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A One-Pot Formal [4 + 2] Cycloaddition Approach to Substituted Piperidines, Indolizidines, and Quinolizidines. Total Synthesis of Indolizidine (−)-209I

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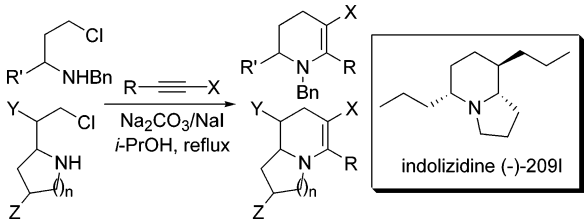

Heating a mixture of substituted *N*-benzyl γ-chloropropylamines, conjugated alkynoates or alkynones, sodium carbonate, and a catalytic amount of sodium iodide in *i*-PrOH at 70−83 °C delivers substituted piperidines in good yields. This transformation goes through a cascade Michael addition/alkylation process and represents a facile one-pot formal [4 + 2] cycloaddition approach to piperidine ring. Using secondary cyclic γ-chloropropylamines as substrates, this process produces substituted indolizidines or quinolizidines. On the basis of this approach, indolizidine (−)-209I is elaborated in 11 steps from methyl 2-hexenoate.

Introduction

Piperidine, indolizidine, and quinolizidine are common skeletons in both natural products[1] and artificial compounds[1a,2] that possess a wide range of biological activities. Accordingly, novel strategies for stereoselective elaboration of these *N*-heterocycles continued to receive considerable attention in the past decades.[1−7] Since both indolizidines and quinolizidines could be assembled from piperidines and piperidones with appropriate substituents, construction of these six-membered rings has become the focus in organic synthesis.[1] Among the emerging methods, one-pot, two-component strategies have been actively pursued because this convergent manner allows high-throughput synthesis. To this end, several elegant [3 + 3] formal cycloaddition methodologies (Figure 1) have been developed.[1a,e] However, little attention has been directed to [4 + 2]-type cycloadditions

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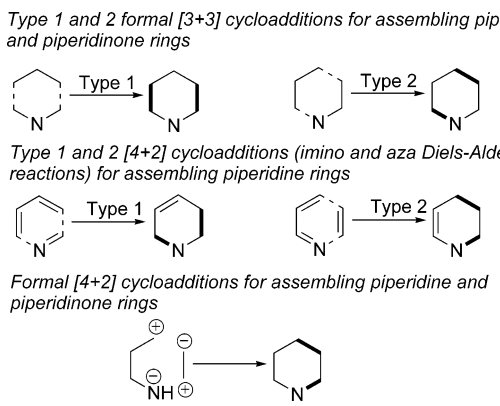
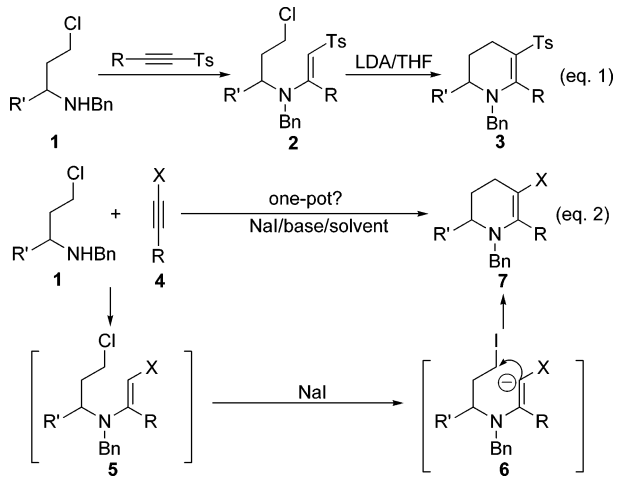


FIGURE 1. [3 + 3] and [4 + 2] cycloadditions to piperidine and piperidinone rings.

SCHEME 1

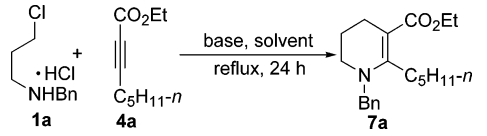


except for using imino and azo Diels−Alder reactions.[1a,e,4] Recently, Ihara and co-workers described a formal [4 + 2] cycloaddition approach to piperidin-2-ones.[5] Herein, we wish to report a facile one-pot formal [4 + 2] cycloaddition approach to piperidine ring.

In 1999, Back and Nakajima reported a cycloaddition strategy to elaborate piperidines **3** via a Michael addition of secondary acyclic γ-chloropropylamines **1** with acetylenic sulfones and subsequent LDA-mediated alkylation (eq 1, Scheme 1).[6] Started from secondary cyclic γ-chloropropylamines, both indolizidine and quinolizidine rings were established via this reaction sequence.[6] Although this two-component methodology showed remarkable efficiency, it is notable that two working-up operations for getting the target molecules were required, and only less conveniently available acetylenic sulfones were utilized while other electron-deficient alkynes were not explored.

The γ-chloropropylamines are relatively stable in the presence of bases compared with the corresponding bromides and iodides that easily undergo an intramolecular or intermolecular S_N2 reaction to give the corresponding substitution products. This is why they were successfully employed as 1,4-difunctional reagents in Back's work.[6] However, for further intramolecular alkylation of their Michael addition products **2**, the poor reactivity of the chloride moiety would be problematic. We envisaged that by adding sodium iodide to the reaction system of γ-chloropropylamines **1** and electron-deficient alkynes **4**, halogen exchange of the Michael addition products **5** would deliver more reactive iodides **6**, which would in turn make direct alkylative cyclization possible (eq 2, Scheme 1). If this process worked well, it would provide a one-pot formal [4 + 2] cycloaddition approach to install the piperidine ring. Indeed, our recent success on elaboration of indolizidines and quinolizidines from γ-chloropropylamines shed a light on this process.[7a]

TABLE 1. Cascade Reaction Process of *N*-Benzyl-3-chloropropylamine 1a and Ethyl 2-Octynoate 4a[a]



entry	base	solvent	yield (%)[b]
1	K_2CO_3	MeCN	0[c]
2	K_2CO_3	DMF	0[c]
3	K_2CO_3	benzene	0[c]
4	K_2CO_3	CH_2Cl_2	0[c]
5	K_2CO_3	*i*-PrOH	56
6	Na_2CO_3	*i*-PrOH	91
7	Na_2CO_3	EtOH	85
8	Na_2CO_3	*i*-PrOH	29[d]

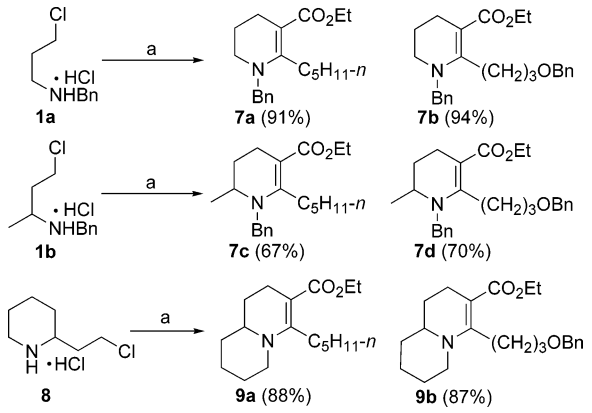
[a] Reaction condition: *N*-benzyl-3-chloropropylamine **1a** (0.33 mmol), ethyl 2-octynoate **4a** (0.24 mmol), base (0.6 mmol), NaI (0.03 mmol), solvent (1 mL), refluxed for 15 h. [b] Isolated yield.[c] **7a** was recovered almost quantitatively. [d] Without addition of NaI.

