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Synthesis of (+)-Lentiginosine and Its Pyrrolizidine Analogue Based on Intramolecular Cyclization of α-Sulfinyl Carbanions

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A synthesis of (+)-lentiginosine and its pyrrolizidine analogue was accomplished in six steps, starting from L-(+)-tartaric acid. The key step of these syntheses involves the intramolecular cyclization of α-sulfinyl carbanions for the construction of the indolizidine or pyrrolizidine ring.

Introduction

Polyhydroxylated indolizidines and pyrrolizidines are important classes of naturally derived compounds. They have received considerable attention due to their interesting structural scaffolds and biological activities such as glycosidase inhibitory activity.[1] A series of these types of compounds, including (–)-swainsonine,[2] (+)-castanospermine,[3] (+)-hyacinthacine A_2,[1b,4] and (+)-lentiginosine (**1**)[5] are widely found in plants and microorganisms (Figure 1). Their intriguing structures and important biological activities have attracted a number of synthetic efforts toward their total syntheses in both racemic and enantiopure forms. We successfully developed a general strategy for the preparation of 1-azabicyclic[*m.n*.0] compounds based on the intramolecular cyclization of α-sulfinyl carbanions.[6] The method was applied as convenient strategies for syntheses of (±)-tashiromine, (±)-indolizidine 167B and 209D,[7] (±)-lupinine,[8] and (+)-swainsonine.[9] To further exploit the synthetic utility of the intramolecular cyclization of α-sulfinyl carbanions as a convenient, general synthetic route to polyhydroxylated 1-azabicyclic compounds, we describe herein a synthesis of (+)-lentiginosine (**1**)[10] and its known pyrrolizidine analogue (**2**)[11] starting from L-(+)-tartaric acid.

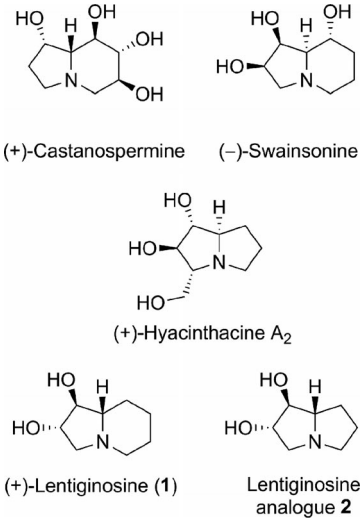

Figure 1. Some biologically active pyrrolizidines and indolizidines.

Results and Discussion

The synthetic sequence is shown in Scheme 1. Sulfinylimides **6a** and **6b** were envisioned as key intermediates for accessing the 1-azabicyclic core structures of (+)-lentiginosine (**1**) and its analogue **2**, respectively.[12] Thus, our investigation began with the synthesis of **6a** and **6b** starting from L-(+)-tartaric acid. Treatment of aminosulfides **3a** and **3b** with L-(+)-tartaric acid in xylene heated to reflux for 15 h afforded the corresponding chiral hydroxyimides **4a** and **4b** in 68 and 72% yields, respectively. Protection of the hydroxyl groups of **4a** and **4b** by employing *tert*-butyldimethylsilyl chloride (TBSCl)/imidazole in *N*,*N*-dimethylformamide (DMF) at 0 °C to room temperature for 1 h provided the corresponding chiral sulfides **5a** and **5b** in 98 and 91% yields, respectively. Oxidation of chiral sulfides **5a** and **5b** by employing $NaIO_4$ in aqueous methanol at 0 °C to room temperature for 17 h furnished the required sulfinylimides **6a** (88% yield) and **6b** (82% yield), each as two diastereomeric mixtures (undetermined diastereomeric ratios).

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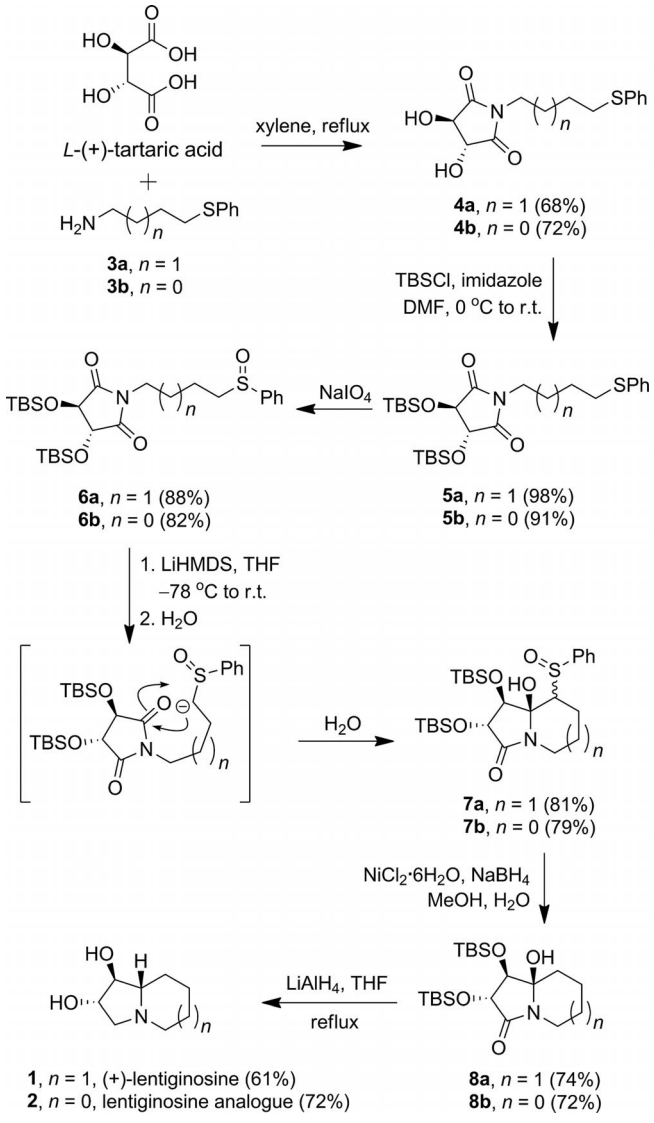
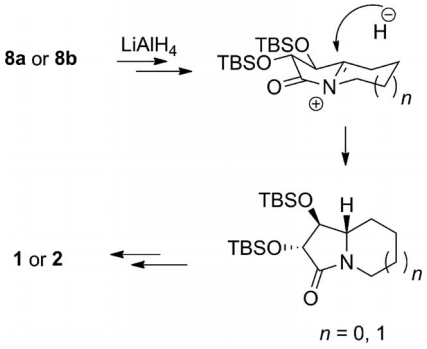


Scheme 1. Synthesis of (+)-lentiginosine (**1**) and its analogue **2**.

With the key sulfinylimides **6a** and **6b** in hand, the intramolecular cyclization of their α-sulfinyl carbanions to the expected dihydroxylated 1-azabicyclic compounds **7a** and **7b** was carried out. Treatment of **6a** with lithium hexamethyldisilazide (LiHMDS; 2.2 equiv.) in tetrahydrofuran (THF) at –78 °C followed by slow warming to room temp. for 4 h afforded the expected cyclized product **7a** in 81% yield as an inseparable mixture of diastereomers. Under similar reaction conditions, **6b** provided **7b** in 79% yield as an inseparable mixture of diastereomers. The formation of **7a** and **7b** resulted from intramolecular cyclization of the initially formed α-sulfinyl carbanion derived from the corresponding sulfinylimides **6** onto the carbonyl group of the imide moiety from the opposite face to the α-substituted OTBS group to provide the cyclized products **7**, in which the hydroxyl group is oriented *cis* to the OTBS group, as shown in Scheme 1. It is worth mentioning that the stereochemistry of **7b** was subsequently assigned by NOE experiments of compound **8b** (see the Supporting Information) after reductive cleavage of the phenylsulfinyl group of **7b**. Therefore, the stereochemistry (hydroxyl group *cis* to the OTBS group) of compounds **7a** and **8a** was assigned on the basis of that of **8b**.

