

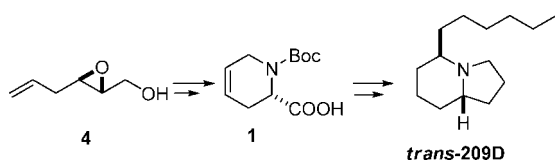
Enantioselective Synthesis of Indolizidine Alkaloid *trans*-209D

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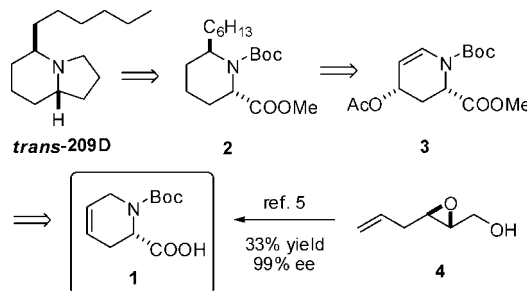
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(*S*)-*N*-Boc-baikiaic acid, readily accessible from enantiomerically enriched 2,3-epoxy-5-hexen-1-ol **4** (prepared by Sharpless asymmetric epoxidation), was used as the starting material in the synthesis of indolizidine alkaloid *trans*-209D, which was obtained in 13 steps and 14% yield from **1** (5% from **4**).

The structural diversity and pharmacological activity associated with alkaloids found in amphibian skin have stimulated research in their synthesis. Many of these compounds have an indolizidine structure. For instance, alkyindolizidine alkaloids,¹ isolated from the skin secretions of certain neotropical frogs of the Dendrobatidae family, have been demonstrated to noncompetitively block neuromuscular transmission.² Although some of these alkaloids (e.g., indolizidines 167B and 209D) have been synthesized by various routes,³ only a few of these give optically active *trans* products.⁴ Polniaszek et al. developed a strategy to obtain the *trans* isomers in ca. 25% overall yield via alkylation of the succinic anhydride moiety using a chiral auxiliary,

SCHEME 1. Retrosynthetic Analysis to Alkyindolizidine Alkaloids



achieving a diastereoselectivity of 4:1.^{4d} Thakahata et al. described an approach that afforded all diastereomers of indolizidines 209D in 92–98% ee.^{4f} This strategy was based on two asymmetric dihydroxylations to construct the two chiral centers, although not always with good selectivities and in less than 5% overall yield from starting materials. More recently, the same authors described a new route to indolizidine *trans*-209D by enantioselective glutaraldehyde allylation using (+)-Ipc₂BOME followed by cyclization with triethylamine to give the chiral starting material.^{4e}

We envisaged that in a synthesis of indolizidines such as *trans*-209D, we could exploit our efficient enantioselective synthesis of *N*-Boc-baikiaic acid **1**.⁵ According to the retrosynthetic analysis shown in Scheme 1, the five-membered ring of the indolizidine could be readily constructed from compound **2**, which in turn would be accessible by functionalization of allylic acetate **3** with a hexyl group. Compound **3**, whose racemic synthesis is known,⁶ would be prepared from enantiomerically pure *N*-Boc-baikiaic acid **1**.

Herein we describe the synthesis of pipercolate **2** from (*S*)-*N*-Boc-baikiaic acid **1** and its subsequent transformation into alkaloid *trans*-209D.

4,5-Dehydropipecolic acid, or baikiaic acid, is a natural product isolated from *Baikiaea plurijuga* and other plants.⁷ Although several papers^{8,9} have reported its synthesis or the preparation of protected related compounds—usually via ring-closing metathesis of allylglycine derivatives⁹—its use as a building block for organic synthesis has been very limited¹⁰ due to a lack of simple methods offering high enantiomeric purity.^{8c,9g,f,j} We

(1) (a) Daly, J. W.; Spande, T. F. In *Alkaloids. Chemical and Biological Perspectives*; Pelletier, S. W., Ed; Wiley, New York, 1986; Vol. 4, Chapter 1. (b) Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albuquerque, E. X. *Neurochem. Res.* **1986**, *11*, 1227. (c) Michael, J. P. In *The Alkaloids: Chemistry and Pharmacology*; Cordell, G., Ed; Academic Press: New York, 2001; Vol. 55, p 91. (d) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 719. (e) Lourenco, A. M.; Maximo, P.; Ferreira, L. M.; Pereira, M. M. A. *Stud. Nat. Prod. Chem* **2002**, *27* (Bioactive Natural Products (part H)), 233. (f) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458. (g) Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M.; Myers, C. W. *Toxicol.* **1978**, *16*, 163. (h) Mensah-Dwumah, M.; Daly, J. W. *Toxicol.* **1978**, *16*, 189.

