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New Access to Indolizidine and Pyrrolizidine Alkaloids from an Enantiopure Proline: Total Syntheses of (−)-Lentiginosine and (1*R*,2*R*,7a*R*)-Dihydroxypyrrolizidine

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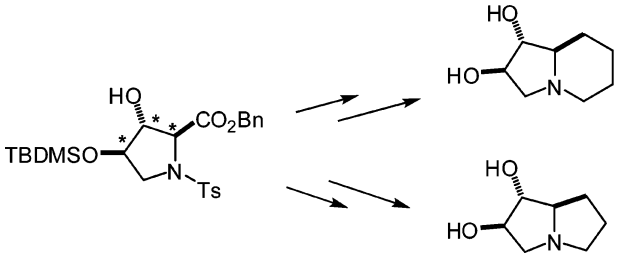

A new approach to the synthesis of indolizidine and pyrrolizidine skeletons is reported. (−)-Lentiginosine and (1*R*,2*R*,7a*R*)-dihydroxypyrrolizidine have both been synthesized in 13 steps from di-*O*-isopropylidene-D-mannitol. The common key intermediate is (−)-dihydroxyproline benzyl ester **10**.

Introduction

The polyhydroxylated indolizidine and pyrrolizidine alkaloids display a wide range of biological activity,[1a−e] mainly as glycosidase inhibitors and anti-HIV agents,[1g−i] and have been the subject of a considerable number of synthetic studies.[2−4] Lentiginosine **1**, *trans*-1,2-dihydroxyindolizidine,[5] was isolated in 1990 from a sample of *Astragalus lentiginosus*,[6] and in spite of its low degree of hydroxylation, it is the most potent inhibitor of amyloglucosidases among azasugars and their analogues. Our group has recently developed a diastereoselective synthesis of highly functionalized 3-hydroxyproline benzyl esters from α-alkoxy N-protected aminoaldehydes and benzyl diazoacetate[7]

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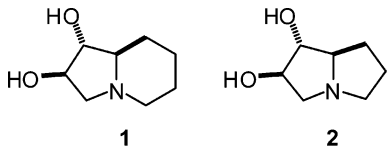

FIGURE 1. Structures of (−)-lentiginosine **1** and (1*R*,2*R*,7a*R*)-dihydroxypyrrolizidine **2**.

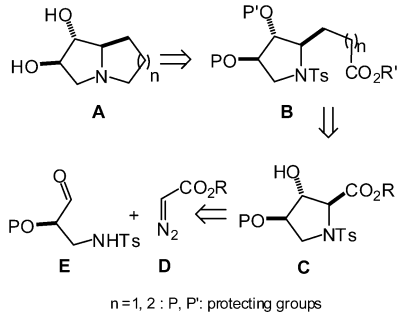

FIGURE 2. Retrosynthetic analysis.

that might find application as part of a general synthetic route to enantiopure indolizidine and pyrrolizidine alkaloids. Our working hypothesis for the mechanism of the proline and THF forming reactions is one in which the diazoester acts as a nucleophile toward the aldehyde or participates in a 1,3-dipolar cycloaddition with the aldehyde.[7] We report here the refinement of this methodology and a new strategy for the synthesis of non-natural (−)-lentiginosine **1** and its pyrrolizidine analogue **2** (Figure 1). This new approach, which allows access to dihydroxyindolizidine (**A**, $n = 2$) or dihydroxypyrrolizidine (**A**, $n = 1$), is illustrated in Figure 2.

Reaction of the enantiopure aldehyde **E** with diazoester **D** should diastereoselectively provide the chiral 3,4-dihydroxyproline ester **C** with a *trans*−*trans* relative configuration. Protection of the hydroxy group and transformation of the ester functionality to a homologated side chain (intermediate **B**) followed by concomitant N-detosylation/cyclization should provide the target molecules **A** after reduction of the lactam and deprotection of the hydroxy groups.

Results and Discussion

Synthesis of the Enantiopure Aldehyde 9. Enantiomerically pure α-hydroxyaldehyde **9** has been synthesized in 25% overall yield and six steps (Scheme 1) from commercially available di-*O*-isopropylidene-D-mannitol **3** (prepared from inexpensive, chiral, naturally occurring compound, D-mannitol). Each molecule of protected D-mannitol **3** provides two molecules of chiral aldehyde **9** after cleavage of the C3−C4 bond. We first used the mild and stereospecific deoxygenation procedure described by Hanessian and co-workers[8a] to convert the vicinal diol **3** into the corresponding *trans*-olefin **4**[8b,c] in 86% yield. Removal of the acetonides using the acidic resin Amberlyst-15 in methanol[9a] led to the known tetraol **5**[9b] in 83% yield. Regioselective bistosylation of the two primary hydroxy groups of **5** was achieved in 66% yield to furnish compound **6** via the bis(dibutylstannylene acetal) intermediate following Dureault's procedure.[10] The secondary hydroxy groups were protected as *tert*-butyldimethylsilyl ethers[11] to provide compound **7** in 92% yield. Reaction of ditosylate **7** and $NaNHTs$[12a] in DMSO at 80 °C led to the bis(*p*-toluenesulfonamide) derivative **8**, which was cleaved by ozone using thiourea[12b] to provide optically pure aldehyde **9** in 81% yield.

