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Concise syntheses of substituted indolizidine alkaloids via cyclization based on α-sulfinyl carbanions: preparation of (±)-indolizidines 167B and 209D, their epimers, and (±)-tashiromine

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Dedicated to Professor Dieter Seebach on the occasion of his 70th birthday

Abstract

(±)-Indolizidines 167B and 209D, their epimers and (±)-tashiromine have been successfully synthesized, starting from simple γ- or α-lactams. The strategy involves the cyclization of α-sulfinyl carbanion onto the carbonyl group of the lactam ring as the key step, leading to the indolizidines containing the phenylsulfinyl group, which are used as precursors for the preparation of the title compounds.

Keywords: Cyclization; α-Sulfinyl carbanion; (±)-Tashiromine; (±)-Indolizidine 167B; (±)-Indolizidine 209D

1. Introduction

Indolizidine alkaloids[1] constitute a class of natural products, which include a large number of pharmaceutically important substances. Tashiromine (**1**) and indolizidines 167B (**2a**) and 209D (**2b**) (Fig. 1) are simple representatives of the series of this class of alkaloids. Tashiromine (**1**) was isolated from the stems of a leguminous plant *Maackia tashiroi*, a deciduous shrub of subtropical Asia.[2,3] Indolizidines 167B (**2a**) and 209D (**2b**) have been isolated from the skin secretions of neotropical frogs of the family Dendrobatidae,[4,5] from Central and South America. These compounds have been shown to function as noncompetitive blockers for muscle type and ganglionic nicotinic receptor channels.[6] Because of the interesting structural features and potent biological activities of these alkaloids and often minute natural abundance, a number of synthetic methodologies of indolizidines have been developed.[3,6,7]

As part of our ongoing research on the cyclization based on the α-sulfinyl carbanions, we have recently reported a general synthetic method for the preparation of 1-azabicyclo[*m.n.*0] alkanes, starting from lactams.[8] In continuation of our successful results, we herein report a concise synthesis of (±)-tashiromine (**1**), (±)-indolizidines 167B (**2a**) and 209D (**2b**), and their epimers. Our retrosynthetic analysis is outlined in Scheme 1. It is anticipated that the syntheses of (±)-tashiromine (**1**) and (±)-indolizidines 167B (**2a**) and 209D (**2b**) would be accomplished by cyclization of α-sulfinyl carbanions onto the carbonyl group of the lactam moiety providing the key intermediates **5** and **6**. The presence of the phenylsulfinyl group in indolizidines **5** and **6** would permit further synthetic transformation at the α-carbon. The intermediate of type **5** (R=H) would be used as the precursor for the preparation of (±)-tashiromine (**1**) by α-hydroxymethylation followed by reductive cleavage of the phenylsulfinyl group. Reductive desulfurization of the resulting indolizidine **6** would provide the

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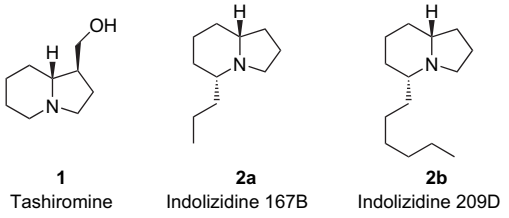


Figure 1.

required indolizidines **2a** and **2b**. We anticipated that the key starting sulfinyl lactam **4** could be easily prepared from lactam **3** by N-alkylation, using 3-bromo-1-phenylsulfanylpropane or 4-bromo-1-phenylsulfanylbutane, followed by oxidation.

2. Results and discussion

2.1. Synthesis of (±)-tashiromine (*1*)

Our investigation began with the preparation of (±)-tashiromine (**1**), starting from commercially available γ-lactam **3a** (R=H; *n*=1). N-Alkylation of γ-lactam **3a** with 4-bromo-1-phenylsulfanylbutane, employing NaH as a base in DMF at 0 °C to room temperature overnight, afforded the corresponding sulfide in 75% yield after column chromatography on silica gel, which was oxidized with $NaIO_4$ in aqueous methanol at 0 °C to give the required starting sulfoxide **4a** (*m*=1; *n*=2) in 70% yield. Cyclization of the sulfoxide **4a** to indolizidine **5** was achieved by treatment with 2.2 equiv of lithium hexamethyldisilazide (LiHDMS) in THF at −78 °C to room temperature overnight, followed by reduction of the resulting crude cyclized product **4aA** with $NaBH_4$ in methanol at 0 °C for 4 h to provide indolizidine **5** in 69% yield as a mixture of inseparable diastereomers. It was found that the cyclized product **4aA** was slowly decomposed during attempted isolation by chromatography on silica gel. It was therefore converted to the corresponding indolizidine **5** by reduction with $NaBH_4$. Compound **4aA** was formed by the intramolecular nucleophilic addition of the initially formed α-sulfinyl carbanion derived from **4a** onto the carbonyl group of the lactam moiety followed by elimination of the hydroxy group during work-up.[8]

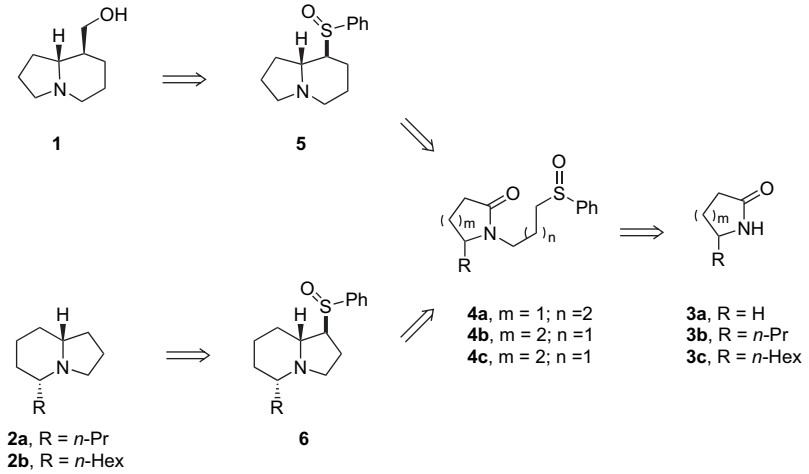
Having the key intermediate indolizidine **5** in hand, the next step was to carry out the α-hydroxymethylation at the α-carbon of the phenylsulfinyl group, following by reductive cleavage. Thus, the α-sulfinyl carbanion of indolizidine **5** generated using lithium diisopropylamide (1.4 equiv) in THF at −78 °C for 1 h was treated with paraformaldehyde (1.2 equiv) to furnish the corresponding diastereomeric mixture of hydroxymethylated indolizidine **7** in 55% yield after chromatography. Pyrolysis of **7** by refluxing in dry toluene in the presence of $CaCO_3$ provided unsaturated indolizidine **8** in 47% yield, which underwent highly stereoselective hydrogenation in ethyl acetate using Pd/C as catalyst to give (±)-tashiromine (**1**) in 86% yield (Scheme 2).

