Pergamon

Tetrahedron 55 (1999) 8905–8914

TETRAHEDRON

Vinylogous Mannich Reactions. Stereoselective Formal Synthesis of Pumiliotoxin 251D

Stephen F. Martin* and Scott K. Bur

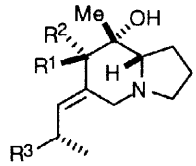
Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas 78712, USA

Received 2 April 1999; accepted 21 April 1999

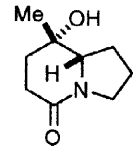
Abstract. A concise synthesis of (-)-**3**, a known precursor of pumiliotoxin 251D, has been completed using a vinylogous Mannich reaction as a key construction. Silyloxyfuran **10** added to methoxypyrrolidine **20** in the presence of TMS-OTf to give a mixture (4.8:1) of **21** and **22** in 57% yield. Reduction and global deprotection of **21** afforded the bicyclic lactam **23**. Raney Nickel mediated extrusion of the hydroxymethyl group from **23** gave (-)-**3**.

Keywords: Mannich reactions; Iminium ions; Asymmetric synthesis; Alkaloids

The structurally diverse and pharmacologically rich indolizidine alkaloids represent attractive targets for natural products synthesis, and numerous strategies have been developed for the efficient construction of these highly functionalized heterocycles in enantiopure form.[1] Among the indolizidines with important biological activity are the approximately 40 pumiliotoxin A and allopumiliotoxin alkaloids having the general structure **1**.[2] One of the simplest members, pumiliotoxin 251D (**2**), isolated from the Ecuadorian frog *Dendrobates tricolor*, was the first alkaloid of this class whose structure was unambiguously determined.[3] Several synthetic routes to **2** have been reported,[4] and the bicyclic lactam **3**, which was first prepared by Gallagher and coworkers in their synthesis of **2**,[4c-e]

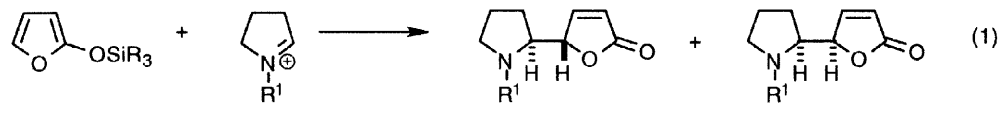


1: R^1, R^2 = H, OH, R^3 = alkyl
2: R^1, R^2 = H, R^3 = *n*-Pr



3

In the context of developing concise entries to a number of alkaloid natural products, we have explored the vinylogous Mannich reaction,[5] an example of which is generally represented by the addition of a trialkylsilyloxyfuran **4** to an iminium ion **5** to give adducts **6** and **7** (eq 1),[6] and the subsequent conversion of the adducts thus obtained into alkaloids.[7] We and others have found that the major diastereomeric product in bimolecular reactions is **6**, although the basis for this selectivity has not been convincingly established.[8-12]

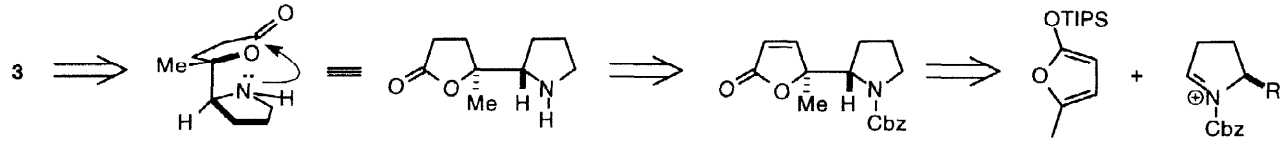


4 **5** **6** **7**

PII: S0040-4020(99)00452-4

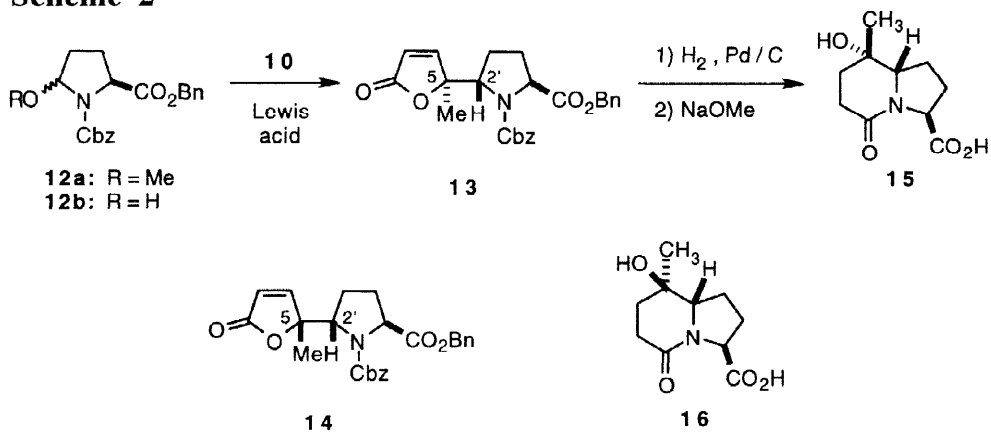
In developing an approach to the asymmetric synthesis of pumiliotoxin 251D (**2**), we reasoned that the bicyclic lactam **3** might be formed by the lactone-lactam rearrangement of the chiral amino lactone **8**, which would be obtained upon refunctionalization of the vinylogous Mannich adduct **9** (Scheme 1). The Cbz nitrogen protecting group on **9** was selected so it could be removed by hydrogenolysis concomitantly with reduction of the unsaturated lactone moiety. Because the relative stereochemical relationship between the two stereogenic centers in **9** corresponds with that in **6**, we anticipated that **9** would be the major product from the addition of the 5-methyl silyloxyfuran **10** to the iminium ion **11** (R = H). This prediction was verified in a series of related studies.[12] The major stereochemical issue was then controlling the absolute stereochemistry in **9**. In principle such control might be achieved by placing a chiral auxiliary on nitrogen or perhaps by using a chiral Lewis acid to induce the addition,[13,14] However, owing to our experience in the asymmetric synthesis of croomine, we adopted an alternative strategy in which a 5-substituted pyrrolidinium ion **11** (R = CO_2Me, CH_2OR', etc.) would serve as the electrophilic partner in the vinylogous Mannich reaction. After directing the facial selectivity in the addition to the intermediate iminium ion, this substituent would be removed.

