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Stereocontrolled enantioselective total synthesis of the [2+2] quadrigemine alkaloids

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Abstract

A unified strategy for enantioselective total synthesis of all stereoisomers of the 2+2 family of quadrigemine alkaloids is reported. In this approach, two enantioselective intramolecular Heck reactions are carried out at the same time on precursors fashioned in four steps from either *meso*- or (+)-chimonanthine to form the two critical quaternary carbons of the peripheral cyclotryptamine rings of these products. Useful levels of catalyst control are realized in either desymmetrizing a *meso* precursor or controlling diastereoselectivity in elaborating C_2-symmetic intermediates. None of the synthetic quadrigemines are identical with alkaloids isolated previously and referred to as quadrigemines A and E. In addition, we report improvements in our previous total syntheses of (+)- or (−)-quadrigemine C that shortened the synthetic sequence to 10 steps and provided these products in 2.2% overall yield from tryptamine.

Keywords

Stereocontrolled total synthesis; alkaloid; enantioselective catalysis; intramolecular Heck reaction

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Supplementary Information Available: Copies of ^{1}H and ^{13}C NMR spectra and HPLC traces, a description of general experimental details, summary of optical rotations reported for quadrigemine C, and HPLC and CD comparisons of synthetic and natural quadrigemine C.

1. Introduction

Alkaloids composed of multiple 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (cyclotryptamine or pyrrolidinoindoline) units have been isolated from a variety of natural sources, including bacteria, fungi, plants and amphibians (Figure 1).[1] In the predominant family of these alkaloids, cyclotryptamine units are joined at their benzylic C3a carbon to generate dimers, trimers and higher-order oligomers. In this linkage, two types of quaternary stereogenic centers are produced: (a) vicinal quaternary carbons joining benzylic (C3a) quaternary stereocenters of two cyclotryptamine units, and (b) aryl-substituted quaternary carbons linking the *peri* (C7) carbon of one pyrrolidinoindoline unit and the benzylic quaternary stereocenter of another. Both types of quaternary stereocenters present formidable challenges for stereocontrolled synthesis. As a result, when our efforts in this area began in 1995, no stereocontrolled methods were available for linking cyclotryptamine fragments at C3a.[2] In the intervening years, this challenging problem in total synthesis has been addressed by a number of researchers and many imaginative methods are currently available.[2,3] Nonetheless, stereocontrolled total synthesis of the more complex members of this group remains largely an unmet challenge.[4]

The first cyclotryptamine alkaloids containing four tricyclic units, quadrigemines A and B, were reported by Perry and Smith in 1978 from the leaves of *Hodgkinsonia frutesecens*.[5,6] Analysis of quadrigemine A revealed a base peak of *m*/*z* 344 corresponding to half the molecular weight of quadrigemine A along with ions *m*/*z* 345 and 690 in the EI mass spectrum. In comparison, quadrigemine B showed a parent ion of *m*/*z* 516, along with ions *m*/*z* 690, 517, and 172. The difference in fragmentation patterns corresponds to the location of the labile σ-bond connecting the 3a′–3a″-vicinal quaternary carbon centers of the chimonanthine subunit. [7] This fragmentation pattern has been used to designate the two groups of constitutional isomers: the [2+2] and [3+1] quadrigemine alkaloids (Figure 1).[8]

Quadrigemines A,[5] C[9], and E[10] are the three reported members of the [2+2] quadrigemine family. The complex NMR spectra and amorphous nature of these higher-order polypyrrolidinoindoline alkaloids has made determination of their three-dimensional structures particularly difficult. The relative and absolute configuration of only quadrigemine C (**1**) is known with certainty (Figure 2). Sévenet, who initially isolated quadrigemine C from an extract of *Psychotria oleoides* found in New Caledonia,[9a] provided evidence for the *R* absolute configuration of the two outer quaternary carbons of **1** by chemical correlation with hodgkinsine, whose absolute and relative configuration had been determined by single-crystal X-ray analysis.[9b,11] However rigorous proof of the absolute configuration of the central chimonanthine unit was not secured until the enantioselective total synthesis of (−)-quadrigemine C was reported by our group in 2002.[4] The optical rotations reported for quadrigemines A, C, and E in alcoholic solvents ($[\alpha]_D$ A, +32 (EtOH);[5] C, +40 (MeOH);[9d] E, +33 (EtOH)[10] are similar; suggesting that these alkaloids, which were isolated by different laboratories, could be identical.[12] Resolving this issue from the published NMR characterization data is impossible, because of differences in the reported NMR solvent and spectrometer field strength. Even if directly comparable data were available for evaluation, the presence of several interconverting low-energy conformations of these alkaloids results in broad peaks on the NMR timescale at 298K.

Attempts to coalesce these signals at elevated temperatures are typically compromised by the lability of σ-bond connecting the vicinal quaternary carbons.[7] Cooling the NMR sample can result in enhanced resolution of the major conformers, as is the case for quadrigemine C;[4,9c] however, fully analyzing these complex spectra is challenging. Quadrigemines A and E, if different from quadrigemine C, could be one of six C_2-symmetric stereoisomers (**5**, **6**, **7** and their enantiomers, Figure 2). Overall there are ten possible [2+2] quadrigemine stereoisomers: 4 enantiomeric pairs and two *meso* compounds (Figure 2).

In an attempt to clarify the structures of quadrigemines A and E, we initiated stereocontrolled total syntheses of the remaining chiral members of the [2+2] quadrigemine alkaloid family. Moreover such an investigation would allow us to investigate the degree of catalyst control achieved in enantioselective Heck cyclizations carried out with C_2-symmetric intermediates; in our original total synthesis of quadrigemine C (**1**), the pivotal enantioselective cyclizations were realized with a *meso* precursor. During these studies, several improvements to our original synthesis of quadrigemine C were attained, allowing the synthetic route to be shortened and the overall yield improved. Finally, with access to an expanded group of [2+2] quadrigemines, the effect of relative and absolute configuration on their antitumor activity was evaluated.

2. Results and discussion

2.1 Inside-out approach to the [2+2] quadrigemines

In the approach we developed to synthesize members of the [2+2] family of quadrigemines, the outer two pyrrolidinoindoline fragments are elaborated simultaneously on a functionalized chimonanthine core (Scheme 1). The formation of decacyclic dioxindole **A** by double enantioselective intramolecular Heck cyclization of dibutenanilide **B** is the pivotal step in this sequence.[13] The Heck cyclization precursor **B** is formed by a double Stille coupling of a chimonanthine diiodide **C** with two equiv of stannane **8**, an intermediate that contains all the heavy atoms of a cyclotryptamine fragment. The natural products *meso*-chimonanthine and its enantiopure C_2-symmetric stereoisomers, which are now readily available by stereocontrolled chemical synthesis,[14,15] serve as the starting point of the synthetic sequence.

2.2 Enantioselective synthesis of [2+2] quadrigemines having a *meso* core

In our initial synthesis of quadrigemine C,[4] *meso*-chimonanthine (**9**) was prepared from oxindole and isatin in 13 steps and ~30% overall yield by a stereocontrolled sequence that we had defined previously.[14b] To expedite access to larger quantities of *meso*-chimonanthine (**9**), we have since adopted the non-stereocontrolled oxidative dimerization method reported by Takayama and co-workers.[16] This method involves the oxidative dimerization of N_b-carbomethoxytryptamine with phenyliodine(III) bis(trifluoroacetate) and a subsequent reduction with Red-Al® to generate *meso*-chimonanthine (**9**) in two steps and 20–30% yield. Willis and coworkers recently improved this procedure by enhancing overall scalability and purification of product **9**.[17] Utilizing our previously published procedure, *meso*-chimonanthine diiodide **10** was prepared from *meso*-chimonanthine in three steps and

66% overall yield by di-Boc protection, di-*ortho*-iodination, and removal of the Boc groups (Scheme 2).[4]

In our first generation synthesis, the Stille cross coupling of *meso*-diiodide **10** with 3 equiv of stannane aryl triflate **8** to provide the *meso*-dibutenanilide **11** was achieved using a catalyst system of $Pd_2dba_3{\cdot}CHCl_3$, tri-2-furylphosphine and CuI in 1-methyl-2-pyrrolindoline (NMP).[4,18] This Stille coupling was sluggish, requiring long reaction times (>36 h) at room temperature, and provided variable yields of **11** (55–71%). In the hope of both accelerating the rate of the reaction and improving the overall yield, several additional conditions for accomplishing this double cross coupling were investigated. Attempts to accelerate the reaction rate by increasing the reaction temperature were thwarted by slow decomposition of the aryl triflate functionality of stannane triflate **8**. The use of fluoride ion (CsF) to accelerate the reaction did not have a substantial effect on improving the overall conversion. [19] The use of copper(I) thiophene-2-carboxylate (CuTC), [20] or CuTC in addition to $[Ph_2PO_2][NBu_4]$[21] did accelerate the reaction rate, but did not improve the yield. After further experimentation, a Stille coupling procedure reported by Corey and co-workers using $Pd(PPh_3)_4$/CuCl/LiCl was found to be optimal.[22] Thus, reaction of *meso*-diiodide **10** with 3 equiv of stannane aryl triflate **8**, 0.5 equiv of $Pd(PPh_3)_4$, 5 equiv of CuCl, and 6 equiv of LiCl in DMSO at room temperature for 20 h provided *meso*-dibutenanilide **11** in 96% yield.

As the outer pyrrolidinoindolines of quadrigemine C (**1**) have the same absolute configuration, our strategy was to utilize an enantioselective intramolecular Heck reaction to access the desired C_1-symmetric dioxindole stereoisomer using a two-directional synthesis strategy.[23] In accordance with the Horeau principle, a double enantioselective transformation has the potential to amplify the enantiopurity of the product over that provided by a single enantioselective transformation.[24] Although the overall yield of the desired product is diminished, the product's enantiomeric purity should by equal to the square of the enantioselectivity of a single reaction.

Several conditions were examined to optimize the double enantioselective Heck cyclization of *meso*-dibutenanilide **11** (Scheme 3, Table 1). Of the diphosphine ligands screened, (*R*)-tol-BINAP in MeCN provided superior diastereo- and enantioselection, providing pentacyclic dioxindole **12** and its two *meso* stereoisomers in a ratio of 9.3:2.0:1.0. The C_1-symmetric product **12** (62%, 90% ee) and the *meso* products **13** and **14** (14% and 7% respectively) [25] were separated by preparative HPLC. The related enantioselective Heck cyclization employed in the enantioselective synthesis of the nonacyclic cyclotryptamine alkaloids hodgkinsines A and B from *meso*-chimonanthine gave a 1:1 ratio of these products in high yield and 79 and 83% ee.[26,27] As the observed enantiomeric purity of the C_1-symmetric product **12** (90% ee) is somewhat less than the predicted (98% ee) from the results in the hodgkinsine series, it can be inferred that the two enantioselective intramolecular Heck reactions are not completely independent. It is important to note that representing these molecules in two dimensions is deceiving. This decrease in enantioselectivity from the predicted model most likely results from stereoinduction across the *meso*-chimonanthine backbone during the second Heck cyclization. A sense that such interactions would be possible can be gleaned from a three-dimensional model of quadrigemine C (Figure 3). Carrying out the cyclization of ditriflate **11** under identical

conditions using (S)- rather than (*R*)-BINAP gave dioxindole *ent*-**12** in 80% yield; the higher selectivity in forming the C_1-symmetric product in this double enantioselective Heck reaction suggests that catalyst and substrate control are matched with the catalyst formed from (*S*)-BINAP.

In our original synthesis of quadrigemine C, diene disulfonamide **12** was hydrogenated at 100 psi using $Pd(OH)_2/C$ in 10:1 EtOH-MeOH at 80 °C to saturate the two double bonds.[4] These conditions often resulted in yields of the tetrahydro product **15** that varied depending upon the batch of substrate and catalyst.[29] Since our initial report, we discovered that including 8 equiv of K_2CO_3 resulted in enhanced reproducibility for this transformation, which we attribute to preventing any acid-catalyzed decomposition[30,31] Additionally, increasing the hydrogen pressure to 1000 psi in EtOH at 80 °C helped to ensure full conversion. Using this procedure, **12** reproducibly was transformed to its tetrahydro congener in yields of 90–95% (Scheme 4). Exposure of this unpurified intermediate to a large excess of Na (50 equiv) in THF/NH_3 containing 4 equiv of *tert*-butanol for 20 min at −78 °C, followed by quenching with NH_4Cl and HPLC purification afforded (−)-quadrigemine C (**1**). Modification of our previous conditions by the incorporation of *tert*-butanol[32]led to significant improvements in reproducibility, reliably yielding (−)-quadrigemine C in 22–24% for the two steps

The improvements made in this second generation synthesis of (−)-quadrigemine C shortened the synthetic sequence to 10 steps and provided (−)-quadrigemine C (**1**), $[\alpha]^{23}_D$ −67 (*c* = 0.2, $CHCl_3$) and $[\alpha]^{23}_D$ −30 (*c* = 0.2, EtOH), in 2.2% overall yield from tryptamine. Synthetic (−)-quadrigemine C showed physical properties (^1H NMR, ^{13}C NMR, HRMS) consistent with those of the natural product,[9a–d] and was indistinguishable from an authentic sample by HPLC and CD analysis.[33,34] Moreover, heating a sample of (−)-quadrigemine C at 100 °C in the presence of dilute aqueous acetic acid gave synthetic (−)-psycholeine (**16**) in 38% yield, which showed ^1H NMR and ^{13}C NMR spectra identical to those reported for the natural product.[9a–c] Using the optimized procedures described herein, *ent*-(+)-quadrigemine C (**2**), $[\alpha]^{23}_D$ +70 (*c* = 0.12, $CHCl_3$) and $[\alpha]^{23}_D$ +19 (*c* = 0.15, EtOH), as well as the two *meso*-quadrigemine congeners **3** and **4** were prepared in an identical fashion (see summary in Table 3).

