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A new synthetic approach to dendrobatid alkaloids

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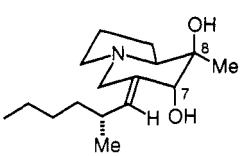
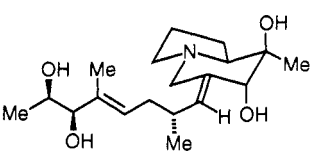
Abstract: A remarkably high regio- and stetreoselective approach for the syntheses of (+)-allopumiliotoxin alkaloids 267A and 339A based on intramolecular nickel(II)/chromium(II)-mediated ring closure has been developed.

South American poison-dart frogs of the family Dendrobatidae have been a rich source of various structurally unique alkaloids.[1] Virtually all of these alkaloids possess high pharmacological activity on nerve and muscle. After the early discovery of four classes of dendrobatid alkaloids that are of the pumiliotoxin C class, the histrionicotoxins, gephyrotoxins, and batrachotoxins, new members of the pumiliotoxin A class and their allo series were isolated and structurally defined.[2] The latter subclass of alkaloids, the allopumiliotoxins, is a group of hydroxy congeners of the pumiliotoxin A class and they are the most complex members of the pumiliotoxin A alkaloid group.[3] For several years, research efforts in our laboratory have been directed toward the development of chiral methods for the total syntheses of dendrobatid alkaloids.[4] This article is concerned with the highly regio- and stereocontrolled approach to (+)-allopumiliotoxins 267A (**1**) and 339A (**2**).

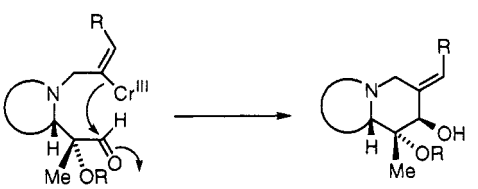


(+)-Allopumiliotoxin 267A (**1**)



(+)-Allopumiliotoxin 339A (**2**)

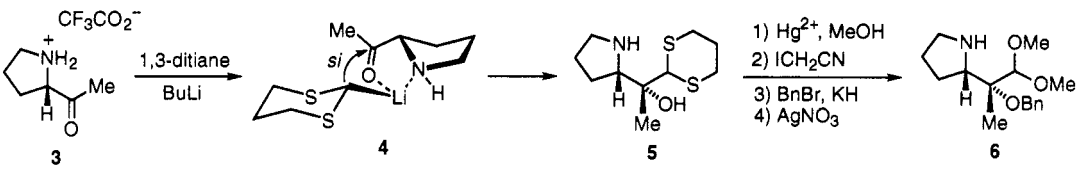
As revealed by the structures shown above, the synthesis of these alkaloids **1** and **2** poses two fundamental problems: (1) the introduction of the axially oriented vicinal dihydroxy groups at C-7 and C-8 to the indolizidine ring and (2) the construction of an exocyclic (*E*)-alkene. To overcome these problems, we envisioned to utilize an intramolecular alkenyl metal approach based on a chromium-mediated coupling reaction[5] in the last step.



3 **4**

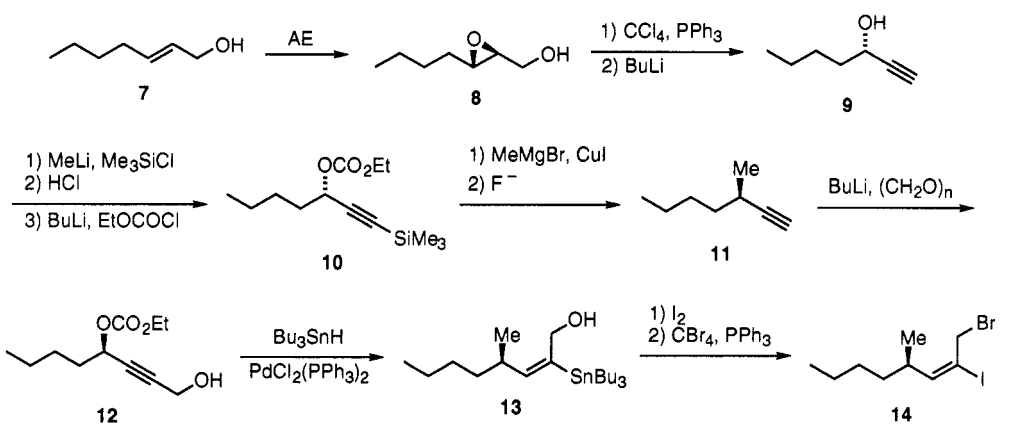
Total Synthesis of (+)-Allopumiliotoxin 267A

