Supporting Information

Development of Hybrid Phospholipid Mimics as Effective Agonists for Liver Receptor Homolog-1

Autumn R. Flynn[†], Suzanne G. Mays[‡], Eric A. Ortlund[§‡], Nathan T. Jui[§†*]

Department of Chemistry[†], Department of Biochemistry[‡], Winship Cancer Institute[§], Emory University, Atlanta, Georgia, 30322, United States

Table of Contents

I. a. General Synthetic Information

All reactions were carried out in oven-dried glassware, equipped with a stir bar and under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Solvents used in anhydrous reactions were purified by passing over activated alumina and storing under argon. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. n-Butyllithium (n-BuLi) was used as a 1.6 M or a 2.5 M solution in hexanes (Aldrich), was stored at 4°C and titrated prior to use. Organic solutions were concentrated under reduced pressure on a rotary evaporator using a water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on 230-400 mesh silica gel. Preparative thin-layer chromatography (PTLC) separations were carried out on 1000μm SiliCycle silica gel F-254 plates. Thin-layer chromatography (TLC) was performed on 250μm SiliCycle silica gel F-254 plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by staining using $KMnO_4$, p-anisaldehyde, or ninhydrin stains.

^{1}H and ^{13}C NMR spectra were obtained from the Emory University NMR facility and recorded on a Bruker Avance III HD 600 equipped with cryo-probe (600 MHz), INOVA 600 (600 MHz), INOVA 500 (500 MHz), INOVA 400 (400 MHz), VNMR 400 (400 MHz), or Mercury 300 (300 MHz), and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, ddd= doublet of doublet of doublets, dtd= doublet of triplet of doublets, b = broad, etc.), coupling constant (Hz), integration, and assignment, when applicable. Data for decoupled ^{13}C NMR are reported in terms of chemical shift and multiplicity when applicable. IR spectra were recorded on a Thermo Fisher Diamond-ATR and reported in terms of frequency of absorption (cm $^{-1}$). High Resolution mass spectra were obtained from the Emory University Mass Spectral facility. Gas Chromatography Mass Spectrometry (GC-MS) was performed on an Agilent 5977A mass spectrometer with an Agilent 7890A gas chromatography inlet. Liquid Chromatography Mass Spectrometry (LC-MS) was performed on an Agilent 6120 mass spectrometer with an Agilent 1220 Infinity liquid chromatography inlet. Preparative High Pressure Liquid chromatography (Prep-HPLC) was performed on an Agilent 1200 Infinity Series chromatograph using an Agilent Prep-C18 30 x 250 mm 10 μm column, or an Agilent Prep-C18 21.2 x 100 mm, 5 μm column. HPLC analyses were performed using the following conditions.

I. b. Evaluation of Compound Purity.

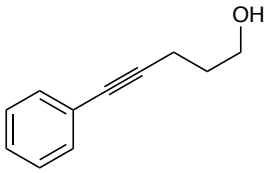
Purity of all tested compounds was determined by HPLC analysis, using the methods given below (as indicated for each compound). All compounds tested *in vitro* were greater than 95% pure (as the indicated *exo* diastereomer), with the exceptions of **13b** (83.9% *exo* and 12.9% *endo*) **11** (91.4% sn1 connectivity, 8.6% sn2 regioisomer) and **12f**, which was of 94.8% purity.

Method A: A linear gradient using water and 0.1 % formic acid (FA) (Solvent A) and MeCN and 0.1% FA (Solvent B); t = 0 min, 50% B, t = 4 min, 99% B (held for 1 min), then 50% B for 1 min, was employed on an Agilent Poroshell 120 EC-C18 2.7 micron, 3.0 mm x 50 mm column (flow rate 1 mL/min) or an Agilent Zorbax SB-C18 1.8 micron, 2.1 mm x 50 mm column (flow

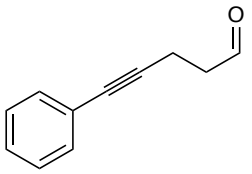
rate 0.8 mL/min). The UV detection was set to 254 nm. The LC column was maintained at ambient temperature.

Method B: An isocratic method using 65% MeCN, 45% water, and 0.1 % FA was employed on an Agilent Poroshell 120 EC-C18 2.7 micron, 3.0 mm x 50 mm column (flow rate 1 mL/min) or an Agilent Zorbax SB-C18 1.8 micron, 2.1 mm x 50 mm column (flow rate 0.8 mL/min). The UV detection was set to 254 nm. The LC column was maintained at ambient temperature.

II. a. *Exo*-selective Enyne Synthesis: Compound 4d



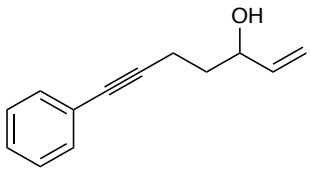
5-phenylpent-4-yn-1-ol: A roundbottom flask equipped with magnetic stir bar was charged with bis(triphenylphosphine)palladium dichloride (347.7 mg, 0.5 mmol, 0.01 equiv) and copper iodide (323.2 mg, 1.7 mmol, 0.03 equiv). The flask was placed under nitrogen and triethylamine (52 mL) was added via syringe. The solution was treated with iodobenzene (10.7 g, 52 mmol, 1.0 equiv), then sparged with nitrogen for 30 minutes. 4-pentyn-1-ol (5.4 g, 64 mmol, 1.2 equiv) was then added via syringe. The sparging needle was removed from the solution and replaced with a vent needle under positive nitrogen pressure. The solution was vigorously stirred at 60°C for 2 hours, at which point the reaction was complete by TLC. The reaction was cooled and precipitated with ether. The entire reaction was filtered over a plug of celite (eluted with ether). The filtrate was concentrated *in vacuo* to afford a rust-colored oil, which was purified on silica (30% EtOAc/hexanes eluent) to afford the title compound as a clear, colorless oil. (8.4 g, >99% yield). Spectral data were consistent with reported values.[1]



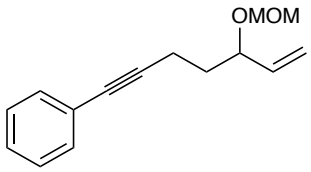
5-phenylpent-4-ynal: Under nitrogen, a solution of oxalyl chloride (4.5 mL, 52 mmol, 1.1 equiv) in DCM (400 mL) was cooled to -78 °C. A solution of dimethylsulfoxide (4.4 mL, 62 mmol, 1.3 equiv) in DCM (30 mL) was added dropwise. After effervescence ceased (ca. 30 minutes), 5-phenylpent-4-yn-1-ol (7.6 g, 48 mmol, 1.0 equiv) was added dropwise in DCM. The reaction mixture was stirred at -78 °C for 1.5 h before the addition of triethylamine (17 mL, 123 mmol, 2.5 equiv). The solution was allowed to warm to room temperature before the addition of saturated ammonium chloride (excess). The reaction mixture was then poured onto water and

[1] K. Fuji, T. Morimoto, K. Tsutsumi, and K. Kakiuchi, *Chem. Comm.*, 2005, 0, 3295-3297.

extracted with EtOAc, dried with $MgSO_4$, concentrated, and purified by silica gel chromatography (10-20% EtOAc/hexanes 6.8 g, 91 %). Spectral data were consistent with reported values.[2]



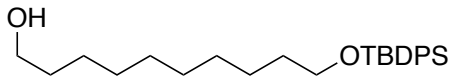
7-phenylhept-1-en-6-yn-3-ol: Under nitrogen, a solution of 5-phenylpent-4-ynal (5.8 g, 37 mmol, 1.0 equiv) in anhydrous THF was cooled to -78 °C. The solution was treated with vinylmagnesium bromide (58 mL of a 1.0M solution in THF, 58 mmol, 1.5 equiv.). The reaction was stirred and allowed to warm to room temperature over 16 h, then saturated ammonium chloride was added. The reaction mixture was poured onto water and extracted with EtOAc, dried with $MgSO_4$, and concentrated before purification on silica (5-10% EtOAc/Hexanes eluent) to give the title compound (5.5 g, 81%). Spectral data are consistent with reported values.[2]



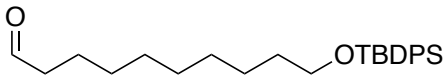
(5-(methoxymethoxy)hept-6-en-1-yn-1-yl)benzene (4d): Under nitrogen, 7-phenylhept-1-en-6-yn-3-ol (1.97 g, 11 mmol, 1.0 equiv) was dissolved in DCM (50 mL), followed by the addition of N,N-diisopropylethylamine (2.3 mL, 13 mmol, 1.2 equiv) and chloromethyl methyl ether (1.2 mL, 16 mmol, 1.5 equiv). The reaction was stirred at 30 °C for 4 h, then cooled to ambient temperature and poured onto water, extracted with DCM, and washed with 1M HCl. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated before purification on silica (5% EtOAc/hexanes eluent) to afford the title compound (2.4 g, 98%).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 2H), 7.32 – 7.22 (m, 3H), 5.70 (ddd, J = 17.6, 10.4, 7.6 Hz, 1H), 5.27 (dt, J = 17.1, 1.4 Hz, 1H), 5.22 (dt, J = 10.4, 1.3 Hz, 1H), 4.73 (d, J = 6.8 Hz, 1H), 4.57 (d, J = 6.7 Hz, 1H), 4.22 (td, J = 7.8, 5.3 Hz, 1H), 3.40 (d, J = 1.5 Hz, 3H), 2.60 – 2.45 (m, 2H), 1.95 – 1.84 (m, 1H), 1.84 – 1.76 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 137.7, 131.5, 128.2, 127.6, 123.9, 117.7, 93.8, 89.4, 81.0, 75.8, 55.5, 34.4, 15.6.

[2] Richard J. Whitby, Jozef Stec, Ray D. Blind, Sally Dixon, Lisa M. Leesnitzer, Lisa A. Orband-Miller, Shawn P. Williams, Timothy M. Willson, Robert Xu, William J. Zuercher, Fang Cai, and Holly A. Ingraham. *J. Med. Chem.* 2011, 54, 2266–2281

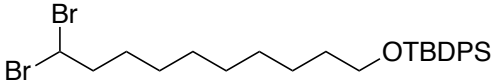
II. b. Representative Dibromoalkane Synthesis: Compound 3g



11-((tert-butyldiphenylsilyl)oxy)undecan-1-ol (S1a): A solution of 1,11-undecanediol (6.9 g, 37 mmol, 2.0 equiv) in THF (100 mL) was treated with imidazole (1.2 g, 18 mmol, 1.0 equiv) and tert-butyldiphenylsilylchloride (TBDPS-Cl, 4.9 g, 18 mmol, 1.0 equiv). The reaction was stirred for 16 h. The entire reaction was passed through celite to remove ammonium salts, then the filtrate was concentrated. The crude oil was purified on silica (5-20% EtOAc/hexanes eluent) to give the desired compound **S1a** as a clear, colorless oil (5.7 g, 74%).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 – 7.61 (m, 4H), 7.45 – 7.32 (m, 6H), 3.68 – 3.54 (t, 4H), 1.64 – 1.44 (m, 4H), 1.37 – 1.21 (m, 14H), 1.03 (s, 9H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 135.6, 134.2, 129.5, 127.5, 64.0, 63.1, 32.8, 32.6, 29.6, 29.5, 29.43, 29.37, 26.9, 25.8, 25.7, 19.2.



11-((tertbutyldiphenylsilyl)oxy)undecanal (S1b): A solution of **S1a** (2.2 g, 5.2 mmol, 1.0 equiv) was dissolved in DCM (100 mL). Trichloroisocyanuric acid (1.35 g, 5.8 mmol, 1.1 equiv) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, 76.7 mg, 0.5 mmol, 0.01 equiv.) were added. The reaction mixture was allowed to stir at room temperature until the reaction was complete by TLC (fewer than 5 minutes). The reaction was quenched with saturated aqueous $NaHCO_3$ and stirred for 5 minutes. The reaction mixture was poured onto water and extracted with DCM three times. The combined organic layers were washed with 1M aqueous HCl, brine, dried with $MgSO_4$, and concentrated. The crude oil was purified on silica (5-10% EtOAc/hexanes eluent) to afford the title compound **S1b** as a clear, colorless oil (2.0 g, 93%)
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.74 (t, J = 1.9 Hz, 1H), 7.65 (m, 4H), 7.42 – 7.33 (m, 6H), 3.63 (td, J = 6.5, 3.4 Hz, 2H), 2.40 (m, 2H), 1.60 (m, 2H), 1.53 (m, 2H), 1.35 – 1.20 (m, 12H), 1.06 – 1.00 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 202.9, 135.5, 134.1, 129.4, 127.5, 63.9, 43.9, 32.5, 29.34, 29.26, 29.1, 26.8, 25.8, 25.7, 19.2.