Results and Discussion

With this idea in mind, a reaction of *N*-benzyl-3-chloropropylamine **1a** with ethyl 2-octynoate **4a** under the action of 0.1 equiv of sodium iodide and 2 equiv of K_2CO_3 was conducted. As summarized in Table 1, in MeCN, DMF, benzene, or CH_2Cl_2 at reflux temperature, this reaction did not give any desired cyclization product **7a**, while **4a** was recovered almost quantitatively (entries 1−4). These results indicated that at these conditions Michael addition did not occur. Since in Back's case[6] this step worked well in these solvents, we reasoned that our problem might result from the relatively poor reactivity of ester **4a** in comparison with acetylenic sulfones. Consequently, some protic solvents that were favorable for Michael addition were tested. We were pleased to find that the reaction in *i*-PrOH worked to provide cyclization product **7a** in 56% yield (entry 5). Further improvement by switching the base to Na_2CO_3 gave the best result (entry 6), which indicated that this process is very sensitive to bases. Changing solvent to ethanol gave slightly low yield (entry 7). Interestingly, without addition of sodium iodide this reaction still produces **7a**, but low yield and isolation of some unreacted **5a** (R′ = H, R = *n*-C_5H_{11}, X = CO_2Et) implied that the halogen exchange was important to ensure this process proceeded well (entry 8).

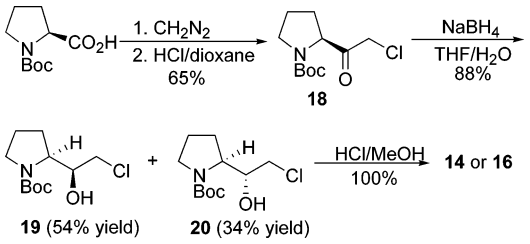
In view of the above encouraging result, reaction of other substituted γ-chloropropylamines with ethyl 2-octynoate **4a** or ethyl 6-benzyloxy-2-hexynoate **4b** was tested for these optimized conditions, and the results were summarized in Scheme 2. In addition to elaboration of 1,2,3-trisubstituted piperidines **7a** and **7b**, this process

SCHEME 2[a]



[a] Reaction conditions: a. ethyl 2-octynoate **4a** or ethyl 6-benzyloxy-2-hexynoate **4b** (1 mmol), substituted γ-chloropropylamine hydrochloride salt (1.4 mmol), Na_2CO_3 (2.5 mmol), NaI (0.1 mmol), *i*-PrOH (2 mL), at reflux temperature for 24 h.

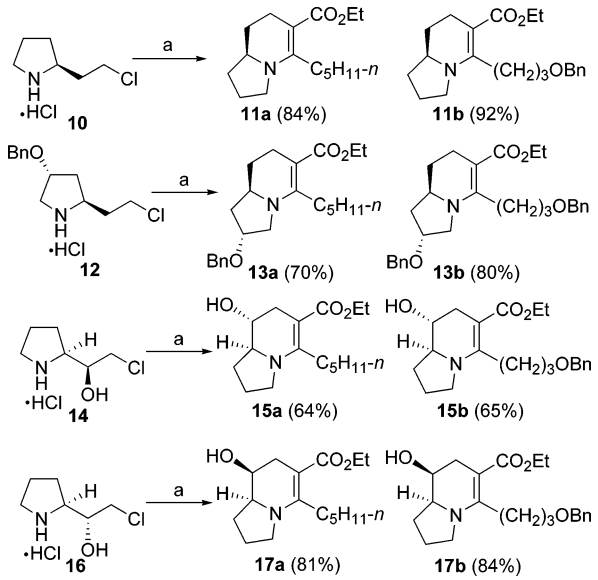
SCHEME 3



was suitable for assembling 1,2,3,6-tetrasubstituted piperidines as evidenced from the formation of **7c** and **7d**. In addition, two 3,4-disubstituted quinolizidines **9** were obtained in good yields by employing a piperidine-embodied γ-chloropropylamine **8** as a building block.

To further demonstrate the usage of our new methodology, four enantiopure pyrrolizidine-embodied γ-chloropropylamines were prepared. The chlorides **10** and **12** were synthesized by a Wolff rearrangement of Boc-protected L-proline or *trans*-4-benzoxy-L-proline[8] and subsequent LAH reduction and chlorination with thionyl chloride. While chlorides **14** and **16** were constructed from HCl cleavage of the corresponding *N*-Boc intermediates **19** and **20** which were produced by $NaBH_4$ reduction of *N*-Boc-L-proline derived chloromethyl ketone **18** as a separable diastereomer mixture (Scheme 3).[9] To our delight, these enantiopure γ-chloropropylamines all worked well for this formal [4 + 2] cycloaddition, providing corresponding 5,6-disubstituted indolizidines **11**, 2,5,6-trisubstituted indolizidines **13**, and 5,6,8-trisubstituted indolizidines **15** and **17** in good to excellent yields (Scheme 4). Obviously, these products should be useful for elaboration of more complicated indolizidines because some of their substituents are ready for further transformations. Noteworthy is that slightly lower yields were observed for **14** in comparison with those of **16**, which implied that the stereochemistry of **16** might be more

SCHEME 4[a]



[a] Reaction conditions: a. ethyl 2-octynoate **4a** or ethyl 6-benzyloxy-2-hexynoate **4b** (1 mmol), substituted γ-chloropropylamine hydrochloride salt (1.4 mmol), Na_2CO_3 (2.5 mmol), NaI (0.1 mmol), *i*-PrOH (2 mL), at reflux temperature for 24 h.

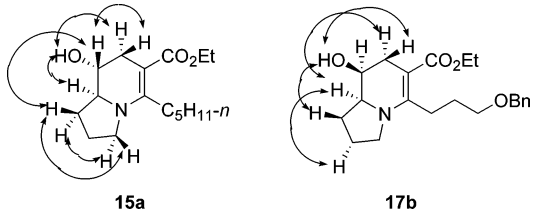


FIGURE 2. NOE correlations of indolizidines **15a** and **17b**.

favorable for a Michael addition or alkylation step. The stereochemistry of indolizidines **15a** and **17b** was established by their NOESY studies as indicated in Figure 2. Through these studies, the configurations at newly generated chiral centers of **19** and **20** were assigned as *R* and *S*, respectively.

