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Extending Pummerer Reaction Chemistry. Development of a Strategy for the Regio- and Stereoselective Oxidative Cyclization of 3-(ω-Nucleophile)-Tethered Indoles

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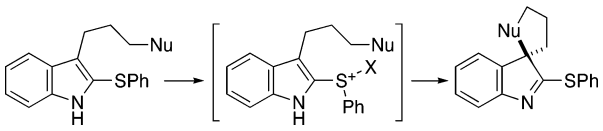
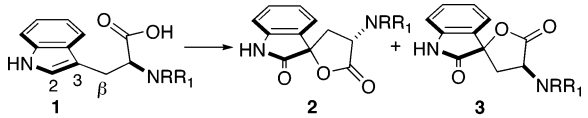


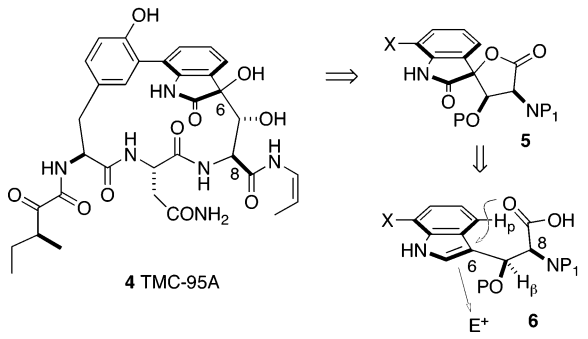
The brominative cyclization of diastereomeric β-silyloxy tryptophan derivatives proceeded with divergent regiochemistry (C(2) or C(3) addition), depending on the relative stereochemistry of the silyloxy substituent. This lack of C(2) vs C(3) regiochemical predictability led to the development of a new approach, which featured Pummerer-type chemistry on an indole C(2) sulfoxide or sulfide substrate, for steering nucleophilic addition to C(3) of the indole. Extension of this transformation from carboxylate nucleophiles to carbon analogues such as allylsilane, silyl enol ether, and silyl ketene iminal bearing substrates led to the formation of spirocyclic oxindole derivatives in good yields with complete regioselectivity for C(3) cyclization and with good diastereoselectivity where relevant.

The oxidative cyclization of tryptophan derivatives has served as a workable strategy for synthesis efforts directed toward members of the tryptoquivaline family of mycotoxins.[1] The scope and limitations of this process are summarized by the conversions of **1** into the diastereomeric products **2** and **3**,[1,2] Scheme 1. With the singular exception shown in entry b,[1a] the diastereoselectivity is typically quite modest. In addition to these discouraging observations, further problems occasionally arise in the form of either (1) product overoxidation[3] or (2) a lack of regiochemical control (C(3) vs C(2)) upon nucleophile addition to the oxidized, electrophilic indole unit.[4] Despite these potential shortcomings of tryptophan oxidative

SCHEME 1



entry	ref.	R, R_1	conditions	yield (%)	2/3 ratio
a	1a	phthalimide	CCl_3SO_2Cl/DMSO	65	2.5:1
b	1a	quinazolinone	$(CH_3SO_2)_2O$/DMSO	66	> 9:1
c	2c	phthalimide	NBS/$NaHCO_3$/t-BuOH	89	not reported
d	2e	Ac, H	t-BuBr/DMSO	67	not reported
e	2f	phthalimide	$Tl(NO_3)_3$	50	2.1:1



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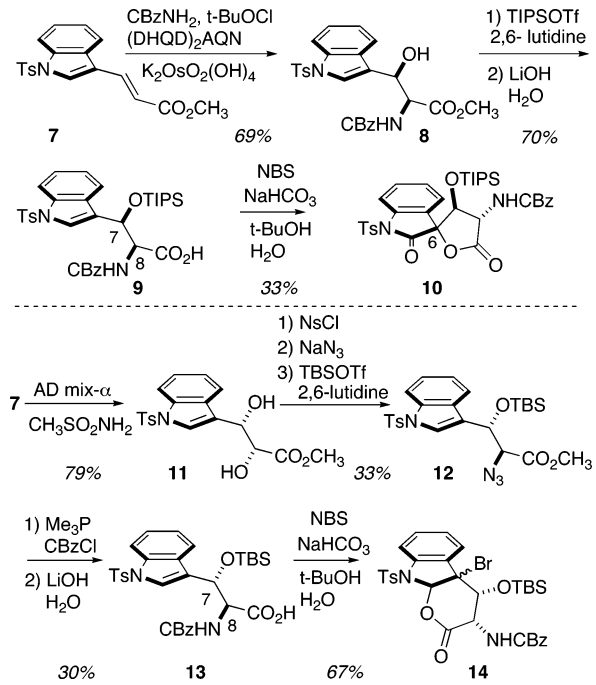
cyclization chemistry, the recent discovery of the complex 20S proteosome inhibitor TMC-95A (**4**)[5] provided motivation to revisit this transform with the goal of designing a possibly biomimetic synthesis of the oxindole core **5** via an oxidative cyclization of the β-oxygenated tryptophan derivative **6**. In this instance, the additional steric interactions engendered between the peri-positioned hydrogen H_p and the group at the β-carbon (H_β vs OP) might provide a bias for cyclization favoring the desired stereochemistry at C(6) (TMC-95A numbering), vide infra. An additional benefit of reaction through **6** might stem from the Felkin-Ahn-type mixing between the now electrophilic C(6) carbon and the adjacent, perpendicularly disposed OP antibond, an electronic advantage not shared with the possible diastereomeric transition state featuring alignment between C(6) and H_β. Although a case for stereochemical control can be made in this tryptophan oxidative cyclization substrate, other potential problems (overoxidation, regioselectivity of cyclization, yield) cannot be so readily addressed by a priori argument.

A project on the oxidative cyclization of species related to **6** was initiated to provide an experimental test of these ideas, with the downstream aim of incorporating any advances in tryptophan oxidative cyclization chemistry into a synthesis of TMC-95A.[6] As it transpired, the cyclization of β-oxygenated tryptophan derivatives proceeded with mixed results (Scheme 2) using documented protocols (cf. Scheme 1, **1** → **2/3**). These disappointing results provided the impetus to develop an alternative approach to tryptophan, and more generally, indole, oxidative cyclizations that proceeds in good-to-excellent yields and without any evidence for product overoxidation or undesired regiochemistry.[7] This approach features an advance in Pummerer reaction chemistry that serves to formally transfer oxidation from sulfur positioned at C(2) of the indole nucleus to C(3), thus enabling bond formation at that site. The details of both the brominative cyclization attempts on β-oxygenated tryptophan derivatives and the emerging Pummerer-triggered oxidative cyclization chemistry are presented below.

The initial foray into oxidative cyclization of β-oxygenated tryptophan derivatives encompassed the two diastereomeric species **9** and **13**, Scheme 2. Substrate **13** has the correct relative stereochemistry at C(7) and C(8) (TMC-95A numbering) for TMC-95A synthesis, whereas **9** would lead to a diastereomeric oxindole product. This study focused on determining the relationship between the C(7) substituents and the emerging stereochemistry

SCHEME 2



at C(6). Based upon the results with **1**, the stereochemistry at the amide-bearing carbon C(8) was not expected to exert much influence on the diastereoselectivity of cyclization, but examining both diastereomers **9** and **13** will test this assumption directly. The synthesis of both cyclization substrates relied on Sharpless asymmetric amidohydroxylation and dihydroxylation,[8] respectively, to set the relative and absolute stereochemistry. The observed enantiomeric excesses for both reactions exceeded 99% (detection limit, HPLC with an OJ-H column). The synthesis of **9** was completed by hydroxyl protection and ester hydrolysis, whereas the sequence that converted diol **11** into the diastereomeric cyclization precursor **13** was more indirect and exploited recent advances from the Boger laboratory on α-azidation chemistry.[9]

In the critical tests of this hypothesis, both **9** and **13** were subjected to a range of oxidative cyclization procedures (cf. Scheme 1, **1** → **2/3**), but it was only with NBS/$NaHCO_3$/*t*-BuOH/H_2O that productive cyclization was observed. The conversion of **9** into the butyrolactone **10** proceeded along orthodox lines, albeit in modest yield. A single diastereomer of **10** was detected, and the stereochemical outcome is nicely rationalized by reaction through the construct **6**. This stereochemical assignment was based upon the observation of a nOe between the hydrogen on C(7) and the peri-positioned aryl hydrogen. It is noteworthy that only the *N*-tosyl substrates **9** and **13** participated in this cyclization—previous scouting experiments with the *N*-H indole analogue of **13** failed to provide cyclized product under any experimental regimen examined.

The cyclization of the stereochemically "correct" isomer **13** was investigated next, and in light of the encouraging

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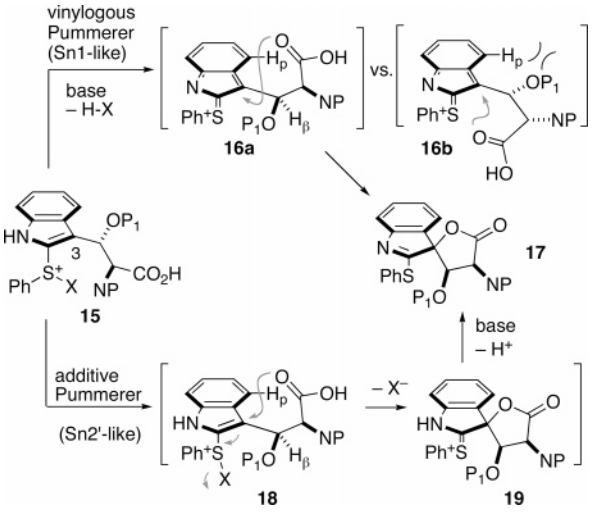
SCHEME 3



result with **9**, formation of the TMC-95A-like diastereomer of **10** was expected. Indeed, exposure of **13** to the successful NBS procedure did provide a single lactone product in good yield, but an unusually low lactone IR absorbance at 1764 cm^{-1} signaled problems (compare 1810 cm^{-1} for **10**; ~ 1800 cm^{-1} for **2/3**). Further spectroscopic characterization pointed to the valerolactone structure **14**, a species that presumably originates with nucleophilic carboxylate attack at C(2) of the indole system. The stereochemical relationship between the ring fusion and the preexisting C(7) and C(8) centers was not determined. This diversion of reactivity to C(2) has been observed previously in indole oxidative cyclizations.[1d] It appears that a lack of regiochemical control has thwarted this approach to the TMC-95A oxindole core. The reasons for the different behavior of **9** and **13** remain a matter of speculation, but problems with eclipsing interactions between the OTBS and NHCBz substituents in a forming five-membered ring derived from **13** (absent with the diastereomeric substrate **9**) might play a role in directing **13** down an alternative path. In this scenario, a regioisomeric six-membered ring transition state, which features a less penalizing gauche-type interaction between the C(7) and C(8) substituents, appears to be preferred. Whatever the reason, it became clear that the brominative cyclization approach to the TMC-95A oxindole fragment **5** was not going to reach fruition.