At this stage, the construction of the core indolizidine and pyrrolizidine scaffolds was achieved. Next, the conversions of **7a** and **7b** into (+)-lentiginosine (**1**) and its analogue **2** were performed. Upon reductive cleavage of the phenylsulfinyl group followed by reduction of the resulting imide, (+)-lentiginosine (**1**) was expected to be obtained. Reductive cleavage of the phenylsulfinyl group of **7a** was accomplished by using a combination of $NiCl_2·6H_2O$/$NaBH_4$[13] in aqueous methanol at 0 °C to room temperature for 30 h. The corresponding indolizidinone **8a** was isolated in 74% yield as a single isomer. Subsequently, reduction of **8a** with $LiAlH_4$[14] in THF heated to reflux furnished (+)-lentiginosine (**1**) in 61% yield. The spectroscopic data and specific optical rotation of the synthesized (+)-lentiginosine (**1**) are consistent with reported values {mp 108–109 °C (MeOH); $[\alpha]_D^{23}$ = +3.3 (*c* = 0.7, MeOH) [ref.[15] m.p. 106 °C; $[\alpha]_D^{20}$ = +3.0 (*c* = 0.7, MeOH)]}. By following a similar synthetic sequence, **7b** was treated with $NiCl_2·6H_2O/NaBH_4$ in aqueous methanol, leading to **8b** (72% yield as a single isomer), which was subjected to $LiAlH_4$-mediated reduction to give the known pyrrolizidine analogue **2** in 72% yield {mp 163–164 °C; $[\alpha]_D^{23}$ = +11.3 (*c* = 0.5, MeOH) [ref.[11] m.p. 164–165 °C; $[\alpha]_D^{23}$ = +11 (*c* = 0.5, MeOH)]}.

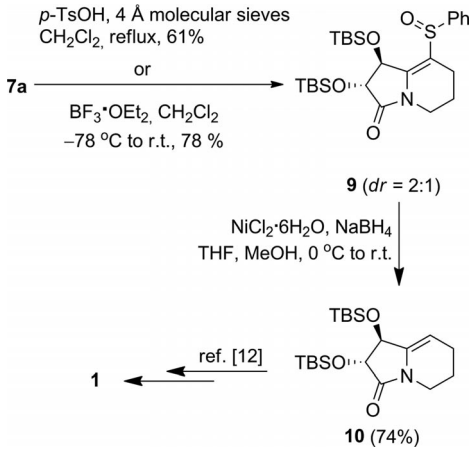
The observed stereochemical outcomes of the reduction reactions mediated by $LiAlH_4$ can be explained by attack of the hydride on the iminium ion derived from **8a** or **8b** taking place from the pseudoaxial direction as governed by stereoelectronic principles (Scheme 2).



Scheme 2. Proposed transition-state for reduction of **8a** and **8b** by $LiAlH_4$.

Alternatively, treatment of **7a** with 10 mol-% *p*TsOH in CH_2Cl_2 at reflux for 2.5 h furnished the corresponding sulfinylindolizidinone **9** in 61% yield as a separable 2:1 diastereomeric mixture. A better yield of **9** (78%) was obtained when **7a** was treated with $BF_3·OEt_2$ at –78 °C to room temperature for 6 h. Our attempted reductive dehydroxylation employing Et_3SiH and $BF_3·OEt_2$ in CH_2Cl_2 at reflux also gave the same result, providing phenylsulfinylindolizidinone **9** in 85% yield (Scheme 3). Reductive cleavage of the phenylsulfinyl group of sulfinylindolizidinone **9** by using

$NiCl_2·6H_2O/NaBH_4$ in THF/MeOH at 0 °C to room temp. for 24 h furnished enantiopure chiral indolizidinone **10** in 74% yield. As reported by Ha and co-workers,[15] indolzidinone **10** was used as a precursor for the synthesis of (+)-lentiginosine by sequential treatment with Et_3SiH/CF_3COOH, desilylation by using CH_3OH/HCl and $LiAlH_4$-mediated reduction.



Scheme 3. An alternative synthesis of (+)-lentiginosine (**1**).

Conclusions

We have demonstrated the synthetic utility of intramolecular cyclization of α-sulfinyl carbanions as a convenient strategy for the synthesis of (+)-lentiginosine (**1**) and its pyrrolizidine analogue (**2**), starting from readily available L-(+)-tartaric acid. Asymmetric syntheses of other polyhydroxylated indolizidines and pyrrolizidines by employing this strategy are under investigation.

Experimental Section

General Methods: ^1H NMR spectra were recorded with a Bruker Advance-300, a Bruker Ascend-400, or a Bruker Advance-500 spectrometer. ^{13}C NMR were recorded with an Advance-300 (75 MHz), Ascend-400 (100 MHz), or Advance-500 (125 MHz) spectrometer in $CDCl_3$ by using tetramethylsilane as an internal standard. Chemical shifts (δ) reported are given in part per million (ppm) downfield from tetramethylsilane. IR spectra were recorded with either a Jasco A-302 or a Perkin–Elmer 683 Infrared spectrometer. Mass spectra were recorded with a Thermo Finnigan Polaris Q mass spectrometer. High-resolution mass spectra were recorded with either a HR-TOF-MS Micromass model VQ-TOF2 or a Finnigan MAT 95 mass spectrometer. Specific rotations were recorded with a Jasco P1020 polarimeter. Melting points were recorded with a Buchi 501 melting-point apparatus.

THF was distilled from sodium-benzophenone ketyl. The molarity of *n*BuLi (in hexane) was determined by titration with diphenylacetic acid in THF at 0 °C. Reactions involving anions were run under an argon atmosphere. All glassware and syringes were oven-dried and kept in a desiccator before use. Hexamethyldisilazane (HMDS), DMF, dichloromethane (CH_2Cl_2) and hexane were dried by distillation over calcium hydride. Methanol was dried by distillation over magnesium turnings. Column chromatography was performed with Merk silica gel 60H (Art. 7734) or 60H (Art. 7736). Reverse-phase chromatography was performed on solid phase extraction (VertiPak, C18-LP Tube). Other common solvents (hexanes, CH_2Cl_2 and ethyl acetate) were distilled before use.

