Nickel-Catalyzed Preparation of Bicyclic Heterocycles: Total Synthesis of (+)-Allopumiliotoxin 267A, (+)-Allopumiliotoxin 339A, and (+)-Allopumiliotoxin 339B

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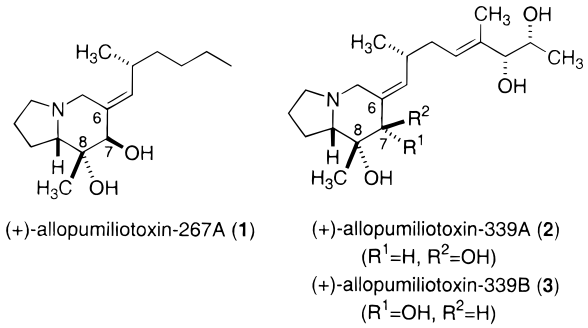
Abstract: A new method for the reductive cyclization of ynals involving a $Ni(COD)_2/PBu_3$ catalyst system to produce allylic alcohols was developed. The triethylsilane-mediated procedure allows preparation of functionally rich pyrrolizidine, indolizidine, and quinolizidine alkaloid frameworks. The method allows the direct introduction of an allylic alcohol moiety with completely stereoselective creation of an exocyclic double bond and highly diastereoselective alcohol introduction relative to preexisting chirality. The total syntheses of (+)-allopumiliotoxin 267A, (+)-allopumiliotoxin 339A, and (+)-allopumiliotoxin 339B were accomplished utilizing an ynal cyclization as the key step. These syntheses provide short and efficient entries to the allopumiliotoxins and highlight the utility of nickel-catalyzed ynal cyclizations in complex synthetic strategies.

Introduction

The allopumiliotoxin alkaloids are the most complex members of the pumiliotoxin class of indolizidine alkaloids.[1,2] The allopumiliotoxins, which are isolated from the skin of Dendrobatid frogs, possess a characteristic 7,8-dihydroxy-8-methyl-6-alkylideneindolizidine ring system (Scheme 1). The characteristic *E*-alkylidene unit varies widely in complexity among the members of this alkaloid class, and both epimers at C-7 have been found in naturally occurring members of this group. The unique structural features of these alkaloids, their scarcity from natural sources, and their potent cardiotonic and myotonic activity have made them important targets for synthesis. Following the initial isolation of members of this natural product class by Daly and co-workers,[1] Overman pioneered the synthesis of the pumiliotoxins.[3] Several generations of synthetic approaches have emerged from the Overman laboratories, including amine/methoxyallene cyclizations, iminium ion/vinylsilane cyclizations, and iodide-promoted iminium ion/alkyne cyclizations. The latter of these strategies was particularly attractive since it allowed construction of the indolizidine skeleton and the 6-alkylidene stereochemistry in a single step. An alternate approach to the allopumiliotoxins involving two key palladium-catalyzed processes was developed by Trost.[4] In this approach, the indolizidine skeleton was assembled by a palladium-catalyzed amine/diene coupling, and the 6-alkylidene side chain was introduced by a palladium-catalyzed vinyl epoxide/allylic sulfone coupling. Kibayashi reported an effective nickel-catalyzed vinyl iodide/aldehyde Nozaki−Kishi coupling[5] to prepare the allopumiliotoxin framework.[6] This approach efficiently allowed introduction of the 6-alkylidene unit from a stereodefined vinyl iodide with simultaneous stereoselective creation of the C-7 stereocenter. Most recently, an extremely short approach to the allopumiliotoxins involving a titanium-mediated alkyne/ester reductive cyclization was reported by Sato.[7] This approach is characterized by the single-step creation of the indolizidine skeleton and 6-alkylidene stereochemistry. Furthermore, the rapid preparation of the cyclization precursor is notable in the Sato approach. Despite the efficiency of these numerous approaches, we envisioned that an aldehyde/alkyne reductive cyclization could potentially provide the most direct approach to the allopumiliotoxins since the indolizidine framework, the 7-hydroxy stereocenter, and the 6-alkylidene double bond would all be constructed in a single step. Herein, we provide a full account of the discovery and development of a nickel-catalyzed ynal cyclization procedure, its application in the synthesis of various nitrogen heterocycles, and the total syntheses of (+)-allopumiliotoxin 267A (**1**), (+)-allopumiliotoxin 339A (**2**), and (+)-allopumiliotoxin 339B (**3**).[8]