Scheme 1



The initial experiments to probe the stereoselectivity of the key vinylogous Mannich reaction were conducted with the chiral methoxy pyrrolidine **12a** and the 5-methyl-2-silyloxyfuran **11** in the presence of various Lewis acids including $BF_3{\cdot}OEt_2$, TMS-OTf, $ZnCl_2$, and $Sc(OTf)_3$ (Scheme 2). However, only traces of the desired Mannich adducts could be detected in the NMR spectra of the crude reaction mixtures. On the other hand, the reaction of the hydroxy pyrrolidine **12b** with **10** in the presence of Et_2AlCl in CH_3CN gave a mixture of **13** and **14** in 48% yield.

Scheme 2

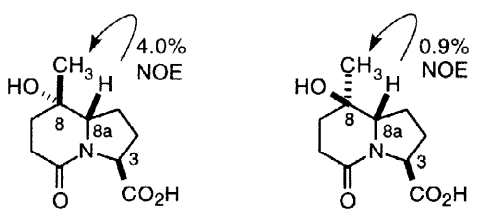


Examination of the ^1H NMR spectrum of the crude reaction mixture revealed four sets of signals (1.0:1.4:4.0:5.8) that arose from the presence of two rotational isomers for each of the two diastereomers **13** and **14**. The ratio of these signals is similar to that reported by Figadère and coworkers for a related reaction, although he attributed the appearance of the four sets of signals to four adducts differing in stereochemistry at the newly

created stereocenters.[11] However, when the ^{1}H NMR spectrum was obtained at 100 °C rather than room temperature, the signals for the diagnostic α-protons of the butenolide moieties coalesced into two sets of doublets at 6.06 and 5.85 ppm in a 1.4:1 ratio.

The major diastereomer was identified as **13** by transformation into the bicyclic lactone **15** whose structure was determined by X-ray analysis. Interestingly, after the initial hydrogenation step in converting **13** into **15**, we obtained a mixture (1:1) of the intermediate amino lactone and the fused bicyclic product **15**. The *O*→*N*-acyl transfer appeared to have been interrupted by protonation of the amino group by the carboxyl function, and treatment of the mixture with base was necessary to complete the formation of **15**. Related lactone-lactam rearrangements have been reported, but base treatment or heat is typically required to promote the reaction.[15] The minor diastereomer **14** was converted in the same fashion into the bicyclic lactam **16**; during this transformation, however, no **16** was detected in the crude mixture after hydrogenation of **14**. Thus, subtle steric factors appear capable of influencing the facility with which these and related lactone-lactam transacylations occur.

The NOE difference spectra of **15** and **16** were compared to complete the structural assignment of **16**, and hence **14**. Irradiation of the bridgehead methine proton at C(8a) in **15** resulted in a 4.0% enhancement in the methyl signal at C(8), whereas irradiation of the bridgehead methine at C(8a) in **16** gave only a 0.9% enhancement of the methyl signal suggesting the two groups are cis in **15** (Figure 1). No enhancement was observed in the resonance for the methine proton at C(3) when either the bridgehead methine at C(8a) or the methyl group at C(8) was irradiated in **15** or **16**. These data suggest that the two compounds are epimeric at the tertiary alcohol center, thereby indicating that the Mannich adducts **13** and **14** were epimeric only at C(5). The configuration of **16** was later confirmed by X-ray analysis of its sodium salt.



15 **16**

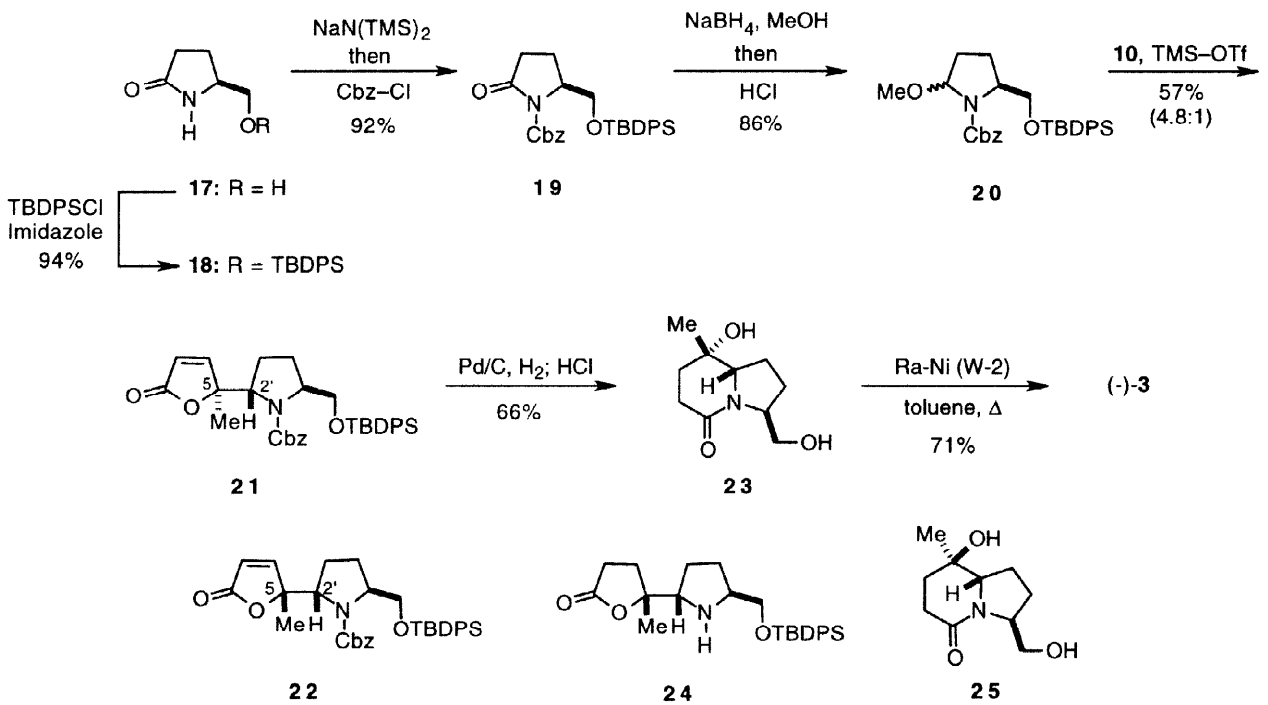
Figure 1. Comparison of NOE difference spectra for **15** and **16**.

