Regioselective Transformation of Malic Acid: A Practical Method for the **Construction of Enantiomerically Pure** Indolizidines

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Selective transformation of readily available chiral building blocks has become a major method for the synthesis of enantiomerically pure bioactive compounds including a large number of natural products.¹ In our previous publications,^{2,3} we have presented the synthesis of enantiomerically pure 1,2- as well as 1,3-amino alcohols employing L-aspartic acid as an educt. The key strategy was a regioselective functionalization of the (dibenzylamino)butanediol 1 (Scheme 1). Application of this methodology gave access to 8a-epi- and 1,8a-diepislaframines **3a**,**b**, both containing an equatorial amino group in position $6.^3$ The *trans*-configuration between positions 6 and 8a is due to a thermodynamically induced epimerization at the stage of the intermediate 2. In contrast, natural slaframine (6), a strong muscarinic agonist,⁴ is characterized by an axial-orientated amino substituent.⁵

As an extension of these studies, we envisioned regioselective functionalization of the (benzyloxy)butanediol **4**,⁶ which should be readily available from (R)-malic acid. Employing the protocol we have presented for **3a**,**b**, we expected this strategy to give access to the 6.8a-transconfigured (1S,6R,8aS)-dihydroxyindolizidine moiety as



a partial structure of the glycosidase inhibitor castanospermine.⁷ Furthermore, a suitable didesoxycastanospermine derivative (5) was planned to give access to natural slaframine (6), when stereospecific $S_N 2$ displacement at position 6 was expected to induce 6,8a-cis stereochemistry.

For the synthesis of a selectively protected butane-1,2,4-triol, (R)-methyl malate (7) was reacted with benzyl bromide, resulting in formation of the benzyl ether 8 (Scheme 2).⁸ Subsequent reduction by $LiAlH_4$ gave the (benzyloxy)butanediol 4. Due to a remote protecting group effect of the N.N-dibenzylamine substituent, we have recently observed regioselective silvlation of the diol 1 by TBDMS-Cl or TBDPS-Cl.³ Analogous regiodifferentiation of a benzyloxy substituent was expected to induce a preferred silvlation of 4 in position 4. Actually, imidazole-assisted reaction of 4 with TBDMS-Cl or TBDPS-Cl resulted in formation of the regioisomers 9a,b and 10a,b as well as the bis-silylation products 11a,b in a 3:2:3 and a 5:1:3.5 ratio, respectively. TBDPS-Cl was the more selective reagent. However, complete separation of the isomers proved to be difficult. In contrast, an improved regioselectivity and easy purification of the major isomer by flash chromatography was observed

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when protection by the sterically demanding TIPS group⁹ was investigated. In this case, 48% of the 4-silvloxy derivative 9c was isolated and only 7% of 10c and 22% of 11c.

For a functionalization of the unprotected HO-group, the synthetic intermediate 9c was subjected to phthalimide under Mitsunobu conditions,¹⁰ giving the protected 1,3-diol 12a in 98% yield (Scheme 3). Subsequent Ndeprotection by hydrazinolysis afforded the primary amine 12b. Removal of the TIPS group was accomplished under acidic conditions (HCl, MeOH) to give 12c (combined yield for both deprotection steps: 91%). Thus, the method provides an efficient approach to chiral 1,3diols. The enantiomeric integrity of the synthesis was established by derivatization of 12b with (S)-1-phenylethyl isocyanate. Subsequent ¹H NMR studies of the urea 12d including doping experiments with the diastereomer obtained by coupling of 12b with (R)-1-phenylethyl isocyanate proved the synthetic material to be isomerically pure.

In analogy to our recent synthesis of enantiomerically pure epi- and diepislaframines **3a**,**b**,³ we envisioned to constructing the indolizidine skeleton by applying methodology developed by Wasserman.¹¹ Thus, treatment of the amino alcohol 12c with the vinyl tricarbonyl reagent 13¹² resulted in formation of the 3-hydroxypyrrole-2carboxylate 14a (Scheme 4). Activation of the terminal HO-group was performed by CBr₄/PPh₃ in CH₂Cl₂ to give the cyclization precursor 14b. Subsequent deprotonation by NaH and intramolecular C-alkylation resulted in formation of the bicyclic β -keto esters **15a** and **15b** as a 1:2 mixture of diastereomers. According to diagnostic coupling constants of the ¹H NMR spectra, the sixmembered rings of 15a and 15b adopt a chair conformation including an equatorial disposition of the benzyloxy substituent for 15a and an axial orientation for 15b. Since epimerization in position 8a was anticipated at a later step, both isomers were expected to be useful for the projected synthesis. Lewis acid assisted reduction of 15a,b gave 16a,b.13 Subsequently, hydrolysis and decarboxylation were induced by TFA to give a 10:1 mixture of the diastereomers 16c and 16d, independently whether 16a or 16b were reacted. According to the observations we have made for the reduction of 2^{3} reaction of the ketones 16c,d with the sterically demanding reagent Li(sBu)₃BH proceeded under complete steric approach control¹⁴ to yield 17a, besides a small amount of its 8a-epimer, which was easily separable by flash

Scheme 4



chromatography. In contrast, reduction by NaBH₄/ MeOH afforded a 1:1 mixture of 17a and the diastereomer 17b. O-Acetylation of 17a and 17b gave 18a and 18b, respectively. Hydrogenolytic debenzylation of 18a was accomplished using Pd/C as a catalyst to afford the didesoxycastanospermine derivative 19. Finally, introduction of a nitrogen substituent at C-6 was investigated. Therefore, 19 was activated by trifluoromethanesulfonic anhydride and the resulting sulfonate was reacted with NaN₃. Instead of the projected inversion at C-6, we observed an equatorial disposition of the azide substituent of the main product 20a and a rearranged structure for the minor product 21a. We reason that this is due to an anchimeric participation of the endocyclic amine resulting in formation of an aziridinium salt. Nucleophilic ring opening of this intermediate by N₃⁻ explains the retention of configuration for 20a and the skeletal migration of 21a. Preferred formation of the rearranged isomer was observed under Mitsunobu conditions.¹⁰ Upon treatment of 19 with phthalimide/PPh3 and DEAD, the pyrrolizdine **21b** was isolated in 55% yield, as well as 19% of 20b. The stereochemistry of 20a was estab-

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lished by catalytic hydrogenation to give 6-epislaframine ent-**3b** and subsequent transformation to the stable *N*-acetyl derivative **20c**. The spectral data were identical with those reported.^{3,5a} The pyrrolizidines **21a** and **21b** were transformed into the acetamide **21c**¹⁵ under standard conditions (H₂, Pd/C or hydrazine, then Ac₂O). In order to generate a "slaframine-like" (S)-configuration at position 6 of the indolizidine skeleton, we envisioned oxidation of the secondary alcohol **19** followed by a diastereoselective reductive amination. Swern oxidation of **19** and subsequent treatment with H₂NOH gave the oxime **22**^{5b} (yield: 81%, isolated in a 3:1 mixture of syn/ antiisomers), which could be transformed into *N*-acetylslaframine (**23**)^{5h,i} according to the protocol reported by Gensler and co-workers for racemic material.^{5b}

Experimental Section

General. THF was distilled from Na/benzophenone and DMF and CH_2Cl_2 from CaH_2 , in all cases immediately before use. All liquid reagents were also purified by distillation. Unless otherwise noted, reactions were conducted under dry N₂. Evaporations of final product solutions were done under vacuo with a rotatory evaporator. Flash chromatography was carried out with 230-400 mesh silica gel. Melting points are uncorrected. Methane was employed for CIMS. NMR spectra were recorded at 400 MHz; spectra were measured as CDCl₃ solutions using TMS as an internal standard. Unless specified otherwise, J values are given in hertz. NMR peak assignments are based on ${}^{1}H^{-1}H$ COSY and ${}^{1}H^{-13}C$ COSY experiments.