2.3 Enantioselective total synthesis of [2+2] quadrigemines having a C_2-symmetric chimonanthine core

The starting material for our studies in this series was (+)-chimonanthine (**17**), which we prepared in gram quantities from α-methoxycarbonyl-L-tryptophan methyl ester using the 8-step biomimetic sequence developed by Movassaghi and co-workers.[14c] The necessary C_2-symmetric diiodide **18** was synthesized, as previously optimized in the *meso*-chimmonanthine series, by di-Boc protection of the aniline nitrogens, di-*ortho*-iodination, and removal of the Boc groups to provide C_2-symmetric diiodide **18** in 72% yield. The di-Stille cross coupling of diiodide **18** with stannane **8** using the recently optimized conditions provided C_2-symmetric dibutenanilide **19** in 98% yield.

We turned to examine the double enantioselective Heck cyclization in the C_2-symmetric series, wherein the chiral substrate would influence diastereoselectivity.[31,35] To examine the inherent substrate bias, the double enantioselective Heck cyclization of ditriflate **19** was carried out initially using *rac*-tol-BINAP, which resulted in modest substrate control to give the C_2- and C_1-symmetric dioxindole products **20** and **21** in a 1.0:2.3 ratio. Utilizing the catalyst generated from 0.5 equiv $Pd(OAc)_2$, 1.0 equiv of (*R*)-tol-BINAP and 4 equiv of 1,2,2,6,6-pentamethylpiperidine (PMP) at 80 °C, various solvents were evaluated. A decrease in solvent polarity from *N*-methylpyrrolidinone (NMP) to THF resulted in a decrease in diastereoselectivity (entries 2–4, Table 2). To some surprise, diastereoselection was inverted in toluene, giving the C_1-symmetric stereoisomer **21** as the major product. The combined yield of the decacyclic dioxindole products **20** and **21** produced in NMP was lower (58%) than we had anticipated. Analysis of the crude product mixture by mass spectrometry identified the formation of byproducts in which one of the pyrrolidinoindoline nitrogens had been acetylated. This product is a likely culprit of the decreased selectivity and undoubtedly arose from the formation of acetic anhydride during the reduction of $Pd(OAc)_2$ by the phosphine ligand.[36] Inclusion of 10 equiv of *N*-methyl-*p*-anisidine as a scavenger for Ac_2O diminished formation of the acetylated byproducts, providing the C_2-symmetric dioxindole **20** and its C_1-symmetric stereoisomer **21** in 4.3:1 ratio and 79% combined yield. Identical Heck cyclization of **19** using Pd-(*S*)-tol-BINAP afforded C_2-symmetric (*S*,*R*,*R*,*S*) dioxindole **22** and dioxindole **21** in a 2:1 ratio and 81% yield. The diastereomeric dioxindole products products were separated by silica gel chromatography and subsequently processed independently to their respective [2+2] quadrigemines.

Utilizing the procedures developed during our optimized total synthesis of quadrigemine C (**1**), pentacyclic dioxindole products **20**–**22** were hydrogenated (1000 psi) with $Pd(OH)_2$/C in EtOH at 80 °C. Subsequent exposure of the resulting tetrahydro products to a large excess of sodium (50 equiv) in THF/*t*-BuOH/NH_3 at −78 °C for 20 min, followed by quenching with NH_4Cl provided the respective [2+2] quadrigemine products **5**–**7**, in 23–29% yield for the final two steps. The yields of the final steps in the total syntheses of the quadrigemine stereoisomers prepared in this study and the optical rotations at the sodium D line of the quadrigemine products are summarized in Table 3. The CD spectra of synthetic quadrigemines **1**, **2**, **5**–**7** are shown in Fig. 4.

The optical rotation data and ^{13}C NMR spectra for the synthetic quadrigemines **5**–**7** confirm that these C_2-symmetic [2+2] quadrigemines are not identical to natural quadrigemines A and E. [37] Moreover, HPLC comparison of these products with a crude isolate of *Psychotria muscosa* showed that these synthetic quadrigemines were not identical to the structurally uncharacterized higher-order polypyrrolidindoline alkaloids identified in this sample by Verotta and coworkers. [38,39] These findings suggest that quadrigemines A and E could be identical to quadrigemine C.

2.4 Antitumor evaluation

A diversity of biological activities–antiviral, antibacterial, antifungal, and anticandidal–are described for quadrigemine alkaloids.[1c] In addition, selected quadrigemines are reported to be analgesics,[31,38,40] antagonists of the somatostain receptor (SRIF),[9b] inhibitors of human

platelet aggregation,[41] and to display cytotoxic activity against solid and blood tumors.[42] To gain some insight into the relationship between the three-dimensional structures of higher-order polypyrrolidinoindoline alkaloids and their antitumor activity, the *in vitro* cytotoxicities of the 2+2 quadrigemines prepared in this study, and several additional polypyrrolindoline alkaloids prepared in our laboratories (depicted in Figure 5), were determined against two invasive cancer cell lines: DU145 (human prostate cancer) and A2058 (human melanoma). Several trends emerge from the cytotoxicity data summarized in Table 4: (a) In general, cytotoxicity increases as a function of molecular weight (increasing number of pyrrolidinoindoline units); only one dodecacyclic alkaloid (the minor *meso*-quadrigemine **4**, entry 3) was less active than the nonacyclic alkaloids (entries 7–11). (b) Relative configuration of higher-order polypyrrolidinoindolines makes only a minor contribution to cytotoxicity. For example, (−)-quadrigemine C is only 2–4 fold more active than the other [2+2] quadrigemine alkaloids. (c) (−)-Psycholeine (**16**), the isomer of (−)-quadrigemine C having a calycanthine core, showed little cytotoxicity (entry 7). The first two of these trends are in accord with cytotoxicity data reported previously for a few cyclotryptamine alkaloids.[42]

3. Conclusion

The inside-out strategy (Scheme 1) that we first introduced in 2002 to synthesize (−)- (**1**) and (+)-quadrigemine C (**2**) is utilized in this investigation to prepare all potential stereoisomers of dodecacyclic quadrigemines having chimonanthine cores (Figure 2). As a prelude to these studies, two steps—the double Stille cross coupling to introduce the heavy atoms of the peripheral cyclotryptamine rings and the subsequent catalytic hydrogenation–were optimized to improve the yields and make these transformations more robust. The second-generation total synthesis of natural (−)-quadrigemine C (**1**) reported herein was accomplished in 10 steps and 2.2% overall yield from tryptamine. This short enantioselective total synthesis, and the other concise constructions of quadrigemine stereoisomers we report, are testaments to the power of two-directional synthesis strategies[23] and the utility of catalytic enantioselective transformations–in this case intramolecular Heck reactions[13]–to stereoselectively generate structurally intricate polycyclic molecules. The total syntheses reported herein are rare examples of using two-directional strategies to stereoselectively elaborate cyclic molecules.[43]

This total synthesis study showed that the previously reported alkaloids referred to as quadrigemines A[5] and E[10] are not identical to any of the synthetic quadrigemine stereoisomers, and most likely are the same as quadrigemine C. In addition, investigations of the *in vitro* antitumor activities of products prepared in this study showed that the relative configuration of the 2+2 family of quadrigemines influences cytotoxicity in only a minor way.

4. Experimental section

Experimental procedures and characterization data for the preparation of compounds **1**, **8**, **11**–**15** have been reported previously.[4]

4.1 Enantioselective total synthesis of quadrigemine C (1) and *ent*-quadrigemine C (*ent*-1)

***meso*-Dibutenanilide 11—**Diiodide **10** (262 mg, 0.44 mmol) and stannane **8** (1.14 g, 1.31 mmol) were combined in a round bottom flask and azeotroped to dryness with dry THF (3 × 6 mL). The mixture was placed under vacuum (1.0 mmHg) for 30 min and then pumped into an inert atmosphere (N_2) drybox. A stirbar followed by $Pd(PPh_3)_4$[44] (252 mg, 0.219 mmol), LiCl (111 mg, 2.60 mmol), and CuCl (216 mg, 2.19 mmol) were added to the flask and the mixture was suspended in dry DMSO (15 mL). The flask was capped and stirred at room temperature in the drybox for 20 h. After removing the flask from the drybox, the black solution was partitioned between 5% *v/v* aqueous solution of NH_4OH (20 mL) and EtOAc (30 mL) and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed consecutively with water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The dark residue was purified by flash column chromatography (10 %KF/SiO_2[45] 100% CH_2Cl_2 → 10:1 CH_2Cl_2/MeOH; product **11** (635 mg, 96%) elutes with 3–5% MeOH in CH_2Cl_2 as a brown foam, which showed ^1H and ^{13}C NMR spectra identical to those reported.[4]

Double enantioselective Heck cyclization of *meso*-dibutenanalide 11—A sample of ditriflate **11** (150 mg, 0.100 mmol) was azeotroped to dryness in benzene (3 × 2 mL) in a sealable Schlenk tube and placed under vacuum (1.0 mm) for 1 h. To the Schlenk flask was added a stirbar, $Pd(OAc)_2$ (23 mg, 0.10 mmol), and (*R*)-tol-BINAP (0.140 g, 0.200 mmol). The flask was evacuated and backfilled with N_2 (3 ×). Dry MeCN (2 mL) and 1,2,2,6,6-pentamethylpiperidine[50] (73 μL, 0.40 mmol) were added and the reaction mixture was degassed using the freeze–pump–thaw technique (3 cycles, liquid N_2 cooling bath, 0.1 mmHg, backfill with N_2). The heterogeneous brown-red mixture was then heated to 80 °C for 16 h. After cooling to room temperature, the deep red solution was partitioned between a 20% *w/w* aqueous solution of NaCN (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2: 100:0 CH_2Cl_2 → 97:3 CH_2Cl_2/MeOH → 94:5:1 CH_2Cl_2/MeOH/NH_4OH → 89:10:1 CH_2Cl_2/MeOH/NH_4OH) to provide a mixture of **12**, **13**, and **14** in a 9:2:1 ratio (ratio determined by reverse-phase HPLC analysis). The three diastereomers could be further purified by preparative reverse-phase HPLC (Phenomenex Gemini-NX, 250 × 21.2 mm), 80:20 MeCN-H_2O (1% NH_4OH), 25 mL/min, UV detection at 254 nm; to afford 74 mg (62%) of **12** (r_t = 30.9 min), 17 mg (14%) of **13** (r_t = 37.6 min), and 8 mg (7%) of **14** (r_t = 23.7 min) as colorless foams.

(*R*,*R*,*S*,*R*)-Isomer 12.[4]—$[\alpha]^{28}_D$ −60, $[\alpha]^{28}_{577}$ −62, $[\alpha]^{28}_{546}$ −72, $[\alpha]^{28}_{435}$ −153, $[\alpha]^{28}_{405}$ −207 (*c* = 0.25, CH_2Cl_2).

Major *meso*-isomer 13—^1H NMR (500 MHz, $(CD_3)_2SO$, 376K) δ 7.49 (d, *J* = 7.5 Hz, 4H), 7.35 (d, *J* = 7.8 Hz, 6H), 7.34–7.31 (m, 4H), 7.27–7.23 (m, 8H), 7.06–7.01 (m, 4H), 6.96 (d, *J* = 7.2 Hz, 2H), 6.79 (d, *J* = 7.8 Hz, 2H), 6.65 (d, *J* = 14.3 Hz, 2H), 6.41 (br s, 2H), 5.32 (d, *J* = 14.2 Hz, 2H), 4.97 (d, *J* = 15.4 Hz, 2H), 4.90 (d, *J* = 15.5 Hz, 2H), 4.25 (br s, 2H), 4.09 (s, 2H), 2.85 (s, 6H), 2.38 (s, 6H), 2.30–2.24 (m, 4H), 1.98–1.94 (m, 2H), 1.78–

1.73 (m, 2H), 1.71 (s, 6H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 376 K) δ 175.9 (C), 148.9 (C), 143.3 (C), 141.3 (C), 135.7 (C), 133.8 (C), 133.7 (C), 130.6 (C), 129.7 (CH), 129.3 (CH), 128.0 (CH), 127.6 (CH), 126.92 (CH), 126.88 (CH), 126.2 (CH), 126.0 (CH), 124.0 (CH), 122.7 (C), 122.0 (CH), 118.6 (C), 116.8 (CH), 110.0 (CH), 108.9 (CH), 82.3 (CH), 61.7 (C), 55.6 (C), 50.8 (CH_2), 42.8 (CH_2), 36.0 (CH_2), 33.8 (CH_3), 31.9 (CH_3), 20.2 (CH_3); IR (thin film) 3358, 2934, 1706, 1610, 1467, 1355, 1162, 745 cm^{-1}; LRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{72}H_{70}N_8O_6S_2H$ 1207.5; found, 1207.5.

