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Asymmetric Total Synthesis of (−)-Alkaloid 223A and Its 6-Epimer

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The enantiopure γ-amino alcohols **7** and **18** are prepared by using the diastereoselective Michael addition of lithium *N*-benzyl (*R*)-α-methylbenzylamide to α,β-unsaturated esters as a key step. The Michael addition of **7** or **18** to an alkynone **8** followed by an intramolecular cyclization afford the cyclic enamine **10** or **20**, which are subjected to the diastereoselective hydrogenation, and the subsequent transformations provide 6-*epi*-alkaloid **223A** and alkaloid **223A**, respectively.

Introduction

From the different species of alkaloid-containing anurans at least 40 indolizidines have been isolated. In the structural view, most of them are 3,5- or 5,8-disubstituted indolizidines.[1,2] The interesting biological activities displayed by these alkaloids such as potent and noncompetitive block action for sodium ion influx, together with the limited amounts isolated from nature, have prompted intensive synthetic studies toward these compounds during the past decades.[1,2] In 1997, Daly and co-workers reported the discovery of alkaloid **223A**, the first trisubstituted indolizidine that was isolated from dendrobatid frogs.[1a] By GC-MS, GC-FTIR, and ^{1}H NMR spectral studies, the structure of this compound was established as (5*R*,6*S*,8*R*,9*S*)- or (5*S*,6*R*,8*S*,9*R*)-6,8-diethyl-5-propylindolizidine **2** (Figure 1).[1a] Very recently, its stereochemistry was revised through total synthesis to the (5*R**,6*R**,8*R**,9*S**) form (Figure 1, compound **1**).[3] During the studies on the synthesis of natural alkaloids from enantiopure β-amino esters,[4] we became interested in the synthesis of this natural indolizidine. The investigations thus undertaken are described here.

Since our synthetic studies started before the appearance of its structural revision, the proposed structure **2** of the alkaloid **223A** was chosen as our target molecule initially. Our synthetic strategy was illustrated in Figure 1: the indolizidine **2** could be assembled from a cyclic enamine **B** using a diastereoselective hydrogenation as a key step, while the intermediate **B** could be obtained through a Michael addition of a γ-amino alcohol **7** to an alkynone **8** and the subsequent intramolecular cyclization.

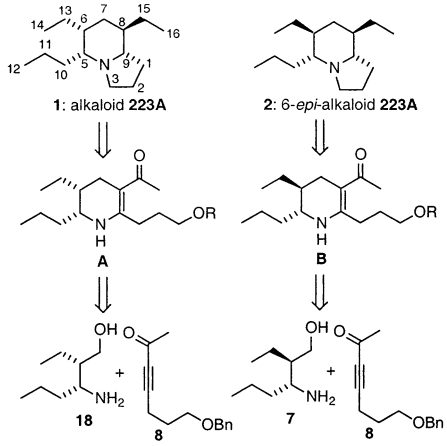

FIGURE 1. Structures and retrosynthetic analysis of alkaloid **223A** and its 6-epimer.

Results and Discussions

As shown in Scheme 1, the required γ-amino alcohol **7** was synthesized from *tert*-butyl 2-hexenoate **3**. Diastereoselective Michael addition of lithium amide generated from *N*-benzyl (*R*)-α-methylbenzylamine to this α,β-unsaturated ester afforded β-amino ester **4**.[5] After hydrogenolysis of **4** the free amino group was reprotected with PhCOCl to provide the amide **5**. Alkylation of **5** with ethyl iodide produced **6** in greater than 96% de determined by HPLC.[6] Next, treatment of **6** with LAH to reduce both the ester and the amide moieties followed by $Pd(OH)_2$/C-catalyzed hydrogenolysis to remove the newly formed benzyl group yielded the amino alcohol **7**.

The Michael addition of **7** to the alkynone **8** worked well to provide the desired enamine **9** in a mixture of

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(2) For reviews, see: (a) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862−2892. (b) Michael, J. P. *Nat. Prod. Rep*. **1993**, 51−72. (c) Michael, J. P. *Nat. Prod. Rep*. **1994**, 17−39.

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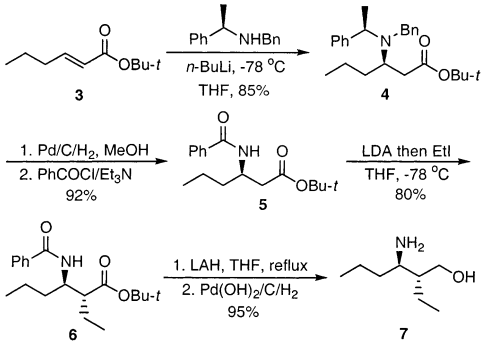
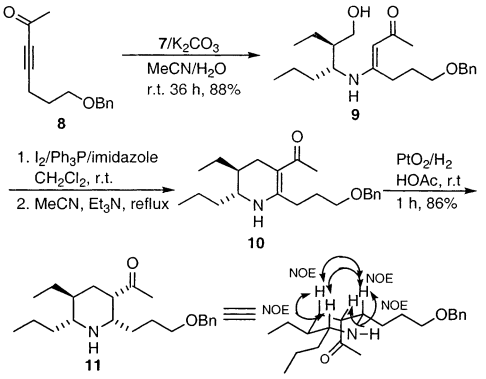
SCHEME 1



SCHEME 2

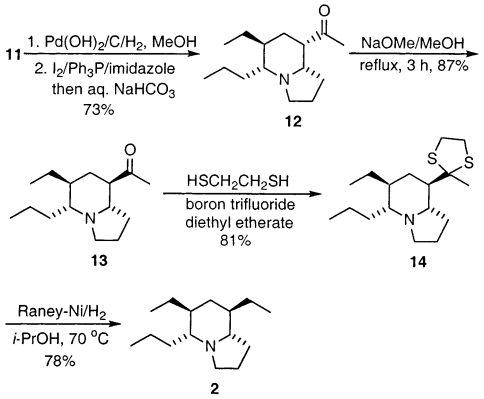


acetonitrile and water with the assistance of K_2CO_3. It was found that the reaction condition of this step was very critical, because when other solvents such as ethanol and DMF or bases were used low yields were observed.[7] Treatment of **9** with I_2/Ph_3P/imidazole in methylene chloride provided the corresponding iodide,[8] which was refluxed in acetonitrile under the action of triethylamine to deliver the cyclic enamine **10**. Next, Pt_2O-catalyzed hydrogenation of **10** was carried out in acetic acid at room temperature and gave the tetrasubstituted piperidine **11** as a single isomer! Its stereochemistry was established by NOE correlations observed as indicated in Scheme 2.

