JOURNAL
OF THE
AMERICAN
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SOCIETY

Application of a Stereospecific Intramolecular Allenylsilane Imino Ene Reaction to Enantioselective Total Synthesis of the 5,11-Methanomorphanthridine Class of *Amaryllidaceae* Alkaloids

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Received March 14, 1997[⊗]

Abstract: Enantioselective total syntheses of the pentacyclic 5,11-methanomorphanthridine *Amaryllidaceae* alkaloids (−)-montanine (**1**), (−)-coccinine (**2**), and (−)-pancracine (**3**) were accomplished using an intramolecular concerted pericyclic allenylsilane imino ene cycloaddition as a key step. These complex natural products were constructed starting from readily available enantiomerically pure epoxy alcohol **15** which was converted to allenylsilane aldehyde **28** *via* an efficient nine-step sequence. The imine generated from aldehyde **28** and iminophosphorane **47** underwent a stereospecific thermal imino ene reaction to afford key intermediate *cis* aminoalkyne **49**. It was possible to transform this compound *via* Lindlar hydrogenation followed by an intramolecular Heck reaction to seven-membered ring tetracycle **51**. This olefinic intermediate could be functionalized through its epoxide to yield α-hydroxymethyl intermediate **54**, and then pentacyclic alcohol **64**. Procedures were then developed to convert this material to the enantiomerically pure alkaloids **1**−**3**. A formal enantioselective total synthesis of (−)-brunsvigine (**4**) was also achieved *via* triol **72**.

Introduction and Background

For decades chemists have been attracted by the *Amaryllidaceae* alkaloids due to their diverse and interesting structures.[1] The 5,11-methanomorphanthridines constitute one of eight classes within this large family of alkaloidal natural products.[2] Three members of the class, (−)-montanine (**1**), (−)-coccinine (**2**), and (−)-manthine (**5**), were first isolated in 1955 by Wildman and co-workers from various *Haemanthus* species (*Haemanthus montanus, Haemanthus coccineus, Haemanthus*

amarylloides, etc.) collected in South Africa.[3] Shortly thereafter, (−)-brunsvigine (**4**) was isolated from *Brunsvigia cooperi* Baker and *Brunsvigia radulosa* Herb.[4,5] (−)-Pancracine (**3**) was found as a minor alkaloid in *Rhodophiala bifida*, a plant which is indigenous to the United States, along with (−)-montanine as the major alkaloid.[6]

The structural assignments of the 5,11-methanomorphanthridine alkaloids were initially based on chemical degradations and interconversions.[5] In 1968, a spectroscopic study of (−)-pancracine (**3**) and some of its derivatives involving proton NMR and mass spectrometry confirmed that alkaloids **1**−**5**

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1997.

(1) For recent reviews, see: (a) Martin, S. F. The *Amaryllidaceae* Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1987; Vol. 30, p 252. (b) Lewis, J. R. *Nat. Prod. Rep.* **1993**, *10*, 291.

(2) For this classification system, see: Dalton, D. R. *The Alkaloids*; Marcel Dekker: New York, 1979; p 197.

(3) Wildman, W. C.; Kaufman, C. J. *J. Am. Chem. Soc.* **1955**, *77*, 1248.

(4) Dry, L. J.; Poynton, M. E.; Thompson, M. E.; Warren, F. L. *J. Chem. Soc.* **1958**, 4701.

(5) Inubushi, Y.; Fales, H. M.; Warnhoff, E. W.; Wildman, W. C. *J. Org. Chem.* **1960**, *25*, 2153.

(6) Wildman, W. C.; Brown, C. L. *J. Am. Chem. Soc.* **1968**, *90*, 6439.

indeed have the structures previously attributed to them.[6] The structure of (−)-brunsvigine (**4**) is firmly based on single crystal X-ray analysis of the *bis-p*-bromobenzoate derivative and its absolute configuration was determined by anomalous dispersion methodology.[7] In general, this group of alkaloids all possess a common bridged pentacyclic skeleton, varying only in the substitution (*i.e.*, methoxyl or hydroxyl) and stereochemistry at C-2 and C-3. Interestingly, a recent report has described the isolation of (+)-montabuphine (**6**), an alkaloid which is apparently in the enantiomeric series.[8,9]
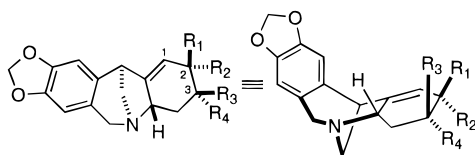
1 (-)-montanine R_1, R_4 = H; R_2 = OMe; R_3 = OH
2 (-)-coccinine R_1 = OMe; R_2, R_4 = H; R_3 = OH
3 (-)-pancracine R_1, R_4 = H; R_2, R_3 = OH
4 (-)-brunsvigine R_1, R_3 = H; R_2, R_4 = OH
5 (-)-manthine R_1, R_4 = H; R_2, R_3 = OMe
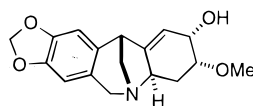
6 (+)-montabuphine

These *Amaryllidaceae* alkaloids display some limited biological activity. For example, (−)-coccinine (**2**) shows convulsive action in high doses [LD_{50} = 17.5 mg/kg (*in vivo*, dog)].[10] Weak hypotensive and convulsive activities are also reported for (−)-montanine (**1**) [LD_{50} = 42 mg/kg (*in vivo*, dog)]. It might be relevant that both physiologically active alkaloids have methyl ether functionality at the C-2 position.

Rather surprisingly, although there has been extensive synthetic effort in the area of *Amaryllidaceae* alkaloids,[1] construction of the 5,11-methanomorphanthridines has received little attention from synthetic organic chemists. However, two groups have recently described successful approaches to total synthesis of the montanine-type alkaloids. In 1991, Overman and Shim described total syntheses of both racemic and (−)-pancracine (**3**) utilizing a clever tandem aza-Cope rearrangement/Mannich cyclization as the pivotal step.[11] In a series of papers, Hoshino and co-workers reported two elegant strategies for total syntheses of these alkaloids, resulting in preparation of **1**-**4** in racemic form.[12]

Retrosynthetic Plan

In 1994 we described the discovery of a novel intramolecular imino ene reaction of an allenylsilane and its application to the

total synthesis of the marine alkaloid papuamine.[13a,b] In subsequent papers we further demonstrated the scope and generality of this type of concerted pericyclic process. In particular, we hoped to apply a stereoselective ene cyclization of the type previously used to generate cyclohexyl systems with adjacent *cis*-amino and -alkynyl moieties (eq 1) to the synthesis of the montanine group of *Amaryllidaceae* alkaloids.
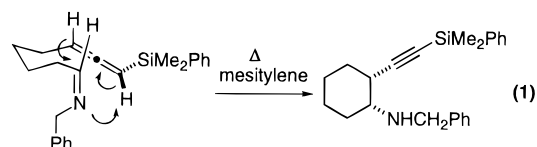
Our general strategy for enantioselective synthesis of the 5,11-methanomorphanthridine alkaloids is outlined in Scheme 1.[16] A key compound is the pentacyclic amine **7**, closely related to an intermediate of Hoshino in which the C-2/C-3 oxygens were not differentially protected, but which could be converted to racemic alkaloids **1**−**4**.[12] The intent was to install the requisite C-1/C-11a double bond at a late stage of the synthetic exercise. We anticipated preparing **7** from hydroxymethyl compound **8** *via* a transannular cyclization of the type used by the Hoshino group.[12] Intermediate **8** was to be generated by hydroboration from the least hindered face of exocyclic olefin **9**.

Unlike the two previous montanine alkaloid total syntheses[11,12] which both used a Pictet−Spengler-type cyclization to create the C-6/C-6a bond connection, we planned to construct tetracyclic intermediate **9** by an intramolecular Heck cyclization of tricyclic bromoalkene **10**, derived from alkyne **11**, generating the C-10a/C-11 bond. Although the use of an intramolecular Heck cyclization to construct a seven-membered ring was precedented,[17] a comparable nitrogen-tethered case had not yet been reported when our synthesis was initiated.[18] We intended to construct alkyne **11** utilizing our intramolecular pericyclic imino ene chemistry of enantiomerically pure allenylsilane imine **12** (*cf.* eq 1) which would be generated by condensation of scalemic allenylsilane aldehyde **13** and a substituted piperonylamine derivative (**14**).

(7) Laing, M.; Clark, R. C. *Tetrahedron Lett.* **1974**, 583.

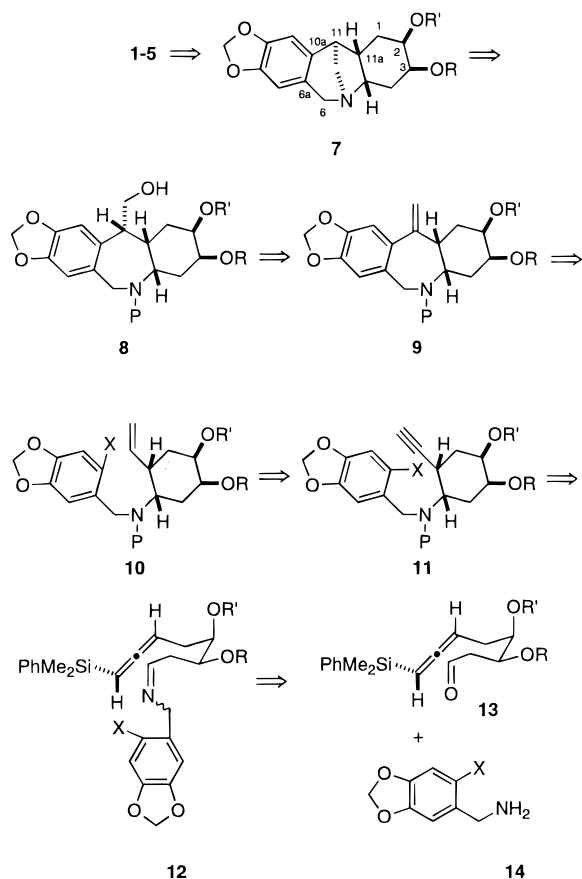(8) Viladomat, F.; Bastida, J.; Codina, C.; Campbell, W. E.; Mathee, S. *Phytochemistry* **1995**, *40*, 307.

(9) The biosynthesis of these alkaloids has been studied: (a) Fuganti, C.; Ghiringhelli, D.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1973**, 430. (b) Wildman, W. C.; Olesen, B. *Ibid.* **1976**, 551.

(10) Southon, I. W.; Buckingham, J. *Dictionary of the Alkaloids*; Chapman & Hall: New York, 1989; pp 229, 735.
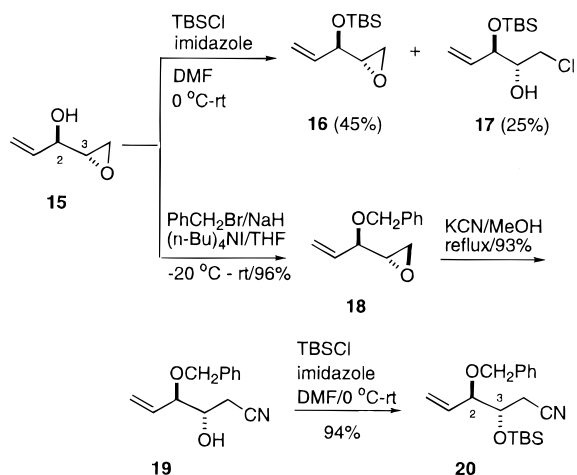
(11) (a) Overman, L. E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005. (b) Overman, L. E.; Shim, J. *J. Org. Chem.* **1993**, *58*, 4662.

(12) (a) Ishizaki, M.; Hoshino, O.; Iitaka Y. *J. Org. Chem.* **1992**, *57*, 7285. (b) Ishizaki, M.; Kurihara, K.; Tanazawa, E.; Hoshino, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 101 and references cited therein. See also: Sanchez, I. H.; Larraza, M. I.; Rojas, I.; Brena, F. K.; Flores, H. J. *Heterocycles* **1985**, 23, 3033.

(13) (a) Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1994**, *116*, 9789. (b) Borzilleri, R. M.; Weinreb, S. M.; Parvez, M. *J. Am. Chem. Soc.* **1995**, *117*, 10905. (c) Jin, J.; Smith, D. T.; Weinreb, S. M. *J. Org. Chem.* **1995**, *60*, 5366. (d) Weinreb, S. M. *J. Heterocycl. Chem.* **1996**, *33*, 1429. (e) Weinreb, S. M.; Smith, D. T.; Jin, J. *Synthesis*, in press. For a review of imino ene reactions, see: Borzilleri, R. M.; Weinreb, S. M. *Synthesis* **1995**, 347.

(14) For intermolecular reactions of allenylsilanes with electrophiles *via* a non-pericyclic process, see: (a) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925. (b) Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870. (c) Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1985**, *107*, 7233. (d) Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407. (e) Becker, D. A.; Danheiser, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 389.

(15) For intramolecular metalloene reactions of allenylsilanes, see: (a) Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J. F. *J. Org. Chem.* **1995**, *60*, 863. (b) Meyer, C.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1996**, *37*, 857. (c) Lorthiois, E.; Marek, I.; Normant, J. F. *Tetrahedron Lett.* **1997**, *38*, 89.

(16) (a) A preliminary account of portions of this work has appeared: Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 2050. (b) Jin, J. Ph.D. Thesis, The Pennsylvania State University, University Park, PA, 1997.

(17) (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130.

