The First Enantioselective Total Syntheses of the Allopumiliotoxin A Alkaloids 267A and 339B

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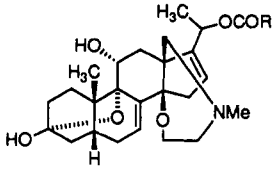
Short, highly stereocontrolled, asymmetric total syntheses of the title amphibian alkaloids are described. In the first stage the indolizidine ketone 11 is assembled from L-proline in enantiomerically pure form. This short sequence proceeds in five laboratory operations and involves the novel intermediacy of an "unprotected" 2-acylpyrrolidine intermediate (Scheme VII). The (*Z*)-alkylidene side chain of the target alkaloids are introduced by stereocontrolled aldol dehydration sequences (Schemes X and XI). These enantioselective total syntheses confirm the structures and absolute configurations of the allopumiliotoxins 267A and 339B.

Skin secretions of Dendrobatid frogs have been known for some time to be venomous.[1-5] Several tribes indigenous to the areas where these amphibians live utilize these poisons to treat their blow gun darts. The batrachotoxins **1**, a group of steroidal alkaloids which differ in the ester groups attached to C-20 of the steroid nucleus, are the most toxic compounds isolated from these frogs. The 1-azaspiro[5.5]undecane ring system is found in compounds produced by *Dendrobates histrionicus*, as exemplified by histrionicotoxin (**2**). Additionally, azacyclic ring systems such as the pyrrolo[1,2-*a*]quinoline and decahydroquinoline are found in the Dendrobatid toxins gephyrotoxin (**3**) and pumiliotoxin C (**4**).



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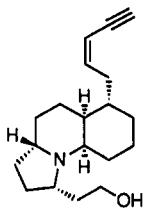

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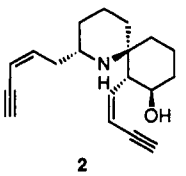

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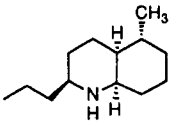

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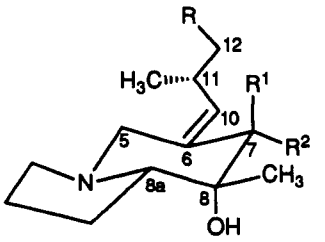
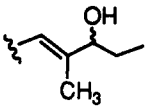
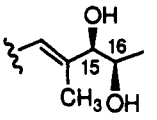
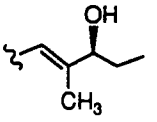
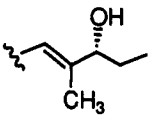
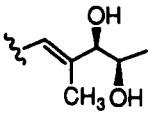
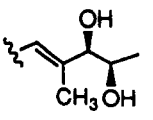
In the 20 years since the initial isolation of pumiliotoxins A (**5**) and B (**6**),[3] Daly and co-workers have discovered more than 20 members of this family of Dendrobatid alkaloids (Table I). The exact constitution of these structurally unusual alkaloids remained elusive until 1980 when an X-ray analysis of the crystalline hydrochloride salt of pumiliotoxin 251D (**7**) revealed both the structure and absolute configuration of this simple toxin.[4,6] From this information, together with NMR and mass spectral data, it was deduced that the pumiliotoxin A family of Dendrobatid alkaloids possessed, as their defining structural element, the (*Z*)-alkylideneindolizidine ring system.[7,8] The pumiliotoxin A alkaloids differ from one another primarily in the nature of the side chain attached to C-12 of the alkylidene appendage. In the case of the most widely studied toxin, pumiliotoxin B, the stereochemistry of the allylic diol moiety of the side chain (*E* alkene and 15*R*,16*R*) was deduced first in model systems[9,10] and then rigorously by total synthesis.[11]

Table I. Representative Pumiliotoxin A Alkaloids



Compound	R	R^1	R^2	PTX
	CH_2CH_3	H	H	237A
7	$CH_2CH_2CH_3$	H	H	251D
5		H	H	A
6		H	H	B
8	$CH_2CH_2CH_3$	OH	H	allo-267A
		OH	H	allo-323B'
		OH	H	allo-323B"
		OH	H	allo-339A
9		H	OH	allo-339B

In addition to the pumiliotoxin A alkaloids previously mentioned, another more highly functionalized group has

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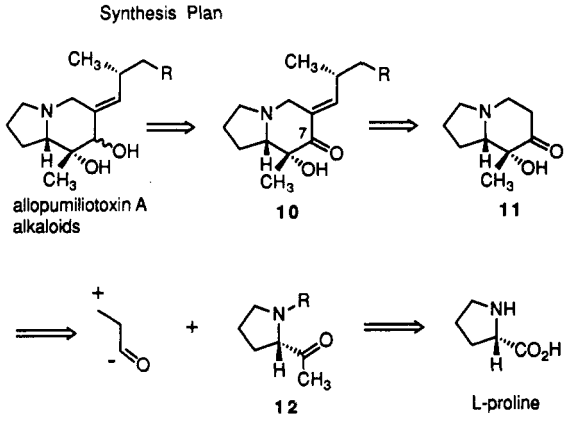
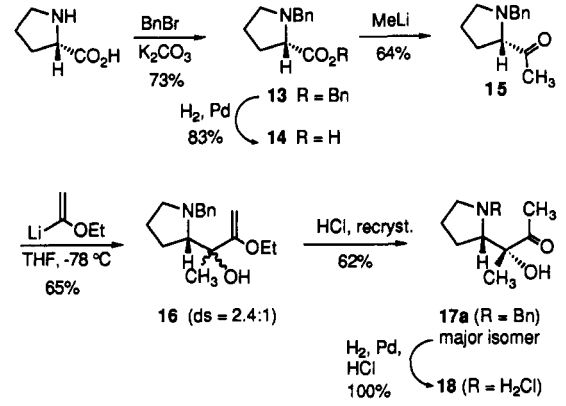
(1) (a) Witkop, B.; Gossinger, E. In *The Alkaloids*; Brossi, A., Eds.; Academic Press: New York, 1983; Vol. 21, Chapter 5. (b) Howard, A. S.; Michael, J. P. *The Alkaloids*; Academic Press: New York, 1986, Vol. 28, p 183.

0022-3263/92/1957-1179$03.00/0

Scheme I



Scheme II



been isolated.[4,12] These compounds, the allopumiliotoxin A alkaloids, contain an additional hydroxyl group on the indolizidine backbone and are the most complex members of this alkaloid family known to date (Table I). At the time our work in this area began, mass spectral analysis had established that the hydroxyl functionality was located at C-7 of the indolizidine ring, but the stereochemistry at this site of the allopumiliotoxin A alkaloids remained undefined.[4] Additionally, NMR spectral data had been interpreted to reveal side chains similar to those found in pumiliotoxins A and B. However, because of the minute amounts of the natural products available, these assignments had not been rigorously confirmed. Representatives of this highly oxygenated family of alkaloids are the allopumiliotoxins 267A (**8**), 323B′, 323B″, 339A, and 339B (**9**), the latter two of which differ from pumiliotoxin B (**6**) solely by incorporation of the C-7 alcohol functionality.

The pumiliotoxin A alkaloids are strong potentiators of cardiac activity.[13-18] The compounds that contain two side chain hydroxyl groups, of which pumiliotoxin B is the most potent, cause a marked increase in both the rate and force of contraction of isolated guinea pig atria. Simple natural toxins, such as pumiliotoxin 251D and synthetic congeners having either no oxidation on the side chain or possessing only protected alcohol functionality, are mild cardiodepressants.[15,18] The stimulatory activity, which is likely mediated by calcium mobilization, has recently been shown to be initiated by the binding of the toxins to voltage-dependent sodium channels.[16-18] This event triggers sodium ion influx and phosphatidylinositol breakdown.[16-18]

Herein we detail our initial synthetic efforts in the allopumiliotoxin A alkaloid area which culminated in the first total syntheses of (+)-allopumiliotoxin 267A (**8**) and (+)-allopumiliotoxin 339B (**9**).[19] These syntheses both established the first synthetic entry to the allopumiliotoxin A alkaloids and rigorously defined the stereostructures of toxins **8** and **9**.[20]

General Synthetic Strategy

Since the allopumiliotoxin A alkaloids differ among themselves mainly in the side chain attached to indolizidine ring, the development of a strategy that would allow for the convergent assembly of a variety of side chain analogues was of prime importance in our synthetic planning.[21] The unresolved issue of the C-7 hydroxyl stereochemistry could presumably by addressed by selective reduction of a C-7 ketone. The thermodynamic preference for a trisubstituted exocyclic enone to exist in an *E* configuration[22] led to the first retrosynthetic intermediate **10** (Scheme I). We envisioned the 6,10 alkylidene double bond as arising from an aldol condensation and

(2) (a) Daly, J. W. *Fort. Chem. Org. Nat.* **1982**, *41*, 205. (b) Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M.; Meyers, C. W. *Toxicon* **1978**, *16*, 163.

(3) (a) Daly, J. W.; Meyers, C. W. *Science* **1967**, *156*, 1970. (b) Meyers, C. W.; Daly, J. W. *Sci. Am.* **1983**, *248*, 120.

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

(5) 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.

(6) Pumiliotoxin 251-D has the *S* absolute configuration at carbon 8a. This carbon is of the same configuration as the related carbons of pumiliotoxin C and L-proline, but opposite to that of gephyrotoxin.[4]

(7) *trans*-Indolizidines are typically more stable than the analogous cis conformers. An axial alcohol at C-8 cf the pumiliotoxin A alkaloids, which can hydrogen bond with the angular nitrogen, should increase this conformational energy difference even more: Crabb, T. A.; Newton, R. F.; Jackson, D. *Chem. Rev.* **1971**, *71*, 109.

(8) For the first total synthesis accomplishment in this area, that of pumiliotoxin 251D, see: Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851.

(9) Tokuyama, T.; Shimada, K., Uemura, M.; Daly, J. W. *Tetrahedron Lett.* **1982**, *23*, 2121.

(10) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355.

(11) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *104*, 4192.

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

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

(14) Albuquerque, E. X.; Warnick, J. E.; Maleque, M. A.; Kaufman, F. C.; Tamburini, R.; Nimit, Y.; Daly, J. W. *Mol. Pharmacol.* **1981**, *19*, 411.

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

(16) Gusovsky, F.; Rossignol, D. P.; McNeal, E. T.; Daly, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 1272.

(17) Rao, K. S.; Warnick, J. E.; Daly, J. W.; Albuquerque, E. X. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 775.

(18) 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. Pharm.* **1990**, *40*, 315.

(19) Portions of this work were previously described in communication form: Overman, L. E.; Goldstein, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 5360.

(20) (a) For a second synthesis of allopumiliotoxin 339B, see: Trost, B. M.; Scanlan, T. C. *J. Am. Chem. Soc.* **1989**, *111*, 4988. (b) A third route to the allopumiliotoxins, which culminated in a very efficient synthesis of (+)-allopumiliotoxin 339A and demonstrated the first practical synthetic entry to the allopumiliotoxin A alkaloids, has recently been disclosed from our laboratories: Overman, L. E.; Robinson, L. A.; Zablocki, J. *J. Am. Chem. Soc.* **1992**, *114*, 368.

(21) When our work began, only two methods of preparing 6-alkylideneindolizidines were known and neither appeared appropriate for the present challenge: (a) Plattner, J. J.; Gless, R. D.; Cooper, G. K.; Rapoport, H. *J. Org. Chem.* **1974**, *39*, 303. (b) Yamagishi, K.; Koshinaka, E.; Ogawa, N.; Mitani, K.; Nishikawa, T.; Kato, H.; Hanaoka, M. *Chem. Pharm. Bull.* **1980**, *28*, 2783.

(22) See, inter alia: Thielke, D.; Wegener, J.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 602.

subsequent dehydration between the 7-oxoindolizidine 11 and an appropriate aldehyde. An attractive route for the generation of 11 could then involve the chelation controlled addition[23] of a 2- or 3-carbon acyl anion equivalent to a suitably protected 2-acetylpyrrolidine 12, followed by elaboration of the piperidine ring. The amino ketone 12 was envisaged to arise from L-proline.

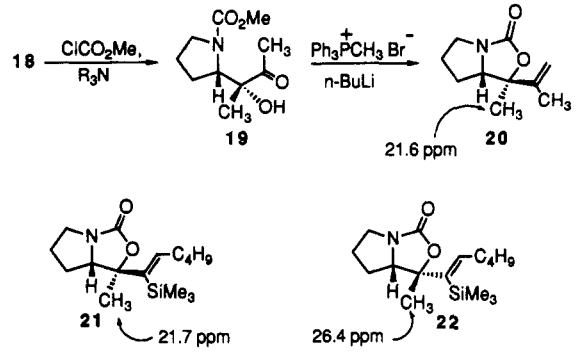
Results and Discussion

A. Preparation of (−)-Indolizidinone 11. Our first concern was the construction of an N-protected 2-acetylpyrrolidine whose reaction with a nucleophile would take place in cyclic Cram fashion to produce the stereochemistry at C-8 needed for the pumiliotoxin A alkaloids. We initially reasoned that the optimum protecting group would be one in which the pyrrolidine nitrogen was protected with a simple alkyl group.[23] The lone pair on the nitrogen should then be free to form a cyclic chelate with the ketone carbonyl and a Lewis acid. This logic, coupled with the possibility of reductive cleavage of the *N*-benzyl linkage, led us to prepare intermediate 15 (Scheme II).

