Total Syntheses of Pumiliotoxin A and Allopumiliotoxin Alkaloids. Interplay of Pharmacologically Active Natural Products and New Synthetic Methods and Strategies

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Contents

I. Introduction

A. Natural Products and Developments in Organic Synthesis

Natural products have played a vital role in the development of organic chemical synthesis. Early in this century, total syntheses of targets such as camphor, tropinone, and hemin established that organic chemistry could be utilized to prepare complex molecules found in nature.[1] With growing understanding of organic reaction mechanisms, conformational analysis and stereochemical principles,[2] increasingly complex natural products yielded to organic synthesis. Landmark total syntheses of cortisone,[3] strychnine,[4] and reserpine[5] by Woodward and associates punctuate the remarkable achievements of multistep chemical synthesis in the 1950s. To this point in time, natural products had served predominantly as foci for establishing that a sequence of properly orchestrated reactions could duplicate the structure of complex target molecules.[6] Emerging in the 1950s was a second role for natural products, that of stimulating the development of new organic synthesis methodology. An early example would be the penicillins, which provided the impetus for Sheehan's development of several new β-lactam syntheses.[7] This work, highlighted by the introduction of carbodiimide-mediated coupling of carboxylic acids and amines, culminated in Sheehan's pioneering synthesis of penicillin V.[8] Two more recent illustrations of the synergy between natural products and new synthetic methodology are found in the development of methods for vicinal functionalization of enones inspired by the prostaglandins[9] and the development of powerful methods for preparing stereochemically complex acyclic polypropionate units provoked initially by the polyether antibiotics.[10]

Natural products isolated from sources that are not readily cultivated or cultured, for example from marine, mammalian, or amphibian sources, are now playing a third role, that of stimulating the development of *practical* organic chemical syntheses. Although the complexity of natural products that can be conquered by total synthesis appears nearly unlimited,[11] few complex organic molecules at present can be obtained through efficient sequences that allow the properties of the target structure to be explored fully. The development of new methodology and synthesis strategies that allow complex target structures to be prepared on meaningful scales, in enantiopure form, is now a central goal of organic synthesis.

B. The Pumiliotoxin A and Allopumiliotoxin Alkaloids

A wide range of biologically active compounds are found in skin secretions of amphibians.[14] Many of these metabolites serve a chemical defense role, being released onto the skin surface from cutaneous granular (poison) glands. A remarkable variety of alkaloids have been isolated in minute quantities from skin extracts of frogs of the family Dendrobatidae.[15] The pumiliotoxin A and allopumiliotoxin classes of den-

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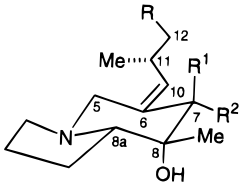
Larry E. Overman was born in Chicago, IL, in 1943. He obtained a B.A. degree from Earlham College in 1965 and completed his doctoral study in 1969 with Professor Howard W. Whitlock, Jr., at the University of Wisconsin. After an NIH postdoctoral fellowship with Professor Ronald Breslow at Columbia University, he joined the faculty at the University of California, Irvine, in 1971, where he is now Distinguished Professor of Chemistry. Dr. Overman is the recipient of the American Chemical Society Award for Creative Work in Synthetic Organic Chemistry and Arthur C. Cope Scholar Award, a Senior Scientist Award of the Alexander von Humboldt Foundation, a Camille and Henry Dreyfus Teacher–Scholar Award, and has been a Fellow of the Guggenheim and Alfred P. Sloan Foundations. Dr. Overman serves on the Board of Directors and Editorial Board of *Organic Reactions*, editorial advisory boards of *Synlett*, *Annual Reports in Heterocyclic Chemistry*, and *Contemporary Organic Synthesis*, and the Tetrahedron Board of Consulting Editors. Dr. Overman's research interests involve the invention of new reactions and strategies in organic synthesis and the total synthesis of complex target molecules.

drobatid alkaloids are a group of approximately 40 heterocycles having general structure **1**. These natu-



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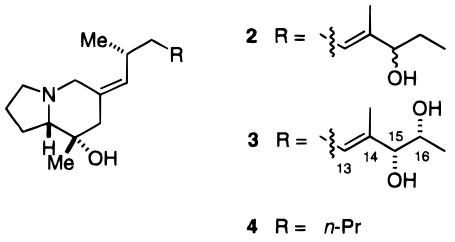
ral products were originally believed to be unique to dendrobatid frogs, but recently have been found to have a wide distribution in amphibians.[16]

Pumiliotoxins A (**2**) and B (**3**) were first isolated from the Panamanian poison frog *Dendrobates pumilio* in 1967.[17] Originally believed to be steroidal alkaloids, the structure of these toxins remained obscure until 1980, when a simpler alkaloid, pumiliotoxin 251D (**4**), was found as a major component of



the basic skin extracts of the Ecuadorian poison frog *Dendrobates tricolor*. X-ray analysis of the crystalline hydrochloride of pumiliotoxin 251D established the structure and absolute configuration of this alkaloid.[18] From this information and NMR and mass spectral data, Daly proposed that the pumiliotoxin A family of dendrobatid alkaloids has the (*Z*)-6-alkylideneindolizidine ring system as its defining structural element. The pumiliotoxin A alkaloids thus differ only in the alkylidene appendage. Total syntheses accomplished in our laboratories, which will be discussed later in this review, were critical in codifying the stereochemistry of pumiliotoxin A alkaloids other than pumiliotoxin 251D. In the case of the most widely pharmacologically investigated toxin, pumiliotoxin B (**3**), the stereochemistry of the allylic diol moiety of the side chain (*E* alkene and 15*R*,16*R*-diol) was deduced first in model systems[19,20] and then rigorously established by total synthesis.[21]

The allopumiliotoxins are hydroxyl congeners of the pumiliotoxin A class and possess a vicinal diol group in the indolizidine ring (**1**, R^1 or R^2 = OH).[14] They are the most complex members of the pumiliotoxin A/allopumiliotoxin alkaloid groups. Because of the minute amount of allopumiliotoxins in dendrobatid frogs, total syntheses have been critical in establishing the relative as well as the absolute configuration in this series (*vide infra*).

Pumiliotoxins A (**2**) and B (**3**) are relatively toxic, with a subcutaneous dose of pumiliotoxin B as low as 20 μg causing death in mice.[17] Early reports that pumiliotoxin B displays both cardiotonic and myotonic activity stimulated interest in this family of dendrobatid alkaloids.[22] Recent pharmacological studies indicate that pumiliotoxin B and certain congeners enhance sodium influx by binding to a unique modulatory site on the voltage-dependent sodium channel.[23] This interaction has been shown to stimulate phosphoinositide breakdown with the effect on this secondary messenger system presumed to be ultimately expressed as cardiotonic and myotonic activities. Structure−activity studies of natural alkaloids and synthetic analogs have shown that the exact nature of the side chain is critical for activity.[23,24] For example, whereas pumiliotoxin B is one of the most potent alkaloids, 15,16-epipumiliotoxin B exhibits much lower cardiotonic and myotonic activity.[24b]

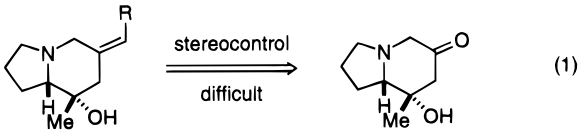
C. Scope of the Review[25]

The important biological activity of the pumiliotoxin A and allopumiliotoxin alkaloids and the inability of natural sources to provide sufficient material for detailed pharmacological evaluation stimulated the evolution of a significant amount of new synthetic chemistry from our laboratories. This review aims to summarize these developments as well as syntheses of pumiliotoxin A and allopumiliotoxin alkaloids accomplished by other workers. The review is organized along chemical lines, rather than by alkaloid structure. This organization will hopefully allow the reader to see potential applications of this new chemistry beyond the pumiliotoxin A/allopumiliotoxin alkaloid arena.

II. Total Syntheses of Pumiliotoxin A Alkaloids Using Iminium Ion–Vinylsilane Cyclizations

A. Retrosynthetic Analysis and Strategy

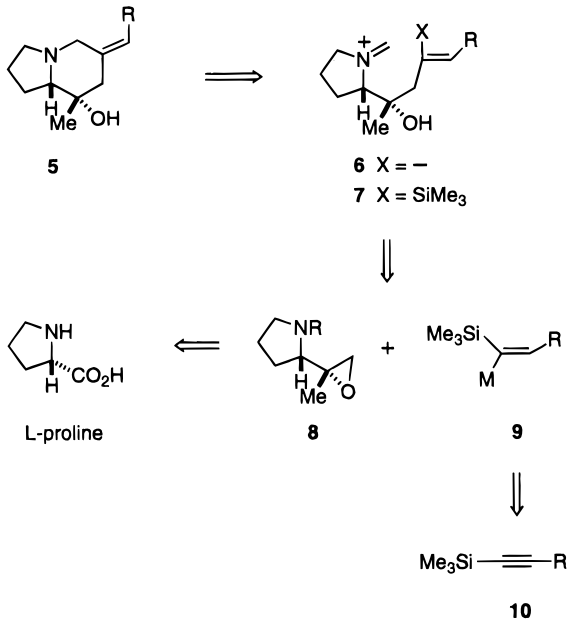
When contemplating the design of a total synthesis strategy for the pumiliotoxin A alkaloids, attention is drawn immediately to the (*Z*)-alkylidene side chain. This unit presents particular problems, since stereocontrolled synthesis of exocyclic alkenes is particularly challenging.[26,27] For example, the prospects for selectively generating the (*Z*)-side chain by Wittig-type functionalization of a progenitor indolizidine ketone are dim (eq 1).[27] Methods that deal with



this stereochemical issue are at the core of the new synthetic methodology developed to prepare the pumiliotoxin A and allopumiliotoxin alkaloids.

Cleavage of a bond β to nitrogen is a fundamental disconnection in alkaloid retrosynthetic analysis, and this retro-Mannich disconnection of alkylideneindolizidine **5** generates the zwitterionic synthon **6** (Scheme 1). Underlying our initial efforts in this area was the perception that the (*Z*)-vinylsilane **7** would be a viable equivalent of this hypothetical intermediate since bimolecular substitution reactions of vinylsilanes with electrophiles had been recently shown to proceed with retention of alkene stereochemistry.[28,29] Our choice of a vinylsilane as a Mannich component was at the time quite daring, since no examples of intramolecular reactions of vinylsilanes with electrophiles were extant. Moreover the reaction of iminium ions with vinylsilanes was also unknown. This latter situation was not surprising, considering the weakly nucleophilic character of vinylsilanes[29,30] and the moderate reactivity of simple iminium electrophiles.[31] Our hope was that the kinetic acceleration provided by intramolecularity would be sufficient to engage these weakly reactive partners. We envisaged assembling the cyclization precursor **7** from the proline-derived epoxide **8** and the vinyl nucleophile **9**. Such a strategy would be particularly attractive if the silyl substituent could

Scheme 1



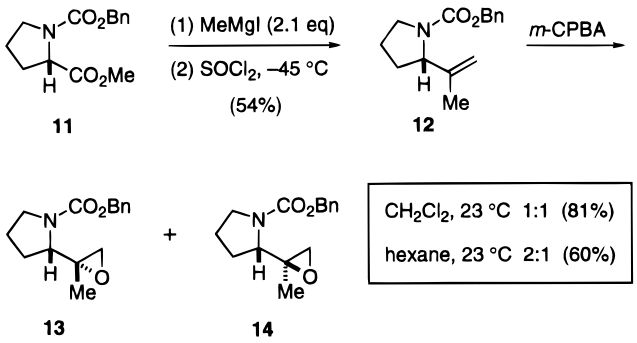
also be exploited to prepare **9**, for example by hydrometalation of silylalkyne **10** (e.g., M = Al, B, Zr).