(18) Cf. (a) Mohanakrishnan, A. K.; Srinivasan, P. C. *Tetrahedron Lett.* **1996**, *37*, 2659. (b) Cornec, O.; Joseph, B.; Merour, J. *Tetrahedron Lett.* **1995**, *36*, 8587.

Scheme 1

Scheme 2

Results and Discussion

Our synthesis began with known scalemic epoxy alcohol **15**[19] which was prepared *via* Sharpless asymmetric epoxidation of commercially available divinyl carbinol (Scheme 2). The epoxy alcohol **15**, which could be consistently prepared in 65% yield on a 25 g scale, showed an ee of >97% as analyzed by ^{19}F NMR of the corresponding Mosher ester. When epoxy alcohol **15** was subjected to silylation conditions,[20] a mixture of epoxy silyl ether **16** and ring-opened chloro alcohol **17** was produced. Thus, at this point we chose instead to use a benzyl ether

(19) (a) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525. (b) Babine, R. E. *Tetrahedron Lett.* **1986**, *27*, 5791. Distillation of epoxide **15** is recommended. It is necessary, however, to remove excess peroxide by chromatography prior to distillation.

(20) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1988**, *53*, 5023.

Scheme 3
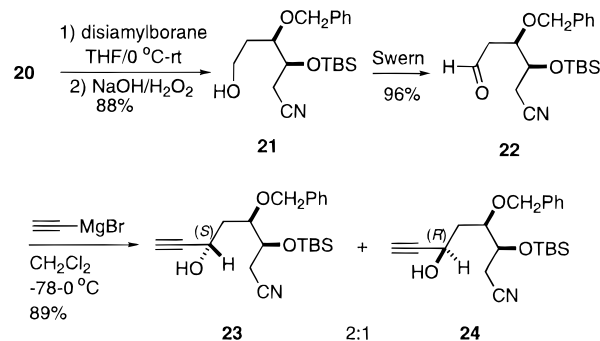
protecting group for the C-2 alcohol (montanine numbering) and found that **15** could be converted cleanly to epoxy ether **18**. Epoxy benzyl ether **18** was opened regioselectively with cyanide ion[21] to produce nitrile alcohol **19** in 93% yield. Alcohol **19** was subsequently silylated to afford intermediate ether **20** (94% yield)[20] having the C-2 and C-3 oxygens differentially protected.

To continue the synthesis, alkene **20** was hydroborated with disiamylborane[22] to regioselectively generate primary alcohol **21**, which then was cleanly oxidized under Swern conditions to yield aldehyde **22** (Scheme 3). Addition of ethynylmagnesium bromide to aldehyde **22** was not particularly stereoselective, affording a chromatographically separable 2/1 mixture of (*S*)-propargyl alcohol **23** and (*R*)-alcohol **24**, respectively.

In order to establish the configuration of alcohols **23** and **24**, as well as to try to improve the stereoselectivity in this phase of the synthesis, we investigated the reactions shown in Scheme 4. Using Jones reagent, the mixture of propargyl alcohols **23**/**24** could be oxidized to acetylenic ketone **25** (82% yield). Attempted asymmetric reduction of ketone **25** with (*S*)-Alpine borane failed, in all attempts giving a complex product mixture.[23] However, enantioselective reduction of ketone **25** using LiAlH4/ Darvon alcohol complex[24] provided a 5.3/1 mixture of **24** and **23** in 84% yield. The configuration of the major isomer **24** was tentatively assigned as (*R*) on the basis of the well-known propensity of Darvon alcohol to generate this configuration in LiAlH4 reductions of alkynyl ketones.[24] Similarly, reduction of ketone **25** with LiAlH4/*ent*-Darvon alcohol[25] provided a 1/4.8 mixture of the alcohols **24**/**23**. Although the selectivity here is somewhat better than in the direct preparation of these propargyl alcohols from aldehyde **22**, the two extra steps involved do not make this sequence an attractive alternative, particularly since it was found that both **23** and **24** can be efficiently used for the total synthesis (*vide infra*).

Thus, (*S*)-propargyl alcohol **23** could be directly acetylated to give the desired (*S*)-acetate **26** in the presence of acetic anhydride, triethylamine, and a catalytic amount of DMAP in 98% yield (Scheme 5). The (*R*)-alcohol **24** can also be converted to the same (*S*)-acetate **26** by a Mitsunobu inversion procedure[26] using diethyl azodicarboxylate, triphenylphosphine, acetic acid, and pyridine (86% yield). Thus, we were able to

(21) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687.

(22) (a) Kabalka, G. W.; Hedgecock, H. C., Jr. *J. Org. Chem.* **1975**, *40*, 1776. (b) Brown, H. C.; Kulkarni, S. U.; Rao, C. G. *Synthesis* **1980**, 151.
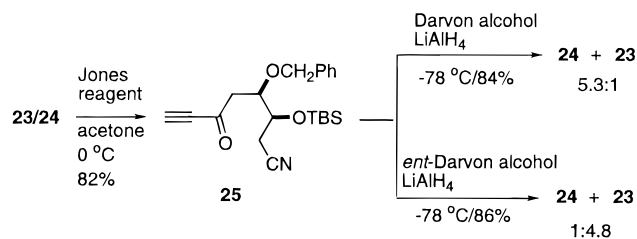
(23) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano A. *J. Am. Chem. Soc.* **1980**, *102*, 867.

(24) (a) Brinkmeyer R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339. (b) Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1980**, *45*, 583.
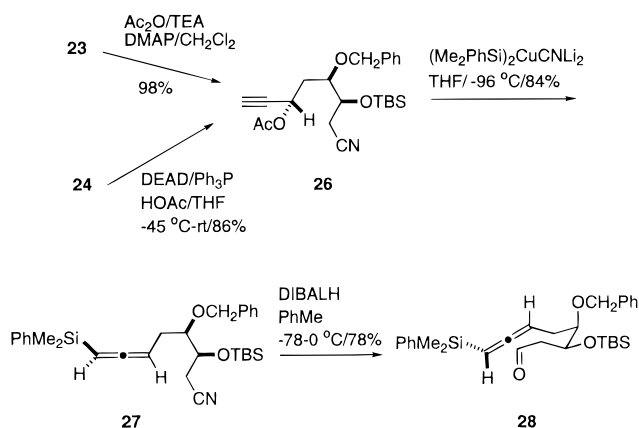
(25) We thank Professor Larry Overman for a sample of *ent*-Darvon alcohol.

(26) Wovkulich, P. M.; Shankaran, K.; Kiegiel, J.; Uskokovic, M. R. *J. Org. Chem.* **1993**, *58*, 832.
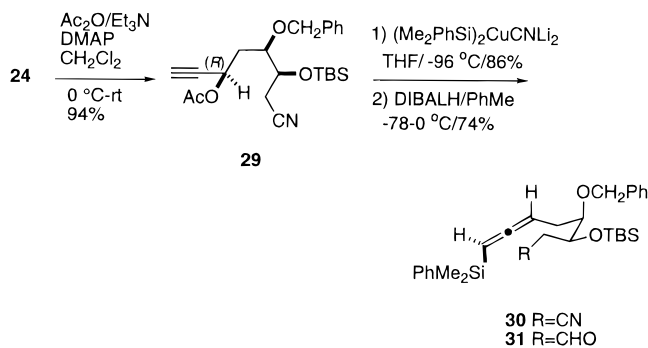
Scheme 4

Scheme 5

Scheme 6

prepare the requisite (*S*)-propargyl acetate **26** efficiently, and we next turned our attention to stereospecific transformation of this propargyl acetate to the (*R*)-allenylsilane needed for the synthesis.

In 1984, Fleming and Terrett reported that silacupration of propargyl acetates stereospecifically affords allenylsilanes via an *anti*-S_N2' process.[27] Fleming's methodology was applied to our system, and thus silacupration of (*S*)-propargyl acetate **26** afforded (*R*)-allenylsilane **27** in 84% yield. This key transformation allowed us to stereospecifically transfer the (*S*)-propargyl acetate configuration of **26** to the desired (*R*)-allene configuration of **27**, which is crucial to our allenylsilane imino ene strategy (*vide infra*). Reduction of nitrile **27** with diisobutylaluminum hydride (DIBALH) produced allenylsilane aldehyde **28** (78% yield). Using the chemistry described here, scalemic allenylsilane aldehyde **28** was prepared efficiently in nine steps and 38% overall yield from chiral epoxy alcohol **15**.

In order to further test the stereospecificity of the silacupration step, diastereomeric propargyl acetate **29** was prepared from (*R*)-alcohol **24** (Scheme 6). Addition of the Fleming silyl cuprate to **29** cleanly yielded (*S*)-allenylsilane nitrile **30** in high yield. DIBALH reduction of **30** then afforded the diastereomeric allenylsilane aldehyde **31**.

(27) Fleming, I.; Terrett, N. K. *J. Organomet. Chem.* **1984**, *264*, 99.

Scheme 7
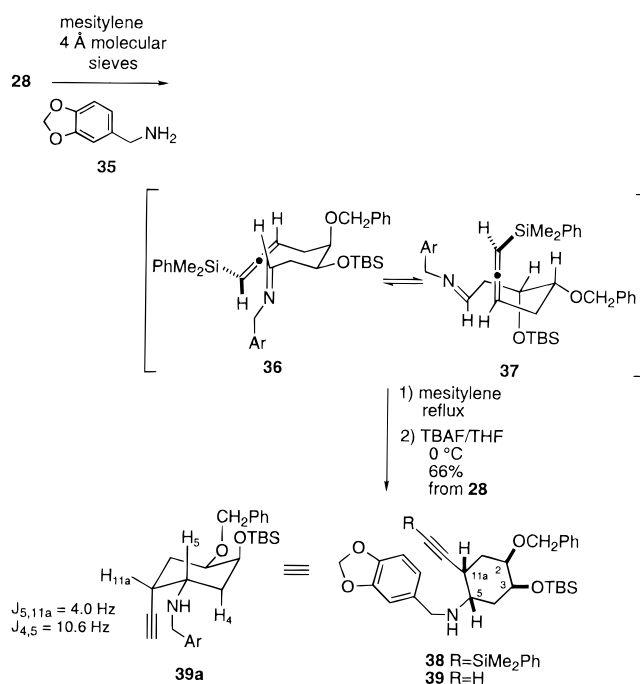
We next investigated synthesis of (6-bromopiperonyl)amine (**33**). This compound was very easily prepared in 64% yield by reductive amination[28] of known 6-bromopiperonal (**32**) (eq 2), which was synthesized by bromination of commercially
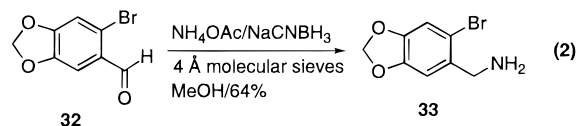
available piperonal.[29] As delineated in our retrosynthetic plan in Scheme 1, an allenylsilane imine (**12**) was to be generated by direct condensation of an allenylsilane aldehyde **13** and a 6-substituted piperonylamine (**14**). However, upon treatment of allenylsilane aldehyde **28** with amine **33** in the presence of 4 Å molecular sieves in benzene-d_6 at room temperature, ^{1}H NMR showed that no allenylsilane imine was formed and only starting materials remained. When this reaction mixture was heated at 50 °C for 12 h, β-elimination product **34** was formed rather than the desired allenylsilane imine (eq 3). The same elimination product was observed when zinc chloride was used as a catalyst at room temperature.
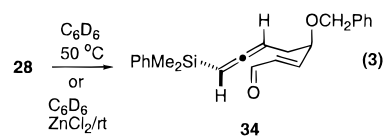
One possible explanation for this unexpected result is that the steric hindrance produced by the *o*-bromine atom in amine **33** slows formation of the desired imine. Therefore, to test this possibility, we decided to employ the system lacking this *ortho* substituent, with the hope of introducing it at a later stage. In fact, an allenylsilane imine could be successfully generated upon treatment of allenylsilane aldehyde **28** with commercially available piperonylamine (**35**) (Scheme 7). When this imine was refluxed in mesitylene for 2 h, we were pleased to find

(28) Ryckman, D. M.; Stevens, R. V. *J. Org. Chem.* **1987**, *52*, 4274.
(29) (a) Jung, M. E.; Lam, P. Y.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087. (b) Khanapure, S. P.; Biehl, E. R. *J. Org. Chem.* **1990**, *55*, 1471.

Scheme 8

Scheme 9

Scheme 10
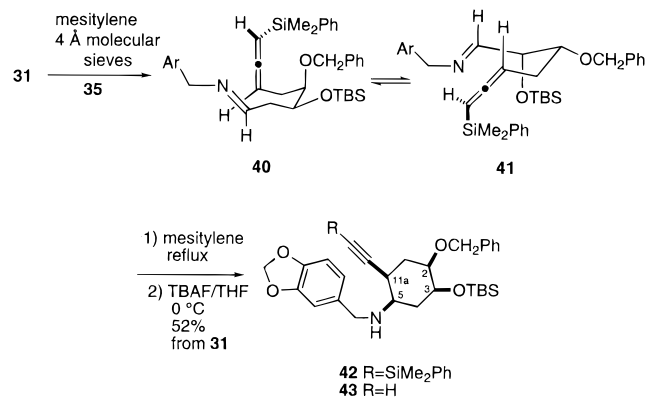
that *cis*-silylacetylene amine **38** was produced as a single stereoisomeric cycloadduct. This silyl acetylene was immediately desilylated to afford *cis*-amino alkyne **39** in 66% yield from aldehyde **28**. We believe that product **38** is generated by a concerted pericyclic imino ene process involving imine conformations **36** and/or **37** (*cf.* eq 1). Inspection of models indicates that both conformations are stereoelectronically capable of undergoing concerted ene reactions.[13] However, it is important to note that both conformations lead to the same cycloadduct **38**.

