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Chiral synthesis of indolizidines 209D and 167B via asymmetric oxidation of sulfides and sulfoxides

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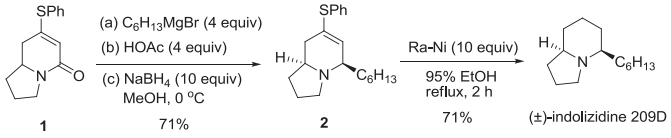
ABSTRACT

Chiral synthesis of indolizidine natural products (−)-209D and (−)-167B, as well as their antipodes, has been achieved through asymmetric oxidation of racemic thio-substituted indolizidines to the chiral sulfoxides and sulfones followed by Raney nickel reduction.

1. Introduction

Many indolizidine alkaloids have been isolated from amphibian skin,[1] some of which show interesting biological activities.[2] Many methods have been developed for the synthesis of these novel compounds.[3] We have previously developed a new aza-Diels–Alder reaction of thio-substituted 3-sulfolenes with *p*-toluenesulfonyl isocyanate (PTSI) to synthesize piperidine derivatives,[4] and have used this method to prepare some indolizidines and quinolizidines.[5] We recently reported that the reaction of thio-substituted indolizidine **1** with hexylmagnesium bromide at room temperature, followed by treatment sequentially with acetic acid and $NaBH_4$/MeOH, gave the vinyl sulfide **2**, which was subsequently converted to (±)-indolizidine 209D by reacting with Ra–Ni in refluxing EtOH (Scheme 1).[6] We have now completed the chiral synthesis of natural products indolizidines (−)-209D and (−)-167B,[7] as well as their antipodes via asymmetric oxidation of racemic sulfides through kinetic resolution.[8]



Scheme 1.

2. Results and discussion

Before using chiral sulfoxides for our studies, we first oxidized compound **1** with *m*CPBA in CH_2Cl_2 at room temperature to give a 1:1.4 diastereomeric mixture of sulfoxides **3**. Compound **3**, when further subjected to hexylmagnesium bromide at room temperature, followed by sequential addition of acetic acid and $NaBH_4$/MeOH, however, did not undergo the expected reaction at the C=O double bond, but gave a mixture of hexyl phenyl sulfoxide (**4**),[9] the C–S cleavage product **5**,[10] and the hexyl-substituted product **6**[11] (Scheme 2). Apparently, the nucleophile attacked the sulfoxide group of compound **3** to afford the cleavage products **4** and **5**, or reacted with the activated C=C double bond to provide the substitution product **6**. We also tried to activate the C=O group of compound **3** with BF_3OEt_2, but a mixture of products **4**–**6** was still obtained.[13]

Having failed to add the carbon nucleophile to the C=O group of compound **3**, we intended to carry out the chiral oxidation of the thio group of compound **2**. We have previously reported asymmetric oxidation of 3-(phenylthio)-3-sulfolene to its sulfoxide using Sharpless oxidation procedures.[12] However, the basic nitrogen atom in compound **2** could be problematic under oxidation conditions. Indeed, attempted oxidation of compound **2** with *m*CPBA in CH_2Cl_2 gave a very low yield of the sulfoxide **7**. We then first treated compound **2** with 1 M sulfuric acid in 95% EtOH, and then with

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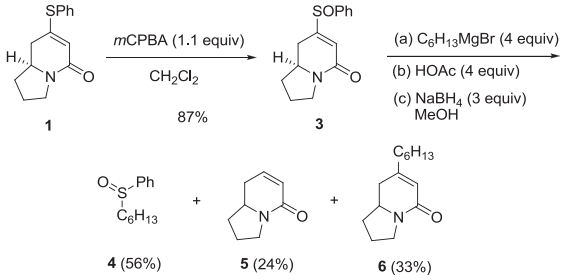
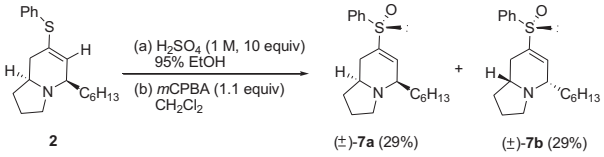


Scheme 2.

*m*CPBA (Scheme 3) to give a 1:1 diastereomeric mixture of sulfoxides **7a** and **7b** (four diastereomers), which could be separated by column chromatography.



