found 512.7988.

Preparation of Disaccharide Fluoride 17. To a solution of phenyl thioglycoside **16** (56 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) at −15 °C was added DAST (21 L, 0.16 mmol) under argon followed by NBS (25 mg, 0.14 mmol). After 15 min at −15 °C, the reaction mixture was poured onto saturated $NaHCO_3$ (5 mL) and extracted with ether (3 × 10 mL). The ether extracts were combined, washed with brine (5 mL), and dried ($MgSO_4$). Evaporation of the solvent followed by flash column chromatography (silica, ether–petroleum ether mixtures) furnished the glycosyl fluoride **17**, (40 mg, 85%) with an anomeric ratio of ca. 5:1 (α:β): R_f 0.24 (30% ether in petroleum ether); IR (neat ν_{max} 2940, 2920, 2880, 2860, 1380, 1240, 1100, 965, 820, 765 cm^{-1}; ^1H NMR (α:β ca. 5:1) δ 5.68 (d, $J_{1,F}$ = 50 Hz, 0.8 H, H-1), 5.34 (d, $J_{1,F}$ = 50 Hz, 0.2 H, H-1), 5.33 (d, $J_{1',2'}$ = 5.0 Hz, 0.8 H, H-1'), 5.29 (d, $J_{1',2'}$ = 5.0 Hz, 0.2 H, H-1'), 3.90 (m, 1 H, H-5), 3.70 (m, 1 H, H-5'), 3.55 (m, 1 H, H-3), 3.45 (m, 1 H, H-3'), 3.38 and 3.34 (two s, 2.4 H each, OCH_3), 3.37 and 3.32 (two s, 0.6 H each, OCH_3), 3.30 and3.14 (dd, J = 9.0, 9.0 Hz, 1 H each, H-4 and H-4'), 2.45 (m, 1 H, H-2_{eq}), 2.30 (dd, J = 15.0, 3.5 Hz, 1 H, H-$2'_{eq}$), 1.60 (m, 1 H, H-2_{ax}), 1.50 (m, 1 H, H-$2'_{ax}$), 1.40 (d, J = 5.0 Hz, 0.6 H, H-6), 1.32 (d, J = 7.5 Hz, 2.4 H, H-6), 1.22 (d, J = 6.0 Hz, 3 H, H-6'), 0.90 (s, 9 H, *-Bu), 0.12 and 0.10 (two s, 3 H each, (Me_2Si); HRMS calcd for $C_{18}H_{39}O_6SiF$ (M^+) 398.6018, found 398.6020.

Preparation of Avermectin B_{1a} Bis(silyl ether) 18. To a suspension of $AgClO_4$ (12 mg, 0.06 mmol), $SnCl_2$ (11 mg, 0.06 mmol), crushed 4-Å molecular sieves (100 mg, dried) in dry ether (1 mL) under argon at −15 °C was added alcohol **12** (52 mg, 0.074 mmol) in ether (1 mL). Addition of fluoride **17** (24 mg, 0.057 mmol), stirring at 0 °C for 16 h, and standard workup as in the preparation of **16**, afforded **18** (38 mg, 62% yield) after flash column chromatography (silica, ether–petroleum ether mixtures): R_f 0.22 (30% ether in petroleum ether); $[\alpha]^{25}_D$ +29.35° (*c* 0.51, CH_2Cl_2); IR (thin film) ν_{max} 3500, 3020, 2970, 2940, 2860, 1710, 1470, 1390, 1260, 1140, 1105, 990, 840 cm^{-1}; ^1H NMR δ 5.86 and 5.75 (two m, 1 H and 3 H, respectively, H-9, H-10, H-11, H-22), 5.55 (dd, J = 10.0, 2.0 Hz, 1 H, H-23), 5.41 (m, 3 H, H-3, H-19, H-1''), 5.00 (m, 1 H, H-15), 4.78 (1 H, H-1'), 4.70 and 4.59 (two d, J = 15.0 Hz, 1 H each, C-8-CH_2O), 4.45 (m, 1 H, H-5), 4.12 (s, 1 H, OH), 3.95 (brs, 1 H, H-13), 3.86 (m, 2 H, H-5' or H-5'', H-17), 3.84 (d, J = 5.5 Hz, 1 H, H-6), 3.65 (m, 3 H, H-5'' or H-5', H-3', H-3''), 3.48 (d, J = 10.0 Hz, 1 H, H-25), 3.45 and 3.35 (two s, 3 H each, OCH_3), 3.40 (brs, 1 H, H-2), 3.21 (dd, J = 8.0, 8.0 Hz, 1H, H-4'), 3.12 (dd, J = 8.0, 8.0 Hz, 1 H, H-4''), 2.51 (m, 1 H, H-12), 2.30 (m, 5 H, H-16, H-24, H -2'$_e$, H -2''$_e$), 2.05 (dd, J = 5.0, 12.0 Hz, 1 H, H-18e), 1.80 (s, 3 H, C-4-CH_3) 1.76 (m, 1 H, H-2'$_a$ or H-2''$_a$), 1.55 (m, 5 H, H-20, H-26, H-27), 1.52 (s, 3 H, C-14-CH_3), 1.25 (d, J = 8.0Hz, 3H, H-6'' or H-6'), 1.22 (d, J = 5.0 Hz, 3 H, H-6'' or H-6'), 1.17 (d, J = 7.5 Hz 3 H, C-12-CH_3), 0.95–0.80 (m, 11 H, H-18a, H-2'$_a$ or H-2''$_a$, H-28, C-24-CH_3, C-26-CH_3), 0.94 and 0.90 (two s, 9 H each, *t*-Bu), 0.15 (s, 6 H, Me_2Si), 0.1 and 0.09 (two s, 3 H each, Me_2Si). Anal. ($C_{60}H_{100}O_{14}Si_2$) C, H.

Avermectin B_{1a} (11). The bis(silyl ether) **18** (22 mg, 0.02 mmol) was dissolved in THF (2 mL) and cooled to 0 °C. *n*-Bu_4NF (1 M in THF, 44 μL, 0.044 mmol) was added and the reaction mixture kept at 0 °C for 16 h. The reaction mixture was flash chromatographed directly (silica, ether–petroleum ether mixture) to afford avermectin B_{1a} (**11**) (15 mg, 89%) identical with an authentic sample by IR, ^1H NMR, MS, TLC, and $[\alpha]^{25}_D$.

Acknowledgment. We express our many thanks to Dr. George Furst of the Department of Chemistry, University of Pennsylvania, for his excellent spectroscopic assistance and helpful comments. We also thank Dr. H. Mrozik of Merck Sharp Dohme, Rahway, NJ, for a generous gift of avermectin B_{1a}. This work was financially supported by the National Institutes of Health, USA, Merck Sharp & Dohme, USA, the A. P. Sloan Foundation, and the Camille and Henry Dreyfus Foundation.

Supplementary Material Available: Listing of ^1H NMR data of **3b**, **4b**, **6b**, **7b**, **3**, **4**, **12**, and **15**, (3 pages). Ordering information is given on any current masthead page.

Enantioselective Total Syntheses of Pumiliotoxin B and Pumiliotoxin 251D. A General Entry to the Pumiliotoxin A Alkaloids via Stereospecific Iminium Ion–Vinylsilane Cyclizations

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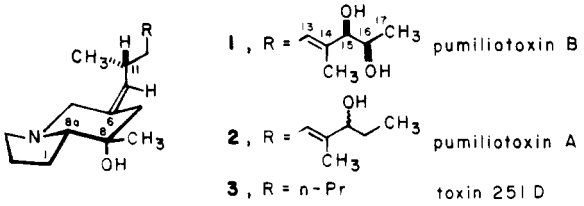
Abstract: Enantioselective total syntheses of pumiliotoxin B (**1**) and pumiliotoxin 251D (**3**) are reported. The synthesis of pumiliotoxin B unambiguously establishes, for the first time, the complete stereostructure of this potentially important cardiac agent. The key synthetic tactic is the use of an iminium ion–vinylsilane cyclization (**6** → **4**, eq 1) to both form the indolizidine ring system and establish the *Z* stereochemistry of the alkylidene side chain.

Pumiliotoxins A (**2**) and B (**1**) were first isolated from the Panamanian poison frog *Dendrobates pumilio* in 1967.[1,2] Originally believed to be steroidal alkaloids, the structure of these toxins remained obscure until 1980 when a simpler alkaloid, pumiliotoxin 251D (**3**), was found as a major component of the basic skin extracts of the Ecuadorian poison frog, *Dendrobates Tricolor*.[3] X-ray analysis of the crystalline hydrochloride of 251D



established the structure and absolute configuration of this toxin[3] and provided the key for partial structure elucidation of the pumiliotoxin A class of dendrobatid alkaloids.[2] These alkaloids, of which pumiliotoxin B is one of the most complex members, have in common the unusual (*Z*)-6-alkylideneindolizidine (1-azabicyclo[4.3.0]nonane) ring system. The stereostructure of the side-

(1) Daly, J. W.; Myers, C. W. *Science (Washington, D.C.)* **1967**, *156*, 970.
(2) For recent reviews of these fascinating poison frog alkaloids, see: (a) Daly, J. W. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 205. (b) Witkop, B.; Gössinger, E. In "The Alkaloids"; Brossi, A., Ed.; Academic: New York, 1983; Vol. 21, Chapter 5.
(3) Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. L.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 830.

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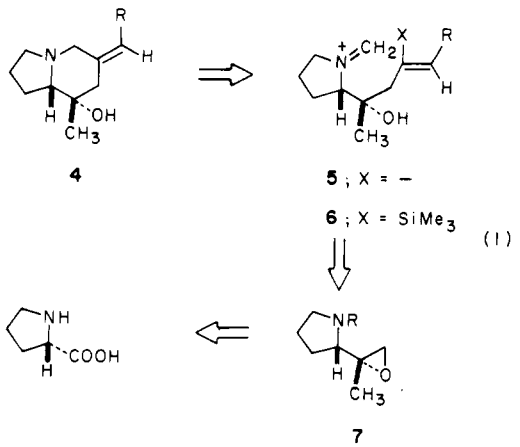
chain allylic diol group of pumiliotoxin B has been established by recent studies[4] to be 15*R*,16*R* (threo relative configuration), although the absolute configuration of the indolizidine portion (C-8, C-8a, C-11) was not rigorously defined.[5]

Pumiliotoxin B has been shown to be a powerful myotonic[6,7] and cardiotonic agent,[7] which selectively effects calcium translocation across membranes.[2] Cardiac activity has been observed with other dendrobatid alkaloids of the pumiliotoxin A class, as well as with some simpler synthetic analogues,[8] although pumiliotoxin B is the most active compound of this group to be studied to date.

Herein we describe a general method for the practical chemical synthesis of the rare pumiliotoxin A alkaloids in enantiomerically pure form. Specifically, we detail our total synthesis of pumiliotoxin 251D[9] and report the first[10] total synthesis of pumiliotoxin B. The latter synthesis unambiguously establishes the complete stereostructure of this potentially important cardiac agent. These syntheses are based on a new method for forming unsaturated azacyclic rings which has potentially broader significance.

General Synthesis Plan

More than ten dendrobatid alkaloids of the pumiliotoxin A class are believed to have the (*Z*)-6-alkylideneindolizidine ring system (**4**) and differ only in the side chain.[2] The development of a convergent method for assembling alkylideneindolizidines of this type, which would allow flexibility in side-chain introduction, was a foremost consideration in our synthesis planning. Of the challenges posed by the bicyclic ring system **4**, perhaps the greatest is control of the exocyclic double-bond stereochemistry, since stereocontrol in the preparation of alkenes that are exocyclic to rings remains a largely unsolved issue.[11] A particularly attractive solution to this problem would be to establish the exocyclic alkene stereochemistry in a cyclization reaction that also forms the piperidine ring, see eq 1. We felt that a vinylsilane might serve

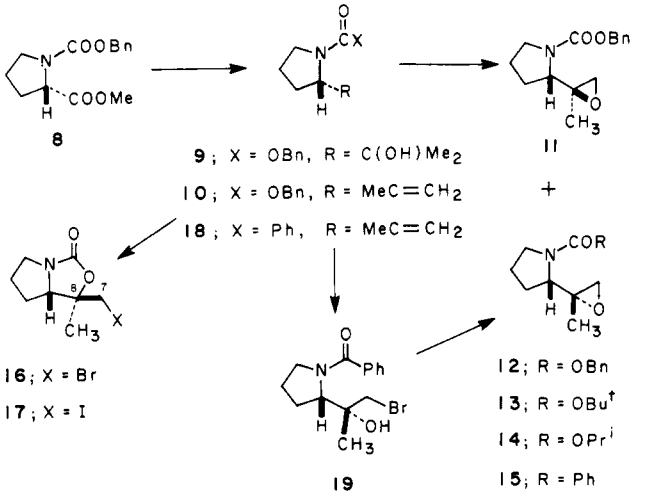


well as a practical equivalent for the vinyl anion functionality in hypothetical intermediate **5**. It had been well established that vinylsilanes undergo electrophilic substitution with retention of configuration,[12] although prior to the investigations described herein there were no examples of the related intramolecular process.[13] We envisioned the construction of vinylsilane **6** from L-proline via epoxide intermediate **7**.

Results and Discussion

Preparation of Epoxides 7. Our first concern was the preparation of epoxide **7** (eq 1) from L-proline. A nonstereoselective route was initially developed with the expectation that the availability of both epoxide isomers would facilitate stereochemical assignments. Methyl *N*-[(benzyloxy)carbonyl]-L-prolinate (**8**)[14] was converted in 86% yield to tertiary alcohol **9** by reaction with 2.15 equiv of MeMgI. Interestingly, MeLi could not be employed in this reaction since it competitively deprotonated **8** at C-2 (confirmed by deuterium incorporation upon quenching with D_2O) as well as reacted at the carbamate group. Alcohol **9** is believed to be enantiomerically pure since the 250-MHz ^1H NMR spectrum of **9** in the presence of 0.3 equiv of tris[3-([(trifluoromethyl)hydroxy]methylene)-*d*-camphorato]europium(III)[15] showed only two methyl singlets at δ 1.73 and 1.42, which result from slow rotation of the carbamate group on the NMR time scale. A sample of racemic **9** analyzed in the same way showed four methyl signals (δ 1.73, 1.60, 1.42, and 1.24) of equal intensity. Dehydration of **9** to give the terminal alkene **10** was best accomplished in tetrahydrofuran (THF) at −45 to −50 °C with $SOCl_2$ and pyridine and provided **10** in 54% overall yield from **8**. Alternate reaction conditions or the use of other dehydrating agents (e.g. $POCl_3$, SO_2Cl_2, RSO_3H, or $MeSO_2Cl$) were less effective and gave larger amounts of the internal alkene isomer.

