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Facile, Stereocontrolled Synthetic Route towards Bis-functionalised Pyrrolizidines

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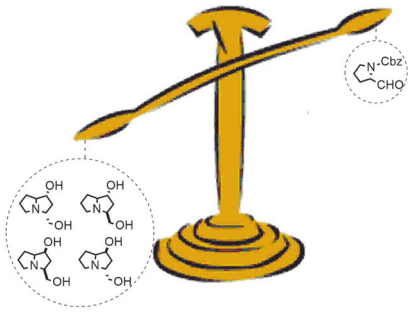

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Abstract A simple and convenient method for the synthesis of bis-functionalised pyrrolizidines starting from readily available *N*-Cbz-L-prolinal is described. This aldehyde was converted within two concise steps to the corresponding aminoepoxides, which were separately subjected to regioselective cyclisation induced by a reductive cleavage of the Cbz protecting group. The versatile and concise strategy holds great potential for practical application in the straightforward preparation of pyrrolizidine-based drugs and natural products.

Key words alkaloids, heterocycles, diastereoselective synthesis, asymmetric epoxidation, cyclisation, tandem reaction

Pyrrolizidines[1] constitute a unique class of omnipresent alkaloids, comprised of a heterobicyclic [3.3.0] scaffold bridged with a centrally positioned nitrogen atom (Figure 1). Some of these compounds are recognized as naturally occurring products isolated from plants, as for instance, *Ageratum houstanium*,[2] *Osyris alba*,[3] *Tephesoris kirilowii*,[4] *Senecio* genus,[5] marine fungus[6] or their strains,[7] *Castanospermum austral*,[8] and *Senecio vulgaris* (**I–VIII**, respectively, Figure 1).[9] Such compounds can be also isolated from ants, butterflies, frogs, and moths.[10] Pyrrolizidine derivatives have been identified as secondary metabolites, whereas their significant bioactivity has been broadly explored in terms of sugar mimics, with a great emphasis put on desired glycosidase inhibitory activities.[11] Therefore, the potential application of pyrrolizidines as therapeutic agents against diabetic diseases, viral infections, and cancer[12–15] have encouraged several research groups to develop efficient approaches towards diastereoselective synthesis of polyhydroxylated and other variously functionalized pyrrolizidines. A number of stereoselective strategies, relying on the use of modified proline derivatives, have so far been brought to light. These have involved, as key synthetic steps, the SmI_2-mediated intramolecular coupling reaction,[16] the Wittig reaction,[17] RCM accelerated by 2nd generation Grubbs catalyst,[18] the Mitsunobu reaction,[19] exhaustive carbonylation under high pressure,[20] $RuCl_2(PPh_3)_3$-assisted[21] and radical cyclisation,[22] intramolecular oxime-olefin cycloaddition,[23] the Ireland–Claisen rearrangement,[24] Cp_2Zr-driven ring contraction,[25] diastereoselective Michael addition,[26] and enzymatic aldol reaction.[27]

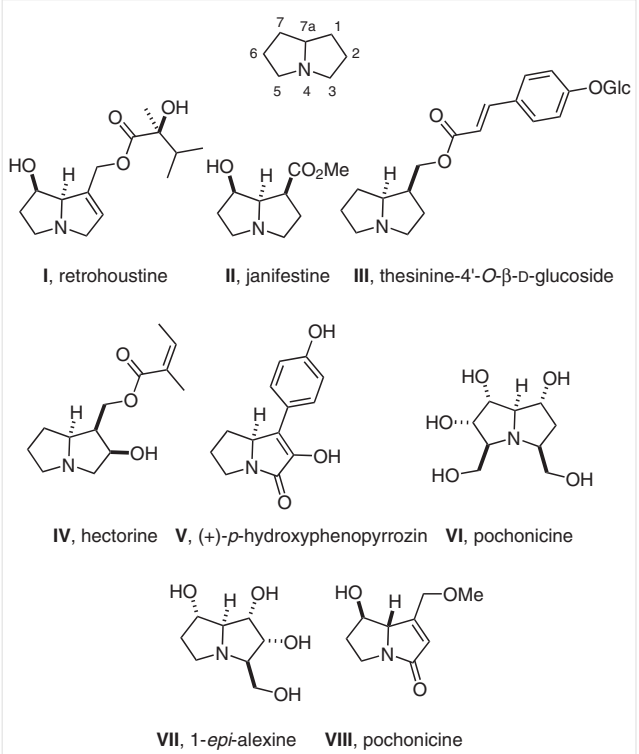
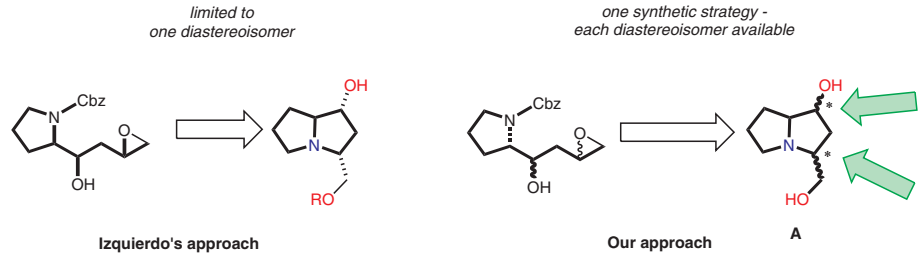