Synthesis of Prolinol 13. Aldehyde **9** was reacted with benzyl diazoacetate with slow addition of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 °C to afford enantiopure proline **10** in 65% yield and β-ketoester byproduct **11** in 24% yield (Scheme 2). We have previously described the synthesis of racemic **10** and shown that it has a *trans*−*trans* relative configuration between the substituents.[7] We were able to obtain reproducible results only when $BF_3{\cdot}OEt_2$ and the aldehyde **9** were rigorously purified, when 3.5 equiv of benzyl diazoacetate and 2.5 equiv of $BF_3{\cdot}OEt_2$ were used, and when $BF_3{\cdot}OEt_2$ was added very slowly (syringe pump). It is interesting to note that, while the yield of proline increased from 37 to 65% from our previous work, β-ketoester **11** was not isolated in our previous work, though in this study, it is formed in 24% yield.

The hydroxy group of proline **10** was then protected using an excess of MEM-Cl and Hunig's base in refluxing $CHCl_3$[13] to provide **12** in 78% yield (Scheme 3). Reduction with $NaBH_4$ in EtOH gave the prolinol **13** in 88% yield, a key intermediate for the synthesis of both the indolizidine and pyrrolizidine skeletons. It should be noted that attempts to protect the free hydroxy group of **10** as the *tert*-butyldimethylsilyl ether failed, likely due to steric hindrance.

To evaluate the enantiomeric purity of proline **10**, NMR examination of chiral MEM-protected proline **12** was performed

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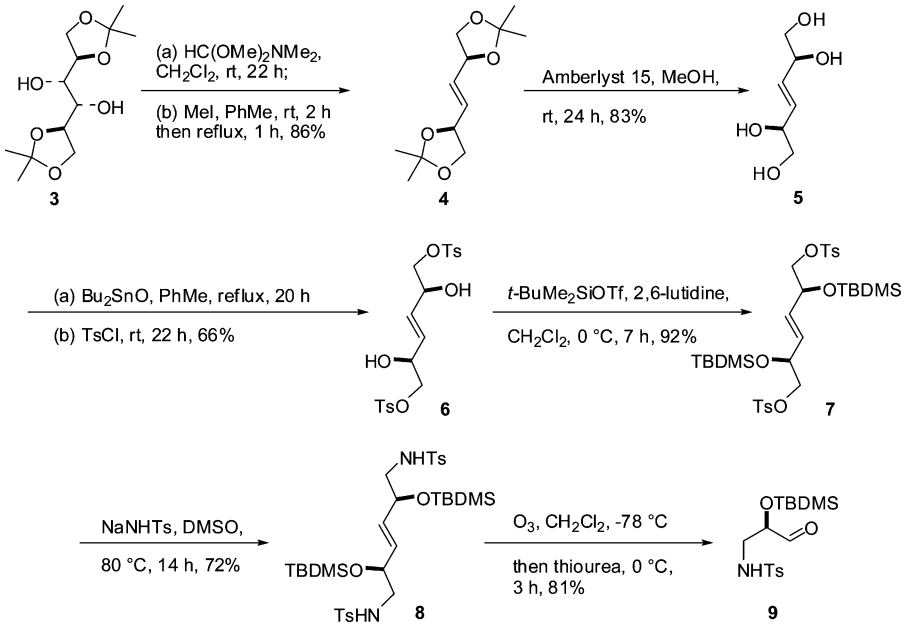
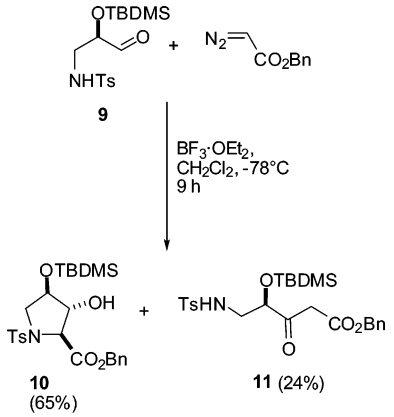
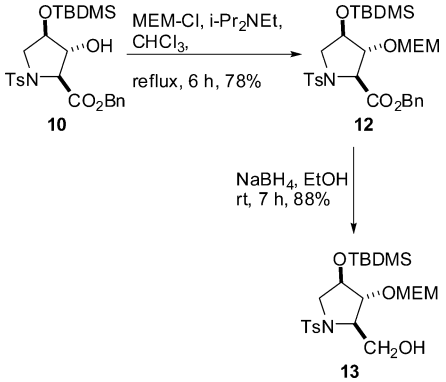
SCHEME 1. Synthesis of Enantiopure Aldehyde 9



SCHEME 2. Synthesis of Enantiopure Dihydroxyproline Benzyl Ester 10



SCHEME 3. Synthesis of the Key Intermediate 13



in the presence of the chiral shift reagent[14] Eu(hfc)$_3$ and compared to racemic **12** (see Supporting Information). This study showed **12** to be >95% ee, and thus no racemization of aldehyde **9** occurred in the reaction with BF_3·OEt_2 and benzyl diazoacetate. Thus, proline **10** must also be >95% ee.

