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Indolidenes and Indolidenium Intermediates in the Synthesis of Cyclopent[*b*]indoles: Mechanistic Studies on Intramolecular Cyclizations

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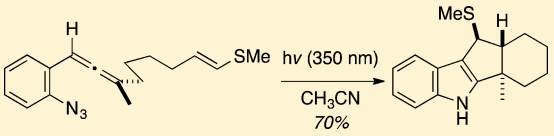
Supporting Information

ABSTRACT: Tetracyclic products featuring predominantly a *trans*-hexahydroindane unit annelated onto the C(2)/C(3) positions of indole can be accessed by intramolecular cyclocondensation of tethered alkenyl sulfides with either indolidene or indolidenium cation intermediates. Studies with geometrically pure *E*- and *Z*-alkenyl sulfide isomers reveal a likely dichotomy of reaction paths that provide mixtures of both regioisomers and stereoisomers of the hexahydroindane adducts.



INTRODUCTION

The Woodward–Hoffmann rules, as systemized in *The Conservation of Orbital Symmetry*,[1] have provided reliable guidance for the broad field of pericyclic reactions for over 50 years. Prompted by the rather brief but timelessly provocative Chapter 12 ("Violations. There are none!"), we sought to explore the possibility that a recently discovered formal $[10\pi + 2\pi]$ photochemical cycloaddition might, in actuality, be a concerted process under the Woodward–Hoffmann umbrella. Legitimate concerted photochemical processes are rare, and pericyclic transformations involving 12π electrons rarer still. Nevertheless, we probed this issue by asking the simplest and most fundamental question with our 12π electron system: Is alkene geometry preserved upon bond formation? This necessary but insufficient condition is a first step in probing concertedness; the experimental evidence is encouraging. The context of this inquiry is a recently reported photoinitiated cascade reaction sequence starting with allenyl azide substrates and passing through a putative indolidene intermediate en route to the $[10\pi + 2\pi]$ cycloaddition product.

Indolidenes and the related indolidenium cations are highly reactive intermediates that are susceptible to nucleophilic addition at the C(3) and C(8) positions (Figure 1). These

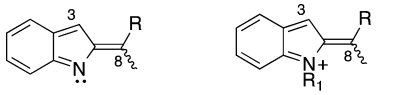


Figure 1. Indolidene and indolidenium electrophiles.

electrophilic species occasionally have been utilized for the formation of C–C bonded products at these positions; they typically have been formed as transient intermediates by removal of a leaving group at the C(8) position of an indole precursor through acid catalysis, rearrangements, and elimination reactions.[2,3,5]

Indolidene and indolidenium cation intermediates have played pivotal roles in the construction of complex natural products.[3,5] For example, the proposed intermediacy of indolidenes and indolidenium cations was first noted by Büchi in the acid-catalyzed condensation of voacangine with vobasinol for the synthesis of the alkaloids voacamine and voacorine.[3a] These highly electrophilic intermediates were reported to be unstable and not isolable. Further efforts through the years have been centered on the synthesis of vinblastine, an alkaloid currently used as a anticancer drug,[4] through the direct coupling of the naturally occurring catharanthine and vindoline via these reactive species.[3] However, it was not until 2009 that Boger et al. reported the use an $FeCl_3$-mediated single-step biomimetic coupling of catharanthine and vindoline via an indolidenium intermediate to generate vinblastine in moderate yield.[3k] Other natural products and their structural analogues also have been accessed through indolidene/indolidenium cation intermediates: actinophyllic acid,[2m,n] aspeverin,[5a] gilbertine,[5b] ibogaine,[3a,5c] mersicarpine,[2l] normacusine,[3a] tronoharine,[2p,5d] voacamine,[3a,5e] yuehchukene,[2e,5f,g] and yuremamine.[5h] In addition, the biomimetic syntheses of borreverine[5i,k] and isoborreverine,[5i] as well as flinderoles B and C,[5i–k] were achieved through dimerization via the intermediacy of these highly reactive species.

Our group has been interested in the preparation and C–C bond-forming processes of these indolidene and indolidenium intermediates. We initially identified novel conditions for the synthesis of indolidene intermediates via the thermolysis or photolysis of allenyl azide substrates (**3**) (Scheme 1).[6] This transformation is presumed to pass through the formation of triazoline intermediate **4**, which extrudes nitrogen to generate

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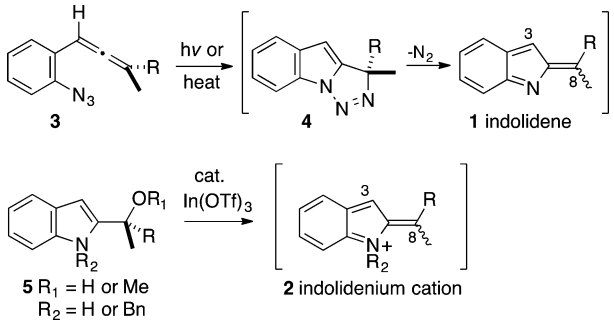
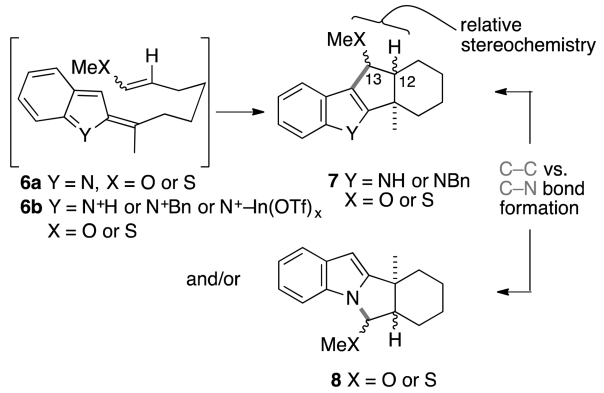
Scheme 1. Generation of Indolidene and Indolidenium Cation Reactive Intermediates



indolidene intermediate **1**. This reactive electrophile subsequently can be intercepted by nucleophiles at either the C(3) or C(8) positions. In addition, we have identified mild experimental conditions for the formation of the putative indolidenium intermediate **2** via the Lewis acid mediated solvolysis of 2-(methyl alcohol) derivatives **5** (Scheme 1).[7] A limitation of allenyl azide substrates **3** is that R ≠ H or the intermediate triazoline readily isomerizes to a triazole product.[6c]

Recently, we reported an intramolecular [3 + 2] cyclocondensation reaction that features the addition of nucleophilic alkenes to these electrophilic intermediates to form cyclopent[*b*]indoles **7** (Scheme 2).[7] Fundamental regiochemical and

Scheme 2. Scope of the Work: Regiochemistry and Stereochemistry of Cyclization as a Function of (a) Alkene Geometry, (b) Nature of X, and (c) Electrophilicity of the Activated Indole (Indolidene vs Indolidenium)



stereochemical questions, such as competition between C−C bond formation (to give **7**) and C−N bond formation (to give **8**), and the stereochemical preference at C(12) and C(13), were brought out in this preliminary investigation.

Herein, we examine the scope of the [3 + 2] cyclocondensation reaction, including the regiochemical and stereochemical outcome as a function of (1) alkene geometry, (2) nature of the nucleophilic alkene, and (3) the electrophilicity of the activated indole derivative. The cyclopent[*b*]indole product maps precisely onto the skeleton of the indolosesquiterpene family of natural products, as illustrated in the representative members lecanindole B[8] (**9**) and penitrem D[9] (**10**), Figure 2.

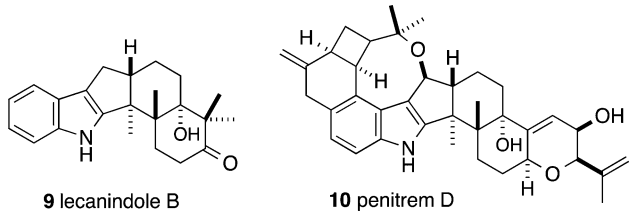


Figure 2. Representative terpene−indole alkaloids.

RESULTS

Substrate Syntheses. The alkenyl sulfide substrate **15a** required for the allenyl azide cyclization was synthesized from known aldehyde **11**[7] via a three-step procedure (Scheme 3). A Wittig reaction on **11** afforded the methyl vinyl sulfide adduct **12a** as a mixture of geometrical isomers in good yield. 2-Azidobenzaldehyde (**13**) was coupled with the anion derived from **12a**, and the resulting alkoxide was trapped with acetic anhydride to afford **14a** in very good yield. The alkenyl sulfide substrate **15a** was obtained by methylating alkyne **14a** using excess Me_2CuBr complex. Importantly, further reaction of the resulting allenyl azide with the organocuprate reagent was not observed. Two allenyl azide substrates with alternate pendant alkenes, the methyl vinyl ether analogue **15b** and a simple alkene **19**, also were accessed using the same approach as that employed for the alkenyl sulfide substrate **15a** (Scheme 3). The *N*-H-containing Lewis acid mediated cyclization precursors **16a** and **16b** were synthesized via either irradiation or thermolysis of their respective allenyl azide substrates **15a** and **15b** in methanol. In addition, the *N*-Bn substrate was prepared successfully by two distinct approaches; either via addition of lithiated indole **22**[10] to the ketone of **21** or by the direct benzylation of the *N*-H species **16b**.

Cyclization Studies. Irradiation of alkenyl sulfide **15a** (1.25:1 *E*/*Z* mixture) at 350 nm in CH_3CN afforded a mixture of products **25**−**27** (Scheme 4 and Table 1, entry 1). The major tricyclized product **25a** featured a C−C bond to C(3) with the *trans* hexahydroindane substructure favored over the *cis* ring juncture alternative (**25a** + **25b**:**25c**) by about 5:1. As a foundational experiment, this result demonstrated the feasibility of the [3 + 2] indolidene-based cyclocondensation sequence for the formation of cyclopent[b]indole products. The structural assignment for compounds **25a**−**c** was secured from a combination of NMR studies including HMBC, HMQC, and DEPT (Scheme 5). The relative stereochemistry of adducts **25a**−**c** was assigned on the basis of the comparison of the observed coupling constant values between H_a−H_b (Scheme 5) with the calculated values for this coupling derived from energy-minimized structures (see the Supporting Information for calculational details). In addition, the alkenyl sulfide moiety was removed from pure **25a** using Superhydride, and the spectral data for the reduced product **28a** were compared to the data reported for authentic **28a** and **28c**, which were prepared by different methods.[2h] A mixture of the *trans*- and *cis*-ring-fused diastereomers (**25a**/**25c** = 3.7:1) also was submitted to the reduction conditions, and the same ratio of *cis*-to-*trans* ring fused products was obtained for the desulfurized products **28a** and **28c** (Scheme 5). The preference for the *trans* stereochemistry at the ring junction addresses the challenges of synthesizing indole-fused *trans* hexahydroindanes, which are less thermodynamically stable than the *cis* isomers.[11]

This photochemical tricyclization reaction displayed a strong solvent effect. Irradiation in the less polar solvents toluene and

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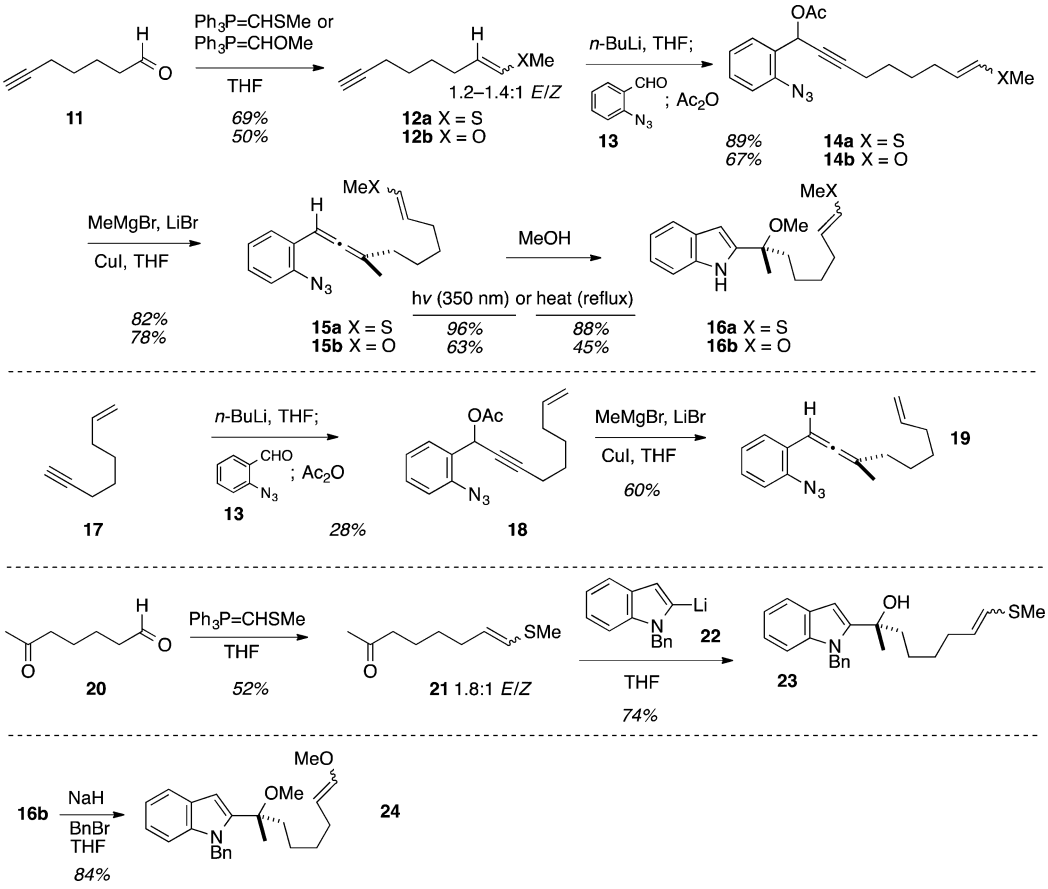
Scheme 3. Substrate Syntheses



