Total Syntheses of All Four Isomers of *cis*-1,2-Dihydroxypyrrolizidine

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Flexibility and ergonomics are, among others, pivotal concerns in organic synthesis, especially where preparation of molecules with potential biological activity is involved. Ideally, for the effects of shape and stereochemistry on biological response to be evaluated, synthetic approaches to a given family of drugs should be amenable to implementation of maximal stereochemical variations and patterns of substitutions in the series. In addition, to minimize the synthetic effort, useful schemes should exploit parallel and repetitive execution of unified protocols of a limited number of optimized transformations and employ readily available synthetic precursors and chemicals. As part of our program for the development of methods for the synthesis of complex carbohydrates and aza-sugars that satisfy the above mentioned concepts,[1] we became interested in the biologically important family of pyrrolizidine alkaloids which feature a range of stereochemical variations and patterns of oxygenation.[2,3] Herein, we report a unified approach to the preparation of all four stereoisomers of *cis*-1,2-dihydroxypyrrolizidine.

Unsaturated γ–substituted γ-lactams of type **3** and **11** were envisioned to be ideal building blocks for the preparation of the oxygenated pyrrolizidine ring sistems. These compounds incorporate the complete seven-carbon skeleton of the final pyrrolizidines and are already equipped with proper substitution and chirality. Noticeably, a conjugate α,β-unsaturation is present, amenable for further substitution. Scheme 1 outlines the sequences by which 1,2-*cis*-dihydroxypyrrolizidines **7**, **8**, *ent*-**7**, and *ent*-**8** were constructed.

Multigram-scale preparation of the two epimeric enantiopairs **3** and **11** was accomplished in excellent yield and stereoselectivity by a divergent $C_3 + C_4$ homologative protocol as previously described.[1e,f] Shortly, $SnCl_4$-assisted coupling of **1** and *ent*-**1** with nitrogen-containing siloxy diene **2** in diethyl ether at −85 °C furnished **3** and *ent*-**3** (80 and 77%), while BF_3-promoted condensation gave rise to the C-4 epimeric couple **11**, *ent*-**11** (70% each). Optimally, the latter pair could be made from the former one via Et_3N-catalyzed C-4 epimerization (90 and 88%).

Lactams **3**, **11**, and their enantiomers are enantiopure crystalline substances with their absolute stereochemistry confirmed by X-ray analyses.[1f] Starting with these intermediates, the sequences shown in Scheme 1 were devised and executed in a parallel and repetitive fashion. Thus, unsaturated lactam **3** was converted to **4** via hydrogenation (Pd–C, NaOAc buffered THF) followed by 6 N aqueous HCl treatment at room temperature (65%). Mesylation of **4**, using excess MsCl in pyridine, led to tri-*O*-mesyl derivative **5** (51%), which was transformed into protected pyrrolizidine **6** by a two-step protocol consisting of carbonyl reduction (BH_3·DMS, THF) followed by DBU-assisted ring closure in refluxing benzene (72%).

For the intermediate **6** to be converted to either **7** or **8**, a divergent protocol had to be employed. Enantioconservative demesylation to the free base **7** was performed by exposing **6** to 6% sodium amalgam in 2-propanol,[4] followed by chromatographic purification (90%). Conversely, recourse to tetrabutylammonium benzoate in refluxing benzene resulted in efficient displacement of the two adjacent OMs groups by the benzoate anion with configurational inversion to produce **10** (60%) which was transformed to the free base **8** upon treatment with catalytic sodium methoxide in methanol (95%).

Paralleling this scheme and exploiting exactly the same chemistry, the pair of enantiomers *ent*-**7** and *ent*-**8** was generated from *ent*-**3** in 21 and 14% yields, respectively, for the entire sequences. Alternatively, reversing the mode of execution of the final transformations, **7** and **8** can be derived from *ent*-**11** via *ent*-**14** (11 and 18%), while the corresponding enantiomers *ent*-**7** and *ent*-**8** sprang from **11** via **14** (11 and 18%).