These discouraging results prompted a reevaluation of the approach but not the overall strategy, as a biomimetic oxidative cyclization theme still held its appeal. In considering what might have gone wrong with **13**, it became apparent that incorporation of some additional driving force might be necessary to overcome the burgeoning eclipsing interactions between OTBS and NHCBz and thereby favor the desired C(3) cyclization pathway over the undesired C(2) alternative. Upon evaluating options along these lines, the idea of coupling C(3)-specific nucleophilic addition with rearomatization of a transient indole-derived aza-orthoquinonedimethane formed from oxidation was intriguing. One manifestation of this strategy is detailed in Scheme 3, where Pummerer chemistry originating with indole C(2) sulfoxide **15** might lead to such an intermediate **16** via a base-promoted loss of H−X (termed the "vinylogous Pummerer reaction"[10]). Cyclization of the carboxylate oxygen into C(3) rather than the thionium ion at C(2), might be favored since it would restore aromaticity, whereas the latter course would not. This process would lead unambiguously to the butyrolactone product **17**, and subsequent hydrolysis of the thioimidate moiety would deliver an oxindole product appropriately functionalized for TMC-95A synthesis. A mechanistic alternative to the vinylogous Pummerer pathway from **15** to **17** may intervene. Termed the "additive Pummerer reaction",[11] this sequence proceeds with Sn2′-like displacement of X by the nucleophile in a presumably concerted manner. As in the vinylogous mechanism, carboxylate attack strictly at C(3) would be expected based upon the construct **18**. The thionium ion-containing product **19** then can deprotonate to furnish the same thioimidate **17**. Irrespective of the mechanistic intricacies, a developing steric interaction between OP_1 and H_p in diastereomeric transition state **16b** (or its additive Pummerer equivalent) should enforce reaction through **16a** and afford the desired stereochemical result.

The exploration of this Pummerer-based oxidative cyclization strategy began, and nearly ended, with the unrewarded attempts to utilize the model *N*-BOC tryptophan derived substrate **22**, Scheme 4. This sulfoxide as a mixture of diastereomers was readily available from *N*-BOC tryptophan in two well-precedented steps.[12] Unfortunately, all attempts to engage this species in Pummerer chemistry failed to deliver even trace amounts of cyclized lactone product. Matters improved considerably when the standard sulfoxide/acylation Pummerer trigger was replaced with an alternative initiation combination, the hypervalent iodine reagent PhI(CN)OTf and sulfide **21**. Use of this iodonium reagent, first introduced by Stang and Zhdankin in 1991,[13] provided the first glimpse of success in these trials as the butyrolactone-containing product **23** was obtained (1:1 mixture of diastereomers) in encouraging yield. Why should the

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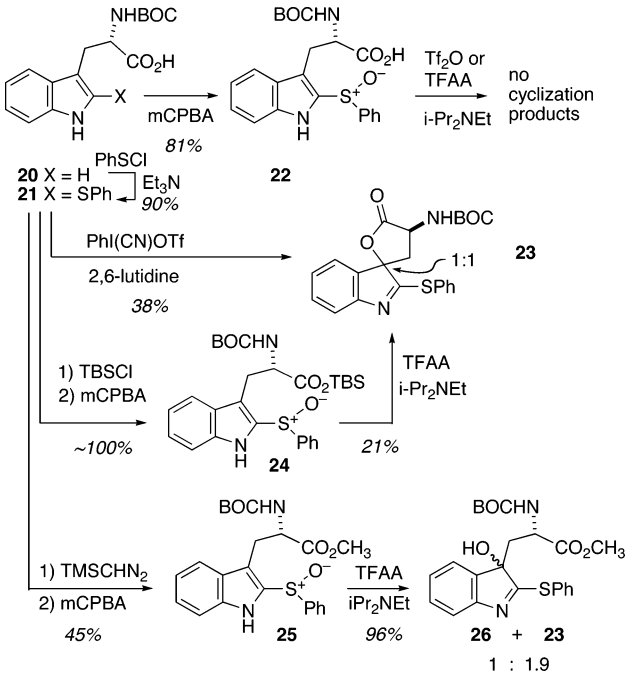
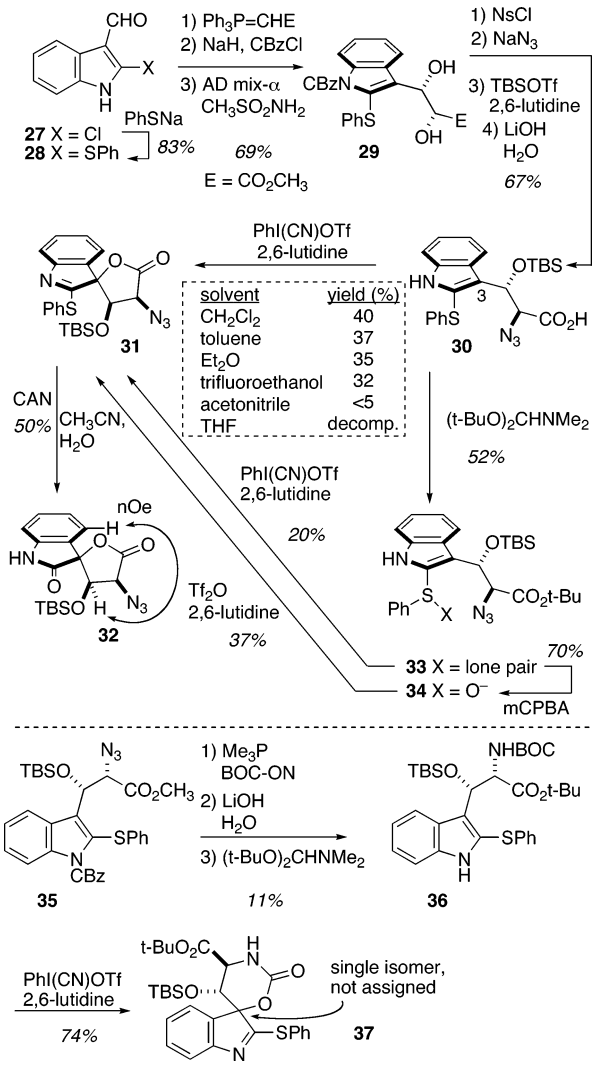
SCHEME 4



iodonium/sulfide initiation work whereas the sulfoxide acylation chemistry failed? Speculation might focus on the culpability of the acid function in **22**, as formation of a mixed anhydride upon exposure to acylation conditions might compete with the desired sulfoxide acylation. This mixed anhydride itself could then acylate the sulfoxide to form a seven-membered ring product whose conformational constraints might make attaining the necessary stereoelectronic alignment between the C(3) p orbital and the scissile S−O bond energetically prohibitive. The sulfide/hypervalent iodonium system, on the other hand would face no such competition, as these reagents do not activate carboxylic acids for acylation. A test of this hypothesis came with use of the sensitive silyl ester sulfoxide substrate **24**, formed by carboxylate silylation and then sulfide oxidation within **21**. Treatment of this sulfoxide with trifluoroacetic anhydride and Hunig's base did furnish the same butyrolactone **23**, again as a 1:1 mixture of diastereomers, in modest yield. No other characterizable materials were isolated from this transformation, and so it is not possible to determine what other competing reactions intervene, although the instability of the TBS-ester may have played a role in the poor yield of the transformation. Later studies with other *N*-BOC substrates (vide infra) suggest that this carbamate unit also serves as a locus of unwanted reactivity that diverts starting material. Attempts to extend Pummerer reactivity to alkyl ester substrates such as the methyl ester **25** did not expand the scope of the transform significantly. The desired butyrolactone product **23** (1:1 mixture of diastereomers) was formed in the typical 30% yield, but in this instance a near equal amount of the C(3)-hydroxylated species **26** was observed also. Presumably, this product resulted from trifluoroacetate trapping (followed by hydrolysis upon workup) of the Pummerer-generated C(3) electrophile in competition with internal delivery of the carboxylate nucleophile. These results, taken together, lend support to the notion that this Pummerer-based strategy for C(3) selective tryptophan

SCHEME 5



oxidative cyclization is indeed feasible. However, the implementation of this idea is beset with a range of competitive reactions that limit yield. Complete regioselectivity for C(3) carboxylate addition is the most valuable asset, although this selectivity has yet to be tested in the more demanding β-oxygenated series of substrates relevant to TMC-95A synthesis.