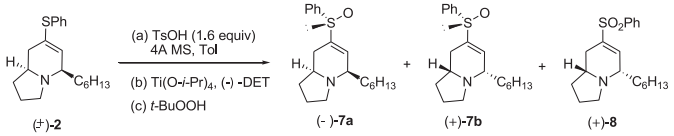
Scheme 3.

Having established that oxidation of compound **2** could be carried out in the presence of sulfuric acid, we then studied the Sharpless asymmetric oxidation[13] of compound **2**. However, the reaction under 1 M H_2SO_4 gave only recovered starting material. We thought that the oxidation might not be compatible with the aqueous system, so we first treated compound **2** with *p*-toluenesulfonic acid and 4 A molecular sieves in toluene before adding the chiral oxidizing agents. The ratio of Ti(O-*i*-Pr)$_4$ to (−)-DET was kept at 1:4 while the amount of *t*-BuOOH (Table 1) was varied. Reaction of compound **2** with 2 equiv of *t*-BuOOH for 12 h at −20 °C (entry 1) gave only recovered starting material **2**; at 0 °C (entry 2) gave a small amount of products (−)-**7a**. The reaction at 25 °C for 12 h (entry 3) yielded only the racemic sulfone **8**, but the reaction at 0 °C for 18 h (entry 4) produced no sulfone (+)-**8**, instead gave an increased amount of (−)-**7a** and (+)-**7b** together with mostly the recovered starting material **2**. We then gradually increased the amount of *t*-BuOOH (entries 5–8) while keeping the reaction at 0 °C for 18 h. It was noted that the amount of sulfoxide (−)-**7a** was greater that of sulfoxide (+)-**7b** in all cases. Under the optimum reaction condition (entry 8), we were able to isolate chiral sulfoxide (−)-**7a** (40%) and chiral sulfone (+)-**8** (41%) by column chromatography. The optical purity of compounds (−)-**7a** and (+)-**8** was determined by chiral HPLC as 99% and 81%, respectively. A pure compound (+)-**8** was obtained by recrystallization from CH_2Cl_2/hexane and its X-ray crystal structure (Fig. 1) indicates the (5*S*,8a*R*) absolute configuration.[14] Consequently, compound (−)-**7a** must have the (5*R*,8a*S*) configuration.

An explanation for the chiral oxidation of compound **2** is shown in Fig. 2. It was reported that with (+)-DET as the chiral ligand, the oxidation of aryl alkyl sulfides proceeds mainly from the *Re* face to give the chiral sulfoxides probably due to steric effect.[13b] In the case of vinyl sulfide **2**, the bicyclic portion would be larger than the phenyl group. So with (−)-DET as the chiral ligand, it is proposed that oxidation of compound **2** occurs faster from the *Si* face to give sulfoxide **A** as the major intermediate. This would explain why sulfoxide (−)-**7a** was formed faster than sulfoxide (+)-**7b** due to steric hindrance of the hexyl group in the latter. Since the amount of sulfoxide (−)-**7a** remained quite steady while the amount of sulfoxide (+)-**7b** diminished with increasing amounts of oxidant *t*-BuOOH, we propose that sulfoxide (+)-**7b** was oxidized faster than sulfoxide (−)-**7a** to the corresponding sulfones **8**. This assumption was proven by subjecting (−)-**7a** and (+)-**7b** separately to 6 equiv of *t*-BuOOH at 0 °C for 6 h. Compound (−)-**7a** remained virtually intact while (+)-**7b** was almost completely converted to sulfone (+)-**8**. Theoretical calculations in the literature proposed that the most favorable conformation of vinyl sulfoxides has the S–O bond *syn* to the C=C double bond (structures **A′** and **B′** in Fig. 2).[15] With this preferred conformation, sulfoxide (−)-**7a** would be more difficult to be further oxidized to the corresponding sulfone (−)-**8** not only due to steric hindrance of the hexyl group, but also because the sulfur lone pair electrons of intermediate **A′** reside in the concave face of the bicyclic system.