Epoxidation of **10** with *m*-chloroperbenzoic acid proceeded without asymmetric induction in CH_2Cl_2 at 25 °C to give a 1:1 mixture of epoxides **11** and **12**. This mixture could be separated



on 25-g scales by chromatography on silica gel to give the desired epoxide **12** as a colorless liquid in 37% yield. The stereoselectivity of this epoxidation was somewhat solvent dependent,[16] and a 2:1 ratio of epoxides **12** and **11** could be realized in hexane at 25 °C. Unfortunately, due to the low solubility of the peracid in hexane this reaction had to be conducted at a dilution which was not convenient for large-scale preparations of **12**. Not surprisingly, **10** could not be epoxidized with *tert*-butyl hydroperoxide in the presence of either $Mo(CO)_6$ or $VO(acac)_2$.[17] Clearly, room for improvement remains in this epoxidation step. Other N-protected

(4) (a) Uemura, M.; Shimada, K.; Tokuyama, T.; Daly, J. W. *Tetrahedron Lett.* **1982**, *23*, 4369. (b) Overman, L. E.; McCready, R. J. *Ibid.* **1982**, *23*, 2355. (c) Tokuyama, T.; Shimada, K.; Uemura, M.; Daly, J. W. *Ibid.* **1982**, *23*, 2121.

(5) The stereochemistry was assumed in analogy with pumiliotoxin 251D to be as shown in **1**.

(6) Albuquerque, E. X.; Warnick, J. E.; Maleque, M. A.; Kaufman, F. C.; Tamburini, R.; Nimit, Y.; Daly, J. W. *Mol. Pharmacol.* **1981**, *19*, 141.

(7) Mensah-Dwumah, M.; Daly, J. W. *Toxicon* **1978**, *16*, 189.

(8) Daly, J. W.; McNeal, E. T.; Overman, L. E.; Ellison, H., submitted for publication.

(9) A preliminary report of this synthesis has appeared: Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851.

(10) This synthesis was first reported at the Great Lakes Regional ACS Meeting, Minneapolis, MN, June 2, 1983.

(11) See: Overman, L. E.; Malone, T. C. *J. Org. Chem.* **1982**, *47*, 5297; and ref 2 and 3 cited therein.

(12) Cf.: Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761.

(13) Subsequent to our first report[9] a number of intramolecular electrophilic cyclizations of vinylsilanes have been described: Burke, S. D.; Murtiashaw, C. W.; Dike, M. S.; Smith-Strickland, S. M.; Saunders, J. O. *J. Org. Chem.* **1981**, *46*, 2400. Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529. Mikami, K.; Kishi, N.; Nakai, T. *Tetrahedron Lett.* **1983**, *24*, 795. Nakamura, E.; Fukuzaki, K.; Kuwajima, I. *J. Chem. Soc., Chem. Commun.* **1983**, 499. Overman, L. E.; Malone, T. C.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993. Reference 11.

(14) Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23*, 3081.

(15) Kime, K. A.; Sievers, R. E. *Aldrichimica Acta* **1977**, *10*, 54.

(16) (a) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 4887. (b) This reaction was first accomplished by Dr. K. Vaughan of this laboratory.

(17) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.

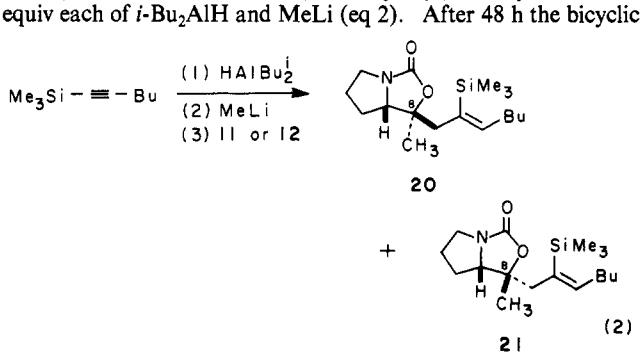
epoxides, e.g., **13** and **14**, were also prepared by this sequence from the corresponding L-proline carbamates.

Alkene **10** did react stereoselectively with *N*-bromosuccinimide (NBS) or iodine[16b] to give the crystalline halocarbamates **16** or **17** with high (>10:1) selectivity.[16] Although **16** and **17** have the desired stereochemistry at C-8,[18] they proved not to be useful synthetic intermediates. Thus, neither **16** nor **17** could be alkylated at C-7 with alkyl or alkenyl cuprates,[19] presumably due to their neopentyl character as well as the presence of the β-oxygen substituent.

The reaction of benzamide alkene **18**[16] at −10 °C with NBS in THF–H_2O (50:1) proceeded with 9:1 stereoselectivity and gave bromohydrin **19** in 50% yield after purification. Treatment of **19** with NaOH provided epoxide **15** in 75% yield. Although this sequence did achieve a stereoselective synthesis of the desired epoxide intermediate, the overall yield from L-proline was no better than for the preparation of **12**.

Incorporation of a Model Side Chain and Proof of the Stereostructures of Epoxides 11 and 12. Although we were unable to determine the stereochemistry of epoxides **11** and **12** by spectroscopic means, characterization was possible after these hindered epoxides were opened to incorporate the elements of a pumiliotoxin A side chain. Our plan from the outset was to use alkyne hydroalumination with its attendant suprafacial stereochemistry to establish the desired *Z* relationship of silicon and what was destined to be the pumiliotoxin A side chain. Eisch had previously established that 1-(trimethylsilyl)-1-alkynes underwent hydroalumination regioselectively to give 1-(trimethylsilyl)-1-alkenylalanes.[20] Although the reaction of alkenylalanes with epoxides was known to be quite inefficient, simple epoxides had been shown to react in good yields with vinyl alanates.[21]

Introduction of the side chain was first explored in a model series that lacked the allylic methyl group at C-11.[18] Epoxide **12** reacted sluggishly in refluxing ether with the silylvinyl alanate formed by sequential treatment of 1-(trimethylsilyl)-1-hexyne[22] with 1 equiv each of *i*-Bu_2AlH and MeLi (eq 2). After 48 h the bicyclic

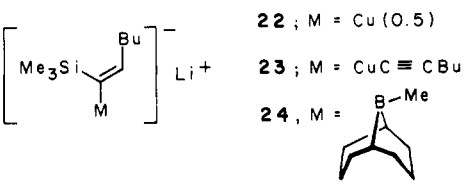


carbamate **20**, which resulted from epoxide opening at C-7 followed by intramolecular alkoxide acylation, was isolated in 33% yield after chromatographic purification. Similar treatment of epoxide **11** provided the diastereomeric bicyclic carbamate **21** in 40% yield.

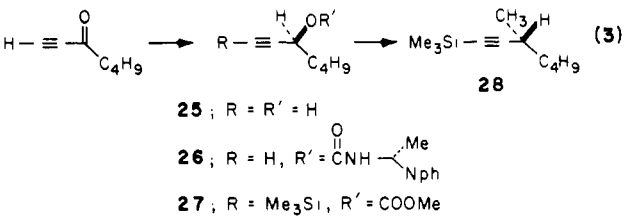
NMR spectra showed that both isomers had an identical (*Z*)-alkene side chain and differed only in the configuration at C-8.[18] The rigid bicyclo[3.3.0]octane ring system of carbamates **20** and **21** allowed structural assignments to be made on the basis of ^{13}C NMR spectra and the expectation[23] that groups of the more sterically congested α face would be shifted upfield. Thus, **20** showed absorptions for the methyl and methylene carbons attached to C-8 at 21.7 and 49.4 ppm, respectively, while these signals were observed at 26.4 and 43.8 ppm for isomer **21**.

Although the yields obtained in the epoxide coupling reaction were initially modest, this one-pot reaction was deemed not without promise since it both introduces the elements of the pumiliotoxin A side chain and establishes the desired *Z* stereochemistry. It should be noted that no epoxides of the complexity of **11** and **12** had previously been successfully coupled with an alkenyl organometallic and that further studies (vide infra) have allowed this key step to be optimized to a significant extent.

Without success, we briefly examined the reaction of epoxide **12** with other alkenyl organometallics prepared from 1-(trimethylsilyl)-1-hexyne. Neither the alkenyl cuprates **22** or **23** nor the alkenyl boronate **24** proved effective.[24]



Enantioselective Synthesis of Pumiliotoxin 251D. The (*R*)-silylalkyne **28**, which would be required for the synthesis of pumiliotoxin 251D (**3**), was prepared as outlined in eq 3. Reduction of 1-heptyn-3-one[25] with *B*-(3-pinanyl)-9-borabicyclo-[3.3.1]nonane (prepared from 92% enantiomerically pure (−)-α-pinine) according to Midland[26] gave (*S*)-1-heptyn-3-ol, $[\alpha]^{25}_D$ −15.0.[27] This material was shown to have an enantiomeric excess (ee) of 82 ± 3% by 250-MHz ^1H NMR analysis of the (*R*)-α-methoxy-α-((trifluoromethyl)phenyl)acetyl ester [(*R*)-MTPA ester].[28] Alternatively, **25** was obtained in >98% enantiomeric purity ($[\alpha]^{25}_D$ −18.8) by chromatographic resolution[29] of the diastereomeric carbamates prepared from racemic 1-heptyn-3-ol and (*R*)-(+)-α-(1-naphthyl)ethylamine.



Carbon silylation of **25** followed by acylation with methyl chloroformate provided **27** in 70% yield. Reaction of **27** with 2 equiv of the mixed cuprate prepared from MeMgBr and CuI using the general procedure of Macdonald and Brinkmeyer[30] gave the (*R*)-silylalkyne **28** ($[\alpha]^{25}_D$ −35.5) in ~50% overall yield from enantiomerically pure **25**. We anticipated[31] that propargylic coupling would occur with inversion of configuration, and our subsequent use of **28** for the synthesis of pumiliotoxin 251D rigorously establishes this stereochemical outcome.[32]

(18) The numbering system used for **1** will be utilized in the discussion of all synthetic intermediates. The proper IUPAC numbering of this intermediate can be found in the Experimental Section of this paper.

(19) To date the only successful conversions accomplished with **16** or **17** have been free radial chain dehalogenations (Bu_3SnD), which were utilized[16] to establish the stereostructure of these intermediates.

(20) Eisch, J. J.; Foxton, M. W. *J. Org. Chem.* **1971**, *36*, 3520. Eisch, J. J.; Damasevitz, G. A. *Ibid.* **1976**, *41*, 2214.

(21) Cf.: Warel, S.; Schmit, G.; Ahlfaenger, B. *Synthesis* **1975**, 632. Negishi, E.; Baba, S.; King, A. O. *J. Chem. Soc., Chem. Commun.* **1976**, 17. Malpass, D. B.; Watson, S. C.; Yeargin, G. S. *J. Org. Chem.* **1977**, *42*, 2712.

(22) Zweifel, G.; Lewis, W. *J. Org. Chem.* **1978**, *43*, 2739.

(23) Cf.: Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972; pp 112–118.

(24) Details can be found in: Bell, K. Ph.D. Thesis, University of California, Irvine, 1981.

(25) Joss, U.; Schallegger, H. *Helv. Chim. Acta* **1969**, *52*, 2465.

(26) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.

(27) A calculated maximum rotation $[\alpha]^{25}_D$ +20.5 (*c* 3.0, dioxane) has been reported for the *R* enantiomer: Vigneron, J.-P.; Bloy, V. *Tetrahedron Lett.* **1979**, 2683. Our calculated maximum rotation for the *S* enantiomer is $[\alpha]^{25}_D$ −19.0 (dioxane).

(28) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

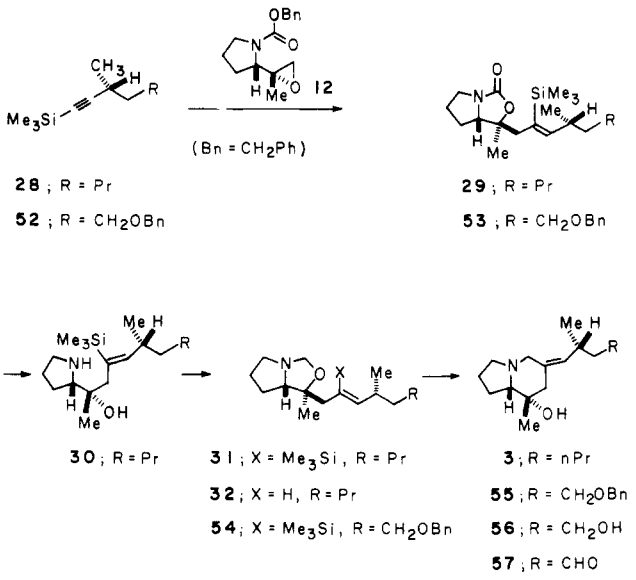
(29) (a) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 1839. (b) Rinaldi, P. L.; Levy, G. C. *Ibid.* **1980**, *45*, 4349. (c) Pirkle, W. H.; Hauske, J. R. *Ibid.* **1977**, *42*, 2781.

(30) Macdonald, T. L.; Reagan, D. R.; Brinkmeyer, R. S. *J. Org. Chem.* **1980**, *45*, 4740.

