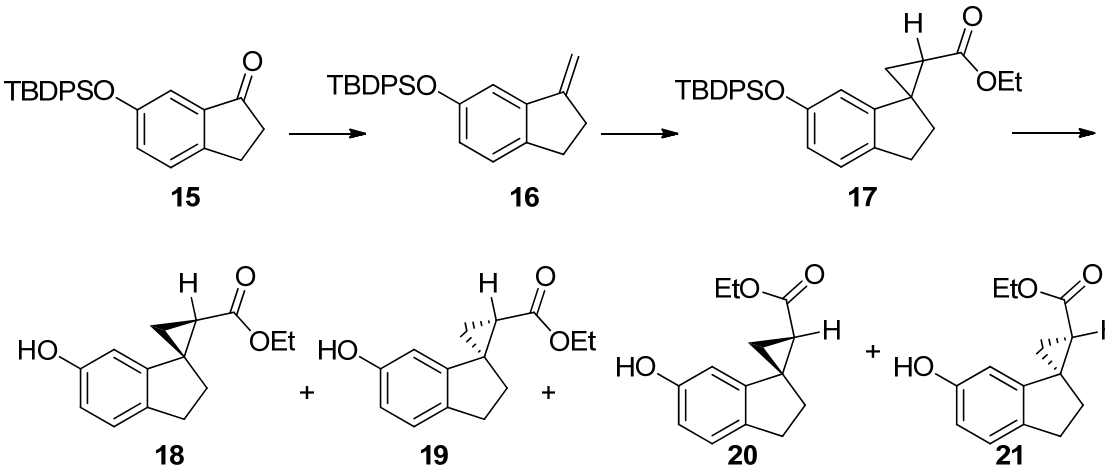
Synthesis of 35. To a solution of **34** (11.45g, 30.9 mmol) and rhodium (ii) acetate, dimer (0.137 g, 0.309 mmol) in refluxing DCM (200 mL) was added ethyl diazoacetate (4.81 mL, 46.3 mmol) in DCM via syringe pump over 60 minutes. The resulting mixture was stirred at 45°C for 1 hour then r.t. for 3 hours. Concentrated and purified by flash chromatography (10% EtOAc in hexanes) to give **35** (9.9 g, 70% yield). MS ESI (pos.) M/E: 457 (M+H).

Synthesis of H2, H3, H4 and H5. To a solution of **35** (9.8 g, 21.5 mmol) in THF (200 mL) was added TBAF (1.0 M, 37.1 mL, 37.1 mmol) in THF. The resulting mixture was stirred at r.t for 1 hour. Concentrated and passed through a short pad of silica gel to give an oil residue after evaporation. Loaded to solid silica gel cartridge and purified by flash chromatography (10%-100% EtOAc in hexanes) to give fraction 1 (determined to be *trans* by NOE) & fraction 2 (determined to be *cis* by NOE). Chiral separation of fraction 1 (*trans* isomers) on OJ-H with 8% IPA/hexanes gave **H2** (526 mg, >99%ee, retention time 14.4 min on OJ-H with 8% IPA/hexanes, $[\alpha]_D$ = -198, $CDCl_3$), and **H5** (500 mg, 98.6%ee, retention time 20.6 min on OJ-H with 8% IPA/hexanes, $[\alpha]_D$ = 191, $CDCl_3$). Chiral separation of fraction 2 (*cis* isomers) on OJ-H with 20% IPA/hexanes gave **H4** (316 mg, >99%ee, retention time 18.9 min on OJ-H with 14% IPA/hexanes, $[\alpha]_D$ = 151, $CDCl_3$), and **H3** (306 mg, 98.5%ee, retention time 27.2 min on OJ-H with 14% IPA/hexanes, $[\alpha]_D$ = -147, $CDCl_3$). Absolute configuration was assigned based on the agreement of calculated vibrational circular dichroism spectra and optical rotations with experimental values. MS ESI (pos.) M/E: 219 (M+H).

VCD and optical rotation agreement for H2 – H5

Head Group	NMR (NOE)	Predicted OR	Exp. OR	VCD
H5	*trans*	+130	+191	consistent
H2	*trans*	-130	-198	consistent
H4	*cis*	+140	+151	consistent
H3	*cis*	-140	-147	consistent

Head groups 18~21



***tert*-Butyl(3-methylene-2,3-dihydro-1H-inden-5-yloxy)diphenylsilane (16).** To a solution of **15** (607 g, 1570 mmol) and triphenylmethylphosphonium bromide (673 g, 1884 mmol) in THF (1000 mL) was added potassium *tert*-butoxide 1.0 M solution in THF) (1884 mL, 1884 mmol) via an addition funnel over 2 hours. The resulting mixture was stirred at room temperature for 16 hours and distilled to remove most of THF. The resulting mixture was suspended in hexanes, passed through a pad of silica gel (1 kg), rinsed with hexanes (total 8 L), and then with 10% EtOAc in hexanes (4 L). The resulting mixture was concentrated to give **16** (600 g, 99% yield). MS ESI (pos.) M/E: 385 (M+H).

Synthesis of 17. To a solution of *tert*-butyl(3-methylene-2,3-dihydro-1H-inden-5-yloxy)diphenylsilane **16** (599.6 g, 1559 mmol) and rhodium (ii) acetate, dimer (2.8 g, 6.3 mmol) in refluxing DCM (1400 mL) was added ethyl diazoacetate (227 mL, 2191 mmol) in DCM via addition funnel over 2 hours. The resulting mixture was stirred at 45 °C for 1 hour and then at room temperature for 2 hours. The reaction mixture was concentrated and passed through a short pad of silica gel (1 kg) with 5% EtOAc in hexanes (8L) to give **17** (588 g, 80% yield) after removal of solvent. MS ESI (pos.) M/E: 471 (M+H).

Synthesis of head groups 18-21. To a solution of **17** (119 g, 253 mmol) in THF (500 mL) was added TBAF (303 mL, 303 mmol) in THF. The resulting mixture was stirred at room temperature for 1 hour. The mixture was then concentrated, redissolved in EtOAc, washed with saturated aqueous NH_4Cl, and concentrated with silica gel (300 g) to give a yellow solid after high vacuum. The solid was loaded into an empty solid load cartridge and purified by flash chromatography (20% EtOAc in hexanes). The collected products were combined and separated by chiral column (ChiralPak AD, 4% IPA/hexanes) to give: **18** (8.3 g, 14% yield, 98%ee, retention time 34.5 min on AD-H with 5% IPA/hexanes, $[\alpha]_D$ = -346,

$CDCl_3$), **19** (8.3 g, 14% yield, 99%ee, retention time 23.9 min on AD-H with 5% IPA/hexanes, $[\alpha]_D$ = 370, $CDCl_3$), **20** (10.0 g, 17% yield, 98%ee, retention time 17.6 min on AD-H with 5% IPA/hexanes, $[\alpha]_D$ = -0.5, $CDCl_3$), **21** (10.0 g, 17% yield, 99%ee, retention time 13.2 min on AD-H with 5% IPA/hexanes, $[\alpha]_D$ = -5, $CDCl_3$). All four products have the same MS, MS ESI (pos.) M/E: 233 (M+H). The relative stereochemistry was assigned based on NMR (NOE) studies. Absolute configuration was assigned based on the comparison of experimental optical rotations (**18-19**) and vibrational circular dichroism spectra (**18-21**) with quantum mechanical calculations on specific enantiomers. The structure of **19** was further confirmed by X-ray analysis of a crystal derivatized from **19** (dibromination followed by hydrolysis). Compound **18**: ^{1}H NMR (400 MHz, *CHLOROFORM-d*), δ ppm 7.06 (1 H, d, *J*=8.0 Hz), 6.64 (1 H, dd, *J*=8.0, 2.3 Hz), 6.19 (1 H, d, *J*=2.3 Hz), 4.14 - 4.22 (2 H, m), 2.86 - 3.03 (2 H, m), 2.21 - 2.35 (2 H, m), 2.00 (1 H, dd, *J*=8.4, 6.1 Hz), 1.61 - 1.69 (1 H, m), 1.39 (1 H, dd, *J*=8.4, 4.9 Hz), 1.24 - 1.31 (3 H, m).

VCD and optical rotation agreement for 18 – 21

Head Group	NMR (NOE)	Predicted OR	Exp. OR	VCD
18	*trans*	-370	-346	consistent
19	*trans*	+370	+370	consistent
20	*cis*	-70	-0.5	consistent
21	*cis*	+70	-5.4	consistent

Experimental VCD spectra and optical rotation – general methodology. VCD spectra were acquired on a BioTools Dual PEM *ChiralIR* instrument. Samples of **18** – **21** and **H2 – H5** were prepared in $CDCl_3$ at concentrations of 45 mg/mL, and spectra acquired (BaF_2 cell, 100 μM path length) for 200 min at room temperature at 4 cm^{-1} resolution, and are solvent subtracted. Optical rotations ($[\alpha]_D$) were measured on a JASCO P-1020 polarimeter. Specific rotations are given as deg/dm, and the concentrations are 0.5~1 g/100 mL in $CDCl_3$ and were recorded at room temperature (22-24 °C).

Theoretical VCD and optical rotation – general methodology. Initial conformational ensembles of a specified enantiomer were obtained via molecular mechanics-based stochastic search (MMFF94 force field, Molecular Operating Environment (MOE); Chemical Computing Group Inc., Montreal, Canada; http://www.chemcomp.com) with relatively exhaustive search and retainment criteria (20 kcal/mol energy window and 0.08 Å RMSD cutoff.) The resultant conformers were subjected to full geometry optimization with the B3LYP functional and 6-31G* basis set, followed by harmonic frequency, VCD rotational strength, and optical rotation (static polarizability model) determination of all resultant, structurally unique conformers within a 3 kcal/mol window with respect to the global minimum. The predicted IR and VCD line spectra for each unique conformer were convolved using a Lorentzian function (γ = 4.0 cm^{-1}), followed by Boltzmann weighting based on the predicted B3LYP/6-31G* relative

free energies (298.15 K) of each conformation and summed to yield final predicted IR and VCD spectra. Vibrational frequencies were scaled by 0.96 for comparison to experiment. Absolute configurations of **18 – 21** and **H2 – H5** were all assigned in this manner. All quantum mechanical calculations were performed with the *Gaussian 03* program system: Frisch *et al*, Gaussian 03, Revision D.01; Gaussian, Inc., Wallingford, CT 2004.

Example of assignment by optical rotation and VCD: 19. 23 structurally unique conformers of the *(S,S)* stereoisomer were located within a free energy window of 3 kcal/mol above the B3LYP/6-31G* global minimum. The predicted optical rotation of **18** and **19** were then determined from the free energy-weighted values predicted for each conformer of the *(S,S)* stereoisomer (found to be **19**) compared to the experimentally measured values. Rotation-based assignments of **H2** – **H5** were performed in a similar manner.

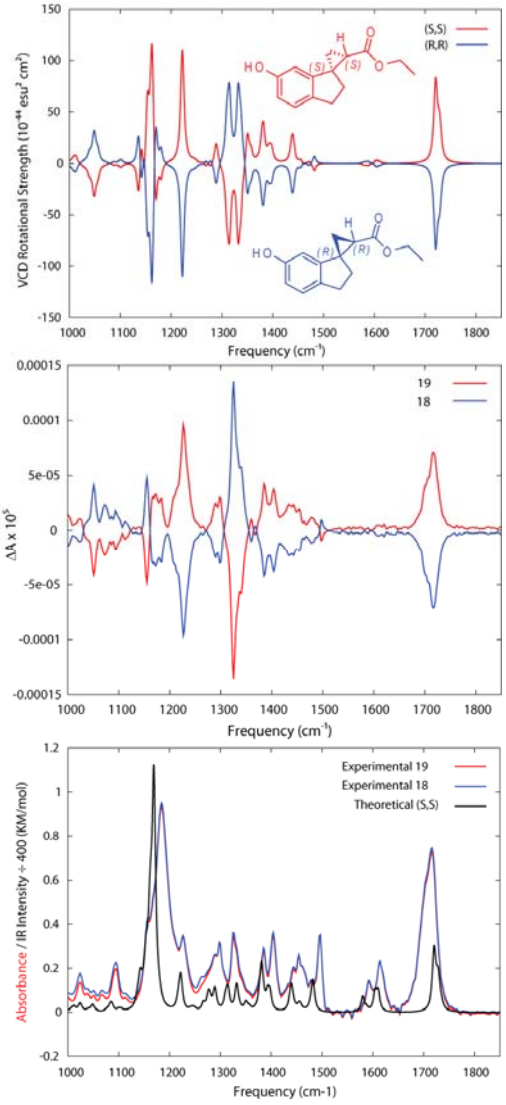
(S,S) Conformer	ΔG_{rel} (kcal/mol)	Boltzmann pop. (298.15 K)	$[\alpha]_D$ (deg.)
Conformation 1	0	0.244303664	+390.03
Conformation 2	0.311	0.144532894	+419.82
Conformation 3	0.452	0.113923566	+288.14
Conformation 4	0.658	0.08046655	+304.21
Conformation 5	0.799	0.06342526	+417.49
Conformation 6	0.807	0.062574624	+425.86
Conformation 7	0.927	0.051102028	+326.51
Conformation 8	0.975	0.047125296	+446.08
Conformation 9	1.005	0.044798561	+455.69
Conformation 10	1.041	0.042157615	+339.52
Conformation 11	1.091	0.038745921	+298.67
Conformation 12	1.187	0.032950188	+314.34
Conformation 13	2.206	0.005901059	+257.26
Conformation 14	2.287	0.005147032	+263.25
Conformation 15	2.379	0.004406774	+350.57
Conformation 16	2.469	0.00378574	+369.68
Conformation 17	2.706	0.002537637	+233.55
Conformation 18	2.752	0.002348072	+304.75
Conformation 19	2.795	0.002183697	+239.41
Conformation 20	2.83	0.002058436	+209.65
Conformation 21	2.832	0.002051499	+324.98
Conformation 22	2.875	0.001907886	+217.64
Conformation 23	2.992	0.001565998	+318.98

Theoretical, Boltzmann-weighted $[\alpha]_D$ for *(S,S)* stereoisomer: +370.42

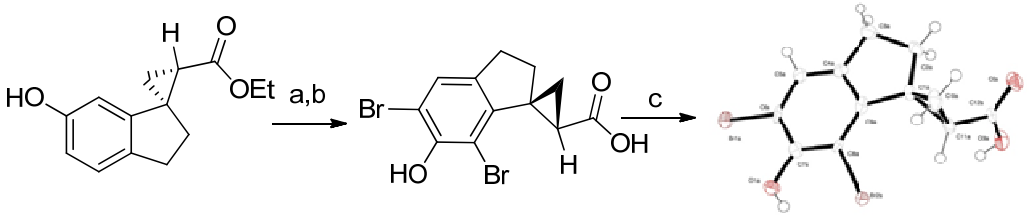
Experimental $[\alpha]_D$ for **18** ($CDCl_3$) : = -346

Experimental $[\alpha]_D$ for **19** ($CDCl_3$) : = +370

Theoretical (B3LYP/6-31G*; top) and experimental VCD (middle) spectra with aligned IR plots (bottom) for 18 and 19.



The configuration of head group **19** in compound **11** was further verified by X-ray analysis of its brominated analog.