Extending these trials to the aforementioned β-oxygenated substrates of interest for TMC-95A synthesis is detailed in Scheme 5. The initial entry point is the C(2) thiophenyl analogue of **13**, compound **30**. This cyclization substrate was prepared via initial substitution of thiophenol for chloride within the known aldehyde **27**.[14,15] Emmons−Horner extension of the aldehyde within **28** afforded an unsaturated methyl ester that was processed through the Sharpless/Boger chemistry (>99% ee in the dihydroxylation, HPLC with an OH-J column) much like the des-thiophenyl version (cf. Scheme 2). In this in-

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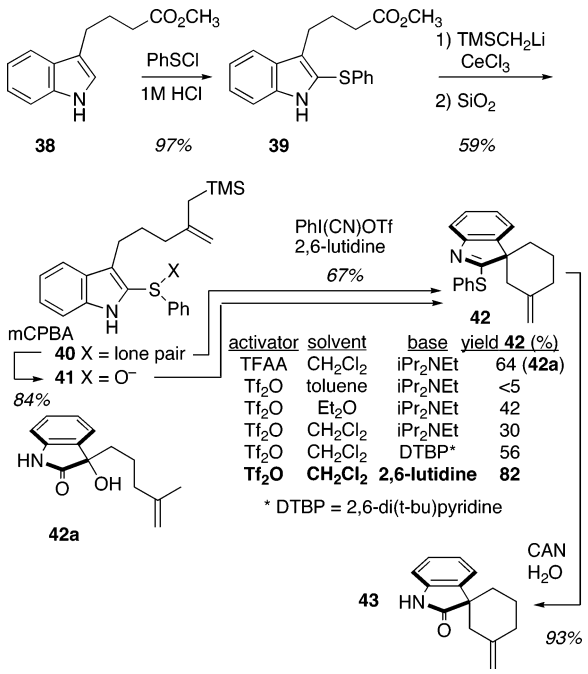
stance, however, the azide function was retained in the cyclization substrate **30**, as attempts to oxidatively cyclize *N*-carbamate versions of **30** led to competitive participation of the carbamate carbonyl as a nucleophile (cf. **36** → **37**). Examination of the PhI(CN)OTf-promoted Pummerer cyclization of **30** included optimization of yield with respect to solvent, temperature, and base. Solvent polarity played the largest role (see Table in Scheme 5), with the best yields observed in the least polar solvents toluene and CH_2Cl_2. Despite extensive exploration of parameter space for this transformation, the yield could not be coaxed above 40%. Cyclization attempts with the sulfoxide derived from **30** were not successful, as anticipated from the results with **22**. The product spirobutyrolactone **31** was formed as a single diastereomer whose relative stereochemistry is in complete accord with the expectations of cyclization through the model transition state **16a** (or its additive Pummerer equivalent **18**). This stereochemical assignment was based the observation of the nOe signal shown with structure **32**. This spirolactone has the correct relative and absolute stereochemistry for use in TMC-95A synthesis, and ceric ammonium nitrate-mediated hydrolysis of the thioimidate function within **31** delivered the expected oxindole product **32** in moderate yield. Further attempts to identify structural perturbations that might lead to improved yield of **31** included the *tert*-butyl esters **33** and **34**. Both species did perform with modest efficiency in the Pummerer process upon exposure to the appropriate initiator (PhI(CN)OTf with the sulfide **33** and Tf_2O with the sulfoxide **34**), but overall, the use of esters in place of the carboxylic acid reside in **30** did not extend the reaction in useful ways.

A reminder that competitive reactions are ever present came with attempts to perform the oxidative cyclization sequence on the *N*-BOC substrate **36**, prepared by azide reduction and in situ acylation within **35**. In this case, the only cyclized material isolated corresponded to C(3)−O bond formation that originated with the carbamate's carbonyl function. As with the earlier substrates featuring β-oxygenation, this material was formed as a single (unassigned) stereoisomer. The contrasting reactions of **36** and its azide analogue **33** illustrate an apparent limitation of this chemistry and suggests that nonparticipating nitrogen protecting groups are a valuable asset.

All successful Pummerer-initiated oxidative cyclizations of tryptophan derivatives examined to date proceeded with complete regiochemical control for C−O bond formation at C(3). This preference was observed even with the β-silyloxy substrates **30**, **33**, and **34**, where eclipsing interactions between the OTBS and N_3 units might have been a cause for concern based on the chemistry of **13**. Nevertheless, these encouraging results with carboxylate nucleophiles prompted exploration of the scope of the oxidative cyclization transform through the use of related carbon-based nucleophiles.

Preparation of the initial nucleophilic carbon-based oxidative cyclization substrate **41** is shown in Scheme 6. The allylsilane function of **41** was chosen for examination first as it is a relatively poor nucleophile (Mayr N = 1.8),[16] and so it should provide a demanding probe of the degree of electrophilicity generated at C(3) via the Pummerer sequence. Curiously, attempted C(2) phenylsulfenylation of ester **38** under basic conditions (PhSCl, Et_3N) afforded only the *N*-SPh product in essentially quantitative yield,

SCHEME 6



a result in sharp contrast to the base-mediated C(2) sulfenylation recorded earlier with acid **20** (Scheme 4). Resorting to acidic sulfenylation conditions did deliver the requisite C(2)-thiophenyl product **39** in excellent yield.[17] Under no set of conditions did the electrophilic sulfenylating agent initiate any detectable oxidative cyclization of the pendant ester or acid moieties. Conversion of ester **39** into allylsilane **40** followed the procedure of Fuchs,[18a] with the modification of including $CeCl_3$ in the nucleophilic addition step.[18b] Omission of this mediator led only the α-trimethylsilyl ketone product (i.e., mono-addition), a result that presumably reflects the ready enolization of that first-formed species. Silica gel-assisted Peterson olefination completed the sequence and delivered sulfide **40**, from which sulfoxide **41** could be derived. It is noteworthy that sulfur oxidation in the presence of the allylsilane moiety did not present a problem in this instance, a favorable chemoselectivity that unfortunately was not borne out with subsequent substrates.

Both iodonium-promoted oxidative cyclization of sulfide **40**, and triflic anhydride initiated Pummerer reaction of sulfoxide **41**, were examined, Scheme 6. The sulfoxide substrate, being the inaugural example of the carbon-nucleophile series, was subjected to an extensive optimization study during which temperature, concentration,

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(17) Bhardari, P.; Crombie, L.; Harper, M. F.; Rossiter, J. T.; Sanders, M.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1685−1697.

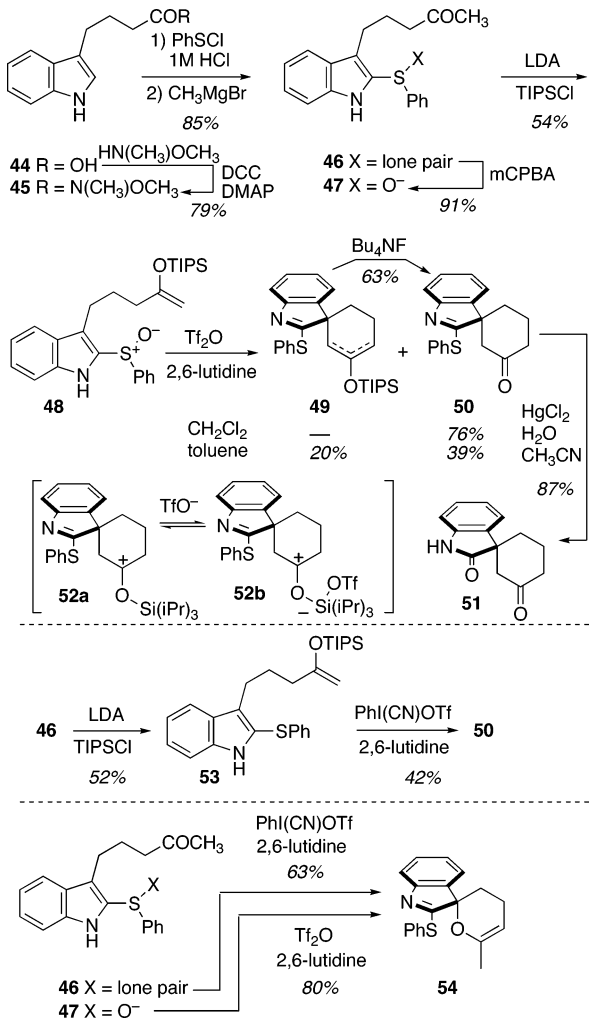
(18) (a) Anderson, M. B.; Fuchs, P. L. *Synth. Commun.* **1987**, *17*, 621−635. (b) Lee, T. V.; Porter, J. R.; Roden, F. S. *Tetrahedron Lett.* **1988**, *29*, 5009−5012.

solvent, base and activator were varied. Select data from this study are shown in Scheme 6. Consideration of these results reveals that (1) a non-nucleophilic counterion is essential for successful C−C bond formation (trifluoroacetate vs triflate) and (2) a sterically hindered pyridine base struck the appropriate balance between basicity and steric bulk. The reaction proceeded essentially instantaneously at −78 °C under the optimized conditions. The exclusive formation of alcohol **42a** from trifluoroacetic anhydride initiation, followed by trifluoroacetate and thioimidate hydrolysis, speaks to the concerns about allylsilane nucleophilicity raised earlier. In this instance, even the weakly nucleophilic trifluoroacetate anion apparently is sufficient to win the competition for the C(3) electrophilic center over the internal allylsilane nucleophile. Of course, clouding this interpretation is the timing of trimethylsilyl loss, an unknown at present. Ceric ammonium nitrate (CAN)-mediated hydrolysis[19] of the thioimidate function within **42** proceeded smoothly to furnish the oxindole-containing product **43** in excellent yield.

The iodonium-initiated Pummerer transform that commenced with sulfide **40** provided the same thioimidate **42** in good but somewhat diminished yield compared with the sulfoxide Pummerer variant. Product formation at even this undistinguished level required extensive optimization studies that highlighted an unexpected (and unexplained) aspect of the hypervalent iodine chemistry: the PhI(CN)OTf reagent was consumed under the reaction conditions in uncharacterized competitive processes, and so the best product yields attended experiments where a 4-fold molar excess of the iodonium reagent was added portion-wise until TLC analysis indicated consumption of starting sulfide. Since both the starting material and the product of this reaction are sulfides, product (over)oxidation was a concern. No such product(s) were detected, and a control experiment documented that **42** was unreactive to PhI(CN)OTf. Apparently, there is a sufficient spread in reactivity between the electron rich sulfide of **40** and the electron deficient sulfide of **42** to allow discrimination with this oxidant. A much stronger oxidant, CAN, is capable of reaction with the sulfide within imidate **42**. Attempts to effect the oxidative cyclization of sulfide **40** with the more common hypervalent iodine reagents PIDA ($PhI(OAc)_2$) or PIFA ($PhI(OCOCF_3)_2$)[20] led to only trace amounts of oxindole **42a** following aqueous workup, although in these trials the starting sulfide **40** was rapidly consumed. The disparate results among the various hypervalent iodine reagents is striking, and perhaps reflects the differential acidic character of the iodonium ligand's conjugate acid (HCN vs HOAc vs $HOCOCF_3$).

