CHAPTER 2

Development of a Diastereoselective 1,2-Addition to Sulfinyl Imines: Application to the Hasubanan Alkaloids[†]

2.1. Introduction

As was illustrated in the previous chapter, the hasubanan alkaloids remain elusive targets for *enantioselective* total synthesis. While their structure comprises a relatively compact, tetracyclic framework, their azapropellane core presents several notable challenges. First, this backbone is structurally defined by a central pair of fully-substituted carbon stereocenters, a motif difficult to access using modern synthetic methods. In addition, the different oxidation patterns that decorate the propellane core introduce variable functionality that can (1) enhance its sterically congested nature, and (2) significantly alter their relative reactivity. The following chapter details our own

[†] Portions of this chapter have been reproduced from published studies (see references 1 and 2) and the supporting information found therein. The research presented in this chapter was completed in collaboration with Kangway V. Chuang, a graduate student in the Reisman group.

efforts toward these alkaloids,[1,2] which have culminated in the efficient enantioselective preparation of several hasubanans.

2.2. Synthetic Approach

2.2.1. Retrosynthetic Analysis. As part of a research program directed towards the synthesis of various alkaloid natural products, we sought to develop a unified strategy for the preparation of several hasubanan alkaloids (Figure 1). More specifically, it was hypothesized that the propellane core of **2**, **4**, and **10** could be readily accessed from an appropriately functionalized dihydroindolone (e.g., **91**) via late-stage introduction of the appropriate peripheral oxidation. The dihydroindolone was anticipated to derive from 4-aminocyclohexadienone **92**, the product of a diastereoselective 1,2-addition of an organometallic nucleophile to a quinone-derived sulfinyl imine (e.g., **93**). Although Swenton and coworkers utilized an intermediate akin to **92** in their synthetic studies toward the erythrina alkaloids, the *enantioselective* preparation of such compounds has not been fully explored.[3] Notably, by varying the identity of the nucleophile, several members of the hasubanan family could be readily accessed.

While attractive from a strategic standpoint, it was recognized that the proposed synthesis presented several challenges. Its successful application to the total synthesis of the hasubanans would require (1) the development of a 1,2-addition reaction to quinone-derived imines *with control over the absolute configuration about the C14-N bond*, and (2) the utilization of a nitrogen protecting group that would prevent any deleterious dienone-phenol rearrangements.[4] Despite numerous reports targeting the preparation enantioenriched chiral amines, the asymmetric synthesis of α,α-disubstituted amines by

nucleophilic 1,2-addition to ketimines—and specifically, benzoquinone-derived imines—remains an underdeveloped arena in organic synthesis.[5,6] Moreover, current *catalytic, asymmetric* syntheses of these structural motifs are limited by the scope of the nucleophile or the *N*-protecting group employed.[7]

With these considerations in mind, it was envisioned that benzoquinone imines derived from *N*-*tert*-butanesulfinamide should fulfill the abovementioned criteria. Pioneering work by Ellman and coworkers has demonstrated that *N*-*tert*-butanesulfinyl aldimines and ketimines undergo nucleophilic additions of organolithium and organomagnesium reagents to furnish *N*-sulfinamides with high diastereoselectivity.[8] Further, in the context of sulfinamide **92,** the electron withdrawing nature of the *N*-sulfinyl group was expected to disfavor any potential dienone-phenol rearrangements. Detailed below are our preliminary studies that demonstrate the feasibility of this approach for the synthesis of hasubanan alkaloids.

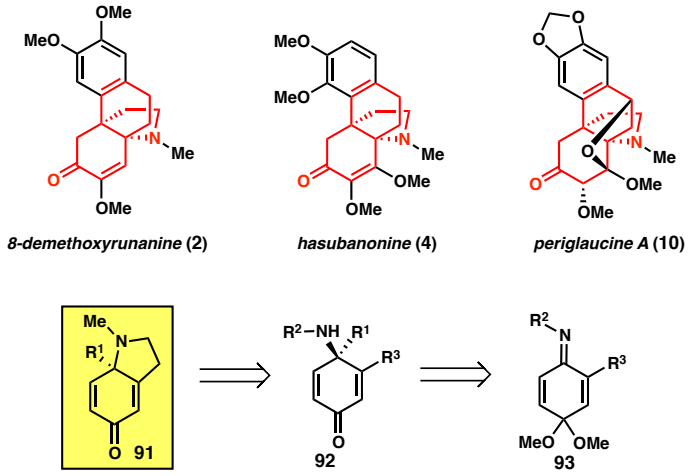


Figure 1. Representative hasubanan alkaloids and proposed strategy.

2.2.2. Development of a Diastereoselective 1,2-Addition to Benzoquinone-Derived t-Butanesulfinimines. At the outset of our studies, we sought to evaluate conditions for the synthesis of benzoquinone-derived sulfinimines (e.g., **96**, Figure 2). Studies by Ellman and coworkers have shown that *N*-sulfinyl ketimines can be readily prepared from the direct condensation of *N*-*tert*-butanesulfinamide with a variety of ketones under mildly Lewis acidic conditions.[6] Our first objective was to determine whether such conditions would be amenable to the synthesis of **96** from quinone monoketal **95**.

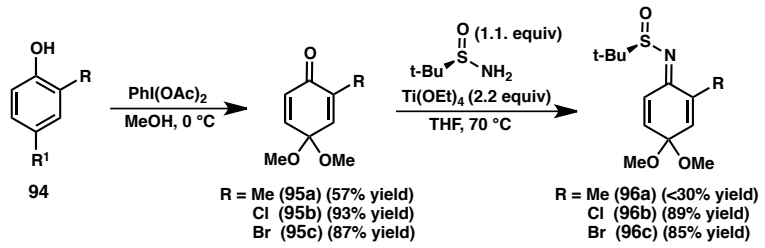


Figure 2. Preparation of quinone-derived sulfinimines.

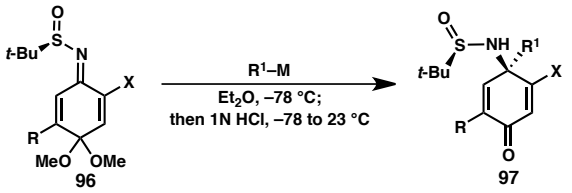
To this end, quinone monoketals **95a-95c** were prepared in one step by oxidation of the corresponding phenols (Figure 2). Our preliminary studies revealed that treatment of **95a** with *N*-*tert*-butanesulfinamide (1.1 equiv) and $Ti(OEt)_4$ (2.2 equiv) in THF at 70 °C for 40 hours furnished sulfinimine **96a**, albeit in low yield. Monitoring the conversion and yield over time indicated that the sulfinimine product was decomposing under the reaction conditions. It was reasoned that utilization of a benzoquinone monoketal bearing an electron-withdrawing substituent would inductively activate the carbonyl towards nucleophilic addition, thereby accelerating the condensation reaction and reducing the

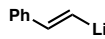
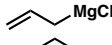
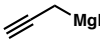
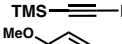
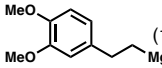
reaction time. Indeed, exposure of **95b** and **95c** to the standard reaction conditions provided **96b** and **96c** in 89% and 85% yield, respectively. In addition to the improved yields of sulfinimine products, halogenated compounds **96b** and **96c** were equipped with functional handles that could be elaborated towards more complex alkaloid intermediates.

With halo-quinone sulfinimines **96b** and **96c** in hand, we turned to evaluating the diastereoselectivity of 1,2-addition reactions of readily available organolithium reagents. To our delight, treatment of chloride **96b** with *n*-BuLi (1.1 equiv) in Et_2O at –78 °C delivered sulfinamide **97a** in 90% yield and 97:3 d.r. (Table 1, entry 1). Importantly, the acidic workup conditions facilitated cleavage of the dimethyl ketal without promoting the formation of dienone migration products. Moreover, the diastereomeric sulfinamide products were easily separated by silica gel chromatography, allowing for the preparation of enantiopure 4-aminocyclohexadienones upon cleavage of the sulfinamide.

High levels of diastereoselectivity were also obtained when bromide **96c** was used (entry 3).[9] A solvent screen revealed ethereal solvents were optimal, with Et_2O or THF providing the highest yields and diastereoselectivities. Use of commercially available alkyllithiums furnished the desired sulfinamides in uniformly high diastereoselectivities for both the chloride and bromide substrates (entries 1, 3-7). On the other hand, 1,2-addition of phenyllithium afforded sulfinamides **97b** and **97h** in moderate d.r. (entries 2 and 8). Interestingly, improved selectivities were observed when *o*-, *m*-, or *p*-tolyllithium was employed (entries 9-11). Vinyl- and alkynyllithium reagents also proved viable nucleophiles for this reaction, providing the corresponding sulfinamides in high d.r. (entries 12, 13, 16). In the case of allyl and propargyl nucleophiles, the readily available Grignard reagents were utilized instead of the corresponding organolithium reagents. The

relative stereochemistry of the newly formed stereogenic center was determined for **97d** by single crystal X-ray diffraction (see Supporting Information) and is consistent with reaction through a closed, chair-like transition state. The stereochemistry of the remaining sulfinamide products was assigned in analogy to **97d**.



entry	X	R		R^1–M (equiv)	pdt	d.r.[a]	yield (%)[b]
1	Cl	H	(**96b**)	*n*-BuLi (1.1)	**97a**	97:3	90
2	Cl	H		PhLi (1.1)	**97b**	78:22	76
3	Br	H	(**96c**)	*n*-BuLi (1.1)	**97c**	98:2	88
4	Br	H		EtLi (1.1)	**97d**	98:2	96
5	Br	H		MeLi (1.1)	**97e**	98:2	91
6	Br	Me	(**96d**)	MeLi (1.1)	**97f**	98:2	91
7	Br	Cl	(**96e**)	MeLi (1.1)	**97g**	97:3	91[c]
8	Br	H		PhLi (1.1)	**97h**	80:20	74
9	Br	H		*o*-MeC_6H_4Li (2.0)	**97i**	97:3	86
10	Br	H		*m*-MeC_6H_4Li (2.0)	**97j**	91:9	79
11	Br	H		*p*-MeC_6H_4Li (2.0)	**97k**	91:9	78
12	Br	H		 (2.0)	**97l**	98:2	68[d]
13	Br	H		 (2.0)	**97m**	98:2	71[d]
14	Br	H		 (1.1)	**97n**	87:13	82[d]
15	Br	H		 (1.1)	**97o**	>97:3	91
16	Br	H		 (2.0)	**97p**	>98:2	99[c,d,e]
17	Br	H		 (1.1)	**97q**	96:4	82[d]

[a]Determined by LCMS. [b]Isolated yield of major diastereomer. [c]Isolated as a mixture of diastereomers. [d]Reaction conducted in THF. [e]Reaction conducted at 0 °C.

Table 1. Scope of diastereoselective 1,2-addition to quinone-derived sulfinimines.

The vinyl halide moiety of the enantioenriched sulfinamide products served as a useful functional handle for further elaboration. For example, vinyl bromide **97e** (R^1 =

Me) undergoes a variety of palladium-catalyzed cross-coupling reactions allowing access to arene-, allyl-, and alkyne-substituted products (Figure 3, **98**, **99**, and **101**, respectively). Alternatively, vinyl bromide **97n** can be coupled with vinyl tributylstannane and treated with Hoveyda-Grubbs second generation catalyst[10] to provide bicycle **100** in excellent yield over two steps.

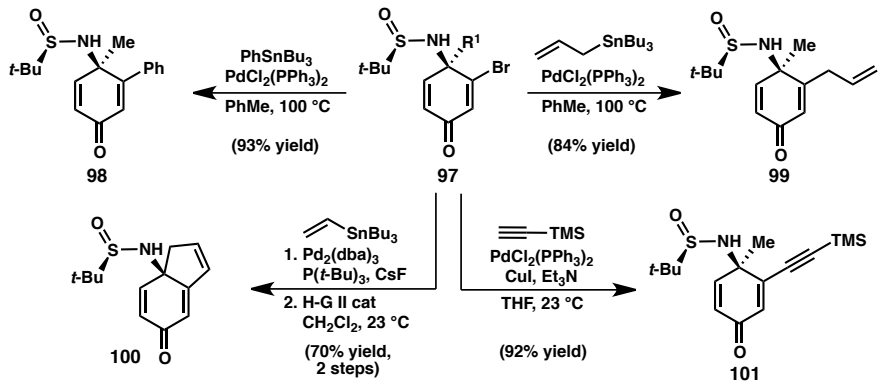


Figure 3. Synthetic transformations of sulfinamide **97**.

Having established a strategy to prepare enantioenriched 4-aminocyclohexadienones, we turned our attention to the synthesis of alkaloid natural products. Although we ultimately sought to target the propellane alkaloids, we recognized that we could readily apply our methodology toward the synthesis of the erythrina alkaloids. Specifically, it was envisioned that the spirocyclic core of 3-(–)-demethoxyerythratidinone (**108**)[11,12] could be derived from **96c** via a one-pot 1,2-addition / intramolecular *N*-alkylation protocol (Figure 4). In the event, addition of aryllithium species **102**[13] to bromosulfinimine **96c** initially generates sulfinamide anion **103**, which upon warming to room temperature delivers spirocycle **104** in 74% yield as a single diastereomer. This

highly convergent reaction provides direct access to the spirocyclic core of **108** with excellent levels of stereocontrol.

To construct the pyrrolidine ring of the natural product, an initial Pd-catalyzed cross-coupling of **104** with vinyl stannane **105** affords enol ether **106** in 85% yield. After considerable experimentation, it was found that brief exposure of **106** to anhydrous HCl in THF at 0 °C resulted in cleavage of the sulfinamide and promoted intramolecular condensation to give indolone **107**. Notably, use of weaker acids or stirring for longer periods resulted in substantially diminished yields due to competitive decomposition of the product. At this point, completion of the synthesis required selective direduction of **107**. In the event, exposure of **107** to heterogeneous hydrogenation conditions furnished **108** in 65% yield. At 6 steps and 26% overall yield, this represents the shortest enantioselective synthesis of **108** reported to date.[14]

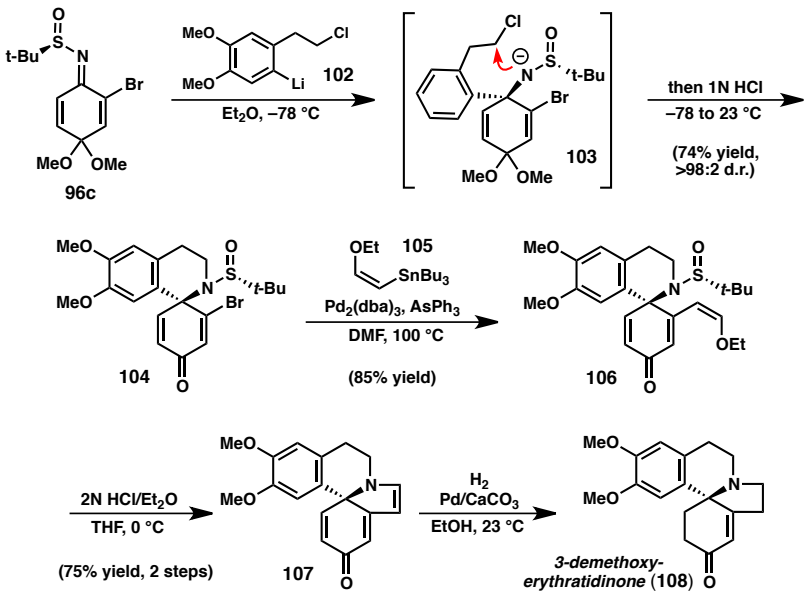


Figure 4. Enantioselective synthesis of (–)-3-demethoxyerythratidinone (**108**).

2.2.3. Synthesis of Hasubanan Alkaloids. Having successfully prepared 3-demethoxyerythratidinone, we turned our attention to the synthesis of the propellane-containing hasubanan alkaloids, initially targeting 8-demethoxyrunanine (**2**)[15] and cepharamine (**1**).[16] Retrosynthetically, an intramolecular Friedel-Crafts-type reaction of dihydroindolone **109** was expected to deliver the propellane core of **2** (Figure 5).[17] On the other hand, we anticipated that intramolecular conjugate addition of **110**, which bears a bromoaryl substituent, should occur from the *o*-position of the arene to deliver the oxidation pattern found in cepharamine. Importantly, the preparation of either dihydroindolone intermediate could be accomplished from sulfinimine **96c** following Grignard addition with an appropriately functionalized nucleophile.

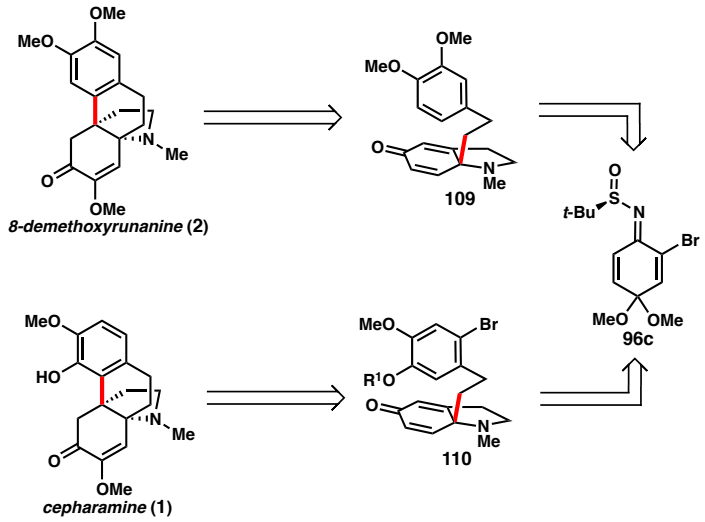


Figure 5. Retrosynthetic analysis for the hasubanan alkaloids.

In the forward sense, addition of Grignard reagent **111** to a solution of sulfinimine **96c** at –78 °C followed by in situ methylation provided sulfinamide **113**, which upon

purification was isolated in 77% as a single diastereomer (Figure 6). In contrast to the previous studies toward 3-demethoxyerythratidinone, AcOH was used for the acidic workup to prevent hydrolysis of the sulfinamide protecting group. Pyrrolidine ring installation was achieved using the previously optimized protocol. Thus, sulfinamide **113** was coupled to vinyl stannane **105** to initially deliver enol ether **115** in excellent yield. Acid-mediated sulfinamide cleavage and cyclization proceeded smoothly to give the corresponding enamine, which was found to be an unstable intermediate. As a result, the crude product was immediately exposed to a mixture of sodium borohydride in AcOH and MeOH to give chromatographically stable dihydroindolone **109** in 96% yield over 2 steps. To access cepharamine, dihydroindolone **117**, which bears a differentially protected phenol, was prepared through an analogous route from **112**.

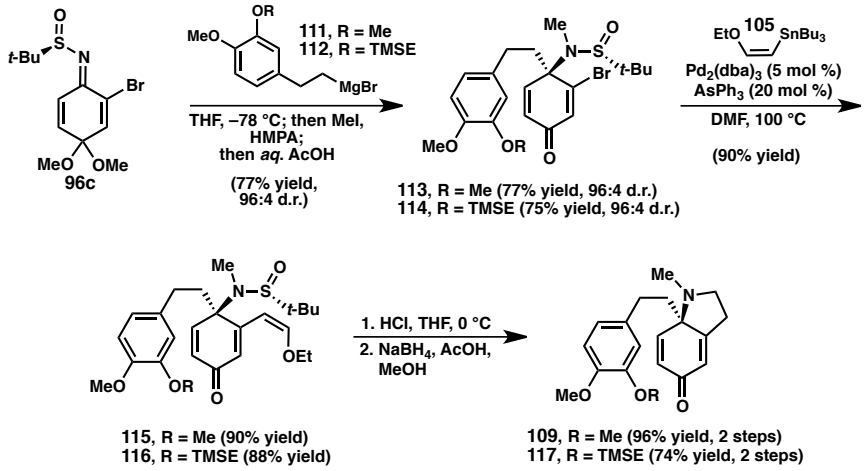


Figure 6. Synthesis of dihydroindolones **109** and **117**.

With dihydroindolones **109** and **117** in hand, we were poised to examine the key intramolecular Friedel-Crafts reaction (Figure 7). After a preliminary screen of Lewis

acids, we were pleased to find that BF_3•OEt_2 promoted the desired cyclization to give propellane **118**, albeit in modest yield. A significant improvement in reactivity was observed when strong Brønsted acids were employed. Indeed, subjection of **109** to triflic acid[18] generates tetracycle **118** as the exclusive cyclization product in 97% yield. The selective addition to the trisubstituted enone olefin is proposed to result from formation of a discrete protonated dienone intermediate that favors the more stable, tertiary carbocation at the C13 position. To access the cepharamine backbone, TMSE-protected phenol **117** was brominated at the C1 position, thereby precluding C1 cyclization to afford the runanine oxidation pattern. Instead, addition of TfOH to the bromide intermediate facilitated cleavage of the TMSE group and cyclization to afford propellane **119**.

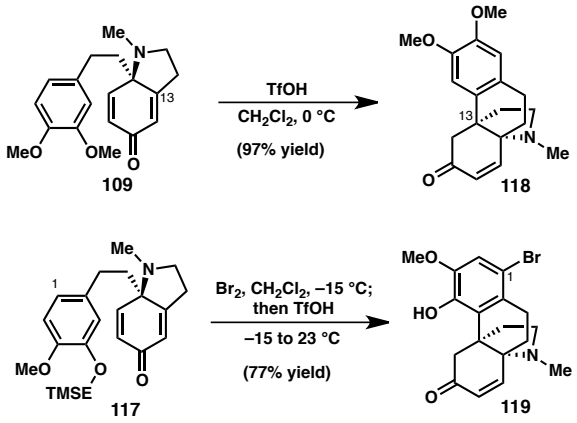


Figure 7. Preparation of aza-propellanes **118** and **119**.

