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Development of the [3 + 2] Annulations of Cyclohexenylsilanes and Chlorosulfonyl Isocyanate: Application to the Total Synthesis of (±)-Peduncularine

Claudia W. Roberson and K. A. Woerpel*

Contribution from the Department of Chemistry, University of California, Irvine, California 92697-2025

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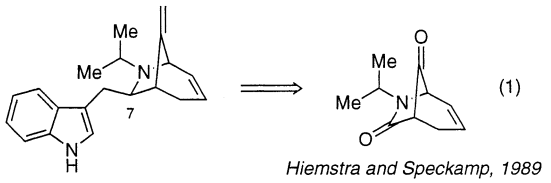
Abstract: The synthesis of (±)-peduncularine was accomplished using the [3 + 2] annulation of an allylic silane with chlorosulfonyl isocyanate to assemble the bicyclic core of the alkaloid. The stereochemistry of the annulation product was employed to control the installation of the indolylmethyl side chain at C-7 with complete stereoselectivity.

Introduction

The alkaloid peduncularine (**1**) was first isolated in 1971[1,2] from the Tasmanian shrub *Aristotelia peduncularis* with the structurally related alkaloids aristoteline, aristoserratine, sorelline, tasmanine, and hobartine.[3] Peduncularine, as well as many other alkaloids isolated from the *Aristotelia* genus, is thought to be derived biogenetically from tryptamine and a rearranged geranyl subunit.[3] These natural products have shown interesting biological activity; in particular, peduncularine has shown cytotoxic activity against breast cancer cell lines.[3]

Peduncularine represents a challenging synthetic target due to its unusual 6-azabicyclo[3.2.1]oct-3-ene core.[4] The only total synthesis of this alkaloid, reported by Hiemstra and Speckamp in 1989,[5] proceeded via the lactam **2** (eq 1). In the past few



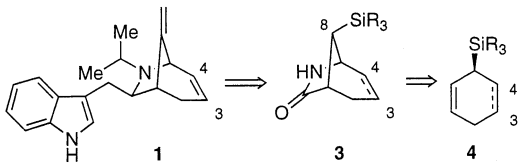
(1)

Hiemstra and Speckamp, 1989

1 **2**

years, three formal syntheses of peduncularine have appeared,[6,7] including our own,[8] targeting the lactam **2**. A formal synthesis involving this advanced intermediate, however, does not address a serious stereochemical problem. In the original total synthesis, the indolylmethyl side chain was introduced without control at the C-7 stereocenter.[5]

We envisioned that the azabicyclic core of peduncularine could be assembled in a single step using a [3 + 2] annulation reaction of a functionalized cyclohexenylsilane[9] such as **4** with chlorosulfonyl isocyanate (eq 2).[8,10,11] These annulation reactions



(2)

1 **3** **4**

(including both the [3 + 2][12] and [2 + 2][13] versions) are powerful tools for the synthesis of both carbocyclic and

* Address correspondence to this author. E-mail: kwoerpel@uci.edu.

(1) Bick, I. R. C.; Bremner, J. B.; Preston, N. W.; Calder, I. C. *J. Chem. Soc., Chem. Commun.* **1971**, 1155−1156.
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(7) Lin, X.; Stien, D.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 2333−2337.
(8) Roberson, C. W.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 621−623.
(9) For examples of 3-silylcyclohexenes as nucleophiles in other reactions, see: (a) Freppel, C.; Poirier, M.-A.; Richer, J.-C.; Maroni, Y.; Manuel, G. *Can. J. Chem.* **1974**, *52*, 4133−4138. (b) Carter, M. J.; Fleming, I.; Percival, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2415−2434. (c) Hayashi, T.; Kabeta, K.; Yamamoto, T.; Tamao, K.; Kumada, M. *Tetrahedron Lett.* **1983**, *24*, 5661−5664. (d) Wickham, G.; Young, D.; Kitching, W. *Organometallics* **1988**, *7*, 1187−1195. (e) Denmark, S. E.; Wallace, M. A.; Walker, C. B. *J. Org. Chem.* **1990**, *55*, 5543−5545. (f) Majetich, G.; Song, J. S.; Ringold, C.; Nemeth, G. A. *Tetrahedron Lett.* **1990**, *31*, 2239−2242. (g) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028−11029. (h) Clive, D. L. J.; Zhang, C. *J. Org. Chem.* **1995**, *60*, 1413−1427. (i) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317−337. (j) Loreto, M. A.; Tardella, P. A.; Tofani, D. *Tetrahedron Lett.* **1995**, *36*, 8295−8298.
(10) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434−1435.
(11) Isaka, M.; Williard, P. G.; Nakamura, E. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2115−2116.
(12) For examples of the [3 + 2] annulation, see: (a) Whitesell, J. K.; Nabona, K.; Deyo, D. *J. Org. Chem.* **1989**, *54*, 2258−2260. (b) Knölker, H.-J.; Jones, P. G.; Pannek, J. B. *Synlett* **1990**, 429−430. (c) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868−9870. (d) Knölker, H.-J.; Foitzik, N.; Goesmann, H.; Graf, R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1081−1083. (e) Danheiser, R. L.; Takahashi, T.; Bertók, B.; Dixon, B. R. *Tetrahedron Lett.* **1993**, *34*, 3845−3848. (f) Akiyama, T.; Yasusa, T.; Ishikawa, K.; Ozaki, S. *Tetrahedron Lett.* **1994**, *35*, 8401−8404. (g) Groaning, M. D.; Brengel, G. P.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 5517−5522. (h) Schinzer, D.; Muller, N.; Fischer, A. K.; Priess, J. W. *Synlett* **2000**, 1265−1268. (i) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949−1952. (j) Angle, S. R.; El-Said, N. A. *J. Am. Chem. Soc.* **2002**, *124*, 3608−3613.

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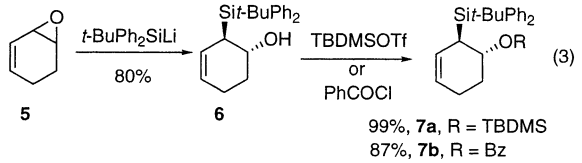
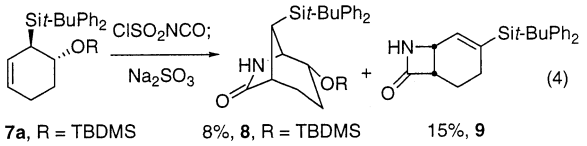
heterocyclic rings.[14,15] The silane **4** would require a functional group suitable for introduction of the C3−C4 double bond of peduncularine. The silyl group at C-8 of annulation product **3** would be oxidized to a hydroxyl group, providing a handle for installation of the exocyclic double bond of **1**. The lactam carbonyl group of **3** would serve as a precursor to an *N*-acyliminium ion, which would be employed to install the side chain at C-7. In this paper, we show that this plan culminates in a stereoselective total synthesis of peduncularine.