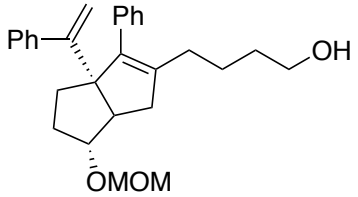


***tert*-butyl((11,11-dibromoundecyl)oxy)diphenylsilane (3g):** Under nitrogen, a solution of triphenylphosphite (4.0 mL, 15 mmol, 1.1 equiv) in DCM (100 mL) was cooled to -78 °C. Bromine (0.8 mL, 16 mmol, 1.1 equiv) and triethylamine (2.2 mL, 16 mmol, 1.1 equiv) were sequentially added dropwise at -78 °C. The reaction was stirred for 5 minutes, then **S1b** (5.8 g, 14 mmol, 1.0 equiv) was added as a solution in DCM (10 mL) via syringe at -78 °C. The reaction was stirred for 5 h and allowed to warm to ambient temperature. The whole reaction was

then poured over a pad of silica. The filtrate was concentrated and purified on a short plug of silica in 100% hexanes to afford the title compound as a clear, colorless oil (7.7 g, 99%).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 – 7.62 (m, 4H), 7.44 – 7.33 (m, 6H), 5.68 (t, J = 6.2 Hz, 1H), 3.63 (t, J = 6.6 Hz, 2H), 2.41 – 2.31 (m, 2H), 1.57 – 1.46 (m, 4H), 1.35 – 1.20 (m, 12H), 1.03 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.1, 129.5, 127.6, 64.0, 46.4, 45.4, 32.5, 29.4, 29.3, 28.2, 28.1, 26.9, 25.7, 19.2.

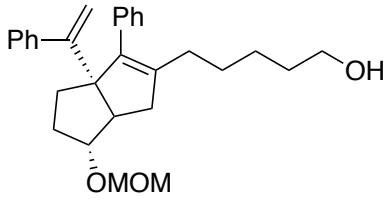
II. c. Cyclization Procedure: Compounds 5a–h

Zirconecene Mediated Cyclization
Hexahydropentalene formation was accomplished through slight modification of Whitby's procedure.[2] Prior to cyclization, all reagents were dried by azeotropic removal of water using benzene. A dry round bottom flask containing bis(cyclopentadienyl)zirconium(IV) dichloride (1.2 equiv) under nitrogen, was dissolved in anhydrous, degassed tetrahydrofuran (THF, 50 mL/mmol enyne) and cooled to -78 °C. The resulting solution was treated with n-BuLi (2.4 equiv.) and the light yellow solution was stirred for 30 minutes. A solution of **4d** (5-(methoxymethoxy)hept-6-en-1-yn-1-yl)benzene (1.0 equiv) in anhydrous, degassed THF (5 mL/mmol) was added. The resulting salmon-colored mixture was stirred at -78 °C for 30 minutes, the cooling bath removed, and the reaction mixture was allowed to warm to ambient temperature with stirring (2.5 hours total). The reaction mixture was then cooled to -78 °C and the required 1,1-dibromoalkane (**3a–3h**, 1.1 equiv) was added as a solution in anhydrous THF (5 mL/mmol) followed by freshly prepared lithium diisopropylamide (LDA, 1.0 M, 1.1 equiv.). After 15 minutes, a freshly prepared solution of lithium phenylacetylide (3.6 equiv.) in anhydrous THF was added dropwise and the resulting rust-colored solution was stirred at -78 °C for 1.5 hours. The reaction was quenched with methanol and saturated aqueous sodium bicarbonate and allowed to warm to room temperature, affording a light yellow slurry. The slurry was poured onto water and extracted with ethyl acetate four times. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The resulting yellow oil was passed through a short plug of silica (20% EtOAc/Hexanes eluent) and concentrated. The crude product was dissolved in THF (50–100 mL) and treated with solid tetrabutylammonium fluoride hydrate (ca. 2.0 equiv.) and the resulting solution stirred at room temperature for 16 h. The reaction mixture was concentrated and purified by silica gel chromatography (20% EtOAc/hexanes eluent) to afford the title compound **5a–5h** as a 7:1 mixture of diastereomers, favoring the desired *exo*-isomer.

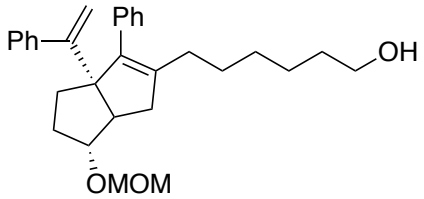


4-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)butan-1-ol (**5a**): According to the general procedure, *tert*-butyl((5,5-

dibromopentyl)oxy)diphenylsilane (798.6 mg, 1.7 mmol) was reacted with **4d** (342.2 mg, 1.5 mmol,) to give the title compound (7:1 dr) as a yellow oil (349.4 mg, 56% over 2 steps).
For the *exo* diastereomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 – 7.11 (m, 10H), 5.03 (d, *J* = 1.5 Hz, 1H), 4.99 (d, *J* = 1.5 Hz, 1H), 4.60 – 4.52 (m, 2H), 3.81 – 3.71 (m, 1H), 3.54 (t, *J* = 6.2 Hz, 2H), 3.29 (s, 3H), 2.47 – 2.35 (m, 1H), 2.31 – 2.26 (m, 1H), 2.09 – 1.99 (m, 4H), 1.78 – 1.54 (m, 4H), 1.52 – 1.35 (m, 3H).
For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.06 (d, *J* = 1.3 Hz, 1H), 4.84 (d, *J* = 1.4 Hz, 1H), 4.00 (td, *J* = 9.8, 6.1 Hz, 1H), 2.64 (dd, *J* = 17.1, 2.4 Hz, 1H), 2.53 (td, *J* = 9.0, 2.2 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4, 144.0, 140.8, 139.7, 137.3, 129.6, 127.8, 127.70, 127.65, 126.6, 114.9, 94.7, 86.7, 69.1, 62.6, 55.2, 52.8, 40.4, 32.7, 32.4, 31.5, 29.4, 24.0.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{27}H_{31}O_2$ $[M\text{-}OCH_3]^+$ 387.2, found 386.9.

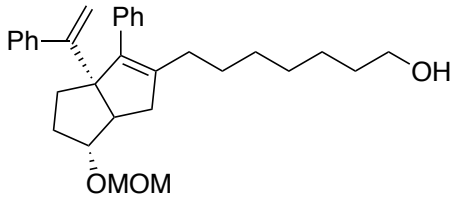


5-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)pentan-1-ol (**5b**): According to the general procedure, *tert*-butyl((6,6-dibromohexyl)oxy)diphenylsilane (529.1 mg, 0.95 mmol) was reacted with **4d** (203.4 mg, 0.88 mmol) to give the title compound (7:1 dr) as a yellow oil (301.0 mg, 70% over 2 steps).
For the *exo* diastereomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 – 7.10 (m, 10H), 5.01 (d, *J* = 1.4 Hz, 1H), 4.97 (d, *J* = 1.4 Hz, 1H), 4.60 – 4.51 (m, 2H), 3.76 (s, 1H), 3.55 (t, *J* = 6.5 Hz, 2H), 3.27 (s, 3H), 2.39 (d, *J* = 8.6 Hz, 1H), 2.29 (dd, *J* = 18.2, 9.6 Hz, 1H), 2.10 – 1.88 (m, 4H), 1.75 – 1.50 (m, 2H), 1.50 – 1.42 (m, 2H), 1.41 – 1.22 (m, 5H).
For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.07 (d, *J* = 1.3 Hz, 1H), 4.84 (d, *J* = 1.4 Hz, 1H), 4.00 (td, *J* = 10.3, 5.8 Hz, 1H), 2.63 (dd, *J* = 17.3, 2.3 Hz, 1H), 2.52 (td, *J* = 9.2, 2.1 Hz, 1H).
LRMS (ESI, APCI) *m/z*: calc'd for $C_{28}H_{33}O_2$ $[M\text{-}OCH_3]^+$ 401.2, found 401.2.

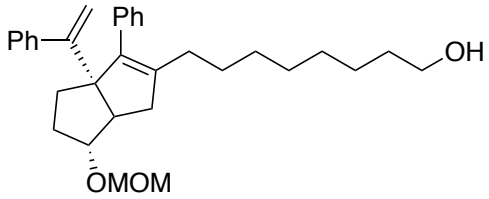


6-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)hexan-1-ol (**5c**): According to the general procedure, *tert*-butyl((7,7-dibromoheptyl)oxy)diphenylsilane (908.2 mg, 1.8 mmol) was reacted with **4d** (355.9 mg, 1.5 mmol) to give the title compound (7:1 dr) as a yellow oil (431.8 mg, 63% over 2 steps).
For the *exo* diastereomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36 – 7.11 (m, 10H), 5.03 (s, 1H), 4.98 (s, 1H), 4.61 – 4.51 (m, 2H), 3.77 (s, 1H), 3.57 (t, *J* = 6.7 Hz, 2H), 3.29 (s, 3H), 2.40 (d, *J* = 9.1,

1.8 Hz, 1H), 2.30 (dd, *J* = 16.9, 9.3 Hz, 1H), 2.10 – 1.96 (m, 4H), 1.79 – 1.53 (m, 2H), 1.54 – 1.45 (m, 2H), 1.43 – 1.23 (m, 7H).
For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.08 (d, *J* = 1.4 Hz, 1H), 4.85 (d, *J* = 1.4 Hz, 1H), 4.01 (td, *J* = 9.8, 5.6 Hz, 1H), 2.65 (dd, *J* = 17.3, 2.2 Hz, 1H), 2.54 (td, *J* = 9.1, 2.3 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 144.1, 141.1, 139.4, 137.4, 134.8, 129.6, 127.8, 127.63, 126.59, 114.9, 94.7, 86.7, 69.1, 62.8, 55.1, 52.8, 40.5, 32.6, 32.41, 31.42, 29.6, 29.4, 27.8, 25.5.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{29}H_{35}O_2$ $[M\text{-}OCH_3]^+$ 415.3, found 415.3.

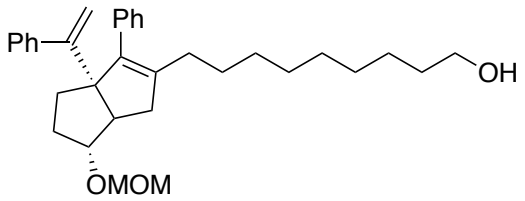


7-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)heptan-1-ol (5d): According to the general procedure, *tert*-butyl((8,8-dibromooctyl)oxy)diphenylsilane (732.9 mg, 1.4 mmol) was reacted with **4d** (287.5 mg, 1.2 mmol) to give the title compound (7:1 dr) as a yellow oil (303.2 mg, 55% over 2 steps).
For the *exo* diastereomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 – 7.02 (m, 10H), 5.05 (s, 1H), 5.00 (s, 1H), 4.62 – 4.56 (m, 2H), 3.79 (s, 1H), 3.66 – 3.60 (m, 2H), 3.30 (s, 3H), 2.41 (d, *J* = 9.4 Hz, 1H), 2.32 (dd, *J* = 17.0, 9.2 Hz, 1H), 2.08 – 1.92 (m, 4H), 1.78 – 1.67 (m, 2H), 1.59 – 1.49 (m, 2H), 1.44 – 1.19 (m, 9H).
For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.08 (d, *J* = 1.3 Hz, 1H), 4.85 (d, *J* = 1.2 Hz, 1H), 4.00 (td, *J* = 9.6, 5.6 Hz, 1H), 2.65 (dd, *J* = 17.4, 2.1 Hz, 1H), 2.53 (td, *J* = 8.9, 2.2 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 144.1, 141.2, 139.3, 137.5, 129.6, 127.8, 127.63, 126.57, 114.9, 94.7, 86.7, 69.1, 63.0, 55.1, 52.8, 40.5, 32.7, 32.4, 31.4, 29.64, 29.58, 29.2, 27.7, 25.6.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{30}H_{37}O_2$ $[M\text{-}OCH_3]^+$ 429.3, found 428.8.

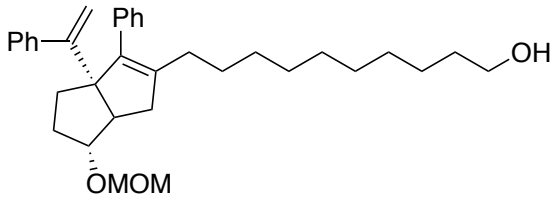


8-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)octan-1-ol (5e): According to the general procedure, *tert*-butyl((9,9-dibromononyl)oxy)diphenylsilane (709.8 mg, 1.3 mmol) was reacted with **4d** (274.4 mg, 1.2 mmol) to afford the title compound (7:1 dr) as a yellow oil (441.5 mg, 78% over 2 steps).
For the *exo* diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.18 (m, 10H), 5.05 (d, *J* = 1.5 Hz, 1H), 5.01 (d, *J* = 1.5 Hz, 1H), 4.63 – 4.53 (m, 2H), 3.79 (s, 1H), 3.62 (t, *J* = 6.7 Hz, 2H), 3.31 (s, 3H), 2.42 (d, *J* = 9.4, 1.8 Hz, 1H), 2.32 (dd, *J* = 16.9, 9.1 Hz, 1H), 2.11 – 1.97 (m, 4H), 1.83 – 1.54 (m, 4H), 1.59 – 1.50 (m, 2H), 1.38 – 1.17 (m, 9H).

For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.08 (d, *J* = 1.3 Hz, 1H), 4.85 (d, *J* = 1.3 Hz, 1H), 4.01 (td, *J* = 9.6, 5.8 Hz, 1H), 2.65 (dd, *J* = 17.4, 2.1 Hz, 1H), 2.53 (td, *J* = 8.9, 2.2 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 144.1, 141.3, 139.3, 137.5, 129.6, 127.8, 127.6, 126.59, 126.55, 114.8, 94.7, 86.7, 69.1, 63.0, 55.1, 52.8, 40.5, 32.8, 32.4, 31.4, 29.7, 29.6, 29.33, 29.27, 27.8, 25.7.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{31}H_{39}O_2$ $[M\text{-}OCH_3]^+$ 443.3, found 442.9.

