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Alyssa Miranda Johnson Date

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Investigation of the Bridgehead Substituent of the Leading LRH-1 Agonists

By

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Master of Science

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Investigation of the Bridgehead Substituent of the Leading LRH-1 Agonists

By

Alyssa Miranda Johnson
B.S., College of Charleston, 2018

Advisor: Nathan T. Jui, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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Abstract

Investigation of the Bridgehead Substituent of the Leading LRH-1 Agonists

By Alyssa Miranda Johnson

Liver Receptor Homolog-1 (LRH-1) is a nuclear receptor of the NR5A class and has been implicated in several disease states, most importantly type 2 diabetes (T2D), and colitis. As a result, the receptor is an attractive therapeutic target and great attention has been given to developing a synthetic modulator for LRH-1. Agonists developed in the Jui lab effectively activate and bind to the receptor (2-fold increases in LRH-1activation levels and low nanomolar binding constants), however, they are held back by their hydrophobicity and biologically unstable substituents. Major modification of the agonists has been impeded by the synthetic difficulty presented by the requisite reaction to produce the characteristic bicyclic hexhydropentalene (6HP) core. We sought to improve the pharmacological traits of our compounds by 1) removing the large, lipophilic styrene, a previously required substituent and 2) modifying the anion capped alkyl tail with various carboxylate surrogates that should both increase the metabolic stability and solubility of the compounds. We successfully overcame the synthetic difficulties presented by our agonists and developed a modular route that excludes the styrene unit; however, these compounds have proven to be more viable as potential LRH-1 antagonists. Replacement of the carboxylate tail with substitutes has proven fruitful and the development of a hybrid combining the most attractive features of previous agonists and the isostere analogues is currently underway.

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Finally, I would like to thank my lab mates in the Jui Lab. Cecie, you are my best friend and I truly value getting to have you as a partner throughout this experience. We entered this program together, joined the same lab, sat in the same office, and I am so grateful that we did. Jeff, thank you for teaching me so much. You have been an amazing mentor to me, and your guidance has been invaluable. Racheal, Kelly, and Cam: thank you for always answering my questions, laughing with me, and supporting me. I feel privileged to have worked with such talented and intelligent chemists during my time at Emory.

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List of Abbreviations:

AcOH: acetic acid

Eq: equivalent

DLPC: dilaurylphosphatidylcoline

DCM: dichloromethane

DMF: dimethylformamide

FP: fluorescence polarization

GSK: GlaxoSmithKline

LRH-1: Liver Receptor Homolog-1

Me: methyl

MeCN: acetonitrile

MeOH: methanol

mg: milligram

mmol: millimole

Ph: phenyl

T2D: type 2 diabetes

TBS: tertbutyl dimethyl silane

tBu: tert-butyl

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TEA: triethylamine

Tf: triflate

THF: tetrahydrofuran

TPAP: tetrapropylammonium perruthenate

6HP: hexahydropentalene

Introduction

Liver Receptor Homolog-1 (LRH-1) is a transcription factor of the NR5A class of nuclear receptors and is known for its role in lipogenesis, bile acid biosynthesis, glucocorticoid synthesis, and embryonic development.[1,2,3,4] LRH-1 is found in a myriad of tissues, most notably the heart, the liver, and the intestine. The abundance of the receptor throughout the body and its role in these vital processes has spurred major interest in developing therapeutics that target LRH-1 for the treatment of metabolic and inflammatory diseases.

Activation of LRH-1 in the liver modulates bile acid synthesis, insulin sensitivity, and glucose homeostasis.[5] These effects are important for treating type 2 diabetes (T2D), as the hallmarks of the disease are insulin resistance as well as increased and unregulated blood-glucose levels.[6] With higher LRH-1 activity, increased bile acid levels reduce lipogenesis and the accumulation of fat in the liver, decreasing liver steatosis.[5] This is desirable because T2D and insulin resistance are known to be tightly correlated to liver steatosis.[5]

In the intestine LRH-1 is a promising therapeutic target for colitis because its activation results in a localized increase in anti-inflammatories and a decrease in pro-inflammatories.[7] This is ideal because colitis is characterized by a chronic inflammation which results in necrosis of the intestinal lining. Current available pharmaceuticals that treat the disease result in an overall decrease in inflammation and bind to excess inflammatory signaling proteins, necessitating a more selective therapeutic. LRH-1 is also known to play a major role in intestinal cell renewal which would be vital in restoring necrotic tissue, a feat current drugs on the market are incapable of doing. Instead, current therapeutic agents focus on alleviating symptoms and preventing future damage.

The endogenous ligand of LRH-1 is unknown, though it is hypothesized that phospholipids, like dilaurylphosphatidylcoline (DLPC) (Figure 1, top left), may serve as native ligands for this important receptor.[8] DLPC has proven the utility of treating LRH-1 as a therapeutic target for T2D. Activation of LRH-1 by DLPC has been shown to restore insulin sensitivity to diet-induced obese mice.[5] Unfortunately, phospholipids are not viable candidates for therapeutics because of their low potency and poor pharmacological properties. Therefore, focus has shifted to synthetic compounds. The first synthetic modulators of LRH-1 were discovered in a high throughput screen done in collaboration between GlaxoSmithKline (GSK) and Dr. Richard J. Whitby (University of Southampton), in which they discovered RJW100 (EC_{50} = 1.1 µM) (Figure 1, bottom left) after a second round of SAR.[9,10] While exciting, the compound's lipophilicity and inadequate EC_{50}, required further improvement. The binding pose of RJW100 was unknown, however, impeding its development into a viable agonist.

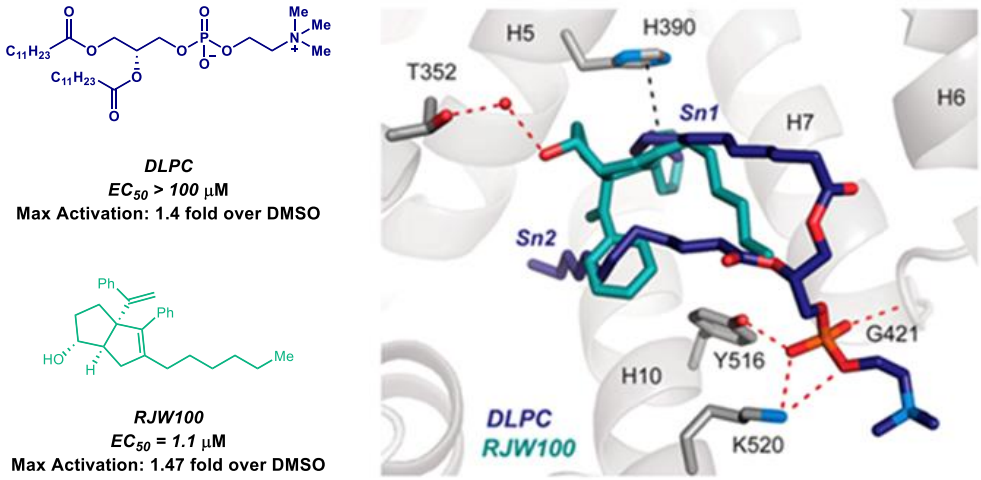


Figure 1. (Left) Previously known modulators of LRH-1 activity. (Right) Crystal structures of DLPC (navy) and RJW100 (teal) bound to LRH-1. Figure adapted from Flynn et al.[11]

The Ortlund lab (Emory University, biochemistry) elucidated the crystal structures of both DLPC and RJW100 bound to LRH-1. It was revealed that the phospholipid achieves LRH-1

activation through a variety of polar interactions at the mouth of the receptor's binding pocket (Figure 1, right).[12] In contrast, the hydroxyl moiety of RJW100 engages in through-water hydrogen bonding deep within the pocket (Figure 1, right).[13] With this new structural and mechanistic information of how LRH-1 is activated, two distinct SAR studies were undertaken: 1) we hypothesized that extension of the tail of RJW100 and termination with a polar group would combine desirable features of both DLPC and RJW100 and 2) we questioned whether elaboration of the hydroxyl group of RJW100 could increase binding and agonism. With these two initial strategies, the Jui lab has indeed shown that synthetic modulators of LRH-1 are capable of reaching high levels of activation and potency (Figure 2).

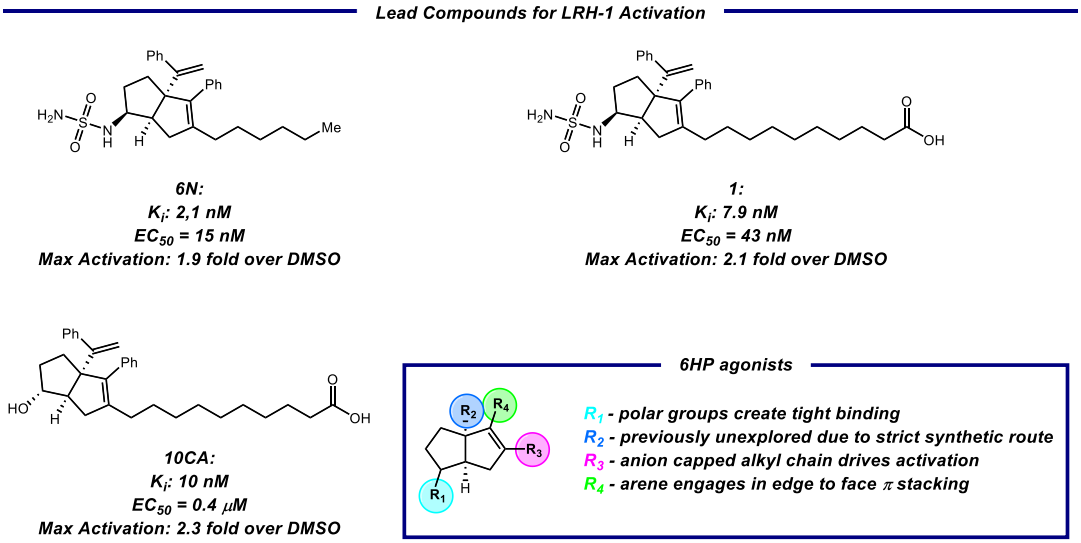


Figure 2. Leading LRH-1 agonists developed in the Jui lab through rational SAR studies

According to these plans, we set out to exploit the same polar contacts made by DLPC at the mouth of the pocket by extending the hexyl tail of RJW100 to 10 carbons and installing a polar group (carboxylate). This work ultimately resulted in LRH-1 agonist 10CA (Figure 2). This compound mimics DLPC through the anionic group and makes the same desired connections as the phospholipid at the mouth of the pocket (Figure 3, Left). 10CA displays a 2-fold increase in LRH-1 activation compared to basal levels (RJW100 had a max LRH-1 activation of 1.47).[11]

Expanding upon the through water connection that RJW100's hydroxyl group engages in prompted the first nanomolar agonist for LRH-1, 6N (Figure 2). By displacing water with a tetrahedral, polar, H-bonding group such as a sulfamide, a direct connection to the Thr352 residue was made as well as peripheral Met345 and Arg393 residues (Figure 3, Right). This modification significantly improved the binding affinity and potency of our compounds to 15 nM (6N).[14] A combination of these modifications led to a hybrid agonist (**1**) (Figure 2) that maintains the tight binding and potency gained in these studies.

