Synthesis of Enantiopure Indolizidine Alkaloids from α-Amino Acids: Total Synthesis of (−)-Indolizidine 167B

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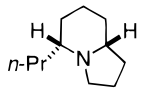
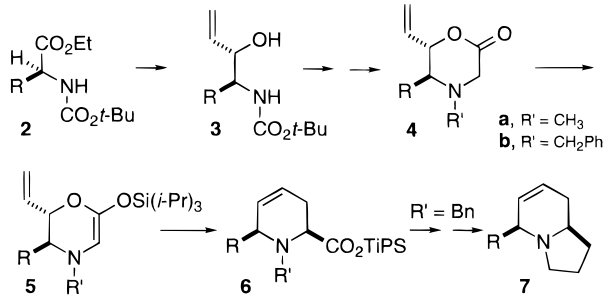
The indolizidine alkaloids display a wide range of biological activity[1] and have been the subject of a considerable number of synthetic studies.[2] The development of general methods for the synthesis of racemic and enantiopure indolizidines remains an area of active investigation.[2] We have developed an enantioselective synthesis of highly functionalized pipecolic esters that might find application as part of a general synthetic route to enantiopure indolizidine alkaloids from readily available α-amino acids.[3] We report here the refinement of the methodology and implementation of this strategy for the synthesis of the naturally occurring indolizidine alkaloid (−)-indolizidine 167B.[4]



(-)-Indolizidine 167B, **1**

(−)-Indolizidine 167B was detected by Daly and co-workers in the skin secretions of neotropical frogs of the genera *Dendrobates* and the family Dendrobatidae.[4,5] The skin secretions of these frogs contain a wide variety of toxic alkaloids that appear to serve as defensive agents. Recent work by Daly and co-workers has shown that the "dendrodaid alkaloids" result from a dietary uptake system which allows accumulation of these poison alkaloids in the skin of the frogs.[6] There have been several previous syntheses of indolizidine 167B.[7,8]

Scheme 1. Proposed Synthesis of Indolizidines



We have previously shown that esters of amino acids **2** could be converted to *N*-methylpipecolic esters **6a** in good yields (Scheme 1).[3a] The key step of the synthetic sequence was a conformationally restricted Claisen rearrangement of silyl ketene acetals **5a** derived from lactones **4a**.[9] The extension of this methodology to the synthesis of indolizidines required removal of the *N*-methyl group to allow introduction of the 5-membered ring of the indolizidine. However, despite considerable effort, this demethylation could not be achieved.[10] Accordingly, we sought to adapt the methodology to the synthesis of *N*-benzylpipecolic esters **6b**, since a benzyl group might be removed under a variety of conditions.

The concise, stereoselective synthesis of *N*-benzyl lactones **4b** from α-amino esters **2** is not straightforward. We have invested substantial effort in the development of a stereoselective route to lactones such as **4** from amino esters **2**[10a] and found that the best method for the conversion of **2** to **3** involves the sequential ester reduction−diastereoselective addition of vinyl organometallics to the resulting aldehyde[11] (or equivalent).[12] This reaction requires an electron-withdrawing group (or alkylidine) on the amine functionality. Whereas, conversion of amino alcohol **3** to lactone **4** requires an alkyl amine that can easily be alkylated with α-haloacetyl halides (or their equivalent) in the presence of the secondary alcohol. We previously showed that alkylation of the *N*-BOC amines **3** with α-haloacetyl halides and their equivalents