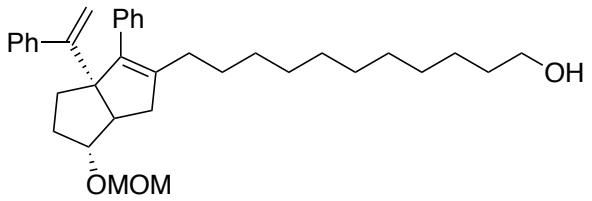


9-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)nonan-1-ol (**5f**): According to the general procedure, *tert*-butyl((10,10-dibromodecyl)oxy)diphenylsilane (577.2 mg, 1.0 mmol) was reacted with **4d** (206.7 mg, 0.9 mmol) to give the title compound (7:1 dr) as a yellow oil (249.6 mg, 57% over 2 steps).
For the *exo* diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.15 (m, 10H), 5.06 (d, *J* = 1.4 Hz, 1H), 5.01 (d, *J* = 1.5 Hz, 1H), 4.62 – 4.56 (m, 2H), 3.80 (s, 1H), 3.62 (t, *J* = 6.7 Hz, 2H), 3.32 (s, 3H), 2.43 (d, *J* = 9.1, 1.7 Hz, 1H), 2.33 (dd, *J* = 16.9, 9.2 Hz, 1H), 2.11 – 1.99 (m, 4H), 1.79 – 1.60 (m, 4H), 1.60 – 1.51 (m, 2H), 1.43 – 1.17 (m, 11H).
For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.09 (d, *J* = 1.4 Hz, 1H), 4.86 (d, *J* = 1.4 Hz, 1H), 4.01 (td, *J* = 9.6, 5.8 Hz, 1H), 2.66 (dd, *J* = 17.3, 2.4 Hz, 1H), 2.54 (td, *J* = 9.0, 2.3 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 144.1, 141.3, 139.2, 137.5, 129.6, 127.8, 127.6, 126.62, 126.56, 114.9, 94.7, 86.7, 69.1, 63.0, 55.2, 52.7, 40.5, 32.8, 32.4, 31.4, 29.7, 29.6, 29.5, 29.4, 29.3, 27.8, 25.7.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{32}H_{41}O_2$ $[M\text{-}CH_3O]^+$ 457.3, found 457.8.



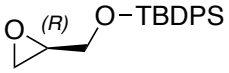
10-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)decan-1-ol (**5g**): According to the general procedure, *tert*-butyl((11,11-dibromoundecyl)oxy)diphenylsilane (1.24 g, 2.2 mmol) was reacted with **4d** (463.9 mmol, 2.0 mmol) to give the title compound (7:1 dr) as a yellow oil (584.1 mg, 58% over 2 steps).
For the *exo* diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.17 (m, 10H), 5.07 (d, *J* = 1.4 Hz, 1H), 5.02 (d, *J* = 1.5 Hz, 1H), 4.64 – 4.56 (m, 2H), 3.81 (p, *J* = 2.1 Hz, 1H), 3.62 (d, *J* = 6.6 Hz, 2H), 3.32 (s, 3H), 2.44 (dq, *J* = 9.2, 1.7 Hz, 1H), 2.35 (dd, *J* = 16.9, 9.2 Hz, 1H), 2.11 – 2.00 (m, 4H), 1.81 – 1.63 (m, 4H), 1.57 (m, 2H), 1.40 – 1.19 (m, 13H).

For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.10 (d, *J* = 1.3 Hz, 1H), 4.87 (d, *J* = 1.4 Hz, 1H), 4.03 (td, *J* = 9.7, 5.6 Hz, 1H), 2.68 (dd, *J* = 17.3, 2.3 Hz, 1H), 2.56 (td, *J* = 9.0, 2.3 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 144.1, 141.3, 139.2, 137.5, 129.6, 127.8, 127.6, 126.62, 126.56, 114.9, 94.7, 86.7, 69.1, 63.0, 55.2, 52.7, 40.5, 32.8, 32.4, 31.4, 29.7, 29.6, 29.5, 29.4, 29.3, 27.8, 25.7.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{33}H_{43}O_2$ $[M\text{-}CH_3O]^+$ 471.3, found 470.9.



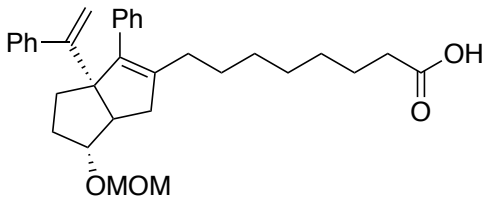
11-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)undecan-1-ol (**5h**): According to the general procedure, *tert*-butyl((12,12-dibromododecyl)oxy)diphenylsilane (703.6 mg, 1.2 mmol) was reacted with **4d** (250.2 mg, 1.1 mmol) to give the title compound (7:1 dr) as a yellow oil (325.7 mg, 58% over 2 steps).
For the *exo* diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.16 (m, 10H), 5.08 (d, *J* = 1.5 Hz, 1H), 5.03 (d, *J* = 1.5 Hz, 1H), 4.65 – 4.56 (m, 3H), 3.82 (s, 1H), 3.64 (t, *J* = 6.7 Hz, 2H), 3.33 (s, 3H), 2.45 (d, *J* = 9.2, 1.7 Hz, 1H), 2.36 (dd, *J* = 16.9, 9.2 Hz, 1H), 2.13 – 2.00 (m, 4H), 1.89 – 1.61 (m, 4H), 1.62 – 1.51 (m, 2H), 1.41 – 1.19 (m, 15H).
For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.11 (d, *J* = 1.4 Hz, 1H), 4.88 (d, *J* = 1.4 Hz, 1H), 4.03 (td, *J* = 9.8, 5.8 Hz, 1H), 2.68 (dd, *J* = 17.3, 2.3 Hz, 1H), 2.57 (td, *J* = 9.0, 2.3 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 144.1, 141.4, 139.2, 137.5, 129.6, 127.8, 127.7, 126.64, 126.58, 114.9, 94.7, 86.8, 69.1, 62.9, 55.2, 52.7, 40.6, 32.8, 32.5, 31.5, 29.7, 29.7, 29.61, 29.58, 29.54, 29.46, 29.4, 27.9, 25.8.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{34}H_{45}O_2$ $[M\text{-}CH_3O]^+$ 485.3, found 484.9.

III. Scheme 1: Synthesis of PL Mimic 11

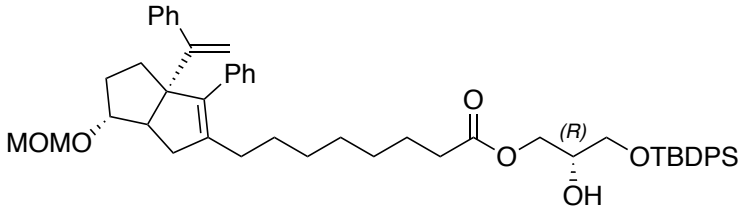


(*R*)-*tert*-butyl(oxiran-2-ylmethoxy)diphenylsilane (**7**): A solution of (*S*)-oxiran-2-ylmethanol (1.1 g, 15 mmol, 1.0 equiv) in THF (50 mL) was treated with TBDPS-Cl (4.9 g, 18 mmol, 1.2 equiv) and imidazole (1.2 g, 18 mmol, 1.2 equiv.) The resulting suspension was stirred for 16 h. The entire reaction was filtered through celite, the filtrate was concentrated, and the crude oil was purified on silica (5% EtOAc/hexanes eluent) to afford the title compound as a clear, colorless oil (3.5g, 74%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 – 7.63 (m, 4H), 7.54 – 7.33 (m, 6H), 3.91 (dd, *J* = 11.8, 3.2 Hz, 1H), 3.75 (dd, *J* = 11.9, 4.7 Hz, 1H), 3.17 (ddt, *J* = 4.9, 4.2, 2.9 Hz, 1H), 2.77 (dd, *J* = 5.2, 4.1 Hz, 1H), 2.65 (dd, *J* = 5.2, 2.7 Hz, 1H), 1.11 (s, 9H). Spectroscopic data are consistent with literature: Díaz, Y.; Bravo, F.; Castillón, S. J. Org. Chem. 1999, 64, 6508.

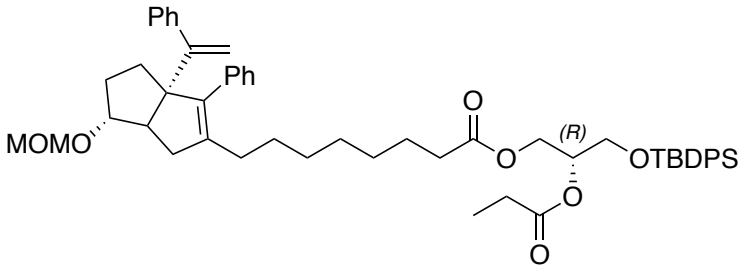


8-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)octanoic acid (6): A solution of **5e** (449.0 mg, 1.2 mmol) in acetonitrile (20 mL) was treated with tetrapropylammonium perruthenate (TPAP, 4.4 mg, 0.01 mmol, 0.1 equiv), N-Methylmorpholine-N-Oxide (NMO, 700.2 mg, 6 mmol, 5.0 equiv.), and water (100 μL, 6 mmol, 5 equiv.). The reaction mixture was allowed to stir until complete by TLC and LCMS, 1-16 h. Upon reaction completion, the reaction mixture was directly concentrated and purified on silica (20-50% EtOAc (containing 0.1% AcOH)/hexanes) to afford the title compound **6** (7:1 dr) as a clear, colorless oil (489.9 mg, 85%).
For the *exo* diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.19 (m, 10H), 5.07 (d, *J* = 1.5 Hz, 1H), 5.02 (d, *J* = 1.5 Hz, 1H), 4.64 – 4.59 (m, 2H), 3.81 (s, 1H), 3.33 (s, 3H), 2.44 (d, *J* = 9.5 Hz, 1H), 2.38 – 2.29 (m, 3H), 2.12 – 1.99 (m, 5H), 1.81 – 1.56 (m, 5H), 1.40 – 1.19 (m, 7H).
For the *endo* diastereomer (characteristic signals): (500 MHz, $CDCl_3$) δ 5.08 (d, *J* = 1.4 Hz, 1H), 4.85 (d, *J* = 1.3 Hz, 1H), 4.01 (td, *J* = 9.1, 5.6 Hz, 1H), 2.64 (d, *J* = 17.5 Hz, 1H), 2.54 (t, *J* = 9.1 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 179.7, 154.5, 144.1, 141.2, 139.4, 137.4, 129.6, 127.8, 127.7, 127.6, 126.62, 126.60, 114.9, 94.7, 86.8, 69.1, 55.1, 52.8, 40.5, 34.0, 32.4, 31.5, 29.6, 29.4, 28.9, 29.0, 27.7, 24.7.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{32}H_{39}O_4$ $[M-H]^-$ 487.3, found 487.2. Calc'd for $C_{31}H_{37}O_3$ $[M-CH_3O]^+$ 457.3, found 456.8.

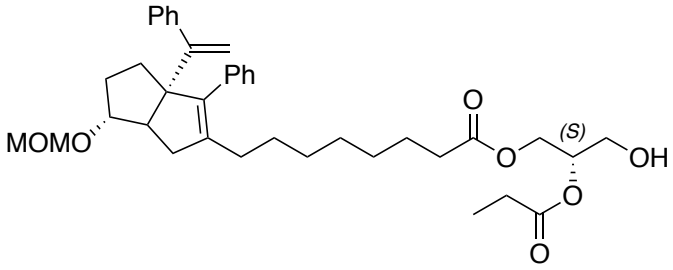


(*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-hydroxypropyl 8-(6-(*exo*)-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)octanoate (**8**): A solution of **6** (111.9 mg, 0.23 mmol) in diethyl ether (1 mL) was treated with co[salen] ((S,S)-(+)-N,N'bix(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamono cobalt (II)) (3.6 mg, 0.006 mmol, 0.03 equiv) and the reaction was allowed to stir for 1 h open to air. After 1 h, the diethylether was evaporated. **7** (76.1 mg, 0.24 mmol, 1.0 equiv) and diisopropylethylamine (40 μL, 0.23 mmol, 1.0 equiv) were added and the reaction was stirred neat at ambient temperature

for 16 h. The crude reaction mixture was directly purified on silica (5-10% EtOAc/hexanes eluent) to give the title compound (7:1 dr) as a clear, colorless oil (44.0 mg, 24%).
For the *exo* diastereomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 4H), 7.47 – 7.18 (m, 16H), 5.05 (d, *J* = 1.4 Hz, 1H), 5.00 (d, *J* = 1.4 Hz, 1H), 4.63 – 4.56 (m, 2H), 4.18 (dd, *J* = 11.5, 4.7 Hz, 1H), 4.15 (dd, *J* = 11.2, 6.3 Hz, 1H), 3.94 (p, *J* = 5.5 Hz, 1H), 3.80 – 3.77 (m, 1H), 3.71 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.66 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.31 (s, 3H), 2.54 (d, *J* = 5.5 Hz, 1H), 2.41 (d, *J* = 9.0 Hz, 1H), 2.32 (dd, *J* = 16.9, 9.3 Hz, 1H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.09 – 1.97 (m, 4H), 1.78 – 1.68 (m, 1H), 1.69 – 1.60 (m, 1H), 1.60 – 1.47 (m, 2H), 1.36 – 1.15 (m, 9H), 1.06 (s, 9H).
For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.08 (d, *J* = 1.3 Hz, 1H), 4.85 (d, *J* = 1.3 Hz, 1H), 4.00 (td, *J* = 9.5, 5.9 Hz, 1H), 2.65 (d, *J* = 17.3 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 154.5, 144.1, 141.2, 139.3, 137.4, 135.73, 135.69, 135.5, 132.9, 129.9, 129.6, 127.8, 127.7, 127.64, 127.61, 126.60, 126.57, 114.9, 94.7, 86.7, 70.1, 69.1, 65.0, 64.5, 63.6, 55.1, 52.8, 40.5, 34.1, 32.4, 31.4, 29.7, 29.5, 29.0, 27.8, 26.9, 26.8, 24.8.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{50}H_{61}O_5Si$ $[M\text{-}OCH_3]^+$ 769.4, found 769.6.