Completion of the syntheses of **1** and **2** required adjustment of the oxidation levels at C7 (Figure 8). Initial attempts to accomplish this objective involved nucelophilic

epoxidation of **118** using hydrogen peroxide and lithium hydroxide in MeOH.[19] Gratifyingly, heating the reaction mixture to 50 °C promoted the formation of 8-demethoxyrunanine (**2**); however, it was isolated in only 15% yield. It was hypothesized that the overall process could be improved by isolating the presumed epoxide intermediate. Under carefully optimized conditions, **118** was cleanly converted to epoxide **120** using *t*-butyl hydroperoxide and Triton B in THF. However, efforts to purify **120** by silica gel chromatography led to isolation of the desired epoxide and an unexpected compound, hemiaminal **121**.[20] Interestingly, prolonged exposure of the crude epoxide to silica gel facilitated conversion to the hemiaminal product, which could now be isolated in 76% yield.

While initially dismayed by this result, we noted that the structural framework of **121** comprises that of the cepharatines, a class of natural products recently reported by Zhang and coworkers.[21] In particular, **121** different from cepharatine D (**123**) by a single oxidation level. With an eye toward completing a synthesis of this new class of natural products, we set out to effect a benzylic oxidation of **121**. Initial attempts to desaturate the C9-C10 bond under radical conditions (e.g., DDQ) failed to provide appreciable amounts of **123**. Given the relative acidity of the C9 protons in **121**, attention was turned to enolization strategies to install the requisite olefin. A survey of reaction conditions revealed that treatment of the potassium enolate of **121** with *N-tert*-butylbenzenesulfinimidoyl chloride (**122**) was optimal,[22] providing cepharatine D in 60% yield.

With access to the cepharatine D, efforts returned to isolation of epoxide **120** en route to 8-demethoxyrunanine. Purification of the crude epoxide on Florisil significantly

suppressed formation of hemiaminal **121**, allowing for isolation of **120** in good yield (Figure 8). From **120**, conversion to the natural product required epoxide opening with MeOH and dehydration to the corresponding enone. After considerable optimization,[23] the epoxide was successfully converted to **2** using tetrabutylammonium methoxide,[24] a reagent found to be uniquely effective for this transformation. Using this route, **2** and cepharatine D (**123**) were both prepared in only 9 steps from commercially available 2-bromo-4-methoxyphenol in 19% and 22% yield, respectively.

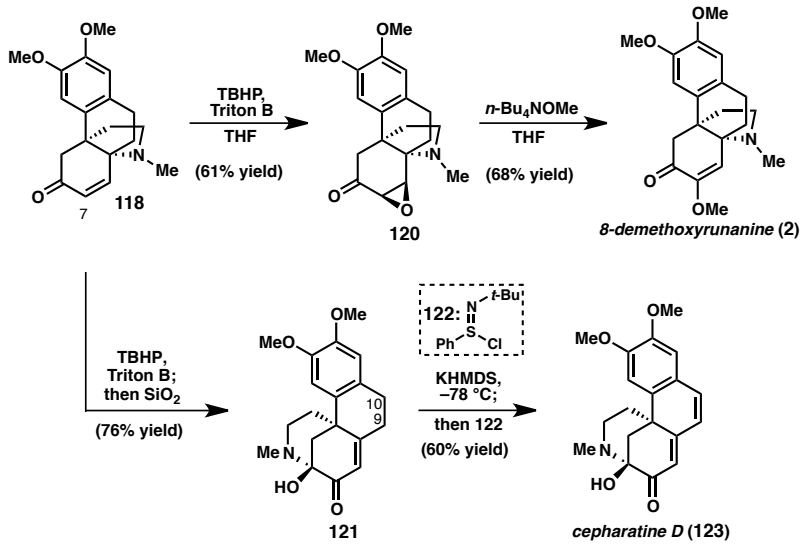


Figure 8. Enantioselective synthesis of 8-demethoxyrunanine and cepharatine D.

After completing a synthesis of **2** and **123**, we turned our attention to the preparation of cepharamine (**1**) from bromo-propellane **119**. Unfortunately, epoxidation of **119** under the previously optimized conditions generated **124** in only 40% yield (Figure 9). Efforts to drive the epoxidation reaction to completion were complicated by competitive oxidative rearrangement of the epoxide product, resulting in the formation of a lactone

byproduct. Moreover, exposure of epoxide **124** to *n*-Bu_4NOMe in THF provided only trace amounts of enol ether **125**. Reasoning that deprotonation of the phenolic O–H might contribute to the poor reactivity observed, several protected variants of **124** were prepared; however, exposure of the corresponding epoxides to a variety of methoxide sources only produced enol ether products in prohibitively low quantities. These studies illustrate how subtle perturbations in the arene oxidation patterns can strikingly alter the reactivity of the aza-propellane framework.

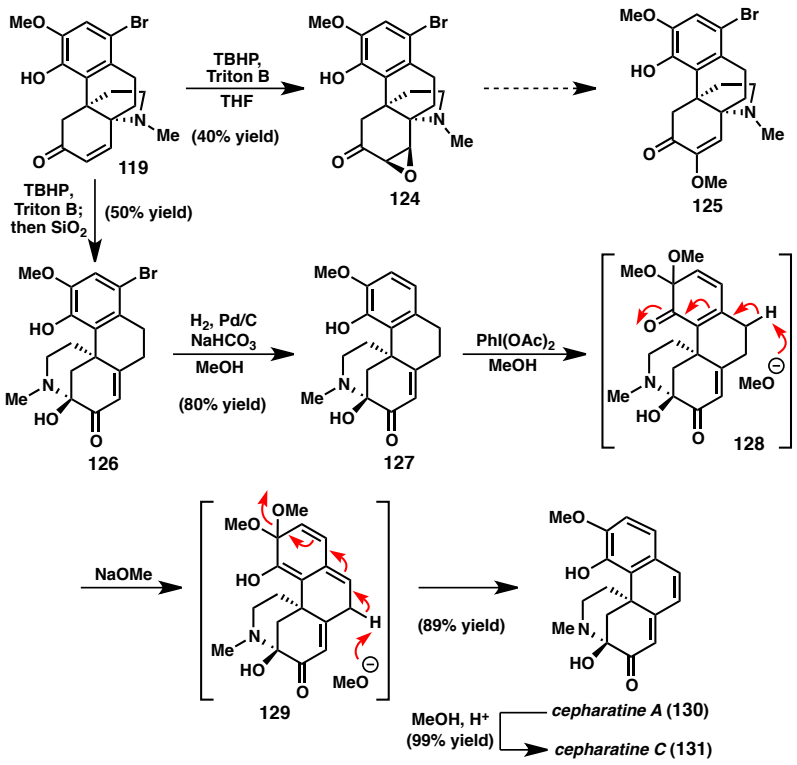


Figure 9. Enantioselective synthesis of cepharatines A and C.

While we were unable to complete a synthesis of cepharamine, we subsequently investigated the conversion of bromo-propellane **119** to cephatines A (**130**) and C (**131**).

Epoxidation of **119** followed by exposure to silica gel provided aminal **126** in 50% yield. Palladium-catalyzed hydrodebromination of **126** proceeded smoothly to generate **127**; however, attempts to oxidize **127** using **122** (see Figure 8) only returned starting material. Rather than protect the phenol moiety, the reactivity of this functional group was exploited to install the desired oxidation. In the event, treatment of phenol **127** with iodobenzene diacetate in MeOH generated *o*-quinone monoketal **128**, which upon rearomatization under basic conditions provided cepharatine A (**130**) in 89% yield. Cepharatine A was readily converted to cepharatine C by exposure to MeOH under acidic reaction conditions. Using this reaction sequence, **130** and **131** could be prepared in 10 and 11 steps, respectively, each in 10% overall yield from commercially available starting materials.

2.3. Concluding Remarks

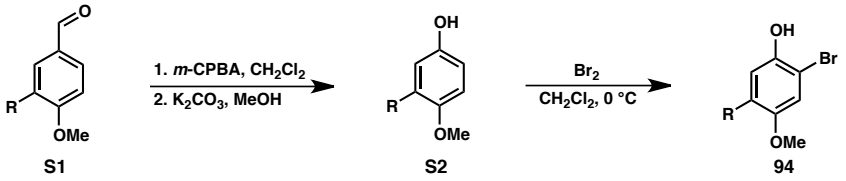
In conclusion, we have developed a unified strategy for the synthesis of 3-demethoxyerythratidinone and several hasubanan alkaloid natural products. Specifically, a highly diastereoselective 1,2-addition of organometallic reagents to benzoquinone-derived *tert*-butanesulfinimines was established, which provides access to enantioenriched 4-aminocyclohexadienone products. This methodology enabled the enantioselective construction of functionalized dihydroindolones, which were found to undergo intramolecular Friedel-Crafts conjugate additions to furnish the propellane cores of several hasubanan alkaloids. As a result of these studies, the first enantioselective total syntheses of 8-demethoxyrunanine and cepharatines A, C, and D were accomplished in 9-11 steps from commercially available starting materials. The versatility of our synthetic

approach is further evidenced in our efforts toward acutumine, a more structurally complex propellane alkaloid. Our synthetic endeavors toward this alkaloid are discussed in the following chapter.

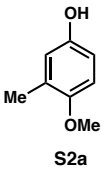
2.4. Experimental Section

2.4.1. Materials and Methods. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), acetonitrile (MeCN), and toluene (PhMe) were dried by passing through activated alumina columns. MeOH was distilled over magnesium oxide and triethylamine (Et_3N) was distilled over calcium hydride. All other commercially obtained reagents were used as received unless specifically indicated. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or $KMnO_4$ staining. Flash column chromatography was performed either as described by Still et al. (Still, W. C., Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923-2925) using silica gel (partical size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Diastereomeric ratios were determined using an Agilent 1190 or 1290 Series LC/MS (λ = 254 nm) using a ZORBAX Eclipse Plus C18 column (RRHD 1.8 μm, 2.1 x 50 mm, 11,072 plates). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) or a Varian Inova 500 (at 500 MHz and 126 MHz respectively), and are reported relative to internal chloroform (^{1}H, δ = 7.26; ^{13}C, δ = 77.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility. HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected.

2.4.2. Procedures and Spectroscopic Data.



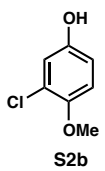
Steps 1 and 2 for phenol preparation: Baeyer-Villiger Oxidation / Saponification. Preparation of 4-methoxy-3-methylphenol (S2a).



S2a

A 50 mL flask was charged with 4-methoxy-3-methylbenzaldehyde (**S1a**) (500 mg, 3.33 mmol, 1 equiv) and CH_2Cl_2 (11 mL). The resulting solution was cooled to 0 °C in an ice-water bath and *m*-CPBA (1.40 g, 70-75%, 5.66 mmol, 1.7 equiv) was added in 3 portions. The resulting suspension was allowed to warm to room temperature, and was stirred for 2 hours at that temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ (11 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give a pale yellow oil. The crude formate ester was dissolved in MeOH (17 mL) and cooled to 0 °C. Solid K_2CO_3 (920 mg, 6.66 mmol) was added in one portion, and the resulting solution was stirred at 0 °C for 15 min. The reaction was quenched with aqueous HCl (9 mL of a 2N solution). The organic solvent was removed by rotary evaporation, and resulting aqueous layer was extracted with Et_2O (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash chromatography (10% EtOAc/Hexanes) to afford **S2a** (361 mg, 78% yield over 2 steps) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (d, J = 8.8 Hz, 1H), 6.66 (d, J = 3.2 Hz, 1H), 6.62 (dd, J = 8.7, 3.1 Hz, 1H), 4.77 (s, 1H), 3.78 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.0, 149.0, 128.1, 118.0, 112.5, 111.3, 56.0, 16.2; IR (NaCl/thin film): 3350, 2950, 2833, 1501, 1465, 1430, 1286, 1217, 1180, 1034 721 cm^{-1}; HRMS (EI+) calc'd for $C_8H_{10}O_2$ $[M+H]^+$ 138.0681, found 138.0685.

Preparation of 3-chloro-4-methoxyphenol (S2b).

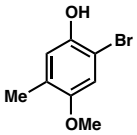


S2b

Prepared from 11.1 mmol of 3-chloro-4-methoxybenzaldehyde (**S1b**) using the above general procedure. The crude product was purified by flash chromatography (5→20% EtOAc/Hexanes) to give **S2b** (1.10 g, 62% yield) as

a beige solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, J = 2.9 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.70 (dd, J = 8.8, 2.9 Hz, 1H), 4.94 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 149.4, 123.0, 117.6, 114.2, 113.5, 56.8; IR (NaCl/thin film): 3400, 2947, 2837, 1500, 1437, 1278, 1209, 1180, 1058, 907, 746 cm^{-1}; HRMS (EI+) calc'd for $C_7H_7O_2Cl$ $[M+H]^+$ 158.0135, found 158.0125.

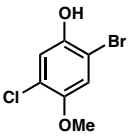
Step 3. Bromination. Preparation of 2-bromo-4-methoxy-5-methylphenol (94d).



94d

A 50 mL flask was charged with phenol **S2a** (300 mg, 2.17 mmol, 1 equiv) and CH_2Cl_2 (11 mL). The resulting solution was cooled to 0 °C in an ice-water bath, and bromine (0.117 mL, 2.28 mmol, 1.05 equiv) was added dropwise. (*Caution! A copious amount of HBr gas is generated as the reaction proceeds. A 16-gauge needle was pierced through the septa to allow the reaction to vent*). The reaction was allowed to stir at 0 °C for 30 min, then quenched with saturated aqueous $NaHCO_3$ (11 mL). The organic layer was washed with water (2 x 10 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography (10% EtOAc/Hexanes) to give **94d** (440 mg, 93% yield) as a beige solid. The spectral data obtained for **94d** is consistent with that reported in the literature.[25]

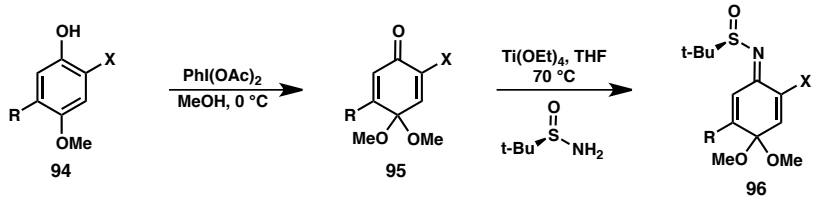
Preparation of 2-bromo-5-chloro-4-methoxyphenol (94e).



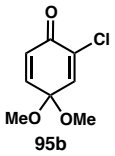
94e

Prepared from 1.26 mmol of phenol **S2b** using the general procedure. **94e** (288 mg, 96% yield) was isolated as a pale beige solid. The crude product was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (s, 1H), 7.01 (s, 1H), 5.17 (s, 1H), 3.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5, 146.6, 123.0, 117.6, 115.4, 107.6, 56.9; IR (NaCl/thin film): 3248, 2969, 1504, 1442, 1400, 1205, 1182, 1073, 859, 784 cm^{-1}; HRMS (EI–) calc'd for $C_7H_7O_2Cl$ $[M–H]^-$ 234.9167, found 234.9198.

General procedure for the preparation of quinone sulfinimine substrates:



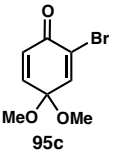
Step 1. Phenolic oxidation. Preparation of chloroquinone 95b.



95b

A 250 mL flask was charged with 2-chloro-4-methoxyphenol (**94b**) (2.00 g, 12.6 mmol, 1.0 equiv) and MeOH (70 mL). The resulting solution was cooled to 0 °C in an ice-water bath and a solution of iodobenzene diacetate (4.47 g, 13.9 mmol, 1.1 equiv) in MeOH (40 mL) was added dropwise via cannula. The reaction was allowed to stir at 0 °C for 10 min, then quenched with saturated aq. $NaHCO_3$ (30mL). The organic solvent was removed by rotary evaporation, and the resulting residue was diluted with Et_2O (60 mL). The aqueous layer was extracted with Et_2O (2 x 50 mL), and the combined organic layers were washed with brine (60 mL), dried over $MgSO_4$, concentrated, and purified by flash chromatography (6:1 Hexanes:EtOAc) to afford **95b** (2.33 g, 98% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, J = 2.9 Hz, 1H), 6.85 (dd, J = 10.3, 2.9 Hz, 1H), 6.36 (d, J = 10.3 Hz, 1H), 3.38 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 143.7, 139.3, 134.0, 128.6, 94.2, 50.6; IR (NaCl/thin film): 2943, 2833, 1684, 1647, 1616, 1331, 1118, 1061, 1036, 1018, 962, 948, 824, 812 cm^{-1}; HRMS (EI+) calc'd for $C_8H_9O_3Cl$ $[M+H]^+$ 188.0240, found 188.0211.

Preparation of bromoquinone 95c.

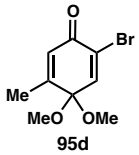


95c

Prepared from 19.7 mmol of 2-bromo-4-methoxyphenol using the general procedure. The quinone product was purified by flash chromatography (10→20% EtOAc/Hexanes) to give **95c** (4.00 g, 87% yield) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 3.2 Hz, 1H), 6.82 (dd, J = 10.3 Hz, 3.2 Hz, 1H), 6.33 (d, J = 10.3 Hz, 1H), 3.34 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 143.9, 143.5, 128.0, 125.7, 94.2, 50.5; IR (NaCl/thin film): 3057, 2944, 2834, 1680, 1644, 1612, 1460, 1375, 1332, 1298, 1280, 1221, 1180, 1119, 1062, 1038, 1010, 964,

939, 823, 742 cm^{-1}; HRMS (EI+) calc'd for $C_8H_9O_3Br$ $[M–OMe]^+$ 200.9551, found 200.9551.[26]

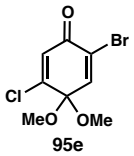
Preparation of bromoquinone 95d.



95d

Prepared from 1.53 mmol of 2-bromo-4-methoxy-5-methylphenol (**94d**) using the general procedure. The quinone product was purified by flash chromatography (0→20% EtOAc/Hexanes) to give **95d** (350 mg, 93% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (s, 1H), 6.33 (q, *J* = 1.5 Hz, 1H), 3.26 (s, 6H), 1.94 (d, *J* = 1.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 156.8, 144.7, 128.0, 127.2, 97.1, 51.2, 16.6; IR (NaCl/thin film): 3315, 3050, 2936, 2832, 1675, 1609, 1437, 1327, 1226, 1104, 1055, 923, 742 cm^{-1}; HRMS (EI+) calc'd for $C_9H_{11}O_3Br$ $[M\text{-}OMe]^+$ 214.9708, found 214.9706.

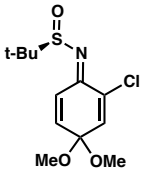
Preparation of dihaloquinone 95e.



95e

Prepared from 0.97 mmol of 2-bromo-5-chloro-4-methoxyphenol (**94e**) using the general procedure. The quinone product was purified by flash chromatography (5→10% EtOAc/Hexanes) to give **95e** (229 mg, 88% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.72 (s, 1H), 3.34 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 153.2, 144.2, 129.5, 126.5, 96.4, 51.7; IR (NaCl/thin film): 3435, 3051, 2940, 2841, 1673, 1612, 1458, 1328, 1105, 1071, 997, 755 cm^{-1}; HRMS (EI+) calc'd for $C_8H_8O_3ClBr$ $[M\text{-}OMe]^+$ 234.9161, found 234.9160.

Step 2. Sulfinamide condensation. Preparation of chlorosulfinimine 96b.

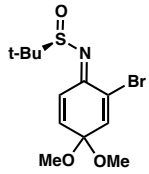


96b

A 50 mL oven-dried Schlenk tube was charged with (*R*)-*tert*-butanesulfinamide (1.78 g, 14.7 mmol, 1.1 equiv) followed by a solution of chloroquinone **95b** (2.64 g, 14.0 mmol, 1.0 equiv) and titanium (IV) ethoxide (6.4 mL, 30.5 mmol, 2.2 equiv) in THF (14 mL). The Schlenk tube was sealed and heated to 70°C in an oil-bath for 72 h while keeping the reaction from light. The reaction was allowed to cool to room temperature, diluted with EtOAc, and slowly poured into a stirring solution of brine (40 mL). The resulting suspension was filtered through a plug of celite and the organic layer was washed with brine (2 x 30 mL). The combined aqueous layers were extracted with EtOAc (40 mL), and the combined

organic layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography (20% EtOAc/Hexanes) to furnish **96b** (3.82 g, 93% yield) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 10.7 Hz, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.45 (dd, *J* = 10.5, 2.7 Hz, 1H), 3.34 (s, 3H), 3.33 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 137.0, 134.0, 133.8, 122.3, 94.2, 60.9, 50.3, 50.2, 23.2; IR (NaCl/thin film): 2961, 2945, 1569, 1457, 1168, 1113, 1082, 1039, 957, 790 cm^{-1}; HRMS (EI+) calc'd for $C_{12}H_{18}NO_3ClS$ $[M+H]^+$ 292.0769, found 292.0769; $[\alpha]_D^{25}$ –344.7 (*c* 0.62, CH_2Cl_2).

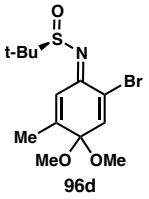
Preparation of bromsulfinimine 96c.