(31) See: Whitesides, G. M.; Fischer, W. F.; San Filippo, J.; Basche, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871. Johnson, C. R.; Dutra, G. A. *Ibid.* **1973**, *95*, 7783. Fouquet, G.; Schlosser, M. *Agnew Chem., Int. Ed. Engl.* **1974**, *13*, 82.

(32) Inversion of configuration in this reaction has been independently demonstrated: Macdonald, T. L.; Brinkmeyer, R. S., personal communication from T.L.M.

Scheme I



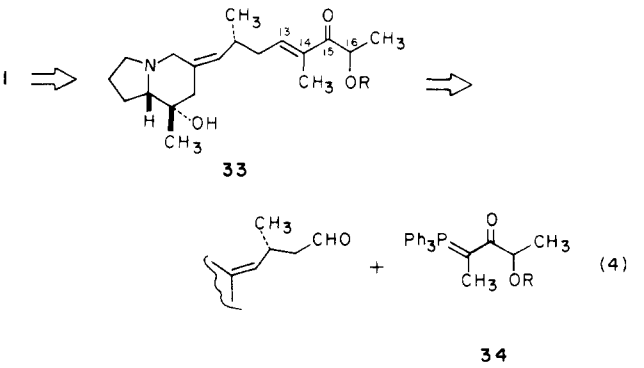
Conversion of **28** to the vinyl alanate followed by reaction of this intermediate with epoxide **12** provided bicyclic carbamate **29** in 38% yield (see Scheme I). The C-11 diastereomer of **29** was not detectable (<1%) by GLC analysis of the crude reaction product. The reaction of **12** with racemic samples of alkyne **28** gave a 1:1 mixture of **29** and its C-11 epimer.[24] These results establish that the optically active sample of alkyne **28** was essentially enantiomerically pure and, thus, that the cuprate displacement reaction occurred with complete inversion of configuration. This preparation of **29** was completed prior to our successful optimization of the alanate coupling reaction. The yield for this step could likely be substantially increased by use of the coupling procedure employed in our later synthesis (vide infra) of pumiliotoxin B.

Hydrolysis of **29** was accomplished in refluxing 3 M ethanolic KOH to give amino alcohol **30** as a colorless liquid in 80% yield.[33] The stability of the vinylsilane group to this quite drastic basic condition is noteworthy. This polar amino alcohol was difficult to purify[33] and was best directly converted to **31** by reaction with paraformaldehyde. Cyclopentaoxazolidine **31** showed a diagnostic AB quartet (J = 6.2 Hz) for the NCH_2O group at δ 4.43 in the ^1H NMR spectrum. Heating this intermediate in refluxing ethanol in the presence of 1 equiv of camphorsulfonic acid cleanly yielded pumiliotoxin 251D (**3**). Chromatographic purification followed by crystallization of the hydrochloride salt from hexane–ethyl acetate afforded pure (+)-pumiliotoxin 251D hydrochloride in 60% yield from **30**. This synthetic sample [mp 206–206.5 °C, $[\alpha]^{25}_D$ +28.0 (c 0.62, MeOH)] was >99.9% pure by capillary GC analysis. The ^1H NMR (250 MHz) and ^{13}C NMR spectra of synthetic (+)-251D hydrochloride in CD_3OD (and the free base in $CDCl_3$) as well as the EI mass spectra were identical with those of the natural material,[3,34] and synthetic (+)-251D hydrochloride was indistinguishable by capillary GLC and TLC (in three solvent systems) analysis from an authentic sample of 251D hydrochloride furnished by Dr. John Daly. Natural pumiliotoxin 251D has not been isolated in large enough quantities to accurately determine its melting point or optical rotation.[3,34] An optical rotation measurement made on a very small sample showed that the natural hydrochloride was dextrorotatory: $[\alpha]^{25}_D$ +17 (c 0.15, MeOH).[34]

A few additional comments concerning the key cyclization reaction are appropriate. If the cyclization step was conducted directly with amino alcohol **30** by treatment with paraformaldehyde (1–3 equiv) and acid (1 equiv) the protodesilylated cyclopentaoxazolidine **32** was formed in variable amounts (up to 90%). This material showed a diagnostic AB quartet at δ 4.42 (J = 6.4 Hz) and two vinylic hydrogens as a multiplet at δ 5.33 in the ^1H NMR spectrum, as well as a molecular ion at m/z 252 in the chemical ionization mass spectrum. Since simple trisubstituted vinylsilanes are stable to protodesilylation in the presence of amine salts,[35] the apparently facile protodesilylation of the conjugate acid of **30** must result from some form of intramolecular participation by the ammonium group. This side reaction was effectively eliminated by converting **30** to the oxozolidine **31** under neutral conditions. Cyclization with 1 equiv of acid was then extremely clean and produced <2% of **32** as a side product. The extent of control of the exocyclic alkene geometry by the Me_3Si group in the cyclization reaction was extremely high, since GC-MS analysis[36] of the crude cyclization product failed to detect any isomers of **3**.

The total synthesis of enantiomerically pure (+)-pumiliotoxin 251D hydrochloride was accomplished by a convergent sequence in nine steps. The overall yield was 6.3% from (*S*)-1-heptyn-3-ol and 3.6% from *N*-[(benzyloxy)carbonyl]-L-proline.

Enantioselective Synthesis of Pumiliotoxin B. Since the stereochemistry of the side chain allylic diol of pumiliotoxin B (**1**) had not been established at the time our synthetic efforts began, we chose the strategy for side-chain elaboration that is illustrated in eq 4. A Wittig reaction with a stabilized ylide[37] should provide



the desired E configuration of the 13,14 double bond, and our hope was that we could then reduce the α'-alkoxy enone functionality of **33** to introduce either the threo or erythro allylic diol grouping. Ylide **34** should be available in either absolute configuration from D- or L-lactic acid.

In our initial model work in this area,[4b] we showed that simple α'-alkoxy enones related to **33** could indeed be reduced with excellent stereoselectivity (17:1 or greater) to give either the threo or erythro allylic diol by utilizing the proper combination of reducing agent and alcohol protecting group. When it became established[4] that pumiliotoxin B had the 15*R*, 16*R* side-chain configuration, the *R* ylide **39** was required. This intermediate was readily prepared, in enantiomerically pure form, from ethyl L-lactate (**35**) as summarized in eq 5.

Mitsunobu[38] inversion of ethyl L-lactate[39,40] at −20 °C in THF cleanly (91% yield) gave the (*R*)-*p*-nitrobenzoyl ester **36**, $[\alpha]^{25}_D$ −13.1 (c 1.17, EtOH). Deacylation of **36** with K_2CO_3 in anhydrous ethanol and protection[41] of the resulting alcohol as the

(33) Purification of this sample on acid washed alumina (Merck, $CHCl_3$ then MeOH) gave a crystalline material (mp 165 °C) which was erroneously characterized in our preliminary communication as amino alcohol **30**. This material is apparently a CO_2 adduct and analyzes correctly for a carbonic acid salt. Partitioning of this solid material between aqueous NaOH and $CHCl_3$ provided **30** as a clear oil. Full characterization data for this solid material is provided in the supplementary material.

(34) Tokuyama, T.; Daly, J. W.; Highet, R. J. *Tetrahedron* **1984**, *40*, 1183.

(35) Unpublished results of Mr. H. Ellison of this laboratory.

(36) A 10-ft column packed with 10% SP-2100 on 100/120 suppelcoport was used.

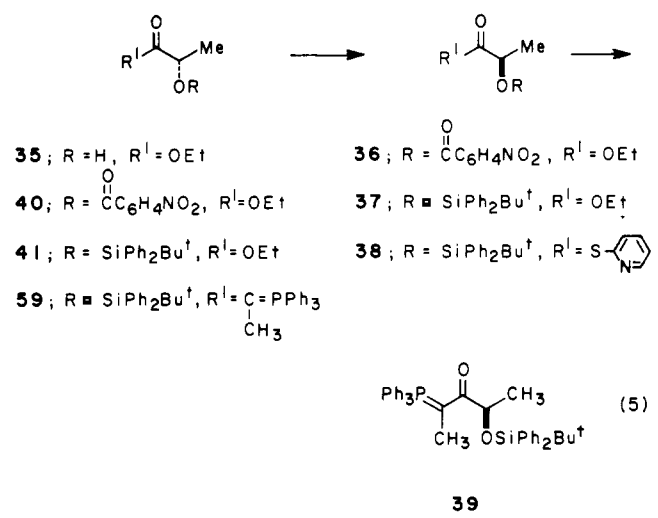
(37) Cf.: House, H. O.; Rasmusson, G. M. *J. Org. Chem.* **1961**, *26*, 4278.

(38) (a) Mitsunobu, I. *Synthesis* **1981**, 1. (b) Kurihara, T. M.Sc. Thesis, Aoyama Gakuin University, 1971.

(39) Purchased from Aldrich Chemical Co., labeled $[\alpha]^{25}_D$ −12 (neat). Rotations of this material are unreliable due to the presence of impurities with high rotation.[40] Commercial samples of ethyl L-lactate are probably ~97% enantiomerically pure.[40] The rotation of pure **37** was identical when prepared from ethyl lactate [measured rotation $[\alpha]^{25}_D$ −10.7 (neat)] obtained from Pettibone World Trade.

(40) Cf.: (a) Johnston, B. D.; Slessor, K. N. *Can. J. Chem.* **1979**, *57*, 233. (b) Hintzer, K.; Koppenhoefer, B.; Schurig, V. *J. Org. Chem.* **1982**, *47*, 3850.

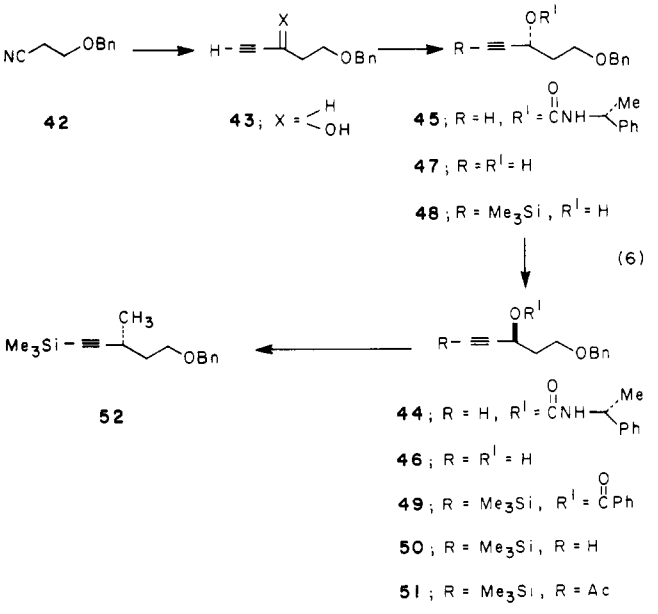
(41) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1977**, *55*, 562.



tert-butyldiphenylsilyl ether provided **37**, $[\alpha]^{25}_D$ + 46.0 (*c* 1.97, EtOH), in 53% yield. There is apparently no loss of enantiomeric purity during this sequence since the *S* enantiomers **40** and **41** prepared directly from ethyl L-lactate showed the following rotations: $[\alpha]^{25}_D$ +12.5 (*c* 2.02, EtOH) and $[\alpha]^{25}_D$ −44.2 (*c* 4.69, EtOH). Conversion of **37** to the desired ylide was accomplished via the 2-pyridinethiol ester[4b] **38** and delivered ylide **39** as an amorphous solid (37% yield from **37**) after chromatographic purification.

On the supposition that pumiliotoxin B would have the same absolute configuration at carbons 8, 8a, and 11 as pumiliotoxin 251D, we assembled indolizidine aldehyde **57** (see Scheme I) from L-proline along the lines of our previous synthesis of pumiliotoxin 251D.

After considering several possibilities for preparing the required (*R*)-silylalkyne **52** from members of the natural "chiral pool",[42] we decided to assemble this intermediate from esters of (*S*)-5-(benzyloxy)-1-(trimethylsilyl)-1-pentyn-3-ol (**50**) using the propargylic inversion procedure we had previously employed to secure the alkyne precursor of the pumiliotoxin 251D side chain, see eq 6. Reduction of the readily available nitrile **42** with *i*-Bu_2AlH



provided 3-(benzyloxy)propanal,[43] which was immediately condensed with ethynyllithium[44] to give the racemic propargylic alcohol **43** in 57% yield after distillation. Chromatographic resolution[29] of the diastereomeric carbamates (**44** and **45**) prepared from **43** and (*R*)-(+)-α-methylbenzylamine followed by carbamate cleavage with Cl_3SiH[29c] gave the *S* alcohol **46** ($[\alpha]^{25}_D$ −23.5) and the *R* alcohol **47** ($[\alpha]^{25}_D$ + 24.3) in yields of 25% and 22% from **43**, respectively. Since carbamate intermediate **45** was 94% isomerically pure and the Pirkle carbamate cleavage procedure is established[29c] to proceed without racemization of the alcohol product, **47** is assigned an enantiomeric purity of 94%. The *S* alcohol **46** was 92 ± 2% enantiomerically pure by 250-MHz ^1H NMR analysis of the corresponding (*R*)-MTPA ester.[28] The absolute configuration assignments for **46** and **47** followed from (a) the elution order of **44** and **45** and the Pirkle-model[29] for chromatographic separations of this type and (b) the direct preparation of **46** from 5-(benzyloxy)-1-pentyn-3-one (**53**) by reduction[26,45] with *B*-(3-pinanyl)-9-borabicyclo[3.3.1]nonane[26] prepared from (−)-α-pinine. Unfortunately, in spite of considerable investigation, enantioselective reduction of 5-(benzyloxy)-1-pentyn-3-one with the Midland reagent[26] was never clean and provided **46** (80% ee) in yields of only ~30%.

