JOC The Journal of Organic Chemistry

Featured Article

pubs.acs.org/joc

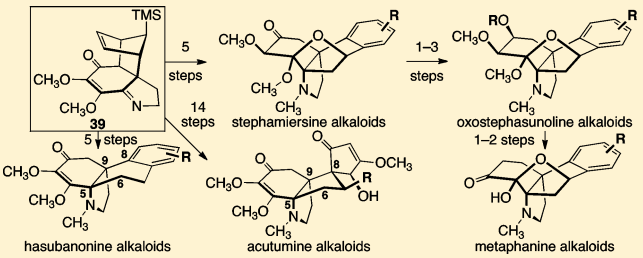
Development of Enantioselective Synthetic Routes to the Hasubanan and Acutumine Alkaloids

Nicholas A. Calandra,[†] Sandra M. King,[†] and Seth B. Herzon*

Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States

Supporting Information

ABSTRACT: We describe a general strategy to prepare the hasubanan and acutumine alkaloids, a large family of botanical natural products that display antitumor, antiviral, and memory-enhancing effects. The absolute stereochemistry of the targets is established by an enantioselective Diels–Alder reaction between 5-(trimethylsilyl)cyclopentadiene (**36**) and 5-(2-azidoethyl)-2,3-dimethoxybenzoquinone (**24**). The Diels–Alder adduct **38** is transformed to the tetracyclic imine **39** by a Staudinger reduction–aza-Wittig sequence. The latter serves as a universal precursor to the targets. Key carbon–carbon bond constructions include highly diastereoselective acetylide additions to the *N*-methyliminium ion derived from **39** and Friedel–Crafts and Hosomi–Sakurai cyclizations to construct the carbocyclic skeleton of the targets. Initially, this strategy was applied to the syntheses of (−)-acutumine (**4**), (−)-dechloroacutumine (**5**), and four hasubanan alkaloids (**1**, **2**, **3**, and **8**). Herein, the synthetic route is adapted to the syntheses of six additional hasubanan alkaloids (**12**, **13**, **14**, **15**, **18**, and **19**). The strategic advantage of 5-(trimethylsilyl)cyclopentadiene Diels–Alder adducts is demonstrated by site-selective functionalization of distal carbon–carbon π-bonds in the presence of an otherwise reactive norbornene substructure. Evaluation of the antiproliferative properties of the synthetic metabolites revealed that four hasubanan alkaloids are submicromolar inhibitors of the N87 cell line.



INTRODUCTION

The hasubanan and acutumine alkaloids are large families of structurally related natural products that share a common tricyclic propellane core (Figure 1).[1] (−)-Hasubanonine (**1**), the first hasubanan alkaloid discovered, was isolated from *Stephania japonica* in 1951.[2] Presently, the hasubanan family contains over 70 alkaloids spanning four subclasses that are defined by the oxidation pattern of the A-ring (see Figure 1).[1c] (−)-Acutumine (**4**) was first isolated from *Sinomenium acutum* in 1929,[3] and to date, 14 additional acutumine alkaloids have been characterized. While the hasubanan alkaloids contain an aromatic ring, the acutumine alkaloids possess a spirocyclic cyclopentenone fragment and a secondary alkyl chloride function (for **4** and **9**). Members of these families exhibit diverse biological effects, including antimicrobial,[4] antiviral (HIV and hepatitis B),[5,6] opioid receptor binding activities,[7] memory-enhancing properties,[8] and selective inhibition of human T-cell proliferation.[9]

The structural challenges and unexplored biological mechanisms of the hasubanan and acutumine alkaloids have engendered significant attention from the synthetic community, and syntheses and synthetic studies date back to as early as 1966. Racemic syntheses of hasubanonine (**1**),[10] metaphanine (**16**),[11] and cepharamine (not shown),[12] and the enantioselective synthesis of (+)-cepharamine,[13] have been reported. In addition, enantioselective syntheses of (−)-8-demethoxyrunanine (not shown) and the related metabolites (−)-cepharatines A, C, and D (not shown),[14] as well as numerous partial and formal syntheses of hasubanan alkaloids,[15,16] have been disclosed. Prior to our work, Castle's synthesis of (−)-acutumine (**4**) stood as the only completed route to any acutumine alkaloid,[17] although several approaches toward (−)-acutumine (**4**) were reported.[18]

We have developed a general and versatile strategy to access the hasubanonine and stephamiersine classes of hasubanan alkaloids, and applied this strategy to the syntheses of (−)-hasubanonine (**1**), (−)-runanine (**2**),[19] (−)-delavayine (**3**),[20] and (+)-periglaucine B (**8**).[5,21] We also modified this approach to access (−)-acutumine (**4**) and (−)-dechloroacutumine (**5**).[22,23] Here we disclose the development of this synthetic strategy and the adaptation of this work to the first enantioselective syntheses of six additional hasubanan alkaloids: (−)-stephabenine (**12**),[24] (+)-*N*,*O*-dimethylstephine (**13**),[24,25] (+)-*N*,*O*-dimethyloxostephine (**14**),[26] (+)-oxostephabenine (**15**),[26] (−)-prostephanaberrine (**18**),[27] and (−)-stephanaberrine (**19**),[27] which comprise the remaining unaddressed oxostephausoline and metaphanine classes of hasubanan alkaloids. We also broaden the strategic application of 5-(trimethylsilyl)cyclopentadiene (**36**) in complex molecule synthesis by demonstrating the site-selective functionalization of unsaturated carbon–carbon bonds in the presence of the

Received: August 26, 2013
Published: September 13, 2013

   dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031–10057

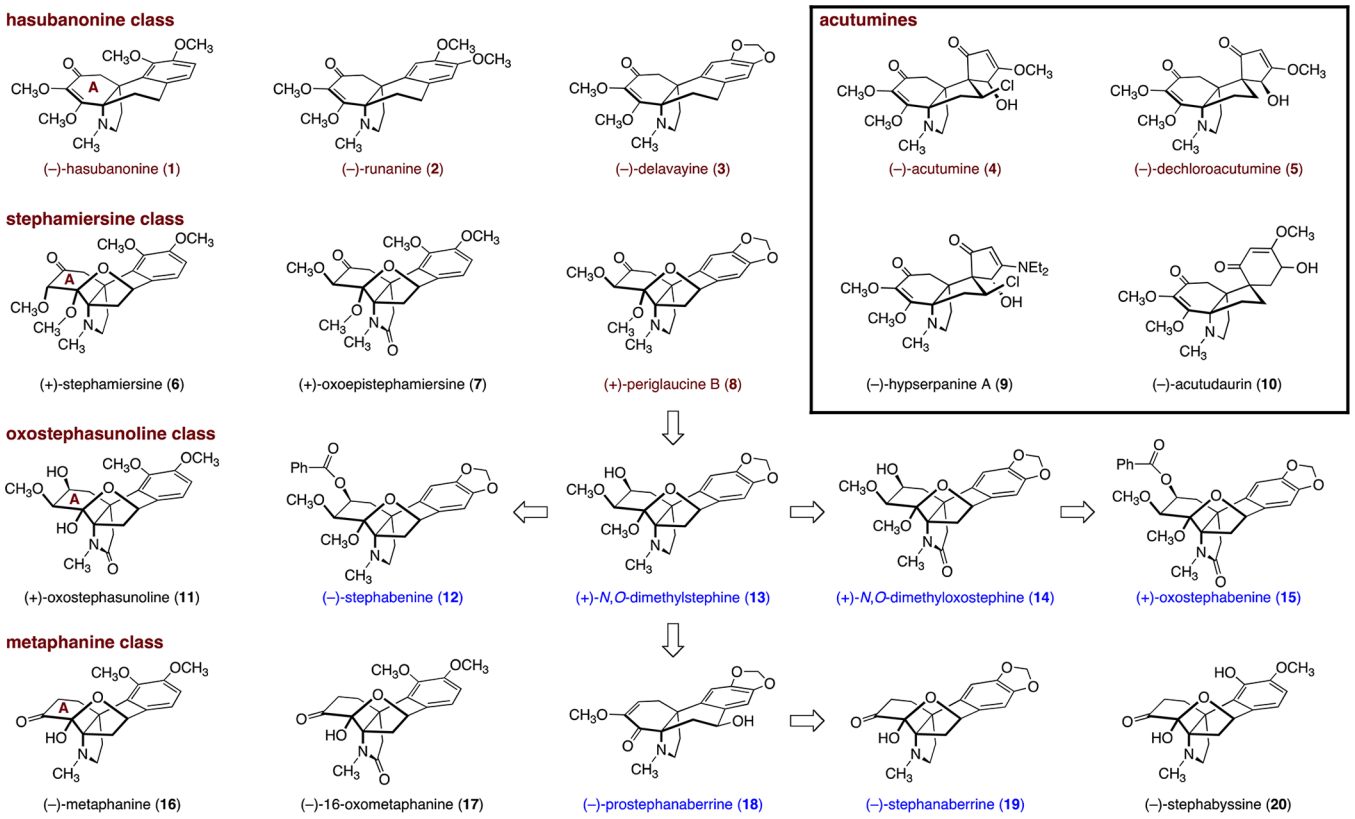


Figure 1. Structures of hasubanan and acutumine alkaloids. Red denotes alkaloids previously prepared. Blue denotes alkaloids synthesized in enantiomerically pure form for the first time herein.

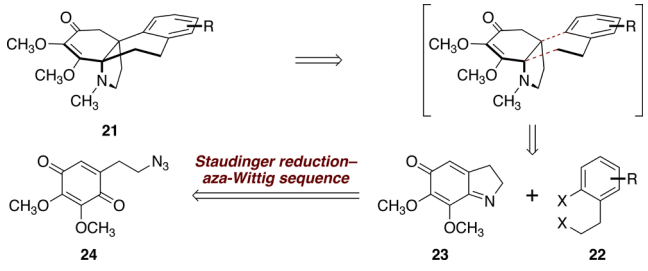
norbornene substructure of the silylcyclopentadiene adducts. Finally, we report the first side-by-side evaluation of the antiproliferative properties of hasubanan and acutumine alkaloids.

RESULTS AND DISCUSSION

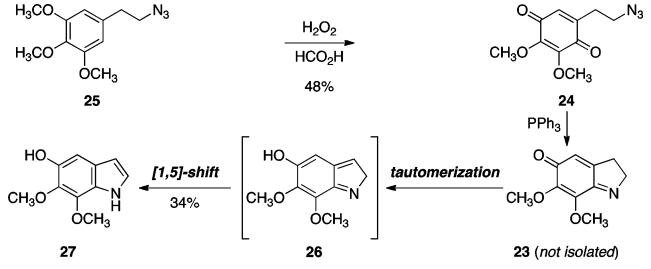
Strategy Development. Given the vast number of alkaloids that constitute the hasubanan and acutumine families, the development of a strategy that would allow access to all compounds within these families was the central element of our synthetic planning. Such an approach would establish general methods for construction of the tetracyclic propellane skeletons of the targets and provide a collection of related alkaloids for use as a basis set in structure–function studies. Our initial efforts focused on the hasubanonine alkaloids. As the aryl ring is the site of variation, we conceived a strategy whereby a bifunctional pronucleophile **22** is added to an iminoquinone such as **23** (Scheme 1). This disconnection provides two fragments of similar complexity and would provide access to diverse hasubanonine alkaloids by variation of **22**. These investigations would also reveal insights into potential pathways for the syntheses of acutumine alkaloids. The iminoquinone **23** was envisioned to derive from the azidoquinone **24** by a Staudinger reduction–aza-Wittig sequence.

Initial efforts focused on the synthesis of the iminoquinone **23** (Scheme 2). 5-(2-Azidoethyl)-1,2,3-trimethoxybenzene

Scheme 1. Strategy To Access the Hasubanonine Alkaloids



Scheme 2. Attempted Synthesis of the Iminoquinone 23



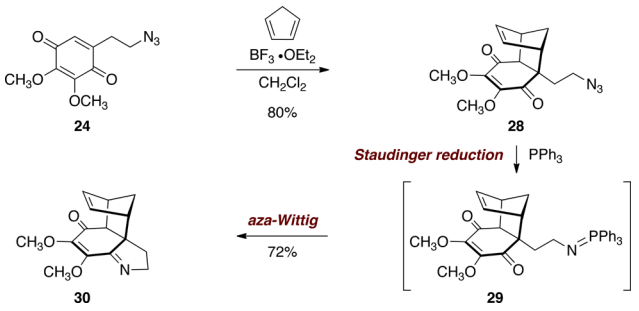
(**25**)[28] was prepared by a chromatography-free three-step sequence. Slow addition of hydrogen peroxide (2.50 equiv) to a solution of **25** in formic acid[29] provided the quinone **24** in 48% yield (20 g scale). The next step of our approach called for reduction of the azide of **24** and condensation of the resulting amine with the vicinal ketone (Staudinger reduction–aza-Wittig sequence) to form the iminoquinone **23**. Under all conditions examined, the desired iminoquinone **23** was not observed; instead, the hydroxyindole **27** was the only isolated product. For example, treatment of the quinone **24** with triphenylphosphine afforded **27** in 34% yield, as well as unidentified decomposition products. The hydroxyindole **27** is

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031–10057

believed to form by a sequence comprising generation of the iminoquinone **23**, tautomerization, and [1,5]-hydrogen atom-shift.[30]

To eliminate this decomposition pathway, we sought to introduce a substituent that would establish a quaternary center within the six-membered ring of **23**, thereby preventing the tautomerization. A number of potential strategies were considered, including derivatization of the less-hindered carbonyl of **24** by selective ketalization or cyanohydrin formation. Ultimately, we pursued a cycloaddition–retrocycloaddition strategy[31] by conducting a Diels–Alder cycloaddition between **24** and cyclopentadiene (Scheme 3).

Scheme 3. Synthesis of the Protected Iminoquinone 30

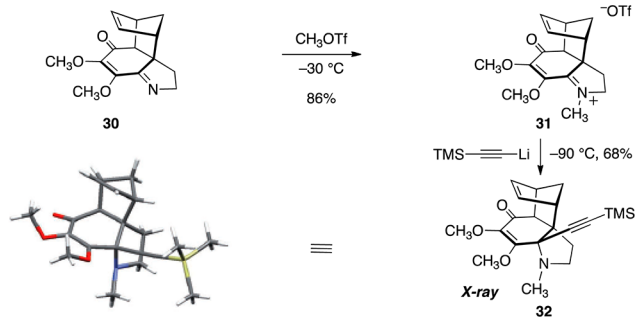


Treatment of the quinone **24** with cyclopentadiene and boron trifluoride etherate complex (20 mol %) formed the Diels–Alder adduct **28** as a single regioisomer and *endo*-diastereomer (80%, ^{1}H NMR analysis). Addition of triphenylphosphine to a solution of **28** in tetrahydrofuran initiated the Staudinger reduction–aza-Wittig sequence, to provide the protected iminoquinone **30** (72%). The triphenylphosphine oxide formed in this reaction was readily removed by acid–base extraction.

With the protected iminoquinone **30** in hand, our attention turned toward the introduction of nucleophiles to the imine functionality. This bond construction requires the site-selective reaction of the more hindered and less electrophilic imine in the presence of the carbonyl. We were also cognizant of the potential for 1,4-addition to the β-positions of either the carbonyl or imine groups. In order to activate the imine toward addition, and to introduce the *N*-methyl group found in almost all of the hasubanan and acutumine alkaloids, the protected iminoquinone **30** was treated with methyl triflate, which formed the iminium ion **31** (86%, Scheme 4). Perhaps reflective of the steric hindrance about the iminium ion, **31** is a stable solid that can be handled in air and stored at −10 °C for prolonged periods of time.

The stable iminium ion **31** provided a practical starting material for development of the nucleophilic addition step. A variety of nucleophiles were evaluated; from these experiments we identified acetylene-based nucleophiles as uniquely suited to effect the desired bond construction. For example, addition of 2-lithio-1-(trimethylsilyl)acetylene to the iminium ion **31** at −90 °C provided the acetylide addition product **32** as a single detectable diastereomer (68%, ^{1}H NMR analysis, Scheme 4). Attempts to add more reactive or bulkier nucleophiles (enolates, alkyl Grignard reagents, or organocopper and zinc reagents), even at −90 °C, led to complications arising from competitive addition to the ketone, addition to both the ketone and the iminium functions, *N*-dealkylation, and, presumably, deprotonation of **31** to generate an extended azomethine ylide.

Scheme 4. Methylation of the Imine 30 and Acetylide Addition to the Resulting Iminium Ion 31[21]



The stereochemical outcome of the addition was unexpected. We anticipated that bond formation *anti* to the cyclopentene substituent would be kinetically favored, but X-ray analysis of the product **32** revealed that the addition occurred from the opposite face, *syn* to the cyclopentene substituent (Scheme 4). Although this face is significantly more congested, the strain associated with *anti* addition to form a *trans*-6,5 ring fusion may render *syn* addition more favorable.[32] DFT calculations [B3LYP/6-31G(d,p)$^{++}$] reveal that the *syn* addition diastereomer **33** is 13.7 kcal/mol lower in energy than the *anti* diastereomer **34** (Figure 2). Regardless, the exceptional diastereoselectivity of this addition established a strategy for control of absolute stereochemistry in the targets.

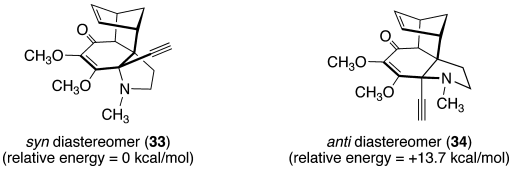
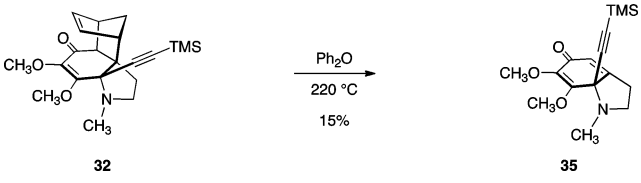


Figure 2. *Syn* and *anti* addition products **33** and **34**.

Thermolytic cleavage of the cyclopentene fragment of **32** was effected by heating in diphenyl ether at 220 °C (Scheme 5).

Scheme 5. Retrocycloaddition of the Acetylide Addition Product 32

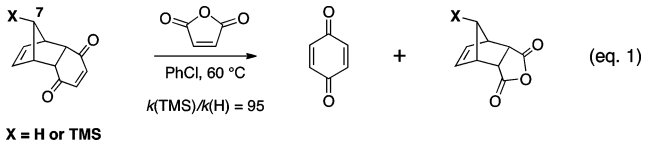


Unfortunately, extensive decomposition of both the starting material and product was observed, and the retrocycloaddition product **35** was obtained in low yield (15%). A variety of Lewis acids were evaluated[33] in an attempt to lower the barrier for the retrocycloaddition; however, no improvements in recovery were observed. At lower temperatures the retrocycloaddition did not proceed.

Although this route provided gram quantities of the addition product **32**, the yield of the retrocycloaddition step impeded progress. To decrease the temperature required for the retrocycloaddition, we investigated the application of trialkylsilyl-substituted cyclopentadiene derivatives. Previous research from Magnus and co-workers established that the Diels–Alder

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031–10057

adduct of 5-(trimethylsilyl)cyclopentadiene (**36**)[34] and 1,4-benzoquinone undergoes retrocycloaddition 95 times faster than the parent cyclopentadiene adduct (eq 1).[35] This rate



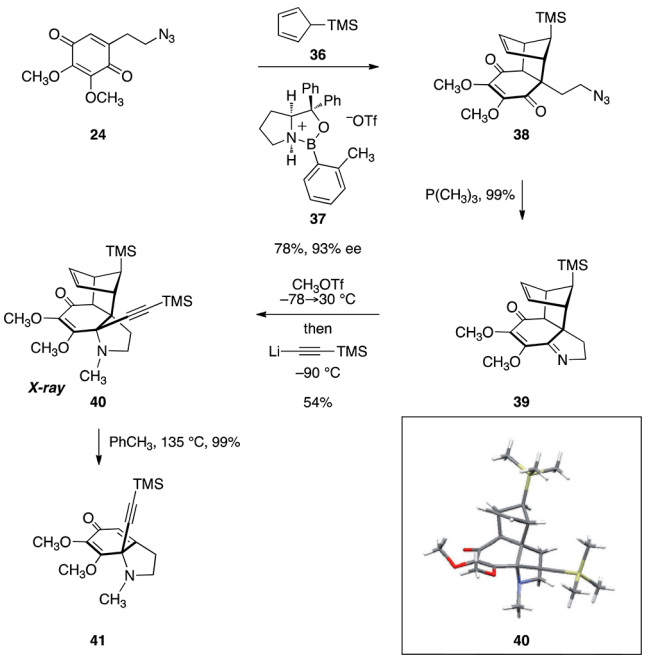
enhancement was proposed to arise from donation of electron density from the silicon−C-7 bonding orbital to the antibonding orbitals of the carbon−carbon bonds that are cleaving in the retrocycloaddition, allowing for progression through a lower energy asynchronous transition state.

We found that the Diels−Alder reaction between 5-(trimethylsilyl)cyclopentadiene (**36**) and the quinone **24** was efficiently promoted by methylaluminum dichloride (30 mol %), to afford the Diels−Alder adduct (not shown) in 31% yield, as a single *endo*-diastereomer and regioisomer (^{1}H NMR and NOE analysis).[36] In the interest of rendering the synthesis enantioselective, we evaluated several chiral Lewis acids for this transformation. In the presence of the protonated form of the Corey−Bakshi−Shibata oxazaborolidine (**37**, 22 mol %),[37] the desired *endo*-adduct **38** was obtained in 78% yield, as a single diastereomer (^{1}H NMR analysis of the unpurified product mixture), and in 93% ee (chiral stationary phase HPLC analysis, Scheme 6). To our knowledge, this is the first application of 5-(trimethylsilyl)cyclopentadiene (**36**) in an enantioselective Diels−Alder reaction.

Staudinger reduction of the *endo*-adduct **38** was conveniently effected using trimethylphosphine, to afford the protected iminoquinone **39** (99%). Although triphenylphosphine could be employed in this step, the product **39** was not stable to acid−base extraction, and chromatographic removal of the triphenylphosphine oxide byproduct was difficult. Due to the electron-donating ability of the trialkylsilyl substituent, the Diels−Alder adduct **38** and the protected iminoquinone **39** undergo retrocycloaddition rapidly in the presence of acid and slowly under neutral conditions at ambient temperature. Furthermore, whereas the 1,3-cyclopentadiene-derived iminoquinone **30** formed the stable and isolable iminium ion **31**, methylation of **39** must be performed at low temperature (−30 °C or lower) to prevent retrocycloaddition. These stability issues notwithstanding, low temperature methylation of **39** (methyl triflate) and addition of 2-lithio-1-(trimethylsilyl)-acetylene formed the acetylide addition product **40** with an efficiency comparable to the parent system (54%). Thermolytic cleavage of the silylcyclopentene substituent proceeded smoothly on heating **40** to 135 °C (toluene, sealed tube), to provide the retrocycloaddition product **41** in quantitative yield. The success of this approach was encouraging, as we now had a handle for control of absolute stereochemistry in the sequence and a mild method for removal of the cyclopentene substituent.

X-ray analysis of the parent (**32**) and trimethylsilyl-substituted (**40**) acetylide addition products allows for direct comparison of their structures (Schemes 4 and 6, respectively). The σ bonds that are broken during the retrocycloaddition are of nearly the same length in both **32** and **40** (1.56−1.57 Å). Thus, in accord with Magnus' earlier studies[35] and as would be expected for an endothermic transformation, we postulate that the effect of the trimethylsilyl substituent is manifested in the transition state for the retrocycloaddition.

Scheme 6. Enantioselective Synthesis of the Acetylide Addition Product 40 and Thermolytic Cleavage of the Silylcyclopentene Protecting Group[21]

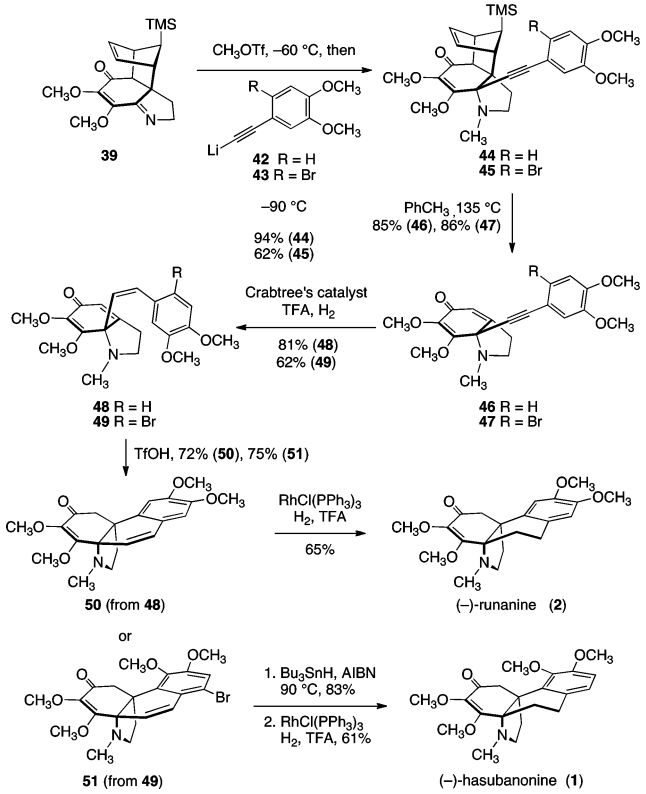


Syntheses of Hasubanonine and Stephamiersine Alkaloids. With efficient, diastereoselective additions to the *N*-methyliminium ion derived from **39**, and a high-yielding method for removal the cyclopentene fragment established, we sought to apply this methodology to the hasubanonine alkaloids (Scheme 7). To access (−)-runanine (**2**), the acetylide **42** was employed. Addition of the acetylide **42** to the *N*-methyliminium ion derived from **39** afforded the addition product **44** as a single detectable diastereomer (94%, ^{1}H NMR analysis). The addition product **44** was transformed to (−)-runanine (**2**) by a four-step sequence. First, the retrocycloaddition was initiated by heating in toluene (135 °C) to provide the dienone **46** (85%). Next, selective hydrogenation of the alkyne of **46** (Crabtree's catalyst)[38] produced the *cis*-alkene **48** (81%). Acid-mediated cyclization of the *cis*-alkene **48** (trifluoromethanesulfonic acid) provided the tetracycle **50** as a single isomer (72%). Finally, hydrogenation of the styrenyl olefin of the tetracycle **50** (Wilkinson's catalyst) afforded (−)-runanine (**2**, 65%).

As (−)-runanine (**2**) and (−)-hasubanonine (**1**) only differ in the positions of the aryl methoxy groups, we anticipated accessing (−)-hasubanonine (**2**) from the semihydrogenation product **48** by overturning the regioselectivity in the cyclization step. Unfortunately, all attempts to override the inherent selectivity using reagent-based strategies were unsuccessful. To overcome this, we installed a halogen blocking group at the less hindered position of the arene.[15p,39] The brominated aryl acetylide **43** was added to the *N*-methyliminium ion derived from **39**, to provide the addition product **45** (62%). Retrocycloaddition (toluene, 135 °C, 86%), followed by semihydrogenation (Crabtree's catalyst,[38] 62%) provided the *cis*-alkene **49**. As anticipated, treatment of the *cis*-alkene **49** with trifluoromethanesulfonic acid promoted bond formation to the more hindered position of the arene, providing the tetracycle **51** as a single isomer (75%). Debromination of the tetracycle **51** (tributyltin hydride) generated the final intermediate (not

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

Scheme 7. Syntheses of (−)-Runanine (2) and (−)-Hasubanonine (1)



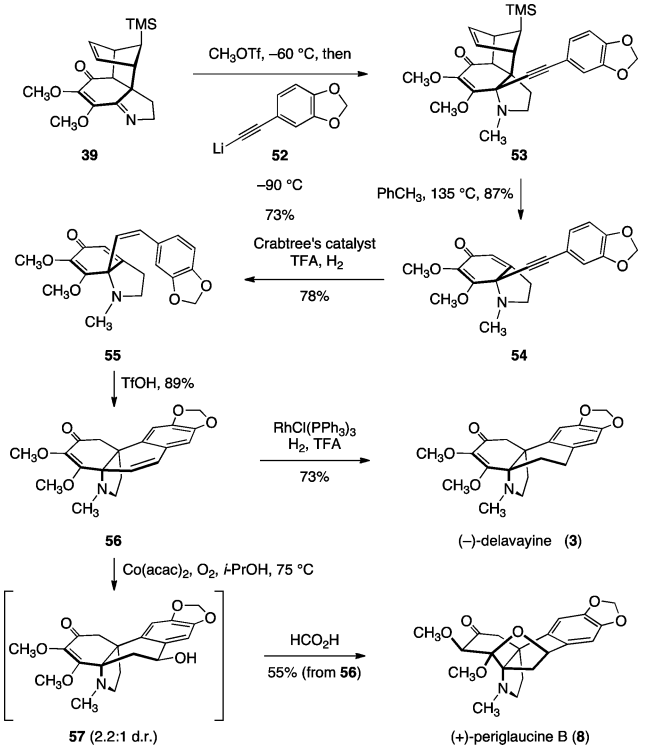
shown, 83%); hydrogenation (Wilkinson's catalyst) furnished (−)-hasubanonine (**1**, 61%).

