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# Convergent Approach to Pumiliotoxin Alkaloids. Asymmetric Total Synthesis of (+)-Pumiliotoxins A, B, and 225F

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A versatile convergent approach for preparing the pumiliotoxin alkaloids has been developed employing Pd(0)-catalyzed cross-coupling reactions between homoallylic organozincs and vinyl iodides. The (*Z*)-iodoalkylidene indolizidine **34**, which served as a common key intermediate, was synthesized through highly stereoselective addition of the chiral silylallene **19** to (*S*)-acetylpyrrolidine followed by a palladium-catalyzed intramolecular carbonylation−cyclization sequence. This synthetic process allowed the first total synthesis of (+)-pumiliotoxin 225F. The intermediate (*Z*)-iodoalkylidene indolizidine **34** obtained was converted to a homoallylzinc chloride derivative and subjected to homoallyl-vinyl cross-coupling with the (*E*)-vinyl iodide **42** using $Pd(PPh_3)_4$ catalyst to give the cross-coupled product **47** with a 1,5-diene side chain. Subsequent deprotection provided (+)-pumiliotoxin A. On the other hand, the (*Z*)-iodoalkylidene indolizidine **34** was transformed into the homoallyl-*tert*-butyl zinc derivative, which underwent palladium-catalyzed cross-coupling with the (*E*)-vinyl iodide **50** and subsequent deprotection to afford (+)-pumiliotoxin B.

## Introduction

Neotropical poison-dart frogs of the family Dendrobatidae have been a rich source of a remarkable variety of alkaloids with structurally unique features and biological significance.[1] Among these natural products, pumiliotoxins A (**6**) and B (**7**), isolated as the major toxic alkaloids from skin extracts of the Panamanian poison frog *Dendrobates pumilio* in 1967,[2] were the first representatives of the pumiliotoxin class. In the late 1970s, a simpler congener, pumiliotoxin 251D (**3**), was isolated from another dendrobatid frog.[3] These dendrobatid alkaloids had been thought to be unique to frogs of the dendrobatid genera. However, during the screening of skin extracts from various genera of other amphibian families, the pumiliotoxin class of alkaloids has been found to have a wide distribution in nondendrobatid frogs and toads, and the number of this class of natural products detected so far now totals up to more than 20.[1d] They are all characterized structurally by a (*Z*)-6-alkylidene-8-hydroxy-8-methylindolizidine ring system differing in only the alkylidene side chain.[1] These molecules have been shown to have modulatory effects on voltage-dependent sodium channels, therefore displaying, in some cases, potent cardiotonic and myotonic activity.[4] For the synthesis of the pumiliotoxins, one significant challenge is the stereoselective incorporation of the (*Z*)-alkylidene side chain at C-6 of the indolizidine nucleus. The selective generation of (*E*)- and (*Z*)-exocyclic olefins has traditionally been attained via $\pi$-bond construction employing the Wittig reaction or aldol condensation, but these methods have often been less than satisfactory. In

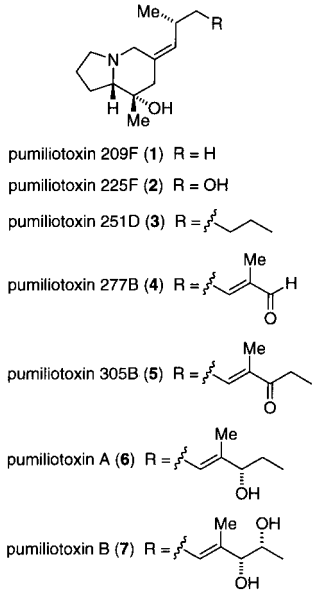


**FIGURE 1.** Representative pumiliotoxin class alkaloids.

(1) (a) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, pp 1−274. (b) Daly, J. W.; Garraffo, H. M.; Spande, T. F. *Alkaloids* **1993**, *43*, 185−288. (c) Daly, J. W. *Alkaloids* **1998**, *50*, 141−169. (d) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Amsterdam, 1999; Vol. 13, pp 1−161.

(2) Daly, J. W.; Myers, C. W. *Science* **1967**, *156*, 970−973.

(3) Daly, J. W.; Tokuyama, T,; Fujiwara, T.; Highet, R. J.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 830−836.

(4) Gusovsky, F.; Padget, W. L.; Creveling, C. R.; Daly, J. W. *Mol. Pharmacol.* **1992**, *42*, 1104−1108 and references therein, and also ref 1.

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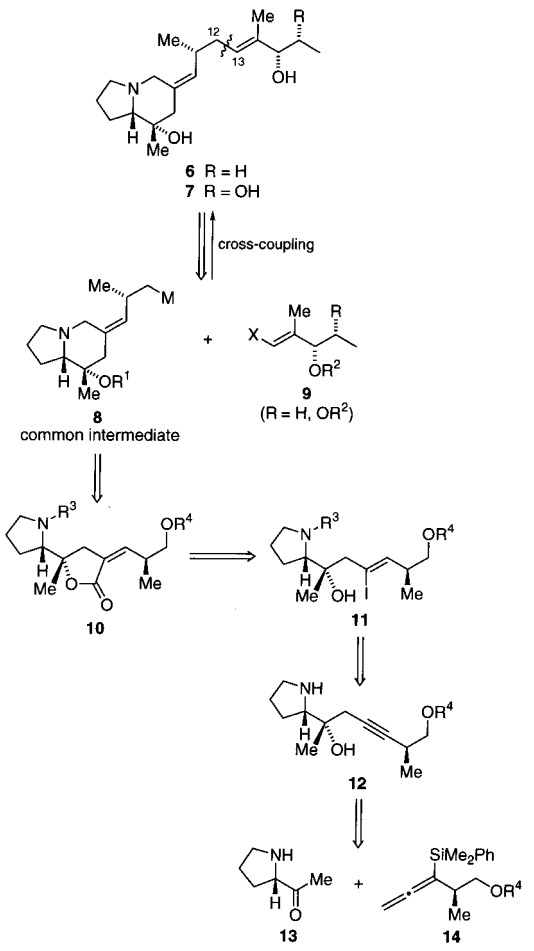
the search for control of the exocyclic alkene geometry as well as the piperidine ring construction, comprehensive efforts by the Overman group[5] have led to the development of the total synthesis of pumiliotoxins 251D (**3**), A (**6**), and B (**7**) via two fundamental approaches based on iminium ion-vinylsilane and iminium ion-alkyne cyclizations. After these pioneering studies, the synthesis of pumiliotoxin 251D (**3**) was reported by Gallagher and co-workers,[6] in which an aldol condensation of a bicyclic lactam was employed to introduce the alkylidene side chain. This intermediate bicyclic lactam was later synthesized by other routes,[7−11] which thus represent formal syntheses of pumiliotoxin 251D. Our own approach to the structural problem presented by this class of alkaloids has thus been to focus on developing stereoselective construction of the (*Z*)-alkylidene indolizidine as a common key intermediate and subsequent assembly of a variety of side chains by means of an organozinc-based homoallyl-vinyl cross-coupling reaction promoted by a palladium(0) catalyst. This process is relevant to a convergent entry into the total synthesis of pumiliotoxins 225F (**2**), A (**6**), and B (**7**).[12]

## Results and Discussion

**Synthetic Strategy.** Since the presence of the (*Z*)-alkylidene indolizidine moiety is the common structural motif shared by not only pumiliotoxins A (**6**) and B (**7**) but also all other pumiliotoxin alkaloids, the strategic disconnection of this class of alkaloids at the C-12−C-13 bond of the alkylidene side chain should be the most appropriate for the efficient and flexible synthesis of these natural products. Our synthetic plan for pumiliotoxins A (**6**) and B (**7**) thus called for connecting two fragments, a metal species **8** of the (*Z*)-alkylidene indolizidine and the alkenyl halides **9**, by cross-coupling reaction (Scheme 1). This approach utilizing **8** with a common fundamental structural unit of the pumiliotoxin alkaloids allows a convergent and general entry into this class of alkaloids. The organic moiety of **8** was anticipated to be obtained through stereoselective addition of a silylallene **14** to (*S*)-acetylpyrrolidine (**13**) followed by a sequence involving an intramolecular carbonylation of a vinyl iodide **11** and cyclization to the indolizidine skeleton as outlined in Scheme 1.

In the critical cross-coupling process between **8** and **9**, one potential problem associated with the transition

**SCHEME 1**




metal-catalyzed homoallyl-alkenyl coupling would be the tendency of the homoallylic metal compounds to undergo *β*-elimination.[13] This problem was overcome by Negishi,[14] who subjected homoallylic organozincs to the palladium-catalyzed conjugate substitution reaction with alkenyl halides to effect the construction of 1,5-dienes. We envisioned that this coupling chemistry associated with the organozincs effects the combination of **8** and **9** through a homoallyl-alkenyl coupling process to yield the 1,5-diene unit, which was expected to be adopted for incorporation of appropriate alkylidene side chains corresponding to pumiliotoxins A and B.

**Synthesis of the (*Z*)-Iodoalkylidene Indolizidine Intermediate.** According to the above discussion, synthesis of the common intermediate (*Z*)-iodoalkylidene indolizidine (**34** in Scheme 5) needed for the preparation of the corresponding zinc reagent was our initial objective. The synthesis began with the dibromo olefin **16**, prepared from O-monosilylated (2*S*)-2-methyl-1,3-propanediol (**15**)[15] via Swern oxidation[15c] followed by treat-

(5) (a) Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851−1853. (b) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192−4201. (c) Overman, L. E.; Lin, N.-H. *J. Org. Chem.* **1985**, *50*, 3669−3670. (d) Overman, L. E.; Sharp, M. J. *Tetrahedron Lett.* **1988**, *29*, 901−904. (e) Lin, N.-H.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062−9072.

(6) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652−2656.

(7) (a) Honda, T.; Hoshi, M.; Tsubuki, M. *Heterocycles* **1992**, *34*, 1515−1518. (b) Honda, T.; Hoshi, M.; Kanai, K.; Tsubuki, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2091−2101.

