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Enantioselective synthesis of (−)-idiospermuline

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Dedicated to Professor K. C. Nicolaou in recognition of his award of the 2003 Tetrahedron Prize

Abstract—The enantioselective total synthesis of the nonacyclic polypyrrolidinoindoline (−)-idiospermuline is described. Stereocontrolled formation of the vicinal quaternary carbon centers is achieved in a single step by dialkylation of an unsymmetrical prostereogenic dienolate with a tartrate-derived chiral dielectrophile. A catalyst-controlled diastereoselective Heck cyclization is employed to form the diaryl-substituted quaternary center.

1. Introduction

Polypyrrolidinoindoline alkaloids are isolated from a wide variety of natural sources including bacteria, fungi and higher plants such as shrubs and trees.[1] Characterized by the linkage of cyclotryptamine subunits through quaternary carbon centers, members of this alkaloid class are characterized by two general structural motifs. The first, seen in *meso*-chimonanthine (**1**) and its C_2-symmetric stereoisomer (−)-chimonanthine (**2**), is a 3a,3a′-bispyrrolidinoindoline moiety linking the benzylic quaternary stereocenters of two pyrrolidinoindoline fragments (Fig. 1). The second, present in higher order members of this alkaloid family, is a 3a,7-bispyrrolidinoindoline unit joining the C7 *peri* position of one pyrrolidinoindoline unit and the benzylic quaternary stereocenter of another. This latter motif is found in quadrigemine C (**3**),[2] idiospermuline (**4**), and numerous other higher order polypyrrolidinoindoline alkaloids.[3] Members of this alkaloid family containing up to eight linked pyrrolidinoindoline fragments have been described.[1] Relative and absolute configuration is known for only the chimonanthines,[1] and some members of the tris-[3,4] and tetrapyrrolidinoindoline groups.[5–7]

Idiospermuline (**4**) was isolated by Duke and co-workers from the seed of *Idiospermum australiense*, a rare tree found in lowland rain forests of North Queensland, Australia.[3] This alkaloid was identified in a search for naturally occurring substances acting on neurochemical transmission. Idiospermuline was subsequently characterized as a μM cholinergic antagonist.[3] Idiospermuline (**4**) is one of the few members of the polypyrrolidinoindoline family whose absolute and relative configuration has been established by single-crystal X-ray crystallography. The C_2-symmetric (−)-chimonanthine moiety embedded within idiospermuline (**4**) is desymmetrized by both the attachment of a third pyrrolidinoindoline subunit at C7′ and the unsymmetrical methyl substitution of its indoline nitrogens. This latter feature is extremely rare in the polypyrrolidinoindoline alkaloids.[1]

As part of ongoing studies aimed at developing chemistry to allow diverse members of the polypyrrolidinoindoline alkaloids to be prepared by stereorational chemical synthesis, we undertook the total synthesis of idiospermuline (**4**). Full details of our successful enantioselective total synthesis of this trispyrrolidinoindoline alkaloid are recorded herein.[8]

2. Results and discussion

2.1. Synthesis plan

Our plan for preparing idiospermuline (**4**) drew heavily on chemistry recently developed to prepare quadrigemine C (**3**) and psycholeine.[5] Disconnection of the pyrrolidine ring of the C7′-linked pyrrolidinoindoline fragment of **4** leads to octacyclic oxindole **5** (Scheme 1). In the first key disconnection, the 3a″ diaryl-substituted quaternary stereocenter of **5** was seen as arising from catalyst-controlled[9] diastereoselective Heck cyclization of (*Z*)-butenanilide **6**. This latter intermediate would logically derive from Stille coupling of bispyrrolidinoindoline iodide **7** and α-stannyl (*E*)-butenanilide **8**.

A major challenge in the synthesis of **4** would be enantioselective preparation of (−)-chimonanthine congener

Keywords: cyclotryptamine alkaloids; dialkylation; Heck cyclization; vicinal quaternary centers.

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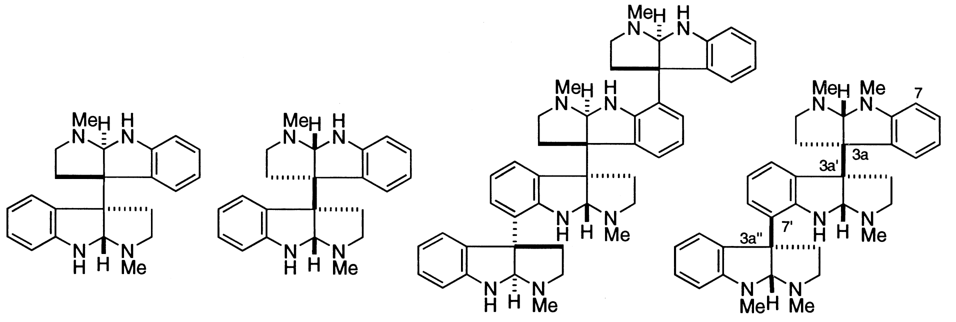
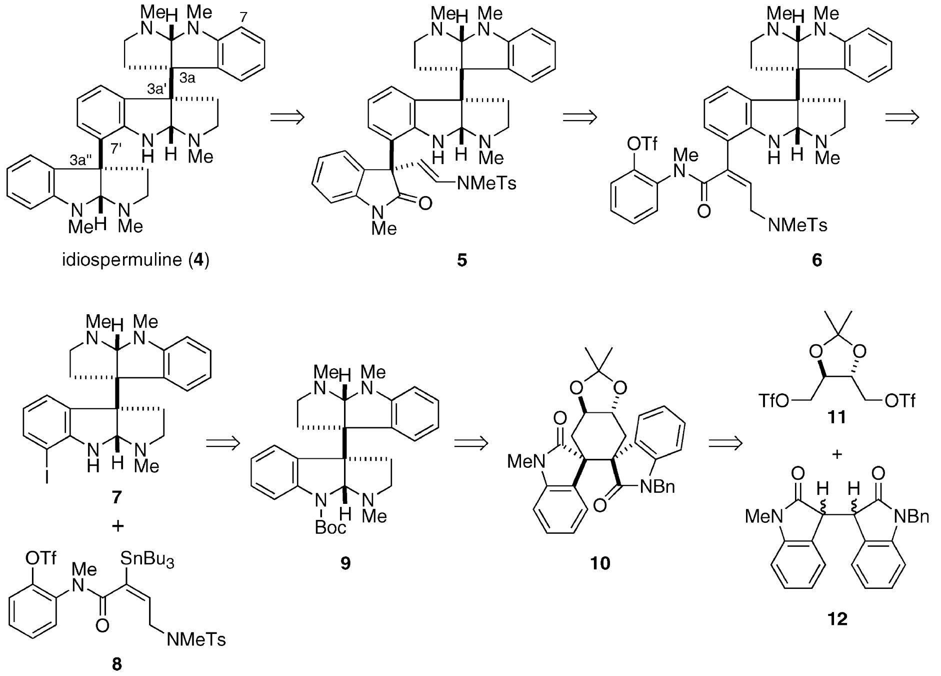


Figure 1. Representative cyclotryptamine alkaloids.

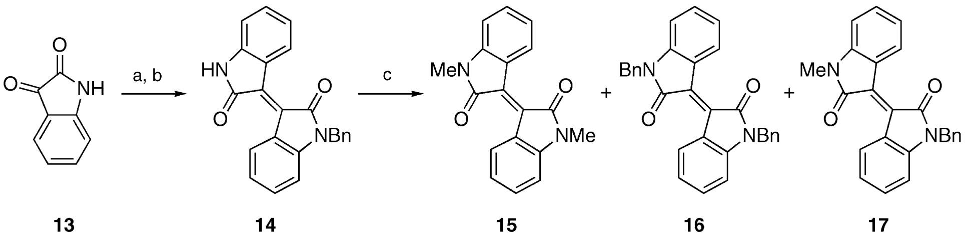


Scheme 1. Retrosynthesis.

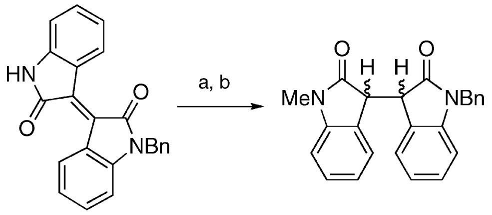
7, an intermediate having both an unsymmetrical methylation pattern and functionality at the *peri* position of only its mono-methylated pyrrolidinoindoline unit. The C7′ iodide of **7** should be available by Boc-directed *ortho*-lithiation[10] of bispyrrolidinoindoline carbamate **9**. This latter intermediate, with its indoline nitrogens differentially functionalized, was seen arising from the hexacyclic *trans*-spirooxindole **10**.[11] In the second key disconnection, **10** would arise by diastereoselective dialkylation of a dienolate derivative of dihydroisoindigo **12** and (*S*)-tartrate-derived ditriflate **11**.[11,12] In this plan, the different substituents on the indoline nitrogens of **9** would arise from the unsymmetrical functionalization of dihydroisoindigo **12**, this latter feature being easily incorporated in the assembly of **12** from isatin and oxindole precursors.

2.2. Preparation of bispyrrolidinoindoline iodide 7

The synthesis of idiospermuline (**4**) began by benzylation of isatin (**13**), followed by condensation of *N*-benzylisatin with oxindole to give mono-protected isoindigo **14** in 75% overall yield (Scheme 2). Methylation of the free oxindole



Scheme 2. *Reaction conditions*: (a) NaH, BnBr, DMF, rt; (b) oxindole, HOAc, HCl, 110°C, (75%, 2 steps); (c) NaH, MeI, DMF, rt.



14 **12**

Scheme 3. *Reaction conditions*: (a) Cs_2CO_3, MeI, DMF, rt; (b) PtO_2, H_2, EtOAc, rt (85%, 2 steps).

nitrogen of **14** initially proved problematic. When this intermediate was exposed to excess MeI and 1.5 equiv. of NaH in DMF at 25°C, a 1:1:2 mixture of isoindigos **15**, **16**, and **17** resulted. We hypothesized that adventitious hydroxide was initiating a retro-aldol/aldol sequence that scrambled the isoindigo products.

To test this hypothesis, symmetrically-protected isoindigos **15** and **16** were synthesized and crossover experiments were performed. These experiments showed that **17** was produced when an equimolar mixture of isoindigos **15** or **16** was treated in DMF with either NaH or NaOH (2 equiv. of base at 25°C in each case). This retro-aldol/aldol scrambling could be prevented by the use of rigorously dried DMF and dry Cs_2CO_3 as the base (Scheme 3). Subsequent catalytic hydrogenation of **17** over PtO_2 provided dihydroisoindigo **12** in 85% overall yield for the 2 steps.

With dihydroisoindigo **12** in hand, diastereoselective dialkylation to form the 3a,3a$'$ vicinal quaternary stereocenters of idiospermuline (**4**) was explored. Previous investigations in our laboratories had shown that the union of prostereogenic bisoxindole dienolates with chiral dielectrophile **11** could efficiently construct contiguous stereogenic quaternary carbon centers. For example, in the synthesis of (+)-chimonanthine, reaction of the LHMDS-derived dienolate of **18** with ditriflate *ent*-**11** in a 9:1 mixture of THF–DMPU at −40°C generated the enantiopure C_2-symmetric product **19** in 55% yield (Scheme 4).[11] However, a preliminary investigation had shown that stereoselection in this reaction was lower when the indoline nitrogens of the dienolate nucleophile were protected with hexyl or cyclohexylmethyl substituents.[13] Whether the *N*-methyl substituent of **12** would lead to an erosion in stereoselection in its union with ditriflate **11** was a pivotal issue to be addressed early in our idiospermuline synthesis endeavor.

Dialkylation of dienolate **20** (derived from unsymmetrical dihydroisoindigo **12**) with ditriflate **11** could generate four different bis-spirooxindole products, **10**, **25**, **26** and **27** (Scheme 5). Preferential formation of the desired *trans* stereoisomer **10** in this union would require two elements of stereocontrol: facial selectivity in the initial alkylation step, and the absence of chelate organization in the subsequent intramolecular alkylation step. Specifically, the bimolecular alkylation must occur from the *Re* face of the dienolate to generate **23** and **24**. However, chemoselectivity in this step would not be required, as both **23** and **24** would evolve to **10** if the second alkylation event occurred with the enolate oxygen and oxindole carbonyl groups oriented away from each other as depicted in Scheme 5.

Salient results of our study of this pivotal dialkylation of dihydroisoindigo **12** with ditriflate **11** are summarized in Table 1. Dialkylation of the LHMDS-derived dienolate of **12** with ditriflate **11** in a 7:3 mixture of THF–HMPA at −40°C, conditions found optimal in an earlier study of dialkylation of related symmetrical dienolates,[13†] delivered **10** in low yield albeit it with good stereoselectivity (Table 1, entry 1). Several reaction variables were investigated to maximize yield of **10**. The best solvents were found to be THF and DME, however, reproducibility was better in THF (Table 1, entries 2–5). Variations in reaction temperatures over the range −30 to −50°C were found to have little effect on stereoselection or yield (Table 1, entries 5–7). However, the yield of the desired product **10** was improved significantly by lowering the substrate concentration and HMPA loading (Table 1, entries 7–11). Carrying out the dialkylation at a substrate concentration of 0.05 M in a 9:1 mixture of THF–HMPA at −40°C provided **10** in 75% yield; the other three stereoisomers, **25**, **26**, and **27**, were isolated in 15% combined yield (Table 1, entry 10).[‡] Substituting DMPU for HMPA resulted in a slight decrease in stereoselection and a corresponding decrease in the yield of **10** (Table 1, entry 12).

