Enantioselective Synthesis of Pumiliotoxin 251D. A Strategy Employing an Allene-Based Electrophile-Mediated Cyclization

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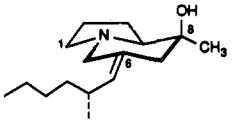
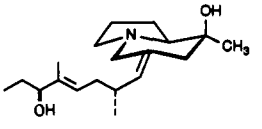
Abstract: The enantioselective synthesis of pumiliotoxin 251D (**1**) (nine steps, 6.3% overall yield) is described in which the Pd^{II}-mediated cyclization of the optically pure allenic amine **6** to give pyrrolidine **7a** plays a central role. The functionality that the allene moiety imparts to **7a** allows for rapid transformation to the enantiomerically pure bicyclic lactam **9**. A stereocontrolled aldol elimination sequence was carried out on **9** to establish the geometry of the exocyclic alkene of **1**.

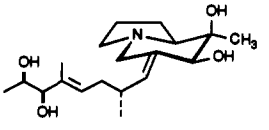
The neotropical "poison-arrow" frogs (family Dendrobatidae) are a rich source of a structurally varied and biologically significant group of alkaloids.[1,2] Those based on the oxygenated indolizidine framework, exemplified by pumiliotoxin 251D (**1**), pumiliotoxin A (**2**), and allopumiliotoxin 339B (**3**), have recently attracted



1, pumiliotoxin 251D



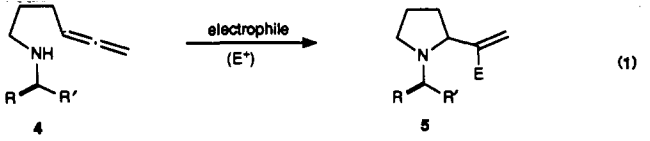
2, pumiliotoxin A



3, *allo*-pumiliotoxin 339B

interest owing to their ability to activate voltage-dependent sodium channels. Access to these materials for use as pharmacological probes is, however, reliant on the exploitation of a scarce natural resource and this limitation, together with the need to generate a range of structural analogues, has stimulated the development of comprehensive synthetic programs from the laboratories of Overman[3] and Trost.[4] Both groups have described the synthesis of key members of this family of alkaloids using various strategies based on (*S*)-proline and its subsequent elaboration to the substituted indolizidine skeleton. The contributions of Overman's group have been of particular significance and have underpinned the recent pharmacological advances that have been made in this area.

Our interest in this field has focused on the synthetic utilization of electrophile-mediated cyclizations incorporating an allene moiety as the π-component as outlined in eq 1.[5] Allenic substrates **4**

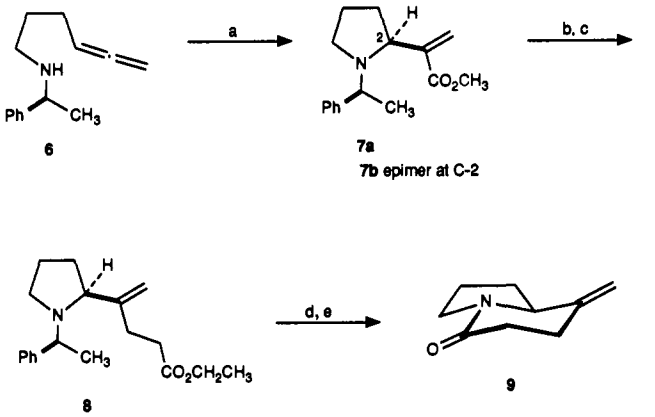


(1)

4 **5**

not only display reactivity toward a range of electrophiles under mild conditions but also provide a synthetically versatile alkenyl residue in the heterocyclic product **5**, a level of functionality that is not available via more conventional alkene-based methods.[6] In this paper, we describe the synthesis of pumiliotoxin 251D (**1**) with an emphasis on stereocontrol in the initial cyclization step

Scheme I. Synthesis of Indolizidine Lactam[a]



[a] (a) 1 mol % $PdCl_2$, CO, CH_3OH, $CuCl_2$; 80%, 1:1 mixture of **7a/b**; (b) Bu^i_2AlH, THF, −78 °C to rt; (c) $(EtO)_3CCH_3$, H^+, 155 °C; 93% from **7a**; (d) NaOH, MeOH; (e) $(CH_3CO)_2O$, 140 °C, 2 h; 76% from **8**.

and, by correct choice of the electrophilic trigger, the rapid elaboration of the indolizidine skeleton. The sequence described not only is efficient but also provides a practical application of the

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(1) (a) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, J. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1, pp 1–274. (b) Daly, J. W.; Myers, C. W.; Whittaker, N. *Toxicon* **1987**, *25*, 1023. (c) Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643. (d) Garraffo, H. M.; Edwards, M. W.; Spande, T. F.; Daly, J. W.; Overman, L. E.; Severini, C.; Erspamer, V. *Tetrahedron* **1988**, *44*, 6795.

(2) For biological studies relating to the pumiliotoxin alkaloids, see: (a) Daly, J. W.; Gusovsky, F.; McNeal, E. T.; Secunda, S.; Bell, M.; Creveling, C. R.; Nishizawa, Y.; Overman, L. E.; Sharp, M. J.; Rossignol, D. P. *Biochem. Pharmacol.* **1990**, *40*, 315. (b) Gusovsky, F.; Rossignol, D. P.; McNeal, E. T.; Daly, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 1272. (c) Daly, J. W.; McNeal, E. T.; Gusovsky, F.; Ito, F.; Overman, L. E. *J. Med. Chem.* **1988**, *31*, 477. (d) Daly, J. W.; McNeal, E. T.; Gusousky, F. *Biochim. Biophys. Acta* **1987**, *930*, 470. (e) Rao, K. S.; Warnick, J. E.; Daly, J. W.; Albuquerque, E. X. *J. Pharmacol. Exp. Ther.* **1987**, *243*, 775. (f) Daly, J. W.; McNeal, E. T.; Overman, L. E.; Ellison, D. H. J. *J. Med. Chem.* **1985**, *28*, 482. (g) Albuquerque, E. X.; Warnick, J. E.; Maleque, M. A.; Kauffman, F. C.; Tamburini, R.; Nimit, Y.; Daly, J. W. *Mol. Pharmacol.* **1981**, *19*, 411.