(8) (a) Cossy, J.; Cases, M.; Gomez-Pardo, D. *Synlett* **1996**, 909−910. (b) Cossy, J.; Cases, M.; Gomez-Pardo, D. *Bull. Soc. Chim. Fr.* **1997**, *134*, 141−144.

(9) Barrett, A. G. M.; Damiani, F. *J. Org. Chem.* **1999**, *64*, 1410−1411.

(10) Martin, S. F.; Bur, S. K. *Tetrahedron* **1999**, *55*, 8905−8914.

(11) Ni, Y.; Zhao, G.; Ding, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3264−3266.

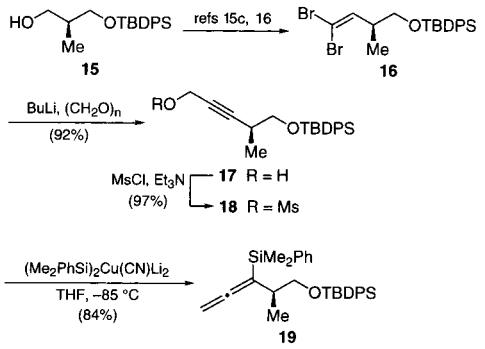
(12) Part of this work has been published in a preliminary form: Hirashima, S.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **1999**, *121*, 9873−9874.

(13) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340−348.

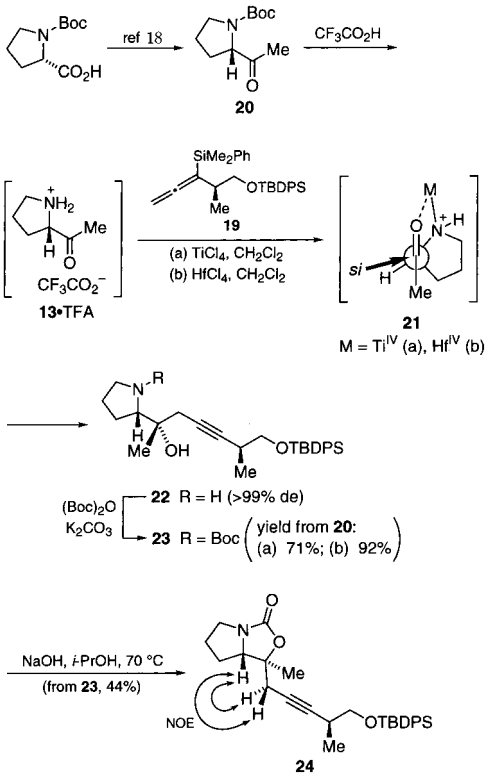
(14) (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298−3299. (b) Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223−5225.

(15) Prepared by a chiron approach from commercial methyl (*R*)-3-hydoxy-2-methylpropionate: (a) Schmittberger, T.; Uguen, D. *Tetrahedron Lett.* **1995**, *36*, 7445−7448. (b) Schmittberger, T.; Uguen, D. *Tetrahedron Lett.* **1997**, *38*, 2837−2840. (c) Matsushima, T.; Mori, M.; Zheng, B.-Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1999**, *47*, 308−321.

**SCHEME 2**



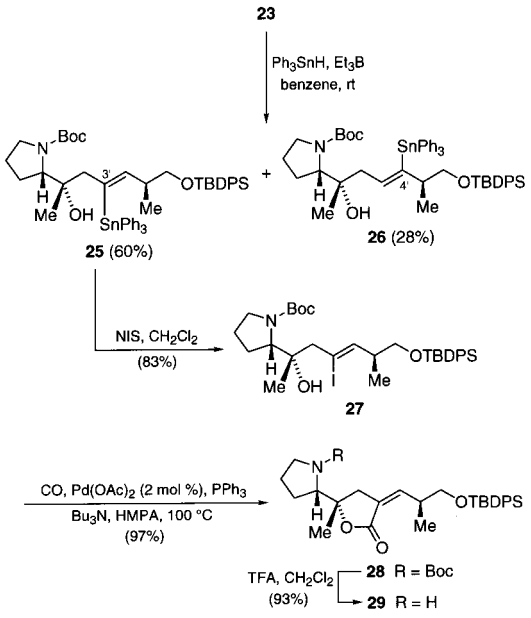

**SCHEME 3**



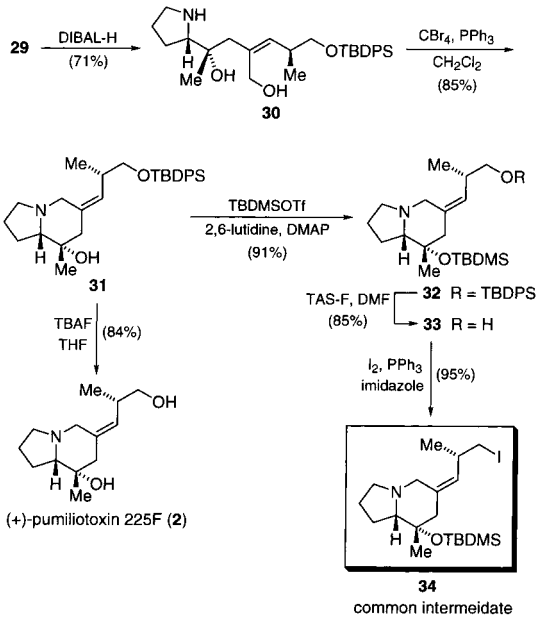

ment with $CBr_4/PPh_3$,[16] which was converted to the propargylic alcohol **17** upon treatment with BuLi and paraformaldehyde (Scheme 2). Construction of the allenylsilane **19** was successfully achieved using Fleming's method[17] by conversion to the mesylate **18** and subsequent treatment with the bis(dimethylphenylsilyl)cuprate reagent at −85 °C in a very short reaction time (3 min).

The trifluoroacetate salt of (*S*)-2-acetylpyrrolidine (**13**), available from the *N*-Boc derivative **20**[18] by deprotection with trifluoroacetic acid, was subjected to titanium(IV) chloride-mediated nucleophilic addition[19] of **19** to afford the desired homopropargylic alcohol **22**, which was isolated as the *N*-Boc derivative **23**, with complete stereocontrol in 71% overall yield; no trace of the other

**SCHEME 4**




**SCHEME 5**




diastereomer was detected by NMR analysis. When the reaction was performed using hafnium(IV) chloride as a Lewis acid, it yielded **23** as a single product more cleanly and in excellent overall yield (92%). The stereochemistry of **22** was determined by a NOESY experiment of the bicyclic carbamate **24** derived from **23** by base treatment. The facial selectivity realized in these propargylations can be rationalized by invoking a Lewis acid-chelate cyclic intermediate **21** involving the chelation of the NH and carbonyl groups with the metal.

Radical-initiated hydrostannylation of **23** proceeded with complete trans selectivity to give the pure (*Z*)-3′-stannyl alkene **25** (60%) after chromatographic separa-

(16) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912−4913.
(17) Fleming, I.; Terrett, N. K. *J. Organomet. Chem.* **1984**, *264*, 99−118.
(18) For preparation of *N*-Boc-(*S*)-2-acetylpyrrolidine (**20**) from *N*-Boc-L-proline, see: (a) Trost, B. M.; Scanlan, T. S. *J. Am. Chem. Soc.* **1989**, *111*, 4988−4990. (b) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179−2290.
(19) For the $TiCl_4$-mediated addition of allenylsilanes to carbonyl compounds, see: (a) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925−3927. (b) Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870−3878.

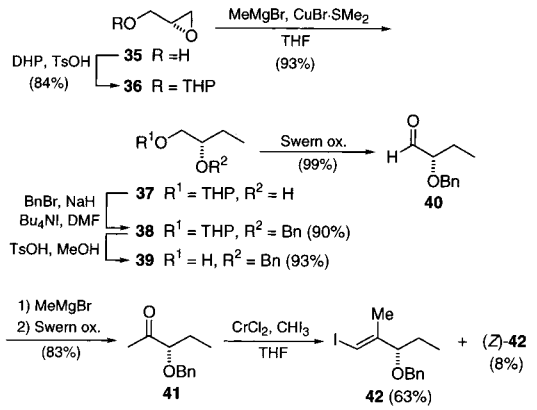
tion from the 4′-stannyl regioisomer **26** (28%) (Scheme 4). The assignment of the (*Z*)-stereochemistry of **25** was made on the basis of the large coupling constant (89.3 Hz) between Sn and the vinylic proton.[20] The regiocontrol of this hydrostannylation process would be rationalized by assuming coordination of a $Ph_3Sn^•$ radical to the OH group[21] and preferential attack of the $Ph_3Sn^•$ radical at the less hindered C-3′. Upon exposure of **25** to *N*-iodosuccinimide, iodolysis took place with complete retention of the (*Z*)-configuration to give the vinyl iodide **27**. Palladium-catalyzed carbonylation[22] of **27** smoothly occurred when treated with carbon monooxide and tributylamine in the presence of catalytic $Pd(OAc)_2$ (2 mol %) and $PPh_3$ (10 mol %) in HMPA at 100 °C,[23] furnishing the lactone **28** in excellent yield (97%). Compound **28** was converted to the amine **29** by *N*-Boc deprotection with TFA.

With the (*Z*)-alkylidene lactone **29** in hand, we next envisaged the construction of the indolizidine framework with the (Z)-alkylidene appendage. Thus, after DIBAL-H reduction, the resulting diol **30** underwent smooth intramolecular cyclodehydration using carbon tetrabromide and $PPh_3$[24] to form the (*Z*)-alkylidene indolizidine **31** in 85% yield (Scheme 5). Subsequent removal of the TBDPS protecting group with tetrabutylammonium fluoride resulted in the first total synthesis of (−)-pumiliotoxin 225F (**2**). The synthetic material displayed spectral properties ($^{13}C$ NMR and MS) that matched those of the natural product.[25] However, the observed rotation of synthetic **2** ($[\alpha]^{24}_D$ −25.3 (*c* 0.25, $CHCl_3$)) was significantly lower than the reported value ($[\alpha]_D$ −87.4 (*c* 0.23, $CHCl_3$)).[25] The reason for this discrepancy in the optical rotation is unclear at present, although it might be attributed to contamination by a small amount of a highly optically active impurity in the natural sample.

