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J Org Chem. Author manuscript; available in PMC 2019 February 02.

Published in final edited form as:

J Org Chem. 2018 February 02; 83(3): 1478–1485. doi:10.1021/acs.joc.7b03032.

Fluorous Phase Approach to α-Hydroxytropolone Synthesis

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Abstract

α-Hydroxytropolones (αHTs) are troponoids that demonstrate inhibition against an array of therapeutically significant targets, making them potential drug leads for several human diseases. We have utilized a recently discovered one-pot three-component oxidopyrylium cycloaddition in a solid-supported synthesis of αHTs. Though the procedure is time efficient and generates assay-ready molecules, the system suffers from low yields and an inability to perform reaction modifications on resin-bound intermediates. In order to combat these issues with the solid-phase platform, we incorporated fluorous tags into our synthetic route. Through the implementation of fluorous phase chemistry, we demonstrate a substantial increase in the overall yield of αHTs, as well as an ability to execute metal-catalyzed cross-coupling and amide coupling on fluorous tagged intermediates. We also show that tagged molecules can be separated from non-fluorous impurities, and vice versa, by utilizing fluorous liquid-liquid and solid-phase extractions. Hence, these proof-of-principle investigations describe the viability of a fluorous phase approach to αHT synthesis, and its potential to serve as a combinatorial technique to produce structurally diverse substrates.

Graphical abstract

Introduction

α-Hydroxytropolones (αHTs) are highly oxygenated troponoids with therapeutic potential against a wide variety of biological targets.[1] Their activity is generally associated with the contiguous array of three oxygen atoms, which bind to and inhibit many bridged dinuclear metalloenzymes (Scheme 1A). Our lab has been investigating an oxidopyrylium cycloaddition/ring-opening procedure that has facilitated the synthesis of a structurally diverse αHT library (Scheme 1B).[2,3] With these molecules in hand, we are currently

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conducting medicinal chemistry studies related to HIV,[4] hepatitis B,[5] herpes simplex virus,[6] aminoglycoside resistance,[7] and fungal pathogens.[8]

During our studies, we recently discovered a one-pot three-component oxidopyrylium cycladdition that generates new oxabicyclic compounds through alcohol incorporation (Scheme 2A).[9,10] Additionally, benzyl alcohol-derived oxabicyclic intermediates produced from this reaction can be directly converted to αHTs when subjected to methanesulfonic acid (Scheme 2B). Considering this information, we developed a solid-phase synthesis of αHTs utilizing polystyrene-supported benzyl alcohol (Scheme 2C).[11] The method is extremely time efficient (i.e. a batch of 8 molecules can be produced in 1.5 days) and provides compounds with assay-ready purity. However, improvements to the system are necessary for it to be completely viable as a combinatorial technique for αHT synthesis. First, though yields for the process are practical for biological screening, they are substantially low overall (i.e. 5-20% yield for 9 substrates). Secondly, the platform does not permit modification of resin-bound intermediates, as conditions for both Suzuki coupling and trifluoroacetic acid (TFA) deprotection cause unintended cleavage (results not reported).

In order to address the issues corresponding with solid-phase synthesis, we turned our attention to a fluorous phase approach. Fluorous phase chemistry allows the successful integration of solution-phase reaction conditions and provides the ability to monitor reactions through conventional analytical techniques that cannot be performed on resin-bound molecules.[12] Also, in relation to traditional organic synthesis, fluorous tagged compounds can be purified easily and efficiently by exclusive techniques based on fluorine-fluorine interactions. These methods include fluorous solid phase extraction (FSPE)[13] and fluorous liquid-liquid extraction (FLLE)[14] that utilize perfluorinated silica and solvents, respectively. The following describes our attempts at synthesizing αHTs by employing fluorous phase synthesis.

Results and Discussion

The integration of fluorous phase chemistry into our synthetic route poses three challenges: 1) verify that fluorous tagged alcohols could successfully be incorporated into oxabicyclic products, 2) assess how well the tagged compounds work with fluorous separation techniques, and 3) demonstrate the capability to remove the tagged segment and form the final product. Our studies began with the preparation of the fluorous tagged benzyl alcohol derivative **10**, which can be generated in high yields through a previously reported approach.[15] Generally, the one-pot three-component oxidopyrylium cycloaddition is conducted under sealed conditions with a surplus of alcohol (5 equivalents in relation to monomeric ylide) to drive the incorporation.[9] Considering the large molecular weight of **10**, slight modifications to our originally optimized procedure were required (Scheme 3A). For instance, the quantity of alcohol was reduced (i.e. stoichiometric with monomeric ylide) to avoid excessive use of starting material. Also, incorporation time was increased to accommodate the lower alcohol concentration. We were able to synthesize the fluorous tagged oxabicyclic compound **11a** with a 34% yield using these adjustments, which is consistent for aryl-containing products obtained through the previously described method.

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However, when larger scale experiments were performed under these sealed conditions, reaction times were significantly increased, yielding little to no incorporation after 6 days. Taking into account our original mechanistic hypothesis for the one-pot three-component oxidopyrylium cycloaddition,[9] we speculated that the lack of conversion was due to the increased generation of methanol (MeOH) that accompanies the scaled up procedure. Since MeOH is more prevalent and trapped within the reactor, the equilibrium of the alcohol incorporation is driven significantly from the fluorous tagged ylide back to **5a**. In order to remove the MeOH byproduct from the reaction, the solvent system was changed to a 2:1 mixture of carbon tetrachloride (CCl_4) and perfluoromethylcyclohexane (C_7F_{14}) and the vessel was exposed to a light stream of argon (Scheme 3B). This solvent combination was chosen not only for its ability to dissolve the quantities of fluorous tagged alcohol necessitated by the reaction but for its higher boiling point (76 °C for both solvents) that supersedes MeOH (64.7 °C). The boiling temperature, along with the argon flow, allows for the evaporation of MeOH without drying out the reaction. Thus, the equilibrium of the alcohol incorporation is shifted towards the product and the reaction time is decreased. With these scale-up alterations, compound **11a** was generated in a 38% yield in approximately 2 days, demonstrating a similar yield to its smaller scale counterpart.

Moving forward, we wanted to test if the newly obtained oxabicyclic product could be purified by fluorous phase separation techniques. Since the fluorine content of **11a** (<50%) is not acceptable for FLLE,[14] we chose FSPE as our starting point. Compound **11a** was purposely contaminated with the non-fluorinated derivative **3a** and loaded onto a 4g column of standard tridecafluoro functionalized silica gel (SiliaBond® Tridecafluoro, Figure 1). Following a typical FSPE procedure,[13] **3a** was extracted with 80% MeOH in water and **11a** was retrieved with acetone. Overall, 94% of **11a** and 93% of **3a** were recovered, proving that FSPE can be used to purify the fluorous tagged oxabicycles.

After demonstrating that it is possible to incorporate fluorous tagged alcohols into our oxabicyclic products and purify them with fluorous extraction, we directed our attention towards the ring-opening/debenzylation phase of **11a** to αHT **4a**. In our previous report,[9] the benzyl-derived oxabicycle **6a** underwent both ring-opening and debenzylation when exposed to liquid- and solid-phase methanesulfonic acid. Upon subjecting **11a** to these conditions, we only observed the ring-opening product, as fluorous tagged tropolone **12a** was isolated in quantitative yields (Scheme 4). The fluorous segment was removed upon returning to our original demethylation procedure (i.e. HBr in acetic acid), and a crude mixture of αHT **4a** and fluorous tagged impurities was obtained. Considering the high fluorine content of the benzylated byproducts (>50%), both FSPE and FLLE were successfully used to purify the final product. With regard to the latter purification method, a 50% solution of methoxyperfluorobutane (HFE-(HFE-7100) in C_7F_{14} proved very effective in separating unwanted contaminants from the αHT (refer to Supp. Info.). Compound **4a** was obtained in 85% yield after FSPE and 95% yield after FLLE.

We found the result described above very promising since it indicates that the electron deficient nature of the fluorous tag introduces stability to our intermediates in harsh media. The added stabilization would allow us to perform modification at multiple stages of our synthetic route, unlike in the case of solid-phase synthesis. To test this hypothesis, we

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synthesized a pair of fluorous tagged oxabicycles (**11j** and **11k**) with functional handles to attempt a series of experiments involving metal catalyzed cross coupling and amide coupling.