Scheme 4. Photochemical [3 + 2] Cyclocondensation of Alkenyl Sulfide Substrate 15a

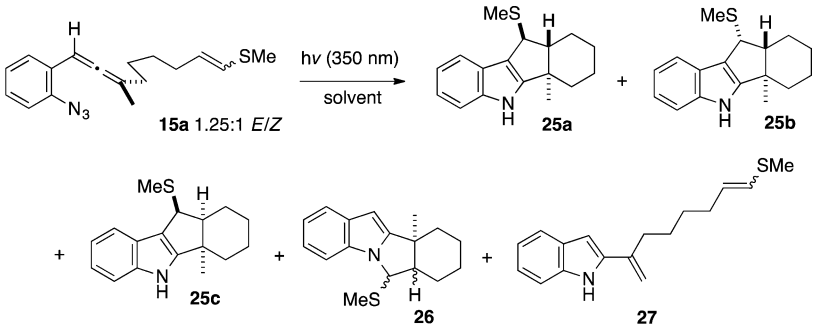


Table 1. Product Yields as a Function of Solvent for the Photochemical [3 + 2] Cyclocondensation of 15a

entry	solvent	25a[a]	25b[a]	25c[a]	26[b]	27[b]
1	CH_3CN	44	2	9	9	3
2	toluene	trace				20
3	CH_2Cl_2	trace			22	
4	DMF	trace				73

[a]Isolated yield of pure **25a**/**25b**/**25c** combined; ratio determined by integration of characteristic signals in the ^{1}H NMR spectrum. [b]Percent yield of isolated, pure products.

CH_2Cl_2 only led to trace amounts of the cyclopent[*b*]indole products (Table 1, entries 2 and 3). In addition, in the more polar solvent DMF, the tricyclized product was not isolated (Table 1, entry 4). Photochemical reaction in the preferred solvent CH_3CN at either lower temperature (0 °C instead of 28 °C as in entry 1) or lower concentration (3 mM vs 10 mM in entry 1) resulted in a mixture of products similar to those observed in entry 1. Inclusion of catalytic amounts of $In(OTf)_3$ or CuI,[6b] under entry 1 conditions, led to decomposition of the starting material, and no characterizable products were identified. Furthermore, the results obtained under thermal conditions did not resemble the results under photochemical conditions; upon reflux in CH_3CN, substrate **15a** was converted largely to the alkene product **27** (40% yield).

The sulfide unit of the nucleophilic alkene was a key component in the success of this [3 + 2] cyclocondensation reaction. In our initial studies, the methyl vinyl ether analogue **15b** was screened under photochemical conditions in CH_3CN, but no characterizable material was isolated. Moreover, when the simple alkene analogue **19** was employed, only a mixture of alkene products **29** was formed via a formal ene-type reaction

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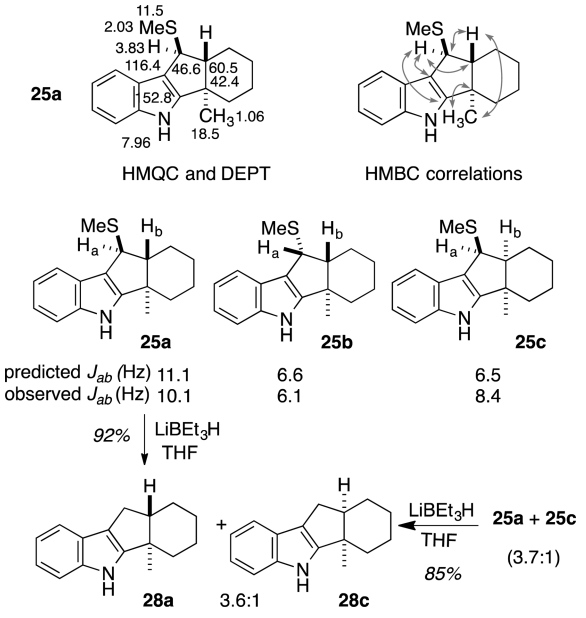
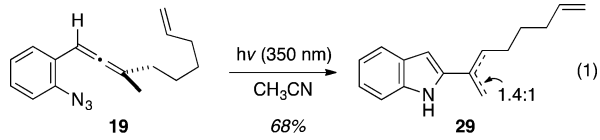
Scheme 5. Structural and Stereochemical Assignments for 25a–c

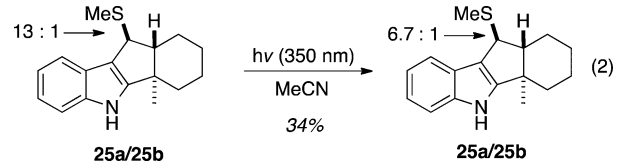


(eq 1). Apparently, there is a mismatch in reactivity between these alkene nucleophiles and the indolidene intermediate, which is overcome by switching to the sulfur analogue.

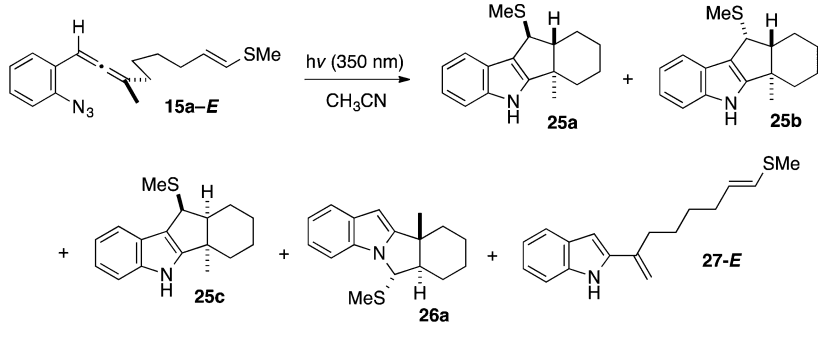


It is worth noting that the cyclization precursor **15a** was used as a mixture of *E* and *Z* isomers (1.25:1 *E*:*Z*). Thus, it was not possible to assess the role that alkene geometry might play in the reaction course. In order to probe this point, the mixture of *E*- and *Z*-alkenyl sulfide allenyl azide isomers **15a** was separated via column chromatography using silver nitrate impregnated silica gel[12] following by a separate chromatography on regular silica gel to remove trace Ag contaminants. Each purified isomer then was subjected to the cyclization conditions (Schemes 6 and 7) at the original 350 nm wavelength, and also, in separate runs, at 300 and 254 nm as well. To our surprise, irradiation of the strictly *E* isomer **15a-*E*** at 350 nm in CH_3CN provided the C–C bonded species **25a** as the predominant product in very good yield with enhanced control of stereochemistry and regiochemistry compared to the reaction of the original *E*/*Z* mixture of substrates (Scheme 6 and Table 2, entry 1). Switching to lower UV wavelengths (300 and 254 nm) also resulted in the formation of the C–C bonded product **25a** as the major product but with decreased yields (Table 2, entries 2 and 3, respectively). On the other hand, irradiation of the *Z* isomer **15a-*Z*** at all three wavelengths afforded the C–C-bonded products as a 1:1 mixture of *trans* (**25a**) and *cis* (**25c**) isomers in very low yields with a plethora of decomposition products (Table 2, entries 4–6). Thus, the encouraging results obtained upon irradiation of the original *E*:*Z* mixture of alkenyl sulfides was largely due to the favorable reactivity of the *E*-alkenyl isomer! The less clean results obtained for the *E*-alkenyl sulfide isomer under the 300 and 254 nm irradiations could be rationalized by examining the UV/vis absorption spectra for the indole-containing product **25a** (see the Supporting Information). The electronic spectrum of the C–C-bonded product **25a** exhibits significant UV absorption at both 254 and 300 nm but very little at 350 nm; thus, product destruction at the lower wavelengths is a real possibility. In fact, control experiments indicated that irradiation of pure **25a** at either 254 nm or at 300 nm led to complete compound destruction within 1 h, whereas only some decomposition of **25a** attended a similar experiment at 350 nm (vide infra).

The cyclization reactions for the *E*- and *Z*-alkenyl sulfide substrates **15a-*E*** and **15a-*Z***, respectively, also were monitored over time, and the results are depicted in Tables 3 and 4. After 30 min, there was 59% conversion of **15a-*E*** to the major C–C bonded product **25a** and only 18% of unreacted **15a-*E*** remained (Table 3, entry 1). At no point was any alkene isomer **15a-*Z*** detected. After 1 h, there was full consumption of the starting material and no formal "ene"-type product **27-*E*** was observed (Table 3, entry 4). When the reaction time was prolonged for an additional 1 h, significant decomposition products resulted. A control experiment showed that irradiation of a mixture of product diastereomers at the MeS-bearing carbon (**25a**:**25b**, 13:1) for 1 h led to a decreased ratio of the isomers (eq 2). Using triphenylmethane as an internal ^1H NMR standard revealed that both isomers **25a**/**25b** slowly decomposed under these conditions, but the major isomer **25a** appeared to decompose faster.



Scheme 6. Photochemical [3 + 2] Cyclocondensation of Pure *E*-Alkenyl Sulfide Substrate 15a-*E*



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Scheme 7. Photochemical [3 + 2] Cyclocondensation of Pure *Z*-Alkenyl Sulfide Substrate 15a-*Z*

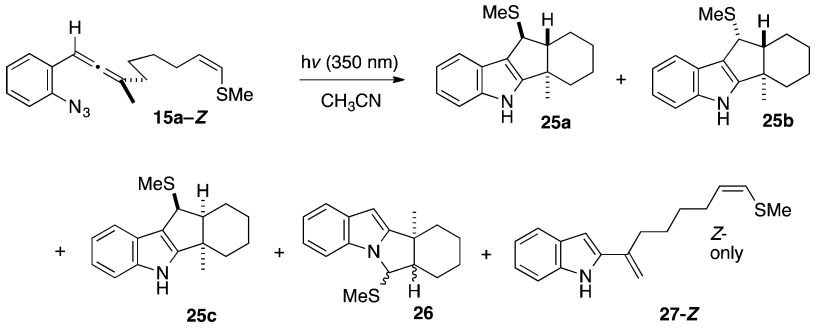

Table 2. Products Yields as a Function of Wavelength for the Photochemical [3 + 2] Cyclocondensation of Pure *E*-Alkenyl Sulfide 15a-*E*

entry	substrate	wavelength (nm)	25a[a]	25b[a]	25c[a]	26a[a]	27-*E* or 27-*Z*[a]
1	**15a-*E***	350	70	3	3	9	
2	**15a-*E***	300	50	3	3	13	2
3	**15a-*E***	254	42	trace	9	5	
4	**15a-*Z***	350	13	2	14	trace	3
5	**15a-*Z***	300	13	2	19	trace	2
6	**15a-*Z***	254	18	1	16	trace	4

[a]Percent yields determined by integration of the ^{1}H NMR spectra of the crude reaction mixtures relative to the internal standard 1,4-dimethoxybenzene.

Table 3. Products Yields as a Function of Reaction Time for the Photochemical [3 + 2] Cyclocondensation of Pure *E*-Alkenyl Sulfide Substrate 15a-*E*

entry	time (min)	15a-*E*[a]	15a-*Z*[a]	25a[a]	25b[a]	25c[a]	26[a]	27-*E*[a]
1	30	18		59	1	1	10	5
2	45	4		66	3	3	6	3
3	50	5		65[b]	5[b]	4[b]	3	4
4	60			70	3	3	9	

[a]Percent yields determined through integration of the ^{1}H NMR spectra of the crude reaction mixtures relative to the internal standard 1,4-dimethoxybenzene. [b]Isolated yield of pure **25a**/**25b**/**25c** combined; ratio by integration of characteristic signals in the ^{1}H NMR spectrum.