(2) (a) Daly, J. W. *Prog. Chem. Org. Nat. Prod.* **1982**, *41*, 205. (b) Daly, J. W.; Myers, C. W.; Whittaker, N. *Toxicol.* **1987**, *25*, 1023. (c) Erspamer, V.; Melchiorri, P. *Trends Pharmacol. Sci.* **1980**, *1*, 391.

(3) For asymmetric syntheses of these compounds, see: (a) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409. (b) Kamimura, A.; Nagata, Y.; Kadowaski, A.; Uchida, K.; Uno, H. *Tetrahedron* **2007**, *63*, 11856. (c) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Tetrahedron Lett.* **2005**, *46*, 2101, and references therein.

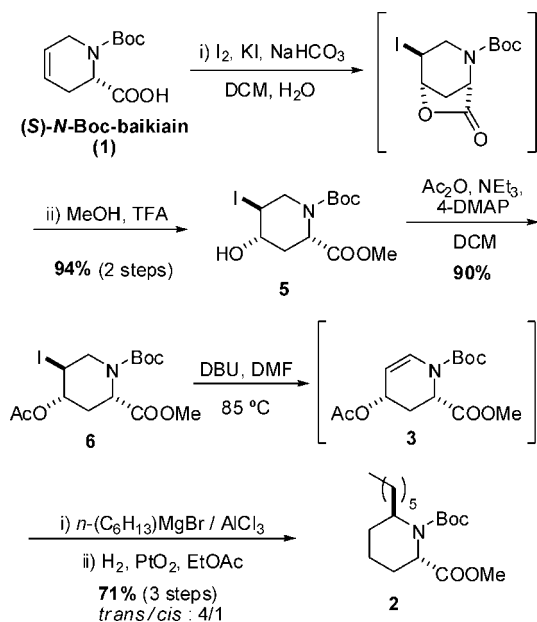
(4) Asymmetric syntheses of indolizidine *trans*-167B: (a) Toyooka, N.; Nemoto, H. *Heterocycles* **2005**, *66*, 549. (b) Kiewel, K.; Tallant, M.; Sulikowski, G. A. *Tetrahedron Lett.* **2001**, *42*, 6621. (c) Yoda, H.; Katoh, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* **2001**, *42*, 2509. (d) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. Asymmetric syntheses of indolizidine *trans*-209D: (e) Takahata, H.; Ichinose, M. *Heterocycles* **2006**, *67*, 407. (f) Takahata, H.; Kubota, M.; Ihara, K.; Okamoto, N.; Momose, T.; Azer, N.; Eldefrawi, A. T.; Eldefrawi, M. E. *Tetrahedron: Asymmetry* **1998**, *9*, 3289. also see ref 4d.

(5) Ginesta, X.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **2002**, *43*, 779.

(6) Hanson, G. J.; Russell, M. A. *Tetrahedron Lett.* **1989**, *30*, 5751.

(7) King, F. E.; King, T. J.; Warwick, A. J. *J. Chem. Soc.* **1950**, 3590.