Further scope exploration of this process revealed that conjugated alkynones were another class of suitable substrates (Scheme 5). At this time it was found that at 70 °C this process gave best results, which implied that the conjugated alkynones have better reactivity than the corresponding alkynoates in this cascade process. Both aliphatic and aromatic ketones were compatible for these reaction conditions, providing substituted 3-acylpiperidines **21**, 3-acylquinolizidines **22**, and 6-acylindolizidines **23** and **24**. In most cases, the yields were excellent, which implied that this process proceeded smoothly. Since the chain length of the alkynones is tunable at both terminals, this success would permit assembling various alkyl-substituted *N*-heterocycles without requirement of chain elongation in later stages as described in many alkaloid synthesis.[1c–e]

As depicted in Scheme 6, the efficiency of the present methodology was tested by a total synthesis of indolizidine (−)-209I **32**, an alkaloid isolated from poison frog skins.[8] According to Davies' procedure,[11] β-amino ester **25** was prepared from methyl 2-hexenoate in 85% yield. LAH reduction of **25** followed by treatment with thionyl

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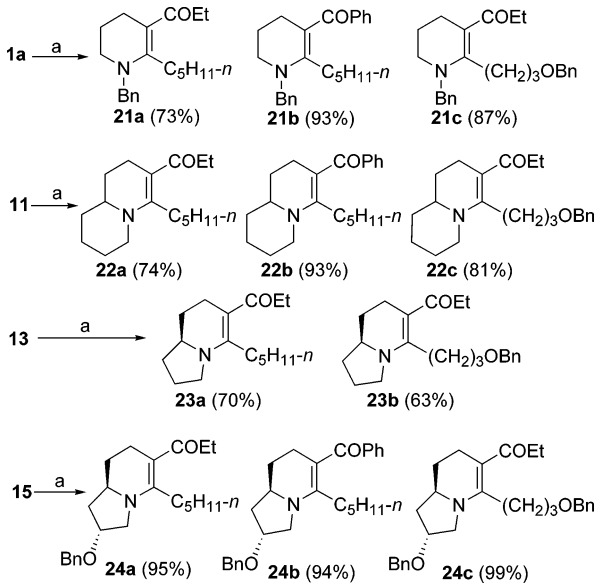
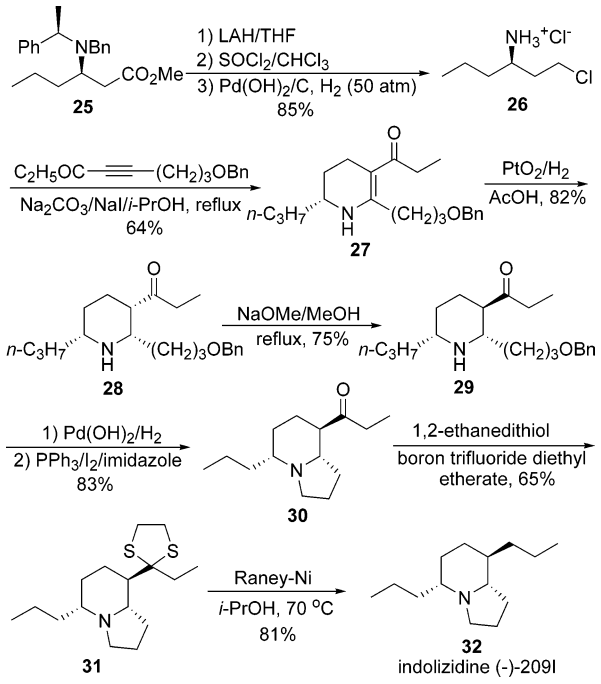
SCHEME 5[a]



[a] Reaction conditions: a. substituted γ-chloropropylamine hydrochloride salt (1.4 mmol), 4-decyn-3-one, 1-phenyl-2-octyn-1-one, or 8-benzoxy-4-decyn-3-one (1 mmol), Na_2CO_3 (2.5 mmol), NaI (0.1 mmol), *i*-PrOH (2 mL), 70 °C, 24 h.

SCHEME 6



chloride and hydrogenolysis provided γ-chloropropylamine **26**. Heating a mixture of **26**, 8-benzyloxy-4-octyn-3-one, sodium carbonate, and a catalytic amount of sodium iodide in *i*-PrOH produced piperidine **27** in 64% yield. Next, hydrogenation of **27** over PtO_2 in acetic acid delivered **28**, which was treated with sodium methoxide in methanol at reflux to give its 3-epimer **29**. After removal of the benzyl-protecting group in **29**, cyclization was carried out under the action of Ph_3P/I_2/imidazole to afford indolizidine **30**. Finally, reduction of ketone moiety in **30** through its 1,3-dithiolane **31** furnished the target molecule **32**. Its analytical data were identical to those reported.[10]

In conclusion, we have demonstrated here a formal [4 + 2] cycloaddition approach to piperidine rings, which is based on a cascade reaction process started from substituted γ-chloropropylamines and two classes of electron-deficient alkynes. This new approach can construct piperidines, indolizidines, and quinolizidines with varying substituents at variable positions. Noteworthy, their benzyloxyl, hydroxyl, ester, and ketone groups are ready for further transformations, which would allow us to assess more complex piperidine-embodied molecules. Further studies toward this goal are in progress.

Experimental Section

General Procedure for Reaction of γ-Chloropropylamines with Conjugated Alkynoates and Alkynones. A mixture of γ-chloropropylamine hydrochloride salt (1.4 mmol), alkynoate or alkynone (1.0 mmol), Na_2CO_3 (2.5 mmol), and NaI (0.1 mmol) in 2 mL of *i*-PrOH was heated at reflux (for alkynoates) or 70 °C (for alkynone) for 24 h. Cooled solution was filtered, and the filtrate was concentrated. The residual oil was purified via chromatography eluting with 1:20 to 1:2 ethyl acetate/petroleum ether to afford pure cyclization product.

1-Benzyl-2-pentyl-1,4,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester 7a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.17 (m, 5H), 4.44 (s, 2H), 4.13 (q, J = 7.5 Hz, 2H), 3.12 (t, J = 5.4 Hz, 2H), 2.86−2.84 (m, 2H), 2.44 (t, J = 6.3 Hz, 2H), 1.80−1.74 (m, 3H), 1.62−1.49 (m, 2H), 1.35−1.25 (m, 6H), 0.89−0.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 159.0, 138.5, 128.8, 127.3, 126.4, 93.2, 58.8, 54.0, 49.4, 32.2, 29.6, 29.2, 24.1, 22.7, 21.8, 14.8, 14.2; IR (film) 1710, 1675, 1558 cm^{-1}; ESI-MS *m/z* 316 (M + H)$^+$; HRMS calcd for $C_{20}H_{30}NO_2$ (M + H)$^+$ 316.2271, found 316.2273.

1-Benzyl-2-(3-benzyloxypropyl)-1,4,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester 7b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.13 (m, 10H), 4.51 (s, 2H), 4.45 (s, 2H), 4.11 (q, J = 7.2 Hz, 2H), 3.54 (t, J = 6.3 Hz, 2H), 3.14 (t, J = 5.4 Hz, 2H), 2.97 (t, J = 7.5 Hz, 2H), 2.47−2.42 (m, 2H), 1.93−1.88 (m, 2H), 2.00−1.74 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.7, 158.4, 138.6, 138.4, 128.6, 128.2, 127.4, 127.3, 127.0, 126.3, 93.4, 72.8, 70.2, 58.6, 53.9, 49.4, 29.3, 26.3, 23.9, 21.7, 14.6; IR (film) 3031, 2235, 1710, 1673, 1558 cm^{-1}; ESI-MS *m/z* 394 (M + H)$^+$; HRMS calcd for $C_{25}H_{32}NO_3$ (M + H)$^+$ 394.2377, found 394.2373.