Figure 1 Widespread alkaloids with a pyrrolizidine scaffold



Scheme 1 A general access to stereochemically diverse pyrrolizidines

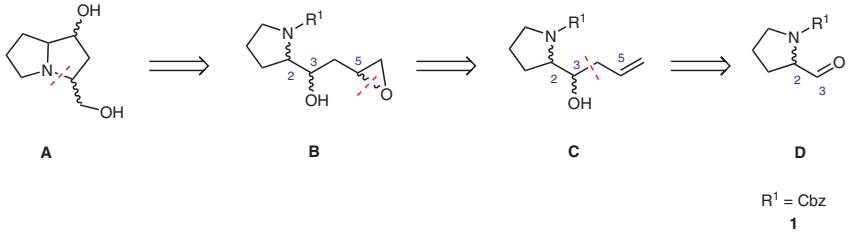
Despite great achievements in the synthesis of various pyrrolizidines, certain drawbacks are still encountered, such as multi-step procedures requiring substrate pre-functionalization, harsh reaction conditions, and costly catalysts. Hence the rational development of more convenient, environment-friendly, and practical methods for assembling pyrrolizidines using readily available oxidants still remains a challenge. Clearly, straightforward and selective oxirane ring formation, followed by rapid ring closure, would be a more practical and economical approach.

The strategies listed above typically aim to synthesize solely one diastereoisomer of alkaloids, as shown in Scheme 1. Izquierdo and co-workers,[28] reported an excellent indium-mediated allylation of L-prolinal[29] that allows *syn*-oriented species to be obtained. Their protocol, however, does not lead to target other possible diastereoisomers.

Herein we report an efficient and versatile protocol that gives straightforward access to the desired diastereoisomer of disubstituted pyrrolizidine scaffolds. In Scheme 1, our synthetic approach to all existing diastereoisomers of 1,3-disubstituted pyrrolizidine core **A** starting from the same precursors as used by Izquierdo et al. is shown and the proposed synthetic strategy towards the preparation of precursors is illustrated in Scheme 2.

This approach opens the way to the precursor **B** and finally to regio- and stereoselective cyclisation, affording diastereoisomerically pure species **8**–**11** (Table 1). Retrosynthetic analysis performed for the assembly of chiral, bis-substituted pyrrolizidine scaffold **A** starts by disconnection of the C3–N4 bond to provide epoxide **B**, as shown in Scheme 2. Thus, the key step for the proposed strategy is envisaged to involve a cascade-type process that starts with NCbz reductive deprotection and consequent rapid, regioselective cyclisation. Epoxide **B** could be established via oxidation of linear homoallyl alcohol **C** affording both *syn*- and *anti*-diastereoisomeric forms, ideally with high stereoselectivity for either of them. Allyl group addition to the parental aldehyde **D**, in turn, leads to the requisite species **C** endowed with two well-defined stereogenic centres. The entire path envisaged for the preparation of the target pyrrolizidines is designed to involve cheap reagents and to proceed under mild conditions, and so may be considered appropriate for further synthetic modifications.