Table 4. Product Yields as a Function of Reaction Time for the Photochemical [3 + 2] Cyclocondensation of Pure *Z*-Alkenyl Sulfide Substrate 15a-*Z*

entry	time (min)	15a-*E*	15a-*Z*[a]	25a[a]	25b[a]	25c[a]	26[a]	27-*Z*[a]
1	30		8	10		11		6
2	60		trace	16	trace	20		12
3	120			13	2	14	trace	3

[a]Percent yields determined by integration of the ^{1}H NMR spectra of the crude reaction mixtures relative to the internal standard 1,4-dimethoxybenzene.

Intriguingly, the formal ene-type product **27-*E*** was observed at early time points while monitoring the time-course of the reaction (Table 3, entries 1–3), but after full consumption of the starting material, it was not detected (Table 3, entry 4). A control experiment indicated that decomposition was the issue, as submitting pure **27-*E*** to the reaction conditions resulted in significant destruction with no characterizable material isolated.

The photochemical reaction of **15a-*E*** also was monitored by taking the UV/vis absorption spectrum of the reaction mixture every minute. Unfortunately, there was no intermediate detected (see the Supporting Information). Thus, the putative indolidene species must be trapped rapidly and never builds up to any detectable concentrations. Attempts to trap this putative indolidene intermediate by spiking the reaction at an intermediate time point with MeOH, which has been shown to outcompete the alkenyl sulfide nucleophile (Scheme 3, **15a** → **16a**), also proved unsuccessful.

The cyclization reaction with the pure *Z*-alkenyl sulfide compound **15a-*Z*** also was monitored over time (Scheme 7). After 30 min, only 21% of the C–C bonded products were present along with 8% of unreacted starting material in addition to decomposition products (Table 4, entry 1). Furthermore, there was absolutely no isomerization of the *Z*-isomer **15a-*Z*** into the *E*-isomer **15a-*E***. The ratio of diastereomeric cyclized products did not change significantly over time and prolonging the reaction resulted in further decomposition. Moreover, there was practically no C–N-bonded products present throughout the reaction process with the *Z*-alkenyl sulfide substrate **15a-*Z*** (Table 4, entries 1–3) compared to a small but detectable amount in the *E*-isomer experiments (Table 3, entries 1–4). In both cases, C–C bond formation is strongly favored over C–N bond formation.

The indolidenium cation chemistry was explored via the Lewis acid-mediated cyclization of **16a** with catalytic amounts of indium triflate in a variety of solvents (Scheme 8). The methanol adduct **16a** was first exposed to indium triflate in toluene, and a mixture of C–C and C–N bonded products was obtained (Table 5, entry 1). Optimization studies revealed that more polar solvents, such as CH_2Cl_2 and CH_3CN, resulted in the formation of the desired C–C bonded products **25a**/**25b** (Table 5, entries 2 and 3). Replacing $In(OTf)_3$ with $Sc(OTf)_3$ led to essentially the same results (Table 5, entry 4 vs entry 3). A control experiment was designed to probe the possibility that isomer **26** was converted into isomer **25** under the reaction conditions in entries 2–4. Resubmitting pure *N*-cyclized product **26** to the same reaction conditions resulted in decomposition, demonstrating that not only did compound **26** fail to isomerize to the C-cyclized product **25**, but also that in these solvents, any C–N bonded product formed was immediately destroyed.

The stereochemistry at the ring junction of the C–C bonded products **25** was exclusively *trans* in toluene solvent. However, there appears to be some erosion of this selectivity in more polar solvents, although still favoring the *trans* stereochemistry at the ring junction (Table 5, entry 1 vs entries 2–4). Thus, the

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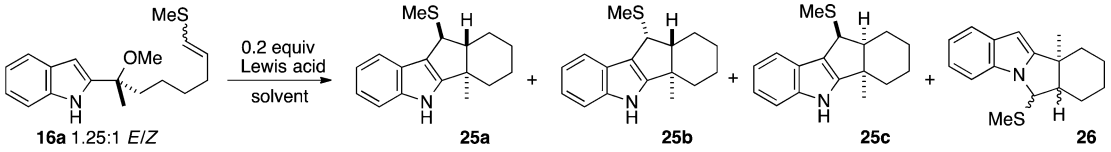
Scheme 8. Lewis Acid Mediated [3 + 2] Cyclocondensation of Alkenyl Sulfide Indole Substrate 16a



16a 1.25:1 *E*/*Z* 25a 25b 25c 26

Table 5. Product Yields as a Function of Lewis Acid and Solvent for the [3 + 2] Cyclocondensation of Alkenyl Sulfide Indole Substrate 16a

entry	acid (0.2 equiv)	solvent	25a[a]	25b[a]	25c[a]	26[b]
1	$In(OTf)_3$	toluene	46	6		38
2	$In(OTf)_3$	CH_2Cl_2	18	2	trace	
3	$In(OTf)_3$	CH_3CN	34	4	13	
4	$Sc(OTf)_3$	CH_3CN	37	5	13	

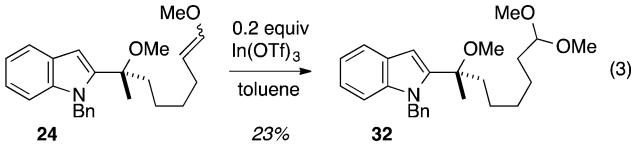
[a]Isolated percent yield of pure **25a**/**25b**/**25c** combined; ratio determined by integration of characteristic signals in the ^1H NMR spectrum [b]Percent yield of isolated, pure product.

results of this Lewis acid mediated cyclization seem to be strongly dependent on the choice of solvent.

Interestingly, when methyl vinyl ether nucleophile substrate **16b** was employed, the desired C−C-bonded product was not observed, even in trace amounts (Scheme 9). Instead, the C−N-bonded product **30** was obtained exclusively as a mixture of diastereomers. The stereochemistry of **30a**−**d** was assigned on the basis of the comparison of the observed coupling constant values between H_a−H_b (Scheme 9) to the calculated values for this coupling derived from energy-minimized structures.

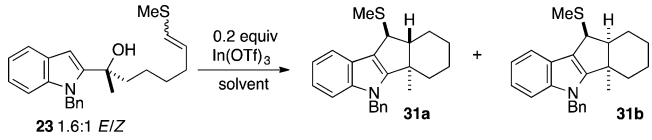
One obvious way to suppress the formation of the *N*-cyclized products in this indolidenium chemistry is to block the indole nitrogen (Scheme 10). Thus, this Lewis acid-mediated cyclization was performed with the *N*-benzylated substrate **23**. The alkenyl sulfide cyclization precursor **23** was exposed to indium triflate in CH_3CN, which resulted in a mixture of epimers **31a** and **31b** in excellent yield (Table 6, entry 1). In an attempt to improve the stereochemical outcome of the cyclization, the less polar solvents toluene and CH_2Cl_2 were screened as well, but they led to a decrease in both overall yield and stereoselectivity (Table 6, entries 2 and 3).

When the methyl vinyl ether equivalent of the *N*-benzylated substrate **24** was exposed to indium triflate, not even trace amounts of the C−C bonded products were observed. Instead, acetal **32** and an unknown dimer (MS and NMR identification) were the sole products isolated (eq 3). In order to suppress



24 23% 32

Scheme 10. Indium Triflate Mediated [3 + 2] Cyclocondensation of *N*-Benzylindole Alkenyl Sulfide Substrate 23



23 1.6:1 *E*/*Z* 31a 31b

Table 6. Product Yields as a Function of Solvent for the $In(OTf)_3$-Mediated [3 + 2] Cyclocondensation of *N*-Benzylindole Alkenyl Sulfide Substrate 23

entry	solvent	31a[a]	31b[a]
1	CH_3CN	61	24
2	toluene	30	12
3	CH_2Cl_2	25	19

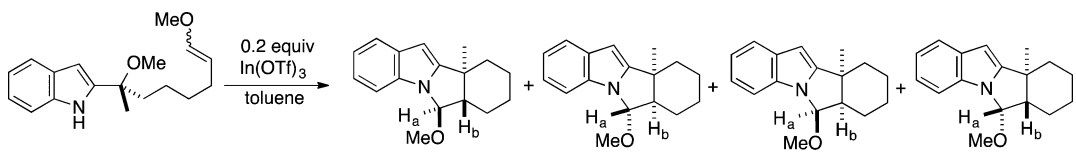
[a]Isolated percent yields of pure **31a**/**31b** combined; ratio determined by integration of characteristic signals in the ^1H NMR spectrum.

dimerization, the concentrations of the reactants were drastically reduced (80 to 4 mM), and although no dimerization was observed, the desired cyclization product could not be detected.

DISCUSSION

The interaction of a putative indolidene or indolidenium cation intermediate with the pendant alkenyl sulfide nominally produces a new C−C bond to C(8) and a new C−C (or C−N) bond to C(3) (or N). The overriding issue of concerted (but not synchronous) bond formation vs stepwise bond formation lies at the heart of any mechanistic description of the overall process. The strongest evidence that speaks to this issue derives from the observed stereochemical outcome of the reactions of the pure *E*- and *Z*-alkenyl sulfide isomers. At one extreme, both *E*- and *Z*-alkenyl sulfide isomers **15a** could be operating via a completely stepwise mechanism perhaps promoted by a photoinitiated single-electron transfer (SET) (Scheme 11). In this scenario, irradiation of **15a** would generate the indolidene intermediate **33** as a mixture of geometrical isomers, which might easily interconvert under irradiation; the calculated barrier to alkene isomerization in a similar model system is about 33 kcal/mol.[6c] In any event, either or both isomers **33**-*E* and **33**-*Z* could undergo

Scheme 9. Lewis Acid Mediated [3 + 2] Cyclocondensation of Enol Ether Indole Substrate 16b



16b 1.5:1 *E*/*Z* 30a 19% 30b 17% 30c 13% 30d 2%

	30a	30b	30c	30d
predicted J_{ab} (Hz)	8.8	5.4	1.0	4.3
observed J_{ab} (Hz)	8.5	5.6	1.0	4.9

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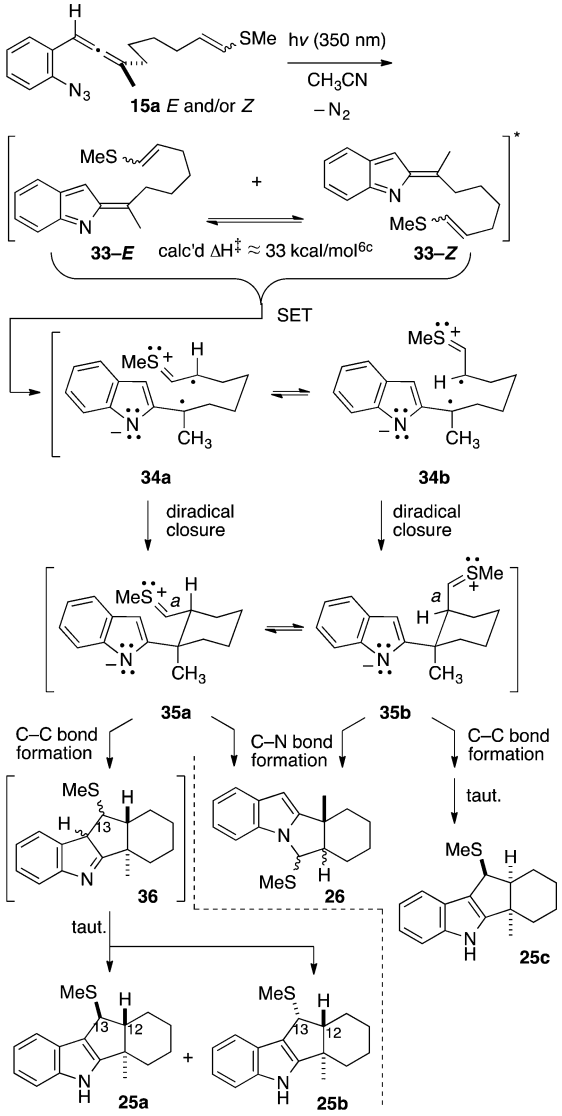
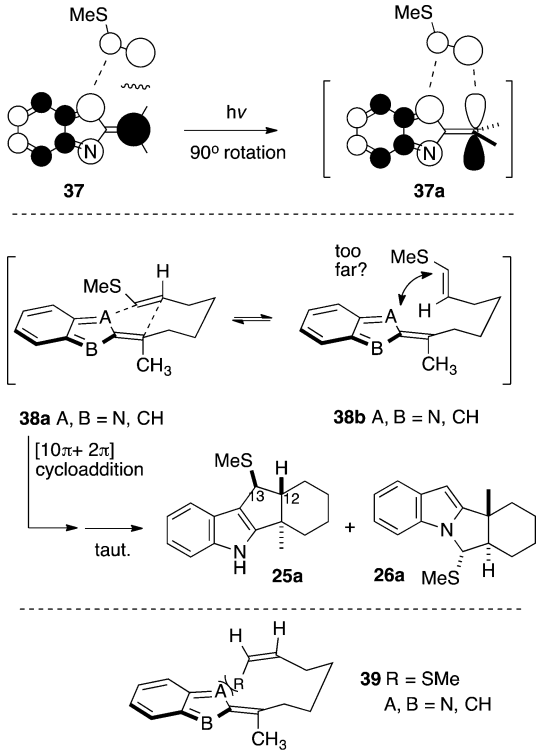
Scheme 11. Stepwise Single Electron Transfer Mediated Mechanistic Proposal for Indolidene Cyclization of 15a To Give Tetracyclic Products