To establish methods to access stephamiersine alkaloids, we targeted the hasubanonine alkaloid (−)-delavayine (**3**), which has the same arene substitution as the stephamiersine alkaloid (+)-perigluacine B (**8**, Scheme 8). We envisioned that (−)-delavayine (**3**) could be converted to (+)-perigluacine B (**8**) by a benzylic oxidation−1,4-addition sequence. Accordingly, the *cis*-alkene **55** was prepared by a three-step sequence comprising acetylide addition (**39** + **52**→**53**, 73%), retrocycloaddition (**53**→**54**, 87%), and semihydrogenation (**54**→**55**, 78%). Acid-mediated cyclization of the *cis*-alkene **55** furnished the tetracycle **56** as a single isomer (89%). Hydrogenation of the tetracycle **56** (Wilkinson's catalyst) afforded (−)-delavayine (**3**, 73%).

At this juncture, we recognized that the final intermediate **56** might be converted directly to (+)-periglaucine B (**8**) by a redox-neutral hydration−1,4-addition sequence. Heating a mixture of the tetracyle **56** and cobalt bis(acetylacetonate) in 2-propanol under an atmosphere of dioxygen[40] produced the hydration product **57** with 2.2:1 diastereoselectivity, in favor of **57**. Addition of excess formic acid directly to the reaction mixture promoted cyclization of **57**, providing (+)-periglaucine B (**8**) in 55% yield (from **56**). Attempts to achieve the hydration step using protic acids alone were unsuccessful.

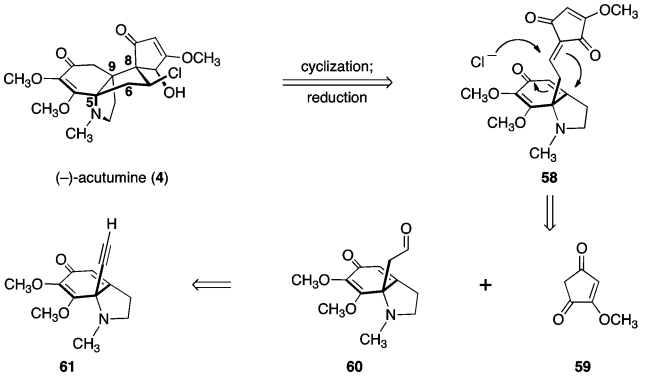
Acutumine Alkaloids. Our attention then focused on adapting this strategy to the syntheses of acutumine alkaloids. Although the acutumine and hasubanan alkaloids share a common propellane core, the acutumine alkaloids contain additional elements of structural complexity. These include two contiguous quaternary stereocenters, a heavily oxidized spirocyclic cyclopentenone, and a secondary alkyl chloride

Scheme 8. Syntheses of (−)-Delavayine (3) and (+)-Periglaucine B (8)



substituent (for **4** and **9**). Retrosynthetically, the C-5−C-6 bond of (−)-acutumine (**4**) would be formed by acetylide addition to the *N*-methyl iminium ion derived from **39** (Scheme 9). The acetylide nucleophile to be employed in

Scheme 9. First-Generation Approach to (−)-Acutumine (4)

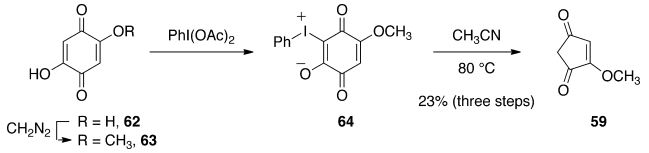


this addition was not immediately apparent. Moreover, the method for stereocontrolled construction of the C-8−C-9 bond, which was formed by a Friedel−Crafts cyclization in our hasubanan work (vide supra), was also not well-defined, and ultimately this step emerged as a significant roadblock. We initially targeted the alkylidene malonate **58**, which was envisioned to form by a Knoevenagel condensation between the diketone **59**[41] and the aldehyde **60**. We postulated that the alkylidene malonate **58** might react by 1,4-addition of chloride anion to generate a stabilized enolate, which could then add to the unsaturated cyclohexenone to yield, following reduction, (−)-acutumine (**4**).

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

The diketone **59** was prepared by a sequence comprising monomethylation of 2,5-dihydroxy-1,4-benzoquinone (**62**) (diazomethane, 1 equiv), followed by formation of the iodonium salt **64** (iodobenzene diacetate, Scheme 10).

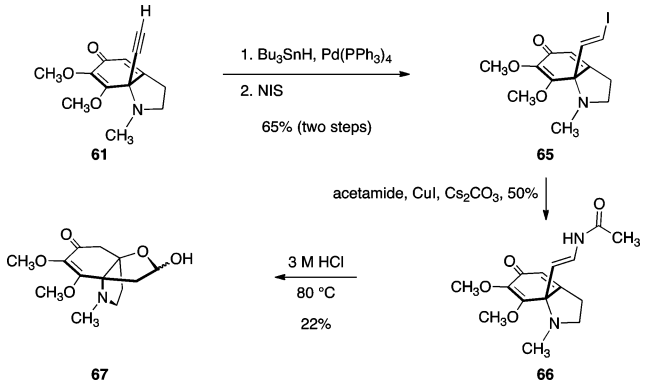
Scheme 10. Synthesis of the Diketone 59



Thermolysis of the iodonium salt **64** in moist acetonitrile (80 °C) provided the diketone **59** (23%, three steps).[42] The diketone **59** may be produced by a sequence comprising Wolff rearrangement, trapping of the resulting acylketene with water, and decarboxylation.

Preparation of the aldehyde **60** proved to be problematic (Scheme 11). Direct hydroboration−oxidation or anti-

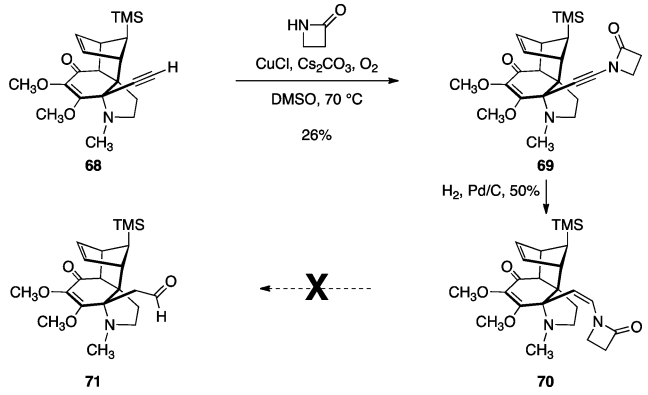
Scheme 11. Synthesis of the Cyclic Hemiacetal 67



Markovnikov hydration[43] of the alkyne **61** (formed by alkyne deprotection and retrocycloaddition of the acetylide addition product **40**)[36] were unsuccessful, and so a less direct route was developed. Palladium-catalyzed hydrostannylation of the alkyne **61** [tributyltin hydride, tetrakis(triphenylphosphine)palladium] provided a vinylstannane (not shown) as a single *trans*-isomer. Iododestannylation of the vinylstannane (*N*-iodosuccinimide) furnished the vinyl iodide **65** (65%, two steps). Copper-mediated coupling of the vinyl iodide **65** with acetamide[44] afforded the enamide **66** (50%). Hydrolysis of the enamide **66** (3 M hydrochloric acid, 80 °C) provided the cyclic hemiacetal **67** (22%), which presumably forms from hydration and cyclization of the aldehyde **60**. Attempts to introduce the diketone **59** to the cyclic hemiacetal **67** were unsuccessful.

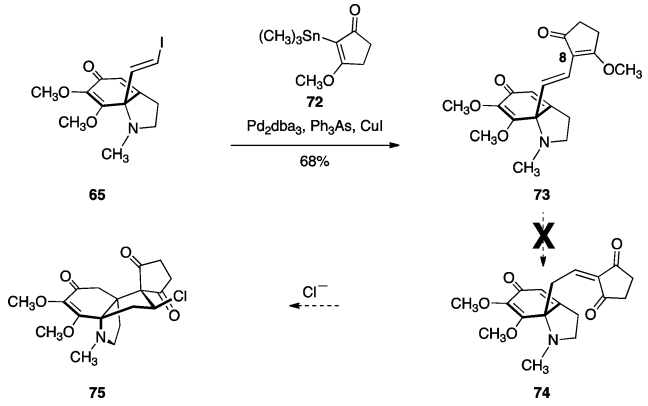
To prevent formation of the cyclic hemiacetal **67**, we attempted to prepare the aldehyde **71**, which bears the silylcyclopentene substituent (Scheme 12). The terminal alkyne **68** (formed by alkyne deprotection of the addition product **40**)[36] was coupled with 2-azetidinone (copper chloride, dioxygen) to yield the ynamide **69** (26%).[45] Semihydrogenation of the ynamide **69** (hydrogen, palladium on carbon) provided the enamide **70** (50%). Unfortunately, all efforts to hydrolyze the enamide function of **70** were unsuccessful. Attempts to introduce the diketone **59** directly to **70** were also unsuccessful.

Scheme 12. Attempted Synthesis of the Aldehyde 71



We then pursued a strategy comprising palladium-catalyzed coupling between the stannane **72** (prepared in two steps and 35% yield from 3-methoxy-2-cyclopent-2-ene-1-one)[36] and the vinyl iodide **65** (Scheme 13). We envisioned that the coupling

Scheme 13. Synthesis of the Stille Coupling Product 73



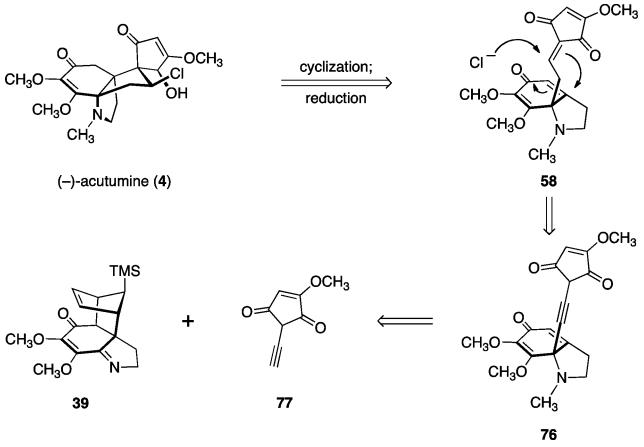
product **73** might be converted to the alkylidene malonate **74**, which could then undergo the conjugate addition−cyclization sequence outlined above (**74**→**75**, see also Scheme 9). Stille coupling of the vinyl iodide **65** and the stannane **72** provided the coupling product **73** (68%). However, attempts to advance **73** were unsuccessful. These difficulties appeared to stem from generation of anionic character at C-8 (see structure **73**, Scheme 13), which led to products derived from pyrrolidine ring-opening and aromatization of the six-membered ring.

The difficulties associated with preparation of the aldehyde **60** led us to conceive a new strategy to access the alkylidene malonate **58** (Scheme 14), whereby a prefunctionalized alkyne **77** containing the desired cyclopentenone fragment would be introduced directly to the *N*-methyliminium ion derived from **39**. Retrocycloaddition of the addition product (not shown) would provide the cyclohexanedienone **76**, a potential precursor to the desired alkylidene malonate **58**.

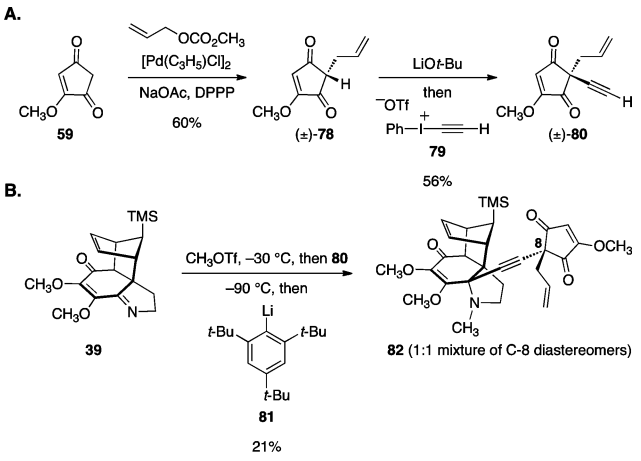
Alkynylation of the diketone **59** directly was problematic, presumably due to isomerization of the product to a highly reactive diacyl allene. Thus, a sequence comprising allylation and alkynylation[46] was developed (34%, two steps, Scheme 15A).[47] Due to the presence of electrophilic ketone substituents within the alkyne **80**, preformation of the lithium acetylide of **80** was not possible. However, we reasoned that the lithium acetylide of **80** might add to the *N*-methyliminium ion derived from **39** selectively if generated in its presence (Scheme

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

Scheme 14. Second-Generation Approach to (−)-Acutumine (4)



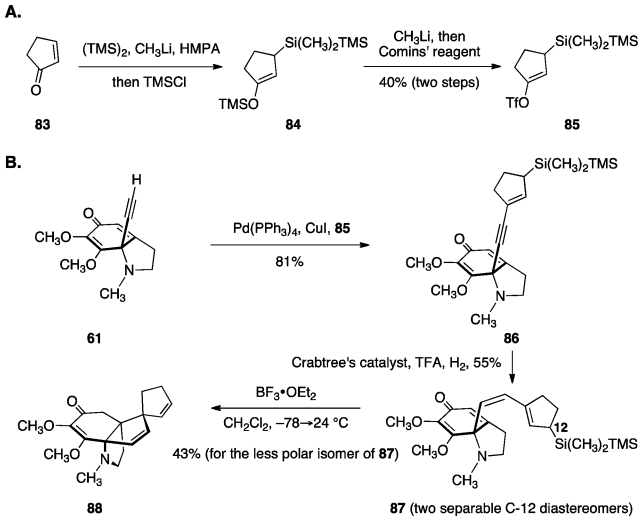
Scheme 15. (A) Synthesis of the Alkyne 80. (B) Addition of the Alkyne 80 to the *N*-Methyliminium Ion Derived from 39



15B). In practice, addition of a solution of 1-lithio-2,4,6-tri-*tert*-butylbenzene (**81**)[48] to a mixture of the alkyne **80** and the *N*-methyliminium ion derived from **39** at −90 °C provided the addition product **82** (21%). Unfortunately, elaboration of the addition product **82** to (−)-acutumine (**4**) was unsuccessful due to difficulties associated with reduction of the sterically hindered alkyne and cleavage of the allyl protecting group.

At this juncture, we reevaluated our approach for the formation of the C-8−C-9 bond of the acutumine alkaloids. As generation of anionic character at C-8 seemed to undermine our strategies, we considered cationic pathways for the formation of the key spirocyclic bond. Toward this end, a model system capable of undergoing an acid-catalyzed Hosomi−Sakurai cyclization[49] was prepared (Scheme 16A). Conjugate addition of dimethyl(trimethylsilyl)silyllithium[50] (methyllithium, hexamethyldisilane) to **83** and trapping with chlorotrimethylsilane provided the enoxysilane **84**. Cleavage of the enoxysilane **84** (methyllithium, −78 °C), followed by the addition of *N*,*N*-bis(trifluoromethylsulfonyl)-5-chloro-2-pyridylamine (Comins' reagent)[51] provided the vinyl triflate **85** (40%, two steps). Sonagashira coupling of the vinyl triflate **85** with the terminal alkyne **61**, followed by semihydrogenation (Crabtree's catalyst),[38] formed two diastereomeric products (see **87**), which could be separated by preparative thin-layer chromatography (55% combined yield, Scheme 16B). The

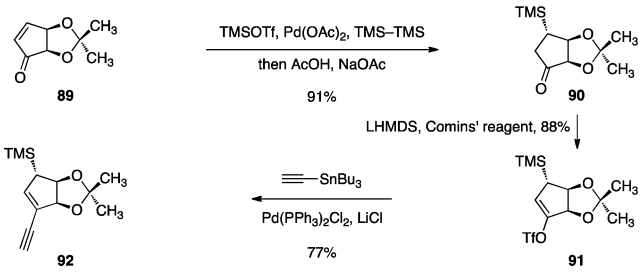
Scheme 16. (A) Synthesis of the Vinyl Triflate 85. (B) Synthesis of the Model Cyclization Product 88



stereochemistry at C-12 of each diastereomer could not be assigned by NMR spectroscopy. We found that treatment of the less polar diastereomer with boron trifluoride etherate complex at 0 °C in dichloromethane provided the cyclization product **88**, as a single detectable isomer (43%, ^{1}H NMR analysis). The more polar diastereomer did not undergo cyclization under any conditions examined.

With a method for the preparation of the acutumine core in hand, our focus turned toward the identification of an enyne that could be elaborated to the targets. Ultimately, we employed the enyne **92**, which was derived from the enone **89** (Scheme 17).[52] Palladium-catalyzed 1,4-disilylation,[53]

Scheme 17. Synthesis of the Enyne 92

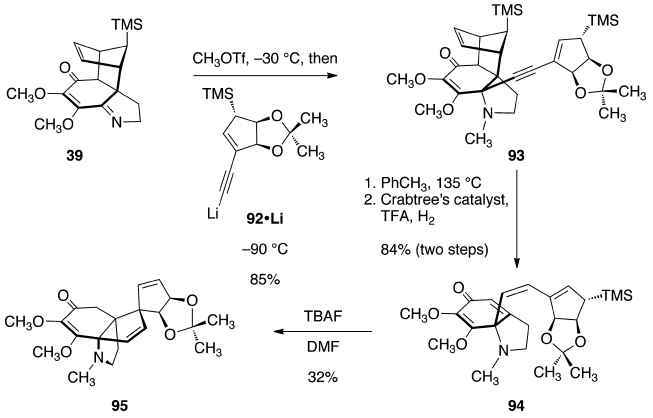


followed by in situ cleavage of the resulting enoxysilane (not shown), provided the *β*-silyl ketone **90** as a single detectable *exo*-diastereomer (91%, ^{1}H and NOE NMR analysis). Deprotonation of **90** and trapping of the resulting enolate with Comins' reagent[51] generated the vinyl triflate **91** (88%). Stille coupling of the vinyl triflate **91** with ethynyltributylstannane formed the enyne **92** (77%).

Addition of the lithiated alkyne **92**·**Li** to the *N*-methyliminium ion derived from **39** provided the 1,2-addition product **93** in 85% yield and as a single detectable diastereomer (^{1}H NMR analysis, Scheme 18). Retrocycloaddition of **93** (toluene, 135 °C) provided a cyclohexanedienone (not shown). Semihydrogenation of the retrocycloaddition product (Crabtree's catalyst)[38] furnished the *cis*-alkene **94** (84%, two steps). In contrast to the model system **87**, attempts to induce cyclization of **94** using Lewis and protic acids led to either decomposition of the substrate, acetonide deprotection, or

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

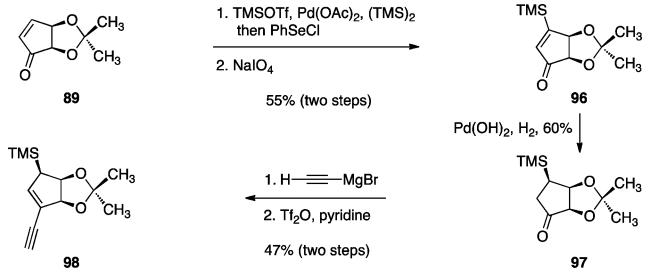
Scheme 18. Synthesis of the Functionalized Cyclization Product 95



elimination of the cyclopentyl oxygen atoms. The failure of the fully functionalized system to cyclize under acidic conditions was surprising. Ultimately, basic/nucleophilic pathways were investigated. Treatment of the cyclization precursor **94** with tetrabutylammonium fluoride induced ring closure to provide the pentacyclic product **95** as a single detectable diastereomer (32%, ^{1}H NMR analysis). Although the yield of this transformation is modest, it forms the two contiguous quaternary centers of the targets with complete stereocontrol.

The low yield for this reaction was initially attributed to an unfavorable steric interaction between the trimethylsilyl group of the cyclopentyl fragment and the cyclohexanedienone of **94**. In an attempt to improve the efficiency of the cyclization, we inverted the stereochemistry of the silyl group (Scheme 19).

Scheme 19. Synthesis of the *endo*-Trimethylsilyl Enyne 98



Beginning with the enone **89**, 1,4-disilylation, followed by in situ selenylation (phenylselenyl chloride) and oxidation (sodium periodate), provided the *β*-(trimethylsilyl)-*α*,*β*-unsaturated ketone **96** (55%, two steps). Hydrogenation of **96** (palladium hydroxide) provided the ketone **97**, as a single detectable diastereomer (^{1}H NMR analysis, 60%). Addition of ethynyl magnesium bromide and dehydration of the resulting alcohol (not shown, trifluoromethanesulfonic anhydride, pyridine) generated the *endo*-trimethylsilyl enyne **98** (47%, two steps).

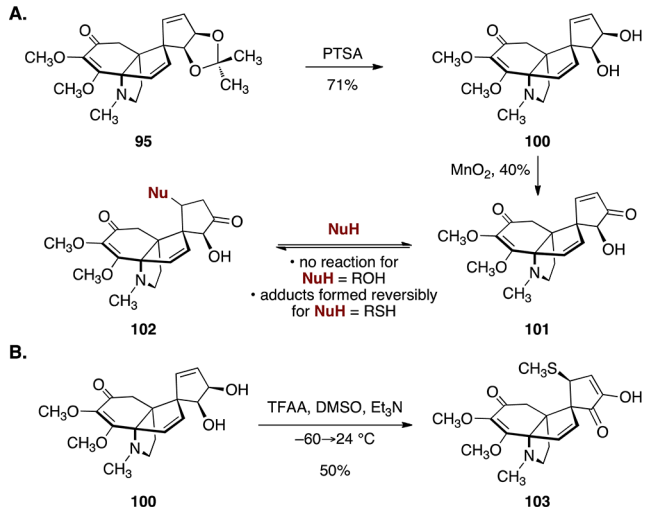
The *endo*-trimethylsilyl cyclization precursor **99** was prepared by an analogous sequence (Scheme 20).[36] As with the *exo*-trimethylsilyl cyclization precursor **94**, attempts to induce cyclization of the *endo*-diastereomer **99** under acidic conditions were unsuccessful. Treatment with tetrabutylammonium fluoride provided the cyclized product **95**, but no improvement in yield was observed (24%). The low yield for this reaction is attributed to decomposition of the substrate to form several

Scheme 20. Cyclization of the *endo*-Trimethylsilyl Cyclization Precursor 99

unidentified products. Given the similar efficiencies of the *endo* and *exo* isomers in the cyclization step, we elected to proceed further with the more acessible *exo* isomer **94**.

To advance the cyclization product **95**, the acetonide was cleaved [*p*-toluenesulfonic acid (PTSA), methanol] to provide the diol **100** (71%, Scheme 21A). At this stage, two major

Scheme 21. (A) Synthesis of the Enone 101. (B) Unexpected Formation of the Methanethiol Addition Product 103



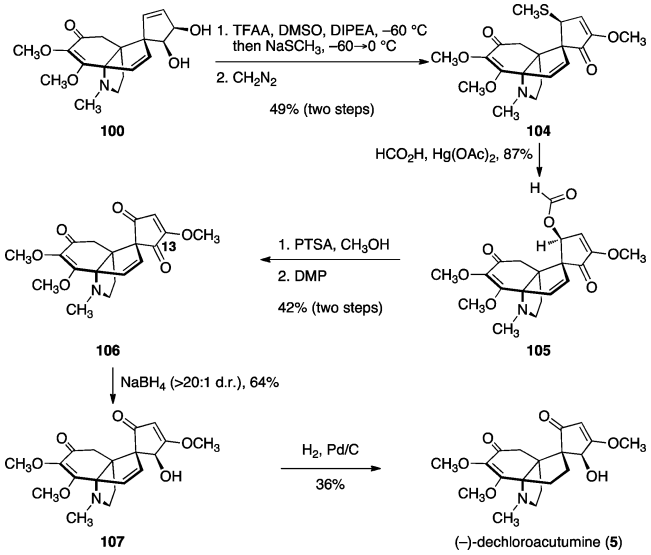
challenges remained. The first involved construction of the *β*-methoxycyclopentenone fragment of (−)-acutumine (**4**) and the second involved introduction of the secondary alkyl chloride. To address the first issue, we investigated selective oxidation of the allylic alcohol of **100** and functionalization of the resulting enone **101**. Treatment of the diol **100** with manganese oxide provided the enone **101** (40%). Treatment with various oxygen-based nucleophiles (e.g., sodium hydrogen peroxide, carboxylate salts, oximes, primary alcohols, and water) did not produce detectable levels of 1,4-addition products **102**, presumably due to steric hindrance about the *β*-position. Although sulfur-based nucleophiles added to the enone **101**, the addition products **102** were formed reversibly and readily reverted to the enone **101** on attempted *S*-functionalization.

To increase the electrophilicity of the system, we investigated two-fold oxidation of the diol **100** to the corresponding enedione.[54,55] Initial experiments employed an excess of dimethylsulfoxide, trifluoroacetic anhydride, and triethylamine (Scheme 21B). Under these conditions, the expected enedione (not shown) was formed in minor amounts, but the major product of these reactions was the sulfide **103** (50%). The sulfide **103** is presumably derived from the enedione by 1,4-addition of methanethiol in situ. While the reaction proceeds to nearly full conversion to **103**, chromatographic purification of **103** was required to separate 4-(diethylamino)-1,1,1-trifluorobut-3-en-2-one, formed by degradation of the triethylamine

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

base under the reaction conditions.[55] The formation of the sulfide **103** was useful because it accomplished the oxidation and 1,4-addition in a single step. The reproducibility and scalability of this transformation were improved by two essential modifications. First, Hünig's base was employed in place of triethylamine, as the former was less prone to decomposition under the conditions of the oxidation. Second, the enedione formed in situ was reproducibly converted (quantitatively) to the 1,4-addition product **103** by addition of a standard solution sodium thiomethoxide (3.30 equiv) directly to the reaction mixture, following the oxidation. Under these modified conditions, the sulfide **103** was obtained in nearly analytically pure form (Scheme 22). Exposure of the unpurified

Scheme 22. Synthesis of (−)-Dechloroacutumine (5)

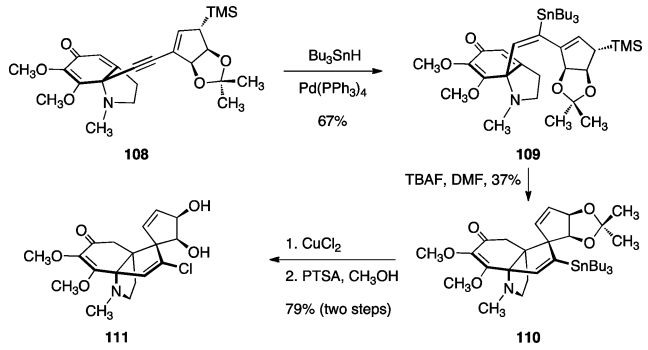


sulfide **103** to diazomethane provided the methyl ether **104** as a single detectable diastereomer (^{1}H NMR analysis, 49%, two steps). The relative stereochemistry of the methanethiol substituent was determined to be that shown by 2D-NOESY analysis.

We then investigated methods to substitute the methanethiol substituent with an oxygen atom (Scheme 22). After considerable experimentation, we found that treatment of the methyl ether **104** with mercuric acetate in formic acid[56] provided the product of stereoretentive substitution of the methanethiol substituent, in the form of the formate **105** (87%). This reaction may proceed by coordination of the thiol to mercury, resulting in elimination to form an extended oxocarbenium ion (not shown) that is trapped by formic acid. The formyl group of **105** was cleaved (PTSA, methanol) to provide an alcohol (not shown). The alcohol was then oxidized (Dess−Martin periodinane)[57] to yield the vinylogous α-diketone **106** (42%, two steps). In the next step, we sought to conduct a site- and stereoselective reduction of the vinylogous diketone **106**. Treatment of **106** with sodium borohydride in ethanol provided the desired alcohol **107**, as a single stereoisomer (^{1}H NMR analysis, 64%). The site selectivity in the reduction of **106** is attributed to the heightened electrophilicity of the C-13 carbonyl group relative to the two other carbonyl functional groups, which are vinylogous esters. The stereoselectivity in the reduction was less predictable but may arise from shielding of the β-face of the C-13 carbonyl by the cyclopentene ring. Heterogenous hydrogenation of **107** (palladium on carbon) provided (−)-dechloroacutumine (**5**) in 36% yield, which was identical to natural material[22] by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, HRMS, and optical rotation.