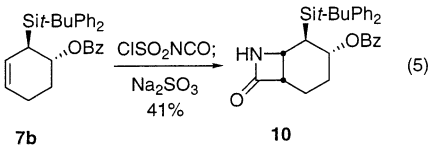
Results and Discussion

Cyclohexenylsilanes as Nucleophiles. Initially, efforts to prepare the functionalized bicyclic core of peduncularine focused on the preparation of cyclohexenylsilanes bearing alkoxy groups at C-4. This functional group pattern was chosen because Hiemstra and Speckamp had introduced the endocyclic double bond by elimination of acetic acid from a C-4 acetoxy derivative.[5] A stereoselective route to β-alkoxysilanes that would be amenable to asymmetric synthesis was developed to evaluate the viability of such a strategy. The cyclohexadiene-derived epoxide **5**[16,17] was treated with *tert*-butyldiphenylsilyllithium to provide the S_N2 product **6** in >99% isomeric purity (eq 3).[18] The resulting alcohol **6** was protected as the TBDMS ether **7a** and as the benzoate **7b**.



Submission of *trans*-substituted cyclohexenylsilanes **7a** and **7b** to annulation reaction conditions did not give acceptable results. Reactions of the allylic silane **7a** with chlorosulfonyl isocyanate led to a low yield of the desired annulation product **8** along with significant amounts of β-lactam **9**, whose structure was suggested by ^{1}H,^{1}H COSY experiments (eq 4). Treatment of the benzoate ester analogue **7b** with chlorosulfonyl isocyanate provided the [2 + 2] annulation[13] product **10** in 41% yield (eq 5). Attempts to optimize the annulations by variation of solvent and temperature were unsuccessful.

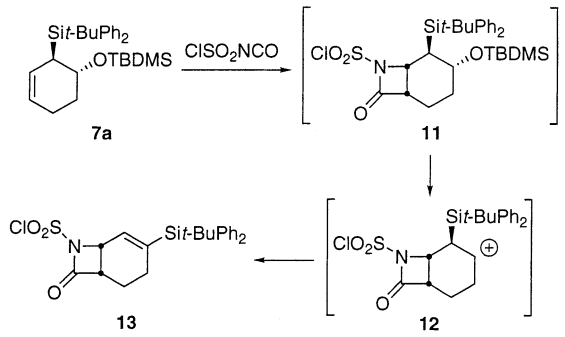




(13) For examples of the [2 + 2] annulation, see: (a) Akiyama, T.; Kirino, M. *Chem. Lett.* **1995**, 723−724. (b) Uyehara, T.; Yuuki, M.; Masaki, H.; Matsumoto, M.; Ueno, M.; Sato, T. *Chem. Lett.* **1995**, 789−790. (c) Akiyama, T.; Yamanaka, M. *Synlett* **1996**, 1095−1096. (d) Knölker, H.-J.; Baum, E.; Schmitt, O. *Tetrahedron Lett.* **1998**, *39*, 7705−7708. (e) Knölker, H.-J.; Baum, G.; Schmitt, O.; Wanzl, G. *Chem. Commun.* **1999**, 1737−1738. (f) Groaning, M. D.; Brengel, G. P.; Meyers, A. I. *Tetrahedron* **2001**, *57*, 2635−2642.
(14) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293−1316.
(15) Knölker, H.-J. *J. Prakt. Chem.* **1997**, *339*, 304−314.

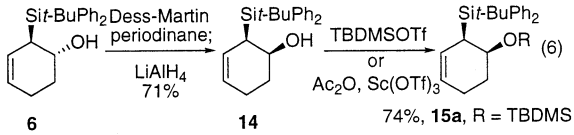
A possible mechanism for the formation of vinylsilane **9** from silyl ether **7a** is shown in Scheme 1. The *N*-chlorosulfonyl

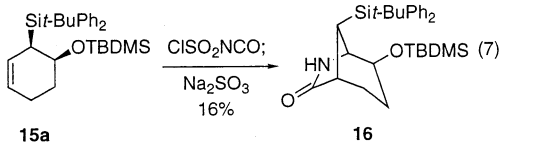
Scheme 1



β-lactam **11** could form initially, in analogy to the reaction of the benzoate derivative (eq 5). Ionization, likely facilitated by chlorosulfonyl isocyanate,[19] would generate β-silyl cation **12**. Silyl group migration and deprotonation would lead to *N*-chlorosulfonyl lactam **13**, which would form lactam **9** upon reductive workup. The fact that this product is so prevalent demonstrates that ionization of groups in the β-position relative to silicon would need to be prevented.

Because solvolysis was a significant side reaction, we evaluated the use of a *cis*-β-alkoxysilane as a potential solution. *cis*-β-Alkoxysilanes undergo solvolysis at a much slower rate than the analogous *trans*-β-alkoxysilanes,[20] increasing the possibility that the [3 + 2] annulation pathway would dominate over elimination. To test this idea, the silanes **15a**,**b** were prepared as shown in eq 6. Acetylation was performed under the Yamamoto conditions for hindered alcohols.[21] Submission of silane **15a** to annulation and reduction conditions resulted in a low yield of annulation product **16** (eq 7), although with none of the solvolysis products. Acetate **15b** provided only decomposition products under analogous annulation conditions. Attempts to optimize these annulations were unsuccessful.





The studies with β-alkoxysilanes indicated that a different approach would be required to install the C3−C4 double bond of peduncularine. Besides the ionization problem encountered with the *trans*-β-alkoxysilane **7a**, the presence of a nearby

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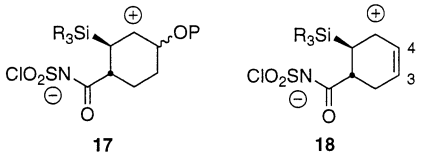
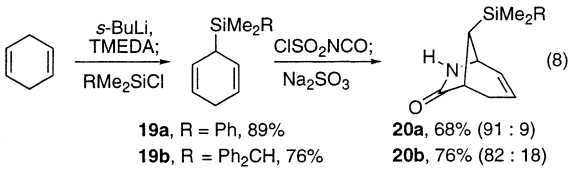
(20) Lambert, J. B.; Wang, G.-T.; Finzel, R. B.; Teramura, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7838−7845.
(21) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560−4567.

alkoxy group could inductively destabilize the carbocation intermediate **17** required to obtain annulation products.[22] Previous investigations of the [3 + 2] annulation reaction indicated that annulation efficiency improved with β-silyl carbocation stability.[10,23−25] Our goal was to identify a structure that would stabilize the β-silyl carbocation and provide a handle to install a double bond. We recognized that incorporation of the double bond at C-3 and C-4 (peduncularine numbering) into the starting nucleophile would provide a stabilized allylic cation intermediate (**18**). In addition to increasing the efficiency of the annulation,

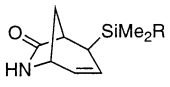


this approach would produce the required C3−C4 double bond of peduncularine directly, thereby reducing the number of steps required to reach the target. This approach, however, would lead to the target as a racemate because the starting cyclohexadienylsilane would be achiral.