photoinitiated single-electron transfer to arrive at the same singlet diradical indole-based zwitterionic species **34**. Continuing with this line of reasoning, this intermediate (**34**) can undergo diradical closure through either of two chairlike transition states extending from **34a** and **34b** to generate the dipolar intermediates **35a** and **35b**, respectively, featuring either a pseudoequatorial thionium cation appendage (e.g., **35a**) or a pseudoaxial thionium cation alternative (e.g., **35b**). The intervention of dipolar intermediates **35a** and **35b** in this SET-based mechanistic proposal is reminiscent of the proposed intermediates operating in the stepwise reaction of alkenes with fulvenes in a formal [6 + 2] manner.[13] Nucleophilic addition of either the indole C(3) carbon or the nitrogen to the sulfur-stabilized carbocation in **35** can result in the formation of cyclized products **25**/**26**, each as a mixture of stereoisomers derived from the newly formed C(12) and C(13) stereogenic positions.

An alternative and highly speculative concerted mechanistic pathway for the *E*-alkenyl sulfide isomer **15a-*E*** merits discussion as well; a formal (and unprecedented) [10π + 2π] photochemical cycloaddition. The basis for this claim lies with the observation that the major cyclized products (**25a** and **26a**) derived from **15a-*E*** retained the geometrical information on the starting alkene (Scheme 12). The LUMO of an indolidene,

Scheme 12. Alternative Mechanistic Proposal for the Indolidene-to-Tetracycle Transformation with the *E*-Alkenyl Substrate 15a-*E*; Possible Intervention of a Concerted Photochemical [10π + 2π] Cycloaddition



as modeled by the simple species **37** (DFT calculation at the B3LYP/6-31G** level with Jaguar V7.8, see the Supporting Information) displays an evident suprafacial symmetry mismatch with the alkenyl sulfide HOMO. However, computational studies by Dreyer and Klessinger on the photochemistry of fulvene suggest a workaround to this problem.[14] They propose that upon excitation fulvene undergoes an approximately 90° rotation about the exocyclic alkene to afford a singlet twisted "alkene". Extrapolating from this model to the related indolidene suggests that a twisted intermediate like **37a** may be accessible. This intermediate, by virtue of its geometry, then might allow sufficient orbital overlap with the alkene HOMO's lobes to achieve concerted but not necessarily synchronous bond formation at C(8) and C(3) (or at N), as illustrated in **38a**. Just the reverse of this cycloaddition process, the concerted (but asynchronous) discharge of N_2 from triazoline **4**, emerged as a viable pathway through computational analysis.[6d] Note that a pseudoaxial placement of the thioalkenyl moiety (e.g., **38b**) would not have the proper juxtaposition for the cycloaddition to occur with equal facility. This concerted pathway might be disfavored for the *Z*-alkene isomer **15a-*Z*** due to untoward steric interactions that could arise between the now pseudoequatorial methylthio appendage and the twisted indolidene moiety in the transition state (modeled as **39**). Thus, it is possible that the *Z* isomer **15a-*Z***, which loses alkene geometrical information upon cyclopentane formation, proceeds through a nonconcerted photoinitiated

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SET process, whereas the *E*-isomer might utilize an unprecedented concerted cycloaddition. In addition, since trace amounts of **25b** and **25c**, which do not retain the stereochemical information on the parent *E*-alkene, were also observed for the *E* isomer, it also could be possible that both the concerted and SET pathways are operating during the course of the **15a-*E*** reaction.

Many cycloadditions with total π electron counts greater than six have been reported;[13,15] both thermal and photochemical conditions have been described, and the evidence in each case for the claim of "cycloaddition" extends no further than noting that the alkene geometrical information on the starting materials is preserved in the products. The subset of higher π electron count 4n cycloaddition claims is much smaller, extending to a $[14\pi + 2\pi]$ thermal reaction of heptafulvene and tetracyanoethylene with the 14π component reacting in an antarafacial manner,[15a] the photochemically promoted $[6\pi + 2\pi]$ addition of singlet oxygen to an azepine,[15b] alkene/benzene $[6\pi + 2\pi]$ photocycloadditions,[15c] and a $[14\pi + 2\pi]$ thermal cycloaddition of dimethyl acetylene dicarboxylate with an annulene.[15d] Interestingly, $[10\pi + 2\pi]$ cycloadditions, promoted by either light or heat, have not yet been described.[16]

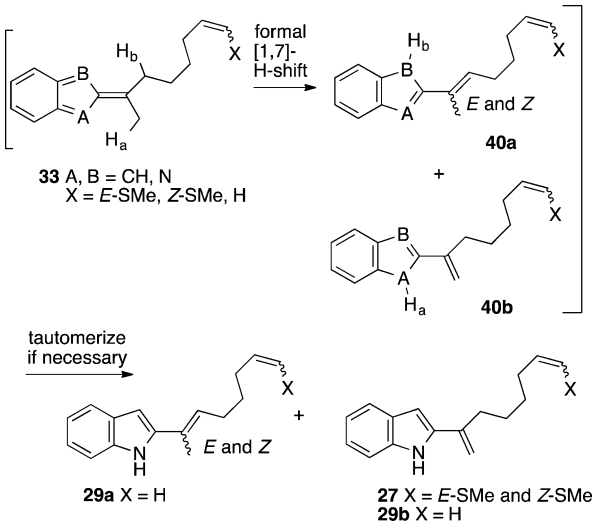
One interesting observation that emerges from the present work is that the product ratios upon reaction of the *E*-alkene isomer **15a-*E*** and the *Z*-alkene isomer **15a-*Z*** are very different. This divergence of results suggests that either (a) these starting materials do not converge in their mechanism to a common intermediate like **34** in the SET proposal or (b) they do converge, but C−C single-bond rotation in this putative common intermediate is slower than closure of the new C−C bond to C(3) (or C−N bond to nitrogen). These possibilities cannot be distinguished at present. If, in fact, C−C bond rotation is faster than ring closure, then (i) the *E*-alkene and the *Z*-alkene isomers must operate through a different mechanism, and (ii) the *Z*-isomer must operate through a stepwise process to account for the loss of alkene geometrical information. This circumstance builds supports the case that a concerted cycloaddition with the *E*-alkene isomer **15a-*E*** occurs upon irradiation.

The formation of the "ene" type product **27** is presumed to occur via a formal [1,7]-hydride shift of H_a (or H_b to form **29**) in the indolidene intermediate **33** to either the C(3) carbon or the nitrogen to afford a mixture of geometrical isomers (**27**/**29**) (Scheme 13). The rate of this formal "ene" type reaction seems to be slow compared to the addition of the alkene under photochemical conditions. If the alkene is not nucleophilic enough, however, the formation of the "ene" type product **27** is favored, as evidenced with the cyclization of the simple alkene nucleophile **19** (eq 1). With this substrate, the alkene isomer **29a** was formed as well.

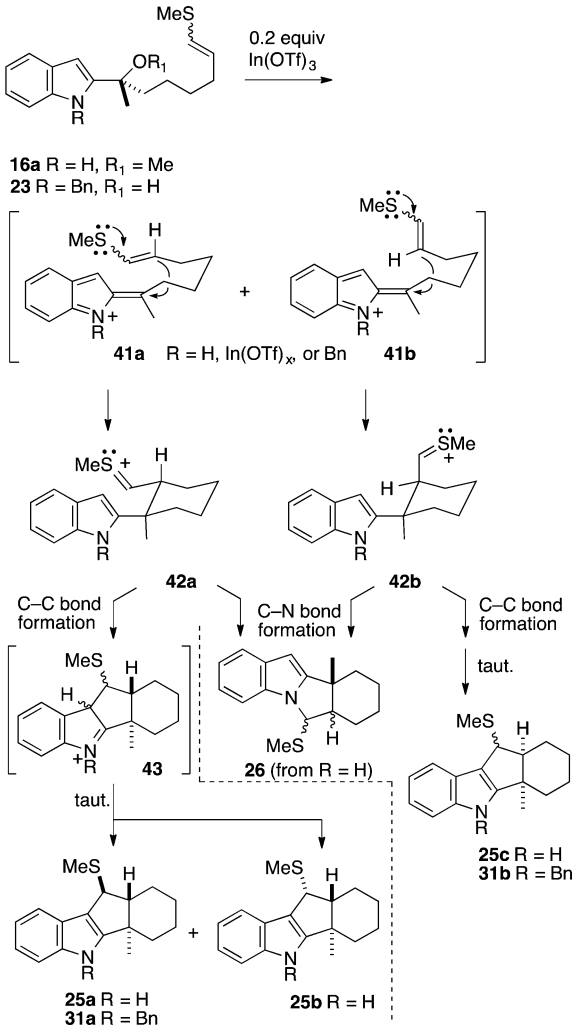
The results for the Lewis acid mediated cyclization can be accommodated by the formation of a putative indolidenium cation intermediate **41**, which then can be captured by either the pseudoequatorially or pseudoaxially aligned alkene nucleophile to afford the sulfur-stabilized cationic intermediate **42** (Scheme 14). This sulfur-stabilized carbocation **42** can be intercepted by either the C(3) carbon (for the R = H and R = Bn systems) or the nitrogen (for the R = H substrate) to generate cyclized products **25**/**26**/**31**, each as a mixture of stereoisomers.

The observed stereoselectivity for the *trans* isomer also can be attributed to the preference for the alkenyl sulfide moiety to reside in a pseudoequatorial position (e. g., **42a**) as opposed to the energetically disfavored pseudoaxial position (e. g., **42b**). Moreover, the exclusive formation of *N*-cyclized products with

Scheme 13. Proposal for the Formation of the Minor Formal "Ene" Products 27 and 29



Scheme 14. Mechanistic Proposal for the $In(OTf)_3$-Mediated Bicyclization of Substrates 16a and 23



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the oxygen-bearing substrate **16b** can be rationalized by noting that in the proposed intermediates **42a** and **42b** the "soft" sulfur-stabilized carbocation might be a better reactivity match for the softer C(3) carbon nucleophile compared to the "hard" oxocarbenium ion, which might prefer the "harder" *N* nucleophile.

In summary, we have demonstrated the utility of indolidene/indolidenium chemistry in [3 + 2] cyclocondensation reactions. We have identified the conditions necessary to perform successful bicyclizations and tricyclizations that likely proceed via indolidenium cation and indolidene intermediates, respectively. The results obtained for the geometrically pure *E*- and *Z*-alkenyl sulfide isomers speak to a possible dichotomy of mechanisms. The *E*-alkenyl sulfide allenyl azide cyclization proved to be a powerful transformation since it not only creates two C−C bonds, one C−N bond, and three fused rings, but it does so with control of both stereochemistry and regiochemistry, and in very good yield. Thus, this chemistry might prove useful for synthesis efforts directed toward the indolosesquiterpenes. Moreover, the remarkable stereoselectivity observed with the *E*-alkenyl sulfide isomer suggests the possibility that a new reaction, a $[10\pi + 2\pi]$ photochemical concerted cycloaddition, might be involved.

EXPERIMENTAL SECTION

General Methods. All reactions were performed using Schlenk glassware unless otherwise indicated. Solvents were purified by passage through activated alumina columns. All reagents were used as supplied without further purification unless otherwise noted. Chromatography specifying "deactivation by triethylamine" indicates that triethylamine was added to the eluent during column packing, after which the column was used with untreated eluent.

General Procedure 1: Irradiation of the Allenyl Azide. The allenyl azide substrate in the indicated solvent (10 mM) under a nitrogen atmosphere was irradiated in a Rayonet photoreactor at 350 nm for the indicated time, with TLC monitoring. When TLC indicated consumption of the starting material, the reaction mixture was concentrated in vacuo and purified by flash column chromatography with the indicated support/eluent.

