Obviously these results limit the applicability of phosphoryl nitrene insertion reactions in directed intramolecular functionalizations, but they do suggest that these nitrenes could be particularly useful as unbiased probes of the environment. Most interstingly, they reveal the limits of transition-state theory in dealing with highly reactive species in solution, in which collision with solvent is more frequent but intramolecular chemistry would be entropically favored. In such cases, the predictions of collision theory are better guides.

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## Enantioselective Total Synthesis of Allopumiliotoxin A Alkaloids 267A and 339B

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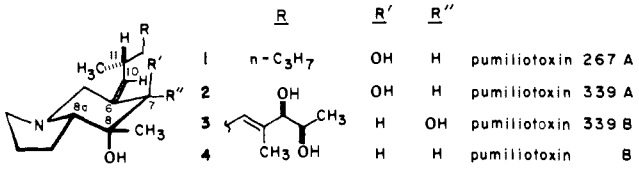
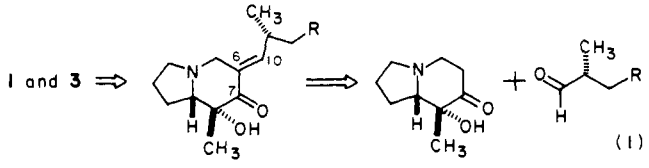
A large variety of pumiliotoxin A alkaloids have been isolated by Daly and co-workers from defensive secretions of neotropical frogs of the species Dendrobatidae.[1-3] The most complex members of this class are the allopumiliotoxins, which contain a hydroxyl group at C-7 of the indolizidine ring. Representative of this group are allopumiliotoxins 267A (**1**), 339A (**2**), and 339B (**3**), the latter




two of which differ[2] from pumiliotoxnin B (**4**)[1,4] only by the appearance of the C-7 hydroxyl group. Stimulated by the marked cardiac activity of members of both the normal and allo classes of pumiliotoxin A alkaloids,[5] we have explored chemical routes to the allopumiliotoxins. Herein we report the first synthetic entry to the allopumiliotoxin A alkaloids. Specifically, we describe enantioselective syntheses of (+)-allopumiliotoxin 267A and (+)-allopumiliotoxin 339B by convergent routes of potentially broad applicability. These syntheses introduce a useful method for generating enantiomerically pure secondary $\alpha$-amino ketones and show that these intermediates react with organolithium reagents stereoselectively *without* racemization.

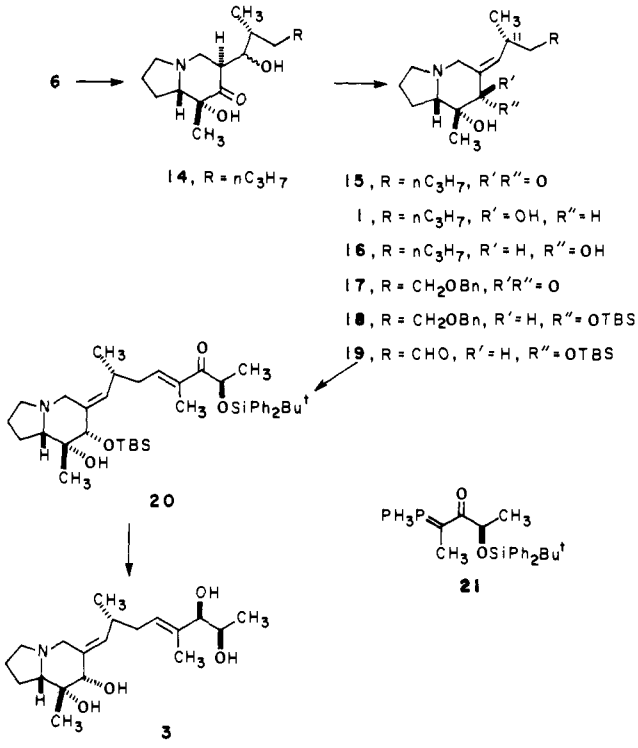
Our general synthesis plan is outlined in eq 1. The thermo-



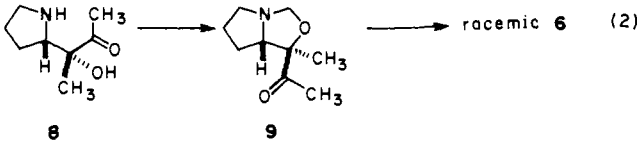

(1)

dynamic preference for enone **5** to adopt an *E* configuration is the key strategic element in controlling the stereochemistry of the alkylidene side chain.[7]

**Scheme I**




We first explored the preparation of indolizidinone **6** by Mannich cyclization of enantiomerically pure[8a] amino ketone **8**[9-11] (eq 2). Treatment of **8** with paraformaldehyde or formalin under