Our approach to construct diastereoisomerically pure, eight-membered bicyclic scaffolds was initiated from readily available Cbz (compatible with all planned functional group transformations) protected L-prolinal **1**. At the initial stage, bearing a highly reactive species, we proposed to introduce novel chiral moieties exploiting a stereocontrolled addition of allyl precursor to the carbonyl group. As was emphasized, the olefin terminus so formed is prone to undergo further functionalization towards desired regioselective ring closure with complete chirality transfer. Note, however, that Li and Zhao[30] explored allylstannanes under acidic conditions. Hall[31] reported addition of allylboropinacolate assisted by combination of Lewis acid ($SnCl_4$) and chiral diol. Both systems promoted *anti*-isomer, while an absence of diol allowed for almost statistical mixture of products and could be considered in the future as an efficient way to increase the ratio of *syn*-oriented diastereoisomer. Nevertheless, we employed allylation of N-protected α-aminoaldehyde **1** with respect to the already reported strategy (demonstrated by our group for the total synthesis of preussine[32] and bulgecinine[33]). This practical variant of



Scheme 2 Retrosynthetic analysis of 1,3-substituted pyrrolizidine analogues

Barbier-type reaction was successfully adopted in the present study (Table 1) and relies on the addition of allyl bromide, zinc dust, and aqueous ammonium chloride to the reaction mixture to give the desired product in high overall yield (90%). From the stereochemical viewpoint the proposed approach gives an access to acceptable ratio of the two products (**2**/**3** = 2:8), which proved to be easily separable by column chromatography. Both diastereoisomers of N-protected homoallyl alcohols were in the next step subjected to epoxidation reaction. Drawing upon previously acquired experience we employed three different variants of catalytic systems based on $VO(acac)_2$ (b), $Ti(Oi\text{-}Pr)_4$ (c), and $Al(Ot\text{-}Bu)_3$ (d) combined with *tert*-butyl hydroperoxide. A compilation of results obtained is displayed in Table 1.

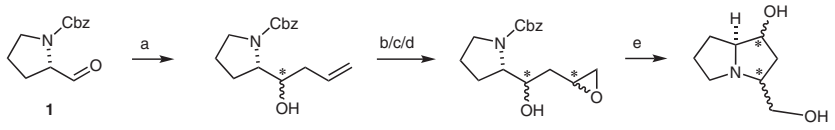
Synthesizing the specific stereoisomer of preussine,[32] we found that under applied conditions (b), the *syn*-isomer was mostly promoted. Faced with the above-mentioned findings we first attempted to employ epoxidation of olefins **2** and **3** assisted by the $VO(acac)_2$/*t*-BuOOH system aimed at selective formation of both *syn*-oriented species (Table 1). The devised protocol paves the way to the anticipated family of epoxides **4**, **5** and **6**, **7** in the ratios 74:26 and 78:22, respectively. Moreover two pairs of epoxides were obtained in moderate 46% and 55% yields.

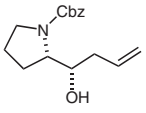
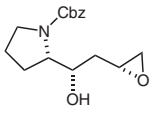
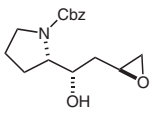
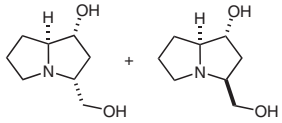
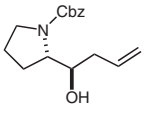
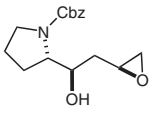
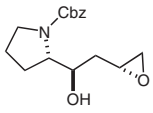
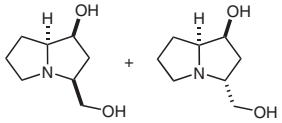
On the basis of our previous experience, the synthesis of the remaining *anti*-oriented epoxides was inspected, taking into account the methods (c) and (d). The examined strategies necessitated a slight increase in the amount of *anti*-arranged isomer (Table 1, 4:**5** = 57:43); nevertheless, the *syn*-arranged compound **4** was still favoured. However, the stereochemical handicap was compensated for with a very good 68% yield. We were very pleased to note a striking difference, over the course of the investigated reaction, struggling against compounds **6** and in particular **7** under specified conditions (d). We readily induced a direction of olefin oxidation with desired shift of ratio towards *anti*-isomer **7** (dr 18:22) with diminished but still acceptable 43% yield (Table 1). All required diastereoisomeric precursors **4**–**7** suit perfectly to carry out the key reaction for a synthesis of target pyrrolizidines **8**–**11**.

We designed the final cyclisation of γ-aminoepoxides to be induced by a sequence of two reactions involving the reductive cleavage of Cbz unit, followed by spontaneous nucleophilic attack of the nitrogen lone pair on the tertiary carbon atom of the oxirane ring. The assembly of pyrrolizidine scaffold was performed by applying reductive cleavage of carbamate masked amine by 10% palladium on charcoal (Degussa type E 101) under a hydrogen atmosphere. The removal of carboxybenzyl protecting group from amine function and its spontaneous S_N2 reaction was monitored by TLC.