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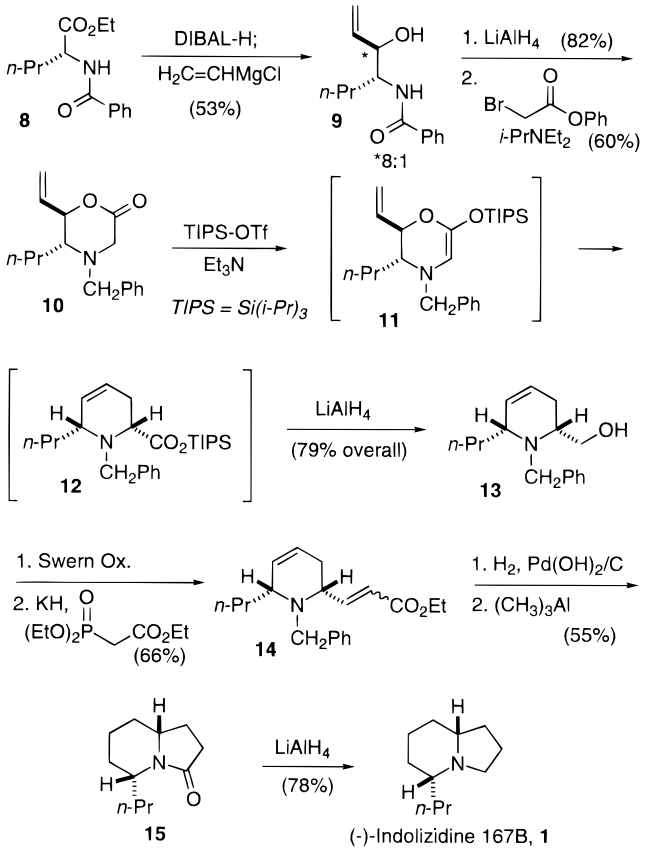
Scheme 2. Total Synthesis of Indolizidine (−)-167B



failed to afford the corresponding lactones (**4**, R′ = CO_2t-Bu).[3,10a] Our synthesis of the indolizidine alkaloid (+)-monomorine[3c] offered a partial solution to this problem. *N*-Benzylpipecolic ester **6b** (R = CH_3) was prepared via removal of the BOC-protecting group in **3** (R = CH_3) followed by reductive amination of the resulting primary amine, lactonization to afford **4b** (R = CH_3), followed by enolization and Claisen rearrangement. The underlying goal of the synthesis of (−)-indolizidine 167B was to develop a more direct synthesis of *N*-benzylpipecolic esters that does not involve a deprotection−reprotection scheme.

Total Synthesis of (−)-Indolizidine 167B. In an effort to circumvent the extra steps required to exchange the BOC protecting group for a benzyl group, we elected to examine a benzoyl group in lieu of a BOC group. The effect of this change on the one-pot DIBAL-H−Grignard reaction[11,12] remained to be seen. If successful, a simple lithium aluminum hydride reduction of the amide would then lead to the desired *N*-benzylamine.