Synthesis of (−)-Lentiginosine. Treatment of prolinol **13** with I_2 and PPh_3 in CH_2Cl_2 in the presence of imidazole at reflux for 12 h afforded iodide **14** in 86% yield (Scheme 4).[15] Excess imidazole was required to prevent cleavage of the protecting groups of **13**. Radical reaction of iodide **14** with methyl acrylate[16] afforded ester **15** in 57% yield. Treatment of **15** with magnesium ribbon in methanol[17] gave lactam **16** in 75% yield after concomitant N-detosylation/cyclization. $LiAlH_4$ reduction of the lactam and cleavage of the *tert*-butyldimethylsilyl ether of **16**, followed by removal of the MEM ether using CBr_4 in refluxing methanol,[18] provided (−)-lentiginosine **1** in 54% yield. Spectral data for **1** were identical to those reported in the literature.[6]

Synthesis of (1*R*,2*R*,7a*R*)-1,2-Dihydroxypyrrolizidine 2. Swern oxidation[19] of prolinol **13** followed by Wittig homologation using (carbethoxymethylene)triphenylphosphorane provided acrylate **17** in 92% yield (Scheme 5). Treatment of **17** with magnesium in methanol failed to afford the expected lactam **19**. Instead, only reduction of the olefin and degradation of the substrate were observed. We were able to obtain the desired product by first reducing the alkene of **17** (H_2, 10% Pd/C) to afford the ester **18** in 93% yield. Treatment of **18** with magnesium afforded lactam **19** in 98% yield. Reduction of the lactam and cleavage of the protecting groups of **19** gave 1,2-dihydroxypyrrolizidine **2**[20] in 51% yield. For characterization purposes, **2** was treated with HCl in methanol to afford the corresponding hydrochloride salt, **2·HCl**.[20]

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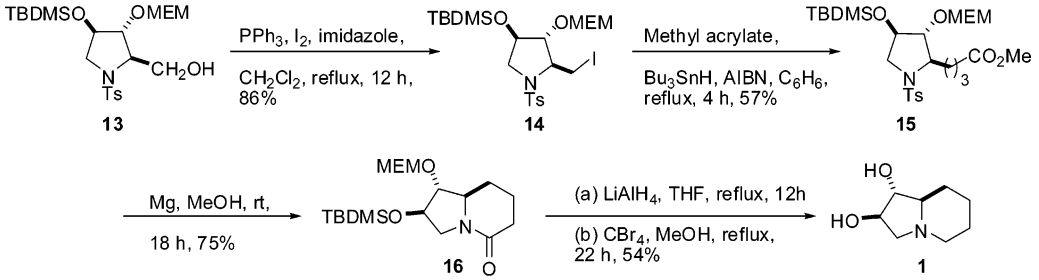
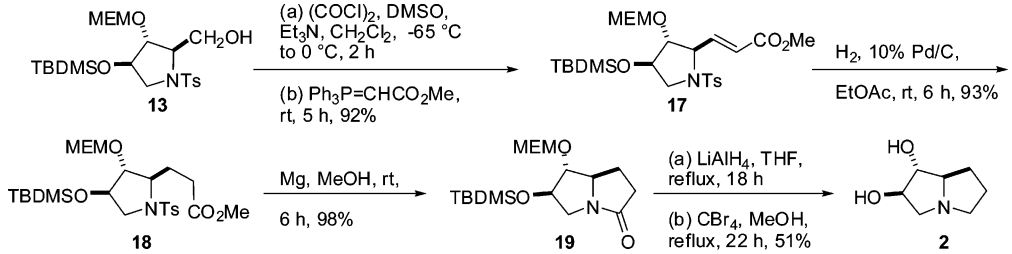
SCHEME 4. Synthesis of (−)-Lentiginosine 1



SCHEME 5. Synthesis of (1*R*,2*R*,7a*R*)-1,2-Dihydroxypyrrolizidine 2



Conclusion

Syntheses of (−)-lentiginosine **1** and (1*R*,2*R*,7a*R*)-1,2-dihydroxyindolizidine **2** were accomplished in seven steps (14 and 29% overall yields) from enantiopure proline **10** obtained from di-*O*-isopropylidene-D-mannitol **3** in six steps (16% overall yield). These syntheses demonstrate the utility of our proline annulation strategy for the synthesis of enantiopure indolizidine and pyrrolizidine alkaloids.

Experimental Section

General Information. HPLC was carried out on a 4.6 × 250 mm column. Flow rate = 0.5 mL/min; the appropriate mixture of hexanes/methanol was used.

(2*R*)-*N*-[2-(*tert*-Butyldimethylsilyloxy)-3-oxopropyl]-4-methylbenzenesulfonamide (9). A solution of **8** (2.70 g, 3.95 mmol) in CH_2Cl_2 (45 mL) at −78 °C was treated with ozone (10 min at 3 psi). Thiourea (0.72 g, 4.09 mmol) was added, and the reaction mixture was stirred for 3 h at 0 °C under argon, filtered through a short pad of Celite, and concentrated. Flash chromatography[21] (2:1 hexanes/EtOAc) gave aldehyde **9** (2.3 g, 81%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 9.57 (s, 1H), 7.73 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 4.74 (br t, J = 6.4 Hz, 1H), 4.10 (t, J = 5.4 Hz, 1H), 3.19 (m, 2H), 2.44 (s, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.1, 143.9, 136.5, 130.0, 127.3, 75.9, 44.9, 25.8, 21.7, 18.2, −4.6, −4.9; IR (CH_2Cl_2) 3365, 2931, 2858, 1735, 1598 cm^{-1}; $[\alpha]_D^{24}$ +1.7 (*c* 10, CH_2Cl_2); MS (FAB, NBA/NaCl) *m*/*z* 380 (MNa^+, 7), 358 (MH^+, 9), 327 (19), 281 (22), 207 (28), 184 (45); HRMS (FAB, NBA/PEG) calcd for $C_{16}H_{28}NO_4SiS$ (MH^+) 358.1508, found 358.1500.