For the formation of the key intermediate (*Z*)-iodoalkylidene indolizidine **34**, **31** was protected as the TBDMS ether **32**. The selective deprotection of the primary TBDPS ether was successfully achieved by using difluorotrimethylsilicate (TAS-F)[26] to provide the primary alcohol **33**, which was then iodinated ($I_2$, $PPh_3$, imidazole) to give **34**.

**Preliminary Experiments of Cross-Coupling Reactions with the Vinyl Iodide.** Having established an efficient route for the synthesis of the indolizidine fragment **34** bearing the 6-alkylidene side chain with the required (*Z*)-configuration, we next examined the preparation of the C-13−C-17 vinylic side chain segment, i.e.,

**SCHEME 6**




(*E*)-vinyl iodide **42** in the homochiral form, which was needed as a coupling partner for the synthesis of (+)-pumiliotoxin A (**6**). Commercially available (*R*)-glycidol (**35**) was protected as the THP ether and underwent copper(I)-catalyzed epoxide ring-opening using methylmagnesium bromide to yield the (*S*)-2-butanol derivative **37** (Scheme 6). After O-benzylation of the secondary alcohol followed by deprotection of the THP group, the resulting primary alcohol **39** was oxidized by the Swern procedure to give the aldehyde **40**, which was converted to (3*S*)-3-(benzyloxy)-2-pentanone (**41**)[27] by the Grignard reaction (MeMgBr) and Swern oxidation sequence. This ketone **41** was subjected to iodo-olefination using the Takai protocol[28] of treatment with $CrCl_2$ and iodoform to produce stereoselectively the chromatographically separable (*E*)-vinyl iodide **42** (63%) and the (*Z*)-isomer (7%).

Preliminary experiments were performed in order to determine the feasibility of this vinyl iodide **42** as the coupling partner in the Pd(0)-catalyzed cross-coupling reaction with the organozinc compound.[29] Hence, the (*R*)-iodide **43**, prepared by iodination of the above-described (*S*)-alcohol **15**,[30] underwent halogen−metal exchange with 2 equiv of *t*-BuLi at −78 °C, followed by transmetalation with 1 equiv of $ZnCl_2$. Subsequent one-pot treatment of the in situ generated alkylzinc reagent **44** with the iodide **42** in the presence of catalytic $Pd(PPh_3)_4$ at room temperature led to the cross-coupled product **45** in 55% yield with complete retention of the (*E*)-geometry (Scheme 7).

**Synthesis of (+)-Pumiliotoxin A.** The stage was then set for the critical homoallyl-vinyl coupling with the (*Z*)-iodoalkylidene indolizidine **34** and the (*E*)-vinyl iodide **42** under conditions similar to those described above. Thus, **34** was subjected to halogen−metal exchange (*t*-BuLi, THF, −110 °C) followed by transmetalation with $ZnCl_2$ to generate the homoallylzinc derivative **46** in situ, which underwent cross-coupling reaction with **42** in the presence of catalytic $Pd(PPh_3)_4$ to give the cross-coupled

(20) In our earlier study, smaller coupling constants (ca. 35 Hz) were observed for (*E*)-stannyl alkenes prepared by syn selective palladium-catalyzed hydrostannylation in a nonradiacal manner. See: Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, *115*, 11393−11409.

(21) Nativi, C.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 820−826.

(22) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318−3326. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327−3331.

(23) Procedure according to Mori, M.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1978**, *43*, 1684−1687.

(24) For intramolecular cyclodehydration of amino alcohols via alkoxyphosphonium salts, see: (a) Stoilova, V.; Trifonov, L. S.; Orahovats, A. S. *Synthesis* **1979**, 105−106. (b) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876−2883.

(25) Tokuyama, T.; Tsujita, T.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron* **1991**, *47*, 5415−5424.

(26) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436−6437.

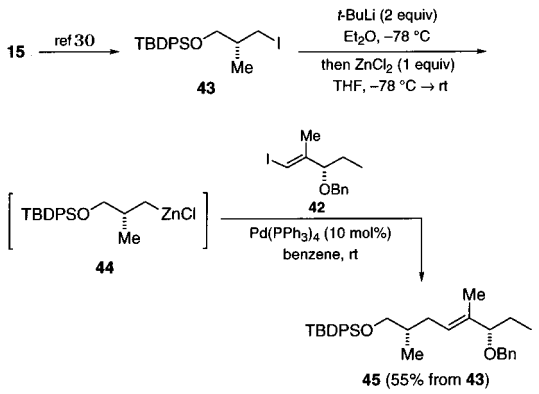
(27) For an alternative synthesis of the ketone **41** from (*S*)-2-methyl-1-penten-3-ol available by Sharpless kinetic resolution, see: ref 5e.

(28) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410

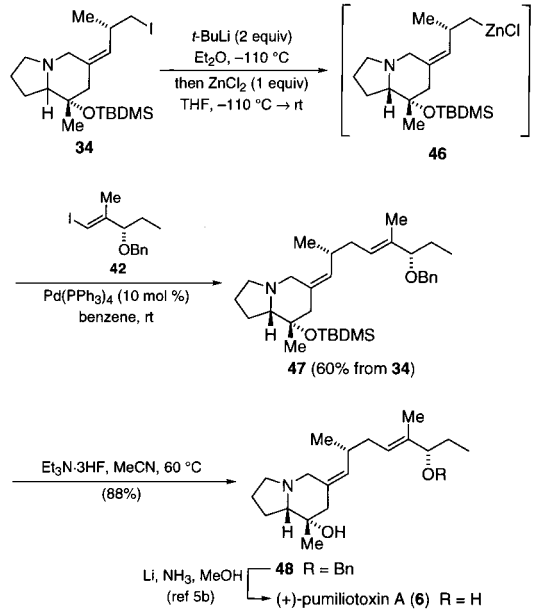
(29) For recent reviews on cross-coupling reactions of zinc organometallics, see: (a) Erdik, E. *Tetrahedron* **1992**, *48*, 9577−9648. (b) Diederich, F., Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998.

(30) For the conversion of the alcohol **15** into the iodide **43**, see the literature cited as 15a,b in ref 15.

**SCHEME 7**



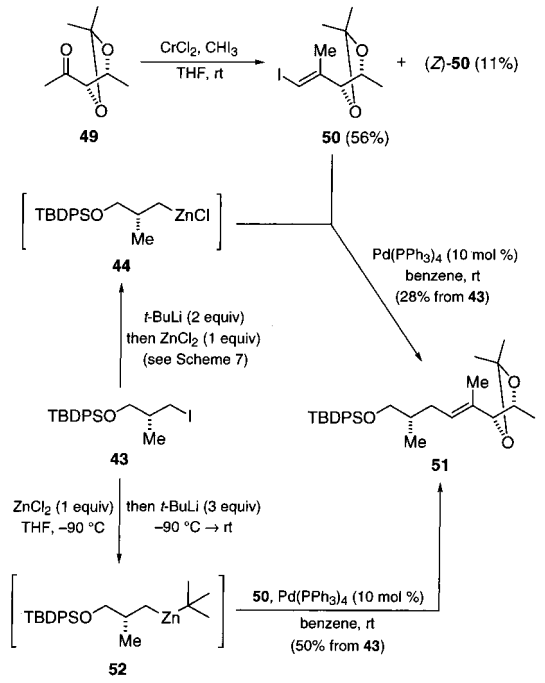

**SCHEME 8**




product **47** in 60% yield from **34** with complete retention of configuration of the stereocenter(s) and (*Z*)-geometry (Scheme 8). When deprotection of the TBDMS group of **47** was carried out using tetrabutylammonium fluoride in DMF at 60 °C, the reaction was very slow and was not complete after 2 days, resulting in 66% yield of the secondary alcohol **48** along with 18% recovery of **47**. However, the use of triethylamine tris(hydrogen fluoride)[31] (MeCN, 60 °C, 24 h) proved to be effective for the silyl deprotection and provided **48** ($[\alpha]^{22}_D$ −2.7 (*c* 0.59, $CHCl_3$), lit.[5c] $[\alpha]^{25}_D$ −2.1 (*c* 0.70, $CHCl_3$)) in 88% yield. Subsequent cleavage of the benzyl ether through the Overman protocol (Li, $NH_3$, MeOH)[5b] produced (+)-pumiliotoxin A (**6**) ($[\alpha]^{25}_D$ +16.7 (*c* 0.84, $CHCl_3$), lit.[5b] $[\alpha]^{23}_D$ +14.9 (*c* 0.65, $CHCl_3$)). The $^1H$ and $^{13}C$ NMR data of synthetic **6** were identical with those of natural pumiliotoxin A.[32]

**Synthesis of (+)-Pumiliotoxin B.** Having achieved the total synthesis of (+)-pumiliotoxin A (**6**) based on the homoallyl-vinyl cross-coupling strategy utilizing the (Z)-iodoalkylidene indolizidine **34** as a key intermediate, we

**SCHEME 9**

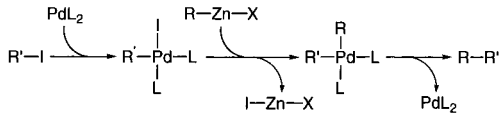



next directed our efforts toward the synthesis of (+)-pumiliotoxin B (**7**) by applying this approach. In this case, the (*E*)-vinyl iodide **50** was needed as a C-13−C-17 side chain fragment for the coupling reaction. Thus, (3*S*,4*R*)-3,4-(isopropylidenedioxy)-2-propanone (**49**)[33] was transformed via iodoolefination using the Takai protocol ($CrCl_2$, $CHI_3$)[28] into the desired (*E*)-vinyl iodide **50** (56%) along with the (*Z*)-isomer (11%). To test the possibility of exploiting the (*E*)-iodide **50** for the organozinc-based cross-coupling reaction, the above-described alkylzinc chloride **44** was allowed to react with **50** under catalytic $Pd(PPh_3)_4$ in a manner similar to that described above for the coupling reaction of the (*E*)-vinyl iodide **42** with the alkylzinc **44**. However, this procedure resulted in the formation of the desired coupled product **51** in low yield (28%) together with a complex mixture (Scheme 9).