(3) (a) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192. (b) Overman, L. E.; Goldstein, S. W. *J. Am. Chem. Soc.* **1984**, *106*, 5360. (c) Overman, L. E.; Lin, N.-H. *J. Org. Chem.* **1985**, *50*, 3669. (d) Overman, L. E.; Lesuisse, D. *Tetrahedron Lett.* **1985**, *26*, 4167. (e) Overman, L. E.; Sharp, M. J. *Tetrahedron Lett.* **1988**, *29*, 901.

(4) Trost, B. M.; Scanlan, T. S. *J. Am. Chem. Soc.* **1989**, *111*, 4988.

(5) (a) Claesson, A.; Sahlberg, C.; Luthman, K. *Acta Chem. Scand. B* **1979**, *33*, 309. (b) Arseniyadis, S.; Gore, J. *Tetrahedron Lett.* **1983**, *24*, 3997. (c) Kinsman, R.; Lathbury, D.; Vernon, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1986**, 244. (d) Arseniyadis, S.; Sartoretti, J. *Tetrahedron Lett.* **1985**, *26*, 729. For reviews relating to electrophilic additions to allenes, see: Jacobs, T. L. In *The Chemistry of the Allenes*; Landor, S. R., Ed.; Academic Press: New York, 1982; Vol. 2, p 349. Smadja, W. *Chem. Rev.* **1983**, *83*, 263.

(6) (a) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 411. (b) Hegedus, L. S. *Tetrahedron* **1984**, *40*, 2415. (c) Gasc, M. B.; Lattes, A.; Perie, J. J. *Tetrahedron* **1983**, *39*, 703. (d) Cardillo, G.; Orena, M. *Tetrahedron* **1990** *46*, 3321.

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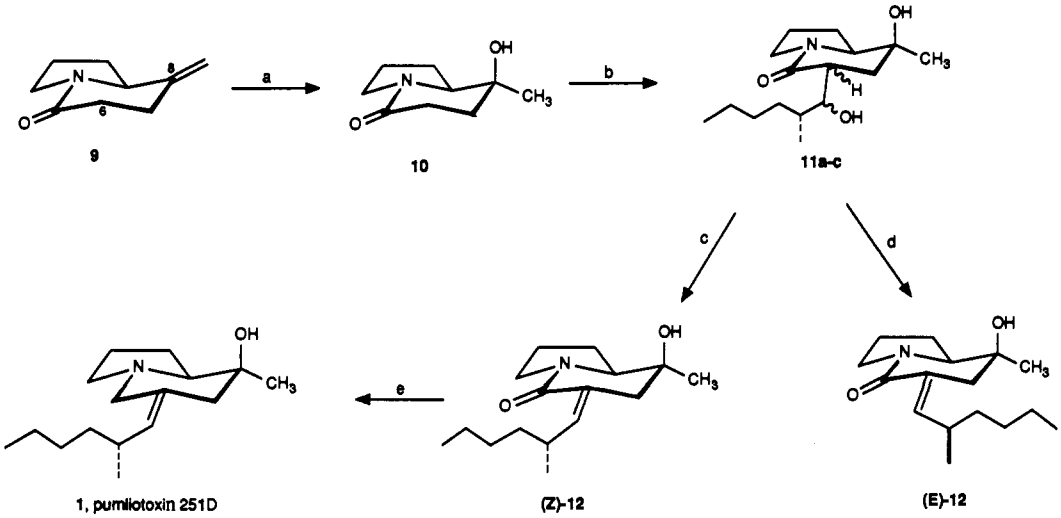
Scheme II. Elaboration of Lactam **9** to Pumiliotoxin 251D[a]



[a](a) $Hg(O_2CCH_3)_2$, H_2O, THF then $NaBH_4$, NaOH; 95% (10:1 mixture at C-8); (b) LDA (2 equivalents), THF, −78 °C, then (R)-2-methylhexanal; 69%; (c) **11a**, DCC, PhMe, $Cu^{I}Cl$, 110 °C (syn); 98%; (d) **11b/c**, CH_3SO_2Cl, C_5H_5N then KOH (anti); 73%, 2.6:1 (E:Z); (e) $LiAlH_4/AlCl_3$ (3:1), Et_2O, rt; 67%.

allene-based methodology adumbrated in eq 1.

Our first objective was to establish the indolizidine framework carrying the functionality appropriate for incorporation of the tertiary hydroxyl at C-8 and the (*Z*)-alkylidene side chain at C-6 (Scheme I). The sequence begins with the enantiomerically pure allenic amine **6**,[7] and it was our intention to utilize the chiral benzylic residue on nitrogen to control the stereochemistry of the new asymmetric center formed in the initial cyclization step. This is a concept that has been realized with reasonable success (up to 81% d.e.) for cyclizations involving Ag^{I} as the electrophilic trigger.[8] However, the corresponding Pd^{II}-mediated processes show a much lower level of selectivity and, in the event, cyclization of **6** under carbomethoxylation conditions[9] provided the 2-substituted pyrrolidines **7a/b** with a negligible level of diastereoselectivity. Although the role of the α-methylbenzyl residue is, in effect, limited to that of a resolving agent, this function is performed efficiently and the desired diastereomer **7a** was isolated in 40% yield on a multigram scale. The absolute stereochemistry of **7a** was, at this stage, unknown but was unambiguously established at a later point in the synthesis by crystallographic analysis (vide infra). To date, we have been unsuccessful in improving the diastereoselectivity of this step using a range of palladium electrophiles modified by chiral, nonracemic ligands, such as (*R*)-BINAP, (*S,S*)-CHIRAPHOS and diethyl L-tartrate.[10] Other benzylic substituents based on (*R*)-phenylglycine have also been examined, but their use within this context is limited by the nature of the transformations used in the latter stages of the synthesis. Electrophiles based on Hg^{II} tend to display a higher level of diastereoselectivity in these cyclization processes and although the initially formed alkenylmercury can be converted, via transmetalation with Li_2PdCl_4 and carbonylation,[12] to the corresponding acrylate, the overall yields of the required products are comparable to those obtained by the direct palladium(II)-mediated cyclization shown in Scheme I.[7]