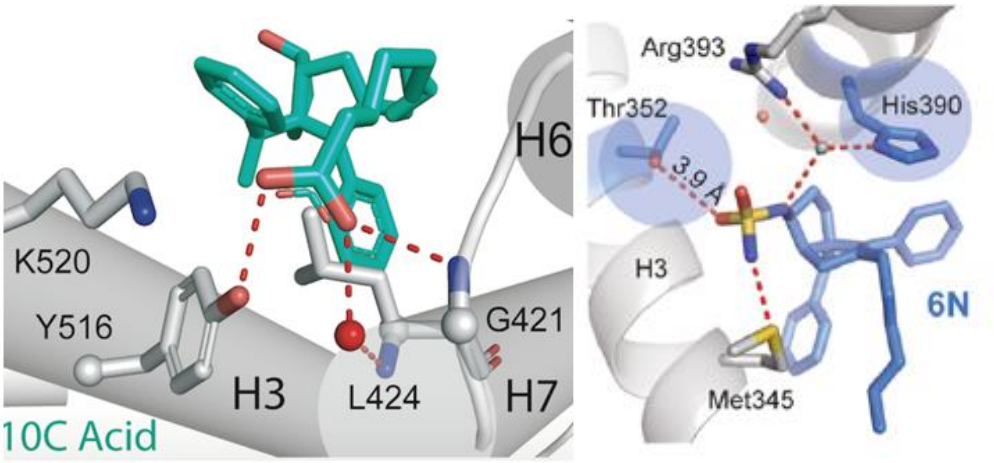


Figure 3. Left: Crystal structure of 10CA in the LRH-1 binding pocket. Right: Crystal structure of 6N in the LRH-1 binding pocket. Figure adapted from Mays et. al.[14]

While these advancements have been substantial in developing probes for LRH-1 biology, in the context of therapeutic development, these agonists are practically hampered by their lipophilicity and an inflexible (functional group intolerant) synthesis that hampers rapid analog production. The compounds in our library contain large, biologically fragile, lipophilic groups resulting in CLogP values over 7, well above suggested values for therapeutics. Meanwhile, harsh reaction conditions (the use of several equivalents of n-butyl lithium), as well as little to no synthetic flexibility, has impeded major modification of the characteristic 6HP core. (Figure 5, top)

Here, we aim to improve solubility and increase synthetic modularity to develop viable therapeutics for diabetes and colitis. We have chosen to investigate the necessity of the lipophilic and metabolically unstable exocyclic styrene (Figure 4, shown in blue). This bridgehead substituent has largely gone uninvestigated due to the strict reaction requirements (Figure 5, middle left) of the cyclization reaction used to create the 6HP core. The cyclization relies on a phenylacetylide-promoted zirconate rearrangement to terminate the reaction, resulting in a 1,1-disubstituted alkene at the bridgehead position. Encouraged by crystal structures suggesting the styrene does not make any specific contacts within the binding pocket (Figure 1, right), we set out to develop a new synthetic route excluding the group. We envisioned its removal would drastically improve solubility while maintaining activity and binding. Elimination of the group would also aid in the biological stability of the compounds due to the ability of the styrene to rapidly undergo a variety of oxidative pathways.[15] In addition, we aimed to further develop the anion capped tail by replacing the carboxylic acid (Figure 4, shown in pink) with various surrogates. The acid moiety presented an opportunity to further elaborate the critical polar contacts the carboxylate makes at the mouth of the pocket. Its replacement would also allow for the introduction of numerous heteroatoms into our agonists which would further improve their solubility.

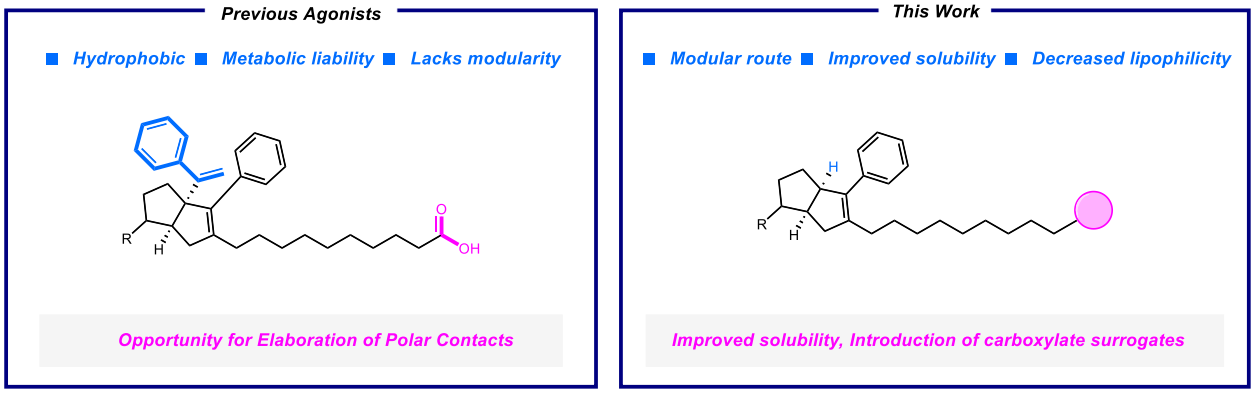
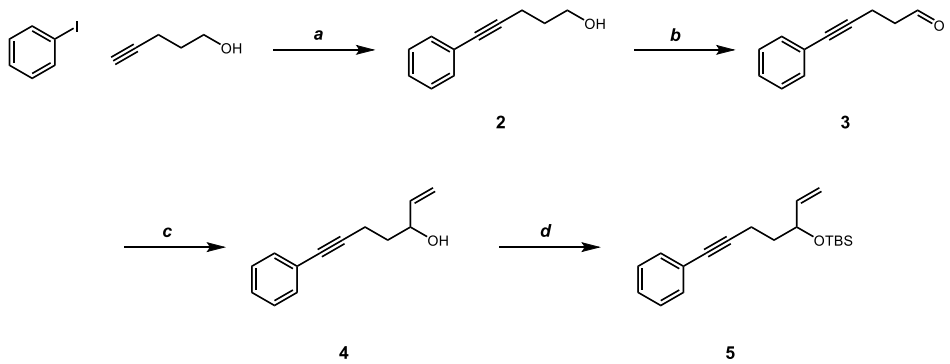


Figure 4. Left: Issues previous agonists developed in the Jui lab face. Right: Goals this work aims to achieve.

Results and Discussion

Removal of the Exocyclic Aromatic Substituent

Synthesis of this new class of LRH-1 agonists bearing no bridgehead substituent followed the typical synthetic route employed by our lab as shown in Scheme 1. This began with a Sonogashira coupling between iodobenzene and pent-4-yn-1-ol to produce **2**. This was followed by oxidation of the primary alcohol to provide a handle for the subsequent Grignard reaction. After the introduction of a vinyl group to produce allylic alcohol **4**, protection of the compound with a silyl group was achieved. This work diverged from the traditional synthetic route after obtaining the requisite enyne (**5**).



Scheme 1. Synthesis of the requisite enyne precursor used for the Pauson-Khand cyclization (*a*) $Pd(PPh_3)_2Cl_2$, CuI, TEA, 60 ℃, 16h; 95% yield. (*b*) $Cu(MeCN)_4PF_6$, NMI, bpy, TEMPO, air, MeCN, 23 ℃, 16 h; 98% yield (*c*) (*i*) $CH_2CHMgBr$, THF, -78 - 23 ℃, 16 h; (*i*) NH_4Cl (*aq*); 68% yield (*d*) TBS-Cl, Imidazole, DCM, 0 - 23℃, 16 h; 91% yield.

To reduce the lipophilicity of our library of agonists we first aimed to remove the exocyclic styrene. To achieve the 6HP core we sought to use a classical Pauson-Khand reaction as an ideal alternative to our previous cyclization conditions because of its mild reaction conditions and scalability (Figure 5, top and middle right). We envisioned that the resulting intermediate **7** could be easily converted to a vinyl triflate, a synthetic handle that would introduce modularity into the previously strict synthetic route to our agonists (Figure 5, bottom). We expected to achieve this transformation by subjecting **7** to conjugate reduction followed by a triflation of the resulting

ketone. Surprisingly, the enone was resistant to a variety of attempts made at reducing the alkene (Table 1).

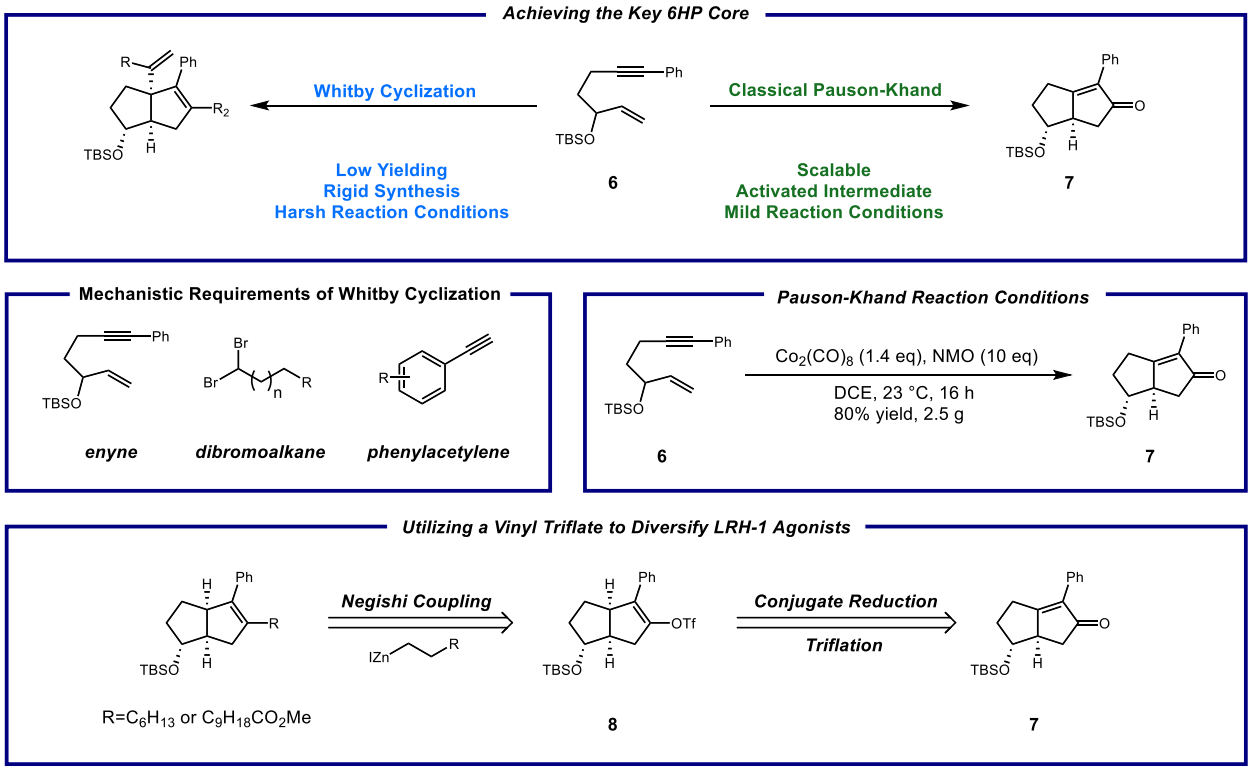
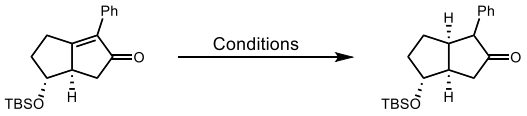


Figure 5. Top: Rationale for developing a more modular synthetic route to the 6HP class of agonists. Middle Left: Required elements of the Whitby Cyclization Middle Right: Pauson-Khand reaction conditions Bottom: Retrosynthesis of coupled Negishi products from **7**.