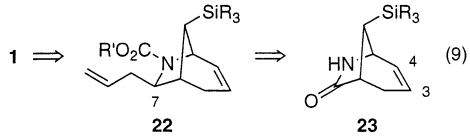
Cyclohexadienylsilanes as Nucleophiles. Cyclohexadienylsilanes proved to be successful partners in the annulation reactions to construct the bicyclic core of peduncularine.[26] These substrates could be prepared easily from commercially available materials. Treatment of 1,4-cyclohexadiene with *sec*-butyllithium and TMEDA followed by quenching with silyl chlorides provided, in high yield, thermally unstable cyclohexadienes **19a**,**b** as single regioisomers (eq 8).[27] The annulation reactions



were performed with **19a**,**b** under the standard conditions (CH_2Cl_2, −45 °C) followed by reduction in situ with 25% aqueous Na_2SO_3 to afford the desired bicyclic lactams **20a**,**b** as mixtures of regioisomers. The minor regioisomers **21a**,**b** were formed by the reaction of the nitrogen nucleophile at the less sterically crowded terminus of the intermediate allylic cation. The isomeric purity could be easily improved by recrystallization.

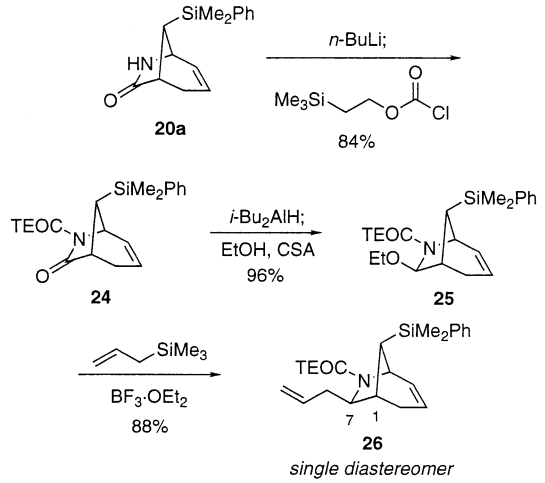


Total Synthesis of Peduncularine. With the bicyclic framework of peduncularine established, the completion of the synthesis was undertaken. As demonstrated in our formal synthesis,[8] the [3 + 2] annulation product **20b** was found to be a valuable intermediate. Our formal synthesis of the Hiemstra and Speckamp[5] intermediate **2** (eq 1) required only six steps from commercially available materials and showcased the use of the $(Ph_2CH)Me_2Si$ group,[28] which had been developed for facile silicon−carbon oxidation.[29−31] This formal synthesis, however, did not address the lack of stereochemical control during installation of the C-7 side chain of peduncularine (vide supra). To solve this problem, we developed a total synthesis that involved the carbamate **22**, which was obtained by allylation of an *N*-acyliminium ion derived from lactam **23** (eq 9).



The critical installation of the C-7 side chain onto the bicyclic core proceeded with high stereoselectivity (Scheme 2). Genera-

Scheme 2



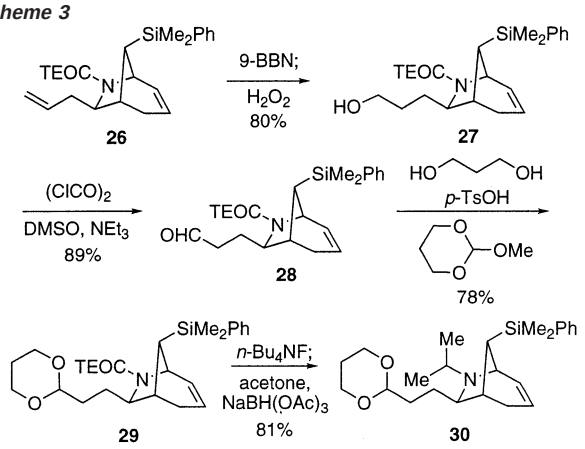
tion of the *N*-acyliminium ion precursor **25** commenced with acylation of lactam **20a** (as a 96:4 mixture of regioisomers) with the trimethylsilylethoxycarbamoyl (TEOC) group.[32] The resulting intermediate **24** was purified by recrystallization to yield >99% isomerically pure material. Selective reduction with *i*-Bu_2AlH followed by treatment of the resultant hemiacetal with ethanol and catalytic acid provided *N*,*O*-acetal **25** as a single acetal epimer. Acetal **25** was then submitted to Hosomi−Sakurai reaction conditions[33,34] to yield the allylated product **26** as a single diastereomer. The allylation proceeded with complete *exo*-selectivity,[35] as indicated by the absence of coupling between

(22) For an example of the successful use of β-alkoxysilanes in [3 + 2] annulations, see: Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461−464.
(23) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. *J. Org. Chem.* **1992**, *57*, 6094−6097.
(24) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1994**, 627−630.
(25) Schinzer, D.; Panke, G. *J. Org. Chem.* **1996**, *61*, 4496−4497.
(26) For other work with cyclohexadienylsilanes, see: (a) Taber, D. F.; Yet, L.; Bhamidipati, R. S. *Tetrahedron Lett.* **1995**, *36*, 351−354. (b) Fujishima, H.; Takeshita, H.; Toyota, M.; Ihara, M. *Chem. Commun.* **1999**, 893−894. (c) Angelaud, R.; Babot, O.; Charvat, T.; Landais, Y. *J. Org. Chem.* **1999**, *64*, 9613−9624.
(27) Ihara, M.; Suzuki, S.; Tokunaga, Y.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2811−2812.
(28) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 1379−1381.
(29) Fleming, I. *Chemtracts: Org. Chem.* **1996**, *9*, 1−64.
(30) Tamao, K. In *Advances in Silicon Chemistry*; JAI Press Inc.: Stamford, CT, 1996; Vol. 3, pp 1−62.
(31) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599−7662.
(32) Shute, R. E.; Rich, D. H. *Synthesis* **1987**, 346−349.
(33) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *17*, 1295−1298.
(34) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856.
(35) This material gave one peak in the GC/MS, although two compounds (presumably rotamers) were evident in the ^{1}H NMR spectrum. To determine whether the carbamate was two rotamers or two diastereoisomers, the alkoxycarbonyl moiety was removed. The resulting amine was found to be a single compound by ^{1}H NMR spectroscopy, indicating that the carbamate was a single diastereomer.

H-7 and H-1 in **26**.[36] Carbamate **26** was sensitive to the Lewis acid (BF_3·OEt_2) at temperatures above −20 °C, so careful control of the reaction temperature and optimization of the isolation procedure were critical to the success of the reaction. Treatment of the reaction mixture with triethylamine was required prior to warming to room temperature to obtain a high yield (88%) of lactam **26**.