Having expended one π-bond of allene **6** in the cyclization step, that remaining was then exploited for further elaboration of **7a** to complete the construction of the bicyclic framework. Reduction of **7a** to the corresponding allylic alcohol followed by treatment of this intermediate under Claisen rearrangement conditions[13] effected homologation to ester **8** in 93% overall yield. Hydrolysis of **8** and reaction of the resulting carboxylate salt with acetic anhydride led directly to the bicyclic lactam **9** as a single enantiomer in 76% yield.[14] This final step not only served to complete the construction of the indolizidine skeleton but, at the same time, effected cleavage of the now redundant α-methylbenzyl residue.[15]

Lactam **9** is a crucial intermediate in this synthesis since it provides the necessary functional elements required for the remaining transformations: the exocyclic methylene allows introduction of the tertiary hydroxyl at C-8, and the lactam carbonyl is a vehicle for the incorporation of the (*Z*)-alkylidene side chain at C-6.

The first of these tasks, hydration of **9**, proceeded smoothly as shown in Scheme II to afford the tertiary alcohol **10** in 95% yield. The hydroxymercuration/reduction procedure used exhibited a high level of stereoselectivity (10:1) in favor of the expected axial alcohol,[16] and although the minor component could be cleanly removed by a single crystallization, it was more convenient to effect purification at the next step. The enantiomeric purity of **10** was also evaluated at this stage by ^1H NMR (270 MHz) using tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) (Eu[hfc]$_3$). This reagent cleanly resolved the corresponding racemate and, within the limits of detection, no trace of *ent*-**10** was observed.

(7) For the preparation of **6** from 4,5-hexadienenitrile and a more comprehensive discussion of the diastereoselectivity available in Pd^{II}-mediated cyclizations of this type see: Fox, D. N. A.; Gallagher, T. *Tetrahedron* **1990**, *46*, 4697.

(8) In Ag^{I}-mediated cyclizations, good diastereoselectivity is observed when the chiral benzylic residue is derived from phenylglycine and so carries an additional ligand capable of coordinating to the electrophile: Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Chem. Soc., Chem. Commun* **1989**, 1073.

(9) (a) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800. (b) Alper, H.; Hartstock, F. W.; Despeyroux, B. *J. Chem. Soc., Chem. Commun.* **1984**, 905. (c) Lathbury, D.; Vernon, P.; Gallagher, T. *Tetrahedron Lett.* **1986**, *27*, 6009. (d) Walkup, R. D.; Park, G. *Tetrahedron Lett.* **1988**, *29*, 5505.

(10) Both *R* and *S* enantiomers of **6** were examined by using these ligands to establish a possible matched/mismatched combination. The efficient palladium-catalyzed asymmetric hydrocarboxylation of alkenes using (*R*)- or (*S*)-1,1-binaphthyl-2,2-diyl ligands has recently been described.[11]

(11) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803.

(12) Larock, R. C. *J. Org. Chem.* **1975**, *40*, 3237. Larock, R. C. *Tetrahedron* **1982**, *38*, 1713, and references cited therein.

(13) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(14) An alternative approach to the synthesis of *rac*-**9** has recently been described: Azzouzi, A.; Dufour, M.; Gramain, J.-C.; Remuson, R. *Heterocycles* **1988**, *27*, 133.

(15) For other examples for cyclization–dealkylation reactions leading to lactams, see: Cooley, J. H.; Evain, E. J. *Synthesis* **1989**, 1, and references cited therein.

(16) For studies relating to the stereoselectivity of the oxymercuration of exocyclic and bicyclic alkenes, see: (a) Brown, H. C.; Hammar, W. J. *J. Am. Chem. Soc.* **1967**, *89*, 1524. (b) Pasto, D. J.; Gontarz, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 7480. (c) Jasserand, D.; Girard, J. P.; Rossi, J. C.; Granger, R. *Tetrahedron* **1976**, *32*, 1535. (d) Senda, Y.; Kamiyama, S.; Imaizumi, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 530.

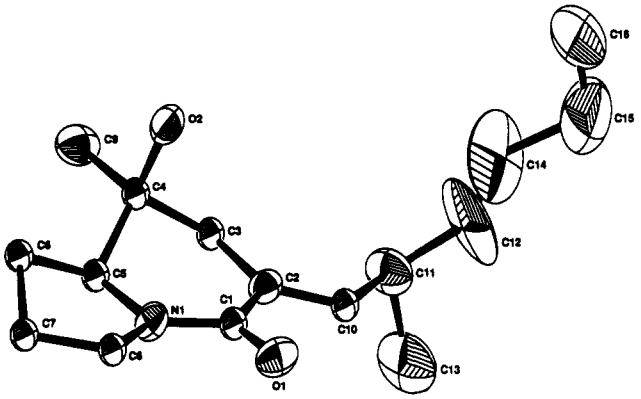


Figure 1. ORTEP diagram for (*E*)-**12**. Thermal ellipsoids represent 30% probability.

