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Enantioselective Total Syntheses of Plectosphaeroic Acids B and C

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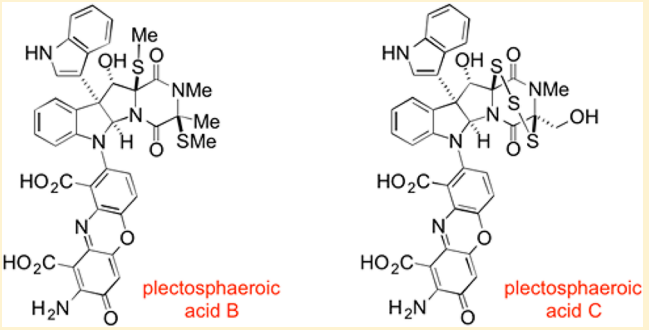
Supporting Information

ABSTRACT: Evolution of the synthetic strategy that culminated in the first total syntheses of the structurally unique plectosphaeroic acids B (**2**) and C (**3**) is described. The successful enantioselective route to (+)-**2** and (+)-**3** proceeds in 6 and 11 steps from the known hexahydro-2*H*-pyrazinopyrrolo[2,3-*b*]indole-1,4-dione **39**, which in turn is available in enantiomerically pure form by chemical synthesis. The central challenge in this synthesis endeavor was uniting the hexahydro-2*H*-pyrazinopyrrolo[2,3-*b*]indole-1,4-dione and cinnabarinic acid fragments of these marine alkaloids. Critical for achieving this successful C−N bond formation was the use of an iodocinnabarinic acid diester in which the amino group was masked with two Boc substituents, a Cu(I) carboxylate complex and the weak base KOAc. The highly congested C−N bond generated in this coupling, in conjunction with the delicate nature of the densely functionalized coupling partners, provided a striking testament to the power of modern copper-mediated amination methods. Two approaches, one stereoselective, for introducing the methylthio substituents of (+)-plectosphaeroic acid B were developed. The epitrisulfide ring of (+)-plectosphaeroic acid C was formed by ring expansion of an epidisulfide precursor.



INTRODUCTION

Epipolythiodioxopiperazines (ETPs) and their methylthio congeners constitute a group of structurally complex and biologically active fungal alkaloids that are characterized structurally by a transannular polysulfide unit joining carbons 3 and 6 of the 2,5-dioxopiperazine ring or thioethers appended at these carbons (Figure 1).[1] A spectrum of biological properties has been reported for this family of natural products, including antimicrobial, antiviral, antifungal, and anticancer activities.[2] Recent attention has focused on the chemotherapeutic potential of ETP molecules, as several studies indicate in vivo selectivity and cytotoxicity toward several cancer variants.[3] These potent activities are generally attributed to the labile S−S σ-bonds of the epidi- or epipolysulfide functionalities.[1]

The plectosphaeroic acids A−C (**1**−**3**) were reported in 2009 by Mauk, Andersen, and co-workers from the marine fungus *Plectosphaerella cucumerina*, which was collected in Barkley Sound, British Columbia, Canada.[4] The constitution and relative configuration of these structurally unique alkaloids were elucidated largely by NMR analysis, whereas the absolute configuration of **1**−**3** was assigned by comparison of circular dichroism (CD) data with values reported for a related group of ETP toxins, the leptosins (e.g., **9**).[5] The plectosphaeroic acids A−C (**1**−**3**) represent a new family of fungal alkaloids that comprise a hexahydro-2*H*-pyrazinopyrrolo[2,3-*b*]indole-1,4-dione moiety **5** containing sulfur functionality and a cinnabarinic acid portion **4**. As both fragments likely arise biosynthetically from tryptophan, the plectosphaeroic acids contain a linear arrangement of four highly modified tryptophan units, a structural feature shared by other, less modified, tryptophan alkaloids such as quadrigemine C[6] and psychotetramine.[7] A number of ETP alkaloids and their methylthio congeners (e.g., **6**−**14**) share a hexahydro-2*H*-pyrazinopyrrolo[2,3-*b*]indole-1,4-dione fragment **5** that is homologous to the northern fragment of **1**−**3**.[8] The southern cinnabarinic acid (**4**) fragment, particularly its 2-amino-phenoxazin-3-one core, is also familiar in natural products, some of which show potential cancer chemotherapeutic applications.[9]

The plectosphaeroic acids (**1**−**3**) were isolated from a program to discover inhibitors of the enzyme indoleamine 2,3-dioxygenase (IDO) from marine sources.[4] Inhibition of IDO has been identified as a potential new approach to cancer therapy in which the immune system would be activated to combat solid tumors.[10] The plectosphaeroic acids (**1**−**3**) and cinnabarinic acid (**4**) were reported to be equipotent (IC_{50} = 2 μM) against human recombinant IDO, whereas T988 A (**10**), which was coisolated with **1**−**3**, was found to be inactive.[11] Considering that some portion of the southern fragment was responsible for IDO inhibition, we became intrigued by the further biological evaluation and the considerable synthetic challenges[12−14] associated with the synthesis of these molecules possessing two antitumor pharmacophores.[15]

Herein, we describe the development of the first total syntheses of (+)-plectosphaeroic acids B (**2**) and C (**3**).[16] The successful approach features a late-stage copper-mediated C−N

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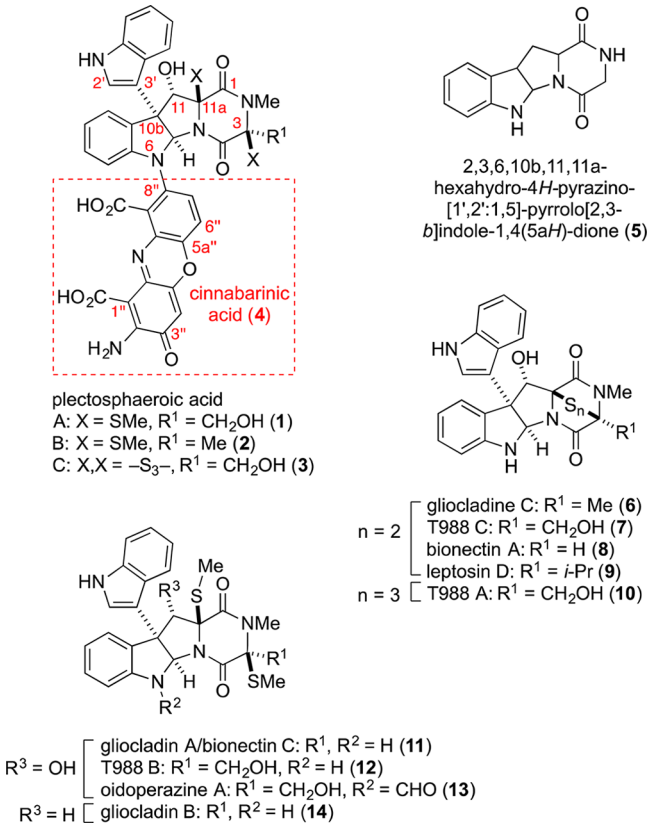


Figure 1. Structures of plectosphaeroic acids A–C and related ETP and methylthio congeners containing the common fragment **5**.

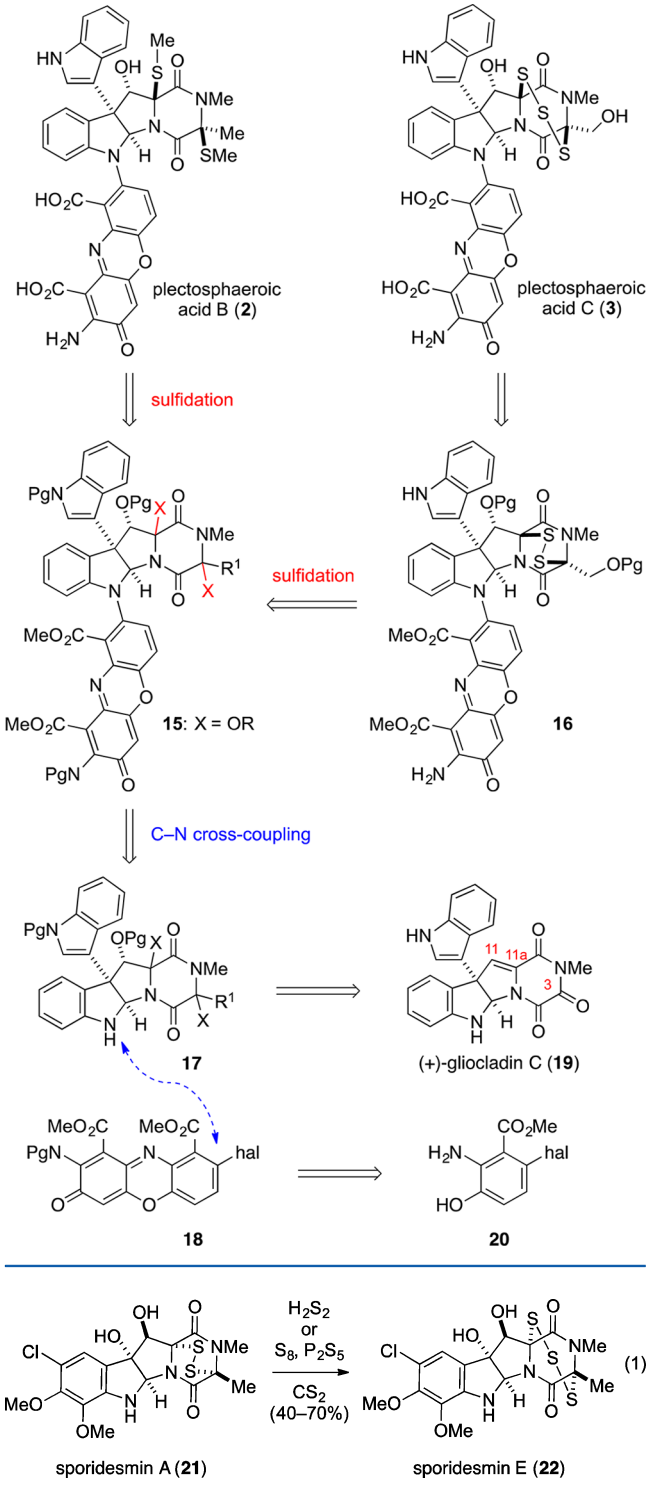
cross-coupling reaction in addition to the stereoselective incorporation of the methylthio or bridging trisulfide substituents into the dioxopiperazine subunits of **2** and **3**. In vitro cytotoxicity of plectosphaeroic acids B (**2**) and C (**3**) and their dimethyl esters against human prostate and melanoma cancer cell lines is described and compared to that of related structures.

RESULTS AND DISCUSSION

Synthesis Plan. Our synthetic planning was guided by several considerations (Scheme 1). The well-recognized sensitivity of epipolythiodioxopiperazines to strong bases and nucleophiles,[1,14] and the similar sensitivity of hexahydro-2*H*-pyrazinopyrrolo[2,3-*b*]indole-1,4-diones that contain a hydroxyl substituent adjacent to the quaternary carbon stereocenter,[17] places limitations on the reactions that could be employed. Certainly we wanted to defer the sulfidation step until a late stage of the synthesis. Precedent from Movassaghi's,[13] Sodeoka's,[18] and our[19] groups suggested that the installation of methylthio or epidithio substituents by thiol trapping of *N*-acyliminium ions derived from intermediate **15** should be possible and likely stereoselective. However, forming the bridging trisulfide functionality of plectosphaeroic acid C (**3**) by a short sequence was less certain.[20] Attractive to us was the potential of ring-expanding the likely more accessible epidisulfide congener **16**, a transformation first described by Taylor and co-workers in 1968 for elaborating naturally obtained sporisdesmin A (**21**) to sporidesmin E (**22**) (eq 1).[21]

Foreseen as a central challenge in these syntheses would be uniting the hexahydro-2*H*-pyrazinopyrrolo[2,3-*b*]indole-1,4-dione and cinnabarinic acid fragments. To maximize convergency, we hoped to forge the key C–N bond as late as possible, for example, between the indoline nitrogen of the pyrazinopyrroloindole fragment **17** and a halogenated congener **18** of cinnabarinic acid. In spite of the remarkable progress recorded in recent years in forging aryl–nitrogen bonds,[22] the hindered nature of the required union and the structural complexity of the coupling partners **17** and **18** were without precedent.[23,24] Hexahydro-2*H*-pyrazinopyrrolo[2,3-*b*]indole-1,4-dione intermediate **17** was envisaged originating from the

Scheme 1. Retrosynthetic Analysis of Plectosphaeroic Acids A–C



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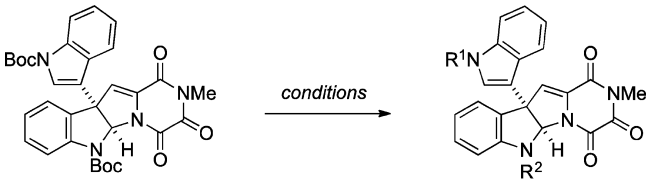
bis(*tert*-butoxycarbonyl) derivative of the natural product (+)-gliocladin C (**19**),[8c,f,12,25] following a sequence our group described recently for preparing gliocladine C (**6**), (+)-T988 C (**7**), and (+)-gliocladin A (**11**).[2c,12] We anticipated that biomimetic, oxidative dimerization of 6-halo-3-hydroxyanthranilic acids **20** would provide access to potential electrophilic coupling partners **18**.[26]

Initial Development of the C−N Cross-Coupling in Model Systems. As an opening phase of this inquiry, we explored the feasibility of joining the two polycyclic fragments of the plectosphaeroic acids. At the time, there were no reports of *N*-arylating structurally complex cyclotryptamines. Thus, we decided to examine initially such conversions with simplified aryl fragments in which a 2-halobenzoic acid would substitute for the cinnabarinic acid electrophile. However, the steric environment and nucleophilicity of the indoline nucleophile of the hexahydro-2*H*-pyrazinopyrrolo[2,3-*b*]indole-1,4-dione would not be easily modeled. As a result, we chose to access an appropriate amine for our preliminary cross-coupling studies from the bis(*tert*-butoxycarbonyl) derivative **23** of (+)-gliocladin C, an intermediate that is available on multigram scale by chemical synthesis.[2c,12]

Salient results from our efforts to deprotect the indoline nitrogen of **23** are summarized in Table 1. Under thermal conditions, the Boc substituent on the indole nitrogen atom was more labile (entries 1 and 2). Lewis acids were more successful, with catalytic amounts of $Sc(OTf)_3$ selectively removing the indoline Boc group to give **25** in 76% yield (entry 3). However, this reaction required careful monitoring to prevent cleavage of the second Boc substituent and proved somewhat unreliable as the reaction was scaled. Thus, an alternative two-step (one-pot) process involving thermal deprotection of both nitrogen atoms of **23**, followed by selective reprotection of the indole nitrogen, was utilized to generate large quantities of the cross-coupling precursor **25** (entry 4).

Table 1. Selective Deprotection of the Bis(*tert*-butoxycarbonyl) Derivative 23 of Gliocladin C



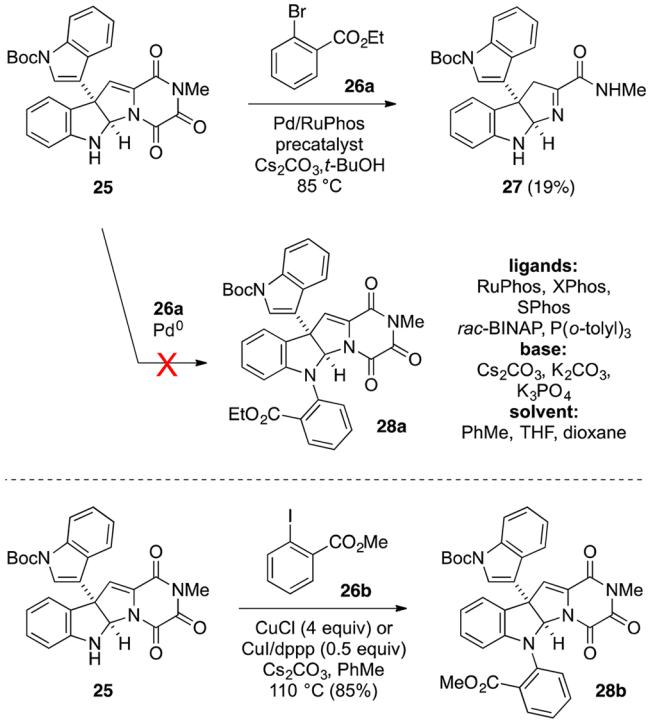
23 **24**: R^1 = H, R^2 = Boc; **25**: R^1 = Boc, R^2 = H

entry	conditions	yield (%)
1	175 °C (neat), 5 min	**24**/**19** (1:1)[a]
2	140 °C (neat), 11 min	**24**/**19**, 83 (3:1)[a,b]
3	$Sc(OTf)_3$ (0.15 equiv), MeCN, 4 h, rt	**25**, 76[b]
4	(i) 175 °C (neat), 15 min; (ii) Boc_2O (1.0 equiv), DMAP, THF	**25**, 95[b]

[a]Relative ratio as determined by ^{1}H NMR. [b]Yield after chromatographic purification.

With indoline **25** in hand, we commenced C−N cross-coupling studies by investigating palladium catalysts (Scheme 2).[27] Attempting to join **25** with ethyl 2-bromobenzoate (**26a**) using 10 mol % of Buchwald's palladacyclic precatalyst ligated with RuPhos[22f,g] and excess Cs_2CO_3 in *t*-BuOH at 85 °C resulted in rapid consumption of **25**. However, *N*-arylation products were not detected from this reaction, which returned ring-fragmentation product **27** in low yield. As the α-oxoimide carbonyl group of trioxopiperazines is quite electrophilic, a property we exploit later in our studies, we reasoned that the *tert*-butoxide anion generated in situ was incompatible with the trioxopiperazine fragment of **25**. Consistent with this result, NaO-*t*-Bu in either THF or toluene decomposed **25**, forming **27**, within hours at 50 °C in the absence of the palladium catalyst.[28] Other strong bases such as LHMDS also consumed **25** at 50 °C, whereas **25** was stable to Cs_2CO_3 in toluene at 85 °C. As a result, our further studies of palladium-catalyzed coupling focused on the use of weak inorganic bases (e.g., Cs_2CO_3, K_2CO_3 and K_3PO_4) in aprotic solvents such as toluene, THF, and 1,4-dioxane. Nevertheless, all attempts to forge the desired C−N bond between **25** and ethyl 2-bromobenzoate (**26a**) or methyl 2-iodobenzoate (**26b**) using catalytic or stoichiometric amounts of palladium(0) and various Buchwald biarylmonophosphine ligands such as RuPhos, XPhos, and SPhos,[22f,g] as well as *rac*-BINAP and tri-*o*-tolylphosphine, were unproductive.

Scheme 2. Investigating Palladium(0)- and Copper(I)-Promoted C−N Cross-Coupling Reactions



Copper(I) salts proved more successful.[22a,b,d,e] After an extensive examination of reaction parameters, it was found that coupling of pyrazinopyrroloindole **25** with 2 equiv of methyl 2-iodobenzoate in the presence of 4 equiv of either CuI, CuBr, or CuCl and 5 equiv of Cs_2CO_3 in toluene at 110 °C for 24 h promoted C−N bond formation to give **28b** as the major product (Scheme 2). Using CuCl, the coupled product **28b** was isolated in 85% yield. Reducing the amount of the copper salt lowered the reaction efficiency, as did replacing Cs_2CO_3 with K_2CO_3 or K_3PO_4. In a brief attempt to develop a catalytic transformation, it was found that the combination of 0.5 equiv of CuI and 1,3-bis(diphenylphosphino)propane (dppp) also furnished **28b** in 85% yield. Having successfully formed the C−N bond in this model system with copper(I), we shifted to the

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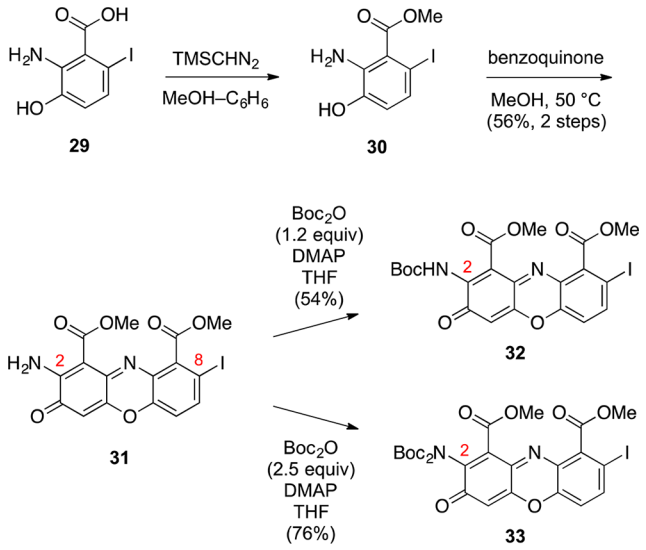
next phase of our studies, introduction of more complex and delicate cinnabarinic acid electrophiles.

C–N Cross-Coupling with Cinnabarinic Acid Derivatives and Initial Attempts To Elaborate the Coupled Products. Our cross-coupling approach required an efficient route for the preparation of cinnabarinic acid derivatives having a halide (or pseudohalide) incorporated at C8 (e.g., **31**) (Scheme 3). As noted previously, such intermediates should be

Scheme 3. Preparation of the 8-Iodophenoxazinone Coupling Partners

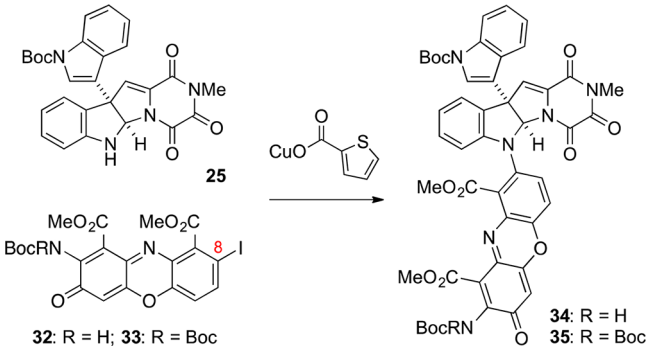


available by oxidative dimerization of 6-halo-3-hydroxyanthranilic acids and derivatives (e.g., **29**).[26,29,30] This transformation could be performed with 3-hydroxy-6-iodoanthranilic acid (**29**);[31] however, we found it more convenient to esterify **29** and then immediately expose the intermediate ester **30** to oxidation with benzoquinone.[32] Simple filtration delivered 2-amino-8-iodophenoxazin-3-one diester **31** in 56% yield from acid **29**. By carefully controlling the amount of Boc_2O used, slow addition of 1.2 equiv or addition of 2–3 equiv, the 2-amino group of **31** was mono- or diprotected to give **32** or **33** in useful yields.[33]

Our efforts to join the two fragments of the plectosphaeroic acids began by attempting to form a C–N bond between the *tert*-butoxycarbonyl derivative **25** of gliocladin C and iodide **32** (Table 2). However, C–N bond formation was not observed using any of the copper(I) conditions that we had identified previously (e.g., excess CuCl, Cs_2CO_3, PhMe, 110 °C). In addition, minor modifications of these conditions also were not fruitful.[34]

A search for an alternate copper reagent,[22a,b,d,e] identified copper(I) thiophene-2-carboxylate (CuTC)[35,36] as particularly effective (Table 2). When **25** was allowed to react with 2 equiv of **32**, 4 equiv of CuTC, and excess Cs_2CO_3 in toluene at 110 °C, coupled product **34** was formed, albeit in low yield (entry 1). The conversion to **34** was improved upon switching to K_2CO_3 as base (entry 2), whereas a change from toluene to dioxane proved detrimental (data not shown). In contrast to our previous observations, substantial hydrodehalogenation and minor amounts of homocoupling of iodide **32** were observed when using CuTC; a result suggesting that this copper complex, unlike other complexes investigated to this point, was more efficient in oxidative addition to the C–I σ-bond of **32**. A potential explanation for the efficacy of CuTC is its increased solubility in nonpolar solvents.[37,38] A breakthrough was made when the electrophile was switched to iodide **33** in which the 2-amino group of the iodophenoxazine was doubly protected. Although the reaction of **25** with 1.5 equiv of **33** in the presence of 3 equiv of CuTC and excess K_2CO_3 in toluene at 110 °C was inefficient (entry 3),[39] carrying out this reaction at **90** °C gave **35** in 48% yield (entry 4). Further reduction of the reaction temperature proved detrimental (entry 5).

Table 2. Optimizing the CuTC-Mediated Cross-Coupling Reaction



entry	iodide	**25**/iodide	CuTC (equiv)	base	temp (°C)	time (h)	yield[a] (%)
1	**32**	1.0:2.0	4	Cs_2CO_3	110	24	**34**, <5
2	**32**	1.0:2.0	4	K_2CO_3	110	24	**34**, 10–20
3	**33**	1.0:1.5	3	K_2CO_3	110	24	**35**, <5[b]
4	**33**	1.0:1.5	3	K_2CO_3	90	24	**35**, 48
5	**33**	1.0:1.5	3	K_2CO_3	80	120	**35**, 19
6	**33**	1.0:1.5	3	K_2CO_3	90	96	**35**, 57
7	**33**	1.0:1.5	6	K_2CO_3	90	24	**35**, 38
8	**33**	1.0:2.3	3	K_2CO_3	90	36	**35**, 67
9	**33**	1.0:3.0	3	K_2CO_3	90	24	**35**, 67

[a]Yields of **34** or **35** after purification by preparatory TLC. [b]Substantial amounts of **32** were observed at this temperature.