At this point, installation of the secondary alkyl chloride substituent was the only remaining challenge toward the synthesis of (−)-acutumine (**4**). Although selective hydrochlorination[58] of **107** was considered, we pursued introduction of the chloride earlier in the synthesis (Scheme 23). Beginning

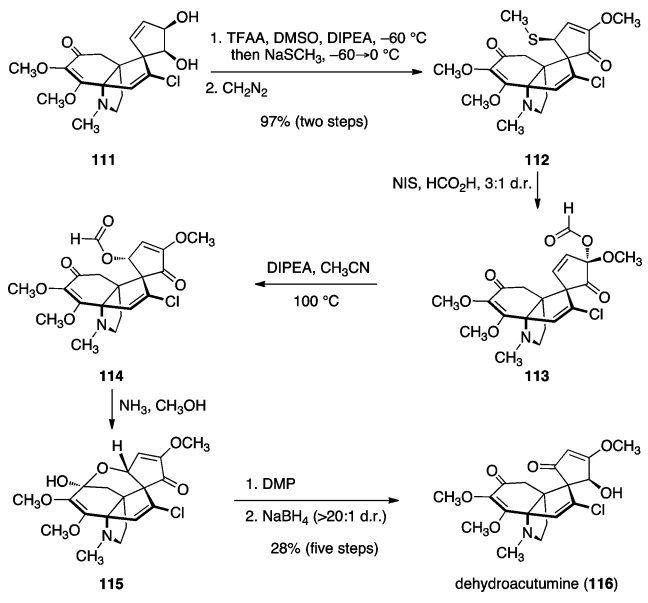
Scheme 23. Synthesis of the Diol 111



with the cyclohexanedienone **108** (formed by retrocycloaddition of **93**, Scheme 18), palladium-catalyzed regio- and stereoselective hydrostannylation [tributyltin hydride, tetrakis(triphenylphosphine)palladium][59] provided the vinylstannane **109** (67%). Activation of **109** with tetrabutylammonium fluoride induced cyclization to furnish the pentacycle **110** as a single detectable diastereomer (37%, ^{1}H NMR analysis). Treatment of the pentacycle **110** with cupric chloride provided a chlorodestannylated product (not shown),[60] that was deprotected (PTSA, methanol) to afford the chlorodiol **111** (79%, two steps).

The diol **111** was exhaustively oxidized to the corresponding enedione (not shown), which was trapped in situ by addition of sodium thiomethoxide (Scheme 24). Exposure of the

Scheme 24. Synthesis of Dehydroacutumine (116)

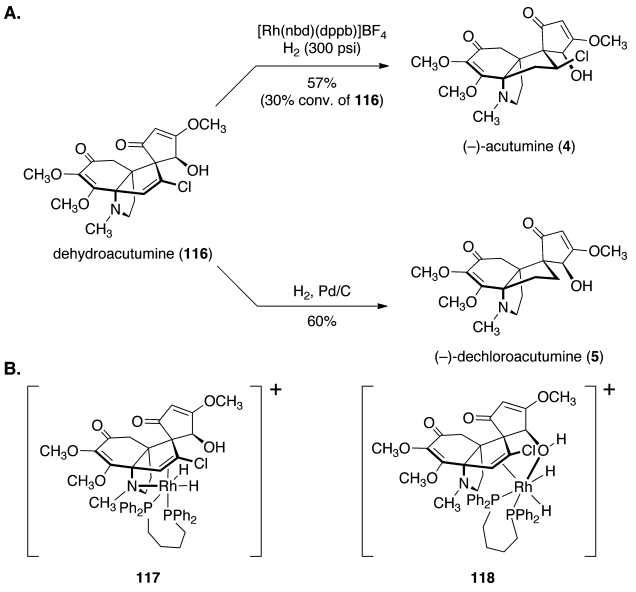


dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

unpurified 1,4-addition product (not shown) to diazomethane provided the methyl ether **112** as a single detectable diastereomer (^{1}H NMR analysis, 97%, two steps). Unfortunately, application of the conditions previously developed for the *ipso* substitution of the methanethiol substituent of **104** with formate (mercuric acetate in formic acid) were unsuccessful when applied to the methyl ether **112**, and the corresponding enedione (not shown) was obtained as the sole isolable product. Upon further experimentation, we found that treatment of **112** with *N*-iodosuccinimide and formic acid[61] resulted in formal S_N2' substitution of the methanethiol substituent, to generate the 1,2-addition product **113** (3:1 d.r.). This change in reactivity is attributed to the increased steric encumbrance introduced by the chlorine atom. Fortunately, the oxygenation pattern of the targets could be obtained by thermolytic rearrangement of **113** (100 °C, acetonitrile),[62] to provide the formate **114**. For reasons that are not apparent, the minor diastereomer formed in the substitution step does not undergo efficient rearrangement. The formyl group of **114** was cleaved (ammonia–methanol) to provide the hemiketal **115**. The hemiketal **115** was then oxidized using the Dess–Martin periodinane[57] to yield a vinylogous α-diketone (not shown). Site- and stereoselective reduction (sodium borohydride, ethanol, >20:1 dr, ^{1}H NMR analysis) provided the final intermediate dehydroacutumine (**116**, 28% over five steps).

(−)-Acutumine (**4**) and (−)-dechloroacutumine (**5**) were both accessible from dehydroacutumine (**116**, Scheme 25A).

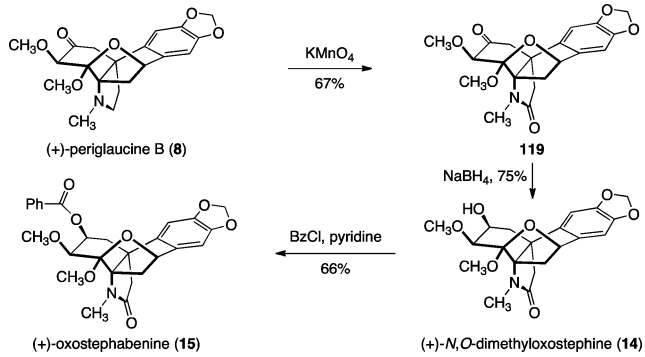
Scheme 25. (A) Syntheses of (−)-Acutumine (4) and (−)-Dechloroacutumine (5). (B) Proposed Substrate–Catalyst Complexes for the Directed Hydrogenation of Dehydroacutumine (116)



Homogeneous hydrogenation[63] of **116** ([Rh(nbd)(dppb)]BF_4, 300 psi H_2) provided (−)-acutumine (**4**) as a single detectable diastereomer (^{1}H NMR analysis; 57% yield of **4** at 30% conversion of **116**). The stereochemical outcome of this step suggests that the reduction of dehydroacutumine (**116**) is directed by coordination of the amine or alcohol functional groups to the catalyst (see structures **117** and **118**, Scheme 25B). (−)-Acutumine (**4**) was formed exclusively at low conversion of dehydroacutumine (**116**), but attempts to achieve higher conversion of **116** using [Rh(nbd)(dppb)]BF_4 led to the formation of (−)-dechloroacutumine (**5**) exclusively, which is indicative of reduction of the C_{sp^3}–Cl bond of **4**. Alternatively, heterogeneous hydrogenation of dehydroacutumine (**116**, palladium on carbon) cleanly furnished (−)-dechloroacutumine (**5**) in 60% yield.

Oxostephasunoline and Metaphanine Alkaloids. With an efficient synthetic route to the stephamiersine alkaloid (+)-periglaucine B (**8**), we were in position to evaluate the transformation of this alkaloid to members of the oxostephasunoline and metaphanine classes, thereby broadening the scope of targets that are accessible by our approach (see Figure 1). These efforts have resulted in the first enantioselective total syntheses of six additional natural products: (−)-stephabenine (**12**), (+)-*N*,*O*-dimethylstephine (**13**), (+)-*N*,*O*-dimethyloxostephine (**14**), (+)-oxostephabenine (**15**), (−)-prostephanaberrine (**18**), and (−)-stephanaberrine (**19**). Each natural product was prepared from synthetic (+)-periglaucine B (**8**) in 1–4 steps. The syntheses of alkaloids in the oxostephasunoline class are shown in Scheme 26. Oxidation of (+)-periglaucine B (**8**)

Scheme 26. Syntheses of Oxostephasunoline Alkaloids

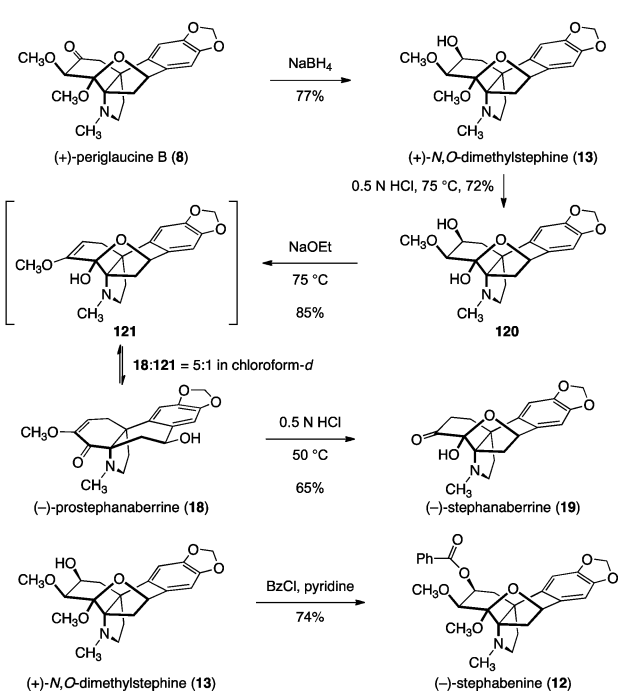


(potassium permanganate) provided the lactam **119** (67%). Stereo- and site-selective reduction of the lactam **119** (sodium borohydride) furnished (+)-*N*,*O*-dimethyloxostephine (**14**) as a single detectable diastereomer (75%, ^{1}H NMR analysis).[64] The selectivity of this reduction is attributed to the concave topology created by the ketal of **119**, which favors addition of hydride from the less-hindered α-face of **119**. Acylation of (+)-*N*,*O*-dimethyloxostephine (**14**, benzoyl chloride) afforded (+)-oxostephabenine (**15**, 66%).

The syntheses of metaphanine alkaloids are shown in Scheme 27A. Reduction of (+)-periglaucine B (**8**, sodium borohydride) afforded (+)-*N*,*O*-dimethylstephine (**13**) as a single detectable diastereomer (77%, ^{1}H NMR analysis). Heating (+)-*N*,*O*-dimethylstephine (**13**) in 0.5 N hydrochloric acid at 75 °C produced the hemiketal **120** (72%).[64] Base-catalyzed dehydration of the hemiketal **120** (sodium ethoxide, 75 °C) furnished (−)-prostephanaberrine (**18**) in 85% yield. It is likely that this elimination proceeds through the chain isomer of **120**. As observed for related alkaloids,[65−67] we found that (−)-prostephanaberrine (**18**) exists as a solvent-dependent mixture of ring and chain isomers (ratio of **18**:**121** = 5:1 in chloroform-*d*). Hydrolysis of (−)-prostephanaberrine (**18**, aqueous hydrochloric acid, 50 °C) cleanly afforded (−)-stephanaberrine (**19**) in 65% yield.[27] Benzoylation of (+)-*N*,*O*-dimethylstephine (**13**, benzoyl chloride) furnished (−)-stephabenine (**12**) in 74% yield (Scheme 27B).

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

Scheme 27. (A) Syntheses of Metaphanine Alkaloids. (B) Synthesis of (−)-Stephabenine (12)



Reactivity Studies of (Trimethylsilyl)cyclopentadiene Diels−Alder Adducts. In our hasubanan and acutumine studies, 5-(trimethylsilyl)cyclopentadiene (**36**) served to stabilize our synthetic intermediates and provide a handle for control of absolute stereochemistry. The ability to remove this blocking group under relatively mild conditions (toluene, 135 °C) suggests it may be of general utility in complex molecule synthesis. Moreover, our X-ray data reveal that the trimethylsilyl group of **40** is oriented above the olefin of the cyclopentene (Scheme 6). This suggested it might be possible to selectively functionalize the alkyne in the presence of the norbornyl alkene, which is typically highly reactive.

To evaluate this, we examined the reactivity of the cyclopentadiene and (trimethylsilyl)cyclopentadiene adducts **33** (formed by deprotection of the addition product **32**)[36] and **68**, respectively, toward hydrogenation, hydrosilylation, and hydrostannylation (Table 1). Exposure of the cyclopentadiene adduct **33** to dihydrogen in the presence of Lindlar's catalyst resulted in rapid reduction of the strained cyclopentenyl olefin and concomitant semihydrogenation of the terminal alkyne (55%, entry 1). Under identical conditions, hydrogenation of the (trimethylsilyl)cyclopentadiene derivative **68** resulted in exclusive semihydrogenation of the alkyne, and no reduction of the cyclopentene was observed (50%, entry 2). Hydrosilylation of the cyclopentadiene adduct **33** (dimethylphenylsilane, Adams' catalyst) led to reduction of the cyclopentenyl olefin and hydrosilylation of the alkyne, to form the reduced vinylsilane **124** (55%, entry 3). Hydrosilylation of the (trimethylsilyl)cyclopentadiene derivative **68** cleanly afforded the vinylsilane **125** (76%), with no reduction of the cyclopentenyl olefin observed (entry 4). However, palladium-catalyzed hydrostannylation of both addition products **33** and **68** [tributyltin hydride, tetrakis(triphenylphosphine)palladium] proceeded without reduction or functionalization of the cyclopentenyl olefin, to provide the vinylstannanes **126** (51%, entry 5) and **127** (78%, entry 6), respectively. This result reflects the higher reactivity of the alkyne functional group of **68** and **33** under these conditions. The terminal alkene **123** could be cleanly hydrosilylated to yield the alkylsilane **128** (56%, entry 7) without any observed reduction of the cycloptenyl olefin. Based on these results, Diels−Alder adducts of 5-(trimethylsilyl)cyclopentadiene (**36**) are anticipated to be stable toward many other metal-catalyzed addition processes, and this capability to selectively functionalize unsaturated carbon−carbon bonds in the presence of the norbornene substructure illustrates the additional versatility of these adducts in multistep sequences. Collectively, the development of enantioselective Diels−Alder reactions employing 5-(trimethylsilyl)cyclopentadiene (**36**), the appreciation that these adducts are stable toward hydrogenation and hydrofunctionalization reactions, and the delineation of mild conditions for their cleavage (toluene, 135 °C), as described herein, may motivate the application of these adducts in other settings.

Cytotoxicity Study. We have evaluated the cyctotoxicity of hasubanan alkaloids, acutumine alkaloids, and synthetic intermediates. The alkaloids were tested against three human cancer cell lines: N87 (gastric), MDA-MB-361-DYT2 (breast), and HT29 (colon). The results are summarized in Table 2. Of the nine alkaloids tested, seven exhibited 50% inhibitory potencies (IC_{50}) in the submicromolar range against the N87 cell line. The most potent alkaloid, (−)-delavayine (**3**), possessed an IC_{50} value of 0.892 μM. (−)-Hasubanonine (**1**), (−)-runanine (**2**), and (+)-periglaucine B (**8**) exhibited IC_{50} values of 0.970, 0.959, and 0.992 μM, respectively. The similar potencies of the compounds suggests the α-methoxy ketone and amine functionality may be important for antiproliferative effects, while the arene substituents are not. For the MDA-MB-361-DYT2 and HT29 cell lines, all alkaloids tested possessed IC_{50} values >1 μM.

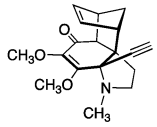
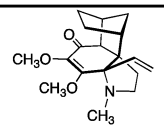
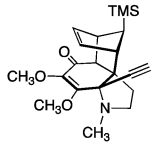
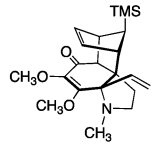
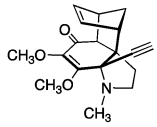
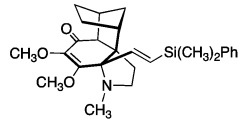
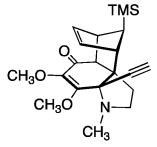
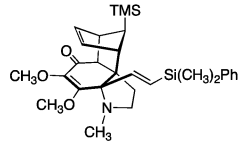
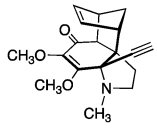
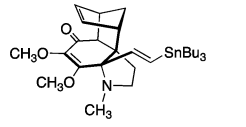
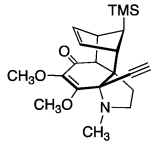
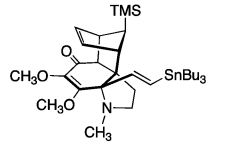
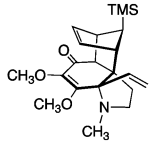
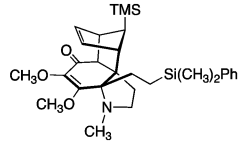
We were pleased to observe that a variety of hasubanan and acutumine alkaloids exhibit nanomolar IC_{50} values against the N87 cell line, since to our knowledge, the only other report of a hasubanan or acutumine alkaloid exhibiting cytotoxicity against a cancer cell line is (−)-acutumine (**4**) [IC_{50} = 13.2 μM against HUT 78 (human T-cells)].[9] In previous studies, (−)-runanine (**2**),[68] (−)-delavayine (**3**),[69] (−)-acutumine (**4**), (−)-dechloroacutumine (**5**), and the acutumine alkaloids (−)-acutumidine, (−)-dechloroacutumidine,[9] and (−)-dauricumine[70] exhibited no cytotoxicity against a variety of mammalian cancer cell lines.

■ CONCLUSION

We have described the evolution of enantioselective synthetic routes to 10 hasubanan and two acutumine alkaloids. Our synthetic routes employ the complex, tetracyclic imine **39** as a precursor to each target. The imine **39** was accessed by a highly enantioselective Diels−Alder reaction employing 5-(trimethylsilyl)cyclopentadiene (**36**) as reaction partner. The *N*-methyliminium ion derived from **39** was found to undergo efficient, diastereoselective addition of lithium acetylide nucleophiles to forge the C-5−C-6 bonds of the targets. The hasubanan skeleton was completed by a Friedel−Crafts cyclization, while the acutumine skeleton was accessed by a late-stage Hosomi−Sakurai cyclization, using a complex dienylsilane substrate. The silylcyclopentene substituent of **39** provided a handle for absolute stereocontrol in the syntheses, and could be removed in high yield by mild thermolysis. Our initial work resulted in the syntheses of (−)-acutumine (**4**), (−)-dechloroacutumine (**5**), and the first enantioselective syntheses of (−)-hasubanonine (**1**), (−)-runanine (**2**),

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

Table 1. Hydrogenation and Hydrofunctionalization of the Terminal Alkynes 33 and 68

Entry	Substrate	Conditions	Product	Yield
1[a]	 **33**	H_2 Lindlar's catalyst	 **122**	55%
2[a]	 **68**	H_2 Lindlar's catalyst	 **123**	50%
3[b]	 **33**	PtO_2 $HSi(CH_3)_2Ph$	 **124**	55%
4[b]	 **68**	PtO_2 $HSi(CH_3)_2Ph$	 **125**	76%
5[c]	 **33**	$Pd(PPh_3)_4$ Bu_3SnH	 **126**	51%
6[c]	 **68**	$Pd(PPh_3)_4$ Bu_3SnH	 **127**	78%
7[b]	 **123**	PtO_2 $HSi(CH_3)_2Ph$	 **128**	56%

[a]Conditions: H_2, Lindlar catalyst (15 mol % Pd), ethyl acetate, 24 °C, 30 min. [b]Conditions: $HSi(CH_3)_2Ph$, PtO_2 (1.60−1.80 equiv), 60 °C, 2−4 h. [c]Conditions: $Pd(PPh_3)_4$ (20−25 mol %), Bu_3SnH, THF, 24 °C, 1 h.

Table 2. Cytotoxicity of Hasubanan and Acutumine Alkaloids Against Cancer Cell Lines

Alkaloid	N87[a] IC_{50} (μM)	MDA-MB-361-DYT2[b] IC_{50} (μM)	HT29[c] IC_{50} (μM)
(−)-hasubanonine (**1**)	0.970	>1	>1
(−)-runanine (**2**)	0.959	>1	>1
(−)-delavayine (**3**)	0.892	>1	>1
(+)-periglaucine B (**8**)	0.992	>1	>1
(−)-dechloroacutumine (**5**)	>1	>1	>1
tetracycle **50**	0.965	>1	>1
tetracycle **56**	>1	>1	>1
dienone **54**	0.989	>1	>1
cis-alkene **49**	0.951	>1	>1

[a]N87 = human gastric cancer cell line. [b]MDA-MB-361-DYT2 = human breast cancer cell line. [c]HT29 = human colon cancer cell line.

(−)-delavayine (**3**), and (+)-periglaucine B (**8**), which encompass the hasubanonine and stephamiersine classes of hasubanan alkaloids. We adapted this route to the syntheses of six additional targets that constitute the unaddressed oxostephasunoline and metaphanine classes of hasubanan alkaloids [(−)-stephabenine (**12**), (+)-*N*,*O*-dimethylstephine

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

(**13**), (+)-*N*,*O*-dimethyloxostephine (**14**), (+)-oxostephabenine (**15**), (−)-prostephanaberrine (**18**), and (−)-stephanaberrine (**19**)]; each was obtained from synthetic (+)-periglaucine B (**8**) in 1−4 steps.

We have further demonstrated the strategic advantages of 5-(trimethylsilyl)cyclopentadiene Diels−Alder adducts in complex molecule synthesis. We developed a highly enantioselective Diels−Alder reaction employing 5-(trimethylsilyl)cyclopentadiene (**36**) as a diene. The trimethylsilyl group of the Diels−Alder adduct is shown to shield the olefin of the cyclopentene fragment, impeding its reactivity toward metal-catalyzed addition reactions. We have demonstrated that the silylcyclopentene substituent is removed in high yield by mild thermolytic cleavage (toluene, 135 °C). Taken together, these data increase the versatility of the silylcyclopentene Diels−Alder adducts, relative to the parent systems, and argue for their application in multistep settings. Additionally, we reported the first side-by-side evaluation of the antiproliferative properties of hasubanan and acutumine alkaloids and showed that (−)-hasubanonine (**1**), (−)-runanine (**2**), (−)-delavayine (**3**), and (+)-periglaucine B (**8**) are submicromolar inhibitors of the N87 (human gastric cancer) cell line. These preliminarily biological data establish a basis set for studying the mechanism of action of hasubanan and acutumine alkaloids. The synthetic chemistry outlined herein is potentially adaptable to many other members of this large family of natural products.

EXPERIMENTAL SECTION

For general experimental procedures, materials, and instrumentation, see the Supporting Information. For clarity, synthetic intermediates not described in the manuscript are numbered in the Experimental Section beginning with **S1**.

Synthesis of the Indole 27. Triphenylphosphine (155 mg, 591 μmol, 1.40 equiv) was added to a stirred solution of the azide **24** (100 mg, 422 μmol, 1 equiv) in tetrahydrofuran (5.0 mL) at 24 °C. The reaction mixture was stirred for 2 h at 24 °C. The product mixture was diluted with dichloromethane (100 mL), and the diluted solution was transferred to a separatory funnel. The organic layer was washed with distilled water (100 mL). The aqueous layer was extracted with dichloromethane (3 × 100 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 30% acetone−hexanes) to afford the indole **27** as a white solid (28.0 mg, 34%): R_f = 0.30 (30% acetone−hexanes; UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.13 (app t, 1H, J = 2.5 Hz), 6.91 (br s, 1H), 6.41 (app t, 1H, J = 2.5 Hz), 5.49 (s, 1H), 4.03 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4 (C), 137.8 (C), 135.9 (C), 124.6 (C), 124.3 (CH), 124.2 (C), 102.8 (CH), 99.4 (CH), 61.6 (CH_3), 60.8 (CH_3); IR (ATR-FTIR), cm^{-1} 3348 (w), 1585 (m), 1343 (m), 1310 (m); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{10}H_{12}NO_3$ 194.0817, found 194.0850.

Synthesis of the Iminium Ion 31. Methyl trifluoromethanesulfonate (489 μL, 4.32 mmol, 1.20 equiv) was added to a solution of the imine **30** [932 mg, 3.60 mmol, 1 equiv; dried by azeotropic distillation with benzene (5 mL)] in ether (7.0 mL) at −78 °C. The reaction vessel was placed in a −30 °C bath, and the mixture was stirred for 30 min at −30 °C. The cooling bath was removed, and the product mixture was allowed to warm over 15 min to 24 °C. The warmed product mixture was concentrated to dryness to afford the iminium ion **31** as a white solid (1.31 g, 86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19−6.17 (m, 1H), 6.11−6.09 (m, 1H), 4.59−4.51 (m, 1H), 4.02−3.93 (m, 7H), 3.73 (s, 3H), 3.53 (br s, 1H), 3.39 (br s, 1H), 3.08 (d, 1H, J = 4.0 Hz), 2.83 (m, 1H), 2.32 (app q, 1H, J = 6.4 Hz), 1.72 (d, 1H, J = 9.6 Hz), 1.66 (d, 1H, J = 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9 (C), 175.9 (C), 154.2 (C), 143.6 (C), 136.2 (CH), 136.0 (CH), 62.0 (CH_3), 61.2 (CH_3), 60.3 (CH_2), 57.4 (C), 56.7 (CH), 54.0 (CH), 50.8 (CH), 50.2 (CH_2), 40.1 (CH_3), 36.4 (CH_2), CF_3 not observed; IR (ATR-FTIR), cm^{-1} 1690 (m), 1640 (m), 1590 (m), 1255 (s), 1030 (s); HRMS-CI (m/z) [M]$^+$ calcd for $C_{16}H_{20}NO_3$ 274.1438, found 274.1443.

Synthesis of the Acetylide Addition Product 32. A solution of *n*-butyllithium in hexanes (2.38 M, 259 μL, 615 μmol, 1.00 equiv) was added to a solution of (trimethylsilyl)acetylene (131 μL, 922 μmol, 1.50 equiv) in tetrahydrofuran (5.0 mL) at −78 °C. The resulting mixture was stirred for 15 min at −78 °C. The cold solution of the lithiated alkyne was then added dropwise via cannula to a solution of the iminium ion **31** (260 mg, 615 μmol, 1 equiv) in tetrahydrofuran (20 mL) at −90 °C. The reaction mixture was stirred for 30 min at −90 °C. The product mixture was allowed to warm over 15 min to 24 °C. The warmed product mixture was concentrated to dryness, and the residue obtained was purified by flash column chromatography (eluting with 60% ethyl acetate−hexanes) to afford the addition product **32** as a clear oil (248 mg, 68%). Spectroscopic data for the acetylide addition product **32** obtained in this way were identical to those previously described.[21]

Synthesis of the Diels−Alder Adduct 38 (Racemic). A solution of methylaluminum dichloride in hexanes (1 M, 633 μL, 633 μmol, 0.30 equiv) was added to a solution of the azidoquinone **24** [500 mg, 2.11 mmol, 1 equiv; dried by azeotropic distillation with benzene (5.0 mL)] and 5-(trimethylsilyl)cyclopentadiene (**36**, 760 μL, 4.22 mmol, 2.00 equiv) in toluene (2.1 mL) at −78 °C. The reaction vessel was placed in a −40 °C bath, and the mixture was stirred for 3 h at −40 °C. The cold product mixture was diluted with ethyl acetate (100 mL) and the cold diluted solution was transferred to a separatory funnel. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate solution (100 mL) and distilled water (100 mL). The washed organic layer was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (eluting with 2% triethylamine−10% ethyl acetate−hexanes) to afford the Diels−Alder adduct **38** as a yellow solid (244 mg, 31%). Spectroscopic data for the Diels−Alder adduct **38** obtained in this way were identical to those previously obtained using the (*S*)-*o*-tol-Corey−Bakshi−Shibata catalyst (**37**).[21]

Methylation of 2,5-Dihydroxy-1,4-benzoquinone (62). A solution of diazomethane in ether (nominally 0.25 M, 29.0 mL, 7.14 mmol, 1 equiv) was added dropwise via syringe to a stirred solution of 2,5-dihydroxy-1,4-benzoquinone (**62**, 1.00 g, 7.14 mmol, 1 equiv) in tetrahydrofuran (29 mL) at 24 °C. The reaction mixture was stirred for 10 min at 24 °C. Excess diazomethane was purged from the product mixture by sparging with dinitrogen (10 min). The sparged product mixture was concentrated to provide the methyl ether **63** as a brown solid (1.16 g). The methyl ether **63** prepared in this way was estimated to be of ∼80% purity (^{1}H NMR analysis) and was used in the subsequent step without purification. An analytically pure sample of the methyl ether **63** was obtained by flash column chromatography (eluting with 5% methanol−dichloromethane): R_f = 0.20 (5% methanol−dichloromethane; CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (br s, 1H), 6.04 (s, 1H), 5.93 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.8 (C), 181.8 (C), 161.6 (C), 155.4 (C), 105.7 (CH), 103.0 (CH), 57.1 (CH_3); IR (ATR-FTIR), cm^{-1} 3530 (br), 1670 (s), 1605 (s), 1545 (s), 1212 (s); HRMS-EI (m/z) [M]$^+$ calcd for $C_7H_6O_4$ 154.0266, found 154.0266.

