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Total Synthesis of Pumiliotoxins 209F and 251D via Late-Stage, Nickel-Catalyzed Epoxide−Alkyne Reductive Cyclization

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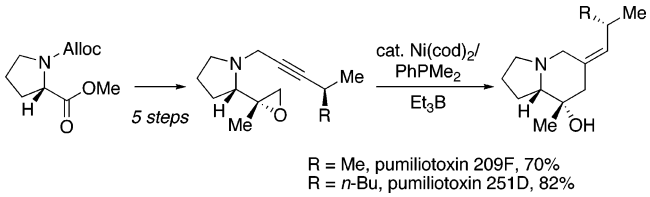
Received June 6, 2007



Pumiliotoxins 209F and 251D were synthesized using highly selective nickel-catalyzed epoxide−alkyne reductive cyclizations as the final step. The exocyclic (*Z*)-alkene found in the majority of the pumiliotoxins was formed stereospecifically and regioselectively, without the use of a directing group on the alkyne, and the epoxide underwent ring opening exclusively at the less hindered carbon to provide the requisite tertiary alcohol. The epoxides were prepared using diastereoselective addition of a sulfoxonium anion to a proline-derived methyl ketone.

The pumiliotoxins were first isolated in 1967 from the *Dendrobates pumilio* frogs in South America.[1,2] The structure and stereochemistry of these alkaloids were initially established via X-ray crytallographic analysis of the hydrochloride salt of pumiliotoxin 251D (**1**)[3] and confirmed by total syntheses of several members of this family of natural products.[4−7] Thirty pumiliotoxins have a (*Z*)-6-alkylideneindolizidine ring system and a tertiary alcohol at C8.

Several different strategies have been developed for the synthesis of the ubiquitous (*Z*)-alkene. Overman used an iminium ion−vinylsilane cyclization to this end in the first total synthesis of pumiliotoxin 251D[6a] and later employed a related iodide-promoted, iminium ion−alkyne cyclization to synthesize more complex pumiliotoxins.[4,8] Gallagher used a stereospecific elimination of a β-hydroxylactam to install the (*Z*)-alkene in the synthesis of pumiliotoxin 251D.[6b] In the synthesis described herein, we have reduced the construction of the pumiliotoxins to simultaneous and stereospecific installation of the exocyclic *Z*-alkene and tertiary alcohol present in the final step of the synthesis.

Our strategy is based on the notion that both of these challenges could be addressed by nickel-catalyzed reductive cyclizations[9] of epoxy alkynes previously developed in our laboratory (Figure 1).[10] However, all of the epoxides in our earlier investigations were monosubstituted (terminal). Thus, a major question in the context of the pumiliotoxins was whether or not 1,1-disubstituted epoxides (e.g., **3a** and **3b**), which we had previously found to be recalcitrant substrates, would undergo reductive cyclization.[11] Furthermore, in order to be used as the final step, the regioselectivity of both alkyne addition and epoxide ring-opening could not depend upon the use of a directing group on the alkyne. Nevertheless, proline-derived ketones **4a** and **4b** and propargyl bromides **5a** and **5b** were attractive precursors and readily available. Accordingly, we began our investigations by preparing these intermediates via chiral ketones **4a** and **4b**.

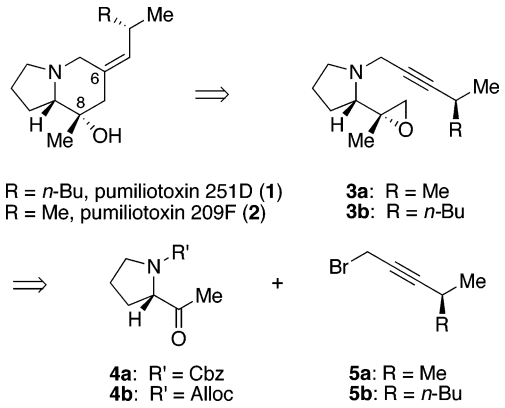


FIGURE 1. Retrosynthetic analysis of the pumiliotoxins.

