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Synthesis of alkylated indolizidine alkaloids via Pummerer mediated cyclization: synthesis of (±)-indolizidine 167B, (±)-5-butylindolizidine and (±)-monomorine I

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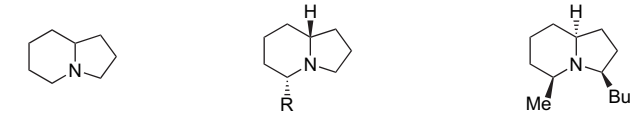
Abstract

The syntheses of indolizidine alkaloids, i.e., (±)-coniceine, (±)-indolizidine 167B, (±)-5-butylindolizidine and (±)-monomorine I via Pummerer cyclization are described. The key step is the transformation of lactam sulfoxide to bicyclic lactam via the Pummerer cyclization.

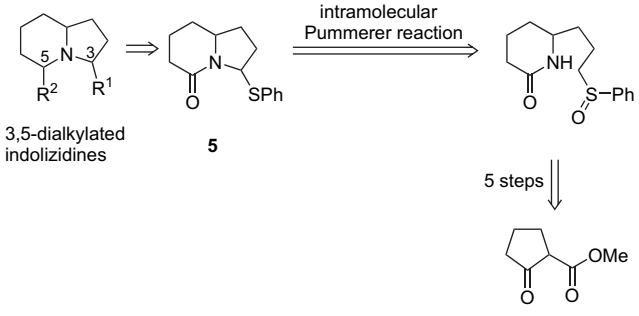
1. Introduction

Indolizidine alkaloids have become important targets for the synthesis in the past few decades due to their vast array of structural diversity and biological activity.[1] A considerable number of synthetic strategies, both racemic and enantioselective syntheses, have been developed for the preparation of substituted indolizidines.[2,3] As witnessed by several review papers, Pummerer-based reaction is a powerful methodology and has been widely used as a key step for the synthesis of nitrogen heterocycles.[4] Our ongoing research interest in sulfur chemistry led us to investigate the Pummerer cyclization as an alternative route to indolizidine alkaloids, i.e., (±)-coniceine (**1**), (±)-indolizidine 167B (**2**), (±)-5-butylindolizidine (**3**) and (±)-monomorine I (**4**) (Scheme 1).

We envisioned the lactam sulfide **5** as a key intermediate leading to 3,5-alkylated indolizidine derivatives. The construction of the bicyclic sulfide **5** should be achieved by the intramolecular Pummerer cyclization of the lactam sulfoxide **6** which, in turn, could be synthesized via a five-step sequence starting from the commercially available methyl 2-oxocyclopentanecarboxylate (Scheme 2).



Scheme 1. Indolizidine alkaloids.



Scheme 2. Synthetic strategy.

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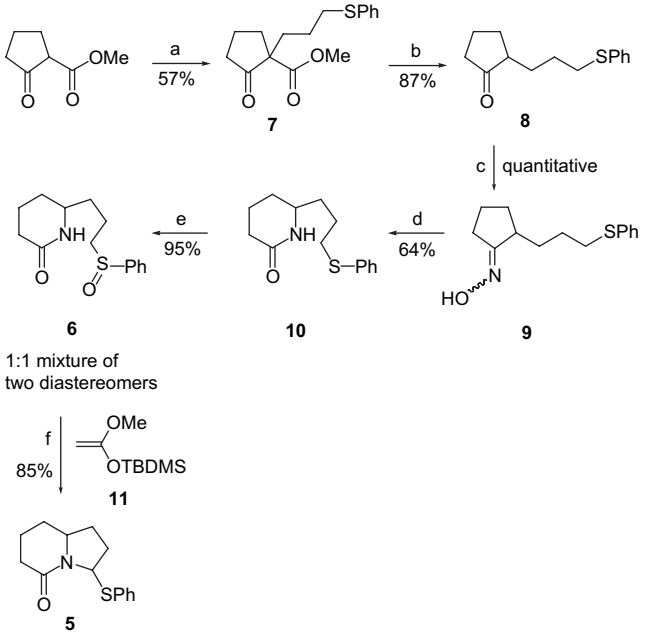
2. Results and discussion

The synthesis of the lactam sulfoxide **6** is outlined in Scheme 3. Alkylation of methyl 2-oxocyclopentanecarboxylate using sodium hydride with 1,3-dibromopropane followed by the reaction with thiophenol in the presence of triethylamine afforded β-ketoester **7**.[5] Krapcho decarboxylation of β-ketoester **7** with NaCN in refluxing DMSO afforded ketosulfide **8** in high yield.[6] The ketosulfide **8** was transformed quantitatively to oxime **9** as a single isomer (^{13}C NMR analysis) by the treatment with hydroxylamine hydrochloride and sodium acetate in aqueous ethanol. Beckmann rearrangement gave lactam sulfide **10** which could be converted to lactam sulfoxide **6** employing $NaIO_4$ in aqueous MeOH. The lactam sulfoxide **6** was obtained as a 1:1 mixture of two diastereomers (^{13}C NMR analysis).



Scheme 3. Reagents and conditions: (a) (i) NaH (1.2 equiv), DMF, 1,3-dibromopropane (3 equiv), rt, 20 h; (ii) PhSH (1.05 equiv), Et_3N (1.25 equiv), THF, 0 °C to rt, 24 h; (b) NaCN (1.2 equiv), DMSO, 160 °C, 3 h; (c) $NH_2OH\cdot HCl$ (1.2 equiv), NaOAc (1.73 equiv), aq EtOH; (d) 1 N NaOH (1.1 equiv), $PhSO_2Cl$ (1.1 equiv), acetone, rt, 24 h; (e) $NaIO_4$ (1.15 equiv), aq MeOH, 0 °C to rt, 24 h; (f) ZnI_2 (10 mol %), **11** (2 equiv), CH_3CN, rt, 24 h.

