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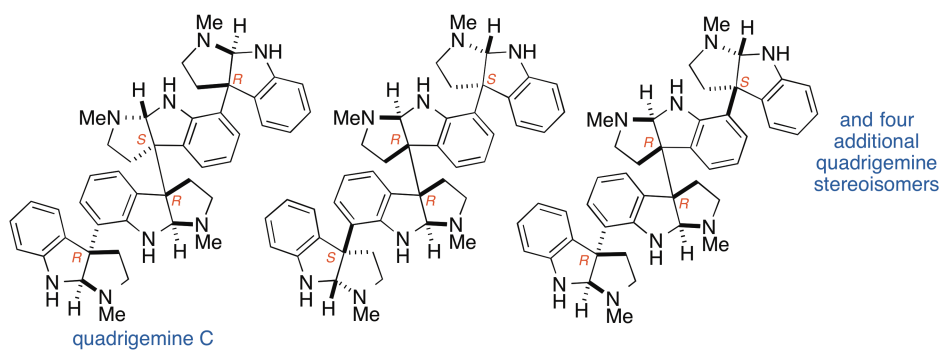
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Graphical Abstract



Dedicated to Professors Jiro Tsuji and Barry Trost in honor of their receipt of the 2015 Tetrahedron Prize

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 -symmetric 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

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

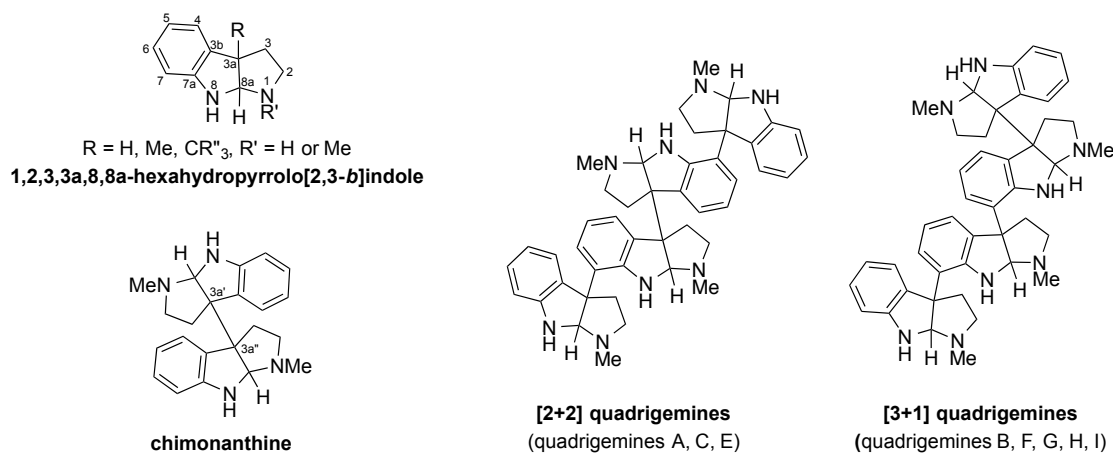


Figure 1. A pyrrolidinoindole fragment and the connectivity of the chimonanthe and quadrigemine alkaloids.

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 frutescens*.^{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 chimonanthe 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 C⁹, and E¹⁰ 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 chimonanthe 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).

