Facile Synthesis of Diastereoisomerically and Optically Pure 2-Substituted Hexahydro-1*H*-pyrrolizin-3-ones

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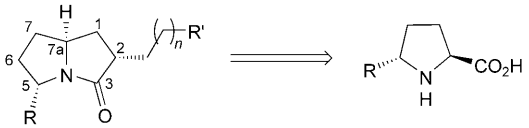
We report a short synthetic route that provides optically active 2-substituted hexahydro-1*H*-pyrrolizin-3-ones in four steps from commercially available Boc (*tert*-but(oxy)carbonyl))-protected proline. Diastereoisomers (−)-**11** and (−)-**12** were assembled from the proline-derived aldehyde (−)-**8** and ylide **9** *via* a *Wittig* reaction and subsequent catalytic hydrogenation (*Scheme 3*). Cleavage of the Boc protecting group under acidic conditions, followed by intramolecular cyclization, afforded the desired hexahydro-1*H*-pyrrolizinones (−)-**1** and (+)-**13**. Applying the same protocol to ylide **19** afforded hexahydro-1*H*-pyrrolizinones (−)-**25** and (−)-**26** (*Scheme 5*). The absolute configuration of the target compounds was determined by a combination of NMR studies (*Figs. 1* and *2*) and X-ray crystallographic analysis (*Fig. 3*).

1. Introduction. – In the course of our search for new, nonpeptidic inhibitors for the enzyme Pin1 [1][2], a peptidyl prolyl *cis/trans* isomerase [3] involved in the control of the cell cycle, that has been proposed as a new anti-cancer target, we became interested in the development of 2-mono- and 2,5-disubstituted 'pyrrolizidin-3-one' (= hexahydro-1*H*-pyrrolizin-3-one = 4-azabicyclo[3.3.0]octan-3-one) derivatives (*Scheme 1*). Only a few examples of diastereoisomerically pure 2,5-disubstituted derivatives have been reported in the literature [4]. A larger number of 2-substituted pyrrolizidinones have been prepared [5], although often as inseparable mixtures of diastereoisomers [6–11]. Here, we describe a versatile new synthesis of diastereoisomerically and optically pure 2-substituted pyrrolizidinones starting from L-proline. The same route is amenable to the preparation of 2,5-disubstituted derivatives, which will be reported later.

Scheme 1. *Synthesis of 2-Mono- and 2,5-Disubstituted Hexahydro-1*H*-pyrrolizin-3-ones Starting from* L*-Proline*

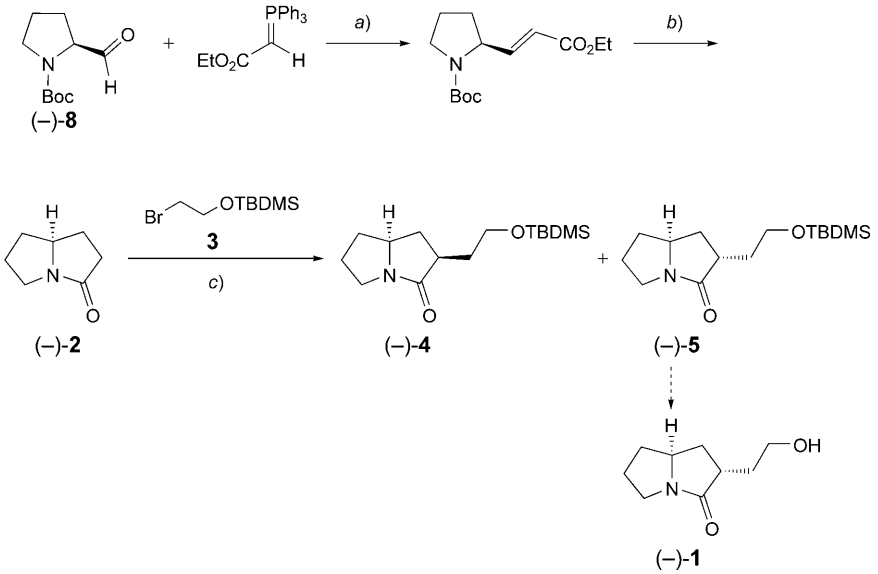


R = H, alkyl
R' = R''O, R'''NH
n = 1, 2

2. Results and Discussion. – In analogy to the synthesis of 2-methyl derivatives described in the literature [5], we envisioned preparing compound (−)-**1** by alkylation

of the parent pyrrolizidinone (−)-**2**. To this end, the bicyclic lactam (−)-**2** was synthesized according to a known procedure with an overall yield of 54% [12]. Treatment of (−)-**2** with LDA (for abbreviations, see *Scheme* captions), followed by addition of bromide **3**, afforded diastereoisomers (−)-**4** and (−)-**5** in a disappointingly low total yield of 27%, which could not be increased upon variation of the reaction conditions (*Scheme 2*). Analogous alkylations with more-potent electrophiles, such as MeI [5], $PhCH_2Br$, and allyl bromide [13], or aldehydes [7], had previously given good results. But to install our functionalized substituents in reasonable yield, another strategy would be required.

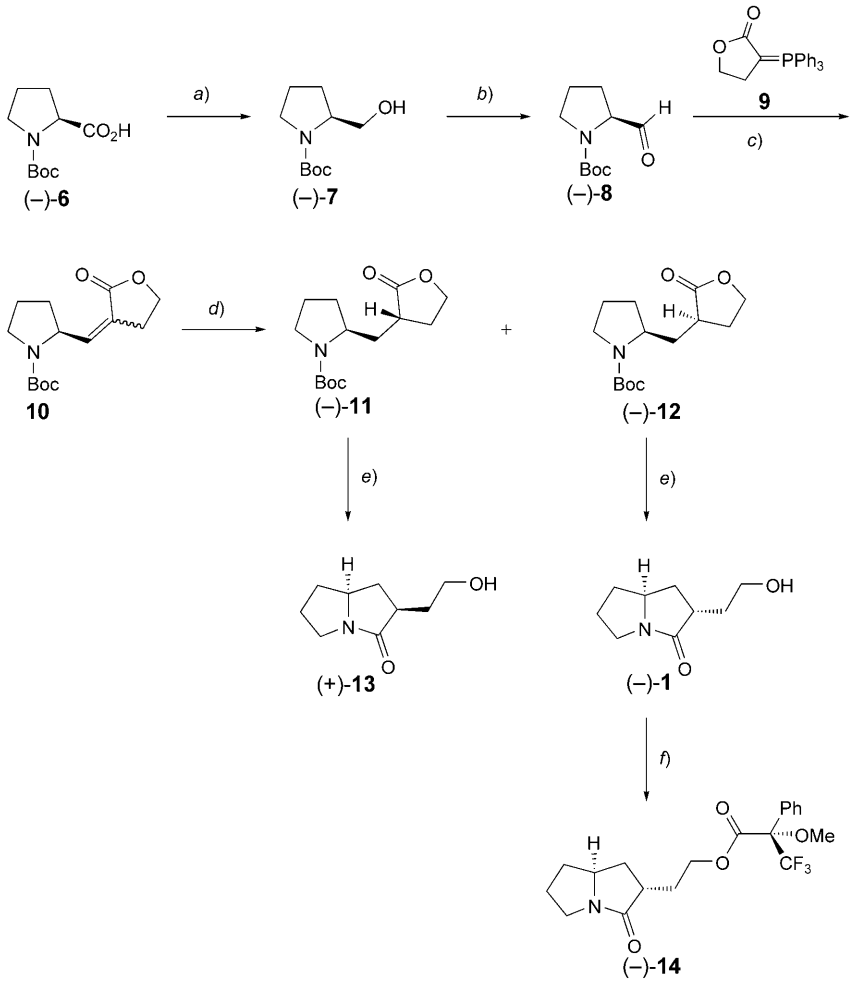
Scheme 2. *First Attempted Synthesis of* (−)-**1**



a) THF, 50°, 21 h; 94%. *b*) 1. Pd/C, H_2, AcOEt, 20°, 6 h; 88%; 2. TFA, CH_2Cl_2, 0°, 1 h; 3. DMAP (cat.), py, Δ, 16 h; 70%. *c*) 1. LDA, THF, −78°, 15 min.; 2. **3**, −78° → 20°, 14 h; 27%. TFA = CF_3COOH, DMAP = 4-(dimethylamino)pyridine, py = pyridine, LDA = lithium diisopropylamide, TBDMS = (*t*-Bu)Me_2Si.