The configuration of dialkylation products **10**, **25**, **26**, and **27** was secured in the following fashion. Bis-spirooxindole **10** was correlated chemically to the enantiomer of C_2-symmetric *trans*-bis-spirooxindole **19** (see Section 4), whose structure had been secured earlier by single-crystal X-ray analysis.[11] Products **26** and **27** were inseparable by silica gel chromatography; however, their derived diols could be resolved. Reprotection of these products provided pure samples of **26** and **27**. The *cis* orientation of the spirooxindole groups in these two stereoisomers was apparent by analysis of their ^1H NMR spectra. As depicted in Figure 2, the chemical shifts of the acetonide methine hydrogens H_a and H_b of **26** and **27** differ by ~1.3 ppm. This difference in chemical shift is expected in the *cis* stereoisomers, because of the proximity of H_a to the oxindole carbonyl and H_b to the nearby arene ring.[11] In contrast, H_a and H_b have nearly identical environments in *trans* stereoisomer **10** as signaled by the nearly identical chemical shifts of these methine hydrogens. The minor *trans* stereoisomer **25** also exhibits coincident chemical shifts for H_a and H_b.

In the dialkylation experiments summarized in Table 1, the undesired *cis*-spirooxindole products **26** and **27** were always formed in a ~1:1 ratio; in the majority of experiments, only trace amounts of the minor *trans*-spirooxindole product **25** was obtained. These observations can be rationalized in the following way. Initial alkylation of the dienolate of **12** with ditriflate **11** from the *Si* face would generate mono-alkylated

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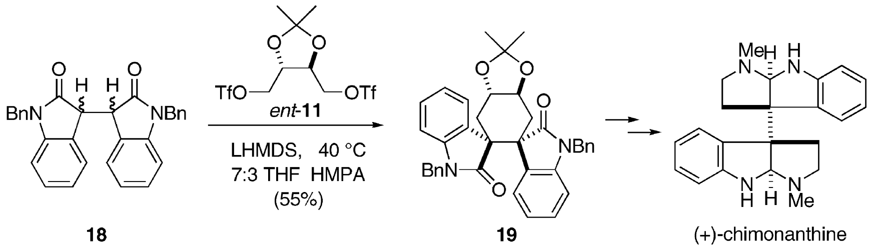
[†] Symmetrical substrates can lead to three possible products, two of which are C_2-symmetric and one C_1-symmetric.

[‡] Dialkylation of *N*,*N*$'$-dibenzyldihydroisoindigo **18** with ditriflate **11** under these conditions provided the corresponding C_2-symmetric product **19** in 80% yield, a notable improvement in efficiency of this previously reported[11] transformation (see Scheme 4).



Scheme 4. Dialkylation of symmetrical *N*,*N*′-bisbenzyldihydroisoindigo **18**.

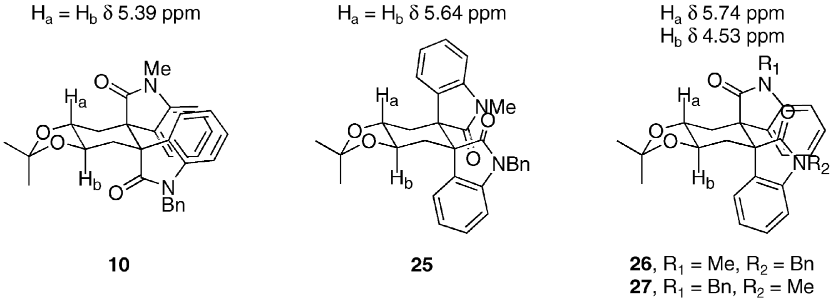
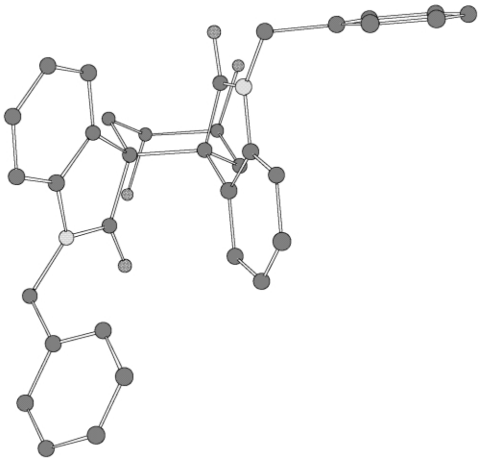


Figure 2. Diagnostic ^1H NMR chemical shifts of dialkylation products **10**, **25**, **26** and **27**.

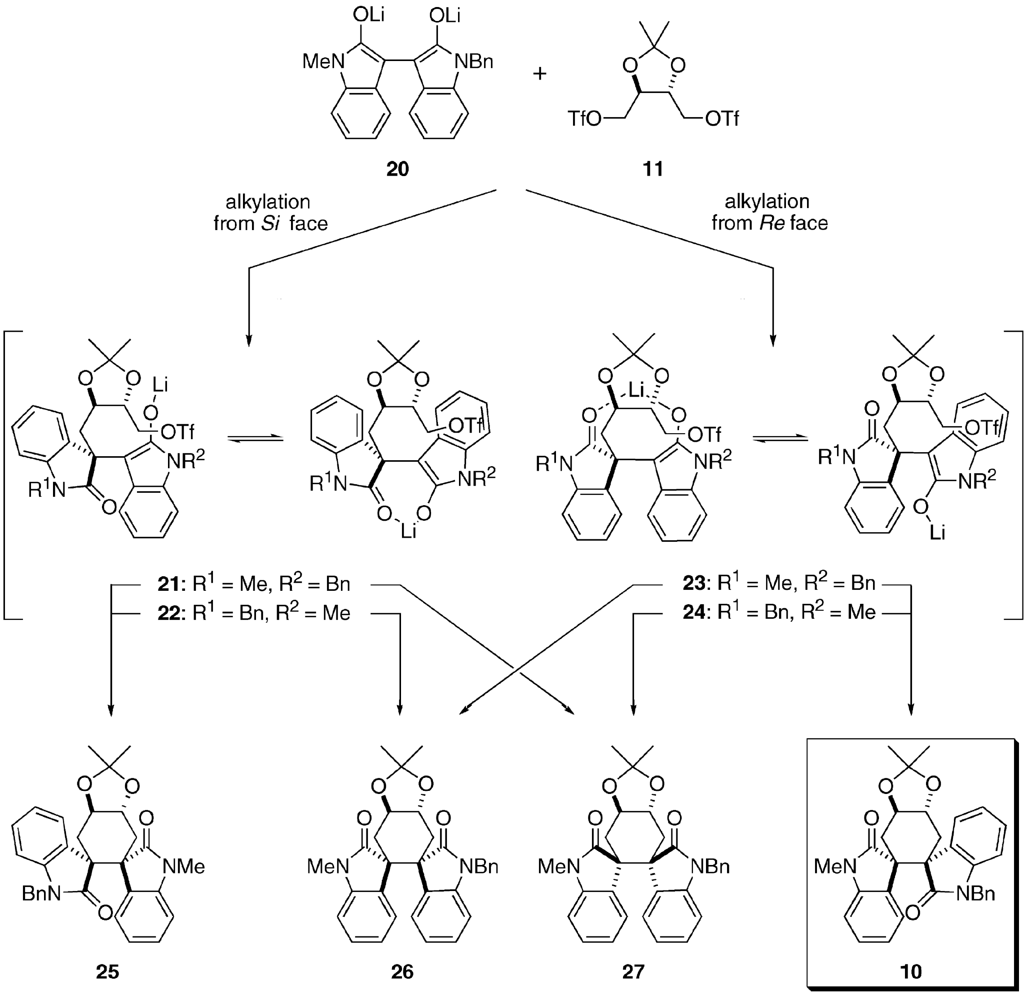
intermediates **21** and **22** (Scheme 5). If the subsequent intramolecular alkylation occurs without chelate organization, *trans*-spirooxindole **25** would be produced. However, this *trans*-spirooxindole isomer would be higher in energy than the other three possible bis-spirooxindole products as both aryl groups of **25** would be axially oriented on the newly formed cyclohexane ring.[§] This destabilizing steric interaction is apparently present to a sufficient extent in the transition state leading to **25** that mono-alkylated intermediates **21** and **22** cyclize preferentially, even in the presence of HMPA, to generate the *cis*-spirooxindole products **26** and **27**. The production of **26** and **27** in nearly equivalent amounts indicates that the closely related nitrogen substituents, methyl and benzyl, have little effect on the site of the initial bimolecular alkylation.

With the vicinal quaternary stereocenters in place, hexacyclic intermediate **10** was elaborated to the differentially protected chiral bispyrrolidinoindoline **9** as summarized in Scheme 6. Removal of the acetonide of **10**, followed by oxidative cleavage of the resulting vicinal diol and immediate reduction of the ensuing dialdehyde with sodium borohydride provided diol **28** in 85% yield over the 3 steps. Reduction of the oxindole[14] carbonyl groups of this intermediate with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®) in refluxing THF triggered in situ condensation to provide the unstable pentacyclic diol **29**. Installation of the nitrogen functionality that would be required to form the outer pyrrolidine rings of **32** was achieved by a double Mitsunobu reaction.[15] This transformation required optimization of a previously employed procedure,[16] because of facile formation of pentacyclic diether **31**. Competitive formation of **31** was minimized by increasing the equivalents of the azide donor and by using a more reactive azide source, HN_3, instead of diphenylphosphoryl azide. In this way, diazide **30** was formed in 75% overall yield from **28**. Staudinger reduction of this diazide and dehydration of the resulting diamine in methanol at 110°C formed the corresponding bispyrrolidinoindoline. Reductive methylation of the pyrrolidine nitrogens of this latter intermediate and subsequent N-debenzylation with Na/NH_3 gave **32** in 75% yield for the 4 steps.



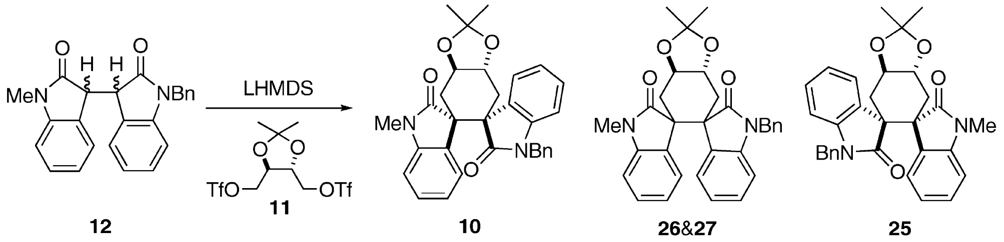
The free indoline nitrogen of bispyrrolidinoindoline **32** was exploited next to introduce iodine selectively at the *peri* position of the mono-methylated pyrrolidinoindoline fragment. Premixing **32** with Boc_2O at −78°C and then slowly adding an excess of NaHMDS followed by quenching at −78°C with saturated aqueous $NaHCO_3$ delivered **9** in 74% yield. Low temperature and slow addition of the base were necessary to prevent alkoxycarbonylation of a pyrrolidine nitrogen, leading ultimately to fragmentation of the 3a,3a′

[§] Single-crystal X-ray analysis shows that the diol derivative of the corresponding isomer in which both nitrogen substituents are benzyl exists in a chair conformation; unpublished studies of J. Larrow



Scheme 5. Intermediates and products potentially generated from dienolate **20** and ditriflate **11**.