The absolute stereochemistry of the four pyrrolizidine bases in this study are believed to be as shown based on the stereochemistry of the intermediates **3** and **11** and the type of chemistry involved. However, since operations on stereocenters were involved in the synthetic plan, confirmation of the assignments was necessary. This was performed on intermediates **6** and **14** and benzoates **9** and **10** by NOE difference spectroscopy (^1H NMR at 300 MHz).[6] For compounds **6** and **9** we observed the relatively strong contacts H7a–H1, H7a–H2, and H7a–H7β, and these results qualitatively imply that H7a is proximate to H1, H2, and H7β (cisoid location). For compounds **10**

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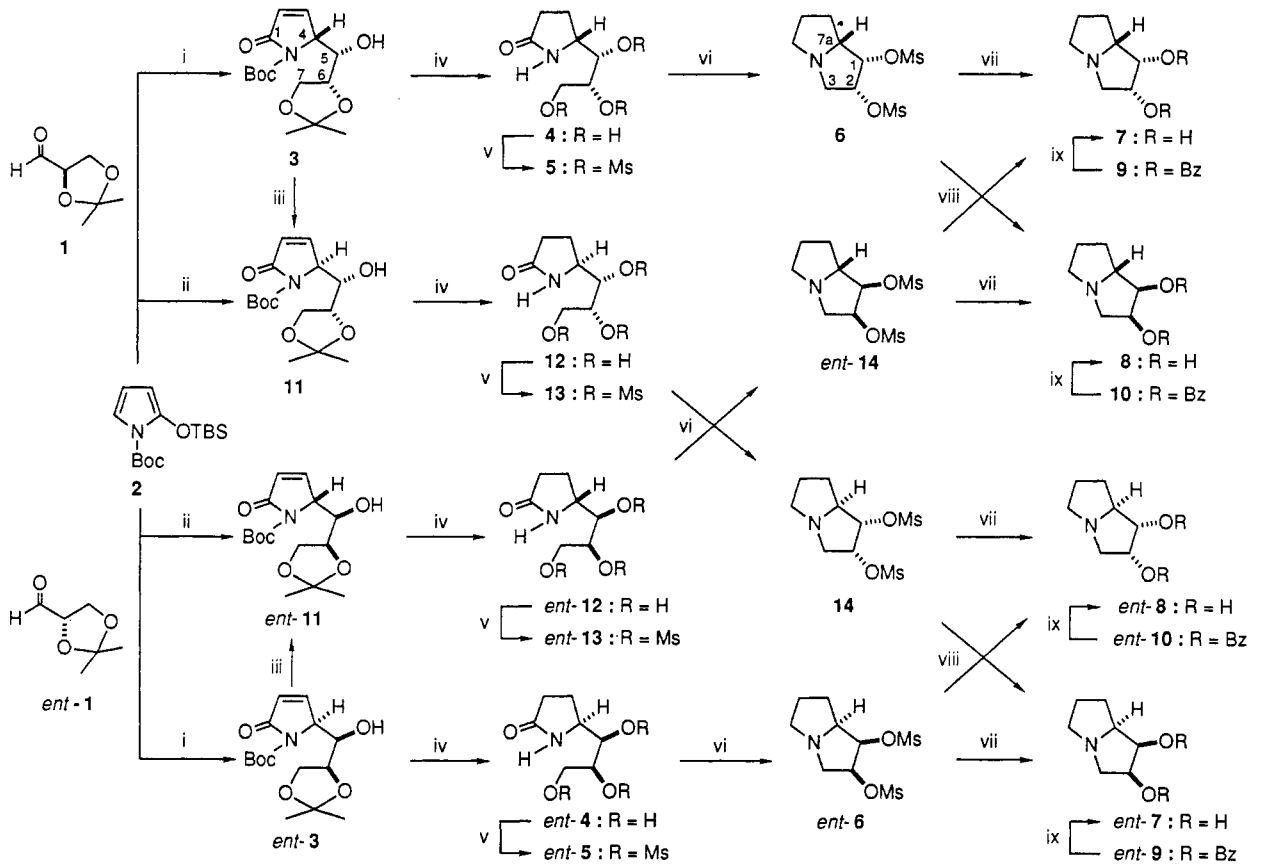
Scheme 1[a]