(2*S*,3*R*,4*R*)-Benzyl-4-(*tert*-butyldimethylsilyloxy)-3-hydroxy-1-(toluene-4-sulfonyl)pyrrolidine-2-carboxylate (10) and (4*R*)-Benzyl-4-(*tert*-butyldimethylsilyloxy)-3-oxo-5-(toluene-4-sulfonylamino)pentanoate (11). To a solution of **9** (450 mg, 1.26 mmol) in CH_2Cl_2 (5 mL) at −78 °C under N_2 was added benzyl diazoacetate (860 mg, 4.89 mmol) in CH_2Cl_2 (2 mL) via cannula. $BF_3{\cdot}OEt_2$ (0.440 mL, 3.50 mmol; freshly distilled over CaH_2; 46 °C/10 mmHg) in CH_2Cl_2 (9.5 mL) was then added over 12 h via syringe pump. The reaction mixture was stirred for an additional 2 h at −78 °C and then poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (4:1 hexanes/EtOAc) gave proline **10** (417 mg, 65%) as a clear oil and β-ketoester **11** (150 mg, 24%) as a clear oil. **10**: ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2H), 7.36 (m, 5H), 7.24 (d, J = 8.2 Hz, 2H), 5.16 (ABq, J = 12.3 Hz, $\Delta\nu$ = 10.9 Hz, 2H), 4.38 (d, J = 2.1 Hz, 1H), 4.35 (br s, 1H), 4.02 (dt, J = 2.6, 5.1 Hz, 1H), 3.61 (dd, J = 5.1, 10.3 Hz, 1H), 3.23 (dd, J = 2.6, 10.3 Hz, 1H), 1.60−1.50 (br s, 1H), 2.40 (s, 3H), 0.81 (s, 9H), −0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 169.3, 143.6, 135.4, 135.3, 129.5, 128.5, 128.2, 128.0, 127.8, 79.9, 75.8, 67.4, 53.9, 25.5, 21.6, 17.9, −5.0, −5.0; IR (neat) 3486, 2947, 2928, 2893, 1759 cm^{-1}; $[\alpha]_D^{24}$ −39.6 (*c* 5, CH_2Cl_2); MS (CI, NH_3) *m*/*z* 523 (MNH_4^+, 5), 506 (MH^+, 100), 350 (67), 260 (13), 216 (41); HRMS (CI, NH_3) calcd for $C_{25}H_{36}NO_6SiS$ (MH^+) 506.2033, found 506.2026. **11** (mixture of keto and enol tautomers, 80:20 by ^{1}H NMR): ^{1}H NMR (keto form, $CDCl_3$) δ 7.76 (d, J = 8.2 Hz, 2H), 7.45 (m, 5H), 7.29 (d, J = 8.2 Hz, 2H), 5.15 (m, 2H), 4.90 (br m, 1H), 3.61 (ABq, J = 16.4 Hz, $\Delta\nu$ = 31.9 Hz, 2H), 3.35−2.98 (m, 2H), 2.42 (s, 3H), 0.87 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (keto form, $CDCl_3$) δ 204.4, 166.9, 143.6, 136.6, 135.1, 127.8, 127.7, 127.4, 127.1, 70.6, 66.1, 46.0, 45.3, 25.7, 21.6, 18.0, −4.6, −4.9; IR ($CDCl_3$) 3547, 3386, 3035, 2931, 2859, 1740, 1719 cm^{-1}; $[\alpha]_D^{24}$ −3.4 (*c* 1, CH_2Cl_2); MS (CI/NH_3) *m*/*z* 523 (MNH_4^+, 32), 375 (100), 332 (69), 213 (18), 184 (41), 174 (14); HRMS (CI/NH_3) calcd for $C_{25}H_{39}N_2O_6SiS$ (MNH_4^+) 523.2298, found 523.2288.

(2*S*,3*R*,4*R*)-Benzyl-4-(*tert*-butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxy)-1-(toluene-4-sulfonyl)pyrrolidine-2-carboxylate (12).[13] To a stirring solution of **10** (340 mg, 0.67 mmol) in $CHCl_3$ (15 mL) at −25 °C under N_2 were added (*i*-Pr_2)NEt (1.8 mL, 10.1 mmol) and then MEM-Cl (0.92 mL, 8.1 mmol).[13] The reaction mixture was allowed to warm to room temperature and then refluxed for 6 h. The mixture was then cooled, and saturated aqueous $NaHCO_3$ (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic extracts were washed with 1 M $KHSO_4$ (20 mL), followed by brine (20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (4:1 hexanes/EtOAc) gave **12** (313 mg, 78%) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2H), 7.36 (m, 5H), 7.22 (d,

(20) The NMR obtained for **2** was the same as the enantiomer synthesized by Ha and co-workers[4f] but totally different from that published by Genisson and co-workers.[4a] We believe that the last authors might have synthesized the hydrochloride form of **2** and not the free base since the spectral data for **2·HCl** are similar to those reported by Genisson and co-workers.[4a]