Table 1. Optimization of the dialkylation reaction

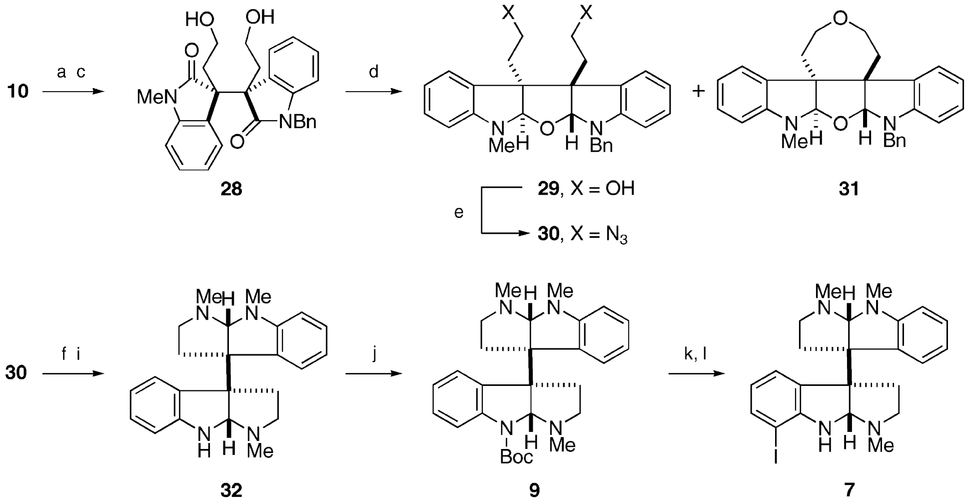


Entry	Solvent	HMPA (%)	Temperature (°C)	Conc. **12** (M)	Ratio[a] **10**:**26** and **27**:**25**	Ratio **10**:**26** and **27**	Yield[a] of **10** (%)
1	THF	42%	−40	0.3	70:7.3:1	9.7:1	55
2	Toluene	30%	−50	0.3	29:14:1	2:1	24[b]
3	Et_2O	30%	−50	0.3	6.6:1.3:1	5:1	12[b]
4	DME	30%	−50	0.3	56:5:1	11:1	18–54
5	THF	30%	−50	0.3	20:3:1	7:1	48
6	THF	30%	−40	0.3	30:3.2:1	7:1	55
7	THF	30%	−30	0.3	33:9:1	3.7:1	46
8	THF	30%	−40	0.05	5:1:2.4	5:1	41
9	THF	20%	−40	0.05	8.6:1.2:1	7:1	45
10	THF	10%	−40	0.05	24:3.5:1	7:1	75[c]
11	THF	5%	−40	0.05	85:10:1	8.5:1	62
12	THF	10% DMPU	−40	0.05	20:5.5:1	3.6:1	51

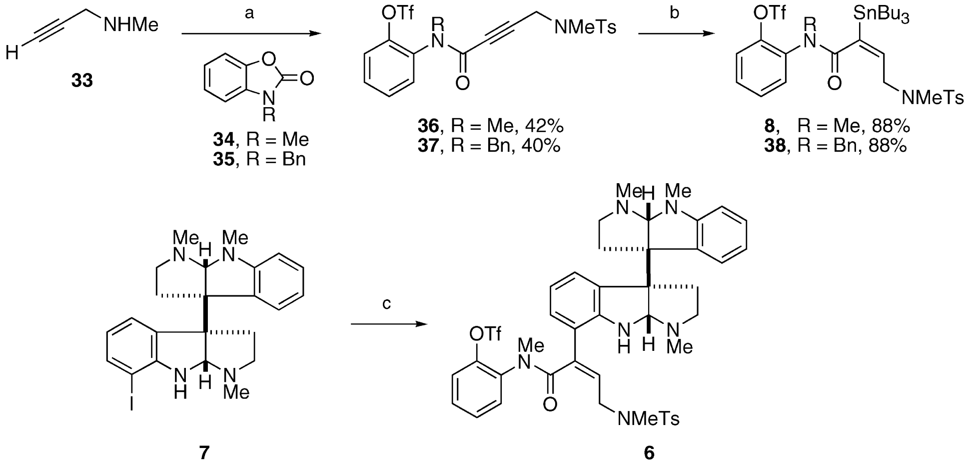
[a] Product ratios and yields determined by ^1H NMR using 3-methylanisole as an internal standard.

[b] Residual starting material was observed in crude reaction mixture.

[c] Isolated yield.



Scheme 6. *Reaction conditions*: (a) CSA, MeOH, CH_2Cl_2, rt; (b) $NaIO_4$, THF, H_2O, rt; (c) $NaBH_4$, MeOH, rt (85%, 3 steps); (d) Red-Al, THF, 67°C; (e) DEAD, PPh_3, HN_3, THF, 0°C (75% from **28**); (f) PPh_3, THF, H_2O; (g) MeOH, 110°C (77%, 2 steps); (h) CH_2O, $NaBH(OAc)_3$; (i) Na, NH_3, THF, −78°C (98%, 2 steps); (j) Boc_2O, NaHMDS, −78°C (74%); (k) (i) TMEDA, *s*BuLi, −78°C; (ii) diiodoethane, −78°C to rt; l) TfOH, CH_2Cl_2 (85%, 2 steps).



Scheme 7. *Reaction conditions*: (a) (i) TMSOTf, *i*-Pr_2NEt, Et_2O, 0°C; (ii) *n*BuLi, −78°C, **34** or **35**; (iii) $PhNTf_2$, −10°C; TsCl, silica gel, rt (42%); (b) $Pd(PPh_3)_4$, Bu_3SnH, THF, 0°C (88%); (c) $Pd_2dba_3·CHCl_3$, P(2-furyl)$_3$, **8**, CuI, NMP, rt (94%).

bond joining the vicinal quaternary carbons. Boc-directed *ortho*-lithiation of **9** with excess *s*BuLi at −78°C, and subsequent quenching of the aryllithium intermediate with an excess of diiodoethane provided, following removal of the Boc group with trifluoromethanesulfonic acid, iodo bispyrrolidinoindoline **7** in 85% yield.[17]

With differentiated bispyrrolidinoindoline **7** now in hand, our attention focused on preparing stannane **8**. For the synthesis of quadridgemine C, analogous stannane **38** was synthesized in 33% yield by a four-step sequence.[5] This sequence proved somewhat less efficient for the production of stannane **8**. As a result, a more convenient two-pot procedure was developed for the synthesis of this intermediate (Scheme 7). Treatment of an ether solution of *N*-methylpropargyl amine (**33**) with TMSOTf and *i*-Pr_2NEt at 0°C, followed by deprotonation of the resulting *N*-silylated alkyne with *n*BuLi at −78°C and sequential addition of *N*-methylbenzoxazolidinone (**34**) and *N*-phenyltriflimide generated the *N*-silyl-protected triflato alkyne amide.[¶] Finally, addition of TsCl and silica gel to the reaction resulted in cleavage of the TMS group and tosylation of the amine to give alkyne amide **36** in 42% yield. Palladium catalyzed hydrostannanylation of **36** generated α-stannyl (*E*)-butenanilide **8** in 88% yield. A similar sequence employing *N*-benzylbenzoxazolidinone (**35**) yielded stannane **38** in similar overall yield. Finally chemoselective palladium catalyzed coupling of stannane **8** with bispyrrolidinoindoline iodide **7**, using conditions we had optimized earlier for related transformations,[5] provided triflato anilide **6** in 94% yield.[18]

With the necessary carbon and nitrogen atoms of the third and final pyrrolidinoindoline subunit of idiospermuline (**4**) installed, our attention focused on diastereoselective

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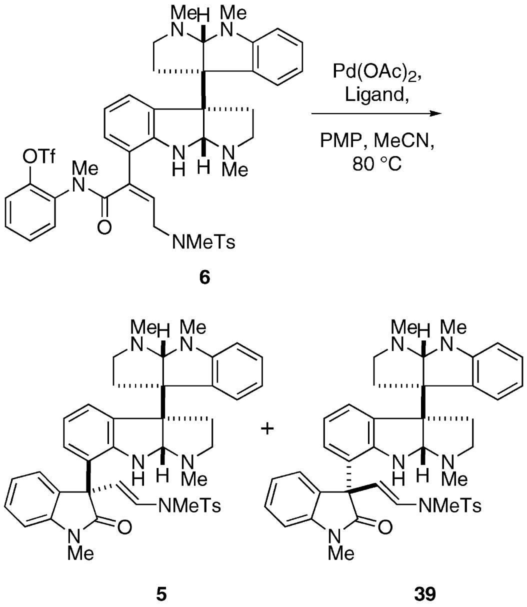
[¶] In situ silyl-protection of the amine was required to prevent competitive formation of the urea.

formation of the remaining diaryl-substituted 3a″ quaternary stereocenter. An asymmetric Heck cyclization[19] was employed in our earlier total synthesis of quadridgemine C (**3**) to desymmetrize an advanced *meso* intermediate to form the diaryl quaternary stereocenters of this alkaloid.[5] We anticipated that related catalyst control would be required to install the final quaternary stereocenter of idiospermuline (**4**) with high diastereoselectivity. Heck cyclizations of **6** were performed initially with achiral chelating bisphosphines such as bis(1,4-diphenylphosphino)butane (dppb). Modest substrate control (2.5:1) was realized in forming the desired 3a″*R* stereoisomer **5** (Table 2, entry 1). This selectivity increased to 6:1 using (*S*)-tol-BINAP,[20] $Pd(OAc)_2$ as the precatalyst (entry 3), 1,2,2,6,6-pentamethylpiperidine (PMP) in acetonitrile at 80°C. Identical cyclization of **6** using (*R*)-tol-BINAP reversed the selectivity, yielding **5** and **39** in a 1:18 ratio (entry 4). The higher diastereoselectivity in the latter case reflects proper matching of substrate and catalyst control.

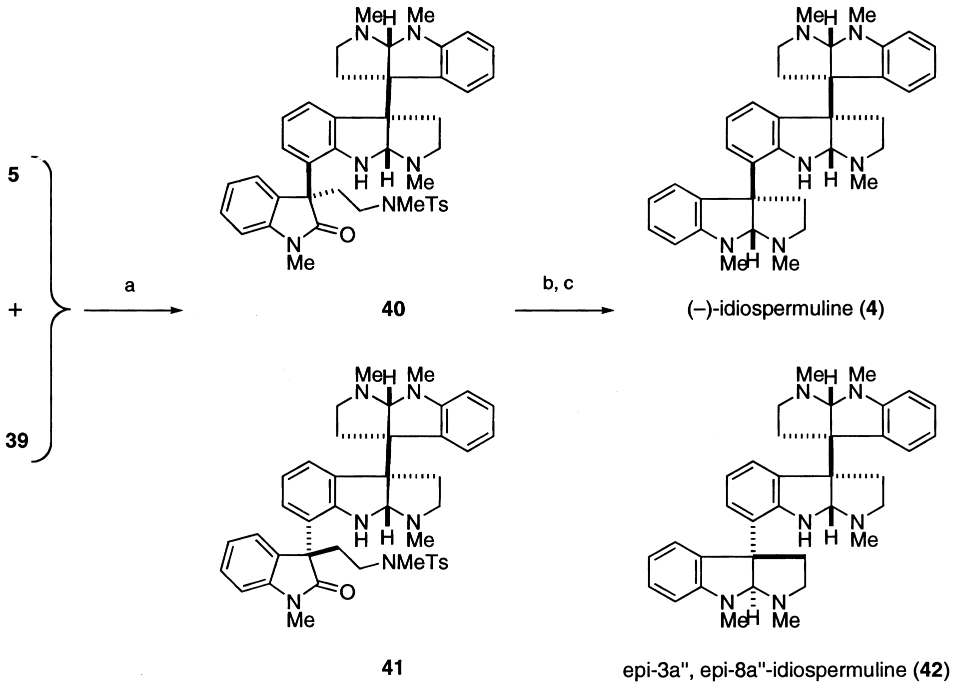
Epimers **5** and **39** proved difficult to separate by flash chromatography. As a result, mixtures enriched in either epimer were advanced to the end of the synthesis where the final products could be separated by preparative HPLC. Catalytic hydrogenation of the 6:1 mixture of **5** and **39** over palladium hydroxide at high hydrogen pressure (1000 psi) provided saturated sulfonamides **40** and **41** (Scheme 8).

Attempts to remove the tosyl group of **40**, reduce the oxindole carbonyl group and cyclize to form idiospermuline

Table 2. Heck cyclization of (*Z*)-butenanilide **6**



Entry	Ligand	Isolated yield (%)	Ratio **5**:**39**
1	Dppb	90	2.5:1
2	*rac*-Tol-BINAP	97	1:2
3	(*S*)-Tol-BINAP	97	6:1
4	(*R*)-Tol-BINAP	99	1:18



Starting Ratio **5** : **39**	Isolated Yields **4** : **42**	Total Yield
6 : 1	47% (**4**) : 16% (**42**)	63%
1 : 18	5% (**4**) : 57% (**42**)	62%

Scheme 8. *Reaction conditions*: (a) $Pd(OH)_2$, H_2 (1000 psi), EtOH, 80°C; (b) Red-Al, toluene, rt; (c) Na, NH_3, THF, −78°C.

in a single transformation with sodium in ammonia at −78°C, conditions employed in our synthesis of quadrigemine C (**3**),[5] met little success. The presence of the methyl group on the oxindole nitrogen perhaps thwarting reduction of the carbonyl group.[21][‖]

This final problem was overcome by reducing the oxindole carbonyl before removal of the tosyl group. Thus, a 6:1 mixture of saturated sulfonamides **40** and **41** was treated with an excess of sodium bis(2-methoxyethoxy)aluminum hydride in toluene at room temperature.[14] The resulting crude product was immediately reduced with excess sodium in ammonia at −78°C. Finally, HPLC purification of the resulting products provided idiospermuline (**4**), $[\alpha]_D = -267$ (*c* 0.85 $CHCl_3$), in 47% overall yield from the mixture of Heck products.[**] Synthetic idiospermuline (**4**) was identical to a natural sample by ^1H NMR, ^{13}C NMR, CD, and HRMS comparisons, as well as by HPLC co-injection. An analogous sequence carried out with a 1:18 mixture of **5** and **39** gave 3a″,8a″-bis-epiidiospermuline (**42**), $[\alpha]_D = -156$ (*c* 0.25 $CHCl_3$), in 57% yield.