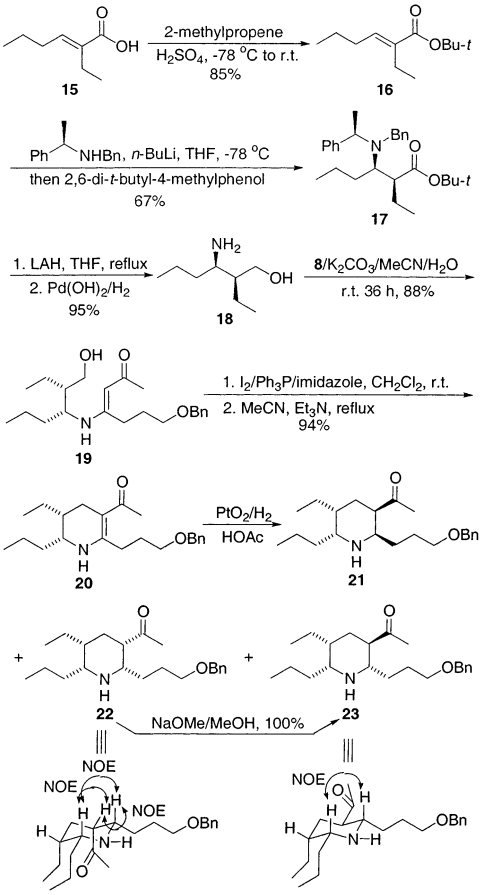
With the piperidine **11** in hand, we finished the total synthesis of **2** by the following transformations (Scheme 3): (1) hydrogenolysis of **11** followed by cyclization mediated with I_2/Ph_3P/imidazole provided indolizidine **12**; (2) isomerization of the 8-acteyl group in **12** from α-form to the thermodynamically stable *β*-form with sodium methoxide afforded **13**; (3) formation of 1,3-dithiolane gave **14**; and (4) hydrogenolysis of **14** with Raney-Ni furnished **2**.

During the studies on the synthesis of **2**, the structural revision report for the alkaloid **223A** was disclosed.[3] This result prompted us to design a new protocol for synthesizing the alkaloid **223A** as illustrated in Figure 1. Obviously, the first problem for us was how to prepare the amino alcohol **18**. We decided to solve this problem by using Davies's procedure.[9] Accordingly, esterification of commercially available acid **15** with 2-methylpropene

SCHEME 3



SCHEME 4



provided α,*β*-unsaturated ester **16** (Scheme 4). After Michael addition of lithium *N*-benzyl (*R*)-α-methylbenzylamide to **16**, the resultant anion was tripped with a sterically hindered proton source to produce **17** in 67% yield and greater than 98% de determined by HPLC.[9] It is notable that 3 equiv of lithium amide was necessary for giving satisfactory yield in this step, probably due to the poor reactivity of **16**. Next, LAH reduction of **17** followed by $Pd(OH)_2$/C-catalyzed hydrogenolysis gave the *γ*-amino alcohol **18** in 95% yield. Subjecting **18** to the Michael addition/cyclization reaction sequence as mentioned above provided the cyclic enamine **20**. After hydrogenation of **20**, three isomers **21** (34% yield), **22** (33% yield), and **23** (22% yield) were isolated and their ster-

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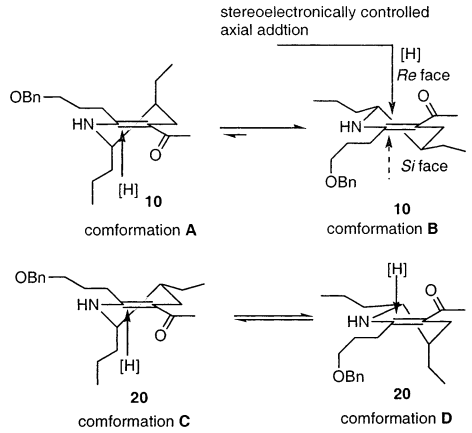
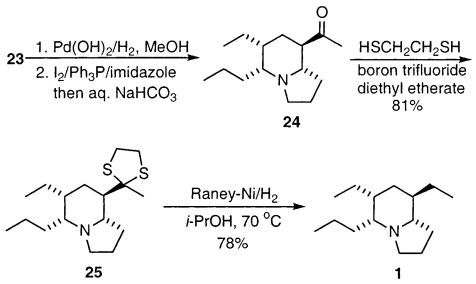


FIGURE 2. Stereochemical course of the hydrogenation of **10** or **20**.

SCHEME 5



eochemistry was established by NOE correlations observed as indicated in Scheme 4. The piperidine **23** might result from the isomerization of **22**, which was proved by complete conversion of **22** to **23** upon treatment with sodium methoxide. This conversion implied that the key intermediate **23** could be obtained from **20** in 55% total yield.

The different stereoselectivity displayed by hydrogenation of the cyclic enamines **10** and **20** could be rationalized by the stereoelectronic control as outlined in Figure 2. When **10** was subjected to hydrogenation it might be preferentially reduced via the transition-state conformation related to conformation **B** with two alkyl groups both at the equatorial positions. A stereoelectronic controlled axial addition of hydrogen from the *Re* face in conformation **B** provided **11** exclusively because in this manner a kinetically favored chairlike transition state could be obtained, while the addition from the *Si* face will be kinetically disfavored to obtain a boatlike transition state.[10] In the case of hydrogenation of compound **20**, two major conformations **C** and **D** with similar stability existed thereby reducing the stereoselectivity.