At the time our synthetic efforts began, no enantiomerically pure 2-acetylpyrrolidines had been reported in the literature. Conditions that allowed for selective N-benzylation of L-proline could not be found. This end result, however, was readily achieved by benzylation of both nitrogen and oxygen to give the dibenzylproline derivative 13, followed by selective benzyl ester hydrogenolysis with $Pd/BaSO_4$ in ethanol. This sequence delivered the tertiary amino acid 14 in 61% overall yield. Treatment of 14 with 2.1 equiv of MeLi followed by an aqueous quench then afforded the enantiomerically pure (vide infra) 2-acetylpyrrolidine 15, $[\alpha]^{25}_D$ −81.2°, in 64% yield.

For our initial foray into the construction of indolizidinone 11, we examined an approach that entailed addition of a two-carbon acyl anion equivalent to ketone 15, followed by nitrogen deprotection and subsequent Mannich cyclization[24] of the resulting secondary amino ketone to form the piperidine ring. 1-Lithio-1-ethoxyethene was chosen as the two-carbon nucleophile, because of both its ease of generation and the mild conditions required for carbonyl liberation. Generation of this anion previously entailed the use of TMEDA,[25] an additive that could potentially destroy the desired cyclic chelate during the addition step. We discovered that slow addition of t-BuLi to an excess of ethyl vinyl ether in THF (ca. 4 M) at −78 °C produced a yellow solution.[26] Careful warming to −22 °C (internal temperature) for 30 min caused this solution to decolorize, quantitatively affording 1-lithio-1-ethoxyethene. This lithium reagent was stable at this temperature for at least 1 h.[27] If the yellow solution was allowed to warm to 0 °C, a lower yield of the anion was realized, owing presumably to deprotonation of THF.[28] Slow addition of ketone 15 to a solution of 1-lithio-1-ethoxyethene at −78 °C afforded a 2.4:1 mixture of addition products 16 in 65% yield. We recommend this (1-alkoxyvinyl)lithium reagent for general use. It is more convenient to generate on a large scale than 1-lithio-1-methoxyethene,[27] since ethyl vinyl ether is less expensive than methyl vinyl ether and also a liquid room temperature.

Scheme III



To establish the stereostructure of the major isomer of 16, the mixture of enol ethers was hydrolyzed with dilute acid to afford ketones 17, from which the major diastereomer 17a was isolated by column chromatography and crystallization. Hydrogenolysis of the *N*-benzyl linkage of 17a in acidic aqueous ethanol gave the corresponding amine hydrochloride salt 18 in high yield.

We had observed during our earlier synthesis of pumiliotoxin 251D (7) that the ^{13}C NMR chemical shift of the C-8 methyl group (pumiliotoxin numbering) in the bicyclic intermediate 21 was shifted ca. 5 ppm upfield of this carbon in the C-8 epimer 22 (Scheme III).[8,29] Amino ketone 18 was converted, therefore, to a structurally related intermediate. Treatment of 18 with methyl chloroformate followed by methylenetriphenylphophorane afforded the bicyclic carbamate 20 in 34% overall yield (Scheme III). Confirmation of the C-8 stereochemistry was then obtained by the observation of the ^{13}C NMR chemical shift for the C-8 methyl group at 21.6 ppm, only 0.1 ppm away from that carbon of the analogous pumiliotoxin 251D intermediate 21. The major isomer produced from the reaction of the *N*-benzylpyrrolidine ketone 15 with 1-lithio-1-ethoxyethene therefore arose from chelation-controlled diastereoselection.

Although we were unable to determine the enantiomeric purity of ketone 17a, amino ketone 18 was readily analyzed.[30] Thus, treatment of 18 with (+)-α-methoxy-α-(trifluoromethyl)phenacetyl chloride gave the corresponding amide, which showed a >98:2 ratio of C-8 methyl signals in its ^1H NMR spectrum. A 1:1 ratio of these signals was seen when a racemic sample of this intermediate was similarly analyzed. This evaluation not only demonstrates that the amino acid 14 and amino ketone 15 had been synthesized with no loss of absolute chirality, but that the subsequent addition to the ketone proceeded with no detectable racemization.

With the stereochemical assignment at C-8 established and the demonstration of the high enantiomeric purity of 16 in hand, we redirected our efforts toward elaboration of 18 (or its precursor 16) to the indolizidinone 11. We initially examined reductive cleavage of the benzyl group of intermediate 16 without success. The ultimate hope was

(23) (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (b) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031. (c) Still, W. C.; Schneider, J. A. *Ibid.* **1980**, *21*, 1035. (d) Still, W. C.; Collum, D. B.; McDonald, J. H. *J. Am.* Chem. *Soc.* **1980**, *102*, 2121. (e) Pierre, J. L.; Handel, H.; Perraud, R. *Tetrahedron Lett.* **1977**, 2013. (f) For a review of facial selectivity in necleophilic additions to α-amino ketones, see: Tramontini, M. *Synthesis* **1982**, 605.

(24) For a brief review, see: Ricca, D. J.; Overman, L. E. Intramolecular Mannich Cyclizations. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991, in press.

(25) Schollköpf, U., Hanssle, P. *Liebigs Ann. Chem.* **1972**, *763*, 208.

(26) Settle, F. A.; Haggerty, M.; Eastham, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 2076.

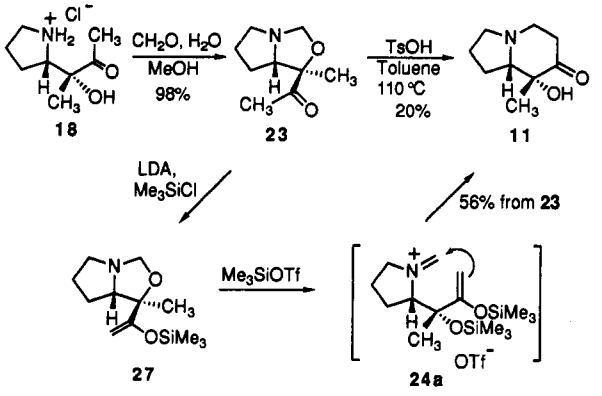
(27) The analogous 1-lithio-1-methoxyethene is produced easily from methyl vinyl ether and t-BuLi at 0 °C: Baldwin, J. E.; Hofle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125.

(28) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 93.

(29) Cf.: Strothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic: New York, 1972: pp 112–8.

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

Scheme IV

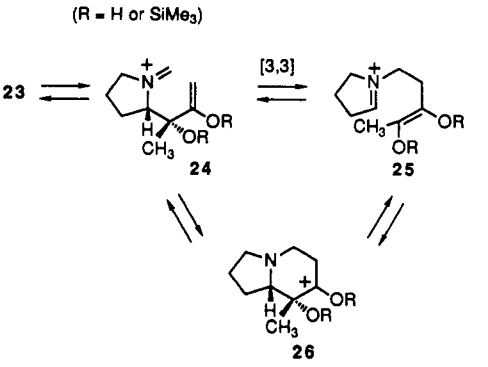


to subsequently effect Mannich cyclization of the enol ether with a formaldiminium ion intermediate derived from the unprotected pyrrolidine nitrogen. Simple sodium in ammonia reductions afforded only recovered starting material, while the addition of various amounts of urea (as a proton source) led to the formation of unidentifiable products.

When formaldehyde was added to the secondary amino ketone salt **18**, however, rapid cyclization occurred in nearly quantitative yield to give not the desired indolizidine, but rather cyclopentaoxazolidine **23** (Scheme IV). The stability of this perhydropyrrolo[1,2-*c*]oxazole was quite remarkable. For example, it was recovered unchanged from refluxing acetic acid, hot aqueous HCl, *p*-toluenesulfonic acid (TsOH) in refluxing acetonitrile, HCl in refluxing acetic acid, and CH_3SO_3H in refluxing toluene. We assumed that under these conditions the equilibrium concentration of ring-opened intermediates was so low that Mannich cyclization was not able to proceed. Success was finally realized under forcing conditions by treating **23** with 2 equiv of TsOH monohydrate in refluxing toluene which was percolated through a Soxhlet thimble containing calcium carbide.[31] The desired indolizidinone **11** was isolated from this reaction in 20% yield. However, when this product was examined by ^1H NMR in the presence of the chiral shift reagent Eu(tfc)$_3$, a doubling of the C-8 methyl absorption signaled that **11** produced in this way was racemic.

This unusual racemization is likely not due to simple epimerization since the two stereogenic centers of **18** or **11** are not obviously labile. A satisfactory explanation for this occurrence can be developed by examining potential reaction intermediates. Acid-promoted ring opening of oxazolidine **23** and keto–enol tautomerization affords **24**, which contains the 2-azonia 1,5-diene unit (Scheme V). Rapid [3,3]-sigmatropic rearrangement[32] could then give rise to intermediate **25**, a compound containing no stereogenic carbons. On the reasonable assumption that the ene diol **25** would not cyclize by a disfavored 5-*endo-trig* pathway,[33] but rather revert to **24**, these events could readily racemize **23**. Alternatively, racemization could proceed stepwise by Mannich cyclization to **26** followed by retro-Mannich cleavage to give **25**. Although from a mechanistic vantage point these two pathways are quite distinct, the formation of the rearranged iminium ion **25** in both cases could result in racemization.[34]

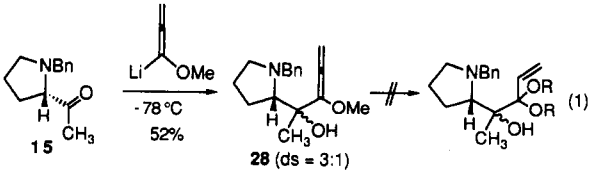
Scheme V



The formation of iminium ion–enol **24** (R = H) from oxazolidine **23** is surely an unfavorable process (Scheme V). The low equilibrium concentration of intermediate **24** is a likely cause for the forcing conditions required to convert **23** to **11**. Therefore, we examined a strategy in which the reversible keto–enol tautomerization and oxazolidine ring opening steps would be rendered irreversible. To this end, **23** was converted to enoxysilane **27** (Scheme IV). Treatment of this intermediate with 1 equiv of trimethylsilyl triflate should in principle product **24a**.[35] In the event, treatment of **27** with 1.1 equiv of trimethylsilyl triflate at 22 °C followed by quenching the reaction with triethylammonium hydrofluoride afforded **11** in 56% overall yield from **23**. To our surprise, **11** produced in this manner was again completely racemic.

The extreme facility of the presumed equilibrium of **24** and **25** (Scheme V) was demonstrated when the silyl-mediated intramolecular Mannich reaction was carried out at −60 °C for 9 h. Although the conversion to the indolizidinone product was low under these conditions (ca. 13%), **11** was again produced in racemic form. It was abundantly clear from these experiments that an intramolecular Mannich reaction could not be employed to assemble the desired indolizidine in asymmetric form.

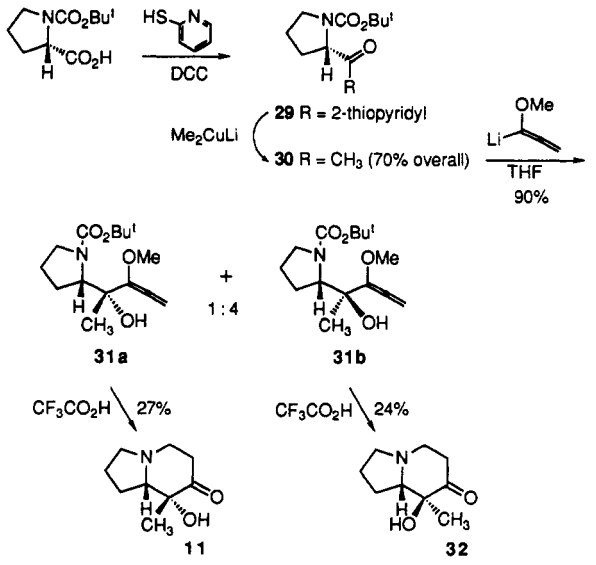
Our attention turned to an alternate sequence in which 1,4-addition of the pyrrolidine nitrogen to an enone would be employed to assemble the indolizidine ring. This ultimately successful approach is formally outlined in Scheme I. As the three-carbon nucleophile, we chose 1-lithio-1-methoxyallene, a reagent that had been the object of earlier attention by the Brandsma[36] and Magnus[37] groups. When this nucleophile was allowed to react at −78 °C with the *N*-benzyl ketone **15**, a 52% yield of tertiary alcohols **28** (a 3:1 mixture of diastereoisomers of undetermined stereochemistry) was produced (eq 1). In the



hope that the alkoxyallene functionality of **28** could be transformed into a more durable structural unit, metha-

(31) Ayers, W. A. *Can. J. Chem.* **1976**, *54*, 473.
(32) For brief reviews of iminium ion sigmatropic rearrangements, see: Blechert, S. *Synthesis* **1989**, 71. Heimgartner, H.; Hansen, J. J.; Schmidt, H. In *Iminium Salts in Organic Chemistry*; Bohme, H., Viehe, H. G., Eds.; Wiley: New York, 1979; Part 2, p 655.
(33) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(34) The interconversion of **24** and **25** not only could racemize **23** but also lead to the formation of other stereoisomers. Diastereomers of **23** (or **11**) were not isolated, however, the low mass balance precludes serious interpretation of this result.
(35) For a previous example of employing enolsilylation to facilitate a Mannich reaction, see: Oppolzer, W.; Hauth, H.; Pfaffli, P.; Wegner, R. *Helv. Chim. Acta* **1977**, *60*, 1801.
(36) (a) Brandsma, L.; Hoff, S.; Arens, J. *Recueil* **1968**, *87*, 916. (b) Brandsma, L.; Vermeer, P.; Meijer, J. *Tetrahedron Lett.* **1976**, 2387.
(37) Magnus, P.; Gange, D. *J. Am. Chem. Soc.* **1978**, *100*, 7746.