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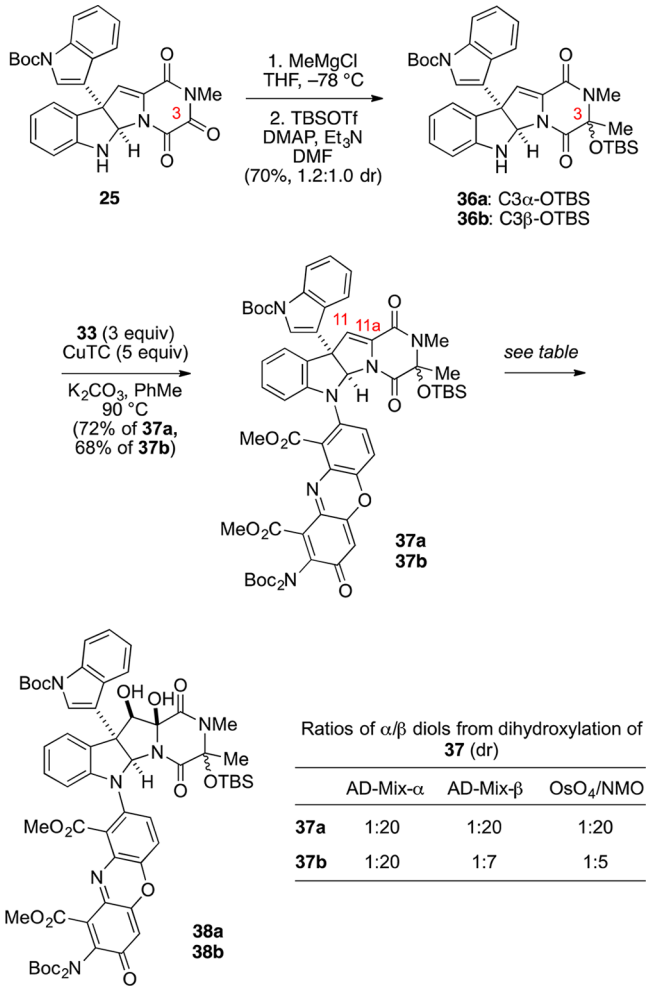
However, additional optimization (entries 6–9) improved the conversion to **35** to 67% yield.[40]

We were encouraged by the successful union of hexahydro-2*H*-pyrazinopyrrolo[2,3-*b*]indole-1,4-dione **25** and iodide **33** to increase the complexity of the amine nucleophile. We chose a measured approach, first by examining whether a potentially delicate *N*,*O*-acetal functionality at C3 would prove problematic. To arrive at a coupling partner of this type, methylmagnesium chloride was added chemoselectively to the α-oxoimide carbonyl group of **25** followed by silylation of the resulting alcohol products to give epimers **36a** and **36b** (1.2:1.0 dr) in 70% yield over two steps (Scheme 4). Submitting these

Scheme 4. Increasing Complexity in the C–N Cross-Coupling and Unexpected Facial Selectivity During Dihydroxylation of the C11,C11a-Double Bond



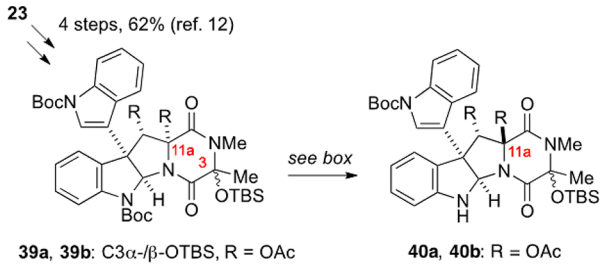
Ratios of α/β diols from dihydroxylation of **37** (dr)			
	AD-Mix-α	AD-Mix-β	OsO_4/NMO
37a	1:20	1:20	1:20
37b	1:20	1:7	1:5

C3-*N*,*O*-acetals to the C–N cross-coupling conditions identified in Table 2 showed that *N*-arylation was efficient with both epimers to give the coupled products **37** in 68–72% yields.

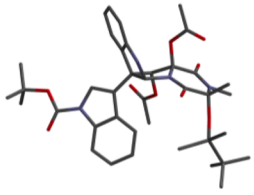
Buoyed by this success, we turned to advance toward the plectosphaeroic acids by dihydroxylation of the alkene double bond of coupled products **37a** and **37b**. In our previous studies with congeners of **37** bearing a Boc protecting group on the indoline nitrogen, we had observed high α-facial selectivity in dihydroxylation of the C11–C11a π bond.[2c,12] To our surprise, oxidation of both **37a** and **37b** with OsO_4/4-methylmorpholine *N*-oxide (NMO), AD-mix α or AD-mix β[41] afforded the undesired, β diols **38a** and **38b** with high stereoselectivity (see the table in Scheme 4).[42] The relative configurations of the syn diol products were assigned from the diagnostic ^{1}H NOE's observed for their C11 methine hydrogens;[12] additionally, the minor isomer obtained from dihydroxylation of **37b** was transformed into bis(methylthio)ether **45b** (vide infra). We were forced to turn to investigate the crucial fragment coupling with more complex hexahydro-2*H*-pyrazinopyrrolo[2,3-*b*]-indole-1,4-dione intermediates already containing oxygen functionality properly installed at C11 and C11a, a strategy that proved ultimately to be successful.

Total Synthesis of (+)-Plectosphaeroic Acid B (2). From the outset of this project, we envisaged the pyrazinopyrroloindole fragment **5** of (+)-plectosphaeroic acid B (**2**) originating from intermediates prepared by our group en route to (+)-gliocladine C (**5**) and congeners.[2c,12] During the synthesis of **5**, the bis(*tert*-butoxycarbonyl) derivative **23** of (+)-gliocladin C was transformed in four efficient steps to products **39a** and **39b** shown in Scheme 5. For the synthesis of

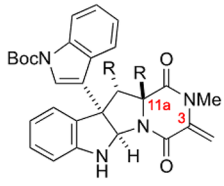
Scheme 5. Deprotection of the Indoline Nitrogen of 39a and 39b



entry	**38**	conditions	yield
1	**39a** or **39b**	i. neat, 175 °C; ii. Boc_2O, DMAP, THF	**40a** or **40b**, 60–80%
2	**39a**	TfOH, CH_2Cl_2, –40 °C	**40a**, 70–80%
3	**39b**	TfOH, CH_2Cl_2, –40 °C	**41**, 82%



X-ray model of **40a**



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2, we needed to remove the Boc group from the indoline nitrogen atom of these intermediates, a task anticipated to be complicated by the various acid-labile functionalities that were present.

Salient results from our efforts to unmask the indoline nitrogen atom of **39a** and **39b** are summarized in Scheme 5. As we were concerned about the sensitivity of these molecules to acid, we initially examined the two-step (single-pot) procedure developed earlier in our studies (entry 1). This sequence provided products **40a** and **40b**, whose relative and absolute configuration was confirmed by single-crystal X-ray analysis, in 60–80% yield.[43] In both products, the configuration of the C11a acetate was inverted during the thermolytic Boc-removal step, consistent with higher thermodynamic stability of a β-C11a-epimer in this ring system. Although this sequence was

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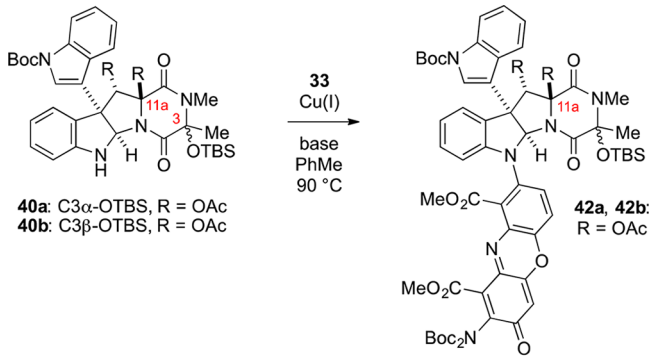
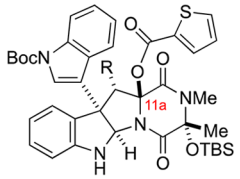
Table 3. C−N Cross-Coupling with Late-Stage Hexahydro-2*H*-pyrazinopyrrolo[2,3-*b*]indole-1,4-dione Intermediates



40a: C3α-OTBS, R = OAc
40b: C3β-OTBS, R = OAc

42a, **42b**: R = OAc



43: R = OAc

entry	indoline[a]	indoline/iodide	Cu(I) (equiv)	base[b]	yield of **42**[c] (%)	yield of **43**[c] (%)
1	**40a**	1:2−3	CuTC (3−6)	K_2CO_3	10−30	5−20
2	**40a**	1:3	CuTC (6)	KOAc	40	<5
3	**40a**	1:3	CuTC (6)	CsOAc	<5	nd[d]
4	**40a** or **40b**	1:3	CuOAc (6)	KOAc	51−58	

[a]All reactions conducted at 0.05 M. [b]Excess base (4−8 equiv) was used. [c]Yields after purification by preparatory TLC. [d]nd = not determined.

best conducted on small scale (multiple vessels containing 40 mg of **39a** or **39b** were run in parallel), it allowed us to secure sufficient quantities of **40a** and **40b** to move forward in the synthesis. Success was registered also in the chemoselective deprotection of **39a** under acidic conditions. Exposure of this epimer to 1.5 equiv of trifluoromethanesulfonic (triflic) acid in CH_2Cl_2 at −40 °C for 2−3 h furnished **40a** in 70−80% yield, also with concomitant inversion of the C11a stereocenter.[44] This transformation required careful monitoring, as prolonged reaction times or an increase in temperature resulted in expulsion of the silyloxy group at C3 to give substantial amounts of α-methylene intermediate **41**. Under identical conditions, epimer **39b** was converted exclusively to elimination product **41** (82% yield). Attempts to prevent the formation of **41** from siloxy epimer **39b** by lowering the reaction temperature, reducing the amount of acid or using silyl triflates (e.g., TMSOTf and TBSOTf) were uniformly unsuccessful.

With convenient access to intermediates **40a** and **40b** in hand, the essential C−N cross-coupling reaction of these more intricate substrates was examined (Table 3). We began by exploring the union of stereoisomer **40a** and cinnabarinic iodide **33**. The CuTC/K_2CO_3 conditions that we had previously found to be optimal with less elaborate intermediates containing a C11,C11a double bond resulted in inefficient conversion to coupled product **42a** (entry 1). A major byproduct formed in this reaction was the C11a thiophene-2-carboxylate analog **43** of the starting diacetate **40a**. As activation of the angular *N*,*O*-acetal appeared unavoidable, to minimize the formation of **43**, KOAc was substituted for K_2CO_3. This change decreased the formation of **43**, giving coupled product **42a** in 40% yield (entry 2). It was eventually found that exposure of **40a** or **40b** to 3 equiv of iodide **33**, 6 equiv of CuOAc and excess KOAc in toluene at 90 °C delivered **42a** and **42b** in 51−58% yield (entry 4).[45]

Two methods were developed for introducing the methylthio substituents of (+)-plectosphaeroic acid B (**2**) (Scheme 6). In the most direct approach, reaction of either *N*,*O*-acetal epimer of dioxopiperazines **42a** or **42b** with a large excess of both $BF_3{\cdot}OEt_2$ and methanethiol at −78 °C with slow warming to room temperature gave an identical 1.3:1.0 separable mixture of bis(methylthio)ethers **44b** and **44a** in high yield (79% from **42a**, 92% from **42b**). The relative configuration of these products was secured from ^{1}H NOE experiments.[46] An identical mixture of epimers was formed when a pure sample of either stereoisomereric product was resubmitted to the reaction conditions, establishing that the thermodynamic ratio of C3 methylthio epimers is produced under these conditions. In addition, this equilibration allowed the undesired C3 α-methylthio epimer **44a** to be recycled. Alternatively, in the sequence we currently prefer, reaction of *N*,*O*-acetals **42** with excess H_2S and $BF_3{\cdot}OEt_2$, followed by alkylation of the resulting thiols with MeI afforded **44b** as a single stereoisomer in 80−88% yield.[47] Bis(methylthio)ether **44b** was prepared on useful scales by both of the procedures summarized in Scheme 6.

The difference in stereochemical outcome of these two sulfidation procedures is striking. Because bis(methylthio)-ethers **44b** and **44a** were established to equilibrate under the acidic conditions of the sulfidation step, a similar thermodynamic equilibration would be expected to occur during the $BF_3{\cdot}OEt_2$-promoted reaction of **42** with H_2S to form the dithiol congeners of **44a** and **44b**. Thus, one potential explanation is a considerably higher thermodynamic stability of the *cis*-dithiol

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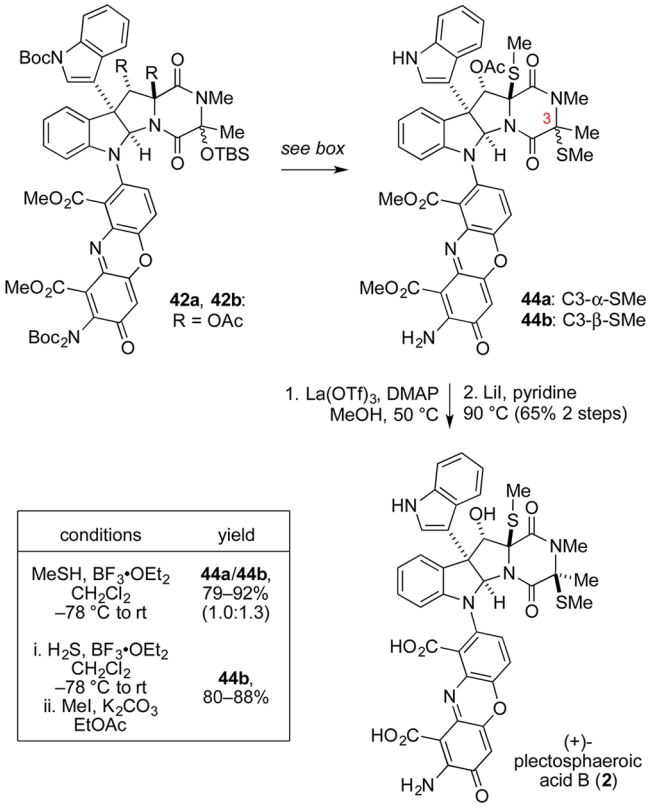
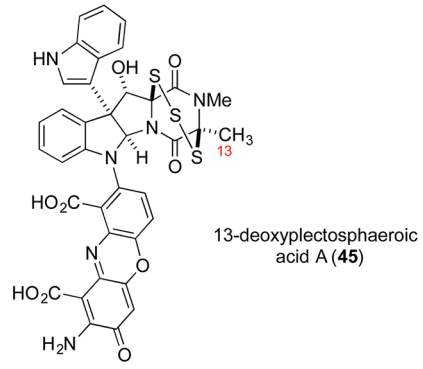
Scheme 6. Completion of the Total Synthesis of Plectosphaeroic Acid B (2)



intermediates. Such a trend was seen in a computational study of *cis*-dithiol and *cis*-bis(methylthio) isomers in closely related model compounds.[48] Alternatively, and in our view more likely, a mixture of dithiol epimers equilibrates[49] during the methylation step, with the observed cis stereoselectivity potentially resulting from intramolecular thio coordination of the intermediate potassium thiolate nucleophile.

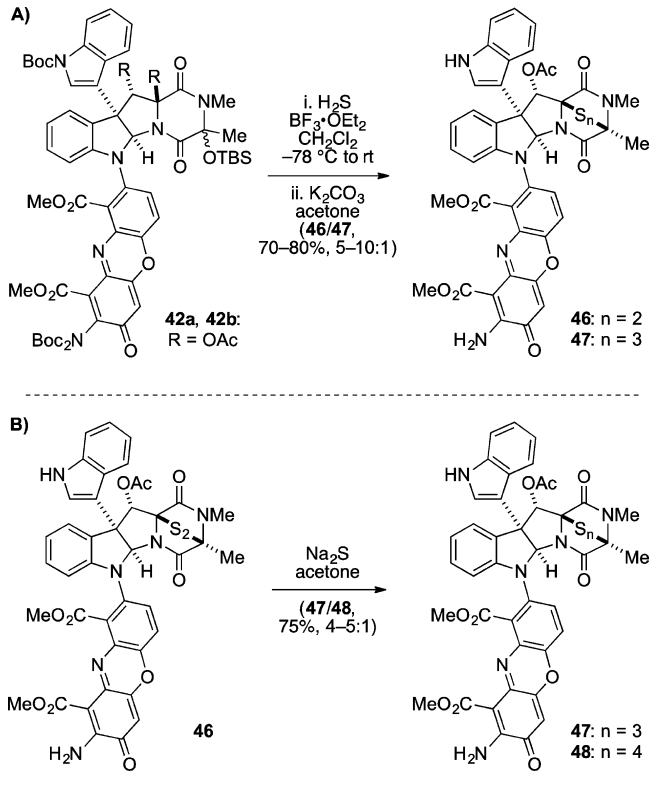
All that remained to finish the total synthesis of plectosphaeroic acid B (**2**) was cleavage of the three ester groups of bis(methylthio) intermediate **44b**. However, the sensitivity of the cinnabarinic acid fragment was worrisome.[50] Methanolysis of the acetyl group at C11 was achieved by exposure of **44b** to excess $La(OTf)_3$ and 1 equiv of DMAP in methanol at 50 °C.[51] In the absence of DMAP, the deprotection step was sluggish, and the resulting product was not stable to prolonged exposure to the reaction conditions. Attempts to promote concomitant hydrolysis of the methyl esters of the phenoxazinone fragment by addition of small amounts of water to this reaction led to decomposition. As a result, the methyl esters were cleaved by classical demethylation with LiI in pyridine at 90 °C.[52] In this way, plectosphaeroic acid B (**2**) was obtained in 65% yield over two steps after purification by HPLC. The optical rotation of synthetic **2**, $[\alpha]_D^{23}$ +228 (*c* 0.08, MeOH), was higher than the value reported for the natural sample, $[\alpha]^{23}_D$ +69.8 (*c* 0.27, MeOH); however, all other spectroscopic data, including CD spectra, compared well.

Total Synthesis of (+)-Plectosphaeroic Acid C (3). As a second total synthesis objective in this area, we selected (+)-plectosphaeroic acid C (**3**) whose synthesis would present two additional challenges: introduction of the bridging trisulfide functionality and incorporation of oxygenation on the one-carbon C3 substituent (Figure 1). We chose to initially address the first obstacle by developing a method to elaborate intermediates prepared en route to (+)-plectosphaeroic acid B to an analogous product containing a trisulfide fragment, 13-deoxyplectosphaeroic acid C (**45**).



The ring-expanding sequence that we eventually implemented to incorporate the epitrisulfide functionality originated from several observations made during our efforts to introduce the methylthio groups of plectosphaeroic acid B (**2**). Specifically, we had observed the formation of epidisulfide **46** (isolated in up to 80% yield) upon exposing *N*,*O*-acetals **42** to excess H_2S and $BF_3{\cdot}OEt_2$ and subsequently to excess K_2CO_3 in acetone in the absence of MeI (Scheme 7A). In addition, minor quantities of **47**, the trisulfide congener of **46**, were also formed from this sequence (10−20% by ^{1}H NMR analysis). When no attempt was made to remove the last traces of H_2S from the crude dithiol intermediate, these products were formed within 30 min in the second step.[53] Consistent with our expectation

Scheme 7. (A) Epipolysulfide Formation and (B) Initial Ring-Expansion Studies



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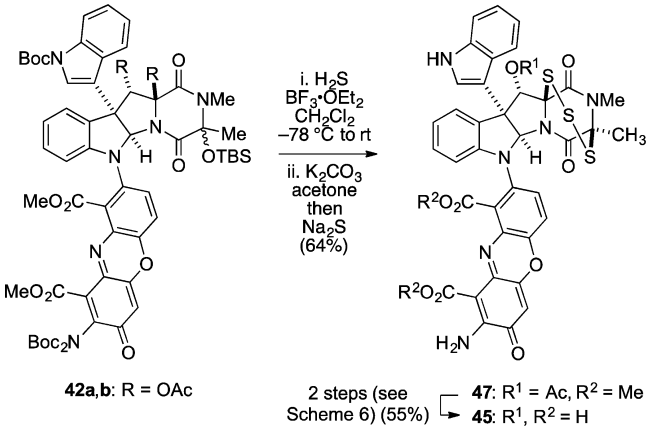
that trisulfide **47** was formed by ring-expansion of epidisulfide precursor **46**,[21,54] exposure of a pure sample of **46** to 1 equiv of Na_2S in acetone at room temperature provided a 4−5:1 mixture of epitrisulfide **47** and epitetrasulfide **48** products in combined yields of up to 75% (Scheme 7B).[55,56]

A streamlined process for installing the epitrisulfide functionality and confirmation that the alcohol and carboxylic acid protecting groups could be removed in the presence of an epitrisulfide was achieved in our successful elaboration of *N,O*-acetals **42** to 13-deoxyplectosphaeroic acid C (**45**) (Scheme 8).

Scheme 8. Epitrisulfide Formation and Preparation of 13-Deoxyplectosphaeroic Acid C (45)

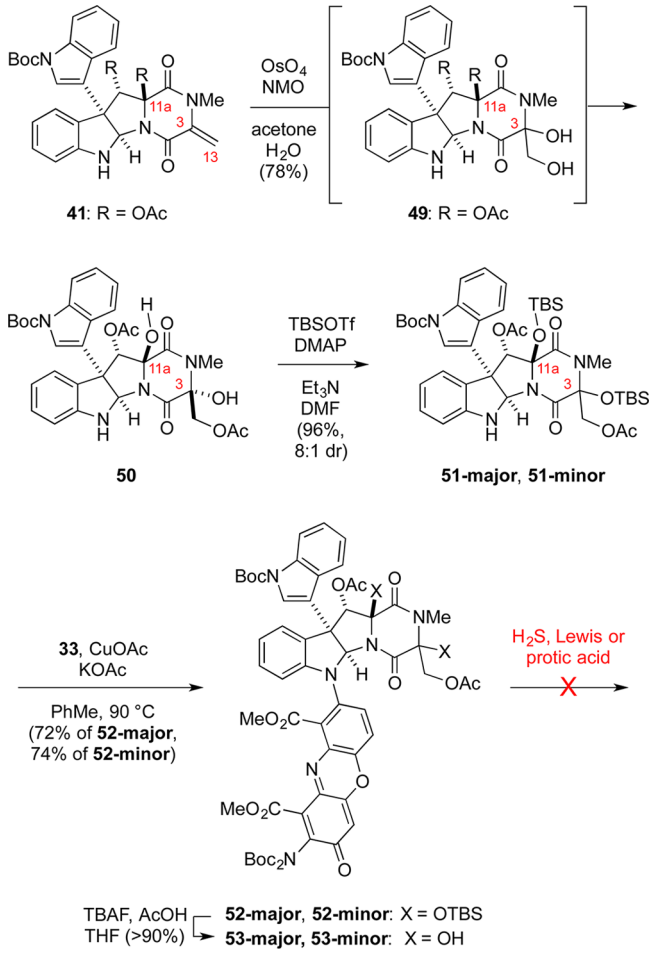


After $BF_3{\cdot}OEt_2$-mediated reaction of **42** with H_2S, the crude dithiol products were dissolved in acetone, followed by sequential additions of K_2CO_3 and Na_2S. In this way, epitrisulfide **47** was isolated in 64% yield from the epimer mixture **42**. To our delight, the two-step sequence for cleaving the ester groups developed en route to (+)-plectosphaeroic acid B (**2**) was not adversely effected by the presence of the epitrisulfide functionality, allowing 13-deoxyplectosphaeroic acid C (**45**) to be prepared in 55% yield from epitrisulfide precursor **47**.

We turned to the synthesis of (+)-plectosphaeroic acid C (**3**) itself. In order to install a hydroxyl group at C13, we envisaged oxidizing the exomethylene double bond of intermediate **41**, a product that could be formed in high yield by the reaction of intermediates **39a** and **39b** with triflic acid (Scheme 5).[57] Oxidation of **41** by reaction with catalytic amounts of OsO_4 in the presence of NMO provided one major product, diol diacetate **50** (Scheme 9). That the acetyl group had been transferred from the angular C11a hydroxyl group of intermediate **49** was apparent from the NMR signals of the methylene group (^{1}H NMR δ 4.42 (d) and 4.29 (d); ^{13}C NMR δ 65.4). Although minor amounts of **49**, in which the C11a acetyl group had not been transferred could be obtained, it was more convenient to promote complete transfer of the acetyl group by stirring the crude reaction product with SiO_2 in ethyl acetate prior to chromatographic purification to yield **50**. Silylation of the tertiary alcohols of **50** furnished pyrazinopyrroloindole **51**, an 8:1 mixture of separable epimers, in 75% overall yield from **41**; these isomers undoubtedly result from inconsequential partial epimerization at C3 during the silylation step.[49]

Joining of the two fragments of (+)-plectosphaeroic acid C (**3**) was accomplished by individually treating epimers **51** with 3 equiv of iodide **33** and 6 equiv of CuOAc in the presence of

Scheme 9. Elaboration of *exo*-Methylene 41 to Intermediates 51 and 52



KOAc in PhMe at 90 °C to give coupled products **52-major** and **52-minor** in 72% and 74% yields, respectively. The increase in efficiency in this C−N coupling step relative to the corresponding *N*-arylation steps in the synthesis of **2** (50−58% yield) is attributable to the enhanced stability of the C3- and C11a-*N,O*-acetals of **51** and **52**. Specifically, *N*-acyliminium ion formation at C3 and C11a would be much less favorable in these intermediates wherein the leaving group is a silyl ether rather than an acetoxy substituent.

