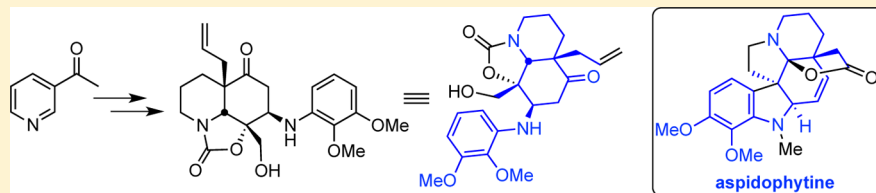


Studies Directed toward the Synthesis of Aspidophytine: Construction of Its Perhydroquinoline Core

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S Supporting Information



ABSTRACT: We have developed an efficient route for the synthesis of the perhydroquinoline core of the indole alkaloid aspidophytine (2), starting from commercially available and inexpensive 3-acetylpyridine. This densely functionalized perhydroquinoline core displays four contiguous stereocenters including an all-carbon quaternary center. The synthetic sequence features a highly effective Diels–Alder reaction using a carbamate-substituted siloxy diene accompanied by a spontaneous intramolecular substitution of the newly formed 3°-alkyl bromide with a carbamate group. The installation of the electron-rich aniline moiety was accomplished via a TBSOTf-mediated intramolecular aza-Michael reaction, and the relative stereochemistry of the aza-Michael product (30) was confirmed by X-ray crystallographic analysis. Among the useful transformations that were developed through this study is a highly enantioselective Diels–Alder reaction of a versatile cyclic carbamate siloxy diene.

INTRODUCTION

Haplophytine (1) is a heterodimeric indole alkaloid first isolated by Snyder and co-workers in 1952 (Figure 1).¹ It is the

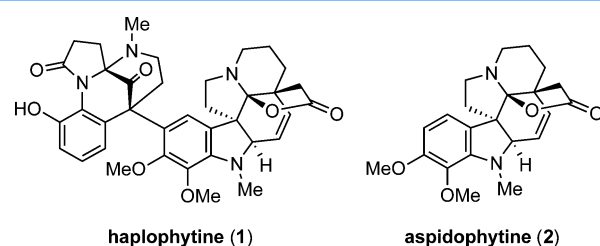


Figure 1. Indole alkaloids haplophytine (1) and aspidophytine (2).

major constituent of an insecticidal/anticochroach powder prepared from the dried leaves of the Mexican plant *Haplophyton cimidum* (family Apocynaceae).² The structure elucidation of haplophytine (1) was accomplished in 1973 after the extensive efforts of Cava, Yates, and Zacharias, which included spectroscopic, crystallographic, and chemical degradation studies.³ More recently, Alam and co-workers reported the isolation of 15 alkaloids from *Haplophyton crooksii* (Apocynaceae), and haplophytine, one of the alkaloids isolated in this study, was found to exhibit moderate *in vitro* inhibition of acetylcholinesterase activity.⁴

Given its highly complex and synthetically challenging structure, it is not surprising that haplophytine has attracted significant attention from leading laboratories in the synthetic community.^{5,6} Many of the initial efforts were directed toward

the total synthesis of its right-hand domain, aspidophytine (2), which is thought to be the key biosynthetic and synthetic precursor to haplophytine (1), as well as the acidic degradation product of the natural product.^{3c} In 1999, Corey and co-workers reported the first total synthesis of aspidophytine, which proceeded through an ingenious tricyclization of a tryptamine derivative. Several other research groups followed up with their own creative solutions to the alkaloid target.⁷ The total synthesis of haplophytine (1) has been accomplished by the groups of Fukuyama/Tokuyama and Nicolaou/Chen.⁶

In 1997, our group contributed amino siloxy dienes to chemists' repertoire of dienes for organic synthesis.^{8,9} Not only are these dienes highly reactive, allowing reactions to take place at considerably lower temperature than well established dienes, but also they give cycloadducts with near complete endo-selectivity with several different types of dienophiles. Of special significance is that these dienes give rise to highly functionalized cycloadducts in which a nitrogen atom has been introduced in a stereocontrolled manner. These attributes make amino siloxy dienes powerful synthons for natural products synthesis, and this capability has been demonstrated by us¹⁰ and others¹¹ through successful total syntheses. For example, in the synthesis of tabersonine (3),^{10b} and subsequently its asymmetric synthesis and that of vindoline,^{10c,d} we constructed the C-ring of the alkaloid by the Diels–Alder

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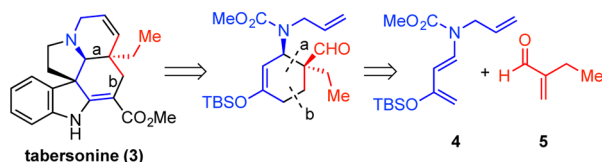
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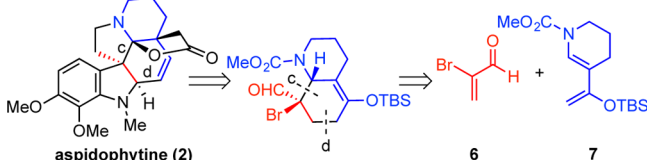
reaction of diene **4** and dienophile **5**, leading to the formation of bonds *a* and *b* (Scheme 1). For the synthesis of

Scheme 1. Alternate Bond Disconnections in the Retrosyntheses of Tabersonine (3) and Aspidophytine (2)

Earlier work: Rawal, 1998, Ref. 10b



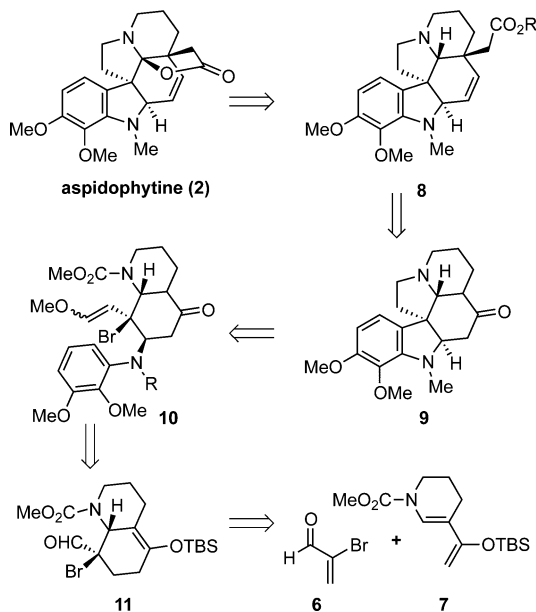
This work:



aspidophytine, we opted to undertake a different strategy to show the versatility of amino and carbamate silyloxy dienes. In this alternate approach, dienophile **6** and diene **7** were selected as the Diels–Alder reaction partners, such that their cycloaddition would construct the alkaloid core via the formation of bonds *c* and *d* instead of *a* and *b* (Scheme 1).

A fuller strategy to aspidophytine (**2**) based on the alternate cycloaddition reaction was devised, as detailed in a retrosynthetic sense in Scheme 2. According to this analysis, the

Scheme 2. Retrosynthesis of Aspidophytine (2)



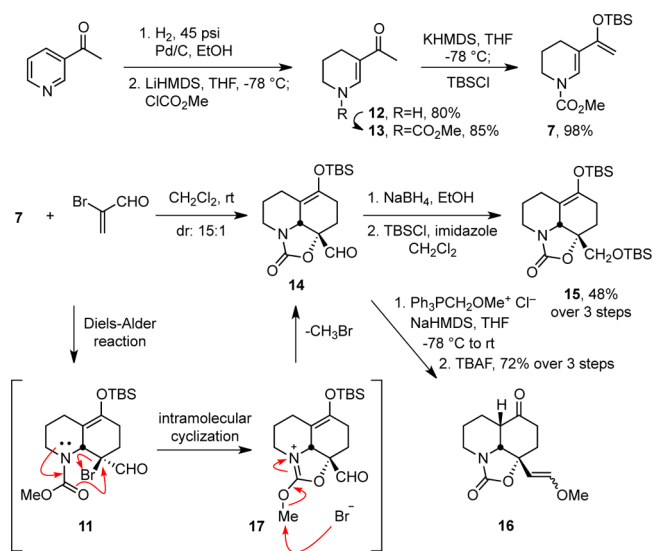
target would be prepared from ester **8** by the oxidative lactone formation methodology that was nicely utilized by Corey and co-workers in their total synthesis of aspidophytine.^{7a} Ester **8** was then expected to be synthesized from ketone **9** by the α -alkylation followed by its conversion to the alkene. A challenging step in the planned sequence was expected to be construction of the all-carbon quaternary center of the indoline unit of **9** from intermediate **10**. Treatment of **10** with a Lewis acid or a silver(I) salt was expected to promote departure of the

bromide, resulting in the formation of a carbocation that would be stabilized by the electron-donating methoxyvinyl group. An intramolecular Friedel–Crafts-type cyclization reaction between the electron-rich aniline ring and the newly formed carbocation would form the needed C–C bond, resulting in the formation of the indoline unit. Intermediate **10** was expected to be synthesized by an intermolecular aza-Michael reaction between the requisite aniline derivative and the enone, which would in turn be obtained from silyl enol ether **11**. Finally, in another pivotal step, the fused bicyclic intermediate **11** would be generated by a Diels–Alder reaction between carbamate silyloxy diene **7** and 2-bromoacrolein (**6**).