Scheme VI

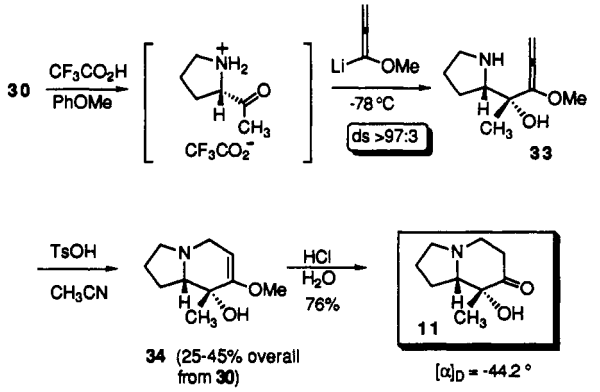


nolysis of **28** in the presence of a variety of acidic catalysts (pyridinium *p*-toluenesulfonate, $BF_3{\cdot}OEt_2$, fumaric acid, and camphorsulfonic acid; with and without trimethyl orthoformate) was attempted. These reactions produced only complex product mixtures, which showed little or no absorbances in the vinyl region of their ^1H NMR spectrum. Attempts to form the ethylene ketal or direct hydrolysis to the corresponding enone also met with little success. Therefore, it was clear that if the methoxyallene functionality were to be employed it would have to be unmasked under extremely mild conditions.

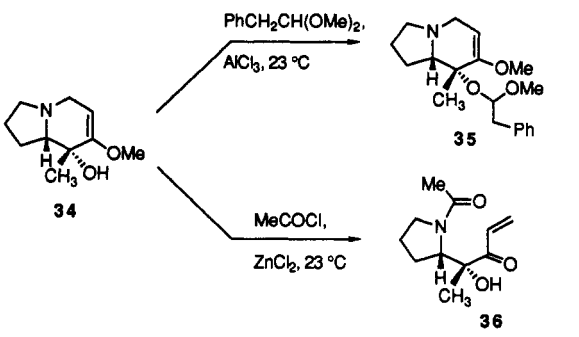
We next turned to combining the three-carbon methoxyallene unit with an *N*-BOC (*tert*-butoxycarbonyl)-protected pyrrolidine ketone, with the expectation that both the BOC and the enol ether groupings could be unraveled under mild acidic conditions. *N*-BOC-L-proline was converted to the thiopyridyl ester **29**, which was then allowed to react with $LiMe_2Cu$ to give the corresponding acetyl pyrrolidine **30**, $[\alpha]_D$ −57.8°, in 70% overall yield (Scheme VI). Treatment of **30** with a slight excess of 1-lithio-1-methoxyallene in the THF at −70 °C then afforded, in 90% yield, the diastereomeric adducts **31a** and **31b** in a 1:4 ratio (vide infra). Attempts to increase the amount of **31a** by modifying both the counterion (addition of $MgBr_2$) and solvent (ether, 1,2-dimethoxyethane, toluene, and Et_3N) served only to lower the amount of **31a** produced. To prove the relative stereochemistry at C-8 and C-8a, the minor isomer **31a** was converted to **11** (27% yield) by treatment with trifluoroacetic acid in CH_2Cl_2 at room temperature. The diastereomeric adduct **31b** was similarly converted to indolizidin-7-one **32** in 24% yield. The undesired Cram mode of stereoselection[38] clearly predominated when the nitrogen of the acetylpyrrolidine electrophile was protected with a carboalkoxy group.

We therefore turned to the ultimately successful strategy in which 1-lithio-1-methoxyallene is coupled with an *unprotected* 2-acetylpyrrolidine. This strategy entailed the potential advantage that chelation stereoselectivity in the addition step might be maximal when the α-amino substituent was a secondary amine.[23f] Although self-condensation of the secondary amino ketone was of some concern, we reasoned that this side reaction could be minimized by

Scheme VII



Scheme VIII



isolating a salt of the amine, and then using excess 1-lithio-1-methoxyallene to liberate the free secondary amine in situ. To this end, the *N*-BOC ketone **30** was deprotected with trifluoroacetic acid and anisole in CH_2Cl_2 to afford the labile 2-acetylpyrrolidine salt (Scheme VII).[39] Direct treatment of this intermediate with 5 equiv of 1-lithio-1-methoxyallene in THF at −78 °C afforded the allenyl pyrrolidine **33** as a *single diastereomer* (diastereoselectivity >97:3).

Allene **33** was remarkably labile, and all attempts at its purification resulted in considerable loss of material. Treatment of crude **33** with slightly less than 1 equiv of anhydrous *p*-toluenesulfonic acid in dry acetonitrile triggered the desired indolizidine-forming cyclization to provide the bicyclic enol ether **34** in 25–40% overall yield from **30**. Conversion of **34** to the 7-indolizidinone **11**, $[\alpha]^{25}_D$ −44.2°, was then accomplished in 76% yield by hydrolysis with 5% aqueous HCl. When **11** prepared in this way was examined by ^1H NMR in the presence of $Eu(tfc)_3$, no splitting of the C-8 methyl group was seen, confirming that this intermediate had finally been accessed in high enantiomeric purity.

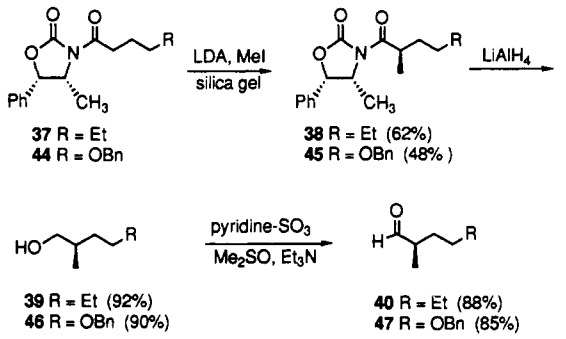
We briefly examined the possibility of employing the bicyclic enol ether **34** as the platform for introducing the alkylidene side chain of the allopumiliotoxin A alkaloids. As a model study, **34** was treated at room temperature with phenylacetaldehyde dimethyl acetal in the presence of $AlCl_3$.[40] The product isolated was not the expected aldol adduct but rather the mixed acetal **35** (Scheme VIII). Pursuing the possibility that a more reactive electrophile might be required, we treated **32** with acetyl chloride in the presence of $ZnCl_2$. However, acylation took place not at carbon, but rather at nitrogen, to give **36** after aqueous quenching. We were forced to turn to indolizidinone **11**

(38) (a) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Felkin, H.; Cherest, M.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (c) Ahn, N. *Top. Cur. Chem.* **1980**, 145. (d) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367.

(39) Suzuki, K.; Endo, N.; Nitta, K.; Sasaki, Y. *Chem. Pharm. Bull.* **1978**, *26*, 2198.

(40) (a) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 295. (b) Povarov, L. S. *Russ. Chem. Rev.* **1965**, *34*, 639.

Scheme IX



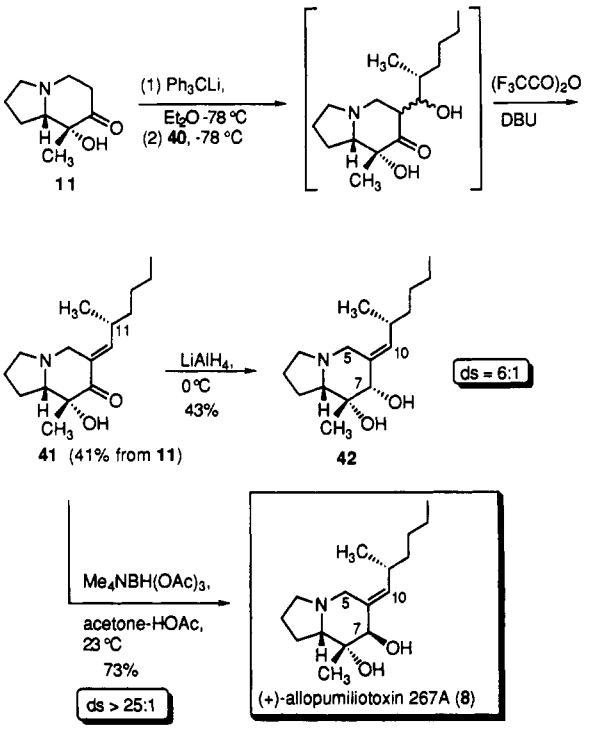
as a potentially more profitable substrate for attaching the side chain.

B. Side-Chain Elaboration and Completion of the Total Syntheses. Our initial synthetic target was the simple allopumilitoxin 267A (8, Table I). Although the stereostructure of the side chain of this target had not been rigorously established, we assumed that it was identical to the side chain of pumiliotoxin 251D. An aldol dehydration sequence for coupling this side chain with the ketoindolizidine 11 would require (*R*)-2-methylhexanal (**40**). To access this aldehyde, (4*R*,5*S*)-4-methyl-5-phenyl-1,3-oxazolidin-2-one[41] was acylated with hexanoyl chloride to give imide **37**. Enolization of **37** with LDA and methylation of the derived enolate following the general Evans protocol[41] occurred with 96% facial selectivity (Scheme IX). Chromatographic separation on silica gel afforded pure **38** in 62% yield. Reduction of **38** with $LiAlH_4$ gave (*R*)-2-methylhexanol (**39**). Parikh–Doering oxidation[42] of **39** then afforded the chromatographically stable aldehyde **40**.[43] When this aldehyde was subsequently reduced with BH_3 and the resulting alcohol esterified as described by Mosher,[30] capillary GC analysis revealed a 99.5:0.5 ratio of diastereomers, confirming that **40** was essentially optically pure (99% ee).

Preliminary model studies of the aldol reaction of indolizidine **11** and hexanal showed that enolization of **11** with tritylllithium in ether followed by aldol condensation at 0 °C was optimal. Some of the more important observations made during these model studies follow. While yields of aldol products were similar with KH, we were wary that an excess of this base would racemize **40**. Enolization of **11** with lithium amides, under both kinetic and thermodynamic conditions, afforded poor yields of the desired aldol products. Utilization of zinc as a counterion improved the aldol yield only marginally.[44] *tert*-Butyllithium could not be employed to enolize **11** since it underwent competitive addition to the carbonyl of **11** at −78 °C in THF. Treatment of **11** with *tert*-butylmagnesium chloride (2.5 equiv) resulted in incomplete enolization at 0 °C; at room temperature, this base occasioned α-ketol equilibration to give **32** and **11** in a 1:1 ratio.

In the key event, treatment of **11** with slightly more than 2 equiv of tritylllithium in ether at 0 °C followed by the addition of 1.05 equiv of aldehyde **40** yielded a mixture of aldol products (Scheme X). These adducts were not characterized but were rather directly dehydrated[45] with

Scheme X



trifluoroacetic anhydride and DBU to give enone **41** in 30% yield (41% yield based on consumed **11**). None of the corresponding *Z* enone was detected. However, **41** produced in this manner was contaminated with about 5% of its C-11 epimer.

The only remaining step of the synthesis of allopumiliotoxin 267A (**8**) was 1,2 reduction of the enone moiety to generate the axial β allylic alcohol. Most reducing agents we investigated delivered hydride predominantly from the β face to give the α (equatorial) alcohol product **42**. The highest yields of this allopumiliotoxin 267A epimer were obtained with $LiAlH_4$, which afforded **42** and (+)-allopumiliotoxin 267A (**8**) in a 6:1 ratio. Separation of this mixture on silica gel provided **42** in 43% yield.

To obtain the natural stereochemistry at C-7, we turned to the use of triacetoxyborohydrides.[46] These mild reducing agents are known to reduce hydroxy ketones by a process involving intramolecular hydride delivery from an alkoxydiacetoxyborohydride intermediate.[47] The reduction of **41** with $NaBH(OAc)_3$ at −23 °C in HOAc–CH_3CN proceeded with only modest (2:1) selectivity for forming the desired *trans*-diol **8**.[48] However, the more selective reductant $Me_4NBH(OAc)_3$[47a] reduced **41** in acetone–HOAc at room temperature to afford (+)-allopumiliotoxin 267A *exclusively*. Treatment of **41** under these conditions for 48 h afforded allopumiliotoxin 267A (**8**) in 73% yield (98% based on consumed **41**) after purification on silica gel.

Analysis of the ^1H NMR coupling constants for the vinylic C-10 hydrogens readily established the stereo-

(41) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(42) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(43) For a related route to this aldehyde, see ref 54. For the preparation of optically pure (*R*)-2-methylhexanol from (*R*)-methyl β-hydroxyisobutyrate, see: Kato, M.; Mori, K. *Agric. Biol. Chem.* **1985**, *49*, 2479.
(44) House, H. O.; Crumrine, D. S.; Reanshi, A. Y.; Olanstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.
(45) Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310.
(46) For a review, see: Gribble, G. W.; Nutaitis, C. F. *Org. Proc. Prep. Int.* **1985**, *17*, 317.
(47) (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. (b) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (c) Gribble, G. W.; Nutaitis, C. F. *Tetrahedron Lett.* **1983**, *24*, 4287.
(48) Cyclohexanones are known to be reduced by $NaBH_4$-acetic acid mixtures, see: Hutchins, R. O.; Su, W.; Sivakumar, R.; Cistone, F.; Stercho, Y. P. *J. Org. Chem.* **1983**, *48*, 3412.

chemistry at C-7 of **8** and **42**. In epimer **42** this hydrogen is coupled (J = 1.8 Hz) to the axial indolizidine hydrogens at both C-5 and C-7. Synthetic **8** produced in this manner was identical with a sample of the natural product[49] by TLC comparisons in three solvent systems, and by capillary GC, 250-MHz ^{1}H NMR and 63-MHz ^{13}C NMR comparisons. The optical rotation of synthetic **8** was $[\alpha]^{25}_D$ +31° (c 0.22, MeOH); a rotation of $[\alpha]^{25}_D$ +24.7° (c 0.2, MeOH) is reported for the natural isolate.[12]

Analogous chemistry was utilized for the preparation of the complex allopumiliotoxin 339B (**9**). Carbons 10–13 of the side chain of this target were also assembled using Evans aldol methodology.[41] This sequence, which began with 4-(benzyloxy)butyric acid,[50] is summarized in Scheme IX. Aldehyde **47**, obtained in this way, showed a rotation of +2.7° at the sodium D line.