Having successfully prepared the lactam sulfoxide **6**, we then explored the ring closure to form a fused bicyclic lactam **5** based upon the Pummerer reaction. Pummerer reaction using trifluoroacetic anhydride in acetonitrile or TMSOTf/Et_3N in CH_2Cl_2 gave the desired lactam sulfide **5** in low yield. Gratifyingly, a satisfactory result was obtained using silicon-induced Pummerer reaction first reported by Kita employing an *O*-silylated ketene acetal.[7,8] Treatment of lactam sulfoxide **6** with 2.0 equiv of *O*-silylated ketene acetal **11** in the presence of a catalytic amount of zinc iodide (10 mol %) in dry CH_3CN at room temperature for 24 h afforded lactam sulfide **5** in high yield (85%) (Scheme 3).

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR analyses showed that the lactam sulfide **5** was obtained as a mixture of two

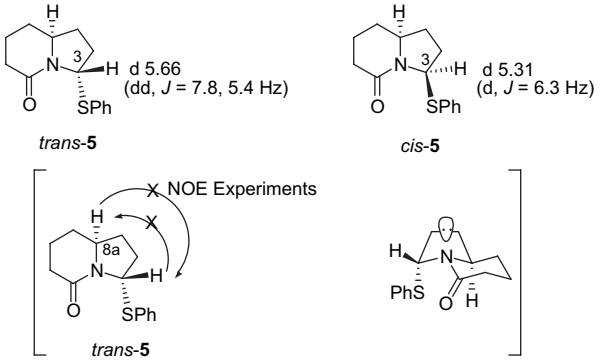
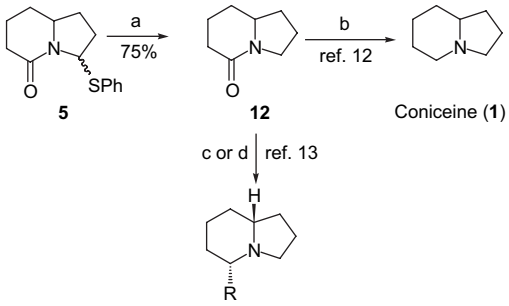


Figure 1. Relative stereochemistry of lactam sulfide **5**.

diastereomers (trans/cis=5:1) (Fig. 1). The H-3 signal of the *trans*-**5** appeared as a doublet of doublets at δ 5.66 (J=7.8 and 5.4 Hz) whereas that of the *cis*-**5** exhibited as a doublet at δ 5.31 with J=6.3 Hz (Fig. 1). The H-3 (equatorial, δ 5.66 ppm) of *trans*-**5** appeared at lower field than H-3 (axial, δ 5.31 ppm) of the *cis*-**5**. This can be explained by a strong deshielding effect by the lone pair electrons of the proximate nitrogen atom.[9] The relative stereochemistry of *trans*-**5** could also be confirmed by NOE experiments as shown in Figure 1. No enhancement in the signal of H-8a was observed when H-3 was irradiated, and vice versa. Desulfurization by treatment of lactam sulfide **5** with tri-*n*-butyltin hydride and AIBN in refluxing toluene furnished bicyclic lactam **12** in good yield (Scheme 4).[10] It is worth mentioning that the known bicyclic lactam **12** was previously synthesized via different routes.[11] Its spectral characteristics are identical to those reported in the literature.[11a,b]

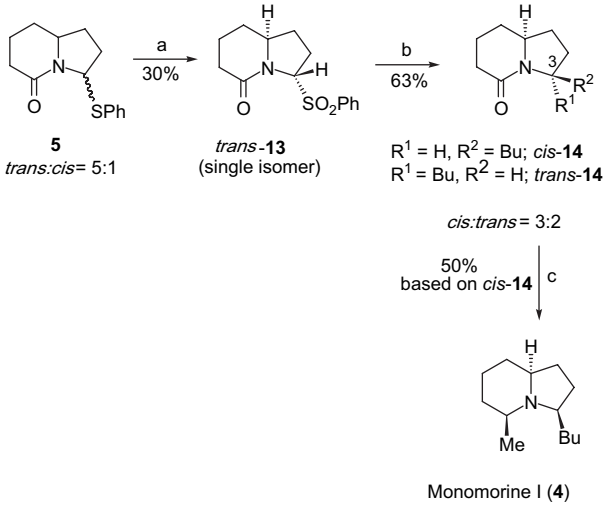


Scheme 4. Synthesis of indolizidine alkaloids **1**–**3**. Reagents and conditions: (a) *n*-Bu_3SnH (2.5 equiv), AIBN (0.3 equiv), toluene, reflux 20 h; (b) $LiAlH_4$ (2.54 equiv), THF, reflux 15 h; (c) (i) *n*-PrMgBr (3 equiv), THF, 0 °C to rt, 4 h; (ii) AcOH then $NaBH_4$ (2 equiv), 0 °C, 1 h; (d) (i) *n*-BuMgCl (3 equiv), THF, 0 °C to rt, 4 h; (ii) AcOH then $NaBH_4$ (2 equiv), 0 °C, 1 h.

The bicyclic lactam **12** was readily transformed to (±)-coniceine (**1**),[12] (±)-indolizidine 167B (**2**)[13] and (±)-5-butylindolizidine (**3**)[13] by following the previously reported procedures (Scheme 4). The spectral data (^{1}H and ^{13}C NMR) of the synthesized **1**[11a,14] and **2**[15] were completely identical to those reported in the literature. The relative stereochemistry of **3** was assigned by comparison with the spectral data of **2**. It is worth mentioning that the relative stereochemical outcome of **2** and **3**

was predicted based on the stereoelectronic principles of Stevens.[16] In addition, compounds **1**, **2** and **3** also exhibited Bohlmann peaks at 2780, 2782 and 2781 cm^{-1}, respectively, in their IR spectra.

