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First regiospecific, enantiospecific total synthesis of gardnerine and gardnutine

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Abstract—The first enantiospecific total synthesis of gardnerine and gardnutine has been achieved from 6-methoxy-D-tryptophan via the asymmetric Pictet–Spengler reaction, a stereocontrolled intramolecular enolate driven palladium-mediated cross-coupling reaction and a chemospecific, regiospecific hydroboration/oxidation sequence as key steps.

Gardnerine and gardnutine are 11-methoxy substituted sarpagine indole alkaloids isolated from the dry roots and stems of *Gardneria nutans*. The structures of these alkaloids were determined by analysis of their ^{1}H NMR spectra,[1] by chemical correlation with the known indole alkaloid ajmaline,[2] as well as by nuclear Overhauser effects (NOE).[3] Important structural features of these natural products include the 11-methoxy group in ring A, the asymmetric centers at C-3(*S*), C-5(*R*), C-6(*R*), C-15(*S*), and C-16(*S*), as well as the *E*-configuration of the olefinic bond at C(19)–C(20), as illustrated in Figure 1. Gardnutine also contains the unique cyclic ether at C(6). Both gardnerine and gardnutine exhibit interesting pharmacological activity.[4–6] For instance, gardnerine exhibited central nervous system depressant activity in mice,[4] and gardnerine showed 25% of the activity of hexamethonium on ganglionic transmission in the rabbit and rat superior cervical ganglion in situ.[5] In addition, gardnerine was found to augment both contractions elicited by nerve and muscle stimulation when it was examined on neuromuscular transmission in a rat limb (in situ), while gardnutine, in contrast, exhibited a long-lasting depressive effect on both types of contraction.[6] Gardnerine, a sarpagine alkaloid, was believed to represent the biogenetic precursor of some Gelsemium alkaloids including 11-methoxykoumine, des-N_a-methoxyhumantenirine, 11-methoxygelsemamide, gelsemicine, and 11-methoxy-19(*R*)-hydroxygelselegine (see Fig. 2). The partial syntheses of these alkaloids were successfully achieved by Sakai and coworkers in biomimetic fashion from gardnerine.[7–11] For example, gardnerine was transformed into 11-methoxykoumine by C–C intramolecular bond formation between the indole π electrons and allyl palladium species at C(20), followed by other steps. Gardnerine was also stereoselectively converted into 11-methoxy-19(*R*)-hydroxygelselegine via a biogenetically hypothetical aziridine intermediate. The conversion of gardnerine into des-N_a-methoxyhumantenirine and gelsemicine involved stereoselective skeletal rearrangements, which included the indole to oxindole transformations. Although gardnerine has been transformed into a variety of alkaloid natural products, no total synthesis of this indole has been achieved. Herein we report the first enantiospecific total synthesis of gardnerine and gardnutine. Bond constructions critical to the synthesis of these two alkaloids include the *E*-ethylidene stereochemistry at C(19)–C(20) and the *S* stereochemistry of the hydroxymethyl function at C(16). In addition, regiospecific

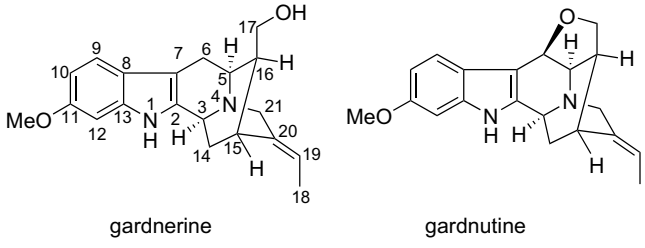

Figure 1. Structures of gardnerine and gardnutine.