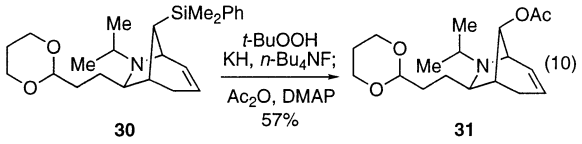
Preparation of the C-7 side chain for installation of the indole ring and construction of the tertiary amine moiety was performed in five steps from the carbamate **26** (Scheme 3). Aldehyde **28**

Scheme 3



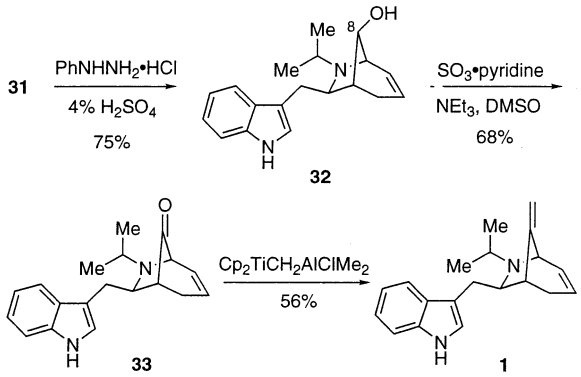
was obtained by hydroboration of **26** with 9-BBN followed by Swern oxidation. Because the carbamate group of **28** was sensitive to acid, the aldehyde was converted to the propanediol acetal in the presence of 2-methoxy-1,3-dioxane.[37] This operation was performed both to protect the aldehyde functionality in the following step and to improve the yield of the Fischer indole synthesis.[38] Liberation of the amino group with *n*-Bu_4NF followed by reductive amination[39] under neutral conditions provided isopropylamine **30**.

Oxidation of the silyl group at C-8 provided a hydroxyl group that could be transformed to the C8−C9 alkene of peduncularine (eq 10). Since the $PhMe_2Si$ group could not be oxidized at the bicyclic lactam stage,[40] this oxidation was performed on a tertiary amine substrate. Using the modified oxidation conditions



developed in our laboratories (*t*-BuOOH, KH, and *n*-Bu_4NF),[41] the phenylsilane **30** was successfully converted to the alcohol (eq 10). Because 5 equiv of *n*-Bu_4NF was needed for the reaction to proceed to completion, the resulting amino alcohol oxidation product was converted to the acetate **31** to facilitate separation from residual *n*-Bu_4NF impurities. While exploring alternate oxidation procedures, we found that displacement of the phenyl

Scheme 4



group on silane **30** could be performed with *t*-BuOK in DMSO.[42] Treatment of the resultant silanol with standard Tamao oxidation conditions (30% H_2O_2, KF, $KHCO_3$) resulted in decomposition, possibly due to *N*-oxide formation.[43] The oxidation conditions developed in our laboratories[41] proved to be the only method that was successful in performing a silicon−carbon oxidation on the phenylsilane of the amine substrate.[44]

The total synthesis of peduncularine was completed in three steps from acetate **31**. The Fischer indole synthesis provided alcohol **32**[5,45] with concomitant deprotection of the C-8 alcohol (Scheme 4). Alcohol **32** was oxidized to the ketone **33** by the mild Parikh−Doering oxidation method.[46] Methylenation of the ketone with freshly prepared Tebbe reagent[47] provided (±)-peduncularine (**1**) with good conversion.

Conclusion

The total synthesis of (±)-peduncularine was accomplished in 16 steps from commercially available materials. The key step of the synthesis is the [3 + 2] annulation of an allylic silane with chlorosulfonyl isocyanate, which provided the distinctive bicyclic core of the natural product. This operation assembled the bicyclic core of the alkaloid in one step, established two stereocenters, and installed functional group handles that were required to complete the synthesis. The stereochemistry of the annulation product was employed to control the installation of the indolylmethyl side chain at C-7 with complete stereoselectivity. The synthesis requires a minimum number of protecting groups that also serve dual roles as activating groups (the TEOC and dioxane units) or functionalities that assist with isolation (the acetate group). The successful synthesis (±)-peduncularine demonstrates the utility of annulation reactions of allylic silanes in the synthesis of natural products.

Experimental Section[48]

3-Dimethylphenylsilyl-1,4-cyclohexadiene (19a). To a cooled (−78 °C) solution of 1,4-cyclohexadiene (10.0 mL, 109 mmol) in 110 mL of THF were added *s*-BuLi (93.0 mL, 1.07 M in cyclohexane, 99 mmol) and TMEDA (15.0 mL, 99.2 mmol). The yellow solution was warmed to −45 °C, and after 2.5 h was treated with neat chlorodimethylphe-

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nylsilane (16.7 mL, 99.2 mmol). After 30 min at −45 °C, the solution was treated with 300 mL of H_2O and warmed to 23 °C. The organic phase was diluted with 200 mL of Et_2O, separated from the aqueous phase, washed with 300 mL of brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes) provided **19a** as an oil (19.0 g, 89%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.36 (m, 3H), 5.65−5.62 (m, 2H), 5.56−5.53 (m, 2H), 2.73−2.65 (m, 1H), 2.59−2.45 (m, 2H), 0.31 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 133.9, 129.0, 127.6, 125.9, 121.9, 30.9, 26.3, −5.4; IR (thin film) 3024, 2820, 1666, 1622 cm^{-1}; HRMS (GC/MS, EI) *m*/*z* calcd for $C_{14}H_{18}Si$ $(M)^+$ 214.1178, found 214.1179.

(1*R,5*R**,8*R**)-8-Dimethylphenylsilyl-6-azabicyclo[3.2.1]oct-3-en-7-one (20a).** To a cooled (−78 °C) solution of **19a** (15.0 g, 70.0 mmol) in 500 mL of CH_2Cl_2 was added chlorosulfonyl isocyanate (6.70 mL, 77.0 mmol). The solution was warmed to −45 °C. After 13 h at −45 °C, the solution was treated with 500 mL of 25% aqueous Na_2SO_3. The biphasic mixture was warmed to 23 °C and stirred for 22 h. The organic phase was separated from the aqueous phase, and the aqueous phase was extracted with 400 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Analysis of the unpurified reaction mixture by ^{1}H NMR spectroscopy showed a 91:9 ratio of **20a**:**21a**. Purification by flash chromatography (1:1 EtOAc/hexanes) provided **20a** and regioisomer **21a** (combined 12.27 g, 68%). Recrystallization provided a pure sample of **20a** as a white solid: mp 115−116 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.37 (m, 3H), 6.14 (m, 1H), 5.98 (br s, 1H), 5.58 (m, 1H), 3.65 (m, 1H), 2.71 (m, 1H), 2.28 (m, 2H), 2.08 (t, J = 3.9 Hz, 1H), 0.372 (s, 3H), 0.366 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 137.5, 133.4, 131.3, 129.2, 128.7, 127.8, 51.1, 41.6, 36.1, 26.9, −2.6, −2.9; IR (KBr) 3203, 3064, 2957, 1683, 1636 cm^{-1}; HRMS (CI/isobutane) *m*/*z* calcd for $C_{15}H_{20}NOSi$ $(M + H)^+$ 258.1314, found 258.1320. Anal. Calcd for $C_{15}H_{19}NOSi$: C, 69.99; H, 7.44; N, 5.44. Found: C, 69.81; H, 7.50; N, 5.47.