Dimethyl (R)-2-(Benzyloxy)succinate (8). To a mixture of (R)-dimethyl malate (8.00 g, 49.3 mmol) and Ag₂O (16.9 g, 73.0 mmol), dissolved in EtOAc (150 mL), was slowly added benzyl bromide (8.65 mL, 73.0 mmol). The mixture was stirred for 15 h at rt. Then it was filtered, the solvent was evaporated, and the residue was purified by flash chromatography (petroleum ether: EtOAc, 85:15) to give 8 (8.02 g, 65%), $[\alpha]^{23}_{D} + 70^{\circ}$ (c = 1.0, CHCl₃). For ent-8: lit.^{8a} $[\alpha]^{23}_{D} - 63^{\circ}$ (CHCl₃, c = 1.6); lit.^{8b} $[\alpha]^{23}_{D} - 68.5^{\circ}$ (c = 11.4, CHCl₃); IR (NaCl) (cm⁻¹) 1740; ¹H NMR δ 2.76–2.86 (m, 2H), 3.68 (s, 3H), 3.77 (s, 3H), 4.40 (dd, J = 7.3, 5.1, 1H), 4.54 (d, J = 11.0, 1H), 4.77 (d, J = 11.0, 1H), 7.27–7.35 (m, 5H); MS (CI) 253 (M + 1). Anal. Calcd for C₁₃H₁₆O₅: C, 61.89; H, 6.39. Found: C, 62.15; H, 6.14.

(**R**)-2-(Benzyloxy)butane-1,4-diol (4). To a solution of LiAlH₄ (40.6 mL, 1 M in THF) was added 8 (7.90 g, 31.2 mmol), dissolved THF (40 mL) at 0 °C. After 4 h, a saturated NaHCO₃ solution and Et₂O were added. The organic layer was separated, dried (MgSO₄), and evaporated to give pure 4 (6.05g, 98%) as a semisolid substance: $[\alpha]^{23}_D$ +15° (c = 1.0, CHCl₃), lit.⁶ $[\alpha]^{23}_D$ +20.6° (c = 1.0, CHCl₃); ¹H NMR δ 1.78–1.94 (m, 2H), 2.26 (brs, 2H, OH), 3.61 (dd, J = 11.0, 3.7), 3.70-3.81 (m, 4H), 4.60 (d, J = 11.7, 1H), 4.64 (d, J = 11.7, 1H), 7.29-7.37 (m); MS (CI) 197 (M + 1), 105 (M - 91). Anal. Calcd for C₁₁H₁₆O₃: C, 67.32; H, 8.22. Found: C, 67.25; H, 8.28.

(R)-2-(Benzyloxy)-4-(tert-butyldimethylsiloxy)-1-butanol (9a), (R)-2-(Benzyloxy)-1-(tert-butyldimethylsiloxy)-1-butanol (10a), and (R)-2-(Benzyloxy)-1,4-(tert-butyldimethylsiloxy)butane (11a). To a mixture of 4 (150 mg, 0.76 mmol) and dimethyl-tert-butylchlorosilane (173 mg, 1.15 mmol) in DMF (20 mL) was added imidazole (156 mg, 2.29 mmol) at 0 °C. After 3 h, saturated NH4Cl solution and Et₂O were added. The organic layer was dried (MgSO₄) and evaporated, and the residue was separated by flash chromatography (petroleum ether:EtOAc, 4:1) to give 11a (46 mg, 15%), followed by a sparingly separable mixture of 9a and 10a (60 mg, 25%, 9a: 10a = 3:2). 11a: colorless oil, $[\alpha]^{23}_D + 24^\circ$ (c = 1.0, CHCl₃); ¹H NMR δ 0.06 (d, J = 6.6, 12H), 0.89 (d, J = 6.6, 18H), 1.63-1.71 (m, 1H), 1.73-1.81 (m, 1H), 3.61-3.77 (m, 5H), 4.57 (d, J = 11.7, 1H), 4.72 (d, J = 11.7, 1H), 7.26-7.31 (m, 2H), 7.33-7.36 (m, 4H); MS (CI) 425 (M + 1). Anal. Calcd for $C_{23}H_{44}O_{3}Si_{2}$: C, 64.88; H, 10.65. Found: C, 65.01; H, 10.53. **9a**: colorless oil; ¹H NMR δ 0.06 (s, 6H), 0.90 (s, 9H), 1.72–1.80 (m, 1H), 1.83–1.95 (m, 1H), 2.41 (t, J = 6.6, 1H, OH), 3.56–3.61 (m, 1H), 3.67–3.77 (m, 4H), 4.56 (d, J = 11.7, 1H), 4.61 (d, J = 11.7, 1H), 7.24–7.31 (m, 1H), 7.34–7.35 (m, 4H); MS (CI) 311 (M + 1), 279 (M – 31). Anal. Calcd for $C_{17}H_{30}O_{3}Si$: C, 65.76; H, 9.74. Found: C, 65.74; H, 10.02. **10a**: colorless oil; ¹H NMR δ 0.08 (s, 6H), 0.90 (s, 9H), 1.75–1.90 (m, 2H), 2.49 (t, J = 5.9, 1H, OH), 3.69–3.78 (m, 5H), 4.59 (d, J = 11.7, 1H), 4.73 (d, J = 11.7), 7.28–7.36 (m, 5H); MS (CI) 311 (M + 1), 279 (M – 31).

(R)-2-(Benzyloxy)-4-(tert-butyldiphenylsiloxy)-1-butanol (9b), (R)-2-(Benzyloxy)-1-(tert-butyldiphenylsiloxy)-4-butanol (10b), and (R)-2-(Benzyloxy)-1,4-(tert-butyldiphenylsiloxy)butane (11b). To a mixture of 4 (150 mg, 0.76 mmol) and tert-butyldiphenylchlorsilane (0.29 mL, 1.15 mmol) in DMF (20 mL) was added imidazole (156 mg, 2.29 mmol) at 0 °C. After 30 min, a saturated NH₄Cl solution and Et₂O were added. The organic layer was separated, dried (MgSO₄), and evaporated, and the residue was separated by flash chromatography (petroleum ether:EtOAc, 85:15), to give 11b (143 mg, 27%), followed by 9b and 10b (160 mg, 48%, 9b:10b 5:1). 11b: colorless oil, $[\alpha]^{23}_{D}$ +13° (c = 1.0); ¹H NMR δ 0.96 (s, 9H,), 0.99 (s, 9H), 1.60-1.68 (m, 1H), 1.77-1.79 (m, 1H), 3.60 (dd, J = 10.3),4.4, 1H), 3.66 (m, 1H), 3.71-3.79 (m, 3H), 4.40 (d, J = 11.7, 1H), 4.58 (d, J = 11.7, 1H), 7.16-7.22 (m, 3H), 7.23-7.36 (m, 14H),7.55-7.65 (m, 8H); MS (CI) 595 (M - 78). Anal. Calcd for C43H52O3Si2: C, 76.74; H, 7.78. Found: C, 76.96; H, 7.57. 9b: $[\alpha]^{23}$ _D -2.5° (c = 1.0, CHCl₃); ¹H NMR δ 1.04 (s, 9H), 1.74-1.81 (m, 1H), 1.84-1.91 (m, 1H), 2.17 (t, J = 6.6, 1H, OH), 3.54-3.60 (m, 1H), 3.72-3.80 (m, 4H), 4.54 (d, J = 11.7, 1H), 4.58 (d, J = 11.7,J = 11.7, 1H, 7.27–7.45 (m, 11H), 7.64–7.66 (m, 4H); MS (CI) 435 (M + 1). Anal. Calcd for $C_{27}H_{34}O_3Si:$ C, 74.61; H, 7.89. Found: C, 74.77; H, 7.73. 10b: ¹H NMR & 1.00 (s, 9H), 1.67-1.79 (m, 2H), 2.23 (t, J = 5.1, 1H, OH), 3.61-3.74 (m, 5H), 4.42(d, J = 11.7, 1H), 4.60 (d, J = 11.7, 1H), 7.21–7.37 (m, 11H), 7.57-7.62 (m, 4H)