The strategy adumbrated in Scheme 1 projects assembly of the target alkaloids from a pyrrolidine epoxide and a variety of alkynylsilane precursors. Such convergency is appealing since the pumiliotoxin A alkaloids differ only in the nature of the alkylidene side chain. The iminium ion–vinylsilane approach to the pumiliotoxin A alkaloids was verified in 1981 in the first total synthesis of (+)-pumiliotoxin 251D[32] and was subsequently employed to achieve the first total syntheses of (+)-pumiliotoxin B[21] and (+)-pumiliotoxin A.[33]

B. Total Synthesis of (+)-Pumiliotoxin 251D

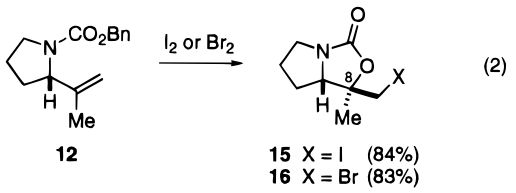
We focused at the outset on the preparation of pyrrolidine epoxide **13** (Scheme 2), with a nonstereoselective route being developed initially. *N*-(Benzyloxycarbonyl)-L-proline methyl ester **11** was first converted to propenyl derivative **12** by reaction with excess MeMgI followed by regioselective dehydration of the resulting tertiary alcohol with thionyl chloride at low temperature.[32] Epoxidation of **12** with *m*-chloroperoxybenzoic acid provided a mixture of epoxides **13** and **14**, which could be separated by careful chromatography. Formation of the desired diastereomer **13** was favored slightly in hexane; however, due to the low solubility of the peracid in this solvent,

Scheme 2



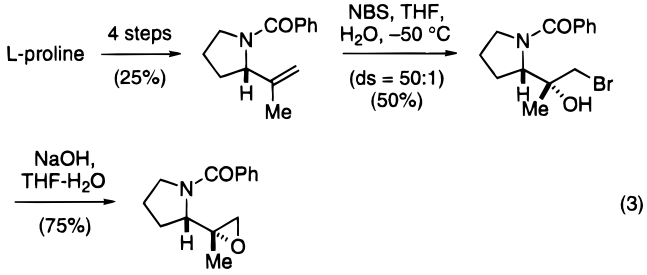
the nonstereoselective epoxidation in CH_2Cl_2 was more readily scaled. In spite of the lack of stereocontrol, this sequence provided epoxide **13** on a 10-g scale in 38% overall yield from **12**.[32]

In an attempt to develop a stereocontrolled synthesis of a pyrrolidine epoxide fragment, the reaction of **12** with I_2 or Br_2 was examined. In this case electrophilic addition proceeded with high stereoselection to yield crystalline halocarbamates **15** or **16** (eq 2).[34] Although **15** and **16** have the desired



(2)

stereochemistry at C(8), they were not competent alkylating agents and did not react with nucleophiles such as alkenyl cuprates. The lack of reactivity of **15** and **16** is not surprising, since these electrophiles are neopentyl and possess a β-oxygen substituent. Using a related halocyclization approach, a stereoselective synthesis of epoxide amides related to **13** was developed. However, this synthesis (eq 3) was longer and offered no advantage over the shorter nonstereoselective preparation of **13**.[34]

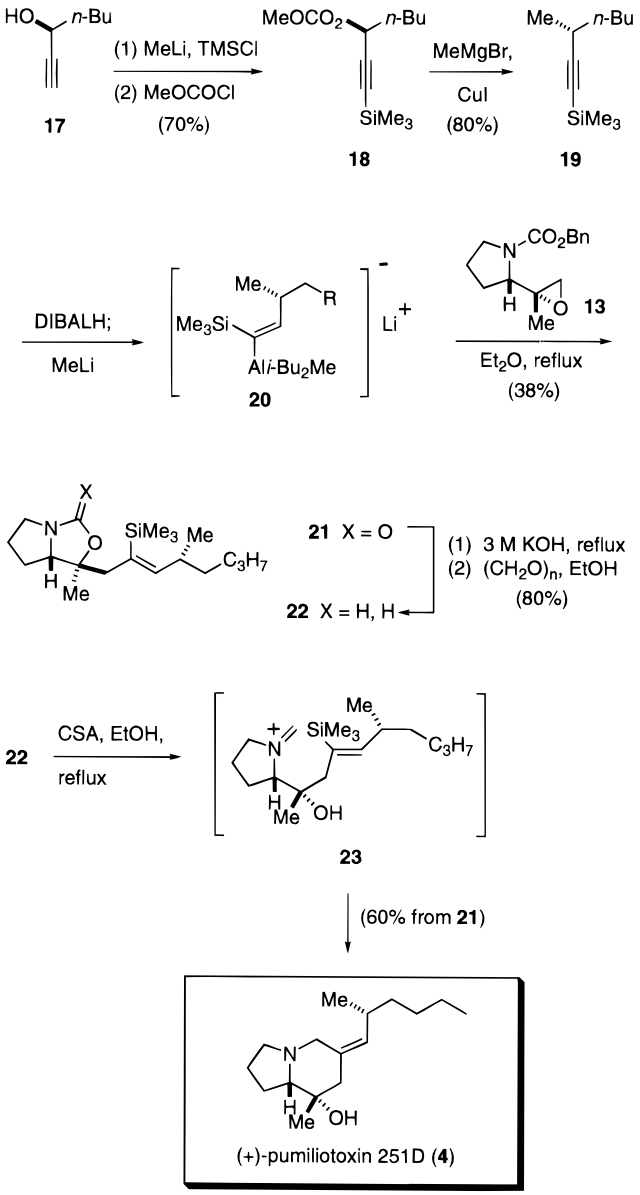


(3)

The preparation of the side chain for (+)-pumiliotoxin 251D (**4**) began with (*S*)-1-heptyn-3-ol (**17**), which was available either from enantioselective reduction[35] of 1-heptyn-3-one or by chromatographic resolution of a carbamate derivative (Scheme 3).[36] The key step in the formation of (*R*)-silylalkyne **19** was stereospecific propargylic displacement of carbonate **18** with the mixed cuprate formed from MeMgBr and CuI.[37]

Vinylalanate **20**, which was generated from **19** following a procedure introduced by Eisch,[38] reacted sluggishly (over 48 h in refluxing ether) with epoxide **13** to provide bicyclic carbamate **21** in 38% yield.[32] Hydrolysis of **21** to the corresponding amino alcohol required refluxing 3 M ethanolic KOH, conditions that notably did not degrade the vinylsilane functionality. Direct reaction of the amino alcohol with paraformaldehyde in refluxing ethanol provided cyclopentaoxazolidine **22**. Subsequent heating of **22** in ethanol in the presence of 1 equiv of camphorsulfonic acid (CSA) generated **23** and smoothly yielded (+)-pumiliotoxin 251D (**4**). Chromatographic purification of **4** followed by crystallization of the hydrochloride salt afforded (+)-pumiliotoxin 251D hydrochloride (**4**·HCl) in 60% overall yield from carbamate **21**. Perfect control of the double bond stereochemistry

Scheme 3



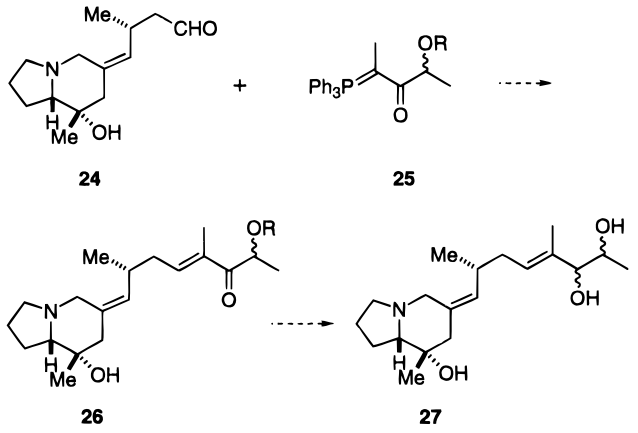
was exerted by the silyl substituent, since no trace of an isomer of **4** was detected by NMR or GC−MS analysis of the crude cyclization product.

This first total synthesis of a pumiliotoxin A alkaloid was accomplished in 13% overall yield from (*S*)-1-heptyn-3-ol (**17**) and 4.7% yield from *N*-(benzyloxycarbonyl)-L-proline. The least satisfactory reaction in the sequence was the coupling of the vinylsilane and epoxide components. Some improvement in this key step was realized in our subsequent synthesis of pumiliotoxin B.

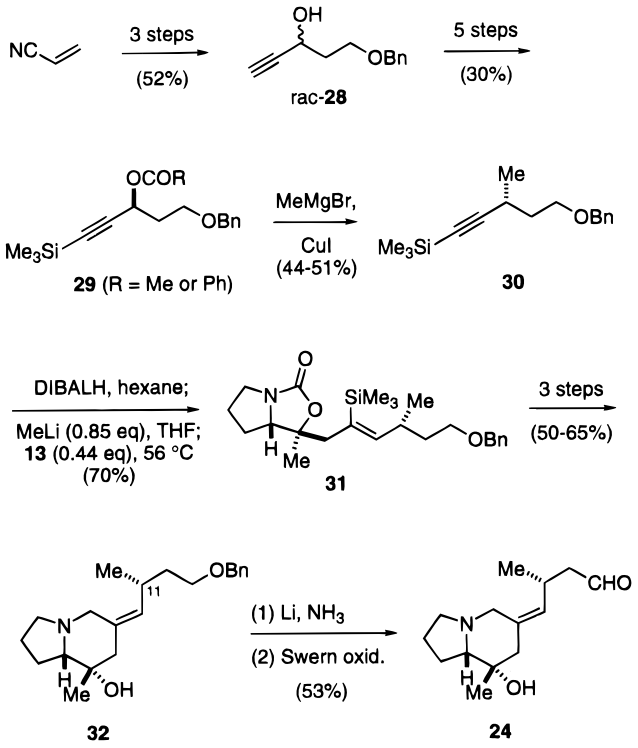
C. Total Synthesis of (+)-Pumiliotoxin B

Since the stereochemistry of the allylic diol side chain of pumiliotoxin B (**3**) had not been defined at the time our synthetic efforts directed toward this more complex target began, we adopted a strategy for side chain elaboration that could provide any one of the four possible diol stereoisomers. Iminium ion−vinylsilane cyclization would be employed to prepare alkylideneindolizidine aldehyde **24** (Scheme 4). Condensation of this intermediate with stabilized ylide

Scheme 4



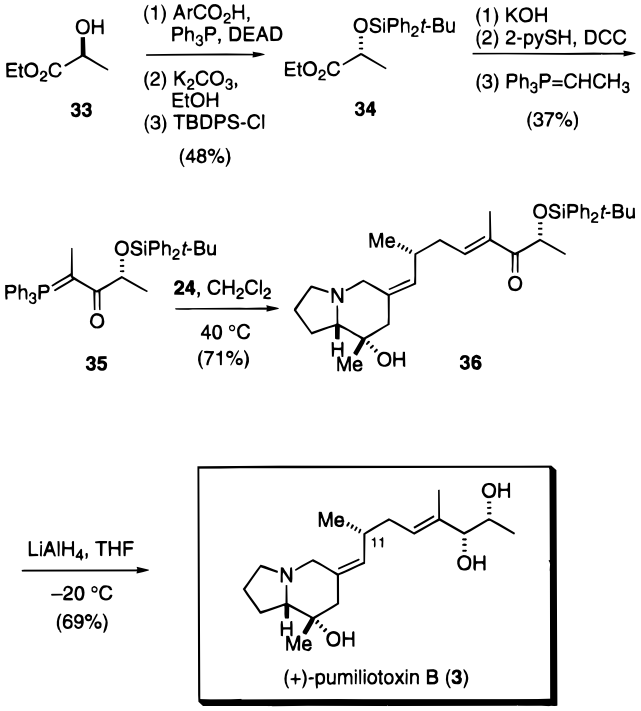
Scheme 5



25 would then provide enone **26** having the requisite *E* configuration of the $\Delta^{13,14}$ double bond. Both enantiomers of the ylide would be available from lactic acid and our hope was that we could reduce the α′-alkoxy enone functionality of **26** selectively to develop either the syn or anti allylic diol functionality in **27**. In our initial experiments in this area, we showed that simple α′-alkoxy enones related to **26** could indeed be reduced with excellent stereocontrol (≥17:1) to give either the syn or anti allylic diol by utilizing the proper combination of reducing agent and alcohol protecting group.[20]

On the supposition that pumiliotoxin B would have the same absolute configuration of the indolizidine portion as pumiliotoxin 251D, we assembled indolizidine aldehyde **24** as summarized in Scheme 5.[21] The strategy for preparing (*R*)-alkynylsilane **30** was similar to that employed in our earlier synthesis of pumiliotoxin 251D. However, in this case, the alkynone that was available from oxidation of *rac*-**28** could not be reduced with high enantioselection using the Midland reagent.[35] A lengthier sequence

Scheme 6

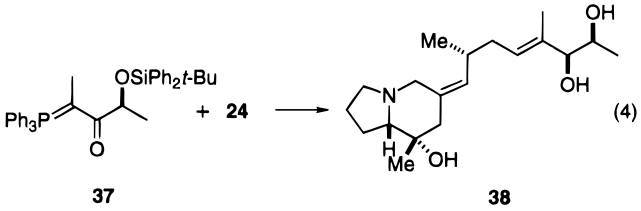


was therefore employed in which both components of the racemate were converged to a single enantiomer. The carbamates formed from *rac*-**28**, phosgene, and (*R*)-α-methylbenzylamine were first separated chromatographically and the resulting diastereomers cleaved to the enantiomeric pair of propargylic alcohols.[36] Acetylation of the (*S*)-alcohol and Mitsunobu inversion of the (*R*)-alcohol with benzoic acid gave (*S*)-propargylic esters **29** (R = Me or Ph) which were each converted to the requisite (*R*)-silylalkyne **30**.[21]

Coupling of the vinylalanate derived from **30** with epoxide **13** was studied in some detail and allowed this key step to be optimized to 70% yield. However, this demanding conversion was still not ideal since an excess of the alanate was required. Hydrolysis of carbamate **31** and iminium ion−vinylsilane cyclization of the resulting amino alcohol proceeded uneventfully to provide (*Z*)-alkylideneindolizidine **32** in 50% to 65% yield. As in the reaction to produce pumiliotoxin 251D, no trace of the corresponding (*E*)-alkylidene isomer was detected. Debenzylation of **32** and oxidation of the resulting alcohol then provided indolizidine aldehyde **24**. A small amount of the C(11) epimer, resulting from the 92% enantiomeric purity of silylalkyne **30**, was conveniently removed at the primary alcohol stage.

