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Development and Scope of the Arene-Fused Domino Michael/Mannich Reaction: Application to the Total Syntheses of *Aspidosperma* Alkaloids (−)-Aspidospermidine, (−)-Tabersonine, and (−)-Vincadifformine

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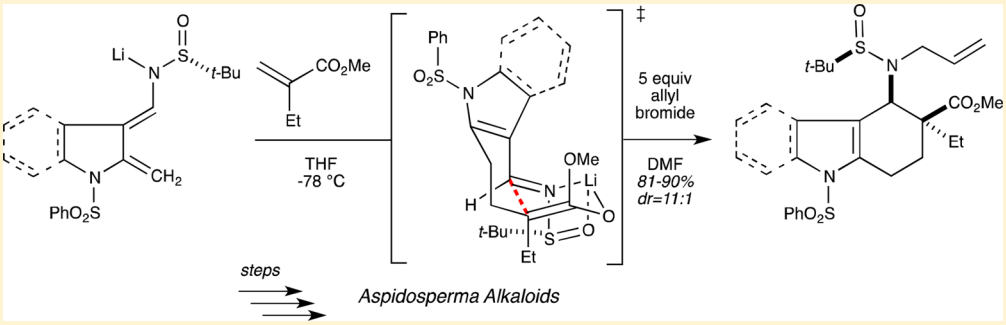
Supporting Information



ABSTRACT: The development and application of the arene-fused domino Michael/Mannich route to the tetrahydrocarbazole (ABE) core of *Aspidosperma* alkaloids is described. The scope of this novel transformation was studied in terms of the nucleophilic component (i.e., *N*-sulfinyl metallodienamine) and the electrophilic component (i.e., Michael acceptor). The successful application of this methodology toward the concise total syntheses of classical indole alkaloids (−)-aspidospermidine, (−)-tabersonine, and (−)-vincadifformine in 10−11 steps, respectively, is also discussed.

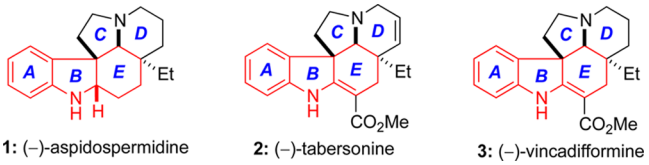
INTRODUCTION

Aspidosperma alkaloids, along with other monoterpene indole alkaloids, have been inspiring research targets for generations of synthetic organic chemists.[1−3] Numerous synthetic strategies have been developed for the construction of complex indole alkaloids, and our efforts in this field have led to the total syntheses of *Strychnos*,[4−8] bis-*Strychnos*,[9] and rearranged *Aspidosperma*[10] indole alkaloids.

In 2013, we reported concise asymmetric total syntheses of three classical members of the *Aspidosperma* alkaloids via a novel arene-fused domino Michael/Mannich/*N*-alkylation route.[11] To the best of our knowledge, this is one of the most efficient routes to (−)-aspidospermidine, (−)-tabersonine, and (−)-vincadifformine (Figure 1). Herein, we present a detailed discussion on the development and the application of the domino Michael/Mannich/*N*-alkylation sequence. Moreover, we discuss the scope of this method as applied to other arene-fused *N*-sulfinyl metallodienamines.

As shown in Figure 1, the structures of three classical *Aspidosperma* alkaloids share a common ABCDE ring system with at least three contiguous stereogenic centers. To develop an efficient and divergent synthetic route to the aforementioned targets, we devoted ourselves to the construction of the ABE tetrahydrocarbazole with suitable functional group handles, which could be further manipulated to install the C and D rings.

To readily access the ABE tetrahydrocarbazole nucleus, we were inspired by Magnus's step-efficient indole-2,3-quinodimethane strategy toward *Aspidosperma* and *Kopsia* alkaloids.[12] The asymmetric sulfinimine methodology developed by Davis[13−16] and expanded by Ellman,[17,18] which remains unparalleled in the construction of nitrogen-containing stereogenic centers, was recruited to render the syntheses enantiospecific. The conjugate addition reactions of *N*-sulfinyl metalloenamines and *α,β*-unsaturated ketones reported by Ellman and co-workers in 2005 further inspired us to test the chemistry of 2,3-indole fused *N*-sulfinyl metalloenamines, which are readily prepared from commercial starting materials.[19] In analogy to Ellman's work, we reasoned the Michael



1: (−)-aspidospermidine 2: (−)-tabersonine 3: (−)-vincadifformine

Figure 1. Structures of (−)-aspidospermidine (**1**), (−)-tabersonine (**2**), and (−)-vincadifformine (**3**).

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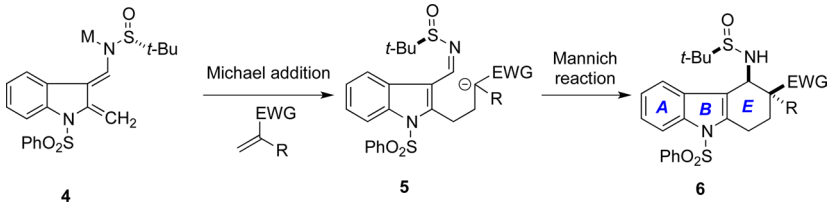
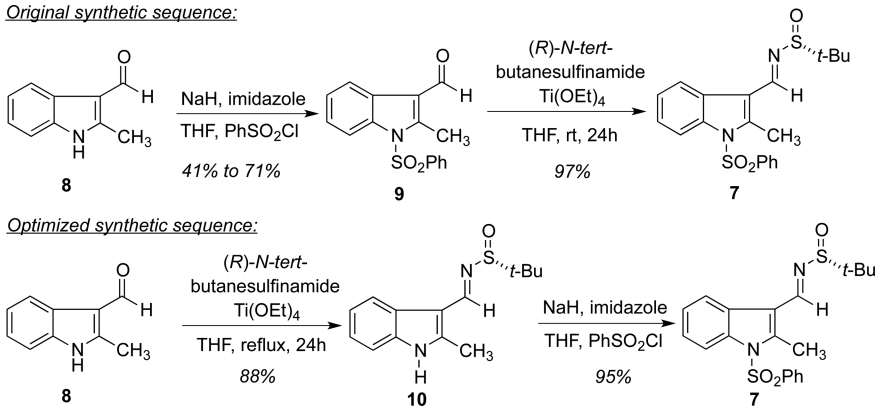
Scheme 1. Proposed Domino-fused Michael/Mannich Reaction of *N*-Sulfinyl Metallodienamines 4



Scheme 2. Synthesis of *N*-Sulfinylimine 7



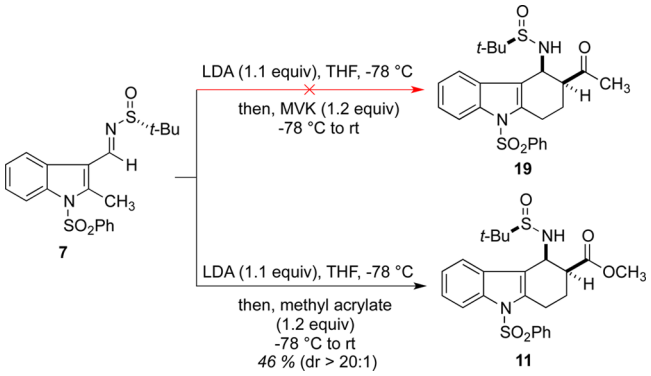
reaction of the *N*-sulfinyl metallodienamine **4** with suitable Michael acceptors would trigger a Mannich reaction, thus making possible the formation of ABE tetrahydrocarbazole **6** via the intermediary enolate **5** (Scheme 1); moreover, the relative and absolute stereochemistry of **6** could be controlled by the *N*-sulfinyl group.

RESULTS AND DISCUSSION

Synthesis of *N*-Sulfinylimine 7. To test the feasibility of our idea, we first needed to generate the *N*-sulfinyl metallodienamines, which were assumed to be obtainable from the treatment of the corresponding *N*-sulfinimines with a strong base. As shown in Scheme 2, *N*-sulfinylimine **7** was easily prepared from the commercially available 2-methyl-indole-3-carboxaldehyde (**8**) by following known methods.[20−22] However, the *N*-sulfonylation reaction of indole **8** was found to be fickle and desired product **9** was obtained in yields ranging from 41% to 71%. Alternatively, reversing the order of events (i.e., first condensing with *N*-sulfinamide followed by *N*-sulfonylation) remedied this problem, thus favorably furnishing *N*-sulfinylimine **7** in high yield and on multigram scale (Scheme 2).

Initial Experiments and Optimization of the Arene-fused Domino Michael/Mannich Reaction. With *N*-sulfinylimine **7** in hand, our focus was turned to optimal conditions for generating the requisite *N*-sulfinyl metallodienamine for the proposed arene-fused domino Michael/Mannich reactions. The common strong base, lithium diisopropylamide (LDA), was initially screened, followed by treatment with methyl vinyl ketone (MVK) as the first Michael acceptor. In the event, deprotonation of **7** with LDA followed by addition of MVK led to a complex mixture with no sign of the domino Michael/Mannich products. However, due to the fact that **7** was completely consumed, it was believed that the metallodienamine did form and react with MVK, but the product **19** might still be in its deprotonated form. This anion would have the ability to undergo further reactions with the reactive Michael acceptor MVK. To test this hypothesis, MVK was replaced with methyl acrylate, a less reactive Michael acceptor, for the domino Michael/Mannich reaction of **7** under the same conditions. To our delight, the desired product **11** was isolated in 46% yield (Scheme 3). No other isomers were able to be isolated at that time.