(*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-2-(propionyloxy)propyl 8-(6-(*exo*)-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)octanoate (**9**): A solution of **8** (44 mg, 0.05 mmol, 1.0 equiv) in DCM (4 mL) was treated with propionyl chloride (18 µL, 0.2 mmol, 4.0 equiv) and DMAP (29.4 mg, 0.24 mol, 4.8 equiv). The reaction was allowed to stir for 4 h. The resulting reaction mixture was directly concentrated and purified on silica (5-10% EtOAc/hexanes eluent) to give the title compound (7:1 dr) as a clear, colorless oil (35.0 mg, 77%).
For the *exo* diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 – 7.60 (m, 4H), 7.50 – 7.16 (m, 16H), 5.23 – 5.14 (m, 1H), 5.06 (s, 1H), 5.02 (s, 1H), 4.62 – 4.58 (m, 2H), 4.41 (dt, *J* = 11.9, 3.4 Hz, 1H), 4.23 (ddd, *J* = 11.8, 6.3, 2.5 Hz, 1H), 3.83 – 3.79 (m, 1H), 3.81 – 3.74 (m, 2H), 3.33 (s, 3H), 2.43 (d, *J* = 8.8 Hz, 1H), 2.38 – 2.20 (m, 5H), 2.11 – 1.97 (m, 4H), 1.80 – 1.71 (m, 1H), 1.71 – 1.60 (m, 1H), 1.60 – 1.51 (m, 2H), 1.42 – 1.13 (m, 9H), 1.12 (t, *J* = 7.6 Hz, 3H), 1.05 (s, 9H).
For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.09 (d, *J* = 1.3 Hz, 1H), 4.87 (d, *J* = 1.4 Hz, 1H), 4.03 (t, *J* = 9.9, 5.9 Hz, 1H), 2.66 (d, *J* = 17.3 Hz, 1H), 2.55 (t, *J* = 8.9 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 173.3, 154.5, 144.1, 141.2, 139.3, 137.4, 135.6, 135.5, 133.1, 133.0, 129.8, 129.6, 127.8, 127.74, 127.72, 127.65, 127.62, 126.61, 126.59, 114.9, 94.8, 86.7, 71.6, 69.1, 62.4, 62.3, 55.1, 52.8, 40.5, 34.1, 32.4, 31.5, 29.7, 29.5, 29.04, 29.03, 27.8, 27.6, 26.7, 24.8, 19.2, 9.0.
LRMS (ESI) *m/z*: calc'd for $C_{53}H_{65}O_6Si$ $[M\text{-}OCH_3]^+$ 825.45504, found 825.45507.



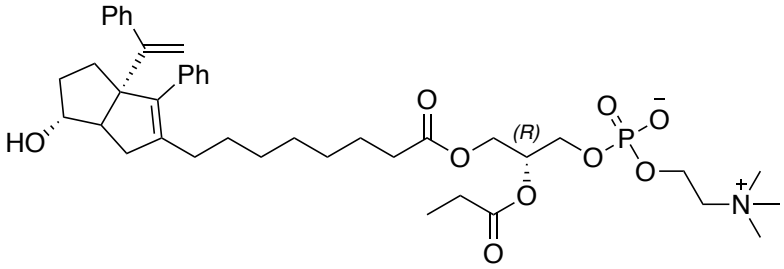
(*S*)-3-hydroxy-2-(propionyloxy)propyl 8-(6-(*exo*)-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)octanoate (**10**): A solution of **9** (35.0 mg, 0.041 mmol, 1.0 equiv) in THF was treated with TBAF (13.2 mg, 0.047 mmol, 1.1 equiv) and stirred for 16 h. The resulting mixture was directly concentrated and purified on silica (20-50% EtOAc/hexanes eluent) to give the desired compound (7:1 dr) as a clear, colorless oil (19.3 mg, 76%).

For the *exo* diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.17 (m, 10H), 5.10 – 5.07 (m, 0H), 5.05 (d, *J* = 1.4 Hz, 1H), 5.00 (d, *J* = 1.4 Hz, 1H), 4.62 – 4.57 (m, 2H), 4.19 (ddd, *J* = 11.5, 4.3, 1.7 Hz, 2H), 4.13 (ddd, *J* = 11.4, 5.8, 2.1 Hz, 2H), 4.12 – 4.04 (m, 1H), 3.81 – 3.76 (m, 1H), 3.73 (s, 1H), 3.31 (s, 3H), 2.45 – 2.27 (m, 6H), 2.09 – 1.98 (m, 4H), 1.79 – 1.53 (m, 4H), 1.36 – 1.19 (m, 8H), 1.15 (t, *J* = 7.2 Hz, 3H).

For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.08 (d, *J* = 1.2 Hz, 1H), 4.85 (d, *J* = 1.4 Hz, 1H), 4.01 (td, *J* = 9.2, 5.7 Hz, 1H), 2.65 (dd, *J* = 17.3, 2.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 173.8, 154.5, 144.1, 141.2, 139.3, 137.4, 129.6, 127.8, 127.64, 127.61, 126.60, 126.57, 114.9, 94.7, 86.7, 69.1, 68.3, 65.1, 65.0, 55.1, 52.8, 40.5, 34.0, 32.4, 31.4, 29.7, 29.5, 29.0, 27.7, 27.4, 24.8.

LRMS (ESI, APCI) *m/z*: calc'd for $C_{37}H_{47}O_6$ $[M\text{-}OCH_3]^+$ 587.3, found 586.8.

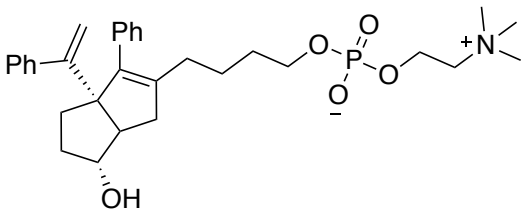


(2*R*)-3-((8-(6-(*exo*)-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)octanoyl)oxy)-2-(propionyloxy)propyl (2-(trimethylammonio)ethyl) phosphate (**11**): A solution of **10** (31.8 mg, 0.05 mmol, 1.0 equiv) in toluene was treated with 2-chloro-1,3,2-dioxaphospholane 2-oxide (10 µL, 0.11 mmol, 2.2 equiv) was added, followed by DMAP (13.1 mg, 0.11 mmol, 2.2 equiv.) The resulting reaction mixture was stirred for 4 h, until reaction was complete by LCMS. The resulting mixture was filtered over a cotton plug to remove excess ammonium salts and concentrated. The crude reaction mixture dissolved in acetonitrile, transferred into a pressure tube, and cooled to -78 °C. Trimethylamine (neat, 2-5mL) was condensed into the pressure tube at -78 °C. The tube was capped, allowed to warm to room temperature, and heated to 90 °C for 16 h. After the reaction was complete, the pressure tube was allowed to cool to ambient temperature before being further cooled to -78 °C and uncapped. The

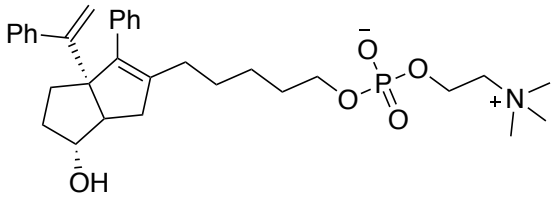
solution was allowed to re-warm to room temperature before being concentrated *inside a fume hood* and used without further purification. The crude reaction mixture was dissolved in acetonitrile, and 2 drops of concentrated HCl was added. The mixture was allowed to stir until the reaction was complete (ca. 5 min, monitored by LCMS), and then concentrated. Purification *via* preparative HPLC on an Agilent 1200 Infinity Series chromatograph using an Agilent Prep-C18 30 x 250 mm 10 µm column, with a linear gradient using water and 0.1% formic acid (FA) (Solvent A) and MeCN and 0.1% FA (Solvent B); t=0 min, 30% B, t = 10 min, 99% B, with a flow rate 40 mL/min, afforded the title compounds **11** as its *exo* diastereomer, as a mixture of regioisomers (2.2 mg, Purity established as a mixture of regioisomers using Method A: >99% (91.3% sn-1 connectivity (desired, shown), 8.6 % sn-2 connectivity). t_R = 0.72 min (sn1), 0.78 min (sn2).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.15 (m, 10H), 5.04 (s, 1H), 4.98 (s, 1H), 4.51 (s, 0H), 4.44 – 4.28 (m, 4H), 4.28 – 4.17 (m, 2H), 4.18 – 4.06 (m, 1H), 3.92 (s, 1H), 3.80 – 3.69 (m, 2H), 3.30 (s, 9H), 2.38 – 2.22 (m, 6H), 2.12 – 1.93 (m, 4H), 1.60 – 1.48 (m, 4H), 1.38 – 1.13 (m, 9H), 1.10 (t, J = 7.5 Hz, 3H).
LRMS (ESI, APCI) *m/z*: calc'd for C_{41} $[M]^+$ 739.4, found 739.6.
HRMS (ESI) *m/z*: calc'd for $C_{41}H_{59}O_9NP$ $[M+H]^+$ 740.3939, found 740.3922. Calc'd for $C_{41}H_{58}O_9NPNa$ $[M+Na]^+$ 762.3747, found 762.3741.

IV. Scheme 2. Phosphorylcholine Synthesis: Compounds 12a–h.

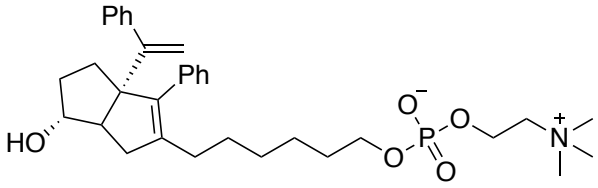
General Procedure:
A solution of the required alcohol (**5a–5h**, 1.0 equiv) in toluene was treated with 2-chloro-1,3,2-dioxaphospholane 2-oxide (2.0 equiv), followed by triethylamine (2.0 equiv). The reaction mixture was stirred for 1-4 h, until reaction was complete by LCMS. The resulting mixture was filtered through a cotton plug to remove ammonium salts and concentrated. The crude reaction mixture was dissolved in acetonitrile, transferred into a pressure tube, and cooled to -78 °C. Trimethylamine (neat, 2-5mL) was condensed into the pressure tube at -78 °C. The tube was capped, allowed to warm to room temperature, and then heated to 90 °C for 16 h. After the reaction was complete, the pressure tube was allowed to cool to ambient temperature before being further cooled to -78 °C and uncapped. The solution was allowed to re-warm to room temperature before being concentrated *inside a fume hood* and used without further purification. The crude reaction mixture was dissolved in acetonitrile, and 2-5 drops of concentrated HCl was added. The mixture was allowed to stir until the reaction was complete (5-30 min, monitored by LCMS), and concentrated. Purification *via* preparative HPLC on an Agilent 1200 Infinity Series chromatograph using an Agilent Prep-C18 30 x 250 mm 10 µm column, with a linear gradient using water and 0.1% formic acid (FA) (Solvent A) and MeCN and 0.1% FA (Solvent B); t=0 min, 30% B, t = 10 min, 99% B, flow rate 40 mL/min, afforded the desired compounds (**12a–12h**) as their *exo* diastereomer as clear, colorless oils.



4-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)butyl (2-(trimethylammonio)ethyl) phosphate (**12a**): **5a** (39.6 mg, 0.1 mmol) was reacted and purified according to the general procedure to give the title compound (9.3 mg, 18% yield over three steps). Purity established as the *exo* diastereomer by Method A: >99%, *exo* t_R = 0.33 min.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.13 (m, 10H), 5.02 (s, 1H), 4.99 (s, 1H), 4.19 (s, 2H), 3.81 (s, 1H), 3.76 (s, 2H), 3.64 (s, 2H), 3.21 (s, 9H), 2.26 – 2.05 (m, 3H), 2.01 – 1.87 (m, 1H), 1.68 – 1.36 (m, 9H).
^{31}P NMR (121 MHz, $CDCl_3$) δ -0.76.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{31}H_{43}O_5NP$ $[M+H]^+$: 540.3, found 540.3.

