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Double Reduction of Cyclic Aromatic Sulfonamides: Synthesis of (+)-Mesembrine and (+)-Mesembranol

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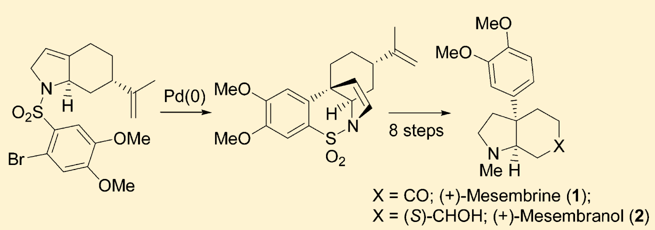
Supporting Information

ABSTRACT: The synthesis of (+)-mesembrine (**1**) and (+)-mesembranol (**2**) has been achieved from the monoterpene (*S*)-(−)-perillyl alcohol. Key transformations include a diastereo- and regioselective Pd-mediated intramolecular Heck reaction, and a double reduction of the resultant cyclic sulfonamide, to afford the *cis*-3a-aryloctahydroindole skeleton.



Mesembrine **1** is a naturally occurring alkaloid isolated from the plant species *Sceletium tortuosum*.[1] Historically, these plants have been used to make a concoction in Southern Africa known as *Channa*, or *Kougoed*. It has been shown that **1** is the major active ingredient of *Channa*, and studies have demonstrated that this naturally occurring alkaloid behaves as a selective serotonin reuptake inhibitor (SSRI).[1,2] This alkaloid, and its congeners, contains the *cis*-3a-aryloctahydroindole nucleus (Figure 1) and has been a popular synthetic target for several decades.[3] The main challenge in the synthesis of these alkaloids is the controlled construction of the sterically hindered, benzylic, quaternary stereogenic center.[4] Another attractive feature of this target is that the *Sceletium* alkaloids are closely structurally related to the *Amaryllidaceae* alkaloids, such as pretazettine (**4**) and the crinane-type alkaloids (e.g., saturated **5** and unsaturated **6**).[5] Additionally, more complex compounds such as strychnine **7** also have embeded within their structure a *cis*-3a-aryloctahydroindole motif.

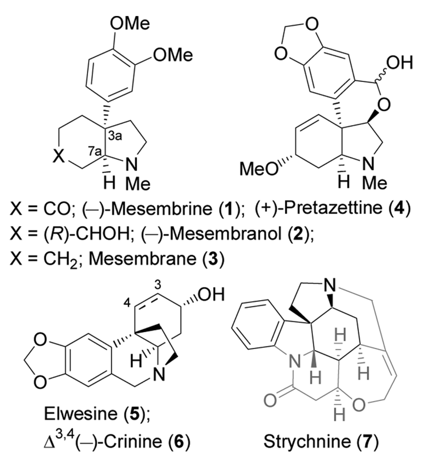
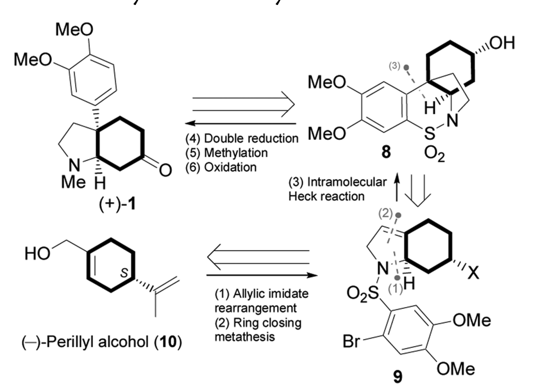


Figure 1. *cis*-3a-Aryloctahydroindole containing alkaloids.

For several years, we[6] have studied the synthesis of cyclic sulfonamides.[7] Our primary motivation for this interest is that certain examples undergo a double-reduction reaction, whereby both the C−S and N−S bonds are cleaved following exposure to lithium, or sodium metal in liquid ammonia.[6a] The cyclic sulfonamide starting materials required for this process may be conveniently accessed by an intramolecular Heck reaction. More recently we have demonstrated that this intramolecular Heck-double reduction sequence can be utilized to access the *cis*-aryloctahydroindole skeleton.[6b]

Having previously achieved the racemic synthesis of mesembrane **3**,[6b] we considered the asymmetric synthesis of this group of alkaloids, in specifically targeting the synthesis of mesembrine **1**. We anticipated that a double reduction reaction of **8** would give access to the naturally occurring alkaloid. In turn a diastereo- and regioselective intramolecular Heck reaction performed on trisubstituted alkene **9** would afford cyclic sulfonamide **8**. It was envisaged that **9** could be assembled as a single enantiomer from the monoterpenoid, (*S*)-perillyl alcohol **10**[8] which will constitute both the source of asymmetry and the cyclohexyl ring (Scheme 1).