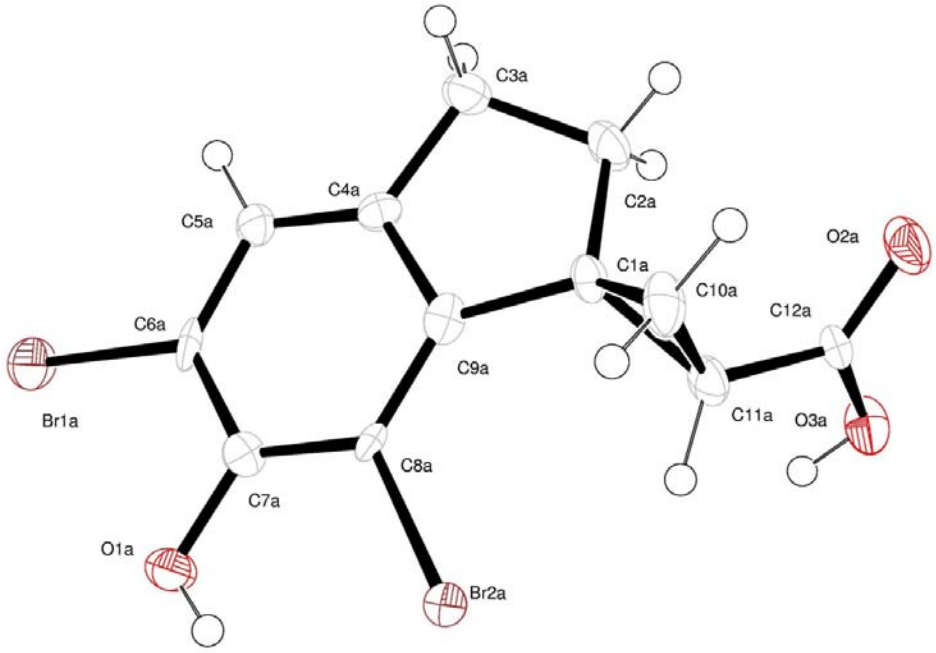
19 **36** **36**

(1S,2S)-5',7'-Dibromo-6'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylic acid (36). To a stirred solution of **19** (0.0465 g, 0.200 mmol) in ethanol (5 mL) was added n-

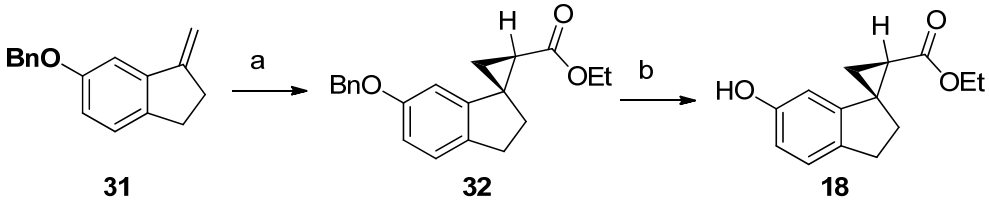
bromosuccinimide (0.0373 mL, 0.440 mmol) , stirred at 23 °C for 16 hours. Loaded directly to silica gel cartridge and purified by flash chromatography (0-50% EtOAc in hexanes). Hydrolysis with 2N LiOH /THF/MeOH (1:2:1 ratio, 5 mL) at 50 °C for 15 hours. Acidified with 2N HCl, diluted with ACN, purified by HPLC to give **36** (0.051 g, 70%). MS ESI (neg.) M/E: 361 (M-H). **36** was crystallized in EtOAc/hexanes to give crystal material, which was dissolved in 1,2-dichloroethane with a few drops of MeOH, and vapor diffused octane into that solution to form bigger crystals (8 of target molecules crystallized to form the asymmetric unit as well as 1,2-dichloroethane). X-ray determination confirmed that it is the assigned stereochemistry (S,S), consistent with VCD and optical rotation assignments of the des-bromo ethyl ester **19**.

X-ray crystal structure.

X-ray data was collected by Frederick J. Hollander and Antonio DiPasquale at UC Berkeley, and submitted to the Cambridge Structural Database (www.ccdc.cam.ac.uk): CCDC 903315.



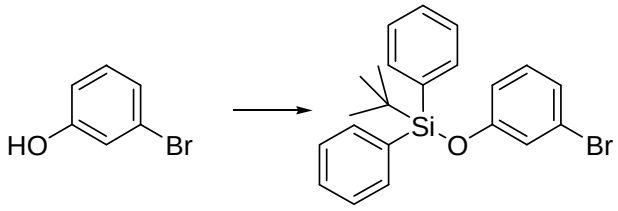
Asymmetric approach to head group 18



(1R,2R)-Ethyl 6'-(benzyloxy)-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylate (32). A mixture of 6-(benzyloxy)-1-methylene-2,3-dihydro-1H-indene [**31**, prepared using the procedure described for the synthesis of **16** from 6-(benzyloxy)-2,3-dihydro-1H-inden-1-one] (100 mg, 423 µmol), 2,6-bis[(4s)-(-)-isopropyl-2-oxazolin-2-yl]pyridine (12.8 mg, 42 µmol) and di-mu-chlorobis[(p-cymene)chlororuthenium (II)] (13.0 mg, 21 µmol) was purged with N_2 and sealed under N_2, then was added degassed THF (8 mL). The solution was heated to 60 °C. To this solution was added ethyl diazoacetate (70.5 µl, 635 µmol) in THF (0.5 mL) via syringe pump over 8 hours. The resulting mixture was cooled to 23 °C, concentrated, loaded to solid silica gel cartridge, and purified by flash chromatography (0%-30% EtOAc in hexanes) to give **32** (128 mg, 94% yield). Chiral HPLC analysis of the crude product revealed 90% *ee* for the desired product **32**.

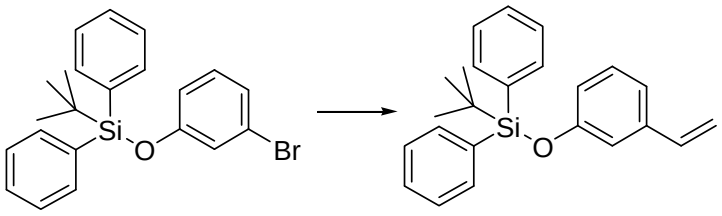
(1R,2R)-Ethyl 6'-hydroxy-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylate (18). A solution of **32** (100 mg, 310 µmol) in EtOAc (5 mL) was added Pd/C (33 mg, 15.5 µmol, 10% weight, 50% wet), charged with a balloon of hydrogen, and stirred at r.t. for 2 hours. Filtered through a pad of Celite and concentrated to give **18** (68 mg, 95%).

Head group H6



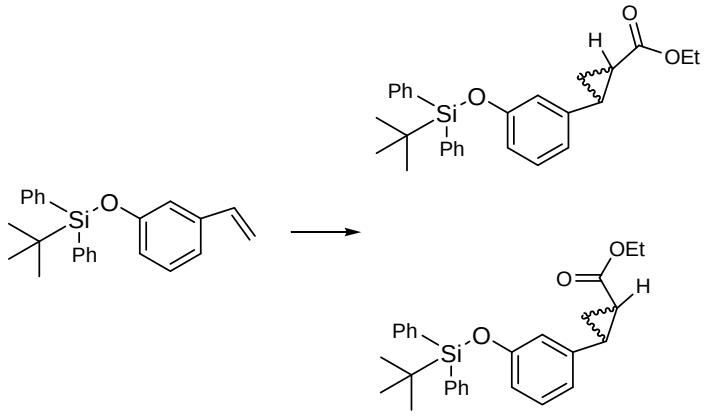
H6.1

(3-Bromophenoxy)(*tert*-butyl) diphenylsilane (H6.1). A mixture of imidazole (8.53 mL, 75.14 mmol), *tert*-butyldiphenylchlorosilane (17.75 mL, 69.36 mmol) and 3-bromophenol (10 g, 57.80 mmol) in DMF (300 mL) was heated at 60°C for 16 hours under N_2. The reaction was then cooled to room temperature, diluted with EtOAc (800 mL), and water was added. The organic layer was separated, and the aqueous solution was extracted with EtOAc (500 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography (0%-10% EtOAc in hexanes) to give **H6.1** (22 g, yield 93%). ^{1}H NMR (500 MHz, $CDCL_3$) δ ppm 7.72-7.76 (4 H, m), 7.36-7.55 (6 H, m), 6.92-7.04 (3 H, m), 6.61-6.63 (1 H, m), 1.12 (9H, s).



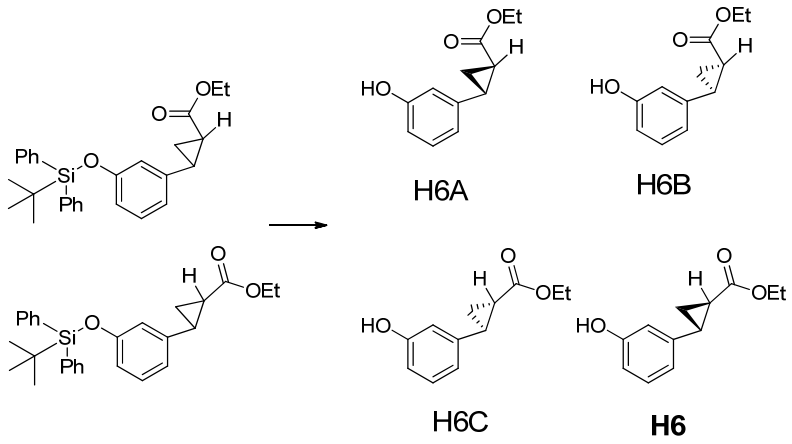
H6.1 **H6.2**

***tert*-Butyldiphenyl(3-vinylphenoxy)silane (H6.2).** Under an argon atmosphere, a mixture of (3-bromophenoxy) (*tert*-butyl) diphenylsilane **H6.1** (10 g, 24.31 mmol), tributyl (vinyl) tin (9.25 g, 29.17 mmol), and tetrakis(triphenylphosphine)palladium (1.40 g, 1.22 mmol) in anhydrous DMF (100 mL) was stirred at 110°C for 2 hours. The solution was diluted with EtOAc (300 mL) and then filtered. The filtrate was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (0%-10% EtOAc in hexanes) to give **H6.2** (8.7 g, 99.8%). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.65 (4 H, dd, *J* = 8.2, 1.6Hz), 7.27-7.38 (6 H, m), 6.94 (1 H, t, *J* = 7.8Hz), 6.77-6.84 (2H, m), 6.46-6.55 (2 H, m), 5.42-5.45 (1H, m), 5.05 (1H, dd, *J* = 10.8, 1.0Hz), 1.04 (9H, s).



H6.2 **H6.3 and H6.4**

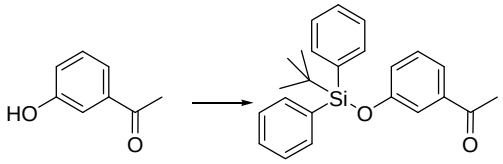
Ethyl 2-(3-(*tert*-butyldiphenylsilyloxy) phenyl) cyclopropane carboxylate (H6.3 and H6.4). To a solution of *tert*-butyldiphenyl (3-vinylphenoxy) silane **H6.2** (8.7 g, 24.265 mmol) and rhodium (ii) acetate dimer (107 mg, 243 μmol) in refluxing DCM (200 mL), was added ethyl diazoacetate (3.775 mL, 36.397 mmol) in DCM (12 mL) via syringe pump over 60 minutes. The resulting mixture was stirred at 45°C for 1 hour and then at room temperature for 2 hours. The mixture was then concentrated, and the residue was purified by flash chromatography (hexanes: EtOAc =5:1, Rf=0.5) to give the mixture of *trans*/*cis* isomers **H6.3** and **H6.4** (7.2g, 66.7%).



H6.3 and H6.4 **H6**

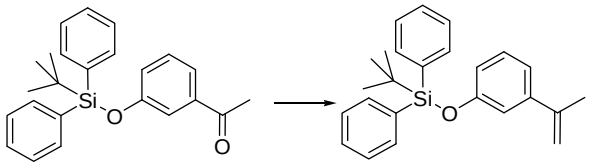
(1R,2R)-ethyl 2-(3-hydroxyphenyl)cyclopropanecarboxylate (H6). To a solution of **H6.3** and **H6.4** (7.2 g, 16.2 mmol) in THF (200 mL) was added 1M solution of TBAF in THF(19.43 mL, 19.43 mmol). The resulting mixture was stirred at room temperature for 1 hour, concentrated, and then purified by column (hexanes: EtOAc = 3:1) to give 6 g of the product as a mixture of *cis*/*trans* isomers in their racemic form. 1 g of the mixture was separated by chiral HPLC (AD-H, 4% IPA/hexanes) to give the four isomers. The *cis* and *trans* isomers were determined by NOESY NMR analysis. **H6** (138 mg, 16.5% yield, 97%ee) is the fourth eluted enantiomer. Mass Spectrum (ESI) m/e = 207.1 [M+1]. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.04 (1 H, t, *J*=8.0 Hz), 6.42 - 6.71 (3 H, m), 6.34 (1 H, br. s.), 4.09 (2 H, q, *J*=7.2 Hz), 2.39 (1 H, ddd, *J*=9.3, 6.6, 4.1 Hz), 1.81 (1 H, dd, *J*=8.4, 4.5 Hz), 1.50 (1 H, ddd, *J*=9.3, 5.1, 4.8 Hz), 1.18-1.22 (4 H, m).

Head group H7



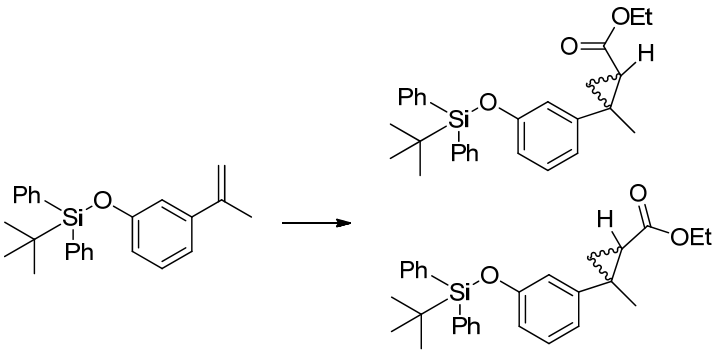
H7.1

1-(3-(*tert*-Butyldiphenylsilyloxy)phenyl)ethanone (**H7.1**). Compound **H7.1** was synthesized using the procedure described for the synthesis of compound **H6.1** using 1-(3-hydroxyphenyl)ethanone in place of 3-bromophenol**.** MS ESI (pos.) M/E: 392.2 (M+18).



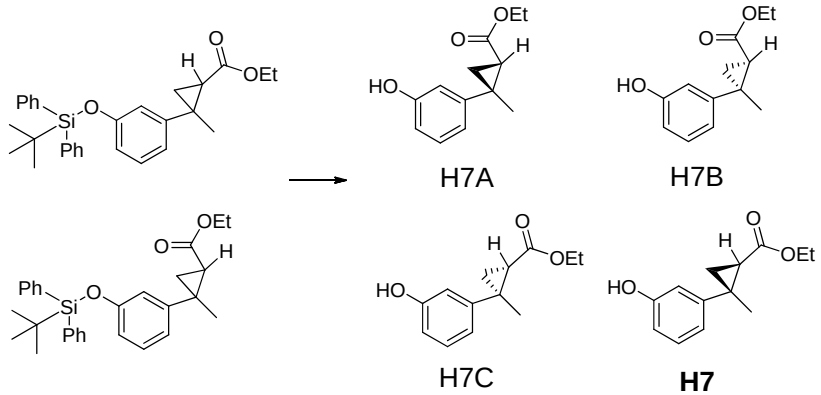
H7.1 **H7.2**

***tert*-Butyldiphenyl(3-(prop-1-en-2-yl)phenoxy)silane** (**H7.2**). To a solution of methyltriphenylphosphonium bromide (15.45 g, 43.25 mmol) and 1N solution of potassium 2-methylpropan-2-olate (43.25 mL, 43.25 mmol) in THF (100 mL) was added **H7.1** (13.5 g, 36.0 mmol) via addition funnel over 10 minutes. The resulting mixture was stirred at room temperature for 1 hour, quenched with a saturated $NaHCO_3$ solution (100 mL), and extracted with EtOAc (300 mL). The combined organic layers were washed with water and brine, died over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (100% hexanes , Rf=0.5) to give **H7.2** (12.5g, 93% yield). MS ESI (pos.) M/E: 391.3 (M+18).