(R)-2-(Benzyloxy)-4-(triisopropylsiloxy)-1-butanol (9c), (R)-2-(Benzyloxy)-1-(triisopropylsiloxy)-4-butanol (10c), and (R)-2-(Benzyloxy)-1,4-(triisopropylsiloxy)butane (11c). A mixture of 4 (14.5 g, 74 mmol), triisopropylchlorosilane (17.4 mL, 81.0 mmol), and imidazole (11.0 g, 160 mmol) in DMF (300 mL) was stirred at rt for 4 h. Then, a saturated NH₄Cl solution and Et₂O were added. The organic layer was separated, dried (MgSO₄), and evaporated, and the residue was separated by flash chromatography (petroleum ether: EtOAc, 9:1), to give 11c (8.28 g, 22%), followed by 9c (12.5 g, 48%) and 10c (1.90 g, 7%). 11c: colorless oil, $[\alpha]^{23}_{D}$ +20° (c = 1.2, CHCl₃); ¹H NMR δ 1.04 (s, 6H), 1.06 (s, 36H), 1.65-1.73 (m, 1H), 1.79-1.87 (m, 1H), 3.68-3.76 (m, 2H), 3.77 - 3.83 (m, 3H), 4.59 (d, J = 11.7, 1H), 4.75 (d, J = 11.7J = 11.7, 1H), 7.25.7.31 (m, 1H), 7.31-7.36 (m, 4H); MS (CI) 509 (M + 1), 465 (M - 43), 335 (M - 173). Anal. Calcd for C₂₉H₅₆O₃Si: C, 68.44; H, 11.09. Found: C, 68.38; H, 11.16. 9c: colorless oil, $[\alpha]^{23}_{D}$ +2.8° (c = 0.8, CHCl₃); ¹H NMR δ 1.05 (s, 3H), 1.07 (s, 18H), 1.77-1.82 (m, 1H), 1.87-1.92 (m, 1H), 2.44 (t, J = 5.8, 1H, OH), 3.58-3.63 (m, 1H), 3.72-3.78 (m, 2H),3.78-3.87 (m, 2H), 4.57 (d, J = 11.7, 1H), 4.63 (d, J = 11.7, 1H),7.26-7.31 (m, 1H), 7.35 (d, J = 4.4, 4H); MS (CI) 353 (M + 1),261 (M - 91). Anal. Calcd for C₂₀H₃₆O₃Si: C, 68.13; H, 10.29. Found: C, 68.16; H, 10.26. 10c: ¹H NMR δ 0.99 (s, 3H), 1.00 (s, 18H), 1.64–1.75 (m, 1H), 1.75–1.87 (m, 1H), 2.38 (t, J = 6.6, 1H, OH), 3.61-3.80 (m, 5H), 4.54 (d, J = 11.7, 1H), 4.68 (d, J = 11.7, 2H), 4.58 (d, J = 11.7, 2H), 11.7, 1H), 7.21–7.25 (m, 1H), 7.28 (d, J = 4.4, 4H).

(*R*)-*N*-(2-(Benzyloxy)-4-((triisopropylsiloxy)butyl))phthalimide (12a). Diethyl azodicarboxylate (6.50 mL, 14 mmol, 38% solution in toluene) was added dropwise to a mixture of 9c (5.01 g, 14.0 mmol), phthalimide (2.09g, 14.0 mmol), and triphenylphosphine (3.73 g, 14.0 mol) in THF (100 mL). The mixture was stirred for 16 h. Then, the solvent was evaporated, and the residue was purified by flash chromatography (CH₂Cl₂: petroleum ether, 3:2) to give 12a (8.8 g, 98%) as a colorless oil: $[\alpha]^{23}_{D}$ +5.3° (*c* = 1.0, CHCl₃); IR (NaCl) (cm⁻¹) 1774, 1720; ¹H NMR δ 1.02 (s, 3H), 1.04 (s, 18H), 1.75–1.83 (m, 2H), 3.76– 3.89 (m, 4H), 3.96–4.02 (m, 1H), 4.57 (d, *J* = 11.7, 1H), 4.60 (d, *J* = 11.7, 1H), 7.08–7.16 (m, 3H); 7.22–7.25 (m, 2H), 7.68 (dd, *J* = 5.1, 2.9, 2H), 7.79 (dd, *J* = 5.1, 2.9, 2H); MS (CI) 482 (M +

⁽¹⁵⁾ The spectroscopic data of **21c** are very similar to those reported and observed for **23**. Structure determination is based on ${}^{1}H^{-1}H$ COSY and ${}^{1}H^{-13}C$ COSY experiments and mass spectroscopy. Diagnostic for **21c** is a ${}^{3}J$ coupling between the NH and neighboring CH₂ protons as well as a characteristic α -cleavage of a CH₂NHAc fragment (see Experimental Section).

1), (EI) 439 (M - 43), 304 (M - 177). Anal. Calcd for $C_{28}H_{39}$ -NO4Si: C, 69.82; H, 8.16; N, 2.91. Found: C, 69.58; H, 8.39; N, 2.93.

(*R*)-2-Benzyloxy-4-triisopropylsiloxy-1-butylamine (12b). A solution of 12a (11.4 g, 24.0 mmol) and hydrazine hydrate (11.5 mL, 238 mmol) in EtOH was refluxed for 16 h. The solvent was then removed, and saturated NaHCO₃ solution was added. After extraction with Et₂O, the organic layer was dried (MgSO₄) and evaporated to leave pure 12b (7.9 g, 95%) as a colorless oil: $[\alpha]^{23}_{D} + 4.8^{\circ}$ (c = 1.9, CHCl₃); ¹H NMR δ 1.05 (s, 3H), 1.06 (s, 18H), 1.68-1.76 (m, 1H), 1.81-1.88 (m, 1H), 2.74 (dd, J = 13.2, 4.4, 1H), 2.91 (dd, J = 13.2, 6.6, 1H), 3.59-3.65 (m, 1H), 3.77-3.85 (m, 2H), 4.55 (d, J = 11.7, 1H), 4.60 (d, J = 11.7, 1H), 7.27-7.35 (m, 5H); MS (CI) 352 (M + 1), 308 (M - 43), 178 (M - 173). Anal. Calcd for C₂₀H₃₇NO₂Si: C, 68.32; H, 10.61; N, 3.98. Found: C, 68.36; H, 10.31; N, 4.24.