Minor *meso*-isomer 14—^{1}H NMR (500 MHz, $(CD_3)_2SO$, 376K) δ 7.42 (d, *J* = 7.8 Hz, 4H), 7.32–7.27 (m, 6H), 7.22 (br s, 14 H), 6.97 (br s, 4H), 6.94 (d, *J* = 7.6 Hz, 2H), 6.70 (br s, 2H), 6.58 (d, *J* = 14.3 Hz, 2H), 5.37 (d, *J* = 14.2 Hz, 2H), 4.98 (d, *J* = 15.8 Hz, 2H), 4.75 (d, *J* = 15.8 Hz, 2H), 2.90 (br s, 2H), 2.85 (s, 6H), 2.69–2.59 (m, 2H), 2.46 (s, 6H), 2.38–2.35 (m, 2H), 2.34 (s, 6H), 2.16–2.09 (m, 2H), 2.04 (br s, 4H), 1.82–1.79 (m, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 376 K) δ 175.9 (C), 148.9 (C), 143.3 (C), 141.3 (C), 135.7 (C), 133.7 (C), 130.6 (C), 129.7 (CH), 129.3 (CH), 129.2 (CH), 128.0 (CH), 127.6 (CH), 126.9 (CH), 126.5 (CH), 126.2 (CH), 125.9 (CH), 124.0 (CH), 122.7 (CH), 122.1 (CH), 118.6 (C), 116.7 (C), 110.1 (CH), 108.9 (CH), 82.3 (CH), 61.7 (C), 55.6 (C), 50.8 (CH_2), 42.8 (CH_2), 36.0 (CH_3), 33.8 (CH_2), 31.8 (CH_3), 20.3 (CH_3); IR (thin film) 3405, 2934, 1710, 1610, 1455, 1359, 1162, 748 cm^{-1}; LRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{72}H_{70}N_8O_6S_2H$ 1207.5; found, 1207.5.

(*S*,*R*,*S*,*S*)-Isomer (*ent*-12)—Carrying out the double Heck cyclization in similar fashion using (*S*)-tol-BINAP and 77 mg (0.051 mmol) of *meso*-dibutenanalide **11** gave as the major product dioxindole ***ent*-12** (51 mg, 83%): ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 376K)[46] δ 7.49–7.45 (m, 4H), 7.36–7.30 (m, 8H), 7.27–7.19 (m, 10H), 7.11 (br d, *J* = 6.4 Hz, 1H), 7.06–6.97 (m, 5H), 6.90 (br d, *J* = 7.7 Hz, 1H), 6.74 (br s, 2H), 6.65 (d, *J* = 15.0 Hz, 1H), 6.61 (d, *J* = 15.8 Hz, 1H), 6.47 (br s, 1H), 6.34 (br s, 1H), 5.42 (d, *J* = 14.3 Hz, 1H), 5.29 (d, *J* = 14.3 Hz, 1H), 5.05 (d, *J* = 15.8 Hz, 1H), 4.98 (d, *J* = 15.5 Hz, 1H), 4.85 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.8 Hz, 1H), 4.40–4.10 (br s, 3H), 2.88 (s, 3H), 2.83 (s, 3H), 2.66 (br t, *J* = 6.7 Hz, 1H), 2.52–2.48 (m, 2H), 2.38 (s, 3H), 2.36 (s, 3H), 2.35–2.30 (m, 1H), 2.29–2.21 (m, 1H), 2.14 (s, 3H), 2.07–1.89 (m, 1H), 1.86–1.82 (m, 1H), 1.78–1.71 (m, 1H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 376 K) δ 176.2 (C), 176.0 (C), 150.0 (C), 149.0 (C), 143.4 (C), 143.3 (C), 141.3 (C), 141.2 (C), 135.66 (C), 135.64 (C), 134.5 (C), 133.9 (C), 133.7 (C), 133.4 (br, C), 130.5 (CH), 130.4 (C), 129.8 (CH), 129.5 (CH), 129.24 (2 peaks, CH), 127.93 (CH), 127.92 (CH), 127.68 (CH), 127.65 (CH), 127.58 (CH), 127.0 (CH), 126.8 (CH), 126.7 (CH), 126.4 (CH), 126.1 (CH), 126.0 (CH), 125.95 (CH), 124.5 (CH), 124.2 (CH), 122.8 (CH), 122.6 (CH), 122.1 (C), 121.9 (C), 118.24 (br, 2 peaks, C), 117.3 (CH), 116.6 (CH), 110.0 (CH), 109.8 (CH), 108.99 (CH), 108.95 (CH), 82.2 (CH), 62.6 (C), 61.8 (C), 55.7 (C), 50.98 (CH_2), 50.97 (CH_2), 42.8 (CH_2), 42.7 (CH_2), 35.8 (br, 2 peaks, CH_2), 34.3 (CH_3), 33.8 (CH_3), 31.79 (CH_3), 31.75 (CH_3), 20.25 (CH_3), 20.23 (CH_3); IR (thin film) 3354, 2930, 1710, 1610, 1359, 1162, 745 cm^{-1}; LRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{72}H_{70}N_8O_6S_2H$ 1207.5; found, 1207.5; $[\alpha]^{23}_D$ +68, $[\alpha]^{23}_{577}$ +69, $[\alpha]^{23}_{546}$ +79, $[\alpha]^{23}_{435}$ +157 (*c* = 0.33, CH_2Cl_2).

(−)-Quadrigemine C (1)—The procedure for hydrogenation of the enesulfonamide side chains and reductive cyclization for the ultimate conversion of tetrahydro intermediate to (−)-quadrigemine C that is reported herein (see the optimized general procedures described for the preparation of (*R*,*R*,*R*,*R*)-quadrigemine **7**) has been found to be more reproducible than the procedure described previously.[4] Using the optimized general procedure for hydrogenation of the enesulfonamide side chains, tetrahydro derivative **15** was prepared in >90% yield: $[\alpha]^{28}_{D}$ −144, $[\alpha]^{28}_{577}$ −154, $[\alpha]^{28}_{546}$ −177, $[\alpha]^{28}_{435}$ −369, $[\alpha]^{28}_{405}$ −492 (*c* = 0.10, CH_2Cl_2). Reduction of this intermediate with Na/NH_3/*t*-BuOH gave (−)-quadrigemine (C) (8.3 mg, 24% overall yield from **12**), $[\alpha]^{23}_{D}$ −67 (*c* = 0.2, $CHCl_3$), HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{44}H_{50}N_8H$ 691.4236; found, 691.4232; NMR and IR and optical rotation data were identical to those reported previously.[4]

***ent*-(+)-Quadrigimine C (2)—**Following the optimized general procedure for hydrogenation of the enesulfonamide side chains, 104 mg of ***ent*-12** was converted to tetrahydro derivative ***ent*-15**. This product was then directly subjected to the optimized reductive cyclization conditions to afford *ent*-(+)-quadrigemine C (**2**) (14 mg, 24%); IR (thin film) 3271, 3054, 2929, 2854, 2791, 1604, 1481, 1452 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{44}H_{50}N_8H$ 691.4236; found, 691.4226; $[\alpha]^{23}_{D}$ +20, $[\alpha]^{23}_{577}$ +17, $[\alpha]^{23}_{546}$ +18, $[\alpha]^{23}_{435}$ +48 (*c* = 0.15, EtOH); $[\alpha]^{23}_{D}$ +70, $[\alpha]^{23}_{577}$ +67, $[\alpha]^{23}_{546}$ +60, $[\alpha]^{23}_{435}$ +110 (*c* = 0.12, $CHCl_3$).

4.2 Synthesis of *meso*-[2+2] quadrigemines

Tetrahydro derivative of the major *meso*-dioxindole isomer 13—Following the optimized general procedure for hydrogenation of the enesulfonamide side chains, tetrahydro-**13** (28.4 mg, 0.024 mmol, 98% yield) was obtained as a colorless solid from 29.6 mg of **13**. ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 396K) δ 7.50 (d, *J* = 8.1 Hz, 4H), 7.33 (d, *J* = 7.6 Hz, 8H), 7.29–7.20 (m, 10H), 7.13 (d, *J* = 6.9 Hz, 2H), 7.09 (t, *J* = 7.1 Hz, 2H), 7.00 (d, *J* = 7.7 Hz, 2H), 6.85 (d, *J* = 7.7 Hz, 2H), 6.50 (br s, 2H), 6.43 (br s, 2H), 4.96 (d, *J* = 15.5 Hz, 2H), 4.85 (d, *J* = 15.5 Hz, 2H), 4.78 (s, 2H), 4.29 (s, 2H), 2.96 (dt, *J* = 5.0, 12.6 Hz, 2H), 2.79 (br s, 2H), 2.70–2.66 (m, 2H), 2.61 (s, 6H), 2.53–2.51 (m, 2H), 2.44–2.40 (m, 2H), 2.38 (s, 6H), 2.35–2.25 (m, 2H), 2.10–2.07 (m, 2H), 1.90 (s, 6H), 1.80–1.77 (m, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 396K) δ 176.8 (C), 149.3 (C), 142.3 (C), 141.8 (C), 135.5 (C), 134.8 (C), 130.0 (C), 128.8 (CH), 127.8 (CH), 127.5 (CH), 127.1 (C), 126.9 (CH), 126.7 (CH), 126.1 (CH), 125.2 (CH), 123.8 (CH), 122.6 (CH), 121.9 (CH), 117.7 (C), 116.9 (CH), 108.7 (CH), 82.6 (CH), 61.7 (C), 53.2 (CH_2), 50.9 (C), 45.1 (CH_2), 42.9 (CH_2), 35.9 (CH_2), 34.1 (CH_3), 33.8 (CH_3), 31.6 (CH_2), 20.0 (CH_3); IR (thin film) 3336, 3060, 2928, 2865, 2791, 1697, 1610, 1487, 1454, 1342 cm^{-1}; LRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{72}H_{74}N_8O_6S_2H$ 1211.5; found, 1211.5.

Tetrahydro derivative of the minor *meso*-dioxindole isomer 14—Following the optimized general procedure for hydrogenation of the enesulfonamide side chains, tetrahydro-**14** (28.2 mg, 0.024 mmol, 94% yield) was obtained as a colorless solid from 31.2 mg of dioxindole **14**. ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 396K) δ 7.45 (d, *J* = 8.2 Hz, 4H), 7.31 (d, *J* = 8.4 Hz, 4H), 7.27–7.21 (m, 8H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 2H), 6.97(d, *J* = 7.8 Hz, 2H), 6.71 (br d, *J* = 7.2 Hz, 2H), 4.89 (d, *J* = 15.7 Hz, 2H), 4.78 (d, *J* =

15.7 Hz, 2H), 4.27 (br s, 2H), 2.95–2.83 (m, 4H), 2.80 (s, 10H), 2.70–2.67 (m, 4H), 2.66–2.63 (m, 2H), 2.61 (s, 6H), 2.41–2.33 (m, 10H), 2.27–2.23 (m, 2H), 2.21 (s, 4H), 1.86 (dd, *J* = 4.7 & 11.4 Hz, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 396K) δ 177.0 (C), 142.3 (C), 141.9(C), 135.6 (C), 134.6 (C), 129.5 (C), 129.8 (CH), 127.7 (CH), 127.2 (CH), 126.9 (C), 126.6 (CH), 126.5 (CH), 126.1 (CH), 125.2 (C), 124.3 (CH), 122.5 (CH), 121.7 (CH), 117.43 (C), 108.8 (CH), 82.0 (CH), 62.1 (C), 53.6 (CH_2), 50.9 (C), 45.4 (CH_2), 42.8 (CH_2), 35.3 (CH_2), 34.3 (CH_3), 33.9 (CH_3), 30.6 (CH_2), 20.0 (CH_3); IR (thin film) 3328, 3060, 2926, 2851, 2789, 1695, 1611, 1488, 1466, 1343 cm^{-1}; LRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{72}H_{74}N_8O_6S_2H$ 1211.5; found, 1211.5.

Major *meso*-quadrigemine isomer—Following the optimized general reductive cyclization procedure, 21 mg (0.017 mmol) of tetrahydro-**13** was transformed to quadrigemine derived from the major *meso*-dioxindole Heck product **13**. The solid was purified by preparative reverse-phase HPLC (Zorbax Extend C18, 100 × 21.2 mm, 80:20 MeOH-H_2O (1% NH_4OH), 16 mL/min, UV detection at 254 nm) to afford 4.8 mg (40%) of the major *meso*-quadrigemine isomer ***(NOTE:** relative configuration was not established; this product is either meso quadrigemine **3** or **4**.)* (r_t = 9.7 min) as a colorless solid. ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 376K) δ 7.43–7.22 (m, 7H), 6.92 (d, *J* = 7.5 Hz, 3H), 6.54 (d, *J* – 16.7 Hz, 2H), 6.17 (s, 2H), 5.65 (s, 3H), 5.13 (s, 1H), 4.96 (br s, 1H), 4.27 (d, *J* = 6.6 Hz, 2H), 3.22 (s, 2H), 3.76 (br s, 7H), 2.57 (d, *J* = 6.9 Hz, 2H), 2.50–2.11 (m, 11H), 1.61 (s, 3H), 1.32–1.28 (m, 4H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 376K) δ 147.0 (C), 146.7 (C), 140.9 (CH), 134.3 (C), 129.1 (CH), 128.2 (CH), 127.0 (CH), 120.5 (CH), 120.1 (C), 118.7 (CH), 107.4 (CH), 107.1 (CH), 100.5 (C), 69.0 (CH), 60.6 (C), 58.0 (C), 54.0 (CH_2), 48.0 (CH_2), 37.7 (CH_2), 37.2 (CH_2), 28.2 (CH_3), 22.9 (CH_3); IR (thin film) 3365, 2923, 2851 1658, 1605, 1451, 1247, 1158, 1035, 744 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{44}H_{50}N_8H$ 691.4236; found, 691.4244.