(1*R,5*R**,8*R**)-8-Dimethylphenylsilyl-7-oxo-6-azabicyclo[3.2.1]-oct-3-ene-6-carboxylic Acid 2-Trimethylsilylethyl Ester (24).** To a cooled (−78 °C) solution of **20a** (20.00 g, 96:4 ratio of **20a**:**21a** by ^{1}H NMR spectroscopy, 74.59 mmol of **20a**) in 600 mL of THF was added *n*-BuLi (40.0 mL, 92 mmol, 2.3 M in hexanes). After 30 min at −78 °C, 2-trimethylsilylethyl chloroformate[32] (155.4 mmol) was added by cannula. Saturated aqueous ammonium chloride solution (600 mL) was added after 45 min at −78 °C, and the reaction mixture was allowed to warm to 23 °C. The organic layer was separated from the aqueous layer, concentrated in vacuo, and azeotropically dried under vacuum with 4 × 200 mL of benzene. Purification by recrystallization (hexanes/EtOAc), followed by recrystallization of the mother liquor, provided **24** in >99% isomeric purity (25.26 g, 84%): mp 113−114 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2H), 7.36 (m, 3H), 6.28 (m, 1H), 5.60 (m, 1H), 4.35 (m, 1H), 4.32−4.23 (m, 2H), 2.84 (m, 1H), 2.30 (m, 2H), 1.93 (t, J = 4.0 Hz, 1H), 1.11−1.06 (m, 2H), 0.377 (s, 3H), 0.374 (s, 3H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 151.1, 136.8, 133.4, 129.8, 129.4, 128.9, 127.9, 64.9, 55.0, 43.8, 32.4, 27.1, 17.6, −1.7, −2.6, −3.0; IR (KBr) 3056, 2957, 1786, 1752, 1700 cm^{-1}; HRMS (CI/ammonia) *m*/*z* calcd for $C_{21}H_{31}NO_3Si_2$ $(M)^+$ 401.1842, found 401.1836. Anal. Calcd for $C_{21}H_{31}NO_3Si_2$: C, 62.80; H, 7.78; N, 3.49. Found: C, 62.90; H, 7.78; N, 3.52.

(1*R,5*R**,7*R**,8*R**)-8-Dimethylphenylsilyl-7-ethoxy-6-azabicyclo-[3.2.1]oct-3-ene-6-carboxylic Acid 2-Trimethylsilylethyl Ester (25).** To a cooled (−78 °C) solution of **24** (10.40 g, 25.89 mmol) in 300 mL of THF was added, over 20 min, a solution of *i*-Bu_2AlH (65.0 mL, 65 mmol, 1.0 M in hexanes). After 1 h, the reaction mixture was treated with 60 mL of saturated aqueous ammonium chloride and warmed to 23 °C. Saturated sodium potassium tartrate solution (200 mL) was added to the solution, and the heterogeneous mixture was concentrated in vacuo. The aqueous layer was washed with 5 × 300 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in 100 mL of EtOH, and to the solution was added camphorsulfonic acid (0.302 g, 1.30 mmol). After 16 h, the solution was treated with 400 mL of saturated aqueous $NaHCO_3$ and diluted with 300 mL of CH_2Cl_2. The organic layer was separated from the aqueous layer and washed with 400 mL of saturated aqueous $NaHCO_3$. The combined aqueous layers were extracted with 800 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (1:1 hexanes/EtOAc to 100% EtOAc) provided **25** as an oil (10.77 g, 96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.35 (m, 3H), 6.29 (m, 0.34H), 6.12 (m, 0.66H), 5.35 (m, 1H), 4.90 (s, 0.66H), 4.74 (s, 0.34H), 4.19−4.05 (m, 3H), 3.71−3.49 (m, 2H), 2.41 (m, 1H), 2.25 (m, 1H), 2.06 (t, J = 3.8 Hz, 0.66H), 2.01−1.94 (m, 1.34H), 1.18 (t, J = 7.0 Hz, 3H), 1.03−0.93 (m, 2H), 0.35 (s, 3H), 0.34 (s, 3H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 155.0, 138.3, 133.6, 132.7, 132.3, 129.0, 127.7, 127.1, 126.9, 95.2, 94.7, 64.3, 64.0, 63.3, 63.2, 54.6, 54.3, 42.2, 41.7, 30.5, 29.72, 29.67, 17.9, 17.7, 15.44, 15.40, −1.6, −1.9, −2.5; IR (thin film) 3034, 2954, 1702 cm^{-1}; HRMS (CI/ammonia) *m*/*z* calcd for $C_{23}H_{37}NO_3Si_2$ $(M)^+$ 431.2312, found 431.2298. Anal. Calcd for $C_{23}H_{37}NO_3Si_2$: C, 63.99; H, 8.64; N, 3.24. Found: C, 63.75; H, 8.72; N, 3.28.

(1*R,5*R**,7*R**,8*R**)-7-Allyl-8-dimethylphenylsilyl-6-azabicyclo-[3.2.1]oct-3-ene-6-carboxylic Acid 2-Trimethylsilylethyl Ester (26).** To a cooled (−78 °C) solution of **25** (4.00 g, 9.27 mmol) in 165 mL of CH_2Cl_2 were added sequentially allyltrimethylsilane (5.90 mL, 37.1 mmol) and BF_3·Et_2O (2.28 mL, 18.5 mmol). The solution was warmed to −45 °C. After 2 h, the reaction mixture was treated with 6.0 mL of NEt_3 and then with 100 mL of H_2O. The heterogeneous solution was allowed to warm to 23 °C. The organic layer was separated from the aqueous layer, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) provided **26** as an oil (3.48 g, 88%, >99% diastereomeric excess by GC/MS of the unpurified reaction mixture): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.35 (m, 3H), 6.27 (0.4H), 6.10 (m, 0.6H), 5.77 (m, 1H), 5.47 (m, 1H), 5.01 (m, 2H), 4.18−4.07 (m, 3H), 3.55 (dd, J = 9.9, 3.2 Hz, 0.6H), 3.46 (dd, J = 9.8, 2.7 Hz, 0.4H), 2.64 (m, 0.6H), 2.55 (m, 0.4H), 2.34 (m, 2H), 2.07−1.96 (m, 2H), 1.70 (t, J = 3.7 Hz, 0.6H), 1.64 (t, J = 3.7 Hz, 0.4H), 0.98 (m, 2H), 0.34 (s, 3H), 0.33 (s, 3H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 155.0, 138.5, 135.9, 135.8, 133.5, 131.6, 131.1, 129.0, 128.1, 127.8, 116.74, 116.69, 66.7, 66.0, 62.9, 62.8, 54.7, 54.6, 39.5, 38.9, 38.6, 38.3, 34.20, 34.16, 31.1, 30.3, 18.0, 17.9, −1.5, −1.9, −2.5; IR (thin film) 3070, 2953, 1695, 1639 cm^{-1}; HRMS (CI/isobutane) *m*/*z* calcd for $C_{22}H_{34}NO_2Si_2$ $(M - C_2H_3)^+$ 400.2128, found 400.2135. Anal. Calcd for $C_{24}H_{37}NO_2Si_2$: C, 67.39; H, 8.72; N, 3.27. Found: C, 67.20; H, 8.76; N, 3.28.

