Articles

Cyclization of Chiral Carbon-Centered Aziridinyl Radicals: A New Route to Azirino[2′,3′:3,4]pyrrolo[1,2-*a*]indoles

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A carbon-centered aziridinyl radical has been generated from the ester of chiral aziridine carboxylic acid **5b**. The resultant radical has been cyclized directly and has been brominated with $CBrCl_3$. The bromo aziridines have also been cyclized reductively in the presence of *n*-Bu_3SnH. Dihydroindole **8b** bears the same relative and absolute stereochemistry as the mitomycin C nucleus.

Introduction

Carbon-centered aziridinyl radicals are species that have not been the subject of extensive study. In 1976, Yamanaka reported the stereospecific reduction of a series of 1,3-diphenyl-2,2-dihaloaziridines in the presence of *n*-Bu_3SnH.[1] The chlorofluoro, bromofluoro, and bromochloro diastereomers were found to reduce stereospecifically signifying slow inversion of the 2-haloaziridinyl radical, an observation in accord with the known behavior of α-chlorocyclopropyl and α-fluorocyclopropyl radicals.[2–4] During the course of our studies, Tamm reported[5,6] the decarboxylation of an aziridine carboxylic acid by the Barton thiohydroxamic acid anhydride method.[7] Our interest in the formation of carbon-centered aziridinyl radicals was stimulated by the possibility that they may, in spite of Yamanaka's observations, undergo rapid inversion and subsequent intramolecular or intermolecular reactions. This expectation was buoyed by our recent success in the generation and cyclization of oxiranyl radicals derived from chiral glycidic acids.[8] The successful cyclization of carbon-centered aziridinyl radicals would permit direct access to reactive mitomycin-like structures, a topic of current interest in the search for effective antitumor agents.[9]

Results and Discussion

The hydroxy aziridine carboxylic acid ester **4a** was prepared in 47% yield from the glycidic ester **1**[10] by the general epoxide → aziridine procedure of Blum (Scheme 1).[11] Tanner[12,13] and Zwanenburg[14] have described the opening of glycidates with azide. The azide opening of the glycidate in Scheme 1 produced a mixture of azido alcohols, which was inconsequential to the eventual formation of the aziridine **2a** although it was formed as a separable 12:1 mixture with its cis isomer. The minor component **2b** was presumed to arise by C_2 epimerization at the azido alcohol stage. A critical aspect of the aziridine formation in the triphenylphosphine reduction was the use of toluene dried with 4 Å molecular sieves to avoid the formation of undesired amino alcohols.

The nitrogens of the aziridines **2** were protected as their Boc derivative. The use of DMAP in conjunction with $(Boc)_2O$ proved crucial to the success of the acylation.[15] The trans isomer **3a** displayed its C_2 hydrogen as a doublet (J = 2.5 Hz) while the cis isomer displayed a doublet (J = 6.6 Hz) for the same hydrogen.[16] The desilylation of **3a** with fluoride to produce aziridinol **4a** proceeded smoothly. However, prolonged exposure of **4a** to the reaction conditions initiated N → O migration of the Boc group to produce aziridine **4c**. Both aziridines **4a** and **4c** proved enantiomerically pure (^1H and ^{19}F NMR) upon derivatization as the Mosher ester, (*R*)-MPTA.[17] The purified alcohol could be stored for at least two weeks at −20 °C.

Alkylation of the sodium salt of 3-cyanoindole with the mesylate of alcohol **4a** gave N-alkylated indole **5a** in low yield (<30%). When the triflate **4b** was prepared in situ and subjected to the alkylation, ester **5a** was isolated in 72% yield. Saponification of the ester with LiOH provided the aziridine carboxylic acid **5b**, which was converted to the thiohydroxamic acid anhydride **5c** through the agency of 2,2′-dithiobis(pyridine N-oxide)/n-Bu_3P.[18]

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1994.

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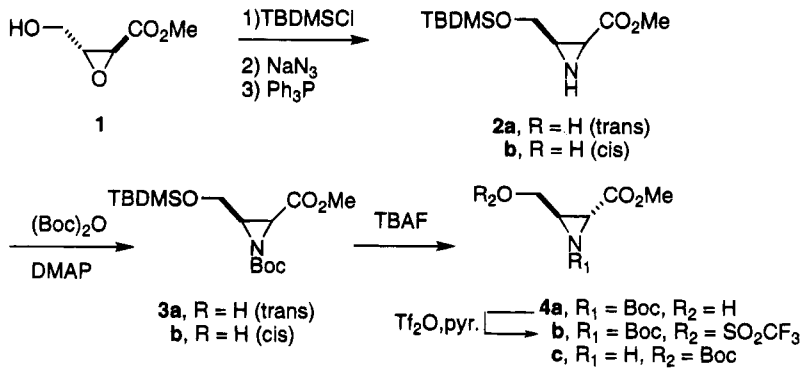
Scheme 1



Photolysis of a degassed solution of thiohydroxamic acid anhydride **5c** (0.05M, CH_2Cl_2) with a 500 W tungsten halogen lamp provided the symmetrical dimer **6** (31%), 2,2′-dipyridyl disulfide (80%), aziridine carboxylic acid **5b** (16%), and trace amounts of indole **7**, a product assigned as cyanohydrin **8a**, and aldehyde **9**, which appeared upon chromatography of the reaction mixture. The structures of the minor components were assigned by a combination of ^{1}H NMR, infrared, and high resolution mass spectroscopy. The aldehyde **9** is believed to arise from hydrolysis of a species such as **15d**, which, although not identified in this study, has been observed using a related thiohydroxamic acid initiator in the aziridine and epoxide series.[8] The cyanohydrin **8a** can arise from attack of the intermediate captodative radical on molecular oxygen followed by reduction, or possibly by attack on *N*-hydroxypyridine-2-thione.[18] The structure of the dimer, which arises by self-coupling of stabilized radicals, was confirmed by single crystal X-ray analysis.[19] The cis relationship of the aziridine ring to the aromatic ring in the dimer has been observed in the epoxide[8] and dioxolane[20] analogs of **6**. Moreover, this cis relationship is found in the mitomycins, and the monomeric units of the dimer have the same absolute stereochemistry as the mitomycins **10.**

The appearance of a significant amount of aziridine carboxylic acid **5b** after photolysis was not the result of incomplete esterification of the acid. Careful ^{1}H NMR analysis showed that the aziridine carboxylic acid was completely converted to the thiohydroxamic acid anhydride **5c** under anhydrous conditions and reappeared after photolysis. This observation may reflect a relatively slow decarboxylation of the intermediate acyloxyl radical, which abstracts a hydrogen atom from a convenient source such as *N*-hydroxypyridine-2-thione,[18] a byproduct of the esterification.