Initially, various palladium catalyzed Suzuki reactions, including systems with $Pd(OAc)_2$/JPhos or $Pd(PPh)_4$, were performed on compound **11j** with benzyl and naphthyl boronic acids to complete conversion. The resulting oxabicycles were subjected to ring-opening/debenzylation conditions, and the corresponding αHTs were synthesized and confirmed through NMR analysis (results not shown). Unfortunately, pure final compounds could not be obtained with these procedures due to the presence of phosphine derived byproducts. Such impurities are not very soluble in the nonfluorous mobile phase of FSPE (80% MeOH in water or 70% acetonitrile (ACN) in water), and hence contaminate the fluorous eluent (acetone or MeOH) to the detriment of subsequent reaction purity.

In order to bypass this issue, we moved towards Suzuki conditions that utilize water-soluble SPhos as the activating ligand (Scheme 5).[16] The phosphine byproducts were significantly removed from the intermediate but large amounts of solvent were still necessary during FSPE to achieve adequate purity (refer to Supp. Info.). However, the resulting bisphenyl oxabicyclic intermediate was successfully converted to pure αHT **4j** after ring-opening/debenzylation. Studies on making purification for metal-catalyzed cross-coupling reactions on our fluorous tagged oxabicyclic products more efficient are currently ongoing. Nevertheless, this data demonstrates that modification through a fluorous phase approach is more tolerated than our previously reported solid-phase synthesis.

Moving forward to amide coupling reactions, compound **11k** was used as a starting point to generate fluorous tagged intermediates with carboxylic acid functionalities (Scheme 6). Through a simple reaction sequence involving an acid-mediated deprotection followed by a ring-opening, **11k** was converted to oxabicycle **11l** and tropolone **12l** near quantitatively. Each of these carboxylic acid derivatives was reacted with piperidine in the presence of PyBOP and N,N-diisopropylethylamine (DIPEA) to either produce compound **11m** in 59% yield or **12m** in 84% yield after FSPE and hexane wash. The corresponding αHT was then obtained by two different paths: 1) ring-opening/debenzylation of oxabicycle **11m** and 2) debenzylation of tropolone **12m**. Both steps were purified by FLLE to separate the fluorous tagged impurities from the final product **4m**, demonstrating a divergent synthetic pathway to access an amide-derived αHT with fluorous phase chemistry.

Taking into account that a secondary amine was used during our initial amide modification experiments, we tested if primary amines could also undergo a two path approach to αHTs (Scheme 7). When oxabicycle **11l** was subjected to PyBOP coupling conditions with 1-naphthylmethylamine, major decomposition was observed and the anticipated amide could not be obtained after FSPE. On the other hand, tropolone **12l** was successfully converted to the corresponding amide-derivative **12n** using the PyBOP procedure outlined above and taken further to αHT **4n** in high yields for both steps. Thus, even though the oxabicycle route is limited to more sterically hindered secondary amines, the tropolone pathway can be used to achieve the coupling of both types of amines.

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Conclusion

In summary, we have demonstrated the first fluorous phase synthesis of αHTs utilizing one-pot three-component oxidopyrylium cycloaddition chemistry. In a prior report, we have shown that this reaction could be leveraged towards incorporation of solid-phase resins.[11] Though the method was time efficient and yielded assay-ready compounds, our solid-supported synthesis resulted in low yields and an inability to modify intermediates while attached to the resin. By incorporating fluorous tags instead of solid supports, we have significantly improved reaction output and generated intermediates that can undergo modification through metal catalyzed cross coupling and amide coupling. Studies are currently ongoing to fully optimize this platform in order to make it a combinatorial technique for αHTs.

Experimental Section

General Information

All starting materials and reagents were purchased from commercially available sources and used without further purification, with the exception of CH_2Cl_2, which was purified on a solvent purification system prior to reactions.[17] ^1H, ^{19}F, and ^{13}C NMR shifts were measured using the solvent residual peak as the internal standard and reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, q = quartet, m = multiplet), coupling constant (Hz), integration. Infrared (IR) spectral bands are characterized as broad (br), strong (s), medium (m), and weak (w). Mass spectra were recorded on a spectrometer by the electrospray ionization (ESI) technique with a time-of-flight (TOF) mass analyzer. Microwave reactions were performed via the Biotage Initiator (external IR temperature sensor). Where noted, reaction products were purified via silica gel chromatography using a Biotage® Isolera Prime, with Biotage® SNAP Ultra 10 g or 25 g cartridges, in a solvent system of ethyl acetate (EtOAc) in hexane. Fluorous solid-phase extraction (FSPE) was performed using columns packed with SiliaBond® Tridecafluoro silica gel.

Synthesis of Fluorous Tagged 3-Benzyloxy-8-Oxabicyclo[3.2.1]octenes: 5-methyl-3-((4-(perfluorooctyl)benzyl)oxy)-6-phenyl-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (11a)

Method A. Dimer **9** (24 mg, 0.0856 mmol), benzyl alcohol **10** (91 mg, 0.172 mmol, 2 equiv.), and CH_2Cl_2 (0.25 M, 344 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 0.5-2 mL), and the reaction mixture was heated to 60 °C in silicon bath oil for 36 hr. Phenyl acetylene (378 μL, 3.44 mmol, 40 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 1 hr. The reaction was then immediately purified by column chromatography (silica (10 g), 0% EtOAc/hexane to 20% EtOAc/hexane gradient over 23 column volumes), giving **11a** as a yellow oil (43 mg, 34% yield). *Method B*,. Dimer **9** (200 mg, 0.714 mmol) and benzyl alcohol **10** (751 mg, 1.43 mmol, 2 equiv.) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 10-20 mL) and the vessel was purged with argon (3x). Carbon tetrachloride (2.75 mL) and perfluoromethylcyclohexane (1.38 mL) were added to the sealed reactor, and the reaction mixture was heated to 60 °C in silicon bath oil for 48 hr under

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argon. Phenyl acetylene (3.14 mL, 28.6 mmol, 40 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 2.5 hr. The reaction mixture was evaporated and purified by column chromatography (silica (25 g), 0% EtOAc/hexane to 15% EtOAc/hexane gradient over 17 column volumes), giving **11a** as a yellow oil (401.9 mg, 38% yield). *FSPE Protocol A*,. A Biotage® SNAP Ultra 10 g cartridge was filled with SiliBond® Tridecafluoro silica gel (4 g) and preconditioned with 50:50 MeOH/H_2O. Compound **11a** (46.4 mg, 0.063 mmol) was contaminated with **3a** (13.5 mg, 0.056 mmol), and the mixture was loaded onto the cartridge in $CHCl_3$. The nonfluorous material was provided by elution with 80:20 MeOH/H_2O (40 mL), while the fluorous component was obtained by elution with acetone (40 mL). The resulting fractions were then concentrated, giving **11a** as a yellow oil (43.4 mg, 94% recovery) and **3a** as a white solid (12.6 mg, 93% recovery). The cartridge was washed with MeOH (40 mL) and acetone (40 mL) prior to reuse, and it was recycled up to 30 times. The 1H NMR for **3a** was consistent with previously reported data.[2a] *Characterization of **11a***. R_f = 0.27 in 15% EtOAc in hexanes. **IR (thin film, KBr)** 3060 (w), 2981 (w), 2935 (w), 1712 (s), 1606 (s), 1211 (s), 1150 (s) cm^{-1}. **^{1}H** Hz, 2H), 7.38 – 7.31 (m, 3H), 7.20 – 7.15 (m, 2H), 6.29 (d, *J* = 2.4 Hz, 1H), 6.24 (s, 1H), 5.02 (d, *J* = 2.5 Hz, 1H), 4.97 (d, *J* = 12.7 Hz, 1H), 4.85 (d, *J* = 12.7 Hz, 1H), 1.64 (s, 3H). **^{19}F NMR (376 MHz, $CDCl_3$)** δ -80.8 (t, *J* = 9.9 Hz, 3F), -110.7 (t, *J* = 14.5 Hz, 2F), -121.1 – -121.4 (m, 2F), -121.7 – -122.1 (m, 6F), -122.56 – -122.89 (m, 2F), -126.0 – -126.2 (m, 2F). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 189.7 (s), 158.8 (s), 144.6 (s), 140.0 (s), 133.0 (s), 128.9 (s), 128.9 (t, *J* = 24.4 Hz), 128.8 (s), 127.4 (s), 127.4 (t, *J* = 6.4 Hz), 126.0 (s), 123.2 (s), 122.0 (s), 86.5 (s), 86.1 (s), 68.8 (s), 22.0 (s). **HRMS (ESI TOF)** *m/z*: $[M + Na]^+$ calcd for $C_{29}H_{17}F_{17}O_3Na$ 759.0802.