Scheme 1



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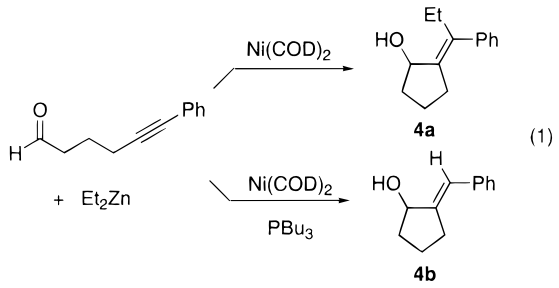
Results and Discussion

Development of an Ynal Reductive Cyclization Procedure. Transition metal-catalyzed reductive cyclizations of dienes, enynes, and diynes have been widely developed with numerous catalyst systems.[9] The corresponding cyclizations of carbonyls with alkenes and alkynes, however, are less well developed. Early metals are effective at promoting the coupling of carbonyls with alkenes and alkynes via the formation of oxametallacycles, but catalytic turnover in these systems is often difficult due to the strength of the early metal−oxygen bond.[10] While very efficient stoichiometric procedures have been developed that are quite broad in scope,[7] the corresponding catalytic procedures have been somewhat elusive. This limitation was partially overcome by Buchwald[11] and Crowe,[12] who demonstrated that titanocene-catalyzed reductive cyclizations of enones and ynones were effective when silanes were employed as the reducing agent. However, the titanium-catalyzed methods were unsuccessful in the formation of rings larger than five-membered and in couplings involving terminal alkynes. A number of late-metal-catalyzed reductive cyclizations involving carbonyls have also been reported. Of particular note are the studies from Mori and Tamaru that described the efficient nickel-catalyzed coupling of diene-aldehydes with triethylsilane,[13] triethylborane,[14] or diethylzinc[14] as the reducing agent. The scope of this procedure is quite broad, and several complex synthetic applications have been reported.[15]

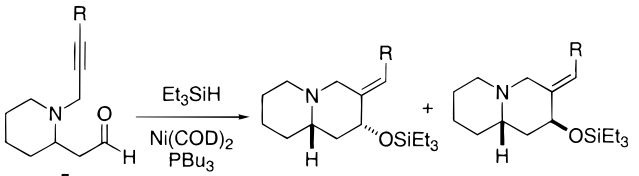
Our group recently reported a procedure for nickel-catalyzed aldehyde-alkyne reductive and alkylative cyclizations involving organozincs.[16] In cyclizations involving a simple ynal and diethylzinc, $Ni(COD)_2$ catalyzed formation of the alkylative cyclization product **4a**, whereas $Ni(COD)_2/PBu_3$ catalyzed formation of the reductive cyclization product **4b** (eq 1). The



(1)

$Ni(COD)_2/PBu_3$ catalyzed procedure appeared to be ideally suited for preparation of the allopumiliotoxin indolizidine framework. However, we quickly found that direct addition of the organozinc to the aldehyde was impossible to suppress as the ynal substrate complexity increased.

