Nickel Catalysis in the Stereoselective Preparation of Quinolizidine, Pyrrolizidine, and Indolizidine Alkaloids: Total Synthesis of (+)-Allopumiliotoxin 267A

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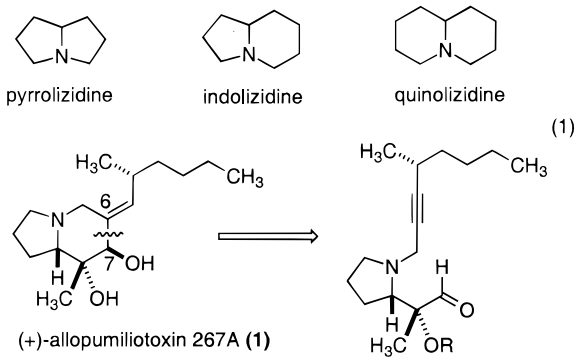
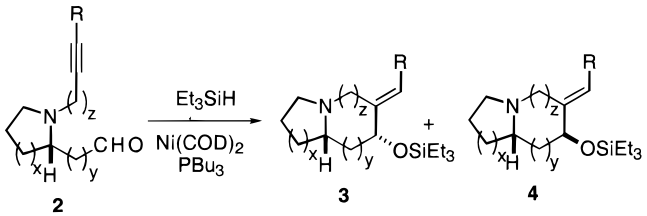
The widespread occurrence and diverse biological activities of quinolizidine, pyrrolizidine and indolizidine alkaloids as well as their utility as research tools in pharmacology have made them important targets in the search for efficient and selective synthetic methods (eq 1).[1] We envisioned that an efficient entry to these classes of alkaloids could be achieved by the application of our recently developed method for the reductive cyclization of ynals.[2] Direct cyclization of an ynal possessing a pyrrolidine or piperidine-containing tether would allow the preparation of each of the above-mentioned classes of alkaloid skeleta. Furthermore, the challenging stereochemical features of the allopumiliotoxin alkaloids[3] such as allopumiliotoxin 267A **(1)** should be particularly well addressed by an ynal reductive cyclization since the C-6/C-7 bond and the stereochemical features at the C-6 and C-7 positions could be directly constructed in a single step.



Unfortunately, our previously reported nickel-catalyzed ynal reductive cyclization method employing diethylzinc as the reducing agent failed completely in the attempted preparation of bicyclic nitrogen heterocycles. Upon treatment of pyrrolidine- and piperidine-functionalized ynals with diethylzinc and catalytic amounts of $Ni(COD)_2$ and PBu_3, only direct addition of the organozinc to the aldehyde was observed. Therefore, we considered alternative reducing agents for the nickel-catalyzed process.

In related classes of metal-catalyzed reductive cyclizations, silanes have served as efficient and chemoselective reducing agents. Crowe[4] and Buchwald[5] have independently developed titanium-catalyzed silane-mediated reductive cyclizations of enals, and Mori has developed nickel-catalyzed silane-mediated reductive cyclizations of dienals.[6] With all-carbon frameworks, hydrosilylation has been coupled with carbocyclization in many different contexts with varying catalyst and substrate structures.[7] However, no catalytic examples of ynal reductive cyclizations involving cyclic templates or Lewis basic functionalities have been reported.

Table 1. Preparation of Bicyclic Nitrogen Heterocycles[a]



entry	*x*	*y*	*z*	R	temp (°C)[b]	product (yield)[c]	**3**:**4** ratio[b,d]
1	2	1	1	Ph	45	**3a** (85%)	90/10
2	2	1	1	Ph	23	**3a** (90%)	98/2
3	2	1	1	Ph	0	**3a** (89%)	>97/<3
4	2	1	1	$SiMe_3$	45	**3b** (93%)	98/2
5	2	1	1	*n*-C_6H_{13}	45	**3c** (83%)	99/1
6	2	1	1	H	45	**3d** (81%)	95/5
7	1	0	1	Ph	50	**4e** (55%)[e]	15/85
8	1	0	1	Me	45	**4f** (42%)[e]	8/92
9	1	0	1	*n*-C_6H_{13}	45	**4g** (51%)[e]	9/91
10	1	0	2	*n*-C_3H_7	45	**4h** (54%)[e]	<3/>97