Transformation of **23** to the alkaloid **223A** was demonstrated in Scheme 5. Hydrogenolysis of **23** and subsequent I_2/Ph_3P/imidazole-mediated cyclization gave the indolizidine **24**. Finally, reduction of the ketone moiety of **24** through the 1,3-dithiolane by Raney-Ni catalyzed hydrogenolysis produced **1**. Its analytical data were all identical with those reported.[3] On the basis of the COSY studies of **1** and **2**, some signals in their ^{1}H NMR spectra were assigned. The ^{1}H NMR spectroscopic data for **1** and **2** were summarized in Table 1. As is apparent, marked differences in chemical shift between the alkaloid 223A and its 6-epimer at the H-5, H-6, and H-7 positions were observed.

TABLE 1. NMR Spectral Data for DCl Salts of the Alkaloid 223A 1 and Its 6-Epimer 2 at 300 MHz (^{1}H) in D_2O

H	1	2
1α	1.56 (m)	1.52 (m)
1β	2.28 (m)	2.16 (m)
2α	1.97 (m)	1.90 (m)
2β	1.88 (m)	1.82 (m)
3α	3.58 (dt, J = 9.6, 2.7 Hz)	3.48 (dt, J = 9.3, 2.6 Hz)
3β	2.95 (q, J = 9.1 Hz)	2.87 (q, J = 9.3 Hz)
5	3.15 (dt, J = 11.0, 3.6 Hz)	2.74 (dd, J = 10.8, 3.9 Hz)
6	1.93 (m)	1.37 (m)
7α	2.04 (m)	1.78 (m)
7β	1.20 (m)	0.85 (q, J = 12.0 Hz)
8	1.55 (m)	1.46
9	2.86 (dt, J = 11.5, 6.0 Hz)	2.78 (dt, J = 11.5, 6.3 Hz)
10	1.68, 1.52	1.60, 1.48
11	1.34, 1.15	1.28, 1.14
13	1.44, 1.12	1.36, 1.12
15	1.39, 1.17	1.37, 1.02
12, 14, 16	0.81, 0.84, 0.86	0.68, 0.71, 0.73

In summary, we have developed two very efficient protocols to synthesize the alkaloid **223A** (11 linear steps and 11.5% overall yield) and its 6-epimer (14 linear steps and 14.4% overall yield). Further application of this strategy to the synthesis of other related alkaloids is in hand.

Experimental Section

General Procedures. Analytically pure ethyl acetate and methanol were used directly without further purification. CH_2Cl_2 and CH_3CN were distilled from CaH_2, and THF was distilled from a deep blue ketyl prior to use. All other solvents were reagent grade quality and used as received. All reactions were run in flame-dried glassware under nitrogen atmosphere unless stated otherwise.

(3*R*,1′*R*)-3-[Benzyl(1-phenylethyl)amino]hexanoic Acid *tert*-Butyl Ester (4). To a stirred solution of (+)-*N*-benzyl-*N*-α-methylbenzylamine (14.9 g, 71 mmol) in 140 mL of dry THF at 0 °C was slowly added *n*-BuLi (1.6 M, 44.38 mL, 71 mmol). After the mixture was stirred for 1 h, the system was put into a dry ice/acetone bath, and a solution of *tert*-butyl 2-hexenoate **3** (10.5 g) in 20 mL of dry THF was added by a syringe for about 40 min. The mixture was stirred for 30 min at −78 °C before saturated aqueous ammonium chloride (60 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography eluting with 1/40 ethyl acetate/petroleum ether to give 20 g (85%) of **4** as a colorless oil. $[\alpha]^{15}_D$ +6 (*c* 0.6, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 10H), 3.81 (m, 2H), 3.41 (d, J = 14 Hz, 1H), 3.31 (m, 1H), 1.91 (ABX, J = 9.3, 3.9 Hz, 2H), 1.22−1.59 (m, 4H), 1.39 (s, 9H), 1.30 (d, J = 7.2 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 143.2, 142.1, 128.16, 128.11, 128.04, 127.92, 126.47, 126.82, 79.81, 58.39, 53.98, 50.09, 37.84, 33.43, 22.65, 28.08, 20.47, 14.06; IR (neat) 2959, 1723 cm^{-1}; EI-MS *m*/*z* 381 (M^+), 290, 238. HRMS calcd for $C_{25}H_{35}NO_2$ 381.2933, found 381.2981.

(3*R*)-3-Benzoylaminohexanoic Acid *tert*-Butyl Ester (5). A solution of **4** (18 g 47.3 mmol) in methanol (250 mL) was hydrogenated over 20% palladium on charcoal (3.6 g) at 50 °C and 50 atm for 12 h. After the mixture was filtered

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through Celite, the filtrate was concentrated to give a colorless oil. This residue was dried in vacuo for 5 h before it was dissolved in 120 mL of CH_2Cl_2 and 27 mL of Et_3N at 0 °C. To this stirring solution was slowly added benzoyl chloride (7 mL, 60 mmol). After the resulting mixture was stirred at room temperature for 5 h, it was washed with aqueous KOH, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography eluting with 1/10 ethyl acetate/petroleum ether to give 12.6 g (92%) of **5**. $[\alpha]^{15}_D$ +36.7 (*c* 1.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 7.2 Hz, 2H), 7.40 (m, 3H), 7.21 (br d, J = 7.1 Hz, 1H), 4.57 (m, 1H), 2.5 (ABX, J = 9.3, 3.9 Hz, 2H), 1.20−1.61 (m, 4H), 1.49 (s, 9H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.46, 166.52, 134.51, 131.16, 128.32, 126.78, 81.05, 46.22, 39.53, 36.30, 27.89, 19.34, 13.76; IR (neat) 3360, 2962, 2847, 1714, 1639, 1166, 718 cm^{-1}; EI-MS *m*/*z* 291 (M^+), 248, 235, 192, 105. HRMS calcd for $C_{17}H_{25}NO_3$ 291.3851, found 291.3821.