1-Benzyl-6-methyl-2-pentyl-1,4,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester 7c: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.24 (m, 3H), 7.19−7.16 (m, 2H), 4.48 (d, J = 17.1 Hz, 1H), 4.47 (d, J = 17.1 Hz, 1H), 4.20−4.05 (m, 2H), 3.32−3.27 (m, 1H), 3.03−2.97 (m, 1H), 2.93 (m, 1H), 2.8−2.75 (m, 1H), 2.36−2.24 (m, 1H), 1.80−1.51 (m, 4H), 1.37−1.25 (m, 7H), 1.06 (q, J = 6.9 Hz, 3H), 0.86 (t, 3H); IR (film) 1675, 1555 cm^{-1}; ESI-MS *m/z* 330 (M + H)$^+$; HRMS calcd for $C_{21}H_{32}NO_2$ (M + H)$^+$ 330.2428, found 330.2430.

1-Benzyl-2-(3-benzyloxypropyl)-6-methyl-1,4,5,6-tetrahydropyridine-3-carboxylic Acid Ethyl Ester 7d: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.11 (m, 10H), 4.55 (d, J = 11.1 Hz, 1H), 4.54 (d, J = 11.1 Hz, 1H), 4.46−4.44 (m, 2H), 4.25−4.06 (m, 2H), 3.59−3.47 (m, 2H), 3.35−3.25 (m, 1H), 3.05−2.94 (m, 3H), 2.63−2.47 (m, 1H), 2.03−1.90 (m, 1H), 1.80−1.51 (m, 3H), 1.29−1.22 (m, 3H), 1.06 (t, J = 6.9 Hz, 3H); IR (film) 3030, 1669, 1550 cm^{-1}; ESI-MS *m/z* 408 (M + H)$^+$; HRMS calcd for $C_{26}H_{34}NO_3$ (M + H)$^+$ 408.2533, found 408.2523.

4-Pentyl-1,6,7,8,9,9a-hexahydro-2*H*-quinolizine-3-carboxylic Acid Ethyl Ester 9a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.02 (q, J = 6.9 Hz, 2H), 3.80 (d, J = 13.5 Hz, 1H), 2.99−2.94 (m, 2H), 2.70−2.61 (m, 2H), 2.33−2.26 (m, 2H), 1.81−1.72 (m,

2H), 1.61−1.21 (m, 12H), 1.20 (t, J = 6.9 Hz, 3H), 0.90 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 158.2, 94.7, 58.7, 57.2, 48.1, 32.7, 32.1, 29.0, 28.8, 28.6, 26.9, 24.8, 22.6, 21.4, 14.7, 14.1; IR (film) 1679, 1560 cm^{-1}; ESI-MS *m/z* 280 (M + H)$^+$; HRMS calcd for $C_{17}H_{30}NO_2$ (M + H)$^+$ 280.2271, found 280.2276.

4-(3-Benzyloxy-propyl)-1,6,7,8,9,9a-hexahydro-2*H*-quinolizine-3-carboxylic Acid Ethyl Ester 9b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.24 (m, 5H), 4.52 (s, 2H), 4.08 (q, J = 6.6 Hz, 2H), 3.99 (d, J = 13.2 Hz, 1H), 3.58 (t, J = 6.0 Hz, 2H), 3.15−3.01 (m, 2H), 2.91−2.80 (m, 1H), 2.71 (t, J = 7.5 Hz, 1H), 2.43−2.32 (m, 2H), 1.86−1.74 (m, 4H), 1.65−1.1.54 (m, 4H), 1.50−1.33 (m, 2H), 1.24 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 157.8, 138.8, 128.4, 127.6, 127.5, 94.8, 73.0, 70.5, 58.8, 57.2, 48.1, 32.7, 28.9, 28.7, 26.9, 25.9, 24.8, 21.3, 14.7; IR (film) 1674, 1558 cm^{-1}; ESI-MS *m/z* 358 (M + H)$^+$; HRMS calcd for $C_{22}H_{32}NO_3$ (M + H)$^+$ 358.2377, found 358.2386.

(*S*)-5-Pentyl-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylic Acid Ethyl Ester 11a: $[\alpha]^{27}_D$ −326.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.10 (q, J = 6.9 Hz, 2H), 3.56 (t, J = 8.4 Hz, 1H), 3.44−3.35 (m, 1H), 3.30−3.22 (m, 1H), 3.01−2.91 (m, 1H), 2.66−2.54 (m, 2H), 2.25−2.03 (m, 3H), 1.96−1.92 (m, 1H), 1.82−1.78 (m, 1H), 1.63−1.58 (m, 1H), 1.52−1.18 (m, 10H), 1.95−1.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.4, 158.0, 90.8, 58.0, 57.9, 46.8, 32.3, 32.0, 30.8, 28.0, 27.7, 24.0, 23.4, 22.2, 14.4, 13.7; IR (film) 1674, 1556 cm^{-1}; ESI-MS *m/z* 266 (M + H)$^+$; HRMS calcd for $C_{16}H_{28}NO_2$ (M + H)$^+$ 266.2115, found 266.2113.

(*S*)-5-(3-Benzyloxypropyl)-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylic Acid Ethyl Ester 11b: $[\alpha]^{23}_D$ −120.7 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.25 (m, 5H), 4.52 (s, 2H), 4.11 (q, J = 6.9 Hz, 2H), 3.63−3.56 (m, 3H), 3.40−3.31 (m, 1H), 3.29−3.18 (m, 1H), 3.15−3.03 (m, 1H), 2.80−2.57 (m, 2H), 2.24−1.75 (m, 8H), 1.47−1.40 (m, 1H), 1.29−1.20 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.6, 157.8, 138.6, 128.1, 127.4, 127.3, 91.2, 72.7, 70.3, 58.2, 58.1, 47.4, 32.5, 28.6, 27.8, 27.7, 24.2, 23.7, 14.6; IR (film) 1670, 1554 cm^{-1}; ESI-MS *m/z* 344 (M + H)$^+$; HRMS calcd for $C_{21}H_{30}NO_3$ (M + H)$^+$ 344.2220, found 344.2218.

(2*R*,9*S*)-2-Benzyloxy-5-pentyl-1,2,3,7,8,8a-hexahydroindolizine-6- carboxylic Acid Ethyl Ester 13a: $[\alpha]^{24}_D$ −111.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.29 (m, 5H), 4.61−4.49 (m, 2H), 4.20−4.07 (m, 3H), 3.67−3.55 (m, 3H), 2.99−2.90 (m, 1H), 2.77−2.55 (m, 2H), 2.40−2.17 (m, 2H), 2.15−2.05 (m, 1H), 1.71−1.16 (m, 11H), 0.97−0.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8, 157.9, 138.0, 128.5, 128.4, 127.7, 127.5, 91.6, 76.4, 70.7, 58.5, 56.1, 53.1, 38.2, 32.4, 31.1, 28.4, 27.8, 24.2, 22.6, 14.7, 14.2; IR (film) 1672, 1554 cm^{-1}; ESI-MS *m/z* 372 (M + H)$^+$; HRMS calcd for $C_{23}H_{34}NO_3$ (M + H)$^+$ 372.2533, found 372.2538.