[a] Key: (i) $SnCl_4$, Et_2O, −85 °C; (ii) $BF_3{\cdot}Et_2O$, Et_2O, −85 °C; (iii) Et_3N, DMAP, CH_2Cl_2, rt; (iv) H_2, THF, NaOAc, Pd on carbon, rt, then 6 N aqueous HCl, rt; (v) $MeSO_2Cl$, pyridine, rt; (vi) $BH_3{\cdot}DMS$, THF, rt, then DBU, benzene, reflux; (vii) for **7**, **8**, *ent*-**7**, and *ent*-**8**: 6% Na/Hg, Et_2O, Pr^iOH, rt; (viii) for **9**, **10**, *ent*-**9**, and *ent*-**10**: $Bu_4N^+BzO^-$, toluene, reflux; (ix) NaOMe, MeOH, rt.

and **14**, no NOE was observed between H7a and H2, while only a weak effect was detected between H7a and H1, corroborating a transoid arrangement of the three protons.

In conclusion, these results establish a chemically efficient strategy for the preparation of the four stereoisomers of *cis*-1,2-dihydroxypyrrolizidine, **7**, **8**, *ent*-**7**, and *ent*-**8**. The syntheses have been accomplished by divergent routes starting from either enantiomer of glyceraldeyde acetonide, **1** or *ent*-**1**, and utilizing *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole (**2**), readily obtainable from pyrrole.[2e]

Experimental Section

Instruments used were described earlier.[1] Preparation of *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole (**2**) was carried out by the method in our precedent paper.[1e] 2,3-*O*-Isopropylidene-D- and -L-glyceraldehyde (**1** and *ent*-**1**) were prepared from D-mannitol and L-ascorbic acid, respectively, according to literature.[7,8]

***N*-(*tert*-Butoxycarbonyl)-6,7-*O*-isopropylidene-2,3-dideoxy-D-*arabino*-hept-2-enono-1,4-lactam (3).** To a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde (**1**, 1.5 g, 11.5 mmol) in anhydrous Et_2O (70 mL) were added **2** (3.4 g, 11.5 mmol) and $SnCl_4$ (1 M in CH_2Cl_2, 17 mL, 17 mmol) under argon at −85 °C. The mixture was stirred at this temperature for 3 h. A saturated aqueous $NaHCO_3$ solution was added at −85 °C and, after ambient temperature was reached, the resulting mixture was extracted with Et_2O (3 × 30 mL). After drying ($MgSO_4$), the solution was evaporated under reduced pressure and the crude product was crystallized from CH_2Cl_2/hexane: 2.9 g (80%), white solid, mp 138–140 °C; $[\alpha]_D$ +197.59° (*c* 0.83, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, 1H, *J* = 6.3, 2.1 Hz), 6.13 (dd, 1H, *J* = 6.3, 1.5 Hz), 4.81 (dt, 1H, *J* = 5.7, 2.4 Hz), 4.09 (ddd, 1H, *J* = 6.0 , 5.7, 3.9 Hz), 4.01 (q, 1H, *J* = 6.0 Hz), 3.94 (dd, 1H, *J* = 8.1, 6.0 Hz), 3.86 (dd, 1H, *J* = 8.1, 6.0 Hz), 3.63 (d, 1H, *J* = 3.9 Hz), 1.57 (s, 9H), 1.37 and 1.32 (2s, each 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 168.9, 150.9, 148.2 126.9, 109.2, 83.8, 75.6, 72.6, 66.4, 65.6, 28.0, 26.4, 25.1. Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.48; H, 7.40; N, 4.47. Found: C, 57.43; H, 7.35; N, 4.32.

***N*-(*tert*-Butoxycarbonyl)-6,7-*O*-isopropylidene-2,3-dideoxy-L-*arabino*-hept-2-enono-1,4-lactam (*ent*-3).** The title compound was prepared from 2,3-*O*-isopropylidene-L-glyceraldehyde *ent*-**1** following the procedure described for its enantiomer **3**: yield 77%; mp 141–142 °C; $[\alpha]_D$ -196.66° (*c* 0.9, $CHCl_3$); ^1H and ^{13}C NMR, see compound **3**. Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.48; H, 7.40; N, 4.47. Found: C, 57.25; H, 7.37; N, 4.51.