Scheme 3. Initial Domino Michael/Mannich Reactions of *N*-Sulfinylimine 7



We reasoned that the treatment of **7** with LDA resulted in the formation of metallodienamine **12**, and the relative and absolute stereocontrol in the domino process can be rationalized by invoking transition state **13**, which is consistent with those posited by both Ellman[23] and Davis (Scheme 4).[13]

Cognizant of the acidity of the protons at the 2-methylindole moiety of *N*-sulfinylimine **7**, which is enhanced due to the electron-withdrawing arene sulfonyl group on indole nitrogen, we started the optimization of the arene-fused domino Michael/Mannich reaction by screening other, slightly weaker bases. Meanwhile, it was speculated that the acidic hydrogen α to the carbomethoxyl group in **11** might cause side reactions, particularly elimination of *N*-sulfinylamine. Thus, the reaction

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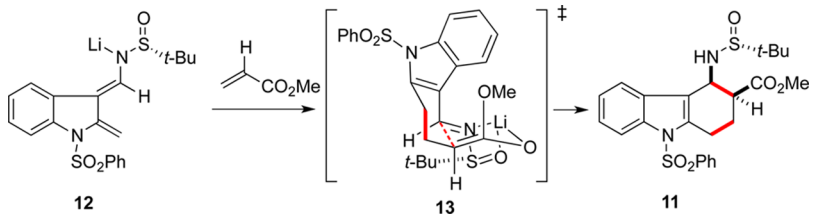
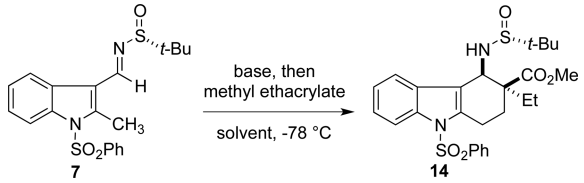
Scheme 4. Proposed Mechanism and Transition State for the Formation of 11



of *N*-sulfinylimine **7** and methyl ethacrylate was selected as the model reaction since the product would bear a quaternary carbon, thus precluding elimination. Furthermore, *Aspidosperma* alkaloids **1**−**3** all possess an ethyl group at C20.

The hexamethyldisilazide bases LHMDS, NaHMDS, and KHMDS were screened, and all provided better results than LDA did. Of the three, LHMDS gave the best result (Table 1, Entry 2). Additional equivalents of LHMDS shortened the reaction time and slightly increased the yield but had a negligible effect on the dr (Table 1, Entry 5). The effect of solvents on the reaction was also examined. The use of Et_2O as solvent resulted in low chemical yields, which is attributed to the low solubility of **7** (Table 1, Entry 6). Since satisfactory results were obtained, no attempts were made to further optimize the reaction conditions.

Table 1. Optimization of the Arene-fused Domino Michael/Mannich Reaction[a]



entry	base	solvent	dr[c]	yield (%)[d]
1	LDA	THF	10:1	40
2	**LHMDS**	**THF**	**11:1**	**93**
3	NaHMDS	THF	6:1	79
4	KHMDS	THF	12:1	77
5[b]	LHMDS	THF	11:1	98
6	LHMDS	Et_2O	7:1	13

[a]Unless otherwise specified, reaction conditions are as follows: **7** (1 equiv, 0.1 mmol) in solvent (3 mL) with base (1.2 equiv), −78 °C, 1 h; then, methyl ethacrylate (1.5 equiv) in solvent (1 mL), −78 °C, 2 h. [b]2.2 equiv of base was used. [c]Determined by ^{1}H NMR. [d]Isolated yields of the major product.

Scope of the Arene-fused Domino Michael/Mannich Reaction with Various Electrophiles. To determine the substrate scope and limitations of our domino Michael/Mannich reaction, a number of Michael acceptors were evaluated (Table 2). As depicted in Table 2, under optimized conditions our arene-fused domino Michael/Mannich reaction appeared to be tolerant toward a variety of functionalities, such as esters, lactones, ketones, aldehydes, and Weinreb amides.

Of all the Michael acceptors screened, acrylates were shown to be the best Michael acceptors in providing products in high chemical yields and good diastereoselectivities (Table 2, Entries 2−3). However, **11** was obtained in relatively low yield (Table 2, Entry 1), mainly owing to the deleterious effect of the acidic proton α to the ester group in the product. An interesting trend of diastereoselectivity was also noticed; that is, the larger the alkyl group α to the ester group, the less diastereoselective the reaction. This can be rationalized by analyzing transition state **13** (Scheme 4). Since the alkyl group occupies the axial position in the transition state, as steric bulk increases, the transition state becomes less favorable.[13,23]

Significantly, the use of the α,β−unsaturated lactone 5,6-dihydro-2-H-pyrane-2-one led to the formation of the tetracyclic product **16**, with formation of three new contiguous stereogenic centers, in good yield (73%) and good diastereoselectivity (dr =9:1, Table 2, Entry 4). The structure of **16** was further confirmed by X-ray analysis, so was the stereochemical course of the arene-fused domino Michael/Mannich reaction (see Supporting Information for details).

It is noteworthy that more electrophilic Michael acceptors, such as α,β-unsaturated aldehydes and ketones, were also compatible with the optimized reaction conditions (Table 2, Entries 5−7). While a modest 40% yield was obtained with α,β-unsaturated ketone MVK, this was a vast improvement over previous efforts using LDA that resulted in no desired product (Scheme 4). We attribute this to the kinetic and thermodynamic acidity of the α-protons on the methyl group of the product **19**. Lastly, the successful use of α,β-unsaturated aldehydes as Michael acceptors (e.g., ethacrolein) would further streamline our syntheses of *Aspidosperma* alkaloids **1**−**3** by obviating additional redox operations.

Interestingly, when methyl propiolate was used as the Michael acceptor, carbazole **20** was obtained in good yield (Table 2, Entry 8), which was believed to be the elimination product of the corresponding tetrahydrocarbazole (Scheme 5). Even though the formation of **20** is not valuable in terms of asymmetric synthesis, it holds great potential for the facile, step-efficient preparation of carbazoles.[24,25]

Finally, when *N*,*O*-dimethyl (i.e., Weinreb) acrylamide was used as the Michael acceptor, no domino Michael/Mannich product was formed at −78 °C, which is consistent with the decreased reactivity of acrylamides vis-à-vis acrylates and acroleins.[26] However, raising the reaction temperature to −20 °C effected the desired process wherein two diastereoisomers were isolated in 62% yield (dr = 1.2:1). The relative stereochemistry of each diastereoisomer was determined by NOE analysis (Figure 2). The poor diastereoselectivity could be attributed to a disrupted transition state caused by the extra chelating group of the Weinreb amide, as well as the higher reaction temperature.

Scope of the Arene-fused Domino Michael/Mannich Reaction. Arene-fused *N*-sulfinimines **24**−**26** were synthesized from their corresponding aldehydes with (*R*)-*N*-*tert*-butanesulfinamide to test the compatibility of these substrates with our 2,3-indole-fused domino Michael/Mannich reaction conditions (Schemes 6). *N*-sulfinimine **24** was obtained in 79% from the condensation of *o*-tolualdehyde (**27**) with (*R*)-*N*-*tert*-butanesulfinamide.[20,21] Similarly, *N*-sulfinimine **25** was obtained from the condensation of 2-methylpyridine-3-carbaldehyde (**28**)[27] in

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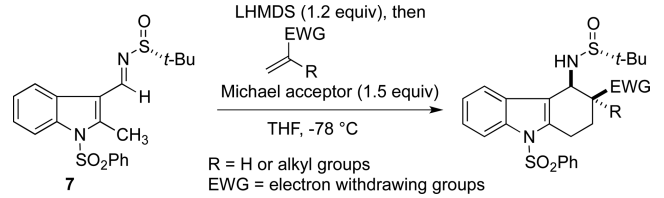
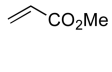
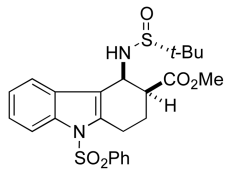
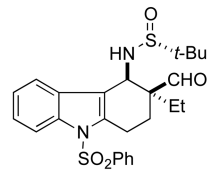
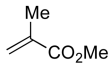
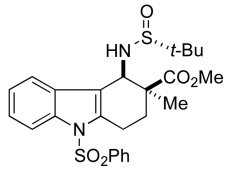
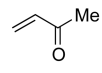
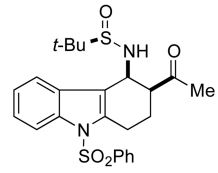
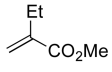
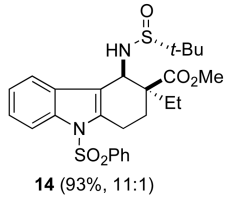
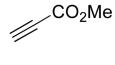
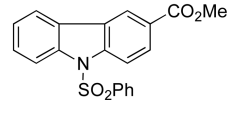
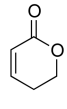
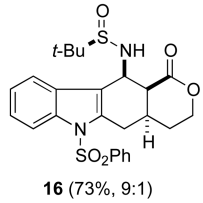
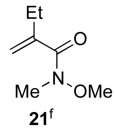
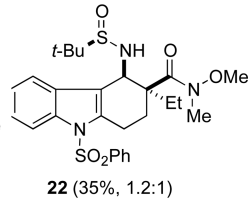
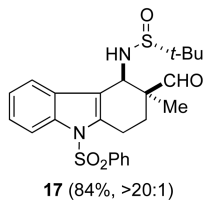
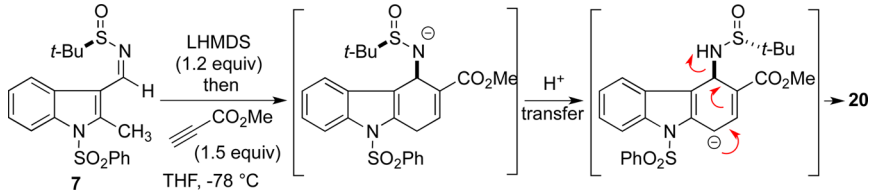
Table 2. Scope of Michael Acceptors[a]