6-(3-bromophenyl)-5-methyl-3-((4-(perfluorooctyl)benzyl)oxy)-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one (11j)

Dimer **9** (200 mg, 0.714 mmol) and benzyl alcohol **10** (751 mg, 1.43 mmol, 2 equiv.) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 10-20 mL), and the vessel was purged with argon (3x). Carbon tetrachloride (2.75 mL) and perfluoromethylcyclohexane (1.38 mL) were added to the sealed reactor, and the reaction mixture was heated to 60 °C in silicon bath oil for 36 hr under argon. 1-Bromo-3-ethynylbenzene (1.72 mL, 14.3 mmol, 20 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 3 hr. The reaction mixture was evaporated and purified by column chromatography (silica (25 g), 0% EtOAc/hexane to 15% EtOAc/hexane gradient over 27 column volumes), giving **11j** as a yellow oil (366.7 mg, 32% yield). Due to the high cost of 1-bromo-3-ethynylbenzene, fractions containing it were also concentrated (2.029 g, 87% recovery (2.321 g would be 100% theoretical yield of unreacted product)). R_f = 0.29 in 15% EtOAc in hexanes. **IR (thin film, KBr)** 3064 (w), 2982 (w), 2936 (w), 1713 (s), 1605 (s), 1588 (m), 1210 (s), 1151 (s) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.52 – 7.44 (m, 3H), 7.38 – (m, 1H), 7.24 – 7.18 (m, 1H), 7.09 – 7.05 (m, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 6.23 (s, 1H), 5.02 (d, *J* = 2.5 Hz, 1H), 4.96 (d, *J* = 12.6 Hz, 1H), 4.85 (d, *J* = 12.6 Hz, 1H), 1.63 (s, 3H). **^{19}F NMR (376 MHz, $CDCl_3$)** δ -80.8 (t, *J* = 9.5 Hz, 3F), -110.7 (t, *J* = 14.5 Hz, 2F), -121.2 (bs, 2F), - – -122.1 (m, 6F), -122.6 – -122.9 (m, 2F), -126.0 – -126.3 (m, 2F). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 189.3 (s), 157.5 (s), 144.7 (s), 139.9 (s), 135.1 (s), 131.8 (s), 130.3 (s),

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129.1 (s), (t, *J* = 24.3 Hz), 127.4 (s), 127.4 (t, *J* = 6.5 Hz), 124.8 (s), 124.5 (s), 123.0 (s), 121.5 (s), 86.4 (s), 86.1 (s), 68.8 (s), 22.0 (s). **HRMS (ESI TOF)** *m/z*: $[M + Na]^+$ calcd for 836.9904; Found 836.9907.

tert-butyl 5-methyl-2-oxo-3-((4-(perfluorooctyl)benzyl)oxy)-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylate (11k)

Dimer **9** (200 mg, 0.714 mmol) and benzyl alcohol **10** (751 mg, 1.43 mmol, 2 equiv.) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 10-20 mL), and the vessel was purged with argon (3x). Carbon tetrachloride (2.75 mL) and perfluoromethylcyclohexane (1.38 mL) were added to the sealed reactor, and the reaction mixture was heated to 60 °C in silicon bath oil for 48 hr under argon. *tert*-Butyl propiolate (1.96 mL, 14.3 mmol, 20 equiv.) was added to the sealed tube, and the reaction mixture was subjected to microwave irradiation at 100 °C for 1 hr. The reaction mixture was evaporated and purified by column chromatography (silica (25 g), 0% EtOAc/hexane to 10% EtOAc/hexane gradient over 24 column volumes), giving **11k** as a white solid (550.5 mg, 51% yield). M.P. = 109-112 °C. R_f = 0.21 in 10% EtOAc in hexanes. **IR (thin film, KBr)** 2982 (w), 2938 (w), 1703 (s), 1615 (m), 1604 (m), 1197 (s), 1146 (s) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 6.98 (d, *J* = 2.5 Hz, 1H), 6.15 (s, 1H), 5.01 (d, *J* = 2.5 Hz, 1H), 4.86 (d, *J* = 12.5 Hz, 1H), 4.79 (d, *J* = 12.5 Hz, 1H), 1.72 (s, 3H), 1.48 (s, 9H). **^{19}F NMR (376 MHz, $CDCl_3$)** δ -80.7 (t, *J* = 9.9 Hz, 3F), -110.7 (t, *J* = 14.5 Hz, 2F), -121.1 –-121.3 (m, 2F), -121.7 – -122.0 (m, 6F), -122.5 – -122.8 (m, 2F), -126.0 – -126.2 (m, 2F). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 188.7 (s), 162.2 (s), 151.1 (s), 143.8 (s), 139.9 (s), 137.6 (s), 128.9 (t, *J* = 24.4 Hz), 127.5 (s), 127.4 (t, *J* = 6.4 Hz), 121.9 (s), 86.0 (s), 85.6 (s), 82.4 (s), 68.6 (s), 28.2 (s), 21.4 (s). **HRMS (ESI-TOF)** *m/z* $[M + Na]^+$ calcd for $C_{28}H_{21}F_{17}O_5Na$ 783.1010 Found 783.1011.

5-methyl-2-oxo-3-((4-(perfluorooctyl)benzyl)oxy)-8-oxabicyclo[3.2.1]octa-3,6-diene-6-carboxylic acid (11l)

Oxabicycle **11k** (435.8 mg, 0.573 mmol) and 50% trifluoroacetic acid in CH_2Cl_2 (2.2 mL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL), and the reaction mixture was subjected to microwave radiation at 70 °C for 2 min. The organic layer was concentrated under reduced pressure and then subjected to azeotropic removal with CH_2Cl_2 (5 × 2 mL), resulting in a yellowish solid. The solid was washed with hexane (5 × 4 mL) and dried under vacuum to give **11l** as an off-white solid (396.7 mg, >95% yield). M.P. = 144-146 °C. R_f = 0.25 in 10% MeOH in CH_2Cl_2. **IR (thin film, KBr)** 2867 (br), 1708 (m), 1676 (s), 1616 (m), 1605 (m), 1199 (s), 1147 (s) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 2.5 Hz, 1H), 6.17 (s, 1H), 5.10 (d, *J* = 2.5 Hz, 1H), 4.84 (d, *J* = 12.3 Hz, 1H), 4.79 (d, *J* = 12.3 Hz, 1H), 1.77 (s, 3H). **^{19}F NMR (376 MHz, $CDCl_3$)** δ -80.9 (t, *J* = 9.9 Hz, 3F), -110.8 (t, *J* = 14.4 Hz, 2F), -121.3 (bs, 2F), -121.8 – -122.1 (m, 6F), -122.8 (bs, 2F), -126.0 – -126.7 (m, 2F). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 188.1 (s), 167.9 (s), 148.9 (s), 143.9 (s), 142.3 (s), 139.6 (s), 129.1 (t, *J* = 24.3 Hz), 127.6 (s), 127.4 (t, *J* = 6.4 Hz), 121.5 (s), 86.3 (s), 85.5 (s), 68.8 (s), 21.3 (s). **HRMS (ESI-TOF)** *m/z*: $[M + Na]^+$ calcd for $C_{24}H_{13}F_{17}O_5Na$ 727.0384 Found 727.0387.

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5-methyl-3-((4-(perfluorooctyl)benzyl)oxy)-6-(piperidine-1-carbonyl)-8-oxabicyclo[3.2.1] octa-3,6-dien-2-one (11m)

A solution of oxabicycle **11l** (60 mg, 0.0852 mmol), PyBOP (48.8 mg, 0.0937 mmol, 1.1 equiv.), and DIPEA (32.6 μL, 0.187 mmol, 2.2 equiv.) in CH_2Cl_2 (0.04 M, 2 mL) was stirred at room temperature for 20 min in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL). Piperidine (9.3 μL, 0.0937 mmol, 1.1 equiv.) was then added to the sealed vessel, and the reaction mixture was subjected to microwave radiation at 85 °C for 5 min. The mixture was concentrated under reduced pressure and purified by FSPE as described in Protocol A. The acetone layer was evaporated, producing a yellow solid. The solid was washed with hexane (5 × 2 mL) to give **11m** as a white solid (38.7 mg, 59% yield). M.P. = 173-175 °C. R_f = 0.29 in 40% EtOAc in hexanes. **IR (thin film, KBr)** 3070 (w), 2942 (m), 2862 (m), 1711 (s), 1609 (s), 1212 (s), 1151 (s) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.58 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 6.35 (s, 1H), 6.29 (d, *J* = 2.4 Hz, 1H), 5.11 (d, *J* = 2.4 Hz, 1H), 4.85 (d, *J* = 12.2 Hz, 1H), 4.80 (d, *J* = 12.2 Hz, 1H), 3.67 – 3.45 (m, 4H), 1.76 – 1.66 (m, 2H), 1.65 – 1.49 (m, 7H). **^{19}F NMR (376 MHz, $CDCl_3$)** δ -80.7 (t, *J* = 9.9 Hz, 3F), -110.7 (t, *J* = 14.4 Hz, 2F), -121.1 – -121.3 (m, 2F), -121.7 – -122.1 (m, 6F), -122.7 (bs, 2F), -125.8 – -126.5 (m, 2F). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 188.3 (s), 163.6 (s), 150.7 (s), 143.9 (s), 140.1 (s), 128.8 (t, *J* = 24.5 Hz), (s), 127.8 (s), 127.3 (t, *J* = 6.5 Hz), 123.6 (s), 87.4 (s), 87.1 (s), 68.7 (s), 47.9 (s), 42.9 (s), 27.0 (s), 25.8 (s), 24.7 (s), 20.7 (s). **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for 772.1350; Found 772.1352.