We have also carried out chiral oxidation of (±)-**2** using (+)-DET as the catalyst (Scheme 4). The reaction of (±)-**2** with (+)-DET was much slower than with (−)-DET. The TLC showed that a significant amount of (±)-**2** was unreacted after 18 h. Thus we monitored the reaction with TLC every 2 h, and found that a reaction time of 36 h

Table 1
Chiral oxidation of compound (±)-**2**[a]



Entry	Ti(O-*i*-Pr)$_4$ (eq)	(−)-DET (eq)	*t*-BuOOH (eq)	Temp (°C)	Time (h)	Ratio of[b]			
						2	**7a**	**7b**	**8**
1	3	12	2	−20	12	100	0	0	0
2	3	12	2	0	12	90	7	3	0
3	3	12	2	25	12	0	0	0	100[c]
4	3	12	2	0	18	60	24	17	0
5	4	16	3	0	18	18	36	22	24
6	5	20	4	0	18	17	49	17	17
7	6	24	5	0	18	6	49	16	29
8	7	28	6	0	18	0	50	0	50

[a] The reaction conditions were as follows: **2** (1 equiv) in toluene was added to a mixture of TsOH (1.6 equiv) and 4 A molecular sieves. The reaction mixture was stirred at room temperature for 10 min, and then a solution of Ti(O-*i*-Pr)$_4$ and (−)-DET in toluene was added and stirred at rt for 10 min before *t*-BuOOH was added (different reaction conditions).

[b] The ratio of **2**:**7a**:**7b**:**8** was determined from the ^{1}H NMR of the crude product. The optical purities were not determined. Their absolute configuration was established by X-ray crystallography and chemical transformations (vide infra).

[c] A racemic mixture of **8** was obtained.

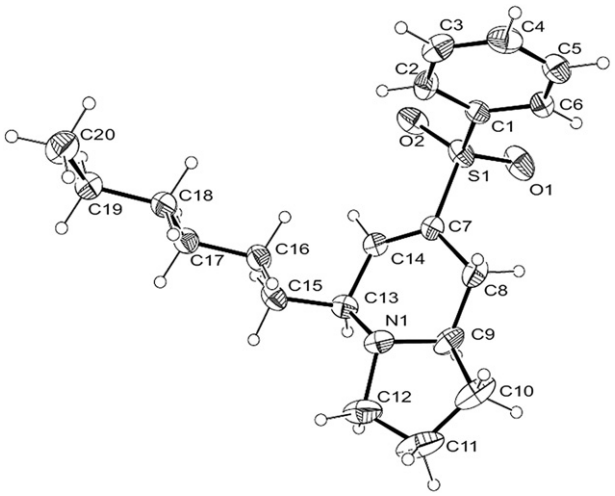


Fig. 1. X-ray crystal structure of chiral sulfone (+)-8.

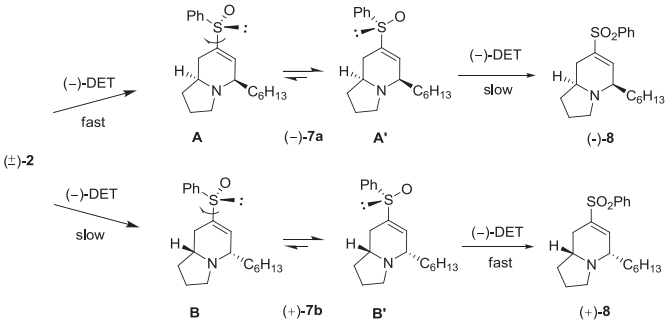
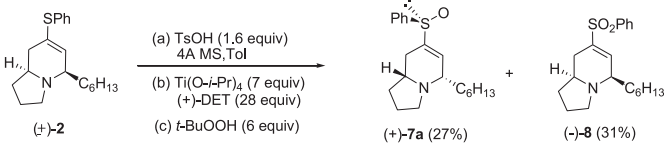


Fig. 2. Chiral oxidation of (±)-2 to (−)-7a and (−)-8.

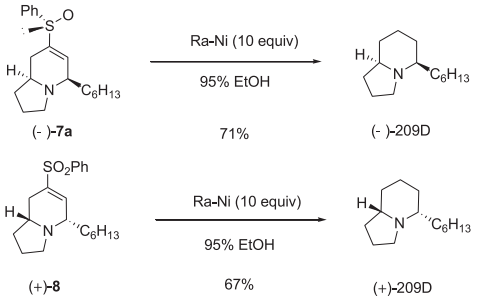


Scheme 4.