We initially targeted the enantioselective approach to the synthesis of (+)-allopumiliotoxin (**1**) by application of the chromium-mediated cyclization mentioned above. To this end, our efforts were directed toward the preparation of the cyclization substrate, which could be disconnected to give the pyrrolidine and side-chain segments. The required pyrrolidine segment **6** was prepared from the trifluoroacetate salt of (*S*)-2-acetylpyrrolidine (**3**) as outlined in Scheme I. Thus, **3** was treated with 2-lithio-1,3-dithiane to produce the tertiary alcohol **5** as a single diastereomer with generation of the desired chirality according to Cram's cyclic model (Scheme I). After acetal exchanging and N-protection by the cyanomethyl group, O-benzylation of the tertiary alcohol (BnBr, KH) followed by de-N-blocking ($AgNO_3$) was carried out to form the pyrrolidine segment **6**.



Scheme I

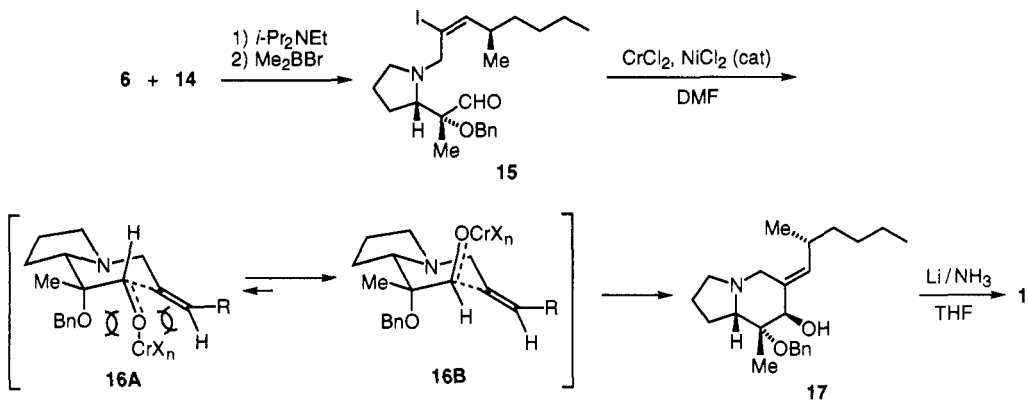
We next turned our attention to elaboration of the alkene side-chain as shown in Scheme II. Asymmetric epoxidation of 2-hexenol (**7**) using diethyl L-tartrate gave the epoxide **8**, which was converted to (*S*)-1-heptyn-3-ol (**9**) under the conditions developed in Takano's laboratory.[6] Following the use of Overman's method,[7] the heptynol **9** was converted to the (*R*)-alkyne **11**, which underwent hydroxymethylation with BuLi and paraformaldehyde to afford the propargy alcohol **12**. Construction of the requisite *E* geometry **13** was successfully achieved by applying stereospecific syn addition to **12** utilizing palladium-catalyzed hydrostannation. Subsequent iododestannation with iodine followed by bromination (CBr_4 and PPh_3) yielded the requested (*E*)-iodoalkenyl segment **14.**