Synthesis of Fluorous Tagged Benzyloxy Tropolones: 2-hydroxy-5-methyl-7-((4-(perfluorooctyl)benzyl)oxy)-4-phenylcyclohepta-2,4,6-trien-1-one (12a)

To a solution of **11a** (135.2 mg, 0.184 mmol) in CH_2Cl_2 (0.16 M, 1.15 mL) was added methanesulfonic acid (477 μL, 7.36 mmol, 40 equiv). The reaction mixture was stirred at room temperature for 1 h, at which time it was quenched with phosphate buffer (pH 7, 0.1 M, 5 mL) and extracted with $CHCl_3$ (3 × 5 mL). The organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield a golden brown solid. This solid was washed with hexane (5 × 2 mL) and dried under vacuum to give **12a** as a light brown solid (131.6 mg, >95% yield). M.P. = Decomposes at 155 °C. **IR (thin film, KBr)** 3220 (br), 2917 (w), 2858 (w), 1575 (m), 1564 (m), 1199 (s), 1148 (s) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.67 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.46 – 7.35 (m, 4H), 7.31 (s, 1H), 7.24 – 7.20 (m, 2H), 5.39 (s, 2H), 2.18 (s, 3H). **^{19}F NMR (376 MHz, $CDCl_3$)** δ -80.8 (t, *J* = 9.9 Hz, 3F), -110.6 (t, *J* = 14.3 Hz, 2F), -121.2 (bs, 2F), -121.6 – -122.1 (m, 6F), -122.7 (bs, 2F), -126.0 – -126.2 (m, 2F). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.5 (s), 160.3 (s), 156.6 (s), 145.2 (s), 143.5 (s), 140.7 (s), 135.0 (s), 128.9 (t, *J* = 24.3 Hz), 128.7 (s), 128.2 (s), 127.9 (s), 127.6 (s), 127.6 (s), 127.5 (t, *J* = 6.5 Hz), 122.3 (s), 71.0 (s), 26.5 (s). **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{29}H_{18}F_{17}O_3$ 737.0979 Found 737.0982.

6-hydroxy-2-methyl-5-oxo-4-((4-(perfluorooctyl)benzyl)oxy)cyclohepta-1,3,6-triene-1-carboxylic acid (12l)

To a solution of **111** (116.1 mg, 0.165 mmol) in CH_2Cl_2 (0.1 M, 1.42 mL) was added trifluoromethanesulfonic acid (58.2 μL, 0.659 mmol, 4 equiv). The reaction mixture was

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stirred at room temperature for 30 min, at which time it was quenched with phosphate buffer (pH 7, 1 M, 5 mL). The CH_2Cl_2 was drained and the remaining residue was extracted with EtOAc (3 × 5 mL). All organics were collected, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a yellow solid. The solid was washed with 50% CH_2Cl_2 in hexanes (6 × 2 mL) and dried under vacuum to give **12l** as a light yellow solid (107.3 mg, 92% yield). M.P. = 163-166 °C. **IR (thin film, KBr)** 3442 (br), 1699 (m), 1570 (m), (s) cm^{-1}. **^{1}H NMR (400 MHz, Acetone)** δ 7.85 (s, 1H), 7.49 (s, 1H), 5.50 (s, 2H), 2.56 (s, 3H). **^{19}F NMR (376 MHz, Acetone)** δ -81.6 (t, *J* = 10.1 Hz, 3F), -110.7 (t, *J* = 14.5 Hz, 2F), -121.6 – -121.9 (m, 2F), -122.2 – -122.6 (m, 6F), -123.2 (bs, 2F), -126.6 – -126.9 (m, 2F). **^{13}C NMR (100 MHz, Acetone)** δ 171.8 (s), 170.2 (s), 160.2 (s), 159.2 (s), 142.5 (s), 137.1 (s), 133.8 (s), 128.9 (s), 128.6 (t, *J* = 24.3 Hz), 127.9 (t, *J* = 6.5 Hz), 125.9 (s), 117.0 (s), 71.0 (s), 25.4 (s). **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd $C_{24}H_{14}F_{17}O_5$ 705.0564 Found 705.0570.

2-hydroxy-5-methyl-7-((4-(perfluorooctyl)benzyl)oxy)-4-(piperidine-1-carbonyl)cyclohepta-2,4,6-trien-1-one (12m)

A solution of tropolone **12l** (50 mg, 0.071 mmol), PyBOP (40.6 mg, 0.0781 mmol, 1.1 equiv.), and DIPEA (27.2 μL, 0.156 mmol, 2.2 equiv.) in EtOAc (0.04 M, 1.67 mL) was stirred at room temperature for 20 min in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL). Piperidine (7.7 μL, 0.0781 mmol, 1.1 equiv.) was then added to the sealed vessel, and the reaction mixture was subjected to microwave radiation at 85 °C for 5 min. The reaction mixture was concentrated under reduced pressure and purified by FSPE as described in Protocol A. The acetone layer was evaporated, producing a yellow solid. The solid was washed with hexane (5 × 2 mL) and dried under vacuum to give **4.30m** as a light yellow solid (45.8 mg, 84% yield). M.P. = 183-186 °C. **IR (thin film, KBr)** 3175 (br), 2942 (w), 2861 (w), 1621 (m), 1568 (m), 1202 (s), 1151 (s) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.93 (bs, 1H), 7.63 (s, 4H), 7.17 (s, 1H), 7.16 (s, 1H), 5.36 (d, *J* = 12.8 Hz, 1H), 5.32 (d, *J* = 12.8 Hz, 1H), 3.84 – 3.75 (m, 1H), 3.69 – 3.61 (m, 1H), 3.27 – 3.13 (m, 2H), 2.34 (s, 3H), 1.76 – 1.62 (m, 4H), 1.60 – 1.43 (m, 2H). **^{19}F NMR (376 MHz, $CDCl_3$)** δ -80.7 (t, *J* = 9.9 Hz, 3F), -110.7 (t, *J* = 14.4 Hz, 2F), -121.1 – -121.3 (m, 2F), -121.7 – -122.0 (m, 6F), -122.5 – -122.8 (m, 2F), -125.9 – -126.3 (m, 2F). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.4 (s), 168.6 (s), 161.2 (s), 157.2 (s), 140.2 (s), 138.6 (s), 132.8 (s), 129.1 (t, *J* = 24.3 Hz), 127.6 (s), 127.5 (t, *J* = 6.5 Hz), 126.6 (s), 116.2 (s), 71.0 (s), 47.9 (s), 42.6 (s), 26.6 (s), 25.7 (s), 24.5 (s), 24.2 (s). **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{29}H_{23}F_{17}NO_4$ 772.1350 Found 772.1351.