Table 1



entry	R	temp (°C)	product (% yield)	6:7 ratio
1	Ph	45	**6a** (85)	90/10
2	Ph	23	**6a** (90)	98/2
3	Ph	0	**6a** (89)	>97/<3
4	*n*-C_6H_{13}	45	**6b** (83)	99/1
5	H	45	**6c** (81)	95/5
6	$SiMe_3$	45	**6d** (93)	98/2

We then examined triethylsilane as a less nucleophilic reducing agent.[17] In contrast to the diethylzinc-promoted process, reductive cyclizations employing triethylsilane were very efficient across a broad range of substrate classes. The quinolizidine ring system[18] **6** was first targeted, via cyclization of ynals **5a**−**d** which possess a piperidine ring in the tether chain (Table 1). Cyclizations proceeded cleanly in several hours at 45 °C in THF to afford high yields and very good diastereoselectivities. Typical catalyst loadings were 10−20 mol % with a 2:1 to 4:1 phosphine−nickel ratio, and substrate concentrations typically ranged from 0.02 to 0.05 M. Upon lowering the reaction temperature to 0 °C, cyclizations required 18−48 h under otherwise identical conditions. At 0 °C, diastereoselectivities were uniformly outstanding across the range of substrates examined. The quinolizidine framework was efficiently produced from ynals that possessed a variety of acetylenic substituents, including aromatic (entry 3) and aliphatic (entry 4) internal alkynes, terminal alkynes (entry 5), and alkynylsilanes (entry 6). The equatorial hydroxyl was selectively produced in all cases. No evidence was obtained for competing reduction of the aldehyde or alkyne without cyclization.

The [3.3.0] bicyclic framework of pyrrolizidine alkaloids[19] was next examined (Table 2). The requisite ynals were quite unstable, and attempts to purify the adducts from Swern oxidation led to extensive decomposition. However, Swern oxidation of alcohols **8a**−**c** followed by simple extraction and concentration afforded aldehydes of sufficient purity to efficiently participate in the nickel-catalyzed cyclizations. The overall two-step procedure of oxidation and cyclization cleanly

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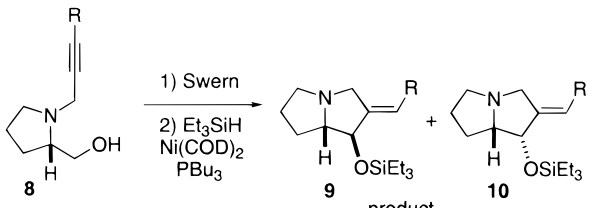
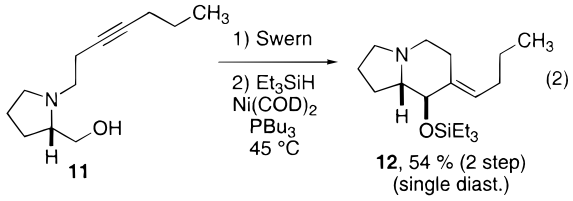
Table 2



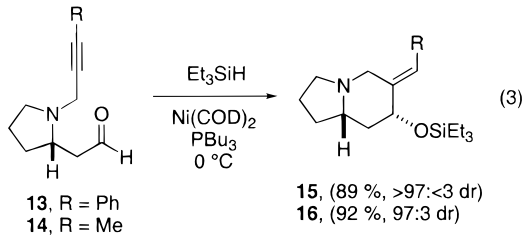
entry	R	temp (°C)	product (% yield)	9:10 ratio
1	Ph	50	**9a** (55)	85/15
2	Me	45	**9b** (42)	92/8
3	*n*-C_6H_{13}	45	**9c** (51)	91/9

afforded pyrrolizidines **9a**−**c** in good yield with very good diastereoselectivities. With this particular substitution pattern, the exo hydroxyl was selectively produced in each case. Both aromatic and aliphatic alkynes participated cleanly in the cyclizations.

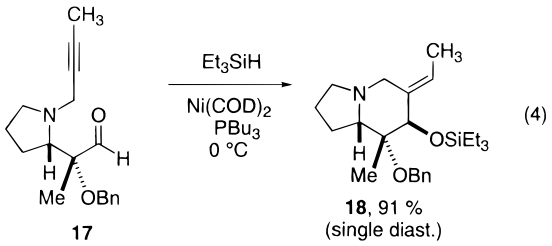
Indolizidines[18c,19c,d,20] that are isomers of the pumiliotoxin skeleton were then produced upon cyclization of the one-carbon homologues of the substrates described above. Again, the requisite aldehydes were unstable, but the crude aldehyde from a Swern oxidation of **11** could be directly cyclized to afford the indolizidine alkaloid **12** as a single diastereomer in good yield (eq 2). Consistent with observations made in the quinolizidine series described above (Table 1), the equatorial hydroxyl of **12** was exclusively produced.