Scheme 1. Retrosynthetic Analysis



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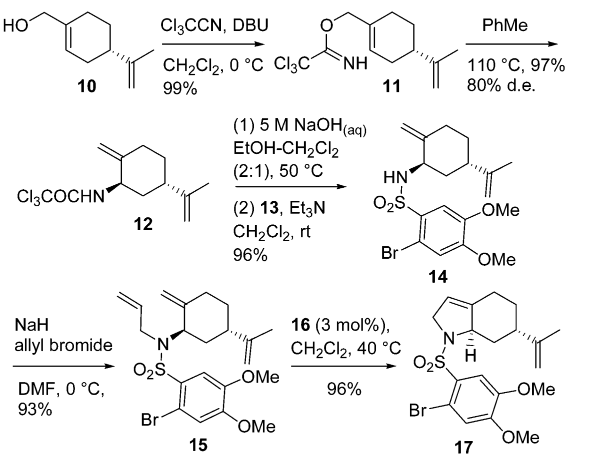
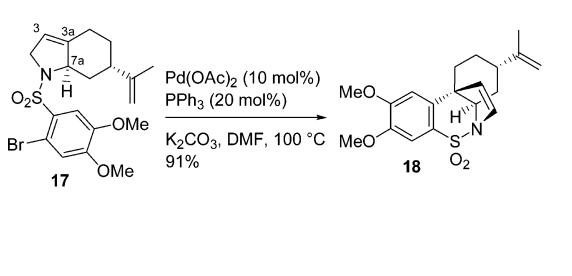
As outlined in Scheme 2, the starting point of the synthesis was conversion of the commercially available (*S*)-perillyl alcohol **10** into the corresponding trichloroacetimidate **11**.[9] An Overman rearrangement[10] was effected on heating imidate **11** to reflux in dry toluene for 5 days, which afforded trichloroacetamide **12** in 97% yield after purification as a 9:1 ratio of diastereoisomers; the major diastereomer contains the correct stereochemistry for (+)-mesembrine (unnatural enantiomer).[11] Presumably the diastereoselectivity observed in this [3,3]-sigmatropic rearrangement arises from a *pseudo*-axial carbon−nitrogen bond formation from a conformer in which the isopropenyl substituent occupies a *pseudo*-equatorial position. The two diastereomers of **12** proved inseparable by column chromatography at this stage. Thus, the mixture of acetamides was cleaved under basic conditions (ethanolic aqueous NaOH)[12] to generate a mixture of diastereomeric primary amines, which, due to volatility,[13] were directly converted into the corresponding sulfonamide with 2-bromo-4,5-dimethoxybenzenesulfonyl chloride **13**. At this point chromatographic separation of diastereomers was possible and the crystalline sulfonamide **14** was isolated (96% in two steps from **12**, based on **13**). X-ray crystallography indicated that the diastereoisomer necessary for the synthesis of (+)-**1** had indeed been obtained.[14] Subsequent alkylation with allyl bromide, utilizing NaH as a base, followed by a ring-closing metathesis (RCM) reaction in the presence of catalytic amounts of Hoveyda−Grubbs second Generation catalyst **16**, efficiently generated the desired *N*-sulfonyldihydropyrrole compound **17** in near-quantitative yield with no interference from the isopropenyl olefin (Scheme 2).

Scheme 2. Synthesis of Heck Precursor 17



With Heck precursor **17** in hand we turned our attention to the planned intramolecular Mizoroki−Heck cyclization (Scheme 3).[15] Pleasingly, using standard conditions, formation of cyclic sulfonamide **18** took place in 91% isolated yield. Two features regarding this cyclization deserve mention. First, the regiochemical outcome of this Heck reaction is unusual, i.e., the selective formation of a quaternary center from an unbiased system, in terms of the size of the newly formed ring. Carbon−carbon bond formation at either carbon 3 or 3a in **17** would proceed via a 6-*exo-trig* mode of cyclization.[16] Second, using this process installation of the quaternary benzylic bond (presented by the alkaloids in Figure 1) was achieved in a stereoselective manner, governed by the stereogenic carbon-7a set following the Overman rearrangement.

Scheme 3. Regio- and Diastereoselective Mizoroki−Heck Reaction of 17



After serving as a nonparticipating bystander in the RCM and Heck process, our next challenge was to consider the conversion of the isopropenyl group in **18** into a functional group that could ultimately become the group present in the target natural products (+)-**1** and (+)-**2**.

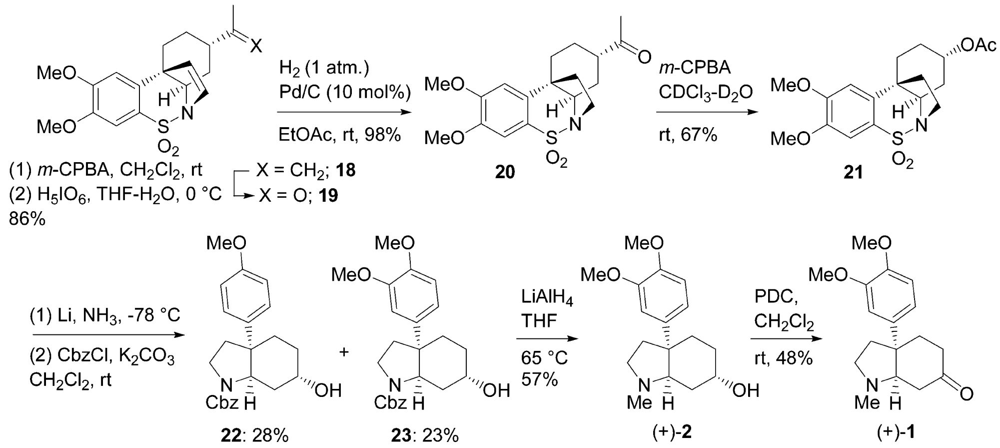
Gratifyingly, a chemoselective epoxidation of the exocyclic alkene proceeded smoothly with a slight excess of *meta*-chloroperbenzoic acid (*m*-CPBA), with the endocyclic alkene remaining unchanged (Scheme 4). The epoxide (not shown), formed as a mixture of diastereoisomers, was then directly treated with periodic acid (H_5IO_6) in a THF−H_2O mixture, which, following ring opening and oxidative cleavage of the resultant 1,2-diol, gave the methyl ketone **19** (86% from **18**).[17] Subsequent hydrogenation of the remaining double bond yielded the saturated cyclic sulfonamide **20** in quantitative yield. Now we were in a position to employ a Baeyer−Villiger oxidation reaction[18] to install an oxygen atom at C-6. Although this reaction proved sluggish, after some optimization, acetate **21** was obtained in 67% yield when 3 equiv of *m*-CPBA were used in a deuterated solvent mixture ($CDCl_3$−D_2O; 1:1), enabling reaction monitoring by ^1H NMR spectroscopy.