Our first attempts at conjugate reduction used standard hydrogenation conditions (Table 1, Entry 1). Rather than returned starting material or the desired product **9**, a complex mixture was observed. Based on LCMS and NMR data, we obtained a mixture of over-reduced products where the carbonyl was also reduced to the corresponding alcohol and fully saturated bicyclic ring system. This produced a variety of diastereomers that could not be identified or separated. This was unexpected, however, Pd/C is capable of interacting the carbonyl's π-system. Monitoring the formation of the byproducts over time, as well as varying the temperature (Table 1, Entry 2), proved ineffective at selecting for the formation of the desired product. We also turned our attention to the effects of solvent, as polar solvents, such as ethanol or methanol, have been shown

to promote rapid hydrogenation.[16,17] We expected that by reducing the polarity the solvent, we could slow the reactivity of our system and gain selectivity for reduction of the alkene (Table 1, Entries 3-5). While we did not successfully isolate the product from these trials, ^{1}H NMR suggested we were, in fact, selecting for more of the desired product when the reaction was done in acetone compared to the more polar solvents screened. Alternative attempts made at conjugate reduction included L-Selectride, known to selectively reduce enones, as well as photoredox methods developed in the Jui lab, however, neither produced any detectable product (Table 1, Entries 6 and 7).



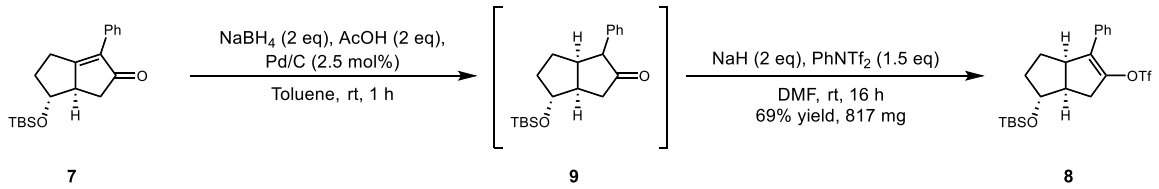
Entry	Conditions	Result
1	H_2, Pd/C, EtOH	Over-reduced products
2	H_2, Pd/C, EtOH, 0 °C	Over-reduced products
3	H_2, Pd/C, Dioxane	Over-reduced products
4	H_2, Pd/C, THF	Over-reduced products
5	H_2, Pd/C, Acetone	Trace product
6	L-Selectride	No observed product
7	Miyake 1, CysH, $NaCHO_2$, Blue LEDs	No observed product
8	**$NaBH_4$, Pd/C, AcOH, PhMe**	**Product is dominant in crude NMR**

Table 1. A variety of conditions attempted to perform the desired conjugate reduction of **7**.

The desired conjugate reduction was finally achieved using a chemoselective borohydride-based method catalyzed by Pd/C (Scheme 2). The chemoselectivity of the method is based on the Pd catalyzed decomposition of the borohydride anion. The active species for the conjugate reduction is the palladium hydride (Pd-H) that forms on the metal surface.[18,19] The proximal aromatic ring may aid in the selectivity of the coordination of the carbon-carbon double bond over the carbonyl π-system as this has been demonstrated in similar conjugated systems.[19] The

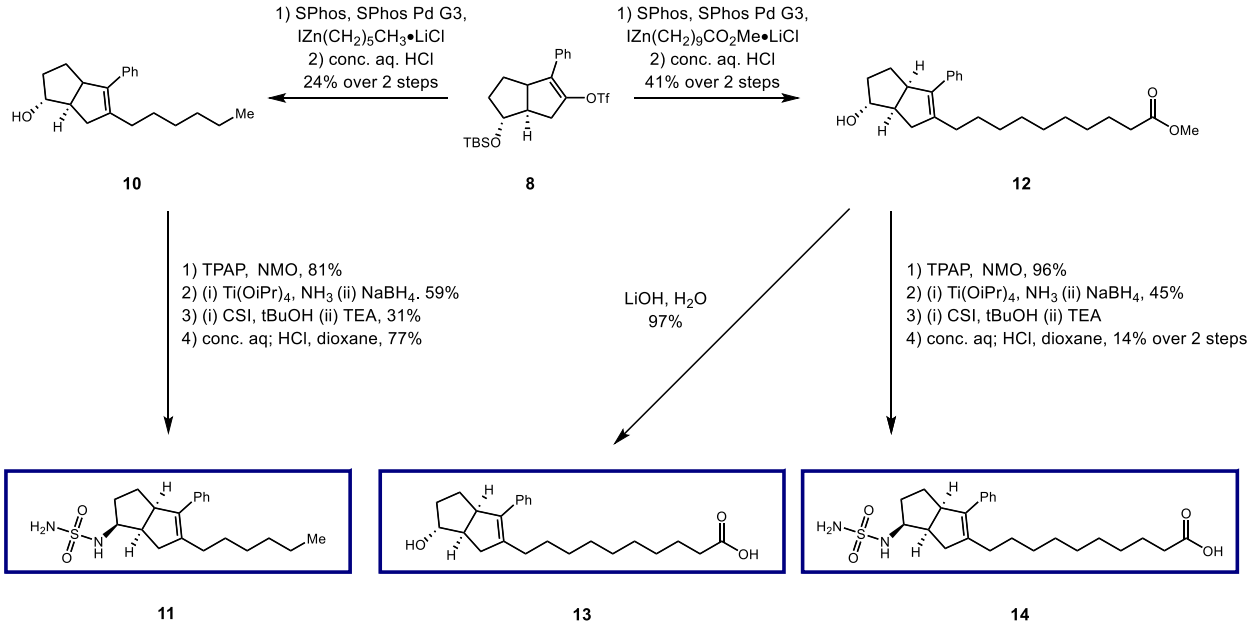
decomposition of the borohydride, as well as the anion's poor solubility in toluene, allowed for a controlled amount of hydrogen to be delivered, allowing this system to avoid overreduction of the enone unlike previous attempts at the transformation.

Despite this promising advancement, we were unable to successfully isolate **9** as rapid decomposition was shown by ^{1}H NMR. We propose the intermediate was undergoing oxidative ring scission upon exposure to air (similar to other cyclopentanone systems that also undergo this decomposition pathway).[20,21] To circumvent decomposition, we placed the crude material under an inert atmosphere and immediately carried it forward. The conjugate reduction and subsequent triflation provided moderate yields that are capable of producing grams worth of valuable triflate (Scheme 2). With this, we now have a modular core that can easily be coupled to various alkyl tails on a sizable scale.



Scheme 2. Optimized reaction conditions to isolate desired vinyl triflate **8**.

The vinyl triflate acted as a synthetic handle for the subsequent Negishi couplings which were followed by TBS deprotection and saponification, producing direct analogues of RJW100 (**10**) and 10CA (**13**) without the bridgehead substituent (Scheme 3). Further modification of **10** and **13** to achieve 6N and 10CA analogues was required. The sulfamide moiety was installed through the oxidation of the exocyclic hydroxyl group, followed by reductive amination with ammonia. The resulting *endo* amine was reacted with freshly prepared boc-protected sulfamoyl chloride. Lastly, the boc-protecting group and the methyl ester were hydrolyzed under acidic conditions to afford **11** and **14**.



Scheme 3. Synthesis of various des-styrene analogues

Using fluorescence polarization (FP) competition ligand binding assays, as well as luciferase activity reporter assays, our collaborators in the Ortlund lab assessed this latest class of LRH-1 agonists. The 6N analogue (**11**) maintained low nanomolar binding affinity (K_i = 56 nM), while the 10CA analogous compound (**13**) had a mid-high nanomolar affinity (K_i = 280 nM). The 10CA/6N analogue (**14**) also possessed a high nanomolar affinity for the receptor (K_i = 521 nM). To our surprise, despite binding quite well to the nuclear receptor, the class of agonists bearing no bridgehead substituent exhibited no measurable activity in the luciferase assays (Figure 6). This suggests that the lipophilic group, while not necessary for binding, is vital for LRH-1 transactivation. Parallel work done in the lab by Jeffery Cornelison aiming to diversify the bridgehead substituent produced a crystal structure of an aniline derivative of 6N (Figure 5). This crystal structure revealed that binding pose of the aniline derivative aligns with that of 6N, however, the analogous bridgehead substituent was flipped in

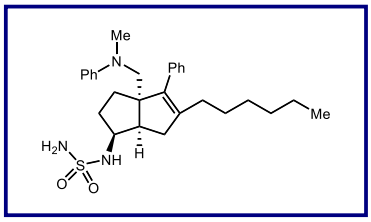


Figure 6. Aniline derivative of 6N produced by fellow members of the Jui Lab

the opposite direction. The pose agrees with our assumption that the bridgehead substituent makes no specific contacts within the pocket, but instead aids in the compound's activity through space-filling and hydrophobic interactions. As a result, we have deemed the lipophilic bridgehead substituent necessary for future iterations of our LRH-1 agonists.

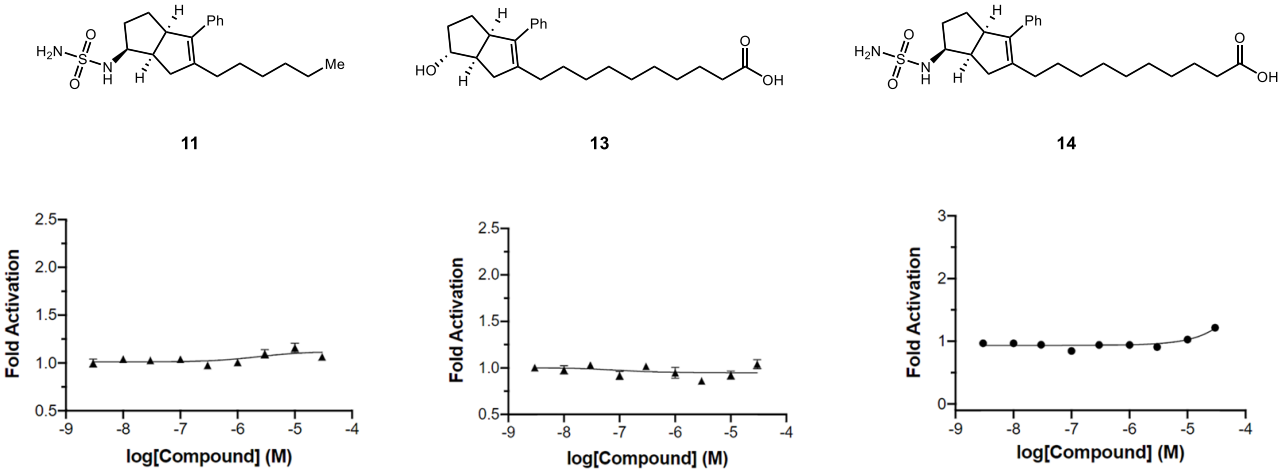


Figure 7. Luciferase reporter data for **11**, **13**, and **14** shown as mean ± SEM from three biological replicates.