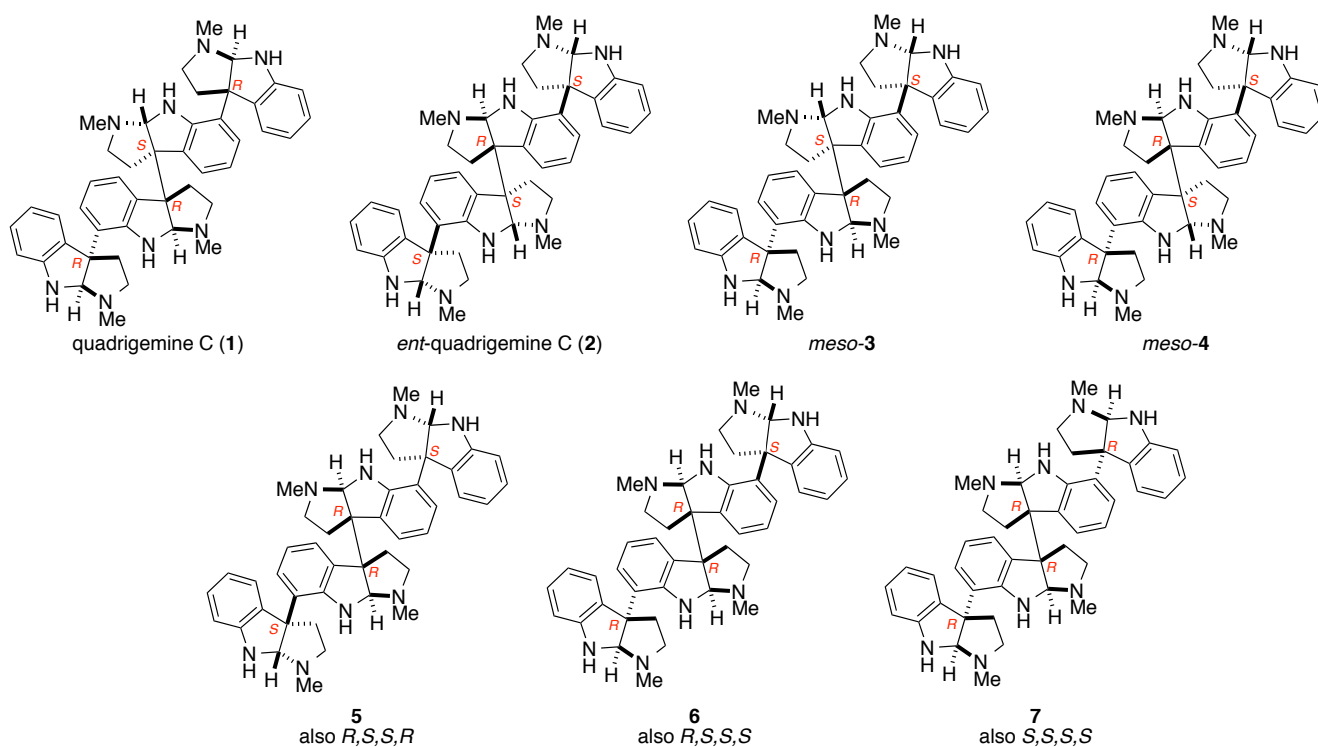


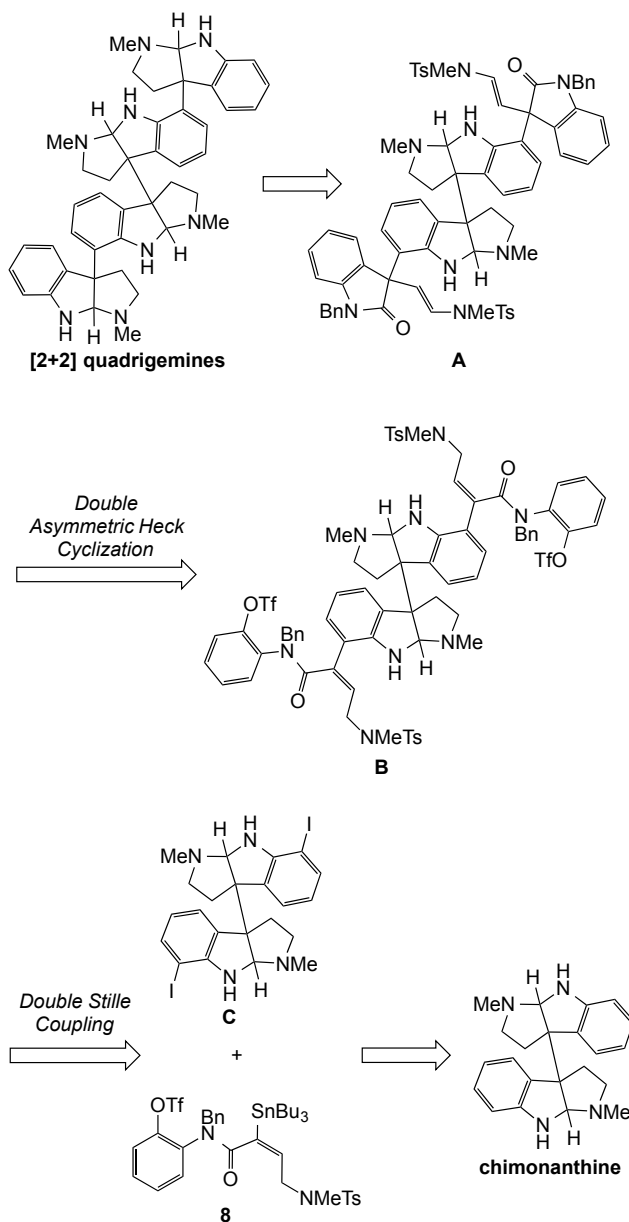
Figure 2. Structure of quadrigemine C and six stereoisomers.

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.

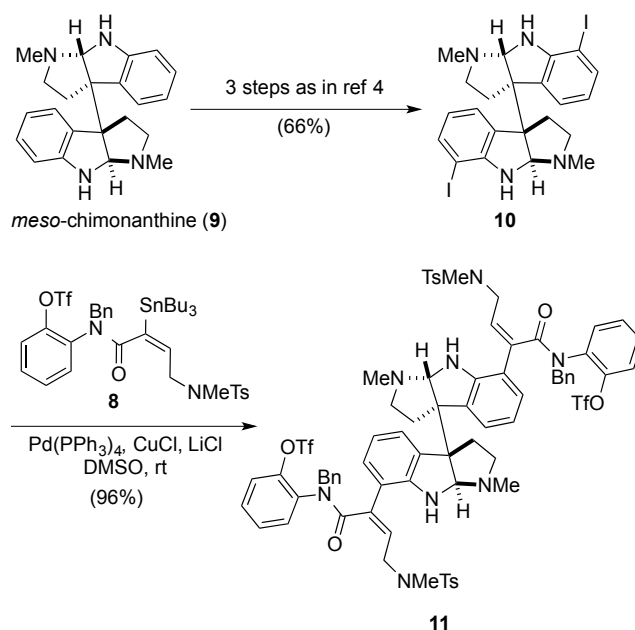


Scheme 1. Retrosynthetic analysis: an inside-out synthetic strategy.

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*₆-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 co-workers 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



Scheme 2. Optimized double-Stillé cross coupling.

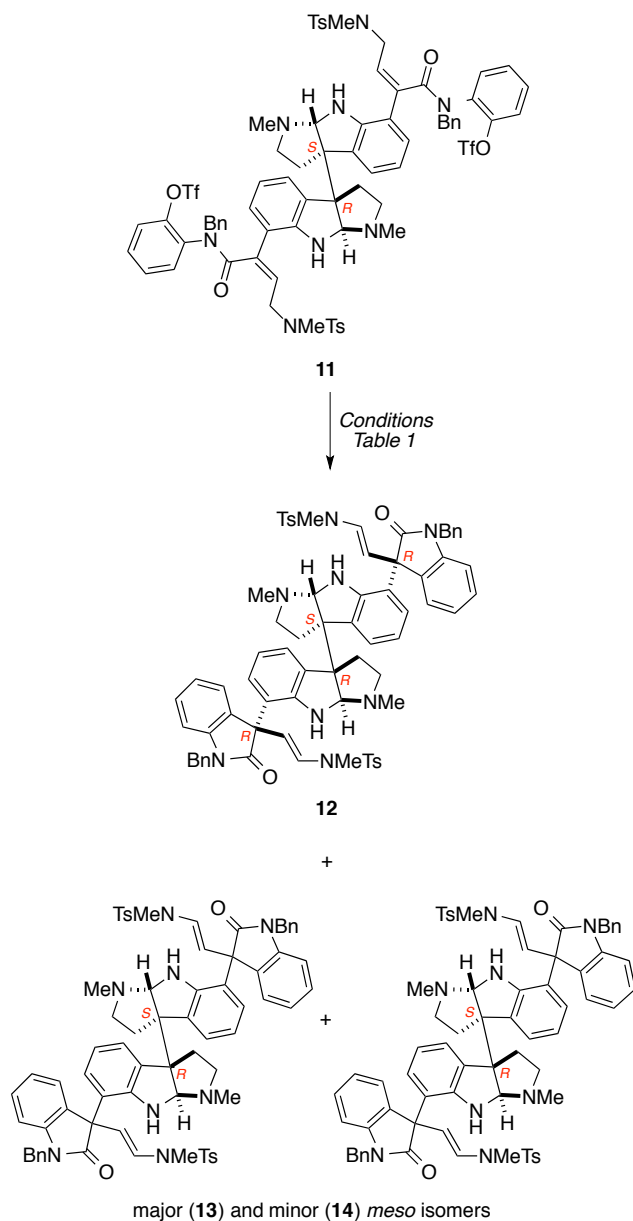
In our first generation synthesis, the Stillé cross coupling of *meso*-diiodide **10** with 3 equiv of stannane aryl triflate **8** to provide the *meso*-dibutenanilide **11** was achieved using a catalyst system of Pd₂dba₃·CHCl₃, tri-2-furylphosphine and CuI in 1-methyl-2-pyrrolidone (NMP).^{4,18} This Stillé 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 $[\text{Ph}_2\text{PO}_2][\text{NBu}_4]$ 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 $\text{Pd}(\text{PPh}_3)_4/\text{CuCl}/\text{LiCl}$ was found to be optimal.²² Thus, reaction of *meso*-diiodide **10** with 3 equiv of stannane aryl triflate **8**, 0.5 equiv of $\text{Pd}(\text{PPh}_3)_4$, 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 be 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.