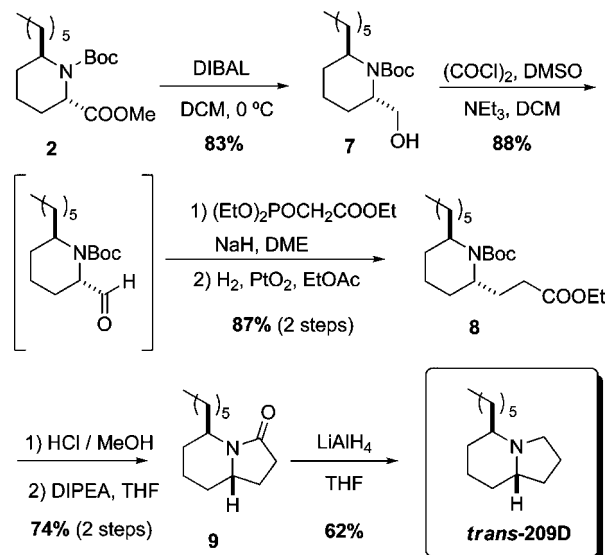
(8) (a) Kraemer, K.; Kazmaier, U. *J. Org. Chem.* **2006**, *71*, 8950. (b) Turner, P. G.; Donohoe, T. J.; Cousins, R. P. C. *Chem. Comm.* **2004**, 1422. (c) Zhang, W.; Xie, W.; Fang, J.; Wang, P. G. *Tetrahedron Lett.* **1999**, *40*, 7929. (d) Rutjes, F. P. J. T.; Veerman, J. J. N.; Meester, W. J. N.; Hiemstra, H.; Schoemaker, H. E. *Eur. J. Org. Chem.* **1999**, 1127. (e) Mazon, A.; Najera, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1855. (f) Herdeis, C.; Engel, W. *Arch. Pharm.* **1993**, *326*, 297. (g) Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707. (h) Burgstahler, W. A.; Aiman, C. E. *J. Org. Chem.* **1960**, *25*, 489. (i) Dobson, N. A.; Raphael, R. A. *J. Chem. Soc.* **1958**, 3642.

SCHEME 2. Synthesis of Methyl (2*S*,6*R*)-1-(*tert*-Butoxycarbonyl)-6-hexylpiperidine-2-carboxylate **2**

started with the preparation of multigram quantities of *N*-Boc-protected baikiaian from 2,3-epoxy-5-hexen-1-ol **4** in accord with our group's previously reported procedure^{5,10a} in 33% overall yield and 99% ee (HPLC of saturated methyl ester, Chiralcel OD).

Enantiomerically pure *N*-Boc-baikiaian was then submitted to iodolactonization followed by methanolysis to give the iodo derivative **5** in excellent overall yield (94%, two steps) (Scheme 2). Alcohol protection afforded uneventfully acetate **6** in excellent yield. Elimination using DBU gave the allylic acetate **3**. However, this compound easily decomposes in solution or on column to give, most probably, methyl (2*S*)-*N*-*tert*-butoxycarbonyl-1,2-dihydropyridine-2-carboxylate. This elimination was confirmed by hydrogenation of the decomposition product, which gave the well-known methyl *N*-Boc-pipecolate. Consequently, compound **3** was immediately used for alkylation in all further procedures.

Unfortunately, all of our attempts at palladium- or copper-catalyzed allylic substitution gave poor yields and/or regio- or stereoselectivities. However, when **3** was treated with hexyl-

SCHEME 3. Synthesis of Indolizidine (–)-(5*R*,9*S*)-**209D**

magnesium bromide/ $AlCl_3$ at -15 °C for 15 min,⁶ the alkylated compound was obtained in good overall yield, high regioselectivity, and acceptable diastereoselectivity (4:1 *trans* to *cis*). The mixture of diastereomers was then hydrogenated and, methyl (2*S*,6*R*)-1-(*tert*-butoxycarbonyl)-6-hexylpiperidine-2-carboxylate **2** could be readily separated from its diastereomer by simple column chromatography (Scheme 2).

To assemble the five-membered ring, compound **2** was treated with DIBAL-H to give alcohol **7**, which was oxidized to the corresponding aldehyde by Swern oxidation in 88% yield (in this case, the Dess–Martin reagent gave only a 74% yield). This aldehyde was then subjected to a Horner–Wadsworth–Emmons reaction¹¹ to obtain the corresponding olefin (96:4 *trans* to *cis* according to 1H NMR), which was immediately hydrogenated in excellent yield. Again, the unsaturated compound decomposed during chromatography. Compound **8** was then treated with methanolic HCl to get the free amine, which formed indolizidinone **9** after cyclization using DIPEA. Finally, amide reduction using $LiAlH_4$ in THF afforded indolizidine (–)-(5*R*,9*S*)-**209D**. Their spectroscopic data were identical to those described in the literature^{4d} (Scheme 3).