To no surprise, this diminished reactivity of the C3- and C11a-*N,O*-acetals complicated the sulfidation step. For example, treating **52-major** with (i) H_2S and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 or $MeNO_2$ at −78 °C to rt, (ii) H_2S and $Sc(OTf)_3$ in MeCN at −78 °C to rt, or (iii) Na_2S in a 1:1 mixture of TFA/$MeNO_2$ at 0 °C to rt were not successful. In these reactions, either sulfur was not incorporated, or after prolonged exposure (i.e., >12 h) decomposition was observed. For this reason, it was decided to convert the oxygen substituents at C3 and C11a to alternate leaving groups. Removal of both silyl groups of **52-major** and **52-minor** upon reaction with TBAF and AcOH in THF gave diols **53-major** and **53-minor** in >90% yields.[58]

By incorporating better leaving groups at C3 and C11a, the total synthesis of (+)-plectosphaeroic acid C (**3**) was successfully completed (Scheme 10).[12,18] After standard acetylation of a mixture of epimeric diols **53** arising from the fragment-coupling and desilylation steps, the 5:1 mixture of tetraacetates **54** was exposed to H_2S and $BF_3{\cdot}OEt_2$ in CH_2Cl_2

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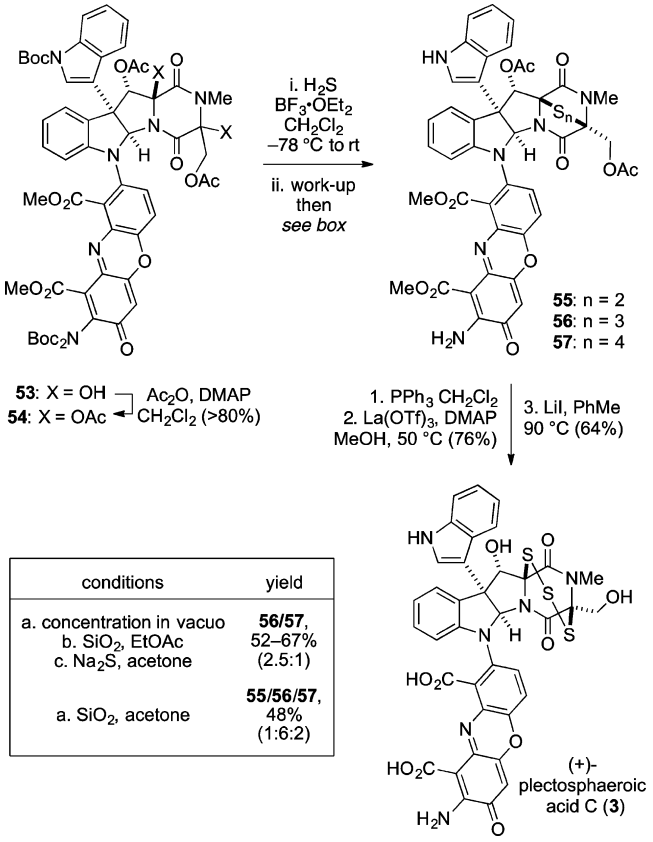
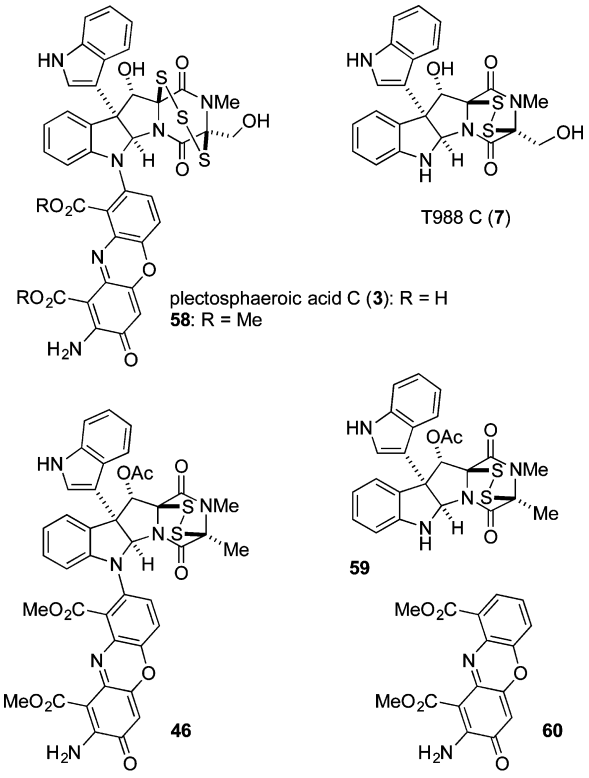
Scheme 10. Completion of the Total Synthesis of Plectosphaeroic Acid C



conditions	yield
a. concentration in vacuo b. SiO_2, EtOAc c. Na_2S, acetone	**56/57**, 52–67% (2.5:1)
a. SiO_2, acetone	**55/56/57**, 48% (1:6:2)

at −78 °C to room temperature. After removing residual H_2S and stirring the crude dithiol products with SiO_2 in ethyl acetate, epidisulfide **55** and epitrisulfide **56** were produced in an 85:15 ratio (by ^1H NMR analysis). Subsequent ring-expansion of this mixture by reaction with Na_2S gave a 2.5:1 mixture of epitrisulfide **56** and epitetrasulfide **57**, respectively. On larger scales (30−60 mg), it was more convenient to process the crude dithiol intermediates without rigorous removal of residual H_2S to yield a 1:6:2 mixture of epidi-, epitri-, and epitetrasulfide products **55**−**57**.[59] As the central S−S σ-bond of tetrasulfides is considerably weaker than the corresponding bonds of disulfides or trisulfides,[60] we were able to selectively reduce the epitetrasulfide component of these mixtures by exposing the reaction product to 1 equiv of triphenylphosphine (relative to the amount of **57**) in CH_2Cl_2 at room temperature.[61] Ensuing cleavage of the remaining ester groups then provided (+)-plectosphaeroic acid C (**3**) in 33% overall yield from tetraacetate **54**. In the final, dealkylative transformation to liberate the carboxylic acids of **3**, switching to the non-coordinating solvent toluene significantly increased the reaction rate,[62] which proved necessary as **3**, unlike its C3 methyl congener **45**, was not stable to prolonged exposure to the reaction conditions. The optical rotation of synthetic **3**, $[\alpha]^{23}_D$ +494 (*c* 0.06, MeOH), was substantially higher than the value reported for the natural sample, $[\alpha]^{23}_D$ +136 (*c* 0.17, MeOH); however, the congruence of all other spectroscopic data, including CD spectra, left little doubt that natural (+)-plectosphaeroic acid C (**3**) had been synthesized.

Preliminary Biological Evaluation. Having synthesized (+)-plectosphaeroic acids B (**2**) and C (**3**), their activities and those of selected related molecules against two invasive cancer cell lines, DU145 (human prostate) and A2058 (melanoma), were determined (Figure 2).[63] It was found that **2**, **3**, and



entry	substrate	DU145 (IC_{50})	A2058 (IC_{50})
1	**2**, **3** or **4**	>5 μM	>5 μM
2	**58**	0.40 μM	0.57 μM
3	**7**	0.53 μM	0.96 μM
4	**46**	0.41 μM	0.26 μM
5	**59**	0.26 μM	0.96 μM
6	**60**	>5 μM	>5 μM

Figure 2. Activity against prostate (DU145) and melanoma (A2508) cancer cell lines.

cinnabarinic acid (**4**)[64] were inactive within the detection limits of the assay (>5 μM) (entry 1). However, the dimethyl ester analog **58** of plectosphaeroic acid C exhibited comparable potency to that of T988 C (**7**) against the two cancer cell lines (entries 2 and 3).[65] Of note, the epidisulfide analogue **46** of plectosphaeroic acid B and the structurally simpler ETP **59** having an identical hexahydro-2*H*-pyrazinopyrrolo[2,3-*b*]-indole-1,4-dione moiety show similar activities (entries 4 and 5). Cinnabarinic acid dimethyl ester (**60**), a moderately active inhibitor of IDO,[11] was inactive (entry 6). In no instance were the corresponding bis(methylthio) congeners active against these cell lines (data not shown). Taken together, these data indicate that (i) only the presence of the epipolysulfide functionality is required for in vitro cytotoxicity activity against the DU145 and A2058 cell lines and (ii) the presence of the carboxylic acid substituents in plectosphaeroic acid C (**3**) is detrimental to its cell-based cytotoxicity.

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CONCLUSION

The first total syntheses of plectosphaeroic acids B (**2**) and C (**3**) are reported, syntheses that confirm the unique structure and absolute configuration of the plectosphaeroic acids.[4] The synthetic sequence to (+)-**2** and (+)-**3** proceeded in 6 and 11 steps from known hexahydro-2*H*-pyrazinopyrrolo[2,3-*b*]indole-1,4-diones **39a** and **39b**, which in turn are available in enantiomerically pure form in 14 steps from indole and isatin.[12] Our approach to these natural products featured the late-stage merger of the cinnabarinic acid and hexahydro-2*H*-pyrazinopyrrolo[2,3-*b*]indole-1,4-dione fragments by a copper-mediated process. The highly congested C−N bond generated in this coupling, in conjunction with the delicate nature of the densely functionalized precursors, provide striking testament to the power of modern copper-mediated amination methods.[22a,b,d,e] The sequence developed in this investigation for stereoselectively introducing the methylthio substituents of **2** and the ring-expanding procedure for fashioning the bridging trisulfide of **3** were essential to simplifying the synthesis of these polyfunctional natural products. We anticipate that the late-stage ring-expansion procedure employed in these syntheses should be of utility for synthesizing tri- and tetrasulfide congeners of other epipolythiodiketopiperazines.

EXPERIMENTAL SECTION

N6-(*tert*-Butoxycarbonyl) derivative of gliocladin C (24). The bis(*tert*-butoxycarbonyl) derivative **23** of gliocladin C[12] (3 mg, 5.1 μmol) was heated in a sealed vial (neat) at 140 °C (preheated oil bath) for 11 min. The reaction mixture was allowed to cool to rt, and then the crude product was directly purified by preparatory thin-layer chromatography (1:1 EtOAc/hexanes) to afford the title compound **24** as a yellow solid (2 mg, 83%; formation of minor quantities of gliocladin C (**19**) also observed, 3:1 **24**/**19**): ^{1}H NMR (500 MHz, acetone-d_6) δ 10.42 (br s, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.46 (d, J = 8.1 Hz), 7.40 (d, J = 7.4 Hz), 7.36 (t, J = 7.6 Hz), 7.33 (d, J = 8.2 Hz), 7.15−7.11 (comp, 3H), 7.02 (s, 1H), 6.94 (t, J = 7.4 Hz), 6.83 (s, 1H), 3.23 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.6 (C), 157.9 (C), 152.7 (C), 150.8 (C), 142.8 (C), 138.6 (C), 135.0 (C), 133.9 (C), 129.7 (CH), 126.3 (C), 125.64 (CH), 125.57 (CH), 125.1 (CH), 124.5 (CH), 123.1 (CH), 120.4 (CH), 119.9 (CH), 118.3 (CH), 115.3 (C), 112.9 (CH), 85.4 (CH), 82.9 (C), 59.2 (C), 28.2 (CH_3), 27.2 (CH_3); IR (film) 3331, 3105, 3058, 2977, 2930, 1714, 1683, 1599, 1478; TLC R_f 0.17 (1:1 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{27}H_{24}N_4O_5Na$ (M + Na)$^+$ 507.1644, found 507.1623.

N1′-(*tert*-Butoxycarbonyl) Derivative of Gliocladin C ((+)-25). *Method A.* A solution of scandium triflate (1.6 mg, 3.3 μmol) and MeCN (50 μL) was added dropwise to a solution of the bis(*tert*-butoxycarbonyl) derivative **23** of gliocladin C (19 mg, 33 μmol) and MeCN (0.33 mL) cooled to 0 °C. The reaction mixture was allowed to warm to rt. After 3 h, the reaction mixture was poured into a mixture of ethyl acetate (EtOAc) (10 mL) and saturated aqueous $NaHCO_3$ (5 mL). The layers were separated, and the aqueous layer was further extracted with EtOAc (2 × 5 mL). The combined organic layers were washed sequentially with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (1:9 EtOAc/hexanes → 3:7 EtOAc/hexanes) to afford the title compound (+)-**25** as a yellow solid (12 mg, 76%).

Method B. The bis(*tert*-butoxycarbonyl) derivative **23** of gliocladin C (150 mg, 260 μmol, concentrated in vacuo from a THF solution into a vial) was heated (neat) under a slight vacuum (160 mmHg) at 180 °C (preheated oil bath) for 20 min (reaction times can vary slightly; removal of both Boc groups of **23** were monitored by TLC). The reaction mixture was allowed to cool to rt, and then THF (4 mL), di-*tert*-butyl dicarbonate (Boc_2O) (56 mg, 260 μmol), and *N*,*N*-dimethyl-4-aminopyridine (DMAP) (6.0 mg, 4.9 μmol) were added to the vial sequentially (under a N_2 atmosphere). After 1 h (in some cases, additional Boc_2O was added to drive the reaction to completion), the reaction mixture was poured into a mixture of EtOAc (20 mL) and saturated aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (1:3 EtOAc/hexanes) to afford the title compound (+)-**25** (118 mg, 95%) as a tan foam: $[\alpha]^{D}_{24}$ +148, $[\alpha]^{577}_{24}$ +144, $[\alpha]^{546}_{24}$ +139 (c = 0.2, CH_2Cl_2); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.15 (d, J = 8.3 Hz, 1H), 7.60 (s, 1H), 7.33 (d, J = 6.9 Hz, 1H), 7.30 (dt, J = 8.3, 1.0 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.15 (dt, J = 7.7, 1.2 Hz, 1H), 7.09 (dt, J = 8.0, 0.9 Hz, 1H), 7.01 (s, 1H), 6.88 (d, J = 7.9 Hz, 1H), 6.75−6.70 (comp, 2H), 6.28 (d, J = 2.6 Hz, 1H), 3.25 (s, 3H), 1.67 (s, 9H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.6 (C), 158.0 (C), 150.7 (C), 150.3 (C), 150.1 (C), 137.9 (C), 133.9 (C), 130.2 (CH), 130.1 (C), 129.0 (C), 125.7 (CH), 125.4 (CH), 125.3 (CH), 124.3 (CH), 123.7 (CH), 122.0 (C), 120.9 (CH), 120.0 (CH), 116.3 (CH), 110.9 (CH), 85.0 (C), 84.0 (CH), 60.6 (C), 28.3 (CH_3), 27.2 (CH_3); IR (film) 3365, 3102, 3064, 2979, 1736, 1686, 1606, 1452; TLC R_f 0.32 (1:1 EtOAc/hexanes), 0.41 (2:98 MeOH/CH_2Cl_2, plate was eluted twice); HRMS (ESI) m/z calcd for $C_{27}H_{24}N_4O_5Na$ (M + Na)$^+$ 507.1644, found 507.1643.

***tert*-Butyl 3-((3a*S*,8a*R*)-2-(Methylcarbamoyl)-8,8a-dihydropyrrolo[2,3-*b*]indol-3a(3*H*)-yl)-1*H*-indole-1-carboxylate (27).** Indoline **25** (12 mg, 25 μmol), Buchwald's palladacyclic precatalyst ligated with RuPhos[66] (1.0 mg, 1.3 μmol), RuPhos (0.5 mg, 1.0 μmol), and Cs_2CO_3 (16 mg, 50 μmol) were added to a 1-dram vial (in a nitrogen-filled glovebox). After *t*-BuOH (100 μL) was added to this mixture, the vial was sealed (with a top, which contained a Teflon-lined septum) and brought outside of the glovebox. Ethyl 2-bromobenzoate (**26a**) (3.3 μL, 21 μmol) was injected into the reaction vessel, and then the reaction mixture was heated at 85 °C (preheated oil bath) for 12 h, at which point the reaction mixture was cooled to rt and EtOAc (400 μL) was added. The mixture was filtered through a short pad of diatomaceous earth, and the filtrate was concentrated in vacuo. The crude residue was purified by preparatory thin layer chromatography (1:4 EtOAc/hexanes) to afford the title compound **27** (2 mg, 19%, with no detectable quantity of the desired coupled product **28a**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (br d, J = 6.3 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.30 (s, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.19 (d, J = 7.3, 1H), 7.18 (t, J = 7.3 Hz, 1H), 7.15−7.11 (comp, 2H), 6.82 (t, J = 7.4, 1H), 6.76 (d, J = 7.8, 1H), 6.02 (s, 1H), 4.67 (s, 1H), 3.85 (d, J = 18.6 Hz, 1H), 3.70 (d, J = 18.6 Hz, 1H), 2.90 (d, J = 5.1 Hz, 1H), 1.63 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C), 162.7 (C), 149.8 (C), 147.5 (C), 150.1 (C), 132.7 (C), 129.3 (CH), 128.6 (C), 125.3 (CH), 124.8 (CH), 123.4 (CH), 123.0 (C), 122.9 (CH), 120.5 (CH), 119.9 (CH), 115.9 (CH), 111.0 (CH), 96.6 (CH), 84.1 (C), 54.9 (C), 48.4 (CH_2), 28.4 (CH_3), 26.2 (CH_3); HRMS (ESI) m/z calcd for $C_{25}H_{26}N_4O_3Na$ (M + Na)$^+$ 453.1903, found 453.1908.

***tert*-Butyl 3-((5a*R*,10b*S*)-6-(2-(Methoxycarbonyl)phenyl)-2-methyl-1,3,4-trioxo-1,2,3,4,5a,6-hexahydro-10b*H*-pyrazino-[1′,2′:1,5]pyrrolo[2,3-*b*]indol-10b-yl)-1*H*-indole-1-carboxylate ((+)-28b).** Indoline **25** (10 mg, 21 μmol), CuCl (8.0 mg, 81 μmol) [or 0.5 equiv of CuI/1,3-bis(diphenylphosphino)propane (dppp)], and Cs_2CO_3 (34 mg, 105 μmol) were added to a 1-dram vial (in a nitrogen-filled glovebox). After PhMe (400 μL, degassed via freeze−pump−thaw cycles prior to use) and methyl 2-iodobenzoate (**26b**) (64 μL, 42 μmol, 10% v/v solution in toluene) were added to this mixture, the vial was sealed (with a Teflon-lined cap) and brought outside of the glovebox. The heterogeneous mixture was stirred at 110 °C (preheated oil bath) for 24 h, at which point the reaction mixture was cooled to rt and EtOAc (400 μL) was added. The mixture was filtered through a short pad of diatomaceous earth, then the filtrate was concentrated in vacuo. The crude residue was purified sequentially by chromatography on silica gel (1:9 EtOAc/hexanes →3:2 EtOAc/hexanes) then preparatory thin layer chromatography (to separate the product from residual, copolar **25**) (1.5% MeOH/CH_2Cl_2) to afford

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the title compound (+)-**28b** (11 mg, 85%) as an orange solid: $[\alpha]^{D}_{24}$ +168, $[\alpha]^{577}_{24}$ +170, $[\alpha]^{546}_{24}$ +174 (c = 0.9, CH_2Cl_2); ^{1}H NMR (500 MHz, 353 K, DMSO-d_6) δ 8.11 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 7.0 Hz, 1H), 7.64 (t, J = 7.1 Hz, 1H), 7.56 (s, 1H), 7.50 (d, J = 7.3 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.36 (t, J = 8.2 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.23 (d, J = 7.2 Hz, 1H), 7.18 (t, J = 7.9 Hz, 1H), 7.08 (dt, J = 7.9, 1.1 Hz, 1H), 7.03 (s, 1H), 6.74 (t, J = 7.4 Hz, 1H), 6.72 (s, 1H), 6.15 (d, J = 7.9 Hz, 1H), 3.44 (s, 3H), 3.17 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (125 MHz, 353 K, DMSO-d_6) δ 165.8 (C), 156.71 (C), 156.66 (C), 149.8 (C), 148.7 (C), 148.6 (C), 139.2 (C), 135.3 (C), 132.9 (CH), 132.0 (C), 130.3 (2 × CH), 128.7 (CH), 127.7 (CH), 127.4 (C), 127.2 (CH), 124.34 (CH), 124.32 (2 × CH), 124.1 (CH), 122.5 (CH), 119.9 (CH), 119.5 (C), 118.5 (CH), 114.7 (CH), 106.7 (CH), 86.6 (CH), 84.1 (C), 58.4 (C), 51.22 (CH_3), 27.4 (CH_3), 26.3 (CH_3); IR (film) 3101, 3054, 2979, 2950, 1731, 1715, 1687, 1598, 1452; TLC R_f 0.35 (1:1 EtOAc/hexanes), 0.50 (2:98 MeOH/CH_2Cl_2, plate was eluted twice); HRMS (ESI) m/z calcd for $C_{35}H_{30}N_4O_7Na$ $(M + Na)^+$ 641.2012, found 641.1995.

6-Iodo-3-methoxy-2-nitrobenzoic Acid (S2). This procedure is a modification of a procedure reported by Fairfax and Yang.[29] To a suspension of 2-methoxy-3-nitrobenzoic acid (**S1**) (10.0 g, 50.7 mmol) in concentrated H_2SO_4 (150 mL) were added Ag_2SO_4 (20.6 g, 65.9 mmol) and iodine (13.5 g, 53.5 mmol). The heterogeneous mixture was shielded from light (by covering the reaction vessel with aluminum foil) and stirred vigorously at rt for 48 h, at which point the reaction mixture was cooled in an ice−water bath and water (200 mL, ice−water mixture) was slowly added to the reaction mixture. *Caution: exotherm or rapid increase in temperature observed over the course of the addition.* The resulting precipitate was separated from the mother liquor by filtration and then dissolved in acetone (200−300 mL). The insoluble material was removed by filtration. The mother liquor was dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound **S2** (12 g, 73%) as a yellow solid in sufficient purity to use in the next step: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.07 (d, J = 8.9 Hz, 1H), 7.24 (d, J = 9.0 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.8 (C), 150.6 (C), 143.0 (CH), 138.7 (C), 134.1 (C), 117.1 (CH), 81.6 (C), 57.2 (CH_3); IR (film) 3074, ∼3000 (broad), 2947, 1713; HRMS (ESI) m/z calcd for $C_8H_6INO_5Na$ $(M + Na)^+$ 345.9189, found 345.9188; mp 178−181 °C.

3-Hydroxy-6-iodo-2-nitrobenzoic Acid (S3). This procedure is a modification of a procedure reported by Fuji and co-workers.[67] To a solution of 6-iodo-3-methoxy-2-nitrobenzoic acid (**S2**) (14.5 g, 44.9 mmol), Et_2S (40 mL), and CH_2Cl_2 (400 mL) was added $AlCl_3$ (21.0 g, 157 mmol) in a portionwise fashion. The reaction mixture was stirred at 40 °C for 48 h (the reaction progress was monitored by ^{1}H NMR of aliquots sampled during the course of the reaction) and then allowed to cool to rt and concentrated under reduced pressure (to approximately 1/3 volume). The crude residue was poured into a mixture of EtOAc (600 mL) and aqueous solution of HCl (0.125 M, 450 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was crystallized (in some cases, precipitated) from CH_2Cl_2 (100 mL) in order to remove minor amounts of the hydrodehalogenated byproduct, 3-hydroxy-2-nitrobenzoic acid (**S4**) (CAS no. 602-00-6) (1:10, **S4**/**S3** by ^{1}H NMR). After removal of the mother liquor by filtration, the product was redissolved in Et_2O to remove residual, purple-colored insoluble material, which was filtered away. The filtrate was concentrated under reduced pressure to afford the title compound **S3** (6.10 g, second crop: 2.10 g; combined 59%) as a tan solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.89 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 168.7 (C), 152.5 (C), 145.0 (CH), 138.6 (C), 137.2 (C), 122.4 (CH), 79.7 (C); IR (KBr) 3411, 3088, ∼3000 (broad), 2898, 2654, 2590, 2526, 1701, 1600, 1442; HRMS (ESI) m/z calcd for $C_7H_3INO_5$ $(M - H)^-$ 307.9056, found 307.9051; mp 174−176 °C dec.

3-Hydroxy-6-iodoanthranilic Acid (29). This procedure is a modification of a procedure reported by Fairfax and Yang.[29] To a solution of 3-hydroxy-6-iodo-2-nitrobenzoic acid (**S3**) (7.3 g, 24 mmol) and THF (200 mL) was added a solution of $Na_2S_2O_4$ (41 g, 240 mmol) and water (100 mL). The reaction mixture was stirred vigorously at 50 °C for 3−4 h and allowed to cool to rt, and EtOAc (300 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford the title compound **29** (4.6 g, 70%) in sufficient purity to use in the next step: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.82 (s, 1H), 7.80 (br s, 2H), 6.93 (d, J = 8.2 Hz, 1H), 6.48 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.0 (C), 144.8 (C), 137.5 (C), 126.8 (CH), 121.4 (C), 116.4 (CH), 80.7 (C); IR (KBr) 3423, 3221, 2921, 1603; HRMS (ESI) m/z calcd for $C_7H_7INO_3$ $(M + H)^+$ 279.9471, found 279.9479; mp 180−182 °C dec.

