JOC Note
pubs.acs.org/joc

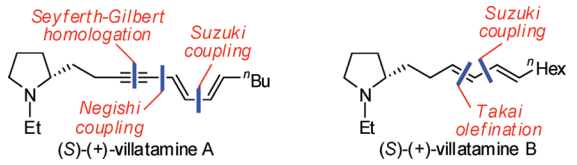
Syntheses and Configuration Determination of (+)-Villatamines A and B, Two Marine Natural Products

Lin Hu,[†,‡] Lihe Zhang,*[,†] and Hongbin Zhai*[,†,‡]

[†]*State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, 38 Xue Yuan Rd, Beijing 100083, China, and* [‡]*Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

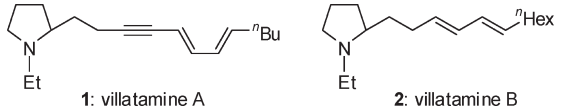
zhaih@mail.sioc.ac.cn; zdszlh@bjmu.edu.cn

Received July 24, 2009



The first total syntheses of (+)-villatamines A and B have been realized in six and five steps, respectively. The stereogenic center present in these two naturally occurring alkaloids should have an (*S*)-configuration based on our results.

(+)-Villatamines A (**1**) and B (**2**) were isolated by Andersen and co-workers 14 years ago from the extract of the flatworm *Prostheceraeus villatus*, the most primitive animals native to the Northeast Atlantic Ocean and North Sea.[1] Villatamine B (**2**) exhibited significant cytotoxicity [in vitro ED_{50} (μg/mL): 11.4 (murine leukemia P388), 2.8 (human breast cancer MCF7), 1.9 (human glioblastoma/astrocytoma U373), 2.8 (human ovarian carcinoma HEY), 1.7 (human colon LOVO), 2.8 (human lung A549)]; on the other hand, the biological properties of villatamine A (**1**) have not been determined yet due to its instability.[1] In addition, the absolute configuration of both compounds remains unaddressed so far.



We recently embarked on an expeditious synthesis of **1** and **2** in an effort both to obtain samples for further biological studies and to determine the absolute configuration of these alkaloids.

Retrosynthetic analysis was conducted (Scheme 1) and the (*S*)-configuration in villatamines A (**1**) and B (**2**) was based upon a somewhat arbitrary assumption. It seems that villatamine A (**1**) can be disconnected, via Negishi and Suzuki coupling reactions, into the following three fragments: (*E*)-1-bromo-2-iodoethylene (**3**),[2] (*E*)-1-hexene-1-boronic acid (**4**),[3] and alkyne **5**. Notably, alkene **3** possesses functional groups having a defined stereochemistry and different reactivities. Analogously, villatamine B (**2**) can be rapidly assembled from Suzuki coupling of iodoalkene **6** and (*E*)-1-octene-1-boronic acid (**7**).[3] Compounds **5** and **6** may in turn be generated from the known proline-derived intermediate **8**[4] by Seyferth−Gilbert homologation and Takai olefination, respectively.

As outlined in Scheme 2, our synthesis of (+)-villatamine A (**1**) commenced from ester **8**,[4] which, after partial reduction[5] with DIBAL-H in toluene at −78 °C, was treated with Bestmann reagent[6] [prepared[7] in situ from dimethyl 2-oxopropylphosphonate (**9**) and *p*-toluenesulfonyl azide in acetonitrile] to form terminal alkyne **5** in 63% overall yield from **8**. Sonogashira reaction ($Pd(PPh_3)_4$, CuI, piperidine, THF, 60 °C)[8] of alkyne **5** and dihaloethylene **3**[2] failed to generate the monocoupling product **10** presumably because of the poor chemoselectivity of **3** displayed under the reaction conditions employed. However, prior conversion (BuLi, THF, −78 °C; $ZnBr_2$, −78 °C) of **5** into an organozinc reagent followed by $Pd(PPh_3)_4$-catalyzed Negishi coupling[9] with **3** at room temperature did form bromo enyne **10**, which was subsequently exposed to boronic acid **4**[3] in the presence of $Pd(PPh_3)_4$ and KOH to give **11** via Suzuki coupling[10] in moderate yield (66%) over two steps. Finally, removal of the Boc group in **11** with *p*-toluenesulfonic acid (TSA) in MeCN at room temperature[11] furnished a secondary amine, which upon reductive amination[12] (MeCHO, HCl, MeOH; $NaBH(OAc)_3$) was smoothly transformed into (+)-villatamine A (**1**) in 62% overall yield for a two-step sequence. The ^1H and ^{13}C NMR data of the synthetic **1** are consistent with those disclosed by Andersen.[1] The optical rotation values ($[\alpha]^{20}_D$) of the free base and trifluoroacetate (TFA) salt were found to be +65.4 (*c* 0.45, MeOH) and +13.8 (*c* 1.65, MeOH), respectively. The