^{1}H NMR indicated that the amino and acetylene groups of **39** have the anticipated *cis* relationship, with a vicinal coupling constant between H_5 and H_{11a} (montanine numbering) of 4.0 Hz (*cf.* **39a**). The coupling constant between H_4 and H_5 is 10.6 Hz, which indicates that these two hydrogens are *trans* diaxial. Although the complete stereochemistry of cycloadduct **39** was not unambiguously established at this time, we eventually were able to convert the brominated analog of **39** to the natural products, thereby confirming the stereochemical assignments (*vide infra*).

In order to further explore the stereospecificity of this imino ene process, we performed the ene cyclization using diastereomeric allenylsilane aldehyde **31**. The allenylsilane imine generated from aldehyde **31** and piperonylamine (**35**) cyclized in refluxing mesitylene for 2 h to give a single product (**42**), which was then desilylated to *cis*-amino alkyne **43** (52% yield over three steps) (Scheme 8). We believe that cycloadduct **42** is generated by a concerted pericyclic imino ene process involving imine conformations **40** and/or **41**. Again, as with **36** and **37**, both of these conformations are capable of undergoing concerted ene reactions, and both lead to the identical cycloadduct **42**. One important aspect of these allenylsilane imino ene reactions which should be reiterated is that the allene absolute configurations in imines **36/37** and **40/41** control the relative stereochemistry created between the pair of substituents at C-2/C-3 *vs* the acetylene and amino groups at C-5/C-11a. As shown in Schemes 7 and 8, the (*R*)-allene configuration of allenylsilane imine **36/37** results in amino alkyne **38** which has these two sets of groups *trans* to each other, and the (*S*)-allene configuration of imine **40/41** results in amino alkyne **42** where these two pairs have a *cis* relationship.

At this juncture we turned to an investigation of the introduction of a bromine at C-6 of the aromatic ring of cyclization product **39** or a derivative.[16b] Despite a number of attempts to effect bromination of various *N*-protected analogs of **39**, as well as with the olefin derived from Lindlar hydrogenation of the alkyne functionality, under no circumstances could we produce a halogenated substrate needed for the projected Heck cyclization. We therefore returned to the
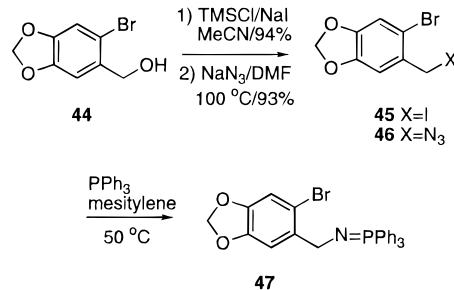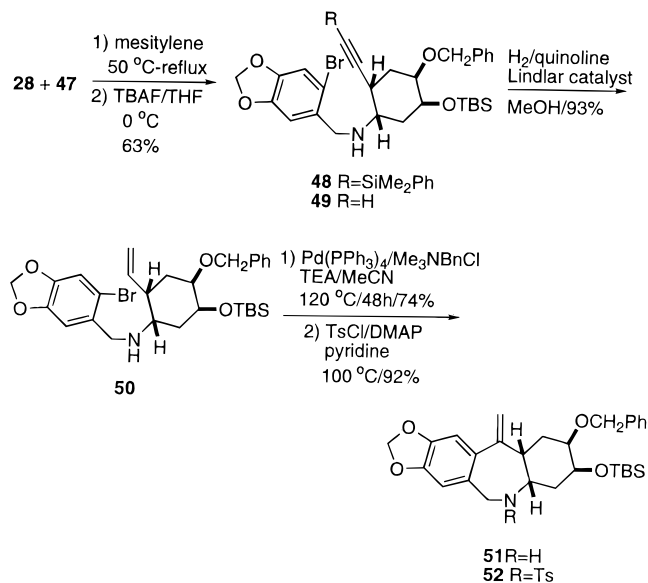
original concept of utilizing a piperonylamine analog already bearing the required C-6 bromine atom.

It is known that aldehydes and ketones can be condensed with iminophosphoranes to generate imines under mild conditions.[30] We thus generated the appropriate iminophosphorane as shown in Scheme 9. Known piperonyl alcohol **44**[29b] was converted to iodide **45** and then to azide **46** in high overall yield. Treatment of this azide with triphenylphosphine produced the iminophosphorane **47**, which without isolation was used for the next step. Iminophosphorane **47** and allenylsilane aldehyde **28** were heated in mesitylene at 50 °C for 12 h, and then at reflux for an additional 2 h, to afford a single ene cyclization product (**48**), which was immediately desilylated to give amino acetylene **49** (63% based upon aldehyde **28**) (Scheme 10). The structure of this cycloadduct was eventually confirmed by correlation with the natural alkaloids (*vide infra*).

It was felt that it would be best to protect the nitrogen of **49** before continuing the synthetic route. However, the amino group in this compound appears to be very hindered, and even under forcing conditions formation of the corresponding *N*-tosyl derivative could not be driven to completion.[16b] Alternatively, we decided to continue with the free amine, and a Lindlar hydrogenation was used to convert alkyne **49** to terminal olefin **50** (93%).[31] We were pleased to find that exposure of bromo olefin **50** to Heck cyclization conditions led to seven-membered

(30) See for example: Lambert, P.; Vaultier, M.; Carrie, R. *J. Chem. Soc., Chem. Commun.* **1982**, 1224.

(31) Amino acetylene **49** could be converted to the *N*-acetyl derivative and reduced to the olefin. This intermediate underwent Heck cyclization at 110 °C in 92% yield to the acetamide of **51**. However, the acetyl group was found to be incompatible with the hydroboration step, and thus this sequence was not pursued.[16b]

Scheme 11
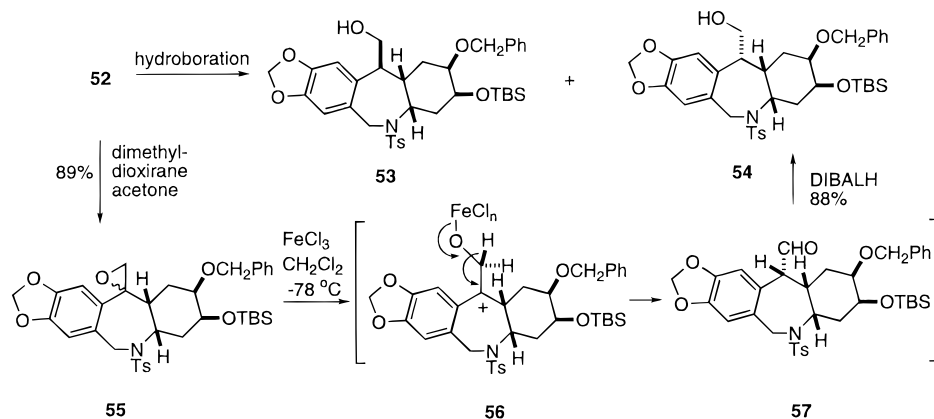
exocyclic alkene **51** in good yield. This compound could then be readily protected as its *N*-tosyl derivative **52**.

With key intermediate **52** in hand, we next turned to studies on the hydroboration of the *exo*-methylene group. Disappointingly, hydroboration of **52** with 1-pyrrolylborane or borane–THF complex led to 1/1 mixtures of stereoisomeric hydroxymethyl compounds **53** and **54** (87% and 67% yields, respectively) (Scheme 11).[16b] The olefinic substrate was found to be unreactive toward disiamylborane and 9-BBN, and with Br$_2$BH–DMS complex, only decomposition occurred.

A search of the literature revealed a possible alternative to the hydroboration of the olefinic moiety of **52**. Danishefsky and McClure have reported[32] an example of an exocyclic alkene being stereoselectively transformed into a hydroxymethyl group *via* a Lewis acid promoted rearrangement of the derived epoxide. Although the olefin here was embedded in a very different ring system from ours, there were enough similarities to warrant investigating a similar sequence. Therefore, an attempt was first made to epoxidize alkene **52** with *m*-chloroperoxybenzoic acid, but only a complex product mixture was produced. However, dimethyldioxirane[33] produced a 2/1 mixture of epoxide diastereoisomers **55** (Scheme 11). This epoxide mixture was unstable to silica gel chromatography and was therefore carried on to the next step without separation. Ring opening of the mixture of epoxide diastereoisomers **55** induced by ferric chloride afforded a single rearrangement product aldehyde (**57**), which was immediately reduced to the desired alcohol diastereoisomer **54**. We believe that the epoxides **55** are opened by the Lewis acid to first generate benzylic carbocation **56**, which then undergoes a 1,2-hydrogen shift from the least hindered β-face to afford the kinetic α-aldehyde **57**. Immediate reduction of aldehyde **57** to alcohol **54** without workup proved crucial, since it was observed that this aldehyde epimerized to the thermodynamically more stable undesired β-epimer on silica gel chromatography. The stereochemistry of alcohol **54** was tentatively assigned as shown on the basis of mechanistic grounds, but this assumption was soon confirmed by subsequent correlation with known compounds (*vide infra*).

After the successful transformation of alkene **52** to the desired hydroxymethyl compound **54**, we turned to construction of the bridged ring system of the montanine alkaloids. Thus, toluenesulfonamide **54** was deprotected by treatment with sodium naphthalenide[34] at −78 °C to generate secondary amine **58** in 96% yield (Scheme 12). Cyclodehydration of amine **58** under

Scheme 12
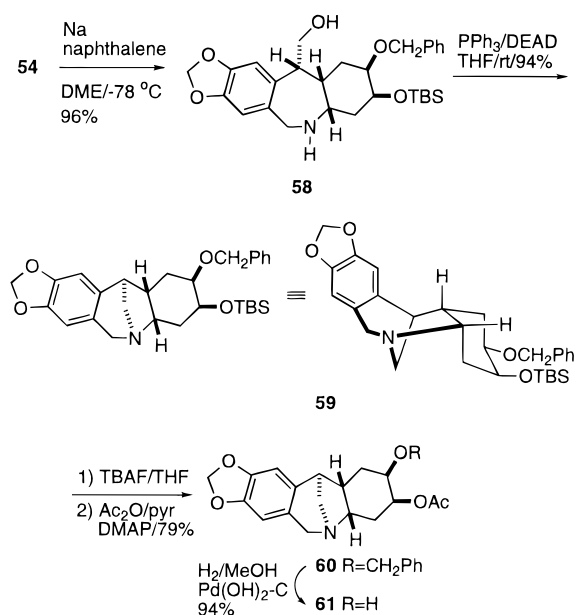
Mitsunobu conditions[35] afforded the bridged pentacyclic intermediate **59** (94%). In order to assure that the structure and stereochemistry assigned to **59** were correct, this intermediate was desilylated and acetylated to afford the known acetate **60**.[12] The ^{1}H NMR (500 MHz) spectrum of our enantiomerically pure acetate **60** was identical to that of a racemic sample provided by Professor Hoshino.[36]

At this stage, difficulties arose in what was anticipated to be a straightforward transformation, *i.e.,* hydrogenolysis of the *O*-benzyl group. Thus, hydrogenation of benzyl ether **59** using palladium on activated carbon in methanol gave no reaction. Using the more reactive Pearlman's catalyst (Pd(OH)$_2$ on carbon) at room temperature, the desired silyl ether alcohol was produced in only about 5% yield along with unreacted benzyl ether. Elevating the temperature of the hydrogenolysis led to a mixture of the desired silyl ether alcohol (21%) and the diol (71%) resulting from loss of the TBS group. Other debenzylation methods such as Birch reduction were also tried unsuccessfully. One possible explanation for the problems in the catalytic hydrogenation is that the steric crowding due to the adjacent *cis-O*-benzyl and bulky OTBS groups in **59** slows the process. In fact, the less crowded acetate benzyl ether **60** could

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(33) (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

(34) McIntosh, J. M.; Matassa, L. C. *J. Org. Chem.* **1988**, *53*, 4452.

(35) (a) Tsunoda, T.; Ozaki, F.; Shirakata, N.; Tamaoka, Y.; Yamamoto, H.; Ito, S. *Tetrahedron Lett.* **1996**, *37*, 2463. (b) Goldstein, D. M.; Wipf, P. *Tetrahedron Lett.* **1996**, *37*, 739.

(36) We are grateful to Professor O. Hoshino for copies of the NMR spectra of intermediate **60**, as well as racemic montanine and coccinine.

Scheme 13

62 R=Ts
63 R=H

64

Scheme 14

65

66

67 R=TBS
68 R=H

(-)-pancracine (**3**)

Scheme 15

69

70

71

(-)-coccinine (**2**)

+

(-)-montanine (**1**)

O-TBS) suffered from low yields. In the best case, the enone could be generated in only 26% yield by oxidation of the saturated ketone with DDQ. It was therefore necessary for us to find a suitable alternative method for enone formation from saturated ketone **65**.

