Enantioselective Total Syntheses of Allopumiliotoxins 267A, 323B′, and 339A. Application of Iodide-Promoted Iminium Ion−Alkyne Cyclizations for Forming Allopumiliotoxin A Alkaloids

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Received May 16, 1996[⊗]

Abstract: A concise, stereocontrolled strategy for the total synthesis of allopumiliotoxin A alkaloids is described. A much improved second generation total synthesis of enantiopure (+)-allopumiliotoxin 267A (**3**) was accomplished in 10 steps and 11% overall yield from the commercially available oxazolidinone precursor of alcohol **32** and 17 steps and 4% overall yield from *N*-[(benzyloxy)carbonyl]-L-proline. The first synthesis of (+)-allopumiliotoxin 323B′ (**4**) rigorously confirms the complete stereostructure of **4** and establishes that the major C(15) epimer isolated from dendrobatid frogs has the 15*S* configuration. The total synthesis of **4** was realized in 5 steps and 17% overall yield from alkyne **39** and aldehyde **20**; the synthesis proceeded in 13 steps and 6% overall yield from (*S*)-2-methyl-1-penten-3-ol and 17 steps and 3.5% overall yield from *N*-[(benzyloxy)carbonyl]-L-proline, the precursors, respectively, of alkyne **39** and pyrrolidine aldehyde **20**. The first total synthesis of allopumiliotoxin 339A (**5**) also confirmed the full stereostructure of this alkaloid. The synthesis of enantiopure **5** was achieved in 5 steps and 32% overall yield from alkyne **45** and pyrrolidine aldehyde **20**; the synthesis proceeded in 17 steps and ∼7% overall yield from *N*-[(benzyloxy)carbonyl]-L-proline and 16 steps and ∼6% overall yield from the commercially available oxazolidinone precursor of **45**. These syntheses provide the best illustrations to date of the substantial utility of iodide-promoted iminium ion−alkyne cyclizations for constructing highly functionalized nitrogen heterocycles.

Amphibians have proven to be a rich source of structurally unique and pharmacologically active alkaloids.[2] The majority of these alkaloids have been isolated from neotropical poison frogs of the family Dendrobatidae. Several members of the pumiliotoxin A class of dendrobatid alkaloids, which now numbers more than 40 alkaloids, display potent cardiotonic and myotonic activities.[2] The pumiliotoxin A alkaloids are characterized by the bicyclic 8-hydroxy-8-methyl-6-alkylideneindolizidine ring system found in pumiliotoxins A (**1**) and B (**2**), the first representatives of this group to be isolated (Figure 1).[3] The allopumiliotoxins contain oxidation at both C(7) and C(8) of the indolizidine ring and are the most complex pumiliotoxin A alkaloids. As of 1993, 15 alkaloids were recognized as members of this subgroup of pumiliotoxin A alkaloids.[2a]

The *trans*-diaxial arrangement of the 7,8-diol of allopumiliotoxins 267A (**3**), 323B′ (**4**), 323B″ (the C(15) epimer of **4**), and 339A (**5**) was established through ^{1}H NMR studies and the failure of these alkaloids to form phenyl boronides or react with periodic acid.[4] The *cis* arrangement of the 7,8-diol is less common.[2] The ready formation of a diboronide upon reaction of allopumiliotoxin 339B (**6**) with phenylboronic acid as well as diagnostic ^{1}H NMR signals demonstrated that this alkaloid

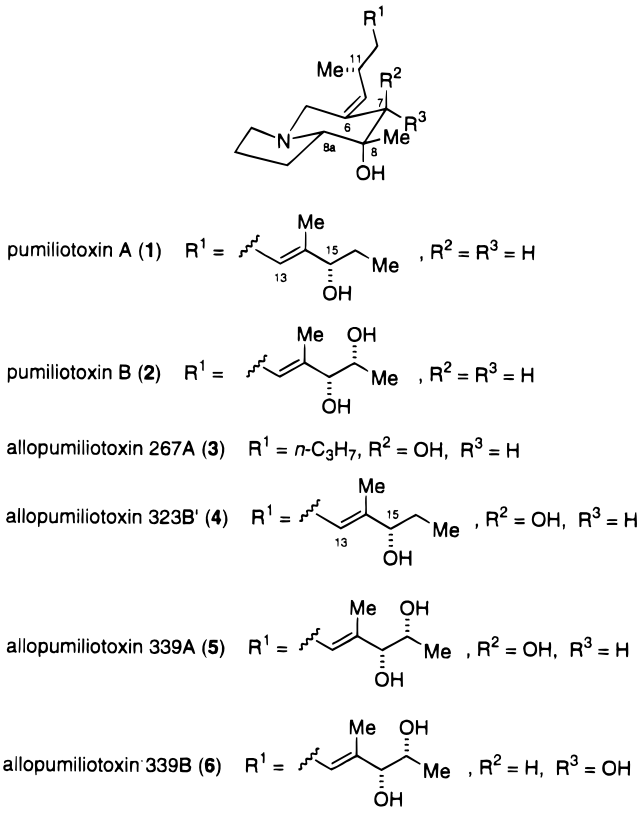

Figure 1. Representative pumiliotoxin A alkaloids.

⊗ Abstract published in *Advance ACS Abstracts,* September 1, 1996.

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(2) For recent 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.

(3) Daly, J. W.; Myers, C. W. *Science* **1967**, *156*, 970.

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

S0002-7863(96)01640-X CCC: $12.00

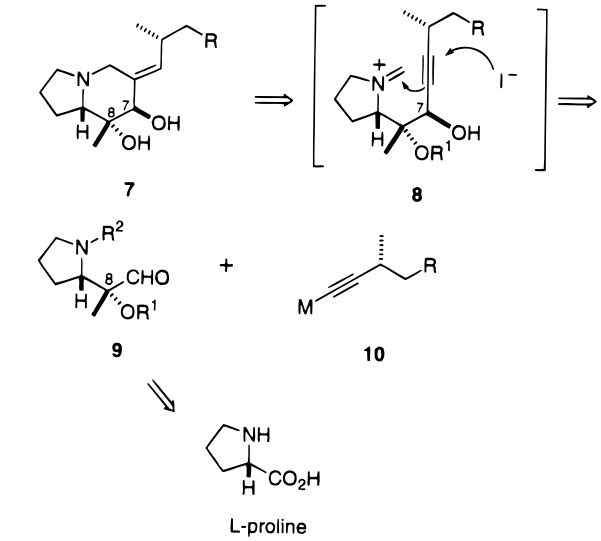
has the *cis*-7,8-diol stereochemistry.[2,4] That the side chains of **3**−**6** are identical to those found in pumiliotoxins 251D, A (**1**), and B (**2**) was surmised initially from correlations of ^{1}H and ^{13}C NMR spectra.[4] The correctness of this assignment for **3** and **6** was confirmed by our initial total syntheses of these alkaloids.[5,6] Allopumiliotoxins containing the *trans*-diaxial arrangement of the 7,8-diol display greater biological activity than their 7α epimers, with allopumiliotoxin 339A (**5**) being the only alkaloid of the pumiliotoxin A family to be more effective than pumiliotoxin B in stimulating sodium influx and phosphoinositide breakdown in guinea pig cerebral cortical synaptoneurosomes.[7]

Since the allopumiliotoxins are found in only minute amounts in dendrobatid frogs,[2] chemical total synthesis has played a role in their structure elucidation and been essential in providing samples of natural alkaloids and analogs for pharmacological studies.[7] The first allopumiliotoxin total syntheses were reported from our laboratories in 1984.[5] In these initial syntheses of **3** and **6**, an aldol reaction was employed to couple indolizidine and side chain fragments while thermodynamic equilibration of an enone intermediate was exploited to establish the proper stereochemistry of the exocyclic alkylidene side-chain.[5,6] However, this approach did not achieve a practical entry to the allopumiliotoxin alkaloids. As a result, we turned to the potential application of iodide-promoted iminium ion−alkyne cyclizations for constructing the allopumiliotoxins, since efficient syntheses of several simpler pumiliotoxin A alkaloids had been realized in this way.[8] In 1992, we reported the first total synthesis of (+)-allopumiliotoxin 339A (**5**) using an iodide-promoted iminium ion−alkyne cyclization as the key step.[9] This synthesis confirmed the full stereostructure of **5** and provided the first practical sequence for obtaining useful amounts of the allopumiliotoxins. In this paper, we summarize the evolution of this improved approach for preparing the allopumiliotoxin alkaloids and document with full details enantioselective total syntheses of (+)-allopumiliotoxin 267A (**3**), (+)-allopumiliotoxin 323B′ (**4**), and (+)-allopumiliotoxin 339A (**5**).[6,10]

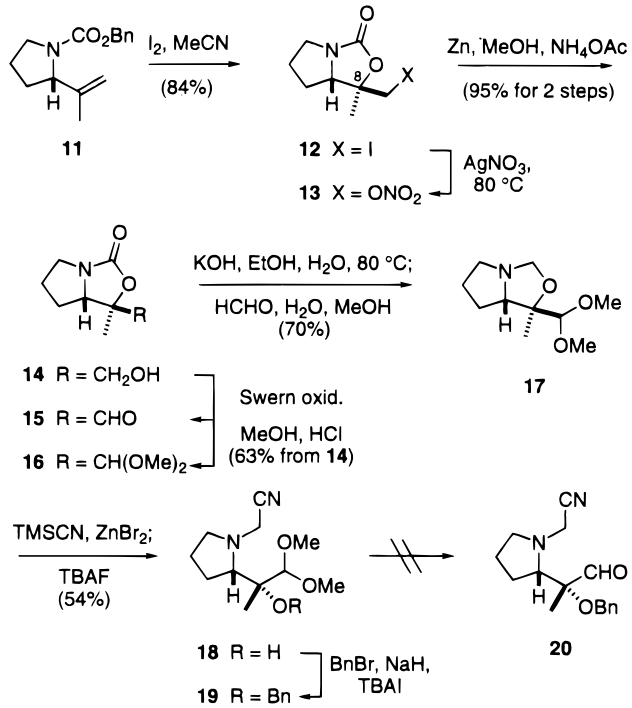
Results and Discussion

Synthesis Plan. A plan for assembling allopumiliotoxins that contain the *trans*-diaxial arrangement of the 7,8-diol is summarized in Scheme 1. The central issue in this strategy is the viability of the pivotal iodide-promoted iminium ion−alkyne cyclization (**8** → **7**) with substrates containing a potentially labile and inductively deactivating propargylic hydroxyl group. The cyclization precursor **8** would come from combination of a proline-derived aldehyde unit **9** with a side-chain acetylide nucleophile. If the C(8) alkoxy substituent of **9** was engaged through chelate organization, the desired *R* stereochemistry at C(7) would result from this coupling step.

Scheme 1



Scheme 2



Preparation of Pyrrolidine Aldehyde 20. After preliminary examination of several possibilities for the pyrrolidine aldehyde fragment, **20** emerged as a viable formulation (Scheme 2). The cyanomethyl protecting group for the pyrrolidine nitrogen was chosen (a) to disfavor, through inductive electron withdrawal, competitive chelation of the carbonyl oxygen and the pyrrolidine nitrogen during the metal acetylide addition step[11] and (b) to serve as a source for the formaldiminium ion during the key cyclization step.[12] Oxazolidinone **12** was a logical starting point for preparing **20**, since this intermediate incorporates the required oxidation at C(8). Crystalline iodide **12** is available by stereoselective iodocyclization of propenylpyrrolidine carbamate **11**, which in turn is readily prepared on a large scale in two steps and 54% overall yield from *N*-[(benzyloxy)carbonyl]-L-proline methyl ester.[13]

(5) (a) Overman, L. E.; Goldstein, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 5360. (b) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179.

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

(7) (a) 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. (b) Daly, J. W.; McNeal, E. T.; Gusovsky, F.; Ito, F.; Overman, L. E. *J. Med. Chem.* **1988**, *31*, 477.

(8) See the preceding paper in this issue for a full account of these investigations.

