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

Peter Gmeiner*,† and Dagmar Junge‡

Pharmazeutisches Institut der Universität Bonn, An der Immenburg 4, D-53121 Bonn, Germany, and Institut für Pharmazie und Lebensmittelchemie der Universität München, Sophienstrasse 10, D-80333 München, Germany

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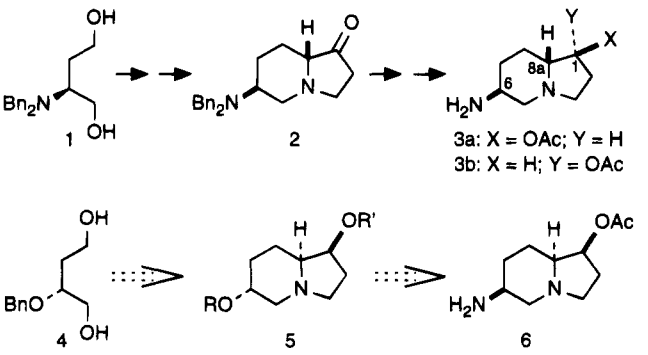
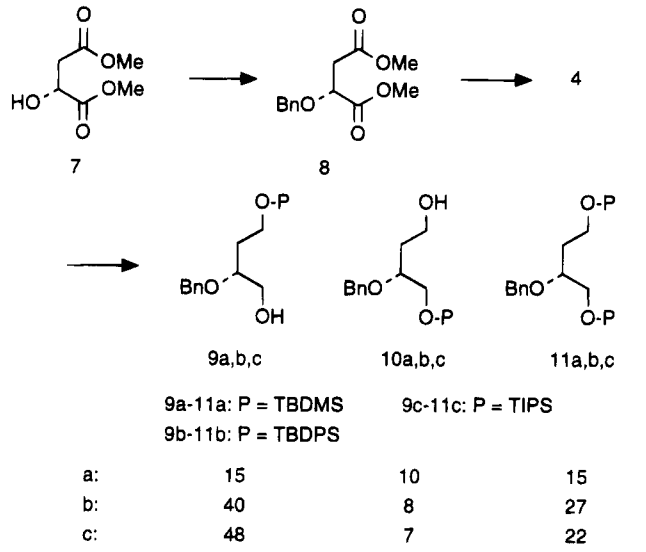
Selective transformation of readily available chiral building blocks has become a major method for the synthesis of enantiomerically pure bioactive compounds including a large number of natural products.[1] In our previous publications,[2,3] we have presented the synthesis of enantiomerically pure 1,2- 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-*trans*-configured (1*S*,6*R*,8a*S*)-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_N2 displacement at position 6 was expected to induce 6,8a-*cis* stereochemistry.

Scheme 1



Scheme 2



a:	15	10	15
b:	40	8	27
c:	48	7	22

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 silylation of the diol **1** by TBDMS-Cl or TBDPS-Cl.[3] Analogous regiodifferentiation of a benzyloxy substituent was expected to induce a preferred silylation 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

† Pharmazeutisches Institut der Universität Bonn.

‡ Institut für Pharmazie und Lebensmittelchemie der Universität München.

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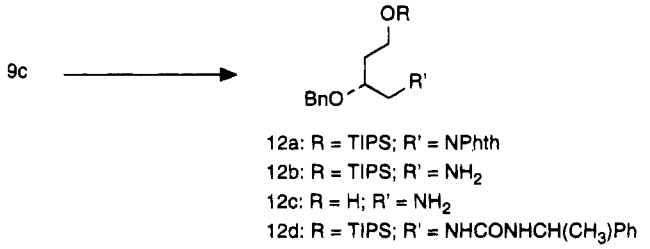
Scheme 3