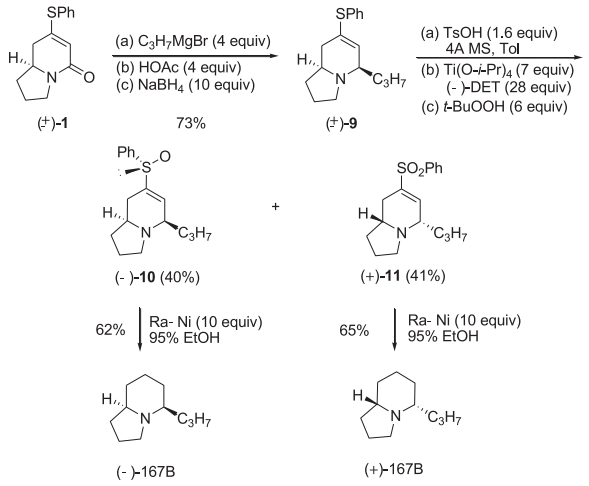
was needed for completion. After purification by column chromatography, we were able to isolate chiral sulfoxide (+)-**7a** (27%, 97% ee), $[\alpha]_D$+26.4 (*c*=0.33, CH_2Cl_2) and (−)-**8** (31%, 91% ee), $[\alpha]_D$−7.2 (*c*=4.0, CH_2Cl_2).

Compounds (−)-**7a** and (+)-**8** were then converted to indolizidines (−)-209D and (+)-209D, respectively by treatment with Raney nickel in refluxing 95% EtOH (Scheme 5). The specific rotation of indolizidine (−)-209D obtained from (−)-**7a**, $[\alpha]_D$−87.5 (*c*=0.03, CH_2Cl_2), was almost identical with that reported for the natural product, $[\alpha]_D$−87.6 (*c*=1, CH_2Cl_2).[16] The specific rotation of indolizidine (+)-209D obtained from (+)-**8**, $[\alpha]_D$+77.0 (*c*=1.15, CH_2Cl_2), indicated that compound (+)-**8** has an *ee* of about 87.9%, which is probably caused by partial formation of (−)-**8** from (−)-**7a** (Fig. 2).

Using a similar method the synthesis of indolizidines (−)-167B and (+)-167B was also achieved (Scheme 6). Sulfoxide (−)-**10** and sulfone (+)-**11** were obtained in 40% and 41%, respectively. Treatment of sulfoxide (−)-**10** with Raney nickel in refluxing 95% EtOH for 2 h provided indolizidine (−)-167B with $[\alpha]_D$−106.8 (*c*=0.01, CH_2Cl_2), which was almost identical with that reported for the natural product, $[\alpha]_D$−106.9 (*c*=1.1, CH_2Cl_2).[17] On the other hand, the specific rotation of indolizidine (+)-167B obtained from (+)-**11**, $[\alpha]_D$+93.8 (*c*=0.16, CH_2Cl_2), indicated that compound (+)-**11** has an *ee* of about 87.7%.



Scheme 5.



Scheme 6.

3. Conclusions

In summary, starting from racemic thio-substituted indolizidine **1**, we have achieved a chemoselective addition of Grignard reagents to the C=O group followed by stereospecific reduction to give *cis*-indolizidines **2** and **9**, which were then asymmetrically oxidized by the Sharpless oxidation to afford chiral sulfoxides (−)-**7a** and (−)-**10**, and their antipodal chiral sulfones (+)-**8** and (+)-**11**, respectively. Treatment of sulfoxides (−)-**7a** and (−)-**10** with Raney nickel provided indolizidines (−)-209D and (−)-167B, whereas the reactions of sulfones (+)-**8** and (+)-**11** with Raney nickel afforded indolizidines (+)-209D and (+)-167B, respectively. We believe this methodology can be applied to the chiral synthesis of other indolizidines and quinolizidines.

4. Experimental section

4.1. General

Melting points were uncorrected. Infrared spectra were recorded on a FTIR spectrophotometer, ν_{max} in cm^{-1}. ^1H NMR spectra were recorded on 300 or 600 MHz spectrometers and are reported in parts per million from tetramethylsilane as the internal standard. ^{13}C NMR spectra were recorded on 75 or 150 MHz spectrometers with complete proton decoupling. Chemical shifts are reported relative to deuterated solvent signals ($CDCl_3$: δ 77.1 ppm). High-resolution mass spectra were obtained using the electron ionization (EI), fast atom bombardment (FAB) or eletrospray ionozation (ESI) method in positive ion mode. Chiral HPLC was carried out with

a DAICEL CHIRALAAK IA column (0.46 cm×25 cm I.D.) using Hexane/IPA=19/1 as eluent (flow rate 0.3 mL/mim) with UV detection at 254 nm.

