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ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE PUMILIOTOXIN A ALKALOIDS VIA REDUCTIVE IMINIUM ION-ALKYNE CYCLIZATIONS. TOTAL SYNTHESIS OF (+)-PUMILIOTOXIN A

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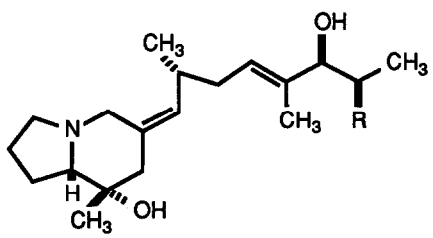
Summary: *A highly practical new route for the enantioselective synthesis of the pumiliotoxin A alkaloids in which the title reaction is a key step is disclosed.*

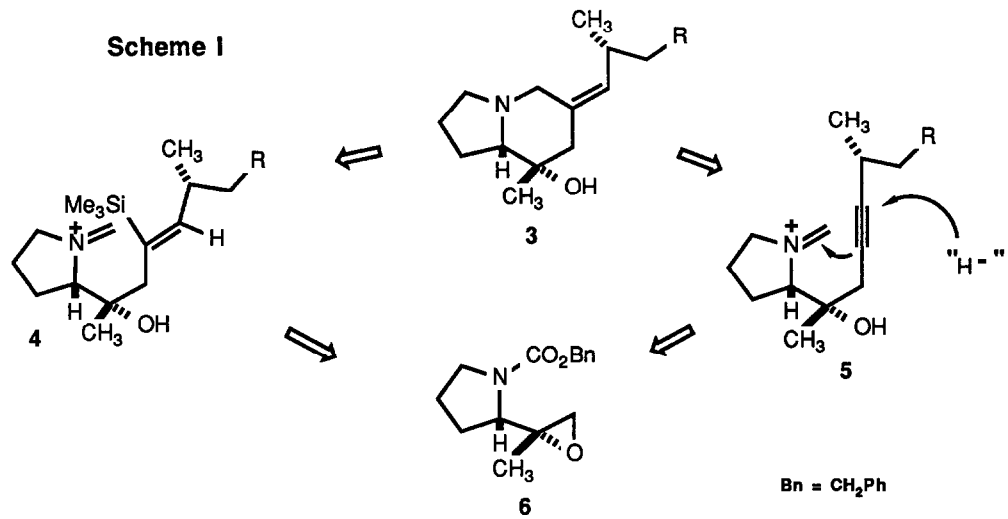
Pumiliotoxin B (**2**) and congeneric alkaloids[1] display marked cardiotonic activity,[2] which in guinea pig atrial preparations is markedly dependent on the nature of the 6-alkylidene side chain.[2bd] Recent studies[2cd,3] indicate that activation of sodium channels and the resulting stimulation of phosphatidylinositol breakdown plays a role in the cardiotonic activity of these alkaloids. Since their effect on membrane sodium channels is similar to that of pyrethroid insecticides,[4] there is considerable current interest also in these alkaloids as models for developing new insecticides.



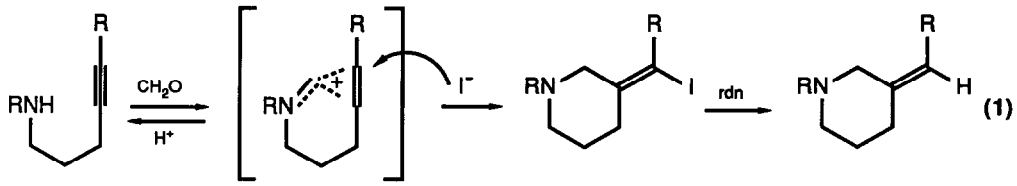
R = H pumiliotoxin A (**1**)
R = OH pumiliotoxin B (**2**)

We have previously detailed[5] a general approach to the pumiliotoxin A alkaloids which involves, in the key step, a stereospecific iminium ion-vinylsilane cyclization (see Scheme I, **4** → **3**). A weakness of this approach is the preparation of the amine precursor of **4** from the coupling of epoxide **6** (derived from *L*-proline) with an α-silyl vinyl anion, since this step is extremely sensitive to experimental details and requires special optimization for every side chain nucleophile. In this Letter we report an alternate cyclization strategy in which the *Z* stereochemistry of the alkylidene side chain evolves from the antarafacial stereochemistry of a "reductive" iminium ion-alkyne cyclization (Scheme I, **5** → **3**). A significant advantage of this approach is the ready availability of the alkynyl pyrrolidine cyclization substrate (amine precursor of **5**) from the coupling of an alkynyl nucleophile with epoxide **6**. The