Dimer **6** underwent disproportionation upon UV photolysis with a medium pressure Hanovia Hg lamp (0.01M THF) to provide indole **7** (22%), two dihydroindoles **8b** (37%) and **8c** (trace), and *N*-acyl enamine **11** (trace). The aldehyde analog of the nitrile **7** has been prepared recently by an alternative route.[9] The stereochemistry of the major dihydroindole **8b** was confirmed by NOE difference experiments. Irradiation of the C_9-H showed a 9.2% enhancement of C_{9a}-H while irradiation of the latter hydrogen caused a 9.8% increase in the C_1-H signal.[21] Not surprisingly, the endo nitrile **8b** is formed as the dominant isomer, which arises by hydrogen atom transfer on the less congested convex face of the captodative radical. Exposure of the endo nitrile **8b** to catalytic Na_2CO_3 in methanol effected equilibration to a 2:1 mixture of the exo and endo nitriles (**8c** and **8b**), respectively. The *N*-acyl enamine **11**, derived from photoisomerization of indole **7**, although not fully characterized, was assigned its structure based upon its mass spectrum [CI, m/z $(M + 1)^+ = 296$]; ^{1}H NMR spectrum, which revealed the vinyl hydrogen as a broadened singlet δ 6.17 and the methylene group at δ 5.05; and IR spectrum, which showed absorptions at 3425, 1730, and 1625 cm^{-1} that could be assigned to the *N*-acyl enamine functionality.

When the UV photolysis of dimer **6** was conducted in the presence of 6 equiv of *n*-Bu_3SnH, the yield of dihydroindole **8b** was unaffected. In addition to the formation of indole **7** and dihydroindole **8c** as minor components, trace amounts of *N*-acyl enamine **11** and its dihydro product **12** were isolated. When the photoreduction of the dimer was conducted in the presence of *n*-Bu_3SnD, less than 10% incorporation of deuterium occurred at the C_9 position in dihydroindole **8b**. The intermediate radical from dimer dissociation undergoes disproportionation faster than it abstracts a hydrogen atom from *n*-Bu_3SnH or at least a deuterium atom from *n*-Bu_3SnD. Moreover, dihydro compound **12** showed complete incorporation of deuterium at C_2 and partial incorporation at C_1. The indole **7** is seen as undergoing light-induced opening of the C_1–N bond followed by hydrogen migration from C_2 to C_1 to afford the imine form of **11**. The hydrogen shift is in accord with the observed photoisomerization of the epoxide **13** to ketone **14**.[8] Complete deuterium incorporation at C_2 can occur through either tautomeric form of **11**.

Because direct photocyclization of thiohydroxamic acid anhydride **5c** in the presence of *n*-Bu_3SnH gave a complex, inseparable mixture whose ^{1}H NMR spectrum indicated the presence of aziridine **15c**, a method was sought to accomplish the cyclization in a two-step process. Accordingly, the thiohydroxamic acid anhydride **5c** (0.04 M) was photolyzed in neat $CBrCl_3$ to afford the stable *cis*- and *trans*-bromoaziridines **15a** and **15b** (5:1) in 25% yield and dibromide **16** (10% yield). The dibromide **16**, which was considered to be a product of ring opening of the bromoaziridines with HBr, could be cyclized to a mixture of the bromoaziridines **15a** and **15b** with NaH in THF. The combined yield of the bromoaziridines **15a** and **15b** was raised to 78% (4:1) by conducting the

(19) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ UK.

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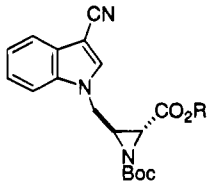
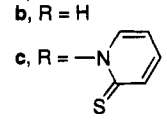
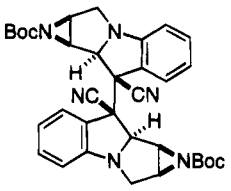
(21) Mitomycin numbering is used in the text. See structure **10**.



5a, R = Me
b, R = H



c, R = —N



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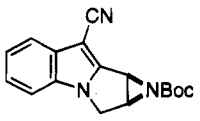

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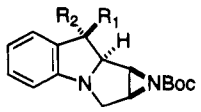
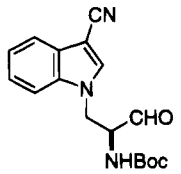


8a, R_1, R_2 = OH, CN
b, R_1 = CN, R_2 = H
c, R_1 = H, R_2 = CN



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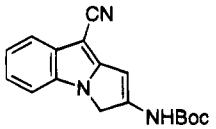

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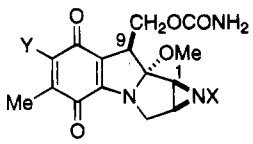
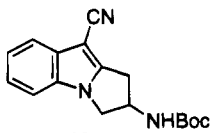


10a, X=H, Y=NH_2 mitomycin C
b, X=Me, Y=NH_2 porfiromycin
c, X=H, Y=OMe mitomycin A