In a next step, we decided to introduce the new substituent during a *Wittig* reaction (*Scheme 3*). The new synthesis started from commercially available Boc-proline (−)-**6** that was reduced according to the procedure of *Pettit et al.* [14]. The resulting Boc-prolinol (−)-**7** was oxidized to the corresponding aldehyde (−)-**8** under mild conditions that are reported to proceed without detectable racemization [14]. The optically active aldehyde (−)-**8** was subjected *in situ* to a *Wittig* reaction with ylide **9**, and the α,β-unsaturated lactone **10** was isolated as an inseparable mixture of (*E*)- and (*Z*)-diastereoisomers. Catalytic hydrogenation with Pd/C afforded the two lactones (−)-**11** and (−)-**12** that were separated by column chromatography. At this point, no structural assignment was possible, and the synthesis was continued with both isomers independently. Acidic removal of the Boc group, followed by cyclization in pyridine with a catalytic amount of DMAP, yielded the desired pyrrolizidinones (+)-**13** and (−)-**1**. NOE Measurements were performed on the two compounds (*Fig. 1*). Upon

Scheme 3. *Synthesis of 2-Substituted Hexahydro-1*H*-pyrrolizinones* (+)-**13** *and* (−)-**1**



a) $BH_3 \cdot THF$, THF, 0° → 20°, 3.5 h; 93%. *b*) $SO_3 \cdot$ py, Et_3N, Me_2SO, 5°, 2.5 h. *c*) **9**, THF, 50°, 22 h; 84% (from (−)-**7**). *d*) H_2, Pd/C, AcOEt, 20°, 14 h; 33% of (−)-**11**, 66% of (−)-**12**. *e*) 1. TFA, CH_2Cl_2, 0°, 1 h; 2. DMAP (cat.), py, Δ, 15 h; 75–77%. *f*) (−)-(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, py, 0°, 2 h; 79%.

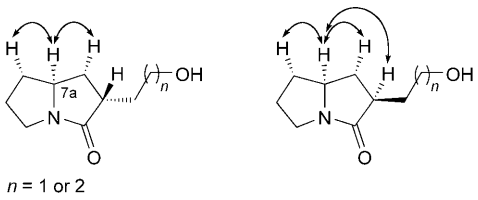


Fig. 1. *NOE Interactions upon irradiation of the* ^{1}*H-NMR resonance of the H-atom at C(7a)*

irradiation of the H-atom at the bridgehead C-atom, C(7a)–H, long-distance interactions were observed, as expected, with the backbone H-atom at C(2) of the *trans*-product (+)-**13**, but not of the *cis*-product (−)-**1**. Thus, in four easy steps, pyrrolizidinone (−)-**1** was obtained in 39% yield, whereas the other diastereoisomer (+)-**13** was isolated in 20% yield.

To demonstrate the optical purity of the newly synthesized compounds, (±)-**1** was prepared. Addition of traces of pyridine during the *Wittig* reaction between aldehyde (−)-**8** and ylide **9** resulted in full racemization of the produced α,β-unsaturated lactone **10**, which was subsequently converted into pyrrolizidinone (±)-**1**. The racemic alcohol (±)-**1** and optically active (−)-**1** were transformed into the corresponding *Mosher* esters **14** [15]. After complete conversion, but before chromatographic purification, the *Mosher* esters were analyzed by ^{19}F-NMR measurements (*Fig. 2*). For the derivative of (±)-**1**, two signals representing the two diastereoisomeric products were found in a 1:1 ratio, as expected. For the derivative of (−)-**1**, only one signal corresponding to pure diastereoisomer (−)-**14** was detected, thereby demonstrating complete retention of configuration at the stereogenic center introduced with Boc-proline (−)-**6**.

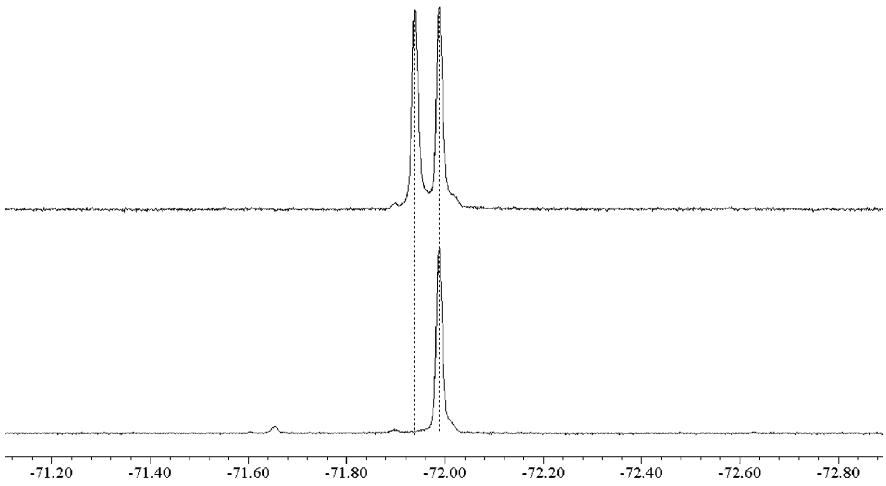
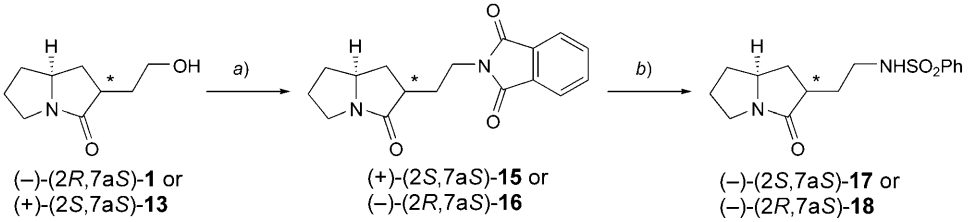


Fig. 2. *^{19}F-NMR Spectra* ($CDCl_3$, 282 MHz) *of the* Mosher *esters derived from* (±)-**1** (top) *and* (−)-**1** (bottom). The spectra of the crude products were recorded.

To install an amine function at the end of the alkyl chain, alcohols (−)-**1** and (+)-**13** were converted *via* a *Mitsunobu* reaction into the corresponding phthalimides (+)-**15** and (−)-**16**, respectively (*Scheme 4*). Subsequent treatment with $MeNH_2$ afforded the corresponding amines. Upon storage, the amines underwent facile epimerization so they were converted directly into the corresponding sulfonamides (−)-**17** and (−)-**18**, respectively.

By slow evaporation of concentrated hexane solutions, suitable single crystals of (+)-**15** and (−)-**16** were obtained to carry out X-ray crystallographic analysis (*Fig. 3*), confirming the previous structural assignments discussed above. The non-planarity of the amide C–N bond in these molecules is appreciable. This is evident from the angular

Scheme 4. *Synthesis of Sulfonamides* (−)-**17** *and* (−)-**18**



a) Phthalimide, PPh_3, DIAD, THF, 20°, 16 h; 76–88%. *b*) 1. 33% $MeNH_2$ in EtOH, 20°, 16 h; 2. $PhSO_2Cl$, Et_3N, CH_2Cl_2, 0°, 2 h; 60–68%. DIAD = Diisopropyl azodicarboxylate. The inversion of absolute configuration at C(2) results from the introduction of a different functional group at the end of the alkyl chain and a subsequent change in priority according to the *CIP* rules.