96c

Prepared from 6.44 mmol of bromoquinone **95c** using the general procedure. The sulfinimine product was purified by flash chromatography (9→33% EtOAc/Hexanes) to yield **96c** (1.91 g, 85% yield) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 10.7 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 6.46 (dd, *J* = 10.5, 2.7 Hz, 1H), 3.35 (s, 3H), 3.34 (s, 3H) 1.33 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.5, 138.4, 137.0, 125.6, 122.1, 94.5, 61.0, 50.33, 50.25, 23.2; IR (NaCl/thin film): 3198, 2958, 2929, 1669, 1597, 1290, 1057, 956, 886 cm^{-1}; HRMS (EI+) calc'd for $C_{12}H_{18}NO_3BrS$ $[M+H]^+$ 336.0264, found 336.0258; $[\alpha]_D^{25}$ –235.6 (*c* 0.80, CH_2Cl_2).

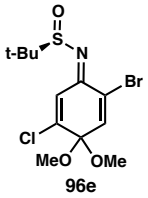
Preparation of quinone sulfinimine 96d.



96d

Prepared from 0.30 mmol of bromoquinone **95d** using the general procedure. The sulfinimine product was purified by flash chromatography (0→20% EtOAc/Hexanes) to yield **96d** (62 mg, 58% yield) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (q, *J* = 1.5 Hz, 1H), 6.88 (s, 1H), 3.22 (s, 3H), 3.20 (s, 3H), 1.90 (d, *J* = 1.5 Hz, 3H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.9, 149.5, 139.4, 127.0, 121.6, 97.2, 60.5, 51.1, 51.0, 23.1, 16.8; IR (NaCl/thin film): 2947, 2830, 1611, 1565, 1456, 1362, 1225, 1109, 1079, 969, 939 cm^{-1}; HRMS (EI+) calc'd for $C_{13}H_{20}NO_3SBr$ $[M+H]^+$ 350.0420, found 350.0423; $[\alpha]_D^{25}$ –261.7 (*c* 0.98, CH_2Cl_2).

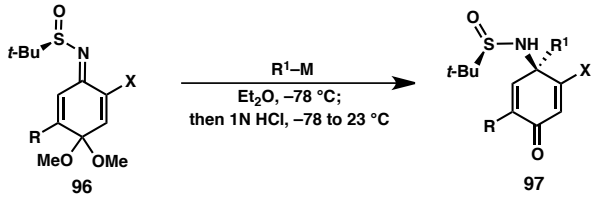
Preparation of quinone sulfinimine 96e.



96e

Prepared from 0.75 mmol of bromoquinone **95e** using the general procedure. The sulfinimine product was purified by flash hromatography (0→20% EtOAc/Hexanes) to yield **96e** (233 mg, 84% yield) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 6.88 (s, 1H), 3.30 (s, 3H), 3.28 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 145.4, 138.5, 126.2, 123.3, 96.4, 61.5, 51.6, 51.5, 23.2; IR (NaCl/thin film): 3078, 2947, 2832, 1596, 1561, 1457, 1363, 1234, 1112, 1081, 1001, 977 cm^{-1}; HRMS (EI+) calc'd for $C_{12}H_{17}NO_3SClBr$ $[M+H]^+$ 369.9874 found 369.9873; $[\alpha]_D^{25}$ –346.2 (*c* 1.54, CH_2Cl_2).

General procedures for the diastereoselective addition of organolithium and organomagnesium reagents to quinone sulfinimine substrates:



96 **97**

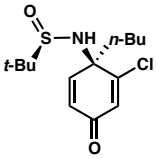
Method A.

An oven-dried 10 mL flask was charged with quinone sulfinimine **96** (0.30 mmol, 1 equiv) and Et_2O (0.6 mL). The resulting solution was cooled to –78 °C in a dry ice-acetone bath, and the organolithium reagent (0.33 mmol, 1.1 equiv) was added dropwise. After stirring at –78 °C for 1 h, the reaction was quenched at that temperature by the addition of aq. 1N HCl (0.6 mL). The reaction mixture was allowed to warm to room temperature and was vigorously stirred for 20 min. The reaction was diluted with EtOAc (30 mL) and washed with saturated aq. $NaHCO_3$ (15 mL). The aqueous layer was extracted with EtOAc (30 mL), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure to provide the crude product, which was analyzed by LC/MS and purified by flash chromatography.

Method B.

An oven-dried 10 mL flask was charged with aryl or vinyl bromide (0.48 mmol, 2.0 equiv) and Et_2O (0.4 mL). The resulting solution was cooled to –78 °C in a dry-ice acetone bath, and *t*-BuLi (0.99 mmol, 1.7 M in pentane, 4.1 equiv) was added dropwise. The resulting solution was warmed to 0 °C and stirred at that temperature for 45 min. The reaction mixture was re-cooled to –78 °C, and a solution of quinone sulfinimine **96** (0.24 mmol, 1 equiv) in Et_2O (0.5 mL) was added dropwise. The resulting suspension was stirred at –78 °C for 1 h, then quenched at that temperature by the addition of aq. 1N HCl (0.5 mL). Reaction work-up was conducted as described in Method A to obtain the crude product, which was analyzed by LC/MS and purified by flash chromatography.

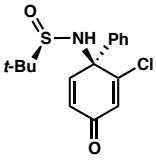
Sulfinamide 97a. Method A.



97a

The reaction was run using quinone sulfinimine **96b** (90 mg, 0.30 mmol) and *n*-BuLi (0.22 mL, 1.5 M in hexanes, 0.33 mmol). The diastereoselectivity was determined by LC/MS: 97:3 d.r. (5→95% $MeCN/H_2O$, t = 0–7 min, 1 mL/min. Minor diastereomer: t_R = 5.3 min, major diastereomer: t_R = 5.6 min). The crude material was purified by flash chromatography (30→80% EtOAc/Hexanes) to provide **97a** (85 mg, 90% yield) as a pale yellow foam. ^1H NMR (500 MHz, $CDCl_3$) δ 6.99 (d, *J* = 10.3 Hz, 1H), 6.53 (d, *J* = 1.5 Hz, 1H), 6.38 (dd, *J* = 10.0, 1.7 Hz, 1H), 3.60 (s, 1H), 2.12 (ddd, *J* = 12.8, 10.5, 6.9 Hz, 1H), 1.67 (ddd, *J* = 12.7, 10.9, 5.5 Hz, 1H), 1.29 (dt, *J* = 14.7, 7.4 Hz, 2H), 1.22 (s, *J* = 5.0 Hz, 9H), 1.12 – 1.01 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.2, 155.9, 150.9, 131.0, 128.7, 62.1, 56.7, 38.8, 25.2, 22.4, 22.3, 13.7; IR (NaCl/thin film): 3198, 2959, 2929, 1660, 1599, 1057, 976, 885 cm^{-1}; HRMS (EI+) calc'd for $C_{14}H_{22}NO_2SCl$ $[M+H]^+$ 304.1133, found 304.1131; $[\alpha]_D^{25}$ –160.7 (*c* 0.50, CH_2Cl_2).

Sulfinamide 97b. Method A.

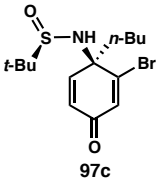


97b

The reaction was run using sulfinimine **96b** (80 mg, 0.27 mmol) and PhLi (0.18 mL, 1.7 M in di-*n*-butyl ether, 0.30 mmol). The diastereoselectivity was determined by LC/MS: 78:22 d.r. (5→95% $MeCN/H_2O$, t = 0–7 min, 1 mL/min. Minor diastereomer: t_R = 4.9 min,

major diastereomer: t_R = 5.1 min). The crude material was purified by flash chromatography (20→80% EtOAc/Hexanes) to give (*R,R*)-**97b** (68 mg, 76% yield) as a pale yellow solid. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.37 (m, 5H), 7.12 (d, *J* = 9.8 Hz, 1H), 6.57 (d, *J* = 1.5 Hz, 1H), 6.40 (dd, *J* = 10.0, 1.7 Hz, 1H), 4.15 (s, 1H), 1.33 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.1, 155.9, 150.5, 137.2, 129.8, 129.4, 129.3, 126.34, 126.23, 64.5, 57.4, 22.6; IR (NaCl/thin film): 3186, 2960, 1658, 1596, 1300, 1062, 976 cm^{-1}; HRMS (EI+) calc'd for $C_{14}H_{22}NO_2ClS$ $[M+H]^+$ 324.0820, found 324.0827; $[\alpha]_D^{25}$ –102.4 (*c* 0.80, CH_2Cl_2). The minor diastereomer ((*R,S*)-**97b**) was obtained as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.32 (m, 5H), 6.80 (d, *J* = 10.3 Hz, 1H), 6.74 (d, *J* = 2.0 Hz, 1H), 6.27 (dd, *J* = 10.0, 1.7 Hz, 1H), 4.53 (s, 1H), 1.36 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.1, 158.0, 148.4, 137.5, 129.8, 129.5, 129.2, 126.9, 125.6, 64.3, 57.4, 22.7; IR (NaCl/thin film): 3186, 2960, 1658, 1596, 1491, 1448, 1378, 1364, 1300, 1062, 976, 958 cm^{-1}; HRMS (EI+) calc'd for $C_{14}H_{22}NO_2ClS$ $[M+H]^+$ 324.0820, found 324.0823; $[\alpha]_D^{25}$ –365.9 (*c* 0.40, CH_2Cl_2).

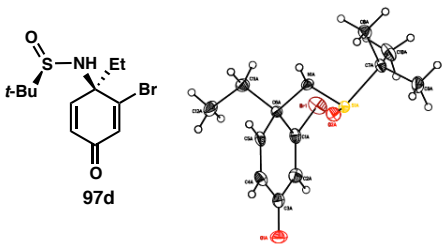
Sulfinamide 97c. Method A.



97c

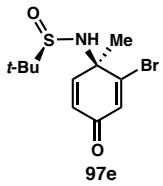
The reaction was run using sulfinimine **96c** (80 mg, 0.24 mmol) and *n*-BuLi (0.18 mL, 1.5 M in hexanes, 0.26 mmol). The diastereoselectivity was determined by LC/MS: 98:2 d.r. (5→95% MeCN/H_2O, t = 0–7 min, 1 mL/min. Minor diastereomer: t_R = 5.4 min, major diastereomer: t_R = 5.7 min). The crude material was purified by flash chromatography (30→90% EtOAc/Hexanes) to furnish **97c** (73 mg, 88% yield) as a pale yellow foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 9.8 Hz, 1H), 6.79 (d, *J* = 2.0 Hz, 1H), 6.41 (dd, *J* = 10.0, 1.7 Hz, 1H), 3.61 (s, 1H), 2.17–2.07 (m, 1H), 1.70–1.59 (m, 2H), 1.35–1.26 (m, 2H), 1.24 (s, 9H), 1.10–1.00 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.5, 151.1, 150.1, 135.3, 128.6, 62.4, 56.8, 39.8, 25.1, 22.6, 22.3, 13.7; IR (NaCl/thin film): 2946, 1567, 1457, 1179, 1110, 1082, 1039, 962, 764 cm^{-1}; HRMS (EI+) calc'd for $C_{14}H_{22}NO_2SBr$ $[M+H]^+$ 348.0627, found 348.0628; $[\alpha]_D^{25}$ –139.0 (*c* 0.50, CH_2Cl_2).

Sulfinamide 97d. Method A.



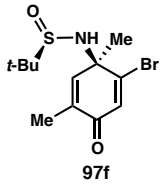
The reaction was run using sulfinimine **96c** (80 mg, 0.24 mmol) and EtLi (0.52 mL, 0.5 M in 90:10 cyclohexane:benzene, 0.26 mmol). The diastereoselectivity was determined by LC/MS: 98:2 d.r. (5→95% MeCN/H_2O, t = 0–7 min, 1 mL/min. Minor diastereomer: t_R = 4.4 min, major diastereomer: t_R = 4.7 min). The crude material was purified by flash chromatography (50→75% EtOAc/Hexanes) to give **97d** (74 mg, 96% yield) as a pale yellow solid. The solid was recrystallized from CH_2Cl_2/pentane to give crystals suitable for single crystal X-ray diffraction. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, *J* = 10.3 Hz, 1H), 6.81 (d, *J* = 1.5 Hz, 1H), 6.43 (dd, *J* = 10.0, 1.7 Hz, 1H), 2.14 (dq, *J* = 13.1, 7.5 Hz, 1H), 1.72 (dq, *J* = 13.1, 7.4 Hz, 1H), 1.24 (s, 9H), 0.76 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.5, 150.8, 149.7, 135.6, 128.9, 63.0, 56.8, 33.3, 22.6, 7.5; melting point: 60 °C (decomposition); IR (NaCl/thin film): 3196, 2970, 1669, 1597, 1286, 1052, 954 cm^{-1}; HRMS (EI+) calc'd for $C_{12}H_{18}NO_2SBr$ $[M+H]^+$ 320.0314, found 320.0318. $[\alpha]_D^{25}$ –160.7 (*c* 1.20, CH_2Cl_2).

Sulfinamide 97e. Method A.



The reaction was run using sulfinimine **96c** (90 mg, 0.27 mmol) and MeLi (0.10 mL, 2.9 M in diethoxymethane, 0.29 mmol). The diastereoselectivity was determined by LC/MS: 98:2 d.r. (5→95% MeCN/H_2O, t = 0–7 min, 1 mL/min. Minor diastereomer: t_R = 4.0 min, major diastereomer: t_R = 4.3 min). The crude material was purified by flash chromatography (50→100% EtOAc/Hexanes) to provide **97e** (75 mg, 91% yield) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 10.3 Hz, 1H), 6.74 (d, *J* = 1.5 Hz, 1H), 6.33 (dd, *J* = 10.0, 1.7 Hz, 1H), 3.63 (s, 1H), 1.61 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.1, 151.9, 151.1, 133.9, 126.7, 58.7, 56.8, 28.1, 22.6; IR (NaCl/thin film): 3139, 2991, 1668, 1636, 1599, 1296, 1048, 960, 884 cm^{-1}; HRMS (EI+) calc'd for $C_{11}H_{16}NO_2SBr$ $[M+H]^+$ 306.0158, found 306.0158; $[\alpha]_D^{25}$ –190.3 (*c* 0.71, CH_2Cl_2).

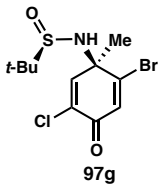
Sulfinamide 97f. Method A.



97f

The reaction was run using sulfinimine **96d** (73 mg, 0.21 mmol) and MeLi (0.08 mL, 2.72 M in diethoxymethane, 0.23 mmol). The diastereoselectivity was determined by LC/MS: 98:2 d.r. (5→95% MeCN/H_2O, t = 0–10 min, 1 mL/min. Minor diastereomer: t_R = 3.0 min, major diastereomer: t_R = 3.3 min). The crude material was purified by flash chromatography (30→80% EtOAc/Hexanes) to provide **97f** (61 mg, 91% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (q, *J* = 1.4 Hz, 1H), 6.72 (s, 1H), 3.59 (s, 1H), 1.93 (d, *J* = 1.5 Hz, 3H), 1.57 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.9, 150.7, 147.4, 133.5, 133.5, 59.0, 56.7, 28.4, 22.6, 15.2; IR (NaCl/thin film): 3125, 2989, 2926, 2870, 1663 1649, 1608, 1460, 1365, 1113, 1040, 1015, 901, 892 cm^{-1}; HRMS (EI+) calc'd for $C_{12}H_{18}NO_2SBr$ $[M+H]^+$ 320.0314, found 320.0316. $[\alpha]_D^{25}$ –168.9 (*c* 1.05, CH_2Cl_2).

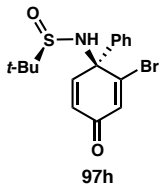
Sulfinamide 97g. Method A.



97g

The reaction was run using sulfinimine **96e** (83 mg, 0.22 mmol) and MeLi (0.091 mL, 2.72 M in diethoxymethane, 0.25 mmol). The diastereoselectivity was determined by LC/MS: 97:3 d.r. (5→95% MeCN/H_2O, t = 0–10 min, 1 mL/min. Minor diastereomer: t_R = 3.1 min, major diastereomer: t_R = 3.4 min). The crude material was purified by flash chromatography (25→70% EtOAc/Hexanes) to provide **97g** (70 mg, 92% yield) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 1H), 6.84 (s, 1H), 3.71 (s, 1H), 1.65 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 151.2, 147.8, 132.6, 131.0, 60.6, 57.0, 28.2, 22.5; IR (NaCl/thin film): 3126, 2981, 2930, 2868, 1674, 1609, 1365, 1334, 1040, 1005, 892, 873 cm^{-1}; HRMS (EI+) calc'd for $C_{11}H_{15}NO_2SClBr$ $[M+H]^+$ 339.9768, found 339.9765. $[\alpha]_D^{25}$ –138.1 (*c* 1.2, CH_2Cl_2).

Sulfinamide 97h. Method A.

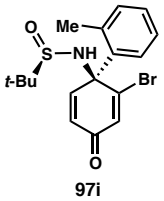


97h

The reaction was run using sulfinimine **96c** (80 mg, 0.24 mmol) and PhLi (0.15 mL, 1.7 M in di-*n*-butyl ether, 0.26 mmol). The diastereoselectivity was determined by LC/MS: 80:20 d.r. (5→95%

MeCN/H_2O, t = 0–7 min, 1 min/mL. Minor diastereomer: t_R = 5.0 min, major diastereomer: t_R = 5.2 min). The crude material was purified by flash chromatography (20→80% EtOAc/Hexanes) to yield (*R,R*)-**97h** (65 mg, 74% yield) as a yellow solid. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 5H), 7.20 (d, *J* = 9.8 Hz, 1H), 6.83 (d, *J* = 1.5 Hz, 1H), 6.40 (dd, *J* = 10.0, 1.7 Hz, 1H), 4.20 (s, 1H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.4, 150.8, 149.9, 137.6, 133.8, 129.31, 129.25, 126.2, 126.0, 64.8, 57.4, 22.8; IR (NaCl/thin film): 3184, 2960, 1669, 1292, 1059, 954 cm^{-1}; HRMS (EI+) calc'd for $C_{16}H_{18}NO_2SBr$ $[M+H]^+$ 368.0314, found 368.0317. $[\alpha]_D^{25}$ – 102.8 (*c* 0.60, CH_2Cl_2). The minor diastereomer ((*R,S*)-**97h**) was obtained as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.33 (m, 5H), 6.97 (d, *J* = 2.0 Hz, 1H), 6.89 (d, *J* = 9.8 Hz, 1H), 6.29 (dd, *J* = 10.0, 1.7 Hz, 1H), 4.56 (s, 1H), 1.37 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.3, 152.5, 148.6, 137.9, 133.6, 129.4, 129.2, 126.8, 125.6, 64.8, 57.4, 22.7; IR (NaCl/thin film): 3287, 2959, 1669, 1295, 1078, 952 cm^{-1}; HRMS (EI+) calc'd for $C_{16}H_{18}NO_2SBr$ $[M+H]^+$ 368.0314, found 368.0313; $[\alpha]_D^{25}$ –281.0 (*c* 0.45, CH_2Cl_2).

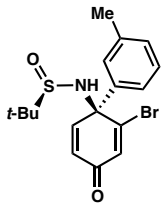
Sulfinamide 97i. Method B.



97i

The reaction was run using quinone sulfinimine **96c** (81 mg, 0.24 mmol), and *o*-bromotoluene (57 μL, 0.48 mmol). The diastereoselectivity was determined by LC/MS: 97:3 d.r. (5% MeCN/H_2O, t = 0–0.5 min; 5→45% MeCN/H_2O, t = 0.5–10.5 min, 1 mL/min. Minor diastereomer: t_R = 8.3 min, major diastereomer: t_R = 8.7 min). The crude material was purified by flash chromatography (25→50% EtOAc/Hexanes) to furnish **97i** (79 mg, 86% yield) as a pale yellow foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.34 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.31 (dt, *J* = 7.3, 1.5 Hz, 1H), 7.16 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.10 (d, *J* = 10.3 Hz, 1H), 6.90 (d, *J* = 1.7 Hz, 1H), 6.48 (dd, *J* = 9.9, 1.7 Hz, 1H), 4.23 (s, 1H), 2.26 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.4, 149.3, 148.5, 136.0, 135.7, 134.2, 133.2, 129.3, 127.4, 127.2, 126.9, 64.8, 57.3, 22.7, 20.7; IR (NaCl/thin film): 3188, 2960, 1666, 1641, 1594, 1291, 1082, 1068, 951 cm^{-1}; HRMS (EI+) calc'd for $C_{17}H_{20}NO_2SBr$ $[M+H]^+$ 382.0471, found 382.0469. $[\alpha]_D^{25}$ –107.7 (*c* 0.60, CH_2Cl_2).

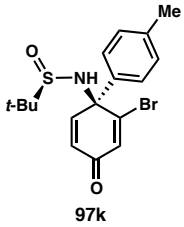
Sulfinamide 97j. Method B.



97j

The reaction was run using sulfinimine **96c** (81 mg, 0.24 mmol) and *m*-bromotoluene (58 μL, 0.48 mmol). The diastereoselectivity was determined by LC/MS: 91:9 d.r. (5→40% MeCN/H_2O, t = 0–0.5 min; 40→50% MeCN/H_2O, t = 0.5–8.5 min, 1 mL/min. Minor diastereomer: t_R = 5.2 min, major diastereomer: t_R = 5.5 min). The crude material was purified by flash chromatography (25→50% EtOAc/Hexanes) to yield **97j** (73 mg, 79% yield) as a pale yellow foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.29 (m, 1H), 7.29–7.26 (m, 1H), 7.19 (d, *J* = 10.3 Hz, 1H), 7.19 (m, 1H), 6.83 (d, *J* = 2.0 Hz, 1H), 6.39 (dd, *J* = 9.8, 1.5 Hz, 1H), 4.19 (s, 1H), 2.37 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.5, 150.9, 150.1, 139.3, 137.5, 133.8, 130.1, 129.2, 126.7, 125.9, 123.2, 64.8, 57.4, 22.8, 21.6; IR (NaCl/thin film): 3188, 2959, 1669, 1595, 1292, 1079, 1062, 954 cm^{-1}; HRMS (EI+) calc'd for $C_{17}H_{20}NO_2SBr$ $[M+H]^+$ 382.0471, found 382.0468. $[\alpha]_D^{25}$ –99.1 (*c* 0.60, CH_2Cl_2).