(2*R*,3*R*)-3-Benzoylamino-2-ethylhexanoic Acid *tert*-Butyl Ester (6). To a stirred solution of **5** (10 g, 34.36 mmol) in 110 mL of dry THF was slowly added LDA (2 M in THF, 38 mL, 76 mmol) by syringe at −78 °C. After the mixture was warmed to −45 °C in about 2 h, the system was cooled to −78 °C again, and then ethyl iodide was added slowly. The resulting mixture was stirred overnight, while warming up to room temperature. The reaction was quenched by adding 20 mL of saturated aqueous ammonium chloride. The organic layer was separated and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography eluting with 1/10 ethyl acetate/petroleum ether to give 8.8 g (85%) of **6** as a white gum. The diastereoisomeric excess was about 96% determined by HPLC. $[\alpha]^{15}_D$ +57.8 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 6.9 Hz, 2H), 7.40 (m, 3H), 7.33 (br d, J = 7.0 Hz, 1H), 4.41 (m, 1H), 2.40 (m, 1H), 1.41−1.62 (m, 6H), 1.46 (s, 9H), 0.89 (t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.37, 166.68, 134.46, 131.15, 128.36, 126.75, 81.23, 50.45, 49.61, 36.66, 27.97, 23.63, 19.34, 13.83, 11.83; IR (neat) 3277, 2959, 2875, 1722, 1636, 1129, 694 cm^{-1}; EI-MS *m*/*z* 319 (M^+), 276. Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.47; H, 9.1; N, 4.38. Found: C, 71.45; H, 9.26; N, 4.23.

(2*R*,3*R*)-3-Amino-2-ethylhexanol (7). A mixture of **6** (8.4 g, 26.3 mmol) and $LiAlH_4$ (3.2 g) in 110 mL of dry THF was refluxed for 12 h. The reaction was quenched by adding ethyl acetate at room temperature. After water was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give a colorless oil. This compound was dissolved in methanol (100 mL) and hydrogenated over 20% palladium hydroxide on charcoal (1.5 g) at 50 °C and 50 atm for 12 h. The mixture was filtered through Celite, and the filtrate was concentrated and purified by a short silica column eluting with 1/5 methanol/ethyl acetate to give 3.6 g (95%) of **7** as a colorless oil. $[\alpha]^{15}_D$ +25 (*c* 1.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (br s, 3H), 3.88 (dd, J = 11.1, 2.1 Hz, 1H), 3.58 (dd, J = 11.1, 5.1 Hz, 1H), 3.01 (q, J = 6.9 Hz, 1H), 1.2−1.6 (m, 7H), 0.89 (dt, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.79, 13.86, 18.9, 21.68, 35.75, 44.5, 54.48, 63.48; IR (neat) 3315, 2960, 1465, 1049 cm^{-1}; EI-MS *m*/*z* 144 ($M^+ - H^+$), 128, 102, 72; HRMS calcd for $C_8H_{19}NO$ 145.1505, found 145.1543.

(1′*R*,2′*R*)-7-Benzyloxy-4-[(2′-hydroxymethyl-1′-propyl)-butyl]aminohept-3-en-2-one (9). To a mixture of **7** (993 mg, 6.85 mmol), compound **8** (1.78 g 8.22 mmol), and K_2CO_3 (900 mg, 6.5 mmol) in 14 mL of CH_3CN was slowly added 15 drops of water to make the system turbid, then the solution was stirred vigorously at 50 °C for 10 h. After the mixture was dried over $MgSO_4$ the solvent was removed in vacuo. The residue was purified via chromatography eluting with 3/1 ethyl acetate/petroleum ether to give 2.1 g (88%) of **9** as a colorless oil. $[\alpha]^{15}_D$ −47.8 (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.92 (s, 1H), 4.51 (s, 2H), 3.50−3.61 (m, 5H), 2.31 (t, J = 8.1 Hz, 2H), 1.98 (s, 3H), 1.82 (m, 2H), 1.21−1.42 (m, 9H), 0.89 (dt, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.03, 13.99, 19.44, 19.98, 28.14, 28.24, 28.61, 34.73, 46.90, 53.29, 61.08, 68.99, 72.77, 93.64, 127.52, 127.59, 128.251, 138.01, 166.88, 194.16; IR (neat) 3368, 2960, 1600, 1519 cm^{-1}; EI-MS *m*/*z* 361 (M^+), 288, 270, 105; HRMS calcd for $C_{22}H_{35}NO_3$ 361.2594, found 361.2570.

(5*S*,6*R*)-2-(3′-Benzyloxy)propyl-3-acyl-5-ethyl-6-propyl-1,4,5,6-tetrahydropyridine (10). To a stirred solution of **9** (542 mg, 1.5 mmol) in 15 mL of dry CH_2Cl_2 were added triphenylphospine (1.18 g, 4.5 mmol), imidazole (306 mg, 4.5 mmol), and iodine (762 mg, 3 mmol) at 0 °C. After the mixture was warmed to room temperature in about 2 h, it was diluted with petroleum ether, and then filtered through Celite. The filtrate was concentrated to give the corresponding iodide compound, which was dissolved in 30 mL of dry CH_3CN. After 0.23 mL of Et_3N was added the resulting solution was refluxed for about 15 h. The mixture was evaporated in vacuo and the residue was purified via chromatography eluting with 4/1 ethyl acetate/petroleum ether to give 410 mg (80%) of **10** as an unstable pale yellow oil. $[\alpha]^{15}_D$ +62 (*c* 1.68, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.72 (br s, 1H), 4.50 (d, J = 3.3 Hz, 2H), 3.5 (m, 2H), 2.9 (m, 1H), 2.8 (m, 2H), 2.5 (dd, J = 13.5, 5.7 Hz, 1H), 2.11 (s, 3H), 1.81 (m, 2H), 1.40−1.12 (m, 8H), 0.89 (dt, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.41, 13.94, 18.41, 24.95, 26.83, 28.25, 29.08, 31.44, 35.99, 37.05, 54.34, 69.56, 72.68, 99.06, 127.45, 127.56, 128.25, 138.336, 156.32, 195.24; IR (neat) 3316, 2962, 1648 cm^{-1}; EI-MS *m*/*z* 343 (M^+), 328, 252, 166. HRMS calcd for $C_{22}H_{33}NO_2$ 343.2464, found 343.2418.