The low yield in the formation of the cross-coupled product **51** was presumably due to accompanying cleavage of the isopropylidene acetal group by a Lewis acidic zinc halide (IZnCl), which would be generated during the coupling process corresponding to the transmetalation between the palladium(II) complex, $R'PdIL_2$, and alkylzinc chloride, RZnCl, as indicated in eq 1 wherein X = Cl.[34] An alternative coupling approach was then considered, and it was envisioned that the generation of the zinc halide, IZnCl, could be avoided by use of diorganozincs, $R_2Zn$ (X = R in eq 1), which are claimed to be more reactive than organozinc halides and undergo transmetalation reactions more readily.[35] Nevertheless, only few reports[36] concerning the palladium-catalyzed[37] cross-coupling reaction using the diorganozinc reagents have been published, and application of this reaction to construction of complex molecules such as natural products had never been described.[38] However, recent reports by Smith et al.[39] demonstrated in natural product syn-

(31) Review: McClinton, M. A. *Aldrichim. Acta* **1995**, *28*, 31−35.
(32) Tokuyama, T.; Daly, J. W.; Highet, R. J. *Tetrahedron* **1984**, *40*, 1183−1190.
(33) For the preparation of **49**, see the literature cited in ref 20.
(34) Cf. ref 29b.
(35) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188.

thesis the efficiency of a functionalized dialkylzinc derivative for the alkyl-vinyl coupling based on the modified Negishi cross-coupling reaction.




(1)

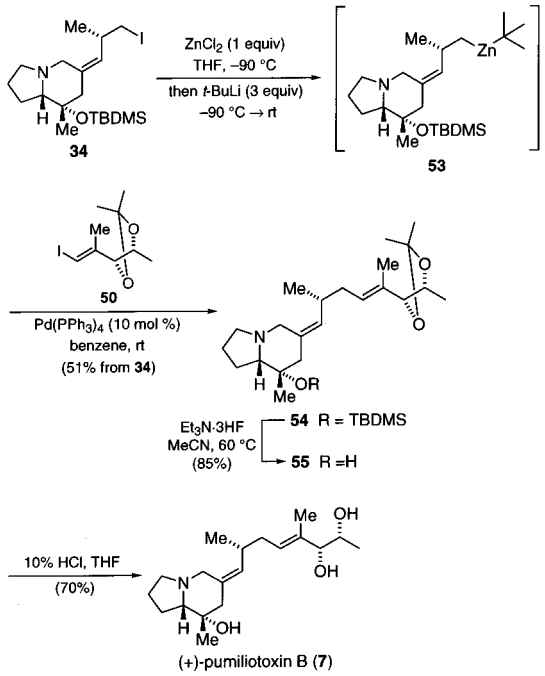
In view of this protocol, we considered employing the dialkylzinc instead of the alkylzinc chloride for the cross-coupling reaction of the vinyl iodide **50**. Hence, the mixed dialkylzinc **52** was prepared in situ by addition of a THF solution containing 1 equiv of $ZnCl_2$ to a solution of the alkyl iodide **43** in ether at −90 °C followed by addition of 3 equiv of *t*-BuLi. After being warmed to room temperature, the resulting mixture was treated with the (*E*)-vinyl iodide **50** along with $Pd(PPh_3)_2$ catalyst, furnishing the cross-coupled product **51** in 50% yield (Scheme 9).

With these results, we were poised to incorporate the homoallyl-vinyl coupling utilizing the diorganozinc for the synthesis of pumiliotoxin B (**7**). Accordingly, we subjected the (*Z*)-iodoalkylidene indolizidine **34** as the homoallylic fragment to the same conditions (1 equiv of $ZnCl_2$, and then 3 equiv of *t*-BuLi) used above in the preparation of the dialkylzinc **52**, leading to the in situ formation of the homoallyl-*tert*-butyl organozinc intermediate **53** (Scheme 10). Subsequent treatment with the (*E*)-vinyl iodide **50** under the palladium(0) catalyst resulted in the desired cross-coupled product **54** in 51% yield. Deprotection of the TBDMS group with $Et_3N{\cdot}3HF$ gave the free secondary alcohol **55**, which was then treated with hydrochloric acid to remove the acetonide protecting group to provide (+)-pumiliotoxin B (**7**) ($[\alpha]^{26}_D$ +22.1 (*c* 0.34, MeOH), lit.[5e] $[\alpha]^{20}_D$ +20.1 (*c* 1.0, MeOH)), which gave spectral data (IR, MS, and $^1H$ and $^{13}C$ NMR) identical with those reported in the literature.[5b]

## Conclusion

The new strategy developed herein has served to demonstrate the potential of the homoallyl-vinyl coupling protocol for a general entry into the convergent asymmetric synthesis of the pumiliotoxin alkaloids. It relies on a palladium(0)-based cross-coupling reaction employing homoallylic zinc molecules derived from the (*Z*)-iodoalkylidene indolizidine which served as an advanced common synthetic intermediate, leading to an efficient approach to the asymmetric synthesis of (+)-pumiliotoxins A and B. To the best of our knowledge, this study provides the first example of utilization of highly functionalized nitrogenous organozinc derivatives in the homoallylic cross-coupling strategy for the natural products synthesis.[40]

**SCHEME 10**




## Experimental Section

***tert*-Butyl (2*S*)-2-[(1*S*,5*S*)-5-{[*tert*-Butyl(diphenyl)silyl]-oxy}-1-hydroxy-1,5-dimethyl-3-hexynyl]-1-pyrrolidinecarboxylate (23).** To a solution of **20** (157 mg, 0.736 mmol) in $CH_2Cl_2$ (4 mL) was added trifluoroacetic acid (588 mg, 5.16 mmol). The mixture was stirred at room temperature for 3 h and then concentrated in vacuo to give (*S*)-2-acetylpyrrolidine trifluoroacetate (**13**·TFA) as a pale yellow oil. The trifluoroacetate obtained was redissolved in $CH_2Cl_2$ (2 mL) and then added to a solution of $HfCl_4$ (708 mg, 2.21 mmol) in $CH_2Cl_2$ (3 mL) at −78 °C. After stirring for 30 min, a solution of **19** (1.04 g, 2.21 mmol) in $CH_2Cl_2$ (2 mL) was added dropwise over 5 min, and the reaction mixture was allowed to warm very slowly to 0 °C over 2 h. To this was added 30% aqueous $K_2CO_3$ (5 mL) followed by di-*tert*-butyl dicarbonate (482 mg, 2.21 mmol). After being stirred at room temperature for 12 h, the mixture was extracted with $CHCl_3$ (3 × 30 mL). The combined extracts were washed with water (10 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the residual oil by chromatography (20:1 hexane−AcOEt) provided **23** (374 mg, 92%) as a colorless oil: $[\alpha]^{24}_D$ −26.6 (*c* 0.28, $CHCl_3$); IR (neat) 3348, 1666 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.11

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(37) In these coupling reactions between the zinc homoenolate and aryl (or vinyl) halides, the $Pd(II)Cl_2$ has been used as a catalyst instead of Pd(0).

(38) For some recent examples of applications of palladium-catalyzed couplings using organozinc halides in natural products synthesis, see: (a) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558−559. (b) Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3158−3175. (c) Smith, A. B., III; Friestad, G. K.; Duan, J. J.-W.; Barbosa, J.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Spoors, P. G.; Bertounesque, E.; Salvatore, B. A. *J. Org. Chem.* **1998**, *63*, 7596−7597. (d) Hu, T.; Panek, J. S. *J. Org. Chem.* **1999**, *64*, 3000−3001. (e) Sasaki, M.; Koike, T.; Sakai, R.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 3923−3926. (f) Masaki, H.; Mizozoe, T.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Tetrahedron Lett.* **2000**, *41*, 4801−4804. (g) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974−9983.

(39) (a) Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011−12012. (b) Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654−8664.

(40) Only a limited number of applications of the palladium-catalyzed homoallyl-alkenyl coupling strategy in natural product synthesis have been published, using non-nitrogenous homoallylic zinc halides. See ref 14 and also: (a) McMurry, J. F.; Bosch, G. K. *J. Org. Chem.* **1987**, *52*, 4885−4893. (b) Asao, K.; Iio, H.; Tokoroyama, T. *Tetrahedron Lett.* **1989**, *30*, 6401−6404. (c) William, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198−11199.

(9H, s), 1.09 (3H, s), 1.21 (3H, d, $J$ = 6.8 Hz), 1.46 (9H, s), 1.60−1.87 (3H, m), 2.03 (1H, br s), 2.30 and 2.35 (2H, AB q, $J$ = 16.8 Hz), 2.61−2.72 (1H, m), 3.17 (1H, ddd, $J$ = 11.0, 7.2, 7.2 Hz), 3.52 (1H, A part of ABX, $J$ = 9.5, 7.9 Hz), 3.63 (1H, br s), 3.72 (1H, B part of ABX, $J$ = 9.5, 5.5 Hz), 4.05 (1H, dd, $J$ = 7.8, 5.7 Hz), 5.68 (1H, br s), 7.35−7.44 (6H m), 7.66−7.69 (4H, m,); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 17.8, 19.3, 22.1, 24.3, 26.9, 28.3, 28.5, 29.2, 31.4, 48.2, 65.4, 68.0, 74.8, 77.5, 80.5, 84.3, 127.7, 129.6, 133.8, 135.6, 157.7; CIMS (isobutane) *m*/*z* 550 ($MH^+$); EIMS *m*/*z* (rel intensity) 549 ($M^+$, 0.02), 448 (0.7), 436 (5), 392 (17), 379 (6), 358 (11), 314 (10), 199 (18), 135 (14), 114 (100). Anal. Calcd for $C_{33}H_{47}NO_4Si$: C, 72.09; H, 8.62; N, 2.55. Found: C, 71.74; H, 8.52; N, 2.62.