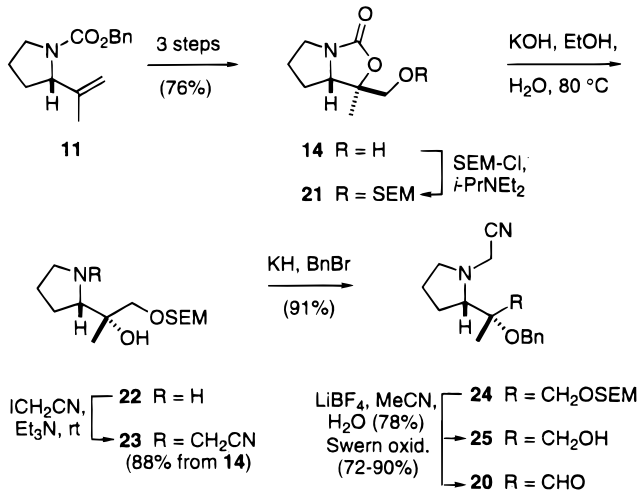
(9) Overman, L. E.; Robinson, L. A.; Zablocki, J. *J. Am. Chem. Soc.* **1992**, *114*, 368.

(10) For syntheses of allopumiliotoxins 267A and 339A by Kibayashi and co-workers and a synthesis of allopumiliotoxin 339B by Trost and Scanlon, see: (a) Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1992**, *114*, 10653. (b) Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, *115*, 11393. (c) Trost, B. M.; Scanlan, T. S. *J. Am. Chem. Soc.* **1989**, *111*, 4988.

(11) The pK_a of aminoacetonitrile is 4.5: Soloway, S.; Lipschitz, A. *J. Org. Chem.* **1958**, *23*, 613.

(12) We often have employed the cyanomethyl group to both protect nitrogen and serve as a formaldiminium source; see, for example: Overman, L. E.; Jacobsen, E. J. *Tetrahedron Lett.* **1982**, *23*, 2355.

Scheme 3



An initial attempt to prepare pyrrolidine aldehyde **20** from iodide **12** is summarized in Scheme 2. Although direct oxidation of **12** to the corresponding aldehyde was undermined by the low reactivity of this neopentyl electrophile,[13] the desired conversion could be accomplished efficiently through a three-step sequence. Thus, heating **12** with 3 equiv of $AgNO_3$ in refluxing acetonitrile cleanly provided nitrate ester **13**. Reduction of this latter intermediate with Zn afforded primary alcohol **14** in crystalline form in 95% overall yield from **12**. Swern oxidation[14] of **14**, followed by direct acetalization of the crude aldehyde product **15** delivered acetal **16** in 63% yield. Base hydrolysis of **16** then provided the corresponding amino alcohol, which was treated directly with formalin to yield cyclopentaoxazolidine **17**. Reaction of **17** with TMS-CN occurred readily in the presence of $ZnBr_2$[15] to deliver **18** in 54% yield after cleavage of the intermediate silyl ether. Protection of the tertiary alcohol of **18** with a benzyl group then yielded **19**. However, acetal **19** did not prove to be a viable precursor of **20**. All attempts to cleave the acetal group of **19** under mildly acidic conditions that were expected to be compatible with the cyanomethylamine group returned only starting material.[16,17] Attempts to remove the group by dealkylation (e.g., with TMSI) led to complex reaction mixtures.[18,19]

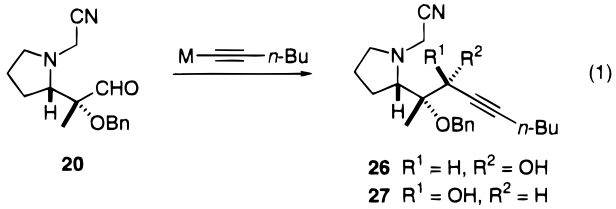
Deferring oxidation of the primary alcohol to the last step allowed pyrrolidine aldehyde **20** to be prepared successfully from **14** by a closely related sequence (Scheme 3). Conversion of **14** to the corresponding SEM ether **21**[20] followed by base hydrolysis provided amino alcohol **22**. Alkylation of this intermediate with iodoacetonitrile yielded cyanomethylamine **23** whose potassium salt could be selectively alkylated on oxygen with benzyl bromide to give **24**. Cleavage of the SEM group with $LiBF_4$ in wet acetonitrile[17] provided primary alcohol **25** in 62% overall yield from **14**. Oxidation of **25** to aldehyde **20** was complicated by facile addition of nucleophiles, for example water, to α-alkoxyaldehyde **20**. After much experimentation, we found that this critical oxidation could be accomplished satisfactorily in the following way. Alcohol **25** was treated at −78 °C with the Swern reagent,[15] and the reaction was allowed to gradually warm to room temperature. Concentration, dilution of the residue with acetone to precipitate the bulk of triethylamine hydrochloride, followed by chromatography of the concentrated filtrate gave **20**, $[\alpha]_D$ +24.7, as a colorless oil. Using this nonaqueous workup, pyrrolidine aldehyde **20** was obtained in yields that ranged, depending upon scale, from 72 to 90%.

Table 1. Addition of 1-Hexynyl Nucleophiles to Aldehyde **20**

reaction conditions			propargylic alcohol products	
metal	solvent	temp, °C	syn:anti[a]	yield, %[b]
ZnBr	Et_2O	−78 → 0		nd[c]
ZnBr	Et_2O−THF (15:1)	−78 → rt		nd
Li	THF	−78	3.2:1	85
Li	Et_2O	−20	2.2:1	(90)
Li	PhMe	−40	1:1	86
Li	C_6H_{14}	−40	2.2:1	(81)
$CeCl_2$	THF	−78 → rt		nd
MgBr	THF	−78	1.8:1	61
Ti(O-*i*-Pr)$_3$	THF	−50	>10:1	80

[a] Ratio of **26**:**27** determined by ^{1}H NMR analysis. [b] Yield of the mixture of propargylic alcohols after purification on silica gel. Yields in parentheses refer to unpurified crude product. [c] Not detected.

Initial Optimization Studies. Preparation of Nor-11-Methylallopumiliotoxin 253A (31). The critical side-chain addition and Mannich cyclization steps were examined in detail using 1-hexyne as a model side-chain component. Since the reaction of simple α-alkoxyaldehydes with alkynyltitanium[21,22] and alkynylzinc[23] nucleophiles had been shown to proceed with high levels of chelate organization, the condensation of these derivatives of 1-hexyne, as well as the corresponding lithium and Grignard reagents, with pyrrolidine aldehyde **20** was examined (eq 1, Table 1).



(1)

The reaction of 1-hexynylzinc bromide with **20** in ether at −78 to 0 °C, according to the general procedure of Mead,[23] did not produce any of the corresponding propargylic alcohols **26** and **27**. Changing the solvent to 15:1 Et_2O−THF to increase the solubility of the zinc reagent also failed to promote addition. Aldehyde **20** is significantly more complex than the α-alkoxy aldehydes studied by Mead and is apparently too hindered to react with a weakly nucleophilic alkynylzinc nucleophile.[24] The related organocerium reagent, prepared according to Imamoto's general procedure,[25] also failed to react with aldehyde **20** in THF at −78 °C to room temperature.[24] 1-Hexynyllithium reacted with **20** within 1 h at −78 °C in THF to give *syn* and

(13) (a) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 4887. (b) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *104*, 4192.

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

(15) Evans, D. A.; Hoffman, J. M.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822.

(16) Conditions examined included: PPTS, acetone, H_2O, rt; oxalic acid, acetone, rt; $LiBF_4$, MeCN, H_2O.[17]

(17) Lipshutz, B. H.; Harvey, D. F. *Synth. Commun.* **1982**, *12*, 267.

(18) Jung, M. E.; Andrus, W. A.; Ornstein, P. L. *Tetrahedron Lett.* **1977**, *18*, 4175.

(19) Standard abbreviations employed are defined in: *J. Org. Chem.* **1996**, *61*, 22A.

(20) Lipshutz, B. H.; Tegram. J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.

(21) Krause, N.; Seebach, D. *Chem. Ber.* **1987**, *120*, 1845.

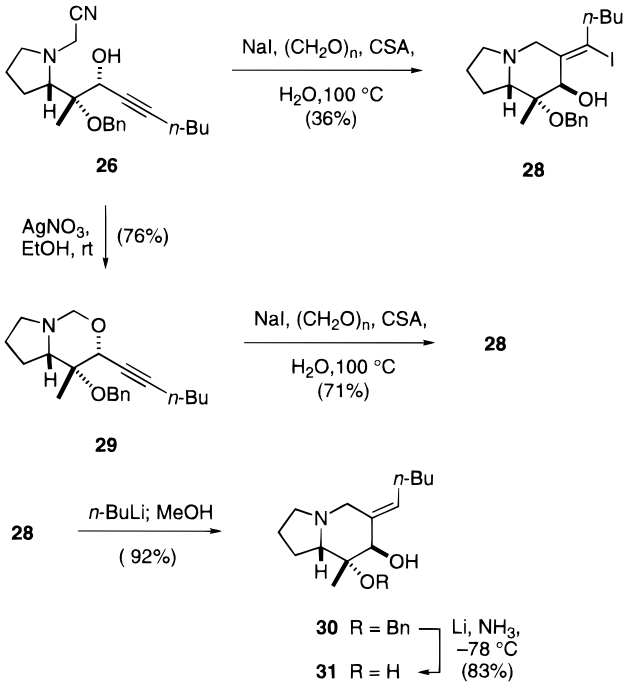
(22) For an earlier report of chelate organization in the addition of alkynyltitanium nucleophiles to tartrate-derived aldehydes, see: Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405.

(23) Mead, K. T. *Tetrahedron Lett.* **1987**, *28*, 1019.

(24) Under identical conditions 1-hexynylzinc and 1-hexynylcerium reagents added in good yield to cyclohexancarboxaldehyde.

(25) Imamoto, T.; Sugiura, Y.; Tagiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

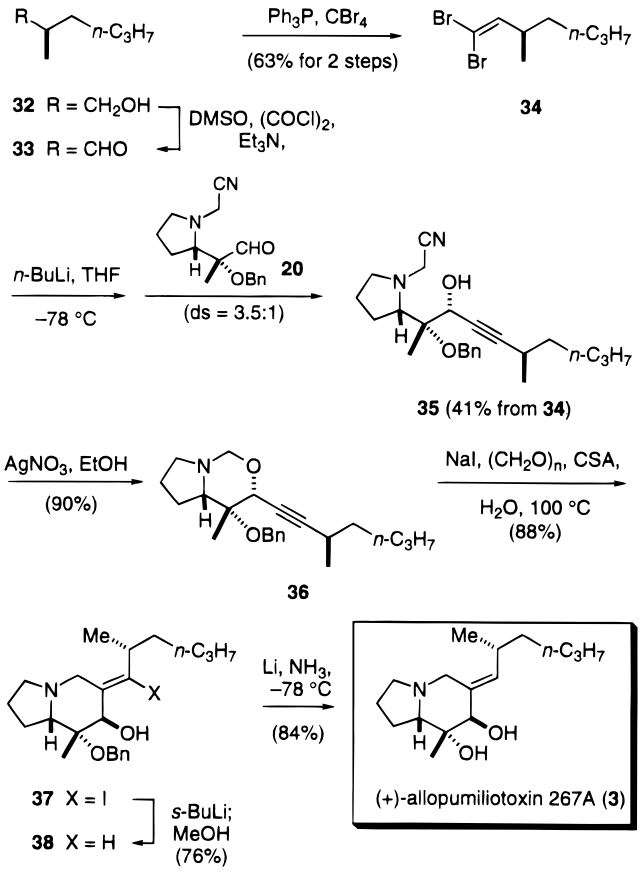
Scheme 4



anti propargylic alcohols **26** and **27** in high yield and a ratio of 3.2:1 (see Table 1). Stereoselectivity with this nucleophile was less in Et_2O, hexanes, or toluene where higher temperatures were required.[26] Addition of 1-hexynylmagnesium bromide, prepared from reaction of 1-hexynyllithium with $MgBr_2 \cdot Et_2O$, with **20** in THF also proceeded with low stereoselectivity. Finally, the titanium nucleophile prepared from reaction of 1-hexynyllithium with chlorotitanium triisopropoxide in THF at −50 °C added to aldehyde **20** with excellent stereoselectivity (>10:1) to give *syn* diastereomer **26** in 80% yield. Unfortunately, with more elaborate alkyne side chains that contained ether and an acetal functionality, addition of the derived titanium triisopropoxide nucleophiles took place with markedly reduced efficiency (*vide infra*). As a result, we have employed the lithium salt of the side-chain nucleophile in our syntheses of the more complex allopumiliotoxins.

