Enantiopure *N*-Acyldihydropyridones as Synthetic Intermediates: Asymmetric Syntheses of Indolizidine Alkaloids (−)-205A, (−)-207A, and (−)-235B

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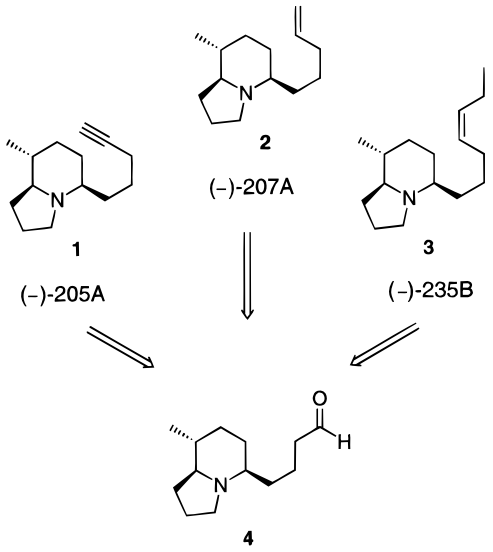
Concise asymmetric syntheses of indolizidine alkaloids (−)-205A, (−)-207A, and (−)-235B were accomplished with a high degree of stereocontrol in eleven steps. Addition of 4-(1-butenyl)-magnesium bromide to 1-acylpyridinium salt **5**, prepared in situ from 4-methoxy-3-(triisopropylsilyl)-pyridine and the chloroformate of (+)-*trans*-2-(α-cumyl)cyclohexanol, gave a 91% yield of diastereomerically pure dihydropyridone **6**. Oxidative cleavage of **6** and subsequent reduction provided alcohol **7** in 81% yield. Removal of the chiral auxilliary and TIPS group (NaOMe; 10% HCl), *N*-acylation with BnOCOCCl, and treatment with NCS/Ph_3P gave chloride **10**. Methylation at C-3, copper-mediated conjugate addition of 4-(benzyloxy)butylmagnesium bromide, and vinyl triflate formation provided **13** in a stereoselective fashion. Catalytic reduction of the vinyl triflate moiety, simultaneous cleavage of the benzyl ether and Cbz groups, and cyclization to give amino alcohol **14** was effected via a one-pot reaction. Oxidation of **14** with the Dess−Martin reagent gave a 97% yield of amino aldehyde **4**. Synthesis of each of the three title alkaloids was accomplished in one step from **4**. The Seyferth−Gilbert reaction provided a 41% yield of (−)-205A. The appropriate Wittig olefination of **4** gave indolizidines (−)-207A and (−)-235B in 70% and 86% yield, respectively.

The indolizidine ring system is found in many biologically active and structurally interesting alkaloids.[1] Although numerous preparations of these alkaloids have been reported,[2] the development of concise enantioselective approaches is still a worthy synthetic goal. We have found that chiral *N*-acyl-2,3-dihydro-4-pyridones are excellent synthetic building blocks due to their facile preparation, the functionality present, their availability in either enantiomerically pure form, good air stability, and the ease of introducing ring substituents in a regio- and stereocontrolled manner.[3] Various alkaloids have been prepared in our laboratories via dihydropyridone intermediates, including indolizidines (±)-209B,[4a] (+)-209D,[2c] (+)-elaeokanine A,[4b] (+)-elaeokanine C,[4b] (−)-septicine,[4c] and (−)-tylophorine.[4c] Recently, several new alkaloids containing the 5-substituted 8-methylindolizine ring system were isolated from skin extracts of neotropical members of the Dendrobatidae family of frogs.[5] These 5,8-disubstituted indolizidines appear to represent an atypical and potent class of noncompetitive blockers for muscle-type and ganglionic nicotinic receptor-channels.[5c] In this paper we report the asymmetric synthesis of three of these indolizidine alkaloids, (−)-205A (**1**), (−)-207A (**2**), and (−)-235B (**3**), from a common intermediate **4**.



Our plan for synthesizing key intermediate **4** (Scheme 1) called for a regio- and stereoselective construction starting with chiral 1-acylpyridinium salt **5**, prepared in

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(4) (a) Comins, D. L.; Zeller, E. *Tetrahedron Lett.* **1991**, *32*, 5889. (b) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1991**, *113*, 6672. (c) Comins, D. L.; Chen, X.; Morgan, L. A. *J. Org. Chem.* **1997**, submitted.

