Efficient Total Syntheses of Pumiliotoxins A and B. Applications of Iodide-Promoted Iminium Ion−Alkyne Cyclizations in Alkaloid Construction

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Abstract: A practical route for the total synthesis of pumiliotoxin A alkaloids is described. The central step is formation of the piperidine ring and establishment of the (*Z*)-alkylidene side chain by an iodide-promoted iminium ion−alkyne cyclization. The total synthesis of (+)-15(*S*)-pumiliotoxin A (**2**) was realized in 5 steps and 32% overall yield from alkyne **36** and epoxide **7**. This synthesis of **2** proceeded in 13 steps and 12% overall yield from (*S*)-2-methyl-1-penten-3-ol (**25**) and 8 steps and 9% overall yield from *N*-[(benzyloxy)carbonyl]-L-proline. The synthesis of (+)-pumiliotoxin B (**3**) was similarly achieved in four steps and 44% overall yield from alkyne **54** and epoxide **7**. The overall yield of enantiopure **3** was 8% from *N*-[(benzyloxy)carbonyl]-L-proline and 10% from (4*S*,5*R*)-4-methyl-5-phenyl-2-oxazolidinone. These syntheses represent substantial improvement over previous routes to these important alkaloids.

A wide variety of structurally unique and pharmacologically active compounds are obtained from amphibians. One unique source is skin secretions of certain brightly colored frogs native to the rain forests of western Colombia and Panama. Likely since pre-Columbian times these frogs have been employed by the Noanamá and Emberá Indians to poison blow darts.[2,3] The first description of darts envenomed with skin secretions of poison frogs dates from 1825 and described the use of a single frog to charge at least 20 blow darts.[3] The chemistry and pharmacology of "poison dart" frogs of the family Dendrobatidae has been pioneered by Witkop, Daly, and co-workers.[4] To date, more than 300 organic compounds, the vast majority of which are unique to Dendrobatid frogs, have been isolated from this amphibian family.[5,6]

The pumiliotoxin A and allopumiliotoxin classes of dendrobatid alkaloids are a group of ~40 alkylideneindolizidine alkaloids that display particularly significant pharmacological activities.[4] Pumiliotoxins A (**2**) and B (**3**) were the second and third dendrobatid alkaloids to be isolated and were initially obtained in 1967 from skin of the Panamanian poison frog *Dendrobates pumilio* (Figure 1).[7] Elucidation of the structure of these alkaloids was complicated by the instability of pumiliotoxins A and B in acid, likely deriving from their allylic hydroxyl group. The structure of these toxins remained unknown until 1980 when a simpler alkaloid, pumiliotoxin 251D (**1**), was isolated as a major alkaloid component of skin extracts of the Ecuadorian poison frog, *Dendrobates tricolor*. Single-crystal X-ray analysis of pumiliotoxin 251D hydrochloride finally provided the key for revealing the constitution of the pumiliotoxin A alkaloids.[8] The allopumiliotoxins are the most complex members of the pumiliotoxin A group of dendrobatid alkaloids and possess oxidation at both carbons 7 and 8 of the indolizidine ring (e.g., **4**, Figure 1).[4]

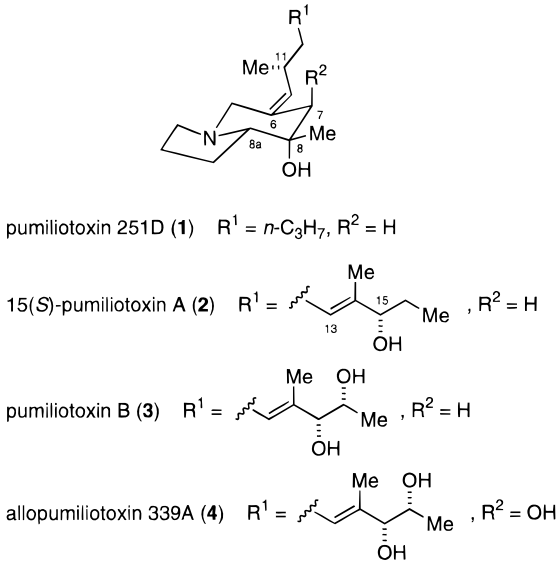

Figure 1. Representative pumiliotoxin A and allopumiliotoxin alkaloids.

Pumiliotoxins A and B are relatively toxic and a subcutaneous dose of pumiliotoxin B of 20 μg can cause death in mice.[7] Recent studies indicate that pumiliotoxin B binds to a unique

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(2) Myers, C. W.; Daly, J. W. *Sci. Am.* **1983**, *248*, 120.

(3) Märki, F.; Witkop, B. *Experentia* **1963**, *19*, 329.

(4) For recent general reviews, see: (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F. *Alkaloids* **1993**, *43*, 185. (b) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1.

(5) For a discussion of the possibility that the skin alkaloids of dendrobatid frogs may have a dietary origin, see: Daly, J. W.; Secunda, S. I. ; Garraffo, H. M.; Spande, T. F.; Wisnieski, A.; Cover, J. F., Jr. *Toxicon* **1994**, *32*, 657.

(6) These alkaloids were originally believed to be unique to dendrobatid frogs but recently have been found to have a wide distribution in amphibians: (a) Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F.; Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod.* **1993**, *56*, 1016. (b) Garraffo, H. M.; Spande, T. F. ; Daly, J. W.; Baldessari, A.; Gros, E. G. *J. Nat. Prod.* **1993**, *56*, 357.

(7) Daly, J. W.; Myers, C. W. *Science* (*Washington, D. C.*) **1967**, *156*, 970.

(8) Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. J.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 830.

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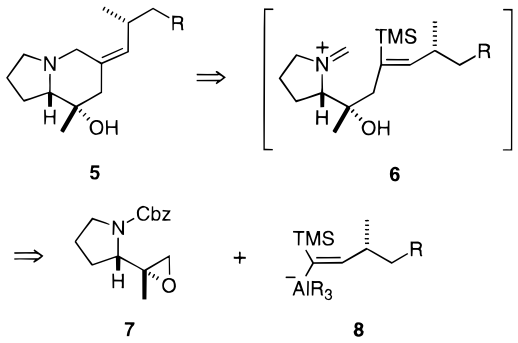
modulatory site on the voltage-dependent sodium channel and enhances sodium influx.[9] This ion flow stimulates phosphoinositide breakdown, which is believed to be ultimately expressed as cardiotonic and myotonic activities. Structure−activity studies of natural alkaloids and synthetic analogs have shown that the structure of the side chain is critical for these pharmacological activities.[9,10] The sodium channel of insects is a well established target for commercial insecticides, and several pumiliotoxin A alkaloids and congeners display useful insecticidal activity.[11]

Early reports of the marked cardiotonic and myotonic activity of pumiliotoxin B,[7] and the unlikelihood that the scarce Central American frogs could provide substantial amounts of these alkaloids, provided the stimulus for our synthetic endeavors in this area.[12] The first syntheses of pumiliotoxin 251D (**1**), pumiliotoxin A (**2**), and pumiliotoxin B (**3**) were reported from our laboratories in the early 1980s.[13−15] Pumiliotoxin A is obtained from amphibian sources as a mixture of C(15) epimers,[4,7] and our initial enantioselective synthesis established that the major epimer had the 15*S* configuration as depicted in Figure 1.[11] Similarly, our first synthesis of pumiliotoxin B rigorously established the full stereostructure of this pharmacologically important member of the pumiliotoxin A family. Herein we describe, with full experimental details, second-generation syntheses of **2** and **3**. These syntheses represent substantial improvement over our initial route and define practical procedures for obtaining gram quantities of these toxins and congeners.[16] The syntheses moreover highlight the utility of nucleophile-promoted iminium ion−alkyne cyclizations for constructing highly functionalized nitrogen heterocycles.

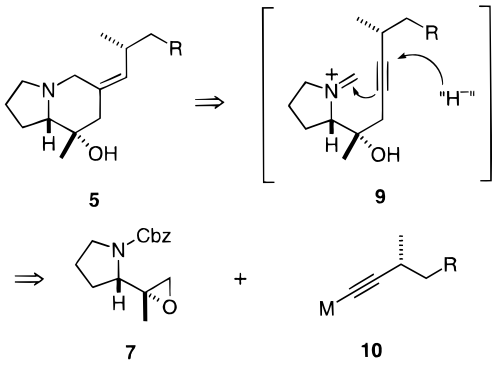
Results and Discussion

A. Synthetic Strategy. Our first-generation syntheses of the pumiliotoxin alkaloids employed a stereospecific iminium ion−vinylsilane cyclization to fashion the (*Z*)-alkylideneindolizidine ring (Scheme 1). Although ring construction in this strategy was efficient and completely stereocontrolled, coupling of the vinylsilane side chain (**8**) and pyrrolidine epoxide (**7**) fragments was often low yielding and required careful optimization for each side chain.[12] An alternate iminium ion cyclization approach to the pumiliotoxin A alkaloids is projected in Scheme 2 in which the stereochemistry of the alkylidene side chain would evolve from the stereoelectronic preference of electrophile−nucleophile pairs to add to alkynes in antarafacial fashion.[17] A "reductive" iminium ion−alkyne cyclization is

Scheme 1



Scheme 2



specifically represented in the conversion **9** → **5**, although we anticipated from the outset that surrogates for a hydride nucleophile would be required. Besides the conceptual simplicity of this strategy, we anticipated that use of a sterically unencumbered alkynyl nucleophile **10** would greatly facilitate joining the pyrrolidine and side-chain components.

B. Initial Model Studies. Synthesis of Nor-11-methylpumiliotoxin 237A (24). We chose initially to examine this new strategy in the synthesis of a simple pumiliotoxin A analog that lacked the C(11) methyl substituent. Since Fried had previously shown that alkynylalanes were excellent reagents for opening epoxides,[18] we began our investigations by examining the reaction of pyrrolidine epoxide **7**[14] and diethyl(1-hexynyl)alane (**12**) (Scheme 3). When 1 equiv of alane **12** (generated from sequential reaction of 1-hexyne (**11**) with *n*-BuLi and Et_2AlCl) was allowed to react with **7** at 0 °C in a mixture of toluene and hexane (7:1) followed by quenching with aqueous NH_4Cl, chlorohydrin **15** was formed as the major product together with a trace amount of alkynol **14**. However, when 2 equiv of alkynylalane **12** was employed, the desired coupled product **14** was formed, after NH_4Cl workup, in 95% yield. These results suggest that the initially formed alane−epoxide complex **13** undergoes ring opening by LiCl more rapidly than rearrangement to the diethylaluminum alkoxide precursor of **14**, while the reaction of this complex with a second equivalent of alane **12** to form ultimately **14** occurs more rapidly than reaction of **13** with LiCl.

Initial attempts to cleave the (benzyloxy)carbonyl group of **14** with a variety of standard reagents (TMSI, BBr_3, Me_2BBr, $AlCl_3$/EtSH, MeLi/LiBr, KOH/EtOH)[19] were not rewarding, with the acidic reagents bringing about partial destruction of the triple bond. The desired deprotection to afford **18** could be accomplished in ∼70% yield using excess $Ba(OH)_2$ in refluxing

(9) Gusovsky, F.; Padgett, W. L.; Creveling, C. R.; Daly, J. W. *Mol. Pharmacol.* **1992**, *42*, 1104, and references cited therein.

(10) (a) Daly, J. W.; McNeal, E. T.; Overman, L. E.; Ellison, D. H. *J. Med. Chem.* **1985**, *28*, 482. (b) Daly, J. W.; McNeal, E. T.; Gusovsky, F.; Ito, F.; Overman, L. E. *J. Med. Chem.* **1988**, *31*, 477. (c) Daly, J. W.; Gusovsky, F.; McNeal, E. T.; Secunda, S.; Bell, M.; Creveling, C. R.; Nishizawa, Y.; Overman, L. E.; Sharp, M. J.; Rossignol, D. P. *Biochem. Pharmacol.* **1990**, *40*, 315. (d) Siegl, P. K. S.; Overman, L. E. *Abstracts International Union of Physiological Sciences*, Vancouver, Canada, July 1986.