3. Conclusion

This total synthesis of idiospermuline (**4**) and that of hodgkinsine, which we reported recently,[22] are the first total syntheses of trispyrrolidinoindoline alkaloids. Starting with isatin, idiospermuline was formed in 6% overall yield by a sequence involving 22 steps (longest linear sequence) and 14 isolated and purified intermediates. This stereocontrolled total synthesis demonstrates for the first time that the dienolate dialkylation chemistry we described earlier for synthesis of symmetrical 3a,3a′-bispyrrolidinoindolines[11] can be employed for enantioselective preparation of unsymmetrical congeners. This synthesis of idiospermuline also provides an additional illustration of the ability of asymmetric intramolecular Heck reactions to generate congested quaternary carbon centers in high yield, and the first demonstration of using such a transformation to elaborate a pyrrolidinoindoline unit at the *peri* position of a chiral 3a,3a′-bispyrrolidinoindoline fragment.

4. Experimental[††]

4.1. Data for compounds

4.1.1. 1-Benzyl-1*H*-indole-2,3-dione. Sodium hydride (19.6 g, 0.49 mol, 60% in oil) was added as one portion to a slurry of isatin (65.5 g, 445 mmol) and anhydrous DMF (800 mL) at rt. After 10 min, benzyl bromide (58 mL, 489 mmol) was added rapidly by syringe. After 15 min, the solution was poured into cold swirling brine and a bright orange solid precipitated. The precipitate was collected by vacuum filtration and subsequently washed with H_2O (400 mL) then hexanes (200 mL) to yield 104.6 g (99%) of 1*H*-indole-2,3-dione. The spectral data was consistent with that reported previously.[23]

4.1.2. 1-Benzyl-1*H*,1′*H*-[3,3′]biindolylidene-2,2′-dione (14). A solution of 1-benzyl-1*H*-indole-2,3-dione[23] (32.7 g, 138 mmol), oxindole (18.3 g, 138 mmol), acetic acid (450 mL) and HCl (5 mL) was heated at 110°C for 6 h. The solution was allowed to cool to rt at which time hexanes (200 mL) were added. A maroon precipitate formed, which was collected by vacuum filtration. This solid was washed with H_2O (200 mL) then hexanes (100 mL), and dried in vacuo to yield 36.8 g (76%) of isoindigo **14** as a maroon solid: mp 225–228°C; ^1H NMR (500 MHz, $(CD_3)_2SO$) 10.99 (s, 1H), 9.15 (t, J=7.5 Hz, 2H), 7.42–7.36 (m, 6H), 7.31 (t, J=6.9 Hz, 1H), 7.09–7.03 (m, 2H), 7.00 (t, J=8.4 Hz, 1H) 6.90 (d, J=7.7 Hz, 1H), 5.06 (s, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$)[‡‡] δ 168.8, 167. 3, 144.3, 143.9, 136.2, 134.3, 133.0, 132.4, 131.8, 129.5, 129.1, 128.7, 127.4, 127.2, 121.9, 121.6, 121.2, 120.9, 109.6, 108.9, 42.7; IR (film) 3134, 3030, 1698, 1606, 1467, 1332 cm^{-1}. Anal. calcd for $C_{23}H_{16}N_2O_2$: C, 78.39; H, 4.58; N, 7.95. Found: C, 78.51; H, 4.74; N, 7.90.

4.1.3. 1′-Benzyl-1-methyl-1*H*,1′*H*-[3,3′]biindolylidene-2,2′-dione (17). Anhydrous DMF (80 mL) was added to **14** (9.89 g, 28.4 mmol) and Cs_2CO_3 (13.1 g, 34.1 mmol). Methyl iodide (2.1 mL, 34 mmol) was added by syringe and the reaction mixture was stirred at rt for 24 h. The mixture then was poured into aqueous NH_4Cl at 0°C and a dark maroon solid precipitated. This solid was collected by vacuum filtration, washed with H_2O (200 mL), then hexanes (100 mL), and dried in vacuo to yield 10.0 g (97%) of isoindigo **17** as a maroon solid: mp 175–177°C; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 9.18 (d, J=8.0 Hz, 2H), 7.49 (dt, J=7.7, 1.1 Hz, 1H), 7.42–7.35 (m, 5H), 7.31 (tt, J=6.9, 1.6 Hz, 1H), 7.12–7.05 (m, 3H), 7.01 (d, J=7.8 Hz, 1H), 5.06 (s, 2H), 3.27 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$)[‡‡] δ 167.2, 167.0, 145.2, 144.0, 136.2, 133.2, 132.9, 132.6, 132.2, 129.3, 129.2, 128.7, 127.4, 127.2, 121.9, 121.8, 120.8, 120.7, 109.0, 108.6, 42.7, 26.1; IR (film) 2926, 1691, 1610, 1471, 1351, 1181, 1096 cm^{-1}. Anal. calcd for $C_{24}H_{18}N_2O_2$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.75; H, 5.09; N, 7.65.

4.1.4. 1′-Benzyl-1-methyl-1,1′,3,3′-tetrahydro-[3,3′]biindolyl-2,2′-dione (12). Platinum (IV) oxide (0.19 g, 0.84 mmol) was added to a dark maroon solution of **17** (6.11 g, 16.7 mmol) and EtOAc (150 mL). The flask was evacuated and backfilled with H_2 (5×) from a balloon. The heterogeneous reaction mixture was stirred vigorously under H_2 (1 atm) until the dark maroon color dissipated. The mixture was then filtered through Celite and the filter cake was washed with EtOAc (100 mL). The filtrate was concentrated in vacuo and the resulting residue was purified on silica gel (3:1 hexanes–EtOAc) to yield 5.41 g (88%) of **12** (a mixture of two stereoisomers) as a colorless foam: ^1H NMR (1.3:1 mixture of stereoisomers, 500 MHz, $CDCl_3$) diagnostic signals: δ 7.36–7.28 (m, 4.7H), 7.21–7.16 (m,

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[‖] To the best of our knowledge, formation of a pyrrolidinoindoline by the original Julian procedure (Na/NH_3)[14] has only been described with oxindole precursors lacking a substituent on nitrogen.

[**] The rotation of **4** was reported as $[\alpha]_D = -2.5$ (*c* 1.0 $CHCl_3$).[3] The rotation of natural **4** measured in our hands (*c*=g/100 mL) is $[\alpha]_D = -241$ (*c* 0.2 $CHCl_3$). We thank Professor Rujee K. Duke for providing a sample of natural idiospermuline.

[††] General experimental details have been described: Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 6379–6387.

[‡‡] Due to the nearly symmetrical nature of this compound, some carbon resonances are coincidental.

4H), 7.09 (t, *J*=7.7 Hz, 1H), 7.05 (t, *J*=6.9 Hz, 2H), 7.02–6.90 (m, 3.4H), 6.84 (t, *J*=8.3 Hz, 2H), 6.78 (t, *J*=6.7 Hz, 1.6H), 6.67 (dd, *J*=14.4, 7.7 Hz, 3.2H), 6.51 (d, *J*=7.3 Hz, 1H), 5.00 (d, *J*=15.2 Hz, 0.8H), 4.97 (br s, 0.8H), 4.95 (d, *J*=15.4 Hz, 0.8H), 4.56 (d, *J*=15.8 Hz, 1H), 4.39 (m, 2.4H), 4.17 (d, *J*=3.4 Hz, 1H), 3.28 (s, 2.3H), 3.21 (s, 3H); ^{13}C NMR (1.3:1 mixture of stereoisomers, 125 MHz, $CDCl_3$) diagnostic signals: δ 176.2, 176.1, 175.3, 174.8, 145.5, 144.4, 144.3, 135.8, 135.7, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.0, 127.9, 127.6, 127.4, 126.4, 125.7, 125.1, 124.9, 124.2, 123.9, 123.8, 123.7, 122.8, 122.7, 122.6, 122.5, 109.6, 109.2, 108.6, 108.2, 46.8, 46.4, 46.3, 44.3, 44.0, 26.6, 26.5; IR (film) 3061, 2934, 1702, 1613, 1490, 1467, 1351, 1089, 911 cm^{-1}. Anal. calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 77.96; H, 5.51; N, 7.54.

4.1.5. (3*S*,3″*S*,3′a*R*,7′a*R*)-1-Benzyl-1″-methyl-2′,2′-dimethyl-3′a,4′,7′,7′a-tetrahydrospiro[3*H*-indole-3,5′(6′*H*)-[1,3]benzodioxole-6′-3″-[3*H*]indole]-2,2″-(1*H*,1″*H*)dione (10). Because of the oxygen sensitivity of this reaction, all solvents and prepared solutions were rigorously sparged for 45 min with Ar prior to their addition to the reaction vessel. A solution of **12** (1.03 g, 2.79 mmol), THF (35 mL) and HMPA (6 mL) was sparged for 45 min with Ar and cooled to −40°C at which time a THF solution of LHMDS (9.3 mL, 0.7 M) was added by syringe pump at a rate of 0.20 mL/min. After 30 min, a THF solution of ditriflate **11** (15.0 mL, 0.2 M) was added using a syringe pump at a rate of 0.20 mL/min. The solution was warmed to −35°C, maintained at −35°C for 12 h (cryocool), then allowed to warm to rt over 1 h. The solution was partitioned between EtOAc (25 mL) and brine (15 mL). The layers were separated and the aqueous layer was washed with EtOAc (2×15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The foam residue was purified on silica gel (5:1 hexanes–EtOAc) to yield 1.03 g (75%) of **10** as a colorless foam: $[\alpha]^{28}_{405}=-698$, $[\alpha]^{28}_{435}=-528$, $[\alpha]^{28}_{546}=-259$, $[\alpha]^{28}_{577}=-224$, $[\alpha]^{28}_{D}=-213$ (*c* 0.94, MeOH); ^1H NMR (500 MHz, C_6D_6) δ 7.37 (dd, *J*=7.2, 1.5 Hz, 1H), 7.34 (d, *J*=7.6 Hz, 1H), 6.95 (t, *J*=3.2 Hz, 3H), 6.90–6.86 (m, 2H), 6.70 (t, *J*=7.7 Hz, 1H), 6.57–6.50 (m, 3H), 5.98 (d, *J*=7.5 Hz, 1H), 5.84 (d, *J*=7.8 Hz, 1H), 5.46–5.39 (m, 2H), 4.63 (d, *J*=15.7 Hz, 1H), 4.29 (d, *J*=15.7 Hz, 1H), 3.34 (m, 2H), 2.52 (s, 3H), 2.18 (dd, *J*=12.7, 3.4 Hz, 1H), 2.09 (dd, *J*=12.7, 3.4 Hz, 1H), 1.57 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 177.6, 177.3, 143.7, 143.0, 136.3, 129.5, 129.4, 129.3, 129.1, 128.9, 128.0, 127.9, 125.4, 125.1, 123.0, 122.8, 110.3, 109.3, 108.1, 74.7, 74.6, 53.7, 53.3, 43.9, 34.1, 33.6, 32.3, 28.0, 25.7, 23.4, 14.7; IR (film) 2980, 1698, 1610, 1370, 1073, 841, 752 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{31}H_{30}N_2O_4$ (M^+) 494.2206, found 494.2206.

A larger scale dialkylation of **12** (4.9 g, 13.3 mmol) proceeded with similar efficiency; however, mixed chromatography fractions were discarded in this case, providing 4.2 g (64%) of pure **10**.

4.1.6. Chemical correlation of 10 with *ent*-19. The *N*-benzyl group of **10** was removed[24] and replaced with a methyl group in the following manner. A solution of **10** (27.2 mg, 0.055 mmol) in Et_2O (1 mL) was cooled to −78°C and a hexane solution of *t*BuLi (0.22 mL, 1.3 M) was added dropwise to generate a bright yellow solution. After 15 min, O_2 was bubbled vigorously through the reaction mixture from a balloon until the yellow color dissipated (10 min). This solution was allowed to warm to rt under an O_2 atmosphere. Saturated aqueous NH_4Cl (1 mL) was added and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was then taken up in DMF (1 mL) and treated sequentially with NaH (10.0 mg, 0.250 mmol, 60% in oil) and MeI (0.22 mL, 3.2 mmol). After 10 min, saturated aqueous $NaHCO_3$ (1 mL) was added and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified on silica gel (5:1 hexanes–EtOAc) to yield 3.2 mg (14%) of the C_2-symmetric (3*S*,3″*S*,3′a*R*,7′a*R*)-1,1″-dimethyl-2′,2′-dimethyl-3′a,4′,7′,7′a-tetrahydrospiro-[3*H*-indole-3,5′(6′*H*)-[1,3]benzodioxole-6′,3″-[3*H*]indole]-2,2″(1*H*,1″*H*)dione (the *N*,*N*′-methyl congener of **10**) as a colorless foam: $[\alpha]^{26}_{405}=-604$, $[\alpha]^{26}_{435}=-446$, $[\alpha]^{26}_{546}=-206$, $[\alpha]^{26}_{577}=-176$, $[\alpha]^{26}_{D}=-167$ (*c* 0.60, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) δ 7.31 (dd, *J*=7.5, 0.9 Hz, 1H), 6.68 (dt, *J*=6.5, 1.2 Hz, 1H), 6.60 (dt, *J*=7.6, 0.9 Hz, 1H), 5.85 (d, *J*=7.6 Hz, 1H), 5.41–5.34 (m, 1H), 3.29–3.22 (m, 1H), 2.52 (s, 3H), 2.05 (dd, *J*=12.5, 3.6 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 177.2, 143.7, 129.4, 128.9, 128.7, 124.8, 122.5, 110.3, 108.0, 74.7, 53.4, 33.2, 28.0, 25.6; IR (film) 2984, 1698, 1613, 1494, 1471, 1374, 1355, 1143, 1069, 756 cm^{-1}. Anal. calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69. Found: C, 72.08; H, 6.65; N, 6.38.