***N*-(*tert*-Butoxycarbonyl)-6,7-*O*-isopropylidene-2,3-dideoxy-D-*ribo*-hept-2-enono-1,4-lactam (11).** To a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde (**1**, 500 mg, 3.85 mmol) in anhydrous Et_2O (20 mL) were added **2** (1.13 g, 3.8 mmol) and $BF_3{\cdot}Et_2O$ (540 mg, 3.8 mmol) under argon at −85 °C. The solution was stirred at this temperature for 5 h, saturated aqueous $NaHCO_3$ solution was added at −85 °C, and, after ambient temperature was reached, the resulting mixture was extracted with Et_2O (3 × 10 mL). After drying ($MgSO_4$), the solution was evaporated in vacuo and the crude product was purified by flash chromatography on silica gel (Et_2O/MeOH 99:1) affording 217 mg (18%) of compound **3** and then 844 mg (70%) of lactam **11** as a white solid: mp 120–122 °C; $[\alpha]_D$ −120.0° (*c* 1.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (dd, 1H, *J* = 6.3, 2.1 Hz), 6.16 (dd, 1H, *J* = 6.3, 2.0 Hz), 4.97 (q, 1H, *J* = 2.1 Hz), 4.20 (m, 1H), 4.15 (td, 1H, *J* = 6.6, 2.2 Hz), 4.03 (m, 2H), 3.49 (d, 1H, *J* = 6.6 Hz), 1.56 (s, 9H), 1.46 and 1.37 (2s, each 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$)

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δ 170.0, 149.7, 147.2, 128.0, 109.9, 83.5, 76.3, 71.4, 67.9, 65.1, 28.1, 26.7, 24.5. Anal. Calcd for: $C_{15}H_{23}NO_6$: C, 57.48; H, 7.40; N, 4.47. Found: C, 57.33; H, 7.30; N, 4.35.

Lactam 11 was also conveniently prepared via epimerization of compound 3. Thus, compound 3 (2.0 g, 6.4 mmol) was dissolved in CH_2Cl_2 (15 mL), and Et_3N (2.0 mL) and DMAP (200 mg) were added. The solution was stirred at rt for 5 h. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were dried over $MgSO_4$ and were evaporated under vacuum. The crude product was purified by flash chromatography on SiO_2 (Et_2O/MeOH 98:2): 1.8 g (90%); white solid; mp 118–120 °C; $[\alpha]_D$ −119.7° (c 0.8, $CHCl_3$); ^1H and ^{13}C NMR identical to those of previously prepared 11.

***N*-(*tert*-Butoxycarbonyl)-6,7-*O*-isopropylidene-2,3-dideoxy-L-*ribo*-hept-2-enono-1,4-lactam (*ent*-11).** The title compound was prepared from *ent*-1 following the procedures described for its enantiomer 11: yield 70 or 88% for alternative procedure; white solid; mp 119–121 °C; $[\alpha]_D$ +121.07° (c 1.3, $CHCl_3$), ^1H and ^{13}C, see compound 11. Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.48; H, 7.40; N, 4.47. Found: C, 57.37; H, 7.36; N, 4.51.

2,3-Dideoxy-D-*arabino*-heptono-1,4-lactam (4). To a solution of 3 (2.0 g, 6.4 mmol) in THF (60 mL) were added NaOAc (200 mg) and 10% Pd on carbon (200 mg) were added. The mixture was hydrogenated for 12 h and then was filtered, and the solution was evaporated under reduced pressure. To the crude product in AcOEt (10 mL) was added a 6 N aqueous HCl solution (15 mL) . The solution was stirred at rt for 2 h and evaporated under reduced pressure. The crude product was then purified by flash chromatography eluting with EtOAc/MeOH 7:3 to afford 4, 730 mg (65%), a glass; $[\alpha]_D$ −32.89° (c 0.46, CH_3OH); ^1H NMR (300 MHz, D_2O) δ 3.96 (m, 1H), 3.70 (m, 1H), 3.52 (m, 2H), 3.43 (m, 1H), 2.27 (m, 3H), 1.90 (m, 1H); ^{13}C NMR (75.4 MHz, D_2O) δ 181.0, 71.5, 70.4, 61.3, 54.2, 28.6, 21.6. Anal. Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00. Found: C, 47.86; H, 7.39; N, 7.92.

