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Modular Strategy for the Synthesis of Functionalized Aryl-Fused Azabicyclo[2.2.2]octanes via Sequential Cu/Pd/Ru Catalysis

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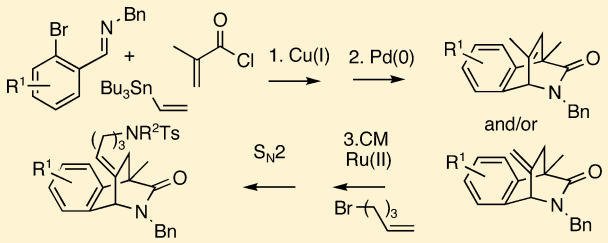
Supporting Information

ABSTRACT: Aryl-fused 2-azabicyclo[2.2.2]octanes were prepared by a novel sequence of Cu-catalyzed three-component coupling of diversely substituted *N*-benzyl *o*-bromoaryl imines with methacryloyl chloride and vinyltributyl stannane followed by Pd-catalyzed Heck annulation. Subsequent diversification of the aryl-fused 2-azabicyclo[2.2.2]octane core was achieved by attaching a flexible linker and a potential second pharmacophore via Ru-catalyzed cross-metathesis and a nucleophilic substitution.



Complex N-heterocyclic structures constitute the core of potent biologically active natural products and synthetic drugs.[1] The isoquinuclidine (2-azabicyclo[2.2.2]octane) motif has been found in diverse types of iboga and iboga-bisindole alkaloids,[2] grandisine B featuring linked isoquinuclidinone and indolizidine cores,[3] and in others[4] like mearsin and dioscorine (Figure 1). Synthetic analogues featuring the benzomorphan-

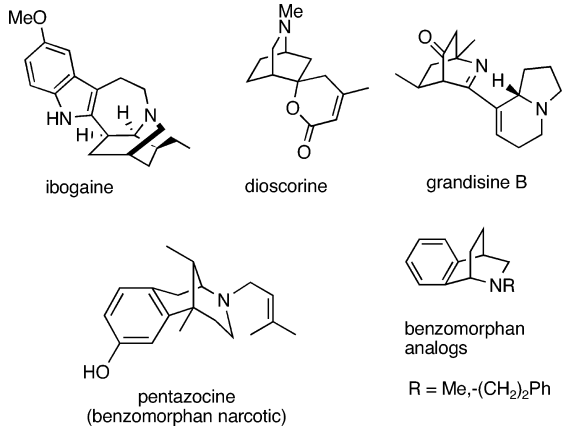


Figure 1. Naturally occurring and synthetic azabicyclooctanes.

related benzo-fused 5,6-benzo-2-azabicyclo[2.2.2]octane cores (Figure 1) have been synthesized,[5] and their potential to exhibit analgesic properties has been studied.[5]

Surprisingly, only an extremely small number of derivatives of aryl-fused 2-azabicyclo[2.2.2]octanes have been isolated or prepared.[6] Synthesis of aryl-fused 2-azabicyclo[2.2.2]octanes via the Diels–Alder reaction with benzyne dienophiles[7] has been limited by the challenging task of diversifying the substitution patterns on the aromatic ring of the benzyne. An intramolecular radical cyclization of tetrahydropyridines providing an access to aryl-fused 2-azabicyclo[2.2.2.]octanes has recently been described.[8] Several other methods for the assembly of the general 2-azabicyclo[2.2.2]octane core have been reported,[9] including Diels–Alder reactions of dihydropyridines.[10] However, these methodologies have not been adopted to the synthesis of the aryl-fused analogues. Furthermore, only in a few instances have parallel syntheses of combinatorial libraries of bridged *N*-heterocycles been achieved.[11] Recently, sequences of intramolecular RCM and Heck reactions were applied toward the construction of structurally related aryl-fused bridged *N*-heterocycles; these however featured different ring-sizes than the 2-azabicyclo[2.2.2]octane core.[12]

We envisioned that a modular method for the assembly of highly functionalized 2-azabicyclo[2.2.2]octanes followed by a process that would link them to other potential pharmacophores could be developed by exploring a strategically designed sequence of multicomponent[13] and transition metal-catalyzed C–C bond-forming reactions.[14] Herein, we describe a new synthetic methodology for a rapid construction of a series of aryl-fused 2-azabicyclo[2.2.2]octanes via a sequence of Cu(I)-catalyzed three-component coupling of various imines, vinyl stannane and methacryloyl chloride, followed by Pd-catalyzed Heck annulation cascade (Scheme 1). Both the electronic properties and positions of the substituents in the aromatic ring of the *N*-benzyl imines **I** were varied to afford a series of acyclic amides **II**. A regioselective Heck cascade consisting of two sequential 6-*exo* cyclizations afforded a mixture of bridged *exo* and *endo* azabicyclooctanes **III** and **IV**, respectively (Scheme 1). Diversification of the allylic C–C bridge in heterocycles **III** and **IV** via Pd-catalyzed allylic acetoxylation was attempted. Ultimately, we identified conditions for a selective synthesis of heterocycles **III** and designed a protocol for their linking to

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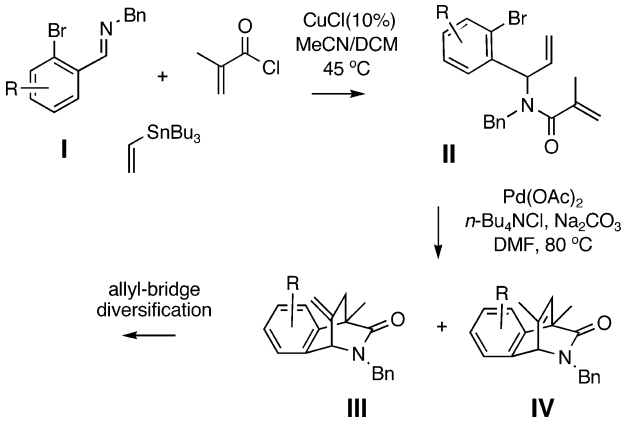
Scheme 1

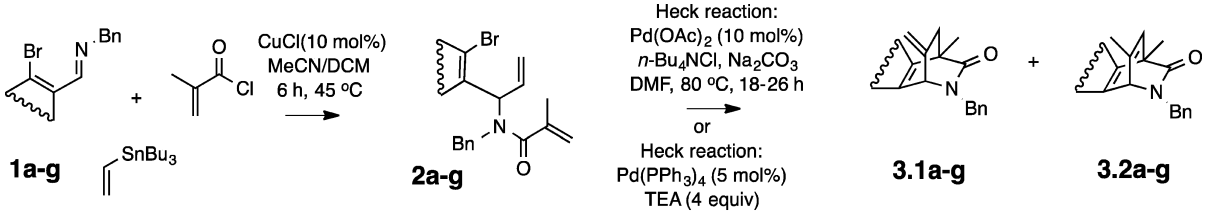


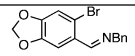
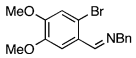
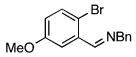
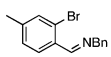
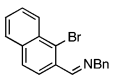
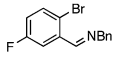
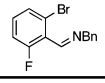
other pharmacophores via Ru-catalyzed cross metathesis and subsequent substitution (vide infra). In contrast to the traditional synthetic methods,[6−10] our protocol is well-suited for the construction of combinatorial libraries of aryl-fused 2-azabicyclo[2.2.2]octanes allowing for systematic variations of the positions of electronically diverse aryl substituents with respect to the fusion of the heterocyclic core, as well as diversifying the nature of the linked pharmacophore.