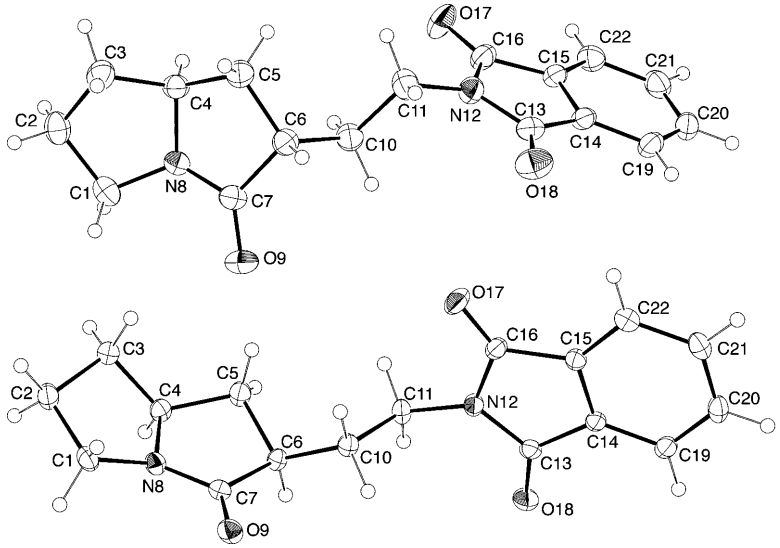


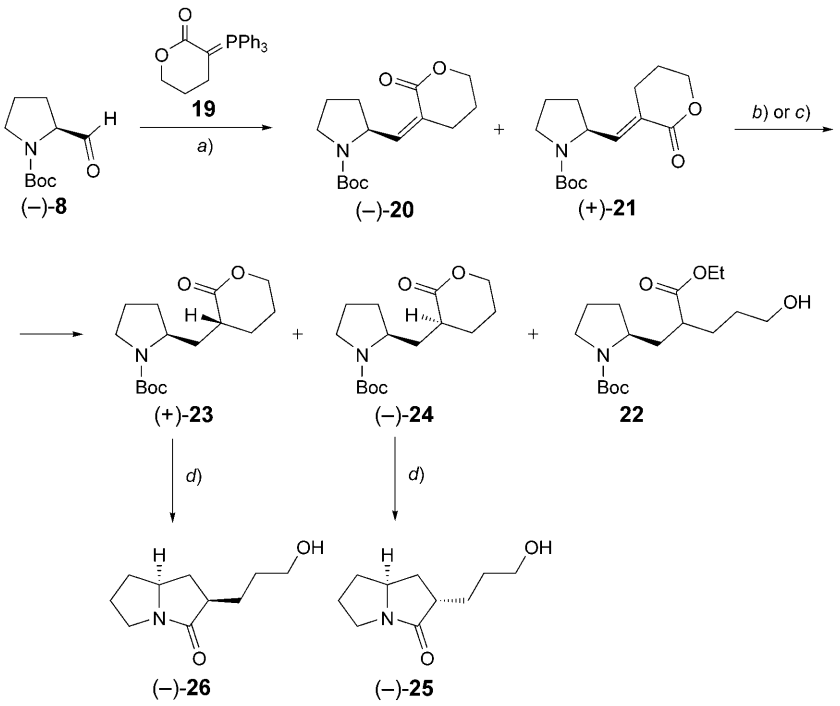
Fig. 3. *X-Ray crystal structures of* (+)-**15** (top) *and* (−)-**16** (bottom). Arbitrary numbering. Atomic displacement parameters obtained at 223 K are drawn at the 30% probability level.

strain (*S*), based on the sum of the three bond angles at N(8) which amounts to 355.27°, and 355.59° for (+)-**15** and (−)-**16**, respectively (note that when *S* is expressed in this way, it does not depend on the bond lengths, as does, for example, the distance of the atom from the plane of its three bonded neighbors). The external angles at N(8) (C(1)−N(8)−C(7)) are 127.73° for (+)-**15**, and 127.51° for (−)-**16**. These values are in the range of those previously reported for pyrrolizidinones. Indeed, for the 18 crystal structures deposited with the *Cambridge Structural Database* (CSD) [16], the external angle is found in a range from 124.27° to 134.08°, and the angular sum in a range from 346.64 to 359.73°. Each five-membered ring exhibits an envelope conformation. The degree of twisting about the N(8)−C(7) bond can be estimated by the two torsional angles ω_1 (C(1)−N(8)−C(7)−C(6)) and ω_2 (C(4)−N(8))−C(7)−O(9)) and the twist angle $\tau = 1/2(\omega_1 + \omega_2)$ (with the side condition $|\omega_1 + \omega_2| < \pi$, which states that a case

with $\omega_1 = -170°$, $\omega_2 = 175°$ should be treated as if $\omega_1 = -170°$, $\omega_2 = -185°$) [17][18]. In the case of a fully planar amide, all three angles would adopt values of $\pm 180°$. The values for (+)-**15**, however, are $\omega_1 = -160.51°$, $\omega_2 = 174.46°$, and $\tau = -173.03°$, and those for (−)-**16** $\omega_1 = 159.84°$, $\omega_2 = 173.15°$, and $\tau = -173.35°$. These values are in good agreement with those reported by *Winkler* for (2*RS*,7a*RS*)-*2*-[4-(bromophenyl)methyl]-pyrrolizidin-3-one ($\omega_1 = -161.5°$, $\omega_2 = 168.0°$, $\tau = -176.8°$) [19].

For the development of Pin1 inhibitors, it was also of interest to elongate the alcohol side chain. For this purpose, ylide **19** was prepared according to a known literature procedure [20]. The first attempt to perform the *Wittig* reaction with Boc-prolinal (−)-**8** under the conditions described above failed, and no trace of the desired product was detected. Changing the solvent from THF to PhMe permitted the use of higher temperatures, which, in turn, allowed the isolation of the α,β-unsaturated lactones (−)-**20** and (+)-**21** in 57% overall yield (*Scheme 5*). Unlike in the γ-lactone series (see above), the (*E*)- and (*Z*)-products were easily separated by column chromatography. According to the hydrogenation protocol (Pd/C, AcOEt) used for compound **10**, the reaction was not complete even after several days. By changing the solvent to EtOH, the reaction took place quickly, but substantial lactone opening was observed, and ethyl ester **22** was isolated as a by-product. The use of PtO_2 appeared to

Scheme 5. *Synthesis of Hexahydro-1*H*-pyrrolizinones* (−)-**25** *and* (−)-**26**.



a) **19**, PhMe, Δ, 48 h; 18% of (−)-**20**, 39% of (+)-**21**. *b*) Pd/C, H_2, EtOH, 20°, 10% of (+)-**23**, 25% of (−)-**24**, 36% of **22**. *c*) PtO_2, H_2, AcOEt, 20°, 60 h; 23% of (+)-**23**, 44% of (−)-**24**. *d*) 1. TFA, CH_2Cl_2, 0°, 1 h; 2. DMAP (cat.), py, Δ, 15 h; 80–92%.

be the best solution; with this catalyst, the reaction went smoothly, and no ring opening was observed. The hydrogenation appeared to be non-selective and, starting from either the (*E*)- or (*Z*)-adduct, gave a mixture of the two diastereoisomers (+)-**23** and (−)-**24** that were separated by column chromatography. Boc Deprotection and subsequent cyclization were achieved by the same protocol as described above. The bicyclic compounds (−)-**25** and (−)-**26** were easily obtained, in 23 and 11% overall yield, respectively. The structural assignments were confirmed by NOE measurements (see *Fig. 1*).

3. Conclusions. – Starting from commercially available Boc-proline ((−)-**6**), we have achieved a facile entry into diastereoisomerically and optically pure 2-substituted pyrrolizidinones in four steps. The complete optical purity of target molecule (−)-**1**, with a 2-hydroxyethyl side chain, was conveniently confirmed by transformation into the corresponding *Mosher* ester, followed by ^{19}F-NMR spectroscopic analysis. X-Ray crystallographic analysis of the phthalimide derivatives (+)-**15** and (−)-**16** revealed nonplanar amide moieties, in agreement with previous structural investigations within this class of compounds. The synthetic route introduced in this study is also amenable to the synthesis of 2,5-disubstituted pyrrolizidinones starting from the appropriately substituted proline derivatives. These developments on the way to inhibitors of Pin1, an enzyme in the cell cycle that attracts interest as an antitumor target, will be reported in due course.