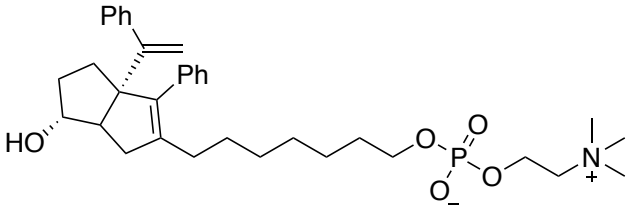


5-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)pentyl (2-(trimethylammonio)ethyl) phosphate (12b): 5b (13.7 mg, 0.03 mmol) was reacted and purified according to the general procedure to give the title compound (2.1 mg, 12% yield over three steps). Purity established as the *exo* diastereomer by Method A: 95.8%, t_R = 0.28 min.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 4H), 7.25 – 7.14 (m, 6H), 4.99 (s, 2H), 4.19 (s, 2H), 3.86 (s, 1H), 3.75 (s, 2H), 3.63 (s, 2H), 3.20 (s, 9H), 2.25 – 2.18 (m, 1H), 2.16 – 2.04 (m, 2H), 1.95 – 1.87 (m, 1H), 1.70 – 1.60 (m, 1H), 1.60 – 1.52 (m, 4H), 1.53 – 1.43 (m, 1H), 1.42 – 1.30 (m, 3H), 1.31 – 1.18 (m, 2H).
^{31}P NMR (121 MHz, $CDCl_3$) δ -0.82.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{32}H_{45}O_5NP$ $[M+H]^+$: 554.3, found 554.2.

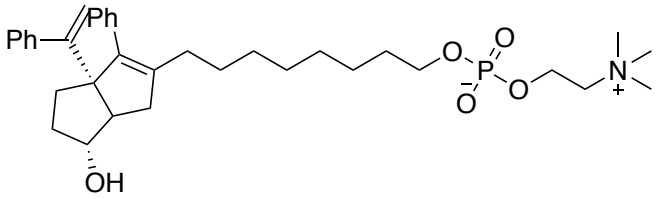


6-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)hexyl (2-(trimethylammonio)ethyl) phosphate (**12c**): **5c** (17.9 mg, 0.04 mmol)was reacted and purified according to the general procedure to give the title compound (6.9 mg, 30% yield over three steps). Purity established as the *exo* diastereomer by Method A: >99%, *exo* t_R = 0.47 min.

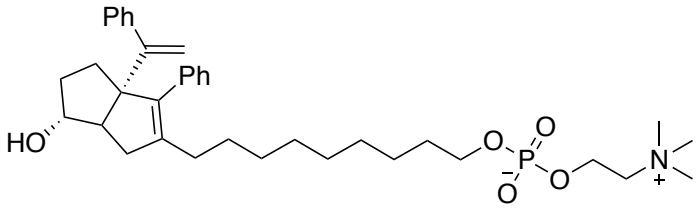
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 4H), 7.28 – 7.12 (m, 6H), 5.03 (s, 1H), 5.01 (s, 1H), 4.24 (s, 2H), 3.88 (s, 1H), 3.80 – 3.67 (m, 4H), 3.28 (s, 9H), 2.28 – 2.05 (m, 3H), 2.01 – 1.80 (m, 1H), 1.72 – 1.49 (m, 3H), 1.40 – 0.82 (m, 10H).
^{31}P NMR (121 MHz, Chloroform-*d*) δ -0.59.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{33}H_{47}O_5NP$ $[M+H]^+$ 568.3, found 568.2.



7-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)heptyl (2-(trimethylammonio)ethyl) phosphate (**12d**): **5d** (128.5 mg, 0.28 mmol) was reacted and purified according to the general procedure to give the title compound (66.1 mg, 41% yield over three steps). Purity established as the *exo* diastereomer by Method B: 95.9%, t_R = 0.48 min.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.11 (m, 10H), 5.02 (s, 1H), 4.99 (s, 1H), 4.21 (s, 2H), 3.87 (s, 1H), 3.77 (s, 2H), 3.67 (s, 1H), 3.25 (s, 9H), 2.29 – 2.16 (m, 1H), 2.15 – 2.02 (m, 2H), 2.00 – 1.90 (m, 1H), 1.72 – 1.57 (m, 3H), 1.57 – 1.48 (m, 3H), 1.37 – 1.14 (m, 9H).
^{13}C NMR (300 MHz, $CDCl_3$) δ 154.6, 144.1, 140.9, 139.6, 137.4, 129.6, 127.8, 127.7, 126.64, 114.7, 81.5, 69.1, 66.1, 65.7, 59.2, 55.7, 54.3, 40.0, 34.2, 32.0, 30.8, 29.5, 29.3, 29.2, 27.6, 25.6.
^{31}P NMR (300 MHz, $CDCl_3$) δ -0.51.
HRMS (ESI) *m/z*: calc'd for $C_{34}H_{49}O_5NP$ $[M+H]^+$: 582.3343, found 582.3338.



8-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)octyl (2-(trimethylammonio)ethyl) phosphate (12e): **5e** (16.7 mg, 0.04 mmol) was reacted and purified according to the general procedure to give the title compound (10.3 mg, 49% yield over three steps). Purity established as the *exo* diastereomer by Method A: >99%, t_R = 0.68 min.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 –7.15 (m, 10H), 5.00 (s, 1H), 4.96 (s, 1H), 4.22 (s, 2H), 3.89 (s, 1H), 3.81 – 3.75 (m, 2H), 3.74 – 3.66 (m, 2H), 3.27 (s, 9H), 2.28 – 2.17 (m, 2H), 2.10 – 2.04 (m, 1H), 1.96 – 1.87 (m, 1H), 1.71 – 1.58 (m, 3H), 1.57 – 1.48 (m, 2H), 1.36 – 1.13 (m, 12H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 154.6, 144.1, 141.0, 139.5, 137.4, 129.6, 127.8, 127.6, 126.61, 126.55, 114.8, 81.7, 69.2, 66.3, 59.1, 55.6, 54.4, 53.4, 40.1, 37.1, 34.3, 32.0, 30.8, 29.4, 29.2, 28.9, 28.8, 27.5, 25.6, 22.6.
^{31}P NMR (300 MHz, $CDCl_3$) δ -0.43.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{35}H_{51}O_5NP$ $[M+H]^+$ 596.3, found 596.3.
HRMS (ESI) *m/z*: calc'd for $C_{35}H_{51}O_5NP$ $[M+H]^+$: 596.3499, found 596.3494.



9-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)nonyl (2-(trimethylammonio)ethyl) phosphate (**12f**): **5f** (66.1 mg, 0.14 mmol) was reacted and purified according to the general procedure to give the title compound (22.3 mg, 27% yield over three steps). Purity established as the *exo* diastereomer using Method A: 94.8%, *exo* $t_R = 0.89$ min.

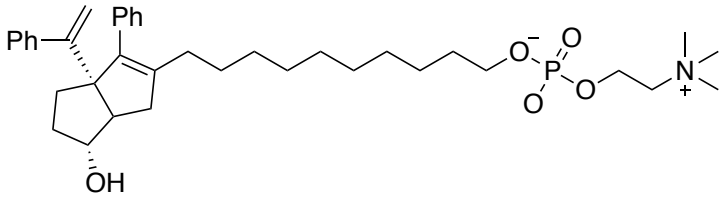
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.14 (m, 10H), 5.01 (d, $J = 7.6$ Hz, 1H), 4.95 (d, $J = 7.9$ Hz, 1H), 4.20 (s, 2H), 3.87 (s, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.25 (s, 9H), 2.27 – 2.18 (m, 2H), 2.06 – 1.98 (m, 2H), 1.94 (p, $J = 7.0$ Hz, 1H), 1.70 – 1.58 (m, 4H), 1.58 – 1.48 (m, 3H), 1.36 – 1.10 (m, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 144.2, 141.1, 139.4, 137.4, 129.7, 127.8, 127.7, 127.6, 126.63, 126.57, 114.9, 81.7, 69.3, 66.2, 65.9, 59.3, 55.7, 54.4, 40.2, 34.2, 32.1, 30.9, 29.5, 29.3, 29.2, 27.7, 27.6, 25.8.

^{31}P NMR (121 MHz, $CDCl_3$) δ -0.73.

LRMS (ESI, APCI) *m/z*: calc'd for $C_{36}H_{53}O_5NP$ $[M+H]^+$ 610.4, found 609.8.

HRMS (ESI) *m/z*: calc'd for $C_{36}H_{53}O_5NP$ $[M+H]^+$: 610.3656, found 610.3655.



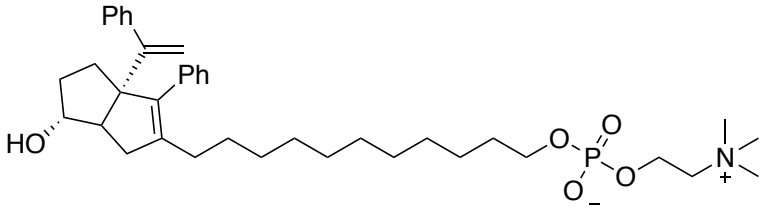
10-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)decyl (2-(trimethylammonio)ethyl) phosphate (**12g**): **5g** (64.5 mg, 0.13 mmol) was reacted and purified according to the general procedure to give the title compound (23.4 mg, 29% yield over three steps). Purity established as the *exo* diastereomer by Method A: 95.8%, $t_R = 0.74$ min.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.14 (m, 10H), 5.03 (d, $J = 4.9$ Hz, 1H), 4.95 (d, $J = 5.0$ Hz, 1H), 4.24 (s, 2H), 3.90 (s, 1H), 3.79 (q, $J = 6.4$ Hz, 2H), 3.74 (s, 2H), 3.28 (s, 9H), 2.34 – 2.23 (m, 2H), 2.10 – 1.92 (m, 3H), 1.64 (q, $J = 10.2$, 6.5 Hz, 2H), 1.56 (t, $J = 7.3$ Hz, 2H), 1.37 – 1.10 (m, 16H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 144.2, 141.1, 139.4, 137.4, 129.7, 127.73, 127.70, 127.6, 126.63, 126.56, 81.7, 69.3, 66.2, 65.9, 59.3, 55.6, 54.3, 40.2, 34.1, 32.2, 30.91, 30.86, 29.6, 29.3, 29.22, 29.17, 27.6, 25.8.

^{31}P NMR (121 MHz, $CDCl_3$) δ -0.75.

LRMS (ESI, APCI) *m/z*: calc'd for $C_{37}H_{55}O_5NP$ $[M+H]^+$: 624.4, found 624.3.



11-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)undecyl (2-(trimethylammonio)ethyl) phosphate (**12h**): **5h** (21.1 mg, 0.4 mmol) was reacted and purified according to the general procedure to give the title compound (5.5 mg, 21% yield over three steps). Purity established as the *exo* diastereomer by Method A: 95.4%, $t_R = 0.74$ min.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.15 (m, 12H), 5.03 (s, 1H), 4.96 (s, 1H), 4.26 (s, 2H), 3.91 (s, 1H), 3.85 – 3.77 (m, 2H), 3.75 (s, 2H), 3.29 (s, 9H), 2.32 (dd, *J* = 16.7, 9.4 Hz, 1H), 2.26 (d, *J* = 9.6 Hz, 1H), 2.10 – 1.94 (m, 4H), 1.71 – 1.61 (m, 3H), 1.61 – 1.53 (m, 2H), 1.38 – 1.14 (m, 16H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 144.2, 141.1, 139.3, 137.4, 129.7, 114.9, 81.7, 69.3, 66.2, 65.9, 59.3, 55.7, 54.4, 40.3, 34.0, 32.2, 31.6, 30.91, 30.86, 29.6, 29.5, 29.43, 29.40, 29.36, 29.3, 29.2, 27.7, 25.8, 22.7.

^{31}P NMR (121 MHz, $CDCl_3$) δ -0.90.

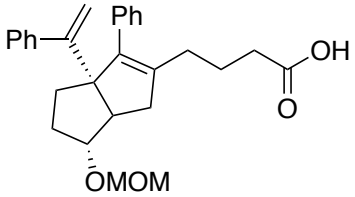
LRMS (ESI, APCI) *m/z*: calc'd for $C_{38}H_{57}O_5NP$ $[M+H]^+$ 638.4, found 637.8

HRMS (ESI) *m/z*: calc'd for $C_{38}H_{57}O_5NP$ $[M+H]^+$: 638.3969, found 638.3974.

V. Scheme 3. Carboxylate Synthesis: Compounds 13a–h.

General Ley-Griffith Oxidation General Procedure:

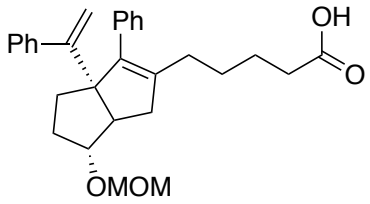
A solution of the required alcohol (**5a–5h**, 1.0 equiv) in acetonitrile was treated with tetrapropylammonium perruthenate (TPAP, 0.1 equiv), N-Methylmorpholine-N-Oxide (NMO, 5 equiv), and water (5 equiv). The reaction mixture was allowed to stir until complete by TLC and LCMS (1-16 h). The reaction mixture was directly concentrated and purified on silica (20-50% EtOAc (containing 0.1% AcOH)/hexanes eluent).