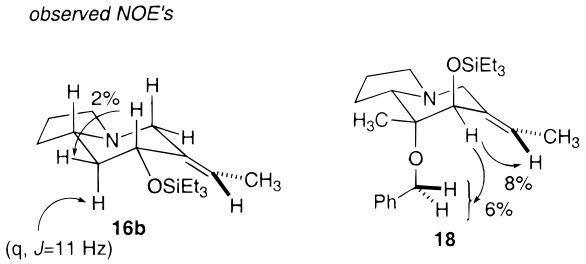
At this juncture, we proceeded to attempt preparation of the allopumiliotoxin indolizidine ring system. On the basis of the results described in Table 1, and eq 2, we suspected that the equatorial hydroxyl, found in (+)-allopumiliotoxin 339B, should be produced in the allopumiliotoxin series. The axial hydroxyl found in allopumiliotoxins 267A and 339A is the more prevalent orientation within the known allopumiliotoxins. As suspected, cyclization at 0 °C of ynals **13** and **14**, which are models of the allopumiliotoxin ring system, led exclusively to indolizidines **15** and **16** in excellent yield and diastereoselectivity (eq 3).



However, cyclization of more highly functionalized model compound **17** that possesses the C-8 tertiary hydroxyl protected as the benzyl ether afforded a surprising result (eq 4). A single diastereomer was obtained, but product **18** possessed the epimeric axial hydroxyl at C-7! These stereochemical assignments were unambiguously determined by an analysis of coupling constants and NOE spectra (Scheme 2).



Scheme 2



The mechanistic basis for this remarkably clean reversal of stereochemistry is unclear; however, we propose the following mechanistic scheme. In the cyclization of substrate **14**, initial complexation of Ni(0) to the alkyne and aldehyde π-systems may be followed by oxidative cyclization to oxametallacycle **20** (Scheme 3).[21] Orientation of the initial π-complex in a *trans*-hydrindane conformation would ultimately lead to production of the equatorial silyloxy substituent. σ-Bond metathesis[22] of the silane and Ni−O bond would afford intermediate **21** which would undergo C−H reductive elimination to afford the observed product **16**. With substrate **17**, inversion at nitrogen could lead to *cis*-hydrindane conformation **22** (Scheme 4). The corresponding *trans*-hydrindane conformation of **22** would be destabilized by electrostatic repulsions involving the ring nitrogen, benzyl ether, and aldehyde. From *cis*-hydrindane conformation **22**, the identical oxidative cyclization/σ-bond metathesis mechanism would afford product **18** with the axial C-7 silyloxy substituent. This proposed mechanism is directly analogous to that proposed by Buchwald and Crowe in titanium-catalyzed reductive cyclizations of enones.[11,12]

It is interesting to compare the selectivities of the nickel-catalyzed ynal cyclizations to the nickel-catalyzed Nozaki−Kishi couplings described by Kibayashi on very closely related systems.[6] Direct comparisons are difficult since the Nozaki−Kishi couplings[5] were carried out in DMF (vs THF in our study) and in the presence of chromium salts that could alter conformational preferences. In the fully functionalized pumiliotoxin framework, very high selectivities for formation of the C-7 axial hydroxyl were observed in both methods. However, in the preparation of less-functionalized quinolizidines **6b** and **26**, the ynal cyclization was highly selective for formation of the equatorial hydroxyl, whereas the Nozaki−Kishi coupling proceeded in a nonselective fashion (Scheme 5).

Total Synthesis of (+)-Allopumiliotoxin 267A, (+)-Allopumiliotoxin 339A, and (+)-Allopumiliotoxin 339B. With the above methodological studies completed, we proceeded to apply the ynal cyclization method in the preparation of allopumil-

(20) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1987; Vol. 5, Chapter 1.