(21) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

J = 8.2 Hz, 2H), 5.15 (s, 2H), 4.64 (ABq, J = 7.0 Hz, $\Delta\nu$ = 26.6 Hz, 2H), 4.56 (d, J = 1.2 Hz, 1H), 4.32 (br s, 1H), 4.18 (dt, J = 2.1, 4.1 Hz, 1H), 3.51−3.59 (m, 3H), 3.45−3.51 (m, 2H), 3.35 (s, 3H), 3.23 (dd, J = 1.7, 11.1 Hz, 1H), 2.40 (s, 3H), 0.81 (s, 9H), −0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 168.8, 143.3, 135.6, 135.4, 129.3, 128.4, 128.1, 127.9, 127.8, 94.6, 84.7, 74.8, 71.6, 67.5, 67.2, 65.6, 59.0, 54.4, 25.6, 21.6, 18.0, −4.9; IR ($CDCl_3$) 3068, 3035, 2931, 1754, 1599 cm^{-1}; $[\alpha]_D^{24}$ −43.9 (c 10, CH_2Cl_2); MS (FAB, NBA/NaCl) m/z 616 (MNa^+, 100), 594 (MH^+, 31), 488 (6), 370 (10), 327 (6), 281 (12), 207 (18); HRMS (FAB, NBA/NaCl) calcd for $C_{29}H_{43}NO_8NaSiS$ (MNa^+) 616.2382, found 616.2376.

(2*R*,3*R*,4*R*)-[4-(*tert*-Butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxy)-1-(toluene-4-sulfonyl)pyrrolidin-2-yl]methanol (13). To a stirring solution of **12** (180 mg, 0.3 mmol) in EtOH(1.0 mL) at 0 °C under N_2 was added $NaBH_4$ (57.0 mg, 1.51 mmol). After stirring at room temperature for 7 h, the reaction mixture was poured into EtOAc (1 mL). The organic layer was combined with 5% aqueous citric acid (5 mL), extracted with EtOAc (3 × 5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (2:1 hexanes/EtOAc) gave prolinol **13** (130 mg, 88%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 4.48 (apparent q, J = 6.7 Hz, 2H), 3.98−3.88 (m, 5H), 3.80 (dd, J = 4.6, 11.5 Hz, 1H), 3.62 (dt, J = 2.0, 5.4 Hz, 1H), 3.51−3.40 (m, 4H), 3.38 (s, 3H), 2.44 (s, 3H), 0.86 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.1, 134.0, 127.9, 94.5, 83.7, 74.5, 71.7, 67.3, 67.2, 64.1, 59.2, 55.3, 25.8, 21.7, 18.1, −4.6, −4.9; IR (CH_2Cl_2) 3503, 2931, 2892, 1598 cm^{-1}; $[\alpha]_D^{24}$ −32.2 (c 7.5, CH_2Cl_2); MS (FAB, NBA) m/z 512 (MNa^+, 58), 490 (MH^+, 19), 414 (100), 222 (24), 155 (29); HRMS (FAB, NBA) calcd for $C_{22}H_{40}NO_7SiS$ (MH^+) 490.2298, found 490.2295.

(2*R*,3*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-iodomethyl-3-(2-methoxyethoxymethoxy)-1-(toluene-4-sulfonyl)pyrrolidine (14). I_2 (114 mg, 0.45 mmol) was added to a stirred solution of PPh_3 (118 mg, 0.45 mmol) in CH_2Cl_2 (2 mL) at room temperature under N_2.[15] After 5 min, imidazole (70 mg, 1.02 mmol) was added. After an additional 5 min, **13** (100 mg, 0.20 mmol) dissolved in CH_2Cl_2 (3 mL) was added via cannula to the reaction mixture, and the resulting solution was refluxed for 12 h. The crude mixture was filtered through Celite, washed with CH_2Cl_2 (20 mL), and concentrated. The residue was dissolved in EtOAc (15 mL), washed with 10% aqueous $Na_2S_2O_3$ (15 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (4:1 hexanes/EtOAc) gave **14** (105 mg, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 4.42 (ABq, J = 6.9 Hz, $\Delta\nu$ = 50.5 Hz, 2H), 4.17 (br s, 1H), 4.08 (br d, J = 4.1 Hz, 1H), 3.79−3.60 (m, 2H), 3.60−3.41 (m, 6H), 3.36 (s, 3H), 3.30 (dd, J = 4.6, 10.3 Hz, 1H), 2.42 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.6, 133.7, 129.4, 127.7, 93.5, 83.5, 74.3, 71.5, 67.1, 67.0, 59.1, 56.3, 25.6, 21.5, 17.9, −5.1, −5.2; IR ($CDCl_3$) 2931, 2892, 2859 1471, 1347 cm^{-1}; $[\alpha]_D^{24}$ −139.0 (c 0.5, CH_2Cl_2); MS (FAB, NBA) m/z 600 (MH^+, 71), 524 (100), 494 (16), 366 (10), 281 (6); HRMS (FAB, NBA/PEG) calcd for $C_{22}H_{39}INO_6SiS$ (MH^+) 600.1335, found 600.1312.