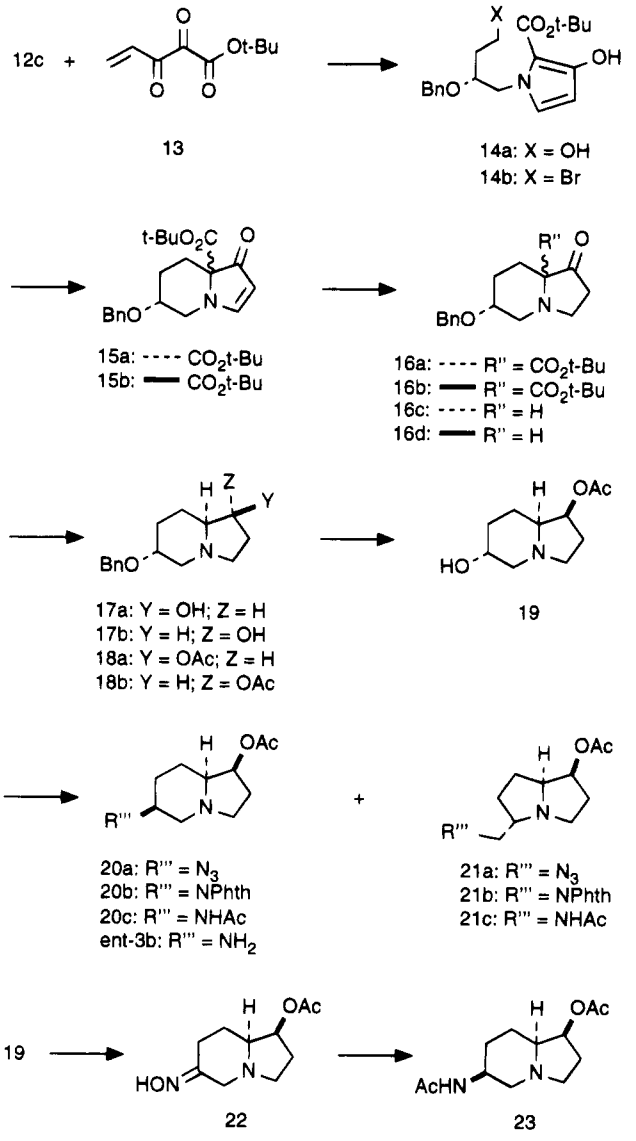
12a: R = TIPS; R' = NPhth
12b: R = TIPS; R' = NH_2
12c: R = H; R' = NH_2
12d: R = TIPS; R' = $NHCONHCH(CH_3)Ph$

when protection by the sterically demanding TIPS group[9] was investigated. In this case, 48% of the 4-silyloxy 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 *N*-deprotection 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 1,3-diols. 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 **13**[12] resulted in formation of the 3-hydroxypyrrole-2-carboxylate **14a** (Scheme 4). Activation of the terminal HO-group was performed by CBr_4/PPh_3 in CH_2Cl_2 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 six-membered 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 control*[14] to yield **17a**, besides a small amount of its 8a-epimer, which was easily separable by flash

Scheme 4



chromatography. In contrast, reduction by $NaBH_4$/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 NaN_3. 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 N_3^- 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/PPh_3 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 (H_2, Pd/C or hydrazine, then Ac_2O). 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 H_2NOH 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 N_2. 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 $CDCl_3$ solutions using TMS as an internal standard. Unless specified otherwise, *J* values are given in hertz. NMR peak assignments are based on $^1H-^1H$ COSY and $^1H-^{13}C$ COSY experiments.

Dimethyl (*R*)-2-(Benzyloxy)succinate (8). To a mixture of (*R*)-dimethyl malate (8.00 g, 49.3 mmol) and Ag_2O (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° (*c* = 1.0, $CHCl_3$,). For *ent*-**8**: lit.[8a] $[\alpha]^{23}_D$ −63° ($CHCl_3$, *c* = 1.6); lit.[8b] $[\alpha]^{23}_D$ −68.5° (*c* = 11.4, $CHCl_3$); 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 $C_{13}H_{16}O_5$: 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 $LiAlH_4$ (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 $NaHCO_3$ solution and Et_2O were added. The organic layer was separated, dried ($MgSO_4$), and evaporated to give pure **4** (6.05g, 98%) as a semisolid substance: $[\alpha]^{23}_D$ +15° (*c* = 1.0, $CHCl_3$), lit.[6] $[\alpha]^{23}_D$ +20.6° (*c* = 1.0, $CHCl_3$); ^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 $C_{11}H_{16}O_3$: 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 NH_4Cl solution and Et_2O were added. The organic layer was dried ($MgSO_4$) 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° (*c* = 1.0, $CHCl_3$); ^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 $C_{23}H_{44}O_3Si_2$: 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 $C_{17}H_{30}O_3Si$: 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 NH_4Cl solution and Et_2O were added. The organic layer was separated, dried ($MgSO_4$), 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 $C_{43}H_{52}O_3Si_2$: C, 76.74; H, 7.78. Found: C, 76.96; H, 7.57. **9b**: $[\alpha]^{23}_D$ −2.5° (*c* = 1.0, $CHCl_3$); ^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, 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 δ 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 NH_4Cl solution and Et_2O were added. The organic layer was separated, dried ($MgSO_4$), 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, $CHCl_3$); ^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* = 11.7, 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 $C_{29}H_{56}O_3Si$: C, 68.44; H, 11.09. Found: C, 68.38; H, 11.16. **9c**: colorless oil, $[\alpha]^{23}_D$ +2.8° (*c* = 0.8, $CHCl_3$); ^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 $C_{20}H_{36}O_3Si$: 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, 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 (CH_2Cl_2: petroleum ether, 3:2) to give **12a** (8.8 g, 98%) as a colorless oil: $[\alpha]^{23}_D$ +5.3° (*c* = 1.0, $CHCl_3$); 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 $^1H-^1H$ COSY and $^1H-^{13}C$ COSY experiments and mass spectroscopy. Diagnostic for **21c** is a ^3J coupling between the NH and neighboring CH_2 protons as well as a characteristic α-cleavage of a CH_2NHAc fragment (see Experimental Section).