H7.2 **H7.3 and H7.4**

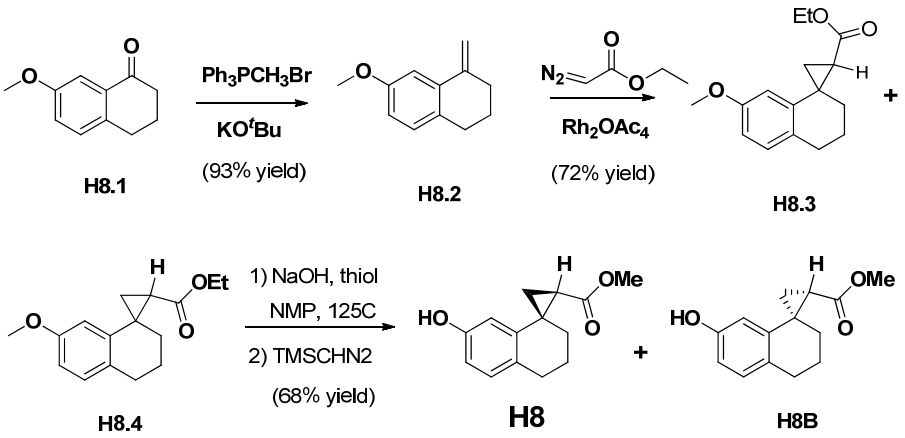
Ethyl 2-(3-(*tert*-butyldiphenylsilyloxy)phenyl)-2-methylcyclopropanecarboxylateand ethyl 2-(3-(*tert*-butyldiphenylsilyloxy)phenyl)-2-methylcyclopropanecarboxylate (H7.3 and H7.4). To a solution of *tert*-butyldiphenyl(3-(prop-1-en-2-yl)phenoxy)silane **H7.2** (12.50 g, 33.55 mmol) and rhodium (ii) acetate, dimer (148 mg, 336 μmol) in refluxing DCM (200 mL) was added ethyl diazoacetate (5.22 mL, 50.33 mmol) in DCM (12 mL) via syringe pump over 60 minutes. The resulting mixture was stirred at 45°C for 1 hour, at room temperature for 2 hours, and was then concentrated. The residue was purified by flash chromatography (hexanes: EtOAc = 20:1, Rf=0.5) to give the mixture of *trans*/*cis* isomers **H7.3** and **H7.4** (10.4g, 67.6%). MS ESI (pos.) M/E: 476.2 (M+18).



H7.3 and H7.4 **H7**

(1R,2R)-Ethyl 2-(3-hydroxyphenyl)-2-methylcyclopropanecarboxylate (H7). To a solution of **H7.3** and **H7.4** (10 g, 21.8 mmol) in THF (200 mL), was added 1M solution of TBAF in THF (26.16 mL, 26.16 mmol). The resulting mixture was stirred at room temperature for 1 hour, concentrated, and passed through a short pad of silica gel to give an oil residue after evaporation. The resulting residue was then purified by flash chromatography (hexanes: EtOAc = 3:1 Rf=0.3 *trans*, 0.2 *cis*) to give a mixture of *cis* isomers **H7A** and **H7B** (1.4g) and *trans* isomers **H7C** and **H7** (1.3g). The *cis* and *trans* isomers were determined by NOESY NMR analysis. The mixture of *trans* isomers (300 mg) was separated by chiral HPLC (AD-H, 4% IPA/hexanes) to give **H7C** (100 mg) as the first eluted enantiomer and **H7** (78 mg, >96% ee) as the second eluted enantiomer. MS ESI (pos.) M/E: 221.1 (M+H). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.18 (1 H, t, *J*=7.8 Hz), 6.76 - 6.93 (2 H, m), 6.71 (1 H, dd, *J*=8.2, 2.7 Hz), 5.39 (1 H, br), 4.22 (2 H, qd, *J*=7.1, 2.2 Hz), 1.98 (1 H, dd, *J*=8.2, 5.9 Hz), 1.53 (3 H, s), 1.37 - 1.50 (2 H, m), 1.32 (3 H, t, *J*=7.2 Hz).

Head group H8



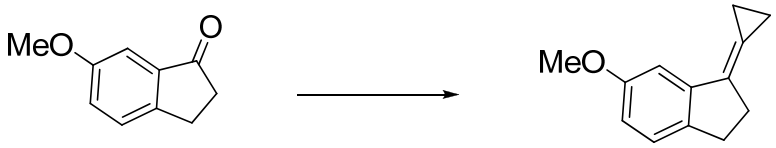
7-Methoxy-1-methylene-1,2,3,4-tetrahydronaphthalene (H8.2). To a solution of 7-methoxy-1-tetralone **H8.1** (26.9 g, 153 mmol) and triphenylmethylphosphonium bromide (65.4 g, 183 mmol) in THF (550 mL) was added potassium *tert*-butoxide (1.0 M solution in THF)(183 mL, 183 mmol) via addition funnel over 1 hour. The resulting mixture was stirred at room temperature for 60 minutes after addition. The reaction was then concentrated and resuspended in hexanes (250 mL). The mixture was passed through a silica gel plug (25g silica) and rinsed with 250 mL of hexanes. Removal of solvent gave **H8.2** (24.5 g, 92 % yield). MS ESI (pos.) M/E: 175 (M+H).

Ethyl 7'-methoxy-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-naphthalene]-2-carboxylate (H8.3 and H8.4). To a solution of **H8.2** (5.23 g, 30.0 mmol) and rhodium (ii) acetate, dimer (0.133 g, 0.30 mmol) in refluxing DCM (200 mL) was added ethyl diazoacetate (4.67 mL, 45.0 mmol) in DCM (12 mL) via

syringe pump over 60 minutes. The resulting mixture was stirred at 45°C for 1 hour and then at room temperature for 2 hours. The reaction was concentrated and purified by flash chromatography (20% EtOAc in hexanes) gave two products with the desired mass (**H8.3** and **H8.4**). **H8.3** (2.88 g) was obtained as oil that became a white solid after a few days, and *NOE* using ^{1}H NMR showed this to be the *cis* product. **H8.4** (3.04 g) was obtained as a colorless oil, and *NOE* using ^{1}H NMR showed this to be the *trans* product. MS ESI (pos.) M/E: 261 (M+H).

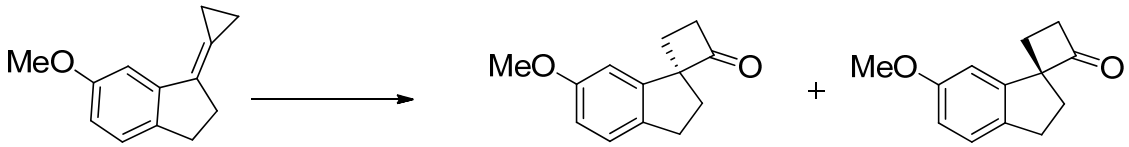
Synthesis of H8. A 100 mL flask was charged with **H8.4** (2.56 g, 9.8 mmol), NMP (22 mL), NaOH (1.77 g, 44.3 mmol), and 1-dodecanethiol (8.25 mL, 34.4 mmol). The mixture was stirred for 24 hours at 125°C, cooled to room temperature, and diluted with 1 N HCl (200 mL) and ether (300 mL). The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated. Flash chromatography purification (10-40% EtOAc/hexanes) gave the desired acid (1.45 g, 68% yield), which was dissolved in 40 mL of benzene and 10 mL of MeOH, treated with (trimethylsilyl)diazomethane (2.0 M in diethyl ether)(8.3 mL, 16.6 mmol) at 0°C for 1 hour. The reaction mixture was concentrated to give methyl 7'-hydroxy-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-naphthalene]-2-carboxylate (1.55 g, 100% yield), which was separated from Chiralcel OJ column (15% IPA/hexanes) to give **H8** (>99%ee, peak 2, 765 mg). MS ESI (pos.) M/E: 233 (M+H). ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 6.95 (1 H, d, *J*=8.2 Hz), 6.60 (1 H, dd, *J*=8.2, 2.5 Hz), 6.20 (1 H, d, *J*=2.5 Hz), 3.63 - 3.75 (3 H, m), 2.79 (2 H, t, *J*=6.3 Hz), 1.98 (1 H, t, *J*=7.4 Hz), 1.90 - 1.95 (2 H, m), 1.80 - 1.90 (1 H, m), 1.65 - 1.76 (1 H, m), 1.56 (2 H, d, *J*=7.0 Hz).

Head group H9



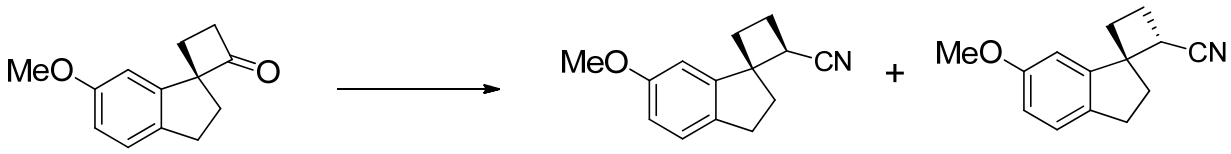
H9.1 **H9.2**

1-Cyclopropylidene-6-methoxy-2,3-dihydro-1H-indene (H9.2). NaH (1.5 g, 62 mmol) was added to a suspension of cyclopropyltriphenyl-phosphonium bromide (24 g, 62 mmol) in THF (100 mL) and the resulting mixture was stirred at r.t. for 2 hrs. Then it was added slowly 6-methoxy-1-indanone (**H9.1**) (5.00 g, 31 mmol) and tris(2-(2-methoxyethoxy)ethyl)amine (1.1 mL, 3.1 mmol). The resulting mixture was stirred at r.t. for 10 min then at 62^{o}C for 4 hrs. The reaction mixture was concentrated and purified by flash chromatography (1:9 EtOAc /hexanes) to give product **H9.2** (4.53g, 79% yield) as solid. MS ESI (pos.) M/E: 187.1 (M+H).



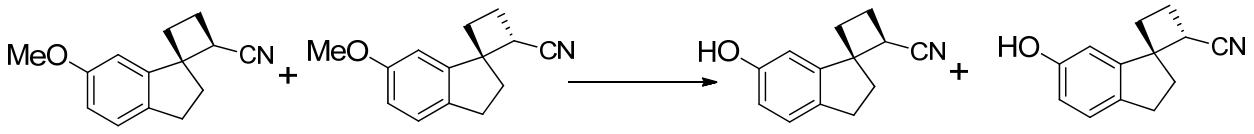
H9.2 **H9.3** **H9.4**

(R)-6'-methoxy-2',3'-dihydrospiro[cyclobutane-1,1'-inden]-2-one (H9.4). At 0-5^{o}C, m-chloroperoxobenzoic acid (5.84 g, 33.8 mmol) was added portion by portion to a solution of 1-cyclopropylidene-6-methoxy-2,3-dihydro-1H-indene (**9.2**) (4.50 g, 24.2 mmol) in DCM (70 mL). It was stirred at 0-5^{o}C for 42 min and then at r.t. for 60 min. The reaction mixture was diluted with DCM (200 mL), washed with 10% NaOH solution and brine and then dried over anhydrous sodium sulfate. It was concentrated and the residue was purified by chromatography (silica gel, eluting with 1:9 EtOAc /hexanes) to give product ketone (1.95 g, 40% yield) as pale yellow oil. MS ESI (pos.) M/E: 203.1 (M+H). Chiral separation was conducted on OD column, eluting with 1% *i*-PrOH /hexanes. Pure enantiomer **H9.3** (0.896 g, oil) (1st peak, retention time 8.4 min) and **H9.4** (1.01g, oil, 21%) (2nd peak, retention time 10.5 min) were obtained. Stereochemistry was assigned based on GPR40 activity of compound **23**.



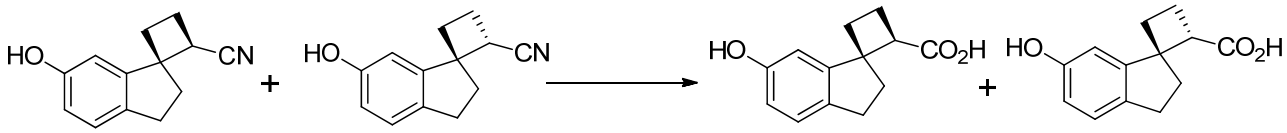
H9.4 **H9.5**

(1S,2R)-6'-methoxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile and (1S,2S)-6'-methoxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile (9.5). At 0-5^{o}C, potassium 2-methylpropan-2-olate (1.66 g, 14.8 mmol) was added in one portion to a solution of **H9.4** (1.00 g, 4.94 mmol) and tosylmethyl isocyanide (1.93 g, 9.89 mmol) in dimethoxyethane (16 mL) and methanol (0.9 mL). After it was stirred at r.t. for 4 hrs, the reaction mixture was poured into water (20 mL) and neutralized with 1N HCl to pH 6-7. It was extracted with EtOAc (3x100 mL) and the combined organic phase was washed with brine, dried over anhydrous sodium sulfate. It was concentrated and the residue was purified by flash chromatography (1:9 EtOAc /hexanes) to give **H9.5** (pale yellow oil, 0.222 g, 21% yield). MS ESI (pos.) M/E: 214.1 (M+H).



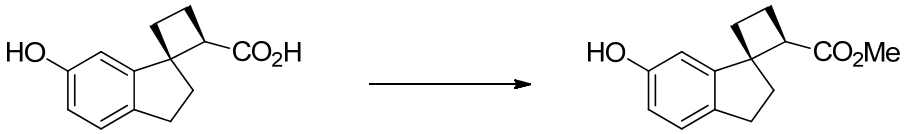
H9.5 **H9.6**

(1S,2R)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile and (1S,2S)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carbonitrile (H9.6). A mixture of **H9.5** (0.217 g, 1.02 mmol) and sodium methanethiolate (0.499 g, 7.12 mmol) in DMF (20 mL) was stirred at 135°C for 3 hrs. The reaction mixture was poured into NH_4Cl solution (20 mL). It was extracted with EtOAc (230 mL). Organic phase was washed with brine, dried over anhydrous sodium sulfate. It was concentrated and the residue was purified by flash chromatography (1:3 EtOAc /hexanes) to give **H9.6** (colorless oil, 0.203g, 100% yield). MS ESI (pos.) M/E: 200.2 (M+H).



H9.6 **H9.7** **H9.8**

(1S,2R)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylic acid (9.7) and (1S,2S)-6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylic acid (9.8). A mixture of **H9.6** (0.203 g, 1.0 mmol) and NaOH (aq., 10%) (6 mL) in ethylene glycol (10 mL) was stirred at 135°C for 2 hrs. It was diluted with water (0.6 mL) and acidified with 1N HCl to pH2-5. The solution was purified by reverse phase HPLC to give **H9.7** (retention time is shorter, white solid, 113 mg, 51% yield) and **H9.8** (retention time is longer, film, 32 mg, 14% yield). **H9.7**: MS ESI (pos.) M/E: 219.1 (M+H).

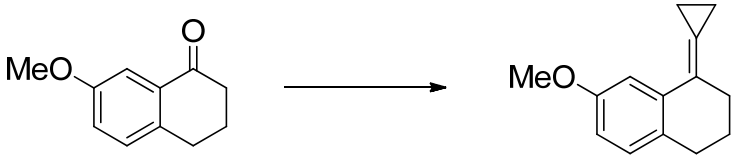


H9.7 **H9**

(1S,2R)-methyl 6'-hydroxy-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylate (H9).

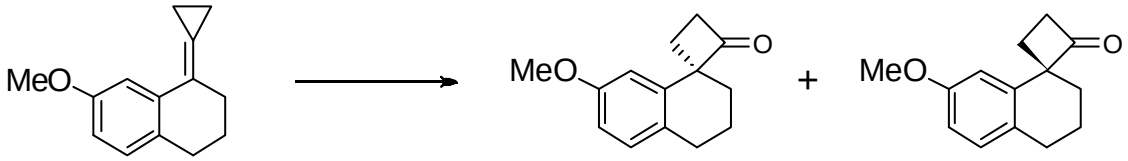
A solution of **H9.7** (0.109 g, 0.50 mmol) in MeOH (12 mL) (containing 4 drops of conc. H_2SO_4) was refluxed for 21 hrs. It was cooled to r.t. and neutralized with $NaHCO_3$ solution. The mixture was concentrated and extracted with ethyl acetate (120 mL). Organic phase was dried over anhydrous sodium sulfate. After removal of solvent, the residue was purified by flash chromatography (10% EtOAc in hexanes) to give **H9** (clear oil, 83 mg, 72% yield) was obtained. MS ESI (pos.) M/E: 250.1 ($M+H_2O$).