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Experimental Part

General. Solvents and reagents were reagent-grade, purchased from commercial suppliers, and used without further purification unless otherwise stated. The following compounds were prepared according to literature procedures: pyrrolizidinone (−)-**2** [12], bromide **3** [21], Boc-prolinol (−)-**7** and Boc-prolinal (−)-**8** [14], ylide **9** [22], and **19** [20]. THF was freshly distilled from sodium benzophenone ketyl, CH_2Cl_2 from CaH_2. Evaporation *in vacuo* was conducted at H_2O aspirator pressure. All products were dried under high vacuum (10^{-2} Torr) before anal. characterization. Column chromatography (CC): SiO_2 *60* (40–63 μm) from *Fluka*, 0–0.3 bar pressure. TLC: SiO_2 *60* F_{245}, *Merck*, visualization by UV light at 245 nm or staining with a soln. of $KMnO_4$ (3 g) and K_2CO_3 (20 g) in 5% aq. NaOH soln. (5 ml) and H_2O (300 ml). M.p.: *Büchi B540* melting-point apparatus; uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter, 1-dm cell, $\lambda = 589$ nm (Na D-line). IR Spectra [cm^{-1}]: *Perkin-Elmer 1600-FTIR* spectrometer. NMR spectra (^{1}H, ^{13}C, ^{19}F, NOE): *Varian Gemini-300*, *Varian Gemini-400*, and *Bruker AMX-500*; spectra were recorded at 20° unless otherwise stated with solvent peak as reference. High-resolution MALDI mass spectra (HR-MS): *IonSpec Ultima*, 2,5-dihydroxybenzoic acid (DHB) as matrix. Elemental analyses were performed by the *Mikrolabor* at the *Laboratorium für Organische Chemie*, *ETH-Zürich*.

General Procedure A (*GP A*) *for the Catalytic Hydrogenation of an α,β-Unsaturated Lactone.* To a soln. of the lactone (35.7 mmol) in AcOEt (500 ml), 10% Pd/C or PtO_2 (10% (*w*/*w*)) was added under Ar. The flask was evacuated and refilled with H_2 (3 ×). The black suspension was stirred at 20° for 21 h under an H_2 atmosphere (atmospheric pressure), and filtered over *Celite*. The filtrate was concentrated *in vacuo* to afford a residue that was purified by CC (SiO_2; hexane/THF 8:2).

General Procedure B (*GP B*) *for the Intramolecular Cyclization of a Lactone.* To an ice-cooled soln. of the lactone (4.8 mmol) in CH_2Cl_2 (20 ml), TFA (5 ml) was added. The mixture was stirred at 0° for 1 h, then concentrated *in vacuo*. The resulting residue was dissolved in pyridine (30 ml). After addition of a cat. amount of DMAP, the mixture was heated to reflux for 16 h. The solvent was removed *in vacuo*, and the resulting residue was purified by CC (SiO_2; CH_2Cl_2/MeOH 95:5).

General Procedure C (*GP C*) *for the Synthesis of a Phthalimide by* Mitsunobu *Reaction.* To a soln. of an alcohol (1.5 mmol), phthalimide (1.7 mmol), and PPh_3 (1.7 mmol) in THF (6 ml), DIAD (1.7 mmol) was added. The mixture was stirred at 20° for 16 h, then evaporated *in vacuo* to afford a residue that was purified by CC (SiO_2; cyclohexane/AcOEt/MeOH 2:1:0.1).

General Procedure D (*GP D*) *for the Conversion of a Phthalimide into a Sulfonamide.* A soln. of the phthalimide (1.3 mmol) in 33% $MeNH_2$ in EtOH (14 ml) was stirred at 20° for 16 h. The volatiles were removed *in vacuo*. The resulting residue was taken up in 10% aq. AcOH and washed with CH_2Cl_2/i-PrOH 3:1. The aq. layer was treated with 1M NaOH until a pH > 12 was reached and extracted with CH_2Cl_2/i-PrOH 3:1. The comb. org. phases were dried ($MgSO_4$) and evaporated *in vacuo*. The resulting amine was dissolved in CH_2Cl_2 (10 ml) and the soln. cooled to 0°. A sulfonyl chloride (1.3 mmol) and Et_3N (1.4 mmol) were added, and the mixture was stirred at 0° for 2 h. The soln. was diluted with CH_2Cl_2 (30 ml) and washed with H_2O and sat. aq. NaCl soln. The aq. layers were extracted with CH_2Cl_2/i-PrOH 3:1. The comb. org. phases were concentrated *in vacuo* to afford a residue that was purified by CC (SiO_2; AcOEt/MeOH 95:5).

*(−)-(2S,7aS)-2-(2-{[(*tert*-Butyl)(dimethyl)silyl]oxy}ethyl)-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizin-3-one* ((−)-**4**) *and (−)-(2*R*,7a*S*)-2-(2-{[(*tert*-Butyl)(dimethyl)silyl]oxy}ethyl)-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizin-3-one* ((−)-**5**). To an ice-cooled soln. of freshly distilled $HN(i\text{-}Pr)_2$ (0.12 ml, 0.83 mmol) in THF (2 ml), 1.6M BuLi in hexane (0.43 ml, 0.69 mmol) was dropwise added. The ice bath was removed, the mixture stirred at 20° for 15 min, then cooled to − 78°. A soln. of (−)-**2** (86 mg, 0.69 mmol) was slowly added. The mixture was stirred at − 78° for 1 h. The cooling bath was removed and the mixture was stirred for 10 min, then cooled again to − 78°. A soln. of **3** (196 mg, 0.82 mmol) in THF (2 ml) was slowly added. The mixture was stirred for 16 h, during which time the temp. rose from − 78° to 20°. Sat. aq. NH_4Cl soln. was added. The mixture was extracted with Et_2O and CH_2Cl_2. The comb. org. phases were dried ($MgSO_4$) and evaporated. The residue was purified by *CC* (SiO_2; CH_2Cl_2/MeOH 98:2), affording (−)-**4** (28 mg, 14%) and (−)-**5** (25 mg, 13%).

Data of (−)-**4**. White solid. M.p. 47–48°. $[\alpha]_D^{20} = -8.6$ ($c = 1.00$, $CHCl_3$). IR (neat): 2954*w*, 2927*m*, 2903*w*, 2879*m*, 2856*w*, 1669*s*, 1485*w*, 1470*w*, 1457*w*, 1448*w*, 1417*m*, 1386*w*, 1359*w*, 1328*m*, 1318*m*, 1304*w*, 1270*w*, 1250*m*, 1103*m*, 1078*m*, 1050*m*, 1023*w*, 1004*w*, 969*m*, 953*m*, 938*w*, 908*m*, 874*m*, 857*m*, 829*s*, 809*m*, 769*s*, 757*m*, 741*m*, 718*m*, 664*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.05 (*s*, 6 H); 0.89 (*s*, 9 H); 1.22–1.50 (*m*, 3 H); 1.93–2.23 (*m*, 4 H); 2.53 (*ddd*, $J = 12.1, 7.8, 6.2$, 1 H); 2.84–2.96 (*m*, 1 H); 3.03–3.10 (*m*, 1 H); 3.49–3.58 (*m*, 1 H); 3.64–3.84 (*m*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): − 5.1; 18.5; 26.2; 27.1; 32.6; 34.4; 36.4; 41.2; 44.1; 59.9; 61.6; 176.1. HR-MALDI-MS: 306.1858 ($[M + Na]^+$, $C_{15}H_{29}NO_2SiNa^+$; calc. 306.1860).

Data of (−)-**5**. Colorless oil. $[\alpha]_D^{20} = -4.7$ ($c = 1.00$, $CHCl_3$). IR (neat): 2953*w*, 2929*w*, 2857*w*, 1690*s*, 1472*w*, 1462*w*, 1408*m*, 1360*w*, 1331*w*, 1287*w*, 1253*m*, 1095*s*, 1006*w*, 939*w*, 913*w*, 832*s*, 774*s*, 726*w*, 663*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.05 (*s*, 6 H); 0.89 (*s*, 9 H); 1.19–1.33 (*m*, 1 H); 1.67–1.79 (*m*, 1 H); 1.91 (*ddd*, $J = 13.1, 9.2, 6.7$, 1 H); 1.94–2.16 (*m*, 5 H); 2.63–2.72 (*m*, 1 H); 3.01–3.09 (*m*, 1 H); 3.52–3.61 (*m*, 1 H); 3.70–3.77 (*m*, 2 H); 3.81–3.90 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): − 5.1; 18.4; 26.0; 26.9; 32.1; 32.2; 35.0; 41.3; 44.2; 60.5; 61.5; 177.6. HR-MALDI-MS: 284.2038 (MH^+, $C_{15}H_{30}NO_2Si^+$; calc. 284.2040). Anal. calc. for $C_{15}H_{29}NO_2Si$ (283.49): C 63.55, H 10.31, N 4.94; found C 63.56, H 10.31, 4.92.