Using the conditions developed for the synthesis of **8**, the aldol condensation between indolizidinone **11** and aldehyde **47** provided a mixture of adducts that was immediately dehydrated to give enone **48** in 27% yield after silica gel chromatography (Scheme XI). Reduction of this intermediate with $CeCl_3$–$NaBH_4$[51] cleanly afforded the α-allylic alcohol **49**, which was isolated in 58% yield after purification. Silylation of alcohol **49** provided **50**. Liberation of the primary alcohol with sodium in ammonia followed by a Swern oxidation[52] afforded aldehyde **52** in 46% yield from **50**.

A sequence identical to the one we employed in our laboratories for assembling the side chain of pumiliotoxin B (**6**)[11a] was now utilized for elaboration of the allylic diol portion of the side chain. Treatment of aldehyde **52** with the enantiomerically pure ylide **53**[11] provided the α'-silyloxy (E)-enone **54** in 55% yield. Threo selective reduction[10] of **54** with $LiAlH_4$ was accompanied by desilylation (presumably by AlH_3) to afford (+)-allopumiliotoxin 339B (**9**) in 44% yield after careful purification on silica gel.

At the time this work was completed, only trace amounts of the natural alkaloid were available for comparison with our synthetic product.[49] Both natural and synthetic pumiliotoxins exhibited identical TLC properties in three solvent systems. Additionally, all ^{1}H NMR signals of synthetic **9** were present in the ^{1}H NMR spectra of a partially decomposed sample of natural **9**. The observed rotation, $[\alpha]^{25}_D$ +8.8° (c 1.0, MeOH) or our synthetic product was higher than the value reported[12] for natural **9**, $[\alpha]^{25}_D$ +4.4° (c 0.5, MeOH). Because of the small amount of the natural material available, the observed rotations of synthetic (+)-allopumiliotoxin 339B at the more intense Hg lines are undoubtedly more reliable: $[\alpha]^{25}_{578}$ +6.9°, $[\alpha]^{25}_{546}$ +7.5°, $[\alpha]^{25}_{435}$ +15°, $[\alpha]^{25}_{405}$ +16°.[53]

Conclusion

The total syntheses detailed herein confirm the stereostructures and absolute configurations of allopumiliotoxins 267A and 339B, structures that had previously been assigned on the basis of spectroscopic data alone.[4,12] The synthetic sequence developed is quite short, convergent, and highly stereocontrolled. These syntheses delineate an aldol approach for appending the alkylidene side chain, which has subsequently been employed to access other pumiliotoxin A alkaloids.[54] These syntheses moreover introduce a useful method for generating enantiomerically pure secondary α-amino ketones and demonstrate that these intermediates react with organolithium reagents stereoselectively without racemization. The total synthesis of (+)-allopumiliotoxin 267A was accomplished in seven steps and ~5% overall yield from *N*-BOC-L-proline. Although the asymmetric total synthesis of (+)-allopumiliotoxin 339B was also notably short, 14 steps from *N*-BOC-L-proline, the overall yield was <1%. Improvements in efficiency will be required before useful amounts of the more complex allopumiliotoxins can be secured in this manner.

Experimental Section[55]

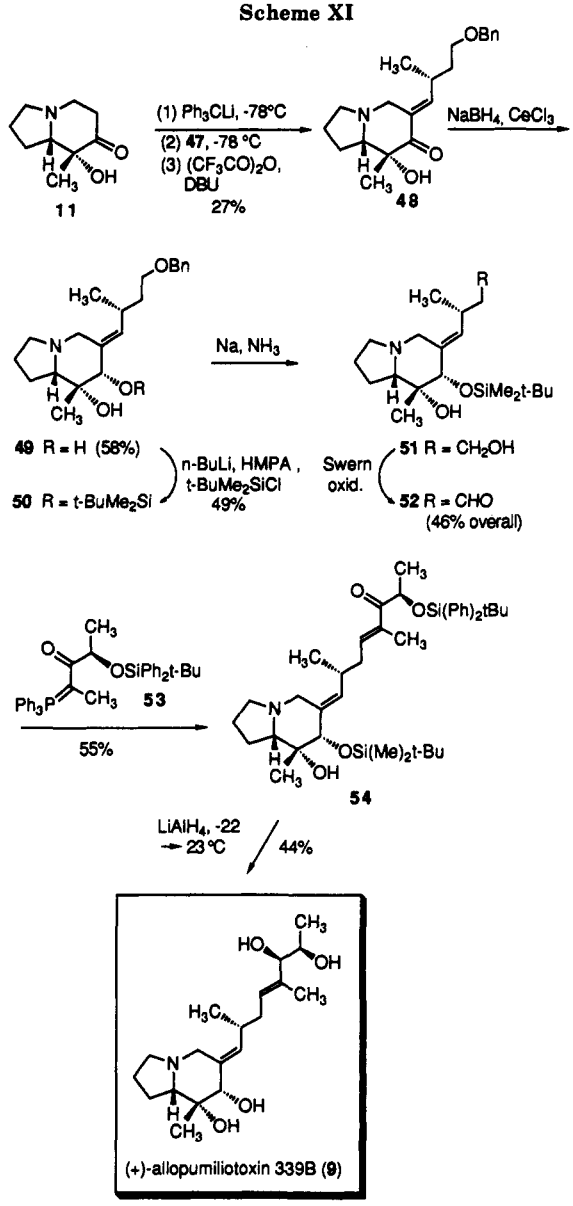
(*S*)-Benzyl 1-Benzylprolinate (13). To L-(−)-proline (69.0 g, 0.600 mol) suspended in dry DMF (1.5 mL) was added anhydrous K_2CO_3 (207 g, 1.5 mol) followed by benzyl bromide (142 mL, 1.20 mol). After 12 h of rapid mechanical stirring, the thick slurry was diluted with an equal volume of ether and filtered. The filtrate was washed with water (4 × 1 L), dried (Na_2SO_4), and concentrated to afford 130 g (73%) of benzyl ester **13** as a thick oil, which was sufficiently pure for the next step. Purification on silica gel (1:99 MeOH–$CHCl_3$) gave a sample contaminated (by ^{13}C and ^{1}H NMR analysis) by only a trace of MeOH: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.4–7.2 (m, 10 H, Ph), 5.12 (d, J = 12 Hz, OC*H*HPh), 5.08 (d, J = 12 Hz, OCH*H*Ph), 3.92 (d, J = 13 Hz, NC*H*HPh), 3.56 (d, J = 13 Hz, NCH*H*Ph), 3.3 (dd, J = 6.0, 8.7 Hz, NCH), 3.03 (m, NC*H*H), 2.5–1.7 (m, 5 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.2, 138.3, 135.7, 128.6, 128.1, 127.8, 126.6, 65.6, 64.6, 57.9, 54.6, 28.8, 22.7; MS (EI) m/e 296, (MH), 220, 160; IR (film) 1739, 1607, 1165 cm^{-1}; $[\alpha]^{25}_D$ −55.1°, $[\alpha]^{25}_{579}$ −57.3°, $[\alpha]_{25434}$ −113° (c 10.1, EtOH).

(*S*)-1-Benzylproline (14). To 800 mg of 10% Pd on $BaSO_4$ (which had been prereduced with H_2) in absolute ethanol (200 mL) was added ester **13** (38.0 g, 129 mmol). The reduction was allowed to proceed at 1 atm until the uptake of H_2 had ceased. The solution was then filtered through Celite and concentrated to a thick slurry, which was triturated with anhydrous ether (6 × 40 mL). The resultant beige powder (21.9 g, 83%, purity >95% by 80 MHz ^{1}H NMR) was used directly in the next step. An analytical sample was prepared by recrystallization twice from $CHCl_3$/ether followed by sublimation (155 °C, 0.4 mm): mp 169–177 °C; ^{1}H NMR (250 MHz, D_2O) δ 7.50 (app s, 5 H, Ph), 4.38 (app s, 2 H, NC*H*$_2$Ph), 3.99 (dd, J = 6.6, 9.6 Hz, NCH), 3.69 (m, NC*H*H), 3.31 (m, NCH*H*), 2.5–1.8 (m, 4 H); ^{13}C NMR (62.9 MHz, D_2O) δ 171.0, 128.3, 127.8, 127.7, 127.0, 66.1, 56.0, 52.3, 26.5, 20.5; MS (CI) m/e 206 (MH), 160, 116; IR ($CHCl_3$) 2960, 1629 cm^{-1}; $[\alpha]^{25}_D$ −34.6°, $[\alpha]^{25}_{579}$ −36.1°, $[\alpha]^{25}_{434}$ −66.9° (c 6.5, 1 N, HCl). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.31; N, 6.82. Found: C, 70.22; H, 7.42; N, 6.89.

(*S*)-1-Benzyl-2-acetylpyrrolidine (15). To a suspension of amino acid **14** (49.7 g, 242 mmol) and ether (200 mL) at 0 °C was added MeLi (306 mL of a 1.66 M solution in ether), and the resulting slurry was heated at reflux for 3 h. Ethyl acetate (20 mL) was added, and reflux was continued for an additional 30 min. The reaction was then quenched into a rapidly stirring

(49) The natural samples of allopumiliotoxin 267A and 339B were kindly supplied to us by Dr. John Daly, National Institutes of Health.
(50) Reppe, W. *Liebigs Ann. Chem.* **1955**, *596*, 191.
(51) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(52) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(53) Trost and Scanlan report the following rotations for allopumiliotoxin 339B: $[\alpha]^{26}_D$ +7.0°, $[\alpha]^{26}_{577}$ +9.0, $[\alpha]^{26}_{435}$ +17.0° (c 0.2, MeOH).[20a]
(54) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652.
(55) General experimental details were provided in ref 11. An ethereal suspension of tritylllithium was prepared in the following way. A hexane solution of *n*-BuLi (4.6 mL, 2.2 M) was added at 0 °C to a solution of Ph_3CH (3.0 g, 12 mmol) and THF, and the reaction mixture was maintained at room temperature for 2 h. After concentration (0.2 mm), the remaining red powder was diluted with 30 mL of ether to give a red-orange suspension. This suspension was transferred by syringe using a wide-bore needle. Pumiliotoxin A alkaloids and their analogs are quite susceptible to air oxidation, presumably at C-5. As a result, chromatography of intermediates containing the 6-alkylideneindolizidine skeleton must be done rapidly and samples must be stored under an atmosphere of Ar or N_2. Due to this lability we also have not found it practical to send compounds with the 6-alkylideneindolizidine skeleton for elemental analysis. The expression "chromatographically pure" is used to describe purified products that showed no detectable impurities by TLC analysis.

Scheme XI



mixture of ether (0.5 L) and NH_4Cl saturated (1 L). The organic layer was removed and the aqueous layer was extracted with ether (2 × 600 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to afford 31.6 g (64%) of ketone **15**, which was sufficiently pure for the next step. Bulb-to-bulb distillation (85 °C, 0.01 mm) provided a sample judged to be ca. 90% pure by ^1H and ^{13}C NMR analysis: ^1H NMR (250 MHz, $CDCl_3$) δ 7.20 (m, 5 H, Ph), 3.83 (d, J = 13 Hz, NC*H*HPh), 3.47 (d, J = 13 Hz, NCH*H*Ph), 3.2–3.0 (m, NCH and NC*H*H), 2.4–1.7 (m, 5 H), 2.10 (s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 210.5, 138.3, 128.4, 127.9, 126.3, 72.9, 58.8, 53.3, 28.2, 24.6, 23.1; MS (CI) m/e 204 (MH) 160, 91; IR (film) 1709, 1605 cm^{-1}; $[\alpha]^{25}_D$ −81.2°, $[\alpha]^{25}_{579}$ 84.8°, $[\alpha]^{25}_{434}$ −191° (c 10.4, EtOH).