Minor *meso*-Quadrigemine isomer—Following the optimized general reductive cyclization procedure, 45 mg (0.037 mmol) of tetrahydro-**14** was converted the quadrigemine derived from the minor *meso*-dioxindole Heck product **14**. The resulting solid was purified by preparative reverse-phase HPLC (Zorbax Extend C18, 100 × 21.2 mm, 80:20 MeOH-H_2O (1% NH_4OH), 10 mL/min, UV detection at 254 nm) to afford 4.0 mg (16%) of minor *meso*-quadrigemine isomer ***(NOTE:** relative configuration was not established; this product is either meso quadrigemine **3** or **4**.)* (r_t = 70.7 min) as a colorless solid. ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 376K) δ 6.98–6.93 (m, 4H), 6.60 (app t, *J* = 7.1 Hz, 2H), 6.54 (d, *J* = 7.8 Hz, 2H), 6.35 (br s, 2H), 5.88 (br s, 2H), 5.71 (br s, 2H), 4.81 (s, 2H), 4.55 (br s, 2H), 3.55 (s, 2H), 2.96 (6H, br s), 2.66–2.58 (m, 4H), 2.50 (s, 4H), 2.08 (br s, 10H), 1.91–1.89 (m, 2H), 1.82–1.81 (m, 2H), 1.27 (s, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 376K) δ 150.9 (C), 149.3 (C), 133.0 (C) 131.8 (C), 126.8 (CH), 124.4 (CH), 123.9 (CH), 122.6 (C), 121.5 (CH), 116.7 (CH), 115.1 (CH), 107.4 (CH), 85.1 (CH), 82.3 (CH), 61.8 (C), 59.6 (C), 51.1 (CH_2), 37.8 (CH_2), 36.3 (CH_2), 34.8 (CH_3), 34.3 (CH_3); HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{44}H_{50}N_8H$ 691.4236; found, 691.4248; IR (thin film) 3271, 2926, 2854, 2791, 1674, 1604, 1486, 1448, 1253, 1246, 1154, 1032, 743 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{44}H_{50}N_8H$ 691.4236; found, 691.4237.

4.3 Enantioselective total synthesis of [2+2] quadrigemines having a C_2-symmetric core

(*R*,*R*)-1,1′-Dimethyl-1,2,3,8,8a,1′,2′,3′,8,8a′-octahydro-1*H*,1*H*′-[3a,3a′]bi[pyrrolo[2,3-*b*]indolyl]-8,8′-dicarboxylic acid di-*tert*-butyl ester (E1)— Following the procedure employed in the *meso* series,[4] a THF solution of sodium bis(trimethylsilyl)amide (15.3 mL, 30.6 mmol, 2 M) was added dropwise via syringe pump over 3 h to a solution of (+)-chimonanthine (2.95 g, 8.51 mmol),[14c] di-*tert*-butyldicarbonate (Boc_2O) (8.16 g, 37.4 mmol), and THF (130 mL) at −78 °C. Upon completion of the addition the solution was maintained for 30 min at −78 °C and then partitioned between saturated aqueous NH_4Cl (50 mL) and EtOAc (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (2:98 → 5:95 MeOH/EtOAc) to yield the di-Boc derivative **E1** as a colorless foam (4.07 g, 87%): ^{1}H NMR (600 MHz, $(CD_3)_2SO$, 373K) δ 7.29 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 7.5 Hz, 2H), 6.98 (dd, *J* = 7.7, 0.9 Hz, 2H), 6.74 (t, *J* = 7.4 Hz, 2H), 2.71–2.67 (m, 2H), 2.47–2.44 (m, 2H), 2.44 (s, 6H), 2.38–2.30 (m, 2H), 2.10–2.06 (m, 2H), 1.57 (s, 18H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, 373K) δ 152.3 (C), 143.0 (C), 135.1 (C), 128.1 (CH), 123.1 (CH), 122.4 (CH), 115.4 (CH), 85.8 (CH), 81.1 (C), 61.1 (C), 52.9 (CH_2), 37.6 (CH_3), 34.4 (CH_2), 28.5 (CH_3); IR (thin film): 2974, 2942, 2793, 1696, 1483, 1384, 1366, 1164 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{32}H_{42}O_4N_4H$ 547.3284; found, 547.3267; $[\alpha]^{23}_D$ +163, $[\alpha]^{23}_{577}$ +168, $[\alpha]^{23}_{546}$ +191, $[\alpha]^{23}_{435}$ +355 (*c* = 0.66, CH_2Cl_2).

(*R*,*R*)-7,7′-diiodo-1,1′-dimethyl-1,2,3,8a,1′,2′,3′,8a′-octahydro-[3a,3a′]bi[pyrrolo[2,3-*b*]indolyl]-8,8′-dicarboxylic acid di-*tert*-butyl ester (E2)— Following the procedure employed in the *meso* series,[4] a cyclohexane solution of *s*-BuLi (23.5 mL, 23.0 mmol, 0.98 M) was added dropwise over 1.5 h maintaining an internal temperature below −70 °C to a solution of dicarbamate **E1** (2.79 g, 5.10 mmol), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine [47] (TMEDA) (4.55 mL, 30.1 mmol) and Et_2O (51 mL) at −78 °C. The solution was aged at −78 °C for 45 min. Then a solution of diiodoethane (14.5 g, 51.0 mmol) and Et_2O (51 mL) was added dropwise by syringe. The resulting solution was maintained at −78 °C for 10 min, then warmed to 0 °C and maintained at 0 °C for 3 h. The mixture was partitioned between saturated aqueous $Na_2S_2O_4$ (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and EtOAc (50 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (100 mL) dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (2:1→0:100 hexane/EtOAc) to provide diiodide **E2** as a beige solid (3.11 g, 84%): ^{1}H NMR (600 MHz, $(CD_3)_2SO$, 373K) δ 7.62 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 7.5 Hz, 2H), 6.74 (t, *J* = 7.7 Hz, 2H), 5.32 (s, 2H), 2.65–2.62 (m, 2H), 2.21–2.18 (m, 2H), 2.05–2.02 (m, 2H), 1.79–1.75 (m, 2H), 1.59 (s, 18H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$, 373K) δ 152.2 (C), 146.6 (C), 139.40 (CH), 126.3 (CH), 124.1(CH), 88.9 (CH), 87.3 (C), 85.8 (C), 82.0 (C), 61.8 (C), 51.9 (CH_2), 36.4 (CH_3), 35.7 (CH_2), 28.4 (CH_3); mp = 197–199 °C; IR (thin film): 2975, 2796, 1702, 1442, 1367, 1352, 1299, 1245, 1158 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{32}H_{40}N_4O_4I_2H$ 799.1218; found, 799.1224; $[\alpha]^{23}_D$ +186, $[\alpha]^{23}_{577}$ +195, $[\alpha]^{23}_{546}$ +225, $[\alpha]^{23}_{435}$ +399, $[\alpha]^{23}_{405}$ 442 (*c* = 0.63, CH_2Cl_2).

(*R*,*R*)-7,7′-diiodo-1,1′-dimethyl-1,2,3,8,8a,1′,2′,3′,8,8a′-octahydro-1*H*,1*H*′-[3a, 3a′]bi[pyrrolo[2,3-*b*]indolyl] (18)—Following the procedure employed in the *meso* series,[4] neat TMSOTf (4.44 mL, 24.5 mmol) was added dropwise to a solution of diiodide **E2** (4.45 g, 5.57 mmol) and CH_2Cl_2 (140 mL). The flask was left open to the air so that adventitious H_2O would create a small amount of triflic acid. After 3 h, the solution was partitioned between saturated aqueous $NaHCO_3$ (50 mL) and CH_2Cl_2 (100 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography with a gradient elution (9:1:0 → 9:1:0.1 CH_2Cl_2/MeOH/Et_3N) to yield **18** as a pale yellow foam (3.28 g, 99%): ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 376K) δ 7.32 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 7.3 Hz, 2H), 6.37 (t, *J* = 7.6 Hz, 2H), 5.56 (s, 2H), 4.88 (br s, 2H), 3.04 (s, 1H), 2.78 (dt, *J* = 2.8, 7.5 Hz, 2H), 2.65 (br s, 3H), 2.61–2.55 (m, 2H), 2.48–2.45 (m, 2H), 2.01–1.97 (m, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 376K) δ 152.3 (C), 135.1 (CH), 133.2 (C), 122.7 (CH), 118.1 (CH), 82.2 (CH), 72.8 (C), 64.3 (C), 50.7 (CH_2), 35.2 (CH_2), 35.1 (CH_3); IR (thin film) 3402, 3062, 2845, 2789, 1596, 1470, 1246, 734 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{22}H_{24}N_4I_2H$ 599.0168; found, 599.0167; mp = 193–195 °C; $[\alpha]^{23}_D$ +363, $[\alpha]^{23}_{577}$ +383, $[\alpha]^{23}_{546}$ +445, $[\alpha]^{23}_{435}$ +909, $[\alpha]^{23}_{405}$ +1058 (*c* = 1.1, CH_2Cl_2).

(*R*,*R*)-Dibutenanalide 19—Diiodide **18** (0.300 g, 0.501 mmol) and stannane **8** (1.31 g, 1.50 mmol) were combined in a round bottom flask and azeotroped in dry THF (3 × 6 mL). The mixture was then placed under vacuum (1.0 mmHg) for 30 min and then pumped into an inert atmosphere (N_2) drybox. A stirbar followed by $Pd(PPh_3)_4$[48] (0.290 g, 0.251 mmol), LiCl (0.128 g, 3.01 mmol), and CuCl (0.250 g, 2.51 mmol) were added to the flask and the mixture was suspended in dry DMSO (17 mL). The flask was capped and stirred at room temperature in the drybox for 20 h. Upon completion the flask was removed from the drybox and the black solution was partitioned between 5% *v*/*v* aqueous solution of NH_4OH (40 mL) and EtOAc (50 mL) and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water (3 × 100 mL) followed by brine (1 × 100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The black residue was purified by flash column chromatography (10%KF/SiO_2[45]: 100:0 CH_2Cl_2 → 98:2 CH_2Cl_2/MeOH 94:5:1 → CH_2Cl_2/MeOH/NH_4OH → 88:10:2 CH_2Cl_2/MeOH/NH_4OH) to provide **19** (0.741g, 98%) as a brown foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ complex due to the presence of multiple conformations on the NMR time-scale, see copy of spectra; ^{13}C NMR (125 MHz, $CDCl_3$) complex due to the presence of multiple conformations on the NMR time-scale, see copy of spectra (only major peaks listed) 134.22, 129.7, 128.8, 128.6, 128.1, 128.0, 127.6, 127.4, 117.1, 83.9, 49.3, 35.8, 29.7, 27.8, 26.8, 21.5, 17.5, 13.6; ^{19}F NMR (376 MHz, $CDCl_3$) −73.6; IR (thin film) 3415, 3063, 2863, 2791, 1649, 1494, 1455, 1421, 1339, 1207, 1162, 893, 736 cm^{-1}; LRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{74}H_{72}N_8F_6O_{12}S_4H$ 1507.4; found, 1507.4; $[\alpha]^{23}_D$ +158, $[\alpha]^{23}_{577}$ +167, $[\alpha]^{23}_{546}$ +192, $[\alpha]^{23}_{435}$ +433, $[\alpha]^{23}_{405}$ 403 (*c* = 0.46, CH_2Cl_2).

Double enantioselective Heck cyclization of (*R*,*R*)-Dibutenanalide 19—Ditriflate **19** (0.200 g, 0.133 mmol) was azeotroped in benzene (3 × 2 mL) in a sealable Schlenk tube and placed under vacuum (1 mm) for 1 h. To the Schlenk flask was added a stirbar followed