Determination of the Enatiomeric Purity of 12b. To a stirred solution of 12b (28 mg, 0.08 mmol) in THF (2 mL) was added (S)-1-phenylethyl isocyanate (11.2 μ L, 0.08 mmol) at 0 °C. After 1 h, the solvent was evaporated to give 12d (40 mg, 100%) as a colorless oil: $[\alpha]^{23}_{D} + 1.6^{\circ} (c = 1.0, CHCl_3)$; IR (NaCl) (cm^{-1}) 1630; ¹H NMR δ 1.03 (s, 3H), 1.04 (s, 18H), 1.36 (d, J =6.6, 3H), 1.64-1.71 (m, 1H), 1.74-1.82 (m, 1H), 3.19 (dt, J =13.9, 5.9, 1H), 3.36-3.42 (m, 1H), 3.58-3.68 (m, 1H), 3.73-3.80 (m, 2H), 4.40 (d, J = 11.7, 1H), 4.50 (d, J = 11.7, 1H), 4.62– 4.63 (m, 1H, NH), 4.71-4.77 (m, 1H), 4.86 (bs, 1H, NH), 7.18-7.35 (m, 10H); MS (CI) 499 (M + 1), 455 (M - 43). Anal. Calcd for C₂₈H₄₆N₂O₃: C, 67.43; H, 9.30; N, 5.62. Found: C, 67.63; H, 9.11; N, 5.60. Coupling using (R)-phenylethyl isocyanate under the same conditions gave the like-diastereomer in 94% yield: $[\alpha]^{23}_{D} + 7.2^{\circ}$ (c = 1.0, CHCl₃); IR (NaCl) (cm⁻¹) 1630; ¹H NMR δ 1.03 (s, 3H), 1.05 (s, 18H), 1.38 (d, J = 6.8, 3H), 1.62– 1.73 (m, 2H), 3.19 (dt, J = 14.1, 6.0, 1H), 3.39 (ddd, J = 13.7, 5.5, 3.8), 3.66-3.71 (m, 1H), 3.72-3.78 (m, 2H), 4.47 (d, J =12.0, 1H), 4.53 (d, J = 12.0, 1H), 4.65 (bs, 1H, NH), 4.68–4.75 (m, 1H), 4.85 (bs, 1H, NH), 7.21-7.33 (m, 10H); MS (CI) 499 (M + 1), 455 (M - 43). Anal. Calcd for $C_{28}H_{16}N_2O_3Si: C, 67.43;$ H, 9.30; N, 5.62. Found: C, 67.58; H, 9.17; N, 5.58.

(*R*)-4-Amino-3-benzyloxy-1-butanol (12c). Compound 12b (9.9 g, 28.0 mmol) was refluxed in a 1:3 mixture of 2 N HCl and EtOH (200 mL) for 15 min. After being cooled to rt, the solvent was evaporated and a saturated NaCl solution and Et₂O were added. The aqueous phase was basified with 2 N NaOH and again extracted with Et₂O. The organic layer was dried (Mg-SO₄), and the solvent was evaporated to leave pure 12c (5.2 g, 96%) as a colorless oil: $[\alpha]^{23}_D - 7^\circ$ (c = 1.0, CHCl₃); ¹H NMR δ 1.85–1.89 (m, 1H), 1.90–1.97 (m, 1H), 2.28 (bs, 2H, NH₂), 2.78 (dd, J = 12.5, 3.7, 1H), 3.04 (dd, J = 12.5, 5.1, 1H), 3.61–3.38 (m, 2H), 3.76–3.82 (m, 1H), 4.53 (d, J = 11.7, 1H), 4.58 (d, J = 11.7, 1H), 7.29–7.38 (m, 5H); MS (CI) 196 (M + 1). Anal. Calcd for C₁₁H₁₇NO₂: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.46; H, 9.01; N, 7.14.

(*R*)-tert-Butyl 1-(2-(Benzyloxy)-4-hydroxybutyl)-3-hydroxypyrrole-2-carboxylate (14a). A mixture of 12c (0.35 g, 1.79 mmol) and 13 (0.36 g, 1.79 mmol) in CH₂Cl₂ (20 mL) was stirred at rt for 30 min. After addition of silica gel (2.7 g), it was stirred for another 16 h. Then, the solution was filtered, the solvent was removed, and the residue was purified by flash chromatography (petroleum ether:EtOAc, 7:3) to give 14a (0.33 g, 51%) as a colorless oil: $[\alpha]^{23}{}_{D}$ -73° (c = 1.0, CHCl₃); IR (NaCl) (cm⁻¹) 1700, 1640; ¹H NMR (MeOD) δ 1.56 (s, 9H), 1.60–1.67 (m, 1H), 1.68–1.77 (m, 1H), 3.61–3.71 (m, 2H), 3.80–3.86 (m, 1H), 3.93–3.99 (m, 1H), 4.00 (d, J = 11.1, 1H), 4.21 (d, J = 11.1, 1H), 4.32 (dd, J = 13.7, 3.0, 1H), 5.71 (d, J = 3.0, 1H), 6.74 (d, J = 3.0, 1H), 7.14 (dd, J = 7.7, 1.7, 2H), 7.23–7.29 (m, 3H); MS (CI) 362 (M + 1). Anal. Calcd for C₂₀H₂₇NO₅: C, 66.62; H, 7.53; N, 3.88. Found: C, 66.53; H, 7.94; N, 3.51.

(*R*)-tert-Butyl 1-(2-(Benzyloxy)-4-bromobutyl)-3-hydroxypyrrole-2-carboxylate (14b). To a solution of 14a (0.77 g, 2.14 mmol) and tetrabromomethane (0.886 g, 2.670 mmol) in CH₂Cl₂ (20 mL) was slowly added triphenylphosphine (0.840 g, 4.272 mmol) at rt. After 30 min, the solvent was evaporated and the residue was purified by flash chromatography (petroleum ether:EtOAc, 93:7) to give 14b (0.8 g, 88%) as a colorless solid: mp 88 °C; [α]²³_D -39° (c = 0.9, CHCl₃); IR (KBr) (cm⁻¹) 1640, 1550; ¹H NMR (MeOD) δ 1.59 (s, 9H), 1.92–1.97 (m, 2H), 3.47–3.55 (m, 2H), 3.92–4.01 (m, 2H), 3.99 (d, J = 11.0, 1H), 4.17 (d, J = 11.0, 1H), 4.34 (dd, J = 12.9, 2.1, 1H), 5.73 (d, J = 2.9, 1H), 6.75 (d, J = 2.9,1H), 7.18 (dd, J = 8.1, 2.2, 2H), 7.24–7.30 (m, 3H); MS (EI) 367 (M – 57), 243 (M – 181). Anal. Calcd for C₂₀H₂₆NO₄Br: C, 56.61; H, 6.18; N, 3.30. Found: C, 56.58; H, 6.37; N, 3.18.