Introduction of Carboxylate Substitutes

Previous modification of the alkyl tail proved fruitful with the identification of 10CA, our most active agonist. As such we hoped to further probe the polar interactions made at the mouth of the pocket to gain enhanced activity. The replacement of the carboxylate moiety with surrogates would also aid in solubilizing our agonists as well as potentially improving their metabolic stability. Several carboxylate substitutes contain multiple heteroatoms and are more resistant to biological manipulation. We produced a variety of analogues (Figure 7, left) including hydroxamic acids, amides, and sulfamates according to a general protocol (Scheme **S1)**.

The most promising initial candidate was serine analogue **19**. This derivative was the most attractive due to both its ability to effectively activate LRH-1 (Figure 7, right) and the significant decrease in the CLogP value of the agonist. Our most effective compound (**1)** has a CLogP value of 7.5 while the serine compound is 6.6. The hydroxamic acid analogue (**15**) was discarded despite its activity due to its ability to act as a siderophore and its low affinity for binding compared to **19** (Ki = 268 nM vs 3.0 nM, respectively).

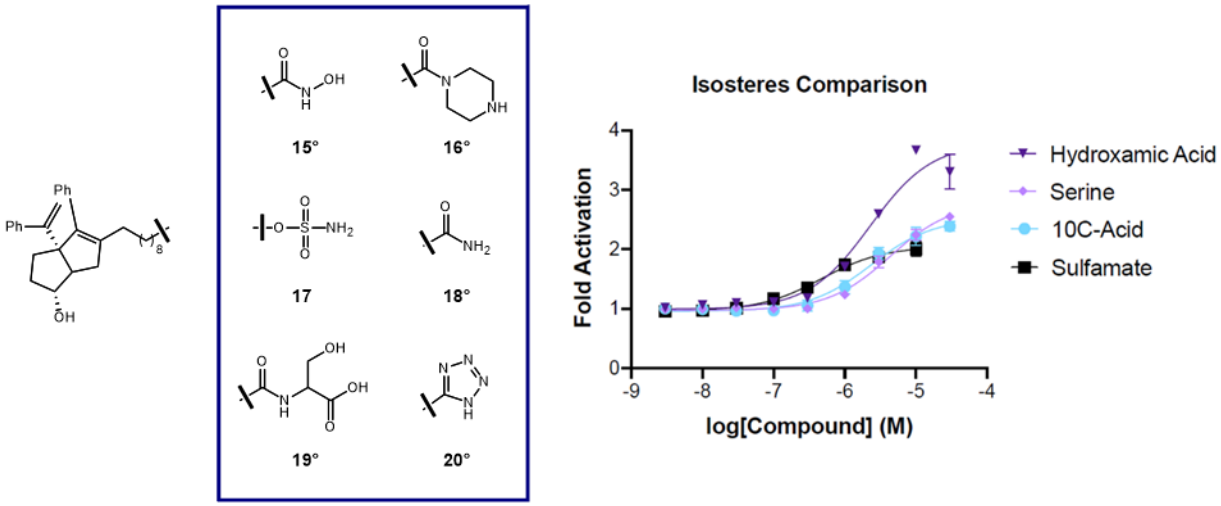
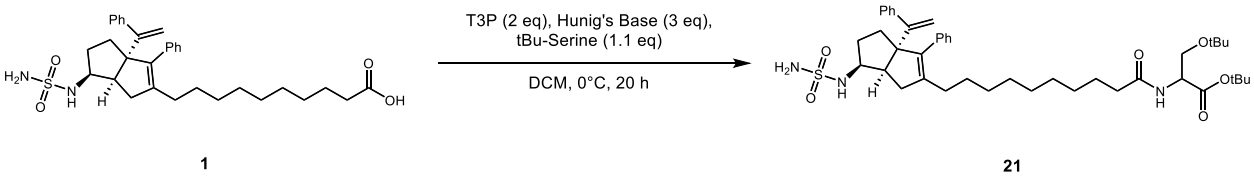


Figure 8. Left: Carboxylate bioisosteres produced in the Jui. Compounds denoted with a ° were synthesized by A. Flynn. Right: Luciferase reporter data comparing the 3 most promising isosteres to 10CA.

With compound **19** in hand, we chose to combine the sulfamide substituent of 6N with the isostere to further improve the efficacy, potency, and solubility of our agonists (Figure 8). We expect that the compound will exhibit similar behavior to **1**, matching 6N and 10CA in efficacy and potency, while also displaying superior solubility compared to its predecessors. Starting from **1**, the carboxylic acid tail was coupled to *tert*-butyl-protected serine using a propylphosphonic anhydride (T3P)-mediated amide coupling to obtain **21** (Scheme 4). Attempts at deprotecting the compound using acidic conditions are currently underway.



Scheme 4. Reaction conditions employed to obtain **21**.

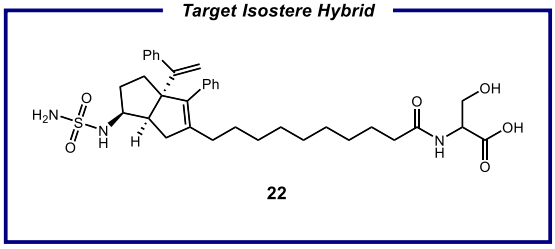


Figure 9. Target hybrid combining the serine headgroup to drive activity and solubility and the sulfamide substituent to drive potency.

Conclusions and Future Work

This work has produced new classes of LRH-1 agonists for the development of viable therapeutics. We successfully developed a synthetic route to agonists with no exocyclic styrene substituent, a large lipophilic group that hindered not only the solubility of our compounds, but also their diversification. Using a chemoselective borohydride-based method we produced analogues of the lab's best agonists that bind with nanomolar affinity to LRH-1. Despite this success in the synthesis, agonists bearing no bridgehead functionality lost all agonistic activity and in fact, induce gene expression profiles similar to compounds aimed at LRH-1 antagonism (Figure 9, left). Specifically, **11** down regulates CYP7A1, a major downstream gene product of LRH-1 that is upregulated when LRH-1 is bound to an agonist. As a result, we have concluded that a large hydrophobic group is required for LRH-1 activation, but the compounds show promise as potential LRH-1 antagonists. Our investigation into further modification of the alkyl chain substituent has produced promising preliminary results, with a serine derivative maintaining efficacy while further solubilizing our compounds.

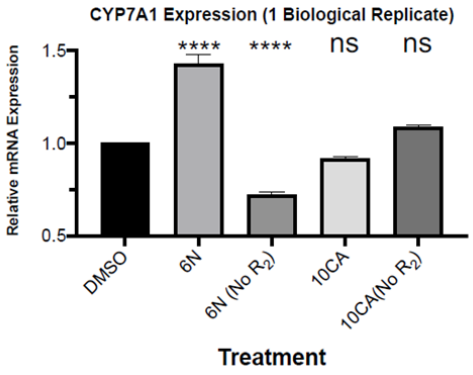


Figure 10. Left: qPCR data comparing the expression of CYP7A1 in cells treated with 6N, 10CA, and their counterparts lacking a bridgehead substituent.

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Experimental:

General 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. 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.

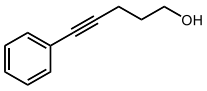
^{1}H and ^{13}C NMR spectra were obtained from the Emory University NMR facility and recorded on a Bruker Avance III HD 600 equipped with cryo-probe (600 MHz), INOVA 600 (600 MHz), INOVA 500 (500 MHz), INOVA 400 (400 MHz), VNMR 400 (400 MHz), or Mercury 300 (300 MHz), and are internally referenced to 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. Liquid Chromatography Mass Spectrometry (LC-MS) was performed on an Agilent 6120 mass spectrometer with an Agilent 1220 Infinity liquid chromatography inlet. Preparative High Performance 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. HPLC analyses were performed using the following conditions.

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, 30% B, t = 4 min, 99% B was employed on 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.

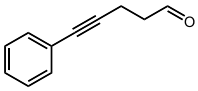
Method B: A linear gradient using water and 0.1 % formic acid (FA) (Solvent A) and MeCN and 0.1% FA (Solvent B); t = 0 min, 70% B, t = 4 min, 99% B was employed on an Agilent Zorbax SB-C18 1.8 micron, 2.1 mm x 50 mm column (flow rate 0.8 mL/min). The UV detection was set to 254 nm. The LC column was maintained at ambient temperature.

Synthesis of agonists bearing no bridgehead substituent

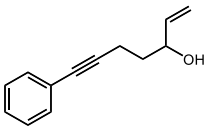


5-phenylpent-4-yn-1-ol (2): Iodobenzene (40 mmol, 4.45 mL), $Pd(PPh_3)Cl_2$ (0.4 mmol, 280 mg), and CuI (1.2 mmol, 228 mg) dissolved in triethylamine (40 mL) and sparged with a nitrogen inlet. After 1 h, a nitrogen inlet was added, sparging stopped, and 4-pentyne-1-ol (48 mmol, 4.5 mL) added. The reaction vessel was then heated to 60 °C for 16 h. Reaction was then cooled to room temperature, exposed to atmosphere and vacuum filtered through a plug of Celite. Filtrate was concentrated under reduced pressure to afford an oil. The crude mixture was purified

by flash chromatography in 5-25% EtOAc/Hexanes (6.124 g, 95% yield). The spectral data reported are consistent with literature. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.36 (m, 2H), 7.29 – 7.25 (m, 3H), 3.81 (t, *J* = 6.1 Hz, 2H), 2.53 (td, *J* = 6.9, 1.3 Hz, 2H), 1.85 (p, *J* = 6.5 Hz, 2H), 1.53 (s, 1H). K. Fuji, T. Morimoto, K. Tsutsumi, and K. Kakiuchi, Chem. Comm., 2005, 0, 3295-3297.

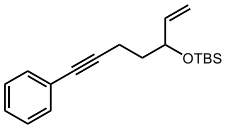


5-phenylpent-4-ynal (3): A round bottom flask was charged with a stir bar, **2** (30.3 mmol, 4.856 g), and MeCN (164 mL). $Cu(MeCN)_4PF_6$ (1.51 mmol, 564.8 mg), bipyridine (1.5 mmol, 236.7 mg), TEMPO (1.51 mmol, 236.7 g), and NMI (3.031 mmol, 241 µL) were each added in single portions to the reaction vessel. The solution was sparged with air over 16 hours. The reaction was diluted with EtOAc and pushed through a plug of silica and concentrated. The oil was isolated (4.795 g, 98 yield) and required no purification. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.84 (t, J = 1.1 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.29 – 7.25 (m, 3H), 2.81 – 2.68 (m, 4H). Park, K. H.; Gung, G. II, Chung, Y. K., Org. Lett. 2004, 6, 1183.