General Procedure 2. Thermolysis of the Allenyl Azide. The allenyl azide in the indicated solvent (10 mM) was heated to reflux and held there, with TLC monitoring. When TLC indicated consumption of the starting material, the solution was concentrated in vacuo, and the product was purified via flash column chromatography with the indicated support/eluent to afford the indicated product.

General Procedure 3. Lewis Acid Mediated Cyclization. A solution of the substrate in the indicated solvent (40−50 mM) was added to a heterogeneous solution of 0.2 equiv of indium triflate in solvent at 0 °C under a N_2 atmosphere (final concentration of substrate: 30−40 mM). The resulting solution was allowed to stir for 1 h under N_2, and then a satd $NaHCO_3$ (aq) solution was added. The aqueous layer was extracted with Et_2O (3×), and the combined organic layers were washed with satd NaCl (aq), dried over Na_2SO_4, and concentrated in vacuo. The product was purified via flash column chromatography with the indicated support/eluent.

General Procedure 4. Removal of Thiomethyl Ether Unit. A 1 M Superhydride solution in THF (5 equiv) was added to a solution of the thiomethyl ether substrate in THF (37 mM) under a N_2 atmosphere. The resulting mixture was stirred for the indicated time, and then a satd NH_4Cl (aq) solution was added. The aqueous layer was extracted with Et_2O (3×), and the combined organic layers were washed with satd NaCl (aq), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via flash column chromatography with the indicated support/eluent.

*Hept-6-ynal (**11**).* To a room-temperature solution of hept-6-yn-1-ol (5.0 g, 45 mmol) in 600 mL of a 2:1 mixture of CH_2Cl_2/DMSO was added triethylamine (31.0 mL, 220 mmol) followed by sulfur trioxide pyridine complex (28.4 g, 178 mmol). The reaction solution was stirred at room temperature for 1 h, at which time the reaction mixture was washed with satd $CuSO_4$ (aq) (2 × 200 mL), distilled water (2 × 200 mL), and satd NaCl (aq) (2 × 200 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash column chromatography, using 10% ethyl acetate in hexanes as eluent, to afford 4.27 g (87%) of alkynal **11** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 2.42 (td, J = 7.2, 1.2 Hz, 2H), 2.16 (td, J = 7.0, 2.6 Hz, 2H), 1.92 (t, J = 2.6 Hz, 1H), 1.81−1.71 (m, 2H), 1.60−1.52 (m, 2H). Spectral data are in agreement with the values published.[17]

*Methyl(oct-1-en-7-yn-1-yl)sulfane (**12a**).* To a 0 °C suspension of ((methylthio)methyl)triphenylphosphonium chloride (9.94 g, 27.7 mmol) in 100 mL of THF was added 1.8 M PhLi in dibutyl ether (14.7 mL, 26.5 mmol). The reaction mixture was allowed to stir for 30 min and then a solution of alkynal **11** (2.77 g, 25.2 mmol) in 100 mL of THF was added dropwise. The resulting suspension was allowed to stir for 3 h at 0 °C, at which time a satd solution of NH_4Cl (aq) (100 mL) was added. The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with satd NaCl (aq) (100 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash column chromatography, using hexanes as eluent, to afford 2.49 g (69%) of thio enol ether **12a** (1.25:1 *E*:*Z*) as a pale yellow oil: IR (neat) 3297, 2360 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, J = 15.0 Hz, 1H, *E* isomer), 5.89 (d, J = 9.4 Hz, 1H, *Z* isomer), 5.47 (m, 1H, *E* and *Z* isomers), 2.30−2.09 (m, 7H), 1.95−1.93 (m, 1H), 1.69−1.39 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.7, 127.2, 126.9, 124.0, 84.4, 68.2, 32.5, 28.5, 28.2, 27.8, 18.2, 17.0, 15.0; LRMS (ESI-TOF) m/z (relative intensity) 154.1 (9%, M); HRMS (ESI-TOF) m/z [M]$^+$ calcd for $C_9H_{14}S$ 154.0816, found 154.0820.

*1-Methoxyoct-1-en-7-yne (**12b**).* To a 0 °C solution of potassium *tert*-butoxide (6.53 g, 58.2 mmol) in 100 mL of THF was added (methoxymethyl)triphenylphosphonium chloride (22.7 g, 66.0 mmol). The mixture was allowed to stir for 15 min, and then a solution of alkynal **11** (4.27 g, 38.8 mmol) in 100 mL of THF was added dropwise. The resulting suspension was allowed to stir for 30 min at 0 °C, at which time the reaction mixture was washed with satd NH_4Cl (aq) (2 × 100 mL), distilled water (2 × 100 mL), and satd NaCl (aq) (2 × 100 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash column chromatography, after deactivation with 2% triethylamine, using 5% ethyl acetate in hexanes as eluent, to afford 2.7 g (50%) of enol ether **12b** (1.7:1 *E*:*Z*) as a pale yellow oil: IR (neat) 3298, 2163 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (d, J = 12.6 Hz, 1H, *E* isomer), 5.85 (dt, J = 6.2, 1.3 Hz, 1H, *Z* isomer), 4.73 (dt, J = 14.6, 7.3 Hz, 1H, *E* isomer), 4.29 (q, J = 7.2 Hz, 1H, *Z* isomer), 3.55 (s, 3H, *Z* isomer), 3.48 (s, 3H, *E* isomer), 2.21−2.13 (m, 2H), 2.10−2.00 (m, 1H), 1.96−1.88 (m, 2H), 1.55−1.43 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 146.2, 106.3, 102.4, 84.5, 68.1, 59.4, 55.7, 29.7, 28.7, 27.9, 27.7, 27.1, 23.1, 18.2; LRMS (ESI-TOF) m/z (relative intensity) 139.1 (44%, M + H$^+$); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_9H_{15}O$ 139.1123, found 139.1117.

*2-Azidobenzaldehyde (**13**).* A solution of 2-nitrobenzaldehyde (7.0 g, 46 mmol) and sodium azide (9.0 g, 140 mmol) in 60 mL of DMF was heated to 60 °C and held at that temperature for 96 h. The reaction mixture was diluted with Et_2O, and the aqueous layer was washed with dichloromethane (5 × 30 mL). The combined organic layers were washed with satd NaCl (aq) (2 × 30 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography, using 0−20% ethyl acetate in hexanes as eluent, to afford 5.60 g (83%) of azidoaldehyde **13** as a pale yellow crystalline solid: mp 32−33 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.23 (s, 1H), 7.79 (dd, J = 7.7, 1.5 Hz, 1H), 7.55 (m, 1H), 7.17 (m, 2H). Spectral data are in agreement with the values published.[18]

*1-(2-Azidophenyl)-9-(methylthio)non-8-en-2-yn-1-yl Acetate (**14a**).* To a solution of thio enol ether **12a** (1.25:1 *E*/*Z*, 2.60 g, 17.1 mmol) in 250 mL of THF at −78 °C was added 2.5 M *n*-BuLi in hexanes (7.5 mL, 19 mmol). The reaction mixture was allowed to stir for 1 h at −78 °C, at which time a solution of azidoaldehyde **13** (2.51

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g, 17.1 mmol) in 75 mL of THF was added dropwise. The resulting solution was allowed to stir for 2.5 h at 0 °C, at which time acetic anhydride (2.0 mL, 19 mmol) was added. The reaction mixture was allowed to stir and warm to room temperature overnight. A saturated solution of NH_4Cl (aq) (100 mL) was added to the reaction mixture, the aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with satd NaCl (aq) (100 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using 5% ethyl acetate in hexanes as eluent to afford 5.20 g (89%) of thio alkynyl azide **14a** (1.25:1 *E*:*Z*) as a viscous light orange oil: IR (neat) 2123, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 7.5 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.18 (m, 2H), 6.61 (s, 1H), 5.95 (d, J = 15.0 Hz, 1H, *E* isomer), 5.87 (d, J = 9.4 Hz, 1H, *Z* isomer), 5.52−5.35 (m, 1H, *E* and *Z* isomers), 2.27−2.21 (m, 5H), 2.14−2.08 (m, 5H), 1.55−1.46 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 137.7, 130.0, 129.2, 128.5, 128.2, 127.0, 123.9, 118.1, 88.0, 61.1, 32.4, 28.5, 28.4, 28.0, 27.8, 27.6, 20.9, 18. 6, 16.9, 14.9; LRMS (ESI-TOF) m/z (relative intensity) 344.1 (30%, M + H^+); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{22}N_3O_2S$ 344.1433, found 344.1430.

*1-(2-Azidophenyl)-9-methoxynon-8-en-2-yn-1-yl Acetate (**14b**).* To a solution of enol ether **12b** (1.7:1 *E*:*Z*, 2.70 g, 19.5 mmol) in 75 mL of THF at −78 °C was added 2.5 M *n*-BuLi in hexanes (8.3 mL, 21 mmol). The reaction mixture was allowed to stir for 45 min, at which time a solution of azidoaldehyde **13** (2.87 g, 19.5 mmol) in 75 mL of THF was cannulated into the reaction mixture. The resulting solution was allowed to stir for 2.5 h at −78 °C, at which time acetic anhydride (2.0 mL, 22 mmol) was added. The reaction mixture was allowed to stir and warm to room temperature overnight. The reaction solution was washed with satd NH_4Cl (aq) (2 × 50 mL), distilled water (2 × 50 mL), and satd NaCl (aq) (2 × 50 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography, after deactivation with 2% triethylamine, using 0−5% ethyl acetate in hexanes as eluent, to afford 4.27 g (67%) of alkynyl azide **14b** (1.7:1 *E*/*Z*) as a viscous light orange oil: IR (neat) 2128, 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, J = 7.6, 1.6 Hz, 1H), 7.39 (td, J = 7.9, 1.4 Hz, 1H), 7.18 (t, J = 7.8 Hz, 2H), 6.16 (t, J = 2.0 Hz, 1H), 6.27 (d, J = 12.6 Hz, 1H, *E* isomer), 5.87 (dt, J = 6.2, 1.5 Hz, 1H, *Z* isomer), 4.68 (dt, J = 14.6, 7.3 Hz, 1H, *E* isomer), 4.29 (q, J = 7.3 Hz, 1H, *Z* isomer), 3.56 (s, 3H, *Z* isomer), 3.49 (s, 3H, *E* isomer), 2.25 (dt, J = 7.1, 1.9 Hz, 2H), 2.09 (s, 3H), 1.93 (q, J = 7.2 Hz, 1H), 1.54−1.17 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 147.2, 146.3, 137.8, 130.1, 129.3, 128.6, 124.9, 118.2, 106.3, 102.5, 88.2, 61.2, 59.4, 55.8, 29.8, 28.8, 27.8, 27.6, 26.9, 23.1, 21.0, 18.6; LRMS (ESI-TOF) m/z (relative intensity) 328.1 (12%, M + H^+); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{22}N_3O_3$ 328.1661, found 328.1666.

*(9-(2-Azidophenyl)-7-methylnona-1,7,8-trien-1-yl)(methyl)-sulfane (**15a**).* To a solution of copper(I) iodide (28.7 g, 151 mmol) and lithium bromide (13.1, 151 mmol) in 2.0 L of THF at 0 °C was added 3 M methylmagnesium bromide in Et_2O (50.0 mL, 151 mmol). The reaction mixture was allowed to stir and warm to room temperature over 1 h, at which time thio alkynyl azide **14a** (1.25:1 *E*/*Z*, 5.17 g, 15.1 mmol) in 100 mL of THF was cannulated into the reaction mixture. The resulting solution was allowed to stir for 30 min. The reaction mixture was washed with satd NH_4Cl (aq) (2 × 200 mL), distilled water (3 × 200 mL), and satd NaCl (aq) (3 × 200 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography, after deactivation with 2% triethylamine, using 0−4% ethyl acetate in hexanes as eluent to afford 3.72 g (82%) of allenyl azide **15a** (1.25:1 *E*/*Z*) as a viscous yellow oil: IR (neat) 2116, 1950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 7.7 Hz, 1H), 7.23−7.18 (m, 1H), 7.13−7.04 (m, 2H), 6.31 (q, J = 2.6 Hz, 1H), 5.93 (d, J = 14.9 Hz, 1H, *E* isomer), 5.86 (d, J = 9.4 Hz, 1H, *Z* isomer), 5.53−5.36 (m, 1H, *E* and *Z* isomers), 2.25 (s, 3H, *Z* isomer), 2.20 (s, 3H, *E* isomer), 2.14−2.02 (m, 4H), 1.80 (d, J = 2.7 Hz, 3H), 1.56−1.42 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 135.9, 128.7, 127.5, 126.7, 124.7, 123.6, 118.4, 103.5, 88.2, 33.8, 32.9, 29.1, 28.9, 28.6, 27.0, 26.8, 18.7, 17.0, 15.0; LRMS (ESI-TOF) m/z (relative intensity) 272.1 (42%, M − N_2 + H^+); HRMS (ESI-TOF) m/z [M − N_2 + H]$^+$ calcd for $C_{17}H_{22}NS$ 272.1473, found 272.1476.