We had originally envisioned that decarboxylation of **15** would deliver (-)-**3**. However, **15** was only sparingly soluble in non-alcoholic solvents, and several attempts to form either the acid chloride of **15** or a mixed anhydride that might be converted to a derivative suitable for decarbonylation were unsuccessful. Moreover, the stereoselectivity in the key vinylogous Mannich reaction was modest. Consequently, an alternate route to (-)-**3** was developed.

Because Hanessian and McNaughton-Smith observed that vinylogous Mannich reactions of iminium ions derived from 2-methoxy-5-pyrrolidine derivatives proceeded with excellent stereoselectivity,[10b] we reasoned that the iminium ion generated from the methoxy pyrrolidine **20** might be a better electrophilic partner for the furan **10** (Scheme 3). Accordingly, commercially available **17** was converted by serial oxygen and nitrogen protection followed by hydride reduction to give **20** in 74% overall yield. Subsequent reaction of **20** with **10** in the presence of trimethylsilyl trifluoromethanesulfonate (TMS–OTf) at -78 °C produced a mixture (3.1:1) of **21** and its C(5) epimer **22** in 61% yield. No C(2') isomeric adducts arising from addition of the furan *syn* to the 5-alkyl substituent in **20** were observed, although small quantities of these products may have escaped detection. The ^{1}H NMR

spectrum of the crude reaction mixture was again complicated by the presence of rotational isomers if the data were acquired at ambient temperature, but at 100 °C, the peaks from the rotamers coalesced so the diastereomeric ratio could be easily determined. Surprisingly, when the vinylogous Mannich reaction was conducted at 0 °C, the ratio of **21** to **22** improved to 4.8:1 (57% yield). A variety of Lewis acids including $Zn(OTf)_2$, $ZnCl_2$, $Cu(OTf)_2$, $Sc(OTf)_3$, $SnCl_2$, and $TiCl_4$ were surveyed as promoters of the addition, and although there was no significant variation in the diastereomeric ratio of products, the highest yield was obtained using TMS-OTf. The structures of **21** and **22** were initially assigned based upon their NMR spectra, but these assignments were ultimately secured by X-ray analyses of their transformation products (*vide infra*).

Scheme 3



Reduction of the carbon-carbon double bond of the major diastereomer **21** by catalytic hydrogenation proceeded with concomitant removal of the carbobenzyloxy (Cbz) protecting group and spontaneous lactone-lactam rearrangement to give, after acid-catalyzed removal of the primary hydroxyl protecting group, the bicyclic lactam **23** in 66% overall yield. This one-pot procedure gave a better overall yield of **23** than the corresponding two-step procedure. As noted previously, the spontaneous lactone-lactam rearrangement to give **23** was somewhat surprising as prior art suggested that, depending on the pairwise stereochemical relationship between C(5) and C(2'), either heating or treatment of the precursor amino lactone with catalytic base would be necessary.[9a,10b] As expected, we observed that reduction of the minor diastereomer **22** cleanly gave the amino lactone **24**, which rearranged to the corresponding fused bicyclic lactam only upon exposure to sodium methoxide; acid-catalyzed removal of the hydroxyl protecting group furnished **25**. The structures of **23** and **25** were unequivocally established by X-ray crystallographic analysis.

Several methods for removing superfluous hydroxymethyl groups have been reported, but the clever use of Raney nickel reported by Krafft and coworkers was appealing because of its simplicity.[16] Thus, heating a mixture of **25** and Raney nickel (W-2) in refluxing toluene produced (-)-**3** in 71% yield, thereby completing the formal asymmetric synthesis of pumiliotoxin 251D (**2**). The quality of the Raney nickel was critical to the successful

removal of the pendant hydroxy methyl group. For example, use of commercially available catalyst failed to promote the reaction to completion, even after prolonged heating. On the other hand, freshly prepared catalyst effected the conversion in approximately 4 h.[17] Although tertiary alcohols may also be slowly deoxygenated under these conditions, only traces of a compound lacking the tertiary hydroxyl group were detected in the ^{1}H NMR spectrum of the crude reaction mixture.

This succinct approach to (-)-**3** further demonstrates the utility of the vinylogous Mannich reaction as a useful construction in alkaloid synthesis. Indeed, the indolizidine ring system, which is produced by an efficient lactone-lactam rearrangement of the initial adduct, is widespread in Nature. The overall yield in the asymmetric synthesis of (-)-**3**, which has a longest linear sequence of 6 steps and requires only 8 chemical steps from commercially available materials, is 16%. Other novel applications of vinylogous Mannich reactions will be reported in due course.

EXPERIMENTAL SECTION

General. Unless otherwise indicated, all reagents were obtained from commercial suppliers and used without further purification. Solvents were dried according to established protocols by distillation under nitrogen from an appropriate drying agent: Tetrahydrofuran (THF) was distilled from potassium/benzophenone, and diethyl ether (Et_2O) was distilled from sodium/benzophenone; dichloromethane (CH_2Cl_2), tetramethyethylenediamine (TMEDA), toluene, and triethylamine (Et_3N) were distilled from calcium hydride. Reactions involving air and/or moisture sensitive reagents were conducted under an argon atmosphere, and glassware was flame-dried under vacuum (<0.1 torr). Flash chromatography was conducted using ICN Biomedicals ICN-SILITech 32-63d silica gel with the indicated solvents. ^{1}H and ^{13}C NMR spectra of compounds were recorded at the indicated field strength at room temperature as solutions in deuteriochloroform ($CDCl_3$) unless otherwise indicated. Chemical shifts are expressed in parts per million downfield from tetramethylsilane (TMS) and were referenced to the solvent. Spectral splitting patterns were designated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplets composed of chemically non-equivalent ^{1}H's; br, broad; app, apparent. Infrared (IR) spectra were recorded either as films on sodium chloride plates or as KBr pellets as indicated. Mass spectra were obtained using chemical ionization (CI) technique.