Synthesis of the Iododonim Ylide 64. Iodobenzene diacetate (3.64 g, 11.3 mmol, 1.50 equiv) was added in one portion to a stirred solution of the unpurified methyl ether **63** (1.16 g, 7.54 mmol, 1 equiv) obtained in the preceding step in dichloromethane (42 mL) at 0 °C. The resulting solution was stirred for 30 min at 0 °C. The cooling bath was removed, and the reaction mixture was allowed to warm over 10 min to 24 °C. The reaction mixture was stirred for 2 h at 24 °C. The yellow product mixture was filtered, and the filter cake was washed with dichloromethane (2 × 100 mL). The washed filter cake was collected and dried in vacuo to provide the iodonium ylide **64** as a yellow solid (2.37 g). The iodonium ylide **64** prepared in this way was estimated to be of ∼80% purity (^{1}H NMR analysis) and was used in the subsequent step without purification. An analytically pure sample

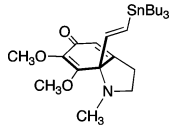
dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

of the iodonium ylide **64** was obtained by flash column chromatography (eluting with 10% methanol–dichloromethane): R_f = 0.40 (10% methanol–dichloromethane; UV); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (d, 2H, J = 7.7 Hz), 7.53 (app t, 1H, J = 7.7 Hz), 7.41 (app t, 2H, J = 7.7), 5.90 (s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.3 (C), 171.4 (C), 170.0 (C), 162.4 (C), 133.2 (2 × CH), 131.1 (2 × CH), 130.6 (CH), 114.3 (C), 104.4 (CH), 97.0 (C), 56.9 (CH_3); IR (ATR FTIR), cm^{-1} 1695 (m), 1600 (s), 1580 (s), 1330 (m), 1200 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{13}H_{10}IO_4$ 356.9624, found 356.9628.

Synthesis of the Diketone 59. The unpurified iodonium salt **64** (2.37 g, 6.66 mmol, 1 equiv) obtained in the preceding step was dissolved in acetonitrile (130 mL) in a 250-mL round-bottomed flask equipped with a reflux condenser. Distilled water (240 μL, 13.3 mmol, 2.00 equiv) was added. The flask was placed in an oil bath that had been preheated to 80 °C. The reaction mixture was stirred and heated for 2 h at 80 °C. The product mixture was allowed to cool over 20 min to 24 °C. The cooled product mixture was concentrated to dryness, and the residue obtained was purified by flash column chromatography (eluting with 30% ethyl acetate–hexanes) to afford the diketone **59** as a yellow solid (189 mg, 23% over three steps). ^{1}H NMR and IR data for the diketone **59** obtained in this way were identical to those previously described:[41] R_f = 0.30 (40% ethyl acetate–hexanes; UV, PAA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (s, 1H), 3.94 (s, 3H), 2.95 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6 (C), 194.8 (C), 172.8 (C), 119.2 (CH), 59.1 (CH_3), 42.4 (CH_2); IR (ATR-FTIR), cm^{-1} 1698 (s), 1600 (s), 1325 (s), 1205 (s), 1100 (s); HRMS-EI (m/z) [M]$^+$ calcd for $C_6H_6O_3$ 126.0317, found 126.0315.

Synthesis of the Acetylide Addition Product 68. Methyl trifluoromethanesulfonate (325 μL, 2.87 mmol, 0.95 equiv) was added to a solution of the imine **39** [1.00 g, 3.02 mmol, 1 equiv; dried by azeotropic distillation with benzene (8.0 mL)] in tetrahydrofuran (20 mL) at −78 °C. The reaction vessel was placed in a −30 °C bath, and the mixture was stirred for 30 min at −30 °C. The mixture was then cooled to −90 °C, and the cooled solution was diluted with tetrahydrofuran (20 mL). In a separate flask, a solution of *n*-butyllithium in hexanes (2.29 M, 1.45 mL, 3.32 mmol, 1.10 equiv) was added to a solution of (trimethylsilyl)acetylene (516 μL, 3.62 mmol, 1.20 equiv) in tetrahydrofuran (20 mL) at −78 °C. The resulting mixture was stirred for 15 min at −78 °C. The cold solution of the lithiated alkyne was then added dropwise via cannula to the iminium ion at −90 °C. The reaction mixture was stirred for 30 min at −90 °C. The product mixture was allowed to warm over 15 min to 24 °C. The warmed product mixture was concentrated to dryness. The residue obtained was dissolved in methanol (20 mL), and potassium carbonate (167 mg, 1.21 mmol, 0.40 equiv) was added. The resulting mixture was stirred for 1 h at 24 °C. The product mixture was diluted with ethyl acetate (300 mL) and the diluted solution was transferred to a separatory funnel. The organic layer was washed with distilled water (2 × 300 mL). The washed organic layer was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (eluting with 40% acetone–hexanes) to afford the addition product **68** as a clear oil (934 mg, 83%). The relative stereochemistry of the addition product **68** was assigned by analogy to related addition products:[21] R_f = 0.80 (60% acetone–hexanes; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (app q, 1H, J = 3.2 Hz), 5.82 (app q, 1H, J = 2.8, Hz), 3.99 (s, 3H), 3.56 (s, 3H), 3.31 (br s, 1H), 3.02 (br s, 1H), 2.90 (d, 1H, J = 4.4 Hz), 2.82 (td, 1H, J = 8.8, 3.6 Hz), 2.56 (s, 1H), 2.43 (dd, 1H, J = 16.8, 9.2 Hz), 2.19 (s, 3H), 2.14–2.01 (m, 2H), 1.15 (s, 1H), −0.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3 (C), 162.9 (C), 139.0 (C), 135.9 (CH), 135.3 (CH), 77.3 (C), 77.0 (CH), 70.3 (C), 65.6 (CH), 61.5 (CH_3), 59.6 (CH_3), 58.4 (CH), 54.4 (C), 54.0 (CH), 50.1 (CH_2), 49.6 (CH), 41.3 (CH_2), 36.3 (CH_3), −0.1 (TMS); IR (ATR-FTIR), cm^{-1} 2950 (br), 1655 (s), 1605 (s), 1450 (m), 1095 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{21}H_{30}NO_3Si$ 372.1995, found 372.2010; $[\alpha]^{20}_D$ +188 (c 3.0, $CHCl_3$).

Synthesis of the Cyclohexanedienone 61. The terminal alkyne **68** (196 mg, 528 μmol, 1 equiv) was dissolved in toluene (11 mL) in a 100-mL round-bottomed flask that had been fused to a Teflon-coated valve. The vessel was sealed, and the sealed reaction vessel was placed in an oil bath that had been preheated to 135 °C. The reaction mixture was stirred and heated for 2 h at 135 °C. The product mixture was allowed to cool over 20 min to 24 °C. The cooled product mixture was concentrated to dryness, and the residue obtained was purified by flash column chromatography (eluting with 25% acetone–hexanes) to afford the cyclohexanedienone **61** as a white solid (109 mg, 89%): R_f = 0.50 (50% acetone–hexanes; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (dd, 1H, J = 1.6, 1.2 Hz), 4.08 (s, 3H), 3.67 (s, 3H), 3.20–3.15 (m, 1H), 2.83–2.67 (m, 2H), 2.58–2.51 (m, 4H), 2.42 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.9 (C), 158.8 (C), 158.5 (C), 137.6 (C), 121.0 (CH), 75.7 (C), 74.7 (CH), 62.5 (C), 61.3 (CH_3), 60.6 (CH_3), 53.8 (CH_2), 38.3 (CH_3), 27.0 (CH_2); IR (ATR-FTIR), cm^{-1} 1690 (s), 1650 (s), 1605 (s), 1215 (s), 1090 (m); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{13}H_{16}NO_3$ 234.1130, found 234.1132; $[\alpha]^{20}_D$ −83 (c 1.0, $CHCl_3$).



S1

Synthesis of the Vinylstannane S1. Tetrakis(triphenylphosphine)palladium (74.4 mg, 64.4 μmol, 0.20 equiv) was added to a solution of the cyclohexanedienone **61** [75.0 mg, 322 μmol, 1 equiv; dried by azeotropic distillation with benzene (3.0 mL)] in tetrahydrofuran (1.0 mL) at 24 °C. Tributyltin hydride (171 μL, 644 μmol, 2.00 equiv) was added dropwise via syringe pump over 1 h at 24 °C. Upon completion of the addition, the product mixture was concentrated to dryness. The residue obtained was purified by flash column chromatography (eluting with 25% acetone–hexanes) to afford the vinylstannane **S1** as a clear oil (118 mg, 70%): R_f = 0.40 (70% ethyl acetate–hexanes; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (app d, 2H, J = 19.2 Hz), 5.96 (d, 1H, J = 19.2 Hz), 4.07 (s, 3H), 3.63 (s, 3H), 3.11–3.04 (m, 1H), 2.90–2.84 (m, 1H), 2.65–2.47 (m, 2H), 2.29 (s, 3H), 1.45–1.37 (m, 6H), 1.27–1.18 (m, 6H), 0.86–0.80 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.3 (C), 161.1 (C), 160.9 (C), 144.4 (CH), 137.5 (CH), 132.1 (CH), 123.4 (C), 75.8 (C), 60.9 (CH_3), 60.8 (CH_3), 52.0 (CH_2), 38.9 (CH_3), 29.2 (CH_2), 27.7 (3 × CH_2), 27.3 (3 × CH_2), 13.8 (3 × CH_3), 9.8 (3 × CH_2); IR (ATR-FTIR), cm^{-1} 2960 (m), 2915 (m), 1650 (s), 1605 (s), 1465 (m); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{25}H_{44}NO_3Sn$ 526.2343, found 526.2381; $[\alpha]^{20}_D$ +189 (c 1.0, $CHCl_3$).

Synthesis of the Vinyl Iodide 65. *N*-Iodosuccinimide (510 mg, 2.27 mmol, 1.40 equiv) was added in one portion to a solution of the vinylstannane **S1** (850 mg, 1.62 mmol, 1 equiv) in dichloromethane (32 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed, and the reaction mixture was allowed to warm over 10 min to 24 °C. The reaction mixture was stirred for 30 min at 24 °C. The product mixture was concentrated to dryness, and the residue obtained was purified by flash column chromatography (eluting with 80% ethyl acetate–hexanes) to afford the vinyl iodide **65** as a clear oil (545 mg, 93%): R_f = 0.20 (90% ethyl acetate–hexanes; UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (d, 1H, J = 15.0 Hz), 6.41 (d, 1H, J = 15.0 Hz), 6.15 (s, 1H), 4.12 (s, 3H), 3.70 (s, 3H), 3.07–3.02 (m, 1H), 2.97–2.92 (m, 1H), 2.69–2.64 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.4 (C), 159.7 (C), 159.1 (C), 141.6 (CH), 137.7 (C), 123.3 (CH), 80.2 (CH), 73.8 (C), 60.8 (2 × CH_3), 52.6 (CH_2), 38.4 (CH_3), 27.6 (CH_2); IR (ATR-FTIR), cm^{-1} 1690 (m), 1645 (s), 1600 (s), 1450 (m), 1205 (m); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{13}H_{17}INO_3$ 362.0253, found 362.0235; $[\alpha]^{20}_D$ +137 (c 1.0, $CHCl_3$).

Synthesis of the Enamide 66. A 10-mL round-bottomed flask that had been fused to a Teflon-coated valve was charged sequentially with the vinyl iodide **65** (50.0 mg, 139 μmol, 1 equiv), acetamide (16.3 mg, 277 μmol, 2.00 equiv), cesium carbonate (68.0 mg, 209 μmol, 1.50 equiv), cuprous iodide (4.0 mg, 20.9 μmol, 0.15 equiv), and tetrahydrofuran (1.0 mL). *N*,*N*′-Dimethylethylenediamine (11.2 μL, 104 μmol, 0.75 equiv) was added and the vessel was sealed. The reaction mixture was stirred and heated for 12 h at 45 °C. The product

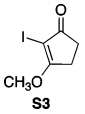
dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031–10057

mixture was allowed to cool over 10 min to 24 °C. The cooled product mixture was diluted with dichloromethane (100 mL), and the diluted solution was transferred to a separatory funnel. Aqueous ammonium hydroxide solution (3%, 100 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 100 mL) and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (eluting with 8% methanol−dichloromethane) to afford the enamide **66** as a yellow oil (20.0 mg, 50%): R_f = 0.50 (10% methanol−dichloromethane; UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, 1H, J = 10.8 Hz), 6.86 (dd, 1H, J = 14.8, 10.8 Hz), 6.18 (br s, 1H), 5.35 (d, 1H, J = 14.8 Hz), 4.13 (s, 3H), 3.69 (s, 3H), 3.01−2.96 (m, 2H), 2.71−2.69 (m, 2H), 2.34 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5 (C), 167.3 (C), 161.4 (C), 160.0 (C), 137.1 (C), 125.0 (CH), 123.5 (CH), 109.3 (CH), 70.0 (C), 61.0 (CH_3), 60.8 (CH_3), 52.4 (CH_2), 38.4 (CH_3), 27.8 (CH_2), 23.4 (CH_3); IR (ATR-FTIR), cm^{-1} 1685 (s), 1650 (s), 1600 (s), 1510 (m), 1285 (m); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{15}H_{21}N_2O_4$ 293.1501, found 293.1512; $[\alpha]^{20}_D$ +164 (c 0.7, $CHCl_3$).

Synthesis of the Hemiacetal 67. The enamide **66** (15.0 mg, 51.4 μmol, 1 equiv) was dissolved in aqueous hydrochloric acid (3 M, 1.0 mL) in a 10-mL round-bottomed flask that had been fused to a Teflon-coated valve. The vessel was sealed, and the sealed reaction vessel was placed in an oil bath that had been preheated to 80 °C. The reaction mixture was stirred and heated for 1 h at 80 °C. The product mixture was allowed to cool over 20 min to 24 °C. The cooled product mixture was diluted with dichloromethane (50 mL), and the diluted solution was transferred to a separatory funnel. The organic layer was washed with saturated aqueous sodium bicarbonate solution (50 mL). The aqueous layer was extracted with dichloromethane (3 × 50 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 50% acetone−hexanes) to afford the hemiacetal **67** as a yellow oil (3.0 mg, 22%): R_f = 0.35 (50% acetone−hexanes; UV, PAA); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (br s, 1H), 5.38 (br s, 1H), 4.07 (s, 3H), 3.67 (s, 3H), 3.11−3.06 (m, 1H), 2.87 (d, 1H, J = 14.5 Hz), 2.56−2.52 (m, 3H), 2.49 (s, 3H), 2.47−2.40 (m, 1H), 2.09 (dd, 1H, J = 13.5, 5.0 Hz), 1.88 (app q, 1H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0 (C), 157.6 (C), 138.3 (C), 100.3 (CH), 89.1 (C), 75.1 (C), 61.1 (CH_3), 60.7 (CH_3), 53.0 (CH_2), 48.7 (CH_2), 40.2 (CH_2), 38.4 (CH_2), 37.0 (CH_3); IR (ATR-FTIR), cm^{-1} 3380 (w), 2920 (w), 1682 (m), 1602 (m), 798 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{13}H_{20}NO_5$ 270.1341, found 270.1344; $[\alpha]^{20}_D$ −110 (c 0.1, $CHCl_3$).

Synthesis of the Ynamide 69. A 25-mL round-bottomed flask was charged sequentially with 2-azetidinone (322 mg, 4.53 mmol, 15.0 equiv), cuprous chloride (59.8 mg, 604 μmol, 2.00 equiv), cesium carbonate (197 mg, 604 μmol, 2.00 equiv), and methyl sulfoxide (3.0 mL). The reaction vessel was evacuated and refilled with dioxygen (balloon). This process was repeated four times, and the reaction vessel was maintained under a positive pressure of dioxygen (balloon). The reaction vessel was placed in an oil bath that had been preheated to 70 °C. A solution of the terminal alkyne **68** (100 mg, 302 μmol, 1 equiv) in methyl sulfoxide (1.0 mL) was added dropwise via syringe pump over 16 h. The product mixture was allowed to cool to 24 °C over 10 min. The cooled product mixture was diluted with ethyl acetate (300 mL), and the diluted solution was transferred to a separatory funnel. The organic layer was washed sequentially with aqueous ammonium hydroxide solution (3%, 200 mL), distilled water (2 × 200 mL), and saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (eluting with 40% acetone−hexanes) to afford the ynamide **69** as a clear oil (35.0 mg, 26%): R_f = 0.60 (50% acetone−hexanes; UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (app q, 1H, J = 2.8 Hz), 5.83 (app q, 1H, J = 2.8, Hz), 3.99 (s, 3H), 3.68 (t, 2H, J = 4.8 Hz), 3.57 (s, 3H), 3.33 (br s, 1H), 3.09 (t, 2H, J = 4.8 Hz), 3.06 (br s, 1H), 2.92 (d, 1H, J = 4.4 Hz), 2.82 (td, 1H, J = 8.8, 3.6 Hz), 2.43 (app q, 1H, J = 8.8 Hz), 2.19 (s, 3H), 2.12−2.06 (m, 2H), 1.16 (s, 1H), −0.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4 (C), 167.0 (C), 163.1 (C), 139.0 (C), 135.8 (CH), 135.5 (CH), 78.9 (C), 70.8 (C), 65.8 (CH), 63.7 (C), 61.5 (CH_3), 59.7 (CH_3), 58.5 (CH), 54.9 (C), 54.1 (CH), 50.3 (CH_2), 49.7 (CH), 43.2 (CH_2), 41.5 (CH_2), 38.2 (CH_2), 36.5 (CH_3), 0.0 (TMS); IR (ATR-FTIR), cm^{-1} 2945 (br), 1790 (s), 1650 (m), 1605 (m), 1090 (m); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{24}H_{33}N_2O_4Si$ 441.2210, found 441.2225; $[\alpha]^{20}_D$ +171 (c 1.0, $CHCl_3$).

Synthesis of the Enamide 70. Palladium on carbon (10 wt % loading, 4.8 mg, 4.5 μmol, 0.10 equiv) was added to a solution of the ynamide **69** (20.0 mg, 45.5 μmol, 1 equiv) in methanol (1.0 mL) at 24 °C. The reaction vessel was evacuated and refilled with dihydrogen (balloon). This process was repeated four times. The reaction mixture was stirred for 30 min at 24 °C under a balloon of dihydrogen. The product mixture was diluted with methanol (5 mL), and the diluted solution was filtered through a pad of Celite. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (eluting with 40% acetone−hexanes) to afford the enamide **70** as a clear oil (10.2 mg, 50%): R_f = 0.50 (40% ethyl acetate−hexanes; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (d, 1H, J = 11.2 Hz), 6.13−6.11 (m, 1H), 5.90−5.88 (m, 1H), 4.33 (d, 1H, J = 11.2 Hz), 3.99 (s, 3H), 3.62−3.58 (m, 5H), 3.36 (br s, 1H), 2.97 (t, 2H, J = 4.8 Hz), 2.86 (br s, 1H), 2.80 (dd, 1H, J = 9.2, 5.2 Hz), 2.61 (d, 1H, J = 4.0 Hz), 2.55−2.49 (m, 1H), 2.26 (s, 3H), 2.11−2.04 (m, 1H), 1.68 (dd, 1H, J = 11.6, 4.0 Hz), 1.28 (s, 1H), −0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6 (C), 167.2 (C), 163.2 (C), 140.2 (C), 136.5 (CH), 135.7 (CH), 119.8 (CH), 113.8 (CH), 71.1 (C), 61.9 (CH_3), 61.0 (CH_3), 60.1 (CH), 57.4 (C), 55.9 (CH), 53.4 (CH), 53.0 (CH_2), 49.8 (CH), 45.3 (CH_2), 40.7 (CH_2), 37.3 (CH_2), 36.3 (CH_3), 0.0 (TMS); IR (ATR-FTIR), cm^{-1} 2920 (br), 1760 (s), 1650 (m), 1600 (m), 1215 (m); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{24}H_{35}N_2O_4Si$ 443.2366, found 443.2357; $[\alpha]^{20}_D$ +26 (c 1.0, $CHCl_3$).



S3

Iodination of the β-Methoxy Enone S2. Iodine (340 mg, 1.34 mmol, 1.00 equiv) and ceric ammonium nitrate (734 mg, 1.34 mmol, 1.00 equiv) were added sequentially to a solution of 3-methoxycyclopent-2-ene-1-one (**S2**, 150 mg, 1.34 mmol, 1 equiv) in acetonitrile (13 mL) at 24 °C. Upon completion of the addition, the reaction mixture was stirred for 1 h at 24 °C. The product mixture was diluted with ethyl acetate (300 mL) and the diluted solution was transferred to a separatory funnel. The organic layer was washed with saturated aqueous sodium thiosulfate solution (300 mL). The washed organic layer was dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (eluting with 80% ethyl acetate−hexanes) to afford the vinyl iodide **S3** as a white solid (183 mg, 57%): R_f = 0.25 (80% ethyl acetate−hexanes; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (s, 3H), 2.87−2.84 (m, 2H), 2.64−2.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6 (C), 189.6 (C), 73.9 (C), 57.6 (CH_3), 32.7 (CH_2), 27.4 (CH_2); IR (ATR-FTIR), cm^{-1} 1665 (s), 1585 (s), 1325 (s), 1290 (s), 1045 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_6H_8IO_2$ 238.9569, found 238.9559.

Synthesis of the Vinylstannane 72. A 10-mL round-bottomed flask that had been fused to a Teflon-coated valve was charged sequentially with the vinyl iodide **S3** (89.0 mg, 374 μmol, 1 equiv), tetrakis(triphenylphosphine)palladium (65.0 mg, 56.1 μmol, 0.15 equiv), hexamethylditin (93.0 μL, 449 μmol, 1.20 equiv), and toluene (3.0 mL). The vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 125 °C. The reaction mixture was stirred and heated for 1.5 h at 125 °C. The product mixture was allowed to cool over 20 min to 24 °C. The cooled product mixture was concentrated to dryness. The residue obtained was purified by flash column chromatography (eluting with 70% ethyl acetate−hexanes) to afford the vinylstannane **72** as a clear oil (64.4

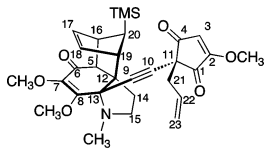
dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

mg, 62%): R_f = 0.30 (70% ethyl acetate−hexanes; UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 3H), 2.75−2.73 (m, 2H), 2.49−2.47 (m, 2H), 0.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.3 (C), 197.0 (C), 117.5 (C), 56.6 (CH_3), 35.5 (CH_2), 28.0 (CH_2), −8.9 (3 × CH_3); IR (ATR-FTIR), cm^{-1} 1680 (m), 1575 (s), 1325 (s), 1275 (s), 1040 (s); HRMS-CI (m/z) [M − CH_3]$^+$ calcd for $C_8H_{13}O_2Sn$ 260.9938, found 260.9944.

Synthesis of the 1,3-Diene 73. A 10-mL round-bottomed flask was charged sequentially with a solution of the vinyl iodide **65** (52.3 mg, 145 μmol, 1 equiv) in benzene (3.0 mL) and a solution of the vinylstannane **72** (40.0 mg, 145 μmol, 1.00 equiv) in benzene (2.0 mL). The resulting solution was concentrated to dryness. Tris(dibenzylideneacetone)dipalladium (33.2 mg, 36.3 μmol, 0.25 equiv), triphenylarsine (44.4 mg, 145 μmol, 1.00 equiv), and cuprous iodide (6.9 mg, 36 μmol, 0.25 equiv) were then added in sequence. The dry mixture was dissolved in *N*,*N*-dimethylformamide (1.5 mL) and the resulting solution was stirred for 12 h at 24 °C. The product mixture was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 80% acetone−hexanes) to afford the 1,3-diene **73** as a clear oil (34.2 mg, 68%): R_f = 0.20 (80% acetone−hexanes; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, 1H, J = 16.4 Hz), 6.21−6.16 (m, 2H), 4.12 (s, 3H), 3.98 (s, 3H), 3.69 (s, 3H), 3.08−2.95 (m, 2H), 2.70−2.65 (m, 4H), 2.47−2.44 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6 (C), 185.3 (C), 185.0 (C), 161.7 (C), 161.1 (C), 137.5 (CH), 128.3 (C), 122.9 (CH), 119.1 (CH), 115.9 (C), 72.2 (C), 60.9 (2 × CH_3), 57.0 (CH_3), 52.4 (CH_2), 38.6 (CH_3), 33.7 (CH_2), 27.8 (CH_2), 24.4 (CH_2); IR (ATR-FTIR), cm^{-1} 1680 (s), 1633 (s), 1600 (s), 1460 (m), 1370 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{19}H_{24}NO_5$, 346.1654, found 346.1621; $[\alpha]^{20}_D$ +209 (c 1.0, $CHCl_3$).

Synthesis of the Allylation Product 78. A 50-mL round-bottomed flask was charged sequentially with the diketone **59** (1.34 g, 10.6 mmol, 2.00 equiv), allylpalladium chloride dimer (205 mg, 532 μmol, 0.10 equiv), 1,3-bis(diphenylphosphine)propane (437 mg, 1.06 mmol, 0.20 equiv), sodium acetate (523 mg, 6.38 mmol, 1.20 equiv), and tetrahydrofuran (10 mL). Allyl acetate (604 μL, 5.32 mmol, 1 equiv) was then added dropwise via syringe pump over 1 h at 24 °C. Upon completion of the addition, the product mixture was concentrated to dryness. The residue obtained was purified by flash column chromatography (eluting with 40% ethyl acetate−hexanes) to afford the allylation product **78** as a white solid (529 mg, 60%): R_f = 0.25 (40% ethyl acetate−hexanes; UV, PAA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (s, 1H), 5.61−5.51 (m, 1H), 5.02−4.91 (m, 2H), 3.87 (s, 3H), 2.79 (t, 1H, J = 5.6 Hz), 2.47 (dd, 2H, J = 6.8, 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2 (C), 197.4 (C), 172.2 (C), 132.2 (CH), 118.7 (CH_2), 118.6 (CH), 58.9 (CH_3), 50.6 (CH), 30.2 (CH_2); IR (ATR-FTIR), cm^{-1} 1760 (m), 1696 (s), 1600 (s), 1222 (m); HRMS-EI (m/z) [M]$^+$ calcd for $C_9H_{10}O_3$ 166.0630, found 166.0629.

Synthesis of the Alkyne 80. A solution of the allylation product **78** [190 mg, 1.14 mmol, 1 equiv; dried by azeotropic distillation with benzene (5.0 mL)] in tetrahydrofuran (11 mL) was added dropwise via cannula to a solution of lithium *tert*-butoxide (100 mg, 1.25 mmol, 1.10 equiv) in tetrahydrofuran (5.0 mL) at 24 °C. Upon completion of the addition, the reaction mixture was stirred for 15 min at 24 °C. A solution of the iodonium salt **79** (518 mg, 1.37 mmol, 1.20 equiv) in tetrahydrofuran (4.0 mL) was then added slowly via cannula to the reaction mixture. Upon completion of the addition, the reaction mixture was stirred for 10 min at 24 °C. The product mixture was concentrated to dryness, and the residue obtained was purified by flash column chromatography (eluting with 40% ethyl acetate−hexanes) to afford the alkyne **80** as a clear oil (122 mg, 56%): R_f = 0.30 (40% ethyl acetate−hexanes; UV, PAA); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.28 (s, 1H), 5.62−5.53 (m, 1H), 5.10−5.06 (m, 2H), 3.96 (s, 3H), 2.66 (d, 2H, J = 7.0 Hz), 2.33 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4 (C), 193.5 (C), 171.3(C), 130.0 (CH), 121.0 (CH_2), 117.4 (CH), 77.5 (C), 73.9 (CH), 59.4 (CH_3), 51.0 (C), 38.8 (CH_2); IR (ATR-FTIR), cm^{-1} 1700 (s), 1601 (s), 1340 (m), 1204 (m); HRMS-EI (m/z) [M]$^+$ calcd for $C_{11}H_{10}O_3$, 190.0630, found 190.0632.