2,3-Dideoxy-L-*arabino*-heptono-1,4-lactam (*ent*-4). The title compound was prepared from *ent*-3 following the procedure described for its enantiomer 4: yield 63%, a glass; $[\alpha]_D$ +32.25° (c 1.21, CH_3OH), ^1H and ^{13}C NMR, see compound 4. Anal. Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00. Found: C, 47.81; H, 7.53; N, 8.12.

2,3-Dideoxy-D-*ribo*-heptono-1,4-lactam (12). The title compound was prepared from 11 following the procedure described for compound 4, to afford 12 as a glass (61%): $[\alpha]_D$ −0.95° (c 0.61, CH_3OH); ^1H NMR (300 MHz, D_2O) δ 3.96 (m, 1H), 3.72 (m, 1H), 3.56 (m, 3H), 2.31 (m, 3H), 2.03 (m, 1H); ^{13}C NMR (75.4 MHz, D_2O) δ 180.0, 69.8, 69.6, 60.9, 54.4, 28.1, 17.8. Anal. Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00. Found: C, 47.81; H, 7.32; N, 8.17.

2,3-Dideoxy-L-*ribo*-heptono-1,4-lactam (*ent*-12). The title compound was prepared from *ent*-11 following the procedure described for compound 4: yield 65%, a glass; $[\alpha]_D$ +1.01° (c 1.12, CH_3OH), ^1H and ^{13}C NMR, see compound 12. Anal. Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00. Found: C, 47.78; H, 7.51; N, 8.13.

5,6,7-Tri-*O*-(methanesulfonyl)-2,3-dideoxy-D-*arabino*-heptono-1,4-lactam (5). To a solution of 4 (1.0 g, 5.7 mmol) in dry pyridine (17 mL), was added methanesulfonyl chloride (3.96 mL, 51 mmol) under argon at rt. The solution was stirred at this temperature for 12 h, H_2O (3mL) was added, and the residue evaporated under reduced pressure. The crude product was purified by flash chromatography eluting with EtOAc/MeOH 8:2 to afford 5 (1.19 g, 51%) as an oil: $[\alpha]_D$ +8.9° (c 0.45, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (s, 1H), 5.04 (ddd, 1H, *J* = 8.1, 4.3, 3.3 Hz), 4.87 (t, 1H, *J* = 4.8 Hz), 4.60 (dd, 1H, *J* = 12.3, 3.3 Hz), 4.42 (dd, 1H, *J* = 12.3, 6.6 Hz), 4.06 (m, 1H), 3.31 (s, 3H), 3.22 (s, 6H), 2.40 (m, 3H), 2.12 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 179.1, 79.8, 76.1, 66.2, 53.4, 39.0, 38.9, 38.0, 29.3, 23.8. Anal. Calcd for $C_{10}H_{19}NO_{10}S_3$: C, 29.34; H, 4.68; N, 3.42. Found: C, 29.47; H, 4.72; N, 3.41.

5,6,7-Tri-*O*-(methanesulfonyl)-2,3-dideoxy-L-*arabino*-heptono-1,4-lactam (*ent*-5). The title compound was prepared from *ent*-4 following the procedure described for its enantiomer 5: yield 52%, an oil; $[\alpha]_D$ −9.1° (c 0.71; CH_3OH), ^1H and ^{13}C NMR, see compound 5. Anal. Calcd for $C_{10}H_{19}NO_{10}S_3$: C, 29.34; H, 4.68; N, 3.42. Found: C, 29.30; H, 4.70; N, 3.51.