4-(Phenylsulfanyl)butan-1-amine (3a):[16] To a suspension of NaH [65% in mineral oil, 835 mg, 22 mmol; washed with anhydrous hexane (3× 15 mL)] in anhydrous DMF (6 mL) was slowly added a solution of phthalimide (2.94 g, 20 mmol) in anhydrous DMF (10 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 1 h until the generation of hydrogen gas ceased, then a solution of 1-bromo-4-phenylsulfanylbutane (5.40 g, 22 mmol) in anhydrous DMF (5 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 2 h, then poured onto ice-water and extracted with EtOAc (3× 50 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. Filtration and evaporation gave a viscous yellow oil of a crude product, which was purified by column chromatography [SiO_2 (Art. 7736); EtOAc/hexanes (1:1)] to give 2-[4-(phenylsulfanyl)butyl]isoindoline-1,3-dione (4.03 g, 65%) as a colorless viscous oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.89–7.79 (m, 2 H, ArH), 7.77–7.68 (m, 2 H, ArH), 7.36–7.20 (m, 4 H, PhH), 7.19–7.11 (m, 1 H, PhH), 3.70 (t, J = 7.0 Hz, 2 H, NCH_2), 2.96 (t, J = 7.1 Hz, 2 H, CH_2SPh), 1.97–1.79 (m, 2 H, CH_2), 1.79–1.62 (m, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3 (2×CO), 136.2 (C), 133.8 (2×CH), 132.0 (2×C), 129.3 (2×CH), 128.8 (2×CH), 125.9 (CH), 123.1 (2×CH), 37.3 (CH_2), 33.1 (CH_2), 27.5 (CH_2), 26.2 (CH_2) ppm. IR (Nujol): $\tilde{\nu}$ = 1719 (s), 1438 (s), 743 (s), 718 (s), 691 (s) cm^{-1}. MS: *m*/*z* (%) = 311 (37) [M^+], 202 (80), 160 (100), 133 (15), 77 (15).

A solution of 2-[4-(phenylsulfanyl)butyl]isoindoline-1,3-dione (3.94 g, 12.6 mmol) in aqueous NaOH (50% w/v, 38 mL) was stirred and heated to reflux for 18 h. After cooling, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4 followed by filtration and evaporation to give analytically pure **3a** (2.06 g, 90%) as a viscous liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.23 (m, 4 H, PhH), 7.17–7.12 (m, 1 H, PhH), 2.91 (t, J = 7.1 Hz, 2 H, CH_2NH_2), 2.67 (t, J = 6.9 Hz, 2 H, CH_2SPh), 1.77 (br. s, 2 H, NH_2), 1.71–1.53 (m, 4 H, 2×CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.6 (C), 128.9 (2×CH), 128.7 (2×CH), 125.6 (CH), 41.3 (CH_2), 33.3 (CH_2), 32.4 (CH_2), 26.3 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3283 (br), 2932 (s), 1651 (s), 1480 (s), 1439 (s), 1088 (s) cm^{-1}. MS: *m*/*z* (%) = 182 (31) [M^+ + 1], 181 (15) [M^+], 165 (34), 135 (20), 123 (9), 109 (16), 91 (8), 72 (100), 65 (18). HRMS (ESI-TOF): calcd. for $C_{10}H_{16}NS$ [M^+ + H] 182.0998; found 182.1020.

3-Phenylsulfanylpropan-1-amine (3b):[17] To a suspension of NaH [65% in mineral oil, 4.51 g, 120 mmol, washed with anhydrous hexane (3×25 mL)] in anhydrous DMF (30 mL) was slowly added a solution of phthalimide (14.71 g, 100 mmol) in anhydrous DMF (95 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 1 h until the generation of hydrogen gas ceased, then a solution of 1-bromo-3-phenylsulfanylpropane (27.74 g, 120 mmol) in anhydrous DMF (125 mL) was slowly added. After stirring at 0 °C for 1 h, the reaction mixture was slowly warmed to room temperature and stirred for 2 h, then it was poured onto ice-water and vigorously stirred. The precipitates were filtered and recrystallized from ethanol to give 2-(3-phenylsulfanylpropyl)isoindoline-1,3-dione (22.46 g, 76%) as white crystals (m.p. 81–82 °C). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.89–7.81 (m, 2 H, ArH), 7.77–7.68 (m, 2 H, ArH), 7.39–7.33 (m, 2 H, PhH), 7.33–7.24 (m, 2 H,

PhH), 7.24–7.15 (m, 1 H, PhH), 3.83 (t, J = 7.0 Hz, 2 H, NCH_2), 2.96 (t, J = 7.3 Hz, 2 H, CH_2SPh), 2.02 (quint., J = 7.1 Hz, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2 (2 × CO), 135.7 (C), 133.9 (2 × CH), 132.0 (2 × C), 129.8 (2 × CH), 128.9 (2 × CH), 126.2 (CH), 123.2 (2 × CH), 36.9 (CH_2), 31.4 (CH_2), 28.1 (CH_2) ppm. IR (Nujol): $\tilde{\nu}$ = 1731 (s), 1411 (s), 865 (s), 840 (m), 687 (m) cm^{-1}. MS: m/z (%) = 297 (62) [M^+], 188 (100), 160 (46).

A solution of 2-(3-phenylsulfanylpropyl)isoindoline-1,3-dione (2.98 g, 10 mmol) in aqueous NaOH (50 w/v, 30 mL) was heated to reflux for 20 h. After cooling, the reaction mixture was diluted with water (20 mL), extracted with EtOAc (3 × 40 mL), and the combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure to give **3b** (1.63 g, 97%). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.25 (m, 4 H, PhH), 7.23–7.15 (m, 1 H, PhH), 3.00 (t, J = 7.2 Hz, 2 H, CH_2NH_2), 2.84 (t, J = 6.8 Hz, 2 H, CH_2SPh), 1.80 (quint., J = 6.9 Hz, 2 H, CH_2), 1.47–1.31 (br. s, 2 H, NH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.5 (C), 129.0 (2 × CH), 128.8 (2 × CH), 125.8 (CH), 40.9 (CH_2), 32.7 (CH_2), 31.0 (CH_2) ppm. IR (Nujol): $\tilde{\nu}$ = 3317 (br), 3276 (br), 2854 (s), 1633 (s), 1557 (s), 1463 (s) cm^{-1}. MS: m/z (%) = 167 (7) [M^+], 165 (28), 151 (16), 147 (15), 123 (22), 121 (23), 109 (36), 95 (52), 81 (74), 77 (50), 67 (100), 55 (93).

(3*R*,4*R*)-3,4-Dihydroxy-1-(4-phenylsulfanylbutyl)pyrrolidine-2,5-dione (4a): A mixture of (+)-L-tartaric acid (659 mg, 4.4 mmol) and **3a** (789 mg, 4.4 mmol) in xylene (10 mL) was heated to reflux overnight (18 h). The precipitates were filtered and recrystallized from CH_2Cl_2 to give **4a** (679 mg, 53%) as a white solid (m.p. 121–122 °C). $[\alpha]_D^{25}$ = +88.3 (c = 1, MeOH). ^1H NMR (300 MHz, [D_6]-acetone): δ = 7.39–7.28 (m, 4 H, PhH), 7.24–7.16 (m, 1 H, PhH), 5.45–5.38 (m, 2 H, 2 × OH), 4.49 (br. d, J = 3.6 Hz, 2 H, 2 × CH), 3.60–3.40 (m, 2 H, NCH_2), 3.00 (t, J = 7.1 Hz, 2 H, CH_2SPh), 1.80–1.70 (m, 2 H, CH_2), 1.70–1.57 (m, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, [D_6]acetone): δ = 175.0 (2 × CO), 137.5 (C), 129.7 (2 × CH), 129.5 (2 × CH), 126.5 (CH), 75.8 (2 × CH), 38.3 (CH_2), 33.0 (CH_2), 27.3 (CH_2), 26.9 (CH_2) ppm. IR (Nujol): $\tilde{\nu}$ = 3359 (br), 1702 (s), 1462 (s), 1376 (s) cm^{-1}. MS: m/z (%) = 295 (100) [M^+], 277 (68), 186 (29), 168 (40), 158 (20), 139 (21), 132 (15), 123 (19), 110 (78). HRMS (ESI-TOF): calcd. for $C_{14}H_{17}NO_4SNa$ [M^+ + Na] 318.0776; found 318.0770.