2-Amino-8-iodo-3-oxo-3*H*-phenoxazine-1,9-dicarboxylic Acid (S5). To a solution of 3-hydroxy-4-iodoanthranilic acid **29** (50 mg, 0.18 mmol) in MeOH (4 mL) was added 1,4-benzoquinone (33 mg, 0.30 mmol, freshly recrystallized from petroleum ether).[11,32] The reaction mixture was maintained at 50 °C for 3 h (the reaction was shielded from light by covering the reaction vessel with aluminum foil), followed by placement in a freezer (−20 °C) for 12 h. The resulting suspension was concentrated under reduced pressure (to approximately 1/2 volume) and then filtered to separate the mother liquor from the precipitate, which was subsequently washed with EtOAc/hexane (10−20 mL, 1:1) to afford the title compound **S5** (25 mg, 66%) as an orange-red solid with no further purification: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.92 (s, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 6.62 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.0 (C), 168.7 (C), 167.9 (C), 152.7 (C), 150.9 (C), 148.1 (C), 142.1 (C), 138.6 (CH), 137.7 (C), 127.7 (C), 118.3 (CH), 105.5 (CH), 92.4 (C), 87.0 (C); IR (KBr) 3402, 3282, 3082, 2917, 1721, 1645, 1578; HRMS (ESI) m/z calcd for $C_{14}H_6IN_2O_6$ $(M - H)^-$ 424.9271, found 424.9274.

Dimethyl 2-Amino-8-iodo-3-oxo-3*H*-phenoxazine-1,9-dicarboxylate (31). To a suspension of 3-hydroxy-4-iodoanthranilic acid **29** (4.4 g, 16 mmol) in a cosolvent mixture of PhMe and MeOH (160, 50 mL, respectively) was slowly added trimethylsilyldiazomethane ($TMSCHN_2$) (8.8 mL, 18 mmol, 2.0 M solution in hexane) with stirring. *Caution: evolution of N_2(g) over the course of the addition.* After 30 min, the resulting solution was poured into a mixture of EtOAc (50 mL) and water (25 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford methyl 3-hydroxy-4-iodoanthranilate (**30**), which was used immediately in the following transformation: TLC R_f 0.45 (3:7 EtOAc/hexanes). To a solution of 2-aminophenol **30** (16 mmol) in MeOH (160 mL) was added 1,4-benzoquinone (3.0 g, 27 mmol, freshly recrystallized from petroleum ether).[11,32] The reaction mixture was maintained at 50 °C for 3 h (the reaction was shielded from light by covering the reaction vessel with aluminum foil), followed by placement in a freezer (−20 °C) for 12 h. The resulting suspension was concentrated under reduced pressure (to approximately 1/2 volume), then filtered to separate the mother liquor from the precipitate, which was subsequently washed with EtOAc/hexane (100 mL, 1:1) to afford the title compound **31** (2.0 g, 56%) as an orange-red solid of sufficient purity to use in the next step: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.00 (br s, 2H), 7.87 (d, J = 7.4 Hz, 1H), 7.39 (d, J = 7.4 Hz, 1H), 6.49 (s, 1H), 3.92 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.4 (C), 167.2 (C), 167.1 (C), 148.9 (C), 148.4 (C), 146.2 (C), 141.3 (C), 138.6 (C), 138.0 (CH), 131.6 (C), 118.4 (CH), 104.3 (CH), 99.0 (C), 86.6 (C), 52.7 (CH_3), 51.6 (CH_3); IR (film) 3446, 3326, 3075, 2948, 2922, 2854, 1730, 1672, 1641, 1575; TLC R_f 0.36 (3:7 EtOAc/hexanes), 0.52 (3:7 EtOAc/hexanes, plate was eluted twice); HRMS (ESI) m/z calcd for $C_{16}H_{11}IN_2O_6Na$ $(M + Na)^+$ 476.9560, found 476.9573; mp 233−235 °C.

Dimethyl 2-((*tert*-Butoxycarbonyl)amino)-8-iodo-3-oxo-3*H*-phenoxazine-1,9-dicarboxylate (32). To a solution of 2-aminophenoxazinone **31** (300 mg, 0.66 mmol) in THF (13 mL) were added

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sequentially Boc_2O (170 mg, 0.79 mmol) and DMAP (16 mg, 0.13 mmol). After 2 h, the reaction mixture was poured into a mixture of EtOAc (60 mL) and saturated aqueous NH_4Cl (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (1:3 EtOAc/hexanes) to afford the title compound **32** (200 mg, 54%; the remainder of mass balance consisted of a copolar mixture of starting material **31** and the bis(*tert*-butoxycarbonyl) derivative **33**) as an orange/red solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.18 (d, J = 8.7 Hz, 1H), 6.48 (s, 1H), 4.03 (s, 3H), 3.92 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0 (C), 166.8 (C), 164.4 (C), 151.1 (C), 148.1 (C), 147.4 (C), 142.6 (C), 141.3 (CH), 141.0 (C), 135.0 (C), 131.9 (C), 118.4 (CH), 116.9 (C), 105.2 (CH), 86.4 (C), 83.0 (C), 53.3 (CH_3), 52.5 (CH_3), 28.2 (CH_3); IR (film) 3330, 2980, 2950, 2917, 2849, 1737, 1631, 1509, 1492; TLC R_f 0.64 (3:7 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{21}H_{19}IN_2O_8Na$ $(M + Na)^+$ 577.0084, found 577.0086.

Dimethyl 2-(Bis(*tert*-butoxycarbonyl)amino)-8-iodo-3-oxo-3*H*-phenoxazine-1,9-dicarboxylate (33). To a THF (88 mL) solution of 2-aminophenoxazinone **31** (2.0 g, 4.4 mmol) were sequentially added Boc_2O (2.3 g, 11 mmol) and DMAP (50 mg, 0.10 mmol). After 2 h (in some cases, additional Boc_2O was added to drive the reaction to completion), the reaction mixture was poured into a mixture of EtOAc (300 mL) and saturated aqueous NH_4Cl (200 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (1:3 EtOAc/hexanes) to afford the title compound **33** (2.2 g, 76%) as a red solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 8.7 Hz, 1H), 6.42 (s, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 1.41 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.9 (C), 166.5 (C), 162.6 (C), 149.2 (C), 148.2 (C), 147.5 (C), 143.5 (C), 142.8 (CH), 141.4 (C), 138.5 (C), 133.8 (C), 131.3 (C), 118.7 (CH), 107.2 (CH), 86.2 (C), 84.2 (C), 53.3 (CH_3), 53.0 (CH_3), 27.9 (CH_3); IR (film) 2980, 2953, 1801, 1745, 1640; TLC R_f 0.48 (3:7 EtOAc/hexanes, plate was eluted twice); HRMS (ESI) m/z calcd for $C_{26}H_{27}IN_2O_{10}Na$ $(M + Na)^+$ 677.0608, found 677.0611.

Cross-Coupled Product ((−)-35). The components of this reaction were combined in a screw-top vial inside a N_2-filled glovebox. The reaction vial was sealed with a Teflon-lined cap, brought outside the glovebox, and heated in an aluminum block for the period of time indicated. The reaction vessel was charged with indoline **25** (10 mg, 21 μmol), phenoxazinone iodide **33** (30 mg, 46 μmol), copper(I) thiophene-2-carboxylate (CuTC)[36] (12 mg, 62 μmol), and K_2CO_3 (11 mg, 83 μmol), and then PhMe (200 μL) was added by syringe. The heterogeneous mixture was stirred at 90 °C for 36 h. After being allowed to cool to rt, the reaction mixture was passed directly through a short plug of silica gel (eluting with EtOAc) to remove the metal salts, then concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (1:19 EtOAc/hexanes → 1:3 EtOAc/hexanes) to afford the title compound (−)-**35** (14 mg, 67%) as a red solid: $[\alpha]^D_{24}$ −68.7, $[\alpha]^{577}_{24}$ −72.2 (c = 0.075, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 7.0 Hz, 1H), 7.68 (d, J = 7.3 Hz, 1H), 7.6−7.5 (comp, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.12 (t, J = 7.3 Hz, 1H), 7.05 (d, J = 4.1 Hz, 1H), 6.96 (d, J = 7.6, 1H), 6.83 (s, 1H), 6.78 (m, 1H), 6.75 (s, 1H), 6.45 (s, 1H), 6.37 (d, J = 7.0 Hz, 1H), 3.84 (s, 3H), 3.63 (s, 3H), 3.41 (s, 3H), 1.70 (s, 9H), 1.43 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1 (C), 165.2 (C), 162.6 (C), 157.2 (C), 157.0 (C), 150.4 (C), 149.6 (C), 149.1 (C), 148.7 (C), 148.5 (CH), 147.3 (C), 143.0 (CH), 138.3 (C), 136.5 (C), 136.3 (C), 135.8 (C), 133.8 (C), 133.5 (CH), 131.6 (C), 131.0 (C), 129.8 (CH), 127.8 (C), 126.9 (C), 126.3 (CH), 125.4 (CH), 124.9 (CH), 124.1 (CH), 123.4 (CH), 120.8 (CH), 119.5 (2 × CH), 119.1 (C), 116.2 (CH), 108.2 (CH), 106.9 (CH), 88.0 (CH), 85.0 (C), 84.2 (C), 59.3 (C), 52.9 (2 × CH_3), 28.4 (CH_3), 27.9 (CH_3), 27.7 (CH_3); IR (film) 3056, 2980, 2952, 2933, 1804, 1741, 1714, 1692, 1642; TLC Rf 0.41 (4:6 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{53}H_{50}N_6O_{15}Na$ $(M + Na)^+$ 1033.3232, found 1033.3240.

***tert*-Butyl 3-((5a*R*,10b*S*)-3-Hydroxy-2,3-dimethyl-1,4-dioxo-1,2,3,4,5a,6-hexahydro-10b*H*-pyrazino[1′,2′:1,5]pyrrolo[2,3-*b*]-indol-10b-yl)-1*H*-indole-1-carboxylate (S6).** This procedure is a modification of a procedure reported by Overman and co-workers.[12] A THF (11 mL) solution of indoline **25** (260 mg, 0.54 mmol) was cooled to −78 °C, and methylmagnesium chloride (540 μL, 1.6 mmol, 2.9 M solution in THF) was added slowly. The reaction mixture was maintained at −78 °C for 3 h, and AcOH (120 μL, 2.0 mmol) was added. The cooling bath was removed, and the reaction mixture was allowed to warm to rt. The solvent was removed under reduced pressure, and H_2O (15 mL) was added to the concentrate. The aqueous phase was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (1:3 EtOAc/hexanes →2:3 EtOAc/hexanes) to afford the title compound **S6** (190 mg, 71%, 3:2 mixture of alcohol epimers) as an amorphous colorless solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, J = 6.4 Hz, 0.6H), 8.08 (d, J = 6.4 Hz, 0.4H), 7.49 (s, 0.6H), 7.46 (s, 0.4H), 7.27 (m, 0.4H), 7.21 (t, J = 7.7 Hz, 0.4H), 7.14 (t, J = 7.5 Hz, 0.4H), 7.08−7.00 comp, 3.8H), 6.94 (d, J = 7.5 Hz, 1H), 6.77−6.72 (comp, 1H), 6.67 (d, J = 7.9 Hz, 0.6H), 6.67 (d, J = 7.8 Hz, 0.4H), 6.59 (s, 1H), 6.57 (s, 1H), 6.20 (d, J = 2.6 Hz, 0.6H), 6.12 (app s, 0.4H), 5.42 (app s, 0.4H), 5.38 (app s, 0.6H), 4.29 (s, 0.6H), 4.25 (s, 0.4H), 3.10 (s, 1.8H), 3.09 (s, 1.2H), 1.73 (s, 3H), 1.68−1.66 (comp, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0 (C), 164.5 (C), 155.7 (2 × C), 149.8 (2 × C), 148.0 (C), 147.9 (C), 136.4 (2 × C), 132.5 (C), 132.2 (C), 129.7 (C), 129.42 (CH), 129.38 (CH), 129.2 (C), 128.1 (2 × C), 125.1 (CH), 124.9 (CH), 124.8 (CH), 124.7 (CH), 123.3 (2 × CH), 123.1 (CH), 123.0 (CH), 121.8 (CH), 121.5 (C), 121.2 (CH), 121.1 (C), 120.2 (CH), 119.9 (CH), 119.8 (CH), 115.8 (CH), 115.7 (CH), 110.0 (CH), 109.8 (CH), 85.3 (C), 84.9 (C) 84.6 (C), 84.5 (C), 83.2 (CH), 83.1 (CH), 59.8 (C), 59.5 (C), 28.44 (CH_3), 28.42 (CH_3), 27.5 (CH_3), 27.3 (CH_3), 26.5 (CH_3), 26.1 (CH_3); IR (film) 3339, 2979, 1734, 1675, 1642, 1453; TLC R_f 0.15 (3:7 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{28}H_{28}N_4O_5Na$ $(M + Na)^+$ 523.1957, found 523.1953.

***tert*-Butyl 3-((5a*R*,10b*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2,3-dimethyl-1,4-dioxo-1,2,3,4,5a,6-hexahydro-10b*H*-pyrazino-[1′,2′:1,5]pyrrolo[2,3-*b*]indol-10b-yl)-1*H*-indole-1-carboxylate (36).** This procedure is a modification of a procedure reported by Overman and co-workers.[12] To a solution of alcohols **S6** (190 mg, 0.38 mmol), DMAP (46 mg, 0.38 mmol), and triethylamine (0.53 mL, 3.8 mmol) in DMF (4.0 mL) maintained at 0 °C was added TBSOTf (0.52 mL, 2.3 mmol) slowly. The cold bath was removed, and the reaction mixture was maintained at rt for 12 h, whereupon EtOAc (20 mL) was added followed by saturated aqueous NH_4Cl (20 mL). The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous phase was further extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (1:3 EtOAc/hexanes →2:3 EtOAc/hexanes) to afford the title compounds **36** as colorless solids (125 mg of the major epimer **36a**, 105 mg of the minor epimer **36b**; 98% overall yield, 1.2:1.0 ratio of C3-epimers). Data for the major, C3α-OTBS epimer, (+)-**36a**: $[\alpha]^D_{24}$ +187, $[\alpha]^{577}_{24}$ +195, $[\alpha]^{546}_{24}$ +220, $[\alpha]^{435}_{24}$ +352 (c = 0.54, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 7.2 Hz, 1H), 7.46 (s, 1H), 7.29 (t, J = 7.2 Hz, 1H), 7.15−7.05 (comp, 3H), 7.02 (d, J = 7.4 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.74 (t, J = 7.4 Hz, 1H), 6.57 (s, 1H), 6.16 (s, 1H), 5.35 (s, 1H), 3.07 (s, 3H), 1.74 (s, 3H), 1.67 (s, 9H), 0.86 (s, 9H), 0.10 (s 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0 (C), 156.0 (C), 149.7 (C), 148.1 (C), 136.4 (C), 132.6 (C), 129.6 (C), 129.3 (CH), 128.2 (C), 125.0 (CH), 124.7 (CH), 123.5 (CH), 123.0 (CH), 121.3 (C), 120.9 (CH), 120.1 (2 × CH), 115.7 (CH), 109.9 (CH), 87.1 (C), 84.3 (C) 83.4 (CH), 59.5 (C), 28.4 (CH_3), 27.8 (CH_3), 26.5 (CH_3), 25.8 (CH_3), 18.4 (C), −3.6 (CH_3), −3.9 (CH_3); IR (film)

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3356, 3054, 2953, 2931, 1736, 1682, 1649, 1607, 1453; TLC R_f 0.38 (3:7 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{34}H_{42}N_4O_5SiNa$ $(M + Na)^+$ 637.2822, found 637.2820. Data for minor, C3β-OTBS epimer, (+)-**36b**: $[\alpha]^D_{24}$ +118, $[\alpha]^{577}_{24}$ +121, $[\alpha]^{546}_{24}$ +134, $[\alpha]^{435}_{24}$ +155 (c = 0.54, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 6.5 Hz, 1H), 7.46 (s, 1H), 7.27 (t, J = 7.1 Hz, 1H), 7.15−7.05 comp, 3H), 6.74 (d, J = 7.4, 1H), 6.74 (d, J = 7.7 Hz, 1H), 6.73 (t, J = 7.6 Hz, 1H), 6.59 (s, 1H), 6.21 (s, 1H), 5.38 (s, 1H), 3.07 (s, 3H), 1.73 (s, 3H), 1.67 (s, 9H), 0.86 (s, 9H), 0.12 (s 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1 (C), 155.6 (C), 149.7 (C), 148.0 (C), 136.4 (C), 132.5 (C), 129.7 (C), 129.3 (CH), 128.2 (C), 125.0 (CH), 124.7 (CH), 123.4 (CH), 123.0 (CH), 121.3 (C), 121.0 (CH), 120.0 (CH), 119.9 (CH), 115.7 (CH), 109.7 (CH), 87.1 (C), 84.4 (C) 83.4 (CH), 59.3 (C), 28.4 (CH_3), 27.9 (CH_3), 27.1 (CH_3), 25.8 (CH_3), 18.5 (C), −3.5 (CH_3), −3.8 (CH_3); IR (film) 3365, 3064, 2979, 1736, 1686, 1606, 1452; TLC R_f 0.44 (3:7 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{34}H_{42}N_4O_5SiNa$ $(M + Na)^+$ 637.2822, found 637.2825.

Cross-Coupled Product (−)-37b (C3β-OTBS epimer). The components of this reaction were combined in a screw-top vial inside a N_2-filled glovebox. The reaction vial was sealed with a Teflon-lined cap, then brought outside the glovebox and heated in an aluminum block for the period of time indicated. The reaction vessel was charged with indoline **36b** (40 mg, 65 μmol), phenoxazinone iodide **33** (130 mg, 200 μmol), copper(I) thiophene-2-carboxylate (CuTC)[36] (63 mg, 330 μmol), and K_2CO_3 (50 mg, 360 μmol), and then PhMe (2.6 mL) was added by syringe. The heterogeneous mixture was stirred at 90 °C for 48 h. After being allowed to cool to rt, the reaction mixture was passed directly through a short plug of silica gel (eluting with EtOAc) to remove the metal salts and then concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (1:19 EtOAc/hexanes →1:3 EtOAc/hexanes) to afford the title compound **37b** (51 mg, 68%) as a red solid: $[\alpha]^D_{24}$ −150 (c = 0.05, MeOH); **37b** was observed as a 9:1 mixture of atropisomers by NMR at 298 K (subsequent data is provided for the major isomer only); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.20 (d, J = 8.3 Hz, 1H), 7.98 (br d, 1H), 7.80−7.70 (comp, 2H), 7.36 (m, 1H), 7.20−7.10 (comp, 4H), 6.77 (t, J = 6.9 Hz, 1H), 6.67 (s, 1H), 6.56 (s, 1H), 6.52 (s, 1H), 6.38 (d, J = 7.9 Hz, 1H), 3.89 (s, 1H), 3.58 (br s, 3H), 3.09 (s, 1H), 1.68 (s, 9H), 1.55 (s, 3H), 1.39 (s, 18H), 0.83 (s, 9H), −0.08 (s, 3H), −0.35 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 180.6 (C), 165.7 (C), 165.4 (C), 163.6 (2 × C), 155.9 (C), 150.3 (C), 150.0 (C), 149.8 (C), 149.6 (C), 147.6 (C), 143.8 (C), 138.9 (C), 137.3 (C), 136.5 (C), 134.8 (CH), 133.4 (C), 131.7 (C), 129.7 (CH), 129.0 (C), 125.66 (CH), 125.59 (CH), 125.4 (C), 123.9 (CH), 121.1 (C), 121.0 (CH), 120.9 (CH), 120.8 (CH), 119.9 (CH), 116.5 (CH), 109.0 (CH), 106.9 (CH), 88.7 (CH), 88.0 (C), 85.1 (C), 83.7 (C), 59.9 (C), 53.2 (CH_3), 52.7 (CH_3), 28.3 (CH_3), 28.0 (CH_3), 27.6 (CH_3), 27.4 (CH_3), 26.3 (CH_3), 19.3 (C), −2.7 (CH_3), −3.4 (CH_3);[68] IR (film) 2977, 2953, 2917, 2850, 1806, 1743, 1701, 1643; TLC Rf 0.35 (3:7 EtOAc/hexanes, plate was eluted twice); HRMS (ESI) m/z calcd for $C_{60}H_{68}N_6O_{15}SiNa$ $(M + Na)^+$ 1163.4409, found 1163.4402.

Sharpless Dihydroxylation Product (−)-38b (C3β-OTBS Epimer). These procedures are modifications of procedures reported by Overman and co-workers.[12] A flask was charged with AD-mix-α (150 mg),[41] (−)-**37b** (15 mg, 13 μmol), methane sulfonamide (6.3 mg, 66 μmol), and $(DHQ)_2PHAL$ (1.3 mg, 1.6 μmol), and then t-BuOH/H_2O/acetone (3:2:1, 3 mL) was added followed by additional $K_2OsO_4{\cdot}H_2O$ (1.2 mg, 3.3 μmol).[69] The resulting heterogeneous mixture was stirred vigorously at rt for 4 h, the reaction was cooled to 0 °C, and solid Na_2SO_3 (450 mg) was added. The cold bath was removed, and the mixture was stirred for 1 h at rt. Water (5 mL) was added to the reaction mixture, which was transferred to a separatory funnel, and then the aqueous phase was extracted with EtOAc (3 × 8 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (1:10 EtOAc/hexanes →2:3 EtOAc/hexanes) to afford the title compound (−)-**38b** (10 mg, 65%, >10:1 dr) as a red solid. The corresponding reaction of (−)-**37b** (10 mg, 8.8 μmol) using AD-mix-β (with additional $K_2OsO_4{\cdot}H_2O$ and $(DHQD)_2PHAL$) provided isomers (−)-**38b** and **S7** (8 mg, 77%, 7:1 dr). The analogous reaction of (−)-**37b** (10 mg, 8.8 μmol) using OsO_4 (22 mg, 2.1 μmol, 2.5 wt % in t-BuOH) and NMO (2 mg, 17 μmol) in acetone/H_2O (4:1, 2 mL) provided isomers (−)-**38b** and **S7** (5 mg, 49%, reaction was quenched prior to full consumption of starting material, 5:1 dr) as red solids. Data for the minor isomer **S7**:[70] ^{1}H NMR (500 MHz, acetone-d_6) δ 8.55 (s 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 7.10 (s, 1H), 7.09 (t, 1H), 6.94 (d, J = 7.3 Hz, 1H), 6.77 (s, 1H), 6.70 (t, J = 7.4 Hz, 1H), 6.53 (s, 1H), 6.30 (d, J = 7.9 Hz, 1H), 6.00 (s, 1H), 5.52 (d, J = 5.7 Hz, 1H), 4.74 (s, 1H), 3.90 (s, 3H), 3.64 (s, 3H), 3.02 (s, 3H), 1.70 (s, 12H), 1.40 (s, 18H), 0.78 (s, 9H), 0.07 (s, 3H), −0.47 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 180.6 (C), 171.2 (C), 166.5 (C), 165.9 (C), 163.7 (C), 150.6 (C), 149.9 (C), 149.5 (C), 149.1 (C), 147.5 (C), 143.5 (C), 138.83 (C), 138.75 (C), 138.0 (C), 136.0 (C), 134.8 (C), 134.0 (C), 133.1 (CH), 131.6 (C), 131.2 (C), 129.5 (CH), 129.1 (CH), 124.7 (CH), 124.4 (CH), 123.4 (CH), 121.1 (CH), 120.7 (CH), 119.8 (CH), 116.9 (C), 116.4 (CH), 109.9 (CH), 106.9 (CH), 88.3 (C), 86.5 (CH), 85.5 (C), 84.6 (C), 83.7 (C), 82.4 (CH), 57.7 (C), 53.2 (CH_3), 52.7 (CH_3), 28.4 (CH_3), 28.0 (CH_3), 27.4 (CH_3), 26.3 (2 × CH_3), 19.4 (C), −2.46 (CH_3), −3.39 (CH_3); TLC R_f 0.07 (2:3 EtOAc/hexanes); LRMS (ESI) m/z calcd for $C_{60}H_{70}N_6O_{17}SiNa$ $(M + Na)^+$ 1197.4, found 1197.5. Data for the major isomer (−)-**38b**: $[\alpha]^D_{24}$ −47.6 (c = 0.03, CH_2Cl_2); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.17 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.70 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 7.3 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.10 (t, J = 7.7 Hz, 1H), 6.76 (d, J = 7.5 Hz, 1H), 6.50 (s, 1H), 6.41 (s, 1H), 6.34 (d, J = 7.5 Hz, 1H), 5.18 (br s, 1H), 5.11 (app s, 1H), 4.72 (br s, 1H), 3.88 (s, 3H), 3.73 (s, 3H), 2.98 (s, 3H), 1.67 (s, 9H), 1.65 (s, 3H), 1.39 (s, 18H), 0.89 (s, 9H), 0.15 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 180.6 (C), 168.5 (C), 166.7 (C), 166.2 (C), 163.7 (C), 150.3 (C), 150.2 (C), 149.8 (C), 149.4 (C), 147.6 (C), 143.6 (C), 138.9 (C), 137.2 (C), 136.6 (C), 136.5 (CH), 135.7 (C), 134.9 (C), 131.8 (C), 129.5 (CH), 129.4 (C), 129.3 (C), 128.7 (CH), 125.4 (CH), 125.1 (CH), 123.8 (CH), 123.0 (C), 121.3 (CH), 119.7 (CH), 119.0 (CH), 116.2 (CH), 108.3 (CH), 106.8 (CH), 86.9 (C), 84.9 (C), 84.5 (C), 83.7 (C), 79.9 (2 × CH), 63.3 (CH_3), 55.6 (C), 52.5 (CH_3), 28.3 (CH_3), 28.0 (CH_3), 27.9 (CH_3), 26.1 (CH_3), 25.0 (CH_3), 18.9 (C), −2.12 (CH_3), −2.96 (CH_3); IR (film) 3457, 2978, 2953, 2932, 2857, 1806, 1740, 1699, 1643, 1371; TLC R_f 0.20 (2:3 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{60}H_{70}N_6O_{17}SiNa$ $(M + Na)^+$ 1197.4464, found 1197.4486. Note, for comparison, the ^{1}H NMR of (−)-**38b** was also obtained in $CDCl_3$: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (br d, J = 5.7 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.60 (s, 1H), 7.51 (br d, 1H), 7.36 (br d, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.9 Hz, 1H), 7.18−7.12 (comp, 2H), 6.83 (t, J = 7.4 Hz, 1H), 6.43 (s, 1H), 6.40 (br s, 1H), 4.96 (s, 1H), 3.87 (s, 3H), 3.81 (br s, 1H), 3.67 (br s, 1H), 3.17 (s, 3H), 3.01 (s, 3H), 1.67 (s, 9H), 1.65 (s, 3H), 1.41 (s, 18H), 0.88 (s, 9H), 0.14 (s, 3H), 0.04 (s, 3H).