The Cu(I)-catalyzed coupling[15] of methacryloyl chloride and vinyl stannane with *N*-benzyl imine, derived from 2-bromo-4,5-methyleneoxy benzaldehyde, afforded amide **2a** in a good yield under conditions analogous to those used in our prior studies[16] (entry 1, Table 1). The two olefins in the amide **2a** are positioned to allow for a regioselective 6-*exo*/6-*exo* two-step Heck cascade reaction.[17] Thus, treatment of amide **2a** with $Pd(OAc)_2$ (10 mol %), TBAC (1 equiv) and Na_2CO_3 (1 equiv) in DMF[18] at 80 °C afforded a chromatographically inseparable mixture of bridged heterocycles **3.1a** (*exo*-olefin) and **3.2a** (*endo*-olefin) in an excellent combined yield (90%) (entry 1, Table 1). The ratio of the *exo*- and *endo*-olefins (1.5:1) was assigned on the basis of well-resolved ^{1}H NMR spectra of the mixture of azabicyclooctanes **3.1a** and **3.2a** (entry 1, Table 1). Initial attempts to eliminate the formation of the double bond isomers by replacing the Na_2CO_3 base with KOAc or TEA (1 equiv each) or by replacing the TBAC/Na_2CO_3 system with PPh_3/Cs_2CO_3 all in DMF were not successful,[19] affording mixtures of the regioisomeric olefins **3.1a** and **3.2a** in 1.5−1.9:1 ratios.

The excellent conversion of the diene **2a** into the heterocycle **3a** points to a high diastereoselectivity of the first 6-*exo* carbopalladation providing palladium(II) intermediate **VIa** instead of its diastereomer **VIb** (Figure 2). Assuming that the palladium(II) intermediate **V** favors the conformation in which the phenyl group in the *N*-benzyl substituent and the vinyl

Table 1. Preparation of Azabicyclooctanes via Pd-Catalyzed Cascade Reaction



Entry	Imine **1**	Amide **2** (%)[a]	Bicyclooctanes by $Pd(OAc)_2$/DMF **3** (%)[b]	Ratio **3.1** : **3.2**[c]	Bicyclooctanes by $Pd(PPh_3)_4$/THF **3.1** (%)[e]
1	**1a** 	**2a** (73)	**3a** (90)	1.5 : 1	**3.1a** (90)
2	**1b** 	**2b** (83)	**3b** (68)	1.3 : 1	**3.1b** (74)
3	**1c** 	**2c** (63)	**3c** (65)	1.3 : 1	-
4	**1d** 	**2d** (74)	**3d** (77)	1.1 : 1	-
5	**1e** 	**2e** (60)	**3e** (65)	2.6 : 1	-
6	**1f** 	**2f** (50)	**3f** (66)	1.2 : 1	-
7	**1g** 	**2g** (77)	**3g** (92)[d]	1 : 1.4	**3.1g** (70)

[a]Isolated yield of a single compound. [b]Combined isolated yield for an inseparable mixture of two regioisomers. [c]Molar ratio of the regioisomers established by ^{1}H NMR. [d]Combined yield of two regioisomers separated by column chromatography. [e]Isolated yield for a single isomer that was formed as the only organic product.

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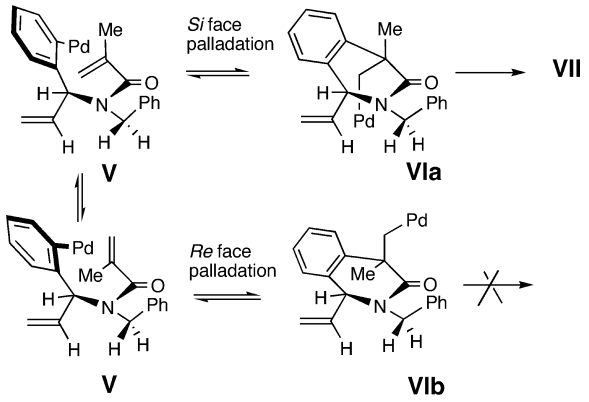


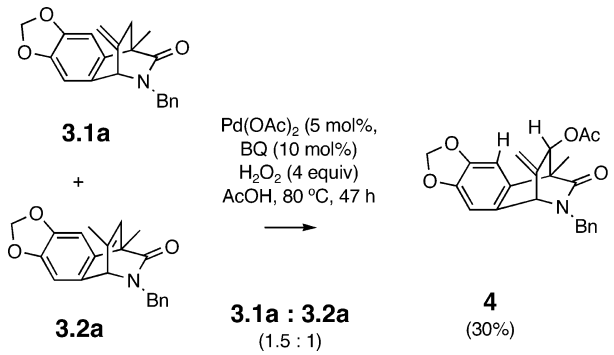
Figure 2. Rationale for diastereoselectivity of the Heck reaction.

group at the stereogenic carbon are located in *anti* orientation (Figure 2), the subsequent carbopalladation step would occur preferentially from the *Si*-face of the disubstituted olefin. The developing transition state for the *Si*-face carbopalladation would be lower in energy due to the palladium(II) center being located at the less sterically encumbered bottom face of the newly created ring. The resulting palladium(II) complex **VIa** features *cis* orentation of the Pd(II) center and the monosubstituted olefin required for the second carbopalladation. Alternatively, equilibrium between diastereomers **VIa** and **VIb** is rapidly established via a facile *β*-carbon elimination/carbopalladation sequence (Figure 2) allowing for a complete conversion of the substrate **2a** into the heterocycle **3a.**

The lack of a significant effect of the choice of base on the ratios of *exo* and *endo* isomers in our case was quite puzzling. Furthermore, the treatment of the mixture of olefins **3.1a** and **3.2a** with acids (H_2SO_4 or TsOH) did not induce a complete isomerization to the internal olefin **3.2a**.[20,21] Reasoning that both regioisomers **3.1** and **3.2** possess an activated allylic C−H bond that may react to yield an identical allylpalladium intermediate that can be used for further diversification of the bridged scaffold, we proceeded to explore the scope of the Cu/Pd-catalyzed reactions with respect to the substitution in the aromatic ring of the imine (Table 1). The reaction sequence proved to have a good scope, affording both the functionalized amides **2b**−**g** (50−83%) and azabicyclooctanes **3b**−**3g** (65−92%) featuring electron-rich (OMe, $-OCH_2O-$), electron-deficient (F), methyl, and fused phenyl groups at different positions in the aromatic ring in very good yields as an inseparable mixture of two regioisomeric olefins (2.6−1.1:1 ratios) (entries 2−7, Table 1). The ^{1}H NMR and ^{13}C NMR spectra for these products proved to be well-resolved, providing analytical data of sufficient quality to fully characterize these compounds in the mixture of olefinic isomers. An exception was the 4-fluorophenyl substituted imine **1g** that afforded azabicyclooctanes **3g.1** and **3g.2** as chromatographically separable compounds (entry 7, Table 1). Disappointingly, imines derived from heterocyclic aldehydes failed to afford the bicyclic products, as revealed by the low yield of the thiophene derivative derived from 3-bromo-2-carbaldehyde thiophene, and the failure of the sequence to afford the 2-azabicyclo[2.2.2]octane product from 2-bromo-3-carbaldehyde pyridine, possibly due to interfering chelation interactions with the palladium catalyst.