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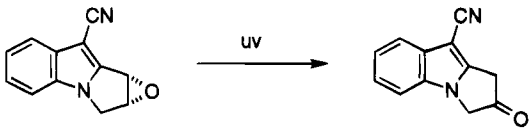
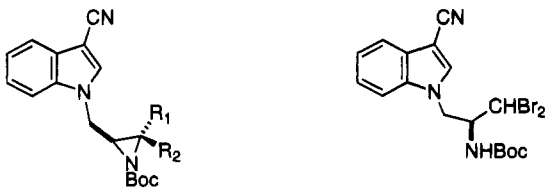


13 **14**



15a, R_1 = H, R_2 =Br
b, R_1 = Br, R_2 = H
c, R_1 = R_2 =H
d, R_1, R_2 = H, 2-S-pyr

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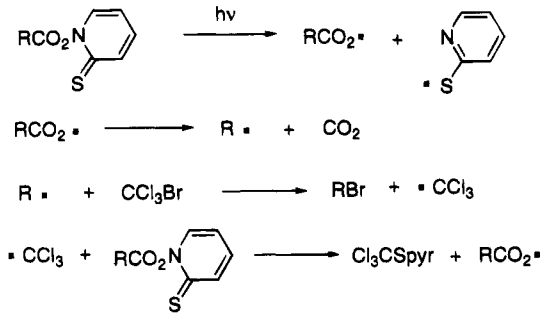
photolysis in the presence of 1 equiv of pyridine to remove traces of HBr. The byproduct of the reaction, 2-pyridyl trichloromethyl sulfide, was formed in 80% yield. This reaction occurs via a radical chain as described in Scheme 2. The major bromoaziridine was assigned the cis stereochemistry based on the larger coupling constant of the aziridine methine hydrogen (J = 5.1 Hz) compared to the *trans*-bromoaziridine (J = 2.3 Hz). Although the appearance in high yield of the cis isomer as the major product was unexpected and no products of cyclization were isolated, the experiment demonstrated that the rate of inversion of the radical is rapid relative to its rate of bromination and cyclization. The formation of the bromoaziridine via a radical process complements the carbanionic routes for electrophilic substitution of aziridines recently reported by Vedejs[22] and Beak.[23]

Scheme 2



When the mixture of bromoaziridines **15a** and **15b** was heated at reflux in toluene in the presence of n-Bu_3SnH and azobis(cyclohexylcarbonitrile) as an initiator, the dimer **6**, dihydroindole **8b**, and uncyclized aziridine **15c** were produced in a 0.8:1.5:1.1 molar ratio (^{1}H NMR) with the dimer being isolated in 35% yield.

Although the yields are moderate and residual material remains on the chromatography column, these techniques for the generation and stereoselective cyclization of carbon-centered radicals of chiral aziridines provide a new and potentially useful route to mitomycin-like substrates. The tendency for the cyclized captodative[24] benzylic radical to dimerize because of its stability may be tempered by the replacement of the cyano group with an alkyl substituent or by conducting the cyclization without a substituent at this position.

Experimental Section

All anhydrous reactions were conducted in oven-dried glassware under N_2, unless otherwise noted. THF was distilled from sodium benzophenone ketyl; CH_2Cl_2 and toluene were distilled from CaH_2. The thiohydroxamic acid anhydride was prepared in aluminum foil-covered flasks, and was degassed (freeze-pump-thaw, 3×) in Pyrex tubes. Workup means the organic phase was dried over $MgSO_4$, filtered, and evaporated in vacuo. Melting points are uncorrected. IR spectra were recorded in $CHCl_3$ solutions. ^{1}H NMR ($CDCl_3$) spectra were recorded at 300 MHz (δ 7.24 ppm); ^{13}C NMR ($CDCl_3$) were recorded at 75.5 MHz (δ 77.0 ppm) unless stated otherwise; ^{19}F NMR ($CDCl_3$) were recorded at 460.2 MHz (CCl_3F, std.). NOE difference spectra were recorded at 500 MHz. The azido alcohol ratio was obtained on a GC equipped with a 29 m x 0.25 mm (i.d.) capilliary column coated with a 0.25μ film of SE-30. Flash chromatography (SiO_2) was conducted as described by Still.[25] Radial chromatography employed a Chromatotron.

Methyl (2*R*,3*R*)-3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-aziridine-2-carboxylate (2a) and Methyl (2*S*,3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]methylaziridine-2-carboxylate (2b). Into a stirred CH_2Cl_2 (100 mL) solution of ethyl (2*S*,3*R*)-4-hydroxy-2,3-epoxybutyrate (**1**) (7.93 g, 60.0 mmol), DMAP (0.42 g, 3.4 mmol), and imidazole (4.51 g, 66.1 mmol) at 0 °C was cannulated over 40 min TBDMSCl (10.90 g, 72.31 mmol) dissolved in CH_2Cl_2 (35 mL). The reaction mixture was stirred for 3 h as the cooling bath was allowed to thaw. The reaction mixture was diluted with CH_2Cl_2, washed several times with water, and the aqueous washes were back extracted with CH_2Cl_2. The combined organic extracts were washed with saturated NH_4Cl, dried over anhydrous Na_2SO_4, filtered, and

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evaporated in vacuo. The crude oil was suitable for the next reaction without further purification. Characterization of the silyl ether was carried out on an oil obtained from flash chromatography ($CHCl_3$): IR 1745 cm^{-1}; ^1H NMR 3.88 (dd, J = 12.2, 2.7 Hz, 1 H), 3.73 (dd, J = 12.2, 3.8 Hz, 1 H), 3.74 (s, 3 H), 3.41 (d, J = 1.8 Hz, 1 H), 3.30–3.26 (m, 1 H), 0.85 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR 169.5, 61.1, 58.1, 52.4, 50.0, 25.7, 18.2, −5.5. Anal. Calcd for $C_{11}H_{22}O_4Si$: C, 53.63; H, 9.00. Found: C, 53.57; H, 8.96.