5-Methyl-2-triisopropylsilyloxyfuran (10). To a solution of Et_3N (9.76 mL, 7.08 g, 70.0 mmol) and 2-(5*H*)-furanone (3.55 mL, 4.20 g, 50.0 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C was added triisopropylsilyl trifluoromethanesulfonate (16.13 mL, 18.39 g, 60.0 mmol) over 15 min. Stirring was continued at 0 °C for 15 min then at rt for 16 h. The amber solution was diluted with Et_2O/petroleum ether (1:1, 250 mL) and washed with cold saturated aqueous $NaHCO_3$ (2 x 150 mL) and then cold saturated aqueous $CuSO_4$ (150 mL). The organic phase was dried ($MgSO_4$) and concentrated to afford a yellow liquid that was distilled (65 °C, 0.35 mmHg) to yield 11.48 g (95%) of 2-triisopropylsilyloxyfuran as a clear, colorless oil. ^{1}H NMR (250 MHz) δ 6.77 (dd, J = 2.2, 1.1 Hz, 1 H), 6.17 (dd, J = 3.1, 2.2 Hz, 1 H), 5.09 (dd, J = 3.1, 1.1 Hz, 1 H), 1.33–1.15 (m, 3H), 1.07 (d, J = 6.7 Hz, 18H); ^{13}C NMR (62.9 MHz) δ 157.0, 131.8, 111.1, 83.4, 17.5, 12.2; IR (film) 1617, 1611 cm^{-1}; mass spectrum (CI) *m/z* 240.1537 [$C_{13}H_{24}O_2Si$ requires 240.1546], 241 (base), 239.

To a solution of 2-triisopropylsilyloxyfuran (25.00 g, 104 mmol) and TMEDA (28.25 mL, 21.75 g, 187 mmol) in anhydrous THF (520 mL) at 0 °C was added a cyclohexane solution of *sec*-butyllithium (1.3 M, 242.86 mL, 187 mmol) over 30 min and stirring continued at 0 °C for 2 h. Iodomethane (25.98 mL, 59.00 g, 416 mmol) was added, and the resulting yellow solution was stirred at rt for 16 h. The mixture was washed with saturated

aqueous $NaHCO_3$ (2 x 250 mL), and the layers were separated. The combined aqueous layers were extracted with Et_2O (3 x 250 mL) and the combined organic layers were washed with saturated aqueous $CuSO_4$ (2 x 250 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The resultant orange oil was filtered through silica gel (100 g, pentane eluant) to afford 24.38 g (95.5%) of **10** as a clear, colorless oil. ^1H NMR (250 MHz, $CDCl_3$) δ 5.73 (dd, J = 3.0, 1.1 Hz, 1 H), 4.96 (d, J = 3.0 Hz, 1 H), 2.14 (d, J = 1.1 Hz, 3 H), 1.35–1.17 (m, 3 H), 1.08 (d, J = 6.7 Hz, 18 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 155.3, 140.9, 106.0, 83.5, 17.7, 13.5), 12.2; IR (film) 1781, 1711, 1625, 1591 cm^{-1}; mass spectrum (CI) *m/z* 254.1612 [$C_{14}H_{26}O_2Si$ (M+1) requires 254.1711], 271, 255 (base), 223.

(5S, 2'S, 5'S)- and (5R, 2'S, 5'S)-1'-Benzyloxycarbonyl-5'-carboxybenzyl-2'-pyrrolidinyl]-5-methylfuran-2(5H)-one (13 and 14). To a solution of *N*-benzyloxycarbonylpyroglutamate benzyl ester[18] (1.554 g, 4.4 mmol) in anhydrous THF (18 mL) at -78 °C was added a solution of Dibal-H in CH_2Cl_2 (1 M, 5.28 mL, 5.28 mmol). The solution was stirred at -78 °C for 1 h. Saturated aqueous potassium sodium tartrate (4 mL) was added, and the mixture was stirred at rt for 30 min. Solid Na_2SO_4 (4 g) was added, and the mixture was stirred for 30 min. Celite (4 g) was added, and the mixture was stirred for 15 min. The mixture was filtered, and the retained solids were washed with Et_2O (3 x 10 mL). The combined filtrates were concentrated to give 1.526 g (98%) of **12** as a clear, colorless oil that was used without further purification.