RESULTS AND DISCUSSION

The required carbamate silyloxy diene **7** was prepared in three steps starting from commercially available and inexpensive 3-acetylpyridine (Scheme 3).¹² Hydrogenation of 3-acetylpyr-

Scheme 3. Diels–Alder Reaction of Diene **7** with 2-Bromoacrolein

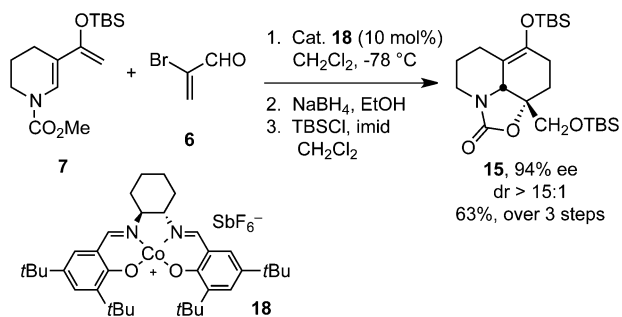


idine under an atmosphere of H₂ at 45 psi pressure using 5% Pd on activated carbon gave the partially reduced vinylogous amide **12** in 80% yield.^{12a} Deprotonation of **12** by LiHMDS and treatment of the resulting anion with ClCO₂Me afforded the vinylogous imide **13** in 85% yield. Finally, deprotonation of the ketone using KHMDS followed by *O*-silylation with TBSCl gave the *N*-carbomethoxy silyloxy diene **7** in 98% yield. The Diels–Alder reaction of diene **7** with 2-bromoacrolein, when performed at room temperature in dry CH₂Cl₂, was found to proceed smoothly in the absence of a catalyst to yield the cycloadduct in a 15:1 diastereomeric ratio (Scheme 3). However, rather than the expected Diels–Alder adduct **11**, oxazolidinone **14** was the major product of this reaction. Subsequent reduction of the aldehyde using NaBH₄ followed by the protection of the resulting primary alcohol with TBSCl/imidazole gave silyl enol ether **15** in 48% isolated yield over three steps. Alternatively, further elaboration of the Diels–Alder adduct through a Wittig–Levine homologation provided the enol–ether as a 1.4:1 mixture of isomers in 72% yield, which on treatment with TBAF removed the silyl ether to reveal ketone **16**.¹³ Formation of the unexpected oxazolidinone can be rationalized as proposed in Scheme 3. The initial Diels–

Alder reaction is expected to give the *endo* cycloadduct **11** based on previous examples with related dienes and dienophiles.^{8c,d} Subsequent intramolecular attack of the electron-rich carbamate oxygen on the α -carbon of the aldehyde would displace Br^- and form methylated oxazolidinone **17**. Finally, demethylation by the nucleophilic attack of Br^- anion would furnish the neutral oxazolidinone **14**. Although $\text{S}_{\text{N}}2$ reactions of 3° -alkyl halides are generally not favorable due to steric reasons, the intramolecular nature of the present reaction, particularly the enforced proximity of the Lewis basic carbamate oxygen to the reaction center, the ultimate formation of a 5-membered ring, and the increased electrophilicity of the alkyl bromide due to the presence of the neighboring aldehyde might account for the facility of this transformation. The direct conversion of the initial DA adduct **11** to oxazolidinone **14** could not be prevented even by running the reaction at low temperature (-78°C). As such, the initial retrosynthetic analysis was modified slightly to include oxazolidinone **14** rather than the bromide **11**.

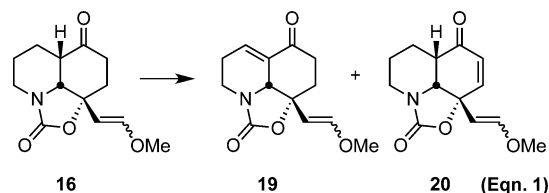
We had shown in the past that the Diels–Alder reactions of carbamate siloxy dienes could be rendered enantioselective by the use of chiral Cr(III)– and Co(III)–salen complexes as catalysts.⁸ Although in those studies we had not examined a diene as elaborate as **7**, consideration of the transition state that we had proposed for the observed enantioselectivity suggested that diene **7** could be a successful partner for the salen catalyzed cycloaddition. Indeed, when the Diels–Alder reaction between **6** and **7** was run at -78°C in the presence of Co–salen catalyst **18** (10 mol %), the desired product (**15**) was obtained with 94% ee and a dr of >15:1 after reduction and TBS protection (63% yield over three steps, Scheme 4). This reaction was carried out successfully on gram scale.

Scheme 4. Enantioselective Diels–Alder Reaction of Diene 7



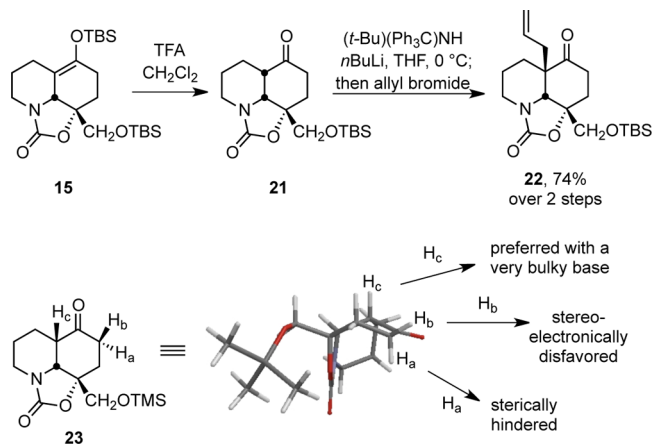
Having established routes that provide efficient access to the cycloadducts through racemic and enantioselective Diels–Alder chemistry, we then used the racemic product to explore methods for introduction of the aniline component, as required in intermediate **10** (Scheme 2). Introduction of unsaturation in the core of the molecule (ketone **16**), to allow installation of the aniline through a Michael reaction, proved more challenging than expected. Attempted use of LDA as a base for kinetic deprotonation followed by selenation with PhSeCl and selenoxide elimination gave primarily the starting ketone, but with the oxazolidinone having been fragmented, along with a small amount of an enone in which the double bond was inside the piperidine ring, indicative of deprotonation and selenation of the more substituted side. Deprotonation with the more hindered LiHMDS left the carbamate untouched, and upon selenation and oxidative elimination afforded a 1:1

mixture of regioisomeric enones, tentatively assigned as **19** and **20** (eq 1).



Given the complications observed with ketone **16**, attention was directed at the elaboration of silyl enol ether **15**. Treatment of **15** with trifluoroacetic acid cleanly afforded ketone **21** with a *cis* ring fusion (Scheme 5). Remarkably, deprotonation of **21**