2.2. Synthesis of indolizidines 167B (*2a*) and 209D (*2b*)

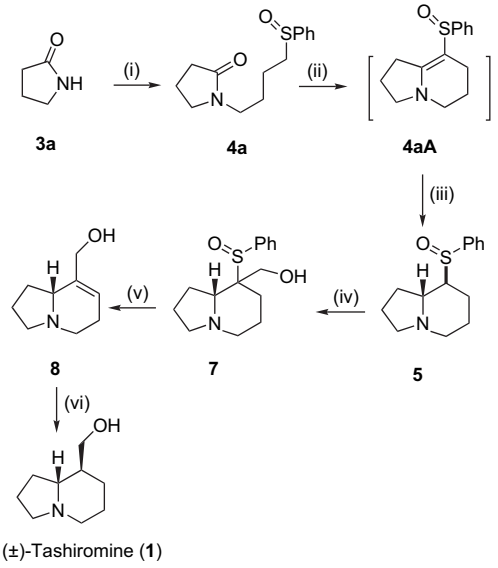
Synthesis of the requisite δ-lactams **3b** and **3c** was achieved by Beckmann rearrangement of oxime derivatives of 2-propylcyclopentanone and 2-hexylcyclopentanone employing NaOH/*p*-TsCl in acetone at room temperature overnight. It was found that inseparable mixtures (4:1) of required δ-lactams **3b/9b** and **3c/9c** were obtained in 67% and 60% yields, respectively. The mixture of **3** and **9** was used directly in the next step (Scheme 3).

Treatment of the mixture of **3b** and **9b** with 1-bromo-3-phenylsulfanylpropane using NaH in DMF at 0 °C overnight afforded **10a** and **11a** in 46% and 14% yields, respectively. Under the same conditions, the mixture of **3c** and **9c** gave **10b** and **11b** in 41% and 12% yields, respectively. Subsequent oxidation of sulfides **10a** and **10b** with $NaIO_4$ in aqueous methanol at 0 °C afforded the corresponding sulfoxides **4b** and **4c** in good yields as diastereomeric mixtures (Scheme 4).

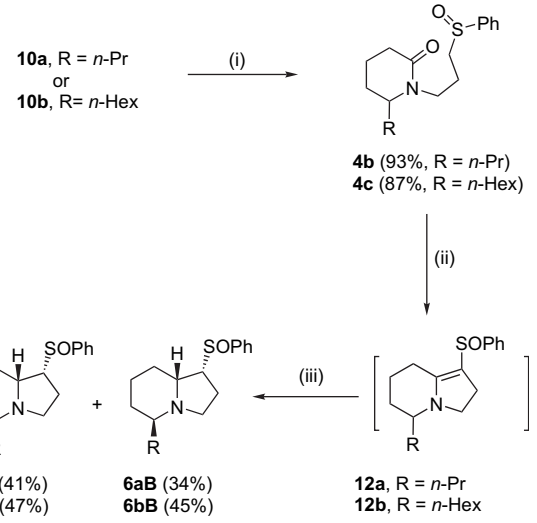
Cyclization of the sulfoxides **4b** and **4c** to the corresponding 1-azabicyclic compounds **12a** and **12b** was accomplished by employing LiHMDS in THF at −78 °C to room temperature overnight. Due to the rapid decomposition of **12a** and



Scheme 1. Retrosynthetic analysis.



Scheme 2. *Reaction conditions*: (i) NaH, DMF, $PhS(CH_2)_4Br$, 0 °C to rt (75%); then $NaIO_4$, MeOH, H_2O, 0 °C to rt overnight (70%); (ii) LiHMDS, THF, −78 °C to rt overnight; (iii) $NaBH_4$, MeOH, 0 °C to rt (69% yield from **4a**); (iv) LDA, THF, $(CH_2O)_n$, −78 °C to rt overnight (55%); (v) toluene, reflux for 8 h (47%); (vi) H_2, Pd/C (86%).



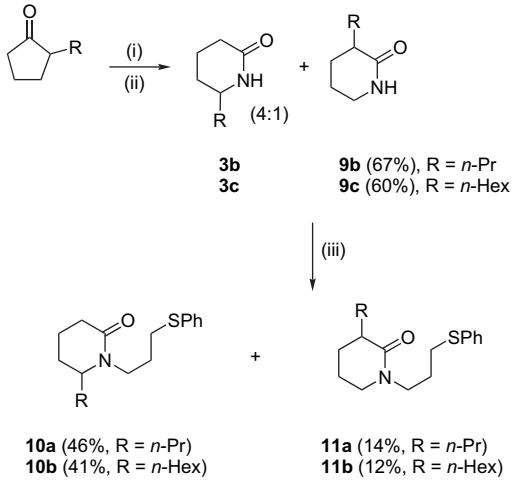
Scheme 4. *Reaction conditions*: (i) $NaIO_4$, MeOH, H_2O, 0 °C to rt overnight; (ii) LiHMDS, THF, −78 °C to rt overnight; (iii) $NaBH_4$, MeOH, 0 °C to rt overnight.

12b during chromatography on silica gel, they were used without purification for the reduction with $NaBH_4$ in MeOH to provide a mixture of two diastereomers of **6aA/6aB** and **6bA/6bB**, respectively, in good overall yields (Scheme 4).

The complete assignment of ^{1}H NMR chemical shifts of **6aA**, **6aB** and **6bA**, **6bB** was made by comparing their ^{1}H NMR spectral data with those of **13** (Fig. 2) (for preparation and complete characterization of **13**, see Supplementary data).

The relative stereochemistry of **6aA/6bA** and **6aB/6bB** was also made by comparison of the chemical shifts of C-5 protons with those of **13**. The chemical shifts of C_5-H_a of **6aA** and **6bA** appear at higher field than C_5-H_e of **6aB** and **6bB**. C_5-H_e of the latter diastereomers resonate at lower field due to strong deshielding effect caused by the proximate nitrogen lone pair electrons.[9] Moreover, compounds **6aA** and **6bA** exhibit strong infrared Bohlmann bands at 2778 and 2783 cm^{-1}, respectively, indicating that the hydrogen on carbon atoms adjacent to the nitrogen oriented trans to lone pair electrons.[10] These characteristic absorption bands in the infrared spectra were not found in compounds **6aB** and **6bB**.

To complete the synthesis of **2a** and **2b** from **6aA** and **6bA** by reductive desulfurization, we began our study with 6% Na(Hg)/MeOH/NaH_2PO_4 or Raney-nickel. All attempts led to unsatisfactory results, providing mainly the recovered starting materials. Fortunately, reductive desulfurization of **6aA** and **6bA** was successfully made by employing nickel boride (Ni_2B).[11] Thus, treatment of **6aA** and **6bA** with Ni_2B, generated in situ from $NiCl_2\cdot 6H_2O$ and $NaBH_4$ in a mixture of MeOH and THF (3:1), at 0 °C to room temperature gave the required (±)-indolizidines 167B (**2a**) and 209 D (**2b**) in 82% and 80% yields, respectively. Their spectroscopic data were



Scheme 3. *Reaction conditions*: (i) $NH_2OH\cdot HCl$, ethanol; (ii) TsCl, NaOH, acetone, rt, overnight; (iii) NaH, DMF, $PhS(CH_2)_3Br$, 0 °C to rt, overnight.