Sharpless Dihydroxylation Product (+)-38a (C3α-OTBS Epimer). Following a similar procedure as described for the formation of (−)-**37b**, indoline (+)-**36a** (40 mg, 65 μmol) and phenoxazinone iodide **33** (130 mg, 200 μmol) were converted to intermediate **37a** (53 mg, 72%) as a red solid: TLC R_f 0.25 (3:7 EtOAc/hexanes, plate was eluted twice), **37a** is copolar with the hydrodehalogenated byproduct of **33** and the yield is based on the corresponding ratio obtained upon ^{1}H NMR analysis. Analytically pure samples of **37a** were not obtained for characterization purposes. Following a similar procedure as described for formation of **38b**, dihydroxylation of **37a** (15 mg, 13 μmol) using AD-mix-α provided the title compound (+)-**38a** (15 mg, 97%, >10:1 dr) as a red solid. The corresponding reaction of **37a** (10 mg, 8.8 μmol) using AD-mix-β (with additional $K_2OsO_4{\cdot}H_2O$ and $(DHQD)_2PHAL$) provided (+)-**38a** (8 mg, 77%, >10:1 dr). The analogous reaction of **37a** (10 mg, 8.8 μmol) using OsO_4 (22 mg, 2.1 μmol, 2.5 wt % in t-BuOH) and NMO (2 mg, 17 μmol) in acetone/H_2O (4:1, 2 mL) provided (+)-**38a** (8 mg, 77%, >10:1 dr). Subsequent data is provided for the major isomer only: $[\alpha]^D_{24}$ +61.8 (c = 0.05, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14

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(br d, J = 7.2 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.69 (s, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.34−7.32 (comp, 2H), 7.17 (app t, J = 7.1 Hz, 1H), 7.15 (app t, J = 6.9 Hz, 1H), 6.81 (app t, J = 7.4 Hz, 1H), 6.45 (comp, 1H), 6.44 (s, 1H), 6.43 (s, 1H), 5.01 (d, J = 2.5 Hz, 1H), 3.98 (br s, 1H), 3.88 (s, 3H), 3.73 (s, 1H), 3.46 (s, 3H), 2.96 (s, 3H), 1.68 (s, 9H), 1.53 (s, 3H), 1.41 (s, 18H), 0.80 (s, 9H), −0.06 (s, 3H), −0.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0 (C), 167.4 (C), 166.2 (C), 165.4 (C), 162.8 (C), 149.8 (C), 149.4 (C), 149.2 (C), 148.5 (C), 146.7 (C), 142.7 (C), 138.3 (C), 137.0 (C), 136.3 (C), 136.0 (C), 134.8 (CH), 134.0 (C), 131.3 (C), 130.2 (CH), 128.2 (C), 127.9 (CH), 127.8 (C), 125.0 (CH), 123.7 (CH), 123.4 (CH), 121.1 (C), 120.9 (CH), 120.4 (CH), 117.3 (CH), 115.6 (CH), 109.3 (CH), 106.8 (CH), 85.9 (C), 84.4 (C), 84.0 (C), 83.5 (C), 82.7 (CH), 78.7 (CH), 54.4 (C), 53.0 (CH_3), 52.7 (CH_3), 28.5 (CH_3), 28.4 (CH_3), 27.9 (CH_3), 27.0 (CH_3), 26.1 (CH_3), 19.0 (C), −2.91 (CH_3), −3.24 (CH_3); IR (film) 3443, 2979, 2951, 2931, 2855, 1805, 1741, 1643; TLC R_f 0.16 (2:3 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{60}H_{70}N_6O_{17}SiNa$ $(M + Na)^+$ 1197.4464, found 1197.4436.

(3*R*,5a*R*,10b*R*,11*S*,11a*S*)-10b-(1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)-3-((*tert*-butyldimethylsilyl)oxy)-2,3-dimethyl-1,4-dioxo-1,2,3,4,5a,6,10b,11-octahydro-11a*H*-pyrazino[1′,2′:1,5]-pyrrolo[2,3-*b*]indole-11,11a-diyl Diacetate ((+)-40a). *Method A.* To a solution of intermediate **39a**[12] (40 mg, 48 μmol) in CH_2Cl_2 maintained at −78 °C was added TfOH (84 μL, 48 μmol, 5% solution in CH_2Cl_2). The reaction mixture was warmed to −40 °C and then maintained at −40 °C for 4 h (note: reaction times may vary; close monitoring was required to prevent further reaction), whereupon it was quenched by the addition of pyridine (10 μL). After 5 min, the mixture was poured into a mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was further extracted with EtOAc (10 mL). The combined organic layers were washed sequentially with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (1:9 EtOAc/hexanes →1:3 EtOAc/hexanes) to afford the title compound (+)-**40a** (28 mg, 80%, in some of these reactions enamide **41** was also isolated as a minor byproduct).

Method B. In multiple sealed vials, intermediate **39a** (5 × 40 mg, 0.048 mmol) was maintained (neat) at 175 °C in a preheated oil bath for 40−50 min. The reaction vessels were allowed to cool to rt, then THF (0.48 mL), DMAP (1 mg) and Boc_2O (10 mg, 0.048 mmol, 0.1 mL of a premade 0.5 M THF solution) were added sequentially to the reaction mixtures. After 1 h, the reaction mixtures were combined and poured into a mixture of EtOAc (20 mL) and saturated aqueous NH_4Cl (10 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (10 mL). The combined organic layers were washed successively with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (1:9 EtOAc/hexanes →1:3 EtOAc/hexanes) to afford the title compound (+)-**40a** (125 mg, 71%; in some of these reactions the bis(*tert*-butoxycarbonyl) derivative (−)-**S8a** was also isolated as a minor byproduct also as a colorless foam)[71] as a colorless foam: $[\alpha]^D_{24}$ +93.8, $[\alpha]^{577}_{24}$ +95.0, $[\alpha]^{546}_{24}$ +100, $[\alpha]^{435}_{24}$ +178 (c 0.14, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (br d, J = 5.5 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.40 (s, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.19 (t, J = 7.8 Hz, 1H), 7.13 (t, J = 7.7 Hz, 1H), 6.92 (t, J = 7.4 Hz, 1H), 6.64 (d, J = 7.8 Hz, 1H), 6.52 (s, 1H), 6.26 (s, 1H), 4.86 (s, 1H), 3.02 (s, 3H), 1.90 (s, 3H), 1.61 (s, 9H), 1.45 (s, 3H), 1.37 (s, 3H), 0.98 (s, 9H), 0.37 (s 3H), 0.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3 (C), 168.13 (C), 168.08 (C), 159.1 (C), 149.5 (C), 147.2 (C), 136.4 (C), 129.5 (C), 129.3 (CH), 128.4 (C), 126.7 (CH), 125.6 (CH), 124.6 (CH), 122.6 (CH), 121.4 (CH), 119.9 (CH), 117.4 (C), 115.6 (CH), 109.7 (CH), 90.6 (C), 87.2 (C) 84.3 (C), 82.4 (CH), 80.9 (CH), 58.5 (C), 28.3 (CH_3), 28.0 (CH_3), 25.9 (CH_3), 24.0 (CH_3), 20.5 (CH_3), 20.4 (CH_3), 18.8 (C), −2.4 (CH_3), −3.1 (CH_3); IR (film) 3372, 2954, 2930, 2856, 1741, 1682, 1609, 1370, 1216; TLC R_f 0.28 (1:3 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{38}H_{48}N_4O_9SiNa$ $(M + Na)^+$ 755.3088, found 755.3083. The relative and absolute configuration of (+)-**40a** was confirmed by single crystal X-ray diffraction of an isopropanol solvate, mp 150−153 °C, formed by slow evaporation of the title compound from isopropanol.[43] Data for bis(*tert*-butoxycarbonyl) derivative (−)-**S8a**: $[\alpha]^D_{24}$ −3.2, $[\alpha]^{577}_{24}$ −3.5, $[\alpha]^{546}_{24}$ −2.8, $[\alpha]^{435}_{24}$ −16.0 (c 0.16, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (br d, J = 6.6 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 7.4 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.40 (s, 1H), 7.34 (s, 1H), 7.32−7.28 (comp, 3H), 7.25 (t, J = 7.6 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 6.11 (s, 1H), 3.03 (s, 3H), 1.90 (s, 3H), 1.61 (s, 9H), 1.49 (s, 9H), 1.43 (2*s*, 6H), 0.98 (s, 9H), 0.43 (s 3H), 0.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3 (C), 168.0 (C), 166.9 (C), 158.9 (C), 151.9 (C), 149.4 (C), 141.9 (C), 136.4 (C), 131.7 (C), 129.3 (CH), 128.0 (C), 127.5 (CH), 125.6 (CH), 124.7 (CH), 123.4 (CH), 122.9 (CH), 121.5 (CH), 116.8 (C), 115.8 (CH), 115.5 (CH), 92.0 (C), 87.1 (C), 84.4 (C), 83.4 (CH), 82.8 (C), 80.1 (CH), 56.9 (C), 28.5 (CH_3), 28.2 (CH_3), 27.9 (CH_3), 26.1 (CH_3), 24.8 (CH_3), 20.5 (CH_3), 20.3 (CH_3), 18.9 (C), −2.38 (CH_3), −2.42 (CH_3); IR (film) 2953, 2929, 2853, 1766, 1740, 1714, 1682, 1484, 1455, 1371; TLC R_f 0.35 (1:3 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{43}H_{56}N_4O_{11}SiNa$ $(M + Na)^+$ 855.3613, found 855.3622.

(3*S*,5a*R*,10b*R*,11*S*,11a*S*)-10b-(1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)-3-((*tert*-butyldimethylsilyl)oxy)-2,3-dimethyl-1,4-dioxo-1,2,3,4,5a,6,10b,11-octahydro-11a*H*-pyrazino[1′,2′:1,5]-pyrrolo[2,3-*b*]indole-11,11a-diyl Diacetate ((+)-40b). Following a similar procedure as described in method B for formation of (+)-**40a**, intermediate **39b**[12] (200 mg, 0.26 mmol) was converted to the title compound (+)-**40b** (110 mg, 63%; in some of these reactions the bis(*tert*-butoxycarbonyl) derivative (−)-**S8b** was also isolated as a minor byproduct also as a colorless foam), which was isolated as a colorless foam: $[\alpha]^D_{24}$ +50.7, $[\alpha]^{577}_{24}$ +52.4, $[\alpha]^{546}_{24}$ +60.5, $[\alpha]^{435}_{24}$ +112, $[\alpha]^{405}_{24}$ +144 (c 0.10, CH_2Cl_2); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.16 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 7.4 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 6.93 (t, J = 7.4 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.52 (s, 1H), 6.49 (d, J = 2.8 Hz, 1H), 6.11 (s, 1H), 3.03 (s, 3H), 1.97 (s, 3H), 1.63 (s, 9H), 1.44 (s, 3H), 1.41 (s, 3H), 0.93 (s, 9H), 0.34 (s 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 168.7 (C), 168.5 (C), 167.7 (C), 160.2 (C), 150.0 (C), 149.9 (C), 137.1 (C), 130.2 (C), 130.0 (CH), 129.2 (C), 126.8 (CH), 125.7 (CH), 125.4 (CH), 123.3 (CH), 121.9 (CH), 119.6 (CH), 119.2 (C), 116.4 (CH), 110.6 (CH), 91.2 (C), 86.9 (C) 85.0 (C), 84.1 (CH), 82.2 (CH), 59.6 (C), 29.4 (CH_3), 28.2 (CH_3), 28.0 (CH_3), 26.3 (CH_3), 20.5 (CH_3), 20.2 (CH_3), 19.2 (C), −2.9 (CH_3), −3.6 (CH_3); IR (film) 3376, 2954, 2917, 2850, 1766, 1740, 1682, 1609, 1371, 1215; TLC R_f 0.25 (3:7 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{38}H_{48}N_4O_9SiNa$ $(M + Na)^+$ 755.3088, found 755.3098. Data for bis(*tert*-butoxycarbonyl) derivative (−)-**S8b**: $[\alpha]^D_{24}$ −20.5, $[\alpha]^{577}_{24}$ −31.4, $[\alpha]^{546}_{24}$ −37.8, $[\alpha]^{435}_{24}$ −82.9 (c 0.18, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (br d, J = 6.4 Hz, 1H), 7.72 (br d, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.40 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.27 (s, 1H), 7.22−7.18 (comp, 2H), 6.11 (s, 1H), 3.04 (s, 3H), 1.94 (s, 3H), 1.61 (s, 9H), 1.55 (s, 9H), 1.45 (s, 3H), 1.33 (s, 3H), 0.92 (s, 9H), 0.33 (s 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8 (C), 167.3 (C), 165.4 (C), 159.6 (C), 152.0 (C), 149.4 (C), 142.1 (C), 136.3 (C), 132.0 (C), 129.3 (CH), 128.0 (C), 127.1 (CH), 125.7 (CH), 124.7 (CH), 123.7 (CH), 122.7 (CH), 120.9 (CH), 116.7 (C), 116.4 (CH), 115.7 (CH), 91.1 (C), 85.9 (C), 84.5 (C), 83.9 (CH), 83.1 (C), 81.8 (CH), 56.9 (C), 28.5 (CH_3), 28.4 (CH_3), 28.3 (CH_3), 28.1 (CH_3), 25.9 (CH_3), 20.5 (CH_3), 20.3 (CH_3), 18.6 (C), −3.2 (CH_3), −4.1 (CH_3); IR (film) 2954, 2917, 2850, 1768, 1737, 1716, 1685, 1476, 1455, 1370; TLC R_f 0.35 (1:3 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{43}H_{56}N_4O_{11}SiNa$ $(M + Na)^+$ 855.3613, found 855.3600.

(5a*R*,10b*R*,11*S*,11a*S*)-10b-(1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)-2-methyl-3-methylene-1,4-dioxo-1,2,3,4,5a,6,10b,11-octahydro-11a*H*-pyrazino[1′,2′:1,5]pyrrolo[2,3-*b*]indole-11,11a-diyl Diacetate ((+)-41). To a solution of intermediate **39b** (100 mg, 0.12 mmol) in CH_2Cl_2 (2.5 mL) maintained at −78 °C was added TfOH (16 μL, 0.18 mmol, 5% solution in CH_2Cl_2). The reaction mixture was warmed to −40 °C, maintained at −40 °C for 4 h (note:

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reaction times may vary, monitoring required to prevent further cleavage of the remaining Boc group), and then quenched by the addition of pyridine (20 μL). After 5 min, the mixture was poured into a mixture of EtOAc (20 mL) and saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was further extracted with EtOAc (10 mL). The combined organic layers were washed successively with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. A second batch of **39b** (220 mg, 0.26 mmol) was processed in a similar fashion. The crude product from both reactions were combined and purified by silica gel chromatography (1:9 EtOAc/hexanes →1:3 EtOAc/hexanes) to afford the title compound (+)-**41** (185 mg, 82%) as a colorless solid: $[\alpha]^{D}_{24}$ +36.0, $[\alpha]^{577}_{24}$ +46.1, $[\alpha]^{546}_{24}$ +44.9, $[\alpha]^{435}_{24}$ +87.9 (*c* 0.13, CH_2Cl_2); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.15 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.48 (s, 1H), 7.33 (t, *J* = 8.2 Hz, 1H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.51 (s, 1H), 6.38 (s, 1H), 6.19 (s, 1H), 5.83 (s, 1H), 5.21 (s 1H), 3.23 (s, 3H), 1.64 (s, 9H), 1.43 (s, 6H); ^{13}C NMR (125 MHz, acetone-d_6) δ 169.9 (C), 168.7 (C), 160.6 (C), 159.0 (C), 150.0 (C), 149.8 (C), 139.1 (C), 137.1 (C), 130.1 (CH), 129.3 (C), 126.8 (CH), 125.9 (CH), 125.5 (CH), 123.5 (CH), 122.2 (CH), 119.7 (CH), 119.0 (C), 116.3 (CH), 110.8 (CH), 103.8 (CH_2), 91.9 (C), 85.0 (C), 83.9 (CH), 81.7 (CH), 58.9 (C), 28.2 (CH_3), 20.30 (CH_3), 20.28 (CH_3);[72] IR (film) 3374, 3055, 2979, 2917, 2849, 1740, 1695, 1615, 1371; TLC R_f 0.28 (3:7 EtOAc/hexanes); HRMS (ESI) *m*/*z* calcd for $C_{32}H_{32}N_4O_8Na$ $(M + Na)^+$ 623.2118, found 623.2111.

Cross-Coupled Product ((+)-42a). The components of this reaction were combined in a screw-top vial inside a nitrogen-filled glovebox. The reaction vial was sealed with a Teflon-lined cap, then brought outside the glovebox and heated in an aluminum block for the period of time indicated. The reaction vessel was charged with indoline **40a** (10 mg, 14 μmol), phenoxazinone iodide **33** (27 mg, 42 μmol), copper(I) acetate (CuOAc) (10 mg, 82 μmol), and KOAc (3.0 mg, 31 μmol), and then PhMe (200 μL) was added by syringe. The reaction mixture was maintained at 90 °C for 8 h. After being allowed to cool to rt, the reaction mixture was passed directly through a short plug of silica gel (eluting with EtOAc) to remove the metal salts, then concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (1:19 EtOAc/hexanes →1:3 EtOAc/hexanes) to afford the title compound (+)-**42a** (10 mg, 58%) as a red solid: $[\alpha]^{D}_{24}$ +43.9 (c 0.063, MeOH). Compound **42a** was observed as a 3:1 mixture of atropisomers by NMR at 298 K: ^{1}H NMR (500 MHz, acetone-d_6) δ 8.21 (d, *J* = 8.3 Hz, 1.33H), 7.76 (d, *J* = 7.5 Hz, 1.33H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.56 (s, 1H), 7.53 (s, 0.33H), 7.51 (d, *J* = 8.1 Hz, 0.33H), 7.41−7.38 (comp, 1.66H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.30−7.19 (comp, 3H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 0.33H), 6.89 (s, 1H), 6.72 (s, 0.33H), 6.69 (d, *J* = 8.0 Hz, 0.33H), 6.48 (s, 1H), 6.44 (s, 0.33H), 6.31 (d, *J* = 7.9 Hz, 1H), 6.20 (s, 1H), 6.11 (s, 0.33H), 3.94 (s, 1H), 3.89 (s, 1H), 3.79 (s, 3H), 3.04 (s, 1H), 3.02 (s, 3H), 2.88 (s, 3H), 2.00 (s, 1H), 1.89 (s, 3H), 1.65 (s, 12H), 1.52 (s, 4H), 1.39 (s, 3H), 1.39 (s, 6H), 1.37 (2*s*, 19H), 1.01 (s, 1H), 0.98 (s, 9H), 0.40 (s, 1H), 0.35 (s, 1H), 0.32 (s 3H), 0.30 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 180.6 (C, major), 170.0 (C, major), 169.6 (C, minor), 168.5 (C, major), 168.3 (C, minor), 168.2 (C, major), 167.4 (C, minor), 166.4 (C, minor), 165.4 (C, major), 163.73 (C, minor), 163.65 (C, major), 159.3 (C, minor), 159.2 (C, major), 151.0 (C, minor), 150.3 (C, minor), 150.2 (C, major), 150.0 (C, major), 149.8 (C, major), 148.8 (C, major), 148.4 (C, minor), 148.2 (C, major), 144.2 (C, major), 144.0 (C, minor), 140.3 (C, minor), 139.0 (C, major), 137.9 (C, minor), 137.33 (C, minor), 137.27 (C, major), 137.0 (C, major), 136.1 (CH, major), 134.83 (CH, minor), 134.75 (C, major), 134.71 (C, major), 131.84 (C, major), 131.79 (C, minor), 131.3 (C, minor), 130.22 (C, major), 130.19 (CH, minor), 130.1 (CH, major), 129.1 (C, major), 128.8 (C, minor), 128.6 (CH, minor), 128.1 (CH, major), 126.1 (CH, major), 125.8 (CH, minor), 125.6 (C, minor), 125.5 (CH, major), 123.6 (CH, major), 123.5 (CH, minor), 122.5 (CH, minor), 122.3 (CH, major), 122.1 (CH, minor), 120.5 (CH, major), 120.4 (CH, minor), 119.4 (CH, major), 118.5 (C, minor), 118.1 (C, major), 116.5 (CH, minor), 116.4 (CH, major), 114.3 (CH, minor), 108.8 (CH, major), 106.8 (CH, major), 106.7 (CH, minor), 92.0 (C, major), 91.5 (C, minor), 88.5 (CH, minor), 88.2 (C, minor), 87.9 (C, major), 86.7 (CH, major), 85.34 (C, minor), 85.25 (C, major), 83.74 (CH, minor), 83.70 (C, major), 83.4 (CH, major), 59.6 (C, minor), 58.5 (C, major), 53.3 (CH_3, minor), 53.2 (CH_3, minor), 53.1 (CH_3, major), 51.8 (CH_3, major), 28.3 (CH_3, major), 28.2 (CH_3, major), 27.93 (CH_3, minor), 27.92 (CH_3, major), 26.35 (CH_3, minor), 26.32 (CH_3, major), 24.83 (CH_3, minor), 24.80 (CH_3, major), 20.5 (CH_3, major), 20.3 (CH_3, major), 20.1 (CH_3, minor), 19.30 (C, minor), 19.28 (C, major), −2.0 (CH_3, minor), −2.3 (CH_3, major), −2.4 (CH_3, minor), −2.7 (CH_3, major);[73] IR (film) 2954, 2918, 2850, 1807, 1744, 1683, 1643, 1578, 1369; TLC Rf 0.10 (3:7 EtOAc/hexanes); HRMS (ESI) *m*/*z* calcd for $C_{64}H_{74}N_6O_{19}SiNa$ $(M + Na)^+$ 1281.4675, found 1281.4697. During preliminary cross-coupling experiments, allowing **40a** to react with varying amounts of **33**, CuTC, and K_2CO_3 in PhMe at 90 °C resulted in the formation of **43** as a tan solid, in minor quantities. Data for thiophene-2-carboxylate adduct (+)-**43**: $[\alpha]^{D}_{24}$ +29.8, $[\alpha]^{577}_{24}$ +38.3, $[\alpha]^{546}_{24}$ +44.0, $[\alpha]^{435}_{24}$ +93.8 (c 0.10, CH_2Cl_2); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.16 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 4.8 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 6.8 Hz, 1H), 7.49 (s, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.3 Hz, 1H), 6.98 (t, *J* = 4.3 Hz, 1H), 6.62 (d, J =1.5 Hz, 1H), 6.56 (s, 1H), 6.49 (s, 1H), 6.48 (d, *J* = 7.8 Hz, 1H), 6.37 (s, 1H), 3.05 (s, 3H), 1.99 (s, 3H), 1.64 (s, 9H), 1.50 (s, 3H), 1.01 (s, 9H), 0.42 (s 3H), 0.32 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 167.9 (C), 167.8 (C), 160.3 (C), 159.0 (C), 149.3 (C), 149.0 (C), 136.5 (C), 135.4 (CH), 135.0 (CH), 131.8 (C), 129.7 (CH), 129.6 (C), 128.5 (C), 128.2 (CH), 126.0 (CH), 125.1 (CH), 124.8 (CH), 122.8 (CH), 121.6 (CH), 119.03 (C), 119.00 (CH), 115.7 (CH), 110.3 (CH), 91.8 (C), 87.3 (C) 84.4 (C), 82.9 (CH), 81.6 (CH), 59.0 (C), 27.65 (CH_3), 27.57 (CH_3), 25.7 (CH_3), 23.9 (CH_3), 19.8 (CH_3), 18.7 (C), −2.9 (CH_3), −3.4 (CH_3); IR (film) 3376, 2954, 2918, 2851, 1765, 1736, 1710, 1683, 1608, 1371, 1218; TLC Rf 0.56 (3:7 EtOAc/hexanes, plate was eluted twice); HRMS (ESI) *m*/*z* calcd for $C_{41}H_{48}N_4O_9SSiNa$ $(M + Na)^+$ 823.2809, found 823.2798.