(3*R*,4*R*)-3,4-Dihydroxy-1-(3-phenylsulfanylpropyl)pyrrolidine-2,5-dione (4b): By following the procedure described for **4a**, the reaction of (+)-L-tartaric acid (1.46 g, 9.7 mmol) and **3b** (1.63 g, 9.7 mmol) in xylene (20 mL) gave **4b** (1.97 g, 72%) as a white solid (m.p. 147–148 °C). $[\alpha]_D^{25}$ = +84.4 (c = 1, MeOH). ^1H NMR (300 MHz, [D_6]-acetone): δ = 7.42–7.28 (m, 4 H, PhH), 7.26–7.17 (m, 1 H, PhH), 5.53–5.25 (br., 1 H, OH), 4.52 (s, 2 H, 2 × CH), 3.69–3.53 (m, 2 H, NCH_2), 2.98 (t, J = 7.3 Hz, 2 H, CH_2SPh), 2.86 (br., 1 H, OH), 1.88 (quint., J = 7.1 Hz, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, [D_6]-acetone): δ = 175.1 (2 × CO), 137.1 (C), 129.8 (4 × CH), 126.8 (CH), 75.8 (2 × CH), 38.0 (CH_2), 31.2 (CH_2), 28.0 (CH_2) ppm. IR (Nujol): $\tilde{\nu}$ = 3272 (br), 1713 (s), 1687 (s), 1463 (s) cm^{-1}. MS: m/z (%) = 281 (100) [M^+], 263 (54), 259 (51), 197 (34), 188 (32), 172 (71), 169 (56), 154 (78), 144 (71), 110 (58), 91 (38), HRMS (ESI-TOF): calcd. for $C_{13}H_{15}NO_4SNa$ [M^+ + Na] 304.0619; found 304.0612.

(3*R*,4*R*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-(4-phenylsulfanylbutyl)pyrrolidine-2,5-dione (5a): To a mixture of **4a** (194 mg, 0.7 mmol) and imidazole (148 mg, 2 mmol) in anhydrous DMF (1 mL) at 0 °C under an argon atmosphere was slowly added a solution of *tert*-butyldimethylsilyl chloride (236 mg, 1.5 mmol) in anhydrous DMF (1 mL). After stirring at room temperature for 1 h, the reaction was quenched with cold water (2 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water, brine, and dried with anhydrous Na_2SO_4. Filtration followed by evaporation gave a crude product, which was purified by column chromatography [SiO_2 (Art. 7736); EtOAc/hexanes, 1:4] to give **5a** (340 mg, 99%) as a colorless viscous oil. $[\alpha]_D^{26}$ = +73.9 (c = 0.5, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 4 H, PhH), 7.22–7.18 (m, 1 H, PhH), 4.46 (s, 2 H, 2 × CHO), 3.54–3.45 (m, 2 H, NCH_2), 2.93 (t, J = 7.2 Hz, 2 H, CH_2SPh), 1.75 (quint., J = 7.7 Hz, 2 H, CH_2), 1.66–1.61 (m, 2 H, CH_2), 0.97 [s, 18 H, 2 × $SiC(CH_3)_3$], 0.24 [s, 6 H, $Si(CH_3)_2$], 0.19 [s, 6 H, $Si(CH_3)_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.4 (2 × CO), 136.1 (C), 129.4 (2 × CH), 128.9 (2 × CH), 126.0 (CH), 76.8 (2 × CH), 38.1 (CH_2), 33.1 (CH_2), 26.7 (CH_2), 26.3 (CH_2), 25.6 (6 × CH_3), 18.2 (2 × C), –4.5 (2 × CH_3), –5.1 (2 × CH_3) ppm. IR (neat): $\tilde{\nu}$ = 1727 (s), 1473 (m), 1361 (s), 1253 (s), 1124 (s) cm^{-1}. MS: m/z (%) = 524 (1) [M^+], 466 (41), 438 (12), 165 (100), 73 (14). HRMS (ESI-TOF): calcd. for $C_{26}H_{45}NO_4SSi_2Na$ [M^+ + Na] 546.2506; found 546.2500.

(3*R*,4*R*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-(3-phenylsulfanylpropyl)pyrrolidine-2,5-dione (5b): By following the procedure described for **5a**, the reaction of **4b** (4.22 g, 15 mmol), imidazole (3.06 g, 45 mmol) and *tert*-butyldimethylsilyl chloride (4.97 g, 33 mmol) in anhydrous DMF (40 mL) gave **5b** (6.85 g, 90%) as a colorless viscous oil after column chromatography [SiO_2 (Art. 7736); EtOAc/hexanes, 1:4]. $[\alpha]_D^{24}$ = +89.3 (c = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.26 (m, 4 H, PhH), 7.25–7.17 (m, 1 H, PhH), 4.48 (s, 2 H, 2 × CHO), 3.72–3.55 (m, 2 H, NCH_2), 2.90 (t, J = 7.2 Hz, 2 H, CH_2SPh), 1.92 (quint., J = 7.1 Hz, 2 H, CH_2), 0.97 [s, 18 H, 2 × $SiC(CH_3)_3$], 0.25 [s, 6 H, $Si(CH_3)_2$], 0.20 [s, 6 H, $Si(CH_3)_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3 (2 × CO), 135.6 (C), 129.9 (2 × CH), 128.9 (2 × CH), 126.3 (CH), 76.8 (2 × CH), 37.7 (CH_2), 31.5 (CH_2), 27.1 (CH_2), 25.6 (6 × CH_3), 18.2 (2 × C), –4.5 (2 × CH_3), –5.1 (2 × CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1719 (s), 1362 (m), 1109 (s) cm^{-1}. MS: m/z (%) = 510 (16) [M^+ + H], 494 (21), 452 (100), 424 (59), 151 (54), 73 (36). HRMS (ESI-TOF): calcd. for $C_{25}H_{43}NO_4SSi_2Na$ [M^+ + Na] 532.2349; found 532.2344.

(3*R*,4*R*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-(4-phenylsulfinylbutyl)pyrrolidine-2,5-dione (6a): To a solution of **5a** (1.05 g, 2 mmol) in methanol (12 mL) at 0 °C was added a solution of $NaIO_4$ (511 mg, 2.4 mmol) in water (3 mL). The mixture was stirred vigorously and slowly warmed to room temperature overnight (18 h). After filtration of the precipitates of $NaIO_3$, the filtrate was extracted with EtOAc (3 × 15 mL) and the combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. Filtration followed by evaporation afforded a crude product, which was purified by column chromatography [SiO_2 (Art. 7734); EtOAc/hexanes, 2:3] to give **6a** (944 mg, 88%) as a mixture of diastereomers as a colorless viscous oil. ^1H NMR (400 MHz, $CDCl_3$): δ (isomers **A** and **B**) = 7.61–7.55 (m, 4 H, PhH **A** and **B**), 7.54–7.44 (m, 6 H, PhH **A** and **B**), 4.43 (s, 4 H, 4 × CHO **A** and **B**), 3.53–3.35 (m, 4 H, 2 × NCH_2 **A** and **B**), 2.86–2.71 (m, 4 H, 2 × CH_2SOPh **A** and **B**), 1.80–1.48 (m, 8 H, 2 × CH_2CH_2 **A** and **B**), 0.92 [s, 36 H, 2 × $SiC(CH_3)_3$ **A** and **B**], 0.20 [s, 12 H, 2 × $Si(CH_3)_2$ **A** and **B**], 0.15 [s, 12 H, 2 × $Si(CH_3)_2$ **A** and **B**] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (isomer **A** marked*) = 173.3 (4 × CO **A** and **B**), 143.6 (C*), 143.5 (C), 131.0 (2 × CH **A** and **B**), 129.2 (4 × CH **A** and **B**), 123.9 (4 × CH **A** and **B**), 76.8 (4 × CH **A** and **B**), 56.1 (CH_2*), 56.0 (CH_2), 37.8 (2 × CH_2 **A** and **B**), 26.6 (CH_2*), 26.5 (CH_2), 25.6 (12 × CH_3 **A** and **B**), 19.4 (CH_2*), 19.3 (CH_2), 18.2 (4 × C **A** and **B**), –4.5 (4 × CH_3 **A** and **B**), –5.1 (4 × CH_3 **A** and **B**) ppm. IR (neat): $\tilde{\nu}$ = 1728 (s), 1716 (s), 1473 (m), 1444 (m), 1361 (s), 1252 (s), 1121 (s), 1048 (m) cm^{-1}. MS: m/z (%) = 540 (41) [M^+ + 1], 483 (76), 398 (43), 356 (29), 328 (31), 165 (28), 74 (57). HRMS (ESI-TOF): calcd. for $C_{26}H_{45}NO_5SSi_2Na$ [M^+ + Na] 562.2455; found 562.2454.

