and DPO (k_1' = 1.85 (+), α = 1.31, Rs = 1.58) using a mixture of ethanol–water (70:30) as eluant.[10] However, in most cases, hexane–2-propanol mixtures were better eluants than ethanol–water mixtures, suggesting that the hydrogen bond and/or dipole–dipole interaction between the stationary phase and racemic compounds play an important role for chiral discrimination. All the packing materials were quite stable under the experimental conditions shown in Figure 1.[11] Phenylcarbamate[12] of β-cyclodextrin was also adsorbed on silica gel and employed as a chiral stationary phase using hexane–2-propanol (99:1) as eluant. No separation was observed with a UV detector, although partial separation was found with a polarimeter detector. This suggests that higher order structures of polysaccharides may be important for effective chiral discrimination.

The present results in addition to the previous one[5] indicate that the various derivatives of polysaccharides will provide useful chiral packing materials especially when they are coated on silica gel.

(10) The column was stable for at least 2 days in this eluant.

(11) The columns were not damaged by water present in hexane–2-propanol mixtures. The phenylcarbamates of low molecular weight may be soluble in ethanol–water mixtures.

(12) This was prepared in the same manner as in the cases of polysaccharides. Elemental analysis indicated that all hydroxy groups were converted into phenylcarbmate groups.

Loss of the Normal Intramolecular Preferential Reactivity with a Highly Nonselective Nitrene

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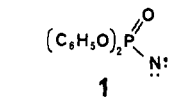
One of the striking successes of transition-state theory has been its explanation of the very high effective concentrations often observed with neighboring groups.[1] Reaction with a group within the same molecule is normally much faster than reaction with a chemically similar solvent; although collision frequencies with solvent molecules will generally be at least comparable to those with the neighboring group, intramolecular reactions are favored by the higher $\Delta S°$ in the activated complex. However, such effects should disappear if a highly reactive species is captured on almost every collision. Then collision frequencies ought to dominate the selectivity, since intrinsic to the idea of $\Delta S°$ is the reversibility of the formation of an activated complex. We have found behavior that seems to correspond to this prediction.

Some years ago[2] we described the photolysis of phosphorazidates to generate phosphorylnitrenes and the reaction of these nitrenes with hydrocarbon solvents. With 2-methylbutane, (diphenoxyphosphoryl)nitrene (**1**) showed a 3.4/1.2/1 preference for tertiary/secondary/primary hydrogens, making it the least selective nitrene known. For instance, (*tert*-butoxycarbonyl)nitrene shows a 160/9/1 preference.[3] However, in contrast to examples in which less selective nitrenes gave intramolecular attack on alkane chains in competition with attack on solvent,[4] we found in subsequent unpublished work[5] that our phosphorylnitrenes attacked only solvent. For example, photolysis of ethyl octyl phosphorazidate (**2**) in cyclohexane affords the cyclohexane nitrene insertion product in 86% yield, and hydrogen abstraction in 14% yield, but



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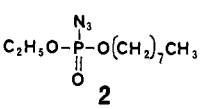

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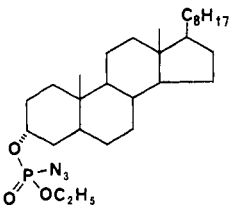

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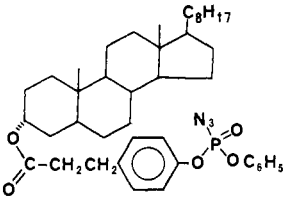

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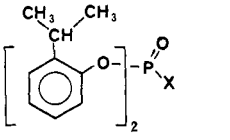
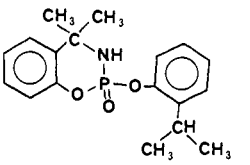


5 X = N_3
6 X = N:
7 X = NH
9 X = NH_2
10 X = NHPh



8

no detectable product from attack on the octyl chain. Even in CH_2Cl_2 or other chlorinated solvents no intramolecular product was detected, and the steroid derivatives **3** and **4** similarly underwent no steroid attack on photolysis. To explore the effect further, we have examined the nitrene **6** derived from bis(*o*-isopropylphenoxy) phosphorazidate (**5**).[6]

The most striking observation was that direct photolysis of **5** (with a medium-pressure Hg lamp and Vycor filter) in cyclohexane solution afforded the cyclohexane insertion product **7**[6] in ca. 70% yield but no detectable amount of the cyclization product **8**[6] or of any other identifiable product resulting from intramolecular reactions. The product of nitrene reduction **9**[6] was also formed in ca. 12% yield. Assays were by G/C calibrated with authentically prepared samples of **7**–**9**; products were also confirmed by isolation and NMR comparison. Photolysis of **5** in CH_2Cl_2 or in tert-butyl alcohol produced various products from solvent attack but no detectable amount (less than 5%) of cyclization product **8**. Thus the nitrene **6** attacks solvent molecules preferentially instead of reacting with the neighboring isopropyl groups.[7]

When a less reactive version of **6** is generated, some intramolecular attack is seen. For instance, photolysis of **5** in benzene solution affords an easily detectable 3% of **8**, along with the major product **10**[6] from reaction with the solvent. This probably reflects stabilizing solvation of nitrene **6** by the benzene; similar results are seen in 1,3,5-trifluorobenzene solvent. Most strikingly, thermolysis of the azide **5** in benzene for 87 h at 120 °C with 15% by weight of dirhodium tetrapivalate[8] affords a 52 ± 8% yield of the cyclization product **8**. Apparently the rhodium–nitrene complex, a nitrenoid, is sufficiently unreactive to show the "normal" preference for intramolecular reactions predicted by transition-state theory.