To the crude epoxy ether dissolved in CH_3OH (235 mL) was added a slurry of NaN_3 (19.59 g, 0.30 mol) and NH_4Cl (6.71 g, 0.13 mol) in H_2O (30 mL). The reaction mixture was heated to reflux over 30 min and was maintained at reflux for 1 h. The cooled reaction mixture was poured into 200 mL each of H_2O, EtOAc, and brine. The organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine and worked up. Flash chromatography (10% EtOAc/hexanes) gave a mixture of azido alcohols (85:11:4; GC) as a colorless oil (13.0 g, 75%): IR 3556 (br), 2112, 1745 cm^{-1}; LRMS (CI) m/z $(M + H)^+$ = 290.15. Anal. Calcd for $C_{11}H_{23}N_3O_4Si$: C, 45.65; H, 8.01; N, 14.52. Found: C, 45.38; H, 8.13; N, 14.25.

Solutions of the azido alcohols (8.10 g, 28.0 mmol) in 26 mL of toluene and Ph_3P (8.86 g, 33.8 mmol) in 60 mL toluene were each stored over 4 Å molecular sieves for 6 h. The azido alcohol solution was cannulated into the refluxing toluene solution of Ph_3P over 1 h followed by an addition of 33 mL of toluene. The solution was heated at reflux for 6 h. [CAUTION: Vigorous gas evolution.] The reaction mixture was subjected to flash chromatography directly (hexanes to remove toluene, 5–20% EtOAc/hexanes) to give aziridines **2a** (5.25 g, 76%) and **2b** (0.43 g, 6%): **2a**: IR 3292, 1729 cm^{-1}; ^1H NMR 3.75 (s, 3 H), 3.7–3.5 (m, 2 H), 2.43 (br s, 2 H), 1.34 (br s, 1 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (62.9 MHz) 172.5, 64.3, 52.1, 39.8, 33.0, 25.7, 18.2, −5.5; HRMS (CI) calcd for $(M + H)^+$ $C_{11}H_{24}NO_3Si$: 246.1525, found 246.1533. Anal. Calcd for $C_{11}H_{23}NO_3Si$: C, 53.85; H, 9.46; N, 5.71. Found: C, 53.89; H, 9.51; N, 5.71. **2b**: IR 3272, 1732 cm^{-1}; ^1H NMR 3.85 (dd, J = 11.1, 5.5 Hz, 1 H), 3.75 (s, 3 H), 3.65 (dd, J = 11.1, 6.7 Hz, 1 H), 2.73 (d, J = 6.3 Hz, 1 H), 2.51 (q, $\langle J \rangle$ = 6.2 Hz, 1 H), 1.48 (br s, 1 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR 170.9, 61.1, 52.1, 39.5, 33.5, 25.6, 18.0, −5.5, −5.6. Anal. Calcd for $C_{11}H_{23}NO_3Si$: C, 53.85; H, 9.46; N, 5.71. Found: C, 53.98; H, 9.53; N, 5.70.

Methyl (2*R*,3*R*)-1-(*tert*-Butyloxycarbonyl)-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]aziridine-2-carboxylate (3a). To a CH_2Cl_2 solution (95 mL) of $(Boc)_2O$ (14.62 g, 67.0 mmol) and aziridine **2a** (5.69 g, 23.2 mmol) was added solid DMAP (0.84 g, 6.88 mmol) in several portions over 5 min at room temperature. Vigorous evolution of CO_2 was observed; the reaction mixture was stirred overnight. The solvent was removed in vacuo, and the residue was purified by flash chromatography (0 to 5% EtOAc/hexanes) to afford **3a** (7.3 g, 91%) as a colorless viscous liquid: $[\alpha]^{22}_D$ = +27.6° (c, 1.16, $CHCl_3$), IR 1742, 1722 cm^{-1}; ^1H NMR 3.86 (dd, J = 11.6, 3.8 Hz, 1 H), 3.78 (s, 3 H), 3.72 (dd, J = 11.6, 4.0 Hz, 1 H), 3.02 (d, J = 2.5 Hz, 1 H), 2.97–2.91 (m, 1 H), 1.44 (s, 9 H), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR 168.8, 158.4, 81.7, 61.0, 52.5, 44.3, 37.8, 28.0, 25.9, 18.4, −5.3. Anal. Calcd for $C_{16}H_{31}NO_5Si$: C, 55.62; H, 9.04; N, 4.05. Found: C, 55.72; H, 9.06; N, 4.03.

Methyl (2*S*,3*R*)-1-(*tert*-Butyloxycarbonyl)-3-[[(*tert*-butyldimethylsilyl)oxy]methyl]aziridine-2-carboxylate (3b). Using the above procedure except that 1.5 equiv of Boc anhydride were used, *cis*-aziridine **2b** provided its *N*-Boc derivative **3b** (85%) after flash chromatography (0–5% ether/hexanes) as a colorless liquid: IR 1748, 1727 cm^{-1}; ^1H NMR 3.91 (dd, J = 11.2, 5.2 Hz, 1 H), 3.70 (s, 3 H), 3.56 (dd, J = 11.2, 7.1 Hz, 1 H), 3.10 (d, J = 6.6 Hz, 1 H), 2.85–2.77 (m, 1 H), 1.38 (s, 9 H), 0.81 (s, 9 H), −0.01 (s, 3 H), −0.03 (s, 3 H); ^{13}C NMR 167.6, 160.0, 82.2, 60.2, 52.2, 43.6, 38.4, 27.7, 25.6, 18.1, −5.5, −5.6. Anal. Calcd for $C_{16}H_{31}NO_5Si$: C, 55.62; H, 9.04; N, 4.05. Found: C, 55.41; H, 8.94; N, 4.02.