Once the stereochemical integrity of this intermediate had been confirmed, the final issue to be addressed was the stereoselective incorporation of the (*Z*)-alkylidene unit at C-6. Previously this problem had been elegantly solved by both Overman[3] and Trost[4] within the context of these indolizidine alkaloids, but the difficulties associated with controlling exocyclic alkene geometry have also been recognized in a more general sense.[17-20]

We focused on an aldol reaction involving lactam **10** to establish the basic carbon framework of the side chain and the use of a stereospecific elimination step to control alkene geometry.[21] An aldol sequence has previously been employed by Overman in his approach to the *allo*-pumiliotoxin series, which carry a hydroxyl residue at C-7, but in this case the required (*E*)-enone geometry was the subject of thermodynamic control.[3b] This solution is not, however, applicable to this present situation, where the target is the thermodynamically disfavored (*Z*)-enelactam, i.e., (*Z*)-**12**. Deprotonation of lactam **10** (10:1 mixture of diastereomers) (LDA, 2 equiv, −78 °C) and addition of the resulting enolate to (*R*)-2-methylhexanal[22] gave a mixture of three aldol adducts **11a–c** in 69% combined yield. One isomer, **11a**, isolated in 27% yield, was exposed to stereospecific syn elimination[26] using DCC and $Cu^{I}Cl$ to give (*Z*)-**12** (98% yield). Application of an anti elimination[27] sequence (CH_3SO_2Cl, KOH) to the remaining inseparable mixture of **11b/c** led to a 2.6:1 mixture of (*E*)- and (*Z*)-**12** (73% combined yield).[28] Therefore, by use of this combination of aldol and complementary elimination procedures, (*Z*)-**12** was arrived at in 39% overall yield from lactam **10**. In addition, the tertiary hydroxyl of **10** did not interfere with either of these steps and this obviated the need for hydroxyl protection throughout this phase of the work.[29] The structure of (*E*)-**12**, which was determined by X-ray crystallographic analysis, is shown in Figure 1. This served primarily to establish the absolute stereochemistry of the initial cycloadduct **7a** but also confirmed both the relative configuration of the tertiary center at C-8 and the geometry of the exocyclic alkene.

Finally, 1,2-reduction of the unsaturated lactam moiety of **12** was achieved by using $LiAlH_4/AlCl_3$[30] to give pumiliotoxin 251D (**1**) in 67% isolated yield, and spectral data (IR, ^1H and ^{13}C NMR) for synthetic **1** and **1**·HCl were correlated with that reported previously.[3a]

The chemistry shown in Schemes I and II represents a novel approach to pumiliotoxin 251D (6.3% yield over nine steps), and we are currently exploring the versatility of this methodology with regard to the synthesis of other members of this class of alkaloids.

Experimental Section

Unless otherwise stated, all solvents were dried and purified before use according to standard procedures.[31] Column chromatography was performed by using Merck silica gel (230–400 mesh), and all high-resolution mass data were obtained on material that was homogeneous by ^1H NMR, ^{13}C NMR, and thin-layer chromatography.

Ethyl 4-[(*S*)-*N*-[(*S*)-α-Methylbenzyl]pyrrolidin-2-yl]-4-pentenoate (8). To a solution of ester **7a** (9.6 g, 37 mmol)[7] [$[\alpha]^{20}_D$ −40.5° (*c* 3.6, $CHCl_3$)] in THF (200 mL) was added dropwise a solution of DiBAl in toluene (1.5 M, 50 mL, 2.0 equiv) at −78 °C, and the reaction mixture was then allowed to warm to room temperature over 30 min. Saturated aqueous ammonium chloride (10 mL) was added, the resulting slurry was then filtered through a pad of Celite, and the solids were washed thoroughly with CH_2Cl_2 to afford, on concentration, *N*-[(*S*)-α-methylbenzyl]-2-(*S*)-[1-(hydroxymethyl)ethenyl]pyrrolidine as a light yellow oil (8.35 g, 98%): [$[\alpha]^{19}_D$ −44.0 (*c* 0.28, $CHCl_3$); IR (film) 3400, 1640, 1600, 1500 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.22–7.37 (5 H, m, Ar *H*), 5.07 (1 H, s, *HC*=), 5.01 (1 H, d, *J* = 2 Hz, *HC*=), 4.58 (1 H, d, *J* = 12 Hz, OC*H*), 4.17 (1 H, d, *J* = 12 Hz, OC*H*), 3.92 (1 H, q, *J* = 7 Hz, PhC*H*), 3.35–3.40 (1 H, m, part of NCH_2), 2.96 (1 H, m, NC*H*C=),

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(21) For a recent example of the use of a stereospecific elimination to control alkene geometry, see: Jones, A. B.; Yamaguchi, M.; Patten, A.; Danishefsky, S. J.; Ragan, J. A.; Smith, D. B.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 17.

(22) (*R*)-2-Methylhexanal was obtained by oxidation (pyridine–SO_3, DMSO) of (*R*)-2-methylhexanol,[23] which was in turn prepared by using Evans' oxazolidinone methodology[24] (see supplementary material). No epimerization was detected in this oxidation step as judged by reduction ($LiAlH_4$) of the aldehyde back to the alcohol and ^1H NMR analysis of the corresponding (*R*)-MTPA [(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid] ester.[25]

(23) Optically pure (*R*)-2-methylhexanol has previously been prepared from (*R*)-methyl β-hydroxyisobutyrate: Kato, M.; Mori, K. *Agric. Biol. Chem.* **1985**, *49*, 2479.

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(27) Bouffard, F. A.; Johnston, D. B. R.; Christensen, B. G. *J. Org. Chem.* **1980**, *45*, 1130. See also: Crowell, T. I.; Wall, A. A.; Kemp, R. T.; Lutz, R. E. *J. Am. Chem. Soc.* **1963**, *85*, 2521.

(28) Unambiguous stereochemical assignments for aldol adducts **11a–c** are not yet available. However **11b/c**, isolated as a 4:1 mixture, does not appear to undergo either syn or anti elimination in a stereospecific fashion. Syn elimination of **11b/c** gave (*E*)-**12** and no trace of (*Z*)-**12**, and the corresponding anti elimination sequence displayed an *E*/*Z* selectivity that was both temperature and base dependent. The diastereoselectivity available in aldol reactions involving lactam enolates is under investigation; see also: Tamaru, Y.; Amino, Y.; Furukawa, Y.; Kagotani, M.; Yoshida, Z. *J. Am. Chem. Soc.* **1982**, *104*, 4018.

(29) In model reactions involving pentanal as the aldehyde component, essentially the same stereochemical results were obtained when the aldol elimination sequence was carried out on either **9** or **10**, although this observation does not exclude participation of the tertiary alkoxide in the reactions of **10**. Attempts to alter the distribution of aldol diastereomers by use of equilibrating conditions, a low-temperature quench, or the corresponding K^+ or Zn^{2+} enolate of **10** were unsuccessful.