(2*R*,9*S*)-2-Benzyloxy-5-(3-benzyloxypropyl)-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylic Acid Ethyl Ester 13b: $[\alpha]^{23}_D$ −87.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33−7.25 (m, 10H), 4.53−4.50 (m, 4H), 4.12−4.05 (m, 3H), 3.73 (q, J_1 = 11.7 Hz, J_2 = 3.6 Hz, 1H), 3.60−3.55 (m, 4H), 3.10−2.95 (m, 1H), 2.83−2.70 (m, 1H), 2.70−2.60 (m, 1H), 2.33−2.21 (m, 2H), 2.10−1.81 (m, 4H), 1.58−1.42 (m, 1H), 1.24 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.7, 157.6, 138.5, 138.1, 128.5, 128.3, 127.7, 127.6, 127.5, 127.4, 91.8, 76.3, 72.9, 70.6, 70.4, 58.5, 56.1, 53.1, 38.3, 28.8, 27.9, 27.8, 24.2, 14.8; IR (film) 1745, 1717 cm^{-1}; ESI-MS *m/z* 450 (M + H)$^+$; HRMS calcd for $C_{28}H_{36}NO_4$ (M + H)$^+$ 450.2639, found 450.2640.

(8*R*,9*S*)-8-Hydroxy-5-pentyl-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylic Acid Ethyl Ester 15a: $[\alpha]^{29}_D$ −241.4 (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.10 (q, J = 7.1 Hz, 2H), 4.00 (s, 1H), 3.59 (t, J = 6.6 Hz, 1H), 3.39−3.36 (m, 2H), 3.05−2.96 (m, 1H), 2.64 (m, 1H), 2.63 (q, J_{AB} = 16.8 Hz, 2H), 2.01−1.92 (m, 5H), 1.51−1.23 (m, 6H), 1.25 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 158.5, 86.6, 62.5, 61.4, 58.6, 47.9, 33.1, 32.3, 31.0, 28.4, 27.0, 23.7, 22.6, 14.6, 14.1; IR (film) 3410, 1674, 1454 cm^{-1}; ESI-MS *m/z* 282 (M + H)$^+$; HRMS calcd for $C_{16}H_{28}NO_3$ (M + H)$^+$ 282.2064, found 282.2063.

(8*R*,9*S*)-5-(3-Benzyloxypropyl)-8-hydroxy-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylic Acid Ethyl Ester 15b: $[\alpha]^{29}_D$ −207.9 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.27 (m, 5H), 4.51 (s, 2H), 4.08 (t, J = 6.9 Hz, 2H), 4.00 (s, 1H), 3.63−3.54 (m, 3H), 3.41−3.35 (m, 2H), 2.63 (AB q, d, J = 15.7 Hz, 2H), 2.05−1.59 (m, 9H), 1.26 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 158.1, 138.5, 128.3, 127.7, 127.5, 87.0, 73.0, 70.3, 62.6, 61.5, 58.6, 48.0, 33.1, 28.8, 27.9, 27.0, 23.7, 14.7; IR (film) 3413, 1721, 1551 cm^{-1}; ESI-MS *m/z* 360 (M + H)$^+$; HRMS calcd for $C_{21}H_{30}NO_4$ (M + H)$^+$ 360.2169, found 360.2160.

(8*S*,9*S*)-8-Hydroxy-5-pentyl-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylic Acid Ethyl Ester 17a: $[\alpha]^{29}_D$ −278.6 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.10 (q, J = 6.3 Hz, 2H), 3.58 (t, J = 8.4 Hz, 1H), 3.50−3.45 (m, 1H), 3.39−3.35 (m, 1H), 3.13−3.09 (m, 1H), 2.95−2.88 (m, 2H), 2.60−2.50 (m, 1H), 2.23−2.15 (m, 1H), 2.05−1.93 (m, 2H), 1.93−1.75 (m, 2H), 1.67−1.56 (m, 2H), 1.50−1.35 (m, 5H), 1.30−1.23 (m, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 160.2, 91.7, 72.2, 65.1, 60.6, 49.7, 36.1, 34.2, 32.3, 32.4, 30.2, 25.8, 24.5, 16.6, 16.0; IR (film) 3384, 1718, 1558, 1448 cm^{-1}; ESI-MS *m/z* 282 (M + H)$^+$; HRMS calcd for $C_{16}H_{28}NO_3$ (M + H)$^+$ 282.2064, found 282.2067.

(8*S*,9*S*)-5-(3-Benzyloxypropyl)-8-hydroxy-1,2,3,7,8,8a-hexahydroindolizine-6-carboxylic Acid Ethyl Ester 17b: $[\alpha]^{29}_D$ −235.6 (*c* 1.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.27 (m, 5H), 4.52 (s, 2H), 4.09 (q, J = 7.1 Hz, 2H), 3.73−3.17 (m, 5H), 3.11−3.06 (m, 2H), 2.90 (dd, J = 15.4, 5.6 Hz, 1H), 2.80−2.73 (m, 1H), 2.33−2.26 (m, 2H), 2.18 (dd, J = 15.4, 10.3 Hz, 1H), 1.97−1.55 (m, 5H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 159.7, 140.5, 130.2, 129.5, 129.4, 91.9, 74.8, 72.2, 72.1, 65.1, 60.6, 49.8, 36.1, 32.4, 30.6, 29.7, 25.8, 16.6; IR (film) 3405, 1720, 1554, 1454 cm^{-1}; ESI-MS *m/z* 360 (M + H)$^+$; HRMS calcd for $C_{21}H_{30}NO_4$ (M + H)$^+$ 360.2169, found 360.2161.

1-(1-Benzyl-2-pentyl-1,4,5,6-tetrahydropyridin-3-yl)-propan-1-one 21a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.27 (m, 3H), 7.19−7.16 (m, 2H), 4.49 (d, 2H), 3.16−3.12 (m, 2H), 2.91−2.86 (m, 2H), 2.51−2.42 (m, 4H), 1.86−1.80 (m, 2H), 1.64−1.59 (m, 2H), 1.20−1.23 (m, 4H), 1.19−1.06 (m, 3H), 0.93−0.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, for two conformers) δ 198.3, 198.1, 159.9, 158.9, 137.9, 128.7, 127.2, 126.3, 102.7, 102.6, 53.7, 53.5, 49.2, 49.1, 40.7, 33.6, 32.1, 31.9, 29.7, 28.7, 25.1, 25.0, 24.8, 22.9, 22.6, 22.5, 21.9, 14.0, 13.2, 9.2; IR (film) 2956, 1716, 1632, 1525 cm^{-1}; ESI-MS *m/z* 300 (M + H)$^+$; Anal. Calcd for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.21; H, 9.79; N, 4.53.