(21) Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2554.

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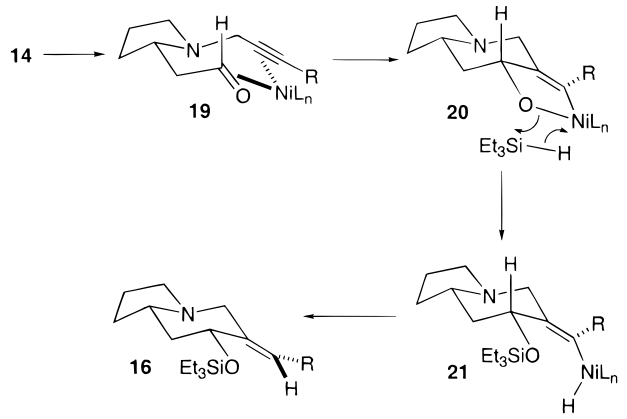
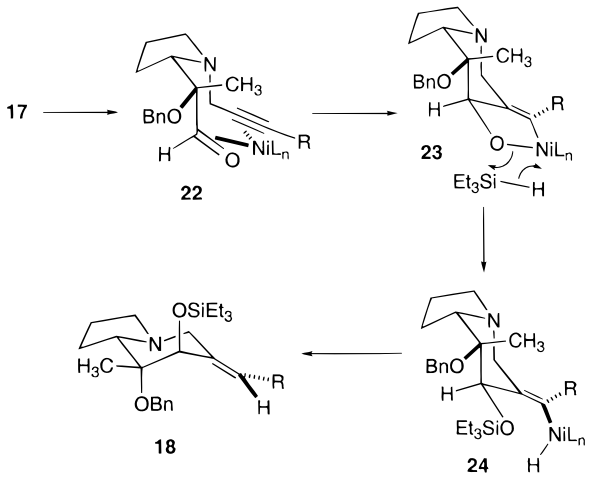
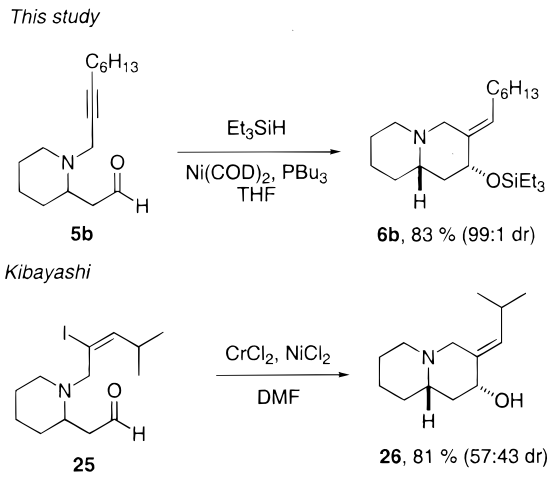
Scheme 3