(1) Kubanek, J.; Williams, D. E.; Silva, E., D.; Allen, T.; Andersen, R. J. *Tetrahedron Lett.* **1995**, *36*, 6189–6192.

(2) (*E*)-1-Bromo-2-iodoethylene is commercial available. For its synthesis, see: Negishi, E.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, *2*, 65–67.

(3) (*E*)-1-Hexene-1-boronic acid (**4**) and (*E*)-1-octene-1-boronic acid (**7**) were prepared according to: Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370–4371.

(4) Grote, R.; Zeeck, A.; Stuempfel, J.; Zaehner, H. *Liebigs Ann. Chem.* **1990**, *6*, 525–530.

(5) Terada, Y.; Arisawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 1269–1272.

(6) Müller, S. G.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–522.

(7) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59–62.

(8) Organ, M. G.; Ghasemi, H.; Valente, C. *Tetrahedron* **2004**, *60*, 9453–9461.

(9) Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* **2003**, *5*, 1597–1600.

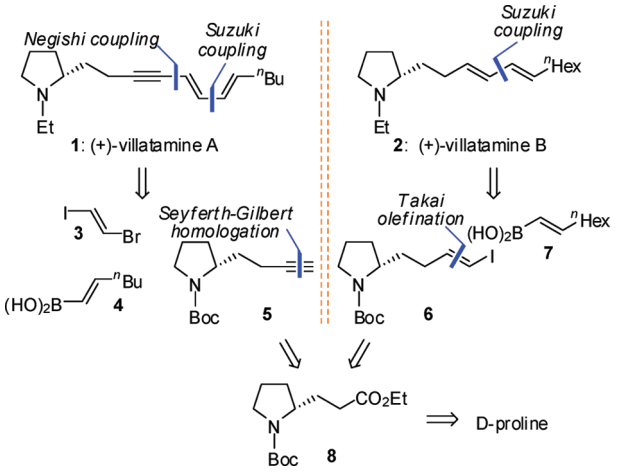
(10) Ozawa, T.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **2001**, *66*, 3338–3347.

(11) Reed, P. E.; Katzenellenbogen, J. A. *J. Org. Chem.* **1991**, *56*, 2624–2634.

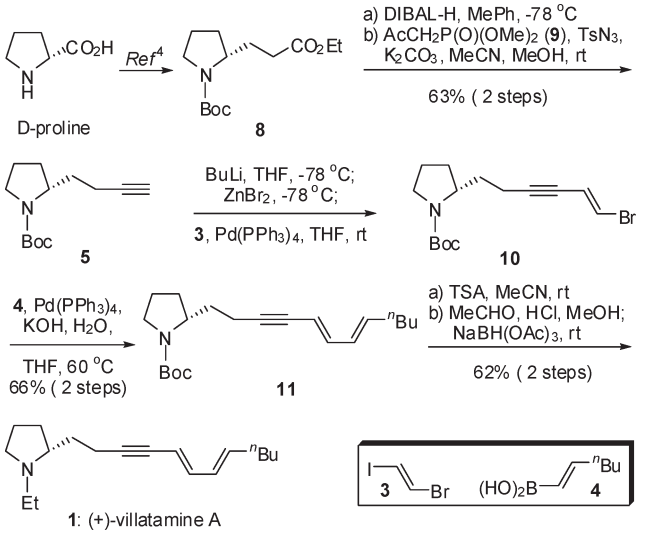
(12) Takebayashi, M.; Hiranuma, S.; Kanie, Y.; Kajimoto, T.; Kanie, O.; Wong, C. H. *J. Org. Chem.* **1999**, *64*, 5280–5291.