(3*R*,4*R*)-3,4-Bis(*tert*-butyldimethylsilyloxy)-1-(3-phenylsulfinylpropyl)pyrrolidine-2,5-dione (6b): By following the procedure described for **6a**, a solution of **5b** (6.69 g, 13 mmol) in methanol (80 mL) was treated with a solution of $NaIO_4$ (3.10 g, 14 mmol) in water (20 mL) to give a colorless oil of **6b** (5.43 g, 79%) after column chromatography [SiO_2 (Art. 7734); EtOAc/hexanes, 1:1] as a mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ (isomers **A** and **B**) = 7.64–7.55 (m, 4 H, PhH **A** and **B**), 7.55–7.43 (m, 6 H, PhH **A** and **B**), 4.45 (s, 2 H, CHO **A**), 4.44 (s, 2 H, CHO **B**), 3.73–3.44 (m, 4 H, 2 × NCH_2 **A** and **B**), 2.89–2.64 (m, 4 H, 2 × C*H*$_2$SOPh **A** and **B**), 2.18–1.97 (m, 2 H, 2 × C*H*H **A** and **B**), 1.97–1.76 (m, 2 H, 2 × CH*H* **A** and **B**), 0.92 [s, 36 H, 4 × SiC(CH$_3$)$_3$ **A** and **B**], 0.20 [s, 12 H, 2 × Si(CH$_3$)$_2$ **A** and **B**], 0.15 [s, 12 H, 2 × Si(CH$_3$)$_2$ **A** and **B**] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ (isomer **A** marked*) = 173.4 (4 × CO **A** and **B**), 143.3 (C), 143.2 (C*), 131.1 (CH*), 131.0 (CH), 129.2 (4 × CH **A** and **B**), 124.0 (2 × CH*), 123.9 (2× CH), 76.8 (4 × CH **A** and **B**), 54.5 (2 × CH_2 **A** and **B**), 37.3 (CH_2*), 37.2 (CH_2), 25.6 (12 × CH_3 **A** and **B**), 20.9 (CH_2), 20.8 (CH_2*), 18.1 (4 × C **A** and **B**), –4.5 (4 × CH_3 **A** and **B**), –5.1 (4 × CH_3 **A** and **B**) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1720 (s), 1445 (m), 1403 (m), 1362 (m), 1111 (m), 1043 (m) cm^{-1}. MS: *m*/*z* (%) = 526 (3) [M$^+$ + H], 468 (100), 314 (49), 210 (26), 167, (76), 149 (35), 73 (34). HRMS (ESI-TOF): calcd. for $C_{25}H_{43}NO_5SSi_2Na$ [M$^+$ + Na] 548.2298; found 548.2293.

(1*R*,2*R*)-1,2-Bis(*tert*-butyldimethylsilyloxy)-8a-hydroxy-8-(phenylsulfinyl)hexahydroindolizin-3(2*H*)-one (7a): To a cooled solution of hexamethyldisilazane (0.88 mL, 4.2 mmol) in anhydrous THF (10 mL) at –78 °C under an argon atmosphere was added dropwise *n*-BuLi (1.48 M in hexane, 2.6 mL, 3.8 mmol). The resulting solution was stirred at –78 °C for 1 h and slowly transferred by using a Teflon tube to a cooled solution of **6a** (927 mg, 1.7 mmol) in THF (10 mL) at –78 °C. The mixture was stirred and slowly warmed to room temperature for 4 h, then the reaction was quenched with water (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. Filtration followed by evaporation gave a yellow oil of a crude product, which was purified by column chromatography [SiO_2 (Art. 7734); EtOAc/hexanes, 2:3] to afford **7a** (749 mg, 81%) as a mixture of diastereomers as a white semi-solid. The following spectroscopic data are of a mixture of two major diastereomers **A** and **B**. ^{1}H NMR (300 MHz, $CDCl_3$): δ (isomer **A** marked*) = 7.63–7.42 (m, 10 H, PhH **A** and **B**), 4.46 (s, 1 H, OH*), 4.37 (d, *J* = 2.1 Hz, 1 H, CHO*), 4.28 (s, 1 H, CHO), 4.18 (d, *J* = 1.6 Hz, 1 H, OH), 4.12 (s, 1 H, CHO), 4.03 (d, *J* = 2.1 Hz, 1 H, CHO*), 3.93–3.81 (m, 2 H, NC*H*H **A** and **B**), 3.18–2.89 (m, 3 H, C*H*SOPh*, NCH*H* **A** and **B**), 2.75–2.64 (m, 1 H, C*H*SOPh), 2.39 (ddd, *J* = 14.0, 13.7, 3.5 Hz, 1 H, C*H*H), 2.18 (ddd, *J* = 13.5, 13.4, 3.8 Hz, 1 H, C*H*H*), 1.97–1.74 (m, 2 H, 2 × C*H*H **A** and **B**), 1.64–1.47 (m, 1 H, CH*H*), 1.47–1.23 (m, 3 H, CH*H*, CH*H*, C*H*H), 0.98–0.89 [m, 36 H, 2 × SiC(CH$_3$)$_3$ **A** and **B**], 0.30–0.21 [m, 24 H, 2 × Si(CH$_3$)$_2$ **A** and **B**] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ (isomer **A** marked*) = 170.1 (CO*), 168.6 (CO), 142.7 (C), 140.8 (C*), 130.8 (CH*), 130.7 (CH), 129.2 (2 × CH), 129.1 (2 × CH*), 124.5 (2 × CH*), 124.0 (2 × CH), 90.3 (C*), 87.7 (C), 79.4 (CH*), 77.2 (CH), 76.6 (CH*), 76.4 (CH), 67.9 (CH), 59.9 (CH*), 36.2 (CH_2), 35.9 (CH_2*), 26.0 (3 × CH_3*), 25.8 (3 × CH_3), 25.7 (3 × CH_3*), 25.6 (3 × CH_3), 24.2 (CH_2), 23.3 (CH_2*), 18.1 (2 × C*), 17.9 (2 × C), 15.3 (CH_2), 15.2 (CH_2*), –3.8 (CH_3), –4.0 (CH_3*), –4.3 (CH_3), –4.4 (2 × CH_3 **A** and **B**), –4.9 (2 × CH_3 **A** and **B**), –5.0 (CH_3*) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3489 (br), 1710 (s), 1464 (m), 1445 (m), 1428 (m), 1259 (m), 1103 (s), 1085 (s), 1048 (m), 873, 1085 (s), 840 (s) cm^{-1}. MS: *m*/*z* (%) = 540 (1) [M$^+$], 442 (51), 424 (43), 328 (73), 310 (100), 170 (37), 168 (33), 139 (22), 122 (28). HRMS (ESI-TOF): calcd. for $C_{26}H_{45}NO_5SSi_2Na$ [M$^+$ + Na] 562.2455; found 562.2457.