5,6,7-Tri-*O*-(methanesulfonyl)-2,3-dideoxy-D-*ribo*-heptono-1,4-lactam (13). The title compound was prepared from 11 following the procedure described for compound 5 to afford 13 as an oil: yield 49%; $[\alpha]_D$ +6.31° (c 0.95, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (bs, 1H), 5.07 (m, 1H), 4.91 (dd, 1H, *J* = 5.1, 3.4 Hz), 4.62 (dd, 1H, *J* = 12.0, 3.4 Hz), 4.45 (dd, 1H, *J* = 12.0, 5.8 Hz), 4.20 (m, 1H), 3.20–3.15 (m, 9H), 2.4–2.12 (m, 4H). Anal. Calcd for $C_{10}H_{19}NO_{10}S_3$: C, 29.34; H, 4.68; N, 3.42. Found: C, 29.38; H, 4.77; N, 3.41.

5,6,7-Tri-*O*-(methanesulfonyl)-2,3-dideoxy-L-*ribo*-heptono-1,4-lactam (*ent*-13). The title compound was prepared from *ent*-11 following the procedure described for compound 5: yield 49%, oil; $[\alpha]_D$ -6.15° (c 1.0, CH_3OH), ^1H and ^{13}C NMR, see compound 13. Anal. Calcd for $C_{10}H_{19}NO_{10}S_3$: C, 29.34; H, 4.68; N, 3.42. Found: C, 29.46; H, 45.72; N, 3.53.

(1*S*,2*R*,7a*R*)-1,2-Di-*O*-(methanesulfonyl)-1,2-dihydroxypyrrolizidine (6). To a solution of 5 (1.0 g, 2.4 mmol) in dry THF (30 mL) was added a solution of BH_3·DMS (2.4 mL, 24 mmol) under argon. The solution was stirred at rt for 8 h and CH_3OH (3 mL) was added. The residue was evaporated under reduced pressure, the crude product was dissolved in benzene (20 mL), and DBU (2 mL) was added. The solution was stirred under reflux for 10 h and then evaporated under reduced pressure. The crude product was purified by flash chromatography eluting with EtOAc/MeOH 8:2 to afford 6: 526 mg (72%), white solid, mp > 250 °C dec; $[\alpha]_D$ +19.2° (c 0.78, $CHCl_3$); ^1H NMR (300 MHz, CD_3OD) δ 5.2–5.1 (m, 2H), 3.70 (m, 1H), 3.42 (dd, 1H, *J* = 9.9, 6.3 Hz), 3.16 (s, 3H), 3.15 (s, 3H), 3.06 (m, 1H), 2.80 (t, 1H, *J* = 9.9 Hz), 2.64 (m, 1H), 2.06–1.73 (m, 4H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 81.3, 79.0, 65.8, 57.1, 55.9, 38.8, 38.0, 27.6, 26.8. Anal. Calcd for $C_9H_{17}NO_6S_2$: C, 36.11; H, 5.72; N, 4.68. Found: C, 36.17, H, 5.63; N, 4.73.

(1*R*,2*S*,7a*S*)-1,2-Di-*O*-(methanesulfonyl)-1,2-dihydroxypyrrolizidine (*ent*-6). The title compound was prepared from *ent*-5 following the procedure described for its enantiomer 6: yield 73%, a glass; $[\alpha]_D$ −18.9° (c 0.93, $CHCl_3$), ^1H and ^{13}C NMR, see compound 6. Anal. Calcd for $C_9H_{17}NO_6S_2$: C, 36.11; H, 5.72; N, 4.68. Found: C, 36.21, H, 5.69; N, 4.75.

(1*S*,2*R*,7a*S*)-1,2-Di-*O*-(methanesulfonyl)-1,2-dihydroxypyrrolizidine (14). The title compound was prepared from 13 following the procedure described for compound 6: yield 68%, white solid: mp > 250 °C dec; $[\alpha]_D$ +3.6° (c 0.55, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ 5.19 (m, 1H), 5.11 (t, 1H, *J* = 4.0 Hz), 3.79 (m, 1H), 3.55 (dd, 1H, *J* = 9.6, 6.0 Hz), 3.13 (s, 3H), 3.12 (s, 3H), 3.11 (m, 1H), 2.85 (t, 1H, *J* = 9.3 Hz), 2.63 (m, 1H), 2.30-1.71 (m, 4H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 80.0, 76.6, 64.9, 56.0, 54.8, 38.8, 38.2, 28.8, 25.9. Anal. Calcd for $C_9H_{17}NO_6S_2$: C, 36.11; H, 5.72; N, 4.68. Found: C, 36.01, H, 5.68; N, 4.71.