Next, palladium-catalyzed oxidative acetoxylation[22] on the mixture of regiosiomers **3.1a**/**3.2a** was studied, seeking to synthesize either a single allylic acetate or a mixture of allylic acetates that would afford a single product following a Tsuji−Trost allylation reaction.[23] The mixture of azabicyclooctanes **3.1a**/**3.2a** was treated with $Pd(OAc)_2$/benzoquinone catalyst and several different stoichiometric oxidants (H_2O_2, *t*-BuOOH, O_2/DMSO) in acetic acid, seeking the best conditions for the preparation of the acetate(s) **4** (Scheme 2). Disappointingly,

Scheme 2



despite extensive variations in the ratios of reaction components, temperature and time, we could only obtain low yields of an identical single diastereomer of the bridge-acetoxylated heterocycle **4**. Under the optimized conditions using $Pd(OAc)_2$ (5 mol %), benzoquinone (10 mol %), H_2O_2 (4 equiv) in acetic acid at (80 °C for 47 h) acetate **4** was isolated in 30% yield. The relative configuration of the new stereocenter was confirmed by NOE ^{1}H NMR spectroscopy, which identified a correlation between the aromatic and aliphatic hydrogens highlighted in the structure of acetate **4** in Scheme 2. The unreacted substrate could be recovered by column chromatography as a mixture of isomers **3.1a**/**3.2a** (1.5:1 by ^{1}H NMR) in 38% yield.

The limited yield of the allylic acetoxylation on the mixture of isomeric heterocycles **3.1a** and **3.2a** prompted us to explore a much broader range of conditions for the initial Heck annulation, including reductive Heck cascade, Heck cascade terminated with CO, or with Suzuki coupling.[24] Although neither of these protocols afforded results competitive with the original method (entry 1, Table 1),[20] we observed that application of THF as the solvent favored the formation of the *exo* isomer **3.1a**. Under optimized conditions, the treatment of amide **2a** with $Pd(PPh_3)_4$ (5 mol %) catalyst and TEA (4 equiv) in anhydrous THF (80 °C, 23 h) delivered the azabicyclooctane **3.1a** in 90% yield as a single product (Scheme 3 and entry 1, Table 1). Conceivably, substituting DMF with THF solvent decreases the stabilization of the hydrido-palladium(II) intermediate formed by *β*-hydride elimination, favoring its decomposition via reductive elimination instead of the readdition that causes the undesired isomerization.[19] In order to assess the generality of the dramatic increase in the regioselectivity delivered by the modified catalytic system, the Heck cyclization catalyzed by $Pd(PPh_3)_4$ with TEA base in the THF solvent was performed with amides **2b** and **2g** under the same conditions as those described for amide **2a** (Scheme 3). In both cases, single regioisomers, e.g., the exocyclic olefins **3.1b** and **3.1g**, were obtained as the sole organic products in 74 and 70% yields, respectively (entries 2 and 7, Table 1).

As a part of the ongoing effort in our group to design strategic reaction sequences involving Pd- and Ru-catalyzed reactions,[25] we considered the diversification of the azabicy-

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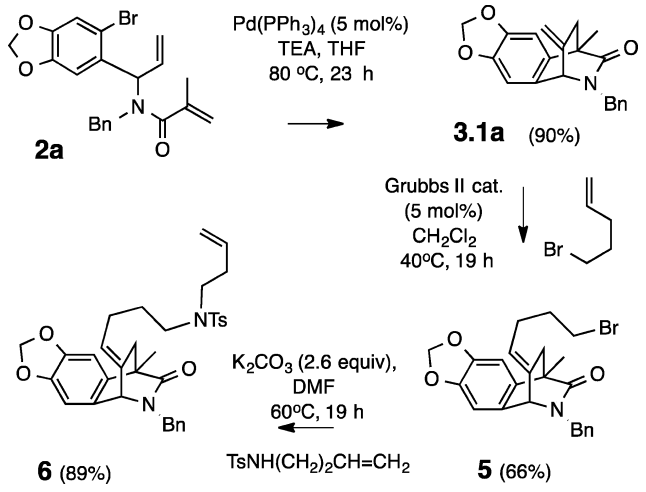
Scheme 3



clooctane **3.1a** via Ru-catalyzed cross-metathesis. The treatment of heterocycle **3.1a** with 1-bromo-4-pentene along with Grubbs II catalyst (10 mol %)[26] provided a good yield of a single stereoisomer of the cross-metathesis product **5** (Scheme 3). The relative stereochemistry in functionalized bicyclooctane **5** was assigned based on NOE ^{1}H NMR experiments that identified a correlation between the vinylic and methine hydrogens in the structure of azabicyclooctane **5** (Scheme 3). The presence of a flexible linker and a reactive leaving group in azabicyclooctane **5** makes it a valuable substrate for the synthesis of structures with two biologically active cores connected by a flexible linker. Such compounds could serve as valuable probes in biomedical research.[27] To validate this concept, azabicyclooctane **5** was reacted with *N*-homoallyl *p*-tolylsulfonamide and K_2CO_3 in DMF (60 °C, 19 h) to afford sulfonamide **6** in an excellent yield (89%) (Scheme 3).

In conclusion, the studies described herein completed the development of a synthetic protocol for the construction of diversely substituted aryl-fused 2-azabicyclo[2.2.2]octanes linked to a second pharmacophore delivered as a nucleophile in the terminal S_N2 reaction. The protocol provides an effective alternative to the limited number of currently available synthetic methods and opens up many options for the preparation of diverse analogues.

EXPERIMENTAL SECTION

General Experimental. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were collected in $CDCl_3$ with internal $CHCl_3$ reference (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). IR spectra were measured in films on NaCl plates. MS were measured under electrospray (ES^+) ionization with time-of-flight (TOF) mass analyzer. Commercial silica gel 60 plates, 0.25 mm thickness, with fluorescent indicator (F-254) were used for thin-layer chromatography (TLC). Retention factors (R_f) for TLC were determined in EtOAc/hexane 1:1 mixture, unless indicated otherwise. Column chromatography was performed with 40−63 mm silica. Solvents and glassware were dried by standard methods.[28] All reactions were performed under dry argon atmosphere. Imines **1** were prepared by a modified literature procedure.[29] Ratios of regioisomers were measured by ^{1}H NMR. Standard workup protocol involving aqueous extraction of the organic phases, drying ($MgSO_4$), and flash chromatography over silica eluting with EtOAc/Hexanes was followed.

General Method for Amides 2a−g. Neat methacryloyl chloride (1.29−5.66 mmol, 125−550 μL, 1.3 equiv) was injected into a solution of imine **1** (0.99−4.33 mmol, 1.0 equiv) and CuCl (10−44 mg, 0.1−0.44 mmol, 0.1 equiv) in acetonitrile (0.27 M). The mixture was stirred at rt for 30 min; a solution of tributylvinyltin (0.381−1.659 g, 1.2−5.23 mmol, 1.2 equiv) in dichloromethane (0.14 M) was added dropwise. The mixture was stirred at 45 °C for 6 h, cooled, diluted with saturated aqueous KF (12 mL), and stirred for 16 h. Standard workup afforded amides **2a−g**. In ^{1}H NMR spectra of amides **2a−g**, signal broadening caused by hindered rotation about the amide bond was observed (see the temperature dependent ^{1}H NMR spectra for **2a** in the Supporting Information). In ^{13}C NMR spectra of amides **2a−g**, broadening of peaks at about 50 and 60 ppm was observed.