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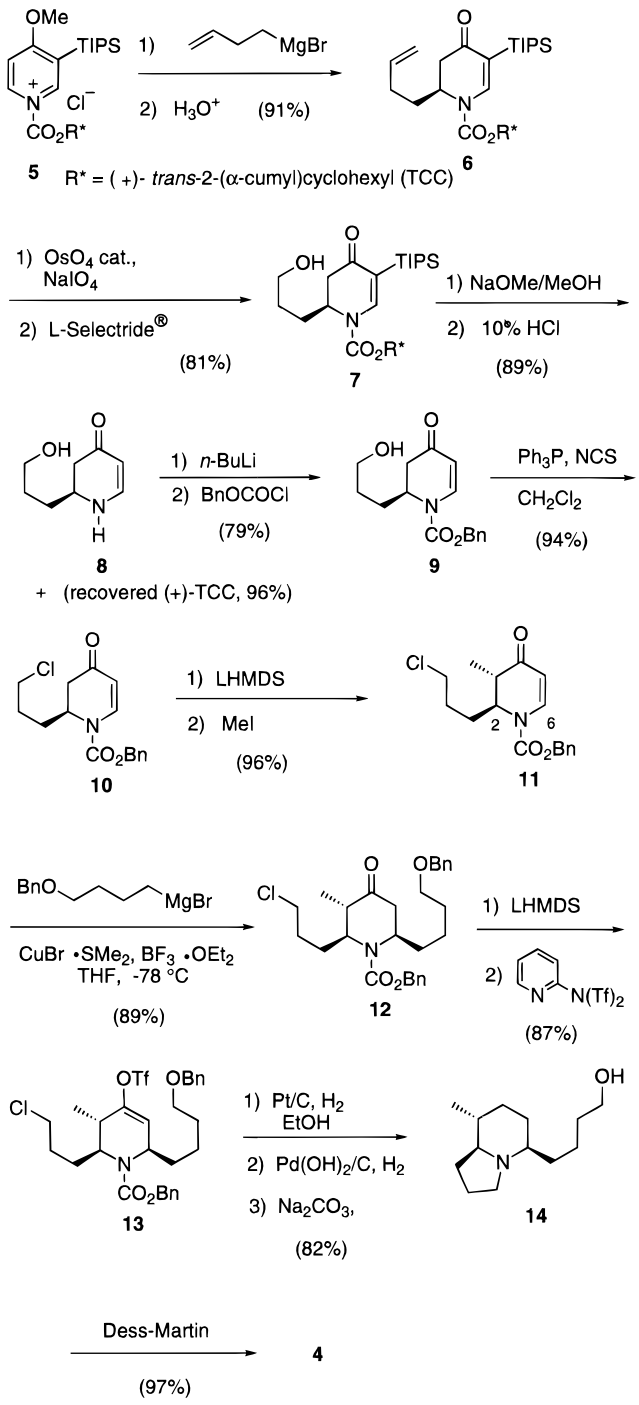
Scheme 1



situ from 4-methoxy-3-(triisopropylsilyl)pyridine[6] and the chloroformate of (+)-*trans*-2-(α-cumyl)cyclohexanol(TCC).[7] The Grignard reagent prepared from commercially available 4-bromo-1-butene was added to 1-acylpyridinium salt **5** using our standard conditions. After workup with aqueous acid, the crude dihydropyridone **6** was obtained in 90% de. Recrystallization from methanol and chromatography of the mother liquor gave a 91% yield of diastereomerically pure **6**. Oxidative cleavage using catalytic OsO_4 and subsequent reduction of the crude aldehyde with L-Selectride provided alcohol **7** in 81% yield. In contrast, reductive workup with sodium boro-

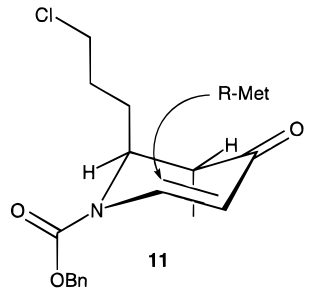


Figure 1. Stereoelectronically preferred axial attack on the chair conformation of **11**.

hydride, or ozonolysis of the terminal alkene followed by reductive workup, resulted in low yields (~25%) of the desired alcohol **7**. Removal of the chiral auxiliary with sodium methoxide in refluxing methanol, subsequent addition of aqueous 10% HCl to effect protodesilylation, and anhydrous workup afforded 89% of the amino alcohol **8** as a white solid. The chiral auxiliary ((+)-TCC) was recovered in 96% yield. Selective *N*-acylation of **8** was effected by deprotonation with 1.05 equiv of *n*-BuLi in THF at −78 °C and addition of benzyl chloroformate to give dihydropyridone **9**. The alcohol to chloride conversion was achieved in 94% yield under mild conditions by treatment of **9** with triphenylphosphine and *N*-chlorosuccinimide to give **10**. Enolate formation using LHMDS in THF and reaction with methyl iodide gave 96% of *trans*-2,3-dihydro-4-pyridone **11**. No *cis*-product or intramolecular alkylated product was evident from the ^{1}H NMR spectrum of the crude product.[8] Treatment of **11** with BF_3·OEt_2, CuBr·DMS, and [4-(benzyloxy)butyl]-magnesium bromide provided an 89% yield of (2*S*,3*S*,6*R*)-piperidone **12**. Presence of the C-2,C-6 *trans*-diastereomer could not be detected by ^{1}H NMR or by HPLC analysis, and none was found during purification by chromatography. Preference for the formation of the *cis*-diastereomer **12** via attack at C-6 of **11** was anticipated based on stereoelectronic arguments and previous results from our laboratories.[3a,9] Due to a strong $A^{(1,3)}$ strain between the alkyl substituent at C-2 and the *N*-acyl group of **11**, the C-2 and C-3 substituents are forced into an axial orientation of a chairlike conformation (see Figure 1). Stereoelectronically preferred axial attack by the organocuprate at C-6 of **11** leads to the observed diastereospecificity.