To a solution of **10** (0.314 g, 1.28 mmol) and **12** (0.453 g, 1.28 mmol) in CH_3CN (3 mL) at rt was added a solution of Et_2AlCl in hexane (1 M, 1.28 mL, 1.28 mmol). The solution was stirred for 30 min, and saturated aqueous potassium sodium tartrate (0.5 mL) was added. The mixture was stirred for 30 min, and solid Na_2SO_4 (1.0 g) was added. After stirring for 1 h, the mixture was filtered, and the retained solids were washed with CH_2Cl_2 (3 x 3 mL). The combined filtrates were dried (Na_2SO_4) and concentrated. The residue was seperated by flash chromatography eluting with a step gradient of Et_2O:hexanes (3:7, 250 mL; 7:13, 100 mL, 2:3, 100 mL; 9:11, 100 mL; 1:1) afforded 0.134 mg (24%) of **13** and 0.121 g (22%) of **14**. For **13:** ^1H NMR (500 MHz, DMSO-d_6,100 °C) δ 7.58 (d, J = 5.6 Hz, 1 H,) 7.36–7.26 (comp, 10 H), 5.86 (d, J = 5.6 Hz, 1 H), 5.02 (s, 4 H), 4.29 (dd, J = 8.0, 1.5 Hz, 1 H) 4.23 (d, J = 9.1 Hz, 1 H), 2.43–2.34 (m, 1 H), 2.12–2.04 (comp, 2 H), 1.89–1.84 (m, 1 H), 1.44 (s, 3 H); ^{13}C NMR (125 MHz) δ 171.2, 171.0, 159.7, 154.0, 135.6, 135.2, 127.8, 127.7, 127.5, 127.4, 127.3, 127.2, 117.5, 90.03, 67.4, 66.1, 65.6, 61.8, 59.8, 28.2, 24.2, 20.7; IR (film) 1759, 1748, 1713 cm^{-1}; mass spectrum *m/z* 436.1747 ($C_{25}H_{26}NO_6$ (M+1) requires 436.1760), 338, 294 (base), 204. For **14**: ^1H NMR (500 MHz) δ 7.71 (d, J = 5.7 Hz, 1 H), 7.36–7.24 (comp, 10 H), 6.07 (d, J = 5.7 Hz, 1H), 5.02 (s, 4 H), 4.39 (d, J = 9.1 Hz, 1 H), 4.27 (d, J = 8.6 Hz, 1 H), 2.34–2.25 (m, 1 H), 2.05–1.95 (m, 1 H), 1.89–1.85 (m, 1 H), 1.83–1.77 (m 1 H), 1.38 (s, 3 H); ^{13}C NMR (125 MHz) δ 171.3, 170.9, 160.2, 154.5, 135.7, 135.2, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 119.0, 89.9, 76.7, 66.3, 65.7, 62.1, 60.1, 28.5, 24.6, 20.3; IR (film) 1752, 1739, 1706 cm^{-1}; mass spectrum *m/z* 436.1767 ($C_{25}H_{26}NO_6$ (M+1) requires 436.1760), 436 (base), 391, 338, 302, 204.

(5R, 6S, 9S)-9-Carboxy-5-hydroxy-5-methyl-1-azabicyclo[4.3.0]nonane-2-one (15). A mixture of 10% Pd on carbon (18 mg, 17 μmol), **13** (73 mg, 168 μmol), and CH_3OH (1 mL) were stirred under H_2 (1 atm) at rt for 16 h. The mixture was then filtered through celite, and the filter cake was washed with CH_3OH (3 x 1 mL). The combined filtrates were concentrated to give 38 mg of a colorless oil. The oil thus obtained was dissolved in a freshly prepared solution of $NaOCH_3$ (1.1 M in CH_3OH, 500 μL, 550 μmol) at rt, and the mixture was stirred for 4 h. A solution of HCl in CH_3OH (2 M, 250 mL) was then added. The mixture was concentrated, and the residual solids were triturated with boiling *sec*-butanol (2 mL). The solids were removed by filtration, and the filtrate was concentrated to give 33 mg (92%) of **15** as a colorless glass. An analytical sample was crystallized from MeOH/*i*–Pr_2O: mp 223–225 °C; ^1H NMR (500 MHz, CD_3OD) δ 4.32 (app t, J = 8.5 Hz, 1 H), 3.62 (dd, J = 10.6,

5.6 Hz, 1 H,), 2.44 (ddd, J = 18.4, 11.6, 7.0 Hz), 2.36–2.30 (comp, 1 H), 1.97–1.91 (comp, 2 H), 1.88–1.72 (comp, 3 H), 1.27 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 178..8, 171.5, 68.2, 68.0, 62.4, 35.5, 29.0, 28.8, 26.6; IR (KBr) 3504, 1690, 1570 cm^{-1}; mass spectrum *m/z* 214.1089 ($C_{10}H_{15}NO_4$ (M+1) requires 214.1079), 214 (base), 196, 168.

(5S, 6S, 9S)-9-Carboxy-5-hydroxy-5-methyl-1-azabicyclo[4.3.0]nonane-2-one, sodium salt (16). A mixture of 10% Pd on carbon (12 mg, 12 μmol), **13** (50 mg, 115 μmol), and CH_3OH (1 mL) were stirred under H_2 (1 atm) at rt for 16 h. The mixture was then filtered through celite, and the filter cake was washed with CH_3OH (3 x 1 mL). The combined filtrates were concentrated to give 24.4 mg of a colorless oil. The oil thus obtained was dissolved in a freshly prepared solution of $NaOCH_3$ (1.1 M in CH_3OH, 500 μL, 550 μmol) at rt, and the mixture was stirred for 4 h. The mixture was concentrated, and the residual solids were triturated with boiling *sec*-butanol (2 mL). The solids were removed by filtration, and the filtrate was concentrated to give 22 mg (81%) of **16** as a colorless glass. An analytical sample was prepared by crystallization from MeOH/acetone: mp >300 °C; ^{1}H NMR (500 MHz, CD_3OD) δ 4.32 (app t, J = 8.3 Hz, 1 H), 3.69 (dd, J = 10.4, 5.6 Hz, 1 H), 2.50 (ddd, J = 18.4, 7.2, 1.5 Hz, 1 H), 2.34–2.25 (comp, 2 H, C8-H), 2.08–1.97 (comp, 2 H), 1.83–1.75 (comp, 2 H), 1.73–1.65 (m, 1 H), 1.12 (s, 3 H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.7, 170.7, 70.1, 68.2, 62.0, 37.0, 30.8, 29.0, 27.6, 19.7; IR (film) 3382, 1560 (br); mass spectrum *m/z* 236.0891 ($C_{10}H_{15}NNaO_4$ (M+1) requires 236.0899), 235 (base), 233, 208, 185, 168.