(1) Cf.: Page, M. I.; Jencks, W. P. *Proc. Nat. Acad. Sci. U.S.A.* **1971**, *68*, 1678.

(2) Breslow, R.; Feiring, A.; Herman, F. *J. Am. Chem. Soc.* **1974**, *96*, 5937.

(3) Cf.: Lwowski, W. "Nitrenes"; Wiley-Interscience: New York, **1979**; p 201.

(4) E.g.: Breslow, D. S.; Prosser, T. J.; Marcantoni, A. F.; Genge, C. A. *J. Am. Chem. Soc.* **1967**, *89*, 2384.

(5) For details, see: Herman, F. Ph.D. Thesis, Columbia University, 1975.

(6) All new compounds were synthesized by an unambiguous scheme and characterized by NMR and mass spectroscopy.

(7) It is hard to imagine a stereoelectronic preference that could explain the lack of intramolecular reaction for nitrenes derived from the entire set of compounds **2**–**5**. The distinction between singlet and triplet states for nitrenes can affect the relative yields of reduction vs. insertion products, but in our systems the striking finding is that the insertion reactions, characteristic of the singlet, prefer the solvent. This preference should in any case not be affected by multiplicity questions. When **5** was irradiated thru a Pyrex filter in cyclohexane with acetophenone as a triplet sensitizer, the principal product was **9**, from reduction of the nitrene, and neither **7** nor **8** could be detected.

(8) For the first report of a rhodium-catalyzed azide insertion reaction, see: Breslow, R.; Gellman, S. *J. Am. Chem. Soc.* **1983**, *105*, 6728.

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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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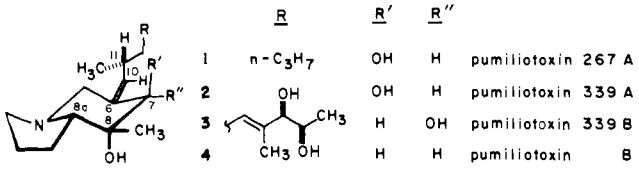
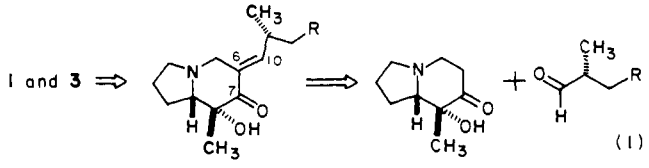
A large variety of pumiliotoxin A alkaloids have been isolated by Daly and co-workers from defensive secretions of neotropical frogs of the species Dendrobatidae.[1-3] The most complex members of this class are the allopumiliotoxins, which contain a hydroxyl group at C-7 of the indolizidine ring. Representative 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 α-amino ketones and show that these intermediates react with organolithium reagents stereoselectively *without* racemization.

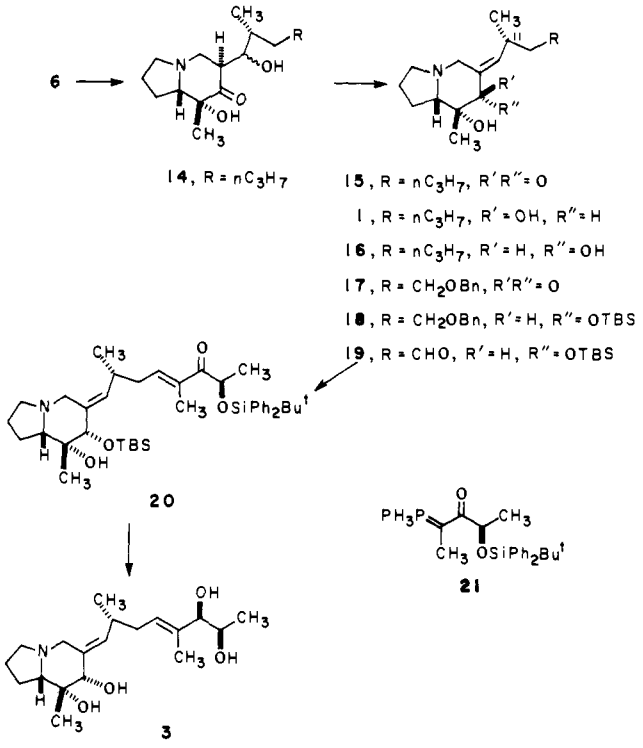
Our general synthesis plan is outlined in eq 1. The thermo-



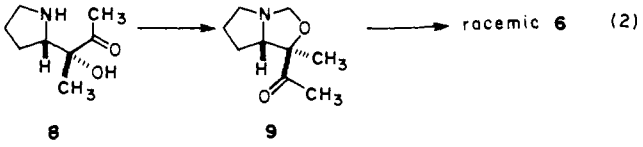
(1)

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 $Eu(tfc)_3$.

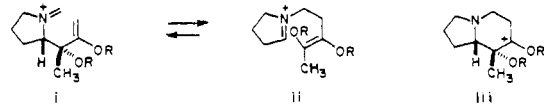
(9) Prepared[10] in six steps (16% overall yield) from L-proline: (1) BnBr (2.0 equiv), K_2CO_3, DMF, 23 °C; (2) H_2, Pd-$BaSO_4$, EtOH; (3) MeLi (2.1 equiv), Et_2O, 40 °C; (4) CH_2=C(OEt)Li, −78 °C, THF, diastereoselectivity = 2.4:1; (5) 0.25 M HCl, THF-H_2O, 0 °C; (6) H_2, Pd-C, HCl-EtOH, 23 °C.

(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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