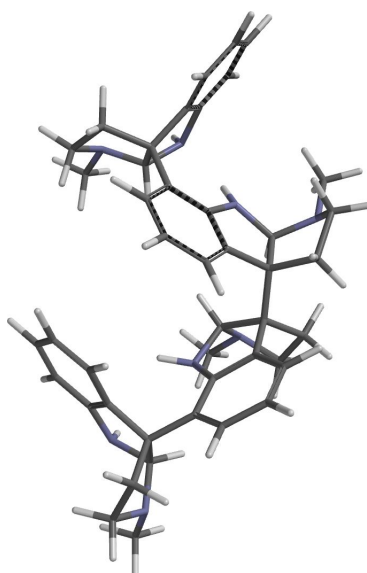


Scheme 3. Double enantioselective Heck cyclization of *meso*-dibutenanilide **11** (one of the *meso* stereoisomers has the *S,S,R,R* absolute configuration and the other the *R,S,R,S* absolute configuration).

Table 1. Optimization of the double enantioselective Heck cyclization of *meso*-dibutenanilide **11**.

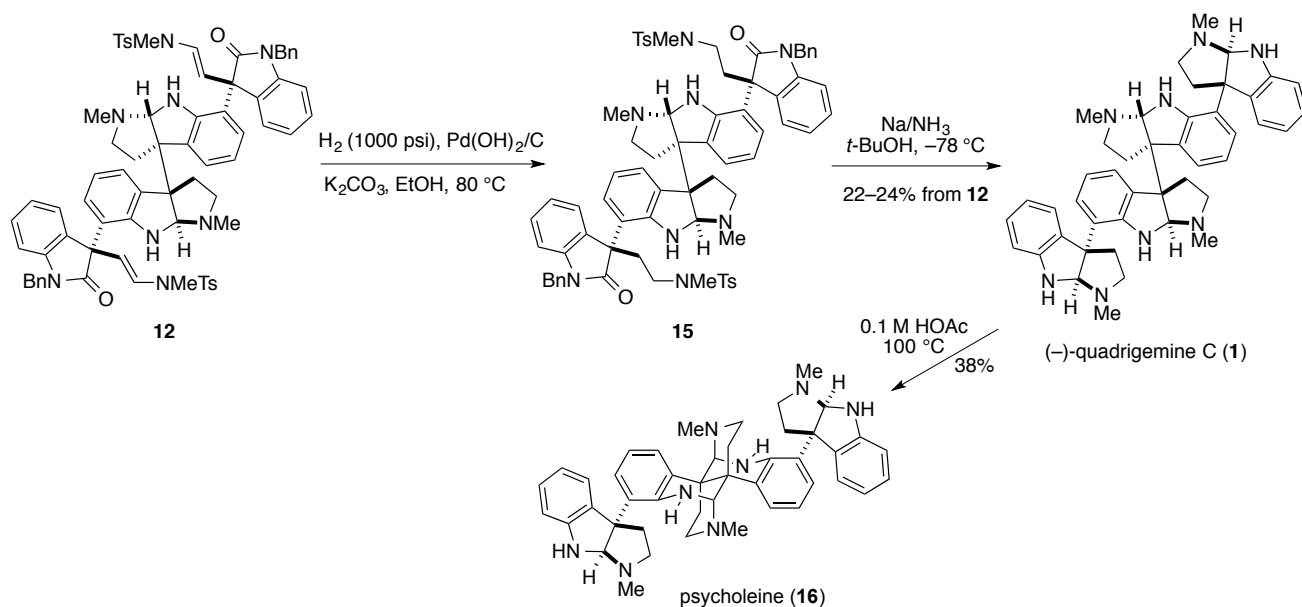
Entry	Conditions ^a	Solvent	ds ratio (12 : 13 : 14) ^b	% ee 12 ^b
1	(<i>R</i>)-BINAP	THF	2.8:1.7:1.0	65
2	(<i>R</i>)-BINAP	DMA	2.5:1.0:1.1	64
3	(<i>R</i>)-BINAP	MeCN	3.5:1.7:1.0	80
4	(<i>R</i>)-BINAP	PhMe	3.1:2.7:1.0	54
5 ^c	(<i>S,S</i>)-BDPP	THF	2.4:1.0:1.5	35
6	(<i>R</i>)-tol-BINAP	THF	7.2:2.0:1.0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

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

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 K₂CO₃ 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/NH₃ containing 4 equiv of *tert*-butanol for 20 min at -78 °C, followed by quenching with NH₄Cl and HPLC purification afforded (-)-quadrigemine C (**1**). Modification of our previous conditions by the incorporation of *tert*-butanol³² led to significant improvements in reproducibility, reliably yielding (-)-quadrigemine C in 22–24% for the two steps

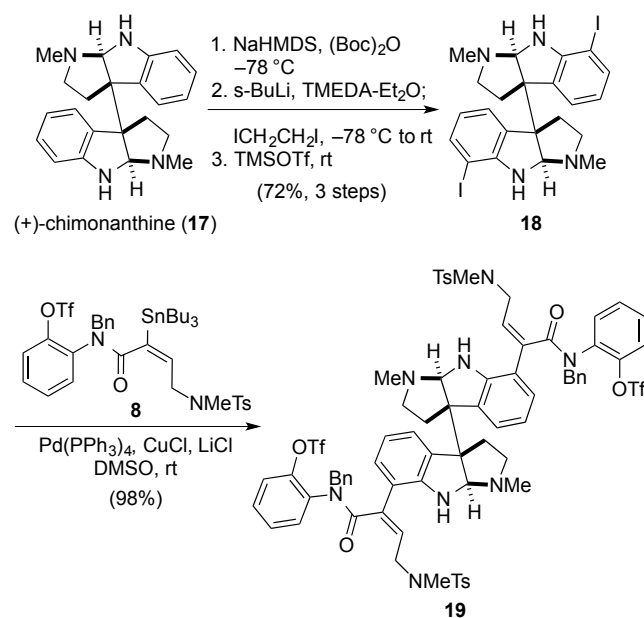


Scheme 4. Completion of an optimized total synthesis of quadrigemine C.