Iodide-promoted cyclization of **26** in H_2O at 100 °C in the presence of 10 equiv of NaI and 1 equiv of camphorsulfonic acid[27] provided the desired (*Z*)-alkylideneindolizidine **28** in 36% yield (Scheme 4).[28] Attempted cyclization under non-aqueous conditions ($(n\text{-Bu})_4NI$, CSA, MeCN, 100 °C, sealed tube) yielded none of the cyclized product.[27,29] The efficiency of the conversion of **26** to **28** was increased by first exposing **26** to 1 equiv of $AgNO_3$ in EtOH to give cyclopentaoxazine **29**. Subsequent reaction of **29** in refluxing H_2O with 10 equiv of NaI, 1 equiv of camphorsulfonic acid, and 2 equiv of paraformaldehyde provided **28**, as a single alkylidene stereoisomer, in 71% yield. The structure of this product was secured by treatment of **28** with 4 equiv of *n*-BuLi followed by protonolysis with MeOH to yield **30**, which upon careful debenzylation with Li/NH_3 at −78 °C gave the nor-11-methyl analog **31** of allopumiliotoxiin 253A in 76% overall yield from **28**. The

Scheme 5



identity of this product with an authentic sample of **31** that we had prepared earlier, using our original vinylsilane−iminium ion cyclization strategy,[30] confirmed both the expected *syn* preference in the reaction of 1-hexynyllithium with **20** and the antarafacial stereochemistry of the iodide-promoted iminium ion−alkyne cyclization.

Enantioselective Total Synthesis of (+)-Allopumiliotoxin 267A (3). This synthesis begins with readily available (*R*)-2-methylhexanol (**32**) (Scheme 5).[5b,31] Swern oxidation[15] of **32** followed by dibromethylenation[32] of the derived crude aldehyde provided **34** in 65% yield. Treatment of **34** with 2.2 equiv of *n*-BuLi at −78 °C in THF to generate the corresponding lithium acetylide followed by addition of aldehyde **20** and chromatographic purification provided the major *syn* adduct **35** in 41% yield. The minor *anti* diastereomer was isolated in 14% yield. Although this one-step sequence was convenient, the yield of **35** undoubtedly would have been higher if the lithium reagent had been generated free of LiBr from the corresponding alkyne (*vide infra*). Reaction of **35** with just less than 1 equiv of $AgNO_3$ in EtOH produced cyclopentaoxazine **36** in high yield. Iodide-promoted cyclization of this intermediate proceeded efficiently using the conditions developed during our earlier model study to deliver alkylideneindolizidine **37** as a single stereoisomer in 80% overall yield from **35**. Conversion of **37** to the corresponding dilithio derivative by treatment with 3.5 equiv of *s*-BuLi at −78 °C in THF, followed by protonolysis provided **38** in 76% yield.[34] Careful debenzylation with Li/NH_3 at −78 °C delivered (+)-allopumiliotoxin 267A(**3**) in 84%

(26) The requirement for higher reaction temperatures in these cases is likely in part due to the lower solubility of 1-hexynyllithium in these solvents.

(27) Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 612.

(28) For a brief review of iminium ion-initiated cyclizations, see: Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 2, Chapter 4.4.

(29) Overman, L. E.; Sarkar, A. K. *Tetrahedron Lett.* **1992**, *33*, 4103.

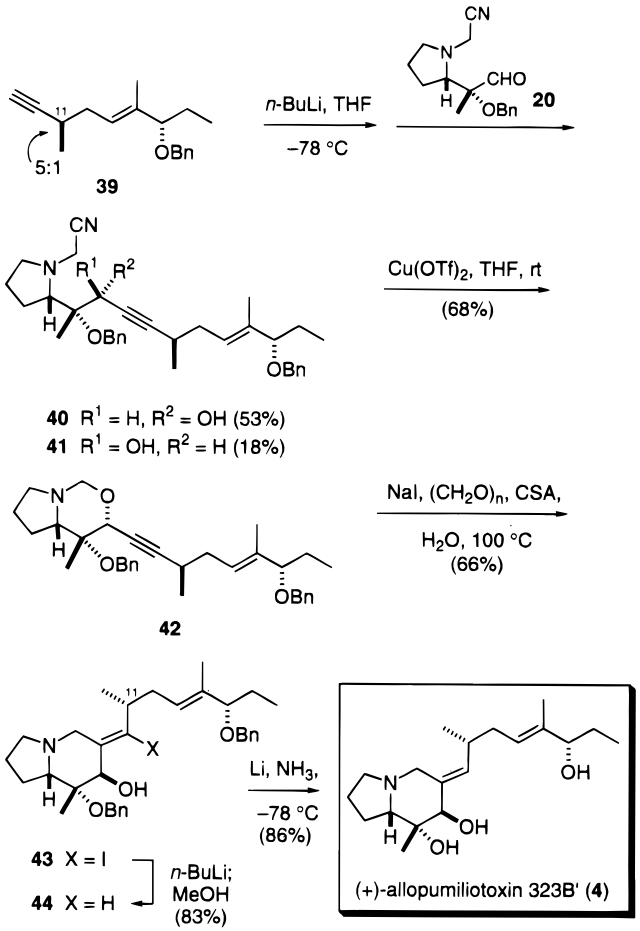
(30) Lett, R. M.; Overman, L. E.; Zablocki, J. *Tetrahedron Lett.* **1988**, *29*, 6541.

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

(32) Corey, E. J.; Fuchs, P. *Tetrahedron Lett.* **1972**, *36*, 3769.

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

Scheme 6



yield. This sample showed $[\alpha]^{20}_D$ +31 (*c* 0.2, MeOH), which is slightly higher than the rotation reported for a dilute solution of the natural isolate, $[\alpha]^{25}_D$ +24.7 (*c* 0.2, MeOH).[4] Synthetic **3** was identical by spectroscopic and chromatographic comparisons with an authentic sample of the natural alkaloid and a sample of **3** prepared earlier in our laboratories.[5]

This much improved second-generation total synthesis of (+)-**3** was accomplished in 10 steps and 11% overall yield from the commercially available oxazolidinone precursor of alcohol **32** and 17 steps and 4% overall yield from *N*-[(benzyloxy)-carbonyl]-L-proline.

Enantioselective Total Synthesis of (+)-Allopumiliotoxin 323B′ (4). The first total synthesis of **4** was accomplished in a similar fashion (Scheme 6). Addition of the alkynyllithium reagent derived from enantiopure alkyne **39** (a 5:1 mixture of C(11) epimers)[8] to aldehyde **20** provided a 3:1 a mixture of *syn* and *anti* alcohols **40** and **41** in 71% combined yield after chromatographic resolution. The major diastereomer **40** was converted in 68% yield to cyclopentaoxazine **42** upon exposure to 2 equiv of $Cu(OTf)_2$ in THF.[35] The yield for this step was less if $AgNO_3$ in EtOH was employed.

Cyclization of **42** occurred cleanly under standard aqueous conditions in the presence of NaI to afford iodoalkylideneindolizidine **43** as a single stereoisomer in 66% yield. At this stage, the C(11) epimer of **43**, which resulted from the low diastereomeric purity of alkyne **39**, could be separated by flash chromatography. Since the C(11) epimer of **43** was isolated in 14% yield, the efficiency of the pivotal iodide-promoted formaldiminium ion−alkyne cyclization was at least 80%. Deiodination of **43** by sequential treatment with *n*-BuLi and MeOH afforded dibenzyl allopumiliotoxin 323B′ (**44**) in 83% yield. Careful debenzylation of **44** with Li/NH_3 at −78 °C then afforded (+)-allopumiliotoxin 323B′ (**4**) in 86% yield. It was critical to quench the reductive debenzylation with solid NH_4Cl after 2 min to avoid reductive scission of the axial C(7) allylic hydroxyl group.[36] Synthetic **4** was indistinguishable from an authentic specimen of (+)-allopumiliotoxin 323B′ by TLC, capillary GLC, and 500 MHz ^{1}H NMR comparisons. The optical rotation of synthetic **4** was $[\alpha]^{23}_D$ +23.8 (*c* 0.42, $CHCl_3$), which compares closely to the rotation reported for material isolated from *Dendrobates pumilio* (a 2:1 mixture of C(15) epimers): $[\alpha]_D$ +22.3 (*c* 1.0, MeOH).[4]

This first synthesis of **4** rigorously confirms the complete stereostructure of **4** and establishes that the major C(15) epimer isolated from dendrobatid frogs has the 15*S* configuration.[2] This synthesis was realized in five steps and 17% overall yield from alkyne **39** and aldehyde **20**.[37] The synthesis proceeded in 13 steps and 6% overall yield from (*S*)-2-methyl-1-penten-3-ol and 17 steps and 3.5% overall yield from *N*-[(benzyloxy)carbonyl]-L-proline, the precursors respectively of alkyne **39** and pyrrolidine aldehyde **20**.

Enantioselective Total Synthesis of (+)-Allopumiliotoxin 339A (5). In a similar fashion, the first synthesis of **5** was completed from pyrrolidine aldehyde **20** and the side-chain alkyne **45** (Scheme 7).[8] The lithium salt of **45** added to aldehyde **20** with the highest degree of chelate organization (4.5:1) we had observed with an alkynyllithium nucleophile. After chromatographic separation, the *syn* adduct **46** was obtained in 68% yield and the minor *anti* isomer **47** in 15% yield. Attempts to improve selectivity by treating the lithium derivative of **45** with $Ti(O\text{-}i\text{-}Pr)_3Cl$ at −50 °C in THF prior to reaction with **20** provided alcohol **46** in a disappointing 10% yield.[21,22] Unconverted aldehyde **20** was isolated from this reaction in 70% yield, although the recovery of alkyne **45** was <40%. This result indicates that this more highly functionalized alkynyltitanium reagent was not stable at the temperatures required to promote its condensation with **20**.

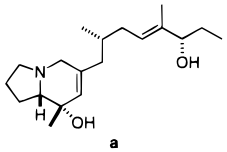
Several conditions were investigated for converting **46** to cyclopentaoxazine **48**. Treatment of **46** with 1 equiv of $AgNO_3$ in EtOH at rt provided **48** in low yield (36%), possibly due to competitive degradation of the side chain. The yield of **48** was improved to 60% when 2 equiv of $Cu(OTf)_2$ in THF was employed; however, the reaction required 20 h to go to completion. Best results were realized upon exposure of **46** to 2.3 equiv of AgOTf in THF, which provided cyclopentaoxazine **48** in 94% yield within 2 h. The yield of this step was quite sensitive to the purity of AgOTf and was significantly lower when older samples of this salt, which undoubtedly contained triflic acid, were employed.

Cyclization of **48** using the standard aqueous conditions we had employed to prepare allopumiliotoxins **3** and **4** provided a mixture of cyclopentaoxazine diol **49** and cyclized triol vinyl iodide **51**. Only traces of the alkylideneindolizidine product **50** that retained the acetonide were isolated. The conversion

(34) Although either *n*- or *s*-BuLi can be employed, *s*-BuLi is preferable since a smaller excess is required to obtain optimum yields.

(35) The contaminating amount of the C(11) epimer could not be removed until the alkylideneindolizidine ring was formed.