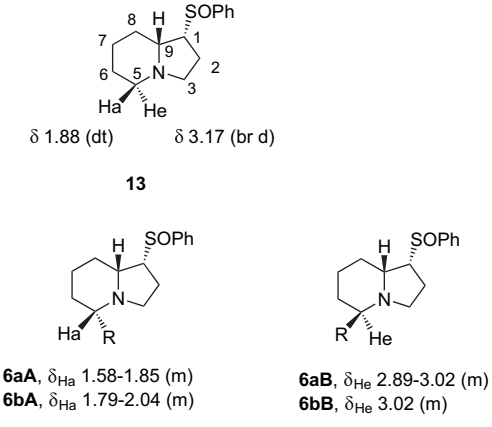
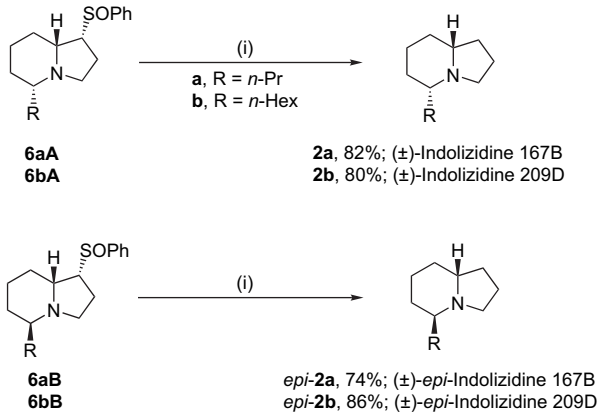


Figure 2. Comparing of ^{1}H NMR data of C-5 protons of compounds **6aA/6aB** and **6bA/6bB** with compound **13**.

consistent with those of the reported values in the literature.[7e] Similarly, under the same reduction conditions, the diastereomers **6aB** and **6bB** furnished the corresponding (±)-*epi*-indolizidine 167B (**2a**) and (±)-*epi*-indolizidine 209D (**2b**)[7e] in 74% and 86% yields (Scheme 5).



Scheme 5. *Reaction conditions*: (i) $NiCl_2 \cdot 6H_2O/NaBH_4$, MeOH/THF (3:1), 0 °C to rt, 2 h.

3. Conclusion

In conclusion, we have developed a concise method for the synthesis of (±)-tashiromine (**1**), (±)-indolizidine 167B (**2a**) and 209D (**2b**), and their epimers, starting from 2-propyl or 2-hexyl substituted δ-lactams, respectively. The synthesis demonstrates the utilities of the cyclization of α-sulfinyl carbanions onto the carbonyl group of the lactam rings as a convenient entry to the indolizidines containing the sulfoxide functional group that can be employed as the key indolizidines for the preparation of the title compounds.

4. Experimental

4.1. General methods

The ^{1}H NMR spectra were recorded on either Bruker DPX-300 (300 MHz) or Bruker Avance-500 (500 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker Avance-500 (500 MHz) spectrometer using tetramethylsilane as an internal standard. The IR spectra were recorded on either a Jasco A-302 or a Perkin–Elmer 683 infrared spectrometer. The mass spectra were recorded using Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded on MS Micromass model VQ-TOF2. Elemental analyses were performed by a Perkin–Elmer Elemental Analyzer 2400 CHN. Melting points were recorded on a Büchi 501 Melting Point Apparatus and uncorrected. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Dry *N*,*N*-dimethylformamide (DMF) was obtained by distilling over calcium hydride. Other common solvents (hexanes, ethyl acetate, methanol, and acetone) were distilled before use. All glasswares and syringes were oven-dried and kept in a dessicator before use. Preparative thin layer chromatography and column chromatography were performed using Merck silica gel $60F_{254}$ (Merck, Art. 7749) and silica gel 60H (Merck, Art. 7736), respectively.

4.2. Preparation of (±)-tashiromine (*1*)

4.2.1. 1-(4-Phenylsulfinylbutyl)pyrrolidin-2-one (*4a*)

General procedure. To a suspension of NaH (1.55 g, 38.7 mmol, 80% suspension in mineral oil) in DMF (58 mL), a DMF (12 mL) solution of γ-lactam (3.0 g, 35 mmol) was slowly added at 0 °C under an argon atmosphere. The reaction mixture was stirred for 1 h until the generation of hydrogen ceased and 1-bromo-4-phenylsulfanylbutane (9.5 g, 38.7 mmol) was then added. After the reaction mixture was stirred at 0 °C to room temperature overnight, it was poured into ice-water and extracted with EtOAc (4×100 mL). The combined organic layers were washed with H_2O and brine, and dried over anhyd Na_2SO_4. Filtration followed by concentration in vacuo gave a residue, which was purified by column chromatography on silica gel (20% EtOAc in hexanes) to give a pale yellow liquid of 1-(4-phenylsulfanylbutyl)pyrrolidin-2-one (6.6 g, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.22 (m, 4H), 7.19–7.13 (m, 1H), 3.38–3.19 (m, 4H), 2.94 (t, *J*=6.5 Hz, 2H), 2.36 (t, *J*=8.0 Hz, 2H), 1.95 (quint, *J*=7.5 Hz, 2H), 1.74–1.56 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 136.3, 129.1 (2C), 128.8 (2C), 125.8, 46.9, 41.7, 33.1, 30.9, 26.0 (2C), 17.8. IR (neat): ν_{max} 1681 (s), 1583 (m), 1480 (s), 1463 (s), 1290 (s), 1267 (s) cm^{-1}. MS: *m*/*z* (%) relative intensity 250 (M^++1, 9), 140 (71), 123 (11), 98 (100), 70 (32), 68 (9). HRMS (ESI): calcd for $C_{14}H_{20}NOS$, 250.1267; found, 250.1232.

A solution of 1-(4-phenylsulfanylbutyl)pyrrolidin-2-one (5.0 g, 20 mmol) in MeOH (11 mL) was slowly added to a suspension of $NaIO_4$ (4.7 g, 22 mmol) in MeOH (48 mL) and H_2O (12 mL) at 0 °C. The mixture was stirred vigorously and slowly warmed up to room temperature overnight (12 h). The precipitates of $NaIO_3$ were filtered and washed several times with EtOAc (3×60 mL). The combined extracts were washed with H_2O and brine, and dried over anhyd Na_2SO_4. Filtration followed by concentration in vacuo gave a pale yellow liquid of a crude product, which was purified by column chromatography (100% EtOAc) to afford a colorless viscous liquid of **4a** (3.75 g, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.31 (m, 2H), 7.31–7.19 (m, 3H), 3.34–3.10 (m, 4H), 2.71–2.52 (m, 2H), 2.08 (t, *J*=7.8 Hz, 2H), 1.78–1.66 (m, 2H), 1.23–1.59 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.2, 142.8, 130.2, 128.5 (2C), 123.2 (2C), 55.3, 46.2, 40.7, 30.2, 25.0, 18.4, 17.1. IR (neat): ν_{max} 1679 (s), 1494 (m), 1464 (s), 1443 (s), 1290 (s), 1087 (s) cm^{-1}. MS: *m*/*z* (%) relative intensity 266 (M^++1, 51), 248 (39), 165 (23), 163 (22), 140 (87), 138 (30), 98 (100), 70 (47). HRMS (ESI): calcd for $C_{14}H_{20}NO_2S$, 266.1216; found, 266.1182.

4.2.2. 8-Phenylsulfinyl-1,2,3,5,6,7,8,9-octahydroindolizine (**5**)

General procedure. A THF (18 mL) solution of **4a** (2.29 g, 8.64 mmol) was added dropwise to a cooled (−78 °C) THF (100 mL) solution of LiHMDS [prepared by reacting *n*-BuLi (1.36 M in hexane; 14 mL, 19 mmol) with THF (93 mL) solution of hexamethyldisilazane (HMDS) (4.3 mL, 20.7 mmol) at −78 °C for 30 min] under an argon atmosphere. The resulting mixture was stirred and slowly warmed up from −78 °C to room temperature overnight (15 h). The resulting yellow solution was quenched with H_2O and extracted with EtOAc (3×100 mL). The combined organic extracts were washed with H_2O and brine, and dried over anhyd Na_2SO_4. Filtration followed by concentration in vacuo afforded a viscous liquid of a crude product **4aA**, which was directly subjected to reduction using $NaBH_4$ as described below.