(2)

a variety of Mannich conditions failed to produce **6** and yielded only the stable cyclopentaoxazolidine **9**.[10] Under forcing conditions (2 equiv TsOH, toluene, 110 °C), **6** was produced in low yield, however, in completely racemic[8b] form. The intramolecular Mannich reaction could be accomplished in 52% overall yield by a new procedure of potential general utility involving treatment of the trimethylsilyl enol ether of **9** with trimethylsilyl trifluoromethanesulfonate[12] (1.1 equiv) at −22 °C (2.5 h, $CH_2Cl_2$, quench with $Et_3NHF$). Remarkably, **6** produced in this manner was again completely racemic. We suggest that this facile racemization may occur via cationic aza-Cope equilibration of an iminium ion intermediate.[13]

(1) Reviews: (a) Daly, J. W. *Prog. Chem. Org. Nat. Prod.* **1982**, *41*, 205. (b) Witkop, B.; Gössinger, E. In "The Alkaloids"; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 21, Chapter 5.

(2) Tokuyama, T.; Daly, J. W.; Highet, R. J. *Tetrahedron* **1984**, *40*, 1183.

(3) These alkaloids have been characterized recently also in nondendrobatid frogs: Daly, J. W.; Highet, R. J.; Myers, C. W. *Toxicon*, in press.

(4) To date, pumiliotoxin B has been the focus of most biological[1,5] and synthetic studies[6] in this area.

(5) Albuquerque, E. X.; Warnick, J. E.; Maleque, M. A.; Kauffman, F. C.; Tamburni, R.; Nimit, Y.; Daly, J. W. *Mol. Pharmacol.* **1981**, *19*, 411. Daly, J. W.; McNeal, E. T.; Overman, L. E.; Ellison, D. H., submitted for publication.

(6) (a) The stereostructure and absolute configuration of (+)-pumiliotoxin B has been confirmed by our recent enantioselective total synthesis.[6b] (b) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192.

(7) For an alternate "kinetic" solution to the demanding problem of exocyclic stereochemistry posed by these natural products, see ref 6b.

(8) Enantiomeric purity was determined by 250-MHz $^1H$ NMR analysis of (a) the corresponding (+)-MTPA amide (Mosher, H. S.; Dale, J. A.; Dull, D. L. *J. Org. Chem.* **1969**, *34*, 2543) or (b) the sample in the presence of the optically active shift reagent $Eu(tfc)_3$.

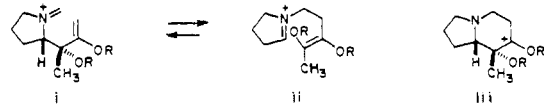
(9) Prepared[10] in six steps (16% overall yield) from L-proline: (1) BnBr (2.0 equiv), $K_2CO_3$, DMF, 23 °C; (2) $H_2$, Pd–$BaSO_4$, EtOH; (3) MeLi (2.1 equiv), $Et_2O$, 40 °C; (4) $CH_2$=C(OEt)Li, −78 °C, THF, diastereoselectivity = 2.4:1; (5) 0.25 M HCl, THF–$H_2O$, 0 °C; (6) $H_2$, Pd–C, HCl–EtOH, 23 °C.

(10) Isolated and purified intermediates showed correct molecular compositions (combustion analysis or high-resolution MS) and appropriate IR, NMR, and mass spectra.

(11) Goldstein, S. W. Ph. D. Thesis, University of California, Irvine, 1984.

(12) The related bimolecular reaction of aminomethyl ethers has been described: Hosomi, A.; Iijima, S.; Sakurai, H. *Tetrahedron Lett.* **1982**, *23*, 547.

(13) The suggested equilibration of i and ii may proceed via iii.

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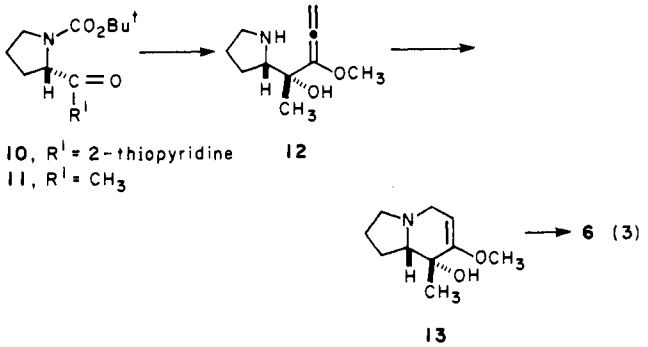
Indolizidinone **6** was successfully prepared in high enantiomeric purity by the sequence outlined in eq 3. Conversion of *N*-