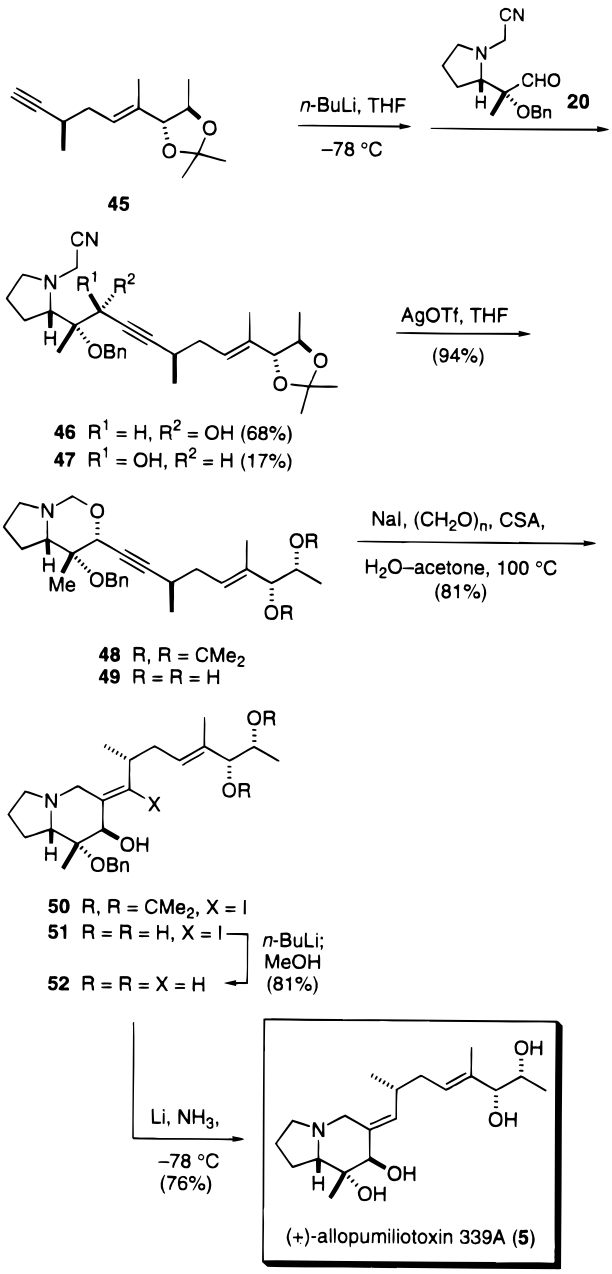
(36) Reaction of **44** with Li/NH_3 for >5 min at −78 °C produced the internal alkene **a** as the major product.



a

(37) The overall yield was 21% when corrected for the isomeric purity of **39**.

Scheme 7



to **51** was much improved by the addition of acetone (10%) to improve the solubility of **48** and **49**. Although extensive optimization studies were not undertaken, the cyclization could be reliably conducted on a small scale by heating a mixture of **48**, 3 equiv of camphorsulfonic, 5 equiv of paraformaldehyde, and a 10:1 mixture of H_2O−acetone in a sealed vial at 100 °C for 2 h. Basic workup, followed by chromatographic purification provided the sensitive vinyl iodide diol **51** in 81% yield. Unfortunately, when the cyclization was conducted on a 50 mg scale, the yield of **51** was reduced. The reason for this difference in yield is not understood; however, the expedience of conducting several simultaneous cyclizations on a 10 mg scale allowed 50 mg of **51** to be obtained.

Since **51** was quite sensitive to light, it was immediately deiodinated by treatment with a large excess of *n*-BuLi at −78 °C in THF followed by protonolysis with MeOH to deliver benzyl allopumiliotoxin 339A (**52**) in 81% yield. Careful debenzylation of this intermediate then provided (+)-allopumiliotoxin 339A (**5**) in 76% yield. Synthetic **5** was indistinguishable from a natural specimen by TLC, 500 MHz ^{1}H NMR, and 125 MHz ^{13}C NMR comparisons. Since ^{1}H NMR spectra of this indolizidene triol are markedly concentration dependent, identity of the synthetic and natural samples was confirmed by 500 MHz ^{1}H NMR analysis of a 1:1 mixture of these samples in $CDCl_3$ and CD_3OD. The optical rotation of synthetic **5**, $[\alpha]^{23}_D$ +68 and $[\alpha]^{23}_{546}$ +90 (*c* 0.5 and 1.0, $CHCl_3$), was slightly higher than the rotation we measured for a small sample of the natural toxin: $[\alpha]^{23}_D$ +52.0 and $[\alpha]^{23}_{546}$ +75.0 (*c* 0.5, $CHCl_3$).

This first total synthesis of allopumiliotoxin 339A also confirmed the full stereostructure of this alkaloid. The total synthesis of enantiopure **5** proceeded in five steps from alkyne **45** and pyrrolidine aldehyde **20**. The synthesis was achieved in 17 steps and ∼7% overall yield from *N*-[(benzyloxy)-carbonyl]-L-proline and 16 steps and ∼6% overall yield from the commercially available oxazolidinone precursor of **45**.

Conclusion. The first total syntheses of **4** and **5**, and a much improved synthesis of the simpler **3**, were accomplished. The former two syntheses rigorously establish the full stereostructure of these complex pumiliotoxin A alkaloids. The synthetic approach to the allopumiliotoxins documented here is sufficiently concise to provide these scarce alkaloids in quantities (10−100 mg) far in excess of that available by isolation. Pharmacological studies of these samples, as well as some simple congeners, have highlighted the sensitivity of biological activity to the stereochemistry of the allopumiliotoxin side chain.[7a,38] The syntheses documented here, together with those described in the accompanying account,[8] underscore the substantial utility of iodide-promoted iminium ion−alkyne cyclizations in constructing highly functionalized nitrogen heterocycles.

Experimental Section[39]

(1*R*,7a*S*)-Tetrahydro-1-methyl-1-(nitratomethyl)-1*H*,3*H*-pyrrolo-[1,2-*c*]oxazol-3-one (13). A solution of $AgNO_3$ (7.2 g, 43 mmol), iodide **12** (4.0 g, 14 mmol), and dry MeCN (15 mL) was heated at reflux for 16 h, during which time AgI precipitated. After cooling to rt, the resulting slurry was filtered and the filtrate was concentrated. Trituration of the gummy residue with EtOAc (7 × 20 mL) left a yellow powder. The combined EtOAc extracts were washed with brine, dried (K_2CO_3), and concentrated to give 3.0 g (∼100% yield) of crude nitratocarbamate **13** as a pale yellow oil, which was used directly in the next step: $[\alpha]^{23}_D$ −50.9 (*c* 3.4, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.61 and 4.55 (AB, J_{AB} = 11.1 Hz, 2H), 3.70 (m, 1H), 3.62 (m, 1H), 3.23 (m, 1H), 2.11 (m, 1H), 1.89 (m, 2H), 1.58 (m, 1H), 1.48 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) 159.4, 78.8, 75.9, 65.0, 45.7, 26.3, 25.4, 18.6 ppm; IR ($CHCl_3$) 1760, 1647, 1277, 830 cm^{-1}; MS (isobutane, CI) *m/z* 217 (MH), 172; HRMS (EI) *m/z* 216.0744 (216.0746 calcd for $C_8H_{12}N_2O_5$).

(1*R*,7a*S*)-Tetrahydro-1-(hydroxymethyl)-1-methyl-1*H*,3*H*-pyrrolo-[1,2-*c*]oxazol-3-one (14). Zinc powder (2.7 g, 41 mmol) was added over 2 min to a stirring solution of nitrate **13** (1.77 g, 8.19 mmol), NH_4OAc (3.2 g, 41 mmol), and MeOH (35 mL) at 0 °C. After 30 min at 0 °C, the slurry was filtered, the zinc residue was washed with MeOH (3 × 50 mL), and the filtrate was concentrated. The resulting residue was partitioned between saturated aqueous NH_4Cl (25 mL) and EtOAc, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were dried (K_2CO_3) and concentrated to afford 1.34 g (95%) of alcohol **14** as a pale yellow oil that solidified upon standing and was sufficiently pure to be used directly in the next step: mp 90−92.5 °C; $[\alpha]^{23}_D$ −69.7 (*c* 3.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.73 (dd, *J* = 10.3, 5.5 Hz, 1H), 3.60 and 3.57 (AB, J_{AB} = 11.8 Hz, 2H), 3.50 (app dt, *J* = 11.5, 3.5 Hz, 1H), 3.30 (br s, 1H), 3.13 (m, 1H), 1.99 (m, 1H), 1.88 (m, 1H), 1.76 (m, 1H), 1.55 (m, 1H), 1.30 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) 160.4, 77.4, 67.4, 64.1, 45.0, 26.1, 25.3, 17.9 ppm; IR ($CHCl_3$)

(38) Bessard, Y.; Daly, J.; Overman, L. E.; Sharp, M. J.; Zablocki, J., manuscript in preparation.

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

3605, 3420, 1735, 1400, 1350, 1060 cm^{-1}; MS (isobutane, CI) *m/z* 172 (MH), 114; HRMS (EI) *m/z* 171.0904 (171.0895 calcd for $C_8H_{13}NO_3$). Anal. Calcd for $C_8H_{13}NO_3$: C 56.13; H, 7.65; N, 8.18. Found: C, 55.97; H, 7.69; N, 8.16.

(1*R*,7a*S*)-Tetrahydro-1-methyl-1-[[2-(trimethylsilyl)ethoxy]methoxy]-methyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (21). A solution of alcohol **14** (800 mg, 4.68 mmol), SEM-Cl (1.7 mL 9.4 mmol), *i*-Pr_2NEt (2.5 mL, 14 mmol), and CH_2Cl_2 (20 mL) was maintained at room temperature for 14 h. The reaction was poured into saturated aqueous $NaHCO_3$ (75 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (75 mL), dried (K_2CO_3), and concentrated to a clear oil. Purification of this residue on silica gel (1:1 hexane−EtOAc) gave 1.40 g (∼100%) of **21**, which solidified upon standing: mp 48−49 °C; $[\alpha]^{23}_D$ −44.7, $[\alpha]_{578}$ −46.3, $[\alpha]_{546}$ −52.8, $[\alpha]_{435}$ −89.0, $[\alpha]_{365}$ −139 (*c* 3.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (s, 2H), 3.75 (m, 1H), 3.55 (m, 5H), 3.21 (m, 1H), 1.35−2.05 (m, 4H), 1.38 (s, 3H), 0.94 (t, J = 8.1 Hz, 2H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 160.3 (s), 95.0 (t), 80.4 (s), 72.6 (t), 65.2 (t), 64.9 (d), 45.5 (t), 26.4 (t), 25.5 (t), 18.9 (q), 17.9 (t), −1.6 (q) ppm; IR (film) 1729, 1250, 835 cm^{-1}; MS (CI, isobutane) *m/z* 302 (MH), 274, 244, 172; HRMS (EI) *m/z* 286.1476 (286.1474 calcd for $C_{13}H_{24}NO_4Si$, M − Me). Anal. Calcd for $C_{14}H_{27}NO_4Si$: C, 55.81; H, 8.97; N, 4.65. Found: C, 55.76; H, 9.08; N, 4.59.

(*R*)-α-Methyl-α-[[[2-(trimethylsilyl)ethoxy]methoxy]methyl]-1-(cyanomethyl)-2(*S*)-pyrrolidinemethanol (23). A carefully degassed solution of **21** (650 mg, 2.2 mmol), KOH (2.4 g, 43 mmol), EtOH (10 mL), and H_2O (2.0 mL) was heated at 80 °C for 16 h under Ar. After cooling to 23 °C, EtOH was removed on a rotary evaporation and the aqueous layer was extracted with THF (100 mL). The organic extract was dried (K_2CO_3) and concentrated to afford crude secondary amine **22** (570 mg) as a pale yellow oil that was homogeneous by ^{1}H NMR analysis: (300 MHz, $CDCl_3$) δ 4.63 (s, 2H), 3.56 (t, J = 7.9 Hz, 2H), 3.36 (s, 2H), 3.12 (m, 1H), 2.90 (m, 1H), 1.52−1.83 (m, 4H), 1.09 (s, 3H), 0.89 (t, J = 7.9 Hz, 2H), −0.03 (s, 9H).