Entry	Michael acceptor	Major product (yield[b], dr[c])	Entry	Michael acceptor	Major product (yield[b], dr[c])
1		 **11** (70%, >20:1)	6		 **18** (86%, 18:1)
2		 **15** (93%, 20:1)	7		 **19** (40%, n.d.[d])
3		 **14** (93%, 11:1)	8		 **20** (68%)
4		 **16** (73%, 9:1)	9[e]	 **21**[f]	 **22** (35%, 1.2:1)
5		 **17** (84%, >20:1)			

[a]Unless otherwise specified, reaction conditions are as follows: **7** (1 equiv, 0.1 mmol) in THF (3 mL) with base (1.2 equiv), −78 °C, 1h; then, methyl ethacrylate (1.5 equiv) in THF (1 mL), −78 °C, 2h. [b]The isolated yield. [c]Determined by ^{1}HNMR. [d]The other diastereomer was not isolated. [e]Reaction temperature: −78 °C to −20 °C. [f]See Experimental Section for the synthesis of **21.**

Scheme 5. Proposed Formation of Carbazole 20 from 7 and Methyl Propiolate



75% yield. The synthesis of furan-fused *N*-sulfinimine **26** started from ethyl 2-methyl-1H-pyrrole-3-carboxylate **29**.[28] Nitrogen protection of **29** with benzenesulfonyl chloride afforded *N*-benzenesulfonyl-protected pyrrole **30** in 96% yield, which was reduced with DIBAL-H and followed by Parikh-Doering oxidation to deliver **31** in 86% overall yield.[29]

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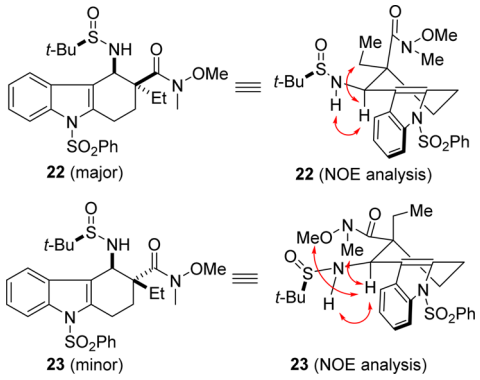


Figure 2. NOE analysis of the diastereoisomers from the arene-fused domino Michael/Mannich reaction with Weinreb amide **21**.

The subsequent Ti-promoted condensation with (*R*)-*N*-*tert*-butanesulfinamide afforded *N*-sulfinimine **26** in 97% yield (Scheme 6).

When *N*-sulfinimines **24** and **25** were subjected to the optimal conditions with methyl ethacrylate as Michael acceptor, no desired product **32** or **33** was detected (Scheme 7). Considering the difficulty with the formation of the corresponding metallodienamines, we also tried other stronger bases (e.g., LDA, *n*-BuLi/diisopropylamine/*t*-BuOK,[30] and *n*-BuLi/TMP[31]). However, those stronger bases either led to the decomposition of *N*-sulfinimines **24** and **25**, or left them intact. Increasing the reaction temperature also proved ineffective.

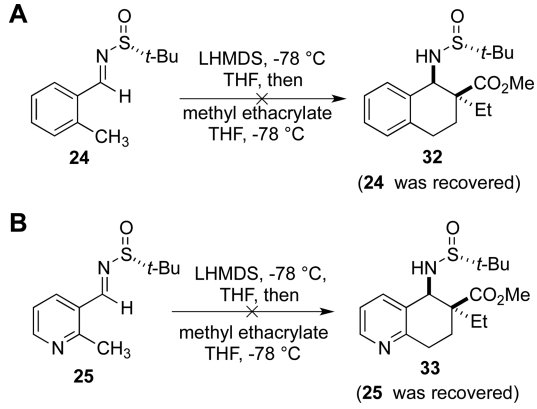
When pyrrole-fused *N*-sulfinimine **26** was subjected to the optimal conditions for the indole-fused analog, no desired products were isolated and *N*-sulfinimine **26** was recovered. However, increasing the reaction temperature to rt after the addition of methyl ethacrylate—much like the case of acrylamide electrophiles in Table 1, Entry 9—resulted in the isolation of the domino Michael/Mannich products **34** and **35** in modest yield and diastereoselectivity (dr =2:1, Scheme 8). The relative stereochemical assignments of **34** and **35** were made from NOE experiments performed on the latter. The absolute stereochemical assignments were based on analogy to the indole-fused variant (Table 1).

2,3-Indole-fused Domino Michael/Mannich/*N*-Alkylation Sequence. After exploring the substrate scope of the arene-fused domino Michael/Mannich sequence, we proposed that there was a possibility to further improve the efficiency of the reaction by trapping the direct domino Michael/Mannich product, the *N*-sulfinyl anion intermediate, with allyl bromide. The resulting domino Michael/Mannich/*N*-alkylation sequence would deliver the tetrahydrocarbazole with an *N*-allyl group which was proved to be useful for the construction of the D ring in *Aspidosperma* alkaloids **1**−**3**.[32,33]

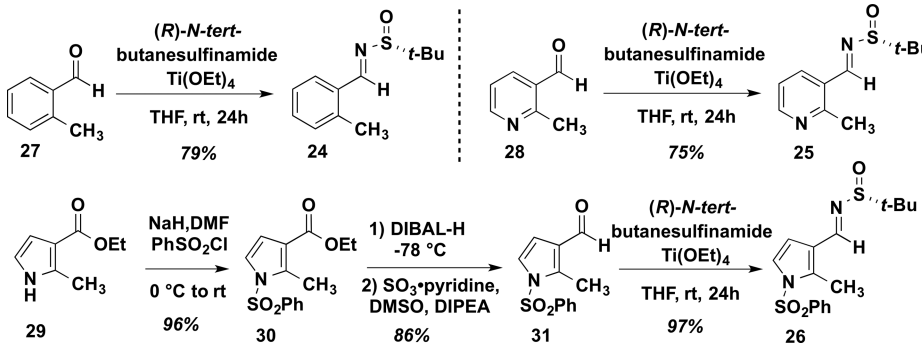
Table 3 shows some of the results from the arene-fused domino Michael/Mannich/*N*-alkylation reaction where *N*-sulfinyl anion intermediate **37** was trapped with allyl bromide. Solvents were found to have a profound effect on the outcome of the telescoped reaction sequence. When using only THF for both the Michael/Mannich and *N*-allylation reactions, no desired *N*-allylated tetrahydrocarbazole **36** was isolated. Instead, the domino Michael/Mannich product **14** was isolated in 90% yield (Table 3, Entry 1). To improve the nucleophilicity of *N*-sulfinyl anion **37**, the polar aprotic solvent DMF was used.[34] However, its incompatibility with the domino Michael/Mannich reaction resulted in complete decomposition of *N*-sulfinylimine **7** (Table 3, Entry 2). A 79% yield of the desired product **36** was obtained when THF was used for the Michael/Mannich reaction and DMF was used for the *N*-allylation step (Table 3, Entry 3). Increasing the ratio of THF/DMF to 1:2 led to a higher yield of **36**. However, the yield was not improved by further increasing the ratio of the solvents (Table 3, Entry 4−5). Finally, the highest yield (up to 90%) was achieved by increasing the equivalents of LHMDS (Table 3, Entry 6).