The improvements made in this second generation synthesis of (-)-quadrigemine C shortened the synthetic sequence to 10 steps and provided (-)-quadrigemine C (**1**), [α]_D²³ -67 ($c = 0.2$, CHCl₃) and [α]_D²³ -30 ($c = 0.2$, EtOH), in 2.2% overall yield from tryptamine. Synthetic (-)-quadrigemine C showed physical properties (¹H NMR, ¹³C 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 ¹³C NMR spectra identical to those reported for the natural product.^{9a-c} Using the optimized procedures described herein, *ent*-(+)-quadrigemine C (**2**), [α]_D²³ +70 ($c = 0.12$, CHCl₃) and [α]_D²³ +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

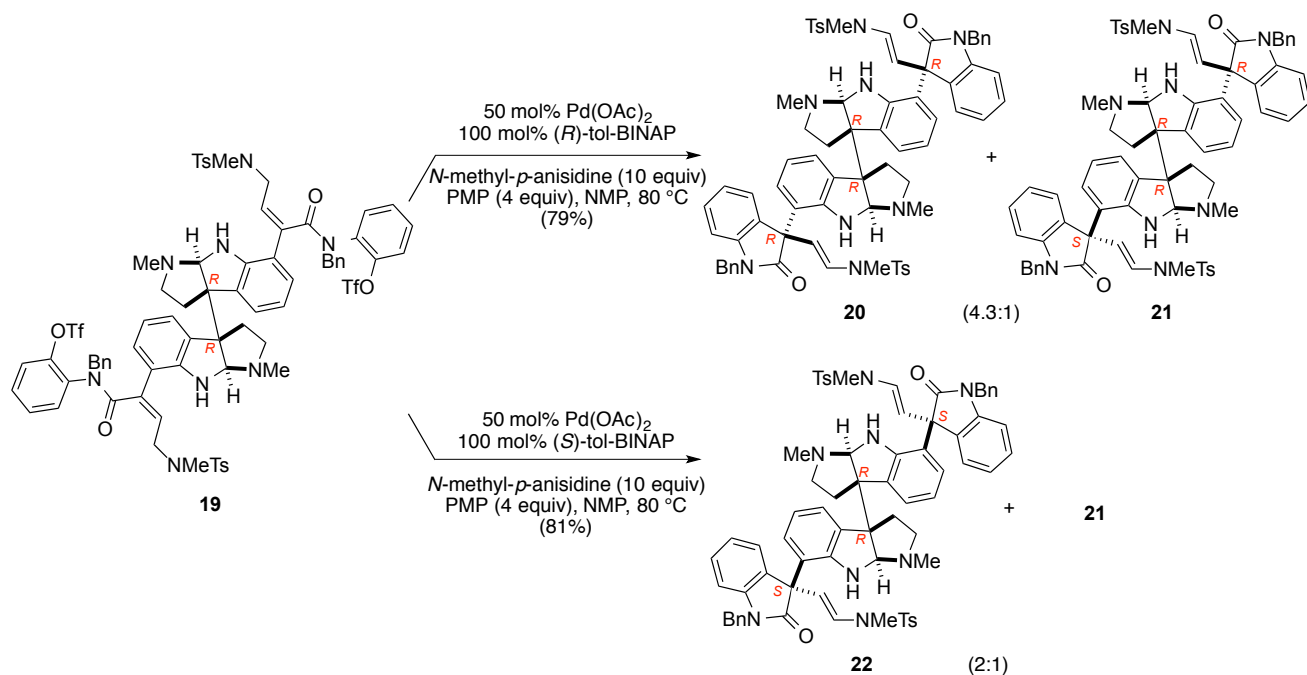
The starting material for our studies in this series was (+)-chimonanthine (**17**), which we prepared in gram quantities from α -methoxycarbonyl-L-tryptophan methyl ester using the 8-step biomimetic sequence developed by Movassaghi and co-workers.^{14c} The necessary C_2 -symmetric diiodide **18** was synthesized, as previously optimized in the *meso*-chimonanthine 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.



Scheme 5. Synthesis of the Heck cyclization precursor in the C_2 -symmetric series.

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 Ac₂O 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 were separated by silica gel chromatography and subsequently processed independently to their respective [2+2] quadrigemines.



Scheme 6. Diastereoselective double Heck cyclization of C_2 -symmetric dibutenanalide **19**.

Table 2. Diastereoselective double Heck cyclization in the C_2 -symmetric series.

Entry	Conditions ^a	Solvent	ds ratio (20:21 ; $C_2:C_1$) ^b
1	<i>rac</i> -tol-BINAP	NMP	1.0:2.3
2	(<i>R</i>)-tol-BINAP	NMP	4.3:1.0
3	(<i>R</i>)-tol-BINAP	MeCN	3.0:1.0
4	(<i>R</i>)-tol-BINAP	THF	2.5:1.0
5	(<i>R</i>)-tol-BINAP	PhMe	1.0:2.3