The second substrate examined, TIPS enol ether sulfoxide **48**, presented the putative C(3) electrophile with a more nucleophilic alkene (Mayr N ~ 5.4),[16] Scheme 7. The synthesis of this substrate began with the commercially available acid **44**, and in a few steps both the sulfide **46** and the sulfoxide **47** were accessed. The formation of sulfoxide **47** had to precede silyl enol ether

SCHEME 7



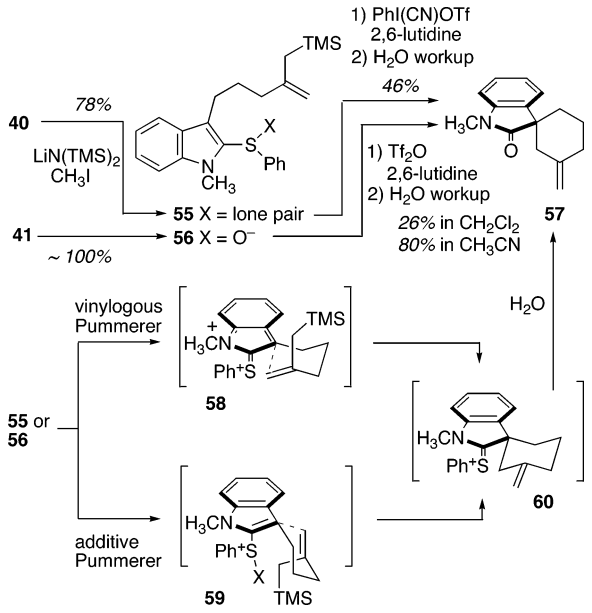
formation, as all attempts to oxidize the sulfur atom within enol ether substrate **53** met with failure. Exposure of sulfoxide **48** to the now optimized reaction conditions (CH_2Cl_2 solvent) led to clean and high-yielding conversion into the expected cyclohexanone-containing product **50**. The thioimidate moiety within **50** was converted efficiently into the oxindole of **51** using mercury-assisted hydrolysis,[21] a procedure that appeared to work better with this substrate than the oxidative hydrolysis approach employed with **42**. Interestingly, similar reaction in the less polar solvent toluene afforded only a 37% yield of the same ketone product **50**, and new spirocycle-containing compounds, the silyl enol ethers **49**, were formed in significant amounts. These product were isolated as a 7:1 ratio of regioisomeric enol ethers, with the minor species favoring enolization toward the quaternary (spiro) ring junction. Both isomers were readily converted into the ketone-containing product **50** upon treatment with fluoride. A rationale for formation of this silyl enol ether product in the less polar solvent is provided by the constructs **52a** and **52b**, presumed intermediates en route to **50** from **48**. In the more polar solvent CH_2Cl_2, formation of the highly charged zwitterion **52b** might be more favorable than in toluene, and this intermediate should rapidly decompose to the ketone

(19) Ho, T.-L.; Ho, H.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791.

(20) (a) Tamura, Y.; Yakura, T.; Shirouchi, Y.; Haruta, J.-i. *Chem. Pharm. Bull.* **1986**, *34*, 1061−1066. (b) Wang, H.-M.; Lin, M.-C.; Chen, L.-C. *Heterocycles* **1994**, *38*, 1519−1526.

(21) Satchell, D. P. N. *Chem. Soc. Rev.* **1977**, *6*, 345−371.

SCHEME 8



product. In contrast, in the less polar solvent toluene, the earlier intermediate **52a** might be intercepted by base to furnish the enol ether product in competition with forming appreciable concentrations of **52b**.

The use of the sulfide/iodonium Pummerer initiation sequence with **53** proceeded in more modest yield than the sulfoxide analogue, but in this instance, only the ketone product **50** was formed. No other characterizable products could be isolated from the reaction mixture, and so the question of where the rest of **53** goes remains open.

The methyl ketones **46** and **47** themselves proved to be competent substrates in this oxidative cyclization. The sulfoxide **47** with Tf_2O initiation and the sulfide **46** with iodonium initiation led in each case to clean conversion, and the sensitive enol ether product **54** was formed uncontaminated by any detectable exocyclic alkene isomer. No attempt was made to hydrolyze the thioimidate function in the presence of the enol ether moiety. That the initial oxidation chemistry is confined, at least in large measure, to the sulfur function is a reminder of the value of using the Pummerer strategy to effect selective oxidation in a polyfunctional molecule. The precise sequence of events that evolves from treating either **46** or **47** with their respective initiators is unknown, and so speculation about the role of an enol nucleophile vs a ketone version of same cannot be addressed directly.

Use of the *N*-methylated substrates **55** and **56** provided some insight into the vinylogous/additive mechanistic dichotomy discussed earlier, Scheme 8. Both the sulfide **55** and the sulfoxide **56** were prepared in good yield by direct methylation of the precursors **40** and **41**, respectively. Treatment of either Pummerer precursor with its appropriate initiator led to the same oxindole product **57** with distinctly different efficiencies. The sulfide/hypervalent iodine system provided product in a yield that never could be improved beyond 46%, despite extensive exploration of reaction parameters. The yield of **57** in the sulfoxide/Tf_2O case varied with solvent, and uniquely for this study, the more polar solvent acetonitrile afforded the highest yield (80%). Note that in all cases, the oxindole product was isolated directly, presumably through facile hydrolysis of an intermediate thionium ion (cf. **60**) upon aqueous workup. Tracking the conversion of either **55** or **56** through to common product **60** via the vinylogous Pummerer intermediate **58** or the additive alternative **59** raises an interesting question about the relative energies of these processes. The additive mechanism proceeds through a transition state (modeled by **59**) that is not likely to be substantially different in energy from the similar one posited for the des methyl series **40**/**41** → **42** (Scheme 4), with the possible exception of a more pronounced steric perturbation introduced by the *N*-CH_3 unit compared with the *N*-H lower homologue. The vinylogous Pummerer mechanism, however, has no *N*-H proton to lose, and so participation by the indole nitrogen's lone pair in the ejection of X- would necessarily deliver an iminium/thionium dicationic intermediate **58**. The energetic consequence of generating a species with adjacent cationic charges is not readily estimated, but this value is likely to bear heavily on the prospects for proceeding through the vinylogous reaction channel from **55** or **56**. The higher yield of **57** in the more polar solvent is certainly consistent with enhanced stabilization of more highly charged intermediates/transition states, but that stabilization could be manifest at points other than **58** or **59** along either mechanistic pathway. Thus, the most plausible explanation for the formation of **57** from **55** or **56** would seem to rely on the Sn2′-like additive pathway, although the alternative vinylogous course cannot be rigorously ruled out. Irrespective of this mechanistic conundrum, acquisition of an oxindole product directly from the oxidative cyclization transformation avoids the discrete thioimidate hydrolysis step and provides a more efficient route to *N*-methyloxindoles from *N*-methylindole precursors.

The final carbon-nucleophile substrate examined in this study featured a very reactive silyl ketene iminal (Mayr N > 10)[16] as the partner for the C(3) electrophile, Scheme 9. In addition, this example introduces an issue of diastereoselectivity upon cyclization. Assembly of the oxidative cyclization precursors **66** (sulfide) and **67** (sulfoxide) commenced with tryptamine (**61**) and passed through the naphthylmethyl carbamate[22−24]-containing species **63** en route to the silyl ketene iminal precursor **64**. The use of this uncommon indole nitrogen protecting group was indicated by the ready loss of the C(2) sulfur moiety upon attempted hydrogenolysis of a CBz analogue. The naphthyl unit within **63** is claimed to be a much better ligand for the Pd catalyst's surface than is a simple phenyl ring, and so the rate of hydrogenolysis of the carbamate should be enhanced compared with other competitive processes relying on Pd-phenyl interactions. Enolization and silylation proceeded smoothly from sulfide **64** to afford the silyl ketene iminal product **66** as a single (*Z*) geometrical isomer. The configurational assignment is based upon comparison of the ^1H and ^{13}C NMR spectra of this species with those of the sulfoxide-derived analogue, a compound whose geometry was secured by observation of an NOE between the alkene proton and the hydrogens of the *tert*-butyl group. The enolization/silylation sequence with the sulfoxide **65** was troublesome, and typically equal parts of **67** and starting

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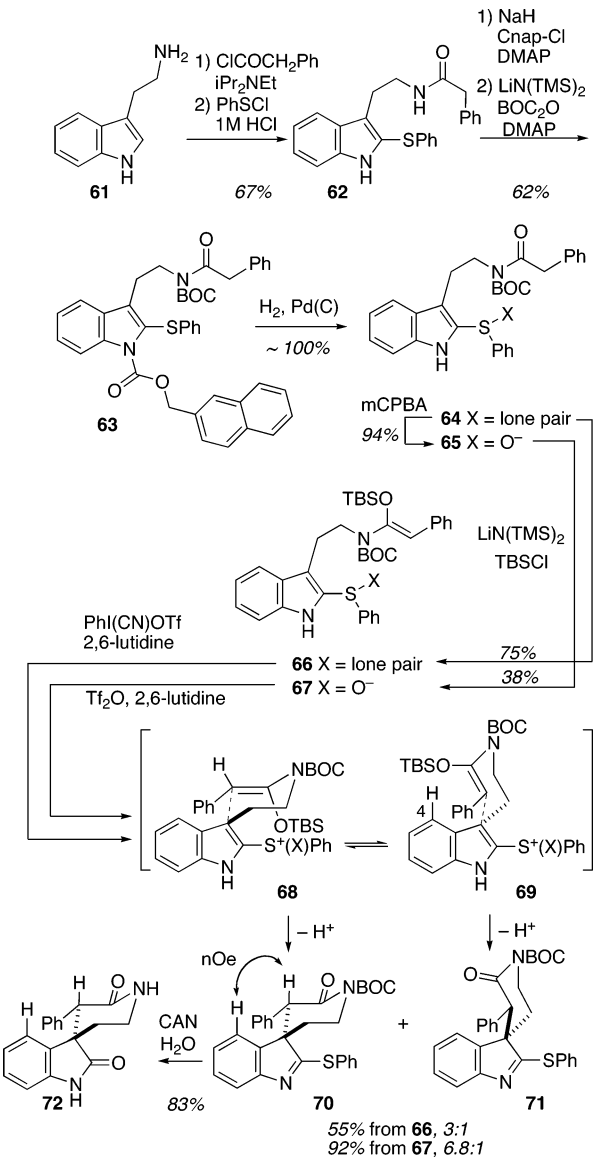
(23) Kim, C. M.; Cole, P. A. *J. Med. Chem.* **2001**, *44*, 2479−2485.