Keywords: Pictet–Spengler reaction; Intramolecular enolate driven palladium-mediated cross-coupling; Hydroboration.
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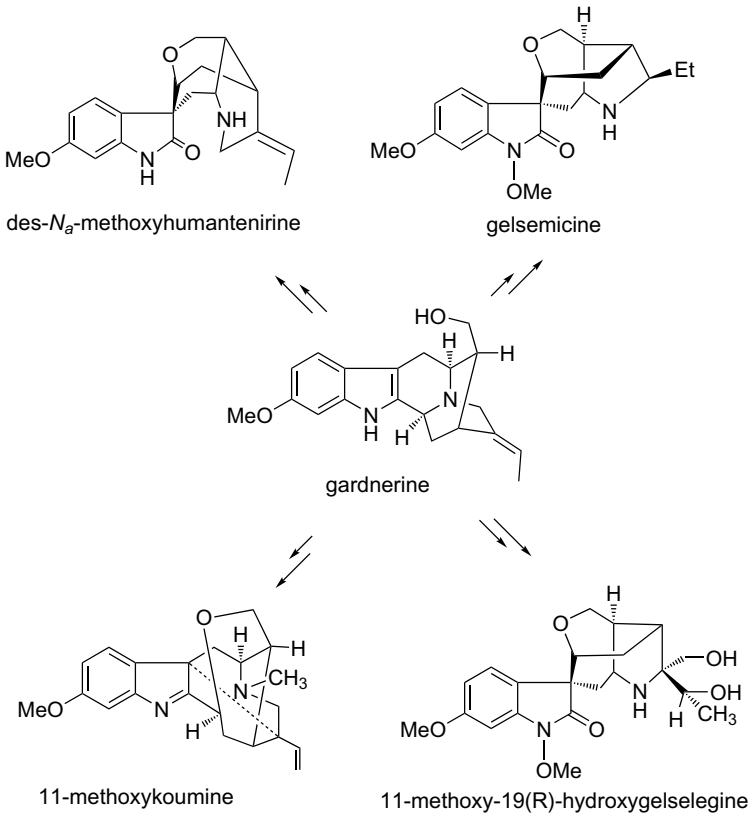
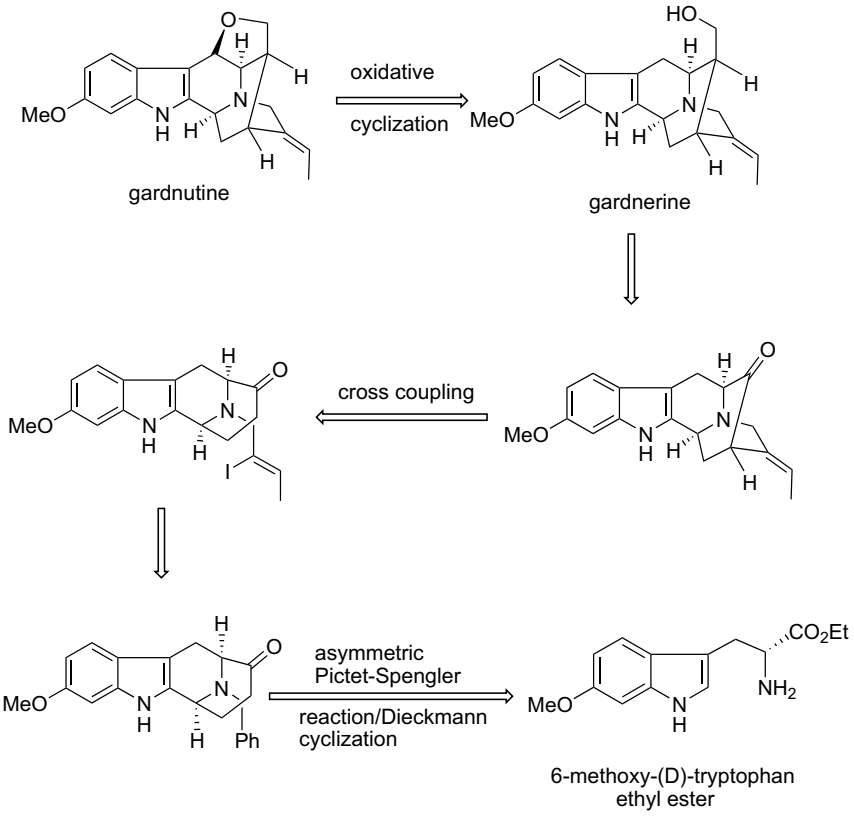