The synthesis of (−)-indolizidine 167B began with the known[13] *N*-benzoyl ethyl ester of D-norvaline **8** which was treated with DIBAL-H followed by vinylmagnesium chloride to afford **9** in 53% yield as an 8:1 mixture of diastereomers (Scheme 2). The yield of this reaction was clearly dependent upon the quality of the Grignard reagent. Reproducible results were obtained with Grignard reagent freshly prepared from vinyl chloride and magnesium.[14] Lithium aluminum hydride reduction afforded the desired amine in 82% yield. Alkylation of the amine with phenyl α-bromoacetate[15] followed by continued stirring of the reaction mixture resulted in lactonization to afford **10** in 60% yield as an 11:1 mixture of diastereomers (GC). The stage was now set for the key Claisen rearrangement. Treatment of **10** with TIPS−OTf followed by reaction at room-temperature overnight afforded a solution of TIPS ester **12** which was immediately treated with lithium aluminum hydride to afford primary alcohol **13** in 79% overall yield from lactone **10**. The silyl ketene acetal derived from the minor diastereomer of lactone **10** failed to undergo Claisen rearrangement, and **13** was obtained as a single diastereomer by ^{1}H and ^{13}C NMR analysis. Oxidation of **13** under Swern conditions[16] followed by homologation with the conjugate base of triethyl phosphonoacetate[17] afforded **14** as a 54:46 mixture of *E*/*Z* isomers (^{1}H NMR) in 74% yield. This proved to be superior to homologation with (carbethoxymethylene)triphenylphosphorane, which afforded **14** as the *E*-isomer (95:5, *E*/*Z*, ^{1}H NMR) in 37% yield. Subjection of the ca. 1:1 *E*/*Z* mixture or enriched *E*-isomer of **14** to hydrogenation/hydrogenolysis conditions (H_2, ammonium formate with Pd/C, PtO_2, or Pd-$(OH)_2$/C) resulted in the formation of several different *N*-benzylamines resulting from scission of the C−N bond in the six-membered ring. The reason for this failed reduction was initially unclear. Corey and Smith[18] encountered problems in a hydrogenation due to what was thought to be sulfur-containing impurities that poisoned the catalyst. Their solution was to stir a THF solution of their compound with sodium carbonate and Pd/C, remove the catalyst, and then carry out the hydrogenation with fresh catalyst. In our case, sulfur impurities might arise from the Swern oxidation. It should be noted that **14** was purified by flash chromatography and homogeneous by NMR and TLC analysis. However, a slight green tint to **14** led us believe that it might contain an impurity that was responsible for the poor behavior in the hydrogenation/hydrogenolysis. Repeated flash chromatography failed to remove this green tint. Accordingly, an ether solution of freshly chromatographed **14** was stirred with potassium carbonate and Pd/C for 2 h. After two cycles, **14** was a clear, colorless oil (66% overall yield from **13**). Hydrogenation/hydrogenolysis of **14** (colorless) with Pearlman's catalyst[19] and hydrogen afforded saturated piperidine−secondary amine in 74% yield. The enantiomer of this compound was previously prepared by Momose and co-workers via a different route.[8b] Treatment of this amino ester with trimethylaluminum[8b,20] afforded lactam **15** in 74% yield. Reduction of **15** with lithium aluminum hydride afforded (−)-indolizidine 167B in 78% yield.[21,8b] Our synthetic

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(21) The synthetic material showed identical ^{1}H NMR and ^{13}C NMR spectra, MS data, and rotation to that reported for the natural product.

material showed spectral characteristics (^{1}H NMR,[8d,f] ^{13}C NMR,[8d,f] and EI mass spectrum[8d]) identical with those reported by other workers.

Conclusion

The synthesis of (−)-indolizidine 167B was accomplished in nine steps (5.8% overall yield) from amino ester **8**. This synthesis demonstrates the utility of our Claisen rearrangement strategy for the synthesis of enantiopure indolizidine alkaloids from readily available α-amino acids. In addition, the synthesis of (−)-indolizidine 167B illustrates the concise route to *N*-benzylpipecolic esters that we have developed. Work is currently ongoing to apply this methodology to the synthesis of other natural products.

Experimental Section

General Information. Capillary GC was carried out using an FID detector on a 25 m HP-101 (methyl silicone) column. The following standard GC parameters were used unless indicated otherwise: flow rate = 60 mL/min; injector temperature = 200 °C; detector temperature = 280 °C; temperature program = 40 to 280 °C at 18 °C/min, initial time = 1 min. The molarity indicated for vinylmagnesium chloride was established by titration with 2,2′-dipyridyl/*sec*-butyl alcohol in methylene chloride.[22] In cases where synthetic intermediates or products were isolated by "aqueous workup (aqueous solution, organic solvent, drying agent)", the procedure was to quench the reaction mixture with the indicated aqueous solution, dilute with the indicated organic solvent, separate the organic layer, extract the aqueous layer several times with the organic solvent, dry the combined organic extracts over the indicated drying agent, and remove the solvent under reduced pressure (water aspirator) with a rotary evaporator. All reactions were run under an atmosphere of nitrogen in flame dried glassware.