SCHEME 9



material **65** were isolated. The basis for the greater sensitivity of sulfoxide **67** to workup/purification compared with **66** is not clear. Subjection of sulfoxide **67** to the optimized Pummerer conditions delivered the expected spirocyclic products **70** and **71** as a 6.8:1 mixture of diastereomers in excellent yield. The stereochemical assignment of the major isomer was discerned by NOE as shown, whereas the minor isomer was assigned by default. Mercury-assisted hydrolysis of the thioimidate function within major isomer **70** was accompanied by imide deprotection, and so amide oxindole **72** was formed in good yield.

The observed diastereoselectivity of this transform can be rationalized by citing major product formation through cyclization of a six-membered chairlike transition state modeled by the additive Pummerer construct **68**. The aryl portion of the indole nucleus occupies a pseudoequatorial location on the forming cyclohexane ring, and so the −S(X)Ph unit must then claim the more sterically demanding psuedoaxial position. The (*Z*) alkene geometry dictates the location of the phenyl ring in this transition state model, and its pseudoequatorial disposition in this case carries through to product. Based upon this analysis, the minor product **71** emerges from the alternative transition state modeled by **69**, where now the indole's aryl ring occupies the psuedoaxial position on the forming six-membered ring, an arrangement that introduces a serious steric clash between C(4)−H of the indole and the axially disposed OTBS and C−H groups of the linking tether. Control experiments indicated that the major and minor isomers did not equilibrate under the reaction conditions. The alternative Pummerer procedure stemming from sulfide **66** treatment with PhI(CN)OTf furnished the same mixture of thioimidate products **70** and **71**, although both yield and diastereoselectivity were compromised compared to the sulfoxide case. The drop in yield appears characteristic of the iodonium/sulfide chemistry relative to the sulfoxide/Tf_2O protocol. However, the diminished diastereoselectivity was surprising, and perhaps reflects a difference in steric demand between −S(+)(OTf)Ph and −S(+)[I(CN)Ph]Ph in transition state model **68**. The presumably larger iodonium-appended species may disfavor **68** more than the sulfoxide-derived alternative, and so reaction through **69** to furnish **71** may be more energetically competitive for the iodonium-derived case.

The application of Pummerer chemistry to the oxidative cyclization of C(3) indole derivatives has extended this venerable transform in new directions. Species with both carboxylate and activated alkene nucleophiles perform satisfactorily to furnish spirocyclic products at C(3) of the indole core. The first-formed thioimidate products can be readily converted to oxindoles. Both yields and diastereoselectivity can be high with certain substrates. Future directions for this work will include development of an asymmetric version of the oxidative cyclization, and applications of this chemistry toward cognate natural products.

Experimental Section

General Procedure A for the Sulfoxide-Initiated Pummerer Rearrangement. Trifluoromethanesulfonic anhydride (Tf_2O) was added to a solution of the corresponding sulfoxide and 2,6-lutidine in the relevant solvent at the indicated temperature. Typically, the reaction was completed in 2 min (TLC). Ice-cold water was added and the cooling bath was removed, allowing the mixture to warm to room temperature. The two layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 30 mL) unless otherwise indicated. The combined organic layers were dried, filtered, and concentrated in vacuo. The crude product was purified via flash column chromatography, eluting with the indicated solvent system.

General Procedure B for the Pummerer-like Reaction Promoted by PhI(CN)OTf. Initially, a small amount of PhI(CN)OTf (about 0.3 equiv) was suspended in the indicated solvent and cooled to the indicated temperature. 2,6-Lutidine was added, and the reaction flask was removed from the cooling bath for a few seconds to dissolve the base and then it was brought again to the indicated temperature. The substrate was dissolved in the indicated solvent and cannulated into the reaction mixture in a dropwise fashion. Further amounts of the iodonium reagent were added in small portions (0.3−0.5 equiv each) every 15 min until the starting material was fully consumed (TLC). Cold water was added, and the bath was removed, allowing the mixture to warm to room temperature. The two layers were separated, and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic

layers were dried, filtered, and concentrated in vacuo. The crude product was purified via flash column chromatography using the indicated solvent system.

Oxindole 10. *N*-Bromosuccinimide (16 mg, 0.09 mmol) was added to a solution of **9** (30 mg, 0.045 mmol) and sodium bicarbonate (8 mg, 0.09 mmol) in *t*-BuOH (340 μL)/H_2O (80 μL) and stirred for 15 h. The reaction solution was concentrated in vacuo, and the residue was purified by flash chromatography using 33% ether in hexanes as the eluent, providing 10 mg (33%) of the product, as a white solid: mp 82−85 °C (sublime); IR ($CDCl_3$) 3452, 1810, 1772, 1725 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.97 (m, 3H), 7.53 (m, 2H), 7.42 (m, 1H), 7.36 (m, 7H), 5.50 (d, J = 7.4 Hz, 1H), 5.35 (d, J = 9 Hz, 1H), 5.22 (d, J = 12 Hz, 1H), 5.09 (d, J = 12 Hz, 1H), 4.61 (m, 1H), 2.42 (s, 3H), 0.84 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 171.7, 156.0, 147.0, 146.6, 141.3, 136.0, 135.0, 132.7, 130.3, 129.0, 128.9, 128.3, 126.1, 125.9, 124.0, 114.3, 83.1, 78.4, 68.0, 57.9, 22.1, 17.9, 12.6; ESI *m/z* (relative intensity) 679.2 (M + H, 35), 696.3 (M + NH_4, 100), 701.2 (M + Na, 70); HRMS calcd for $C_{35}H_{42}N_2O_8SSi$ (M + NH_4) 696.2775, found 696.2778. Anal. Calcd for $C_{35}H_{42}N_2O_8SSi$: C, 61.92; H, 6.24; N, 4.13; S, 4.72. Found: C, 61.31; H, 6.13; N, 4.01; S, 4.68.

Benzyl [4a-Bromo-4-(*tert*-butyldimethylsilanyloxy)-2-oxo-9-(toluene-4-sulfonyl)-2,3,4,4a,9,9a-hexahydropyrano-[2,3-*b*]indol-3-yl]carboxylate (14). *N*-Bromosuccinimide (250 mg, 1.5 mmol) was added to a solution of **13** (200 mg, 0.32 mmol) and $NaHCO_3$ (120 mg, 1.4 mmol) in *t*-BuOH (5.5 mL)/H_2O (1.3 mL) and stirred for 15 h. The reaction solution was concentrated in vacuo and purified by flash chromatography using 33% ether in hexanes as the eluent, providing 150 mg (67%) of lactone **14**, as a white solid: mp 92−95 °C; IR ($CDCl_3$) 3426, 1764, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.42 (m, 9H), 6.62 (s, 1H), 5.61 (d, J = 4.4 Hz, 1H), 5.23 (m, 3H), 4.32 (dd, J = 4.4, 1.4 Hz, 1H), 2.40 (s, 3H), 0.95 (s, 9H), 0.27 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 155.6, 145.3, 139.9, 135.8, 135.2, 131.9, 130.3, 130.0, 128.8, 128.6, 128.3, 128.1, 125.8, 124.9, 115.2, 98.1, 74.1, 67.5, 63.5, 54.3, 26.1, 21.9, 18.6, −3.5, −4.1; APCIMS *m/z* (relative intensity) 701.1 (M + H, 85), 703.1 (^{81}Br, 100); HRMS calcd for $C_{32}H_{37}BrN_2O_7SSi$ (M + H) 701.1352, found 701.1373. Anal. Calcd for $C_{32}H_{37}BrN_2O_7SSi$: C, 54.77; H, 5.31; N, 3.99; S, 4.57. Found: C, 54.76; H, 5.30; N, 3.91; S, 4.57.

Lactone 23 from Sulfide 21. Sulfide **21** (500 mg, 1.21 mmol) was cooled to −78 °C in CH_2Cl_2 (40 mL). 2,6-Lutidine (400 μL, 3.46 mmol) was added followed by PhI(CN)OTf (1.12 g, 2.96 mmol). The reaction solution was slowly warmed to room temperature and stirred there for 15 h. The reaction solution was added to water (25 mL), extracted with CH_2Cl_2 (3 × 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 2/1 hexanes/Et_2O as the eluent to yield 190 mg (38%) of **23** as a white solid (1:1 mixture of diastereomers).

Methyl 3-(2-Benzenesulfinyl-1*H*-indol-3-yl)-2-*tert*-butoxycarbonylaminopropionate (25). Trimethylsilyldiazomethane (2 M in hexanes, 808 μL, 1.62 mmol) was added to acid **21** (500 mg, 1.21 mmol) in benzene (5 mL) and methanol (5 mL). The reaction solution was stirred for 45 min and then concentrated in vacuo. The crude product was purified by flash chromatography using 1/2 ether/hexanes as the eluent to yield 330 mg (64%) of the methyl ester as a white solid: mp 104−106 °C; IR ($CDCl_3$) 3458, 1741, 1710 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.33 (m, 8H), 5.15 (d, J = 8.0 Hz, 1H), 4.66 (m, 1H), 3.61 (s, 3H), 3.44 (dd, J = 14.3, 5.5 Hz), 3.31 (dd, J = 14.3, 6.3 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.8, 155.3, 137.2, 136.6, 129.4, 128.1, 127.1, 126.3, 123.9, 123.8, 120.3, 119.5, 117.7, 111.2, 79.9, 54.3, 52.5, 28.4, 14.3; ESI *m/z* (relative intensity) 449.1 (M + Na, 100); HRMS calcd for $C_{23}H_{26}N_2O_4S$ 449.1511 (M + Na), found 449.1502.