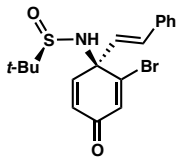
Sulfinamide 97k. Method B.



97k

The reaction was run using sulfinimide **96c** (80 mg, 0.24 mmol) and *p*-bromotoluene (81 mg, 0.48 mmol). The diastereoselectivity was determined by LC/MS: 91:9 d.r. (5→30% MeCN/H_2O, t = 0–0.5 min; 30→50% MeCN/H_2O, t = 0.5–10.5 min, 1 mL/min. Minor diastereomer: t_R = 8.2 min, major diastereomer: t_R = 8.7 min). The crude material was purified by flash chromatography (25→60% EtOAc/Hexanes) to provide **97k** (72 mg, 78% yield) as a pale yellow foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (app d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 9.8 Hz, 1H), 6.81 (d, *J* = 1.5 Hz, 1H), 6.38 (dd, *J* = 10.0, 1.7 Hz, 1H), 4.17 (s, 1H), 2.36 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.5, 160.0, 150.2, 139.4, 134.6, 133.7, 130.0, 126.1, 125.8, 64.7, 57.4, 22.8, 21.1; IR (NaCl/thin film): 3186, 2959, 2920, 1668, 1292, 1079, 1062, 955 cm^{-1}; HRMS (EI+) calc'd for $C_{17}H_{20}NO_2SBr$ $[M+H]^+$ 382.0471, found 382.0470. $[\alpha]_D^{25}$ –84.7 (*c* 0.50, CH_2Cl_2).

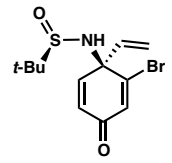
Sulfinamide 97l. Method B.



97l

The reaction was run in THF using sulfinimide **96c** (80 mg, 0.24 mmol) using β-bromostyrene[27] (87 mg, 0.48 mmol). The diastereoselectivity was determined by LC/MS: 98:2 d.r. (5→50% MeCN/H_2O, t = 0–10 min; 50→100% MeCN/H_2O, t = 10–13 min, 1 mL/min. Minor diastereomer: t_R = 11.6 min, major diastereomer: t_R = 11.8 min). The crude material was purified by flash chromatography (25→90% EtOAc/Hexanes) to furnish **97l** (64 mg, 68% yield) as a pale yellow solid.[28] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.37 (m, 2H), 7.37–7.29 (m, 3H), 7.25 (d, *J* = 9.8 Hz, 1H), 6.79 (d, *J* = 1.5 Hz, 1H), 6.69 (d, *J* = 16.1 Hz, 1H), 6.44 (dd, *J* = 10.0, 1.7 Hz, 1H), 6.19 (d, *J* = 16.1 Hz, 1H), 3.92 (s, 1H), 1.30 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.1, 149.7, 149.0, 135.0, 134.0, 133.8, 129.1, 128.8, 127.02, 127.00, 126.9, 62.4, 57.2, 22.7, 22.4; IR (NaCl/thin film): 3189, 2960, 1669, 1596, 1293, 1060, 955, 735 cm^{-1}; HRMS (EI+) calc'd for $C_{18}H_{20}NO_2SBr$ $[M+H]^+$ 394.0471, found 394.0476. $[\alpha]_D^{25}$ –115.0 (*c* 0.65, CH_2Cl_2).

Sulfinamide 97m. Method A.

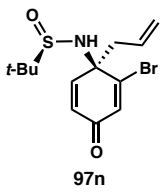


97m

The reaction was run in THF using sulfinimine **96c** (80 mg, 0.24 mmol) and vinyllithium[29] (0.48 mmol). The diastereoselectivity was determined by LC/MS: 98:2 d.r. (5→50% MeCN/H_2O, t = 0–10 min, 1 mL/min. Minor diastereomer: t_R = 7.9 min, major diastereomer: t_R = 8.3 min). The crude material was purified by flash chromatography (40→90% EtOAc/Hexanes) to yield **97m** (55 mg, 72% yield) as a yellow foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, *J* = 9.8 Hz, 1H), 6.76 (d, *J* = 1.0 Hz, 1H), 6.39 (dd, *J* = 10.0, 1.2 Hz, 1H), 5.87 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.45 (d, *J* = 10.7 Hz, 1H), 5.45 (d, *J* = 17.1 Hz, 1H), 3.82 (s, 1H), 1.27 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.0, 149.6, 148.5, 136.4, 134.1, 127.1, 119.3, 62.6, 57.2, 22.6; IR (NaCl/thin film): 3186, 2959, 1669, 1594, 1294, 1060, 954 cm^{-1}; HRMS (EI+) calc'd for $C_{12}H_{16}NO_2SBr$ $[M+H]^+$ 318.0158, found 318.0161. $[\alpha]_D^{25}$ –175.9 (*c* 0.85, CH_2Cl_2).

Sulfinamide 97n. Method A.

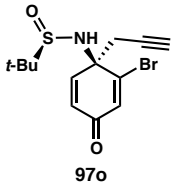
The reaction was run in THF using sulfinimide **96c** (80 mg, 0.24 mmol) and allylmagnesium chloride (0.13 mL, 2.0 M in THF, 0.26 mmol). The diastereoselectivity



97n

was determined by LC/MS: 87:13 d.r. (5→40% MeCN/H_2O, t = 0–0.5 min; 40→60% MeCN/H_2O, t = 0.5–5.5 min, 1 mL/min. Minor diastereomer: t_R = 3.0 min, major diastereomer: t_R = 3.4 min). The crude material was purified by flash chromatography (30→80% EtOAc/Hexanes) to give (*R,R*)-**97n** (49 mg, 82% yield) as a pale yellow solid. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 10.0 Hz, 1H), 6.79 (d, *J* = 1.8 Hz, 1H), 6.39 (dd, *J* = 10.0, 1.8 Hz, 1H), 5.52 (dddd, *J* = 17.1, 10.1, 7.7, 7.1 Hz, 1H), 5.26–5.22 (m, 1H), 5.22–5.20 (m, 1H), 3.77 (s, *J* = 10.4 Hz, 1H), 2.75 (ddt, *J* = 13.2, 7.1, 1.0 Hz, 1H), 2.57 (ddt, *J* = 13.2, 7.8, 1.0 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.2, 150.6, 149.7, 135.4, 128.8, 128.2, 122.1, 61.6, 57.1, 44.6, 22.6. IR (NaCl/thin film): 3196, 2959, 1669, 1597, 1056, 957 cm^{-1}; HRMS (EI+) calc'd for $C_{13}H_{18}NO_2SBr$ $[M+H]^+$ 332.0314, found 332.0316. $[\alpha]_D^{25}$ –129.0 (*c* 0.6, CH_2Cl_2). The minor diastereomer ((*R,S*)-**97n**) was obtained as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (d, *J* = 10.3 Hz, 1H), 6.76 (d, *J* = 1.5 Hz, 1H), 6.39 (dd, *J* = 10.0, 1.7 Hz, 1H), 5.47 (ddt, *J* = 17.1, 10.3, 7.3 Hz, 1H), 5.20 –5.13 (m, 2H), 3.95 (s, 1H), 2.70 – 2.59 (m, 2H), 1.26 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.1, 152.0, 148.3, 133.8, 129.7, 128.7, 121.2, 61.8, 56.9, 43.9, 22.5; IR (NaCl/thin film): 3195, 2956, 1670, 1595, 1070, 955, 883 cm^{-1}; HRMS (EI+) calc'd for $C_{13}H_{18}NO_2S^{81}Br$ $[M+H]^+$ 333.0221, found 333.0209. $[\alpha]_D^{25}$ –95.7 (*c* 0.80, CH_2Cl_2).

Sulfinamide 97o. Method A.

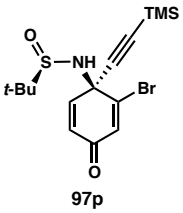


97o

The reaction was run using quinone sulfinimine **96c** (80 mg, 0.24 mmol) and propargylmagnesium bromide (0.48 mL, 0.55 M in Et_2O, 0.26 mmol). The diastereoselectivity was determined to be >97:3 by ^{1}H NMR. The crude material was purified by flash chromatography (25→75% EtOAc/Hexanes) to give **97o** (72 mg, 91% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 10.3 Hz, 1H), 6.85 (d, *J* = 1.7 Hz, 1H), 6.40 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.12 (s, 1H), 3.02 (dd, *J* = 16.6, 2.7 Hz, 1H), 2.61 (dd, *J* = 16.6, 2.7 Hz, 1H), 2.27 (t, *J* = 2.7 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.7, 150.0, 147.7, 136.2, 127.6, 76.0, 74.7, 60.1, 57.2, 31.5, 22.6; IR (NaCl/thin film): 3283,

3128, 2962, 1671, 1600, 1377, 1308, 1278, 1047, 1036, 957 cm^{-1}; HRMS (EI+) calc'd for $C_{13}H_{16}NO_2SBr$ $[M+H]^+$ 330.0158, found 330.0159. $[\alpha]_D^{25}$ –94.6 (*c* 1.05, CH_2Cl_2).

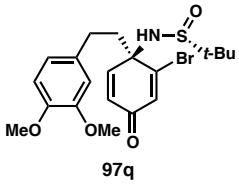
Sulfinamide 97p. Method A.



97p

The reaction was run in THF at 0 °C using quinone sulfinimine **96c** (40 mg, 0.12 mmol) and lithium (trimethylsilyl)acetylide[30] (0.24 mmol). The diastereoselectivity was determined by LC/MS: >98:2 d.r. (30→50% MeCN/H_2O, t = 0–10 min; 50→70% MeCN/H_2O, t = 10–15 min, 1 mL/min. Minor diastereomer: t_R = 11.6 min, major diastereomer: t_R = 12.0 min). The crude material was purified by flash chromatography (10→40% EtOAc/Hexanes) to give **97p** (46 mg, 99% yield) as a pale yellow foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 9.8 Hz, 1H), 6.73 (d, *J* = 1.7 Hz, 1H), 6.36 (dd, *J* = 9.9, 1.7 Hz, 1H), 4.00 (s, 1H), 1.26 (s, 9H), 0.20 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.5, 147.2, 146.1, 133.5, 126.4, 98.1, 93.7, 57.2, 56.5, 22.5, –0.6; IR (NaCl/thin film): 3185, 2960, 1673, 1599, 1292, 1251, 1076, 955, 845 cm^{-1}; HRMS (EI+) calc'd for $C_{15}H_{22}NO_2SSiBr$ $[M+H]^+$ 388.0397, found 388.0401. $[\alpha]_D^{25}$ –41.0 (*c* 0.50, CH_2Cl_2).

Sulfinamide 97q. Method A.

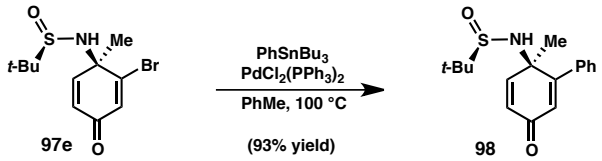


97q

The reaction was run in THF using quinone sulfinimine **96c** (270 mg, 0.80 mmol) and (3,4-dimethoxyphenethyl)magnesium bromide[31] (1.6 mL, 0.55 M in THF, 0.88 mmol). The diastereoselectivity was determined by LC/MS: 96:4 d.r. (30→50% MeCN/H_2O, t = 0–10 min, 1 mL/min. Minor diastereomer: t_R = 5.8 min, major diastereomer: t_R = 7.2 min). The crude material was purified by flash chromatography (50→100% Hexanes/EtOAc) to provide **97q** (301 mg, 82% yield) as a pale yellow foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 10.0 Hz, 1H), 6.87 (d, *J* = 1.7 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.66 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.62 (d, *J* = 2.0 Hz, 1H), 6.46 (dd, *J* = 10.0, 1.7 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.67 (s, 1H), 2.47 – 2.27 (m, 3H), 2.04 – 1.93 (m, 1H), 1.23 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.3, 150.7, 149.6, 149.0, 147.7, 135.6, 132.0, 128.8, 120.1, 111.5, 111.4, 62.2, 56.8, 56.0, 55.9, 41.8, 29.2, 22.5; IR (NaCl/thin film): 3246, 2958, 2835, 1669, 1645, 1596, 1516, 1465, 1258, 1236, 1157,

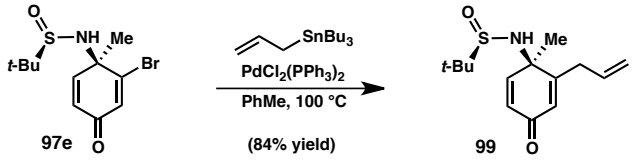
1060, 1027, 730 cm^{-1}; HRMS (EI+) calc'd for $C_{20}H_{26}NO_4SBr$ $[M+H]^+$ 456.0839, found 456.0841. $[\alpha]_D^{25}$ –63.3 (*c* 1.15, CH_2Cl_2).

Preparation of dienone 98.



Sulfinamide **97e** (51.9 mg, 0.169 mmol), $PdCl_2(PPh_3)_2$ (5.6 mg, 8.0 μmol), and $PhSnBu_3$ (75 mg, 0.20 mmol) were dissolved in PhMe (1 mL), and the resulting solution was heated to 100°C for 3 hours. The reaction mixture was cooled to room temperature, filtered through a plug of silica gel, and rinsed with EtOAc (15 mL). The filtrate was concentrated in vacuo and purified by flash chromatography (20→70% CH_2Cl_2/EtOAc) to afford phenyldienone **98** as a white solid (47.8 mg, 0.158 mmol, 93% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.47 (m, 2H), 7.37–7.35 (m, 3H), 7.09 (d, *J* = 10.0 Hz, 1H), 6.37 (d, *J* = 2.0 Hz, 1H), 6.30 (dd, *J* = 10.0 Hz, 2.0 Hz, 1H), 3.55 (s, 1H), 1.72 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.7, 159.5, 154.0, 137.2, 129.5, 129.1, 128.6, 128.2, 126.2, 57.4, 56.6, 28.0, 22.3; IR (NaCl/thin film): 3434, 3151, 2986, 2958, 2930, 2868, 1660, 1626, 1570, 1472, 1457, 1364, 1290, 1274, 1147, 1114, 1040, 893, 813, 763, 705 cm^{-1}; HRMS (ES+) calc'd for $C_{17}H_{22}NO_2S$ $[M+H]^+$ 304.1366, found 304.1358; $[\alpha]_D^{25}$ –134.2 (*c* 0.81, CH_2Cl_2).

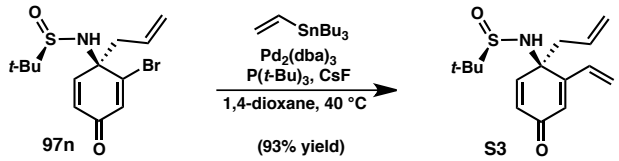
Preparation of dienone 99.



Sulfinamide **97e** (48 mg, 0.16 mmol), $PdCl_2(PPh_3)_2$ (5.5 mg, 7.8 μmol), and allyltributyltin (62 mg, 0.19 mmol) were dissolved in PhMe (1 mL), and the resulting solution was heated to 100°C for 3 hours. The reaction mixture was cooled to room temperature, filtered through a plug of silica gel, and rinsed with EtOAc (15 mL). The

resulting solution was concentrated in vacuo and the crude residue was purified by flash chromatography (20→70% EtOAc/CH_2Cl_2) to afford dienone **99** (35.1 mg, 0.131 mmol, 84% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, *J* = 10.0 Hz, 1H), 6.22 (dd, *J* = 9.8, 2.0 Hz, 1H), 6.19 (app. q, *J* = 1.6 Hz, 1H), 5.75 (m, 1H), 5.20 (dq, *J* = 10.0, 1.2 Hz, 1H), 5.14 (dq, *J* = 17.0, 1.5 Hz, 1H), 3.55 (s, 1H), 3.15 (dddd, *J* = 17.3, 6.3, 2.8, 1.4 Hz, 1H), 2.99 (dddd, *J* = 17.3, 7.3, 2.3, 1.3 Hz, 1H), 1.48 (s, 3H), 1.20 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.5, 160.5, 153.6, 133.5, 128.4, 126.7, 118.9, 57.2, 56.4, 34.7, 26.3, 22.5; IR (NaCl/thin film): 3128, 2983, 2964, 2928, 2870, 1672, 1635, 1460, 1419, 1388, 1363, 1285, 1270, 1157, 1064, 1043, 916, 892, 810 cm^{-1}; HRMS (ES+) calc'd for $C_{14}H_{22}NO_2S$ $[M+H]^+$ 268.1366, found 268.1376. $[\alpha]_D^{25}$ –82.7 (*c* 0.70, CH_2Cl_2).

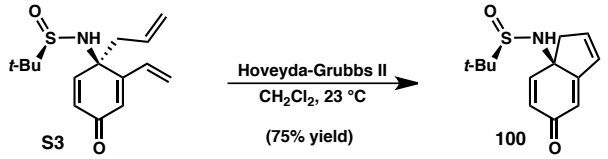
Preparation of trienone S3.



Sulfinamide **97n** (100 mg, 0.30 mmol), $Pd_2(dba)_3$ (4.1 mg, 0.0045 mmol), P(*t*-Bu)$_3$ (3.7 mg, 0.018 mmol), CsF (101 mg, 0.66 mmol), and vinyltributylstannane (93μL, 0.32 mmol), and 1,4-dioxane (3.0 mL) were sequentially added to a Schlenk tube. The solution was then stirred and degassed via 3 freeze-pump-thaw cycles, then heated to 40°C for 20 hours. The solution was cooled and filtered through a plug of silica, rinsed with EtOAc (30 mL), and concentrated to afford a brown oil. Flash chromatography (1→5% MeOH/CH_2Cl_2) afforded trienone **S3** (78 mg, 0.28 mmol, 93% yield) as a bright yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (d, *J* = 10.1 Hz, 1H), 6.46 (d, *J* = 1.8 Hz), 6.42 (ddd, *J* = 17.4, 11.0, 0.6 Hz, 1H), 6.23 (dd, *J* = 10.1, 2.0 Hz, 1H), 5.79 (dd, *J* = 17.5, 1.0 Hz, 1H), 5.40 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.45–5.35 (m, 1H), 5.08–5.00 (m, 2H), 3.88 (s, 1H), 2.55–2.43 (m, 2H), 1.11 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.9, 155.3, 151.8, 132.1, 129.5, 127.9, 125.7, 121.1, 120.8, 59.0, 56.5, 43.5, 22.5; IR (NaCl/thin film): 3197, 2980, 2960, 2234, 1663, 1624, 1474, 1420, 1390, 1364, 1295, 1192, 1175,

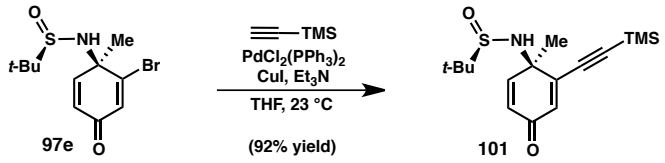
1154, 1057, 992, 9224, 895, 818, 734 cm^{-1}; HRMS (ES+) calc'd for $C_{15}H_{22}NO_2S$ $[M+H]^+$ 280.1366, found 280.1376; $[\alpha]_D^{25}$ –247.5 (*c* 0.92, CH_2Cl_2).

Preparation of bicycle 100.



To a solution of trienone **S3** (18 mg, 0.065 mmol) in CH_2Cl_2 (0.75 mL) was added Hoveyda-Grubbs II catalyst (2.6 mg, 4.6 μmol). The solution was stirred at 23°C for 3 hours, then concentrated and purified by flash chromatography (1→5% MeOH/CH_2Cl_2) to afford bicycle **100** (14 mg, 0.058 mmol, 88% yield) as a white crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 9.8, 0.7 Hz, 1H), 6.58 (dt, *J* = 5.2 Hz, 2.6 Hz, 1H), 6.47 (dt, *J* = 5.8, 2.0 Hz, 1H), 6.25 (dd, *J* = 9.8, 1.7 Hz, 1H), 6.13 (d, *J* = 1.5 Hz, 1H), 3.43 (s, 1H), 2.77 (t, *J* = 2.2 Hz, 2H), 1.12 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.3, 166.7, 145.5, 143.7, 130.9, 130.6, 120.2, 61.7, 56.4, 43.4, 22.3; IR (NaCl/thin film): 3152, 2979, 2918, 2866, 1726, 1653, 1634, 1597, 1561, 1474, 1457, 1379, 1362, 1289, 1190, 1050, 1037, 929, 891, 865, 811, 740 cm^{-1}; HRMS (ES+) calc'd for $C_{13}H_{17}NO_2S$ $[M+H]^+$ 252.1058, found 252.1061; $[\alpha]_D^{25}$ –80.4 (*c* 0.29, CH_2Cl_2).

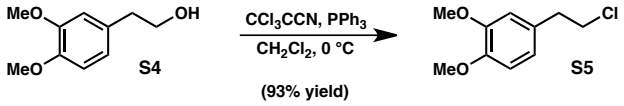
Preparation of dienone 101.