6-hydroxy-2-methyl-N-(naphthalen-1-ylmethyl)-5-oxo-4-((4-(perfluorooctyl)benzyl)oxy) cyclohepta-1,3,6-triene-1-carboxamide (12n)

A solution of tropolone **12l** (51.7 mg, 0.0734 mmol), PyBOP (42 mg, 0.0807 mmol, 1.1 equiv.), and DIPEA (28.1 μL, 0.161 mmol, 2.2 equiv.) in EtOAc (0.04 M, 1.67 mL) was stirred at room temperature for 20 min in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL). 1-Naphthylmethylamine (11.8 μL, 0.0807 mmol, 1.1 equiv.) was then added to the sealed vessel, and the reaction mixture was subjected to microwave radiation at 85 °C for 5 min. The reaction mixture was concentrated under reduced pressure and purified

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by FSPE as described in Protocol A. The acetone layer was evaporated, producing a yellow solid. The solid was washed with hexane (5 × 2 mL) and ACN (5 × 2 mL) and dried under vacuum to give **12n** as a light yellow solid (53.8 mg, 87% yield). M.P. = 175-177 °C. **IR (thin film, KBr)** 3239 (br), 1666 (m), 1541 (m), 1199 (s), 1146 (s)

Synthesis of α-Hydroxytropolones: 2,7-dihydroxy-4-methyl-5-phenylcyclohepta-2,4,6-trien-1-one (4a)

FSPE Purification. Tropolone **12a** (50 mg, 0.068 mmol) and 33% HBr in acetic acid (197 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL), and the reaction mixture was heated to 120 °C in silicon bath oil for 1 hr. The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 0.1 M, 5 mL), and extracted with $CHCl_3$ (3 × 5 mL). The organic layer was evaporated under reduced pressure and purified by FSPE as described in Protocol A. The 80:20 MeOH/H_2O layer was concentrated to yield **4a** as a white solid (13.2 mg, 85% yield). The ^{1}H NMR for **4.24a** was consistent with previously reported data.[7] *FLLE Purification, Protocol A*. Tropolone **4.30a** (50.5 mg, 0.0686 mmol) and 33% HBr in acetic acid (199 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL), and the reaction mixture was heated to 120 °C in silicon bath oil for 1 hr. The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 0.1 M, 5 mL), and extracted with $CHCl_3$ (3 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give a crude oil. The residue was taken up in ACN (2 mL) and washed with 50% HFE-7100 in perfluoromethylcyclohexane (5 × 2 mL). The ACN layer was concentrated to yield **4.24a** as a brown oil (15.5 mg, >95% yield). The ^{1}H NMR for **4.24a** was consistent with previously reported data.[7]

4-([1,1'-biphenyl]-3-yl)-2,7-dihydroxy-5-methylcyclohepta-2,4,6-trien-1-one (4j)

FSPE Protocol B. Compund **11j** (36.1 mg, 0.0443 mmol), phenyl boronic acid (54 mg, 0.443 mmol, 10 equiv.), water soluble SPhos (23 mg, 0.0443 mmol, 1 equiv.), K_2CO_3 (61.2 mg, 0.443 mmol, 10 equiv.), $Pd(OAc)_2$ (5 mg, 0.0222 mmol, 0.5 equiv.) and 33% ACN in water (0.01 M, 4.5 mL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL), and the reaction mixture was heated to 50 °C in silicon bath oil for 5 hr. The reaction mixture was cooled to room temperature and immediately loaded to a Biotage SNAP Ultra 10 g cartridge that was filled with SiliBond® Tridecafluoro silica gel (4 g) and preconditioned with 30:70 ACN/H_2O. Any remaining residue in the reactor was loaded onto the column with $CHCl_3$, and the nonfluorous material was provided by elution with ACN/H_2O (0% ACN/H_2O to 70% ACN/H_2O gradient over 12 column volumes) and MeOH/H_2O (80% MeOH/H_2O over 3 column volumes). The fluorous component was obtained by elution with MeOH (100% MeOH over 5 column volumes) and the resulting fractions were then concentrated, giving **S2** as a yellow oil (26.4 mg, 73% crude yield).

To a solution of oxabicycle **S2** (26.4 mg, 0.0325 mmol) in CH_2Cl_2 (0.1 M, 325 μL) was added trifluoromethanesulfonic acid (11.5 μL, 0.13 mmol, 4 equiv.). The reaction mixture was allowed to stir for 30 minutes, after which time it was quenched with phosphate buffer (pH 7, 0.1 M, 5 mL) and extracted with $CHCl_3$ (3 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was then

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dissolved in 33% HBr in acetic acid (100 μL) and heated to 120 °C for 1 hr in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL). The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 0.1 M, 5 mL), and extracted with $CHCl_3$ (3 × 5 mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated to give a crude oil. The residue was purified by FLLE according to Protocol A, giving **4j** as a brown oil (8.9 mg, 90% yield over two steps). **IR (thin film, KBr)** 3248 (br), 3059 (w), 2928 (w), 1525 (s), 1277 (s), 1231 (s) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.65 – 7.59 (m, 4H), 7.55 (s, 1H), 7.54 – 7.42 (m, 4H), 7.40 – 7.34 (m, 1H), 7.24 – 7.20 (m, 1H), 2.31 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 167.3, 157.9, 156.6, 144.2, 143.8, 141.8, 140.6, 139.2, 129.2, 129.0, 127.8, 127.3, 127.3, 127.2, 126.6, 124.5, 124.3, 26.6. **HRMS (ESI-TOF)** *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}O_3$ 305.1172 Found 305.1176.

2,7-dihydroxy-4-methyl-5-(piperidine-1-carbonyl)cyclohepta-2,4,6-trien-1-one (4m)

Method A. To a solution of oxabicycle **11m** (39.4 mg, 0.0511 mmol) in CH_2Cl_2 (0.1 M, 511 μL) was added trifluoromethanesulfonic acid (18 μL, 0.204 mmol, 4 equiv.). The reaction mixture was allowed to stir for 30 minutes, after which time it was quenched with phosphate buffer (pH 7, 0.1 M, 5 mL) and extracted with $CHCl_3$ (3 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure producing a brown residue. The crude mixture was then dissolved in 33% HBr in acetic acid (150 μL), and heated to 120 °C for 1 hr in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL). The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 0.1 M, 5 mL), and extracted with $CHCl_3$ (3 × 5mL). The organic layer was then dried over Na_2SO_4, filtered, and concentrated to give a crude oil. The residue was purified by FLLE according to Protocol A, giving **4m** as a brown oil (10.4 mg, 77% yield over two steps). *Method B*. Tropolone **12m** (40 mg, 0.0518 mmol) and 33% HBr in acetic acid (150 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL), and the reaction mixture was heated to 120 °C in silicon bath oil for 1 hr. The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 0.1 M, 5 mL), and extracted with $CHCl_3$ (3 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give a crude oil. The residue was purified by FLLE according to Protocol A, giving **4m** as a brown oil (12.5 mg, 92% yield). *Characterization of 4m*. **IR (thin film, KBr)** 3246 (br), 2940 (s), 2859 (m), 1627 (s), 1541 (s), 1265 (s), 1232 (s) cm^{-1}. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (s, 1H), 7.27 (s, 1H), 3.86 – 3.77 (m, 1H), 3.70 – 3.62 (m, 1H), 3.25 – 3.13 (m, 2H), 2.41 (s, 3H), 1.77 – 1.44 (m, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.7, 168.2, 158.3, 157.8, 137.5, 137.0, 124.3, 118.6, 47.9, 42.7, 26.5, 25.7, 24.5, 24.1. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{14}H_{18}NO_4$ 264.1230 Found 264.1230.

4,6-dihydroxy-2-methyl-N-(naphthalen-1-ylmethyl)-5-oxocyclohepta-1,3,6-triene-1-carboxamide (4n)

Tropolone **12n** (53 mg, 0.0628 mmol) and 33% HBr in acetic acid (185 μL) were placed in a sealed tube reactor (Biotage® microwave reaction vial, 2-5 mL), and the reaction mixture was heated to 120 °C in silicon bath oil for 1 hr. The reaction mixture was cooled to room temperature, quenched with phosphate buffer (pH 7, 0.1 M, 5 mL), and extracted with

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$CHCl_3$ (3 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give a crude oil. The residue was purified by FLLE according to Protocol A, giving **4n** as a brown oil (18.8 mg, 89% yield). **IR (thin film, KBr)** 3263 (br), 3060 (m), 1697 (s), 1640 (s), 1536 (s), 1248 (s) cm^{-1}. **^{1}H NMR (400 MHz, Acetone)** δ 8.28 (d, *J* = 8.3 Hz, 1H), 8.02 (bs, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.64 – 7.46 (m, 4H), 7.42 (s, 1H), 7.34 (s, 1H), 5.07 (d, *J* = 5.7 Hz, 2H), 2.42 (s, 3H). **^{13}C NMR (100 MHz, Acetone)** δ 169.9, 169.1, 159.7, 158.3, 138.7, 138.0, 135.2, 134.9, 132.5, 129.6, 129.1, 127.6, 127.2, 126.8, 126.3, 124.7, 124.3, 119.9, 42.1, 24.3. **HRMS (ESI-TOF)** *m/z*: $[M + H]^+$ calcd for $C_{20}H_{18}NO_4$ 336.1230 Found 336.1233.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors are grateful for financial support from the National Institutes of Health (SC1GM111158). NMR data was in part collected at the City University of New York Advanced Science Research Center (CUNY ASRC), and we thank Dr. James Aramini for his assistance in the collection of this data.