***tert*-Butyl (2*S*)-2-[(1*S*,3*Z*,5*S*)-6-{[*tert*-Butyl(diphenyl)silyl]oxy}-1-hydroxy-1,5-dimethyl-3-(triphenylstannyl)-3-hexynyl]-1-pyrrolidinecarboxylate (25).** To a solution of **23** (708 mg, 1.29 mmol) in benzene was added triphenyltin hydride (2.26 g, 6.44 mmol) followed by triethylborane (1.06 M solution in hexane, 0.608 mL, 0.644 mmol), and the mixture was stirred at room temperature. After 5 days, the mixture was diluted with AcOEt (100 mL), washed with water (10 mL) and brine (10 mL), and dried ($MgSO_4$). Removal of the solvent by evaporation in vacuo followed by chromatography (100:1 hexane−AcOEt) afforded **25** (707 mg, 60%) as a white amorphous powder: $[\alpha]^{26}_D$ +21.4 (*c* 0.43, $CHCl_3$); IR (neat) 3303, 1663 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.94 (3H, d, $J$ = 6.5 Hz), 1.05 (3H, s), 1.07 (9H, s), 1.48 (9H, s), 1.50−1.76 (3H, m), 1.94 (1H, br s), 2.42 and 2.60 (2H, AB q, $J$ = 12.5 Hz), 2.44−2.61 (1H, m), 3.04 (1H, br s), 3.45 (2H, s), 3.58 (1H, br s), 3.80 (1H, br t, $J$ = 7.0 Hz), 5.43 (1H, br s), 6.25 (1H, d, $J$ = 9.9 Hz, $J_{Sn-H}$ = 89.3 Hz) 7.33−7.46 (15H, m), 7.61−7.75 (10H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 17.8, 19.3, 21.3, 24.2, 26.9, 28.0, 28.4, 41.9, 48.1, 49.2, 66.2, 68.4, 76.9, 80.2, 127.5, 127.9, 128.1, 128.3, 129.4, 133.8, 134.0, 135.7, 137.2, 137.4, 137.6, 141.9, 149.2, 157.7; EIMS *m*/*z* (rel intensity) 824 ($M^+$ − Ph, $Sn^{120}$, 11), 822 ($M^+$ − Ph, $Sn^{118}$, 9), 724 (6), 653 (100). Anal. Calcd for $C_{51}H_{63}NO_4SiSn$: C, 68.00; H, 7.05; N, 1.55. Found: C, 67.71; H, 6.99; N, 1.62.

Further elution provided the (*Z*)-4′-stannyl regioisomer **26** (1.29 g, 28%) as a white amorphous powder: $[\alpha]^{26}_D$ −41.7 (*c* 0.44, $CHCl_3$); IR (neat) 3349, 1663 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.72 (3H, s), 1.02 (9H, s), 1.09 (3H, d, $J$ = 6.7 Hz), 1.34−1.50 (4H, m), 1.45 (9H, s), 2.08−2.17 (2H, m), 2.81 (1H, sextet, $J$ = 6.7 Hz), 2.94 (1H, dt, $J$ = 10.6, 7.0 Hz), 3.45 (1H, dd, $J$ = 9.6, 7.7 Hz), 3.49 (1H, br s), 3.66−3.70 (2H, m), 6.00 (1H, br s), 6.76 (1H, br s, $J_{Sn-H}$ = 88.7 Hz), 7.28−7.43 (15H, m), 7.48−7.63 (10H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 18.3, 19.3, 20,8, 24.0, 26.9, 27.8, 28.4, 45.1, 46.8, 48.1, 66.2, 68.6, 75.7, 80.5, 127.5, 127.6, 128.2, 128.5, 128.7, 129.4, 134.0, 135.6, 137.0, 137.2, 137.4, 139.4, 139.9, 145.3, 158.0; EIMS *m*/*z* (rel intensity) 824 ($M^+$ − Ph, $Sn^{120}$, 4), 822 ($M^+$ − Ph, $Sn^{118}$, 3), 770 (6), 750 (11), 653 (100). Anal. Calcd for $C_{51}H_{63}NO_4SiSn$: C, 68.00; H, 7.05; N, 1.55. Found: C, 67.63; H, 7.14; N, 1.61.

***tert*-Butyl (2*S*)-2-[(1*S*,3*Z*,5*S*)-6-{[*tert*-Butyl(diphenyl)silyl]oxy}-1-hydroxy-3-iodo-1,5-dimethyl-3-hexynyl]-1-pyrrolidinecarboxylate (27).** To an ice-cooled, stirred solution of **25** (656 mg, 0.728 mmol) in $CH_2Cl_2$ (7.3 mL) was added solid *N*-iodosuccinimide (492 mg, 2.18 mmol) in one portion. After being stirred for 30 min, the mixture was diluted with $Et_2O$ (150 mL), washed successively with 5% aqueous $NaHSO_3$ (10 mL), water (10 mL), and brine (10 mL), and dried ($MgSO_4$). After concentration in vacuo, the residue was purified by chromatography (20:1 hexane−AcOEt) to give **27** (409 mg, 83%) as a colorless oil: $[\alpha]^{26}_D$ +5.3 (c 0.57, $CHCl_3$); IR (neat) 3345, 1665 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.06 (12H, s), 1.07 (3H, d, $J$ = 6.3 Hz), 1.47 (9H, s), 1.66−1.77 (2H, m), 1.78−1.91 (1H, m), 1.99−2.09 (1H, m), 2.67−2.85 (3H, m), 3.23 (1H, dt, $J$ = 11.0, Hz), 3.54−3.65 (3H, m, including dd at 3.56 ppm, $J$ = 9.7, 6.4 Hz, and dd at 3.63 ppm, $J$ = 9.7, 5.8 Hz), 4.05 (1H, dd, $J$ = 8.1, 3.7 Hz), 5.41 (1H, br s), 5.61 (1H, d, $J$ = 8.1 Hz) 7.36−7.43 (6H, m), 7.67−7.69 (4H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 16.0, 19.3, 22.4, 24.3, 26.9, 28.5, 44.8, 48.2, 54.3, 64.8, 67.3, 77.1, 80.5, 98.7, 127.6, 129.5, 133.8, 135.7, 142.8, 158.1; CIMS (isobutane) *m*/*z* 678 ($MH^+$); EIMS *m*/*z* (rel intensity) 677 ($M^+$, 0.2), 620 (0.4), 576 (6), 564 (14), 520 (100), 486 (69), 429 (48). Anal. Calcd for $C_{33}H_{48}INO_4Si$: C, 58.48; H, 7.14; N, 2.07. Found: C, 58.13; H, 7.06; N, 1.99.

***tert*-Butyl (2*S*)-2-[(2*S*,4*Z*)-4-((2*S*)-3-{[*tert*-Butyl(diphenyl)silyl]oxy}-2-methylpropylidene)-2-methyl-5-oxotetrahydro-2-furanyl]-1-pyrrolidinecarboxylate (28).** To a solution of **27** (409 mg, 0.603 mmol) in hexamethylphosphoramide (6.0 mL) were added palladium(II) acetate (3.0 mg, 0.012 mmol), triphenylphosphine (16.0 mg, 0.0603 mmol), and tributylamine (134 mg, 0.723 mmol). The air in the reaction vessel was evacuated, and a balloon of carbon monoxide gas was attached. The mixture was heated to 100 °C and stirred for 4 h. After being cooled, the mixture was diluted with AcOEt (100 mL) and washed successively with 1 N aqueous HCl (10 mL), water (3 × 10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and chromatographed (10:1 hexane−AcOEt) to afford **28** (338 mg, 97%) as a colorless oil: $[\alpha]^{28}_D$ −32.2 (*c* 0.52, $CHCl_3$); IR (neat) 1755, 1688 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.04 (9H, s), 1.10 (3H, d, $J$ = 6.6 Hz), 1.26 (6H, br s), 1.37 (3H, br s), 1.44 (3H, br s), 1.71 (1H, br s), 1.88 (1H, br s), 1.95−2.12 (2H, br m), 2.48 (1H, dd, $J$ = 16.4, 1.9 Hz), 2.92 (1H, br s), 3.30−3.65 (4H, m, including dd at 3.59 ppm, $J$ = 9.5, 4.5 Hz), 3.90 (1H, br s), 4.00 (1H, d, $J$ = 8.3 Hz), 5.95 (1H, d, $J$ = 9.9 Hz), 7.35−7.41 (6H, m), 7.65−7.67 (4H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 17.2, 19.3, 24.7, 25.2, 26.5, 26.9, 28.3, 28.5, 34.3, 39.0, 47.3, 63.2, 67.8, 79.7, 85.8, 126.3, 127.6, 129.5, 133.6, 133.9, 135.7, 143.0, 156.4, 169.0; CIMS (isobutane) *m*/*z* 578 ($MH^+$); EIMS *m*/*z* (rel intensity) 578 ($M^+$ + 1, 0.1), 521 (0.2), 504 (2), 464 (58), 446 (18), 420 (23), 402 (12), 386 (26), 342 (45), 204 (33), 199 (39), 170 (18), 135 (42), 114 (100). Anal. Calcd for $C_{34}H_{47}NO_5Si$: C, 70.67; H, 8.20; N, 2.42. Found: C, 70.43; H, 8.08; N, 2.39.