(2*S*,3*S*,5*S*,6*R*)-2-(3′-Benzyloxy)propyl-3-acyl-5-ethyl-6-propylpiperidine (11). Compound **10** (208 mg, 0.6 mmol) was dissolved in glacial acid (40 mL) and hydrogenated over platinum dioxide (10 mg) at room temperature and 1 atm for 1 h. It was then filtered through Celite, and the filtrate was concentrated and diluted with saturated aqueous $NaHCO_3$. The aqueous layer was extracted several times with ethyl acetate and the combined organic layers were dried over $MgSO_4$. The solution was concentrated and the residue was purified via chromatography eluting with 4/1 ethyl acetate/petroleum ether to give 180 mg (86%) of **11** as a colorless oil. $[\alpha]^{15}_D$ −3.0 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.48 (s, 2H), 3.44 (m, 2H), 2.72 (m, 1H), 2.51 (dt, J = 7.2, 2.9 Hz, 1H), 2.17 (dt, J = 7.5, 3.0 Hz, 1H), 2.15 (s, 3H), 2.01 (dt, J = 11.4, 2.1 Hz, 1H), 1.12−1.72 (m, 13H), 0.89 (dt, J = 7.2, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.33, 14.31, 18.16, 24.61, 27.07, 30.62, 31.23, 32.40, 35.26, 36.74, 49.09, 58.07, 60.20, 70.25, 72.74, 127.35, 127.50, 128.18, 138.40, 212.67; IR (neat) 2959, 2870, 1702, 1455, 1354 cm^{-1}; EI-MS *m*/*z* 344 ($M^+ - H^+$), 302, 254, 196; HRMS calcd for $C_{22}H_{35}NO_2$ 345.2630, found 345.2591.

(5*R*,6*S*,8*S*,9*S*)-8-Acyl-6-ethyl-5-propyloctahydroindolizine (12). Compound **11** (180 mg, 0.52 mmol) was dissolved in 10 mL of methanol and then hydrogenated over 20% palladium hydroxide on charcoal (60 mg) at ordinary temperature and pressure for 12 h. The mixture was then filtered through Celite, and the filtrate was concentrated to give a colorless oil. To a stirred solution of the above compound in 15 mL of dry CH_2Cl_2 were added triphenylphospine (352 mg), imidazole (92 mg), and iodine (228 mg) at 0 °C. After the solution was warmed to room temperature in about 2 h, the mixture was washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by chromatography eluting with 4/1 ethyl acetate/petroleum ether containing a drop of ethylamine to give 90 mg (73%) of **12**. $[\alpha]^{15}_D$ −45.2 (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15 (dt, J = 9.0, 3.3 Hz, 1H), 2.74 (br d, J = 3.2 Hz, 1H), 2.28 (s, 3H), 2.17 (m, 1H), 2.01 (dt, J = 13.0, 3.6 Hz, 1H), 1.91 (q, J = 8.4 Hz, 1H), 1.21−1.50 (m, 13H), 0.89 (dt, J = 7.2 Hz, 6H); IR (neat) 2959, 1697, 1460, 1351 cm^{-1};

EI-MS *m*/*z* 238 ($M^+ + H^+$), 194; HRMS calcd for $C_{15}H_{27}NO$ 237.2133, found 237.2174.

(5*R*,6*S*,8*R*,9*S*)-8-Acyl-6-ethyl-5-propyloctahydroindolizine (13). To 2 mL of dry methanol were added 2.5 mg of sodium and a solution of **12** (25 mg) in 1 mL of dry MeOH at room temperature. After the mixture was refluxed for about 3 h, the solvent was evaporated off. The residue was triturated with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and evaporated in vacuo. The residue was purified via chromatography eluting with 1/3 to 1/1 ethyl acetate/petroleum ether to give 20 mg (87%) of **13**. $[\alpha]^{15}_D$ −48.7 (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.11 (dt, J = 8.5, 3.2 Hz, 1H), 2.41 (dt, J = 11.0, 3.2 Hz, 1H), 2.16 (s, 3H), 2.02−1.81 (m, 4H), 1.71−1.12 (m, 12H), 0.89 (t, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.89, 14.64, 17.22, 22.08, 24.30, 28.73, 29.68, 32.50, 33.02, 39.15, 51.00, 55.14, 65.10, 66.52, 211.07; IR (neat) 2959 1709, 1460 cm^{-1}; EI-MS *m*/*z* 237 (M^+), 194; HRMS calcd for $C_{15}H_{27}NO$ 237.2112, found 237.2130.

(5*R*,6*S*,8*R*,9*S*)-8-(2-Methyl-[1,3]-dithiolan-2-yl)-6-ethyl-5-propyloctahydroindolizine (14). A solution of compound **13** (10 mg, 0.042 mmol) and ethane-1,2-dithiol (0.07 mL, 0.84 mmol) in 2 mL of CH_2Cl_2 was cooled to 0 °C before $BF_3{\cdot}OEt_2$ (0.03 mL, 0.21 mmol) was added. After the mixture was stirred for 30 min it was warmed to rt, and then stirred for an additional 12 h. The suspension was diluted with 10 mL of CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. The solution was concentrated in vacuo and the residue was purified via chromatography eluting with 1/5 ethyl acetate/petroleum ether to yield 10.6 mg (81%) of **14** as a pale yellow oil. $[\alpha]^{15}_D$ −41.4 (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.31−3.20 (m, 5H), 2.15 (dt, J = 12.1, 3.2 Hz, 1H), 2.01−1.89 (m, 5H), 1.71 (s, 3H), 1.62−1.11 (m, 10H), 1.01 (q, J = 12.0 Hz, 1H), 0.89 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.01, 14.74, 17.39, 20.74, 24.54, 29.62, 30.34, 32.84, 36.05, 37.49, 39.71, 51.66, 52.17, 67.16, 67.71, 70.83; IR (neat) 2958, 2874, 2786, 1458 cm^{-1}; EI-MS *m*/*z* 313 (M^+), 270; HRMS calcd for $C_{17}H_{31}NS_2$ 313.1887, found 313.1892.