Our earlier work on the double reduction reaction had shown that, using lithium, or sodium metal in liquid ammonia, partial loss of the *para*-methoxy group to the sulfonyl moiety takes place.[6a,19] Thus, when we subjected sulfonamide **21** to lithium (20 equiv) in liquid ammonia, we isolated, following aqueous workup, appoximately a 1:1 mixture of mono- and dimethoxy substituted amino alcohols. During this reaction, in addition to the reductive sulfonyl excision, ammonia also facilitated a deacetylation process to reveal the secondary alcohol.

The crude mixture of amino alcohols was then submitted to benzyl chloroformate (CbzCl) in CH_2Cl_2 with potassium carbonate. This afforded carbamates **23** (23%) and **22** (28%), which proved readily separable by flash column chromatography. Although the reduction in yield associated with the partial methoxy cleavage was detrimental in relation to the synthesis of (+)-**1**, the monomethoxy side product is synthetically useful since other alkaloids belonging to the *Sceletium* family (for example, (+)-dihydro-*O*-methylsceletenone and joubertiamine) possess this type of aromatic substitution.[20]

Previously,[6b] we have reduced the Cbz-protecting group strategically to reveal a methyl group on the nitrogen atom.[21] Thus, when compound **23** was treated with lithium aluminum hydride the *N*-methyl-amino alcohol **2** was obtained in moderate yield. This amino alcohol **2** is in fact the enantiomer of the naturally occurring alkaloid mesembranol,[22] which is also a known intermediate[3i] on route to the target molecule mesembrine. To complete the synthesis of (+)-**1** an oxidation of the secondary alcohol in (+)-mesembranol was carried out. In our hands, despite numerous attempts and different conditions,[23] the optimum conditions proved to be pyridinium

Scheme 4. Conversion of 18 to 21, Its Double Reduction, and the Synthesis of (+)-Mesembrine 1 and (+)-Mesembranol 2



dichromate (PDC) in anhydrous CH_2Cl_2, which gave (+)-**1** in 48% yield with data consistent to those reported in the literature.[3f] The Wolff–Kishner reduction of mesembrine (**1**) has been reported to generate mesembrane (**3**).[24]

In conclusion, we have reported the stereoselective, total synthesis of (+)-**1**, (+)-**2** from the inexpensive, chiral alcohol (*S*)-perillyl alcohol **10**. During this synthesis the sulfonamide functional group and the benzyl carbamate groups were both used in strategic bond formation reactions, which therefore did not require nonproductive, additional deprotection steps. The partial methoxy cleavage observed, following the double reduction, enables the access of monomethoxy members of the *Sceletium* alkaloid family.[20] Based on the route developed, the natural enantiomer of mesembrine would be accessible using noncommercially available (*R*)-(+)-perillyl alcohol, which can be prepared by a biotransformation.[8b] It is additionally notable that certain members of the *Amaryllidaceae* family of natural products exhibit alternate stereochemistry to that found in the *Sceletium* family (e.g., **6**, Figure 1).[5b,25]

■ EXPERIMENTAL SECTION

General Directions. Reagents were obtained from commercial suppliers and were used without further purification. Anhydrous dimethylformamide (DMF) and toluene (PhMe) were used as supplied and stored under an inert gas at room temperature. Anhydrous tetrahydrofuran (THF) was distilled under nitrogen from the sodium-benzophenone ketyl radical. Dichloromethane was distilled, under nitrogen, from CaH_2. Thin-layer chromatography was performed on silica coated aluminum sheets (60 F_{254}). Flash column chromatography was performed under moderate pressure using flash silica 60 Å (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded using 300, 400, and 500 MHz instruments as indicated. Reported assignments are based on two-dimensional $^1H-^1H$ and $^1H-^{13}C$ spectra. Deuterochloroform was used as the solvent, and chemical shifts are given in ppm relative to the standard reference tetramethylsilane, or residual chloroform. Samples for infrared spectroscopy were recorded as films on KBr plates using an FT-IR spectrometer. Optical rotation measurements were recorded at 589 nm, 25 °C and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Melting points are uncorrected and were recorded on recrystallized material (from indicated solvent), or material directly obtained following purification by flash column chromatography. High resolution mass spectra (ESI-HRMS) were obtained using a mass spectrometer with a TOF mass analyzer.

(*S*)-(4-(Prop-1-en-2-yl)cyclohex-1-enyl)methyl 2,2,2-Trichloroacetimidate 11. A solution of **10** (1.04 mL, 6.58 mmol, 1 equiv) in anhydrous CH_2Cl_2 (30 mL) was cooled to 0 °C. 1,8-Diazabicyloc[5.4.0]undec-7-ene[26] (1.17 mL, 7.9 mmol, 1.2 equiv) and trichloroacetonitrile (0.98 mL, 9.87 mmol, 1.5 equiv) were added sequentially. Stirring was continued for 2 h during which period room temperature was reached. The reaction mixture was then filtered through a plug of silica washing with CH_2Cl_2, and the filtrate was concentrated *in vacuo* to give the imidate (1.92 g, 99%) as an orange liquid. The thus obtained imidate **11** was used without further purification. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.27 (s, 1H, NH), 5.89–5.81 (m, 1H, CH), 4.77–4.69 (m, 2H, CH_2), 4.68 (s, 2H, CH_2), 2.24–2.19 (m, 1H, CH), 2.20–2.13 (m, 3H, CH_2), 2.06–1.97 (m, 1H, CH_2), 1.87 (m, 1H, CH_2), 1.74 (s, 3H, CH_3), 1.58–1.46 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9 (C), 149.7 (C), 132.4 (C), 126.2 (CH), 108.9 (CH_2), 91.8 (C), 73.3 (CH_2), 40.9 (CH), 30.6 (CH_2), 27.5 (CH_2), 26.4 (CH_2), 20.98 (CH_3).