After 20 hours, readily obtained bicyclic products were purified by means of column chromatography separation, providing each of envisaged compounds. The outlined methodology provided an excess of each of the anticipated, diastereoisomerically pure pyrrolizidines **8**–**11**, which were isolated with the same ratio as their oxirane-featured precursors. We found that no epimerisation occurred during

Table 1 D iasteroselective Synthesis of Pyrrolizidines **8**–**11**[a]



Allyl substrate	*syn*-Epoxide	*anti*-Epoxide	Overall yield (%)	Ratio of epoxides[b] *syn*/*anti*	Separated pyrrolizidines[c]	dr[c]
 **2**	 **4**	 **5**	46[d]	74:26	 **8**, 80% + **9**, 81%	74:26
			50[e]	58:42		58:42
			68[f]	57:43		57:43
 **3**	 **6**	 **7**	55[d]	78:22	 **10**, 84% + **11**, 85%	78:22
			76[e]	37:63		37:63
			43[f]	12:88		12:88

[a] Reaction conditions: (a) allyl bromide, Zn, NH_4Cl; (b) $VO(acac)_2$/*t*-BuOOH; (c) $Ti(Oi\text{-}Pr)_4$/*t*-BuOOH; (d) $Al(Ot\text{-}Bu)_3$/*t*-BuOOH; (e) H_2, cat. 10% Pd/C (Degussa).
[b] Ratio of formed epoxide determined by NMR analysis.
[c] Pyrrolizidines isolated with diastereomeric ratio corresponding to the ratio of starting epoxides.
[d] Reagent used: $VO(acac)_2$/*t*-BuOOH.
[e] Reagent used: $Ti(Oi\text{-}Pr)_4$/*t*-BuOOH.
[f] Reagent used: $Al(Ot\text{-}Bu)_3$/*t*-BuOOH.

the cyclisation, as was corroborated by ^{1}H NMR spectra of products. No indolizidine by-products were found either. The combined yields of individually isolated cyclised product pairs **8**, **9** and **10**, **11** were 80–85%. Successfully isolated diastereoisomerically pure pyrrolizidines **8**–**11** were subjected to NMR analyses aimed at stereochemical structure elucidation. The ^{1}H–^{13}C correlation spectra allowed for precise assignment of all resonance signals. Subsequently, the analysis of two-dimensional NOE experiment for each of the synthesised products allowed us to determine the relative configurations, taking advantage of strong nuclear Overhauser effects, which were observed mainly for protons located at the stereogenic centres. In this context, all spectra recorded for target compounds **8**–**11** were analysed in detail (the accurate assignment and spectra interpretation are depicted in Supporting Information), shedding light on diverse correlations detected for (i) the separated signals of methylene protons (geminal inequality) in the pyrrolizidine ring and (ii) geminal coupling between hydroxyl protons with other spatial protons.

In order to corroborate spectral analyses, we made an attempt to get more insight into structural attributes of pyrrolizidine motif in a solid state. The mono crystals of diastereosimerically pure compound **8** suitable for X-ray crystal structure analysis were obtained by a slow evaporation from methanol. The molecular structure is shown in Figure 2. Single crystal X-ray diffraction unambiguously prove the stereochemical identity of compound **8**, and confirmed the accuracy of stereochemical assignment supported by NMR technique for all of target species **8**–**11**.

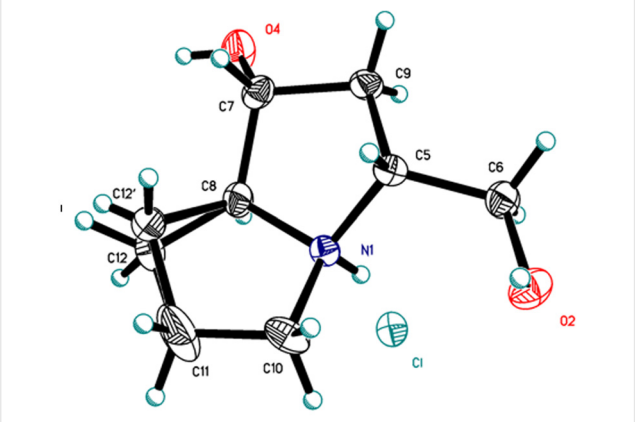


Figure 2 Molecular structure of pyrrolizidines **8** determined by single crystal X-ray diffraction[33]

In conclusion, we have developed a cheap, readily synthetic protocol towards each of the designed and expected diastereoisomers of pyrrolizidines **8**–**11**, functionalised with two different substituents. The conducted epoxidation does not require additional, sophisticated ligands, while the key synthetic step based on tandem deprotection–cyclisation provides a great opportunity to produce the required pyrrolizidines with well-defined stereochemistry. The established protocol may potentially be transferrable to the synthesis of amine-terminated pyrrolizidines, utilising an asymmetric azidiration as a source of the exo-amine group.