(2*S*)-α-Methyl-α-1-(1-ethoxyethenyl)-1-benzylpyrrolidinemethanol (16). To a solution of ethyl vinyl ether (19.1 mL, 200 mmol) and THF (50 mL) at −78 °C was added t-BuLi (33.3 mL of a 1.65 M solution in hexanes) over 5 min. By use of an internal thermometer and adjustment of the CO_2/acetone bath, the yellow solution was kept at −22 ● 3 °C for 15 min. The bath was then replaced with a CO_2/CCl_4 (−22 °C) bath for an additional 30 min, then the clear solution of the anion was cooled to −78 °C. A solution of ketone **15** (10.2 g, 50.0 mmol) and THF (10 mL) was then added over 20 min and the reaction was maintained at −78 °C for 1 h. The reaction was quenched by pouring into a rapidly stirring mixture of ether (100 mL) and water (200 mL), the organic layer was removed and the aqueous phase was extracted with ether (2 × 200 mL). The combined organic layers were dried (K_2CO_3), concentrated, and purified on silica gel (1:9 Et_3N–hexanes) to afford 8.92 g (65%) of a mixture of the α-(*S*) and α-(*R*) diastereomers in a 2.4:1 ratio: ^{13}C NMR (62.9 MHz, $CDCl_3$) α-(*S*) isomer δ 168.0, 140.5, 128.8, 128.2, 126.8, 80.1, 73.2, 67.1, 62.9, 60.5, 55.0, 27.1, 24.4, 24.1, 14.6; α-(*R*) isomer: δ 166.2, 140.2, 128.3, 128.3, 126.9, 79.5, 75.2, 69.9, 62.7, 60.5, 55.0, 27.1, 24.4, 24.1, 14.6; MS (CI) m/e 276, (MH) 160; IR (film) 3450, 1610 cm^{-1}.

(*R*)-α-Methyl-α-acetyl-1-benzyl-2(*S*)-pyrrolidinemethanol (17a). To an HCl solution (220 mL of a 0.3 M aqueous solution which had been evacuated and refilled with Ar × 3) at 0 °C was added a solution of enol ethers **16** (8.80 g, 32.0 mmol) and THF (40 mL). The resulting solution was stirred at 0 °C for 2.5 h, basified with solid K_2CO_3 (until pH 11), and extracted with ether (3 × 100 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated to afford 7.59 g (96%) of a mixture of ketones **17a** and the (*S*) epimer **17b**. Analysis of this mixture by 80-MHz ^1H NMR showed two quaternary methyl singlets at δ 1.25 and 1.37 in a 2.4:1 ratio. Chromatography (silica gel, 1:9 Et_3N–hexane) afforded chromatographically pure **17a** in 62% yield (4.90 g) from **16**. Recrystallization from pentane gave an analytical sample of the major isomer **17a**: mp 69–70 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.4–7.2 (m, 5 H, Ph), 3.72 (d, J = 14 Hz, NC*H*HPh), 3.36 (d, J = 14 Hz, NCH*H*Ph), 3.35 (t, J = 7.3 Hz, NCH), 2.91 (dt, J = 5.9, 10 Hz, NC*H*H), 2.41 (dt, J = 7.3, 10 Hz, NCH*H*), 2.30 (s, $COCH_3$), 1.95–1.8 (m, 2 H), 1.85–1.7 (m, 2 H), 1.23 (s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 215.5, 139.4, 128.3 (4 C), 126.9, 79.8, 69.1, 60.4, 54.7, 26.8, 26.1, 23.9, 22.4; MS (CI) m/e 248 (MH), 160; IR ($CHCl_3$) 3400, 1704 cm^{-1}; $[\alpha]^{25}_D$ −22.1°, $[\alpha]^{25}_{579}$ −22.6°, $[\alpha]^{25}_{434}$ −26.8° (c 4.3, EtOH). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.57; H, 8.99; N, 5.52.

(*R*)-α-Methyl-α-acetyl-2(*S*)-pyrrolidinemethanol (18). A mixture of amino ketone **17a** (3.10 g, 11.3 mmol), ethanol (70 mL), 3 N, HCl (7.53 mL, 22.6 mmol), and 10% Pd–C (150 mg) was kept under 1 atm of H_2 until no more starting material was seen by TLC analysis (1:9 Et_3N–hexanes). The mixture was then filtered through Celite and concentrated to a thick slurry. After azeotropic removel of water with 1,2-dichloroethane, 2.1 g (100%) of chromatographically pure amine hydrochloride **18** was isolated as an off-white powder. An analytical sample of **18** was prepared by several recrystallizations from $CHCl_3$–ether: mp 152–153 °C; $[\alpha]^{25}_D$ +2.5°, $[\alpha]^{25}_{579}$ +2.5°, $[\alpha]^{25}_{546}$ +2.1°, $[\alpha]^{25}_{434}$ −5.8° (c 2.4, EtOH). Anal. Calcd for $C_8H_{16}NO_2Cl$: C, 49.64; H, 8.27; N, 7.23. Found: C, 49.70; H, 7.92; N, 7.18.

A portion of **18** was partitioned between aqueous K_2CO_3 (pH 11) and ether. The ether layers were dried (K_2CO_3) and concentrated to give the free amine: ^1H NMR (250 MHz, $CDCl_3$) δ 4.10 (br s, OH and NH), 3.48 (, J = 7.7 Hz, NCH), 2.90 (m, NCH_2), 2.23 (s, $COCH_3$), 1.9–1.6 (m, 4 H), 1.19 (s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 213.6, 79.2, 63.5, 74.1, 25.6, 25.5, 24.9, 22.4; MS (CI) m/e 158 (MH) 70; IR ($CHCl_3$) 3500–3200, 1710 cm^{-1}.

Tetrahydro-(1*R*,7a*S*)-1-acetyl-1-methyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole (23). To a solution of amine hydrochloride **18** (134 mg, 0.693 mmol) and methanol (1 mL) was added aqueous formaldehyde (1.5 mL of a 37% solution). After stirring for 15 min, the solution was adjusted to pH 11 (K_2CO_3) and extracted with ether (3 × 5 mL). The combined organic layers were dried (K_2CO_3) and concentrated to give 115 mg (98%) of oxazolidine **23**, which showed trace impurities by ^1H NMR analysis but was >90% pure by ^{13}C NMR analysis: ^1H NMR (250 MHz, $CDCl_3$) δ 4.56 (d, J = 6.8 Hz, NC*H*HO), 4.30 (d, J = 6.8 Hz, NCH*H*O), 3.76 (dd, J = 4.0, 7.7 Hz, NCH), 3.13 (m, NC*H*H), 2.74 (m, NCH*H*), 2.23 (s, $COCH_3$), 2.1–1.7 (m, 4 H), 1.29 (s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 213.9, 87.4, 86.2, 67.6, 54.4, 27.1, 26.4, 25.1, 20.5; MS (CI) m/e 170 (MH), 125, 83; IR (film) 1712 cm^{-1}; $[\alpha]^{25}_D$ −32.5°, $[\alpha]^{25}_{579}$ −33.2°, $[\alpha]^{25}_{434}$ −85.7°.

Preparation of Racemic (8*R,8a*S**)-8-Hydroxy-8-methyl-7(1*H*)-octahydroindolizinone (11) by Protic Acid Promoted Cyclization of Oxazolidine 23.** A solution of *p*-toluenesulfonic acid monohydrate (450 mg, 2.36 mmol) and toluene (15 mL) was heated at reflux through a Soxhlet thimble containing CaC_2 (oil bath = ca. 145 °C). A solution of oxazolidine **23** (200 mg, 1.18 mmol) and toluene (1 mL) was then added, and reflux was continued for 3 h, whereupon the reaction was allowed to cool to room temperature. The toluene was decanted, and the resultant

brown oil was treated with aqueous K_2CO_3 (pH 11). After extraction with ether (3 × 10 mL), the combined organic layers were dried (K_2CO_3) and concentrated. Purification on silica gel (1:9 Et_3N–hexanes) afforded 40 mg (20%) of racemic indolizidine 11, which showed no detectable impurities by ^{13}C NMR analysis: ^1H NMR (250 MHz, $CDCl_3$) δ 3.81 (br s, OH), 3.26 (ddd, J = 1.2, 7.5, 10 Hz, H-5a), 3.17 (m, H-3a), 3.06 (ddd, J = 7.5, 12, 14 Hz, H-6a), 2.30 (m, H-3b), 2.35 (ddd, J = 3.5, 10, 12 Hz, H-5b), 2.24 (ddd, J = 1.2, 3.8, 14 Hz, H-6b), 2.16 (m, H-8a), 2.0–1.6 (m, H-1, H-2), 1.18 (s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 209.3, 75.6, 72.6, 54.2, 50.4, 36.6, 23.7, 23.0, 17.0; MS (EI) m/e 169 (M, 19), 83 (100), 70 (26); IR ($CDCl_3$) 3450, 2875, 2808, 1726 cm^{-1}.

(1*R*,7a*S*)-Tetrahydro-1-[1-[(trimethylsilyl)oxy]-ethenyl]-1-methyl-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one (27). To a solution of LDA [from diisopropylamine (3.43 mL, 24.5 mmol), THF (15 mL), and *n*-BuLi (14.6 mL of a 1.53 M solution in hexanes at 0 °C)] cooled to −78 °C was added a solution of oxazolidine **23** (3.45, 20.4 mmol) and THF. After 1 h at −78 °C, Me_3SiCl (3.1 mL, 24.5 mmol) was added, and after 15 min the reaction mixture was allowed to warm to room temperature and stirred there for 30 min. After concentration under vacuum, the resulting slurry was diluted with dry pentane (50 mL) and filtered through Celite. Concentration followed by bulb-to-bulb distillation afforded 3.44 g (70%) of ca. 90% pure (by ^{13}C NMR analysis) enol ether **27**: ^1H NMR (250 MHz, $CDCl_3$) δ 4.49 (d, J = Hz, NC*H*HO), 4.43 (d, J = 6.5 Hz, NCH*H*O), 4.43 (d, J = 1.2 Hz, C=C*H*H), 3.99 (d, J = 1.2 Hz, C=CH*H*), 3.58 (dd, J = 3.4, 7.8 Hz, NCH), 3.1 (m, NC*H*H), 2.78 (m, NCH*H*), 2.1–1.7 (m, H-6, H-7), 1.29 (s, CH_3), 0.22 (s, $SiMe_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 160.9, 84.9, 84.0, 81.6, 69.2, 53.3, 26.9, 25.7, 22.5, −0.3; MS (CI) m/e 242 (MH); IR ($CDCl_3$) 2700, 1632, 1000 cm^{-1}; $[\alpha]^{25}_D$ −38.6°, $[\alpha]^{25}_{579}$ −40.2°, $[\alpha]^{25}_{434}$ −75.4° (*c* 9.6, toluene).

Preparation of Racemic Indolizidine 11 from Trimethylsilyl Triflate Promoted Cyclization of Enol Ether 27. Enol ether **27** (383 mg, 1.59 mmol) was azeotroped to dryness with toluene (2 × 1 mL), diluted with dry CH_2Cl_2 (3.5 mL), and cooled to −22 °C. Trimethylsilyl triflate (0.32 mL, 1.75 mmol) was added, and the reaction mixture was maintained at −22 °C for 2.5 h. The reaction was then quenched by the addition of Et_3NHF (3.5 mL of a 1 M solution in CH_2Cl_2), the cooling bath was removed, and the reaction mixture was allowed to stir at ambient temperature for 1 h. The reaction mixture was then washed with a saturated K_2CO_3 solution (10 mL), and this was then reextrcted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried (K_2CO_3) and concentrated to afford 204 mg (76%) of chromatographically pure racemic indolizidine 11.

(*S*)-*S*-2-Pyridinyl 1-[(1,1-Dimethylethoxy)carbonyl]-2-pyrrolidinecarbothioate (29). To a solution of *N*-(*tert*-butoxycarbonyl)-L-proline (50.0 g, 233 mmol), 2-mercaptopyridine (25.8 g, 233 mmol), and CH_2Cl_2 was added a solution of dicyclohexylcarbodiimide (48.0 g, 233 mmol) and CH_2Cl_2 (50 mL) over 20 min. The resulting solution was stirred overnight at room temperature and then concentrated to a thick slurry. Dilution with ether (250 mL), filtration through Celite, and concentration afforded 79 g (ca. 100%) of the oil thioester. Recrystallization from 1:1 ether–hexanes gave 62.5 g (87%) of pure **28** as a yellow powder. An analytical sample was prepared by further recrystallization from 1:4 ether–hexanes: mp 69–71 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 8.7–8.5 (m, pyridine H-6), 7.8–7.2 (m, pyridine H-3,4,5), 3.7–3.4 (m, NCH_2), 2.4–1.8 (m, 4 H), 1.50 (s, t-Bu); ^{13}C NMR (62.9 MHz, $CDCl_3$), δ 177.1, 176.7, 176.0, 155.1, 154.0, 114.0, 113.9, 80.3, 80.2, 58.9, 58.7, 46.6, 46.2, 30.6, 29.4, 28.1, 24.1, 23.5; MS (CI) m/e 309 (MH), 142, 114, 70; IR ($CDCl_3$) 1695, 1390 cm^{-1}; $[\alpha]^{24}_D$ −133.3°, $[\alpha]^{25}_{579}$ −139.2° (*c*, 5.8, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}N_2O_3S$: C, 58.42; H, 6.54; N, 9.08. Found: C, 58.39; H, 6.56; N, 9.08.