The methyl ester (330 mg, 0.77 mmol) was cooled to 0 °C in CH_2Cl_2 (15 mL). *m*-Chloroperbenzoic acid (132 mg, 0.76 mmol) was added, and the reaction solution was stirred at 0 °C for 90 min. The reaction solution was added to $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 × 10 mL), washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 4/1 ether/hexanes as the eluent to yield 240 mg (71%) of **25** as a white solid (1:1 mixture of diastereomers): IR ($CDCl_3$) 3439, 1741, 1708 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 8.58 (s, 1H), 8.53 (s, 1H), 7.72 (m, 4H), 7.64 (m, 2H), 7.52 (m, 6H), 7.29 (m, 6H), 7.16 (m, 2H), 5.35 (d, J = 8.2 Hz, 1H), 5.24 (d, J = 8.0 Hz, 1H), 4.73 (m, 2H), 3.74 (s, 3H), 3.64 (s, 3H), 3.59 (d, J = 5.9 Hz, 1H), 3.50 (m, 3H), 1.46 (s, 9H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 173.2, 172.2, 155.3, 155.1, 143.3, 143.2, 137.8, 137.7, 134, 133.7, 131.2, 129.6, 129.5, 127.3, 127.2, 125.5, 125.2, 120.7, 120.6, 120.3, 120.2, 116.3, 115.8, 112.7, 112.6, 80.2, 80.1, 54.3, 54.2, 52.7, 52.6, 28.5, 28.4, 14.3; ESI *m/z* (relative intensity) 465.1 (M + Na, 100); HRMS calcd for $C_{23}H_{26}N_2O_5S$ 465.1460 (M + Na), found 465.1465.

Methyl 2-*tert*-Butoxycarbonylamino-3-(3-hydroxy-2-phenylsulfanyl-3*H*-indol-3-yl)propionate (26) and (23) from 25. Diisopropylethylamine (86 μL, 0.49 mmol) was added to a solution of **25** (88 mg, 0.20 mmol) in CH_2Cl_2 (8 mL) at −78 °C and stirred for 5 min. Trifluoroacetic anhydride (36 μL, 0.26 mmol) was added, and the reaction solution was slowly warmed to room temperature over 3 h and stirred there for 15 h. Additional diisopropylethylamine (86 μL, 0.49 mmol) and then trifluoroacetic anhydride (36 μL, 0.26 mmol) were added, and the reaction solution was stirred for 48 h. The reaction solution was added to water (10 mL), extracted with CH_2Cl_2 (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 1/1 ether/hexanes as the eluent to yield 52 mg (63%) of **23** as a white solid (1:1 mixture of diastereomers) and 29 mg (33%) of **26** as a white solid (1:1 mixture of diastereomers). **26**: IR ($CDCl_3$) 1745, 1714 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 8.00 (d, J = 12.2 Hz, 1H), 7.72 (m, 4H), 7.46 (m, 7H), 7.33 (m, 4H), 7.17 (m, 2H), 5.35 (bs, 1H), 5.09 (bs, 1H), 4.57 (bs, 1H), 4.25 (bs, 1H), 3.68 (s, 3H), 3.65 (s, 3H), 2.71 (dd J = 14.4, 5 Hz, 1H), 2.56 (dd, J = 14.6, 9.4 Hz, 1H), 2.34 (dd J = 14.4, 9.0 Hz, 1H), 2.26 (dd, J = 14.7 Hz, 3.6 Hz, 1H), 1.44 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 184.8, 172.4, 154.0, 153.9, 138.6, 134.8, 134.7 130.7, 130.5, 129.7, 129.6, 125.5, 125.3, 123.5, 123.0, 120.3, 86.6, 86.3, 80.8, 77.4, 52.8, 28.5 (2 carbons), 23.8; ESI *m/z* (relative intensity) 443.1 (M + H, 85), 465.1 (M + Na, 100); HRMS calcd for $C_{23}H_{26}N_2O_5S$ 443.1641 (M + H), found 443.1644.

Spiro Butyrolactone Thioimidate 31. A solution of **30** (20 mg, 0.043 mmol) in CH_2Cl_2 (1 mL) was cooled to −78 °C. 2,6-Lutidine (15 μL, 0.13 mmol) followed by PhI(CN)OTf (41 mg, 0.11 mmol) were added, and the reaction solution was slowly warmed to room temperature over 45 min and stirred there for 15 h. The reaction solution was added to water (3 mL), extracted with CH_2Cl_2 (3 × 5 mL), washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude products were purified by flash chromatography using 20% Et_2O in hexanes as the eluent to yield 8 mg (40%) of **31** as an orange oil: IR ($CDCl_3$) 2116, 1803, 1524 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 2H), 7.49 (m, 3H), 7.34 (m, 2H), 7.22 (m, 2H), 5.03 (d, J = 9.5 Hz, 1H), 4.56 (d, J = 9.5 Hz, 1H), 0.79 (s, 9H), 0.00 (s, 3H), −0.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 169.8, 154.7, 134.5, 134.0, 132.0, 129.9, 129.6, 126.9, 125.7, 122.8, 120.2, 93.2, 79.2, 63.6, 25.3, 17.7, −5.2, −5.9; ESI *m/z* (relative intensity) 467.1 (M + H, 100); HRMS calcd for $C_{23}H_{26}N_4O_3SSi$ (M + H) 467.1573, found 467.1591.

Oxindole 32. Cerium(IV) ammonium nitrate (42 mg, 0.077 mmol) was added to a solution of **31** (30 mg, 0.06 mmol) in CH_3CN/H_2O (4.5 mL, 5/1) and stirred for 15 h. The reaction

solution was extracted with EtOAc (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 1/1 hexanes/Et_2O as the eluent to yield 12 mg (50%) of **32** as a white solid: mp 128−130 °C; IR ($CDCl_3$) 3432, 2117, 1807, 1752 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.41 (m, 1H), 7.15 (m, 1H), 6.91 (d, J = 7.7 Hz, 1H), 4.93 (d, J = 5.1 Hz, 1H), 4.51 (d, J = 5.1 Hz), 0.87 (s, 9H), −0.06 (s, 3H), −0.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 170.1, 142.4, 132.1, 125.2, 123.9, 123.6, 110.8, 83.1, 79.9, 62.7, 25.4, 17.8, 0.2, −5.5; ESI *m/z* (relative intensity) 392.2 (M + NH_4, 100), 375.2 (M + H, 16); HRMS calcd for $C_{17}H_{22}N_4O_4Si$ (M + H) 375.1489, found 375.1454. Anal. Calcd for $C_{17}H_{22}N_4O_4Si$: C, 54.53; H, 5.92; N, 14.96. Found: C, 54.32; H, 5.94; N, 14.73.

***tert*-Butyl 2-Azido-3-(*tert*-butyldimethylsilanyloxy)-3-(2-phenylsulfanyl-1*H*-indol-3-yl)propionate (33).** *N*,*N*-Dimethylformamide di-*tert*-butyl acetal (232 μL, 0.97 mmol) was added to a solution of acid **30** (87 mg, 0.19 mmol) in toluene (3 mL). The reaction solution was brought to 55 °C and held there for 15 h. The reaction solution was added to water (5 mL), extracted with ethyl acetate (3 × 5 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 1/5 ether/hexanes as the eluent to yield 50 mg (52%) of **33** as a colorless oil: IR ($CDCl_3$) 3458, 2115, 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.06 (d, J = 7.7 Hz, 1H), 7.34 (m, 8H), 5.83 (d, J = 4.4 Hz, 1H), 3.70 (m, 1H), 1.40 (s, 9H), 0.94 (s, 9H), 0.09 (s, 3H), −0.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 137.2, 136.2, 129.8, 129.0, 127.6, 127.1, 124.0, 123.1, 121.9, 121.5, 121.0, 111.2, 83.1, 71.9, 69.0, 28.6, 26.2, 18.5, −4.3, −5.2; ESI *m/z* (relative intensity) 547.1 (M + Na, 100); HRMS calcd for $C_{27}H_{36}N_4O_3SSi$ 547.2175 (M + Na), found 547.2162.

***tert*-Butyl 2-Azido-3-(2-benzenesulfinyl-1*H*-indol-3-yl)-3-(*tert*-butyldimethylsilanyloxy)propionate (34).** Sulfide **33** (153 mg, 0.29 mmol) was cooled to 0 °C in CH_2Cl_2 (9 mL). *m*-Chloroperbenzoic acid (49 mg, 0.28 mmol) was added, and the reaction solution was stirred at 0 °C for 20 min. The reaction solution was added to satd $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 × 10 mL), washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 2/1 ether/hexanes as the eluent to yield 107 mg (70%) of **34** as a white solid (1:1 mixture of diastereomers) and 45 mg of recovered **33** (30%): IR ($CDCl_3$) 3430, 2115, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 7.94 (d, J = 8.0 Hz, 1H), 7.84 (m, 4H), 7.78 (d, J = 2.0 Hz, 1H), 7.49 (m, 3H), 7.44 (m, 3H), 7.41 (m, 3H), 7.34 (m, 2H), 7.23 (m, 2H), 7.14 (m, 2H), 5.84 (d, J = 3.6 Hz, 1H), 5.74 (d, J = 4.4 Hz, 1H), 3.57 (bs, 1H), 3.46 (bs, 1H), 0.94 (s, 18H), 0.94 (s, 9H), 0.86 (s, 9H), 0.17 (s, 3H), 0.07 (s, 3H), −0.01 (s, 3H), −0.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 167.6, 167.4, 143.8, 143.3, 137.6, 137.0, 136.8, 134.1, 132.4, 132.0, 131.8, 131.7, 129.7, 129.7, 128.8, 128.8, 126.6, 126.3, 126.3, 125.6, 125.2, 125.1, 121.1, 120.9, 119.4, 112.5, 83.5, 83.4, 70.3, 70.2, 68.7, 68.3, 28.1, 28.1, 18.4, 18.3, 0.2, −4.6, −5.2, −5.3**;** ESI *m/z* (relative intensity) 563.2 (M + Na, 100); HRMS calcd for $C_{27}H_{36}N_4O_4SSi$ 563.2124 (M + Na), found 563.2133.