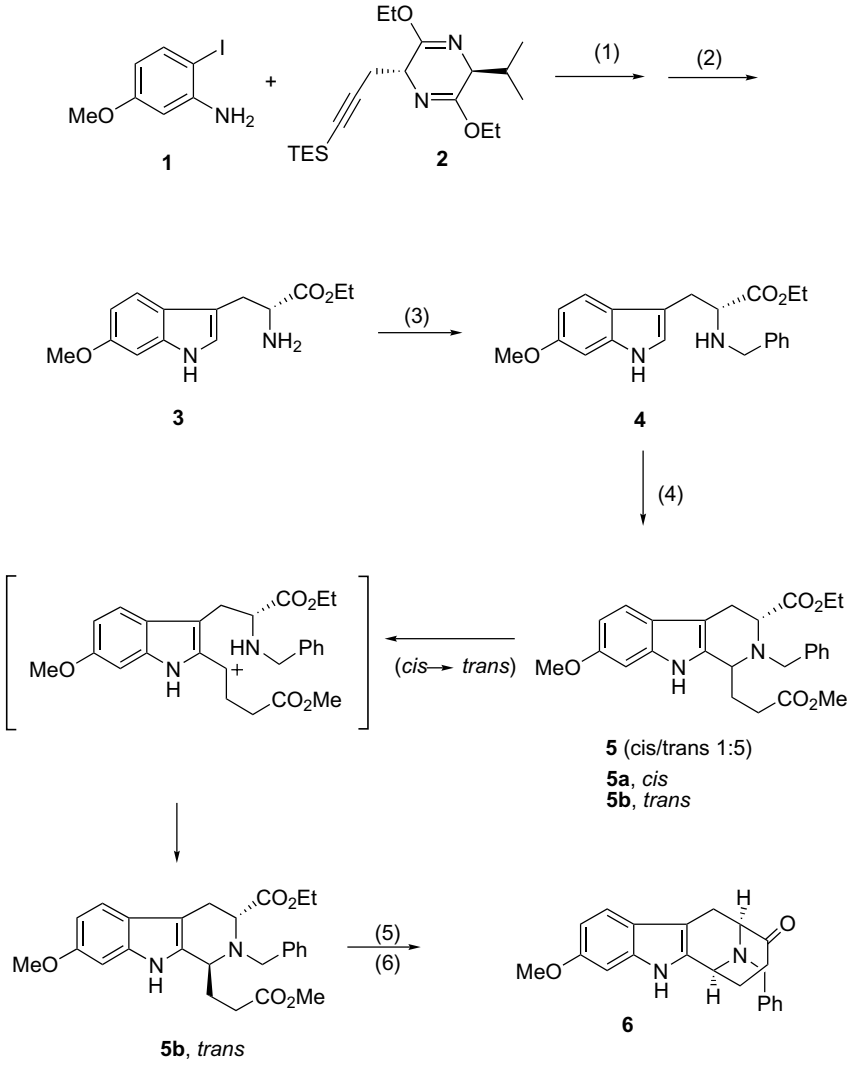
Figure 2. Examples of partial synthesis of gelsemium alkaloids from gardnerine.



Scheme 1. Retrosynthetic analysis.

incorporation of the 11-methoxy group into the indole was of paramount importance to success.

Based on the previous work on the total synthesis of indole alkaloids via the asymmetric Pictet–Spengler reaction,[12] the synthesis of gardnerine required 6-methoxy-(D)-tryptophan as the chiral transfer agent and starting material (Scheme 1). The 6-methoxy-(D)-tryptophan ethyl ester **3** was prepared from Larock heteroannulation between iodoaniline **1** and the propargyl unit **2** in the presence of $Pd(OAc)_2$, LiCl, and Na_2CO_3 at 100 °C on large scale (300 g) in 77% yield.[13] Hydrolysis of the Schöllkopf chiral auxiliary, accompanied by concomitant loss of the indole-2-silyl group during treatment with aqueous 2 N HCl in THF provided optically active 6-methoxy-D-tryptophan ethyl ester in a single step in 90% yield. This approach had also been employed for the regiospecific preparation of the 7-methoxy-(D)-tryptophan on large scale as well.[14] Ester **3** was then employed to construct the N_a-*H*-11-methoxy-tetracyclic ketone, as shown in Scheme 2. The primary amine in **3** was converted into the N_b-benzyl tryptophan **4** by reductive amination. The Pictet–Spengler condensation between the N_b-benzylamine **4** and the aldehyde afforded a mixture (at C-1) of *trans*- and *cis*-diester **5** in a ratio of 5:1 in high yield. Addition of 1 equiv of TFA into the mixture rapidly epimerized the *cis*-diester into the *trans*-diester presumably through a carbocationic intermediate via the scission of the C(1)–N(2) bond.[15] It is important to note, the epimerization of this 7-methoxy substituted N_a-H cis isomer **5a** into the trans diastereomer **5b** was completed in 30 min. In the parent system devoid of the methoxy group in ring A, the epimerization was slower and took several days to go to completion. The epimerization of this 7-methoxy substituted N_a-H cis diastereomer **5a** was also completed faster than that of the related 7-methoxy substituted N_a-CH_3 system, which took 7 h. The faster rate for **5a** to **5b** could be explained by stabilization of the carbocationic intermediate via resonance. The latter phenomena was recently investigated by study of the stable conformations of both the trans and cis diastereomers in the