(*S*)-1-[(1,1-Dimethylethoxy)carbonyl]-2-acetylpyrrolidine (30). To a solution of crystalline CuBr–SMe_2 (32.6 g, 161 mmol), Me_2S (150 mL), and ether (300 mL) was added MeLi (1.26 M solution in ether) slowly until the reaction mixture had changed from clear to a yellow (precipitate) and then back again to clear. This cuprate solution was then cooled to −78 °C, and a solution of thioester **29** (45.0 g, 146 mmol), ether (150 mL), and Me_2S (150 mL) was added via a dry ice–acetone-jacketed addition funnel. The addition was carefully monitored so that the internal temperature of the reaction solution was always <−70 °C. After 45 min, the reaction was quenched by the addition of pH 8 ($N-H_3-NH_4Cl$) buffer (200 mL). After this mixture had warmed to room temperature, the aqueous layer was removed and the organic phase diluted with ether (200 mL) and washed with pH 8 buffer (3 × 100 mL). After drying (Na_2SO_4), the organic layer was filtered through a short pad of silica gel and the resulting clear solution was concentrated to afford 29.3 g (94%) of product. Two crops of crystals from pentane provided 25.2 g (81%) of chromatographically pure **30** as thin clear plates. An analytical sample was prepared by further recrystallization from pentane: mp 38 °C; ^1H NMR (250 MHz, toluene-d_8, 80 °C) δ 4.05–3.95 (m, NCH), 3.3–3.2 (m, NCH_2), 1.83 (s, $COCH_3$), 1.7–1.2 (m, 4 H), 1.37 (s, t-Bu); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 208.1, 154.6, 153.8, 80.1, 79.8, 65.7, 65.2, 46.8, 46.6, 29.8, 29.7, 28.4, 28.3, 26.3, 25.6, 24.4, 23.7; MS (EI) m/e 170 (28), 114 (68), 70 (100); IR ($CDCl_3$) 1740, 1690, 1400 cm^{-1}; $[\alpha]^{25}_D$ −57.8°, $[\alpha]^{25}_{578}$ −60.0°, $[\alpha]^{25}_{435}$ −115°, $[\alpha]^{25}_{365}$ −182.5° (*c* 4.3, $CHCl_3$). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.04; H, 9.04; N, 6.55.

(*R*)-α-Methyl-α-(1-methoxypropadienyl)-2(*S*)-pyrrolidinemethanol (33). After ketone **30** (640 mg, 3.00 mmol) was dried by azeotroping to dryness with toluene (2 mL), trifluoroacetic acid (2 mL), anisole (2 g, 20 mmol), and CH_2Cl_2 (2 mL) were added at 23 °C. After 15 min this solution was concentrated, and the resulting oil was azeotroped to dryness with CH_2Cl_2 (3 × 2 mL) and then toluene (2 × 2 mL).

In another flask, *n*-BuLi (6.38 mL of a 2.35 M solution in hexanes) was added to a −78 °C solution of methoxyallene (1.15 g, 16.4 mmol) and THF (15 mL), and the resulting light yellow solution was kept at −78 °C for 30 min.[36] A solution of the crude amine salt prepared above and THF (10 mL) was then added at such a rate that the temperature of the reaction was maintained <−70 °C. The reaction mixture was maintained at −78 °C for an additional 15 min and then quenched into a mixture of brine (50 mL) and ether (50 mL, which had been degassed by evacuating and refilling 3× with Ar). After removing the organic layer, the aqueous layer was extracted with ether (2 × 50 mL) and the combined organic layers were dried (K_2CO_3) and concentrated. Purification of the crude product on silica gel (5:2:92 Et_3N–MeOH–Et_2O) afforded 234 mg (43%) of the highly labile crystalline aminoallene **33**, which showed no impurities by ^1H and ^{13}C NMR analysis: mp 55.5–59 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 5.57 (d, J = 7.4 Hz, C=C*H*H), 5.55 (d, J = 7.4 Hz, C=CH*H*), 3.42 (s, OCH_3), 3.3–3.4 (m, NCH), 2.97 (m, NCH_2), 1.9–1.6 (m, $NCH_2CH_2CH_2$), 1.35 (s, CCH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.2, 140.4, 95.2, 71.7, 63.5, 56.5, 46.5, 25.6, 25.4, 22.4; MS (CI) m/e 184 (MH), 166, 70; IR ($CDCl_3$) 3350, 1952, 1090 cm^{-1}.

(8*R*,8a*S*)-7-Methoxy-8-hydroxy-8-methyl-1,2,3,5,8,8a-hexahydroindolizine (34). Trifluoroacetic acid (25 mL) was added to a solution of ketone **30** (4.68 g, 22.0 mmol), anisole (14.3 g, 132 mmol), and CH_2Cl_2 (25 mL). After the reaction had proceeded for 15 min, the flask was evacuated and the solvents were removed under reduced pressure. The remaining liquid was triturated with dry pentanes (5 × 200 mL) and azetroped with toluene (20 mL), and the residue was then allowed to react with 1-lithio-1-methoxyallene as previously described for the synthesis of **33**.

The isolated crude aminoallene **33** was azotroped with toluene (20 mL) and then diluted with dry acetontrile (50 mL). Anhydrous *p*-toluenesulfonic acid was added until the solution was just acidic (as measured with pHydrin paper). Immediately, triethylamine was added dropwise until the solution was basic to Litmus paper. The solution was then heated to 40 °C for 8 h. The reaction mixture was then quenched by pouring it into a 5% K_2CO_3 solution (25 mL) and then diluting the mixture with ether (100 mL). The organic layer was removed, and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic layers were dried (K_2CO_3), filtered through Celite, and concentrated to give a black oil. Purication of this crude product on silica gel (1:9 Et_3N–hexanes) afforded 1.16 g (29%) of crystalline enol ether **34**, which was sufficiently pure to be employed in the next step. An analytical sample was prepared by recrystallization from hexanes: mp 76–76.5 °C; ^1H NMR (250 MHz, $CDCL_3$) δ 4.59 (dd, J = 1.8, 5.1 Hz, H-6), 3.54 (s, OCH_3), 3.47 (dd, J = 5.1, 15 Hz, H-5a), 3.2–3.1 (m, H-3a), 2.77 (app. d, J = 15 Hz, H-5b), 2.70 (br s, OH), 2.3–2.2 (m, H-3b, H-8a), 2.0–1.7 (m, H-1,2), 1.21 (s, CCH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 158.9, 92.9, 70.3, 70.2, 54.8 (2C), 50.9, 22.8, 22.5,

19.9; MS (CI) m/e 184 (MH), 114, 70; IR ($CDCl_3$) 3460, 2790, 2710, 1651 cm^{-1}; $[\alpha]^{25}_D$ +187.8°, $[\alpha]^{25}_{578}$ +195.9°, $[\alpha]^{25}_{435}$ +408.0°. Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.38; H, 9.37; N, 7.59.

Preparation of Enantiomerically Pure (-)-Indolizidine 11 from 34. To 150 mL of a 5% HCl solution (previously vigorously degassed by evacuation and refilling 3× with Ar) was added enol ether **34** (2.11 g, 11.5 mmol), and the reaction mixture was maintained at ambient temperature for 14 h. The aqueous solution was then extracted with ether (3 × 100 mL), adjusted to pH 11 with K_2CO_3, and extracted with ethyl acetate (3 × 100 mL). The combined ethyl acetate layers were dried (K_2CO_3) and concentrated to give 1.48 g (76%) of chromatographically pure **11**. An analytical sample was prepared by further chromatography on silica gel as previously detailed: $[\alpha]^{25}_D$ -44.2°, $[\alpha]^{25}_{578}$ -45.5°, $[\alpha]^{25}_{546}$ -49.6° (c 4.7, $CHCl_3$); HRMS calcd for $C_9H_{15}NO_2$ 169.1103, found 169.1101.

(*R*)-2-Methylhexanal (40). The general procedure of Parikh and Doering was followed:[42] A solution of pyridine-SO_3 complex (955 mg, 6.0 mmol) and Me_2SO (5 mL) was added to 0 °C to a solution of alcohol **39** (232 mg, 2.0 mmol), Et_3N (1.05 mL, 14 mmol), and Me_2SO (1 mL). The ice bath was removed, and the reaction mixture was allowed to stir at 23 °C for 1 h, and then was quenched by pouring rapidly into a mixture of saturated NH_4Cl (25 mL) and ether (25 mL). The organic layer was removed and washed with saturated NH_4Cl (3 × 25 mL) and water (3 × 25 mL), dried ($CaSO_4$), and concentrated using a rotary evaporator at ca. 200 mm to afford the crude aldehyde. Purification on silica gel (1:19 ether–pentane) gave 0.20 g (88%) of pure **40**: ^1H NMR (250 MHz, $CDCl_3$) δ 9.62 (d, J = 2.3 Hz, CHO), 2.31 (m, 2 H, H-2), 1.8–1.2 (m, 6 H), 1.09 (d, J = 7.0 Hz, $CHCH_3$), 0.90 (m, CH_3); $[\alpha]^{25}_D$ -19.7°, $[\alpha]^{25}_{578}$ -20.9°, $[\alpha]^{25}_{435}$ -54.2°, $[\alpha]^{25}_{365}$ -133.2° (c 5.8, $CHCl_3$).

(8*R*,8a*S*)-8-Hydroxy-8-methyl-6-((*Z*)-2(*R*)-methylhexylidene)octahydroindolizin-7-one (41). A solution of indolizidine **11** (164 mg, 0.97 mmol) and ether (1 mL) was cooled to 0 °C. A suspension of tritylllithium in ether (ca. 0.3 M) was then added until the reaction mixture remained pink for 5 min. Neat (*R*)-2-methylhexanal (145 mL, 10.2 mmol) was added all at once, and the resulting mixture was stirred at 0 °C for 5 min and then quenched into 40 mL of rapidly stirring pH 8 (NH_3/NH_4Cl) buffer. The mixture was extracted with ether (5 × 10 mL), and the combined organic layers were dried ($CaSO_4$) and concentrated.

The crude aldol diastereomers were dried by azeotroping with toluene (3 × 1 mL), and then CH_2Cl_2 (2 mL) and 4-(dimethylamino)pyridine (ca. 10 mg) were added. After cooling to -46 °C, DBU (0.88 mL, 5.9 mmol) was added followed by trifluoroacetic anhydride (0.70 mL, 4.9 mmol). After 1 h at this temperature, the solution was allowed to warm to 0 °C, additional DBU (0.10 mL, 0.67 mmol) was added, and the reaction mixture was maintained at ambient temperature for 15 min. After quenching with 5 mL of pH 8 (NH_3/NH_4Cl) buffer, the aqueous phase was adjusted to pH 9 with NH_4OH and extracted with ether (3 × 10 mL). The combined organic extracts were dried ($CaSO_4$) and purified on silica gel (hexanes to 1:9 Et_3N–hexanes) to give 77 mg (30%) of enone **41**, which was contaminated with a small amount (ca. 5%) of the C-11 methyl epimer. Additional chromatography provided a sample of **41**, which was >90% pure by ^1H and ^{13}C NMR analysis: ^1H NMR (250 MHz, $CDCl_3$) δ 6.52 (ddd, J = 1.6, 2.6, 11 Hz, H-10), 4.03 (dd, J = 1.6, 14 Hz, H-5a), 3.7 (br s, OH), 3.35–3.25 (m, H-3a), 2.97 (dd, J = 2.6, 14 Hz, H-5b), 2.5–2.25 (m, H-8a, H-3b, H-11), 2.0–1.8 (m, H-1, H-2), 1.4–1.1 (m, H-12, H-13, H-14), 1.26 (s, H-9), 1.02 (d, J = 6.6 Hz, H-16), 0.87 (t, J = 6.8 Hz, H-15); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.4, 148.2, 129.8, 77.5, 73.3, 69.4, 55.4, 52.3, 36.5, 33.1, 30.0, 23.8, 23.0, 20.1, 18.0, 14.2; MS (EI) m/e 265 (M, 30), 139 (30), 70 (100); IR ($CDCl_3$) 3450, 2800, 2740, 1694, 1618 cm^{-1}; $[\alpha]^{25}_D$ -6.5°, $[\alpha]^{25}_{578}$ -6.6°, $[\alpha]^{25}_{435}$ +1.2° (c 1.1, $CHCl_3$); HRMS calcd for $C_{16}H_{27}NO_2$ (265.2042, found, 265.2043.

Basification of the quenched aldol solution with NaOH to pH 11 followed by extraction with ethyl acetate (3 × 10 mL), drying (K_2CO_3), and concentration provided 42 mg (27%) of chromatographically pure unconsumed indolidizine **11**.

Preparation of Indolizidinediol 42 by $LiAlH_4$ Reduction of Enone 41. A solution of $LiAH_4$ (1 M in THF, 0.24 mmol) was added dropwise at 0 °C to a solution of enone **41** (62 mg, 0.23 mmol) and THF (1 mL). When TLC analysis indicated that no more enone was present, the reaction was quenched by the sequential addition of water (8 mL), 15% NaOH (8 mL), and water (25 mL). The resulting mixture was diluted with ether and filtered through Celite to afford a 1:6 mixture (by ^1H NMR analysis) of **8** and **42**. Purification on silica gel (1:9 MeOH–$CHCl_3$) afforded the equatorial alcohol stereoisomer **42** (26.5 mg, 43%) and the axial alcohol stereoisomer **8** (2.2 mg, 4%). **42**: ^1H NMR (250 MHz, $CDCl_3$) δ 5.47 (ddd, J = 1.8, 1.8, 9.9 Hz, H-10), 3.80 (d, J = 12 Hz, H-5a), 3.67 (br s, H-7), 3.1–3.0 (m, H-3a), 2.45–2.3 (m, H-3b), 2.38 (ddd, J = 1.2, 1.2, 12 Hz, H-5b), 2.3–2.15 (m, H-11), 2.1–2.0 (m, H-8a), 1.85–1.7 (m, H-1, H-2), 1.4–1.1 (m, H-12, H-13, H-14), 1.22 (s, H-9), 0.98 (d, J = 6.6 Hz, H-16), 0.86 (t, J = 7.1 Hz, H-15); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 132.7, 131.9, 71.7, 70.8, 54.7, 52.0, 37.6, 32.1, 30.0, 23.8, 23.0, 22.0 (2 C), 20.4, 14.3; MS (EI) m/e 267 (M, 38), 250 (77), 149 (84), 114 (33), 112 (39), 70 (100); IR ($CDCl_3$) 3560, 3480, 2875, 2800 cm^{-1}; $[\alpha]^{25}_D$ -19.2°, $[\alpha]^{25}_{578}$ -19.8°, $[\alpha]^{25}_{546}$ -22.9°, $[\alpha]^{25}_{435}$ -4.1°, $[\alpha]^{25}_{365}$ -70.1° (c 1.3, MeOH).