When it was established[19,20] that pumiliotoxin B (**3**) had the 15*R*,16*R* syn diol configuration, the (*R*)-ylide **35** was required to complete the synthesis of **3** (Scheme 6). Phosphorane **35** was readily prepared in enantiomerically pure form from ethyl L-lactate (**33**) as summarized in Scheme 6. Mitsunobu inversion of **33** followed by deacylation and protection of the resulting secondary alcohol as a *tert*-butyldiphenylsilyl ether provided **34**. Conversion of **34** to ylide **35** was then accomplished in 37% overall yield by way of the 2-pyridinethiol ester intermediate.[39]

Condensation of phosphorane **35** with indolizidine aldehyde **24** provided (*E*)-enone **36**. Reduction of **36** with $LiAlH_4$ in THF at −20 °C occurred with high Felkin−Anh stereoselection[20] and was accompanied by desilylation to provide pumiliotoxin B (**3**) directly in 69% yield. Synthetic **3** was indistinguishable from an authentic specimen of the amphibian alkaloid by spectroscopic, optical, chromatographic, and pharmacological criteria. Although these comparisons left little doubt about the identity of the synthetic and natural toxins, it was deemed prudent to verify that a diastereomer of **3** differing in absolute configuration at the two stereogenic carbons of the indolizidine ring and the C(11) allylic methyl group could indeed be distinguished. Although such a sample was not easily accessible, its enantiomer **38** could be prepared from indolizidine aldehyde **24** and (*S*)-ylide **37** (eq 4). Indolizidinetriol **38** displayed physical and spec-



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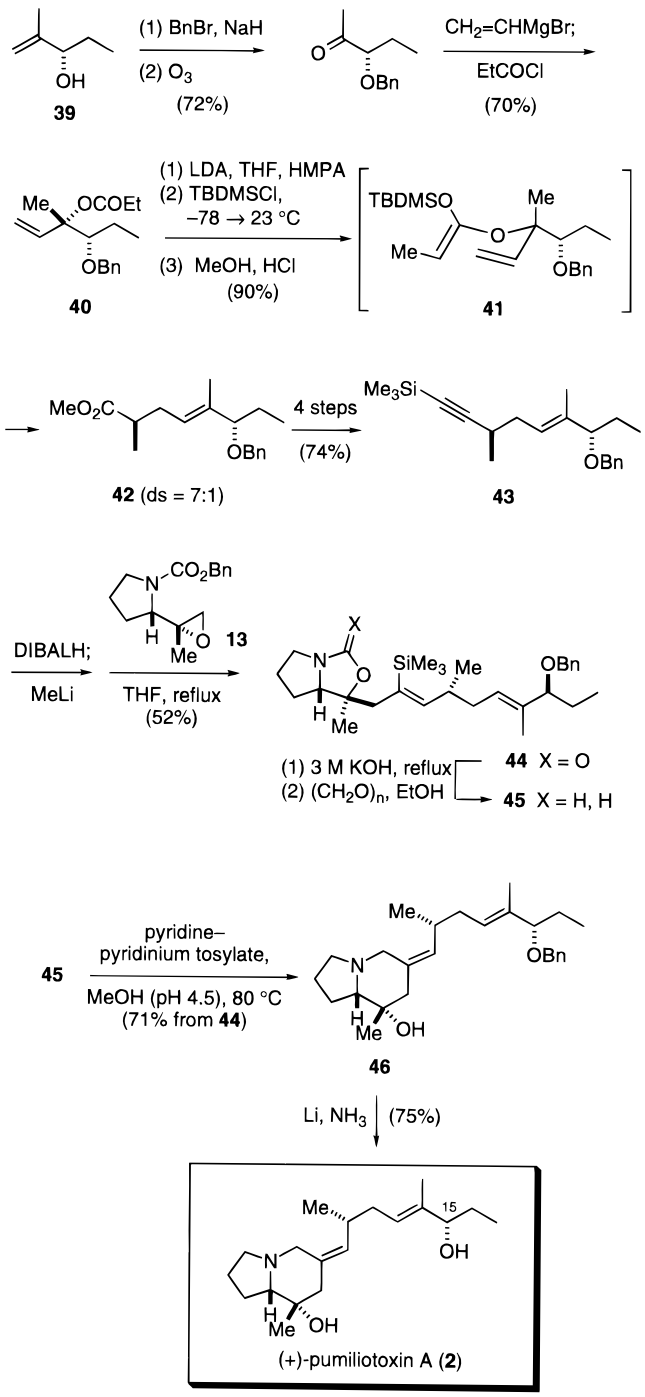
troscopic properties nearly identical to those of pumiliotoxin B (**3**); however, it could be distinguished from **3** by careful high-field ^1H NMR comparisons.

This initial synthesis of (+)-pumiliotoxin B (**3**), which confirmed the full stereostructure of the alkaloid, proceeded in 10 steps and 4.2% yield from *N*-(benzyloxycarbonyl)-L-proline and in 17 steps and 1.6% yield from acrylonitrile. The synthesis was efficient enough to prepare 150 mg of **3** for pharmacological investigations. A number of analogs of pumiliotoxin B were synthesized in similar fashion and pharmacological investigations of these congeners contributed to initial definition of structure−activity relationships in this series.[24a,b] One of these analogs having the anti (15*R*,16*S*) configuration of the allylic diol was later found in the skin of an Australian myobatrachid frog.[40]

D. Total Synthesis of (+)-Pumiliotoxin A

Pumiliotoxin A is typically isolated from dendrobatid frogs as a mixture of C(15) epimers.[14] On the expectation that the major epimer would have the same configuration at C(15) as pumiliotoxin B, silylalkyne **43** was prepared from (*S*)-2-methyl-1-penten-3-ol (**39**)[41] by the eight-step route summarized in Scheme 7.[33] The most interesting step in this efficient sequence is Ireland−Claisen rearrangement[42] of the (*Z*)-silylketene acetal derivative of tertiary propionate ester **40**, which provided **42** and its C(11) epimer in a ratio of 7:1 after esterification. Stereoselection in the formation of **42** is in accord with preferential rearrangement through chair topography **41** and is notably high for Ireland−Claisen rearrangement of a tertiary allylic ester. Standard transformations converted octenoate **42** to silylalkyne **43**. Chromatographic separation of the minor C(11) epimer could not be realized with any acyclic intermediate and had to await construction of the alkylideneindolizidine ring system.

Scheme 7



Coupling of 2 equiv of the alanate derivative of **43** with epoxide **13** in refluxing THF provided cyclopentaoxazolidinone **44** in 52% yield. Hydrolysis of **44** and treatment of the resulting amino alcohol with paraformaldehyde provided **45**. Desired cyclization of this intermediate required careful pH control to minimize solvolysis of the allylic benzyl ether. Iminium ion−vinylsilane cyclization was best realized in methanol buffered with pyridine−pyridinium tosylate and provided alkylideneindolizidine **46** in 71% overall yield from **44**. Debenzylation of **46** and separation of ~15% of the unnatural 11*S* epimer provided 15*S*-**2**, which was identical in all respects with the major C(15) epimer of natural (+)-pumiliotoxin A.[33]

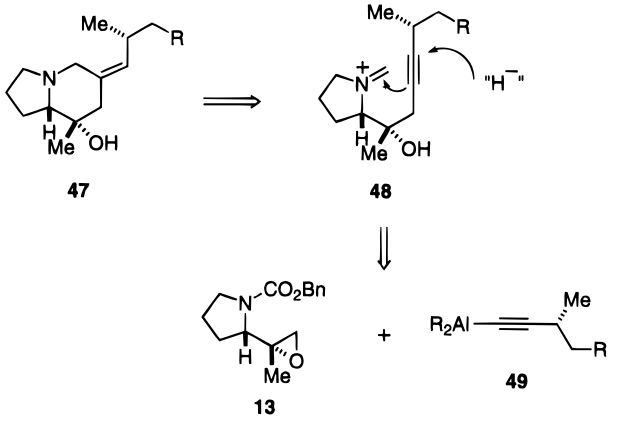
The synthesis of (+)-15(*S*)-pumiliotoxin A summarized in Scheme 7 was accomplished in 13 steps and 8.2% overall yield from (*S*)-2-methyl-1-penten-3-ol and 9 steps and 5.7% overall yield from *N*-(benzyloxycarbonyl)-L-proline. This synthesis is the most efficient achieved using the iminium ion−vinylsilane cyclization strategy and provides an excellent illustration of the compatibility of this cyclization reaction with complex functionality such as the allylic ether group of the side chain.

III. Total Syntheses of Pumiliotoxin A and Allopumiliotoxin Alkaloids Using Iodide-Promoted Iminium Ion–Alkyne Cyclizations

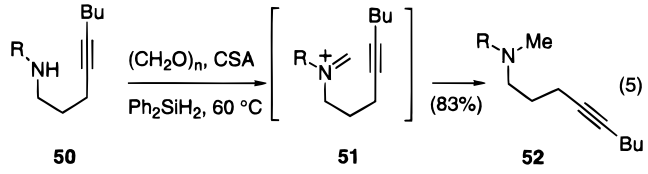
A. Retrosynthetic Analysis and Strategy

A major drawback to the iminium ion−vinylsilane cyclization route to the pumiliotoxin A alkaloids is the coupling of the vinylsilane side chain and pyrrolidine epoxide fragments. This step requires special optimization for each side chain nucleophile and often is low yielding. An alternative, conceptually simpler approach to the pumiliotoxin A alkaloids is outlined in Scheme 8. In this plan the *Z* stereochemistry of the alkylidene side chain evolves from the stereoelectronic preference for electrophile−nucleophile pairs to add to alkynes in an antarafacial fashion.[43] A "reductive" iminium ion−alkyne cyclization is specifically represented in the conversion **48** → **47**, although from the outset we anticipated that surrogates for a hydride nucleophile would be required. One anticipated advantage of this new approach was the expected facility of coupling epoxide **13** with a side chain alkyne nucleophile. On the basis of earlier studies of Fried and co-workers, alkynylalane **49** was the obvious choice for this nucleophile.[44]

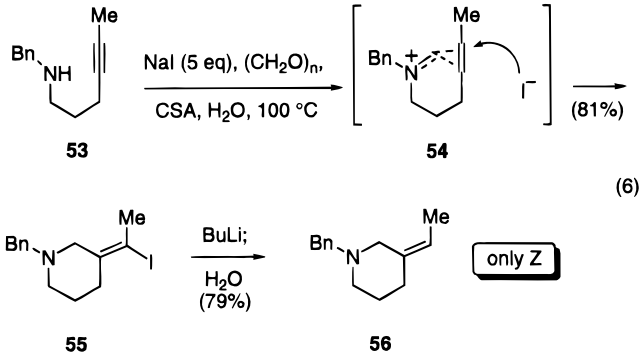
Scheme 8



Initially we briefly examined Mannich cyclizations of 4-alkynylamines in the presence of reducing agents such as silicon hydrides (e.g., **50** → **52**, R = *p*-methoxybenzyl, eq 5). Not surprisingly, the major product formed from these attempted cyclizations was the *N*-methylamine resulting from simple reduction of formaldiminium ion intermediate **51**.[45]



Although alkynes are not sufficiently nucleophilic to react with simple iminium ion electrophiles,[31,46] we discovered in 1988 that Mannich cyclizations of alkynes are possible in the presence of reactive external nucleophiles.[47] Iodide is particularly effective and cyclizations with this promoter can be carried out under a wide variety of conditions.[48] An example of a cyclization under aqueous conditions is the conversion of **53** → **55**, which takes place in 70%−90% yield to afford solely the (*E*)-1-iodoethylidene stereoisomer (eq 6).[48a] Since the vinyl iodide functionality can be reduced with retention of double bond geometry, net reductive cyclization can be realized in two steps.