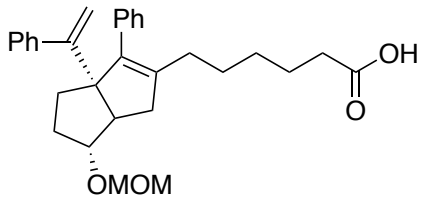
4-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)butanoic acid (S2a): 5a (262.8 mg, 0.63 mmol) was reacted and purified according to the general procedure to give the title compound as a clear, colorless oil (161.2 mg, 59%).

For the *exo* diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 – 7.05 (m, 10H), 5.07 (s, 1H), 5.01 (s, 1H), 4.66 – 4.52 (m, 2H), 3.80 (s, 1H), 3.31 (s, 3H), 2.45 (d, *J* = 8.9 Hz, 1H), 2.37 – 2.20 (m, 2H), 2.13 – 1.98 (m, 4H), 1.81 – 1.57 (m, 3H), 1.36 – 1.18 (m, 3H).

For the *endo* diastereomer (characteristic signals): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (s, 1H), 4.88 (s, 1H), 4.06 – 3.98 (m, 1H), 2.67 (d, *J* = 17.8 Hz, 1H).
^{13}C NMR (126 MHz, cdcl$_3$) δ 179.0, 154.3, 143.9, 140.6, 139.7, 137.1, 129.5, 127.80, 127.75, 127.7, 126.8, 115.0, 94.7, 86.6, 69.1, 55.2, 52.8, 40.3, 33.6, 32.4, 31.5, 29.1, 22.9.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{27}H_{29}O_3$ $[M\text{-}OCH_3]^+$ 401.2, found 400.8.

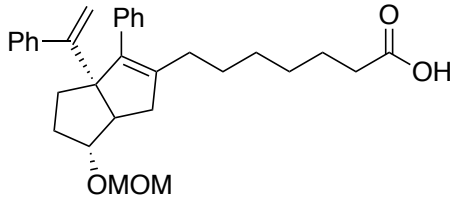


5-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)pentanoic acid (S2b): 5b (50.6 mg, 0.12 mmol) was reacted and purified according to the general procedure to give the title compound as a clear, colorless oil. (41.2 mg, 79 %).
For the *exo* diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.14 (m, 10H), 5.06 (d, *J* = 1.4 Hz, 1H), 5.02 (d, *J* = 1.4 Hz, 1H), 4.63 – 4.57 (m, 2H), 3.80 (s, 1H), 3.32 (s, 3H), 2.43 (d, *J* = 9.2 Hz, 1H), 2.35 – 2.26 (m, 3H), 2.10 – 2.00 (m, 4H), 1.79 – 1.53 (m, 4H), 1.46 – 1.20 (m, 3H).
For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.07 (d, *J* = 1.3 Hz, 1H), 4.85 (d, *J* = 1.3 Hz, 1H), 3.99 (dt, *J* = 9.6, 5.8 Hz, 1H), 2.63 (dd, *J* = 17.2, 1.8 Hz, 1H), 2.54 (dd, *J* = 9.5, 2.2 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 179.5, 154.3, 144.0, 140.4, 139.9, 137.2, 129.5, 127.8, 127.7, 127.6, 126.7, 126.6, 114.9, 86.6, 69.1, 55.1, 52.7, 40.3, 32.4, 31.4, 29.9, 29.3, 27.2, 24.6.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{29}H_{33}O_4$ $[M\text{-}H]^-$ 445.2, found 445.1. Calc'd for $C_{28}H_{31}O_3$ $[M\text{-}OCH_3]^+$ 415.2, found 415.2.

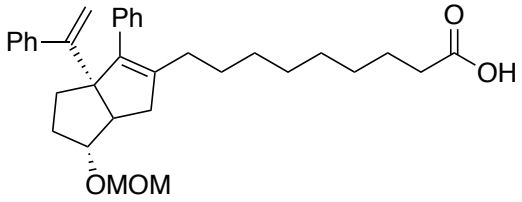


6-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)hexanoic acid (S2c): 5c (45.8 mg, 0.10 mmol) was reacted and purified according to the general procedure to give the title compound as a clear, colorless oil (35.5 mg, 75 %).
For the *exo* diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.11 (m, 10H), 5.05 (d, *J* = 1.4 Hz, 1H), 5.02 (d, *J* = 1.5 Hz, 1H), 3.80 (s, 1H), 3.33 (s, 3H), 2.41 (d, *J* = 8.7 Hz, 1H), 2.38 – 2.29 (m, 2H), 2.24 (dd, *J* = 17.0, 8.9 Hz, 1H), 2.12 – 1.98 (m, 4H), 1.79 – 1.49 (m, 7H), 1.47 – 1.18 (m, 4H).
For the *endo* diastereomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.06 (d, *J* = 1.3 Hz, 1H), 4.84 (d, *J* = 1.3 Hz, 1H), 4.00 (td, *J* = 9.8, 5.8 Hz, 1H), 2.63 (dd, *J* = 17.4, 2.2 Hz, 1H), 2.53 (td, *J* = 9.0, 2.2 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 179.5, 144.1, 140.7, 139.5, 137.2, 129.6, 127.72, 127.69, 127.66, 126.66, 126.65, 115.0, 82.0, 69.3, 60.4, 53.4, 40.1, 34.0, 32.0, 31.6, 29.4, 29.0, 27.4, 27.0, 22.6, 21.1.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{30}H_{35}O_4$ $[M-H]^-$ 459.3, found 459.3. Calc'd for $C_{29}H_{33}O_3$ $[M-OCH_3]^+$ 429.2, found 429.3.

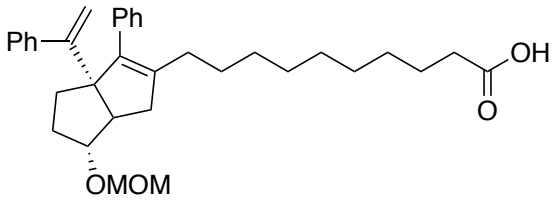


7-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)heptanoic acid (S2d): 5d (303.1 mg, 0.66 mmol) was reacted and purified according to the general procedure to give the title compound as a clear, colorless oil (126.3 mg, 40%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.02 (m, 10H), 5.05 (d, *J* = 1.5 Hz, 1H), 5.00 (d, *J* = 1.5 Hz, 1H), 4.66 – 4.52 (m, 2H), 3.79 (s, 1H), 3.31 (s, 3H), 2.42 (d, *J* = 9.3, 1.7 Hz, 1H), 2.40 – 2.27 (m, 3H), 2.10 – 1.97 (m, 4H), 1.79 – 1.50 (m, 4H), 1.52 – 1.18 (m, 7H).
For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.08 (d, *J* = 1.4 Hz, 1H), 4.85 (d, *J* = 1.4 Hz, 1H), 4.01 (td, *J* = 9.1, 5.8 Hz, 1H), 2.64 (d, *J* = 17.5 Hz, 1H), 2.54 (t, *J* = 9.1 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 179.5, 154.5, 144.1, 141.1, 139.4, 137.4, 134.6, 129.6, 127.8, 127.7, 126.6, 114.9, 94.7, 86.7, 69.1, 55.1, 52.8, 40.5, 33.9, 32.4, 31.4, 29.6, 29.2, 28.8, 27.6, 24.5.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{31}H_{37}O_4$ $[M-H]^-$ 473.3, found 473.4.

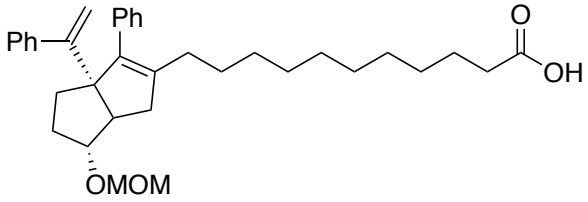


9-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)nonanoic acid (S2f): **5f** (559.0 mg, 1.1 mmol) was reacted and purified according to the general procedure to give the title compound as a clear, colorless oil (489.9 mg, 85%).
For the *exo* diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 10H), 5.05 (d, *J* = 1.4 Hz, 1H), 5.00 (d, *J* = 1.5 Hz, 1H), 4.65 – 4.57 (m, 2H), 3.80 (d, *J* = 2.1 Hz, 1H), 3.32 (d, *J* = 0.7 Hz, 3H), 2.42 (d, 1H), 2.37 – 2.29 (m, 3H), 2.10 – 1.98 (m, 4H), 1.69 – 1.58 (m, 5H), 1.44 – 1.08 (m, 11H).
For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.09 (d, *J* = 1.3 Hz, 1H), 4.85 (d, *J* = 1.4 Hz, 1H), 4.02 (td, *J* = 9.8, 5.4 Hz, 1H), 2.65 (dd, *J* = 17.7, 2.1 Hz, 1H), 2.54 (td, *J* = 9.4, 2.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.2, 154.5, 144.1, 141.3, 139.3, 137.4, 129.6, 127.8, 127.6, 126.61, 126.57, 114.9, 94.6, 86.8, 69.1, 55.1, 52.8, 40.5, 33.9, 32.4, 31.4, 29.7, 29.5, 29.2, 29.1, 29.0, 27.7, 24.7.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{33}H_{41}O_4$ $[M-H]^-$ 501.3, found 501.4. Calc'd for $C_{32}H_{39}O_3$ $[M-CH_3O]^+$ 471.3, found 470.8.



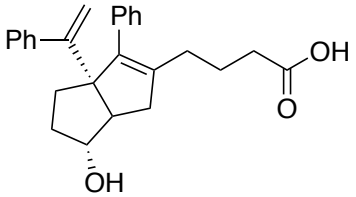
10-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)decanoic acid (S2g): **5g** (584.5 1.2 mmol) was reacted and purified according to the general procedure to give the title compound as a clear, colorless oil (498.2 mg, 88%).
For the *exo* diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.18 (m, 10H), 5.05 (d, J = 1.4 Hz, 1H), 5.01 (d, J = 1.5 Hz, 1H), 4.61 – 4.59 (m, 2H), 3.80 (s, 1H), 3.32 (s, 3H), 2.42 (d, J = 9.2, 1.7 Hz, 1H), 2.38 – 2.29 (m, 3H), 2.11 – 1.97 (m, 4H), 1.70 – 1.59 (m, 5H), 1.37 – 1.18 (m, 13H).
For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.09 (d, J = 1.3 Hz, 1H), 4.86 (d, J = 1.3 Hz, 1H), 4.02 (td, J = 9.7, 5.5 Hz, 1H), 2.65 (dd, J = 17.7, 2.2 Hz, 1H), 2.54 (td, J = 9.3, 2.2 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 179.4, 154.5, 144.1, 141.3, 139.2, 137.5, 129.6, 127.8, 127.6, 126.61, 126.56, 114.9, 94.7, 86.7, 69.1, 55.1, 52.7, 40.5, 34.0, 32.4, 31.4, 29.7, 29.6, 29.30, 29.26, 29.2, 29.0, 27.8, 24.7.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{34}H_{43}O_4$ $[M-H]^-$ 515.3, found 515.1. Calc'd for $C_{33}H_{41}O_3$ $[M-CH_3O]^+$ 485.3, found 484.9.



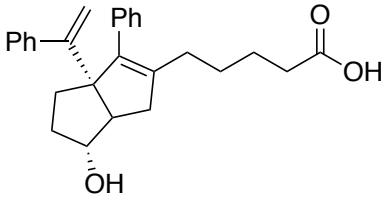
11-(6-*exo*-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)undecanoic acid (**S2h**): **5h** (325.7 mg, 0.63 mmol) was reacted and purified according to the general procedure to give the title compound as a clear, colorless oil (334.0 mg, > 99 %).
For the *exo* diastereomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 10H), 5.05 (d, J = 1.2 Hz, 1H), 5.00 (d, J = 1.2 Hz, 1H), 4.64 – 4.58 (m, 2H), 3.80 (s, 1H), 3.32 (s, 3H), 2.42 (d, J = 8.8 Hz, 1H), 2.38 – 2.30 (m, 3H), 2.11 – 1.98 (m, 4H), 1.72 – 1.59 (m, 5H), 1.44 – 1.17 (m, 16H).
For the *endo* diastereomer (characteristic signals): **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 5.09 (d, J = 1.2 Hz, 1H), 4.86 (d, J = 1.2 Hz, 1H), 4.02 (td, J = 9.4, 5.7 Hz, 1H), 2.66 (dd, J = 17.6, 2.2 Hz, 1H), 2.54 (td, J = 9.9, 2.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.2, 154.5, 144.1, 141.4, 139.2, 137.5, 129.6, 127.8, 127.63, 126.60, 126.55, 114.9, 94.7, 86.7, 69.1, 55.1, 52.7, 40.5, 33.9, 32.4, 31.4, 29.7, 29.6, 29.38, 29.36, 29.3, 29.2, 29.0, 27.8, 24.7.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{35}H_{46}O_4$ $[M-H]^-$ 529.3, found 529.5. Calc'd for $C_{34}H_{43}O_3$ $[M-CH_3O]^+$ 499.3, found 498.9.