Application of the 2,3-Indole-fused Michael/Mannich Reaction in the Syntheses of *Aspidosperma* Alkaloids 1−3. After developing new methodology for the construction of ABE tetrahydrocarbazole framework of *Aspidosperma* alkaloids, and exploring its generality with different Michael acceptors and donors, we applied this methodology toward the step-

Scheme 7. Attempted Domino Michael/Mannich Reaction of (A) Benzene- and (B) Pyridine-fused *N*-Sulfinimines



Scheme 6. Syntheses of Benzene-, Pyridine-, and Pyrrole-fused *N*-Sulfinimines 24−26



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Scheme 8. Domino Michael/Mannich Reaction of Pyrrole-fused *N*-Sulfinimines

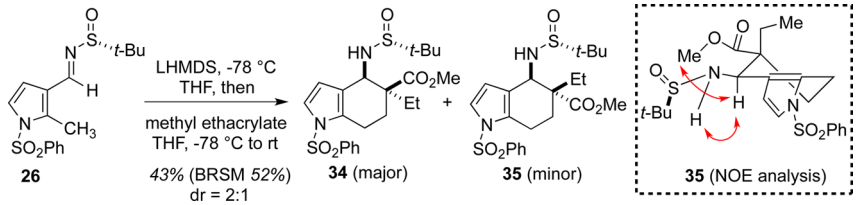
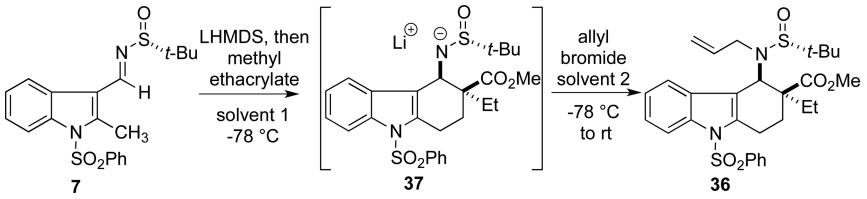


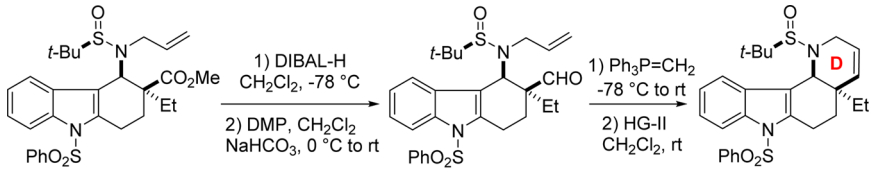
Table 3. Optimization of the 2,3-Indole-fused Domino Michael/Mannich/*N*-Alkylation Reaction[a]



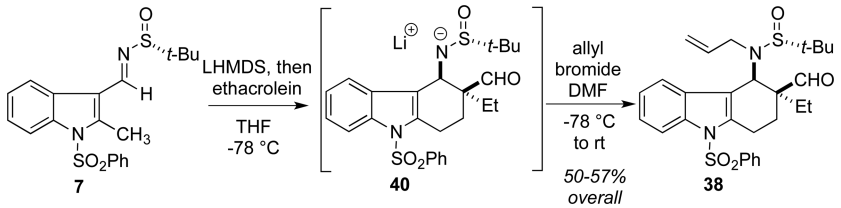
entry	LHMDS (equiv)	allyl bromide (equiv)	solvent 1/Solvent 2 (v/v)	yield (%)[b]
1	1.2	5	THF/THF	[c]
2	1.2	5	DMF/DMF	[d]
3	1.2	5	THF/DMF (1:1)	83
4	1.2	5	THF/DMF (1:2)	88
5	1.2	5	THF/DMF (1:4)	79
6[e]	2.2	5	THF/DMF (1:4)	90

[a]Unless otherwise specified, reaction conditions are as follows: **7** (1 equiv, 0.1 mmol) in solvent 1, LHMDS (1.2 or 2.2 equiv), −78 °C, 1 h; then, methyl ethacrylate (1.5 or 3 equiv), −78 °C, 2 h; then allyl bromide (5 equiv) in solvent 2, −20 °C to rt, 16 h. [b]Isolated yields. [c]The domino product **14** was isolated (90% yield). [d]No product was isolated. [e]3 equiv of methyl ethacrylate was used.

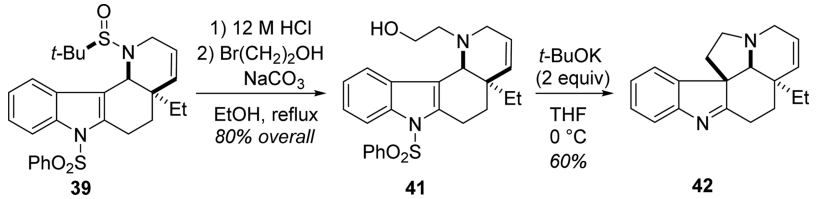
Scheme 9. Construction of the *Aspidosperma* Dehydropiperidine D Ring



Scheme 10. Alternative Route to Aldehyde 38



Scheme 11. Construction of the C Ring



efficient, asymmetric total syntheses of (−)-aspidospermidine (**1**), (−)-tabersonine (**2**), and (−)-vincadifformine (**3**).[11]

Since we had established facile access to 2,3-indole-fused domino Michael/Mannich/*N*-alkylation product **36**, the next stage of the synthesis called for ring-closing metathesis (RCM) of the D ring, a strategy employed by Rawal in the *Aspidosperma* series.[32,33] To this end, the methyl ester group in **36** was converted to a requisite terminal olefin via the intermediary aldehyde **38**. This goal was best accomplished by sequential reduction to the alcohol with DIBAL-H and

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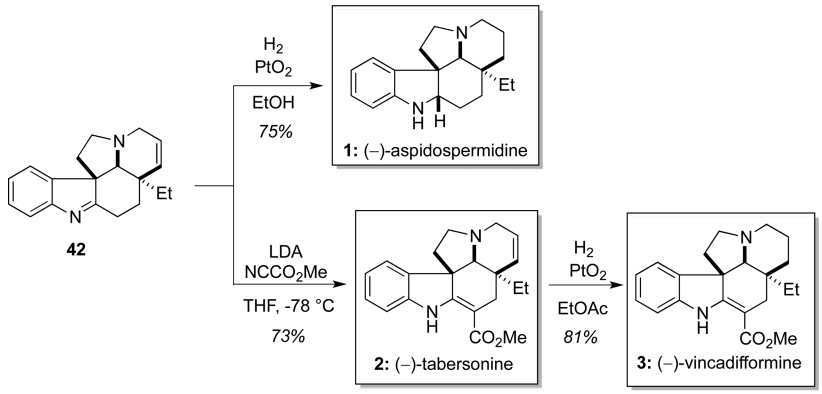
Scheme 12. Endgame for *Aspidosperma* Alkaloids 1−3



oxidation with the Dess−Martin periodinane (DMP) in 98% overall yield.[35] Wittig methylenation of **38** and ring-closing metathesis under the agency of 10 mol% Hoveyda−Grubbs second generation catalyst (HG-II)[36] delivered ABDE tetracycle **39** in 90% overall yield (Scheme 9).

As previously noted, a more step-efficient route would be possible if an α,β-unsaturated aldehyde (i.e., ethacrolein) was used for the 2,3-indole-fused domino Michael/Mannich/*N*-allylation, which would lead to aldehyde **38** in one step and avoid redox processes. Thus, anion **40** from the 2,3-indole-fused domino Michael/Mannich reaction sequence could be trapped with allyl bromide to give **38** in one step from *N*-sulfinimine **7**. However, the yield of this more direct route to **38** was lower (50−57% overall) than the acrylate variant (83−90% overall), which is attributed to the reactivity of the aldehyde moiety under the reaction conditions (Scheme 10).

With ABDE tetracycle **39** in hand, we were poised to construct the final C ring (Scheme 11). To this end, we recruited the step-efficient process developed by Bosch and Rubiralta wherein *t*-BuOK was utilized for transferring the *N*-benzenesulfonyl protecting group from indole to the primary hydroxyl group in **41**, which resulted in spirocyclization leading to pentacyclic indolenine **42**.[37,38]

To access substrate **41** for the Bosch−Rubiralta process, the *N*-sulfinyl group in **39** was first removed with methanolic HCl. Subsequent *N*-alkylation of the gramine intermediate was effected with 2-bromoethanol and Na_2CO_3 (refluxing EtOH) to deliver alcohol **41** in 80% overall yield. Thus, the Bosch−Rubiralta spirocyclization was realized by the addition of 2 equiv of *t*-BuOK in THF at 0 °C to afford indolenine **42** in 60% yield (Scheme 11).

Indolenine **42** served as a key intermediate in the endgame of *Aspidosperma* alkaloids **1−3**. Global hydrogenation of **42** with Adams's catalyst and H_2 in EtOH at room temperature delivered (−)-aspidospermidine (**1**) in a single step (75% yield). Alternatively, metalation of indolenine **42** with LDA to access a metalloenamine intermediate and subsequent addition of Mander's reagent furnished (−)-tabersonine (**2**) in 73% yield.[39−42] The hydrogenation of **2** with Adams's catalyst and H_2 in EtOAc afforded (−)-vincadifformine (**3**) in 81% yield (Scheme 12). Spectral data for **1−3** (e.g., ^{1}H and ^{13}C NMR, IR, optical rotation) were in complete agreement with those reported in the literature.[11]

3. CONCLUSION

In summary, a novel asymmetric 2,3-indole-fused domino Michael/Mannich reaction sequence for the rapid assembly of the tetrahydrocarbazole (ABE) framework of *Aspidosperma* alkaloids was developed. The reaction scope of both nucelophilic and electrophilic partners was explored. The methodology was employed in the concise asymmetric total syntheses of classical targets (−)-aspidospermidine (**1**, 10 steps, 27% overall yield), (−)-tabersonine (**2**, 10 steps, 26% overall yield), and (−)-vincadifformine (**3**, 11 steps, 22% overall yield) from commercial starting materials. Other key steps include (1) ring-closing metathesis to prepare the D ring and (2) the Bosch−Rubiralta spirocyclization to prepare the C ring.