(11) 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.

(12) For a recent review of the total synthesis of pumiliotoxin A and allopumiliotoxin alkaloids, see: Franklin, A.; Overman, L. E. *Chem. Rev.* **1996**, *96*, 505.

(13) Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851.

(14) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192.

(15) Overman, L. E.; Lin, N.-H. *J. Org. Chem.* **1985**, *50*, 3669.

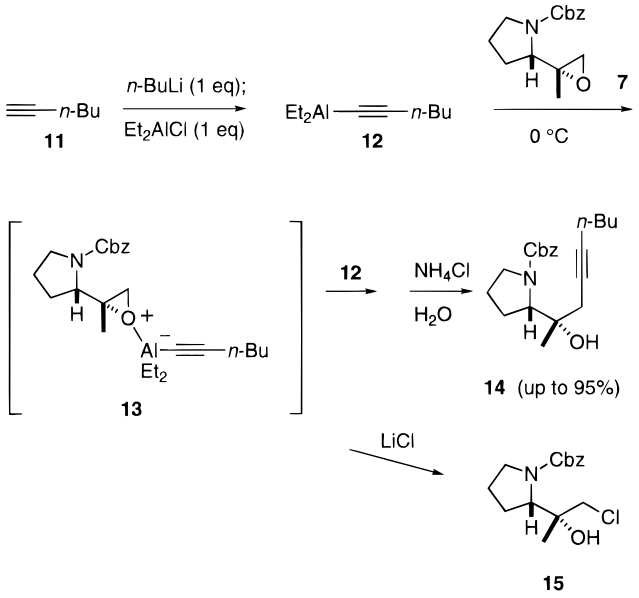
(16) This second generation synthesis of pumiliotoxin A has been reported in preliminary form: Overman, L. E.; Sharp, M. J. *Tetrahedron Lett.* **1988**, *29*, 901.

(17) Patai, S. *Chemistry of the Carbon−Carbon Triple Bond*, Wiley: New York, 1978.

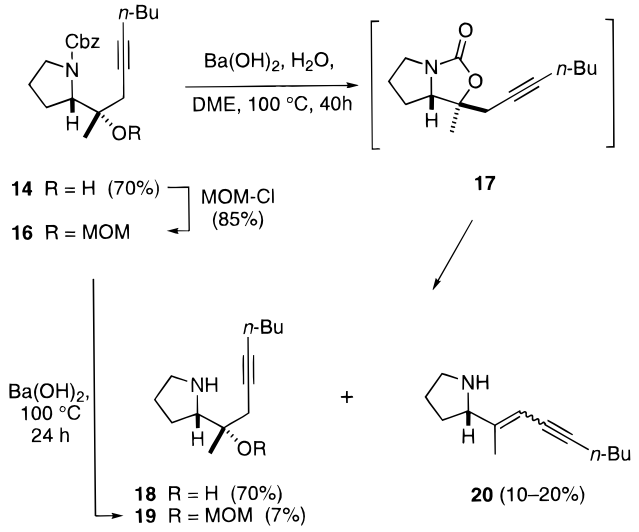
(18) (a) Fried, J.; Lin, C.-H.; Ford, S. H. *Tetrahedron Lett.* **1969**, 1379. (b) Fried, J.; Lin, C. H.; Sih, J. C.; Dalven, P.; Cooper, G. F. *J. Am. Chem. Soc.* **1972**, *94*, 4342.

(19) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley: New York, 1991; pp 335−338.

Scheme 3



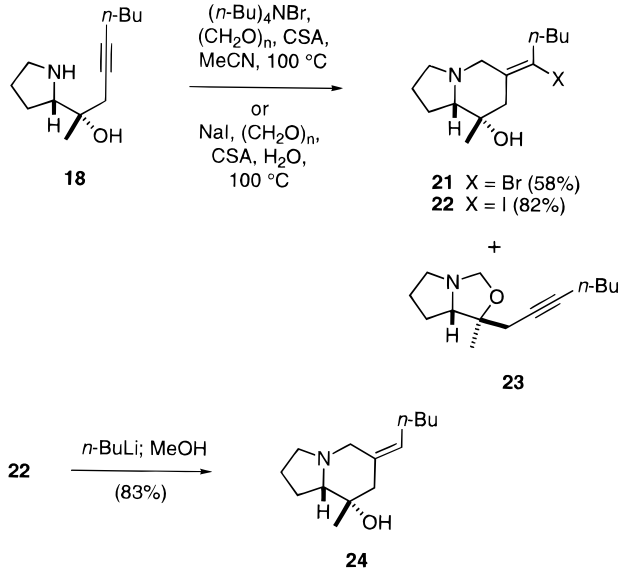
Scheme 4



DME−H_2O (Scheme 4). The moderate yield realized in this step was traced to competitive formation of enyne amine **20**. The oxazolidinone **17**, the likely intermediate in these conversions, could be prepared independently from **14** by reaction with LiOH at 60 °C. Subsequent treatment of **17** with $Ba(OH)_2$ in refluxing glyme−H_2O produced **18** and **20** in approximately the same yield and ratio as from **14**, supporting the intermediacy of the oxazolidinone in the direct hydrolysis. To determine whether the undesired elimination step would be less favorable if the homopropargylic oxygen was not acylated, MOM ether **16** was prepared from tertiary alcohol **14**. Not surprisingly, cleavage of the (benzyoxy)carbonyl group of this latter intermediate with $Ba(OH)_2$ was quite slow, providing only 7% of the secondary amine **19** after 24 h. Unfortunately, homopropargylic elimination was less affected and enyne **20** was isolated in 20% yield along with 68% of recovered **16**. Since amino alcohol **18** and enyne amine **20** were separated easily by silica gel chromatography, direct $Ba(OH)_2$ cleavage of the Cbz group was deemed workable, if not ideal.

The critical conversion of **18** to the alkylideneindolizidine ring system was attempted using the two conditions shown in Scheme 5, which earlier had proven effective for the synthesis

Scheme 5



of 3-alkylidenepiperidines from 4-alkynylamines.[20] Using 5 equiv of $(n\text{-Bu})_4NBr$ as the cyclization promoter and acetonitrile as solvent (in a sealed tube at 100 °C), the bromoalkylideneindolizidine **21** was isolated in 58% yield together with 18% of the oxazolidine **23**. The cyclization was more efficiently accomplished in H_2O in the presence of 10 equiv of NaI as the promoter and yielded the corresponding iodide **22** in 82% yield. Within the limits of detection by 300 MHz ^1H NMR and capillary GC analysis, both cyclizations afforded only the (*E*)-alkylidene product. Iodide **22** was quite sensitive to light and could not be stored without appreciable losses, so it was directly deiodinated by treatment at −78 °C in ether with 2.5 equiv of *n*-BuLi followed by protonation of the resulting vinyllithium alkoxide with MeOH to afford **24** in 83% yield. This sample was indistinguishable from an authentic sample,[14] thus confirming the expected antarafacial stereochemistry of the pivotal cyclization step.

C. Enantioselective Total Synthesis of (+)-15(*S*)-Pumiliotoxin A (2). The challenge in synthesizing the side chain of pumiliotoxin A is relating the C(11) and C(15) stereocenters, which are insulated by a *trans*-propenyl unit.[21] The strategy we chose to employ was to begin with the C(15) stereocenter, use it to introduce a temporary stereocenter at C(14), and then utilize the latter to deliver the C(11) stereocenter and *E* unsaturation through Ireland−Claisen rearrangement (Scheme 6).[22] The preparation starts with (*S*)-2-methyl-1-penten-3-ol (**25**), which at the time was obtained by Sharpless kinetic resolution.[23] Benzylation of the sodium salt of this alcohol followed by careful ozonolysis of the derived benzyl ether **26** at −78 °C in MeOH provided α-benzyloxy ketone **27** in 72% overall yield. Careful monitoring of the oxidation step by TLC was required to avoid oxidation of **27** to the corresponding benzoate ester. Condensation of **27** with vinylmagnesium bromide in THF occurred with a high degree of chelate

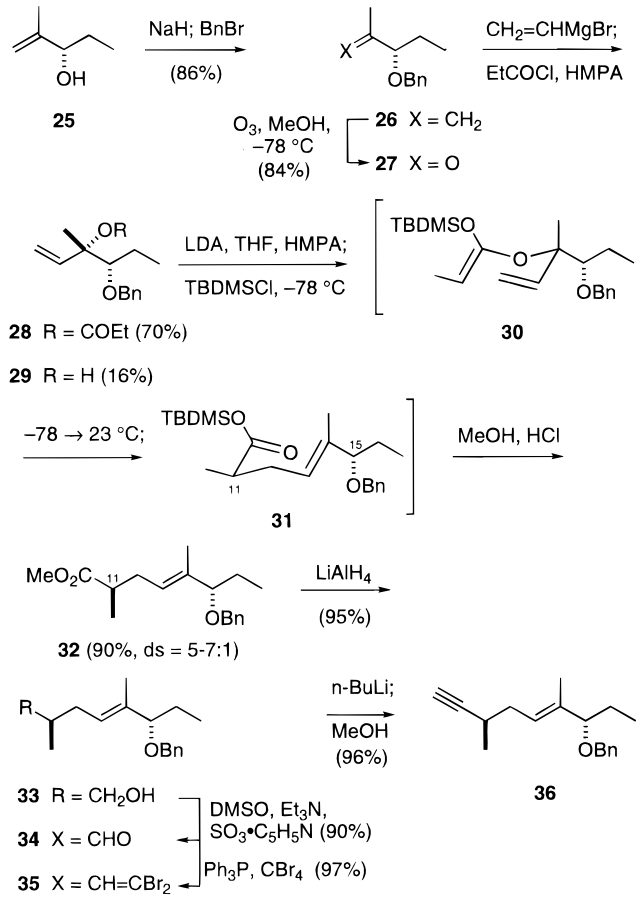
(20) (a) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612. (b) Arnold, H.; Overman, L. E.; Sharp, M. J.; Witschel, M. C. *Org. Synth.* **1991**, *70*, 111.

(21) We employ pumiliotoxin A numbering for synthetic intermediates in the Results and Discussion. IUPAC names (and numbering) for synthetic intermediates is provided in the Experimental Section. Standard abbreviations we use are defined in *J. Org. Chem.* **1996**, *61*, 22A.