Carbon silylation of the resolved *S* alcohol **46** gave **50**, which was acetylated to provide the *S* acetate **51** in 55% yield. The related *S* benzoate **49** was prepared in 75% overall yield from the *R* alcohol **47** by carbon silylation followed by Mitsunobu[38] inversion with benzoic acid. The reaction[30] of either **49** or **51** with $Me_2CuMgBr$ in THF at 23 °C gave **52** in yields of 44–51% after chromatographic purification. Silylalkyne **52** showed a rotation at the sodium D line of −64.0 (*c* 2.26, $CHCl_3$) when prepared from *S* alcohol **46** and −64.4 (*c* 1.42, $CHCl_3$) when produced from the *R* enantiomer **47**. On the basis of our previous demonstration that this cuprate coupling reaction occurs with complete inversion of configuration, alkyne **52** was assigned the *R* configuration and an enantiomeric purity of ~93%. This enantioconvergent sequence proceeded with acceptable efficiency and provided the (*R*)-silylalkyne **52** on gram scales and 14% overall yield from racemic alcohol **43**.

Considerable effort was expended in optimizing the reaction of epoxide **12** with the vinylalanate reagent formed from alkyne **52** (Scheme I). Although **52** was not cleanly hydroaluminated with 1 equiv of *i*-Bu_2AlH in ether, this reaction was successfully accomplished using hexane as the solvent. Protonolysis of the vinylalane intermediate produced in this way cleanly (^1H NMR analysis) gave the (*Z*)-alkene reduction product of **52**, confirming that hydroalumination of **52** was also suprafacial[20] in this noncoordinating solvent. Previous experience[8,46] had shown that vinyl alanate coupling reactions of epoxide **12** were faster in refluxing THF than in ether, and that the major competing reaction pathway was deacylation of **12**. The key observation was that **12** was rapidly destroyed by excess MeLi in refluxing THF, presumably due to cleavage[47] of the carbamate group. Thus, product yields were dramatically improved if the alanate reagent was prepared using a deficiency of MeLi. The optimum procedure was to treat silylalkyne **52** sequentially at room temperature with *i*-Bu_2AlH (1 equiv) and MeLi (0.85 equiv) followed by reaction of this reagent with epoxide **12** (0.44 equiv) at 60 °C. These conditions routinely afforded **53** in 70–77% yield from **12**. Bicyclic carbamate **53** showed a diagnostic IR absorption at 1760 cm^{-1} for the carbonyl of the five-membered ring carbamate group.[48] Importantly, the 250-MHz ^1H NMR spectrum of the crude reaction product showed <7% of the C-11 epimer of **53**. The product of coupling reactions of **12** and racemic samples of silylalkyne **52** showed two

(42) For example, two conceivable precursors would be (*R*)-3-methyl-4-pentenoic acid (which is available from (−)-citronellene: Ireland, R. E.; McGarvey, G. I.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B.; Taisrivongs, S. *J. Am. Chem. Soc.* **1980**, *102*, 6178) or (*S*)-3-hydroxy-4-pentynal (which is available from (*S*)-malic acid or D-ribonolactone: Barton, D. H. R.; Bĕnĕchie, M.; Khuong-Huu, F. *Tetrahedron Lett.* **1982**, 651).

(43) Cf.: Gaiffe, A.; Launay, C. R. *Acad. Sci., Ser. C* **1968**, 1379–1380. Diisobutylaluminum hydride is a more convenient reducing agent than Raney Ni and provides 3-(benzyloxy)propanal of useful purity in 88% crude yield from 3-(benzyloxy)propanitrile.

(44) Midland, M. M. *J. Org. Chem.* **1975**, *40*, 2250.

(45) Results of Dr. D. Lesuisse of this laboratory.

(46) Studies of H. Ellison of this laboratory.

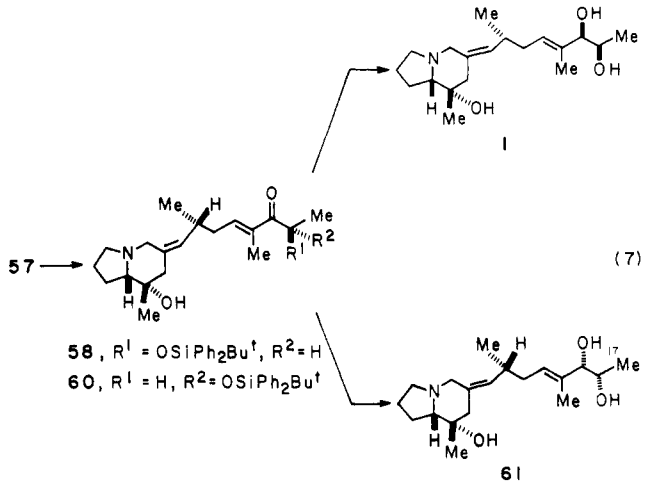
(47) Cf.: Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629. Buckley, T. F., III; Rapoport, H. *Ibid.* **1981**, *103*, 6157.

(48) Nakanishi, K.; Solomon, P. H. "Infrared Absorption Spectroscopy", 2nd ed.; Holden Day: San Francisco, 1977.

diagnostic doublets of equal intensity for the C-11 Me groups of the two diastereomeric products: δ 0.99 (**53**), 0.97 (C-11 epimer of **53**). We also briefly examined the reaction of the vinyl alanate produced from **52** with the epoxide carbamates **13** and **14**, which have *tert*-butoxycarbonyl and isopropoxycarbonyl nitrogen protecting groups. These intermediates offered no advantage over **12**.

Base hydrolysis of **53** at 90 °C followed by reaction of the crude amino alcohol at room temperature with aqueous formalin provided cyclopentaoxazolidine **54**, which was cleanly cyclized to the desired (*Z*)-alkylideneindolizidine **55** when treated with 1 equiv of camphorsulfonic acid in refluxing acetonitrile. Chromatographic purification routinely provided **55** in yields of 50–65%. As in the cyclization reaction to produce pumiliotoxin 251D, no chromatography fraction corresponding to the (*E*)-alkylidene isomer of **55** was detected. Conventional debenzylation (Li/NH_3) provided **56**, $[\alpha]^{25}_D$ −22.1. Separation of small amounts of the C-11 epimer of **56** was easily accomplished by chromatography on silica gel. Oxidation of **56** with the Swern reagent[49] afforded the important indolizidine aldehyde intermediate **57** in 53% overall yield from **55**.

Wittig reaction of aldehyde **57** with ylide **39** was readily accomplished in refluxing CH_2Cl_2, without complications from ylide racemization, to provide a single enone **58** in 71% yield, see eq 7. No trace of the (*Z*)-enone isomer of **58** could be seen in the



250-MHz ^1H NMR spectrum of the crude reaction product, although ~0.5% of what is believed to be the *Z* isomer was isolated from one large-scale enone preparation.

Threo selective reduction[4b] of **58** with excess $LiAlH_4$ (−20 °C → room temperature, THF) was accompanied by desilylation[50] to give pumiliotoxin B directly. Purification by radial chromatography on silica gel provided **1**, as a 15:1 mixture of threo and erythro isomers, in 74% yield. Although we have not yet successfully resolved these isomers by capillary GC[51] or high-performance LC, their ratio was easily determined by ^1H NMR analysis of the cyclic boronide esters[4a] formed from the addition of excess (*p*-bromophenyl)boronic acid: **1** δ 4.37 (C-15 H), 4.29 (C-16 H); C-15 epimer of **1** δ 4.89 (C-15 H), 4.79 (C-16 H). A center fraction from a second chromatographic purification was 95% isomerically pure and showed optical properties, $[\alpha]^{25}_D$ +19.3 (*c* 1.00, MeOH),[52] essentially identical with those of natural pumiliotoxin B [$[\alpha]^{25}_D$ +20.5 (*c* 1.00, MeOH);[34] $[\alpha]^{25}_D$ +19.8 (*c* 2.28, MeOH), our determination]. Synthetic **1** was also indistinguishable from a natural sample of pumiliotoxin B provided by Dr. John Daly by ^1H NMR (250 and 500 MHz in $CDCl_3$ and C_6D_6), ^{13}C NMR, TLC, mass spectral, and capillary GC comparisons.[53] Most significantly, synthetic pumiliotoxin B showed cardiotonic effects on isolated guinea pig atria preparations[7] comparable to those of the natural toxin.[54]

Although the comparisons just enumerated left little doubt about the identity of our synthetic material, we thought it nonetheless important to verify that a diastereomer, which differed from **1** in absolute configuration at carbons 8, 8a, and 11,[5] would indeed be distinguishable. Although such a sample was not easily accessible, its enantiomer **61** was readily prepared from enone **60**. This enone was assembled from aldehyde **57** and the *S* ylide **59** (see eq 5), which was prepared directly from ethyl L-lactate. Indolizidine triol **61**, $[\alpha]^{25}_D$ +15.7 (*c* 1.4, MeOH), showed a characteristic doublet ^1H NMR absorption (250 MHz, $CDCl_3$) at δ 1.08 (J = 6.1 Hz) for the C-17 methyl group, which was clearly distinguishable from the corresponding signal (δ 1.11, J = 6.0 Hz) of pumiliotoxin B. Since the C-11 epimer of **1** was also clearly distinguishable from **1** by ^1H NMR analysis (see Experimental Section), these results unambiguously establish the complete stereochemistry of pumiliotoxin B to be as shown in structure **1**.

The total synthesis of (+)-pumiliotoxin B was accomplished in a convergent fashion from *N*-[(benzyloxy)carbonyl]-L-proline, ethyl L-lactate, and *dl*-5-(benzyloxy)-1-pentyn-3-ol (**43**). The longest linear sequence was 13 steps, and the overall yield was 1.8% from *N*-[(benzyloxy)carbonyl]-L-proline and 1.3% from alcohol **43**.

Conclusion

Pumiliotoxin 251D (**3**) and pumiliotoxin B (**1**) have been prepared for the first time. Significantly, the synthesis of pumiliotoxin B unambiguously establishes the complete stereostructure of this potentially important cardiac agent. The convergent sequence outlined in eq 1 has been demonstrated to be a *practical* route for the chemical synthesis of enantiomerically pure pumiliotoxin A alkaloids. The preparation of pumiliotoxin B in gram quantities by this route seems clearly feasible, since we have already prepared ~200 mg of **1** in this fashion. Perhaps more significantly, this convergent synthetic approach should allow a variety of pumiliotoxin B analogues of general structure **4** to be readily assembled. Several simple analogues have already been prepared in our laboratory and demonstrated to be biologically active.[8]

The efficiency of this approach to the pumiliotoxin A alkaloids stems in large part from the use of an iminium ion–vinylsilane cyclization to both form the indolizidine ring and control the stereochemistry of the alkylidene side chain. This tactic is an example of a potentially more general stereocontrolled method for preparing exocyclic alkenes in which stereochemistry is established in an acyclic precursor and then transferred to the desired cyclic product via a stereospecific cyclization reaction.[11]

Experimental Section[55]

Benzyl (*S*)-2-(1-Methylethenyl)-1-pyrrolidinecarboxylate (10). A solution of MeMgI was prepared from Mg (18.5 g, 0.76 mol), MeI (108

(49) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(50) Preliminary experiments indicate that this fortuitous deprotection is caused by AlH_3.

(51) (a) A 15-m SE-30 silica capillary column (4000 plates/m) was used for this analysis. (b) The erythro isomer of **1** was also not resolved on a OV-17 capillary column.

(52) This rotation is likely little effected by the presence of the small amount of the erythro isomer, since the erythro analogue of **1** which has the 15*R*,16*S* configuration showed $[\alpha]^{25}_D$ +19.0 (*c* 1.00, MeOH).

(53) Considering the many sites for intermolecular association, it is not surprising that the ^1H NMR spectra of pumiliotoxin B is markedly solvent dependent. Thus comparisons of samples from different sources must be made at identical concentrations or with mixtures from the two sources. The one exception we have found is MeOH, in which the ^1H NMR spectrum of **1** is nearly concentration independent.

(54) These biological comparisons[7] were kindly made by Dr. J. Daly.

(55) General experimental details were described recently: Overman, L. E., Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373. In cases where synthetic intermediates or products were isolated by "isolation (organic solvent, drying agent)" the procedure was to extract the quenched reaction several times with the indicated organic solvent, wash the organic layer with saturated $NaHCO_3$(aq), dry the combined organic layers with the indicated drying agent, and remove the solvent with a rotary evaporator at reduced pressure. Thionyl chloride was purified by successive distillations from quinoline and triisopropylphosphite. Unless indicated otherwise, all chromatographies were done with E. Merck silica gel (40–63 μm). Radial chromatography was done with a Harrison Research Chromatotron. All reactions were conducted under an argon atmosphere. Reactions were degassed to remove dissolved O_2 by successive evacuation at 23 °C and refilling with Ar. Room temperature is reported as 23 °C.

g, 0.76 mol), and dry ether (400 mL). A solution of methyl carbobenzoxy-L-prolinate[14] [92.5 g, 0.352 mol, $[\alpha]^{25}_D$ −57.5° (c 5.03, MeOH), prepared in quantitative yield from commerically available carbobenzoxy-L-proline by Fisher esterification] and dry ether (400 mL) was added at such a rate that the stirred solution refluxed gently. After the addition was complete, the reaction was heated at reflux for 1 h, cooled to 0 °C, and quenched by dropwise addition of saturated NH_4Cl (300 mL, buffered to pH 8 with NH_4OH). Isolation (ether, Na_2SO_4) gave 80 g (86%) of **9**,[56] which was >90% pure by ^1H NMR analysis and suitable for the dehydration step.