General Deprotection Procedure:
A solution of **S2a-S2h** (1.0 equiv) in acetonitrile was treated with 2-5 drops of concentrated aqueous HCl and stirred until complete by TLC and LCMS (5-30 min). The resulting solution was directly purified *via* preparatory HPLC on an Agilent 1200 Infinity Series chromatograph using an Agilent Prep-C18 30 x 250 mm 10 µm column, with a linear gradient using water and 0.1% formic acid (FA) (Solvent A) and MeCN and 0.1% FA (Solvent B); t=0 min, 50% B, t = 10 min, 99% B, flow rate 40 mL/min, to afford the desired compounds as their *exo* diastereomer as clear, colorless oils (**13a–13h**).

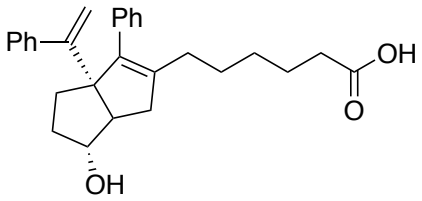


4-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)butanoic acid (**13a**): **S2a** (169.2 mg, 0.39 mmol) was reacted and purified according to the general procedure to give the title compound as a clear, colorless oil (47.8 mg, 31%). Purity was established as the *exo* diastereomer by Method A: >99%, *exo* t_R = 1.63 min.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.16 (m, 10H), 5.08 (d, *J* = 1.4 Hz, 1H), 5.00 (d, *J* = 1.4 Hz, 1H), 3.97 (s, 1H), 2.42 – 2.36 (m, 1H), 2.37 – 2.31 (m, 2H), 2.30 – 2.23 (m, 2H), 2.14 – 2.06 (m, 4H), 1.75 – 1.65 (m, 5H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7, 154.4, 144.0, 140.4, 139.6, 137.0, 129.6, 127.8, 127.7, 126.81, 126.75, 115.2, 82.0, 69.4, 55.7, 40.1, 34.0, 33.8, 32.0, 29.1, 22.9.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{26}H_{27}O_3$ $[M-H]^-$ 387.2, found 387.1.
HRMS calcd for $C_{26}H_{27}O_3$ $[M-H]^-$: 387.1966, found 387.1969.

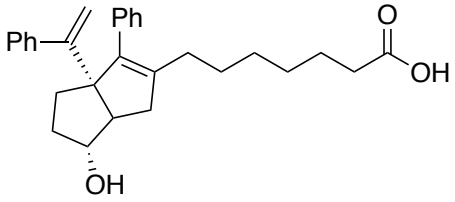


5-(6-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)pentanoic acid (13b): S2b (40.6 mg, 0.09 mmol) was reacted according to the general procedure and purified on silica (20-50% EtOAc (0.1% AcOH)/hexanes eluent) to give the title compound as a mixture of diastereomers as a clear, colorless oil (36.1 mg, >99%). Purity was established as a mixture of diastereomers by Method B: 96.8% (83.9% *exo* 12.9% *endo*), *exo* t_R =1.07 min, *endo* t_R =1.28 min.
For the *exo* diastereomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.56 – 6.96 (m, 10H), 5.05 (d, *J* = 1.4 Hz, 1H), 4.97 (d, *J* = 1.4 Hz, 1H), 3.93 (s, 1H), 2.38 – 2.23 (m, 4H), 2.13 – 1.97 (m, 5H), 1.74 – 1.62 (m, 3H), 1.53 (p, *J* = 7.4 Hz, 2H), 1.44 – 1.32 (m, 2H).

For the *endo* diastereomer (characteristic signals): ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.07 (d, *J* = 1.6 Hz, 1H), 4.94 (d, *J* = 1.4 Hz, 1H), 4.20 (td, *J* = 9.0, 5.7 Hz, 1H), 2.64 (dd, *J* = 17.3, 2.0 Hz, 1H), 2.50 (td, *J* = 8.6, 1.9 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 154.5, 144.1, 140.3, 139.8, 137.2, 129.7, 127.8, 127.7, 126.8, 126.7, 115.1, 82.0, 69.4, 55.8, 40.1, 34.0, 33.5, 32.1, 29.3, 27.2, 24.6.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{27}H_{30}O_3$ $[M-H]^-$ 401.2, found 401.5. Calc'd for $C_{27}H_{29}O_2$ $[M-OH]^+$ 385.2, found 385.2
HRMS calc'd for $C_{27}H_{31}O_3$ $[M+H]^+$: 403.2268, found 403.2266.

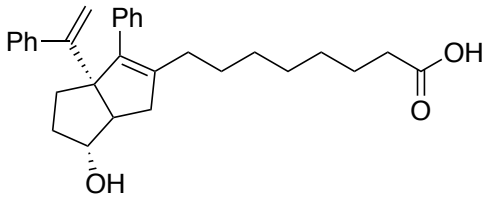


6-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)hexanoic acid (**13c**): **S2c** (169.6 mg, 0.37 mmol) was reacted and purified according to the general procedure to give the title compound as a clear, colorless oil (94.3 mg, 61%). Purity was established as the *exo* diastereomer by Method A: >99%, *exo* t_R = 2.26 min.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 – 7.05 (m, 10H), 5.05 (d, *J* = 1.5 Hz, 1H), 4.97 (d, *J* = 1.4 Hz, 1H), 3.93 (s, 1H), 2.36 – 2.21 (m, 4H), 2.10 – 1.97 (m, 5H), 1.73 – 1.61 (m, 3H), 1.59 – 1.51 (m, 2H), 1.34 (p, *J* = 7.6 Hz, 2H), 1.28 – 1.20 (m, 2H).
^{13}C NMR (126 MHz, $cdcl_3$) δ 179.4, 154.5, 144.1, 140.7, 139.5, 137.3, 129.6, 127.8, 127.70, 127.68, 126.7, 115.0, 82.1, 69.3, 55.7, 40.2, 34.0, 33.8, 32.0, 29.5, 29.0, 27.4, 24.5.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{28}H_{31}O_3$ $[M-H]^-$ 415.2, found 414.9. Calc'd for $C_{28}H_{31}O_2$ $[M-OH]^+$ 399.2, found 399.2
HRMS calc'd for $C_{28}H_{32}O_3Na$ $[M+Na]^+$: 439.2235, found 439.2237.

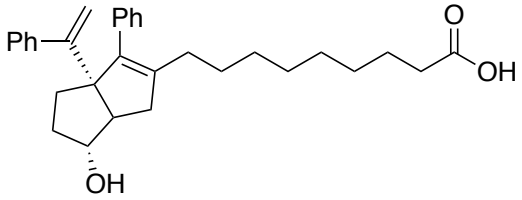


7-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)heptanoic acid (**13d**): **S2d** (126.3 mg, 0.27 mmol) was reacted and purified according to the general procedure to give the title compound as a clear, colorless oil (95.3 mg, 83%). Purity was established as the *exo* diastereomer by Method A: >99%, *exo* t_R = 2.53 min.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.14 (m, 9H), 5.05 (d, *J* = 1.5 Hz, 1H), 4.97 (d, *J* = 1.4 Hz, 1H), 3.93 (s, 1H), 2.38 – 2.25 (m, 4H), 2.11 – 1.97 (m, 4H), 1.76 – 1.47 (m, 4H), 1.33 (p, *J* = 7.6 Hz, 2H), 1.29 – 1.14 (m, 6H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 179.9, 154.5, 144.1, 140.9, 139.3, 137.3, 129.7, 127.74, 127.70, 127.66, 126.7, 115.0, 82.1, 69.3, 55.6, 40.2, 34.0, 33.9, 32.0, 29.6, 29.2, 28.8, 27.6, 24.6.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{29}H_{33}O_3$ $[M-H]^-$ 429.3, found 429.3. Calc'd for $C_{29}H_{33}O_2$ $[M-OH]^+$ 413.2, found 413.28

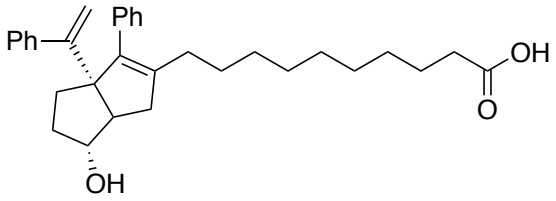
HRMS calc'd for $C_{29}H_{33}O_3$ [M-H]$^-$: 429.2435, found 429.2378.



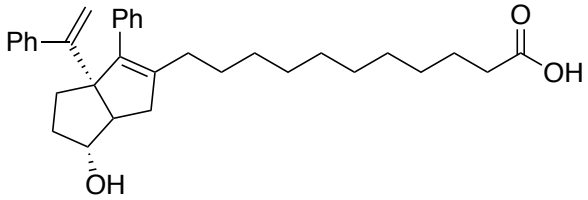
8-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)octanoic acid (**13e**): **S2e** (147.2 mg, 0.30 mmol) was reacted and purified according to the general procedure to give the title compound as a clear, colorless oil (95.9 mg, 72%). Purity was established as the *exo* diastereomer by Method A: >97.3%, t_R = 2.84 min.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 – 7.13 (m, 10H), 5.05 (s, 1H), 4.97 (s, 1H), 3.93 (s, 1H), 2.37 – 2.22 (m, 5H), 2.09 – 1.94 (m, 5H), 1.79 – 1.58 (m, 6H), 1.38 – 1.16 (m, 5H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 180.0, 154.5, 144.1, 141.0, 139.2, 137.3, 129.7, 127.74, 127.68, 127.6, 126.7, 115.0, 82.1, 69.3, 55.6, 40.2, 34.0, 33.8, 32.0, 29.4, 28.94, 28.88, 27.7, 24.6, 21.0.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{30}H_{35}O_3$ [M-H]$^-$ 443.3, found 443.2. Calc'd for $C_{30}H_{35}O_2$ [M-OH]$^+$ 427.3, found 427.4
HRMS calc'd for $C_{30}H_{35}O_3$ [M-H]$^-$: 443.2592, found 443.2593



9-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)nonanoic acid (**13f**): **S2f** (39.4 mg, 0.83 mmol) was reacted and purified according to the general procedure to give the title compound as a clear, colorless oil (34.3 mg, 90%). Purity was established as the *exo* diastereomer by Method A: >99%, t_R = 3.22 min.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.15 (m, 10H), 5.07 (d, *J* = 1.4 Hz, 1H), 4.99 (d, *J* = 1.4 Hz, 1H), 3.95 (s, 1H), 2.39 – 2.27 (m, 5H), 2.12 – 1.97 (m, 5H), 1.76 – 1.56 (m, 6H), 1.40 – 1.15 (m, 7H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 179.5, 154.6, 144.1, 141.1, 139.2, 137.4, 129.7, 127.74, 127.71, 127.6, 126.7, 126.6, 115.0, 82.1, 69.3, 55.7, 40.2, 34.0, 32.1, 29.6, 29.5, 29.2, 29.1, 29.0, 24.7.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{31}H_{37}O_3$ [M-H]$^-$ 457.3, found 457.3. Calc'd for $C_{31}H_{37}O_2$ [M-OH]$^+$ 441.3, found 440.8
HRMS (ESI) *m/z* : calc'd for for $C_{31}H_{37}O_3$ [M-H]$^-$ 457.2748, found 457.2749.