Scheme 2. Reagents and conditions: (1) $Pd(OAc)_2$, Na_2CO_3, LiCl, DMF, 100 °C, 77%; (2) aq HCl, THF 90% (3) PhCHO, EtOH, rt; $NaBH_4$, −5 °C, 90%; (4) $HCOCH_2CH_2CO_2Me$, CH_2Cl_2, HOAc, rt, overnight, then 1% TFA/CH_2Cl_2 (1 equiv TFA), rt, 30 min, 92%; (5) NaH (60%, 8 equiv), MeOH (4 equiv), toluene, reflux; (6)33% KOH, dioxane, reflux, two steps, 60%.

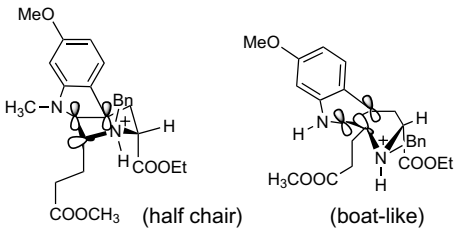
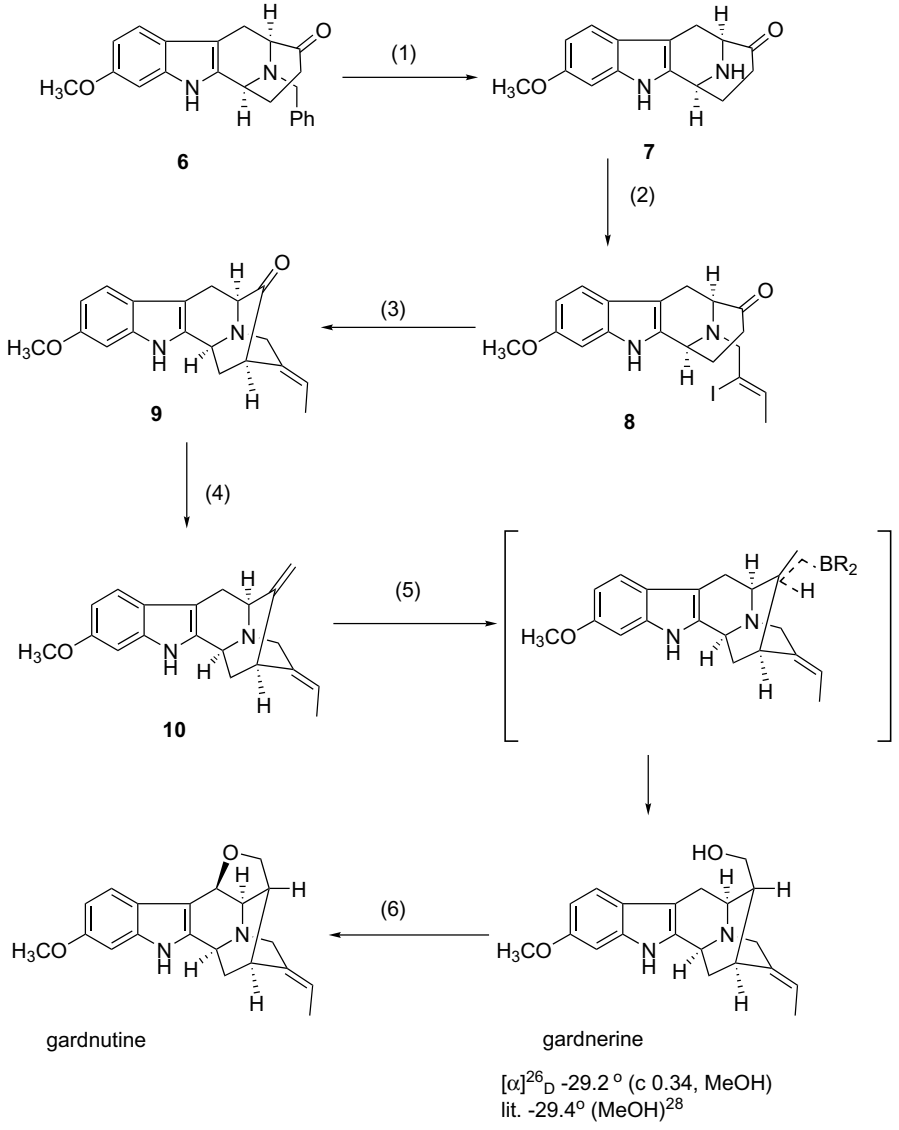


Figure 3. Proposed electronic orbital alignment in the *cis* N_a-CH_3 (left) and N_a-H (right) diesters.