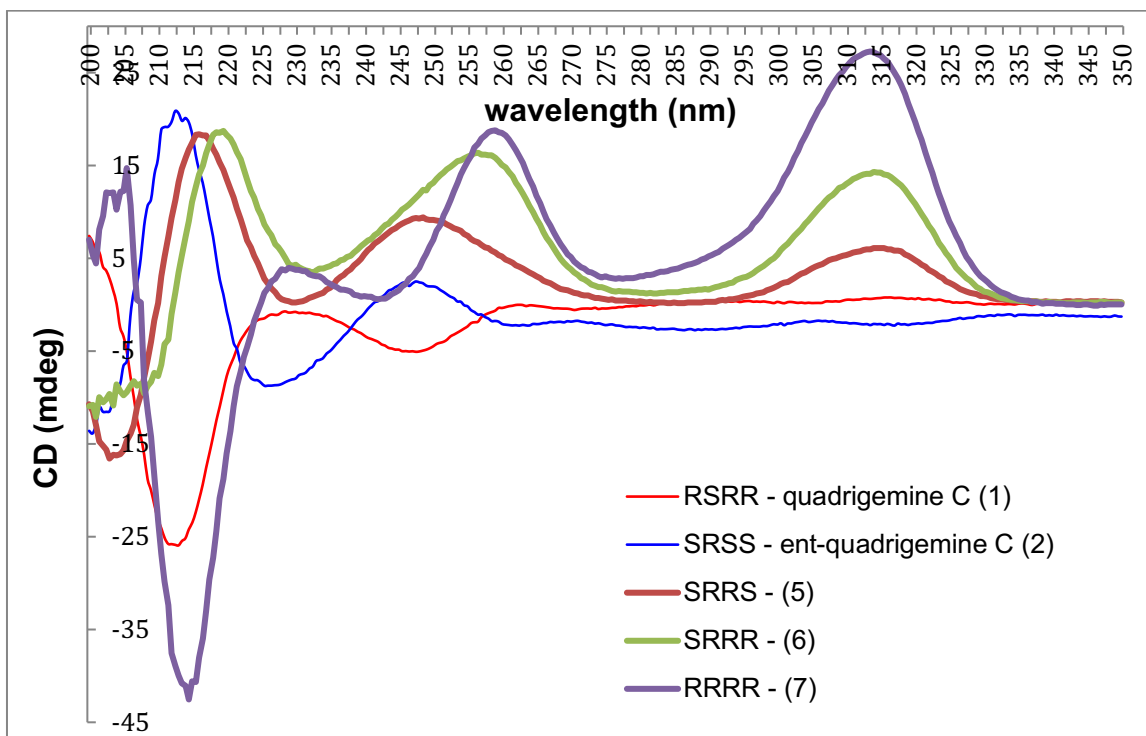
^a 50 mol% Pd(OAc)₂, 100 mol% phosphine ligand, 4.0 equiv 1,2,2,6,6-pentamethylpiperidine (PMP), 80 °C; ^b ratio determined by HPLC

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/NH₃ at –78 °C for 20 min, followed by quenching with NH₄Cl 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.

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 (<i>R,S,R,R</i>)-quadrigemine C	22–24%	–30 (–67) ^b
<i>ent</i> - 12	2 (<i>S,R,S,S</i>)- <i>ent</i> -quadrigemine C	24%	+20 (+70) ^b
13	major <i>meso</i> -quadrigemine ^{c,e}	40%	–
14	minor <i>meso</i> -quadrigemine ^{d,e}	16%	–
20	7 (<i>R,R,R,R</i>)	23%	+277
21	6 (<i>S,R,R,R</i>)	29%	+140
22	5 (<i>S,R,R,S</i>)	29%	+231

^a $[\alpha]_D$ taken in EtOH. ^b $[\alpha]_D$ taken in CHCl₃. ^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**.



^a all data taken $\sim 2.9 \times 10^{-4}$ M in EtOH

Figure 4. Circular dichroism of [2+2] quadrigemines^a

The optical rotation data and ^{13}C NMR spectra for the synthetic quadrigemines **5–7** confirm that these C_2 -symmetric [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 somatostatin 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 polypyrrolidindoline alkaloids and their antitumor activity, the *in vitro* cytotoxicities of the [2+2] quadrigemines prepared in this study, and several additional polypyrrolidindoline

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

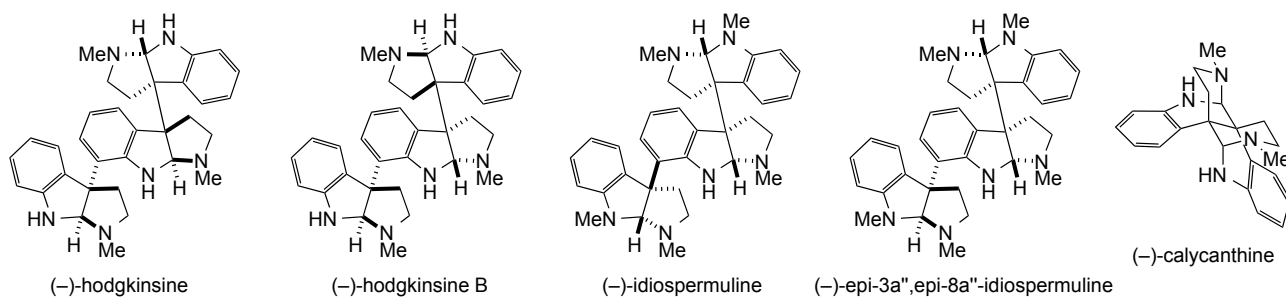


Figure 5: Additional pyrrolidinoindoline alkaloids.

Table 4. Cytotoxic activity against prostate cancer (DU145) and melanoma (A2508) cell lines (IC₅₀).^a

Entry	Compound	DU145	A2058
1	(–)-quadrigemine C (1)	2.2 μM	1.7 μM
2	<i>meso</i> -quadrigemine ^{a,c}	4 μM	5 μM
3	<i>meso</i> -quadrigemine ^{b,c}	>10 μM	>10 μM
4	(<i>S,R,R,S</i>)-quadrigemine (5)	8.8 μM	4.1 μM
5	(<i>S,R,R,R</i>)-quadrigemine (6)	4.7 μM	3.5 μM
6	(<i>R,R,R,R</i>)-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	(–)- <i>epi</i> -idiospermuline	>10 μM	>10 μM
12	<i>meso</i> -chimonanthine (9)	>10 μM	>10 μM
13	(–)-chimonanthine (<i>ent</i> - 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**.

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 strategies²³ and the utility of catalytic enantioselective transformations—in this case intramolecular Heck reactions¹³—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 A⁵ and E¹⁰ 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 x 6 mL). The mixture was placed under vacuum (1.0 mmHg) for 30 min and then pumped into an inert atmosphere (N₂) drybox. A stirbar followed by Pd(PPh₃)₄⁴⁴ (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 NH₄OH (20 mL) and EtOAc (30 mL) and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed consecutively with water and brine. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The dark residue was purified by flash column chromatography (10 %KF/SiO₂⁴⁵ 100% CH₂Cl₂ → 10:1 CH₂Cl₂/MeOH; product **11** (635 mg, 96%) elutes with 3–5% MeOH in CH₂Cl₂ as a brown foam, which showed ¹H and ¹³C 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 x 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 N₂ (3 x). Dry MeCN (2 mL) and 1,2,2,6,6-pentamethylpiperidine⁵⁰ (73 μL, 0.40 mmol) were added and the reaction mixture was degassed using the freeze–pump–thaw technique (3 cycles, liquid N₂ cooling bath, 0.1 mmHg, backfill with N₂). 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 x 20 mL). The combined organic layers were washed with water and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂: 100:0 CH₂Cl₂ → 97:3 CH₂Cl₂/MeOH → 94:5:1 CH₂Cl₂/MeOH/NH₄OH → 89:10:1 CH₂Cl₂/MeOH/NH₄OH) 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 x 21.2 mm), 80:20 MeCN-H₂O (1% NH₄OH), 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 $[\alpha]_D^{28} -60$, $[\alpha]_{577}^{28} -62$, $[\alpha]_{546}^{28} -72$, $[\alpha]_{435}^{28} -153$, $[\alpha]_{405}^{28} -207$ ($c = 0.25$, CH₂Cl₂).