(5*R*,6*S*,8*R*,9*S*)-6,8-Diethyl-5-propyloctahydroindolizine (2). To a solution of dithioacetal **14** (8 mg, 0.026 mmol) in *i*-PrOH (3 mL) was added Raney nickel (1 g). The resulting mixture was vigorously stirred under hydrogen atmosphere (1 atm) at 70 °C. After completion of the reaction monitored by TLC, the mixture was filtered through Celite. The filtrate was concentrated and purified by a short silica column (EA: MeOH 100:1) to give 4.5 mg (78%) **2** as a volatile colorless oil. Data for its DCl salt: $[\alpha]^{15}_D$ −19.7 (*c* 0.26, $CHCl_3$); ^{1}H NMR (300 MHz, D_2O) δ 3.48 (dt, J = 9.3, 2.6 Hz, 1H), 2.87 (q, J = 9.3 Hz, 1H), 2.78 (dt, J = 11.5, 6.3 Hz, 1H), 2.74 (dd, J = 10.8, 3.9 Hz, 1H), 2.16 (m, 1H), 1.89 (m, 2H), 1.78 (m, 1H), 1.68−1.48 (m, 4H), 1.46−1.32 (m, 3H), 1.23 (m, 1H), 1.18−0.95 (m, 3H), (m, 11H), 0.85 (q, J = 12.0 Hz, 1H), 0.75−0.69 (m, 9H); ^{13}C NMR (75 MHz, D_2O) δ 9.10, 9.30, 13.12, 15.19, 18.71, 22.97, 24.37, 26.37, 29.39, 32.40, 37.69, 39.34, 50.71, 67.15, 71.19; IR (neat) 2960, 2875, 2781, 1459 cm^{-1}; EI-MS *m*/*z* 223 (M^+), 180; HRMS calcd for $C_{15}H_{29}N$ 223.3975, found 223.3991.

2-Ethylhex-2-enoic Acid *tert*-Butyl Ester (16). Isobutylene (40 mL) was condensed into a Schlenk tube containing acid **15** (14.2 g, 0.1 mol) at −70 °C. After sulfuric acid (0.5 mL) was added, the vessel was sealed and warmed to room temperature slowly. After 3 days at room temperature, the vessel was cooled to −70 °C before opening and excessive isobutylene was released by slowly warming the solution to room temperature. The crude product was directly purified via chromatography eluting with 1/5 ethyl acetate/petroleum ether to yield 16.8 g (85%) of **16** as a volatile colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.6 (t, J = 7.5 Hz, 1H), 2.28 (q, J = 7.8 Hz, 2H), 2.12 (q, J = 7.2 Hz, 2H), 1.46 (s and m, 11H), 0.91 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.78, 140.213, 135.17, 79.27, 30.05, 27.86, 27.58, 21.93, 19.77, 13.63; IR (neat) 2968, 2876, 1707, 1458 cm^{-1}; EI-MS *m*/*z* 198 (M^+), 155, 143; HRMS calcd for $C_{12}H_{22}O_2$ 198.1644, found 198.1668.

(2*S*,3*R*,1′*R*)-3-[Benzyl(1′-phenylethyl)amino]-2-ethylhexanoic Acid *tert*-Butyl Ester (17). To a stirred solution of (+)-*N*-benzyl-*N*-α-methylbenzylamine (10.5 g, 50 mmol) in 30 mL of dry toluene was slowly added *n*-BuLi (1.6 M, 31 mL, 50 mmol) at 0 °C. After the mixture was stirred for 1 h, the system was put into a dry ice/acetone bath. To this solution was added *tert*-butyl 2-ethyl-2-hexenoate **16** (3.96 g 20 mmol) in dry toluene (20 mL) by syringe over about 40 min. The mixture was stirred for 1 h at −78 °C and then warmed to −40 °C over 1 h. The solution was maintained at this temperature for 1 h before it was recooled to −78 °C. Precooled THF (−78 °C, 200 mL) was added swiftly by cannula to the reaction mixture, which was then stirred for a further 30 min at −78 °C. Finally, a precooled solution of 2,6-di-*tert*-butyl-4-methylphenol (18 g, 100 mmol) in THF (−78 °C, 20 mL) was added swiftly by cannula to the reaction mixture, which was then stirred for a further 10 min at −78 °C, and warmed to room temperature over 1 h. Evaporation of the mixture in vacuo left a residue that was partitioned between brine and diethyl ether and the combined organic layers were dried over $MgSO_4$ and the solvent removed in vacuo. The residue was purified via chromatography eluting with 1/100 ethyl acetate/petroleum ether to yield 5.5 g (67%) of **17** as a colorless oil. The diastereoisomeric excess was about 98% determined by HPLC. $[\alpha]^{15}_D$ +43 (*c* 1.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.21 (m, 10H), 3.91 (dq, J = 14, 3.5 Hz, 3H), 2.82 (m, 1H), 2.21 (m, 1H), 1.52−1.23 (m, 4H), 1.41 (s, 9H), 1.26 (d, J = 6.9 Hz, 3H), 0.94 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H), 0.66 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.10, 144.82, 142.65, 128.23, 128.03, 128.00, 127.95, 127.88, 126.99, 126.66, 126.28, 79.83, 60.06, 51.16, 32.76, 28.04, 24.97, 21.08, 19.95, 14.29. 11.89; IR (neat) 2966, 2874, 1725, 1455 cm^{-1}. EI-MS *m*/*z* 409 (M^+), 366, 319, 192, 91. HRMS calcd for $C_{27}H_{39}NO_2$ 409.2474, found 409.2455.

(2*S*,3*R*)-3-Amino-2-ethylhexanol (18). A mixture of **17** (5.5 g 13.4 mmol) and $LiAlH_4$ (1.5 g) in dry THF (60 mL) was refluxed for 12 h. The reaction was quenched by adding ethyl acetate at room temperature. After water was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give a colorless oil. This compound was dissolved in methanol (50 mL) and hydrogenated over 20% palladium hydroxide on charcoal (600 mg) at 50 °C and 50 atm for 12 h. The mixture was filtered through Celite, and the filtrate was concentrated and purified by a short silica column eluting with 1/5 methanol/ethyl acetate to give 1.8 g (95%) of **18** as a colorless oil. $[\alpha]^{15}_D$ −1.5 (*c* 1.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (br s, 3H), 3.71 (dd, J = 12.1, 3.4 Hz, 1H), 3.50 (dd, J = 12.1, 5.6 Hz, 1H), 3.12 (m, 1H), 1.61−1.22 (m, 7H), 0.89 (dt, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.24, 13.93, 18.03, 19.74, 35.27, 44.53, 55.07, 64.55; IR (neat) 3325, 2962, 1569, 1069 cm^{-1}; EI-MS *m*/*z* 144 ($M^+ - H^+$), 126, 114, 102, 72; HRMS calcd for $C_8H_{19}NO$ 145.1462, found 145.1458.