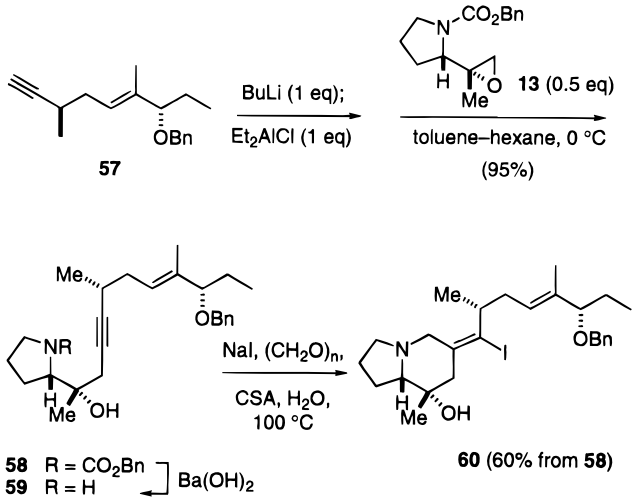


The synthetic strategy outlined in Scheme 8 has proven to be particularly powerful for the preparation of both pumiliotoxin A[39,49] and allopumiliotoxin alkaloids[50] as well as many structural analogs.[51]

B. Efficient Total Syntheses of Pumiliotoxins A and B

The alkyne−iminium ion cyclization strategy was first utilized to prepare 15(*S*)-pumiliotoxin A (**2**) (Scheme 9).[49] Successive treatment of alkyne **57**, which was available from our earlier studies (Scheme 7),[33] with *n*-BuLi, Et_2AlCl, and epoxide **13** provided coupling product **58** in 95% yield. To minimize competitive opening of epoxide **13** with LiCl, 2 equiv of the alkynylalane nucleophile were employed. In contrast to our earlier vinylsilane route, however, unreacted alkyne **57** could be efficiently recovered during chromatographic purification of **58**, allowing the key coupling step to be accomplished in near quantitative yield with net use of stoichiometric quantities of **57** and **13**. The benzyloxycarbonyl group of **58** was next cleaved with $Ba(OH)_2$ in refluxing H_2O−glyme to provide amino alcohol **59**. The yield for this step was only ~80%, since dehydration to form the enyne was a surprisingly competitive process. Iodide-promoted cyclization of the formaldiminium ion formed from **59** provided isomerically pure alkylideneindolizidine **60** in 60% overall yield from **58**. The efficiency of the cyclization step was very high, since 15% of 11-epi-**60** (resulting from the minor diastereomer of **57**)[33] was also isolated during chromatographic purification of **60**. Deiodination of **60** followed by cleavage of the benzyl

Scheme 9



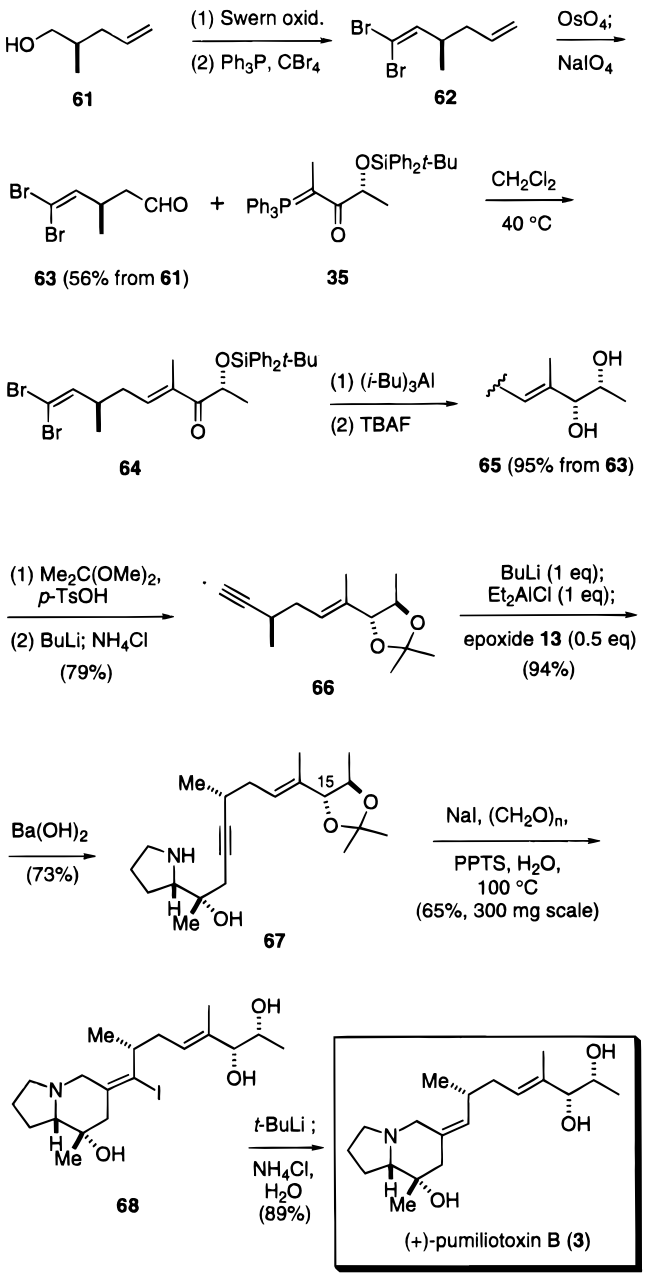
protecting group provided (+)-(15*S*)-pumiliotoxin A (**2**) in 75% yield.

This synthesis of (+)-15(*S*)-pumiliotoxin A was realized in five steps and 43% overall yield from the alkyne and epoxide components **57** and **13**; the synthesis proceeded in 13 steps and 14.4% overall yield from (*S*)-2-methyl-1-penten-3-ol (**39**) and eight steps and 8.8% overall yield from *N*-(benzyloxycarbonyl)-L-proline.

Pumiliotoxin B has recently been prepared for the first time in a practical fashion by a related convergent strategy.[39] An optimized synthesis of alkyne **66**, which embodies the full side chain of pumiliotoxin B, is summarized in Scheme 10.[39,50] This preparation begins with (*R*)-2-methyl-4-pentenol (**61**), which is readily available by Evans asymmetric alkylation.[52] Oxidation of **61** to the corresponding aldehyde and dibromomethylenation provided diene **62**. Reflecting electron withdrawal by the bromine substituents, this diene underwent regioselective osmylation of the terminal vinyl group. Cleavage of the resulting diol provided dibromopentenal **63** in 56% overall yield from **61**. Condensation of **63** with phosphorane **35**, followed by reduction of the resulting α′-siloxyenone **64** with triisobutylaluminum[20] and final removal of the *tert*-butyldiphenylsilyl protecting group, provided the syn diol **65** in nearly quantitative yield from aldehyde **63**. Generation of the acetonide and standard conversion of the dibromoalkene to the terminal alkyne then provided **66**. This eight-step synthesis proceeded in an excellent overall yield of 42% from pentenol **61**.

As in our earlier synthesis of pumiliotoxin A, the alkyne side chain was coupled with pyrrolidine epoxide **13** in high yield. Hydrolytic cleavage of the

Scheme 10



carbamate group from the resulting adduct with Ba(OH)$_2$ provided alkynylamine **67** in 68% overall yield. Iodide-promoted cyclization of the formaldiminium ion generated from this intermediate was examined in some detail. Optimum results were obtained with 1.5 equiv of the weak proton acid pyridinium *p*-toluenesulfonate (PPTS), which promoted cyclization and isopropylidene cleavage while minimizing competitive solvolysis of the allylic C(15)−O bond. Under these conditions, **67** was stereoselectively transformed to the iodoalkylideneindolizidine **68** in 65% yield on a 300-mg scale. Deiodination of **68** by treatment with a large excess of *t*-BuLi at −78 °C followed by protonolysis provided (+)-pumiliotoxin B (**3**) in 89% yield.

The synthesis summarized in Scheme 10 allowed 500 mg of (+)-pumiliotoxin B (**3**) to be prepared in a short time for biological and structural investigations.[39] The overall yield of enantiopure **3** was 8% from *N*-(benzyloxycarbonyl)-L-proline and 10% from

(4*S*,5*R*)-4-methyl-5-phenyl-2-oxazolidinone, the commercially available precursor[52] of (*R*)-2-methyl-4-pentenol.

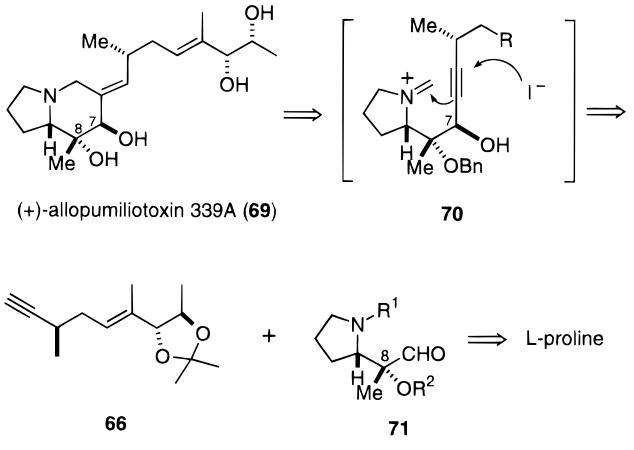
C. Total Synthesis of Allopumiliotoxin 339A

The allopumiliotoxins, which contain oxidation at both C(7) and C(8) of the indolizidine ring, are the most complex members of the dendrobatid indolizidine alkaloids. They are extremely scarce in nature and chemical synthesis has been required to fully define the structures of these rare alkaloids. Allopumiliotoxins containing a β-oriented C(7) hydroxyl group display greater biological activity than their α-epimers, with allopumiliotoxin 339A (**69**) being the only alkaloid of this group to be more effective than pumiliotoxin B in stimulating sodium influx and phosphoinositide breakdown in guinea pig cerebral cortical synaptoneurosomes.[24c] The first allopumiliotoxin total syntheses were accomplished in our laboratories using an aldol reaction to couple the indolizidine and side chain fragments.[53] These syntheses, as well as total syntheses of allopumiliotoxin alkaloids accomplished in the Trost[54] and Kibayashi[55] laboratories, will be discussed later in this review.