***N*-Phenylcarbonyl-D-Norvaline Ethyl Ester (8).** Thionyl chloride (28.9 mL, 388 mmol) was added dropwise over 10 min to absolute ethanol (325 mL) at 0 °C.[13a] D-Norvaline (6.49 g, 10.2 mmol) was added and the resulting solution was refluxed for 10 h. The solution was then concentrated in vacuo. Aqueous workup (saturated aqueous $NaHCO_3/NH_4OH$, 5/1, v/v, 50 mL; benzene, K_2CO_3) afforded D-norvaline ethyl ester (7.85 g, 98%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (q, J = 7.1 Hz, 2H), 3.42 (t, J = 5.6 Hz, 1H), 1.85−1.36 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 60.7, 54.3, 37.1, 18.9, 14.3, 13.8; IR (neat) 3383, 3317, 2962, 2875, 1733 cm^{-1}; $[\alpha]^{25}_D$ −10.0° (c = 0.0245, 5 N HCl), lit.[13b] $[\alpha]^{25}_D$ +9.5° (c = 2, 5 N HCl) for L-norvaline ethyl ester. D-Norvaline ethyl ester (1.48 g, 10.2 mmol) was dissolved in CH_2Cl_2 (20 mL) and the resulting solution was cooled to 0 °C. Triethylamine (4.20 mL, 33.1 mmol) and benzoyl chloride (2.97 mL, 25.6 mmol) were added sequentially, and the resulting solution was warmed to rt and stirred for 24 h. The reaction mixture was then poured into pH 7 phosphate buffer (50 mL). Aqueous workup (CH_2Cl_2, K_2CO_3) afforded 2.45 g of crude product. Flash chromatography (3:1 hexanes/ethyl acetate) followed by crystallization from hexanes (200 mL, stirred 2 h at −25 °C) afforded **8** (2.36 g, 94%) as white needles: mp 58−59 °C, (lit.[13c] mp 59 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 7.0, Hz, 2H), 7.48 (m, 3H), 6.68 (d, J = 6.8 Hz, 1H), 4.90−4.80 (m, 1H), 4.25 (q, J = 7.1 Hz, 2H), 2.05−1.35 (m, 4H), 1.30 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 167.0, 134.1, 131.7, 128.6, 127.0, 61.5, 52.5, 34.8, 18.6, 14.2, 13.7; IR (CCl_4) 3694, 3437, 2965, 1732, 1662, 1516, 1485 cm^{-1}; $[\alpha]^{25}_D$ +15.9 ° (c = 0.014, abs EtOH), lit.[13c] $[\alpha]^{19}_D$ +7.98 ° (c = 0.0138, "alcoholic solution, d = 0.8").

(3*R*,4*R*)-3-Hydroxy-4-[(*N*-phenylcarbonyl)amino]-1-heptene (9). A solution of DIBAL-H (0.73 mL, 4.1 mmol) in hexanes (0.73 mL) was added dropwise over 10 min to a stirried −78 °C solution of ester **8** (510 mg, 2.05 mmol) in CH_2Cl_2 (7 mL). The rate of addition was adjusted as needed to maintain a temperature of −75 °C. The resulting solution was stirred for 20 min. Freshly prepared vinylmagnesium chloride[14] (7.0 mL of a 0.88 M solution in THF, 6.16 mmol) was then added slowly, again the rate of addition was continuously adjusted to maintain a temperature of −75 °C. Immediately after the addition was complete, the reaction flask was placed in an ice bath and allowed to slowly warm to rt. After stirring for 18 h, the reaction mixture was slowly poured into stirring 1 N HCl (25 mL) at 0 °C. Aqueous workup (ether, K_2CO_3) afforded 530 mg of crude product. Flash chromatography (1:1 hexanes/ethyl acetate) afforded **9** (255 mg, 53%, 8:1 mixture of diastereomers, ^{1}H NMR) as a white solid: mp 87−89 °C; ^{1}H NMR (300 MHz, $CDCl_3$, major diastereomer) δ 7.75 (d, J = 7.1 Hz, 2H), 7.45 (m, 3H), 6.31 (d, J = 8.3 Hz, 1H), 5.93 (ddd, J = 17.2, 10.5, 5.7 Hz, 1H), 5.32 (d, J = 17.2 Hz, 1H), 5.19 (d, J = 10.5 Hz, 1H), 4.28 (m, 1H), 4.22−4.12 (m, 1H), 2.05 (bs, 1H), 1.73−1.58 (m, 2H), 1.51−1.39 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer) δ 168.0, 138.4, 134.6, 131.4, 128.5, 127.0, 116.0, 74.2, 53.7, 34.1, 19.5, 14.0; IR (CCl_4) 3616, 3443, 2962, 2934, 1655, 1516, 1274 cm^{-1}; MS (Cl, NH_3) m/z 234 (MH^+, 100), 216 (50), 176 (55), 122 (56), 105 (95); HRMS calcd for $C_{14}H_{20}NO_2$ (M + H) 234.1494, found 234.1487; $[\alpha]^{25}_D$ + 33.5° (c = 0.0498, CH_2Cl_2).