4. EXPERIMENTAL SECTION

General Information. All reactions containing moisture or air sensitive reagents were performed in oven-dried glassware under nitrogen or argon. Tetrahydrofuran, diethyl ether and dichloromethane were passed through two columns of neutral alumina prior to use. 2-Methylenebutyric acid and methyl ethacrylate were prepared according to the procedure of Chen.[43] All other reagents were purchased from commercial sources and used without further purification. All solvents for workup procedures were used as received. Flash column chromatography was performed according to the procedure of Still[44] using 60 Å silica gel with the indicated solvents. For all ring-closing metathesis reactions, CH_2Cl_2 was deaerated by bubbling argon (1 min/mL). Thin layer chromatography was performed on $60F_{254}$ silica gel plates. Detection was performed using UV light, $KMnO_4$ stain, PMA stain, and subsequent heating. Infrared spectra (IR) were measured on a Fourier transform infrared spectrometer (FT-IR). ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz instrument in $CDCl_3$ at 298 K. Chemical shifts are indicated in parts per million (ppm) and internally referenced to residual solvent signals. Splitting patterns are abbreviated as follows: s (singlet), d (doublet), bs (broad singlet), bd (broad doublet), t (triplet), q (quartet), and m (multiplet). High-resolution mass spectra (HRMS) were obtained on a time-of-flight (TOF) mass spectrometer using an electrospray ionization (ESI) source.

*(R,E)-2-Methyl-N-((2-methyl-1H-indol-3-yl)methylene)propane-2-sulfinamide (**10**).* A mixture of 2-methyl-3-formylindole **8** (2 g, 12.56 mmol), (*R*)-*tert*-butanesulfinamide (1.83 g, 15.1 mmol) and $Ti(OEt)_4$ (8.6 g, 37.7 mmol) in THF (50 mL) was stirred at 70 °C overnight. The reaction was quenched with brine (30 mL) and the resulting suspension was filtered through a short pad of Celite. The solid cake was washed with ethyl acetate, and the separated organic layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc/hexanes (1:4 to 1:1) to afford 2.9 g (88% yield) of *N*-sulfinimine **10** as an off-white foam. $[\alpha]_D^{20}$ + 74.9 (*c* 1.1, $CHCl_3$); IR (neat) 3197, 2980, 2361, 2341, 1592, 1572, 1459, 1362, 1339, 1247, 1048, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.83 (s, 1H), 8.26−8.19 (m, 1H), 7.38−7.33 (m, 1H), 7.26−7.20 (m, 2H), 2.57 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3,

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144.2, 135.8, 126.1, 123.0, 122.0, 121.2, 110.9, 110.9, 56.9, 22.4, 12.1; HRMS (ESI) calc'd for $C_{14}H_{18}N_2OS$ + H = 263.1218, found 263.1227.

General Procedure for the Optimization of the Arene-fused Domino Michael/Mannich Reaction. To a stirred solution of sulfinimine **7** (40 mg, 0.1 mmol) in THF or diethyl ether (3 mL) was added base (0.12 or 0.22 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 1 h. Then a solution of methyl ethacrylate (17 mg, 0.15 mmol) in THF or diethyl ether (1 mL) was added at −78 °C. Stirring was continued at −78 °C for 2 h. The reaction was quenched with saturated aq. NH_4Cl (4 mL) at −78 °C. The cooling bath was removed and the mixture was warmed to rt. The organic layer was separated, washed with brine (4 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (1:1 to 4:1) to afford **14** as a white foam.

General Procedure for the Arene-fused Domino Michael/Mannich Reaction with Various Electrophiles. To a stirred solution of *N*-sulfinimine **7** (40 mg, 0.1 mmol) in THF (3 mL) was added LHMDS (1.0 M in THF, 0.12 mL, 0.12 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 1 h. Then a solution of Michael acceptor (0.15 mmol) in THF (1 mL) was added at −78 °C. Stirring was continued at −78 °C for 2 h. The reaction was quenched with saturated aq. NH_4Cl (4 mL) at −78 °C. The cooling bath was removed and the mixture was warmed to rt. The organic layer was separated, washed with brine (4 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography.

*Methyl (3S,4S)-4-(((R)-tert-Butylsulfinyl)amino)-9-(phenylsulfonyl)-2,3,4,9-tetra-hydro-1H-carbazole-3-carboxylate (**11**).* The title product **11** was obtained as a white foam (34 mg, 70% yield) after purification by silica gel flash column chromatography eluting with EtOAc/hexanes (1:1 to 4:5). $[\alpha]_D^{20}$ + 16.4 (*c* 1.1, $CHCl_3$); IR (neat) 3287, 2954, 2359, 1724, 1449, 1371, 1203, 11173, 1066, 984, 750, 727, 687, 593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.75−7.67 (m, 3H), 7.57−7.51 (m, 1H), 7.42 (dt, *J* = 7.5, 1.7 Hz, 2H), 7.33−7.23 (m, 2H), 4.98 (dd, *J* = 7.2, 3.9 Hz, 1H), 4.53 (d, *J* = 7.2 Hz, 1H), 3.75 (s, 3H), 3.20 (dt, *J* = 18.5, 5.1 Hz, 1H), 3.06−2.92 (m, 2H), 2.33−2.17 (m, 2H), 1.13 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 138.9, 136.4, 136.4, 133.7, 129.3, 128.8, 126.2, 124.6, 123.6, 119.8, 117.8, 114.2, 56.2, 52.1, 49.7, 45.1, 23.5, 22.8, 21.2; HRMS (ESI) calc'd for $C_{24}H_{28}N_2O_5S_2$ + H = 489.1518, found 489.1513.

*Methyl (3S,4R)-4-(((R)-tert-Butylsulfinyl)amino)-3-methyl-9-(phenylsulfonyl)-2,3,4,9-tetrahydro-1H-carbazole-3-carboxylate (**15**).* The title product **15** was obtained as a white foam (47 mg, 93% yield) after purification by silica gel flash column chromatography eluting with EtOAc/hexanes (1:1 to 4:5). $[\alpha]_D^{20}$ − 7.5 (*c* 1.55, $CHCl_3$); IR (neat) 3314, 2954, 2359, 1733, 1449, 1371, 1172, 1145, 1066, 749, 728, 594 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (dt, *J* = 5.9, 3.5 Hz, 1H), 7.73−7.69 (m, 2H), 7.65 (dt, *J* = 7.7, 3.5 Hz, 1H), 7.55−7.50 (m, 1H), 7.43−7.38 (m, 2H), 7.34−7.28 (m, 2H), 4.72 (d, *J* = 6.1 Hz, 1H), 4.07 (d, *J* = 6.1 Hz, 1H), 3.79 (s, 3H), 3.26 (ddd, *J* = 18.8, 6.4, 1.6 Hz, 1H), 2.91−2.82 (m, 1H), 2.24 (ddd, *J* = 14.0, 11.4, 6.4 Hz, 1H), 2.11−2.03 (m, 1H), 1.07 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 138.9, 136.8, 136.1, 133.7, 129.2, 126.0, 124.8, 123.7, 119.4, 115.9, 114.2, 56.0, 53.7, 52.2, 47.3, 24.4, 22.7, 21.4, 19.6; HRMS (ESI) calc'd for $C_{25}H_{30}N_2O_5S_2$ + H = 503.1674, found 503.1681.

*(R)-2-Methyl-N-((4aR,11S,11aS)-1-oxo-6-(phenylsulfonyl)-1,3,4,4a,5,6,11,11a-octahydropyrano[4,3-b]carbazol-11-yl)-propane-2-sulfinamide (**16**).* The title product **16** was obtained as a white foam (37 mg, 73% yield) after purification by silica gel flash column chromatography eluting with EtOAc/dichloromethane (1:1 to 4:5). $[\alpha]_D^{20}$ + 18.1 (*c* 1.38, $CHCl_3$); IR (neat) 3277, 2980, 2361, 1730, 1448, 1389, 1370, 1228, 1182, 1151, 1127, 1062, 1035, 750, 729, 686, 593 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.70−7.63 (m, 3H), 7.53−7.47 (m, 1H), 7.41 (dd, *J* = 10.7, 4.8 Hz, 2H), 7.29−7.22 (m, 1H), 7.21−7.14 (m, 1H), 5.86 (d, *J* = 11.2 Hz, 1H), 4.90 (dd, *J* = 11.2, 4.8 Hz, 1H), 4.52−4.37 (m, 2H), 3.76 (t, *J* = 4.8 Hz, 1H), 3.48−3.33 (m, 1H), 2.79−2.69 (m, 2H), 2.36−2.30 (m, 1H), 2.01−1.90 (m, 1H), 1.32 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 138.4, 136.5, 133.8, 133.5, 129.3, 128.6, 126.2, 124.4, 123.3, 120.9, 118.0, 114.3, 65.5, 56.3, 54.0, 44.3, 30.4, 30.3, 27.2, 22.9; HRMS (ESI) calc'd for $C_{25}H_{28}N_2O_5S_2$ + Na = 523.1337, found 523.1322.