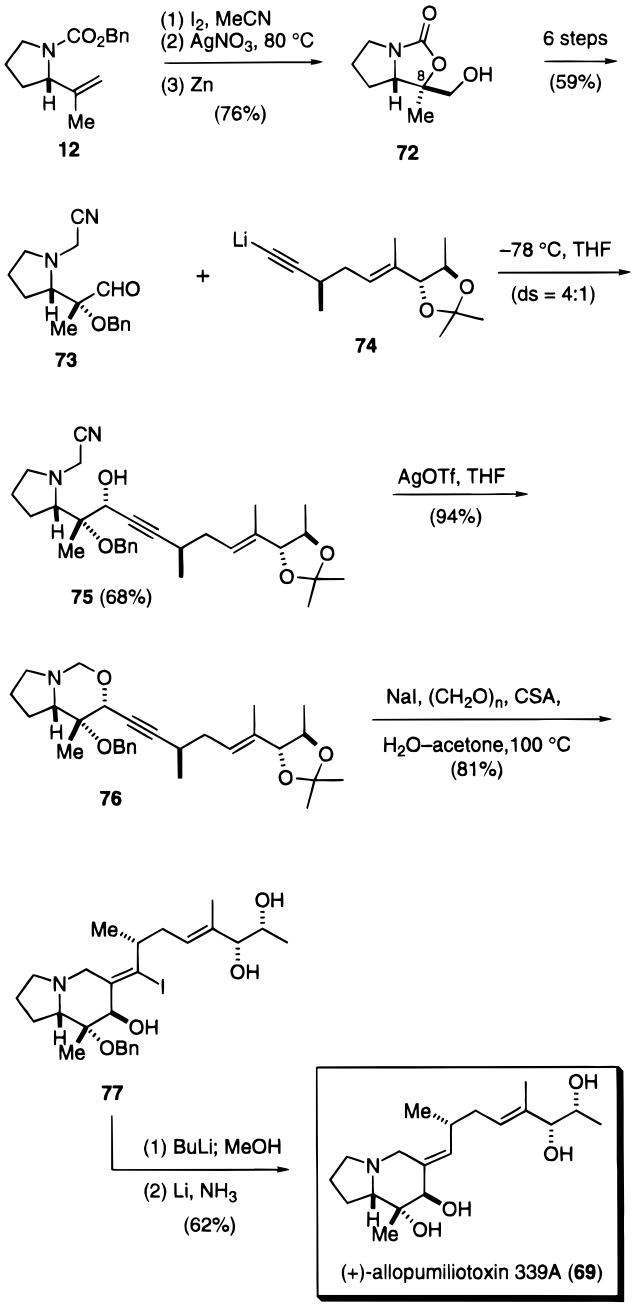
A practical synthetic entry to the allopumiliotoxin alkaloids was recently demonstrated in our synthesis of (+)-allopumiliotoxin 339A (**69**).[50,56] The strategy employed in this endeavor is enunciated in Scheme 11. The central issue examined in the synthesis was the viability of the pivotal iodide-promoted iminium ion−alkyne cyclization with a substrate (**70**) that contained a potentially labile and inductively deactivating C(7) propargylic hydroxyl group. The cyclization precursor **70** comes from the combination of proline-derived aldehyde **71** with side chain alkyne **66**. To obtain the desired *R* stereochemistry at C(7), the protecting groups of **71** were chosen to favor chelate-organization by the C(8) alkoxy substituent in the condensation of aldehyde **71** with an acetylenic salt of **66**.

After examining several possibilities for the pyrrolidine aldehyde fragment, **73** emerged as a viable formulation (Scheme 12). The electron-withdrawing cyanomethyl protecting group in this intermediate was chosen to disfavor competitive chelation with the pyrrolidine nitrogen during the carbonyl addition step. Pyrrolidine aldehyde **73** was obtained from the propenyl proline derivative **12** through an efficient

Scheme 11



Scheme 12



nine-step sequence.[56] Iodocyclization of **12** yielded a single bicyclic carbamate product (**15** of eq 2), which was converted to alcohol **72** by way of the nitrate ester. Appropriate adjustments of protecting groups and the oxidation level of C(7) provided **73** in 45% overall yield from **12**.

Addition of alkynyllithium **74**, prepared from deprotonation of **66** with *n*-BuLi, to the α-benzyloxy aldehyde **73** occurred in good yield with 4:1 stereoselectivity. The resulting alcohol stereoisomers could be separated on silica gel to provide the major isomer **75** in 68% yield. When the corresponding alkynyl diisopropoxytitanium nucleophile derived from **74**[57] was allowed to react with **73**, higher (10:1) facial selectivity was observed; however, the yield of this addition reaction was unacceptably low. The corresponding zinc reagent[58] did not add to **73**.

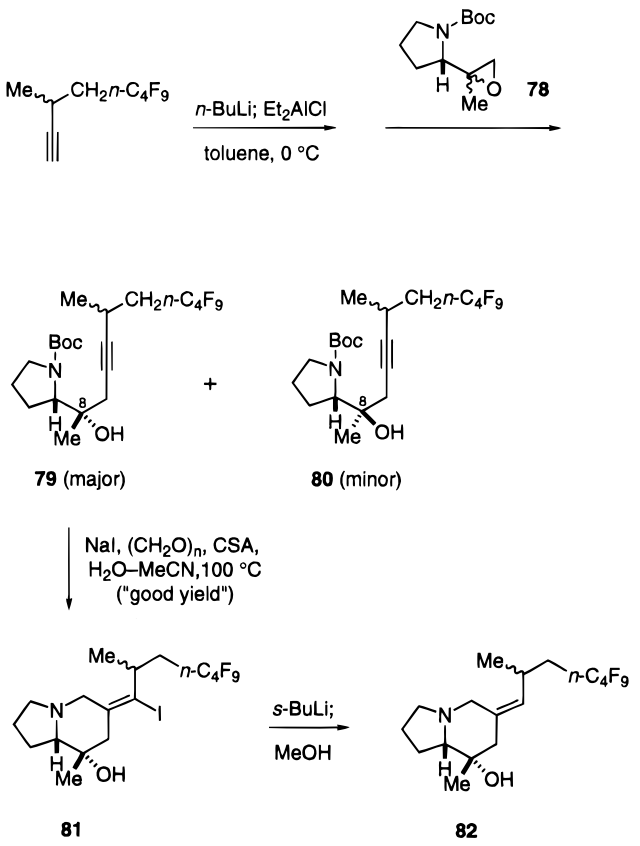
Treatment of **75** with silver triflate proceeded smoothly to provide cyclopentaoxazine **76** in high yield and set the stage for the key cyclization step. Iodide-promoted cyclization of **76** took place as desired at 100 °C with loss of the isopropylidene group to afford alkylideneindolizidine **77** in 76% overall yield from **75**. As in the related cyclizations in the pumiliotoxin A series, no stereoisomers of **77** were detected. Deiodination of **77** followed by careful cleavage of the C(8) benzyl ether provided (+)-allopumiliotoxin 339A (**69**) in 62% yield.

The synthesis of enantiopure (+)-allopumiliotoxin 339A (**69**) was reasonably direct and proceeded in 16 steps and 7.5% overall yield from *N*-(benzyloxycarbonyl)-L-proline and 16 steps and 6% overall yield from the commercially available enantiopure oxazolidine precursor of **74**.

D. A Simplified Procedure for Preparing Pumiliotoxin 251D Analogs

The sodium channel is an established target site for commercial insecticides[59] and pumiliotoxin A alkaloids have been shown to bind to a unique site of this channel.[23] It is not surprising, therefore, that analogs of the pumiliotoxin A alkaloids have been investigated as potential insecticides. In a recent report, DowElanco scientists describe the preparation of pumiliotoxin 251D and a series of 13 analogs using iodide-promoted iminium ion−alkyne cyclizations as well as a study of the toxicity of these agents to larvae of the important cotton pest *Heliothis virescens*.[51] Two minor modifications of our synthesis were introduced and merit note. Firstly these workers employed the mixture of epoxides **13** and **14** resulting from peracid epoxidation of propenyl pyrrolidine **12** (see Scheme 2), or the (*tert*-butoxy)carbonyl analogs **78**, directly in the coupling step with the alkynylalane precursor of the alkylidene side chain (Scheme 13). The epoxide epimer with the natural C(8) stereochemistry reacts faster and chromatographic separation of the C(8) epimeric product alcohols is facile,[60] making this sequence preferable to separation of the epoxide epimers in cases where the side chain fragment is not precious. Although yields and experimental details were not specified, these workers also reported that the Boc-protected amino alcohol **79** could be directly cyclized to the iodoalkylideneindolizidine precursor **81** of pumiliotoxin 251D analog **82**. This second modification is potentially quite significant, since $Ba(OH)_2$ cleavage of the benzyloxycarbonyl protecting group is the most problematic step in the pumiliotoxin A/allopumiliotoxin synthesis strategy developed in our laboratories.

Scheme 13



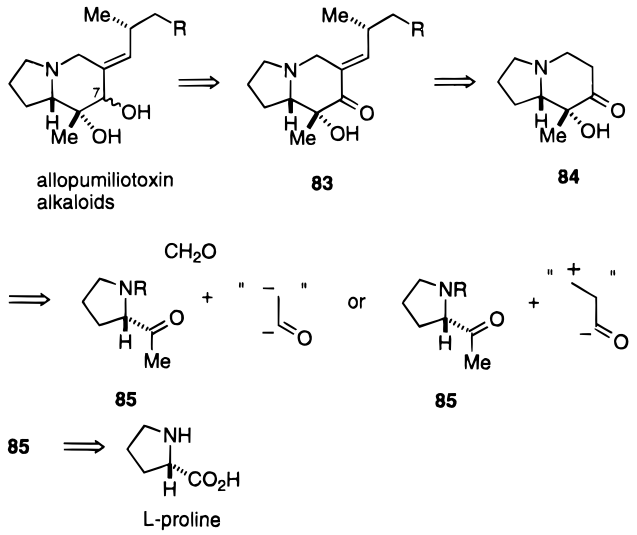
IV. Alternative Strategies for Pumiliotoxin A and Allopumiliotoxin Synthesis

A. Aldol Attachment of the Alkylidene Side Chain

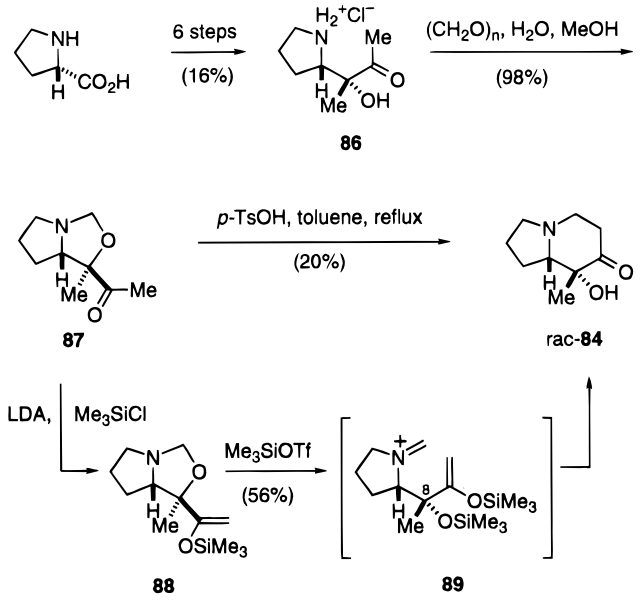
1. Total Synthesis of Allopumiliotoxins 267A and 339B

A third approach that we have employed[53] for the introduction of the alkylidene side chain is the aldol−dehydration sequence illustrated in Scheme 14. The additional oxygenation at C(7) of the allopumiliotoxins provides an opportunity to employ the corresponding enone **83** to control the alkylidene geometry due to the thermodynamic preference of trisubstituted exocyclic enones to exist in an (*E*)-configuration. We planned to introduce the side chain through aldol addition of an appropriate aldehyde to indolizidinone **84** with a subsequent dehydration giving **83**. Again, L-proline was our preferred starting material for assembly of the indolizidine skeleton, and two distinct synthetic strategies were open to us: addition of a two-carbon acyl anion equivalent to a suitably protected 2-acetylpyrrolidine **85** followed by Mannich ring closure or addition of a three-carbon nucleophile and subsequent elaboration of the piperidine ring by *N*-alkylation.