Following an identical procedure, *ent*-**19** (44 mg, 0.025 mmol) was converted to its C_2-symmetric *N*,*N*′-methyl congener, (3*S*,3″*S*,3′a*R*,7′a*R*)-1,1″-dimethyl-2′,2′-dimethyl-3′a,4′,7′,7′a-tetrahydrospiro[3*H*-indole-3,5′(6′*H*)-[1,3]benzodioxole-6′,3″-[3*H*]indole]-2,2″(1*H*,1″*H*)dione, in 33% yield.

4.1.7. Isolation of pure samples of hexacycles 26 and 27. The *cis* products **26** and **27** were collected as an inseparable ~1:1 mixture from several dialkylation reactions. A 0.250 g (0.505 mmol) sample of this mixture was dissolved in CH_2Cl_2 (3 mL) and MeOH (3 mL) and treated with (±)-camphorsulfonic acid (0.012 g, 0.051 mmol) at rt. This solution was maintained at rt for 4 h at which time it was concentrated and purified on silica gel (6:1 EtOAc–hexanes) to yield 0.10±0.01 g of each stereoisomer.

The pure vicinal diols were separately reprotected by treatment with 2,2-dimethoxypropane (8.3 g, 80 mmol) and (±)-camphorsulfonic acid (7.0 mg, 0.03 mmol) in acetone (2.5 mL) at rt for 12 h. The reaction was quenched with solid $NaHCO_3$, and the resulting mixture was filtered and concentrated. The resulting residue was purified on silica gel (3:1 hexanes–EtOAc) to yield 0.069 g (63%) of isomer **A** and 0.078 g (72%) of isomer **B**. It has not been established which of these *cis*-bis-spirooxindole stereoisomers is **26** and which is **27**.

Data for hexacycle **A**. ^1H NMR (400 MHz, C_6D_6) δ 7.56 (d, *J*=7.5 Hz, 1H), 7.28 (d, *J*=7.3 Hz, 2H), 7.05

(t, J=7.7 Hz, 2H), 6.99–6.93 (m, 2H), 6.74 (dt, J=7.6, 1.0 Hz, 1H), 6.58 (dt, J=7.8, 1.2 Hz, 1H), 6.29–6.24 (m, 2H), 6.05 (d, J=7.2 Hz, 2H), 5.74 (ddd, J=13.8, 9.2, 4.6 Hz, 1H), 4.93 (d, J=15.7 Hz, 1H), 4.71 (d, J=15.7 Hz, 1H), 4.53 (ddd, J=13.4, 9.3, 4.1 Hz, 1H), 3.73 (t, J=12.2 Hz, 1H), 2.60 (t, J=12.7 Hz, 1H), 2.26 (dd, J=13.1, 4.6 Hz, 1H), 2.20 (s, 3H), 1.92 (dd, J=11.9, 4.2 Hz, 1H), 1.56 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 176.7, 175.3, 144.7, 144.0, 137.2, 131.5, 129.2, 129.16, 129.1, 129.0, 127.8, 127.4, 125.0, 121.9, 121.6, 110.3, 109.3, 109.1, 76.2, 74.1, 56.0, 52.7, 44.7, 35.6, 33.5, 28.0, 27.7, 25.9; IR (film) 2930, 1718, 1610, 1471, 1351 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{30}N_2O_4$ (M+Na) 517.2103, found 517.2122.

Data for hexacycle **B**. ^{1}H NMR (400 MHz, C_6D_6) δ 7.57 (d, J=7.4 Hz, 1H), 6.92 (d, J=7.2 Hz, 1H), 6.86 (t, J=7.6 Hz, 2H), 6.81 (dt, J=7.7, 1.1 Hz, 1H), 6.74 (dt, J=7.7, 1.2 Hz, 1H), 6.67 (dt, J=7.6, 1.2 Hz, 1H), 6.29 (dt, J=7.6, 1.0 Hz, 1H), 6.15–6.10 (m, 3H), 6.061 (d, J=7.6 Hz, 1H), 6.059 (d, J=7.6 Hz, 1H), 5.73 (ddd, J=13.8, 9.3, 4.6 Hz, 1H), 4.79 (d, J=16.4 Hz, 1H), 4.53 (ddd, J=13.4, 9.3, 4.1 Hz, 1H), 3.74 (t, J=6.4 Hz, 1H), 3.71 (d, J=16.4 Hz, 1H), 2.79 (s, 3H), 2.56 (t, J=12.5 Hz, 1H), 2.14 (dd, J=13.0, 4.6 Hz, 1H), 1.96 (dd, J=11.8, 4.1 Hz, 1H), 1.57 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 176.4, 175.5, 145.1, 143.5, 135.8, 131.4, 129.2, 129.13, 129.08, 127.44, 127.39, 126.6, 125.3, 122.0, 121.6, 110.4, 110.3, 108.1, 76.0, 74.0, 56.23, 52.6, 43.5, 34.9, 33.4, 28.0, 27.7, 26.4; IR (film) 2934, 1710, 1610, 1471, 1351, 1077 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{31}H_{30}N_2O_4$ (M+Na) 517.2103, found 517.2090.

4.1.8. 1′-Benzyl-3,3′-bis-(2-hydroxyethyl)-1-methyl-1,1′,3,3′-tetrahydro-[3*S*,3′*S*]biindolyl-2,2′-dione (28). Camphorsulfonic acid (0.244 g, 1.05 mmol) was added to a solution of **10** (5.21 g, 10.5 mmol), MeOH (50 mL), and CH_2Cl_2 (50 mL) at rt. After 3 h, the solvent was removed in vacuo and the residue was purified on silica gel (1:1 EtOAc–hexanes–9:1 EtOAc–hexanes) to yield 4.67 g (98%) of the corresponding vicinal diol as a colorless foam: $[\alpha]^{26}_{405}=-665$, $[\alpha]^{26}_{435}=-507$, $[\alpha]^{26}_{546}=-254$, $[\alpha]^{26}_{577}=-219$, $[\alpha]^{26}_{D}=-208$ (*c* 0.79, MeOH); ^{1}H NMR (500 MHz, C_6D_6) δ 7.32 (d, J=1.5 Hz, 1H), 7.28 (d, J=7.5 Hz, 1H), 7.00–6.96 (m, 5H), 6.69 (dt, J=7.7, 1.1 Hz, 1H) 6.55 (m, 3H), 6.01 (d, J=7.2 Hz, 1H), 5.87 (d, J=7.7 Hz, 1H), 5.02–4.98 (m, 2H), 4.61 (d, J=15.7 Hz, 1H), 4.39 (d, J=15.7 Hz, 1H), 3.33–3.28 (m, 2H), 2.58 (s, 3H), 2.45–2.02 (br s, 2H), 1.93–1.85 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6)‡‡ δ 178.1, 177.9, 143.7, 143.1, 136.6, 130.2, 130.1, 129.2, 128.9, 128.7, 127.8, 125.0, 124.7, 122.9, 122.8, 109.2, 108.1, 70.9, 70.8, 53.4, 53.0, 44.0, 36.9, 36.3, 25.9; IR (film) 3428, 2936, 1695, 1610, 1490, 1467, 1378, 1050, 752, 698 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{28}H_{26}N_2O_4$ (M$^+$) 454.1893, found 454.1888.

Sodium periodate (22.0 g, 102 mmol) was added to a solution of the vicinal diol (4.67 g, 10.3 mmol), H_2O (65 mL) and THF (65 mL) at rt. After 12 h, saturated aqueous NH_4Cl (100 mL) was added and the phases were separated. The aqueous layer was extracted with EtOAc (3×25 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue was dissolved in MeOH (100 mL) and treated portion-wise with $NaBH_4$ (2.72 g, 71.9 mmol). After 10 min, the reaction mixture was concentrated in vacuo and the residue was partitioned between EtOAc (50 mL) and H_2O (40 mL). The aqueous layer was extracted with EtOAc (3×25 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue was purified on silica gel (9:1 EtOAc–hexanes) to yield 4.06 g (87%) of **28** as a colorless foam: $[\alpha]^{25}_{405}=-722$, $[\alpha]^{25}_{435}=-544$, $[\alpha]^{25}_{546}=-266$, $[\alpha]^{25}_{577}=-229$, $[\alpha]^{25}_{D}=-218$ (*c* 0.84, MeOH); ^{1}H NMR (500 MHz, C_6D_6) δ 7.20 (d, J=7.5 Hz, 2H), 7.10–7.04 (m, 4H), 6.98 (t, J=7.4 Hz, 1H), 6.73 (dt, J=7.7, 1.0 Hz, 1H), 6.60–6.53 (m, 3H), 6.08 (dd, J=6.7, 2.1 Hz, 1H), 5.97 (d, J=7.7 Hz, 1H), 5.01 (d, J=15.8 Hz, 1H), 4.28 (d, J=15.8 Hz, 1H), 3.68–3.60 (m, 2H), 3.58–3.50 (m, 2H), 3.35–3.25 (m, 2H), 2.97–2.93 (m, 2H), 2.66 (s, 3H), 1.98–1.80 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6)‡‡ δ 179.1, 178.9, 144.4, 143.9, 136.7, 129.2, 128.7, 128.6, 128.5, 128.2, 127.9, 124.8, 124.4, 122.2, 121.9, 109.3, 108.0, 60.0, 59.9, 55.2, 55.1, 44.6, 33.3, 33.1, 26.0; IR (film) 3397, 2949, 2883, 1687, 1610, 1490, 1467, 1378, 1050, 926 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{28}H_{28}N_2O_4$ (M$^+$) 456.2049, found 456.2045.

4.1.9. 5-Benzyl-(5a*R*,6a*R*,11b*S*,11c*S*)-bis(2-azidoethyl)-7-methyl-5,5a,6a,7-tetrahydrofuro[2,3-*b*:5,4-*b*′]diindole (30). A THF solution of diol **28** (50 mL, 0.18 M) was transferred to a sealed tube and the solution was sparged with N_2 for 30 min. A toluene solution of Red-Al® (30 mL, 65 wt%) was added to the sealed tube slowly by syringe to avoid vigorous H_2 evolution. After the addition was complete, the tube was sealed and the solution heated at 67°C. After 1.5 h, the solution was allowed to cool to rt and then added slowly to a swirling saturated aqueous solution of NaF (500 mL) at 0°C. The layers were separated and the aqueous layer was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was azeotroped with benzene (2×50 mL). The resulting unstable pentacyclic diol **29** was used directly in the Mitsunobu reaction.

A solution of this crude pentacyclic diol **29** and PPh_3 (22.2 g, 84.5 mmol) in THF (75 mL) was cooled to 0°C and a toluene solution of HN_3 (56.0 mL, 1.56 M) was added by syringe. To this solution, diethyl azodicarboxylate (14.0 mL, 88.9 mmol) was added using a syringe pump at a rate of 0.16 mL/min. The resulting solution was allowed to warm to rt where it was maintained for 30 min before being quenched by the addition of silica gel (5 g). The residual solvent was removed in vacuo and the resulting residue was purified on silica gel (10:1 petroleum ether–EtOAc) to provide 3.27 g (75%) of **30** as a colorless oil: ^{1}H NMR (500 MHz, C_6D_6) δ 7.17 (d, J=7.1 Hz, 2H), 7.10 (s, 1H), 7.09–7.01 (m, 3H), 6.97 (dt, J=7.8, 1.2 Hz, 1H), 6.80 (dt, J=6.9, 0.8 Hz, 2H), 6.68 (ddd, J=10.2, 7.5, 7.5 Hz, 2H), 6.29 (d, J=7.8 Hz, 1H), 6.2 (d, J=7.8 Hz, 1H), 4.74 (s, 1H), 4.63 (s, 1H), 4.23 (s, 2H), 2.54 (s, 3H), 2.50–2.44 (m, 4H), 1.20–1.84 (m, 2H), 1.71 (ddd, J=13.6, 9.1, 7.0 Hz, 1H), 1.65 (ddd, J=13.3, 9.4, 6.6 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6)‡‡ δ 151.2, 150.7, 138.8, 129.7, 129.6, 129.2, 129.0, 127.9, 126.5, 126.3, 118.7, 118.6, 108.1, 107.8, 103.0, 101.7, 61.4, 61.3, 50.0, 48.6, 48.5, 35.8, 35.6, 31.6; IR (film) 3053, 2926, 2088, 1702, 1602, 1486, 1355, 1258 cm^{-1};

HRMS (FAB) *m/z* calcd for $C_{28}H_{28}N_8O$ (M^+) 492.2386, found 492.2375. Anal. calcd for $C_{28}H_{28}N_8O$: C, 68.27; H, 5.73; N, 22.75. Found: C, 68.08; H, 5.84; N, 22.37.