82 (1:1 mixture of C-11 diastereomers)

Synthesis of the Acetylide Addition Product 82. Methyl trifluoromethanesulfonate (46.0 μL, 407 μmol, 1 equiv) was added to a solution of the imine **39** [135 mg, 407 μmol, 1 equiv; dried by azeotropic distillation with benzene (5 mL)] in tetrahydrofuran (6.0 mL) at −78 °C. The reaction vessel was placed in a −30 °C bath, and the mixture was stirred for 30 min at −30 °C. The mixture was then cooled to −90 °C, and the cooled solution was diluted with tetrahydrofuran (6.0 mL). A solution of the alkyne **80** (85 mg, 447 μmol, 1.10 equiv) in tetrahydrofuran (5.0 mL) was then added. In a separate flask, a solution of *n*-butyllithium in hexanes (2.30 M, 230 μL, 529 μmol, 1.30 equiv) was added to a solution of 2,4,6-tri-*tert*-butylbromobenzene (**81**, 172 mg, 529 μmol, 1.30 equiv) in tetrahydrofuran (5 mL) at −78 °C. The resulting mixture was stirred for 15 min at −78 °C. The cold solution of the lithiated arene was then added dropwise via cannula to the solution of the alkyne **80** and the iminium ion at −90 °C. The reaction mixture was stirred for 30 min at −90 °C. The product mixture was allowed to warm over 15 min to 24 °C. The warmed product mixture was concentrated to dryness. The residue obtained was purified by flash column chromatography (eluting with 40% acetone−hexanes) to afford the addition product **82** as a clear oil (45.0 mg, 21%, 1:1 mixture of C-11 diastereomers): R_f = 0.40 (40% acetone−hexanes; UV, PAA); ^{1}H NMR (500 MHz, $CDCl_3$, overlapping mixture of C-11 diastereomers) δ 6.30 (s, 1H, H_3), 6.10−6.07 (m, 1H, H_{18}), 5.81−5.79 (m, 1H, H_{17}), 5.76−5.71 (m, 1H, H_{22}), 5.18−5.12 (m, 2H, H_{23}), 4.00 (s, 3H, C_8-OCH_3), 3.92 (s, 3H, C_2-OCH_3), 3.56 (s, 3H, C_7-OCH_3), 3.31 (br s, 1H, H_{16}), 2.95 (br s, 1H, H_{19}), 2.88 (d, 1H, J = 4.0 Hz, H_5), 2.79−2.76 (m, 1H, H_{15}), 2.73 (app d, 2H, J = 7.5 Hz, H_{21}), 2.38 (q, 1H, J = 9.0 Hz, H_{15}), 2.16 (br s, 3H, NCH_3), 2.09−2.05 (m, 1H, H_{14}), 2.00−1.96 (m, 1H, H_{14}), 1.12 (s, 1H, H_{20}), −0.08 (s, 9H, TMS); ^{13}C NMR (125 MHz, $CDCl_3$, overlapping mixture of C-11 diastereomers) δ 195.2 (C), 194.9 (C), 194.1 (C), 171.1 (C), 163.1 (C), 139.4 (C), 135.8 (CH), 135.7 (CH), 130.7 (CH), 120.6 (CH_2), 117.0 (CH), 83.4 (C), 80.0 (C), 70.5 (C), 66.1 (CH), 61.5 (CH_3), 59.7 (CH_3), 59.4 (CH_3), 58.8 (CH), 54.8 (C), 54.1 (CH), 51.6 (C), 50.5 (CH_2), 49.4 (CH), 41.6 (CH_2), 39.0 (CH_2), 36.6 (CH_3), −0.1 (TMS); IR (ATR-FTIR), cm^{-1} 2947 (w), 1701 (m), 1656 (m), 1602 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{30}H_{38}NO_6Si$ 536.2468, found 536.2450; $[\alpha]^{20}_D$ +138 (c 1.0, $CHCl_3$).

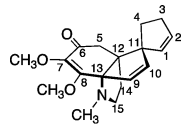
Synthesis of the Vinyl Triflate 85. Methyllithium (1.10 M, 3.55 mL, 3.90 mmol, 1.30 equiv) was added to a solution of hexamethyldisilane (1.84 mL, 9.00 mmol, 3.00 equiv) in hexamethylphosphoramide (4.0 mL) at 0 °C, and the resulting red solution was stirred for 30 min at 0 °C. The mixture was then cooled to −78 °C, and the cooled solution was diluted with tetrahydrofuran (20 mL). Cyclopent-2-ene-1-one (**83**, 251 μL, 3.00 mmol, 1 equiv) was added, and the resulting solution was stirred for 20 min at −78 °C. Chlorotrimethylsilane (457 μL, 3.60 mmol, 1.20 equiv) was then added dropwise via syringe, and stirring was continued for an additional 30 min at −78 °C. The product mixture was allowed to warm over 15 min to 24 °C. The warmed product mixture was diluted with hexanes (200 mL) and the diluted solution was transferred to a separatory funnel. The organic layer was washed with distilled water (4 × 200 mL). The washed organic layer was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated to provide an enoxysilane as a clear oil (520 mg). The product obtained in the preceding step was dissolved in tetrahydrofuran (10 mL) and cooled to 0 °C. Methyllithium (1.10 M, 1.98 mL, 2.18 mmol, 1.20 equiv based on the mass of the unpurified enoxysilane obtained in the preceding step) was added and the mixture was stirred for 30 min at 0 °C. A solution of Comins' reagent (857 mg, 2.18 mmol, 1.20 equiv) in tetrahydrofuran (5.0 mL) was then added slowly via cannula to the cold solution. Upon completion of the addition, the reaction mixture was stirred for 1 h at 0 °C. The product mixture was allowed to warm over 15 min to 24 °C. The warmed product mixture was concentrated

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

to dryness and the residue obtained was purified by flash column chromatography (eluting with 100% hexanes) to afford the vinyl triflate **85** as a clear oil [280 mg, 40% (two steps)]: R_f = 0.30 (100% hexanes; $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.60 (br s, 1H), 2.61−2.51 (m, 2H), 2.28−2.12 (m, 1H), 2.11−2.08 (m, 1H), 1.97−1.90 (m, 1H), 0.09 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8 (C), 120.9 (CH), 31.5 (CH_2), 28.9 (CH), 23.8 (CH_2), −1.8 (TMS), −5.7 (CH_3), −6.0 (CH_3), CF_3 not observed; IR (ATR-FTIR), cm^{-1} 2945 (w), 1410 (s), 1251 (m), 1202(s), 1146 (s). Anal. Calcd for $C_{11}H_{21}F_3O_3SSi_2$: C, 38.13; H, 6.11. Found: C, 38.37; H, 5.97.

Synthesis of the Enyne 86. A 25-mL round-bottomed flask that had been fused to a Teflon-coated valve was charged sequentially with a solution of the terminal alkyne **61** (40.0 mg, 172 μmol, 1 equiv) in benzene (2.0 mL) and a solution of the vinyl triflate **85** (89.3 mg, 258 μmol, 1.50 equiv) in benzene (3.0 mL). The resulting solution was concentrated to dryness. Tetrakis(triphenylphosphine)palladium (39.7 mg, 34.4 μmol, 0.20 equiv) and cuprous iodide (6.54 mg, 34.4 μmol, 0.20 equiv) were then added in sequence. The dry mixture was dissolved in tetrahydrofuran (3.0 mL). Triethylamine (3.0 mL) was added, and the resulting solution was deoxygenated by three freeze−pump−thaw cycles. The vessel was then sealed under vacuum, and the deoxygenated solution was stirred and heated for 50 min at 50 °C. The product mixture was allowed to cool over 10 min to 24 °C. The cooled product mixture was diluted with dichloromethane (100 mL) and the diluted solution was transferred to a separatory funnel. Aqueous ammonium hydroxide solution (3%, 100 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 100 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (eluting with 30% acetone−hexanes) to afford the enyne **86** as a clear oil (60.0 mg, 81%): R_f = 0.70 (50% acetone−hexanes; UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (br s, 1H), 5.96 (br s, 1H), 4.13 (s, 3H), 3.73 (s, 3H), 3.20 (td, 1H, J = 9.0, 2.5 Hz), 2.88−2.82 (m, 1H), 2.76−2.73 (m, 1H), 2.61−2.55 (m, 4H), 2.48−2.40 (m, 2H), 2.16−2.10 (m, 2H), 1.87−1.82 (m, 1H), 0.07 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.3 (C), 159.7 (C), 159.4 (C), 142.4 (CH), 137.9 (C), 120.8 (CH), 120.1 (C), 84.7 (C), 81.4 (C), 63.4 (C), 61.4 (CH_3), 60.7 (CH_3), 54.0 (CH_2), 38.6 (CH_3), 37.0 (CH_2), 35.5 (CH), 27.3 (CH_2), 26.3 (CH_2), −1.6 (3 × CH_3), −5.1 (CH_3), −5.5 (CH_3); IR (ATR-FTIR), cm^{-1} 2948 (w), 1692 (m), 1660 (s), 1602 (s), 1203 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{23}H_{36}NO_3Si_2$, 430.2234, found 430.2219; $[\alpha]^{20}_D$ −90 (c 1.0, $CHCl_3$).

Synthesis of the 1,3-Diene 87. Trifluoroacetic acid (12.8 μL, 168 μmol, 1.20 equiv) was added to a solution of the enyne **86** (60.0 mg, 140 μmol, 1 equiv) in benzene (3.0 mL) at 24 °C. The resulting solution was concentrated to dryness. The residue obtained was dissolved in dichloromethane (3.0 mL), and the flask was purged with dihydrogen by three evacuation-refill cycles. The resulting solution was maintained under an atmosphere of dihydrogen (balloon). A solution of Crabtree's catalyst (113 mg, 140 μmol, 1.00 equiv) in dichloromethane (1.0 mL) was added dropwise via syringe pump over 1 h at 24 °C. Upon completion of the addition, the product mixture was diluted with dichloromethane (50 mL), and the diluted solution was transferred to a separatory funnel. The organic layer was washed with saturated aqueous sodium bicarbonate solution (50 mL). The aqueous layer was extracted with dichloromethane (3 × 50 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 40% acetone−hexanes) to afford the 1,3-diene **87** as a clear oil (33.0 mg, 55%). **87**, less polar diastereomer: R_f = 0.50 (40% acetone−hexanes; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11−6.06 (m, 2H), 5.43−5.40 (m, 2H), 4.10 (s, 3H), 3.71 (s, 3H), 3.23−3.16 (m, 1H), 2.92−2.86 (m, 1H), 2.71−2.55 (m, 2H), 2.34−2.31 (m, 2H), 2.27 (s, 3H), 2.09−2.03 (m, 2H), 1.79−1.73 (m, 1H), 0.05 (s, 9H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8 (C), 161.2 (C), 159.7 (C), 138.4 (C), 136.1 (C), 134.5 (CH), 131.3 (CH), 127.2 (CH), 122.8 (CH), 70.9 (C), 60.8 (2 × CH_3), 51.9 (CH_2), 38.3 (CH_3), 37.1 (CH_2), 34.6 (CH), 28.1 (CH_2), 26.4 (CH_2), −1.6 (3 × CH_3), −5.2 (CH_3), −5.6 (CH_3); IR (ATR-FTIR), cm^{-1} 2950 (w), 1686 (m), 1640 (m), 1602 (m); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{23}H_{38}NO_3Si_2$, 432.2390, found 432.2407; $[\alpha]^{20}_D$ +102 (c 0.5, $CHCl_3$). **87**, more polar diastereomer: R_f = 0.48 (40% acetone−hexanes; UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14−6.13 (m, 1H), 6.06 (d, 1H, J = 12.0 Hz), 5.54 (d, 1H, J = 12.0 Hz), 5.39 (m, 1H), 4.12 (s, 3H), 3.72 (s, 3H), 3.21−3.15 (m, 1H), 2.83−2.78 (m, 1H), 2.56−2.53 (m, 2H), 2.27−2.25 (m, 2H), 2.23 (s, 3H), 2.07−2.02 (m, 2H), 1.79−1.74 (m, 1H), 0.04 (s, 9H), −0.04 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.9 (C), 161.4 (C), 158.9 (C), 137.8 (C), 135.1 (C), 134.5 (CH), 131.4 (CH), 128.6 (CH), 123.8 (CH), 71.0 (C), 60.9 (CH_3), 60.6 (CH_3), 51.5 (CH_2), 38.4 (CH_3), 36.8 (CH_2), 34.4 (CH), 27.8 (CH_2), 26.5 (CH_2), −1.6 (3 × CH_3), −5.2 (CH_3), −5.6 (CH_3); IR (ATR-FTIR), cm^{-1} 2940 (w), 1687 (m), 1648 (s), 1602 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{23}H_{38}NO_3Si_2$, 432.2390, found 432.2408; $[\alpha]^{20}_D$ −30 (c 0.5, $CHCl_3$).



88

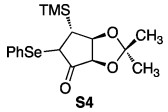
Synthesis of the Tetracycle 88. Boron trifluoride diethyl etherate complex (5.88 μL, 46.4 μmol, 2.00 equiv) was added to a solution of the less polar diastereomer of the 1,3-diene **87** (10.0 mg, 23.2 μmol, 1 equiv) in dichloromethane (2.0 mL) at −78 °C. The resulting solution was stirred for 30 min at −78 °C. The cooling bath was removed, and the reaction mixture was allowed to warm over 10 min to 24 °C. The reaction mixture was stirred for an additional 30 min at 24 °C. The product mixture was diluted with dichloromethane (25 mL), and the diluted solution was transferred to a separatory funnel. The organic layer was washed with saturated aqueous sodium bicarbonate solution (25 mL). The aqueous layer was extracted with dichloromethane (3 × 25 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 60% acetone−hexanes) to afford the tetracycle **88** as a clear oil (3.0 mg, 43%). The relative stereochemistry of the tetracycle **88** was determined by 1D-NOE analysis ($CDCl_3$, 500 MHz): 1 × H_{14} → H_1 3.6%; R_f = 0.20 (40% acetone−hexanes; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (d, 1H, J = 7.5 Hz, H_{10}), 5.93−5.91 (m, 1H, H_1), 5.90 (d, 1H, J = 7.5 Hz, H_9), 5.70−5.68 (m, 1H, H_2), 4.10 (s, 3H, C_8-OCH_3), 3.67 (s, 3H, C_7-OCH_3), 3.11−3.04 (m, 1H, H_{15}), 2.65−2.62 (m, 1H, H_{15}), 2.56 (s, 3H, NCH_3), 2.49−2.44 (m, 2H, H_5), 2.31−2.25 (m, 2H, H_3), 2.07−2.03 (m, 1H, H_{14}), 1.91−1.84 (m, 1 H, H_4), 1.61−1.43 (m, 2H, 1 × H_{14}, 1 × H_4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0 (C), 163.7 (C, detected by HMBC), 142.4 (CH), 136.6 (C), 134.1 (CH), 133.9 (CH), 127.9 (CH), 79.6 (C), 67.8 (C), 60.7 (CH_3), 60.5 (CH_3), 56.6 (C), 54.8 (CH_2), 42.7 (CH_2), 38.6 (CH_3), 35.4 (CH_2), 33.1 (CH_2), 32.0 (CH_2); IR (ATR-FTIR), cm^{-1} 2920 (w), 1678 (s), 1601 (s), 1085 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{18}H_{24}NO_3$, 302.1756, found 302.1750; $[\alpha]^{20}_D$ +110 (c 0.2, $CHCl_3$).

Synthesis of the 1,3-Diene 94. Trifluoroacetic acid (114 μL, 1.49 mmol, 1.20 equiv) was added to a solution of the retrocycloaddition product **108** (550 mg, 1.24 mmol, 1 equiv) in benzene (6.0 mL) at 24 °C. The resulting solution was concentrated to dryness. The residue obtained was dissolved in dichloromethane (25 mL) and the flask was purged with dihydrogen by three evacuation−refill cycles. The resulting solution was maintained under an atmosphere of dihydrogen (balloon). A solution of Crabtree's catalyst (1.00 g, 1.24 mmol, 1.00 equiv) in dichloromethane (10 mL) was added dropwise via syringe pump over 1 h at 24 °C. Upon completion of the addition, the product mixture was diluted with dichloromethane (200 mL), and the diluted solution was transferred to a separatory funnel. The organic layer was washed with saturated aqueous sodium bicarbonate solution (200

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

mL). The aqueous layer was extracted with dichloromethane (3 × 200 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (eluting with 60% ethyl acetate–hexanes) to afford the 1,3-diene **94** as a clear oil (472 mg, 86%): R_f = 0.20 (60% ethyl acetate–hexanes; UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08 (s, 1H), 6.03 (d, 1H, J = 13.0 Hz), 5.75 (br s, 1H), 5.34 (d, 1H, J = 13.0 Hz), 4.97 (d, 1H, J = 5.5 Hz), 4.48 (d, 1H, J = 5.5 Hz), 4.06 (s, 3H), 3.67 (s, 3H), 3.20–3.14 (m, 1H), 2.72–2.69 (m, 1H), 2.51–2.47 (m, 2H), 2.17 (s, 3H), 2.13 (br s, 1H), 1.33 (s, 3H), 1.31 (s, 3H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.4 (C), 160.0 (C), 159.8 (C), 138.3 (C), 135.5 (CH), 134.1 (C), 129.5 (CH), 127.1 (CH), 123.4 (CH), 109.1 (C), 87.8 (CH), 80.4 (CH), 72.1 (C), 60.9 (2 × CH_3), 51.4 (CH_2), 42.8 (CH), 38.7 (CH_3), 27.8 (CH_2), 27.6 (CH_3), 26.0 (CH_3), −2.8 (TMS); IR (ATR-FTIR), cm^{-1} 2949 (w), 1680 (m), 1625 (s), 1602 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{24}H_{36}NO_5Si$, 446.2363, found 446.2371; $[\alpha]^{20}_D$ +125 (c 5.0, $CHCl_3$).

Synthesis of the Tetracycle 95. A solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 1.11 mL, 1.11 mmol, 1.05 equiv) was added dropwise via syringe to a solution of the allylic silane **94** [472 mg, 1.06 mmol, 1 equiv; dried by azeotropic distillation with benzene (10 mL)] in *N*,*N*-dimethylformamide (21 mL) at −10 °C. The resulting brown mixture was stirred for 20 min at −10 °C. The cold product mixture was diluted with dichloromethane (300 mL), and the diluted solution was transferred to a separatory funnel. Distilled water (300 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 300 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 60% acetone–hexanes) to afford the tetracycle **95** as a yellow oil (126 mg, 32%). The relative stereochemistry of the tetracycle **95** was assigned by analogy to the cyclization product **110**:[23] R_f = 0.25 (60% acetone–hexanes; UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (d, 1H, J = 5.6 Hz), 6.01 (d, 1H, J = 5.6 Hz), 5.80 (dd, 1H, J = 6.0, 2.0 Hz), 5.41 (d, 1H, J = 6.0 Hz), 5.08 (d, 1H, J = 6.0 Hz), 4.56 (d, 1H, J = 6.4 Hz), 4.09 (s, 3H), 3.66 (s, 3H), 3.20–3.15 (m, 1H), 2.59–2.53 (m, 5H), 2.25 (d, 1H, J = 17.2 Hz), 2.18–2.11 (m, 1H), 1.72–1.66 (m, 1H), 1.45 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7 (C), 163.0 (C), 138.7 (CH), 137.7 (CH), 137.1 (C), 131.1 (CH), 128.5 (CH), 111.5 (C), 83.9 (CH), 82.2 (CH), 79.9 (C), 71.4(C), 60.8 (CH_3), 60.4 (CH_3), 55.9 (C), 54.4 (CH_2), 43.6 (CH_2), 38.5 (CH_3), 36.8 (CH_2), 27.0 (CH_3), 25.2 (CH_3); IR (ATR-FTIR), cm^{-1} 2920 (s), 1710 (s), 1675 (s), 1600 (s), 1282 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{21}H_{28}NO_S$, 374.1967, found 374.1969; $[\alpha]^{20}_D$ +127 (c 1.0, $CHCl_3$).

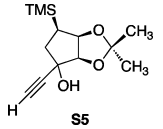


S4

Synthesis of the α-Phenylselenyl Ketone S4. A 100-mL round-bottomed flask was charged sequentially with the enone **89** (600 mg, 3.90 mmol, 1 equiv), palladium acetate (87.8 mg, 390 μmol, 0.10 equiv), and toluene (13 mL). The resulting mixture was cooled to 0 °C. Hexamethyldisilane (956 μL, 4.10 mmol, 1.20 equiv) and trimethylsilyl trifluoromethanesulfonate (70.4 μL, 390 μmol, 0.10 equiv) were then added sequentially to the cooled solution. Upon completion of the addition, the reaction mixture was stirred for 20 min at 0 °C. Phenylselenyl chloride (786 mg, 4.10 mmol, 1.05 equiv) was then added in one portion, and the resulting mixture was stirred for 5 min at 0 °C. The cooling bath was removed, and the reaction mixture was allowed to warm over 10 min to 24 °C. The reaction mixture was stirred for 1 h at 24 °C. The product mixture was diluted with ethyl acetate (150 mL), and the diluted solution was transferred to a separatory funnel. Saturated aqueous sodium bicarbonate solution (150 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 150 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (eluting with 5% acetone–hexanes) to afford the α-phenylselenyl ketone **S4** as a clear oil (1.11 g, 74%). The relative stereochemistry of the trimethylsilyl group of **S4** was assigned by analogy to the β-trimethylsilyl ketone **90**.[23] The relative stereochemistry of the phenylselenyl substituent of **S4** was not rigorously established: R_f = 0.30 (5% acetone–hexanes; UV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.65 (m, 2H), 7.31–7.29 (m, 3H), 4.77 (d, 1H, J = 5.2 Hz), 4.18 (dd, 1H, J = 5.2, 0.8 Hz), 3.54 (t, 1H, J = 2.0 Hz), 1.92 (d, 1H, J = 2.0 Hz), 1.64 (s, 3H), 1.36 (s, 3H), 0.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.2 (C), 134.7 (2 × CH), 131.4 (C), 129.3 (2 × CH), 128.4 (CH), 112.6 (C), 78.7 (2 × CH), 43.2 (CH), 34.5 (CH), 26.8 (CH_3), 25.1 (CH_3), −3.0 (TMS); IR (ATR-FTIR), cm^{-1} 1742 (m), 1265 (m), 1075 (m), 832 (s); HRMS-CI (m/z) [M + Na]$^+$ calcd for $C_{17}H_{24}O_3SeSiNa$ 407.0558, found 407.0560; $[\alpha]^{20}_D$ −175 (c 1.0, $CHCl_3$).

Synthesis of the β-(Trimethylsilyl)-α,β-unsaturated Ketone 96. Sodium bicarbonate (146 mg, 1.74 mmol, 1.60 equiv) and sodium periodate (351 mg, 1.64 mmol, 1.50 equiv) were added in sequence to a solution of the α-phenylselenyl ketone **S4** (420 mg, 1.09 mmol, 1 equiv) in methanol and water (1:1 v/v, 8.0 mL) at 24 °C. The resulting mixture was stirred for 5 h at 24 °C. The product mixture was diluted with ethyl acetate (100 mL), and the diluted solution was transferred to a separatory funnel. Distilled water (100 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (eluting with 15% ethyl acetate–hexanes) to afford the β-(trimethylsilyl)-α,β-unsaturated ketone **96** as a clear oil (183 mg, 74%): R_f = 0.30 (10% ethyl acetate–hexanes; UV, $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.28 (s, 1H), 5.29 (d, 1H, J = 5.5 Hz), 4.38 (d, 1H, J = 5.5 Hz), 1.40 (s, 3H), 1.34 (s, 3H), 0.26 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.7 (C), 180.7 (C), 140.7 (CH), 115.2 (C), 82.3 (CH), 76.8 (CH), 27.8 (CH_3), 26.6 (CH_3), −1.9 (TMS); IR (ATR-FTIR), cm^{-1} 1722 (s), 1265 (m), 1070 (m), 840 (s); HRMS-CI (m/z) [M + Na]$^+$ calcd for $C_{11}H_{18}O_3SiNa$ 249.0923, found 249.0943; $[\alpha]^{20}_D$ +24 (c 1.0, $CHCl_3$).

Synthesis of the *endo*-Silane 97. Palladium hydroxide (10 wt % loading, 250 mg, 236 μmol, 0.10 equiv) was added to a solution of the β-(trimethylsilyl)-α,β-unsaturated ketone **96** (517 mg, 2.29 mmol, 1 equiv) in methanol (30 mL) at 24 °C. The reaction vessel was evacuated and refilled using a balloon of dihydrogen. This process was repeated four times. The reaction mixture was stirred for 50 min at 24 °C under a balloon of dihydrogen. The product mixture was diluted with methanol (20 mL), and the diluted solution was filtered through a pad of Celite. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (eluting with 10% ethyl acetate–hexanes) to afford the *endo*-silane **97** as a white solid (313 mg, 60%). The relative stereochemistry of the trimethylsilyl substituent of **97** was assigned by analogy to the enyne **98** (vide infra). R_f = 0.20 (10% ethyl acetate–hexanes; $KMnO_4$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (app t, 1H, J = 4.4 Hz), 4.11 (td, 1H, J = 5.2, 1.2 Hz), 2.40 (ddd, 1H, J = 19.2, 13.2, 0.8 Hz), 2.21 (ddd, 1H, J = 19.2, 8.8, 0.8 Hz), 1.40–1.34 (m, 4H), 1.31 (s, 3H), −0.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6 (C), 112.0 (C), 80.2 (CH), 79.6 (CH), 34.8 (CH_2), 26.8 (CH_3), 24.9 (CH_3), 24.0 (CH), −2.0 (TMS); IR (ATR-FTIR), cm^{-1} 2953 (w), 1747 (s), 1250 (m), 1110 (m), 835 (s); HRMS-CI (m/z) [M + Na]$^+$ calcd for $C_{11}H_{20}O_3SiNa$ 251.1079, found 251.1089; $[\alpha]^{20}_D$ −288 (c 1.0, $CHCl_3$).

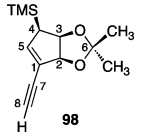


S5

Synthesis of the Propargylic Alcohol S5. A solution of ethynylmagnesium bromide in tetrahydrofuran (0.5 M, 4.11 mL,

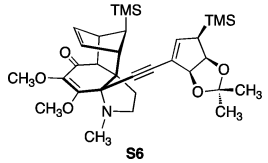
dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031–10057

2.06 mmol, 1.50 equiv) was added dropwise via syringe to a solution of the *endo*-silane **97** [313 mg, 1.37 mmol, 1 equiv; dried by azeotropic distillation with benzene (6 mL)] in tetrahydrofuran (7.0 mL) at −78 °C. The resulting solution was stirred for 30 min at −78 °C. The cooling bath was removed, and the reaction mixture was stirred for an additional 30 min at 24 °C. The product mixture was diluted with ethyl acetate (100 mL), and the diluted product mixture was transferred to a separatory funnel. Distilled water (100 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated to provide the propargylic alcohol **S5** as a white solid (335 mg, 96%). The propargylic alcohol **S5** prepared in this way was determined to be of >95% purity (^{1}H NMR analysis) and was used in the subsequent step without purification. The relative stereochemistry of the trimethylsilyl substituent of **S5** was assigned by analogy to the enyne **98** (vide infra). The relative stereochemistry of the alkyne substituent of **S5** was not rigorously established: R_f = 0.35 (25% ether−hexanes; $KMnO_4$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (app t, 1H, J = 4.8 Hz), 4.34 (dd, 1H, J = 5.6, 0.8 Hz), 3.00 (s, 1H), 2.47 (s, 1H), 2.01 (dd, 1H, J = 12.0, 5.6 Hz), 1.76 (dd, 1H, J = 14.4, 12.4 Hz), 1.43 (s, 3H), 1.30 (s, 3H), 1.22−1.16 (m, 1H), 0.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.8 (C), 85.8 (CH), 84.3 (CH), 83.0 (C), 75.8 (C), 73.3 (CH), 39.6 (CH_2), 28.9 (CH), 25.9 (CH_3), 24.4 (CH_3), −1.4 (TMS); IR (ATR-FTIR), cm^{-1} 2932 (w), 1390 (m), 1245 (m), 1080 (m), 835 (s); HRMS-ES (m/z) [M + Na]$^+$ calcd for $C_{13}H_{22}O_3SiNa$ 277.1236, found 277.1236; $[\alpha]^{20}_D$ +60 (c 1.0, $CHCl_3$).



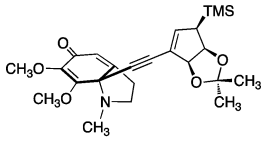
98

Synthesis of the Enyne 98. Pyridine (2.12 mL, 26.4 mmol, 20.0 equiv) and a solution of trifluoromethanesulfonic anhydride in dichloromethane (1 M, 1.98 mL, 1.98 mmol, 1.50 equiv) were added sequentially to a solution of the propargylic alcohol **S5** (335 mg, 1.32 mmol, 1 equiv) in dichloromethane (5.0 mL) at 0 °C. The resulting mixture was stirred for 2 h at 0 °C. The product mixture was diluted with dichloromethane (100 mL), and the diluted solution was transferred to a separatory funnel. Saturated aqueous sodium bicarbonate solution (100 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 100 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 10% ether−hexanes) to afford the enyne **98** as a white solid (153 mg, 49%). The relative stereochemistry of the C-4 trimethylsilyl group of **98** was determined by analysis of vicinal coupling constants (J_{H3-H4} = 6.0 Hz): R_f = 0.80 (20% ether−hexanes; UV, PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (br s, 1H, H_5), 5.09 (d, 1H, J = 6.0 Hz, H_2), 4.82 (app t, 1H, J = 6.0 Hz, H_3), 3.02 (s, 1H, H_8), 2.20−2.19 (m, 1H, H_4), 1.42 (s, 3H, C_6−CH_3), 1.31 (s, 3H, C_6−CH_3), 0.01 (s, 9H, TMS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2 (CH), 122.6 (C), 109.9 (C), 87.5 (CH), 80.6 (CH), 79.5 (C), 79.2 (CH), 41.5 (CH), 27.0 (CH_3), 25.2 (CH_3), −1.2 (TMS); IR (ATR-FTIR), cm^{-1} 3283 (w), 2975 (w), 1250 (m), 835 (s); HRMS-CI (m/z) [M + Na]$^+$ calcd for $C_{13}H_{20}O_2SiNa$ 259.1127, found 259.1130; $[\alpha]^{20}_D$ −49 (c 1.0, $CHCl_3$).