(5*R*,6*R*)-6-Ethenyl-4-(phenylmethyl)-5-propyl-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (10). A solution of **9** (8:1 mixture of diastereomers, 1.90 g, 8.13 mmol) in THF (25 mL) was added dropwise to a stirring suspension of $LiAlH_4$ (1.24 g, 32.5 mmol) in THF (40 mL) at 0 °C. The resulting suspension was refluxed for 3 h and cooled to 0 °C, and H_2O (1.25 mL), 15% NaOH (1.25 mL), and H_2O (3.75 mL) were sequentially added. The resulting suspension was allowed to warm to rt, stirred for 1 h, filtered through Celite, and concentrated to afford 2.21 g of crude product as a yellow oil. Flash chromatography (1:3 hexanes/ethyl acetate, 4% triethylamine) afforded (3*R*,4*R*)-3-hydroxy-4-[*N*-(phenylmethyl)amino]-1-heptene (1.47 g, 82%, 8:1 mixture of diastereomers, ^{1}H NMR) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$, major diastereomer) δ 7.41−7.25 (m, 5H), 5.84 (ddd, J = 16.9, 10.4, 6.2 Hz, 1H), 5.35 (d, J = 17.1 Hz, 1H), 5.20 (d, J = 10.4 Hz, 1H), 3.86−3.79 (m, 2H), 3.80 (partially obscured ABq, J = 12.7 Hz, $\Delta\nu$ = 27.1 Hz, 2H), 2.54 (dt, J = 6.6, 5.1 Hz, 1H), 1.61−1.22 (m, 5H), 0.94 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer) δ 140.1, 139.4, 128.4, 128.0, 127.1, 116.3, 73.6, 61.2, 51.5, 33.0, 19.0, 14.3; IR (neat) 3612, 3363, 3030, 3007, 2961, 2874, 1455, 1089, 1029 cm^{-1}. Freshly distilled phenyl α-bromoacetate (1.86 g, 8.59 mmol) in CH_3CN, (25 mL) was added to a stirred solution of the above *N*-benzylamine (1.56 g, 7.16 mmol) and diisopropylethylamine (5.1 mL, 29 mmol) in CH_3CN (75 mL) at 0 °C.[15] The resulting solution was warmed to rt and stirred for 12 h. Diethylamine (0.296 mL, 2.86 mmol) was then added to remove excess phenyl α-bromoacetate and the resulting solution was allowed to stir for 1 h. The reaction mixture was concentrated (0.01 mmHg, 30 min) and the resulting oil was diluted with ether (30 mL) and stirred for 5 min to precipitate amine salts. The organic layer was then decanted away from the precipitate. The precipitate was washed with ether (4 × 30 mL) and the combined ether solutions were concentrated to afford crude lactone. Flash chromatography (8:1 hexanes/ethyl acetate) afforded 2.95 g of lactone **10** contaminated with phenol. The phenol was inseparable from **10** by chromatography but could be removed by conversion to phenyl acetate followed by flash chromatography. Acetic anhydride (0.600 mL, 6.33 mmol) was added to a stirred solution of the above crude lactone (2.95 g) in pyridine (10 mL) at rt. The resulting solution was allowed to stir for 4 h and then concentrated. Flash chromatography (4:1 hexanes/ethyl acetate) afforded lactone **10** (1.10 g, 60%) as a clear oil (11:1 mixture of diastereomers by capillary GC analysis, major t_R = 37.3 min, minor t_R = 37.7 min): ^{1}H NMR (300 MHz, $CDCl_3$, major diastereomer) δ 7.31 (m, 5H), 5.98 (ddd, J = 17.1, 10.4, 6.7 Hz, 1H), 5.42 (d, J = 16.8 Hz, 1H), 5.34 (d, J = 10.1 Hz, 1H), 4.72 (t, J = 6.2 Hz, 1H), 3.67 (ABq, J = 13.1 Hz, $\Delta\nu$ = 21.8 Hz, 2H), 3.36 (ABq, J = 18.0 Hz, $\Delta\nu$ = 24.6 Hz, 2H), 2.72 (q, J = 5.9 Hz, 1H), 1.65−1.38 (m, 4H), 0.94 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer) δ 168.6, 137.2, 135.1, 128.7, 128.5, 127.6, 118.9, 81.8, 59.6, 57.3, 50.9, 28.0, 19.1, 14.1 IR (neat) 2960, 2933, 1748, 1212 cm^{-1}; MS (EI, 50 eV) m/z 259 (M^+,