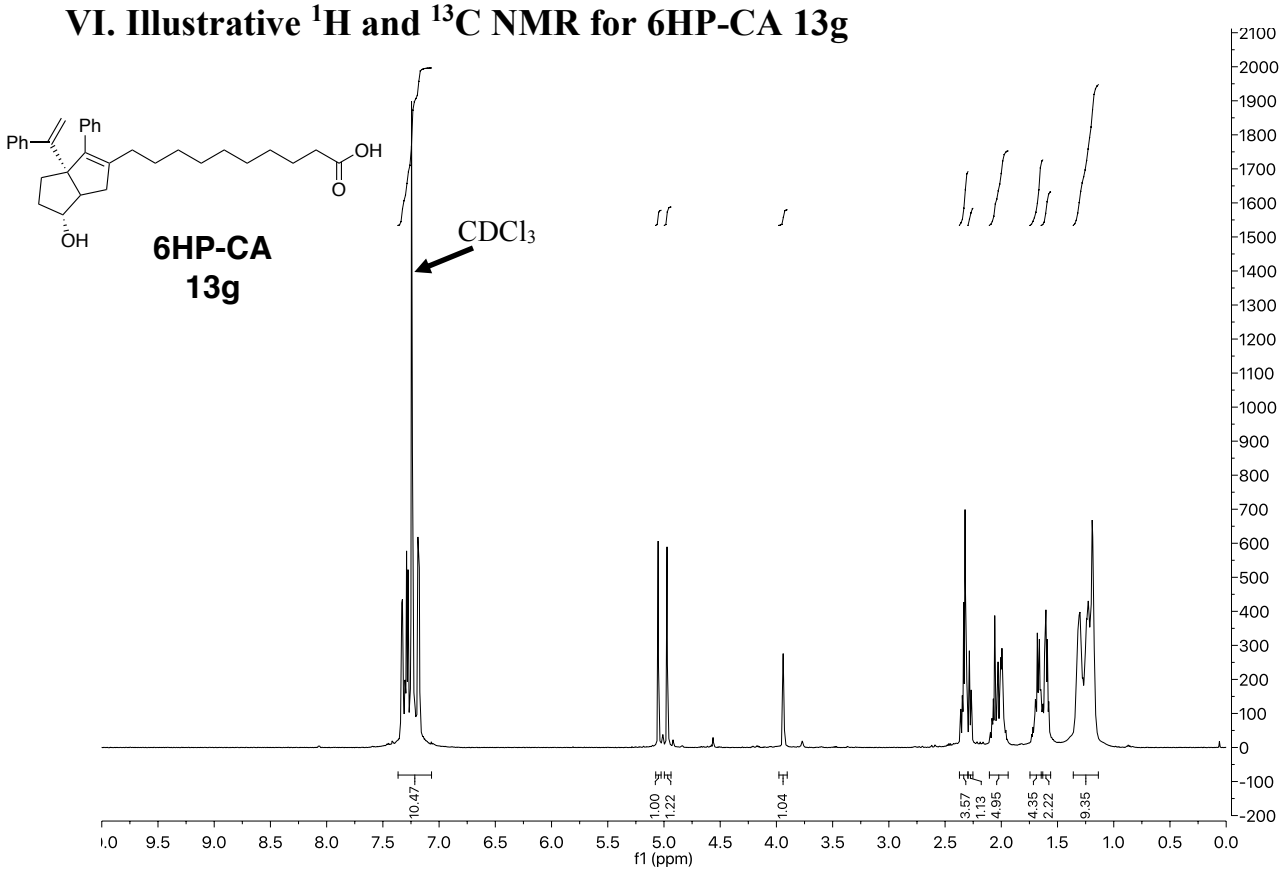


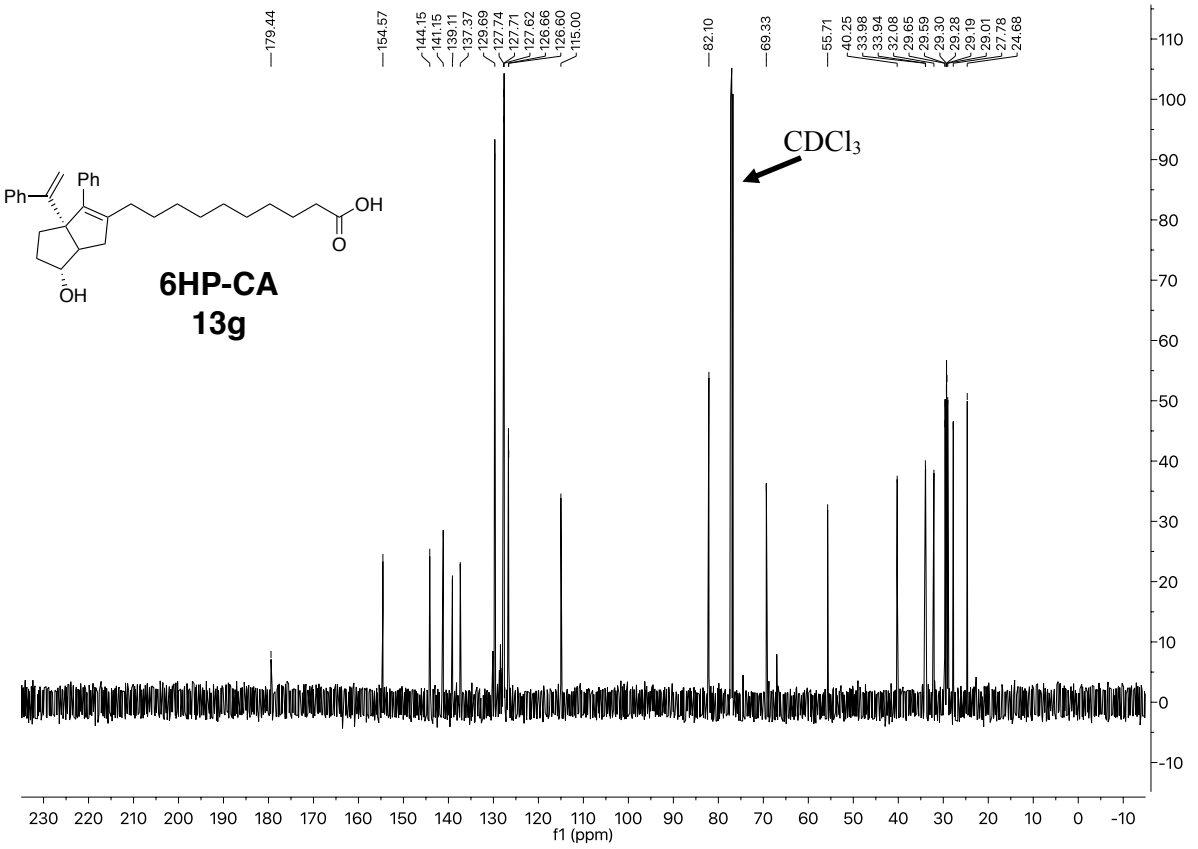
10-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)decanoic acid (6HP-CA, 13g): **S2g** (498.2 mg, 0.96 mmol) was reacted and purified according to the general procedure to give the title compound as a clear, colorless oil (434.9 mg, 95%). Purity was established as the *exo* diastereomer using Method A: 98.5%, t_R = 3.64 min.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.15 (m, 10H), 5.07 (d, *J* = 1.6 Hz, 1H), 4.99 (d, *J* = 1.6 Hz, 1H), 3.95 (s, 1H), 2.41 – 2.24 (m, 5H), 2.15 – 1.94 (m, 5H), 1.75 – 1.50 (m, 6H), 1.42 – 1.09 (m, 9H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 179.4, 154.6, 144.2, 141.2, 139.1, 137.4, 129.7, 127.74, 127.71, 127.6, 126.7, 126.6, 115.0, 82.1, 69.3, 55.7, 40.3, 34.0, 33.9, 32.1, 29.7, 29.6, 29.30, 29.28, 29.2, 29.0, 27.8, 24.7.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{32}H_{39}O_3$ $[M-H]^-$ 471.3, found 471.3. Calc'd for $C_{32}H_{39}O_2$ $[M-OH]^+$ 455.3, found 454.8
HRMS (ESI) *m/z*: calc'd for $C_{32}H_{39}O_3$ $[M-H]^-$ 471.2905, found 471.2882.
FT-IR (neat): 3360(b), 1708 (s) cm^{-1}.



11-(6-*exo*-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)undecanoic acid (13h): **S2h** (38.9 mg, 0.07 mmol) was reacted and purified according to the general procedure to give the title compound as a clear, colorless oil (30.8 mg, 87%). Purity was established as the *exo* diastereomer by Method A: 98.0%, *exo* t_R = 3.71 min.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.12 (m, 10H), 5.07 (d, *J* = 1.4 Hz, 1H), 4.99 (d, *J* = 1.5 Hz, 1H), 3.99 – 3.92 (s, 1H), 2.38 – 2.26 (m, 5H), 2.11 – 1.98 (m, 5H), 1.75 – 1.58 (m, 6H), 1.36 – 1.17 (m, 11H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 179.4, 154.6, 144.2, 141.2, 139.1, 137.4, 129.7, 127.74, 127.71, 127.6, 126.7, 126.6, 115.0, 82.1, 69.3, 55.7, 40.2, 34.0, 33.9, 32.1, 29.7, 29.6, 29.4, 29.3, 29.2, 29.0, 27.8, 24.7.
LRMS (ESI, APCI) *m/z*: calc'd for $C_{33}H_{41}O_3$ $[M-H]^-$ 485.3, found 485.3. Calc'd for $C_{33}H_{41}O_2$ $[M-OH]^+$ 469.3, found 468.9
HRMS (ESI) *m/z* : calc'd for $C_{33}H_{41}O_3$ $[M-H]^-$ 485.3061, found 485.3065.

VI. Illustrative ^{1}H and ^{13}C NMR for 6HP-CA 13g



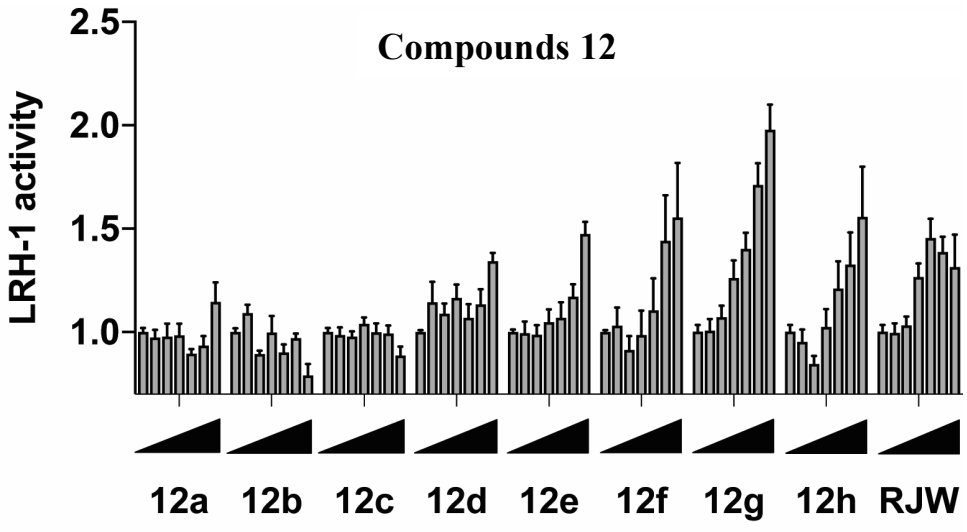


VII. Detailed Biological Procedures.

We performed cellular assays with HeLa cells which were reverse-transfected with three vectors: (1) full-length, human LRH-1 in a PCl vector, (2) a firefly reporter (pGL3 Basic) with a portion of the SHP promoter cloned upstream of the firefly luciferase gene, and (3) a constitutively active vector expressing Renilla luciferase under control of the cytomegalovirus (CMV) promoter. The following day, cells were treated with each compound or vehicle control for 24 hours (in the case of all synthetic compounds, vehicle was DMSO). In most cases, six points in the concentration range of 0.03—30 μM were used, with a final DMSO concentration of 0.3% in all wells. Luciferase expression was measured using the DualGlo Kit (Promega). Firefly luciferase signal was normalized to Renilla luciferase signal in each well. EC_{50} values were calculated using three-parameter curve-fitting (GraphPad Prism, v.7). Assays were conducted in triplicate with at least two independent biological replicates.

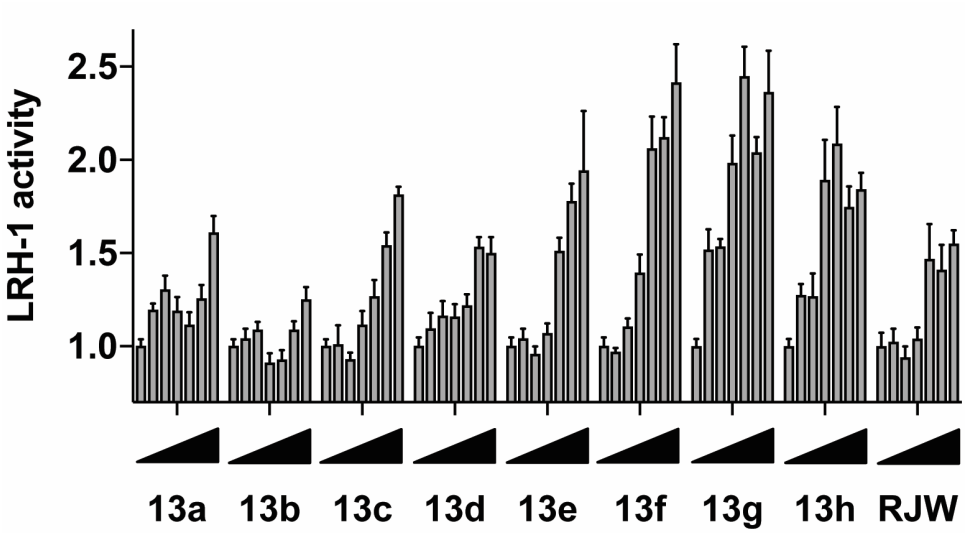
DLPC was purchased from Avanti Polar Lipids (Alabaster, AL) and dissolved in ethanol for delivery to cells (with a final concentration of 0.3% ethanol in each well). A concentration range of 0-100 μM was used. Fold change in LRH-1 activation for DLPC-treated cells was calculated relative to response in cells treated with 0.3% ethanol vehicle alone.

VIII. Additional Activity Data.



Compound	EC_{50} (μM)	Maximum LRH-1 Activity (curve fit)	Maximum LRH-1 Activity (SEM)
12a	N/A	inactive	--
12b	N/A	inactive	--
12c	N/A	inactive	--
12d	N/A	inactive	--
12e	>30	4	7
12f	2 +/- 3	2.3	0.2
12g	5 +/- 2	2.1	0.1
12h	5.1 +/- 0.5	1.4	0.06

Compounds 13



Compound	EC_{50} (μM)	Maximum LRH-1 Activity (curve fit)	Maximum LRH-1 Activity (SEM)
13a	N/A	inactive	--
13b	N/A	inactive	--
13c	9 +/- 3	2	0.1
13d	4 +/- 3	1.6	0.1
13e	4 +/- 2	2.1	0.1
13f	1.8 +/- 0.7	2.5	0.1
13g (6HP-CA)	0.4 +/- 0.4	2.3	0.2
13h	0.3 +/- 0.3	1.9	0.1