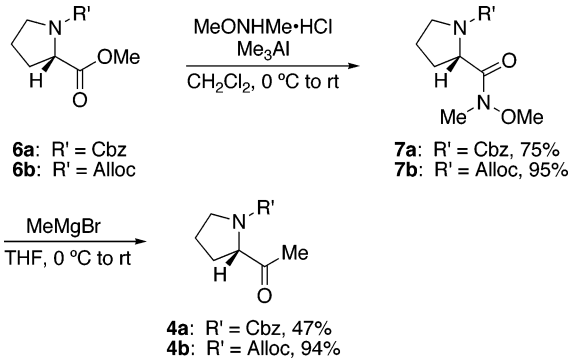
Treatment of carbamate-protected proline methyl esters **6a** and **6b**[12] with *N*,*O*-dimethylhydroxylamine hydrochloride and trimethylaluminium afforded Weinreb amides **7a** and **7b**,

(1) Daly, J. W.; Myers, C. W. *Science* **1967**, *156*, 970−973.
(2) For a recent review of pumiliotoxins, see: Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556−1575.
(3) Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. J.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 830−836.
(4) For a review of pumiliotoxin syntheses, see: Franklin, A. S.; Overman, L. E. *Chem. Rev.* **1996**, *96*, 505−522.
(5) Total syntheses of pumiliotoxin 209F: (a) Overman, L. E.; Lesuisse, D. *Tetrahedron Lett.* **1985**, *26*, 4167−4170. (b) Kibayashi, C.; Aoyagi, S. *Synth. Org. Chem. Jpn.* **1999**, *57*, 981−992. 8-*epi*-Pumiliotoxin 209F: (c) Sudau, A.; Münch, W.; Bats, J.-W.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2002**, 3315−3325.
(6) Total syntheses of pumiliotoxin 251D: (a) Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851−1853. (b) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652−2656. (c) Racemic 251D: Bargar, T. M.; Lett, R. M.; Johnson, P. L.; Hunter, J. E.; Chang, C. P.; Pernich, D. J.; Sabol, M. R.; Dick, M. R. *J. Agric. Food Chem.* **1995**, *43*, 1044−1051. (d) See also ref 5c.
(7) Formal syntheses of pumiliotoxins: (a) Honda, T.; Hoshi, M.; Kanai, K.; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2091−2101. (b) Cossy, J.; Cases, M.; Pardo, D. G. *Synlett* **1996**, 909−910. (c) Barrett, A. G. M.; Damiani, F. *J. Org. Chem.* **1999**, *64*, 1410−1411. (d) Martin, S. F.; Bur, S. K. *Tetrahedron* **1999**, *55*, 8905−8914. (e) Ni, Y.; Zhao, G.; Ding, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3264−3266. (f) Wang, B.; Fang, K.; Lin, G.-Q. *Tetrahedron Lett.* **2003**, *44*, 7981−7984.
(8) Overman, L. E.; Sharp, M. J. *Tetrahedron Lett.* **1988**, *29*, 901−904.
(9) In the syntheses of several allopumiliotoxins, Montgomery utilized a diastereoselective nickel-catalyzed alkyne−aldehyde reductive cyclization to establish the (*Z*)-alkene and the configuration of a secondary alcohol: (a) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098−6099. (b) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950−6954. (c) Review: Montgomery, J. *Angew. Chem.* **2004**, *43*, 3890−3908.
(10) Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076−8077.

10.1021/jo071132e CCC: $37.00
Published on Web 08/14/2007

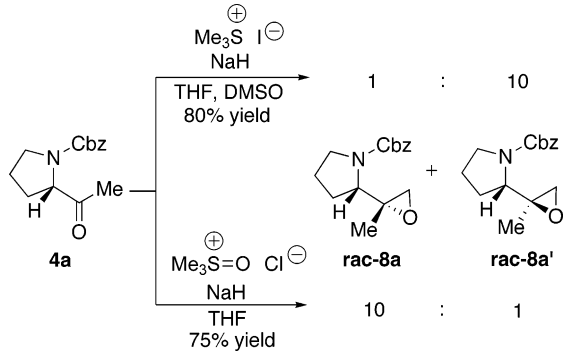
respectively, in good yield (Scheme 1). Conversion of these amides to ketones **4a** and **4b** proceeded in a similarly straightforward manner, setting the stage for investigation of the step that would set the stereogenic center corresponding to the tertiary alcohol in the natural products.[13]