tert-*Butyl (2*S*)-2-[(2,3,4,5-Tetrahydro-2-oxofuran-3-ylidene)methyl]pyrrolidine-1-carboxylate* (**10**). To a soln. of (−)-**8** (6.06 g, 30.4 mmol) in THF (150 ml), ylide **9** (21.10 g, 60.9 mmol) was added. The resulting suspension was stirred at 50° for 24 h. The solids were removed by filtration, and the filtrate was evaporated. CC (SiO_2; hexane/AcOEt 7:3) furnished **10** (6.82 g, 84%) as a 1:2 mixture of (*E*)- and (*Z*)-diastereoisomers. White solid. M.p. 91 → 121°. IR (neat): 2972*w*, 2910*w*, 1739*s*, 1678*s*, 1479*w*, 1436*w*, 1387*s*, 1364*s*, 1308*m*, 1249*m*, 1203*s*, 1167*s*, 1105*s*, 1026*s*. ^{1}H-NMR (300 MHz, 363 K, $C_2D_2Cl_4$): 1.37 (*s*, 2.7 H); 1.38 (*s*, 6.3 H); 1.53–1.94 (*m*, 3 H); 2.10 (*ddd*, $J = 15.3, 12.5, 7.8, 0.7$ H); 2.18–2.30 (*m*, 0.3 H); 2.74–2.87 (*m*, 1.4 H); 2.94–3.06 (*m*, 0.6 H); 3.29–3.49 (*m*, 2 H); 4.23–4.39 (*m*, 2.7 H); 5.30–5.37 (*m*, 0.3 H); 6.09 (*dt*, $J = 8.4, 2.3, 0.3$ H); 6.54 (*dt*, $J = 8.1, 2.8, 0.7$ H). ^{13}C-NMR (125 MHz, 363 K, $C_2D_2Cl_4$): 24.1; 24.9; 28.6; 28.8; 31.8; 32.9; 46.7; 46.8; 54.3; 56.5; 65.5 (2 ×); 79.2; 79.5; 79.6; 79.8; 122.7; 124.7; 140.9; 145.7; 154.2; 154.4; 169.3; 171.1. HR-MALDI-MS: 290.1357 ($[M + Na]^+$, $C_{14}H_{21}NO_4Na^+$; calc. 290.1368). Anal. calc. for $C_{14}H_{21}NO_4$ (267.32): C 62.90, H 7.92, N 5.24; found C 63.02, H 7.92, N 5.10.

*(−)-*tert*-Butyl (2*S*)-2-{[(3*S*)-2,3,4,5-Tetrahydro-2-oxofuran-3-yl]methyl}pyrrolidine-1-carboxylate* ((−)-**11**) *and (−)-*tert*-Butyl (2*S*)-2-{[(3*R*)-2,3,4,5-Tetrahydro-2-oxofuran-3-yl]methyl}pyrrolidine-1-carboxylate* ((−)-**12**). *GP A*, starting from **10** (9.50 g, 35.7 mmol), afforded, after purification, (−)-**11** (3.18 g, 33%) and (−)-**12** (6.36 g, 66%).

Data of (−)-**11**. White solid. M.p. 59–60°. $[\alpha]_D^{20} = -13.6$ ($c = 1.00$, $CHCl_3$). IR (neat): 2966*w*, 2903*w*, 2881*w*, 1754*s*, 1684*s*, 1478*w*, 1465*w*, 1397*s*, 1364*s*, 1309*w*, 1252*w*, 1212*m*, 1157*s*, 1100*s*, 1024*s*. ^{1}H-NMR (300 MHz, 363 K, $C_2D_2Cl_4$): 1.42 (*s*, 9 H); 1.62–2.19 (*m*, 7 H); 2.46–2.55 (*m*, 2 H); 3.24 (*ddd*, $J = 11.2, 7.0, 4.9$, 1 H); 3.41

(*ddd*, J = 11.2, 7.4, 7.4, 1 H); 3.92–4.00 (*m*, 1 H); 4.11 (*dt*, J = 8.1, 6.4, 1 H); 4.26 (*dt*, J = 8.9, 2.7, 1 H). ^{13}C-NMR (125 MHz, 363 K, $C_2D_2Cl_4$): 23.8; 28.9; 29.8; 31.5; 36.3; 37.3; 46.6; 55.6; 66.7; 79.5; 155.1; 179.3. HR-MALDI-MS: 292.1513 ([M + Na]$^+$, $C_{14}H_{23}NO_4Na^+$; calc. 292.1525). Anal. calc. for $C_{14}H_{23}NO_4$ (269.34): C 62.43, H 8.61, N 5.20; found C 62.36, H 8.47, N 5.16.

Data of (−)-**12**. White solid. M.p. 103–104°. $[\alpha]_D^{20}$ = − 39.7 (c = 1.00, $CHCl_3$). IR (neat): 2976*w*, 2869*w*, 1746*s*, 1698*s*, 1684*s*, 1455*m*, 1392*s*, 1380*s*, 1368*s*, 1348*m*, 1252*m*, 1153*s*, 1128*m*, 1098*s*, 1019*s*. ^{1}H-NMR (300 MHz, 363 K, $C_2D_2Cl_4$): 1.42 (*s*, 9 H); 1.62–2.03 (*m*, 7 H); 2.32–2.49 (*m*, 2 H); 3.23–3.41 (*m*, 2 H); 3.78–3.86 (*m*, 1 H); 4.12 (*dt*, J = 8.9, 6.6, 1 H); 4.28 (*dt*, J = 8.9, 3.1, 1 H). ^{13}C-NMR (125 MHz, 363 K, $C_2D_2Cl_4$): 23.4; 28.7; 29.0; 30.4; 35.9; 37.4; 46.3; 56.0; 66.4; 79.2; 154.4; 178.9. HR-MALDI-MS: 292.1514 ([M + Na]$^+$, $C_{14}H_{23}NO_4Na^+$; calc. 292.1525). Anal. calc. for $C_{14}H_{23}NO_4$ (269.34): C 62.43, H 8.61, N 5.20; found C 62.54, H 8.52, N 5.16.

*(−)-(2*R*,7a*S*)-2,3,5,6,7,7a-Hexahydro-2-(hydroxyethyl)-1*H*-pyrrolizin-3-one* ((−)-**1**). *GP B*, starting from (−)-**12** (1.30 g, 4.8 mmol), afforded (−)-**1** (616 mg, 75%). Yellow oil. $[\alpha]_D^{20}$ = − 18.8 (c = 1.00, $CHCl_3$). IR (neat): 3382*w*, 2939*w*, 2877*w*, 1660*s*, 1418*m*, 1330*m*, 1288*m*, 1208*w*, 1046*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.23–1.35 (*m*, 1 H); 1.77–1.86 (*m*, 1 H); 1.90–2.21 (*m*, 6 H); 2.71–2.80 (*m*, 1 H); 3.04–3.12 (*m*, 1 H); 3.47 (br. *s*, 1 H); 3.53–3.62 (*m*, 1 H); 3.78–3.87 (*m*, 2 H); 3.88–3.94 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.8; 32.0; 32.8; 35.4; 41.3; 45.6; 60.8; 61.8; 178.0. HR-MALDI-MS: 192.0995 ([M + Na]$^+$, $C_9H_{15}NO_2Na^+$; calc. 192.1000). Anal. calc. for $C_9H_{15}NO_2$ (169.22): C 63.88, H 8.93, N 8.28; found C 63.87, H 8.88, N 8.35.

*(+)-(2*S*,7a*S*)-2,3,5,6,7,7a-Hexahydro-2-(hydroxyethyl)-1*H*-pyrrolizin-3-one* ((+)-**13**). *GP B*, starting from (−)-**11** (538 mg, 2.0 mmol), afforded (+)-**13** (260 mg, 77%). Yellow oil. $[\alpha]_D^{20}$ = + 25.4 (c = 1.01, $CHCl_3$). IR (neat): 3388*w*, 2927*w*, 2876*w*, 1659*s*, 1455*m*, 1423*m*, 1330*m*, 1288*m*, 1183*w*, 1144*w*, 1049*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.31–1.40 (*m*, 1 H); 1.45 (*dt*, J = 12.2, 8.8, 1 H); 1.66–1.71 (*m*, 1 H); 1.83 (br. *s*, 1 H); 1.89–1.96 (*m*, 1 H); 2.00–2.11 (*m*, 2 H); 2.12–2.19 (*m*, 1 H); 2.49 (*ddd*, J = 12.2, 7.7, 6.1, 1 H); 2.95–3.02 (*m*, 1 H); 3.07–3.12 (*m*, 1 H); 3.50–3.56 (*m*, 1 H); 3.67–3.72 (*m*, 1 H); 3.76–3.81 (*m*, 1 H); 3.83–3.89 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 27.0; 32.3; 34.4; 36.5; 41.1; 47.9; 60.5; 62.1; 176.1. HR-MALDI-MS: 192.0997 ([M + Na]$^+$, $C_9H_{15}NO_2Na^+$; calc. 192.1000). Anal. calc. for $C_9H_{15}NO_2$ (169.22): C 63.88, H 8.93, N 8.28; found C 63.89, H 8.81, N 8.33.