(1′*R*,2′*S*)-7-Benzyloxy-4-[(2′-hydroxymethyl-1′-propyl)-butyl]aminohept-3-en-2-one (19). To a mixture of **18** (990 mg, 6.85 mmol), compound **8** (1.78 g, 8.22 mmol), and K_2CO_3 (900 mg, 6.5 mmol) in CH_3CN (14 mL) was slowly added 15 drops of water to make the system turbid, then the mixture was stirred vigorously at 50 °C for 10 h. After the mixture was dried over $MgSO_4$ it was concentrated in vacuo. The residue was purified via chromatography eluting with 3/1 ethyl acetate/petroleum ether to yield 2.1 g (88%) of **19** as a colorless oil. $[\alpha]^{15}_D$ −50.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 5H), 4.88 (s, 1H), 4.47 (s, 2H), 3.82 (m, 1H), 3.61 (dd, J = 8.4, 3.3 Hz, 1H), 3.40 (m, 3H), 2.31 (d, J = 7.6 Hz, 2H), 1.90 (s, 3H), 1.81 (m, 3H), 1.52−1.23 (m, 8H), 0.89 (dt, J = 7.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.51, 13.99, 18.74, 19.78, 27.95, 28.19, 28.65, 35.86, 46.78, 52.35, 61.31, 69.00, 72.80, 93.58, 127.50, 127.59, 128.28, 137.99, 167.181, 194.19;

IR (neat) 3369, 2961, 1600, 1567 cm^{-1}; EI-MS *m/z* 361 (M^+), 288, 270, 91; HRMS calcd for $C_{22}H_{35}NO_3$ 361.2662, found 361.2697.

(5*R*,6*R*)-2-(3′-Benzyloxy)propyl-3-acyl-5-ethyl-6-propyl-1,4,5,6-tetrahydropyridine (20). To a stirred solution of **19** (300 mg, 0.83 mmol) in dry CH_2Cl_2 (8 mL) were added triphenylphospine (654 mg, 2.48 mmol), imidazole (168 mg, 2.48 mmol), and iodine (419 mg, 1.66 mmol) at 0 °C. After the solution was warmed to room temperature in about 2 h, the mixture was diluted with petroleum ether and then filtered through Celite. The filtrate was concentrated to give the corresponding iodide compound, which was dissolved in dry CH_3CN (15 mL). After Et_3N (0.115 mL) was added the mixture was refluxed for about 15 h. The solution was evaporated in vacuo and the residue was purified via chromatography eluting with 4/1 ethyl acetate/petroleum ether to yield 263 mg (94%) of **20** as an unstable pale yellow oil. $[\alpha]^{15}_D$ +48 (*c* 1.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.72 (br s, 1H), 4.50 (d, J = 6.9 Hz, 2H), 3.52 (t, J = 6.1 Hz, 2H), 3.11 (m, J = 3.1 Hz, 1H), 2.70 (t, J = 7.2 Hz, 2H), 2.41 (dd, J = 10, 3.6 Hz, 1H), 2.12 (s, 3H), 1.81 (m, 2H), 1.73−1.12 (m, 8H), 0.89 (dt, J = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.30, 14.33, 19.55, 23.12, 28.50, 28.70, 29.44, 31.89, 32.00, 37.12, 53.72, 70.01, 73.12, 100.33, 127.84, 127.98, 128.62, 138.68, 157.01, 195.55; IR (KBr) 3295, 2961, 1717, 1619 cm^{-1}; EI-MS *m/z* 343 (M^+), 328, 252, 166; HRMS calcd for $C_{22}H_{33}NO_2$ 343.2458, found 343.2432.

Compounds 21, 22, and 23. The cyclic enamine **20** (332 mg, 0.97 mmol) was dissolved in glacial acid (40 mL) and then hydrogenated over platinum dioxide (12 mg) at ordinary temperature and pressure for 1 h. After the mixture was filtered through Celite, the filtrate was concentrated and diluted with saturated aqueous $NaHCO_3$. EtOAc-extract work-up followed by chromatography eluting with 5/1 ethyl acetate/petroleum ether and 100/1 ethyl acetate/methanol to give 116 mg (34%) of **21**, 110 mg (33%) of **22**, and 72 mg (22%) of **23**.

(2*R*,3*R*,5*R*,6*R*)-2-(3′-Benzyloxy)propyl-3-acyl-5-ethyl-6-propylpiperidine (21). $[\alpha]^{15}_D$ +12 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.48 (s, 2H), 3.45 (m, 2H), 2.79 (br m, 2H), 2.12 (s, 3H), 1.72−1.11 (m, 15H), 0.89 (dt, J = 7.0 Hz, 6H); IR (neat) 2958, 2879, 1705, 1455, 1154 cm^{-1}; ESI-MS *m/z* 346 ($M^+ + H^+$); HRMS calcd for $C_{22}H_{35}NO_2$ 345.2730, found 345.2740.

(2*S*,3*S*,5*R*,6*R*)-2-(3′-Benzyloxy)propyl-3-acyl-5-ethyl-6-propylpiperidine (22). $[\alpha]^{15}_D$ −20.5 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.52 (s, 2H), 3.41 (m, 2H), 2.66 (m, 1H), 2.59 (m, 1H), 2.49 (m, 1H), 2.30 (dt, J = 14.5, 2.6 Hz, 1H), 2.17 (s, 3H), 1.79−1.11 (m, 13H), 0.89 (dt, J = 7.2 Hz, 6H); IR (neat) 2959, 2871, 1707, 1455, 1354 cm^{-1}; EI-MS *m/z* 344 ($M^+ - H^+$), 302, 254, 196; ESI-HRMS calcd for $C_{22}H_{36}NO_2$ 346.2732 ($M^+ + H^+$), found 346.2740.