Methyl (2*R*,3*R*)-1-(*tert*-Butyloxycarbonyl)-3-(hydroxymethyl)aziridine-2-carboxylate (4a). Tetra-n-butylammonium fluoride (13.6 mL of 1.0M/THF, 13.6 mmol) was added dropwise to a THF (25 mL) solution of aziridine **3a** (3.15 g, 9.1 mmol). After 15 min the reaction mixture was poured into a mixture of EtOAc (140 mL), H_2O (70 mL), and saturated NH_4Cl (30 mL). The layers were separated and the aqueous phase was washed with EtOAc. The combined organic extracts were washed with brine, and worked up. Flash chromatography (30–50% EtOAc/hexanes) afforded **4a** as a viscous colorless liquid (1.91 g, 91%): IR 3671–3164, 1743, 1724 cm^{-1}; ^1H NMR 3.96 (ddd, J = 12.3, 6.1, 2.8 Hz, 1 H), 3.77 (s, 3 H), 3.67 (ddd, J = 12.3, 7.3, 4.3 Hz, 1 H), 3.08 (d, J = 3.1 Hz, 1 H), 3.04–2.99 (m, 1 H), 1.91 (t, $\langle J \rangle$ = 6.6 Hz, 1 H, O*H*), 1.45 (s, 9 H); ^{13}C NMR 168.4, 158.8, 82.1, 59.9, 52.4, 43.8, 37.4, 27.7; HRMS (CI) calcd for $(M + H)^+$ $C_{10}H_{18}NO_5$: 232.1185, found 232.1182. Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.34 (−0.6%); H, 7.40; N, 5.93; the (*R*)-MPTA Mosher ester was prepared: ^1H NMR 3.55 (OMe); ^{19}F NMR −73.63 ppm. In addition, less than 5% of the aziridine **4c**, in which the Boc group migrated to the hydroxyl, was isolated: IR (cm^{-1}) 3269 (weak), 1741, 1733; ^1H NMR 3.99 (dd, J = 11.6, 6.0 Hz, 1 H), 3.91 (dd, J = 11.6, 5.7 Hz, 1 H), 3.72 (s, 3 H), 2.59–2.51 (m, 1 H), 2.44 (dd, J = 7.5, 2.3 Hz, 1 H), 1.43 (s, 9 H); ^{13}C NMR 172.1, 153.0, 82.5, 67.5, 52.6, 36.3, 33.4, 27.6; CIMS m/z $(M + H)^+$ = 232.15; the (*R*)-MPTA Mosher amide was prepared: ^1H NMR 3.50 (OMe); ^{19}F NMR −69.43 ppm; HRMS (CI) calcd for $(M + H)^+$ $C_{10}H_{18}NO_5$ 232.1185, found 232.1189.

Methyl (2*R*,3*S*)-1-(*tert*-Butyloxycarbonyl)-3-[1-(3-cyanoindolyl)methyl]aziridine-2-carboxylate (5a). To a solution of 3-cyanoindole (2.35 g, 16.50 mmol) in THF (16 mL) was added dropwise $NaN(TMS)_2$ (16.5 mL, 1.0 M/THF, 16.5 mmol) over 10 min at room temperature. The mixture was stirred for an additional 1.5 h. In the meantime, trifluoromethanesulfonic acid anhydride (1.46 mL, 8.68 mmol) was added dropwise over 13 min into a cooled (−25 °C) CH_2Cl_2 (22 mL) solution of aziridinol **4a** (1.91 g, 8.26 mmol) and pyridine (0.74 mL, 9.14 mmol) and stirred for 15 min. The heterogeneous indole solution was cooled to −25 °C, and the triflate was rapidly transferred by cannulation. The solvent bath was removed and the reaction mixture was stirred for 2 h. The resultant brick-red solution was quenched with saturated NH_4Cl, partitioned between EtOAc and H_2O, and reextracted with EtOAc. The combined organic phases were washed with brine, and worked up. Flash chromatography of the residue (50% ether/hexanes) recovered excess 3-cyanoindole and indole **5a** as a white foam (2.11 g, 72%): IR 2224, 1747, 1730 cm^{-1}; ^1H NMR 7.77 (s, 1 H), 7.76 (dd, J = 6.9, 1.0 Hz, 1 H), 7.43 (dd, J = 7.6, 1.1 Hz, 1 H), 7.36–7.27 (m, 2 H), 4.47 (dd, J = 14.8, 3.5 Hz, 1 H), 4.12 (dd, J = 14.8, 6.8 Hz, 1 H), 3.76 (s, 3 H), 3.20–3.15 (m, 1 H), 2.90 (d, J = 2.4 Hz, 1 H), 1.34 (s, 9 H); ^{13}C NMR 167.1, 157.2, 135.5, 134.7, 127.6, 124.0, 122.2, 119.8, 115.3, 110.3, 86.7, 82.5, 52.6, 47.2, 41.3, 38.9, 27.6. Anal. Calcd for $C_{19}H_{21}N_3O_4$: C, 64.20; H, 5.96; N, 11.83. Found: C, 64.05; H, 5.97; N, 11.76.

(2*R*,3*S*)-1-(*tert*-Butyloxycarbonyl)-3-[1-(3-cyanoindolyl)-methyl]aziridine-2-carboxylic Acid (5b). A solution of LiOH (0.286 g, 11.94 mmol) in H_2O (15 mL) was added to a THF (45 mL) solution of ester **5a** (2.10 g, 5.91 mmol) cooled in an ice–water bath. After 1.5 h most of the solvent was removed in vacuo. The remaining material was dissolved in H_2O and washed with CH_2Cl_2. The solution was cooled in an ice bath and acidified to pH 4–5 with cold 5% HCl. The acid was thoroughly extracted with EtOAc. The combined organic extracts were washed with brine and worked up to afford acid **5b** as a white foam (1.79 g, 89%): IR 3246–2695, 2223, 1734 cm^{-1}; ^1H NMR 11.05 (br s, 1 H, conc dependent), 7.74 (s, 1 H), 7.68 (d, J = 7.3 Hz, 1 H), 7.42 (d, J = 7.9 Hz, 1 H), 7.33–7.23 (m, 2 H), 4.47 (dd, J = 14.9, 3.2 Hz, 1 H), 4.07 (dd, J = 14.9, 6.7 Hz, 1 H), 3.19–3.15 (m, 1 H), 2.91 (d, J = 2.4 Hz, 1 H), 1.27 (s, 9 H); ^{13}C NMR 170.7, 157.7, 135.4, 135.0, 127.5, 124.1, 122.4, 119.7, 115.4, 110.4, 86.2, 83.1, 47.0, 41.7, 38.6, 27.5; HRMS (CI) calcd for $(M + H)^+$ $C_{18}H_{20}N_3O_4$: 342.1454, found 342.1453.