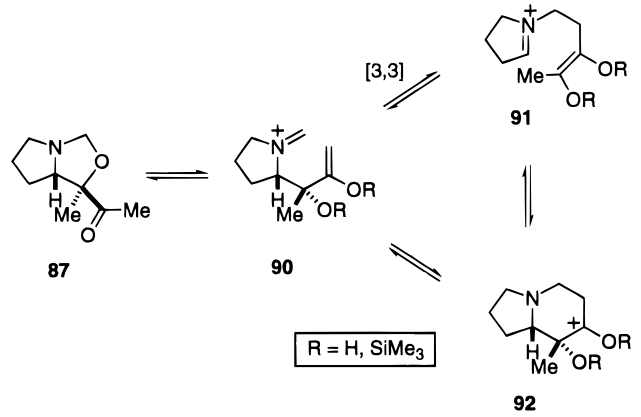
Scheme 14



Scheme 15



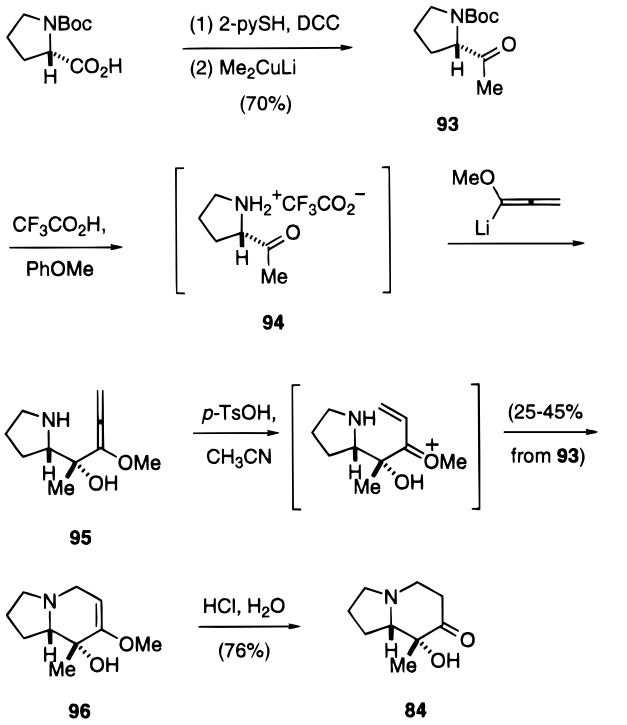
Scheme 16



Synthesis of indolizidinone **84** proved more demanding than originally envisioned as initial efforts directed toward the intramolecular Mannich approach were undermined in an unexpected way. The pyrrolidine ketone **86** was first prepared from L-proline by way of a 2-acetylpyrrolidine intermediate in an unoptimized six-step sequence (Scheme 15).[53] Addition of formaldehyde to this amino ketone led to cyclopentaoxazolidine **87**. This intermediate proved to be very robust, requiring forcing acidic conditions to promote any degree of Mannich cyclization. Unfortunately, the indolizidine product *rac*-**84** that was formed in low yield exhibited no optical rotation. An improved yield of **84** was secured by way of a silyl-mediated intramolecular Mannich reaction of enoxysilane derivative **88**.[61] When **88** was exposed to TMSOTf, *O*-silylation of the C(8) oxygen apparently occurred preventing re-equilibration of **89** to **88**, thus facilitating cyclization. This reaction, however, also yielded racemic indolizidinone *rac*-**84**.

This unexpected racemization has been rationalized in terms of a rapid equilibration of iminium ion intermediates (Scheme 16).[53] [3,3]-Sigmatropic rearrangement of **90** would give rise to an achiral intermediate **91** which is likely to revert to *rac*-**90** in preference to undergoing a disfavored 5-endo-trig cyclization. Alternatively, racemization could occur

Scheme 17

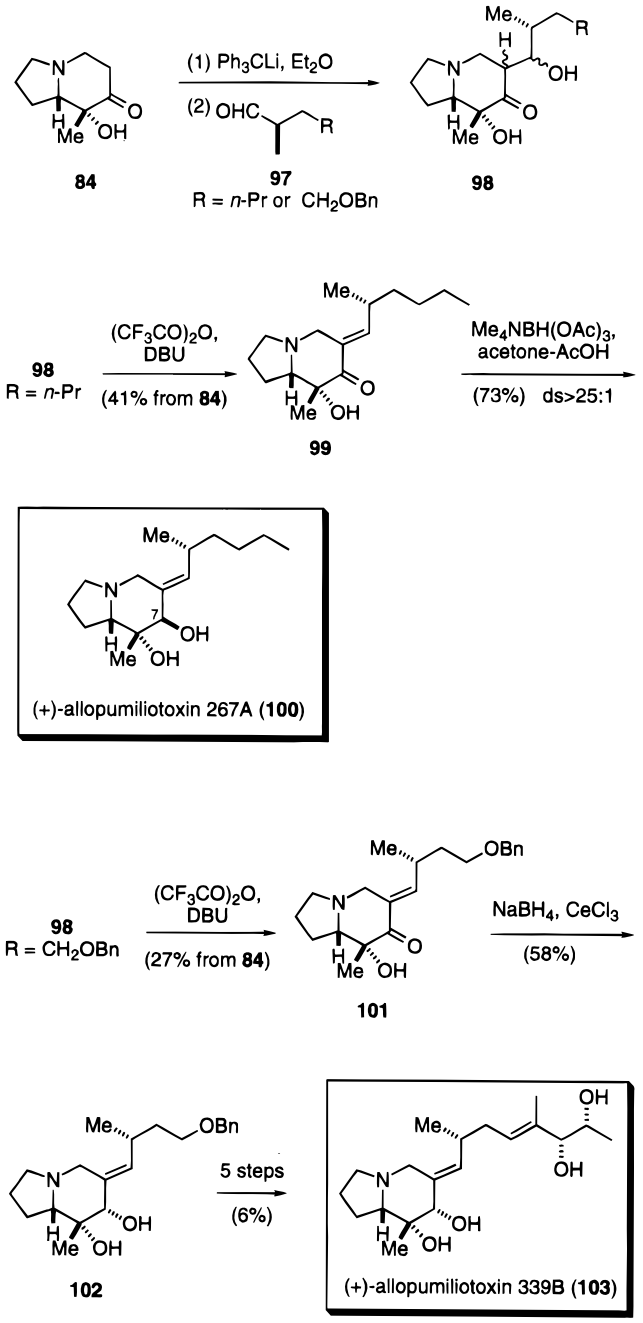


by a stepwise Mannich−retro-Mannich sequence (**90** → **92** → **91**).

A successful strategy for the synthesis of **84** was developed based on ring formation by 1,4-addition of the pyrrolidine nitrogen to an enone.[53] The latter intermediate was derived from condensation of 2-acetylpyrrolidine **93** with an appropriate three-carbon nucleophile (Scheme 17). Optimum conditions involved addition of 1-lithio-1-methoxyallene to *unprotected* 2-acetylpyrrolidine **94**, where chelate organization led to excellent diastereoselection (>97:3). In contrast, related addition reactions to 2-acetylpyrrolidines bearing acyl or alkyl substitution on nitrogen proceed with low stereoselectively.[53] Allene **95** could not be purified; however, treatment of the crude alkylation product with less than 1 equiv of *p*-toluenesulfonic acid under anhydrous conditions gave bicyclic enol ether **96** in 25%−45% overall yield from **93**. Hydrolysis of **96** then provided the target indolizidinone **84** in 76% yield and high enantiomeric purity.

Model studies on the aldol reaction of indolizidinone **84** with simple aldehydes indicated that the use of tritylllithium for deprotonation of **84**, with subsequent aldol condensation at 0 °C, would give the best results. Synthesis of side chain aldehydes **97** was achieved using Evans chiral alkylation methodology.[62] Addition of **97** (R = *n*-Pr) to the lithium enolate of **84** at 0 °C gave a mixture of aldol adducts **98** (R = *n*-Pr) which were dehydrated directly using trifluoroacetic anhydride and DBU to afford exclusively the (*E*)-enone **99** in 41% yield (Scheme 18). The final step in the synthesis of (+)-allopumiliotoxin 267A (**100**) required stereoselective 1,2-reduction of **99**. Simple hydride reducing agents gave predominantly the incorrect C(7) stereochemistry resulting from attack from the β face of **99**. Although a small amount of allopumiliotoxin 267A (**100**) was obtained by this route, attention turned to the use of triac-

Scheme 18



etoxyborohydride reagents, which had been shown to reduce hydroxy ketones in an intramolecular fashion via alkoxydiacetoxyborohydride intermediates.[63] Reduction of **99** with $Me_4NBH(OAc)_3$ gave exclusively (+)-allopumiliotoxin 267A (**100**), thus completing the first total synthesis of an allopumiliotoxin alkaloid.[53a]

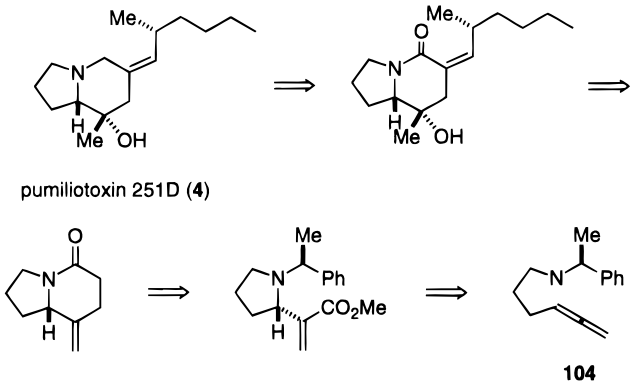
The synthesis of allopumiliotoxin 339B (**103**) was completed in an analogous fashion by employing aldehyde **97** (R = CH_2OBn) in the aldol reaction. In this synthesis, reduction of enone **101** from the β face was required and Luche's $NaBH_4-CeCl_3$ conditions[64] proved optimal, yielding only the equatorial alcohol **102** in 58% yield. Elaboration of the alkylidene side chain using the sequence employed in our first synthesis of (+)-pumiliotoxin B[21] finalized the first total synthesis of (+)-allopumiliotoxin 339B (**103**).[53b]

The overall yields in these initial total syntheses of the allopumiliotoxin alkaloids were quite low: (+)-allopumiliotoxin 267A (**100**) was prepared in nine steps and 5.6% overall yield from *N*-(*tert*-butoxycarbonyl)-L-proline, while (+)-allopumiliotoxin 339B (**103**) was prepared in an overall yield of <1% from the same commercial precursor. However, these syntheses were significant in establishing that the absolute configuration of these alkaloids is 7*R*,8*R*,8a*S*,11*R* and 7*S*,8*R*,8a*S*,11*R*,15*R*,16*R*, respectively, as depicted in Scheme 18. Due to the minute amount of allopumiliotoxins present in dendrobatid frogs, allopumiliotoxins 267A (**100**) and 339B (**103**) had been represented as 7R*,8R*,11S* and 7R*,8R*,11S*,15R*,16R*, with the configuration at 8a undefined, in the original report of their isolation earlier in 1984.[65]

2. Total Synthesis of Pumiliotoxin 251D

Gallagher and co-workers also employed an aldol−dehydration strategy in their synthesis of pumiliotoxin 251D.[66] However, in this case the alkylidene moiety was introduced by a stereospecific elimination of a β-hydroxylactam to give the thermodynamically *disfavored* (*Z*) ene lactam geometry as illustrated in Scheme 19.

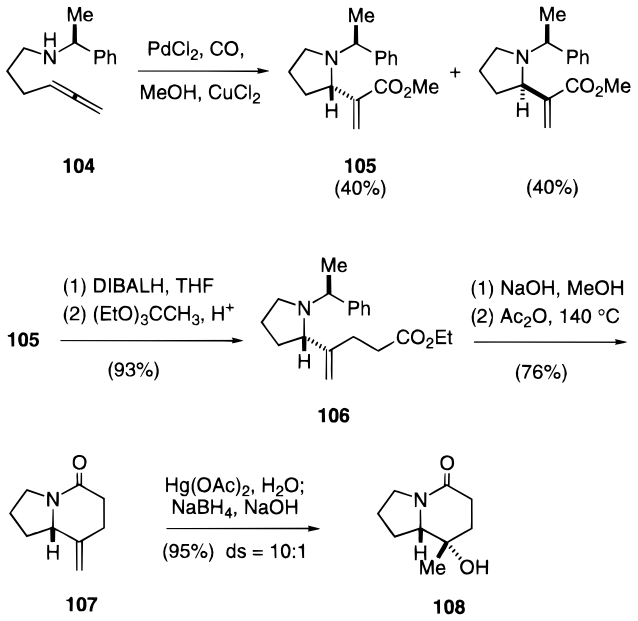
Scheme 19



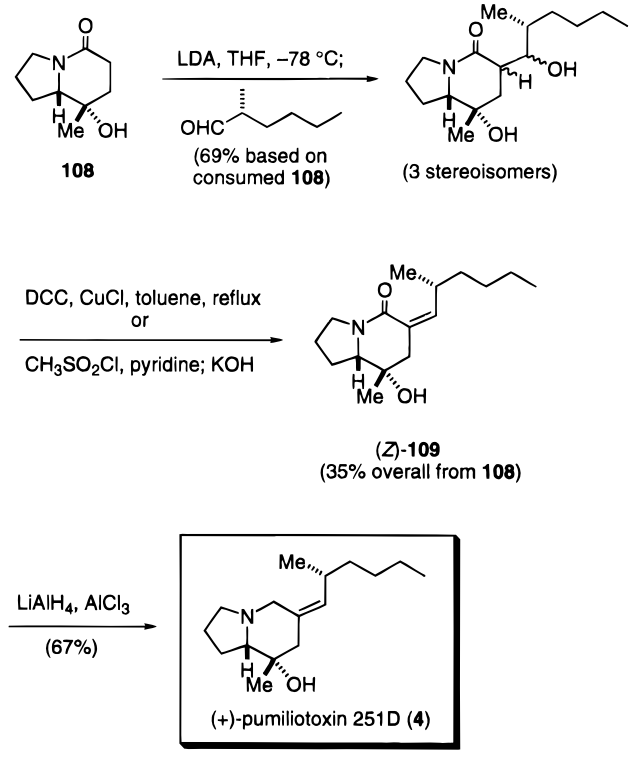
Assembly of the aldol precursor proceeded rapidly with the pivotal step being a palladium-catalyzed cyclization of an allenic amine.[67] It was hoped that asymmetric induction from the chiral benzylic residue of enantiomerically pure amine **104**[68] would control the stereochemical outcome of the cyclization process. In the event, no selectivity was realized in the Pd(II)-mediated cyclization of **104** under carbomethoxylation conditions,[69] with the role of the α-methylbenzyl moiety being reduced to that of a resolving agent (Scheme 20). No improvement in selectivity was observed using enantiopure chiral ligands or by variation of the chiral auxiliary. Although a related Hg(II)-mediated cyclization proved to be more stereoselective, the additional synthetic manipulations required to generate the corresponding acrylate rendered this approach comparable to the Pd(II)-mediated sequence in terms of overall yield.[66]