Major *meso*-isomer **13**. ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 (CH₂), 42.8 (CH₂), 36.0 (CH₂), 33.8 (CH₃), 31.9 (CH₃), 20.2 (CH₃); IR (thin film) 3358, 2934, 1706, 1610, 1467, 1355, 1162, 745 cm⁻¹; LRMS-ESI (m/z) [M + H]⁺ calcd for C₇₂H₇₀N₈O₆S₂H 1207.5; found, 1207.5.

Minor *meso*-isomer **14**. ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 (CH₂), 42.8 (CH₂), 36.0 (CH₃), 33.8 (CH₂), 31.8 (CH₃), 20.3 (CH₃); IR (thin film) 3405, 2934, 1710, 1610, 1455, 1359, 1162, 748 cm⁻¹; LRMS-ESI (m/z) [M + H]⁺ calcd for C₇₂H₇₀N₈O₆S₂H 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%): ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 (CH₂), 50.97 (CH₂), 42.8 (CH₂), 42.7 (CH₂), 35.8 (br, 2 peaks, CH₂), 34.3 (CH₃), 33.8 (CH₃), 31.79 (CH₃), 31.75 (CH₃), 20.25 (CH₃), 20.23 (CH₃); IR (thin film) 3354, 2930, 1710, 1610, 1359, 1162, 745 cm⁻¹; LRMS-ESI (*m/z*) [M + H]⁺ calcd for C₇₂H₇₀N₈O₆S₂H 1207.5; found, 1207.5; [α]²³_D +68, [α]²³₅₇₇ +69, [α]²³₅₄₆ +79, [α]²³₄₃₅ +157 (*c* = 0.33, CH₂Cl₂).

(–)-Quadrigimine C (**1**). The procedure for hydrogenation of the enesulfonamide side chains and reductive cyclization for the ultimate conversion of tetrahydro intermediate to (–)-quadrigimine C that is reported herein (see the optimized general procedures described for the preparation of (*R,R,R,R*)-quadrigimine **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: [α]²⁸_D –144, [α]²⁸₅₇₇ –154, [α]²⁸₅₄₆ –177, [α]²⁸₄₃₅ –369, [α]²⁸₄₀₅ –492 (*c* = 0.10, CH₂Cl₂). Reduction of this intermediate with Na/NH₃/*t*-BuOH gave (–)-quadrigimine (C) (8.3 mg, 24% overall yield from **12**), [α]²³_D –67

($c = 0.2$, CHCl_3), HRMS-ESI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{44}\text{H}_{50}\text{N}_8\text{H}$ 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*-(+)-quadrigimine C (**2**) (14 mg, 24%); IR (thin film) 3271, 3054, 2929, 2854, 2791, 1604, 1481, 1452 cm^{-1} ; HRMS-ESI (m/z) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{44}\text{H}_{50}\text{N}_8\text{H}$ 691.4236; found, 691.4226; $[\alpha]^{23}_{\text{D}} +20$, $[\alpha]^{23}_{577} +17$, $[\alpha]^{23}_{546} +18$, $[\alpha]^{23}_{435} +48$ ($c = 0.15$, EtOH); $[\alpha]^{23}_{\text{D}} +70$, $[\alpha]^{23}_{577} +67$, $[\alpha]^{23}_{546} +60$, $[\alpha]^{23}_{435} +110$ ($c = 0.12$, CHCl_3).

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

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**. ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$, 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, $(\text{CD}_3)_2\text{SO}$, 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) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{72}\text{H}_{74}\text{N}_8\text{O}_6\text{S}_2\text{H}$ 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**. ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 (CH₂), 50.9 (C), 45.4 (CH₂), 42.8 (CH₂), 35.3 (CH₂), 34.3 (CH₃), 33.9 (CH₃), 30.6 (CH₂), 20.0 (CH₃); IR (thin film) 3328, 3060, 2926, 2851, 2789, 1695, 1611, 1488, 1466, 1343 cm⁻¹; LRMS-ESI (*m/z*) [M + H]⁺ calcd for C₇₂H₇₄N₈O₆S₂H 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 x 21.2 mm, 80:20 MeOH-H₂O (1% NH₄OH), 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.**) (*t*_r = 9.7 min) as a colorless solid. ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 (CH₂), 48.0 (CH₂), 37.7 (CH₂), 37.2 (CH₂), 28.2 (CH₃), 22.9 (CH₃); IR (thin film) 3365, 2923, 2851 1658, 1605, 1451, 1247, 1158, 1035, 744 cm⁻¹; HRMS-ESI (*m/z*) [M + H]⁺ calcd for C₄₄H₅₀N₈H 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 x 21.2 mm, 80:20 MeOH-H₂O (1% NH₄OH), 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. ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 (CH₂), 37.8 (CH₂), 36.3 (CH₂), 34.8 (CH₃), 34.3 (CH₃); HRMS-ESI (m/z) [M + H]⁺ calcd for C₄₄H₅₀N₈H 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 C₄₄H₅₀N₈H 691.4236; found, 691.4237.