A rapidly stirring solution of **9** (15.8 g, 60.0 mmol) and dry THF (600 mL) was cooled to −45 to −50 °C (internal temperature). Cold $SOCl_2$ (6.6 mL, 90 mmol) was added dropwise from a dry ice-cooled addition funnel, followed by a cold solution of Et_3N (170 mL, 1.2 mol). Care was taken during both additions to keep the reaction temperature between −45 and −50 °C. The reaction mixture was maintained at −45 to −50 °C for 0.5 h and then allowed to warm to room temperature. The reaction was quenched onto ice (~100 g), and the crude product was isolated (ether, Na_2SO_4). Purification on silica gel (4:1 hexane–ethyl acetate) gave 9.3 g (54% overall from methyl carbobenzoxy-L-prolinate) of pure **10** as a colorless liquid: >99% pure by GLC analysis;[51a] $[\alpha]^{25}_D$ −27.9 (c 6.05, MeOH); IR (film) 1700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$)[57] δ 7.2–7.4 (m, Ph), 5.13 (br s, CH_2Ph), 4.7–4.85 (m, $=CH_2$), 4.2–4.35 (m, CHN), 3.4–3.6 (m, CH_2N), 1.5–2.1 (m), 1.72 and 1.68 (s, CH_3); ^{13}C NMR (23 MHz, $CDCl_3$) δ 154.4, 145.1, ($C=CH_2$), 137.0, 128.0 (2 C), 127.4 (3 C), 109.2 ($C=CH_2$), 66.3, 62.2, 46.7, 30.7, 23.0, 18.9; MS (isobutane CI), m/z 246 (MH), 202, 138, 114, 91; MS (EI), m/z 245.1411 (245.1416 calcd for $C_{15}H_{19}NO_2$).

Dehydration reactions run more concentrated (~0.3 M) on an 80-g scale routinely gave **10** in 40–50% overall yield from methyl carbobenzoxy-L-prolinate.

Benzyl (S)-2-(2(R)-Methyloxiranyl)-1-pyrrolidinecarboxylate (12) and Diastereomeric Epoxide (11). A solution of **10** (30.6 g, 0.125 mol) and CH_2Cl_2 (85 mL) was cooled to 0 °C and solid *m*-chloroperbenzoic acid (85%, 37.8 g, 0.186 mol) was added over 10 min to this rapidly stirring solution. The reaction was maintained at 25 °C for 3 h and then diluted with CH_2Cl_2 (100 mL). This solution was washed successively with 25 mL of 10% Na_2SO_3, 5% $NaHCO_3$, and brine. After drying (Na_2SO_4), the organic phase was concentrated to give 32.0 g of a 1:1 mixture[47a] of epoxides **11** and **12**. Purification using a Waters Prep LC-500 chromatograph (two silica prepPAK columns, 93:2:5 hexane–ethyl acetate–triethylamine) gave 12.0 g of epoxide **12** (37%) and 14.5 g of the slower eluting epoxide **11** (44%) as colorless liquids after bulb-to-bulb distillation (oven temp = 120–130 °C, 0.15 mm). **12**: a colorless liquid, HPLC[58] (k′ = 5.9, 3:1 hexane–ethyl acetate); $[\alpha]^{25}_D$ −72.6 (c 2.84, MeOH); IR (film) 1705, 1410, 1100 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$)[57] δ 7.3–7.4 (m, Ph), 5.11 (br s, CH_2Ph), 3.8–4.2 (m, CHN), 3.3–3.5 (m, CH_2N), 2.35–2.7 (m, CH_2O), 1.5–2.2 (m), 1.34 and 1.27 (br s, Me); ^{13}C NMR (23 MHz, $CDCl_3$) δ 155.2, 137.0, 128.3 (2 C), 127.75 (2 C), 66.8, 59.4, 58.8, 52.2, 47.1, 28.0, 24.0, 19.5; MS (isobutane CI), m/z 262 (MH), 218, 204, 160, 154, 114, 91; MS (EI), m/z 261.1385 (261.1364 calcd for $C_{15}H_{19}NO_3$). **11**: a colorless liquid HPLC[58] (k′ = 7.1, 3:1 hexane–ethyl acetate); $[\alpha]^{25}_D$ −8.0 (c 5.9, MeOH); IR (film) 1705, 1410, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$)[57] 7.2–7.4 (m, Ph), 5.0–5.2 (m, CH_2Ph), 3.35–3.7 (m, CHN and CH_2N), 2.4–2.95 (m, OCH_2), 1.8–2.15 (m), 1.25 and 1.18 (br s, Me); ^{13}C NMR (23 MHz, $CDCl_3$) 155.2, 136.8, 128.4 (2 C), 128.0 (3 C), 66.9, 61.8, 57.4, 56.0, 47.6, 28.1, 23.9, 16.5; MS (isobutane CI), m/z 262 (MH), 204, 172, 160, 154, 114, 91.

(1S,7aS)-Tetrahydro-1-methyl-1-[2-(trimethylsilyl)-2(Z)-heptenyl]-1H,3H-pyrrolo[1,2-c]oxazol-3-one (20). The vinylalanate reagent was generated by using a modification of procedures reported by Eisch.[20] Neat *i*-Bu_2AlH (5.4 mL, 30 mmol) was added dropwise at 23 °C to a solution of 1-(trimethylsilyl)-1-hexyne (4.96 g, 32.2 mmol)[22] and dry ether (80 mL). The resulting solution was heated at reflux for 1 h and cooled to room temperature, and MeLi (28.0 mL of a 1.15 M solution in ether) was added dropwise. After 0.5 h, a solution of epoxide **12** (3.85 g, 14.8 mmol) and dry ether (120 mL), was added and the resulting solution was heated at reflux for 2 days. After cooling to room temperature, the reaction mixture was diluted with ether (300 mL) and extracted with 5% sodium/potassium tartarate solution (100 mL). The organic layer was washed with H_2O (100 mL) and brine (100 mL) and dried (Na_2SO_4). Chromatography on silica gel (85:15 hexane–ethyl acetate) gave 1.52 g (33%) of pure **20** as a colorless liquid: $[\alpha]^{25}_D$ −8.9 (c 0.18, $CHCl_3$), >99% pure by GLC analysis;[51a] IR (film) 1730–1770, 1250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.08 (t, J = 7.3 Hz, =CH), 3.5–3.7 (m, CHHN and CHN), 3.1–3.2 (m, CHHN), 2.68 (d, J = 13.8 Hz, CHHC=C), 2.26 (d, J = 13.8 HZ, CHHC=C), 2.1–1.7 (m), 1.25 (s, Me), 1.2–1.3 (m), 0.88 (t, J = 6.4 Hz, CH_2Me), 0.17 (s, Me_3Si); ^{13}C NMR (23 MHz, C_6D_6) δ 160.7 (s, C=O), 150.0 (d, C=CH), 134.4 (s, C=CH), 82.0 (s, C-1), 68.4, (d, CHN), 49.4 (t, CH_2O), 46.2 (t, NCH_2), 33.0 (t, $C=CCH_2CH_2$), 32.8 (t, $C=CH_2CH_2$, 27.2 (t, CH_2CH_2N), 26.1 (t, CH_2CHN), 23.1 (t, CH_2CH_3), 21.7 (q, $OCMe$), 14.6 (q, CH_2Me), 1.1 (q, Me_3Si); MS (isobutane, CI), m/z 310 (MH), 294, 186, 156, 139, 114.

(1R,7aS)-Tetrahydro-1-methyl-1-[2-(trimethylsilyl)-2(Z)-heptenyl]-1H,3H-pyrrolo[1,2-c]oxazol-3-one (21). The reaction of epoxide **11** with 1-(trimethylsilyl)-1-hexyne was conducted in an identical fashion to give **21** in 40% yield: IR (film) 1720–1760, 1245 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.05 (t, J = 8 Hz, CH=C), 3.4–3.7 (m, CHHN and CHN), 3.1–3.2 (m, CHHN), 2.67 (d, J = 14.0 Hz, CHHC=C), 2.09 (d, J = 14.2 Hz, CHHC=C), 2.0–2.2 (m), 1.2–1.9 (m), 1.39 (s, Me), 0.88 (app t, J = 6.4 Hz, CH_2Me), 0.17 (s, Me_3Si); ^{13}C NMR (23 MHz, C_6D_6) δ 161.0 (s, C=O), 149.3 (d, C=CH), 134.6 (s, C=CH), 81.2 (s, C-1) 70.5 (d, CHN), 46.2 (t, NCH_2), 43.8 (t, CH_2CO), 32.9 (t, $C=CCH_2CH_2$), 26.6 (t, CH_2CH_2N), 26.4 (q, $OCMe$), 25.8 (t, CH_2CHN), 23.2 (CH_2Me), 14.6 (CH_2Me), 1.10 (q, Me_3Si); MS (isobutane, CI), m/z 310 (MH), 186, 156, 139, 114.

(S)-1-Heptyn-3-ol (25). Using the general procedure developed by Pirkle,[29a] racemic 1-heptyn-3-ol (30.0 g, 0.268 mol) was converted to the chloroformate ester and reacted with (R)-(+)-α-(1-naphthyl)ethylamine [45.8 g, 0.268 mol, $[\alpha]^{25}_D$ +75.8 (neat)] to give 82 g of a mixture of diastereomeric carbamates.

A 13-g sample of this mixture was separated by silica gel chromatography (9:1 hexane–ethyl acetate, two silica prePAK columns, Waters LC-500 liquid chromatograph) to give 6.3 g of the S,R diastereomer **26** (HPLC[58] k′ = 3.6, purity = 98.5%, 9:1 hexane–ethyl acetate) and 6.0 g of the R,R diastereomer[56] (HPLC[58] k′ = 2.9, purity = 95.5%, 9:1 hexane–ethyl acetate). **26**: mp 107–110 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.2–7.4 (m, Ph), 5.2–5.3 (m, OCH), 4.95–5.05 (m, NH), 4.75–4.95 (m, CHN), 2.42 (d, J = 2.1 Hz, HC≡C), 1.7–1.9 (m), 1.49 (br d, J = 6.7 Hz, NCH*Me*), 1.2–1.5 (m), 0.8–0.9 (m). MS (EI), m/z 309 (2%), 214 (60%), 170 (51%), 156 (37%), 155 (100%), 129 (86%).

Carbamate **26** (6.3 g, 20 mmol) was cleaved to the alcohol with Cl_3SiH (3.4 g, 25 mmol) as described by Pirkle.[29c] Bulb-to-bulb distillation gave 1.53 g (68% from **26**) of (S)-1-heptyn-3-ol (**25**): 99% pure by GLC analysis,[51a] $[\alpha]^{25}_D$ −18.8 (c 5.2, dioxane).[27] 250-MHz ^1H NMR analysis of the (R)-MTPA ester[28] of **25** indicated an enantiomeric purity of >98%.

(S)-1-Heptyn-3-ol was also prepared by enantioselective reduction using the procedure of Midland.[26] Reaction of 1-heptyne-3-one[25] (8.20 g, 74.5 mmol) with the reagent prepared from (−)-α-pinene [25.3 g, 186 mmol, $[\alpha]^{25}_D$ −47.3 (neat), 92% ee][26] and 9-borabicyclo[3.3.1]nonane (327 mL of 0.5 M solution in THF) afforded, after purification on silica gel (9:1 hexane–ethyl acetate) and short-path distillation (bp 76 °C, 25 mm), 5.87 g (70%) of **25**: 99% pure by GLC analysis;[51a] $[\alpha]^{25}_D$ −15.0 (c 2.60, dioxane). The (R)-MTPA ester[28] of this sample showed cleanly separated signals for the C-1 hydrogens of the two diastereomers at δ 2.54 and 2.50 in the 250-MHz ^1H NMR spectrum.

(R)-3-Methyl-1-(trimethylsilyl)-1-heptyne (28). MeLi (380 mL of a 1.3 M solution in ether) was added dropwise to a cold solution of the S alcohol **25** (25.0 g, 223 mmol, $[\alpha]^{25}_D$ −15.0) and ether (200 mL) at a rate such that the reaction temperature did not rise above −50 °C. The resulting solution was allowed to warm to 23 °C and was then heated at reflux for 0.5 h. After cooling to −60 °C, Me_3SiCl (60.8 g, 0.56 mol) was added dropwise, and the resulting mixture was allowed to warm to 23 °C overnight. Filtration followed by concentration of the filtrate gave the crude disilylated product, which was O-desilylated by dissolving it in a mixture of 3 N HCl (200 mL) and THF (700 mL). After 3 h, isolation (ether, $MgSO_4$) and chromatography (4:1 hexane-ethyl acetate) gave 32.8 g (80%) of (S)-1-(trimethylsilyl)-1-heptyn-3-ol: IR (film) 3620, 3460, 2170 cm^{-1}.

A 1.86-g (10.1 mmol) sample of this alcohol was converted to the methyl carbonate derivative exactly as described by Macdonald[30] to give 2.13 g (87%) of the pure silyl carbonate **27**: 98% pure by GLC analysis;[51a] $[\alpha]^{25}_D$ −69.9 (c 3.35, $CHCl_3$); IR (film) 2175, 1705, 1260 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.23 (t, J = 6.4 Hz, OCH), 3.80 (s, Me), 1.6–1.8 (m), 1.3–1.5 (m), 0.91 (apparent t, J = 7.1 Hz, CH_2Me), 0.17 (s, Me_3Si); ^{13}C NMR (23 MHz, C_6D_6) δ 155.7, 103.6, 91.2, 68.8, 54.9, 35.4, 27.8, 22.9, 14.0, 0.25; MS (isobutane CI), m/z 242 (MH), 167, 149, 93, 89, 73. Preparation of **27** from enantiomerically pure alcohol **25** provided **27**: $[\alpha]^{25}_D$ −87.6 (c 5.3, $CHCl_3$).

Reaction of **27** (100 mg, 0.413 mmol, $[\alpha]^{25}_D$ −69.9) with the copper reagent prepared in THF (3 mL) from CuI (52.2 g, 0.826 mmol) and

(56) Spectral and analytical data for a pure sample of this compound may be found in the supplementary material.

(57) Many signals in the ^1H and ^{13}C NMR spectra of this sample are doubled due to carbamate conformational isomers.

(58) A Du Pont Zorbax PSM 60 column was used for this analysis.