Scheme 5. Regioselective Allylation of Ketone 21



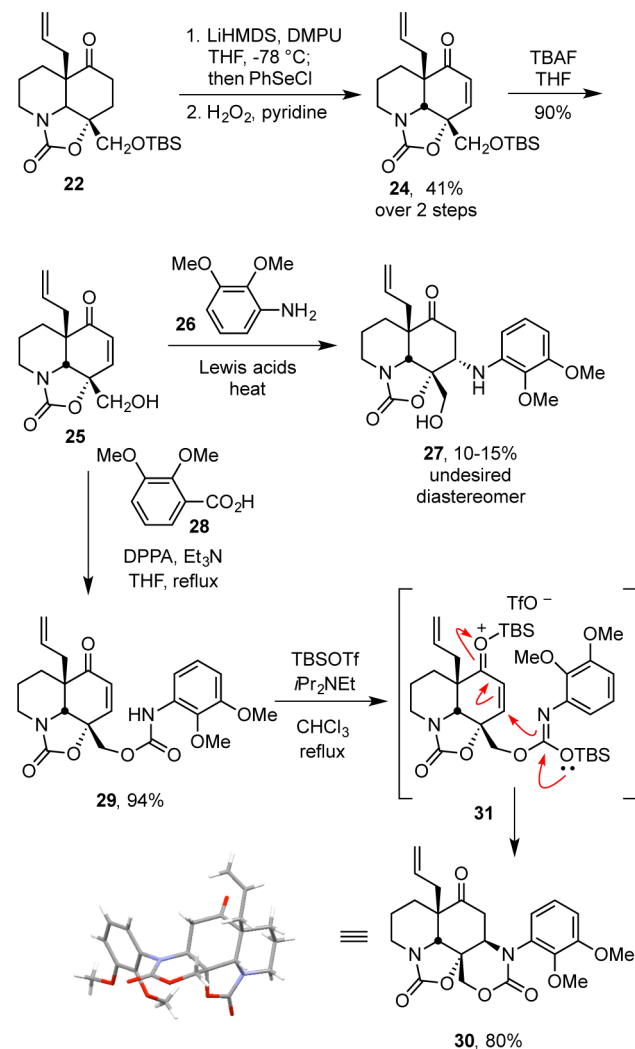
with the extremely bulky base $(t\text{-Bu})(\text{Ph}_3\text{C})\text{NHLi}$ ¹⁴ followed by the reaction of the resulting enolate with allyl bromide allowed the formation of the needed quaternary center with ketone **22** being isolated in 74% yield over two steps. Initially, the relative configuration of this product was assigned through the nuclear Overhauser effect (NOE) correlations obtained from its NOESY spectrum. This assignment was later confirmed unequivocally through the X-ray crystallographic analysis of a more advanced intermediate (compound **30**, see below). Finally, it is worth mentioning that the use of $(t\text{-Bu})(\text{Ph}_3\text{C})\text{NHLi}$ was crucial for the success of this transformation as less bulky bases such as LiHMDS or LiTMP were found to give a ca. 1:1 mixture of regioisomeric enolates, as noted for ketone **16**.

At first glance, these observations seem untenable, given that the bulkier base has promoted formation of the enolate from the sterically more hindered position. However, this counter-intuitive situation can be better understood by considering the conformation of the molecule in conjunction with the steric and stereoelectronic requirements for enolate formation. The energy-minimized structure¹⁵ of the TMS-protected analogue **23** is shown in Scheme 5. While H_b appears to be sterically the most accessible proton for enolate formation, its abstraction is stereoelectronically disfavored due to the poor alignment of the σ -bond of the C–H with the $\text{C}=\text{O}$ π^* orbital. On the other hand, H_a , which is more properly oriented for deprotonation, is shielded from the base, especially a very bulky base, as it is positioned in the concave region of the tricyclic framework. Finally, even though H_c is situated on a tertiary carbon, it is positioned on the convex face of the molecule, and its abstraction is stereoelectronically favored (better $\sigma_{\text{C-H}}-\pi^*_{\text{C=O}}$

overlap). The above rationale may explain the surprising observation that deprotonation by a bulky base is favored at the more substituted position of bicyclic ketone **21**.

We next investigated the oxidation of ketone **22** to enone **24** (Scheme 6). After an extensive screening of the common

Scheme 6. Intramolecular Aza-Michael Reaction



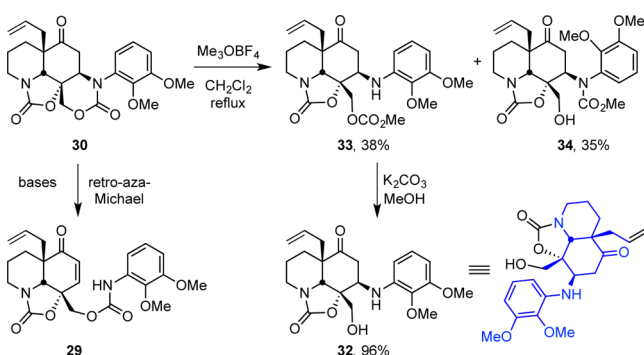
methods available for this transformation, we found the selenoxide elimination method to be the highest yielding.¹⁶ Formation of the enolate with LiHMDS in a mixture of DMPU and THF and its subsequent treatment with PhSeCl gave the α -selenylated product with a dr of 10:3. Oxidation of this intermediate with H₂O₂ followed by elimination of PhSeOH afforded enone **24** in 41% yield over two steps. It should be noted that this reaction was performed using 3.81 g of ketone **22** and afforded a useful amount (1.56 g) of the enone product. The deprotection of the TBS-protected alcohol proceeded uneventfully and provided the free alcohol **25** in 90% yield. Similar to the above case, this step was also performed on gram scale (1.56 g of **24**) and afforded the free alcohol product in 87% yield (0.95 g of **25**).

With enone **25** in hand, we next sought to perform the aza-Michael reaction that would form the C–N bond required for construction of the indoline unit (Scheme 6). For this purpose, 2,3-dimethoxyaniline (**26**) was prepared in two steps from 2,3-dimethoxybenzoic acid, following a reported procedure.¹⁷ First,

the uncatalyzed reaction between enone **25** and aniline **26** was tested. However, when the reaction was carried out in CH₃CN (room temperature, then 80 °C) or in CH₃OH (room temperature, then 60 °C), none or only trace amounts of the conjugate addition product were obtained. Lewis acid catalyzed intermolecular aza-Michael reactions of amine and aniline derivatives with α,β -unsaturated carbonyl compounds have been investigated extensively, and several of the reported conditions were investigated.¹⁸ Among the different Lewis acids examined as catalysts for this reaction, the most promising result was obtained when a mixture of **25** and excess 2,3-dimethoxyaniline (**26**) in the presence of ZrOCl₂·8H₂O¹⁹ was heated at 110 °C for 24 h, which provided the aza-Michael product **27** in 13% yield along with 60% recovered enone. Disappointingly, this aza-Michael product was later determined to be the undesired diastereomer, formed through the attack of the aniline derivative from the α -face of the enone.

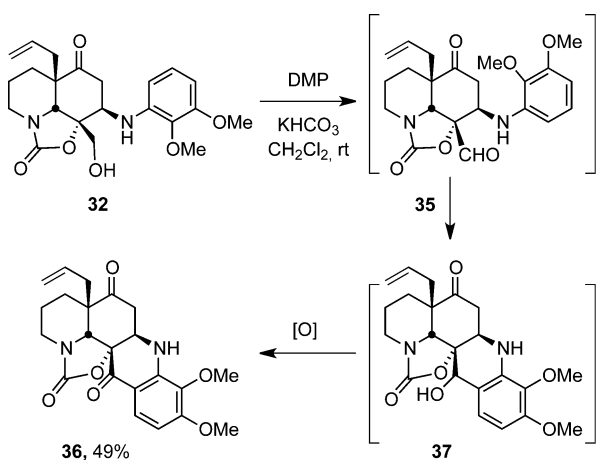
To overcome formation of the undesired diastereomer, we explored the use of an intramolecular cyclization strategy.²⁰ Such an aza-Michael addition was expected not only to give the correct configuration but also to be more favorable based on entropic considerations. Initial attempts using silicon and aminal tethers to achieve this goal proved to be unfruitful. Attention was then directed to the utilization of a carbamate tether to deliver the nucleophile. The tethering was achieved by heating a mixture of **25**, 2,3-dimethoxybenzoic acid (**28**), DPPA,²¹ and Et₃N in refluxing THF, which gave the carbamate product **29** in 94% isolated yield (Scheme 6). We next sought to investigate the key intramolecular aza-Michael reaction. Unfortunately, basic conditions using NaH, KHMDS (catalytic or stoichiometric amounts), or KHMDS/18-crown-6 did not give any desired cyclization product.²² We were delighted to see, however, that the cyclic carbamate **30** was obtained in 80% isolated yield when the reaction was carried out using TBSOTf and Hunig's base (*i*-Pr₂NEt) in refluxing CHCl₃. It is likely that the carbamate reacts with TBSOTf in the presence of Hunig's base to form the *O*-silyl imidate intermediate (**31**). Additional TBSOTf can silylate the enone carbonyl, which would promote an aza-Michael reaction by the imidate nitrogen, so as to give the desired product **30**, after desilylation during hydrolytic workup. The structure of the cyclic carbamate **30** was established unequivocally through ¹H and ¹³C NMR, HRMS, and X-ray crystallographic analysis. The crystal structure also confirmed the relative stereochemical assignments of the previous intermediates.