(22) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(23) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

Scheme 6

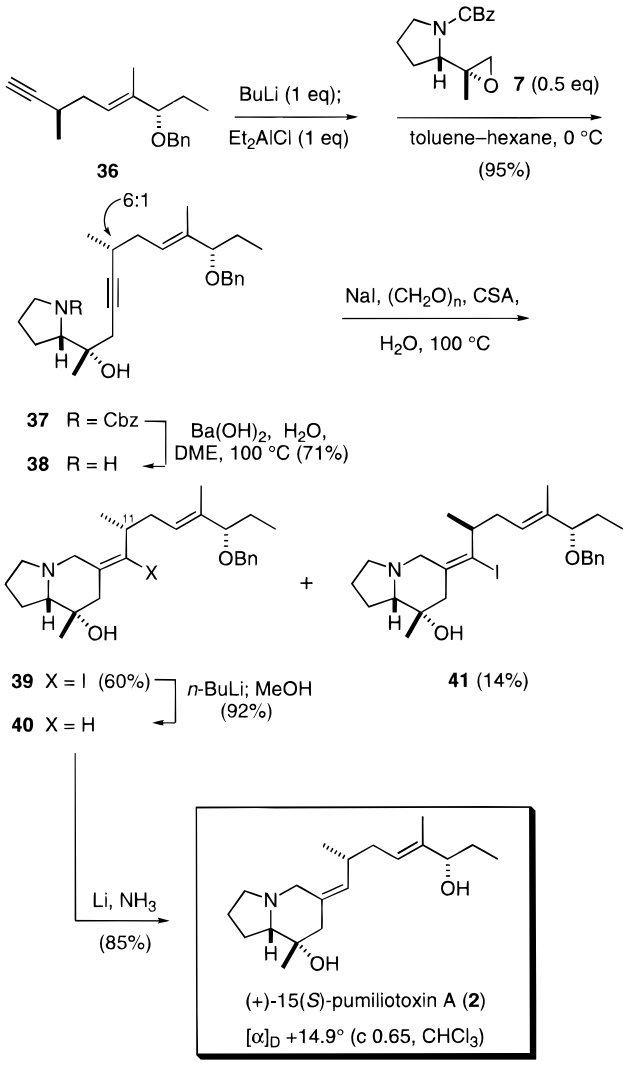


organization[24] to afford exclusively the *syn* hydroxy ether **29** upon hydrolytic quenching.[25] Addition of HMPA and propionyl chloride allowed the intermediate alkoxide to be trapped with moderate efficiency to provide propionate ester **28** (70% yield) directly along with alcohol **29** (16%). The (*Z*)-silylketene acetal derivative **30** was generated by sequential reaction of **28** with LDA at −78 °C in THF containing 23 vol % HMPA followed by silylation according to Ireland's procedure.[22] This intermediate underwent Claisen rearrangement upon warming to room temperature to deliver, after Fisher esterification, ester **32** and its C(11) epimer in 90% yield. Diastereoselection in this conversion ranged from 5:1 to 7:1, and is in accord with preferential rearrangement of **30** ⇀ **31** through a chair topography transition state having the larger 1-(benzyloxy)propyl group in an equatorial orientation. We were unable to separate the epimers of **32**, or the corresponding epimers of acyclic intermediates derived from them, and consequently removal of the unwanted 11*S*-epimer had to await formation of the alkylideneindolizidine ring.

Reduction of ester **32** provided alcohol **33**, which was most efficiently oxidized to aldehyde **34** by the Parikh−Doering procedure.[26] Dibromethylenation of **34**[27] then provided **35**, which upon sequential treatment with *n*-BuLi and MeOH delivered alkyne **36** in 96% yield. The synthesis of **36** (a ∼6:1 mixture of C(11) epimers) was accomplished in this fashion in 37% overall yield from (*S*)-2-methyl-1-penten-3-ol by way of seven isolated and purified intermediates.

(24) See, inter alia: Still, W. C.; McDonald, J. H., III *Tetrahedron Lett.* **1980**, *21*, 1031.
(25) We use exclusively to denote that no stereoisomer was detectable by careful high-field ^{1}H NMR analysis of the crude product.
(26) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(27) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769.

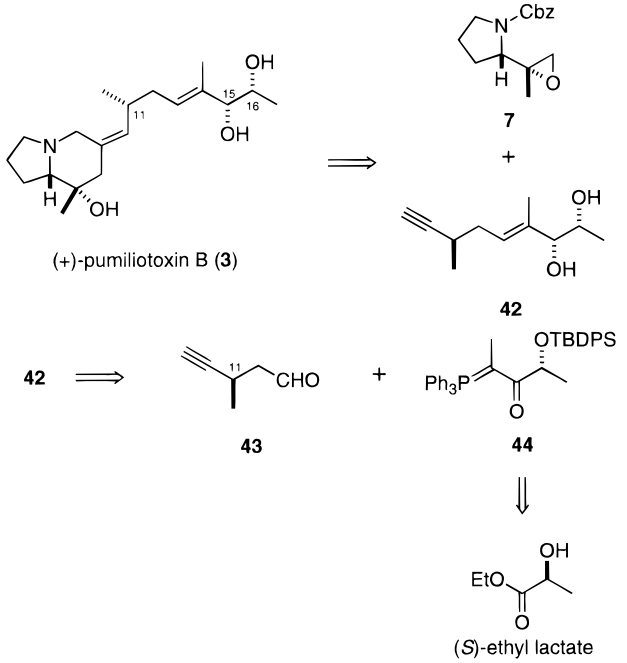
Scheme 7



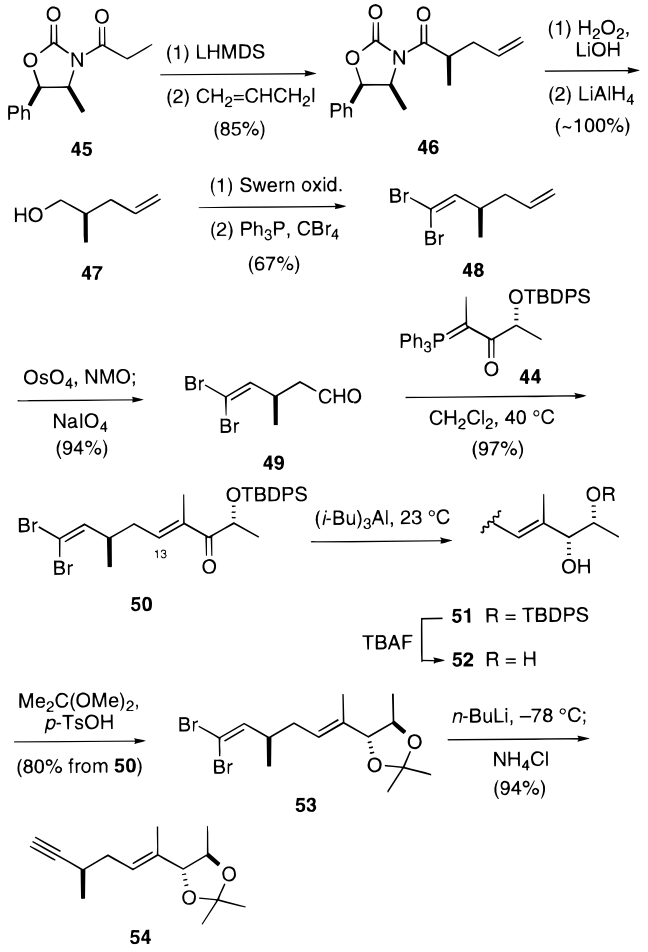
The synthesis of **2** was easily completed from alkyne **36** and epoxide **7** as summarized in Scheme 7. Coupling of **7** with 2 equiv of the diethylaluminum derivative of **36** proceeded efficiently to provide **37** in 95% yield. Since the nonpolar unreacted alkyne **36** was easily recovered in near quantitative yield, this key coupling step proceeded in excellent yield with net use of stoichiometric amounts of the coupling partners. Hydrolysis of **37** with hot aqueous $Ba(OH)_2$ then provided the secondary amine **38** in 71% yield. Iodide-promoted formaldiminium ion cyclization of **38** took place efficiently in H_2O at 100 °C, as in our earlier model study, to provide **39** and its C(11) epimer **40** in 80% yield. This mixture of C(11) epimers was readily separated on silica gel to give **39** (60% yield) and **41** (14% yield). Vinyl iodide **39** was immediately deiodinated by sequential treatment with *n*-BuLi and MeOH to provide the known[15] pumiliotoxin A precursor **40** in 75% yield (92% based on consumed **39**). Finally, careful debenzylation[15] of **40** provided **2** in 85% yield. This material was indistinguishable from an authentic specimen by TLC, capillary GLC, and 500 MHz ^{1}H NMR comparisons. The optical rotation of **2** prepared in this way was +14.9 (*c* 0.65, $CHCl_3$), which compares closely to the rotation reported[4b] for material isolated from *D. pumilio* (a 2:1 mixture of C(15) epimers): $[\alpha]_D$ +14.2 (*c* 0.51, $CHCl_3$) and that reported earlier by us[15] for synthetic **2**: $[\alpha]_D$ +13.9 (*c* 0.80, $CHCl_3$).

This improved synthesis of **2** was realized in five steps and 32% overall yield from alkyne **36** and epoxide **7**. The synthesis

Scheme 8



Scheme 9



proceeded in 13 steps and 12% overall yield from (*S*)-2-methyl-1-penten-3-ol (**25**), and 8 steps and 9% overall yield from *N*-[(benzyloxy)carbonyl]-L-proline, the commercially available precursor of pyrrolidine epoxide **7**.[14]

D. Enantioselective Total Synthesis of (+)-Pumiliotoxin B (3). We next turned our attention to the preparation of **3** by a related convergent sequence (Scheme 8). In this case, the *syn*-enynediol **42** would be required for coupling with pyrrolidine epoxide **7**. In our first total synthesis of **3**, we had employed the lactate-derived ylide **44** at the last stage of the synthesis to incorporate the five terminal carbons of the pumiliotoxin B side chain, with the C(15) stereocenter being introduced thereafter by Felkin selective reduction of an α-siloxy enone intermediate.[14,28] Utilization of a similar strategy to prepare the pumiliotoxin B side-chain fragment **42** would require access to (*R*)-3-methyl-4-pentynal (**43**) or an equivalent six-carbon fragment.[29]

Due to the expected volatility of ynal **43**, we chose as the six-carbon fragment the dibromo precursor **49**, which was best assembled by the sequence summarized in Scheme 9. Allylation of enantiopure propionyl oxazolidinone **45**, as described by Evans and co-workers in the enantiomeric series,[31] provided **46** as a single diastereomer in 85% yield. Removal of the oxazolidinone auxiliary with basic hydrogen peroxide,[32] followed by direct $LiAlH_4$ reduction of the crude acid provided (*R*)-2-methyl-4-penten-1-o1 (**47**) in excellent overall yield. Oxidation[33] of **47** to the corresponding aldehyde and then dibromomethylenation under standard conditions[27] provided dibromodiene **48** in 67% overall yield. Regioselective osmylation of the terminal vinyl group of this intermediate was readily accomplished to deliver aldehyde **49** in 94% yield after periodate cleavage. This intermediate was confirmed to be >95% ee by Mosher analysis[34] of the primary alcohol obtained by $NaBH_4$ reduction of **49**. This three-step sequence provided dibromopentenal **49** in a satisfactory 64% overall yield from pentenol **47**.

Condensation of **49** with phosphorane **44**[14] afforded exclusively (*E*)-enone **50**, which showed a diagnostic signal at δ 6.29 in the ^{1}H NMR spectrum for the C(13) vinylic hydrogen. Felkin selective reduction of α′-siloxyenone **50** with triisobutylaluminum[28] at room temperature in pentane and removal of the *tert*-butyldiphenylsilyl protecting group of **51** with TBAF provided *syn* diol **52**. Condensation of **52** with 2,2-dimethoxypropane then yielded acetonide **53**. The conversion of **50** to **53** could be accomplished in this way without purification of intermediates in 80% overall yield. Finally, generation of the alkyne from the dibromoalkene was accomplished under standard conditions to provide **54** in 94% yield. This eight-step sequence delivered the pumiliotoxin B side-chain precursor **54** with complete stereocontrol in an excellent overall yield of 46% from pentenol **47**.

A critical improvement in the preparation of the lactate-derived ylide **44** was essential in evolving this practical synthesis of the pumiliotoxin B side chain. In our earlier preparation of ylide **44**, the condensation with ethylidenetriphenylphosphorane was accomplished with a thiopyridyl ester of the lactate fragment.[14] Although this sequence was satisfactory for small-scale preparations of **44**, on larger scale, the purity and yield of the ylide prepared in this way was never high. The consequence of this problem was magnified by the dramatic effect the purity

(28) This sequence was first worked out during our early structural investigations: Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2741.

(29) An early, less efficient, route for preparing the pumiliotoxin B side chain was described in preliminary form.[30]

(30) Overman, L. E.; Robinson, L. A.; Zablocki, J. *J. Am. Chem. Soc.* **1992**, *114*, 368.