Iodoacetonitrile (450 mg, 2.7 mmol) was added over 1 min to a solution of this sample of **22** (570 mg), Et_3N (840 mg, 8.3 mmol), and THF (10 mL) at room temperature. After 2 h at room temperature, the reaction was diluted with saturated aqueous $NaHCO_3$ (30 mL) and extracted with EtOAc (3 × 80 mL); the organic extract was washed with brine (15 mL), dried (K_2CO_3), and concentrated. The resulting residue was purified in a silica gel (3:2 hexane−EtOAc) to give cyanomethylamine **23** (610 mg, 88% from **14**) as a pale yellow oil: $[\alpha]^{23}_D$ −38.7, $[\alpha]_{578}$ −40.2, $[\alpha]_{546}$ −45.8, $[\alpha]_{435}$ −77.6, $[\alpha]_{365}$ −122 (*c* 3.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (s, 2H), 3.90 (ABq, J = 17.2 Hz, Δ = 132.5 Hz, 2H), 3.63 (m, 2H), 3.40 (ABq, J = 10.0 Hz, Δ = 28.5 Hz, 2H), 3.04 (m, 1H), 2.90 (m, 1H), 2.70 (m, 1H), 1.21−1.95 (m, 4H), 1.11 (s, 3H), 0.94 (m, 2H), 0.02 (s, 9H): ^{13}C NMR (75 MHz, $CDCl_3$) 116.5, 95.5, 75.3, 74.7, 65.9, 65.6, 54.5, 43.3, 27.5, 23.5, 18.9, 18.0, −1.5 ppm; IR (film) 3616−3567, 3515−3300, 2232 cm^{-1}; MS (CI, isobutane) *m/z* 315 (MH), 288, 158; HRMS (EI) *m/z* 314.2010 (314.2025 calcd for $C_{15}H_{30}N_2O_3Si$). Anal. Calcd for $C_{15}H_{30}N_2O_3Si$: C, 57.32; H, 9.55; N, 8.92. Found C, 57.61; H, 9.67; N, 8.90.

(*R*)-α-Methyl-α-[[[2-(trimethylsilyl)ethoxy]methoxy]methyl]-1-(cyanomethyl)-2(*S*)-pyrrolidine(benzyloxy)methane (24). A solution of alcohol **23** (1.50 g, 4.78 mmol), benzyl bromide (1.6 g, 9.6 mmol), and THF (4 mL) was added dropwise over 3 min to a rapidly stirred suspension of KH (∼0.3 g, 7.2 mmol, prewashed with 4 mL of dry hexane) and THF (4 mL). The solution exotherms to reflux upon combination of the reagents. After 30 min, the reaction mixture was added dropwise to EtOAc (300 mL), and the organic solution was washed with brine (2 × 50 mL). After drying (K_2CO_3) and concentration, the residue was purified on silica gel (4:1 hexane−EtOAc) to give 1.76 g (91%) of **24** as a pale yellow oil: $[\alpha]_D$ −42.9, $[\alpha]_{578}$ −44.6, $[\alpha]_{546}$ −50.9, $[\alpha]_{435}$ −86.8 (*c* 3.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.38 (m, 5H), 4.68 (s, 2H), 4.56 (ABq, J = 11.3 Hz, Δ = 16.7 Hz, 2H), 3.86 (ABq, J = 17.1 Hz, Δ = 123.5 Hz, 2H), 3.61 (m, 2H), 3.62 (ABq, J = 11.1 Hz, Δ = 71.9 Hz, 2H), 3.20 (m, 1H), 3.06 (m, 1H), 2.71 (m, 1H), 1.57−2.03 (m, 4H), 1.20 (s, 3H), 0.94 (t, J = 8.5 Hz, 2H), 0.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 139.2, 128.2, 127.2, 127.1, 116.9, 95.0, 81.0, 70.2, 65.3, 64.7, 54.6, 43.5, 27.6, 23.6, 18.1, 15.2, −1.5 ppm; IR (film) 2231, 1249, 836 cm^{-1}; MS (CI, isobutane) *m/z* 405 (MH), 378, 248, 147; HRMS (EI) *m/z* 404.2504 (404.2495 calcd for $C_{22}H_{36}N_2O_3Si$).

(*R*)-α-Methyl-α-(hydroxymethyl)-1-cyanomethyl-2(*S*)-pyrrolidine-(benzyloxy)methane (25). Following the general procedure of Lipshutz,[17] a mixture of **24** (419 mg, 1.04 mmol), $LiBF_4$ (1.9 g, 20 mmol), and 10:1 MeCN−H_2O (5 mL) was maintained at 70 °C for 2 h and then concentrated. The residue was dissolved in EtOAc (100 mL), and this solution was washed with brine (2 × 30 mL). After drying (K_2CO_3) and concentration, purification of the residue by radial chromatography (silica gel, 1 mm plate, 3:2 hexane−EtOAc) gave 222 mg (78%) of **25** as a colorless oil: $[\alpha]^{23}_D$ −46.7, $[\alpha]_{578}$ −48.4, $[\alpha]_{546}$ −55.1, $[\alpha]_{435}$ −93.9, $[\alpha]_{365}$ −148 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.38 (m, 5H), 4.51 (ABq, J = 11.2 Hz, Δ = 7.8 Hz, 2H) 3.82 (ABq, J = 17.2 Hz, Δ = 154.4 Hz, 2H), 3.81 (dd, J = 12.1, 3.0 Hz, 1H), 3.48 (dd, J = 12.1, 8.0 Hz, 1H), 3.15 (m, 1H), 3.09 (m, 1H), 2.71 (m, 1H), 2.65 (m, 1H), 1.76−2.02 (m, 4H), 1.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 138.6, 128.5, 127.5, 127.2, 116.5, 80.4, 66.4, 65.2, 63.8, 54.8, 43.6, 27.4, 23.8, 15.8 ppm; IR (film) 3625−3200, 2231 cm^{-1}; MS (CI, isobutane) *m/z* 275 (MH), 249, 248; HRMS (EI) *m/z* 248.1671 (248.1650 calcd for $C_{15}H_{22}NO_2$, M − CN). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.07; H, 8.03; N, 10.22. Found: C, 70.02; H, 8.11, N, 10.17.

(*R*)-α-Methyl-α-formyl-1-(cyanomethyl)-2(*S*)-pyrrolidine(benzyloxy)methane (20). Following the general procedure of Swern,[14] a stirring solution of oxalyl chloride (270 mg, 2.1 mmol, freshly distilled) and dry CH_2Cl_2 (11 mL) was cooled to −78 °C and DMSO (300 μL, 4 mmol, distilled from CaH_2 and stored over 4 Å sieves) was added dropwise over 3 min. The resulting mixture was stirred at −78 °C for 10 min, and a solution of alcohol **25** (238 mg, 0.87 mmol) and CH_2Cl_2 (1 mL) was added dropwise over 2 min. The reaction was maintained at −78 °C for an additional 30 min, and then Et_3N (750 μL) was added dropwise over 3 min. The resulting slurry was stirred at −78 °C for 10 min and allowed to gradually warm to room temperature over 20 min. Concentration, dilution of the residue with acetone (25 mL), filtration, and a second concentration gave the crude aldehyde as a yellow oil that was contaminated with DMSO and Et_3N·HCl. Purification of this residue on silica gel (4:1 hexane−ethyl acetate) gave 183 mg (77%) of nearly pure **20** as a colorless oil: $[\alpha]^{23}_D$ +24.7, $[\alpha]_{578}$ +27.3, $[\alpha]_{546}$ +37.2, $[\alpha]_{435}$ +144 (*c* 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.29−7.39 (m, 5H), 4.45 (ABq, J = 11.4 Hz, Δ = 96.8 Hz, 2H) 3.86 (ABq, J = 17.3 Hz, Δ = 193.5 Hz, 2H), 3.20 (m, 1H), 3.07 (m, 1H), 2.71 (m, 1H), 1.55−1.87 (m, 4H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 203.5, 137.7, 128.2, 116.0, 86.4, 66.7, 63.6, 54.0, 42.9, 26.3, 23.8, 11.9 ppm; IR (film) 2237, 1731 cm^{-1}; MS (CI, isobutane) *m/z* 273 (MH); HRMS (EI) *m/z* 246.1498 (246.1494 calcd for $C_{15}H_{20}NO_2$, M − CN).

(*R*)-1,1-Dibromo-3-methylheptene (34). Following the general procedure of Swern,[14] a solution of oxalyl chloride (410 mg, 3.3 mmol) and CH_2Cl_2 (7 mL) was cooled to −78 °C and a solution of DMSO (460 μL, 6.5 mmol) and CH_2Cl_2 (2 mL) was added dropwise; the resulting solution was allowed to stir for 3 min. A solution of (*R*)-2-methylhexanol[5b] (342 mg, 2.95 mmol) and CH_2Cl_2 (4 mL) was added dropwise at −78 °C, and after 15 min, Et_3N (570 μL, 4.1 mmol) was added slowly. After 5 min, the cooling bath was removed and the reaction was allowed to warm to room temperature. The reaction mixture then was washed 1:1 H_2O−brine (2 × 20 mL), dried ($MgSO_4$), and concentrated to give 375 mg of crude aldehyde **33**, which was immediately used in the next step.

Following the general procedure of Corey and Fuchs,[32] a solution of Ph_3P (3.09 g, 11.8 mmol) and CH_2Cl_2 (7.5 mL) was added dropwise at −15 °C to a solution of CBr_4 (1.96 g, 5.90 mmol; passed through activity 1 alumina immediately prior to use) and CH_2Cl_2 (6 mL). After 20 min at −10 °C, the orange solution was cooled to −78 °C. A solution of this sample of crude aldehyde **33** and CH_2Cl_2 (3 mL) then was added dropwise, and the resulting solution was maintained at −78°C for 10 min and then at −20 °C for 30 min. The solution was poured into pentane (150 mL), and the resulting mixture was filtered through Celite. The gummy residue was taken up in CH_2Cl_2 (10 mL), pentane was added, and the resulting mixture was filtered. This process was repeated 3×, and the combined filtrates were concentrated (0 °C bath; 20 mm). This residue was suspended in pentane (50 mL), and

after 3 h at −15 °C, this mixture was filtered. The concentrated filtrate (rotary evaporation at 0 °C, 20 mm) was purified on silica gel (pentane) to give 522 mg (65% for two steps) of **34** as a colorless, nonviscous liquid: ^{1}H NMR (50 MHz, $CDCl_3$) δ 6.17 (d, J = 9.0 Hz, 1H), 2.42 (m, 1H), 1.4−1.2 (m, 6H), 1.00 (d, J = 6.5 Hz, 3H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 87.1, 38.3, 35.8, 29.3, 22.7, 19.2, 14.0 ppm; IR (CCl_4) 2962, 2929, 2873, 1457, 732 cm^{-1}; HRMS (EI) *m/e* 269.9465 (269.9442 calcd for $C_8H_{14}{}^{79}Br^{81}Br$, MH).