***N*-Benzyl-*N*-(1-(6-bromobenzo[*d*][1,3]dioxol-5-yl)allyl)-methacrylamide (2a).** (1.304 g, 73%); white solid: mp 100−110 °C; R_f = 0.57; ^{1}H NMR δ 7.16 (t, *J* = 7.1 Hz, 2H), 7.13 (d, *J* = 6.7 Hz, 1H), 7.02 (d, *J* = 7.3 Hz, 2H), 6.80 (s, 2H), 6.11 (d, *J* = 4.1 Hz, 1H), 5.99−5.96 (m, 0.7H), 5.94 (d, *J* = 1.4 Hz, 1H), 5.94−5.93 (m, 0.3H), 5.91 (d, *J* = 1.4 Hz, 1H), 5.37 (br s, 1H), 5.26 (s, 1H), 5.18 (t, *J* = 8.2 Hz, 2H), 4.77 (br s, 1H), 4.38 (br s, 1H), 2.01 (s, 3H); ^{13}C NMR δ 21.4, 48.5, 62.7, 102.0, 110.5, 113.0, 115.6, 116.5, 118.1, 126.7, 127.2 (2C), 128.1 (2C), 128.0, 128.9, 135.9, 138.0, 147.5, 148.0, 173.7; IR (cm^{-1}) 1647, 1618; HRMS calcd for $C_{21}H_{20}BrNO_3Na$ $(M + Na)^+$ 436.0524, found 436.0516.

***N*-Benzyl-*N*-(1-(2-bromo-4,5-dimethoxyphenyl)allyl)meth-acrylamide (2b).** (355 mg, 83%); clear oil: R_f = 0.40; ^{1}H NMR δ 7.17−7.12 (m, 3H), 7.00 (d, *J* = 7.3 Hz, 2H), 6.84 (br s, 1H), 6.76 (s, 1H), 6.08 (dt, *J* = 5.3, 1.5 Hz, 1H), 5.99 (ddd, *J* = 17.1, 10.4, 5.3 Hz, 1H), 5.36 (br s, 1H), 5.26 (br s, 1H), 5.21 (s, 0.5H), 5.19 (s, 1H), 5.17 (s, 0.5H), 4.69 (br s, 1H), 4.43 (br s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 2.02 (s, 3H); ^{13}C NMR δ 21.3, 47.8, 56.2, 56.3, 63.0, 113.5, 115.5, 115.7, 115.9, 118.2, 126.8, 127.3 (2C), 128.1 (2C), 129.6, 135.9, 138.0, 140.7, 148.3, 149.2, 173.7; IR (cm^{-1}) 1647, 1620, 1252; HRMS calcd for $C_{22}H_{24}BrNO_3Na$ $(M + Na)^+$ 452.0837, found 452.0835.

***N*-Benzyl-*N*-(1-(2-bromo-5-methoxyphenyl)allyl)methacryl-amide (2c).** (399 mg, 63%); yellow oil: R_f = 0.58; ^{1}H NMR δ 7.33−7.27 (m, 1H), 7.16−7.12 (m, 3H), 7.02 (d, *J* = 7.2 Hz, 2H), 6.85 (d, *J* = 3.1 Hz, 1H), 6.61 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.13 (br s, 1H), 5.97 (ddd, *J* = 17.2, 10.4, 5.4 Hz, 1H), 5.36 (d, *J* = 8.1 1H), 5.24 (s, 1H), 5.20 (q, *J* = 1.1 Hz, 0.5H), 5.18 (s, 1H), 5.16 (q, *J* = 1.0 Hz, 0.5H), 4.69 (br s, 1H), 4.54 (d, *J* = 13.0 Hz, 1H), 3.72 (s, 3H), 1.99 (s, 3H) ^{13}C NMR δ 21.3, 47.3, 55.6, 63.3, 114.8, 115.6, 115.7, 117.0, 118.6, 126.8, 127.3 (2C), 128.1 (2C), 122.8, 135.4, 138.1, 138.9, 140.6, 159.0, 173.8. IR (cm^{-1}) 1647, 1624; HRMS calcd for $C_{21}H_{22}BrNO_2Na$ (M + Na)$^+$ 422.0732, found 422.0744.

***N*-Benzyl-*N*-(1-(2-bromo-4-methylphenyl)allyl)methacryl-amide (2d).** (1.213 g, 74%); clear oil: R_f = 0.54; ^{1}H NMR δ 7.21 (br s, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 6.7 Hz, 3H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.98 (d, *J* = 6.9 Hz, 2H), 6.14 (br s, 1H), 5.98 (ddd, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.34 (d, *J* = 6.7 Hz, 1H), 5.25 (s, 1H), 5.18 (q, *J* = 1.1 Hz, 0.5H), 5.17 (br s, 1H), 5.15 (q, *J* = 1.1 Hz, 0.5H), 4.65 (br s, 1H), 4.46 (d, *J* = 10.2 Hz, 1H), 2.24 (s, 3H), 1.99 (s, 3H); ^{13}C NMR δ 20.7, 21.3, 47.1, 63.0, 115.5, 118.1, 125.3, 126.6, 127.3 (2C), 128.0 (2C), 128.3, 130.4, 133.7, 134.8, 135.8, 138.1, 139.9, 140.6, 173.8; IR (cm^{-1}) 1649, 1620; HRMS calcd for $C_{21}H_{23}BrNO$ $(M + H)^+$ 384.0963, found 384.0963.

***N*-Benzyl-*N*-(1-(1-bromonaphthalen-2-yl)allyl)methacryl-amide (2e).** (252 mg, 60%); yellow oil: R_f = 0.32; ^{1}H NMR δ 8.25 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.56 (td, *J* = 8.2, 1.2 Hz, 1H), 7.51 (td, *J* = 8.1, 1.3 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.06 (br s, 2H), 7.01 (d, *J* = 7.3 Hz, 3H), 6.47 (d, *J* = 5.4 Hz, 1H), 6.12 (ddd, *J* = 16.8, 10.4, 5.4 Hz, 1H), 5.36 (d, *J* = 10.0 Hz, 1H), 5.23 (s, 1H), 5.18 (q, *J* = 1.0 Hz, 1.5H), 5.14 (q, *J* = 1.1 Hz, 0.5H), 4.70 (d, *J* = 12.6 Hz, 1H), 4.63 (d, *J* = 15.7 Hz, 1H), 1.97 (s, 3H); ^{13}C NMR δ 21.2, 31.1, 64.0, 115.6, 118.5, 126.0, 126.8, 126.8, 127.1, 127.1 (2C), 127.7 (2C), 127.7, 128.0, 128.0, 128.1, 132.4, 134.1, 135.6, 136.1, 138.1, 140.7, 173.8; IR (cm^{-1}) 1647, 1624; HRMS calcd for $C_{24}H_{22}BrNONa$ $(M + Na)^+$ 442.0782, found 442.0784.

***N*-Benzyl-*N*-(1-(2-bromo-5-fluorophenyl)allyl)methacryl-amide (2f).** (193 mg, 50%); yellow oil: R_f = 0.61; ^{1}H NMR δ 7.34−7.27 (m, 1H), 7.23−7.09 (m, 3H), 7.04 (dd, *J* = 9.6, 3.0 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 2H), 6.78 (dt, *J* = 8.4, 2.9 Hz, 1H), 6.13 (d, *J* = 5.0 Hz, 1H), 5.96 (ddd, *J* = 17.2, 10.4, 5.3 Hz, 1H), 5.39 (br d, *J* = 6.8 Hz, 1H), 5.24 (s, 1H), 5.21−5.17 (m, 2H), 4.72 (br s, 1H), 4.48 (br s,

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1H), 2.00 (s, 3H); ^{13}C NMR δ 21.3, 48.2, 62.7, 115.7, 116.7 (d, J = 21.3 Hz), 118.0 (d, J = 23.8 Hz), 119.0, 119.4 (d, J = 2.5 Hz), 126.9, 127.2 (2C), 128.0 (d, J = 82.5 Hz), 128.2 (2C), 134.4 (d, J = 8.8 Hz), 134.8, 137.8, 140.2, 162.0 (d, J = 246.3 Hz), 173.7; IR (cm^{-1}) 1647, 1624; HRMS calcd for $C_{20}H_{20}BrFNO$ (M + H)$^+$ 388.0712, found 388.0719.