Lactone 31 from 33. A solution of **33** (45 mg, 0.086 mmol) in CH_2Cl_2 (2.5 mL) was cooled to −78 °C. 2,6-Lutidine (37 μL, 0.32 mmol) followed by PhI(CN)OTf (51 mg, 0.13 mmol) were added, and the reaction solution was slowly warmed to room temperature over 45 min and stirred there for 15 h. The reaction solution was added to water (3 mL), extracted with ethyl acetate (3 × 5 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude products were purified by flash chromatography using 10% Et_2O in hexanes as the eluent to yield 8 mg (20%) of **31** as an orange oil.

Lactone 31 from 34. 2,6-Lutidine (17 μL, 0.15 mmol) was added to **34** (22 mg, 0.041 mmol) in CH_3CN (1 mL) and cooled to −40 °C. A solution of Tf_2O (17 μL, 0.10 mmol) in CH_3CN (1 mL) was added, and the reaction solution was stirred for 36 h. The reaction solution was added to satd $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (3 × 5 mL), washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude products were purified by flash chromatography using 1/4 ether/hexanes as the eluent to yield 7 mg (37%) of **31** as an orange oil.

***tert*-Butyl 2-*tert*-Butoxycarbonylamino-3-(*tert*-butyldimethylsilanyloxy)-3-(2-phenylsulfanyl-1*H*-indol-3-yl)propionate (36).** Trimethylphosphine (0.95 mL, 1 M in THF, 0.95 mmol) was slowly added to a solution of **35** (200 mg, 0.32 mmol) in THF (4 mL), and stirring was continued for 45 min. The reaction solution was cooled below −20 °C, BOC-ON (230 mg, 0.93 mmol) in THF (1 mL) was added, and the reaction solution was warmed to room temperature and stirred for 15 h. The reaction mixture was added to water (10 mL), extracted with CH_2Cl_2 (3 × 10 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 20% ether in hexanes as the eluent, providing 160 mg (72%) of the Boc protected amine as a colorless oil: IR ($CDCl_3$) 3550, 1743, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.84 (m, 2H), 7.51 (m, 4H), 7.38 (m, 6H), 5.94 (d, J = 2.6 Hz, 1H), 5.72 (d, J = 9.8 Hz, 1H), 5.26 (s, 2H), 4.72 (dd, J = 9.8, 2.3 Hz, 1H), 3.76 (s, 3H) 1.14 (s, 9H), 0.86 (s, 9H), −0.07 (s, 3H), −0.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 155.5, 151.2, 138.1, 137.3, 134.7, 133.3, 131.2, 129.6, 129.2 (2 carbons), 128.9, 128.7, 128.5, 126.4, 126.1, 125.7, 123.0, 115.7, 80.5, 72.1, 69.2, 66.4, 52.7, 28.1, 25.8, 15.2, −3.5, −4.7; ESI *m/z* (relative intensity) 713.2 (M + Na, 90); HRMS calcd for $C_{37}H_{46}N_2O_7SiS$ 713.2693 (M + Na), found 713.2673.

The Boc-protected amine (160 mg, 0.23 mmol) and LiOH·H_2O (33 mg, 0.79 mmol) were stirred for 15 h in THF/H_2O (15 mL, 4/1). The reaction mixture was acidified with 1 M HCl (5 mL), extracted with CH_2Cl_2 (3 × 5 mL), washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 50% ether in hexanes as the eluent, providing 31 mg (25%) of the acid as a yellow solid.

N,*N*-Dimethylformamide di-*tert*-butyl acetal (72 μL, 0.30 mmol) was added to a solution of the acid from above (31 mg, 0.057 mmol) in toluene (2 mL). The reaction solution was brought to 55 °C and held there for 15 h. The reaction solution was added to water (5 mL), extracted with ethyl acetate (3 × 5 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 1/5 ether/hexanes as the eluent to yield 50 mg (52%) of **36** as a colorless oil: IR ($CDCl_3$) 3692, 3458, 1712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (s,1H), 7.89 (d, J = 7.8 Hz, 1H), 7.23 (m, 7H), 7.10 (m, 1H), 5.66 (d, J = 3.1 Hz, 1H), 5.52 (d, J = 10 Hz, 1H), 4.44 (dd, J = 9.7, 3.1 Hz, 1H), 1.38 (s, 9H), 1.19 (s, 9H), 0.85 (s, 9H), −0.08 (s, 3H), −0.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 155.2, 136.9, 131.2, 131.0, 129.2, 129.0, 127.9, 127.0, 126.4, 126.3, 123.1, 119.9, 110.5, 81.6, 79.2, 70.8, 61.0, 28.3, 28.1, 25.8, 18.0, −4.7, −5.7; ESI *m/z* (relative intensity) 621.2 (M + Na, 100); HRMS calcd for $C_{32}H_{46}N_2O_5SiS$ 621.2794 (M + Na), found 621.2795.

Cyclic Carbamate 37. A solution of **36** (3 mg, 0.005 mmol) in CH_2Cl_2 (1 mL) was cooled to −78 °C. 2,6-Lutidine (2 μL, 0.017 mmol) followed by PhI(CN)OTf (3 mg, 0.008 mmol) were added,and the reaction solution was slowly warmed to room temperature over 45 min and stirred there for 15 h. The reaction solution was added to water (3 mL), extracted with ethyl acetate (3 × 5 mL), washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude products were purified by flash chromatography using 50% Et_2O in hexanes as the eluent to yield 2 mg (74%) of **37** as a colorless oil: IR ($CDCl_3$) 3691, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (m, 2H), 7.54 (m, 3H), 7.39 (m, 3H), 7.12 (td J = 7.1, 1.6 Hz, 1H), 5.93 (s, 1H), 4.71 (m, 1H), 4.68 (d, J = 2.6 Hz,

1H), 1.60 (s, 9H), 0.80 (s, 9H), 0.00 (s, 3H), −0.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 166.2, 154.2, 152.4, 135.8, 135.0, 131.1, 130.3, 129.9, 127.6, 127.0, 125.6, 120.2, 85.5, 77.6, 69.5, 58.3, 30.1, 26.3, 18.5, −4.0, −4.6; ESI *m/z* (relative intensity) 604.1 (M + Na); HRMS calcd for $C_{28}H_{36}N_2O_5SiS$ 563.2012 (M + Na), found 563.2018.

2-(Phenylthio)indolenine 42 from Sulfoxide 41. According to general procedure A, trifluoromethanesulfonic anhydride (52 μL, 0.309 mmol), allylsilane sulfoxide **41** (60.4 mg, 0.153 mmol), and 2,6-lutidine (54 μL, 0.464 mmol) in dry CH_2Cl_2 (30 mL) at −75 °C were combined. A bright yellow color was observed instantaneously, and the reaction was completed in 2 min as evidenced by TLC. The residual material was purified via flash column chromatography using 10% Et_2O in hexanes as eluent. The product indolenine **42**, 38.4 mg of a colorless oil that solidifies slowly upon standing, was isolated in 82% yield: mp 95−98 °C; IR (thin film) 1515 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74−7.66 (m, 2H), 7.53−7.43 (m, 5H), 7.29 (td, J = 7.6, 1.2 Hz, 1H), 7.09 (td, J = 7.5, 1.1 Hz, 1H), 4.98 (d, J = 1.7 Hz, 1H), 4.71 (d, J = 1.6 Hz, 1H), 2.73 (d, J = 13.1 Hz, 1H), 2.60 (d, J = 13.4 Hz, 1H), 2.37−2.27 (m, 1H), 2.13 (d, J = 13.2 Hz, 1H), 2.13−1.93 (m, 3H), 1.54 (d, J = 13.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.0, 154.4, 143.81, 143.78, 134.6, 129.5, 129.3, 128.7, 127.9, 124.4, 123.6, 119.8, 111.6, 60.2, 41.8, 34.2, 34.1, 23.0; APCIMS *m/z* (relative intensity) 306.1 (M + H, 100) 197.1 (M − PhS, 15); HRMS calcd for $C_{20}H_{19}NS$ (M + H) 306.1311, found 306.1296. Anal. Calcd for $C_{20}H_{19}NS$: C, 78.65; H, 6.27; N, 4.59; S, 10.50. Found: C, 78.78; H, 6.42; N, 4.62; S, 10.79.

2-(Phenylthio)indolenine 42 from Sulfide 40. Following general procedure B, sulfide **40** (16.8 mg, 0.040 mmol) in 4 mL of CH_2Cl_2 was added to a mixture of 2,6-lutidine (14 μL, 0.12 mmol) and PhI(CN)OTf (5.0 mg, 0.013 mmol) in 0.9 mL of CH_2Cl_2 at 0 °C. The remaining iodonium reagent (57 mg, 0.15 mmol) was added in small portions. The product **42** was isolated via flash column chromatography, eluting with 10% Et_2O−hexanes as a white solid, 8.1 mg (67%).