Published on Web 08/27/2009 DOI: 10.1021/jo901606r

SCHEME 1. Retrosynthetic Analysis of 1 and 2



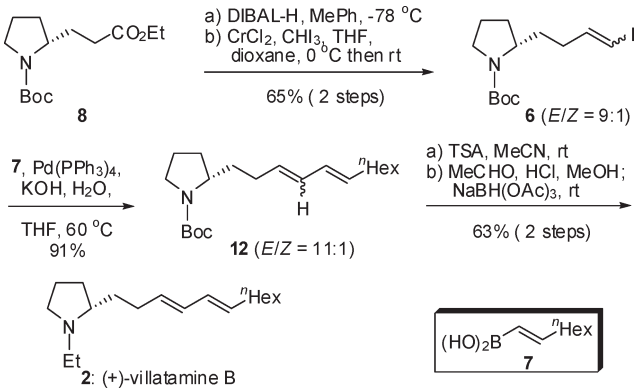
SCHEME 2. Synthesis of (+)-Villatamine A



latter is prominently different in magnitude from that reported[1] for the natural sample of **1** [[α]$_D$ = +49 (MeOH), TFA salt] but has the same sign, therefore suggesting the initially assumed (*S*)-configuration in (+)-villatamine A to be correct.

The synthesis of (+)-villatamine B (**2**) turned out to be quite straightforward (Scheme 3). Starting from the aldehyde obtained by partial reduction[5] of ester **8**[4] with DIBAL-H, Takai olefination[13] ($CrCl_2$, CHI_3, THF, dioxane, 0 °C then room temperature) provided alkenyl iodide **6** (*E*/*Z* = 9:1[14]) in 65% overall yield for the two steps. Then, under essentially the same reaction conditions used for connecting **10** and **4**, Suzuki coupling[10] of **6** with (*E*)-1-octene-1-boronic acid[3] (**7**) was performed to afford conjugated dienes **12** (*E*/*Z* = 11:1[14]) in 91% combined yield. To conclude the total synthesis, deprotection[11,15] of the Boc group and the subsequent reductive

SCHEME 3. Synthesis of (+)-Villatamine B



amination[12,15] successfully produced (+)-villatamine B (**2**) in 63% yield (over two steps). The ^{1}H and ^{13}C NMR data of the synthetic sample of (+)-villatamine B are also in accord with those documented in the literature.[1] The [α]$^{20}_D$ values of the free base and TFA salt of the synthetic compound were +55.2 (*c* 0.42, MeOH) and +15.1, (*c* 0.60, MeOH), respectively. The latter perfectly agrees in both magnitude and sign with that published for Andersen's sample of **2** [[α]$_D$ = +15 (MeOH), TFA salt].[1] Obviously, the stereocenter in (+)-villatamine B should also have an (*S*)-configuration.

In summary, the first total syntheses of (+)-villatamine A (6 steps, 26% overall yield) and (+)-villatamine B (5 steps, 37% overall yield) have been accomplished in enantiomerically pure form from the proline-derived ester **8** by an efficient strategy. The stereogenic center present in these two naturally occurring alkaloids should have an (*S*)-configuration based on our results.

Experimental Section

(*S*)-*tert*-Butyl 2-(But-3-ynyl)pyrrolidine-1-carboxylate (5). To a cooled solution of **8** (1.53 g, 5.64 mmol) in MePh (35 mL) was added DIBAL-H (1.0 M in toluene, 6.8 mL, 6.8 mmol) under N_2 atmosphere at −78 °C. The mixture was stirred at −78 °C for 3 h, and the reaction was quenched by the addition of MeOH and saturated aqueous Rochelle's salt solution. The solution was stirred at rt until separation of organic and aqueous layers was achieved. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude aldehyde was used for the next step without further purification.