***N*-Benzyl-*N*-(1-(2-bromo-6-fluorophenyl)allyl)methacrylamide (2g).** (473 mg, 77%); yellow oil: R_f = 0.68; ^{1}H NMR δ 7.29 (d, J = 7.8 Hz, 1H), 7.20 (t, J = 7.2 Hz, 2H), 7.12 (t, J = 7.1 Hz, 1H), 7.08 (d, J = 7.4 Hz, 2H), 7.01 (dt, J = 8.2, 5.8 Hz, 1H), 6.90 (ddd, J = 11.0, 8.5, 0.8 Hz, 1H), 6.41 (br s, 1H), 6.13−6.06 (m, 1H), 5.22 (d, J = 10.3 Hz, 1H), 5.13−5.09 (m, 3H), 4.88−4.80 (m, 2H), 1.83 (s, 3H); ^{13}C NMR) δ 20.8, 49.2, 60.7, 115.5, 115.7 (d, J = 23.8 Hz), 118.2, 125.8 (d, J = 6.3 Hz), 126.2 (2C), 126.7, 127.3, 128.3 (2C), 128.7, 129.2 (d, J = 3.8 Hz), 130.0 (d, J = 8.8 Hz), 133.4, 139.7 (d, J = 196.3 Hz), 161.6 (d, J = 250.0 Hz), 173.7; IR (cm^{-1}) 1649, 1624; HRMS calcd for $C_{20}H_{20}FBrNO$ (M + H)$^+$ 388.0712, found 388.0704.

General Method for Azabicyclooctanes 3.1a−g and 3.2a−g. A solution of amide **2a−g** (0.25−3.67 mmol, 1.0 equiv) in DMF (4−30 mL, 0.12 M) was injected into a vessel containing sodium carbonate (27−390 mg, 0.26−3.68 mmol, 1.0 equiv), tetrabutylammonium chloride (70 mg-1.012 g, 0.25−3.57 mmol, 1.0 equiv) and palladium acetate (6−83 mg, 0.024−0.37 mmol, 0.1 equiv). The mixture was stirred at 80 °C for 18−26 h. Standard workup afforded a mixture of azabicyclooctanes **3.1a−g** and **3.2a−g**. In ^{13}C NMR spectra, the signals for the minor regioisomer are provided in brackets.

(5*R,8*S**)-11-Benzyl-8-methyl-6-methylene-5,6,7,8-tetrahydro-5,8-(epiminomethano)naphtho[2,3-*d*][1,3]dioxol-10-one (3.1a) and (5*R**,8*S**)-11-Benzyl-6,8-dimethyl-5,8-dihydro-5,8-(epiminomethano)naphtho[2,3-*d*][1,3]dioxol-10-one (3.2a).** (1.103 g, 90%); clear oil, 1.5:1.0 ratio of **3.1a**:**3.2a**: R_f = 0.52; ^{1}H NMR δ 7.33−7.24 (m, 3H), 7.13−7.08 (m, 2H), 6.83 (s, 0.4H), 6.80 (s, 0.6H), 6.63 (s, 0.4H), 6.52 (s, 0.6H), 6.02 (p, J = 2.0 Hz, 0.4H), 5.95 (d, J = 2.0 Hz, 0.6H), 5.93 (d, J = 2.0 Hz, 0.4H), 5.91 (d, J = 1.0 Hz, 0.6H), 5.90 (d, J = 1.5 Hz, 0.4H), 4.87 (t, J = 2.0 Hz, 0.6H), 4.79 (d, J = 15.3 Hz, 0.6H), 4.78 (d, J = 14.9 Hz, 0.4H), 4.70 (t, J = 2.0 Hz, 0.6H), 4.50 (s, 0.6H), 4.44 (d, J = 2.0 Hz, 0.4H), 4.37 (d, J = 15.0 Hz, 0.6H), 4.13 (d, J = 15.0 Hz, 0.4H), 2.51 (dt, J = 16.5, 2.0 Hz, 0.6H), 2.18 (dt, J = 16.0, 2.0 Hz, 0.6H), 1.80 (s, 1.2H), 1.67 (s, 1.8H) 1.61 (d, J = 1.4 Hz 1.2H); ^{13}C NMR δ [14.3], 16.2, [18.0], 38.7, 47.3, 48.3, [49.2], [54.0], [63.8], 64.5, 101.2, [101.3], 103.8, [104.08], 104.12, [104.2], 107.8, 127.6, [127.7], 128.1 (2C), [128.3 (2C)], 128.6 (2C), [128.7 (2C)], 133.0, [134.6], 135.2, [136.6], 136.8, [137.1], [139.3], 143.5, [144.8], [145.5], 146.2, [147.27], 147.29, 174.7, [174.9]; IR (cm^{-1}) 1740, 1682; HRMS calcd for $C_{21}H_{19}NO_3Na$ (M + Na)$^+$ 356.1263, found 356.1253.

Single Isomer 3.1a. THF (4 mL) was injected into a vessel containing solid amide **2a** (142 mg, 0.34 mmol, 1.0 equiv) and tetrakis(triphenylphosphine)palladium (20 mg, 0.02 mmol, 0.05 equiv), followed by neat triethylamine (138 mg, 190 μL, 1.36 mmol, 4.0 equiv). The mixture was stirred at 80 °C for 23 h. Standard workup afforded azabicyclooctane **3.1a** (102 mg, 90%) as a white solid: mp 120−124 °C; R_f = 0.52; ^{1}H NMR δ 7.29−7.23 (m, 3H), 7.10 (d, J = 1.9, 1H), 7.08 (d, J = 1.3, 1H), 6.80 (s, 1H), 6.52 (s, 1H), 5.95 (d, J = 1.5 Hz, 1H), 5.91 (d, J = 1.5 Hz, 1H), 4.87 (t, J = 2.3 Hz, 1H), 4.79 (d, J = 15.3 Hz, 1H), 4.70 (t, J = 1.9 Hz, 1H), 4.50 (s, 1H), 4.38 (d, J = 15.3 Hz, 1H), 2.57 (dt, J = 16.1 Hz, J = 2.2 Hz, 1H), 2.16 (dt, J = 16.2 Hz, J = 2.2 Hz, 1H), 1.67 (s, 3H). ^{13}C NMR δ 16.2, 38.7, 47.3, 48.3, 64.5, 101.2, 103.8, 104.1, 107.8, 127.6, 128.1 (2C), 128.6 (2C), 133.0, 135.2, 136.8, 143.5, 146.2, 147.3, 174.7; IR (cm^{-1}) 1666. HRMS calcd for $C_{21}H_{19}NO_3Na$ (M + Na)$^+$ 356.1263, found 356.1262.

