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Stereoselective Synthesis of Tricyclic Diproline Analogues that Mimic a PPII Helix: Structural Consequences of Ring-Size Variation

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Polycyclic proline-derived scaffolds (ProMs) have recently demonstrated their value as conformationally defined dipeptide analogs for the modular construction of secondary structure mimetics, specifically interfering with PPII helix-mediated protein–protein interactions. We disclose the stereoselective synthesis of two new tricyclic amino acid scaffolds (ProM-4 and ProM-8) that differ from the first generation scaffold ProM-1 by the size of ring A. Conformational preferences and subtle structural differences of the three homologous scaffolds were analyzed by X-ray crystallography, computational calculations, and NMR spectroscopy. *N*-*tert*-butoxycarbonyl(Boc)-3-(1-propenyl)azetidine-2-carboxylic acid was prepared from L-aspartic acid through β-lactam intermediates. The corresponding piperidine-based building block *rac*-*N*-Boc-3-vinylpipecolic acid was synthesized by Cu-catalyzed 1,4-addition of vinyl-MgBr to methyl *N*-Boc-2,3-dehydropipecolate. Target molecules were prepared through peptide coupling of the respective ring A building blocks with *cis*-5-vinylproline *tert*-butyl ester and subsequent ring-closing metathesis. Selective deprotection of a *tert*-butyl carbamate (*N*-Boc protecting group) in the presence of a *tert*-butyl ester was achieved with trifluoroacetic acid at 0 °C.

Introduction

The selective modulation of protein-protein interactions by means of synthetic small molecules represents a challenging research task at the interface of chemistry, biology and medicine.[1] In this context, protein domains specialized in recognition of so-called proline-rich motifs (PRMs) have recently attracted attention as potential drug targets.[2] To be recognized by their specific binding domains, PRMs must adopt a left-handed polyproline type 2 (PPII) helix secondary structure.[3] Recently, we envisioned that suitable interface inhibitors could possibly be developed by replacing flexible Pro-Pro units of proline-rich peptide chains by synthetic diproline analogs ("ProMs") rigidified in a PPII helix conformation.[4] After inspecting molecular models we devised and stereoselectively synthesized tricyclic scaffold **1a** (ProM-1), in which a vinylidene unit bridges two proline rings such that the system is forced to adopt an almost perfect PPII helix conformation (Figure 1). And indeed, we found that a Pro-Pro unit within a PRM peptide, which specifically binds to the Fyn-SH3 domain, could be substituted by **1a** without loss of binding affinity.[4a]

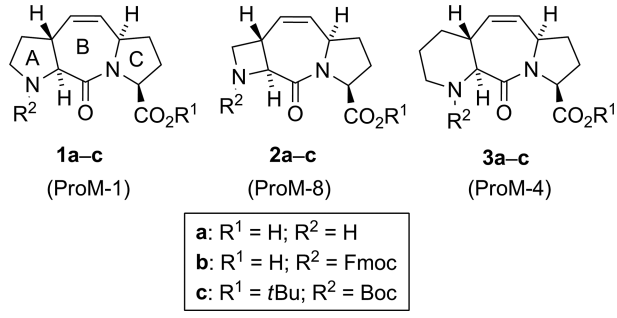

Figure 1. The diproline analog ProM-1 and its lower and higher homologs ProM-8 and ProM-4, respectively, as tricyclic scaffolds rigidified in a PPII helix conformation.

During investigations we learned, however, that not all diproline units of a PRM can just be replaced by **1a** and that, following our approach, the development of efficient and selective ligands for specific PRM-binding domains will require a combination of different ProMs with various conformational and steric features.[5] Consequently, we were interested in the lower and higher homologues of **1a**, i.e. azetidine- and piperidine-based scaffolds **2a** (ProM-8) and **3a** (ProM-4), respectively, which differ from **1a** (ProM-1) only in the size of the "eastern" heterocyclic ring (ring A). We here report the stereoselective synthesis of fluorenylmethyloxycarbonyl (Fmoc)-protected scaffolds **2b** and **3b** as well as the conformational analysis of these tricyclic ring systems based on data from X-ray crystallography, NMR spectroscopy and quantum chemical calculations.

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Results and Discussion

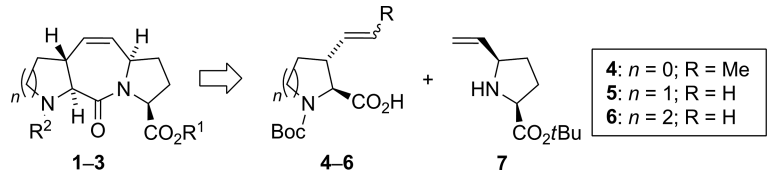
Synthetic Strategy

We decided to follow a similar strategy for the synthesis of **1b**[4] by building up the tricyclic scaffolds **2b** and **3b**, respectively, through peptide coupling and subsequent ring-closing metathesis (Scheme 1).[5] Therefore, a crucial challenge of the present study was the stereoselective synthesis of the required building blocks of type **4**, **6** and **7**.

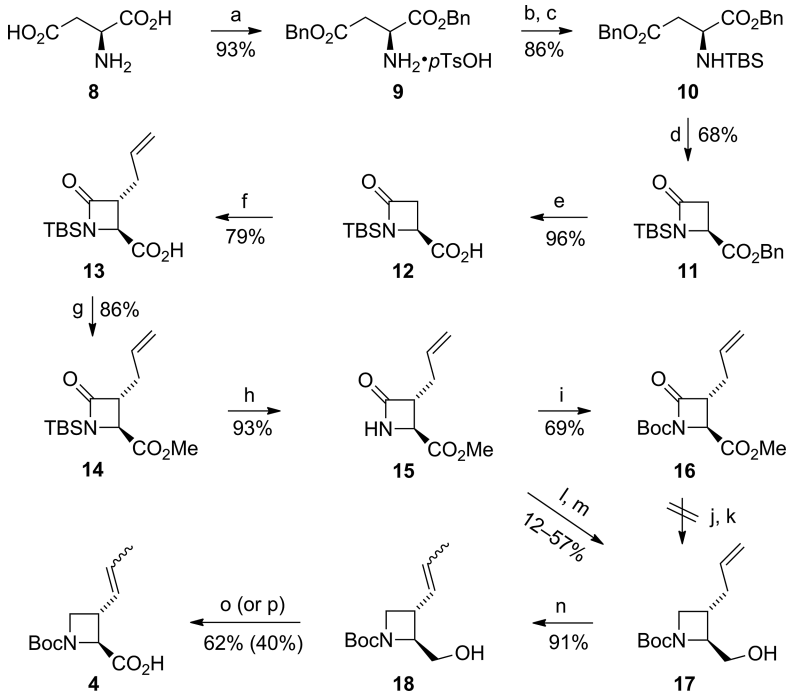
Synthesis of the Azetidine Building Block 4

The synthesis of *N*-*tert*-butoxycarbonyl-(Boc-)protected azetidine building block **4** (Scheme 2) began with conversion of inexpensive L-aspartic acid (**8**) into β-lactam **13** by following the route of Baldwin.[6] For this purpose, **8** was first converted into its dibenzyl ester, which was isolated as crystalline hydro tosylate **9**. After treatment with aqueous K_2CO_3 the (sensitive) free amine was directly *N*-protected with *tert*-butyldimethylsilyl (TBS) chloride to give **10** on a 15-gram scale. Screening of different Grignard reagents (R-MgCl; R = *t*Bu, Bu, Et, *i*Pr) revealed that the cyclization of **10** was most efficiently achieved with *t*BuMgCl to afford β-lactam **11** in 68% yield after (a first) chromatographic purification.[6,7] Hydrogenolytic cleavage of the benzyl ester (H_2, Pd/C) and subsequent *trans*-diastereoselective allylation of carboxylic acid **12** (through dianion formation) afforded **13** in good overall yield ($dr > 95:5$).[6a,8]

Although treatment of **13** with diazomethane in Et_2O/MeOH afforded methyl ester **14** in high yield, various attempts to convert β-lactams **13** or **14** into the corresponding azetidine derivative through amide reduction (deoxygenation)[9] failed. We tried a variety of reagents such as $LiAlH_4$,[10] diisobutylaluminium hydride (DIBAL-H),[11] $LiEt_3BH$[12] and AlH_2Cl (generated from DIBAL-H and $AlCl_3$)[13] under different conditions, but this resulted either in the opening of the four-membered ring or afforded an inseparable mixture of products. Therefore, we decided to change the *N*-protecting group. Cleavage of the TBS group



Scheme 1. Strategy for the synthesis of compounds of type **1**–**3**.