Since the vinyl triflate **13** was needed, several unsuccessful attempts were made to trap the resulting enolate from the conjugate addition of **11** with triflating reagents.[10] Although vinyl triflates have been prepared by in situ trapping of enolates prepared from copper-mediated conjugate addition reactions,[10,11] the presence of BF_3·OEt_2 in our reaction prevented vinyl triflate formation. Since the use of BF_3·OEt_2 was needed to obtain a high yield and the desired stereoselectivity in the formation of **12**,[9] an additional step was used to

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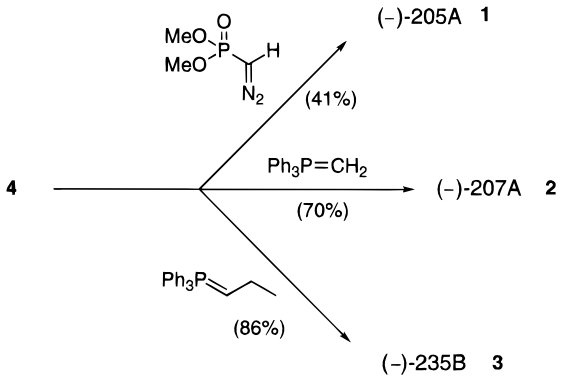
Scheme 2



prepare vinyl triflate **13**. Regiospecific enolate formation was accomplished by deprotonation of **12** with 1.1 equiv of LHMDS in THF at −78 °C. Subsequent addition of *N*-(2-pyridyl)triflimide[10] provided the vinyl triflate **13** in 87% yield. At this point, the synthetic plan called for complete reduction of the vinyl triflate moiety of **13**, simultaneous cleavage of the benzyl ether and Cbz groups, and cyclization to give the amino alcohol **14**. We were able to accomplish this via a one-pot reaction. Catalytic hydrogenation of the vinyl triflate in EtOH using 5% Pt/C and 20% $Pd(OH)_2/C$ as catalysts, and then heating the mixture with Na_2CO_3 for 1 h, afforded the desired indolizidine **14** in 82% yield. Oxidation of **14** with the Dess−Martin periodinane[12] gave a 97% yield of amino aldehyde **4**. The synthesis of each of the three target indolizidine alkaloids was completed in one step from amino aldehyde **4** as shown in Scheme 2. Using the Seyferth−Gilbert reaction,[13] treatment of **4** with methyl diazomethyl phosphate and potassium *tert*-butoxide provided a 41% yield of indolizidine 205A (**1**). Wittig olefination of **4** with methylenetriphenylphosphorane gave indolizidine 207A (**2**) in 70% yield. Finally, treatment of **4** with 2.5 equiv of *n*-propylenetriphenylphosphorane under high dilution and "salt free" conditions[14] at −78 °C → rt provided an 86% yield of (−)-indolizidine 235B (**3**). All three synthetic alkaloids exhibited IR and ^1H and ^{13}C NMR spectral data in agreement with the reported values for the natural products.[5] Samples of our synthetic alkaloids had identical MS and FTIR spectra and GC retention times as the natural compounds (see Acknowledgment).

In summary, a strategy for the synthesis of the 5-substituted 8-methylindolizidine ring system has been developed and utilized in the preparation of indolizidines (−)-205A, (−)-207A, and (−)-235B.[15] These three natural products were constructed enantioselectively in eleven steps from readily available 4-methoxy-3-(triisopropylsilyl)pyridine via the common amino aldehyde intermediate **4**. The three stereocenters of the indolizidines are formed with a high degree of control of relative and absolute stereochemistry. The route is general and broadens the scope of 1-acyl-2,3-dihydro-4-pyridones as chiral building blocks for the enantioselective preparation of various alkaloid natural products.

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Experimental Section[6]

(+)-(2*S*)-2-(3′-Butenyl)-1-[((((1*S*,2*R*)-*trans*-2-(α-cumyl)cyclohexyl)oxy)carbonyl]-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (6). Magnesium turnings (5.48 g, 225.4 mmol) were mechanically stirred at rt overnight under argon, and then 50 mL of anhydrous THF was added to the flask. Neat 4-bromo-1-butene (7.65 mL, 75.35 mmol) was added dropwise at 0 °C. The mixture was stirred 20 min at rt, 1 h at 0 °C, and 2 h at rt to form the Grignard reagent.

Into a separate flask containing a solution of 4-methoxy-3-(triisopropylsilyl)pyridine (10.0 g, 37.7 mmol) in 280 mL of anhydrous toluene was added a solution of the chloroformate of (+)-*trans*-2-(α-cumyl)cyclohexanol (11.63 g, 41.44 mmol) in 80 mL of anhydrous toluene at −42 °C. The reaction mixture was stirred at −42 °C for 1.5 h, and then 70 mL of THF was added. The mixture was cooled to −78 °C. The previously prepared Grignard reagent was transferred dropwise via a double-tipped stainless steel needle to the flask containing the newly formed chiral *N*-acylpyridinium salt solution, and the mixture was stirred at −78 °C for 4 h. Saturated aqueous oxalic acid (100 mL) was added, and the reaction mixture was warmed to rt and then was stirred overnight. The aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine and dried over anhydrous K_2CO_3. Filtration and concentration in vacuo gave 23.24 g (de 90%) of the crude product. Crystallization from 5% H_2O/MeOH yielded 15.24 g (de 100%) of the desired (2*R*)-2,3-dihydro-4-pyridone **6**. The mother liquor was concentrated and purified by radical PLC (silica gel, 2−5% EtOAc/hexanes) to yield another 3.68 g (de 99.8%) of **6**: $[\alpha]^{25}_D$ +62.9 (*c* 0.34, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.71 (s, 1 H), 7.20−7.39 (m, 5 H), 7.11 (t, 1 H, J = 6.6 Hz), 5.63 (br s, 1 H), 4.77−5.15 (m, 3 H), 2.76 (br s, 1 H), 1.60−2.50 (series of m, 8 H), 1.12−1.45 (series of m, 15 H), 1.05 and 1.01 (two d, 18 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.7, 152.5 and 152.1 (due to rotamers), 147.4, 137.1, 128.1, 125.1, 115.2, 110.2, 78.0, 51.0, 40.1, 39.4, 33.5, 30.7, 29.9, 29.5, 26.8, 25.8, 24.6, 21.7, 18.82, 18.77, 11.1; IR (KBr): 3085, 3020, 1712, 1660 cm^{-1}. Anal. Calcd for $C_{34}H_{53}NO_3Si$: C, 74.00; H, 9.68; N, 2.54. Found: C, 73.93; H, 9.68; N, 2.53.