MeMgBr (0.53 mL of a 3.1 M solution in ether) was accomplished using the procedure detailed by Macdonald.[30] TLC analysis showed that the reaction was complete after 1 h at 0 °C. Saturated NH_4Cl (5 mL) and hexane (10 mL) were added; the organic layer was separated and washed with NH_4Cl solution (5 mL) and dried (Na_2SO_4). Concentration and purification of the residue by chromatography (hexane) gave 60 mg (80%) of **28** as a colorless liquid: >97% pure by GLC analysis;[51a] $[\alpha]^{25}_D$ −27.7 (*c* 2.0, $CHCl_3$, ~80% ee); IR ($CHCl_3$) 2175, 1460, 1250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.3–2.5 (m, CHC≡C), 1.2–1.5 (m), 1.14 (d, *J* = 7.0 Hz, CH*Me*), 0.90 (apparent t, *J* = 7.1 Hz, CH_2*Me*); ^{13}C NMR (23 MHz, $CDCl_3$) 112.3, 83.9, 36.6, 29.5, 26.8, 22.5, 21.0, 14.0, 0.31; MS (isobutane CI), *m/z* 183 (MH), 167, 109, 99, 73; MS (EI), *m/z* 182.1479 (182.1491 calcd for $C_{11}H_{22}Si$).

Enantiomerically pure alkyne **28** [$[\alpha]^{25}_D$ −35.5 (*c* 5.0, $CHCl_3$), 98% pure by GLC analysis[51a]] was obtained similarly in ~70% yield from enantiomerically pure carbonate **27** ($[\alpha]^{25}_D$ −87.6).

(1*S*,7a*S*)-Tetrahydro-1-methyl-1-[2-(trimethylsilyl)-4(*R*)-methyl-2-(*Z*)-octenyl]-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (29). By the procedure described for the preparation of **20**, alkyne **28** (439 mg, 2.41 mmol, $[\alpha]^{25}_D$ −27.7) was combined with epoxide **12** (300 mg, 1.15 mmol, $[\alpha]^{25}_D$ −72.6) to give 147 mg (38%) of an 8.5:1 mixture (by GLC or ^{13}C NMR analysis) of **29** and its C-11 epimer. This mixture proved impossible to separate by chromatography. Use of enantiomerically pure **28** ($[\alpha]^{25}_D$ −33.5) in this sequence provided diastereomerically pure **29** in similar yield. Characterization data for **29**: $[\alpha]^{25}_D$ −45.6 (*c* 7.0, $CHCl_3$); IR (film) 1760, 1250, 1050 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.86 (d, *J* = 10 Hz, CH=C), 3.5–3.7 (m, C*H*HN and CHN), .3.1–3.2 (m, CH*H*N), 2.3–2.6 (m), 2.0–2.1 (m), 1.4–2.0 (m), 1.30 (s, C-1 Me), 1.1–1.4 (m), 0.96 (d, *J* = 6.2 Hz, CH*Me*), 0.88 (br t, *J* = 6.4 Hz, CH_2*Me*); ^{13}C NMR (23 MHz, $CDCl_3$) δ 160.5, 156.3, 131.0, 82.6, 67.1, 48.4, 45.3, 37.1, 36.7, 29.6, 26.8, 25.9, 23.1, 22.2, 20.8, 14.0, 0.85; MS (isobutane CI), *m/z* 338 (MH), 186, 139, 114; MS (EI), *m/z* 322.2207 (322.2157 calcd for $C_{18}H_{32}NO_2Si$, M − Me).

The C-11 epimer of **29** showed characteristic signals in the 250-MHz ^1H NMR spectrum at δ 5.84 (d, *J* = 10.7 Hz), 0.94 (d, *J* = 6.6 Hz).

Pumiliotoxin 251D (3). A carefully degassed solution of **29** (230 mg, 0.68 mmol, contaminated with ~4% of the C-11 diastereomer), KOH (770 mg, 14 mmol), ethanol (3.3 mL), and H_2O (0.9 mL) was heated at reflux for 24 h. The reaction mixture was then concentrated, the residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (5 mL), and the organic layer was separated and washed several times with H_2O. After drying (Na_2SO_4), concentration gave 176 mg (87%) of crude amino alcohol **30** as a colorless oil.[33] This polar material could not be purified without significant losses and was used directly in the cyclization step: MS(isobutane CI), *m/z* 312 (MH), 114, 73, 70; MS (EI), *m/z* 296.2408 (296.2428 calcd for $C_{17}H_{34}NOSi$, M − Me).

A mixture of a portion of this sample of **30** (58.5 mg, 0.188 mmol), paraformaldehyde (11.3 mg, 0.376 mmol), and absolute EtOH (0.6 mL) was sealed in a 5-mL ampule and heated at 80 °C for 2–4 h. After cooling to 23 °C unreacted paraformaldehyde was removed by filtration, and the filtrate was concentrated to give the crude oxazolidine **31**: ^1H NMR (250 MHz, $CDCl_3$) δ 5.78 (d, *J* = 10 Hz, C=CH), 4.43 (AB q, *J* = 6.25 Hz, Δν = 14.9 Hz, NCHHO), 3.3–3.4 (m, NCH), 3.1–3.2 (m, NC*H*H), 2.7–2.8 (m, NCH*H*), 2.34 (d, *J* = 13.6 Hz, C*H*HC=C), 2.09 (d, *J* = 13.6 Hz, CH*H*C=C), 2.2–2.4 (m), 1.7–2.0 (m), 1.2–1.4 (m), 1.10 (s, Me), 0.94 (d, *J* = 6.2 Hz, CH*Me*), 0.88 (t, *J* = 6.5 Hz, CH_2*Me*), 0.15 (s, Me_3Si); MS (isobutane CI), *m/z* 324 (MH), 126, 125, 114, 84, 83, 73, 70.

A solution of this oxazolidine sample, camphorsulfonic acid (21.8 mg, 0.087 mmol), and absolute EtOH (0.6 mL) was sealed in a glass ampule and heated at 80 °C for 1 day. The reaction was then concentrated, the residue was partitioned between CH_2Cl_2 (20 mL) and $NaHCO_3$ (5 mL, saturated aqueous), and the organic layer was dried (Na_2SO_4). The CH_2Cl_2 was removed by distillation through a 30-cm concentric tube column at atmospheric pressure (due to the volatility of **3**, substantial losses occurred if CH_2Cl_2 was removed with a rotary evaporator in vacuo). Purification of the residue on silica gel (825:10:1 $CHCl_3$–*i*-PrOH–12 N NH_4OH) gave 26.2 mg of **3**. GLC analysis[51a] showed that this sample contained **3** (95.4%), its C-11 epimer (3.6%), and protodesilylated oxazolidine **32** (1%): $[\alpha]^{25}_D$ −3.08 (*c* 1.6, $CHCl_3$); IR ($CDCl_3$) 3500, 1660, 1465 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.05 (d, *J* = 9.5 Hz, H-10), 3.78 (d, *J* = 12.1 Hz, H-5α), 3.07 (m, H-3α) 2.6 (br s, OH), 2.34 (d, *J* = 12.1 Hz, H-5β), 2.3–2.5 (m, H-11), 2.1–2.3 (m, H-3β), 2.17 (br apparent s, two H-7), 1.9–2.0 (m, H-8a), 1.1–1.4 (m), 1.16 (s, C-8 Me), 0.98 (d, *J* = 6.2 Hz, C-11 Me), 0.87 (apparent t, *J* = 6.8 Hz, CH_2*Me*); ^{13}C NMR (23 MHz, $CDCl_3$) 134.8, 129.8, 71.8, 68.3, 54.6, 53.2, 48.9, 37.5, 32.1, 29.7, 24.3, 23.3, 22.8, 21.7, 21.1, 14.1; MS (EI), *m/z* 251 (MH, 3%), 166 (43%), 112 (10%), 70 (100%).

The hydrochloride salt (60% overall yield from **29**) was prepared in ether and recrystallized from hexane–ethyl acetate (3×) to give an analytical specimen of (+)-pumiliotoxin 251D hydrochloride: mp 206–206.5 °C (evacuated sealed tube); 100% pure by GLC analysis;[51a] $[\alpha]^{25}_D$ +28.0 (*c* 0.62, MeOH), $[\alpha]^{25}_{546}$ +32.0 (*c* 0.62, MeOH); ^1H NMR (250 MHz, CD_3OD) δ 5.34 (d, *J* = 9.5 Hz, H-10), 4.38 (d, *J* = 13 Hz, H-5α), 2.43 (d, *J* = 17.5 Hz, C-7 H), 2.36 (d, *J* = 17.5 Hz, C-7 H), 1.29 (s, C-8 Me), 1.04 (d, *J* = 6.5 Hz, C-11 Me), 0.89 (t, *J* = 7.3 Hz, CH_2*Me*); ^{13}C NMR (CD_3OD) δ 140.5, 125.4, 73.4, 68.7, 54.0, 52.1, 47.3, 38.3, 33.3, 30.7, 26.1, 23.7, 22.8, 21.5, 20.6, 14.4; MS (EI), *m/z* 251.2240 (251.249 calcd for $C_{16}H_{29}NO$, 69%), 166 (24%), 112 (7%), 84 (19%), 70 (100%).

(8*S*,8a*S*)-8-Hydroxy-8-methyl-6(*Z*)-(2(*S*)-methylhexylidene)octahydroindolizidine. C-11 *epi*-Pumiliotoxin-251D. This isomer was isolated from hydrolysis and cyclization of bicyclic carbamate samples that contained ~15% of the C-11 diastereomer of **29**: IR (film) 3520, 1460 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.04 (d, *J* = 9.1 Hz, H-10), 3.78 (d, *J* = 11 Hz, H-5α), 3.06 (m, H-3α), 2.70 (br s, OH), 2.36 (d, *J* = 11 Hz, H-5β), 1.2–2.2 (m), 1.13 (s, C-8 Me), 0.89 (d, *J* = 6.6 Hz, C-11 Me), 0.87 (t, *J* = 6.8 Hz, CH_2*Me*); MS (CI), *m/z* 252 (MH), 234, 166, 84. epi-C_{11}-251D hydrochloride: $[\alpha]^{25}_D$ +9.41 (*c* 0.42, MeOH) 100% pure by GLC analysis;[51a] ^{13}C NMR (CD_3OD) δ 140.7, 125.3, 73.5, 68.6, 54.2, 52.1, 47.3, 38.1, 33.3, 30.7, 26.0, 24.0, 22.9, 21.3, 20.6, 14.4.

Ethyl (*R*)-2-((4-Nitrobenzoyl)oxy)propionate (36). A modification of one of Mitsunobu's procedures[38b] was employed. A solution of Ph_3P (3.14 g, 12 mmol) and THF was added dropwise at −20 °C to a rapidly stirred solution of diethyl azodicarboxylate (2.0 mL, 12 mmol) and THF (2 mL). A white precipitate appeared within 0.5 h. A solution of 4-nitrobenzoic acid (1.67 g, 10 mmol) and THF (15 mL) was added dropwise at −20 °C, the resulting mixture was stirred at −20 °C for 0.5 h, and ethyl L-lactate (**35**) (2.0 mL, 18 mmol, $[\alpha]^{20}_D$ −12 (neat), Aldrich Chemical Co.) was then added by drops. The cooling bath was removed, and the reaction mixture was allowed to stir for 27 h. Concentration gave an orange oil, which was diluted with ether and filtered to remove a white solid. Purification of the filtrate by chromatography (1:1 hexane–ethyl acetate) gave 2.42 g (91%) of pure **36** as a low-melting white solid: mp 42–43 °C (from hexane), $[\alpha]^{25}_D$ −13.1 (*c* 1.17, EtOH); IR (film) 1720, 1430, 1280, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 8.2–8.35 (m, aryl H), 5.35 (q, *J* = 7.0 Hz, OCH), 4.25 (q, *J* = 7.1 Hz, OCH_2), 1.67 (d, *J* = 7.0 Hz, OCH*Me*), 1.30 (t, *J* = 7.1 Hz, CH_2*Me*); MS (isobutane CI), *m/z* 268 (MH), 222, 150, 120, 71; MS (EI), *m/z* 267.0742 (267.0743 calcd for $C_{12}H_{13}NO_6$).

Ethyl 2(*R*)-((*tert*-Butyldiphenylsilyl)oxy)propanoate (37). A mixture of **36** (1.66 g, 6.22 mmol), K_2CO_3 (850 mg, 6.2 mmol, flame dried), and absolute EtOH (10 mL) was stirred at 23 °C for 15 min. Filtration and concentration of the filtrate gave crude ethyl D-lactate, which was immediately silylated at 23 °C (6 h) in DMF (10 mL) with *tert*-butyldiphenylsilyl chloride (1.8 mL, 7.0 mmol) and imidazole (950 mg, 14 mmol). Aqueous workup (ether, $MgSO_4$) gave a viscous oil, which was chromatographed (7:1 hexane–ethyl acetate) to give 1.18 g (53%) of pure **37** as a colorless liquid: $[\alpha]^{25}_D$ +46.0 (*c* 1.97, EtOH), IR (film) 1762, 1110, 1140 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.3–7.7 (m, Ph), 4.27 (q, *J* = 6.7 Hz, OCH), 4.02 (q, *J* = 7.1 Hz, OCH_2), 1.37 (d, *J* = 6.7 Hz, CH*Me*), 1.14 (t, *J* = 7.1 Hz, CH_2*Me*), 1.10 (s, *t*-Bu); MS (EI), *m/z* 299.1104 (299.1103 calcd for $C_{17}H_{19}SiO_3$, M − Bu, 72%), 227 (70%), 199 (100%).

***S*-(2-Pyridinyl) 2-(*R*)-((*tert*-Butyldiphenylsilyl)oxy)propanthioate (38).** A solution of **37** (775 mg, 2.17 mmol), KOH (620 mg, 8.8 mmol), and MeOH (10 mL) was maintained at 23 °C for 10 h and then concentrated. Acidification with 1 N HCl (20 mL), extraction with ether, and drying of the organic extract ($MgSO_4$) provided the corresponding crude acid (579 mg, 82%) as a colorless liquid. This material was immediately esterified in ethyl acetate (10 mL) by reaction with 2-pyridinethiol (222 mg, 2.0 mmol), and dicyclohexylcarbodiimide (474 mg, 2.33 mmol) at 23 °C for 9 h. After separation of the precipitate by filtration, the filtrate was washed with brine, dried ($MgSO_4$), and concentrated to give a yellow oil. Purification on silica gel (4:1 hexane–ethyl acetate) gave 620 mg (68% from **37**) of **38** (purity ~90% by ^1H NMR analysis) as a colorless oil: IR (film) 1715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 8.6–8.7 (m, C-6 pyridinyl H), 7.2–7.8 (m, pyridinyl H), 4.44 (q, *J* = 6.6 Hz, OCH), 1.26 (d, *J* = 6.6 Hz, CH*Me*), 1.18 (s, *t*-Bu); MS (isobutane CI), 422 (MH), 279, 257, 225, 112, 89.