To a suspension of K_2CO_3 (2.34 g, 17.0 mmol) and *p*-toluenesulfonylazide (1.34 g, 6.79 mmol) in MeCN (65 mL) was added dimethyl-2-oxopropylphosphonate (1.13 g, 6.80 mmol). The mixture was stirred at rt for 2 h. A solution of the above-mentioned aldehyde in MeOH (15 mL) was added and the mixture was stirred for additional 10 h. The volatiles were removed in vacuo, and the residue was diluted with Et_2O (100 mL) and water (30 mL). The aqueous layer was separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The volatiles were removed in vacuo, and the residue was purified by chromatography on silica gel (EtOAc/petroleum ether, 15:1) to give **5** (795 mg, 63%) as a colorless oil: [α]$^{20}_D$ +51.7 (*c* 1.00, MeOH); IR (film) *ν* 3309, 3253, 2973, 2932, 2877, 2119, 1693, 1454, 1395, 1251, 1172, 1101, 911, 865, 772, 631; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 1.47 (s, 9H), 1.38−1.62 (m, 1H), 1.62−1.75 (m, 1H), 1.75−2.10 (m, 5H), 2.10−2.31 (m, 2H), 3.20−3.50 (m, 2H), 3.75−3.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) *δ* 15.5, 22.9, 23.6, 28.4, 29.8, 30.4,

(13) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.
(14) The *E*/*Z* ratio was deduced from the line integrals of ^{1}H NMR spectrum.
(15) This was conducted under similar conditions used for the transformations on **11**.

33.0, 33.2, 45.9, 46.3, 56.3, 56.5, 68.2, 68.3, 78.9, 79.1, 83.7, 84.0, 154.5 (extra peaks appeared due to the presence of rotamers); MS (ESI) m/z 246.4 (M + Na); HRMS (ESI) calcd for $C_{13}H_{21}NO_2$ + Na 246.1465, found 246.1463.

(*S*)-*tert*-Butyl 2-((5*E*,7*E*)-Dodeca-5,7-dien-3-ynyl)pyrrolidine-1-carboxylate (11). To a solution of terminal alkyne **5** (167 mg, 0.748 mmol) in THF (5 mL) was added BuLi (0.40 mL, 2.25 M in hexane, 0.90 mmol) at −78 °C. The resultant solution was stirred at −78 °C for 30 min, followed by addition of a solution of anhydrous $ZnBr_2$ (202 mg, 0.897 mmol) in THF (1.5 mL). The mixture thus obtained was stirred at −78 °C for 5 min and then warmed to 0 °C over 25 min. To this was added via cannula a mixture of (*E*)-1-iodo-2-bromoethylene (209 mg, 0.898 mmol) and $Pd(PPh_3)_4$ (87 mg, 0.075 mmol) in THF (2.5 mL) at 0 °C. The mixture was stirred at rt for 2 h. After quenching with saturated aqueous $NaHCO_3$ solution, the mixture was extracted with ether. The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product **10** was used for the next step without further purification.

To a solution of the above-mentioned **10** in THF (7 mL) was added $Pd(PPh_3)_4$ (87 mg, 0.075 mmol) under N_2 atmosphere. The resultant mixture was stirred at rt for 5 min. To this mixture was added dropwise a solution of (*E*)-1-hexenylboronic acid (144 mg 1.13 mmol) in aqueous KOH solution (1 M, 3.4 mL, 3.40 mmol). The mixture was heated at 60 °C for 10 h with stirring and then diluted with ether (30 mL) and H_2O (5 mL). The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was submitted to chromatography (EtOAc/petroleum ether, 1:30) to provide **11** (164 mg, 66%) as a yellowish oil: $[\alpha]^{20}_D$ +9.8 (*c* 1.35, MeOH); IR (film) ν 3017, 2958, 2926, 2855, 2202, 1696, 1456, 1392, 1366, 1254, 1171, 1120, 1100, 983, 772; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.8 Hz, 3H), 1.17−1.61 (m, 5H), 1.46 (s, 9H), 1.62−2.19 (m, 7H), 2.19−2.47 (m, 2H), 3.20−3.48 (m, 2H), 3.74−3.91 (m, 1H), 5.45 (d, J=15.6 Hz, 1H), 5.62−5.83 (m, 1H), 5.92−6.14 (m, 1H), 6.47 (dd, J = 15.0, 11.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 13.8, 16.5, 16.8, 22.1, 22.9, 23.7, 28.5, 29.6, 29.8, 30.4, 30.9, 31.1, 32.3, 32.6, 33.2, 33.6, 45.9, 46.4, 56.4, 56.7, 78.9, 79.1, 80.0, 91.2, 91.6, 109.1, 109.6, 129.62, 137.1, 141.0, 154.5 (extra peaks appeared due to the presence of rotamers); MS (ESI) m/z 232.1 (M − Boc), 332.3 (M + H), 354.2 (M + Na); HRMS (ESI) calcd for $C_{21}H_{33}NO_2$ + H 332.2584, found 332.2582.