(1-Benzyl-2-pentyl-1,4,5,6-tetrahydropyridin-3-yl)phenylmethanone 21b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35−7.14 (m, 10H), 4.02 (s, 2H), 3.18 (t, J = 4.8 Hz, 2H), 2.54 (t, J = 6.3 Hz, 2H), 1.77 (t, J = 5.4 Hz, 2H), 1.67 (t, J = 7.8 Hz, 2H), 1.34−1.26 (m, 2H), 1.15−1.07 (m, 2H), 0.97−0.90 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, for two conformers) δ 201.6, 156.2, 138.1, 137.9, 129.4, 128.9, 128.5, 128.4, 127.2, 127.1, 113.0, 55.5, 48.3, 41.1, 31.5, 25.6, 24.6, 22.3, 21.5, 13.9; IR (film) 3030, 1604, 1548, 1494 cm^{-1}; ESI-MS *m/z* 348 (M + H)$^+$; Anal. Calcd for $C_{24}H_{29}NO$: C, 82.95; H, 8.41; N, 4.03. Found: C, 82.55; H, 8.48; N, 3.95.

1-[1-Benzyl-2-(3-benzyloxypropyl)-1,4,5,6-tetrahydropyridin-3-yl]propan-1-one 21c: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.12 (m, 10H), 4.55−4.45 (m, 4H), 3.60−3.53 (m, 2H), 3.18−3.13 (m, 2H), 3.00−2.88 (m, 2H), 2.60−2.44 (m, 4H), 1.98−1.81 (m, 4H), 1.19−1.05 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, for two conformers) δ 198.3, 197.1, 160.2, 158.6, 138.8, 138.7, 138.0, 137.9, 128.7, 128.3, 128.2, 127.6, 127.5, 127.3, 127.2, 126.4, 126.3, 102.7, 72.8, 72.6, 70.4, 70.3, 53.8, 53.6, 49.4, 49.2, 37.1, 33.6, 29.0, 26.8, 25.0, 22.0, 13.3, 9.1; IR (film) 3030, 1716, 1627, 1520 cm^{-1}; ESI-MS *m/z* 378 (M + H)$^+$; Anal. Calcd for $C_{25}H_{31}NO_2$: C, 79.54; H, 8.28; N, 3.71. Found: C, 79.24; H, 8.30; N, 3.79.

1-(4-Pentyl-1,6,7,8,9,9a-hexahydro-2*H*-quinolizin-3-yl)-propan-1-one 22a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.95 (t, J = 12.0 Hz, 1H), 3.12−3.06 (m, 1H), 3.06−2.96 (m, 1H), 2.76 (t, J = 12.6 Hz, 2H), 2.47−2.34 (m, 4H), 1.93−1.84 (m, 2H), 1.71−1.56 (m, 4H), 1.52−1.26 (m, 8H), 1.12−1.04 (m, 3H), 0.92−0.86 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, for two conformers) δ 198.7, 198.5, 159.1, 158.0, 104.0, 103.9, 57.2, 47.8, 47.6, 40.9, 33.8, 32.9, 32.0, 31.9, 29.0, 28.5, 26.9, 26.8, 25.0, 24.7, 22.6, 22.3, 14.1, 14.0, 9.4; IR (film) 1635, 1525, 1443 cm^{-1}; ESI-MS *m/z* 264 (M + H)$^+$; Anal. Calcd for $C_{17}H_{29}NO$: C, 77.51; H, 11.10; N, 5.32. Found: C, 77.61; H, 11.19; N, 5.13.

(4-Pentyl-1,6,7,8,9,9a-hexahydro-2*H*-quinolizin-3-yl)-phenylmethanone 22b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.35 (m, 3H), 7.27−7.15 (m, 2H), 3.16−3.10 (m, 2H), 2.62−2.54 (m, 2H), 2.49−2.25 (m, 2H), 2.04−1.98 (m, 1H), 1.86−1.82 (m, 1H), 1.77−1.68 (m, 2H), 1.65−1.58 (m, 2H), 1.52−1.40 (m, 3H), 1.34−1.23 (m, 3H), 1.16−1.04 (m, 1H), 0.97−0.83 (m, 2H), 0.81−0.77 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, for two conformers) δ 200.5, 155.5, 138.3, 128.5, 128.4, 127.9, 110.5, 57.7, 49.8, 40.8, 33.1, 31.6, 29.6, 26.5, 25.6, 24.5, 22.3, 21.9, 13.9; IR (film) 1605, 1547 cm^{-1}; ESI-MS *m/z* 312 (M + H)$^+$; Anal. Calcd for $C_{21}H_{29}NO$: C, 80.98; H, 9.38; N, 4.50. Found: C, 80.69; H, 9.54; N, 4.28.

1-[4-(3-Benzyloxypropyl)-1,6,7,8,9,9a-hexahydro-2*H*-quinolizin-3-yl]propan-1-one 22c: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.24 (m, 5H), 4.52 (AB q, d, J = 12.0 Hz, 2H), 4.11−3.93 (m, 1H), 3.63−3.50 (m, 2H), 3.12−2.95 (m, 2H), 2.95−2.72 (m, 2H), 2.54−2.34 (m, 4H), 1.95−1.77 (m, 4H), 1.68−1.50 (m, 3H), 1.49−1.38 (m, 3H), 1.12−1.03 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, for two conformers) δ 198.5, 197.2, 159.2, 157.5, 138.8, 128.2, 127.5, 127.4, 127.3, 103.9, 103.8, 72.8, 72.6, 70.5, 70.2, 57.1, 47.7, 47.5, 37.1, 33.7, 32.8, 28.8, 28.7, 26.8, 26.0, 25.1, 24.6, 22.2, 22.1, 12.9, 9.2; IR (film) 3029, 1629, 1523 cm^{-1}; ESI-MS *m/z* 342 (M + H)$^+$; Anal. Calcd for $C_{22}H_{31}NO_2$: C, 77.38; H, 9.15; N, 4.10. Found: C, 77.36; H, 9.34; N, 4.02.

(*S*)-1-(5-Pentyl-1,2,3,7,8,8a-hexahydroindolizin-6-yl)-propan-1-one 23a: $[\alpha]^{19}_D$ −232.9 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.66−3.57 (m, 1H), 3.45−3.36 (m, 1H), 3.26−3.18 (m, 1H), 3.11−2.94 (m, 1H), 2.75−2.53 (m, 2H), 2.46−2.30 (m, 3H), 2.19−2.09 (m, 2H), 1.99−1.92 (m, 1H), 1.86−1.79 (m, 1H), 1.63−1.52 (m, 2H), 1.51−1.24 (m, 6H), 1.90−1.03 (m, 3H), 0.95−0.85 (m, 3H); IR (film) 1625, 1516 cm^{-1}; ESI *m/z* 250 (M + H)$^+$.