**(3*Z*,5*S*)-3-((2*S*)-3-{[*tert*-Butyl(diphenyl)silyl]oxy}-2-methylpropylidene)-5-methyl-5-[(2*S*)-pyrrolidinyl]dihydro-2(3*H*)-furanone (29).** To a solution of **28** (693 mg, 1.20 mmol) in $CH_2Cl_2$ (8.0 mL) was added trifluoroacetic acid (1.37 g, 12.0 mmol), and the resulting solution was stirred at room temperature. After 2 h, the mixture was made basic by addition of 30% aqueous $K_2CO_3$ (10 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the residual oil by chromatography (700:10:1 $CHCl_3$−MeOH−29% $NH_4OH$) provided **29** (534 mg, 93%) as a colorless oil: $[\alpha]^{28}_D$ +36.4 (*c* 1.06, $CHCl_3$); IR (neat) 3361, 1749 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.040 (3H, d, $J$ = 6.6 Hz), 1.043 (9H, s), 1.38 (3H, s), 1.47−1.57 (1H, m), 1.71−1.89 (3H, m), 2.55 (1H, dd, $J$ = 16.3, 2.2 Hz), 2.83−2.95 (3H, m), 3.17 (1H, t, $J$ = 7.8 Hz), 3.58 (1H, A part of ABX, $J$ = 9.7, 6.1 Hz), 3.61 (1H, B part of ABX, $J$ = 9.7, 5.3 Hz), 3.89−3.99 (1H, m), 6.05 (1H, dt, $J$ = 10.0, 2.2 Hz), 7.35−7.44 (6H, m), 7.63−7.68 (4H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 16.8, 19.4, 24.2, 26.0, 26.5, 26.9, 34.1, 38.8, 47.2, 65.6, 68.2, 84.4, 125.9, 127.7, 129.6, 133.8, 135.7, 146.1, 169.2; CIMS (isobutane) *m*/*z* 478 ($MH^+$); EIMS *m*/*z* (rel intensity) 477 ($M^+$, 0.4), 420 (8), 342 (4), 204 (9), 199 (10), 135 (13), 70 (100); HRMS (EI) calcd for $C_{29}H_{39}NO_3Si$ ($M^+$) 477.2699, found 477.2703.

**(3*Z*,5*S*)-3-((2*S*)-3-{[*tert*-Butyl(diphenyl)silyl]oxy}-2-methylpropylidene)-4-[(2*S*)-pyrrolidinyl]-1,4-pentanediol (30).** To a cooled (−30 °C), stirred solution of **29** (449 mg, 0.940 mmol) in toluene (7 mL) was added dropwise diisobutylaluminum hydride (1.01 M solution in toluene, 2.79 mL, 2.82 mmol). After the mixture was stirred at −30 °C for 30 min, 30% aqueous $K_2CO_3$ (1 mL) was added, and the mixture was stirred at room temperature for 1 h. The resulting cloudy solution was dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude oil, which was purified by chromatography (300:10:1 $CHCl_3$−MeOH−29% $NH_4OH$) to provide **30** (321 mg, 71%) as a colorless oil: $[\alpha]^{24}_D$ −4.0 (*c* 0.53, $CHCl_3$); IR (neat) 3307 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl3) $\delta$ 0.98 (3H, d, $J$ = 6.7 Hz), 1.05 (9H, s), 1.09 (3H, s), 1.49−1.66 (2H, m),

1.70−1.79 (2H, m), 2.24 and 2.30 (2H, AB q, $J$ = 13.6 Hz), 2.75−2.85 (3H, m), 3.05 (1H, dd, $J$ = 8.1, 7.2 Hz), 3.47 (1H, A part of ABX, $J$ = 9.7, 6.9 Hz), 3.52 (1H, B part of ABX, $J$ = 9.7, 6.1 Hz), 3.8 (2H, br), 4.06 and 4.17 (2H, AB q, $J$ = 12.4 Hz), 5.11 (1H, d, $J$ = 9.5 Hz), 7.36−7.44 (6H, m), 7.65−7.67 (4H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 17.7, 19.3, 23.6, 26.6, 26.7, 26.9, 35.2, 46.8, 49.9, 61.3, 66.0, 68.8, 73.0, 127.6, 129.6, 133.8, 135.4, 135.6, 136.4; CIMS (isobutane) $m/z$ 482 ($MH^+$); EIMS $m/z$ (rel intensity) 481 ($M^+$, 0.3), 424 (9), 406 (6), 199 (15), 137 (11), 114 (15), 70 (100); HRMS (EI) calcd for $C_{29}H_{43}NO_3Si$ ($M^+$) 481.3012, found 481.3017.

**(6*Z*,8*S*,8a*S*)-6-((2*S*)-3-{[*tert*-Butyl(diphenyl)silyl]oxy}-2-methylpropylidene)-8-methyloctahydro-8-indolizinol (31).** To an ice-cooled, stirred solution of **30** (51.0 mg, 0.106 mmol) in $CH_2Cl_2$ (0.7 mL) was added triphenylphosphine (42.0 mg, 0.159 mmol) followed by carbon tetrabromide (49.0 mg, 0.148 mmol). After being stirred at room temperature for 1 h, the mixture was diluted with $CHCl_3$ (50 mL), washed with 1 N aqueous NaOH (3 mL) and brine (10 mL), and dried ($MgSO_4$). Evaporation of the solvent in vacuo and purification of the residue by chromatography (500:50:1 $CHCl_3$−MeOH−29% $NH_4OH$) provided **31** (42.0 mg, 85%) as a colorless oil: $[\alpha]^{24}_D$ +25.6 (*c* 1.14, $CHCl_3$); IR (neat) 3507, 2787 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.01 (3H, d, $J$ = 6.7 Hz), 1.04 (9H, s), 1.12 (3H, s), 1.61−1.73 (4H, m), 1.90−1.98 (1H, m), 2.06 and 2.14 (2H, AB q, $J$ = 13.7 Hz), 2.10−2.21 (1H, m), 2.24 (1H, d, $J$ = 12.0 Hz), 2.55−2.68 (2H, m), 2.79−3.07 (1H, m), 3.38 (1H, A part of ABX, $J$ = 9.7, 6.5 Hz), 3.43 (1H, B part of ABX, $J$ = 9.7, 7.1 Hz), 3.65 (2H, d, $J$ = 12.0 Hz), 5.02 (1H, d, $J$ = 9.3 Hz), 7.35−7.44 (6H, m), 7.63−7.65 (4H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 17.7, 19.3, 21.1, 23.2, 24.3, 26.9, 35.0, 48.8, 53.2, 54.6, 68.4, 68.7, 71.7, 127.6, 129.6, 130.8, 132.2, 134.0, 135.6; CIMS (isobutane) $m/z$ 464 ($MH^+$); EIMS $m/z$ (rel intensity) 463 ($M^+$, 5), 406 (10), 328 (2), 199 (13), 166 (100).

**(−)-Pumiliotoxin 225F (2).** To a stirred solution of **31** (45.0 mg, 0.097 mmol) in THF (1.0 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.194 mL, 0.194 mmol), and the mixture was stirred at room temperature. After 2 h, the mixture was diluted with $CHCl_3$ (50 mL), washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product obtained was purified by chromatography (400:10:1 $CHCl_3$−MeOH−29% $NH_4OH$) to afford **2** (18.5 mg, 84%) as a colorless oil: $[\alpha]^{24}_D$ −25.5 (*c* 0.33, $CHCl_3$); IR (neat) 3407, 2794 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.99 (3H, d, $J$ = 6.7 Hz), 1.14 (3H, s), 1.64−1.78 (4H, m), 1.97−2.03 (1H, m), 2.15 and 2.20 (2H, AB q, $J$ = 14.1 Hz), 2.19−2.28 (1H, m), 2.41 (1H, d, $J$ = 12.0 Hz), 2.62−2.73 (2H, m), 3.04−3.08 (1H, m), 3.29 (1H, A part of ABX, $J$ = 10.5, 8.2 Hz), 3.46 (1H, B part of ABX, $J$ = 10.5, 5.9 Hz), 3.84 (1H, d, $J$ = 12.0 Hz), 5.04 (1H, d, $J$ = 9.5 Hz); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 17.3, 21.1, 23.2, 24.3, 35.2, 49.0, 53.3, 54.5, 67.8, 68.5, 71.7, 130.3, 134.2; CIMS (isobutane) $m/z$ 226 ($MH^+$); EIMS $m/z$ (rel intensity) 225 ($M^+$, 11), 194 (16), 166 (79), 112 (16), 70 (100); HRMS (EI) calcd for $C_{13}H_{23}NO_2$ ($M^+$) 225.1729, found 225.1720.

**(6*Z*,8*S*,8a*S*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-((2*S*)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-2-methylpropylidene)-8-methyloctahydroindolizine (32).** To an ice-cooled, stirred mixture of **31** (213 mg, 0.459 mmol), 4-(dimethylamino)-pyridine (6.0 mg, 0.046 mmol), and 2,6-lutidine (151 mg, 1.41 mmol) in $CH_2Cl_2$ (1.5 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (364 mg, 1.38 mmol). The resulting mixture was stirred at 0 °C for 30 min, and the reaction was quenched by addition of 1 N aqueous NaOH (10 mL). After extraction with $Et_2O$ (3 × 40 mL), the combined extracts were washed with water (10 mL) and then brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by chromatography (750:50:1 $CHCl_3$−MeOH−29% $NH_4OH$) gave **32** (241 mg, 91%) as a colorless oil: $[\alpha]^{22}_D$ +17.5 (*c* 1.14, $CHCl_3$); IR (neat) 2773 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.069 (3H, s), 0.074 (3H, s), 0.85 (9 H, s), 1.00 (3H, d, $J$ = 6.6 Hz), 1.04 (9H, s), 1.14 (3H, s), 1.59−1.82 (5H, m), 2.02 and 2.20 (2H, AB q, $J$ = 14.5 Hz), 2.02−2.08 (1H, m), 2.28 (1H, d, $J$ = 12.4 Hz), 2.60−2.71 (1H, m), 3.00−3.04 (1H, m), 3.38 and 3.42 (2H, AB q, $J$ = 10.2 Hz), 3.68 (1H, d, $J$ = 12.0 Hz), 4.85 (1H, d, $J$ = 9.4 Hz), 7.34−7.43 (6H, m), 7.64−7.66 (4H, m); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ −1.7, 17.5, 18.6, 19.3, 21.3, 23.5, 26.2, 26.9, 28.0, 34.9, 48.3, 52.8, 54.5, 68.9, 72.5, 72.8, 127.6, 128.3, 129.5, 133.3, 134.1, 135.7; EIMS $m/z$ (rel intensity) 577 ($M^+$, 10), 520 (9), 388 (3), 280 (100), 176 (10), 135 (16); HRMS (EI) calcd for $C_{35}H_{55}NO_2Si_2$ ($M^+$) 577.3771, found 577.3793.