*Separation of E- and Z-Alkenyl Sulfide Isomers **15a**.* The *E*- and *Z*-alkenyl sulfide allenyl azide isomers were separated via column chromatography using silver nitrate impregnated silica gel[12] and 0−5% Et_2O in hexanes as the eluent. A second column chromatography was performed for each stereoisomer, using 100% hexanes as the eluent, to remove any trace amount of silver.

*(E)-(9-(2-Azidophenyl)-7-methylnona-1,7,8-trien-1-yl)(methyl)-sulfane (**15a-E**):* IR (neat) 2360, 2338, 2023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 7.7 Hz, 1H), 7.23−7.18 (m, 1H), 7.13−7.03 (m, 2H), 6.31 (s, 1H), 5.95 (d, J = 14.9 Hz, 1H), 5.44−5.35 (m, 1H), 2.20 (s, 3H), 2.14−2.02 (m, 4H), 1.79 (s, 3H), 1.56−1.42 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 136.1, 128.0, 127.6, 127.5, 127.4, 124.8, 123.8, 118.5, 103.6, 88.4, 33.8, 33.0, 29.2, 26.9, 18.8, 15.1; LRMS (ESI-TOF) m/z (relative intensity) 272.1 (27%, M − N_2 + H^+); HRMS (ESI-TOF) m/z [M − N_2 + H]$^+$ calcd for $C_{17}H_{22}NS$ 272.1473, found 272.1476.

*(Z)-(9-(2-Azidophenyl)-7-methylnona-1,7,8-trien-1-yl)(methyl)-sulfane (**15a-Z**):* IR (neat) 2116, 1950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 7.7 Hz, 1H), 7.23−7.18 (m, 1H), 7.13−7.04 (m, 2H), 6.31 (q, J = 2.6 Hz, 1H), 5.86 (d, J = 9.4 Hz, 1H), 5.53−5.45 (m, 1H), 2.25 (s, 3H), 2.14−2.02 (m, 4H), 1.80 (d, J = 2.7 Hz, 3H), 1.56−1.41 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 136.1, 128.8, 128.0, 127.6, 127.5, 126.9, 124.8, 118.5, 103.7, 88.3, 33.9, 29.0, 28.7, 27.2, 18.8, 17.2; LRMS (ESI-TOF) m/z (relative intensity) 272.1 (72%, M − N_2 + H^+); HRMS (ESI-TOF) m/z [M − N_2 + H]$^+$ calcd for $C_{17}H_{22}NS$ 272.1473, found 272.1461.

*Irradiation of E-Alkenyl Sulfide Isomer (**15a-E**).* Following general procedure 1, a solution of *E*-alkenyl sulfide **15a-*E*** (100 mg, 0.33 mmol) in 36 mL of acetonitrile was irradiated through Pyrex at 350 nm for 50 min and then concentrated in vacuo. The crude product was purified via basic Al_2O_3 flash chromatography using 0−8% ethyl acetate in hexanes as eluent to afford 0.067 g (74%) of **25** as a mixture of stereoisomers (**25a**/**25b**/**25c**, 16:1.3:1). In addition, 3% of the C−N-bonded product **26a**, 4% of the formal "ene"-type product **27**, and 5% of starting material **15a-*E*** also were isolated.

25a: IR (neat) 3396 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.82−7.79 (m, 1H), 7.34−7.31 (m, 1H), 7.17−7.15 (m, 2H), 3.83 (d, J = 10.0 Hz, 1H), 2.30−2.15 (m, 1H), 2.03 (s, 3H), 2.02−1.92 (m, 2H), 1.82−1.30 (m, 6H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 139.3, 124.6, 120.9, 120.1, 118.6, 116.4, 111.8, 60.5, 46.7, 42.4, 34.9, 26.8, 21.9, 21.2, 18.5, 11.5; LRMS (ESI-TOF) m/z (relative intensity) 272.1 (12%, M + H^+); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{22}NS$ 272.1473, found 272.1468.

26a: ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 7.0 Hz, 1H), 7.55 (d, J = 7.0 Hz, 1H), 7.15−7.04 (m, 2H), 6.13 (s, 1H), 4,95 (d, J = 10.3 Hz, 1H), 2.31−2.19 (m, 1H), 2.19−2.05 (m, 1H), 2.02−1.87 (m, 2H), 1.85 (s, 3H), 1.80−1.62 (m, 3H), 1.61−1.49 (m, 1H), 1.46−1.31 (m, 1H), 1.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 133.0, 132.4, 120.9, 120.8, 119.5, 110.6, 90.9, 63.9, 56.8, 40.2, 34.7, 26.2, 21.2, 20.9.1, 19.3, 9.9; LRMS (ESI-TOF) m/z (relative intensity) 272.1 (43%, M + H^+); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{22}NS$ 272.1473, found 272.1452.

*Irradiation of the E-Alkenyl Sulfide Isomer **15a-E** Monitored by UV/vis Absorption.* A diluted solution of the *E* isomer **15-*E*** in acetonitrile (estimate concentration: < 100 μM) was irradiated at 350 nm in a quartz cuvette and monitored every minute with a UV−vis absorption spectrophotometer (see the Supporting Information for the resulting graph of the absorption spectra over time). The cyclization reaction with the *Z* alkene was also monitored with the UV−vis absorption spectrophotometer, and the spectrum looked almost identical to the spectrum obtained for the *E* isomer.

*1-Azido-2-(9-methoxy-3-methylnona-1,2,8-trien-1-yl)benzene (**15b**).* To a solution of copper(I) iodide (24.8 g, 130 mmol) and lithium bromide (11.3 g, 130 mmol) in 1.5 L of THF at 0 °C was added 3 M methylmagnesium bromide in Et_2O (43.4 mL, 130 mmol). The reaction mixture was allowed to stir and warm to room temperature over 30 min, at which time alkynyl azide **14b** (1.7:1 *E*:*Z*, 4.27 g, 13.0 mmol) in 125 mL of THF was cannulated into the

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reaction mixture. The resulting solution was allowed to stir for 45 min. The reaction mixture was washed with satd NH_4Cl (aq) (2 × 500 mL), distilled water (10 × 500 mL), and satd NaCl (aq) (2 × 500 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography, after deactivation with 2% triethylamine, using 0−4% ethyl acetate in hexanes as eluent, to afford 2.88 g (78%) of allenyl azide **15b** (1.7:1 *E*:*Z*) as a viscous yellow/orange oil: IR (neat) 2117, 1951 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (dd, J = 7.7, 1.4 Hz, 1H), 7.21−7.07 (m, 3H), 6.31 (p, J = 3.1 Hz, 1H), 6.24 (d, J = 12.6 Hz, 1H, *E* isomer), 5.85 (dt, J = 6.2, 1.4 Hz, 1H, *Z* isomer), 4.69 (dt, J = 14.6, 7.3 Hz, 1H, *E* isomer), 4.31 (q, J = 7.3 Hz, 1H, *Z* isomer), 3.55 (s, 3H, *Z* isomer), 3.47 (s, 3H, *E* isomer), 2.10−2.05 (m, 3H), 1.80 (s, 3H), 1.52−1.28 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 147.0, 146.1, 135.9, 127.9, 127.4, 124.7, 118.3, 106.7, 103.7, 103.6, 102.9, 88.1, 59.4, 55.8, 33.8, 30.4, 29.4, 27.4, 27.1, 26.8, 23.6, 18.7; LRMS (ESI-TOF) m/z (relative intensity) 256.2 (63%, M − N_2 + H^+); HRMS (ESI-TOF) m/z [M − N_2 + H]$^+$ calcd for $C_{17}H_{22}NO$ 256.1701, found 256.1688.

*2-(2-Methoxy-8-(methylthio)oct-7-en-2-yl)-1H-indole (**16a**).* Method A: Following general procedure 2, a solution of allenyl azide **15a** (1.25:1 *E*:*Z*, 0.51 g, 1.7 mmol) in 175 mL of methanol was brought to reflux and held there for 84 h. At that time, concentration of the reaction mixture led to a crude product that was purified via SiO_2 flash chromatography using 5% ethyl acetate in hexanes as eluent to afford 0.46 g (88%) of methanol adduct **16a** (1.25:1 *E*/*Z*) as a viscous yellow oil. Method B: Following general procedure 1, a solution of thio allenyl azide **15a** (1.25:1 *E*/*Z*, 50.0 mg, 0.17 mmol) in 17 mL of methanol was irradiated through Pyrex at 350 nm for 1.8 h. The reaction mixture was concentrated in vacuo and purified as in method A: yield 23 mg (45%, 1.25:1 *E*/*Z*); IR (neat) 3307 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 7.1 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H), 6.35 (s, 1H), 5.92 (d, J = 15.0 Hz, 1H, *E* isomer), 5.83 (d, J = 9.4 Hz, 1H, *Z* isomer), 5.51−5.30 (m, 1H, *E* and *Z* isomers), 3.11 (s, 3H), 2.25 (s, 3H, *E* isomer), 2.19 (s, 3H, *Z* isomer), 2.07 (p, J = 6.9 Hz, 2H), 1.89 (q, J = 6.6 Hz, 2H), 1.59 (s, 3H), 1.37−1.10 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 135.8, 128.6, 128.1, 127.3, 126.7, 123.7, 121.7, 120.3, 119.5, 110.8, 100.7, 50.6, 40.7, 40.6, 32.9, 29.8, 29.1, 28.9, 23.5, 23.4, 22.1, 17.0, 15.0; LRMS (ESI-TOF) m/z (relative intensity) 304.2 (40%, M + H^+); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{26}NOS$ 304.1735, found 304.1723.

*2-(2,8-Dimethoxyoct-7-en-2-yl)-1H-indole (**16b**).* Method A: Following general procedure 2, allenyl azide **15b** (1.7:1 *E*/*Z*, 0.77 g, 2.7 mmol) in 50 mL of methanol was brought to reflux and held there for 120 h. At that time, concentration of the reaction mixture led to a crude product that was purified via SiO_2 flash chromatography, after deactivation with 2% triethylamine, using 10% ethyl acetate in hexanes as eluent, to afford 0.75 g (96%) of methanol adduct **16b** (1.7:1 *E*/*Z*) as a viscous yellow oil. Method B: Following general procedure 1, a solution of thio allenyl azide **15b** (1.7:1 *E*/*Z*, 50.0 mg, 0.18 mmol) in 17 mL of methanol was irradiated through Pyrex at 350 nm for 20 min. The reaction mixture was concentrated in vacuo and purified as in method A: yield 33 mg (63%, 1.7:1 *E*:*Z*); IR (neat) 3308 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 7.1 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.35 (d, J = 1.9 Hz, 1H), 6.23 (d, J = 12.6 Hz, 1H, *E* isomer), 5.83 (d, J = 6.2 Hz, 1H, *Z* isomer), 4.66 (dt, J = 12.6, 7.3 Hz, 1H, *E* isomer), 4.28 (q, J = 7.3 Hz, 1H, *Z* isomer), 3.55 (s, 3H, *Z* isomer), 3.45 (s, 3H, *E* isomer), 3.10 (s, 3H), 1.91−1.83 (m, 3H), 1.58 (s, 3H), 1.43−1.03 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 146.1, 142.3, 135.9, 128.1, 121.7, 120.3, 119.5, 110.8, 106.7, 102.8, 100.7, 59.4, 55.8, 50.5, 40.5, 31.0, 30.0, 27.5, 23.3, 22.1; LRMS (ESI-TOF) m/z (relative intensity) 288.2 (58%, M + H^+); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{26}NO_2$ 288.1964, found 288.1982.

*(9-(2-Azidophenyl)-7-methylnona-1,7,8-trien-1-yl)(methyl)-sulfane (**19**).* To a solution of alkene **17**[19] (0.21 g, 1.4 mmol) in 22 mL of THF at −78 °C was added 2.5 M *n*-BuLi in hexanes (0.56 mL, 1.4 mmol). The reaction mixture was allowed to stir for 30 min at −78 °C, at which time a solution of azidoaldehyde **13** (0.15 g, 1.4 mmol) in 5 mL of THF was added dropwise. The resulting solution was allowed to stir for 1.5 h at 0 °C, at which time acetic anhydride (0.16 mL, 1.7 mmol) was added. The reaction mixture was allowed to stir and warm to room temperature overnight. A saturated solution of NH_4Cl (aq) (10 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with satd NaCl (aq) (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using 0−5% ethyl acetate in hexanes as eluent to afford 0.12 g (28%) of **18** as a light yellow oil.