4.2. (±)-7-(Phenylsulfinyl)-2,3,8,8a-tetrahydroindolizin-5(1*H*)-one (3)

To a solution of compound **1** (122 mg, 0.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added *m*CPBA (145 mg, 70%, 0.55 mmol) in small portions. The reaction mixture was stirred at room temperature for 17 h, and $Na_2S_2O_3$ (0.5 g), and H_2O (10 mL) were added sequentially. After stirring for 10 min, the solvent was removed under vacuum, and saturated sodium bicarbonate was added. The mixture was extracted with ethyl acetate, dried ($MgSO_4$), and evaporated. The crude product was purified by flash chromatography on basic alumina using ethyl acetate/hexane (4: 1) as eluent to give an approximately 1:1.4 diastereomeric mixture of sulfoxides **3** (113 mg, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.62–7.56 (4H, m), 7.52–7.47 (6H, m), 6.65 (1H, d, J=2.7 Hz), 6.61 (1H, d, J=2.7 Hz), 3.71–3.56 (4H, m), 3.45–3.33 (2H, m), 2.81 (1H, dd, J=4.6, 16.6 Hz), 2.37 (1H, dd, J=4.6, 16.6 Hz), 2.20–2.12 (2H, m), 2.03–1.93 (2H, m), 1.87–1.64 (4H, m), 1.59–1.45 (2H, m); ^{13}C NMR ($CDCl_3$) δ 161.4, 161.0, 155.7 (×2), 141.4, 141.1, 132.2, 131.6, 129.8, 129.6, 126.4, 125.5, 124.6, 124.3, 57.1, 57.0, 44.3, 44.2, 33.2 (×2), 28.4, 24.6, 23.1, 23.0; IR (ATR, film) v: 3060, 2973, 2951, 2881, 1656, 1603, 1444, 1050 cm^{-1}; EIMS (rel intensity) m/z 261 (5), 244 (15), 136 (12), 91 (7), 77 (21), 70 (100), 67 (18); HRMS m/z calcd for $C_{14}H_{15}NO_2S$ 261.0823, found 261.0822.

4.3. Reaction of compound 3 to give products 4, 5 and 6

To a solution of compound **3** (52 mg, 0.20 mmol) in THF (3 mL) at room temperature was added slowly another solution of $C_6H_{13}MgBr$ (0.80 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature for 6 h, and then cooled in an ice bath. Acetic acid (0.025 mL) was then added dropwise. The mixture was stirred for 10 min, and $NaBH_4$ (80 mg, 2 mmol), and methanol (2 mL) were added sequentially. After stirring for 30 min, the solvent was removed under vacuum, and saturated sodium bicarbonate solution was added. The mixture was extracted with ethyl acetate, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using Et_3N/ethyl acetate/hexane (1:2:20) as eluent to give compound **4** (23 mg, 56%),[9] compound **5** (6.5 mg, 24%),[10] and compound **6** (14.7 mg, 33%).[11]

4.4. (±)-*cis*-5-Hexyl-7-(phenylsulfinyl)-1,2,3,5,8,8a-hexahydroidoindolizine (7a) and (7b)

A mixture of compound **2** (50 mg, 0.158 mmol) and H_2SO_4 (1 M, 0.15 mL) in 95% EtOH (2 mL) was stirred at room temperature for 30 min, and then *m*CPBA (42 mg, 70%, 0.174 mmol) was added in small portions. The reaction mixture was stirred at room temperature for 17 h, and $Na_2S_2O_3$ (0.2 g) and H_2O (2 mL) were added sequentially. After stirring for 10 min, the solvent was removed under vacuum, and saturated sodium bicarbonate was added. The mixture was extracted with ethyl acetate, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on basic alumina (deactivated with 10% water) using ethyl acetate/hexane (4:1) as eluent to give compound **7a** (15.2 mg, 29%) and compound **7b** (15.3 mg, 29%), both as a colorless oil. Compound **7a**: ^{1}H NMR ($CDCl_3$) δ 7.56–7.53 (2H, m), 7.48–7.41 (3H, m), 6.56 (1H, t, J=1.8 Hz), 3.26 (1H, dt, J=3.0, 8.7 Hz), 2.94–2.86 (1H, m), 2.49 (1H, dt, J=16.5, 3.3 Hz), 2.23 (1H, ddt, J=3.6, 6.9, 10.0 Hz), 2.03 (1H, q, J=8.7 Hz), 1.94–1.84 (1H, m), 1.82–1.64 (4H, m), 1.56–1.40 (3H, m), 1.37–1.23 (7H, m), 0.88 (3H, t, J=6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 142.7, 142.3, 136.7, 130.5, 129.0, 124.6, 63.3, 60.4, 51.9, 33.3, 31.8, 30.3, 29.5, 25.6, 25.1, 22.6, 21.2, 14.1; IR (ATR, film) v: 3049, 2951, 2928, 2857, 2786, 1044 cm^{-1}; EIMS (rel intensity) m/z 314 (15), 247 (18), 246 (100), 204 (37), 137 (47), 136 (19), 120 (22); HRMS m/z calcd for $C_{20}H_{29}NOS$ 331.1970, found 331.1971. Compound **7b**: ^{1}H NMR ($CDCl_3$) δ 7.62–7.57 (2H, m), 7.48–7.43 (3H, m), 6.52 (1H, t, J=1.8 Hz), 3.28 (1H, dt, J=3.0, 8.4 Hz), 2.93–2.86 (1H, m), 2.22 (1H, ddt, J=3.6, 6.0, 9.9 Hz), 2.15–2.00 (2H, m), 1.93–1.64 (5H, m), 1.60–1.40 (2H, m), 1.37–1.23 (8H, m), 0.88 (3H, t, J=6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 142.7, 141.3, 132.5, 131.1, 129.2, 125.4, 63.3, 60.5, 51.8, 33.3, 31.7, 30.4, 29.5, 29.1, 24.9, 22.5, 21.2, 14.0; IR (ATR, film) v: 3060, 2956, 2928, 2862, 2797, 1723, 1689, 1087 cm^{-1}; FABMS (rel intensity) m/z 332 (M+H, 100), 331 (13), 330 (46), 314 (74), 206 (47), 70 (88); FAB-HRMS m/z calcd for $C_{20}H_{29}NOS$ 331.1970, found 331.1972.