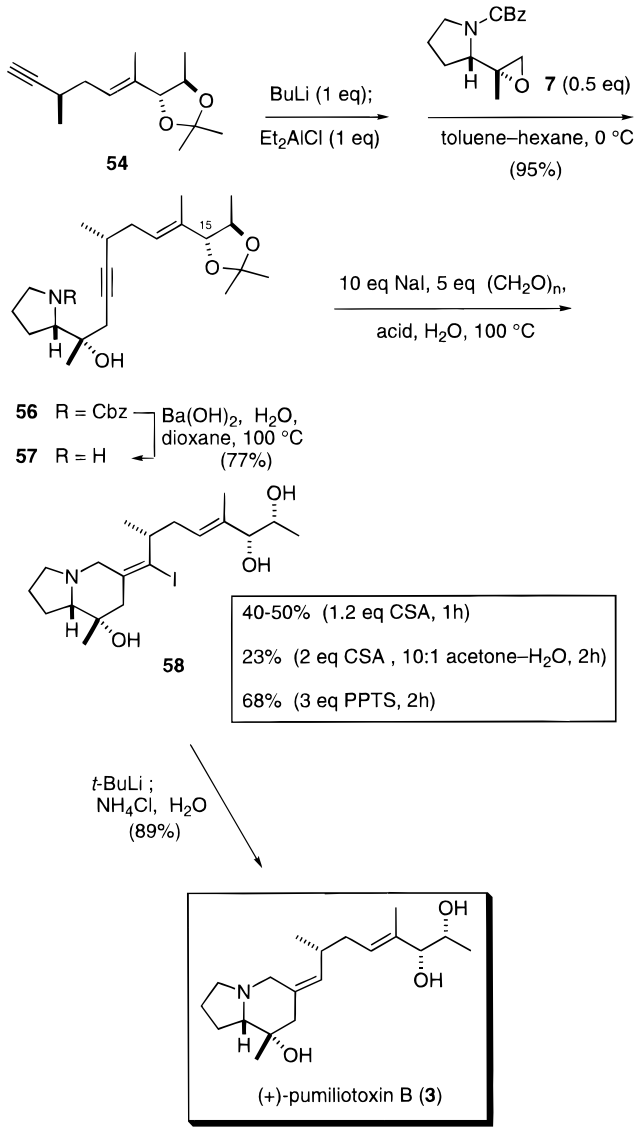
(31) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

(32) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83.

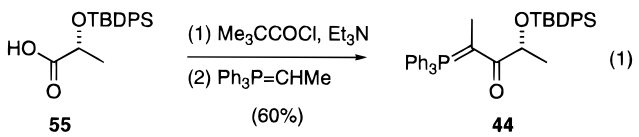
(33) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

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

Scheme 10



of **44** had on its condensation with pentenal **49**. Significant improvement in the synthesis of **44** was achieved when (*R*)-2(-*tert*-butyldiphenylsiloxy)propanoic acid (**55**)[14] was activated for coupling with ethylidenetriphenylphosphorane as the pivaloyl mixed anhydride (eq 1). This simple modification allowed ylide



(1)

44 to be conveniently prepared on 10−20 g scales and 25% overall yield from ethyl (*S*)-lactate.

The acetonide-protected alkyne side chain **54** was coupled with pyrrolidine epoxide **7** (Scheme 10), exactly as in our earlier synthesis of pumiliotoxin A, to afford **56** in 95% yield. In early chromatography fractions, the 1 equiv excess of **54** was recovered in 97% of theory. Hydrolytic removal of the carbamate group from adduct **56** with $Ba(OH)_2$ provided alkynylamine **57**. This step was faster using a 1.5:1 mixture of dioxane−H_2O (rather than DME−H_2O) as solvent and delivered **57** in 77% yield. As before, elimination to form the corresponding enyne was the predominant side reaction. In an attempt to side step this problem, we briefly examined whether the (benzyloxy)carbonyl protecting could be removed from epoxide **7** prior to the coupling step. However, attempted hydrogenolysis of epoxide **7** under a variety of conditions provided either intractable product mixtures or returned **7**.[35]

Iodide-promoted cyclization of the formaldiminium ion generated from **57** was examined in some detail. As summarized in Scheme 10, the yield of iodoalkylideneindolizidine **58** was only modest when iodide-promoted cyclization was carried out in the presence of a slight excess of camphorsulfonic acid (CSA). On the assumption that competing solvolysis at C(15) was occurring, we turned to the weak acid pyridinium *p*-toluenesulfonate (PPTS). When 1 equiv of PPTS was employed, iodide-promoted formaldiminium ion alkyne cyclization took place efficiently to give **58** and the corresponding acetonide. To simplify product isolation, 3 equiv of PPTS was employed, which resulted in both cyclization and isopropylidene cleavage to afford **58** in 51−68% yield on scales ranging from 50 to 500 mg. Again this pivotal cyclization reaction occurred with high stereoselectivity, since no trace of a stereoisomer of **58** was seen by 500 MHz ^{1}H NMR analysis of the cyclization product. Immediate deiodination of **58** by treatment with a large excess of *t*-BuLi at −78 °C, followed by protonolysis with degassed aqueous NH_4Cl, provided **3** in 89% yield. This material, $[\alpha]^{23}_D$ +20.1 (*c* 1.0, MeOH), was identical in all respects to a natural specimen and a sample of **3** prepared earlier in our laboratories.[14]

The synthesis of pumiliotoxin B summarized in Schemes 9 and 10 was sufficiently efficient that 500 mg of **3** could be prepared for biological and structural investigations. The overall yield of enantiopure **3** was 8% from *N*-[(benzyloxy)carbonyl]-L-proline and 10% from (4*S*,5*R*)-4-methyl-5-phenyl-2-oxazolidinone, the commercially available precursor of acyloxazolidinone **45**.[31]

Conclusion

The pumiliotoxin A alkaloids have proven to be valuable research tools in pharmacology and may serve as models for the development of new myotonic or cardiotonic agents.[4,9,10] The threatened existence of dendrobatid frogs in nature,[4] and the absence of alkaloids in captive-raised dendrobatid frogs,[36] highlight the importance of developing efficient syntheses of the pumiliotoxin A alkaloids. The iminium ion−alkyne cyclization route to the pumiliotoxin A alkaloids is sufficiently concise that 50−500 mg of the natural toxins can be prepared conveniently. Besides providing access to substantial quantities of the natural alkaloids, this chemistry readily can provide gram quantities of simple congeners.[10c,11,37]

The least satisfactory stage in the synthesis route documented here is removal of the (benzyloxy)carbonyl protecting group in the presence of the homopropargylic alcohol unit. A potential solution to this problem, introduced by Dow−Elanco chemists in their preparation of pumiliotoxin 251D and simpler analogs for insecticidal evaluation,[11] would be to employ the *tert*-butoxycarbonyl (BOC) analog of epoxide **7**[14] in coupling with the alkyne side chain. As they demonstrated in one case (and should be possible with many side chains), direct treatment of the derived adduct with NaI, formaldehyde, and acid can lead directly to the iodoalkylideneindolizidine product.[11]

The use of iodide-promoted formaldiminium ion−alkyne cyclizations to achieve efficient synthetic entry to the allopumiliotoxin alkaloids is described in the accompanying paper.[38]

(35) Hydrogenolysis conditions screened included: transfer hydrogenation with cyclohexene and Pd/C; transfer hydrogenation with formic acid and Pd/C or Pd black; H_2/Pd/C; H_2/PtO_2.

(36) Daly, J. W.; Secunda, S. I.; Gorraffo, H. M.; Spande, T. F.; Wisnieski, A.; Nishihiva, C.; Cover, J. F. *Toxicon* **1992**, *30*, 887.

(37) Bessard, Y.; Overman, L. E.; Rabinowitz, M. H., to be submitted.

Experimental Section[39]

(3*S*)-2-Methyl-3-(benzyloxy)pentene (26). To a stirred suspension of 1.6 g (33 mmol) of 50% sodium hydride dispersion in 20 mL of dry tetrahydrofuran was added 1.66 g (16.6 mmol) of (*S*)-2-methyl-1-penten-3-ol (**25**; $[\alpha]^{25}_D$ −4.9, *c* 0.63, $CHCl_3$). After the mixture was stirred 1 h at rt, 2.6 mL (21 mmol) of benzyl bromide and a catalytic amount of Me_4NCl were added and the resultant reaction mixture was stirred at room temperature for an additional 17 h. The reaction was then quenched by addition of saturated aqueous NH_4Cl, and the resulting mixture was extracted with ether (3 × 50 mL). The combined ether layers were washed with brine (50 mL) and dried ($MgSO_4$). Concentration provided 3 g of residue that was purified by flash chromatography on silica gel (100:1 hexane−Et_2O) to give 2.6 g (86%) of **26** as a colorless oil: R_f 0.70 (10:1 hexane−ether); $[\alpha]^{25}_D$ −26.7 (*c* 0.45, $CHCl_3$); IR ($CHCl_3$) 2974, 2941, 2879, 1657, 1456, 1066 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.26−7.35 (m, 5H), 4.98 (m, 1H), 4.93 (m, 1H), 4.40 (ABq, 2H, J = 12 Hz), 3.63 (t, 1H, J = 6.9 Hz), 1.71 (br s, 3H), 1.30−1.66 (m, 2H), 0.88 (t, 3H, J = 7.4 Hz); MS (isobutane, CI) *m/e* 191 (MH), 173, 161, 91; HRMS (EI) *m/e* 161.0985 (161.0966 calcd for $C_{11}H_{13}O$, M − C_2H_5).

(3*S*)-(Benzyloxy)-2-pentanone (27). A solution of **26** (1.0 g, 5.2 mmol) and 20 mL of MeOH was cooled to −78 °C, and O_3 was bubbled through the solution for 2 h. The reaction was carefully monitored by TLC analysis, and O_3 was purged with a stream of N_2 as soon as **26** was no longer detected. The reaction then was quenched by adding Me_2S (8 mL, 100 mmol) at −78 °C, and the resulting solution was allowed to warm to rt. Concentration then provided 2.5 g of residue that was chromatographed on silica gel (20:1 hexane−ether) to give 840 mg (84%) of ketone **27** as a colorless oil: R_f 0.42 (4:1 hexane−ether) $[\alpha]^{25}_D$ −113 (*c* 2.6, $CHCl_3$); IR ($CHCl_3$) 3030, 3000, 2960, 2900, 1725, 1505, 1450, 1390, 1130, 1080 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.34−7.38 (m, 5H), 4.53 (ABq, 2H, J = 11.7 Hz), 3.72 (t, 1H, J = 6.0 Hz), 2.19 (s, 3H), 1.68−1.80 (m, 2H), 0.87 (t, 3H, J = 7.2 Hz); MS (isobutane, CI) *m/e* 193 (MH), 91; HRMS (EI) *m/e* 192.1147 (192.1150 calcd for $C_{12}H_{16}O_2$).

(3*R*,4*S*)-3-Methyl-4-(benzyloxy)-1-hexene-3-yl propionate (28). Following the general procedure of Still,[24] a solution of vinylmagnesium bromide (12 mmol, 1 M solution in THF) and 20 mL of THF was added dropwise to a solution of ketone **27** (2.00 g, 10.4 mmol) and 6 mL of THF at room temperature over a 10 min period. After 3 h, HMPA (2.2 mL, 13 mmol) was added and after an additional 15 min propionyl chloride (1.8 mL, 20 mmol, freshly distilled from quinoline) was added dropwise. After the reaction was left overnight at rt, it was quenched with saturated aqueous NH_4Cl solution and diluted with ether (50 mL). The aqueous layer was separated and extracted with ether (3 × 100 mL); the combined organic layers were washed with H_2O (2 × 25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated to give a light yellow oil. This crude product was bulb-to-bulb distilled and further purified by chromatography on silica gel (100:1 hexane−ether) to afford (in order of elution) 2.0 g (70%) of ester **28** (R_f 0.50, 4:1 hexane−ether) and 346 mg (16%) of the corresponding alcohol **29** (R_f 0.25, 4:1 hexane−ether), both as colorless oils. Ester **28** exhibited the following spectral characteristics: $[\alpha]^{25}_D$ −10.2 (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 2950, 1735, 1460, 1360, 1280, 1240, 1145, 1100, cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.26−7.37 (m, 5H), 6.04 (dd, 1H, J = 10.9, 17.5 Hz), 5.25 (dd, 1H, J = 17.7, 1.0 Hz), 5.21 (dd, 1H, J = 11, 1.1 Hz), 4.88 (ABq, 2H, J = 11.3 Hz), 3.70 (dd, 1H, J = 2.8, 9.6 Hz), 2.29 (q, 1H, J = 8.0 Hz), 1.64 (s, 3H), 1.32−1.59 (m, 2H), 1.11 (t, 3H, J = 7.5 Hz), 0.98 (t, 3H, J = 7.4 Hz); MS (isobutane, CI) *m/e* 203 (MH − C_3H_6O); HRMS (EI) *m/e* 247.1318 (247.1329 calcd for $C_{17}H_{34}O_3$, M − C_2H_5).