In conclusion, we have shown the suitability of enantiomerically pure *N*-Boc-baikiaian (**1**) as starting material for a stereocontrolled synthesis of indolizidine alkaloid *trans*-**209D**, which was prepared in 13 steps and 14% yield. The starting material was efficiently prepared from enantiomerically enriched 2,3-epoxy-5-hexen-1-ol (**4**), which in turn is readily available by Sharpless asymmetric epoxidation.

Experimental Section

Methyl (2*S*,4*S*,5*S*)-1-(*tert*-Butoxycarbonyl)-4-hydroxy-5-iodopiperidine-2-carboxylate (5**).** A mixture of (*S*)-*N*-Boc-baikiaian (2.6 g, 11.4 mmol), I_2 (8.71 g, 34.3 mmol), KI (11.3 g, 68.6 mmol), and $NaHCO_3$ (1.92 g, 22.9 mmol) in water (50 mL) and dichloromethane (100 mL) was stirred at rt for 72 h. Then, $Na_2S_2O_3$ was added until the yellow color disappeared. The aqueous layer was extracted with dichloromethane (3×110 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo, yielding (1*S*,4*S*,5*S*)-2-(*tert*-butoxycarbonyl)-4-iodo-6-oxa-7-oxo-2-

(11) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

(9) (a) Binder, J. B.; Blank, J. J.; Raines, R. T. *Org. Lett.* **2007**, *9*, 4885. (b) Maechling, S.; Zaja, M.; Blechert, S. *Adv. Synth. Catal.* **2005**, *347*, 1413. (c) Halbach, T. S.; Mix, S.; Fischer, D.; Maechling, S.; Krause, J. O.; Sievers, C.; Blechert, S.; Nuyken, O.; Buchmeiser, M. R. *J. Org. Chem.* **2005**, *70*, 4687. (d) Varray, S.; Lazaro, R.; Martinez, J.; Lamaty, F. *Organometallics* **2003**, *22*, 2426. (e) Cho, J. H.; Kim, B. M. *Org. Lett.* **2003**, *5*, 531. (f) Kinderman, S. S.; Doodeman, R.; Van Beijma, J. W.; Russcher, J. C.; Tjen, K. C. M. F.; Kooistra, T. M.; Mohaselzadeh, H.; Van Maarseveen, J. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 736. (g) Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2602. (h) Varray, S.; Lazaro, R.; Martinez, J.; Lamaty, F. *Eur. J. Org. Chem.* **2002**, 2308. (i) Varray, S.; Gauzy, C.; Lamaty, F.; Lazaro, R.; Martinez, J. *J. Org. Chem.* **2000**, *65*, 6787. (j) Tjen, K. C. M. F.; Kinderman, S. S.; Hiemstra, H.; Rutjes, F. P. J. T.; Schoemaker, H. E. *Chem. Commun.* **2000**, 699. (k) Veerman, J. J. N.; Van Maarseveen, J. H.; Visser, G. M.; Kruse, C. G.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **1998**, 2583. (l) Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677. (m) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606. (n) Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855.

(10) See, for example (a) Alegret, C.; Ginesta, X.; Riera, A. *Eur. J. Org. Chem.* **2008**, 1789–1796. (b) Herdeis, C.; Engel, W. *Arch. Pharm.* **1993**, *326*, 297–301. (c) Mazaleyra, J. P.; Rage, I.; Xie, J.; Savrda, J.; Wakselman, M. *Tetrahedron Lett.* **1992**, *33*, 4453–4456. (d) Fujita, Y.; Irreverre, F.; Witkop, B. *J. Am. Chem. Soc.* **1964**, *86*, 1844–1846. Also see ref. ⁶

azabicyclo[3.2.1]octane (3.96 g, 98%) as a slightly yellow solid, which was used in next step without further purification: R_f (hexane/EtOAc 3/1) = 0.50; mp = 88–89 °C; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 1.50 (s, 9H), 2.23–2.31 (m, 1H), 2.94 (d, J = 12.8 Hz, 1H), 3.70–3.86 (m, 1H), 4.18–4.32 (m, 1H), 4.33–4.45 (m, 1H), 4.61–4.87 (m, 1H), 4.96 (t, J = 4.8 Hz, 1H) ppm.