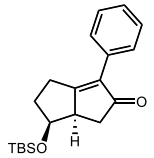


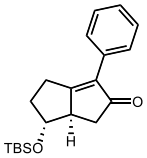
7-phenylhept-1-en-6-yn-3-ol (4): To an oven-dried 3-neck flask equipped with a stir bar was added **3** (32.7 mmol, 5.46 g) in THF (327 mL). The solution was cooled to -78 °C before the addition of vinylmagnesium bromide in THF (1.0 M, 49.0 mmol, 49.0 mL). The reaction was stirred and allowed to warm to room temperature over 16 hours before quenching with saturated ammonium chloride. The reaction mixture was poured over water and extracted with ethyl acetate, dried with Na_2SO4, and concentrated to an oil. The crude mixture was purified by flash chromatography in 10-20% EtOAc/Hexanes (4.1139 g, 68% yield). The spectral data

reported are consistent with literature. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.35 (m, 2H), 7.28 – 7.24 (m, 3H), 5.89 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.28 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.14 (dt, *J* = 10.4, 1.3 Hz, 1H), 4.35 – 4.29 (m, 1H), 2.59 – 2.44 (m, 2H), 1.86 – 1.75 (m, 2H). 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



tert-butyldimethyl((7-phenylhept-1-en-6-yn-3-yl)oxy)silane (5): To a flame dried 3-neck flask equipped with a stir bar and Imidazole (25.8 mmol, 1.75 g) and evacuated and backfilled with nitrogen 3 times. DCM (30 mL) was added to the flask and cooled to 0 °C. Compound **4** (8.586 mmol, 1.60 g) was dissolved in DCM (20 mL) and added to the reaction solution. TBS-Cl (12.878 mmol, 1.94 g) was then added slowly as a solution in DCM (30 mL) and allowed to come to room temp over 16 hours. The reaction was quenched with H_2O and washed with H_2O and brine 2 times each. The organic layers were combined and pushed through a silica plug before being concentrated under reduced pressure to afford the title compound (2.34 g, 91% yield) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 2H), 7.30 – 7.24 (m, 3H), 5.86 – 5.76 (m, 1H), 5.19 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.06 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.29 (tdd, *J* = 6.9, 5.0, 1.3 Hz, 1H), 2.54 – 2.37 (m, 2H), 1.83 – 1.68 (m, 2H), 0.90 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H). 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



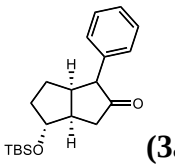


(6,6a)-6-((tert-butyldimethylsilyl**)oxy)-3-phenyl-4,5,6,6a-tetrahydropentalen-2(1H)-one (7):** A round-bottom flask was charged with a stirbar, **5** (13.25 mmol, 3.98 g), $Co_2(CO)_8$ (18.56 mmol, 6.35 g), and 1,2-DCE (530 ml). The resulting solution was stirred at 23 ºC while sparging with nitrogen for 3 h. The sparge was then removed and NMO (132.5 mmol, 15.53 g) added in small portions, using an ice bath to keep reaction approximately 23 ºC as necessary, then continued to stir at 23 ºC for 16 h. The reaction was then pushed through a plug of silica and filtrate concentrated under reduced pressure to a white solid. The crude product was purified by flash chromatography over silica with 1-10% EtOAc/hexane eluent to separate the two diastereomers, with the *exo* isomer (2.5124 g) eluting first then the *endo* isomer (978.1 mg) both as white solids (80% yield of combined diastereomers).

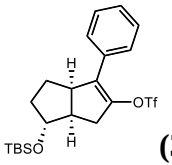
endo diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.0 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.33 – 7.27 (m, 1H), 4.31 (t, *J* = 3.9 Hz, 1H), 3.05 – 2.94 (m, 1H), 2.95 – 2.68 (m, 2H), 2.55 (d, *J* = 5.0 Hz, 2H), 2.35 – 2.21 (m, 1H), 2.04 (ddd, *J* = 13.7, 8.0, 2.6 Hz, 1H), 1.00 – 0.63 (m, 9H), 0.04 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.4, 183.1, 135.6, 132.2, 128.4, 128.3, 127.7, 70.6, 50.9, 37.5, 36.5, 25.9, 25.5, 18.2, -4.4, -4.8. HPLC method A **LRMS** (ESI, APCI) m/z: calc'd for $C_{20}H_{29}O_2Si$ $(M+H)^+$ 329.2, found 328.9.

exo diastereomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.0 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.28 (tt, *J* = 7.4, 2.0 Hz, 1H), 3.76 (td, *J* = 9.2, 7.4 Hz, 1H), 3.04 (dt, *J* = 18.2, 9.5 Hz, 2H), 2.79 (dd, *J* = 17.9, 6.3 Hz, 1H), 2.69 – 2.58 (m, 1H), 2.31 (dd, *J* = 18.1, 3.1 Hz, 1H), 2.27 – 2.18 (m, 1H), 2.13 – 2.00 (m, 1H), 0.89 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ

207.9, 180.5, 136.3, 131.4, 128.5, 128.4, 128.1, 77.6, 51.8, 41.6, 35.3, 26.5, 26.0, 18.2, -4.4, -4.5. HPLC method A **LRMS** (ESI, APCI) m/z: calc'd for $C_{20}H_{29}O_2Si$ $(M+H)^+$ 329.2, found 328.9.

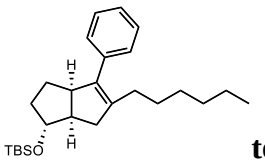


(3a,4,6a)-4-((tert-butyldimethylsilyl**)oxy)-1-phenylhexahydropentalen-2(1H)-one (9):** A round-bottom flask was charged with a stirbar, **7** (2.55 mmol, 839.3 mg), and palladium on carbon (2.5 mol%, 272.3 mg) and then evacuated and backfilled with nitrogen four times. Dry toluene (15 mL) and acetic acid (5.12 mmol, 293 µL) were added to the reaction flask and allowed to stir at 23 °C. The reaction flask was opened briefly and $NaBH_4$ (5.12 mmol, 193.6 mg) was added under positive pressure. The reaction was allowed to stir for 1 h and then quenched with 0.1 M HCl until bubbling ceased before exposing to the atmosphere. The reaction solution was made basic using saturated $NaHCO_3$ solution and quickly extracted two times with EtOAc. The resultant organic layers were dried over Na_2SO_4 and filtered through Celite. Filtrate was concentrated under reduced vacuum to produce a milky oil which was immediately evacuated and backfilled with nitrogen four times to avoid decomposition in air. The oil was then dissolved in dry benzene under nitrogen and was used without further purification in subsequent steps.



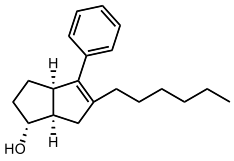
(3a,6,6a)-6-((tert-butyldimethylsilyl**)oxy)-3-phenyl-1,3a,4,5,6,6a-hexahydropentalen-2-yl** trifluoromethanesulfonate **(8):** A flame-dried round-bottom flask was charged with a stirbar and NaH (60% dispersion in mineral oil, 5.1 mmol, 204 mg) then evacuated and backfilled with nitrogen four times. Dry DMF (26 ml) was then added, and the reaction flask was cooled to 0 ºC. **9** (approximately 2.55 mmol) was added slowly as a solution in dry benzene

via syringe. After stirring at 0 ºC for 2 h, $PhNTf_2$ (3.83 mmol, 1.366g) was added as a solid and reaction put back under nitrogen. The resulting mixture was allowed to warm to 23 ºC and stirred 16 h. The mixture was then quenched with EtOAc before exposing to atmosphere and further diluting with EtOAc and H_2O. The organic layer was washed four times with H_2O then brine, dried over Na_2SO_4, and filtered. Filtrate was concentrated under reduced pressure to obtain a brown oil. The crude product was purified by flash chromatography on silica with EtOAc/hexane eluent (1-10%) to obtain the title compound as a clear oil (817 mg, 69% over 2 steps from conjugate reduction). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.7 Hz, 2H), 7.36 (t, J = 7.2 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 3.97 (q, J = 3.8 Hz, 1H), 3.70 (t, J = 8.6 Hz, 1H), 3.07 (dd, J = 17.1, 10.2 Hz, 1H), 2.62 (t, J = 9.8 Hz, 1H), 2.49 (dt, J = 17.0, 3.6 Hz, 1H), 2.11 – 1.99 (m, 1H), 1.73 – 1.51 (m, 2H), 1.43 – 1.35 (m, 1H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.1, 132.5, 131.9, 128.5, 128.3, 128.0, 118.3 (q, *J* = 320.4 Hz), 80.3, 46.8, 45.7, 36.4, 33.5, 28.1, 25.8, 18.0, -4.6, -4.8.



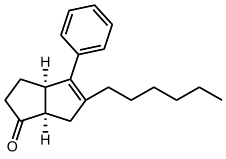
tert-butyl(((1,3a,6a)-5-hexyl-4-phenyl-1,2,3,3a,6,6a-hexahydropentalen-1-yl)oxy)dimethylsilane **(S1):** A round-bottom flask was charged with a stirbar and LiCl (15 mmol, 636 mg) then heated to 140 ºC under vacuum for 10 minutes before cooling again to 23 ºC. Once cooled, zinc (30 mesh, 22.5 mmol, 1.47 g) was added and re-heated to 140 ºC under vacuum for 10 minutes. While cooling back to 23 ºC, the flask was backfilled with nitrogen and evacuated three times. Once the flask cooled, dry THF was added (15 ml) and began stirring vigorously. To the vigorously stirred suspension was added 1,2-dibromoethane (0.75 mmol, 60 µl), trimethylsilyl chloride (0.15 mmol, 10.5 µl), and two drops of a 1M solution of I_2 in dry THF under nitrogen.

Once the yellow color of the I_2 had disappeared (about 10 minutes), 1-iodohexane (15 mmol, 2.21 ml) was added neat via syringe and the solution was heated to reflux for 10 seconds then to 50 ºC. After stirring at 50 ºC for 4 h, a titer for the hexylzinc iodide of 0.50 M was obtained by colorimetric titration of an aliquot with a 1M solution of I_2 in dry THF (equivalence point reached when I_2 color persists with stirring). A separate flame-dried reaction vial was charged with a stirbar, **8** (0.108 mmol, 50 mg), SPhos G3 (5.4 µmol, 4.2 mg), and SPhos (10.8 µmol, 4.4 mg). The reaction vial was evacuated and backfilled with nitrogen four times then dry THF (0.3 ml) added and the resulting solution stirred at 50 ºC. After 5 minutes hexylzinc iodide solution added (0.324 mmol, 0.648 ml) via syringe. The resulting mixture was heated to 50 ºC for 16 h before cooling back to 23 ºC and pushing through a plug of silica with ethyl acetate. Filtrate concentrated under reduced pressure to a black oil. The crude product was used in subsequent steps without further purification.