[a] Typical conditions: $Ni(COD)_2$ (10 mol %), PBu_3 (20 mol %), Et_3SiH (5 equiv) in THF. [b] Diastereoselectivities in reactions carried out at 45−50 °C were not optimized. [c] Isolated yield for the major diastereomer. [d] Determined by crude ^1H NMR spectra. [e] Overall yields for two steps (oxidation and cyclization) from the propargyl amino alcohol derivatives.

We report here that $Ni(COD)_2/PBu_3$ is a highly effective catalyst system for the triethylsilane-mediated reductive cyclization of ynals that allows preparation of functionally rich pyrrolizidine, indolizidine, and quinolizidine alkaloid frameworks. The cyclization method allows the direct introduction of an allylic alcohol moiety with completely stereoselective introduction of an exocyclic double bond and highly diastereoselective alcohol introduction relative to preexisting chirality. Entries 1−6 describe quinolizidine alkaloid preparation, entries 7−9 describe pyrrolizidine alkaloid preparation, and entry 10 describes the preparation of an indolizidine alkaloid (Table 1). While the mechanism for this process has not been established (vide infra), it appears that both 1,2- and 1,3-induction relative to preexisting stereocenters is quite good across the range of substrates examined. The allylic alcohol functionality produced may be further manipulated to potentially provide access to many natural product classes that possess the requisite skeletal frameworks.

The allopumiliotoxin alkaloids, isolated from dendrobatid frogs, are members of the indolizidine class.[3] Members of this alkaloid family possess a vicinal diol flanked by an *E*-alkylidene side chain. Syntheses of members of this alkaloid class have been completed by Overman,[8] Trost,[9] Kibayashi,[10] and Sato.[11] While each of these

(1) For a representative review on the isolation of members of these natural product classes, see: Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162.
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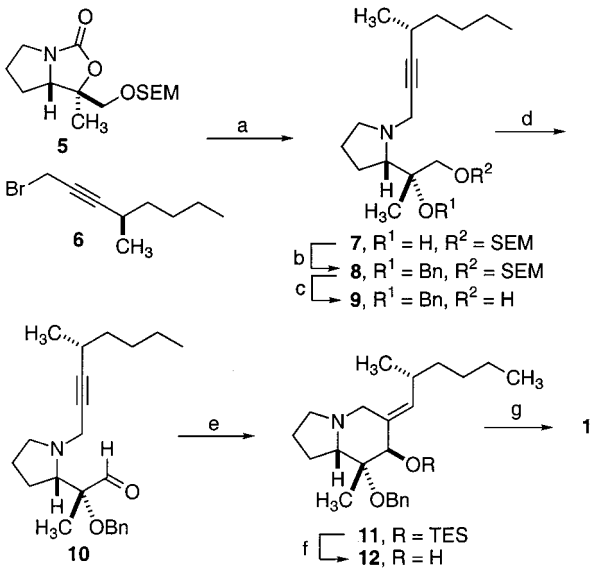
Scheme 1[a]