To a solution of this compound (3.96 g, 11.2 mmol) in MeOH (60 mL) was added TFA (0.86 mL, 11.2 mmol). After 6 h. of stirring at rt, more TFA (0.86 mL, 11.2 mmol) was added, and the resulting solution was stirred 2 h. Then the solvent was evaporated, yielding a yellow solid. Crystallization from hot toluene gave pure **5** (4.15 g, 94% two steps) as a white solid: R_f (hexane/EtOAc 3/1) = 0.17; mp = 170–173 °C; $[\alpha]_D = -16.6$ (c 1.1, CHCl_3); IR (film) ν_{max} 3433, 2974, 1745, 1671 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 1.49 (s, 9H), 2.32 (dd, J = 14.8, 1.7 Hz, 1H), 2.61 (br, 1H), 2.70 (dd, J = 14.8, 6.7 Hz, 1H), 3.61–3.73 (m, 1H), 3.74 (s, 3H), 4.07 (d, J = 14.7 Hz, 1H), 4.16–4.23 (m, 2H), 4.59–5.06 (m, 1H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 28.5 (CH_3), 28.5 (CH_2), 29.0 (br, CH), 44.0 (br, CH_2), 50.1 (CH), 52.6 (CH_3), 69.2 (CH), 81.1 (C), 155.2 (C), 173.1 (C) ppm; MS (ESI+) m/z 408 [(M + Na) $^+$, 30], 286 [(M – 99) $^+$, 100]; HRMS (ESI+) calcd for $\text{C}_{12}\text{H}_{20}\text{INNaO}_5$ 408.0278, found 408.0276.

Methyl (2S,4S)-4-Acetoxy-1-(tert-butoxycarbonyl)-1,2,3,4-tetrahydropiperidine-2-carboxylate (3). To a solution of **6** (0.77 g, 1.79 mmol) in anhydrous DMF (58 mL) was added DBU (0.806 mL, 5.37 mmol). The resulting mixture was stirred at 85 °C during 25 min. Then, the reaction mixture was cooled to rt and concentrated in vacuo, obtaining compound **3** (0.55 g, >100%) as a slight yellow oil, which was used in the next steps without further purification: R_f (hexane/EtOAc 3/2) = 0.64; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 1.47 (s, 9H), 1.52* (s, 9H), 1.96 (s, 3H), 2.04–2.13 (m, 1H), 2.60–2.70 (m, 1H), 3.74 (s, 3H), 4.74 (dd, J = 6.2, 1.9 Hz, 1H), 4.90* (dd, J = 6.1, 2.1 Hz, 1H), 5.01 (ddd, J = 8.0, 5.7, 1.6 Hz, 1H), 5.10* (ddd, J = 7.2, 6.1, 1.6 Hz, 1H), 5.15–5.20 (m, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.21* (d, J = 8.4 Hz, 1H) ppm.

Methyl (2S,6R)-1-(tert-Butoxycarbonyl)-6-hexylpiperidine-2-carboxylate (2). To a solution of AlCl_3 (1.91 g, 14.4 mmol) in dichloromethane (40 mL) at –78 °C was added dropwise a solution of *n*-hexylmagnesium bromide (21.5 mL 2 M, 43.1 mmol) in diethyl ether. Then the solution was warmed to 0 °C and stirred 15 min. After that, the solution was cooled again to –15 °C and was added via cannula to a solution containing the crude reaction of compound **3** (see above) in dichloromethane (40 mL) at –15 °C and stirred for 50 min. A solution of citric acid (0.5 M, 16 mL) was then added, and after 10 min. the resulting mixture was filtered through Celite. The layers were separated, the aqueous layer was extracted with EtOAc (3 \times 15 mL), and the combined organic layers were dried over MgSO_4 and concentrated in vacuo to yield a brown oil. Column chromatography afforded 0.42 g of a 4/1 mixture of trans/cis isomers as a colorless oil: R_f (hexane/EtOAc 3/1) = 0.66–0.70; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 0.85–0.92 (m, 3H), 1.22–1.36 (m, 8H), 1.45 (s, 9H), 1.50* (s, 9H), 1.57–1.78 (m, 2H), 2.28–2.72 (m, 2H), 3.68 (s, 3H), 3.69* (s, 3H), 4.12–4.41 (m, 1H), 4.43–4.68 (m, 1H), 5.67–5.91 (m, 2H) ppm.