(2*S*,3*R*,5*R*,6*R*)-2-(3′-Benzyloxy)propyl-3-acyl-5-ethyl-6-propylpiperidine (23). $[\alpha]^{15}_D$ −23.6 (*c* 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.52 (s, 2H), 3.41 (t, J = 6.2 Hz, 2H), 2.80 (dt, J = 9.0, 2.7 Hz, 1H), 2.62 (m, 1H), 2.41 (dt, J = 11.0, 3.0 Hz, 1H), 1.90 (dd, J = 11.1, 3.3 Hz, 1H), 2.11 (s, 3H), 1.63−1.24 (m, 13H), 0.89 (dt, J = 7.2, 6H); IR (neat) 2959, 2871, 1705, 1455, 1361 cm^{-1}; ESI-MS *m/z* 346 ($M^+ + H^+$). ESI-HRMS calcd for $C_{22}H_{36}NO_2$ 346.2751 ($M^+ + H^+$), found 346.2741.

Epimerization of Compound 22. To a freshly prepared solution of sodium methoxide (1 mmol) in methanol was added a solution of **22** (1 mmol) in dry MeOH at room temperature. The mixture was refluxed for about 3 h before the solvent was evaporated off. The residue was triturated with water and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$. After removal of solvents, the residue was subjected to a short FC (PE:EA 1:1) to afford **23** in quantitative yield.

(5*R*,6*R*,8*R*,9*S*)-8-Acyl-6-ethyl-5-propyloctahydroindolizine (24). A mixture of **23** (110 mg, 0.31 mmol) and 10 mL of methanol was hydrogenated over 20% palladium hydroxide on charcoal (60 mg) at ordinary temperature and pressure for 12 h. It was then filtered through Celite, and the filtrate was concentrated to give a colorless oil.

To a stirred solution of the above compound in dry CH_2Cl_2 (15 mL) were added triphenylphospine (282 mg), imidazole (75 mg), and iodine (182 mg) at 0 °C. After the mixture was warmed to room temperature in about 2 h, it was washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over $MgSO_4$. The solution was evaporated in vacuo and the residue was purified via chromatography eluting with 4/1 ethyl acetate/petroleum ether containing a drop of ethylamine to give 54 mg (74%) of **24** as a colorless oil: $[\alpha]^{15}_D$ −79.2 (*c* 0.98, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.11 (dt, J = 9.1, 2.0 Hz, 1H), 2.50 (dt, J = 9.6, 3.2 Hz, 1H), 2.16 (s, 3H), 2.11−1.82 (m, 5H), 1.70−1.13 (m, 11H), 0.89 (dt, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.59, 14.72, 18.02, 19.21, 20.64, 29.26, 29.66, 30.87, 33.43, 36.77, 51.14, 51.35, 66.34, 66.55, 211.67; IR (neat) 2959, 2873, 2783, 1714, 1463 cm^{-1}; EI-MS *m/z* 237 (M^+), 194; HRMS calcd for $C_{15}H_{27}NO$ 237.2102, found 237.2138.

(5*R*,6*R*,8*R*,9*S*)-6-Ethyl-8-(2-methyl-[1,3]-dithiolan-2-yl)-5-propyloctahydroindolizine (25). To a solution of compound **24** (30 mg, 0.126 mmol) and ethane-1,2-dithiol (0.21 mL, 2.5 mmol) in CH_2Cl_2 (2 mL) was added $BF_3{\cdot}OEt_2$ (0.09 mL, 0.63 mmol) at 0 °C. After the mixture was stirred for 30 min it was warmed to rt, and then stirred for an additional 12 h. The suspension was diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified via chromatography eluting with 1/5 ethyl acetate/petroleum ether to afford 31 mg (81%) of **25** as a pale yellow oil. $[\alpha]^{15}_D$ −67.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32−3.12 (m, 5H), 2.15 (dt, J = 11.1, 3.2 Hz, 1H), 1.68 (s, 3H), 2.01−1.73 (m, 6H), 1.61−1.23 (m, 10H), 0.89 (dt, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2, 14.5, 17.9, 18.9, 20.4, 29.4, 30.5, 33.3, 33.5, 37.2, 37.3, 39.8, 47.6, 51.7, 66.8, 68.9, 70.9; IR (neat) 2960, 2875, 2785, 1425 cm^{-1}; EI-MS *m/z* 313 (M^+), 270; HRMS calcd for $C_{17}H_{31}NS_2$ 313.1887, found 313.1875.

(5*R*,6*R*,8*R*,9*S*)-6,8-Diethyl-5-propyloctahydroindolizine (1). To a solution of dithioacetal **25** (16 mg, 0.052 mmol) in *i*-PrOH (3 mL) was added Raney nickel (1.5 g). The resulting mixture was vigorously stirred under hydrogen atmosphere (1 atm) at 70 °C. After completion of the reaction monitored by TLC, the mixture was filtered through Celite. The filtrate was concentrated and purified by a short silica column (EA:MeOH 100:1) to give 9 mg (78%) of **1** as a volatile colorless oil. Data for its DCl salt: $[\alpha]^{15}_D$ −38.4 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, D_2O) δ 3.58 (dt, J = 9.6, 2.7 Hz, 1H), 3.15 (dt, J = 11.0, 3.6 Hz, 1H), 2.95 (q, J = 9.1 Hz, 1H), 2.86 (dt, J = 11.5, 6.0 Hz, 1H), 2.28 (m, 1H), 2.05 (dd, J = 13.2, 2.5 Hz, 1H), 1.97−1.88 (m, 3H), 1.74−1.37 (m, 7H), 1.22−1.12 (m, 4H), 0.88−0.80 (m, 9H); ^{13}C NMR (75 MHz, D_2O) δ 11.4, 13.0, 14.7, 18.5, 19.3, 20.2, 26.0, 27.7, 31.3, 31.4, 36.9, 36.8, 52.7, 68.1, 73.8; IR (neat) 2960, 2871, 2781, 1456 cm^{-1}; EI-MS *m/z* 223 (M^+), 180; HRMS calcd for $C_{15}H_{29}N$ 223.3976, found 223.3958.

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Supporting Information Available: ^{1}H NMR or ^{13}C NMR spectra for compounds **1**, **2**, **9**−**11**, **13**, **14**, **19**, **20**, and **23**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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