[1a*S*,8*S*,8(1a′*S*,8′*S*,8a′*S*,8b′*R*),8a′*S*,8b′*R*]-1a,1a′,8,8′,8a,-8a′,8b,8b′-Octahydro-[8,8′-bi-8*H*-azirino[2′,3′:3,4]pyrrolo-[1,2-*a*]indole]-8,8′-dicarbonitrile (6). To a stirred mixture of carboxylic acid **5b** (390 mg, 1.14 mmol) and 2,2′-dithiobis-

(pyridine *N*-oxide) (390 mg, 1.49 mmol) in CH_2Cl_2 (4 mL) at 0 °C and protected from light (Al foil) was added rapidly n-Bu_3P (370 μL, 1.49 mmol). The reaction mixture was stirred at room temperature for 1 h to obtain the lemon-colored solution of thiohydroxamic acid anhydride **5c**. The solution was transferred into a pyrex tube, diluted with CH_2Cl_2 (19 mL), degassed, and photolyzed with a 500 W tungsten halogen lamp (half-immersed in an ice–water bath) with vigorous stirring for 3 h. The reaction mixture was diluted with CH_2Cl_2 and extracted with dilute $NaHCO_3$. The basic solution was acidified with cold 5% HCl and subjected to an aqueous workup to recover carboxylic acid **5b** (16%), which was contaminated with N-hydroxypyridine-2-thione. The original CH_2Cl_2 layer was worked up and the residue was subjected to flash chromatography (20–50% EtOAc/hexanes) to give 2,2′-dipyridyl disulfide (~80%) and impure dimer **6**, which was carefully triturated with Et_2O to obtain dimer **6** as a pure white solid. The Et_2O wash was concentrated and subjected to radial chromatography ($CHCl_3$) to afford additional dimer (103 mg, 31%). Crystallization of a sample from $CHCl_3/Et_2O$ provided rod-shaped crystals containing $CHCl_3$ of crystallization (X-ray sample). A CH_2Cl_2 solution of the crystals gave $CHCl_3$-free crystals: mp 202–204 °C dec; IR 1715, 1602, 1483 (no CN absorption) cm^{-1}; ^1H NMR 7.87 (d, J = 7.6 Hz, 2 H), 7.27 (td, $\langle J \rangle$ = 7.5, 1.1 Hz, 2 H), 6.92 (td, $\langle J \rangle$ = 7.5, 0.6 Hz, 2 H), 6.53 (d, J = 8.0 Hz, 2 H), 3.71 (br s, 2H), 3.60 (d, J = 12.6 Hz, 2 H), 3.25 (dd, J = 12.6, 1.9 Hz, 2 H), 3.04 (dd, J = 4.7, 1.8 Hz, 2 H), 2.90–2.86 (m, 2 H), 1.33 (s, 18 H); ^{13}C NMR 160.2, 154.9, 131.5, 125.8, 124.1, 120.7, 116.9, 110.2, 81.9, 68.8, 53.8, 52.3, 43.2, 41.9, 27.7; HRMS (FAB) calcd for $(M + H)^+$ $C_{34}H_{37}N_6O_4$: 593.2876, found 593.2899. Anal. Calcd for $C_{34}H_{36}N_6O_4$: C, 68.90; H, 6.12; N, 14.18. Found: C, 68.77; H, 6.17; N, 14.08.

From the flash chromatography, trace amounts of impure indole **7**, amino aldehyde **9**, and a compound assigned the structure of cyanohydrin **8a** were isolated. Further chromatography (10–20% Et_2O/hexanes) gave pure materials. **7**: IR 2222, 1715 cm^{-1}; ^1H NMR 7.71–7.67 (m, 1 H), 7.29–7.19 (m, 3H), 4.71 (d, J = 12.5 Hz, 1 H), 4.16 (dd, J = 12.5, 3.7 Hz, 1H), 4.09 (d, J = 4.0 Hz, 1 H), 3.98 (t, $\langle J \rangle$ = 3.6 Hz, 1 H), 1.08 (s, 9 H); HRMS (CI) calcd for $(M + H)^+$ $C_{17}H_{18}N_3O_2$: 296.1399, found 296.1396. **9**: IR 3434, 2224, 1736, 1708 cm^{-1}; ^1H NMR (CD_2Cl_2, δ 5.32) 9.67 (s, 1 H), 7.74 (d, J = 7.8 Hz, 1 H), 7.60 (s, 1 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.39–7.28 (m, 2 H), 5.23 (br d, J = 6.3 Hz, 1 H), 4.72 (dd, J = 14.9, 5.2 Hz, 1 H), 4.61 (dd, J = 14.9, 6.5 Hz, 1 H), 4.36–4.29 (td, J = 7.6, 5.6 Hz, 1 H), 1.42 (s, 9 H); HRMS (CI) calcd for $(M + H)^+$ $C_{17}H_{20}N_3O_3$: 314.1505, found 314.1507. **8a**: IR 1716, 1607, 1481 cm^{-1}; ^1H NMR 7.40 (d, J = 7.8 Hz, 1 H), 7.28 (t, $\langle J \rangle$ = 7.7 Hz, 1 H), 6.87 (t, $\langle J \rangle$ = 8.0 Hz, 1 H), 6.58 (d, J = 8.1 Hz, 1 H), 4.11 (d, J = 2.2 Hz, 1 H), 3.64 (d, J = 12.6 Hz, 1 H), 3.38–3.32 (m, 2 H), 3.23 (dd, J = 4.7, 1.9 Hz, 1 H), 3.10 (s, 1 H, conc dependent), 1.37 (s, 9 H); ^{13}C NMR 160.4, 154.7, 132.2, 128.6, 124.1, 120.6, 117.6, 111.2, 82.2, 76.8, 73.5, 52.2, 42.6, 41.5, 27.8; HRMS calcd for $C_{17}H_{19}N_3O_3$: 313.1426, found 313.1423.