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26), 175 (17), 160 (14), 146 (11), 91 (100); HRMS calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1579; $[\alpha]^{25}_D$ +59.46° (*c* = 0.0124, $CHCl_3$).

(2*R*,6*R*)-6-(Hydroxymethyl)-*N*-(phenylmethyl)-2-propyl-1,2,5,6-tetrahydropyridine (13). Triisopropylsilyl trifluoromethanesulfonate (1.45 mL, 5.37 mmol) was added to a stirred solution of lactone **10** (1.10 g, 4.24 mmol) and triethylamine (1.4 mL, 9.9 mmol) in benzene (20 mL) at rt. The mixture was allowed to stir for 18 h. The reaction flask was immersed in an ice bath, and ether (5 mL) and $LiAlH_4$ (434 mg, 1.14 mmol) were added. The mixture was then warmed to rt, stirred for 2 h, and cooled to 0 °C, and H_2O (0.45 mL), 15% NaOH (0.45 mL), H_2O (1.35 mL) were sequentially added. The resulting suspension was stirred for 2 h, filtered through Celite, and concentrated to afford 1.90 g of a pale yellow oil. Flash chromatography (4:1 hexanes/ethyl acetate) afforded **13** (819 mg, 79%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.35 (m, 5H), 5.81−5.73 (m, 1H), 5.69 (m, 1H), 3.81 (s, 2H), 3.44 (partially obscured q, *J* = 10.1 Hz, 1H), 3.38 (m, 1H), 3.12−3.00 (m, 2H), 2.90 (bs, 1H), 2.33 (dm, *J* = 17.8, 1H), 1.74 (dm, *J* = 17.7 Hz, 1H), 1.55−1.21 (m, 4H), 0.82 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 128.9, 128.8, 128.4, 127.2, 122.6, 63.0, 60.4, 57.3, 56.4, 39.0, 22.2, 20.1, 14.0; IR (neat) 3027, 2956, 2931, 2872, 1453, 1027 cm^{-1}; MS (CI/NH_3) *m*/*z* 246 (MH^+, 49), 214 (91), 202 (71), 91 (100); HRMS calcd for $C_{16}H_{24}NO$ (M + H) 246.1858, found 246.1862; $[\alpha]^{25}_D$ −76.1° (*c* = 0.0117, $CHCl_3$). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.00; H, 9.82; N, 5.69. Found: C, 77.98; H, 9.53; N, 5.58.