(1*R,5*R**,7*R**,8*R**)-8-Dimethylphenylsilyl-7-(3-hydroxypropyl)-6-azabicyclo[3.2.1]oct-3-ene-6-carboxylic Acid 2-Trimethylsilylethyl Ester (27).** To a solution of **26** (0.152 g, 0.355 mmol) in 2 mL of THF was added solid 9-BBN dimer (0.130 g, 1.07 mmol). After 1 h at 23 °C, the reaction mixture was treated, sequentially, with 0.75 mL of EtOH, 0.25 mL of 6 M NaOH, and 0.5 mL of 30% aqueous H_2O_2. The heterogeneous solution was heated to 50 °C for 1 h. Once cooled to 23 °C, the mixture was diluted with 5 mL of Et_2O and 2 mL of H_2O. The aqueous layer was saturated with K_2CO_3, separated from the organic layer, and extracted with 5 mL of Et_2O. The combined organic layers were washed with 10 mL of brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) provided **27** as an oil (0.126 g, 80%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.37 (m, 3H), 6.27 (m, 0.2H), 6.10 (m, 0.8H), 5.46 (m, 1H), 4.16−4.05 (m, 3H), 3.67 (m, 2H), 3.56 (dd, J = 9.4, 2.9 Hz, 0.8H), 3.40 (dd, J = 9.9, 2.6 Hz, 0.2H), 2.82 (br s, 0.8H), 2.41−2.36 (m, 1H), 2.26 (s, 0.2H), 2.21 (s, 0.8H), 2.04−1.97 (m, 1H), 1.90−1.77 (m, 2H), 1.68 (s, 0.2H), 1.66−1.33 (m, 3H), 0.98 (m, 2H), 0.35 (s, 3H), 0.34 (s, 3H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 155.2, 138.4, 133.5, 131.7, 131.0, 129.1, 128.1, 127.8, 127.7, 66.6, 63.0, 62.6, 62.1, 54.5, 54.4, 40.5, 40.3, 34.3, 34.2, 31.4, 30.93, 30.86, 30.5, 30.3, 29.6, 17.9, 17.8, −1.5, −1.9, −2.5; IR (thin film)

3453, 3032, 2951, 1694 cm^{-1}; HRMS (CI/ammonia) *m*/*z* calcd for $C_{24}H_{40}NO_3Si_2$ $(M + H)^+$ 446.2546, found 446.2548. Anal. Calcd for $C_{24}H_{39}NO_3Si_2$: C, 64.67; H, 8.82; N, 3.14. Found: C, 64.45; H, 8.85; N, 3.13.

(1*R,5*R**,7*R**,8*R**)-8-Dimethylphenylsilyl-7-(3-oxopropyl)-6-azabicyclo[3.2.1]oct-3-ene-6-carboxylic Acid 2-Trimethylsilylethyl Ester (28).** To a cooled (−78 °C) solution of DMSO (0.622 mL, 8.77 mmol) in 25 mL of CH_2Cl_2 was added oxalyl chloride (0.384 mL, 4.38 mmol). After 1 h, a solution of **27** (1.15 g, 2.58 mmol) in 10 mL of CH_2Cl_2 was added. Triethylamine (2.70 mL, 19.4 mmol) was added to the solution after 1 h at −78 °C. The reaction mixture was allowed to warm to 23 °C, stirred for 1 h, and poured into 40 mL of H_2O. The organic layer was separated from the aqueous layer, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) provided **28** as an oil (1.02 g, 89%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (t, J = 1.6 Hz, 1H), 7.50 (m, 2H), 7.36 (m, 3H), 6.28 (m, 0.33H), 6.10 (m, 0.67H), 5.45 (m, 1H), 4.16−4.05 (m, 3H), 3.52 (dd, J = 7.8, 5.5 Hz, 0.67H), 3.40 (dd, J = 9.0, 4.0 Hz, 0.33H), 2.52−2.36 (m, 3H), 2.19 (m, 1H), 2.02 (m, 2H), 1.75−1.63 (m, 2H), 1.00−0.96 (m, 2H), 0.35 (s, 3H), 0.34 (s, 3H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 201.2, 155.4, 155.0, 138.0, 133.2, 131.5, 131.0, 128.9, 127.6, 127.3, 66.8, 66.1, 63.1, 63.0, 54.9, 41.8, 40.9, 34.3, 34.2, 31.6, 30.8, 27.5, 18.1, −1.2, −1.6, −2.3; IR (thin film) 3033, 2953, 2897, 2720, 1725, 1694 cm^{-1}; HRMS (CI/ammonia) *m*/*z* calcd for $C_{24}H_{38}NO_3Si_2$ $(M + H)^+$ 444.2390, found 444.2395. Anal. Calcd for $C_{24}H_{37}NO_3Si_2$: C, 64.96; H, 8.40; N, 3.16. Found: C, 64.92; H, 8.52; N, 3.16.

(1*R,5*R**,7*R**,8*R**)-8-Dimethylphenylsilyl-7-(2-[1,3]dioxan-2-ylethyl)-6-azabicyclo[3.2.1]oct-3-ene-6-carboxylic Acid 2-Trimethylsilylethyl Ester (29).** A solution of aldehyde **28** (0.041 g, 0.092 mmol) in 1 mL of THF was treated with 1,3-propanediol (0.073 mL, 1.0 mmol), 2-methoxy-1,3-dioxane[37] (0.040 g, 0.33 mmol), and a crystal of *p*-TsOH. After 20 min, the reaction mixture was diluted with 5 mL of Et_2O and treated with 5 mL of saturated aqueous $NaHCO_3$. The organic layer was separated from the aqueous layer, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) provided **29** as an oil (0.036 g, 78%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (m, 2H), 7.35 (m, 3H), 6.26 (m, 0.35H), 6.07 (m, 0.65H), 5.44 (m, 1H), 4.52 (t, J = 5.1 Hz, 0.65H), 4.49 (t, J = 5.1 Hz, 0.35H), 4.14−4.04 (m, 5H), 3.75−3.70 (m, 2H), 3.48 (dd, J = 9.7, 3.3 Hz, 0.65H), 3.38 (dd, J = 9.7, 2.6 Hz, 0.35H), 2.36 (m, 1H), 2.28 (m, 1H), 2.08−1.84 (m, 3H), 1.69−1.59 (m, 3H), 1.44−1.26 (m, 2H), 1.00−0.88 (m, 2H), 0.34 (s, 3H), 0.33 (s, 3H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 155.2, 138.6, 133.5, 131.8, 131.2, 129.0, 127.9, 127.8, 127.6, 102.3, 102.1, 67.52, 66.82, 66.77, 62.8, 62.7, 54.5, 40.4, 39.4, 34.2, 33.0, 32.9, 31.3, 30.4, 29.1, 28.5, 25.8, 17.9, −1.5, −1.8, −2.5; IR (thin film) 3032, 2953, 1694 cm^{-1}; HRMS (FAB+) *m*/*z* calcd for $C_{27}H_{43}NO_4Si_2$ $(M)^+$ 501.2730, found 501.2725. Anal. Calcd for $C_{27}H_{43}NO_4Si_2$: C, 64.63; H, 8.63; N, 2.79. Found: C, 64.78; H, 8.63; N, 2.76.