UV Photolysis of Dimer 6. A THF (6.4 mL) solution of dimer **6** (36.4 mg, 0.0614 mmol) was degassed, followed by bubbling argon through the solution for 10 min. Photolysis with 450 W Hanovia Hg lamp for 3.5 h gave crude material upon removal of the THF whose ^1H-NMR spectrum showed the presence of dihydroindole **8b**, and indole **7** (1:1). Baseline material was removed with a short silica gel column (10–20% EtOAc/hexanes) followed by radial chromatography ($CHCl_3$) to afford dihydroindole **8b** (13.7 mg, 37%) and indole **7** (8.0 mg, 22%). Dihydroindole **8b:** mp 142–143 °C (CH_2Cl_2, hexanes; colorless needles); $[\alpha]^{23}_D$ = +128.6° (*c*, 0.56, $CHCl_3$); IR 2248 (weak), 1716, 1605, 1483 cm^{-1}; ^1H NMR 7.21 (d, J = 7.60, 1 H), 7.14 (td, $\langle J \rangle$ = 7.7, 0.8 Hz, 1 H), 6.79 (td, $\langle J \rangle$ = 7.5, 0.6 Hz, 1 H), 6.50 (d, J = 7.9 Hz, 1 H), 4.44 (d, J = 10.3 Hz, 1 H), 4.26 (dd, J = 10.3, 2.0 Hz, 1 H), 3.64 (d, J = 12.6 Hz, 1 H), 3.35–3.30 (m, 2 H), 3.21 (dd, J = 4.7, 1.9 Hz, 1 H), 1.37 (s, 9 H); ^{13}C NMR 160.4, 153.7, 129.7, 124.4, 123.7, 120.1, 117.1, 110.2, 81.8, 66.1, 53.0, 42.9, 42.4, 32.6, 27.8; HRMS (EI) calcd for $C_{17}H_{19}N_3O_2$: 297.1477, found 297.1477. Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.65; H, 6.44; N, 14.14. Found: C, 68.01 (−0.64%); H, 6.46; N, 14.03.

UV Photolysis of Dimer 6 in the Presence of *n*-Bu_3SnH. A THF (12 mL) solution of dimer **6** (70.0 mg, 0.118 mmol) was degassed as described above. *n*-Bu_3SnH (195 μL, 0.703 mmol) was added, and the solution was photolyzed for 7.5 h. The crude ^1H NMR showed the presence of *trans*-dihydroindole **8c**, indole **12**, indole **7**, and dihydroindole **8b** in a respective ratio of 0.2:0.7:1.0:2.0. Flash chromatography (5–20% EtOAc/hexanes) effected the separation of dihydroindole **8b** (25.3 mg, 36%) from the other products. A second flash chromatography of the remaining combined fractions gave indole **12**: IR 3440, 2218, 1712 cm^{-1}; ^1H NMR (CD_2Cl_2, δ 5.32) 7.70–7.64 (m, 1 H), 7.37–7.21 (m, 3 H), 5.05 (br s, 1 H), 4.95 (br s, 1 H), 4.45 (dd, J = 11.0, 6.7 Hz, 1 H), 4.03 (dd, J = 11.0, 4.3 Hz, 1 H), 3.57 (dd, J = 17.3, 7.6 Hz, 1 H), 3.08 (dd, J = 17.3, 4.8 Hz, 1 H), 1.45 (s, 9 H); HRMS (EI) calcd for $C_{17}H_{19}N_3O_2$: 297.1477, found 297.1475.

Equilibration of Dihydroindoles 8b and 8c. Equilibration of the C_9 position of dihydroindole **8c** or **8b** (5.5 mg) with sodium carbonate/methanol (10 mol%, 1.5 mL) gave a 2:1 mixture, respectively. Flash chromatography (0–10% EtOAc/hexanes) gave dihydroindole **8c**: IR 2244 (weak), 1718, 1603, 1485 cm^{-1}; ^1H NMR 7.20 (d, J = 7.5 Hz, 1 H), 7.16 (t, $\langle J \rangle$ = 7.6 Hz, 1 H), 6.80 (t, $\langle J \rangle$ = 7.1 Hz, 1 H), 6.49 (d, J = 8.0 Hz, 1 H), 4.61 (d, J = 5.3 Hz, 1 H), 4.41 (dd, J = 5.3, 2.3 Hz, 1 H), 3.51 (d, J = 12.1 Hz, 1 H), 3.41 (dd, J = 12.1, 1.8 Hz, 1 H), 3.31 (dd, J = 4.7, 2.3 Hz, 1 H), 3.26 (dd, J = 4.7, 1.8 Hz, 1 H), 1.38 (s, 9H); HRMS (EI) calcd for $C_{17}H_{19}N_3O_2$: 297.1477, found 297.1478.