To a solution of the mixture (0.42 g, 1.28 mmol) in EtOAc (20 mL) was added $\text{PtO}_2 \cdot \text{H}_2\text{O}$ (0.042 g, 20 wt %) and the resulting mixture was stirred under H_2 at atmospheric pressure. After 3 h, the mixture was filtered through Celite and concentrated in vacuo. The mixture of isomers (413 mg, 71%, three steps) was separated by chromatography to afford 0.32 g of **(2S,6R)-2** (55% from **6**) as a colorless oil and 91 mg of **(2S,6S)-2** (15% from **6**). **(2S,6R)-2**: R_f (hexane/EtOAc 3/1) = 0.63; $[\alpha]_D = -32.8$ (c 1.1, CHCl_3); IR (film) ν_{max} 2931, 2858, 1752, 1698 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 0.88 (t, J = 6.8 Hz, 3H), 1.21–1.36 (m, 8H), 1.44 (s, 9H), 1.46–1.69 (m, 5H), 1.69–1.81 (m, 1H), 1.87 (dq, J = 14.1, 7.0 Hz, 1H), 1.92–2.03 (m, 1H), 3.72 (s, 3H), 3.98–4.07 (m, 1H), 4.09 (dd, J = 7.2, 5.1 Hz, 1H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 14.2 (CH_3), 16.7 (CH_2), 22.7 (CH_2), 24.5 (CH_2), 25.8 (br, CH_2), 26.9 (CH_2), 28.5 (CH_3), 29.3 (CH_2), 32.0 (CH_2), 32.9 (br, CH_2),

52.0 (CH_3), 52.1 (br, CH), 54.3 (CH), 80.2 (C), 156.0 (C), 173.7 (C) ppm; MS (ESI+) m/z 350 [(M + Na) $^+$, 18], 328 [(M + H) $^+$, 4], 228 [(M – 99) $^+$, 100]; HRMS (ESI+) calcd for $\text{C}_{18}\text{H}_{34}\text{NO}_4$ 328.2482, found 328.2484.

(2R,6S)-1-(tert-Butoxycarbonyl)-2-hexyl-6-(hydroxymethyl)piperidine (7). To a solution of **2** (0.287 g, 0.877 mmol) in dichloromethane (10 mL) at 0 °C was added dropwise a 1 M DIBAL-H solution (2.6 mL, 2.63 mmol) in hexane and the mixture stirred for 1.5 h at this temperature. To this solution were added dichloromethane (5 mL), water (5 mL), and 2 M HCl (5 mL). The mixture was allowed to warm to rt, and the layers were separated. The aqueous layer was extracted with dichloromethane (3 \times 15 mL), and the combined organic layers were dried over MgSO_4 and concentrated in vacuo to give a brown oil which was purified by column chromatography to yield **7** (0.22 g, 83%) as a colorless oil: R_f (hexane/EtOAc 3/1) = 0.51; $[\alpha]_D = -28.3$ (c 0.8, CHCl_3); IR (film) ν_{max} 3425, 2930, 2857, 1688, 1672 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 0.89 (t, J = 6.8 Hz, 3H), 1.19–1.35 (m, 8H), 1.46 (s, 9H), 1.35–1.47 (m, 1H), 1.50–1.74 (m, 7H), 3.41–3.49 (m, 1H), 3.73 (dd, J = 11.9, 3.5 Hz, 1H), 3.79 (dd, J = 11.9, 7.0 Hz, 1H), 4.06–4.14 (m, 1H), 4.27 (br, 1H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 14.2 (CH_3), 17.7 (CH_2), 22.8 (CH_2), 26.6 (CH_2), 26.7 (CH_2), 27.7 (CH_2), 28.6 (CH_3), 29.3 (CH_2), 31.4 (CH_2), 32.0 (CH_2), 53.4 (CH), 54.9 (CH), 66.7 (CH_2), 80.0 (C), 156.3 (C) ppm; MS (ESI+) m/z : 322 [(M + Na) $^+$, 83], 300 [(M + H) $^+$, 22], 244 [(M – 55) $^+$, 100]; HRMS (ESI+) calcd for $\text{C}_{17}\text{H}_{34}\text{NO}_3$ 300.2533, found 300.2530.