(1*R,5*R**,7*R**,8*R**)-8-Dimethylphenylsilyl-7-(2-[1,3]dioxan-2-ylethyl)-6-isopropyl-6-azabicyclo[3.2.1]oct-3-ene (30).** A solution of **29** (0.581 g, 1.16 mmol) in 15 mL of CH_3CN was treated with *n*-Bu_4NF (1.85 mL, 1.9 mmol, 1.0 M in THF) at 65 °C for 6 h. Upon being cooled to 23 °C, the reaction mixture was concentrated in vacuo. Purification by flash chromatography (90:10:1 CH_2Cl_2/MeOH/NEt_3) provided the amine as an impure residue which was used in the subsequent step. Repurification of an aliquot provided a pure sample of the deprotected amine as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.33 (m, 3H), 5.92 (m, 1H), 5.44 (m, 1H), 4.51 (t, J = 5.0 Hz, 1H), 4.07 (m, 2H), 3.73 (m, 2H), 3.50 (dd, J = 5.8, 3.4 Hz, 1H), 2.90 (t, J = 7.0 Hz, 1H), 2.33 (m, 1H), 2.15 (m, 1H), 2.10−2.00 (m, 2H), 1.89 (m, 1H), 1.69−1.47 (m, 3H), 1.41−1.31 (m, 3H), 0.34 (s, 3H), 0.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 133.1, 131.8, 128.4, 127.2, 126.5, 101.8, 66.63, 66.62, 64.8, 55.2, 41.6, 35.0, 32.9, 31.5, 25.8, −1.5, −2.1; IR (thin film) 3322, 3022, 2849, 1640 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{32}NO_2Si$ $(M + H)^+$ 358.2202, found 358.2198.

The deprotected amine (1.16 mmol) and acetone (0.426 mL, 5.80 mmol) were mixed in 12 mL of CH_3CN and then treated with sodium triacetoxyborohydride (0.369 g, 1.74 mmol). The mixture was stirred for 14 h at 23 °C until the reactant was consumed (as determined by GC analysis). The reaction mixture was diluted with 30 mL of CH_2Cl_2 and treated with 40 mL of saturated aqueous $NaHCO_3$. The organic layer was separated from the aqueous layer, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (95:5:1 CH_2Cl_2/MeOH/NEt_3) provided **30** as an oil (0.377 g, 81% over two steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.30 (m, 3H), 5.82 (m, 1H), 5.57 (m, 1H), 4.46 (m, 1H), 4.07−4.03 (m, 2H), 3.72−3.66 (m, 2H), 3.47 (m, 1H), 2.68 (septet, J = 6.2 Hz, 1H), 2.30 (m, 1H), 2.15−1.98 (m, 3H), 1.82 (m, 1H), 1.72 (t, J = 3.7 Hz, 1H), 1.59−1.53 (m, 3H), 1.40−1.35 (m, 1H), 1.28 (m, 1H), 1.07 (d, J = 6.4 Hz, 3H), 1.05 (d, J = 6.2 Hz, 3H), 0.33 (s, 3H), 0.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 133.5, 129.6, 128.6, 128.4, 127.4, 102.1, 71.5, 66.6, 57.1, 51.0, 41.4, 35.6, 33.5, 33.2, 30.7, 25.6, 23.7, 22.6, −1.6, −2.3; IR (thin film) 3020, 2964, 1643 cm^{-1}; HRMS (CI/ammonia) *m*/*z* calcd for $C_{24}H_{38}NO_2Si$ $(M + H)^+$ 400.2672, found 400.2674. Anal. Calcd for $C_{24}H_{37}NO_2Si$: C, 72.13; H, 9.33; N, 3.50. Found: C, 71.90; H, 9.38; N, 3.52.

Acetic Acid (1*R,5*R**,7*R**,8*R**)-7-(2-[1,3]Dioxan-2-ylethyl)-6-isopropyl-6-azabicyclo[3.2.1]oct-3-en-8-yl Ester (31).** To a cooled (−45 °C) suspension of KH (0.113 g, 2.86 mmol) in 1 mL of DMF was added *tert*-butyl hydroperoxide (0.12 mL, 0.9 mmol, 70% in H_2O) dropwise. After being warmed to 23 °C, the reaction mixture was treated with a solution of **30** (0.052 g, 0.13 mmol) in 2 mL of DMF. After 10 min, *n*-Bu_4NF (0.715 mL, 0.72 mmol, 1.0 M in THF) was added to the reaction mixture. Immediately after addition was complete, the solution foamed vigorously. The flask was fitted with a reflux condenser, and the solution was heated to 65 °C for 4 h. Once cooled to 23 °C, the reaction mixture was treated with 10 mL of EtOAc and 10 mL of saturated aqueous $Na_2S_2O_3$. The organic layer was separated from the aqueous layer, and the aqueous layer was washed with 2 × 10 mL of EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (90:10:1 CH_2Cl_2/MeOH/NEt_3) to provide the impure alcohol: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (m, 1H), 5.78 (m, 1H), 4.49 (t, J = 4.8 Hz, 1H), 4.41 (t, J = 4.6 Hz, 1H), 4.10−4.07 (m, 2H), 3.76−3.71 (m, 2H), 3.50 (t, J = 4.6 Hz, 1H), 2.83 (septet, J = 6.3 Hz, 1H), 2.54 (m, 1H), 2.37 (m, 1H), 2.10−2.00 (m, 2H), 1.94 (m, 1H), 1.67−1.46 (m, 4H), 1.34−1.31 (m, 1H), 1.08 (d, J = 6.2 Hz, 3H), 1.06 (d, J = 6.4 Hz, 3H). A solution of the alcohol in 1 mL of CH_2Cl_2 was treated with acetic anhydride (0.123 mL, 1.30 mmol), triethylamine (0.091 mL, 0.65 mmol), and a crystal of DMAP. After 30 min at 23 °C, the reaction mixture was concentrated in vacuo. Purification by flash chromatography (95:5 CH_2Cl_2/MeOH) provided acetate **31** as an oil (0.024 g, 57%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.70 (m, 1H), 5.12 (t, J = 4.8 Hz, 1H), 4.50 (t, J = 4.7 Hz, 1H), 4.08 (dd, J = 10.8, 4.9 Hz, 2H), 3.74 (td, J = 12.1, 2.2 Hz, 2H), 3.65 (t, J = 4.7 Hz, 1H), 2.83 (septet, J = 6.3 Hz, 1H), 2.42 (m, 1H), 2.34 (m, 1H), 2.22 (m, 1H), 2.06 (m, 1H), 2.03 (s, 3H), 1.92−1.87 (m, 1H), 1.68−1.44 (m, 4H), 1.32 (m, 1H), 1.05 (d, J = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 129.1, 125.8, 102.0, 71.0, 68.1, 66.81, 66.78, 55.5, 50.5, 40.1, 33.2, 32.8, 32.7, 25.9, 23.1, 22.7, 21.2; IR (thin film) 3021, 2964, 2846, 2730, 2655, 1737, 1642 cm^{-1}; HRMS (CI/ammonia) *m*/*z* calcd for $C_{18}H_{30}NO_4$ $(M + H)^+$ 324.2175, found 324.2174. Anal. Calcd for $C_{18}H_{29}NO_4$: C, 66.85; H, 9.04; N, 4.33. Found: C, 66.49; H, 9.16; N, 4.34.