by $Pd(OAc)_2$ (30 mg, 0.13 mmol), (*R*)-tol-BINAP (0.181 g, 0.266 mmol), and *N*-Me-*p*-anisidine (0.143 g, 1.33 mmol). The flask was evacuated and backfilled with N_2 (3 times). The mixture was then suspended in 1-methyl-2-pyrrolidinone (4.4 mL)[49] and 1,2,2,6,6-pentamethylpiperidine[50] (97 μL, 0.53 mmol). The reaction mixture was degassed using the freeze–pump–thaw technique (3 cycles, liquid N_2 cooling bath, 0.1 mmHg, backfill with N_2). The heterogeneous brown-red mixture was heated to 80 °C for 16 h. After cooling to room temperature the deep red solution was partitioned between a 20% *w/w* aqueous solution of NaCN (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 ×20 mL). The combined organic layers were washed with water (3 × 40 mL) followed by brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2: 100:0 CH_2Cl_2 → 97:3 CH_2Cl_2/MeOH → 94:5:1 CH_2Cl_2/MeOH/NH_4OH → 89:10:1 CH_2Cl_2/MeOH/NH_4OH) to provide eluting first C_1-symmetric dioxindole **21** (17.0 mg, 11%) followed by C_2-symmetric dioxindole **20** (74.0 mg, 46%) as tan foams: (*R*,*R*,*R*,*R*)-dioxindole **20**: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 376K) δ 7.47 (d, *J* = 8.3 Hz, 4H), 7.33 (d, *J* = 8.1 Hz, 4H), 7.31 (dd, *J* = 7.8, 1.1 Hz, 2H), 7.20 (dd, *J* = 6.0, 1.9 Hz, 4H), 7.13 (dd, *J* = 5.7, 1.9 Hz, 8H), 7.01 (d, *J* = 7.1 Hz, 2H), 6.95 (d, *J* = 7.8 Hz, 2H), 6.70 (br d, *J* = 7.2 Hz, 2H), 6.62 (d, *J* = 14.3 Hz, 2H), 6.41 (d, *J* = 7.8 Hz, 2H), 6.14 (t, *J* = 7.7 Hz, 2H), 5.45 (d, *J* = 14.3 Hz, 2H), 4.95 (d, *J* = 15.9 Hz, 2H), 4.90 (d, *J* = 15.9 Hz, 2H), 4.83 (br s, 4H), 2.90 (s, 6H), 2.63 (br m, 2H), 2.37 (s, 6H), 2.37–2.31 (m, 2H), 2.21 (br s, 6H), 1.80–1.77 (m, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 376K) δ 176.3 (C), 149.3 (C), 143.3 (C), 141.4 (C), 135.7 (C), 135.0 (C), 133.9 (C), 130.4 (CH), 129.4 (CH), 129.2 (CH), 127.8 (CH), 126.5 (CH), 126.3 (CH), 125.9 (CH), 125.2 (CH), 124.7 (CH), 121.9 (CH), 121.7 (CH), 118.6 (C), 117.0 (CH), 109.8 (CH), 109.0 (CH), 82.8 (CH), 78.5 (C), 62.5 (C), 55.7 (C), 50.1 (CH_2), 42.5 (CH_2), 34.9 (CH_2), 34.5 (CH_3), 31.8 (CH_3), 20.2 (CH_3); IR (thin film) 3367, 3061, 3032, 2853, 2788, 1700, 1647, 1609, 1466, 1355, 1246, 1159, 743 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{72}H_{70}N_8O_6S_2H$ 1207.4938; found, 1207.4950; $[\alpha]^{23}_D$ +28, $[\alpha]^{23}_{577}$ +29, $[\alpha]^{23}_{546}$ +34, $[\alpha]^{23}_{435}$ +74 (*c* = 1.6, CH_2Cl_2). (*S*,*R*,*R*,*R*)-Dioxindole **21**: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 376K) δ 7.51 (d, *J* = 13.6 Hz, 2H), 7.48 (d, *J* = 13.6 Hz, 2H), 7.44–7.19 (overlapping multiplets, 16H), 7.11–7.03 (m, 6H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.74 (br d, *J* = 6.4 Hz, 1H), 6.63 (dd, *J* = 14.3, 3.7 Hz, 2H), 6.57 (br dd, *J* = 10.6, 7.9 Hz, 2H), 6.40 (t, *J* = 7.5 Hz, 1H), 6.28 (t, *J* = 7.1 Hz, 1H), 5.45 (d, *J* = 14.3 Hz, 1H), 5.34 (d, *J* = 14.3 Hz, 1H), 5.01 (d, *J* = 9.1 Hz, 1H), 4.97 (s, 2H), 4.85 (d, *J* = 15.8 Hz, 1H), 4.68 (br s, 1H), 4.44 (br s, 1H), 4.37 (br s, 1H), 2.92 (s, 3H), 2.90 (s, 3H), 2.65–2.58 (m, 1H), 2.48–2.41 (m, 1H), 2.40 (s, 3H), 2.39 (s, 3H), 2.27–2.26 (m, 2H), 2.22–2.19 (m, 1H), 2.18 (s, 3H), 2.02–1.98 (m, 1H), 1.82 (s, 3H), 1.77 (br dd, *J* = 11.9, 4.9 Hz, 1H), 1.69–1.66 (m, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 376 K) δ 176.3 (C), 175.9 (C), 149.2 (C), 148.4 (C), 143.35 (C), 143.31 (C), 141.4 (C), 141.3 (C), 135.8 (C), 135.6 (C), 134.7 (C), 134.2 (C), 133.9 (C), 133.8 (C), 130.6 (C), 130.5 (C), 129.5 (CH), 129.4 (CH), 129.28 (CH), 129.26 (CH), 127.94 (CH), 127.91 (CH), 127.8 (CH), 127.7 (CH), 127.0 (CH), 126.9 (CH), 126.7 (CH), 126.5 (CH), 126.45 (CH), 126.0 (CH), 125.9 (CH), 125.7 (CH), 125.6 (CH), 124.5 (CH), 124.2 (CH), 122.3 (CH), 122.1 (CH), 121.9 (CH), 119.1 (C), 118.7 (C), 117.2 (CH), 116.7 (CH), 110.2 (CH), 110.0 (CH), 109.0 (CH), 108.9 (CH), 83.2 (CH), 83.0 (CH), 62.2 (C), 61.9 (C), 55.7 (C), 55.6 (C), 50.4 (CH_2), 50.3 (CH_2), 42.8 (CH_2), 42.6 (CH_2), 35.2 (CH_2), 35.1 (CH_2), 34.5 (CH_3), 34.3 (CH_3), 31.84 (CH_3), 31.78 (CH_3), 20.27 (CH_3), 20.24

(CH_3); IR (thin film) 3378, 3060, 2857, 2790, 1703, 1609, 1465, 1356, 1159, 742 cm^{-1}; LRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{72}H_{70}N_8O_6S_2H$ 1207.5; found, 1207.5; $[\alpha]^{23}_D$ +116, $[\alpha]^{23}_{577}$ +121, $[\alpha]^{23}_{546}$ +142, $[\alpha]^{23}_{435}$ +298, $[\alpha]^{23}_{405}$ +276 (*c* = 0.80, CH_2Cl_2).

Following the same procedure utilizing (*S*)-tol-BINAP instead of (*R*)-tol-BINAP, dibutenanilide **19** (0.282 mg, 0.187 mmol) was converted into C_2-symmetric dioxindole product **22** and C_1-symmetric isomer **21**. These products were purified by column chromatography (SiO_2: 100:0 $CHCl_3$ → 98:2 $CHCl_3$/MeOH → 94:3:1 $CHCl_3$/MeOH/NH_4OH → 94:5:1 $CHCl_3$/MeOH/NH_4OH) to elute first C_2-symmetric **22** (123 mg, 55%) followed by C_1-symmetric **21** (87.0 mg, 39%) as tan foams. (*S*,*R*,*R*,*S*)-dioxindole **22**: ^1H NMR (500 MHz, $(CD_3)_2SO$, 376K) δ 7.50 (d, *J* = 8.2 Hz, 4H), 7.40 (t, *J* = 6.3 Hz, 8H), 7.32 (t, *J* = 6.9 Hz, 4H), 7.28 (dt, *J* = 1.9, 9.0 Hz, 4H), 7.07 (dd, 7.2, 14.8 Hz, 8H), 6.90 (d, *J* = 7.7 Hz, 2H), 6.68 (d, *J* = 7.9 Hz, 2H), 6.64 (d, *J* = 14.3 Hz, 2H), 6.44 (t, *J* = 7.8 Hz, 2H), 5.34 (d, *J* = 14.3 Hz, 2H), 4.97 (d, *J* = 15.8 Hz, 2H), 4.95 (d, *J* = 15.7 Hz, 2H), 4.39 (br d, 12.6 Hz, 2H), 2.90 (s, 6H), 2.40 (m, 8H), 2.25–2.19 (m 2H), 2.01–1.90 (m, 2H), 1.80 (s, 6H), 1.65–1.62 (m, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 376K) δ 176.0 (C), 148.6 (C), 143.4 (C), 141.3 (C), 135.7 (C), 133.8 (C), 130.5 (CH), 129.6 (CH), 129.3 (CH), 127.9 (CH), 127.7 (CH), 127.0 (CH), 126.9 (CH), 126.5 (C), 126.99 (CH), 125.95 (CH), 124.2 (CH), 122.7 (CH), 122.1 (CH), 118.8 (C), 116.8 (CH), 110.2 (CH), 108.9 (CH), 83.3 (CH), 61.9 (C), 55.7 (C), 50.6 (CH_2), 42.8 (CH_2), 35.3 (CH_2), 34.2 (CH_3), 31.8 (CH_3), 20.3 (CH_3); IR (thin film) 3417, 3376, 3061, 3032, 2867, 2791, 2244, 1708, 1650, 1609, 1485, 1465, 1357, 1247, 1160, 732 cm^{-1}; LRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{72}H_{70}N_8O_6S_2H$ 1207.5; found, 1207.5; $[\alpha]^{23}_D$ +147, $[\alpha]^{23}_{577}$ +156, $[\alpha]^{23}_{546}$ +184, $[\alpha]^{23}_{435}$ +379, $[\alpha]^{23}_{405}$ +201 (*c* = 0.81, CH_2Cl_2).

4.4 Optimized general Procedure for Hydrogenation of the enesulfonamide side chains of the dioxindole Heck products

Synthesis of the tetrahydro derivative of 20—A solution of **20** (140 mg, 0.116 mmol) in warm EtOH (4.0 mL) was added to a glass sleeve containing $Pd(OH)_2/C$ (0.28 g, 20 wt %), K_2CO_3 (130 mg, 0.928 mmol) and a stirbar. The sleeve was fitted inside a pressure reactor (Parr bottle 250 mL) and sealed. The Parr bottle was charged with hydrogen gas (1000 psi) and heated to 80 °C for 24 h. After cooling to room temperature and venting the mixture was filtered through Celite® and the filter cake was washed with $CHCl_3$ saturated with NH_3 (20 mL). The washes were concentrated to afford the tetrahydro derivative of **20** (139 mg, 99%) as a colorless foam. An analytical sample was obtained by column chromatography (SiO_2: 100:0 CH_2Cl_2 → 97:3 CH_2Cl_2/MeOH → 94:5:1 CH_2Cl_2/MeOH/NH_4OH → 89:10:1 CH_2Cl_2/MeOH/NH_4OH) to provide 121 mg (96%) of **21** as a colorless foam: ^1H NMR (500 MHz, $(CD_3)_2SO$, 396K) δ 7.54 (d, *J* = 8.2 Hz, 4H), 7.31 (overlapping signals d and m, d; *J* = 8.0 Hz, 8H), 7.18 (t, *J* = 7.2 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 2H), 7.10 (d, *J* = 7.2 Hz, 4H), 7.02 (t, *J* = 6.8 Hz, 2H), 6.96 (t, *J* = 7.4 Hz, 4H), 6.89 (d, *J* = 7.9 Hz, 2H), 6.77 (d, *J* = 7.5 Hz, 2H), 6.33 (d, *J* = 7.7 Hz, 2H), 6.04 (t, *J* = 7.6 Hz, 2H), 5.77 (br s, 2H), 4.97 (d, *J* = 15.8 Hz, 2H), 4.75 (d, *J* = 15.8 Hz, 2H), 3.07–3.01 (m, 2H), 2.91–2.86 (m, 4H), 2.81 (br s, 4H), 2.63 (s, 6H), 2.38 (s, 6H), 2.37 (s, 6H), 2.32–2.23 (m, 2H), 1.93–1.87 (m, 2H) 1.26 (br s, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 396K) δ 177.2 (C), 149.6 (C), 142.3 (C), 141.9 (C), 135.3 (C), 134.6 (C), 129.4 (C), 128.8 (CH), 127.62

(CH), 127.57 (CH), 126.3 (CH), 126.2 (CH), 126.1 (CH), 124.7 (CH), 124.5 (CH), 121.7 (CH), 121.4 (CH), 118.0 (C), 117.7 (C), 117.3 (CH), 108.9 (CH), 82.8 (CH), 62.4 (C), 53.8 (C), 50.1 (CH_2), 45.5 (CH_2), 42.5 (CH_2), 34.7 (CH_2), 34.6 (CH_2), 33.9 (CH_3), 30.0 (CH_3), 20.0 (CH_3); IR (thin film) cm^{-1}; 3334, 3060, 3031, 2857, 2788, 1695, 1611 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{72}H_{74}N_8O_6S_2H$ 1211.5251; found, 1211.5251; $[\alpha]^{23}_D$ −40, $[\alpha]^{23}_{577}$ −43, $[\alpha]^{23}_{546}$ −51, $[\alpha]^{23}_{435}$ −102, $[\alpha]^{23}_{405}$ −121 (*c* = 1.5, CH_2Cl_2).

Tetrahydro derivative of 22—Following the optimized general procedure for the hydrogenation of the enesulfonamide side chains, 125 mg of **22** yielded 121 mg (96%) of the tetrahydro derivative of **22**: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 396K) δ 7.51 (d, *J* = 7.9 Hz, 4H), 7.38–7.34 (m, 8H), 7.30–7.27 (m, 8H), 7.17 (d, *J* = 7.0 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 2H), 6.94 (d, *J* = 6.8 Hz, 2H), 6.72 (d, *J* = 7.8 Hz, 2H), 6.42 (t, *J* = 7.3 Hz, 2H), 5.23 (s, 2H), 4.95 (d, *J* = 16.4 Hz, 2H), 4.89 (d, *J* = 15.3 Hz, 2H), 4.41 (s, 2H), 2.95–2.91 (m, 2H), 2.84–2.80 (m, 4H), 2.65 (s, 6H), 2.49–2.42 (m, 2H), 2.39 (s, 6H), 2.36–2.31 (m, 2H), 2.27–2.24 (m, 2H), 2.14–1.11 (m, 2H), 2.00 (s, 6H), 1.75–1.71 (m, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 396K) δ 177.0 (C), 148.9 (C), 142.3 (C), 141.8 (C), 135.6 (C), 134.8 (C), 129.8 (C), 128.8 (CH), 127.8 (CH), 127.6 (CH), 126.9 (CH), 126.7 (CH), 126.2 (CH), 125.1 (CH), 124.0 (CH), 122.8 (CH), 121.9 (CH), 117.8 (C), 116.8 (CH), 116.7 (C), 108.8 (CH), 83.8 (CH), 61.7 (C), 53.3 (C), 50.9 (CH_2), 45.2 (CH_2), 42.9 (CH_2), 35.0 (CH_3), 34.8 (CH_3), 33.9 (CH_2), 31.5 (CH_2), 20.0 (CH_3); IR (thin film) 3320, 3057, 3033, 2851, 2790, 1692, 1610 cm^{-1}; LRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{72}H_{74}N_8O_6S_2H$ 1211.5; found, 1211.5; $[\alpha]^{23}_D$ +254, $[\alpha]^{23}_{577}$ +269, $[\alpha]^{23}_{546}$ +312, $[\alpha]^{23}_{435}$ +625 (*c* = 1.1, CH_2Cl_2).