(1*R,4*S**)-10-Benzyl-6,7-dimethoxy-4-methyl-2-methylene-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-9-one (3.1b) and (1*R**,4*S**)-10-Benzyl-6,7-dimethoxy-2,4-dimethyl-1,4-dihydro-1,4-(epiminomethano)naphthalen-9-one (3.2b).** (166 mg, 68%); yellow oil, 1.3:1.0 ratio of **3.1b**:**3.2b**: R_f = 0.31; ^{1}H NMR δ 7.29−7.23 (m, 3H), 7.10 (dd, J = 7.8, 2.2 Hz, 1H), 7.07 (dd, J = 7.6, 2.0 Hz, 1H), 6.87 (s, 0.44H), 6.82 (s, 0.56H), 6.66 (s, 0.44H), 6.56 (s, 0.56H), 6.05 (p, J = 1.9 Hz, 0.44H), 4.88 (t, J = 2.2 Hz, 0.56H), 4.83 (d, J = 15.3 Hz, 0.56H), 4.73 (d, J = 15 Hz, 0.44H), 4.71 (t, J = 1.9 Hz, 0.56H), 4.53 (s, 0.56H), 4.48 (d, J = 2.1 Hz, 0.44H), 4.38 (d, J = 15.3 Hz, 0.56H), 4.22 (d, J = 15.1 Hz, 0.44H), 3.90 (s, 1.68H), 3.88 (s, 1.32H), 3.80 (s, 1.32H), 3.79 (s, 1.68H), 2.60 (dt, J = 16.2, 2.2 Hz, 0.56H), 2.19 (dt, J = 16.2, 2.1 Hz, 0.56H), 1.84 (s, 1.32H), 1.71 (s, 1.68H) 1.65 (d, J = 1.8 Hz, 1.32H); ^{13}C NMR δ [14.2], 16.1, [18.1], 38.8, 47.1, 48.3, [49.2], [53.8], 56.3, 56.4, [56.4], [56.5], [63.7], 64.4, 106.3, 106.5, [106.6], [107.1], 107.6, 127.5, [127.7], 128.1 (2C), [128.4 (2C)], 128.6 (2C), [128.7 (2C)], 131.9, [133.5], 134.8, [135.3], 136.9, [137.1], [137.4], 143.7, [146.3], [146.7], 147.2, [147.8], 148.6, 174.9, [175.0]; IR (cm^{-1}) 1668, 1607; HRMS calcd for $C_{22}H_{24}NO_3$ (M + H)$^+$ 350.1756, found 350.1758.

Single Isomer 3.1b. Reaction with $Pd(PPh_3)_4$ catalyst, TEA in THF as described for **3.1a** afforded **3.1b** (65 mg, 74%); clear oil. For ^{1}H NMR spectra, see the Supporting Information.

(1*R,4*S**)-10-benzyl-7-methoxy-4-methyl-2-methylene-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-9-one (3.1c) and (1*R**,4*S**)-10-Benzyl-7-methoxy-2,4-dimethyl-1,4-dihydro-1,4-(epiminomethano)naphthalen-9-one (3.2c).** (54 mg, 65%); clear oil, 1.3:1.0 ratio of **3.1c**:**3.2c**: R_f = 0.31; ^{1}H NMR δ 7.32−7.23 (m, 3H), 7.18 (d, J = 8.3 Hz, 0.56H), 7.15 (d, J = 8.2 Hz, 0.44H), 7.13 (dd, J = 1.8, 8.1 Hz, 0.88H), 7.10 (dd, J = 2.1, 7.8 Hz, 1.12H), 6.79 (dd, J = 8.4, 2.6 Hz, 0.56H), 6.69 (d, J = 2.5 Hz, 0.44H), 6.61 (d, J = 2.5 Hz, 0.22H), 6.59 (d, J = 2.5 Hz, 0.78H), 6.04 (p, J = 1.9 Hz, 0.44H), 4.90 (t, J = 2.3 Hz, 0.56H), 4.82 (d, J = 15.1 Hz, 0.44H), 4.76 (d, J = 15.3 Hz, 0.56H), 4.73 (t, J = 1.9 Hz, 0.56H), 4.56 (s, 0.56H), 4.48 (d, J = 2.1 Hz, 0.44H), 4.44 (d, J = 15.3 Hz, 0.56H), 4.11 (d, J = 15.1 Hz, 0.44H), 3.76 (s, 1.32H), 3.75 (s, 1.68H), 2.60 (dt, J = 16.2, 2.2 Hz, 0.56H), 2.19 (dt, J = 16.3, 2.2 Hz, 0.56H), 1.83 (s, 1.32H), 1.70 (s, 1.68H) 1.62 (d, J = 1.8 Hz, 1.32H) ; ^{13}C NMR δ [14.1], 15.9, [18.0], 38.9, 46.7, 48.3, [49.1], [53.3], 55.5, [56.6], [63.9], 64.8, 108.4, 108.6, [109.1], [109.7], 112.3, [121.8], 123.1, 127.5, [127.7], 128.1 (2C), [128.4 (2C)], 128.6 (2C), [128.7 (2C)], [133.4], 135.0, 136.7, [136.9], [137.2], 140.6, 143.5, [144.0], [146.4], [157.6], 158.7, [175.0], 175.1; IR (cm^{-1}) 1612, 1612; HRMS calcd for $C_{21}H_{21}NO_2Na$ (M + H)$^+$ 342.1470, found 342.1466.

(1*R,4*S**)-10-Benzyl-4,6-dimethyl-2-methylene-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-9-one (3.1d) and (1*R**,4*S**)-10-Benzyl-2,4,6-trimethyl-1,4-dihydro-1,4-(epiminomethano)naphthalen-9-one (3.2d).** (146 mg, 77%); yellow oil, 1.1:1.0 ratio of **3.1d**:**3.2d**: R_f = 0.53; ^{1}H NMR δ 7.32−7.23 (m, 3H), 7.14 (s, 0.53H), 7.12 (s, 0.47), 7.11−7.08 (m, 2H), 6.98 (s, 0.47), 6.97 (s, 0.53), 6.91 (d, J = 7.5 Hz, 0.53H), 6.85 (d, J = 7.3, 0.47H), 6.02 (p, J = 1.7 Hz, 0.47H), 4.89 (t, J = 2.3 Hz, 0.53H), 4.83 (d, J = 15.1 Hz, 0.47H), 4.76 (d, J = 15.3 Hz, 0.53H), 4.70 (t, J = 1.8 Hz, 0.53H), 4.58 (s, 0.53H), 4.51 (d, J = 2.1 Hz, 0.47H), 4.44 (d, J = 15.3 Hz, 0.53H), 4.08 (d, J = 15.1 Hz, 0.47H), 2.60 (dt, J = 16.2, 2.2 Hz, 0.53H), 2.37 (s, 1.59H), 2.33 (s, 1.41H), 2.19 (dt, J = 16.2, 2.2 Hz, 0.53H), 1.84 (s, 1.41H), 1.71 (s, 1.59H), 1.61 (d, J = 1.8 Hz, 1.41H); ^{13}C NMR δ [14.0], 15.8, [18.0], 21.6, [21.7], 38.7, [47.3], 48.3, 49.1, [54.0], [63.6], 64.4, 107.9, [121.3], 121.8, [122.4], 123.0, [125.4], 127.3, 127.5, [127.7], 128.1 (2C), [128.3 (2C)], 128.6 (2C), [128.7 (2C)], [134.4], 135.7, 136.5, 136.9, [137.2], [137.6], 139.8, 141.2, [143.7], [144.8], [147.0], [174.7], 174.8; IR (cm^{-1}) 1672, 1495; HRMS calcd for $C_{21}H_{22}NO$ (M + H)$^+$ 304.1701, found 304.1698.