(1*R,5*R**,7*R**,8*R**)-7-(1*H*-Indol-3-ylmethyl)-6-isopropyl-6-azabicyclo[3.2.1]oct-3-en-8-ol (32).** A solution of 1.5 mL of 4% aqueous sulfuric acid was heated to 50 °C for 30 min. Phenylhydrazine hydrochloride (0.025 g, 0.17 mmol) was added to the heated solution,

and the solid was allowed to dissolve over 10 min. The heated solution was transferred to a flask containing acetal **31** (0.051 g, 0.16 mmol). This mixture was heated at reflux for 1 h. After being cooled to 23 °C, the reaction mixture was treated with 2 mL of saturated aqueous $NaHCO_3$ solution and 4 mL of EtOAc. The organic phase was separated from the aqueous phase, and the aqueous phase was washed with 2 × 5 mL of EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (90:10:0.5 CH_2Cl_2/MeOH/NEt_3) provided **32** as a white foam (0.035 g, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.19 (m, 1H), 7.11 (m, 1H), 6.99 (s, 1H), 5.98 (m, 1H), 5.84 (m, 1H), 4.54 (m, 1H), 3.61 (t, J = 4.6 Hz, 1H), 2.99 (m, 2H), 2.89−2.79 (m, 2H), 2.40 (m, 1H), 2.20 (m, 1H), 1.90 (br s, 1H), 1.81−1.77 (m, 1H), 1.28 (d, J = 6.4 Hz, 3H), 1.16 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 130.9, 127.7, 127.3, 122.0, 121.7, 119.3, 119.1, 114.9, 111.1, 69.4, 69.1, 58.7, 51.0, 41.5, 34.5, 32.1, 23.3, 22.7; IR (KBr) 3291, 3040, 2936, 1653, 1617, 1457, 1100, 739 cm^{-1}; HRMS (CI/ammonia) m/z calcd for $C_{19}H_{25}N_2O$ $(M + H)^+$ 297.1967, found 297.1965.

(1*R,5*R**,7*R**)-7-(1*H*-Indol-3-ylmethyl)-6-isopropyl-6-azabicyclo-[3.2.1]oct-3-en-8-one (33).** To a solution of **32** (0.013 g, 0.040 mmol) in 0.6 mL of DMSO were added sulfur trioxide−pyridine complex (0.043 g, 0.27 mmol) and triethylamine (0.050 mL, 0.36 mmol). After 20 min at 23 °C, the reaction mixture was treated with 3 mL of saturated aqueous $NaHCO_3$ solution and 3 mL of EtOAc. The organic layer was separated from the aqueous layer, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc to 1:3 hexanes/EtOAc) provided **33** as a foam (0.008 g, 68%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (br s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.20 (td, J = 8.0, 1.0 Hz, 1H), 7.13 (td, J = 7.9, 1.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 5.92 (m, 1H), 5.80 (m, 1H), 3.58 (d, J = 5.2 Hz, 1H), 3.30−3.26 (m, 2H), 3.13 (dd, J = 14.9, 2.6 Hz, 1H), 2.74 (ddt, J = 18.1, 5.0, 2.5 Hz, 1H), 2.67 (dd, J = 14.8, 10.7 Hz, 1H), 2.43 (m, 2H), 1.39 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 136.2, 130.3, 130.0, 127.5, 122.2, 121.9, 119.3, 118.8, 113.1, 111.2, 66.6, 61.1, 50.2, 49.7, 41.5, 33.6, 22.7, 22.4; IR (thin film) 3411, 3049, 2970, 1760, 1637 cm^{-1}; HRMS (CI/ammonia) m/z calcd for $C_{19}H_{23}N_2O$ $(M + H)^+$ 295.1810, found 295.1807.

(±)-Peduncularine (1). To a cooled (−45 °C) solution of **33** (0.025 g, 0.085 mmol) in 0.5 mL of THF was added Tebbe reagent[47] (0.340 mL, 0.34 mmol, 1.0 M in toluene). The reaction mixture was maintained at −45 °C for 30 min and then slowly warmed to 0 °C over 2.5 h. The reaction mixture was warmed to 23 °C and stirred for 3 h. The solution was diluted with 1 mL of THF and treated with 0.2 mL of 15% aqueous NaOH. After being stirred for 1 h, the heterogeneous mixture was filtered, and the precipitate was washed with 3 × 5 mL of Et_2O. The filtrates were combined and concentrated in vacuo. Purification by flash chromatography (75:25 hexanes/EtOAc to 75:25:1 hexanes/EtOAc/NEt_3) provided **1** (0.014 g, 56%) as a solid:[5,49] mp 145−147 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (br s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.99 (s, 1H), 5.95 (ddt, J = 9.3, 5.2, 2.0 Hz, 1H), 5.69 (dt, J = 9.3, 2.8 Hz, 1H), 4.95 (s, 1H), 4.82 (s, 1H), 3.84 (d, J = 5.0 Hz, 1H), 3.00 (septet, J = 6.2 Hz, 1H), 2.95 (d, J = 15.4 Hz, 1H), 2.89 (d, J = 11.3 Hz, 1H), 2.71 (dd, J = 14.7, 11.4 Hz, 1H), 2.50 (br d, J = 4.1 Hz, 1H), 2.46 (ddt, J = 17.6, 4.6, 2.4 Hz, 1H), 2.07 (ddt, J = 17.6, 3.3, 1.7 Hz, 1H), 1.31 (d, J = 6.3 Hz, 3H), 1.17 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 136.2, 130.6, 128.4, 127.8, 122.0, 121.3, 119.3, 119.0, 115.0, 111.0, 101.4, 69.8, 60.4, 50.9, 45.9, 40.1, 34.2, 23.6, 22.7; IR (KBr) 3416, 2969, 1684, 1626 cm^{-1}; HRMS (CI/ammonia) m/z calcd for $C_{20}H_{24}N_2$ $(M)^+$ 292.1939, found 292.1938.

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Supporting Information Available: Additional experimental details and selected spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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