Tetrahydro derivative of 21—Following the optimized general procedure for the hydrogenation of the enesulfonamide side chains, 230 mg of **21** yielded 224 mg (97%) of tetrahydro derivative of **21**: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 396K) δ 7.50 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 7.1 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 4H), 7.30–7.23 (m, overlapping signals, 8H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.16–7.07 (m, 4H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 7.3 Hz, 1H), 6.80 (d, *J* = 7.3 Hz, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 6.36 (t, *J* = 7.5 Hz, 1H), 6.27 (t, *J* = 7.4 Hz, 1H), 5.44 (d, *J* = 3.9 Hz, 1H), 5.18 (s, 1H), 4.96 (d, *J* = 15.6 Hz, 1H), 4.90 (s, 2H), 4.89 (d, *J* = 15.4 Hz, 1H), 4.70 (br s, 1H), 4.43 (br s, 1H), 3.03–2.98 (m, 1H), 2.97–2.89 (m, 2H), 2.80 (br s, 3H), 2.68–2.61 (m, 1H), 2.66 (s, 3H), 2.65 (s, 3H), 2.44–2.40 (m, 2H), 2.39 (s, 3H), 2.37 (s, 3H), 2.34–2.31 (m, 2H), 2.30 (s, 3H), 2.28–2.25 (m, 2H), 2.15–2.10 (m, 1H), 2.00 (s, 3H), 1.84–1.81 (m, 1H), 1.75–1.72 (m, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 396K) δ 177.2 (C), 176.9 (C), 149.5 (C), 148.8 (C), 142.30 (C, overlapping signal), 142.30 (C, overlapping signal), 141.89 (C), 141.86 (C), 135.63 (C), 135.57 (C), 135.2 (C), 134.8 (C), 134.7 (C), 134.5 (C), 129.8 (C), 129.6 (C), 128.85 (CH, overlapping signal), 128.85 (CH, overlapping signal), 127.76 (CH, overlapping signal), 127.67 (CH, overlapping signal), 127.71 (CH), 127.6 (CH), 126.9 (CH), 126.7 (CH), 126.6 (CH), 126.3 (CH), 126.2 (CH), 126.1 (CH), 124.9 (CH), 124.7 (CH), 124.4 (CH), 124.0 (CH), 122.3 (CH), 122.0 (CH), 121.84 (CH), 121.77 (CH), 118.5 (C), 117.7 (CH), 117.4 (C), 116.8 (CH), 108.8 (CH), 108.7 (CH), 83.6 (CH), 82.9 (CH), 62.3 (C), 61.9 (C), 53.7 (C), 53.3 (C), 50.6 (CH_2), 50.3 (CH_2), 45.4 (CH_2), 45.2 (CH_2), 42.9 (CH_2), 42.8 (CH_2), 35.0 (CH_2), 34.9 (CH_2), 34.8 (CH_3), 34.7 (CH_3), 33.92 (CH_3), 33.87 (CH_3), 31.3 (CH_2), 30.6 (CH_2), 20.05 (CH_3), 20.03 (CH_3); IR

(thin film) 3334, 3058, 2852, 2789, 1693, 1610 cm^{-1}; LRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{72}H_{74}N_8O_6S_2H$ 1211.5; found, 1211.5; $[\alpha]^{23}_D$ +148, $[\alpha]^{23}_{577}$ +155, $[\alpha]^{23}_{546}$ +180, $[\alpha]^{23}_{435}$ +360, $[\alpha]^{23}_{405}$ +410 (*c* = 0.87, CH_2Cl_2).

4.5 Optimized general procedure for reductive cyclization to form dodecacyclic alkaloid products

Preparation of (*R*,*R*,*R*,*R*)-quadrigemine 7—*Caution!!! Ammonia gas is toxic and should only be used in a well-ventilated fume hood.* Ammonia was condensed in a 2-neck flask cooled to −78 °C and fitted with a cold finger filled with dry ice and isopropanol. After condensing ~20 mL NH_3(l) a small piece of sodium (~25 mg) was added to provide a deep blue color. Using a wide-bore cannula approximately 10 mL of ammonia was distilled into another 2-neck flask cooled to −78 °C and fitted with a cold finger filled with dry ice and isopropanol. The tetrahydro derivative of **20** (68.0 mg, 0.056 mmol) in dry THF (3 mL) was added to the liquid NH_3. *Tert*-butanol (42 μL, 0.448 mmol) was added followed by slow addition of small pieces of sodium metal (65 mg, 2.8 mmol). The heterogeneous solution was stirred vigorously at −78 °C as the solution slowly changed from clear yellow, green-brown, to blue. After persistence of the blue color for 20 min the reaction was quenched at −78 °C by slowly adding solid NH_4Cl (~190 mg). The blue color disappeared and a cloudy colorless precipitate formed. The flask was allowed to slowly warm to room temperature while open to the atmosphere and the ammonia permitted to evaporate. Water (20 mL) was added to the heterogeneous mixture and extracted with $CHCl_3$ (sat with NH_3; 3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and the residue was purified by reverse phase HPLC to yield (*R*,*R*,*R*,*R*)-quadrigemine **7** (8.8 mg, 23% from **20**): Analytical reverse-phase HPLC (Zorbax Extend C18, 250 × 4.6 mm), 72:28–>85:15 MeOH-H_2O (1% NH_4OH) over 40 min, 1.0 mL/min, UV detection at 254 nm (r_t = 24.8 min); ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 376K) δ 6.93 (app t, *J* = 7.1 Hz, 2H), 6.87 (d, *J* = 7.4 Hz, 2H), 6.70–6.67 (m, 3H), 6.57 (app t, *J* = 7.0 Hz, 2H), 6.50 (d, *J* = 7.7 Hz, 2H), 6.20 (br app t, *J* = 7.7 Hz, 1H), 5.81 (br s, 1H), 5.75 (br s, 1H), 4.77 (br s, 1H), 4.71 (br s, 2H), 3.89–2.82 (m, 7H), 2.61 (br s, 1H), 2.41 (s, 7H), 2.36 (s, 5H), 2.26–2.23 (m, 2H), 1.83–1.79 (m, 3H), 1.34–1.25 (m, 6H), 0.85 (app t, *J* = 7.1 Hz, 2H); ^{1}H NMR (500 MHz, C_6D_6, 345K) δ 7.10 (d, *J* = 6.9 Hz, 2H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 2H), 6.96 (br s, 1H), 6.76 (t, *J* = 7.3 Hz, 2H), 6.48 (br s, 1H), 6.42 (d, *J* = 7.5 Hz, 1H), 5.92 (s, 1H), 5.05 (s, 1H), 4.86 (s, 1H), 3.46 (br s, 1H), 3.14–3.10 (m, 1H), 2.78 (t, *J* = 7.8 Hz, 2H), 2.70–2.68 (m, 3H), 2.60–2.56 (m, 3H), 2.55–2.51 (m, 3H), 2.49 (s, 3H), 2.40 (br s, 5H), 2.25 (s, 4H), 1.94 (t, *J* = 8.1 Hz, 4H), 1.85 (dd, *J* = 5.0 & 11.1 Hz, 1H), 1.32–1.28 (m, 3H); ^{13}C NMR (125 MHz, C_6D_6, 345K) δ 151.8 (C), 150.8 (C), 133.7 (C), 126.5 (CH), 125.7 (CH), 119.6 (CH), 117.4 (CH), 109.8 (CH), 88.2 (CH), 84.8 (CH), 64.3 (C), 61.9 (C), 53.0 (CH_2), 51.8 (CH_2), 48.9 (CH), 39.3 (CH_2), 37.4 (CH_2), 36.2 (CH_3), 35.9 (CH_3), 30.7 (C), 29.5 (CH), 18.1 (C); IR (thin film) 3379, 3270, 3053, 2930, 2855, 2789, 1604, 1485, 1466, 1248, 1153, 1036, 908, 737 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{44}H_{50}N_8H$ 691.4236; found, 691.4237; $[\alpha]^{23}_D$ +277, $[\alpha]^{23}_{577}$ +283, $[\alpha]^{23}_{546}$ +328, $[\alpha]^{23}_{435}$ +656 (*c* = 0.20, EtOH).

(*S*,*R*,*R*,*S*)-quadrigemine (5)—Following the optimized general for the reductive cyclization, the tetrahydro derivative of **22** (71 mg, 0.059 mmol) was converted to **5** (11.9

mg, 29%): Analytical reverse-phase HPLC (Zorbax Extend C18, 250 × 4.6 mm), 72:28–>85:15 MeOH-H_2O (1% NH_4OH) over 40 min, 1.0 mL/min, UV detection at 254 nm: (r_t = 29.4 min); ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 376K) δ 6.98–6.94 (overlapping doublets, 6H), 6.86 (d, *J* = 7.2 Hz, 2H), 6.61 (t, *J* = 7.1 Hz, 2H), 6.56 (d, *J* = 7.6 Hz, 2H), 6.37 (t, *J* = 7.5 Hz, 2H), 6.05 (br s, 2H), 5.88 (br s, 2H), 4.84 (s, 2H), 4.72 (s, 2H), 2.94–2.90 (m, 8H), 2.76–2.69 (m, 2H), 2.41 (s, 6H), 2.37–2.34 (m, 2H), 2.13 (s, 6H), 1.90–1.88 (m, 2H), 1.78–1.75 (m, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 376K) δ 150.9 (C), 148.9 (C), 132.8 (C), 131.7 (C), 127.6 (CH), 126.8 (CH), 124.5 (CH), 123.8 (CH), 122.9 (C), 116.6 (CH), 115.0 (CH), 107.5 (CH), 85.5 (CH), 83.2 (CH), 61.9 (C), 59.6 (C), 51.2 (CH_2), 50.9 (CH_2), 37.9 (CH_2), 35.4 (CH_2), 34.8 (CH_3), 34.7 (CH_3); IR (thin film) cm^{-1}; 3379, 3245, 3050, 2858, 2791, 1683, 1604, 1486 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{44}H_{50}N_8H$ 691.4236; found, 691.4223; $[\alpha]^{23}_D$ +279, $[\alpha]^{23}_{577}$ +289, $[\alpha]^{23}_{546}$ +332, $[\alpha]^{23}_{435}$ +690 (*c* = 0.27, EtOH).

(*S*,*R*,*R*,*R*)-Quadrigemine 6—Following the optimized general procedure for the reductive cyclization, the tetrahydro derivative of **21** (73 mg, 0.06 mmol) was converted to **6** (11.9 mg, 29%): Analytical reverse-phase HPLC (Zorbax Extend C18, 250 × 4.6 mm), 72:28–>85:15 MeOH-H_2O (1% NH_4OH) over 40 min, 1.0 mL/min, UV detection at 254 nm: (r_t = 27.3 min); ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 376K) δ 6.98 (d, *J* = 7.1Hz, 2H), 6.95 (d, *J* = 3.3 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 3H), 6.83 (d, *J* = 7.2 Hz, 1H), 6.79 (t, *J* = 8.1 Hz, 2H), 6.62–6.57 (m, 2H), 6.54 (dd, *J* = 5.7, 7.1 Hz, 2H), 6.34 (t, *J* = 7.2 Hz, 1H), 6.28 (t, *J* = 7.3 Hz, 1H), 6.00 (s, 1H), 5.86 (s, 1H), 5.82 (s, 1H), 5.75 (s, 1H), 4.80 (s, 2H), 4.69 (br s, 1H), 4.56 (br s, 1H), 2.68–2.61 (m, 3H), 2.47– 2.43 (m, 5H), 2.41 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H), 2.31–2.26 (m, 2H), 2.14–2.11 (m, 1H), 2.10 (s, 3H), 1.89–1.82 (m, 3H), 1.77–1.73 (m, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 376K) δ 151.9 (C), 149.9 (C), 127.9 (C), 125.7 (C), 117.7 (CH), 117.5 (C), 116.4 (CH), 116.0 (CH), 108.5 (CH), 87.1 (CH), 86.5 (CH), 84.3 (CH), 83.9 (CH), 70.5 (CH), 63.0 (C), 60.7 (C), 52.3 (CH_2), 51.8 (CH_2), 39.0 (CH_2), 38.9 (CH_2), 36.2 (CH_3), 35.9 (CH_3); IR (thin film) 3378, 3055, 2852, 2791, 1698, 1603, 1486, 1456 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{44}H_{50}N_8H$ 691.4236; found, 691.4237; $[\alpha]^{23}_D$ +347, $[\alpha]^{23}_{577}$ +367, $[\alpha]^{23}_{546}$ +435, $[\alpha]^{23}_{435}$ +854 (*c* = 0.10, EtOH).