All starting materials and reagents were obtained from commercial suppliers and used without further purification. TLC was performed on silica gel 60 F_{254} plates, spots were detected by fluorescence quenching under UV light at 254 nm. Column chromatography was performed on silica gel 60 (0.040–0.063 mm). All experimental manipulations with anhydrous solvents were carried out in flame-dried glassware under an inert atmosphere of argon. Degassed solvents were obtained by three freeze-pump-thaw cycles.

All NMR spectra were recorded at 25 °C in DMSO-d_6 by Varian VNMRS 500 MHz spectrometer. ^{1}H NMR (500.16 MHz) spectra were referenced to the solvent residual proton signal (DMSO-d_6, δ_H = 2.50). ^{13}C NMR (128.54 MHz) with total decoupling of protons were referenced to the solvent (DMSO-d_6, δ_C = 39.52). HRMS spectra were obtained with an LSI, EI, ESI-TOF mass spectrometer in MeOH or MeCN. Optical rotations were measured at room temperature using a Jasco J-815 polarimeter. IR spectra were recorded on Jasco 6200 FTIPR spectrophotometer. Melting points were measured with a Büchi M565 melting point apparatus and are uncorrected. Elemental analyses were obtained using the elemental analyser Vario (Elementar) EL III analyser.

Allylation of NCbz-Protected L-Prolinal 1

The aldehyde **1** (1.165 g, 5 mmol) was dissolved in of THF (10 mL) and cooled down in a crushed ice bath to 0 °C. Subsequently, sat. aq NH_4Cl (2.5 mL) and Zn dust (650 mg, 10 mmol) were added at once. The resulting mixture was vigorously stirred and allyl bromide (0.605 g, 5 mmol) was carefully added dropwise. The reaction mixture was allowed to warm up to r.t. and the mixture was stirred for the next 2 h. The reaction was terminated by the addition of aq 0.5 M HCl (40 mL) and Et_2O (40 mL). The crude mixture was stirred till the solution became transparent. The aqueous layer was extracted with Et_2O (2 × 20 mL). Organic layers were separated, combined, and dried (anhyd $MgSO_4$). The solvent was removed under reduced pressure. The obtained homoallyl alcohols **2** and **3** (1.4g, 0.35 g) were purified by column chromatography separation.

(2*S*,1′*S*)-2-(1′-Hydroxybut-3′-en-1′-yl)-1-(carbobenzyloxy)pyrrolidine (2)[34,35]

Colorless oil; yield: 1.4 g (80%); $[\alpha]_D$ –64.8 (*c* 0.8, $CHCl_3$).

IR ($CHCl_3$): 3383, 1670, 1421, 1358 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.29 (m, 5 H), 6.03–5.90 (m, 1 H), 5.17–5.08 (m, 4 H), 4.49 (br s, 1 H), 3.97–3.89 (m, 1 H), 3.69–3.56 (m, 2 H), 3.40–3.33 (m, 1 H), 2.40–2.31 (m, 1 H), 2.20–2.11 (m, 1 H), 1.99 (m, 1 H), 1.87 (m, 1 H), 1.79 (m, 1 H), 1.73–1.67 (m, 1 H).

^{13}C NMR (128.5 MHz, $CDCl_3$): δ = 157.96, 136.48, 134.65, 128.51, 128.09, 127.95, 117.18, 74.86, 67.41, 62.85, 47.23, 39.20, 28.36, 24.16.

HRMS LSI (+): *m*/*z* ($[M + H]^{+\cdot}$) calcd for $C_{16}H_{22}NO_3$: 276.1600; found: 276.1602.

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.35; H, 7.59; N, 5.07.

(2*S*,1′*R*)-2-(1′-Hydroxybut-3′-en-1′-yl)-1-(carbobenzyloxy)pyrrolidine (3)[34,35]

Colorless oil; yield: 0.35 mg (20%); $[\alpha]_D$ –56.7 (*c* 1.0, $CHCl_3$).