(S)-(-)-5-Diphenyl*tert*-butylsilyloxymethyl-2-pyrrolidinone (18). A solution of (*S*)-(-)-5-hydroxymethyl-2-pyrolidinone (**17**) (3.394 g, 29.5 mmol), imidazole (5.021 g, 73.8 mmol), and chlorodiphenyl*tert*-butylsilane (9.730 g, 35.4 mmol) in DMF (150 mL) was stirred at rt for 36 h. The solvent was evaporated, and the residual oil was partitioned between sat. aq. $NaHCO_3$ (50 mL) and CH_2Cl_2 (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residual oil was purified by flash chromatography eluting with EtOAc/hexanes (2:3) to afford **18** (9.798 g, 94%) as a viscous oil which turned into a glass upon standing and whose spectral data are in accord with the literature.[19]

(S)-(-)-5-Diphenyl*tert*-butylsilyloxymethyl-*N*-benzyloxycarbonyl-2-pyrrolidinone (19). To a solution of **18** (5.303 g, 15 mmol) in anhydrous THF (45 mL) at -78 °C was added a solution of sodium hexamethyldisilazide (1 M in THF, 18 mL, 18 mmol). The mixture was stirred for 30 min at -78 °C, whereupon benzyl chloroformate (3.071 g, 18 mmol) was added. The mixture was stirred at -78 °C for 1 h, the cooling bath was removed, and the mixture was stirred at rt for 3 h. Aq. HCl (0.5 M, 30 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL), and the combined organics were dried (Na_2SO_4) and concentrated. The residual oil was purified by flash chromatography eluting with EtOAc/hexanes (1:4) to give **19** (6.767 g, 92%) as a viscous oil. ^{1}H NMR (300 MHz) δ 7.67–7.58 (comp, 5 H), 7.49–7.28 (comp, 10 H), 5.21 (d, J = 12.3 Hz, 1 H), 5.14 (d, J = 12.3 Hz, 1 H), 4.30–4.25 (m, 1 H), 3.92 (dd, J = 10.7, 3.9 Hz, 1 H), 3.73 (dd, J = 10.7, 2.3 Hz, 1 H), 2.85 (dt, J = 17.5, 10.5 Hz, 1 H), 2.53–2.43 (m, 1 H), 2.18–2.12 (comp, 2 H), 1.06 (s, 9 H); ^{13}C NMR (75.5 MHz) δ 175.3, 152.0, 136.2, 136.1, 135.8, 133.5, 129.1, 128.8, 128.7, 128.4, 68.4, 65.4, 59.3, 32.8, 27.4, 21.8, 19.7; IR (film) 1792, 1751, 1718 cm^{-1}; mass spectrum (CI) *m/z* 488.2253 ($C_{29}H_{34}NO_4Si$ (M+1) requires 488.2257), 198, 276, 320, 430, 444 (base), 488.

(5S, 2'S, 5'S)- and (5R, 2'S, 5'S)-1'-Benzyloxycarbonyl-5'-diphenyl*tert*-butylsilyloxymethyl-2'-pyrrolidinyl-5-methylfuran-2(5H)-one (21 and 22). To a solution of **19** (4.394 g, 9.0 mmol) in MeOH (45.0 mL) at -10 °C was added $NaBH_4$ (2.724 g, 72.0 mmol) in 4 equal portions over 1 h. The mixture was stirred at -10

°C for an additional 30 min, whereupon conc. HCl was added to adjust the pH to 2. The mixture was stirred for an additional 15 min and then neutralized with sat. aq. $NaHCO_3$. The mixture was concentrated and partitioned between H_2O (25 mL) and CH_2Cl_2 (15 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford **20** as an oily mixture of two anomers (4.314 g, 86%) that was use without further purification.

To a solution of **10** (0.608 g, 2.4 mmol) and **20** (1.000 g, 2.0 mmol) in Et_2O (10 mL) at 0 °C was added TMS-OTf (0.044 mg, 36μL, 0.2 mmol). The mixture was stirred at 0 °C for 36 h, whereupon sat. aq. $NaHCO_3$ (10 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The resulting oil was purified by flash chromatography eluting with EtOAc/hexanes (3:17) to afford, in order of elution, pure **21** (0.476 g), a mixture of **21** and **22** (0.053 g), and pure **22** (0.113 g) as viscous oils for a total of 0.642 g (57%). For **21**: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.61–7.53 (comp, 7 H), 7.40 7.36 (comp, 6 H), 7.30–7.21 (comp, 3 H), 5.76 (d, J = 5.6 Hz, 1 H), 5.02 (d, J = 12.3 Hz, 1 H), 4.83 (d, J = 12.3 Hz, 1 H), 4.19 (d, J = 7.9 Hz, 1 H), 3.80–3.74 (comp, 3 H), 2.26–2.13 (comp, 2 H), 2.04 (dd, J = 12.2, 7.0 Hz, 1 H), 1.97 (dd, J = 11.4, 7.0 Hz, 1 H), 1.42 (s, 3 H), 1.01 (s, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 171.1, 159.9, 153.5, 135.8, 134.4, 132.8, 132.7, 129.1, 127.6, 127.2, 127.1, 116.7, 90.5, 63.4, 62.1, 58.8, 26.8, 26.1, 24.3, 20.9, 18.2; IR (film) 1760, 1697 cm^{-1}; mass spectrum (CI) *m/z* 570.2686 ($C_{34}H_{40}NO_5Si$ (M+1) requires 570.2676), 570 (base), 472, 338, 260. For **22**: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.70 (d, J = 5.7 Hz, 1 H), 7.61–7.55 (comp, 6 H), 7.45–7.36 (comp, 6 H), 7.25 (b s, 3 H), 6.02 (d, J = 5.7 Hz, 1 H), 5.08 (d, J = 12.5 Hz, 1 H), 4.90 (d, J = 12.5 Hz, 1 H), 4.19 (d, J = 7.7 Hz, 1 H), 3.94–3.89 (m, 1 H), 3.88–3.64 (m, 1 H), 3.78 (dd, J = 9.8, 2.6 Hz, 1 H), 2.18–2.03 (comp, 2 H), 2.00–1.95 (m, 1 H), 1.80 (q, J = 5.6 Hz, 1 H), 1.38 (s, 3 H), 1.00 (s, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 170.8, 160.5, 153.9, 135.9, 134.4, 132.8, 132.7, 129.1, 127.6, 127.1, 126.8, 118.5, 90.2, 65.9, 63.3, 62.4, 58.9, 27.1, 26.1, 24.7, 20.3, 18.2; IR (film) 1751, 1698 cm^{-1}; mass spectrum (CI) *m/z* 570.2673 ($C_{34}H_{40}NO_5Si$ (M+1) requires 570.2676), 570 (base), 488, 472, 338.