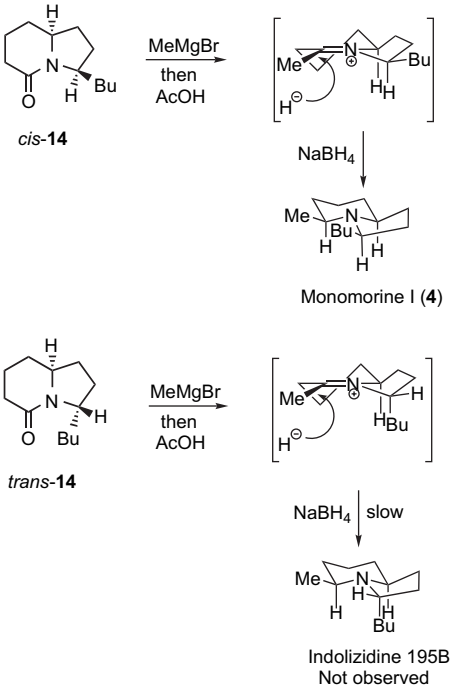
To further demonstrate the synthetic utility of the key intermediate lactam sulfide **5**, the synthesis of (±)-monomorine I (**4**) was undertaken (Scheme 5). It was planned to install the butyl substituent of monomorine I using Ley's protocol.[17] Therefore, treatment of lactam sulfide **5** using *m*-CPBA in CH_2Cl_2 yielded the corresponding sulfone **13** as a single diastereomer (trans) after column chromatography followed by crystallization. The sulfone **13** was treated with the butyl organometallic reagent prepared from *n*-butylmagnesium chloride and zinc chloride to yield alkylated lactam **14** which consists of two inseparable diastereomers (cis/trans=3:2) as determined by ^{1}H NMR (500 MHz) analysis. The relative stereochemistry of **14** was assigned by comparison with the ^{13}C NMR spectrum of the known *cis*-**14**, which was reported by Jones and co-workers.[18] The H-3 proton of *cis*-**14** appeared as a triplet at δ 3.96 ppm (J=7.6 Hz), which corresponded well with the value reported by Jones and co-workers (δ 3.94 ppm, multiplet).[18] The H-3 proton of *trans*-**14** exhibited a multiplet between δ 4.12 and 4.04 ppm. According to the published procedure, treatment of **14** (3:2 mixture of cis/trans) with methylmagnesium bromide followed by acidification and $NaBH_4$ reduction gave the desired (±)-monomorine I (**4**) as a single isomer in 50% yield (based on *cis*-**14**) as shown in Scheme 5.[2c] It should be emphasized that the other possible product, (±)-indolizidine 195B derived from the reaction of *trans*-**14** was not isolated. In addition, ^{1}H NMR of the crude material also did not show, to significant degree, the presence of a multiplet signal at δ 3.31–3.26 (1H) belonging to (±)-indolizidine 195B.[19] This could be attributed to a slower rate of reduction of the iminium ion intermediate due to steric hindrance from the *n*-butyl substituent at the pseudoaxial position. The unreacted iminium ion was believed to undergo



5
trans:cis = 5:1

trans-**13**
(single isomer)

Scheme 5. Synthesis of (±)-monomorine I (**4**). Reagents and conditions: (a) *m*-CPBA (2.1 equiv), CH_2Cl_2, 0 °C to rt, 16 h; (b) *n*-BuMgCl (2 equiv), $ZnCl_2$ (1.2 equiv), CH_2Cl_2, 0 °C to rt, 24 h; (c) (i) MeMgBr (3.5 equiv), THF, reflux, 5 h; (ii) AcOH then $NaBH_4$ (11.6 equiv), 0 °C, 2 h.



Scheme 6.

hydrolysis during aqueous work-up, leading to water soluble salt. The stereochemical outcome of this reaction could be explained based on the stereoelectronic principles of Stevens.[16] Thus, addition of methylmagnesium bromide followed by acidification afforded an iminium ion intermediate, which was reduced from the pseudoaxial direction to give the target (±)-monomorine I (**4**) as a single isomer (Scheme 6). The spectral data (^{1}H and ^{13}C NMR) of (±)-monomorine I (**4**) were identical to those reported in the literature.[19]

3. Conclusion

We have described an alternative route for the preparation of 3-alkyl- and 3,5-dialkylindolizidines. The synthesis was achieved starting from the commercially available methyl 2-oxocyclopentanecarboxylate by the exploitation of silicon-induced Pummerer reaction as the key step to form the key precursor lactam sulfide **5** (six steps, 26%). Transformation of the lactam sulfide **5** to (±)-coniceine (**1**), (±)-indolizidine 167B (**2**), (±)-5-butylindolizidine (**3**) and (±)-monomorine I (**4**) was carried out according to the existing procedures.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 (300 MHz) or a Bruker AV-500 (500 MHz) spectrometer using $CDCl_3$ as a solvent with tetramethylsilane as an internal standard. Chemical shifts (δ) reported are given in parts per million (ppm) and the coupling constants (J) are in hertz (Hz). Melting points were determined on electrothermal

melting point apparatus (Electrothermal 9100) and were uncorrected. The IR spectra were recorded on a Jasco A-302 spectrometer or a Perkin Elmer 683 Infrared spectrometer. The EI mass spectra were recorded by using a Thermo Finnigan Polaris Q mass spectrometer. The high-resolution mass spectra (HRMS) were recorded on a Bruker Esquire apparatus. Elemental analyses were performed by a Perkin Elmer Elemental Analyzer 2400 CHN. Column chromatography was performed using silica gel 60 (70–230 mesh). Preparative thin layer chromatography (PLC) was performed with silica gel 60 PF_{254}. Analytical TLC was performed with silica gel 60 PF_{254} aluminium sheet with 0.2 mm layer of silica gel. The plates of radial chromatography were prepared by using silica gel 60 PF_{254} with $CaSO_4 \cdot 1/2H_2O$.