Oxindole 43. Cerium(IV) ammonium nitrate (133 mg, 0.243 mmol) was added in one portion to a solution of phenylthioindolenine **42** (73.7 mg, 0.241 mmol) in 1:5 water−CH_3CN (4.8 mL). The clear solution was stirred for 24 h, during which time the color changed from bright yellow to orange and back to yellow. The mixture was partitioned between water (10 mL) and EtOAc (10 mL), and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic fractions were dried with $MgSO_4$, filtered, and concentrated in vacuo. The yellow oily residue obtained was purified with flash column chromatography eluting with 50% Et_2O in hexanes. The oxindole **43** as a white solid (47.9 mg, 93%) was recovered: mp 119−121 °C; IR (thin film) 3212, 1708 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (br s, 1H), 7.42 (d, J = 7.4 Hz, 1H), 7.22 (tdd, J = 7.7, 1.2, 0.3 Hz, 1H), 6.98 (m, 2H), 4.91 (d, J = 1.6 Hz, 1H), 4.67 (d, J = 1.4 Hz, 1H), 2.66 (d, J = 13.6 Hz, 1H), 2.52 (dt, J = 13.4, 3.6 Hz, 1H), 2.29 (td, J = 12.3, 5.4 Hz, 1H), 2.16 (d, J = 13.3 Hz, 1H), 2.03 (td, J = 12.2, 4.7 Hz, 1H), 1.90 (m, 2H), 1.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.9, 144.3, 140.2, 134.6, 127.8, 125.4, 121.9, 111.2, 110.1, 49.9, 40.6, 34.2, 33.0, 22.6; APCIMS *m/z* (relative intensity) 214.1 (M + H, 100). Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57; O, 7.50. Found: C, 78.80; H, 7.19; N, 6.54.

2-(Phenylthio)indolenine 50 from Sulfoxide 48. Following general procedure A, trifluoromethanesulfonic anhydride (82 μL, 0.49 mmol) was added to a solution of sulfoxide **48** (117 mg, 0.244 mmol) and 2,6-lutidine (85 μL, 0.73 mmol) in dry CH_2Cl_2 (48 mL) at −75 °C. The residual material was purified via flash column chromatography, eluting with 20% Et_2O in hexanes. The product **50**, 56.9 mg (76%), was isolated as a white solid: mp 140 °C; IR (thin film) 1719, 1515 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.65 (m, 2H), 7.50−7.41 (m, 4H), 7.28 (ddd, J = 7.3, 1.3, 0.3 Hz, 1H), 7.18 (ddd, J = 7.5, 1.6, 0.7 Hz, 1H), 7.09 (ddd, J = 7.2, 1.2, 0.4 Hz, 1H), 2.92 (d, J = 14.0 Hz, 1H), 2.65 (m, 2H), 2.33 (m, 3H), 2.24 (dt, J = 14.1, 1.6 Hz, 1H), 1.69 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 183.5, 154.1, 142.4, 134.6, 129.59, 129.56, 128.6, 128.2, 124.5, 122.9, 120.2, 61.6, 47.5, 40.9, 33.2, 22.7; APCIMS *m/z* (relative intensity) 308.1 (M + H, 100); HRMS calcd for $C_{19}H_{17}NOS$ (M + H) 308.1104, found 308.1095. Anal. Calcd for $C_{19}H_{17}NOS$: C, 74.23; H, 5.57; N, 4.56; S, 10.43. Found: C, 73.94; H, 5.69; N, 4.47; S, 10.47.

2-(Phenylthio)indolenine 50 from Sulfide 53. Following general procedure B, sulfide **53** (18.8 mg, 0.040 mmol) in 4 mL of CH_3CN was added to a mixture of 2,6-lutidine (14 μL, 0.12 mmol) and PhI(CN)OTf (8.0 mg, 0.021 mmol) in 0.5 mL of CH_3CN at 0 °C. The remaining iodonium reagent (8.0 mg, 0.021 mmol) was added in a single portion. The product **50** was isolated via flash column chromatography, eluting with 20% Et_2O in hexanes, 5.2 mg (42%).

2′-(Phenylsulfenyl)-3-(triisopropylsilanyloxy)spiro-[cyclohex-3-ene-1,3′-indole] and 2′-(Phenylsulfenyl)-3-(triisopropylsilanyloxy)spiro[cyclohex-2-ene-1,3′-indole (49). Following general procedure A, Tf_2O (15 μL, 0.09 mmol) was added dropwise to a solution of sulfoxide **48** (22.0 mg, 0.046 mmol) and 2,6-lutidine (16 μL, 0.14 mmol) in toluene (4.6 mL) at −75 °C. A mixture of compounds was obtained and separated via preparative TLC. The major product was indolenine **50** (5.4 mg, 39%), which was isolated along with the inseparable mixture of indolenines **49** (major and minor components) in 17.5% and 2.5% yield, respectively, as revealed by ^{1}H NMR: IR (thin film) 2866, 1516 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (m, 2H), 7.48−7.36 (m, 5H), 7.31−7.24 (m, 1H), 7.09 (td, J = 7.5, 0.8 Hz, 1H), 5.12 (s, 1H, major), 4.47 (s, 1H, minor), 2.77 (d, J = 17.2 Hz, 1H, major), 2.43−2.33 (m, 2H, major; m, 2H, minor), 2.05−1.97 (m, 1H, major; m, 4H, minor), 1.98 (d, J = 17.2 Hz, 1H, major), 1.46 (d, J = 10.8 Hz, 1H, major), 1.21 (m, 3H), 1.11 (d, J = 6.7 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.9, 154.3, 148.6, 144.1, 134.6, 129.5, 129.3, 128.6, 128.1, 124.3, 123.3, 119.7, 102.2, 58.6, 36.6, 30.2, 21.5, 18.3, 12.8; LRMS (APCI+) *m/z* (relative intensity) 464.3 (M + H, 100); HRMS calcd for $C_{28}H_{37}NOSSi$ (M + H) 464.2438, found 464.2416. Anal. Calcd for $C_{28}H_{37}NOSSi$: C, 72.52; H, 8.04; N, 3.02; S, 6.91. Found: C, 72.47; H, 7.84; N, 3.13; S, 6.94.

2-(Phenylthio)indolenine 70 from Sulfoxide 67. Following general procedure A, trifluoromethanesulfonic anhydride (19 μL, 0.113 mmol) was added to a solution of sulfoxide **67** (55% silyl ketene iminal, 61.9 mg, 0.055 mmol of silyl ketene iminal) and 2,6-lutidine (20 μL, 0.172 mmol) in dry CH_2Cl_2 (5.9 mL) at −75 °C. After 5 min, ice-cold water was added, and the cooling bath was removed, allowing the mixture to warm to room temperature. The residual material was purified via preparative thin-layer chromatography using 10% Et_2O in benzene as eluent. The desired product was obtained as a mixture of diastereomers (24.5 mg, 92%, 6.8:1 ratio of **70** to **71**). Major diastereomer **70** (white solid): mp 186−187 °C; IR (thin film) 1770, 1717, 1509 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.46−7.35 (m, 4H), 7.18−7.02 (m, 8H), 4.62 (ddd, J = 13.7, 6.8, 5.9 Hz, 1H), 4.22 (s, 1H), 3.99 (ddd, J = 13.6, 7.6, 5.7 Hz, 1H), 2.44 (m, 2H), 1.60 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.4, 169.4, 153.7, 153.1, 142.8, 134.2, 132.4, 130.7, 129.5 (two carbons), 128.7, 128.2, 127.8, 127.6, 124.9, 121.2, 119.8, 83.9, 62.8, 57.2, 42.4, 31.5, 28.3; APCIMS *m/z* (relative intensity) 485.3 (M + H, 100); HRMS calcd for $C_{29}H_{28}N_2O_3S$ (M + H) 485.1893, found 485.1872.

***tert*-Butyl [1-(*tert*-Butyldimethylsilanyloxy)-2-phenylvinyl]-[2-(2-phenylsulfenyl-1*H*-indol-3-yl)ethyl] Carbamate (66).** A mixture of sulfide **64** (259 mg, 0.532 mmol) and TBSCl (277 mg, 1.84 mmol) was dissolved in THF (5.3 mL) and treated with LiHMDS (1.0 M in THF, 4.25 mL, 4.25 mmol) at −75 °C. The reaction mixture was slowly warmed to 0 °C (over 3 h), and the solution was poured into ice-cold water. The aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography of the crude product using water-deactivated silica

(20 g water, 80 g silica) and eluting with 10% Et_2O in hexanes provided the desired product **66** as a yellow oil (240 mg, 75%) as a *Z*-double bond isomer: IR (thin film) 3309 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.75 (m, 1H), 7.40 (m, 2H), 7.32−7.21 (m, 4H), 7.20−7.07 (m, 5H), 7.07−7.02 (m, 2H), 5.30 (br s, 1H), 3.58 (m, 2H), 3.30 (m, 2H), 1.50 (s, 9H), 0.92 (s, 9H), 0.04 (s, 6H); LRMS (APCI+) *m/z* (relative intensity) 601.3 (M + H, 57), 545.2 (M + H − C_4H_8, 100), 501.2 (M + H − C_4H_8 − CO_2, 9).

2-(Phenylthio)indolenine 70 from Sulfide 66. Following general procedure B, sulfide **66** (40.5 mg, 0.067 mmol) in 3.4 mL of CH_2Cl_2 was added to a mixture of 2,6-lutidine (47 μL, 0.40 mmol) and PhI(CN)OTf (13.0 mg, 0.034 mmol) in 1 mL of CH_2Cl_2 at −78 °C. The remaining iodonium reagent (91 mg, 0.24 mmol) was added portionwise. The product was purified via preparative TLC using 10% Et_2O in benzene. The indolenines **70/71** were recovered as an inseparable mixture of diastereomers (17.9 mg, 55%, 3.2:1).

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Supporting Information Available: Copies of ^1H NMR and ^{13}C NMR spectra for compounds **8**, **12**, **13**, **22**−**26**, **30**, **31**, **33**, **34**, **36**, **37**, **42a**, **51**, **53**, **56**, **64**, **66**, **67**, and **72** and full experimental descriptions for the preparation of **8**, **9**, **11**−**13**, **21**−**23**, **28**−**30**, **39**−**41**, **42a**, **46**−**48**, **51**, **53**−**57**, **62**−**65**, **67**, and **72**. This material is available free of charge via the Internet at http://pubs.acs.org.

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