Elaboration of acrylate ester **105** to the aldol precursor **108** proceeded in five steps (Scheme 20). Claisen rearrangement of the allylic alcohol derived from **105** first gave **106** which underwent hydrolysis

Scheme 20



Scheme 21

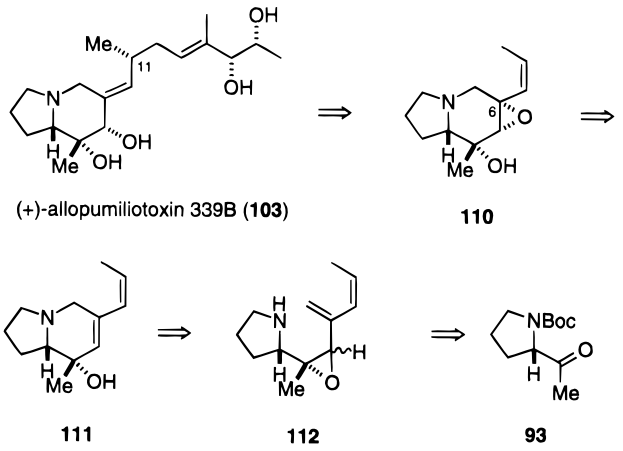


and cyclization to give unsaturated lactam **107** in 71% overall yield from **105**.[70] Stereoselective introduction of the axial tertiary alcohol was achieved using a hydroxymercuration−reduction sequence (95% yield, ds = 10:1). Addition of (*R*)-2-methylhexanal to the lithium enolate of lactam **108** gave a mixture of three aldol isomers together with 23% of recovered **108** (Scheme 21). Stereospecific syn elimination of one isomer, isolated in 27% yield, using DCC−CuCl[72] yielded exclusively the desired (*Z*)-ene lactam (*Z*-**109**), while anti elimination (CH_3SO_2Cl, KOH)[73] of the remaining inseparable mixture of isomers gave a 2.6:1 mixture of (*E*)- and (*Z*)-**109**. Deoxygenation of (*Z*)-**109** with $LiAlH_4$−$AlCl_3$ completed the synthesis of (+)-pumiliotoxin 251D (**4**). This total synthesis proceeded in 6.3% overall yield from allenic amine **104** and 1.3% overall yield from lithium acetylide−ethylene diamine complex, the commercially available precursor of **104**.

B. Synthesis of Allopumiliotoxin 339B Using Pd(0) Catalysis

Trost and Scanlan employed a Pd(0)-mediated cyclization of vinyl epoxide **112** to forge the piperidine ring in their synthesis of allopumiliotoxin 339B (**103**) (Scheme 22).[54] Although π-allylpalladium intermediates had previously been shown to facilitate the endo cyclization mode in the formation of medium rings,[74] this synthesis provided the first example of a Pd(0)-mediated 6-endo cyclization reaction.[75] A second notable feature of Trost's strategy is the control of both the C(11) stereochemistry and the alkylidene geometry through an intermolecular Pd(0)-mediated allylic alkylation of **110**, where the Pd catalyst mediates chirality transfer from the indolizidine ring to the side chain.

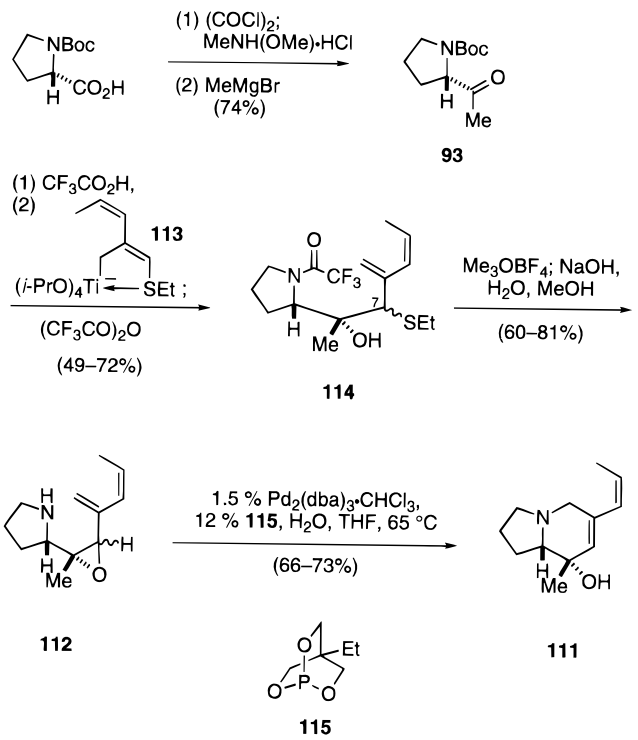
Scheme 22



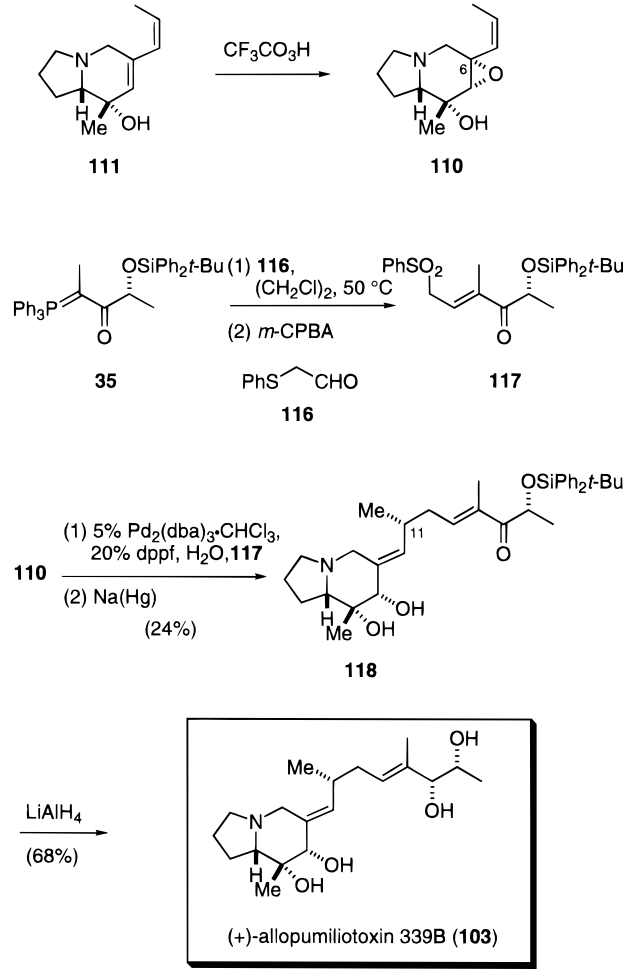
Cyclization precursor **112** was generated by chelation-controlled addition of allyltitanium intermediate **113** to the unprotected 2-acetylpyrrolidine generated from ketone **93** (Scheme 23), an intermediate that earlier had been used in our initial syntheses of the allopumiliotoxin alkaloids.[53] The lack of stereocontrol at C(7) during this addition was ultimately insignificant since a nonstereogenic center was generated at C(7) in the subsequent cyclization step. *S*-Methylation of **114** followed by base treatment provided epoxide **112** in 60%−81% yield. Although a variety of Pd(0) catalysts promoted the cyclization of **112**, optimal results were obtained using $Pd_2(dba)_3{\cdot}CHCl_3$ and phosphite ligand **115** in the presence of water as a proton source providing indolizidine **111** in 63% to 73% yield.

Indolizidine vinyl epoxide **110** was then generated by hydroxyl-directed epoxidation of the trifluoroacetate salt of **111**, while its alkylation partner **117** was derived from the known ylide **35**[21] and phenylthioethanal (**116**).[76] The Pd(0)-mediated alkylation again benefited from the addition of water and gave a single alkylideneindolizidine **118** in 24% yield after reductive desulfonylation (Scheme 24). The perfect chirality transfer from C(6) to C(11) observed in this

Scheme 23



Scheme 24



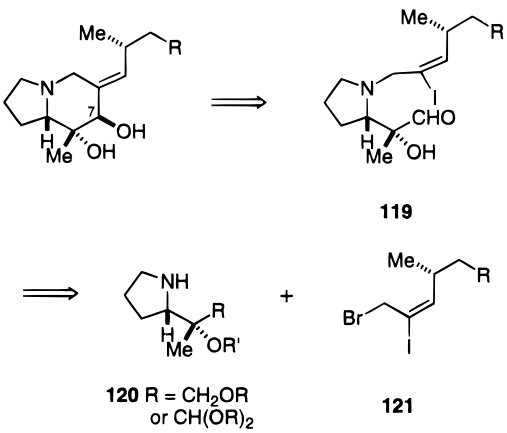
reaction is attributed to the ability of a Pd template to control the conformation of the intermediate π-allyl species. Reduction−desilylation[34] of **118** then gave (+)-allopumiliotoxin 339B in 68% yield.

The Trost−Scanlan synthesis of allopumiliotoxin 339B (**103**) was accomplished in only 11 steps from *N*-(*tert*-butoxycarbonyl)-L-proline. However, the overall yield was <3% due largely to the low efficiency of the bimolecular π-allylpalladium alkylation step.[77] This imaginative synthesis demonstrated that endocyclic π-allylpalladium cyclizations can be employed to form six-membered rings as well as highlighted the utility of cationic π-allylpalladium electrophiles to relate remote stereocenters.

C. Synthesis of Allopumiliotoxins 267A and 339A Using a Nozaki–Kishi Cyclization

Kibayashi and co-workers utilized an intramolecular Nozaki−Kishi cyclization[78] as the central step in their efficient approach to the allopumiliotoxins (Scheme 25).[55,79] This pivotal step generates the indolizidine framework, installs the (*E*)-alkylidene side chain, and establishes the C(7) hydroxyl stereochemistry in a single operation. Cyclization precursor **119** was derived from the coupling of allylic bromide **121** with an appropriately protected pyrrolidine fragment **120**.

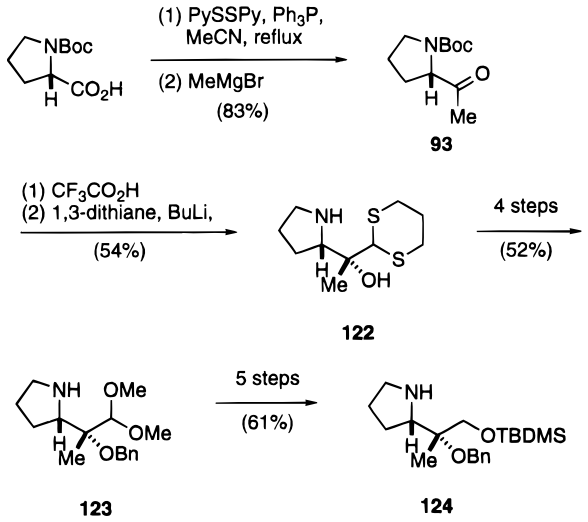
Scheme 25



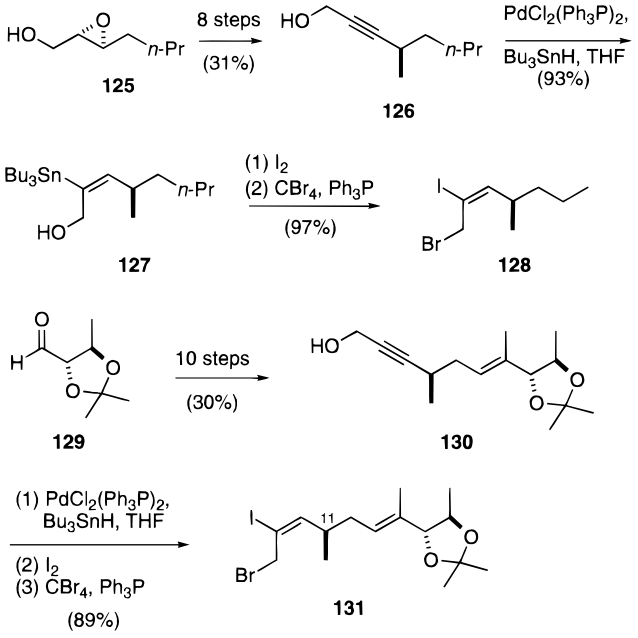
Enantioselective synthesis of the pyrrolidine unit proceeds along lines similar to earlier allopumiliotoxin syntheses,[53,54] where chelation-controlled addition of 2-lithio-1,3-dithiane to the trifluoroacetate salt of (*S*)-2-acetylpyrrolidine proceeded with complete diastereoselection to give alcohol **122** in 54% yield from **93** (Scheme 26). A four-step sequence of protecting group manipulations was then required to generate allopumiliotoxin 267A precursor **123.** A further five steps were required in the allopumiliotoxin 339A synthesis to prepare **124**. In this case the presence of an isopropylidene moiety in the side chain precluded unmasking of the dimethoxyacetal of **123** after the alkylation step.