*(−)-2-[(2*R*,7a*S*)-2,3,5,6,7,7a-Hexahydro-3-oxo-1*H*-pyrrolizin-2-yl]ethyl (2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate* ((−)-**14**). To an ice-cooled soln. of (−)-**1** (61 mg, 0.36 mmol) in pyridine (2 ml), (−)-(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (100 mg, 0.40 mmol) was added. The mixture was stirred at 0° for 2 h, then diluted with Et_2O. The mixture was washed with H_2O, 1N HCl, H_2O, 5% aq. Na_2CO_3 soln., sat. aq. NaCl soln., dried (Na_2SO_4), and evaporated to afford (−)-**14** (110 mg, 79%). Pale yellow oil. $[\alpha]_D^{20}$ = − 49.5 (c = 1.00, $CHCl_3$). IR (neat): 2951*w*, 2879*w*, 1746*m*, 1683*s*, 1452*w*, 1418*w*, 1331*w*, 1266*m*, 1258*m*, 1163*s*, 1120*m*, 1081*w*, 1020*m*, 998*m*, 964*w*, 915*w*, 882*w*, 820*w*, 766*w*, 718*m*, 698*m*, 646*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.15–1.31 (*m*, 1 H); 1.83–2.23 (*m*, 7 H); 2.55–2.64 (*m*, 1 H); 2.99–3.08 (*m*, 1 H); 3.51–3.60 (*m*, 4 H); 3.75–3.85 (*m*, 1 H); 4.39–4.52 (*m*, 2 H); 7.38–7.43 (*m*, 3 H); 7.50–7.53 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.8; 30.7; 31.6; 32.0; 41.4; 43.7; 55.5; 60.4; 64.8; 84.6 (*q*, ^2J(C,F) = 27.5); 123.2 (*q*, ^1J(C,F) = 287.7); 127.2; 128.4; 129.5; 132.1; 166.3; 176.2. HR-MALDI-MS: 408.1386 ([M + Na]$^+$, $C_{19}H_{22}NO_4F_3Na^+$; calc. 408.1393). Anal. calc. for $C_{19}H_{22}NO_4F_3$ (385.38): C 59.22, H 5.75, N 3.63; found C 59.10, H 5.74, N 3.85.

*(+)-2-{2-[(2*S*,7a*S*)-2,3,5,6,7,7a-Hexahydro-3-oxo-1*H*-pyrrolizin-2-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione* ((+)-**15**). *GP C*, starting from (−)-**1** (245 mg, 1.5 mmol), afforded (+)-**15** (395 mg, 76%). White solid. M.p. 106–109°. $[\alpha]_D^{20}$ = + 20.2 (c = 1.00, $CHCl_3$). IR (neat): 2944*w*, 2889*w*, 2863*w*, 1770*m*, 1708*s*, 1681*s*, 1454*m*, 1434*m*, 1399*s*, 1371*s*, 1332*m*, 1189*m*, 1069*m*, 1012*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.22–1.34 (*m*, 1 H); 1.79–2.24 (*m*, 7 H); 2.56–2.65 (*m*, 1 H); 3.04 (*ddd*, J = 11.7, 8.6, 3.3, 1 H); 3.57 (*ddd*, J = 11.7, 7.8, 7.8, 1 H); 3.77–3.92 (*m*, 3 H); 7.70–7.74 (*m*, 2 H); 7.81–7.85 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.8; 30.9; 31.6; 32.1; 36.3; 41.4; 44.7; 60.4; 123.2; 132.0; 133.9; 168.1; 176.4. HR-MALDI-MS: 299.1390 (MH^+, $C_{17}H_{19}N_2O_3^+$; calc. 299.1396). Anal. calc. for $C_{17}H_{18}N_2O_3$ (298.34): C 68.44, H 6.08, N 9.39; found C 68.46, H 6.22, N 9.27. X-Ray crystal structure: see *Fig. 3*.

*(−)-2-{2-[(2*R*,7a*S*)-2,3,5,6,7,7a-Hexahydro-3-oxo-1*H*-pyrrolizin-2-yl]ethyl}-1*H*-isoindole-1,3(2*H*)-dione* ((−)-**16**). *GP C*, starting from alcohol (+)-**13** (204 mg, 1.2 mmol), afforded (−)-**16** (318 mg, 88%). White solid. M.p. 159–161°. $[\alpha]_D^{20}$ = − 13.7 (c = 1.00, $CHCl_3$). IR (neat): 2971*w*, 2951*w*, 2866*w*, 1769*w*, 1707*s*, 1675*s*, 1456*w*, 1437*m*, 1403*s*, 1374*s*, 1333*m*, 1189*m*, 1050*m*, 1011*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.24–1.36 (*m*, 1 H); 1.43 (*dt*, J = 12.1, 8.7, 1 H); 1.59–1.72 (*m*, 1 H); 1.93–2.13 (*m*, 3 H); 2.28–2.39 (*m*, 1 H); 2.63 (*ddd*, J = 12.1, 7.7, 6.1, 1 H); 2.75–2.86 (*m*, 1 H); 3.01–3.08 (*m*, 1 H); 3.49 (*ddd*, J = 11.5, 7.8, 7.8, 1 H); 3.75–3.84 (*m*, 3 H); 7.70–7.74 (*m*, 2 H); 7.81–7.87 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 27.0; 30.4; 32.4; 35.7; 36.2; 41.1; 44.6; 59.6; 123.1;

132.0; 133.8; 168.2; 174.4. HR-MALDI-MS: 299.1388 (MH^+, $C_{17}H_{19}N_2O_3^+$; calc. 299.1396). Anal. calc. for $C_{17}H_{18}N_2O_3$ (298.34): C 68.44, H 6.08, N 9.39; found C 68.41, H 6.01, N 9.31. X-Ray crystal structure: see *Fig. 3*.

*(−)-*N*-{2-[(2*S*,7a*S*)-2,3,5,6,7,7a-Hexahydro-3-oxo-1*H*-pyrrolizin-2-yl]ethyl}benzenesulfonamide* ((−)-**17**). *GP D*, starting from (+)-**15** (400 mg, 1.3 mmol) and $PhSO_2Cl$ (0.17 ml, 1.3 mmol), afforded (−)-**17** (244 mg, 60%). Colorless oil. $[\alpha]_D^{20} = -41.9$ ($c = 1.00$, $CHCl_3$). IR (neat): 3151*w*, 2943*w*, 2877*w*, 1659*s*, 1446*m*, 1325*s*, 1155*s*, 1093*m*, 690*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.21–1.32 (*m*, 1 H); 1.79–1.86 (*m*, 1 H); 1.88–2.17 (*m*, 6 H); 2.62 (*ddd*, $J = 16.1, 8.0, 4.0$, 1 H); 3.01–2.24 (*m*, 3 H); 3.54 (*ddd*, $J = 11.8, 7.9, 7.9$, 1 H); 3.78–3.88 (*m*, 1 H); 5.75–5.79 (*m*, 1 H); 7.47–7.59 (*m*, 3 H); 7.86–7.90 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.8; 32.0; 32.2; 32.8; 41.3; 42.0; 45.0; 60.6; 126.9; 128.9; 132.3; 140.2; 176.9. HR-MALDI-MS: 331.1089 ($[M + Na]^+$, $C_{15}H_{20}N_2O_3SNa^+$; calc. 331.1092). Anal. calc. for $C_{15}H_{20}N_2O_3S$ (308.40): C 58.42, H 6.54, N 9.08; found C 58.49, H 6.73, N 9.17.