We expected that regioselective conversion of ketone **65** to a kinetic silyl enol ether, followed by oxidation, should be feasible. Therefore, ketone **65** was first cleanly converted to the silyl enol ether **66** following the procedure developed by Corey and Gross.[40] Although oxidation of silyl enol ether **66** to α,β-unsaturated ketone **67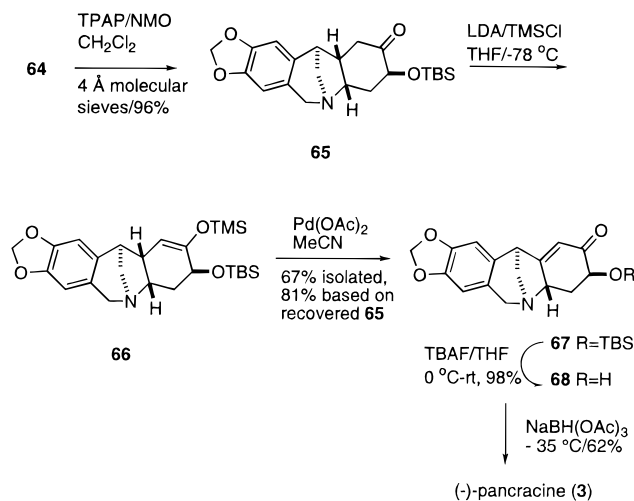** with DDQ[41] was unsuccessful, we were pleased to find that **66** was converted to the desired enone by the Saegusa method (Pd(OAc)$_2$ in acetonitrile)[42] in 67% isolated yield (81% yield based on recovered starting ketone **65**) for the two steps.

Conversion of enone **67** to the 5,11-methanomorphanthridine alkaloids **1**−**3** proved to be straightforward. Desilylation of **67** with tetrabutylammonium fluoride produced the known α-hydroxy enone **68**[11] in 98% yield. ^{1}H NMR, ^{13}C NMR, and low- and high-resolution mass spectra of our synthetic **68** were identical to those previously reported by Overman and Shim.[11,43] The optical rotation [[α]$^{23}_{546}$ = −55.9° (*c* = 0.272, MeOH), [α]$^{23}_{D}$ = −50.7° (*c* = 0.272, MeOH)] of our synthetic material was in good agreement with that reported [[α]$^{25}_{546}$ = −47.7° (*c* = 0.10, MeOH)].[11] Overman and Shim have found that enantiomerically pure **68** could be reduced to (−)-pancracine (**3**) with sodium triacetoxyborohydride in 62% yield.[11]

We could also prepare (−)-coccinine (**2**) from **68** by the chemistry shown in Scheme 15. Dimethyl ketal **69** was synthesized in 91% yield by treatment of enone **68** with *p*-toluenesulfonic acid and trimethyl orthoformate in methanol. When **69** was treated with DIBALH in toluene at room temperature,[12] it underwent both ketone reduction and cleavage of the TBS group to afford (−)-coccinine (**2**) in 81% yield. (−)-Montanine (**1**) was also produced in this reaction as a minor product (8%). We believe that the large OTBS group in intermediate **70** shields the β face of the molecule, therefore leading to (−)-coccinine (**2**) as the major diastereoisomer of the reduction. The formation of a small amount of (−)-montanine (**1**) is possibly due to some silyl group cleavage prior to hydride reduction of the ketal (*vide infra*). The ^{1}H NMR
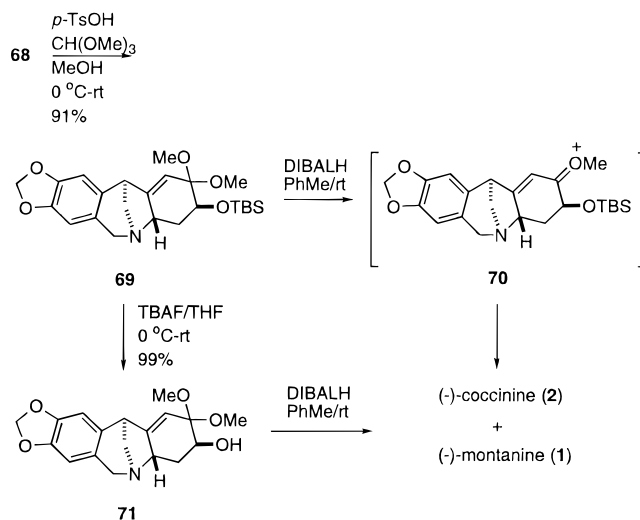
be hydrogenated using Pearlman's catalyst in methanol at room temperature to produce the corresponding alcohol acetate **61** in 94% yield. Although alcohol **61** might potentially be used in the synthesis, the extra deprotection and reprotection steps required did not make this sequence very attractive. Since it also seemed possible that the basic nitrogen in **59** was also contributing to the slow rate of benzyl group hydrogenolysis,[37] it was decided to return to *N*-protected tetracyclic sulfonamide **54**.

Indeed catalytic hydrogenation of *N*-tosyl compound **54** using Pd/C in methanol at room temperature produced the desired alcohol **62** in 97% yield (Scheme 13). Deprotection of toluenesulfonamide **62** then afforded amino diol **63** (96% yield). Cyclodehydration of **63** under standard Mitsunobu conditions did generate the desired bridged intermediate **64**, but in only 42% yield. We were pleased to find, however, that treatment of **63** with imidazole, triphenylphosphine, and iodine[38] at 0 °C for 10 min produced **64** in 82% overall yield for the three steps from **54**.

With pentacyclic alcohol **64** now in hand, the stage was set for introduction of the C-1/C-11a double bond and effecting the final functional group tranformations to produce the natural products. Thus, alcohol **64** was cleanly oxidized to ketone **65** with *N*-methylmorpholine *N*-oxide and tetrapropylammonium perruthenate[39] in the presence of 4 Å molecular sieves (Scheme 14). In Hoshino's synthesis,[12] all attempts to form an enone from a ketone very closely related to **65** (*O*-benzyl rather than

(37) *Cf.* Czech, B. P.; Bartsch, R. A. *J. Org. Chem.* **1984**, *49*, 4076.
(38) (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978. (b) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187.
(39) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(40) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.
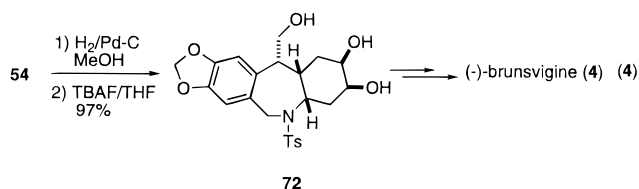(41) Fleming, I.; Paterson, I. *Synthesis* **1979**, 736.
(42) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(43) We thank Professor Larry Overman for copies of the ^{1}H and ^{13}C NMR spectra of intermediate **68** and a sample of (−)-pancracine.

spectrum of our synthetic (−)-coccinine (**2**) was identical to that of Hoshino's racemic material.[12,36] The optical rotation [[α]$^{25}_D$ = −161° (c = 0.101, EtOH)] of our synthetic **2** was consistent with that reported for natural (−)-coccinine [[α]$^{27}_D$ = −188.8° (c = 1.9, EtOH)].[3] The ^{13}C NMR spectrum and low- and high-resolution mass spectra of our synthetic **2** also confirmed the structural assignment.

Interestingly, when α-hydroxy ketal **71**, generated from desilylation of ketal **69**, was treated with DIBALH in toluene (Scheme 15), (−)-montanine (**1**) (41% isolated, 47% based on recovered starting material) along with (−)-coccinine (**2**) (39% isolated, 44% based on recovered starting material) was formed. Therefore, without the bulky silyl ether group α to the ketal, the diastereoselectivity of the DIBALH reduction drops sharply. The ^{1}H NMR spectrum of our synthetic (−)-montanine (**1**) was identical to that obtained by Hoshino and co-workers.[12,36] The optical rotation [[α]$^{25}_D$ = −83° (c = 0.06, CHCl$_3$)] of our synthetic (−)-**1** corresponded with that reported for natural (−)-montanine [[α]$^{26}_D$ = −87.6° (c = 0.6, CHCl$_3$)].[3] The identity of our synthetic (−)-**1** was also confirmed by its ^{13}C NMR spectrum, HMBC NMR, and low- and high-resolution mass spectra.

In addition, alcohol **54** was debenzylated and desilylated to the known triol **72**[12] in 97% yield (eq 4). Hoshino and co-

workers have previously converted triol **72** to racemic brunsvigine (**4**) in several steps.[12] Therefore, we have also completed a formal enantioselective total synthesis of (−)-brunsvigine (**4**).

Conclusion

We have developed a new type of thermal intramolecular concerted ene reaction of allenylsilane imines which has been successfully used in total syntheses of the 5,11-methanomorphanthridine *Amaryllidaceae* alkaloids (−)-montanine (**1**), (−)-coccinine (**2**), and (−)-pancracine (**3**). These complex pentacyclic natural products were synthesized from readily available enantiomerically pure epoxy alcohol **15** in about 25 steps. The key features of the synthetic strategy include (1) a stereospecific thermal imino ene cyclization of allenylsilane imine derived from aldehyde **28** to afford key intermediate amino alkyne **48**, (2) an intramolecular Heck reaction of bromo alkene **50** to produce a seven-membered ring containing tetracycle **51**, and (3) stereospecific formation of hydroxymethyl compound **54** *via* epoxidation of the alkene **52**, followed by a Lewis acid catalyzed epoxide ring opening/rearrangement. We plan to use this and related methodology in approaches to other natural product targets.

Experimental Section

General Methods. Low-resolution mass spectra (MS) were obtained at 50−70 eV by electron impact (EI). Chemical ionization mass spectra (CIMS) were obtained using isobutane as a carrier gas. Optical rotations were obtained at ambient temperature. Flash chromatography was performed using EM Science silica gel 60. Analytical and preparative TLC were performed on EM silica gel 60 PF$_{254}$. HPLC was done using a Beckman Ultrasphere SI 5 mm, 10.0 mm × 25 cm column. All chemicals were purchased from Aldrich Chemical Co. unless otherwise noted. THF, benzene, and ether were dried over and distilled from sodium/benzophenone ketyl. CH$_2$Cl$_2$, toluene, NEt$_3$, DMF, pyridine,

and mesitylene were distilled from CaH$_2$, and methanol was distilled from magnesium turnings.

Preparation of Benzyl Ether Epoxide 18. To a solution of 5.00 g (50.0 mmol) of scalemic epoxide **15** (>97% ee),[19] 7.1 mL (60.0 mmol) of benzyl bromide, and 1.85 g (5.00 mmol) of tetrabutylammonium iodide in 125 mL of dry THF at −20 °C under argon was added 1.39 g (55.0 mmol, 95%) of NaH. The mixture was allowed to warm to room temperature (rt) over 2 h. After the mixture was stirred at rt for another 2 h, 80 mL of saturated aqueous NH$_4$Cl solution was added at 0 °C. The mixture was stirred for 10 min and extracted three times with 60 mL portions of ether. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1/19), to produce benzyl ether **18** as a clear oil (9.12 g, 96%): [α]$^{20}_D$ = −12.2° (c = 0.97, benzene); ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.69 (dd, J = 2.6, 5.3 Hz, 1 H), 2.78 (dd, J = 4.0, 5.3 Hz, 1 H), 3.08−3.12 (m, 1 H), 3.82−3.87 (m, 1 H), 4.46 (d, J = 12.1 Hz, 1 H), 4.64 (d, J = 12.1 Hz, 1 H), 5.36−5.38 (m, 1 H), 5.40−5.42 (m, 1 H), 5.86 (ddd, J = 7.3, 10.9, 16.7 Hz, 1 H), 7.27 −7.37 (m, 5 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 44.5, 53.0, 70.4, 79.1, 119.3, 127.4, 127.5 (2 C), 128.2 (2 C), 134.3, 138.0; IR (film) 3080−2940, 2930−2780 cm^{-1}; CIMS m/z (relative intensity) 190 (M$^+$ + H, 0.5), 189 (M$^+$, 0.7), 173 (1), 107 (11), 91 (100); HRMS calcd for C$_{12}$H$_{14}$O$_2$ 190.0994, found 190.1001.

Preparation of Nitrile 19. To a solution of 1.80 g (9.50 mmol) of epoxide **18** in 40 mL of MeOH under argon was added 0.93 g (14.3 mmol) of KCN. The mixture was gently refluxed at 70 °C for 2.5 h. After the mixture was cooled to rt, 40 mL of water was added. The aqueous layer was extracted three times with 80 mL portions of ether. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1/2), to produce nitrile **19** as a yellow oil (1.92 g, 93%): [α]$^{20}_D$ = −57.7° (c = 1.03, benzene); ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.56 (d, J = 5.8 Hz, 2 H), 3.35 (br d, J = 5.3 Hz, 1 H), 3.79−3.92 (m, 2 H), 4.39 (d, J = 11.5 Hz, 1 H), 4.64 (d, J = 11.5 Hz, 1 H), 5.40−5.50 (m, 2 H), 5.79 (ddd, J = 7.5, 10.5, 17.1 Hz, 1 H), 7.14−7.43 (m, 5 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 21.4, 68.8, 70.4, 81.8, 117.7, 121.2, 127.58 (2 C), 127.64, 128.2 (2 C), 133.7, 137.3; IR (film) 3600−3200, 2750 cm^{-1}; CIMS m/z (relative intensity) 218 (M$^+$ + H, 78), 91 (100); HRMS calcd for C$_{13}$H$_{15}$NO$_2$ 217.1103, found 217.1117.