Cross-Coupled Product ((+)-42b). Following a similar procedure as described for formation of **42a**, intermediate (+)-**40b** (17 mg, 23 μmol) was converted to the title compound (+)-**42b** (15 mg, 51%), which was isolated as a red solid: $[\alpha]^{D}_{24}$ +28.0 (*c* 0.053, MeOH); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.22 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.56 (s, 1H), 7.41−7.38 (comp, 3H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.79 (s, 1H), 6.48 (s, 1H), 6.34 (d, *J* = 7.6 Hz, 1H), 6.11 (s, 1H), 3.78 (s, 3H), 3.04 (s, 3H), 2.84 (s, 3H), 1.96 (s, 3H), 1.65 (s, 9H), 1.59 (s, 3H), 1.40 (2*s*, 21H), 0.98 (s, 9H), 0.24 (s 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 180.6 (C), 169.4 (C), 168.3 (C), 167.8 (C), 165.3 (C), 163.6 (C), 159.8 (C), 150.1 (C), 150.0 (C), 149.7 (C), 149.0 (C), 148.1 (C), 144.2 (C), 139.0 (C), 137.22 (C), 137.17 (CH), 136.7 (CH), 134.79 (C), 134.76 (C), 131.9 (C), 130.1 (CH), 129.8 (C), 129.1 (C), 127.9 (CH), 126.1 (CH), 125.6 (CH), 123.3 (CH), 121.8 (CH), 120.6 (CH), 119.4 (CH), 118.3 (C), 116.5 (CH), 108.9 (CH), 106.9 (CH), 91.6 (C), 88.0 (CH), 87.1 (C), 85.3 (C), 84.3 (CH), 83.4 (C), 59.0 (C), 53.1 (CH_3), 51.7 (CH_3), 29.4 (CH_3),[74] 28.2 (CH_3), 28.1 (CH_3), 27.9 (CH_3), 26.2 (CH_3), 20.6 (CH_3), 20.1 (CH_3), 19.2 (C), −2.8 (CH_3), −3.1 (CH_3); IR (film) 2979, 2952, 2929, 2851, 1807, 1768, 1747, 1687, 1577, 1370; TLC R_f 0.24 (4:6 EtOAc/hexanes); HRMS (ESI) *m*/*z* calcd for $C_{64}H_{74}N_6O_{19}SiNa$ $(M + Na)^+$ 1281.4675, found 1281.4680.

Bis(methylthio)ether (44). *Method A.* Hydrogen sulfide (bp −60 °C, ca. 200 μL) was condensed at −78 °C in a thick-walled, glass pressure tube fitted with a rubber septum. A solution of (+)-**42a** (5.0 mg, 4.0 μmol) in CH_2Cl_2 (400 μL) and $BF_3{\cdot}OEt_2$ (10 μL, 80 μmol) were injected sequentially into the reaction vessel maintained at −78 °C. The rubber septum was replaced by a Teflon screw cap, which was used to seal the vessel. The cold bath was removed and the reaction mixture was allowed to warm to rt *behind a blast shield*. After 1 h, the reaction mixture was cooled to −78 °C, and the Teflon cap was replaced by the rubber septum, which was equipped with a needle vented to base (KOH/isopropanol) and bleach traps (attached in

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series). The cooling bath was removed and the resulting brown suspension was allowed to warm up to rt. Upon evolution of the majority of hydrogen sulfide gas, an argon-filled balloon was attached (by needle) to fully purge the reaction mixture, which was subsequently poured into a mixture of EtOAc (2 mL) and saturated aqueous NH_4Cl (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 mL). The combined organic layers were washed with brine (4 mL), dried over Na_2SO_4 and filtered. To this solution was immediately added MeI (20 μL, 200 μmol) and K_2CO_3 (14 mg, 100 μmol). *Performing the S-alkylation step prior to any further manipulations prevented competitive oxidation of the dithiol intermediate to the undesired epidisulfide congener.* The reaction mixture was stirred for 12 h at rt and then poured into a mixture of EtOAc (10 mL) and saturated aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by preparatory thin layer chromatography (6/4 EtOAc/hexanes) to afford the title compound (−)-**44b** (3.0 mg, 88%) as a single diastereomer (by ^{1}H NMR analysis). In corresponding experiments with *N,O*-acetal intermediate (+)-**42b** (10 mg, 8.0 μmol), the title compound (−)-**44b** (5.5 mg, 80%) was obtained in similar efficiency and diastereoselectivity as a red solid.

Method B. Methanethiol (bp 6 °C, ca. 200 μL) was condensed at −78 °C in a thick-walled, glass pressure tube fitted with a rubber septum. A solution of (+)-**42a** (23 mg, 18 μmol) in CH_2Cl_2 (400 μL) and $BF_3{\cdot}OEt_2$ (30 μL, 240 μmol) was injected sequentially into the reaction vessel maintained at −78 °C. The rubber septum was replaced by a Teflon screw cap, which was used to seal the vessel. The cold bath was removed, and the reaction mixture was allowed to warm to rt *behind a blast shield*. After 1 h, the reaction mixture was cooled back down to −78 °C, and the Teflon cap was replaced by the rubber septum, which was equipped with a needle vented to base (KOH/isopropanol) and bleach traps (attached in series). The cooling bath was removed and the resulting brown suspension was allowed to warm to rt. Upon evolution of the majority of methanethiol gas, an argon-filled balloon was attached (by needle) to fully purge the reaction mixture, which was subsequently poured into a mixture of EtOAc (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. This reaction was conducted three times consecutively, and then the crude residues were combined for purification by preparatory thin layer chromatography (6/4 EtOAc/hexanes) to afford the title compound (−)-**44b** (21 mg, 45%) and (−)-**44a** (16 mg, 34%) as red solids. In corresponding experiments with (+)-**42b** (30 mg, 24 μmol), the title compound (−)-**44b** and (−)-**44a** were obtained in similar efficiency (19 mg, 92% overall) and diastereoselectivity (1.3:1 dr, respectively) as a red solid. Data for *cis*-bis(methylthio)ether (−)-**44b**: $[\alpha]^D_{24}$ −142, $[\alpha]^{577}_{24}$ −168, $[\alpha]^{546}_{24}$ −217 (*c* 0.050, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.71−7.67 (comp, 2H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.26 (s, 1H), 7.16−7.13 (comp, 1H), 7.10 (s, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 2.5 Hz, 1H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.45 (s, 1H), 6.29 (s, 1H), 6.22 (d, *J* = 7.8 Hz, 1H), 3.75 (s, 3H), 3.10 (s, 3H), 2.65 (s, 3H), 2.16 (s, 3H), 2.00 (s, 3H), 1.87 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5 (C), 169.1 (C), 168.9 (C), 166.1 (C), 163.8 (C), 163.5 (C), 150.8 (C), 150.2 (C), 149.4 (C), 145.9 (C), 141.1 (C), 137.3 (C), 135.6 (C), 134.7 (C), 132.0 (C), 131.4 (CH), 129.7 (C), 129.6 (CH), 126.1 (C), 126.0 (CH), 124.2 (CH), 122.3 (CH), 121.1 (CH), 120.1 (CH), 118.8 (CH), 117.4 (CH), 112.9 (C), 111.8 (CH), 107.7 (CH), 105.0 (CH), 98.2 (C), 86.1 (CH), 81.2 (CH), 72.6 (C), 67.2 (C), 57.5 (C), 51.6 (CH_3), 51.3 (CH_3), 29.2 (CH_3), 23.7 (CH_3), 20.5 (CH_3), 16.4 (CH_3), 14.6 (CH_3); IR (film) 3412, 3308, 2947, 2918, 2849, 1745, 1668, 1581, 1374; TLC R_f 0.38 (1:1 EtOAc/hexanes, plate was eluted twice); HRMS (ESI) *m*/*z* calcd for $C_{43}H_{38}N_6O_{10}S_2Na$ $(M + Na)^+$ 885.1989, found 885.1968. Note, for comparison, the ^{1}H NMR of (−)-**44b** was also obtained in acetone-d_6: ^{1}H NMR (500 MHz, acetone-d_6) δ 10.37 (s, 1H), 7.73 (d, *J* = 7.3 Hz, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.2−7.1 (comp, 3H), 7.07 (s, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.44 (s, 1H), 6.30 (s, 1H), 6.16 (d, *J* = 7.8 Hz, 1H), 3.73 (s, 3H), 3.08 (s, 3H), 2.69 (s, 3H), 2.13 (s, 3H), 2.05 (s, 3H), 1.85 (s, 3H), 1.29 (s, 3H). Data for *trans*-bis(methylthio)ether (−)-**44a**: $[\alpha]^D_{24}$ −103, $[\alpha]^{577}_{24}$ −110, $[\alpha]^{546}_{24}$ −136 (*c* 0.11, CH_2Cl_2); **44a** was observed as a 4:1 mixture of atropisomers by NMR at 298 K (subsequent data is provided for the major isomer only); ^{1}H NMR (500 MHz, acetone-d_6) δ 10.39 (s, 1H), 7.73 (d, *J* = 7.3 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.2−7.1 (comp, 3H), 7.05 (t, *J* = 7.8 Hz, 1H), 7.04 (s, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.45 (s, 1H), 6.23 (s, 1H), 6.19 (d, *J* = 7.9 Hz, 1H), 3.73 (s, 3H), 3.11 (s, 3H), 2.62 (s, 3H), 2.16 (s, 3H), 2.12 (s, 3H), 1.74 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 179.0 (C), 169.3 (C), 168.6 (C), 166.2 (C), 165.1 (C), 163.6 (C), 151.3 (C), 151.2 (C), 150.4 (C), 146.8 (C), 142.1 (C), 138.7 (C), 136.4 (C), 135.1 (C), 132.6 (C), 132.1 (CH), 130.9 (C), 130.1 (CH), 127.2 (CH), 127.1 (C), 125.1 (CH), 122.5 (CH), 121.9 (CH), 119.8 (CH), 119.3 (CH), 118.2 (CH), 112.98 (CH), 112.96 (C), 108.1 (CH), 105.3 (CH), 87.3 (CH), 81.6 (CH), 74.5 (C), 73.8 (C), 58.6 (C), 51.7 (CH_3), 51.2 (CH_3), 30.2 (CH_3), 25.2 (CH_3), 20.3 (CH_3), 16.1 (CH_3), 13.2 (CH_3);[75] IR (film) 3389, 3307, 2947, 2917, 2849, 1747, 1667, 1581, 1377; TLC R_f 0.28 (1:1 EtOAc/hexanes, plate was eluted twice); HRMS (ESI) *m*/*z* calcd for $C_{43}H_{38}N_6O_{10}S_2Na$ $(M + Na)^+$ 885.1989, found 885.1960.

(+)-Plectosphaeroic Acid B (2).[4] To a solution of *cis*-bis(methylthio)ether (−)-**44b** (8.0 mg, 9.3 μmol) in MeOH (0.10 mL) were added lanthanum(III) trifluoromethanesulfonate (56 mg, 93 μmol) and DMAP (1.4 mg, 11 μmol). The reaction mixture was maintained at 45 °C. After 5 h (the consumption of the starting material was monitored by TLC, heating times varied in some instances), the reaction mixture was allowed to cool to rt and then poured into a mixture of EtOAc (10 mL) and saturated aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by preparatory thin-layer chromatography (7:3 EtOAc/hexanes) to afford the deacetylated, C11-secondary alcohol intermediate (6.0 mg, contaminated with a closely eluting byproduct arising from the in situ hydrolysis of a methyl ester group) as a red solid. This solid was dissolved in pyridine (0.10 mL), and LiI (50 mg, 370 μmol) was added to the solution. The reaction mixture was stirred for 12 h at 90 °C (formation of product was observed by RP-18 TLC), allowed to cool to rt, and poured into a mixture of EtOAc (5 mL) and 1 N HCl (2 mL). The layers were separated, and the organic layers was washed with 1 N HCl (2 × 2 mL). The combined aqueous layers were extracted with EtOAc (4 mL), the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by reverse-phase HPLC (step-gradient eluting 20%, 40%, 60%, 65%, 70%, 75%, 90% MeOH/H_2O + 0.1% TFA) to afford plectosphaeroic acid B (**2**) (4.8 mg, 65% over two steps, eluting at 75% MeOH/H_2O + 0.1% TFA) as a red solid: $[\alpha]^D_{24}$ +228 (*c* 0.08, MeOH), compare with reported value $[\alpha]^D_{24}$ +69.8 (*c* 0.27, MeOH) of the natural sample; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.85 (s, 1H), 9.72 (s, 1H), 8.91 (s, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.36 (comp, 2H), 7.09 (m, 1H), 7.06 (m, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.74 (s, 1H), 6.68 (s, 1H), 6.56 (t, *J* = 7.4 Hz, 1H), 5.98 (d, *J* = 7.9 Hz, 1H), 5.73 (br s, 1H), 5.44 (br s, 1H), 2.93 (s, 3H), 2.14 (s, 3H), 1.88 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.1 (C), 168.9 (C), 167.2 (C), 163.6 (C), 163.5 (C), 152.6 (C), 151.0 (C), 149.1 (C), 147.6 (C), 141.2 (C), 137.1 (C), 135.0 (C), 133.4 (C), 133.3 (C), 130.7 (CH), 127.9 (CH), 127.4 (C), 125.3 (C), 122.5 (CH), 122.4 (CH), 121.5 (CH), 120.9 (CH), 118.6 (CH), 118.0 (CH), 117.8 (CH), 115.9 (C), 111.4 (CH), 106.7 (CH), 105.5 (CH), 92.4 (C), 86.1 (C), 78.6 (CH), 74.1 (C), 66.3 (C), 58.6 (C), 28.5 (CH_3), 22.6 (CH_3), 15.7 (CH_3), 13.9 (CH_3); RP-18 TLC R_f 0.57 (4:1

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MeOH/H_2O); HRMS (ESI) m/z calcd for $C_{39}H_{31}N_6O_9S_2$ $(M - H)^-$ 791.1594, found 791.1610.

C3-*epi*-Plectosphaeroic acid B ((+)-S9). Following a procedure similar to that described for formation of plectosphaeroic acid B (**2**), (−)-**44a** (18 mg, 19 μmol) was converted to the title compound (+)-**S9** (8.0 mg, 48%), which was isolated as a red solid: $[\alpha]^D_{24}$ +236 (c 0.062, MeOH); **S9** was observed as an 8:1 mixture of atropisomers by NMR at 298 K (subsequent data is provided for the major isomer only); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.87 (s, 1H), 9.72 (s, 1H), 8.91 (s, 1H), 8.00 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.6−7.5 (comp, 2H), 7.35 (d, J = 8.1 Hz, 1H), 7.31 (s, 1H), 7.1−7.0 (comp, 2H), 6.93 (t, J = 7.7 Hz, 1H), 6.69 (s, 1H), 6.68 (s, 1H), 6.60 (t, J = 7.3 Hz, 1H), 6.10 (br s, 1H), 6.01 (d, J = 7.9 Hz, 1H), 5.41 (s, 1H), 2.97 (s, 3H), 2.10 (s, 3H), 1.71 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.1 (C), 168.9 (C), 167.1 (C), 164.7 (C), 162.8 (C), 152.6 (C), 150.9 (C), 149.3 (C), 147.6 (C), 141.2 (C), 137.1 (C), 135.2 (C), 133.2 (2 × C), 130.6 (CH), 128.7 (CH), 127.6 (C), 125.3 (C), 122.9 (CH), 122.4 (CH), 121.4 (CH), 120.9 (CH), 118.6 (CH), 118.3 (CH), 117.7 (CH), 115.8 (C), 111.4 (CH), 106.9 (CH), 105.5 (CH), 92.4 (C), 86.7 (CH), 78.7 (CH), 75.4 (C), 73.3 (C), 58.7 (C), 29.4 (CH_3), 25.1 (CH_3), 15.3 (CH_3), 12.3 (CH_3); IR (film) 3374, 3270, 3062, 2919, 2850, 1681, 1588, 1487, 1385; RP-18 TLC R_f 0.53 (4:1 MeOH/H_2O); HRMS (ESI) m/z calcd for $C_{39}H_{31}N_6O_9S_2$ $(M - H)^-$ 791.1594, found 791.1595.

Epidisulfidedioxopiperazine ((−)-46). A similar procedure for sulfidation as described for formation of **44** using H_2S and $BF_3{\cdot}OEt_2$ was followed, except the organic layer upon quenching of this step was concentrated under reduced pressure and the resulting crude mixture was redissolved in acetone (0.5 mL) and K_2CO_3 (14 mg, 100 μmol) was added. The mixture was subsequently processed in a similar fashion. Using this procedure, intermediate **42a** and **42b** (5−10 mg/run) were converted to epidisulfide (−)-**46** containing minor amounts of trisulfide (+)-**47** (3−6 mg, 70−80%, 5−10:1 ratio of products). An alternative procedure for the S−S bond-forming step involved adding SiO_2 (100 mg; instead of K_2CO_3) to the crude mixture obtained from sulfidating 26 mg of **42** dissolved in acetone (0.5 mL). The resulting heterogeneous mixture was vigorously stirred for 24 h (reaction times varied) and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by preparatory thin layer chromatography (7:3 EtOAc/hexanes) to afford (−)-**46** and (+)-**47** (12 mg, 70%, 7:1 ratio) as a red solid: $[\alpha]^D_{24}$ −23.8, $[\alpha]^{577}_{24}$ −33.2 (c 0.12, MeOH); ^{1}H NMR (500 MHz, acetone-d_6) δ 10.42 (br s, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.3 Hz, 1H), 7.64 (m, 1H), 7.51 (d, J = 9.0 Hz, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 7.3 Hz, 1H), 7.15 (t, J = 7.2 Hz, 1H), 7.05 (d, J = 2.1 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 7.01 (s, 1H), 6.44 (s, 1H), 6.42 (br d, J = 7.2 Hz, 1H), 6.36 (s, 1H), 3.74 (s, 3H), 3.01 (s, 3H), 2.60 (br s, 3H), 1.91 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 178.9 (C), 169.2 (C), 169.0 (C), 166.3 (C), 164.1 (C), 162.8 (C), 151.1 (C), 150.4 (C), 149.4 (C), 146.7 (C), 141.7 (C), 138.8 (C), 134.4 (C), 132.8 (CH), 132.3 (C), 130.7 (C), 130.5 (CH), 127.5 (CH), 127.4 (C), 126.1 (CH), 125.9 (CH), 122.7 (CH), 122.3 (CH), 120.6 (CH), 120.1 (CH), 117.6 (CH), 113.0 (CH), 111.7 (C), 109.1 (CH), 105.2 (CH), 99.1 (C), 86.8 (CH), 80.6 (CH), 77.2 (C), 76.2 (C), 60.6 (C), 51.8 (CH_3), 51.4 (CH_3), 27.6 (CH_3), 20.4 (CH_3), 18.0 (CH_3); IR (film) 3411, 3323, 3055, 2950, 2917, 2849, 1737, 1703, 1578, 1489; TLC R_f 0.33 (4:6 EtOAc/hexanes, plate was eluted twice); HRMS (ESI) m/z calcd for $C_{41}H_{32}N_6O_{10}S_2Na$ $(M + Na)^+$ 855.1519, found 855.1542.

Epitrisulfidedioxopiperazine ((+)-47). *Method A.* Hydrogen sulfide (bp −60 °C, ca. 400 μL) was condensed at −78 °C in a thick-walled, glass pressure tube fitted with a rubber septum. A solution of **42** (12 mg, 9.5 μmol) in CH_2Cl_2 (400 μL) and $BF_3{\cdot}OEt_2$ (20 μL, 160 μmol) were injected sequentially into the reaction vessel maintained at −78 °C. The rubber septum was replaced by the corresponding Teflon screw cap, which was used to seal the vessel. The cold bath was removed and the reaction mixture was allowed to warm to rt *behind a blast shield*. After 1 h, the reaction mixture was cooled to −78 °C, the Teflon cap was replaced by the rubber septum, which was equipped with a needle vented to base (KOH/isopropanol) and bleach traps (attached in series). The cooling bath was removed and the resulting brown suspension was allowed to warm up to rt. Upon evolution of the majority of hydrogen sulfide gas, an argon-filled balloon was attached (by needle) to fully purge the reaction mixture, which was subsequently poured into a mixture of EtOAc (2 mL) and saturated aqueous NH_4Cl (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 mL). The combined organic layers were washed with brine (4 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in acetone (1 mL) and K_2CO_3 (10 mg, 72 μmol) was added. The resulting heterogeneous mixture was stirred for 1 h, at which point Na_2S (0.7 mg, 9.0 μmol) was added. The reaction mixture was stirred for 12 h at rt, then poured into a mixture of EtOAc (10 mL) and saturated aqueous NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by preparatory thin layer chromatography (6:4 EtOAc/hexanes) to afford the title compound (+)-**47** (5.0 mg, 64%) as a red solid.[76]

Method B. To a solution of disulfide (−)-**46** (5.0 mg, 6.0 μmol) was added Na_2S (0.50 mg, 6.4 μmol). The reaction mixture was stirred for 1 h at rt, then poured into a mixture of EtOAc (20 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. An identical reaction was conducted on 9 mg of (−)-**46**. The crude residue from both reactions was combined for purification by preparatory thin layer chromatography (3:7 EtOAc/hexanes) to afford the title compound (+)-**47** and **48** (11 mg, 75%; 5:1 ratio). Data for epitrisulfide (+)-**47**: $[\alpha]^D_{24}$ +61.3, $[\alpha]^{577}_{24}$ +64.9, $[\alpha]^{546}_{24}$ +72.4 (c 0.12, MeOH); ^{1}H NMR (500 MHz, acetone-d_6) δ 10.38 (br s, 1H), 8.19 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.27 (t, J = 7.7 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.04 (s, 1H), 6.99 (t, J = 7.5 Hz, 1H), 6.95 (s, 1H), 6.47 (s, 1H), 6.43 (d, J = 8.1 Hz, 1H), 6.33 (s, 1H), 3.74 (s, 3H), 3.21 (s, 3H), 2.66 (s, 3H), 1.74 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 179.0 (C), 169.2 (C), 168.5 (C), 166.8 (C), 166.4 (C), 164.1 (C), 152.4 (C), 151.1 (C), 150.4 (C), 146.8 (C), 142.1 (C), 138.8 (C), 135.4 (C), 135.2 (C), 132.7 (CH), 132.4 (C), 131.3 (CH), 127.7 (C), 127.2 (2 × CH), 127.0 (C), 122.6 (CH), 122.0 (CH), 120.3 (CH), 120.1 (CH), 117.9 (CH), 113.0 (CH), 111.3 (C), 109.5 (CH), 105.3 (CH), 99.1 (C), 85.9 (CH), 85.7 (C), 84.1 (CH), 73.2 (C), 58.4 (C), 51.8 (CH_3), 51.4 (CH_3), 29.6 (CH_3), 21.4 (CH_3), 20.7 (CH_3);[77] IR (film) 3410, 3313, 3056, 2997, 2948, 2917, 2849, 1738, 1686, 1579, 1488; TLC R_f 0.40 (4:6 EtOAc/hexanes, plate was eluted twice; compare with R_f 0.37 for **48**); HRMS (ESI) m/z calcd for $C_{41}H_{32}N_6O_{10}S_3Na$ $(M + Na)^+$ 887.1240, found 887.1238. Only minor quantities of tetrasulfide **48** suitable for mass spectrometric analysis could be obtained in pure form: HRMS (ESI) m/z calcd for $C_{41}H_{32}N_6O_{10}S_4Na$ $(M + Na)^+$ 919.0961, found 919.0952).

C13-Deoxyplectosphaeroic Acid C ((+)-45). Following a similar procedure as described for formation of **2**, intermediate (+)-**47** (5 mg, 5.8 μmol) was converted to acid (+)-**45** (2.6 mg, 55%) as a red solid: $[\alpha]^D_{24}$ +416, (c 0.06, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.85 (s, 1H), 9.72 (s, 1H), 8.90 (s, 1H), 8.01 (d, J = 8.7 Hz, 1H), 7.97 (d, J = 8.9 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.38−7.35 (comp, 2H), 7.11−7.04 (comp, 3H), 6.71 (t, J = 7.5 Hz, 1H), 6.68 (s, 1H), 6.64 (s, 1H), 6.33 (d, J = 7.0 Hz, 1H), 6.28 (d, J = 8.0 Hz, 1H), 5.53 (d, J = 6.9 Hz, 1H), 3.06 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 178.1 (C), 168.9 (C), 167.5 (C), 166.3 (C), 163.3 (C), 152.6 (C), 150.9 (C), 150.5 (C), 147.6 (C), 141.2 (C), 137.1 (C), 135.3 (C), 132.1 (C), 131.3 (CH), 129.8 (C), 129.3 (CH), 127.3 (C), 125.1 (C), 125.0 (CH), 122.6 (C), 121.1 (CH), 121.0 (CH), 119.5 (CH), 118.8 (CH), 117.3 (CH), 113.7 (C), 111.5 (CH), 108.7 (CH), 105.5 (CH), 92.5 (C), 86.8 (C), 85.7 (CH), 81.8 (CH), 71.9 (C), 58.4 (C), 27.8 (CH_3), 20.7 (CH_3); IR (film) 3363, 3243, 2954, 2916, 2849, 1681, 1584, 1481; RP-18 TLC R_f 0.36 (7:3 MeOH/H_2O); HRMS (ESI) m/z calcd for $C_{37}H_{25}N_6O_9S_3Na_2$ $(M - H + 2Na)^+$ 839.0641, found 839.0637.