Preparation of (+)-Allopumiliotoxin 267A (8) by $Me_4NBH(OAc)_3$ Reduction of Enone 41. The general procedure of Evans was employed.[47a] Tetramethylammonium triacetoxyborohydride (161 mg, 0.613 mmol) was placed in an oven-dried 10-mL test tube containing a magnetic stir bar. The tube was sealed with a rubber septum and flushed with N_2. Acetone (3.4 mL, freshly distilled from $CaSO_4$) was added by syringe followed by glacial acetic acid (70 μL, 16 equiv, dried by azeotropic distillation with benzene followed by fractional distillation from CrO_3). The suspension was stirred at ambient temperature (24 °C) for 15 min. A solution of octahydroindolizin-7-one **41** (20.3 mg, 0.0766 mmol) and acetone (0.2 mL) was then added by syringe, and the reaction mixture was allowed to stir at ambient temperature under N_2 for 48 h. The reaction was quenched by the addition of 1 mL of saturated NH_4Cl, and half of the acetone was removed under a stream of nitrogen. The residue was diluted with EtOAc (10 mL) and water (1 mL), and the aqueous layer was decanted. The organic layer was washed with 1 M Na_2CO_3 (2 × 2 mL) and brine followed by drying over K_2CO_3 to give 19.8 mg of crude yellow oil whose 300-MHz ^1H NMR spectrum showed starting enone **41** and allopumiliotoxin 267A (**8**) in a ratio of 1:3 with no trace of the C-7 epimer. Purification on 1.6 g of silica gel ($CHCl_3$–MeOH–NH_4OH, 20:1:0.1) provided starting material (5.2 mg, 25%) and allopumiliotoxin 267A (15.0 mg, 0.562 mmol, 73%): $[\alpha]^{25}_D$ +31°, $[\alpha]^{25}_{405}$ +87°, $[\alpha]^{25}_{435}$ +68°, $[\alpha]^{25}_{546}$ +50°, $[\alpha]^{25}_{577}$ +40° (c 0.22, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 5.33 (dd, J = 9.5, 1.5 Hz, H-10), 3.71 (s, H-7), 3.60 (d, J = 12.5 Hz, H-5a), 3.1 (m, H-3a), 2.91 (bs, OH), 2.71 (bd, J = 12 Hz, H-5b), 2.50–2.45 (m, H-8a), 2.41–2.37 (m, H-11), 2.4–2.2 (m, H-3b), 1.8–1.6 (m, H-1, H-2), 1.4–1.1 (m, H-12, H-13, H-14), 1.21 (s, H-9), 0.97 (d, J = 6.5 Hz, C-11 Me), 0.87 (t, J = 7.2 Hz, H-15); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 133.4, 80.9, 70.3, 65.2, 54.3, 48.9, 37.1, 32.0, 29.7, 22.8, 22.7, 21.2 (2 carbons), 20.6. 14.1; IR (CCl_4) 3623, 3473, 2876, 2858, 1742 cm^{-1}; HRMS calcd for $C_{16}H_{29}NO_2$ 267.2198, found 267.2196.

(*R*)-4-(Benzyloxy)-2-methylbutanal (47). Oxidation of alcohol **46** (291 mg, 1.50 mmol) as directed for the synthesis of **40** gave the crude aldehyde, which was purified on silica gel (1:9 ethyl acetate–hexanes) to afford 246 mg (85%) of chromatographically pure **47** as an oil. This sample was used immediately in the aldol step. **47**: ^1H NMR (250 MHz, $CDCl_3$) δ 9.64 (d, J = 1.6 Hz, CHO), 7.3 (m, 5 H, Ph), 4.48 (s, CH_2Ph), 3.53 (dt, J = 2.5, 6.0, Hz, H-4), 2.54 (dq, J = 1.5, 6.8 Hz, H-2), 2.06 (ddt, J = 5.9, 7.1, 14 Hz, H-3), 1.69 (ddd, J = 6.2, 12, 14 Hz, H-3), 1.10 (d, J = 7.1 Hz, $CHCH_3$); MS (EI) m/e 107 (85), 91 (100); IR (CCl_4) 1732, 1092 cm^{-1}; $[\alpha]^{25}_D$ +2.7°, $[\alpha]^{25}_{578}$ +2.8°, $[\alpha]^{25}_{435}$ +5.4°, (c 3.6, MeOH).

(8*R*,8a*S*)-8-Hydroxy-8-methyl-6-[(*Z*)-2(*R*)-methyl-4-(benzyloxy)butylidene]octahydroindolizin-7-one (48). A solution of indolizidine **11** (169 mg, 1.00 mmol) was deprotonated with tritylllithium and allowed to undergo an aldol reaction with aldehyde **47** (246 mg, 1.28 mmol) as described for the preparation of **41**. The crude aldol adducts were then dehydrated (as described for the preparation of **41**) to give, after purification on silica gel (1:9 Et_3N–hexanes), 91 mg (27%) of chromatographically pure enone **48**, which was judged to be >95% pure by ^1H NMR analysis: ^1H NMR (250 MHz, $CDCl_3$) δ 7.3 (m, 5 H, Ph), 6.48 (ddd, J = 1.6, 2.5, 11 Hz, H-10), 4.45 (s, CH_2Ph), 4.02 (dd, J = 1.4, 14 Hz, H-5a), 3.7 (br s, OH), 3.5–3.3 (m, H-13), 3.18 (m, H-3a), 2.94 (dd,

J = 2.6, 14 Hz, H-5b), 2.64 (m, H-11), 2.4–2.2 (m, H-8a and H-3b), 2.0–1.5 (m, H-1, H-2, H-12), 1.25 (s, H-9), 1.04 (d, J = 6.7 Hz, $CHCH_3$); MS (EI) m/e 343 (M, 10), 91 (62), 70 (100); IR (CCl_4) 3450, 2870, 2790, 1720, 1622 cm^{-1}; $[\alpha]^{25}_D$ −16.0°, $[\alpha]^{25}_{578}$ −16.4°, $[\alpha]^{25}_{546}$ −17.9° (c 4.3, MeOH).

Basification of the aldol quench, as described in the previous example, allowed for the isolation of 49 mg (29%) of chromatographically pure indolizidine **11**.

(8*R*,8a*S*)-8-Hydroxy-8-methyl-6-[(*Z*)-2(*R*)-methyl-4-(benzyloxy)butylidene]octahydroindolizin-7-ol (49). To a solution of enone **48** (91 mg, 0.27 mmol) and ethanol (2 mL) was added $CeCl_3$ heptahydrate (148 mg, 0.40 mmol) followed by $NaBH_4$ (10.4 mg, 0.30 mmol).[51] After being stirred for 5 min, the reaction mixture was quenched with brine (2 mL) and extracted with ether (4 × 3 mL). The combined organic extracts were dried (K_2CO_3) and concentrated to afford 53 mg (58%) of chromatographically pure diol **49**, which showed no detectable impurities by ^{13}C NMR analysis: ^1H NMR (250 MHz, $CDCl_3$) δ 7.3 (m, 5 H, Ph), 5.46 (ddd, J = 1.8 1.8, 10 Hz, H-10), 4.45 (s, CH_2Ph), 3.83 (d, J = 12 Hz, H-5a), 3.65 (m, H-7), 3.5–3.3 (m, H-13), 3.03 (m, H-3a), 2.68 (m, H-11), 2.38 (br s, OH), 2.30 (ddd, J = 1.3, 1.3, 12 Hz, H-5b), 2.2–1.9 (m, H-8a and H-3b), 1.85–1.6 (m, H-1, H-2, H-12), 1.21 (s, H-9), 1.01 (d, J = 6.7 Hz, $CHCH_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$), δ 138.7, 133.6, 130.7, 128.8, 128.5, 127.8, 127.6, 73.1, 71.7, 70.8, 68.6, 54.5, 51.8, 37.4, 28.7, 23.7, 22.0, 21.8, 20.4; MS (EI) m/e 345 (M, 2), 182 (100), 91 (68), 70 (86); IR (CCl_4) 3500, 2870, 2790 cm^{-1}; $[\alpha]^{25}_D$ −35.0°, $[\alpha]^{25}_{578}$ −36.2°, $[\alpha]^{25}_{546}$ −41.6° (c 2.2, MeOH).

(8*R*,8a*S*)-7-[[(Dimethylethyl)dimethylsilyl]oxy]-8-hydroxy-8-methyl-6-[(*Z*)-2(*R*)-methyl-4-(benzyloxy)butylidene]octahydroindolizine (50). To a solution of alcohol **49** (17.7 mg, 0.0513 mmol), THF (1 mL), and HMPA (0.5 mL) at −78 °C was added *n*-BuLi (73 mL of a 2.2 M solution in hexanes, 0.16 mmol). After the solution was kept at −78 °C for 20 min, it was warmed to 0 °C for 10 min, and then t-$BuMe_2SiCl$ (150 mg, 1.00 mmol) was added. After 15 min the reaction was quenched by the addition of 10% aqueous K_2CO_3 and extracted with ether (4 × 2 mL). The combined organic layers were washed with water (4 × 2 mL) and brine (1 mL), dried (K_2CO_3), and concentrated. Purification on silica gel (3:97 MeOH–$CHCl_3$) gave 11.6 mg (49%) of chromatographically pure silyl ether **50**, which showed no detectable impurities by ^1H NMR analysis: ^1H NMR (250 MHz, $CDCl_3$) δ 7.3–7.2 (m, 5 H, Ph), 5.41 (ddd, J = 1.0 1.8, 10 Hz, H-10), 4.46 (s, CH_2Ph), 3.83 (d, J = 14 Hz, H-5a), 3.76 (d, J = 2.0 Hz, H-7), 3.4–3.3 (m, H-13), 2.93 (m, H-3a), 2.70 (m, H-11), 2.27 (app d, J = 12 Hz, H-5b), 2.2–2.0 (m, H-8a and H-3b), 2.0–1.6 (m, H-1, H-2, H-12), 1.14 (s, H-9), 1.03 (d, J = 6.6 Hz, $CHCH_3$), 0.96 (s, t-Bu), 0.16 (s, $SiCH_3$), 0.08 (s, $SiCH_3$); MS (EI) m/e 459 (M, 6), 296 (61), 91 (100), 73 (73), 72 (65); IR (CCl_4) 3530, 2865, 2780, 1109 cm^{-1}; $[\alpha]^{25}_D$ −23.1°, $[\alpha]^{25}_{578}$ −22.8°, $[\alpha]^{25}_{435}$ −47.3°, $[\alpha]^{25}_{365}$ −76.5° (c 0.6, MeOH).

(8*R*,8a*S*)-7-[[(Dimethylethyl)dimethylsilyl]oxy]-8-hydroxy-8-methyl-6-[(*Z*)-2(*R*)-methyl-4-hydroxybutylidene]octahydroindolizine (51). To a solution of benzyl ether **50** (21 mg, 0.046 mmol), THF (2 mL), and ammonia (2 mL) at −78 °C was added 2 small (ca. 1 mm^3) pieces of sodium metal. The cooling bath was removed, and the solution was allowed to reflux for 30 min. The blue solution was recooled to −78 °C, and solid NH_4Cl was added until the solution turned clear. After allowing the ammonia to evaporate, brine (3 mL) was added and the aqueous phase was extracted with ether (3 × 5 mL). The combined organic layers were dried (K_2CO_3) and concentrated. Purification on silica gel (1:9 Et_3N–$CHCl_3$) gave 8.9 mg (55%) of chromatographically pure diol **51**, which showed no detectable impurities by ^1H NMR analysis: ^1H NMR (250 MHz, $CDCl_3$) δ 5.44 (dd, J = 1.5, 10 Hz, H-10), 3.82 (d, J = 15 Hz, H-5a), 3.80 (s, H-7), 3.6–3.8 (m, H-13), 3.06 (m, H-3a), 2.7 (m, H-11), 2.42 (br d, J = 15 H, H-5b), 2.28 (s, OH), 2.3–2.0 (m, H-8a and H-3b), 1.9–1.4 (m, H-1, H-2, H-12), 1.15 (s, H-9), 1.05 (d, J = 6.5 Hz, $CHCH_3$), 0.97 (s, t-Bu), 0.09 (s, $SiCH_3$), 0.03 (s, $SiCH_3$); MS (EI) m/e 369 (M, 17), 75 (79), 73 (74), 70 (100); IR (CCl_4) 3550–3300, 2855, 2790, 1595 cm^{-1}; $[\alpha]^{25}_D$ −7.6°, $[\alpha]^{25}_{578}$ −9.9°, $[\alpha]^{25}_{546}$ −20°, $[\alpha]^{25}_{365}$ −30° (c 0.4, MeOH); HRMS calcd for $C_{20}H_{39}NO_3Si$ 369.2699, found 369.2708.