References

1. For lead examples, see Piettre SR, Ganzhorn A, Hoflack J, Islam K, Hornsperger J-M. J Am Chem Soc. 1997; 119:3201–3204.Himmel DM, Maegley KA, Pauly TA, Bauman JD, Das K, Dharia C, Clark AD Jr, Ryan K, Hickey MJ, Love RA, Hughes SH, Bergqvist S, Arnold E. Structure. 2009; 17:1625–1635. [PubMed: 20004166] Didierjean J, Isel C, Querré F, Mouscadet J-F, Aubertin A-M, Valnot J-Y, Piettre SR, Marquet R. Antimicrob Agents Chemother. 2005; 49:4884–4894. [PubMed: 16304149] Tavis JE, Cheng X, Hu Y, Totten M, Cao F, Michailidis E, Aurora R, Meyers MJ, Jacobsen EJ, Parniak MA, Sarafianos SG. PLoS Pathog. 2013; 9:e1003125. [PubMed: 23349632] Hu Y, Cheng X, Cao F, Huang A, Tavis JE. Antiviral Res. 2013; 99:221–229. [PubMed: 23796982] Tavis JE, Wang H, Tollefson AE, Ying B, Korom M, Cheng X, Cao F, Davis KL, Wold WSM, Morrison LA. Antimicrob Agents Chemother. 2014; 58:7451–7461. [PubMed: 25267681] For recent reviews, see Meck C, D'Erasmo MP, Hirsch DR, Murelli RP. Med Chem Commun. 2014; 5:842–852.Liu N, Song W, Schienebeck CM, Zhang M, Tang W. Tetrahedron. 2014; 70:9281–9305. [PubMed: 25400298]
2. (a) Meck C, Mohd N, Murelli RP. Org Lett. 2012; 14:5988–5991. [PubMed: 23167954] (b) Williams YD, Meck C, Mohd N, Murelli RP. J Org Chem. 2013; 78:11707–11713. [PubMed: 24171600]
3. For other examples of oxidopyrylium cycloaddition/ring-opening sequences in troponoid synthesis, see: Zhang M, Liu N, Tang W. J Am Chem Soc. 2013; 135:12434–12438. [PubMed: 23930656] Adlington RM, Baldwin JE, Mayweg AVW, Pritchard GJ. Org Lett. 2002; 4:3009–3011. [PubMed: 12182611]
4. Murelli RP, D'Erasmo MP, Hirsch DR, Meck C, Masaoka T, Wilson JA, Zhang B, Pal RK, Gallicchio E, Beutler JA, Le Grice SFJ. Med Chem Commun. 2016; 7:1783–1788.
5. Lomonosova E, Daw J, Garimallaprabhakaran AK, Agyemang NB, Ashani Y, Murelli RP, Tavis JE. Antiviral Res. 2017; 144:164–172. [PubMed: 28633989]
6. Ireland PJ, Tavis JE, D'Erasmo MP, Hirsch DR, Murelli RP, Cadiz MM, Patel BS, Gupta AK, Edwards TC, Korom M, Moran EA, Morrison LA. Antimicrob Agents Chemother. 2016; 60:2140–2149. [PubMed: 26787704]
7. Hirsch DR, Cox G, D'Erasmo MP, Shakya T, Meck C, Mohd N, Wright GD, Murelli RP. Bioorg Med Chem Lett. 2014; 24:4943–4947. [PubMed: 25283553]

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8. Donlin MJ, Zunica A, Lipnicky A, Garimallaprabhakaran AK, Berkowitz AJ, Grigoryan A, Meyers MJ, Tavis JE, Murelli RP. Antimicrob Agents Chemother. 2017; 61:e02574–16. [PubMed: 28167553]
9. D'Erasmo MP, Meck C, Lewis CA, Murelli RP. J Org Chem. 2016; 81:3744–3751. [PubMed: 27018974]
10. For seminal work on the intermolecular oxidopyrylium cycloaddition, see: Wender PA, Mascareñas JL. Tetrahedron Lett. 1992; 33:2115–2118.
11. D'Erasmo MP, Masaoka T, Wilson JA, Hunte EM Jr, Beutler JA, Le Grice SFJ, Murelli RP. Med Chem Commun. 2016; 7:1789–1792.
12. For reviews on fluorous phase chemistry, see: Dobbs AP, Kimberley MR. J Fluorine Chem. 2002; 118:3–17.Zhang W. Chem Rev. 2004; 104:2531–2556. [PubMed: 15137799] Zhang W. Chem Rev. 2009; 109:749–795. [PubMed: 19146385]
13. (a) Curran DP. Synlett. 2001:1488–1496.(b) Zhang W, Curran DP. Tetrahedron. 2006; 62:11837–11865. [PubMed: 18509513]
14. (a) Yu MS, Curran DP, Nagashima T. Org Lett. 2005; 7:3677–3680. [PubMed: 16092848] (b) Chu Q, Yu MS, Curran DP. Tetrahedron. 2007; 63:9890–9895. [PubMed: 20631912]
15. Kasahara T, Kondo Y. Chem Commun. 2006:891–893.
16. (a) Anderson KW, Buchwald SL. Angew Chem Int Ed. 2005; 44:6173–6177.(b) Pathak TP, Miller SJ. J Am Chem Soc. 2013; 135:8415–8422. [PubMed: 23692563]
17. Pangborn AB, Giardello MA, Grubbs RH, Rosen RK, Timmers FJ. Organometallics. 1996; 15:1518–1520.

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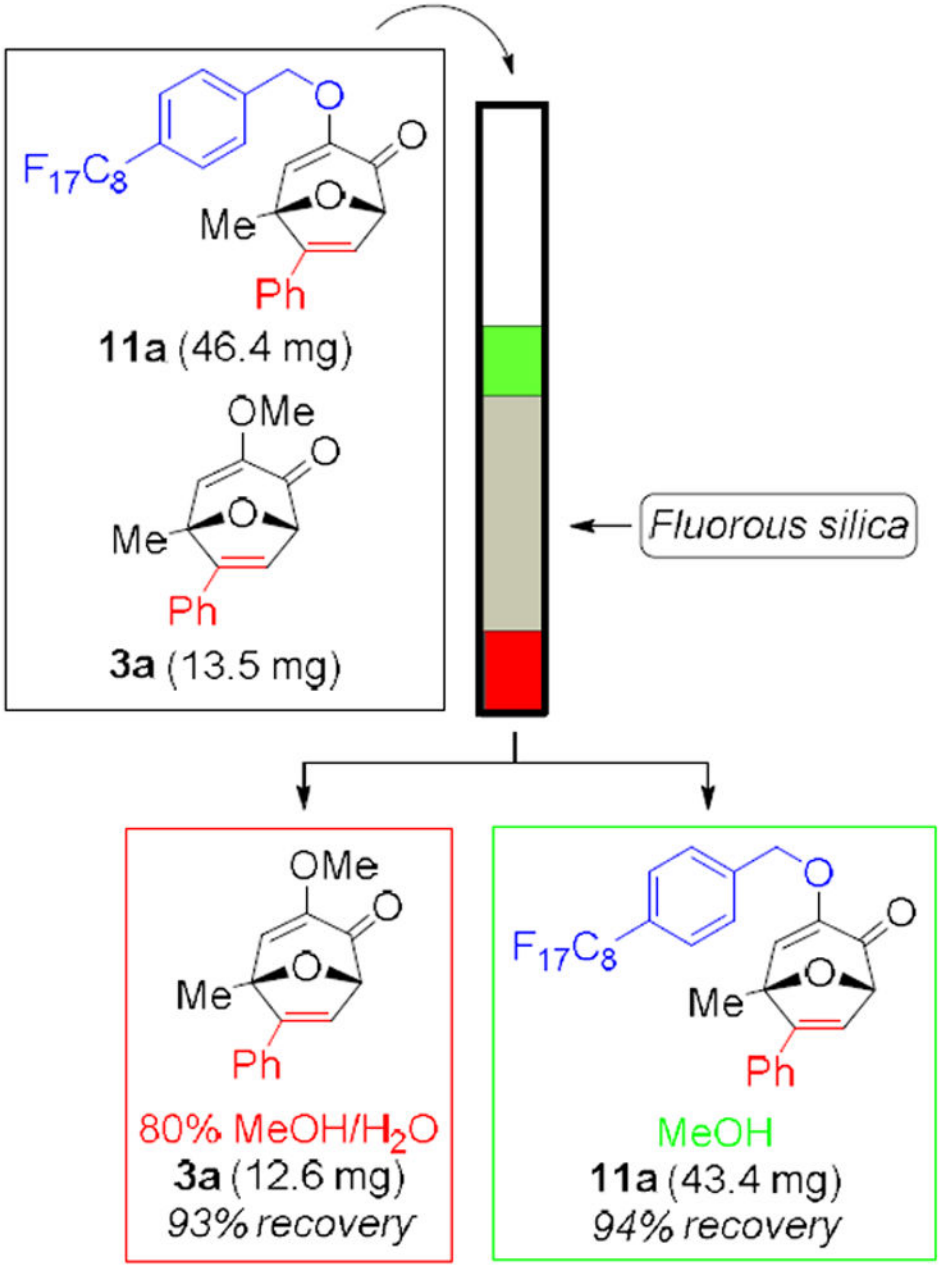

Figure 1.
Overview of FSPE on a mixture of fluorous **11a** and nonfluorous **3a**.