Scheme 2. Synthesis of azetidine building block **4**. *Reagents and conditions:* (a) BnOH, *p*TsOH, benzene, 105 °C, 8 h; (b) K_2CO_3, CH_2Cl_2; (c) TBSCl, DMAP, Et_3N, CH_2Cl_2, room temp., 16 h; (d) *t*BuMgCl, Et_2O, room temp., 16 h; (e) H_2, Pd/C, THF, room temp., 24 h; (f) LDA (2.2 equiv.), allyl bromide, THF, room temp., 3 h, $KHSO_4$ (aq.); (g) CH_2N_2, MeOH, room temp., 1 h; (h) CsF, MeOH, room temp., 1 h; (i) Boc_2O, DMAP, Et_3N, CH_2Cl_2, room temp., 16 h; (j) $LiBEt_3H$, THF, –78 °C, 1 h; (k) $BF_3{\cdot}OEt_2$, Et_3SiH, CH_2Cl_2, –78 °C, 3 h; (l) $LiAlH_4$, THF, room temp., 76 h; (m) Boc_2O, CH_2Cl_2, room temp., 6 h; (n) $RhCl_3{\cdot}3H_2O$, EtOH, reflux, 16 h; (o) TEMPO, BAIB, $NaHCO_3$, H_2O/MeCN, room temp., 3 h; (p) Jones reagent, acetone, room temp., 3 h.

with cesium fluoride gave **15** from which *N*-Boc derivative **16** was obtained under standard conditions. Attempts to convert **16** into azetidine **17** by subsequent treatment with $LiEt_3BH$ and Et_3SiH only resulted in the formation of an acyclic amino alcohol. However, the desired azetidine was finally obtained by reduction of unprotected β-lactam **15** with 4 equiv. of $LiAlH_4$[10a,10b] followed by *N*-Boc protection. On a small scale, product **17** was obtained in 57% yield (over 2 steps) but lower yields (12–36%) were observed when the reaction sequence was repeated on a multi mmol scale. Nevertheless, with substantial amounts of **17** in hand, completion of the synthesis could be attempted. Isomerization of the allyl to a propenyl side chain was achieved in 91% yield by treatment of **17** with $RhCl_3$ trihydrate (10 mol-%) in EtOH[14] to afford **18** (*E*/*Z* = 3.1:1). The final oxidation of the alcohol functionality with Jones reagent gave acid **4** in moderate yield (40%) after chromatographic purification. As an alternative, oxidation of **18** was performed by using the protocol of Epp and Widlandski[15] that uses catalytic amounts of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) in the presence of 2 equiv. of bis(acetoxy) iodobenzene (BAIB)[16] in 1:1 MeCN/H_2O (62% yield). In this case, no chromatographic purification was required as, after basic extraction, carboxylic acid **4** was obtained in pure form. The *trans*-configuration was confirmed by 2D NMR spectroscopy (H,H-COSY, NOESY).

Synthesis of Piperidine Building Block *rac*-6

In analogy to our synthesis of 3-vinylproline derivatives[4b] we decided to synthesize corresponding piperidine system **6** through Cu-catalyzed 1,4-addition of vinylmagnesium bromide to a *N*-protected dehydroamino acid intermediate.[17] By starting from racemic pipecolic acid (*rac*-**19**) double protected derivative *rac*-**21** was prepared through methyl ester formation (MeOH, $SOCl_2$) and *N*-Boc protection (Boc_2O, Et_3N) (Scheme 3). Without purification, product *rac*-**21** was obtained in nearly quantitative yield and then converted into dehydro derivative **22** by applying the bromination/elimination protocol of Kublitskii and Trukhan.[18] Thus, after α-lithiation of *rac*-**21** with lithium bis(trimethylsilyl)amide (LiHMDS) in tetrahydrofuran (THF) at –30 °C, bromination at –90 °C and final elimination of the unstable bromo intermediate (by stirring with aqueous citric acid), α,β-unsaturated ester **22** was obtained in 71% isolated yield, and its structure was confirmed by X-ray crystallography (Figure 2). The Cu-catalyzed 1,4-vinylation (1.5 equiv. of vinyl-MgBr, 0.2 equiv. of $CuBr{\cdot}SMe_2$, –35 °C, 6 h) afforded desired *trans*-product *rac*-**23** in 32% isolated yield after separation of the minor *cis*-isomer (and side products resulting from 1,2-addition to the ester group) by column chromatography. Finally, the ester was hydrolyzed with LiOH in H_2O/THF/MeOH at 50 °C to afford carboxylic acid building block *rac*-**6** without epimerization at C2.

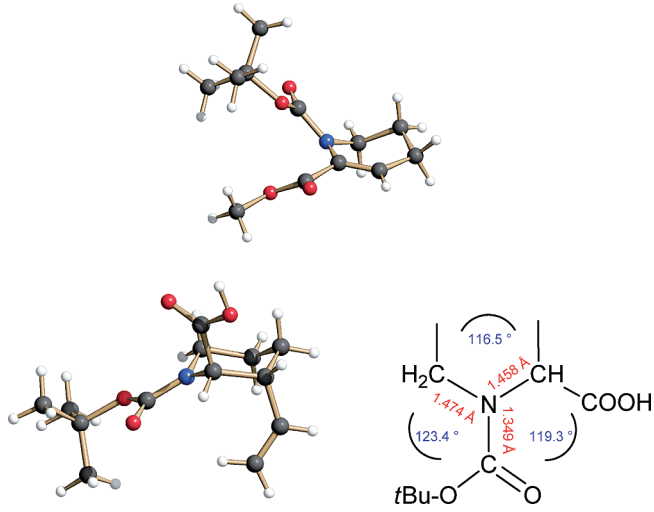
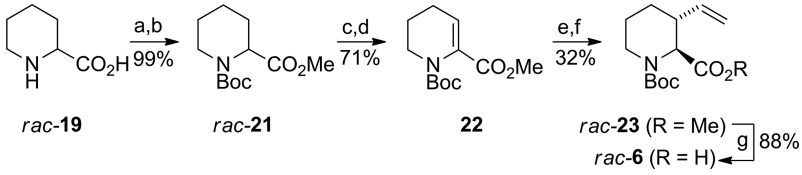


Figure 2. Structure of **22** (top) and *rac*-**6** (bottom) in the crystalline state; the bond lengths and angles around the N atom of **6** are shown separately.

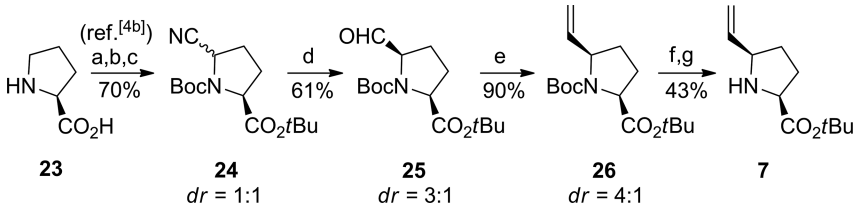
The required *trans*-configuration of *rac*-**6** was confirmed by X-ray crystal structure analysis (Figure 2). Interestingly, both *C*-bound substituents at the aza-cyclohexane chair demand an axial position in this case (to minimize repulsive steric interactions) whereas the carbamate C–N bond clearly exhibits double bond character, with a C–N bond length of 1.35 Å. The angular sum (359.2°) indicates almost perfect planar geometry at the nitrogen center.

Synthesis of Pyrolidine Building Block 7

cis-Vinylproline building block **7**, required for both ProM-4 and ProM-8, was synthesized according to a strategy developed in our laboratory (Scheme 4).[4b] A crucial step of this synthesis is the conversion of nitrile **24**, which is readily prepared in three steps from (*S*)-proline (**23**), into aldehyde **25**. In the original procedure, **24** was stirred with *Raney*-Ni under an atmosphere of hydrogen in slightly basic



Scheme 3. Synthesis of building block *rac*-**6**. *Reagents and conditions:* (a) $SOCl_2$, MeOH, room temp., 16 h; (b) Boc_2O, Et_3N, dioxane/H_2O, room temp., 8 h; (c) LiHMDS, THF, –30 °C, 3.5 h; (d) Br_2, –90 °C, 1 h to room temp., then citric acid H_2O, 30 min; (e) vinyl-MgBr, $CuBr{\cdot}SMe_2$, THF, –35 °C, 6 h, then NH_4Cl, H_2O; (f) column chromatography; (g) LiOH, THF/MeOH/H_2O, 50 °C, 5 h.