(6R,8aS)-tert-Butyl-6-(Benzyloxy)-5,6,7,8-tetrahydro-1oxo-8a(1H)-indolizinecarboxylate (15a) and (6R,8aR)-tert-Butyl-6 (Benzyloxy)-5,6,7,8-tetrahydro-1-oxo-8a(1H)-indolizinecarboxylate (15b). To a suspension of sodium hydride (0.14 g, 6.00 mmol) in THF (40 mL) was slowly added a solution of 14b (1.16 g, 2.73 mmol) in THF (20 mL) at 0 °C. When the production of hydrogen ceased, the mixture was stirred for 30 min at 40 °C. After addition of a saturated NH4Cl solution, the product was extracted with ether, and the organic layer was dried (MgSO₄) and evaporated. The residue was separated by flash chromatography (petroleum ether: EtOAc, 4:1) to give 15a (0.62 g, 65%) followed by 15b (0.27 g, 28%). 15a (colorless solid); mp 110 °C; $[\alpha]^{23}_{D}$ +382° (c = 0.95, CHCl₃); IR (KBr) (cm⁻¹) 1730, 1660, 1540; ¹H NMR δ 1.40 (s, 9H, t-Bu), 1.50 (tt, J = 13.7, 3.0,1H, 7- H_{ax}), 1.82 (dt, $J = 13.7, 3.4, 1H, 8-H_{ax}$), 1.96–2.02 (m, 1H, $7-H_{eq}$), 2.38 (dt, $J = 13.3, 3.4, 1H, 8-H_{eq}$), 3.38 (dd, J = 13.7, 2.1, 3.38) 1H, 5-H_{ax}), 3.55-3.61 (m, 2H, 5-H_{eq} + 6-H_{eq}), 4.36 (d, J = 12.0, 1H, OCH₂Ph), 4.48 (d, J = 12.0, 1H, OCH₂Ph), 4.93 (d, J = 3.0, 1H, 2-H), 7.19–7.27 (m, 5H, H_{ar}), 7.65 (d, J = 3.0, 1H, 3-H); ¹³C NMR δ 24.8, 25.5, 27.9, 51.2, 70.2, 72.0, 73.1, 82.7, 94.7, 127.3, 127.7, 128.5, 138.0, 165.0, 165.3, 198.3; MS (CI) 344 (M + 1), 288 (M - 57, tBu). Anal. Calcd for C₂₀H₂₅NO₄: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.83; H, 7.68; N, 3.86. 15b (yellowish solid): mp. 122 °C; $[\alpha]^{23}_{D}$ -273° (c = 0.9, CHCl₃); IR (KBr) (cm⁻¹) 1730, 1660, 1540; ¹H NMR; δ (ppm) 1.42-1.47 (m, 1H, 8-Hax), 1.47 (s, 9H, COOtBu), 1.47-1.49 (m, 1H, 7-Hax), 2.18- $2.22 \text{ (m, 1H, 7-H_{eq})}, 2.71 \text{ (dt, } J = 12.4, 3.0, 1H, 8-H_{eq}), 3.23 \text{ (dd,}$ $J = 12.8, 10.3, 1H, 5-H_{ax}), 3.38-3.46 \text{ (m, 1H, 6-H_{ax})}, 3.78 \text{ (ddd, })$ $J = 12.4, 5.1, 1.7, 1H, 5-H_{eq}$, 4.53 (d, $J = 11.5, 1H, OCH_2Ph$), $4.62 (d, J = 11.5, 1H, OCH_2Ph), 4.96 (d, J = 3.0, 1H, 2-H), 7.31-$ 7.39 (m, 5H, H_{ar}), 7.75 (d, J = 3.0, 1H, 3-H); MS (CI) 344 (M + 1), 388 (M - 57). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.93; H, 7.57; N, 4.06.

(6R,8aS)-tert-Butyl 6-(Benzyloxy)-2,3,5,6,7,8-hexahydro-1-oxo-8a(1H)-indolizinecarboxylate (16a). To a solution of 15a (0.95 g, 2.76 mmol) in THF (100 mL) was added BF_3 Et₂O (0.44 mL, 3.59 mmol) at -78 °C. After 5 min, LiEt₃BH (Super Hydride, 1 M in THF, 3.58 mL) was added and stirring was continued for 1 h. Then, a saturated NaCl solution and a saturated NaHCO₃ solution were added. After extraction with Et_2O , the organic layer was dried (MgSO₄) and evaporated. The residue was purified by flash chromatography (petroleum ether: EtOAc 4:1 to give 16a (0.72 g, 76%) as a colorless oil: $[\alpha]^{23}D$ +59° (c = 1.0, CHCl₃); IR (NaCl) (cm⁻¹) 1760, 1720; ¹H NMR δ 1.46 (s, 9H, COOtBu), 1.61–1.72 (m, 1H, 7- H_{ax}), 1.82 (dt, $J = 13.7, 4.7, 1H, 8-H_{ax}$), 2.0–2.1 (m, 2H, 7- $H_{eq} + 8-H_{eq}$), 2.48 (t, J $= 6.4, 2H, 2-H_2$, 3.11-3.17 (m, $2H, 5-H_2$), 3.32-3.37 (m, 1H, 3-H), 3.40–3.45 (m, 1H, 3-H), 3.52 (bs, 1H, 6-H_{eq}), 4.52 (d, J =12.4, 1H, OCH₂Ph), 4.58 (d, J = 12.4, 1H, OCH₂Ph), 7.27-7.34 (m, 5H, H_{ar}); MS (CI) 346 (M + 1), 244 (M - 101). Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.62; H, 7.76; N, 4.08.

(6R,8aR)-tert-Butyl 6-(Benzyloxy)-2,3,5,6,7,8-hexahydro-1-oxo-8a(1H)-indolizinecarboxylate (16b). Compound 15b (0.40 g, 1.18 mmol), BF3 Et2O (0.19 mL, 1.52 mmol), and LiEt3-BH (Super Hydride, 1 M in THF, 1.52 mL, 1.52 mmol) were reacted and worked up as described for 16a to give 16b (0.32 g, 80%) as a colorless solid: mp 49 °C: $[\alpha]^{23}_{D} - 86^{\circ} (c = 1.0, CHCl_3);$ IR (NaCl) (cm⁻¹) 1760, 1720; ¹H NMR δ 1.33 (dt, J = 13.3, 3.4, 1H, 8-H_{ax}), 1.45-1.52 (m, 1H, 7-H_{ax}), 1.46 (s, 9H, COOtBu), 2.10-2.14 (m, 1H, 7-H_{eq}), 2.33 (dt, J = 13.3, 3.4, 1H, 8-H_{eq}), $2.45-2.50 \text{ (m, 2H, 2-H_2)}, 2.90 \text{ (dd, } J = 11.5, 10.3, 1H, 5-H_{ax}),$ $3.09-3.14 \text{ (m, 1H, 3-H)}, 3.18 \text{ (ddd}, J = 12.0, 5.1, 1.7, 1H, 5-H_{eq}),$ 3.38-3.43 (m, 1H, 3-H), 3.51-3.57 (m, 1H, 6-H_{ax}), 4.55 (d, J =12.0, 1H, OCH₂Ph), 4.60 (d, J = 12.0, 1H; OCH₂Ph), 7.27-7.31 $(m, 1H, H_{ar,p}), 7.32 - 7.34 \ (m, 4H, H_{ar,o+m}); \ ^{13}C \ NMR \ (CDCl_3) \ 26.5,$ 27.8, 28.1, 36.0, 46.2, 51.1, 70.5, 71.2, 72.5, 82.5, 127.5, 127.6, 128.4, 138.5, 168.0, 209.0; MS (EI) 244 (M-101). Anal. Calcd for C20H27NO4: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.60; H, 7.92, N, 3.95.