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***tert*-Butyl 3-((3*R*,5a*R*,10b*R*,11*S*,11a*S*)-11-Acetoxy-3-(acetoxymethyl)-3,11a-dihydroxy-2-methyl-1,4-dioxo-1,2,3,4,5a,6,11,11a-octahydro-10b*H*-pyrazino[1′,2′:1,5]pyrrolo[2,3-*b*]indol-10b-yl)-1*H*-indole-1-carboxylate ((+)-50).** To a solution of enamide (+)-**41** (70 mg, 0.12 mmol), NMO (28 mg, 0.24 mmol), and a cosolvent mixture of acetone and H_2O (1.2 and 0.3 mL, respectively) was added OsO_4 (60 μL, 6 μmol, 2.5 wt % solution in *t*-BuOH). The reaction mixture was stirred for 2 h at rt and then poured into a mixture of EtOAc (10 mL) and 10% aqueous sodium thiosulfate. The layers were separated and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed sequentially with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4 ,and concentrated under reduced pressure. The crude residue was redissolved in EtOAc (1 mL) and SiO_2 (100 mg) was added. The resulting suspension was stirred for 1 h at rt (reaction times can vary; the reaction was monitored for consumption of the minor product, **49** by TLC: R_f 0.12, 7:3 EtOAc/hexanes), and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (3:7 → 7:3 EtOAc/hexanes) to afford the title compound (+)-**50** (58 mg, 78%) as a colorless solid: $[\alpha]^{D}_{24}$ +140, $[\alpha]^{577}_{24}$ +145, $[\alpha]^{546}_{24}$ +162, $[\alpha]^{435}_{24}$ +330 (*c* 0.48, CH_2Cl_2); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.13 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.46 (s, 1H), 7.40 (d, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.80 (t, *J* = 7.4 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.47 (s, 1H), 6.25 (s, 1H), 6.20 (s, 1H), 5.50 (s, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 4.29 (d, *J* = 11.3 Hz, 1H), 2.99 (s, 3H), 1.90 (s, 3H), 1.63 (s, 9H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 170.6 (C), 168.8 (C), 166.7 (C), 165.3 (C), 150.0 (C), 149.9 (C), 137.0 (C), 130.1 (C), 129.8 (CH), 129.5 (C),126.1 (CH), 125.6 (CH), 125.3 (CH), 123.3 (CH), 122.6 (CH), 119.9 (C), 119.2 (CH), 116.1 (CH), 110.6 (CH), 90.6 (C), 84.8 (C), 84.7 (CH), 83.8 (CH), 80.8 (CH), 65.4 (CH_2), 58.5 (C), 28.2 (CH_3), 27.6 (CH_3), 20.9 (CH_3), 20.7 (CH_3); IR (film) 3365, 2979, 2917, 2849, 1740, 1650, 1453, 1370; TLC R_f 0.27 (7:3 EtOAc/hexanes); HRMS (ESI) *m*/*z* calcd for $C_{32}H_{34}N_4O_{10}Na$ (M + Na)$^+$ 657.2173, found 657.2175.

***tert*-Butyl 3-((5a*R*,10b*R*,11*S*,11a*S*)-11-Acetoxy-3-(acetoxymethyl)-3,11a-bis((*tert*-butyldimethylsilyl)oxy)-2-methyl-1,4-dioxo-1,2,3,4,5a,6,11,11a-octahydro-10b*H*-pyrazino[1′,2′:1,5]pyrrolo[2,3-*b*]indol-10b-yl)-1*H*-indole-1-carboxylate (51).** To a solution of **50** (200 mg, 0.32 mmol), DMAP (38 mg, 0.31 mmol), and triethylamine (0.41 mL, 3.2 mmol) in DMF (3.2 mL) maintained at 0 °C was added TBSOTf (0.360 mL, 1.6 mmol) slowly. The cold bath was removed, and the reaction mixture was maintained at rt for 12 h, whereupon EtOAc (30 mL) was added followed by saturated aqueous NH_4Cl (20 mL). The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous phase was further extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed sequentially with 10% aqueous LiCl (2 × 15 mL) and brine (15 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (1:10 EtOAc/hexanes →1:3 EtOAc/hexanes) to afford the title compounds **51** as colorless solids (230 mg of the major epimer **51-major**, 30 mg of the minor epimer **51-minor**; 96% overall yield, 8:1 ratio of C3-epimers). Data for the major epimer, (+)-**51-major**: $[\alpha]^{D}_{24}$ +126.8, $[\alpha]^{577}_{24}$ +131, $[\alpha]^{546}_{24}$ +152, $[\alpha]^{435}_{24}$ +293, $[\alpha]^{405}_{24}$ +396 (*c* 0.34, CH_2Cl_2); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.13 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.41 (s, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.51 (d, *J* = 2.2 Hz, 1H), 6.48 (br s, 1H), 6.25 (s, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 4.33 (d, *J* = 11.5 Hz, 1H), 3.14 (s, 3H), 2.11 (s, 3H), 1.62 (s, 9H), 1.41 (s, 3H), 1.00 (s, 9H), 0.44 (s, 9H), 0.40 (s, 3H), 0.28 (s, 3H), 0.20 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 170.3 (C), 168.7 (C), 165.5 (C), 163.5 (C), 150.0 (2 × C), 137.0 (C), 130.5 (CH), 129.6 (C), 129.4 (C), 126.1 (CH), 125.7 (CH), 125.3 (CH), 123.1 (CH), 122.5 (CH), 120.8 (C), 119.9 (CH), 116.2 (CH), 111.2 (CH), 92.5 (C), 86.7 (C), 84.9 (C), 83.6 (CH), 80.9 (CH), 69.0 (CH_2), 59.0 (C), 30.1 (CH_3), 28.2 (CH_3), 26.7 (CH_3), 26.2 (CH_3), 20.9 (CH_3), 20.7 (CH_3), 19.9 (C), 18.6 (C), −2.4 (CH_3), −2.8 (CH_3), −3.7 (CH_3), −4.2 (CH_3); IR (film) 3380, 2954, 2929, 2856, 1756, 1739, 1694, 1678, 1454, 1371; TLC R_f 0.61 (3:7 EtOAc/hexanes); HRMS (ESI) *m*/*z* calcd for $C_{44}H_{62}N_4O_{10}Si_2Na$ (M + Na)$^+$ 885.3902, found 885.3907. Data for the minor epimer, (+)-**51-minor**: $[\alpha]^{D}_{24}$ +57.7, $[\alpha]^{577}_{24}$ +58.3, $[\alpha]^{546}_{24}$ +69.1, $[\alpha]^{435}_{24}$ +140.0, $[\alpha]^{405}_{24}$ +190 (*c* 0.34, CH_2Cl_2); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.14 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 7.4 Hz, 1H), 7.40 (s, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.86 (t, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.55 (br s, 1H), 6.53 (d, *J* = 3.2 Hz, 1H), 6.16 (s, 1H), 4.72 (d, *J* = 10.9 Hz, 1H), 4.50 (d, *J* = 10.9 Hz, 1H), 3.02 (s, 3H), 2.15 (s, 3H), 1.62 (s, 9H), 1.38 (s, 3H), 0.94 (s, 9H), 0.48 (s, 9H), 0.43 (s, 3H), 0.21 (s, 3H), 0.14 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 170.2 (C), 168.8 (C), 164.2 (C), 160.1 (C), 150.2 (C), 149.9 (C), 137.0 (C), 130.3 (CH), 129.9 (C), 129.6 (C), 127.0 (CH), 125.8 (CH), 125.3 (CH), 123.4 (CH), 122.3 (CH), 120.7 (C), 119.4 (CH), 116.2 (CH), 110.9 (CH), 91.8 (C), 86.8 (C), 84.9 (C, CH), 81.5 (CH), 65.7 (CH_2), 59.1 (C), 28.2 (CH_3), 28.1 (CH_3), 26.40 (CH_3), 26.36 (CH_3), 21.1 (CH_3), 20.7 (CH_3), 19.2 (C), 18.7 (C), −2.4 (CH_3), −3.1 (CH_3), −3.6 (CH_3), −3.7 (CH_3); IR (film) 3380, 2954, 2928, 2856, 1754, 1740, 1681, 1454, 1372; TLC R_f 0.47 (3:7 EtOAc/hexanes); HRMS (ESI) *m*/*z* calcd for $C_{44}H_{62}N_4O_{10}Si_2Na$ (M + Na)$^+$ 885.3902, found 885.3905.

Cross-Coupled Product ((+)-52-major). Following a similar procedure as described for formation of **42a**, intermediate (+)-**51-major** (3 runs in parallel: 50 mg, 58 μmol per run) and phenoxazinone iodide **33** (114 mg, 170 μmol per run) were converted to (+)-**52-major** (168 mg combined, 72%) as an orange solid: $[\alpha]^{D}_{24}$ +26.2 (*c* 0.052, MeOH); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.19 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 7.4 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.66−7.62 (comp, 3H), 7.50 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.3 Hz, 1H), 6.99 (s, 1H), 6.49 (s, 1H), 6.31 (s, 1H), 6.30 (d, 1H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.34 (d, *J* = 11.3 Hz, 1H), 3.83 (s, 3H), 3.12 (s, 3H), 3.09 (s, 3H), 2.15 (s, 3H), 1.65 (s, 9H), 1.38 (s, 18H), 1.35 (s, 3H), 0.93 (s, 3H), 0.55 (s, 3H), 0.25 (s, 3H), 0.21 (s, 3H), 0.18 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 180.6 (C), 170.2 (C), 168.4 (C), 165.60 (C), 165.55 (C), 163.6 (C), 163.5 (C), 150.0 (C), 149.7 (C), 149.3 (C), 147.9 (C), 144.1 (C), 139.0 (C), 137.2 (C), 137.0 (C), 136.2 (CH), 135.8 (C), 134.8 (C), 131.9 (C), 130.7 (C), 129.6 (CH), 129.4 (C), 127.2 (CH), 126.0 (CH), 125.4 (CH), 123.1 (CH), 122.7 (CH), 120.9 (CH) 119.8 (C), 118.9 (CH), 116.3 (CH), 109.9 (CH), 106.9 (CH), 93.9 (C), 86.5 (CH), 86.2 (C), 85.1 (C), 83.9 (CH), 83.7 (C), 65.4 (CH_2), 58.1 (C), 53.1 (CH_3), 52.1 (CH_3), 28.2 (CH_3), 27.9 (CH_3), 26.6 (CH_3), 26.4 (CH_3), 21.1 (CH_3), 20.5 (CH_3), 19.9 (C), 18.8 (C), −2.4 (CH_3), −2.8 (CH_3), −3.7 (CH_3), −3.9 (CH_3);[78] IR (film) 2956, 2929, 2856, 1807, 1746, 1712, 1679, 1461, 1371; TLC R_f 0.45 (3:7 EtOAc/hexanes); HRMS (ESI) *m*/*z* calcd for $C_{70}H_{88}N_6O_{20}Si_2Na$ (M + Na)$^+$ 1411.5490, found 1411.5460.

Cross-Coupled Product (52-minor). Following a similar procedure as described for formation of **42a**, intermediate (+)-**51-minor** (30 mg, 35 μmol) and phenoxazinone iodide **33** (68 mg, 100 μmol per run) were converted to **52-minor** (36 mg, 74%) as an orange solid: ^{1}H NMR (500 MHz, acetone-d_6) δ 8.20 (d, *J* = 8.2 Hz, 1H), 7.70−7.64 (comp, 3H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.43 (s, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.89 (s, 1H), 6.48 (s, 1H), 6.29 (d, *J* = 7.9 Hz, 1H), 6.21 (s, 1H), 4.64 (d, *J* = 10.8 Hz, 1H), 4.55 (d, *J* = 10.8 Hz, 1H), 3.78 (s, 3H), 3.03 (s, 3H), 2.78 (s, 3H), 2.19 (s, 3H), 1.64 (s, 9H), 1.36 (s, 18H), 1.35 (s, 3H), 0.96 (s, 3H), 0.57 (s, 3H), 0.28 (s, 3H), 0.15 (s, 3H), 0.15 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 180.6 (C), 170.1 (C), 168.6 (C), 165.3 (C), 164.32 (C), 164.25 (C), 163.6 (C), 150.0 (C), 149.7 (C), 149.5 (C), 147.9 (C), 143.9 (C), 139.0 (C), 137.3 (C), 136.4 (C), 135.7 (CH), 134.8 (C), 133.5 (C), 132.1 (C), 132.0 (C), 130.5 (CH), 129.8 (C), 129.7 (C), 128.1 (CH), 126.1 (CH), 125.4 (CH), 123.5 (CH), 122.3 (CH), 120.6 (CH) 119.6 (C), 119.1 (CH), 116.3 (CH), 109.3 (CH), 106.8 (CH), 92.6 (C), 87.31 (C), 87.29 (CH), 85.12 (C), 85.05 (CH), 83.7 (C), 65.4 (CH_2), 58.3 (C), 53.1 (CH_3), 51.6 (CH_3), 28.2 (CH_3), 27.9 (CH_3), 26.6 (CH_3), 26.3 (CH_3), 21.2 (CH_3), 20.6 (CH_3), 19.3 (C),

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18.8 (C), −2.0 (CH_3), −2.2 (CH_3), −3.3 (CH_3), −3.6 (CH_3); IR (film) 2952, 2929, 2856, 1806, 1747, 1712; TLC R_f 0.20 (3:7 EtOAc/hexanes, copolar with iodide **32**); HRMS (ESI) m/z calcd for $C_{70}H_{88}N_6O_{20}Si_2Na$ $(M + Na)^+$ 1411.5490, found 1411.5490.

C3,C11a-Dihydroxydioxopiperazine ((−)-53-major). Tetra-*n*-butylammonium fluoride (TBAF) (85 μL, 85 μmol, 1.0 M in THF) was added to a solution of intermediate (+)-**52-major** (56 mg, 40 μmol), acetic acid (AcOH) (7.0 μL, 12 μmol), and THF (0.40 mL) at 0 °C. The reaction mixture was maintained at 0 °C for 30 min then poured into a mixture of EtOAc (10 mL) and saturated aqueous NH_4Cl (5 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (2 × 5 mL). The combined organic layers were washed successively with saturated aqueous NH_4Cl (2 × 5 mL) and brine (5 mL), dried over Na_2SO_4, and then concentrated under reduced pressure. The crude product was purified by silica gel chromatography (7:3 EtOAc/hexanes) to afford the title compound **(−)-53-major** as a red solid (45 mg, 96%): $[\alpha]^D_{24}$ −94.4 (*c* 0.050, CH_2Cl_2); ^1H NMR (500 MHz, acetone-d_6) δ 8.19 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.64−7.60 (comp, 2H), 7.57 (s, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.00 (s, 1H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.49 (s, 1H), 6.32 (s, 1H), 6.29 (d, *J* = 7.8 Hz, 1H), 6.17 (s, 1H), 6.01 (s, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 3.87 (s, 3H), 3.86 (d, 1H), 3.24 (s, 3H), 2.94 (s, 3H), 2.08 (s, 3H), 1.67 (s, 9H), 1.40 (s, 3H), 1.39 (s, 18H); ^{13}C NMR (125 MHz, acetone-d_6) δ 180.6 (C), 170.3 (C), 168.5 (C), 166.8 (C), 166.0 (C), 165.3 (C), 163.8 (C), 150.2 (C), 150.1 (C), 150.0 (C), 149.7 (C), 147.7 (C), 144.0 (C), 138.9 (C), 137.4 (C), 137.2 (C), 136.4 (CH), 136.1 (C), 134.8 (C), 131.6 (C), 130.9 (C), 130.0 (CH), 129.3 (C), 126.7 (CH), 125.9 (CH), 125.4 (CH), 123.4 (CH), 122.7 (CH), 120.3 (CH) 119.1 (C), 119.0 (CH), 116.2 (CH), 109.1 (CH), 106.8 (CH), 91.6 (C), 86.1 (CH), 85.1 (C), 84.6 (C), 84.3 (CH), 83.7 (C), 64.7 (CH_2), 57.7 (C), 53.1 (CH_3), 52.3 (CH_3), 28.2 (CH_3), 27.9 (CH_3), 27.5 (CH_3), 21.0 (CH_3), 20.5 (CH_3); IR (film) 3360, 2981, 2952, 2933, 2918, 2849, 1806, 1747, 1644, 1371; TLC R_f 0.17 (7:3 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{58}H_{60}N_6O_{20}Na$ $(M + Na)^+$ 1183.3760, found 1183.3765.

Acetylated Intermediate (54). Tetra-*n*-butylammonium fluoride (TBAF) (310 μL, 0.31 mmol, 1.0 M in THF) was added to a solution of intermediate epimers **52** (227 mg, 5:1 ratio of epimers, 0.16 mmol), acetic acid (AcOH) (25 μL, 0.40 mmol) and THF (0.40 mL) at 0 °C. The reaction mixture was maintained at 0 °C for 30 min then poured into a mixture of EtOAc (10 mL) and saturated aqueous NH_4Cl (5 mL). The layers were separated, and the aqueous layer was further extracted with EtOAc (2 × 5 mL). The combined organic layers were washed successively with saturated aqueous NH_4Cl (2 × 5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The diol intermediates **53** were of sufficient purity to be taken forward without further purification. To a solution of this intermediate in CH_2Cl_2 (7.3 mL) was added DMAP (142 mg, 1.2 mmol) and acetic anhydride (50 μL, 0.52 mmol). The resulting mixture was maintained for 12 h at rt, then poured into a mixture of EtOAc (30 mL) and saturated aqueous NH_4Cl (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed successively with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, then concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel (1:5 EtOAc/hexanes →6:4 EtOAc/hexanes) to afford the title compounds **54** (175 mg, 86% over two steps, 5:1 ratio of epimers) as a deep red solid: Analytical samples for both epimers were obtained. Data for **(−)-54-major**: $[\alpha]^D_{24}$ −45.8, $[\alpha]^{577}_{24}$ −48.6 (*c* 0.058, CH_2Cl_2); ^1H NMR (500 MHz, acetone-d_6) δ 8.17 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 7.3 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.48 (s, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.28−7.22 (comp, 2H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.98 (s, 1H), 6.49 (s, 1H), 6.43 (s, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 4.86 (d, *J* = 11.9 Hz, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 3.81 (s, 3H), 3.00 (s, 3H), 2.80 (s, 3H), 2.23 (s, 3H), 1.65 (s, 9H), 1.50 (s, 3H), 1.47 (s, 3H), 1.39 (s, 3H), 1.37 (s, 18H); ^{13}C NMR (125 MHz, acetone-d_6) δ 180.6 (C), 170.2 (C), 169.5 (C), 169.4 (C), 168.8 (C), 165.5 (C), 163.7 (C), 163.3 (C), 160.6 (C), 150.1 (C), 150.0 (C), 149.7 (C), 148.7 (C), 148.0 (C), 144.1 (C), 139.0 (C), 137.2 (2 × C), 135.4 (CH), 134.83 (C), 134.77 (C), 131.8 (C), 130.8 (C), 130.3 (CH), 129.4 (C), 128.0 (CH), 126.3 (CH), 125.5 (CH), 124.0 (CH), 123.4 (CH), 120.8 (CH) 119.3 (CH), 117.7 (C), 115.9 (CH), 109.1 (CH), 106.9 (CH), 92.8 (C), 87.6 (CH), 86.7 (C), 85.2 (C), 83.7 (C), 83.0 (CH), 64.6 (CH_2), 57.7 (C), 53.1 (CH_3), 51.8 (CH_3), 29.4 (CH_3), 28.2 (CH_3), 27.9 (CH_3), 20.9 (CH_3), 20.7 (CH_3), 20.4 (CH_3), 20.3 (CH_3); IR (film) 2979, 2917, 2849, 1806, 1747, 1694, 1644, 1369; TLC R_f 0.18 (1:1 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{62}H_{64}N_6O_{22}Na$ $(M + Na)^+$ 1267.3971, found 1267.3987. **Data for (+)-54-minor**: $[\alpha]^D_{24}$ +50.5 (*c* 0.043, CH_2Cl_2); ^1H NMR (500 MHz, acetone-d_6) δ 8.23 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 7.4 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.55 (s, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.98 (s, 1H), 6.59 (s, 1H), 6.46 (s, 1H), 6.39 (d, *J* = 7.9 Hz, 1H), 4.75 (d, *J* = 11.4 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 3.80 (s, 3H), 3.05 (s, 3H), 2.87 (s, 3H), 2.20 (s, 3H), 2.12 (s, 3H), 1.65 (s, 9H), 1.47 (s, 3H), 1.46 (s, 3H), 1.37 (s, 18H); ^{13}C NMR (125 MHz, acetone-d_6) δ 180.6 (C), 170.2 (C), 168.7 (C), 168.5 (C), 167.4 (C), 165.6 (C), 163.7 (C), 162.1 (C), 162.0 (C), 150.1 (C), 150.0 (C), 149.7 (C), 149.2 (C), 147.7 (C), 144.0 (C), 138.9 (C), 137.5 (CH), 137.3 (C), 136.6 (C), 135.1 (C), 134.8 (C), 131.6 (C), 130.3 (CH), 130.0 (C), 129.4 (C), 128.0 (CH), 126.3 (CH), 125.6 (CH), 123.6 (CH), 122.1 (CH), 120.5 (CH) 118.9 (CH), 117.9 (C), 116.5 (CH), 108.8 (CH), 106.8 (CH), 91.7 (C), 87.20 (CH), 87.17 (C), 85.3 (C), 83.7 (C), 83.2 (CH), 64.2 (CH_2), 57.8 (C), 53.1 (CH_3), 51.8 (CH_3), 29.2 (CH_3), 28.2 (CH_3), 27.9 (CH_3), 21.1 (CH_3), 21.0 (CH_3), 20.6 (CH_3), 20.6 (CH_3); IR (film) 2979, 2917, 2848, 1806, 1747, 1703, 1644, 1370; TLC R_f 0.11 (1:1 EtOAc/hexanes); HRMS (ESI) m/z calcd for $C_{62}H_{64}N_6O_{22}Na$ $(M + Na)^+$ 1267.3971, found 1267.3956.

Dimethyl 8-((4*S*,6a*R*,11b*R*,12*S*,12a*S*)-12-Acetoxy-4-(acetoxymethyl)-11b-(1*H*-indol-3-yl)-14-methyl-5,13-dioxo-4,5,11b,12-tetrahydro-4,12a-(epiminomethano)[1,2,3,5]trithiazepino[5′,4′:1,5]pyrrolo[2,3-*b*]indol-7(6a*H*)-yl)-2-amino-3-oxo-3*H*-phenoxazine-1,9-dicarboxylate ((+)-56). *Method A.* Hydrogen sulfide (bp −60 °C, ca. 0.20 mL) was condensed at −78 °C in a thick-walled, glass pressure tube fitted with a rubber septum. A solution of **54** (3 runs in series: 30 mg, 50 mg, 60 mg; 5:1 mixture of epimers) in CH_2Cl_2 (0.60 mL) and $BF_3{\cdot}OEt_2$ (30 μL, 0.24 mmol) were injected sequentially into the reaction vessel maintained at −78 °C. The rubber septum was replaced by a Teflon screw cap, which was used to seal the vessel. The cold bath was removed and the reaction mixture was allowed to warm to rt *behind a blast shield*. After 1 h, the reaction mixture was cooled to −78 °C, the Teflon cap was replaced by the rubber septum, which was equipped with a needle vented to base (KOH/isopropanol) and bleach traps (attached in series). The cooling bath was removed and the resulting brown suspension was allowed to warm up to rt. Upon evolution of the majority of hydrogen sulfide gas, an argon-filled balloon was attached (by needle) to fully purge the reaction mixture, which was subsequently poured into a mixture of EtOAc (2 mL) and saturated aqueous NH_4Cl (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 mL). The combined organic layers were washed with brine (4 mL), dried over Na_2SO_4, and concentrated under reduced pressure (residual volatile components were not rigorously removed). The crude residue was immediately dissolved in acetone (1 mL) and 400 wt % of SiO_2 (120, 150, 180 mg, respectively) was added. The resulting heterogeneous mixture was stirred vigorously for 12−48 h (reaction times were found to be variable and required monitoring for completion; see Table S4 (Supporting Information) for more details) and then filtered, and the filtrate was concentrated under reduced pressure. The residue from all three reactions was purified by silica gel chromatography (3:7 EtOAc/hexanes) to afford a mixture of ETP products, disulfide **55**, trisulfide **56** and tetrasulfide **57** (50 mg, 48%, 1:6:2 ratio of products, determined by ^1H NMR) as an orange solid.