(2*R*,3*S*,4*R*)-Methyl-4-[4-(*tert*-butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxy)-1-(toluene-4-sulfonyl)pyrrolidin-2-yl]butyrate (15). A solution of Bu_3SnH (0.094 mL, 0.35 mmol) and AIBN (8.5 mg, 0.052 mmol) in C_6H_6 (1 mL) was added via syringe pump over 4 h to a refluxing solution of **14** (105 mg, 0.175 mmol), methyl acrylate (0.16 mL, 1.75 mmol), and AIBN (5.5 mg, 0.035 mmol) in C_6H_6 (1.5 mL) under N_2.[16] After an additional 0.5 h, the reaction mixture was cooled and concentrated. The residue was dissolved in CH_3CN (10 mL), washed with hexanes (2 × 5 mL), and concentrated. Flash chromatography (4:1 hexanes/EtOAc) gave **15** (56 mg, 57%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 4.41 (ABq, J = 6.7 Hz, $\Delta\nu$ = 22.1 Hz, 2H), 3.98 (br m, 1H), 3.78 (br m, 1H), 3.68 (s, 3H), 3.53 (partially obscured br t, J = 6.7 Hz, 1H), 3.50−3.41 (m, 3H), 3.37 (s, 3H), 3.35 (m, 1H), 2.37 (s, 3H), 2.35 (m, 2H), 1.94−1.85 (m, 2H), 1.75−1.60 (m, 2H), 1.43−1.26 (m, 2H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.9, 143.3, 134.6, 129.5, 127.9, 94.0, 84.1, 75.1, 71.6, 67.2, 65.6, 59.2, 55.0, 51.7, 34.0, 33.4, 25.7, 21.9, 21.6, −4.9; IR (CH_2Cl_2) 2954, 2888, 2859, 1732 cm^{-1}; $[\alpha]_D^{22}$ −46.7 (c 1.3, CH_2Cl_2); MS (FAB, NBA) m/z 582 (MNa^+, 10), 560 (MH^+, 6), 496 (5), 474 (4), 401 (6), 355 (5), 281 (21); HRMS (FAB, NBA/NaCl) calcd for $C_{26}H_{45}NO_8NaSiS$ (MNa^+) 582.2533, found 582.2539.

(1*R*,2*R*,9a*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-(2-methoxyethoxymethoxy)hexahydroindolizidin-5-one (16). To a stirred suspension of activated Mg ribbon (43.0 mg, 0.090 mmol) in MeOH (2 mL) under N_2 at room temperature was added **15** (50.0 mg, 0.09 mmol) dissolved in MeOH (2 mL) via cannula.[17] After 15 h at room temperature, the reaction mixture was concentrated, and the residue was dissolved in EtOAc (10 mL), filtered through a short pad of Celite, and concentrated. Flash chromatography (1:3 hexanes/EtOAc) gave **16** (25.0 mg, 75%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.82 (ABq, J = 6.7 Hz, $\Delta\nu$ = 35.8 Hz, 2H), 4.19 (dd, J = 6.2, 13.3 Hz, 1H), 3.82−3.58 (m, 4H), 3.58−3.52 (m, 2H), 3.46 (dd, J = 6.2, 12.3 Hz, 1H), 3.39 (s, 3H), 3.40−3.28 (partially m, 1H), 2.47−2.16 (m, 3H), 2.02−1.90 (m, 1H), 1.78−1.56 (m, 1H), 1.52−1.22 (m, 1H), 0.86 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.2, 95.6, 86.6, 74.3, 71.8, 67.4, 61.0, 59.2, 50.0, 31.0, 27.4, 25.8, 20.8, −4.2, −4.8, IR (CH_2Cl_2) 3054, 2931, 2888, 2858, 1634 cm^{-1}; $[\alpha]_D^{24}$ +16.2 (c 0.85, CH_2Cl_2); MS (CI/NH_3) m/z 374 (MH^+, 100), 316 (42), 286 (11), 133 (28); HRMS (CI/NH_3) calcd for $C_{18}H_{36}NO_5Si$ (MH^+) 374.2363, found 374.2369.