A 10 mL flask was charged with sulfinamide **97e** (50 mg, 0.16 mmol), $PdCl_2(PPh_3)_2$ (6.0 mg, 8 μmol), CuI (3.0 mg, 16 μmol), and THF (0.8 mL). Nitrogen was bubbled through the resulting suspension for 20 minutes, then Et_3N (0.8 mL) and ethynyltrimethylsilane (25 μL, 0.18 mmol) were added. The reaction mixture was allowed to stir 1 hour at room temperature, then filtered through Celite, rinsed with EtOAc, concentrated, and purified by flash chromatography (0→70% EtOAc/CH_2Cl_2) to

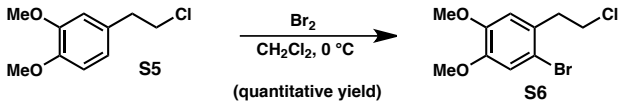
provide dienone **101** (49 mg, 92% yield) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, *J* = 10.1 Hz, 1H), 6.44 (d, *J* = 2.0 Hz, 1H), 6.28 (dd, *J* = 10.3, 2.0 Hz, 1H), 3.62 (s, 1H), 1.60 (s, 3H), 1.22 (s, 9H), 0.21 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.7, 152.1, 143.7, 133.6, 127.5, 107.4, 100.8, 56.4, 56.3, 27.9, 22.4, –0.5; IR (NaCl/thin film): 3139, 2960, 2253, 2149, 1662, 1623, 1586, 1364, 1251, 1105, 1043, 897, 843 cm^{-1}; HRMS (ES+) calc'd for $C_{16}H_{25}NO_2SSi$ $[M+H]^+$ 324.1454, found 324.1463; $[\alpha]_D^{25}$ –191.8 (*c* 1.13, CH_2Cl_2).

Preparation of 3,4-dimethoxyphenethyl chloride (S5).



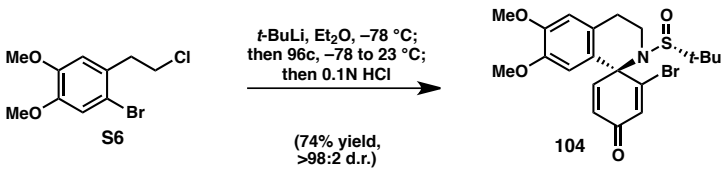
To a solution of 3,4-dimethoxyphenethanol (**S4**) (4.72g, 25.9 mmol) in CH_2Cl_2 (250 mL) at 0°C was added PPh_3 (13.6 g, 51.8 mmol). The solution was stirred for 10 minutes, and CCl_3CCN (3.89 mL, 38.9 mmol) was added dropwise via syringe over 5 minutes. The solution was stirred at 0 °C for 10 min and then slowly warmed to room temperature. After stirring for an additional 45 minutes, the reaction mixture was concentrated and purified by flash chromatography (5→20% EtOAc/Hexanes) to afford chloride **S5** (4.82 g, 24.0 mmol, 93 % yield) as a clear colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.30 Hz, 1H), 6.76 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.73 (d, *J* = 2.0 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.68 (t, *J* = 7.5 Hz, 2H), 3.00 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9, 147.9, 130.6, 120.7, 112.0, 111.2, 55.8, 55.8, 45.1, 38.7; IR (NaCl/thin film): 3000, 2956, 2909, 2867, 2934, 1607, 1591, 1516, 1464, 1418, 1325, 1260, 1232, 1191, 1146, 1027, 914, 854, 809, 767 cm^{-1}; HRMS (ES+) calc'd for $C_{10}H_{13}O_2Cl$ $[M+H]^+$ 200.0604, found 200.0591.

Preparation of 2-bromo-3,4-dimethoxyphenethyl chloride (S6).



To a solution of chloride **S5** (4.82 g, 24.0 mmol) in CH_2Cl_2 (240 mL) at 0°C was added bromine (1.25 mL, 24.2 mmol) dropwise via syringe. (*Caution! A copious amount of HBr gas is generated as the reaction proceeds. A needle was pierced through the septa to allow the reaction to vent*). The solution was stirred at 0°C for 10 minutes, warmed to room temperature, and stirred for another 20 minutes. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (50 mL) and washed with saturated $NaHCO_3$ (3 x 100 mL). The combined aqueous layers were extracted with CH_2Cl_2 (50 mL), and the combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography (5→20% EtOAc/Hexanes) to afford bromide **S6** (6.70 g, 24.0 mmol, quantitative yield) as white needles. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.77 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.71, (t, *J* = 7.3 Hz, 2H), 3.12 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.6, 148.3, 129.2, 115.6, 114.2, 113.9, 56.2, 56.1, 43.5, 39.1; IR (NaCl/thin film): 3009, 2955, 2940, 2906, 2836, 1602, 1576, 1510, 1469, 1461, 1451, 1435, 1382, 1344, 1266, 1254, 1217, 1166, 1033, 959, 856, 834, 865, 834, 802, 759 cm^{-1}; HRMS (ES+) calc'd for $C_{10}H_{12}O_2Cl^{81}Br$ $[M+H]^+$ 279.9689, found 279.9691.

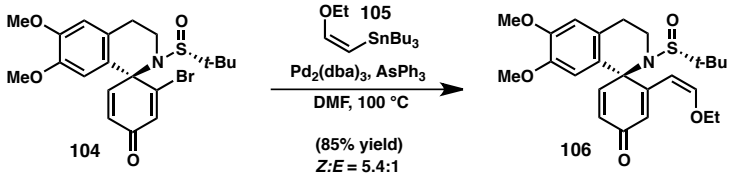
Preparation of sulfinamide 104.



To a solution of aryl bromide **S6** (506 mg, 1.8 mmol) in Et_2O (18 mL) at –78°C was added a solution of *t*-BuLi (1.6 M in pentane, 1.31 mL, 2.1 mmol) dropwise via syringe, and the resulting mixture was stirred 2 hours at –78 °C. A solution of sulfinimine **96c** (495 mg, 1.5 mmol) in Et_2O (3 mL) was added over 5 minutes. The reaction mixture was stirred 1 hour at –78°C, then allowed to warm to room temperature and stirred for an additional hour. The reaction was quenched by the slow addition of aqueous HCl (0.1 N) and stirred for 30 minutes. The biphasic mixture was diluted with EtOAc (60 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 20 mL). The combined aqueous layers were back extracted with EtOAc (1 x 25 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated to give a light brown oil. The diastereoselectivity was

determined by LC/MS: >98:2 d.r. (5→95% MeCN/H_2O, t = 0–10 min, 1 mL/min. Minor diastereomer: t_R = 3.7 min, major diastereomer: t_R = 4.0 min). Flash chromatography (10→30% EtOAc/CH_2Cl_2) afforded tricyclic dienone **104** (491 mg, 1.08 mmol, 74% yield) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 9.8Hz, 1H), 6.77 (d, *J* = 1.5 Hz, 1H), 6.63 (s, 1H), 6.42 (dd, *J* = 9.8, 1.5 Hz, 1H), 6.32 (s, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 3.52 (dt, *J* = 13.2, 4.4 Hz, 1H), 3.33 (ddd, *J* = 13.2, 9.8, 2.9 Hz, 1H), 3.03 (ddd, *J* =15.4, 10.0, 3.9 Hz, 1H), 2.79 (dt, *J* = 15.4, 3.8 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.7, 153.0, 149.6, 149.1, 148.3, 133.5, 128.5, 126.0, 122.7, 111.5, 109.1, 66.7, 59.2, 56.1, 55.8, 38.5, 29.0, 24.4; IR (NaCl/thin film): 2958, 2925, 2855, 1669, 1644, 1594, 1516, 1436, 1363, 1298, 1262, 1230, 1199, 1126, 1076, 1022, 954, 915, 796, 731 cm^{-1}; HRMS (EI+) calc'd for $C_{20}H_{24}BrNO_4S$ $[M+H]^+$ 454.0682, found 454.0697; $[\alpha]_D^{25}$ –17.3 (*c* 0.39, CH_2Cl_2).

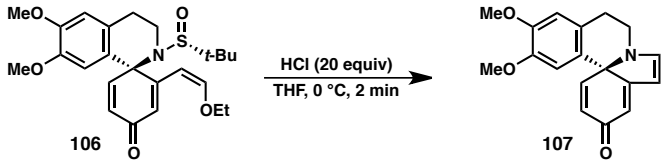
Preparation of trienone 106.



To a solution of dienone **104** (238 mg, 0.52 mmol) in DMF (10 mL) was added $Pd_2(dba)_3$ (14 mg, 0.016 mmol), $AsPh_3$ (19 mg, 0.063 mmol) and stannane **105** (164 mg, 0.63 mmol). N_2 was then bubbled through the solution for 30 minutes, and the reaction was then stirred at 100°C for 1 hour. Upon cooling to room temperature, the reaction mixture was passed through a plug of Celite, rinsed and diluted with Et_2O (40 mL), and washed with H_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash chromatography (35→100% EtOAc/Hexanes) to afford trienone **106** (~5.4:1 mixture of *Z:E*-isomers by ^{1}H NMR) as a tan solid (199 mg, 0.446 mmol, 85% yield). *Z*-**106**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (d, *J* = 10.0 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 6.59 (s, 1H), 6.36 (dd, *J* = 10.0, 2.0 Hz, 1H), 6.34 (s, 1H), 6.28 (d, *J* = 7.3 Hz, 1H), 4.46 (d, *J* = 7.1 Hz, 1H), 3.97–3.90 (m, 2H), 3.84 (s, 3H), 3.67 (s, 3H), 3.49 (ddd, *J* = 13.1, 4.3, 3.4 Hz, 1H), 3.17 (ddd, *J* = 13.1, 11.3, 2.8 Hz, 1H), 3.05

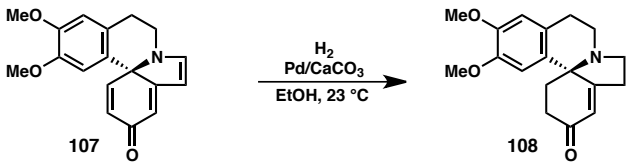
(ddd, *J* = 15.5, 11.2, 4.0 Hz, 1H), 2.81 (dt, *J* = 15.5, 3.0 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.19 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.4, 155.4, 153.3, 148.5, 148.1, 147.3, 127.6, 127.2, 126.8, 125.0, 111.3, 109.9, 102.8, 70.4, 63.9, 58.4, 56.0, 55.8, 38.1, 29.0, 24.1, 15.4. IR (NaCl/thin film): 2979, 2959, 2932, 1658, 1625, 1574, 1516, 1464, 1360, 1262, 1249, 1124, 1072, 1038, 1021, 893, 795 cm^{-1}; HRMS (ES+) calc'd for $C_{24}H_{32}NO_5S$ $[M+H]^+$ 446.1996, found 446.2006. *E*-**106** gave the following diagnostic resonances by ^{1}H NMR (500 MHz, $CDCl_3$): 7.18 (d, *J* = 10.0 Hz, 1H), 6.89 (d, *J* = 13.0 Hz, 1H), 5.09 (d, *J* = 13.2 Hz).

Preparation of enamine 107.



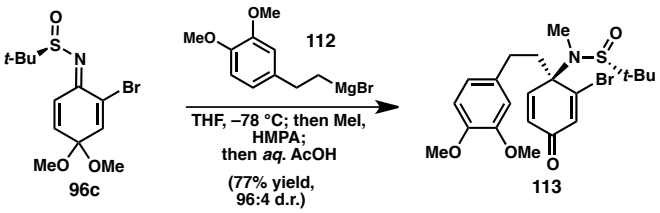
To a solution of trienone **106** (50 mg, 0.11 mmol) in THF (2.2 mL) at 0 °C was added a solution of HCl (2.0 M solution in Et_2O, 1.1 mL, 2.2 mmol) dropwise by syringe. The reaction was allowed to stir 2 min at 0 °C, then quenched by the addition of aq. NaOH (10% w/w, 4 mL) and stirred for an additional 5 minutes. The mixture was diluted with H_2O (5 mL) and extracted with EtOAc (4 x 10 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography (10→20% EtOAc/ CH_2Cl_2) to afford enamine **107** (29 mg, 0.098 mmol, 88% yield) as a bright orange solid. $[\alpha]^{25}_D$ –1307 (*c* 0.72, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (d, *J* = 9.8 Hz, 1H), 6.99 (d, *J* = 3.4 Hz, 1H), 6.85 (s, 1H), 6.53 (s, 1H), 6.06 (dd, *J* = 9.8 Hz, 2.0 Hz, 1H), 6.03 (d, *J* = 1.5 Hz, 1H), 5.62 (d, *J* = 3.4 Hz, 1H), 3.83 (s, 1H), 3.78 (ddd, *J* = 14.2 Hz, 6.8 Hz, 1.0 Hz, 1H), 3.74 (s, 1H), 3.56 (ddd, *J* = 14.2 Hz, 12.7 Hz, 4.4 Hz, 1H), 2.93 (ddd, *J* = 16.9 Hz, 12.5 Hz, 6.4 Hz, 1H), 2.75 (dd, 16.4 Hz, 4.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.5, 172.8, 152.9, 148.6, 148.0, 143.6, 127.8, 125.7, 124.6, 112.7, 111.4, 107.5, 105.2, 71.3, 55.9, 55.8, 42.1, 28.5; IR (NaCl/thin film): 2992, 2955, 2936, 2835, 1636, 1605, 1571, 1523, 1513, 1455, 1450, 1442, 1402, 1356, 1333, 1256, 1218, 1204, 1190, 1166, 1140, 1111, 1081, 1068, 1039, 1001, 895, 852, 784, 731 cm^{-1}; HRMS (ES+) calc'd for $C_{18}H_{18}NO_3$ $[M+H]^+$ 296.1281, found 296.1272.

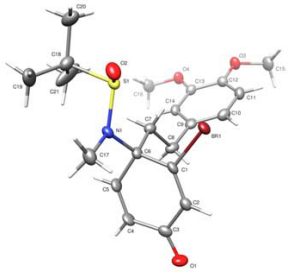
Preparation of (–)-3-demethoxyerythratidinone (108).



To a solution of enamine **107** (20 mg, 0.068 mmol, 1.0 equiv) in EtOH (3.3 mL) was added Pd on $CaCO_3$ (14 mg, 5 wt %, 7.0 μmol, 0.1 equiv). The solution was placed under an atmosphere of H_2 and was stirred 3 hours at room temperature. The reaction was filtered through a plug of Celite, rinsed with EtOAc, concentrated, and purified by flash chromatography (0→20% acetone/CH_2Cl_2) to afford (–)-3-demethoxyerythratidinone (**108**) as a pale yellow oil (13 mg, 0.043 mmol, 65% yield). $[\alpha]^{25}_D$ –296.5 (*c* 0.57, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (s, 1H), 6.56 (s, 1H), 6.11 (app. s, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.49 (ddd, *J* = 14.4, 11.7, 6.6 Hz, 1H), 3.24 (dd, *J* = 14.4 Hz, 7.6 Hz, 1H), 3.12–3.00 (m, 2H), 2.86 (q, *J* = 7.7 Hz, 1H), 2.77–2.68 (m, 1H), 2.62–2.50 (m, 3H), 2.46 (dd, *J* = 18.3, 4.2 Hz, 1H), 2.31 (ddd, *J* = 12.5, 5.6, 2.0 Hz, 1H), 2.24 – 2.15 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.5, 169.2, 148.3, 146.8, 125.7, 124.8, 123.4, 112.8, 110.3, 63.5, 56.0, 55.9, 45.7, 40.1, 36.1, 32.8, 28.7, 21.4; IR (NaCl/thin film): 2928, 2848, 1667, 1509, 1464, 1329, 1253, 1229, 1205, 1165, 1106 cm^{-1}; HRMS (ES+) calc'd for $C_{18}H_{21}NO_3$ $[M+H]^+$ 300.1600, found 300.1606.

Preparation of sulfinamide 113.

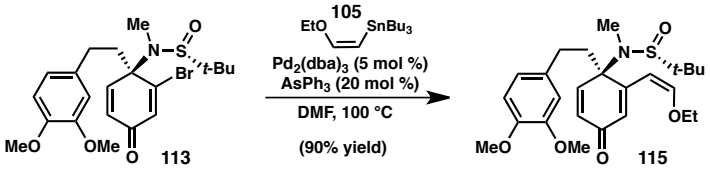




To a solution of sulfinimine **96c** (2.96 g, 8.80 mmol, 1.0 equiv) in THF (17 mL) at –78 °C was added a solution of Grignard reagent **112** (0.67M solution in THF, 14.3 mL, 9.6 mmol) dropwise by syringe. The solution was then stirred at –78 °C for one hour, then MeI (1.6 mL, 26.1 mmol, 3.0 equiv) and hexamethylphosphoramide (HMPA) (4.5 mL, 26.1 mmol, 3.0 equiv) were sequentially added by syringe, and the solution stirred at

–78 °C for ten minutes. The solution was then warmed to 23 °C and stirred for 2 hours, then quenched by the addition of aqueous AcOH (10% v/v, 31 mL). After 3.5 hours, the mixture was diluted with H_2O (100 mL) and extracted with EtOAc (3 x 150 mL) and washed with H_2O (3 x 100 mL). The organic layers were then combined, washed with saturated aqueous $NaHCO_3$ (150 mL), then brine (150 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a clear brown oil. The diastereoselectivity was determined by LC/MS: 96:4 dr (5→95% MeCN/H_2O, t = 0–10 min, 1 mL/min. Major diastereomer: t_R = 4.2 min, minor diastereomer: t_R = 4.8 min). Flash chromatography (30% to 80% EtOAc in Hexanes) afforded sulfinamide **113** as a white crystalline solid (3.18 g, 6.76 mmol, 77% yield). Recrystallization of **113** by vapor diffusion (CH_2Cl_2 into a solution of **113** in PhMe) afforded crystals suitable for single crystal X-ray diffraction. Melting Point: 136–138 °C; $[\alpha]^{25}_D$: +22.7 (*c* 0.85, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (d, *J* = 1.7 Hz, 1H), 6.82 (d, *J* = 10.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.66 (dd, *J* = 6.1 Hz, 2.0 Hz, 2H), 6.62 (d, *J* = 2.0 Hz, 1H), 6.44 (dd, *J* = 9.8 Hz, 1.7 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.81 (td, 12.3 Hz, 4.9 Hz, 1H), 2.47 (s, 3H), 2.39 – 2.24 (m, 2H), 1.84 (td, *J* = 12.5 Hz, 5.2 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.0, 150.7, 150.1, 148.9, 147.7, 136.4, 132.4, 129.6, 120.1, 111.7, 111.3, 68.7, 59.2, 55.9, 55.8, 38.2, 29.9, 26.7, 24.2; IR (NaCl/thin film): 3042, 2934, 2864, 2833, 1669, 1592, 1516, 1464, 1419, 1377, 1360, 1258, 1238, 1156, 1140, 1077, 1028, 951, 885, 819, 788; HRMS (ES+) calc'd for $C_{21}H_{29}BrNO_4S$ $[M+H]^+$ 470.0995, found 470.1003.

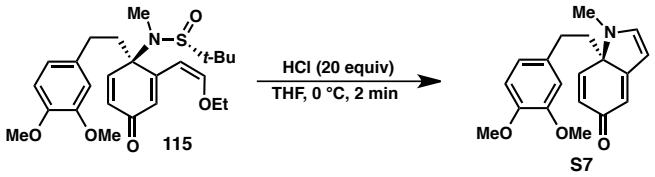
Preparation of enol ether 115.



To a solution of sulfinamide **113** (2.30 g, 4.89 mmol) in DMF (49 mL) was added $Pd_2(dba)_3$ (224 mg, 0.245 mmol, 0.5 equiv), $AsPh_3$ (299 mg, 0.979 mmol, 0.20 equiv), and stannane **105** (1.8 mL, 5.4 mmol, 1.1 equiv). The solution was degassed with N_2 for 30 minutes, then heated and stirred at 100 °C for 1 hour. Upon cooling to room

temperature, the solution was passed through a plug of Celite, diluted with EtOAc (300 mL), and washed with H_2O (3 x 150 mL). The aqueous layers were combined and back-extracted with EtOAc (3 x 100 mL), and the combined organic layers dried over $MgSO_4$, filtered, and concentrated in vacuo to afford brown oil. Flash chromatography (50% to 100% EtOAc in Hexanes) afforded **115** (>10:1 mixture of *Z:E* isomers by ^{1}H NMR) as a tan solid (2.02 g, 4.37 mmol, 91% yield). $[\alpha]_D^{25}$: –80 (*c* 1.07, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 1.8 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.54 (d, *J* = 2.0 Hz, 1H), 6.53 (d, *J* = 10.0 Hz, 1H), 6.35 (dd, *J* = 10.0 Hz, 2.0 Hz, 1H), 5.15 (d, *J* = 7.0 Hz, 1H), 4.05 (q, *J* = 7.0 Hz, 2H), 3.81 (s, 3H), 3.81 (s, 3H), 2.53 – 2. 42 (m, 1H), 2.42 (s, 3H), 2.32 – 2.26 (m, 2H), 1.88 – 1.80 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.21 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.6, 154.7, 153.5, 149.4, 148.7, 147.4, 133.3, 130.4, 128.7, 119.9, 111.7, 111.2, 98.7, 70.8, 66.5, 58.8, 55.8, 55.7, 38.3, 29.9, 27.0, 24.4, 15.3; IR (NaCl/thin film): 2958, 2934, 2835, 1660, 1623, 1575, 1516, 1464, 1455, 1303, 1261, 1238, 1180, 1156, 1238, 1180, 1156, 1141, 1099, 1055, 1030, 959, 935, 896, 804, 765, 735; HRMS (EI+) calc'd for $C_{25}H_{36}NO_3S$ $[M+H]^+$ 462.2309, found 462.2320.

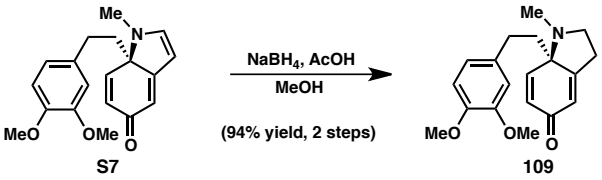
Preparation of enamine S7.