(6R, 8aS)-6-(Benzyloxy)-2,3,6,7,8,8a-hexahydro-5(1H)-indolizinone (16c) and (6R, 8aR)-6-(Benzyloxy)-2,3,6,7,8,8a-hexahydro-5(1H)-indolizinone (16d). TFA (9.57 mL, 0.12 mol) was added dropwise to a solution of 16a or 16b (0.72 g,

2.08 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred for 3 h and then cooled to 0 °C, when saturated NaHCO3 solution was added. After extraction with Et₂O, the organic layer was dried (MgSO₄) and evaporated. The residue was purified by flash chromatography (petroleum ether: EtOAc, 65:35), to give a mixture of 16c and 16d (0.43 g, 85% 16c:16d = 10:1): ¹H NMR (major isomer) δ 1.16–1.30 (m, 2H, 7-H_{ax} + 8-H_{ax}), 1.95 (m, 1H, $8-H_{eq}$, 2.06–2.11 (m, 1H, 8a-H), 2.07 (dd, J = 10.4, 9.8, 1H, 5-Hax), 2.16-2.19 (m, 1H, 7-Heq), 2.27-2.31 (m, 2H, 2-H₂), 2.47 (q, J = 8.6, 1H, 3-H), 3.15-3.20 (m, 1H, 3-H), 3.34 (ddd, J = 3.15)10.3, 4.7, 1.3, 1H, 5-H_{eq}), 3.46-3.53 (m, 1H, 6-H), 4.50 (d, J =11.5, 1H, OCH₂Ph), 4.54 (d, J = 11.5, 1H, OCH₂Ph), 7.19-7.29(m, 5H, H_{ar}); ¹³C NMR (major isomer) δ 23.5 (H₂C-8), 30.2 (H₂C-7), 36.5 (H₂C-2), 49.4 (H₂C-3), 57.8 (H₂C-5), 68.7 (HC-8a), 70.8 (OCH2Ph), 74.1 (HC-6), 127.5 (OCH2Ph: HCar,p), 127.6 (OCH2-Ph: HCar,m), 128.4 (OCH2Ph: HCar,o), 138,4 (OCH2Ph: Car,i), 212.8 (C-1); MS (CI) 246 (M + 1), 138 (M - 107). Anal. Calcd for C₁₅H₁₉NO₂: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.29; H, 7.96: N. 5.61

(1S,6R,8aS)-6-(Benzyloxy)-1,2,3,5,6,7,8,8a,-octahydro-1-indolizinole (17a) and (1R,6R,8aS)-6-(Benzyloxy)-1,2,3,5,6,7,8,8a-octahydro-1-indolizinol (17b). A. To a solution of crude 16c,d (80 mg, 0.33 mmol) in MeOH (10 mL) was added NaBH₄ (12.4 mg, 0.33 mmol) at 0 °C. After the solution was stirred for 1 h, 2 N HCl (1 mL) was added, followed by addition of a saturated NaHCO₃ solution and Et₂O. The organic layer was separated, dried (MgSO₄), and evaporated, and the residue was separated by flash chromatography (CH₂Cl₂:MeOH, 95:5) to give 17a (34 mg, 42%) followed by 17b (34 mg, 42%) both as colorless oils.

B. To a solution of crude 16c,d (0.42 g, 1.7 mmol) in THF (70 mL) was added Li(sBu)₃BH (L-Selectride, 1 M in THF, 1.87 mL) at -78 °C. After the solution was stirred for 30 min at -78 °C, a saturated NaHCO3 solution was added and the mixture was extracted with Et₂O. The organic layer was dried (MgSO₄) and evaporated and the residue purified by flash chromatography (CH₂Cl₂:MeOH, 9:1) to yield 17a (0.28 g, 66%) and in small amounts the 8a-epimer, derived from 16d (0.04 g, 8%), both as colorless oils. 17a: $[\alpha]^{23}_{D} + 41^{\circ} (c = 1.0, CHCl_{3});$ 1 H NMR δ 1.20–1.30 (m, 1H), 1.44–1.54 (m, 1H), 1.62–1.74 (m, 3H), 1.84 (dd, J = 10.3, 9.8, 1H), 2.01 (q, J = 8.9, 1H), 2.09-2.18 (m, 2H), 3.02 (dt, J = 8.9, 2.1, 1H), 3.33 (ddd, J = 10.3, 4.3, 4.3)1.7, 1H), 3.46-3.53 (m, 1H), 3.99 (bs, 1H), 4.49 (d, J = 12.0, 1H), 4.53 (d, J = 12.0, 1H), 7.19–7.27 (m, 5H); MS (CI) 248 (M + 1), 228 (M - 19), 140 (M - 107). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.84; H, 8.61; N, 5.62. **17b**: $[\alpha]^{23}_{D} - 8^{\circ} (c = 0.4, \text{CHCl}_3); {}^{1}\text{H NMR } \delta 1.20 - 1.27 (m, 2\text{H}),$ 1.54-1.62 (m, 1H), 1.83-1.87 (m, 1H), 1.99-2.06 (m, 1H), 2.01 (dd, J = 10.3, 9.8, 1H), 2.18-2.21 (m, 1H), 2.26-2.33 (m, 1H),2.45 (q, J = 8.9, 1H), 2.95 (dt, J = 8.9, 2.1, 1H), 3.30 (ddd, J = 100)10.3, 4.6, 1.2, 1H), 3.50–3.58 (m, 1H), 3.87–3.92 (m, 1H), 4.55 (d, J = 12.0, 1H), 4.58 (d, J = 12.0, 1H), 4.58 (d, J = 12.0, 1H), 7.25–7.30 (m, 1H), 7.31-7.34 (m, 4H). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.34; H, 8.45; N, 5.26. (1S,6S,8aR)-epimer: $[\alpha]^{23}_{D} - 16^{\circ} (c = 1.0, CHCl_3); {}^{1}H NMR \delta$ 1.30-1.38 (m, 1H), 1.58-1.68 (m, 1H), 1.71-1.76 (m, 2H), 1.88-1.99 (m, 2H), 2.05-2.18 (m, 3H), 3.14 (dt, J = 8.9, 2.5, 1H), 3.32(dt, J = 11.9, 2.1, 1H), 3.59 - 3.61 (m, 1H), 4.06 (bs, 1H), 4.53 (d, 1H), 4.53 (d, 1H))J = 12.4, 1H, 4.62 (d, J = 12.4, 1H), 7.26–7.28 (m, 1H), 7.29– 7.38 (m, 4H); MS (CI) 248 (M + 1). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.63; H, 8.91; N, 5.52.

(1S,6R,8aS)-6-(Benzyloxy)-1,2,3,5,6,7,8,8a-octahydroindolizinyl Acetate (18a). Compound 17a (0.29 g, 1.18 mmol) was dissolved in pyridine (3 mL). After addition of Ac₂O (3 mL), the mixture was stirred for 4 h at rt. The reaction mixture was evaporated, and the residue was purified by flash chromatography (petroleum ether: EtOAc, 2:3), to give 18a (0.31 g, 90%) as a colorless oil: $[\alpha]^{23}_{D} + 4^{\circ} (c = 1.0, \text{CHCl}_3); \text{IR} (\text{NaCl}) (\text{cm}^{-1})$ 1730; ¹H NMR δ 1.18–1.29 (m, 1H), 1.34–1.44 (m, 1H), 1.64– 1.70 (m, 1H), 1.71-1.77 (m, 1H), 1.79-1.87 (m, 1H), 1.82 (dd, J = 10.25, 9.8, 1H), 1.98 (s, 3H), 2.05 (q, J = 9.0, 1H), 2.08–2.15 (m, 1H), 2.18-2.27 (m, 1H), 3.05 (dt, J = 9.0, 1.7, 1H), 3.39 (ddd, J = 10.25, 4.7, 1.7, 1H), 3.47 - 3.55 (m, 1H), 4.49 (d, J = 12.0, 1H), 4.52 (d, J = 12.0, 1H); 5.11–5.14 (m, 1H); 7.17–7.23 (m, 1H), 7.24-7.26 (m, 4H); MS (CI) 290 (M + 1), 230 (M - 59), 182 (M - 107). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.28; H, 7.84; N, 5.29.