*(R)-N-((3S,4R)-3-Formyl-3-methyl-9-(phenylsulfonyl)-2,3,4,9-tetrahydro-1H-carbazol-4-yl)-2-methylpropane-2-sulfinamide (**17**).* The title product **17** was obtained as a white foam (40 mg, 84% yield) after purification by silica gel flash column chromatography. $[\alpha]_D^{20}$ −15.5 (*c* 2.8, $CHCl_3$); IR (neat) 3218, 2960, 2361, 1722, 1448, 1370, 1172, 1149, 1051, 982, 749, 728, 686, 591, 573 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 7.0 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.35−7.27 (m, 2H), 4.69 (d, *J* = 6.2 Hz, 1H), 4.17 (d, *J* = 6.2 Hz, 1H), 3.29 (dd, *J* = 19.0, 4.6 Hz, 1H), 3.00−2.86 (m, 1H), 2.23−2.09 (m, 1H), 1.93 (dd, *J* = 13.9, 6.1 Hz, 1H), 1.04 (s, 9H), 1.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.7, 139.2, 137.1, 136.4, 134.2, 129.7, 129.5, 126.5, 125.3, 124.2, 119.8, 116.8, 114.7, 56.6, 52.6, 50.2, 23.7, 23.1, 21.5, 17.1; HRMS (ESI) calc'd for $C_{24}H_{28}N_2O_4S_2$ + H = 473.1569, found 473.1577.

*(R)-N-((3S,4R)-3-Ethyl-3-formyl-9-(phenylsulfonyl)-2,3,4,9-tetrahydro-1H-carbazol-4-yl)-2-methylpropane-2-sulfinamide (**18**).* The title product **18** was obtained as a white foam (42 mg, 86% yield) after purification by silica gel flash column chromatography eluting with EtOAc/hexanes (1:1 to 4:5). $[\alpha]_D^{20}$ −39.0 (*c* 2.2, $CHCl_3$); IR (neat) 3215, 2966, 2361, 1721, 1449, 1370, 1213, 1171, 1149, 1055, 1026, 982, 749, 727, 686, 592, 573 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 1H), 8.19−8.13 (m, 1H), 7.71 (dt, *J* = 8.6, 1.6 Hz, 2H), 7.66−7.62 (m, 1H), 7.56−7.50 (m, 1H), 7.43−7.37 (m, 2H), 7.34−7.25 (m, 2H), 4.76 (d, *J* = 6.2 Hz, 1H), 4.02 (d, *J* = 6.2 Hz, 1H), 3.30−3.21 (m, 1H), 2.91−2.79 (m, 1H), 2.10−2.06 (m, 2H), 1.54 (dq, *J* = 15.0, 7.5 Hz, 1H), 1.43−1.34 (m, 1H), 1.02 (s, 9H), 0.76 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.8, 138.8, 136.7, 136.4, 133.8, 129.3, 129.1, 126.1, 124.8, 123.9, 119.2, 116.5, 114.3, 56.2, 53.6, 50.9, 22.9, 22.6, 21.1, 20.2, 8.4; HRMS (ESI) calc'd for $C_{25}H_{30}N_2O_4S_2$ + H = 487.1725, found 487.1716.

*(R)-N-((3S,4S)-3-Acetyl-9-(phenylsulfonyl)-2,3,4,9-tetrahydro-1H-carbazol-4-yl)-2-methylpropane-2-sulfinamide (**19**).* The title product **19** was obtained as a colorless gum (19 mg, 40% yield) after purification by silica gel flash column chromatography eluting with 100% diethyl ether. $[\alpha]_D^{20}$ − 8.8 (*c* 1.38, $CHCl_3$); IR (neat) 2980, 2360, 2341, 1701, 1449, 1371, 1173, 1148, 1090, 1063, 985, 750, 726, 687, 592, 574 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.0 Hz, 1H), 7.74−7.67 (m, 3H), 7.55−7.50 (m, 1H), 7.45−7.40 (m, 2H), 7.30−7.21 (m, 2H), 4.86 (dd, *J* = 8.1, 4.4 Hz, 1H), 4.59 (d, *J* = 8.1 Hz, 1H), 3.38−3.32 (m, 1H), 3.11 (dt, *J* = 18.3, 6.0 Hz, 1H), 3.00 (dt, *J* = 12.7, 6.0 Hz, 1H), 2.39−2.30 (m, 1H), 2.29 (s, 3H), 2.17−2.11 (m, 1H), 1.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 138.8, 136.3, 136.0, 133.7, 129.2, 128.8, 126.2, 124.4, 123.5, 120.1, 118.1, 114.2, 56.0, 51.7, 50.4, 29.2, 22.8, 22.7, 22.4; HRMS (ESI) calc'd for $C_{24}H_{28}N_2O_4S_2$ + Na = 495.1388, found 495.1391.

*Methyl 9-(Phenylsulfonyl)-9H-carbazole-3-carboxylate (**20**).* The title product **20** was obtained as a white foam (25 mg, 68% yield) after purification by silica gel flash column chromatography eluting with EtOAc/hexanes (3:7). IR (neat) 2949, 2361, 1716, 1446, 1366, 1250, 1176, 1120, 1099, 975, 756, 745, 729, 685, 599 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.63−8.59 (m, 1H), 8.40−8.37 (m, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 8.21−8.17 (m, 1H), 7.99−7.95 (m, 1H), 7.86−7.82 (m, 2H), 7.54 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.51−7.45 (m, 1H), 7.43−7.39 (m, 1H), 7.37−7.32 (m, 2H), 3.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 141.0, 138.8, 137.7, 134.1, 129.2, 128.7, 128.0, 126.4, 126.3, 125.9, 125.7, 124.3, 122.0, 120.3, 115.0, 114.6, 52.2; HRMS (ESI) calc'd for $C_{20}H_{15}NO_4S$ + H = 366.0800, found 366.0802.

*N-Methoxy-N-methyl-2-methylenebutanamide (**21**).* *N*,*N*-Carbonyldiimidazole (501 mg, 3.09 mmol) was added slowly to a stirred solution of 2-methylenebutyric acid (300 mg, 3 mmol) in acetonitrile (2 mL) at rt. After 30 min, *N*,*O*-dimethylhydroxylamine (351 mg, 3.6 mmol) was added, followed by addition of a solution of trimethylamine (0.51 mL, 3.6 mmol) in acetonitrile (1 mL). The stirring was continued at rt for 24 h. The resulting suspension was filtered through a short pad of Celite and the filter cake was washed with ethyl acetate.

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The filtrate was concentrated in vacuo. The residue was redissolved in ethyl acetate (20 mL) and washed with a 5% solution of sodium carbonate (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was used in the next reaction without further purification. The residue was purified by flash column chromatography eluting with EtOAc/hexanes (3:7 to 1:1) to afford 281 mg (65% over 2 steps) of the Weinreb amide as a colorless oil. IR (neat) 2921, 2360, 2342, 1654, 1559, 1458, 1378, 999 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.26 (s, 1H), 5.21 (s, 1H), 3.65 (s, 3H), 3.24 (s, 3H), 2.35 (q, J = 7.4 Hz, 2H), 1.08 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 146.2, 114.4, 61.1, 33.4, 26.4, 11.8; HRMS (ESI) calc'd for $C_7H_{13}NO_2$ + H = 144.1025, found 144.1015.

*(3S,4R)-4-(((R)-tert-Butylsulfinyl)amino)-3-ethyl-N-methoxy-N-methyl-9-(phenylsulfonyl)-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide (**22**).* The title product **22** was obtained as an off-white gum (19 mg, 35% yield) after purification by silica gel flash column chromatography eluting with EtOAc/hexanes (1:1 to 100% EtOAc). $[\alpha]_D^{20}$ −65.8 (c 0.95, $CHCl_3$); IR (neat) 2964, 1647, 1453, 1371, 1174, 1148, 1089, 1068, 995, 750, 728, 595 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.18−8.12 (m, 1H), 7.69 (dd, J = 8.5, 1.1 Hz, 2H), 7.67−7.65 (m, 1H), 7.54−7.49 (m, 1H), 7.41−7.37 (m, 2H), 7.33−7.27 (m, 2H), 5.06 (d, J = 5.7 Hz, 1H), 3.90 (d, J = 5.7 Hz, 1H), 3.78 (s, 3H), 3.27 (s, 3H), 3.24−3.18 (m, 1H), 2.77 (ddd, J = 18.7, 12.2, 6.2 Hz, 1H), 2.31 (dd, J = 14.6, 6.2 Hz, 1H), 2.14−2.06 (m, 1H), 1.60 (dq, J = 14.6, 7.5 Hz, 1H), 1.30−1.24 (m, 1H), 0.99 (s, 9H), 0.82 (t, J = 7.5 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 138.9, 136.9, 136.7, 133.6, 129.5, 129.2, 126.0, 124.7, 123.6, 119.5, 116.6, 114.3, 60.6, 56.1, 53.0, 52.5, 34.0, 22.7, 22.6, 21.8, 21.5, 9.3; HRMS (ESI) calc'd for $C_{27}H_{35}N_3O_5S_2$ + Na = 568.1916, found 568.1932.