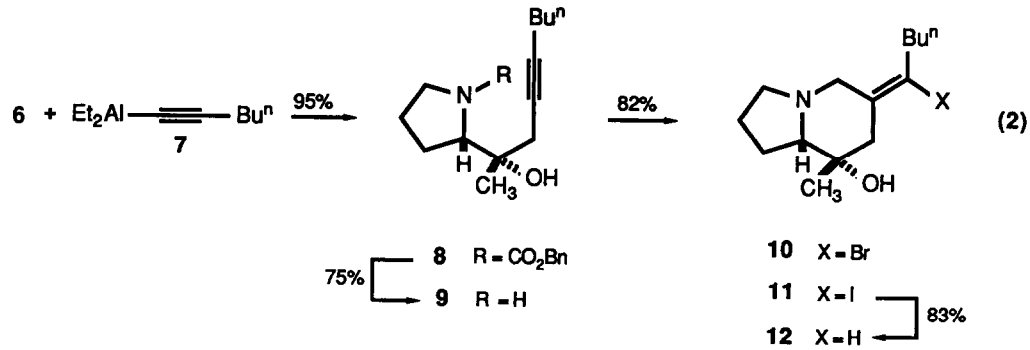
Scheme I



conceptual basis for this new approach is the two step sequence outlined in eq 1, which accomplishes net antarafacial addition of an internal iminium cation and an external hydride anion to an alkyne. This useful method stems from our recent discovery[6] that simple alkynes, although unreactive with intramolecular iminium ions in non-nucleophilic environments, cyclize stereoselectively with these weak electrophiles when iodide, or other strong carbon nucleophiles are present.

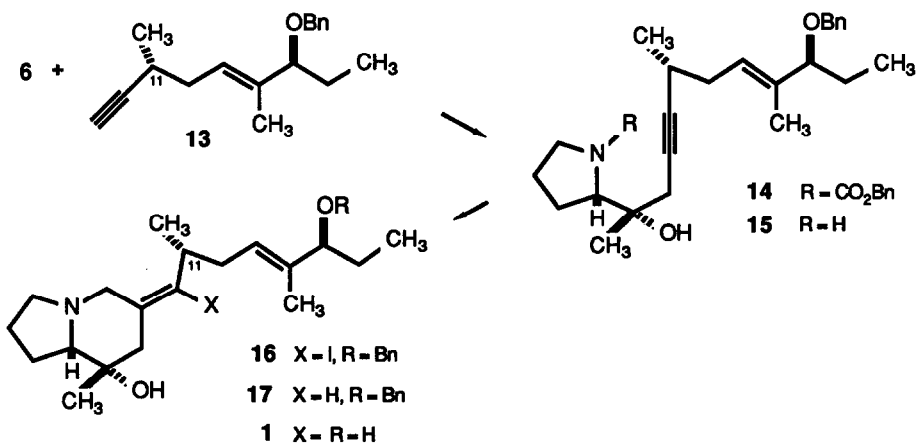


Since Fried had previously demonstrated[7] that alkynylalanes are excellent reagents for opening epoxides, the reaction of epoxide **6** with diethyl(1-hexynyl)alane (**7**) was examined for assembling the model cyclization precursor **9** (see eq 2). This reaction occurred cleanly at 0°C (100 mg/mL in 7:1 toluene-hexane, 2 equiv of **7**) to provide the desired coupled product **8**[8] in >90% yield. Initial attempts to cleave the benzyloxycarbonyl group of **8** with a variety of standard reagents were not rewarding.[9] However, the desired deprotection was accomplished using 0.15 *M* $Ba(OH)_2$[10] (reflux for 40 h in 3:2 glyme-H_2O) to afford the desired alkynyl amine **9**[8] in 75% yield. Cyclization of the formaldiminium ion derived from **9** (5 equiv of paraformaldehyde, 1 equiv of camphorsulfonic acid, CH_3CN, 100°C, 1 h) in the presence of 5 equiv of $(n\text{-}Bu)_4NBr$ gave the bromo alkylidene indolizidine **10**[8] in 58% yield. The desired cyclization was more efficiently accomplished under aqueous conditions (50 mg/mL, 100°C, 1 h) in the presence of 10 equiv of NaI to provide the corresponding vinyl iodide **11**[8] in 82% yield. The stereoselectivity of both cyclizations was complete to limits of detection by 300 MHz ^1H NMR and capillary GC. Treatment of **11** (75 mg/mL) with n-BuLi (2.2 equiv, -78°C, ether) followed by quenching with methanol provided nor-11-methylpumiliotoxin **237A (12)**[11] in 83% yield.