Preparation of Silyl Ether 20. To a solution of 5.20 g (24.0 mmol) of alcohol **19** in 120 mL of DMF at 0 °C under argon was added 6.53 g (96.0 mmol) of imidazole, followed by 7.22 g (48.0 mmol) of *tert*-butyldimethylsilyl chloride. After the mixture was stirred for 16 h at rt, 100 mL of water was added. The mixture was extracted three times with 100 mL portions of ether. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (3/97), to produce silyl ether **20** as a clear oil (7.47 g, 94%): [α]$^{20}_D$ = −25.7° (c = 1.21, benzene); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.12 (s, 3 H), 0.18 (s, 3 H), 0.96 (s, 9 H), 2.53 (dd, J = 4.3, 16.8 Hz, 1 H), 2.74 (dd, J = 5.6, 16.8 Hz, 1 H), 3.83−3.87 (m, 1 H), 3.93−3.97 (m, 1 H), 4.45 (d, J = 11.5 Hz, 1 H), 4.66 (d, J = 11.5 Hz, 1 H), 5.39−5.47 (m, 2 H), 5.79 (ddd, J = 7.2, 11.0, 18.1 Hz, 1 H), 7.27−7.39 (m, 5 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ −4.9, −4.5, 17.8, 22.8, 25.6 (3 C), 70.6, 70.7, 82.3, 117.6, 120.3, 127.6, 127.7 (2 C), 128.2 (2 C), 134.8, 137.7; IR (film) 3100−2840, 2250 cm^{-1}; CIMS m/z (relative intensity) 332 (M$^+$ + H, 33), 91 (100); HRMS calcd for C$_{15}$H$_{20}$NO$_2$Si (M$^+$ − t-Bu) 274.1263, found 274.1254.

Preparation of Alcohol 21. To 44.2 mL (44.2 mmol) of borane−THF complex (1.0 M solution in THF) under argon at 0 °C was added dropwise 9.84 mL (88.4 mmol) of 2-methyl-2-butene. After being stirred for 1 h at 0 °C, the mixture was added dropwise through a cannula to a solution of 12.19 g (36.8 mmol) of alkene **20** in 75 mL of THF at 0 °C under argon. The mixture was stirred for 6 h at rt. After the mixture was cooled to −20 °C, 23.7 mL of H$_2$O$_2$ (30% in H$_2$O) and 77.3 mL of aqueous 3 M NaOH solution were added slowly. The resulting mixture was stirred at rt for 10 min and extracted three times with 80 mL portions of ether. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes

(1/2), to produce alcohol **21** as a clear oil (11.28 g, 88%): $[\alpha]^{20}_D =$ +4.9° ($c = 1.08$, benzene); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.14 (s, 3 H), 0.18 (s, 3 H), 0.95 (s, 9 H), 1.69−1.82 (m, 2 H), 2.21 (br s, 1 H), 2.52 (dd, J = 4.5, 16.8 Hz, 1 H), 2.70 (dd, J = 6.2, 16.8 Hz, 1 H), 3.71−3.75 (m, 3 H), 4.01−4.08 (m, 1 H), 4.62 (d, J = 11.2 Hz, 1 H), 4.78 (d, J = 11.2 Hz, 1 H), 7.27−7.40 (m, 5 H); ^{13}C NMR (75 Mz, CDCl$_3$) δ −4.9, −4.6, 17.8, 22.2, 25.6 (3 C), 33.0, 59.3, 70.9, 73.4, 79.7, 117.9, 127.9 (3 C), 128.4 (2 C), 137.7; IR (film) 3600−3300, 2250 cm^{-1}; CIMS m/z (relative intensity) 350 (M$^+$ + H, 92), 91 (100); HRMS calcd for C$_{19}$H$_{31}$NO$_3$Si 349.2073, found 349.2060.

Preparation of Aldehyde 22. To a solution of 13.7 mL (27.4 mmol) of oxalyl chloride (2.0 M solution in CH$_2$Cl$_2$) in 30 mL of dry CH$_2$Cl$_2$ at −78 °C under argon was slowly added a solution of 4.30 mL (60.4 mmol) of DMSO in 12 mL of dry CH$_2$Cl$_2$ while the mixture was kept below −65 °C. After the mixture was stirred for 10 min at −78 °C, 6.39 g (18.3 mmol) of alcohol **21** in 10 mL of CH$_2$Cl$_2$ was added below −65 °C. The mixture was stirred at −78 °C for 30 min and triethylamine (15.3 mL (109.9 mmol)) was added at −78 °C. The mixture was allowed to warm to rt, and 30 mL of water was added. The aqueous layer was extracted three times with 50 mL portions of CH$_2$Cl$_2$. The combined organic layers were washed with aqueous 5% HCl solution, and brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1/5), to produce aldehyde **22** as a clear oil (6.10 g, 96%): $[\alpha]^{20}_D = -4.7°$ ($c = 1.12$, benzene); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.14 (s, 3 H), 0.17 (s, 3 H), 0.95 (s, 9 H), 2.50 (dd, J = 4.3, 16.8 Hz, 1 H), 2.693 (dd, J = 5.0, 16.8 Hz, 1 H), 2.695 (dd, J = 1.9, 5.4 Hz, 2 H), 3.99−4.07 (m, 2 H), 4.63 (d, J = 11.2 Hz, 1 H), 4.68 (d, J = 11.2 Hz, 1 H), 7.30−7.37 (m, 5 H), 9.76 (t, J = 1.9 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ −5.0, −4.8, 17.7, 22.5, 25.4 (3 C), 44.6, 70.0, 72.8, 76.5, 117.2, 127.7 (2 C), 127.8, 128.3 (2 C), 137.2, 199.7; IR (film) 2980−2800, 2250, 1725 cm^{-1}; CIMS m/z (relative intensity) 348 (M$^+$ + H, 100); HRMS calcd for C$_{18}$H$_{26}$NO$_3$Si (M$^+$ − Me) 332.1682, found 332.1675.

Preparation of Propargyl Alcohols 23 and 24. To a solution of 5.45 g (15.71 mmol) of aldehyde **22** in 80 mL of dry CH$_2$Cl$_2$ under argon at −78 °C was added dropwise 34.6 mL (17.30 mmol) of ethynylmagnesium bromide (0.5 M solution in THF), and the mixture was slowly warmed to 0 °C. After the mixture was stirred for 12 h at 0 °C, 50 mL of 5% aqueous HCl solution was added at 0 °C. The mixture was warmed to rt and stirred for 10 min. The aqueous layer was extracted three times with 50 mL portions of ether. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with CH$_2$Cl$_2$, to produce **23** and **24** as clear oils. **23** (3.47 g, 59%): $[\alpha]^{20}_D = +10.0°$ ($c = 1.10$, benzene); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.16 (s, 3 H), 0.19 (s, 3 H), 0.97 (s, 9 H), 1.79−2.05 (m, 2 H), 2.50 (dd, J = 4.6, 16.8 Hz, 1 H), 2.51 (d, J = 2.0 Hz, 1 H), 2.68 (dd, J = 6.7, 16.8 Hz, 1 H), 3.78−3.84 (m, 1 H), 4.04−4.10 (m, 1 H), 4.52−4.58 (m, 1 H), 4.59 (d, J = 11.2 Hz, 1 H), 4.79 (d, J = 11.2 Hz, 1 H), 7.30−7.36 (m, 5 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ −5.1, −4.6, 17.8, 21.9, 25.6 (3 C), 38.9, 59.6, 71.1, 73.5 (2 C), 79.5, 84.1, 117.9, 127.78, 127.83 (2 C), 128.3 (2 C), 137.6; IR (film) 3600−3200, 2990−2800, 2250, 2110 cm^{-1}; CIMS m/z (relative intensity) 374 (M$^+$ + H, 90), 91 (100), HRMS calcd for C$_{21}$H$_{31}$NO$_3$Si 373.2073, found 373.2057. **24** (1.76 g, 30%): $[\alpha]^{20}_D = +23.5°$ ($c = 1.30$, benzene); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.16 (s, 3 H), 0.20 (s, 3 H), 0.97 (s, 9 H), 1.80−1.93 (m, 2 H), 2.50 (dd, J = 4.5, 16.8 Hz, 1 H), 2.51 (d, J = 2.1 Hz, 1 H), 2.66 (dd, J = 6.6, 16.8 Hz, 1 H), 3.96−4.00 (m, 1 H), 4.02−4.07 (m, 1 H), 4.51−4.57 (m, 1 H), 4.64 (d, J = 10.9 Hz, 1 H), 4.84 (d, J = 10.9 Hz, 1 H), 7.29−7.38 (m, 5 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ −5.0, −4.6, 17.8, 21.9, 25.6 (3 C), 37.9, 59.0, 71.0, 73.1, 73.8, 79.1, 84.4, 117.9, 127.9, 128.0 (2 C), 128.4 (2 C), 137.4; IR (film) 3600−3200, 2990−2800, 2250, 2110 cm^{-1}; CIMS m/z (relative intensity) 374 (M$^+$ + H, 90), 91 (100); HRMS calcd for C$_{21}$H$_{31}$NO$_3$Si 373.2073, found 373.2057.

Preparation of (S)-Propargyl Acetate 26 from (S)-Propargyl Alcohol 23. To a solution of 656 mg (1.76 mmol) of propargyl alcohol **23** in 15 mL of CH$_2$Cl$_2$ at 0 °C under argon were added 0.49 mL (3.52 mmol) of triethylamine and a catalytic amount of DMAP, followed by the dropwise addition of 0.25 mL (2.64 mmol) of acetic anhydride. After the mixture was stirred for 12 h at rt, 10 mL of saturated aqueous NaHCO$_3$ solution was added, and stirring was continued for 15 min. The aqueous layer was extracted three times with 15 mL portions of CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1/5), to produce propargyl acetate **26** as a clear oil (714 mg, 98%): $[\alpha]^{20}_D = -1.7°$ ($c = 1.27$, benzene); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.14 (s, 3 H), 0.18 (s, 3 H), 0.96 (s, 9 H), 1.88−2.02 (m, 2 H), 2.04 (s, 3 H), 2.46 (dd, J = 4.4, 16.9 Hz, 1 H), 2.54 (d, J = 2.0 Hz, 1 H), 2.65 (dd, J = 6.6, 16.9 Hz, 1 H), 3.76−3.82 (m, 1 H), 4.02−4.06 (m, 1 H), 4.60 (d, J = 11.2 Hz, 1 H), 4.77 (d, J = 11.2 Hz, 1 H), 5.50 (ddd, J = 2.0, 6.4, 8.5 Hz, 1 H), 7.27−7.36 (m, 5 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ −5.1, −4.7, 17.7, 20.6, 21.9, 25.5 (3 C), 36.2, 61.4, 71.0, 73.5, 74.5, 78.5, 80.3, 117.6, 127.7 (3 C), 128.2 (2 C), 137.4, 169.1; IR (film) 3260, 2240, 2105, 1740 cm^{-1}; CIMS m/z (relative intensity) 416 (M$^+$ + H, 100); HRMS calcd for C$_{23}$H$_{33}$NO$_4$Si 415.2179, found 415.2158.

Preparation of (S)-Propargyl Acetate 26 from (R)-Propargyl Alcohol 24. To a solution of 280 mg (0.751 mmol) of propargyl alcohol **24**, 788 mg (3.00 mmol) of Ph$_3$P, 0.12 mL (1.50 mmol) of pyridine, and 0.22 mL (3.75 mmol) of acetic acid in 10 mL of THF was added a solution of 523 mg (3.00 mmol) of DEAD in 2 mL of THF at −45 °C under argon. After being stirred at 0 °C for 16 h, the mixture was taken up in 50 mL of ether and washed with saturated aqueous NaHCO$_3$, 5% aqueous HCl solution, and brine. The organic layer was dried over MgSO$_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1/5), to produce propargyl acetate **26** as a clear oil (266 mg, 86%).

Preparation of Allene Nitrile 27. To a mixture of 427 mg (61.5 mmol) of lithium shot in 12 mL of dry THF under argon at 0 °C was added dropwise a solution of 2.103 g (12.3 mmol) of dimethylphenylsilyl chloride in 2 mL of dry THF, and the mixture was warmed to rt. After being stirred for 12 h, the red solution was added to a suspension of CuCN (552 mg, 6.15 mmol) in 80 mL of dry THF under argon at 0 °C, and the mixture was stirred for 30 min. A solution of 2.556 g (6.15 mmol) of propargyl acetate **26** in 10 mL of dry THF was added to the mixture at −96 °C by syringe pump over 15 min. After being stirred for 4 h at −90 °C, the mixture was poured into 100 mL of saturated aqueous NH$_4$Cl solution. The mixture was stirred for 1 h and extracted three times with 100 mL portions of ether. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1/19), to produce allene **27** as a clear oil (2.54 g, 84%): $[\alpha]^{20}_D = -29.1°$ ($c = 1.12$, benzene); ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.11 (s, 3 H), 0.16 (s, 3 H), 0.37 (s, 6 H), 0.94 (s, 9 H), 2.28−2.40 (m, 2 H), 2.49 (dd, J = 4.2, 16.8 Hz, 1 H), 2.76 (dd, J = 5.3, 16.8 Hz, 1 H), 3.51−3.56 (m, 1 H), 3.94−3.99 (m, 1 H), 4.62 (s, 2 H), 4.81−4.91 (m, 1 H), 5.07−5.12 (m, 1 H), 7.30 −7.59 (m, 10 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ −4.6 (2 C), −2.3 (2 C), 17.9, 22.6, 25.7 (3 C), 29.2, 69.9, 72.9, 78.8, 81.1, 81.3, 117.9, 127.8 (4 C), 128.4 (2 C), 129.2, 133.6 (2 C), 133.9, 138.0, 138.2, 211.5; IR (film) 3080−2840, 2240, 1930 cm^{-1}; EIMS m/z (relative intensity) 491 (M$^+$, 3), 434 (8), 81 (100); HRMS calcd for C$_{29}$H$_{41}$NO$_2$Si$_2$ 491.2676, found 491.2675.