The key step in the construction of the alkenyliodide side chain fragments **128** and **131** was Pd-catalyzed stereospecific syn hydrostannation of propargylic alcohols **126** and **130**, reactions that proceeded with 96%−98% regioselectivity (Scheme 27).

Scheme 26



Scheme 27

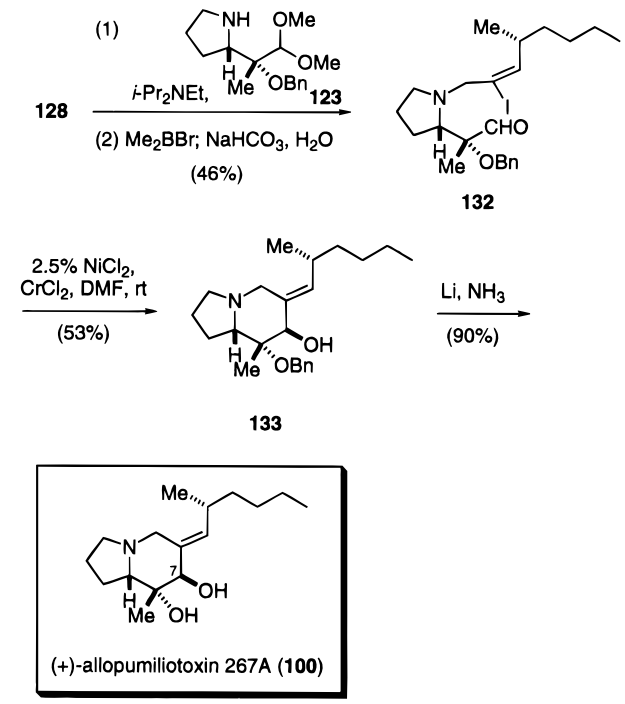


Propargylic alcohol **126** was prepared[32,80] from epoxy alcohol **125**, itself obtained by Sharpless epoxidation of (*E*)-2-hepten-1-ol. The more elaborate propargylic alcohol **130** was assembled in 10 steps from D-4-deoxythreose derivative **129**[81] using Evans methodology[62] to establish the C(11) stereocenter.

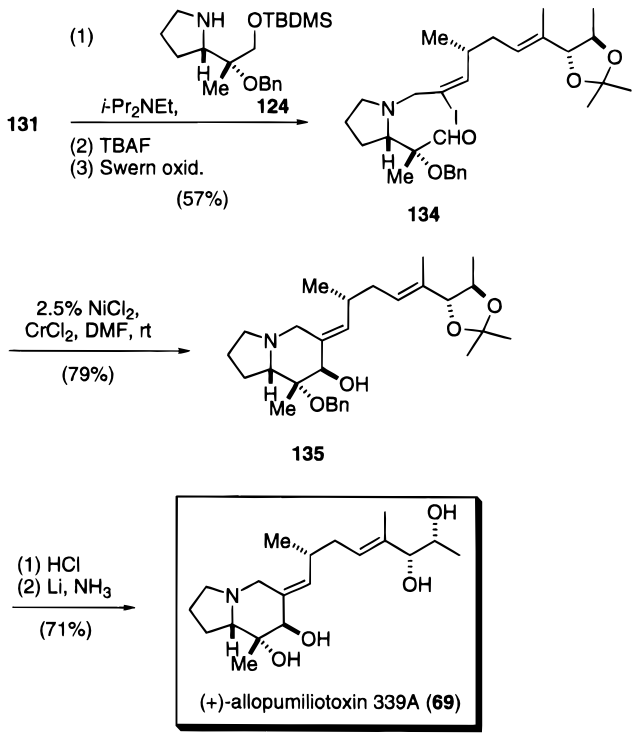
Alkylation of allylic bromide **128** with pyrrolidine **123** followed by acetal cleavage provided **132**, the iodoaldehyde precursor of allopumiliotoxin 267A, in 46% yield (Scheme 28). Similar alkylation of **131** with pyrrolidine diol derivative **124** followed by cleavage of the silyl ether and oxidation afforded the related precursor **135** of allopumiliotoxin 339A (Scheme 29).

Chromium−nickel-mediated[78] cyclization of both **132** and **134** proceeded under mild conditions with complete retention of alkene geometry to give single products, the C(7) axial alcohols **133** and **135**, respectively (Schemes 28 and 29). The excellent stereoselection observed in the formation of the C(7)

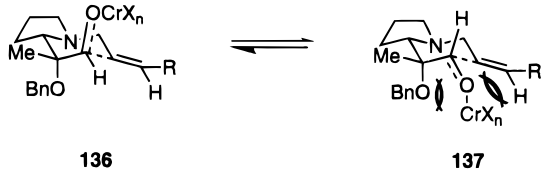
Scheme 28



Scheme 29



stereocenter was attributed to reaction through a chairlike transition state (eq 7). Cyclization con-



(7)

former **137** is destabilized by allylic 1,3 strain between the quasi equatorial chromium alkoxide and

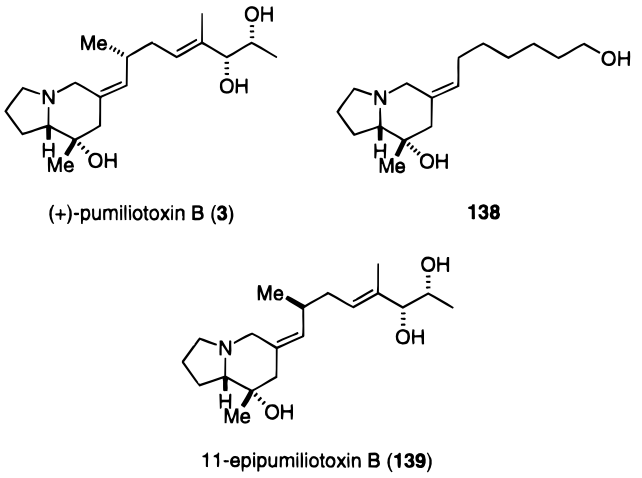
the alkene and, more importantly, by steric hindrance and electrostatic repulsion between the benzyloxy and chromium alkoxide group bearing a partial negative charge. Neither of these interactions exist in the preferred transition structure **136**.

Reductive cleavage of the benzyl group of **133** gave (+)-allopumiliotoxin 267A (**100**) in 90% yield, while cleavage of the isopropylidene group of **135** and subsequent debenzylation provided (+)-allopumiliotoxin 339A (**69**) in 71% yield (Schemes 28 and 29). The total synthesis of allopumiliotoxin 267A (**100**) summarized in Schemes 26−28 proceeded in 12 steps and 5.1% yield from *N*-(*tert*-butoxycarbonyl)-L-proline and 15 steps and 6.1% yield from epoxy alcohol **125**.[82] The synthesis of allopumiliotoxin 339A was similarly efficient, proceeding in 19 steps and 4.5% yield from *N*-(*tert*-butoxycarbonyl)-L-proline and 24 steps and <4% yield from L-threonine.

V. Conclusion

The pumiliotoxin A alkaloids have proven to be valuable research tools in pharmacology and may serve as models for the development of new myotonic or cardiotonic agents as well as insecticides.[14] As this review has documented, a number of innovative syntheses of the pumiliotoxin A and allopumiliotoxin alkaloids have been developed during the past 15 years. Syntheses accomplished in our laboratories played an important role in defining the full stereostructure of many of these amphibian alkaloids.[32,33,40,53] The iminium ion−vinylsilane,[21,32,33] and particularly the iminium ion−alkyne[49,50] cyclization routes to the pumiliotoxin A and allopumiliotoxin alkaloids are sufficiently efficient that 50−500 mg of the natural toxins and gram quantities of simple congeners can be conveniently prepared in academic or industrial discovery research laboratories. The route to the allopumiliotoxins originated by Kibayashi and coworkers[55,79] would also appear capable of preparing similar quantities of the allopumiliotoxins. The significance of these synthetic accomplishments is heightened by the absence of alkaloids in captive-raised dendrobatid frogs[83] and the scarcity and threatened existence of these frogs in nature.

Besides providing access to substantial quantities of the natural alkaloids, chemical total synthesis has provided numerous analogs of the pumiliotoxin A and allopumiliotoxin alkaloids which have contributed substantially to defining structure−activity relationships. For example, it is now clear that cardiotonic and myotonic activities in the pumiliotoxin A series are markedly dependent on the structure of the alkylidene side chain.[24] Thus, while pumiliotoxin B shows powerful effects on the rate (chronotropic) and force (intropic) of contractures of guinea pig atria at 6 μM, the C(11) epimer **138** shows virtually no effect at 54 μM and simple analogs such as **139** are cardiac depressants.[24a,b] Similar dramatic structural effects are seen on sodium flux and phosphoinositide breakdown in guinea pig brain synaptoneurosomes: **138**, 12 ± 3 (Na) and 6 ± 2 (PI); **139**, 21 ± 1 (Na) and 11 ± 2 (PI) (% of response relative to pumiliotoxin B).[24b,c] The requirement for the *R* configuration at C(11) is also seen in structure−activity relationship studies of pumiliotoxin-based insecticides,[51] while polar substitutents on the side chain decrease insecticide activity.[84] The fact that the C(11) stereochemistry is important is not surprising due to the conformational constraints on the C(10)−C(11) σ-bond that arise from allylic interactions.[51,85,86]



Several of the new chemistries developed in response to the synthetic challenge posed by the pumiliotoxin and allopumiliotoxin alkaloids have proven to have general utility in organic synthesis. Foremost among these are iminium ion−vinylsilane cyclizations, which have been employed as a central strategic element in a number of total syntheses.[30,31,87] Figure 1 depicts four representative natural products that have been prepared in this way. Three of the examples are plant alkaloids from different families (*Corynanthe*,[88] *Amaryllidaceae*,[89] and *Elaeokarpus*[90]) and one an antibiotic from a *Streptomyces* species.[91] The particular utility of vinylsilanes as terminators of cationic cyclization reactions extends far beyond Mannich chemistry[92−94] and was summarized in an earlier review.[30]

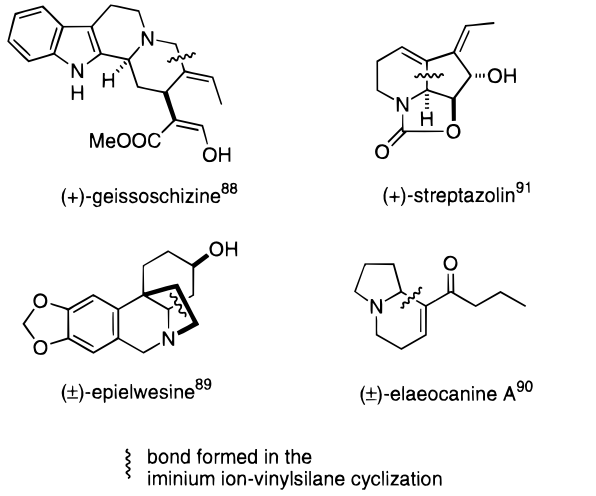


Figure 1. Total syntheses of representative other natural products employing iminium ion−vinylsilane cyclizations as key steps.

Acknowledgments

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