2,2,2-Trichloro-*N*-((1*R*,5*S*)-2-methylene-5-(prop-1-en-2-yl)-cyclohexyl)acetamide 12. A solution of imidate **11** (1.9 g, 6.42 mmol) in anhydrous toluene (60 mL) was heated to reflux for 5 days (oil bath temperature 130 °C). Once cooled, the mixture was concentrated under pressure to give a brown oil, which was flushed through a pad of silica (*c*-Hex/EtOAc, 3:1) to afford acetamide **12** (1.85 g, 97%) as a golden yellow liquid. R_f = 0.6 (*c*-Hex/EtOAc, 3:1); $[\alpha]_D^{20}$ = +40.3 (*c* = 2.0, $CHCl_3$); IR (KBr, dep. from CH_2Cl_2) 3435, 3369, 3083, 2939, 2858, 1708, 1645, 1504, 893, 821 cm^{-1}; HRMS (ESI): calcd for $C_{12}H_{17}NO^{35}Cl_3$ ([M + H]$^+$): 296.0376, found 296.0365; ^1H NMR ($CDCl_3$, 500 MHz): δ 6.85–6.72 (m, 1H, NH), 4.97 (s, 1H, CH_2), 4.89 (s, 1H, CH_2), 4.78 (s, 1H, CH_2), 4.76 (s, 1H, CH_2), 4.55 (dt, *J* = 8.0, 4.5 Hz, 1H, CH), 2.35 (dt, *J* = 14.0, 4.5 Hz, 1H, CH_2), 2.25–2.19 (m, 2H, CH/CH_2), 2.03 (m, 1H, CH_2), 1.85 (m, 1H, CH_2), 1.72 (s, 4H, CH_2/CH_3), 1.47 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.6 (CO), 147.5 (C), 144.6 (C), 111.9 (CH_2), 110.1 (CH_2), 92.9 (C), 53.5 (CH), 39.4 (CH), 36.1 (CH_2), 31.7 (CH_2), 30.7 (CH_2), 21.1 (CH_3).

2-Bromo-4,5-dimethoxy-*N*-((1*R*,5S)-2-methylene-5-(prop-1-en-2-yl)cyclohexyl)benzene Sulfonamide 14. A solution of **12** (2.20 g, 7.46 mmol) in EtOH–CH_2Cl_2 (2:1, 12 mL) was treated with 5 M NaOH (5 mL), and the reaction was heated to 50 °C for 15 h.[12] Once the reaction cooled, CH_2Cl_2 (20 mL) was added and the organic layer was washed with brine (1 × 20 mL), dried ($MgSO_4$), and filtered. The crude amine–CH_2Cl_2 solution was treated with 2-bromo-4,5-dimethoxybenzene-1-sulfonyl chloride **13** (1.78 g, 5.64 mmol, 0.76 equiv) and Et_3N (0.9 mL, 6.77 mmol, 1.2 equiv) at 0 °C. Stirring was continued for 5 h, and the reaction gradually warmed to room temperature. The reaction mixture was washed once with H_2O, and the organic layer was dried over $MgSO_4$. The crude product, obtained after solvent removal and filtration, was purified by column chromatography (*c*-Hex/EtOAc, 6:1) which gave the *title* compound **14** (2.30 g, 96% - based on **13**) as a light yellow solid. R_f = 0.3 (*c*-Hex/EtOAc, 3:1); Mp 100–102 °C; $[\alpha]_D^{20}$ = +62.5 (*c* = 2.0, $CHCl_3$); IR (KBr, dep. from CH_2Cl_2) 3081, 2937, 1464, 1360, 1331, 1161, 1132, 690 cm^{-1}; HRMS (ESI): calcd for $C_{18}H_{24}NO_4S^{79}BrNa$ ([M + Na]$^+$): 452.0507, found 452.0515; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.56 (s, 1H, ArH), 7.09 (s, 1H, ArH), 5.34 (d, J = 6.0 Hz, 1H, NH), 4.71−4.64 (m, 1H, CH_2), 4.65−4.57 (m, 2H, CH_2), 4.53 (s, 1H, CH_2), 3.91 (s, 3H, CH_3), 3.89 (s, 4H, CH_3/CH), 2.28 (tt, J = 12.0, 3.0 Hz, 1H, CH), 2.19−2.09 (m, 2H, CH_2), 1.93 (dq, J = 13.5, 3.0 Hz, 1H, CH_2), 1.83−1.74 (m, 1H, CH_2), 1.63 (s, 3H, CH_3), 1.50−1.41 (m, 1H, CH_2), 1.25 (td, J = 12.0, 5.0 Hz, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.3 (C), 148.3 (C), 147.9 (C), 145.2 (C), 131.2 (C), 116.9 (CH), 114.2 (CH), 111.6 (CH), 111.5 (CH_2), 109.6 (CH_2), 56.6 (CH), 56.5 (CH_3), 56.4 (CH_3), 38.9 (CH), 37.9 (CH_2), 32.2 (CH_2), 30.4 (CH_2), 20.9 (CH_3).