To a solution of the crude product **4aA** in MeOH (21 mL) at 0 °C under argon atmosphere, $NaBH_4$ (3.9 g, 103.6 mmol) was gradually added over 15 min. The mixture was stirred at room temperature overnight, diluted with 1 N NaOH (63 mL) and H_2O (38 mL), and extracted with EtOAc (3×100 mL). The combined organic extracts were washed with brine, dried over anhyd Na_2SO_4, and concentrated. The crude product was purified by column chromatography (SiO_2, 10% MeOH in EtOAc containing 0.15% NH_4OH solution) to afford a mixture of three diastereomers of **5** (1.49 g, 69% yield).

F_1 (less polar) was obtained as a yellow viscous liquid of a mixture of two diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64–7.58 (m, 2H, Ar*H*), 7.57–7.42 (m, 8H, Ar*H*), 3.13 (dt, *J*=8.6, 1.9 Hz, 1H), 3.09–3.01 (m, 3H), 2.81–2.79 (m, 1H), 2.52–2.35 (m, 4H), 2.32–2.18 (m, 2H), 2.18–1.98 (m, 2H), 1.98–1.43 (m, 13H), 1.26–1.22 (m, 1H), 1.07 (dq, *J*=12.6, 4.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3, 141.2, 131.2, 130.5, 128.9 (2C), 128.9 (2C), 125.4 (2C), 124.2 (2C), 66.1, 65.7, 63.8, 63.4, 53.9, 53.2, 51.7, 29.4, 29.2, 24.8, 24.2, 23.4, 20.9, 20.6, 18.1. IR (neat): ν_{max} 2939 (s), 2788 (s), 1582 (w), 1478 (m), 1461 (m), 1443 (s), 1362 (s), 1086 (s), 1045 (s), 749 (s) cm^{-1}. MS: *m*/*z* (%) relative intensity 250 (M^++1, 13), 124 (53), 123 (85), 122 (100), 96 (47). HRMS (EI): calcd for $C_{14}H_{20}NOS$, 250.1260; found, 250.1259.

F_2 (more polar) was obtained as a colorless viscous liquid of a single diastereomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64–7.52 (m, 2H, Ar*H*), 7.49–7.36 (m, 3H, Ar*H*), 3.16–2.92 (m, 3H), 2.57–2.39 (m, 1H), 2.41–1.59 (m, 8H), 1.58–1.34 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.4, 130.7, 129.2 (2C), 124.6 (2C), 63.9, 63.3, 54.4, 51.9, 25.8, 22.8, 21.3, 20.9. IR (neat): ν_{max} 2938 (s), 2786 (s), 1582 (w), 1442 (s), 1041 (s), 753 (s) cm^{-1}. MS: *m*/*z* (%) relative intensity 250 (M^++1, 1), 232 (100), 122 (63), 96 (35), 94 (14). HRMS (ESI): calcd for $C_{14}H_{20}NOS$, 250.1260; found, 250.1262.

4.2.3. [1,2,3,5,6,7,8,9-Octahydro-8-(phenylsulfinyl)indolizin-8-yl]methanol (**7**)

n-BuLi (1.36 M in hexane; 4.0 mL, 5.4 mmol) was added to a cooled (−78 °C) THF (5 mL) solution of diisopropylamine (0.86 mL, 6 mmol) under an argon atmosphere. After stirring at −78 °C for 30 min, a THF (12 mL) solution of **5** (1.0 g, 4 mmol) was added dropwise and allowed to stir for 30 min. Paraformaldehyde (145 mg, 4.8 mmol) was added as a solid to the resulting solution at −78 °C and the resulting mixture was allowed to stir and slowly warmed up to room temperature overnight (15 h). The resulting yellow solution was quenched with H_2O and extracted with EtOAc (3×70 mL). The combined organic extracts were washed with H_2O and brine, and dried over anhyd Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography (SiO_2, 10% MeOH in EtOAc) to afford a pale yellow viscous liquid of **7** (0.62 g, 55% yield) as a mixture of three diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79–7.70 (m, 3H), 7.56–7.39 (m, 12H), 4.42 (d, *J*=11.7 Hz, 1H), 4.17–4.06 (m, 2H), 3.81 (d, *J*=11.4 Hz), 3.51 (d, *J*=12.7 Hz, 1H), 3.31 (d, *J*=10.6 Hz, 1H), 3.23–3.13 (m, 3H), 3.13–2.94 (m, 3H), 2.76–2.59 (m, 1H), 2.49–1.52 (m, 31H), 1.43–1.39 (m, 1H), 1.21–1.03 (m, 2H), 0.82 (dt, *J*=4.79, 13.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 138.6, 137.8, 131.8 (2C), 131.6 (2C), 128.9 (2C), 128.7 (2C), 126.7 (2C), 126.2 (3C), 125.9 (2C), 69.9, 67.7, 67.6, 66.2, 64.6, 62.5, 62.4, 61.2, 60.4, 54.1, 53.9, 53.6, 52.8, 52.3, 52.2, 29.7, 28.1, 27.2, 25.3, 24.4, 23.9, 22.7, 22.6, 21.8, 20.9, 20.9, 20.6. IR (neat): ν_{max} 3367 (br), 2709 (s), 1582 (w), 1475 (w), 1443 (s), 1032 (s), 749 (s), 699 (s) cm^{-1}. MS: *m*/*z* (%) relative intensity 280 (M^++1, 1), 153 (32), 136 (100), 122 (15). HRMS (ESI): calcd for $C_{15}H_{22}NO_2S$, 280.1366; found, 280.1353.

4.2.4. (1,2,3,5,6,8a-Hexahydroindolizin-8-yl)methanol (**8**)

A toluene (15 mL) solution of **7** (0.32 g, 1.17 mmol) in the presence of $CaCO_3$ was stirred at reflux under an argon atmosphere for 8 h. $CaCO_3$ was filtered off and the filtrate was evaporated to dryness to give a crude product, which was purified by preparative thin layer chromatography (SiO_2, 30% MeOH in EtOAc) to give a pale brown liquid of **8** (89 mg, 47% yield). ^{1}H NMR (300 Hz, $CDCl_3$): δ 5.61 (br s, 1H), 4.25 (br s, 1H), 3.98 (br s, 2H), 3.20 (t, 1H, *J*=7.8 Hz), 2.88–2.79 (m, 1H), 2.65–2.79 (m, 2H), 2.59–2.46 (m, 1H), 2.15 (br s, 2H), 2.19–2.06 (m, 1H), 1.91–1.63 (m, 2H), 1.56–1.42 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4, 120.1, 64.5, 60.1, 52.9, 46.3, 27.9, 24.7, 22.1. IR (neat): ν_{max} 3351 (br), 2876 (s), 2729 (s), 1663 (m), 1576 (w), 1457 (s), 1434 (s), 1062 (s), 1018 (s) cm^{-1}. MS: *m*/*z* (%) relative intensity 154 (M^++1, 36), 152 (36), 136 (16), 122 (100), 120 (23), 94 (14), 79 (12). HRMS (ESI): calcd for $C_9H_{16}NO$, 154.1226; found, 154.1230.