(1*R*,2*R*)-1,2-Bis(*tert*-butyldimethylsilyloxy)-7a-hydroxy-7-(phenylsulfinyl)tetrahydro-1*H*-pyrrolizin-3(2*H*)-one (7b): By following the procedure described for **7a**, a solution of **6b** (7.33 g, 14 mmol) in anhydrous THF (70 mL) was treated with a solution of LiHMDS [prepared by reacting hexamethyldisilazane (7 mL, 33 mmol) in THF (70 mL) with *n*BuLi (1.31 M in hexane, 23.4 mL, 31 mmol)] at –78 °C to room temperature for 3 h. Purification by column chromatography [SiO_2 (Art. 7734); EtOAc/hexanes, 2:3] afforded **7b** (5.79 g, 79%) as a mixture of diastereomers as a white semi-solid. The following spectroscopic data are of a mixture of two major diastereomers **A** and **B**. ^{1}H NMR (400 MHz, $CDCl_3$): δ (isomer **A** marked*) = 7.47–7.41 (m, 4 H, PhH **A** and **B**), 7.41–7.32 (m, 6 H, PhH **A** and **B**), 4.53–4.43 (br., 2 H, OH **A** and **B**), 4.38 (d, *J* = 6.6 Hz, 2 H, CHO **A** and **B**), 3.91 (d, *J* = 6.6 Hz, 2 H, CHO **A** and **B**), 3.53 (ddd, *J* = 10.9, 8.3, 5.3 Hz, 2 H, NC*H*H **A** and **B**), 3.26–3.15 (m, 2 H, NCH*H* **A** and **B**), 2.86–2.72 (m, 4 H, 2 × C*H*SOPh and 2 × C*H*H **A** and **B**), 1.69–1.56 (m, 2 H, CH*H* **A** and **B**), 0.88 [s, 18 H, 2 × SiC(CH$_3$)$_3$*], 0.79 [s, 18 H, 2 × SiC(CH$_3$)$_3$], 0.15 (s, 6 H, 2 × SiCH$_3$*), 0.11 (s, 6 H, 2 × SiCH$_3$*), 0.06 (s, 6 H, 2 × SiCH$_3$), 0.00 (s, 6 H, 2 × SiCH$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (isomer **A** marked*) = 171.1 (CO*), 168.8 (CO), 142.6 (C*), 141.3 (C), 131.0 (2 × CH **A** and **B**), 129.4 (2 × CH), 129.2 (2 × CH*), 124.2 (2 × CH), 124.0 (2 × CH*), 99.4 (C*), 92.1 (C), 80.7 (CH*), 79.0 (CH), 77.9 (CH*), 76.4 (CH), 69.7 (CH), 62.8 (CH*), 40.8 (CH_2), 39.8 (CH_2*), 26.0 (3 × CH_3*), 25.9 (3 × CH_3), 25.6 (3 × CH_3*), 25.5 (3 × CH_3), 22.8 (CH_2*), 21.7 (CH_2), 18.3 (C*), 18.0 (C), 17.9 (C*), 17.8 (C), –3.7 (CH_3), –3.9 (CH_3*), –4.3 (CH_3), –4.4 (CH_3*), –4.5 (CH_3), –4.6 (CH_3*), –4.7 (CH_3), –5.2 (CH_3*) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3421 (br), 1718 (s), 1445 (m), 1424 (m), 1336 (m), 1256 (m), 1121 (m), 1086 (m), 840 (s) cm^{-1}. MS: *m*/*z* (%) = 526 (2) [M$^+$], 507 (14) [M$^+$ – H_2O], 467 (36), 450 (30), 382 (24), 342 (100), 286 (23), 250 (20), 210 (26), 149 (51), 73 (47). HRMS (ESI-TOF): calcd. for $C_{25}H_{43}NO_5SSi_2Na$ [M$^+$ + Na] 548.2298; found 548.2293.

(1*S*,2*R*)-1,2-Bis(*tert*-butyldimethylsilyloxy)-8-(phenylsulfinyl)-1,2,6,7-tetrahydroindolizin-3(5*H*)-one (9); Preparation with Et_3SiH and BF_3·OEt_2: To a cooled solution of **7a** (196 mg, 0.36 mmol) in anhydrous CH_2Cl_2 (5 mL) at –78 °C was added Et_3SiH (0.6 mL, 3.5 mmol) followed by BF_3·OEt_2 (0.12 mL, 1.1 mmol). The mixture was vigorously stirred and slowly warmed to room temperature for 14 h, then the reaction was quenched with saturated $NaHCO_3$ solution, diluted with water, and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water and brine, then dried with anhydrous Na_2SO_4. After removal of solvent, the crude product was purified by column chromatography [SiO_2 (Art. 7734); EtOAc/hexanes, 2:3] to give **9** (133 mg, 85%; 2:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy) as a white semi-solid. Partial separation of both diastereomers could be achieved by radial chromatography (hexanes to EtOAc/hexanes, 1:1) to give two pure fractions of F_1 and F_2.

Fraction F$_1$ was obtained as a viscous oil (less polar, 46 mg): $[\alpha]_D^{26}$ = +180.8 (*c* = 0.5, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.64 (m, 2 H, PhH), 7.50–7.47 (m, 3 H, PhH), 5.07 (s, 1 H, CHO), 4.21 (s, 1 H, CHO), 3.75 (dt, *J* = 13.2, 5.2 Hz, 1 H, NC*H*H), 3.35 (dt, *J* = 13.2, 6.6 Hz, 1 H, NCH*H*), 2.52 (dt, *J* = 16.5, 5.1 Hz, 1 H, C*H*H), 1.88–1.74 (m, 2 H, CH_2), 1.65–1.56 (m, 1 H, CH*H*), 0.93 [s, 9 H, SiC(CH$_3$)$_3$], 0.91 [s, 9 H, SiC(CH$_3$)$_3$], 0.26 [s, 6 H, Si(CH$_3$)$_2$], 0.17 [s, 6 H, Si(CH$_3$)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6 (CO), 146.8 (C), 142.2 (C), 130.0 (CH), 128.8 (2 × CH), 125.2 (2 × CH), 116.3 (C), 77.3 (CH), 73.8 (CH), 39.0

(CH_2), 25.8 (6 × CH_3), 19.9 (CH_2), 18.2 (C), 17.9 (C), 16.5 (CH_2), –4.0 (CH_3), –4.1 (CH_3), –4.2 (CH_3), –5.0 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 1736 (s), 1657 (s), 1216 (s), 835 (s) cm^{-1}. MS: *m*/*z* (%) = 522 (1) [M^+ + H], 464 (100), 298 (33), 149 (18), 122 (11), 75 (11), 73 (14). HRMS (ESI-TOF): calcd. for $C_{26}H_{43}NO_4SSi_2Na$ [M^+ + Na] 544.2349; found 544.2340.