To a solution of enol ether **115** (318.3 mg, 0.668 mmol) in THF (13 mL) at 0 °C was added a solution of hydrochloric acid (2.0 M solution in Et_2O, 7.0 mL, 14 mmol) dropwise by syringe over 1 minute. The reaction was allowed to stir 2 additional minutes at 0 °C and then quenched by the addition of aqueous potassium hydroxide (10% w/v, 10 mL) and stirred an additional 10 minutes. The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a red foam that was used immediately in the next step without further purification. A sample was purified by flash chromatography (1% to 5% MeOH in CH_2Cl_2) for characterization purposes: $[\alpha]_D^{25}$:

–1650 (*c* 0.41, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): 6.98 (dd, *J* = 9.9 Hz, 0.6 Hz, 1H), 6.89 (d, *J* = 3.2 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 6.60 (dd, *J* = 8.2 Hz, 2.1 Hz, 1H), 6.56 (d, *J* = 2.2 Hz, 1H), 6.16 (dd, *J* = 9.8 Hz, 1.7 Hz, 1H), 5.88 (d, *J* = 1.5 Hz, 1H), 5.47 (dd, *J* = 3.3, 0.6 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.04 (s, 3H), 2.41–2.30 (m, 2H), 2.08–1.98 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): 184.7, 174.5, 153.4, 148.8, 147.4, 140.1, 132.9, 131.1, 120.1, 111.7, 111.3, 109.8, 99.6, 72.6, 55.8, 55.8, 45.8, 31.5, 29.1. IR (NaCl/thin film): 2934, 2834, 1631, 1592, 1568, 1515, 1465, 1313, 1260, 1237, 1156, 1108, 1089, 1050, 1028, 977, 884, 830, 766; HRMS (ES+) calc'd for $[M+H]^+$ 312.1594, found 312.1585.

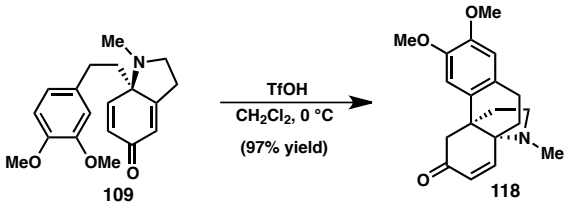
Preparation of dihydroindolone 109.



To a solution of crude enamine **S7** (220 mg) in MeOH (14 mL) at 0 °C was added a solution of $NaBH_4$ (50 mg, 1.32 mmol) in AcOH (5 mL), dropwise by syringe. The solution was stirred at 0 °C for 10 minutes before warming to 20 °C and stirring continued for 1 hour. The reaction was cooled to 0 °C and quenched by the slow addition of potassium hydroxide (30% w/v, 20 mL). The solution was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were then combined, dried over Na_2SO_4, filtered, concentrated under reduced pressure to afford an orange oil. Purification by flash chromatography (2% to 4% MeOH in CH_2Cl_2) gave amine **109** as a yellow oil (200 mg, 0.638 mmol, 96% yield over two steps). $[\alpha]_D^{25}$: –40.6 (*c* 0.89, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, *J* = 10.0 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.61 (dd, *J* = 8.2 Hz, 2.1 Hz, 1H), 6.57 (d, *J* = 2.0 Hz, 1H), 6.32 (dd, *J* = 10.0, 1.6 Hz, 1H), 6.18 (dt, *J* = 2.3, 1.5 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.16 (ddd, *J* = 10.5, 8.6, 4.2 Hz, 1H), 3.07–2.99 (m, 1H), 2.81–2.67 (m, 2H), 2.40 (s, 3H), 2.39–2.31 (m, 1H), 2.27–2.17 (m, 1H), 1.90–1.79 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.6, 166.9, 148.8, 147.4, 145.9, 133.6, 130.2, 123.3, 119.8, 111.6, 111.3, 66.5, 55.9, 55.8, 51.6, 36.5,

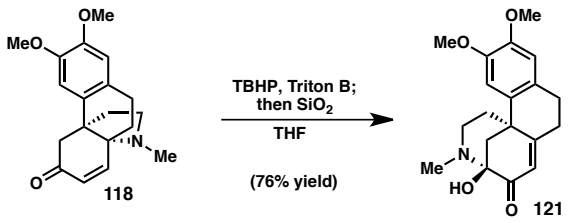
32.0, 29.6, 27.8; IR (NaCl/thin film): 2934, 2834, 2789, 1667, 1642, 1606, 1590, 1515, 1464, 1452, 1418, 1259, 1464, 1452, 1259, 1234, 1176, 1152, 1028, 890, 809, 764; HRMS (EI+) calc'd for $C_{19}H_{24}NO_3$ $[M+H]^+$ 314.1751, found 314.1748.

Preparation of propellane 118.



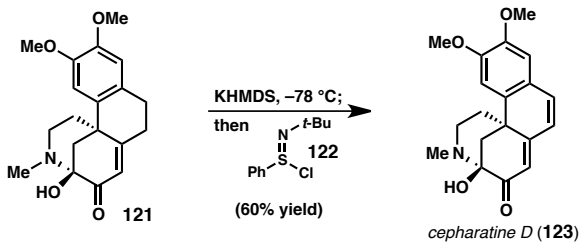
To a solution of dihydroindolone **109** (370 mg, 1.18 mmol, 1.0 equiv) in CH_2Cl_2 (24 mL) at 0 °C was added TfOH (0.522 mL, 5.90 mmol, 5.0 equiv) dropwise by syringe. The solution was stirred for 5 minutes and quenched with saturated aqueous $NaHCO_3$ (50 mL). The mixture was then washed with additional aqueous $NaHCO_3$ (3 x 50 mL), and the combined aqueous layers were back extracted with CH_2Cl_2 (100 mL). The organic layers were then combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a tan foam. Flash chromatography (1% to 2% MeOH in CH_2Cl_2) afforded propellane **118** as a white foam (360 mg, 1.15 mmol, 97% yield). $[\alpha]_D^{25}$: –243 (*c* 0.44, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (d, *J* = 10.4 Hz, 1H), 6.69 (s, 1H), 6.53 (s, 1H), 6.14 (dd, *J* = 10.4 Hz, 1.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.98–2.84 (m, 2H), 2.91 (dd, *J* = 16.5 Hz, 1.1 Hz, 1H), 2.60–2.54 (m, 1H), 2.56 (d, *J* = 16.5 Hz, 1H), 2.47–2.40 (m, 1H), 2.45 (s, 3H), 2.32–2.22 (m, 1H), 2.07–1.97 (m, 2H), 1.82–1.71 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.8, 150.3, 147.9, 147.1, 135.7, 129.9, 126.3, 111.1, 110.5, 63.1, 56.1, 55.8, 51.6, 49.5, 48.3, 36.2, 33.3, 25.1, 24.6; IR (NaCl/thin film): 2929, 2851, 2832, 2790, 2252, 1681, 1610, 1515, 1464, 1452, 1356, 1255, 1207, 1140, 1068, 1035, 1010, 916, 886, 856, 730; HRMS (EI+) calc'd for $C_{19}H_{24}NO_3$ $[M+H]^+$ 314.1751, found 314.1748.

Preparation of hemiaminal 121.



To a solution of enone **118** (93.8 mg, 0.299 mmol, 1.0 equiv) in THF (3.0 mL) was added *tert*-butylhydroperoxide (TBHP) (214 μL of a 70% aq. solution, 1.50 mmol, 5.0 equiv) and Triton B (110 μL of a 40% solution in methanol, 0.239 mmol, 0.8 equiv) dropwise by syringe, and the solution stirred 17 hours at room temperature. The reaction was then quenched by the addition of a solution of saturated aqueous $Na_2S_2O_3$ (7 mL) and stirred for an additional 30 minutes. H_2O (15 mL) was added, the solution extracted with CH_2Cl_2 (3 x 20 mL). The organic layers combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a clear oil. The oil was then redissolved in CH_2Cl_2 (2 mL), then loaded onto dry silica gel and allowed to sit for 2 hours. Flash chromatography (60 to 100% EtOAc in hexanes) afforded hemiaminal **121** as a white foam (75.0 mg, 0.228 mmol, 76% yield). $[\alpha]_D^{25}$: –204 (*c* 0.65, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.57 (s, 1H), 6.21 (s, 1H), 4.27 (br s, 1H), 3.85 (s, 3H), 3.85 (s, 3H), 3.02 (ddd, *J* = 12.2, 5.3, 1.6 Hz, 1H), 2.94–2.81 (m, 2H), 2.67–2.57 (m, 2H), 2.46 (td, *J* =12.5, 3.7 Hz, 1H), 2.45 (d, *J* = 12.5 Hz, 1H), 2.28 (td, *J* =13.3, 5.3 Hz, 1H), 2.24 (s, 3H), 2.12 (dd, *J* = 12.5, 2.9 Hz, 1H), 1.70–1.64 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.5, 168.0, 148.2, 147.6, 132.2, 127.2, 124.8, 111.0, 108.5, 83.1, 55.9, 55.8, 49.2, 46.8, 43.5, 36.3, 35.9, 31.2, 29.8; IR (NaCl/thin film): 3468, 2933, 2848, 1666, 1619, 1517, 1465, 1354, 1259, 1228, 1187, 1124, 1089, 1006, 914, 870, 789, 729; HRMS (EI+) calc'd for $C_{19}H_{24}NO_4$ $[M+H]^+$ 330.1700, found 330.1713.

Preparation of cepharatine D (123).



To a solution of hemiaminal **121** (30 mg, 91 μmol, 1.0 equiv) in THF (1.8) mL at –78 °C was added a solution of KHMDS in THF (0.21 mL of a 0.9 M solution in THF, 0.191 mmol, 2.1 equiv). The yellow solution was stirred at –78 °C for 10 minutes, then warmed to 0 °C and stirred for 20 minutes. The solution was again cooled to –78 °C, and a solution of **122** (27.6 mg, 0.128 mmol, 1.4 equiv) in THF (0.25 mL) was added dropwise. After 50 minutes, the solution was quenched with saturated aqueous NH_4Cl (20 mL), warmed to room temperature, and extracted with EtOAc (3 x 20 mL). The organic layers were then combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (1 to 2 % MeOH in CH_2Cl_2) afforded (–)-cepharatine D (**123**) as a bright yellow foam (18.0 mg, 55.0 μmol, 60% yield). $[\alpha]_D^{25} = -227$ (*c* 0.51, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.74 (d, *J* = 9.5 Hz, 1H), 6.72 (s, 1H), 6.32 (d, *J* = 9.3 Hz, 1H), 6.15 (s, 1H), 4.42 (br s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.87 (ddd, *J* = 12.6, 5.1, 1.6 Hz, 1H), 2.75 (d, *J* = 12.2 Hz, 1H), 2.62 (td, *J* = 12.7, 3.7 Hz, 1H), 2.31 (dd, 12.2, 2.9 Hz, 1H), 2.24 (s, 3H), 1.98 (td, *J* = 13.1, 5.1 Hz, 1H), 1.58 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.4, 161.4, 150.3, 147.9, 135.9, 135.5, 124.2, 123.5, 123.2, 111.6, 107.6, 83.0, 56.1, 56.0, 46.8, 56.0, 46.8, 45.0, 43.7, 38.1, 36.0; ^{1}H NMR (500 MHz, CD_3OD) δ 7.07 (s, 1H), 6.90 (s, 1H), 6.84 (d, *J* = 9.3 Hz, 1H), 6.37 (d, *J* = 9.3 Hz, 1H), 6.10 (s, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 2.82 (dd, *J* = 12.7, 4.9 Hz, 1H), 2.68 (d, *J* = 12.2 Hz, 1H), 2.56 (td, *J* = 12.8, 3.5 Hz, 1H), 2.23 (d, *J* = 12.2, 2.8 Hz, 1H), 2.21 (s, 3H), 1.92 (td, *J* = 13.2, 5.1 Hz, 1H), 1.58 – 1.50 (m, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 194.7, 162.7, 151.8, 149.6, 137.1, 136.9, 126.0, 125.4, 124.1, 113.5, 109.5, 84.7, 56.7, 56.6, 47.9, 46.4, 44.9, 39.0, 36.7; IR (NaCl/thin film): 3455, 2925, 2843, 1732, 1650, 1608, 1554, 1516, 1463, 1376, 1340, 1275, 1235, 1190, 1135, 1081, 877, 784; HRMS (EI+) calc'd for $C_{19}H_{21}NO_4$ $[M+H]^+$ 328.1543, found 330.1552.

Comparison of Spectroscopic Data for Natural[32] and Synthetic (–)-Cepharatine D

^{1}H NMR Data (both spectra are referenced to 3.30 ppm)

Reported[3]	Synthetic
7.06 (s, 1H)	7.07 (s, 1H)
6.89 (s, 1H)	6.90 (s, 1H)
6.84 (d, *J* = 9.2 Hz, 1H)	6.84 (d, *J* = 9.3 Hz, 1H)
6.36 (d, *J* = 9.2 Hz, 1H)	6.37 (d, *J* = 9.3 Hz, 1H)
6.10 (s, 1H)	6.10 (s, 1H)
3.92 (s, 3H)	3.91 (s, 3H)
3.83 (s, 3H)	3.84 (s, 3H)
2.90 (m, 1H)	2.82 (dd, *J* = 12.7, 4.9 Hz, 1H)
2.67 (d, *J* = 12.0 Hz, 1H)	2.68 (d, *J* = 12.2 Hz, 1H)
2.66 (m, 1H)	2.56 (td, *J* = 12.8, 3.5 Hz, 1H)
2.19 (m, 1H)	2.23 (d, *J* = 12.2, 2.8 Hz, 1H)
2.18 (s, 3H)	2.21 (s, 3H)
2.02 (m, 1H)	1.92 (td, *J* = 13.2, 5.1 Hz, 1H)
1.59 (m, 1H)	1.58 – 1.50 (m, 1H)

^{13}C NMR Comparsion Data (both spectra are referenced to 49.0 ppm)

Reported	Synthetic
194.7	194.7
162.7	162.7
151.7	151.8
149.5	149.6
137.0	137.1
136.9	136.9
126.0	126.0
125.3	125.4
124.1	124.1
113.4	113.5
109.3	109.5
84.7	84.7
56.6	56.7
56.5	56.6
47.8	47.9
46.4	46.4
44.8	44.9
39.0	39.0
36.7	36.7

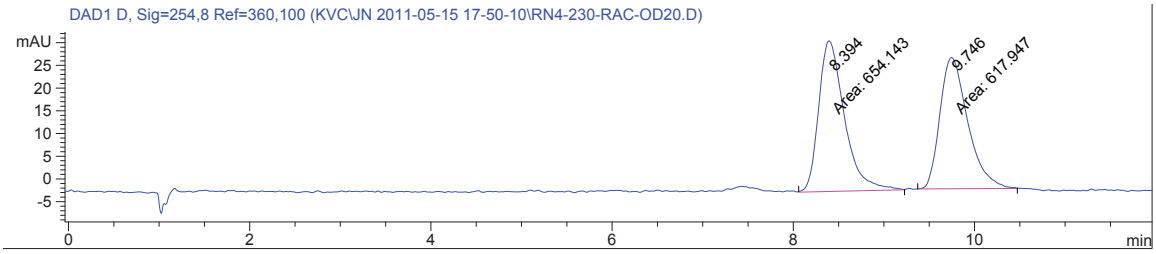
Optical Rotation[33]

Natural	Synthetic
$[\alpha]_D^{17}$: –321 (*c* 1.01, MeOH)	$[\alpha]_D^{17}$: –227 (*c* 0.51, MeOH)

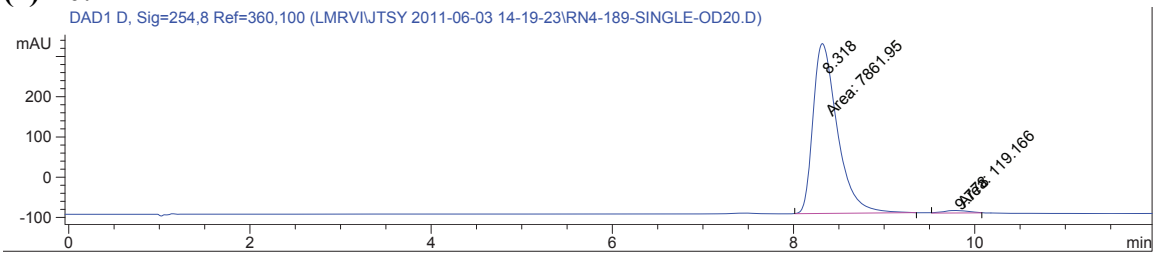
Chiral SFC Traces

Method Information: OD-H column, 20% IPA, 12.0 minutes.

***rac*-10:**

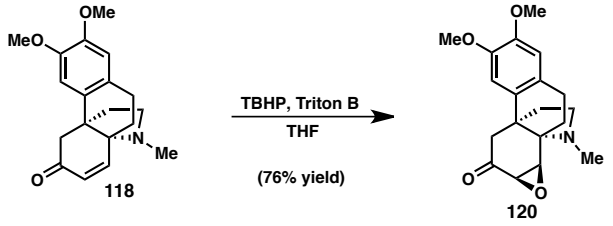


(–)-10:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.318	MM	0.3103	7861.95264	422.33008	98.5069
2	9.778	MM	0.3079	119.16633	6.45073	1.4931
Totals :				7981.11897	428.78081	

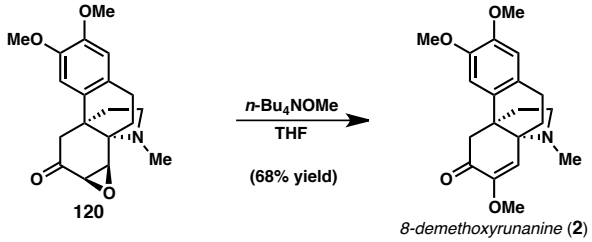
Preparation of epoxyketone 120.



To a solution of enone **118** (62.6 mg, 0.200 mmol, 1.0 equiv) in THF (2.0 mL) was added TBHP (143 μL of a 70% aq. solution, 1.0 mmol, 3.0 equiv) and Triton B (73 μL of a 40% solution in methanol, 0.16 μmmol, 0.8 equiv) dropwise by syringe, and the solution stirred 17 hours at room temperature. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (6 mL) and stirred an additional 30 minutes. H_2O (15 mL) was then added, the solution extracted with CH_2Cl_2 (3 x 20 mL), and the organic layers

combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a clear oil. Flash chromatography (30 to 50% EtOAc in hexanes) on Florisil afforded epoxyketone **120** as a white foam (40.0 mg, 0.075 mmol, 61% yield). $[\alpha]_D^{25}$: +30 (*c* 0.70, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 1H), 6.52 (s, 1H), 3.84 (s, 2H), 3.82 (s, 2H), 3.49 (d, *J* = 3.9 Hz, 1H), 3.32 (dd, *J* = 3.8, 1.0 Hz, 1H), 2.95 (d, *J* = 14.0 Hz, 1H), 2.77 (m, 3H), 2.63 (dt, *J* = 16.0, 3.9 Hz, 1H), 2.56 (s, 3H), 2.50 (dd, *J* = 14.0, 1.0 Hz, 1H), 2.21–2.16 (m, 2H), 2.10 (ddd, *J* = 13.2, 8.0, 5.3 Hz, 1H), 2.01–1.94 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.1, 147.8, 147.2, 134.5, 127.4, 110.7, 110.1, 60.5, 60.4, 56.0, 56.0, 55.7, 52.5, 51.4, 45.8, 37.2, 33.3, 24.9, 24.33; IR (NaCl/thin film): 2934, 2833, 2792, 1716, 1610, 1516, 1464, 1454, 1358, 1330, 1256, 1202, 1142, 1070, 1005, 973, 873, 853, 801, 733; HRMS (EI+) calc'd for $C_{19}H_{23}NO_4$ $[M+H]^+$ 330.1700, found 330.1710.

Preparation of 8-Demethoxyrunanine (2).



To epoxyketone **120** (40.8 mg, 0.124 mmol, 1.0 equiv) was added a freshly prepared solution of *n*-Bu_4NOMe[24] (2.5 mL of a 0.5 M solution in THF, 1.2 mmol, 10 equiv) by syringe and the solution was then heated to 50 °C for 11 hours. The reaction was then cooled, diluted with brine (10 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were then combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to isolate a brown oil that was purified by flash chromatography (SiO_2 deactivated with 0.5% Et_3N, 40 to 80% EtOAc in Hexanes) to isolate synthetic (–)-8-demethoxyrunanine (**2**) as a white foam (29.1 mg, 84.8 mmol, 68% yield). $[\alpha]_D^{20}$: –185 (*c* 0.51, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (s, 1H), 6.52 (s, 1H), 5.64 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.65 (s, 3H), 3.04 (d, *J* = 16.6 Hz, 1H), 2.92 (td, *J* = 9.3, 3.7 Hz, 1H), 2.87 (ddd, *J* = 15.9, 12.8, 4.9 Hz), 2.66 (d, *J* =16.4 Hz, 1H), 2.55 (ddd, *J* = 15.9, 5.0, 2.8 Hz, 1H), 2.44–

2.37 (m, 1H), 2.42 (s, 3H), 2.26 (ddd, J = 13.3, 9.6, 6.2 Hz, 1H), 2.09–1.99 (m, 2H), 1.80 (ddd, J = 13.9, 12.8, 5.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 151.2, 147.9, 147.1, 135.3, 126.4, 114.7, 111.1, 110.6, 63.7, 56.0, 55.8, 55.0, 51.5, 49.6, 48.1, 36.4, 33.5, 26.7, 25.0; IR (NaCl/thin film): 2926, 2848, 2832, 2787, 1693, 1624, 1515, 1463, 1451, 1376, 1356, 1282, 1257, 1217, 1205, 1156, 1136, 1114, 1095, 1066, 1051, 1013, 962, 883, 858, 800, 731, 665 cm^{-1}; HRMS (EI+) calc'd for $C_{20}H_{26}NO_4$ $[M+H]^+$ 344.1856, found 344.1863.