Characterization data for alcohol **29**: $[\alpha]^{25}_D$ −21.2 (*c* 0.82, $CHCl_3$); IR ($CHCl_3$) 3857, 3676, 2975, 2940, 2878, 1645, 1206, 1097 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.25−7.36 (m, 5H), 5.98 (dd, 1H, J = 10.7, 17.3 Hz), 5.33 (dd, 1H, J = 16.9, 1.4 Hz), 5.14 (dd, 1H, J = 1.4 Hz, 9.3 Hz), 4.66 (s, 2H), 3.21 (dd, 1H, J = 9.5, 8.6 Hz), 2.30−2.3, (m, 1H), 1.49−1.69 (m, 2H), 1.25 (s, 3H), 1.02 (t, 3H, J = 7.4 Hz).

Methyl (2*R*,6*S*)-6-(benzyloxy)-2,5-dimethyl-4(*Z*)-enoate (32). Following the general procedure of Ireland,[22] a solution of LDA was prepared from *n*-BuLi (0.8 mL of a 2.50 M solution in hexane, 2.0 mmol) and diisopropylamine (0.30 mL, 2.1 mmol) in 3.3 mL of anhydrous THF at 0 °C under an Ar atmosphere. After 15 min at 0 °C, HMPA (1.6 mL) was added dropwise over 5 min and the stirred reaction mixture was cooled to −78 °C. After 15 min at −78 °C, ester **28** (500 mg, 1.81 mmol) was added dropwise. The reaction solution changed from light yellow to orange during the addition. The reaction was maintained at −78 °C for 1 h (the color was yellow at the end of this period), then a solution of TBDMS-Cl (0.35 g, 2.4 mmol) and THF (2.0 mL) was added in one portion, and the resulting solution was maintained at room temperature for 4.5 h. The reaction then was diluted with pentane (25 mL) and washed with H_2O (2.5 mL). The aqueous layer was acidified to pH 4.5 with 1 M HCl and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to afford crude **31** as a light yellow oil.

This material was dissolved in 25 mL of methanol, and 0.6 mL of 12 M HCl was added. After the reaction was maintained at room temperature overnight, it was concentrated and the residue was dissolved in ether (100 mL) and washed sequentially with saturated aqueous $NaHCO_3$(10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the resulting residue was chromatographed on silica gel (10:1 hexane−ether) to provide 475 mg (90%) of ester **32** as a ∼6:1 mixture of epimers (by ^1H NMR analysis): R_f 0.38 (4:1 hexane−ether); $[\alpha]^{25}_D$ −32.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3011, 2985, 1713, 1456, 1383, 1196, 1170, 1055 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.25−7.36 (m, 5H), 5.30 (t, 1H, J = 7.4 Hz), 4.31 (ABq, 2H, J = 12.0 Hz), 3.66 (s, 3H), 3.53 (t, 1H, J = 7.0 Hz), 2.26−2.56 (m, 3H), 1.49−1.69 (m, 2H), 1.59 (s, 3H), 1.19 (d, 3H, J = 6.9 Hz, minor isomer), 1.18 (d, 3H, J = 6.8 Hz, major isomer), 0.82 (t, 3H, J = 7.5 Hz); MS (isobutane, CI) *m/e* 183 (MH − $C_6H_5CH_2OH$); HRMS (EI) *m/e* 261.1490 (261.1483 calcd for $C_{18}H_{26}O_3$, M − C_2H_5).

(2*R*,6*S*)-2,5-Dimethyl-6-(benzyloxy)-4(*Z*)-octen-1-o1 (33). A solution of ester **32** (420 mg, 1.37 mmol) and dry Et_2O (4 mL) was added dropwise to a mixture of $LiAlH_4$ (76 mg, 2 mmol) and dry Et_2O (8 mL) at 0 °C. After being stirred for 1 h at 0 °C, the reaction was quenched by successive dropwise addition of H_2O (76 μL), 15% aqueous NaOH (76 μL) and water (0.23 mL) and allowed to stir at room temperature for 1 h. The reaction then was filtered through a pad of anhydrous $MgSO_4$, the filtrate was concentrated, and the residue was chromatographed on silica gel (1:1 hexane−ether) to afford 342 mg (95%) of alcohol **33** as a ∼7:1 mixture of epimers (by ^1H NMR analysis): R_f 0.05 (4:1 hexane−ether); $[\alpha]^{25}_D$ −29 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 3802, 3635, 3449, 2968, 2938, 2879, 1456, 1094, 1024 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.37 (br t, 1H, J = 7.4 Hz), 4.35 (ABq, 2H, J = 12.0 Hz), 3.56 (t, 1H, J = 7 Hz), 3.52 (m, 2H), 1.93−2.21 (m, 2H), 1.62−1.78 (m, 2H), 1.59 (s, 3H) 1.43−1.58 (m, 1H), 0.95 (d, 3H, J = 6.7 Hz, minor isomer), 0.93 (d, 3H, J = 6.7 Hz, major isomer), 0.84 (t, 3H, J = 7.5 Hz); MS (isobutane, CI) *m/e* 263 (MH), 155, 137, 107, 95, 91; HRMS (EI) *m/e* 233.1557 (233.1541 calcd for $C_{17}H_{26}O_2$, M − C_2H_5).

(2*R*,6*S*)-2,5-Dimethyl-6-(benzyloxy)-4(*Z*)-octenal (34). To a solution of alcohol **33** (600 mg, 2.3 mmol), Et_3N (2.2 mL, 16 mmol), and Me_2SO (5.7 mL) was added 1.1 g (6.9 mmol) of pyridine sulfur trioxide at rt.[26] After being stirred for 1 h at rt, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution. The aqueous layer was separated and extracted with ether (3 × 25 mL); the combined organic layers were dried ($MgSO_4$) and concentrated to afford 750 mg of a light yellow oil. Rapid purification of this oil on silica gel (10:1 hexane−ether) gave 535 mg (90%) of aldehyde **34** as a colorless oil, which was used immediately in the next step: R_f 0.42 (10:1 hexane−ether); $[\alpha]^{25}_D$ −43.3 (*c* 1.9, $CHCl_3$); IR ($CHCl_3$) 3019, 2973, 2944, 1732, 1518, 1457, 1069, 1027 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.67 (d, 1H, J = 1.3 Hz), 7.31 (m, 5H), 4.33 (ABq, 2H, J = 11.9 Hz), 3.54 (t, 1H, J = 7.0 Hz), 2.40−2.52 (m, 1H), 2.18−2.24 (m, 1H), 1.45−1.70 (m, 2H), 1.60 (s, 3H), 1.13 (d, 3H, J = 6.9 Hz, minor isomer), 1.12 (d, 3H, J = 7.0 Hz, major isomer), 0.83 (t, 3H, J = 7.4 Hz); MS (isobutane, CI) *m/e* 153 (MH − $PhCH_2OH$, 100).

(3*R*,7*S*)-2,6-Dimethyl-7-(benzyloxy)-1,1-dibromo-1,5(*Z*)-nonadiene (35). The general procedure of Corey and Fuchs was followed.[27] To a mixture of Ph_3P (3.2 g, 12 mmol), CBr_4 (2.0 g, 6 mmol, freshly

(38) Caderas, C.; Lett, R. M.; Overman, L. E.; Rabinowitz, J.; Robinson, L. A.; Sharp, M. J.; Zablocki, J., following paper in this issue.

(39) For general experimental details, see: Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.

sublimed) and CH_2Cl_2 (30 mL) was added 280 mg (2.0 mmol) of anhydrous K_2CO_3. After being stirred for 30 min at rt, a solution of aldehyde **34** (535 mg, 2.05 mmol) and CH_2Cl_2 (15 mL) was added and the resulting mixture was stirred at room temperature for 45 min. The reaction then was poured into pentane (400 mL), the resulting mixture was filtered, and the filtrate was concentrated. The residue was washed exhaustively with EtOAc, the combined extracts were concentrated, and the residue was chromatographed on silica gel (10:1 hexane−ether) to provide 835 mg (97%) of dibromide **35** as a colorless oil, which was a ∼6:1 mixture of epimers (by ^{1}H NMR analysis): R_f 0.69 (10:1 hexane−ether); $[\alpha]^{25}_D$ −14.9 (*c* 0.90, $CHCl_3$); IR ($CHCl_3$) 2968, 2936, 1613, 1455, 1378 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 5H), 6.74 (d, 1H, J = 9.4 Hz), 5.34 (t, 1H, J = 7.2 Hz), 4.37 (ABq, 2H, J = 11.9 Hz), 3.57 (t, 1H, J = 7.0 Hz), 2.62 (m, 1H), 2.10−2.23 (m, 2H), 1.46−1.75 (m, 2H), 1.59 (s, 3H), 1.06 (d, 3H, J = 6.6 Hz, major isomer), 1.02 (d, 3H, J = 6.8 Hz, minor isomer), 0.86 (t, 3H, J = 7.4 Hz, major isomer), 0.90 (t, 3H, J = 7.5 Hz, minor isomer); MS (isobutane, CI) *m/e* 309 (MH − $PhCH_2OH$, 100).

(3*R*,7*S*)-3,6-Dimethyl-7-(benzyloxy)-5(*E*)-nonen-1-yne (36). Under an argon atmosphere, *n*-BuLi (0.30 mL of a 2.1 M solution in hexane, 0.63 mmol) was added dropwise to a solution of dibromide **36** (125 mg, 0.30 mmol) and THF (4.0 mL) at −78 °C. This solution was maintained at −78 °C for 45 min and then quenched with MeOH (0.2 mL). The resulting mixture was allowed to warm to room temperature and then was partitioned between CH_2Cl_2 (50 mL) and brine (20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (50:1 hexane−ether) gave 74 mg (96%) of **36** as a clear oil, which was a ∼6:1 mixture of epimers (by ^{1}H NMR analysis): IR (film) 3308, 2967, 2874, 1454, 1068, 697, 630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.22 (m, 5H), 5.43 (br t, 1H, J = 7.3 Hz), 4.38 (ABq, 2H, J = 11.9 Hz, major isomer), 4.37 (ABq, 2H, J = 11.9 Hz, minor isomer), 3.58 (t, 1H, J = 7.0 Hz), 2.54 (m, 1H), 2.30 (m, 2H), 2.06 (d, 1H, J = 2.4 Hz), 1.78−1.45 (m, 4H), 1.64 (s, 3H), 1.23 (d, 3H, J = 6.7 Hz), 0.82 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 139.7, 137.0, 128.9, 128.5, 127.9, 126.8, 89.5, 87.2, 70.2, 69.0, 35.3, 27.2, 26.7, 21.2, 11.4, 11.1 ppm; HRMS (EI) *m/e* 227.1438 (227.1436 calcd for $C_{16}H_{19}O$, M − C_2H_5).