***N*-Allyl-2-bromo-4,5-dimethoxy-*N*-((1*R*,5*S*)-2-methylene-5-(prop-1-en-2-yl)cyclohexyl)benzene Sulfonamide 15.** A solution of **14** (150 mg, 0.35 mmol) dissolved in DMF (4 mL) was cooled to 0 °C. Sodium hydride (60% w/w in mineral oil, 22 mg, 0.525 mmol, 1.5 equiv) was added, and the mixture was stirred for 0.5 h. Allyl bromide (0.04 mL, 0.42 mmol, 1.2 equiv) was added in a dropwise fashion. Stirring was continued for 15 h during which period room temperature was reached. EtOAc (10 mL) and H_2O (10 mL) were added, and the phases were separated. The aqueous layer was further extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried over $MgSO_4$. The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex/EtOAc, 6:1) to yield the *title compound* **15** (152 mg, 93%) as a white solid. R_f = 0.5 (*c*-Hex/EtOAc, 3:1); Mp 78−80 °C; $[\alpha]_D^{20}$ = −8.8 (c = 0.8, $CHCl_3$); IR (KBr, dep. from CH_2Cl_2) 2846, 1584, 1503, 1437, 1360, 1330, 1158, 1116, 598 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{29}NO_4S^{79}Br$ ([M + H]$^+$): 470.1001, found 470.0986; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (s, 1H, ArH), 7.08 (s, 1H, ArH), 5.87 (ddt, J = 16.5, 10.5, 6.0 Hz, 1H, CH), 5.18 (d, J = 17.0 Hz, 1H, CH_2), 5.09 (d, J = 11.0 Hz, 1H, CH_2), 4.84 (s, 1H, CH_2), 4.81−4.76 (m, 2H, CH_2), 4.72 (s, 1H, CH_2), 4.51 (dd, J = 8.5, 4.5 Hz, 1H, CH), 4.19 (ddt, J = 17.0, 6.0, 1.5 Hz, 1H, CH_2), 4.03 (ddt, J = 17.0, 6.0, 1.5 Hz, 1H, CH_2), 3.91 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 2.24−2.18 (m, 1H, CH), 2.10−2.04 (m, 2H, CH_2), 2.02−1.95 (m, 2H, CH_2), 1.64 (s, 3H, CH_3), 1.60−1.57 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.1 (C), 147.7 (C), 146.7 (C), 145.9 (C), 135.9 (CH), 132.5 (C), 117.3 (CH_2), 117.2 (CH), 114.9 (CH), 112.3 (C), 110.8 (CH), 110.6 (CH), 58.6 (CH), 56.6 (CH_3), 56.5 (CH_3), 48.9 (CH_2), 39.5 (CH), 35.3 (CH_2), 31.2 (CH_2), 30.5 (CH_2), 21.9 (CH_3).

(6*S*,7a*R*)-1-(2-Bromo-4,5-dimethoxyphenylsulfonyl)-6-(prop-1-en-2-yl)-2,4,5,6,7,7a-hexahydro-1*H*-indole 17. Under N_2, a degassed solution of **15** (500 mg, 1.06 mmol, 1 equiv) in CH_2Cl_2 (40 mL) was treated with Hoveyda−Grubbs second generation catalyst **16** (20 mg, 0.0321 mmol, 3 mol %). Stirring was continued at 40 °C for 15 h. Once cooled, the solvent was removed under reduced pressure. Purification by flash column chromatography (*c*-Hex/EtOAc, 6:1) gave **17** (450 mg, 96%) as a viscous oil. R_f = 0.4 (*c*-Hex/EtOAc, 3:1); $[\alpha]_D^{20}$ = +1.6 (c = 1.1, $CHCl_3$); IR (KBr, dep. from CH_2Cl_2) 2872, 1585, 1503, 1465, 1439, 1360, 1330, 1158, 1116 cm^{-1}; HRMS (ESI): calcd for $C_{19}H_{25}NO_4S^{79}Br$ ([M + H]$^+$): 442.0688, found 442.0706; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55 (s, 1H, ArH), 7.13 (s, 1H, ArH), 5.23 (s, 1H, CH), 4.89 (s, 1H, CH_2), 4.81 (s, 1H, CH_2), 4.48−4.42 (m, 1H, CH), 4.34−4.29 (m, 1H, CH_2), 4.21−4.15 (m, 1H, CH_2), 3.91 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 2.45−2.44 (m, 1H, CH_2), 2.41 (s, 1H, CH), 2.32−2.26 (m, 1H, CH_2), 2.19−2.12 (m, 1H, CH_2), 2.09−2.04 (m, 1H, CH_2), 1.71 (s, 3H, CH_3), 1.52−1.42 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 152.0 (C), 147.7 (C), 144.9 (C), 141.9 (C), 130.8 (C), 117.6 (CH), 113.9 (CH), 113.5 (CH), 112.1 (C), 111.4 (CH_2), 62.8 (CH), 56.4 (CH_3), 56.3 (CH_3), 55.0 (CH_2), 38.5 (CH), 36.8 (CH_2), 28.3 (CH_2), 24.3 (CH_2), 22.6 (CH_3).