Scheme 4. Synthesis of building block **7**. *Reagents and conditions:* (a) *t*BuOH, Boc_2O, Et_3N, room temp., 4 h; DMAP, room temp., 16 h; HCl (1 N), 50 °C, 1 h; (b) –2 e^-, 260 mA, MeOH, Bu_4NBF_4, 0 °C, 2.32 F mol^{-1}; (c) TMSCN, TMSOTf (1 vol.-%), CH_2Cl_2, –40 °C, 1.5 h; (d) H_2, *Raney*-Ni, Py/AcOH/H_2O, 50 °C, 5 h; (e) KHMDS, Ph_3PCH_3Br, THF, room temp. 1 h, then –78 °C to room temp., 2.5 h; (f) TMSOTf, CH_2Cl_2, 0 °C, 5 min; (g) separation of diastereomers by column chromatography.

medium (pyridine, water, acetic acid) at 80 °C to afford the product after 72 h in only moderate yield (51%) as a 1.7:1 (*cis*/*trans*) mixture of diastereomers. By bubbling a continuous flow of hydrogen through the reaction mixture and by lowering the temperature to 50 °C the reaction proceeded faster and product **25** was obtained after only 5 h in higher yield (61%) and with significantly improved diastereoselectivity (*cis*/*trans* = 3:1).

The conversion of the aldehyde into a vinyl side chain was achieved in 90% yield through Wittig reaction by using oven-dried Ph_3PCH_3Br and KHMDS to afford **26**, still as a mixture of diastereomers (*cis*/*trans* = 4:1). After selective cleavage of the *N*-Boc protection group with trimethylsilyl trifluoromethanesulfonate (TMSOTf), the diastereomers could be separated by column chromatography and desired *cis*-3-vinylproline ester **7** was obtained as a pure diastereomer in 43% isolated yield on a multi-gram scale.

Synthesis of Tricyclic Scaffold 2b (Fmoc-ProM-8)

The synthesis of ProM-8 (as its Fmoc derivative **2b**) was concluded as shown in Scheme 5. Building blocks **4** and **7** were connected through peptide coupling [by using (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP)] to give dipeptide **27** in 78% yield. After treatment of **27** with 10 mol-% of Grubbs II catalyst in CH_2Cl_2 at reflux temperatures, the tricyclic product **2c** was obtained in 46% yield. The yield of the ring closing metathesis reaction could not be significantly improved by increasing the amount of catalyst, by prolonging the reaction time, or by running the reaction at lower temperature. The final conversion of **2c** into **2b** was achieved by following our standard procedure[4b] by global deprotection [with trifluoroacetic acid (TFA)] and subsequent Fmoc-protection of the amino function to afford target compound **2b** in 76% yield.

Synthesis of Tricyclic Scaffold 3b (Fmoc-ProM-4)

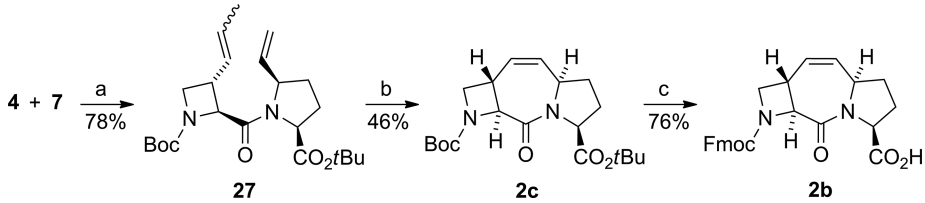
By employing building blocks *rac*-**6** and **7** the synthesis of **3b** (Fmoc-ProM-4) was performed in a similar fashion as described above for the synthesis of **2b** (Scheme 6). Thus, PyBOP coupling of *rac*-**6** with **7** cleanly afforded **28** as an expected mixture of diastereomers, which could not be separated. However, subsequent ring-closing metathesis (by using 20 mol-% of Grubbs II catalyst) proceeded smoothly, and the two diastereomeric tricyclic products were readily separable by column chromatography. Thus, both isomers, i.e. **3c** and *dia*-**3c**, were isolated in pure form in 42% yield each.

The relative configuration of **3c** and *dia*-**3c**, respectively, was unambiguously assigned by X-ray crystallography (see Figure 3), which also revealed the preferred conformation of the tricyclic scaffolds.

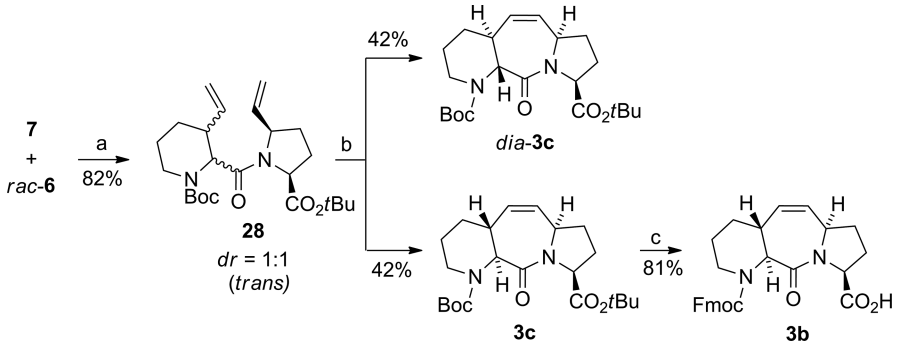
By having successfully constructed the ring system of ProM-4 with the correct configuration, the final conversion of **3c** into Fmoc-protected derivative **3b** was performed (in 81% yield) by following the established procedure (Scheme 6).

We also converted diastereomeric cyclization product *dia*-**3c** into corresponding Fmoc derivative *dia*-**3b** under standard conditions (Scheme 7). Of note, we found that selective cleavage of the *N*-Boc group is also possible in the presence of the *tert*-butyl ester function. Thus, when *dia*-**3c** was treated with an excess TFA at 0 °C (instead of at room temp) for 1 h followed by Fmoc-protection of deprotected intermediate **29**, ester *dia*-**3d** was obtained in 76% yield.

To probe whether TFA-mediated selective cleavage of a *N*-Boc carbamate in the presence of a *tert*-butyl ester function can also be applied to other substrates, we chose L-*N*-Boc *tert*-butylproline **30** as a model substrate, which had served as an intermediate in the synthesis of building block **7** (see Scheme 4). And indeed, treatment of **30** with an ex-



Scheme 5. Synthesis of **2b** (Fmoc-ProM-8). *Reagents and conditions:* (a) PyBOP, DIPEA, MeCN, room temp., 16 h; (b) Grubbs II catalyst (10 mol-%), CH_2Cl_2, reflux, 24 h; (c) TFA, CH_2Cl_2, room temp., 1 h; $NaHCO_3$, Fmoc-Cl, THF, room temp., 16 h.



Scheme 6. Synthesis of **3b** (Fmoc-ProM-4). *Reagents and conditions:* (a) PyBOP, DIPEA, MeCN, room temp., 20 h; (b) Grubbs II catalyst (20 mol-%), CH_2Cl_2, reflux, 48 h; (c) TFA, CH_2Cl_2, room temp., 1 h; $NaHCO_3$, Fmoc-Cl, THF, room temp., 16 h.

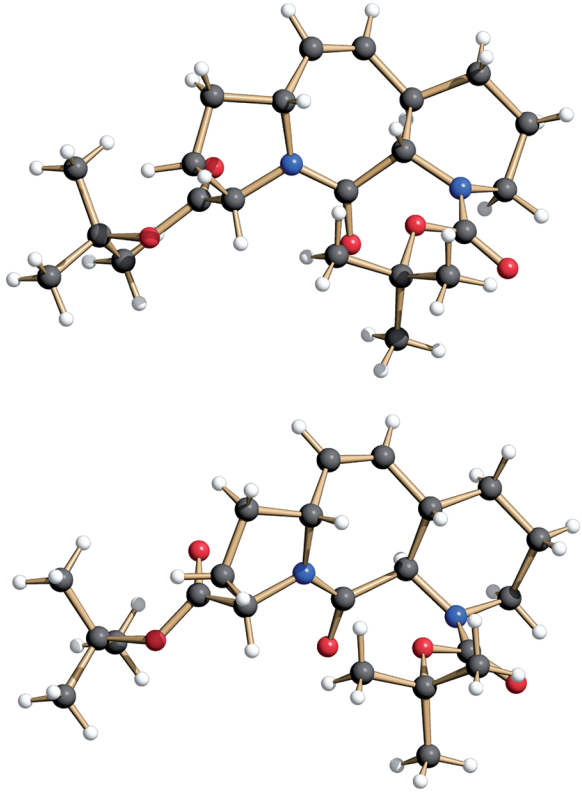
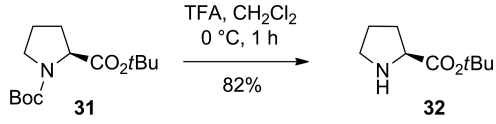


Figure 3. Structure of tricyclic scaffolds **3c** (top) and *dia*-**3c** (bottom) in the crystalline state.