***E*- and *Z*-(2*R*,6*R*)-6-[(3-Ethoxycarbonyl)propen-1-yl]-1-(phenylmethyl)-2-propyl-1,4,5,6-tetrahydropyridine (14).** A solution of DMSO (0.27 mL, 3.9 mmol) in CH_2Cl_2 (2 mL) was added to a stirred solution of oxalyl chloride (0.20 mL, 2.3 mmol) in CH_2Cl_2 (4 mL) at −78 °C over 5 min.[16] A solution of alcohol **13** (189 mg, 0.770 mmol) in CH_2Cl_2 (4 mL) was added and the resulting solution was stirred for 30 min at −78 °C. Triethylamine (0.75 mL, 5.4 mmol) in CH_2Cl_2 (2 mL) was then added, and the reaction mixture was allowed to warm to rt over 20 min and then poured into stirring H_2O (10 mL). Aqueous workup (CH_2Cl_2, K_2CO_3) and concentration afforded the unstable aldehyde, which was immediatly diluted with THF (5 mL). KH (177 mg of a 35% w/w solution in mineral oil, 1.54 mmol) was washed with hexanes (2 × 10 mL) and then diluted with THF (25 mL). Triethyl phosphonoacetate (0.46 mL, 2.3 mmol) was added and the mixture stirred at rt for 30 min and then cooled to −78 °C. The THF solution of the above aldehyde was slowly added and the reaction mixture was allowed to warm to rt and stirred for 7 h. The mixture was poured into stirring H_2O (25 mL). Aqueous workup (ethyl acetate, K_2CO_3) afforded crude product (579 mg) as a brown oil. Flash chromatography (95:5 hexanes/ethyl acetate) afforded **14** (179 mg, 74%) as a bright green oil. This material contained a minor impurity that poisoned the Pd catalyst in the next step.[18] The impurity was removed by stirring a solution of **14** (bright green oil, 179 mg, 0.570 mmol), K_2CO_3, (100 mg), and Pd/C (5%, 100 mg) in ether (12 mL) for 2 h. The reaction mixture was filtered and the solids were rinsed with $CHCl_3$ (6 × 25 mL). The combined washings were concentrated and the procedure was repeated one additional time to afford ester **14** (159 mg, 66%; 46:54, *Z*/*E* by ^{1}H NMR) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$, 46:54 *Z*/*E* mixture of isomers) δ 7.30 (m, 10H), 6.83 (dd, *J* = 15.8, 8.3 Hz, 1H), 6.11 (dd, *J* = 11.4, 9.6 Hz, 1H), 5.70 (m, 5H), 4.45 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 4H), 3.76 (s, 4H), 3.45 (br dd *J* = 13.9, 7.01 Hz, 1H), 3.38 (br dd *J* = 13.6, 6.0 Hz, 1H) 3.13 (bs, 2H), 2.10 (bs, 4H), 1.65−1.19 (m, 14H), 1.25 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 46:54 *Z*/*E* mixture of isomers) δ 166.3, 166.1, 152.6, 151.3, 141.0, 140.1, 130.1, 129.8, 128.6, 128.3, 128.1, 127.9, 126.6, 126.4, 122.7, 122.3, 120.9, 119.1, 60.2, 60.0, 59.3, 58.7, 58.1, 57.3, 56.7, 36.4, 31.3, 29.9, 18.7, 18.1, 14.3; IR (neat) 3029, 2957, 1720, 1650, 1454, 1180 cm^{-1}; MS (DCI/NH_3) *m*/*z* 314 (MH^+, 100), 270 (45), 91 (44); HRMS calcd for $C_{20}H_{28}NO_2$ (M + H) 314.2110, found 314.2120; $[\alpha]^{25}_D$ −97.3° (*c* = 0.0203, CH_2Cl_2).