Scheme 4

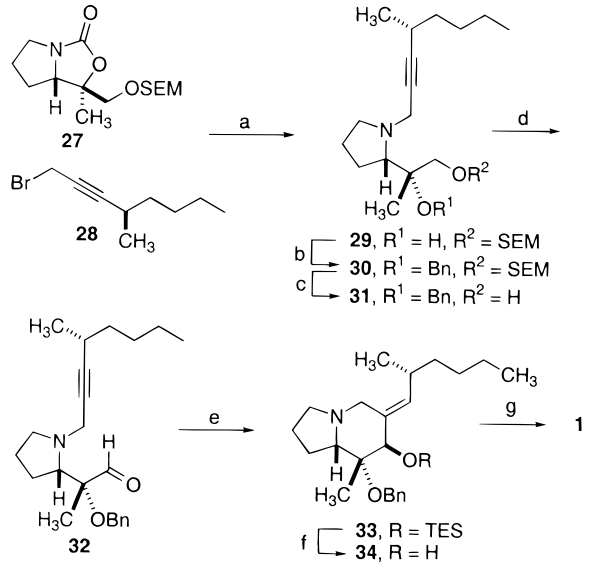


Scheme 5



iotoxin 267A (Scheme 6). For our studies, we relied on the excellent procedures developed by Overman,[3] Kibayashi,[6] and Sato[7] in the preparation of the requisite cyclization precursors. Accordingly, oxazolidinone **27**[3c] was prepared from L-proline methyl ester. Oxazolidinone hydrolysis with KOH in ethanol followed by propargylation with enantiopure bromide **28**[7] afforded substrate **29** in 74% yield for the two-step conversion. Benzylation of the tertiary hydroxyl followed by primary hydroxyl deprotection and oxidation led to cyclization substrate **32** in high yield. Aldehyde **32** was then treated with triethylsilane (5 equiv), $Ni(COD)_2$ (0.2 equiv), and tributylphosphine (0.4 equiv) in THF at 0 °C for 18 h to afford bicycle **33** as a single diastereomer in 95% yield. Careful inspection of the crude 500 MHz ^{1}H NMR spectrum revealed no trace of the C-7 epimer or C-6 *Z*-alkylidene. Deprotection of the triethylsilyl ether with HF·pyridine and the benzyl ether with Li°/NH_3 afforded (+)-allopumiliotoxin 267A (**1**) that was identical in all respects with synthetic material kindly provided by Overman.[3c]

Scheme 6[a]



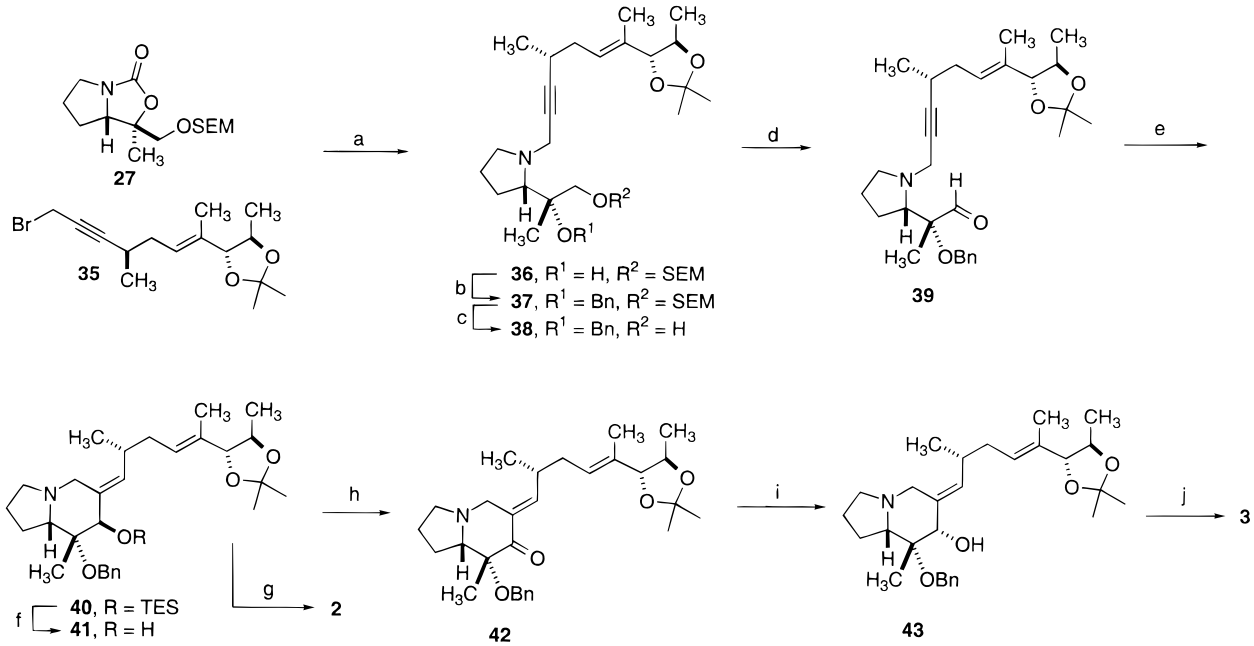
[a] Conditions: (a) I. KOH, EtOH; Ii. **28**, *i*-Pr_2NEt, THF, 74 % for Two Steps. (b) BnBr, KH, THF, 83 %. (c) NBu_4F, Molecular Sieves, THF, 94 %. (d) $Cl_2(CO)_2$, DMSO, Et_3N, 93 %. (e) Et_3SiH, $Ni(COD)_2$, PBu_3, THF, 95 %. (f) HF·Pyridine, THF, 92 %. (g) Li°, NH_3, THF, 88 %.