(2*R*,3*S*)-1-(*tert*-Butyloxycarbonyl)-2-bromo-3-[1-(3-cyanoindolyl)methyl]aziridine (15a) and (2*S*,3*S*)-1-(*tert*-Butyloxycarbonyl)-2-bromo-3-[1-(3-cyanoindolyl)methyl]-aziridine (15b). Indolecarboxylic acid **5b** (115 mg, 0.337 mmol) was converted to its thiohydroxamic acid anhydride **5c** as described above. CH_2Cl_2 was removed in vacuo, and the crude residue was transferred into a pyrex photolysis tube with distilled $CBrCl_3$ (8 mL) and degassed. Pyridine (28 μL, 0.346 mmol) was added, the vessel was half immersed in an ice–water bath and stirred vigorously as irradiation (1.5 h) was conducted with a 500 W tungsten halogen lamp. Without removing the $CBrCl_3$, the reaction mixture was submitted to flash chromatography (0–10% EtOAc/hexanes) followed by radial chromatography (0.5% MeOH/$CHCl_3$) to afford bromoaziridine **15a** and **15b** (100 mg, 78%, **15a:15b** = 4:1; early and late fractions gave pure material), 2-pyridyl trichloromethyl sulfide (64 mg, 80%), and 2, 2′-dipyridyl disulfide in variable yield. **15a**: mp 124.5–125.6 °C (Et_2O/hexanes; colorless needles); IR 2224, 1734 cm^{-1}; ^1H NMR 7.86 (s, 1 H), 7.78 (d, J = 7.6 Hz, 1 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.40–7.29 (m, 2 H), 4.70 (d, J = 5.1 Hz, 1 H), 4.51 (dd, J = 15.1, 5.1 Hz, 1 H), 4.36 (dd, J = 15.1, 6.7 Hz, 1 H), 2.87–2.82 (m, 1 H), 1.34 (s, 9 H); ^{13}C NMR 157.8, 135.5, 134.8, 127.8, 124.0, 122.4, 119.9, 115.5, 110.5, 86.8, 83.6, 46.9, 40.7, 39.9, 27.5; LRMS (CI) m/z $(M + H)^+$ = 376.20, 378.20. Anal. Calcd for $C_{17}H_{18}N_3O_2Br$: C, 54.39; H, 4.84; N, 11.20. Found: C, 54.33; H, 4.88; N, 11.22. **15b**: IR 2223, 1730 cm^{-1}; ^1H NMR 7.76 (d, J = 7.6 Hz, 1 H), 7.69 (s, 1 H), 7.44–7.28 (m, 3 H), 4.48 (dd, J = 15.1, 3.5 Hz, 1 H), 4.24 (dd, J = 15.1, 5.9 Hz, 1 H), 4.03 (d, J = 2.3 Hz, 1 H), 3.09–3.04 (m, 1 H), 1.40 (s, 9 H); ^{13}C NMR 156.2, 135.5, 135.0, 127.8, 124.4, 122.6, 120.2, 115.6, 110.2, 87.0, 83.9, 46.5, 43.4, 36.4, 27.9; HRMS(CI) calcd for $(M + H)^+$ $C_{17}H_{19}N_3O_2Br$: 376.0661, found 376.0659.

[1-[3,3-Dibromo-2(*S*)-[(*tert*-Butyloxycarbonyl)amino]-propyl]-3-cyanoindole (16). When pyridine was omitted from the above experiment, dibromide **16** could be isolated upon radial chromatography: IR 3426, 2225, 1717 cm^{-1}; ^1H NMR 7.77 (d, J = 7.8 Hz, 1 H), 7.62 (s, 1 H), 7.57 (d, J = 8.1 Hz, 1 H), 7.42–7.30 (m, 2 H), 5.67 (br d, J = 2.7 Hz, 1 H), 4.96 (br d, J = 8.6 Hz, 1 H), 4.59 (dd, J = 13.5, 5.8 Hz, 1 H), 4.55–4.44 (m, 1 H), 4.38 (dd, J = 13.5, 6.9 Hz, 1 H), 1.38 (s, 9H); LRMS (CI) m/z $(M + H)^+$ = 456.00, 457.95, 459.95; HRMS (CI) calcd for $(M + H)^+$ $C_{17}H_{20}N_3O_2Br_2$ (^{79}Br, ^{81}Br): 457.9902, found 457.9908.

Reductive Cyclization of Bromoaziridines 15a and 15b. A mixture of bromoaziridines **15a** and **15b** (4:1, 48.4 mg, 0.129 mmol) and azobis(cyclohexylcarbonitrile) (11.7 mg, 0.047 mmol) were dissolved in toluene (2.8 mL). *n*-Bu_3SnH (71 μL, 0.256 mmol) was added, and the solution was heated at reflux

for 3.5 h. A short SiO_2 column was employed to remove the toluene and the unconsumed n-Bu_3SnH. The ^1H NMR spectrum of the mixture showed the presence of dimer **6**, dihydroindole **8b**, and uncyclized aziridine **15c** in a ratio of 0.8:1.5:1.1. Flash chromatography (10–40% EtOAc/hexanes) afforded the dimer **6** (13.3 mg, 35%) and a mixture of **8b** and **15c**, which was separated by radial chromatography ($CHCl_3$). **15c:** IR 2223, 1726 cm^{-1}; ^1H NMR 7.90 (s, 1 H), 7.75 (d, J = 7.9 Hz, 1 H), 7.44 (d, J = 7.8 Hz, 1 H), 7.34–7.28 (m, 2 H), 4.47 (dd, J = 14.7, 3.2 Hz, 1 H), 3.95 (dd, J = 14.7, 7.4 Hz, 1 H), 2.80–2.70 (m, 1H), 2.41 (d, J = 6.2 Hz, 1 H), 2.04 (d, J = 3.5 Hz, 1 H), 1.34 (s, 9 H); ^{13}C NMR 161.2, 135.5, 135.1, 127.7, 123.9, 122.2, 119.9, 115.8, 110.4, 86.3, 82.1, 48.6, 35.9, 29.6, 27.7; HRMS (CI) calcd for $(M + H)^+$ $C_{17}H_{20}N_3O_2$: 298.1556, found 298.1557.

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