(1*R*,2*S*,7a*R*)-1,2-Di-*O*-(methanesulfonyl)-1,2-dihydroxypyrrolizidine (*ent*-14). The title compound was prepared from *ent*-13 following the procedure described for compound 6: yield 63%, white solid; mp > 250 °C dec; $[\alpha]_D$ −3.2° (c 0.73, CH_3OH); ^1H and ^{13}C, see compound 14. Anal. Calcd for $C_9H_{17}NO_6S_2$: C, 36.11; H, 5.72; N, 4.68. Found: C, 36.27, H, 5.79; N, 4.65.

(1*S*,2*R*,7a*R*)-1,2-Dihydroxypyrrolizidine (7) (Demesylation Procedure). Compound 6 (110 mg, 0.37 mmol), anhydrous 2-propanol (2.2 mL), anhydrous ethyl ether (9 mL), and 6.0% sodium amalgam (1.32 g) were added under argon. The mixture was stirred overnight, the solvent was evaporated and the remaining mixture was purified by flash chromatography eluting with a 5:5:2 CH_2Cl_2/MeOH/30% aqueous NH_4OH solvent mixture to afford 7: 47 mg (90%), an oil; $[\alpha]_D$ −7.46° (c 0.50, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 4.21 (q, 1H, *J* = 4.1 Hz), 3.77 (dd, 1H, *J* = 5.7, 4.5 Hz), 4.20 (m, 1H), 3.12 (dd, 1H, *J* = 11.4, 3.9 Hz), 2.96 (m, 1H), 2.75 (dd, 1H, *J* = 11.7, 4.5 Hz), 2.57 (m, 1H), 2.1–1.7 (m, 4H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 78.7, 73.7, 69.6, 60.0, 56.6, 31.0, 26.4. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.63; H, 8.98; N, 9.87.

(1*R*,2*S*,7a*S*)-1,2-Dihydroxypyrrolizidine (*ent*-7). The title compound was prepared from *ent*-6 following the procedure described for its enantiomer 7: yield 87%, an oil; $[\alpha]_D$ +7.46° (c 0.67, CH_3OH), ^1H and ^{13}C NMR, see compound 7. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.77; H, 9.29; N, 9.90.

(1*R*,2*S*,7a*R*)-1,2-Dihydroxypyrrolizidine (8). The title compound was prepared from *ent*-14 following the procedure

described for compound 7: yield 91%, an oil; $[\alpha]_D$ +23.86° (c, 0.88, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 4.30 (q, 1H, J = 3.6 Hz), 3.96 (dd, 1H, J = 6.6, 3.9 Hz), 3.88 (m, 1H), 3.54 (dd, 1H, J = 12.0, 3.2 Hz), 3.32 (m, 1H), 3.07 (dd, 1H, J = 12.3, 4.2 Hz), 2.99 (dt, 1H, J = 12.0, 6.3 Hz), 2.18 (m, 1H), 2.03 (m, 2H), 1.91 (m, 1H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 77.7, 72.9, 70.5, 59.6, 56.2, 29.7, 25.6. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.81; H, 9.10; N, 9.81.

(1*S*,2*R*,7a*S*)-1,2-Dihydroxypyrrolizidine (*ent*-8). The title compound was prepared from **14** following the procedure described for compound **7**: yield 87%, an oil; $[\alpha]_D$ −23.55° (c 0.97, CH_3OH) ^1H and ^{13}C NMR, see compound **8**. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78%. Found: C, 58.61; H, 9.21; N, 9.82.