4.1.10. 1,8,1′-Trimethyl-2,3,8,8a*R*,2′,3′,8′,8′a*S*-octahydro-1*H*,1′*H*-[3a*S*,3′a*S*]bipyrrolo[2,3-*b*]indole (32). Tetrahydrofuran (70 mL) and H_2O (1 mL) were added to a flask containing **30** (3.51 g, 7.13 mmol) at rt. To this solution, PPh_3 (4.67 g, 17.8 mmol) was added. After 12 h, the solution was concentrated in vacuo and azeotroped with benzene (2×50 mL). The residue was taken up in MeOH (50 mL), transferred to a sealed tube and heated at 110°C for 12 h. The solution was concentrated in vacuo and purified on silica gel (10:1 CH_2Cl_2–MeOH) to yield 2.32 g (77%) of 8′-benzyl-8-methyl-2,3,8,8a*R*,2′,3′,8′,8′a*R*-octahydro-1*H*-1′*H*-[3a*S*,3′a*S*]bipyrrolo[2,3-*b*]indole as a colorless foam: $[\alpha]^{27}_{405}=-887$, $[\alpha]^{27}_{435}=-601$, $[\alpha]^{27}_{546}=-241$, $[\alpha]^{27}_{577}=-200$, $[\alpha]^{27}_{D}=-189$ (*c* 0.84, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.23 (m, 6H), 7.17 (d, *J*=7.3 Hz, 1H), 7.07 (ddd, *J*=15.4, 7.7, 7.7 Hz, 1H), 7.03 (ddd, *J*=15.4, 7.7, 7.7 Hz, 1H), 6.58 (ddd, *J*=13.9, 7.4, 7.1 Hz, 2H), 6.26 (d, *J*=7.9 Hz, 2H), 4.50 (s, 1H), 4.45 (d, *J*=16.2 Hz, 1H), 4.43 (s, 1H), 4.35 (d, *J*=16.2 Hz, 1H), 3.05–2.95 (m, 2H), 2.78 (s, 3H), 2.57–2.43 (m, 4H), 2.27–2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)[‡‡] δ 153.0, 152.1, 139.0, 131.2, 131.1, 128.6, 128.5, 128.4, 127.1, 126.8, 124.3, 124.2, 116.3, 116.1, 105.0, 104.8, 87.3, 85.9, 62.1, 62.0, 48.0, 45.9, 45.8, 39.3, 38.8, 30.8; IR (film) 3331, 3049, 2937, 1602, 1490, 1351, 1158, 1027, 733 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{30}N_4$ (M+Na) 423.2549, found 423.2537.

An aqueous solution of formaldehyde (3.2 mL, 42.5 mmol, 37%, wt/wt) was added to a flask containing this product (1.80 g, 4.25 mmol) and MeOH (50 mL). The solution turned opaque white and $NaBH(OAc)_3$ (9.00 g, 42.5 mmol) was added. After 10 min, the solution was partitioned between saturated aqueous $NaHCO_3$ (100 mL) and EtOAc (75 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×50 mL) and $CHCl_3$ (saturated with NH_3) (3×20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was azeotroped with benzene (2×50 mL) then heptane (2×25 mL) to yield 1.83 g (95%) of 8′-benzyl-1,8,1′-trimethyl-2,3,8,8a*R*,2′,3′,8′,8′a*R*-octahydro-1*H*,1′*H*-[3a*S*,3′a*S*]bipyrrolo[2,3-*b*]indole as a colorless foam, which was of sufficient purity for further use. A comparable sample was purified on silica gel (10:1 CH_2Cl_2–MeOH) for characterization: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 353 K) δ 7.42–7.36 (m, 4H), 7.29 (t, *J*=6.9 Hz, 1H), 7.06 (d, *J*=7.2 Hz, 1H), 7.01 (d, *J*=7.3 Hz, 1H), 6.95 (dt, *J*=6.7, 1.1 Hz, 1H), 6.88 (dt, *J*=6.8, 1.1 Hz, 1H), 6.55–6.47 (dd, *J*=7.4, 7.4 Hz, 1H and dd, *J*=7.4, 7.4 Hz, 1H), 6.29 (d, *J*=7.8 Hz, 1H), 6.20 (d, *J*=7.8 Hz, 1H), 4.57 (d, *J*=16.3 Hz, 1H), 4.50 (s, 1H), 4.44 (d, *J*=16.3 Hz, 1H), 4.39 (s, 1H), 2.95 (s, 3H), 2.68–2.60 (m, 2H), 2.57–2.45 (m, 3H), 2.41–2.35 (m, 1H and s, 3H), 2.23 (s, 3H), 2.01–1.90 (m, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 353 K)[‡‡] δ 152.2, 151.6, 138.8, 132.3, 132.2, 127.7, 127.3, 127.1, 126.8, 126.1, 123.1, 123.0, 116.1, 115.8, 105.4, 104.9, 91.4, 91.3, 62.2, 61.9, 51.8, 51.7, 51.1, 38.6, 37.6, 34.7, 34.6, 33.9; IR (film) 3049, 2930, 2795, 1602, 1490, 1351, 1258, 1158, 1027 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{34}N_4$ (M+H) 451.2862, found 451.2869.

A two-neck flask fitted with a liquid NH_3 condenser was charged with sodium metal (0.93 g, 40.6 mmol) under a positive flow of N_2. The reaction flask and condenser were cooled to −78°C. A separate three-neck flask with an attached bubbler was cooled to −78°C and NH_3 (50 mL) was condensed directly from the tank into this flask. The NH_3 was redistilled from the 3-neck flask into the reaction vessel through a cannula to create a dark blue solution. A THF solution of 8′-benzyl-1,8,1′-trimethyl-2,3,8,8a*R*,2′,3′,8′,8′a*R*-octahydro-1*H*,1′*H*-[3a*S*,3′a*S*]bipyrrolo[2,3-*b*]indole (40 mL, 0.10 M) was added to this dark blue solution. Following complete addition, MeOH (5 mL) was added immediately at −78°C and the mixture became clear. This solution was allowed to warm slowly to rt allowing NH_3 to evaporate. The resulting THF solution was partitioned between EtOAc (30 mL) and saturated aqueous NH_4Cl (40 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×30 mL) and $CHCl_3$ (saturated with NH_3) (3×30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was azeotroped with benzene (2×50 mL) to yield 1.46 g (100%) of **32** as a colorless foam, which was of sufficient purity for further use. A comparable sample was purified on silica gel (10:1:0.01 CH_2Cl_2–MeOH–NH_4OH) for characterization: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 373 K) δ 7.08 (dd, *J*=7.4, 0.8 Hz, 1H), 6.99 (d, *J*=7.4 Hz, 1H), 6.92 (dt, *J*=7.7, 1.2 Hz, 1H), 6.84 (dt, *J*=7.6, 1.2 Hz, 1H), 6.49–6.41 (m, 2H and d, *J*=7.8 Hz, 1H), 6.28 (d, *J*=7.8 Hz, 1H), 5.83 (br s, 1H), 4.55 (s, 1H), 4.45 (s, 1H), 2.96 (s, 3H), 2.68–2.59 (m, 2H), 2.51–2.42 (m, 3H), 2.40–2.36 (m, 1H and s, 3H), 2.33 (s, 3H), 2.0–1.86 (m, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 373 K)[‡‡] δ 152.3, 151.2, 132.4, 127.0, 126.7, 123.1, 122.7, 115.9, 115.7, 107.2, 104.9, 91.1, 84.0, 62.1, 62.0, 51.3, 51.2, 36.9, 35.6, 34.9, 34.6, 34.4; IR (film) 3385, 2934, 2791, 1602, 1490, 1251, 1154, 1023, 733 cm^{-1}; HRMS (CI) *m/z* calcd for $C_{23}H_{28}N_4$ (M^+) 360.2314, found 360.2314.

4.1.11. 1,1′,8′-Trimethyl-1,2,3,8a*R*,2′,3′,8′,8′a*R*-octahydro-1′*H*-[3a*S*,3′a*S*]bi[pyrrolo[2,3-*b*]indolyl]-8-carboxylic acid *tert*-butyl ester (9). A THF solution of di-*tert*-butyl dicarbonate (Boc_2O, 8.8 mL, 0.56 M) was added to a solution of **32** (1.48 g, 4.12 mmol) and THF (100 mL) at −78°C. To this solution, NaHMDS (15 mL, 1.0 M in THF) was added using a syringe pump at a rate of 0.16 mL/min. The resulting solution was maintained at −78°C and carefully monitored by TLC. Upon complete consumption of starting material, $NaHCO_3$ (5 mL) was added immediately by syringe at −78°C. The solution was allowed to warm to rt and was then partitioned between saturated aqueous NH_4Cl (50 mL) and EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL), and $CHCl_3$ (saturated with NH_3) (1×20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified on silica gel using gradient elution (10:1 CH_2Cl_2–MeOH–10:1:0.01 CH_2Cl_2–MeOH–NH_4OH) to yield 1.41 g (74%) of **9** as a colorless oil: $[\alpha]^{27}_{405}=-685$, $[\alpha]^{27}_{435}=-505$, $[\alpha]^{27}_{546}=-242$, $[\alpha]^{27}_{577}=-206$, $[\alpha]^{27}_{D}=-198$ (*c* 0.55, CH_2Cl_2); ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 353 K) δ 7.44 (d, *J*=7.9 Hz, 1H), 7.24 (d, *J*=7.6 Hz, 1H), 7.07 (dt, *J*=8.3, 1.2 Hz, 1H), 6.94–6.88 (m, 3H), 6.42 (t, *J*=7.3 Hz, 1H), 6.24 (d, *J*=7.7 Hz, 1H), 5.09 (s, 1H), 4.35 (s, 1H), 2.91

(s, 3H), 2.66–2.61 (m, 2H), 2.50–2.38 (m, 4H), 2.39 (s, 3H), 2.37 (s, 3H), 2.09–1.99 (m, 2H), 1.59 (s, 9H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 353 K) δ 151.6, 151.5, 142.4, 135.2, 131.4, 127.6, 127.1, 123.5, 122.1, 121.8, 115.9, 114.6, 105.1, 90.9, 84.9, 80.1, 61.5, 60.4, 52.1, 51.7, 37.3, 36.8, 34.4, 33.9, 33.2, 27.6; IR (film) 2934, 2795, 1698, 1602, 1482, 1251, 1162, 1023, 745 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{36}N_4O_2$ (M+H$^+$) 461.2917, found 461.2917.

4.1.12. 7-Iodo-1,1′,8′-trimethyl-2,3,8,8a*S*,2′3′8′8′a*R*-octahydro-1*H*,1′*H*-[3a*S*,3′a*S*]bipyrrolo[2,3-*b*]indole (7). A pentane solution of *s*-BuLi (2.1 mL, 1.2 M) was added dropwise to a solution of **9** (0.392 g, 0.851 mmol), TMEDA (0.40 mL, 2.6 mmol), and Et_2O (10 mL) at −78°C. The solution was maintained at −78°C for 45 min, at which time an Et_2O solution of diiodoethane (8.1 mL, 1.05 M) was added by syringe. Upon complete addition of diiodoethane, the solution was warmed to 0°C where it was maintained for 20 min and then allowed to warm to rt. The solution was partitioned between saturated aqueous $Na_2S_2O_4$ (20 mL) and CH_2Cl_2 (20 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified on silica gel using gradient elution (10:1 CH_2Cl_2–MeOH–10:1:0.01 CH_2Cl_2–MeOH–NH_4OH) to yield 0.455 g (90%) of the *tert*-butoxycarbonyl protected bispyrrolidinoindoline monoiodide as a colorless foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J*=7.8 Hz, 1H), 7.16 (d, *J*=7.1 Hz, 1H), 7.06 (t, *J*=7.5 Hz, 1H), 6.98 (d, *J*=7.1 Hz, 1H), 6.73 (t, *J*=7.7 Hz, 1H), 6.59 (t, *J*=7.4 Hz, 1H), 6.33 (d, *J*=7.8 Hz, 1H), 5.14 (br s, 1H), 4.38 (br s, 1H), 2.99 (s, 3H), 2.70–2.61 (m, 2H), 2.54–2.47 (m, 1H and s, 3H), 2.43 (s, 3H), 2.36–2.29 (m, 1H), 2.27–2.21 (m, 2H), 2.07–2.01 (m, 1H), 1.87–1.81 (m, 1H), 1.59 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$)[‡‡] δ 152.4, 146.5, 139.8, 139.1, 131.9, 128.6, 125.6, 124.5, 123.9, 117.0, 106.0, 92.2, 88.0, 84.8, 81.6, 62.6, 61.8, 52.9, 52.3, 38.8, 36.6, 35.3, 34.5, 28.3; IR (film) 2934, 2798, 1718, 1606, 1494, 1444, 1351, 1247, 1158, 1046, 1023 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{35}IN_4O_2$ (M+Na$^+$) 609.1702, found 609.1705.