(1*R*,6*R*,8a*S*)-6-(Benzyloxy)-1,2,3,5,6,7,8,8a-octahydroindolizinyl Acetate (18b). Compound 17b (27 mg, 0.11 mmol) was reacted and worked up as described for 18a to give 18b (23 mg, 88%) as a colorless solid: mp 27 °C; $[\alpha]^{23}_{D} - 18^{\circ}$ (c = 1.0, CHCl₃); IR (KBr) (cm⁻¹) 1740; ¹H NMR δ 1.17–1.29 (m, 2H), 1.49–1.57 (m, 2H), 1.88–1.96 (m, 2H), 1.98 (s, 3H), 2.09–2.13 (m, 1H), 2.23–2.38 (m, 2H), 2.86–2.90 (m, 1H), 3.27 (ddd, J = 10.25, 4.7, 1.7, 1H), 3.44–3.51 (m, 1H), 4.48 (d, J = 12.0, 1H); 4.52 (d, J = 12.0, 1H), 4.64–4.69 (m, 1H), 7.18–7.26 (m, 5H). Anal. Calcd for C₁₇H₂₃NO₃: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.21; H, 7.86; N, 4.31.

(1S,6R,8aS)-6-Hydroxy-1,2,3,5,6,7,8,8a-octahydroindolizinyl Acetate (19). A mixture of 18a (0.31 g, 1.07 mmol) and Pd/C (10%, 0.16 g) in AcOH (20 mL) was stirred for 16 h under a balloon of hydrogen. After filtration, the filtrate was evaporated. The residue was dissolved in a saturated NaHCO₃ solution and extracted with CH₂Cl₂. The organic layer was dried and evaporated to give 19 (0.19 g, 88%) as a yellowish oil: $[\alpha]^{23}$ D +7.5° (c = 0.95, CHCl₃); IR (NaCl) (cm⁻¹) 3390, 1730; ¹H NMR δ 1.15–1.25 (m, 1H), 1.39–1.49 (m, 1H), 1.64–1.70 (m, 1H), 1.64–1.75 (m, 1H), 1.78 (dd, J = 10.3, 10.3, 1H), 1.81–1.86 (m, 1H), 1.90–2.16 (m, 2H), 1.99 (s, 3H), 2.17–2.29 (m, 1H), 3.07 (dt, J = 9.0, 1.7, 1H), 3.28 (ddd, J = 10.3, 4.7, 1.7, 1H), 3.74–3.81 (m, 1H), 5.12–5.16 (m, 1H); MS (CI) 200 (M + 1), 140 (M - 59). Anal. Calcd for C₁₀H₁₇NO₃: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.88; H, 8.53; N, 6.50.

(1S,6R,8aS)-6-Azido-1,2,3,5,6,7,8,8a-octahydroindolizinyl Acetate (20a) and (1S,5S,7aS)-5-Azidomethyl-2,3,5,6,7, 7a-hexahydropyrrolizinyl Acetate (21a). To a solution of 19 (86 mg, 0.43 mmol) and triethylamine (71 μ L, 0.51 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of trifluoromethanesulfonic anhydride (70.3 μ L, 0.47 mmol) in CH₂Cl₂ (1 mL) at 0 °C. The solution was stirred for 2 h. Then, a suspension of NaN₃ (200 mg) in DMF (10 mL) was added. After 1 h, a saturated NH4Cl solution and Et2O were added. The organic layer was separated, dried (MgSO₄), and evaporated, and the residue was purified by flash chromatography (petroleum ether:EtOAc, 1:1), to give 20a (38 mg, 40%), followed by 21a (10 mg, 11%). **20a** (colorless oil): $[\alpha]^{23}_{D} - 6.5^{\circ} (c = 1, CHCl_3);$ IR (NaCl) (cm⁻¹) 2100, 1740; ¹H NMR δ 1.29–1.39 (m, 1H), 1.47-1.57 (m, 1H), 1.76-1.85 (m, 2H), 1.87-1.94 (m, 1H), 1.91 (dd, J = 10.3, 9.7, 1H), 2.07 (s, 3H), 2.07-2.18 (m, 1H), 2.13 (q, 1H))J = 9.0, 1H, 2.27–2.36 (m, 1H), 3.16 (dt, J = 9.0, 1.7, 1H), 3.34 (ddd, J = 10.3, 4.3, 1.7, 1H), 3.48 - 3.55 (m, 1H), 5.20 - 5.24 (m, 1H))1H); MS (CI) 225 (M + 1), 182 (M - 42). **21a**: $[\alpha]^{23}D - 47^{\circ} (c = 1)^{12}$ 0.7, CHCl₃); IR (NaCl) (cm⁻¹) 2100, 1740; ¹H NMR δ 1.63–1.81 (m, 3H), 2.02-2.35 (m, 3H), 2.08 (s, 3H), 2.69 (dt, J = 10.3, 6.4)1H), 2.83-2.89 (m, 1H), 3.18-3.27 (m, 2H), 3.24 (dd, J = 6.0, 2.1, 1H), 3.72-3.77 (m, 1H, 6-H), 5.11-5.14 (m, 1H, 1-H); MS (CI) 225 (M + 1), 182 (M - 42).

(1S,6R,8aS)-6-(Phthalimido)-1,2,3,5,6,7,8,8a-octahydroindolizinyl Acetate (20b) and (1S,5S,8aS)-5-(Phthalimido)methyl)-2,3,5,6,7,7a-hexahydro-1(1H)-pyrrolizinyl Acetate (21b). To a solution of 19 (56 mg, 0.28 mmol), phthalimide (41 mg, 0.28 mmol), and triphenylphosphine (74 mg, 0.28 mmol) in THF (5 mL) was slowly added diethyl azodicarboxylate (38% in toluene, 128 $\mu L,$ 0.28 mmol). After 16 h, the solvent was evaporated and the residue was purified by flash chromatography (CH₂Cl₂:MeOH, 95:5) to give 20b (17.7 mg, 27%) and 21b (34.7mg, 55%). **20b**: $[\alpha]^{23}_{D}$ -6° (c = 0.75, CHCl₃); ¹H NMR δ 1.58-1.68 (m, 1H), 1.82-1.90 (m, 3H), 2.06-2.16 (m, 1H), 2.10 (s, 3H), 2.19 (q, J = 9.0, 1H), 2.26–2.37 (m, 2H), 2.84 (dd, J =10.7, 10.7, 1H), 3.12 (dd, J = 10.7, 4.3, 1H), 3.18 (dt, J = 9.4, 1.7, 1H), 4.45-4.53 (m, 1H), 5.25-5.28 (m, 1H), 7.71 (dd, J =5.6, 3.0, 2H), 7.82 (dd, J = 5.6, 3.0, 2H); MS (CI) 329 (M + 1), 269 (M - 59). Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 66.04; H, 6.43; N, 8.04. **21b**: $[\alpha]^{23}D - 32^{\circ}(c)$ = 0.6, CHCl₃); IR (NaCl) 2940, 1740, 1710; ¹H NMR δ 1.59– $1.65\,(m,\,1H),\,1.71-1.83\,(m,\,2H),\,1.96-2.16\,(m,\,3H),\,2.04\,(s,\,3H),$ 2.67 (dt, J = 10.6, 6.4, 1H), 2.99-3.06 (m, 1H), 3.12 (dt, J = 9.8),2.6, 1H), 3.63 (dd, 13.7, 7.3, J = 13.7, 7.3, 1H), 3.73-3.78 (m, 2H), 5.08-5.11 (m, 1H), 7.72 (dd, J = 5.5, 3.0, 2H), 7.85 (dd, J= 5.5, 3.0, 2H); MS (CI) 329 (M + 1), 168 (M - 160, CH₂NPhth). Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 66.19; H, 6.34; N, 7.98.