(5R, 6S, 9S)-5-Hydroxy-9-hydroxymethyl-5-methyl-1-azabicyclo[4.3.0]nonane-2-one (23). A mixture of 10% Pd on carbon (0.081 mg, 0.08 mmol) and **21** (0.436 g, 0.77 mmol) in MeOH (8.0 mL) were stirred under H_2 (1 atm) for 12 h, whereupon a solution of HCl (1 M in MeOH, 8.0 mL, 8 mmol) was added. The mixture was stirred at 0 °C for 36 h. Solid $NaHCO_3$ (1.0 g) was added, and the mixture was stirred at rt for 1 h. The mixture was filtered through celite, and the retained solids were washed with MeOH (2 x 1 mL). The combined filtrates were concentrated to give a waxy solid that was crystallized from CH_3CN to give **23** (0.072 g, 47%) as white needles. The mother liquor was purified by flash chromatography eluting with MeOH/CH_2Cl_2 (3:47) to give additional **23** (0.029 g, 19%). Mp 177–178 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 4.12–4.04 (m, 1 H), 3.79 (dd, J = 11.2, 3.9 Hz, 1 H), 3.57 (dd, J = 11.2, 4.4 Hz, 1 H), 3.48 (dd, J = 10.8, 5.4 Hz, 1 H), 2.53–2.28 (comp, 2 H), 2.08–2.00 (m, 1 H), 1.96–1.65 (comp, 5 H), 1.26 (s, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 171.2, 67.7, 67.0, 63.7, 60.8, 34.5, 28.4, 25.8, 25.2, 25.1; IR (KBr) 3327, 3224, 1606 cm^{-1}; mass spectrum *m/z* 200.1292 (calculated for $C_{10}H_{18}NO_3$ (M+1) requires 200.1287), 200 (base) 182, 168.

(5R, 2'S, 5'S)- 5'-Diphenyl*tert*-butylsilyloxymethyl-2'-pyrrolidinyl-5-methylfuran-2(5H)-one (24). A mixture of 10% Pd on carbon (0.1054 g, 0.1 mmol) and **22** (0.5886 g, 1.03 mmol) in MeOH (5 mL) were stirred under H_2 (1 atm) for 12 h. The reaction mixture was filtered through celite, and the retained solids were washed with MeOH (2 x 5 mL). The combined filtrates were concentrated, and the residual oil was purified by flash chromatography eluting with Et_2O/hexanes (3:2) to afford **24** (0.152 g, 35%) as a clear, colorless oil. ^{1}H NMR

(300 MHz) δ 7.68–7.65 (comp , 4 H), 7.47–7.37 (comp, 6 H), 3.59 (dd, J = 10.2, 4.4 Hz, 1 H), 3.51 (dd, J = 10.2, 6.0 Hz, 1 H), 3.42 (app t, J = 7.9 Hz, 1 H), 3.33 (dt, J = 10.7, 6.0 Hz, 1 H), 2.70 (ddd, J = 17.5, 10.9, 6.4 Hz, 1 H), 2.63–2.52 (m, 1 H), 2.35 (ddd, J = 12.4, 10.9, 7.1 Hz, 1 H), 2.07 (br s, 1 H), 1.91–1.71 (comp, 3 H), 1.63–1.51 (m, 1 H), 1.46–1.29 (m, 1 H), 1.34 (s, 3 H), 1.08 (s, 9 H); ^{13}C NMR (75 MHz) δ 177.9, 136.2, 136.1, 134.1, 134.0, 130.3, 128.4, 90.0, 66.4, 64.3, 60.6, 30.4, 28.5, 28.3, 27.5, 27.3, 25.0, 19.9; IR (film) 3355, 1770 cm^{-1}; mass spectrum *m/z 438.2457* ($C_{26}H_{36}NO_3Si$ (M+1) requires 438.2464), 438 (base), 360, 338, 243, 211, 182.

(5S, 6S, 9S)-5-Hydroxy-9-hydroxymethyl-5-methyl-1-azabicyclo[4.3.0]nonane-2-one (25). To a solution of **24** (0.081 g, 0.19 mmol) in MeOH (1 mL) at 0 °C was added a solution of NaOMe (1 M in MeOH, 0.17 mL, 0.17 mmol). The solution was stirred for 4 h, and a solution of HCl in MeOH (1 M, 1 mL, 1 mmol) was then added. The mixture was stirred at 0 °C for an additional 36 h. An aqueous solution of NaOH (6 M, 0.20 mL) was added, and the mixture was concentrated under reduced pressure. The residual waxy solid was triturated with hot CH_3CN (2 mL), and the solids were then removed by filtration. Upon cooling, **25** crystallized from the filtrate as thin white needles (0.019 mg, 51%): mp 148–149 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 4.11–4.03 (m, 1 H), 3.81 (dd, J = 11.2, 4.1 Hz, 1 H), 3.57 (dd, J = 11.2, 4.1 Hz, 1 H), 3.53 (dd, J = 10.7, 5.5 Hz, 1 H), 2.52 (ddd, J = 18.5, 7.2, 2.1 Hz, 1 H), 2.29 (ddd, J = 18.5, 11.4, 7.3 Hz, 1 H), 2.07–2.20 (comp, 2 H), 1.91 (dt, J = 12.1, 7.3 Hz, 1 H), 1.81- 1.74 (comp, 2 H), 1.72–1.56 (m, 1 H), 1.12 (s, 3 H); ^{13}C NMR (75 MHz, CD_3OD) δ 171.6, 70.0, 68.7, 63.9, 61.6, 36.6, 31.0, 27.0, 26.2, 20.1; IR (KBr) 3352, 3164, 1603 cm^{-1}; mass spectrum *m/z* 200.1286 ($C_{10}H_{18}NO_3$ (M+1) requires 200.1287), 200 (base), 182, 168, 154.