Fraction F_2 was obtained as viscous oil (more polar, 34 mg): $[\alpha]_D^{26}$ = –120.7 (*c* = 1.7, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.40 (m, 5 H, PhH), 5.00 (s, 1 H, CHO), 4.20 (s, 1 H, CHO), 3.75–3.61 (m, 1 H, NC*H*H), 3.43–3.29 (m, 1 H, NCH*H*), 2.56 (dt, *J* = 16.3, 5.1 Hz, 1 H, C*H*H), 1.95–1.73 (m, 2 H, C*HH*), 1.73–1.55 (m, 1 H, CH*H*), 0.97 [s, 9 H, $SiC(CH_3)_3$], 0.95 [s, 9 H, $SiC(CH_3)_3$], 0.31 (s, 3 H, $SiCH_3$), 0.26 (s, 3 H, $SiCH_3$), 0.25 (s, 3 H, $SiCH_3$), 0.20 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9 (CO), 146.4 (C), 143.0 (C), 130.2 (CH), 129.0 (2 × CH), 124.4 (2 × CH), 116.7 (C), 76.8 (CH), 73.1 (CH), 39.0 (CH_2), 25.8 (3 × CH_3), 25.7 (3 × CH_3), 19.9 (CH_2), 18.2 (C), 18.0 (C), 16.6 (CH_2), –4.1 (CH_3), –4.2 (CH_3), –4.6 (CH_3), –5.0 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 1727 (s), 1658 (s), 1216 (s), 834 (s) cm^{-1}. MS: *m*/*z* (%) = 522 (1) [M^+ + H], 464 (100), 298 (27), 149 (8), 122 (7), 73 (10). HRMS (ESI-TOF): calcd. for $C_{26}H_{43}NO_4SSi_2Na$ [M^+ + Na] 544.2349; found 544.2349.

Preparation of 9 with *p*-TsOH: A solution of **7a** (135 mg, 0.25 mmol) in anhydrous CH_2Cl_2 (5 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid (*p*TsOH) in the presence of 4 Å molecular sieves. The reaction mixture was vigorously stirred and heated to reflux for 2.5 h. After cooling, the reaction mixture was filtered and washed with CH_2Cl_2. The filtrate was evaporated to dryness to give a crude product, which was purified by column chromatography [SiO_2 (Art. 7734); EtOAc/hexanes, 2:3] to give **9** (80 mg, 61%) as a white semi-solid.

Preparation of 9 with BF_3·OEt_2: To a cooled solution of **7a** (113 mg, 0.2 mmol) in anhydrous CH_2Cl_2 (2.5 mL) at –78 °C was added BF_3·OEt_2 (0.07 mL, 0.6 mmol). The mixture was stirred and slowly warmed to room temperature for 6 h, then the reaction was quenched with saturated $NaHCO_3$ solution, diluted with water, and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with water and brine, then dried with anhydrous Na_2SO_4. Purification by column chromatography [SiO_2 (Art. 7734); EtOAc/hexanes, 2:3] gave **9** (89 mg, 78%) as a white semi-solid.

(1*S*,2*R*)-1,2-Bis(*tert*-butyldimethylsilyloxy)-1,2,6,7-tetrahydroindolizin-(5*H*)-one (10):[15] To a solution of the diastereomeric mixture of **9** (89 mg, 0.17 mmol) and $NiCl_2$·$6H_2O$ (405 mg, 1.7 mmol) in anhydrous MeOH (1.5 mL) and anhydrous THF (0.5 mL) at 0 °C was added portionwise $NaBH_4$ (202 mg, 5.3 mmol). The mixture was vigorously stirred and slowly warmed to room temperature for 1 h. Upon completion of the reaction, the precipitate of Ni_2B was removed by filtration and the filtrate was concentrated by evaporation. The resulting mixture was diluted with water and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine and dried with anhydrous Na_2SO_4. After solvent removal, the crude product was purified by column chromatography [SiO_2 (Art. 7734); EtOAc/hexanes, 1:4] to give **10** (51 mg, 74%) as a colorless viscous oil. $[\alpha]_D^{22}$ = +115.8 (*c* = 6.0, $CHCl_3$) [ref.[15] $[\alpha]_D^{24}$ = +111.1 (*c* = 6.02, $CHCl_3$)]. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.95–4.87 (m, 1 H, CHO), 4.62–4.54 (m, 1 H, CHO), 4.17 (dd, *J* = 5.3, 1.2 Hz, 1 H, CH), 3.87–3.71 (m, 1 H, NC*H*H), 2.94 (ddd, *J* = 16.5, 9.9, 3.3 Hz, 1 H, NCH*H*), 1.96–1.87 (m, 2 H, CHC*HH*), 1.49–1.34 (m, 2 H, C*HH*), 0.93 [s, 18 H, 2 × $SiC(CH_3)_3$], 0.21 (s, 3 H, $SiCH_3$), 0.20 (s, 3 H, $SiCH_3$), 0.18 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7 (CO), 137.8 (C), 98.9 (CH), 78.1 (CH), 76.0 (CH), 38.3 (CH_2), 25.8 (3 × CH_3), 25.7 (3 × CH_3), 21.4 (CH_2), 20.5 (CH_2), 18.2 (C), 17.9 (C), –4.0 (CH_3), –4.2 (CH_3), –4.4 (CH_3), –4.5 (CH_3) ppm. IR (Nujol): $\tilde{\nu}$ = 1716 (s), 1463 (s), 1255 (s), 1099 (s) cm^{-1}. MS: *m*/*z* (%) = 397 (2) [M^+], 352 (32), 334 (48), 302 (9), 277 (59), 260 (100), 242 (43), 226 (51), 196 (30), 165 (25), 75 (78).

(1*R*,2*R*)-1,2-Bis(*tert*-butyldimethylsilyloxy)-8a-hydroxyhexahydroindolizin-3(2*H*)-one (8a): To a solution of **7a** (203 mg, 0.38 mmol) and $NiCl_2$·$6H_2O$ (905 mg, 3.8 mmol) in anhydrous MeOH (3.5 mL) and anhydrous THF (1.2 mL) at 0 °C was added portionwise $NaBH_4$ (431 mg, 11.4 mmol). The mixture was stirred and slowly warmed to room temperature for 30 h. Ni_2B was then removed by filtration and the filtrate was evaporated to dryness. The residue was diluted with water, extracted with EtOAc (3 × 10 mL), and the combined extracts were washed with brine and dried with anhydrous Na_2SO_4. Filtration followed by evaporation afforded a crude product, which was purified by column chromatography [SiO_2 (Art. 7736); EtOAc/hexanes, 3:7] to give **8a** (115 mg, 74%) as a single isomer as a white semi-solid. $[\alpha]_D^{24}$ = +6.2 (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.90 (dd, *J* = 13.2, 4.9 Hz, 1 H, NC*H*H), 3.85 (d, *J* = 1.9 Hz, 1 H, CHO), 3.79 (d, *J* = 1.9 Hz, 1 H, CHO), 2.97 (dt, *J* = 13.2, 3.4 Hz, 1 H, NCH*H*), 2.93 (d, *J* = 1.7 Hz, 1 H, OH), 1.89–1.65 (m, 5 H, C*H*H, C*HH*, C*HH*), 1.44–1.28 (m, 1 H, CH*H*), 0.19 [s, 9 H, $SiC(CH_3)_3$], 0.18 [s, 9 H, $SiC(CH_3)_3$], 0.11 [s, 6 H, $Si(CH_3)_2$], 0.10 [s, 6 H, $Si(CH_3)_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$):δ = 170.6 (CO), 89.8 (C), 79.0 (CH), 76.8 (CH), 36.9 (CH_2), 29.6 (CH_2), 25.7 (3 × CH_3), 25.6 (3 × CH_3), 24.1 (CH_2), 18.9 (CH_2), 18.0 (2 × C), –4.5 (CH_3), –4.6 (CH_3), –4.8 (CH_3), –5.1 (CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3404 (br), 1698 (s), 1447 (m), 1259 (m), 1172 (m) cm^{-1}. MS: *m*/*z* (%) = 416 (1) [M^+ + H], 374 (19), 358 (100), 340 (33), 208 (20), 198 (21), 170 (17), 149 (36), 73 (24). HRMS (ESI-TOF): calcd. for $C_{20}H_{41}NO_4SSi_2Na$ [M^+ + Na] 438.2472; found 438.2466.