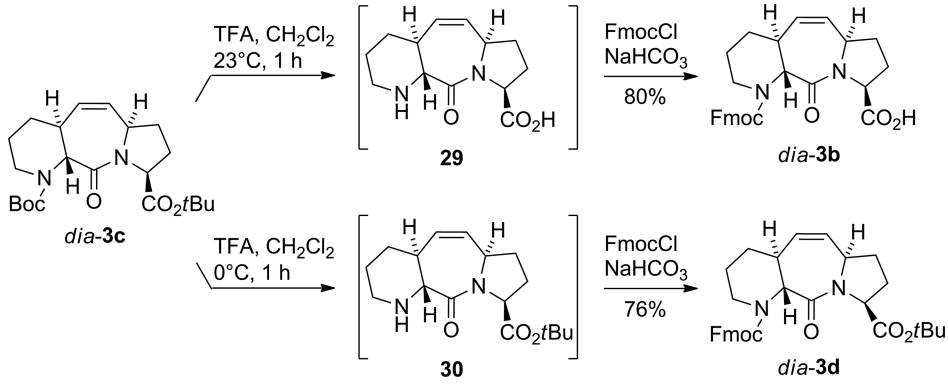
cess of TFA in CH_2Cl_2 at 0 °C resulted in a clean transformation to afford amine **31** in 82% isolated yield (Scheme 8).



Scheme 8. Selective *N*-Boc deprotection of *tert*-butyl ester **30**.

Conformational Analysis

As mentioned in the introduction, an important aspect of the present study was to create a homologues series of rigid scaffolds that mimic a diproline unit in the PPII helix conformation (i.e. **1**, **2** and **3**), which differ slightly in their geometry. By having successfully achieved the syntheses, we next performed a careful conformational analysis to identify the structural consequences of ring-size variation. For this purpose we calculated the energy minima of all possible rotamers of *N*-Boc-protected *tert*-butyl esters **1c**, **2c** and **3c** by using TURBOMOLE 6.3[19] in combination with geometry optimization (functional: TPSS; basis set: TZVPP) and successive frequency calculations. As Figure 4 shows, the calculated geometry of the tricyclic core structure of **1c** almost perfectly matches the geometry of this compound in the crystalline state. Even the conformation of the Boc pro-



Scheme 7. Global deprotection or selective *N*-Boc cleavage of *dia*-**3c** by treatment with excess TFA at either 23 °C or 0 °C, respectively, and subsequent Fmoc protection.

tecting groups differs only slightly between the calculated and the X-ray structure of **1c**.[20]

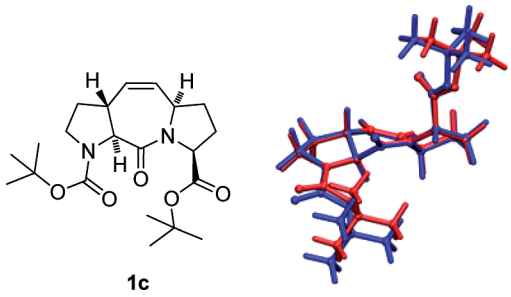


Figure 4. Structure of **1c** in the crystalline state (red) relative to the calculated minimum conformation (blue).

To structurally compare three homologues compounds **1c**, **2c**, and **3c** we superimposed the central amide units of the calculated lowest energy conformers as shown in Figure 5. Obviously, the geometry of rings B and C (including the *tert*-butyl ester side chain) is almost identical for all three compounds, whereas subtle but significant deviations emerge from the variation of the A-ring size. Most notably, the twist of the pseudo-dipeptidic core structure differs in the three structures, as indicated by the different exit vectors defined by the exocyclic N–C bond at ring A. Also, the steric demand of the lipophilic part of ring A decreases in the homologous series from **3c** to **1c** to **2c**.

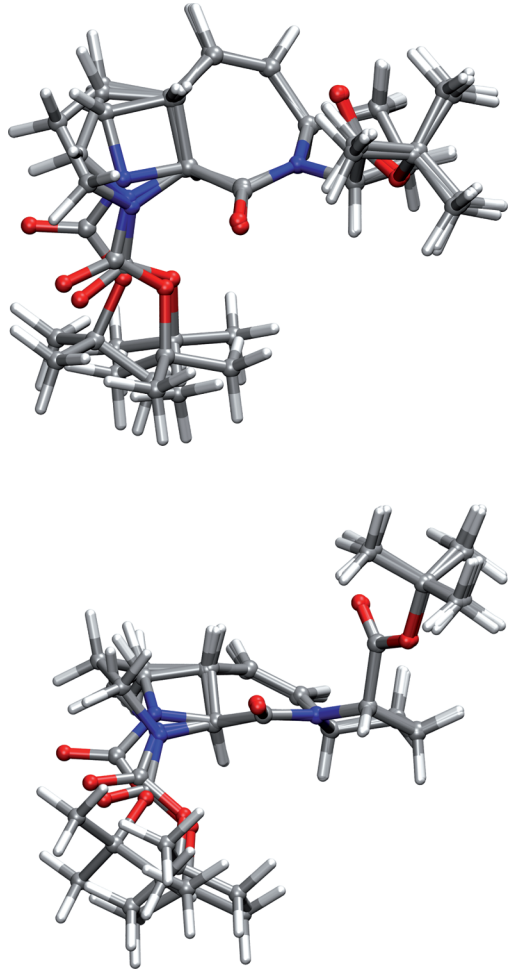


Figure 5. Comparison of the (calculated) geometries of **1c**, **2c**, and **3c**. The superimposed structures are shown from two different perspectives.

Another interesting aspect is the effect of the ring size on the structural flexibility of the three systems as reflected by their different NMR spectroscopic behavior. In contrast to **1c**, which shows two major signal sets in the ^{1}H NMR ($CDCl_3$, 300 MHz, 20 °C) spectrum that represents two distinct conformations (rotamers; ratio 2:1) along the C–N bond of the *N*-Boc unit, the corresponding spectrum of azetidine derivative **2c** exhibits only a single set of signals. This observation reflects a lower rotational barrier. In the case of piperidine derivative **3c**, the ^{1}H NMR spectrum (300 or 600 MHz) at room temperature did not allow any assignments because of severe signal broadening (coalescence) and the presence of superimposed rotamer signals. However, at lower temperatures (below –30 °C) two major rotamers are detected (ratio 1:1.5). All in all it could be shown that modified systems ProM-4 (**3c**) and ProM-8 (**2c**) exhibit a slower conformational dynamic relative to original system **1c** (ProM-1) with five-membered ring C.

Conclusions

In summary, we have elaborated stereoselective synthetic routes to homo- and nor-proline derivatives **4** and *rac*-**6**, to complete a homologues series of 3-vinylproline-related building blocks, which were subsequently employed for the construction of the new tricyclic scaffolds ProM-4 and ProM-8 (as their Fmoc-protected derivatives **2b** and **3b**). Like the original scaffold ProM-1, these compounds represent conformationally defined diproline mimetics, rigidified in a PPII conformation. Subtle structural differences between the three scaffolds were identified by careful conformational analysis (based on X-ray data and quantum chemical calculations). In addition, differences in the conformational dynamics were revealed by NMR spectroscopic measurements. The new scaffolds described here will be employed in future as modules of our ProM-based construction kit for the modeling-guided development of specific small molecule interface inhibitors for (so far undruggable) PPII-mediated protein–protein interactions.

Experimental Section

General: All oxygen- or moisture-sensitive reactions were carried out under an argon atmosphere. All glassware was flame-dried under vacuum before use and flushed with argon. Solids were added under a continuous flow of argon. Syringes and cannulas were flushed with argon before use. If not otherwise indicated, chemicals were employed without further purification. All solvents were dried and distilled before use. THF was distilled from sodium/benzophenone under argon. Dichloromethane was distilled from calcium hydride under argon. Dry acetonitrile was purchased from Acros (99.5%, extra dry over molecular sieves). The concentration of Grignard reagents was determined by titration against iodine dissolved in a solution of LiCl (0.5 M) in THF. NMR spectra were

recorded at room temp with a Bruker DPX 300, Avance II 300, DRX 500, Avance II$^+$ 600. The spectra are reported by using the following abbreviations to express the multiplicities: s = singlet, d = doublet, t = triplet, dd = double doublet, td = triple doublet, tt = triple triplet, ddd = double double doublet, qd = tetra doublet, m = multiplet, br. s = broad singlet. Most ^{13}C NMR spectra were recorded with a DeptQ or APT sequence with complete proton decoupling. The non-trivial assignments are based on H,H-COSY, HMQC, HMBC, NOESY and single proton NOE spectra. Preparative electrolysis was performed with a Voltcraft VLP-1602 Pro power supply and Didac-Tec 48 × 28 mm graphite plate electrode. Commercial methanol was used without further purification. IR spectra were recorded in ATR mode (attenuated total reflection) at room temp on a Paragon 100 FTIR spectrometer from Perkin–Elmer. The absorptions are characterized by the abbreviations w (weak), medium (m) strong (s). HRMS and low-resolution MS were measured with a Finnigan MAT 900s (ESI). Melting points were determined with a Büchi B-545 in open capillary tubes or with a Wagner und Munz Mikro-Heiztisch System PolyTherm A. Analytical thin layer chromatography was performed on silica coated alumina plates that contained a fluorescent indicator, visualized by UV light, by treatment with a cerium reagent [prepared by dissolving phosphomolybdic acid (2 g) and $Ce(SO_4)_2$ (1 g) in a mixture of concentrated H_2SO_4 (10 mL) and water (90 mL)] or with a $KMnO_4$ solution (0.5% solution in 1 M NaOH) followed by heating. Flash column chromatography was conducted by using either silica gel DAVISIL®LC60A 40–63 μm from GRACE DIVISION or Allox N for column chromatography 50–200 μm, Brockmann I from ACROS. X-ray measurements were carried out with a Nonius Kappa CCD diffractometer. Optical rotation was measured with a Perkin–Elmer Polarimeter 343 with a cuvette path length of 10 cm. Concentrations are given in g/100 mL of solvent.