(+)-(2*S*)-1-[(((1*S*,2*R*)-*trans*-2-(α-Cumyl)cyclohexyl)oxy)carbonyl]-2-(3′-hydroxypropyl)-5-(triisopropylsilyl)-2,3-dihydro-4-pyridone (7). A stirred solution of **6** (1.04 g, 1.88 mmol) in 80 mL of H_2O/THF (1:1) was treated with $NaIO_4$ (3.66 g, 17.1 mmol) and OsO_4 (0.12 mL, 1.88 × 10^{-2} mmol, 4 wt % in H_2O) and stirred for 19 h at rt. The reaction mixture was filtered through Celite and extracted with methylene chloride. The extracts were dried over anhydrous K_2CO_3. Filtration and concentration gave a clear oil that was dissolved in THF (40 mL) and treated with L-Selectride (2.1 mL, 2.1 mmol, 1.0 M solution in THF) at −78 °C. After stirring for 1 h, 5.0 mL of water and 1 g of sodium perborate tetrahydrate ($NaBO_3 \cdot 4H_2O$) was added, and stirring was continued for 3 h as the reaction mixture warmed to rt. Drying over anhydrous K_2CO_3, filtration, concentration, and purification by radial PLC (silica gel, 30−50% EtOAc/hexanes) gave 0.85 g (81%) of the desired dihydropyridone **7** as a white solid: mp 119−121 °C; $[\alpha]^{27.5}_D$ +66.2 (*c* 0.52, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.71 (br s, 1 H), 7.19−7.40 (m, 5 H), 7.11 (t, 1 H, J = 6.7 Hz), 4.85 (br s, 1 H), 3.49 (d, 3 H, J = 5.5 Hz), 2.66 (br s, 1 H), 1.65−2.50 (series of m, 7 H), 1.08−1.45 (m, 17 H), 1.01 and 1.04 (two

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doublets due to rotamers, 18 H, $J = 7.6$ Hz); ^{13}C NMR($CDCl_3$, 75 MHz) δ 196.9, 152.7 and 152.1 (doublet due to rotamers), 147.4, 128.0, 125.0, 110.1, 78.1, 62.1, 51.2 and 50.9 (doublet due to rotamers), 40.2, 39.3, 33.4, 30.9, 28.5, 26.8, 25.8, 24.6, 21.3, 18.8, 18.7, and 11.0; IR (KBr) 3434, 3088, 3022, 1717, 1658 cm^{-1}. Anal. Calcd for $C_{33}H_{53}NO_4Si$: C, 71.30; H, 9.61; N, 2.52. Found: C, 71.36; H, 9.58; N, 2.48.

(−)-(2*S*)-2-(3′-Hydroxypropyl)-2,3-dihydro-4-pyridone (8). To a stirred solution of **7** (4.30 g, 7.74 mmol) in 20 mL of MeOH was added sodium methoxide (7.0 mL, 30.9 mmol, 4.37 M (25%) in MeOH). After refluxing for 3.5 h, and cooling to rt, aqueous HCl (16.9 mL, 46.4 mmol, 2.74 M (10%)) was added. The mixture was stirred at rt for 15 min, and then the methanol was removed in vacuo (0 °C). An aqueous workup was avoided by adding THF and drying the mixture with anhydrous K_2CO_3. Filtration and concentration yielded 3.56 g of the crude product. Purification by radial PLC (silica gel, 10% MeOH/EtOAc/1% TEA) gave 3.25 g (96%) of the chiral auxiliary ((+)-TCC) and 1.064 g (89%) of the desired 2,3-dihydro-4-pyridone **8** as a white semisolid: $[\alpha]^{27}_D$ −430 (*c* 0.30, MeOH); ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.16 (t, 1 H, $J = 6.9$ Hz), 5.35 (br s, 1 H), 5.02 (d, 1 H, $J = 7.3$ Hz), 3.60−3.72 (m, 3 H), 2.30−2.51 (m, 2 H), 1.18−1.82 (series of m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.2, 151.4, 98.6, 62.3, 53.2, 42.1, 31.0, 28.4; IR (NaCl, neat): 3266, 3044, cm^{-1}. HRMS calcd for $C_8H_{13}NO_2$ 155.09460 (M^+), found 155.09442.