(+)-Villatamine A (1). To a solution of the Boc-protected amine **11** (67.0 mg, 0.202 mmol) dissolved in MeCN (2 mL) was added *p*-toluenesulfonic acid monohydrate (115 mg, 0.605 mmol). The resultant solution was stirred at rt for 10 h. After concentration, the residue was treated with saturated aqueous $NaHCO_3$ solution, followed by extraction with CH_2Cl_2 (5 mL × 3). The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude secondary amine was used for the next step without further purification.

A solution of the above-mentioned crude secondary amine in MeOH (2 mL) was made acidic (pH = 4) with methanolic hydrogen chloride solution. After acetaldehyde (26.7 mg, 0.606 mmol) was added, the mixture was stirred at rt for 30 min, followed by the addition of triacetoxyborohydride (129 mg, 0.609 mmol). The mixture thus obtained was stirred at rt for 12 h. The volatiles were evaporated in vacuo, and the residue was treated with saturated aqueous $NaHCO_3$ solution, followed by extraction with CH_2Cl_2 (5 mL × 3). The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. After removing the volatiles, the residue was purified by chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:20) to give **1** (32.6 mg, 62%) as a yellowish oil: $[\alpha]^{20}_D$ +65.4 (*c* 0.45, MeOH); IR (film) ν 3020, 2961, 2930, 2872, 2789, 2211, 1729, 1641, 1453, 1369,1261, 1098, 982, 801; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 6.8 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H), 1.20−1.57 (m, 6H), 1.62−1.84 (m, 2H), 1.84−2.02 (m, 2H), 2.02−2.22 (m, 4H), 2.22−2.50 (m, 3H), 2.81−2.97 (m, 1H), 3.11−3.25 (m, 1H), 5.47 (d, J = 15.2 Hz, 1H), 5.75 (dt, J = 14.8, 7.2 Hz, 1H), 5.98−6.12 (m, 1H), 6.47 (dd, J = 15.2, 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 13.7, 13.9, 16.9, 22.0, 22.2, 30.2, 31.2, 32.4, 33.2, 48.3, 53.6, 63.7, 79.9, 91.8, 109.2, 129.7, 137.1, 141.0. MS (EI, 70 eV) m/z (relative intensity) 260 (1.6), 259 (7.6), 244 (4.8), 231 (10.6), 230 (21.6), 216 (20.5), 202 (9.7), 188 (9.5), 162 (9.4), 100 (9.0), 98 (100), 70 (11.4), 41 (5.8); HRMS (ESI) calcd for $C_{18}H_{29}N$ + H 260.2373, found 260. 2377. **1**·TFA: $[\alpha]^{25}_D$ +13.8 (*c* 1.65, MeOH); IR (film) ν 3019, 2962, 2931, 2874, 2696, 2218, 1778, 1740, 1673, 1459, 1261, 1201, 1019, 985, 799, 719, 705; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, 7.2 Hz, 3H), 1.40 (t, 7.2 Hz, 3H), 1.17−1.50 (m, 4H), 1.78−2.48 (m, 9H), 2.54−2.71 (m, 1H), 2.79−3.02 (m, 2H), 3.24−3.53 (m, 2H), 3.83−4.02 (m, 1H), 5.43 (d, 15.6 Hz, 1H), 5.78 (dt, 14.8, 7.2 Hz, 1H), 6.06 (dd, 14.8, 10.8 Hz, 1H), 6.48 (dd, 15.6, 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 10.2, 13.9, 16.9, 21.7, 22.2, 29.2, 29.4, 31.1, 32.4, 49.0, 53.0, 66.7, 81.8, 88.3, 108.2, 129.4, 138.2, 142.0. ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 0.89 (t, 6.9 Hz, 3H), 1.37 (t, 7.2 Hz, 3H), 1.24−1.44 (m, 4H), 1.77−2.24 (m, 7H), 2.24−2.48 (m, 2H), 2.61 (dt, 17.2, 5.7 Hz, 1H), 2.82−3.01(m, 2H), 3.25−3.48 (m, 2H), 3.78−3.93 (m, 1H), 5.46 (d, 15.6 Hz, 1H), 5.81 (dt, 15.3, 7.3 Hz, 1H), 6.08 (dd, 15.3, 10.5 Hz, 1H), 6.49 (dd, 15.5, 10.7 Hz, 1H); ^{13}C NMR (CD_2Cl_2, 75.47 MHz) δ 10.6, 14.2, 17.5, 22.4, 22.8, 29.9, 30.1, 33.0, 49.3, 53.1, 67.0, 82.0, 89.3, 109.0, 130.0, 138.7, 142.4; HRMS (ESI) calcd for $C_{18}H_{30}N^+$ 260.2373, found 260. 2377.