1), (EI) 439 (M − 43), 304 (M − 177). Anal. Calcd for $C_{28}H_{39}NO_4Si$: 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 $NaHCO_3$ solution was added. After extraction with Et_2O, the organic layer was dried ($MgSO_4$) and evaporated to leave pure **12b** (7.9 g, 95%) as a colorless oil: $[\alpha]^{23}_D$ +4.8° (*c* = 1.9, $CHCl_3$); ^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 $C_{20}H_{37}NO_2Si$: 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 μL, 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° (*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 $C_{28}H_{46}N_2O_3$: 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° (*c* = 1.0, $CHCl_3$); 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 Et_2O were added. The aqueous phase was basified with 2 N NaOH and again extracted with Et_2O. The organic layer was dried ($MgSO_4$), and the solvent was evaporated to leave pure **12c** (5.2 g, 96%) as a colorless oil: $[\alpha]^{23}_D$ −7° (*c* = 1.0, $CHCl_3$); ^1H NMR δ 1.85−1.89 (m, 1H), 1.90−1.97 (m, 1H), 2.28 (bs, 2H, NH_2), 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 $C_{11}H_{17}NO_2$: 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 CH_2Cl_2 (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, $CHCl_3$); 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 $C_{20}H_{27}NO_5$: 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 CH_2Cl_2 (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; $[\alpha]^{23}_D$ −39° (*c* = 0.9, $CHCl_3$); 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 $C_{20}H_{26}NO_4Br$: C, 56.61; H, 6.18; N, 3.30. Found: C, 56.58; H, 6.37; N, 3.18.

(6*R*,8a*S*)-*tert*-Butyl-6-(Benzyloxy)-5,6,7,8-tetrahydro-1-oxo-8a(1*H*)-indolizinecarboxylate (15a) and (6*R*,8a*R*)-*tert*-Butyl-6 (Benzyloxy)-5,6,7,8-tetrahydro-1-oxo-8a(1*H*)-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 NH_4Cl solution, the product was extracted with ether, and the organic layer was dried ($MgSO_4$) 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, $CHCl_3$); 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, 1H, 5-H_{ax}), 3.55−3.61 (m, 2H, 5-H_{eq} + 6-H_{eq}), 4.36 (d, *J* = 12.0, 1H, OCH_2Ph), 4.48 (d, *J* = 12.0, 1H, OCH_2Ph), 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); ^{13}C 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 $C_{20}H_{25}NO_4$: 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, $CHCl_3$); IR (KBr) (cm^{-1}) 1730, 1660, 1540; ^1H NMR; δ(ppm) 1.42−1.47 (m, 1H, 8-H_{ax}), 1.47 (s, 9H, COOtBu), 1.47−1.49 (m, 1H, 7-H_{ax}), 2.18−2.22 (m, 1H, 7-H_{eq}), 2.71 (dt, *J* = 12.4, 3.0, 1H, 8-H_{eq}), 3.23 (dd, *J* = 12.8, 10.3, 1H, 5-H_{ax}), 3.38−3.46 (m, 1H, 6-H_{ax}), 3.78 (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.