(+)-(2*S*)-1-[(Benzyloxy)carbonyl]-2-(3′-hydroxypropyl)-2,3-dihydro-4-pyridone (9).[4a] To a stirred solution of **8** (0.992 g, 6.39 mmol) in THF at −78 °C was added *n*-butyllithium (2.10 mL, 6.71 mmol, 3.19 M solution in *n*-hexane). After stirring at −78 °C for 1 h, benzyl chloroformate (0.91 mL, 6.39 mmol) was added, and the reaction mixture was stirred for 1.5 h. Because TLC analysis of the reaction mixture indicated the presence of starting dihydro-4-pyridone, an additional portion of benzyl chloroformate (0.30 mL, 2.1 mmol) was added. Stirring was continued for an additional 30 min, 0.2 mL of water was added, and the reaction mixture was warmed to rt. The crude solution was dried over K_2CO_3, filtered, and concentrated to give 2.41 g of the crude product. Purification by radial PLC (silica gel, EtOAc/hexanes) yielded 1.457 g (79%) of the desired hydroxy 2,3-dihydro-4-pyridone **9** as a clear oil: $[\alpha]^{25.5}_D$ +103 (*c* 0.37, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, 1 H, $J = 7.7$ Hz), 7.40 (s, 5 H), 5.18−5.38 (m, 3 H), 4.66 (apparent q, 1 H, $J = 5.9$ Hz), 3.60 (apparent t, 2 H, not resolved adequately to obtain *J* values), 2.83 (dd, 1 H, $J = 6.6$ and 16.6 Hz), 2.46 (d, 1 H, $J = 16.7$ Hz), 1.35−1.90 (m, 5 H); ^{13}C NMR ($CDCl_3$, MHz) δ 192.9, 152.3, 141.4, 134.7, 128.5 (2 carbons), 128.2, 106.9, 68.8, 61.7, 53.0, 39.5, 28.4, 26.9; IR (NaCl, neat): 3427, 3089, 3067, 1724, 1663, 1600 cm^{-1}.

(+)-(2*S*)-1-[(Benzyloxy)carbonyl]-2-(3′-chloropropyl)-2,3-dihydro-4-pyridone (10). Triphenylphosphine (3.88 g, 14.8 mmol) was added in one portion to a solution of **9** (2.85 g, 9.86 mmol) in 30 mL of anhydrous CH_2Cl_2 at −42 °C, and the mixture was stirred until homogeneous. *N*-Chlorosuccinimide (1.98 g, 14.8 mmol) was added in one portion, and the mixture was stirred at −42 °C for 30 min after becoming homogeneous. After warming to rt, the stirring was continued for 4 h, 0.5 mL of anhydrous methanol was added, and the mixture was stirred for 20 min. The solvents were removed in vacuo, and the residue was redissolved in diethyl ether, filtered through Celite, and concentrated. The crude product was purified by radial PLC to yield 2.85 g (94%) of the desired dihydropyridone **10** as a clear oil: $[\alpha]^{27.5}_D$ +111.6 (*c* 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, 1 H, $J = 7.6$ Hz), 7.39 (s, 5 H), 5.15−5.40 (m, 3 H), 4.63 (br s, 1 H), 3.46 (br s, 2 H), 2.84 (dd, 1 H, $J = 6.5$ and 16.6 Hz), 2.41 (d, 1 H, $J = 16.5$ Hz), 1.55−1.95 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.4, 152.4, 141.2, 134.8, 128.8, 128.7, 128.5, 107.3, 69.1, 52.7, 44.1, 40.0, 28.7, 28.1; IR (NaCl, neat): 3089, 3066, 1725, 1670, 1603 cm^{-1}; Anal. Calcd for $C_{16}H_{18}NO_3Cl$: C, 62.44; H, 5.89; N, 4.55. Found: C, 62.31; H, 5.91; N, 4.55.

(+)-(2*S*,3*S*)-1-[(Benzyloxy)carbonyl]-2-(3′-chloropropyl)-3-methyl-2,3-dihydro-4-pyridone (11). Lithium bis(trimethylsilyl)amide (10.9 mL, 10.9 mmol, 1.0 M solution in THF) was added dropwise to a solution of **10** (2.80 g, 9.08 mmol) in 100 mL of THF at −78 °C. After stirring for 1 h at −78 °C, methyl iodide (1.70 mL, 27.3 mmol) was added dropwise. Stirring was continued for 2 h at −78 °C, the reaction mixture was slowly warmed to −10 °C and was then stored in a freezer overnight (−5 to −10 °C). After warming to rt, 25 mL of water was added, and the crude mixture was extracted with diethyl ether. The combined organic extracts were dried over anhydrous K_2CO_3 for 15 min (drying over K_2CO_3 for longer times may cause epimerization at C-3). Filtration and concentration in vacuo gave 3.18 g of the crude product. Purification by radial PLC (silica gel, 10−30% EtOAc/hexanes) yielded 2.82 g (96%) of the desired 2,3-dihydropyridone **11** as a clear oil: $[\alpha]^{27.5}_D$ +29.7 (*c* 0.385, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (br s, 1 H), 7.39 (s, 5 H), 5.28 (shoulder at 5.24) (s, 3 H), 4.32 (br s, 1 H), 3.46 (br s, 2 H), 2.38 (apparent q, 1 H, $J = 6.7$ and 7.2 Hz), 1.55−1.95 (m, 4 H, $J = 6.6$ and 7.1 Hz), 1.20 (d, 3 H, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.8, 152.9, 139.9, 134.7, 128.5, 128.2, 105.2, 68.9, 58.6, 44.0, 43.8, 28.6, 28.2, 16.7; IR (NaCl, neat): 3090, 3066, 3034, 1726, 1668, 1602 cm^{-1}. Anal. Calcd for $C_{17}H_{20}NO_3Cl$: C, 63.45; H, 6.26; N, 4.35. Found: C, 63.39; H, 6.27; N, 4.38.

1-Bromo-4-(benzyloxy)butane.[16] Sodium hydroxide (20.0 g, 505 mmol) was carefully added to 40 mL of deionized water at 0 °C. To the solution was added benzyl alcohol (10.35 mL, 100 mmol), 1,4-dibromobutane (59.7 mL, 500 mmol), and tetrabutylammonium hydrogen sulfate (1.70 g, 5.0 mmol). The reaction mixture was stirred at rt overnight, poured into 500 mL of H_2O, and was extracted with hexanes. The organic extracts were washed with brine, dried over anhydrous K_2CO_3, and concentrated in vacuo. The crude product was purified by distillation (bp 101−105 °C, 0.40 mmHg) to yield 20.72 g (85%) of the desired product [67.2 g of 1,4-dibromobutane was recovered (bp 31−41 °C, 0.35−0.5 mmHg)]: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20−7.45 (m, 5 H), 4.50 (s, 2 H), 3.51 (t, 2 H, $J = 6.2$ Hz), 3.44 (t, 2 H, $J = 6.8$ Hz), 1.98 (quintet, 2 H, $J = 7.9$ Hz), 1.76 (quintet, 2 H, $J = 6.0$ Hz).