A CH_2Cl_2 (25 mL) solution of this crude product (1.23 g, 2.1 mmol) was treated with TMSOTf (1.2 mL, 6.3 mmol) at rt. The flask was left open to the atmosphere and a drop of H_2O (~0.01 mL) was added. After 10 min the solution turned pink and was partitioned between saturated aqueous $NaHCO_3$ (20 mL) and CH_2Cl_2 (15 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3×10 mL) and $CHCl_3$ (saturated with NH_3) (1×15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified on silica gel with gradient elution (20:1:0–10:1:0.01 CH_2Cl_2–MeOH–Et_3N) to yield 0.96 g (94%) of **7** as a colorless foam: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 383 K) δ 7.24 (d, *J*=7.8 Hz, 1H), 7.10 (d, *J*=7.4 Hz, 1H), 7.01 (d, *J*=7.2 Hz, 1H), 6.95 (t, *J*=8.5 Hz, 1H), 6.50 (t, *J*=7.6 Hz, 1H), 6.34–6.28 (m, 2H), 5.67 (s, 1H), 4.81 (br s, 1H), 4.62 (br s, 1H), 3.00 (s, 3H), 2.92–2.84 (m, 2H), 2.82–2.73 (m, 2H), 2.51–2.46 (m, 2H and s, 3H), 2.43 (s, 3H), 2.02–1.94 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 152.3, 136.2, 133.2, 132.3, 128.3, 124.2, 123.5, 119.5, 116.9, 111.0, 106.0, 91.9, 83.6, 74.5, 65.3, 62.9, 52.4, 52.3, 37.6, 36.6, 35.6, 34.5; IR (film) 3397, 2930, 2791, 1602, 1494, 1471, 1351, 1251, 1158, 1023 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{27}IN_4$ (M+Na$^+$) 509.1178, found 509.1163.

4.1.13. Trifluoromethanesulfonic acid 2-(methyl{4-[methyl(toluene-4-sulfonyl)amino]but-2-ynonyl}amino)-phenyl ester (36). Diisopropylethylamine (5.0 mL, 28.7 mmol) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (5.0 mL, 26.1 mmol) were added sequentially to an Et_2O solution of *N*-methylpropargylamine (75 mL, 0.35 M) at 0°C. A colorless precipitate formed immediately upon addition of TMSOTf. This mixture was maintained at 0°C for 10 min, then warmed to rt. The reaction mixture then was filtered through a Schlenk filter to give a clear yellow solution. This solution was cooled to −78°C and a hexane solution of *n*-BuLi (12.5 mL, 2.6 M) was added. After 10 min, 3-methylbenzoxazolinone (**34**) (3.89 g, 26.1 mmol) was added as a solid with positive N_2 flow followed by THF (30 mL). The solution was warmed to −20°C and maintained at this temperature for 2 h at which time *N*-phenylbis(trifluoromethanesulfonimide) (9.32 g, 26.1 mmol) was added as a solid under positive N_2 flow. The solution was warmed to −10°C and after 30 min at −10°C, tosyl chloride (4.98 g, 26.1 mmol) and silica gel (3 g) were added. This mixture was stirred and allowed to warm to rt. After 6 h at rt, additional silica gel was added and the mixture was concentrated in vacuo, loaded onto a silica gel column, and purified using gradient elution (3:1 hexanes–EtOAc–1:2 hexanes–EtOAc) to yield 4.66 g (41%) of **36** as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) a mixture of rotamers, only major peaks are listed δ 7.75 (d, *J*=8.3 Hz, 2H), 7.47 (dt, *J*=7.6, 1.8 Hz, 1H), 7.44–7.40 (m, 2H), 7.37 (dd, *J*=8.0, 1.5 Hz, 1H), 7.32 (d, *J*=8.0 Hz, 2H), 7.28 (dd, *J*=6.0, 1.6 Hz, 1H), 3.99 (d, *J*=18.1 Hz, 1H), 3.77 (d, *J*=18.1 Hz, 1H), 2.45 (s, 3H), 2.44 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) a mixture of rotamers, only major peaks are listed δ 152.8, 145.2, 144.0, 135.42, 130.6, 130.3, 129.7, 129.3, 127.6, 122.6, 117.1, 84.8, 78.3, 39.6, 35.7, 33.9, 21.4; IR (film) 3069, 2247, 1659, 1498, 1351, 1212, 1162, 1139 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{19}F_3N_2O_6S_2$ (M+Na$^+$) 527.0534, found 527.0540.

4.1.14. Trifluoromethanesulfonic acid 2-(benzyl{4-[methyl(toluene-4-sulfonyl)amino]but-2-ynonyl}amino)-phenyl ester (37). Following the procedure used to prepare **36**, *N*-methylpropargyl amine (150 mL, 0.33 M) and 3-benzylbenzoxazolinone[25] (11.1 g, 49.3 mmol) were elaborated to give a crude product which was purified using gradient elution (5:1 hexanes–EtOAc–1:3 hexanes–EtOAc) to yield 11.3 g (40%) of **37** as a yellow oil. Spectral data for **37** was identical to that previously published.[9]

4.1.15. Trifluoromethanesulfonic acid 2-{methyl[4-[methyl(toluene-4-sulfonyl)amine]-2-(tributylstannyl)-but-2*E*-enoyl]amino}phenyl ester (8). Degassed (sparged with Ar for 1 h) THF (80 mL) was added to a flask charged with **36** (4.66 g, 9.24 mmol) and the solution was cooled to 0°C. Under a positive Ar flow, $Pd(PPh_3)_4$ (0.39 g, 0.37 mmol) was added to this solution. A THF solution of Bu_3SnH (10.0 mL, 0.93 M) then was added dropwise at 0°C over 20 min using a syringe pump. After 2 h, the solution was concentrated and the residue was purified on silica gel using gradient elution (3:1 hexanes–EtOAc–2:1 hexanes–EtOAc) to yield 6.44 g (88%) of **8** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) a ~1:1 mixture of rotamers, only major peaks are listed δ 7.71 (dd, J=8.2, 6.6 Hz), 7.46–7.33 (m), 7.30–7.27 (m), 5.74 (ddd, J_{Sn-H}=21.5 Hz, J=6.5, 6.5 Hz), 3.86 (m,), 3.29 (s), 3.28 (s), 2.76 (s), 2.73 (s), 2.46 (s), 2.45 (s), 1.81 (s), 1.65–1.51 (m), 1.40 (t, J=7.3 Hz), 1.35 (t, J=7.3 Hz,), 1.28 (t, J=7.3 Hz), 1.24 (t, J=7.3 Hz), 1.10 (tt, J_{Sn-H}=26.2 Hz, J=8.3 Hz), 0.94 (t, J=7.3 Hz), 0.89 (t, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) a ~1:1 mixture of rotamers, only major peaks are listed δ 172.6, 172.3, 145.7, 143.2, 136.6, 134.6, 129.6, 127.4, 121.9, 119.6, 117.1, 53.4, 50.9, 38.4, 34.6, 34.4, 28.7 (t), 28.5 (t), 27.1 (d), 21.3, 13.5, 10.7 (d); IR (film) 2926, 1640, 1602, 1424, 1212, 1162 cm^{-1}; HRMS (ESI) m/z calcd for $C_{32}H_{47}F_3N_2O_6SnS_2$ (M+H$^+$) 797.1932, found 797.1923, calcd for (M+Na$^+$) 819.1751, found 819.1761.

4.1.16. *E*-Butenanilide 6. A solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (21 mg, 0.020 mmol), P(2-furyl)$_3$ (19 mg, 0.08 mmol) and *N*-methylpyrrolidinone (NMP) (1 mL) was charged to a base-washed, sealable reaction flask and sparged with Ar for 1 h. In a separate flask, a solution of **7** (97 mg, 0.200 mmol), **8** (0.237 g, 0.298 mmol) and NMP (1 mL) was sparged with Ar for 1 h and then transferred to the catalyst solution. The resulting dark green solution was degassed using the freeze-pump-thaw technique (3×, −78°C cooling bath, 0.05 mm). Copper (I) iodide (39 mg, 0.20 mmol) was added in one portion under positive Ar flow and the flask was sealed. The solution was maintained at rt for 36 h at which time it was partitioned between an aqueous solution of NH_4OH (10 mL, 5% in H_2O) and EtOAc (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×5 mL) and CH_2Cl_2 (2×10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified on silica gel using gradient elution (10:1 CH_2Cl_2–MeOH–10:1:0.5 CH_2Cl_2–MeOH–NH_4OH) to yield 0.162 g (94%) of **6** as a colorless foam: ^{1}H NMR (500 MHz, CD_2Cl_2, 200 K) a mixture of rotamers,[§§] only major peaks are listed δ 7.59 (t, J=9.7 Hz, 2H), 7.37 (t, J=9.3 Hz, 2H), 6.28 (d, J=7.6 Hz, 0.5H), 6.12 (d, J=7.7 Hz, 0.5H), 5.86 (t, J=7.6 Hz, 0.3H), 5.62 (d, J=7.4 Hz, 0.3H), 4.85 (br s, 1H), 4.77 (br s, 1H), 4.67 (br s, 0.5H), 4.61 (br s, 0.5H), 3.21 (s, 1.3H), 3.07 (s, 2H), 2.95 (s, 2H), 2.91 (s, 1H), 2.58 (s, 1H), 2.54 (s, 2H), 2.45–2.38 (m, 9H), 2.31 (s, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2) a mixture of rotamers, only major peaks are listed δ 169.4, 147.1, 144.7, 143.9, 134.5, 131.2, 129.6, 127.4, 121.9, 117.2,110.8, 110.8, 105.5, 90.5 (br), 84.5 (br), 62.1, 49.0, 36.9, 34.6, 21.4; IR (film) 3416, 2937, 1648, 1602, 1498, 1216, 1162, 1139 cm^{-1}; HRMS (ESI) m/z calcd for $C_{43}H_{47}F_3N_6O_6S_2$ (M+H$^+$) 887.2849, found 887.2876.

4.1.17. Heck cyclization of 6 with (*S*)-tol-BINAP to form 3a″*R*-enamine 5. A sealed tube was charged with **6** (0.162 g, 0.188 mmol), $Pd(OAc)_2$ (4 mg, 0.019 mmol), (*S*)-tol-BINAP (26 mg, 0.038 mmol), MeCN (2 mL, previously sparged with Ar for 3 h) and 1,2,2,6,6-pentamethylpiperidine (0.14 mL, 0.75 mmol). This solution was sparged with Ar for 15 min until the solution was a deep red color. The reaction vessel was sealed and heated at 80°C for 18 h at which time it was allowed to cool to rt and partitioned between saturated aqueous NaCN (10 mL) and EtOAc (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×10 mL) and CH_2Cl_2 (2×10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified on silica gel using gradient elution (10:1 CH_2Cl_2–MeOH–10:1:0.05 CH_2Cl_2–MeOH–NH_4OH) to yield 0.130 g (97%) of **5** and **39** as a 6:1 mixture of epimers (determined by analytical HPLC: Zorbax Extend-C18, 5 μm, 250×4.6 mm, 70:30 MeCN–H_2O (1% NH_4OH), 1 mL/min, UV detection at 254 nm). For characterization of **5**, a comparable sample was purified by reverse-phase HPLC: Zorbax Extend-C18, 5 μm, 150×21.2 mm, 70:30 CH_3CN–H_2O (1% NH_4OH), 16 mL/min, UV detection at 254 nm) $[\alpha]^{27}_{405}$=−472, $[\alpha]^{27}_{435}$=−353, $[\alpha]^{27}_{546}$=−165, $[\alpha]^{27}_{577}$=−141, $[\alpha]^{27}_{D}$=−133 (c 0.64, MeOH); ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 360 K) δ 7.52 (d, J=8.3 Hz, 2H), 7.46 (ddd, J=7.7, 7.7, 1.3 Hz, 1H), 7.43 (d, J=8.0 Hz, 2H), 7.21 (t, J=7.5 Hz, 1H), 7.17 (d, J=7.9 Hz, 1H), 7.01 (d, J=7.9 Hz, 1H), 6.91 (d, J=7.6 Hz, 1H), 6.87 (t, J=7.6 Hz, 1H), 6.74 (br d, J=7.2 Hz, 1H), 6.66 (d, J=7.2 Hz, 1H), 6.60 (d, J=14.3 Hz, 1H), 6.45 (t, J=7.6 Hz, 1H), 6.34 (t, J=7.4 Hz, 1H), 6.22 (d, J=7.8 Hz, 1H), 5.37 (d, J=14.3 Hz, 1H), 4.45 (br s, 1H), 4.35 (br s,1H), 4.19 (br d, J=3.6 Hz, 1H), 3.24 (s, 3H), 2.91 (s, 3H), 2.89 (s, 3H), 2.60–2.52 (m, 2H), 2.44 (s, 3H), 2.42–2.36 (m, 2H), 2.35 (s, 3H), 2.32–2.26 (m, 1H), 2.22–2.17 (m, 1H), 2.15 (s, 3H), 1.89–1.85 (m, 1H), 1.80 (ddd, J=11.8, 5.6, 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 360 K) δ 176.0, 152.3, 149.1, 143.5, 142.4, 134.8, 133.6, 132.6, 130.0, 129.41, 129.38, 128.1, 126.9, 126.1, 125.7, 124.3, 122.5, 122.1, 122.0, 120.0, 117.2, 115.9, 110.1, 108.5, 104.9, 91.0, 82.8, 61.96, 61.92, 55.5, 51.1, 50.7, 36.9, 34.7, 34.63, 34.59, 31.8, 25.7, 20.4 (one ^{13}C signal is apparently overlapping with another at this field strength); IR (film) 3385, 2930, 1702, 1602, 1459, 1351, 1254, 1158 cm^{-1}; HRMS (ESI) m/z calcd for $C_{42}H_{46}N_6O_3S$ (M+H$^+$) 715.3430, found 715.3421.