Supplementary Material

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37. Obtaining NMR spectra in d_6-DMSO at 376K of the [2+2] qudrigemine products **1**, **2**, *meso*-**3**, *meso*-**4**, and **5–7** resulted in some simplification of the spectra by reducing the number of significant conformers present. However, these samples gradually decomposed during extended acquisition time at this temperature. NMR samples, which were clear and colorless solutions at the outset, eventually turned dark brown; partial degradation under the analysis conditions could be confirmed by HPLC analysis.
38. Verotta L, Peterlongo F, Elisabetsky E, Amador TA, Nunes DS. J Chromatogr A. 1999; 841:165–176.
39. Extract was from *P. muscosa* collected at Benfica, Brazil in Feb 1997 by Verotta and co-workers.
40. (a) Amador TA, Elisabetsky E, Souza DO. Neurochem Res. 1996; 21:97–102. [PubMed: 8833229] (b) Amador TA, Verotta L, Nunes DS, Elisabetsky E. Planta Med. 2000; 66:770–772. [PubMed: 11199142] (c) Amador TA, Verotta L, Nunes DS, Elisabetsky E. Phytomedicine. 2001; 8:202–6. [PubMed: 11417913] (d) Verotta L, Orsini F, Sbacchi M, Scheildler MA, Amador TA, Elisabetsky E. Bioorg Med Chem. 2002; 10:2133–2142. [PubMed: 11983509]

41. Beretz A, Roth-Georger A, Corre G, Kuballa B, Anton R, Cazenave JP. Planta Med. 1985; 51:300–303. [PubMed: 17340518]

42. (a) Roth A, Kuballa B, Bounthanh C, Cabalion P, Sévenet T, Beck JP, Anton R. Planta Med. 1986; 52:450–453. [PubMed: 3494261] (b) Adjibadé Y, Kuballa B, Cabalion P, Jung ML, Beck JP, Anton R. Planta Med. 1989; 52:567–568. [PubMed: 2616674] (c) Adjibadé Y, Saad H, Kuballa B, Beck JP, Sévenet T, Cabalion P, Anton R. J Ethnopharmacol. 1990; 29:127–136. (d). [PubMed: 2374427]

43. Such strategies have generally been employed to elaborate acyclic chains, see reference 23.

44. Prepared as described: Coulson DR. Inorg Syntheses. 1972; 13:121–124.

45. 10% KF/SiO_2 was prepared as described: Harrowven DC, Guy IL. Chem Comm. 2004:1968–1969. [PubMed: 15340625]

46. NMR spectra were nearly identical to those obtained previously for the enantiomer.[4] The slight changes observed likely result from differences in the concentrations of the NMR samples.

47. TMEDA was distilled from CaH_2 immediately prior to use.

48. Prepared as describe by Coulson DR. Inorg Syntheses. 1972; 13:121–124.

49. Dried by first azeotroping with benzene, followed by distillation from 4Å MS under vacuum and stored over 4Å MS.

50. Dried by distillation under vacuum from CaH_2.

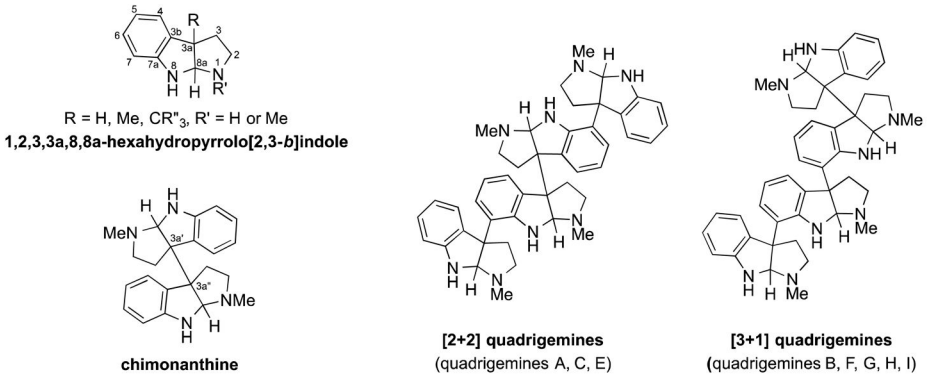


Figure 1.

A pyrrolidinoindoline fragment and the connectivity of the chimonanthine and quadrigemine alkaloids.

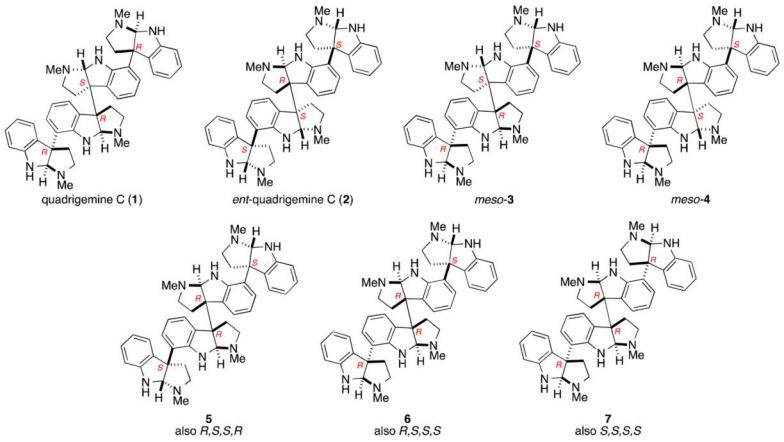


Figure 2.
Structure of quadrigemine C and six stereoisomers.

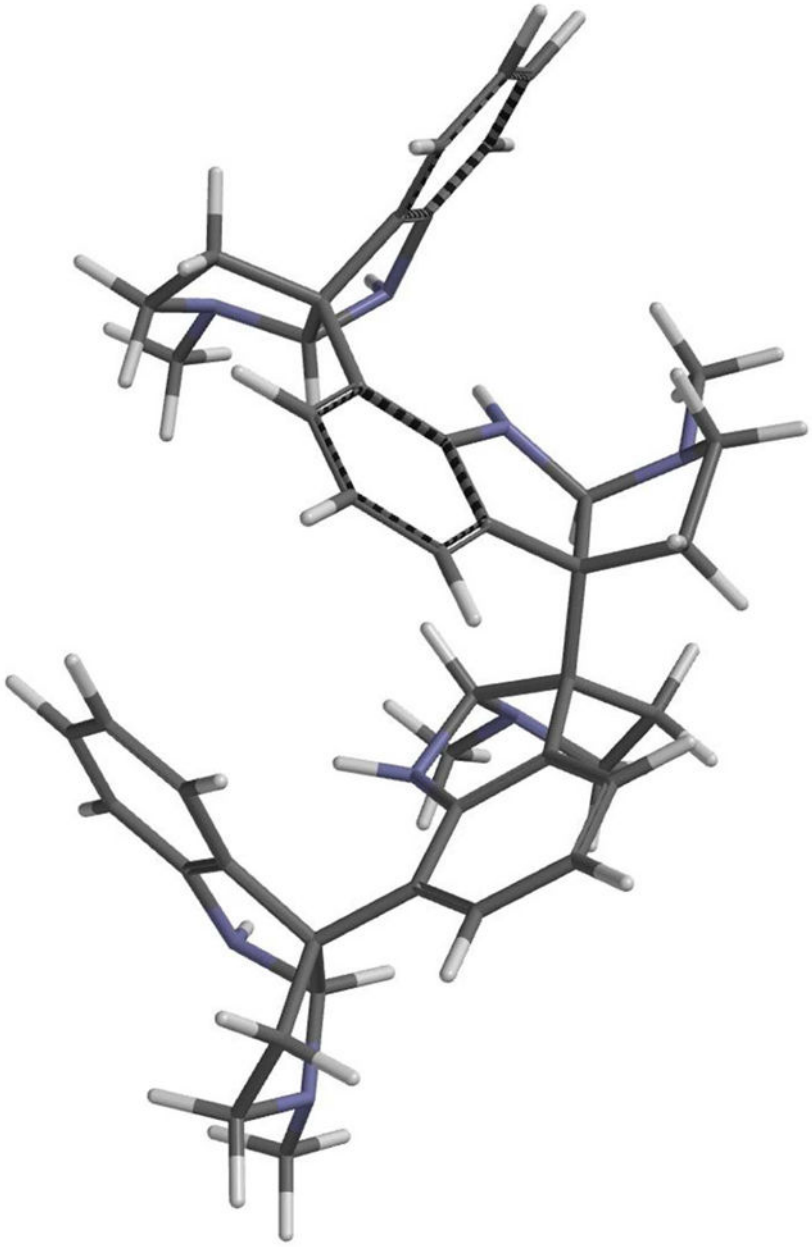


Figure 3.
Model of a low-energy conformation of quadrigemine C.[28]

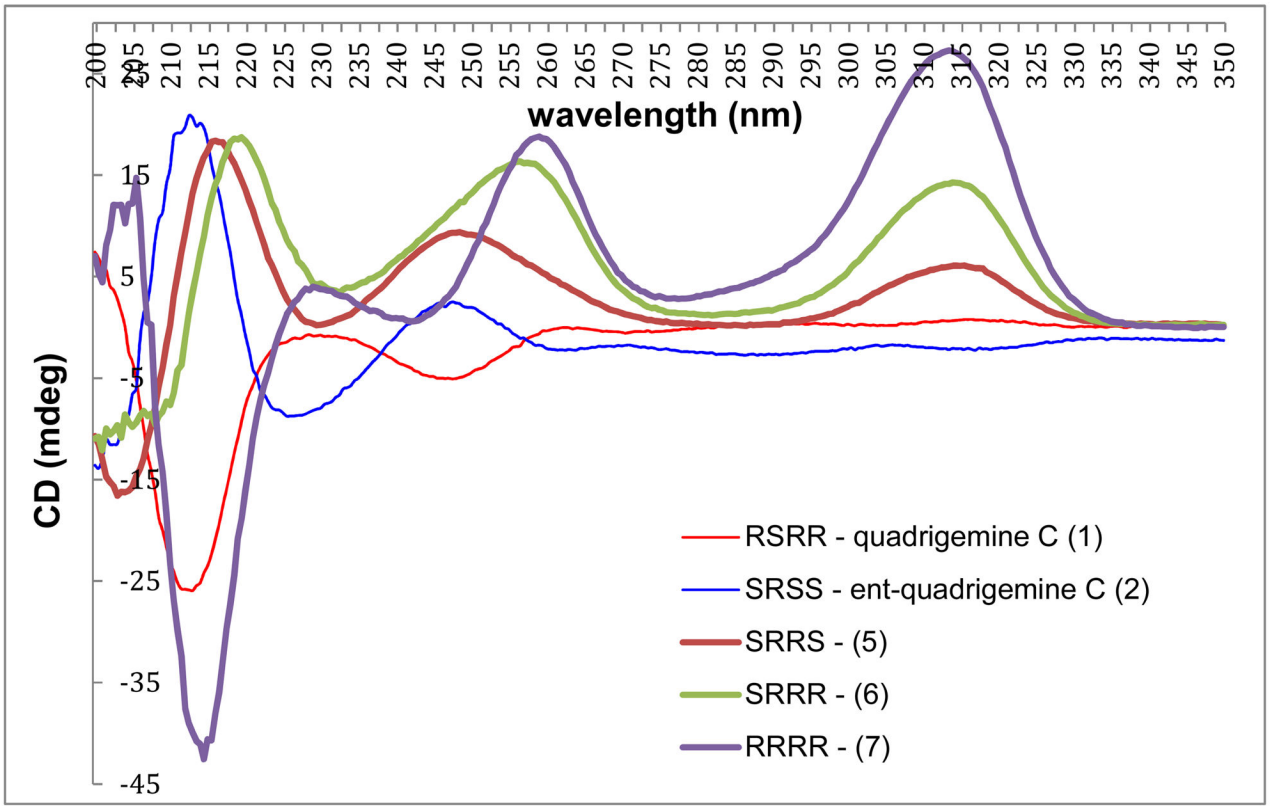


Figure 4.

Circular dichroism of [2+2] quadrigemines[a]