SCHEME 1. Synthesis of Proline-Derived Ketone 4



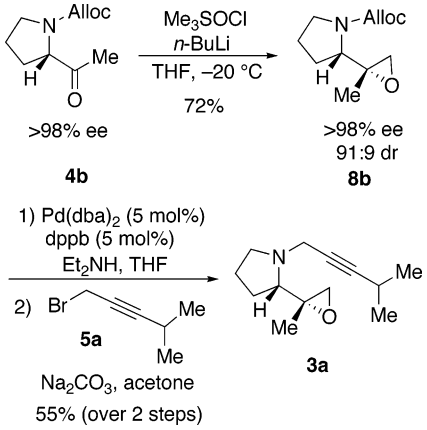
Application of the Corey−Chaykovsky[14] sulfur−ylide epoxidation method provided stereochemically complementary results, depending on which sulfonium reagent was employed.[15] When Cbz-protected ketone **4a** was subjected to dimethylsulfonium methylide, the undesired diastereomer (epoxide **8a**) was formed with high selectivity (>10:1 dr) in good yield, but both diastereomers were optically *inactive*, suggesting rapid racemization of the proline derivative prior to a highly diastereoselective epoxide formation (Scheme 2). Gratifyingly, when dimethyloxosulfonium methylide was used, the desired diastereomer (**8a**) was afforded in good yield and in a highly diastereoselective fashion (>10:1 dr). It was further discovered that the carbamate group was required to impart the high diastereoselectivity during the epoxidation, as other proline-derived ketones gave a 1:1 mixture of diastereomers.[16] The dimethylsulfonium methylide reagent often exhibits kinetic control of stereoselectivity. In a Felkin−Ahn analysis of the reaction at hand, the nucleophile would approach anti to the carbamate group, leading to the observed diastereomer (**8a**, undesired). Conversely, diastereoselective dimethylsulfoxonium methylide addition reactions tend to be under thermodynamic control. Epoxide **8a** (desired) may thus be favored under these conditions because of the reversible nature of the addition process and a greater thermodynamic stability of either a subsequent intermediate or of **8a** itself.[17]

SCHEME 2



Attempts to remove the Cbz group from epoxide **8a** unfortunately led to a complex mixture of products under all conditions evaluated. We thus turned our attention to the Alloc series and found that the conditions that provided high dr in the Cbz series (NaH, trimethylsulfoxonium chloride) gave similar results with Alloc-protected ketone **4b**. However, although the desired product had formed with high diastereoselectivity, it was optically inactive, suggesting that racemization of ketone **4b** had occurred prior to the epoxidation. A careful examination of reagents and reaction conditions revealed that the racemization could be prevented by the use of *n*-BuLi (instead of NaH) at a lower reaction temperature (Scheme 3).[18] This sequence provided epoxide **8b** with high diastereoselectivity and optical purity. Removal of the Alloc group was effected with catalytic $Pd(dba)_2$ and dppb in the presence of excess diethylamine.[19] The free amine was treated with propargyl bromide **5a**[20] (Na_2CO_3/acetone) to form epoxy alkyne **3a**, thus setting the stage for the critical nickel-catalyzed step.

SCHEME 3. Synthesis of Epoxy Alkyne 3a (209F Precursor)



Under reaction conditions routinely used in intermolecular nickel-catalyzed coupling reactions between alkynes and terminal epoxides,[9] no conversion of epoxy alkyne substrate **3a** was observed (Table 1, entry 1). However, conducting the reaction in the absence of an additional solvent did lead to the formation of small amounts of the desired product, pumiliotoxin 209F (**2**). The largest increase in yield was imparted by

(11) Molinaro, C.; Jamison, T. F. Unpublished results.

(12) (a) Cbz-Pro methyl ester is commericially available. (b) Alloc-Pro methyl ester was prepared in quantitative yield from Pro methyl ester and allyl chloroformate; see: Yamada, Y.; Takahashi, W.; Asada, Y.; Holiuchi, J.; Takeda, K.; Harigaya, Y. *Chem. Pharm. Bull.* **2004**, *52*, 1082−1085.