(*S*)-*tert*-Butyl 2-(4-Iodobut-3-enyl)pyrrolidine-1-carboxylate (6). To a cooled solution of **8** (247 mg, 0.910 mmol) in MePh (8 mL) was added DIBAL (1.0 M in toluene, 1.0 mL, 1.00 mmol) under N_2 atmosphere at −78 °C. The mixture was stirred at −78 °C for 3 h, and the reaction was quenched by the addition of MeOH and saturated aqueous Rochelle's salt solution. The solution was stirred at rt until separation of organic and aqueous layers was achieved. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude aldehyde was used for the next step without further purification.

To a suspension of anhydrous $CrCl_2$ (671 mg, 5.46 mmol) in THF (5 mL) and dioxane (2 mL) was added a solution of the above-mentioned aldehyde and iodoform (717 mg, 1.82 mmol) in THF (3 mL) under Ar atmosphere. After eing stirred at rt for 1 h, the reaction mixture was poured into water (25 mL) followed by extraction with EtOAc (15 mL × 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The volatiles were removed in vacuo, and the residue was purified by chromatography on silica gel (EtOAc/petroleum ether, 1:20) to give **6** (E/Z = 9:1, 208 mg, 65%) as a colorless oil: $[\alpha]^{20}_D$ +22.1 (*c* 2.15, MeOH); IR (film) ν 3044, 2971, 2929, 2867, 1693, 1453, 1392, 1365, 1250, 1171, 1121, 1100, 943, 858, 766; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20−2.22 (m, 8H), 1.46 (s, 9H), 3.16−3.52 (m, 2H), 3.60−3.91 (m, 1H), 6.02 (d, J = 11.4 Hz, 1H), 6.52 (dt, J = 11.1 Hz, 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 23.0, 23.8, 28.5, 29.9, 30.5, 32.7, 32.9, 33.0, 33.2 (extra peaks appeared due to the presence of rotamers); MS (ESI) m/z 373.9 (M + Na); HRMS (ESI) calcd for $C_{13}H_{22}INO_2$ + Na 374.0587, found 374.0592.

(*S*)-*tert*-Butyl 2-((3*E*,5*E*)-Dodeca-3,5-dienyl)pyrrolidine-1-carboxylate (12). To a solution of **6** (38.0 mg, 0.108 mmol) in THF (3 mL) was added $Pd(PPh_3)_4$ (12.5 mg, 0.0110 mmol) under N_2 atmosphere, and the resultant mixture was stirred at rt for 5 min. Then a solution of (*E*)-1-octenylboronic acid (34.0 mg, 0.218 mmol) in aqueous KOH solution (1 M, 0.65 mL, 0.650 mmol) was added dropwise. The mixture was heated at 60 °C for 3 h with stirring and then diluted with ether (20 mL) and H_2O (5 mL). The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was submitted to