(5R, 6S)-5-Hydroxy-5-methyl-1-azabicyclo[4.3.0]nonane-2-one ((-)-3). Raney nickel (W-2)[17] (0.300 g) was washed with H_2O (8 x 1 mL), *i*-PrOH (2 x 1 mL), and toluene (1 x 1 mL). To the Raney nickel was added **21** (0.050 g, 0.25 mmol) and toluene (2 mL). The mixture was heated at 140 °C for 4 h, was cooled to rt, and the solids were removed by filtration through celite. The retained solids were washed with boiling MeOH (2 x 1 mL), and the combined filtrates were concentrated. The residual oil was purified by flash chromatography eluting with $MeOH/CH_2Cl_2$ (1:19) to give (-)-**3** as a white solid. An analytical sample was prepared by crystallization from EtOAc/*i*-Pr_2O: mp 94–95 °C (lit mp 90–92 °C;[4b] 89-91 °C[4e]); $[\alpha]^{22}_D$ -55.0° (c 0.79 $CHCl_3$){lit $[\alpha]^{21}_D$ -47.0° (c 0.97, $CHCl_3$);[4b] $[\alpha]^{29}_D$ -53.0° (c 0.97, $CHCl_3$)[4e]}; ^{1}H NMR (300 MHz) δ 3.51 (dd, J = 9.3, 4.6 Hz, 2 H), 3.37 (dd, J = 9.9, 5.8 Hz, 1 H), 2.53 (ddd, J = 18.3, 11.4, 7.3 Hz, 1 H), 2.37 (dd, J = 18.3, 6.6 Hz, 1 H), 2.18 (br s, 1H), 2.01–1.69 (comp, 6 H,), 1.30 (s, 3 H); ^{13}C NMR (75 MHz) δ 169.1, 67.3, 66.2, 45.7, 34.9, 28.0 26.3, 26.2, 21.9; IR (film) 3380, 1620 cm^{-1}; mass spectrum *m/z* 170.1177 ($C_9H_{16}NO_2$ (M+1) requires 170.1181), 170 (base), 152.

Acknowledgments. We thank the National Institutes of Health and the Robert A. Welch Foundation for supporting this research. We also thank Dr. Vincent M. Lynch for performing X-ray crystallographic analyses of compounds **15**, **16**, **23**, and **25**.

References and Notes

1. For a review of simple indolizidines, see Takahata, H.; Momose, T. in "the Alkaloids"(Cordell, G. A. Ed.), Vol. 44, p 189-256. Academic Press, New York, 1993.
2. For a review of the syntheses of pumiliotoxin A and allopumiliotoxin alkaloids, see Overman, L. E.; Franklin, A. S. *Chem. Rev.* **1996**, *96*, 505–522. For a study on the biological activity of pumiliotoxins, see

Bargar, T. M.; Lett, R. M.; Johnson, P. L.; Hunter, E. J.; Chang, C. P.; Pernich, D. J.; Sabol, M. R.; Dick, M. R. *J. Agric. Food Chem* **1995**, *43*, 1044–1051.

3. Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. J.; Karle, I. L. *J. Am. Chem. Soc*, **1980**, *102*, 830–836.
4. (a) Overman, L. E.; Bell, K. L., Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192–4201. (b) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652–2656. (c) Honda, T.; Hoshi, M.; Kanai, K.; Tsubukim, M. *J. Chem. Soc., Perkin. Trans. I* **1994**, 2091–2101. (d) Cossy, J.; Cases, M.; Pardo, D. G. *Bull. Chem. Soc. Fr.* **1997**, *134*, 141–144. (e) Barrett, A. G. M.; Damaini, F. *J. Org. Chem.* **1999**, *64*, 1410–1411.
5. For a recent review of the Mannich reaction, see: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1045.
6. For a review of the reactions of trialkylsilyloxyfurans with electrophiles, see: (a) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607–626. See also (b) Casiraghi, G.; Rassu, G. *Tetrahedron* **1990**, *46*, 5807–5824. (c) Pelter, A.; Ward, R. S.; Sirit, A. *Tetrahedron: Asym.* **1994**, *5*, 1745–1762. (d) Harding, K. E.; Coleman, M. T.; Liu, L. T. *Tetrahedron Lett.* **1991**, *32*, 3795–3798.
7. (a) Martin, S. F.; Liras, S. *J. Am. Chem. Soc.* **1993**, *115*, 10450–10451. (b) Martin, S. F.; Clark, C. C.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236–3242. (c) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299–3300.
8. (a) Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, 55–57. (b) Martin, S. F.; Bur, S. K. *Tetrahedron Lett.* **1997**, *38*, 7641–7644.
9. (a) Morimoto, Y.; Nishida, K.; Hayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 5773–5776. (b) Morimoto, Y.; Iwahashi, M. *Synlett* **1995**, 1221–1222.
10. (a) Hanessian, S.; Raghavan, S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1697–1702. (b) Hanessian, S.; McNaughton-Smith, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1567–1572.
11. Pichon, M.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1996**, *37*, 7963–7966.
12. Martin, S. F.; Barr, K. J. Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc* . submitted.
13. For example, see: (a) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868–4874. (b) Sato, K.; Koga, T.; Masuya, K.; Tanino, K.; Kuwajima, I. *Synlett*, **1996**, 751–752. (c) Comins, D. L.; Zhang, Y.; Zheng, X. *Chem. Commun.* **1998**, 2509–2510.
14. For example, see: (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153–7152. (b) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474–2475. (c) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242–4243. (d) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548–4549.
15. For example, see in: Rebek, Jr., J.; Tai, D. F.; Shue, Y.-K. *J. Am. Chem. Soc.* **1984**,*106*, 1813-1819. See also refs 9a,10b.
16. Krafft, M. E.; Crooks, W. J. III; Zorc, B.; Milczanowski, S. E. *J. Org. Chem.* **1988**, *53*, 3158–3163.
17. Mozingo, R. *Org. Syntheses Coll. Vol. 3*, **1955**, 181–183.
18. August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W. *J. Chem. Soc., Perkin. Trans. I* **1996**, 507–514.
19. Pickering, L.; Malhi, B. S.; Coe, P. L., Walker, R. T. *Nucleosides & Nucleotides* **1994**, *13*, 1493–1506.