Head group H10



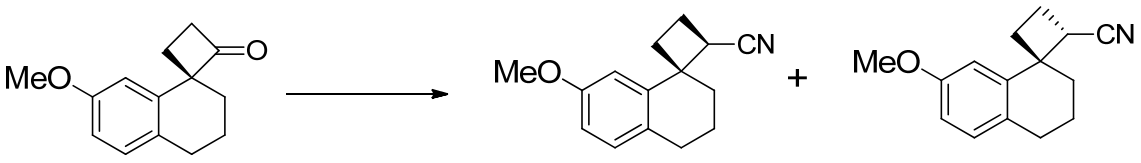
H8.1 **H10.2**

1-Cyclopropylidene-7-methoxy-1,2,3,4-tetrahydronaphthalene (H10.2). H10.2 was synthesized according to the procedure for **H9.2** from **H8.1**.



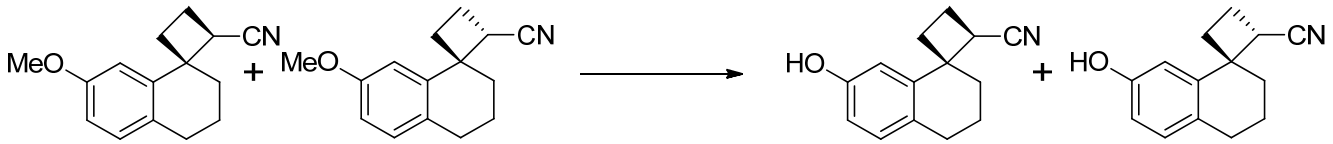
H10.2 **H10.3** **H10.4**

(S)-7'-Methoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalen]-2-one or (R)-7'-Methoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalen]-2-one (H10.3). H10.3 was synthesized according to the procedure for **H9.3** from **H10.2**. The racemic product: MS ESI (pos.) M/E: 217.1 (M+H). Chiral separation was conducted on OD column, eluting with 1% *i*-PrOH /hexanes. Pure enantiomer **H10.3** (1.35g, white solid, 49% yield) (1st peak, retention time 8.06 min) and **H10.4** (1.37g, white solid, 49% yield) (2nd peak, retention time 11.6 min) were obtained. Stereochemistry was assigned according to analogy to **H9.3**.



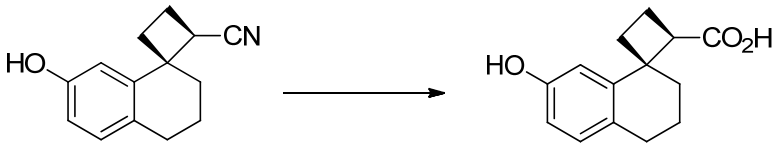
H10.4 **H10.5**

(1R,2S)-7'-methoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile and (1R,2R)-7'-methoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile (H10.5). **H10.5** (220 mg, 17% yield) was synthesized according to the procedure for **H9.5** from **H10.4**. MS ESI (pos.) M/E: 245.2 ($M+H_2O$).



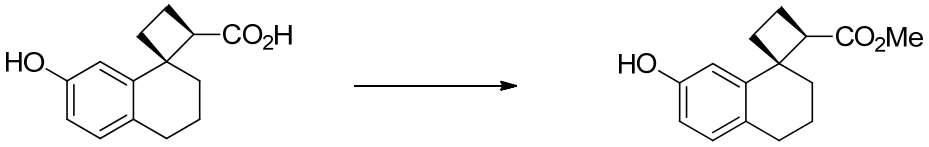
H10.5 **H10.6**

(1R,2S)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile and (1R,2R)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carbonitrile (H10.6). **H10.6** (203 mg, 100% yield) was synthesized according to the procedure for **H9.6** from **H10.5**. MS ESI (pos.) M/E: 231.1 (M+H).



H10.6 **H10.7**

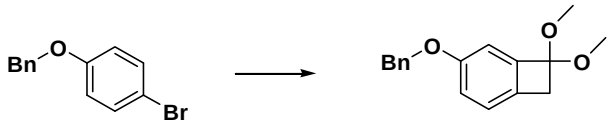
(1R,2R)-7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylic acid (H10.7). H10.7 (1^{st} peak from reverse phase HPLC, 49 mg, 22% yield) was synthesized according to the procedure for **H9.7** from **H10.6**. MS ESI (neg.) M/E: 231.1 (M-H).



H10.7 **H10**

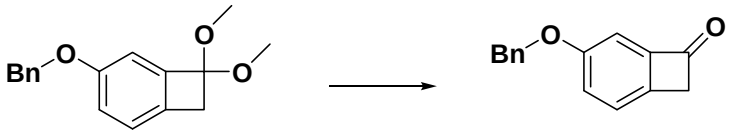
(1R,2R)-methyl 7'-hydroxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylate (H10). H10 was synthesized according to the procedure for **H9** from **H10.7**. MS ESI (pos.) M/E: 247.2 (M+H).

Head group H11



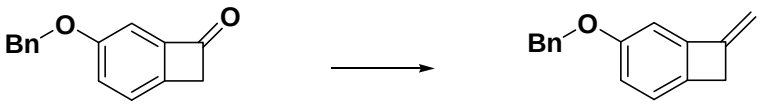
H11.1

5-(Benzyloxy)-1,1-dimethoxy-1,2-dihydrocyclobutabenzene (H11.1). To a 6 mL THF solution of 1-(benzyloxy)-4-bromobenzene (500 mg, 1900 µmol, Sigma-Aldrich) and ketene dimethyl acetal (359 µL, 3800 µmol) was added neat sodium amide (107 µL, 3800 µmol). The resulting mixture was heated to 80°C and stirred for 48 hours. After the reaction was complete, it was quenched by slow addition of water (10 mL). The resulting mixture was then extracted with EtOAc (20 mL). The organic layer was washed with brine and dried over $MgSO_4$. Solvent was removed in the presence of silica gel, and the residue was purified by flash chromatography with 20% EtOAc/hexanes to afford desired product **H11.1** (274 mg, yield, 60%). MS ESI (pos.) m/e: 271.1 $(M+H)^+$.



H11.1 **H11.2**

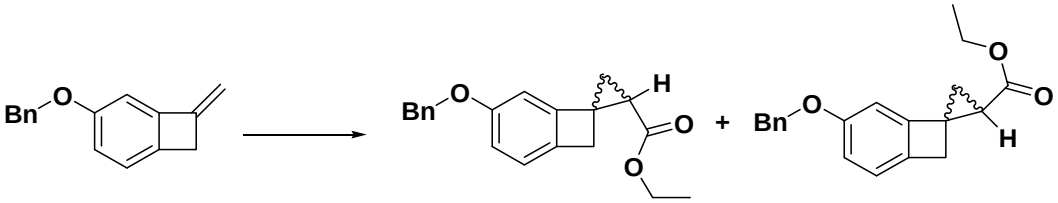
5-(Benzyloxy)cyclobutabenzen-1(2H)-one (H11.2). H11.1 (270 mg, 1.00 mmol) was dissolved in 6 mL 5:1 THF and water. To this solution was added 0.5 mL 1N HCl, and the resulting mixture was stirred for 1 hour. The resulting mixture was then diluted with 20 mL EtOAc and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in the presence of silica gel. The residue was then purified by flash chromatography with 10% EtOAc/hexanes to afford **H11.2** (204 mg, yield, 91.1%). MS ESI (pos.) m/e: 225.1 $(M+H)^+$.



H11.2 **H11.3**

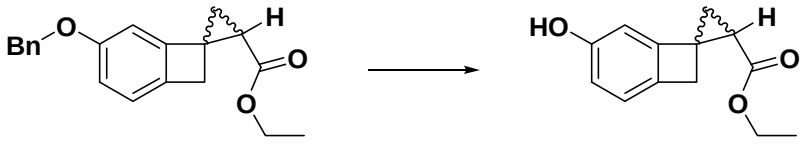
5-(Benzyloxy)-1-methylene-1,2-dihydrocyclobutabenzene (H11.3). H11.2 (13.0 g, 58.0 mmol) was dissolved in 300 mL THF. The resulting solution was cooled to 0°C in an ice-water bath.

Methyltriphenylphosphonium bromide (24.8 g, 69.6 mmol) was added and some yellow solid appeared. Potassium 2-methylpropan-2-olate (69.6 mL, 69.6 mmol) was then added dropwise over an hour. The reaction was stirred at 0°C for another hour and then quenched by addition of 200 mL saturated $NaHCO_3$. The THF solvent was evaporated by vacuum and the residue was extracted twice with 200 mL EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and then concentrated in the presence of silica gel. The residue was purified by flash chromatography with 10% EtOAc/hexanes to afford **H11.3** (4.1 g, 31.8%). MS ESI (pos.) m/e: 223.1 $(M+H)^+$.



H11.3 **H11.4** **H11.5**

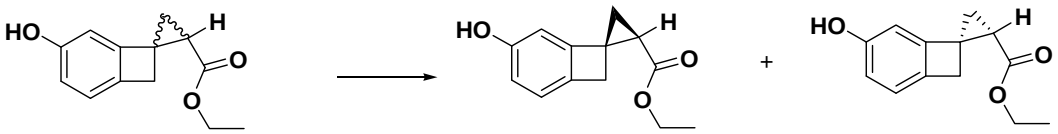
Ethyl 4-(benzyloxy)spiro[bicyclo[4.2.0]octane-7,1'-cyclopropane]-1,3,5-triene-2'-carboxylate (H11.4 and H11.5). **H11.3** (1.77 g, 7.96 mmol) was dissolved in 64 mL DCM. To this solution was added rhodium (ii) acetate dimer (0.176 g, 0.398 mmol). The resulting mixture was then refluxed at 45°C for 30 minutes. Ethyl diazoacetate (1.36 g, 11.9 mmol) was added to the refluxed solution via syringe pump over 1 hour. After completion, the reaction was stirred for another hour. The solution was then filtered through Celite, concentrated in the presence of silica gel and purified by flash chromatography (5% EtOAc/hexanes) to give compound **H11.4** (0.85 g, 35%) and compound **H11.5** (0.85 g, 35%). NMR confirmed that **H11.4** was the *trans* isomer and **H11.5** was the *cis* isomer. Compound **H11.4**: MS ESI (pos.) m/e: 309.1 $(M+H)^+$. ^1H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 7.28 - 7.44 (5 H, m), 7.01 (1 H, dd, *J*=8.0, 0.6 Hz), 6.84 (1 H, dd, *J*=7.9, 2.2 Hz), 6.66 (1 H, s), 5.02 (1 H, d, *J*=3.9 Hz), 4.98 - 5.06 (1 H, m), 4.05 (2 H, qd, *J*=7.1, 3.4 Hz), 3.15 - 3.29 (2 H, m), 2.30 (1 H, dd, *J*=8.4, 6.1 Hz), 1.64 (1 H, dd, *J*=8.5, 4.8 Hz), 1.55 - 1.60 (1 H, m), 1.13 - 1.18 (3 H, m).



H11.4 **H11.6**

Ethyl 4-hydroxyspiro[bicyclo[4.2.0]octane-7,1'-cyclopropane]-1,3,5-triene-2'-carboxylate (H11.6). **H11.4** (700 mg, 2.27 mmol) was dissolved in 5 mL MeOH. To this solution was added 10% palladium on carbon (242 mg, 0.227mmol) and a balloon of H_2 was placed over the reaction. The reaction mixture

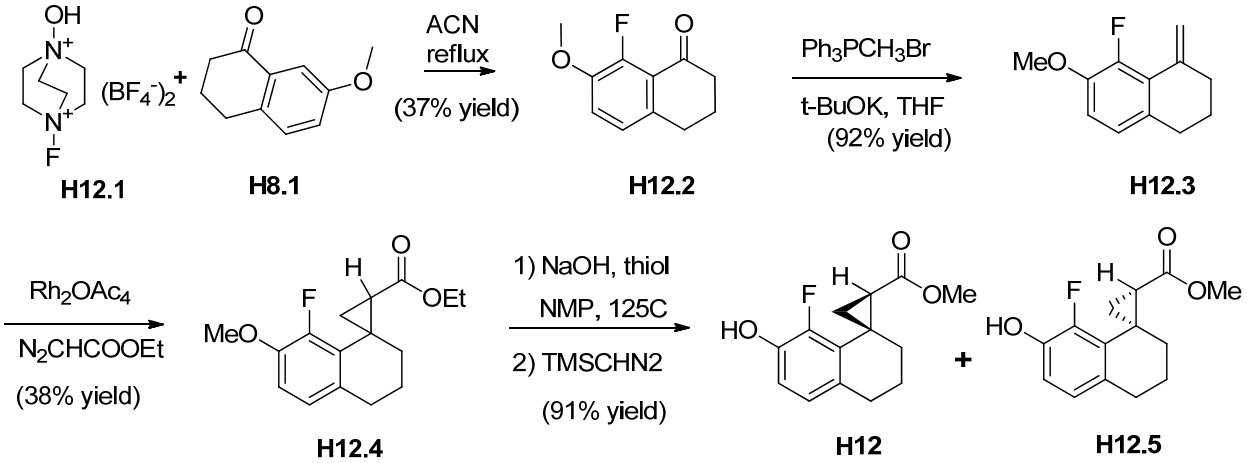
was stirred for 1 hour, and the catalyst was then removed by filtration. The filtrate was concentrated down in the presence of silica gel and purified by flash chromatography with 30% EtOAc/hexanes to give 250 mg compound **H11.6** (yield, 50.1%). MS ESI (pos.) m/e: 218.2 $(M+H)^+$.



H11.6 **H11** **H11.7**

Ethyl (2'*R*,7*S*)-4-hydroxyspiro[bicyclo[4.2.0]octane-7,1'-cyclo propane]-1,3,5-triene-2'-carboxylate (H11). Racemate **H11.6** (350 mg, 1.60 mmol) was resolved by chiral HPLC (Chiral OJ column, 10% IPA/hexanes). The second peak corresponded to **H11** (152 mg, 43%). The stereochemistry of **H11** and **H11.7** was determined by their chiral HPLC retention times compared to those of **18** and **19.**

Head group H12



H12.1 **H8.1** **H12.2** **H12.3**

H12.4 **H12** **H12.5**

8-Fluoro-7-methoxy-3,4-dihydronaphthalen-1(2H)-one (H12.2). To a solution of 7-methoxy-1-tetralone **H8.1** (199 g, 1130 mmol) in ACN (1200 mL) was added **H12.1** (200.0 g, 622 mmol) (NFTh, 400 g on alumina), and the suspension was heated under reflux for 1.5 hours. The solvent was removed and the residue was redissolved in DCM (1500 mL). The resulting mixture was filtered, concentrated, and purified by flash chromatography (0% to 20% then 40% EtOAc in hexanes) to give 8-fluoro-7-methoxy-3,4-dihydronaphthalen-1(2H)-one **H12.2** (74 g, 37%). (Reference: Stojan Stavber, Chemical Communication 2000, 1323). MS ESI (pos.) M/E: 195 (M+H).

8-Fluoro-7-methoxy-1-methylene-1,2,3,4-tetrahydronaphthalene (H12.3). To a solution of **H12.2** (44.0 g, 227 mmol) and triphenylmethylphosphonium bromide (97.1 g, 272 mmol) in THF (1000 mL)

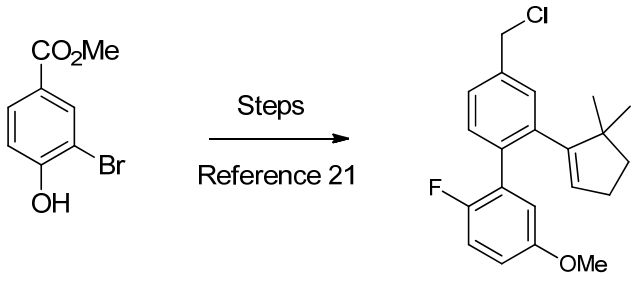
was added potassium *tert*-butoxide (1.0 M solution in THF)(272 mL, 272 mmol) via addition funnel over 3 hours. The resulting mixture was stirred at room temperature for 30 minutes after addition. The solvent was removed and the residue was resuspended in hexanes (1 L). The resulting mixture was passed through a silica gel plug (50 g silica) and rinsed with 1L of hexanes. Removal of solvent gave **H12.3** (40.1 g, 92.1% yield). MS ESI (pos.) M/E: 193 (M+H).