We next investigated the hydrolysis of the six-membered cyclic carbamate moiety of **30** to afford the desired amino alcohol product **32** (Scheme 7). This transformation is fraught with complications, as there are two different carbamates in **30**, one a five-membered ring, an oxazolidinone unit, and the other a six-membered ring carbamate that is susceptible to a retro-Michael reaction. A noteworthy aspect of the latter is that the amine component is an aniline derivative, which would render the carbonyl carbon of this carbamate more electron-deficient and hence more susceptible to nucleophiles. This anticipated higher reactivity, in particular, suggested that it might be possible to accomplish selective hydrolysis of the six-membered ring carbamate over the five-membered one. The above rationale notwithstanding, the hydrolysis step proved quite challenging. Under basic conditions, using LiOH in THF/H₂O or LiOH/LiCl in MeOH, only the retro-aza-Michael reaction was observed, and the open carbamate **29** was obtained as the sole product. On the other hand, acidic conditions using

Scheme 7. Conversion of Carbamate 30 to Amino Alcohol 32

TMSCl in MeOH (room temperature, then 50 °C), HCl in EtOH/H₂O, or TsOH in MeOH (room temperature, then 60 °C) gave no reaction. In addition, when **30** was treated with TMSBr in CH₂Cl₂ at room temperature and at 40 °C, no reaction was observed, and the starting material was returned intact. We were delighted to find, however, that treatment of **30** with Meerwein's salt²³ (Me₃OBF₄) in refluxing CH₂Cl₂ followed by aqueous workup gave isomeric carbonate **33** and carbamate **34** in 38% and 35% yields, respectively (Scheme 7). The hydrolysis of the carbonate group of **33** using K₂CO₃ in MeOH afforded the amino alcohol product **32** in 96% yield.

Finally, with amino alcohol **32** in hand, we investigated its oxidation to aldehyde **35**, which could be further elaborated through Wittig–Levine olefination followed by a Friedel–Crafts cyclization to give the desired indoline. Surprisingly, when **32** was treated with Dess–Martin periodinane (DMP)²⁴ in CH₂Cl₂ at room temperature, ketone **36** was obtained in 49% yield as the major product (Scheme 8). Compound **36** has

Scheme 8. Conversion of Alcohol 32 to Ketone 36

a bright yellow color, presumably due to the electronic push–pull system generated by the *o*-aminoacetophenone moiety. The formation of this unexpected product is the consequence of three successive reactions. The initial oxidation of alcohol **32** evidently generates aldehyde **35**, which then undergoes an intramolecular Friedel–Crafts type cyclization to give rise to **37** with formation of a six-membered ring. Further oxidation of the alcohol can then afford the observed ketone **36**. Unfortunately, despite several different conditions examined, including a variety of oxidants [inter alia, TPAP/NMO and TEMPO/

Phi(OAc)₂], the oxidation could not be stopped after only the first stage, to allow isolation of aldehyde **35** as the major product. For example, the effects of the amount of the oxidant, reaction time, and the presence of pyridine as a buffering reagent on the reaction outcome were investigated, but to little avail. By limiting the amount of the oxidant, it was possible to isolate a small amount of alcohol **37**, with even less of aldehyde **35**, but this method did not provide a usable solution to the problem. What oxidation attempts clearly demonstrated is that the electron-rich aniline will readily participate in a Friedel–Crafts cyclization, and this understanding will help shape the development of a revised endgame to aspidophytine.

CONCLUSIONS

In summary, we have developed an efficient, stereocontrolled route for the synthesis of the perhydroquinoline core of the indole alkaloid aspidophytine (**2**). The key Diels–Alder reaction of carbamate siloxy diene **7** with 2-bromoacrolein (**6**) proceeded smoothly to give a cycloadduct that underwent a spontaneous intramolecular substitution reaction between the newly formed 3°-alkyl bromide and the carbamate group. Importantly, this central cycloaddition can be rendered enantioselective by the use of the chiral Co(III)–salen catalyst **18** to afford compound **15** in 94% ee. The electron-rich aniline moiety was installed via a TBSOTf-mediated intramolecular aza-Michael reaction, and the relative configuration of the product (**30**) was established by X-ray crystallographic analysis. Finally, initial studies to oxidize the primary alcohol group in **32** led to the formation of ketone **36** via a series of reactions including an intramolecular Friedel–Crafts type cyclization between the electron-rich aniline and the newly formed aldehyde. While key elements of the strategy have proven effective, the rapidity of the unwanted cyclization reaction will necessitate revision of the endgame of the synthesis, and results from those studies will be reported in due course.

EXPERIMENTAL SECTION

General Information. All air-sensitive reactions were performed using oven-dried glassware under N₂ or Ar atmosphere. Reactions were monitored by TLC on silica gel 60 Å F254 plates visualized by UV and KMnO₄ or Hanessian's staining solutions. Flash column chromatography was performed on 32–63 μm flash silica gel. NMR spectra were measured at 500 MHz for ¹H spectra and 125 MHz for ¹³C spectra and calibrated from residual solvent signals (chloroform at 7.26 ppm and DMSO at 2.50 ppm for ¹H spectra; chloroform at 77.0 ppm and DMSO at 39.51 ppm for ¹³C spectra). Infrared spectra were measured on NaCl plates. Melting points are uncorrected. High-resolution mass spectra (ESI) were obtained using an ion trap mass analyzer.

Dichloromethane (CH₂Cl₂), toluene, and tetrahydrofuran (THF) were purified by passage over activated alumina using a commercial solvent purification system. Hunig's base (*i*Pr₂NEt) was distilled under nitrogen and stored at 0 °C over KOH pellets.

Methyl 5-(1-((*tert*-Butyldimethylsilyloxy)vinyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (7**).** A solution of vinylogous imide **13** (668 mg, 3.65 mmol) in 5 mL of anhydrous THF was added dropwise over 10 min to a solution of KHMDs (8.75 mL, 0.5 M in toluene, 4.38 mmol) in THF (10 mL) at –78 °C. The resulting solution was warmed to –55 °C over 1 h and then cooled to –78 °C. A solution of TBSCl (659 mg, 4.38 mmol) in 5 mL of THF was added dropwise, and the reaction mixture was warmed to room temperature over 2 h. The suspension was filtered through Celite, rinsed with Et₂O, and then concentrated in vacuo to a yellow oil. Kugelrohr bulb-to-bulb distillation (225 °C, 0.3 mmHg) afforded pure diene **7** (1.06 g, 98%) as a pale yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.50–7.38

(m, 1H), 4.25 (s, 1H), 4.17 (s, 1H), 3.76 (s, 3H), 3.60–3.53 (m, 2H), 2.19–2.15 (m, 2H), 1.90–1.81 (m, 2H), 0.99 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.6, 154.1, 123.8, 114.3, 89.1, 53.2, 41.9, 25.9, 21.9, 21.3, 18.3, –4.5; IR (film) 2955, 2858, 1716, 1647, 1260, 1129 cm^{-1} ; MS (CI Pos) calcd for $\text{C}_{15}\text{H}_{28}\text{NO}_3\text{Si}$ 298.1, found 298.1.

(±)-(3¹R,9aS)-7-((tert-Butyldimethylsilyloxy)methyl)-9a-(((tert-butylidimethylsilyloxy)methyl)-3¹,5,6,8,9,9a-hexahydro-2H,4H-oxazolo[5,4,3-ij]quinolin-2-one (15). To a stirred solution of diene **7** (3.79 g, 12.7 mmol) in 25 mL of anhydrous CH_2Cl_2 was added a solution of 2-bromoacrolein **6** (1.89 g, 14.0 mmol) in 10 mL of CH_2Cl_2 dropwise, at room temperature, under nitrogen. The reaction was observed to be exothermic. The resulting mixture was stirred for 2 h, at which time additional 2-bromoacrolein (0.24 g, 1.8 mmol) was added. At the end of 3 h, all volatiles were evaporated in vacuo to afford the crude Diels–Alder cycloadduct as a yellow oil (dr = 15:1 by ^1H NMR analysis).

The crude product was dissolved in 30 mL of anhydrous EtOH and cooled to 0 °C. NaBH_4 (722 mg, 19.1 mmol) was added portionwise, and the resulting mixture was stirred at 0 °C for 20 min and at room temperature overnight. It was then quenched with saturated NaHCO_3 solution, causing gas evolution. The mixture was stirred for 30 min, diluted with CH_2Cl_2 , and filtered by suction. The aqueous phase was extracted four times with CH_2Cl_2 , and the combined organic phase was dried over MgSO_4 . Filtration and concentration in vacuo afforded crude alcohol product (3.82 g) as a light yellow solid.

The crude alcohol (3.03 g) was dissolved in 25 mL of anhydrous CH_2Cl_2 , and imidazole (1.82 g, 26.7 mmol) was added at room temperature, under nitrogen. A solution of TBSCl (1.61 g, 10.7 mmol) in 5 mL of CH_2Cl_2 was then added slowly, and the reaction mixture was stirred for 2 days at room temperature. It was then quenched with H_2O , and the aqueous phase was extracted four times with CH_2Cl_2 . The combined organic phase was dried over MgSO_4 , filtered, and concentrated in vacuo to afford a yellow oil. Purification by flash column chromatography (EtOAc/hexanes 1:7) gave pure **15** (2.22 g, 48% over three steps) as a white solid.