(2*S*,4a*R*,10a*S*)-6,7-Dimethoxy-4a,10-etheno-2,3,4,4a,10,10a-hexahydro-1*H*-2-isopropenyl-9-thia-10-aza-phenanthrene 9,9-dioxide 18. Under N_2, a solution of **17** (105 mg, 0.24 mmol, 1 equiv) dissolved in DMF (2 mL) was degassed under a steady stream of nitrogen (*ca.* 0.5 h). To this solution was added $Pd(OAc)_2$ (6 mg, 0.024 mmol, 10 mol %), PPh_3 (12 mg, 0.048 mmol, 20 mol %), and K_2CO_3 (66 mg, 0.48 mmol, 2 equiv), and the mixture was heated to 110 °C for 15 h. The reaction vessel was cooled, and EtOAc (10 mL) and H_2O (10 mL) were added. The resultant aqueous layer was further extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 6:1→4:1) affording the Heck product **18** (79 mg, 91%) as a colorless solid. R_f = 0.3 (*c*-Hex/EtOAc, 2:1); Mp 63−66 °C; $[\alpha]_D^{20}$ = +10 (c = 0.5, $CHCl_3$); IR (KBr, dep. from CH_2Cl_2) 2920, 1562, 1470, 1361, 1334, 1146 cm^{-1}; HRMS (ESI): calcd for $C_{19}H_{23}NO_4SNa$ ([M + Na]$^+$): 384.1245, found 384.1245; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.16 (s, 1H, ArH), 6.64 (s, 1H, ArH), 6.23 (d, J = 3.5 Hz, 1H, CH), 6.16 (d, J = 3.5 Hz, 1H, CH), 4.94 (s, 1H, CH_2), 4.90 (s, 1H, CH_2), 4.74 (dd, J = 11.0, 6.0 Hz, 1H, CH), 3.90 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 2.48 (s, 1H, CH), 2.46−2.39 (m, 1H, CH_2), 2.16−2.12 (m, 2H, CH_2), 2.11−2.05 (m, 1H, CH_2), 1.98−1.90 (m, 1H, CH_2), 1.75 (s, 3H, CH_3), 1.69−1.65 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.1 (C), 149.6 (C), 144.5 (C), 138.7 (C), 138.3 (CH), 132.5 (CH), 125.1 (C), 112.6 (CH_2), 109.4 (CH), 105.3 (CH), 69.7 (CH), 56.4 (CH_3), 56.3 (CH_3), 48.4 (C), 37.3 (CH), 29.4 (CH_2), 23.2 (CH_2), 22.8 (CH_2), 22.5 (CH_3).

(2*S*,4a*R*,10a*S*)-2-Acetyl-6,7-dimethoxy-4a,10-etheno-2,3,4,4a,10,10a-hexahydro-1*H*-9-thia-10-aza-phenanthrene 9,9-dioxide 19. A solution of **18** (296 mg, 0.819 mmol, 1 equiv) dissolved in CH_2Cl_2 (10 mL) was treated with *m*-CPBA (77% w/w, 275 mg, 1.23 mmol, 1.5 equiv) at room temperature. After 15 h, sodium sulfite sat. (10 mL) and $NaHCO_3$ sat. (10 mL) were added and the reaction mixture was allowed to stir for 0.5 h, after which the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL), dried over $MgSO_4$, and reduced under pressure to afford the crude epoxide. The crude epoxide dissolved in THF−H_2O (2:1, 12 mL) was treated to H_5IO_6 (446 mg, 1.64 mmol, 2 equiv) at 0 °C. Stirring was continued for 15 h during which period room temperature was reached. Et_2O (20 mL) and H_2O (15 mL) were added, and the phases separated. The resultant aqueous layer was further extracted with Et_2O (2 × 20 mL), and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product which was purified by flash column chromatography (*c*-Hex/EtOAc, 2:1→1:2) affording the *title* compound **19** (255 mg, 86%) as a white solid. R_f = 0.1 (*c*-Hex/EtOAc, 1:1); Mp 78−81 °C; $[\alpha]_D^{20}$ = −5.7 (c = 1.4, $CHCl_3$); IR (KBr, dep. from CH_2Cl_2) 2945, 2854, 1705, 1599, 1352, 1330, 1158, 1149 cm^{-1}; HRMS (ESI): calcd for $C_{18}H_{21}NO_5SNa$ ([M + Na]$^+$): 386.1038, found 386.1039; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11 (s, 1H, ArH), 6.58 (s, 1H, ArH), 6.18 (d, J = 3.5 Hz, 1H, CH), 6.13 (d, J = 3.5 Hz, 1H, CH), 4.82 (dd, J = 10.5, 6.5 Hz, 1H, CH), 3.86 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 2.82 (s, 1H, CH), 2.41 (dd, J = 14.0, 6.5 Hz, 1H, CH_2), 2.26−2.23 (m, 2H, CH_2), 2.16 (s, 3H, CH_3), 1.81−1.73 (m, 1H, CH_2), 1.72−1.65 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 210.1 (C), 151.0 (C), 149.6 (C), 138.2 (C), 137.7 (CH), 132.6 (CH), 125.0 (C), 109.3 (CH), 105.3 (CH), 69.5 (CH), 56.3 (CH_3), 56.2 (CH_3), 48.0 (C), 45.4 (CH), 28.1 (CH_3), 27.6 (CH_2), 23.7 (CH_2), 22.4 (CH_2).