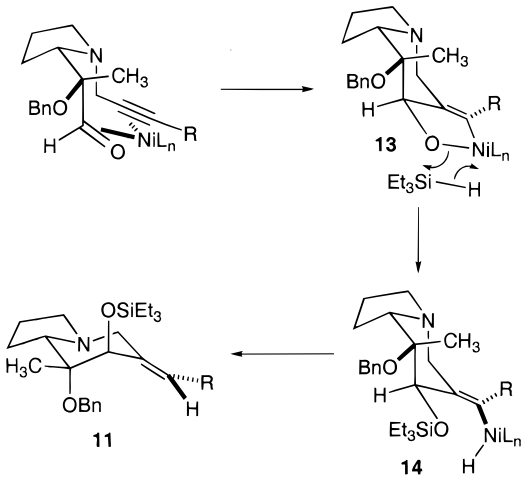
[a] (a) i. KOH, EtOH; ii. **6**, *i*-Pr_2NEt, THF, 74% for two steps. (b) BnBr, KH, THF, 83%. (c) NBu_4F, molecular sieves, THF, 94%. (d) $Cl_2(CO)_2$, DMSO, Et_3N, 93%. (e) Et_3SiH, $Ni(COD)_2$, PBu_3, THF, 95%. (f) HF·pyridine, THF, 92%. (g) Li°, NH_3, THF, 88%.

previous approaches provided elegant contributions, we envisioned that simultaneous construction of the alkaloid skeleton and stereoselective introduction of the C-7 hydroxyl and C-6 alkylidene unit in the preparation of allopumiliotoxin 267A would provide an important contribution to this field.

With this plan in mind, oxazolidinone **5** was conveniently prepared from L-proline methyl ester by the Overman procedure (Scheme 1).[8c] Oxazolidinone hydrolysis with KOH in ethanol followed by propargylation with enantiopure bromide **6** afforded substrate **7** in 74% yield for the two-step conversion. Benzylation of the tertiary hydroxyl followed by primary hydroxyl deprotection and oxidation led to cyclization substrate **10** in high yield. Aldehyde **10** 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 **11** as a single diastereomer in 95% yield. Careful inspection of the crude 500 MHz 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.

We speculate that the reaction mechanism of the nickel-catalyzed process proceeds by oxidative cyclization to oxametallacycle **13** via a *cis*-hydrindane conformation (Scheme 2).[12] Sigma bond metathesis of triethylsilane and the nickel/oxygen bond of **13** would afford nickel hydride **14**, which would directly afford the observed product **11** upon CH bond reductive elimination. The involvement of highly organized oxametallacycles could explain the high levels of diastereoselectivity obtained in the pumiliotoxin series as well as in the simpler model systems (Table 1). Although we are unaware of any examples of sigma bond

Scheme 2



metathesis involving a nickel/oxygen bond and a silicon/hydrogen bond, other classes of sigma bond metatheses involving late transition metals have been reported.[7e,13] Interestingly, Ojima reported that a $Rh_2Co_2(CO)_{12}$-catalyzed hydrosilylation with cyclization of ynals afforded cyclic vinylsilanes rather than silyl ethers, with a complete reversal of the regiochemistry noted in the nickel-catalyzed process.[14] To examine the possibility that alkyne hydrometalation followed by addition to the aldehyde was involved, a competition experiment was carried out. A 1:1:1 mixture of aldehyde **10**, SEM-protected substrate **8**, and triethylsilane in THF was treated with $Ni(COD)_2/PBu_3$. After 16 h at 0 °C, an 85% yield (based on **10**) of cyclized product **11**, a 15% yield of recovered aldehyde **10**, and a quantitative recovery of ether **8** were obtained. Furthermore, substrate **8** was recovered unchanged after extended exposure to $Ni(COD)_2$, PBu_3, and Et_3SiH at elevated temperatures. A similar competition experiment between aldehyde **10** and heptaldehyde afforded high yields of cyclized product **11** with no evidence for reduction of heptaldehyde. These results appear to be most consistent with an oxametallacycle mechanism in which the cooperative influence of both an aldehyde and an alkyne component is required for a reaction to occur.

In conclusion, a new method for the reductive cyclization of ynals has been developed. The method was demonstrated to be efficient and highly stereoselective in the preparation of a variety of quinolizidine, indolizidine, and pyrrolizidine alkaloids. A total synthesis of (+)-allopumiliotoxin 267A was carried out which highlights the utility of nickel-catalyzed ynal cyclizations in complex synthetic strategies.

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Supporting Information Available: Experimental procedures 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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