**10**, $R^1$ = 2-thiopyridine **12**
**11**, $R^1$ = $CH_3$



**13**

BOC-L-Pro to thioester **10**[10] and subsequent reaction with $LiMe_2Cu$ provided methyl ketone **11**[10] (mp 38 °C; $[\alpha]_D$ −57.8°, *c* 4.3, $CHCl_3$) in 70% yield. Treatment of **11** with $CF_3COOH$ (23 °C, anisole, $CH_2Cl_2$) followed by concentration and immediate reaction (−78 °C, THF) of the resulting trifluoroacetate salt with 5 equiv of 1-lithio-1-methoxyallene[14] afforded **12** as the only detectable product. This extremely labile adduct, which results from cyclic-Cram diastereoselectivity, could not be purified without extensive decomposition. However, treatment of crude **12** with slightly less than 1 equiv of dry *p*-toluenesulfonic acid ($CH_3CN$, 23 °C) gave the bicyclic enol ether **13**[10] (mp 76–77 °C) in 35–40% overall yield from **11**. Hydrolysis of **13** (5% HCl, 23 °C) provided indolizidinone **6**[10] ($[\alpha]^{25}_D$ −44.2°, *c* 4.7 $CHCl_3$; >95% ee[8b]) in 76% yield.

The alkylidene side chain was introduced in the following fashion (see Scheme I). Conversion of **6** to its lithium dianion ($Ph_3CLi$, $Et_2O$, 0 °C) followed by reaction with (*R*)-2-methylhexanal[15] (0 °C, 5 min) gave a ~1:1 mixture of two major aldol diastereomers **14**.[16] Direct dehydration [$(CF_3CO)_2O$, DBU, DMAP, 0 °C][17] of this mixture gave **15**[10] ($[\alpha]^{25}_D$ −6.5°, *c* 1.1, $CHCl_3$) as the major product in 41% overall yield from **6**.[18] Reduction of **15** with $NaBH_4$–$CeCl_3$[19] produced the equatorial alcohol **16**[10,20] in essentially quantitative yield. Similar stereoselectivity was seen with a variety of other hydride reducing agents. Reduction of **15** with $LiAlH_4$ (0 °C, THF) provided a 6:1 mixture of **16** and **1**, from which pure (+)-allopumiliotoxin 267A ($[\alpha]^{25}_D$ +12.8°, *c* 0.1, MeOH) could be isolated in low yield.[21]

The more complex allopumiliotoxin 339B (**3**) was prepared in a related fashion. An aldol-dehydration sequence identical with that described above provided enone **17**[10] ($[\alpha]_D$ −16.0°, *c* 4.2, MeOH) in 37% overall yield from **6** and (*R*)-4-(benzyloxy)-2-methylbutanal.[15] Reduction ($NaBH_4$–$CeCl_3$,[19] 58% yield) of **17** followed by selective protection (BuLi, HMPA, −78 °C; excess *t*-$BuMe_2SiCl$; 49% yield) of the resulting secondary alcohol provided **18**.[10] This intermediate was converted to aldehyde **19** (83% yield) and treated with the enantiomerically pure ylide **21**[6b] to provide the (*E*)-enone **20**[10] ($[\alpha]^{25}_D$ −1.8°, *c* 0.4, MeOH; 55% yield) by a sequence identical with the one we had previously employed[6b] to prepared **4**. Threo-selective reduction of **20** ($LiAlH_4$, −20 °C)[6b,24] followed by desilylation[6b] afforded (+)-allopumiliotoxin 339B (**3**) ($[\alpha]^{25}_D$ + 8.8°, *c* 1.0, MeOH) in 49% yield after chromatographic purification.[25]

The total syntheses recorded here confirm the stereostructures and absolute configurations of allopumiliotoxins 267A and 339B, which had previously been assigned[2] on the basis of spectroscopic data alone. The synthetic sequence developed is concise, stereocontrolled, and potentially quite general. However, improvements in efficiency are required before useful amounts of the allopumiliotoxins could be secured in this manner for testing. Our investigations in this area are continuing.

**Acknowledgment.** We particularly thank Dr. J. W. Daly for comparison samples of **1** and **3** and Professor D. Evans for the complete experimental details for ref 15. This study was supported by PHS Grant HL-25854-02-06 and NSF instrumentation grants.

**Supplementary Material Available:** NMR spectra and spectroscopic and analytical data for **1**, **3**, **6**, **13**, **15**, and **18** (8 pages). Ordering information is given on any current masthead page.