4.2. Methyl 1-(3-phenylsulfanylpropyl)-2-oxocyclopentanecarboxylate (7)

To a suspension of NaH (6.28 g, 144.0 mmol; 55–65% suspension in mineral oil) in DMF (100 mL), methyl 2-oxocyclopentanecarboxylate (15.2 mL, 120.0 mmol) was slowly added at room temperature under an argon atmosphere. The reaction mixture was further stirred until the evolution of hydrogen gas ceased (2 h) before 1,3-dibromopropane (36 mL, 360.0 mmol) was added. After the reaction mixture was stirred at room temperature for 20 h, it was poured into ice-water and extracted with hexanes (4×200 mL). The combined organic layers were washed with water (2×100 mL), brine (2×100 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated and distilled under reduced pressure to remove the unreacted 1,3-dibromopropane (32 °C, 0.8 mmHg). The resulting bromide was obtained as an orange liquid (27.78 g, ca. 105.6 mmol), which was used in the next step without further purification. Thiophenol (11.3 mL, 110.0 mmol) was added dropwise at 0 °C to a solution of Et_3N (18.4 mL, 132.0 mmol) in THF (340 mL) under an argon atmosphere. The resulting mixture was stirred at 0 °C for 0.5 h. To this mixture, was slowly added a solution of crude bromide (27.78 g, ca. 105.6 mmol) in THF (60 mL). After being stirred and slowly warmed up to room temperature for 24 h, the reaction mixture was diluted with water (100 mL) and extracted with hexanes (4×100 mL). The combined organic layers were washed with brine (100 mL), water (100 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude yellow liquid, which was purified by column chromatography on silica gel (30×8.0 cm, 1:4 ethyl acetate/hexanes eluent) to provide **7** (19.87 g, 57% yield) as a pale yellow liquid: analytical TLC on silica gel, 1:4 ethyl acetate/hexanes, R_f=0.25. IR (neat): ν_{max} 2953 (C–H), 1750 (C=O, ester), 1725 (C=O, ketone) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.32–7.26 (4H, m), 7.19–7.15 (1H, m), 3.67 (3H, s), 2.95–2.85 (2H, m), 2.53–2.48 (1H, m), 2.40 (1H, ddd, J=18.9, 8.7, 5.4 Hz), 2.25 (1H, dt, J=18.9, 8.4 Hz), 2.11–1.50 (7H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.3, 171.2, 136.3, 129.2, 128.8, 125.9, 60.1, 52.4, 37.7, 33.8, 32.9, 32.8, 24.5, 19.5. MS (EI): *m/z* (%) relative intensity 293 (M^++1, 29), 292 (M^+, 25), 215 (100), 183 (35), 123 (62), 109 (7), 106 (16), 95 (11), 81 (10), 79 (7), 67 (12). Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.72; H, 6.89. Found: C, 65.83; H, 6.75.

4.3. 2-(3-Phenylsulfanylpropyl)cyclopentanone (8)

A mixture of methyl 1-(3-phenylsulfanylpropyl)-2-oxocyclopentanecarboxylate (**7**) (5.84 g, 20.0 mmol), sodium cyanide (1.18 g, 24.0 mmol) and DMSO (40 mL) was stirred at 160 °C for 3 h under an argon atmosphere. After cooling, the reaction mixture was poured into ice-water and extracted with hexanes (4×100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated (in vacuo). The residue was purified by column chromatography on silica gel (25×3.5 cm, 1:3 ethyl acetate/hexanes eluent) to afford **8** (4.07 g, 87% yield) as colourless oil: analytical TLC on silica gel, 1:3 ethyl acetate/hexanes, R_f=0.38. IR (neat): ν_{max} 2938 (C–H), 1736 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.22 (4H, m), 7.19–7.14 (1H, m), 2.99–2.84 (2H, m), 2.35–1.65 (9H, m), 1.55–1.34 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 220.8, 136.5, 128.97, 128.8, 125.7, 48.6, 38.0, 33.5, 29.5, 28.8, 27.1, 20.6. MS (EI): *m/z* (%) relative intensity 235 (M^++1, 31), 234 (M^+, 45), 125 (100), 110 (8), 95 (10), 79 (7), 67 (6), 55 (7). Anal. Calcd for $C_{14}H_{18}OS$: C, 71.75; H, 7.74. Found: C, 71.55; H, 7.94.

4.4. 2-(3-Phenylsulfanylpropyl)cyclopentanone oxime (9)

A solution of 2-(3-phenylsulfanylpropyl)cyclopentanone (**8**) (3.78 g, 16.18 mmol) in EtOH (30.0 mL) was added to a solution of hydroxylamine hydrochloride (1.35 g, 19.42 mmol) and sodium acetate (2.30 g, 27.96 mmol) in water (20.0 mL). This mixture was stirred for 4 h at reflux and then for 18 h at room temperature. The reaction mixture was evaporated to remove EtOH, extracted with ethyl acetate (3×100 mL), washed with brine (50 mL), dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent left thick oil, which was crystallized from ethyl acetate/hexanes, yielding **9** (4.03 g, quantitatively) as a white solid: analytical TLC on silica gel, 1:4 ethyl acetate/hexanes, R_f=0.28, mp=79–81 °C. IR (KBr): ν_{max} 3261 (O–H), 2952 (C–H) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.24 (4H, m), 7.18–7.13 (1H, m), 6.50–5.50 (1H, br), 2.98–2.85 (2H, m), 2.63–2.34 (2H, m), 2.10–1.30 (9H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 136.7, 129.0, 128.8, 125.7, 42.7, 33.6, 31.6, 31.3, 27.3, 27.1, 22.4. MS (EI): *m/z* (%) relative intensity 250 (M^++1, 14), 233 (16), 232 (83), 149 (29), 140 (10), 123 (19), 122 (36), 109 (7), 105 (8), 97 (100), 94 (11), 79 (11), 77 (8), 67 (6), 65 (6). Anal. Calcd for $C_{14}H_{19}NOS$: C, 67.43; H, 7.68; N, 5.62. Found: C, 67.58; H, 7.63; N, 5.36.