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2.24 (1 H, m, part of NCH_2), 1.76–1.94 (3 *H*, m, part of CH_2CH_2), 1.66 (1 H, m, part of CH_2CH_2), 1.48 (3 H, d, J = 7 Hz, CH_3), 1.26 (1 H, s, O*H*); ^{13}C NMR (68 MHz, $CDCl_3$) δ 147.71 (C), 140.44 (C), 128.31 (CH), 128.09 (CH), 127.18 (CH), 114.01 (CH_2), 66.62 (CH), 65.49 (CH_2), 60.07 (CH), 48.85 (CH_2), 30.42 (CH_2), 23.77 (CH_2), 21.24 (CH_3); *m/e* (EI) 231, 216, 174. HRMS Calcd for $C_{15}H_{21}NO$: 231.1623. Found: 231.1633. This material was used in the next step without further purification.

To a solution of this allylic alcohol (8.15 g, 35 mmol) in triethyl orthoacetate (150 mL) was added a catalytic quantity of trimethylacetic acid, and the reaction mixture was heated to 155 °C, with a Claisen head and receiver attached, to collect ethanol produced. After 1 h, the reaction mixture was cooled, the solvent evaporated in vacuo, and the residue diluted with ethyl acetate (30 mL), washed with saturated aqueous sodium bicarbonate (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by chromatography, eluting with 30% ethyl acetate/petroleum ether, afforded recovered allylic alcohol (1.08 g) and ester **8** (8.72 g, 95% based on recovered alcohol) as a light yellow oil, (*S,S*)-**8**: $[\alpha]^{22}_D$ −23.2° (*c* 0.17, $CHCl_3$); IR (film) 1720, 1640, 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.20–7.34 (5 H, m, Ar *H*), 5.18 and 4.84 (2 H, 2 × s, 2 × *HC*=), 4.16 (2 H, q, J = 7 Hz, OCH_2), 3.72 (1 H, q, J = 7 Hz, PhC*H*), 2.95–3.03 (2 H, m, $NCHC$=C, part of NCH_2), 2.31–2.60 (4 H, m, $CO_2CH_2CH_3$, H_2CC=), 2.18 (1 H, m, part of NCH_2), 1.48–1.88 (4 H, m, 2 × CH_2), 1.39 (3 H, d, J = 7 Hz, PhCCH_3), 1.27 (3 H, t, J = 7 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.46 (C), 151.31 (C), 141.94 (C), 128.15 (CH), 127.79 (CH), 126.63 (CH), 109.60 (CH_2), 66.07 (CH), 60.23 (CH_2), 59.81 (CH), 49.07 (CH_2), 32.73 (CH_2), 31.49 (CH_2), 26.56 (CH_2), 22.93 (CH_2), 21.47 (CH_3), 14.21 (CH_3); *m/e* (EI) 301, 286, 196, 174. HRMS Calcd for $C_{19}H_{27}NO_2$ (M^+): 301.2039. Found: 301.2039.

(8a*S*)-8-Methyleneoctahydro-5-indolizidinone (9). To a solution of ester **8** (1.29 g, 4.3 mmol) in methanol (60 mL) was added powdered sodium hydroxide (2.41 g, 14 equiv), and the reaction mixture was heated to reflux for 30 min. The solution was then cooled, and solvent was removed in vacuo. Acetic anhydride (50 mL) was added cautiously to the resulting solid, and once the addition was complete, the reaction mixture was heated to reflux for 2 h. After this time, the solution was cooled, diluted with CH_2Cl_2 (100 mL), and washed with aqueous sodium hydroxide (2 M, 20 mL). The organic phase was dried (Na_2SO_4) and evaporated in vacuo to afford a residue which was chromatographed on silica gel, eluting with ethyl acetate, to yield lactam **9** as a colorless oil (491 mg, 76%), (*S*)-**9**: bp (bulb to bulb) 165 °C (0.1 Torr); $[\alpha]^{20}_D$ −98.3 (*c* 1.2, $CHCl_3$); IR (film) 1620 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.98 and 4.92 (2 H, 2 × s, *HC*=), 4.01 (1 H, m, $NCHC$=CH_2), 3.44–3.69 (2 H, m, NCH_2), 2.38–2.51 and 2.16–2.25 (4 H, 2 × m, $COCH_2$, H_2CC=C), 2.05 (1 H, m, part of CH_2CH_2), 1.63–1.94 (3 H, m, part of CH_2CH_2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 169.38 (C), 143.46 (C), 109.15 (CH_2), 60.85 (CH), 44.66 (CH_2), 32.57 (CH_2), 30.94 (CH_2), 29.45 (CH_2), 22.25 (CH_2); *m/e* (EI) 151, 136. HRMS Calcd for $C_9H_{13}NO$ (M^+): 151.0996. Found: 151.0983.

(8S,8a*S*)-8-Hydroxy-8-methyloctahydro-5-indolizidinone (10). To a suspension of mercuric acetate (195 mg, 0.61 mmol) in THF/water (1:1, 4 mL) was added a solution of lactam **9** (71 mg, 0.47 mmol) in THF (2 mL) at room temperature. The reaction mixture was stirred for 3 h, and then aqueous sodium hydroxide (2 M, 1 mL) was added followed by a solution of sodium borohydride (10 mg, 0.26 mmol) in aqueous sodium hydroxide (2 M, 1 mL). After 5 min, the suspension was filtered through Celite, and the solids were washed well with CH_2Cl_2. Separation of the organic layer, saturation of the aqueous layer with sodium chloride, and further extraction with CH_2Cl_2 (2 × 30 mL) afforded, after drying (Na_2SO_4) and evaporation of the combined organic layers, a light gray residue. This was taken up in ethyl acetate and once again filtered through a plug of Celite to afford, on evaporation, hydroxylactam **10** as a colorless glass (10:1 mixture, 76 mg, 95%), which was used without further purification. A sample of diastereomerically pure **10** was obtained by recrystallization from petroleum ether/ether: mp 90–92 °C; $[\alpha]^{21}_D$ −47.0° (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) 3380, 1620 cm^{-1}; 1H NMR (270 MHz, $CDCl_3$) δ 3.55 (2 H, dd, J = 11, 5 Hz, NCH_2), 3.37 (1 H, dd, J = 10, 5.5 Hz, NC*H*), 2.71 (1 H, s, O*H*), 2.56 (1 H, ddd, J = 19.5, 10.5, 7.5 Hz, part of $COCH_2$), 2.40 (1 H, dd, J = 19.5, 7.5 Hz, part of $COCH_2$), 1.68–2.03 (6 H, m, 3 × CH_2), 1.31 (3 H, s, CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 169.18 (C), 67.08 (C), 66.20 (CH), 45.64 (CH_2), 34.87 (CH_2), 27.99 (CH_2), 26.30 (CH_3), 26.08 (CH_2), 21.83 (CH_2); *m/e* (EI) 169, 111, 83, 70. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.6; H, 9.1; N, 7.9. Found: C, 63.9; H, 8.9; N, 8.3.