(14) Brandsma, L.; Hoff, S.; Arens, J. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916.
(15) Conveniently prepared by using the chiral enolate chemistry of Evans: Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(16) A variety of other aldol conditions (e.g., variations in base, solvent, temperature and counterion) were found to be inferior. The presence of a secondary amine was clearly deleterious.
(17) Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310.
(18) None of the *Z* diastereomer of **15** was detected, although a trace amount (~5%) of the C-11 epimer of **15** was produced, and 27% of **6** was recovered unchanged. The C-11 epimer is believed to arise from the ~10% of enone formed directly in the aldol step. Identical condensation[11] of **6** with racemic 2-methylhexanal provided a 1:1 mixture of **15** and its C-11 epimer.
(19) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(20) An axial hydrogen at C-7 shows characteristic allylic coupling in the 250-MHz $^1H$ NMR spectrum: H-10 of **16** $\delta$ 5.47 (dt, $J_{10,11}$ = 9.9, $J_{5\beta,10}$ = $J_{7\beta,10}$ = 1.8 Hz), H-10 of **1** $\delta$ 5.34 (dd, $J_{10,11}$ = 9.7, $J_{5\beta,10}$ = 1.5 Hz).
(21) Synthetic **1** was identical with a natural sample[22] by TLC (three solvents), capillary GC, 250-MHz $^1H$ NMR, and 63-MHz $^{13}C$ NMR comparisons. A rotation at the sodium D line of +24.7° (*c* 0.17, MeOH) has been reported[2] for a very dilute sample of natural **1**.[23]
(22) Kindly supplied by Dr. J. Daly.
(23) Until more of this material is isolated from natural sources, the significance (if any) of the discrepancies observed in the rotations of the synthetic and natural allopumiliotoxins cannot be established.
(24) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355.
(25) Pumiliotoxin 339B is remarkably unstable to storage and only trace amounts of the natural alkaloid were available[22] for comparison. Synthetic **3** exhibited the same $R_f$ by TLC analysis (three solvents) as a natural sample, and all $^1H$ NMR signals (250 MHz) observed for synthetic **3** were seen in an identical spectrum of impure natural **3**. A rotation at the sodium D line of +4.4° (*c* 0.5, MeOH) has been reported[2] for a very dilute sample of natural **3**.[23]

## The $C_3H_4$ Surface

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Interconversions of the stable $C_3H_4$ isomers, methylacetylene, allene, cyclopropene, propenylidene, vinylmethylene, and cyclopropylidene are of considerable interest; these involve diradical formation, ring opening and closing, and various hydrogen shifts. In addition, they also serve as a model for much larger systems. Many experiments[1-3] and theoretical calculations[4-8] have been

(1) (a) Hutton, R. S.; Manion, M. L.; Roth, H. D.; Wessermann, E. *J. Am. Chem. Soc.* **1974**, *96*, 4680. (b) Palmer, G. E.; Bolton, J. R.; Arnold, D. R. *Ibid.* **1974**, *96*, 3708. (c) Chapman, O. L.; Chedekel, M.; Pacansky, J.; Rosenquist, N.; Roth, R.; Sheridan, R. S., unpublished results.
(2) (a) York, E. J.; Dittmar, W.; Stevenson, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 5680. (b) Bradley, J. H.; West, K. O. *J. Chem. Soc., Faraday Trans. 1* **1975**, *71*, 967. (c) Lifshitz, A.; Frenklack, M.; Burcat, A. *J. Phys. Chem.* **1975**, *79*, 1148. (d) Walsh, R. *J. Chem. Soc., Faraday Trans.* **1976**, *72*, 2137. (e) Bailey, I. M.; Walsh, R. *J. Chem. Soc., Faraday Trans. 1* **1978**, *74*, 1146. (f) Hopf, H.; Priebe, H.; Walsh, R. *J. Am. Chem. Soc.* **1980**, *102*, 1210.
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(4) (a) Hoffmann, R.; Zeiss, G. D.; Van Dine, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 1485. (b) Davis, J. H.; Goddard, III, W. A.; Bergman, R. G. *Ibid.* **1976**, *98*, 4015; **1977**, *99*, 2424. (c) Feller, D.; Borden, W. T.; Davidison, E. R. *J. Phys. Chem.* **1983**, *87*, 4833.
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(6) (a) Shaad, L. J.; Burnelle, L. A.; Dressler, K. P. *Theor. Chim. Acta* **1969**, *15*, 91. (b) Dykstra, C. E. *J. Am. Chem. Soc.* **1977**, *99*, 2060. (c) Staemmler, V. *Theor. Chim. Acta* **1977**, *45*, 89. (d) Rauk, A.; Drake, A. F.; Mason, S. F. *J. Am. Chem. Soc.* **1979**, *101*, 2284.

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