N_a-H and N_a-CH_3 series by analysis of the conformations by NMR spectroscopy and X-ray analysis.[16] It was found, the N_a-H trans diastereomer **5b** as well as the N_a-methyl cis and trans diastereomers existed with a half-chair C-ring in the preferred conformer in solution, while the N_a-H cis diastereomer **5a** adopted a boat-like C-ring (Fig. 3) in the preferred conformer. Since the cis isomer **5a** existed in a half boat-like conformation in which the δ^* orbital of the C(1)–N(2) bond was approximately parallel with the π electrons of the indole ring, this stabilized the scission of the C(1)–N(2) bond by π orbital overlap with the indole. In the half-chair conformation, the δ^* orbital would be perpendicular to the π electrons of the indole system, consequently generation of the carbocationic intermediate would be more difficult. Furthermore, epimerization of the *cis*-N_a-H diester with the boat-like conformation took place more rapidly than the related *cis*-N_a-methyl case which existed in the half-chair conformation. After complete conversion of **4** into the *trans*-diester **5b** via the asymmetric Pictet–Spengler reaction, the Dieckmann cyclization, decarboxylation process under basic conditions, provided 11-methoxy ketone **6** in good yield.

The tetracyclic ketone **6** was then converted into gardnerine and gardnutine, as illustrated in Scheme 3. The



Scheme 3. Reagents and conditions: (1) Pd/C, EtOH/HCl, 90%; (2) (*Z*)-1-bromo-2-iodo-2-butene, THF, K_2CO_3, reflux, 95%; (3) 5% $Pd(OAc)_2$, 20% PPh_3, 1 equiv Bu_4NBr, 4 equiv K_2CO_3, DMF/H_2O (9:1), 65 °C, 80%; (4) CH_3PPh_3Br, KOtBu, benzene, rt, 2 h, 85%; (5) 9-BBN; $NaOH/H_2O_2$, rt, 1 h, 70%; (6) DDQ, THF, reflux, 1 h, 92%.

N_b-benzyl group of **6** was removed via catalytic hydrogenation, and this was followed by alkylation with (*Z*)-1-bromo-2-iodo-2-butene to provide ketone **8**. When this ketone **8** was heated in DMF/H_2O (9/1) with $Pd(OAc)_2$, PPh_3, K_2CO_3, and Bu_4NBr at 65 °C, the pentacyclic ketone **9** was obtained in 80% yield. The C(19)–C(20) *E*-ethylidene function in ketone **9** had been established in stereospecific fashion with this enolate-driven palladium-catalyzed intramolecular cyclization.[17–23] Recently, we reported the C(19)–C(20) *Z*-ethylidene function of (−)-koumidine could be introduced in a similar fashion, when PCy_3 was employed as the ligand instead of PPh_3.[24] The Wittig reaction of ketone **9** was then carried out with methyltriphenylphosphonium bromide in benzene in the presence of potassium *tert*-butoxide to afford diene **10** in high yield. The 9-BBN reagent was chosen as the hydroborating agent to maximize the chemoselectivity of the process. The use of bulky hydroborating agents permits differentiation between the disubstituted and hindered trisubstituted olefinic moieties in diene **10**. The C(19)–C(20) double bond in the related sapargine indole alkaloids reacted with both BH_3·DMS and BH_3·THF, however, they did not react with thexyl borane or 9-BBN.[25] In addition, carbon atom (16) of the C(16)–C(17) olefinic site had been selectively hydroborated to provide the 16(*S*) alcohol during the synthesis of (+)-koumine,[26] (*E*)16-epinormacusine B and (*E*)16-epiaffinisine.[27] Gardnerine was obtained as the only detectable diastereomer when 9-BBN was employed as the hydroborating agent, followed by the usual oxidative work up. The ^1H NMR spectrum, ^{13}C spectrum, and optical rotation of synthetic gardnerine (see Ref. 32) were in excellent agreement with those of natural gardnerine.[1,28] Further oxidative cyclization of gardnerine with DDQ in THF afforded gardnutine in 92% yield. The use of DDQ to form 6-oxygen substituted tetrahydro β-carbolines was reported from our laboratory several years ago,[29] following the earlier work of Oikawa and Yonemitsu.[30,31] Thus, a concise, stereospecific total synthesis of gardnerine and gardnutine has been completed from 6-methoxy-(D)-tryptophan **3** in 9 (20% overall yield) and 10 steps (18% overall yield), respectively.