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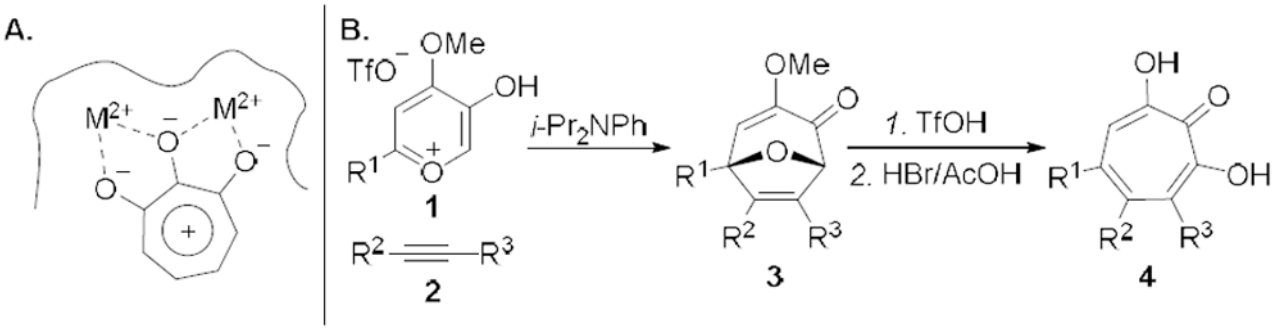

Scheme 1.

(A) The most favorable binding mode of αHTs to dinuclear metalloenzymes. (B) Oxidopyrylium cycloaddition/ring-opening route used to synthesize αHTs.

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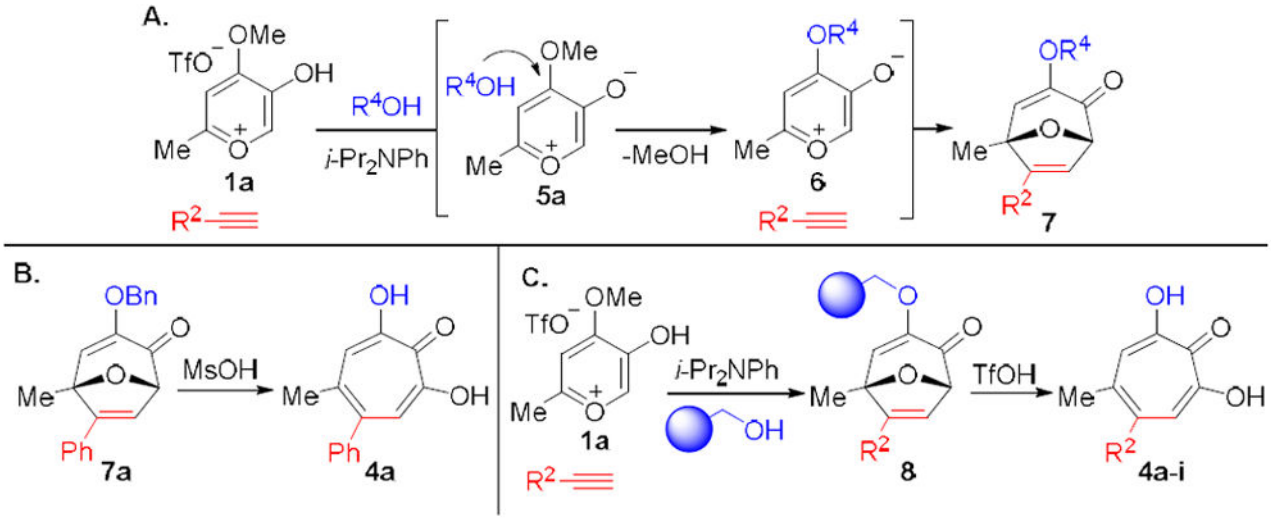

Scheme 2.

(A) Illustration of three-component oxidopyrylium cycloaddition, highlighting alcohol incorporation. (B) Utilization of three-component oxidopyrylium cycloaddition in αHT synthesis. (C) Overview of solid-phase synthesis of αHTs

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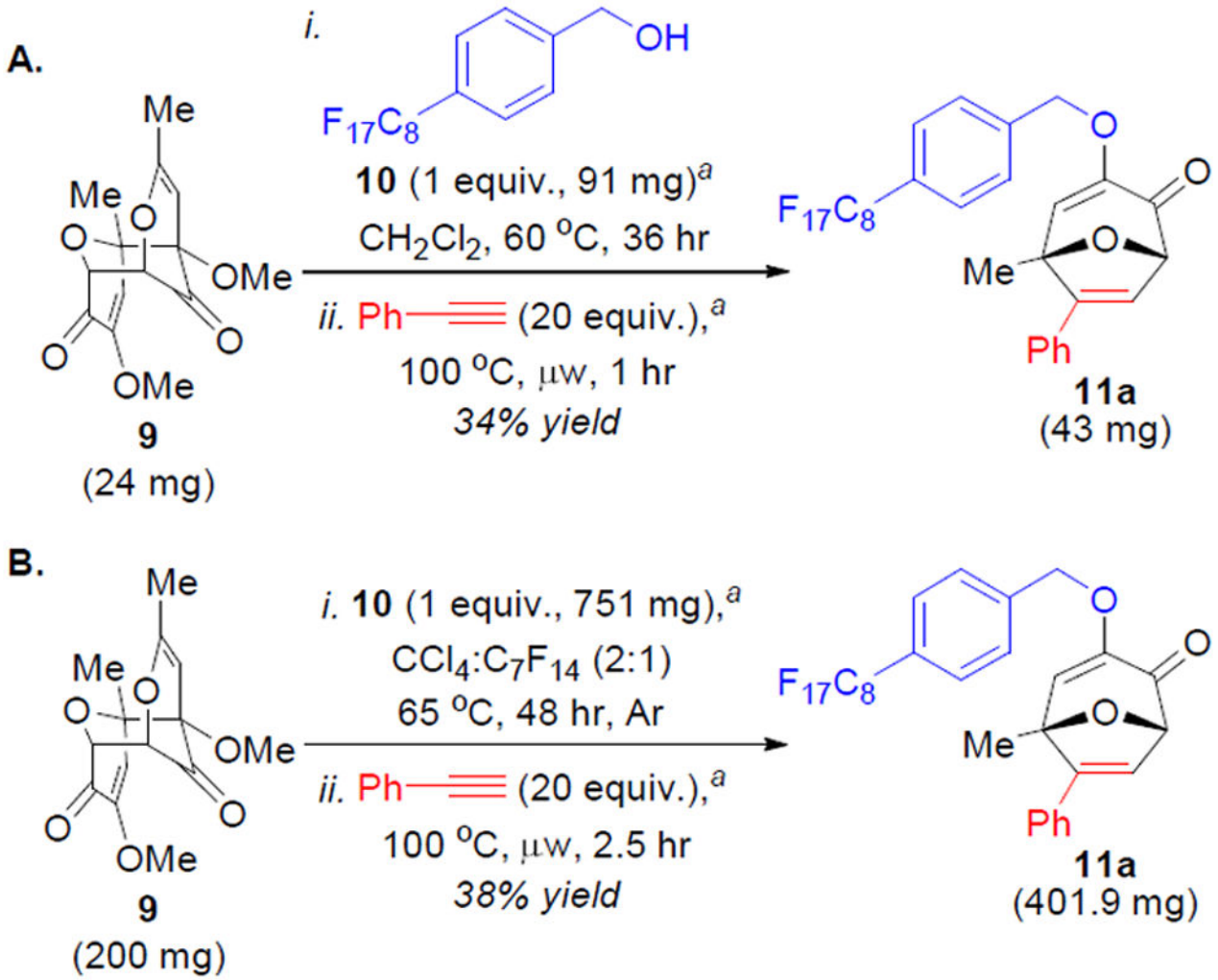
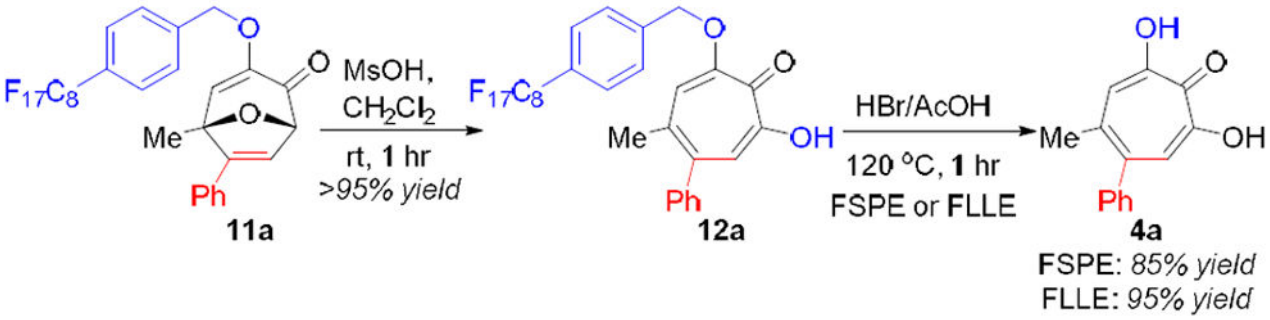