(13) Epimerization of ketones **4a** and **4b** was not observed (chiral GC analysis).

(14) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364.

(15) For a discussion on kinetic vs. thermodynamic control in sulfur ylide addition reactions, see: Johnson, C. R.; Schroeck, C. W.; Shanklin, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 7424−7431.

(16) For a discussion on sulfur-ylide epoxidation of similar pyrrolidines, see: Fray, M. J.; Thomas, E. J.; Wallis, J. D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 395−401.

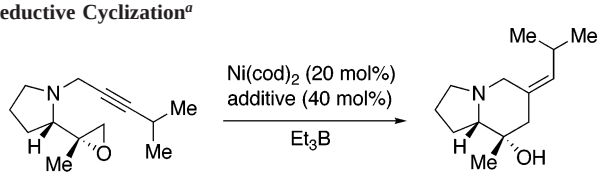
(17) For a discussion of substrate control in sulfur−ylide epoxidations, see: Li, H-H; Dai, L-X, Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341−2372 and references cited therein.

(18) Racemization could also be prevented by using less NaH (150 mol%) and by lowering the reaction temperature, but conversion to product was much slower. See the Supporting Information for details.

(19) Genêt, J. P.; Blart, E.; Savignac, M.; Lemeune, S.; Lemaire-Audoire, S.; Bernard, J. M. *Synlett* **1993**, 680−682.

(20) Propargyl bromide **5a** was prepared by treatment of 4-methylpent-2-yn-1-ol with CBr_4 and PPh_3 in CH_2Cl_2. See the Supporting Information for details.

TABLE 1. Synthesis of Pumiliotoxin 209F via Nickel-Catalyzed Reductive Cyclization[a]



entry	solvent added	*T* (°C)	Et_3B (mol %)	phosphine additive	isolated yield (%)
1	Et_2O	23	250	PBu_3	0
2	none	23	250	PBu_3	9
3	none	65	250	PBu_3	53
4	none	65	150	PBu_3	61
5	none	65	150	$PCyp_3$	0
6	none	65	150	PMe_2Ph	70

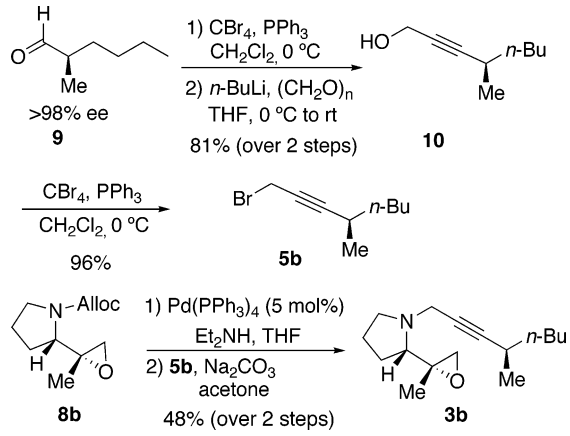
[a] See the Supporting Information for experimental details.

conducting the reaction at slightly elevated temperature (entry 3). By lowering the amount of Et_3B to 150 mol %, which also considerably increased the concentration of the reaction, the yield appreciated further (entry 4). The phosphine employed also had a dramatic effect on the yield. The larger tricyclopentylphosphine ($PCyp_3$) was inferior to tributylphosphine (PBu_3), and the smaller PMe_2Ph was superior to all phosphines evaluated (entries 5 and 6).[21−23] Under the optimum conditions, the nickel-catalyzed reductive cyclization of epoxy alkyne **2a** proceeded in 70% yield to produce pumiliotoxin 209F (**2**).