L-Aspartic Acid Dibenzyl Ester *p*-Toluenesulfonate (9):[21] To L-aspartic acid **8** (90.0 g, 0.676 mol) and benzyl alcohol (422 mL, 4.057 mol) in benzene (650 mL) was added *p*-toluenesulfonic acid monohydrate (160.7 g, 0.845 mol) at 80 °C before heating the mixture to reflux for 8 h under removal of water by means of a Dean–Stark apparatus. After cooling to room temp the solvent was removed under reduced pressure. The remaining white solid was washed with methyl *tert*-butyl ether (MTBE; 3 × 1 L) and dried for 8 h at 80 °C in vacuo to give sulfonate **9** (306.9 g, 0.630 mol, 93%) as a white solid. $[\alpha]_D^{20}$ = +6.9 (*c* = 1.100 , $CHCl_3$) {ref.[21] $[\alpha]_D^{20}$ = +5.2 (*c* = 1.000 , $CHCl_3$)}, m.p. 158 °C {ref.[21] 155–156 °C}. R_f = 0.54 (EtOAc/cyclohexane = 1:1). ^1H NMR: (300 MHz, $CDCl_3$): δ = 2.25 (s, 3 H, 7-H), 3.00–3.20 (qd, *J* = 18.1, 4.7 Hz, 2 H, 3-H), 4.48 (s, 1 H, 4-H), 4.88–5.04 (m, 4 H, 5-H), 6.98 (d, *J* = 7.8 Hz, 2 H, 9-H), 7.16–7.25 (m, 10 H, H-Ar), 7.71 (d, *J* = 7.8 Hz, 2 H, 10-H), 8.39 (br. s, 3 H, -NH_3^+) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 21.3 (C7), 33.8 (C3), 49.6 (C2), 67.1; 68.2 (C5), 126.1 (C10), 126.2–128.4 (C-Ar_t), 128.8 (C9), 134.5; 135.1 (C6), 140.2 (C11), 141.3 (C8), 167.9 (C1), 169.8 (C4) ppm. IR: $\tilde{\nu}$ = 3446 (w), 3026 (m), 2948 (m), 1745 (s), 1731 (s), 1592 (m), 1529 (m), 1183 (m), 1126 (m), 1034 (s), 1010 (s), 695 (s) cm^{-1}. GC–MS (EI): *m*/*z* (%) = 314 (1), 178 (32), 91 (100), 65 (16).

Dibenzyl (*S*)-2-(*tert*-Butyldimethylsilylamino)succinate (10): Sulfonate **9** (152.3 g, 0.314 mol) was dissolved in aqueous K_2CO_3 (1 M, 2 L) and the solution was extracted with CH_2Cl_2 (3 × 1 L). The combined organic layers concentrated in vacuo and the crude product (yellow oil) was dissolved in CH_2Cl_2 (1.5 L). After addition of TBSCl (43.7 g, 0.290 mol), 4-(dimethylamino)pyridine (DMAP; 1.7 g, 0.014 mol) and Et_3N (88.5 mL, 0.635 mol) the mixture was stirred for 16 h under argon before it was quenched with saturated aqueous NH_4Cl (1.2 L). After extraction with CH_2Cl_2 (1.5 L) the combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine (1.2 L) and dried with $MgSO_4$. After removal of the solvent under reduced pressure succinate **10** was obtained as yellow oil (116.0 g, 0.271 mol, 86%), which was used without further purification. $[\alpha]_D^{20}$ = –18.4 (*c* = 0.930, $CHCl_3$). R_f = 0.32 (Et_2O/cyclohexane = 1:1). ^1H NMR: (300 MHz, $CDCl_3$): δ = 0.01; 0.13 (2 × s, 6 H, 7-H), 0.86 (s, 9 H, 9-H), 2.67–2.82 (m, 2 H, 3-H), 3.88–3.96 (m, 1 H, 2-H), 5.06–5.17 (m, 4 H, 5-H), 7.26–7.35 (m, 10 H, H-Ar) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$): δ = –5.2; –3.7 (C7), 0.8 (C8), 25.9 (C9), 41.8 (C3), 52.5 (C2), 66.4; 66.7 (C5), 128.2–128.4 (C-Ar_t), 135.6 (C1, C4), 170.5 (C1), 174.3 (C4) ppm. IR: $\tilde{\nu}$ = 3381 (w), 3031 (w), 2949 (s), 2852 (m), 1732 (s), 1596 (w), 1496 (m), 1454 (s), 1406 (m), 1378 (m), 1250 (s), 1210 (s), 1152 (s), 1026 (m), 1002 (s), 829 (s), 749 (s), 695 (s) cm^{-1}. GC–MS (EI): *m*/*z* (%) = 428 (1), 412 (2), 370 (24), 292 (30), 178 (19), 91 (100), 57 (2).

Benzyl (*S*)-1-(*tert*-Butyldimethylsilyl)-4-oxoazetidine-2-carboxylate (11):[6a] Under argon atmosphere dibenzyl aspartate **10** (44.2 g, 0.103 mol) was dissolved in Et_2O (500 mL) and the solution was cooled to 0 °C before *t*BuMgCl (56.5 mL, 0.113 mol, 2.0 M in Et_2O) was added dropwise over 45 min. The resulting yellow suspension was stirred at room temp overnight before the mixture was quenched at 0 °C with saturated aqueous NH_4Cl (100 mL) and extracted with Et_2O (2 × 200 mL). The combined organic layers were washed with H_2O (200 mL) and brine (200 mL), dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by chromatography (SiO_2, EtOAc/cyclohexane = 1:3) to give β-lactam **11** (21.7 g, 0.070 mol, 68%) as a yellow oil. $[\alpha]_D^{20}$ = –38.4 (*c* = 0.500, $CHCl_3$) {ref.[6a] $[\alpha]_D^{20}$ = –61.2 (*c* = 1.550 , $CHCl_3$)}. R_f = 0.61 (EtOAc/cyclohexane = 1:2). ^1H NMR: (300 MHz, $CDCl_3$): δ = 0.06; 0.24 (2 × s, 6 H, 8-H), 0.93 (s, 9 H, 10-H), 3.04/3.31 (2 × m, 2 H, 3-H), 4.06 (m, 1 H, 2-H), 5.18 (s, 2 H, 6-H), 7.36 (s, 5 H, H-Ar) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$): δ = –6.4; –6.0 (C8), 18.4 (C9), 26.1 (C10), 43.9 (C3), 48.7 (C2), 67.2 (C6), 128.5–128.6 (C-Ar_t), 134.9 (C7), 171.0 (C4), 172.0 (C5) ppm. IR: $\tilde{\nu}$ = 2946 (m), 2927 (m), 2855 (m), 1740 (s), 1496 (w), 1469 (m), 1347 (m), 1275 (s), 1172 (s), 1076 (s), 1012 (s), 936 (m), 823 (s), 748 (s), 696 (s) cm^{-1}. GC–MS (EI): *m*/*z* (%) = 320 (1), 262 (2), 91 (100), 57 (10).