Ethyl 8'-fluoro-7'-methoxy-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-naphthalene]-2-carboxylate (H12.4). To a solution of **H12.3** (4.18 g, 21.7 mmol) and rhodium (ii) acetate, dimer (0.0961 g, 0.217 mmol) in refluxing DCM (200 mL) was added ethyl diazoacetate (3.38 mL, 32.6 mmol) in DCM via syringe pump over 40 minutes. The resulting mixture was stirred at 45°C for 1 hour and then at room temperature for 2 hours. Solvent was removed and the residue was purified by flash chromatography (20% EtOAc in hexanes) giving two products with the desired mass. The *cis* product (2.31 g) was obtained as an oil that became a white solid after a few days. The *trans* product **H12.4** (2.31 g), was obtained as a colorless oil, and confirmed by NOESY NMR. MS ESI (pos.) M/E: 279 (M+H).

Synthesis of H12. A 100 mL flask was charged with **H12.4** (2.30 g, 8.26 mmol), NMP (20 mL), sodium hydroxide (1487 mg, 37.2 mmol), and 1-dodecanethiol (6936 µl, 28.9 mmol). The mixture was stirred for 16 hours at 125°C, cooled to room temperature, and diluted with 1 N HCl (200 mL) and ether (300 mL). The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (10-40% EtOAc/hexanes) gave desired the acid (1.77 g, 91% yield). The acid was then dissolved in 40 mL of benzene and 10 mL of MeOH, treated with (trimethylsilyl)diazomethane (2.0 M in diethyl ether)(8.3 mL, 16.6 mmol) at 0°C for 1 hour. Solvent was removed from the resulting mixture to give methyl 8'-fluoro-7'-hydroxy-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-naphthalene]-2-carboxylate (1.88 g, 99% yield), which was separated using a Chiralcel OJ column (15% IPA/hexanes) to give **H12** (>99%ee, peak 2, 796 mg) and **H12.5** (>99%ee, peak 1, 780 mg). MS ESI (pos.) M/E: 251 (M+H).

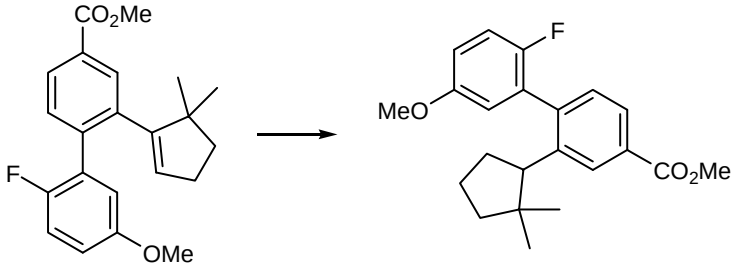
Synthesis of tail intermediates

Synthesis of T1 was reported in reference 21 (compound **26**) cited in manuscript.



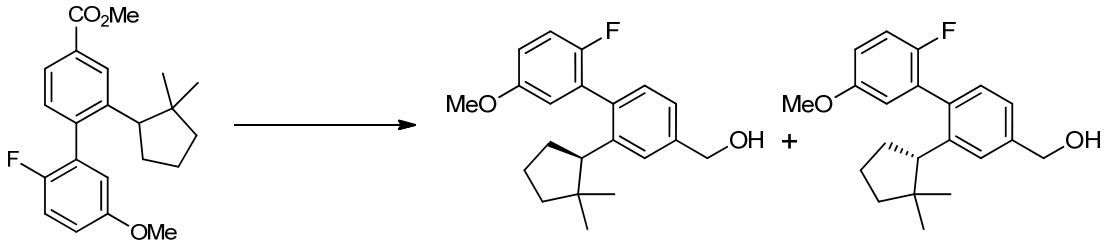
T1

Synthesis of tail intermediates 33 and T2.



T2.1 (**25** from reference 21) **T2.2**

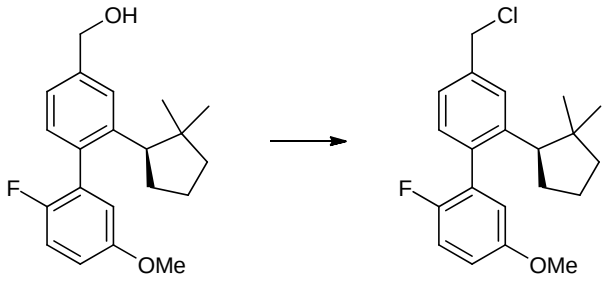
Methyl 2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-carboxylate (T2.2). To a stirred solution of **T2.1** (0.660 g, 1.86 mmol) in MeOH (20.00 mL, 1.86 mmol) at 23°C was added Pd/C (0.0198 g, 0.186 mmol). The resulting mixture was stirred under an atmosphere of hydrogen for 16 hours. The reaction mixture was then filtered and concentrated in *vacuo* to give **T2.2** as a clear oil (0.600 g, 90.4% yield).



T2.2 **T2.3** **T2.4**

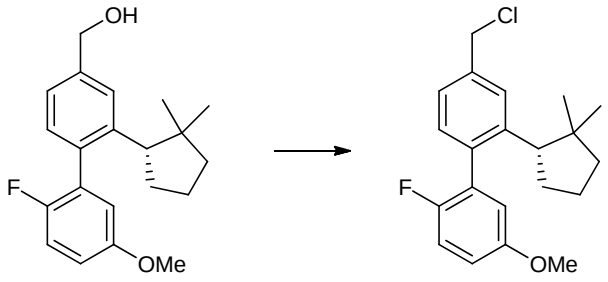
(2-((1S)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methanol and (2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methanol (T2.3 and T2.4). To a stirred solution of **T2.2** (0.500 g, 1.4 mmol) in THF (7.0 mL, 1.4 mmol) at 0°C was added

LAH (1.4 mL, 1.4 mmol). After addition, the reaction was stirred for 1.5 hours. 1N NaOH (aq, 5 mL) was then added to quench the reaction, and the mixture was extracted with EtOAc (20 mL). The organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting product was then purified by flash chromatography (0-20% EtOAc/hexanes) to give a mixture of **T2.3** and **T2.4** (0.442 g, 96% yield). Chiral separation was accomplished on Chiracel-OD (3%IPA in hexanes) to provide **T2.3** (retention time 38 min on Chiralcel-OD, 2% IPA in hexanes) and **T2.4** (retention time 15.5 min on Chiralcel-OD, 2% IPA in hexanes).



T2.3 **33**

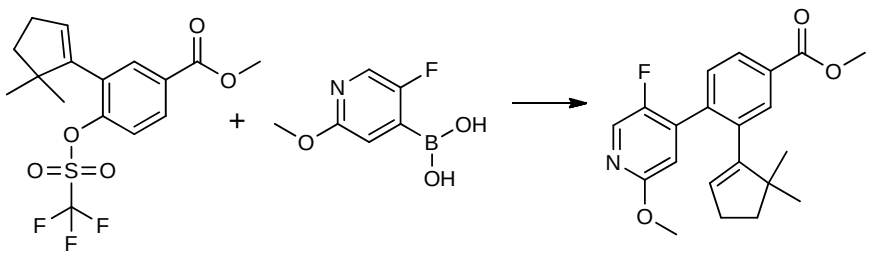
4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl (33). Thionyl chloride (1.5 mL, 20 mmol) was added to a stirred solution of **T2.3** (3.28 g, 10.0 mmol) in DCM (100 mL, 10.0 mmol) and DMF (0.77 mL, 10.0 mmol) at 0°C. Stirring was continued at room temperature for 2 hours. The reaction mixture was then concentrated in vacuo and purified by flash chromatography (0-10% EtOAc in hexanes) to give the desired product **33** (3.00 g, 87 % yield) as a clear oil.



T2.4 **T2**

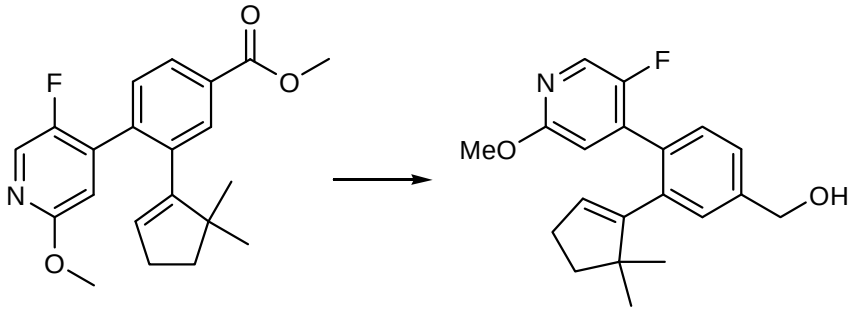
4-(Chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl (T2). T2 was prepared from **T2.4** using the procedure for **33** from **T2.3**.

Synthesis of tail intermediate T3



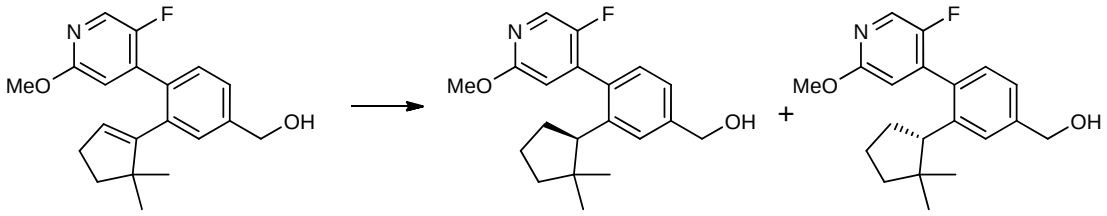
T3.1 (**21.5** from reference 21) **T3.2**

[001] Methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)benzoate (T3.2). To a flask with methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(trifluoromethylsulfonyloxy)benzoate **T3.1** (404 mg, 1068 µmol) was added $Pd(PPh_3)_4$ (123 mg, 107 µmol), potassium carbonate (443 mg, 3203 µmol), 5-fluoro-2-methoxypyridin-4-ylboronic acid (456 mg, 2669 µmol). The mixture was degassed, and DMF (3 mL) was added. The reaction was stirred overnight at 87°C and worked up with EtOAc (20 mL) and water (20 mL). Flash chromatography (0-50% EtOAc/hexanes) afforded methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)benzoate **T3.2 (**295 mg, 78%).



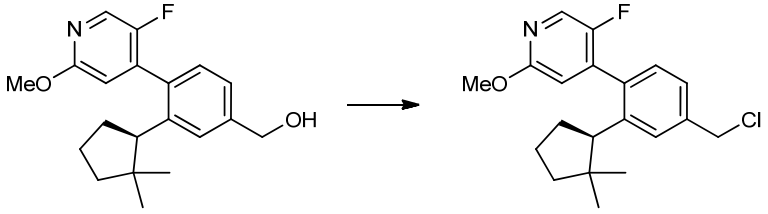
T3.2 **T3.3**

(3-(5,5-Dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)phenyl)methanol (T3.3). To methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)benzoate **T3.2** (295 mg, 830 µmol) was added THF (10 mL). The mixture was cooled to 0°C, and LAH (1660 µL, 1660 µmol) was added dropwise. The reaction was stirred at room temperature for 1 hour, and was quenched with water (20 mL) and a small amount of Rochelle's salt solution. Purification by flash chromatography (0-60% EtOAc/hexanes) afforded (3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)phenyl)methanol **T3.3** (201 mg) as an oil (74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm. 7.24 (s, 2H), 7.09 - 7.21 (m, 1H), 6.84 - 6.96 (m, 1H), 6.68-6.72 (m, 2H), 5.43 (s, 1H), 4.65 (s, 2H), 3.66 (s, 3H), 2.17 (td, 2H), 1.77 (b, 1H), 1.58 (t, 2H), 0.78 (s, 6H). MS ESI (pos.) m/e: 309.1 $(M\text{-}HO)^+$, 345.2 $(M+H_3O)^+$.



T3.3 **T3.4** **T3.5**

(3-((R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-methoxypyridin-4-yl)phenyl)methanol (T3.4). To a flask with (3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)phenyl)methanol **T3.3** (50 mg, 0.153 mmol) was added 10 mg 10% Pd on Carbon, 1.2 mL EtOAc and 1.2 mL MeOH. The flask was purged with hydrogen and then stirred under a hydrogen balloon for 2 hours. LC/MS showed the completion of the reaction. The reaction was filtered through a pad of Celite and rinsed with EtOAc. Two additional reactions were run with the same condition on 70 mg and 81 mg scale. Then the three batches of the reactions (a total of 201 mg of **T3.3**) were combined and purified on chiral OD column in four equal portions with 3% IPA/hexanes to afford **T3.4** (54 mg, 98% ee, the later-eluting enantiomer) and **T3.5** (78 mg, 100% ee). The mixed fraction was repurified on chiral column to afford an additional 28 mg of **T3.4** (>99% ee). MS ESI (pos.) m/e: 330.1 $(M+H)^+$.

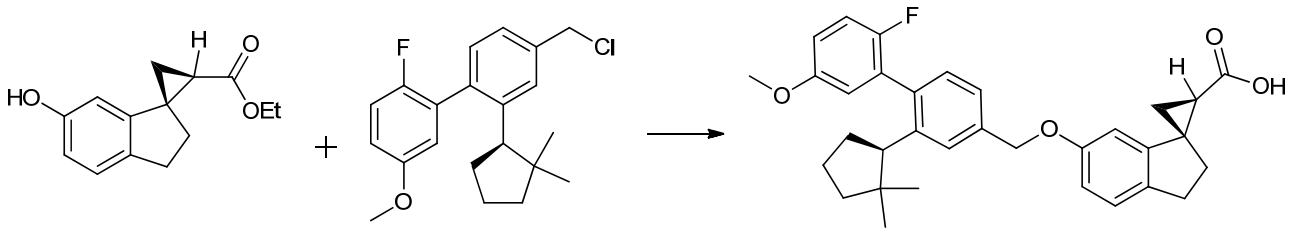


T3.4 **T3**

4-(4-(Chloromethyl)-2-((S)-2,2-dimethylcyclopentyl)phenyl)-5-fluoro-2-methoxypyridine or 4-(4-(chloromethyl)-2-((R)-2,2-dimethylcyclopentyl)phenyl)-5-fluoro-2-methoxypyridine (T3). The same procedure used to prepare **33** from **T2.3** was applied to make **T3** from **T3.4** (28 mg, >99% ee). Compound **T3** was obtained as an oil (27 mg, 91%). MS ESI (pos.) m/e: 348.1 $(M+H)^+$.

Preparation of final compounds.

General procedure to prepare final compounds as exemplified by 26:

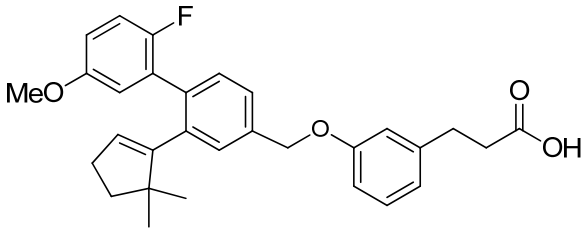


18 **33** **26**

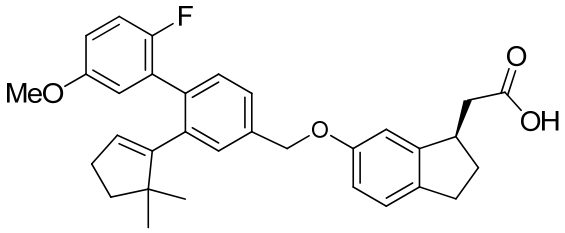
(1*R*,2*R*)-6'-((2-((*R*)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylic acid (26). Note: this general procedure was used for all final compounds reported in the Letter, unless otherwise stated. To a stirred solution of **33** (10.0 mg, 28.8 μmol) and **18** (6.57 mg, 28.3 μmol) in DMSO (1 mL) was added Cs_2CO_3 (12.0 mg, 36.7 μmol). The resulting mixture was stirred at 23 °C for 16 hours and then aqueous LiOH (2N, 0.5 mL) and MeOH (1 mL) were added, and the mixture was stirred at 50 °C for 15 hours. The mixture was acidified with aqueous HCl (2N, 0.6 mL), diluted with ACN, and purified by HPLC (reverse phase, C18, 0.1% TFA in water/0.1% TFA in ACN, 10-95%) to give **26** (10.5 mg, 72% yield) as white solid.