In conclusion, the first regiospecific, enantiospecific total synthesis of gardnerine and gardnutine has been achieved from 6-methoxy-D-tryptophan **3** via the asymmetric Pictet–Spengler reaction. A stereocontrolled intramolecular enolate driven palladium-mediated cross-coupling reaction and a chemospecific, regiospecific hydroboration/oxidation were also key steps in this route. Since Sakai et al. had earlier converted gardnerine into 11-methoxykoumine,[7] des-N_a-methoxyhumantenirine,[8] 11-methoxygelsemamide,[9] gelsemicine,[10] and 11-methoxy-19(*R*)-hydroxygelselegine,[11] this work also constituted a formal total synthesis of these alkaloids.

Acknowledgements

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References and notes

1. Sakai, S.; Kubo, A.; Haginiwa, J. *Tetrahedron Lett.* **1969**, *19*, 1485.
2. Sakai, S.; Kubo, A.; Hamamoto, T.; Wakabayashi, M.; Takahashi, K.; Ohtani, Y.; Haginiwa, J. *Tetrahedron Lett.* **1969**, *19*, 1489.
3. Sakai, S.; Kubo, A.; Hamamoto, T.; Wakabayashi, M.; Takahashi, K.; Ohtani, H.; Haginiwa, J. *Chem. Pharm. Bull.* **1973**, *21*, 1783.
4. Harada, M.; Ozaki, Y.; Murayama, S.; Sakai, S.; Haginiwa, J. *Yakugaku Zasshi* **1971**, *91*, 997.
5. Harada, M.; Ozaki, Y. *Chem. Pharm. Bull.* **1978**, *26*, 48.
6. Harada, M.; Ozaki, Y. *Chem. Pharm. Bull.* **1976**, *24*, 211.
7. Sakai, S.; Yamanaka, E.; Kitajima, M.; Yokota, M.; Aimi, N.; Wongseripatana, S.; Ponglux, D. *Tetrahedron Lett.* **1986**, *27*, 4585.
8. Takayama, H.; Masubuchi, K.; Kitajima, M.; Aimi, N.; Sakai, S. *Tetrahedron* **1989**, *45*, 1327.
9. Takayama, H.; Kitajima, M.; Sakai, S. *Tetrahedron* **1994**, *50*, 5363.
10. Kitajima, M.; Takayama, H.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1573.
11. Takayama, H.; Kitajima, M.; Sakai, S. *Tetrahedron* **1994**, *50*, 11813.
12. Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; Cook, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 6998.
13. Liu, X.; Deschamps, J. R.; Cook, J. M. *Org. Lett.* **2002**, *4*, 3339.
14. Zhou, H.; Liao, X.; Cook, J. M. *Org. Lett.* **2004**, *6*, 249.
15. (a) Zhang, L. H.; Gupta, A. K.; Cook, J. M. *J. Org. Chem.* **1989**, *54*, 4708; (b) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, K. M.; Deng, L.; Bennett, D. W.; Cook, J. M.; Watson, W. H.; Krawiec, M. *J. Org. Chem.* **1997**, *62*, 44; (c) Cox, E. D.; Li, J.; Hamaker, K.; Yu, P.; Cook, J. M. *Chem. Commun.* **1996**, 2478; (d) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
16. Han, D; Liu, X; Cook, J. M. Mechanistic Study on the Asymmetric Pictet–Spengler Reaction: Evidence Supporting the Carbocationic Pathway, 227th ACS National Meeting, Anaheim, CA, United States, March 28–April 1, 2004.
17. Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454.
18. Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11.
19. Birman, V. B.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 7219.
20. Wang, T.; Cook, J. M. *Org. Lett.* **2000**, *2*, 2057.
21. Solé, D.; Peidro, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225.
22. Solé, D.; Vallverdu, L.; Solans, X.; Font-Bardia, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587.
23. Solé, D.; Diab, F.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 5749.
24. Cao, H.; Yu, J.; Wearing, X. Z.; Zhang, C.; Liu, X.; Deschamps, J.; Cook, J. M. *Tetrahedron Lett.* **2003**, *44*, 8013.
25. Liu, X. Ph.D Thesis., University of Wisconsin—Milwaukee, Milwaukee, WI, 2002.
26. Magnus, P.; Mugrage, B.; Deluca, M.; Cain, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 786.
27. Yu, J.; Liao, X.; Cook, J. M. *Org. Lett.* **2002**, *4*, 4681.
28. Takayama, H.; Nitta, W.; Kitajima, M.; Aimi, N.; Sakai, S. *J. Nat. Prod.* **1994**, *57*, 521.