Benzyl 2-[(1*S*,5*R*,9*S*)-9-benzyloxy-1-hydroxy-1,5,8-trimethyl-3-undec-7(*E*)-en-3-ynyl]-1(*S*)-pyrrolidinecarboxylate (37). Under an Ar atmosphere, *n*-BuLi (0.43 mL of a 2.1 M solution in hexanes, 0.90 mmol) was added dropwise to a solution of **36** (240 mg, 0.95 mmol) and anhydrous toluene (1.5 mL) at 0 °C. After 15 min, Et_2AlCl (0.51 mL of a 1.8 M solution in toluene) was added dropwise to this stirring solution. The resulting mixture was stirred for 1 h at 0 °C during which time LiCl precipitated. A solution of the epoxide **7** (119 mg, 0.456 mmol) and dry toluene (0.5 mL) was then added dropwise. The resulting mixture was stirred at 0 °C, for 15 min and then quenched with saturated aqueous NH_4Cl (20 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (2:1 hexane−ethyl acetate) gave 210 mg (95%) of alcohol **37** as a clear oil, which was a ∼6:1 mixture of epimers (by ^{1}H NMR analysis): $[\alpha]^{25}_D$ −37.6 (*c* 8.9, $CHCl_3$); IR (film) 3386, 1674, 1410, 1356, 1114, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.24 (m, 10H), 5.46 (br t, 1H, J = 6.5 Hz), 5.38 (br s, 1H), 5.15 (s, 2H), 4.31 (ABq, 2H, J = 11.9 Hz, major isomer), 4.30 (ABq, 2H, J = 11.9 Hz, minor isomer), 4.22 (m, 1H), 3.73 (m, 1H), 3.58 (t, 1H, J = 6.9 Hz), 3.26 (m, 1H), 2.60−1.42 (m, 11H), 1.60 (s, 3H), 1.18 (d, 3H, J = 6.8 Hz), 1.12 (s, 3H), 0.85 (t, 3H, J = 7.4 Hz); MS (CI, isobutane) *m/e* 518 (MH), 410, 392, 302, 258; HRMS (EI) *m/e* 488.2789 (488.2801 calcd for $C_{31}H_{38}NO_4$, M − C_2H_5).

(*S*)-2-[(1*S*,5*R*,9*S*)-9-(Benzyloxy)-1-hydroxy-1,5,8-trimethyl-7(*E*)-undecyen-3-nyl]pyrrolidine (38). A mixture of carbamate **37** (234 mg, 0.453 mmol), DME (10 mL), H_2O (6 mL), and $Ba(OH)_2{\cdot}8H_2O$ (710 mg, 2.2 mmol) was heated at reflux under an Ar atmosphere for 50 h. The resulting mixture was allowed to cool to rt, and CO_2 gas was bubbled through the solution to precipitate barium salts. Filtration, concentration of the filtrate, and purification of the residue by chromatography (10:10:0.1 hexane−ethyl acetate−Et_3N) gave 123 mg (71%) of **38** as a clear oil, which was a ∼6:1 mixture of epimers (by ^{1}H NMR analysis) at C(11): $[\alpha]^{23}_D$ −40.3, (*c* 0.92, $CHCl_3$); IR (film) 3437, 3356, 2966, 2966, 3933, 1456, 1375, 1331, 1068, 731, 693 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5H), 5.43 (br t, 1H, J = 7.2 Hz), 4.37 (ABq, 2H, J = 11.9 Hz, major isomer), 4.36 (ABq, 2H, J = 11.8 Hz, minor isomer), 3.56 (t, 1H, J = 6.9 Hz), 3.30 (m, 1H), 2.97 (m, 1H), 2.50 (m, 1H), 2.31−2.17 (m, 3H), 1.79−1.37 (m, 8H), 1.60 (s, 3H), 1.19 (s, 3H), 1.17 (d, 3H, J = 6.9 Hz), 0.85 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 139.7, 136.5, 128.9, 128.3, 127.9, 127.2, 87.2, 77.9, 72.4, 70.1, 64.2, 47.5, 35.7, 32.9, 27.1, 26.9, 26.6, 23.5, 21.6, 11.4, 10.9; HRMS (EI) *m/e* 292.2282 (292.2276 calc for $C_{18}H_{30}NO_2$, M-Bn).

(8*S*,8a*S*)-8-Hydroxy-8-methyl-(6*E*)-[(2*R*,4*E*,6*S*)-6-(benzyloxy)-2,5-dimethyl-1-iodo-4-octenylidene]octahydroindolizine (39). A solution of **38** (100 mg, 0.26 mmol), camphorsulfonic acid (77 mg, 0.31 mmol), NaI (460 mg, 3.1 mmol), and H_2O (2.5 mL) was heated in a sealed vial at 100 °C for 1 h. The resulting mixture was allowed to cool to room temperature and then was partitioned between CH_2Cl_2 (40 mL) and 1 M aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by chromatography (2:1 hexane−ethyl acetate) gave 82 mg (60%) of **39** as an unstable yellow oil (lower R_f) and 20 mg (14%) of the C(11) epimer **41** (higher R_f). Characterization data for **39**: $[\alpha]^{23}_D$ −16.0 (*c* 1.0, $CHCl_3$); IR (film) 3362, 2967, 2874, 1454, 1395, 1310, 1095, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5H), 5.16 (br t, 1H, J = 6.9 Hz), 4.29 (ABq, 2H, J = 11.8 Hz), 4.12 (d, 1H, J = 12.6 Hz), 3.50 (t, 1H, J = 6.9 Hz), 3.06 (m, 1H), 3.01 (d, 1H, J = 14.7 Hz), 2.61 (br s, 1H), 2.44 (d, 1H, J = 12.9 Hz), 2.40−2.00 (m, 4H), 1.93 (d, 1H, J = 14.6 Hz), 1.80−1.42 (m, 6H), 1.62 (s, 3H), 1.13 (s, 3H), 1.08 (d, 3H, J = 6.3 Hz), 0.83 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 139.7, 136.3, 135.8, 128.9, 128.4, 127.9, 126.9, 120.9, 87.4, 72.5, 70.2, 69.6, 55.6, 54.8, 54.5, 39.9, 36.7, 27.1, 24.9, 23.9, 23.6, 23.2, 22.0, 11.9, 11.0 ppm; MS (CI, isobutane) *m/e* 524 (MH), 416, 396, 290; HRMS (EI) *m/e* 416.1431 (416.1456 calcd for $C_{19}H_{31}NOI$, M − OBn).

(8*S*,8a*S*)-8-Hydroxy-8-methyl-(6*Z*)-[(2*R*,4*E*,6*S*)-6-(benzyloxy)-2,5-dimethyl-4-octenylidene]octahydroindolizidine (40). Under an Ar atmosphere, *n*-BuLi (0.20 mL of a 2.1 M solution in hexane, 0.41 mmol) was added dropwise to a solution of the vinyl iodide **39** (72 mg, 0.14 mmol) and dry Et_2O (1.0 mL) at −78 °C. The resulting solution was maintained at −78 °C for 20 min and then MeOH (30 μL) was added. The resulting mixture was allowed to warm to room temperature and then was partitioned between CH_2Cl_2 (20 mL) and brine (10 mL). The organic layer was separated, dried (K_2CO_3), and concentrated. Purification of the residue by chromatography (100:1:0.1 $CHCl_3$−MeOH−12 M NH_4OH) gave 41 mg (75%) of **40** (92% based on consumed starting material) as a clear oil that was identical to an authentic sample:[15] $[\alpha]_D$ −2.1, $[\alpha]_{577}$ −1.9, $[\alpha]_{546}$ −2.6 (*c* 0.70, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 5.27 (t, 1H, J = 7.2 Hz), 5.10 (d, 1H, J = 9.6 Hz), 4.32 (ABq, 2H, J = 11.9 Hz), 3.80 (d, 2H, 1H, J = 11.7 Hz), 3.52 (t, 1H, J = 6.9 Hz), 3.06 (m, 1H), 2.66 (br s, 1H), 2.52 (m, 1H), 2.34 (d, 1H, J = 11.8 Hz), 2.20 (m, 1H), 2.10 (ABq, 2H, J = 13.8 Hz), 2.05−1.90 (m, 3H), 1.79−1.48 (m, 6H), 1.56 (s, 3H), 1.11 (s, 3H), 1.01 (d, 3H, J = 6.6 Hz), 0.83 (t, 3H, J = 7.3 Hz).

(+)-15(*S*)-Pumiliotoxin A (2). Under an Ar atmosphere, a solution of **40** (40 mg, 0.10 mmol), anhydrous THF (5 mL), and liquid NH_3 (∼20 mL) was treated with excess Li until the blue color persisted for several minutes. Then MeOH (1 mL) and saturated aqueous NH_4Cl (5 mL) were added, and the resulting mixture was allowed to warm to rt. This mixture was diluted with brine (10 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried (K_2CO_3) and concentrated; the residue was purified (50:1:0.1 $CHCl_3$−MeOH−12 NH_4OH) to give 26 mg (85%) of (+)-15(*S*)-pumiliotoxin A (**2**), which was identical by TLC, ^{1}H NMR, and ^{13}C NMR comparisons to the major epimer of the natural isolate: $[\alpha]^{23}_D$ +14.9 (*c* 0.65, $CHCl_3$).

(2*R*)-2-Methyl-4-pentenol (47). A solution of aqueous 30% H_2O_2 (4.4 mL, 40 mmol) and LiOH (0.46 g, 19 mmol, in 6 mL of H_2O) was added to a solution of imide **46** (2.63 g, 9.63 mmol, prepared from the (4*S*,5*R*)-propionyloxazolidinone **45** exactly as described by Evans and co-workers for the enantiomer) and THF−H_2O (48 mL of a 3:1 solution) at 0 °C.[31,32] After 1 h, excess peroxide was quenched by the addition of 1.5 M Na_2SO_3 (29 mL, 43 mmol) and the mixture was concentrated. The resulting residue (pH ∼10) was washed with CH_2-

Cl_2 (3 × 50 mL), and the aqueous phase was acidified to pH 1 with 1 M HCl and extracted into Et_2O (3 × 50 mL). The combined ethereal extracts were dried ($MgSO_4$) and concentrated to give the crude acid as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.13−5.04 (m, 2H), 2.56 (sextet, 1H, J = 6.9 Hz), 2.50−2.15 (m, 2H), 1.19 (d, 3H, J = 6.9 Hz).

A solution of $LiAlH_4$ (12.5 mL of a 1 M solution in Et_2O) was added dropwise to a solution of this sample of (*R*)-2-methyl-4-pentenoic acid and Et_2O (42 mL) at 0 °C. The resulting mixture was stirred at room temperature for 4 h and then cooled to 0 °C. Excess hydride was quenched by the addition of H_2O (475 μL), 15% aqueous NaOH (475 μL), and H_2O (1.42 mL). Anhydrous Na_2SO_4 was added, and the resulting suspension was stirred at room temperature for 12h. Filtration through Celite and removal of solvent by distillation at atmospheric pressure gave alcohol **47** (0.96 g, 100%) as a light yellow oil that was sufficiently pure for the next step: $[\alpha]^{23}_D$ +2.6 (*c* 1.5, $CHCl_3$); $[\alpha]_D$ −2.3 (*c* 1.0, $CHCl_3$) is reported for the enantiomer).[31]

(*R*)-1,1-Dibromo-3-methyl-1,5-hexadiene (48). Following the general procedure of Swern,[33] a solution of oxalyl chloride (5.9 g, 47 mmol) and CH_2Cl_2 (100 mL) was cooled to −78 °C and a solution of DMSO (7.3 g, 94 mmol) and CH_2Cl_2 (10 mL) was added dropwise from a pressure-equalizing dropping funnel. After 5 min, a solution of alcohol **47** (4.25 g, 42.5 mmol) and 30 mL of CH_2Cl_2 was added dropwise from a second addition funnel. The mixture was maintained at −78 °C for 20 min, and then Et_3N (22 g, 210 mmol) was added over 5 min, during which time the reaction became a colorless heterogeneous mixture. After being stirred for 5 min, the bath was removed and the reaction mixture was allowed to warm to room temperature over 1.5 h. Water (70 mL) then was added, and the resulting mixture was washed with 1 M HCl (4 × 50 mL), saturated aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). After filtration, the solution was concentrated by distillation (bath temperature 60 °C) under reduced pressure (160 mm) to a final volume of 50 mL. The resulting CH_2Cl_2 solution of the crude aldehyde was used directly in the next step. An aliquot was examined by ^{1}H NMR and found to be contaminated only with solvent: 300 MHz ($CDCl_3$) δ 9.66 (d, 1H, J = 1.2 Hz), 5.76 (m, 1H), 5.09 (m, 2H), 2.45 (m, 2H), 2.18 (m, 1H), 1.11 (d, 3H).