Synthesis of **26** on a large scale: To a stirred solution of **33** (8.90 g, 25.66 mmol) and **18** (5.48 g, 25.16 mmol) in DMSO (100 mL) was added Cs_2CO_3 (10.65 g, 32.70 mmol). The resulting mixture was stirred at 23 °C for 3 hours. The reaction mixture was extracted with EtOAc (500 mL) and water (500 mL), and the organic layer was concentrated in reduced pressure and purified by flash chromatography (5% EtOAc in hexanes) to give the corresponding ethyl ester as a colorless oil (12.00 g, 88% yield). The ester was redissolved in THF (76 mL) and EtOH (38 mL), added aqueous LiOH (2N, 38 mL), and the mixture was stirred at 50 °C for 15 hours. The mixture was acidified with aqueous HCl (2N, 50 mL), diluted with EtOAc (100 mL), washed with water and brine, dried over $MgSO_4$ and concentrated to give **26** (11.34 g, 87% yield, two steps) as a white solid (chemical purity: 99.7% by HPLC at 210 nm; chiral purity: >99% ee). ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 7.42 - 7.51 (1 H, m), 7.25 - 7.35 (1 H, m), 7.13 - 7.24 (2 H, m), 7.02 (1 H, d, *J*=8.3 Hz), 6.92 - 6.98 (1 H, m), 6.82 (1 H, dd, *J*=6.1, 3.2 Hz), 6.66 - 6.76 (1 H, m), 6.35 (1 H, d, *J*=2.2 Hz), 5.03 - 5.14 (2 H, m), 3.74 (3 H, s), 2.70 - 2.86 (3 H, m), 2.28 - 2.38 (1 H, m), 1.94 - 2.10 (3 H, m), 1.76 (1 H, td, *J*=8.5, 4.8 Hz), 1.54 - 1.65 (2 H, m), 1.44 - 1.54 (1 H, m), 1.24 - 1.34 (1 H, m), 1.22 (1 H, dd, *J*=6.1, 3.4 Hz), 0.96 (1 H, dd, *J*=8.3, 3.2 Hz), 0.60 - 0.70 (3 H, m), 0.45 -

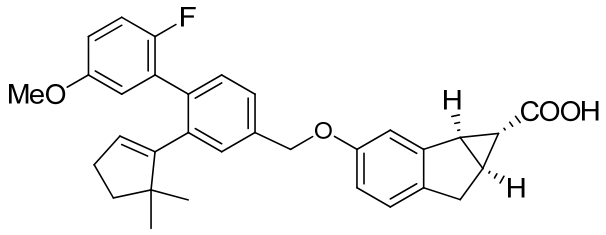
0.56 (3 H, m). ^{13}C NMR (126 MHz, *CHLOROFORM-d*) δ ppm 174.63, 157.81, 155.33, 154.80, 154.70, 153.97, 152.92, 152.11, 150.28, 140.52, 140.19, 136.62, 136.51, 135.62, 135.40, 135.32, 130.10, 130.01, 129.90, 129.75, 129.64, 129.49, 127.85, 127.14, 125.29, 124.70, 124.36, 117.31, 116.36, 115.71, 115.50, 113.96, 112.53, 105.18, 105.14, 69.28, 69.24, 55.66, 55.63, 50.84, 50.01, 42.79, 42.42, 41.70, 41.52, 34.28, 33.16, 31.98, 31.48, 30.44, 29.40, 28.69, 28.04, 23.43, 23.39, 21.54, 21.37, 21.14. HRMS (TOF) Calculated for $C_{33}H_{34}FO_4^-$ [M-H]$^-$: 513.2447, found: 513.2456.



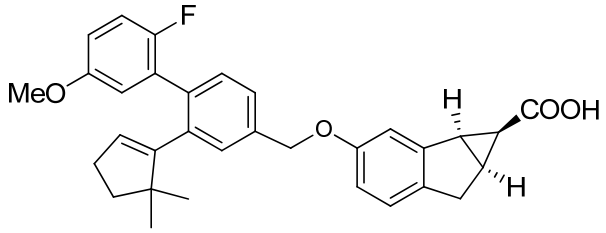
3-(3-((2-(5,5-dimethylcyclopent-1-en-1-yl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)phenyl)propanoic acid (3). Prepared from methyl 3-(4-hydroxyphenyl)propanoate and **T1** using general procedure. ^{1}H NMR (500 MHz, *ACETONITRILE-d*$_3$) δ ppm 7.40 (1 H, dd, *J*=7.9, 1.6 Hz), 7.30 - 7.35 (2 H, m), 7.21 (1 H, t, *J*=7.9 Hz), 6.99 - 7.05 (1 H, m), 6.88 - 6.91 (1 H, m), 6.81 - 6.88 (4 H, m), 5.51 (1 H, s), 5.13 (2 H, s), 3.74 (3 H, s), 2.86 (2 H, t, *J*=7.7 Hz), 2.58 (2 H, t, *J*=7.7 Hz), 2.20 - 2.24 (2 H, m), 1.61 - 1.67 (2 H, m), 0.84 (6 H, s). HRMS (TOF) Calculated for $C_{30}H_{30}FO_4^-$ [M-H]$^-$: 473.2134, found: 473.2144.



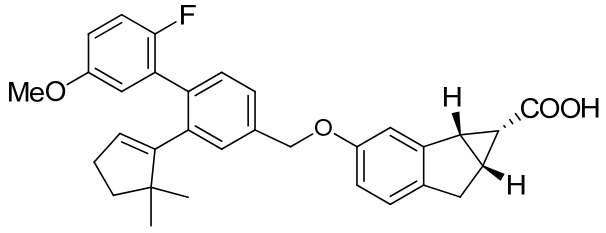
(*R*)-2-(6-((2-(5,5-Dimethylcyclopent-1-en-1-yl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-2,3-dihydro-1H-inden-1-yl)acetic acid (4). Prepared from **H1** and **T1** using general procedure. ^{1}H NMR (500 MHz, *DMSO-d*$_6$) δ ppm 7.40 (1 H, dd, *J*=7.9, 1.6 Hz), 7.29 (1 H, d, *J*=7.8 Hz), 7.27 (1 H, d, *J*=1.5 Hz), 7.07 - 7.13 (2 H, m), 6.94 (1 H, d, *J*=2.0 Hz), 6.88 (1 H, dt, *J*=9.0, 3.5 Hz), 6.82 (1 H, dd, *J*=6.1, 3.2 Hz), 6.80 (1 H, dd, *J*=8.2, 2.3 Hz), 5.50 (1 H, s), 5.11 (2 H, s), 3.70 (3 H, s), 2.66 - 2.82 (3 H, m), 2.23 - 2.32 (2 H, m), 2.18 (2 H, td, *J*=7.0, 2.2 Hz), 1.64 (1 H, dd, *J*=12.5, 7.8 Hz), 1.59 (2 H, t, *J*=7.0 Hz), 1.13 (1 H, s), 0.78 (6 H, d, *J*=3.2 Hz). HRMS (TOF) Calculated for $C_{32}H_{32}FO_4^-$ [M-H]$^-$: 499.2290, found: 499.2294.



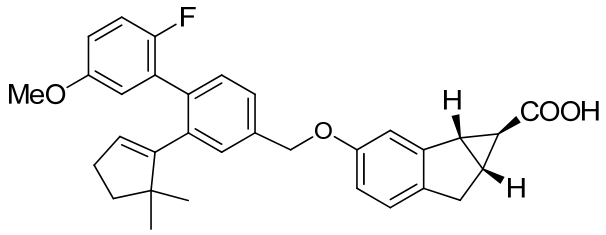
(1*R*,1a*R*,6a*S*)-3-((2-(5,5-dimethylcyclopent-1-en-1-yl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-1,1a,6,6a-tetrahydrocyclopropa[a]indene-1-carboxylic acid (5). Prepared from **H2** and **T1** using general procedure. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.37 - 7.42 (1 H, m), 7.34 (1 H, d, *J*=8.0 Hz), 7.29 (1 H, d, *J*=1.4 Hz), 7.08 (1 H, d, *J*=8.2 Hz), 7.04 (1 H, d, *J*=2.3 Hz), 6.93 - 7.01 (1 H, m), 6.76 - 6.85 (3 H, m), 5.53 (1 H, s), 5.09 (2 H, s), 3.76 (3 H, s), 3.24 (1 H, dd, *J*=17.4, 6.1 Hz), 2.98 - 3.07 (2 H, m), 2.53 (1 H, td, *J*=6.4, 3.2 Hz), 2.25 (2 H, td, *J*=7.0, 2.4 Hz), 1.66 (2 H, t, *J*=7.0 Hz), 1.26 (1 H, t, *J*=2.7 Hz), 0.86 (6 H, s). HRMS (TOF) Calculated for $C_{32}H_{30}FO_4^-$ [M-H]$^-$: 497.2134, found: 497.2148.



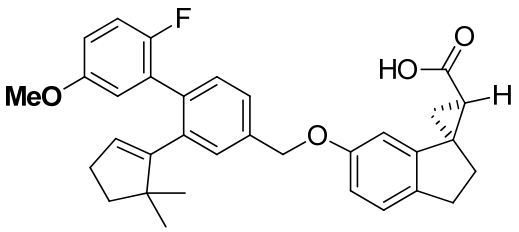
(1*S*,1a*R*,6a*S*)-3-((2-(5,5-dimethylcyclopent-1-en-1-yl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-1,1a,6,6a-tetrahydrocyclopropa[a]indene-1-carboxylic acid (6). Prepared from **H3** and **T1** using general procedure. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.37 - 7.41 (1 H, m), 7.33 (1 H, d, *J*=8.0 Hz), 7.30 (1 H, d, *J*=1.6 Hz), 7.04 (1 H, d, *J*=8.2 Hz), 6.92 - 7.00 (2 H, m), 6.76 - 6.84 (3 H, m), 5.53 (1 H, s), 5.06 (2 H, s), 3.76 (3 H, s), 3.30 (1 H, d, *J*=17.0 Hz), 3.15 (1 H, dd, *J*=17.3, 6.7 Hz), 2.95 - 3.02 (1 H, m), 2.36 (1 H, d, *J*=7.6 Hz), 2.25 (2 H, td, *J*=7.0, 2.3 Hz), 2.00 - 2.07 (1 H, m), 1.66 (2 H, t, *J*=7.0 Hz), 0.86 (6 H, s). HRMS (TOF) Calculated for $C_{32}H_{30}FO_4^-$ [M-H]$^-$: 497.2134, found: 497.2149.



(1*R*,1a*S*,6a*R*)-3-((2-(5,5-dimethylcyclopent-1-en-1-yl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-1,1a,6,6a-tetrahydrocyclopropa[a]indene-1-carboxylic acid (7). Prepared from **H4** and **T1** using general procedure. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.37 - 7.41 (1 H, m), 7.33 (1 H, d, *J*=8.0 Hz), 7.29 - 7.31 (1 H, m), 7.04 (1 H, d, *J*=8.2 Hz), 6.92 - 7.00 (2 H, m), 6.76 - 6.84 (3 H, m), 5.53 (1 H, s), 5.06 (2 H, s), 3.76 (3 H, s), 3.30 (1 H, d, *J*=16.8 Hz), 3.15 (1 H, dd, *J*=17.0, 6.8 Hz), 2.95 - 3.02 (1 H, m), 2.32 - 2.40 (1 H, m), 2.25 (2 H, td, *J*=7.0, 2.4 Hz), 2.03 (1 H, t, *J*=8.2 Hz), 1.66 (2 H, t, *J*=7.0 Hz), 0.86 (6 H, s). HRMS (TOF) Calculated for $C_{32}H_{30}FO_4^-$ [M-H]$^-$: 497.2134, found: 497.2147.

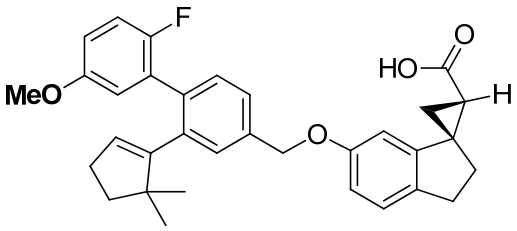


(1*S*,1a*S*,6a*R*)-3-((2-(5,5-dimethylcyclopent-1-en-1-yl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-1,1a,6,6a-tetrahydrocyclopropa[a]indene-1-carboxylic acid (8). Prepared from **H5** and **T1** using general procedure. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.38 - 7.42 (1 H, m), 7.32 - 7.36 (1 H, m), 7.29 (1 H, d, *J*=1.4 Hz), 7.08 (1 H, d, *J*=8.2 Hz), 7.04 (1 H, d, *J*=2.3 Hz), 6.93 - 7.01 (1 H, m), 6.77 - 6.84 (3 H, m), 5.53 (1 H, s), 5.09 (2 H, s), 3.76 (3 H, s), 3.24 (1 H, dd, *J*=17.5, 6.2 Hz), 2.98 - 3.07 (2 H, m), 2.54 (1 H, td, *J*=6.4, 3.2 Hz), 2.25 (2 H, td, *J*=7.0, 2.3 Hz), 1.66 (2 H, t, *J*=7.0 Hz), 1.23 - 1.28 (1 H, m), 0.86 (6 H, s). HRMS (TOF) Calculated for $C_{32}H_{30}FO_4^-$ [M-H]$^-$: 497.2134, found: 497.2141.

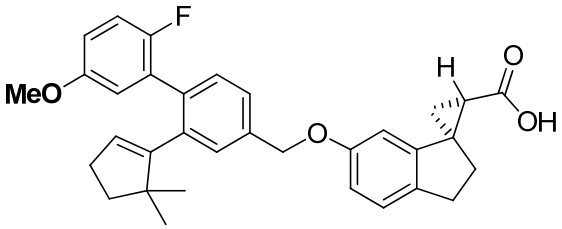


(1*S*,2*R*)-6'-((2-(5,5-dimethylcyclopent-1-en-1-yl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylic acid (9). Prepared from **21** and **T1** using general procedure. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.37 - 7.41 (1 H, m), 7.31 - 7.34 (1 H, m), 7.29 (1 H, d, *J*=1.6 Hz), 7.10 (1 H, d, *J*=8.0 Hz), 6.93 - 7.00 (1 H, m), 6.76 - 6.89 (4 H, m), 5.49 - 5.55 (1 H, m), 5.00 (2 H, q, *J*=11.7 Hz), 3.76 (3 H, s), 2.95 - 3.06 (1 H, m), 2.83 (1 H, dd, *J*=15.1, 7.8 Hz), 2.41 (1 H, dt, *J*=12.8, 9.4 Hz), 2.25 (2 H, td, *J*=7.0, 2.3 Hz), 2.11 (1 H, dd, *J*=7.9, 6.4 Hz), 1.92 (1 H, ddd, *J*=12.8, 7.8, 1.5 Hz), 1.87 (1 H, t, *J*=5.9 Hz), 1.66 (2 H, t, *J*=7.0 Hz), 1.47 (1 H, dd,

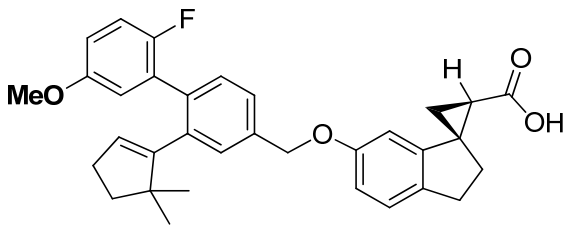
J=7.9, 5.4 Hz), 0.87 (3 H, s), 0.86 (3 H, s). HRMS (TOF) Calculated for $C_{33}H_{32}FO_4^-$ [M-H]$^-$: 511.2290, found: 511.2298.