Thioester **38** was not stable to storage and was used immediately in the next reaction.

(*R*)-2-((*tert*-Butyldiphenylsilyloxy)-4-(triphenylphosphoranylidene)-3-pentanone (39). A solution of *sec*-BuLi (1.91 mL of a 1.15 M solution in cyclohexane) was added at 23 °C to a rapidly stirred suspension of ethyltriphenylphosphonium bromide (816 mg, 2.20 mmol, finely ground and dried in vacuo for 2 days at 200 °C) and THF (15 mL). Over the period of 10 min the white suspension changed to a dark red solution. A solution of **38** (421 mg, 1.00 mmol) and THF (5 mL) was added by drops, the resulting orange suspension was stirred at 23 °C for 20 min

and was then filtered through Celite. Aqueous workup (ether, K_2CO_3) gave 690 mg of a yellow oil. This material was purified by radial chromatography (4-mm silica gel plate, 1:1 hexane–ethyl acetate) to give 323 mg (54%) of **39** as a nearly pure light yellow amorphous solid: IR (film) 1518, 1440, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.3–7.8 (m, Ph), 4.56 (q, J = 6.5 Hz, CHO), 1.58 (d, J = 6.8 Hz, P=CMe), 1.32 (d, J = 6.5 Hz, CH*Me*), 1.08 (s, *t*-Bu); MS (CI), m/z 601 (MH), 317, 279, 263, 185, 85.

Ylide **39** of this purity was successfully stored for over 1 month at 23 °C.

5-(Benzyloxy)-1-pentyn-3-ol (43). Known 3-(benzyloxy)propanal[43] was reliably prepared on 0.1–0.4-mol scales by the following procedure. A solution of *i*-Bu_2AlH (36 mL in 150 mL of hexane, 200 mmol) was added dropwise at 0 °C to a stirred solution of 3-(benzyloxy)propanitrile (24.1 g, 150 mmol, available on mol scales from acrylonitrile and benzyl alcohol[43]) and THF (400 mL). The reaction was allowed to warm to 23 °C and after 1 h was carefully quenched by adding it dropwise to a rapidly stirred mixture of 1 M tartaric acid (700 mL) and ether (300 mL) at 0 °C. Isolation (ether, $MgSO_4$) gave 21.8 g (88%) of crude 3-(benzyloxy)propanal as a light yellow oil. Although this material may be purified by rapid distillation or chromatography, fragmentation to acrolein and benzyl alcohol can be a significant complication.

A solution of this crude aldehyde sample and THF (80 mL) was added dropwise to a solution of 1-ethynyllithium (prepared from 150 mmol of BuLi and excess acetylene as described by Midland[44]) at −75 °C. The reaction was maintained at −75 °C for 0.5 h and then allowed to warm to 23 °C. After 2 h, the reaction was quenched at 0 °C by adding excess NH_4Cl (saturated aqueous solution), and the crude organic product was isolated (ether, $MgSO_4$) and distilled to give 14.8 g of **43**. Chromatographic purification of the distillation residue (5:1 hexane–ethyl acetate) provided an additional 1.60 g of pure **43** (57% total yield from **42**): bp 97 °C, 0.5 mm; IR (film) 3200–3600, 2112, 1100 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) 7.2–7.4 (m, Ph), 4.55–4.65 (m, C*H*OH), 4.53 (br s, OCH_2Ph), 3.8–3.9 (eight-line m, CH_2CHHO), 3.63–3.71 (eight-line m, CH_2CHHO), 3.28 (br d, $J \sim 6$ Hz, OH), 2.45 (d, J = 2.0 Hz, C≡CH), 1.90–2.15 (m); MS (isobutane CI), m/z 191 (MH), 173, 155, 145, 191, 73; MS (EI), m/z 190.0983 (190.0994 calcd for $C_{12}H_{14}O_2$).

Resolution of 5-(Benzyloxy)-1-pentyn-3-ol. By the general procedure described by Pirkle,[29a] racemic **43** (14.8 g, 77.7 mmol) was converted to the chloroformate ester and condensed with (*R*)-(+)-α-methylbenzylamine [10.0 mL, 77.6 mmol, $[\alpha]^{25}_D$ +39 (neat)] to give 25 g of a mixture of carbamates **44** and **45**. Chromatographic separation (two silica prePAK columns, Waters LC-500, 6:1 hexane–ethyl acetate) gave 9.58 g (37%) of the more polar *S,R* diastereomer **44**[56] and 8.55 g (33%) of the less polar *R,R* diastereomer **45**.[56] Analytical HPLC analysis[58] (6:1 hexane–ethyl acetate) showed that this sample of **44** was 92% diastereomerically pure, while **45** was 94% diastereomerically pure. When this separation was done on smaller scales, **44** could be obtained with a diastereomer purity of >98%.

Cleavage of **44** (4.60 g, 13.6 mmol) with Cl_3SiH (20 mmol) as described by Pirkle[29c] gave 1.74 g (67%) of (*S*)-5-(benzyloxy)-1-pentyn-3-ol (**46**) as a colorless liquid after chromatographic purification (5:1 hexane–ethyl acetate): $[\alpha]^{25}_D$ −23.5 (*c* 1.89, $CHCl_3$). Similar cleavage of **45** gave 2.95 g (67%) of (*R*)-5-(benzyloxy)-1-pentyn-3-ol (**47**): $[\alpha]^{25}_D$ +24.3 (*c* 2.60, $CHCl_3$).

The (*R*)-MTPA ester of racemic samples of alcohol **43** showed diagnostic signals in the 250-MHz ^1H NMR spectrum ($CDCl_3$) for the two diastereomers at δ 4.44 and 4.53 (OCH_2Ph), 3.50 and 3.63 (d, OMe), and 2.53 and 2.57 (d, J = 3.5 Hz, C≡CH). The δ 2.5–2.6 region of the (*R*)-MTPA ester prepared from *S* alcohol **46** showed doublets in a ratio of 96:4 at δ 2.53 and 2.57, respectively, corresponding to an enantiomeric purity of 92%.

(*S*)-5-(Benzyloxy)-1-(trimethylsilyl)-1-pentyn-3-yl Benzoate (49). The *R* alcohol **47** (2.94 g, 15.5 mmol, $[\alpha]^{25}_D$ +24.3) was silylated at C-1, as described for the preparation of **27**, to give 3.57 g (88%) of silylalkyne **48** after purification on silica gel (5:1 hexane–ethyl acetate): $[\alpha]^{25}_D$ +20.8 (*c* 5.08, $CHCl_3$).

Diethyl azodicarboxylate (2.84 mL, 17.2 mmol) was added dropwise at 23 °C to a stirred solution of **48** (3.47 g, 13.2 mmol), Ph_3P (4.51 g, 17.2 mmol), benzoic acid (2.1 g, 17.2 mmol), and THF (50 mL).[38] After 4 h, concentration gave an oil, which was diluted with ether and filtered. The filtrate was purified by chromatography (20:1 hexane–ethyl acetate) to afford 4.08 g (85%) of **49** as a pure colorless oil: $[\alpha]^{25}_D$ −17.7 (*c* 3.39, $CHCl_3$); IR (film) 2179, 1723, 1270, 1105 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.0–8.1 (m, 2 H, Ph), 7.2–7.6 (m, 8 H, Ph), 5.82 (t, J = 6.7 Hz, CHO), 4.50 (s, CH_2Ph), 3.6–3.71 (m, CH_2O), 2.14–2.31 (m), 0.15 (s, Me_3Si); MS (isobutane CI), m/z 367 (MH), 245, 217, 195, 173, 155, 123, 105, 91, 73; MS (EI), m/z 275.1110 (275.1103 calcd for $C_{15}H_{19}O_3Si$, M − CH_2Ph).

(*S*)-5-(Benzyloxy)-1-(trimethylsilyl)-1-pentyn-3-yl Acetate (51). By use of the procedure described for the preparation of **27**, the *S* alcohol **46** (2.65 g, 14.4 mmol, $[\alpha]^{25}_D$ −23.5) was silylated at C-1 to give, after chromatography (5:1 hexane–ethyl acetate), 2.50 g (65%) of silylalkyne **50**:[56] $[\alpha]^{25}_D$ −22.8 (*c* 1.00, $CHCl_3$).

Acetylation [Ac_2O (1.5 equiv), 4-(dimethylamino)pyridine (0.25 g), and pyridine (50 mL)] of a 4.60-g (17.6 mmol) sample of **50** gave, after purification on silica gel (4:1 hexane–ethyl acetate), 4.57 g (85%) of acetate **51** as a colorless liquid:[56] $[\alpha]^{25}_D$ −57.9 (*c* 2.95, $CHCl_3$); MS (EI), m/z 304.1514 (304.1494 calcd for $C_{17}H_{24}O_3Si$).

(*R*)-5-(Benzyloxy)-3-methyl-1-(trimethylsilyl)pentyne (52). By use of the general procedure of Macdonald,[30] a solution of the *S* acetate **51** (4.50 g, 14.8 mmol) and THF (15 mL) was added at 23 °C by drops to the cuprate reagent prepared in THF (75 mL) from CuI (2.81 g, 29.6 mmol) and MeMgBr (31 mL of a 1.9 M solution in ether). After 10 min at 23 °C, the reaction was quenched by adding it dropwise to an excess of NH_4Cl (saturated aqueous). Isolation (ether, $MgSO_4$) and chromatographic purification (20:1 hexane–ethyl acetate) gave 1.98 g (51%) of **52** as colorless liquid: 98.7% pure by GLC[51a] analysis; $[\alpha]^{25}_D$ −64.0 (*c* 2.26, $CHCl_3$); IR (film) 2167, 1252, 1100 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.2–7.4 (m, Ph), 4.52 (s, OCH_2Ph), 3.61 (apparent t, J = 6.5 Hz, CH_2CH_2O), 2.6–2.75 (m, C≡CCH), 1.65–1.80 (m), 1.18 (d, J = 7.0 Hz, Me), 0.13 (s, Me_3Si); MS (isobutane CI), m/z 261 (MH), 233, 187, 171, 129, 103, 91, 79, 73; MS (EI), m/z 245.1368 (245.1362 calcd for $C_{15}H_{21}OSi$, M − Me).

The identical procedure was also used to prepare **52** from benzoate **49** (3.98 g, 10.8 mmol): yield 1.23 g (44%); $[\alpha]^{25}_D$ −64.4 (*c* 1.42, $CHCl_3$).

(1*S*,7a*S*)-Tetrahydro-1-methyl-1-[6-(benzyloxy)-4(*R*)-methyl-2-(trimethylsilyl)-2(*Z*)-hexenyl]-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (53). Neat *i*-Bu_2AlH (0.85 mL, 4.8 mmol) was added dropwise at 23 °C to a solution of **52** (1.23 g, 4.74 mmol) and hexane (3 mL). After 0.5 h THF (8 mL) was added followed by the dropwise addition of MeLi (2.6 mL of a 1.33 M solution in ether, 3.5 mmol). The color changed from colorless to light pink when the last drop of MeLi was added, and slowly changed over 0.5 h to light yellow as this solution was maintained at 23 °C. A solution of epoxide **12** (520 mg, 1.99 mmol) and THF (2 mL) was then added, and the resulting solution was heated at 60 °C for 25 h. Workup as described for the isolation of **20** gave a yellow oil, which was purified by chromatography (4:1 hexane–ethyl acetate) to give 637 mg (77% based on **12**) of **53** as a colorless oil: $[\alpha]^{25}_D$ −39.2 (*c* 1.05, $CHCl_3$); IR (film) 1760 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.2–7.4 (m, Ph), 5.87 (d, J = 10.6 Hz, =CH), 4.48 (AB quartet, J = 11.9 Hz, OCH_2Ph), 3.53–3.66 (m, NCH and NC*H*H), 3.46 (apparent t, J = 6.8 Hz, CH_2O), 3.05–3.2 (m, NCH*H*), 2.55–2.65 (m, =CHC*H*), 2.56 (AB quartet, J = 13.7 Hz, CH_2C=), 1.5–2.2 (m), 1.30 (s, C-8 Me), 0.99 (d, J = 6.6 Hz, CH*Me*), 0.17 (s, Me_3Si); MS (isobutane CI), m/z 416 (MH), 372, 186, 139, 107, 91, 70; MS (EI), m/z 400.2306 (400.2307 calcd for $C_{23}H_{34}NO_3Si$, *M* − Me).

(8*S*,8a*S*)-8-Hydroxy-8-methyl-6(*Z*)-[4-(benzyloxy)-2(*R*)-methylbutylidene]octahydroindolizidine (55). A carefully degassed solution of **53** (527 mg, 1.27 mmol), KOH (1.8 g, 25 mmol), EtOH (1.6 mL), and H_2O (0.4 mL) was heated at 90 °C for 12 h. After cooling to 23 °C, 37% aqueous formalin (1 mL) and MeOH (2 mL) were added dropwise. After 4 h the reaction was concentrated and the crude oxazolidine **54** (496 mg) was isolated (CH_2Cl_2, K_2CO_3):[56] MS (isobutane CI), m/z 402 (MH).