4.2.5. (±)-Tashiromine (**1**)

To a suspension of 10% Pd/C (40 mg, 0.038 mmol) in EtOAc (2 mL), an EtOAc (3 mL) solution of **8** (58 mg, 0.38 mmol) was slowly added at room temperature under hydrogen atmosphere. The reaction mixture was allowed to stir overnight (15 h) followed by filtration over Celite. The filtrate was evaporated in vacuo to give a crude product, which was purified by preparative thin layer chromatography (Al_2O_3,

100% EtOAc) to give a pale yellow viscous liquid of (±)-tashiromine (**1**) (51 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64–3.52 (m, 1H), 3.49–3.38 (m, 1H), 3.14–3.01 (m, 2H), 2.17–1.36 (m, 11H), 1.11–0.99 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.5, 65.6, 54.0, 52.6, 44.2, 28.9, 27.4, 24.9, 20.6. IR (neat): ν_{max} 3392 (br), 2799 (s), 1648 (m), 1445 (m) cm^{-1}. MS: *m/z* (%) relative intensity 156 (M^++1, 100), 154 (74), 136 (39), 110 (26), 84 (64). HRMS (ESI): calcd for $C_9H_{18}NO$, 156.1383; found, 156.1393. The spectroscopic data are consistent with the literature.[2,3f,3g]

4.3. Preparation of (±)-indolizidine 167B (**2a**) and 209D (**2b**)

4.3.1. 6-Propyl-2-piperidone (**3b**)[12]

General procedure. To a solution of hydroxylamine hydrochloride (0.28 g, 4.0 mmol) and NaOH (0.22 g) in EtOH (5 mL) was added a solution of 2-propylcyclopentanone (0.39 g, 3.1 mmol) in EtOH (1 mL). The mixture was stirred at reflux for 2 h, poured into ice-water after cooling to room temperature, and extracted with EtOAc (3×15 mL). The combined organic layers were washed with H_2O and brine, and dried over anhyd Na_2SO_4. Filtration followed by evaporation gave a crude product of a *syn*- and *anti*-mixture of 2-propylcyclopentanone oxime. A solution of the crude product of 2-propylcyclopentanone oxime (0.41 g, 2.9 mmol) in acetone (3.8 mL) was treated with 1 N NaOH (5 mL) at 0 °C and *p*-TsCl (0.72 g, 3.8 mmol) in acetone (2.2 mL) was added dropwise. Aftre stirring the resulting mixture for 18 h at 25 °C, it was diluted with H_2O (8 mL) and extracted with EtOAc (3×15 mL). The combined organic extracts were washed with H_2O and brine, and dried over anhyd Na_2SO_4. The crude product was purified by column chromatography (SiO_2, 30% EtOAc in hexanes) to afford a white solid of a 4:1 mixture of 6-propylvalerolactam (**3b**) and 3-propylvalerolactam (**9b**) (0.293 g, 67% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.61 (br s, 1H), 6.42 (br s, 1H), 3.39–3.31 (m, 1H), 3.31–3.19 (m, 2H), 2.44–2.16 (m, 3H), 1.99–1.20 (m, 16H), 0.92 and 0.91 (each t, *J*=7.1 Hz, 2×3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3, 172.4, 52.7, 42.2, 40.6, 38.9, 33.5, 31.2, 28.2, 25.9, 21.1, 20.0, 19.6, 18.4, 13.9, 13.8. IR (Nujol): ν_{max} 1667 (s), 1462 (s), 1403 (m), 1377 (s), 1333 (m) cm^{-1}. MS: *m/z* (%) relative intensity 143 (M^++2, 9), 142 (M^++1, 100), 98 (50), 70 (29).

4.3.2. 6-Hexyl-2-piperidone (**3c**)

According to the general procedure described for **3b**, hydroxylamine hydrochloride (2.02 g, 29.01 mmol) in an ethanol (50 mL) solution of NaOH (30 mmol) was reacted with a solution of 2-hexylcyclopentanone (3.88 g, 23.10 mmol). The crude product obtained from the above reaction was treated with 1 N NaOH (30 mL) and a solution of *p*-TsCl (5.68 g, 29.82 mmol) in acetone (17 mL). After the usual work-up, the crude product was purified by column chromatography (SiO_2, 30% EtOAc in hexanes) to afford a yellow liquid of a 4:1 mixture of 6-hexylvalerolactam (**3c**) and 3-hexylvalerolactam (**9c**) (2.54 g, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.55 (br s, 1H), 6.34 (br s, 1H), 3.37–3.17 (m, 3H), 2.43–2.13 (m, 3H), 1.96–1.12 (m, 28H), 0.91–0.79 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, 172.4, 53.0, 42.2, 40.8, 36.8, 31.6, 31.5, 31.4, 31.2, 29.2, 29.0, 28.2, 26.8, 25.9, 25.1, 22.5, 22.4, 21.2, 19.6, 13.9, 13.9. IR (Nujol): ν_{max} 1668 (s), 1485 (s), 1469 (s), 1403 (s), 1377 (m), 1346 (m) cm^{-1}. MS: *m/z* (%) relative intensity 184 (M^++1, 8), 183 (M^+, 9), 112 (22), 99 (21), 98 (100), 70 (58), 55 (70). HRMS (ESI): calcd for $C_{11}H_{21}NONa$, 206.1521; found, 206.1522.

4.3.3. Preparation of a mixture of 6-alkyl-1-(3-phenylsulfanylpropyl)piperidin-2-one **10** and 3-alkyl-1-(3-phenylsulfanylpropyl)piperidin-2-one **11**

*4.3.3.1. A mixture of 6-propyl-1-(3-phenylsulfanylpropyl)piperidin-2-one (**10a**) and 3-propyl-1-(3-phenylsulfanylpropyl)piperidin-2-one (**11a**). General procedure*. To a suspension of NaH (1.01 g, 33.75 mmol, 80% suspension in mineral oil) in DMF (80 mL), a DMF (7 mL) solution of a 4:1 mixture of **3b** and **9b** (3.16 g, 22.41 mmol) was slowly added at 0 °C under an argon atmosphere. The reaction mixture was stirred for 1 h until the generation of hydrogen ceased and 1-bromo-3-phenylsulfanylpropane (6.20 g, 26.84 mmol) was then added. After the reaction mixture was stirred at 0 °C to room temperature overnight (15 h), it was quenched with water and extracted with EtOAc (4×80 mL). The combined organic layers were washed with H_2O and brine, and dried over anhyd Na_2SO_4. Filtration followed by concentration in vacuo gave a residue, which was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give a pale yellow liquid of **10a** (2.99 g, 46% yield) and **11a** (0.94 g, 14% yield).

Compound **10a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.21 and 7.19–7.11 (each m, 5H), 3.86 (ddd, *J*=14.1, 8.0, 5.6 Hz, 1H), 3.31–3.21 (m, 1H), 2.99 (ddd, *J*=13.7, 8.3, 5.6 Hz, 1H), 2.91 (t, *J*=7.2 Hz, 2H), 2.38–2.26 (m, 2H), 1.99–1.09 (m, 10H), 0.91 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 136.9, 129.8 (2C), 129.5 (2C), 126.5, 57.2, 45.1, 35.4, 32.5, 31.9, 27.7, 26.7, 19.9, 17.7, 14.6. IR (neat): ν_{max} 1637 (s), 1585 (m), 1473 (s), 1418 (m), 1360 (m) cm^{-1}. MS: *m/z* (%) relative intensity 292 (M^++1, 8), 183 (12), 182 (100), 113 (22). HRMS (ESI): calcd for $C_{17}H_{25}NONaS$, 314.1555; found, 314.1553.

Compound **11a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.09 (m, 5H), 3.47–3.28 (m, 2H), 3.23–3.08 (m, 2H), 2.83 (t, *J*=7.4 Hz, 2H), 2.25–2.13 (m, 1H), 1.92–1.13 (m, 10H), 0.85 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 136.2, 129.1 (2C), 128.8 (2C), 125.9, 48.1, 46.3, 41.2, 34.0, 31.1, 26.8, 26.2, 21.6, 20.1, 14.0. IR (neat): ν_{max} 1636 (s), 1584 (m), 1490 (s), 1464 (s), 1439 (s), 740 (s) cm^{-1}. MS: *m/z* (%) relative intensity 292 (M^++1, 1), 291 (M^+, 2), 183 (13), 182 (100), 154 (15).