4.5. (−)-(5*R*,8a*S*)-5-Hexyl-7-(phenylsulfinyl)-1,2,3,5,8,8a-hexahydroindolizine ((−)-7a) and (+)-(5*S*,8a*R*)-5-hexyl-7-(phenylsulfonyl)-1,2,3,5,8,8a-hexahydroindolizine ((+)-8)

A mixture of compound **2** (50 mg, 0.158 mmol), TsOH (43 mg, 0.253 mmol) and powdered 4 A molecular sieves (0.5 g) in toluene (2 mL) was stirred at room temperature for 10 min. A solution of Ti(O-*i*-Pr)$_4$ (0.33 mL, 1.106 mmol) and (−)-DET (0.759 mL, 4.424 mmol) in tolune (2 mL) was added, stirred for 10 min, and then cooled in an ice bath before *t*-BuOOH (0.119 mL, 80%, 0.948 mmol) was added. The mixture was stirred at 0 °C for 18 h, and then $Na_2S_2O_3$ (0.5 g) and H_2O (2 mL) were added sequentially. After stirring for 20 min, the solvent was removed under vacuum, and saturated sodium bicarbonate solution (20 mL) was added. The mixture was extracted with ethyl acetate (3×20 mL). Since severe emulsion resulted, we used centrifugation to separate the aqueous and organic layers. The combined organic layers were then dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on basic alumina (deactivated with 10% water) using ethyl acetate/hexane (1:6) as eluent to give compound (−)-**7a** (21 mg, 40%) and compound (+)-**8** (23 mg, 41%). (−)-**7a**: a colorless liquid, chiral HPLC R_t=34.96 min, $[\alpha]_D$−26.9 (c=1.15, CH_2Cl_2), the spectral data, of which are the same as the (±)-**7a**. (+)-**8**: a white solid, chiral HPLC R_t=24.56 min, $[\alpha]_D$+6.4 (c=1.00, CH_2Cl_2); mp 42.4–44.1 °C (recryst. CH_2Cl_2/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.85–7.82 (2H, m), 7.61–7.46 (3H, m), 6.92 (1H, t, J=2.0 Hz), 3.26 (1H, dt, J=2.8, 8.4 Hz), 2.92–2.85 (1H, m), 2.50 (1H, dt, J=16.2, 3.0 Hz), 2.25 (1H, ddt, J=3.8, 6.6, 10.2 Hz), 2.04 (1H, q, J=9.0 Hz), 1.98–1.64 (5H, m), 1.58–1.35 (3H, m), 1.32–1.20 (7H, m), 0.87 (3H, t, J=6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 140.0, 139.3, 138.5, 133.1, 129.1, 127.9, 62.7, 60.2, 51.6, 32.9, 31.6, 30.2, 30.1, 29.4, 24.9, 22.5, 21.2, 14.0; IR (ATR, film) v: 3060, 2951, 2928, 2857, 2791, 1306, 1153 cm^{-1}; EIMS (rel intensity) m/z 347 (M$^+$, 1), 263 (22), 262 (100), 206 (16), 120 (23); HRMS m/z calcd for $C_{20}H_{29}NO_2S$ 347.1919, found 347.1915.