Catalysis of the Enantioselective Diels–Alder Reaction by Co(III)–salen Catalyst 18. A solution of diene **7** (1.87 g, 6.27 mmol) in 10 mL of CH_2Cl_2 was added slowly to a cooled (–78 °C) solution of catalyst **18**^{8d} (526 mg, 0.63 mmol) in CH_2Cl_2 (40 mL). A solution of 2-bromoacrolein **6** (1.95 g, 14.4 mmol) in CH_2Cl_2 (10 mL) was then added dropwise over 30 min. The resulting solution was stirred at –78 °C for 2.5 h and then concentrated in vacuo to a black oil. The crude product was co-concentrated with CH_2Cl_2 (3 × 50 mL) to remove any remaining bromomethane. The crude aldehyde was dissolved in 60 mL of ethanol and cooled to 0 °C. NaBH_4 (356 mg, 9.41 mmol) was carefully added in portions, and the resulting brown mixture was stirred at room temperature for 20 min. Brine (60 mL) and Et_2O (100 mL) were then added carefully. The organic layer was washed three times with H_2O , dried over MgSO_4 , and then filtered and concentrated in vacuo. The crude product was dissolved in CH_2Cl_2 (60 mL) and treated with imidazole (854 mg, 12.5 mmol) and TBSCl (1.42 g, 9.41 mmol) sequentially at room temperature. The reaction mixture was stirred for 16 h, and then H_2O (50 mL) was added. The aqueous layer was extracted three times with CH_2Cl_2 , and the combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo to a brown oil. Purification by flash column chromatography (10% EtOAc in hexanes) gave **15** (1.78 g, 63% over three steps, 94% ee) as a brown oil: ^1H NMR (500 MHz, CDCl_3) δ 3.88 (s, 1H), 3.85 (dd, J = 13.5, 5.0 Hz, 1H), 3.68 (d, J = 10.3 Hz, 1H), 3.54 (d, J = 10.3 Hz, 1H), 2.99–2.93 (m, 2H), 2.30–2.25 (m, 1H), 2.05–1.99 (m, 2H), 1.97–1.92 (m, 1H), 1.70–1.64 (m, 2H), 1.53–1.43 (m, 1H), 0.93 (s, 9H), 0.88 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 156.8, 143.9, 110.3, 79.0, 65.8, 57.6, 41.9, 26.6, 26.1, 25.83, 25.76, 25.6, 24.0, 18.2, 18.1, –3.7, –4.0, –5.48, –5.51; IR (film) 2954, 2930, 2857, 1761, 1688, 1367, 1254, 1107, 839 cm^{-1} ; HRMS (ESI) calcd for $(\text{C}_{23}\text{H}_{43}\text{NO}_4\text{Si}_2)_\text{Na}^+$ ($M + \text{Na}$)⁺ 476.2623, found 476.2626; HPLC: OD-H, 98% hexanes, 2% *i*-PrOH, 0.8 mL/min, 7.4 min (minor), 8.2 min (major).

(±)-(3¹R,6aS,9aS)-9a-(((tert-Butyldimethylsilyloxy)methyl)-octahydro-2H,7H-oxazolo[5,4,3-ij]quinoline-2,7-dione (21). To a solution of the silyl enol ether **15** (1.726 g, 3.8 mmol) in 12 mL of anhydrous CH_2Cl_2 was added trifluoroacetic acid (TFA, 0.88 mL, 11.4 mmol) at room temperature, under nitrogen. The color of the solution first turned brown-red and then pink as the reaction proceeded. After 1 h, the reaction mixture was quenched with saturated NaHCO_3 solution and turned yellow with evolution of gas. The aqueous phase was extracted three times with CH_2Cl_2 . The combined organic phase was dried over MgSO_4 , filtered, and concentrated in vacuo to afford a yellow oil, which solidified upon standing in the refrigerator to give **21** a yellow-white solid (1.282 g). The crude product was clean enough to be used directly in the next step. Purification of a portion of the crude product by flash column chromatography (EtOAc/hexanes 1:4 to 1:3 to 1:2) gave analytically pure ketone **21** as a white solid: ^1H NMR (500 MHz, CDCl_3) δ 3.95 (d, J = 4.7, 1H), 3.80–3.76 (m, 1H), 3.72 (d, J = 10.4 Hz, 1H), 3.63 (d, J = 10.4 Hz, 1H), 2.77 (dt, J = 12.7, 3.7 Hz, 1H), 2.57–2.52 (m, 1H), 2.47–2.35 (m, 3H), 2.09 (dt, J = 14.7, 5.5 Hz, 1H), 2.01 (dq, J = 14.8, 2.7 Hz, 1H), 1.48–1.34 (m, 3H), 0.85 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 209.3, 155.1, 79.7, 67.4, 57.5, 43.6, 40.7, 33.7, 26.3, 25.6, 22.5, 19.9, 18.0, –5.6; IR (film) 2953, 2930, 2857, 1751, 1716, 1436, 1258, 1137, 1120, 1095, 1052, 839 cm^{-1} ; HRMS (ESI) Calcd for $(\text{C}_{17}\text{H}_{29}\text{NO}_4\text{Si})\text{Na}^+$ ($M + \text{Na}$)⁺ 362.1758, found 362.1750.

(±)-(3¹R,6aR,9aS)-6a-Allyl-9a-(((tert-butylidimethylsilyloxy)methyl)octahydro-2H,7H-oxazolo[5,4,3-ij]quinoline-2,7-dione (22). *t*-Bu(Ph_3C)NH (1.142 g, 3.62 mmol) was dissolved in 7 mL of anhydrous THF in a flask containing 4 Å molecular sieves, and the resulting solution was transferred to an oven-dried, 50 mL Schlenk flask under nitrogen. The solution was cooled to 0 °C, and *n*-BuLi (1.50 mL, 3.47 mmol, 2.3 M in hexanes) was added dropwise. The resulting orange-brown mixture was stirred at 0 °C for 1 h, and then a solution of ketone **21** (1.069 g, 3.15 mmol) in 11 mL of anhydrous THF was added dropwise over 10 min. Within a short time, the color turned light brown-orange, and the reaction mixture was stirred at room temperature for 2 h. Allyl bromide (410 μL , 4.73 mmol) was then added, and the reaction was allowed to proceed for 17 h. It was then quenched with H_2O , and the aqueous phase was extracted four times with CH_2Cl_2 . The combined organic phase was dried over MgSO_4 , filtered, and concentrated in vacuo to afford a brown oil. Purification by flash column chromatography (EtOAc/hexanes, 1:2) gave pure ketone **22** (888 mg, 74% over two steps) as a light yellow oil: ^1H NMR (500 MHz, CDCl_3) δ 5.65 (ddt, J = 17.4, 10.1, 7.4 Hz, 1H), 5.13 (dd, J = 10.1, 0.9 Hz, 1H), 5.04 (dd, J = 16.9, 1.5 Hz, 1H), 3.84–3.81 (m, 1H), 3.80 (d, J = 10.6 Hz, 1H), 3.76 (s, 1H), 3.66 (d, J = 10.6 Hz, 1H), 2.70 (dt, J = 12.8, 3.4 Hz, 1H), 2.53–2.41 (m, 3H), 2.36 (dd, J = 14.4, 7.2 Hz, 1H), 2.26 (dt, J = 15.0, 5.5 Hz, 1H), 2.11 (dd, J = 14.5, 7.6 Hz, 1H), 2.06 (dq, J = 15.0, 2.5 Hz, 1H), 1.56–1.52 (m, 1H), 1.35–1.25 (m, 1H), 1.15 (dt, J = 13.6, 3.7 Hz, 1H), 0.90 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 210.3, 155.2, 131.3, 119.4, 80.4, 67.8, 61.1, 49.2, 40.8, 40.6, 33.8, 30.3, 26.8, 25.8, 21.3, 18.2, –5.4, –5.5; IR (film) 3077, 2952, 2931, 2857, 1760, 1712, 1640, 1434, 1257, 1140, 1093, 840 cm^{-1} ; HRMS (ESI) calcd for $(\text{C}_{20}\text{H}_{33}\text{NO}_4\text{Si})\text{Na}^+$ ($M + \text{Na}$)⁺ 402.2071, found 402.2061.

(±)-(3¹R,6aR,9aS)-6a-Allyl-9a-(((tert-butylidimethylsilyloxy)methyl)-3¹,4,5,6,6a,9a-hexahydro-2H,7H-oxazolo[5,4,3-ij]quinoline-2,7-dione (24). To a solution of ketone **22** (3.809 g, 10.0 mmol) in 40 mL of anhydrous THF and 3.5 mL of anhydrous DMPU was added LiHMDS (13.0 mL, 13.0 mmol, 1.0 M in THF) dropwise over 5 min, at –78 °C, under nitrogen. The resulting dark brown-red solution was stirred at the same temperature for 30 min followed by the addition of a solution of PhSeCl (2.298 g, 12.0 mmol) in 10 mL of THF over 10 min. The reaction mixture was stirred at –78 °C for 4 h and then warmed to room temperature. It was then quenched with H_2O (40 mL), and the aqueous phase was extracted once with EtOAc (50 mL). The organic phase was washed with H_2O (25 mL), dried over MgSO_4 , filtered, and concentrated in vacuo to afford a dark-colored oil. Purification by flash column chromatography (EtOAc/hexanes 1:3 to 1:2) gave the selenylated product (4.438 g) as a brown oil (dr 10:3 by ^1H NMR analysis).