(6*R*,8a*S*)-*tert*-Butyl 6-(Benzyloxy)-2,3,5,6,7,8-hexahydro-1-oxo-8a(1*H*)-indolizinecarboxylate (16a). To a solution of **15a** (0.95 g, 2.76 mmol) in THF (100 mL) was added $BF_3{\cdot}Et_2O$ (0.44 mL, 3.59 mmol) at −78 °C. After 5 min, $LiEt_3BH$ (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 $NaHCO_3$ solution were added. After extraction with Et_2O, the organic layer was dried ($MgSO_4$) 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, $CHCl_3$); 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, OCH_2Ph), 4.58 (d, *J* = 12.4, 1H, OCH_2Ph), 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.

(6*R*,8a*R*)-*tert*-Butyl 6-(Benzyloxy)-2,3,5,6,7,8-hexahydro-1-oxo-8a(1*H*)-indolizinecarboxylate (16b). Compound **15b** (0.40 g, 1.18 mmol), $BF_3{\cdot}Et_2O$ (0.19 mL, 1.52 mmol), and $LiEt_3BH$ (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° (*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 (m, 2H, 2-H_2), 2.90 (dd, *J* = 11.5, 10.3, 1H, 5-H_{ax}), 3.09−3.14 (m, 1H, 3-H), 3.18 (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, OCH_2Ph), 4.60 (d, *J* = 12.0, 1H; OCH_2Ph), 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 $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.60; H, 7.92, N, 3.95.

(6*R*, 8a*S*)-6-(Benzyloxy)-2,3,6,7,8,8a-hexahydro-5(1*H*)-indolizinone (16c) and (6*R*, 8a*R*)-6-(Benzyloxy)-2,3,6,7,8,8a-hexahydro-5(1*H*)-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 $NaHCO_3$ solution was added. After extraction with Et_2O, the organic layer was dried ($MgSO_4$) 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-H_{ax}), 2.16−2.19 (m, 1H, 7-H_{eq}), 2.27−2.31 (m, 2H, 2-H_2), 2.47 (q, J = 8.6, 1H, 3-H), 3.15−3.20 (m, 1H, 3-H), 3.34 (ddd, J = 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, OCH_2Ph), 4.54 (d, J = 11.5, 1H, OCH_2Ph), 7.19−7.29 (m, 5H, H_{ar}); ^{13}C NMR (major isomer) δ 23.5 (H_2C-8), 30.2 (H_2C-7), 36.5 (H_2C-2), 49.4 (H_2C-3), 57.8 (H_2C-5), 68.7 (HC-8a), 70.8 (OCH_2Ph), 74.1 (HC-6), 127.5 (OCH_2Ph: $HC_{ar,p}$), 127.6 (OCH_2-Ph: $HC_{ar,m}$), 128.4 (OCH_2Ph: $HC_{ar,o}$), 138,4 (OCH_2Ph: $C_{ar,i}$), 212.8 (C-1); MS (CI) 246 (M + 1), 138 (M − 107). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.29; H, 7.96; N, 5.61.

(1*S*,6*R*,8a*S*)-6-(Benzyloxy)-1,2,3,5,6,7,8,8a,-octahydro-1-indolizinole (17a) and (1*R*,6*R*,8a*S*)-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 $NaBH_4$ (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 $NaHCO_3$ solution and Et_2O. The organic layer was separated, dried ($MgSO_4$), and evaporated, and the residue was separated by flash chromatography (CH_2Cl_2: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)$_3$BH (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 $NaHCO_3$ solution was added and the mixture was extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated and the residue purified by flash chromatography (CH_2Cl_2: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° (c = 1.0, $CHCl_3$); ^1H 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, 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° (c = 0.4, $CHCl_3$); ^1H NMR δ 1.20−1.27 (m, 2H), 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 = 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), 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. **(1*S*,6*S*,8a*R*)-epimer**: $[\alpha]^{23}_D$ −16° (c = 1.0, $CHCl_3$); ^1H NMR δ 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, 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.

(1*S*,6*R*,8a*S*)-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 Ac_2O (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° (c = 1.0, $CHCl_3$); IR (NaCl) (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° (c = 1.0, $CHCl_3$); 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 $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.21; H, 7.86; N, 4.31.

(1*S*,6*R*,8a*S*)-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 $NaHCO_3$ solution and extracted with CH_2Cl_2. 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, $CHCl_3$); 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 $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.88; H, 8.53; N, 6.50.