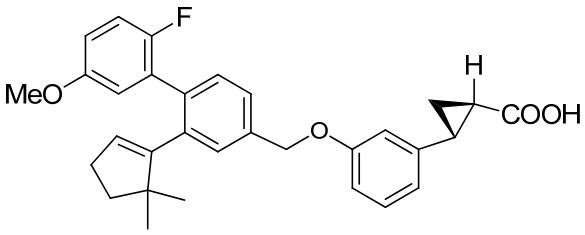
(1*R*,2*S*)-6'-((2-(5,5-dimethylcyclopent-1-en-1-yl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylic acid (10). Prepared from **20** and **T1** using general procedure. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.36 - 7.41 (1 H, m), 7.30 - 7.35 (1 H, m), 7.28 (1 H, d, *J*=1.6 Hz), 7.10 (1 H, d, *J*=8.2 Hz), 6.93 - 7.01 (1 H, m), 6.76 - 6.88 (4 H, m), 5.52 (1 H, s), 4.99 (2 H, q, *J*=11.6 Hz), 3.76 (3 H, s), 2.96 - 3.06 (1 H, m), 2.82 (1 H, dd, *J*=15.5, 7.6 Hz), 2.41 (1 H, dt, *J*=13.2, 9.3 Hz), 2.25 (2 H, td, *J*=7.0, 2.3 Hz), 2.11 (1 H, dd, *J*=7.9, 6.4 Hz), 1.92 (1 H, ddd, *J*=12.9, 7.9, 1.6 Hz), 1.87 (1 H, t, *J*=5.9 Hz), 1.66 (2 H, t, *J*=7.0 Hz), 1.46 (1 H, dd, *J*=7.8, 5.5 Hz), 0.87 (3 H, s), 0.86 (3 H, s). HRMS (TOF) Calculated for $C_{33}H_{32}FO_4^-$ [M-H]$^-$: 511.2290, found: 511.2299.



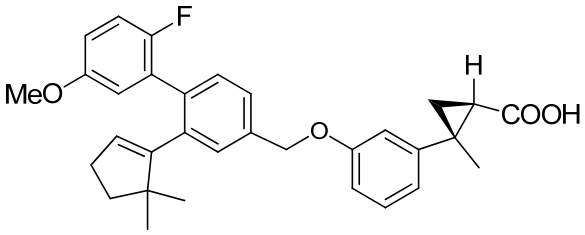
(1*S*,2*S*)-6'-((2-(5,5-dimethylcyclopent-1-en-1-yl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylic acid (11). Prepared from **19** and **T1** using general procedure. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.36 - 7.40 (1 H, m), 7.33 (1 H, d, *J*=8.4 Hz), 7.28 (1 H, s), 7.14 (1 H, d, *J*=8.2 Hz), 6.93 - 7.01 (1 H, m), 6.85 (1 H, dd, *J*=8.3, 2.4 Hz), 6.75 - 6.82 (2 H, m), 6.36 (1 H, d, *J*=2.3 Hz), 5.50 - 5.55 (1 H, m), 5.06 (2 H, s), 3.76 (3 H, s), 2.98 (2 H, t, *J*=7.1 Hz), 2.35 - 2.44 (1 H, m), 2.28 - 2.34 (1 H, m), 2.25 (2 H, td, *J*=7.0, 2.3 Hz), 1.99 - 2.06 (1 H, m), 1.61 - 1.74 (3 H, m), 1.50 (1 H, dd, *J*=8.3, 4.8 Hz), 0.86 (6 H, s). HRMS (TOF) Calculated for $C_{33}H_{32}FO_4^-$ [M-H]$^-$: 511.2290, found: 511.2301.



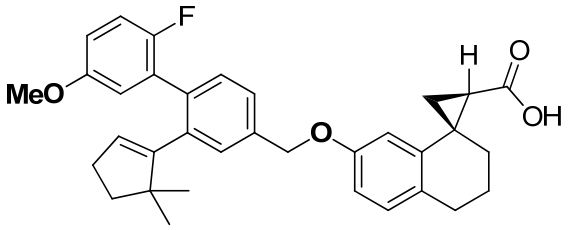
(1*R*,2*R*)-6'-((2-(5,5-dimethylcyclopent-1-en-1-yl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylic acid (12). Prepared from **18** and **T1** using general procedure. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.36 - 7.41 (1 H, m), 7.33 (1 H, d, *J*=8.4 Hz), 7.28 (1 H, s), 7.14 (1 H, d, *J*=8.2 Hz), 6.97 (1 H, t, *J*=9.2 Hz), 6.85 (1 H, dd, *J*=8.2, 2.3 Hz), 6.77 - 6.82 (2 H, m), 6.36 (1 H, d, *J*=2.3 Hz), 5.53 (1 H, s), 5.06 (2 H, s), 3.76 (3 H, s), 2.95 - 3.01 (2 H, m), 2.27 - 2.43 (3 H, m), 2.25 (2 H, td, *J*=7.0, 2.3 Hz), 2.02 - 2.06 (1 H, m), 2.02 (1 H, s), 1.64 - 1.72 (3 H, m), 1.50 (1 H, dd, *J*=8.4, 4.9 Hz), 0.86 (6 H, s). HRMS (TOF) Calculated for $C_{33}H_{32}FO_4^-$ [M-H]$^-$: 511.2290, found: 511.2304.



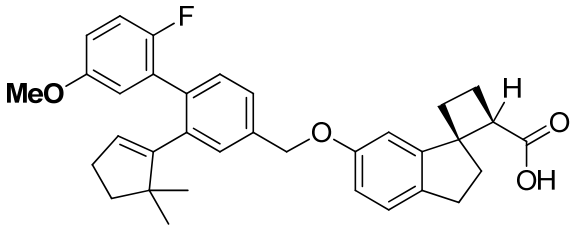
(1*R*,2*R*)-2-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)cyclopropanecarboxylic acid (13). Prepared from **H6** and **T1** using general procedure. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.12 - 7.33 (4 H, m), 6.64 - 6.89 (6 H, m), 5.45 (1 H, t, J=2.7 Hz), 5.01 (2 H, s), 3.68 (3 H, s), 2.51 (1 H, dd, J=3.9, 2.7 Hz), 2.17 (2 H, td, J=7.0, 2.7 Hz), 1.83-1.86(1 H, m), 1.55 - 1.62 (3 H, m), 1.33 (1 H, ddd, J=8.5, 6.7, 4.7 Hz), 0.78 (6H, s). HRMS (TOF) Calculated for $C_{31}H_{30}FO_4^-$ [M-H]$^-$ 485.2134, found: 485.2143.



(1*R*,2*R*)-2-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-2-methylcyclopropane carboxylic acid (14). Prepared from **H7** and **T1** using general procedure. 1H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.15 - 7.33 (4 H, m), 6.70 - 6.93 (6 H, m), 5.45 (1 H, t, *J*=2.7 Hz), 5.02 (2 H, s), 3.68 (3 H, s), 2.17 (2 H, td, *J*=7.0, 2.7 Hz), 1.93 (1 H, dd, *J*=8.2, 5.9 Hz), 1.58 (2 H, t, *J*=7.0 Hz), 1.51 (3 H, s), 1.38 - 1.44 (2 H, m), 0.77 (6 H, s). HRMS (TOF) Calculated for $C_{32}H_{32}FO_4^-$ $[M-H]^-$ 499.2290, found: 499.2292.

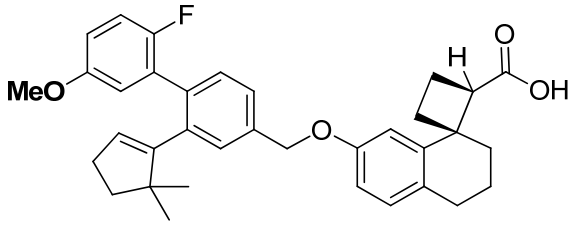


(1*R*,2*R*)-7'-((2-(5,5-dimethylcyclopent-1-en-1-yl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-2-carboxylic acid (22). Prepared from **H8** and **T1** using general procedure. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.76 (1 H, dd, *J*=7.9, 1.5 Hz), 7.34 - 7.40 (2 H, m), 7.11 (1 H, d, *J*=8.0 Hz), 7.03 (1 H, d, *J*=8.4 Hz), 6.97 (1 H, t, *J*=9.2 Hz), 6.80 (2 H, td, *J*=5.9, 2.8 Hz), 6.36 (1 H, d, *J*=2.3 Hz), 5.53 (1 H, s), 5.05 (2 H, s), 3.76 (3 H, s), 2.83 (2 H, t, *J*=6.3 Hz), 2.25 (2 H, td, *J*=7.0, 2.3 Hz), 1.97 - 2.00 (3 H, m), 1.84 - 1.92 (1 H, m), 1.74 - 1.83 (1 H, m), 1.62 - 1.71 (3 H, m), 1.55 - 1.60 (1 H, m), 1.13 (6 H, s). HRMS (TOF) Calculated for $C_{34}H_{34}FO_4^-$ $[M-H]^-$ 525.2447, found: 525.2457.

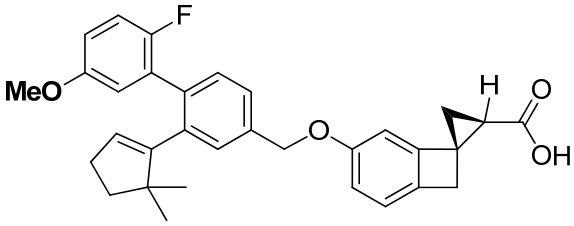


(1*S*,2*R*)-6'-((2-(5,5-dimethylcyclopent-1-en-1-yl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-2',3'-dihydrospiro[cyclobutane-1,1'-indene]-2-carboxylic acid (23). Prepared from **H9**

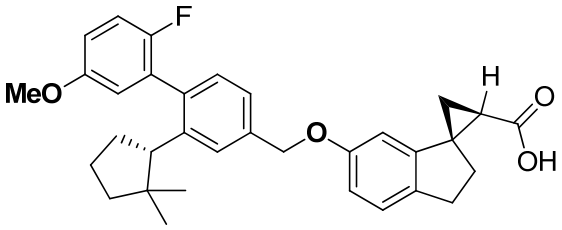
and **T1** using general procedure. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.40 - 7.45 (1 H, m), 7.30 - 7.38 (2 H, m), 7.12 (1 H, d, *J*=8.2 Hz), 7.04 (1 H, d, *J*=2.2 Hz), 6.94 - 7.00 (1 H, m), 6.86 (1 H, dd, *J*=8.3, 2.2 Hz), 6.77 - 6.82 (2 H, m), 5.53 (1 H, s), 5.12 (2 H, s), 3.76 (3 H, s), 3.37 (1 H, t, *J*=8.3 Hz), 2.74 - 2.90 (2 H, m), 2.35 - 2.48 (2 H, m), 2.22 - 2.30 (3 H, m), 2.05 - 2.21 (4 H, m), 1.67 (2 H, t, *J*=7.0 Hz), 0.87 (6 H, s). HRMS (TOF) Calculated for $C_{34}H_{34}FO_4^-$ $[M-H]^-$: 525.2447, found: 525.2445.



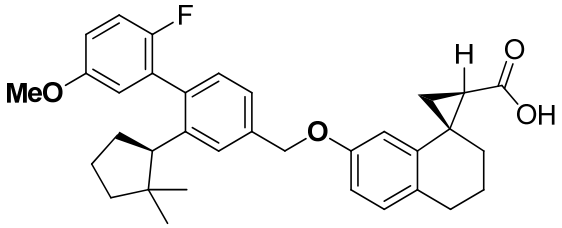
(1*R*,2*R*)-7'-((2-(5,5-dimethylcyclopent-1-en-1-yl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-naphthalene]-2-carboxylic acid (24). Prepared from **H10** and **T1** using general procedure. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.42 (1H, m), 7.32-7.36 (2H, m), 7.20 (1H, m), 6.92-7.03 (2H, m), 6.76-6.85 (3H, m), 5.53(1H, s), 5.12 (2H, s), 3.76 (3H, s), 3.64 (1H, s), 2.69 (2H, m), 2.43 (1H, m), 2.25 (2H, m), 2.10-2.20 (2H, m), 1.94-2.05 (3H, m), 1.65-1.85 (4H, m), 0.86 (6H, s). HRMS (TOF) Calculated for $C_{35}H_{36}FO_4^-$ $[M-H]^-$: 539.2603, found: 539.2614.



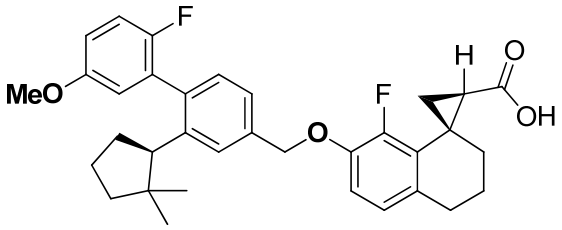
(1'*S*,2'*R*)-4-((2-(5,5-dimethylcyclopent-1-en-1-yl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)spiro[bicyclo[4.2.0]octa[1,3,5]triene-7,1'-cyclopropane]-2'-carboxylic acid (25). Prepared from **H11** and **T1** using general procedure. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.38 (1H, m), 7.26 - 7.34 (2 H, m), 6.93 - 7.02 (2 H, m), 6.87 - 6.91 (2 H, m), 6.80 - 6.78 (2 H, m), 5.52 (1 H, s), 5.03 (2 H, s), 3.76 (3 H, s), 3.31 (2 H, m), 2.25 (3 H, br.), 1.81 (1 H, d, *J*=5.5 Hz), 1.64 - 1.69 (2 H, m), 0.85 (6 H, d, *J*=3.9 Hz). HRMS (TOF) Calculated for $C_{32}H_{30}FO_4^-$ $[M-H]^-$: 497.2134, found: 497.2146.



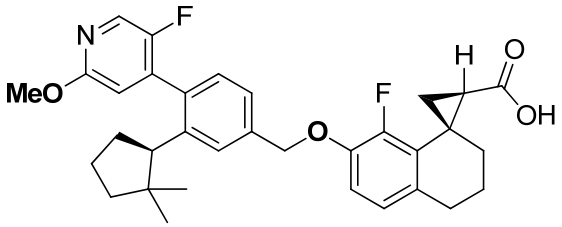
(1*R*,2*R*)-6'-((2-((*S*)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-2',3'-dihydrospiro[cyclopropane-1,1'-indene]-2-carboxylic acid (27). Prepared from **18** and **T2** using general procedure. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.38 - 7.45 (1 H, m), 7.28 - 7.34 (1 H, m), 7.17 - 7.26 (1 H, m), 7.14 (1 H, d, *J*=8.2 Hz), 6.98 - 7.09 (1 H, m), 6.82 - 6.88 (2 H, m), 6.78 (1 H, dd, *J*=5.8, 3.2 Hz), 6.35 (1 H, d, *J*=2.0 Hz), 5.01 - 5.12 (2 H, m), 3.80 (3 H, s), 2.91 - 3.05 (3 H, m), 2.84 (1 H, ddd, *J*=10.5, 8.3, 2.2 Hz), 2.34 - 2.43 (1 H, m), 2.25 - 2.34 (1 H, m), 2.16 (1 H, ddt, *J*=17.4, 8.8, 4.1, 4.1 Hz), 1.94 - 2.08 (2 H, m), 1.73 - 1.86 (1 H, m), 1.61 - 1.72 (2 H, m), 1.46 - 1.57 (2 H, m), 1.32 - 1.43 (1 H, m), 0.66 - 0.74 (3 H, m), 0.54 - 0.64 (3 H, m). HRMS (TOF) Calculated for $C_{33}H_{34}FO_4^-$ [M-H]$^-$ 513.2447, found: 513.2452.



(1*R*,2*R*)-7'-((2-((*R*)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-2-carboxylic acid (28). Prepared from **H8** and **33** using general procedure. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.36 - 7.45 (1 H, m), 7.28 - 7.34 (1 H, m), 7.17 - 7.25 (1 H, m), 6.97 - 7.11 (2 H, m), 6.73 - 6.90 (3 H, m), 6.32 - 6.38 (1 H, m), 5.00 - 5.11 (2 H, m), 3.80 (3 H, s), 2.98 (1 H, dd, *J*=10.3, 8.5 Hz), 2.79 - 2.87 (3 H, m), 2.10 - 2.21 (1 H, m), 1.94 - 2.08 (4 H, m), 1.84 - 1.94 (1 H, m), 1.73 - 1.84 (2 H, m), 1.61 - 1.71 (2 H, m), 1.47 - 1.60 (2 H, m), 1.34 - 1.42 (1 H, m), 1.27 (3 H, s), 0.65 - 0.76 (3 H, m), 0.57 - 0.62 (3 H, m). HRMS (TOF) Calculated for $C_{34}H_{36}FO_4^-$ [M-H]$^-$: 527.2603, found: 527.2605.