*4.3.3.2. A mixture of 6-hexyl-1-(3-phenylsulfanylpropyl)piperidin-2-one (**10b**) and 3-hexyl-1-(3-phenylsulfanylpropyl)piperidin-2-one (**11b**).* According to the general procedure described for **10a**, a 4:1 mixture of **3c** and **9c** (4:1) (1.40 g,

7.65 mmol) in DMF (3 mL) was treated with NaH (0.29 g, 9.58 mmol, 80% suspension in mineral oil) and 1-bromo-3-phenylsulfanylpropane (2.11 g, 9.13 mmol) in DMF (16 mL) to afford a crude product, which was purified by column chromatography (SiO_2, 50% EtOAc in hexanes) to give a pale yellow liquid of **10b** (1.0412 g, 41% yield) and **11b** (0.3094 g, 12% yield).

Compound **10b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.13 (m, 5H), 3.88 (ddd, J=13.8, 8.2, 6.0 Hz, 1H), 3.32–3.21 (m, 1H), 3.00 (ddd, J=13.7, 8.2, 5.7 Hz, 1H), 2.93 (t, J=7.2 Hz, 2H), 2.39–2.28 (m, 2H), 2.02–1.09 (m, 16H), 0.90 (t, J=6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 136.2, 129.1 (2C), 128.8 (2C), 125.9, 56.8, 44.4, 32.5, 31.8, 31.6, 31.2, 29.1, 27.0, 26.0, 26.0, 22.5, 17.0, 14.0. IR (neat): ν_{max} 1640 (s), 1585 (w), 1470 (s), 1439 (s), 1275 (m), 738 (s) cm^{-1}. MS: *m/z* (%) relative intensity 334 (M^++1, 4), 225 (15), 224 (100). HRMS (ESI): calcd for $C_{20}H_{31}NONaS$, 356.2024; found, 356.2024.

Compound **11b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.10 (m, 5H), 3.54–3.34 (m, 2H), 3.29–3.13 (m, 2H), 2.90 (t, J=7.3 Hz, 2H), 2.30–2.17 (m, 1H), 1.98–1.17 (m, 16H), 0.96–0.79 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 136.1, 128.9 (2C), 128.6 (2C), 125.7, 47.9, 46.1, 41.2, 31.7, 31.5, 30.9, 29.1, 26.8, 26.6, 26.1, 22.4, 21.5, 13.8. IR (neat): ν_{max} 1637 (s), 1584 (m), 1490 (m), 1465 (m), 1439 (m), 1352 (m) cm^{-1}. MS: *m/z* (%) relative intensity 334 (M^++1, 3), 225 (15), 224 (100), 196 (14), 168 (15).

*4.3.3.3. 6-Propyl-1-(3-phenylsulfinylpropyl)piperidin-2-one (**4b**).* According to the general procedure as described for **4a**, a solution of **10a** (0.21 g, 0.72 mmol) in MeOH (0.5 mL) was reacted with $NaIO_4$ (0.16 g, 0.75 mmol) in MeOH (1.6 mL) and H_2O (0.4 mL). The crude product obtained was purified by column chromatography (SiO_2, 100% EtOAc) to afford a colorless viscous liquid of **4b** (0.204 g, 93% yield) as a 1:1 mixture of two diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65–7.58 and 7.57–7.45 (each m, 2×5H), 4.02–3.87 (m, 2H), 3.40–3.22 (m, 2H), 3.05–2.68 (m, 6H), 2.42–2.22 (m, 4H), 2.21–1.11 (m, 20H), 0.94 (t, J=7.2 Hz, 3H), 0.93 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 170.2, 143.6, 143.5, 130.8 (4C), 129.1 (4C), 123.9, 123.8, 56.2, 56.2, 54.7, 54.5, 43.8, 43.6, 34.6, 34.6, 31.8, 31.7, 26.0, 25.9, 20.5, 20.5, 19.2 (2C), 16.9 (2C), 13.9 (2C); IR (neat): ν_{max} 3055 (w), 2955 (m), 2872 (m), 1634 (s), 1473 (m), 1446 (m), 1086 (m), 1045 (m), 751 (m) cm^{-1}. MS: *m/z* (%) relative intensity 308 (M^++1, 7), 290 (29), 182 (100), 180 (27), 112 (67). HRMS (ESI): calcd for $C_{17}H_{25}NO_2NaS$, 330.1504; found, 330.1511.

*4.3.3.4. 6-Hexyl-1-(3-phenylsulfinylpropyl)piperidin-2-one (**4c**).* According to the general procedure described for **4a**, a solution of **10b** (2.38 g, 7.15 mmol) in MeOH (5 mL) was treated with a suspension of $NaIO_4$ (1.68 g, 7.85 mmol) in MeOH (16 mL) and H_2O (4 mL). The crude product was purified by column chromatography (SiO_2, 100% EtOAc) to afford a colorless viscous liquid of **4c** (2.18 g, 87% yield) as a mixture of two diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66–7.57 and 7.57–7.44 (each m, 2×5H), 4.03–3.88 (m, 2H), 3.40–3.19 (m, 2H), 3.05–2.67 (m, 6H), 2.42–2.20 (m, 4H), 2.19–1.08 (m, 32H), 0.89 (t, J=6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 170.2, 143.6, 143.5, 130.8 (4C), 129.1 (4C), 123.9, 123.8, 56.5, 56.4, 54.7, 54.5, 43.8, 43.6, 32.5, 32.4, 31.8, 31.7, 31.6 (2C), 29.1 (2C), 25.9 (4C), 22.4 (2C), 20.5, 20.5, 16.9 (2C), 13.9 (2C). IR (neat): ν_{max} 1634 (s), 1471 (s), 1444 (m), 1087 (m), 1046 (s), 749 (m) cm^{-1}. MS: *m/z* (%) relative intensity 350 (M^++1, 3), 224 (100), 222 (29), 138 (20), 112 (69). HRMS (ESI): calcd for $C_{20}H_{31}NO_2NaS$, 372.1973; found, 372.1974.

*4.3.3.5. 1-Phenylsulfinyl-5-propyl-1,2,3,5,6,7,8,9-octahydroindolizine (**6a**).* According to the general procedure for the preparation of **5**, a THF (12 mL) solution of **4b** (1.86 g, 6.06 mmol) was treated with LiHMDS (14.4 mmol) to afford a crude product (1.73 g, 5.99 mmol), which was dissolved in methanol (30 mL) followed by treatment with $NaBH_4$ (1.49 g, 39.4 mmol) in a small portion over 15 min. The crude product obtained was purified by column chromatography (SiO_2, 2% MeOH in EtOAc containing 0.15% NH_4OH solution) to afford two separated diastereomers of **6aA** and **6aB**.

F_1 (less polar) was obtained as a yellow solid of **6aA** [0.72 g, 41% yield; mp 66–68 °C (EtOAc)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.21 (m, 5H), 3.09 (dt, J=8.4, 1.1 Hz, 1H), 2.91–2.78 (m, 1H), 2.23–2.04 (m, 2H), 1.85–1.58 (m, 5H), 1.50–1.30 (m, 2H), 1.28–0.90 (m, 6H), 0.68 (t, J=7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.8, 130.2, 128.9 (2C), 124.2 (2C), 66.8, 66.4, 63.9, 50.5, 36.3, 29.7, 27.6, 24.9, 18.6, 17.6, 14.4. IR (Nujol): ν_{max} 2778 (s), 1441 (s), 1047 (s), 751 (s) cm^{-1}. MS: *m/z* (%) relative intensity 292 (M^++1, 5), 274 (83), 164 (34), 124 (60), 122 (100).