Preparation of Allene Aldehyde 28. To a solution of 1.705 g (3.47 mmol) of allene nitrile **27** in 35 mL of dry toluene under argon at −78 °C was added 6.25 mL (6.25 mmol) of DIBALH (1.0 M solution in hexanes). After the mixture was slowly warmed to 0 °C over 2 h, 20 mL of aqueous 5% HCl solution was added. The mixture was stirred for 20 min, and was extracted three times with 50 mL portions of ether. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (2/98), to produce allene aldehyde **28** as a clear oil (1.33 g, 78%): $[\alpha]^{20}_D = -20.9°$ ($c = 0.98$, benzene); ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.07 (s, 3 H), 0.09 (s, 3 H), 0.35 (s, 6 H), 0.88 (s, 9 H), 2.20−2.36 (m, 2 H), 2.50 (ddd, J = 2.4, 5.4, 16.1 Hz, 1 H), 2.69 (ddd, J = 2.5, 5.6, 16.1 Hz, 1 H), 3.39−3.47 (m, 1 H), 4.23−4.31 (m, 1 H), 4.56 (d, J = 11.5 Hz, 1 H), 4.64 (d, J = 11.5 Hz, 1 H), 4.82−4.93 (m, 1 H), 5.06−5.12 (m, 1 H), 7.26−7.58 (m, 10 H), 9.81 (dd, J = 2.4, 2.5 Hz, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ −4.7, −4.5, −2.2 (2 C), 17.9, 25.8 (3 C), 29.9, 47.3, 70.3, 72.8, 79.7, 81.1, 82.8, 127.6, 127.7 (2 C), 127.8 (3

C), 128.3 (2 C), 129.1, 133.6 (2 C), 138.2, 201.3, 211.4; IR (film) 3080−2840, 2700, 1930, 1720 cm^{-1}; CIMS *m/z* (relative intensity) 495 (M$^+$ + H, 2), 477 (4), 437 (3), 91 (100); HRMS calcd for C$_{29}$H$_{42}$O$_3$Si$_2$ 494.2672, found 494.2689.

Preparation of (R)-Propargyl Acetate 29. Following the procedure for preparation of (S)-propargyl acetate **26** from (S)-propargyl alcohol **23**, (R)-propargyl alcohol **24** (196 mg, 0.525 mmol) was converted to (R)-propargyl acetate **29** (206 mg, 94%): ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.10 (s, 3 H), 0.13 (s, 3 H), 0.91 (s, 9 H), 1.94−2.08 (m, 2 H), 1.98 (s, 3 H), 2.45 (dd, *J* = 4.9, 17.0 Hz, 1 H), 2.46 (d, *J* = 2.2 Hz, 1 H), 2.68 (dd, *J* = 6.3, 17.0 Hz, 1 H), 3.59−3.67 (m, 1 H), 3.97−4.08 (m, 1 H), 4.50 (d, *J* = 11.1 Hz, 1 H), 4.71 (d, *J* = 11.1 Hz, 1 H), 5.41−5.51 (m, 1 H), 7.28−7.37 (m, 5 H); IR (film) 3260, 2240, 2105, 1740 cm^{-1}; CIMS *m/z* (relative intensity) 416 (M$^+$ + H, 100); HRMS calcd for C$_{23}$H$_{33}$NO$_4$Si 415.2179, found 415.2158.

Preparation of Allene Nitrile 30. Following the procedure for preparation of allene **27**, propargyl acetate **29** (402 mg, 0.969 mmol) was converted to allene **30** (408 mg, 86%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.11 (s, 3 H), 0.16 (s, 3 H), 0.37 (s, 6 H), 0.94 (s, 9 H), 2.15−2.46 (m, 2 H), 2.49 (dd, *J* = 4.1, 16.8 Hz, 1 H), 2.74 (dd, *J* = 5.9, 16.8 Hz, 1 H), 3.56 (q, *J* = 5.6 Hz, 1 H), 3.92−4.00 (m, 1 H), 4.65 (s, 2 H), 4.80−4.90 (m, 1 H), 5.10−5.16 (m, 1 H), 7.30 −7.57 (m, 10 H); IR (film) 3080−2840, 2240, 1930 cm^{-1}; EIMS *m/z* (relative intensity) 491 (M$^+$, 3), 434 (8), 81 (100); HRMS calcd for C$_{29}$H$_{41}$NO$_2$Si$_2$ 491.2676, found 491.2675.

Preparation of Allene Aldehyde 31. Following the procedure for preparation of aldehyde **28**, nitrile **30** (408 mg, 0.831 mmol) was converted to aldehyde **31** (303 mg, 74%): ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.03 (s, 3 H), 0.05 (s, 3 H), 0.31 (s, 6 H), 0.85 (s, 9 H), 2.16−2.26 (m, 2 H), 2.48 (ddd, *J* = 2.3, 5.1, 16.2 Hz, 1 H), 2.68 (ddd, *J* = 2.3, 5.9, 16.2 Hz, 1 H), 3.43−3.52 (m, 1 H), 4.23−4.33 (m, 1 H), 4.59 (d, *J* = 11.6 Hz, 1 H), 4.69 (d, *J* = 11.6 Hz, 1 H), 4.85 (q, *J* = 7.3 Hz, 1 H), 5.04−5.12 (m, 1 H), 7.29−7.58 (m, 10 H), 9.84 (t, *J* = 2.3 Hz, 1 H); IR (film) 3080−2840, 2700, 1930, 1720 cm^{-1}; CIMS *m/z* (relative intensity) 495 (M$^+$ + H, 2), 477 (4), 437 (3), 91 (100); HRMS calcd for C$_{29}$H$_{42}$O$_3$Si$_2$ 494.2672, found 494.2689.

Preparation of Cycloadduct 39. To a solution of 580 mg (1.17 mmol) of aldehyde **28** in 20 mL of mesitylene was added a solution of 186 mg (1.23 mmol) of piperonylamine (**35**) in 3 mL of mesitylene at rt under argon. After stirred at rt for 1 h, the mixture was refluxed for 2 h. The mixture was cooled to 0 °C, and 20 mL of THF and 1.17 mL (1.17 mmol) of tetrabutylammonium fluoride (1.0 M solution in THF) were added. After the mixture was stirred at 0 °C for 1 h, 20 mL of water was added. The mixture was extracted three times with 30 mL portions of ether. The combined organic layers were washed with brine, dried over K$_2$CO$_3$. and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1/19), to produce amine **39** as a yellow oil (378 mg, 66% from aldehyde **28**): ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.03 (s, 6 H), 0.83 (s, 9 H), 1.45−1.63 (m, 2 H), 1.75−1.97 (m, 2 H), 2.06 (d, *J* = 2.5 Hz, 1 H), 2.97−3.04 (m, 1 H), 3.05−3.15 (m, 1 H), 3.58−3.68 (m, 1 H), 3.62 (d, *J* = 12.9 Hz, 1 H), 3.73 (d, *J* = 12.9 Hz, 1 H), 4.12−4.18 (m, 1 H), 4.45−4.62 (m, 2 H), 5.92 (s, 2 H), 6.71−6.79 (m, 2 H), 6.83 (s, 1 H), 7.25−7.35 (m, 5 H); IR (film) 3300, 2100 cm^{-1}; EIMS *m/z* (relative intensity) 493 (M$^+$, 2), 436 (7); HRMS calcd for C$_{29}$H$_{39}$NO$_4$Si 493.2648, found 493.2625.

Preparation of Cycloadduct 43. Following the procedure for preparation of amine **39**, aldehyde **31** (27 mg, 0.0547 mmol) was converted to cycloadduct **43** (14 mg, 52% from **31**): ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.48−1.54 (m, 2 H), 2.01−2.13 (m, 1 H), 2.13 (d, *J* = 2.4 Hz, 1 H), 2.25−2.35 (m, 1 H), 2.63−2.71 (m, 1 H), 2.72−2.85 (m, 1 H), 3.41-3.51 (m, 1 H), 3.70−3.87 (m, 3H), 4.64 (d, *J* = 12.6 Hz, 1 H), 4.70 (d, *J* = 12.6 Hz, 1 H), 5.94 (s, 2 H), 6.74 (d, *J* = 7.8 Hz, 2 H), 6.82 (dd, *J* = 1.2, 7.8 Hz, 1 H), 6.97 (s, 1 H), 7.23−7.42 (m, 5 H); IR (film) 3300, 2100 cm^{-1}; EIMS *m/z* (relative intensity) 493 (M$^+$, 2), 436 (7); HRMS calcd for C$_{29}$H$_{39}$NO$_4$Si 493.2648, found 493.2625.

Preparation of Azide 46. To a solution of 274 mg (1.19 mmol) of bromo alcohol **44**[29b] in 5 mL of MeCN at rt under argon was added 357 mg (2.38 mmol) of NaI, followed by slow addition of 0.30 mL (2.38 mmol) of TMSCl. After being stirred at rt for 15 min, the mixture was taken up in CH$_2$Cl$_2$ and washed with water, 10% aqueous Na$_2$S$_2$O$_3$

solution, and brine. The organic layer was dried over MgSO$_4$ and concentrated *in vacuo* to produce iodide **45** as a white solid suitable for use in the next step without further purification (381 mg, 94%): ^{1}H NMR (200 MHz, CDCl$_3$) δ 4.48 (s, 2 H), 5.97 (s, 2 H), 6.88 (s, 1 H), 6.96 (s, 1 H).

To a solution of 0.810 g (2.38 mmol) of iodide **45** in 10 mL of DMF at rt was added 0.232 g (3.57 mmol) of sodium azide. After the mixture was stirred at 100 °C for 2 h, 10 mL of water was added. The mixture was extracted three times with 10 mL portions of ether. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated *in vacuo* to produce azide **46** as colorless crystals suitable for use in the next step without further purification (0.565 g, 93%): mp 38−39 °C; ^{1}H NMR (200 MHz, CDCl$_3$) δ 4.38 (s, 2 H), 6.01 (s, 2 H), 6.88 (s, 1 H), 7.06 (s, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 54.4, 102.0, 109.8, 112.9, 114.5, 127.9, 147.6, 148.4; IR (CDCl$_3$) 2899, 2096 cm^{-1}; CIMS *m/z* (relative intensity) 257 (21), 255 (M$^+$, 21), 215 (100), 213 (M$^+$ − N$_3$, 98); HRMS calcd for C$_8$H$_6$BrN$_3$O$_2$ 254.9644, found 254.9654.

Preparation of Cycloadduct 49. To a solution of 399 mg (1.56 mmol) of azide **46** in 16 mL of dry mesitylene under argon was added 410 mg (1.56 mmol) of Ph$_3$P. The mixture was stirred at 50 °C for 4 h. To the above solution was added 736 mg (1.49 mmol) of aldehyde **28** in 4 mL of mesitylene by cannula. After being stirred at 50 °C for 16 h, the mixture was refluxed for 2 h. The mixture was cooled to 0 °C, and 20 mL of THF and 1.49 mL (1.49 mmol) of tetrabutylammonium fluoride (1.0 M solution in THF) were added. After the mixture was stirred at 0 °C for 1 h, 20 mL of water was added. The mixture was extracted three times with 20 mL portions of ether. The combined organic layers were washed with brine, dried over K$_2$CO$_3$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1/19), to produce amine **49** as a clear oil (535 mg, 63% from aldehyde **28**): $[\alpha]^{20}_D$ = −3.9° (*c* = 2.58, benzene); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.08 (s, 3 H), 0.077 (s, 3 H), 0.89 (s, 9 H), 1.62−1.72 (m, 1 H), 1.86−2.06 (m, 3 H), 2.11 (d, *J* = 2.5 Hz, 1 H), 3.05 (dt, *J* = 3.9, 10.5 Hz, 1 H), 3.13−3.20 (m, 1 H), 3.69 (ddd, *J* = 2.4, 4.3, 9.8 Hz, 1 H), 3.75 (d, *J* = 13.9 Hz, 1 H), 3.83 (d, *J* = 13.9 Hz, 1 H), 4.19−4.21 (m, 1 H), 4.55 (d, *J* = 11.8 Hz, 1 H), 4.61 (d, *J* = 11.8 Hz, 1 H), 5.95 (d, *J* = 1.2 Hz, 1 H), 5.96 (d, *J* = 1.2 Hz, 1 H), 6.97 (s, 1 H), 7.00 (s, 1 H), 7.25−7.38 (m, 5 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ −5.0, −4.5, 18.1, 25.8 (3 C), 29.0, 29.6, 31.1, 50.5, 51.1, 68.0, 70.5, 71.6, 76.2, 83.8, 101.5, 110.0, 112.6, 113.9, 127.2, 127.4 (2 C), 127.8, 128.2 (2 C), 138.9, 147.2, 147.4; IR (film) 3600−3100, 3080−2800, 2090 cm^{-1}; CIMS *m/z* (relative intensity) 574 (13), 572 (M$^+$ + H, 12); HRMS calcd for C$_{29}$H$_{38}$BrNO$_4$Si 571.1754, found 571.1747.