(+)-Lentiginosine (1): To a suspension of $LiAlH_4$ (25 mg, 0.65 mmol) in anhydrous THF (0.35 mL) was added dropwise a solution of **8a** (53 mg, 0.13 mmol) in anhydrous THF (0.5 mL) at room temperature. The resulting mixture was heated to reflux for 18 h. After cooling at 0 °C, water (0.5 mL) was carefully added followed by 1 N NaOH (0.5 mL) and the resulting mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure to give a crude viscous oil, which was purified by solid phase extraction on reverse phase [C18-LP, MeOH/CH_3CN, 2:3] to give **1** (12 mg, 61%) as a white solid [m.p. 108–109 °C (MeOH)]; $[\alpha]_D^{23}$ = +3.3 (*c* = 0.7, MeOH) [ref.[15] m.p. 106 °C; $[\alpha]_D^{20}$ = +3.0 (*c* = 0.7, MeOH)]. ^1H NMR (400 MHz, D_2O): δ = 4.20–4.11 (m, 1 H, CH), 3.74 (dd, *J* = 8.7, 3.3 Hz, 1 H, CH), 3.17–3.05 (m, 1 H, NC*H*H), 3.04–2.94 (m, 1 H, NCH), 2.93–2.81 (m, 1 H, NC*H*H), 2.41–2.19 (m, 2 H, NCH*H*, NCH*H*), 2.06–1.92 (m, 1 H, C*H*H), 1.92–1.78 (br. d, 2 H, 2 × OH), 1.78–1.65 (m, 1 H, CH*H*), 1.61–1.43 (m, 1 H, C*H*H), 1.43–1.20 (m, 3 H, C*H*H, CH*H*, CH*H*) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 81.9 (CH), 74.9 (CH), 68.4 (CH), 59.6 (CH_2), 52.3 (CH_2), 26.7 (CH_2), 23.3 (CH_2), 22.3 (CH_2) ppm. IR (Nujol): $\tilde{\nu}$ = 3270 (br), 1136 (s), 1106 (s), 677 (s) cm^{-1}. MS: *m*/*z* (%) = 157 (6) [M^+], 149 (19), 129 (16), 121 (19), 117 (16), 111 (23), 109 (16), 105 (16), 97 (37), 95 (42), 83 (30), 67 (100).

(1*R*,2*R*)-1,2-Bis(*tert*-butyldimethylsilyloxy)-7a-hydroxytetrahydro-1*H*-pyrrolizin-3(2*H*)-one (8b):[15] By following the procedure descried for **8a**, a solution of **7b** (203 mg, 0.38 mmol) and $NiCl_2$·$6H_2O$ (905 mg, 3.8 mmol) in anhydrous MeOH (3.5 mL) and anhydrous THF (2 mL) was treated with $NaBH_4$ (431 mg, 11.4 mmol) at 0 °C to room temperature for 30 h to give a crude product, which was purified by column chromatography [SiO_2 (Art. 7736); EtOAc/hexanes, 3:7] to give **8b** (51 mg, 74%) as a single isomer as a white

solid (m.p. 104–105 °C); $[\alpha]_D^{25}$ = +43.3 (*c* = 1, $CHCl_3$)]. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.55–4.45 (m, 1 H, CH), 3.98 (d, *J* = 7.7 Hz, 1 H, CH), 3.75 (s, 1 H, OH), 3.51–3.42 (m, 1 H, NC*H*H), 3.38–3.26 (m, 1 H, NCH*H*), 2.40–2.20 (m, 1 H, C*H*H), 2.14–1.97 (m, 2 H, 2 ×CH*H*), 1.68–1.50 (m, 1 H, CH*H*), 0.94 [s, 18 H, 2 × $SiC(CH_3)_3$], 0.20 (s, 3 H, $SiCH_3$), 0.18 (s, 3 H, $SiCH_3$), 0.14 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3 (CO), 91.5 (C), 80.7 (CH), 78.9 (CH), 41.4 (CH_2), 38.8 (CH_2), 25.8 (3 × CH_3), 25.7 (3 × CH_3), 24.1 (CH_2), 18.3 (C), 17.8 (C), –4.3 (2 × CH_3), –4.6 (CH_3), –4.8 (CH_3) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3523 (br), 1717 (s), 1259 (s), 1123 (s) cm^{-1}. MS: *m*/*z* (%) = 403 (6) [M^+ + H], 385 (100), 345 (43), 212 (16),185 (33), 157 (29). HRMS (ESI-TOF): calcd. for $C_{19}H_{39}NO_4SSi_2Na$ [M^+ + Na] 424.2315; found 424.2315.

(1*S*,2*S*,7a*S*)-1,2-Dihydroxypyrrolizidine (2): A solution of **8b** (600 mg, 1.5 mmol) in anhydrous THF (5 mL) was added to a suspension of $LiAlH_4$ (286 mg, 7.5 mmol) in anhydrous THF (4 mL) at room temperature. The mixture was heated to reflux for 18 h, then, after cooling at 0 °C, water (4 mL) was carefully added to the reaction mixture followed by addition of 1 N NaOH (4 mL). The resulting mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure to give a crude viscous oil, which was purified by solid-phase extraction on reverse phase [C18-LP, CH_3CN/MeOH (2:3)] to give lentiginosine analogue **2** (154 mg, 72%) as a white solid (m.p. 163–164 °C); $[\alpha]_D^{23}$ = +11.3 (*c* = 0.5, MeOH) [ref.[11] m.p. 164–165 °C; $[\alpha]_D^{23}$ = +11 (*c* = 0.5, MeOH)]. ^1H NMR (400 MHz, CD_3OD): δ = 4.04 (ddd, *J* = 7.1, 5.8, 5.8 Hz, 1 H, CH), 3.64 (dd, *J* = 5.8, 5.8 Hz, 1 H, CH), 3.26–3.17 (m, 2 H, NC*H*H, NCH), 2.92 (ddd, *J* = 10.4, 6.0, 6.0 Hz, 1 H, NC*H*H), 2.72 (ddd, *J* = 10.4, 6.4, 6.4 Hz, 1 H, NCH*H*), 2.54 (dd, *J* = 10.6, 7.2 Hz, 1 H, NCH*H*), 2.03–1.84 (m, 2 H, C*H*H, C*H*H), 1.84–1.65 (m, 2 H, CH*H*, CH*H*) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 83.0 (CH), 78.7 (CH), 70.7 (CH), 59.6 (CH_2), 56.6 (CH_2), 31.4 (CH_2), 26.2 (CH_2) ppm. IR (Nujol): $\tilde{\nu}$ = 3271 (br), 1136 (s), 1105 (m), 1095 (s), 677 (s) cm^{-1}. MS: *m*/*z* (%) = 143 (6) [M^+], 83 (72), 82 (64), 78 (21), 70 (42), 67 (18), 55 (100), 54 (60). HRMS (ESI-TOF): calcd. for $C_7H_{14}NO_2$ [M^+ + H] 144.1025; found 144.1023.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra of compounds **1**–**10**.

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