(*R*)-2-Methylhexanal.[22] To a solution of (*R*)-2-methylhexanol (58 mg, 0.50 mmol) in DMSO (2 mL) was added triethylamine (0.43 mL, 6.9 equiv) followed by a solution of pyridine/sulfur trioxide complex (240 mg, 3.4 equiv) in DMSO (2 mL). After stirring at room temperature for 30 min, the solution was diluted with water (5 mL) and extracted with 1:1 ether/30–40 petroleum ether (3 × 10 mL). The combined organic layers were washed with water (3 × 10 mL) and dilute aqueous hydrochloric acid (3 × 10 mL) and dried (Na_2SO_4). Removal of solvents in vacuo at 0 °C afforded (*R*)-2-methylhexanal in essentially quantitative yield, which was used in the aldol reactions described below without further purification.

Aldol Adducts 11a–c. A solution of the hydroxylactam **10** (10:1 mixture, 76 mg, 0.45 mmol) in THF (2 mL) was added to a solution of LDA in THF (0.094 M, 10 mL, 2.1 equiv) at −78 °C. After 30 min at −78 °C, a solution of (*R*)-2-methylhexanal (58 mg, 1.1 equiv) in THF (1 mL) was added, and the reaction mixture was then warmed to 0 °C over 30 min. Saturated aqueous ammonium chloride solution (1 mL) was added, and the products were extracted by using ethyl acetate (3 × 30 mL). The extracts were dried (Na_2SO_4) and concentrated in vacuo, and the residue was purified by flash chromatography, eluting with 20% ethyl acetate/petroleum ether to give the three aldol components **11a–c** in 69% combined yield, based on recovered **10** (17.5 mg). Aldol **11a** (25.8 mg) was isolated as colorless crystals: mp 151–152 °C (ether/petroleum ether); $[\alpha]^{21}_D$ −7.8° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3400, 1610 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.03 (1 H, dd, J = 8.5, 2.5 Hz, C*H*OH), 3.51–3.56 (2 H, m, NCH_2), 3.43 (1 H, m, NC*H*), 2.80 (1 H, ddd, J = 11.5, 7.5, 3 Hz, COC*H*), 1.74–1.99 (8 H, m, 3 × ring CH_2, 2 × O*H*), 1.47–1.56 (1 H, m, MeC*H*), 1.32 (3 H, s, CH_3), 1.09–1.37 (6 H, m, 3 × CH_2), 0.97 (3 H, d, J = 6.5 Hz, $CHCH_3$), 0.90 (3 H, t, J = 6.5 Hz, CH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ (carbonyl not observed) 75.44 (CH), 68.08 (C), 65.78 (CH), 46.12 (CH_2), 41.52 (CH), 35.26 (CH), 34.96 (CH_2), 32.63 (CH_2), 28.90 (CH_2), 26.56 (CH_3), 26.24 (CH_2), 22.96 (CH_2), 22.06 (CH_2), 15.47 (CH_3), 14.11 (CH_3); *m/e* (CI) 284; *m/e* (EI) 265, 226, 198, 169, 70. HRMS Calcd for $C_{16}H_{27}NO_2$ ($M - H_2O$)$^+$: 265.2042. Found: 265.2054.

Aldols **11b,c** (41.5 mg) were obtained as an inseparable mixture of isomers: IR ($CHCl_3$) 3400, 1610 cm^{-1}. HRMS Calcd for $C_{16}H_{27}NO_2$ ($M - H_2O$)$^+$: 265.2042. Found: 265.2054. Overlapping signals complicated ^1H NMR analysis, and this mixture was not characterized further.

(8*S*,8a*S*)-8-Hydroxy-8-methyl-6(*Z*)-[2(*R*)-methylhexylidene]octahydro-5-indolizidinone [(*Z*)-12]. To a solution of the aldol **11a** (22 mg, 0.078 mmol) in toluene (2 mL) was added DCC in toluene (0.36 M, 0.25 mL, 1.2 equiv) and cuprous chloride (9 mg, 1.9 equiv), and the reaction mixture was heated to reflux for 24 h. After this time, dilute aqueous ammonia (5 mL) was added, and the mixture was extracted with ethyl acetate (3 × 10 mL); the extracts were dried ($MgSO_4$) and concentrated in vacuo to afford, on chromatography, eluting with 30% ethyl acetate/petroleum ether (*Z*)-**12** (20.4 mg, 98%) as colorless crystals: mp 135–138 °C (ether/petroleum ether); $[\alpha]^{21}_D$ −28.0° (*c* 0.40, $CHCl_3$); IR ($CHCl_3$) 3400, 1650, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (1 H, dd, J = 9.5, 2 Hz, *HC*=), 3.81 (1 H, m, MeC*H*), 3.56 (2 H, dd, J = 9.5, 5 Hz, NCH_2), 3.46 (1 H, dd, J = 10.5, 6 Hz, NC*H*), 2.70 (1 H, dd, J = 15, 2 Hz, part of H_2CC=C), 2.44 (1 H, d, J = 15 Hz, part of H_2CC=C), 1.75–2.03 (5 H, m, 2 × ring CH_2, O*H*), 1.19–1.34 (6 H, m, 3 × CH_2), 1.27 (3 H, s, CH_3), 0.97 (3 H, d, J = 6.5 Hz, $CHCH_3$), 0.86 (3 H, t, J = 7 Hz, CH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 163.80 (C), 152.28 (CH), 122.86 (C), 67.69 (C), 66.52 (CH), 47.03 (CH_2), 45.54 (CH_2), 37.17 (CH_2), 32.43 (CH), 29.58 (CH_2), 26.08 (CH_2), 25.17 (CH_3), 22.87 (CH_2), 22.15 (CH_2), 20.73 (CH_3), 14.04 (CH_3); *m/e* (EI) 265, 222, 149, 120, 91. HRMS Calcd for $C_{16}H_{27}NO_2$ (M^+): 265.2039. Found: 265.2047.