(*S*)-2-[(1*R*,2*R*,5*R*)-1-(Benzyloxy)-1,5-dimethyl-2-hydroxy-3-nonynyl]-1-(cyanomethyl)pyrrolidine (35). A hexane solution of *n*-BuLi (0.35 mL, 0.76 mmol, 2.2 M) was added dropwise at −78 °C to a solution of dibromoalkene **34** (98 mg, 0.36 mmol) and 1.3 mL of THF. After 2 h, this solution was added via cannula to a −78 °C solution of aldehyde **20** (90 mg, 0.33 mmol, azeotropically dried with toluene 3× prior to use) and THF (2 mL). After the temperature was maintained at of −78 °C for 0.5 h, the reaction was placed in a −50 °C bath and was maintained at this temperature for an additional 8 h. Saturated aqueous NH_4Cl (2 mL) was added, and the resulting mixture was partitioned between ether (20 mL) and H_2O (2 mL). The aqueous layer was extracted with ether (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue on silica gel (10:1 hexanes−EtOAc) gave 18 mg (14%) of the *anti* alcohol as a colorless oil followed by the major *syn* isomer **35** (51 mg, 41%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (m, 5H), 5.01 (AB, J = 11.0 Hz, 1H), 4.66 (AB, J = 11.0 Hz, 1H), 4.33 (d, J = 7.8 Hz, 1H), 3.86 (AB, J = 17.1 Hz, 1H), 3.62 (AB, J = 17.1 Hz, 1H), 3.18 (m, 1H), 3.08 (m, 1H), 2.93 (d, J = 8.1 Hz, 1H), 2.70 (m, 1H), 2.48 (m, 1H), 1.98 (m, 1H), 1.9−1.7 (m, 3H), 1.6−1.2 (m, 4H), 1.42 (s, 3H), 1.18 (d, J = 6.9 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, benzene-d_6) 139.6, 128.7, 116.8, 91.6, 82.3, 80.4, 67.2, 66.6, 66.4, 54.8, 43.7, 36.9, 30.0, 27.9, 26.4, 24.2, 22.9, 21.2, 15.6, 14.3 ppm; IR (neat) 3478, 2872, 2860, 2830, 1497, 1454, 1377 cm^{-1}; MS (CI, isobutane) *m/e* 383 (MH), 356, 257, 232, 192, 107; HRMS (CI, isobutane) *m/e* 383.2677 (383.2698 calcd for $C_{24}H_{35}N_2O_2$, MH).

(*S*)-2-[(1*R*,2*S*,5*R*)-1-(Benzyloxy)-1,5-dimethyl-2-hydroxy-3-nonynyl]-1-(cyanomethyl)pyrrolidine: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (m, 5H), 5.84 (s, 1H), 4.67 (s, 1H), 4.63 (AB, J = 11.0 Hz, 1H), 4.45 (AB, J = 11.0 Hz, 1H), 4.29 (AB, J = 17.4 Hz, 1H), 3.57 (AB, J = 17.4 Hz, 1H), 3.57 (m, 1H), 3.15 (m, 1H), 2.77 (m, 1H), 2.50 (m, 1H), 2.1−1.8 (m, 4H), 1.6−1.3 (m, 4H), 1.27 (s, 3H), 1.20 (d, J = 6.9 Hz, 3H), 0.91 (t, J = 6.9 Hz, 3H); IR (CCl_4) 3480, 2965, 2932, 2875, 1485, 1457 cm^{-1}; HRMS (CI, isobutane) *m/e* 383.2677 (383.2698 calcd for $C_{24}H_{35}N_2O_2$, MH).

(7*R*,8*R*,8a*S*)-8-(Benzyloxy)-8-methyl-7-[(3*R*)-3-methyl-1-heptynyl]-6-oxaocthydroindolizidine (36). A solution of alcohol **35** (71 mg, 0.19 mmol), $AgNO_3$ (30 mg, 0.18 mmol) and ethanol (3 mL) was stirred in the dark at room temperature for 20 h. The reaction mixture then was diluted with EtOAc (15 mL) and was washed with 1 M NaOH (5 mL), H_2O (5 mL), and brine, dried (K_2CO_3), and concentrated. The resulting oil was purified on silica gel (3:1 hexanes−EtOAc) to give 60 mg (90%) of oxazine **36** as a colorless oil: $[\alpha]^{20}_D$ −87, $[\alpha]_{405}$ −655, $[\alpha]_{435}$ −589, $[\alpha]_{546}$ −535, $[\alpha]_{577}$ −482 (*c* 0.11, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.2−7.4 (m, 5H), 5.21 (d, J = 11.5 Hz, 1H), 4.82 (d, J = 11.5 Hz, 1H), 4.78 (d, J = 10.0 Hz, 1H), 4.42 (d, J = 10.0 Hz, 1H), 4.13 (d, J = 1.0 Hz, 1H), 3.43 (app q, J = 7.5 Hz, 1H), 2.77 (dd, J = 7.0, 3.5 Hz, 1H), 2.62 (m, 1H), 2.47 (m, 1H), 2.12 (m, 1H), 1.9−1.7 (m, 3H), 1.5−1.2 (m, 4H), 1.26 (s, 3H), 1.15 (d, J = 7.0 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 128.1, 127.0, 126.8, 92.6, 82.0, 76.4, 75.1, 74.6, 67.5, 67.2, 49.6, 36.3, 29.6, 26.1, 25.3, 22.9, 22.5, 20.7, 18.6, 14.0 ppm; IR (neat) 2964, 2931, 2871, 1454, 1167 cm^{-1}; MS (CI, isobutane) *m/e* 356 (MH), 354, 256, 248, 192, 165, 147; HRMS (CI, isobutane) *m/e* 356.2566 (356.2589 calcd for $C_{23}H_{34}NO_2$, MH).

(7*S*,8*R*,8a*S*)-8-(Benzyloxy)-7-hydroxy-8-methyl-6-(*E*)-[(2*R*)-2-methylpentylidene]octahydroindolizidine (38). A mixture of oxazine **36** (67 mg, 0.19 mmol), camphorsulfonic acid monohydrate (CSA; 50 mg, 0.20 mmol), NaI (283 mg, 1.89 mmol), paraformaldehyde (14 mg, 0.47 mmol), H_2O (2 mL), and a stir bar was sealed in a 5 mL pressure bottle, immersed in a preheated (100 °C) oil bath, and vigorously stirred for 1 h. The mixture was allowed to cool to room temperature and was partitioned between brine and CH_2Cl_2; the organic layer was washed with brine, dried ($MgSO_4$), and concentrated. Purification of the residue on silica gel (20:1.0:01 $CHCl_3$−MeOH−NH_4OH) provided 80 mg (88%) of the unstable vinyl iodide **37**: IR (film) 3418, 3363, 1636 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (m, 5H), 4.90 (s, 1H), 4.64 (AB, J = 12.3 Hz, 1H), 4.60 (AB, J = 12.3 Hz, 1H), 4.03 (d, J = 12.9 Hz, 1H), 3.09 (m, 1H), 2.87 (d, J = 12.9 Hz, 1H), 2.52 (dd, J = 9.6, 6.0 Hz, 1H), 2.32−2.18 (m, 2H), 2.1−1.9 (m, 1H), 1.9−1.8 (m, 1H), 1.7 (br s, 3H), 1.4−1.1 (m, 4H), 1.29 (s, 3H), 1.02 (d, J = 6.3 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 140.2, 138.2, 128.0, 127.1, 126.9, 123.3, 81.1, 76.7, 66.3, 65.5, 53.5, 51.0, 38.9, 36.9, 29.3, 22.8, 22.7, 21.2, 19.0, 14.1 ppm.

A cyclohexane solution of *s*-BuLi (0.47 mL, 0.58 mmol) was added dropwise at −78 °C to a solution of the vinyl iodide **37** (80 mg, 0.17 mmol) and THF (3.5 mL). After 1.75 h, MeOH (0.2 mL) was added and the resulting solution was allowed to warm to room temperature and then was diluted with EtOAc (10 mL). This solution was washed with saturated aqueous NH_4Cl (2 × 1 mL), 1 M aqueous Na_2CO_3 (2 × 1 mL), and brine, dried (K_2CO_3), and concentrated. Purification of the residue on silica gel (20:1:0.1 $CHCl_3$−MeOH−NH_4OH) gave 45 mg (76%) of benzyl ether **38** as an amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4−7.2 (m, 5H), 5.27 (d, J = 10.0 Hz, 1H), 4.59 (AB, J = 12.5 Hz, 1H), 4.56 (AB, J = 12.5 Hz, 1H), 4.07 (s, 1H), 3.71 (d, J = 12.5 Hz, 1H), 3.12 (app t, J = 7.5 Hz, 1H), 2.74 (d, J = 12.5 Hz, 1H), 2.43 (m, 2H), 2.15 (m, 1H), 1.97 (m, 1H), 1.9−1.6 (m, 5H), 1.4−1.1 (m, 3H), 1.26 (s, 3H), 1.00 (d, J = 6.5 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 140.3, 136.7, 134.0, 128.0, 127.2, 126.9, 76.4, 76.2, 66.5, 64.5, 54.4, 48.7, 37.4, 31.8, 29.6, 22.8, 21.0, 20.8, 18.8, 14.1 ppm; HRMS (EI) *m/e* 357.2691 (357.2668 calcd for $C_{23}H_{35}NO_2$, M).

(+)-Allopumiliotoxin 267A (3). Lithium wire (4 mg, 0.5 mmol, containing 1% Na) was added in small pieces to a solution of benzyl ether **38** (12 mg, 0.034 mmol), THF (2 mL), and NH_3 (4 mL, freshly distilled) at −78 °C. After the last piece of Li was added, the reaction was stirred for 6 min, the cooling bath was removed, and the clear solution was stirred vigorously until a deep blue color developed (1 min). After an additional 30 s, dry MeOH (1 mL) was added followed by saturated aqueous NH_4Cl (1 mL). The NH_3 was allowed to evaporate, and the residue was taken up in EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (3 × 1 mL), the combined organic extracts were dried and (K_2CO_3) concentrated, and the residue was purified on silica gel (20:1:0.1 $CHCl_3$−MeOH−NH_4OH) to give 8.2 mg (90%) of **3**, which was 93% pure by capillary GLC analysis: $[\alpha]^{20}_D$ +31; $[\alpha]_{405}$ +87, $[\alpha]_{435}$ +68, $[\alpha]_{546}$ +50, $[\alpha]_{577}$ +40 (*c* 0.22, MeOH). Synthetic **3** showed TLC mobility and 250 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, and mass spectra that were indistinguishable from those of a natural specimen.

(*S*)-2-[(1*R*,2*R*,5*R*,7*E*,9*S*)-1,9-(Dibenzyloxy)-2-hydroxy-1,5,8-trimethyl-7-undecen-2-ynyl]-1-(cyanomethyl)pyrrolidine (40). A hexane solution of *n*-BuLi (0.45 mL, 2.05 *M*) was added dropwise to a solution of alkyne **39** (244 mg, 0.953 mmol, previously dried by azeotroping 2× with benzene) and THF (2 mL) over 3 min at 0 °C. After an additional 40 min at 0 °C, the reaction was cooled to −78 °C and a solution of aldehyde **20** (162 mg, 0.596 mmol, previously dried by azeotroping with benzene) and THF (3 mL) was added dropwise. After 1.5 h at −78 °C, the reaction was allowed to warm to −40 °C over 20 min and then was recooled to −78 °C and quenched by the addition of saturated aqueous NH_4Cl (1.5 mL). After allowing the reaction to warm to room temperature, it was diluted with brine (20 mL) and extracted with EtOAc (2 × 100 mL). After drying (K_2CO_3) and concentration, the residue was purified by radial chromatography (silica gel, 2 mm plate, 9:1−3:1 hexane−EtOAc) to give 165 mg (53%) of the major *syn* diastereomer **40** as a colorless oil and 56 mg (18%) of the minor *anti* diastereomer **41**. Characterization data for **40**: $[\alpha]^{23}_D$ −90.1, $[\alpha]_{577}$ −94.3, $[\alpha]_{546}$ −107.6, $[\alpha]_{435}$ −184 $[\alpha]_{405}$ −221 (*c* 2.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.37 (m, 10H), 5.44 (br t, J = 7.0 Hz), 4.85 (ABq, J = 10.9 Hz, $\Delta\nu$ = 175.8 Hz), 4.36 (ABq, J = 11.8 Hz, $\Delta\nu$ =124.5 Hz), 4.30 (br s, 1H), 3.73 (ABq, J = 17.2 Hz, $\Delta\nu$ = 118.0 Hz, 2H), 3.56 (t, J = 7.0 Hz, 1H), 3.18 (m, 1H), 3.08 (m, 1H), 2.96 (br s, 1H), 2.70 (m, 2H), 1.48−1.98 (m, 6H), 1.61 (s, 3H), 1.41 (s, 3H), 1.22 (d, J = 6.9 Hz, 3H), 0.85 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9 (s), 138.6 (s), 136.3 (s), 128.5 (d), 128.2 (d), 127.6 (d), 127.5 (d), 127.3 (d), 126.0 (d), 125.8 (d), 116.7 (s),

91.4 (s), 86.6 (d), 82.3 (s), 79.4 (s), 69.6 (t), 66.8 (d), 66.5 (t), 66.3 (d), 54.9 (t), 44.0 (t), 34.5 (t), 27.8 (t), 26.4 (t), 26.3 (d), 24.1 (t), 20.3 (q), 14.9 (q), 10.8 (q), 10.3 (q) ppm; IR (film) 3606−3250, 2244 cm^{-1}; MS (CI, isobutane) *m/e* 529 (MH), 502; HRMS (EI) *m/e* 528.3346 (528.3352 calcd for $C_{34}H_{44}N_2O_3$).