4.3 Enantioselective total synthesis of [2+2] quadrigemines having a C₂-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 (Boc₂O) (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 NH₄Cl (50 mL) and EtOAc (50 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄, 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%): ^1H NMR (600 MHz, $(\text{CD}_3)_2\text{SO}$, 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, $(\text{CD}_3)_2\text{SO}$, 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 (CH₂), 37.6 (CH₃), 34.4 (CH₂), 28.5 (CH₃); IR (thin film): 2974, 2942, 2793, 1696, 1483, 1384, 1366, 1164 cm^{-1} ; HRMS-ESI (m/z) [$\text{M} + \text{H}$]⁺ calcd for $\text{C}_{32}\text{H}_{42}\text{O}_4\text{N}_4\text{H}$ 547.3284; found, 547.3267; $[\alpha]_{\text{D}}^{23} +163$, $[\alpha]_{577}^{23} +168$, $[\alpha]_{546}^{23} +191$, $[\alpha]_{435}^{23} +355$ ($c = 0.66$, 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*]indoly]-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'*-tetramethylethylenediamine⁴⁷ (TMEDA) (4.55 mL, 30.1 mmol) and Et₂O (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 Et₂O (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 Na₂S₂O₄ (50 mL), saturated aqueous NaHCO₃ (50 mL), and EtOAc (50 mL). The phases were separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (100 mL) dried over MgSO₄, 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%): ^1H NMR (600 MHz, $(\text{CD}_3)_2\text{SO}$, 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, $(\text{CD}_3)_2\text{SO}$, 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 (CH₂), 36.4 (CH₃), 35.7 (CH₂), 28.4 (CH₃); 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 $\text{C}_{32}\text{H}_{40}\text{N}_4\text{O}_4\text{I}_2\text{H}$ 799.1218; found, 799.1224; [α]²³_D +186, [α]²³₅₇₇ +195, [α]²³₅₄₆ +225, [α]²³₄₃₅ +399, [α]²³₄₀₅ 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 x 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 $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{Et}_3\text{N}$) to yield **18** as a pale yellow foam (3.28 g, 99%): ¹H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$, 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); ¹³C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$, 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 $\text{C}_{22}\text{H}_{24}\text{N}_4\text{I}_2\text{H}$ 599.0168; found, 599.0167; mp = 193–195 °C; [α]²³_D +363, [α]²³₅₇₇ +383, [α]²³₅₄₆ +445, [α]²³₄₃₅ +909, [α]²³₄₀₅ +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 x 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 $\text{Pd}(\text{PPh}_3)_4$ 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 x 30 mL). The combined organic layers were washed with water (3 x 100 mL) followed by brine (1 x 100 mL). The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The black residue was purified by flash column chromatography (10%KF/SiO₂⁴⁵: 100:0 CH₂Cl₂ → 98:2 CH₂Cl₂/MeOH 94:5:1 → CH₂Cl₂/MeOH/NH₄OH → 88:10:2 CH₂Cl₂/MeOH/NH₄OH) to provide **19** (0.741g, 98%) as a brown foam: ¹H NMR (500 MHz, CDCl₃) δ complex due to the presence of multiple conformations on the NMR time-scale, see copy of spectra; ¹³C NMR (125 MHz, CDCl₃) 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; ¹⁹F NMR (376 MHz, CDCl₃) -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 C₇₄H₇₂N₈F₆O₁₂S₄H 1507.4; found, 1507.4; [α]²³_D +158, [α]²³₅₇₇ +167, [α]²³₅₄₆ +192, [α]²³₄₃₅ +433, [α]²³₄₀₅ 403 (*c* = 0.46, CH₂Cl₂).

Double enantioselective Heck cyclization of (*R,R*)-Dibutenanalide **19**. Ditriflate **19** (0.200 g, 0.133 mmol) was azeotroped in benzene (3 x 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 N₂ (3 times). The mixture was then suspended in 1-methyl-2-pyrrolidinone (4.4 mL)⁴⁹ and 1,2,2,6,6-pentamethylpiperidine⁵⁰ (97 μL, 0.53 mmol). The reaction mixture was degassed using the freeze-pump-thaw technique (3 cycles, liquid N₂ cooling bath, 0.1 mmHg, backfill with N₂). 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 x 20 mL). The combined organic layers were washed with water (3 x 40 mL) followed by brine (1 x 20 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂: 100:0 CH₂Cl₂ → 97:3 CH₂Cl₂/MeOH → 94:5:1 CH₂Cl₂/MeOH/NH₄OH → 89:10:1 CH₂Cl₂/MeOH/NH₄OH) 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**: ¹H NMR (500 MHz,

(CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 (CH₂), 42.5 (CH₂), 34.9 (CH₂), 34.5 (CH₃), 31.8 (CH₃), 20.2 (CH₃); 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 C₇₂H₇₀N₈O₆S₂H 1207.4938; found, 1207.4950; [α]_D²³ +28, [α]₅₇₇²³ +29, [α]₅₄₆²³ +34, [α]₄₃₅²³ +74 (c = 1.6, CH₂Cl₂). (*S,R,R,R*)-Dioxindole **21**: ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 (CH₂), 50.3 (CH₂), 42.8 (CH₂), 42.6 (CH₂), 35.2 (CH₂), 35.1 (CH₂), 34.5 (CH₃), 34.3 (CH₃), 31.84 (CH₃), 31.78 (CH₃), 20.27 (CH₃),

20.24 (CH₃); IR (thin film) 3378, 3060, 2857, 2790, 1703, 1609, 1465, 1356, 1159, 742 cm⁻¹; LRMS-ESI (*m/z*) [M + H]⁺ calcd for C₇₂H₇₀N₈O₆S₂H 1207.5; found, 1207.5; [α]²³_D +116, [α]²³₅₇₇ +121, [α]²³₅₄₆ +142, [α]²³₄₃₅ +298, [α]²³₄₀₅ +276 (*c* = 0.80, CH₂Cl₂).

Following the same procedure utilizing (*S*)-tol-BINAP instead of (*R*)-tol-BINAP, dibutenanilide **19** (0.282 mg, 0.187 mmol) was converted into C₂-symmetric dioxindole product **22** and C₁-symmetric isomer **21**. These products were purified by column chromatography (SiO₂: 100:0 CHCl₃ → 98:2 CHCl₃/MeOH → 94:3:1 CHCl₃/MeOH/NH₄OH → 94:5:1 CHCl₃/MeOH/NH₄OH) to elute first C₂-symmetric **22** (123 mg, 55%) followed by C₁-symmetric **21** (87.0 mg, 39%) as tan foams. (*S,R,R,S*)-dioxindole **22**: ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 (CH₂), 42.8 (CH₂), 35.3 (CH₂), 34.2 (CH₃), 31.8 (CH₃), 20.3 (CH₃); 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 C₇₂H₇₀N₈O₆S₂H 1207.5; found, 1207.5; [α]²³_D +147, [α]²³₅₇₇ +156, [α]²³₅₄₆ +184, [α]²³₄₃₅ +379, [α]²³₄₀₅ +201 (*c* = 0.81, CH₂Cl₂).