To a solution of copper(I) iodide (1.04 g, 3.36 mmol) and lithium bromide (0.474 g, 5.45 mmol) in 70.0 mL of THF at 0 °C was added 3.0 M methylmagnesium bromide in Et_2O (1.80 mL, 5.45 mmol). The reaction mixture was allowed to stir and warm to room temperature over 1 h, at which time substrate **18** (0.162 g, 0.545 mmol) in 7 mL of THF was added to the reaction mixture. The resulting solution was allowed to stir for 30 min and diluted with 50 mL of Et_2O. The reaction mixture was washed with satd NH_4Cl (aq) (2 × 200 mL), distilled water (3 × 200 mL), and satd NaCl (aq) (3 × 200 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using 100% hexanes as eluent to afford 0.082 g (60%) of allenyl azide **19** as a viscous yellow oil: IR (neat) 2120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 7.7 Hz, 1H), 7.23−7.18 (m, 1H), 7.13−7.04 (m, 2H), 6.31−6.22 (m, 1H), 5.88−5.67 (m, 1H), 5.05−4.85 (m, 2H), 2.13−1.90 (m, 4H), 1.80 (d, J = 2.7 Hz, 3H), 1.56−1.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 139.0, 136.1, 128.1, 127.6 (2), 124.9, 118.5, 114.5, 103.7, 88.4, 34.0, 33.7, 28.7, 27.1, 18.8; LRMS (ESI-TOF) m/z (relative intensity) 226.1 (43%, M − N_2 + H^+); HRMS (ESI-TOF) m/z [M − N_2 + H]$^+$ calcd for $C_{16}H_{20}N$ 226.1596, found 226.1604.

*8-(Methylthio)oct-7-en-2-one (**21**).* A solution of [(methylthio)-methyl]triphenylphosphonium chloride (0.97 g, 2.7 mmol) and 1.8 M PhLi in dibutyl ether (1.5 mL, 2.7 mmol) in 5 mL of THF was stirred at −78 °C for 45 min. This solution was added dropwise to a solution of alkynal **20**[20] (0.315 g, 2.46 mmol) in 10 mL of THF. The resulting suspension was allowed to stir for 2 h at room temperature, at which time a satd solution of NH_4Cl (aq) (15 mL) was added. The aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organic layers were washed with satd NaCl (aq) (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using 5% ethyl acetate in hexanes as eluent to afford 0.22 g (52%) of ketone **21** as a viscous light yellow oil (mixture of 2 isomers, *E*:*Z* 1.8:1): IR (neat) 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, J = 15.0 Hz, 1H, *E* isomer), 5.88 (d, J = 9.4 Hz, 1H, *Z* isomer), 5.53−5.38 (m, 1H, *E* and *Z* isomers), 2.43−2.41 (m, 2H), 2.25 (s, 3H, *Z* isomer), 2.21 (s, 3H, *E* isomer), 2.12−2.08 (m, 5H), 1.61−1.57 (m, 2H), 1.38−1.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3, 209.2, 128.4, 127.2, 127.0, 124.2, 43.6, 43.6, 33.0, 30.0, 29.1, 28.8, 28.5, 23.5, 23.4, 23.3, 17.2, 15.2; LRMS (EI-TOF) m/z (relative intensity) 172.1 (22%, M); HRMS (EI-TOF) m/z [M]$^+$ calcd for $C_9H_{16}OS$ 172.0922, found 172.0927.

*2-(1-Benzyl-1H-indol-2-yl)-8-(methylthio)oct-7-en-2-ol (**23**).* To a solution of 1-benzyl-2-bromo-1*H*-indole[21] (0.52 g, 1.8 mmol) in 75 mL of THF at −78 °C was added 2.5 M *n*-BuLi in hexanes (0.72 mL, 1.8 mmol) dropwise, and the mixture was warmed to 0 °C and stirred for 20 min. The reaction mixture was then cooled to −78 °C, and a solution of ketone **21** (0.26 g, 1.5 mmol, *E*/*Z* 1.8:1) in 5 mL of THF was cannulated into the reaction mixture. The resulting solution was warmed to room temperature and stirred for 3 h. A satd NH_4Cl (aq) solution (20 mL) was added at that time, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with satd NaCl (aq) (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using 5% ethyl acetate in hexanes as eluent to afford 0.42 g (74%) of alcohol **23** as a viscous yellow oil (mixture of 2 isomers, *E*/*Z* 1.8:1): IR (neat) 3402 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61−7.59 (m, 1H), 7.24−7.18 (m, 3H), 7.14−7.05 (m, 3H), 6.93 (d, J = 7.0 Hz, 2H), 6.46 (s, 1H), 5.93−5.81 (m, 2H), 5.71 (d, J = 17.4 Hz, 1H), 5.44−5.29 (m, 1H, *E* and *Z* isomers), 2.23 (s, 3H, *Z* isomer), 2.18 (s, 3H, *E* isomer), 1.99−1.81 (m, 4H), 1.73−1.68 (m, 4H), 1.43−0.96 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1,

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144.0, 138.9 (2), 138.6, 138.5, 128.7, 128.6, 127.5, 127.1 (2), 126.8 (2), 125.6, 123.7, 122.0, 121.9, 120.5, 119.8 (2), 110.2, 100.7, 100.6, 72.8, 48.3, 41.9 (2), 32.9, 29.5, 28.9 (3), 24.2 (2), 17.1, 15.1; LRMS (AP-TOF) m/z (relative intensity) 362.2 (59%, M − OH + H^+); HRMS (ESI-TOF) m/z [M − OH + H]$^+$ calcd for $C_{24}H_{28}NS$ 362.1942, found 362.1939.

*(S)-1-Benzyl-2-(2,8-dimethoxyoct-7-en-2-yl)-1H-indole (**24**).* A solution of substrate **16b** (0.132 g, 0.459 mmol) and KOH (0.077 g, 1.4 mmol) in 6.6 mL of DMF was stirred at 0 °C for 1 h. Benzyl bromide (82 μL, 0.69 mmol) was added, and the reaction mixture was allowed to stir at room temperature for 1 h. Water (5 mL) and diethyl ether (5 mL) were added, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with satd NaCl (aq) (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using 100% benzene as eluent to afford 0.145 g (84%) of the benzylated product **24** as a viscous light yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.63−7.59 (m, 1H), 7.27−7.18 (m, 3H), 7.13−7.07 (m, 3H), 6.97 (d, J = 7.0 Hz, 2H), 6.50 (s, 1H), 6.18 (d, J = 12.6 Hz, 1H, *E* isomer), 5.94, (dd, J = 17.4, 3.3 Hz, 1H), 5.81 (d, J = 6.2 Hz, 1H, *Z* isomer), 5.64, (d, J = 17.4 Hz, 1H), 4.63−4.54 (m, 1H, *E* isomer), 4.23 (q, J = 7.2 Hz, 1H), 3.53 (s, 3H, *Z* isomer), 3.45 (s, 3H, *E* isomer), 3.02 (s, 3H), 1.95−1.65 (m, 4H), 1.59 (s, 3H), 1.15−0.80 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 147.1, 146.1, 141.5, 141.4, 138.8, 138.6, 128.6, 127.2 (2), 126.9, 126.8, 125.9, 122.1, 122.0, 120.5, 119.8 (2), 110.4, 106.8, 103.8, 103.7, 103.0, 77.9, 59.5, 56.0, 50.7, 47.7, 40.3, 40.2, 30.9, 29.9, 27.6, 24.1, 23.9, 23.8, 23.1; LRMS (ESI-TOF) m/z (relative intensity) 378.2 (100%, M + H^+); HRMS (EIS-TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{32}NO_2$ 378.2433, found 378.2438.

*4a-Methyl-10-(methylthio)-1,2,3,4,4a,5,10,10a-octahydroindeno-[1,2-b]indole (**25a/25b/25c**), 10a-Methyl-6-(methylthio)-6a,7,8,9,10,10a-hexahydro-6H-isoindolo[2,1-a]indole (**26**), and 2-(8-(Methylthio)octa-1,7-dien-2-yl)-1H-indole (**27**).* In acetonitrile: Following general procedure 1, a solution of thio allenyl azide **15a** (1.25:1 *E*/*Z*, 50 mg, 0.17 mmol) in 17 mL of acetonitrile was irradiated through Pyrex at 350 nm for 2.5 h. The reaction mixture was concentrated in vacuo. The crude product was purified via basic Al_2O_3 flash chromatography using 0−4% ethyl acetate in hexanes as eluent to afford 26 mg (55%) of the C-cyclized products **25** as a viscous yellow oil (mixture of three isomers, 18:1:4, **25a**/**25b**/**25c**) as well as 1 mg (3%) of the alkene **27** and 4 mg (9%) of the *N*-cyclized products **26** as a mixture of three isomers. The major isomer **25a** was isolated via preparatory HPLC and fully characterized (vide infra). The isomers' relative stereochemistries were determined by the comparison of ^{1}H NMR coupling constants for H_a to predicted values. The predicted values were generated from structures optimized via molecular mechanics calculations. It is not possible to distinguish between the structures **25b** and **25c** by this method; however, a mixture of the three isomers were subjected to desulfurization conditions (vide infra) and the ^{1}H NMR spectral data of the reduction (desulfurization) product from **25c** was found to match those of the *cis*-fused isomer.[2h] In dichloromethane: yield 20% of the alkene product **27** (only trace amounts of the desired C-cyclized product were seen by ^{1}H NMR). In toluene: yield 22% of the *N*-cyclized product **26** as a mixture of 3 isomers (only trace amounts of the C-cyclized product were seen by ^{1}H NMR). Another stereoisomer of the *N*-cyclized product (labeled as **26b**) was isolated and fully characterized, but the ring juncture stereochemistry could not be assigned. In DMF: yield 73% of the formal "ene" product **27** (only trace amounts of the C-cyclized product were seen by ^{1}H NMR).

26b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (t, J = 7.0 Hz, 2H), 7.15−7.04 (m, 2H), 6.10 (s, 1H), 5.50 (d, J = 6.0 Hz, 1H), 2.70 (q, J = 6.3 Hz, 1H), 2.46 (s, 3H), 2.10−1.75 (m, 4H), 1.65−1.35 (m, 4H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 133.5, 133.0, 121.0, 120.9, 120.0, 119.9, 91.7, 70.1, 53.4, 40.3, 35.5, 27.0, 24.4, 24.1, 22.3, 18.0; LRMS (ESI-TOF) m/z (relative intensity) 272.1 (12%, M + H^+); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{22}NS$ 272.1473, found 272.1468.

27: IR (neat) 3395, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.21 (t, J = 7.1 Hz, 1H), 7.12 (t, J = 7.3 Hz, 1H), 6.57 (m, 1H), 6.02 (d, J = 15.0 Hz, 1H, *E* isomer), 5.91 (d, J = 9.4 Hz, 1H, *Z* isomer), 5.58−5.40 (m, 1H, *E* and *Z* isomers), 5.33 (s, 1H), 5.09 (s, 1H), 2.56−2.49 (m, 2H), 2.28 (s, 3H, *E* isomer), 2.23 (s, 3H, *Z* isomer), 2.22−2.13 (m, 2H), 1.70−1.60 (m, 2H), 1.56−1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 138.2, 136.5, 128.8, 127.0, 122.7, 120.8, 120.0, 110.7, 109.3, 101.0, 34.2, 29.0, 28.8, 28.6, 17.2; LRMS (ESI-TOF) m/z (relative intensity) 272.1 (36%, M + H^+); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{22}NS$ 272.1473, found 272.1461.

*Irradiation of the C−C-Bonded Product **25**.* A solution of the C-cyclized product **25a**/**25b** (0.021 g, 0.078 mmol) in 9.4 mL of acetonitrile was irradiated through Pyrex at 350 nm for 1 h and concentrated. Triphenylmethane (0.019 g, 0.078 mmol) was added as an internal standard and the ^{1}H NMR of the mixture showed significant decomposition. The major isomer **25a** appeared to decompose faster than the minor isomer **25b**, therefore changing the isomers ratio (13:1 → 6.7:1). ^{1}H NMR yield of **25a**/**25b**: 34%.