4.5. 6-(3-Phenylsulfanylpropyl)piperidin-2-one (10)

A solution of 2-(3-phenylsulfanylpropyl)cyclopentanone oxime (**9**) (0.75 g, 3.0 mmol) in acetone (7.0 mL) was treated with 1 N NaOH (3.3 mL, 3.3 mmol) at 0 °C. To this stirred mixture was added benzenesulfonyl chloride (0.42 mL,

3.3 mmol) dropwise, and the resulting mixture was stirred at room temperature (24 h). The reaction mixture was poured into water and extracted with ethyl acetate (3×50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to afford crude mixture as yellow oil. The crude material was purified by column chromatography on silica gel (30×4.0 cm, 1% MeOH/CH_2Cl_2 eluent) to afford **10** (0.48 g, 64% yield) as a white solid: analytical TLC on silica gel, 2% MeOH/CH_2Cl_2, R_f=0.34, mp=106–108 °C. IR (KBr): ν_{max} 3194 (N–H), 2950 (C–H), 1663 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.26 (4H, m), 7.21–7.16 (1H, m), 6.48 (1H, br s), 3.37 (1H, br m), 2.93 (2H, t, J=6.0 Hz), 2.42–2.22 (2H, m), 1.90–1.87 (2H, m), 1.73–1.60 (5H, m), 1.39–1.25 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 136.0, 129.3, 128.9, 126.1, 52.8, 35.7, 33.5, 31.0, 28.0, 24.9, 19.4. MS (EI): *m/z* (%) relative intensity 250 (M^++1, 19), 249 (M^+, 21), 216 (22), 185 (16), 174 (26), 141 (10), 140 (100), 135 (17), 126 (35), 113 (22), 112 (40), 98 (54), 96 (25), 84 (14), 83 (18), 82 (34), 79 (5), 77 (6), 71 (32), 55 (31). Anal. Calcd for $C_{14}H_{19}NOS$: C, 67.43; H, 7.68; N, 5.62. Found: C, 67.56; H, 7.82; N, 5.52.

4.6. 6-(3-Benzenesulfinylpropyl)piperidin-2-one (*6*)

A solution of 6-(3-phenylsulfanylpropyl)piperidin-2-one (**10**) (1.37 g, 5.50 mmol) in MeOH (25 mL) was slowly added at 0 °C to a solution of $NaIO_4$ (1.35 g, 6.33 mmol) in water (15 mL). The mixture was stirred vigorously and slowly warmed up to room temperature for 20 h. The white precipitates of $NaIO_3$ were filtered and washed several times with CH_2Cl_2. The filtrate was diluted with water and extracted with CH_2Cl_2 (3×100 mL). The combined extracts were washed with water (50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by radial chromatography (chromatotron; 2 mm plate, gradient 0–10% MeOH/ethyl acetate eluent) to provide a white solid of **6** (1.39 g, 95% yield) as a 1:1 mixture of two diastereomers: analytical TLC on silica gel, 5% MeOH/$CHCl_3$, R_f=0.26, mp=115.0–115.2 °C. IR (KBr): ν_{max} 3204 (N–H), 2940 (C–H), 1660 (C=O), 1480, 1447, 1409, 1301, 1145, 1088, 1036 (S=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.64–7.60 (2×2H, m, Ar*H*), 7.56–7.49 (2×3H, m, Ar*H*), 6.79 (1H, br s, –CON*H*), 6.73 (1H, br s, –CON*H*), 3.44–3.33 (2×1H, br m, CONHC*H*–), 2.87–2.75 (2×2H, m, –CH_2SOPh), 2.41–2.32 (2×1H, m, –CH_2–), 2.31–2.23 (2×1H, m, –CH_2–), 1.93–1.78 (2×3H, m, –CH_2–), 1.76–1.50 (2×4H, m, –CH_2–), 1.40–1.29 (2×1H, m, –CH_2–). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.65 (*C*=O), 172.59 (*C*=O), 143.6 (*C*), 143.5 (*C*), 131.05 (*C*H), 131.0 (*C*H), 129.2 (4×*C*H), 123.9 (4×*C*H), 56.6 (*C*H_2), 56.4 (*C*H_2), 52.63 (*C*H), 52.57 (*C*H), 35.64 (*C*H_2), 35.58 (*C*H_2), 31.1 (2×*C*H_2), 27.83 (*C*H_2), 27.80 (*C*H_2), 19.44 (*C*H_2), 19.40 (*C*H_2), 18.1 (*C*H_2), 17.9 (*C*H_2). MS (EI): *m/z* (%) relative intensity 266 (M^++1, 7), 248 (33), 140 (67), 139 (10), 138 (82), 136 (25), 135 (12), 126 (18), 112 (14), 110 (15), 98 (27), 97 (26), 96 (100), 84 (11), 82 (18), 79 (11), 78 (25), 77 (11), 70 (24), 67 (9), 55 (38), 51 (13). Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.55; H, 7.05; N, 5.40.