(*S*)-1-(*tert*-Butyldimethylsilyl)-4-oxoazetidine-2-carboxylic Acid (12):[6a] To a solution of β-lactam **11** (25.3 g, 0.079 mol) in THF (130 mL) was added Pd/C (2.0 g) and the mixture was intensively stirred under an atmosphere of hydrogen (balloon) at room temp for 24 h. The suspension was filtered with THF (150 mL) through a short pad of Celite® and the solvent was removed under reduced pressure to give carboxylic acid **12** (17.5 g, 0.076 mol, 96%) as a white solid, which was used without further purification. $[\alpha]_D^{20}$ = –77.1 (*c* = 0.500, $CHCl_3$) {ref.[6a] $[\alpha]_D^{20}$ = –71.7 (*c* = 1.030 , $CHCl_3$)}, m.p. 142 °C {ref.[6a] 147–148 °C}. R_f = 0.38 (EtOAc/cyclohexane = 2:1). ^1H NMR: (300 MHz, $CDCl_3$): δ = 0.16; 0.30 (2 × s, 6 H, 6-H), 0.96 (s, 9 H, 8-H), 3.11 (dd, *J* = 15.3, 2.6 Hz, 1 H, 3-H_β), 3.40 (dd, *J* = 15.3, 6.0 Hz, 1 H, 3-H_α), 4.07 (dd, *J* = 5.9, 2.7 Hz, 1 H, 2-H), 9.05 (br. s, 1 H, -COOH) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$): δ = –6.3; –6.6 (C6), 18.5 (C7), 26.1 (C8), 43.8 (C3), 48.6 (C2), 171.5 (C5), 180.0 (C4) ppm. IR: $\tilde{\nu}$ = 2922 (s), 2853 (s), 2706 (m), 2593 (m), 2506 (m), 1734 (s), 1684 (s), 1464 (m), 1341 (s), 1315 (s), 1254 (s), 1215 (s), 1186 (s), 1104 (m), 1086 (m), 1022 (m), 1003 (m), 964 (m), 839 (s), 820 (s), 781 (s), 681 (m) cm^{-1}.

(2*S*,3*R*)-3-Allyl-1-(*tert*-butyldimethylsilyl)-4-oxoazetidine-2-carboxylic Acid (13):[6a] Under an argon atmosphere, a Schlenk tube was charged with carboxylic acid **12** (16.7 g, 0.073 mol) in THF (100 mL) and the solution was cooled to 0 °C. A solution of lithium diisopropylamide (LDA; 0.153 mol) in THF, freshly prepared in a

separate flask, was then added dropwise over 10 in through a cannula to give a deep red solution. After 15 min, allyl bromide (13.9 mL, 0.160 mol) was added at 0 °C and the now pale yellow solution was allowed to stir at room temp for 3 h. After addition of aqueous $KHSO_4$ (1 M, 700 mL), the mixture was extracted with EtOAc (700 mL). The organic phases were washed with aqueous $KHSO_4$ (1 M, 700 mL) and brine (700 mL), dried with $MgSO_4$ and concentrated under reduced pressure to give β-lactam **13** (15.5 g, 0.058 mol, 79%) as a white solid. $[\alpha]_D^{20}$ = –69.1 (c = 1.000, $CHCl_3$) {ref.[6a] $[\alpha]_D^{20}$ = –68.6 (c = 1.000 , $CHCl_3$)}, m.p. 136 °C (2 × Et_2O/hexane) {ref.[6a] 112–114 °C}. R_f = 0.48 (MeOH/CH_2Cl_2 = 1:30). ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 0.13; 0.30 (2 × s, 6 H, 9-H), 0.96 (s, 9 H, 11-H), 2.44–2.61 (m, 2 H, 6-H), 3.42 (m, 1 H, 3-H), 3.81 (m, 1 H, 2-H), 5.17 (t, J = 12.7 Hz, 2 H, 8-H), 5.74–5.88 (td, J = 16.9, 6.9 Hz, 1 H, 7-H), 8.77 (br. s, 1 H, -COOH) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$): δ = –6.4; –5.9 (C9), 18.6 (C10), 26.1 (C11), 32.4 (C6), 53.8 (C2), 56.9 (C3), 118.5 (C8), 133.1 (C7), 173.9 (C5), 178.1 (C4) ppm. IR: $\tilde{\nu}$ = 2927 (s), 2853 (s), 2593 (m), 1742 (s), 1703 (s), 1640 (m), 1469 (m), 1413 (m), 1326 (s), 1253 (s), 1183 (s), 1153 (s), 1096 (s), 1068 (s), 1004 (m), 986 (m), 918 (s), 840 (s), 824 (s), 780 (s), 681 (s) cm^{-1}.

Methyl (2*S*,3*R*)-3-Allyl-1-(*tert*-butyldimethylsilyl)-4-oxoazetidine-2-carboxylate (14): A solution of carboxylic acid **13** (15.5 g, 0.058 mol) in MeOH (150 mL) was cooled to 0 °C and a freshly prepared solution of CH_2N_2 (450 mL, 0.250 mol–0.280 mol in Et_2O) was added carefully. The mixture was stirred at room temp for 1 h. After careful removal of the solvent and all volatile compounds the crude product was purified through a pad of silica (EtOAc/cyclohexane = 1:2) to give β-lactam **14** (14.0 g, 0.049 mol, 86%) as a yellow oil. $[\alpha]_D^{20}$ = –49.3 (c = 1.000, $CHCl_3$). R_f = 0.61 (EtOAc/cyclohexane = 1:4). ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 0.09; 0.28 (2 × s, 6 H, 10-H), 0.95 (s, 9 H, 12-H), 2.46–2.53 (m, 2 H, 7-H), 3.33–3.37 (dd, J = 9.0, 3.8 Hz, 1 H, 3-H), 3.75 (s, 3 H, 6-H), 3.77 (d, J = 2.0 Hz, 1 H, 2-H), 5.11–5.19 (m, 2 H, 9-H), 5.74–5.85 (m, 1 H, 8-H) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$): δ = –6.4; –5.9 (C10), 18.5 (C11), 32.4 (C7), 52.3 (C6), 54.0 (C2), 56.7 (C3), 118.2 (C9), 133.3 (C8), 172.6 (C5), 173.4 (C4) ppm. IR: $\tilde{\nu}$ = 2928 (s), 2856 (s), 1749 (s), 1640 (m), 1470 (s), 1435 (s), 1390 (m), 1363 (s), 1280 (s), 1256 (s), 1200 (s), 1176 (s), 1153 (s), 1068 (s), 1026 (s), 1003 (m), 918 (s), 824 (s), 773 (s), 679 (s) cm^{-1}. GC–MS (EI): m/z (%) = 284 (2), 268 (1), 242 (1), 226 (92), 198 (6), 116 (100), 100 (95), 41 (19). HRMS (ESI): calcd. for [M + H]$^+$ 284.16692; found 284.16764.

1-*tert*-Butyl 2-Methyl (2*S*,3*R*)-3-Allyl-4-oxoazetidine-1,2-dicarboxylate (16): Methyl ester **14** (0.600 g, 2.112 mmol) was dissolved in MeOH (21 mL) and CsF (0.481 g, 3.168 mmol) was added. The mixture was stirred at room temp for 1 h before the solvent was removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 (20 mL) and washed with aqueous $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to give a yellow oil (0.340 g), which was dissolved in CH_2Cl_2 (4 mL) in an argon-flushed Schlenk tube. Then, Boc_2O (0.877 g, 4.022 mmol), Et_3N (0.28 mL, 2.011 mmol) and DMAP (0.246 g, 2.013 mmol) were carefully added to give an orange solution (CAUTION: gas evolution!), which was stirred at room temp for 16 h before the solvent was removed under reduced pressure. The residue was purified by chromatography (SiO_2, EtOAc/cyclohexane = 1:2) to give β-lactam **16** (0.363 g, 1.348 mmol, 64%) as a yellow oil. $[\alpha]_D^{20}$ = –45.5 (c = 1.000, $CHCl_3$). R_f = 0.68 (EtOAc/cyclohexane = 1:2). ^{1}H NMR (mixture of rotamers) (300 MHz, $CDCl_3$): δ = 1.50 (s, 9 H, 12-H), 2.43–2.67 (m, 2 H, 7-H), 3.25–3.31 (m, 1 H, 3-H), 3.80 (s, 3 H, 6-H), 4.11 (d, J = 2.9 Hz, 1 H, 2-H), 5.16–5.22 (m, 2 H, 9-H), 5.72–5.86 (tt, J = 13.6, 6.8 Hz, 1 H, 8-H) ppm. ^{13}C NMR (mixture of rotamers) (75 MHz, $CDCl_3$): δ = 27.9 (C12), 31.8. (C7), 52.7 (C2), 54.2 (C3), 54.9 (C6), 84.0 (C11), 118.8 (C9), 132.2 (C8), 164.8 (C10), 169.6 (C4), 175.2 (C5) ppm. IR: $\tilde{\nu}$ = 3073 (w), 2978 (m), 2926 (w), 1806 (vs.), 1749 (s), 1724 (vs.), 1640 (w), 1473 (m), 1436 (s), 1366 (vs.), 1318 (vs.), 1253 (s), 1203 (s), 1143 (vs.), 1076 (s), 1016 (s), 990 (m), 920 (m), 853 (m), 806 (w), 770 (s), 736 (w) cm^{-1}. GC–MS (EI): m/z (%) = 196 (4), 168 (3), 153 (2), 126 (14), 111 (15), 84 (6), 67 (29), 57 (100), 41 (36). HRMS (ESI): calcd. for [M + Na]$^+$ 292.11554; found 284.11556.