(*S*)-1-[5-(3-Benzyloxypropyl)-1,2,3,7,8,8a-hexahydroindolizin-6-yl]propan-1-one 23b: $[\alpha]^{24}_D$ −269.7 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.23 (m, 5H), 4.52 (AB q, d, J = 12.0 Hz, 2H), 3.69−3.52 (m, 3H), 3.46−3.37 (m, 1H), 3.28−3.20 (m, 1H), 3.10−3.03 (m, 1H), 2.88−2.63 (m, 1H), 2.70−2.23 (m, 4H), 2.16−2.11 (m, 2H), 2.02−1.74 (m, 4H), 1.49−1.39 (m, 1H), 1.37−1.23 (m, 1H), 1.20−1.05 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, for two conformers) δ 197.2, 195.9, 160.3, 158.6, 138.9, 138.8, 128.2, 127.6, 127.5, 127.3, 101.3, 72.9, 72.6, 70.6, 70.4, 58.3, 47.2, 46.9, 37.0, 33.5, 32.5, 29.7, 28.6, 28.4, 28.2, 25.5, 25.0, 24.8, 23.6, 22.2, 12.4, 9.1; IR (film) 1621, 1513 cm^{-1}; ESI *m/z* 328 (M + H)$^+$.

(2*R*,9*S*)-1-(2-Benzyloxy-5-pentyl-1,2,3,7,8,8a-hexahydroindolizin-6-yl) propan-1-one 24a: $[\alpha]^{24}_D$ −164.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.26 (m, 5H), 4.54 (AB q, d, J = 12.0 Hz, 2H), 4.16 (t, J = 4.2 Hz, 1H), 3.67−3.57 (m, 3H), 2.97−2.85 (m, 1H), 2.75−2.51 (m, 1H), 2.47−2.30 (m, 5H), 2.16−2.12 (m, 1H), 1.64−1.25 (m, 8H), 1.06 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H); IR (film) 1623, 1515 cm^{-1}; ESI-MS *m/z* 356 (M + H)$^+$; Anal. Calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.40; H, 9.55; N, 3.69.

(2*R*,9*S*)-(2-Benzyloxy-5-pentyl-1,2,3,7,8,8a-hexahydroindolizin-6-yl)-phenylmethanone 24b: $[\alpha]^{24}_D$ −124.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47−7.26 (m, 10H), 4.56 (AB q, d, J = 12.0 Hz, 2H), 4.20 (m, 1H), 3.70−3.63 (m, 3H), 2.73−2.46 (m, 3H), 2.42−2.33 (m, 2H), 2.10−2.04 (m, 1H), 1.60−1.43 (m, 4H), 1.29−1.21 (m, 4H), 0.90−0.85 (m, 3H); IR (film) 1718, 1599, 1498 cm^{-1}; ESI-MS *m/z* 404 (M + H)$^+$; Anal. Calcd for $C_{27}H_{33}NO_2$: C, 80.36; H, 8.24; N, 3.47. Found: C, 80.03; H, 8.41; N, 3.28.

(2*R*,9*S*)-1-[2-Benzyloxy-5-(3-benzyloxypropyl)-1,2,3,7,8,-8a-hexahydroindolizin-6-yl]propan-1-one 24c: $[\alpha]^{24}_D$ −136.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.24 (m, 10H), 4.54−4.49 (m, 4H), 4.16−4.09 (m, 1H), 3.79−3.68 (m, 1H), 3.64−3.51 (m, 4H), 3.02−2.98 (m, 1H), 2.91−2.82 (m, 1H), 2.58−2.30 (m, 5H), 2.16−2.10 (m, 1H), 2.04−1.78 (m, 2H), 1.54−1.49 (m, 1H), 1.29−1.19 (m, 1H), 1.17−1.03 (m, 3H); IR (film) 1719, 1623 cm^{-1}; ESI-MS *m/z* 434 (M + H)$^+$; Anal. Calcd for $C_{28}H_{35}NO_3$: C, 77.56; H, 8.14; N, 3.23. Found: C, 77.37; H, 8.36; N, 3.18.

(*R*)-1-Chloro-3-hexylamine Hydrochloride Salt 26. To a stirred suspension of LAH (1.63 g, 42.8 mmol) in dry THF (80 mL) was added dropwise β-amino ester **25** (15.12 g, 42.8 mmol) in dry THF (40 mL) at 0 °C. After the reaction mixture was stirred at 20 °C for 1 h, water (1.5 mL), 15% NaOH (1.5 mL), and more water (1.5 mL) were added successively. Stirring was continued until a white precipitate formed, then it was filtered through Celite, and the filtrate was dried over $MgSO_4$, concentrated, and purified via chromatography to give 13.24 g (100%) of β-amino alcohol as a viscous oil.

To a stirred solution of the above oil (5.00 g, 16.18 mmol) in $CHCl_3$ (50 mL) was slowly added a solution of $SOCl_2$ (1.8 mL, 24.3 mmol) in $CHCl_3$ (10 mL) at 0 °C. The reaction mixture was refluxed for 1 h and then evaporated. The residue was dissolved directly in methanol (60 mL) and hydrogenated over 20% $Pd(OH)_2$ (1.00 g) under 50 atm hydrogen atmosphere at 30 °C for 48 h. The reaction mixture was filtered off, and the filtrate was concentrated in a vacuum to afford 2.37 g (85%) of crude **26** as a light yellow solid, which was used directly due to its instability. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.47−8.42 (m, 3H), 3.86−3.85 (m, 1H), 3.73−3.70 m, 1H), 3.51−3.50 (m, 1H), 2.27−2.25 (m, 1H), 2.15−2.13 (m, 1H), 1.76−1.51 (m, 4H), 0.99 (t, J = 6.6 Hz, 3H).

(*R*)-1-[2-(3-Benzyloxypropyl)-6-propyl-1,4,5,6-tetrahydropyridin-3-yl]-propan-1-one 27. A mixture of **26** (347 mg, 2.01 mmol), **7e** (331 mg, 1.44 mmol), Na_2CO_3 (381 mg, 3.60 mmol), and NaI (22 mg, 0.14 mmol) in *i*-PrOH (5 mL) was refluxed for 30 h. The precipitate was filtered through Celite. The residue was concentrated and chromatographed to afford 312 mg (66%) of **27** as yellow oil. $[\alpha]^{28}_D$ +81.1 (*c* 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.28 (m, 5H), 4.53−4.50 (m, 3H), 3.13 (s, 1H), 2.78−2.72 (m, 2H), 2.45−2.25 (m, 4H), 1.94−1.86 (m, 4H), 1.45−1.26 (m, 5H), 1.10−1.02 (m, 3H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.9, 158.7, 140.4, 130.3, 129.6, 129.5, 102.6, 74.8, 71.7, 52.8, 39.9, 35.0, 33.8, 30.4, 29.4, 25.0, 20.7, 16.0, 10.7; IR (film) 3301, 1712, 1604, 1455 cm^{-1}; ESI-MS *m/z* 330 (M + H)$^+$; HRMS calcd for $C_{21}H_{32}NO_2$ (M + H)$^+$ 330.2428, found 330.2411.