S6

Synthesis of the Acetylide Addition Product S6. Methyl trifluoromethanesulfonate (121 μL, 1.07 mmol, 0.95 equiv) was added to a solution of the imine **39** [374 mg, 1.13 mmol, 1 equiv; dried by azeotropic distillation with benzene (5 mL)] in tetrahydrofuran (11 mL) at −78 °C. The reaction vessel was placed in a −30 °C bath, and the mixture was stirred for 30 min at −30 °C. The mixture was then cooled to −90 °C, and the cooled solution was diluted with tetrahydrofuran (11 mL). In a separate flask, a solution of *n*-butyllithium in hexanes (2.29 M, 738 μL, 1.69 mmol, 1.50 equiv) was added to a solution of the enyne **98** [400 mg, 1.69 mmol, 1.50 equiv; dried by azeotropic distillation with benzene (5 mL)] in tetrahydrofuran (11 mL) at −78 °C. The resulting mixture was stirred for 15 min at −78 °C. The cold solution of the lithiated alkyne was then added dropwise via cannula to the iminium ion at −90 °C. The reaction mixture was stirred for 30 min at −90 °C. The product mixture was allowed to warm over 15 min to 24 °C. The warmed product mixture was concentrated to dryness and the residue obtained was purified by flash column chromatography (eluting with 20% acetone−hexanes) to afford the alkyne addition product **S6** as a clear oil (340 mg, 52%). The relative stereochemistry of the acetylide addition product **S6** was assigned by analogy to related addition products:[21] R_f = 0.45 (30% acetone−hexanes; UV, PAA). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26−6.25 (m, 1H), 6.01 (br s, 1 H), 5.83−5.81 (m, 1H), 5.12 (d, 1H, J = 5.5 Hz), 4.78 (app t, 1H, J = 5.5 Hz), 4.00 (s, 3H), 3.60 (s, 3H), 3.34 (br s, 1H), 3.15 (br s, 1H), 2.94−2.93 (m, 1H), 2.85−2.81 (m, 1H), 2.52 (app q, 1H, J = 9.0 Hz), 2.26 (s, 3H), 2.17−2.07 (m, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.15 (s, 1H) 0.12 (s, 9H), −0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.5 (C), 163.7 (C), 139.4 (C), 138.9 (CH), 136.4 (CH), 135.3 (CH), 124.3 (C), 109.8 (C), 88.2 (CH), 85.6 (C), 85.4 (C), 80.9 (CH), 71.0 (C), 66.1 (CH), 61.6 (CH_3), 59.7 (CH_3), 58.8 (CH), 55.2 (C), 54.1 (CH), 50.6 (CH_2), 49.6 (CH), 41.8 (CH_2), 41.0 (CH), 36.8 (CH_3), 27.7 (CH_3), 26.3 (CH_3), 0.0 (TMS), −1.2 (TMS); IR (ATR-FTIR), cm^{-1} 2950 (m), 1654 (s), 1612 (s), 1250 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{32}H_{48}NO_5Si_2$, 582.3071, found 582.3064; $[\alpha]^{20}_D$ +180 (c 1.0, $CHCl_3$).



S7

Synthesis of the Cyclohexanedienone S7. The acetylide addition product **S6** (46.0 mg, 79.2 μmol, 1 equiv) was dissolved in toluene (4.0 mL) in a 10-mL round-bottomed flask that had been fused to a Teflon-coated valve. The vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 135 °C. The reaction mixture was stirred and heated for 1 h at 135 °C. The product mixture was allowed to cool over 20 min to 24 °C. The cooled product mixture was concentrated to dryness, and the residue obtained was purified by flash column chromatography (eluting with 30% acetone−hexanes) to afford the cyclohexanedienone **S7** as a clear oil (29.0 mg, 83%): R_f = 0.25 (30% acetone−hexanes; UV, PAA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (br s, 1H), 5.97 (br s, 1H), 5.03 (d, 1H, J = 5.6 Hz), 4.77 (app t, 1H, J = 5.6 Hz), 4.13 (s, 3H), 3.73 (s, 3H), 3.21 (td, 1H, J = 9.2, 2.8 Hz), 2.92−2.77 (m, 2H), 2.62−2.55 (m, 4H), 2.16−2.14 (m, 1H), 1.36 (s, 3H), 1.30 (s, 3H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.3 (C), 159.5 (C), 159.2 (C), 141.6 (CH), 138.1 (C), 123.2 (C), 121.0 (CH), 109.9 (C), 87.8 (CH), 82.9 (C), 82.8 (C), 80.8 (CH), 63.4 (C), 61.6 (CH_3), 60.7 (CH_3), 54.0 (CH_2), 41.3 (CH), 38.6 (CH_3), 27.4 (CH_3), 27.3 (CH_2), 26.0 (CH3), −1.2 (TMS); IR (ATR-FTIR), cm^{-1} 2923 (w), 1652 (s), 1612 (s), 1205 (s), 1090 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{24}H_{34}NO_5Si$ 444.2206, found 444.2197; $[\alpha]^{20}_D$ −54 (c 0.5, $CHCl_3$).

Synthesis of the 1,3-Diene 99. Trifluoroacetic acid (6.01 μL, 78.6 μmol, 1.20 equiv) was added to a solution of the cyclohexanedienone product **S7** (29.0 mg, 65.5 μmol, 1 equiv) in benzene (2.0 mL) at 24 °C. The resulting solution was concentrated to dryness. The residue obtained was dissolved in dichloromethane (1.5 mL), and the flask was purged with dihydrogen by three evacuation−refill cycles. The resulting solution was maintained under an atmosphere of dihydrogen (balloon). A solution of Crabtree's catalyst (52.7 mg, 65.5 μmol, 1.00 equiv) in dichloromethane (1.0 mL) was added dropwise

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

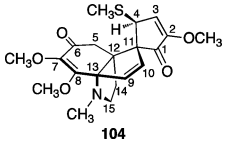
via syringe pump over 1 h at 24 °C. Upon completion of the addition, the product mixture was diluted with dichloromethane (50 mL), and the diluted product mixture was transferred to a separatory funnel. The organic layer was washed with saturated aqueous sodium bicarbonate solution (50 mL). The aqueous layer was extracted with dichloromethane (3 × 50 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 60% ethyl acetate−hexanes) to afford the 1,3-diene **99** as a clear oil (25.0 mg, 86%): R_f = 0.20 (60% ethyl acetate−hexanes; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08−6.05 (m, 2H), 5.58−5.55 (m, 2H), 4.87 (d, 1H, J = 6.0 Hz), 4.73 (app t, 1H, J = 6.0 Hz), 4.11 (s, 3H), 3.69 (s, 3H), 3.20−3.13 (m, 1H), 2.80−2.74 (m, 1H), 2.54−2.50 (m, 2H), 2.20 (s, 3H), 2.03 (br s, 1H), 1.32 (s, 3H), 1.25 (s, 3H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8 (C), 161.1 (C), 159.4 (C), 137.7 (C), 134.4 (C), 134.2 (CH), 130.4 (CH), 128.8 (CH), 123.2 (CH), 109.3 (C), 88.2 (CH), 81.0 (CH), 71.6 (C), 60.8 (CH_3), 60.6 (CH_3), 51.4 (CH_2), 40.6 (CH), 38.4 (CH_3), 27.5 (CH_2), 27.1 (CH_3), 25.3 (CH_3), −1.2 (TMS); IR (ATR-FTIR), cm^{-1} 2949 (w), 1680 (m), 1650 (s), 1602 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{24}H_{36}NO_5Si$, 446.2363, found 446.2365; $[\alpha]^{20}_D$ +260 (c 1.0, $CHCl_3$).

Synthesis of the Tetracycle 95. A solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 142 μL, 142 μmol, 1.05 equiv) was added dropwise via syringe to a solution of the allylic silane **99** [60.0 mg, 135 μmol, 1 equiv; dried by azeotropic distillation with benzene (6.0 mL)] in *N*,*N*-dimethylformamide (2.7 mL) at −10 °C. The resulting brown mixture was stirred for 20 min at −10 °C. The cold product mixture was diluted with dichloromethane (100 mL), and the diluted solution was transferred to a separatory funnel. Distilled water (100 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 100 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 60% acetone−hexanes) to afford the tetracycle **95** as a yellow oil (12.0 mg, 24%). Spectroscopic data for the tetracycle **95** obtained in this way were identical to those obtained by cyclization of the allylic silane **94**.[23]

Synthesis of the Diol 100. A solution of the tetracycle **95** (60.0 mg, 161 μmol, 1 equiv) in methanol (3.2 mL) was added to a 10-mL round-bottomed flask that had been fused to a Teflon-coated valve. Water (145 μL, 8.05 mmol, 50.0 equiv) and *p*-toluenesulfonic acid (61.0 mg, 322 μmol, 2.00 equiv) were then added in sequence. The vessel was sealed, and the sealed vessel was placed in an oil bath that had been preheated to 60 °C. The reaction mixture was stirred and heated for 4 h at 60 °C. The product mixture was allowed to cool over 10 min to 24 °C. The cooled product mixture was diluted with dichloromethane (100 mL), and the diluted solution was transferred to a separatory funnel. Saturated aqueous sodium bicarbonate solution (100 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 100 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 10% methanol−dichloromethane) to afford the diol **100** as a clear oil (38.0 mg, 71%): R_f = 0.20 (10% methanol−dichloromethane; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (d, 1H, J = 6.0 Hz), 5.96 (dd, 1H, J = 6.0, 2.8 Hz), 5.80 (d, 1H, J = 6.0 Hz), 5.76 (d, 1H, J = 6.0 Hz), 4.54 (dd, 1H, J = 6.0, 2.8 Hz), 4.10 (s, 3H), 4.02 (d, 1H, J = 6.0 Hz), 3.68 (s, 3H), 2.97−2.91 (m, 1H), 2.83−2.77 (m, 1H), 2.56 (s, 3H), 2.51−2.42 (m, 3H), 1.59−1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2 (C), 162.1 (C), 140.3 (CH), 138.3 (CH), 137.5 (C), 132.4 (CH), 128.9 (CH), 79.6 (C), 73.9 (CH), 73.6 (CH), 69.3 (C), 60.9 (CH_3), 60.6 (CH_3), 56.4 (C), 54.3 (CH_2), 44.5 (CH_2), 38.0 (CH_3), 32.4 (CH_2); IR (ATR-FTIR), cm^{-1} 1675 (s), 1600 (s), 1455 (s), 1205 (s), 1082 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{18}H_{24}NO_5$, 334.1654, found 334.1683; $[\alpha]^{20}_D$ +100 (c 0.5, $CHCl_3$).

Synthesis of the Enone 101. Trifluoroacetic acid (13.4 μL, 176 μmol, 1.50 equiv) was added to a solution of the diol **100** (39.0 mg, 117 μmol, 1 equiv) in benzene (2.0 mL) at 24 °C. The resulting solution was concentrated to dryness. The residue obtained was dissolved in *N*,*N*-dimethylformamide (6.0 mL), and manganese dioxide (203 mg, 2.34 mmol, 20.0 equiv) was added. The resulting mixture was stirred for 1 h at 24 °C. An additional portion of manganese dioxide (306 mg, 3.52 mmol, 30.0 equiv) was added, and the resulting mixture stirred for an additional 2 h at 24 °C. Sodium bicarbonate (98.3 mg, 1.17 mmol, 10.0 equiv) was added, and the mixture was stirred 5 min at 24 °C. The product mixture was diluted with ethyl acetate (10 mL), and the diluted solution was filtered through a pad of Celite. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 80% acetone−hexanes) to afford the enone **101** as a clear oil (15.4 mg, 40%): R_f = 0.20 (80% acetone−hexanes; UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, 1H, J = 6.4 Hz), 6.30 (d, 1H, J = 6.4 Hz), 6.16 (d, 1H, J = 6.0 Hz), 5.65 (d, 1H, J = 6.0 Hz), 4.15 (s, 3H), 4.08 (s, 1H), 3.72 (s, 3H), 3.16−3.11 (m, 1H), 2.97 (br s, 1H), 2.71−2.46 (m, 7H), 1.68−1.61 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6 (C), 193.5 (C), 163.4 (C), 162.9 (CH), 136.8 (C), 135.8 (CH), 131.8 (CH), 131.0 (CH), 79.5 (C), 75.5 (CH), 68.1 (C), 61.0 (CH_3), 60.6 (CH_3), 55.6 (CH_2), 54.5 (C), 43.7 (CH_2), 38.4 (CH_3), 35.4 (CH_2); IR (ATR-FTIR), cm^{-1} 2920 (w), 1715 (s), 1674 (s), 1600 (s), 1082 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{18}H_{22}NO_5$ 332.1498, found 332.1525; $[\alpha]^{20}_D$ +258 (c 0.4, $CHCl_3$).

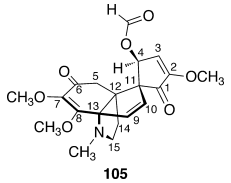
Synthesis of the Methanethiol Addition Product 103. Trifluoroacetic anhydride (38.0 μL, 270 μmol, 6.00 equiv) was added dropwise via syringe to a solution of methyl sulfoxide (26.0 μL, 360 μmol, 8.00 equiv) in dichloromethane (1.8 mL) at −60 °C. The resulting solution was stirred for 10 min at −60 °C. A solution of the diol **100** [15.0 mg, 45.0 μmol, 1 equiv; dried by azeotropic distillation with benzene (2.0 mL)] in dichloromethane (1.0 mL) was then added dropwise via syringe. The transfer was quantified with dichloromethane (2 × 500 μL). The resulting solution was stirred for 1.5 h at −60 °C. Triethylamine (125 μL, 900 μmol, 20.0 equiv) was then added dropwise via syringe, and stirring was continued for an additional 1.5 h at −60 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to 24 °C. The reaction mixture was stirred for 2 h at 24 °C. The product mixture was diluted with dichloromethane (25 mL), and the diluted solution was transferred to a separatory funnel. The organic layer was washed with aqueous potassium phosphate buffer solution (pH 7, 25 mL). The aqueous layer was extracted with ethyl acetate (2 × 25 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by preparative thin-layer chromatography (eluting with 10% methanol−dichloromethane) to afford the thiol addition product **103** as a yellow oil (8.5 mg, 50%). The stereochemistry of the methanethiol substituent was determined by 2D-NOESY analysis of the methyl ether **104** (vide infra): R_f = 0.60 (10% methanol−dichloromethane; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (d, 1H, J = 3.6 Hz), 6.44 (d, 1H, J = 6.0 Hz), 5.95 (d, 1H, J = 6.0 Hz), 4.12 (s, 3H), 3.70 (s, 3H), 3.67 (d, 1H, J = 3.6 Hz), 3.12−3.03 (m, 1H), 2.68−2.59 (m, 3H), 2.56 (s, 3H), 2.51 (d, 1H, J = 18.4 Hz), 1.93 (s, 3H), 1.18−1.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1 (C), 193.4 (C), 163.9 (C), 153.2 (C), 135.9 (C), 135.2 (CH), 134.4 (CH), 127.8 (CH), 80.3 (C), 67.1 (C), 60.8 (CH_3), 60.7 (CH_3), 57.1 (C), 54.5 (CH_2), 48.5 (CH), 41.8 (CH_2), 38.3 (CH_3), 34.2 (CH_2), 15.1 (CH_3); IR (ATR-FTIR), cm^{-1} 1704 (m), 1660 (m), 1602 (m), 1082 (m); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{19}H_{24}NO_5S$ 378.1375, found 378.1379; $[\alpha]^{20}_D$ +193 (c 1.0, $CHCl_3$).



104

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

Synthesis of the Methanethiol Addition Product 104. Trifluoroacetic anhydride (125 μL, 901 μmol, 3.00 equiv) was added dropwise via syringe to a solution of methyl sulfoxide (128 μL, 1.80 mmol, 6.00 equiv) in dichloromethane (6.0 mL) at −60 °C. The resulting solution was stirred for 10 min at −60 °C. A solution of the diol **100** [100 mg, 300 μmol, 1 equiv; dried by azeotropic distillation with benzene (5.0 mL)] in dichloromethane (3.0 mL) was then added dropwise via syringe. The transfer was quantified with dichloromethane (2 × 1.0 mL). The resulting solution was stirred for 1.5 h at −60 °C. *N,N*- Diisopropylethylamine (522 μL, 3.00 mmol, 10.0 equiv) was then added dropwise via syringe, and stirring was continued for an additional 1.5 h at −60 °C. A solution of sodium thiomethoxide (69.4 mg, 990 μmol, 3.30 equiv) in methanol (6.0 mL) was then added to the cold solution via syringe. The resulting mixture was stirred for 5 min at −60 °C and was then placed in an ice bath. The reaction mixture was stirred for 1 h at 0 °C. The product mixture was transferred to a separatory funnel that had been charged with dichloromethane (200 mL) and aqueous potassium phosphate buffer solution (pH 7, 150 mL). The layers that formed were separated, and the organic layer was washed sequentially with aqueous potassium phosphate buffer solution (pH 7, 3 × 150 mL) and saturated aqueous sodium chloride solution (150 mL). The washed organic layer was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was dissolved in tetrahydrofuran (10 mL). A solution of diazomethane in ether (nominally 0.66 M, 13.6 mL, 9.00 mmol, 30.0 equiv) was added dropwise via syringe at 24 °C. The reaction mixture was stirred for 10 min at 24 °C. Excess diazomethane was purged from the reaction vessel by sparging with nitrogen (10 min). The product mixture was concentrated to provide the methyl ether **104** as an orange solid (58.0 mg, 49%). The methyl ether **104** prepared in this way was determined to be of >95% purity (^{1}H NMR analysis) and was used in the subsequent step without purification. The stereochemistry of the methanethiol substituent was determined by 2D-NOESY analysis ($CDCl_3$, 500 MHz): $H_4 \leftrightarrow 1 \times H_5$; R_f = 0.40 (10% methanol−dichloromethane; UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.41 (d, 1H, J = 6.0 Hz, H_{10}), 6.34 (d, 1H, J = 3.5 H, H_3), 5.97 (d, 1H, J = 6.0 Hz, H_9), 4.10 (s, 3H, C_8-OCH_3), 3.76 (s, 3H, C_2-OCH_3), 3.69 (s, 3H, C_7-OCH_3), 3.66 (d, 1H, J = 3.5 Hz, H_4), 3.08−3.03 (m, 1H, H_{15}), 2.65−2.57 (m, 2H, $1 \times H_{15}$, $1 \times H_5$), 2.55− 2.48 (m, 5H, $1 \times H_{14}$, $1 \times H_5$, NCH_3), 1.90 (s, 3H, SCH_3), 1.14−1.09 (m, 1H, H_{14}); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7 (C), 193.6 (C), 164.3 (C), 158.0 (C), 135.8 (C), 135.0 (CH), 134.9 (CH), 124.9 (CH), 80.4 (C), 68.1 (C), 60.8 (CH_3), 60.7 (CH_3), 57.6 (C), 57.0 (CH_3), 54.6 (CH_2), 48.4 (CH), 42.0 (CH_2), 38.4 (CH_3), 34.3 (CH_2), 15.4 (CH_3); IR (ATR-FTIR), cm^{-1} 2940 (w), 1710 (s), 1677 (s), 1602 (s), 1089 (s); HRMS-CI (m/z) $[M + H]^+$ calcd for $C_{20}H_{26}NO_5S$, 392.1532, found 392.1552; $[\alpha]^{20}_D$ +313 (c 1.0, $CHCl_3$).



105

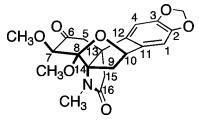
Synthesis of the Formic Acid Addition Product 105. Mercuric acetate (36.7 mg, 115 μmol, 3.00 equiv) was added in one portion to a solution of the methyl ether **104** (15.0 mg, 38.4 μmol, 1 equiv) in formic acid (1.0 mL) at 24 °C. The resulting solution was stirred for 1 h at 24 °C. The product mixture was diluted with dichloromethane (25 mL), and the diluted solution was transferred to a separatory funnel that had been charged with ice-cold saturated aqueous sodium bicarbonate solution (25 mL). The aqueous layer was extracted with dichloromethane (3 × 25 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 5% methanol−dichloromethane) to afford the formic acid addition product **105** as a yellow oil (13.0 mg, 87%). The relative stereochemistry of the formic acid addition product **105** was determined by 1D-NOE analysis ($CDCl_3$, 500 MHz): $H_4 \rightarrow 1 \times H_5$ 1.8%; R_f = 0.30 (5% methanol−dichloromethane; UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H, C_4-OCHO), 6.38 (d, 1H, J = 6.0 Hz, H_9), 6.32 (d, 1H, J = 3.5 Hz, H_3), 5.86 (d, 1H, J = 3.5 Hz, H_4), 5.70 (d, 1H, J = 6.0 Hz, H_{10}), 4.13 (s, 3H, C_8-OCH_3), 3.82 (s, 3H, C_2-OCH_3), 3.72 (s, 3H, C_7-OCH_3), 3.04 (dd, 1H, J = 16.5, 7.0 Hz, H_{15}), 2.71−2.65 (m, 2H, $1 \times H_{15}$, $1 \times H_5$), 2.56−2.51 (m, 5H, $1 \times H_{14}$, $1 \times H_5$, NCH_3), 1.21−1.17 (m, 1H, H_{14}); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4 (C), 191.7 (C), 162.8 (C), 160.7 (C), 158.7 (CH), 135.5 (CH), 135.3 (C), 131.3 (CH), 119.0 (CH), 79.4 (C), 71.3 (C), 65.4 (CH), 59.9 (CH_3), 59.8 (CH_3), 56.9 (CH_3), 55.1 (C), 53.7 (CH_2), 41.0 (CH_2), 37.4 (CH_3), 33.5 (CH_2); IR (ATR-FTIR), cm^{-1} 2930 (w), 1714 (s), 1669 (m), 1628 (m), 1602 (s), 1152 (m); HRMS-CI (m/z) $[M + H]^+$ calcd for $C_{20}H_{24}NO_7$ 390.1553, found 390.1537; $[\alpha]^{20}_D$ +298 (c 0.5, $CHCl_3$).

Synthesis of the Vinylogous α-Diketone 106. *p*-Toluenesulfonic acid (31.7 mg, 167 μmol, 5.00 equiv) was added in one portion to a solution of the formic acid addition product **105** (13.0 mg, 33.4 μmol, 1 equiv) in methanol (3.0 mL) at 24 °C. The resulting solution was stirred for 3 h at 24 °C. The product mixture was diluted with dichloromethane (25 mL), and the diluted solution was transferred to a separatory funnel. The organic layer was washed with saturated aqueous sodium bicarbonate solution (25 mL). The aqueous layer was extracted with dichloromethane (3 × 25 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was used directly in the following step. The Dess−Martin periodinane (28.3 mg, 66.8 μmol, 2.00 equiv) was added in one portion to a solution of the residue obtained in the preceding step in dichloromethane (3.0 mL) at 24 °C. The resulting mixture was stirred for 30 min at 24 °C. A mixture of saturated aqueous sodium thiosulfate solution, saturated aqueous sodium bicarbonate solution, and distilled water (1:1:1, v/v/v, 5 mL) was then added. The resulting mixture was stirred vigorously for 2 h at 24 °C. The biphasic mixture was diluted with dichloromethane (25 mL), and the diluted solution was transferred to a separatory funnel. The layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 25 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate and the dried solution was filtered. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (eluting with 5% methanol−dichloromethane) to provide the vinylogous α-diketone **106** as a yellow oil (5.0 mg, 42%): R_f = 0.25 (5% methanol−dichloromethane; UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (d, 1H, J = 6.0 Hz), 6.37 (s, 1H), 5.56 (d, 1H, J = 6.0 Hz), 4.15 (s, 3H), 3.99 (s, 3H), 3.73 (s, 3H), 3.01−2.96 (m, 1H), 2.72−2.67 (m, 1H), 2.62−2.56 (m, 5H), 2.49 (d, 1H, J = 18.0 Hz), 1.32−1.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6 (C), 195.9 (C), 192.1 (C), 172.9 (C), 163.2 (C), 138.8 (CH), 136.9 (C), 129.4 (CH), 119.2 (CH), 80.6 (C), 70.3 (C), 60.9 (CH_3), 60.4 (CH_3), 59.3 (CH_3), 56.7 (C), 54.3 (CH_2), 43.4 (CH_2), 38.4 (CH_3), 34.9 (CH_2); IR (ATR-FTIR), cm^{-1} 2925 (w), 1699 (s), 1670 (m), 1604 (s), 1210 (m); HRMS-CI (m/z) $[M + H]^+$ calcd for $C_{19}H_{22}NO_6$ 360.1447, found 360.1437; $[\alpha]^{20}_D$ +155 (c 0.2, $CHCl_3$).

Synthesis of Dehydrodechloroacutumine (107). Sodium borohydride (1.6 mg, 43 μmol, 2.0 equiv) was added to a solution of the vinylogous α-diketone **106** (7.8 mg, 22 μmol, 1 equiv) in ethanol (1.0 mL) at 0 °C. The resulting mixture was stirred for 20 min at 0 °C. The product mixture was diluted with ethyl acetate (10 mL), and the diluted solution was transferred to a separatory funnel. Saturated aqueous sodium chloride solution (10 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, and the combined organic layers were dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash column chromatography (eluting with 10% methanol−dichloromethane) to afford dehydrodechloroacutumine (**107**) as a yellow oil (5.0 mg, 64%). The stereochemistry of the newly formed secondary alcohol was

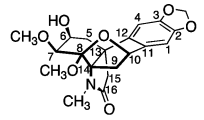
determined by transformation of **107** to (−)-dechloroacutumine (**5**, vide infra): R_f = 0.20 (10% methanol−dichloromethane; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (d, 1H, J = 6.0 Hz), 5.80 (d, 1H, J = 6.0 Hz), 5.26 (s, 1H), 4.74 (s, 1H), 4.13 (s, 3H), 3.91 (s, 3H), 3.75 (s, 3H), 2.97−2.95 (m, 1H), 2.81−2.75 (m, 1H), 2.60 (d, 1H, J = 18.0 Hz), 2.56 (s, 3H), 2.49 (d, 1H, J = 18.0 Hz), 2.36−2.29 (m, 1H), 1.70−1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6 (C), 192.9 (C), 185.6 (C), 162.3 (C, detected by HMBC), 137.9 (C), 134.2 (CH), 133.1 (CH), 104.1 (CH), 79.9 (C), 73.0 (C), 72.6 (CH), 60.7 (CH_3), 60.5 (CH_3), 59.2 (CH_3), 55.6 (C), 53.9 (CH_2), 43.8 (CH_2), 38.2 (CH_3), 37.1 (CH_2); IR (ATR-FTIR), cm^{-1} 3400 (w), 2918 (w), 1675 (m), 1600 (s), 1089 (m); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{19}H_{24}NO_6$ 362.1604, found 362.1611; $[\alpha]^{20}_D$ +35 (c 0.2, $CHCl_3$).

(−)-Dechloroacutumine (5). Palladium on carbon (10 wt % loading, 8.8 mg, 8.3 μmol, 1.0 equiv) was added to a solution of dehydrodechloroacutumine [**107**, 3.0 mg, 8.3 μmol, 1 equiv; dried by azeotropic distillation with benzene (1.0 mL)] in ethyl acetate (1.5 mL) at 24 °C. The reaction vessel was evacuated and refilled using a balloon of dihydrogen. This process was repeated four times. The reaction mixture was stirred for 20 min at 24 °C under a balloon of dihydrogen. The product mixture was diluted with ethyl acetate (5 mL), and the diluted solution was filtered through a pad of Celite. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 10% methanol−dichloromethane) to afford (−)-dechloroacutumine (**5**) as a white solid (1.1 mg, 36%). Spectroscopic data for (−)-dechloroacutumine obtained in this way were identical to those obtained by heterogeneous hydrogenation of dehydroacutumine (**116**).[23]



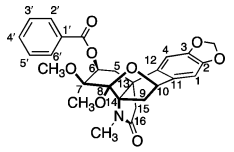
119

Synthesis of the Lactam (119). A solution of potassium permanganate in acetone−water (1:1 v/v; 24.3 mM, 1.30 mL, 2.43 equiv) was added dropwise via syringe to a stirred solution of (+)-periglaucine B (**8**) [5.0 mg, 13.4 μmol, 1 equiv; dried by azeotropoic distillation with benzene (500 μL)] in acetone−water (2:1 v/v, 1.3 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed, and the reaction mixture was allowed to warm to 24 °C. The reaction mixture was stirred for 3 h at 24 °C. The product mixture was diluted with dichloromethane (3.0 mL), and the diluted solution was transferred to a separatory funnel. An aqueous solution of sulfuric acid and sodium bisulfite solution (5% sulfuric acid by volume, 10% sodium bisulfite by weight, 3.0 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 3.0 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 33% acetone−hexanes initially, grading to 50% acetone−hexanes, one step) to afford the lactam **119** as a white solid (3.5 mg, 67%): R_f = 0.48 (50% acetone−hexanes; CAM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (s, 1H, H_4), 6.53 (s, 1H, H_1), 5.95 (d, 1H, J = 1.5 Hz, 1 × OCH_2O), 5.94 (d, 1H, J = 1.5 Hz, 1 × OCH_2O), 4.83 (d, 1H, J = 6.0 Hz, H_{10}), 4.11 (s, 1H, H_7), 3.59 (s, 3H, C_8-OCH_3), 3.50 (s, 3H, C_7-OCH_3), 3.13 (s, 3H, NCH_3), 3.01−2.93 (m, 2H, 1 × H_5, 1 × H_9), 2.67 (d, 1H, J = 16.5 Hz, H_{15}), 2.64−2.58 (m, 2H, 1 × H_5, 1 × H_{15}), 1.64 (d, 1H, J = 11.0 Hz, H_9); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2 (C), 172.8 (C), 148.5 (C), 146.3 (C), 134.0 (C), 130.5 (C), 107.5 (CH), 106.1 (CH), 105.6 (C), 101.5 (CH_2), 88.3 (CH), 75.9 (CH), 73.9 (C), 59.7 (CH_3), 52.5 (CH_3), 49.6 (CH_2), 47.2 (C), 45.2 (CH_2), 33.4 (CH_2), 28.5 (CH_3); IR (ATR-FTIR), cm^{-1} 2924 (w), 1738 (m), 1697 (s), 1486 (s), 1038 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{20}H_{22}NO_7$ 388.13908, found 388.13930; $[\alpha]^{20}_D$ +110 (c 1.0, $CHCl_3$).