(2)

Pumiliotoxin A (**1**), the parent alkaloid of the pumiliotoxin A class, was efficiently prepared in a similar fashion (see eq 3). Thus, successive treatment of optically active alkyne **13**[12] (90 mg/mL in toluene, a 5:1 mixture of C-11[12b] epimers) at 0°C with 1 equiv of n-BuLi (2.1 *M* in hexane), 1 equiv of Et_2AlCl (1.8 *M* in toluene) and after 1 h with 0.5 equiv of epoxide **6** (240 mg/mL in toluene, 0°C, 15 min) afforded the desired coupled product **14**[8,12b] in 95% yield.[13] Since unreacted alkyne **13** is recovered quantitatively during chromatographic purification of **14**, this coupling step is accomplished in excellent yield with the net use of **stoichiometric quantities** of side chain and epoxide. Hydrolysis of carbamate **14**, as in the model series, with 0.15 *M* $Ba(OH)_2$ (50 h at reflux in 5:3 glyme-H_2O) followed by iodide-promoted iminium ion cyclization in H_2O (**15** 40 mg/mL, 1.2 equiv of camphorsulfonic acid, 2 equiv of paraformaldehyde, 12 equiv of NaI, 100°C, 1 h) provided, after chromatographic purification on silica gel, the isomerically pure alkylidene indolizidine **16**,[8] $[\alpha]_D$ -16.0 (c 1.04, $CHCl_3$), in 60% yield. The yield for the cyclization step was >75%, since 15% of 11-epi-**16**, which is derived from the minor diastereomer[12] of alkyne **13**, was also isolated. Deiodination of **16** (70 mg/mL, 3 equiv n-BuLi, ether, -78°C; CH_3OH quench) provided **17**, which was deprotected, as previously described,[5c] to afford (+)-(15*S*)-pumiliotoxin A[11], $[\alpha]_D$ + 14.9° (c 0.65, $CHCl_3$)[14], in 75% overall yield from **16**.



(3)

This report demonstrates the utility of nucleophile-promoted[6a] iminium ion-alkyne cyclizations for the synthesis of pumiliotoxin A alkaloids. Using this approach, (+)-pumiliotoxin A of high enantiomeric purity[14] was prepared in 5 steps and 43% overall yield from the readily available[5] intermediates **6** and **13**. The experimental simplicity of this sequence and the fact that the side chain is consumed stoichiometrically in the coupling step combine to make this sequence a highly *practical* method for preparing the pumiliotoxin A alkaloids and related analogs.

Acknowledgment. This investigation was supported by PHS Grant HL-25854. NMR and mass spectra were determined at Irvine with spectrometers purchased with the assistance of NSF Shared Instrumentation Grants.

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7. Fried, J.; Lin, C.H.; Ford, S.H. *Tetrahedron Lett.* **1969**, 1379. Fried, J.; Lin, C.H.; Sih, J.C.; Dalven, P.; Cooper, G.F. *J. Am. Chem. Soc.* **1972**, *94*, 4342.

8. New compounds showed ^{1}H NMR, ^{13}C NMR, IR, and high resolution mass spectra consistent with their assigned structures. Yields refer to isolated product purified by chromatography.

9. Many of the reagents examined (Me_3SiI, BBr_3, Me_2BBr, BF_3/EtSH, $AlCl_3$/EtSH, MeLi/LiBr, KOH/EtOH) caused partial destruction of the alkyne.

10. Bailey, T.R.; Garigipati, R.S.; Morton, J.A.; Weinreb, S.M. *J. Am. Chem. Soc.* **1984**, *106*, 3240.

11. This product was identical with material prepared by our earlier[5] synthesis.

12. (a) Prepared in 96% yield from the corresponding[5c] 1,1-dibromoalkene (e.e. 94-97%) by successive treatment with n-BuLi and CH_3OH. (b) This sample was a 5:1 mixture of epimers at the propargylic carbon (C-11, using the numbering system of pumiliotoxin A).

13. This step can be accomplished in 74-78% yield using 1.4 equiv of alkyne **13**.

14. Pumiliotoxin A isolated from *Dendrobates pumilio*, which is a 2:1 mixture of C-15 epimers, shows[1a,5c] the following optical rotation: $[\alpha]_D$ + 14.2° (c 0.51, $CHCl_3$).

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