IR (film): 3432, 2975, 1697, 1682, 1420, 1109 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.29 (m, 5 H), 5.95–5.70 (m, 1 H), 5.17–5.05 (m, 4 H), 4.01–3.78 (m, 1 H), 3.61 (m, 1 H), 3.38–3.31 (m, 2 H), 2.22–2.11 (m, 2 H), 2.02–1.72 (m, 4 H).

^{13}C NMR (128.5 MHz, $CDCl_3$): δ = 156.23, 136.62, 135.29, 134.90, 128.43, 127.96, 127.83, 117.20, 117.03, 71.84, 71.60, 66.99, 62.94, 61.33, 47.66, 38.31, 37.41, 26.62, 25.57, 24.30, 24.108.

HRMS LSI (+): *m*/*z* ([M + H]$^{+\cdot}$) calcd for $C_{16}H_{22}NO_3$: 276.1600; found: 276.1590.

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.77; H, 7.66; N, 5.03.

Epoxidation of Homoallyl Alcohols 2 and 3 Using the Catalytic System V^{5+}/*t*-BuOOH; General Procedure

An oven-dried and argon-flushed, three-necked round-bottomed flask was charged with a solution of the homoallyl alcohol **2** or **3** (3 mmol) in anhyd CH_2Cl_2 (30 mL), followed by $VO(acac)_2$ (30 mg, 4 mol%) and 4 M *tert*-butyl hydroperoxide in CH_2Cl_2 (1.13 mL, 1.5 mol equiv). The reaction was stirred at r.t. for at least 20 h until no further progress of the reaction was observed by TLC. The reaction was terminated by the addition of aq 1% $Na_2S_2O_5$ (until a greenish-blue colour change of the aqueous layer appeared). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (anhyd $MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (Table 1).

Epoxidation of Homoallyl Alcohols 2 and 3 Using the Al^{3+}/*t*-BuOOH System; General Procedure

An oven-flamed and argon flushed three-necked round bottomed flask was charged with corresponding homoallyl alcohol (3 mmol), Al(O*t*-Bu)$_3$ (1.11 g, 4.5 mmol), and anhyd benzene (15 mL). The resulting mixture was cooled to 5 °C, and a 4 M solution of *tert*-butyl hydroperoxide in CH_2Cl_2 (1.51 mL, 6 mmol) was added. The reaction was stirred at 5 °C for the next 5–9 hours, until no further reaction progress of the reaction was observed by TLC. Afterwards, Et_2O (150 mL) and H_2O (30 mL) were added and the resulting mixture was vigorously stirred at r.t. for 15 min. The aqueous layer was separated and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried (anhyd $MgSO_4$) and the solvents were evaporated under reduced pressure. The residue was purified by column chromatography (Table 1).

Epoxidation of Homoallyl Alcohols 2 and 3 Using the Ti^{4+}/*t*-BuOOH System; General Procedure

An oven-dried and argon-flushed, three-necked round-bottomed flask was charged with the corresponding homoallyl alcohol **2** or **3** (3 mmol), anhyd CH_2Cl_2 (12 mL), and activated 3Å molecular sieves (150 mg). The resulting solution was cooled down to –15 °C. Consecutively, a 4 M solution of *tert*-butyl hydroperoxide in CH_2Cl_2 (1.51 mL, 6 mmol) and Ti(O*i*-Pr)$_4$ (853 mg, 893 µL, 3 mmol) were added dropwise and the mixture was stirred under an argon atmosphere until no further progress of the reaction was observed by TLC. Afterwards, CH_2Cl_2 (40 mL) and H_2O (20 mL) were then added and the mixture was stirred at 0 °C for 15 min. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (anhyd $MgSO_4$) and the solvent was evaporated under a reduced pressure. The residue was purified by column chromatography (Table 1).

A label 'x' given instead of the proton number in the description of ^1H NMR spectrum denotes the molar fraction of one of the diastereoisomers, which occur in the product mixture.

Mixture of (2*S*,1′*R*,3′*S*)-2-(3′,4′-Epoxy-1′-hydroxbut-1′-yl)-1-(carbobenzyloxy)pyrrolidine (4) and (2*S*,1′*R*,3′*R*)-2-(3′,4′-Epoxy-1′-hydroxbut-1′-yl)-1-carbobenzyloxy)pyrrolidine (5)

Colourless oil.