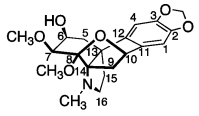
(+)-*N*,*O*-dimethyloxostephine (**14**)

(+)-*N*,*O*-Dimethyloxostephine (14). Sodium borohydride (0.8 mg, 20 μmol, 4 equiv) was added to a solution of the lactam **119** [2.0 mg, 5.2 μmol, 1 equiv; dried by azeotropic distillation with benzene (500 μL)] in ethanol (500 μL) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C. The product mixture was diluted with ethyl acetate (3.0 mL), and the diluted solution was transferred to a separatory funnel. Saturated aqueous sodium chloride solution (3.0 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 3.0 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by preparative thin-layer chromatography (eluting with 5% methanol−ethyl acetate) to afford (+)-*N*,*O*-dimethyloxostephine (**14**) as a white solid (1.5 mg, 75%): R_f = 0.40 (5% methanol−ethyl acetate; UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (s, 1H, H_4), 6.57 (s, 1H, H_1), 5.96 (d, 1H, J = 1.5 Hz, 1 × OCH_2O), 5.95 (d, 1H, J = 1.5 Hz, 1 × OCH_2O), 4.88 (d, 1H, J = 6.0 Hz, H_{10}), 4.14−4.08 (m, 1H, H_6), 3.60 (s, 3H, C_8-OCH_3), 3.46 (s, 3H, C_7-OCH_3), 3.44 (d, 1H, J = 4.0 Hz, H_7), 3.01 (s, 3H, NCH_3), 2.96 (dd, 1H, J = 11.0, 6.5 Hz, $H_{9\beta}$), 2.58 (d, 1H, J = 16.5 Hz, $H_{15\alpha}$), 2.45 (d, 1H, J = 16.0 Hz, $H_{15\beta}$), 2.40 (dd, 1H, J = 15.0, 3.5 Hz, $H_{5\beta}$), 2.34 (d, 1H, J = 10.0 Hz, OH), 1.97 (dd, 1H, J = 14.8, 2.8 Hz, $H_{5\alpha}$), 1.64 (d, 1H, J = 11.0 Hz, $H_{9\alpha}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3 (C), 148.6 (C), 145.9 (C), 134.6 (C), 132.3 (C), 108.0 (CH), 105.8 (CH), 102.2 (C), 101.4 (CH_2), 82.0 (CH), 76.2 (CH), 73.7 (C), 66.1 (CH), 57.0 (CH_3), 52.4 (CH_3), 45.8 (CH_2), 43.6 (C), 41.0 (CH_2), 33.3 (CH_2), 28.2 (CH_3); IR (ATR-FTIR), cm^{-1} 3541 (w), 2920 (w), 2158 (m), 1697 (s), 1486 (m); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{20}H_{24}NO_7$, 390.15473, found 390.15513. Natural: $[\alpha]^{22}_D$ +222 (c 1.02, $CHCl_3$).[26] Synthetic: $[\alpha]^{20}_D$ +127 (c 1.0, $CHCl_3$).



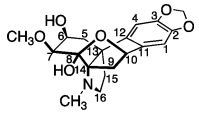
(+)-oxostephabenine (**15**)

(+)-Oxostephabenine (15). Benzoyl chloride (6.0 μL, 52 μmol, 14 equiv) was added to a solution of (+)-*N*,*O*-dimethyloxostephine (**14**) [1.4 mg, 3.6 μmol, 1 equiv; dried by azeotropic distillation with benzene (500 μL)] in pyridine (360 μL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C. The product mixture was allowed to warm over 10 min to 24 °C. The warmed product mixture was concentrated to dryness, and the residue obtained was purified by preparative thin-layer chromatography (eluting with 25% acetone−hexanes) to afford (+)-oxostephabenine (**15**) as a clear, colorless oil (1.2 mg, 66%): R_f = 0.13 (25% acetone−hexanes; UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47−7.41 (m, 3H, H_2', H_4', H_6'), 7.27−7.22 (m, 2H, H_3', H_5'), 6.61 (s, 1H, H_1), 6.47 (s, 1H, H_4), 5.75 (d, 1H, J = 1.5 Hz, 1 × OCH_2O), 5.55−5.51 (m, 1H, H_6), 5.24 (d, 1H, J = 1.5 Hz, 1 × OCH_2O), 4.96 (d, 1H, J = 6.0 Hz, H_{10}), 3.62 (s, 3H, C_8-OCH_3), 3.60 (d, 1H, J = 4.5 Hz, H_7), 3.43 (s, 3H, C_7-OCH_3), 3.05 (s, 3H, NCH_3), 2.96 (dd, 1H, J = 11.0, 6.0 Hz, $H_{9\beta}$), 2.53 (app d, 2H, J = 16.5 Hz, $H_{5\beta}$, $H_{15\alpha}$), 2.44 (d, 1H, J = 16.5 Hz, $H_{15\beta}$), 2.15 (dd, 1H, J = 15.5, 2.5 Hz, $H_{5\alpha}$), 1.69 (d, 1H, J = 10.5 Hz, $H_{9\alpha}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4 (C), 166.1 (C), 148.1 (C), 145.5 (C), 133.5 (C), 132.6 (C, CH), 129.8 (2 × CH), 129.3 (C), 127.6 (2 × CH), 107.0 (CH), 106.4 (CH), 101.4 (C), 100.9 (CH_2), 81.9 (CH), 76.0 (CH), 73.8 (C), 66.4 (CH), 57.9 (CH_3), 52.1 (CH_3), 45.8 (CH_2), 43.6 (C), 36.8 (CH_2), 33.1 (CH_2), 28.3 (CH_3); IR (ATR-FTIR), cm^{-1} 2923 (w), 1705 (s), 1486 (m), 1279 (s), 1098 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{27}H_{28}NO_8$ 494.18094, found 494.18003. Natural: $[\alpha]^{20}_D$ +65 (c 1.04, $CHCl_3$).[26] Synthetic: $[\alpha]^{20}_D$ +44 (c 1.0, $CHCl_3$).



(+)-*N,O*-dimethylstephine (**13**)

(+)-*N,O*-Dimethylstephine (13). Sodium borohydride (2.5 mg, 66 μmol, 2.5 equiv) was added to a solution of (+)-periglaucine B (**8**) [10.0 mg, 26.8 μmol, 1 equiv; dried by azeotropic distillation with benzene (1.0 mL)] in ethanol (2.7 mL) at 0 °C. The reaction mixture was stirred for 15 min at 0 °C. The product mixture was diluted with ethyl acetate (5.0 mL), and the diluted solution was transferred to a separatory funnel. Saturated aqueous sodium chloride solution (5.0 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 5% methanol−ethyl acetate) to afford (+)-*N,O*-dimethylstephine (**13**) as a clear, colorless oil (7.8 mg, 77%). Natural: R_f = 0.54 (10% methanol−chloroform).[24] Synthetic: R_f = 0.59 (10% methanol−chloroform; UV, CAM), 0.35 (5% methanol−ethyl acetate; UV, CAM): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (s, 1H, H_4), 6.52 (s, 1H, H_1), 5.92 (d, 1H, J = 1.5 Hz, 1 × OCH_2O), 5.90 (d, 1H, J = 1.5 Hz, 1 × OCH_2O), 4.82 (d, 1H, J = 6.5 Hz, H_{10}), 4.14−4.09 (m, 1H, H_6), 3.64 (d, 1H, J = 4.0 Hz, H_7), 3.53 (s, 3H, C_8-OCH_3), 3.44 (s, 3H, C_7-OCH_3), 3.40−3.33 (m, 1H, H_{16}), 2.69 (dd, 1H, J = 11.0, 6.5 Hz, $H_{9\beta}$), 2.55−2.50 (m, 1H, H_{16}), 2.53 (s, 3H, NCH_3), 2.29 (dd, 1H, J = 14.5, 3.5 Hz, H_5), 2.23−2.18 (m, 1H, H_5), 2.20 (d, 1H, J = 10.0, OH), 1.97−1.91 (m, 1H, H_{15}), 1.89−1.81 (m, 1H, H_{15}), 1.51 (d, 1H, J = 11.0 Hz, $H_{9\alpha}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0 (C), 145.0 (C), 138.2 (C), 132.5 (C), 108.1 (CH), 105.4 (CH), 104.0 (C), 101.0 (CH_2), 81.9 (CH), 77.0 (CH, detected by HMQC), 75.7 (C), 67.4 (CH), 56.9 (CH_3), 54.0 (CH_2), 51.8 (CH_3), 49.9 (C), 41.0 (CH_2), 38.5 (CH_3), 37.6 (CH_2), 29.5 (CH_2); IR (ATR-FTIR), cm^{-1} 3543 (w), 2937 (m), 1485 (s), 1258 (m), 1037 (s); HRMS-CI (m/z) $[M + H]^+$ calcd for $C_{20}H_{26}NO_6$, 376.17546, found 376.17560. Natural: $[\alpha]^{22}_D$ +122 (c 1.23, $CHCl_3$).[25] Synthetic: $[\alpha]^{20}_D$ +75 (c 1.23, $CHCl_3$).

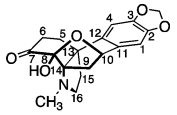


120

Synthesis of the Hemiketal (120). Aqueous hydrochloric acid (0.5 N, 2.0 mL) was added to (+)-*N,O*-dimethylstephine (**13**) [7.8 mg, 21 μmol, 1 equiv; dried by azeotropic distillation with benzene (1.0 mL)] in a 20-mL vial that had been charged with a Teflon-coated stir bar. The vial was sealed with a Teflon-lined cap, and the sealed vial was placed in an oil bath that had been preheated to 75 °C. The reaction mixture was stirred and heated for 4 h at 75 °C. The product mixture was allowed to cool over 10 min to 24 °C. The cooled product mixture was diluted with ethyl acetate (5.0 mL), and the diluted solution was transferred to a separatory funnel. Saturated aqueous sodium bicarbonate solution (5.0 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by preparative thin-layer chromatography (eluting with 10% methanol−ethyl acetate) to afford the hemiketal **120** as a white solid (5.5 mg, 72%). R_f = 0.24 (10% methanol−ethyl acetate; UV, CAM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 1H, H_4), 6.51 (s, 1H, H_1), 5.92 (d, 1H, J = 0.8 Hz, 1 × OCH_2O), 5.90 (d, 1H, J = 0.8 Hz, 1 × OCH_2O), 4.84 (d, 1H, J = 6.0 Hz, H_{10}), 4.19−4.12 (m, 1H, H_6), 4.01 (s, 1H, C_8-OH), 3.60 (d, 1H, J = 3.6 Hz, H_7), 3.47 (s, 3H, C_7-OCH_3), 3.37 (app q, 1H, J = 8.7 Hz, H_{16}), 2.91 (dd, 1H, J = 10.4, 6.4 Hz, H_9), 2.60−2.51 (m, 1H, H_{16}), 2.57 (s, 3H, NCH_3), 2.53 (d, 1H, J = 10.4 Hz, C_6-OH), 2.33 (dd, 1H, J = 14.4, 3.6 Hz, H_5), 2.20 (dd, 1H, J = 14.4, 2.4 Hz, H_5), 2.02−1.85 (m, 2H, H_{15}), 1.57 (d, 1H, J = 10.8 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0 (C), 145.0 (C), 138.1 (C), 132.7 (C), 108.2 (CH), 105.2 (CH), 102.4 (C), 101.0 (CH_2), 79.7 (CH), 76.1 (CH), 73.4 (C), 65.8 (CH), 56.8 (CH_3), 53.9 (CH_2), 49.6 (C), 41.5 (CH_2), 38.0 (CH_3), 37.8 (CH_2), 29.5 (CH_2); IR (ATR-FTIR), cm^{-1} 3525 (w), 2936 (br), 1485 (s), 1259 (m), 1036 (s); HRMS-CI (m/z) $[M + H]^+$ calcd for $C_{19}H_{24}NO_6$ 362.15981, found 362.15947; $[\alpha]^{20}_D$ +102 (c 1.0, $CHCl_3$).

121 1:5 (−)-prostephanaberrine (**18**)

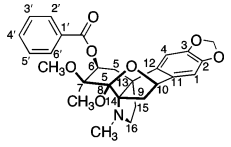
(−)-Prostephanaberrine (18). A solution of sodium ethoxide in ethanol (1.28 M, 93.8 μL, 125 μmol, 10.0 equiv) was added to a solution of the hemikteal **120** [4.5 mg, 13 μmol, 1 equiv; dried by azeotropic distillation with benzene (1.0 mL)] in ethanol (2.7 mL) in a 20-mL vial that had been charged with a Teflon-coated stir bar. The vial was sealed with a Teflon-lined cap, and the sealed vial was placed in an oil bath that had been preheated to 75 °C. The reaction mixture was stirred and heated for 20 min at 75 °C. The product mixture was allowed to cool over 10 min to 24 °C. The cooled product mixture was diluted with ethyl acetate (5.0 mL), and the diluted solution was transferred to a separatory funnel. Water (5.0 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by preparative thin-layer chromatography (eluting with 5% methanol−dichloromethane) to afford (−)-prostephanaberrine (**18**) as a yellow solid (3.5 mg, 85%). Synthetic (−)-prostephanaberrine (**18**) exists as a solvent-dependent mixture of ring and chain isomers (ratio of **18**:**121** = 5:1 in chloroform-*d*). Natural (−)-prostephanaberrine (**18**) is reported to exist only in the chain form **18** in chloroform-*d*.[27] This isolation report for natural (−)-prostephanaberrine (**18**) notes that natural (−)-prometaphanine,[65] (−)-prostephabyssine,[66] and (−)-16-oxoprometaphanine,[67] alkaloids differing from (−)-prostephanaberrine (**18**) by aromatic substitution pattern, each exist as a solvent-dependent equilibrium mixture with the corresponding hemiketal: R_f = 0.43 (5% methanol−dichloromethane; UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$, * denotes **121**) δ 7.02 (s, 1H, H_1), 6.73 (s, 1H, H_4), 6.69 (s, 1H, H_4*), 6.56 (s, 1H, H_1*), 5.93 (d, 1H, J = 1.5 Hz, 1 × OCH_2O), 5.91 (d, 1H, J = 1.5 Hz, 1 × OCH_2O), 5.90 (d, 1H, J = 1.5 Hz, 1 × OCH_2O*), 5.89 (d, 1H, J = 1.5 Hz, 1 × OCH_2O*), 5.67 (dd, 1H, J = 6.3, 3.3, H_6), 4.82 (d, 1H, J = 5.5 Hz, H_{10}*), 4.73 (dd, 1H, J = 9.5, 5.5, H_{10}), 4.46 (dd, 1H, J = 6.0, 2.0 Hz, H_6*), 4.13 (s, 1H, OH*), 3.61 (s, 3H, C_7-OCH_3), 3.57−3.51 (m, 1H, H_{16}*), 3.52 (s, 3H, C_7-OCH_3*), 2.87 (dd, 1H, J = 16.8, 1.8 Hz, H_5*), 2.84−2.77 (m, 3H, $H_{5\beta}$, H_{16}, $H_{9\beta}$*), 2.65 (s, 3H, NCH_3*), 2.64−2.54 (m, 3H, $H_{5\alpha}$, H_{16}, H_{16}*), 2.57 (s, 3H, NCH_3), 2.44 (dd, 1H, J = 16.8, 6.8 Hz, H_5*), 2.39 (dd, 1H, J = 13.5, 5.5 Hz, $H_{9\beta}$), 2.30−2.23 (m, 1H, H_{15}), 2.20−2.13 (m, 1H, H_{15}), 1.97−1.91 (m, 2H, 2 × H_{15}*), 1.82 (dd, 1H, J = 13.5, 9.5 Hz, $H_{9\alpha}$), 1.67 (d, 1H, J = 11.0 Hz, $H_{9\alpha}$*); ^{13}C NMR [125 MHz, $CDCl_3$, (−)-prostephanaberrine (**18**) only] δ 195.7 (C), 151.5 (C), 147.4 (C), 146.1 (C), 137.3 (C), 131.2 (C), 112.2 (CH), 106.4 (CH), 106.3 (CH), 101.0 (CH_2), 69.6 (C), 66.2 (CH), 55.1 (CH_3), 51.2 (CH_2), 49.4 (C), 36.4 (CH_2), 35.8 (CH_3), 34.7 (CH_2), 32.0 (CH_2); IR (ATR-FTIR), cm^{-1} 3446 (br), 2923 (w), 1670 (s), 1484 (s), 1241 (s), 1037 (s); HRMS-CI (m/z) $[M + H]^+$ calcd for $C_{19}H_{22}NO_5$, 344.14925, found 344.14823. Natural: $[\alpha]^{15}_D$ −219.1 (c 0.25, $CHCl_3$).[27] Synthetic: $[\alpha]^{20}_D$ −132 (c 0.25, $CHCl_3$).



(−)-stephanaberrine (**19**)

dx.doi.org/10.1021/jo401889b | J. Org. Chem. 2013, 78, 10031−10057

(−)-Stephanaberrine (19). Aqueous hydrochloric acid (0.5 N, 930 μL) was added to (−)-prostephanaberrine (**18**) [3.2 mg, 9.3 μmol, 1 equiv; dried by azeotropic distillation with benzene (1.0 mL)] in a 20-mL vial that had been charged with a Teflon-coated stir bar. The vial was sealed with a Teflon-lined cap and the sealed vial was placed in an oil bath that had been preheated to 50 °C. The reaction mixture was stirred and heated for 4 h at 50 °C. The product mixture was allowed to cool over 10 min to 24 °C. The cooled product mixture was diluted with ethyl acetate (5.0 mL), and the diluted solution was transferred to a separatory funnel. Saturated aqueous sodium bicarbonate solution (5.0 mL) was added, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL), and the organic layers were combined. The combined organic layers were dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated, and the residue obtained was purified by preparative thin-layer chromatography (eluting with 5% methanol−ethyl acetate) to afford (−)-stephanaberrine (**19**) as a white solid (2.0 mg, 65%): R_f = 0.51 (5% methanol−ethyl acetate; UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (s, 1H, H_4), 6.64 (s, 1H, H_1), 5.95 (s, 2H, OCH_2O), 5.08 (s, 1H, OH), 4.98 (d, 1H, J = 6.0 Hz, H_{10}), 3.43−3.36 (m, 1H, H_{16}), 2.74 (dd, 1H, J = 11.0, 6.5 Hz, $H_{9\beta}$), 2.58−2.51 (m, 3H, H_5, H_6, H_{16}), 2.57 (s, 3H, NCH_3), 2.21−2.16 (m, 1H, H_6), 2.09−2.00 (m, 2H, H_5, H_{15}), 1.97−1.91 (m, 1H, H_{15}), 1.67 (d, 1H, J = 11.0 Hz, $H_{9\alpha}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8 (C), 148.2 (C), 145.6 (C), 134.7 (C), 134.2 (C), 106.9 (CH), 106.1 (CH), 101.2 (CH_2), 98.4 (C), 78.1 (C), 77.3 (CH), 53.9 (CH_2), 51.0 (C), 38.3 (CH_3), 36.2 (CH_2), 36.0 (CH_2), 32.3 (CH_2), 30.9 (CH_2); IR (ATR-FTIR), cm^{-1} 3455 (w), 2951 (w), 1727 (s), 1486 (s), 1258 (s), 1025 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{18}H_{20}NO_5$ 330.13360, found 330.13320. Natural: $[\alpha]^{23}_D$ −47.5 (c 0.78, $CHCl_3$).[27] Synthetic: $[\alpha]^{20}_D$ −44 (c 0.78, $CHCl_3$).



(−)-stephabenine (**12**)

(−)-Stephabenine (12). Benzoyl chloride (6.0 μL, 52 μmol, 11 equiv) was added to a solution of (+)-*N*,*O*-dimethylstephine (**13**) [1.8 mg, 4.8 μmol, 1 equiv; dried by azeotropic distillation with benzene (500 μL)] in pyridine (480 μL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C. The product mixture was allowed to warm over 10 min to 24 °C. The warmed product mixture was concentrated to dryness, and the residue obtained was purified by preparative thin-layer chromatography (eluting with 5% methanol−dichloromethane) to afford (−)-stephabenine (**12**) as a clear, colorless oil (1.7 mg, 74%). Natural: R_f = 0.56 (3% methanol−7% acetone−chloroform).[24] Synthetic: R_f = 0.55 (3% methanol−7% acetone−chloroform; UV, CAM), R_f = 0.35 (5% methanol−dichloromethane; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.38 (m, 3H, H_2', H_4', H_6'), 7.22 (app t, 2H, J = 7.8 Hz, H_3', H_5'), 6.58 (s, 1H, H_1), 6.44 (s, 1H, H_4), 5.70 (d, 1H, J = 1.6 Hz, 1 × OCH_2O), 5.57−5.51 (m, 1H, H_6), 5.15 (d, 1H, J = 1.6 Hz, 1 × OCH_2O), 4.91 (d, 1H, J = 6.0 Hz, H_{10}), 3.81 (d, 1H, J = 4.4 Hz, H_7), 3.55 (s, 3H, C_8-OCH_3), 3.44−3.36 (m, 1H, H_{16}), 3.41 (s, 3H, C_7-OCH_3), 2.70 (dd, 1H, J = 10.8, 6.4 Hz, $H_{9\beta}$), 2.58 (s, 3H, NCH_3), 2.52 (td, 1H, J = 10.4, 3.6, H_{16}), 2.46−2.35 (m, 2H, H_5), 1.93−1.79 (m, 2H, H_{15}), 1.55 (d, 1H, J = 10.8 Hz, $H_{9\alpha}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3 (C), 147.6 (C), 144.6 (C), 137.1 (C), 133.5 (C), 132.3 (CH), 129.9 (2 × CH), 129.6 (C), 127.5 (2 × CH), 107.0 (CH), 106.1 (CH), 103.3 (C), 100.6 (CH_2), 81.6 (CH), 77.2 (CH), 75.5 (C), 67.9 (CH), 57.7 (CH_3), 53.9 (CH_2), 51.6 (CH_3), 49.6 (C), 38.6 (CH_3), 37.5 (CH_2), 36.6 (CH_2), 29.3 (CH_2); IR (ATR-FTIR), cm^{-1} 2937 (w), 1709 (s), 1502 (m), 1484 (s), 1279 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{27}H_{30}NO_7$, 480.20168, found 480.20113. Natural: $[\alpha]^{16}_D$ −15.24 (c 1.65, $CHCl_3$).[24] Synthetic: $[\alpha]^{20}_D$ −15 (c 1.65, $CHCl_3$).

Synthesis of the Acetylide Addition Product 33. Methyl trifluoromethanesulfonate (132 μL, 1.17 mmol, 0.95 equiv) was added to a solution of the imine **30** [320 mg, 1.24 mmol, 1 equiv; dried by azeotropic distillation with benzene (5 mL)] in tetrahydrofuran (10 mL) at −78 °C. The reaction vessel was placed in a −30 °C bath, and the mixture was stirred for 30 min at −30 °C. The mixture was then cooled to −90 °C, and the cooled solution was diluted with tetrahydrofuran (10 mL). In a separate flask, a solution of *n*-butyllithium in hexanes (2.18 M, 596 μL, 1.30 mmol, 1.05 equiv) was added to a solution of (trimethylsilyl)acetylene (223 μL, 1.61 mmol, 1.30 equiv) in tetrahydrofuran (10 mL) at −78 °C. The resulting mixture was stirred for 15 min at −78 °C. The cold solution of the lithiated alkyne was then added dropwise via cannula to the iminium ion at −90 °C. The reaction mixture was stirred for 30 min at −90 °C. The product mixture was allowed to warm over 15 min to 24 °C. The warmed product mixture was concentrated to dryness, and the residue obtained was used directly in the next step. Potassium carbonate (171 mg, 1.24 mmol, 1.00 equiv) was added to a solution of the residue obtained in the preceding step in methanol (10 mL) at 24 °C. The resulting mixture was stirred for 1 h at 24 °C. The product mixture was diluted with ethyl acetate (300 mL), and the diluted solution was transferred to a separatory funnel. The organic layer was washed with distilled water (2 × 300 mL). The washed organic layer was dried over sodium sulfate, and the dried solution was filtered. The filtrate was concentrated and the residue obtained was purified by flash column chromatography (eluting with 100% ethyl acetate) to afford the addition product **33** as a white solid (215 mg, 58%): R_f = 0.50 (100% ethyl acetate−hexanes; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (app q, 1H, J = 2.8 Hz), 5.89 (app q, 1H, J = 3.2, Hz), 3.97 (s, 3H), 3.53 (s, 3H), 3.22 (br s, 1H), 2.96 (br s, 1H), 2.84−2.78 (m, 2H), 2.53 (s, 1H), 2.40 (q, 1H, J = 8.8 Hz), 2.16 (s, 3H), 2.03 (dd, 2H, J = 8.8, 6.4 Hz), 1.48 (d, 1H, J = 8.4 Hz), 1.38 (dt, 1H, J = 7.2, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3 (C), 162.8 (C), 138.8 (C), 136.4 (CH), 135.5 (CH), 77.2 (C), 76.8 (CH), 70.2 (C), 62.7 (CH), 61.4 (CH_3), 59.5 (CH_3), 55.4 (CH), 52.8 (C), 50.9 (CH), 50.0 (CH_2), 47.3 (CH_2), 40.8 (CH_2), 36.1 (CH_3); IR (ATR-FTIR), cm^{-1} 2985 (br), 1648 (s), 1602 (s), 1275 (s), 1085 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{18}H_{22}NO_3$ 300.1600, found 300.1616.

Synthesis of the Alkene 122. Lindlar's catalyst (53.1 mg, 25.1 μmol, 0.15 equiv) was added to a solution of the acetylide addition product **33** (50.0 mg, 167 μmol, 1 equiv) in ethyl acetate (4.0 mL) at 24 °C. The reaction vessel was evacuated and refilled using a balloon of dihydrogen. This process was repeated four times. The reaction mixture was stirred for 30 min at 24 °C under a balloon of dihydrogen. The product mixture was diluted with ethyl acetate (5 mL), and the diluted product mixture was filtered through a pad of Celite. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 50% ethyl acetate−hexanes) to afford the terminal olefin **122** as a white solid (28.0 mg, 55%): R_f = 0.80 (80% ethyl acetate−hexanes; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (d, 1H, J = 16.8, 10.4 Hz), 5.40 (dd, 1H, J = 16.8, 2.4 Hz), 5.25 (dd, 1H, J = 10.4, 2.4 Hz), 4.07 (s, 3H), 3.72 (s, 3H), 2.87 (t, 1H, J = 8.0 Hz), 2.74 (br s, 1H), 2.67−2.60 (m, 1H), 2.32 (s, 3H), 2.29 (d, 1H, J = 5.2 Hz), 2.10 (app d, 1H, J = 5.2 Hz), 1.88−1.80 (m, 1H), 1.61 (app d, 1H, J = 10.0 Hz), 1.48−1.28 (m, 2H), 1.41−1.28 (m, 3H), 1.24−1.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6 (C), 164.5 (C), 139.0 (CH), 138.3 (C), 115.5 (CH_2), 70.6 (C), 61.3 (CH_3), 60.6 (CH_3), 56.4 (CH), 55.2 (C), 51.0 (CH_2), 46.1 (CH), 43.9 (CH), 38.4 (CH_2), 37.5 (CH_2), 35.3 (CH_3), 25.7 (CH_2), 23.7 (CH_2); IR (ATR-FTIR), cm^{-1} 2961 (br), 1655 (s), 1600 (s), 1450 (m), 1248 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{18}H_{26}NO_3$ 304.1913, found 304.1918.