To a solution of the selenylated product (4.438 g) in 60 mL of CH_2Cl_2 were added sequentially anhydrous pyridine (2.0 mL, 24.9 mmol) and H_2O_2 (2.8 mL, 24.9 mmol, 30% solution in H_2O) at room temperature, under air. Heat evolution was observed after a few minutes and the reaction mixture was cooled to 0 °C. It was stirred at 0 °C for 10 min and then at room temperature for 30 min, at which point it turned almost colorless. The reaction mixture was then quenched with 30 mL of a 1:1 mixture of saturated $\text{Na}_2\text{S}_2\text{O}_3$ and NaHCO_3 solutions. The aqueous phase was extracted three times with EtOAc , and the combined organic phase was dried over MgSO_4 , filtered, and concentrated in vacuo to afford an orange oil. Purification by flash column chromatography (EtOAc /hexanes 1:3) gave pure enone **24** (1.564 g, 41% over two steps) as a colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 6.48 (dd, $J = 10.4, 1.4$ Hz, 1H), 6.13 (d, $J = 10.4$ Hz, 1H), 5.64 (ddt, $J = 17.4, 10.1, 7.5$ Hz, 1H), 5.15 (dt, $J = 10.1, 0.7$ Hz, 1H), 5.05 (dq, $J = 6.9, 1.4$ Hz, 1H), 4.00 (d, $J = 11.7$ Hz, 1H), 3.89 (d, $J = 1.3$ Hz, 1H), 3.84 (d, $J = 11.7$ Hz, 1H), 3.78 (dd, $J = 12.7, 5.1$ Hz, 1H), 2.69 (dt, $J = 12.8, 3.5$ Hz, 1H), 2.50–2.46 (m, 1H), 2.32 (dd, $J = 14.0, 7.2$ Hz, 1H), 2.20 (dd, $J = 14.0, 7.7$ Hz, 1H), 1.65–1.60 (m, 1H), 1.39 (ddq, $J = 13.5, 5.1, 3.5$ Hz, 1H), 1.14 (dt, $J = 13.7, 3.8$ Hz, 1H), 0.91 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 198.7, 154.5, 139.3, 130.8, 130.0, 120.0, 79.2, 65.4, 60.8, 47.5, 41.4, 41.1, 28.7, 25.8, 20.9, 18.3, –5.3, –5.4; IR (film) 2953, 2929, 2856, 1767, 1686, 1415, 1256, 1150, 1091, 839 cm^{-1} ; HRMS (ESI) calcd for $(\text{C}_{20}\text{H}_{31}\text{NO}_4\text{Si})\text{Na}^+$ ($M + \text{Na}$) $^+$ 400.1915, found 400.1907.

(±)-(3¹R,6aR,9aS)-6a-Allyl-9a-(hydroxymethyl)-3¹,4,5,6,6a,9a-hexahydro-2H,7H-oxazolo[5,4,3-ij]quinoline-2,7-dione (25). To a solution of the silyl ether **24** (181 mg, 0.48 mmol) in 5 mL of anhydrous THF was added TBAF (0.72 mL, 0.72 mmol, 1.0 M in THF) at room temperature, under nitrogen. Upon addition of TBAF, the color of the solution turned orange immediately. After 45 min, the reaction mixture was quenched with H_2O , and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over MgSO_4 , filtered, and concentrated in vacuo to afford an orange oil. Purification by flash column chromatography (EtOAc /hexanes, 2:1 to 3:1) gave pure alcohol **25** (113 mg, 90%) as a colorless oil.

This reaction was performed on a gram-scale using silyl ether **24** (1.564 g, 4.1 mmol), TBAF (6.2 mL, 6.2 mmol, 1.0 M in THF), and anhydrous THF (30 mL) using the same procedure. Alcohol **25** was obtained in 87% yield (953 mg): ^1H NMR (500 MHz, CDCl_3) δ 6.49 (dd, $J = 10.4, 1.5$ Hz, 1H), 6.14 (d, $J = 10.4$ Hz, 1H), 5.62 (ddt, $J = 17.0, 10.1, 7.7$ Hz, 1H), 5.16 (dt, $J = 10.0, 0.7$ Hz, 1H), 5.06 (dq, $J = 16.9, 1.4$ Hz, 1H), 4.03 (dd, $J = 13.0, 5.3$ Hz, 1H), 4.01 (s, 1H), 3.77–3.71 (m, 2H), 3.45 (br s, 1H), 2.73 (dt, $J = 12.8, 3.5$ Hz, 1H), 2.50–2.46 (m, 1H), 2.28 (dd, $J = 14.0, 7.0$ Hz, 1H), 2.22 (dd, $J = 14.0, 7.8$ Hz, 1H), 1.65–1.61 (m, 1H), 1.39 (ddq, $J = 13.5, 5.1, 3.5$ Hz, 1H), 1.14 (dt, $J = 13.7, 3.8$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 198.5, 154.9, 138.6, 130.5, 130.3, 120.2, 79.8, 64.1, 59.9, 47.5, 41.2, 41.1, 28.6, 20.8; IR (film) 3415 (br), 2935, 2866, 1759, 1684, 1436, 1387, 1293, 1145, 1109, 1027 cm^{-1} ; HRMS (ESI) calcd for $(\text{C}_{14}\text{H}_{17}\text{NO}_4)\text{Na}^+$ ($M + \text{Na}$) $^+$ 286.1050, found 286.1046.

(±)-(3¹R,6aR,9aS)-6a-Allyl-9-((2,3-dimethoxyphenyl)amino)-9a-(hydroxymethyl)octahydro-2H,7H-oxazolo[5,4,3-ij]quinoline-2,7-dione (27). A mixture of alcohol **25** (20 mg, 0.076 mmol), 2,3-dimethoxyaniline **26** (106 mg, 0.69 mmol), and $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ (12 mg, 0.038 mmol) was stirred in an Eppendorf tube at 110 °C for 24 h. The reaction mixture was then diluted with CH_2Cl_2 , filtered, and concentrated in vacuo to give a black oil. Purification by flash column chromatography (EtOAc /hexanes 2:1) afforded the aza-Michael addition product **27** (4 mg, 13%) along with unreacted alcohol **25** (12 mg, 60%): ^1H NMR (500 MHz, CDCl_3) δ 6.91 (t, $J = 8.2$ Hz, 1H), 6.38 (dd, $J = 8.4, 1.2$ Hz, 1H), 6.24 (d, $J = 8.3$ Hz, 1H), 5.74 (ddt, $J = 17.3, 10.1, 7.5$ Hz, 1H), 5.22 (dt, $J = 10.1, 0.7$ Hz, 1H), 5.15 (dd, $J = 16.9, 1.5$ Hz, 1H), 4.62 (d, $J = 10.7$ Hz, 1H), 4.28 (ddd, $J = 13.3, 10.7, 4.2$ Hz, 1H), 4.06 (dd, $J = 11.6, 3.5$ Hz, 1H), 3.98 (s, 1H), 3.88–3.79 (m, 8H), 2.83 (dd, $J = 18.4, 4.2$ Hz, 1H), 2.78 (dt, $J = 12.7, 3.7$ Hz, 1H), 2.53–2.50 (m, 1H), 2.43–2.36 (m, 2H), 2.27 (dd, $J = 14.5, 7.6$ Hz, 1H), 2.15 (dd, $J = 7.6, 4.1$ Hz, 1H), 1.37–1.27 (m, 2H);

^{13}C NMR (125 MHz, CDCl_3) δ 208.5, 154.8, 153.1, 140.0, 136.3, 131.0, 124.5, 120.2, 104.7, 102.7, 82.4, 64.3, 61.1, 60.1, 55.8, 49.8, 48.8, 41.0, 40.9, 40.5, 30.3, 21.2; IR (film) 3397 (br), 2934, 1751, 1711, 1601, 1512, 1481, 1438, 1419, 1296, 1264, 1146, 1063 cm^{-1} ; HRMS (ESI) calcd for $(\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_6)\text{Na}^+$ ($M + \text{Na}$) $^+$ 439.1840, found 439.1832.