chromatography (EtOAc/petroleum ether, 1:50) to provide **12** (*E*/*Z* = 11:1, 33.0 mg, 91%) as a colorless oil: $[\alpha]^{20}_{D}$ +17.0 (*c* 2.15, MeOH); IR (film) ν 3012, 2962, 2927, 2857, 1697, 1458, 1393, 1365, 1261, 1173, 1102, 1015, 987, 869, 799; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.20−1.54 (m, 9H), 1.46 (s, 9H), 1.58−1.98 (m, 5H), 1.98−2.24 (m, 4H), 3.20−3.48 (m, 2H), 3.63−3.89 (m, 1H), 5.45−5.75 (m, 2H), 5.89−6.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 14.1, 22.6, 23.0, 23.7, 28.5, 28.8, 29.3, 29.5, 29.6, 30.3, 30.5, 31.7, 32.6, 32.6, 33.6, 34.3, 46.0, 46.4, 56.7, 56.9, 78.9, 130.1, 130.6, 130.8, 131.3, 132.5, 132.8, 154.6 (extra peaks appeared due to the presence of rotamers); MS (ESI) *m*/*z* 236.1 (M − Boc), 336.2 (M + H), 358.2 (M + Na); HRMS (ESI) calcd for $C_{21}H_{37}NO_2$ + H 336.2897, found 336.2897.

(+)-Villatamine B (2). To a solution of **12** (30.0 mg, 0.0890 mmol) in MeCN (1 mL) was added *p*-toluenesulfonic acid monohydrate (50.7 mg, 0.267 mmol). The resultant solution was stirred for 10 h. After concentration, the residue was treated with saturated aqueous $NaHCO_3$ solution, followed by extraction with CH_2Cl_2 (3 mL × 3). The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude secondary amine was used for the next step without further purification.

A solution of the above-mentioned crude secondary amine in MeOH (1 mL) was made acidic (pH = 4) with methanolic hydrogen chloride solution. After acetaldehyde (11.7 mg, 0.267 mmol) was added, the mixture was stirred at rt for 30 min, followed by the addition of triacetoxyborohydride (56.5 mg, 0.267 mmol). The mixture thus obtained was stirred at rt for 12 h. The volatiles were evaporated in vacuo, and the residue was treated with saturated aqueous $NaHCO_3$ solution, followed by extraction with CH_2Cl_2 (3 mL × 3). The organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. After removal of the volatiles, the residue was purified by chromatography on silica gel (MeOH/CH_2Cl_2, 1:20) to give **2** (14.8 mg, 63%) as a yellowish oil: $[\alpha]^{20}_{D}$ +55.2 (*c* 0.41, MeOH); IR (film) ν 3015, 2960, 2926, 2855, 2787, 1727, 1454, 1376, 1283, 1254, 1183, 1106, 980, 810, 725; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.11 (t, *J* = 7.0 Hz, 3H), 1.18−1.55 (m, 10H), 1.55−2.44 (m, 11H), 2.80−3.03 (m, 1H), 3.10−3.30 (m, 1H), 5.45−5.78 (m, 2H), 5.85−6.15 m, 2H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 13.5, 14.0, 21.7, 22.6, 28.8, 29.3, 29.7, 30.3, 31.7, 32.6, 33.5, 48.1, 53.4, 64.5, 130.1, 130.4, 131.6, 132.7; MS (ESI) *m*/*z* 264.2 (M + H); HRMS (MALDI) calcd for $C_{18}H_{33}N$ + H 264. 2686, found 264.2689. **2**·TFA: $[\alpha]^{20}_{D}$ +15.1 (*c* 0.60, MeOH); IR (film) ν 3017, 2958, 2927, 2854, 2662, 1675, 1460, 1414, 1200, 1132, 989, 828, 800, 720; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.19−1.46 (m, 8H), 1.78−1.95 (m, 2H), 1.95−2.13 (m, 5H), 2.13−2.38 (m, 3H), 2.78−2.94 (m, 2H), 2.97−3.12 (m, 1H), 3.35−3.51 (m, 1H), 3.83−4.01 (m, 1H), 5.45 (dt, *J* = 14.4, 6.8 Hz, 1H), 5.62 (dt, *J* = 14.4, 6.9 Hz, 1H), 5.98 (dd, *J* = 14.4, 10.4 Hz, 1H), 6.04 (dt, *J* = 14.4, 10.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 10.3, 14.1, 21.5, 22.6, 28.8, 29.2, 29.4, 29.7, 29.9, 31.7, 32.6, 48.8, 52.8, 67.5, 128.2, 129.4, 132.5, 134.3; HRMS (ESI) calcd for $C_{18}H_{30}N^+$ 264.2686, found 264. 2685.

Acknowledgment. Financial support was provided by grants from NSFC (20625204, 20632030, 90713007, 207-72141) and MOST_863 (2006AA09Z405, 2006AA09Z446).

Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.