Anti Elimination of Aldols 11b,c; (*E*)- and (*Z*)-12. To an ice-cold solution of **11b,c** (12.6 mg, 0.045 mmol) in pyridine (2 mL) was added methanesulfonyl chloride (10 μL, 3.0 equiv.). The reaction mixture was allowed to warm to room temperature and stirred for 15 min. After this time, 2 M hydrochloric acid (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and concetrated in vacuo, and the residue was purified by chromatography eluting with ethyl acetate/petroleum ether (3:1), to give the corresponding isomeric mesylates (11.8 mg) as a colorless oil. This mixture was dissolved in methanol (3 mL), powdered potassium hydroxide (25.0 mg, 9.9 equiv) added, and the reaction mixture gradually warmed to reflux over 45 min. After 2 h at reflux, the reaction mixture was cooled, diluted with water (5 mL), and extracted with ethyl acetate (3 × 10 mL), and the extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography, eluting with ethyl acetate/petroleum ether (3:1), afforded (*Z*)-**12** (2.1 mg) and the (*E*)-**12** as a colorless solid (6.5 mg) in a combined yield of 73%. Further purification of (*E*)-**12** by recrystallization from CH_2Cl_2/petroleum ether yielded colorless crystals: mp 175–176 °C; $[\alpha]^{17}_D$ −43.3° (*c* 0.33, $CHCl_3$); IR ($CHCl_3$) 3400, 1660, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.81 (1 H, dd, J = 10, 2 Hz, *HC*=), 3.55–3.66 (2 H, m, NCH_2), 3.50 (1 H, dd, J = 9, 4 Hz, NC*H*), 2.76 (1 H, d, J = 16 Hz, part of H_2CC=), 2.40 (1 H, dd, J = 16, 2 Hz, part of H_2CC=), 2.36–2.44 (1 H, m, MeC*H*),

1.76-2.04 (4 H, m, 2 × ring CH_2), 1.21-1.43 (7 H, m, 3 × CH_2, OH), 1.31 (3 H, s, CH_3), 0.97 (3 H, d, J = 6.5 Hz, $CHCH_3$), 0.87 (3 H, t, J = 7 Hz, CH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 163.77 (C), 147.71 (CH), 124.16 (C), 67.82 (C), 65.81 (CH), 46.25 (CH_2), 39.53 (CH_2), 36.56 (CH_2), 32.79 (CH), 29.68 (CH_2), 26.40 (CH_2), 25.27 (CH_3), 22.80 (CH_2), 22.22 (CH_2), 19.79 (CH_3), 13.98 (CH_3); *m/e* (EI) 265, 222. HRMS Calcd for $C_{16}H_{27}NO_2$ (M^+): 265.2039. Found: 265.2039.

Pumiliotoxin 251D (1) and 1·HCl.[3a] To a solution of (*Z*)-**12** (16 mg, 0.06 mmol) in ether (2 mL) was added a solution of aluminum hydride in ether (0.18 M, 1.8 mL, 5.4 equiv) at room temperature. After 10 min, the reaction was quenched with saturated aqueous sodium sulfate solution and filtered, and the solids were washed with CH_2Cl_2. Addition of methanolic HCl to the resulting solution effected complete conversion to the hydrochloride salt, and evaporation in vacuo afforded pumiliotoxin 251D hydrochloride as a colorless solid (11.7 mg, 67%). Recrystallization from ether/petroleum ether yielded colorless crystals. **1**·HCl:[32] mp 200-201 °C (evacuated sealed capillary); $[\alpha]^{20}_D$ +23.6° (*c* 0.11, MeOH); $[\alpha]^{20}_{546}$ +36.1° (*c* 0.11, MeOH); ^{1}H NMR (270 MHz, CD_3OD) δ 5.32 (1 H, d, J = 10 Hz, *H*-10), 4.36 (1 H, d, J = 13 Hz, *H-5β*), 3.05-3.59 (4 H, m, *H-3β*, N*H*, *H-5α*, *H-11*), 2.43) (1 H, d, J = 15 Hz, *H-7*), 2.36 (1 H, d, J = 15 Hz, *H*-7), 1.77-2.18 (6 H, m, 2 × *H*-1, 2 × *H-2*, *H-3α*, *H-8*a), 1.12-1.35 (6 H, m, 2 × *H*-12, 2 × *H*-13, 2 × *H*-14), 1.28 (3 H, s, *C-8Me*), 1.03 (3 H, d, J = 6.5 Hz, *C-11Me*), 0.89 (3 H, t, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR (68 MHz, CD_3OD) δ 140.93, 125.75, 74.05 68.96, 54.33, 52.64, 47.68, 38.60, 33.76, 31.10, 26.30, 24.10, 22.13, 21.76, 20.89, 14.69. Pumiliotoxin 251D (**1**) was obtained by neutralization of the hydrochloride salt with saturated aqueous sodium bicarbonate solution, followed by extraction of the free base with CH_2Cl_2. The extracts were dried (Na_2SO_4), and the solvents were removed in vacuo at 0 °C to avoid loss of the relatively volatile base. **1**: IR ($CHCl_3$) 3400, 1660 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.04 (1 H, d, J = 9.5 Hz, *H*-10), 3.79 (1 H, d, J = 12 Hz, *H-5β*), 3.08 (1 H, m, *H-3β*), 2.35 (1 H, d, J = 12 Hz, *H-5α*), 2.37 (1 H, m, *H-11*), 2.17 (1 H, m, *H-3α*), 2.14 (2 H, br s, 2 × *H-7*), 1.98 (1 H, m, *H-8a*), 1.66-1.78 (4 H, m, 2 × *H-1*, 2 × *H-2*), 1.11-1.34 (7 H, m, 2 × *H-12*, 2 × *H-13*, 2 × *H-14*, O*H*), 1.13 (3 H, s, *C-8Me*), 0.97 (3 H, d, J = 6.5 Hz, *C-11Me*), 0.88 (3 H, t, J = 7 Hz, CH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 134.70 (CH), 129.74 (C), 71.68 (CH), 68.31 (C), 54.65 (CH_2), 53.16 (CH_2), 48.81 (CH_2), 37.43 (CH_2), 32.05 (CH), 29.71 (CH_2), 24.26 (CH_3), 23.22 (CH_2), 22.80 (CH_2), 21.67 (CH_3), 21.05 (CH_2), 14.11 (CH_3); *m/e* (EI) 251, 166, 112, 70. HRMS Calcd for $C_{16}H_{29}NO$ (M^+): 251.2249. Found: 251.2253.