In addition to representing the first example of a successful nickel-catalyzed cyclization between a 1,1-disubstituted epoxide and an alkyne, a noteworthy element of selectivity was that the six-membered ring was formed exclusively. The other alkyne addition regioisomer would have led to a seven-membered ring containing an alkene. This isomer was not observed, likely because cis addition to the alkyne, a process that occurs with very high fidelity, would lead to a highly strained trans alkene in the seven-membered ring as the carbon−carbon bond formed. In a similar vein, no evidence of epoxide opening at the more hindered carbon, which would lead to a five-membered ring, was observed. We believe that the sense of epoxide-opening regioselectivity is largely dictated by this difference in steric hindrance, and it is also possible that the Ni complex reacts with the epoxide *first*, which in turn classifies addition to the alkyne as a 6-*exo-dig* cyclization.[10]

To investigate the utility and scope of this cyclization further and to take advantage of the high degree of convergence in this strategy, pumiliotoxin 251D (**1**) was also synthesized. Substitution of the appropriate propargyl electrophile for **5a** (Scheme 3) would provide the necessary educt for the nickel-catalyzed reductive cyclization. In other words, after preparation of propargyl bromide **5b**,[24] only two new transformations would

SCHEME 4. Synthesis of Epoxy Alkyne 3b (251D Precursor)

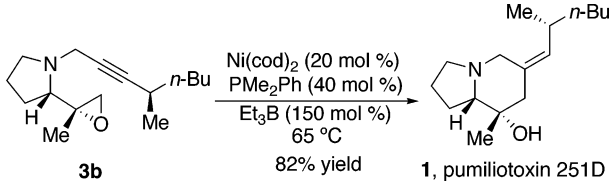


be required to convert a known intermediate in the 209F synthesis to pumiliotoxin 251D.

The route to pumiliotoxin 251D thus began with synthesis of alcohol **10** from aldehyde **9**[25] using the Corey−Fuchs reaction (Scheme 4).[26] This alcohol was converted to bromide **5b**, and epoxide **3b** was afforded by alkylation of the primary amine prepared previously.

As was the case in the pumiliotoxin 209F studies, the final step of the 251D synthesis, nickel-catalyzed reductive cyclization of epoxy alkyne **3b** proceeded smoothly, affording the natural product in 82% yield as a single diastereomer and regioisomer (Scheme 5).

SCHEME 5. Synthesis of Pumiliotoxin 251D via Nickel-Catalyzed Reductive Cyclization



In summary, pumiliotoxin 209F was synthesized in seven steps (longest linear sequence) in 25% overall yield, and pumiliotoxin 251D was synthesized in nine linear steps from commercial materials in 17% overall yield. Both syntheses utilized a novel cyclization reaction, an intramolecular, nickel-catalyzed reductive coupling of a 1,1-disubstituted epoxide, and an alkyne. In this way, the tertiary homoallylic alcohol and exocyclic trisubstituted alkene moieties present in this family of natural products were prepared in the final step of each total synthesis. For these reasons, this strategy shows promise for entry into other members of the pumiliotoxin family by way of a common intermediate.

Experimental Section

(*S*)-Allyl 2-((*R*)-2-Methyloxiran-2-yl)pyrrolidine-1-carboxylate (8b). Me_3SOCl (0.096 g, 0.75 mmol) was dissolved in THF (7 mL) and *n*-BuLi (0.22 mL, 0.55 mmol, 2.5 M in hexanes) was added dropwise at rt. The reaction was stirred at rt for 4.5 h and

(21) Other phosphine ligands evaluated include P(*n*-octyl)$_3$, P(*o*-anisyl)$_3$, P(CH$_2$CH$_2$CN)$_3$, P(OEt)Ph$_2$, P(OEt)$_2$Ph, and P(OEt)$_3$.

(22) The cone angles of PBu_3 and PMe_2Ph are 132° and 122°, respectively: Rahman, M. M.; Liu, H.-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1−7.

(23) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741−2770.

(24) Preparation of bromide **5b**: Okamoto, S.; Iwakubo, M.; Kobayashi, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 6984−6990.

(25) Synthesis of aldehyde **9** in 56% yield over four steps: Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179−1190.