29. (a) Cain, M.; Mantei, R.; Cook, J. M. *J. Org. Chem.* **1982**, *47*, 4933; (b) Wang, T.; Xu, Q.; Yu, P.; Liu, X.; Cook, J. M. *Org. Lett.* **2001**, *3*, 345.
30. Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213.
31. Oikawa, Y.; Yoshioka, T.; Mohri, K.; Yonemitsu, O. *Heterocycles* **1979**, *12*, 1457.
32. Compound **3**: $[\alpha]$ −5.07° (*c* 0.71, $CHCl_3$); IR (NaCl) 3365, 1730, 1625 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, 3H, *J* = 7.1 Hz), 1.60 (br s, 2H), 3.0 (dd, 1H, *J* = 14.3, 7.7 Hz), 3.22 (dd, 1H, *J* = 14.4, 4.8 Hz), 3.78 (m, 1H), 3.81 (s, 3H), 4.15 (q, 2H, *J* = 7.2 Hz), 6.80 (m, 2H), 6.90 (d, 1H, *J* = 2.0 Hz), 7.45 (d, 1H, *J* = 8.5 Hz), 8.15 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 30.7, 54.5, 54.9, 60.8, 94.7, 109.2, 111.0, 119.1, 121.8, 121.9, 136.5, 156.1, 175.2; MS (CI) (*m*/*e*): 263 (M^++1, 100). Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.12; H, 6.87; N, 10.69. Found: C, 63.96; H, 6.98; N, 10.54.
Compound **10**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.66 (dt, 3H, *J* = 6.8, 1.9 Hz), 1.89 (ddd, 1H, *J* = 12.0, 3.9, 2.4 Hz), 2.12 (ddd, 1H, *J* = 11.7, 9.6, 1.8 Hz), 2.95 (dd, 1H, *J* = 15.5, 1.5 Hz), 3.14 (dd, 1H, *J* = 15.6, 5.0 Hz), 3.32 (dd, 1H, *J* = 3.9, 1.4 Hz), 3.68 (d, 2H, *J* = 1.5 Hz), 3.81 (s, 3H), 3.83–3.85 (m, 1H), 4.14 (dd, 1H, *J* = 9.3, 1.7 Hz), 4.84 (d, 2H, *J* = 2.4 Hz), 5.26 (q, 1H, *J* = 6.8 Hz), 6.76 (dd, 1H, *J* = 8.4, 2.2 Hz), 6.80 (d, 1H, *J* = 1.9 Hz), 7.35 (d, 1H, *J* = 8.4 Hz), 7.93 (br s, 1H). ^1H NMR (300 MHz, CD_3OD): δ 1.67 (dt, 3H, *J* = 6.8, 1.8 Hz), 1.90 (ddd, 1H, *J* = 12.3, 4.2, 2.6 Hz), 2.20 (td, 1H, *J* = 11.4, 2.1 Hz), 3.00 (dd, 1H, *J* = 16.8, 2.1 Hz), 3.11 (dd, 1H, *J* = 16.5, 4.8 Hz), 3.42 (dd, 1H, *J* = 4.2, 1.7Hz), 3.65 (d, 1H, *J* = 16.5 Hz), 3.76 (dt, *J* = 13.0, 3.1 Hz), 3.81 (s, 3H), 3.87 (dd, 1H, *J* = 4.6, 2.2 Hz), 4.21 (d, 1H, *J* = 10.1 Hz), 4.88 (d, 2H, *J* = 2.7 Hz), 5.32 (q, 1H, *J* = 6.9 Hz), 6.66 (dd, 1H, *J* = 8.6, 2.2 Hz), 6.84 (d, 1H, *J* = 2.1 Hz), 7.28 (d, 1H, *J* = 8.5 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ 11.0, 25.5, 35.5, 36.3, 50.5, 54.6, 54.9, 56.7, 94.4, 103.0, 104.2, 107.9, 114.9, 117.6, 121.6, 135.7, 136.2, 137.4, 151.8, 155.9. EIMS (*m*/*e*, relative intensity): 306 (M^+, 72), 305 (100), 199 (39), 198 (60). This material was used directly in the next step.