Preparation of Alkene 50. To a solution of 311 mg (0.545 mmol) of alkyne **49** in 25 mL of MeOH were added 31.1 mg of Lindlar catalyst and 5 drops of quinoline. After being stirred under 1 atm of hydrogen at rt for 19 h, the mixture was filtered through a small plug of Celite and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1/9), to produce alkene **50** as a white foam (290 mg, 93%): $[\alpha]^{20}_D$ = +1.2° (*c* = 0.48, benzene); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.03 (s, 3 H), 0.94 (s, 9H), 1.75−1.83 (m, 2 H), 1.90−1.98 (m, 2 H), 2.75−2.81 (m, 1 H), 2.99−3.05 (m, 1 H), 3.65−3.71 (m, 1 H), 3.71 (d, *J* = 13.7 Hz, 1 H), 3.78 (d, *J* = 13.7 Hz, 1 H), 4.20−4.25 (m, 1 H), 4.58−4.77 (m, 2 H), 5.06−5.18 (m, 2 H), 5.82−5.97 (m, 1 H), 5.96 (s, 2 H), 6.88 (s, 1 H), 7.00 (s, 1 H), 7.27−7.41 (m, 5 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ −4.8, −4.6, 18.1, 25.9 (3 C), 28.9 (br), 33.4 (br), 38.7 (br), 51.2, 53.7 (br), 68.9, 71.4 (br), 76.4 (br), 101.6, 110.1, 112.7, 114.0, 116.1 (br), 127.1, 127.3 (2 C), 128.1 (2 C), 132.7, 133.0, 139.4, 147.2 (2 C); IR (film) 3340−3280, 3060−2800 cm^{-1}; EIMS *m/z* (relative intensity) 573 (M$^+$, 2); HRMS calcd for C$_{29}$H$_{40}$BrNO$_4$Si 573.1910, found 573.1878.

Heck Cyclization of Bromo Alkene 50. To a solution of 293 mg (0.511 mmol) of alkene **50** in 8 mL of dry CH$_3$CN in a sealed tube were added 177 mg (0.153 mmmol) of Pd(PPh$_3$)$_4$, 0.85 mL (6.13 mmol) of triethylamine, and 190 mg (1.02 mmol) of trimethylbenzylammonium chloride. After the mixture was deoxygenated under vacuum three times, the tube was sealed under argon and heated at 120 °C for 48 h. After being cooled to rt, the mixture was filtered through a small plug of Celite and concentrated *in vacuo*. The residue was purified by flash

chromatograghy on silica gel, eluting with triethylamine/ethyl acetate/hexanes (1/10/90), to produce tetracyclic alkene **51** as a white foam (187 mg, 74%): $[\alpha]^{20}_D = -5.5°$ (*c* = 0.73, benzene); ^{1}H NMR (200 MHz, CDCl$_3$) δ −0.02 (s, 6 H), 0.86 (s, 9 H), 1.39−1.62 (m, 3 H), 2.24 (dt, *J* = 3.6, 12.5 Hz, 1 H), 2.89−2.99 (m, 1 H), 3.26−3.29 (m, 1 H), 3.56−3.59 (m, 1 H), 3.70 (s, 2 H), 3.94 (ddd, *J* = 3.2, 3.6, 11.2 Hz, 1 H), 4.63 (d, *J* = 12.4 Hz, 1 H), 4.78 (d, *J* = 12.4 Hz, 1 H), 4.88 (d, *J* = 2.0 Hz, 1 H), 5.17 (d, *J* = 2.0 Hz, 1 H), 5.91 (s, 2 H), 6.60 (s, 1 H), 6.66 (s, 1 H), 7.23−7.41 (m, 5 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ −4.7, −4.6, 18.2, 25.9 (3 C), 29.9, 38.0, 42.0, 54.2, 62.2, 69.1, 72.2, 77.4, 100.9, 108.3, 109.8, 114.8, 127.1, 127.4 (2 C), 128.1 (2 C), 132.1, 135.5, 139.7, 146.1, 146.3, 153.5; IR (CDCl$_3$) 3066, 2954−2857, 1630, 1612 cm^{-1}; EIMS *m/z* (relative intensity) 493 (M$^+$, 9); HRMS calcd for C$_{29}$H$_{39}$NO$_4$Si 493.2648, found 493.2629.

Preparation of Toluenesulfonamide 52. To a solution of 125 mg (0.254 mmol) of amine **51** in 5 mL of pyridine were added 12.5 mg of DMAP and 97.0 mg (0.508 mmol) of toluenesulfonyl chloride. The mixture was stirred at 100 °C for 20 h. After the mixture was cooled to 0 °C, 10 mL of saturated aqueous NaHCO$_3$ solution was added, and stirring was continued for 15 min. The aqueous layer was extracted three times with 10 mL portions of ether. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1/4), to produce toluenesulfonamide **52** as a white foam (151 mg, 92%): $[\alpha]^{20}_D = -13.1°$ (*c* = 0.73, benzene); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.08 (s, 6 H), 0.96 (s, 9 H), 1.42−1.84 (m, 3 H), 2.01−2.11 (m, 1 H), 2.39 (s, 3 H), 2.49−2.55 (m, 1 H), 3.46−3.54 (m, 1 H), 4.11−4.17 (m, 1 H), 4.26−4.34 (m, 2 H), 4.35−4.50 (m, 1 H), 4.47 (d, *J* = 12.3 Hz, 1 H), 4.58 (d, *J* = 12.4 Hz, 1 H), 4.98 (s, 1 H), 5.07 (s, 1 H), 5.95 (d, *J* = 1.2 Hz, 1 H), 5.96 (d, *J* = 1.2 Hz, 1 H), 6.45 (s, 1 H), 6.75 (s, 1 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 7.26−7.41 (m, 5 H), 7.53 (d, *J* = 7.9 Hz, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ −4.9, −4.6, 18.2, 21.4, 22.6, 25.8 (3 C), 31.5, 40.7, 47.4, 52.7, 68.3, 70.2, 74.0, 101.1, 108.9 (2 C), 117.0, 127.1 (2 C), 127.47 (2 C), 127.55 (2 C), 128.3 (2 C), 129.4 (2 C), 137.3, 137.7, 138.7, 142.8, 146.8, 147.3, 150.2; IR (CDCl$_3$) 3050−2800, 1599 cm^{-1}; EIMS *m/z* (relative intensity) 647 (M$^+$, 0.4), 590 (63); HRMS calcd for C$_{36}$H$_{45}$NO$_6$SSi 647.2737, found 647.2698.

Preparation of Alcohol 54. To a solution of 59.0 mg (0.0912 mmol) of alkene **52** in 4 mL of acetone at −20 °C under argon was added 3.0 mL (0.30 mmol) of dimethyldioxirane^{33} (0.1 M solution in acetone). The mixture was stirred at −20 °C for 4 h and was concentrated *in vacuo*. The crude epoxides **55** were produced as a white foam (54 mg, 89%, 2/1 mixture of diastereoisomers determined by the integration of ^{1}H NMR spectrum of the crude product) and were used for the next step immediately.

To a solution of 80.0 mg (0.121 mmol) of the above mixture of epoxides in 5 mL of dry CH$_2$Cl$_2$ at −78 °C under argon was added 58.9 mg (0.363 mmol) of anhydrous FeCl$_3$. After the mixture was stirred at −78 °C for 30 min, 0.60 mL (0.60 mmol) of DIBALH (1.0 M solution in hexanes) was added at −78 °C. After the mixture was stirred at 0 °C for 10 min, 5 mL of 5% aqueous HCl solution was added. The mixture was extracted three times with 10 mL portions of CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1/2), to produce alcohol **54** as a white foam (70.6 mg, 88%): $[\alpha]^{20}_D = +0.9°$ (*c* = 1.05, benzene); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.01 (s, 3 H), 0.03 (s, 3H), 0.89 (s, 9 H), 1.20−1.36 (m, 1 H), 1.48−1.79 (m, 2 H), 2.32−2.45 (m, 1 H), 2.44 (s, 3 H), 2.49−2.53 (m, 1 H), 3.04−3.08 (m, 1 H), 3.17−3.21 (m, 1 H), 3.71−3.75 (m, 1 H), 3.83−3.93 (m, 2 H), 4.14−4.17 (m, 1 H), 4.32−4.65 (m, 4 H), 5.94 (s, 2 H), 6.28 (s, 1 H), 6.67 (s, 1 H), 7.27−7.40 (m, 7 H), 7.73 (d, *J* = 7.8 Hz, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ −4.9, −4.6, 18.1, 21.5, 25.4, 25.9 (3 C), 29.7, 36.2, 36.8, 43.2, 51.6, 62.4, 68.1, 70.8, 74.7, 101.1, 106.0, 109.4, 127.0 (2 C), 127.5 (2 C), 127.6 (2 C), 128.4 (2 C), 129.8, 132.9, 137.0, 138.6, 139.0, 143.2, 146.1, 147.9; IR (CDCl$_3$) 3622 cm^{-1}; EIMS *m/z* (relative intensity) 665 (M$^+$, 1); HRMS calcd for C$_{32}$H$_{38}$NO$_7$SSi (M$^+$ − *t*-Bu) 608.2138, found 608.2160.

Preparation of Pentacyclic Amine 64. To a solution of 90.0 mg (0.135 mmol) of alcohol **54** in 15 mL of MeOH was added 18 mg of 10% palladium on carbon. After being stirred under 1 atm of hydrogen

at rt for 24 h, the mixture was filtered through a small plug of Celite and concentrated *in vacuo*. The crude diol **62** was suitable for use in the next step without further purification.

To a solution of 1.05 g (8.19 mmol) of naphthalene in 5 mL of dry DME was added 0.20 g (8.70 mmol) of sodium. The mixture was stirred at rt for 2 h, during which time the solution turned a deep blue color. To a solution of the above crude diol **62** in 4 mL of DME at −78 °C under argon was added the above blue solution dropwise by cannula until the solution maintained its blue color. The mixture was quenched with 5 mL of saturated aqueous NaHCO$_3$ solution, and was extracted three times with 10 mL portions of ethyl acetate. The combined organic layers were dried over K$_2$CO$_3$ and concentrated *in vacuo* to produce the crude amine **63**.

To the above crude amine **63** dissolved in 1.5 mL of CH$_3$CN and 3 mL of ether were added 71 mg (0.271 mmol) of PPh$_3$, 28 mg (0.411 mmol) of imidazole, and 69 mg (0.271 mmol) of I$_2$ at 0 °C under argon. After being stirred at 0 °C for 15 min, the mixture was quenched with 5 mL of saturated aqueous NaHCO$_3$ solution and 2 mL of saturated aqueous Na$_2$S$_2$O$_3$ solution, and was extracted three times with 10 mL portions of ether. The combined organic layers were dried over K$_2$CO$_3$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with CH$_2$Cl$_2$/MeOH/NH$_4$OH (97/2/1), to produce pentacyclic amine **64** as a clear oil (44.8 mg, 82% from alcohol **54**): $[\alpha]^{20}_D = +55.4°$ (*c* = 0.16, MeOH); ^{1}H NMR (360 MHz, CDCl$_3$) δ 0.10 (s, 3 H), 0.17 (s, 3 H), 0.89 (s, 9 H), 1.42 (ddd, *J* = 3.9, 12.7, 14.4 Hz, 1 H), 1.57 (ddd, *J* = 3.7, 9.3, 14.0 Hz, 1 H), 1.95 (ddd, *J* = 2.4, 5.9, 14.4 Hz, 1 H), 2.02 (dd, *J* = 6.5, 19.7 Hz, 1 H), 2.53 (d, *J* = 2.4 Hz, 1 H), 2.54−2.62 (m, 1 H), 2.90 (d, *J* = 11.5 Hz, 1H), 2.92 (s, 1 H), 3.05 (dd, *J* = 2.4, 11.4 Hz, 1 H), 3.24 (q, *J* = 6.7 Hz, 1 H), 3.72 (d, *J* = 16.7 Hz, 1 H), 3.86−3.94 (m, 1 H), 4.03−4.09 (m, 1 H), 4.27 (d, *J* = 16.7 Hz, 1 H), 5.878 (d, *J* = 1.5 Hz, 1 H), 5.883 (d, *J* = 1.5 Hz, 1 H), 6.45 (s, 1 H), 6.50 (s, 1 H); ^{13}C NMR (90 MHz, CDCl$_3$) δ −2.8, −2.2, 18.1, 25.8 (3 C), 32.3, 33.2, 43.6, 45.5, 52.8, 61.0, 61.1, 66.0, 68.0, 100.2, 106.4, 107.1 (2 C), 136.4, 145.7, 146.4; IR (CDCl$_3$) 3500, 3155, 2858−2955, 1794 cm^{-1}; EIMS *m/z* (relative intensity) 403 (M$^+$, 28), 387 (M$^+$ − OH, 10), 346 (M$^+$ − *t*-Bu, 100); HRMS calcd for C$_{22}$H$_{33}$NO$_4$Si 403.2179, found 403.2146.