^1H NMR (500 MHz, DMSO-d_6; 350 K): δ = 7.36–7.26 (m, 5 H), 5.08–5.06 (m, 2 H), 4.64–4.48 (m, 1 H), 3.95–3.83 (m, 2 H), 3.56–3.44 (m, 1 H), 3.31–3.24 (m, 1 H), 3.03–2.94 (m, 1 H), 2.67 (m, x H), 2.60 [m, (1 – x) H], 2.41 (m, x H), 2.35 [m, (1 – x) H], 1.92–1.68 (m, 4 H), 1.66–1.56 [m, (1 – x) H], 1.54-1.36 [m, (1 + x) H].

^{13}C NMR (128.5 MHz, DMSO-d_6; 350 K): δ (**4**) = 154.62, 136.74, 127.83, 127.19, 126.98, 69.33, 65.53, 60.86, 49.32, 46.66, 45.42, 34.96, 26.09, 23.08; δ (**5**) = 154.62, 136.74, 127.83, 127.19, 126.98, 68.94, 65.53, 61.12, 49.19, 46.66, 46.20, 35.33, 25.86, 23.08.

HRMS LSI (+): *m*/*z* calcd ([M + Na]$^{+\cdot}$) for $C_{16}H_{21}NO_4Na$: 314.1368; found: 314.1339.

Mixture of (2*S*,1′*R*,3′*S*)-2-(3′,4′-Epoxy-1′-hydroxbut-1′-yl)-1-(carbobenzyloxy)pyrrolidine (6) and (2*S*,1′*R*,3′*R*)-2-(3′,4′-Epoxy-1′-hydroxbut-1′-yl)-1-(carbobenzyloxy)pyrrolidine (7)

Colourless oil.

^1H NMR (500 MHz, DMSO-d_6; 350 K): δ = 7.35–7.25 (m, 5 H), 5.11–5.03 (m, 2 H), 4.59 (d, *J* = 5.6 Hz, x H), 4.54 [d, *J* = 5.7 Hz, (1–x) H], 4.04–3.95 (m, 1 H), 3.75–3.71 (m, 1 H), 3.49–3.43 (m, 1 H), 3.31–3.25 (m, 1 H), 2.97–2.91 (m, 1 H), 2.67 (m, x H), 2.63 [m, (1 – x) H], 2.44–2.38 (m, 1 H), 2.01–1.92 (m, 2 H), 1.81–1.67 [m, (3 – x) H], 1.59 (m, x H), 1.42–1.32 (m, 1 H).

^{13}C NMR (128.5 MHz, DMSO-d_6; 350 K): δ (**6**) = 153.87, 136.79, 127.84, 127.18, 126.98, 67.72, 65.38, 61.40, 49.12, 46.44, 45.53, 37.01, 24.26, 23.29; δ (**7**) = 153.87, 136.79, 127.84, 127.18, 126.98, 67.72, 65.38, 61.40, 48.96, 46.44, 45.94, 36.58, 24.26, 23.29.

HRMS EI: *m*/*z* ([M]$^{+\cdot}$) calcd for $C_{16}H_{21}NO_4$: 291.1471; found: 291.1474.

Cyclisation of γ-Aminoepoxides; General Procedure

A three-necked round-bottomed flask was charged with a mixture of epoxy alcohol **4**/**5** or **6**/**7** (2.0 mmol) and MeOH (40 mL). The resulting solution was degassed, subsequently catalyst 10% Pd/C (Degussa, type E 101, 40 mg) was added at once and the reaction mixture was vigorously stirred at r.t. under H_2 for 20 h. Afterwards, the crude product was filtered through a pad of Celite. The residual solvent was removed under reduced pressure. The crude material was subjected to column chromatography to purify and separate the formed diastereoisomers.

(1*R*,3*R*,7a*S*)-1-Hydroxy-3-hydroxymethylpyrrolizidine (8)

Pale-yellow crystals; yield: 129 mg (81%, 0.83 mmol); mp 82–88 °C (CH_2Cl_2/pentane); $[\alpha]_D$ –3.2 (*c* 1.0, MeOH).

IR ($CHCl_3$): 3602, 3350, 2966, 1449, 1091, 1021 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 4.82 (br s, 1 H), 4.41 (br s, 1 H), 3.67 (dt, *J* = 8.9, 6.4, 6.4 Hz, 1 H), 3.34 (d½ABq, *J* = 5.5 Hz, J_{AB} = 10.5 Hz, 1 H), 3.26 (d½ABq, *J* = 6.0 Hz, J_{AB} = 10.5 Hz, 1 H), 3.06 (m, 1 H), 2.75 (ddd, *J* = 10.7, 7.3, 6.1 Hz, 1 H), 2.64 (m, 1 H), 2.58 (m, 1 H), 2.04 (dt, *J* = 12.0, 6.1, 6.1 Hz, 1 H), 1.77–1.67 (m, 1 H), 1.67–1.60 (m, 1 H), 1.60–1.48 (m, 2 H), 1.42 (ddd, *J* = 12.0, 9.6, 9.2 Hz, 1 H).