*4a-Methyl-10-(methylthio)-1,2,3,4,4a,5,10,10a-octahydroindeno-[1,2-b]indole (**25a/25b/25c**) and 10a-Methyl-6-(methylthio)-6a,7,8,9,10,10a-hexahydro-6H-isoindolo[2,1-a]indole (**26**).* In acetonitrile: Following general procedure 3, indole **16a** (77 mg, 0.25 mmol, 1.25:1 *E*/*Z*) in 6.5 mL of acetonitrile was cannulated into a suspension of indium triflate (0.029 g, 0.051 mmol) in 0.5 mL of acetonitrile at 0 °C. The resulting solution was allowed to stir for 1 h, and then a satd $NaHCO_3$ (aq) solution (5 mL) was added. The aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organic layers were washed with satd NaCl (aq) (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using 5% ethyl acetate in hexanes as eluent to afford 35 mg (51%) of the C-cyclized product as a mixture of 3 isomers (**25a**/**25b**/**25c**, 8:1:3) as a viscous yellow oil. In dichloromethane: yield 20% of the C-cyclized product as a mixture of two isomers (**25a**/**25b**, 8:1). In toluene: yield 52% of the C-cyclized product as a mixture of two isomers (**25a**/**25b**, 8:1) and 38% of the *N*-cyclized product **26** as a mixture of three isomers.

*2-(8-(Methylthio)octa-1,7-dien-2-yl)-1H-indole (**27**).* Following general procedure 2, allenyl azide **15a** (1.25:1, *E*/*Z*, 50.0 mg, 0.17 mmol) in 50 mL of acetonitrile was brought to reflux and held there for 20 h. At that time, concentration of the reaction mixture led to a crude product that was purified via basic Al_2O_3 flash chromatography using 2% ethyl acetate in hexanes as eluent to afford 0.018 g (40%, 1.25:1 *E*/*Z*) of the alkene **27** as a viscous yellow oil (only trace amounts of the cyclized product **25a** were observed by ^{1}H NMR).

*(4aR,10aS)-4a-Methyl-1,2,3,4,4a,5,10,10a-octahydroindeno[1,2-b]indole (**28a**).* Following general procedure 4, a 1 M Superhydride solution in THF (0.60 mL, 0.55 mmol) was added to a solution of the cyclized adduct **25a** (30 mg, 0.11 mmol) in THF (3 mL) under a N_2 atmosphere. The resulting mixture was stirred for 12 h at room temperature, and then a satd NH_4Cl (aq) solution (5 mL) was added. The aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with satd NaCl (aq) (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via basic Al_2O_3 flash chromatography using 5% ethyl acetate in hexanes as eluent to afford 23 mg (92%) of the desulfurized product **28a** as a viscous light yellow oil: IR (neat) 3402 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.49−7.44 (m, 1H), 7.35−7.30 (m, 1H), 7.12−7.07 (m, 2H), 2.73−2.66 (m, 1H), 2.47−2.31 (m, 2H), 2.04−1.98 (m, 1H), 1.88−1.82 (m, 1H), 1.74−1.65 (m, 4H), 1.50−1.30 (m, 2H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 139.3, 125.2, 120.3, 119.6, 118.6, 116.8, 111.6, 55.7, 42.2, 34.9, 28.0, 26.8, 24.7, 21.3, 17.1; LRMS (ESI-TOF) m/z (relative intensity) 226.2 (96%, M + H^+); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{20}N$ 226.1613, found 226.1596.

*4a-Methyl-1,2,3,4,4a,5,10,10a-octahydroindeno[1,2-b]indole (**28a/28c**).* Following general procedure 4, a 1 M Superhydride solution in THF (0.61 mL, 0.55 mmol) was added to a solution of the cyclized adduct **25** (33 mg, 0.12 mmol, 3.7:1 **25a**/**25c**) in THF (4 mL) under a N_2 atmosphere. The resulting mixture was stirred for 12 h at room temperature, and then a satd NH_4Cl (aq) solution (5 mL) was added. The aqueous layer was extracted with Et_2O (3 × 10 mL),

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and the combined organic layers were washed with satd NaCl (aq) (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via basic Al_2O_3 flash chromatography using 5% ethyl acetate in hexanes as eluent to afford 23 mg (85%) of the desulfurized product **28** as a mixture of two isomers (**28a**/**28c**, 3.6:1). The structural assignment of **28c** is based upon comparison of its ^{1}H NMR values to the ^{1}H NMR values of the authentic *cis*-fused isomer **28c** published by Harrison and co-workers.[2h]

*(E)-2-(Octa-2,7-dien-2-yl)-1H-indole (**29a**/**29b**).* Following general procedure 1, a solution of alkene **19** (10 mg, 0.039 mmol) in 4.0 mL of acetonitrile was irradiated through Pyrex at 350 nm for 1.5 h and then the solution was concentrated in vacuo. The crude product was purified via basic Al_2O_3 flash chromatography using 0−5% ethyl acetate in hexanes as eluent to afford 6.0 mg (68%) of the elimination product as a mixture of two inseparable regioisomers (**29a**/**29b**, 1.4:1): IR (neat) 2162 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.61 (q, J = 8.1 Hz, 1H), 7.34 (q, J = 8.0 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.10 (t, J = 7.3 Hz, 1H), 6.56 (s, 1H **29a**), 6.48 (s, 1H, **29b**), 5.90−5.77 (m, 1H), 5.53−5.59 (m, 1H, **29b** *E* or *Z* isomer), 5.45−5.35 (m, 1H, **29b** *E* or *Z* isomer), 5.32 (s, 1H, **29a**), 5.08 (s, 1H, **29a**), 5.05−4.92 (m, 2H), 2.55 (t, J = 7.6 Hz, 2H, **29a**), 2.45−2.35 (q, J = 7.5 Hz, 2H, **29b** *Z* or *E* isomer), 2.33−2.23 (q, J = 7.4 Hz, 2H, *Z* or *E* isomer), 2.20−2.04 (m, 2H for **29a**, and 5H for **29b**), 1.70−1.33 (m, 4H for **29a**, and 2H for **29b**); ^{13}C NMR (75 MHz, $CDCl_3$) δ **29a**: 140.1, 139.0, 138.2, 136.5, 128.9, 122.7, 120.8, 120.1, 114.6, 110.7, 109.2, 101.0, 34.3, 33.74, 28.8, 28.6; LRMS (ESI-TOF) m/z (relative intensity) 226.2 (38%, M + H$^+$); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{20}N$ 226.1596, found 226.1606.

*6-Methoxy-10a-methyl-6a,7,8,9,10,10a-hexahydro-6H-isoindolo-[2,1-a]indole (**30a**−**d**).* Following general procedure 3, a solution of methanol adduct **16b** (200 mg, 0.70 mmol) in 8 mL of toluene was added to a suspension of In(OTf)$_3$ (78 mg, 0.14 mmol) in 1 mL of toluene at 0 °C. The resulting solution was allowed to stir for 8 h. The reaction mixture was washed with satd $NaHCO_3$ (aq) (2 × 10 mL), distilled water (2 × 10 mL), and satd NaCl (aq) (2 × 10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via spherical SiO_2 flash chromatography, after deactivation with 2% triethylamine, using 0−5% ethyl acetate in hexanes as eluent to afford 91 mg (51%) of **30** as a pale yellow oil (mixture of four diastereomers in a ratio of 10:9:7:1, **30a**/**30b**/**30c**/**30d**). Compound **30b** was isolated and characterized (*vide infra*). The remaining isomers' identities were provisionally determined by the comparison of ^{1}H NMR coupling constants for H_a to predicted values. These values were generated from structures optimized via molecular mechanics calculations. LC−LRMS and LC−HRMS were employed to ensure that all isomers did indeed have the appropriate mass.

30b: IR (neat) 2359 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.14 (t, J = 7.0 Hz, 1H), 7.08 (t, J = 7.0 Hz, 1H), 6.14 (s, 1H), 5.47 (d, J = 5.6 Hz, 1H), 3.63 (s, 3H), 2.42 (m, 1H), 1.94−1.71 (m, 5H), 1.61−1.44 (m, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 133.2, 132.7, 120.7, 120.5, 119.6, 110.2, 91.5, 90.8, 58.3, 52.0, 38.3, 36.5, 23.5, 22.9, 22.4, 21.6; LRMS (ESI-TOF) m/z (relative intensity) 256.1 (100%, M + H$^+$, all isomers); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{22}NO$ 256.1701, found 256.1692.

*(4aR,10S,10aR)-5-Benzyl-4a-methyl-10-(methylthio)-1,2,3,4,4a,5,10,10a-octahydroindeno[1,2-b]indole (**31a**/**31b**).* In acetonitrile: Following general procedure 3, a solution of alcohol **23** (52 mg, 0.14 mmol, *E*/*Z* 1.6:1) in acetonitrile (3 mL) was added to a suspension of indium triflate (15 mg, 0.027 mmol) in 0.5 mL of acetonitrile at 0 °C. The resulting solution was allowed to stir for 15 min, and then Et_2O (5 mL) and a satd $NaHCO_3$ (aq) solution (5 mL) were added. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were washed with satd NaCl (aq) (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via SiO_2 flash chromatography using hexanes as eluent to afford 42 mg (85%) of the cyclized product as viscous yellow oil (mixture of two isomers, **31a**:**31b**, 2.6:1). In dichloromethane: yield 44% (**31a**/**31b**, 1.6:1). In toluene: yield 42% (**31a**/**31b**, 2.6:1).

31a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−7.90 (m, 1H), 7.30−7.25 (m, 3H), 7.17−7.08 (m, 3H), 7.05−6.98 (m, 2H), 5.34 (s, 2H), 3.88 (d, J = 10.0 Hz, 1H), 2.27−2.19 (m, 1H), 2.05 (s, 3H), 2.02−1.96 (m, 1H), 1.43−1.83 (m, 1H), 1.78−1.50 (m, 4H), 1.37−1.30 (m, 2H), 1.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 140.2, 138.0, 128.7, 127.4, 126.0, 124.6, 120.8, 119.8, 118.7, 115.8, 110.1, 60.7, 48.0, 46.5, 43.1, 35.4, 26.6, 21.9, 21.2, 18.1, 11.5; LRMS (ESI-TOF) m/z (relative intensity) 362.2 (59%, M + H$^+$); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{28}NS$ 362.1942, found 362.1948. A pure sample of **31b** could not be isolated; hence, its structural assignment is based upon analogy to the results of the nonbenzylated series. The tentative stereochemical assignment is based upon analysis at the MeS-C*H* coupling constant.

*1-Benzyl-2-(2,8,8-trimethoxyoctan-2-yl)-1H-indole (**32**).* Following general procedure 3, a solution of methanol adduct **24** (0.027 mg, 0.074 mmol) in 1 mL of toluene was added to a suspension of In(OTf)$_3$ (78 mg, 0.14 mmol) in 0.2 mL of toluene at −10 °C. The resulting solution was allowed to stir for 2 h at that temperature. A saturated solution of $NaHCO_3$ (aq) (5 mL) was added, the aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were washed with satd NaCl (aq) (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified via spherical SiO_2 flash chromatography using 0−5% ethyl acetate in hexanes as eluent to afford 7 mg (23%) of **32** as a clear oil. There were no trace amounts of the desired C−C bonded product: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.57 (m, 1H), 7.30−7.18 (m, 3H), 7.15−7.05 (m, 3H), 6.98 (d, J = 7.4 Hz, 2H), 6.49 (s, 1H), 5.94 (d, J = 17.5 Hz, 1H), 5.63 (d, J = 17.5 Hz, 1H), 4.27 (t, J = 5.7 Hz, 1H), 3.27 (s, 6H), 3.02 (s, 3H), 1.79 (t, J = 7.8 Hz, 2H), 1.59 (s, 3H), 1.48 (q, J = 7.2 Hz, 2H), 1.20−0.80 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 138.8, 138.6, 128.6, 127.2, 126.8, 125.9, 122.1, 120.5, 119.8, 110.4, 104.5, 103.8, 77.9, 76.8, 52.7, 52.6, 50.6, 47.7, 40.4, 32.5, 29.5, 24.6, 24.5, 23.1; LRMS (ESI-TOF) m/z (relative intensity) 410.2 (87%, M + H$^+$); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{36}NO_3$ 410.2695, found 410.2711.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01777.

Detailed calculation procedures, including prediction of coupling constants and determination of the molecular orbital for the LUMO of the indolidene; UV/vis absorption spectra for compounds **15a-*E***, **15a-*Z***, **25a**, and the *E* isomer **15a-*E*** irradiation over time; ^{1}H and ^{13}C NMR spectra for **12a,b**, **14a**, **14b**, **15a**, **15a-*E***, **15a-*Z***, **15b**, **16a,b**, **19**, **21**, **23**, **24**, **25a** (plus HMBC, HMQC, DEPT), **26a,b**, **27**, **28a**, **29a**/**b**, **30b**, **31a**/**b**, and **32** (plus DEPT) (PDF)

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Notes

The authors declare no competing financial interest.

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