(1S,6R,8aS)-6-Acetamido-1,2,3,5,6,7,8,8a-octahydroindolizyl Acetate (20c) A. Compound 20b (5 mg, 0.015 mmol) and hydrazine hydrate ($22 \ \mu$ L, 0.45 mmol) in EtOH (3 mL) were refluxed for 4 h. After evaporation of the solvent, pyridine (0.3 mL) and acetic acid anhydride (0.3 mL) were added and the mixture was stirred for another 4 h. Then, the solvents were evaporated, and the residue was filtered on a short silica gel column (CHCl₃:MeOH 95:5) to give **20c** (2 mg, 55%).

B: A mixture of **20a** (30 mg, 0.134 mmol) and Pd/C (10% 10 mg) in MeOH (3 mL) was stirred for 16 h under a balloon of hydrogen at rt. The reaction mixture was filtered, and the solvent was evaporated. After addition of pyridine (0.5 mL), and acetic acid anhydride (0.5 mL) it was stirred for 4 h. Then the mixture was evaporated, and the residue was filtered on a short silica gel column (CHCl₃:MeOH, 95:5) to give **20c** (14 mg, 43%) as colorless crystals: mp 203 °C; [α]²³_D +12.4° (c = 0.75, CHCl₃), for *ent*-**20c**; lit.³ [α]²³_D -12° (c = 0.7, CHCl₃). Spectroscopic data are identical with those reported for *ent*-**20c** (lit.³).

(1S,5S,7aS)-5-(Acetamidomethyl)-2,3,5,6,7,7a-hexahydropyrrolizinyl Acetate (21c). A solution of 21b (16 mg, 0.05 mmol) and hydrazine hydrate (88 µL, 1.8 mmol) in EtOH (3 mL) was refluxed for 4 h. The solvent was then removed, and the residue was stirred with pyridine (0.5 $\ensuremath{\,mL}\xspace)$ and acetic acid anhydride (0.5mL) for another 4 h. After evaporation, the residue was filtered on a short silica gel column (CHCl3:MeOH 95:5) to give **21c** (8 mg, 69%) as a colorless oil: $[\alpha]^{23}_{D} - 40^{\circ} (c =$ 0.8, CHCl₃); IR (NaCl) (cm⁻¹) 3280, 1740, 1660; ¹H NMR δ 1.63-1.72 (m, 1H), 1.74 - 1.79 (m, 2H), 1.96 - 2.09 (m, 2H), 2.05 (s, 3H),2.07 (s, 3H), 2.11-2.15 (m, 1H), 2.65-2.71 (dt, J = 10.3, 6.4,1H), 2.89-2.95 (m, 1H), 3.13-3.17 (m, 1H), 3.19-3.25 (m, 1H), 3.28-3.35 (m, 1H), 3.71-3.76 (m, 1H), 5.13-5.16 (m, 1H), 6.19 (bs, 1H, NH); MS (CI) 241 (M + 1), 181 (M - 59), 168 (M - 72, CH_2Ac). Anal. $C_{12}H_{20}N_2O_3$: C, 59.98; H, 8.39; N, 11.66. Found: C, 59.10; H, 8.81; N, 10.96.

(1S,6R,8aS)-6-Amino-1,2,3,5,6,7,8,8a-octahydroindolizinyl Acetate (ent-3b). A mixture of 20a (5 mg, 0.02 mmol) and Pd/C in MeOH was stirred for 16 h at rt under a balloon of hydrogen. The reaction mixture was filtered, and the solvent was evaporated to give ent-3b (3 mg, 68%) as a colorless oil. Spectroscopic data are identical to those reported for 3b and ent-3b (lit.^{3,5j,m}).

(15,8aS)-6-(Hydroxyimino)-1,2,3,5,6,7,8,8a-octahydroindolizinyl Acetate (22). To a mixture of oxalyl chloride (5.0 $\mu L,\,0.006~mmol)$ in $CH_2Cl_2\,(0.5~mL)$ were added at $-60~^\circ C~DMSO$ $(9.0 \ \mu L, 0.012 \ mmol)$ dissolved in CH_2Cl_2 (0.05 mL) and subsequently, 19 (12 mg, 0.006 mmol), also dissolved in CH₂Cl₂ (0.05 mL). The mixture was stirred for 15 min, when Et₃N (40 μ L, 0.03 mmol) was added. After 5 min, a saturated NaHCO₃ solution was added. After extraction with CH₂Cl₂, the organic layer was dried (MgSO₄) and evaporated. The residue was heated in a mixture of EtOH (2 mL), pyridine (1 mL), and H₂-NOH·HCl (15 mg, 0.22 mmol) for 4 h at 80 °C. After a further 16 h at rt, the mixture was concentrated and CH₂Cl₂ and saturated NaHCO3 were added. The organic layer was separated, dried (MgSO₄), and evaporated, and the residue was purified by flash chromatography (CH₂Cl₂:MeOH, 95:5) to give 22 (12 mg, 81%, 3:1 mixture of syn/anti isomers) as a colorless oil. Spectroscopic data (IR, ¹H NMR) are identical to those reported for racemic 22 (lit.5b).

(1S,6S,8aS)-6-Acetamido-1,2,3,5,6,7,8,8a-octahydroindolizinyl Acetate (23). According to ref 5b, a mixture of 22 (10 mg, 0.047 mmol) and PtO₂ in EtOH (3.5 mL) and concentrated HCl (0.2 mL) was stirred for 16 h at rt under a balloon of hydrogen. The reaction mixture was filtered, and the solvent was evaporated. Then, pyridine (1.5 mL) and Ac₂O (1 mL) were added to the residue. After being stirred for 3 h at rt, the mixture was concentrated and the residue was purified by flash chromatography (CH₂Cl₂: MeOH, 97:3) to give 23 (2 mg, 20%) as a colorless solid: mp 130-135 °C (ref 5j, 139-141 °C); ¹H NMR & 1.41-1.48 (m, 1H), 1.48-1.57 (m, 1H), 1.73-1.82 (m, 1H), 1.87-1.93 (m, 1H), 1.95-1.98 (m, 1H), 2.01 (s, 3H), 2.02-2.11 (m, 2H), 2.09 (s, 3H), 2.18 (dd, J = 11.1, 2.5, 1H), 2.25-2.33 (m, 1H), 3.03 (d, J)J = 11.5, 1H), 3.09 (td, J = 9.4, 1.7, 1H), 4.18 (dt, J = 8.1, 2.6, 11H), 5.25 (ddd, J = 7.7, 5.1, 2.5, 1H), 6.31 (d, J = 6.4,NH); MS (CI) 241 (M + 1).

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