Minor *anti* diastereomer **41**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.38 (m, 10H), 5.44 (t, J = 7.1 Hz, 1H), 4.20−4.65 (m, 6H), 3.06 (m, 1H, 2H), 2.71 (m, 1H), 2.62 (m, 1H), 2.30 (m, 2H), 1.48−2.10 (m, 6H), 1.63 (s, 3H), 1.25 (d, J = 7.0 Hz, 3H), 1.24 (s, 3H), 0.86 (t, J = 7.5 Hz, 3H).

(7*R*,8*R*,8a*S*)-8-(Benzyloxy)-7-[(3*R*,5*E*,7*S*)-7-(benzyloxy)-3,6-dimethyl-5-decen-1-ynyl]-8-methyl-6-oxaoctahydroindolizidine (42). A solution of alcohol **40** (60 mg, 0.11 mmol), $Cu(OTf)_2$ (82 mg, 0.23 mmol), and dry THF (3 mL) was stirred at room temperature. A gray precipitate formed slowly over a 19 h period. The reaction then was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL), and the resulting mixture was extracted with EtOAc (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL), dried (K_2CO_3), and concentrated. Purification of the residue by radial chromatography on silica gel (1 mm plate, 2:1 hexane−EtOAc) gave 38 mg (68%) of **42** as a clear oil: $[\alpha]^{23}_D$ −89.0, $[\alpha]_{577}$ −93.5, $[\alpha]_{546}$ −106, $[\alpha]_{435}$ −181, $[\alpha]_{405}$ −217 (*c* 2.1, $CHCl_3$); IR (film) 2237 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23−7.39 (m, 10H), 5.41 (m, 1H), 5.01 (ABq, J = 11.6 Hz, $\Delta\nu$ = 198.1 Hz, 2H), 4.54 (ABq, J = 10.0 Hz, $\Delta\nu$ = 197.2 Hz, 2H), 4.34 (ABq, J = 11.9 Hz, $\Delta\nu$ = 130.3 Hz, 2H), 4.07 (br s, 1H), 3.53 (t, J = 6.9 Hz, 1H), 3.42 (m, 1H), 2.72 (m, 1H), 2.55−2.65 (m, 2H), 2.3 (m, 2H), 1.48−2.01 (m, 6H), 1.58 (s, 3H), 1.25 (s, 3H), 1.17 (d, J = 6.9 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 140.1 (s), 139.0 (s), 136.2 (s), 128.2 (d), 128.0 (d), 127.6 (d), 127.2 (d), 127.0 (d), 126.8 (d), 126.1 (d), 92.0 (s), 86,6 (d), 81.8 (t), 76.6 (s), 74.9 (d), 74.5 (s), 69.5 (t), 67.3 (d), 67.2 (d), 49.4 (t), 34.5 (t), 26.4 (t), 26.3 (d), 25.2 (t), 22.8 (t), 20.1 (q), 18.5 (q), 10.7 (q), 10.3 (q) ppm; MS (CI, isobutane) *m/e* 502 (MH), 394; HRMS (EI) *m/e* 410.2682 (410.2695 calcd for $C_{26}H_{36}NO_3$ M − $PhCH_2$).

(7*R*,8*R*,8a*S*)-8-(Benzyloxy)-7-hydroxy-8-methyl-6-(*Z*)-[(2*R*,4*E*,6*S*)-6-(benzyloxy)-2,5-dimethyl-1-iodo-4-octenylidene]octahydroindolizidine (43). A solution of **41** (88 mg, 0.18 mmol), camphorsulphonic acid (44 mg, 0.18 mmol), paraformaldehyde (11 mg, 0.35 mmol), NaI (260 mg, 1.8 mmol), and H_2O (4.5 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 (50 mL) and 1 M $NaHCO_3$ (30 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL), and the combined organic layers were dried (K_2CO_3) and concentrated. Purification of the residue on silica gel (50:1:0.1 $CHCl_3$−MeOH−NH_4OH) gave 73 mg (66%) of **43** as a colorless oil that was homogeneous by TLC analysis (high R_f) and 15 mg (14%) of the C(11) epimer (low R_f). Characterization data for **43**: IR (film) 3387, 2968, 2931, 2875, 1456, 1056, 912 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25−7.09 (m, 10H), 5.13 (bt, J = 7.3 Hz, 1H), 4.75 (br s, 1H), 4.51 (ABq, J = 12.2 Hz, $\Delta\nu$ = 14.4 Hz, 2H), 4.25 (ABq, J = 11.8 Hz, $\Delta\nu$ = 64.9 Hz, 2H), 3.90 (d, J = 12.8 Hz, 1H), 3.43 (t, J = 6.9 Hz, 1H), 2.98 (br t, J = 7.0 Hz, 1H), 2.80 (d, J = 12.8 Hz, 1H), 2.45−2.29 (m, 2H), 2.17−1.33 (m, 8H), 1.53 (s, 3H), 1.16 (s, 3H), 0.97 (d, J = 6.3 Hz, 3H), 0.74 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 140.0, 138.9, 138.5, 136.1, 128.2, 128.0, 127.7, 127.3, 127.1, 126.9, 125.6, 121.9, 86.6, 80.8, 76.8, 69.7, 66.1, 65.5, 53.4, 50.8, 39.2, 35.4, 26.3, 22.8, 22.4, 21.2, 18.9, 11.2, 10.3 ppm; MS (CI, isobutane) *m/e* 630 (MH), 522, 502, 410, 396, 364, 300, 147, 107, 91; HRMS (EI) *m/e* 538.1806 (538.1818 calcd for $C_{26}H_{37}NO_3I$, M − $PhCH_2$).

(7*R*,8*R*,8a*S*)-8-(Benzyloxy)-7-hydroxy-8-methyl-6-(*E*)-[(2*R*,4*E*,6*S*)-6-(benzyloxy)-2,5-dimethyl-4-octenylidine]octahydroindolizidine (44). A hexane solution of *n*-BuLi (0.28 mL, 2.05 M, 0.58 mmol) was added dropwise to a solution of **43** (66 mg, 0.11 mmol) and dry THF (4.0 mL) at −78 °C. This solution was maintained at −78 °C for 1 h and MeOH (100 mL) was added. The resulting solution was allowed to warm to room temperature and then was partitioned between $CHCl_3$ (50 mL) and brine (30 mL). The organic layer was separated, dried (K_2CO_3), and concentrated. Purification of the residue on silica gel (50:1:0.1 $CHCl_3$−MeOH−NH_4OH) gave 44 mg (83%) of **44** as a colorless oil that was homogeneous by TLC analysis: $[\alpha]^{23}_D$ +2.5, $[\alpha]_{577}$ +5.6, $[\alpha]_{546}$ +5.4, $[\alpha]_{435}$ +10.6, $[\alpha]_{405}$ +14.1 (*c* 1.1 $CHCl_3$); IR (film) 3431, 2962, 1456, 1093, 1056, 750, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.20 (m, 10H), 5.37−5.28 (m, 3H), 4.57 (ABq, J = 12.8 Hz, $\Delta\nu$ = 8.3 Hz, 2H), 4.36 (ABq, J = 11.9 Hz, $\Delta\nu$ = 60.9 Hz, 2H), 4.07 (s, 1H), 3.72 (d, J = 13.3 Hz, 1H), 3.55 (t, J = 7.0 Hz, 1H), 3.12 (t, J = 8.2 Hz, 1H), 2.75 (d, J = 12.2 Hz, 1H), 2.62−2.40 (m, 2H), 1.58 (s, 3H), 1.26 (s, 3H), 1.04 (d, J = 6.5Hz, 3H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 140.2, 138.9, 136.0, 135.4, 134.1, 128.2, 128.0, 127.7, 127.3, 127.2, 126.9, 126.9, 86.8, 76.5, 75.9, 69.6, 66.3, 64.5, 54.3, 48.5, 35.4, 32.2, 26.2, 22.8, 20.9, 20.5, 18.7, 10.9, 10.4 ppm; MS (CI, isobutane) *m/e* 504 (MH), 396, 380, 288, 272, 107, 91; HRMS (EI) *m/e* 412.2845 (412.2852 calcd for $C_{26}H_{38}NO_3$, M − $PhCH_2$).

(+)-Allopumiliotoxin 323 B′ (4). A solution of **44** (15 mg, 0.030 mmol), THF (1.0 mL), and NH_3 (5 mL, freshly distilled) was cooled to −78 °C and treated with excess Li until the blue color persisted for 2 min. The reaction was then quenched by the addition of solid NH_4Cl. This mixture was allowed to warm to room temperature and then was diluted with 1 M aqueous Na_2CO_3 (10 mL) and extracted with $CHCl_3$ (3 × 15 mL). After drying (K_2CO_3) and concentration, the residue was purified on silica gel (15:1:0.1 $CHCl_3$−MeOH−NH_4OH) to give 6.5 mg (86%) of **4** as a colorless oil: $[\alpha]^{23}_D$ +23.8, $[\alpha]_{577}$ +19.8, $[\alpha]_{546}$ +25.0, $[\alpha]_{435}$ +52.9, $[\alpha]_{405}$ +66.2 (*c* 0.42 $CHCl_3$). Synthetic **4** showed TLC mobility and 250 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, and mass spectra that were indistinguishable from those of a natural specimen.

(*S*)-2-[(1*R*,2*R*,5*R*,7*E*,9*R*,10*R*)-1-(Benzyloxy)-2-hydroxy-9,10-*O*-isopropylidene-1,5,8-trimethyl-7-undecen-3-ynyl]-1-(cyanomethyl)pyrrolidine (46). Following the procedure described for preparation of **40**, a solution of the alkyne **45** (150 mg, 0.68 mmol) and THF (1.4 mL) was treated with *n*-BuLi (300 μL, 2.2 M in hexanes, 0.66 mmol) at −15 °C. The resulting dark anion solution was maintained at −15 °C for 15 min and then cooled to −78 °C. A solution of aldehyde **20** (140 mg, 0.51 mmol) and THF (1.6 mL) was added dropwise, and the resulting solution was maintained at −78 °C for 2.5 h. Workup provided a dark oil that was purified on silica gel (8:1 hexane−EtOAc) to give 43 mg (17%) of the *anti* diastereomer **47** and 172 mg (68%) of the *syn* isomer **46**. Also isolated were recovered alkyne **45** (51 mg, 34%) and aldehyde **20** (21 mg, 15%). Characterization data for **46**: $[\alpha]^{22}_D$ −73.6, $[\alpha]_{577}$ −73.5, $[\alpha]_{546}$ −79.4, $[\alpha]_{435}$ −118 (*c* 0.9, $CHCl_3$); IR (film) 3463, 2982, 2250, 1455, 1379, 1239, 1103, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, ArH, 5H), 5.57 (dt, J = 7.1, 0.9 Hz, 1H), 4.82 (ABq, J_{AB} = 10.9 Hz, $\Delta\nu_{AB}$ = 98.3, 2H), 4.31 (br d, J = 4.9 Hz, 1H), 3.86 (m, 2H), 3.73 (ABq, J_{AB} = 17.2 Hz, $\Delta\nu_{AB}$ = 74.4 Hz, 2H), 3.18 (dd, J = 8.9, 5.1 Hz, 1H), 3.07 (dt, J = 3.7, 5.7 Hz, 1H), 2.99 (br d, J = 7.3 Hz, OH, 1H), 2.69 (m, 1H), 2.59 (dq, J = 7.0, 1.7 Hz, 1H), 2.25 (m, 2H), 1.97 (m, 2H), 1.83−1.68 (m, 2H), 1.65 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.20 (d, J = 4.5 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 138.6, 132.9, 128.4, 127.5, 127.0, 116.7, 107.9, 91.1, 88.4, 82.3, 79.6, 74.2, 66.8, 66.5, 66.2, 54.8, 43.9, 34.6, 27.8, 27.4, 26.8, 26.0, 24.0, 20.2, 16.9, 14.9, 11.7 ppm; MS (CI, isobutane) *m/e* 495 (MH), 468, 437, 410, 304, 246; HRMS (CI) *m/e* 495.3225 (495.3223 calcd for $C_{30}H_{43}N_2O_4$, MH).