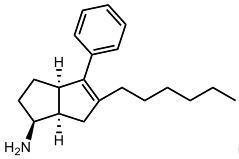


(1,3a,6a)-5-hexyl-4-phenyl-1,2,3,3a,6,6a-hexahydropentalen-1-ol (10): A round-bottom flask was charged with a stirbar and **S1** (approximately 0.108 mmol). The material was suspended in MeOH (2 ml) and DCM was added until all of **S1** had dissolved. The resulting solution was stirred at 23 ºC and two drops of concentrated hydrochloric acid added. After 1 h the reaction was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$, H_2O twice, then brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to collect a crude mixture. The crude mixture was purified by flash chromatography over silica with 10-30% EtOAc/hexanes eluent to collect the title compound (7.5 mg, 24% yield over 2 steps). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (t, J = 7.4 Hz, 2H), 7.23 (dd, J = 7.4, 1.4 Hz, 1H), 7.20

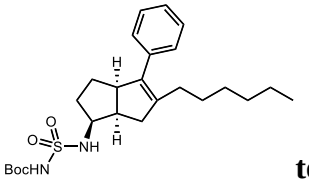
– 7.17 (m, 2H), 4.02 (q, J = 3.5 Hz, 1H), 3.73 (t, J = 8.3 Hz, 1H), 2.77 (dd, J = 17.2, 10.0 Hz, 1H), 2.59 (t, J = 9.2 Hz, 1H), 2.26 (dt, J = 17.1, 3.2 Hz, 1H), 2.19 – 2.09 (m, 1H), 2.09 – 2.00 (m, 1H), 1.91 – 1.82 (m, 1H), 1.69 – 1.61 (m, 1H), 1.61 – 1.54 (m, 1H), 1.48 – 1.33 (m, 3H), 1.31 – 1.18 (m, 6H), 0.87 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.3, 138.2, 137.7, 128.5, 128.0, 126.2, 81.3, 53.3, 48.3, 41.2, 33.4, 31.7, 29.3, 29.2, 28.2, 27.8, 22.6, 14.1. HPLC method B **LRMS** (ESI, APCI) m/z: calc'd for $C_{20}H_{27}$ $(M\text{-}OH)^+$ 267.2, found 267.0.



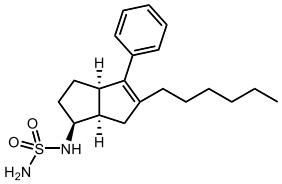
(3a,6a)-5-hexyl-4-phenyl-3,3a,6,6a-tetrahydropentalen-1(2H)-one (S2): A reaction vial was charged with a stirbar, **10** (0.574 mmol, 163.2 mg), and MeCN (5.7 ml). The resulting solution stirred at 23 ºC then TPAP (57 µmol, 20.2 mg) and NMO (5.73 mmol, 672.2 mg) added. The reaction solution continued to stir until **10** was consumed by TLC before eluting through a plug of silica. The resulting crude material was then loaded on silica and eluted with 5-10% EtOAc/hexanes to collect the title compound (130.8 mg, 81% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 (t, J = 7.7 Hz, 2H), 7.26 (tt, J = 6.8, 1.3 Hz, 1H), 7.16 (d, J = 8.1, 1.1 Hz, 2H), 3.96 – 3.91 (m, 1H), 2.78 – 2.62 (m, 3H), 2.24 – 1.89 (m, 5H), 1.87 – 1.81 (m, 1H), 1.43 – 1.31 (m, 2H), 1.29 – 1.13 (m, 6H), 0.85 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 224.2, 141.1, 137.3, 137.0, 128.2,3126.6, 50.9, 48.8, 39.4, 36.1, 31.6, 29.3, 29.2, 27.9, 23.9, 22.6, 14.0. HPLC method B **LRMS** (ESI, APCI) m/z: calc'd for $C_{20}H_{26}O$ $(M+H)^+$ 283.2, found 283.0.



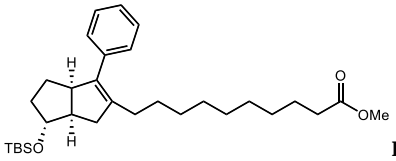
(1,3a,6a)-5-hexyl-4-phenyl-1,2,3,3a,6,6a-hexahydropentalen-1-amine (S3): A reaction vial was charged with a stirbar, **S2** (0.463 mmol, 130.8 mg), $Ti(O^iPr)_4$ (0.694 mmol, 211 µl), and EtOH (4.6 ml) and then sealed. A solution of NH_3 in MeOH (7N, 9.26 mmol, 1.323 ml) was then injected and the resulting solution was stirred at 23 ºC for 6 h before unsealing vial and adding $NaBH_4$ (1.389 mmol, 52.5 mg) and continuing stirring at 23 ºC for 16 h. Reaction was then diluted with EtOAc and saturated aqueous Rochelle's salt and sonicated for 5 min. The resulting slurry was washed two times with saturated aqueous Rochelle's salt, H_2O, then brine. The organic layer was dried over Na_2SO_4, filtered, and filtrate concentrated under reduced pressure to collect the crude material. Crude material purified by flash chromatography on silica with 5:95:0 to 30:69:1 EtOAc:hexanes:Et_3N eluent to collect the title compound as a single diastereomer (99.5 mg, 59% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 (t, J = 7.6 Hz, 2H), 7.23 – 7.17 (m, 3H), 3.59 (t, J = 8.8 Hz, 1H), 3.36 – 3.28 (m, 1H), 2.80 – 2.72 (m, 1H), 2.58 (dt, J = 17.3, 3.5 Hz, 1H), 2.42 (dd, J = 17.3, 9.8 Hz, 1H), 2.21 – 2.13 (m, 1H), 2.13 – 2.04 (m, 1H), 1.71 – 1.64 (m, 1H), 1.60 – 1.46 (m, 1H), 1.46 – 1.32 (m, 2H), 1.33 – 1.17 (m, 9H), 0.86 (t, J = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.2, 138.6, 138.2, 128.5, 127.9, 126.1, 55.9, 53.9, 43.1, 35.8, 33.8, 31.7, 29.3, 28.6, 28.3, 22.6, 14.1. HPLC method B **LRMS** (ESI, APCI) m/z: calc'd for $C_{20}H_{29}N$ $(M+H)^+$ 284.2, found 284.0.



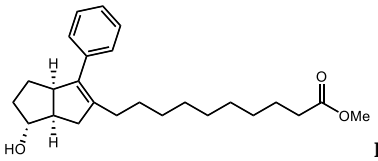
tert-butyl (N-((1,3a,6a)-5-hexyl-4-phenyl-1,2,3,3a,6,6a-hexahydropentalen-1-yl)sulfamoyl**)carbamate (S4):** An oven-dried vial was charged with a stirbar, ^{t}BuOH (1.23 mmol, 91.7 mg), and DCM (12.5 ml) then evacuated under reduced pressure and backfilled with nitrogen three times and cooled to 0 ºC. Chlorosulfonyl isocyanate (1.125 mmol, 97 µl) was then added dropwise via syringe and the solution allowed to warm to 23 ºC over 90 minutes. A 2.64 ml portion of this solution was added slowly via syringe to a solution of **S3** (0.225 mmol, 63.9 mg) and Et_3N (0.451 mmol, 63 µl) in DCM (2.25 ml) at 0 ºC under nitrogen. This combined solution was allowed to warm to 23 ºC gradually 16 h then diluted with EtOAc. The diluted solution was washed with three times with NH_4Cl then H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and filtrate concentrated under reduced pressure to collect the crude material. Crude material purified by flash chromatography on silica with 10:90:0 to 50:49:1 EtOAc:hexanes:Et_3N to give the title compound (32.7 mg, 31% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (t, J = 7.4 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 7.19 – 7.15 (m, 2H), 5.18 (d, J = 7.6 Hz, 1H), 3.76 (dtd, J = 9.7, 7.7, 5.6 Hz, 1H), 3.61 (t, J = 8.7 Hz, 1H), 2.95 (qd, J = 7.9, 5.7 Hz, 1H), 2.55 (d, J = 6.1 Hz, 2H), 2.21 – 2.13 (m, 1H), 2.13 – 2.04 (m, 1H), 1.83 – 1.75 (m, 1H), 1.69 – 1.50 (m, 2H), 1.50 (s, 9H), 1.49 – 1.34 (m, 2H), 1.33 – 1.17 (m, 7H), 0.86 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.1, 139.4, 138.1, 137.5, 128.4, 128.1, 126.4, 83.7, 58.4, 52.9, 41.5, 36.9, 31.6, 30.2, 29.3, 29.2, 28.2, 28.0, 27.9, 22.6, 14.1. HPLC method B **LRMS** (ESI, APCI) m/z: calc'd for $C_{21}H_{30}N_2O_4S$ $(M\text{-}C_4H_8)^+$ 406.2, found 406.8.



N-((1)-5-hexyl-4-phenyl-1,2,3,3a,6,6a-hexahydropentalen-1-yl)sulfamide **(11):** A reaction vial was charged with a stirbar, **S4** (70 µmol, 32.7 mg), and dioxane (530 µL). The solution was frozen in an ice bath and then allowed to slowly warm to 23 ºC. As soon was the entire solution had re-melted, cold concentrated HCl (176 µL) was added so the solution was 3:1 Dioxane: HCl. The solution was allowed to slowly warm to 23 ºC and continue reacting at 40 °C until **S4** was consumed. The reaction solution was diluted with EtOAc and washed four times with H_2O then twice with brine. The organic layer was dried over Na_2SO_4, filtered, and filtrate concentrated under reduced pressure to collect the crude material. This crude material was purified by flash chromatography on silica with 10-40% EtOAc/hexanes to collect the title compound (19.8 mg, 77% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30 (d, J = 7.3 Hz, 2H), 7.20 (tt, J = 7.2, 1.3 Hz, 1H), 7.16 – 7.13 (m, 2H), 4.53 (s, 2H), 4.44 (d, J = 7.7 Hz, 1H), 3.84 – 3.77 (m, 1H), 3.60 (t, J = 8.4 Hz, 1H), 2.96 (dddd, J = 8.4, 4.6, 0.4 Hz, 1H), 2.57 – 2.45 (m, 2H), 2.18 – 2.10 (m, 1H), 2.10 – 2.02 (m, 1H), 1.85 – 1.79 (m, 1H), 1.63 – 1.55 (m, 2H), 1.49 – 1.34 (m, 3H), 1.28 – 1.16 (m, 6H), 0.83 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.2, 138.3, 137.5, 128.4, 128.1, 126.4, 57.9, 53.0, 41.3, 36.9, 31.6, 30.9, 29.3, 29.3, 28.3, 27.9, 22.61, 14.1. HPLC method B **LRMS** (ESI, APCI) m/z: calc'd for $C_{25}H_{30}N_2O_2S$ $(M+H)^+$ 363.2, found 362.9.

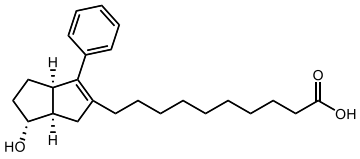


methyl 10-((3a,6,6a)-6-((tert-butyldimethylsilyl**)oxy)-3-phenyl-1,3a,4,5,6,6a-hexahydropentalen-2-yl)decanoate (S5):** A flame-dried reaction vial was charged with a stirbar, **8** (0.700 mmol, 323.8 mg), Sphos G3 (35 µmol, 27.3 mg), and SPhos (70 µmol, 28.7 mg). The reaction vial was evacuated and backfilled with nitrogen four times then THF (2.3 ml) added and began heating to 50 ºC. After 10 minutes, a previously prepared alkylzinciodide solution was added (0.7 M, 2.1 mmol, 3 ml) via syringe. The resulting mixture continued to stir at 50 ºC 16 h before cooling back to 23 ºC and pushing through a silica plug with ethyl acetate. The crude product was carried on to subsequent steps without further purification.