*(−)-*N*-{2-[(2*R*,7a*S*)-2,3,5,6,7,7a-Hexahydro-3-oxohexahydro-1*H*-pyrrolizin-2-yl]ethyl}benzenesulfonamide* ((−)-**18**). *GP D*, starting from (−)-**16** (200 mg, 0.7 mmol) and $PhSO_2Cl$ (0.08 ml, 0.7 mmol), afforded (−)-**18** (139 mg, 68%). White solid. M.p. 141–142°. $[\alpha]_D^{20} = -106.0$ ($c = 0.99$, $CHCl_3$). IR (neat): 3326*w*, 2956*w*, 2927*w*, 2869*w*, 1694*m*, 1641*s*, 1453*m*, 1320*s*, 1148*s*, 1098*s*, 753*s*, 688*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.43–1.64 (*m*, 3 H); 1.74–2.05 (*m*, 4 H); 2.39–2.55 (*m*, 2 H); 3.16–3.25 (*m*, 1 H); 3.31–3.44 (*m*, 3 H); 3.82–3.90 (*m*, 1 H); 5.55 (br. *s*, 1 H); 7.49–7.62 (*m*, 3 H); 7.82–7.86 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.1; 28.3; 30.7; 38.3; 38.8; 40.4; 48.6; 59.4; 127.4; 129.0; 132.5; 137.8; 179.7. HR-MALDI-MS: 331.1085 ($[M + Na]^+$, $C_{15}H_{20}N_2O_3SNa^+$; calc. 331.1092). Anal. calc. for $C_{15}H_{20}N_2O_3S$ (308.40): C 58.42, H 6.54, N 9.08; found C 58.44, H 6.83, N 8.83.

*(−)-*tert*-Butyl (2*S*)-2-[(*Z*)-(3,4,5,6-Tetrahydro-2-oxo-2*H*-pyran-3-ylidene)methyl]pyrrolidine-1-carboxylate* ((−)-**20**) *and (+)-*tert*-Butyl (2*S*)-2-[(*E*)-(3,4,5,6-Tetrahydro-2-oxo-2*H*-pyran-3-ylidene)methyl]pyrrolidine-1-carboxylate* ((+)-**21**). To a soln. of (−)-**8** (1.70 g, 8.45 mmol) in PhMe (40 ml), **19** (6.09 g, 16.90 mmol) was added. The resulting mixture was heated to reflux for 48 h, then cooled to 20° and filtered. The filtrate was evaporated *in vacuo*. CC (SiO_2; hexane/AcOEt 7:3 → 1:1) afforded (−)-**20** (428 mg, 18%) and (+)-**21** (928 mg, 39%).

Data of (−)-**20**: White solid. M.p. 99–101°. $[\alpha]_D^{20} = -51.9$ ($c = 1.00$, $CHCl_3$). IR (neat): 2977*w*, 2881*w*, 1708*s*, 1680*s*, 1645*w*, 1475*w*, 1443*w*, 1402*s*, 1365*m*, 1347*w*, 1278*w*, 1234*m*, 1164*s*, 1121*s*, 1076*m*, 1007*w*, 981*w*, 971*w*, 918*m*, 899*m*, 886*m*, 860*w*, 764*m*, 655*w*. ^{1}H-NMR (300 MHz, 363 K, $C_2D_2Cl_4$): 1.37 (*s*, 9 H); 1.55–1.66 (*m*, 1 H); 1.73–1.91 (*m*, 4 H); 2.23–2.35 (*m*, 1 H); 2.45–2.56 (*m*, 2 H); 3.33 (*dt*, $J = 10.9, 6.9$, 1 H); 3.43 (*dt*, $J = 10.9, 6.9$, 1 H); 4.14–4.27 (*m*, 2 H); 5.00–5.07 (*m*, 1 H); 5.90–5.94 (*m*, 1 H). ^{13}C-NMR (75 MHz, 363 K, $C_2D_2Cl_4$): 23.7; 24.5; 28.9; 29.5; 33.1; 47.1; 56.7; 68.8; 79.2; 123.9; 149.9; 154.5; 165.0. HR-MALDI-MS: 304.1519 ($[M + Na]^+$, $C_{15}H_{23}NO_4Na^+$; calc. 304.1519). Anal. calc. for $C_{15}H_{23}NO_4$ (281.35): C 64.04, H 8.24, N 4.98; found C 64.28, H 8.14, N 4.90.

Data of (+)-**21**: White solid. M.p. 123–126°. $[\alpha]_D^{20} = +20.0$ ($c = 1.00$, $CHCl_3$). IR (neat): 2971*w*, 2918*w*, 1691*s*, 1638*m*, 1481*w*, 1436*w*, 1398*s*, 1364*m*, 1348*w*, 1309*m*, 1274*w*, 1247*s*, 1166*s*, 1146*s*, 1118*m*, 1098*s*, 1076*m*, 1044*w*, 1014*w*, 977*w*, 926*m*, 886*w*, 869*w*, 771*m*, 739*m*, 645*w*. ^{1}H-NMR (300 MHz, 363 K, $C_2D_2Cl_4$): 1.38 (*s*, 9 H); 1.58–1.68 (*m*, 1 H); 1.74–1.97 (*m*, 4 H); 2.03–2.15 (*m*, 1 H); 2.36–2.47 (*m*, 1 H); 2.70–2.81 (*m*, 1 H); 3.32–3.47 (*m*, 2 H); 4.22–4.26 (*m*, 2 H); 4.37–4.44 (*m*, 1 H); 6.79 (*dt*, $J = 8.7, 2.3$, 1 H). ^{13}C-NMR (75 MHz, 363 K, $C_2D_2Cl_4$): 23.0; 23.8; 24.4; 28.8; 32.0; 46.8; 54.9; 68.7; 79.6; 125.0; 146.4; 154.1; 166.0. HR-MALDI-MS: 304.1519 ($[M + Na]^+$, $C_{15}H_{23}NO_4Na^+$; calc. 304.1519). Anal. calc. for $C_{15}H_{23}NO_4$ (281.35): C 64.04, H 8.24, N 4.98; found C 64.27, H 8.14, N 5.01.

*(+)-*tert*-Butyl (2*S*)-2-{[(3*R*)-3,4,5,6-Tetrahydro-2-oxo-2*H*-pyran-3-yl]methyl}pyrrolidine-1-carboxylate* ((+)-**23**) *and (−)-*tert*-Butyl (2*S*)-2-{[(3*S*)-3,4,5,6-Tetrahydro-2-oxo-2*H*-pyran-3-yl]methyl}pyrrolidine-1-carboxylate* ((−)-**24**). *GP A*, starting from (−)-**20** (670 mg, 2.38 mmol) or (+)-**21** (670 mg, 2.38 mmol), afforded, after purification, (+)-**23** (182 mg, 27%) and (−)-**24** (358 mg, 53%).

Data of (+)-**23**: White solid. M.p. 94–96°. $[\alpha]_D^{20} = +20.3$ ($c = 1.00$, $CHCl_3$). IR (neat): 2968*w*, 2918*w*, 2876*w*, 1722*m*, 1694*s*, 1480*w*, 1446*w*, 1379*s*, 1694*s*, 1480*w*, 1446*w*, 1379*s*, 1365*s*, 1345*w*, 1328*w*, 1311*m*, 1283*m*, 1258*m*, 1248*m*, 1220*w*, 1158*s*, 1113*m*, 1099*s*, 1076*s*, 1033*w*, 985*w*, 975*w*, 960*m*, 910*w*, 897*w*, 881*w*, 861*w*, 847*w*, 770*m*, 730*w*, 671*m*, 647*w*. ^{1}H-NMR (300 MHz, 363 K, $C_2D_2Cl_4$): 1.31–1.62 (*m*, 3 H); 1.42 (*s*, 9 H); 1.70–1.99 (*m*, 5 H); 2.24 (*ddd*, $J = 13.9, 7.2, 5.3$, 2 H); 2.47–2.57 (*m*, 1 H); 3.23 (*ddd*, $J = 10.9, 7.5, 5.0$, 1 H); 3.34–3.43 (*m*, 1 H); 3.93–4.01 (*m*, 1 H); 4.22 (*t*, $J = 5.9$, 2 H). ^{13}C-NMR (75 MHz, 363 K, $C_2D_2Cl_4$): 22.4; 23.7; 25.7; 28.9; 31.6; 37.1; 37.7; 46.4; 55.2; 68.3; 79.2; 154.9; 174.2. HR-MALDI-MS: 306.1676 ($[M + Na]^+$, $C_{15}H_{25}NO_4Na^+$; calc. 306.1676). Anal. calc. for $C_{15}H_{25}NO_4$ (283.37): C 63.58, H 8.89, N 4.94; found C 63.73, H 8.90, N 4.90.