(1*S*,6*R*,8a*S*)-6-Azido-1,2,3,5,6,7,8,8a-octahydroindolizinyl Acetate (20a) and (1*S*,5*S*,7a*S*)-5-Azidomethyl-2,3,5,6,7,7a-hexahydropyrrolizinyl Acetate (21a). To a solution of **19** (86 mg, 0.43 mmol) and triethylamine (71 μL, 0.51 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of trifluoromethanesulfonic anhydride (70.3 μL, 0.47 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The solution was stirred for 2 h. Then, a suspension of NaN_3 (200 mg) in DMF (10 mL) was added. After 1 h, a saturated NH_4Cl solution and Et_2O were added. The organic layer was separated, dried ($MgSO_4$), 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° (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, 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); MS (CI) 225 (M + 1), 182 (M − 42). **21a**: $[\alpha]^{23}_D$ −47° (c = 0.7, $CHCl_3$); 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).

(1*S*,6*R*,8a*S*)-6-(Phthalimido)-1,2,3,5,6,7,8,8a-octahydroindolizinyl Acetate (20b) and (1*S*,5*S*,8a*S*)-5-(Phthalimido)-methyl)-2,3,5,6,7,7a-hexahydro-1(1*H*)-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 μL, 0.28 mmol). After 16 h, the solvent was evaporated and the residue was purified by flash chromatography (CH_2Cl_2:MeOH, 95:5) to give **20b** (17.7 mg, 27%) and **21b** (34.7mg, 55%). **20b**: $[\alpha]^{23}_D$ −6° (c = 0.75, $CHCl_3$); ^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° (c = 0.6, $CHCl_3$); 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, CH_2NPhth). 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.

(1*S*,6*R*,8a*S*)-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 μL, 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 ($CHCl_3$: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 ($CHCl_3$:MeOH, 95:5) to give **20c** (14 mg, 43%) as colorless crystals: mp 203 °C; $[\alpha]^{23}_D$ +12.4° (c = 0.75, $CHCl_3$), for *ent*-**20c**; lit.[3] $[\alpha]^{23}_D$ −12° (c = 0.7, $CHCl_3$). Spectroscopic data are identical with those reported for *ent*-**20c** (lit.[3]).

(1*S*,5*S*,7a*S*)-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 mL) and acetic acid anhydride (0.5mL) for another 4 h. After evaporation, the residue was filtered on a short silica gel column ($CHCl_3$:MeOH 95:5) to give **21c** (8 mg, 69%) as a colorless oil: $[\alpha]^{23}_D$ −40° (c = 0.8, $CHCl_3$); 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.

(1*S*,6*R*,8a*S*)-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]).

(1*S*,8a*S*)-6-(Hydroxyimino)-1,2,3,5,6,7,8,8a-octahydroindolizinyl Acetate (22). To a mixture of oxalyl chloride (5.0 μL, 0.006 mmol) in CH_2Cl_2 (0.5 mL) were added at −60 °C DMSO (9.0 μL, 0.012 mmol) dissolved in CH_2Cl_2 (0.05 mL) and subsequently, **19** (12 mg, 0.006 mmol), also dissolved in CH_2Cl_2 (0.05 mL). The mixture was stirred for 15 min, when Et_3N (40 μL, 0.03 mmol) was added. After 5 min, a saturated $NaHCO_3$ solution was added. After extraction with CH_2Cl_2, the organic layer was dried ($MgSO_4$) and evaporated. The residue was heated in a mixture of EtOH (2 mL), pyridine (1 mL), and H_2NOH·HCl (15 mg, 0.22 mmol) for 4 h at 80 °C. After a further 16 h at rt, the mixture was concentrated and CH_2Cl_2 and saturated $NaHCO_3$ were added. The organic layer was separated, dried ($MgSO_4$), and evaporated, and the residue was purified by flash chromatography (CH_2Cl_2: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]).

(1*S*,6*S*,8a*S*)-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 PtO_2 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 Ac_2O (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 (CH_2Cl_2: MeOH, 97:3) to give **23** (2 mg, 20%) as a colorless solid: mp 130−135 °C (ref 5j, 139−141 °C); ^1H NMR δ 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 = 11.5, 1H), 3.09 (td, J = 9.4, 1.7, 1H), 4.18 (dt, J = 8.1, 2.6, 1H), 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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