Method B. The procedure described above was followed for processing **54** (10 mg, 8.0 μmol), except upon quenching the sulfidation step, the crude residue was dissolved in EtOAc (2 mL) and concentrated under reduced pressure three additional cycles prior to

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the addition of EtOAc (1 mL) and SiO_2 (40 mg). Upon purification, an inseparable mixture of ETP products, disulfide **55** and trisulfide **56** (7 mg, 7:1 ratio of products, determined by ^{1}H NMR), as an orange solid was obtained. To a solution of this mixture of ETPs **55** and **56** (7 mg, 7.8 μmol) in acetone (1 mL) was added Na_2S (0.60 mg, 7.6 μmol). The resulting heterogeneous mixture was stirred for 0.5 h at rt and then poured into a mixture of EtOAc (2 mL) and saturated aqueous NH_4Cl (2 mL). The combined organic layers were washed with brine (4 mL), dried over Na_2SO_4, and then concentrated under reduced pressure to afford a mixture of ETP products, trisulfide **56** and tetrasulfide **57** (2.5:1 ratio of products, determined by ^{1}H NMR).[79] The mixture was dissolved in CH_2Cl_2 (0.5 mL) then Ph_3P (40 μL, 0.05 M solution in CH_2Cl_2) was added. After 0.5 h, the mixture was eluted through a short column of silica gel (1:2 EtOAc/hexanes, then 2:1 EtOAc/hexanes) to afford the title compound (+)-**56** (5.0 mg, 67%) as a red solid: $[\alpha]^{D}_{24}$ +47.3, $[\alpha]^{577}_{24}$ +49.5, $[\alpha]^{546}_{24}$ +53.9 (*c* 0.06, CH_2Cl_2); ^{1}H NMR (500 MHz, acetone-d_6) δ 10.41 (br s, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 7.70−7.67 (comp, 2H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 2.5 Hz, 1H), 7.00 (d, *J* = 7.4 Hz, 1H), 6.94 (s, 1H), 6.46 (s, 1H), 6.43 (d, *J* = 8.0 Hz, 1H), 6.36 (s, 1H), 4.65 (d, *J* = 12.3 Hz, 1H), 4.36 (d, *J* = 12.3 Hz, 1H), 3.73 (s, 3H), 3.27 (s, 3H), 2.68 (s, 3H), 1.96 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 179.0 (C), 169.9 (C), 169.2 (C), 168.5 (C), 166.7 (C), 166.4 (C), 162.1 (C), 152.3 (C), 151.1 (C), 150.4 (C), 146.8 (C), 142.1 (C), 138.8 (C), 135.3 (C), 135.0 (C), 132.8 (CH), 132.4 (C), 131.4 (CH), 127.5 (C), 127.2 (CH), 127.04 (CH), 126.95 (C), 122.7 (CH), 121.8 (CH), 120.4 (CH), 120.2 (CH), 118.0 (CH), 113.0 (CH), 111.3 (C), 109.4 (CH), 105.3 (CH), 99.1 (C), 86.0 (CH), 85.1 (C), 84.0 (CH), 74.9 (C), 61.6 (CH_2), 58.6 (C), 51.8 (CH_3), 51.4 (CH_3), 28.5 (CH_3), 20.6 (CH_3), 20.6 (CH_3); IR (film) 3394, 3322, 2917, 2849, 1746, 1694, 1576, 1486; TLC R_f 0.25 (4:6 EtOAc/hexanes); HRMS (ESI) *m*/*z* calcd for $C_{43}H_{34}N_6O_{12}S_3Na$ (M + Na)$^+$ 945.1295, found 945.1281. Data for epidisulfidedioxopiperazine **55**: ^{1}H NMR (500 MHz, acetone-d_6) δ 10.40 (br s, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.71 (d, *J* = 7.4 Hz, 1H), 7.64 (m, 1H), 7.69−7.62 (comp, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.21−7.16 (comp, 2H), 7.08−7.04 (comp, 2H), 7.02 (s, 1H), 6.44 (d, 1H), 6.43 (s, 2H), 6.39 (s, 1H), 4.82 (d, *J* = 12.7 Hz, 1H), 4.77 (d, *J* = 12.7 Hz, 1H), 3.71 (s, 3H), 3.10 (s, 3H), 2.60 (br s, 3H), 2.11 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 178.9 (C), 170.1 (C), 169.1 (C), 169.0 (C), 166.2 (C), 163.8 (C), 161.1 (C), 151.0 (C), 150.4 (C), 149.3 (C), 146.7 (C), 141.7 (C), 138.8 (C), 138.7 (C), 132.8 (CH), 132.3 (C), 131.4 (C), 130.6 (CH), 127.6 (CH), 127.42 (C), 127.38 (C), 126.0 (CH), 122.7 (CH), 122.3 (CH), 120.7 (CH), 120.2 (CH), 117.6 (CH), 113.0 (CH), 111.5 (C), 109.4 (CH), 105.2 (CH), 99.0 (C), 86.9 (CH), 80.3 (CH), 77.3 (C), 77.1 (C), 60.9 (CH_2), 60.8 (C), 51.8 (CH_3), 51.5 (CH_3), 28.5 (CH_3), 20.6 (CH_3), 20.5 (CH_3); TLC R_f 0.25 (4:6 EtOAc/hexanes); HRMS (ESI) *m*/*z* calcd for $C_{43}H_{34}N_6O_{12}S_2Na$ (M + Na)$^+$ 913.1574, found 913.1587.

Plectosphaeroic Acid C Dimethyl Ester ((+)-58). To a solution of ETP (+)-**56** (11 mg, 11 μmol) in MeOH (0.30 mL) were added lanthanum(III) trifluoromethanesulfonate (66 mg, 110 μmol) and DMAP (1.6 mg, 12 μmol). The reaction mixture was maintained at 45 °C. After 5 h (the consumption of the starting material was monitored by TLC), the reaction mixture was allowed to cool to rt and then poured into a mixture of EtOAc (10 mL) and saturated aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by preparatory thin layer chromatography (7:3 EtOAc/hexanes) to afford intermediate (+)-**58** (7.0 mg, 76%) as a red solid:[80] $[\alpha]^{D}_{24}$ +181.4, $[\alpha]^{577}_{24}$ +190.0, $[\alpha]^{546}_{24}$ +203.6 (*c* 0.07, CH_2Cl_2); ^{1}H NMR (500 MHz, acetone-d_6) δ 10.25 (br s, 1H), 8.02 (d, *J* = 8.7 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 7.3 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.32 (s, 1H), 7.18−7.11 (comp, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.3 Hz, 1H), 6.78 (s, 1H), 6.47 (s, 1H), 6.45 (d, *J* = 7.7 Hz, 1H), 5.52 (d, *J* = 4.8 Hz, 1H), 5.17 (d, *J* = 4.8 Hz, 1H), 4.25 (app t, *J* = 7.0 Hz, 1H), 3.99 (dd, *J* = 12.5, 6.4 Hz, 1H), 3.86 (s, 3H), 3.82 (dd, *J* = 12.5, 7.6 Hz, 1H), 3.37 (s, 3H), 3.24 (s, 3H), 1.96 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 179.0 (C), 169.2 (C), 168.4 (C), 167.5 (C), 164.1 (C), 151.9 (C), 151.1 (C), 150.3 (C), 146.7 (C), 141.9 (C), 138.6 (C), 136.3 (C), 135.0 (C), 132.5 (CH), 132.4 (C), 130.6 (CH), 130.2 (C), 127.4 (C), 126.7 (CH), 125.0 (CH), 122.5 (CH), 122.4 (CH), 120.5 (CH), 120.0 (CH), 117.9 (CH), 114.3 (C), 112.5 (CH), 109.9 (CH), 105.3 (CH), 99.2 (C), 87.6 (C), 87.1 (CH), 84.4 (CH), 76.6 (C), 61.9 (CH_2), 59.5 (C), 52.4 (CH_3), 51.9 (CH_3), 27.8 (CH_3); IR (film) 3390, 3323, 2951, 2918, 2849, 1738, 1681, 1582; TLC R_f 0.41 (7:3 EtOAc/hexanes, plate was eluted twice); HRMS (ESI) *m*/*z* calcd for $C_{39}H_{30}N_6O_{10}S_3Na$ (M + Na)$^+$ 861.1083, found 861.1087.

(+)-Plectosphaeroic Acid C (3). To a solution of ETP (+)-**58** (5.0 mg, 6.0 μmol) in PhMe (0.10 mL) was added LiI (3 mg, 22 μmol). The reaction mixture was stirred for 1 h at 90 °C (formation of product was observed by RP-18 TLC), a second portion of LiI (3 mg, 22 μmol) was added, and the reaction mixture was heated for 1 h at 90 °C. This sequence was repeated two more times (total: 12 mg of LiI, 4 h at 90 °C) before the reaction was allowed to cool to rt and poured into a mixture of EtOAc (5 mL) and 0.1% aqueous TFA (2 mL). The layers were separated, the aqueous layers were extracted with EtOAc (4 mL), and then the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. This reaction was conducted in series on 1, 2, 5, 5 mg scales (processed identically), and then the crude residue from all four reactions was purified by reverse-phase HPLC (step-gradient eluting 20%, 40%, 50%, 60%, 70%, 95% MeCN/H_2O + 0.1% TFA) to afford plectosphaeroic acid C (**3**) (9 mg, 64%, eluting at 60% MeCN/H_2O + 0.1% TFA) as a red solid: $[\alpha]^{D}_{24}$ +494 (*c* 0.06, MeOH), compare with reported value $[\alpha]^{D}_{24}$ +136 (*c* 0.17, MeOH) of the natural sample; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.86 (br s, 1H), 9.72 (br s, 1H), 8.92 (br s, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.37 (m, 1H), 7.36 (m, 1H), 7.10 (t, *J* = 7.0 Hz, 1H), 7.06 (comp, 2H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.70 (s, 1H), 6.68 (s, 1H), 6.45 (br s, 1H), 6.32 (d, *J* = 7.8 Hz, 1H), 5.54 (s, 1H), 5.48 (br s, 1H), 3.78 (m, 1H), 3.61 (m, 1H), 3.11 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 178.1 (C), 168.9 (C), 167.5 (C), 166.8 (C), 162.1 (C), 152.7 (C), 150.8 (C), 150.3 (C), 141.1 (C), 137.1 (C), 135.5 (C), 132.0 (C), 131.2 (CH), 129.8 (C), 129.3 (CH), 127.4 (C), 125.1 (C, CH), 122.6 (CH), 121.1 (2 × CH), 119.5 (CH), 118.8 (CH), 117.3 (CH), 113.8 (C), 111.5 (CH), 108.7 (CH), 105.6 (CH), 92.5 (C), 86.3 (C), 85.7 (C), 81.7 (CH), 75.6 (C), 59.5 (CH_2), 58.5 (C), 27.3 (CH_3); RP-18 TLC R_f 0.50 (1:1 MeCN/H_2O); HRMS (ESI) *m*/*z* calcd for $C_{37}H_{25}N_6O_{10}S_3$ (M − H)$^-$ 809.0794, found 809.0779.

Cinnabarinic Acid (4).[11,32b,c] This procedure is a modification of a procedure reported by Manthey and co-workers.[32b] To a solution of 3-hydroxyanthranilic acid (**S10**) (350 mg, 2.3 mmol) and EtOH (200 mL) was added 1,4-benzoquhinone (420 mg, 3.3 mmol, freshly recrystallized). The reaction mixture was maintained at 40 °C for 12 h and then cooled to rt, and the desired product (250 mg, 72%) was filtered away from the mother liquor as an orange/red solid in sufficient purity. The spectroscopic data obtained for the product matched previously reported data:[32c] ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.72 (br s 1H), 8.78 (br s, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 6.60 (s, 1H).

Dimethyl 2-Amino-9-iodophenoxazin-3-one 1,10-dicarboxylate (60).[81] To a solution of 3-hydroxyanthranilic acid methyl ester (**S11**)[82] (280 mg, 1.7 mmol) and EtOH (56 mL) was added 1,4-benzoquinone (310 mg, 2.8 mmol, freshly recrystallized). The reaction mixture was maintained at 40 °C for 24 h and then cooled to rt and concentrated in vacuo. The crude residue was suspended in ethyl acetate/hexanes (1:1, 60 mL), and the desired product (160 mg, 56%) was filtered away from the mother liquor as an orange/red solid in sufficient purity. The spectroscopic data obtained for the product matched previously reported data:[11] ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.8 (br s, 2H), 7.65 (d, *J* = 6.1 Hz, 1H), 7.59−7.54 (m, 2H), 6.49 (s, 1H), 3.89 (s, 3H), 3.83 (s, 3H).

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■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of new compounds, CD spectra for **2** and **3**, CIF for **40a** and details of the X-ray analysis, complete author listing for ref 3b, and additional experimental and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(26) (a) Ruan, J. W.; Huang, Z. S.; Huang, J. F.; Du, C. J.; Huang, S. L.; Shi, Z.; Fu, L. W.; Gu, C. Q. *Chin. Chem. Lett.* **2006**, *17*, 1141−1144. (b) Giurg, M.; Piekielska, K.; Gębala, M.; Ditkowski, B.; Wolański, M.; Peczyńska−Czoch, W.; Mlochowski, J. *Synth. Commun.* **2007**, *37*, 1779−1789 and references therein..

(27) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067.

(28) As judged by TLC analysis.

(29) 3-Hydroxy-6-iodoanthranilic acid (**29**) was prepared in a fashion analogous to the reported three-step synthesis of 6-bromo-3-hydroxyanthranilic acid; see: Fairfax, D. K.; Yang, Z. Benzoxazole Carboxamides for Treating CINV and IBS-D. US Patent 2006/183769 A1, 08/17/2006. See the Experimental Section for details.

(30) These reactions presumably proceed via the intermediacy of an iminoquinone prior to cyclocondensation with a second equivalent of the aminophenol.

(31) The benzoquinone-mediated dimerization of carboxylic acid **29** proceeded in 66% yield; see the Experimental Section for details.

(32) (a) Osman, A.; Bassioumi, I. *J. Am. Chem. Soc.* **1960**, *82*, 1607−1609. (b) Manthey, M. K.; Pyne, S. G; Truscott, R. J. W. *Biochem. Biophys. Acta* **1990**, *1034*, 207−210. (c) Christen, S.; Southwell-Keely, P. T.; Stocker, R. *Biochemistry* **1992**, *31*, 8090−8097.

(33) The bromide analogues of **32** and **33** were prepared in an analogous fashion. See the Supporting Information of ref 16 for details.

(34) For example, altering the ratio of coupling partners (a range of molar ratios from 2:1 to 1:6 **25**/**32** were examined) or adding stoichiometric quantities of copper and ligands (e.g., CuI and dppp or bpy) were unsuccessful. Switching to amine bases (e.g., Et_3N, pyridine) and polar aprotic solvents (e.g., THF, dioxane, DMA, DMF or NMP) commonly used in copper-promoted C−N cross-couplings were either ineffective or led to decomposition of **25**. In all reactions, iodide **32** was recovered largely intact with little to no hydrodehalogenation or homocoupling being detected.

(35) For an early example of the use of CuTC in cross-couplings, see: (a) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749. For CuTC in a related C−N cross-coupling, see: (b) Li, G.; Padwa, A. *Org. Lett.* **2011**, *13*, 3767−3769.

(36) It was found that the source of copper(I) thiophene-2-carboxylate (CAS No. 68986-76-5) was important. We used reagent purchased from Sigma-Aldrich Co.

(37) (a) Kubo, T.; Katoh, C.; Yamada, K.; Okano, K.; Tokuyama, H.; Fukuyama, T. *Tetrahedron* **2008**, *64*, 11230−11236. (b) Komori, T.; Satoh, N.; Yokoshima, S.; Fukuyama, T. *Syn Lett.* **2011**, *13*, 1859−1862.

(38) A parallel study investigating palladium(0) for this C−N cross-coupling was also conducted. Although hydrodehalogenation and homocoupling of **32** was observed (using 0.1−1.0 equiv of Pd_2dba_3 and RuPhos, Cs_2CO_3/K_2CO_3, toluene/dioxane), no formation of **34** was detected in any of these reactions.

(39) One Boc-protecting group of **33** was cleaved under these conditions, and a significant amount of the mono(*tert*-butoxycarbonyl) congener **32** was detected.

(40) The corresponding bromide of **33** was much less efficient, giving rise to **35** in 8% yield under the conditions of Table 2, entry 8.

(41) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263−4265.

(42) At present, the origin of this unexpected reversal in facial selectivity is not understood.

(43) (a) α-Epimer **40a**: CCDC 922842. (b) The β-epimer, **40b**, provided single crystals allowing its relative and absolute configuration to be confirmed by X-ray analysis; however, the data set did not refine to a high level.

(44) Use of TMSOTf also proved effective under similar conditions, although optimal conditions were not identified, whereas $Sc(OTf)_3$, $BF_3{\cdot}OEt_2$, TMSI, TFA, or formic acid led to extensive decomposition of **39a** or formation of multiple byproducts.

(45) For previous use of CuOAc in C−N cross-couplings, see ref 37 and: Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2007**, 2147−2151.

(46) See the Supporting Information for details.

(47) Signals attributable to the undesired C3 α-methylthio epimer **44a** were not apparent in the ^{1}H NMR of the crude mixture of this two-step sequence.

(48) The lowest energy *cis*-dithiol epimer of closely related model compounds (see the Supporting Information) is calculated (B3-LYP/def2-TZVP) to be 2.5 (or 2.0; when zero-point energies are incorporated) kcal/mol more stable than its C3 epimer, whereas this difference is 0.9 (or 0.8; when zero-point energies are incorporated) kcal/mol in the bis(methylthio)ether series; however, this difference is likely magnified by an intramolecular HS···HS hydrogen bond in these gas-phase calculations.

(49) For experimental evidence of the equilibration of dioxopiperazines by reversible ring-opening of hemiaminal intermediates, see ref 2c. For similar equilibration of thiohemiaminal intermediates, see: (a) Herscheid, J. D. M.; Tijhuis, M. W.; Noordik, J. H.; Ottenheijm, H. C. J. *J. Am. Chem. Soc.* **1979**, *101*, 1159−1162. (b) Fukuyama, T.; Nakatsuka, S.-I.; Kishi, Y. *Tetrahedron* **1981**, *37*, 2045−2078.

(50) For the lability of aminophenoxazinones, see: Bolognese, A.; Piscitelli, C.; Scherillo, G. *J. Org. Chem.* **1983**, *48*, 3649−3652.

(51) Zhao, H.; Pendri, A.; Greenwald, R. B. *J. Org. Chem.* **1998**, *63*, 7559−7562.

(52) McMurry, J. E. *Org. React* **1976**, *24*, 187−224.

(53) It was crucial to perform the *S*-alkylation step described in Scheme 6 immediately after aqueous quenching of the sufidation (without concentrating the organic layer under reduced pressure) to minimize competitive oxidation of the dithiol intermediate to epidisulfide **46**.

(54) For related ring-expansions of ETPs, see: (a) Murdock, K. C. *J. Med. Chem.* **1974**, *17*, 827−835. (b) Ottenheijm, H. C. J.; Herscheid, J. D. M.; Kerkhoff, G. P. C.; Spande, T. F. *J. Org. Chem.* **1976**, *41*, 3433−3438. (c) Coffen, D. L.; Katonak, D. A.; Nelson, N. R.; Sancilio, F. D. *J. Org. Chem.* **1977**, *42*, 948−952. (d) Curtis, P. J.; Greatbanks, D.; Hesp, B.; Cameron, A. F.; Freer, A. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 180−189. (e) Kirby, G. W.; Rao, G. V.; Robins, D. J.; Stark, W. M. *Tetrahedron Lett.* **1986**, *27*, 5539−5540. (f) Pedras, M. S. C.; Séguin-Swartz, G.; Abrams, A. R. *Phytochemistry* **1990**, *29*, 777−782.

(55) Resubmitting this mixture of ETPs to these conditions did not increase conversion to **48**. Allowing either **47** or **48** individually to react with 1 equiv of Na_2S returned this mixture of tri- and tetrasulfide

ETPs. Addition of an excess of Na_2S resulted in decomposition. These are heterogeneous reactions, and it is difficult to draw conclusions from this study. However, a possible explanation for these results is that upon formation of epitrisulfude **47**, a second molecule of Na_2S reopens the polysulfide ring. The corresponding mixture of ETPs would be obtained from competing ring-closing mechanisms: nucleophilic ring closure (with concomitant expulsion of one sulfur atom) to return **47** or formation of the tetrasulfide bridge of **48**.

(56) We also examined the use of Na_2S_4 for this transformation. Exposing disulfide **46** to 1 equiv of Na_2S_4 in acetone gave a 1.4:1 mixture of ETPs **47** and **48**. Resubmitting this product mixture to these conditions brought about no change. In none of these experiments were products containing more than four sulfur atoms detected by MS analysis.

(57) On larger scales (0.1−0.3 g), it was most convenient to expose a mixture of **39a,b** to TfOH in CH_2Cl_2 at −25 °C to promote complete expulsion of the oxygen substituent at C3. However, a portion of the Boc group on the indole nitrogen atom was cleaved under these conditions and could be selectively protected by subsequent treatment of the crude mixture with a corresponding amount of Boc_2O in the presence of DMAP in THF prior to isolation of **41** in 67% yield.

(58) Attempts to sulfidate the major diol product **53** were unsuccessful. Endeavoring to activate the alcohol groups of **53-major** in the presence of H_2S in MeCN with $Hf(OTf)_3$, a Lewis acid with high oxophilicity but reduced thiophilicity that was utilized by Boyer and Movassaghi in their total synthesis of gliocladin B (**14**),[13a] failed to yield the desired dithiol product.

(59) This sequence required careful monitoring, as reaction times were variable; for additional details, see the Supporting Information.

(60) Pickering, T. L.; Saunders, K. J.; Tobolsky, A. V. *J. Am. Chem. Soc.* **1967**, *89*, 2364−2367.

(61) See refs 8a,d, 54b, and: (a) Hino, T.; Sato, T. *Chem. Pharm. Bull.* **1974**, *22*, 2866−2874. For a mechanistic study on desulfurization of ETPs, see: (b) Herscheid, J. D. M.; Tijhuis, M. W.; Noordik, J. H.; Ottenheijm, H. C. J. *J. Am. Chem. Soc.* **1979**, *101*, 1159−1162.

(62) Fisher, J. W.; Trinkle, K. L. *Tetrahedron Lett.* **1994**, *35*, 2505−2508.

(63) Cell viability was determined by Dr. Sangkil Nam at the Beckman Research Institute, City of Hope Comprehensive Cancer Center, using a MTS metabolic activity assay as described by the supplier (Promega); see: Nam, S.; Williams, A.; Vultur, A.; List, A.; Bhalla, K.; Smith, D.; Lee, F. Y.; Jove, R. *Mol. Cancer Ther.* **2007**, *6*, 1400−1405.

(64) A synthetic sample of cinnabarinic acid (**4**) and the dimethyl ester **60** were prepared in a fashion similar to that described for preparation of **31**. See the Experimental Section for details.

(65) The synthesis and in vitro cytotoxicity activity of T988 C (**7**), **59** and related ETPs against DU145 and A2025 were previously reported and used in the present context for comparison. See ref 2c.

(66) The Pd/RuPhos precatalyst (CAS No. 1028206-60-1) is commercially available.

(67) Node, M.; Kawabata, T.; Ohta, K.; Fujimoto, M.; Fujita, E.; Fuji, K. *J. Org. Chem.* **1984**, *49*, 3641−3643.

(68) In the ^{13}C NMR spectrum of (−)-**37b**, two quaternary carbons were not detected or coincided with another carbon resonance.

(69) Additional $K_2OsO_4{\cdot}H_2O$ and $(DHQ)_2PHAL$ were needed in order to consume all starting material.

(70) The relative configuration of **S7** was confirmed chemically by elaboration to **44b** in two steps: (i) acetylation of the alcohols and (ii) sulfidation by the two-step procedure (vide infra).

(71) This two-step sequence gave yields ranging from 60−80% yields on various scales (5−100 mg of **39a**).

(72) In the ^{13}C spectrum of **41**, one tertiary carbon coincided with the solvent peak (acetone) and was assigned by an HMQC experiment.

(73) In the ^{13}C NMR spectrum of **42a**, multiple carbons of the minor atropisomer were not detected or coincided with other carbon resonances.

(74) In the ^{13}C NMR spectrum of **42b**, this carbon coincided with the acetone-d_6 (solvent) peaks and was assigned by DEPT and HMQC experiments.

(75) In the ^{13}C NMR spectrum of **44a**, a quaternary carbon was not detected or coincided with another carbon resonance.

(76) A corresponding experiment (**42a**: 4 mg, 3.2 μmol) was conducted wherein Na_2S_4 (0.6 mg, 3.4 μmol) was used instead of Na_2S. A mixture of (+)-**47** and **48** (64%, 1.4:1 ratio of products) was obtained upon purification.

(77) In the ^{13}C NMR spectrum of **47**, overlapping carbons were assigned by HMQC, DEPT, and HMBC experiments.

(78) In the ^{13}C NMR spectrum of **52-major**, one quaternary carbon was not detected or coincided with another carbon resonance.

(79) The addition of small amounts of Na_2S proved challenging. In some cases, adjusting the amount of Ph_3P added in the subsequent step to selectively decompose the corresponding tetrasulfide ETP **57** was employed.

(80) At this step, the resulting di-, tri-, and tetrasulfide ETP products could be efficiently separated by preparatory thin-layer chromatography: R_f 0.38, 0.41, 0.29, respectively (7:3 EtOAc/hexanes, plate was eluted twice).

(81) See ref 11 and: (a) Angyal, S. J.; Bullock, E. B.; Hangar, W. E.; Howell, W. C.; Johnson, A. W. *J. Chem. Soc.* **1952**, 1592−1602. (b) Bolognese, A.; Piscitelli, C.; Scherillo, G. *J. Org. Chem.* **1983**, *48*, 3649−3652.

(82) The procedure for preparation of 3-hydroxyanthranilic acid methyl ester from 3-hydroxyanthranilic acid has been described; see: Fielder, D. A.; Collins, F. W. *J. Nat. Prod.* **1995**, *58*, 456−458.