*(3R,4R)-4-(((R)-tert-Butylsulfinyl)amino)-3-ethyl-N-methoxy-N-methyl-9-(phenylsulfonyl)-2,3,4,9-tetrahydro-1H-carbazole-3-carboxamide (**23**).* The title product **23** was obtained as an off-white gum (15 mg, 27% yield) after purification by silica gel flash column chromatography eluting with EtOAc/hexanes (1:1 to 100% EtOAc). $[\alpha]_D^{20}$ −14.0 (c 0.73, $CHCl_3$); IR (neat) 2965, 1638, 1452, 1368, 1172, 1150, 1092, 1056, 998, 750, 728, 686, 596 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11−8.05 (m, 1H), 7.64 (d, J = 7.5 Hz, 2H), 7.59−7.56 (m, 1H), 7.49−7.43 (m, 1H), 7.38−7.32 (m, 2H), 7.25−7.22 (m, 2H), 5.26 (d, J = 6.5 Hz, 1H), 3.66 (s, 3H), 3.39−3.33 (m, 1H), 3.16 (d, J = 6.5 Hz, 2H), 2.90 (s, 3H), 2.59−2.46 (m, 1H), 2.10 (dq, J = 14.8, 7.5 Hz, 1H), 1.85−1.75 (m, 2H), 1.08 (s, 9H), 0.95 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 139.4, 136.8, 136.7, 133.2, 128.9, 128.8, 126.2, 124.3, 123.5, 120.2, 118.9, 114.4, 60.3, 56.5, 52.5, 51.2, 33.3, 26.6, 26.1, 23.3, 22.7, 8.7; HRMS (ESI) calc'd for $C_{27}H_{35}N_3O_5S_2$ + Na = 568.1916, found 568.1900.

General Procedure for the One-Pot Arene-fused Domino Michael/Mannich/*N*-Allylation Reaction. To a stirred solution of sulfinimine **7** (40 mg, 0.1 mmol) in THF (3 mL) was added LHMDS (0.12 or 0.22 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 1 h. A solution of methyl ethacrylate (0.15 or 0.3 mmol) in THF (1 mL) was added at −78 °C. Stirring was continued at −78 °C for 2 h. Then a solution of allyl bromide (60.5 mg, 0.5 mmol) in DMF was added. The reaction mixture was warmed to rt and stirred overnight. The reaction was quenched with saturated aq. NH_4Cl (20 mL) and diluted with H_2O (12 mL), followed by extraction with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (3 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting EtOAc/hexanes (3:7) to afford **31** as a white foam.

*o-Tolualdehyde N-t-Butyl Sulfinimine (**24**).* A mixture of *o*-tolualdehyde **27** (1.15 mL, 10 mmol), (*R*)-*tert*-butanesulfinamide (1.45 g, 12 mmol), and $Ti(OEt)_4$ (6.2 mL, 30 mmol) in THF (50 mL) was stirred at rt overnight. The reaction was quenched with brine (10 mL) and the resulting suspension was filtered through a short pad of Celite. The solid cake was washed with ethyl acetate, and the separated organic layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc/hexanes (1:9) to afford 1.76 g (79%) of **24** as a pale yellow oil. $[\alpha]_D^{20}$ −141.8 (c 2.75, $CHCl_3$); IR (neat) 3491, 2959, 2925, 2359, 1604, 1589, 1567, 1456, 1362, 1082, 758, 716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.91 (dd, J = 7.5, 1.1 Hz, 1H), 7.39 (td, J = 7.5, 1.3 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 3.8 Hz, 1H), 2.61 (s, 3H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 139.4, 132.1, 131.9, 131.3, 129.4, 126.3, 57.5, 22.5, 19.9; HRMS (ESI) calc'd for $C_{12}H_{17}NOS$ + H = 224.1109, found 224.1102.

*2-Methylpyridine-3-carboxaldehyde N-t-Butyl Sulfinimine (**25**).* A mixture of 2-methylpyridine-3-carboxaldehyde **28** (0.28 g, 2.31 mmol), (*R*)-*tert*-butanesulfinamide (0.34 g, 2.8 mmol), and $Ti(OEt)_4$ (1.9 mL, 9.16 mmol) in THF (20 mL) was stirred at rt overnight. The reaction was quenched with brine (5 mL) and the resulting suspension was filtered through a short pad of Celite. The solid cake was washed with ethyl acetate, and the separated organic layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc/hexanes (1:1)→EtOAc (100%) to afford 390 mg (75%) of **25** as a pale yellow oil. $[\alpha]_D^{20}$ − 193.7 (c 1.0, $CHCl_3$); IR (neat) 3522, 2980, 2961, 2360, 2340, 1598, 1581, 1435, 1363, 1084, 805, 729, 708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.61 (dd, J = 4.8, 1.8 Hz, 1H), 8.19 (dd, J = 7.9, 1.8 Hz, 1H), 7.26 (dd, J = 7.9, 4.8 Hz, 1H), 2.83 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3, 158.8, 151.8, 136.4, 127.8, 121.6, 57.8, 22.8, 22.5; HRMS (ESI) calc'd for $C_{11}H_{16}N_2OS$ + H = 225.1062, found 225.1061.

*Ethyl 2-Methylpyrrole-1-benzenesulfonyl-3-carboxylate (**30**).* To a suspension of NaH (60% in mineral oil, 68 mg, 1.7 mmol) in DMF (5 mL) was added a solution of ethyl 2-methylpyrrole-1-H-3-carboxylate (235 mg, 1.53 mmol) in DMF (10 mL) at 0 °C. The reaction mixture was stirred at rt for 30 min. Then the resulting reaction mixture was cooled to 0 °C, followed by slow addition of $PhSO_2Cl$ (0.29 mL, 2.27 mmol). The reaction mixture was allowed to warm to rt and the stirring was continued at rt overnight. The reaction was quenched with saturated aq. NH_4Cl (20 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (4 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc/hexanes (1:9) to afford 433 mg (96%) of **30** as a colorless oil. IR (neat) 2980, 2361, 1707, 1372, 1298, 1174, 1156, 1137, 1089, 729, 686, 596 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.83−7.81 (m, 1H), 7.65−7.62 (m, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.29 (d, J = 3.5 Hz, 1H), 6.62 (d, J = 3.5 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.62 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 138.4, 136.9, 134.2, 129.6, 127.1, 120.9, 117.6, 111.9, 60.1, 14.3, 11.9; HRMS (ESI) calc'd for $C_{14}H_{15}NO_4S$ + Na = 316.0619, found 316.0611.

*2-Methylpyrrole-1-benzenesulfonyl-3-methanol (**30−1**).* To a stirred solution of **30** (420 mg, 1.43 mmol) in CH_2Cl_2 (15 mL), was added DIBAL (1.0 M in CH_2Cl_2, 1.72 mL, 1.72 mmol) slowly at −78 °C. The reaction mixture was stirred at −78 °C for 30 min. Then another portion of DIBAL (1.0 M in CH_2Cl_2, 1.72 mL, 1.72 mmol) was added. The stirring was continued at −78 °C for another 30 min. The reaction was quenched with a saturated solution of Rochelle's salt (10 mL) at −78 °C. The resulting mixture was allowed to warm to rt and vigorously stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (1 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was used in the next reaction without further purification.

*2-Methylpyrrole-1-benzenesulfonyl-3-carboxaldehyde (**31**).* To a solution of the above alcohol **30−1** (359 mg, 1.43 mmol) in CH_2Cl_2 (15 mL) were added DMSO (1.42 mL, 20 mmol), DIPEA (0.8 mL, 4.59 mmol), and SO_3·pyridine (682 mg, 4.28 mmol) at rt. The reaction mixture was stirred at rt for 30 min. The reaction was quenched with addition of H_2O (12 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (1 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc/hexanes (1:4) to

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afford 305 mg (86%) of **31** as a white solid. mp = 74.4−75.8 °C; IR (neat) 2980, 2851, 2361, 1670, 1558, 1420, 1369, 1291, 1177, 1152, 1088, 1019, 725, 685, 650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.88−7.85 (m, 2H), 7.70−7.66 (m, 1H), 7.59−7.56 (m, 2H), 7.34 (d, J = 3.6 Hz, 1H), 6.65 (d, J = 3.6 Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.4, 138.7, 138.1, 134.6, 129.7, 127.2, 126.0, 122.5, 109.8, 11.2; HRMS (ESI) calc'd for $C_{12}H_{11}NO_3S$ + H = 250.0538, found 250.0529.

*2-Methylpyrrole-1-benzenesulfonyl-3-carboxaldehyde N-t-Butyl Sulfinimine (**26**).* A mixture of **31** (0.3 g, 1.2 mmol), (*R*)-*tert*-butanesulfinamide (175 mg, 1.44 mmol), and $Ti(OEt)_4$ (1 mL, 4.8 mmol) in THF (12 mL) was stirred at rt overnight. The reaction was quenched with brine (5 mL) and the resulting suspension was filtered through a short pad of Celite. The solid cake was washed with ethyl acetate, and the separated organic layer was washed with brine (1 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc/hexanes (1:4 to 3:7) to afford 410 mg (97%) of 2-methylpyrrole-1-benzenesulfonyl-3-carboxaldehyde *N*-*t*-butyl sulfinimine as a pale gum. $[\alpha]_D^{20}$ −214.3 (*c* 1.3, $CHCl_3$); IR (neat) 2980, 2361, 2340, 1592, 1372, 1291, 1187, 1177, 1155, 1078, 1020, 728, 590 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.86−7.84 (m, 2H), 7.68−7.63 (m, 1H), 7.58−7.52 (m, 2H), 7.36 (d, J = 3.6 Hz, 1H), 6.68 (d, J = 3.6 Hz, 1H), 2.52 (s, 3H), 1.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 138.4, 135.5, 134.4, 129.6, 127.1, 123.0, 122.6, 110.0, 57.3, 22.4, 11.3; HRMS (ESI) calc'd for $C_{16}H_{20}N_2O_3S_2$ + H = 353.0994, found 353.0985.