(−)-(2*S*,3*S*,6*R*)-1-[(benzyloxy)carbonyl]-2-(3′-chloropropyl)-3-methyl-6-[4′-(benzyloxy)butyl]-4-piperidone (12). To a mixture of freshly ground magnesium turnings (0.457 g, 18.8 mmol) in 20 mL of anhydrous THF at rt was added 1,2-dibromoethane (0.15 mL, 1.71 mmol). After stirring at rt for 1 h, the $MgBr_2$/THF solution was removed and discarded. Residual $MgBr_2$ was removed by washing the magnesium with anhydrous THF. Fresh THF (40 mL) and a portion of 4-(benzyloxy)-1-bromobutane (3.24 mL, 17.1 mmol) were added to the flask. When the reaction initiated, the flask was cooled to 0 °C and the remainder of 4-(benzyloxy)-1-bromobutane was added. The mixture was stirred until most of the magnesium had reacted. Additional magnesium (0.21 g, 8.5 mmol) was added, and stirring was continued for 1 h at rt to give the Grignard reagent.

In a separate flask, copper(I) bromide−dimethyl sulfide complex (3.51 g, 17.1 mmol) was added to 70 mL of anhydrous THF and cooled to −78 °C. The Grignard of 4-(benzyloxy)-1-bromobutane was added slowly via a double-tipped stainless steel needle. Stirring for 1 h at −78 °C produced an orange solution that appeared to be almost homogeneous. Boron trifluoride etherate (2.10 mL, 17.1 mmol) was added, and stirring was continued for 5 min. To the newly formed BF_3·-OEt_2/organocopper complex was added (over a 1.5 h period) a solution of **11** (2.75 g, 8.55 mmol) in 35 mL of anhydrous THF. After stirring for 2 h at −78 °C, 40 mL of aqueous 20% NH_4Cl/NH_4OH (50:50) was added, and the mixture was allowed to warm to rt. After exposure to air and stirring for several min, the mixture turns blue. The crude mixture was extracted with diethyl ether. The organic extracts were washed with brine and dried over anhydrous K_2CO_3 for 15 min. Filtration and concentration in vacuo gave 5.26 g of the crude product as a dark oil. Purification by radial PLC (silica gel, 10−30% EtOAc/hexanes) yielded 3.70 g (89%) of the desired 2,6-*cis*-piperidone **12** as a clear oil: $[\alpha]^{24.5}_D$ −3.0 (*c* 0.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20−7.45 (m, 10 H), 5.08−5.22 (appears as a doublet at 5.15 ppm with sidebands at 5.20 and 5.11 ppm, 2 H, $J = 2.2$ Hz), 4.50 (br s, 1 H), 4.47 (s, 2 H), 4.35 (br s 1 H), 3.48 (br s, 2 H), 3.42 (t, 2 H, $J = 5.2$ Hz), 2.81 (dd, 1 H, $J = 9.2$ and 15.8 Hz), 2.40 (q, 1 H, $J = 6.6$ Hz), 2.31 (dd, 1 H, $J = 4.5$ and 15.5 Hz), 1.25−1.90 (series of m, 10 H), 1.18

(d, 3 H, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.3, 156.1, 138.4, 136.2, 128.4, 128.1, 128.0, 127.8, 127.4, 127.3, 72.6, 69.7, 67.5, 58.5, 52.7, 47.8, 44.2, 40.2, 37.0, 33.7, 29.6, 29.1, 23.1, 16.6; IR (NaCl, neat): 3088, 3063, 3031, 1715, 1694, 1605, cm^{-1}. HRMS calcd for $C_{28}H_{36}NO_4Cl$ 485.23330 (M^+), found 485.23252.