**(2*S*,3*Z*)-3-((8*S*,8a*S*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-8-methylhexahydro-6(5*H*)-indolizinylidene)-2-methyl-1-propanol (33).** To an ice-cooled, stirred solution of **32** (241 mg, 0.417 mmol) in DMF (2.6 mL) was added tris(dimethylamino)sulfur (trimethylsilyl)difluoride (1.30 M solution in DMF, 0.481 mL, 0.625 mmol), and the resulting solution was stirred at 0 °C for 1 h and then at room temperature for an additional 6 h. After addition of saturated aqueous $NaHCO_3$ (10 mL) followed by extraction with AcOEt (3 × 40 mL), the combined extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo to give a residue, which was purified by chromatography (300:10:1 $CHCl_3$−MeOH−29% $NH_4OH$) to provide **33** (120 mg, 85%) as a colorless oil: $[\alpha]^{24}_D$ −21.4 (*c* 0.45, $CHCl_3$); IR (neat) 3331, 2774 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.08 (3H, s), 0.09 (3H, s), 0.85 (9H, s), 0.96 (3H, d, $J$ = 6.7 Hz), 1.17 (3H, s), 1.59−1.80 (4H, m), 1.94 (1H, dd, $J$ = 7.6, 6.4 Hz), 2.10−2.21 (1H, m), 2.11 and 2.27 (2H, AB q, $J$ = 14.4 Hz), 2.49 (1H, d, $J$ = 12.2 Hz), 2.63−2.74 (1H, m), 3.00−3.06 (1H, m), 3.27 (1H, A part of ABX, $J$ = 10.4, 8.3 Hz), 3.45 (1H, B part of ABX, $J$ = 10.4, 5.7 Hz), 3.80 (1H, d, $J$ = 12.2 Hz), 4.89 (1H, d, $J$ = 9.5 Hz); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ −1.7, 17.1, 18.6, 21.3, 23.5, 26.1, 28.0, 35.0, 48.3, 52.6, 54.5, 68.0, 72.3, 72.9, 127.9, 135.3; EIMS $m/z$ (rel intensity) 339 ($M^+$, 24), 324 (8), 282 (60), 207 (53), 176 (100), 84 (97); HRMS (EI) calcd for $C_{19}H_{37}NO_2Si$ ($M^+$) 339.2594, found 339.2577.

**(6*Z*,8*S*,8a*S*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-[(2*S*)-3-iodo-2-methylpropylidene]-8-methyloctahydroindolizine (34).** To an ice-cooled, stirred solution of **33** (241 mg, 0.417 mmol) in $CH_2Cl_2$ (1.5 mL) were successively added imidazole (30.0 mg 0.442 mg), triphenylphosphine (116 mg, 0.368 mmol), and iodine (93.0 mg, 0.368 mmol), and the mixture was warmed to room temperature. After the mixture was stirred for 8 h, saturated aqueous $Na_2SO_3$ (5 mL) was added, and the mixture was extracted with AcOEt (4 × 10 mL). The combined extracts were washed with saturated aqueous $Na_2SO_3$ (3 mL) followed by brine (3 mL) and dried ($MgSO_4$). Concentration in vacuo followed by purification by chromatography (1500:30:1 $CHCl_3$−MeOH−29% $NH_4OH$) provided **34** (63.0 mg, 95%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.07 (3H, s), 0.08 (3H, s), 0.85 (9H, s), 1.09 (3H, d, $J$ = 6.5 Hz), 1.16 (3H, s), 1.60−1.80 (4H, m), 1.86−1.93 (1H, m), 2.08−2.16 (1H, m), 2.10 and 2.26 (2H, AB q, $J$ = 14.0 Hz), 2.48 (1H, d, $J$ = 12.3 Hz), 2.65−2.75 (1H, m), 3.01−3.05 (1H, m), 3.05 (2H, d, $J$ = 6.6 Hz), 3.74 (1H, d, $J$ = 12.3 Hz), 4.89 (1H, d, $J$ = 9.2 Hz); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ −1.7, 15.9, 18.6, 21.3, 21.6, 23.4, 26.1, 27.9, 34.5, 48.2, 52.8, 54.6, 72.4, 72.7, 128.7, 134.3.

**(6*Z*,8*S*,8a*S*)-6-[(2*R*,4*E*,6*S*)-6-(Benzyloxy)-2,5-dimethyl-4-octenylidene]-8-{[*tert*-butyl(dimethyl)silyl]oxy}-8-methyloctahydroindolizine (47).** A pentane solution of *t*-BuLi (1.54 M, 0.122 mL, 0.188 mmol) was added to cooled (−110 °C) $Et_2O$ (0.20 mL), and to this solution was added a solution of **34** (42.0 mg, 0.0934 mmol) in $Et_2O$ (0.20 mL). After the mixture was stirred at −110 °C for 30 min, zinc chloride (0.50 M solution in THF, 0.187 mL, 0.0935 mmol) was introduced slowly and the resulting mixture was allowed to warm slowly to room temperature over 2 h. To this mixture was added a solution containing **42** (38.0 mg, 0.121 mmol) and tetrakis-(triphenylphosphine)palladium(0) (10.8 mg, 0.00935 mmol) in benzene (0.50 mL). After being stirred at room temperature for 3 h, the mixture was diluted with AcOEt (50 mL), washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product obtained was puri-

fied by chromatography (1500:30:1 $CHCl_3$−MeOH−29% $NH_4OH$) to provide **47** (28.5 mg, 60%) as a colorless oil: $[\alpha]^{21}_D$ −4.1 (*c* 1.05, $CHCl_3$); IR (neat) 2773 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.08 (3H, s), 0.09 (3H, s), 0.83 (3H, d, $J$ = 7.5 Hz), 0.86 (9H, s), 1.00 (3H, d, $J$ = 6.6 Hz), 1.13 (3H, s), 1.45−1.55 (1H, m), 1.55 (3H, s), 1.61−1.80 (5 H, m), 1.87 (1H, br s), 1.96−2.16 (3H, m), 2.02 and 2.22 (2H, AB q, $J$ = 14.4 Hz), 2.43 (1H, br d, $J$ = 12.1 Hz), 2.47−2.59 (1H, m), 3.05 (1H, br t, $J$ = 6.2 Hz), 3.52 (1H, t, $J$ = 7.0 Hz), 3.80 (1H, d, $J$ = 12.2 Hz), 4.20 and 4.43 (2H, AB q, $J$ = 12.0 Hz), 4.94 (1H, d, $J$ = 9.5 Hz), 5.28 (1H, t, $J$ = 7.0 Hz), 7.23−7.35 (5H, m); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ −1.72, −1.68, 10.5, 10.7, 18.6, 21.1, 21.3, 23.5, 26.2, 26.5, 28.0, 32.4, 35.8, 48.2, 52.7, 54.5, 69.5, 72.3, 72.8, 87.0, 127.3, 127.7, 127.8, 128.3, 131.1, 131.6, 134.8, 139.3; CIMS (isobutane) *m*/*z* 512 ($MH^+$); EIMS *m*/*z* (rel intensity) 511 ($M^+$, 22), 454 (24), 420 (45), 404 (85), 307 (31), 280 (72), 176 (45), 91 (100); HRMS (EI) calcd for $C_{32}H_{53}NO_2Si$ ($M^+$) 511.3846, found 511.3838.

**(6*Z*,8*S*,8a*S*)-6-[(2*R*,4*E*,6*S*)-6-(Benzyloxy)-2,5-dimethyl-4-octenylidene]-8-methyloctahydro-8-indolizinol (48).** To a solution of **47** (11.5 mg, 0.0225 mmol) in acetonitrile (4.0 mL) was added triethylamine tris(hydrogen fluoride) (363 mg, 2.25 mmol) followed by $Et_3N$ (27 mg, 0.27 mmol). This mixture was stirred and heated to 60 °C, and stirring was continued for 24 h. After the mixture was cooled, saturated aqueous $NaHCO_3$ (5 mL) was added, and the resulting mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo to give a crude oil, which was purified by chromatography (1000:10:1 $CHCl_3$−MeOH−29% $NH_4OH$), affording **48** (7.8 mg, 88%) as a colorless oil: $[\alpha]^{22}_D$ −2.7 (c 0.59, $CHCl_3$); IR (neat) 3507, 2787 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.83 (3H, $J$ = 7.4 Hz), 1.02 (3H, d, $J$ = 6.6 Hz), 1.11 (3H, s), 1.45−1.78 (6H, m), 1.55 (3H, s), 1.93 (1H, m), 1.96−2.10 (2H, m), 2.05 and 2.25 (2H, AB q, $J$ = 13.9 Hz), 2.16−2.25 (1H, m), 2.34 (1H, d, $J$ = 11.8 Hz), 2.46−2.57 (1H, m), 2.65 (1H, br s), 3.06 (1H, m), 3.51 (1H, t, $J$ = 7.0 Hz), 3.79 (1H, d, $J$ = 11.8 Hz), 4.20 and 4.43 (2H, AB q, $J$ = 12.0 Hz), 5.10 (1H, d, $J$ = 9.6 Hz), 5.27 (1H, t, $J$ = 7.1 Hz), 7.24−7.35 (5H, m); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 10.4, 10.8, 21.1, 21.4, 23.3, 24.3, 26.5, 32.6, 35.6, 48.9, 53.3, 54.6, 68.4, 69.5, 71.7, 86.9, 127.3, 127.5, 127.7, 128.3, 130.4, 133.9, 135.0, 139.2; CIMS (isobutane) *m*/*z* 398 ($MH^+$); EIMS *m*/*z* (rel intensity) 397 ($M^+$, 5), 306 (45), 290 (74), 206 (27), 193 (49), 166 (92), 91 (100), 70 (72); HRMS (EI) calcd for $C_{26}H_{39}NO_2$ ($M^+$) 397.2981, found 397.2987.