(2*S*,4a*R*,10a*S*)-2-Acetyl-6,7-dimethoxy-4a,10-ethano-2,3,4,4a,10,10a-hexahydro-1*H*-9-thia-10-aza-phenanthrene 9,9-dioxide 20. A mixture of **19** (300 mg, 0.826 mmol, 1 equiv) and 10% w/w Pd/C (9 mg, 0.083 mmol) in EtOAc (20 mL) was stirred under an atmosphere of hydrogen (1 atm) for 19 h. The mixture was filtered through Celite (washed with EtOAc 3 × 20 mL), and solvent removal under reduced pressure afforded the alkane compound **20** (295 mg, 98%) as an oil. R_f = 0.1 (*c*-Hex/EtOAc, 1:1); $[\alpha]_D^{20}$ = −5.4 (c = 3.7, $CHCl_3$); IR (KBr, dep. from CH_2Cl_2) 2981, 1703, 1601, 1321, 1156 cm^{-1}; HRMS (EI): calcd for $C_{18}H_{23}NO_5S$ ([M]$^+$): 365.1297, found 365.1306; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (s, 1H, ArH), 6.69 (s, 1H, ArH), 4.28 (dd, J = 12.0, 5.5 Hz, 1H, CH), 3.92 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 3.87−3.81 (m, 1H, CH_2), 3.59 (ddd, J = 14.0, 10.0, 4.0 Hz, 1H, CH_2), 2.83 (s, 1H, CH), 2.36−2.39 (m, 3H, CH_2), 2.28−2.20 (m, 1H, CH_2), 2.18 (s, 3H, CH_3), 1.95−1.87 (m, 1H, CH_2), 1.82 (ddt, J = 18.5, 9.0, 4.5 Hz, 1H, CH_2), 1.70 (ddd, J = 13.0, 9.5, 4.0 Hz, 1H, CH_2), 1.64−1.55 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 209.6 (C), 152.4 (C), 148.7 (C), 139.4 (C), 126.9 (C), 108.0 (CH), 106.1 (CH), 64.3 (CH), 56.3 (CH_3), 56.2

(CH_3), 45.9 (CH_2), 45.7 (CH), 44.3 (C), 33.3 (CH_2), 28.1 (CH_3), 27.6 (CH_2), 25.4 (CH_2), 21.6 (CH_2).

(2*S*,4a*R*,10a*S*)-2-Acetoxy-6,7-dimethoxy-4a,10-ethano-2,3,4,4a,10,10a-hexahydro-1*H*-9-thia-10-aza-phenanthrene 9,9-dioxide 21. A solution of ketone **20** (120 mg, 0.329 mmol, 1 equiv) dissolved in $CDCl_3$–D_2O (2.0 mL, 1:1) was treated with *m*-CPBA 77% pure (221 mg, 0.986 mmol, 3 equiv) at room temperature. The reaction was periodically monitored by ^1H NMR until all starting material was consumed (after approximately 48 h). Sodium sulfite sat. (5 mL) and $NaHCO_3$ sat. (5 mL) were added, and the reaction mixture was allowed to stir for 0.5 h, after which the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), dried over $MgSO_4$, and reduced under pressure to afford the crude acetate which was purified by flash column chromatography (*c*-Hex/EtOAc, 2:1→1:2) affording the *title* compound **21** (125 mg, 67%) as a white solid. R_f = 0.5 (*c*-Hex/EtOAc, 1:2); Mp 110–113 °C; $[\alpha]_D^{20}$ = −28.6 (*c* = 1.8, $CHCl_3$); IR (KBr, dep. from CH_2Cl_2) 2956, 2849, 1729, 1160, 1567, 1509, 1331, 1322, 1159, 1130 cm^{-1}; HRMS (ESI): calcd for $C_{18}H_{23}NO_6SNa$ ($[M + Na]^+$): 404.1144, found 404.1137; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.27 (s, 1H, ArH), 6.78 (s, 1H, ArH), 5.23 (s, 1H, CH), 4.39 (dd, *J* = 12.0, 5.5 Hz, 1H, CH), 3.94 (s, 3H, CH_3), 3.92 (s, 3H, CH_3) 3.90–3.85 (m, 1H, CH_2), 3.65–3.58 (m, 1H, CH_2), 2.37–2.29 (m, 3H, CH_2), 2.18–2.13 (m, 1H, CH_2), 2.05 (s, 1H, CH_2), 2.03 (s, 3H, CH_3), 1.81–1.78 (m, 1H, CH_2), 1.77–1.73 (m, 1H, CH_2), 1.59–1.52 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4 (C), 152.5 (C), 148.8 (C), 139.1 (C), 126.9 (C), 108.03 (CH), 106.1 (CH), 68.4 (C), 63.9 (C), 56.4 (CH_3), 56.2 (CH_3), 45.9 (CH_2), 44.1 (C), 33.1 (CH_2), 30.7 (CH_2), 24.8 (CH_2), 23.8 (CH_2), 21.4 (CH_3).