Data of (−)-**24**: White solid. Mp. 90–91°. $[\alpha]_D^{20} = -54.9$ ($c = 1.00$, $CHCl_3$). IR (neat): 2961*w*, 2870*w*, 1738*m*, 1728*m*, 1664*s*, 1477*w*, 1453*w*, 1392*s*, 1363*m*, 1314*w*, 1256*m*, 1168*s*, 1105*s*, 1069*m*, 1061*m*, 993*w*, 956*w*, 943*w*, 915*w*, 871*w*, 859*w*, 771*m*, 730*w*, 674*w*, 644*w*. ^{1}H-NMR (300 MHz, 363 K, $C_2D_2Cl_4$): 1.41 (*s*, 9 H); 1.54–1.99 (*m*,

9 H); 1.99–2.11 (*m*, 1 H); 2.41–2.51 (*m*, 1 H); 3.21–3.40 (*m*, 2 H); 3.86–3.93 (*m*, 1 H); 4.23 (*dd*, $J = 6.5, 5.0$, 2 H). ^{13}C-NMR (75 MHz, 363 K, $C_2D_2Cl_4$): 22.3; 23.6; 25.4; 28.9; 30.9; 36.9; 37.8; 46.4; 55.7; 68.1; 79.2; 154.6; 174.2. HR-MALDI-MS: 306.1675 ($[M + Na]^+$, $C_{15}H_{25}NO_4Na^+$; calc. 306.1676). Anal. calc. for $C_{15}H_{25}NO_4$ (283.37): C 63.58, H 8.89, N 4.94; found C 63.58, H 8.80, N 4.96.

*(−)-(2*S*,7a*S*)-2,3,5,6,7,7a-Hexahydro-2-(3-hydroxypropyl)-1*H*-pyrrolizin-3-one* ((−)-**25**). *GP B*, starting from (−)-**24** (160 mg, 0.95 mmol), afforded (−)-**25** (160 mg, 92%). Yellow oil. $[\alpha]_D^{20} = -17.3$ ($c = 1.00$, $CHCl_3$). IR (neat): 3378*w*, 2938*w*, 2876*w*, 1654*s*, 1450*m*, 1425*m*, 1331*w*, 1288*w*, 1202*w*, 1176*w*, 1145*w*, 1056*m*, 985*w*, 907*w*, 880*w*, 720*w*, 667*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.20–1.35 (*m*, 1 H); 1.61–1.87 (*m*, 4 H); 1.90–2.18 (*m*, 5 H); 2.30 (br. *s*, 1 H); 2.64–2.72 (*m*, 1 H); 3.06 (*ddd*, $J = 11.8, 8.7, 3.7$, 1 H); 3.56 (*ddd*, $J = 11.8, 7.8, 7.8$, 1 H); 3.62–3.74 (*m*, 2 H); 3.83–3.92 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.9; 29.0; 30.4; 32.3; 32.7; 41.2; 46.5; 60.6; 62.6; 177.5. HR-MALDI-MS: 206.1153 ($[M + Na]^+$, $C_{10}H_{17}NO_2Na^+$; calc. 206.1151).

*(−)-(2*R*,7a*S*)-2,3,5,6,7,7a-Hexahydro-2-(3-hydroxypropyl)hexahydro-1*H*-pyrrolizin-3-one* ((−)-**26**). *GP B*, starting from (+)-**23** (150 mg, 0.53 mmol), afforded (−)-**26** (78 mg, 80%). Yellow oil. $[\alpha]_D^{20} = -4.5$ ($c = 1$, $CHCl_3$). IR (neat): 3384*w*, 2928*w*, 2865*w*, 1659*s*, 1454*m*, 1424*m*, 1331*w*, 1288*w*, 1213*w*, 1183*w*, 1143*w*, 1057*m*, 1036*w*, 878*w*, 719*m*, 622*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.23–1.51 (*m*, 3 H); 1.53–1.73 (*m*, 2 H); 1.87–2.18 (*m*, 5 H); 2.49 (*ddd*, $J = 12.1, 7.8, 6.2$, 1 H); 2.76–2.87 (*m*, 1 H); 3.04–3.12 (*m*, 1 H); 3.48–3.57 (*m*, 1 H); 3.59–3.71 (*m*, 2 H); 3.75–3.85 (*m*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.6; 26.9; 30.6; 32.4; 35.7; 41.0; 46.4; 59.6; 62.1; 175.8. HR-MALDI-MS: 206.1152 ($[M + Na]^+$, $C_{10}H_{17}NO_2Na^+$; calc. 206.1151). Anal. calc. for $C_{10}H_{17}NO_2$ (183.25): C 65.54, H 9.35, N 7.64; found C 65.35, H 9.42, N 7.75.

*X-Ray Crystal Structure of (+)-***15**. Crystal data at 223(2) K for $C_{17}H_{18}N_2O_3$ ($M_r = 298.33$): orthorhombic, space group $P2_12_12_1$ (No. 19), $D_c = 1.316$ g cm^{-3}, $Z = 4$, $a = 7.8001(2)$ Å, $b = 8.7746(2)$ Å, $c = 22.0016(5)$ Å, $V = 1505.85(6)$ Å^3. *Bruker-Nonius Kappa-CCD* diffractometer, MoK_α radiation, $\lambda = 0.7107$ Å. A colorless crystal (linear dimensions *ca*. $0.2 \times 0.2 \times 0.18$ mm) was obtained by slow evaporation of a conc. hexane soln. The structure was solved by direct methods (SIR97) [23] and refined by full-matrix least-squares analysis (SHELXL-97) [24], using an isotropic extinction correction and $w = 1/[\sigma^2(F_o^2) + (0.04532P)^2 + 0.1883P]$, where $P = (F_o^2 + 2F_c^2)/3$. All heavy atoms of (+)-**15** were refined anisotropically, H-atoms isotropically, whereby H-positions are based on stereochemical considerations. Final $R(F) = 0.038$, w$R(F^2) = 0.092$ for 218 parameters and 2998 reflections with $I > 2\sigma(I)$ and $2.50 < \theta < 27.47°$ (corresponding R values based on all 3409 reflections are 0.046 and 0.098, resp.).

*X-Ray Crystal Structure of (−)-***16**. Crystal data at 153(2) K for $C_{17}H_{18}N_2O_3$ ($M_r = 298.33$): orthorhombic, space group $P2_12_12_1$ (No. 19), $D_c = 1.352$ g cm^{-3}, $Z = 4$, $a = 7.6825(2)$ Å, $b = 8.7790(3)$ Å, $c = 21.7314(9)$ Å, $V = 1465.67(9)$ Å^3. *Bruker-Nonius Kappa-CCD* diffractometer, MoK_α radiation, $\lambda = 0.7107$ Å. A colorless crystal (linear dimensions *ca*. $0.15 \times 0.13 \times 0.10$ mm) was obtained by slow evaporation of a conc. hexane soln. The structure was solved by direct methods (SIR97) [23] and refined by full-matrix least-squares analysis (SHELXL-97) [24], using an isotropic extinction correction, and $w = 1/[\sigma^2(F_o^2) + (0.0454P)^2 + 0.2969P]$, where $P = (F_o^2 + 2F_c^2)/3$. All heavy atoms of (−)-**16** were refined anisotropically, H-atoms isotropically, whereby H-positions are based on stereochemical considerations. Final $R(F) = 0.042$, w$R(F^2) = 0.095$ for 218 parameters and 2717 reflections with $I > 2\sigma(I)$ and $1.87 < \theta < 27.49°$ (corresponding R values based on all 3280 reflections are 0.058 and 0.104, resp.).

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-270197 and CCDC-270198. Copies of the data can be obtained, free of charge, on application to the *CCDC*, 12 union Road, Cambridge CB2 1EZ UK (fax: + 44(1223)336033; e-mail:deposit@ccdc.cam.ac.uk).

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