Comparison of Spectroscopic Data for Natural[15] and Synthetic 8-demethoxyrunanine

^{1}H NMR Comparison Data

Reported	Synthetic
6.65 (s, 1H)	6.67 (s, 1H)
6.51 (s, 1H)	6.52 (s, 1H)
5.63 (s, 1H)	5.64 (s, 1H)
3.82 (s, 3H)	3.84 (s, 3H)
3.81 (s, 3H)	3.83 (s, 3H)
3.63 (s, 3H)	3.65 (s, 3H)
3.04 (d, J = 16.4 Hz, 1H)	3.04 (d, J = 16.6 Hz, 1H)
2.84 (m, 1H)	2.92 (td, J = 9.3, 3.7 Hz, 1H)
2.84 (m, 1H)	2.87 (ddd, J = 15.9, 12.8, 4.9 Hz)
2.65 (d, J = 16.4 Hz, 1H)	2.66 (d, J =16.4 Hz, 1H)
2.55 (ddd, J = 16.0, 4.8, 2.8 Hz, 1H)	2.55 (ddd, J = 15.9, 5.0, 2.8 Hz, 1H)
2.41 (s, 3H)	2.42 (s, 3H)
2.39 (m, 1H)	2.44 – 2.37 (m, 1H)
2.25 (m, 1H)	2.26 (ddd, J = 13.3, 9.6, 6.2 Hz, 1H)
2.05 (m, 1H)	2.09 – 1.99 (m, 2H)
2.01 (ddd, J = 14.0, 4.8, 2.8 Hz, 1H)	–
1.79 (ddd, J = 14.0, 13.2, 4.8 Hz, 1H)	1.80 (ddd, J = 13.9, 12.8, 5.1 Hz, 1H)

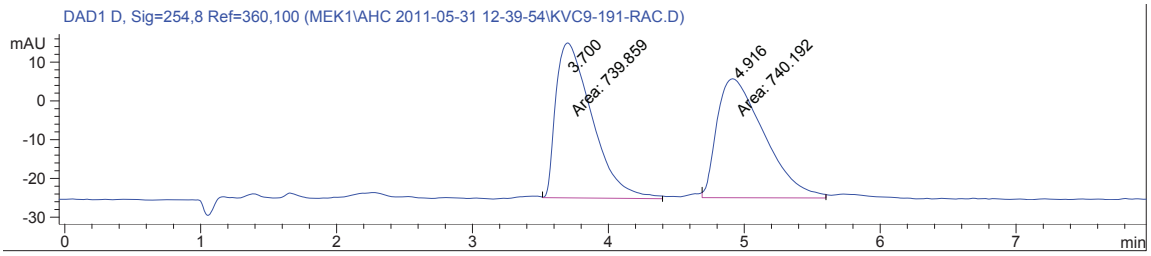
^{13}C NMR Comparison Data

Reported	Synthetic
193.2	193.2
151.1	151.2
147.8	147.9
147.0	147.0
135.2	135.3
126.3	126.4
114.6	114.7
111.0	111.1
110.4	110.6
63.7	63.8
56.0	56.1
55.7	55.8
54.9	55.1
51.4	51.5
49.5	49.7
48.0	48.1
36.3	36.4
33.4	33.5
26.6	26.7
24.8	25.0

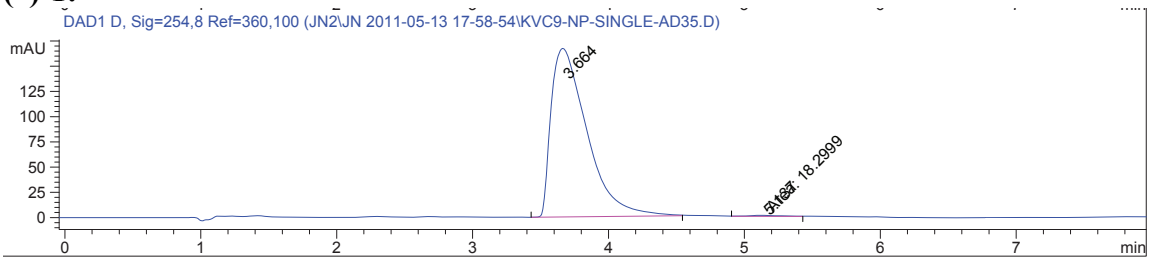
Optical Rotation[34]

Natural	Synthetic
$[\alpha]_D^{20}$: –244 (c 0.48, $CHCl_3$)	$[\alpha]_D^{20}$: –185 (c 0.51, $CHCl_3$)

Chiral SFC Traces:
Method Information:AD column, 35% IPA, 8.0 minutes.
***rac*-1:**



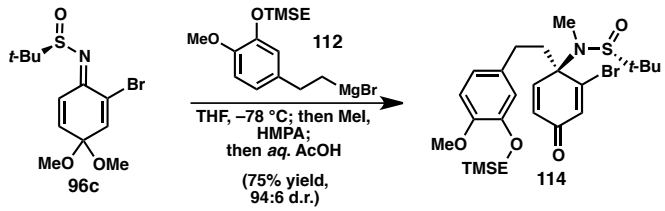
(–)-1:



Signal 2: DAD1 D, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.664	BB	0.2798	3058.54810	166.89442	99.4052
2	5.137	MM	0.2913	18.29991	1.04703	0.5948
Totals :				3076.84801	167.94145	

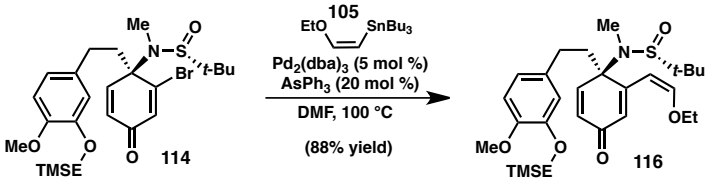
Preparation of sulfinamide 114.



To a solution of bromosulfinimine **96c** (2.49 g, 7.42 mmol) in THF (15 mL) at –78 °C was added a solution of Grignard reagent **112**[35] (0.51M solution in THF, 16.0 mL, 8.16 mmol) dropwise by syringe. The solution was then stirred at –78 °C for one hour, then MeI (1.4 mL, 22 mmol) and HMPA (3.9 mL, 22 mmol) sequentially added dropwise by syringe, and the solution stirred at –78 °C for 10 minutes. The solution was then warmed

to 23 °C and stirred for an additional 2 hours, then quenched by the addition of aqueous AcOH (10% v/v, 30 mL). After 3.5 hours, the mixture was diluted with EtOAc (150 mL), washed with H_2O (3 x 100 mL), and the aqueous layers combined and back extracted with EtOAc (3 x 100 mL). The ethereal layers were then combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a brown oil. The diastereoselectivity was determined by LC/MS: 96:4 d.r. (5→95% MeCN/H_2O, t = 0–10 min, 1 mL/min. Major diastereomer: t_R = 6.7 min, minor diastereomer: t_R = 7.2 min). Flash chromatography (20% to 50% EtOAc in Hexanes) afforded sulfinamide **114** as a white solid foam (3.09 g, 5.55 mmol, 75% yield). $[\alpha]_D^{25}$: +16.9 (*c* 0.92, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (d, *J* = 1.8 Hz, 1H), 6.81 (d, *J* = 10.0 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.64 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.59 (d, *J* = 2.0 Hz, 1H), 6.43 (dd, *J* = 10.0, 1.8 Hz, 1H), 4.12–4.04 (m, 2H), 3.81 (s, 3H), 2.80 (td, *J* = 12.3, 5.0 Hz, 1H), 2.46 (s, 3H), 2.38–2.22 (m, 2H), 1.84 (td, *J* = 12.4, 5.2 Hz, 1H), 1.21 (s, 9H), 1.21–1.16 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 183.1, 150.7, 150.1, 148.3, 148.2, 136.4, 132.2, 129.6, 120.0, 113.4, 111.7, 68.8, 66.3, 59.2, 55.9, 38.2, 29.8, 26.7, 24.2, 17.8, –1.4; IR (NaCl/thin film): 3045, 2951, 2900, 2866, 2834, 1670, 1640, 1592, 1515, 1463, 1455, 1442, 1425, 1360, 1292, 1253, 1236, 1156, 1137, 1079, 1055, 1032, 950, 886, 859, 839, 786; HRMS (EI+) calc'd for $C_{25}H_{38}BrNO_4SSi$ $[M+Na]^+$ 578.1366, found 578.1555.

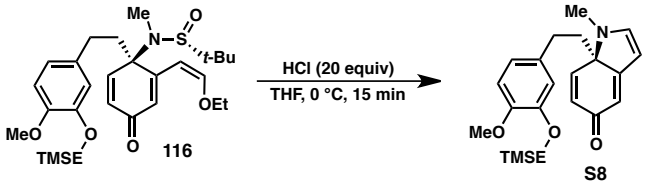
Preparation of enol ether 116.



To a solution of sulfinamide **114** (1.28 g, 2.30 mmol) in DMF (19 mL) was added $Pd_2(dba)_3$ (105 mg, 0.115 mmol), $AsPh_3$ (141 mg, 0.460 mmol), and stannane **105** (0.84 mL, 2.53 mmol). The solution was degassed with N_2 for 30 minutes, then heated and stirred at 100 °C for 1 hour. Upon cooling to room temperature, the solution was passed through a short plug of Celite, diluted with EtOAc (200 mL), and washed with H_2O (3 x 100 mL). The aqueous layers were combined and back extracted with EtOAc (3 x 75

mL), then the organic layers combined, washed with brine (250 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a light brown oil. Flash chromatography (50% to 100% EtOAc in hexanes) afforded **116** (>10:1 mixture of *Z:E*-isomers by ^{1}H NMR) as a tan solid (1.11 g, 88% yield). $[\alpha]_D^{25}$: –66 (*c* 1.34, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, *J* = 2.0 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.61 (d, *J* = 7.1 Hz, 1H), 6.59 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.55 (d, *J* = 10.0 Hz, 1H), 6.55 (d, *J* = 2.2 Hz, 1H), 6.38 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.17 (d, *J* = 7.3 Hz, 1H), 4.09–4.02 (m, 4H), 3.81 (s, 3H), 2.51 (ddd, *J* = 12.7, 10.3, 7.1 Hz, 1H), 2.45 (s, 3H), 2.33–2.26 (m, 2H), 1.90–1.80 (m, 1H), 1.35 (t, *J* = 7.08 Hz, 3H), 1.24 (s, 9H), 1.21–1.16 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 186.7, 154.8, 153.6, 149.5, 148.2, 148.0, 133.2, 130.5, 128.8, 119.9, 113.5, 111.6, 98.8, 70.7, 66.6, 66.3, 58.9, 55.9, 38.3, 29.9, 27.1, 24.4, 17.8, 15.4, –1.4; IR (NaCl/thin film): 2952, 2899, 2834, 1661, 1623, 1576, 1515, 1453, 1384, 1302, 1258, 1157, 1137, 1099, 1055, 957, 896, 859, 839, 803, 767 cm^{-1}; HRMS (EI+) calc'd for $C_{29}H_{45}NO_5SSi$ $[M+H]^+$ 547.2860, found 548.2850.

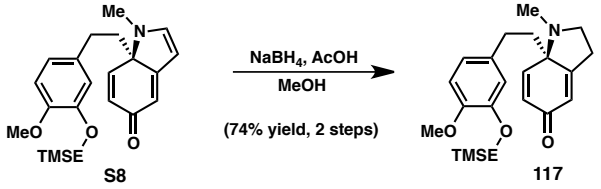
Preparation of Enamine S8.



To a solution of enol ether **116** (702 mg, 1.28 mmol) in THF (12.8 mL) at 0 °C was added a solution of HCl (2.0 M solution in Et_2O, 12.8 mL, 25.6 mmol) dropwise by syringe over 1 minute. The reaction was allowed to stir 15 minutes at 0 °C and then quenched by the addition of aqueous KOH (10% w/v, 13 mL), and stirred for an additional 5 minutes. The mixture was then diluted with H_2O (50 mL), and extracted with EtOAc (3 x 50 mL). The organic layers were then combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to isolate a bright red foam. Column chromatography (2% MeOH in CH_2Cl_2) afforded a red foam of adequate purity for the next step. $[\alpha]_D^{25}$: –1185 (*c* 0.22, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99 (dd, *J* = 9.7, 0.5 Hz, 1H), 6.89 (d, *J* = 3.17 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.59 (d, *J* = 8.1, 2.2

Hz, 1H), 6.55 (d, J = 2.0 Hz, 1H), 6.18 (dd, J = 9.9, 1.6 Hz, 1H), 5.91 (d, J = 1.5 Hz, 1H), 5.49 (dd, J = 3.3, 0.6 Hz, 1H), 4.08–4.04 (m, 2H), 3.81 (s, 3H), 3.05 (s, 1H), 2.42–2.31 (m, 2H), 2.11–1.99 (m, 2H), 1.19–1.16 (m, 2H), 0.08 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 184.8, 174.5, 153.3, 148.3, 148.0, 140.1, 132.8, 131.2, 120.0, 113.6, 111.7, 110.0, 99.7, 72.7, 66.4, 56.0, 45.7, 31.6, 29.1, 17.9, –1.4; IR (NaCl/thin film): 2951, 2916, 1631, 1569, 1514, 1424, 1248, 1157, 1137, 1108, 108, 1050, 1032, 859, 837, 649; HRMS (EI+) calc'd for $C_{23}H_{31}NO_3Si$ $[M+H]^+$ 398.2146, found 398.2149.

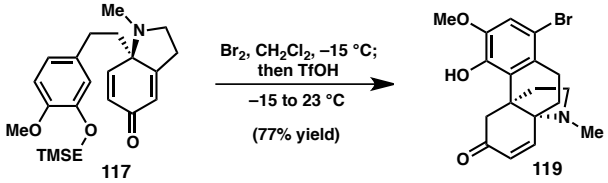
Preparation of dihydroindolone 117.



To a solution of enamine **S8** in MeOH (26 mL) at 23 °C was added a solution of $NaBH_4$ (97 mg, 2.56 mmol) in AcOH (9.8 mL), dropwise by syringe. The solution was stirred at 20 °C for 1 hour, then a second portion of $NaBH_4$ (97 mg, 2.56 mmol) in AcOH (9.8 mL) was added and stirring was continued for an additional hour. The reaction was cooled to 0 °C in an ice/water bath and neutralized by the slow addition of aqueous KOH (30% w/v, 65 mL). The solution was then diluted with H_2O (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash chromatography (2% MeOH in CH_2Cl_2) to afford dihydroindolone **117** as a yellow oil (379 mg, 0.948 mmol, 77% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (d, J = 10.0 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.61 (dd, J = 8.1, 2.0 Hz, 1H), 6.56 (d, J = 1.7 Hz, 1H), 6.34 (dd, J = 10.0, 1.5 Hz, 1H), 6.20 (app d, J = 1.7 Hz, 1H), 4.10–4.05 (m, 2H), 3.82 (s, 3H), 3.18 (ddd, J = 10.5, 8.5, 4.2 Hz, 1H), 3.05 (td, J = 10.0, 7.0 Hz, 1H), 2.79–2.68 (m, 2H), 2.42 (s, 3H), 2.36 (ddd, J = 13.9, 10.7, 6.4 Hz, 1H), 2.22 (ddd, J = 14.0, 10.9, 6.5 Hz, 1H), 1.90–1.81 (m, 2H), 1.22–1.17 (m, 2H), 0.08 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 186.7, 167.0, 148.2, 147.9, 146.0, 133.5, 130.2, 123.3, 119.8, 113.4, 111.6, 66.6, 66.3, 56.0, 51.6, 36.5, 32.0, 29.6, 27.8, 17.9, –1.4; IR (NaCl/thin film): 2949, 2850, 1669, 1644, 1606, 1589,

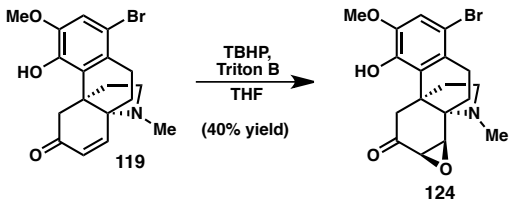
1514, 1442, 1424, 1305, 1253, 1234, 1176, 1150, 1137, 1032, 1013, 942, 890, 859, 839, 695; HRMS (EI+) calc'd for $C_{23}H_{33}NO_3Si$ $[M+H]^+$ 400.2302, found 400.2283.

Preparation of propellane 119.



To a solution of dihydroindolone **117** (414 mg, 1.04 mmol) in CH_2Cl_2 (21 mL) at –15 °C was added Br_2 (80 μL, 1.55 mmol) dropwise by syringe. The solution was stirred for 20 minutes, then TfOH (550 μL, 6.22 mmol) was added dropwise by syringe and the solution was warmed to room temperature. After 12 minutes, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL), diluted with CH_2Cl_2 (60 mL), and washed with aqueous $NaHCO_3$ (2 x 100 mL). The aqueous layers were extracted with CH_2Cl_2 (100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a light brown foam. Flash chromatography (20 to 30% EtOAc in hexanes) afforded propellane **119** as an off-white solid (302 mg, 0.798 mmol, 77% yield). $[\alpha]_D^{25}$: –226 (*c* 0.42, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (s, 1H), 6.82 (d, *J* = 10.3 Hz, 1H), 6.15 (dd, *J* = 10.4, 1.1 Hz, 1H), 5.95 (s, 1H), 3.86 (s, 3H), 3.62 (dd, *J* = 16.6, 1.2 Hz, 1H), 2.89–2.81 (m, 2H), 2.69–2.55 (m, 2H), 2.44 (s, 3H), 2.41–2.36 (m, 1H), 2.04–1.96 (m, 2H), 1.77–1.69 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 199.3, 149.7, 145.4, 143.2, 130.8, 130.2, 127.4, 114.0, 112.9, 63.2, 56.4, 51.6, 48.0, 43.8, 33.4, 33.2, 25.8, 24.8; IR (NaCl/thin film): 3338, 2926, 2850, 2790, 1673, 1601, 1470, 1436, 1420, 1388, 1357, 1314, 1314, 1276, 1235, 1125, 1064, 1038, 879, 785. HRMS (EI+) calc'd for $C_{18}H_{20}BrNO_3$ $[M+H]^+$ 378.0699, found 378.0683.

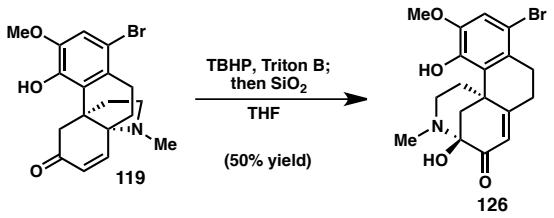
Preparation of epoxyketone 124.



To a solution of enone **119** (13.3 mg, 0.035 mmol) in THF (0.70 mL) at 28 °C was added TBHP (100 μL of a 5.5M solution in decane, 0.550 mmol) and Triton B (0.05 mL of a 40% solution in methanol, 105 μmol) dropwise by syringe, and the solution stirred for 16 hours at 28 °C. The reaction was quenched by the addition of saturated aqueous - $Na_2S_2O_3$ (2 mL) and stirred for an additional 30 minutes. H_2O (10 mL) was added, and the solution was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a clear oil. Flash chromatography (1 to 2% MeOH in CH_2Cl_2) on Florisil afforded epoxyketone **124** as a white foam (5.3 mg, 0.014 mmol, 40% yield). $[\alpha]^{25}_D$: –11 (*c* 0.24, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (s, 1H), 5.93 (s, 1H), 3.84 (s, 3H), 3.51 (d, *J* = 3.91 Hz, 1H), 3.29 (dd, *J* = 3.91, 1.0 Hz, 1H), 3.21 (dd, *J* = 14.2, 1.0 Hz, 1H), 2.95–2.81 (m, 2H), 2.74–2.64 (m, 1H), 2.67 (d, *J* = 13.9 Hz, 1H), 2.58 (ddd, *J* = 16.6, 11.8, 6.3 Hz, 1H), 2.51 (s, 3H), 2.42 (ddd, *J* = 14.4, 9.3, 6.8 Hz), 2.20–2.09 (m, 2H), 2.06–1.96 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 207.4, 145.3, 142.8, 130.3, 127.8, 113.9, 113.0, 60.7, 59.2, 56.4, 55.6, 51.8, 51.4, 40.3, 34.0, 33.3, 25.7, 23.2; IR (NaCl/thin film): 3420, 2937, 2791, 1717, 1603, 1470, 1436, 1356, 1313, 1277, 1238, 876 cm^{-1}; HRMS (EI+) calc'd for $C_{18}H_{20}BrNO_4$ $[M+H]^+$ 394.0648, found 394.0632.

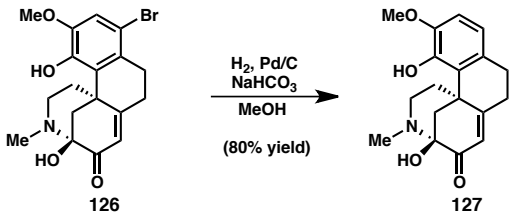
Longer reaction times resulted in higher conversion, but led to oxidative rearrangement of the desired epoxide into an unidentified lactone side product: ^{1}H NMR (300 MHz, $CDCl_3$): 6.99 (s, 1H), 4.44 (d, *J* = 1.9 Hz, 1H), 3.83 (s, 3H), 3.04–2.83 (m, 5H), 2.83–2.64 (m, 3H), 2.36 (s, 3H), 2.20 (ddd, *J* = 18.4, 12.7, 4.0 Hz, 3H), 2.04–1.80 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.4, 145.2, 142.1, 130.1, 127.1, 115.0, 114.0, 85.0, 80.4, 73.9, 56.3, 55.6, 54.4, 41.9, 34.2, 27.3, 23.7; IR (NaCl/thin film): 3351, 2930, 2849, 2791, 1784, 1605, 1470, 1434, 1292, 1274; HRMS (EI+) calc'd for $C_{18}H_{20}BrNO_5$ $[M+H]^+$ 410.0598, found 410.0599.