(1*R*,2*R*)-7'-((2-((*R*)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methoxy)-8'-fluoro-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-2-carboxylic acid (29). Prepared from **H12** and **33** using general procedure. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.37 - 7.46 (1 H, m), 7.29 - 7.35 (1 H, m), 7.16 - 7.25 (1 H, m), 6.97 - 7.09 (1 H, m), 6.79 - 6.89 (3 H, m), 6.77 (1 H, dd, *J*=5.9, 3.1 Hz), 5.11 (2 H, s), 3.80 (3 H, s), 2.75 - 2.90 (3 H, m), 2.54 (1 H, t, *J*=7.3 Hz), 2.34 (1 H, dd, *J*=8.0, 4.9 Hz), 2.15 (1 H, dtd, *J*=13.1, 8.8, 8.8, 4.0 Hz), 1.96 - 2.08 (2 H, m), 1.87 - 1.95 (1 H, m), 1.76 - 1.86 (2 H, m), 1.59 - 1.76 (2 H, m), 1.52 (1 H, ddt, *J*=12.6, 8.4, 4.2, 4.2 Hz), 1.31 - 1.45 (2 H, m), 0.64 - 0.72 (3 H, m), 0.52 - 0.64 (3 H, m). HRMS (TOF) Calculated for $C_{34}H_{35}F_2O_4^-$ [M-H]$^-$ 545.2509, found: 545.2515.



(1*R*,2*R*)-7'-((3-((*R*)-2,2-Dimethylcyclopentyl)-4-(5-fluoro-2-methoxypyridin-4-yl)benzyl)oxy)-8'-fluoro-3',4'-dihydro-2'H-spiro[cyclopropane-1,1'-naphthalene]-2-carboxylic acid (30). Prepared from **H12** and **T3**. Reaction was performed similarly to the large scale synthesis of **26** by starting with 4.0 g of the corresponding head group **H12**, **30** was obtained as a white solid (7.17 g, 82% yield, chemical purity: 99.5% by HPLC at 210 nm; chiral purity: >99% de). ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 8.18 (1 H, s), 7.43 - 7.58 (1 H, m), 7.28 - 7.41 (1 H, m), 7.20 (1 H, d, *J*=7.4 Hz), 6.92 (1 H, t, *J*=8.2 Hz), 6.68 - 6.83 (2 H, m), 5.15 (2 H, s), 3.86 (3 H, s), 2.57 - 2.78 (3 H, m), 2.10 - 2.21 (1 H, m), 1.95 - 2.08 (2 H, m), 1.90 (1 H, t, *J*=7.3 Hz), 1.77 (1 H, d, *J*=5.5 Hz), 1.55 - 1.70 (5 H, m), 1.50 (1 H, ddd, *J*=12.3, 8.1, 4.6 Hz), 1.24 - 1.38 (1 H, m), 0.92 (1 H, dt, *J*=6.7, 3.3 Hz), 0.60 (3 H, br. s.), 0.45 - 0.56 (3 H, m). HRMS (TOF) Calculated for $C_{34}H_{34}F_2NO_4^-$ [M-H]$^-$ 546.2461, found: 546.2462.

Panel screen data against 101 receptors:

In vitro panel screen data was collected at Cerep (http://www.cerep.fr). The specific ligand binding to the receptors is defined as the difference between the total binding and the nonspecific binding determined in the presence of an excess of unlabelled ligand. The results (POC %) are expressed as a **percent inhibition of control specific binding** (100-((measured specific binding/control specific binding) x 100)) obtained in the presence of a test compound.

Receptor Name	POC (%)		
	2	**26**	**30**
A3R_Human	97	97	96
TXA2 synthetase_Human	96	88	95
COX2_ACE	97	85	88
CXCR2_Human	93	73	84
COX1_ACE	88	71	90
A1R_Human	88	38	70
TRH1_Human	86	20	63
NETr_Human	85	34	45
CCKR B_Human	82	44	47
H4 R_Human	79	33	-7
Dopamine D1 R_Human	78	49	49
Opioid Kns R_Rat	71	45	59
DATr_Human	67	-15	-6
CCKR A_Human	62	22	19
CaN WCon_Rat	6	73	87
Angiotensin II R 1_Human	6	14	12
H1 R_Human	22	3	24
M2 R_Human	47	23	47
V1a R_Human	0	1	7
CA II_Human	-2	5	9
nAchR a4b2_Rat	4	8	6
CB 2_Human	10	1	0
M1 R_Human	45	22	26
BLT R_Human	10	16	16
Cys Lt 1 R_Human	-3	-20	-2
NK1 R_Human	-6	9	-18
PAF R_Human	7	4	-3
Glu NMDAP_Rat	-8	-22	-42
P2X ns_Rat	-6	-3	-4
P2Y R_Rat	42	27	25
VPAC2_Human	3	-191	-160
Alpha 1 ns R_Rat	5	2	-1

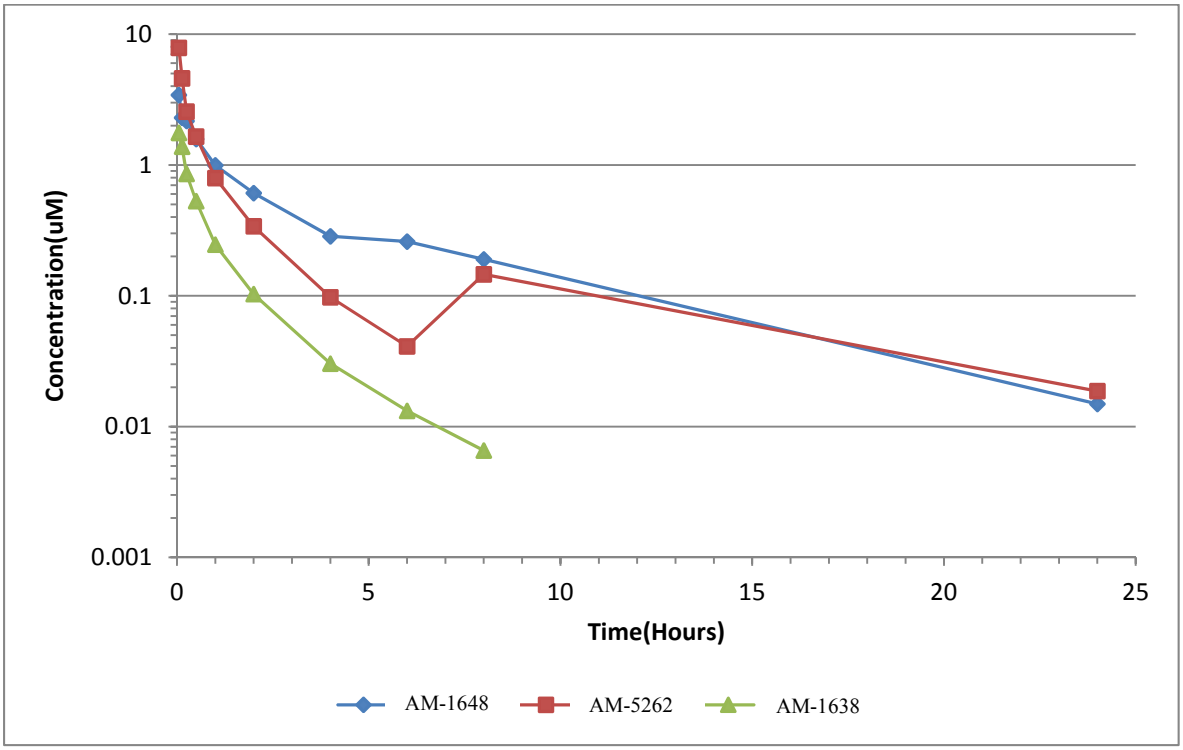
GABA A_Rat	6	5	7
H2 R_Human	9	-9	-3
MT ns R_Human	11	-2	5
M3 R_Human	52	8	12
5-HT1a R_Human	32	-11	19
Angiotensin II R 2_Human	-6	2	-11
BKR 2_Human	-2	13	8
CCR1_Human	0	1	-4
ETa R_Human	5	5	-10
Gal 2 R_Human	12	0	-8
5-HT3 R_Human	-19	-3	-7
AR_Human	33	13	25
CB 1_Human	0	6	-4
Alpha 2 ns R_Rat	11	7	7
A2aR_Human	-15	-34	10
CaL DHP_Rat	59	27	60
Na 2ns_Rat	20	14	17
VPAC 1_Human	-4	-3	-47
A2bR_Human	-10	-27	-9
Sigma ns R_Rat	-5	7	15
ETb R_Human	5	-8	-6
GABA B 1b_Human	-6	-8	6
Glu AMPA_Rat	-3	-9	10
Opioid Mu R_Human	43	36	50
CGRP Receptor_Human	-2	-2	-8
5-HTTr_Human	3	-11	1
BKR 1_Human	12	52	16
H3 R_Human	0	43	2
NK2 R_Human	8	0	3
NK3 R_Human	-1	0	-8
MCR4_Human	1	9	0
Beta 1 R_Human	2	10	15
CHT1_Human	22	28	6
GAT ns_Rat	27	20	2
Glu KA_Rat	10	6	1
Glu NMDA_Rat	13	-3	15
Glu NMDAG_Rat	21	16	-14
MAO A_Human	5	-11	4
MAO B_Human	34	38	11
GlyR_Rat	10	2	-3
KATP_Rat	4	6	1
SKCa_Rat	-2	-5	-11
CRF1_Human	-37	-9	-23

ER ns_Human	6	5	-7
adenosine transporter_Guinea Pig	29	53	31
PDE2_in vitro	8	2	5
PDE3_Human	-9	-2	4
PDE4_in vitro	3	-5	3
PDE5_Human	16	1	-5
PDE6_Bovine	6	6	-3
MMP1_Human	2	5	11
MMP7_Human	-2	-3	2
PTP1B_Human	7	10	6
NEP_Human	14	6	-5
tryptase _Human	20	2	5
ATPase (Na+/K+)_Pig	15	17	16
ACE_Human	44	56	13
elastase_Human	-5	-11	-1
OT R_Rat	-4	9	1
cBZR_Rat	15	13	7
MMP3_Human	15	-2	1
SSTns R_in vitro	8	15	-9
EDG-2_Human	-30	-33	1
cNOS_in vitro	35	1	6
TP R_Human	11	20	2
angiotensin converting enzyme_Human	26	8	-34
BACE 1_Human	2	7	1
MMP9_Human	-3	12	20
MMP2_Human	-10	6	4

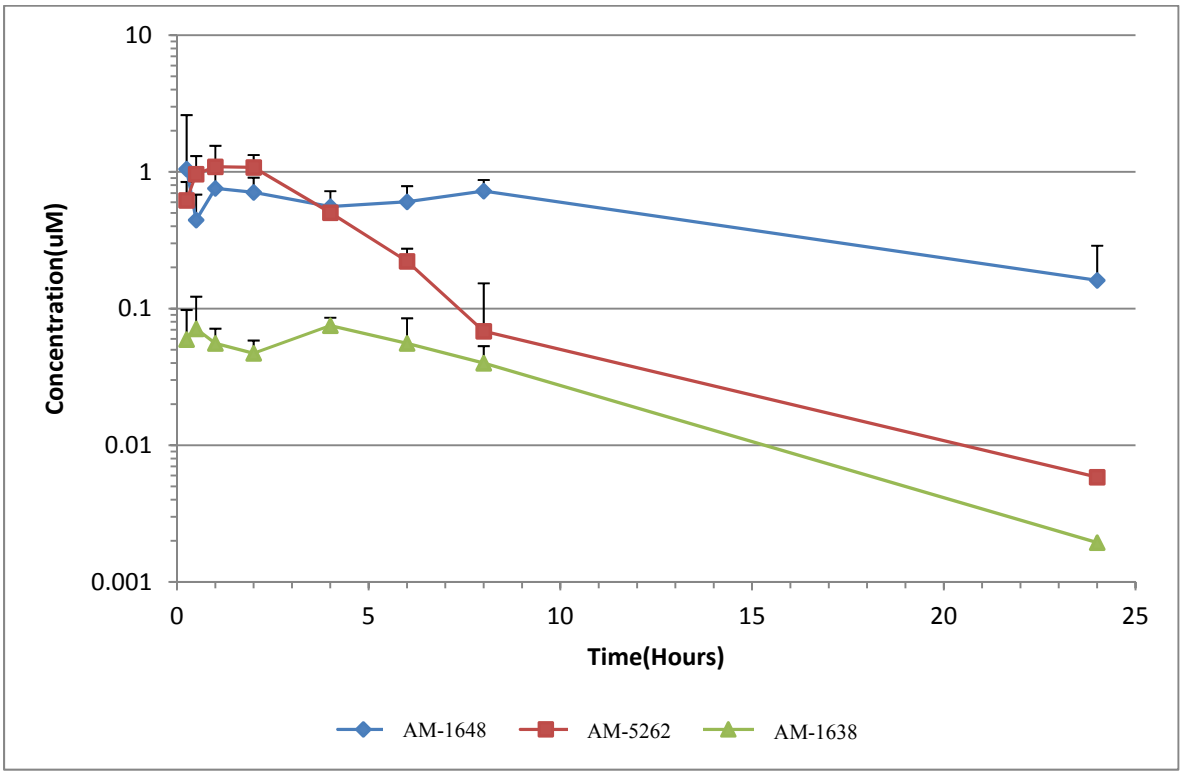
Overlay of rat pharmacokinetic experiments:

The improvement of rat pharmacokinetic profiles can be better seen with the overlays of corresponding experiment data curves. Compounds were dosed as DMSO solution for *iv* dosing. For *po* dosing, all three compounds were dosed as suspensions in 1%Tween 80_1%methyl cellulose_98%water. Please note that the rat bioavailability of AM-1638 (**2**) was reported as 72% (in reference 21) using a different formulation (10% Pluronic F68, 3% Tween 80). In this paper it is more appropriate to compare the three compounds using the same formulation. Standard Sprague Dawley rats were used for all experiments.

Overlay of rat *iv* PK:



Overlay of rat *po* PK:



Binding data from reciprocal competition experiments:

Methods

Equilibrium binding experiments: The assay was performed in a 96 well plate containing either 5 μg of membrane protein expressed human FFA1 receptor for [^{3}H] AMG 837 binding or 20 μg per well for [^{3}H] AMG1638 and incubated at room temperature for 4 h. Non–specific binding was determined in presence of 10 μM of either cold AMG 837 (**1**) or AM-1638 (**2**). The details of membrane preparation and binding and data analysis are reported in Lin et al 2012 (Reference 28, in manuscript).

Results

Binding experiments with two different radiolabel ligands allows one to detect both the allosteric and competitive binding sites. Here we examined the ability of the cold synthetic ligands AMG 837 (**1**), AM-1638 (**2**) and AM-5262 (**26**) to modulate the binding of [3H] AMG 837 and [3H] AM-1638 on membranes expressing FFA1 receptor.

Equilibrium binding assay was performed with 5nM [^{3}H] AMG 837. As expected, AMG 837, fully inhibited the specific [3H] AMG 837 binding with log affinity of 8.5 ± 0.09. However, both AM-1638 and AM-5262 strongly enhanced the specific binding of [3H] AMG 837 indicating positive cooperativity. The data analyzed using the allosteric ternary complex model gave a log affinity for AM-5262 occupied receptor 8.6 ± 0.13. The log affinity for occupied AM-1638 was 8.56 ± 0.14 and close to that reported earlier (Lin et al., 2012, reference 28). Cross-interaction experiments with 10 nM [^{3}H] AM-1638, as expected showed that AM-5262 competed fully to zero specific binding of AM-1638. Binding of AMG 837 displayed positive cooperativity by two fold with radiolabeled AM-1638.