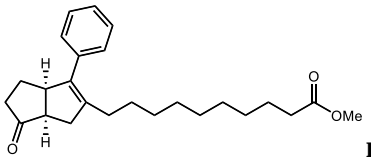


methyl 10-((3a,6,6a)-6-hydroxy-3-phenyl-1,3a,4,5,6,6a-hexahydropentalen-2-yl)decanoate (12): A round-bottom flask was charged with a stirbar and **8** (0.311 mmol, 155.1 mg). The material was suspended in MeOH (10 ml) and DCM was added until it dissolved. The resulting solution was stirred at 23 ºC and two drops of concentrated hydrochloric acid added. After stirring 16 h, the reaction was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$, H_2O twice, then brine. The organic layer was dried over Na2SO4, filtered and concentrated under reduced pressure to collect a crude mixture. The crude mixture was purified by flash chromatography over silica with 10-30% EtOAc/hexanes eluent to collect the title compound (106.3 mg, 41% yield over 2 steps from Negishi coupling). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.4 Hz, 1H), 7.18 (d, J = 7.8 Hz, 2H), 4.01 (q, J = 3.3 Hz, 1H), 3.72 (t, J = 8.8 Hz, 1H), 3.67 (s, 3H), 2.76 (dd, J = 17.1, 9.9 Hz, 1H),

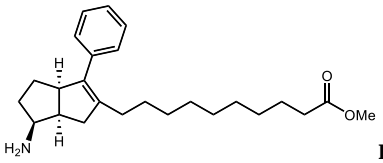
2.58 (t, J = 9.2 Hz, 1H), 2.30 (t, J = 7.6 Hz, 2H), 2.25 (dt, J = 17.1, 3.1 Hz, 1H), 2.17 – 2.09 (m, 1H), 2.08 – 2.00 (m, 1H), 1.90 – 1.81 (m, 1H), 1.69 – 1.52 (m, 4H), 1.44 – 1.32 (m, 2H), 1.32 – 1.17 (m, 11H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.3, 138.3, 138.2, 137.7, 128.4, 128.0, 126.2, 81.3, 53.3, 51.4, 48.4, 41.1, 34.1, 33.4, 29.5, 29.4, 29.3, 29.2, 29.1, 28.2, 27.8, 24.9. HPLC method B **LRMS** (ESI, APCI) m/z: calc'd for $C_{25}H_{35}O_2$ $(M\text{-}OH)^+$ 367.3, found 366.9.



10-((3a,6,6a)-6-hydroxy-3-phenyl-1,3a,4,5,6,6a-hexahydropentalen-2-yl)decanoic acid (13): A reaction vial was charged with a stirbar, **12** (0.287 mmol, 106.3 mg), $LiOH{\cdot}H_2O$ (2.87 mmol, 68.7 mg), and 2 ml of 5:1 THF/H_2O solution. The resulting suspension was stirred at 50 ºC 16 h. The reaction was then acidified with 1 M HCl, diluted with EtOAc and H_2O. The aqueous layer was extracted three times with EtOAc and the organic layers were combined, washed twice with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (100 mg, 97% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.29 (t, J = 7.6 Hz, 2H), 7.19 (tt, J = 7.4, 1.5 Hz, 1H), 7.16 – 7.13 (m, 2H), 3.99 (q, J = 3.6 Hz, 1H), 3.69 (t, J = 10.6 Hz, 1H), 2.73 (dd, J = 16.9, 9.8 Hz, 1H), 2.55 (t, J = 9.2 Hz, 1H), 2.32 (t, J = 7.5 Hz, 2H), 2.22 (dt, J = 17.1, 3.2 Hz, 1H), 2.13 – 2.06 (m, 1H), 2.06 – 1.97 (m, 1H), 1.86 – 1.78 (m, 1H), 1.65 – 1.57 (m, 3H), 1.57 – 1.51 (m, 1H), 1.41 – 1.31 (m, 1H), 1.32 – 1.27 (m, 1H), 1.28 – 1.09 (m, 11H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 179.4, 138.26, 138.25, 137.6, 128.4, 128.0, 126.2, 81.4, 53.3, 48.3, 41.1, 34.0, 33.3, 29.5, 29.3, 29.3, 29.2, 29.1, 29.0, 28.1, 27.8, 24.7. HPLC method B **LRMS** (ESI, APCI) m/z: calc'd for $C_{24}H_{33}O_2$ $(M\text{-}OH)^+$ 353.2, found 353.0.

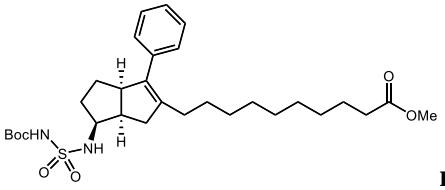


methyl 10-((3a,6a)-6-oxo-3-phenyl-1,3a,4,5,6,6a-hexahydropentalen-2-yl)decanoate (S6): A reaction vial was charged with a stirbar, **13** (0.185 mmol, 71.0 mg), and MeCN (1.8 ml). The resulting solution stirred at 23 ºC then TPAP (18.5 µmol, 20.2 mg) and NMO (1.85 mmol, 216.3 mg) were added. The reaction solution continued to stir until **13** was consumed by TLC before eluting through a plug of silica. The resulting crude material was then loaded on silica and eluted with 5-10% EtOAc/hexanes to collect the title compound (67.6 mg, 96% yield).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.3 Hz, 2H), 7.29 – 7.19 (m, 1H), 7.15 – 7.11 (m, 2H), 3.95 – 3.88 (m, 1H), 3.65 (s, 3H), 2.76 – 2.60 (m, 3H), 2.27 (t, *J* = 7.4 Hz, 2H), 2.24 – 2.04 (m, 2H), 2.02 – 1.75 (m, 3H), 1.59 (q, *J* = 7.6 Hz, 2H), 1.41 – 1.29 (m, 2H), 1.30 – 1.11 (m, 11H). HPLC method B **LRMS** (ESI, APCI) m/z: calc'd for $C_{25}H_{34}O_3$ $(M+H)^+$ 383.3, found 382.9.

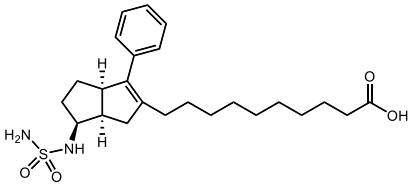


methyl 10-((3a,6,6a)-6-amino-3-phenyl-1,3a,4,5,6,6a-hexahydropentalen-2-yl)decanoate (S7): A reaction vial was charged with a stirbar, **S6** (0.210 mmol, 80.3 mg), $Ti(O^iPr)_4$ (0.315 mmol, 95 µl), and EtOH (2.1 ml) and then sealed. A solution of NH_3 in MeOH (7N, 4.20 mmol, 599 µl) was then injected and the resulting solution was stirred at 23 ºC for 6 h before unsealing the vial and adding $NaBH_4$ (0.630 mmol, 23.8 mg) and continuing stirring at 23 ºC for 16 h. Reaction was then diluted with EtOAc and saturated aqueous Rochelle's salt and sonicated for 5 min. The resulting slurry was washed two times with saturated aqueous Rochelle's salt, H_2O, then brine. The organic layer was dried over Na_2SO_4, filtered, and filtrate

concentrated under reduced pressure to collect the crude material. Crude material purified by flash chromatography on silica with 5:95:0 to 30:69:1 EtOAc:hexanes:Et_3N eluent to collect the title compound as a single diastereomer (36.1 mg, 45% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.2 Hz, 2H), 7.22 – 7.18 (m, 1H), 7.18 – 7.14 (m, 2H), 3.65 (s, 3H), 3.57 (t, *J* = 8.8 Hz, 1H), 3.37 – 3.25 (m, 1H), 2.74 (qd, *J* = 8.4, 4.2 Hz, 1H), 2.55 (dt, *J* = 17.2, 3.1 Hz, 1H), 2.40 (dd, *J* = 17.1, 9.7 Hz, 1H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.20 – 2.04 (m, 2H), 1.64 – 1.46 (m, 2H), 1.48 – 1.28 (m, 2H), 1.30 – 1.17 (m, 14H). HPLC method B **LRMS** (ESI, APCI) m/z: calc'd for $C_{25}H_{37}NO_2$ $(M+H)^+$ 384.2, found 383.9.

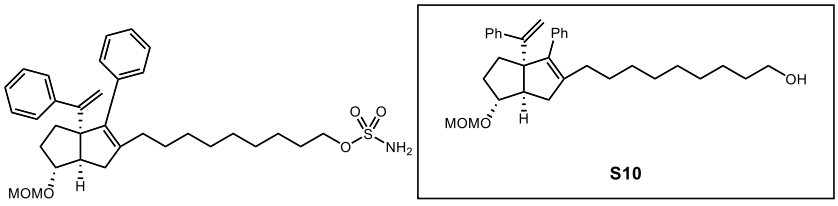


methyl 10-((3a,6,6a)-6-((N-(tert-butoxycarbonyl)sulfamoyl)amino)-3-phenyl-1,3a,4,5,6,6a-hexahydropentalen-2-yl)decanoate (S8): An oven-dried vial was charged with a stirbar, *t*BuOH (1.23 mmol, 91.7 mg), and DCM (11.2 ml) then evacuated under reduced pressure and backfilled with nitrogen three times and cooled to 0 ºC. Chlorosulfonyl isocyanate (1.125 mmol, 97 µl) was then added dropwise via syringe and the solution allowed to warm to 23 ºC over 90 minutes. A 1.63 ml portion of this solution was added slowly via syringe to a solution of **S7** (0.148 mmol, 57.0 mg) and Et_3N (0.297 mmol, 41 µl) in DCM (1.47 ml) at 0 ºC under nitrogen. This combined solution was allowed to warm to 23 ºC gradually 16 h then diluted with EtOAc. The diluted solution was washed with three times with NH_4Cl then H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and filtrate concentrated under reduced pressure to collect the crude material. The material was carried forward without purification.

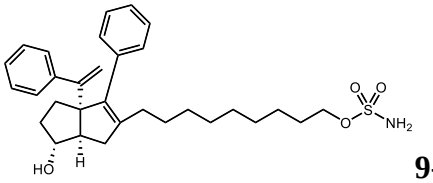


10-((3a,6,6a)-3-phenyl-6-(sulfamoylamino)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)decanoic acid (14): A reaction vial was charged with a stirbar, **S8** (67 µmol, 38.1 mg), and dioxane (507 µL). The solution was frozen in an ice bath and then allowed to slowly warm to 23 ºC. As soon as the entire solution had re-melted, cold concentrated HCl (169 µL) was added so the solution was 3:1 Dioxane: HCl. The solution was allowed to slowly warm to 23 ºC and continue reacting at 40 °C until **S8** was consumed. The reaction solution was diluted with EtOAc and washed four times with H_2O then twice with brine. The organic layer was dried over Na_2SO_4, filtered, and filtrate concentrated under reduced pressure to collect the crude material. This crude material was purified by flash chromatography on silica with 30-45% EtOAc/hexanes to collect the title compound (4.4 mg, 14% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.6 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.1 Hz, 2H), 4.96 (d, *J* = 7.8 Hz, 1H), 4.55 (s, 2H), 3.76 (dtd, *J* = 10.3, 7.8, 5.6 Hz, 1H), 3.55 (t, *J* = 8.7 Hz, 1H), 2.97 – 2.90 (m, 1H), 2.50 – 2.42 (m, 2H), 2.28 (t, *J* = 7.2 Hz, 2H), 2.15 – 2.09 (m, 1H), 2.01 – 1.95 (m, 1H), 1.81 – 1.75 (m, 1H), 1.63 – 1.48 (m, 2H), 1.44 – 1.31 (m, 2H), 1.30 – 1.24 (m, 2H), 1.26 – 1.17 (m, 11H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 177.02, 139.16, 138.37, 137.60, 128.45, 128.13, 126.46, 57.95, 53.10, 41.21, 36.95, 33.28, 30.63, 29.70, 29.11, 28.98, 28.58, 28.42, 28.29, 27.90, 27.82, 24.20. HPLC method B **LRMS** (ESI, APCI) m/z: calc'd for $C_{24}H_{36}N_2O_4S$ $(M+H)^+$ 449.2, found 448.8.