4.1.18. Heck cyclization of 6 with (*R*)-tol-BINAP to form 3a″*S*-enamine 39. Following the procedure employed to cyclize **6** with (*S*)-tol-BINAP, **6** (0.117 g, 0.136 mmol), $Pd(OAc)_2$ (3 mg, 0.014 mmol), and (*R*)-tol-BINAP (18 mg, 0.027 mmol) yielded 96 mg (99%) of **39** and **5** as an 18:1 mixture of epimers as determined by ^{1}H NMR. For characterization of **39**, a comparable sample was purified by reverse-phase HPLC: Zorbax Extend-C18, 5 μm, 150×21.2 mm, 70:30 CH_3CN–H_2O (1% NH_4OH), 16 mL/min, UV detection at 254 nm) $[\alpha]^{27}_{405}$=−587, $[\alpha]^{27}_{435}$=−438, $[\alpha]^{27}_{546}$=−203, $[\alpha]^{27}_{577}$=−174, $[\alpha]^{27}_{D}$=−165 (c 0.51, CH_2Cl_2); ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 360 K) δ 7.57 (d, J=8.3 Hz, 2H), 7.45 (d, J=7.9 Hz, 2H), 7.43–7.38 (m, 2H), 7.20–7.13 (m, 3H), 7.05 (d, J=7.2 Hz, 1H), 6.93 (t, J=7.5 Hz, 1H), 6.64 (d, J=14.3 Hz, 1H), 6.62 (d, J=6.8 Hz, 1H), 6.48 (t, J=7.5 Hz, 2H), 6.30 (d, J=7.7 Hz, 1H), 5.35 (d, J=14.3 Hz, 1H), 4.90 (s, 1H), 4.27 (s, 1H), 4.16 (s, 1H), 3.25 (s, 3H), 2.93 (s, 3H), 2.92 (s, 3H), 2.44 (s, 3H), 2.43–2.38 (m, 4H), 2.35–2.31 (m, 1H), 2.30 (s, 3H), 2.24–2.19 (m, 1H), 1.95 (s, 3H), 1.90–1.84 (m, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 360 K) δ 176.1, 152.3, 149.0, 143.6, 142.3, 134.7, 133.6, 132.4, 130.6, 129.4, 128.0, 127.2,

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[§§] Attempts to resolve peaks in the ^{1}H NMR at high temperature led to extensive decomposition, low temperature ^{1}H and ^{13}C were performed to decrease the rate of conformer interconversion.

126.1, 125.8, 124.3, 123.1, 123.0, 122.9, 122.0, 119.2, 116.9, 115.9, 110.3, 108.5, 105.1, 91.0, 84.0, 61.6, 55.8, 51.4, 51.3, 37.0, 35.4, 34.8, 34.5, 31.8, 25.8, 20.4 (two ^{13}C signals are apparently overlapping with others at this field strength); IR (film) 3385, 2930, 1702, 1602, 1459, 1351, 1254, 1158 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{42}H_{46}N_6O_3S$ ($M+H^+$) 715.3430, found 715.3428.

4.1.19. Catalytic hydrogenation of 5 to form *N*-tosylamine 40. A 6:1 mixture of **5**, and **39** (0.142 g, 0.198 mmol, generated from Heck cyclization of **6** with (*S*)-tol-BINAP), $Pd(OH)_2/C$ (0.150 g, 20 wt%), and EtOH (3 mL) was stirred in a glass sleeve within a pressure reactor (Parr bomb, 120 cm^3) under 1500 psi of H_2 at 80°C for 48 h. The reaction vessel was cooled and the mixture taken up in a syringe and pushed through a nylon filter (0.45 μm, *d*=3 cm). The glass sleeve and filter were repeatedly washed with hot MeOH (50 mL). The resulting solution was concentrated to afford 0.127 g (90%) of **40** (which was contaminated with the corresponding amount of **41**). This crude product was taken on directly to the next step. For characterization of **40**, a comparable sample was purified by reverse-phase HPLC: Zorbax Extend-C18, 5 μm, 150×21.2 mm, 70:30 CH_3CN-H_2O (1% NH_4OH), 16 mL/min, UV detection at 254 nm. Diagnostic data for **40**: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 360 K) δ 7.52 (d, *J*=8.3 Hz, 2H), 7.44 (dt, *J*=6.5, 2.4 Hz, 1H), 7.39 (d, *J*=8.0 Hz, 2H), 7.20 (t, *J*=7.4 Hz, 1H), 7.14 (d, *J*=7.1 Hz, 1H), 7.10 (d, *J*=7.8 Hz, 1H), 6.88 (d, *J*=7.2 Hz, 1H), 6.83 (t, *J*=7.5 Hz, 1H), 6.78 (d, *J*=7.2 Hz, 1H), 6.69 (d, *J*=7.8 Hz, 1H), 6.46 (t, *J*=7.6 Hz, 1H), 6.32 (t, *J*=7.3 Hz, 1H), 6.20 (d, *J*=7.9 Hz, 1H), 5.05 (br d, *J*=3.9 Hz, 1H), 4.57 (br s, 1H), 4.40 (br s, 1H), 3.21 (s, 3H), 2.90 (s, 3H), 2.90–2.83 (m, 2H), 2.64 (s, 3H), 2.65–2.62 (m, 3H), 2.42 (s, 3H), 2.41–2.37 (m, 1H), 2.36 (s, 3H), 2.35–2.29 (m, 1H), 2.27 (s, 3H), 2.23–2.18 (m, 1H), 1.90–1.80 (m, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 360 K) δ 176.9, 152.3, 149.7, 143.0, 142.6, 135.2, 134.3, 132.6, 129.5, 129.1, 128.1, 126.9, 126.4, 124.8, 124.1, 122.4, 122.1, 121.9, 119.2, 117.4, 115.9, 108.4, 104.9, 91.0, 82.7, 62.0, 61.9, 53.4, 51.0, 50.6, 45.4, 36.9, 34.9, 34.8, 34.7, 34.1, 30.5, 25.6, 20.3 (one ^{13}C signal is apparently overlapping with another at this field strength); IR (film) 2934, 1695, 1606, 1494, 1347, 1162; HRMS (ESI) *m/z* calcd for $C_{42}H_{48}N_6O_3S$ ($M+H^+$) 717.3587, found 717.3569.

4.1.20. Idiospermuline (4). A toluene solution of Red-Al® (0.1 mL, 65 wt%) was added to a solution of **40** (contaminated with ~15% of **41**) (26 mg, 0.037 mmol) in toluene (2 mL) at rt. After 15 min, the solution was cooled to 0°C and EtOAc (3 mL) was added dropwise. The resulting solution was concentrated in vacuo and placed under high vacuum for 1 h. The residue was dissolved in THF (5 mL) and added to the Na/NH_3 solution described below.

A two-neck reaction vessel fitted with a liquid NH_3 condenser and magnetic stir bar was charged with sodium metal (20 mg, 0.87 mmol) under a positive flow of N_2. The reaction flask and condenser were cooled to −78°C. A separate three-neck flask with an attached bubbler was cooled to −78°C and NH_3 (50 mL) was condensed directly from the tank into this flask. The NH_3 was redistilled from the three-neck flask into the reaction vessel (20 mL) through a cannula to create a dark blue solution. The THF solution of the crude Red-Al® reduction product was added dropwise to the dark blue solution at −78°C. After 10 min, NH_4Cl (1.0 g) was added to the solution at −78°C. The mixture was warmed slowly to rt, partitioned between saturated aqueous NH_4Cl (10 mL) and EtOAc (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×5 mL) and $CHCl_3$ (saturated with NH_3) (3×10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by preparative HPLC (Zorbax Extend 5 μm C18, 250×15.5 mm, 80:20 MeOH–1% NH_4OH in H_2O, 16 mL/min, UV detection at 254 nm, retention time 10.6 min) to provide 9.2 mg (46% over 3 steps from **5**) of idiospermuline (**4**) as an amorphous solid. Additionally, 3.5 mg (17%) of 3a″,8a″-bis-epiidiospermuline (**42**) was isolated (retention time 13.5 min). Data for synthetic **4**: HRMS (ESI) *m/z* calcd for $C_{35}H_{42}N_6$ ($M+H^+$) 547.3549, found 547.3543. Other spectral (^{1}H and ^{13}C NMR in $CDCl_3$) and analytical properties (TLC and HPLC: Zorbax Extend 5 μm C18, 250×4.60 mm, 80:20 MeOH–1% NH_4OH in H_2O, 0.8 mL/min, UV detection at 254 nm) were indistinguishable from those of a sample of natural **4**; the CD spectrum in MeOH at 0.2 mg/mL of synthetic **4** compared well with that the CD spectrum in MeOH at 0.1 mg/mL taken of authentic **4**.[3] Copies of ^{1}H and ^{13}C NMR spectra of synthetic idiospermuline have been deposited as Supporting Information for Ref. 8.

4.1.21. Catalytic hydrogenation of 39 to form *N*-tosylamine 41. Following the procedure employed for the catalytic hydrogenation of **5**, a 1:18 mixture of **5** and **39** (0.191 g, 0.267 mmol, generated from Heck cyclization of **5** with (*R*)-tol-BINAP), and $Pd(OH)_2/C$ (0.134 g, 20 wt%), yielded 0.171 g (89%) of **41**, (which was contaminated with the corresponding amount of **40**). This crude product mixture was taken on directly to the next step. For characterization of **41**, a comparable sample was purified by reverse-phase HPLC: Zorbax Extend-C18, 5 μm, 150×21.2 mm, 70:30 CH_3CN-H_2O (1% NH_4OH), 16 mL/min, UV detection at 254 nm. Diagnostic data for **41**: ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 360 K) δ 7.55 (d, *J*=8.2 Hz, 2H), 7.40 (m, 3H), 7.23 (d, *J*=6.9 Hz, 1H), 7.17 (t, *J*=7.4 Hz, 1H), 7.11 (d, *J*=7.8 Hz, 1H), 7.06 (d, *J*=6.2 Hz, 1H), 6.97 (d, *J*=7.3 Hz, 1H), 6.90 (t, *J*=7.5 Hz, 1H), 6.65 (d, *J*=7.7 Hz, 1H), 6.47 (t, *J*=7.6 Hz, 1H), 6.40 (t, *J*=7.3 Hz, 1H), 6.27 (d, *J*=7.8 Hz, 1H), 5.91 (br s, 1H), 4.23 (br s, 1H) 3.21 (s, 3H), 2.90 (s, 3H), 2.92–2.89 (m, 1H), 2.82–2.75 (m, 1H), 2.65 (s, 3H), 2.66–2.55 (m, 2H), 2.40 (s, 3H), 2.42–2.35 (m, 3H), 2.30 (s, 3H), 2.33–2.25 (m, 2H), 2.24–2.19 (m, 1H), 2.17 (s, 3H), 1.90–1.83 (m, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 360 K) δ 177.1, 152.3, 149.5, 143.0, 142.6, 135.1, 134.6, 132.2, 129.5, 129.2, 128.0, 127.1, 126.4, 125.1, 124.3, 123.0, 122.9, 121.9, 118.3, 116.9, 115.8, 108.5, 105.1, 91.0, 84.5, 61.8, 61.7, 53.7, 51.5, 51.4, 45.3, 36.9, 35.9, 34.8, 34.7, 34.6, 33.9, 30.4, 25.7, 20.4; HRMS (ESI) *m/z* calcd for $C_{42}H_{48}N_6O_3S$ ($M+H^+$) 717.3587, found 717.3599.

4.1.22. 3a″,8a″-Bis-epiidiospermuline (42). Following the procedure employed to furnish idiospermuline (**4**) from **40**, the crude catalytic hydrogenation product **41** (contaminated with ~5% of **40**) (33 mg, 0.046 mmol) was converted to

14.2 mg (57% from **39**) of **42** as an amorphous solid. Additionally, 1.2 mg (5%) of idiospermuline (**4**) was isolated. Characterization data for **42**: $[\alpha]^{28}_{405}=-492$, $[\alpha]^{28}_{435}=-372$, $[\alpha]^{28}_{546}=-187$, $[\alpha]^{28}_{577}=-164$, $[\alpha]^{28}_{\mathrm{D}}=-156$ (c 0.25, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J=7.0 Hz, 1H), 7.12 (t, J=7.6 Hz, 1H and m, 1H), 7.05–6.90 (m, 3H), 6.74 (t, J=7.3 Hz, 1H), 6.60–6.52 (m, 1H), 6.48 (d, J=7.8 Hz, 1H), 6.42–6.28 (m, 2H), 4.58 (s, 1H), 4.50–4.30 (m, 2H), 3.00 (s, 3H), 2.99–2.94 (m, 1H), 2.94 (s, 3H), 2.88–2.78 (m, 1H), 2.68–2.59 (m, 2H), 2.53–2.38 (m, 5H) 2.50 (s, 3H), 2.45 (s, 3H), 2.20 (s, 3H), 2.05–1.88 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 153.0, 149.3, 133.2, 132.6, 132.4, 128.1, 128.0, 125.9, 125.2, 123.8, 117.7, 116.6, 115.1, 107.1, 105.9, 95.0, 91.7, 84.7, 62.7, 62.3, 59.6, 52.8, 52.7, 38.5, 37.4, 36.8, 36.5, 35.7, 35.4; IR (film) 3250, 2934, 2791, 1602, 1494, 1251, 1154, 1034 cm^{-1}; HRMS (ESI) m/z calcd for $C_{35}H_{42}N$ $(M+H^+)$ 547.3549, found 547.3541.

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