^{13}C NMR (128.5 MHz, DMSO-d_6): δ = 75.51, 71.48, 66.36, 65.13, 54.47, 38.50, 29.75, 24.58.

HRMS ESI (+): *m*/*z* ([M + H]$^{+}$) calcd for $C_8H_{16}NO_2$: 158.1181; found: 158.1213.

(1*R*,3*S*,7a*S*)-1-Hydroxy-3-hydroxymethylpyrrolizidine (9)

Yellowish oil; yield: 109 mg (80%, 0.7 mmol); $[\alpha]_D$ –5.2 (*c* 1.0, MeOH).

IR ($CHCl_3$): 3605, 3351, 2970, 1449, 1109, 1065, 1019 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.80 (br s, 2 H), 3.82 (m, 1 H), 3.58 (d½ABq, *J* = 7.2 Hz, J_{AB} = 11.2 Hz, 1 H), 3.50 (d½ABq, *J* = 5.6 Hz, J_{AB} = 11.2 Hz, 1 H), 3.37 (m, 1 H), 3.22 (dt, *J* = 7.7, 7.7, 1.9 Hz, 1 H), 2.75–2.70 (m, 1 H), 2.68–2.62 (m, 1 H), 2.00 (m, 1 H), 1.79–1.69 (m, 2 H), 1.62–1.52 (m, 2 H), 1.34 (m, 1 H).

^{13}C NMR (128.5 MHz, DMSO-d_6): δ = 74.45, 74.32, 62.24, 59.96, 46.28, 34.86, 28.87, 25.89.

HRMS EI (+): *m*/*z* ([M + H]$^{+}$) calcd for $C_8H_{15}NO_2$: 157.1103; found: 157.1101.

(1*S*,3*S*,7a*S*)-1-Hydroxy-3-hydroxymethylpyrrolizidine (10)

Yellowish oil; yield: 165 mg (84%, 1.06 mmol); $[\alpha]_D$ +15.4 (*c* 0.15, MeOH).

IR ($CHCl_3$): 3603, 3350, 2970, 1447, 1108, 1065, 1018 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6; 363 K): δ = 4.74 (br s, 2 H), 4.00 (m, 1 H), 3.53 (m, 2 H), 3.21 (m, 1 H), 3.03–2.97 (m, 1 H), 2.81 (m, 1 H), 2.66–2.60 (m, 1 H), 2.10 (dt, *J* = 13.4, 6.8, 6.8 Hz, 1 H), 1.88–1.79 (m, 2 H), 1.73–1.64 (m, 1 H), 1.59–1.52 (m, 2 H).

^{13}C NMR (128.5 MHz, DMSO-d_6; 363 K): δ = 69.39, 68.77, 60.82, 60.05, 46.77, 36.50, 25.89, 22.77.

HRMS EI: *m*/*z* ([M]$^{+}$) calcd for $C_8H_{15}NO_2$ 157.1103; found: 157.1106.

(1*S*,3*R*,7a*S*)-1-Hydroxy-3-hydroxymethylpyrrolizidine (11)

Yellowish oil; yield: 163 mg (85%, 1.09 mmol); $[\alpha]_D$ +11.7 (*c* 1.0, MeOH).

IR (KBr): 3604, 3352, 2966, 1447, 1096, 1023 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 4.65 (br s, 2 H), 3.97 (m, 1 H), 3.45 (m, 1 H), 3.39 (d½ABq, *J* = 5.6 Hz, J_{AB} = 10.7 Hz, 1 H), 3.30 (d½ABq, *J* = 5.7 Hz, J_{AB} = 10.7 Hz, 1 H), 2.92–2.86 (m, 2 H), 2.58 (ddd, *J* = 9.6, 7.0, 6.8 Hz, 1 H), 1.93–1.86 (m, 2 H), 1.80 (m, 1 H), 1.70–1.55 (m, 2 H), 1.48 (m, 1 H).

^{13}C NMR (128.5 MHz, DMSO-d_6): δ = 70.72, 69.34, 66.98, 62.24, 54.25, 38.76, 26.60, 23.66.

HRMS EI: *m*/*z* ([M]$^{+}$) calcd for $C_8H_{15}NO_2$: 157.1103; found: 157.1101.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609582.

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