Scheme II

Coupling of the two segments **6** and **14** followed by acetal cleavage afforded (*E*)-iodoalkenyl aldehyde **15**. Intramolecular Ni(II)/Cr(II)-mediated cyclization of **15** smoothly proceeded through the alkenylchromium(III) intermediate **16**, exclusively giving rise to **17** with the required axial C-7 hydroxy group (Scheme III). The extremely high degree of diastereoselectivity in this process can be explained by the chair-like transition state **16B**, in which the benzyloxy and chromium(III) alkoxide groups must

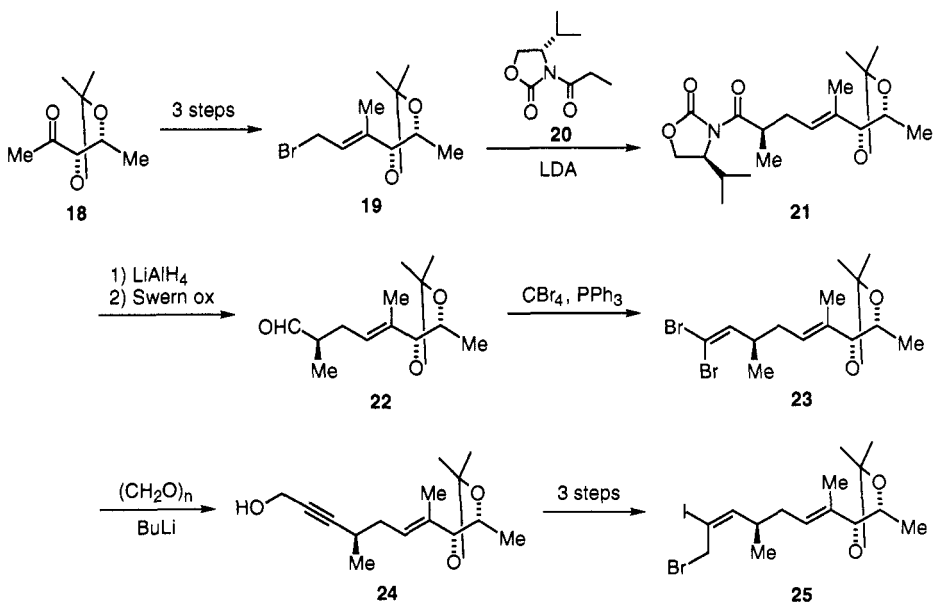
be antiperiplanar to avoid an unfavorable allylic 1,3-strain between the quasiequatorial chromium alkoxide and the olefin and, more importantly, a steric/polar effect between the benzyloxy group and the chromium alkoxide group bearing a partial negative charge. These interactions are matched in destabilizing the alternative equatorial predictable conformer **16A**. Completion of the synthesis of (+)-allopumiliotoxin (**1**) was accomplished via reductive cleavage of the benzyl group of **17** under the Birch conditions.



Scheme III

Total Synthesis of (+)-Allopumiliotoxin 339A

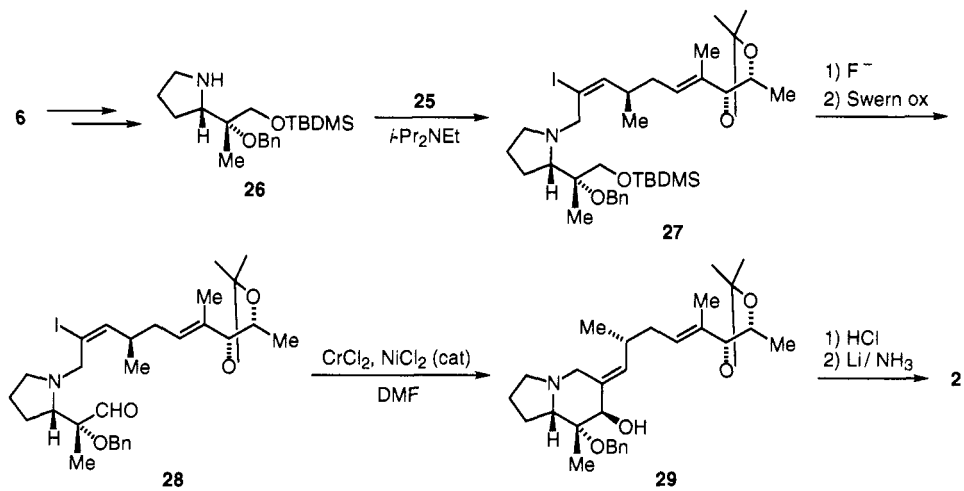
We further investigated extension of the above convergent strategy to the preparation of allopumiliotoxin 339A (**2**). Toward this end, the sequence began with the elaboration of the side-chain segment **25** as depicted in Scheme IV. Thus, the methyl ketone **18** was transformed into the allyl bromide **19** in a straightforward manner involving Horner–Emmons condensation. Evans alkylation of the (*S*)-oxazolidone derivative **20** with **19** provided **21** with virtually complete diastereoselection. After