**(+)-Pumiliotoxin A (6).** A solution of **48** (13.4 mg, 0.0337 mmol) in THF (2 mL) was added to liquid $NH_3$ (1 mL) at −78 °C. To this was added excess lithium in several small portions until the blue color persisted. Once the blue color persisted for 2 min, the reaction mixture was quenched by addition of MeOH (0.5 mL) followed by saturated aqueous $NH_4Cl$ (1 mL), and the ammonia was allowed to evaporate at room temperature. To the resulting slurry was added saturated aqueous $NaHCO_3$ (5 mL), and the mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were washed with brine (2 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product obtained was purified by chromatography (500:10:1 $CHCl_3$−MeOH−29% $NH_4OH$) to give **6** (8.4 mg, 81%) as a colorless oil: $[\alpha]^{25}_D$ +16.7 (*c* 0.84, $CHCl_3$); IR (neat) 3421, 2791 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.84 (3H, $J$ = 7.4 Hz), 0.99 (3H, d, $J$ = 6.6 Hz), 1.12 (3H, s), 1.49−1.78 (6H, m), 1.56 (3H, s), 1.88−2.05 (3H, m), 2.08 and 2.14 (2H, AB q, $J$ = 13.9 Hz), 2.17−2.25 (1H, m), 2.33 (1H, d, $J$ = 11.8 Hz), 2.42−2.53 (1H, m), 2.64 (1H, br s), 3.05 (1H, m), 3.77 (1H, d, $J$ = 11.8 Hz), 3.88 (1H, t, $J$ = 6.7 Hz), 5.07 (1H, d, $J$ = 9.5 Hz), 5.30 (1H, t, $J$ = 7.1 Hz); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 10.1, 11.3, 21.1, 21.2, 23.2, 24.3, 27.7, 32.5, 35.5, 48.8, 53.3, 54.6, 68.4, 71.7, 79.5, 125.0, 130.3, 133.8, 137.7; EIMS *m*/*z* (rel intensity) 307 ($M^+$, 13), 290 (6), 278 (4), 193 (19), 166 (100), 70 (38); HRMS (EI) calcd for $C_{19}H_{33}NO_2$ ($M^+$) 307.2511, found 307.2517.

**(6*Z*,8*S*,8a*S*)-8-{[*tert*-Butyl(dimethyl)silyl]oxy}-8-methyl-6-{(2*R*,4*E*)-2-methyl-5-[(4*R*,5*R*)-2,2,5-trimethyl-1,3-dioxolan-4-yl]-4-hexenylidene}octahydroindolizine (54).** To a cooled (−90 °C), stirred solution of **34** (55.0 mg, 0.122 mmol) in $Et_2O$ (0.5 mL) was added zinc chloride (0.50 M solution in THF, 0.244 mL, 0.122 mmol), and the mixture was stirred at −90 °C. After 30 min, *t*-BuLi (1.60 M solution in pentane, 0.229 mL, 0.366 mmol) was added dropwise, and the resulting mixture was allowed to warm slowly to room temperature over 2 h. The flask was then covered completely with aluminum foil to afford protection from light, and a solution containing **50** (25.1 mg, 0.0889 mmol) and tetrakis(triphenylphosphine)palladium(0) (14.1 mg, 0.0122 mmol) in benzene (0.6 mL) was added. The mixture was stirred in the dark for 3 h and then diluted with $Et_2O$ (10 mL) and water (10 mL). The aqueous layer was separated and extracted with $Et_2O$ (3 × 10 mL), and the combined organic layers were washed with brine (5 mL) and dried ($MgSO_4$). Concentration in vacuo followed by chromatography (1000:10:1 $CHCl_3$−MeOH−29% $NH_4OH$) provided **54** (30.0 mg, 51%) as a colorless oil: $[\alpha]^{24}_D$ −14.7 (*c* 0.91, $CHCl_3$); IR (neat) 2778 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.080 (3H, s), 0.083 (3H, s), 0.85 (9H, s), 0.96 (3H, d, $J$ = 6.6 Hz), 1.16 (3H, s), 1.21 (3H, d, $J$ = 5.7 Hz), 1.42 (6H, s), 1.62 (3H, s), 1.57−1.80 (5H, m), 1.91−2.17 (4H, m), 2.23 (1H, 1/2AB q, $J$ = 14.2 Hz), 2.40−2.55 (2H, m), 3.03 (1H, td, $J$ = 7.2, 1.0 Hz), 3.77 (1H, d, $J$ = 12.3 Hz), 3.80−3.90 (2H, m, including d at 3.84 ppm, $J$ = 3.3 Hz), 4.93 (1H, d, $J$ = 9.2 Hz), 5.44 (1H, td, $J$ = 7.2, 0.7 Hz); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ −1.72, −1.69, 11.7, 17.1, 18.6, 20.9, 21.3, 23.5, 26.2, 27.0, 27.5, 28.0, 32.2, 35.8, 48.0, 52.2, 54.2, 72.0, 72.9, 74.4, 88.8, 107.9, 128.6, 130.8, 131.5, 131.8; EIMS *m*/*z* (relative intensity) 477 ($M^+$, 30), 462 (11), 420 (14), 391 (13), 357 (12), 334 (30), 307 (74), 280 (44), 253 (60), 225 (31), 176 (59), 162 (50), 148 (44), 91 (66), 84 (94), 73 (100); HRMS (EI) calcd for $C_{28}H_{51}NO_3Si$ ($M^+$) 477.3643, found 477.3638.

**(6*Z*,8*S*,8a*S*)-8-Methyl-6-{(2*R*,4*E*)-2-methyl-5-[(4*R*,5*R*)-2,2,5-trimethyl-1,3-dioxolan-4-yl]-4-hexenylidene}octahydro-8-indolizinol (55).** The silyl ether **54** (28.0 mg, 0.0586 mmol) was treated with triethylamine tris(hydrogen fluoride) (944 mg, 5.86 mmol) and $Et_3N$ (70 mg, 0.69 mmol) as described above for desilylation of **47**. Workup and chromatography (500:10:1 $CHCl_3$−MeOH−29% $NH_4OH$) afforded **55** (18.0 mg, 85%) as a colorless oil: $[\alpha]^{27}_D$ +6.4 (*c* 0.88, $CHCl_3$); IR (neat) 3509, 2788 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.98 (3H, d, $J$ = 6.6 Hz), 1.13 (3H, s), 1.20 (3H, d, $J$ = 5.6 Hz), 1.41 (6H, s), 1.61 (3H, s), 1.64−1.77 (4H, m), 1.91−2.05 (3H, m), 2.09 and 2.14 (2H, AB q, $J$ = 14.7 Hz), 2.17−2.26 (1H, m), 2.35 (1H, d, $J$ = 11.8 Hz), 2.40−2.53 (1H, m), 2.55−2.75 (1H, br s), 3.06 (1H, m), 3.77 (1H, d, $J$ = 11.8 Hz), 3.79−3.89 (2H, m, including d at 3.84 ppm, $J$ = 3.2 Hz), 5.08 (1H, d, $J$ = 9.5 Hz), 5.43 (1H, td, $J$ = 7.2, 0.7 Hz); $^{13}C$ NMR (100.6 MHz, $CDCl_3$) $\delta$ 11.7, 17.1, 21.1, 23.2, 24.3, 27.0, 27.5, 32.4, 35.7, 48.8, 53.2, 54.5, 68.4, 71.7, 74.4, 88.7, 107.9, 128.4, 130.4, 131.7, 133.8; EIMS *m*/*z* (relative intensity) 363 ($M^+$, 29), 348 (16), 206 (32), 194 (44), 166 (100), 91 (14), 70 (46); HRMS (EI) calcd for $C_{22}H_{37}NO_3$ ($M^+$) 363.2773, found 363.2782.

**(+)-Pumiliotoxin B (7).** To a solution of **55** (16.0 mg, 0.0440 mmol) in THF (0.34 mL) was added 10% aqueous HCl (0.34 mL) at room temperature. After the mixture was stirred for 30 min, saturated aqueous $NaHCO_3$ (2 mL) was added, and the resulting mixture was extracted with $CHCl_3$ (3 × 5 mL). The combined extracts were washed with brine (3 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the crude product by chromatography (100:10:1 $CHCl_3$−MeOH−29% $NH_4OH$) afforded **7** (10.0 mg, 70%) as a colorless oil: $[\alpha]^{26}_D$ +22.1 (*c* 0.34, MeOH); IR (neat) 3401, 2793 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.00 (3H, d, $J$ = 6.6 Hz), 1.11 (3H, d, $J$ = 6.2 Hz), 1.13 (3H, s), 1.58 (3H, s), 1.65−1.78 (4H, m), 1.89−2.07 (3H, m), 2.09 and 2.14 (2H, AB q, $J$ = 13.8 Hz), 2.18−2.26 (1H, m), 2.35 (1H, d, $J$ = 11.8 Hz), 2.44−2.55 (1H, m), 2.65 (1H, br s), 3.05 (1H, m), 3.70 (1H, d, $J$ = 7.1 Hz), 3.71−3.80 (2H, m), 5.06 (1H, d, $J$ = 9.6 Hz), 5.39 (1H, t, $J$ = 7.2

Hz); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 12.2, 18.9, 21.1, 21.3, 23.2, 24.3, 32.5, 35.5, 48.8, 53.2, 54.5, 68.4, 68.8, 71.7, 82.7, 127.5, 130.5, 133.7, 135.2; EIMS *m*/*z* (relative intensity) 323 ($M^+$, 53), 306 (17), 278 (46), 206 (27), 194 (41), 193 (29), 176 (21), 166 (100), 70 (16); HRMS (EI) calcd for $C_{19}H_{33}NO_3$ ($M^+$) 323.2460, found 323.2457.

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**Supporting Information Available:** Detailed experimental procedures for the preparation of compounds **17**−**19**, **24**, **36**−**42**, **45**, **50**, and **51** and copies of $^1$H NMR spectra for compounds **2**, **6**, **7**, **29**−**34**, **40**, **45**, **47**, **48**, **50**, (*Z*)-**50**, **51**, **54**, and **55**. This material is available free of charge via the Internet at http://pubs.acs.org.

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