(1*R,4*S**)-12-Benzyl-4-methyl-2-methylene-1,2,3,4-tetrahydro-1,4-(epiminomethano)phenanthren-11-one (3.1e) and (1*R**,4*S**)-12-Benzyl-2,4-dimethyl-1,4-dihydro-1,4-(epiminomethano)phenanthren-11-one (3.2e).** (123 mg, 65%); yellow solid, 2.3:1.0 ratio of **3.1e**:**3.2e**: mp 110−120 °C; R_f = 0.52; ^{1}H NMR δ 8.69 (d, J = 8.8 Hz, 0.7H), 8.65 (d, J = 8.9 Hz, 0.3H), 7.84 (d, J = 8.2 Hz, 0.7H), 7.82 (d, J = 7.7 Hz, 0.3H), 7.68 (d, J = 8.1 Hz, 0.7H), 7.59 (d, J = 8.0 Hz, 0.3H), 7.50 (ddd, J = 8.5, 6.8, 1.6 Hz, 0.7H), 7.48−7.42 (m, 1H), 7.37 (ddd, J = 8.0, 6.8, 0.9 Hz, 0.3H), 7.30−7.28 (m, 1H), 7.25−7.22 (m, 2.4H), 7.14−7.12 (m, 1H), 7.11 (s, 0.3H), 7.09−7.07 (m, 1.3H), 6.16 (p, J = 2.0 Hz, 0.3H), 4.97 (t, J = 2.3 Hz, 0.7H), 4.90 (d, J = 15.3 Hz, 0.7H), 4.79 (d, J = 15.1 Hz, 0.3H), 4.75 (t, J = 1.9 Hz, 0.7H), 4.69 (s, 0.7H), 4.64 (d, J = 2.3 Hz, 0.3H), 4.41 (d, J = 15.3 Hz, 0.7H), 4.23 (d, J = 15.1 Hz, 0.3H), 2.62 (dt, J = 16.4, 2.2 Hz, 0.7H), 2.48 (dt, J = 16.4, 2.2 Hz, 0.7H), 2.44 (s, 0.9H), 2.32 (s, 2.1H), 1.67 (d, J = 1.8 Hz, 0.9H); ^{13}C NMR δ [18.0], [20.1], 21.9, 40.4, 48.3,

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[49.4], 51.1, [57.8], [64.8], 65.4, 108.1, [121.0], 121.3, [124.0], 124.4, [124.7], 125.1, [126.3], 126.4, [126.9], 127.6, 127.7, 128.1 (2C), [128.4 (2C)], [128.5], 128.6 (2C), [128.8 (2C)], [129.5], 129.7, 130.9, [130.9], [133.2], 134.3, [135.0], 136.8, [137.0], [137.5], 138.8, [139.6], [142.8], 143.0, [146.8], 174.9, [175.0]; IR (cm^{-1}) 1668, 1607; HRMS calcd for $C_{24}H_{21}NONa$ $(M + Na)^+$ 362.1521, found 362.1521.

(1*R,4*S**)-10-Benzyl-7-fluoro-4-methyl-2-methylene-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-9-one (3.1f) and (1*R**,4*S**)-10-Benzyl-7-fluoro-2,4-dimethyl-1,4-dihydro-1,4-(epiminomethano)naphthalen-9-one (3.2f).** (129 mg, 66%); orange oil, 1.2:1.0 ratio of **3.1f**:**3.2f**: R_f = 0.50; ^{1}H NMR δ 7.30−7.27 (m, 2H), 7.26 (d, J = 1.8 Hz, 1H), 7.23 (dd, J = 8.4, 5.0 Hz, 0.53H), 7.18 (dd, J = 9.0, 5.0 Hz, 0.47H), 7.11 (dd, J = 7.8, 2.1 Hz, 0.94H), 7.07 (dd, J = 7.7, 2.8 Hz, 1.06H), 6.96 (ddd, J = 9.2, 8.4, 2.6 Hz, 0.53H), 6.81−6.77 (m, 0.94H), 6.73 (dd, J = 8.0, 2.5 Hz, 0.53H), 6.05 (p, J = 1.8 Hz, 0.47H), 4.93 (t, J = 2.4 Hz, 0.53H), 4.81 (d, J = 2.7 Hz, 0.47H), 4.77 (d, J = 2.4 Hz, 0.53H), 4.76 (t, J = 2.0 Hz, 0.53H), 4.57 (s, 0.53H), 4.50 (d, J = 2.1 Hz, 0.47H), 4.41 (d, J = 15.2 Hz, 0.53H), 4.15 (d, J = 15.1 Hz, 0.47H), 2.61 (dt, J = 16.3, 2.2 Hz, 0.53H), 2.19 (dt, J = 16.2, 2.2 Hz, 0.53H), 1.84 (s, 1.41H), 1.71 (s, 1.59H), 1.63 (d, J = 1.8 Hz, 1.41H); ^{13}C NMR δ [14.1], 16.0, [18.0], 38.5, 47.1, 48.3, [49.2], [53.7], [63.5], 64.3, 109.0, [109.8 (d, J = 22.5 Hz)], 110.0 (d, J = 23.8 Hz), [111.6 (d, J = 21.3 Hz)], 111.1 (d, J = 21.3 Hz), [122.2 (d, J = 8.8 Hz)], 123.7 (d, J = 7.5 Hz), 127.7, [127.85], 128.1 (2C), [128.4 (2C)], 128.7 (2C), [128.8 (2C)], 136.6, [136.88], 136.9 (d, J = 2.5 Hz), [140.3 (d, J = 2.5 Hz)], [141.1 (d, J = 7.5 Hz)], 142.9, 144.6 (d, J = 7.5 Hz), [146.4], 160.3 (d, J = 113.8 Hz), [162.3 (d, J = 113.8 Hz)], 174.4; IR (cm^{-1}) 1672, 1603; HRMS calcd for $C_{20}H_{19}FNO$ $(M + H)^+$ 308.1451, found 308.1446.

(1*R,4*S**)-10-Benzyl-8-fluoro-4-methyl-2-methylene-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-9-one (3.1g) and (1*R**,4*S**)-10-Benzyl-8-fluoro-2,4-dimethyl-1,4-dihydro-1,4-(epiminomethano)naphthalen-9-one (3.2g). 3.1g** (30 mg, 38%), yellow oil **3.2g** (41.8 mg, 54%), clear oil.

3.1g: R_f = 0.5 (EtOAc/hexane 1:2.3); ^{1}H NMR δ 7.29−7.26 (m, 1H), 7.26−7.21 (m, 3H), 7.12−7.10 (m, 2H), 7.07 (d, J = 7.6 Hz, 1H), 6.89 (dt, J = 8.5, 0.8 Hz, 1H), 5.02 (s, 1H), 4.96 (t, J = 2.4 Hz, 1H), 4.75 (t, J = 2.0 Hz, 1H), 4.72 (d, J = 15.1 Hz, 1H), 4.49 (d, J = 15.1 Hz, 1H), 2.62 (dt, J = 16.3, 2.2 Hz, 1H), 2.21 (dt, J = 16.3, 2.2 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR δ 16.0, 38.3, 47.8, 48.6, 57.9, 108.9, 113.9 (d, J = 20 Hz), 118.0 (d, J = 3.8 Hz), 125.8 (d, J = 18.8 Hz), 127.6, 128.1 (2C), 128.7 (2C), 129.1 (d, J = 7.5 Hz), 136.5, 142.2, 144.4 (d, J = 5 Hz), 155.8 (d, J = 246.3 Hz), 174.3; IR (cm^{-1}) 1676, 1622; HRMS calcd for $C_{20}H_{19}FNO$ $(M + H)^+$ 308.1451, found 308.1450.

3.2g: R_f = 0.55 (EtOAc/hexane 1:2.3); ^{1}H NMR δ 7.33−7.28 (m, 3H), 7.14 (dd, J = 7.9, 2.0 Hz, 2H), 7.08−7.06 (m, 2H), 6.81−6.77 (m, 1H), 6.05 (p, J = 1.9 Hz, 1H), 4.96 (d, J = 2.1 Hz, 1H), 4.83 (d, J = 15.0 Hz, 1H), 4.12 (d, J = 15.0 Hz, 1H), 1.86 (s, 3H), 1.62 (d, J = 1.8 Hz, 3H); ^{13}C NMR δ 14.2, 17.9, 49.3, 54.5, 57.2, 113.0 (d, J = 21.3 Hz), 117.2 (d, J = 2.5 Hz), 127.4 (d, J = 7.5 Hz), 127.8, 128.4 (2C), 128.5 (d, J = 20.0 Hz), 128.8 (2C), 134.8, 136.8, 146.4, 148.4 (d, J = 5 Hz), 156.0 (d, J = 243.8 Hz), 174.5; IR (cm^{-1}) 1682, 1622; HRMS calcd for $C_{20}H_{19}FNO$ $(M + H)^+$ 308.1451, found 308.1442.