F_2 (more polar) was obtained as a yellow solid of **6aB** [0.60 g, 34% yield; mp 81–83 °C (EtOAc)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.33 (m, 5H), 3.02–2.89 (m, 3H), 2.85 (dt, J=8.6, 2.5 Hz, 1H), 2.55 (q, J=8.0 Hz, 1H), 2.38–2.23 (m, 1H), 1.96–1.55 (m, 4H), 1.53–1.00 (m, 7H), 0.83 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 130.3, 128.8 (2C), 124.1 (2C), 65.9, 56.9, 55.1, 48.1, 26.9, 26.2, 25.7, 20.6, 19.1, 17.5, 14.2. IR (Nujol): ν_{max} 2780 (m), 1582 (w), 1457 (m), 1441 (m), 1041 (s), 748 (m) cm^{-1}. MS: *m/z* (%) relative intensity 292 (M^++1, 21), 274 (75), 122 (100), 96 (21). HRMS (ESI): calcd for $C_{17}H_{25}NONaS$, 314.1555; found, 314.1549.

*4.3.3.6. 1-Phenylsulfinyl-5-hexyl-1,2,3,5,6,7,8,9-octahydroindolizine (**6b**).* According to the general procedure described for **5**, the reaction of LiHMDS (15.4 mmol) in THF (77 mL) with a THF (14 mL) solution of **4c** (2.42 g, 6.93 mmol) gave a viscous liquid of a crude product (2.20 g, 6.65 mmol). The crude product obtained was dissolved in MeOH (34 mL) and treated with $NaBH_4$ (1.62 g, 42.63 mmol). After the usual work-up, the crude product was purified by column chromatography (SiO_2, 2% MeOH in EtOAc containing 0.15%

NH_4OH solution) to afford two separated diastereomers **6bA** and **6bB**.

F_1 (less polar) was obtained as a yellow solid of **6bA** [1.08 g, 47% yield; mp 54–56 °C (EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 7.59–7.37 (m, 5H), 3.09 (t, J=8.2 Hz, 1H), 3.05 (ddd, J=9.3, 7.7, 6.0 Hz, 1H), 2.42–2.26 (m, 2H), 2.04–1.79 (m, 5H), 1.72–1.52 (m, 2H), 1.47–1.10 (m, 12H), 0.88 (t, J=6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 130.3, 128.9 (2C), 124.2 (2C), 66.8, 66.4, 64.2, 50.6, 34.0, 31.7, 29.8, 29.6, 27.7, 25.5, 24.9, 22.5, 17.6, 14.0. IR (Nujol): ν_{max} 2783 (s), 1441 (s), 1376 (s), 1084 (s), 1045 (s), 751 (s), 704 (s) cm^{-1}. MS: *m/z* (%) relative intensity 334 (M^++1, 1), 316 (30), 122 (100), 94 (16).

F_2 (more polar) was obtained as a yellow solid of **6bB** [1.04 g, 45% yield; mp 58–60 °C (EtOAc)]. ^1H NMR (300 MHz, $CDCl_3$): δ 7.88–7.59 (m, 5H), 3.10–2.91 (m, 3H), 2.91 (dt, J=8.6, 2.3 Hz, 1H), 2.62 (q, J=8.0 Hz, 1H), 2.47–2.24 (m, 1H), 2.03–1.63 (m, 4H), 1.60–1.06 (m, 13H), 0.88 (t, J=6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 130.3, 128.8 (2C), 124.1 (2C), 65.9, 56.9, 55.4, 48.1, 31.8, 29.5, 27.4, 27.1, 25.8, 23.5, 22.5, 19.2, 17.5, 14.0; IR (Nujol): ν_{max} 2783 (m), 1461 (m), 1039 (s), 750 (m) cm^{-1}. MS: *m/z* (%) relative intensity 334 (M^++1, 1), 316 (29), 248 (10), 123 (25), 122 (100). HRMS (ESI): calcd for $C_{20}H_{32}NOS$, 334.2205; found, 334.2209.

*4.3.3.7. (±)-Indolizidine 167B (**2a**). General procedure*. A stirred solution of **6aA** (0.21 g, 0.72 mmol) and $NiCl_2\cdot 6H_2O$ (1.56 g, 6.56 mmol) in a 1:3 mixture of THF and MeOH (6 mL) was cooled to 0 °C. $NaBH_4$ (0.79 g, 20.79 mmol) was added in small portions within 20 min at such a rate that the temperature was kept below 10 °C. The mixture was stirred at room temperature for 2 h. The black precipitate was filtered off over Celite and washed with hexanes (3×20 mL). The combined extracts were washed with H_2O and brine, and dried over anhyd Na_2SO_4. Filtration followed by concentration in vacuo gave a colorless liquid of a crude product, which was purified by column chromatography (Al_2O_3, hexanes) to afford a colorless liquid of (±)-indolizidine 167B (**2a**) (0.098 g, 82% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 3.29 (dt, J=8.7, 2.2 Hz, 1H, C_3-H_e), 1.97 (q, J=9.0 Hz, 1H, C_3-H_a), 1.93–1.09 (m, 16H), 0.91 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.6, 64.3, 52.0, 37.4, 31.5, 31.3, 31.1, 25.2, 20.9, 19.6, 15.0. IR (neat): ν_{max} 2781 (s), 1458 (m), 1129 (m), 1056 (w) cm^{-1}. MS: *m/z* (%) relative intensity 168 (M^++1, 6), 124 (100), 96 (73), 81 (21). The spectroscopic data were consistent with the literature.[7e]

*4.3.3.8. (±)-epi-Indolizidine 167B (epi-**2a**)*. According to the general procedure described for (±)-indolizidine 167B (**2a**), a reaction of **6aB** (0.28 g, 0.96 mmol), $NiCl_2\cdot 6H_2O$ (2.08 g, 8.75 mmol), and $NaBH_4$ (1.14 g, 30 mmol) in a mixture of THF (2.5 mL) and MeOH (7.5 mL) gave a pale yellow liquid of a crude product, which was purified by column chromatography (Al_2O_3, 100% hexanes) to afford a colorless liquid of *epi*-**2a** (0.118 g, 74% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 3.01–2.93 (m, 1H), 2.88 (dt, J=8.9, 3.4 Hz, 1H, C_3-H_e), 2.71 (q, J=8.2 Hz, 1H, C_3-H_a), 2.63–2.52 (m, 1H), 1.91–1.31 (m, 14H), 0.94 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.8, 55.8, 49.3, 31.5, 31.0, 28.0, 26.5, 21.4, 21.3, 19.8, 14.9; IR (neat): ν_{max} 2930 (s), 2872 (s), 2804 (m), 1457 (m) cm^{-1}. MS: *m/z* (%) relative intensity 168 (M^++1, 9), 167 (M^+, 67), 150 (26), 149 (100), 124 (40), 122 (38), 96 (31), 55 (25). The spectroscopic data were consistent with the literature.[7e]