(26) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769−3772.

then cooled to −20 °C, and the slurry was added to the ketone **4b** (0.099 g, 0.5 mmol), dissolved in THF (2 mL), dropwise via cannula over 20 min. The reaction was stirred at −20 °C for 32 h and quenched with 0.1 M $NaHSO_4$ (10 mL).[7] The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the organic extracts were washed with brine (50 mL) and dried over Na_2SO_4. The solution was filtered and concentrated in vacuo and was purified by flash column chromatography (3:7 EtOAc/hexanes) to give alloc-protected epoxide **8b** (0.076 g, 72% yield, 91:9 dr favoring desired diastereomer, >98% ee, as determined by chiral GC): R_f 0.41 (1:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) (reported as ∼1:1 mixture of rotamers) δ 5.97−5.90 (m, 2H), 5.31 (dd, J = 10.4, 1.1 Hz, 2H), 5.20 (dd, J = 10.4, 1.1 Hz, 2H), 4.68−4.52 (m, 4H), 4.06 (d, J = 6.4 Hz, 1H), 3.94 (d, J = 6.4 Hz, 1H), 3.62−3.28 (m, 4H), 2.63 (d, J = 4.6 Hz, 2H), 2.53 (d, J = 4.6 Hz, 2H), 2.10−1.67 (m, 8H), 1.35 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) (reported as ∼1:1 mixture of rotamers) δ 155.6, 155.3, 133.3, 117.5, 117.4, 65.9, 59.5, 59.0, 52.6, 52.4, 47.7, 47.2, 29.0, 27.8, 24.6, 23.9, 19.9, 19.6; IR (thin film NaCl) 3057, 2980, 2882, 1702, 1648, 1405, 1350, 1335, 1277, 1186, 1121, 1098, 919, 774 cm^{-1}; HRMS (ESI) m/z 234.1105 [M + Na; calcd for $C_{11}H_{17}NO_3$ 234.1101]; $[\alpha]_D$ = −80.8 (23 °C, 589 nm, 0.45 g/100 mL, $CHCl_3$).

(*S*)-2-((*R*)-2-Methyloxiran-2-yl)-1-(4-methylpent-2-ynyl)pyrrolidine (3a). $Pd(dba)_2$ (0.086 g, 0.15 mmol) and dppb (0.064 g, 0.15 mmol) were combined in a glove box. Alloc-protected epoxide **8b** (0.317 g, 1.5 mmol) in THF (4 mL) was added followed by addition of diethylamine (2.3 mL, 22.5 mmol). The reaction was stirred at rt for 2 h and then filtered through a plug of Celite with ether (10 mL) to removed the palladium catalyst andas concentrated in vacuo to form free amine. The amine was dissolved in acetone (15 mL), Na_2CO_3 (0.398 g, 3.75 mmol) and propargyl bromide **5a** (0.290 g, 1.8 mmol) were added, and the reaction was allowed to stir at rt for 16 h. The solvent was removed in vacuo, and the compound was purified by flash column chromatography using a solvent gradient (1:19 to 3:7 EtOAc/hexanes) to give amine **3a** as a pale yellow oil (0.17 g, 55% yield over the two steps, 91:9 dr retained): R_f 0.51 (1:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) (reported as a 10:1 mixture of diastereomers, asterisk denotes minor diastereomer) δ 3.60 (dd, J = 16.7, 1.9 Hz, 1H), 3.49* (dd, J = 16.7, 1.9 Hz, 0.1H), 3.41* (dd, J = 16.7, 1.9 Hz, 0.1H), 3.31 (dd, J = 16.7, 1.9 Hz, 1H), 3.08 (t, J = 7.3 Hz, 1H), 2.96* (t, J = 7.3 Hz, 0.1H), 2.77* (d, J = 5.3 Hz, 0.1H), 2.62−2.48 (m, 4H), 2.27 (t, J = 7.33 Hz, 1H), 1.89−1.70 (m, 4H), 1.33 (s, 3H), 1.29* (s, 0.3H), 1.60 (d, J = 6.9 Hz, 6H) 1.15* (d, J = 6.9 Hz, 0.6H); ^{13}C NMR (125 MHz, $CDCl_3$) (major and minor peaks reported) δ 91.2, 90.4, 74.7, 73.9, 66.8, 65.4, 58.1, 57.4, 54.0, 53.5, 53.2, 51.0, 42.6, 41.8, 28.4, 27.8, 23.6, 23.5, 23.3, 23.1, 20.8, 20.7, 16.8, 16.7; IR (thin film NaCl) 3035, 2969, 2873, 2813, 2242, 1462, 1444, 1400, 1368, 1319, 1180, 1123, 1095, 1067, 909 cm^{-1}; HRMS (ESI) m/z 208.1695 [M + H; calcd for $C_{13}H_{21}NO$ 208.1696]; $[\alpha]_D$ = −40.4 (23 °C, 589 nm, 0.2 g/100 mL, $CHCl_3$).