4.7. 3-(Phenylsulfanyl)hexahydro-indolizin-5-one (*5*)

A solution of ZnI_2 (40 mg, 0.12 mmol) in CH_3CN (5 mL) was added to a solution of 6-(3-benzenesulfinylpropyl)piperidin-2-one (**6**) (0.253 g, 0.952 mmol) in CH_3CN (20 mL) at room temperature under an argon atmosphere. Subsequently, *tert*-butyl-1-(methoxyvinyloxy)dimethylsilane (0.42 mL, 1.91 mmol) was added to the reaction mixture. The solution was stirred at room temperature for 24 h before it was quenched by the addition of a saturated $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by radial chromatography (chromatotron; 1 mm plate, gradient 20–50% ethyl acetate/hexanes eluent) to provide **5** (0.200 g, 85% yield, trans/cis=5:1 determined by ^1H NMR) as a colourless oil: analytical TLC on silica gel, 3:2 ethyl acetate/hexanes, R_f=0.30. IR ($CHCl_3$): ν_{max} 3003 (C–H), 1635 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, minor isomer marked*): δ 7.58–7.50 (4H, m, *o*-Ar*H* of major and minor isomers), 7.33–7.25 (6H, m, *m*- and *p*-Ar*H* of major and minor isomers), 5.66 (1H, dd, J=7.8, 5.4 Hz, C_3–*H*), 5.31* (1H, d, J=6.3 Hz, C_3–*H*), 3.45–3.34 (2H, m, C_{8a}–*H* of major and minor isomers), 2.49–2.38 (2H, m, C_6–*H* of major and minor isomers), 2.37–2.19 (4H, m, C_2–*H* and C_6–*H* of major and minor isomers), 2.15–2.02 (4H, m, C_1–*H* and C_8–*H* of major and minor isomers), 2.00–1.82 (4H, m, C_2–*H* and C_7–*H* of major and minor isomers), 1.69–1.53 (2H, m, C_7–*H* of major and minor isomers), 1.45–1.37 (2H, m, C_1–*H* of major and minor isomers), 1.32* (1H, qd, J=12.1, 4.6 Hz, C_8–*H*), 1.22 (1H, qd, J=12.5, 3.0 Hz, C_8–*H*). ^{13}C NMR (125 MHz, $CDCl_3$, minor isomer marked*): δ 169.7*, 168.3 (C=O), 134.8, 134.1* (2×*C*H, C-2′ and C-6′), 132.8, 131.2* (*C*, C-1′), 128.8*, 128.7 (2×*C*H, C-3′ and C-5′), 128.1, 127.8* (CH, C-4′), 65.1*, 63.0 (*C*H, C-3), 60.1*, 58.1 (*C*H, C-8a), 32.6*, 32.0 (*C*H_2, C-1), 31.5, 31.4* (*C*H_2, C-6), 30.5, 30.3* (*C*H_2, C-2), 29.3, 29.0* (*C*H_2, C-8), 20.9*, 20.5 (*C*H_2, C-7). MS (EI): *m/z* (%) relative intensity 248 (M^++1, 35), 247 (M^+, 2), 139 (10), 138 (M^+–SPh, 100), 120 (7), 111 (7), 110 (18), 96 (14), 82 (11), 67 (5). Anal. Calcd for $C_{14}H_{17}NOS$: C, 67.98; H, 6.93; N, 5.66. Found: C, 67.58; H, 6.64; N, 5.32. HRMS (ESI) calcd for $C_{14}H_{18}NOS$ $[M+H]^+$: 248.1109; found: 248.1107.

4.8. 5-Oxoindolizidine (*12*)

3-(Phenylsulfanyl)hexahydro-indolizin-5-one (**5**) (0.978 g, 3.95 mmol) was dissolved in toluene (15 mL) and tri-*n*-butyltin hydride (2.83 mL, 9.88 mmol) was added. Subsequently, a solution of azo(bis)isobutyronitrile (0.195 g, 1.19 mmol) in toluene (5 mL) was added to the reaction mixture. The resulting mixture was refluxed at 120 °C (20 h). After cooling to room temperature, toluene was removed in vacuo and the

residue was dissolved in acetonitrile (100 mL). This solution was washed with hexanes (4×30 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography on silica gel (20×2.5 cm, 2% MeOH/CH_2Cl_2 eluent) to afford **12** (0.410 g, 75% yield) as a colourless oil: analytical TLC on silica gel, 2% MeOH/CH_2Cl_2, R_f=0.21. IR (neat): ν_{max} 1635 (C=O) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.63–3.50 (1H, m), 3.50–3.30 (2H, m), 2.50–2.20 (2H, m), 2.16–2.03 (2H, m), 2.00–1.83 (2H, m), 1.82–1.55 (2H, m), 1.50–1.15 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 59.2, 44.7, 33.4, 30.8, 29.0, 22.0, 21.0. MS (EI): *m/z* (%) relative intensity 141 (M^++2, 28), 139 (M^+, 54), 111 (54), 105 (28), 99 (49), 97 (61), 85 (48), 83 (55), 81 (55), 71 (82), 69 (49), 67 (48), 57 (100), 55 (58). HRMS (ESI) calcd for $C_8H_{13}NONa$ $[M+Na]^+$: 162.0895; found: 162.0925. The spectral characteristics (^1H and ^{13}C NMR) of **12** are identical with those reported in the literature.[11a,b]

4.9. (±)-Indolizidine 167B (*2*)