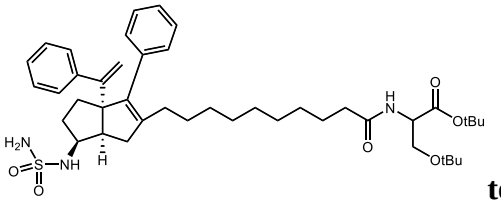
Synthesis of Carboxylate Isosteres



9-((3a,6,6a)-6-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)nonyl sulfamate (S9): An oven dry vial was charged with a stir bar and evacuated and backfilled with nitrogen 3 times. Chlorosulfonyl isocyanate (5.74 mmol, 0.500 mL) was added and placed at 0 °C. Formic acid (5.74 mmol, 0.216 mL) was added to the reaction solution and was allowed to come to room temperature over 16 hours. In a separate oven dry vial **9-((3a,6,6a)-6-(methoxymethoxy)-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)nonan-1-ol (S10**, prepared as previously reported)[11] (0.14 mmol, 70.6 mg) was placed under an inert atmosphere and dissolved in DMA (1 mL). The freshly prepared sulfamoyl chloride (28 µL) was added to the reaction vessel and stirred at room temperature for 16 hours. The solution was diluted with EtOAc and washed 4 times with 1 M LiCl, once with H_2O, and once with brine. The organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica using 5-30% EtOAc/hexanes eluent to collect the title compound (37.9 mg, 46% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 5H), 7.24 – 7.22 (m, 3H), 7.20 – 7.11 (m, 2H), 5.04 (d, *J* = 30.3 Hz, 2H), 4.81 (s, 2H), 4.57 (s, 2H), 4.17 (t, *J* = 6.6 Hz, 2H), 3.77 (s, 1H), 3.30 (s, 3H), 2.39 (d, *J* = 9.2 Hz, 1H), 2.30 (dd, *J* = 17.0, 9.2 Hz, 1H), 2.12 – 1.94 (m, 4H), 1.78 – 1.53 (m, 4H), 1.40 – 1.14 (m, 13H). HPLC method B **LRMS** (ESI, APCI) m/z: calc'd for $C_{33}H_{45}NO_5S$ $(M\text{-}OCH_3)^+$ 536.2, found 535.8.



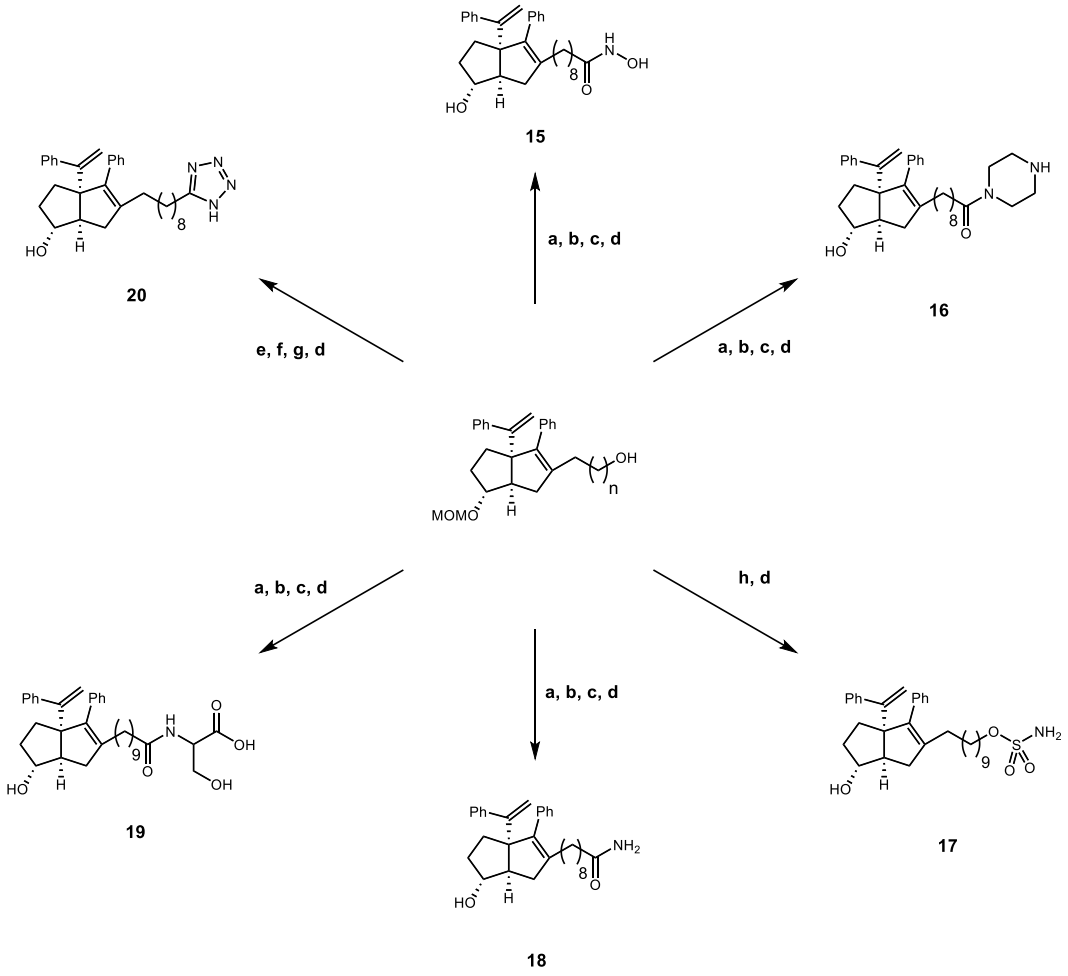
9-((3a,6,6a)-6-hydroxy-3-phenyl-3a-(1-phenylvinyl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)nonyl sulfamate (17): In a reaction vial, **S9** (66 µmol, 37.9 mg) was dissolved in MeCN and a stir bar was added. Concentrated HCl (4 drops) was added to the reaction and it was monitored by LCMS. After all of the starting material was consumed the reaction was concentrated under reduced pressure. The crude material was purified by reverse phase liquid chromatography using a 50-99% MeCN/H_2O gradient over 25 minutes to afford the title compound (14 mg, 40% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 4H), 7.28 – 7.23 (m, 4H), 7.24 – 6.94 (m, 2H), 5.03 (d, *J* = 40.6 Hz, 2H), 4.80 (s, 2H), 4.20 (t, *J* = 6.6 Hz, 2H), 3.95 (s, 1H), 2.36 (dd, *J* = 16.7, 9.3 Hz, 1H), 2.29 (d, *J* = 9.5 Hz, 1H), 2.12 – 1.95 (m, 4H), 1.77 – 1.65 (m, 4H), 1.36 (dd, *J* = 13.8, 7.4 Hz, 2H), 1.33 – 1.05 (m, 11H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.58, 144.15, 141.06, 139.22, 137.36, 129.69, 127.74, 127.71, 127.62, 126.66, 126.60, 115.00, 82.09, 71.52, 69.35, 55.82, 40.23, 34.00, 32.10, 29.61, 29.48, 29.23, 29.18, 28.93, 28.77, 27.71, 25.39. HPLC method B **LRMS** (ESI, APCI) m/z: calc'd for $C_{31}H_4NO_5S$ $(M+H)^+$ 524.2, found 523.8.



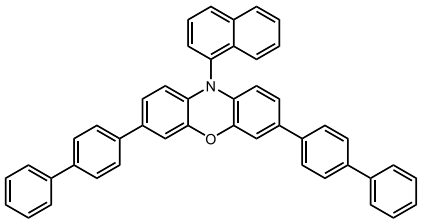
tert-butyl O-(tert-butyl)-N-(10-((3a,6,6a)-3-phenyl-3a-(1-phenylvinyl)-6-(sulfamoylamino)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)decanoyl)serinate (19): An oven dry vial was charged with *tert*-Butyl serine •HCl (7.9 µmol, 2 mg) and a stir bar. The vial was evacuated and backfilled 3 times with nitrogen. As a solution in DCM (0.1 mL), **1** (7.3 µmol, 4 mg) (prepared as previously reported)[21] was added the reaction

vessel followed by Hunig's base (21 µmol, 3.7 µL). The reaction was cooled to 4 °C and T3P (50% in EtOAc, 14.5 µmol, 8.6 µL) was added. The reaction stirred for 20 hours before being quenched at 0 °C with H_2O. The reaction solution was extracted with DCM two times, after which the organic layers were combined and washed with brine. After drying over Na_2SO_4, the solution was filtered and concentrated under reduced pressure. The crude material was purified by reverse phase liquid chromatography using a 75-99% MeCN/H_2O gradient over 20 minutes to afford the title compound (2.5 mg, 45% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 8H), 7.16 (d, *J* = 7.3 Hz, 2H), 5.38 – 5.29 (m, 2H), 5.00 (d, *J* = 55.1 Hz, 2H), 4.65 – 4.57 (m, 1H), 4.53 (s, 2H), 4.39 (t, *J* = 7.9 Hz, 1H), 3.83 – 3.72 (m, 2H), 3.49 (dd, *J* = 8.6, 2.9 Hz, 1H), 2.60 (t, *J* = 8.8 Hz, 1H), 2.41 (dd, *J* = 16.7, 7.2 Hz, 1H), 2.26 – 2.16 (m, 2H), 2.09 – 1.92 (m, 4H), 1.74 – 1.67 (m, 2H), 1.67 – 1.57 (m, 3H), 1.44 (s, 9H), 1.40 – 1.15 (m, 11H), 1.12 (s, 9H). HPLC method B **LRMS** (ESI, APCI) m/z: calc'd for $C_{43}H_{63}N_3O_6S$ $(M+H)^+$ 750. 2, found 749.6.

Supplementary Figures



Scheme S1: (*a)* TPAP, NMO. (*b*) CDI, Hunig's Base, (*c*) Amine, temp. (*d*) HCl. (*e*) Ms-Cl, NEt_3 (*f)* NaCN, (*g*) NaN_3 (*h*) (i) Chlorosulfonyl isocyanate, Formic Acid



Miyake 1

Figure S1: Photocatalyst employed to conjugately reduce enone **7**.