Gardnerine: $[\alpha]_D$ −29.2° (*c* 0.31, MeOH), lit. $[\alpha]_D$ −29.4° (MeOH). ^1H NMR (500 MHz, $CDCl_3$): δ 1.66 (dt, 3H, *J* = 6.8, 1.8 Hz), 1.84 (dd, 2H, *J* = 8.5, 2.5 Hz), 2.17–2.23 (m, 1H), 2.89–2.99 (m, 3H), 3.30 (dd, 1H, *J* = 10.5, 2.0 Hz), 3.58 (dd, 2H, *J* = 10.5, 6.5 Hz), 3.61 (d, 1H, *J* = 3.3 Hz), 3.69 (dt, 1H, *J* = 16.8, 1.7 Hz), 3.85 (s, 3H), 4.12 (dd, 1H, *J* = 7.8, 5.2 Hz), 5.25 (q, 1H, *J* = 6.8 Hz), 6.78 (dd, 1H, *J* = 8.5, 2.2 Hz), 6.85 (d, 1H, *J* = 2.2 Hz), 7.36 (d, 1H, *J* = 8.5 Hz), 8.10 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.2, 23.1, 26.9, 27.6, 42.7, 50.5, 52.9, 56.1, 56.7, 61.8, 95.6, 106.4, 109.2, 114.4, 119.1, 121.2, 135.9, 137.6, 139.9, 156.6.
^1H NMR (500 MHz, acetone-d_6): δ 1.63 (dt, 3H, *J* = 6.8, 2.2 Hz), 1.73–1.85 (m, 2H), 2.14–2.15 (m, 1H), 2.80–2.96 (m, 3H), 3.17 (dd, 1H, *J* = 11.0, 9.0 Hz), 3.48–3.54 (m, 2H), 3.56–3.59 (m, 2H), 3.78 (s, 3H), 4.10 (dd, 1H, *J* = 9.8, 2.7 Hz), 5.21 (q, 1H, *J* = 6.8 Hz), 6.67 (dd, 1H, *J* = 8.5, 2.3 Hz), 6.89 (d, 1H, *J* = 2.3 Hz), 7.28 (d, 1H, *J* = 8.5 Hz), 9.82 (br s, 1H). ^{13}C NMR (125 MHz, acetone-d_6) 12.4, 22.8, 26.8, 27.4, 43.2, 50.2, 52.9, 55.2, 56.6, 60.2, 95.2, 105.7, 108.5, 112.5, 118.5, 121.3, 136.9, 137.8, 142.2, 156.3. EIMS (*m*/*e*, relative intensity): 324 (M^+, 66), 323 (70), 293 (39), 199 (100), 198 (100).
Gardnutine: ^1H NMR (500 MHz, $CDCl_3$): δ 1.67 (d, 3H, *J* = 6.8 Hz), 1.84 (t, 1H, *J* = 11.5 Hz), 2.02 (dt, 1H, *J* = 13.5, 3.3 Hz), 2.32 (qd, 1H, *J* = 11.5, 3.5 Hz), 2.85 (q, 1H, *J* = 3.0 Hz), 3.50 (t, 1H, *J* = 9.6 Hz), 3.74 (br s, 2H), 3.82 (dd, 1H, *J* = 11.5, 7.5 Hz), 3.87 (s, 3H), 3.87 (t, 1H, *J* = 9.0 Hz), 4.00 (dd, 1H, *J* = 10.3, 2.4 Hz), 5.33 (q, 1H, *J* = 6.9 Hz), 5.63 (d, 1H, *J* = 7.5 Hz), 6.84 (dd, 1H, *J* = 8.6, 2.2 Hz), 6.87 (d, 1H, *J* = 2.1 Hz), 7.59 (d, 1H, *J* = 8.6 Hz), 7.91 (br s, 1H). EIMS (*m*/*e*, relative intensity): 322 (M^+, 48), 212 (31), 199 (75), 198 (100).