(1*R*,2*R*,8a*R*)-1,2-Dihydroxyindolizidine (1), ((−)-Lentiginosine). $LiAlH_4$ (14.0 mg, 0.374 mmol) was added to a solution of **16** (35 mg, 0.094 mmol) in THF (3 mL) at 0 °C under N_2. After stirring for 5 min, the suspension was refluxed for 6 h. The suspension was then cooled to 0 °C, and water (0.4 mL), 15% aqueous NaOH (0.8 mL), water (0.4 mL) and Na_2SO_4 were sequentially added. The crude mixture was filtered through a short pad of Celite, rinsed with EtOAc (20 mL), and concentrated. The reduction was incomplete by ^{1}H NMR analysis, and the crude product was resubmitted to treatment with $LiAlH_4$ (14.0 mg, 0.374 mmol) in THF (3 mL) at 0 °C under N_2. After stirring for 5 min, the suspension was refluxed for 12 h. Workup as above afforded 24 mg of crude product. The crude product was then dissolved in MeOH (1 mL), and CBr_4 (62.0 mg, 0.188 mmol) was added. The resulting solution was refluxed under N_2 for 22 h and then concentrated. Flash chromatography (80:19:1 CH_2Cl_2/MeOH/30% NH_4OH) gave the known[5a] compound **1** (8 mg, 54%) as a white solid: mp = 106−108 °C (lit.[5a] mp = 106−107 °C); ^{1}H NMR (D_2O) δ 4.04 (ddd, J = 2.1, 3.9, 7.4 Hz, 1H), 3.62 (dd, J = 3.8, 8.5 Hz, 1H), 2.93 (br d, J = 10.8 Hz, 1H), 2.81 (dd, J = 1.5, 11.3 Hz, 1H), 2.59 (dd, J = 7.7, 11.3 Hz, 1H), 2.02 (dt, J = 2.9, 11.6 Hz, 1H), 1.91 (m, 2H), 1.79 (m, 1H), 1.62 (br d, J = 15.4 Hz, 1H), 1.43 (m, 1H), 1.23 (br t, J = 9.2 Hz, 2H); ^{13}C NMR (D_2O) δ 85.1, 77.8, 70.6, 62.4, 54.7, 29.8, 26.2, 25.2; IR (neat) 3757, 3692, 2986 cm^{-1}; $[\alpha]_D^{23}$ −2.5 (c 1.2, MeOH), $[\alpha]_D^{25}$ −4.2 (c 1.2, MeOH) (lit.[5b] $[\alpha]_D$ −3.05 (c 1.0, MeOH), $[\alpha]_D^{23}$ −1.6 (c 0.24, MeOH),[5a] $[\alpha]_D^{25}$ −4.5 (c 0.8, MeOH)[5i]); MS (EI+) m/z 157 (M^+, 21), 140 (11), 126 (9), 97 (100); HRMS (EI+) calcd for $C_8H_{15}NO_2$ (M^+) 157.1103, found 157.1106.

Methyl-(2*R*,3*R*,4*R*)-[4-(*tert*-butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxy)-1-(toluene-4-sulfonyl)pyrrolidin-2-yl]acrylate (17). DMSO (0.16 mL, 2.2 mmol) in CH_2Cl_2 (0.65 mL) was added carefully to a stirring solution of $(COCl)_2$ (0.095 mL, 1.1 mmol) in CH_2Cl_2 (1.2 mL) at −60 °C under N_2.[19] The reaction mixture was stirred for 15 min at −60 °C, and then alcohol **13** (310 mg, 0.63 mmol) in CH_2Cl_2 (2.5 mL) was added via cannula. After an additional 15 min, Et_3N (0.70 mL, 5.05 mmol) was added. The reaction mixture was kept at −50 °C for 0.5 h and then warmed in a brine−ice bath for 1.5 h. CH_2Cl_2 (6 mL) and methyl-(triphenylphosphoranylidene)acetate (450 mg, 1.34 mmol) were added, and the reaction mixture was allowed to warm up to room temperature. After 5 h, H_2O (5 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined

organic extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (2:1 hexanes/EtOAc) gave **17** (315 mg, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 6.96 (dd, J = 6.9, 15.9 Hz, 1H), 6.08 (d, J = 15.9 Hz, 1H), 4.50 (ABq, J = 7.2 Hz, $\Delta\nu$ = 21.3 Hz, 2H), 4.26 (d, J = 7.2 Hz, 1H), 4.08 (m, 1H), 3.83 (br s, 1H), 3.72 (s, 3H), 3.49 (s, 4H), 3.48 (partially obscured dd, J = 4.1, 10.7 Hz, 1H), 3.41 (partially obscured dd, J = 1.7, 10.3 Hz, 1H), 3.37 (s, 3H), 2.43 (s, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.4, 145.8, 143.5, 129.5, 127.8, 122.1, 94.5, 86.0, 74.9, 71.6, 67.4, 65.8, 59.2, 55.2, 51.6, 25.7, 21.7, 18.0, −4.8; IR ($CDCl_3$) 2932, 2887, 2859, 1715, 1664 cm^{-1}; $[\alpha]_D^{24}$ −101.7 (*c* 4, CH_2Cl_2); MS (FAB, NBA) *m*/*z* 566 (MNa^+, 62), 544 (MH^+, 44), 468 (53), 270 (27). HRMS (FAB, NBA/PEG) calcd for $C_{25}H_{42}NO_8SiS$ (MH^+) 544.2400, found 544.2424.

Methyl-(2*R*,3*R*,4*R*)-3-[4-(*tert*-butyldimethylsilyloxy)-3-(2-methoxyethoxymethoxy)-1-(toluene-4-sulfonyl)pyrrolidin-2-yl]propionate (18). To a solution of **17** (300 mg, 0.55 mmol) in EtOAc (15 mL) at room temperature under N_2 was added 10% Pd/C (120 mg, 0.027 mmol). A balloon of H_2 was then attached, and the reaction mixture was stirred for 6 h. The suspension was then filtered through a short pad of Celite and concentrated. Flash chromatography (2:1 hexanes/EtOAc) gave **18** (280 mg, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 4.43 (ABq, J = 6.9 Hz, $\Delta\nu$ = 37.5 Hz, 2H), 3.94 (overlapping dt, J = 1.8, 3.8 Hz, 1H), 3.75 (t, J = 1.5 Hz, 1H), 3.70 (s, 3H), 3.52−3.43 (m, 5H), 3.37 (s, 3H), 3.42−3.29 (partially obscured m, 2H), 2.67−2.42 (m, 2H), 2.42 (s, 3H), 2.26−2.02 (m, 2H), 0.85 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 173.7, 143.3, 134.6, 129.4, 128.1, 94.0, 84.8, 75.3, 71.8, 67.3, 64.7, 59.2, 55.3, 51.7, 30.9, 25.9, 21.7, 18.2, −4.8; IR (neat) 2930, 1734, 1598 cm^{-1}; $[\alpha]_D^{24}$ −26.8 (*c* 5, CH_2Cl_2); MS (FAB, NBA) *m*/*z* 568 (MNa^+, 84), 546 (MH^+, 75), 470 (22), 281 (29), 207 (23). HRMS (FAB, NBA/PEG) calcd for $C_{25}H_{44}NO_8SiS$ (MH^+) 546.2557, found 546.2568.