(±)-((3¹R,6aR,9aS)-6a-Allyl-2,7-dioxo-5,6,6a,7-tetrahydro-2H,4H-oxazolo[5,4,3-ij]quinolin-9a(3¹H)-yl)methyl (2,3-Dimethoxyphenyl)carbamate (29). To a solution of 2,3-dimethoxybenzoic acid **28** (109 mg, 0.6 mmol) in anhydrous THF (1.0 mL) were added, sequentially, DPPA (129 μL , 0.6 mmol), Et_3N (113 μL , 0.8 mmol), and a solution of alcohol **25** (105 mg, 0.4 mmol) in THF (1.5 mL) at room temperature, under nitrogen. The resulting clear, pale-yellow solution was heated to 70 °C and stirred at this temperature for 7 h. It was then cooled to room temperature and quenched with saturated NaHCO_3 solution (5 mL). The aqueous phase was extracted with EtOAc (3 × 15 mL), and the combined organic phase was dried over MgSO_4 , filtered, and concentrated in vacuo to give a light yellow oil. Purification by flash column chromatography (EtOAc /hexanes, 1:2 to 1:1) afforded carbamate **29** (166 mg, 94%) as a colorless oil which solidified upon standing in the refrigerator: ^1H NMR (500 MHz, CDCl_3 , 295 K) δ 7.70 (br s, 1H), 7.50 (br s, 1H), 7.04 (t, $J = 8.4$ Hz, 1H), 6.67 (dd, $J = 8.4, 1.3$ Hz, 1H), 6.59 (dd, $J = 10.4, 1.6$ Hz, 1H), 6.19 (d, $J = 10.4$ Hz, 1H), 5.62 (dddd, $J = 16.8, 10.2, 8.2, 6.6$ Hz, 1H), 5.16 (d, $J = 9.9$ Hz, 1H), 5.09 (dd, $J = 16.9, 1.3$ Hz, 1H), 4.60 (d, $J = 12.4$ Hz, 1H), 4.48 (d, $J = 12.4$ Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.83 (d, $J = 1.5$ Hz, 1H), 3.83–3.79 (m, 1H), 2.77 (dt, $J = 12.8, 3.5$ Hz, 1H), 2.54–2.50 (m, 1H), 2.38 (dd, $J = 14.1, 6.5$ Hz, 1H), 2.26 (dd, $J = 14.1, 8.2$ Hz, 1H), 1.68–1.64 (m, 1H), 1.46–1.37 (m, 1H), 1.17 (dt, $J = 13.7, 3.7$ Hz, 1H); ^{13}C NMR (500 MHz, CDCl_3 , 323 K) δ 7.66 (d, $J = 8.3$ Hz, 1H), 7.41 (br s, 1H), 7.01 (t, $J = 8.4$ Hz, 1H), 6.66 (d, $J = 8.3$ Hz, 1H), 6.56 (dd, $J = 10.4, 1.5$ Hz, 1H), 6.16 (d, $J = 10.4$ Hz, 1H), 5.62 (dddd, $J = 16.9, 10.2, 8.0, 6.7$ Hz, 1H), 5.15 (d, $J = 10.2$ Hz, 1H), 5.08 (dd, $J = 16.9, 1.4$ Hz, 1H), 4.59 (d, $J = 12.3$ Hz, 1H), 4.48 (d, $J = 12.4$ Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.82–3.79 (m, 2H), 2.74 (dt, $J = 12.8, 3.4$ Hz, 1H), 2.55–2.49 (m, 1H), 2.37 (dd, $J = 14.2, 6.6$ Hz, 1H), 2.25 (dd, $J = 14.2, 8.0$ Hz, 1H), 1.66–1.62 (m, 1H), 1.47–1.37 (m, 1H), 1.15 (dt, $J = 13.7, 3.7$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3 , 323 K) δ 197.6, 154.1, 152.3, 152.2, 137.8, 137.7, 131.4, 130.5, 130.3, 124.1, 120.1, 111.4, 107.9, 77.2, 65.8, 61.7, 60.8, 56.0, 47.6, 41.3, 41.2, 28.9, 20.8; IR (film) 3321, 2941, 1766, 1686, 1606, 1535, 1481, 1462, 1422, 1233, 1205, 1057, 1028, 920 cm^{-1} ; HRMS (ESI) calcd for $(\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_7\text{Na})^+$ ($M + \text{Na}$) $^+$ 465.1632, found 465.1652.

(±)-(4aS,4a¹R,10aR,12aR)-10a-Allyl-1-(2,3-dimethoxyphenyl)hexahydro-2H,4H,6H,8H-[1,3]oxazino[4,5-h]oxazolo[5,4,3-ij]quinoline-2,6,11(1H)-trione (30). To a solution of carbamate **29** (109 mg, 0.25 mmol) in 1.5 mL of anhydrous CHCl_3 were added sequentially $i\text{-Pr}_2\text{NEt}$ (174 μL , 1.0 mmol) and TBSOTf (574 μL , 2.5 mmol) at room temperature under nitrogen. The reaction mixture was heated to 60 °C and stirred at this temperature for 18 h. It was then cooled to room temperature and quenched with a saturated NaHCO_3 solution. The aqueous phase was extracted three times with CH_2Cl_2 , and the combined organic phase was dried over MgSO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography (4% MeOH in CHCl_3) afforded cyclized carbamate product **30** (87 mg, 80%) as a white solid: mp 239–240 °C dec; ^1H NMR (500 MHz, CDCl_3 , 295 K) δ 7.09 (t, $J = 8.2$ Hz, 1H), 6.95 (dd, $J = 8.4, 1.3$ Hz, 1H), 6.75 (br d, $J = 7.8$ Hz, 1H), 5.60 (ddt, $J = 17.0, 10.1, 7.6$ Hz, 1H), 5.22 (d, $J = 9.9$ Hz, 1H), 5.18 (dd, $J = 16.9, 1.2$ Hz, 1H), 4.86 (d, $J = 12.1$ Hz, 1H), 4.65 (dd, $J = 12.1, 1.4$ Hz, 1H), 4.31 (br s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.79 (dd, $J = 12.8, 4.5$ Hz, 1H), 3.75 (s, 1H), 2.76–2.68 (m, 2H), 2.55 (dd, $J = 15.5, 5.0$ Hz, 1H), 2.50–2.46 (m, 2H), 2.30 (dd, $J = 14.2, 7.9$ Hz, 1H), 1.67–1.64 (m, 1H), 1.42–1.30 (m, 1H), 1.17 (dt, $J = 8.0, 3.2$ Hz, 1H); ^{13}C NMR (500 MHz, $\text{DMSO}-d_6$, 353 K) δ 7.09–7.07 (m, 2H), 6.76 (dd, $J = 6.1, 3.4$ Hz, 1H), 5.57 (ddt, $J = 17.2, 10.1, 7.3$ Hz, 1H), 5.32 (d, $J = 12.3$ Hz, 1H), 5.19 (dd, $J = 17.0, 1.8$ Hz, 1H), 5.11 (dd, $J = 10.1, 1.9$ Hz, 1H), 4.62 (dd, $J = 12.3, 2.0$ Hz, 1H), 4.05 (ddd, $J = 12.4, 5.1, 1.8$ Hz, 1H), 3.95 (s, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.57–3.54 (m, 1H), 3.21 (t, J

= 13.5 Hz, 1H), 2.70 (dt, $J = 12.3, 3.2$ Hz, 1H), 2.56 (dd, $J = 14.2, 7.2$ Hz, 1H), 2.34–2.26 (m, 3H), 1.59–1.55 (m, 1H), 1.30–1.20 (m, 1H), 1.13 (dt, $J = 13.5, 3.4$ Hz, 1H); ^{13}C NMR (125 MHz, DMSO- d_6 , 353 K) δ 205.4, 153.6, 153.1, 150.1, 145.2, 132.8, 130.7, 123.0, 121.4, 119.1, 113.1, 74.9, 66.6, 62.1, 60.4, 59.7, 55.8, 48.5, 40.7, 40.3, 39.8, 27.4, 19.8; IR (film) 2941, 2840, 2252, 1771, 1710, 1590, 1489, 1477, 1436, 1267, 1231, 1183, 1002, 922, 851 cm^{-1} ; HRMS (ESI) calcd for $(\text{C}_{27}\text{H}_{27}\text{N}_2\text{O}_7)^+$ ($\text{M} + \text{H}$) $^+$ 443.1813, found 443.1820.

Compounds 33 and 34. To a solution of **30** (17.6 mg, 0.04 mmol) in 1.5 mL of anhydrous CH_2Cl_2 was added Me_3OBF_4 (24 mg, 0.16 mmol), and the resulting mixture was stirred at 32–34 °C under nitrogen for 3 h. It was then cooled to room temperature and quenched with H_2O . The aqueous phase was extracted three times with CH_2Cl_2 , and the combined organic phase was dried over MgSO_4 , filtered, and concentrated in vacuo. Purification by PTLC (EtOAc/hexanes, 2:1) afforded **33** (7.1 mg, 38%) and **34** (6.6 mg, 35%).