*Methyl (4R,5S)-4-(((R)-tert-Butylsulfinyl)amino)-5-ethyl-1-((phenylperoxy)thio)-4,5,6,7-tetrahydro-1H-indole-5-carboxylate (**34**).* To a stirred solution of 2-methylpyrrole-1-benzenesulfonyl-3-carboxaldehyde *N*-*t*-butyl sulfinimine **26** (40 mg, 0.11 mmol) in THF (2 mL) was added LHMDS (1.0 M in THF, 0.13 mL, 0.13 mmol) at −78 °C. The resulting mixture was stirred at −78 °C for 1 h. Then a solution of methyl ethacrylate (20 mg, 0.17 mmol) in THF (1 mL) was added at −78 °C. The reaction mixture was allowed to warm to rt and the stirring was continued overnight. The reaction was quenched with saturated aq. NH_4Cl (4 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (1 × 4 mL). The combined organic layers were washed with brine (1 × 4 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc/hexanes (3:7 to 1:1) to afford 8 mg of **26**, and 14 mg (27%) of **34** as a white foam. $[\alpha]_D^{20}$ −90.4 (*c* 1.1, $CHCl_3$); IR (neat) 2970, 2360, 2341, 1735, 1718, 1448, 1370, 1185, 1127, 1067, 755, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73−7.71 (m, 2H), 7.62−7.58 (m, 1H), 7.51−7.48 (m, 2H), 7.24 (d, J = 3.4 Hz, 1H), 6.37 (d, J = 3.4 Hz, 1H), 4.38−4.35 (m, 2H), 3.63 (s, 3H), 2.79 (dt, J = 17.8, 5.4 Hz, 1H), 2.57−2.47 (m, 1H), 2.08−2.02 (m, 1H), 1.94 (dt, J = 14.1, 5.4 Hz, 1H), 1.65 (dq, J = 14.8, 7.5 Hz, 1H), 1.42 (dq, J = 14.8, 7.5 Hz, 1H), 1.14 (s, 9H), 0.78 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 139.1, 133.7, 129.7, 129.3, 126.5, 122.5, 121.9, 113.0, 56.0, 56.0, 51.7, 51.7, 26.3, 23.3, 22.9, 20.0, 8.8; HRMS (ESI) calc'd for $C_{22}H_{30}N_2O_5S_2$ + Na = 489.1494, found 489.1486.

*Methyl (4R,5R)-4-(((R)-tert-Butylsulfinyl)amino)-5-ethyl-1-((phenylperoxy)thio)-4,5,6,7-tetrahydro-1H-indole-5-carboxylate (**35**).* The same procedure was followed as the one for the synthesis of **34**. The residue was purified by flash column chromatography eluting with EtOAc/hexanes (3:7 to 1:1) to afford 8 mg (16%) of **35** as a pale gum. $[\alpha]_D^{20}$ −104.1 (*c* 0.76, $CHCl_3$); IR (neat) 2980, 2360, 2341, 1725, 1558, 1448, 1370, 1238, 1185, 1126, 1068, 754, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72−7.65 (m, 2H), 7.61−7.58 (m, 1H), 7.51−7.48 (m, 2H), 7.21 (d, J = 3.2 Hz, 1H), 6.29 (d, J = 3.2 Hz, 1H), 4.70 (d, J = 7.1 Hz, 1H), 3.37 (s, 3H), 3.35 (d, J = 7.1 Hz, 1H), 2.82−2.78 (m, 1H), 2.68−2.58 (m, 1H), 2.12−2.08 (m, 1H), 1.78 (dq, J = 14.6, 7.3 Hz, 1H), 1.72−1.67 (m, 1H), 1.63−1.55 (m, 1H), 1.16 (s, 9H), 0.87 (t, J = 7.3 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 139.1, 133.6, 130.2, 129.3, 126.5, 123.8, 122.0, 112.7, 56.2, 53.3, 51.4, 51.1, 28.2, 25.0, 22.7, 20.8, 8.7; HRMS (ESI) calc'd for $C_{22}H_{30}N_2O_5S_2$ + Na = 489.1494, found 489.1485.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02551.

NMR spectra (^1H and ^{13}C) for **10**, **11**, **15**, **16**, **17**, **18**, **19**, **20**, **21**, **22**, **23**, **24**, **25**, **30**, **31**, **26**, **34**, and **35** (PDF)

X-ray crystallographic data of compound **16** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Saxton, J. E. *Nat. Prod. Rep.* **1997**, *14*, 559.
(2) Saxton, J. E. In *The Alkaloids: Chemistry and Biology*; Geoffrey, A. C., Ed.; Academic Press: 1998; Vol. *51*, p 1.
(3) Saxton, J. E. In *The Alkaloids: Chemistry and Biology*; Geoffrey, A. C., Ed.; Academic Press: 1998; Vol. *50*, p 343.
(4) Sirasani, G.; Andrade, R. B. *Org. Lett.* **2009**, *11*, 2085.
(5) Sirasani, G.; Andrade, R. B. *Org. Lett.* **2011**, *13*, 4736.
(6) Sirasani, G.; Andrade, R. B. In *Strategies and Tactics in Organic Synthesis*; Michael, H., Ed.; Academic Press: 2013; Vol. *9*, p 1.
(7) Sirasani, G.; Paul, T.; Dougherty, W.; Kassel, S.; Andrade, R. B. *J. Org. Chem.* **2010**, *75*, 3529.
(8) Teijaro, C. N.; Zhao, S.; Kokkonda, P.; Andrade, R. B. *Synthesis* **2015**, *47*, 1547.
(9) Kokkonda, P.; Brown, K. R.; Seguin, T. J.; Wheeler, S. E.; Vaddypally, S.; Zdilla, M. J.; Andrade, R. B. *Angew. Chem., Int. Ed.* **2015**, *54*, 12632.
(10) Zhao, S.; Sirasani, G.; Vaddypally, S.; Zdilla, M. J.; Andrade, R. B. *Angew. Chem., Int. Ed.* **2013**, *52*, 8309.
(11) Zhao, S.; Andrade, R. B. *J. Am. Chem. Soc.* **2013**, *135*, 13334.
(12) Gallagher, T.; Magnus, P.; Huffman, J. *J. Am. Chem. Soc.* **1982**, *104*, 1140.
(13) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993.
(14) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003.
(15) Zhou, P.; Chen, B.-C.; Davis, F. A. In *Advances in Sulfur Chemistry*; Raynor, C. M., Ed.; JAL Press: Samford, CT, 2000; Vol. *2*, p 249.10.1016/S1874-5296(00)80020-0
(16) Davis, F. A.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13.
(17) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.
(18) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.
(19) Peltier, H. M.; Ellman, J. A. *J. Org. Chem.* **2005**, *70*, 7342.
(20) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

DOI: 10.1021/acs.joc.6b02551
J. Org. Chem. 2017, 82, 521−531

(21) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403.
(22) Mohanakrishnan, A. K.; Srinivasan, P. C. *J. Org. Chem.* **1995**, *60*, 1939.
(23) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12.
(24) Sureshbabu, R.; Mohanakrishnan, A. K. *J. Heterocycl. Chem.* **2012**, *49*, 913.
(25) Sureshbabu, R.; Balamurugan, R.; Mohanakrishnan, A. K. *Tetrahedron* **2009**, *65*, 3582.
(26) Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, *2008*, 3707.
(27) Kovalskiy, D. A.; Perevalov, V. P. *Chem. Heterocycl. Compd.* **2009**, *45*, 1053.
(28) Bellur, E.; Görls, H.; Langer, P. *J. Org. Chem.* **2005**, *70*, 4751.
(29) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(30) Pasquinet, E.; Rocca, P.; Godard, A.; Marsais, F.; Queguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3807.
(31) Si, C.; Myers, A. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 10409.
(32) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523.
(33) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628.
(34) Senter, T. J.; Fadeyi, O. O.; Lindsley, C. W. *Org. Lett.* **2012**, *14*, 1869.
(35) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(36) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
(37) Rubiralta, M.; Diez, A.; Bosch, J.; Solans, X. *J. Org. Chem.* **1989**, *54*, 5591.
(38) Cheng, B.; Sunderhaus, J. D.; Martin, S. F. *Org. Lett.* **2010**, *12*, 3622.
(39) Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685.
(40) Mander, L. N.; Shing, T. K. M.; Yeung, Y. Y. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd, 2001.
(41) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966.
(42) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1992**, *70*, 256.
(43) Kuang, Y. Y.; Chen, F. E. *Org. Prep. Proced. Int.* **2005**, *37*, 184.
(44) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

DOI: 10.1021/acs.joc.6b02551
J. Org. Chem. 2017, 82, 521−531