(8*R*,8a*S*)-7-[[(Dimethylethyl)dimethylsilyl]oxy]-8-hydroxy-8-methyl-6-[(*Z*)-2(*R*)-methyl-4-oxobutylidene]-octahydroindolizine (52). To a solution of freshly distilled oxalyl chloride (5.4 μL, 0.062 mmol) and CH_2Cl_2 (0.1 mL) at −78 °C was added Me_2SO (8.9 mL, 0.12 mmol).[52] After 10 min, a solution of diol **51** (9.9 mg, 0.025 mmol) and CH_2Cl_2 (0.2 mL) was added. After 20 min, Et_3N (26 mL, 0.19 mmol) was added, the cooling bath was removed, and the reaction mixture was allowed to warm to ambient temperature. The reaction was quenched with brine (1 mL) and extracted with ether (4 × 2 mL), and the combined organic layers were then dried (K_2CO_3) and concentrated. Purification on silica gel (1:9 Et_3N–hexanes) gave 8.2 mg (83%) of chromatographically pure aldehyde **52**: ^1H NMR (250 MHz, $CDCl_3$) δ 9.68 (t, J = 2.1 Hz, CHO), 5.46 (ddd, J = 1.1, 2.0, 10 Hz, H-10), 3.87 (d, J = 12 Hz, H-5a), 3.76 (d, J = 2.1 Hz, H-7), 3.1 (m, H-3a, H-11), 2.39 (ddd, J = 2.0, 3.5, 7.6 Hz, H-12), 2.3–1.9 (m, H-8a, H-5b, H-3b), 1.9–1.6 (m, H-1, H-2), 1.14 (s, H-9), 1.10 (d, J = 6.7 Hz, $CHCH_3$), 0.97 (s, t-Bu), 0.08 (s, $SiCH_3$), 0.01 (s, $SiCH_3$); MS m/e (EI) 211 (78), 73 (100), 70 (84); IR (CCl_4) 3510, 2860, 2790, 2710, 1728 cm^{-1}; $[\alpha]^{25}_D$ −4.0°, $[\alpha]^{25}_{578}$ −3.2°, $[\alpha]^{25}_{546}$ −4.2°, $[\alpha]^{25}_{435}$ −8.0° (c, 0.6, MeOH).

(8*R*,8a*S*)-7-[[(Dimethylethyl)dimethylsilyl]oxy]-8-hydroxy-8-methyl-6-[(*Z*)-2(*R*),5-dimethyl-7-[[(dimethylethyl)diphenylsilyl]oxy]-6-oxo-4-octen-1-ylidene]octahydroindolizine (54). To a degassed solution of aldehyde **52** (8.2 mg, 0.021 mmol) and CH_2Cl_2 (0.2 mL) was added ylide **53**[11] (30 mg, 0.50 mmol), and the reaction mixture was heated in a 60 °C oil bath for 72 h. The contents of the reaction vessel were then purified on silica gel (1:9 Et_3N–hexanes) to give 7.8 mg (55%) of chromatographically pure enone **54**, which showed only trace impurities by ^1H NMR analysis: ^1H NMR (250 MHz, $CDCl_3$) δ 7.8–7.3 (m, 5 H, Ph), 6.23 (dt, J = 1.2, 7.5 Hz, H-13), 5.46 (dd, J = 1.3, 9.3 Hz, H-10), 4.87 (q, J = 6.7 Hz, H-16), 3.74 (d, J = 2.0 Hz, H-7), 3.70 (d, J = 11 Hz, H-5a), 3.1 (m, H-3a), 2.5 (m, H-11), 2.4–2.00 (m, H-8a, H-5b, H-3b, H-12), 1.9–1.6 (m, H-1 and H-2), 1.37 (d, J = 6.7 Hz, $=CCH_3$), 1.19 (s, H-9), 1.19 (s, $Si(CH_3)_3$), 1.0 (m, H-17 and $CHCH_3$), 0.11 (s, $SiCH_3$), 0.06 (s, $SiCH_3$); MS (EI) m/e 689 (M, 2), 323 (100), 211 (54), 135 (62), 73 (81); IR (CCl_4) 3500, 2860, 1675, 1100 cm^{-1}; $[\alpha]^{25}_D$ −1.8°, $[\alpha]^{25}_{546}$ −2.1°, $[\alpha]^{25}_{435}$ −3.6° (c 0.4, MeOH); HRMS calcd for $C_{41}H_{63}NO_4Si$ 689.4295, found 689.4317.

(+)-Allopumiliotoxin 339B (9). A solution of enone **54** (8.7 mg, 0.013 mmol) and THF (0.5 mL) was slowly added to a suspension of $LiAlH_4$ (2 mg, 0.05 mmol) in THF (0.5 mL) at −78 °C. After stirring at −22 °C for 1 h, the reaction mixture was allowed to warm to room temperature and stirred for an additional hour. The reaction was then quenched by the addition of $NaSO_4 \cdot 10H_2O$ (ca. 100 mg) followed by $CHCl_3$ (5 mL). After 1 h of stirring, the reaction mixture was filtered through Celite, and the Celite was washed with ether (2 mL). The organic layer was dried (K_2CO_3) and concentrated. Purification on silica gel (1:9 Et_3N–$CHCl_3$) gave 1.9 mg (44%) of chromatographically pure (+)-allopumiliotoxin 339B. This sample was judged to be >95% pure by ^1H NMR analysis and deteriorated within days if stored in $CDCl_3$: ^1H NMR (250 MHz, $CDCl_3$) δ 5.52 (ddd, J = 1.9, 1.9, 10 Hz, H-10), 5.39 (dt, J = 1.1, 7.6 Hz, H-13), 3.79 (d, J = 12 Hz, H-5a), 3.78 (app dd, J = 6.9, 13 Hz, H-16), 3.71 (d, J = 6.9 Hz, H-15), 3.66 (dd, J = 1.1, 1.6 Hz, H-7), 3.07 (m, H-3a), 2.5 (m, H-11), 2.39 (app dd, J = 1.8, 12 Hz, H-5b), 2.3–1.9 (m, H-8a, H-3b, H-12), 1.8–1.6 (m, H-1 and H-2), 1.60 (d, J = 1.2 Hz, $=CCH_3$), 1.22 (s, H-9), 1.11 (d, J = 6.1 Hz, H-17), 1.01 (d, J = 6.6 Hz, H-18); MS (EI) m/e 339 (M, 9), 182 (91), 114 (40), 70 (100); IR (CCl_4) 3500, 2855, 2785, 2745, 1252, 1085 cm^{-1}; $[\alpha]^{25}_D$ +8.8°, $[\alpha]^{25}_{578}$ +6.9°, $[\alpha]^{25}_{546}$ +7.5°, $[\alpha]^{25}_{435}$ +15°, $[\alpha]^{25}_{407}$ +17°, $[\alpha]^{25}_{404}$ +16°, $[\alpha]^{25}_{365}$ +29°, $[\alpha]^{25}_{334}$ +40° (c 1.0, MeOH); HRMS calcd for $C_{19}H_{33}NO_4$ 339.2409, found 339.2416.

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Registry No. **8**, 73376-38-2; **9**, 91550-04-8; **11**, 91550-05-9; **13**, 83528-04-5; **14**, 31795-93-4; **15**, 138052-86-5; **16** (isomer 1), 138052-87-6; **16** (isomer 2), 138052-88-7; **17a**, 138052-89-8; **17b**,

138052-90-1; **18**, 91550-06-0; **18**·HCl, 138052-91-2; **19**, 138052-92-3; **20**, 138052-93-4; **23**, 91550-07-1; **27**, 138052-94-5; **28** (isomer 1), 138052-95-6; **28** (isomer 2), 138052-96-7; **29**, 33857-76-0; **30**, 91550-08-2; **31a**, 138052-97-8; **31b**, 138052-98-9; **32**, 138128-10-6; **33**, 91550-09-3; **34**, 91550-10-6; **35** (isomer 1), 138052-99-0; **35** (isomer 2), 138128-11-7; **36**, 138053-00-6; **37**, 131636-15-2; **38**, 131636-16-3; **39**, 66050-98-4; **40**, 132151-88-3; **41**, 91550-12-8; **42**, 91604-59-0; **43**, 10385-30-5; **44**, 138053-01-7; **45**, 138053-02-8; **46**, 96154-47-1; **47**, 91550-14-0; **48**, 91550-13-9; **49**, 138053-03-9; **50**, 91550-15-1; **51**, 138053-04-0; **52**, 91550-16-2; **53**, 90246-35-8; **54**, 91550-17-3; $MeOCH{=}C{=}CH_2$, 13169-00-1; $PhCH_2CH(OMe)_2$, 101-48-4; $ClCO(CH_2)_3Et$, 142-61-0; L-proline, 147-85-3; *N*-(*tert*-butoxycarbonyl)-L-proline, 15761-39-4; 2-mercaptopyridine, 2637-34-5; (4*R*,5*S*)-4-methyl-5-phenyloxazolidinone, 77943-39-6.

Supplementary Material Available: Experimental procedures and characterization data for intermediates **19**, **20**, **28**, **31**, **32**, **35**, **36**, **37**, **38a**, **39**, **43**, **44**, **45a**, and **46**; procedures for forming **11** and **31a**; ^1H and/or ^{13}C NMR spectra for **8**, **9**, **11**, **13**, **15**, **16**, **19**, **20**, **23**, **27**, **32**, **33**, **35**, **36**, **38**, **41**, **42**, **43**, **45**, **46**, **47**, **48**, **49**, **50**, **51**, **52** and **54** (35 pages). Ordering information is given on any current masthead page.

Stereospecific Enammonium–Iminium Rearrangements in a Benzo[*a*]quinolizidine System

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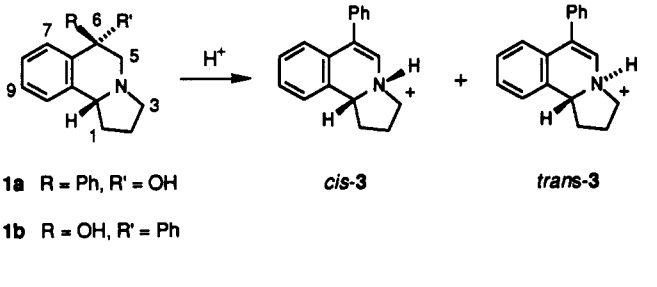
Reductive deoxygenation of amino alcohols **5a**·HBr or **5b**·HBr with borane–THF in trifluoroacetic acid produced a 68:32 mixture of amines **8a** and **8b**. This is a significant departure from the 8:92 ratio of amines **2a**:**2b** obtained in the reduction of amino alcohols **1a**·HBr or **1b**·HBr. The diminished trans selectivity with **5** arises from a reduced bias for a cis ring fusion in the N-protonated 6,6 system relative to the 5,6 system. By proton NMR, we observed dehydration of **5a**·HBr in CF_3CO_2D to a 75:25 mixture of enammonium salts *trans*-**6**:*cis*-**6**, each of which rearranged stereospecifically to give a 75:25 mixture of iminium salts *cis*-**7**:*trans*-**7**. Rate data for this rearrangement were acquired and computationally analyzed. The dehydration of free base **5b** in CF_3CO_2D was also studied. In this case, we were able to characterize the rate of disappearance of **5b**, as well as the rate of the stereospecific enammonium–iminium rearrangement. We also address slow, "post-rearrangement" epimerization at ring position 7, H/D exchange at ring position 6, and mechanistic aspects of the overall process.

Recently, we identified an unusual stereospecific 1,3 proton migration from nitrogen to carbon in the context of an enammonium–iminium rearrangement (Scheme I).[1] This process, which appears to occur substantially through a tight solvent cage, is crucial to the high stereoselectivity obtained in the deoxygenation of pyrroloisoquinoline **1a** or **1b** with borane–THF/trifluoroacetic acid to a mixture of **2a** and **2b** highly enriched in **2b**.[1] In this reduction a mixture of enammonium salts **3**, strongly biased to the cis-fused form (*cis*-**3**), rearranges to a mixture of iminium salts **4**, highly enriched in the trans diastereomer (*trans*-**4**), regardless of the stereochemistry of the original amino alcohol. The stereospecificity was reflected by virtually identical isomer ratios at the enammonium and iminium stages of the reaction (*trans*-**3**:*cis*-**3** = *cis*-**4**:*trans*-**4**; by ^1H NMR). As far as the independent diastereomeric pathways are concerned, we deemed the rearrangement of the major diastereomers, *cis*-**3** → *trans*-**4**, to be >98% stereospecific, but we were only able to estimate a level of stereospecificity of >80% for the minor rearrangement, *trans*-**3** → *cis*-**4**, because of the small populations involved. By the same token, we could only measure reaction rates for the major pathway, not the minor one.

To address these issues further, we required a related system in which the ratio of trans- and cis-fused enammonium salts would be closer to 50:50. Consequently, we explored the corresponding benzo[*a*]quinolizidine system, represented by amino alcohols **5a** and **5b** (Scheme II). The derived enammonium salts, *cis*-**6** and *trans*-**6**, now have a junction of two six-membered rings at the nitrogen bridgehead, reducing the thermodynamic preference for the cis-fused form.[2] As a valuable side benefit, we expected this endeavor to test our explanation for the origin

Scheme I



(1) (a) Maryanoff, B. E.; McComsey, D. F.; Mutter, M. S.; Sorgi, K. L.; Maryanoff, C. A. *Tetrahedron Lett.* **1988**, *29*, 5073. (b) Sorgi, K. L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1990**, *112*, 3567. (Please note that the stereochemical descriptors used in these papers are consistent with the descriptors used herein: "cis-fused" and "trans-fused" for the ring fusion in **3** and **6**, and "cis" and "trans" for the relative stereochemistry between the phenyl substituent and the angular proton in **2**, **4**, **7**, and **8**.)

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