(−)-(2*S*,3*S*,6*R*)-6-[4′-(Benzyloxy)butyl]-1-[(benzyloxy)carbonyl]-2-(3′-chloropropyl)-3-methyl-4-[(trifluoromethanesulfonyl)oxy]-1,2,3,6-tetrahydropyridine (13). To a stirred solution of LHMDS (8.31 mL, 8.31 mmol, 1.0 M solution in THF) in 25 mL of anhydrous THF at −78 °C was added dropwise a solution of **12** (3.673 g, 7.556 mmol) in 11 mL of anhydrous THF via a double-tipped stainless steel needle. After the reaction mixture was stirred at −78 °C for 1.5 h, a solution of 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-pyridine[10] (4.06 g, 11.3 mmol) in 8.0 mL of THF was added via a double-tipped stainless steel needle (Note: The *N*-(2-pyridyl)triflimide was pumped under high vacuum for 1 h prior to use). The reaction was stirred for 2 h at −78 °C, and 0.25 mL of water was added. The mixture was diluted with diethyl ether and dried over anhydrous K_2CO_3. Filtration through Celite and silica gel and concentration in vacuo gave 9.04 g of the crude vinyl triflate. Purification in three separate portions by radial PLC (silica gel, CH_2Cl_2/hexanes, CH_2Cl_2, then 20% EtOAc/hexanes) yielded 4.08 g (87%) of the desired vinyl triflate **13** as a clear oil: $[\alpha]^{23.7}_D$ −74.1 (*c* 0.885, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (s, 10 H), 5.73 (dd, 1 H, $J =$ 3.4 and 22.0 Hz), 5.05−5.23(m, 2 H), 4.19−4.72 (m, 4 H), 3.32−3.60 (m, 4 H), 2.39 (apparent sextet, 1 H, $J = 7.4$ Hz), 1.21−1.90 (m, 10 H), 1.16 and 1.11 (two d due to rotamers, 3 H, $J =$ 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.0 and 1.55 (due to rotamers), 149.8 and 149.3 (due to rotamers), 138.5, 136.2, 128.5, 128.3, 128.2, 127.9, 127.5, (124.8, 120.5, 116.3, 112.0) (CF_3), 116.0 and 115.4 (due to rotamers), 72.8, 69.8 and 69.7 (due to rotamers), 67.7 and 67.5 (due to rotamers), 56.2 and 55.7 (due to rotamers), 52.0 and 51.7 (due to rotamers), 44.3 and 44.1 (due to rotamers), 37.7 and 37.6 (due to rotamers), 36.0, 35.2, 31.4 and 31.3 (due to rotamers), 29.3, 23.2, 17.6; IR (NaCl, neat): 3089, 3065, 3032, 1701, 1604 cm^{-1}. HRMS calcd for $C_{29}H_{35}NO_6SClF_3$ 618.19040 (M^+), found 618.18840.

(−)-(5*R*,8*R*,8a*S*)-5-(4′-Hydroxybutyl)-8-methyloctahydroindoline (14). A flask containing a solution of **13** (305 mg, 0.493 mmol) in 5 mL of absolute EtOH at rt was purged with argon. To this solution was added 122 mg (40 wt %) of 5% platinum on carbon. The mixture was stirred overnight under a hydrogen atmosphere at balloon pressure. The flask was again purged with argon and 61 mg (20 wt %) of palladium hydroxide (Pearlman's catalyst, 20% on carbon/31% H_2O) was added. The reaction mixture was stirred for 13 h at rt under a hydrogen atmosphere at balloon pressure, and then argon was bubbled through the solution for 5 min. Sodium carbonate (105 mg, 0.99 mmol) was added, and the reaction mixture was heated at reflux for 1.5 h. After cooling to rt, the solution was filtered through Celite and concentrated in vacuo. The crude residue was dissolved in methylene chloride, filtered through Celite, and purified by column chromatography (basic alumina, 0−50% EtOAc/hexanes) to give 85 mg (82%) of the desired amino alcohol **14** as a dark oil: $[\alpha]^{24}_D$ −95.1 (*c* 0.45, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.64 (t, 2 H, $J = 6.3$ Hz), 3.32 (dt, 1 H, $J = 2.1$ and 7.0 Hz), 1.20−2.25 (series of m, 18 H), 0.95 (dq, 1 H, $J = 4.4$ and 11.8 Hz), 0.89 (d, 3 H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 71.1, 63.3, 61.4, 51.3, 35.6, 33.6, 33.0, 32.6, 30.4, 28.4, 21.8, 19.8, 18.4; IR (NaCl, neat): 3353 (br), 2932, 1699 (br) cm^{-1}. HRMS calcd for $C_{13}H_{25}NO$ 211.19360 (M^+), found 211.19279.

(−)-(5*R*,8*R*,8a*S*)-5-(3-Formylpropyl)-8-methyloctahydroindoline (4). A solution of **14** (0.423 g, 2.00 mmol) in 20 mL of anhydrous CH_2Cl_2 was transferred via a double-tipped stainless steel needle into a solution of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (1.10 g, 2.6 mmol) (the Dess−Martin 12-I-5 triacetoxyperiodinane)[12] in 20 mL of CH_2Cl_2 at rt. After stirring for 2.5 h at rt, the reaction mixture was transferred via a double-tipped needle into a stirred solution of 10 mL of saturated aqueous $NaHCO_3$ and 2.5 g of sodium thiosulfate ($Na_2S_2O_3 \cdot 5H_2O$). Stirring was continued at rt until the solution appeared homogeneous. The crude reaction mixture was extracted with diethyl ether. The combined organic extracts were washed with brine and dried over anhydrous K_2CO_3. Filtration through Celite and concentration yielded 0.406 g (97%) of the desired amino aldehyde **4** as a dark oil, which was used without further purification. $[\alpha]^{25}_D$ −86.0 (*c* 0.24, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.77 (s 1 H), 3.23 (t, 2 H, $J = 6.8$ Hz), 2.44 (t, 2 H, $J = 7.1$ Hz), 1.83−2.10 (m, 4 H), 1.10−1.83 (m, 10 H), 0.96 (dq, 1 H, $J =$ 4.1 and 13.4 Hz), 0.87 (d, 3 H, $J = 6.4$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.2, 71.3, 63.0, 51.7, 44.1, 36.4, 34.0, 33.5, 31.0, 29.0, 20.3, 18.7, 18.3; IR (NaCl, neat): 2950, 2871, 2781, 1726, 1694 cm^{-1}. HRMS calcd for [$C_{13}H_{23}NO$ + H] 210.18580 [(M + H)$^+$], found, 210.18568.