To a −14 °C solution of Ph_3P (61 g, 230 mmol) and CH_2Cl_2 (230 mL) was added a solution of CBr_4 (38 g, 115 mmol; freshly sublimed) and CH_2Cl_2 (50 mL) by syringe pump over 15 min.[27] (The CH_2Cl_2 solution of CBr_4 was passed through activity I basic Al_2O_3 immediately prior to use. Failure to remove traces of HBr caused, in some runs, partial epimerization of the sensitive aldehyde.) The resulting solution was then cooled to −78 °C, and the solution of the aldehyde (∼43 mmol) was added by syringe pump over 20 min. The reaction vessel was placed in an ice bath and allowed to stir at 0 °C for 1.5 h. The reaction mixture was poured into 1 L of pentane, and the precipitate was removed by filtration through Celite. The solid residue was dissolved in 50 mL of CH_2Cl_2, reprecipitated with 200 mL of pentane, and filtered (this process was repeated a total of three times). The combined pentane filtrates were concentrated at room temperature (130 mm), and the resulting liquid was purified on silica gel (pentane) to give dibromodiene **48** (7.23 g, 67% from alcohol **47**) as a clear liquid: $[\alpha]^{20}_D$ +3.5; $[\alpha]_{405}$ +18.9, $[\alpha]_{435}$ +11.3, $[\alpha]_{546}$ +7.1, $[\alpha]_{577}$ +6.2 (*c* 0.39, $CHCl_3$); IR (film) 2962, 2871, 1641, 1615, 1454, 786 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (d, 1H, J = 9.5 Hz), 5.73 (m, 1H), 5.03 (m, 2H), 2.59 (m, 1H), 2.10 (m, 2H), 1.02 (d, 3H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 143.4, 135.5, 116.8, 87.7, 40.0, 38.0, 18.6 ppm; MS *m/e* 253.9091 (253.9128 calcd for $C_7H_{10}{}^{79}Br^{81}Br$).

(*R*)-5,5-Dibromo-3-methyl-4-pentenal (49). To a solution of *N*-methylmorpholine *N*-oxide (4.0 g, 30 mmol) and 20 mL of 5:2 acetone-water was added a solution of OsO_4 in *tert*-butyl alcohol (2.8 g, 2.5% w/w, ∼0.3 mmol of OsO_4), and the heterogeneous mixture was stirred vigorously. Dibromodiene **48** (7.0 g, 27 mmol) then was added dropwise, and the flask containing the diene was rinsed with 1 mL of acetone, which also was added to the reaction mixture. The biphasic mixture was stirred at room temperature for 14 h and then quenched by the addition of $Na_2S_2O_4$ (1 g), Florisil (10 g), and H_2O (50 mL). This mixture was neutralized to pH 7 with 1 M HCl and then was concentrated. The resulting aqueous suspension was acidified further to pH 1 with 1 M HCl and extracted with EtOAc (4 × 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a ∼1:1 mixture of diastereomeric diols (by ^{1}H NMR analysis) as a slightly brown viscous oil (7.6 g, 96%). This mixture was used directly in the next step.

The diols were dissolved in 70 mL of THF, and $NaIO_4$ (8.5 g, 40 mmol) was added with stirring in one portion. Water (70 mL) then was added over 5 min to the stirred slurry. After 1 h, ∼30 mL of the THF was removed by concentration (100 mm) at rt. The resulting white slurry was extracted with ether (4 × 50 mL), washed with brine, dried ($MgSO_4$), and concentrated to give aldehyde **49** (6.59 g, 94% from diene **48**) as a brown oil that was ∼90% pure by GLC analysis and was sufficiently pure for use in the next step.

A pure sample of **49** was obtained by silica gel chromatography (9:1 hexanes−EtOAc): $[\alpha]_D^{20}$ −24 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 6.32 (d, 1H, J = 9.3 Hz), 3.10 (m, 1H), 2.51 (m, 2H), 1.14 (d, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 200.3, 141.5, 89.3, 49.0, 33.1, 19.0 ppm.

(3*R*,5*E*,8*R*)-8-*tert*-Butyldiphenylsiloxy-1,1-dibromo-3,6-dimethyl-7-oxo-1,5-nonadiene (50). A solution of pure ylide **44** (1.66 g, 2.77 mmol), crude aldehyde **49** (251 mg, ∼1 mmol), and CH_2Cl_2 (6 mL) was carefully deoxygenated with dry N_2 for 0.5 h and then heated at reflux for 48 h under a N_2 atmosphere. Concentration gave an orange oil that was purified on silica gel (20:1 hexane−EtOAc) to give enone **50** (560 mg, 97%) as a light yellow oil: $[\alpha]^{22}_D$ +1.6, $[\alpha]_{577}$ +1.9, $[\alpha]_{546}$ +4.1, $[\alpha]_{435}$ +19.2 (*c* 2.7, $CHCl_3$); IR (film) 2931, 1684, 1473, 1428, 1148, 1113, 1093 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.30 (m, 10H), 6.29 (app dt, 1H, J = 7.3, 1.3 Hz), 6.13 (d, 1H, J = 9.4 Hz), 4.80 (q, 1H, J = 6.8 Hz), 2.51 (m, 1H), 2.15 (m, 2H), 1.65 (br s, 3H), 1.34 (d, 3H, J = 6.8 Hz), 1.09 (s, 9H), 0.97 (d, 3H, J = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 142.6, 138.9, 136.2, 135.9, 135.7, 133.7, 133.2, 129.7, 127.6, 127.5, 88.6, 71.4, 37.9, 34.8, 26.9, 22.1, 19.2, 18.9, 11.9 ppm; MS (isobutane CI) *m/e* 521 (M − *t*-Bu), 501 (M − Ph), 420, 393; HRMS (EI) *m/e* 520.9962 (520.9970 calcd for $C_{23}H_{25}Br_2O_2Si$, M − *t*-Bu). Anal. Calcd for $C_{27}H_{34}Br_2O_2Si$: C, 56.07; H, 5.88. Found: C, 57.28; H, 5.95.

(3*R*,5*E*,7*R*,8*R*)-8-(*tert*-Butyldiphenylsiloxy)-1,1-dibromo-3,6-dimethyl-7-hydroxy-1,5-nonadiene (51). A solution of enone **50** (270 mg, 0.47 mmol) and pentane (8.5 mL) was treated dropwise with triisobutylaluminum (0.94 mL of a 1 M solution in toluene) at rt.[28] The initially colorless solution became bright yellow during addition of the first equivalent of triisobutylaluminum, and then faded to colorless upon addition of the second equivalent. The reaction was maintained at room temperature for 1 h and then quenched by the addition of saturated aqueous NH_4Cl (10 mL). Rochelle's salt was added, and the mixture was stirred vigorously for 20 min. The resulting mixture was extracted into EtOAc (5 × 10 mL), and the organic phase was dried (Na_2SO_4). Concentration gave **51** (270 mg, 98%) as a pale yellow oil, which appeared to be a single stereoisomer by ^{1}H NMR analysis and was used without further purification.

A sample of **51** was purified on silica gel (20:1 hexane−EtOAc) to provide a pure specimen: $[\alpha]^{22}_D$ −10.9, $[\alpha]_{577}$ −1.3, $[\alpha]_{546}$ +11.4, $[\alpha]_{435}$ +72.8, $[\alpha]_{405}$ +84.3 (*c* 2.7, $CHCl_3$); IR (film) 3566, 2931, 1616, 1590, 1473, 1218, 1113 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75−7.32 (m, 10H), 6.18 (d, 1H, J = 9.4 Hz), 5.43 (t, 1H, J = 6.9 Hz), 3.86 (m, 1H), 3.81 (m, 1H), 2.84 (d, 1H, J = 2.5 Hz), 2.50 (m, 1H), 2.06 (app t, 2H, J = 7.0 Hz), 1.46 (s, 3H), 1.07 (s, 9H), 0.98 (d, 3H, J = 6.7 Hz), 0.92 (d, 3H, J = 6.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 143.6, 135.9, 135.8, 134.0, 133.0, 129.8, 129.7, 127.8, 127.5, 125.6, 87.6, 82.5, 71.6, 38.4, 33.6, 27.0, 20.1, 19.3, 18.7, 12.3 ppm; MS (EI) *m/e* 523, 445, 283, 199; HRMS (EI) *m/e* 523.0111, (523.0127 calcd for $C_{23}H_{27}Br^{79}Br^{81}O_2Si$, M − *t*-Bu).

(3*R*,5*E*,7*R*,8*R*)-1,1-Dibromo-7,8-dihydroxy-3,6-dimethyl-1,5-nonadiene (52). Tetrabutylammonium fluoride (2.0 mL of a 1 M solution in THF) was added dropwise to a solution of **51** (568 mg, 0.98 mmol) and THF (18 mL) at rt. The resulting solution was maintained at room temperature for 2 h and was concentrated. The residue was dissolved in EtOAc (20 mL) and washed with brine (2 × 20 mL), dried (Na_2SO_4), and concentrated to give **52** (335 mg, 100%) as a yellow oil, which was used without further purification.

A sample of **52** was purified on silica gel (3:2 hexane−EtOAc) for characterization: $[\alpha]^{23}_D$ +4.3, $[\alpha]_{577}$ +4.6, $[\alpha]_{546}$ +7.3, $[\alpha]_{435}$ +21.6, $[\alpha]_{405}$ +26.8 (*c* 2.5, $CHCl_3$); IR (film) 3416, 2928, 1615, 1456, 1374,

1023 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.19 (d, 1H, J = 9.4 Hz), 5.44 (t, 1H, J = 7.1 Hz), 3.78 (m, 1H), 3.73 (m, 1H), 2.54 (m, 1H), 2.37 (br s, 1H), 2.10 (app t, 2H, J = 7.2 Hz), 1.62 (s, 3H), 1.11 (d, 3H, J = 6.3 Hz), 1.02 (d, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 143.4, 136.4, 126.0, 87.8, 82.7, 68.9, 38.5, 33.6, 18.9, 18.8, 12.1 ppm.

(3*R*,5*E*,7*R*,8*R*)-1,1-Dibromo-3,6-dimethyl-7,8-*O*-isopropylidene-1,5-nonadiene (53). A solution of diol **52** (335 mg, 0.98 mmol), acetone (14 mL), and TsOH (38 mg, 0.20 mmol) was maintained at room temperature for 30 h. Concentration followed by purification of the residue on silica gel (20:1 hexane−EtOAc) gave acetonide **53** (313 mg, 84%) as a colorless oil: $[\alpha]^{23}_D$ +1.7, $[\alpha]_{577}$ +1.4, $[\alpha]_{546}$ +1.7, $[\alpha]_{435}$ +5.9, $[\alpha]_{405}$ +9.5 (*c* 4.5, $CHCl_3$); IR (film) 2985, 1613, 1455, 1379, 1240, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.20 (d, 1H, J = 9.4 Hz), 5.49 (t, 1H, J = 7.3 Hz), 3.88 (m, 2H), 2.54 (m, 1H), 2.12 (app t, 2H, J = 7.2 Hz), 1.66 (br s, 3H), 1.43 (app s, 6H), 1.24 (d, 3H, J = 5.5 Hz), 1.02 (d, 3H, J = 6.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) 143.4, 133.1, 126.4, 108.0, 88.3, 87.8, 74.6, 38.4, 33.7, 27.5, 26.9, 18.7, 17.1, 11.8 ppm; MS (isobutane CI) *m/e* 383, 325, 323, 267, 217; HRMS (EI) *m/e* 383.0032 (383.0044 calcd for $C_{14}H_{23}Br^{79}Br^{81}O_2$, M). Anal. calcd for $C_{14}H_{23}Br_2O_2$: C, 43.89; H, 6.05; Br, 41.71. Found: C, 44.11; H, 5.80; Br, 41.69.