Scheme IV

reductive removal of the oxazolidone auxiliary on **21** with $LiAlH_4$, the resulting aldehyde **22** was converted to the propargyl alcohol **24** as outlined in Scheme IV. In a manner similar to that described above for the preparation of **14**, **24** was converted to the (*E*)-alkylidene segment **25** in three steps in stereospecific and highly regioselective manners.

The alkylidene segment **25** was coupled with the pyrrolidine segment **26**, available from **6**, to give **27**, which was converted to the (*E*)-iodoalkenyl aldehyde **28** as summarized in Scheme V. On treatment of **28** with Ni(II)/Cr(II), intramolecular coupling proceeded smoothly to give exclusively **29**. The same stereochemical argument as described for **16** should hold for this process. Sequential removal of the isopropylidene and benzyl protecting groups provided (+)-allopumiliotoxin (**2**).



Scheme V

REFERENCES

1. J. W. Daly and T. F. Spande, In *Alkaloids: Chemical and Biological Perspectives*, S. W. Pelletier, Ed., Vol. 4, pp. 1–274, Wiley-Interscience, New York (1986).
2. (a) J. W. Daly, T. Tokuyama, T. Fujisawa, R. J. Hight, and I. L. Karle, *J. Am. Chem. Soc.*, **102**, 830 (1980). (b) T. Tokuyama, J. W. Daly, and R. J. Hight, *Tetrahedron*, **40**, 1183 (1984). (c) T. Tokuyama, T. Tsujita, H. M. Garraffo, T. F. Spande, and J. W. Daly, *ibid.*, **47**, 5415 (1991).
3. For total syntheses of allopumiliotoxins, see: (a) L. E. Overman and S. W. Goldstein, *J. Am. Chem. Soc.*, **106**, 5360 (1984). (b) B. M. Trost and T. S. Scanlan, *ibid.*, **111**, 4988 (1989). (c) L. E. Overman, L. A. Robinson, and J. Zablocki, *ibid.*, **114**, 368 (1992). (c) S. W. Goldstein, L. E. Overman, and M. Rabinowitz, *J. Org. Chem.*, **57**, 1179 (1992).
4. (a) N. Yamazaki and C. Kibayashi, *J. Am. Chem. Soc.*, **111**, 1396 (1989). (b) Y. Shishido and C. Kibayashi, *J. Org. Chem.*, **57**, 2876 (1992). (c) N. Machinaga and C. Kibayashi, *ibid.*, **57**, 5178 (1992).
5. (a) K. Takai, K. Kimura, T. Kuroda, T. Hiyama, and H. Nozaki, *Tetrahedron Lett.*, **24**, 5281 (1983). (b) K. Takai, M. Tagashima, T. Kuroda, K. Oshima, K. Utimoto, and H. Nozaki, *J. Am. Chem. Soc.*, **108**, 6084 (1986). (c) H. Jin, J. Uenishi, W. J. Christ, and Y. Kishi, *ibid.*, **108**, 5644 (1986).
6. S. Takano, K. Samizu, K. Sugihara, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1344 (1989).
7. L. E. Overman, L. B. Kenneth, and F. Ito, *J. Am. Chem. Soc.*, **106**, 4192 (1984).