Scheme 3.

Newly optimized conditions with fluorous tagged benzyl alcohol **10** for small scale (A) and scale-up (B) procedures.

[a]Equivalents are calculated on the basis of monomeric ylide.



Scheme 4.

Ring-Opening/debenzylation of **11a** to corresponding αHT **4a**.

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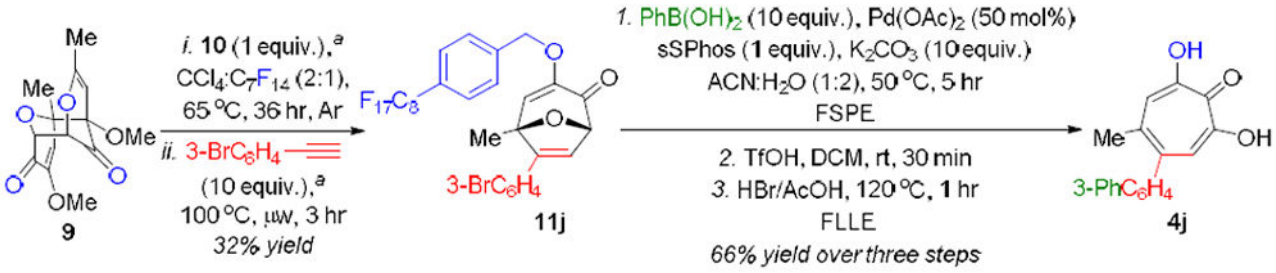

Scheme 5.

Overview of Suzuki cross-coupling route to αHT **4j**.

[a]Equivalents are calculated on the basis of monomeric ylide.

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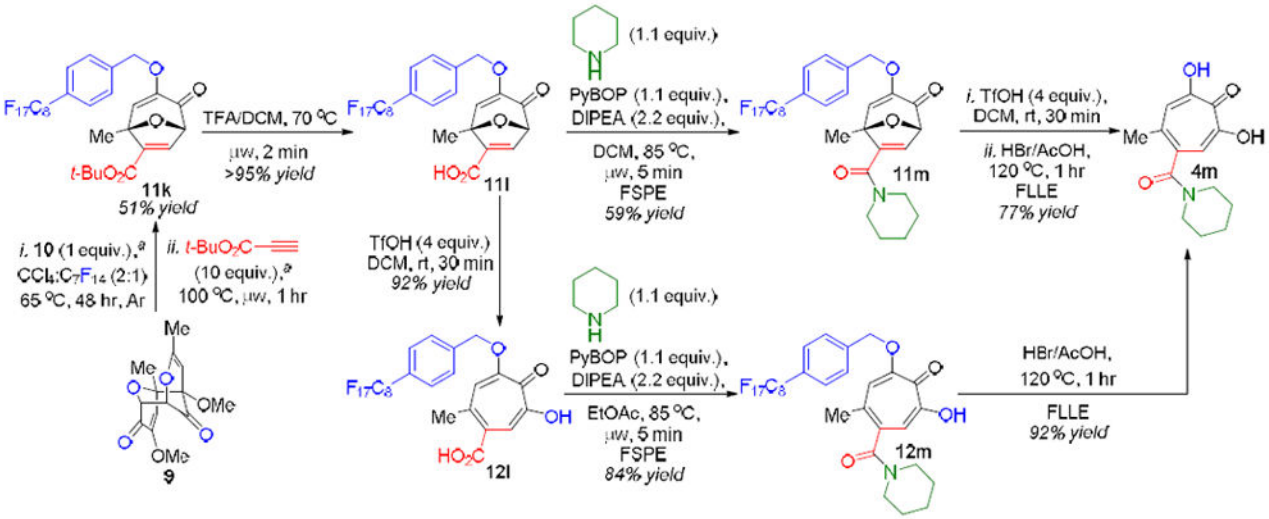

Scheme 6.

Overview of divergent amide coupling on fluorous tagged oxabicycle and tropolone with piperidine to αHT **4m**.

[a]Equivalents are calculated on the basis of monomeric ylide.

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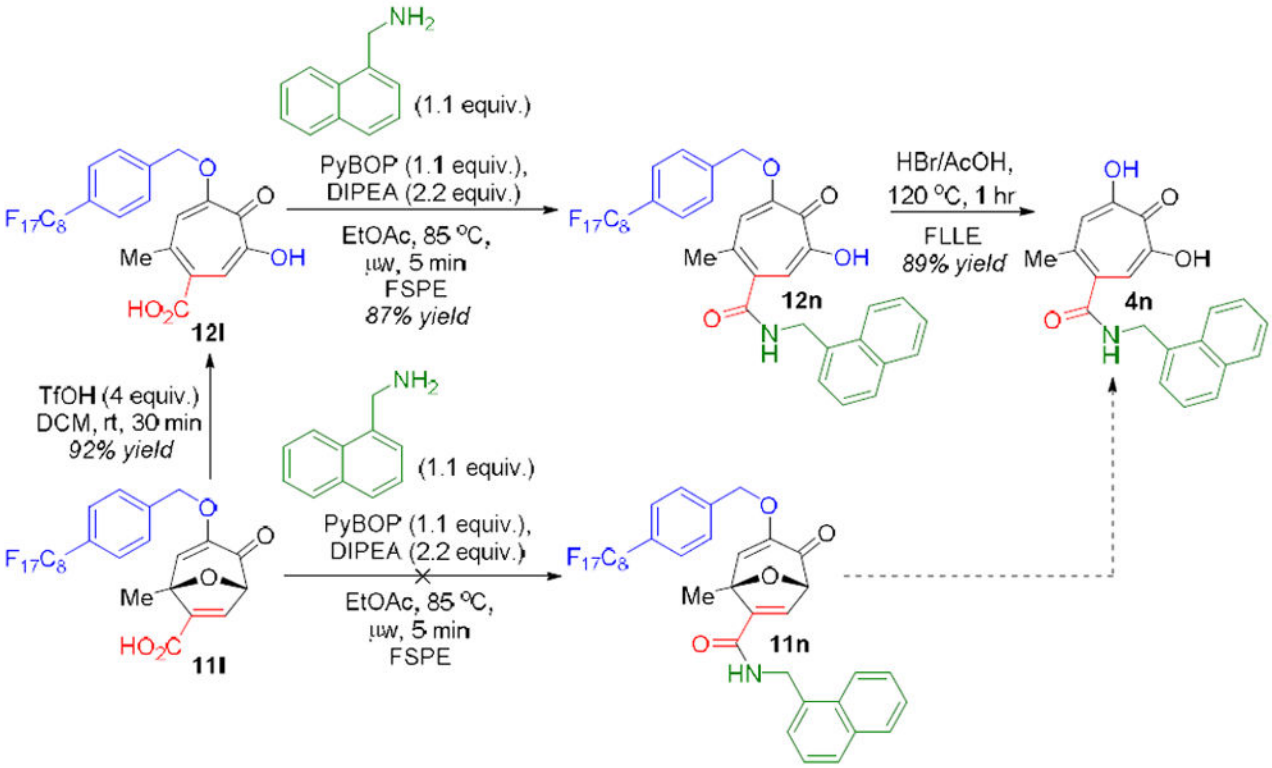

Scheme 7.

Overview of divergent amide coupling on fluorous tagged oxabicycle and tropolone with primary amine to αHT **4n**.

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