(3*R*,5*E*,7*R*,8*R*)-3,6-Dimethyl-7,8-*O*-isopropylidene-5-nonen-1-yne (54). A solution of **53** (93 mg, 0.24 mmol) and THF (4.6 mL) was cooled to −78 °C. A hexane solution of *n*-BuLi (260 μL, 2.4 M in hexane, 0.62 mmol) was added dropwise, and the resulting mixture was stirred at −78 °C for 1.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (1 mL) and allowed to warm to rt. This mixture was extracted with EtOAc (5 x 2 mL), and the organic phase was dried (Na_2SO_4) and concentrated; the residue was purified on silica gel (20:1 hexane−EtOAc) to give alkyne **54** (50 mg, 94%) as a colorless oil: $[\alpha]^{23}_D$ −10.1, $[\alpha]_{577}$ −11.0, $[\alpha]_{546}$ −12.3, $[\alpha]_{435}$ −20.3, $[\alpha]_{40}$ −22.9 (*c* 2.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (t, 1H, J = 7.1 Hz), 3.89 (m, 2H), 2.51 (m, 1H), 2.24 (m, 2H), 2.04 (d, 1H, J = 2.3 Hz), 1.66 (br s, 3H), 1.42 (app s, 6H), 1.22 (d, 3H, J = 5.6 Hz), 1.17 (d, 3H, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 133.0, 126.7, 108.0, 88.4, 88.4, 74.5, 68.4, 34.5, 27.5, 26.9, 25.7, 20.3, 17.0, 11.7 ppm; IR (film) 3311, 2985, 2145, 1456, 1379, 1239, 1037 cm^{-1}; MS (EI) *m/e* 222 (M), 207, 183; HRMS (CI, isobutane) *m/e* 223.1723 (223.1698 calcd for $C_{14}H_{23}O_2$, MH). Anal. calcd for $C_{14}H_{22}O_2$: C, 75.68; H, 9.91. Found: C, 75.64; H, 9.95.

(*R*)-2-(*tert*-Butyldiphenylsiloxy)-4-(triphenylphosphoranylidene)-3-pentanone (44). Triethylamine (0.71 mL) was added dropwise to a solution of acid **55**[14] (1.53 g, 4.66 mmol) and THF (45 mL) at −77 °C (internal temperature). Pivaloyl chloride (0.55 mL, 4.5 mmol) was added dropwise, and the resulting solution was allowed to warm to 0 °C over 2 h and then was maintained at 0° for 1 h.

A solution of PhLi (7.6 mL of a 2.0 M solution in 7:3 cyclohexane−Et_2O, 15.2 mmol) was added slowly to a stirred suspension of ethyltriphenylphosphonium bromide (5.65g, 15.2 mmol) and THF (45 mL) at 0 °C, producing an orange solution. After being stirred at 0 °C for 0.5 h, the ylide solution was added dropwise by syringe to the crude mixed anhydride solution, which had been recooled to −78 °C. The rate of addition was controlled so that the internal temperature was maintained below −70 °C throughout the addition. The reaction was maintained at −78 °C for 1 h, allowed to warm to room temperature over 2 h, and then was quenched by the addition of saturated aqueous NH_4Cl (100 mL). The ylide was extracted into EtOAc (3 × 50 mL), and the organic phase was washed sequentially with saturated aqueous $NaHCO_3$ (2 × 50 mL) and brine (2 × 50 mL) and dried (Na_2SO_4). Concentration gave an orange oil, which was purified on silica gel (2:3 hexane−EtOAc) to give the known[14] ylide **44** as a light yellow amorphous solid (1.66 g, 62%).

(*S*)-2-[(1*S*,5*R*,7*E*,9*R*,10*R*)-1-Hydroxy-9,10-*O*-isopropylidene-1,5,8-trimethyl-7-undecen-3-ynyl]-1-(carbobenzyloxy)pyrrolidine (56). To a solution of alkyne **54** (310 mg, 1.40 mmol) and toluene (2.1 mL) at 0 °C was added *n*-BuLi (0.53 mL, 2.40 M in hexanes), and the resulting solution was maintained at 0 °C for 15 min. Diethylaluminum chloride (1.27 mL, 1.0 M in hexanes) was added dropwise, and the heterogeneous reaction mixture was stirred at 0 °C for 1 h. A solution of epoxide **7** (168 mg, 0.642 mmol, azeotropically dried with toluene) and 0.7 mL toluene was added dropwise, and the resulting mixture was stirred at 0 °C for 2 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (3 mL), water (1 mL), and Rochelle's salt (0.5 g) and then was stirred vigorously for 1 h. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined extracts were dried ($MgSO_4$) and concentrated. Purification of the resulting oil on silica gel (7:3−1:1 hexanes−ether) gave recovered alkyne **54** (164 mg, 98% of theory) and adduct **56** (294 mg, 95%) as a colorless oil whose ^1H NMR spectrum showed the presence of a mixture of carbamate rotamers: $[\alpha]^{20}_D$ −19 $[\alpha]_{405}$ −68, $[\alpha]_{435}$ −58, $[\alpha]_{546}$ −41 (*c* 2.0, $CHCl_3$); IR (film) 3369, 2981, 2977, 2246, 1677, 1356 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.4−7.3 (m, 5H), 5.61 (brs, 1H), 5.34 (brs, 1H), 5.15 (app s, 2H), 4.19 (brs, 1H), 3.85 (m, 2H), 3.74 (brs, 1H), 3.29 (m, 1H), 2.51 (m, 1H), 2.40 (AB, 1H, J = 17.3 Hz), 2.32 (AB, 1H, J = 17.3 Hz), 2.29−2.10 (m, 3H), 1.90 (brs, 1H), 1.75 (m, 2H), 1.66 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.22 (d, 3H, J = 6.0 Hz), 1.15 (bd, 3H, J = 7.0 Hz), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 136.3, 132.3, 128.5, 128.0, 127.9, 127.6, 107.8, 88.5, 74.9, 74.3, 67.5, 65.7, 48.0, 35.1, 31.3, 28.1, 27.5, 27.4, 26.9, 26.8, 26.0, 24.3, 20.7, 17.0, 17.0, 11.6 ppm; HRMS (CI, isobutane) *m/e* 484.3002 (484.3062 calcd for $C_{29}H_{42}NO_5$, MH).

(*S*)-2-[(1*S*,5*R*,7*E*,9*R*,10*R*)-1-Hydroxy-9,10-*O*-isopropylidene-1,5,8-trimethyl-7-undecen-3-ynyl]pyrrolidene (57). A mixture of $Ba(OH)_2 \cdot H_2O$ (1.34 g, 4.24 mmol), carbamate **56** (294 mg, 0.609 mmol), and 21 mL of 1,4-dioxane−H_2O (1.5:1) was placed in a preheated 100 °C oil bath and heated without stirring for 14 h. The reaction mixture was allowed to cool to room temperature and then was partitioned between a mixture of brine (50 mL), saturated aqueous NH_4Cl (20 mL), and EtOAc (60 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were dried (K_2CO_3) and concentrated. Purification of the resulting oil on silica gel (1:1 hexanes−EtOAc and then 8:1:0.1 $CHCl_3$−MeOH−12 M NH_4OH) gave **57** as a clear oil (164 mg, 77%): $[\alpha]^{20}_D$ −20, $[\alpha]_{405}$ −199, $[\alpha]_{435}$ −231, $[\alpha]_{546}$ −16, $[\alpha]_{577}$ −13 (*c* 0.37, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.57 (t, 1H, J = 7.0 Hz), 4.05 (br m, 1H), 3.88 (m, 2H), 3.44 (t, 1H, J = 8.0 Hz), 3.11 (m, 1H), 3.04 (m, 1H), 2.49 (m, 1H), 2.40 (m, 2H), 2.20 (m, 3H), 1.9−1.7 (m, 4H), 1.65 (s, 3H), 1.42 (s, 6H), 1.23 (s, 3H), 1.21 (d, 3H, J = 5.5 Hz), 1.14 (d, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 132.5, 127.5, 108.0, 88.6, 87.0, 74.4, 71.8, 64.4, 46.7, 35.2, 32.3, 27.5, 26.9, 26.1, 26.0, 25.8, 23.1, 20.8, 17.0 ppm; IR (film) 3351, 2980, 2932, 1455, 1378, 1240 cm^{-1}; MS (CI, isobutane) *m/e* 350.2666 (350.2695 calcd for $C_{21}H_{36}NO_3$, MH).

(+)-Pumiliotoxin B (3). Due to the sensitivity of vinyl iodide **58** to room light, the following manipulations were done in glassware wrapped with aluminum foil. A mixture of alkynylamine **57** (523 mg, 1.50 mmol), NaI (2.2 g, 15 mmol), paraformaldehyde (220 mg, 7.5 mmol), pyridinium *p*-toluenesulfonate (1.13 g, 4.50 mmol), and H_2O (50 mL) contained in a 60 mL Fisher−Porter pressure bottle was placed in a 105 °C oil bath and stirred for 2 h. The reaction mixture was allowed to cool to room temperature and then was partitioned between EtOAc and 1:1 1 M aqueous Na_2CO_3−brine. The layers were separated, the aqueous phase was saturated with NaCl and extracted with EtOAc (3 × 40 mL), and the combined organic layers were dried (K_2CO_3) and concentrated. Purification of the residue on silica gel (20:1:0.1 $CHCl_3$−MeOH−12 M NH_4OH) provided **58** (344 mg, 51%) as a clear oil, which was immediately deiodinated. Yields as high as 68% were realized in this step in smaller scale runs. Characterization data for **58**: IR (film) 3405, 2971, 2930, 2798, 1702, 1450, 1423, 1372, 1128, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.29 (t, J = 6.0 Hz, 1H), 4.07 (dd, 1H, J = 12.2, 1.0 Hz), 3.75 (m, 1H), 3.69 (d, 1H, J = 6.5 Hz), 3.04 (m, 1H), 2.99 (app d, 1H, J = 15 Hz), 2.55 (brs, 1H), 2.48 (bd, 1H, J = 12.0 Hz), 2.3−1.9 (m, 6H), 1.8−1.6 (m, 6H), 1.64 (s, 3H), 1.17 (s, 3H, Me), 1.12 (d, 3H, J = 6.5 Hz), 1.06 (d, 3H, J = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 136.0, 125.8, 82.0, 71.7, 69.1, 68.7, 54.8, 54.0, 53.9, 39.3, 35.9, 24.5, 23.1, 22.5, 21.5, 18.9, 13.0 ppm.

To a solution of the crude vinyl iodide **58** (344 mg, ∼0.75 mmol) and THF (13.5 mL) cooled in a −78 °C bath was added dropwise a solution of *tert*-butyllithium (2.8 mL, 1.5 M in pentane). After 15 min at −78 °C, the stirring yellow solution was quenched by cautious addition of degassed saturated aqueous NH_4Cl (5 mL). The resulting colorless mixture was allowed to warm to room temperature with vigorous stirring and then was partitioned between brine (50 mL) and EtOAc (50 mL); the aqueous layer was saturated with NaCl and

extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (K_2CO_3) and concentrated, and the residue was purified on silica gel (20:1:0.1 $CHCl_3$−MeOH−12 M NH_4OH) to give **3** (221 mg, 89%) as a colorless oil. This sample, $[\alpha]^{20}_D$ +20.1 (*c* 1.0, MeOH), was identical with authentic samples of natural and synthetic[14] **3** by TLC, 500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, IR, and mass spectrometric comparisons.

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