Synthesis of the Terminal Alkene 123. Lindlar's catalyst (86.0 mg, 40.4 μmol, 0.15 equiv) was added to a solution of the terminal alkyne **68** (100 mg, 270 μmol, 1 equiv) in ethyl acetate (5.0 mL) at 24 °C. The reaction vessel was evacuated and refilled using a balloon of dihydrogen. This process was repeated four times. The reaction mixture was stirred for 30 min at 24 °C under a balloon of dihydrogen. The product mixture was diluted with ethyl acetate (5 mL), and the diluted solution was filtered through a pad of Celite. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 30% ethyl acetate−hexanes) to afford the terminal alkene **123** as a clear oil (50.0 mg, 50%): R_f = 0.40 (30%

ethyl acetate–hexanes; UV, CAM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.10–6.09 (m, 1H), 5.88–5.87 (m, 1H), 5.74 (dd, 1H, J = 17.0, 10.5 Hz), 5.51 (dd, 1H, J = 17.0, 2.5 Hz), 5.26 (dd, 1H, J = 10.5, 2.5 Hz), 3.98 (s, 3H), 3.59 (s, 3H), 3.35 (br s, 1H), 2.93 (app t, 1H, J = 7.0 Hz), 2.71 (br s, 1H), 2.67–2.61 (m, 2H), 2.28 (s, 3H), 2.07–2.01 (m, 1H), 1.65–1.62 (m, 1H), 1.26 (s, 1H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.1 (C), 164.7 (C), 139.9 (C), 139.2 (CH), 136.0 (CH), 135.8 (CH), 115.1 (CH_2), 71.4 (C), 61.4 (CH_3), 60.9 (CH_3), 60.1 (C), 55.9 (CH), 55.3 (CH), 53.6 (CH), 52.3 (CH_2), 49.5 (CH), 39.6 (CH_2), 35.4 (CH_3), −0.1 (TMS); IR (ATR-FTIR), cm^{-1} 2950 (br), 1650 (s), 1602 (s), 1245 (s), 1215 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{21}H_{32}NO_3Si$, 374.2151, found 374.2169; $[\alpha]^{20}_D$ +106 (c 1.0, $CHCl_3$).

Synthesis of the Vinylsilane 124. Platinum oxide (30.0 mg, 134 μmol, 1.60 equiv) was added portionwise to a solution of the acetylide addition product **33** (25.0 mg, 83.6 μmol, 1 equiv) in dimethylphenyl silane (1.9 mL) in a 10-mL round-bottomed flask that had been fused to a Teflon-coated valve at 24 °C. The vessel was sealed, and the sealed reaction vessel was stirred and heated for 4 h at 60 °C. The product mixture was allowed to cool over 20 min to 24 °C. The cooled product mixture was diluted with ethyl acetate (5 mL), and the diluted solution was filtered through a pad of Celite. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 30% ethyl acetate–hexanes) to afford the vinylsilane **124** as a clear oil (20.0 mg, 55%): R_f = 0.60 (50% ethyl acetate–hexanes; UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.55 (m, 2H), 7.37–7.35 (m, 3H), 6.21 (d, 1H, J = 18.5 Hz), 6.17 (d, 1H, J = 18.5 Hz), 4.04 (s, 3H), 3.72 (s, 3H), 2.91 (t, 1H, J = 8.0 Hz), 2.75 (br s, 1H), 2.67–2.62 (m, 1H), 2.33 (s, 3H), 2.29 (d, 1H, J = 5.0 Hz), 2.03 (br d, 1H, J = 3.5 Hz), 1.81–1.75 (m, 1H), 1.61 (br s, 1H), 1.51–1.35 (m, 3H), 1.31–1.28 (m, 2H), 1.23–1.21 (m, 1H), 0.37 (s, 3H), 0.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6 (C), 164.6 (C), 149.1 (CH), 139.6 (C), 138.5 (C), 134.0 (2 × CH), 129.0 (CH), 127.8 (2 × CH), 127.0 (CH), 71.8 (C), 61.2 (CH_3), 60.6 (CH_3), 56.4 (CH), 55.4 (C), 51.2 (CH_2), 46.3 (CH), 43.8 (CH), 38.6 (CH_2), 37.6 (CH_2), 35.4 (CH_3), 25.7 (CH_2), 23.7 (CH_2), −1.8 (CH_3), −2.0 (CH_3); IR (ATR-FTIR), cm^{-1} 2958 (br), 1656 (s), 1600 (s), 1250 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{26}H_{36}NO_3Si$ 438.2464, found 438.2479.

Synthesis of the Vinylsilane 125. Platinum oxide (25.0 mg, 110 μmol, 1.60 equiv) was added portionwise to a solution of the terminal alkyne **68** (25.0 mg, 67.4 μmol, 1 equiv) in dimethylphenylsilane (1.5 mL) in a 10-mL round-bottomed flask that had been fused to a Teflon-coated valve at 24 °C. The vessel was sealed, and the sealed reaction vessel was placed in an oil bath that had been preheated to 60 °C. The reaction mixture was stirred and heated for 2 h at 60 °C. The product mixture was allowed to cool over 20 min to 24 °C. The cooled product mixture was diluted with ethyl acetate (5 mL), and the diluted solution was filtered through a pad of Celite. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 30% acetone–hexanes) to afford the vinylsilane **125** as a clear oil (26.0 mg, 76%): R_f = 0.70 (30% acetone–hexanes; UV, CAM); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.57 (m, 2H), 7.37–7.36 (m, 3H), 6.29 (d, 1H, J = 18.5 Hz), 5.94–5.90 (m, 2H), 5.84–5.83 (m, 1H), 3.93 (s, 3H), 3.58 (s, 3H), 3.34 (br s, 1H), 2.95 (dd, 1H, J = 9.0, 6.0 Hz), 2.66–2.61 (m, 2H), 2.59 (br s, 1H), 2.27 (s, 3H), 2.00–1.95 (m, 1H), 1.62–1.58 (m, 1H), 1.23 (s, 1H), 0.40 (s, 3H), 0.39 (s, 3H), −0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.1 (C), 164.7 (C), 149.5 (CH), 140.2 (C), 139.5 (C), 136.2 (CH), 135.6 (CH), 134.0 (2 × CH), 129.0 (CH), 127.9 (2 × CH), 126.2 (CH), 72.5 (C), 61.3 (CH), 60.8 (CH_3), 60.2 (CH_3), 56.2 (CH), 55.7 (C), 53.4 (CH), 52.5 (CH_2), 49.4 (CH), 40.0 (CH_2), 35.5 (CH_3), −0.3 (TMS), −1.9 (CH_3), −2.0 (CH_3); IR (ATR-FTIR), cm^{-1} 2955 (br), 1648 (m), 1602 (m), 1250 (s), 1215 (m); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{29}H_{42}NO_3Si_2$ 508.2703, found 508.2705; $[\alpha]^{20}_D$ +148 (c 1.0, $CHCl_3$).

Synthesis of the Vinylstannane 126. Tetrakis(triphenylphosphine)palladium (24.1 mg, 20.9 μmol, 0.25 equiv) was added to a solution of the terminal alkyne **33** [25.0 mg, 83.6 μmol, 1 equiv; dried by azeotropic distillation with benzene (3.0 mL)] in tetrahydrofuran (1.0 mL) at 24 °C. Tributyltin hydride (88.6 μL, 334 μmol, 4.00 equiv) was added dropwise via syringe pump over 1 h at 24 °C. Upon completion of the addition, the product mixture was concentrated to dryness. The residue obtained was purified by flash column chromatography (eluting with 30% ethyl acetate–hexanes) to afford the vinylstannane **126** as a clear oil (25.0 mg, 51%): R_f = 0.35 (30% ethyl acetate–hexanes; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (d, 1H, J = 18.8 Hz) 6.19–6.17 (m, 1H), 5.99–5.97 (m, 1H), 5.80 (d, 1H, J = 18.8 Hz) 3.97 (s, 3H), 3.59 (s, 3H), 3.29 (br s, 1H), 2.95 (app t, 1H, J = 7.2 Hz), 2.73–2.64 (m, 3H), 2.27 (s, 3H), 2.02–1.94 (m, 1H), 1.62–1.50 (m, 8H), 1.42–1.25 (m, 7H), 0.94–0.88 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3 (C), 165.5 (C), 147.5 (CH), 140.0 (C), 136.4 (CH), 136.2 (CH), 126.7 (CH), 73.0 (C), 60.7 (CH_3), 60.2 (CH_3), 58.8 (CH), 54.2 (CH), 53.0 (C), 52.5 (CH), 50.4 (CH_2), 47.6 (CH_2), 39.6 (CH_2), 35.4 (CH_3), 29.4 (3 × CH_2), 27.4 (3 × CH_2), 13.9 (3 × CH_3), 9.8 (3 × CH_2); IR (ATR-FTIR), cm^{-1} 2920 (br), 1718 (s), 1655 (s), 1602 (s), 1280 (s); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{30}H_{50}NO_3Sn$ 592.2813, found 592.2817.

Synthesis of the Vinylstannane 127. Tetrakis(triphenylphosphine)palladium (62.8 mg, 54.4 μmol, 0.20 equiv) was added to a solution of the terminal alkyne **68** (90.0 mg, 272 μmol, 1 equiv) in tetrahydrofuran (2.7 mL) at 24 °C. Tributyltin hydride (144 μL, 544 μmol, 2.00 equiv) was added dropwise via syringe pump over 1 h at 24 °C. Upon completion of the addition, the product mixture was concentrated to dryness. The residue obtained was purified by flash column chromatography (eluting with 20% ethyl acetate–hexanes) to afford the vinylstannane **127** as a clear oil (140 mg, 78%): R_f = 0.45 (30% ethyl acetate–hexanes; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (d, 1H, J = 18.8 Hz) 6.07–6.06 (m, 1H), 5.87–5.85 (m, 1H), 5.79 (d, 1H, J = 18.8 Hz) 3.94 (s, 3H), 3.57 (s, 3H), 3.34 (br s, 1H), 2.92 (app t, 1H, J = 7.2 Hz), 2.68–2.64 (m, 3H), 2.25 (s, 3H), 2.02–1.94 (m, 1H), 1.56–1.51 (m, 7H), 1.35–1.30 (m, 6H), 1.24 (s, 1H), 0.94–0.87 (m, 15H), −0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2 (C), 165.4 (C), 147.7 (CH), 140.0 (C), 136.1 (CH), 135.6 (CH), 126.6 (CH), 73.0 (C), 61.2 (CH_3), 60.7 (CH_3), 60.1 (CH), 55.9 (C, CH), 53.5 (CH), 52.3 (CH_2), 49.4 (CH), 39.9 (CH_2), 35.4 (CH_3), 29.3 (3 × CH_2), 27.3 (3 × CH_2), 13.9 (3 × CH_3), 9.8 (3 × CH_2), −0.1 (TMS); IR (ATR-FTIR), cm^{-1} 2915 (br), 1650 (m), 1605 (m), 1250 (m), 1215 (m); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{33}H_{58}NO_3SiSn$ 664.3208, found 664.3207; $[\alpha]^{20}_D$ +115 (c 2.0, $CHCl_3$).

Synthesis of the β-Silylethyl Derivative 128. Platinum oxide (27.4 mg, 121 μmol, 1.80 equiv) was added portionwise to a solution of the terminal alkene **123** (25.0 mg, 67.0 μmol, 1 equiv) in dimethylphenylsilane (1.5 mL) in a 10-mL round-bottomed flask that had been fused to a Teflon-coated valve at 24 °C. The vessel was sealed, and the sealed reaction vessel was placed in an oil bath that had been preheated to 60 °C. The reaction mixture was stirred and heated for 2 h at 60 °C. The product mixture was allowed to cool over 20 min to 24 °C. The cooled product mixture was diluted with ethyl acetate (5 mL), and the diluted solution was filtered through a pad of Celite. The filtrate was concentrated, and the residue obtained was purified by flash column chromatography (eluting with 25% ethyl acetate–hexanes) to afford the β-silylethyl derivative **128** as a clear oil (19.0 mg, 56%): R_f = 0.60 (60% ethyl acetate–hexanes; UV, CAM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.55 (m, 2H), 7.38–7.36 (m, 3H), 5.91–5.89 (m, 1H), 5.80–5.78 (m, 1H), 3.85 (s, 3H), 3.57 (s, 3H), 3.28 (br s, 1H), 2.86–2.82 (m, 2H), 2.71–2.70 (app d, 1H, J = 4.0 Hz), 2.51–2.44 (m, 1H), 2.26 (s, 3H), 2.13–2.06 (m, 1H), 1.72–1.65 (m, 2H), 1.44–1.36 (m, 1H), 1.26 (s, 1H), 1.10–0.98 (m, 2H), 0.31 (s, 6H), −0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0 (C), 167.0 (C), 140.3 (C), 139.8 (C), 135.7 (CH), 135.5 (CH), 133.8 (2 × CH), 129.0 (CH), 127.9 (2 × CH), 69.9 (C), 63.3 (CH_3), 61.0 (CH_3), 59.7 (CH), 56.0 (CH), 54.3 (CH), 53.3 (CH_2), 52.6 (C), 49.5 (CH), 40.6 (CH_2), 37.2 (CH_3), 29.2 (CH_2), 11.2 (CH_2), 0.02 (TMS), −2.9 (2 × CH_3); IR (ATR-FTIR), cm^{-1} 2915 (s), 1730 (s), 1652 (m), 1600 (m), 1460 (m); HRMS-CI (m/z) [M + H]$^+$ calcd for $C_{29}H_{44}NO_3Si_2$ 510.2860, found 510.2830; $[\alpha]^{20}_D$ +85 (c 0.2, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures, materials, instrumentation, comparison of NMR data for natural and synthetic alkaloids, and catalog of NMR and IR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: seth.herzon@yale.edu.

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Andreas Maderna, Dr. Frank Loganzo, and My-Hanh Lam (Pfizer) for cytotoxicity studies and Professor Steven L. Castle (Brigham Young University) for a generous sample of natural (−)-acutumine (**4**). Financial support from the Department of Defense (NDSEG fellowship to S.M.K.), the Division of Organic Chemistry of the American Chemical Society (Graduate Research Fellowship to N.A.C., sponsored by Boehringer Ingelheim), the National Science Foundation (CHE-1151563), the Searle Scholars Program, and Yale University is gratefully acknowledged. S.B.H. is a fellow of the Alfred P. Sloan and David and Lucile Packard Foundations, a Cottrell Scholar of the Research Corporation for Science Advancement, and a Camille Dreyfus Teacher−Scholar.

■ REFERENCES

(1) (a) Bentley, K. W. Morphine Alkaloids. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1971; Vol. *13*, pp 1−163. (b) Inubushi, Y.; Ibuka, T. The Hasubanan Alkaloids. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1977; Vol. *16*, pp 393−430. (c) Matsui, M. Hasubanan Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. *33*, pp 307−347. (d) King, S. M.; Herzon, S. B. The Hasubanan and Acutumine Alkaloids. In *The Alkaloids*; Knölker, H.-J., Ed.; Academic Press.: London, 2014; Vol. *73*, in press.

(2) (a) Kondo, H.; Satomi, M.; Odera, T. *Ann. Rept. ITSUU Lab.* **1951**, *2*, 1. (b) Tomita, M.; Ibuka, T.; Inubushi, Y.; Watanabe, Y.; Matsui, M. *Tetrahedron Lett.* **1964**, *5*, 2937. (c) Tomita, M.; Ibuka, T.; Inubushi, Y.; Watanabe, Y.; Matsui, M. *Chem. Pharm. Bull.* **1965**, *13*, 538.

(3) (a) Goto, K.; Sudzuki, H. *Bull. Chem. Soc. Jpn.* **1929**, *4*, 220. (b) Tomita, M.; Okamoto, Y.; Kikuchi, T.; Osaki, K.; Nishikawa, M.; Kamiya, K.; Sasaki, Y.; Matoba, K.; Goto, K. *Tetrahedron Lett.* **1967**, *8*, 2421. (c) Sugimoto, Y.; Inanaga, S.; Kato, M.; Shimizu, T.; Hakoshima, T.; Isogai, A. *Phytochemistry* **1998**, *49*, 1293.

(4) Semwal, D. K.; Rawat, U. *Planta Med.* **2009**, *75*, 378.

(5) Yan, M.-H.; Cheng, P.; Jiang, Z.-Y.; Ma, Y.-B.; Zhang, X.-M.; Zhang, F.-X.; Yang, L.-M.; Zheng, Y.-T.; Chen, J.-J. *J. Nat. Prod.* **2008**, *71*, 760.

(6) Cheng, P.; Ma, Y.-b.; Yao, S.-y.; Zhang, Q.; Wang, E.-j.; Yan, M.-h.; Zhang, X.-m.; Zhang, F.-x.; Chen, J.-j. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5316.

(7) Carroll, A. R.; Arumugan, T.; Redburn, J.; Ngo, A.; Guymer, G. P.; Forster, P. I.; Quinn, R. J. *J. Nat. Prod.* **2010**, *73*, 988.

(8) Qin, G.-W.; Tang, X.-C.; Lestage, P.; Caignard, D.-H.; Renard, P. *Acutumine and Acutumine Compounds, Synthesis and Use*. Patent WO2004000815A1, 2003.

(9) Yu, B.-W.; Chen, J.-Y.; Wang, Y.-P.; Cheng, K.-F.; Li, X.-Y.; Qin, G.-W. *Phytochemistry* **2002**, *61*, 439.

(10) (a) Ibuka, T.; Tanaka, K.; Inubushi, Y. *Tetrahedron Lett.* **1970**, 4811. (b) Ibuka, T.; Tanaka, K.; Inubushi, Y. *Chem. Pharm. Bull.* **1974**, *22*, 782.

(11) (a) Ibuka, T.; Tanaka, K.; Inubushi, Y. *Tetrahedron Lett.* **1972**, *13*, 1393. (b) Ibuka, T.; Tanaka, K.; Inubushi, Y. *Chem. Pharm. Bull.* **1974**, *22*, 907.

(12) (a) Inubushi, Y.; Kitano, M.; Ibuka, T. *Chem. Pharm. Bull.* **1971**, *19*, 1820. (b) Kametani, T.; Nemoto, H.; Kobari, T.; Shishido, K.; Fukumoto, K. *Chem. Ind. (London, U.K.)* **1972**, 538.

(13) Schultz, A. G.; Wang, A. *J. Am. Chem. Soc.* **1998**, *120*, 8259.

(14) (a) Chuang, K. V.; Navarro, R.; Reisman, S. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 9447. (b) For a recent synthesis of (±)-cepharatine A, see: Magnus, P.; Seipp, C. *Org. Lett.* **2013**, *15*, 4870.

(15) (a) Tomita, M.; Ibuka, T.; Kitano, M. *Tetrahedron Lett.* **1966**, *7*, 6233. (b) Ibuka, T.; Kitano, M. *Chem. Pharm. Bull.* **1967**, *15*, 1944. (c) Tomita, M.; Kitano, M.; Ibuka, T. *Tetrahedron Lett.* **1968**, *9*, 3391. (d) Evans, D. A. *Tetrahedron Lett.* **1969**, *10*, 1573. (e) Evans, D.; Bryan, C.; Wahl, G. *J. Org. Chem.* **1970**, *35*, 4122. (f) Keely, S. L., Jr; Martinez, A. J.; Tahk, F. C. *Tetrahedron* **1970**, *26*, 4729. (g) Evans, D. A.; Bryan, C. A.; Sims, C. L. *J. Am. Chem. Soc.* **1972**, *94*, 2891. (h) Kametani, T.; Kobari, T.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1972**, 288. (i) Belleau, B.; Wong, H.; Monkovic, I.; Perron, Y. G. *J. Chem. Soc., Chem. Commun.* **1974**, 603. (j) Kametani, T.; Kobari, T.; Shishido, K.; Fukumoto, K. *Tetrahedron* **1974**, *30*, 1059. (k) Monkovic, I.; Wong, H.; Belleau, B.; Pachter, I. J.; Perron, Y. G. *Can. J. Chem.* **1975**, *53*, 2515. (l) Monkovic, I.; Wong, H. *Can. J. Chem.* **1976**, *54*, 883. (m) Shiotani, S.; Kometani, T. *Tetrahedron Lett.* **1976**, *17*, 767. (n) Bruderer, H.; Knopp, D.; Daly, J. J. *Helv. Chim. Acta* **1977**, *60*, 1935. (o) Schwartz, M. A.; Wallace, R. A. *Tetrahedron Lett.* **1979**, *20*, 3257. (p) Trauner, D.; Porth, S.; Opatz, T.; Bats, J. W.; Giester, G.; Mulzer, J. *Synthesis* **1998**, 653. (q) Jones, S. B.; He, L.; Castle, S. L. *Org. Lett.* **2006**, *8*, 3757. (r) Nguyen, T. X.; Kobayashi, Y. *J. Org. Chem.* **2008**, *73*, 5536. (s) Nielsen, D. K.; Nielsen, L. L.; Jones, S. B.; Toll, L.; Asplund, M. C.; Castle, S. L. *J. Org. Chem.* **2009**, *74*, 1187. (t) Jones, S. B.; He, L.; Castle, S. L. *Org. Lett.* **2009**, *11*, 785.

(16) Pihko, A. J.; Koskinen, A. M. P. *Tetrahedron* **2005**, *61*, 8769.

(17) (a) Reeder, M. D.; Srikanth, G. S. C.; Jones, S. B.; Castle, S. L. *Org. Lett.* **2005**, *7*, 1089. (b) Li, F.; Castle, S. L. *Org. Lett.* **2007**, *9*, 4033. (c) Li, F.; Tartakoff, S. S.; Castle, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 6674. (d) Li, F.; Tartakoff, S. S.; Castle, S. L. *J. Org. Chem.* **2009**, *74*, 9082.

(18) (a) Matoba, K.; Karibe, N.; Yamazaki, T. *Chem. Pharm. Bull.* **1982**, *30*, 3906. (b) Matoba, K.; Karibe, N.; Yamazaki, T. *Chem. Pharm. Bull.* **1984**, *32*, 2639. (c) Waller, D. L.; Stephenson, C. R. J.; Wipf, P. *Org. Biomol. Chem.* **2007**, *5*, 58. (d) Moreau, R. J.; Sorensen, E. J. *Tetrahedron* **2007**, *63*, 6446. (e) Navarro, R.; Reisman, S. E. *Org. Lett.* **2012**, *14*, 4354.

(19) Zhi-Da, M.; Ge, L.; Guang-Xi, X.; Iinuma, M.; Tanaka, T.; Mizuno, M. *Phytochemistry* **1985**, *24*, 3084.

(20) (a) Fadeeva, I. I.; Il'inskaya, T. N.; Perel'son, M. E.; Kuzovkov, A. D. *Chem. Nat. Compd.* **1970**, *6*, 139. (b) Fadeeva, I. I.; Il'inskaya, T. N.; Perel'son, M. E.; Kuzovkov, A. D. *Chem. Nat. Compd.* **1971**, *7*, 756. (c) Patra, A. *Phytochemistry* **1987**, *26*, 2391.

(21) Herzon, S. B.; Calandra, N. A.; King, S. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 8863.

(22) (a) Sugimoto, Y.; Inanaga, S.; Kato, M.; Shimizu, T.; Hakoshima, T.; Isogai, A. *Phytochemistry* **1998**, *49*, 1293. (b) Sugimoto, Y.; Matsui, M.; Takikawa, H.; Sasaki, M.; Kato, M. *Phytochemistry* **2005**, *66*, 2627.

(23) King, S. M.; Calandra, N. A.; Herzon, S. B. *Angew. Chem., Int. Ed.* **2013**, *52*, 3642.

(24) Kondo, S.; Matsui, M.; Watanabe, Y. *Chem. Pharm. Bull.* **1983**, *31*, 2574.

(25) Van Wyk, A. J.; Wiechers, A. *J. South Afr. Chem. Inst.* **1974**, *27*, 95.

(26) Yamamura, Y.; Matsui, M. *J. Nat. Prod.* **1985**, *48*, 746.

(27) Matsui, M.; Yamamura, Y. *J. Nat. Prod.* **1986**, *49*, 588.

(28) Soderquist, J. A.; Kock, I.; Estrella, M. E. *Org. Process Res. Dev.* **2006**, *10*, 1076.

(29) Orita, H.; Shimizu, M.; Hayakawa, T.; Takehira, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1652.
(30) Related intramolecular redox processes have been employed in the syntheses of 5-hydroxyindole derivatives, see: Stoffman, E. J. L.; Clive, D. L. J. *Org. Biomol. Chem.* **2009**, *7*, 4862.
(31) For reviews on cycloaddition−retrocycloaddition strategies, see: (a) Ichihara, A. *Synthesis* **1987**, 207. (b) Klunder, A. J. H.; Zhu, J.; Zwanenburg, B. *Chem. Rev.* **1999**, *99*, 1163.
(32) (a) Bachmann, W. E.; Ross, A.; Dreiding, A. S.; Smith, P. A. S. *J. Org. Chem.* **1954**, *19*, 222. (b) Eliel, E. L.; Pillar, C. *J. Am. Chem. Soc.* **1955**, *77*, 3600.
(33) Grieco, P. A.; Abood, N. *J. Org. Chem.* **1989**, *54*, 6008.
(34) Ashe, A. J. *J. Am. Chem. Soc.* **1970**, *92*, 1233.
(35) Magnus, P.; Cairns, P. M.; Moursounidis, J. *J. Am. Chem. Soc.* **1987**, *109*, 2469.
(36) See the Experimental Section.
(37) (a) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (b) Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800.
(38) (a) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205. (b) Suggs, J. W.; Cox, S. D.; Crabtree, R. H.; Quirk, J. M. *Tetrahedron Lett.* **1981**, *22*, 303.
(39) Ramanathan, A.; Jimenez, L. S. *Synthesis* **2010**, *2010*, 217.
(40) Mukaiyama, T.; Isayama, S.; Inoki, S.; Kato, K.; Yamada, T.; Takai, T. *Chem. Lett.* **1989**, 449.
(41) Sheley, C. F.; Shechter, H. *J. Org. Chem.* **1970**, *35*, 2367.
(42) Papoutsis, I.; Spyroudis, S.; Varvoglis, A. *Tetrahedron Lett.* **1994**, *35*, 8449.
(43) Grotjahn, D. B.; Lev, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 12232.
(44) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.
(45) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.
(46) Stang, P. J.; Arif, A. M.; Crittell, C. M. *Angew. Chem., Int. Ed.* **1990**, *29*, 287.
(47) Suzuki, T.; Uozumi, Y.; Shibasaki, M. *J. Chem. Soc., Chem. Commun.* **1991**, 1593.
(48) Yoshifuji, M.; Nakamura, T.; Inamoto, N. *Tetrahedron Lett.* **1987**, *28*, 6325.
(49) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673.
(50) Krohn, K.; Khanbabaee, K. *Angew. Chem., Int. Ed.* **1994**, *33*, 99.
(51) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.
(52) Smith, A. B., III; Han, Q.; Breslin, P. A. S.; Beauchamp, G. K. *Org. Lett.* **2005**, *7*, 5075.
(53) Ogoshi, S.; Tomiyasu, S.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2002**, *124*, 11598.
(54) Huang, S. L.; Omura, K.; Swern, D. *Synthesis* **1978**, *1978*, 297.
(55) Amon, C. M.; Banwell, M. G.; Gravatt, G. L. *J. Org. Chem.* **1987**, *52*, 4851.
(56) Liu, G.; Wang, Z. *Synthesis* **2001**, 119.
(57) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(58) Gaspar, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5758.
(59) Alami, M.; Ferri, F. *Synlett* **1996**, 755.
(60) Takeda, T.; Kanamori, F.; Matsusita, H.; Fujiwara, T. *Tetrahedron Lett.* **1991**, *32*, 6563.
(61) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331.
(62) Overman, L. E. *Angew. Chem., Int. Ed.* **1984**, *23*, 579.
(63) (a) Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348. (b) Crabtree, R. H.; Davis, M. W. *Organometallics* **1983**, *2*, 681. (c) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. (d) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866.
(64) Matsui, M.; Watanabe, Y.; Ibuka, T.; Tanaka, K. *Chem. Pharm. Bull.* **1975**, *23*, 1323.
(65) Tomita, M.; Ibuka, T.; Inubushi, Y. *Tetrahedron Lett.* **1964**, *5*, 3617.
(66) Kupchan, S. M.; Liepa, A. J.; Fujita, T. *J. Org. Chem.* **1973**, *38*, 151.
(67) Watanabe, Y.; Matsui, M.; Uchida, M. *Phytochemistry* **1975**, *14*, 2695.
(68) Jin, H.-Z.; Wang, H.-B.; Wang, Y.-B.; Lin, L.-P.; Ding, J.; Qin, G.-W. *Zhongguo Tianran Yaowu* **2007**, *5*, 112.
(69) Likhitwitayawuid, K.; Angerhofer, C. K.; Chai, H.; Pezzuto, J. M.; Cordell, G. A.; Ruangrungsi, N. *J. Nat. Prod.* **1993**, *56*, 1468.
(70) Min, Y.; Choi, S.; Lee, K. *Arch. Pharmacal Res.* **2006**, *29*, 627.