(−)-(5*R*,8*R*,8a*S*)-5-(4′-Pentynyl)-8-methyloctahydroindoline [(−)-Indolizidine 205A] (1). To a stirred slurry of potasium *tert*-butoxide (15 mg, 0.13 mmol) in 1.0 mL of anhydrous THF (−78 °C) was added a solution of methyl diazomethyl phosphonate (20 mg, 0.13 mmol) in 2.0 mL of anhydrous THF. The reaction mixture was stirred at −78 °C for 5 min. A solution of crude **4** (25 mg, 0.118 mmol) in 2.0 mL of anhydrous THF was added via a double-tipped stainless steel needle. The reaction mixture was stirred at −70 °C for 14 h, and then 20 mL of H_2O was added. The resulting mixture was extracted with dichloromethane (3 × 25 mL). The combined extracts were dried over anhydrous K_2CO_3, filtered through Celite, and concentrated. Purification by column chromatography (neutral alumina, 0−1% EtOAc/hexanes) gave 10 mg (41%) of (−)-indolizidine 205A (**1**) as a clear oil: $[\alpha]^{27.5}_D$ −82.3 (*c* 0.26, MeOH); lit.[15c] $[\alpha]^{24}_D$ −81.7 (*c* 0.36, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.26 (dt, 1 H, $J = 2.1$ and 8.7 Hz), 2.19 (apparent dt, 2 H, $J = 2.5$ and 6.8 Hz), 2.05−1.14 (series of m, 16 H), 0.95 (apparent dt, 1 H, $J = 3.6$ and 12.4 Hz), 0.87 (d, 3 H, $J = 6.5$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 84.4, 71.4, 68.3, 63.0, 51.8, 36.5, 33.8, 33.7, 31.3, 29.1, 24.8, 20.4, 18.83, 18.79; IR (NaCl, neat) 3313, 2951, 2119 cm^{-1}.

(−)-(5*R*,8*R*,8a*S*)-5-(4′-Pentenyl)-8-methyloctahydroindoline [(−)-Indolizidine 207A] (2). To a stirred solution of methyltriphenylphosphonium bromide (0.114 g, 0.319 mmol) in 3.0 mL of anhydrous THF at rt was added potassium bis-(trimethylsilyl)amide (0.64 mL, 0.319 mmol, 0.5 M solution in toluene). The yellow reaction mixture was stirred for 20 min at rt and cooled to 0 °C. Then crude **4** (22.3 mg, 0.106 mmol) in 3.0 mL of anhydrous THF was slowly added via a double-tipped stainless steel needle. The reaction mixture was slowly warmed to rt and stirred for 15 min. The organic solvents were removed in vacuo. The crude residue was dissolved in methylene chloride and filtered through Celite. Concentration in vacuo gave the crude product. Purification by radial PLC (silica gel, 15% THF/hexanes/1% TEA) gave 15.4 mg (70%) of (−)-indolizidine 207A (**2**) as a clear oil: $[\alpha]^{22.5}_D$ −103.2 (*c* 0.47, $CHCl_3$); lit.[15b] $[\alpha]^{28}_D$ −86.5 (*c* 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.70−5.90 (m, 2 H), 4.86−5.08 (m, 2 H), 3.26 (dt, 1 H, $J = 2.0$ and 8.7 Hz), 1.12−2.15 (series of m, 17 h), 0.95 (m, 1 H, $J = 4.5$ and 13.8 Hz), 0.87 (d, 3 H, $J =$ 6.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8, 114.4, 71.3, 63.3, 51.8, 36.5, 34.1 (2 carbons), 33.6, 31.2, 29.0, 25.1, 20.3, 18.9.

(−)-(5*R*,8*R*,8a*S*)-8-Methyl-5-[4(*Z*)-heptenyl]octahydroindolidine [(−)-Indolizidine 235B] (3). To a stirred solution of *n*-propyltriphenylphosphonium bromide (0.175 g, 0.454 mmol) in 15.0 mL of anhydrous THF (rt) was added sodium bis(trimethylsilyl)amide (0.45 mL, 0.454 mmol, 1.0 M solution in THF). After stirring for 1 h at rt, the orange reaction mixture was cooled to −78 °C, and crude **4** (38.0 mg, 0.182 mmol) in 50 mL of anhydrous THF was added dropwise via a double-tipped stainless steel needle. The reaction mixture was stirred at −78 °C for 3 h, slowly warmed to rt, and stirred overnight. Methanol (1.0 mL) was added, the solution was stirred for 1 h, water (0.5 mL) was added, and the crude mixture was dried over anhydrous K_2CO_3. Filtration and concentration in vacuo gave 0.162 g of the crude product. Purification by radial PLC (silica gel, 20% EtOAc/hexanes/0.5% NH_4OH) yielded 36.9 mg (86%) of (−)-indolizidine 235 B (**3**) as a clear oil: $[\alpha]^{24}_D$ − 88.0 (*c* 1.0, MeOH); lit.[15b] $[\alpha]^{28}_D$ −85.4 (*c* 0.79, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.21−5.43 (m, 2 H), 3.26 (dt, 1 H, $J = 1.8$ and 8.1 Hz), 1.80−2.10 (m, 8 H), 1.55−1.80 (m, 5 H), 1.14−1.55 (m, 7 H), 0.95 (t, 3 H, $J = 7.5$

Hz), 0.87 (d, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.8, 129.0, 71.4, 63.4, 51.8, 36.6, 34.3, 33.7, 31.3, 29.1, 27.4, 26.0, 20.5, 20.4, 18.9, 14.3; IR (NaCl, neat): 3004, 2961, 2932, 2871, 2850, 2778, 2700, 1457, 1374, 1332, 1242, 1220, 1163, 1132, 975 cm^{-1}.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **1**−**3**, **8**, and **12**−**14** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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