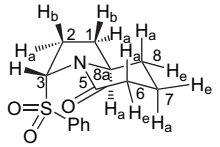
5-Oxoindolizidine (**12**) (0.182 g, 1.31 mmol) was dissolved in dry THF (4.0 mL) and the solution was brought to 0 °C (ice-bath). To this solution, was slowly added *n*-propylmagnesium bromide (2.0 mL of a 2.0 M solution in THF, 4.0 mmol). The reaction mixture was warmed to room temperature and further stirred for additional 4 h. The reaction mixture was cooled to 0 °C (ice-water bath) and glacial acetic acid (0.4 mL) was added, followed by $NaBH_4$ (0.100 g, 2.62 mmol). The ice-bath was removed and the mixture was stirred for 1 h. Subsequently, diethyl ether (20 mL) was added and the solution was washed with 7.5% KOH (10 mL). The aqueous layer was extracted with diethyl ether (20 mL), and the combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography on Al_2O_3 (type 507 C neutral, 8×0.7 cm, 1:6 diethyl ether/hexanes eluent) to afford (±)-indolizidine 167B (**2**) (0.072 g, 33% yield) as a colourless oil: IR (neat): ν_{max} 2957 (C–H), 2857, 2782 (Bohlmann band), 2710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.20 (1H, td, *J*=8.6, 2.2 Hz), 1.90 (1H, q, *J*=8.9 Hz), 1.82–1.48 (9H, m), 1.45–1.00 (7H, m), 0.84 (3H, t, *J*=7.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 65.0, 63.7, 51.6, 36.9, 31.1, 30.9, 30.6, 24.7, 20.4, 19.1, 14.5. MS (EI): *m/z* (%) relative intensity 168 (M^++1, 5), 167 (M^+, 49), 166 (5), 150 (11), 149 (10), 125 (8), 124 (100), 121 (6), 97 (5), 95 (6), 83 (6), 81 (7), 71 (8), 57 (7). The spectral characteristics (^1H and ^{13}C NMR) of (±)-indolizidine 167B (**2**) are identical with those reported in the literature.[15]

4.10. (±)-5-Butylindolizidine (*3*)

5-Oxoindolizidine (**12**) (0.091 g, 0.654 mmol) was dissolved in dry THF (2.0 mL) and the solution was brought to 0 °C (ice-bath). To this solution, was slowly added *n*-butylmagnesium chloride (1.0 mL of a 2.0 M solution in THF, 2.0 mmol). The reaction mixture was warmed to room temperature and further stirred for additional 4 h. The reaction mixture was cooled to 0 °C (ice-water bath) and glacial acetic acid (0.2 mL) was added, followed by $NaBH_4$ (0.050 g, 1.31 mmol). The ice-bath was removed and the mixture was stirred for 1 h. Subsequently, diethyl ether (40 mL) was added and the solution was washed with 7.5% KOH (20 mL). The aqueous layer was extracted with diethyl ether (40 mL), and the combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography on Al_2O_3 (type 507 C neutral, 8×0.7 cm, 1:6 diethyl ether/hexanes eluent) to afford **3** (0.060 g, 51% yield) as a colourless oil: IR (neat): ν_{max} 2932 (C–H), 2860, 2781 (Bohlmann band), 2709, 1457 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.20 (1H, td, *J*=8.6, 1.9 Hz), 1.90 (1H, q, *J*=8.9 Hz), 1.81–1.52 (9H, m), 1.43–1.01 (9H, m), 0.83 (3H, t, *J*=6.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 65.2, 63.9, 51.4, 34.1, 30.7, 30.6, 30.4, 28.0, 24.6, 23.0, 20.3, 14.0. MS (EI): *m/z* (%) relative intensity 182 (M^++1, 1), 181 (M^+, 3), 180 (18), 149 (2), 138 (3), 125 (10), 124 (100), 122 (4), 97 (2), 96 (20), 94 (2), 81 (2), 79 (2), 77 (1), 67 (2). HRMS (ESI) calcd for $C_{12}H_{24}N$ $[M+H]^+$: 182.1908; found: 182.1941.

4.11. trans-3-(Benzenesulfonyl)hexahydroindolizin-5-one (*trans-13*)

A solution of 3-(phenylsulfanyl)hexahydro-indolizin-5-one (**5**) (1.044 g, 4.22 mmol) in CH_2Cl_2 (20 mL) was slowly added to a solution of *m*-CPBA (1.52 g, 8.86 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The mixture was stirred vigorously and slowly warmed up to room temperature for 16 h before it was quenched by the addition of saturated $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with water (30 mL), brine (30 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography on silica gel (30×3.0 cm, 4:1 ethyl acetate/hexanes eluent) followed by crystallization from ethyl acetate/hexanes to provide *trans*-**13** (0.355 g, 30% yield) as a white solid (Fig. 2): analytical TLC on silica gel, 4:1 ethyl acetate/hexanes, R_f=0.25, mp=116–118 °C. IR (KBr): ν_{max} 2978 (C–H), 1651 (C=O), 1585, 1435, 1406, 1331, 1309 (O=S=O), 1152 (O=S=O), 1084, 733, 690 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.91–7.89 (2H, m), 7.67–7.64 (1H, m), 7.56–7.53 (2H, m), 5.63 (1H, dd, *J*=9.1, 4.2 Hz), 3.99–3.93 (1H, m), 2.69–2.62 (1H, m), 2.42–2.35 (1H, m), 2.31–2.23 (1H, m), 2.21–2.14 (2H, m), 2.11–2.03 (1H, m), 1.88–1.82 (1H, m), 1.74–1.63 (1H, m), 1.60–1.52 (1H, m), 1.27–1.18 (1H, m). ^{13}C NMR (125 MHz,



trans-**13**

Figure 2.

$CDCl_3$): δ 169.5, 138.3, 134.9, 130.1, 129.8, 76.0, 60.1, 33.1, 32.0, 30.1, 23.1, 21.0. MS (EI): *m/z* (%) relative intensity 279 (M^+, 2), 168 (2), 167 (13), 150 (4), 149 (36), 139 (11), 138 (M^+-SO_2Ph, 100), 137 (6), 120 (12), 111 (7), 110 (25), 109 (7), 95 (28), 82 (25), 81 (10), 80 (17), 71 (10), 67 (15), 57 (11), 55 (13). HRMS (ESI) calcd for $C_{14}H_{18}NO_3S$ $[M+H]^+$: 280.1007; found: 280.1005.