Diastereomer **47**: $[\alpha]^{22}_D$ −20.8, $[\alpha]_{577}$ −24.7, $[\alpha]_{546}$ −25.6, $[\alpha]_{435}$ −32.4 (*c* 2.0, $CHCl_3$); IR (film) 3438, 3294, 2982, 2250, 1455, 1380, 1239, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, ArH, 5H), 5.94 (br s, OH, 1H), 5.59 (t, J = 7.2 Hz, 1H), 4.65 (d, J = 1.2 Hz, 1H), 4.53 (ABq, J_{AB} = 10.8 Hz, $\Delta\nu_{AB}$ = 52.9 Hz, 2H), 3.92 (ABq, J_{AB} = 17.3 Hz, $\Delta\nu_{AB}$ = 204.9 Hz, 2H), 3.88 (m, 2H), 3.54 (dd, J = 8.3, 4.4 Hz, 1H), 3.15 (m, 1H), 2.77 (dt, J = 10.2, 7.0 Hz, 1H), 2.61 (dq, J = 6.9, 1.6 Hz, 1H), 2.27 (m, 2H), 2.05 (m, 2H), 1.90 (m, 2H), 1.68 (s, 3H), 1.42 (s, 6H), 1.26 (s, 3H), 1.23 (d, J = 5.5 Hz, 3H), 1.21 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.9, 133.0, 128.3, 128.1, 127.4, 127.1, 127.0, 117.1, 107.9, 91.5, 88.3, 80.3, 79.1, 74.3, 69.5, 66.7, 63.7, 55.1, 44.4, 34.7, 27.4, 27.0, 26.8, 26.0, 24.9, 20.3, 18.6, 17.0, 11.6 ppm; MS (CI, isobutane) *m/e* 495, 468, 437, 410, 304; HRMS (CI) *m/e* 495.3223 (495.3223 calcd for $C_{30}H_{43}N_2O_4$ (MH).

(7*R*,8*R*,8a*S*)-8-(Benzyloxy)-7-[(3*R*,5*E*,7*R*,8*R*)-3,6-dimethyl-7,8-*O*-isopropylidene-5-decen-1-ynyl]-8-methyl-6-oxaoctahydroindolizidine (48). Silver triflate (25 mg, 0.097 mmol) was added in one portion to a solution of the alcohol **46** (20 mg, 0.041 mmol) and THF (1.5 mL) at room temperature. The reaction was protected from light and

was stirred at room temperature for 3h. The resulting mixture was diluted with saturated aqueous $NaHCO_3$ (2 mL) and then basified (pH 9) with 12 M NH_4OH (~5 drops). This mixture was extracted into EtOAc (4 × 5 mL), the organic phase was dried (K_2CO_3) and concentrated, and the residue was and purified on silica gel (3:2 hexane−EtOAc) to give 18 mg (94%) of oxazine **48** as a clear oil: $[\alpha]^{22}_D$ −66.5, $[\alpha]_{577}$ −67.7, $[\alpha]_{546}$ −75.8, $[\alpha]_{435}$ −118 (*c* 2.2, $CHCl_3$); IR (film) 3026, 2980, 2244, 1455, 1378, 1239, 1174, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, ArH, 5H), 5.57 (t, J = 7.0 Hz, 1H), 5.0 (ABq, J_{AB} = 11.6 Hz, $\Delta\nu_{AB}$ = 115.5 Hz, 2H), 4.60 (ABq, J_{AB} = 10.0 Hz, $\Delta\nu_{AB}$ = 106.4 Hz, 2H), 4.12 (d, J = 1.8 Hz, 1H), 3.84 (m, 2H), 3.43 (dd, J = 15.1, 7.7 Hz, 1H), 2.78 (dd, J = 7.2, 3.7 Hz, 1H), 2.60 (m, 2H), 2.23 (m, 2H), 2.02 (m, 2H), 1.82 (m, 2H), 1.63 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.27 (s, 3H), 1.19 (d, J = 5.2 Hz, 3H), 1.14 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 140.5, 133.3, 128.4, 127.4, 127.2, 127.1, 108.2, 92.1, 88.7, 82.3, 75.4, 74.9, 74.7, 67.8, 67.6, 49.9, 34.8, 27.8, 27.2, 26.4, 25.6, 23.2, 20.3, 18.9, 17.4, 12.0 ppm; MS (CI, isobutane) *m/e* 468, 410, 304, 246, 165; HRMS (CI) *m/e* 468.3096 (468.3113 calcd for $C_{29}H_{42}NO_4$, MH).

(7*R*,8*R*,8a*S*)-8-(Benzyloxy)-7-hydroxy-8-methyl-6-(*E*)-[(2*R*,6*R*,7*R*)-6,7-dihydroxy-2,5-dimethyl-4-(*E*)-octenylidene]octahydroindolizidine (52). A mixture of oxazine **48** (9 mg, 0.019 mmol), CSA (14 mg, 0.056 mmol), paraformaldehyde (3 mg, 0.10 mmol), NaI (28 mg, 0.19 mmol), H_2O (750 μL), acetone (75 μL), and a small stirring bar was placed in a 20 dr sealable vial. The vial was tightly capped, lowered into a hot (100 °C) oil bath, and stirred for 2 h. After being cooled to room temperature, the vial was carefully opened, diluted with 1 M aqueous Na_2CO_3 (2 mL), and extracted with CH_2Cl_2 (5 × 5 mL). The organic phase was dried (K_2CO_3) and concentrated, and the residue was purified on silica gel (9:1:0.15 $CHCl_3$−MeOH−NH_4OH) to give 8.5 mg (81%) of indolizidine iodide **51** as a colorless oil. This product decomposed rapidly upon storage or in room light and was immediately deiodinated. Diagnostic data for **51**: IR (film) 3401 (br), 2975, 1455, 1216, 1052 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, ArH, 5H), 5.25 (dd, J = 10.3, 4.2 Hz, 1H), 4.77 (s, 2H), 4.59 (s, 2H), 3.89 (d, J = 12.9 Hz, 1H), 3.82 (t, J = 6.0 Hz, 1H), 3.67 (d, J = 5.9 Hz, 1H), 3.01 (d, J = 12.7 Hz, 1H), 2.95 (dt, J = 8.0, 3.0 Hz, 1H), 2.70 (dd, J = 10.2, 3.5 Hz, 1H), 2.52−1.67 (m, 7H), 1.68 (s, 3H), 1.28 (s, 3H), 1.13 (d, J = 6.4 Hz, 3H), 1.10 (d, J = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, MeOH-d_4) 139.8, 138.4, 136.6, 127.8, 127.1, 125.8, 125.0, 82.9, 80.1, 78.3, 68.9, 66.3, 65.6, 53.0, 50.2, 39.4, 35.1, 22.5, 22.0, 21.8, 20.8, 18.7, 18.1, 11.5 ppm.

A hexane solution of *n*-BuLi (580 μL, 2.1 M) was added dropwise to a stirring solution of a comparable sample of vinyl iodide **51** (27 mg, 0.049 mmol) and THF (6 mL) at −78 °C. After 1.5 h, the reaction was quenched by the addition of MeOH (2 mL) and the resulting solution was allowed to warm to room temperature. After concentration, the residue was purified on silica gel (9:1:0.15 $CHCl_3$−MeOH−NH_4OH) to give 17 mg (81%) of indolizidine triol **52** as a clear oil: $[\alpha]^{23}_D$ +3.6, $[\alpha]_{577}$ −33.6, $[\alpha]_{546}$ −30.9 (*c* 1.0, $CHCl_3$); IR (film) 3380 (br), 2958, 2798, 1455, 1374, 1217, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.28 (m, ArH, 5H), 5.38 (m, 1H), 5.23 (d, J = 10.1 Hz, 1H), 4.55 (m, 2H), 4.09 (s, 1H), 3.76 (m, 1H), 3.67 (m, 1H), 3.50 (d, J = 12.3 Hz, 1H), 3.00 (m, 1H), 2.88 (d, J = 12.1 Hz, 1H), 2.72−2.33 (m, 3H), 2.10−1.65 (m, 6H), 1.56 (s, 3H), 1.29 (s, 3H), 1.12 (d, J = 6.2 Hz, 3H), 1.08 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 140.6, 135.8, 135.0, 134.4, 128.8, 128.1, 128.0, 127.9, 127.7, 83.0, 75.9, 69.1, 66.8, 65.1, 55.1, 49.3, 36.2, 33.3, 30.4, 23.5, 21.8, 19.8, 19.2, 14.8, 13.0 ppm; MS (CI, isobutane) *m/e* 430, 338, 267, 236, 186; HRMS (CI) *m/e* 430.2953 (430.2957 calcd for $C_{26}H_{40}NO_4$, MH).

Allopumiliotoxin 339A (5). Following the procedure described for the formation of **4**, Li (38 mg, 6 mmol, containing 2% Na) was added at −78 °C to a stirring solution of benzyl ether **52** (11 mg, 0.026 mmol) and 2:1 NH_3−THF (19 mL). The solution became deep blue within 3 min, 30 s later MeOH (3.5 mL) was added, and 3 min thereafter saturated aqueous NH_4Cl (7 mL) was added. The crude residues from two identical reactions were combined and purified on silica gel (9:1:0.15 $CHCl_3$−MeOH−NH_4OH) to give 13.5 mg (76%) of **5** as a colorless oil: $[\alpha]^{22}_D$ +68.2, $[\alpha]_{577}$ +75.0, $[\alpha]_{546}$ +90.0 (*c* 1.0, $CHCl_3$). A natural sample isolated from *D. pumilio* showed $[\alpha]^{22}_D$ +52.0, $[\alpha]_{577}$ +60.3, $[\alpha]_{546}$ +75.0 (*c* 0.5, $CHCl_3$), while a rotation of +29.4 (*c* 1.0, MeOH) is reported for allopumiliotoxin 339A.[4] Synthetic **5** exhibited TLC mobility and ^{13}C NMR and mass spectra indistinguishable from those of the natural product. Moreover, a 1:1 mixture of synthetic and natural **5** was homogeneous by TLC comparisons and by 500 MHz ^1H NMR analysis in $CDCl_3$ and CD_3OD.

Acknowledgment. This paper is dedicated with respect and affection to Nelson Leonard on the occasion of his 80th birthday. This research was supported by grants from the National Heart, Lung, and Blood Institute of the National Institutes of Health (HL-25854). NMR and mass spectra were determined at Irvine with instrumentation acquired with the assistance of the NSF Shared Instrumentation program. We particularly thank Dr. John Daly, Chief, Laboratory of Bioorganic Chemistry NIDDK, NIH, for samples of natural allopumiliotoxins 267A, 323B′ and 339A.

Supporting Information Available: Experimental procedures and characterization data for compounds **26**−**31** (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA961640Y