(2*S*,3*S*,6*R*)-1-[2-(3-Benzyloxypropyl)-6-propylpiperidin-3-yl]propan-1-one 28. To a solution of **28** (260 mg, 0.79 mmol) in acetic acid (20 mL) was added PtO_2 (40 mg). The mixture was hydrogenated under 1 atm hydrogen atmosphere at room temperature for 1 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. To this residue was added aqueous solution of $NaHCO_3$ and extracted with ethyl acetate for two times. The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography to give 214 mg (82%) of **28**. $[\alpha]^{28}_D$ −26.4 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34−7.27 (m, 5H), 4.48 (s, 2H), 3.49−3.41 (m, 2H), 2.68−2.36 (m, 5H), 1.98−1.93 (m, 1H), 1.79−1.64 (m, 4H), 1.50−1.30 (m, 7H), 1.15−1.04 (m, 1H), 1.00 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 217.7, 140.4, 130.2, 129.5, 129.4, 74.8, 72.3, 60.4, 58.2, 49.0, 41.4, 38.8, 33.1, 29.5, 29.1, 21.0, 16.2, 9.5; IR (film) 3032, 1701,1455 cm^{-1}; ESI-MS *m/z* 332 (M + H)$^+$; HRMS calcd for $C_{21}H_{34}NO_2$ (M + H)$^+$ 332.2584, found 332.2568.

(2*S*,3*R*,6*R*)-1-[2-(3-Benzyloxypropyl)-6-propylpiperidin-3-yl]propan-1-one 29. A mixture of sodium (18 mg, 0.785

mmol) and anhydrous MeOH (10 mL) was stirred for 10 min. To this solution was added **28** (260 mg, 0.785 mmol). The reaction mixture was refluxed for 12 h and then cooled to room temperature. The solvent was removed under reduced pressure, and the residue was purified by column chromatography to give 196 mg (75%) of **29** as colorless oil. $[\alpha]^{20}_D$ −40.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33−7.26 (m, 5H), 4.47 (s, 2H), 3.44 (t, J = 6.3 Hz, 2H), 2.82 (dt, J = 9.9, 3.0 Hz, 1H), 2.56−2.41 (m, 3H), 2.38−2.27 (m, 1H), 1.88−1.83 (m, 1H), 1.73−1.55 (m, 4H), 1.49−1.30 (m, 8H), 1.02 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.9, 138.9, 128.7, 128.0, 127.8, 73.2, 70.7, 57.8, 56.3, 56.2, 39.7, 36.9, 32.3, 31.8, 29.4, 26.4, 19.4, 14.6, 7.9; IR (film) 3032, 1708, 1455 cm^{-1}; ESI-MS *m/z* 332 $(M + H)^+$; HRMS calcd for $C_{21}H_{34}NO_2$ $(M + H)^+$ 332.2584, found 332.2581.

(5*R*,8*R*,9*S*)-1-(5-Propyloctahydroindolizin-8-yl)propan-1-one 30. A mixture of **29** (196 mg, 0.592 mmol) in anhydrous MeOH (10 mL) was hydrogenated over 20% palladium hydroxide on charcoal (30 mg) under 1 atm hydrogen atmosphere at 25 °C for 20 h. After the mixture was filtered, the filtrate was concentrated in a vacuum to provide the crude alcohol.

To a stirred solution of the above alcohol in dry CH_2Cl_2 (20 mL) was added triphenylphosphine (465 mg, 1.78 mmol), imidazole (121 mg, 1.78 mmol), and iodine (300 mg, 1.18 mmol) at 0 °C. After the reaction mixture was warmed to room temperature in about 2 h, saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over Na_2SO_4. The solution was evaporated in vacuo, and the residue was purified via chromatography to afford 107 mg (83%) of **30** as colorless oil. $[\alpha]^{20}_D$ −84.4 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.24 (dt, J = 2.7, 9.0 Hz, 1H), 2.55−2.38 (m, 3H), 2.12−1.82 (5H), 1.79−1.62 (m, 3H), 1.46−1.13 (m, 7H), 1.04 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 213.5, 65.4, 62.8, 54.7, 51.0, 36.8, 36.0, 30.4, 29.0, 28.4, 20.4, 18.9, 14.5, 7.6; IR (film) 1712 cm^{-1}; ESI-MS *m/z* 224 $(M + H)^+$; HRMS calcd for $C_{14}H_{26}NO$ $(M + H)^+$ 224.2009, found 224.2020.

(5*R*,8*R*,9*S*)-8-(2-Ethyl-[1,3]dithiolan-2-yl)-5-propyloctahydroindolizine 31. To a solution of **30** (110 mg, 0.493 mmol) in dry CH_2Cl_2 (10 mL) were added ethane-1,2-dithiol (0.8 mL) and $BF_3{\cdot}OEt_2$ (0.36 mL) at 0 °C. After the mixture was stirred for 30 min, it was warmed to room temperature and then stirred for an additional 12 h. The suspension was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure, and the residue was purified by column chromatography to give 96 mg (65%) of **31** as colorless oil. $[\alpha]^{20}_D$ −66.2 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.32−3.15 (m, 5H), 2.32−2.17 (m, 1H), 2.00−1.73 (m, 9H), 1.73−1.54 (m, 2H), 1.49−1.23 (m, 6H), 1.11 (t, J = 6.9 Hz, 3H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 69.9, 65.1, 52.6, 52.2, 41.4, 40.8, 37.9, 36.1, 32.3, 31.2, 31.1, 30.9, 21.9, 20.5, 15.9, 12.0; IR (film) 1709 cm^{-1}; ESI-MS *m/z* 300 $(M + H)^+$; HRMS calcd for $C_{16}H_{30}NS_2$ 300.1814, found 300.1822.

(5*R*,8*R*,9*S*)-5,8-Dipropyloctahydroindolizine 32 (Indolizidine (−)-209I). To a solution of dithioacetal **31** (88 mg, 0.294 mmol) in *i*-PrOH (10 mL) was added Raney nickel (1.5 g). The resulting mixture was stirred at 70 °C for 10 h and then filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography to give 49 mg (81%) of **32** as colorless oil. $[\alpha]^{22}_D$ −92.1 (*c* 1.0, $CHCl_3$); $[\alpha]^{24}_D$ −126.5 (*c* 0.19, CH_3COCH_3) (lit:[10c] $[\alpha]^{29}_D$ −123.4 (*c* 0.71, CH_3COCH_3)); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.27 (dt, J = 8.7, 1.8 Hz, 1H), 2.00−1.87 (m, 2H), 1.87−1.80 (m, 2H), 1.78−1.67 (m, 2H), 1.65−1.59 (m, 2H), 1.50−1.35 (m, 5H), 1.48−1.15 (m, 5H), 1.04 (m, 1H), 0.92−0.86 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.4, 63.5, 51.8, 41.0, 36.8, 35.6, 31.0, 30.4, 29.1, 20.4, 19.6, 19.1, 14.5, 14.4; IR (film) 1643 cm^{-1}; ESI-MS *m/z* 210 $(M + H)^+$; HRMS calcd for $C_{14}H_{28}N$ $(M + H)^+$ 210.2216, found 210.2221.

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Supporting Information Available: Copies of ^1H NMR and ^{13}C NMR spectra for compounds **7**, **9**, **11**, **13**, **15**, **17**, and **21**−**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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