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 %), K₂CO₃ (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 CHCl₃ saturated with NH₃ (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 (SiO₂: 100:0 CH₂Cl₂ → 97:3 CH₂Cl₂/MeOH → 94:5:1 CH₂Cl₂/MeOH/NH₄OH → 89:10:1 CH₂Cl₂/MeOH/NH₄OH) to provide 121 mg (96%) of **21** as a colorless foam: ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 (CH₂), 45.5 (CH₂), 42.5 (CH₂), 34.7 (CH₂), 34.6 (CH₂), 33.9 (CH₃), 30.0 (CH₃), 20.0 (CH₃); IR (thin film) cm⁻¹; 3334, 3060, 3031, 2857, 2788, 1695, 1611 cm⁻¹; HRMS-ESI (*m/z*) [*M* + *H*]⁺ calcd for C₇₂H₇₄N₈O₆S₂H 1211.5251; found, 1211.5251; [α]²³_D -40, [α]²³₅₇₇ -43, [α]²³₅₄₆ -51, [α]²³₄₃₅ -102, [α]²³₄₀₅ -121 (*c* = 1.5, CH₂Cl₂).

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**: ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 (CH₂), 45.2 (CH₂), 42.9 (CH₂), 35.0 (CH₃), 34.8 (CH₃), 33.9 (CH₂), 31.5 (CH₂), 20.0 (CH₃); IR (thin film) 3320, 3057, 3033, 2851, 2790, 1692, 1610 cm⁻¹; LRMS-ESI (*m/z*) [M + H]⁺ calcd for C₇₂H₇₄N₈O₆S₂H 1211.5; found, 1211.5; [α]²³_D +254, [α]²³₅₇₇ +269, [α]²³₅₄₆ +312, [α]²³₄₃₅ +625 (*c* = 1.1, CH₂Cl₂).

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**: ¹H NMR (500 MHz, (CD₃)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); ¹³C NMR (125 MHz, (CD₃)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 (CH₂), 50.3 (CH₂), 45.4 (CH₂), 45.2 (CH₂), 42.9 (CH₂), 42.8 (CH₂), 35.0 (CH₂), 34.9 (CH₂), 34.8 (CH₃), 34.7 (CH₃), 33.92 (CH₃), 33.87 (CH₃), 31.3 (CH₂), 30.6 (CH₂), 20.05 (CH₃), 20.03 (CH₃); IR (thin film) 3334, 3058, 2852, 2789, 1693, 1610 cm⁻¹; LRMS-ESI (*m/z*) [M + H]⁺ calcd for

C₇₂H₇₄N₈O₆S₂H 1211.5; found, 1211.5; [α]_D²³ +148, [α]₅₇₇²³ +155, [α]₅₄₆²³ +180, [α]₄₃₅²³ +360, [α]₄₀₅²³ +410 (*c* = 0.87, CH₂Cl₂).

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

Preparation of (*R,R,R,R*)-quadrigimine **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 NH₃(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 NH₃. *Tert*-butanol (42 μ L, 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 NH₄Cl (~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 CHCl₃ (sat with NH₃; 3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered, concentrated under reduced pressure, and the residue was purified by reverse phase HPLC to yield (*R,R,R,R*)-quadrigimine **7** (8.8 mg, 23% from **20**): Analytical reverse-phase HPLC (Zorbax Extend C18, 250 x 4.6 mm), 72:28→85:15 MeOH-H₂O (1% NH₄OH) over 40 min, 1.0 mL/min, UV detection at 254 nm (*r*_t = 24.8 min); ¹H NMR (500 MHz, (CD₃)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); ¹H NMR (500 MHz, C₆D₆, 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) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{44}\text{H}_{50}\text{N}_8\text{H}$ 691.4236; found, 691.4237; $[\alpha]^{23}_{\text{D}} +277$, $[\alpha]^{23}_{577} +283$, $[\alpha]^{23}_{546} +328$, $[\alpha]^{23}_{435} +656$ ($c = 0.20$, 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 x 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); ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$, 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, $(\text{CD}_3)_2\text{SO}$, 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) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{44}\text{H}_{50}\text{N}_8\text{H}$ 691.4236; found, 691.4223; $[\alpha]^{23}_{\text{D}} +279$, $[\alpha]^{23}_{577} +289$, $[\alpha]^{23}_{546} +332$, $[\alpha]^{23}_{435} +690$ ($c = 0.27$, 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 x 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); ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$, 376K) δ 6.98 (d, $J = 7.1$ Hz, 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, $(\text{CD}_3)_2\text{SO}$, 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) $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{44}\text{H}_{50}\text{N}_8\text{H}$ 691.4236; found, 691.4237; $[\alpha]^{23}_{\text{D}} +347$, $[\alpha]^{23}_{577} +367$, $[\alpha]^{23}_{546} +435$, $[\alpha]^{23}_{435} +854$ ($c = 0.10$, EtOH).

Supplementary Information Available: Copies of ^1H 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.

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²⁵ The relative configuration of the major and minor *meso*-dioxindole products was not possible by spectroscopic means. In addition, we were unsuccessful in crystallizing the two *meso*-quadrigenines that were prepared from these dioxindole intermediates. As a result, the relative configuration of these two products (*i.e.*, which is **3** and which is **4**) is unknown.

²⁶ Conditions: 10 mol% Pd(OAc)₂, 20 mol% (*R*)-tol-BINAP, 4.0 equiv PMP, MeCN at 80 °C.²⁷

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²⁸ Computational model of the lowest energy conformation of (–)-quadrigenine C identified by Monte Carlo conformational searching using the MMMF force field and final optimization by DFT calculation at the EDF2-631G* level. Calculations performed using Spartan 14, Wavefunction, Inc.

²⁹ Hydrogenation catalysts such as Rh/Al₂O₃, Ru/Al₂O₃, Pt₂O, Ir(COD)(PCy₃)PyPF₆, Pd/C, and Pd(OAc)₂ evaluated using a H₂ atmosphere or under transfer hydrogenation conditions were less effective.

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- ³⁴ The origin of the apparent discrepancy between the levorotatory optical rotation in ethanol that we observe for *ent*-quadrigemine C, $[\alpha]_{23}^D -30$ ($c = 0.2$), and that reported for natural quadrigemine C in methanol, $[\alpha]_D +40$ ($c = 0.2$),^{9d} is unclear, as CD spectra of synthetic quadrigemine C and natural quadrigemine C in methanol under the same conditions are identical.³³ Moreover, we observe $[\alpha]_{23}^D +20$ ($c = 0.2$) for *ent*-quadrigemine C.
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⁴⁸ Prepared as describe by Coulson, D. R. *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 CaH₂.