Preparation of hemiaminal 126.



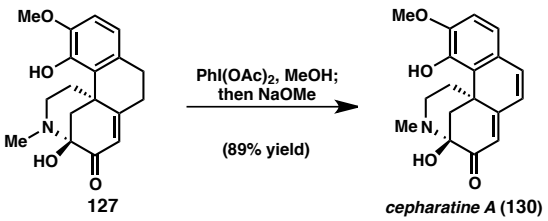
To a solution of enone **119** (106 mg, 0.279 mmol) in THF (5.6 mL) was added TBHP (1.01 mL of a 5.5M solution, 5.58 mmol) and Triton B (0.64 mL of a 40% solution in MeOH, 1.40 mmol) dropwise by syringe, and the solution stirred for 18.5 hours. The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (10 mL) and saturated NH_4Cl (5 mL), and stirred for an additional 30 minutes. The solution was extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a clear oil. The oil was then redissolved in CH_2Cl_2 and concentrated onto dry SiO_2 and allowed to sit for 2 hours. Flash chromatography (1 to 4% MeOH in CH_2Cl_2) afforded hemiaminal **126** as a light yellow foam (55.2 mg, 0.140, 50% yield). $[\alpha]_D^{25} = -179$ (*c* 0.79, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01 (s, 1H), 6.19 (br s, 1H), 6.16 (d, *J* = 1.3 Hz, 1H), 4.17 (br s, 1H), 3.88 (s, 3H), 3.42 (d, *J* = 12.7 Hz, 1H), 3.36 (td, *J* = 13.2, 5.6 Hz, 1H), 3.28–3.21 (m, 1H), 3.01 (ddd, *J* = 12.2, 5.5, 1.4 Hz, 1H), 2.65–2.53 (m, 2H), 2.52–2.43 (m, 2H), 2.21 (s, 3H), 1.91 (dd, *J* = 12.7, 2.7 Hz, 1H), 1.42 (dddd, *J* = 13.5, 4.1, 2.6, 1.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.8, 167.6, 145.9, 144.1, 128.4, 127.2, 123.8, 113.7, 113.6, 83.2, 77.3, 77.0, 76.8, 56.4, 49.1, 44.8, 42.0, 36.1, 31.7, 31.1, 29.1; IR (NaCl/thin film): 3447, 2929, 2841, 1665, 1599, 1471, 1436, 1275, 1234, 1179, 1-83, 1035, 885; HRMS (EI+) calc'd for $C_{18}H_{20}BrNO_4$ $[M+H]^+$ 394.0648, found 330.0649.

Preparation of dihydrocepharatine A (127).



To a solution of hemiaminal **126** (32.8 mg, 0.083 mmol) in MeOH (0.83 mL) was added solid $NaHCO_3$ (42 mg, 0.50 mmol) and Pd/C (3.2 mg of 10 wt % Pd on activated carbon). The solution was placed under an atmosphere of H_2 and the stirred for 1.5 hours at room temperature. The reaction was diluted with EtOAc, filtered through a plug of Celite, and concentrated under reduced pressure to isolate a yellow oil. Flash chromatography (1 to 4% MeOH in CH_2Cl_2) afforded hemiaminal **127** as a white foam (20.8 mg, 0.066 mmol, 80% yield). $[\alpha]_D^{25} = -284$ (*c* 0.21, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 (d, *J* = 8.3 Hz, 1H), 6.61 (app d, *J* = 8.3 Hz, 1H), 6.19 (br s, 1H), 6.15 (d, *J* = 1.2 Hz, 1H), 4.18 (br s, 1H), 3.88 (s, 2H), 3.44 (d, *J* = 12.7 Hz, 1H), 3.34 (td, *J* = 13.2, 5.6 Hz, 1H), 3.01 (ddd, *J* = 12.2, 5.5, 1.4 Hz, 1H), 2.97–2.90 (m, 1H), 2.61–2.42 (m, 3H), 2.22 (s, 3H), 1.99 (dd, *J* = 12.7, 2.7 Hz, 1H), 1.41 (dddd, *J* = 13.5, 4.1, 2.7, 1.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.1, 168.7, 145.6, 144.5, 129.4, 125.5, 124.0, 119.3, 109.1, 83.3, 77.3, 77.0, 76.8, 56.2, 49.2, 44.5, 42.2, 36.1, 31.7, 31.1, 29.3; IR (NaCl/thin film): 3469, 2934, 2842, 2801, 1664, 1484, 1440, 1277, 1234, 1189, 1079, 965; HRMS (EI+) calc'd for $C_{18}H_{21}NO_4$ $[M+H]^+$ 316.1543, found 316.1541.

Preparation of cepharatine A (130).



To a solution of hemiaminal **127** (14.1 mg, 44.8 μmol) in MeOH (0.89 mL) at 0 °C was added a solution of $PhI(OAc)_2$ (15.1 mg, 47 μmol, 1.05 equiv) dropwise by syringe. The solution was stirred for 20 minutes before a solution of NaOMe (0.5 M in MeOH, 0.224 mmol, 5.0 equiv) was added dropwise by syringe. After 5 minutes, the reaction was warmed to room temperature, stirred for 20 minutes, then quenched with saturated aqueous NH_4Cl (5 mL). The reaction was diluted with H_2O, extracted with EtOAc (3 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a yellow-orange oil. Flash chromatography on silica gel (1 to 3% MeOH in CH_2Cl_2) afforded **130** (12.5 mg, 40.0 μmol, 89% yield) as a yellow-

orange foam. $[\alpha]^{15}_{D} = -537$ (*c* 0.38, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 6.78 (d, *J* = 8.3 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.70 (d, *J* = 9.3 Hz, 1H), 6.29 (d, *J* = 9.3 Hz, 1H), 6.28 (br s, 1H), 6.12 (s, 1H), 4.29 (br s, 1H), 3.93 (s, 3H), 3.91 (d, *J* = 13.0 Hz, 1H), 2.91–2.84 (m,1H), 2.74–2.58 (m, 2H), 2.24 (s, 3H), 2.22 (dd, *J* = 13.0 Hz, 1H), 1.38 (ddd, *J* = 6.1, 4.7, 2.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.1, 161.4, 148.1, 144.4, 136.0, 125.6, 125.5, 124.1, 123.4, 121.3, 108.7, 83.2, 56.2, 46.6, 44.4, 43.5, 36.2, 31.2; IR (NaCl/thin film): 3447, 2929, 2839, 1648, 1609, 1563, 1483, 1440, 1273, 1239, 1192, 1272, 1075, 969 cm^{-1}; HRMS (EI+) calc'd for $C_{18}H_{19}NO_4$ $[M+H]^+$ 314.1387, found 314.1393.

Comparison of Spectroscopic Data for Natural and Synthetic[36] (–)-Cepharatine A

^{1}H NMR Data (both spectra are referenced to 7.27 ppm)

Reported	Synthetic
6.79 (d, *J* = 8.4 Hz, 1H)	δ 6.79 (d, *J* = 8.2 Hz, 1H),
6.77 (d, *J* = 8.4 Hz, 1H)	6.77 (d, *J* = 8.2 Hz, 1H)
6.71 (d, *J* = 9.6 Hz, 1H)	6.71 (d, *J* = 9.3 Hz, 1H)
6.29 (d, *J* = 9.6 Hz, 1H)	6.30 (d, *J* = 9.4 Hz, 1H)
-	6.29 (br s, 1H)
6.13 (s, 1H)	6.13 (s, 1H)
4.32 (br s, 1H)	4.30 (br s, 1H)
3.94 (s, 3H)	3.94 (s, 3H)
3.95 (d, *J* = 12.8 Hz, 1H)	3.92 (d, *J* = 13.0 Hz, 1H)
2.90 (m, 1H)	2.92 – 2.85 (m, 1H)
2.74 (m, 1H)	2.75 – 2.59 (m, 2H)
2.66 (m, 1H)	-
2.25	2.25 (s, 3H)
2.19 (m, 1H)	2.23 (dd, *J* = 13.0, 2.7 Hz, 1H),
1.40 (m, 1H)	1.38 (ddd, *J* = 6.1, 4.7, 2.2 Hz, 1H)

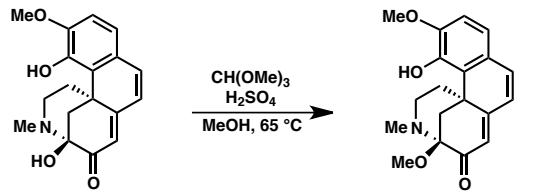
^{13}C NMR Comparsion Data (referenced to 77.0 ppm)

Reported	Synthetic
194.0	194.1
161.6	161.4
148.1	148.1
144.4	144.4
136.1	136.0
125.5	125.6
125.4	125.5
124.0	124.1
123.3	123.4
121.2	121.3
108.7	108.7
83.2	83.2
56.1	56.2
46.6	46.6
44.3	44.4
43.4	43.5
36.2	36.2
31.1	31.2

Optical Rotation

Natural	Synthetic
$[\alpha]^{15}_{D}$: –716 (*c* 0.98, $CHCl_3$)	$[\alpha]^{15}_{D}$ = –537 (*c* 0.38, $CHCl_3$)

Preparation of cepharatine C (131).



cepharatine A (130) *cepharatine C* (131)

To a solution of cepharatine A (7.5 mg, 23.0 μmol mmol) in MeOH (0.46 mL) was added trimethyl orthoformate (0.05 mL) and H_2SO_4 (0.050 mL of a 1M solution in methanol). The solution was then stirred for 1 hour at 65 °C, cooled to room temperature, then slowly quenched with saturated aqueous $NaHCO_3$ (3 mL). The reaction was extracted with EtOAc (4 x 3 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to isolate a yellow oil. Flash chromatography (0.5 to 4% MeOH in CH_2Cl_2) afforded cepharatine C (**131**) as a yellow-orange foam (7.4 mg, 22.6 μmol, 99% yield). $[\alpha]^{16}_D$ = –550 (*c* 0.38, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.65 (d, *J* = 9.3 Hz, 1H), 6.26 (t, *J* = 4.7 Hz, 1H), 6.26 (s, 1H), 6.07 (s, 1H), 3.94 (d, *J* = 12.5 Hz, 1H), 3.94 (s, 3H), 3.38 (s, 3H), 2.90–2.81 (m, 1H), 2.64–2.53 (m, 1H), 2.20 (s, 1H), 2.15 (dd, *J* = 12.4, 2.6 Hz, 1H), 1.44–1.34 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 191.7, 158,0, 147.8, 144.2, 135.0, 126.7, 125.9, 125.5, 123.6, 121.1, 108.7, 87.4, 56.2, 48.6, 46.6, 43.7, 38.8, 36.6, 31.3; ^{1}H NMR (300 MHz, CD_3OD): δ 6.88 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 9.4 Hz, 1H), 6.30 (d, *J* = 9.5 Hz, 1H), 6.02 (s, 1H), 4.14 (d, *J* = 12.5 Hz, 1H), 3.89 (s, 3H), 3.31 (s, 3H), 2.83 (ddd, *J* = 11.7, 4.8, 1.6 Hz, 1H), 2.66 (td, *J* = 12.8, 4.8 Hz, 1H), 2.51 (ddd, *J* = 12.9, 11.6, 3.4 Hz, 1H), 2.10 (s, 3H), 2.02 (dd, *J* = 12.5, 1.3 Hz, 1H), 1.34–1.27 (m, 1H); ^{13}C NMR (126 MHz, CD_3OD): δ 193.4, 162.6, 150.8, 146.4, 137.9, 126.8, 126.7, 126.5, 123.7, 122.6, 110.5, 88.9, 56.6, 47.7, 45.4, 40.2, 36.9, 32.0; IR (NaCl/thin film): 3338, 2923, 2849, 1658, 1612, 1566, 1483, 1440, 1296, 1274, 1083, 1022, 878 cm^{-1}; HRMS (EI+) calc'd for $C_{19}H_{21}NO_4$ $[M+H]^+$ 328.1543, found 330.1546.

Comparison of Spectroscopic Data for Natural and Synthetic (–)-Cepharatine C

^{1}H NMR Data (both spectra are referenced to 3.30 ppm)

Reported	Synthetic
6.88 (d, *J* = 8.4 Hz, 1H)	6.88 (d, *J* = 8.4 Hz, 1H)
6.80 (d, *J* = 9.2 Hz, 1H)	6.79 (d, *J* = 8.2 Hz, 1H)
6.77 (d, *J* = 8.4 Hz, 1H)	6.76 (d, *J* = 9.4 Hz, 1H)
6.30 (d, *J* = 9.2 Hz, 1H)	6.30 (d, *J* = 9.5 Hz, 1H)
6.03 (s, 1H)	6.02 (s, 1H)
4.14 (d, *J* = 12.4 Hz, 1H)	4.14 (d, *J* = 12.5 Hz, 1H)
3.90 (s, 3H)	3.89 (s, 3H)
3.31 (s, 3H)	3.31 (s, 3H)
2.85 (m, 1H)	2.83 (ddd, *J* = 11.7, 4.8, 1.6 Hz, 1H)
2.69 (m, 1H)	2.66 (td, *J* = 12.8, 4.8 Hz, 1H)
2.55 (m, 1H)	2.51 (ddd, *J* = 12.9, 11.6, 3.4 Hz, 1H)
2.10 (s, 3H)	2.10 (s, 3H)
2.02 (m, 1H)	2.02 (dd, *J* = 12.5, 1.3 Hz, 1H)
1.29 (m, 1H)	1.34 – 1.27 (m, 1H)

^{13}C NMR Comparsion Data (both spectra are referenced to 49.0 ppm)

Reported	Synthetic
193.6	193.5
162.7	162.6
150.8	150.8
146.5	146.5
137.9	137.9
126.8	126.8
126.7	126.7
126.4	126.5
123.7	123.7
122.6	122.6
110.4	110.5
88.8	88.9
56.6	56.6
49.0	–[37]
47.7	47.7
45.4	45.4
40.1	40.2
36.9	36.9
32.0	32.0

Optical Rotation

Natural	Synthetic
$[\alpha]^{20}_{D}$: –332 (*c* 1.01, MeOH)	$[\alpha]^{15}_{D}$ = –550 (*c* 0.56, MeOH)

2.5. Notes and References

(1) Chuang, K. V.; Navarro, R.; Reisman, S. E. *Chem. Sci.* **2011**, *2*, 1086–1089.

(2) Chuang, K. V.; Navarro, R.; Reisman, S. E. *Angew. Chem. Int. Ed.* **2011**, *50*, 9447–9451.

(3) (a) Chou, C. T.; Swenton, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 6898–6899. (b) Swenton, J. S.; Bonke, B. B.; Clark, W. M.; Chen, C.-P.; Martin, K. V. *J. Org. Chem.* **1990**, *55*, 2027–2034.

(4) Wilds, A. L.; Djerassi, C. *J. Am. Chem. Soc.* **1946**, *68*, 1715–1719.

(5) For a review, see: Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873–888.

(6) Auxiliary-based approaches: (a) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268–269; (b) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686–5687; (c) Canales, E.; Hernandez, E.; Soderquist, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 8712–8713.

(7) Catalytic asymmetric approaches: (a) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687–7691; (b) Yazaki, R.; Nitabaru, T.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 14477–14479; (c) Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 500–501; (d) Du, Y.; Xu, L.-W.; Shimizu, Y.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 16146–16147; (e) Wieland, L. C.; Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 570–576; (f) Lauzon, C.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2743–2745; (g) Fu, P.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 5530–5541; (h) Shintani, R.; Takeda, M.; Tsuji, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 13168–13169.

(8) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995.

(9) When *n*-BuLi is used, the debrominated product is observed in approximately 5% yield.

(10) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(11) Barton, D. H. R.; Gunatilaka, A. A. L.; Letcher, R. M.; Lobo, A. M. F. T.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 874.

(12) (–)-**108** is the unnatural antipode. Both enantiomers of *tert*-butanesulfinamide are readily accessible; use of (*S*)-*tert*-butanesulfinamide should provide access to the natural enantiomer.

(13) Jakiela, D. J.; Helquist, P.; Jones, L. D. *Org. Synth.* **1984**, *62*, 74–85.

(14) For previous enantioselective syntheses, see: (a) Tsuda, Y.; Hosoi, S.; Ishida, K.; Sangai, M. *Chem. Pharm. Bull.* **1994**, *42*, 204–213; (b) Allin, S. M.; Streetley, G. B.; Slater, M.; James, S. L.; Martin, W. P. *Tetrahedron Lett.* **2004**, *45*, 5493–5496; (c) Zhang, F.; Simpkins, N. S.; Wilson, C. *Tetrahedron Lett.* **2007**, *48*, 5942–5947.

(15) Wang, X.; Jin, H.; Li, Z.; Qin, G. *Fitoterapia* **2007**, *78*, 593–595.

(16) Tomita, M.; Kozuka, M. *Tetrahedron Lett.* **1966**, *7*, 6229–6232.

(17) Gensler, W. J.; Bluhm, A. L. *J. Org. Chem.* **1956**, *21*, 336–339.

(18) Li, W.-D. Z.; Wang, X.-W. *Org. Lett.* **2007**, *9*, 1211–1214.

(19) Antony, P.; Sigüeiro, R.; Huet, T.; Sato, Y.; Ramalanjaona, N.; Rodrigues, L. C.; Mouriño, A.; Moras, D.; Rochel, N. *J. Med. Chem.* **2010**, *53*, 1159–1171.

(20) Castle and coworkers have isolated a similar intermediate during synthetic studies toward the hasubanans: Nielsen, D. K.; Nielsen, L. L.; Jones, S. B.; Toll, L.; Asplund, M. C.; Castle, S. L. *J. Org. Chem.* **2009**, *74*, 1187–1199.

(21) He, L.; Zhang, Y.-H.; Guan, H.-Y.; Zhang, J.-X.; Sun, Q.-Y.; Hao, X.-J. *J. Nat. Prod.* **2011**, *74*, 181–184.

(22) Mukaiyama, T.; Matsuo, J.-I.; Kitagawa, H. *Chem. Lett.* **2000**, 1250–1251.

(23) All other reaction conditions screened provided hemiaminal **121** as the major product or led to significant decomposition.

(24) Di Bussolo, V.; Caselli, M.; Romano, M. R.; Pineschi, M.; Crotti, P. *J. Org. Chem.* **2004**, *69*, 8702–8708.

(25) Vyvyan, J. R.; Loitz, C.; Looper, R. E.; Mattingly, C. S.; Peterson, E. A.; Staben, S. T. *J. Org. Chem.* **2004**, *69*, 2461–2468.

(26) McKillop, A.; Perry, D. H.; Edwards, M.; Antus, S.; Farkas, L.; Nogradi, M.; Taylor, E. C. *J. Org. Chem.* **1976**, *41*, 282–287.

(27) Brown, H. C.; Subrahmanyam, C.; Hamaoka, T.; Ravindran, N.; Bowman, D. H.; Misumi, S.; Unni, M. K.; Somayaji, V.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6068–6075.

(28) The product isolated contained <2% minor diastereomer and 3% cis addition

product.

(29) Liu, H.; Tomooka, C. S.; Xu, S. L.; Yerxa, B. R.; Sullivan, R. W.; Xiong, Y.; Moore, H. W. *Org. Synth.* **1999**, *76*, 189.

(30) Raminelli, C.; Gargalaka, J., Jr.; Silveira, C. C.; Comasseto, J. V. *Tetrahedron* **2007**, *63*, 8801–8809.

(31) To a suspension of Mg turnings (239 mg, 9.8 mmol) in THF (1 mL) was added DIBAL-H (1 mol %). The resulting suspension was heated to reflux, and a solution of 3,4-dimethoxyphenethyl bromide (1 g, 4.1 mmol) in THF (4 mL) was added dropwise. The reaction was maintained at reflux for 1.5 hrs, then cooled to room temperature and used for the sulfinimine addition reaction.

(32) ^{1}H NMR data for cepharatine D was found to be inconsistent with the spectral data provided in the isolation paper. See ref. 21.

(33) It was noted that synthetic (–)-cepharatine D produced a significantly lower specific rotation than reported by the isolation paper. To eliminate the possibility of racemization during the reaction sequence, racemic **123** was synthesized using racemic *tert*-butylsulfinamide by an identical sequence, and the enantiomeric excess of synthetic **123** was determined to be > 98% ee by chiral SFC (see Chiral SFC Traces).

(34) It was noted that synthetic (–)-8-demethoxyrunanine produced a significantly lower specific rotation than reported by the isolation paper. Racemic **2** was synthesized using racemic *tert*-butylsulfinamide*;* the enantiomeric excess of synthetic **2** was determined to be > 98% ee by chiral SFC.

(35) Grignard reagent **112** was prepared in analogy to 3,4-dimethoxyphenethyl)magnesium bromide. See ref. 31.

(36) It was noted that synthetic (–)-cepharatine A produced a lower specific rotation than that reported. It is inferred, based on the total syntheses of 8-demethoxyrunanine and cepharatine D, that the lower observed rotation does not necessarily imply any loss of enantiomeric excess.

(37) The corresponding resonance is obscured by the residual solvent peak. Acquisition in $CDCl_3$ shows the analogous signal at δ 48.6 ppm.