(2S,6R)-1-(tert-Butoxycarbonyl)-2-[2-(ethoxycarbonyl)ethyl]-6-hexylpiperidine (8). To a solution of oxalyl chloride (0.092 mL, 1.06 mmol) in dichloromethane (2.7 mL) at –78 °C was added, under stirring, DMSO (0.151 mL, 2.12 mmol). After 20 min, a solution of alcohol **7** (0.16 g, 0.531 mmol) in dichloromethane (1.3 mL) was added via cannula and the stirring maintained for 30 min at the same temperature. Then, NEt_3 (0.37 mL, 2.65 mmol) was added, and the solution was allowed to stir for an additional 45 min at the same temperature. After that, the solution was allowed to warm to rt, and the aqueous layer was extracted with dichloromethane (3 \times 2 mL). The combined organic layers were washed with 5% HCl (2 mL) and dried over MgSO_4 . The solvent was removed, yielding the corresponding aldehyde (0.14 g, 88%) that was immediately used in the next step without further purification: $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 0.85–0.93 (m, 3H), 1.18–1.79 (m, 16H), 1.46 (s, 9H), 3.54–3.62 (m, 1H), 3.93–4.12 (m, 1H), 9.34 (d, J = 3.2 Hz, 1H) ppm.

To a mixture of NaH (0.013 g, 0.553 mmol) in DME (1.1 mL) was added triethyl phosphonoacetate (0.111 mL, 0.553 g). After 1 h of stirring at rt, the crude aldehyde (0.14 g, 0.461 mmol) in DME (1.1 mL) was added via cannula. The resulting mixture was stirred for 48 h. Then, water (0.7 mL) was added, the aqueous layer was extracted with Et_2O (3 \times 2 mL), and the combined organic layers were dried over MgSO_4 and concentrated in vacuo. The crude product, containing **(2S,6R)-1-(tert-butoxycarbonyl)-2-[2-(ethoxycarbonyl)ethylene]-6-hexylpiperidine** (0.17 g, 99%, *E/Z* = 96/4) was used in the next step without purification: R_f (hexane/EtOAc 4/1) = 0.65; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 0.89 (t, J = 6.8 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.24–1.32 (m, 8H), 1.44 (s, 9H), 1.42–1.46 (m, 1H), 1.53–1.80 (m, 6H), 1.86–1.97 (m, 1H), 3.86–3.96 (m, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.35–4.42 (m, 1H), 5.80 (dd, J = 15.8, 1.8 Hz, 1H), 7.02 (dd, J = 15.8, 5.0 Hz, 1H) ppm.

A mixture of the previous crude product (0.17 g) and $\text{PtO}_2 \cdot \text{H}_2\text{O}$ (0.017 g, 10 wt %) in EtOAc (5 mL) was stirred under H_2 at atmospheric pressure. After 5 h, the mixture was filtered through Celite and concentrated in vacuo. The crude product was purified by chromatography to afford **8** (0.15 g, 87% yield in two steps) as a colorless oil: R_f (hexane/EtOAc 4/1) = 0.65; $[\alpha]_D = -18.1$ (c 1.1, CHCl_3); IR (film) ν_{max} 2930, 2857, 1737, 1688 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 0.88 (t, J = 6.8 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.20–1.34 (m, 8H), 1.46 (s, 9H), 1.52–1.86 (m, 9H), 2.08

(ddt, $J = 13.7, 9.0, 6.9$ Hz, 1H), 2.25–2.41 (m, 2H), 3.64–3.77 (m, 2H), 4.12 (q, $J = 7.1$ Hz, 2H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 14.2 (CH_3), 14.4, (CH_3), 15.7 (CH_2), 22.8 (CH_2), 24.9 (CH_2), 25.6 (CH_2), 27.2 (CH_2), 28.7 (CH_3), 29.4 (CH_2), 29.6 (CH_2), 32.0 (CH_2), 32.1 (CH_2), 33.9 (CH_2), 51.7 (CH), 52.6 (CH), 60.4 (CH_2), 79.2 (C), 155.8 (C), 173.8 (C) ppm; MS (CI- CH_4) m/z 370 [(M + H) $^+$, 51], 270 [(M – 99) $^+$, 100]; HRMS (CI- CH_4) calcd for $\text{C}_{21}\text{H}_{39}\text{NO}_4$ 369.2879, found 369.2872.