A mixture of this oxazolidine sample, paraformaldehyde (180 mg, 6.0 mmol), camphorsulfonic acid (650 mg, 2.8 mmol), and acetonitrile (10 mL) was heated at 80 °C for 13 h. Isolation (ether, K_2CO_3) gave a brown oil, which was purified by radial chromatography (silica gel, 50:1:0.1 $CHCl_3$–MeOH–12 N NH_4OH) to afford 219 mg (52%) of **55** as a light yellow oil: pure by TLC analysis; $[\alpha]^{23}_D$ −25.5 (*c* 2.33, $CHCl_3$); IR (film) 3200–3600, 1100 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.2–7.4 (m, Ph), 5.02 (br d, J = 9.7 Hz, =CH), 4.45 (apparent s, OCH_2Ph), 3.82 (d, J = 11.8 Hz, H-5α), 2.29 (br d, J = 11.8 Hz, H-5β), 1.13 (s, C-8 Me), 1.00 (d, J = 6.6 Hz, C-11 Me); MS (isobutane CI), m/z 330, 166, 107, 91, 83, 70; MS (EI), m/z 329.2338 (329.2355 calcd for $C_{21}H_{31}NO_2$).

(8*S*,8a*S*)-8-Hydroxy-8-methyl-6(*Z*)-(4-hydroxy-2(*R*)-methylbutylidene)octahydroindolizidine (56). A solution of **55** (164 mg, 0.500 mmol), THF (8 mL), and NH_3 (8 mL) was treated with excess Li until the blue color persisted for 3 h. Addition of excess NH_4Cl was followed by evaporation of the NH_3 and isolation with $CHCl_3$ (K_2CO_3) to give, after radial chromatography (silica gel, 20:1:0.1 $CHCl_3$–MeOH–12 N NH_4OH), 73.1 mg (61%) of **56** as a colorless oil: isomerically pure by TLC analysis (R_f 0.4, C-11 epimer R_f 0.5; 10:1:0:0.1 $CHCl_3$–MeOH–12 N NH_4OH), $[\alpha]^{25}_D$ −22.1 (*c* 1.87, $CHCl_3$); IR (film) 3100–3600, 1670 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.06 (br d, J = 9.8 Hz, =CH), 3.82 (d, J = 11.8 Hz, H-5α), 3.45–3.65 (m, CH_2O), 3.0–3.12 (m,

NC*H*H), 2.7 (br s, OH), 2.55–2.70 (m, =CC*H*), 2.37 (br d, J = 11.9 Hz, H-5β), 2.17–2.3 (m, NCH*H*), 2.14 (AB q, J = 14.0 Hz, CH_2C=), 1.5–2.3 (m), 1.14 (s, C-8 Me), 1.02 (d, J = 6.6 Hz, C-11 Me); MS (EI), m/z 239.1876 (239.1885 calcd for $C_{14}H_{25}NO_2$).

This alcohol could be stored in a freezer under Ar for several months with only slight decomposition.

(8*S*,8a*S*)-8-Hydroxy-8-methyl-6(*Z*)-[4-oxo-2(*R*)-methylbutylidene]octahydroindolizidine (57). Alcohol **56** (240 mg, 1.00 mmol) was oxidized with oxalyl chloride (3 mmol) and Me_2SO(6 mmol) by using the general procedure developed by Swern[49] to give, after radial chromatography (silica gel, 25:1:0.1 $CHCl_3$–MeOH–12 N NH_4OH), 211 mg (88%) of **57** as a slightly impure pale yellow oil: $[\alpha]^{25}_D$ −25.9 (c 0.63, $CHCl_3$); IR (film) 3100–3700, 1718, 1030 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.67 (t, J = 2.0 Hz, CHO); MS (isobutane CI), m/z 238 (MH), 117, 99.

This aldehyde was not stable to storage and was used immediately in the olefination step.

(8*S*,8a*S*)-8-Hydroxy-8-methyl-6(*Z*)-[6-oxo-2(*R*),5-dimethyl-7(*R*)-(*tert*-butyldiphenylsiloxy)-4(*E*)-octenylidene]octahydroindolizidine (58). A carefully degassed solution of **57** (53.3 mg, 0.224 mmol), ylide **39** (194 mg, 0.323 mmol), and CH_2Cl_2 (1 mL) was heated at reflux for 5 days. Concentration and purification of the residue by radial chromatography (silica gel, 40:1:0.1 $CHCl_3$–MeOH–NH_4OH) gave 136 mg of a light yellow oil, which was a ~2:1 mixture of **58** and Ph_3PO. This mixture was difficult to separate and it was typically used directly in the reduction step, since Ph_3PO and **1** are easy to separate by chromatography.

A 30-mg portion of this crude oil was purified by careful preparative TLC (R_f 0.3, 40:1 $CHCl_3$–MeOH, eluted twice), to give 19.3 mg (71%) of chromatographically homogeneous **58** as a colorless oil: $[\alpha]^{25}_D$ +13.2 (c 0.87, MeOH); IR (film) 3100–3600, 1685, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.2–7.7 (m, Ph), 6.19 (br t, J = 7.3 Hz, CH=CCO), 5.01 (br d, J = 9.8 Hz, =CH), 4.69 (q, J = 6.8 Hz, CHOR), 3.74 (d, J = 11.7 Hz, H-5α), 3.2–3.1 (m), 2.5–1.6 (m), 1.54 (br s, =CMe), 1.24 (d, J = 6.8 Hz, ROCH*Me*), 1.08 (s, C-8 Me), 1.00 (s, *t*-Bu), 0.89 (d, J = 6.5 Hz, CH*Me*); MS (isobutane CI), m/z 560 (MH), 304, 279, 257, 231; MS (EI), m/z 559.3463 (559.3480 calcd for $C_{35}H_{49}NO_3Si$).

(+)-Pumiliotoxin B (1). A solution of pure enone **58** (14.6 mg, 0.026 mmol) and THF (0.5 mL) was added dropwise at −20 °C to a rapidly stirred suspension of $LiAlH_4$ (8 mg, 0.2 mmol) and THF (1.5 mL). After 0.5 h, the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 2 h, $Na_2SO_4 \cdot 10H_2O$ (0.1 g) was added followed by $CHCl_3$ (5 mL), and the resulting mixture was stirred rapidly for 2 h and then filtered through Celite. The concentrated filtrate was purified by radial chromatography (silica gel, 10:1:0.1 $CHCl_3$–MeOH–12 N NH_4OH) to give 6.2 mg (74%) of **1** as a colorless oil. This sample was chromatographically homogeneous but contained 6% of the erythro diastereomer (^1H NMR analysis of the *p*-bromophenyl boronides). An analytical specimen of synthetic **1** was obtained from the center cut of a chromatographic purification of a larger sample of comparable material: $[\alpha]^{25}_D$ +19.3, $[\alpha]^{25}_{578}$ +19.7, $[\alpha]^{25}_{546}$ +23.0, $[\alpha]^{25}_{435}$ +40.2 (c 1.00, MeOH); IR (film) 3100–3600, 1455, 1375, 1310, 1090, 1028, 966 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 4.7 mg/0.5 mL) δ 5.39 (br t, J = 6.7 Hz, H-13), 5.06 (br d, J = 9.6 Hz, H-10), 3.7–3.9 (m, H-5α and H-16), 3.70 (apparent d, J = 7.1 Hz, H-15), 3.0–3.1 (m, H-3α) 2.66 (br s, OH), 2.42–2.57 (m, H-11), 2.34 (br d, J = 11.7 Hz, H-5β), 1.65–2.3 (m), 1.58 (br s, H-19), 1.13 (s, H-9), 1.11 (d, J = 6.0 Hz, H-17), 1.00 (d, J = 6.6 Hz, H-18); ^{13}C NMR (63 MHz, $CDCl_3$) δ 135.4, 133.9, 130.7, 127.6, 82.9, 71.8, 69.0, 68.6, 54.7, 53.4, 49.0, 35.7, 32.6, 24.5, 23.4, 21.5, 21.3, 19.1, 12.4; MS (EI), m/z 323.2466 (323.2460 calcd for $C_{19}H_{33}NO_3$, 18%), 306 (10%), 278 (40%), 206 (23%), 194 (53%), 193 (31%), 176 (16%), 166 (100%), 70 (98%).

An authentic sample of natural pumiliotoxin B provided by Dr. J. Daly showed the following optical properties: $[\alpha]^{25}_D$ +19.8, $[\alpha]^{25}_{578}$ +19.8, $[\alpha]^{25}_{546}$ +21.3, $[\alpha]^{25}_{435}$ +35.8 (c 2.28, MeOH).

(8*S*,8a*S*)-8-Hydroxy-8-methyl-6(*Z*)-[6(*R*),7(*R*)-dihydroxy-2(*S*),5-dimethyl-4(*E*)-octenylidene]octahydroindolizidine. C-11 *epi*-Pumiliotoxin B. This isomer was isolated from preparations of **1** which utilized bicyclic carbamate samples which contained 50% of the C-11 epimer of **53**: IR (film) 3100–3600, 1450, 1373, 1310, 1265, 1110, 1020, 966 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 9.0 mg/0.5 mL) 5.51 (br t, J ~ 6 Hz, H-13), 4.98 (d, J = 10.0 Hz, H-10), 3.65–3.9 (m, H-5α, H-15, H-16), 3.09 (br t, J = 7.7 Hz, H-3α), 1.6–2.65 (m), 1.62 (br s, H-19), 1.15 (d, J = 5.9 Hz, H-17), 1.15 (s, H-9), 1.03 (d, J = 6.5 Hz, H-18); MS (EI) m/z 323.2464 (323.2460 calcd for $C_{19}H_{33}NO_3$, 9%), 278 (24%), 306 (14%), 278 (34%), 206 (23%), 194 (24%), 193 (25%), 176 (13%), 166 (84%), 70 (100%).

(8*S*,8a*S*)-8-Hydroxy-8-methyl-6(*Z*)-[6-oxo-2(*R*),5-dimethyl-7(*S*)-(*tert*-butyldiphenylsiloxy)-4(*E*)-octenylidene]octahydroindolizidine (60). Aldehyde **57** (30 mg, 0.13 mmol) was condensed with the *S* ylide **59** (240 mg, 0.40 mmol), exactly as described for the preparation of **58**, to give 133 mg of enone **60**, which was contaminated with Ph_3PO. A 30-mg sample was further purified by preparative TLC (R_f 0.4, 20:1 $CHCl_3$–MeOH) to give 8.5 mg (54%) of **60** as a chromatographically homogeneous light yellow oil:[56] IR (film) 1685 cm^{-1}; MS (isobutane CI), m/z 560 (MH).

(8*S*,8a*S*)-8-Hydroxy-8-methyl-6(*Z*)-[6(*S*),7(*S*)-dihydroxy-2(*R*),5-dimethyl-4(*E*)-octenylidene]octahydroindolizidine (61). Enone **60** (9.0 mg, 0.016 mmol) was reduced with $LiAlH_4$, and resulting diol was purified, exactly as described for the preparation of **1**, to afford 3.8 mg (73%) of **61** as a light yellow oil: $[\alpha]^{25}_D$ +15.7 (c 1.4, MeOH); IR (film) 3100–3600, 1455, 1375, 1311, 1090, 1030, 969 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.38 (br t, J = 6.8 Hz, =CH), 5.06 (br d, J = 9.6 Hz, CH), 3.7–3.9 (m, H-5α and C*H*(OH)Me), 3.69 (apparent d, J = 7.4 Hz, =CC*H*OH), 1.59 (br s, =CMe), 1.13 (s, Me), 1.08 (d, J = 6.1 Hz, C(OH)*Me*), 1.01 (d, J = 6.1 Hz, CH*Me*); MS (EI), m/z 323.2466 (323.2460 calcd for $C_{19}H_{33}NO_3$, 8%), 306 (2%), 278 (12%), 206 (15%), 194 (28%) 193 (28%), 176 (14%), 166 (98%), 70 (100%).

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Registry No. 1, 67016-65-3; **3**, 73376-35-9; **3**·HCl, 73395-60-5; **3** (*epi*-C_{11})·HCl, 90319-46-3; **8**, 5211-23-4; **9**, 51207-68-2; **10**, 51207-70-6; **11**, 77733-66-5; **12**, 77733-65-4; **20**, 77733-69-8; **21**, 77790-27-3; **25**, 51703-66-3; **25** (*R*-MTPA ester), 90246-51-8; **26**, 65337-07-7; **26** (*R*,*R* diastereiomer), 65391-25-5; **27**, 77733-63-2; **28**, 77733-64-3; **29**, 77733-70-1; **29** (C-11 epimer), 90319-51-0; **30**, 90246-29-0; **31**, 90246-30-3; **31** (C-11 epimer), 73376-35-9; **32**, 90246-31-4; **36**, 90246-32-5; **37**, 90246-33-6; **38**, 90246-34-7; **39**, 90246-35-8; **42**, 6328-48-9; (±)-**43**, 90246-36-9; **44**, 90246-37-0; **45**, 90246-38-1; **46**, 90319-47-4; **46** ((*R*)-MTPA ester), 90246-40-5; **35**, 687-47-8; **47**, 90319-48-5; **47** ((*R*)-MTPA ester), 90246-39-2; **49**, 90246-41-6; **50**, 90246-50-7; **51**, 90246-42-7; **52**, 90246-43-8; **53**, 90246-44-9; **54**, 90246-46-1; **55**, 90246-45-0; **56**, 90246-47-2; **57**, 90246-48-3; **58**, 90246-49-4; **59**, 83108-27-4; **60**, 90319-49-6; **61**, 90319-50-9; (*S*)-1-(trimethylsilyl)-1-heptyn-3-ol, 90246-28-9; 1-(trimethylsilyl)hexyne, 3844-94-8; (*R*)-α-(1-naphthyl)-ethylamine, 3886-70-2; 1-heptyn-3-one, 26119-02-8; 2-pyridinethiol, 2637-34-5; 3-(benzyloxy)propanal, 19790-60-4; 1-ethynyllithium, 1111-64-4; (±)-1-heptyn-3-ol, 51586-58-4; 4-nitrobenzoic acid, 62-23-7; ethyltriphenylphosphonium bromide, 1530-32-1.

Supplementary Material Available: Experimental data for compounds **9**, **26**, **30**, **44**, **45**, **50**, **51**, and **54** (3 pages). Ordering information is given on any current masthead page.