(5*R*,9*R*)-5-Propylindolizidin-3-one (15). To a solution of **14** (100 mg, 0.318 mmol) in absolute ethanol (3 mL) was added Pearlman's catalyst[19] $Pd(OH)_2$/C (10%, 60.0 mg). The mixture was pressurized in a Parr hydrogenator to 30 PSI, heated to 60 °C, and shaken for 1.5 h. After cooling, the reaction mixture was diluted with $CHCl_3$ (10 mL) and saturated aqueous Na_2CO_3 (10 mL). Aqueous workup ($CHCl_3$, K_2CO_3) afforded (2*R*,6*R*)-6-[(3-ethoxycarbonyl)propyl]-2-propylpiperidine (53.3 mg, 74%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.1 Hz, 2H), 2.51−2.39 (m, 2H), 2.34 (t, *J* = 7.7 Hz, 2H), 1.80−1.56 (m, 6H), 1.40−1.27 (m, 5H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.07−0.93 (m, 2H), 0.88 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 60.3, 56.7, 56.3, 39.6, 32.6, 32.4, 32.3, 31.0, 24.7, 19.1, 14.2; IR (CCl_4) 2930, 2873, 1737, 1300, 1190, 1110 cm^{-1}; $[\alpha]^{25}_D$ −1.09° (*c* = 0.0128, CH_2Cl_2). Trimethylaluminum[20] (0.14 mL of a 2.0 M solution in benzene, 0.28 mmol) was added dropwise to a stirred solution of the above secondary amine (53 mg, 0.23 mmol) in benzene (12 mL) at 0 °C. The resulting solution was refluxed for 43 h, cooled to rt, and poured into stirring 1 N HCl (25 mL). Aqueous workup (CH_2Cl_2, K_2CO_3) afforded crude product (50.6 mg) as an oil. Flash chromatography (2:3 hexanes/ethyl acetate) afforded **15** (31.0 mg, 74%) as a clear, colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42−3.31 (m, 1H), 3.22−3.11 (m, 1H), 2.40−2.26 (m, 3H), 2.14−2.00 (m, 1H), 1.85−1.58 (m, 4H), 1.57−1.19 (m, 6H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 59.6, 57.3, 34.5, 31.9, 31.8, 29.5, 25.1, 22.7, 20.1, 14.1; IR (CCl_4) 2935, 2873, 2861, 1693, 1423, 1251 cm^{-1}; MS (EI$^+$, 20 eV) *m*/*z* 181 (M^+, 7), 139 (16), 138 (100), 110 (6); HRMS calcd for $C_{11}H_{19}NO$ 181.1467, found 181.1465; $[\alpha]^{25}_D$ −27.6° (*c* = 0.021, CH_2Cl_2), lit.[8b] $[\alpha]^{25}_D$ +28.1° (*c* = 1.125, CH_2Cl_2) for (+)-enantiomer.

(−)-Indolizidine 167B (1). $LiAlH_4$ (11.3 mg, 0.29 mmol) was added to a solution of **20** (14 mg, 0.077 mmol) in ether at 0 °C. The resulting suspension was refluxed for 3 h, and cooled to 0 °C, and H_2O (0.011 mL), 15% NaOH (0.011 mL), H_2O (0.033 mL) were sequentially added. The resulting suspension was stirred for 20 min, filtered through Celite, and concentrated to afford **1** (10.0 mg, 78%) as a gold oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (dt, *J* = 1.8, 8.6 Hz, 1H), 1.95 (q, *J* = 9.0 Hz, 1H), 1.88−1.52 (m, 8H), 1.50−1.06 (m, 8H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.0, 63.7, 51.6, 36.9, 31.0, 30.9, 30.6, 24.7, 20.4, 19.1, 14.5; IR (CCl_4) 2933, 2873, 2859, 1458, 1381, 1177, 1127 cm^{-1}; MS (EI, 20 eV) *m*/*z* 167 (M^+, 9), 166 (5), 125 (25), 124 (100), 96 (26), 70 (8); HRMS calcd for $C_{11}H_{21}N$ 167.1674, found 167.1671; $[\alpha]^{25}_D$ −116.6° (*c* = 0.0042, CH_2Cl_2), lit.[13f] $[\alpha]_D$ −111.3° (*c* = 1.3, CH_2Cl_2).

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Supporting Information Available: Copies of NMR spectra for compounds **1** (−)-indolizidine 167B, **8**, **9**, **10**, **13**, **14**, and **15**, a procedure for the synthesis of *E*-**14,** and ^{1}H NMR spectral data (16 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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