Pumiliotoxin 209F (2). In a glovebox, $Ni(cod)_2$ (5.6 mg, 0.02 mmol) and PMe_2Ph (5.7 μL, 0.04 mmol) were placed into an oven-dried, sealed tube, which was sealed with a rubber septum and Teflon cap. The tube was removed from the glovebox and placed under argon, and triethylborane (22 μL, 0.15 mmol) was added via syringe. The resulting solution was stirred for 5 min, and the epoxy alkyne **3a** (21 mg, 0.10 mmol) was added dropwise via microsyringe. The reaction was heated to 65 °C and allowed to stir for 16 h. The solution was then cooled to rt, and ether (2 mL) was added to dilute the solution at which point the septum was removed and the reaction was stirred 30 min open to air to promote quenching of the catalyst. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (1:49 to 1:19 MeOH/$CHCl_3$) to give pumiliotoxin 209F (**2**) as a colorless oil (14.6 mg, 70% yield, 1 diastereomer): R_f 0.33 (1:9 MeOH/$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (d, J = 9.2 Hz, 1H), 3.80 (d, J = 11.9 Hz, 1H), 3.07 (t, J = 8.3 Hz, 1H), 2.67 (s, 1H), 2.60−2.55 (m, 1H), 2.36 (d, J = 11.9 Hz, 1H), 2.24−2.20 (m, 1H), 2.12 (d, J = 13.8 Hz, 1H), 2.09 (d, J = 13.8 Hz, 1H), 1.98 (t, J = 5.0 Hz, 1H), 1.79−1.65 (m, 4H), 1.14 (s, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 129.4, 71.9, 68.6, 54.6, 53.1, 48.9, 26.96, 24.5, 23.7, 23.6, 23.4, 21.3; IR (thin film NaCl) 3512, 2959, 2874, 2785, 2743, 1464, 1445, 1424, 1396, 1376, 1321, 1309, 1297, 1275, 1216, 1175, 1150, 1098, 967 cm^{-1}; HRMS (ESI) m/z 210.1852 [M + H; calcd for $C_{13}H_{23}NO$ 210.1849]; $[\alpha]_D$ = −12.8 (23 °C, 589 nm, 0.3 g/100 mL, $CHCl_3$).

Pumiliotoxin 251 D (1): same experimental procedure as **2**; R_f 0.30 (1:9 MeOH/$CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (d, J = 9.5 Hz, 1H), 3.78 (d, J = 12.0 Hz, 1H), 3.07−3.03 (m, 1H), 2.67 (s, 1H), 2.42−2.30 (m, 1H), 2.34 (d, J = 12.0 Hz, 1H), 2.25−2.15 (m, 1H), 2.15−2.12 (m, 2H), 2.00−1.90 (m, 1H), 1.78−1.60 (m, 4H), 1.32−1.10 (m, 6H), 1.14 (s, 3H), 0.97 (d, J = 6.5 Hz, 3H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.7, 130.0, 71.8, 68.4, 54.7, 53.3, 48.9, 37.6, 32.2, 29.8, 24.4, 23.3, 22.9, 21.8, 21.2, 14.2; IR (thin film NaCl) 3418, 2982, 2909, 2872, 1660, 1465, 1420, 1324, 1305, 1291, 1176, 1121, 1072, 939, 913, 871 cm^{-1}; HRMS (ESI) m/z 252.2321 [M + H; calcd for $C_{16}H_{29}NO$: 252.2322]; $[\alpha]_D$ = −9.3 (23 °C, 589 nm, 0.05 g/100 mL, $CHCl_3$).

Acknowledgment. This work was supported by the National Institutes of General Medical Sciences (Grant No. GM-063755). We are grateful to Ms. Li Li for obtaining mass spectrometric data for all compounds (MIT Department of Chemistry Instrumentation Facility, which is supported in part by the NSF (Grant Nos. CHE-9809061 and DBI-9729592) and the NIH (Grant No. 1S10RR13886-01)).

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO071132E