(32) Literature data[3a] for (+)-pumiliotoxin 251D hydrochloride (**1**·HCl): mp 206-206.5 °C (evacuated sealed capillary); $[\alpha]^{25}_D$ +28.0° (*c* 0.62, MeOH); $[\alpha]^{25}_{546}$ +32.0° (*c* 0.62, MeOH).

Acknowledgment. We thank Professor L. E. Overman for copies of ^{1}H and ^{13}C NMR spectra of both pumiliotoxin 251D and related synthetic model systems. Financial support for this work was received from the Science and Engineering Research Council (Quota award, GR/C/88130, GR/E/57024).

Registry No. 1, 73376-35-9; **1**·HCl, 73395-60-5; **6**, 126179-87-1; **7a**, 131636-08-3; **7a** alcohol, 131636-10-7; **7b**, 131636-09-4; **8**, 131636-11-8; **9**, 131636-12-9; **10**, 131722-93-5; 8-*epi*-**10**, 131722-95-7; **11**, 131636-13-0; (*Z*)-**12**, 131636-14-1; (*E*)-**12**, 131722-94-6; (*R*)-2-methylhexanal, 132151-88-3; (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone, 77943-39-6; hexanoyl chloride, 142-61-0; *N*-hexanoyl-4(*R*)-methyl-5(*S*)-phenyl-2-oxazolidinone, 131636-15-2; 4(*R*)-methyl-*N*-[2(*R*)-methylhexanoyl]-5-(*S*)-phenyl-2-oxazolidinone, 131636-16-3; (*R*)-2-methylhexanol, 66050-98-4.

Supplementary Material Available: Experimental details for the preparation of (*R*)-2-methylhexanol and tables giving the crystallographic data, the final coordinates and equivalent thermal parameters, bond lengths and angles, and dihedral angles for (*E*)-**12** (8 pages). Ordering information is given on any current masthead page.

Bromination of Imidazoles Coordinated to Cobalt(III). Kinetics and Mechanism of Bromination of $RImH^{3+}$ Systems (R = $(NH_3)_5Co$), Wheland Intermediates, and Preassociation or Diffusion Control

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Abstract: The bromination of $RImH^{3+}$ and several Me- (2-, 3-, 4-, 5-, and 2,4-) and Br- (4-, 5-, and 4,5-) substituted imidazole complexes of the pentaamminecobalt(III) ion (R = $(NH_3)_5Co^{3+}$) has been studied in aqueous solution at 25.0 °C, I = 1.0 or 0.1 M ($NaClO_4$). Reactions are generally fast and result in polybromination when more than one C site is available, even when less than stoichiometric amounts of Br_2 are used. Site reactivity order is C-4 > C-5 ≫ C-2 for both the neutral (**11**) and anionic (**12**) ligands. Br_2 is a much more powerful electrophile than Br_3^-. The pH dependence of monobromination is complex for the neutral ligand **11** and suggests proton abstraction from a Wheland addition intermediate (CoHBr) is rate-determining at acidic pHs; both spontaneous and OH^--catalyzed pathways are observed. At more neutral pHs, bromine addition becomes rate-determining. Reaction of the anionic ligand **12** is very fast with rate constants up to 3.4 × 10^{10} M^{-1} s^{-1} (for R-2,4-Me_2Im^{2+}). For such species, preassociation with Br_2 before proton abstraction is suggested as an alternative mechanism. For R-3-$MeIm^{3+}$ (*N*-methyl derivative), reaction via the ammine conjugate base is suggested for the OH^--catalyzed reaction. The effects of deuterium substitution and temperature on the reaction rate are discussed.

Introduction

When imidazole is treated with an equal amount of bromine in aqueous or nonaqueous solution, the major product is 2,4,5-tribromoimidazole,[1] eq 1. A similar result occurs with N- and C-substituted imidazoles,[2-4] all nonsubstituted carbons are readily brominated in the presence of even limited amounts of bromine, eq 2. This inability to prepare mono- (especially) and dibrominated imidazoles has resulted in more circuitous routes being devised for these synthetically useful precursors.[5]

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(5) For example, 4(5)-bromoimidazole can be made by reducing 2,4,5-tribromoimidazole with aqueous Na_2SO_3[1] and 4,5-dibromoimidazole by treatment of the same starting material with triphenylphosphine in ethanol: *Chem. Abstr.* **1965**, *63*, 16369. 2-Bromoimidazole and 2,4(5)-dibromoimidazole can be made as a mixture by treating 2,5-dibromoimidazole-4-carboxy-*p*-bromoanilide with concentrated HBr in a sealed tube: King, H.; Murch, W. O. *J. Chem. Soc.* **1923**, *123*, 621.

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