Preparation of Ketone 65. To a solution of 31.0 mg (0.0769 mmol) of alcohol **64** in 4 mL of dry CH$_2$Cl$_2$ under argon were added 0.5 g of 4 Å molecular sieves and 27.0 mg (0.230 mmol) of *N*-methylmorpholine *N*-oxide at rt. After 10 min, 2.70 mg (0.00769 mmol) of tetrapropylammonium perruthenate was added. After being stirred at rt for 24 h, the mixture was filtered through a small plug of Celite and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with CH$_2$Cl$_2$/MeOH/NH$_4$OH (97/2/1), to produce ketone **65** as a clear oil (29.6 mg, 96%): $[\alpha]^{20}_D = -81.7°$ (*c* = 0.28, MeOH); ^{1}H NMR (360 MHz, CDCl$_3$) δ 0.06 (s, 3 H), 0.10 (s, 3 H), 0.85 (s, 9 H), 1.88 (ddd, *J* = 3.0, 11.5, 14.4 Hz, 1 H), 2.30−2.36 (m, 1 H), 2.36 (dd, *J* = 13.0, 15.6 Hz, 1 H), 2.50 (dd, *J* = 5.8, 15.6 Hz, 1 H), 2.62 (d, *J* = 2.6 Hz, 1 H), 2.61−2.70 (m, 1 H), 3.01 (d, *J* = 11.9 Hz, 1H), 3.16 (dd, *J* = 2.7, 11.9 Hz, 1 H), 3.42−3.53 (m, 1 H), 3.78 (d, *J* = 17.6 Hz, 1 H), 3.95 (dd, *J* = 3.2, 3.3 Hz, 1 H), 4.32 (d, *J* = 17.6 Hz, 1 H), 5.89 (s, 2 H), 6.47 (s, 1 H), 6.49 (s, 1 H); ^{13}C NMR (90 MHz, CDCl$_3$) δ −2.8, −2.0, 18.2, 25.7 (3 C), 35.4, 40.5, 46.1, 46.9, 51.9, 60.5, 60.6, 71.2, 100.7, 106.5, 107.0, 125.3, 135.4, 145.8, 146.5, 209.1; IR (CDCl$_3$) 3155, 2857−2955, 1794, 1725 cm^{-1}; EIMS *m/z* (relative intensity) 401 (M$^+$, 6), 344 (M$^+$ − *t*-Bu, 100); HRMS calcd for C$_{22}$H$_{31}$NO$_4$Si 401.2022, found 401.2040.

Preparation of Enone 67. To a solution of 0.19 mL (1.36 mmol) of diisopropylamine in 4 mL of dry THF at 0 °C under argon was added 0.54 mL (1.35 mmol) of *n*-BuLi (2.5 M solution in hexanes). After 10 min, the solution was cooled to −78 °C. Freshly distilled TMSCl (0.85 mL, 6.70 mmol) was added to the above solution at −78 °C, followed by dropwise addition of a solution of 27.0 mg (0.0673 mmol) of ketone **65** in 1 mL of THF. After the mixture was stirred for 5 min, 1.9 mL (13.6 mmol) of triethylamine was added. The mixture was allowed to warm to 0 °C over 1 h. The mixture was quenched with 5 mL of saturated aqueous NaHCO$_3$ solution and extracted three times with 10 mL portions of ether. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude silyl enol ether **66** was immediately used for the next step without further purification.

To the above crude **66** dissolved in 3.4 mL of dry MeCN was added 151 mg (0.673 mmol) of Pd(OAc)$_2$ at rt under argon. After being stirred for 50 h at rt, the mixture was quenched with 5 mL of saturated aqueous NaHCO$_3$ solution and extracted three times with 5 mL portions of ether. The combined organic layers were dried over K$_2$CO$_3$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with CH$_2$Cl$_2$/MeOH/NH$_4$OH (97/2/1), to produce 4.7 mg of starting ketone **65** and 18.0 mg of enone **67** (67% isolated yield, 81% based on recovered starting ketone) as clear oils. **67**: [α]$^{20}_D$ = +12.8° (*c* = 0.13, MeOH); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.04 (s, 3 H), 0.13 (s, 3 H), 0.85 (s, 9 H), 1.90 (ddd, *J* = 3.0, 11.8, 12.6 Hz, 1 H), 2.41 (ddd, *J* = 2.7, 4.7, 12.6 Hz, 1 H), 3.16 (s, 2 H), 3.42 (s, 1 H), 3.86 (d, *J* = 17.1 Hz, 1 H), 3.87−3.96 (m, 1 H), 4.06−4.10 (m, 1 H), 4.40 (d, *J* = 17.1 Hz, 1 H), 5.83−5.86 (m, 1 H), 5.93 (d, *J* = 1.4 Hz, 1 H), 5.94 (d, *J* = 1.4 Hz, 1 H), 6.53 (s, 1 H), 6.59 (s, 1 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ −5.2, −4.7, 18.2, 25.7 (3 C), 39.7, 46.5, 54.8, 60.0, 60.8, 71.6, 101.0, 106.9, 107.7, 115.7, 124.5, 130.2, 146.3, 147.5, 176.9, 195.5; IR (CDCl$_3$) 3155, 2874−2978, 1794, 1676 cm^{-1}; EIMS *m/z* (relative intensity) 399 (M$^+$, 8), 342 (M$^+$ − *t*-Bu, 100); HRMS calcd for C$_{22}$H$_{29}$NO$_4$Si 399.1866, found 399.1831.

Preparation of α-Hydroxy Enone 68. To a solution of 3.0 mg (0.0075 mmol) of siloxy enone **67** in 1 mL of THF at 0 °C was added 11.3 μL (0.0113 mmol) of tetrabutylammonium fluoride (1.0 M solution in THF). After being stirred at 0 °C for 2 h and for another 2 h at rt, the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with CH$_2$Cl$_2$/MeOH/NH$_4$-OH (92.5/5/2.5), to produce α-hydroxy enone **68** as a clear oil (2.1 mg, 98%): [α]$^{23}_{546}$ = −55.9° (*c* = 0.272, MeOH), [α]$^{23}_D$ = −50.7° (*c* = 0.272, MeOH) (lit.[11] [α]$^{25}_{546}$ = −47.7° (*c* = 0.10, MeOH)). ^{1}H NMR (500 MHz, CDCl$_3$), ^{13}C NMR (125 MHz, CDCl$_3$), and low- and high-resolution mass spectra were identical to those previously reported.[43]

Preparation of (−)-Coccinine (2). To a solution of 11.6 mg (0.0291 mmol) of enone **68** in 1 mL of dry MeOH at 0 °C under argon was added 32 μL (0.289 mmol) of trimethyl orthoformate and 8.3 mg (0.044 mmol) of *p*-toluenesulfonic acid monohydrate. The solution was slowly warmed to rt over 2 h and stirred at rt for 2 h. Saturated aqueous NaHCO$_3$ solution (2 mL) was added, and the mixture was extracted three times with 5 mL portions of ether. The combined organic layers were dried over K$_2$CO$_3$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with CH$_2$Cl$_2$/MeOH/NH$_4$OH (97/2/1), to produce ketal **69** as a clear oil (11.8 mg, 91%): ^{1}H NMR (360 MHz, CDCl$_3$) δ 0.07 (s, 3 H), 0.11 (s, 3 H), 0.82 (s, 9 H), 1.78 (dt, *J* = 1.8, 12.3 Hz, 1 H), 2.19 (dt, *J* = 4.6, 12.3 Hz, 1 H), 3.03 (d, *J* = 11.7 Hz, 1 H), 3.08 (dd, *J* = 2.0, 11.7 Hz, 1 H), 3.19−3.26 (m, 1 H), 3.25 (s, 6 H), 3.63 −3.72 (m, 1 H), 3.74 (d, *J* = 16.6 Hz, 1 H), 4.07−4.10 (m, 1 H), 4.31 (d, *J* = 16.6 Hz, 1 H), 5.58 (t, *J* = 2.0 Hz, 1 H), 5.89 (s, 2 H), 6.46 (s, 1 H), 6.54 (s, 1 H); EIMS *m/z* (relative intensity) 445 (M$^+$, 49); HRMS calcd for C$_{24}$H$_{35}$NO$_5$Si 445.2284, found 445.2245.

To a solution of 5.6 mg (0.0126 mmol) of ketal **69** in 1 mL of dry toluene at rt under argon was added 0.125 mL (0.125 mmol) of DIBALH (1.0 M solution in hexanes). After the solution was stirred at rt for 12 h, 2 drops of saturated aqueous Na$_2$SO$_4$ solution was added, the mixture was stirred for 30 min, and 2 mL of CH$_2$Cl$_2$/MeOH/NH$_4$-OH (92.5/5/2.5) was added. After being stirred for 30 min, the mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with CH$_2$Cl$_2$/MeOH/NH$_4$OH (92.5/5/2.5), to produce (−)-coccinine (**2**) as a clear oil (3.1 mg, 81%) whose ^{1}H NMR (500 MHz, CDCl$_3$), and low- and high-resolution mass spectra were identical to those previously reported:[12,36] [α]$^{25}_D$ = −161° (*c* = 0.101, EtOH) (lit.[3] [α]$^{27}_D$ = −188.8° (*c* = 1.9, EtOH)); ^{13}C NMR (125 MHz, CDCl$_3$) δ 36.0, 46.0, 55.7, 56.7, 58.1, 61.2, 65.6, 77.7, 100.8, 106.9, 107.8, 111.9, 125.0, 132.1, 145.9, 146.8, 156.1. (−)-Montanine (**1**) (0.3 mg, 8%) was produced as a minor product.

Preparation of (−)-Montanine (1). To a solution of 8.1 mg (0.018 mmol) of ketal silyl ether **69** in 1 mL of THF at 0 °C was added 0.18 mL (0.18 mmol) of tetrabutylammonium fluoride (1.0 M solution in THF). After being stirred at rt for 20 h, the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with CH$_2$Cl$_2$/MeOH/NH$_4$OH (92.5/5/2.5), to produce ketal alcohol **71** as a clear oil (6.0 mg, 99%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.70 (ddd, *J* = 1.7, 11.9, 12.5 Hz, 1 H), 2.37 (dt, *J* = 4.4, 12.5 Hz, 1 H), 2.51 (br s, 1 H), 3.05 (d, *J* = 11.1 Hz, 1 H), 3.11 (dd, *J* = 1.9, 11.1 Hz, 1 H), 3.24−3.28 (m, 1 H), 3.28 (s, 3 H), 3.32 (s, 3 H), 3.64 −3.74 (m, 1 H), 3.85 (d, *J* = 16.8 Hz, 1 H), 4.06−4.11 (m, 1 H), 4.32 (d, *J* = 16.8 Hz, 1 H), 5.58 (t, *J* = 2.1 Hz, 1 H), 5.88 (d, *J* = 1.4 Hz, 1 H), 5.90 (d, *J* = 1.4 Hz, 1 H), 6.50 (s, 1 H), 6.55 (s, 1 H); EIMS *m/z* (relative intensity) 331 (M$^+$, 100); HRMS calcd for C$_{18}$H$_{21}$NO$_5$ 331.1420, found 331.1410.

To a solution of 5.0 mg (0.015 mmol) of hydroxy ketal **71** in 1 mL of dry toluene at 0 °C under argon was added 0.15 mL (0.15 mmol) of DIBALH (1.0 M solution in hexanes). After the solution was allowed to warm to rt slowly and stirred for 27 h, 2 drops of saturated aqueous Na$_2$SO$_4$ solution was added, the mixture was stirred for 30 min, and 2 mL of CH$_2$Cl$_2$/MeOH/NH$_4$OH (92.5/5/2.5) was added. After being stirred for 30 min, the mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with CH$_2$Cl$_2$/MeOH/NH$_4$OH (92.5/5/2.5), to produce starting ketal **71** (0.6 mg, 12%), (−)-coccinine (**2**) (1.8 mg, 39% isolated yield, 44% based on recovered starting material), and (−)-montanine (**1**) (1.9 mg, 41% isolated yield, 47% based on recovered starting material). (−)-Montanine (**1**): ^{1}H NMR (500 MHz, CDCl$_3$) and low- and high-resolution mass spectra were identical to those previously reported.[12,36] [α]$^{25}_D$ = −83° (*c* = 0.06, CHCl$_3$) (lit.[3] [α]$^{26}_D$ = −87.6° (*c* = 0.6, CHCl$_3$)); ^{13}C NMR (125 MHz, CDCl$_3$) δ 32.7, 45.6, 55.4, 57.6, 58.7, 60.9, 69.2, 79.8, 100.7, 106.8, 107.3, 112.9, 124.8, 132.5, 145.9, 146.7, 154.3.

Preparation of Triol 72. To a solution of 21.0 mg (0.0316 mmol) of alcohol **54** in 4 mL of MeOH was added 25 mg of 10% palladium on carbon. After being stirred under hydrogen at rt for 20 h, the mixture was filtered through a small plug of Celite and concentrated *in vacuo*. The residue was dissolved in 3 mL of THF, and 0.063 mL (0.063 mmol) of tetrabutylammonium fluoride (1.0 M solution in THF) was added. After being stirred at rt for 3 h, the mixture was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with CHCl$_3$/MeOH (97/3), to produce triol **72** as a clear oil (14.0 mg, 97%): [α]$^{20}_D$ = −51.9° (*c* = 0.91, MeOH); ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.00−1.10 (m, 1 H), 1.34−1.42 (m, 1 H), 1.78 −1.95 (m, 1 H), 2.32−2.42 (m, 1 H), 2.43 (s, 3 H), 3.08−3.14 (m, 1 H), 3.36−3.40 (m, 1 H), 3.75−3.95 (m, 4 H), 4.11−4.20 (m, 2 H), 4.79 (d, *J* = 14.6 Hz, 1 H), 5.93 (s, 2 H), 6.46 (s, 1 H), 6.79 (s, 1 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.69 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 21.5, 26.9, 34.0, 34.7, 44.6, 54.1, 61.8, 63.4, 67.5, 68.5, 101.1, 105.9, 110.0, 127.2 (2 C), 128.9, 129.9 (2 C), 133.2, 135.5, 143.7, 145.7, 147.5; IR (CDCl$_3$) 3600−3250 cm^{-1}; EIMS *m/z* (relative intensity) 461 (M$^+$, 22); HRMS calcd for C$_{23}$H$_{27}$NO$_7$S 461.1508, found 461.1531.

Supporting Information Available: Experimental details for the reactions in eqs 2 and 3 and Schemes 4 and 12 (4 pages). See any current masthead page for ordering and Internet access instructions.