Methyl (2*S*,3*R*)-3-Allyl-4-oxoazetidine-2-carboxylate (15): Methyl ester **14** (14.0 g, 49.4 mmol) was dissolved in MeOH (500 mL). After addition of CsF (11.3 g, 74.1 mmol) the mixture was stirred at room temp for 1 h. After removal of the solvent under reduced pressure the crude product was diluted with CH_2Cl_2 (500 mL) and washed with aqueous solution of $NaHCO_3$ (500 mL), distilled H_2O (500 mL) and brine (500 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to give amine **15** (7.8 g, 46.1 mmol, 93%) as a light brown oil, which was used without further purification. $[\alpha]_D^{20}$ = –3.3 (c = 1.000, $CHCl_3$). R_f = 0.33 (MeOH/CH_2Cl_2 = 1:30). ^{1}H NMR: (300 MHz, $CDCl_3$): δ = 2.41–2.59 (m, 2 H, 7-H), 3.32 (t, J = 6.7 Hz, 1 H, 3-H), 3.73 (s, 3 H, 6-H), 3.87 (d, J = 1.7 Hz, 1 H, 2-H), 5.08–5.18 (t, J = 14.4 Hz, 2 H, 9-H), 5.72–5.85 (m, 1 H, 8-H), 6.76 (br. s, 1 H, -NH) ppm. ^{13}C NMR: (75 MHz, $CDCl_3$): δ = 32.0 (C7), 52.4 (C6), 52.5 (C2), 56.4 (C3), 118.0 (C9), 133.0 (C8), 169.1 (C5), 171.5 (C4) ppm. IR: $\tilde{\nu}$ = 3273 (m), 3073 (m), 2946 (m), 2846 (w), 1733 (s), 1653 (m), 1640 (m), 1540 (m), 1436 (m), 1363 (m), 1280 (m), 1263 (m), 1206 (s), 1106 (m), 1053 (m), 993 (m), 920 (m), 760 (m) cm^{-1}. GC–MS (EI): m/z (%) = 169 (1), 111 (48), 84 (20), 67 (100), 39 (34). HRMS (ESI): calcd. for [M + Na]$^+$ 192.06311; found 192.06253.

***tert*-Butyl (2*S*,3*S*)-3-Allyl-2-(hydroxymethyl)azetidine-1-carboxylate (17):** Under argon atmosphere β-lactam **15** (0.200 g, 1.182 mmol) was dissolved in THF (3 mL) and cooled to 0 °C. After dropwise addition of a $LiAlH_4$ solution (5.9 mL, 5.91 mmol, 1 M in THF) the mixture was stirred under an argon atmosphere at room temp for 76 h and quenched at 0 °C with H_2O (0.3 mL). After stirring for 15 min aqueous NaOH (15 wt.-%, 0.3 mL) was added. Stirring was continued for 15 min before addition of H_2O (0.6 mL). After stirring for further 30 min, the slurry was filtered with CH_2Cl_2 (10 mL) through a plug of Celite®. Removal of the solvent gave a pale yellow oil (0.220 g), which was dissolved under an argon atmosphere in CH_2Cl_2 (3 mL) and stirred with Boc_2O (0.515 g, 2.360 mmol) at room temp for 6 h. After removal of the solvent under reduced pressure the crude product was purified by chromatography (SiO2, EtOAc/cyclohexane = 1:2) to give alcohol **17** (0.152 g, 0.669 mmol, 57%) as a light yellow oil. For reproduced reactions on scales above 2 mmol up to 8 mmol the yield decreased to 12–36%. $[\alpha]_D^{20}$ = –2.7 (c = 1.000, $CHCl_3$). R_f = 0.41 (EtOAc/cyclohexane = 1:2). ^{1}H NMR (mixture of rotamers) (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, 11-H), 2.30–2.31 (m, 3 H, 3-H, 6-H), 3.48–3.51 (m, 1 H, 4-H_β), 3.72 (m, 2 H, 5-H), 3.84–3.89 (m, 1 H, 4-H_α), 3.98–4.10 (m, 1 H, 2-H), 4.10–4.20 (br. s, 1 H, -OH), 4.99–5.05 (m, 2 H, H7), 5.59–5.73 (m, 1 H, H6) ppm. ^{13}C NMR (mixture of rotamers) (75 MHz, $CDCl_3$): δ = 27.7; 28.3 (C11), 30.8 (C3), 37.2 (C6), 52.0 (C4), 66.2 (C5), 68.8 (C2), 80.3 (C9), 116.8 (C8), 134.3 (C7), 152.4 (C9) ppm. IR: $\tilde{\nu}$ = 3410 (b), 3071 (w), 2973 (s), 2928 (m), 2880 (m), 1738 (m), 1694 (s), 1667 (s), 1476 (s), 1408 (s), 1364 (s), 1279 (s), 1252 (s), 1139 (s), 1085 (s), 1034 (s), 990 (s), 913 (s), 857 (s), 771 (s) cm^{-1}. GC–MS (EI): m/z (%) = 227 (1), 211 (1), 196 (18), 171 (9), 57 (100). HRMS (ESI): calcd. for [M + Na]$^+$ 250.14136; found 250.14020.

***tert*-Butyl (2*S*,3*S*)-2-(Hydroxymethyl)-3-(prop-1-en-1-yl)azetidine-1-carboxylate (18):** Under an argon atmosphere $RhCl_3 \cdot 3H_2O$ (0.008 g, 0.030 mmol) was stirred in EtOH (2 mL) at 70 °C for 30 min. Alcohol **17** (0.140 g, 0.616 mmol) in EtOH (1 mL) was added to the reaction vessel. The mixture was heated to reflux for 16 h (reaction progress detected by GC–MS), cooled to room temp and filtered with EtOAc (20 mL) through a plug of silica. The crude product was purified by chromatography (SiO_2, EtOAc/cyclohexane = 1:2) to give propenyl alcohol **18** (0.128 g, 0.563 mmol, 91%) as a light yellow oil. $[\alpha]_D^{20}$ = –6.6 (*c* = 0.300, $CDCl_3$). R_f = 0.48 (EtOAc/cyclohexane = 1:2). ^{1}H NMR (mixture of rotamers) (300 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, 11-H), 1.60; 1.68 (2 × d, *J* = 5.3 Hz, & 4.8 Hz, 3 H, 8-H, *E*/*Z*-ratio = 3.1:1), 2.84 (br. s, 1 H, 3-H), 3.59–3.66 (m, 1 H, 4-H_β), 3.71–3.74 (m, 2 H, 5-H), 3.87–3.99 (m, 1 H, 4-H_α), 4.13 (br. s, 1 H, -OH), 5.47–5.59 (m, 2 H, 6-H, 7-H) ppm. ^{13}C NMR (mixture of rotamers) (75 MHz, $CDCl_3$): δ = 13.2; 17.8 (C8), 28.3 (C11), 34.3 (C3), 52.6 (C4), 65.8 (C5), 69.5; 70.0 (C2), 80.4 (10), 126.8; 127.7 (C7), 129.7; 129.9 (C6), 157.4 (C9) ppm. IR: $\tilde{\nu}$ = 3421 (b), 2969 (m), 2928 (m), 2880 (m), 1740 (m), 1697 (s), 1672 (s), 1477 (m), 1453 (m), 1391 (s), 1365 (s), 1275 (s), 1252 (s), 1140 (vs.), 1088 (m), 1038 (m), 965 (m), 931 (w), 856 (w), 772 (w) cm^{-1}. GC–MS (EI): *m*/*z* (%) = 196 (3), 171 (2), 154 (8), 96 (34), 80 (9), 68 (30), 57 (100), 41 (65). HRMS (ESI): calcd. for $[M + Na]^+$ 250.14136; found 250.14128.

(2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-3-(prop-1-en-1-yl)azetidine-2-carboxylic Acid (4). Method A: Propenyl alcohol **18** (0.200 g, 0.880 mmol), BAIB (0.624 g, 1.936 mmol), $NaHCO_3$ (0.148 g, 1.760 mmol) and TEMPO (0.028 g, 0.176 mmol) were dissolved in a mixture of H_2O/MeCN (1:1, 8 mL) and stirred at room temp for 3 h. Aqueous NaOH (7 mL, 1 M) was added until pH 10. The mixture was diluted with MTBE (60 mL) and the separated aqueous layer was washed with MTBE (2 × 50 mL). The combined wash phases were extracted with H_2O (50 mL). The aqueous layers were acidified with HCl (20 mL, 1 M) until pH < 1 and extracted with MTBE (3 × 60 mL). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure to give azetidinecarboxylic acid **4** (0.132 g, 0.547 mmol, 62%) as a colorless oil in excellent purity.