*4.3.3.9. (±)-Indolizidine 209D (**2b**)*. According to the general procedure described for (±)-indolizidine 167B (**2a**), the reaction of **6bA** (0.23 g, 0.69 mmol), $NiCl_2\cdot 6H_2O$ (1.63 g, 6.86 mmol), and $NaBH_4$ (0.79 g, 20.79 mmol) in a mixture of THF (2 mL) and MeOH (6 mL) gave a pale yellow liquid of a crude product, which was purified by column chromatography (Al_2O_3, hexanes) to afford a colorless liquid of (±)-indolizidine 209D (**2b**) (0.116 g, 80% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 3.26 (dt, J=8.7, 2.0 Hz, 1H, C_3-H_e), 1.97 (q, J=8.8 Hz, 1H, C_3-H_a), 1.92–1.07 (m, 22H), 0.89 (app t, J=6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.6, 64.5, 52.1, 35.2, 32.4, 31.5, 31.4, 31.1, 30.3, 26.4, 25.3, 23.2, 21.0, 14.6; IR (neat): ν_{max} 2781 (s), 1457 (m), 1381 (m), 1129 (m) cm^{-1}. MS: *m/z* (%) relative intensity 210 (M^++1, 6), 149 (35), 124 (100), 96 (43). The spectroscopic data were consistent with the literature.[7e]

*4.3.3.10. (±)-epi-Indolizidine 209D (epi-**2b**)*. According to the general procedure described for (±)-indolizidine 167B (**2a**), a reaction of **6bB** (0.236 g, 0.71 mmol), $NiCl_2\cdot 6H_2O$ (1.64 g, 6.90 mmol), and $NaBH_4$ (0.79 g, 20.79 mmol) in a mixture of THF (2 mL) and MeOH (6 mL) gave a pale yellow liquid of a crude product, which was purified by column chromatography (Al_2O_3, 100% hexanes) to afford a colorless liquid of *epi*-**2b** (0.127 g, 86% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 2.97–2.87 (m, 1H, C_5-H), 2.82 (dt, J=8.8, 3.2 Hz, 1H, C_3-H_e), 2.64 (q, J=8.4 Hz, 1H, C_3-H_a), 2.53–2.40 (m, 1H), 1.94–1.01 (m, 20H), 0.92–0.79 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5, 55.1, 48.7, 31.9, 31.2, 30.6, 29.6, 27.6, 27.5, 23.4, 22.6, 20.8, 19.3, 14.0. IR (neat): ν_{max} 2929 (s), 2859 (s), 2804 (m), 1459 (m) cm^{-1}. MS: *m/z* (%) relative intensity 209 (M^+, 2), 149 (28), 124 (100), 96 (53). The spectroscopic data were consistent with the literature.[7e]

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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.2008.01.008.

References and notes

1. (a) Michael, J. P. *Nat. Prod. Rep.* **2000**, *17*, 579–602; (b) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520–542; (c) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458–475.
2. Ohmiya, S.; Kubo, H.; Otomatsu, H.; Saito, K.; Murakoshi, I. *Heterocycles* **1990**, *30*, 537–542.
3. For some recent syntheses of tashiromine, see: (a) Belanger, G.; Larouche-Gauthier, R.; Menard, F.; Nantel, M.; Barabe, F. *J. Org. Chem.* **2006**, *71*, 704–712; (b) McElhinney, A. D.; Marsden, S. P. *Synlett* **2005**, 2528–2530; (c) Dieter, R.; Chen, N.; Watson, R. T. *Tetrahedron* **2005**, *61*, 3221–3230; (d) Dieter, R. K.; Watson, R. T. *Tetrahedron Lett.* **2002**, *43*, 7725–7728; (e) Banwell, M. G.; Beck, D. A. S.; Smith, J. A. *Org. Biomol. Chem.* **2004**, *2*, 157–159; (f) Kim, S.-H.; Kim, S.-I.; Lai, S.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 6771–6775; (g) Bates, R. W.; Boonsombat, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 654–656; (h) David, O.; Blot, J.; Bellec, C.; Fargeau-Bellassoued, M.-C.; Haviari, G.; Celereir, J.-P.; Lhommet, G.; Gramain, J.-C.; Gardette, D. *J. Org. Chem.* **1999**, *64*, 3122–3133; (i) Gage, J. L.; Branchaud, B. P. *Tetrahedron Lett.* **1997**, *38*, 7007–7010; (j) Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 1613–1620.
4. (a) Daly, J. W.; Spande, T. F. Amphibian Alkaloids: Chemistry, Pharmacology and Biology. *Alkaloid: Chemical and Biological Perspective*; Pelletier, S. W., Ed.; Wiley: New York, NY, 1986; Vol. 4, pp 1–274; (b) Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M. *Toxicon* **1978**, *16*, 163–188; (c) Daly, J. W.; Myers, C. W.; Whittaker, N. *Toxicon* **1987**, *25*, 1023–1095.
5. (a) Michael, J. P. *Alkaloids*; Cordell, G. A., Ed.; Academic: London, 2001; Vol. 55, pp 91–258; (b) Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, T. K.; Albequerque, E. X. *Neurochem. Res.* **1986**, *11*, 1227–1240.
6. For some recent syntheses of indolizidine 167B, see: (a) Peroche, S.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron Lett.* **2001**, *42*, 4617–4619; (b) Michael, J. P.; Gravestock, D. *Pure Appl. Chem.* **1997**, *69*, 583–588; (c) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919–1928; (d) Zaminer, J.; Stapper, C.; Blechert, S. *Tetrahedron Lett.* **2002**, *43*, 6739–6741; (e) Back, T. G.; Nakajima, K. *Org. Lett.* **1999**, *1*, 261–263; (f) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C.; Canet, I. *Tetrahedron Lett.* **1999**, *40*, 1661–1664.
7. For some recent syntheses of indolizidine 209D, see: (a) Chênevert, R.; Ziarani, G. M.; Morin, M. P.; Dasser, M. *Tetrahedron: Asymmetry* **1999**, *10*, 3117–3122; (b) Comins, D. L.; Zhang, Y.-M. *J. Am. Chem. Soc.* **1996**, *118*, 12248–12249; (c) Takahata, H.; Kubota, M.; Ihara, K.; Okamoto, N.; Momose, T.; Azer, N.; Eldefrawi, A. T.; Eldefrawi, M. E. *Tetrahedron: Asymmetry* **1998**, *9*, 3289–3301; (d) Kim, G.; Jung, S.-D.; Kim, W.-J. *Org. Lett.* **2001**, *3*, 2985–2987; (e) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688–4693; (f) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543–4552.
8. Pohmakotr, M.; Numechai, P.; Prateeptongkum, S.; Tuchinda, P.; Reutrakul, V. *Org. Biomol. Chem.* **2003**, *1*, 3495–3497.
9. Fleurant, A.; Saliou, C.; Célérier, P.; Platzer, N.; Moc, T. V.; Lhommet, G. *J. Heterocycl. Chem.* **1995**, *32*, 255–258.
10. Hamlow, H. P.; Okuda, S.; Nakagawa, N. *Tetrahedron Lett.* **1964**, 2553–2559 and references cited.
11. (a) Euerby, M. R.; Waigh, R. D. *Synth. Commun.* **1986**, *16*, 779–784; (b) Back, T. G.; Yang, K.; Krouse, H. R. *J. Org. Chem.* **1992**, *57*, 1986–1993.
12. Keith, W. R.; Metz, S.; Moore, W. M.; Connor, J. R.; Currie, M. G.; Fok, K. F.; Hagen, T. J.; Hansen, D. W., Jr.; Jerome, G. M.; Manning, P. T.; Pitzele, B. S.; Toth, M. V.; Trivedi, M.; Zupec, M. E.; Tjoeng, F. S. *J. Med. Chem.* **1998**, *41*, 96–101.