Single Isomer 3.1g. Reaction with $Pd(PPh_3)_4$ catalyst, TEA in THF as described for **3.1a** afforded **3.1g** (85 mg, 70%); yellow oil. For ^{1}H NMR spectra, see the Supporting Information.

(5*R,7*S**,8*S**)-11-Benzyl-8-methyl-6-methylene-10-oxo-5,6,7,8-tetrahydro-5,8-(epiminomethano)naphtho[2,3-*d*][1,3]-dioxol-7-yl acetate (4).** A solution of azabicyclooctane **3a** (207 mg, 0.62 mmol, 1.0 equiv) in acetic acid (3 mL) was injected into a vessel containing benzoquinone (7 mg, 0.065 mmol, 0.1 equiv) and $Pd(OAc)_2$ (7 mg, 0.033 mmol, 0.05 equiv). 30% aqueous H_2O_2 (78 μL, 2.55 mmol, 4.1 equiv) was added, and the mixture was stirred at 75 °C for 47 h. Standard workup afforded azabicyclooctane **4** (73 mg, 30%) as a yellow oil and recovered **3a** (38%) with the isomer ratio unchanged.

4: mp 96−99 °C; R_f = 0.40; ^{1}H NMR δ 7.26−7.27 (m, 3H), 7.15−7.13 (m, 2H), 6.83 (s, 1H), 6.49 (s, 1H), 5.96 (d, J = 1.4 Hz, 1H), 5.93 (d, J = 1.5 Hz, 1H), 5.37 (s, 1H), 5.01 (d, J = 1.5 Hz, 1H), 4.94 (d, J = 1.8 Hz, 1H), 4.72 (d, J = 15.2 Hz, 1H), 4.58 (d, J = 15.3 Hz, 1H), 4.51 (s, 1H), 2.15 (s, 3H), 1.61 (s, 3H); ^{13}C NMR δ 12.9, 21.3, 48.6, 51.5, 63.0, 73.9, 101.5, 103.6, 105.4, 112.0, 127.7, 128.3 (2C), 128.6 (2C), 131.4, 133.8, 136.5, 143.9, 147.0, 147.6, 171.2, 171.7; IR (cm^{-1}) 1740, 1672; HRMS calcd for $C_{23}H_{21}NO_5Na$ $(M + Na)^+$ 414.1317, found 414.1319.

(5*R,8*S**,*E*)-11-Benzyl-6-(4-bromobutylidene)-8-methyl-5,6,7,8-tetrahydro-5,8-(epiminomethano)naphtho[2,3-*d*][1,3]-dioxol-10-one (5).** A solution of azabicyclooctane **3.1a** (39 mg, 0.12 mmol, 1.0 equiv) in dichloromethane (5 mL) was injected into a pressure tube containing the Grubbs II catalyst (5 mg, 0.0059 mmol, 0.05 equiv), followed by neat 5-bromo-1-pentene (21 μL, 0.18 mmol, 1.5 equiv). The pressure tube was flushed with argon and sealed, and the mixture was stirred at 40 °C for 19 h. The crude product was purified by preparative TLC to afford bromide **5** (35 mg, 66%) as a colorless oil: R_f = 0.41; ^{1}H NMR δ 7.29−7.27 (m, 2H), 7.26−7.25 (m, 1H), 7.11 (dd, J = 8.0, 1.9 Hz, 2H), 6.81 (s, 1H), 6.53 (s, 1H), 5.94 (d, J = 1.5 Hz, 1H), 5.91 (d, J = 1.5 Hz, 1H), 5.14 (dt, J = 7.1, 2.1 Hz, 1H), 4.62 (d, J = 15.2 Hz, 1H), 4.51 (d, J = 15.2 Hz, 1H), 4.45 (s, 1H), 3.25 (dd, J = 6.6, 2.3 Hz, 2H), 2.46 (d, J = 16.1 Hz, 1H), 2.10 (d, J = 16.1 Hz, 1H), 2.02−1.93 (m, 2H), 1.79 (p, J = 6.9 Hz, 2H), 1.70 (s, 3H); ^{13}C NMR δ 16.5, 27.1, 32.0, 33.2, 36.7, 47.3, 48.3, 64.7, 101.2, 103.6, 104.1, 121.2, 127.6, 128.2 (2C), 128.6 (2C), 133.2, 135.2, 136.5, 136.9, 146.1, 147.1, 174.7; IR (cm^{-1}) 1666; HRMS calcd for $C_{24}H_{24}BrNO_3Na$ $(M + Na)^+$ 476.0837, found 476.0847.

***N*-((*E*)-4-((5*R**,8*S**)-11-Benzyl-8-methyl-10-oxo-7,8-dihydro-5,8-(epiminomethano)naphtho[2,3-*d*][1,3]dioxol-6(5*H*)-ylidene)butyl)-*N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (6).** A solution of bromide **5** (37 mg, 0.081 mmol, 1.0 equiv) in DMF (2 mL) was added dropwise at rt to the mixture of *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (27 mg, 0.12 mmol, 1.5 equiv) and anhydrous K_2CO_3 (29 mg, 0.21 mmol, 2.6 equiv) in DMF (1 mL). The mixture was stirred at 60 °C for 19 h, and the crude product was purified by preparative TLC yielding sulfonamide **6** (43 mg, 89%) as a clear oil: R_f = 0.40; ^{1}H NMR δ 7.63 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.25 (s, 1H), 7.23 (s, 2H), 7.08 (dd, J = 7.5, 2.0 Hz, 2H), 6.80 (s, 1H), 6.50 (s, 1H), 5.92 (dd, J = 18.9, 1.3 Hz, 2H), 5.71−5.63 (m, 1H), 5.19 (tt, J = 7.1, 2.0 Hz, 1H), 5.03 (dq, J = 7.5, 1.5 Hz, 1H), 5.00 (t, J = 1.0 Hz, 1H), 4.74 (d, J = 15.2 Hz, 1H), 4.44 (s, 1H), 4.38 (d, J = 15.2 Hz, 1H), 3.10 (hept, J = 7.5 Hz, 2H), 3.00 (td, J = 6.9, 1.8 Hz, 2H), 2.41 (s, 3H), 2.38 (d, J = 16.9 Hz, 1H), 2.22 (q, J = 7.6 Hz, 2H), 2.03 (d, J = 16.5 Hz, 1H), 1.81 (hept, J = 7.4 Hz, 2H), 1.70 (s, 3H), 1.49 (p, J = 7.4 Hz, 2H); ^{13}C NMR δ 16.5, 21.6, 25.9, 28.3, 33.4, 36.7, 47.3, 47.9, 48.1, 48.2, 64.6, 101.2, 103.6, 104.1, 117.2, 122.0, 127.2 (2C), 127.5, 128.1 (2C), 128.6 (2C), 129.8 (2C), 133.3, 134.7, 135.3., 135.7, 136.88, 136.91, 143.3, 146.1, 147.1, 174.7; IR (cm^{-1}) 1663, 1479; HRMS calcd for $C_{35}H_{39}N_2O_5S$ $(M + H)^+$ 599.2580, found 599.2573.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds prepared in this study, variable temperature ^{1}H NMR for compound **2a**, data from NOE experiments on compounds **4** and **5** and quantitative GC−MS data for compounds **3a**−**g**. This material is available free of charge via Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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