(±)-((3¹R,6aR,9R,9aS)-6a-Allyl-9-((2,3-dimethoxyphenyl)-amino)-2,7-dioxohexahydro-2H,4H-oxazolo[5,4,3-*ij*]quinolin-9a(3¹H)-yl)methyl methyl carbonate (33): ^1H NMR (500 MHz, CDCl_3) δ 6.96 (t, $J = 8.3$ Hz, 1H), 6.47 (d, $J = 8.1$ Hz, 1H), 6.41 (dd, $J = 8.3, 1.0$ Hz, 1H), 5.71 (ddt, $J = 17.3, 10.1, 7.3$ Hz, 1H), 5.19 (d, $J = 10.2$ Hz, 1H), 5.16 (dd, $J = 16.9, 1.4$ Hz, 1H), 4.78 (d, $J = 12.4$ Hz, 1H), 4.52 (d, $J = 12.5$ Hz, 1H), 4.19 (d, $J = 8.4$ Hz, 1H), 4.10–4.06 (m, 1H), 3.92 (s, 1H), 3.87–3.83 (m, 4H), 3.80 (s, 3H), 3.76 (s, 3H), 2.79–2.73 (m, 3H), 2.60 (dd, $J = 14.4, 7.1$ Hz, 1H), 2.55 (app d, $J = 13.6$ Hz, 1H), 2.32 (dd, $J = 14.4, 7.6$ Hz, 1H), 1.68–1.64 (m, 1H), 1.37–1.21 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 208.0, 155.0, 154.7, 152.4, 140.1, 135.9, 130.5, 124.6, 120.2, 105.3, 103.3, 82.1, 67.5, 61.1, 60.2, 56.1, 55.7, 55.3, 48.6, 42.7, 41.6, 41.2, 30.8, 21.1; IR (film) 2917, 2849, 1756, 1716, 1602, 1481, 1457, 1442, 1264 cm^{-1} ; HRMS (ESI) calcd for $(\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_8)\text{Na}^+$ ($\text{M} + \text{Na}$) $^+$ 497.1894, found 497.1887.

(±)-Methyl ((3¹R,6aR,9R,9aS)-6a-allyl-9a-(hydroxymethyl)-2,7-dioxooctahydro-2H,4H-oxazolo[5,4,3-*ij*]quinolin-9-yl)(2,3-dimethoxyphenyl)carbamate (34): ^1H NMR (500 MHz, CDCl_3 , 295 K) δ 7.06 (major rotamer, t, $J = 8.2$ Hz, 1H), 6.99 (minor rotamer, t, $J = 8.2$ Hz, 1H), 6.83 (major rotamer, dd, $J = 8.1, 1.6$ Hz, 1H), 6.88 (major rotamer, dd, $J = 8.4, 1.5$ Hz, 1H), 6.85 (minor rotamer, dd, $J = 8.4, 1.4$ Hz, 1H), 6.64 (minor rotamer, br d, $J = 7.6$ Hz, 1H), 5.63–5.55 (m, 1H), 5.17–5.12 (m, 2H), 4.55 (minor rotamer, br s, 1H), 4.43–4.39 (major rotamer, m, 1H), 4.13–3.98 (m, 4H), 3.91–3.82 (m, 6H), 3.73–3.66 (m, 4H), 3.61–3.55 (m, 1H), 2.98 (dd, $J = 14.1, 7.3$ Hz, 1H), 2.82 (dd, $J = 14.1, 4.1$ Hz, 1H), 2.61–2.48 (m, 2H), 2.36 (dd, $J = 14.1, 7.4$ Hz, 1H), 1.62–1.56 (m, 1H), 1.48–1.31 (m, 1H), 1.07–0.98 (m, 1H); IR (film) 3415 (br), 2951, 2849, 1763, 1713, 1590, 1478, 1451, 1310, 1077, 1011 cm^{-1} ; HRMS (ESI) calcd for $(\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_8)\text{Na}^+$ ($\text{M} + \text{Na}$) $^+$ 497.1894, found 497.1890.

(±)-((3¹R,6aR,9R,9aS)-6a-Allyl-9-((2,3-dimethoxyphenyl)-amino)-9a-(hydroxymethyl)octahydro-2H,7H-oxazolo[5,4,3-*ij*]quinoline-2,7-dione (32). To a solution of the carbonate **33** (11.9 mg, 0.025 mmol) in 2.0 mL of MeOH was added K_2CO_3 (10.4 mg, 0.075 mmol). The resulting mixture was stirred for 30 min, at which time TLC analysis showed full consumption of the starting material. It was then quenched with saturated NH_4Cl solution (3 mL) and diluted with H_2O (5 mL), and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried over MgSO_4 , filtered, and concentrated in vacuo. Purification by flash column chromatography (EtOAc:hexanes, 1:1 to 2:1) gave pure **32** (10.0 mg, 96%) as a colorless oil: ^1H NMR (500 MHz, CDCl_3) δ 6.95 (t, $J = 8.3$ Hz, 1H), 6.42 (d, $J = 8.5$ Hz, 1H), 6.40 (d, $J = 8.4$ Hz, 1H), 5.74 (ddt, $J = 17.3, 10.1, 7.4$ Hz, 1H), 5.19 (d, $J = 10.8$ Hz, 1H), 5.17 (d, $J = 17.4$ Hz, 1H), 4.31 (br d, $J = 6.5$ Hz, 1H), 4.20 (d, $J = 12.8$ Hz, 1H), 4.07–4.02 (m, 1H), 4.04 (s, 1H), 3.85–3.80 (m, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 2.79–2.70 (m, 3H), 2.66–2.57 (m, 2H), 2.53 (app d, $J = 13.6$ Hz, 1H), 2.36 (dd, $J = 14.4, 7.5$ Hz, 1H), 1.66–1.63 (m, 1H), 1.38–1.16 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 208.7, 155.2, 152.5, 140.3, 135.9, 130.9, 124.6, 120.1, 105.2, 103.1, 84.1, 63.7, 60.6, 60.2, 55.9, 55.8, 48.6, 42.9, 41.5, 41.2, 30.8, 21.2; IR (film) 3377 (br), 2932, 2854, 1747, 1715, 1602, 1516, 1481, 1306, 1263, 1219, 1138 cm^{-1} ;

HRMS (ESI) calcd for $(\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_6)\text{Na}^+$ ($\text{M} + \text{Na}$) $^+$ 439.1840, found 439.1837.

(±)-36. To a solution of alcohol **32** (5.6 mg, 0.013 mmol) in 0.6 mL of anhydrous CH_2Cl_2 was added DMP (8.6 mg, 0.02 mmol) and a few crystals of KHCO_3 . The resulting mixture was stirred at room temperature, under nitrogen for 5 h, and then quenched with a 1:1 mixture of saturated $\text{Na}_2\text{S}_2\text{O}_3$ and NaHCO_3 solutions. The aqueous phase was extracted three times with CH_2Cl_2 , and the combined organic phase was dried over MgSO_4 , filtered, and concentrated in vacuo. Purification by PTLC (EtOAc/hexanes, 2:1) afforded **36** (2.7 mg, 49%) as a bright yellow oil: ^1H NMR (500 MHz, CDCl_3) 26 δ 7.72 (d, $J = 9.1$ Hz, 1H), 6.54 (d, $J = 9.1$ Hz, 1H), 5.55 (dddd, $J = 16.8, 10.0, 8.3, 6.7$ Hz, 1H), 4.99 (d, $J = 10.1$ Hz, 1H), 4.88 (s, 1H), 4.65 (dd, $J = 16.9, 1.4$ Hz, 1H), 4.26 (dt, $J = 3.8, 1.5$ Hz, 1H), 4.06 (s, 1H), 3.94 (s, 3H), 3.89–3.86 (m, 1H), 3.80 (s, 3H), 2.88–2.75 (m, 3H), 2.48–2.45 (m, 1H), 2.37 (dd, $J = 14.2, 6.7$ Hz, 1H), 2.29 (dd, $J = 14.2, 8.3$ Hz, 1H), 1.63–1.60 (m, 1H), 1.32–1.21 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 208.9, 186.7, 158.1, 154.6, 144.0, 134.0, 131.2, 125.5, 120.1, 112.0, 104.9, 77.7, 62.3, 60.5, 56.1, 55.2, 48.6, 41.8, 41.2, 41.0, 31.1, 21.3; IR (film) 3328 (br), 2934, 2850, 1764, 1712, 1667, 1608, 1525, 1479, 1346, 1272, 1211, 1037 cm^{-1} ; HRMS (ESI) calcd for $(\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_6)\text{K}^+$ ($\text{M} + \text{K}$) $^+$ 451.1266, found 451.1262.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01574.

X-ray crystallographic data for **30** (CIF)

HPLC chromatograms for **15** and ^1H and ^{13}C NMR spectra (PDF)

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Notes

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