(6*R*,7*R*,8a*R*)-6-(*tert*-Butyldimethylsilyloxy)-7-(2-methoxyethoxymethoxy)pyrrolizidin-3-one (19). The procedure given for the preparation of **16** was carried out using Mg ribbon (250 mg, 10.3 mmol) in MeOH (8 mL) and **18** (280 mg, 0.51 mmol) in MeOH (8 mL), stirring for 6 h. Flash chromatography (3:1 hexanes/EtOAc) gave **19** (180 mg, 98%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.77 (s, 2H), 4.30 (dd, J = 3.8, 8.9 Hz, 1H), 3.81−3.63 (m, 4H), 3.60−3.52 (m, 3H), 3.39 (s, 3H), 3.24 (dd, J = 5.4, 12.1 Hz, 1H), 2.62 (m, 1H), 2.34 (m, 2H), 1.96 (m, 1H), 0.85 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 176.9, 95.5, 87.3, 77.4, 71.8, 67.5, 65.1, 59.2, 49.6, 33.7, 26.7, 25.8, 18.1, −4.6; IR ($CDCl_3$) 2930, 2892, 2858, 1684 cm^{-1}; $[\alpha]_D^{24}$ −0.6 (*c* 2, CH_2Cl_2); MS (CI, NH_3) *m*/*z* 360 (MH^+, 100), 302 (10), 272 (22); HRMS (CI, NH_3) calcd for $C_{17}H_{34}NO_5Si$ (MH^+) 360.2206, found 360.2201.

(1*R*,2*R*,7a*R*)-1,2-Dihydroxypyrrolizidine (2). The procedure given for the preparation of **1** was carried out using **19** (50.0 mg, 0.139 mmol), $LiAlH_4$ (21.0 mg, 0.556 mmol) in THF (4.4 mL), then CBr_4 (92.0 mg, 0.278 mmol) in MeOH (1.5 mL). Flash chromatography (50:5:1 CH_2Cl_2/MeOH/30% NH_4OH) gave **2** (10.0 mg, 51%) as a white solid: mp = 141−143 °C; ^{1}H NMR (CD_3OD) δ 4.09 (q, J = 6.0 Hz, 1H), 3.75 (t, J = 4.9 Hz, 1H), 3.29−3.19 (m, 2H), 3.00−2.94 (m, 1H), 2.79−2.71 (m, 1H), 2.56 (dd, J = 6.0, 11.0 Hz, 1H), 2.10−1.70 (m, 4H); ^{13}C NMR (CD_3OD) δ 82.6, 78.6, 71.2, 59.6, 56.7, 31.3, 26.3; IR (CH_2Cl_2) 3684, 3600, 2986 cm^{-1}; $[\alpha]_D^{24}$ −6.4 (*c* 1, MeOH) (lit.[5f] $[\alpha]_D^{25}$ +7.6 (*c* 1.3, MeOH)); MS (EI^+) *m*/*z* 143 (M^+, 17), 83 (100), 70 (39); HRMS (EI^+) calcd for $C_7H_{13}NO_2$ (M^+) 143.0946, found 143.0941.

(1*R*,2*R*,7a*R*)-1,2-Dihydroxypyrrolizidine hydrochloride (2-HCl). HCl (0.05 mL) was added to a solution of **2** (10.0 mg) in MeOH (2 mL) and stirred for 2 min at room temperature. Na_2SO_4 was added, and the suspension was filtered on a short pad of Celite and concentrated. The residue was rinsed with dry Et_2O (5 mL) and dried under vacuum to give **2-HCl** (8 mg) as a white solid: mp = 174−176 °C; ^{1}H NMR (CD_3OD) δ 4.30 (m, 1H), 4.16 (br s, 1H), 4.02 (br t, J = 8.7 Hz, 1H), 3.80−3.67 (m, 1H), 3.72 (partially obscured dd, J = 4.1, 12.8 Hz, 1H), 3.40−3.30 (m, 1H), 2.40−2.10 (m, 4H), 2.02−1.85 (m, 2H), ^{13}C NMR (CD_3OD) δ 81.0, 80.1, 78.9, 61.4, 60.0, 31.4, 28.6; $[\alpha]_D^{24}$ −11.2 (*c* 1.6, MeOH).

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Supporting Information Available: Detailed procedures for the preparation of **4**, **5**, **6**, **7**, and **8**; copies of ^{1}H and ^{13}C NMR spectra for all the compounds described in this paper; determination of the enantiopurity of proline **10** using shift reagent Eu(hfc)$_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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