The identical strategy was pursued in the syntheses of allopumiliotoxins 339A and 339B (Scheme 7). Propargyl bromide **35** was prepared by bromination of the corresponding propargyl alcohol[6a] with carbon tetrabromide and triphenylphosphine in CH_2Cl_2 in 93% yield. Hydrolysis of oxazolidinone **27** as before followed by *N*-propargylation with bromide **35** proceeded cleanly. Benzylation of the tertiary hydroxyl followed by primary hydroxyl deprotection and oxidation under Swern conditions led to cyclization substrate **39** in 67% yield for the three-step conversion. Cyclization of substrate **39** with triethylsilane (5.0 equiv), $Ni(COD)_2$ (0.2 equiv), and tributylphosphine (0.8 equiv) proceeded in a completely diastereoselective fashion in THF at −10 to 0 °C in 18 h to afford silyl ether **40** in 93% isolated yield. Silyl ether **40** was deprotected with HF·pyridine to afford alcohol **41**, which serves as the branchpoint for the preparation of allopumiliotoxins 339A (**2**) and 339B (**3**). Further deprotection[6a] of alcohol **41** with 3 N HCl and then Li°/NH_3 afforded synthetic (+)-allopumiliotoxin 339A (**2**) that exhibited melting point, optical rotation, and NMR data consistent with that previously reported.[3c,6a]

Alcohol **41** was then oxidized under Swern conditions to enone **42**, and reduction with $CeCl_3/NaBH_4$[23] in methanol afforded equatorial hydroxyl **43** in 95% yield as a single diastereomer. The procedure for this selective reduction had previously been reported by Overman in a simpler system.[3a] Deprotection of this material with 3 N HCl and then Li°/NH_3 afforded synthetic (+)-allopumiliotoxin 339B (**3**) that exhibited optical rotation and NMR data consistent with that previously reported.[3a,4]

(23) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

Scheme 7[a]



[a] Conditions: (a) I. KOH, EtOH; Ii. 35, *i*-Pr_2NEt, THF, 92% for Two Steps. (b) BnBr, KH, THF, 82 %. (c) NBu_4F, Molecular Sieves, THF, 92 %. (d) $Cl_2(CO)_2$, DMSO, Et_3N, 89 %. (e) Et_3SiH, $Ni(COD)_2$, PBu_3, THF, 93 %. (f) HF·Pyridine, THF, 87 %. (g) I. 3N HCl/THF, 92 %; Ii. Li°, NH_3, THF, 80 %. (h) $Cl_2(CO)_2$, DMSO, Et_3N, 86 %. (i) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 95 %. (j) I. 3N HCl/THF, 91 %; Ii. Li°, NH_3, THF, 82 %.

Conclusions

The studies described herein detail the development of a nickel-catalyzed procedure for the reductive cyclization of ynals. The method is particularly useful for generating cyclic allylic alcohols with a stereodefined exocyclic double bond. With a variety of heterocyclic templates, the diastereoselectivites with respect to preexisting stereocenters were shown to be uniformly excellent. The total syntheses of (+)-allopumiliotoxin 267A, (+)-allopumiliotoxin 339A, and (+)-allopumiliotoxin 339B were completed in a highly efficient and stereoselective fashion utilizing the ynal cyclization procedure as a key step. These studies underscore the utility of nickel-catalyzed ynal cyclizations in the preparation of highly functionalized heterocycles.

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Supporting Information Available: Full experimental details and copies of ^1H NMR spectra of all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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