4.12. 3-(Butyl)hexahydroindolizin-5-one (*14*)

A solution of *n*-butylmagnesium chloride (2.0 M solution in THF, 1.1 mL, 2.18 mmol) was slowly added to a solution of anhydrous zinc chloride (1 M solution in THF, 1.31 mL, 1.31 mmol) in dry CH_2Cl_2 (6.5 mL) at 0 °C and the mixture was stirred under argon for 30 min to afford the organozinc species. A solution of *trans*-**13** (0.304 g, 1.089 mmol) in dry CH_2Cl_2 (5.5 mL) was then slowly added to the organozinc species and stirring was continued at 0 °C to room temperature for 24 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography on silica gel (15×1.5 cm, 60% ethyl acetate/hexanes eluent) to afford **14** (0.130 g, 63% yield, cis/trans=3:2 determined by ^1H NMR) as a colourless oil: analytical TLC on silica gel, 60% ethyl acetate/hexanes, R_f=0.37. IR (neat): ν_{max} 2955 (C−H), 2933, 2861, 1623 (C=O), 1466, 1451, 1413, 1373, 1328 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.12−4.04 (1H, m, C_3−*H* of *trans*-**14**), 3.96 (1H, t, *J*=7.6 Hz, C_3−*H* of *cis*-**14**), 3.46−3.40 (1H, m, C_{8a}−*H* of *trans*-**14**), 3.37 (1H, tdd, *J*=11.3, 5.0, 3.0 Hz, C_{8a}−*H* of *cis*-**14**), 2.45 (1H, dd, *J*=18.0, 6.2 Hz, C_6−*H* of *trans*-**14**), 2.39−2.21 (3H, m; 2H for C_6−*H* of *cis*-**14** and 1H for C_6−*H* of *trans*-**14**), 2.12−1.85 (9H, m; 4H for *cis*-**14** and 5H for *trans*-**14**), 1.83−1.62 (6H, m; 3H for each isomer), 1.61−1.52 (1H, m, *cis*-**14**), 1.49−1.42 (1H, m, *trans*-**14**), 1.39−1.14 (11H, m; 6H for *cis*-**14** and 5H for *trans*-**14**), 0.90 (3H, t, *J*=7.1 Hz, $-CH_3$ of *trans*-**14**), 0.89 (3H, t, *J*=7.2 Hz, $-CH_3$ of *cis*-**14**). ^{13}C NMR (125 MHz, $CDCl_3$, minor isomer marked*): δ_C 169.4, 168.7* (C=O), 59.9, 58.7* (*C*H, C-8a), 57.3, 57.0* (*C*H, C-3), 34.1* (CH_2), 33.0* (CH_2), 32.4 (CH_2), 31.6* (CH_2), 31.3 (CH_2), 31.0 (CH_2), 29.4* (CH_2), 29.3 (CH_2), 28.8 (CH_2), 28.7* (CH_2), 27.6* (CH_2), 27.5 (CH_2), 22.7* (CH_2), 22.6 (CH_2), 21.1 (CH_2), 20.8* (CH_2), 14.0 (CH_3 of both isomers). MS (EI): *m/z* (%) relative intensity 197 (M^++2, 14), 196 (M^++1, 96), 195 (M^+, 14), 166 (6), 152 (6), 139 (29), 138 (M^+-Bu, 100), 120 (11), 111 (6), 110 (26), 95 (20), 82 (19), 67 (9). HRMS (ESI) calcd for $C_{12}H_{22}NO$ $[M+H]^+$: 196.1701; found: 196.1715. The spectral characteristics (^1H and ^{13}C NMR) of *cis*-**14** are identical with those reported in the literature.[18]

4.13. (±)-Monomorine I (*4*)

A solution of methylmagnesium bromide (3.0 M solution in diethyl ether, 0.2 mL, 0.6 mmol) was added dropwise to a solution of **14** (a mixture of cis/trans=3:2, 0.033 g, 0.17 mmol) in THF (4 mL) at room temperature under an argon atmosphere. The mixture was brought to refluxing temperature for 5 h. The reaction was cooled to 0 °C followed by the addition of glacial acetic acid (0.2 mL) and $NaBH_4$ (0.076 g, 2.0 mmol) in MeOH (2 mL). After being stirred at 0 °C for 2 h, the mixture was diluted with water (20 mL), and made alkaline with saturated aqueous $NaHCO_3$ before it was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography on Al_2O_3 (8×0.7 cm, 1:6 diethyl ether/hexanes eluent) to afford (±)-monomorine I (**4**) (0.010 g, 50% yield (based on *cis*-**14**)) as colourless oil: ^1H NMR (300 MHz, $CDCl_3$): δ 2.50−2.30 (1H, m), 2.28−2.10 (1H, m), 2.08−1.95 (1H, m), 1.85−1.52 (5H, m), 1.50−1.00 (11H, m), 1.08 (3H, d, *J*=6.1 Hz), 0.82 (3H, t, *J*=6.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 67.2, 62.9, 60.3, 39.7, 35.9, 31.0, 30.3, 29.8, 29.4, 24.9, 22.9, 22.8, 14.1. MS (EI): *m/z* (%) relative intensity 196 (M^++1, 3), 195 (M^+, 1), 180 (M^+-Me, 11), 139 (11), 138 (M^+-Bu, 100), 124 (8), 110 (4), 95 (6), 70 (17). The spectral characteristics (^1H and ^{13}C NMR) of (±)-monomorine I ((±)-**4**) are identical with those reported in the literature.[19]

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