4.6. (+)-(5*S*,8a*R*)-5-Hexyl-7-(phenylsulfinyl)-1,2,3,5,8,8a-hexahydroidoindolizine ((+)-7a) and (−)-(5*R*,8a*S*)-5-hexyl-7-(phenylsulfonyl)-1,2,3,5,8,8a-hexahydroidoindolizine ((−)-8)

A mixture of compound **2** (100 mg, 0.317 mmol), TsOH (86 mg, 0.506 mmol) and powdered 4 A molecular sieves (0.5 g) in toluene (2 mL) was stirred at room temperature for 10 min. A solution of Ti(O-*i*-Pr)$_4$ (0.66 mL, 1.212 mmol) and (+)-DET (1518 mL, 8.848 mmol) in toluene (2 mL) was added, stirred for 10 min, and then cooled in an ice bath before *t*-BuOOH (0.238 mL, 80%, 1.902 mmol) was added. The mixture was stirred at 0 °C for 36 h, and then $Na_2S_2O_3$ (0.5 g) and H_2O (2 mL) were added sequentially. After stirring for 20 min, the solvent was removed under vacuum, and saturated sodium bicarbonate solution was added. The mixture was extracted with ethyl acetate, dried ($MgSO_4$) and evaporated.

The crude product was purified by flash chromatography on basic alumina using ethyl acetate/hexane (1:6) as eluent to give compound (+)-**7a** (28 mg, 27%) and compound (−)-**8** (34 mg, 31%). (+)-**7a**: a colorless liquid, $[\alpha]_D$+26.4 (c=0.33, CH_2Cl_2), (−)-**8**: a white solid, chiral HPLC R_t=8.5 min (94.8%), 9.6 min (5.2%), $[\alpha]_D$−7.2 (c=4.0, CH_2Cl_2).

4.7. Indolizidine (−)-209D

A mixture of compound (−)-**7a** (30 mg, 0.090 mmol) and a W-2 Ra–Ni (100 mg) in 95% EtOH (5 mL) was heated at reflux under nitrogen for 2 h. The solid was filtered off, and the residue was evaporated under vacuum in an ice bath. The crude product was purified by flash chromatography using Et_3N/ethyl acetate/hexane (1:1:20) as eluent to give indolizidine (−)-209D (13.5 mg, 71%) as a colorless liquid, $[\alpha]_D$−87.5 (c=0.03, CH_2Cl_2); Lit. $[\alpha]_D$−87.6 (c=1, CH_2Cl_2).[16]

4.8. Indolizidine (+)-209D

A mixture of compound (+)-**8** (36 mg, 0.104 mmol) and a W-2 Ra–Ni (90 mg) in 95% EtOH (5 mL) was heated at reflux under nitrogen for 6 h. The solid was filtered off, and the residue was evaporated under vacuum in an ice bath. The crude product was purified by flash chromatography using Et_3N/ethyl acetate/hexane (1:1:20) as eluent to give indolizidine (+)-209D (14.5 mg, 67%) as a colorless liquid, $[\alpha]_D$+77.0 (c=1.15, CH_2Cl_2).

4.9. (±)-*cis*-7-(Phenylthio)-5-propyl-1,2,3,5,8,8a-hexahydroindolizine (9)

To a solution of compound **1** (50 mg, 0.20 mmol) in THF (3 mL) at room temperature was added slowly another solution of C_3H_7MgBr (0.80 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature for 6 h, and then cooled in an ice bath. Acetic acid (0.025 mL) was then added dropwise. The mixture was stirred for 10 min, and $NaBH_4$ (80 mg, 2 mmol), and methanol (2 mL) were added sequentially. After stirring for 30 min, the solvent was removed under vacuum, and saturated sodium bicarbonate solution was added. The mixture was extracted with ethyl acetate, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using Et_3N/ethyl acetate/hexane (1:2:20) as eluent to give compound **9** (40.1 mg, 73%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.36–7.18 (5H, m), 5.99 (1H, t, J=1.5 Hz), 3.34 (1H, dt, J=2.4, 8.5 Hz), 2.81 (1H, br s), 2.39–2.11 (3H, m), 2.06 (1H, q, J=9.0 Hz), 1.98–1.64 (4H, m), 1.58–1.22 (4H, m), 0.94 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 134.5, 134.0, 130.4, 130.1, 128.8, 126.5, 63.7, 61.4, 52.1, 36.8, 36.0, 30.4, 21.2, 18.4, 14.4; IR (ATR, film) ν: 3059, 2956, 2931, 2870, 2785, 1475 cm^{-1}; FABMS (rel intensity) 274 (M+H, 8), 270 (8), 251 (20), 250 (100), 248 (12), 208 (38), 206 (23), 164 (11); HRMS m/z calcd for $C_{17}H_{24}NS$ 274.1629 (M^+ + 1), found 274.1625.