[a]all data taken ~2.9×10^{-4} M in EtOH

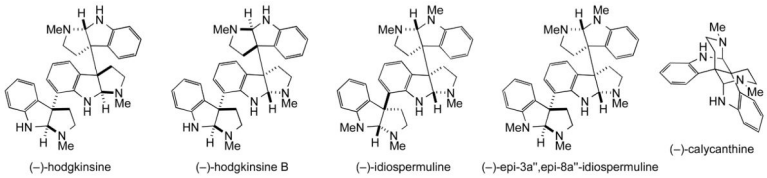
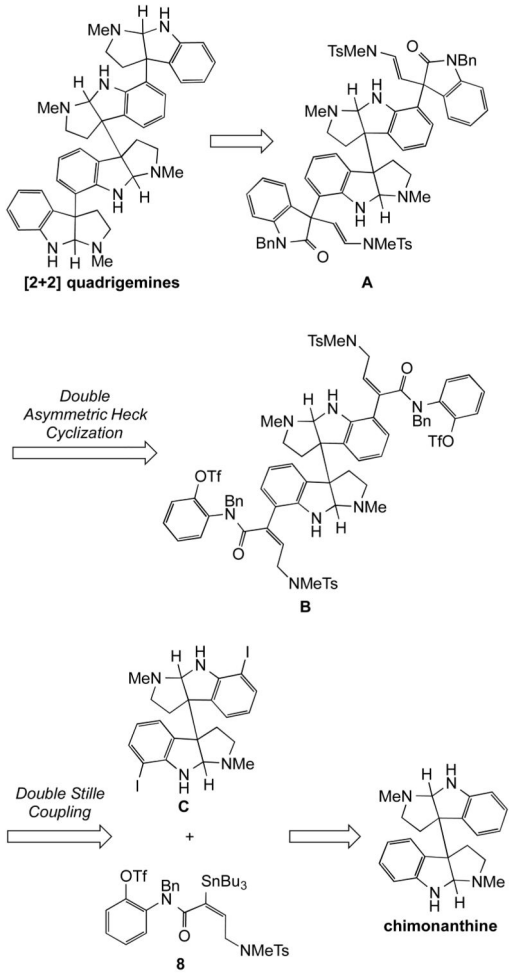
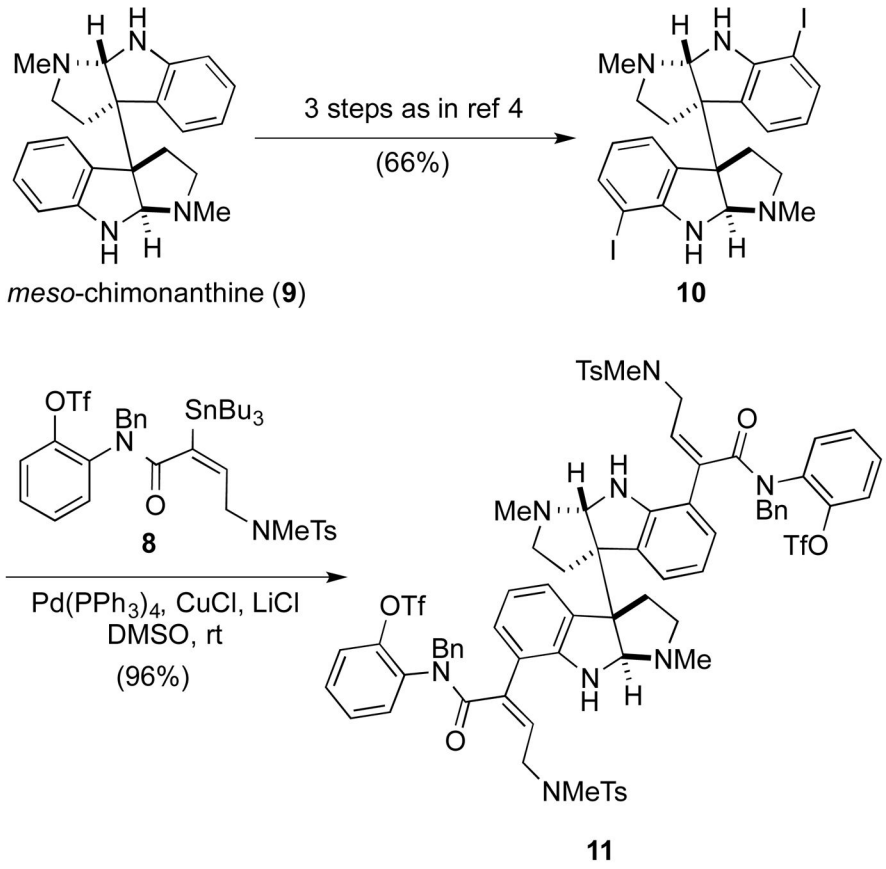


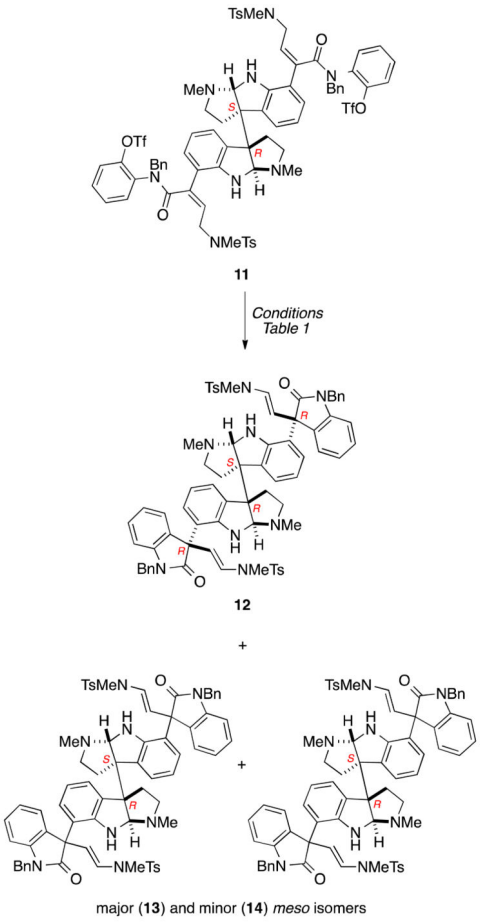
Figure 5.
Additional pyrrolidinoinoline alkaloids.



Scheme 1.
Retrosynthetic analysis: an inside-out synthetic strategy.

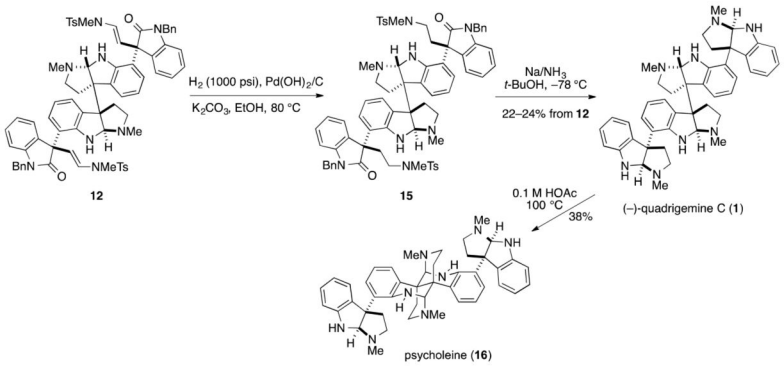


Scheme 2.
Optimized double-Stille cross coupling.



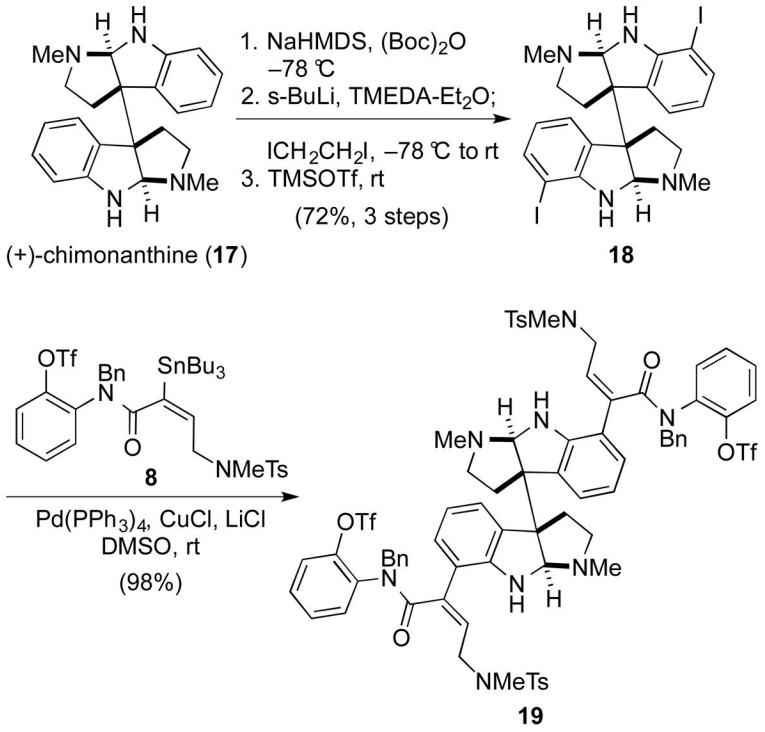
Scheme 3.

Double enantioselective Heck cyclization of *meso*-dibutenanilide **11** (one of the meso stereoisomers has the *S*,*S*,*R*,*R* absolute configuration and the other the *R*,*S*,*R*,*S* absolute configuration).



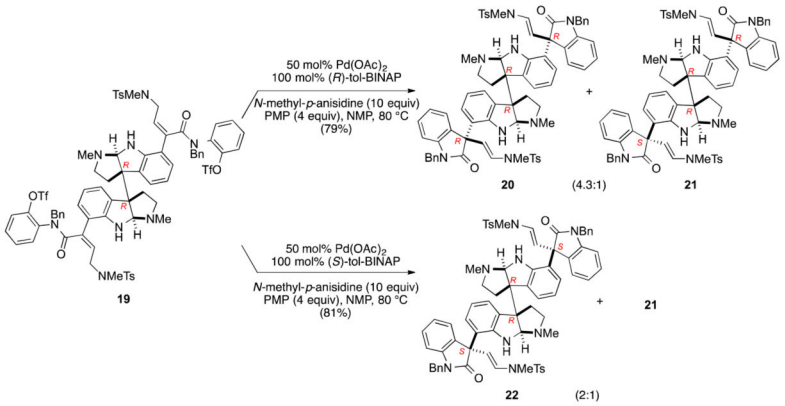
Scheme 4.

Completion of an optimized total synthesis of quadrigemine C.



Scheme 5.

Synthesis of the Heck cyclization precursor in the C_2-symmetric series.



Scheme 6.

Diastereoselective double Heck cyclization of C_2-symmetric dibutenanalide **19**.

Table 1

Optimization of the double enantioselective Heck cyclization of *meso*-dibutenanilide **11**.

Entry	Conditions[a]	Solvent	ds ratio (12:13:14)[b]	% ee 12[b]
1	(*R*)-BINAP	THF	2.8:1.7:1.0	65
2	(*R*)-BINAP	DMA	2.5:1.0:1.1	64
3	(*R*)-BINAP	MeCN	3.5:1.7:1.0	80
4	(*R*)-BINAP	PhMe	3.1:2.7:1.0	54
5[c]	(*S*,*S*)-BDPP	THF	2.4:1.0:1.5	35
6	(*R*)-tol-BINAP	THF	7.2:2.0:1.0	85
7	(*R*)-tol-BINAP	DMA	6.7:1.2:1.0	81
8	(*R*)-tol-BINAP	NMP	5.6:1.2:1.0	80
9	(*R*)-tol-BINAP	NMP	5.1:1.7:1.0	79
10	(*R*)-tol-BINAP	MeCN	9.3:2.0:1.0	90

[a] 50 mol% $Pd(OAc)_2$, 100 mol% phosphine ligand, 4 equiv 1,2,2,6,6-pentamethylpiperidine (PMP), 80 °C;

[b] ratio determined by HPLC;

[c] *ent*-**12** was formed preferentially.

Table 2

Diastereoselective double Heck cyclization in the C_2-symmetric series.

Entry	Conditions[a]	Solvent	de ratio (20:21; C_2:C_1)[b]
1	*rac*-tol-BINAP	NMP	1.0:2.3
2	(*R*)-tol-BINAP	NMP	4.3:1.0
3	(*R*)-tol-BINAP	MeCN	3.0:1.0
4	(*R*)-tol-BINAP	THF	2.5:1.0
5	(*R*)-tol-BINAP	PhMe	1.0:2.3

[a] 50 mol% $Pd(OAc)_2$, 100 mol% phosphine ligand, 4.0 equiv 1,2,2,6,6-pentamethylpiperidine (PMP), 80 °C;

[b] ratio determined by HPLC

Table 3

Yield of the final two steps in the synthesis of [2+2] quadrigemines and their optical rotations.

Starting Material	Product	Yield (over 2 steps)	$[\alpha]_D^a$
12	**1** (*R*,*S*,*R*,*R*)-quadrigemine C	22–24%	−30 (−67)[b]
ent-**12**	**2** (*S*,*R*,*S*,*S*)-*ent*-quadrigemine C	24%	+20 (+70)[b]
13	major *meso*-quadrigemine[c,e]	40%	–
14	minor *meso*-quadrigemine[d,e]	16%	–
20	**7** (*R*,*R*,*R*,*R*)	23%	+277
21	**6** (*S*,*R*,*R*,*R*)	29%	+140
22	**5** (*S*,*R*,*R*,*S*)	29%	+231

[a] $[\alpha]_D$ taken in EtOH.

[b] $[\alpha]_D$ taken in $CHCl_3$.

[c] The dodecacyclic product resulting from transformation of the major *meso* Heck product **13**;

[d] The dodecacyclic product resulting from transformation of the minor *meso* Heck product **14**;

[e] The relative configuration could not be confirmed, the product is either *meso* quadrigemine **3** or **4**.

Table 4

Cytotoxic activity against prostate cancer (DU145) and melanoma (A2508) cell lines (IC_{50}).[a]

Entry	Compound	DU145	A2058
1	(−)-quadrigemine C (**1**)	2.2 μM	1.7 μM
2	*meso*-quadrigemine[a,c]	4 μM	5 μM
3	*meso*-quadrigemine[b,c]	>10 μM	>10 μM
4	(*S*,*R*,*R*,*S*)-quadrigemine (**5**)	8.8 μM	4.1 μM
5	(*S*,*R*,*R*,*R*)-quadrigemine (**6**)	4.7 μM	3.5 μM
6	(*R*,*R*,*R*,*R*)-quadrigemine (**7**)	5.0 μM	4.1 μM
7	(−)-psycholeine (**16**)	>10 μM	>10 μM
8	(−)-hodgkinsine	7.2 μM	7.2 μM
9	(−)-hodgkinsine B	8.0 μM	8.1 μM
10	(−)idiospermuline	>10 μM	>10 μM
11	*(−)-epi*-idiospermuline	>10 μM	>10 μM
12	*meso*-chimonanthine (**9**)	>10 μM	>10 μM
13	(−)-chimonanthine (*ent*-**17**)	>10 μM	>10 μM
14	(−)-calycanthine	>10 μM	>10 μM

[a] The dodecacyclic product resulting from transformation of the major *meso* Heck product **13**;

[b] The dodecacyclic product resulting from transformation of the minor *meso* Heck product **14**;

[c] The relative configuration could not be confirmed, the product is either *meso* quadrigemine **3** or **4**.