(1*S*,2*R*,7a*R*)-1,2-*O*-Dibenzoyl-1,2-dihydroxypyrrolizidine (9) (Inversion Procedure). Compound *ent*-**14** (70 mg, 0.24 mmol) was dissolved in 4 mL of toluene containing tetrabutylammonium benzoate (450 mg, 1.24 mmol). After the solution was heated under reflux for 8 h, H_2O (5 mL) was added and the resulting mixture extracted with toluene (3 × 5 mL). The organic layer was dried with $MgSO_4$ and then evaporated under reduced pressure. The crude product was purified by flash chromatography, eluting with 9:1 CH_2Cl_2/MeOH to afford **9**: yield 50 mg (60%), a glass; $[\alpha]_D$ −22.5° (c 0.60, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (m, 4H), 7.52 (m, 3H), 7.37 (m, 3H), 5.74 (q, 1H, J = 5.0 Hz), 5.33 (t, 1H, J = 5.4 Hz), 3.89 (q, 1H, J = 6.0 Hz), 3.53 (dd, 1H, J = 12.3, 4.8 Hz), 3.23 (m, 1H), 3.17 (dd, 1H, J = 12.0, 5.1 Hz), 2.70 (m, 1H), 2.05–1.50 (m, 4H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.8, 133.1, 129.7, 128.3, 77.4, 73.5, 67.0, 56.8, 56.0, 30.2, 26.1. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.63; H, 6.15; N, 4.07.

(1*R*,2*S*,7a*S*)-1,2-*O*-Dibenzoyl-1,2-dihydroxypyrrolizidine (*ent*-9). The title compound was prepared from **14** following the procedure described for its enantiomer **9**: yield 58%, an oil; $[\alpha]_D$ +22.3° (c 0.56, $CHCl_3$); ^1H and ^{13}C NMR, see compound **9**. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.62; H, 6.07; N, 4.01.

(1*R*,2*S*,7a*R*)-1,2-*O*-Dibenzoyl-1,2-dihydroxypyrrolizidine (10). The title compound was prepared from **6** following the procedure described for compound **9**: yield 60%, a glass; $[\alpha]_D$ +36.05° (c 2.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 4H), 7.52 (m, 2H), 7.35 (m, 4H), 5.73 (q, 1H, J = 4.5 Hz), 5.31 (t, 1H, J = 5.1 Hz), 3.82 (dt, 1H, J = 7.5, 5.7 Hz), 3.47 (dd, 1H, J = 12.3, 4.5 Hz), 3.15 (dd, 1H, J = 12.3, 5.1 Hz), 3.13 (m, 1H), 2.66 (m, 1H), 2.13 (m, 1H), 1.88 (m, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 165.9, 133.1, 129.7, 128.3, 77.5, 73.7, 66.9, 56.9, 56.0, 30.3, 26.1. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.82; H, 6.13; N, 3.83.

(1*S*,2*R*,7a*S*)-1,2-*O*-Dibenzoyl-1,2-dihydroxypyrrolizidine (*ent*-10). The title compound was prepared from *ent*-**6** following the procedure described for compound **9**: yield 61%, a glass; $[\alpha]_D$ -35.78° (c 1.1, $CHCl_3$), ^1H and ^{13}C NMR, see compound **10**. Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.85; H, 6.03; N, 3.81.

(1*S*,2*R*,7a*R*)-1,2-Dihydroxypyrrolizidine (7) (Debenzoylation Procedure). Compound **9** (30 mg, 0.085 mmol) was dissolved in methanol (2 mL) and treated with few drops of a 1 mM methanolic NaOH solution. The mixture was allowed to stir at rt for 30 min and then evaporated to give crude pyrrolizidine **7** which was purified by flash chromatography on silica gel eluting with a 5:5:2 CH_2Cl_2/MeOH/30% aqueous NH_4OH solvent mixture. Yield 12 mg (98%); physical and spectroscopic data, see the above demesylation procedure.

(1*R*,2*S*,7a*S*)-1,2-Dihydroxypyrrolizidine (*ent*-7). The title compound was prepared from *ent*-**9** following the procedure described for its enantiomer **7**: yield 96%; physical and spectroscopic data, see the above demesylation procedure.

(1*R*,2*S*,7a*R*)-1,2-Dihydroxypyrrolizidine (8). The title compound was prepared from **10** following the procedure described for compound **7**: yield 95%; physical and spectroscopic data, see the above demesylation procedure.

(1*S*,2*R*,7a*S*)-1,2-Dihydroxypyrrolizidine (*ent*-8). The title compound was prepared from *ent*-**10** following the procedure described for compound **7**: yield 97%; physical and spectroscopic data, see the above demesylation procedure.

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