(5R,8aS)-5-Hexylhexahydroindolizin-3(2H)-one (9). Compound **8** (0.060 g, 0.162 mmol) was treated with a 1 M solution of HCl (2 mL) in methanol. After 2 h of stirring at rt, the solvent was eliminated yielding (2R,6S)-2-hexyl-6-[2-(methoxycarbonyl)ethyl]piperidine hydrochloride (0.056 g, >100%) as a solid, which was used without further purification: ^1H NMR (CDCl_3 , 400 MHz) δ 0.88 (t, $J = 6.3$ Hz, 3H), 1.19–1.45 (m, 9H), 1.58–1.86 (m, 5H), 1.86–2.12 (m, 4H), 2.25–2.41 (m, 1H), 2.48–2.63 (m, 2H), 3.30–3.50 (m, 2H), 3.69 (s, 3H), 9.39 (br, 2H) ppm.

The previous crude product was dissolved in THF (1.5 mL) and treated with DIPEA. The resulting mixture was heated to reflux and stirred for 15 h. After that, the solvent was removed and the crude purified by chromatography to yield **9** (0.026 g, 74% in two steps) as a colorless oil: R_f (hexane/EtOAc 3/1) = 0.51; $[\alpha]_D = -42.2$ (c 1.0, CHCl_3); IR (film) ν_{max} 2930, 2856, 1687 cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz) δ 0.87 (t, $J = 6.7$ Hz, 3H), 1.06–1.36 (m, 9H), 1.36–1.68 (m, 7H), 1.84 (dm, $J = 3.0$ Hz, 1H), 2.17 (dtd, $J = 13.0, 7.2, 7.1$ Hz, 1H), 2.32–2.38 (m, 2H), 3.56 (dddd, $J = 11.1, 7.0, 6.8, 3.5$ Hz, 1H), 4.19 (dd, $J = 13.5, 7.0$ Hz, 1H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 14.2 (CH_3), 19.1, (CH_2), 22.8 (CH_2),

25.4 (CH_2), 26.5 (CH_2), 27.6 (CH_2), 29.4 (CH_2), 30.2 (CH_2), 30.5 (CH_2), 31.9 (CH_2), 34.0 (CH_2), 48.2 (CH), 53.3 (CH), 173.7 (C) ppm; MS (CI- CH_4) m/z 224 [(M + H) $^+$, 100]; HRMS (CI- CH_4) calcd for $\text{C}_{14}\text{H}_{26}\text{NO}$ 224.2014, found 224.2014.

(5R,9S)-5-Hexylindolizidine (trans-209D). A solution of **9** (0.028 g, 0.125 mmol) in THF (4 mL) was added via cannula to a mixture of LiAlH_4 (0.017 g, 0.439 mmol) in THF (2 mL) and refluxed for 2 h. After that, the reaction mixture was cooled to 0 °C and quenched with water (0.017 mL), 15% NaOH (0.017 mL), and water again (0.050 mL). After 10 min, Na_2SO_4 was added; the reaction mixture filtered through Celite and the solvent was eliminated in vacuo. The crude product was purified by chromatography yielding indolizidine **trans-209D** (16 mg, 62%) as a colorless oil. Spectroscopic data were in agreement with those reported in the literature:^{4d} $[\alpha]_D = -7.5$ (c 0.4, CH_2Cl_2) [lit.^{4d} for **(5S,9R)-209D** $[\alpha]_D = +8.1$ (c 1, CH_2Cl_2).

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Supporting Information Available: General methods, preparation of **6**, and ^1H and ^{13}C NMR spectra of compounds **2**, **5–9**, and **trans-209D**. This material is available free of charge via the Internet <http://pubs.acs.org>.

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