4.10. (−)-(5*R*,8a*S*)-7-(Phenylsulfinyl)-5-propyl-1,2,3,5,8,8a-hexahydroindolizine ((−)-10) and (+)-(5*S*,8a*R*)-7-(phenylsulfonyl)-5-propyl-1,2,3,5,8,8a-hexahydroindolizine ((+)-11)

Using a procedure similar to that for the preparation of (−)-**7a** and (+)-**8**, compound (±)-**9** (100 mg, 0.36 mmol) gave compound (−)-**10** (41.6 mg, 40%), $[\alpha]_D$−15.8 (c=0.95, CH_2Cl_2), and compound (+)-**11** (45.1 mg, 41%), $[\alpha]_D$+3.8 (c=1.00, CH_2Cl_2). (−)-**10**: ^{1}H NMR ($CDCl_3$) δ 7.58–7.53 (2H, m), 7.49–7.40 (3H, m), 6.61 (1H, br s), 3.27 (1H, dt, J=2.8, 8.5 Hz), 2.90 (1H, br s), 2.50 (1H, dt, J=16.2, 3.0 Hz), 2.26 (1H, ddt, J=3.6, 6.3, 9.9 Hz), 2.04 (1H, q, J=9.0 Hz), 1.97–1.85 (1H, m), 1.83–1.64 (3H, m), 1.56–1.40 (1H, m), 1.38–1.22 (2H, m), 0.95 (3H, t, J=7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 142.7, 142.3, 136.9, 130.6, 129.2, 124.7, 63.2, 60.6, 52.1, 35.6, 30.4, 25.7, 21.3, 18.6, 14.5; IR (ATR, film) ν: 3053, 2951, 2927, 2868, 2786, 1045 cm^{-1}; EIMS (rel intensity) m/z 247 (18), 246 (100), 204 (46), 198 (18), 164 (24), 137 (70), 136 (28), 120 (32), 70 (60); HRMS m/z calcd for $C_{17}H_{23}NOS$ 289.1500, found 289.1485. (+)-**11**: ^{1}H NMR ($CDCl_3$) δ 7.85–7.81 (2H, m), 7.61–7.46 (3H, m), 6.92 (1H, t, J=2.0 Hz), 3.26 (1H, dt, J=2.4, 8.7 Hz), 2.89 (1H, br s), 2.55 (1H, dt, J=15.9, 3.0 Hz), 2.34–2.22 (1H, m), 2.04 (1H, q, J=9.0 Hz), 1.99–1.81 (2H, m), 1.80–1.62 (3H, m), 1.59–1.32 (3H, m), 1.31–1.19 (1H, m), 0.92 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 140.0, 139.3, 138.5, 133.2, 129.1, 128.0, 62.6, 60.2, 51.7, 35.1, 30.3, 30.2, 21.3, 18.2, 14.3; IR (ATR, film) ν: 3055, 2958, 2929, 2868, 2786, 1305, 1152 cm^{-1}; FABMS (rel intensity) m/z 306 (M^++H, 48), 250 (21), 208 (18), 180 (20); HRMS m/z calcd for $C_{17}H_{24}NO_2S$ 306.1528, found 306.1524.

4.11. Indolizidine (−)-167B

Using a procedure similar to that for the preparation of indolizidine (−)-209D, compound 10 (30 mg, 0.103 mmol) gave (−)-167B (11.3 mg, 65%), $[\alpha]_D$−106.8 (c=0.01, CH_2Cl_2); lit. $[\alpha]_D$−106.9 (c=1.1, CH_2Cl_2).[17]

4.12. Indolizidine (+)-167B

Using a procedure similar to that for the preparation of indolizidine (+)-209D, compound (+)-11 (35 mg, 0.103 mmol) gave (+)-167B (11.9 mg, 62%), $[\alpha]_D$+93.8 (c=0.16, CH_2Cl_2).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.04.054.

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