(+)-Mesembranol [(3a*R*,6*S*,7a*R*)-3a-(3,4-Dimethoxyphenyl)-1-methyloctahydro-1*H*-indol-6-ol] 2. Under N_2, small pieces of Li (32 mg, 4.57 mmol, 20 equiv) were added to NH_3 (*ca.* 75 mL) at −78 °C. The mixture was stirred for 1 h before a solution of **21** (87 mg, 0.228 mmol, 1 equiv) in THF (5 mL + 5 mL to wash flask) was added in a dropwise fashion. Stirring was continued for 0.5 h at −78 °C before the addition of solid NH_4Cl (*ca.* 2 g). The NH_3 was allowed to evaporate on warming to room temperature, and the residue was dissolved in CH_2Cl_2 (15 mL). A 1 M solution of NaOH (to pH 12) was added, and the resultant aqueous layer was further extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure afforded a separable mixture of 3a-(3,4-dimethoxyphenyl)-octahydroindol-6-ol (LRMS (ESI): calcd for $C_{16}H_{24}NO_3$ ($[M + H]^+$): found 278.17) and 3a-(4-methoxyphenyl)octahydroindol-6-ol (LRMS (ESI): calcd for $C_{15}H_{22}NO_2$ ($[M + H]^+$): found 247.16). The crude mixture was dissolved in CH_2Cl_2 (30 mL) and treated subsequently with benzyl chloroformate (0.05 mL, 0.342 mmol, 1.5 equiv) and K_2CO_3 (315 mg, 2.28 mmol, 10 equiv). Stirring was continued at room temperature for 4 h before the addition of H_2O (30 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined layers were dried over $MgSO_4$. Following filtration and solvent removal, column chromatography (*c*-Hex/EtOAc, 6:1→1:1) afforded **23** (22 mg, 23%) and **22** (24 mg, 28%); [(3a*R*,6*S*,7a*R*)-benzyl 3a-(3,4-dimethoxyphenyl)-6-hydroxyoctahydro-1*H*-indole-1-carboxylate **23**: HRMS (ESI): calcd for $C_{23}H_{27}NO_4Na$ ($[M + Na]^+$): 404.1838, found 404.1853; (3a*R*,6*S*,7a*R*)-benzyl 6-hydroxy-3a-(4-methoxyphenyl)octahydro-1*H*-indole-1-carboxylate **22**: HRMS (ESI): calcd for $C_{24}H_{29}NO_5Na$ ($[M + Na]^+$): 434.1943, found 434.2012]. Under N_2, a solution of **23** (52 mg, 0.127 mmol, 1 equiv) dissolved in anhydrous THF (4 mL) was treated with $LiAlH_4$ (15 mg, 0.38 mmol, 3 equiv). The reaction mixture was heated to reflux for 3 h. Once cooled, EtOAc (10 mL) was added followed by 1 M NaOH (1 mL). H_2O (10 mL) was added, and the phases were separated. The aqueous layer was further extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and purified by column chromatography ($CHCl_3$/MeOH, 8:1) to afford the *title* compound **2** (9 mg, 57%) as a light pink solid. R_f = 0.18 ($CHCl_3$/MeOH, 8:1); Mp 111–114 °C; $[\alpha]_D^{20}$ = +25.2 (*c* = 0.7, $CHCl_3$) lit. −24 (*c* = 0.2, $CHCl_3$);[22] IR (KBr, dep. from CH_2Cl_2) 3355, 1655, 1454, 1410 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{26}NO_3$ ($[M + H]^+$): 292.1913, found 292.1906; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.91–6.77 (m, 2H, ArH), 6.82–6.79 (m, 1H, ArH), 4.01 (m, 1H, CH), 3.88 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 3.30–3.23 (m, 1H, CH_2), 2.80 (s, 1H, CH), 2.38 (s, 3H, CH_3), 2.34–2.30 (m, 1H, CH_2), 2.21–2.16 (m, 1H, CH_2), 2.04 (dd, *J* = 8.0, 3.0 Hz, 2H, CH_2), 1.97–1.87 (m, 1H, CH_2), 1.86–1.82 (m, 1H, CH_2), 1.80–1.71 (m, 1H, CH_2), 1.59–1.49 (m, 1H, CH_2), 1.25–1.16 (m, 1H, CH_2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 148.9 (C), 147.2 (C), 139.0 (C), 118.9 (CH), 111.0 (CH), 110.6 (CH), 70.2 (CH), 66.7 (CH), 56.1 (CH_3), 56.0 (CH_3), 54.4 (CH_2), 47.3 (C), 40.7 (CH_2), 40.2 (CH_2), 34.9 (CH_2), 33.1 (CH_2), 32.8 (CH_2).

(+)-Mesembrine [(3a*R*,7a*R*)-3a-(3,4-Dimethoxyphenyl)-1-methylhexahydro-1*H*-indol-6(2*H*)-one] 1. Under N_2, a solution of **2** (6 mg, 0.02 mmol, 1 equiv) dissolved in anhydrous CH_2Cl_2 (5 mL) was treated with PDC (23 mg, 0.062 mmol, 3 equiv). The reaction mixture was allowed to stir at room temperature for 2 h. A solution of 0.1 M NaOH (2 mL) was added, and the reaction was allowed to stir for an additional 2 h before the addition of CH_2Cl_2 (10 mL). The organic layer was washed with H_2O (10 mL), and the phases were separated. The organic layer was further extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and reduced under pressure. Purification by column chromatography ($CHCl_3$/Me_2CO, 6:1) afforded the *title* compound as a brown oil (6 mg, 48%). R_f = 0.2 ($CHCl_3$/Me_2CO, 6:1); $[\alpha]_D^{20}$ = +43 (*c* = 0.8, MeOH) (+28.2 (*c* = 2.8, $CHCl_3$)) lit. +53 (*c* = 0.53, MeOH),[3f] lit. −61.6 (*c* = 0.2, MeOH);[3b] IR (KBr, dep. from CH_2Cl_2) 1709, 1653, 1456 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{24}NO_3$ ($[M + H]^+$): 290.1756, found 290.1766; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.95–6.87 (m, 2H, ArH), 6.84 (d, *J* = 8.5 Hz, 1H, ArH), 3.90 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.14–3.11 (m, 1H, CH_2), 2.96–2.92 (m, 1H, CH), 2.60 (s, 2H, CH_2), 2.49–2.37 (m, 2H, CH_2), 2.37–2.27 (m, 4H, CH_2/CH_3), 2.24–2.19 (m, 2H, CH_2), 2.15–2.09 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 211.6 (CO), 149.2 (C), 147.7 (C), 140.4 (C), 118.1 (CH), 111.2 (CH), 110.1 (CH), 70.5 (CH), 56.2 (CH_3), 56.1 (CH_3), 55.0 (CH_2), 47.7 (C), 46.7 (CH_2), 40.2 (CH_3), 39.0 (CH_2), 36.4 (CH_2), 35.4 (CH_2).

■ ASSOCIATED CONTENT

Supporting Information

Copies of proton and carbon NMR spectra and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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