Method B: To freshly prepared chromic acid (1.16 mL, 2.6 M) propenyl alcohol **18** (68.2 mg, 0.030 mmol) in acetone (3.0 mL) was added dropwise at 0 °C and stirred after warming to room temp for 3 h. After quenching with *i*PrOH (5 mL) and H_2O (5 mL) the mixture was extracted with EtOAc (3 × 10 mL) and the organic layer was dried with $MgSO_4$. After removal of the solvent the residue was purified by chromatography (SiO_2, EtOAc/cyclohexane = 1:2 + 1 vol.-% AcOH) to give azetidinecarboxylic acid **4** (29.6 mg, 0.012 mmol, 40%) with slight impurities. $[\alpha]_D^{20}$ = –70.2 (*c* = 0.350, $CHCl_3$). R_f = 0.22 (MeOH/CH_2Cl_2 = 1:50 + 1 vol.-% AcOH). ^{1}H NMR (mixture of rotamers) (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, 11-H), 1.65; 1.70 (2 × d, *J* = 5.3, 4.8 Hz, 8-H, *E*/*Z*-ratio = 3.1:1), 3.25 (m, 1 H, 3-H), 3.64–3.73 (m, 1 H, 4-H_β), 4.01–4.14 (m, 1 H, 4-H_α), 4.44 (m, 1 H, 2-H), 5.53–5.72 (s, 2 H, 6-H, 7-H), 10.95 (br. s, 1 H, -COOH) ppm. ^{13}C NMR (mixture of rotamers) (75 MHz, $CDCl_3$): δ = 13.2; 17.7 (C8), 28.1 (C11), 36.4 (C3), 52.9; 53.6 (C4), 66.1; 66.6 (C2), 81.6 (C10), 128.4; 128.9; 129.0 (C6, C7), 156.7 (C9), 173.5 (C5) ppm. IR: $\tilde{\nu}$ = 2974 (w), 2926 (w), 2886 (w), 1737 (w), 1703 (s), 1659 (s), 1477 (w), 1413 (s), 1392 (s), 1366 (s), 1281 (w), 1246 (w), 1140 (s), 965 (m), 895 (w), 855 (m), 770 (m), 730 (w), 683 (w) cm^{-1}. HRMS (ESI): calcd. for $[M - H]^-$ 240.12303; found 240.12379.

(*rac*)-2-(Methoxycarbonyl)piperidin-1-ium Chloride (*rac*-20):[22] To a suspension of D/L-pipecolic acid *rac*-**19** (10.0 g, 0.077 mol) in MeOH (78 mL) was carefully added $SOCl_2$ (7.3 mL, 0.101 mol) at 0 °C over 1 h (***CAUTION***: gas evolution!). After stirring at room temp for 16 h the solvent was removed under reduced pressure. The white solid was washed with Et_2O (5 × 70 mL) and dried overnight under vacuo to give hydrochloride ***rac*-20** (13.7 g, 0.076 mol, 99%) as a white solid, m.p. 208–209 °C {ref.[22] 206–207 °C}. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.68–2.04 (m, 6 H, 3-H, 4-H, 5-H), 2.88–3.19 (m, 2 H, 6-H), 3.74 (s, 3 H, 8-H), 4.05 (m, 1 H, 2-H), 9.65 (br. s, 2 H, -NH_2^+) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 21.5 (C4), 21.6 (C5), 26.0 (C3), 43.7 (C6), 53.2; 55.9 (C2, C8), 169.6 (C7) ppm. IR: $\tilde{\nu}$ = 3372 (m), 2946 (w), 2900 (w), 2700 (m), 2526 (m), 2413 (w), 1742 (s), 1630 (m), 1583 (w), 1433 (m), 1360 (w), 1330 (w), 1273 (m), 1225 (m), 1206 (m), 1080 (w), 1030 (m), 886 (m) cm^{-1}. GC–MS (EI): *m*/*z* (%) = 143 (2), 128 (1), 100 (1), 84 (100), 56 (34), 41 (7).

1-*tert*-Butyl 2-Methyl (*rac*)-Piperidine-1,2-dicarboxylate (*rac*-21):[23] To a solution of hydrochloride *rac*-**20** (10.0 g, 0.056 mol) in dioxane/water (240 mL, 1:1) was added Boc_2O (14.6 g, 0.067 mol) and Et_3N (18 mL, 0.128 mol). After stirring at room temp for 8 h and acidification (HCl, 2 N) to pH 4 the mixture was extracted with EtOAc (500 mL). The organic layer was washed with brine (500 mL), dried with $MgSO_4$ and concentrated under reduced pressure to give pipecolic carboxylate *rac*-**21** (13.5 g, 0.056 mol, 100%) as a light yellow oil. R_f = 0.66 (EtOAc/cyclohexane = 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16–1.65 (m, 14 H, 3-H, 4-H, 5-H_β, 11-H), 2.13–2.18 (m, 1 H, 5-H_α), 2.88; 3.92 (2 × m, 2 H, 6-H), 3.69 (s, 3 H, 8-H), 4.69–4.85 (m, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7 (C4), 24.7 (C5), 26.8 (C3), 28.2 (C11), 41.0; 42.0 (C6), 51.9 (C8), 53.7; 54.8 (C2), 79.8 (C10), 155.9 (C9), 172.3 (C7) ppm. IR: $\tilde{\nu}$ = 2972 (m), 2938 (m), 2859 (w), 1807 (w), 1741 (s), 1692 (s), 1446 (m), 1391 (s), 1338 (s), 1246 (s), 1204 (s), 1154 (s), 1073 (m), 1043 (m), 1007 (m), 929 (m), 874 (m), 771 (w) cm^{-1}. GC–MS (EI): *m*/*z* (%) = 243 (1), 184 (27), 142 (35), 128 (100), 110 (2), 84 (100), 57 (100).

1-*tert*-Butyl 2-Methyl 5,6-Dihydropyridine-1,2(4*H*)-dicarboxylate (22):[18] Under an argon atmosphere pipecolic carboxylate *rac*-**21** (7.1 g, 29.2 mmol) was dissolved in THF (30 mL) and cooled to –30 °C. A solution of LiHMDS (32.3 mL, 1 M in THF) was added over 2 h and stirring of the resulting mixture was continued at –30 °C for 1.5 h. Then the yellow solution was cooled –90 °C (N_2, He×) and bromine (1.65 mL, 32.3 mmol) was added dropwise (***CAUTION***: efficient cooling and stirring required!) over 1 h. Afterwards the cooling bath was removed allowing the mixture to warm to room temp, aqueous citric acid (40 mL, 1 M) was added. The mixture was stirred at room temp for 30 min and the phases were diluted with EtOAc (200 mL). The organic layer was washed with H_2O (2 × 200 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography (SiO_2, EtOAc/cyclohexane = 1:2) to give a light yellow oil. Colorless crystals of carboxylate **22** (5.0 g, 20.6 mmol, 71%) were obtained after recrystallization (Et_2O/Hex = 1:2), m.p. 68 °C {ref.[18] 73–75 °C}. R_f = 0.54 (EtOAc/cyclohexane = 1:2), 0.44 (EtOAc/cyclohexane = 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9 H, 11-H), 1.76–1.80 (m, 2 H, 5-H), 2.14–2.26 (m, 2 H, 4-H), 3.54–3.57 (m, 2 H, 6-H), 3.75 (s, 1 H, 8-H), 5.57 (t, *J* = 2.8 Hz, 1 H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6 (C5), 22.9 (C4), 27.9 (C11), 41.3; 43.0 (C6), 51.8; 53.6 (C8), 81.2 (C10), 121.8 (C3), 132.7 (C2), 153.0 (C9), 165.5 (C7) ppm. IR: $\tilde{\nu}$ = 2975 (m), 2948 (m), 2880 (w), 1730 (s), 1696 (s), 1643 (m), 1453 (m), 1361 (s), 1336 (s), 1250 (s), 1152 (s), 1066 (s), 962 (m), 873 (m), 771 (s), 730 (w) cm^{-1}. GC–MS (EI): *m*/*z* (%) = 241 (4), 168 (19), 141 (92), 126 (46), 109 (10), 82 (44), 57 (100), 41 (53).

1-*tert*-Butyl 2-Methyl (*rac*/*trans*)-3-Vinylpiperidine-1,2-dicarboxylate (*rac*-23): Under argon atmosphere vinyl-MgBr (118.0 mL, 47.2 mmol, 0.4 M in THF) was cooled to –35 °C and $CuBr{\cdot}SMe_2$ (1.3 g, 6.3 mmol) was added. The suspension was stirred at –35 °C for 1 h and carboxylate **22** (7.6 g, 31.5 mmol) was added. After stirring at –35 °C for 6 h the mixture was quenched with aqueous NH_4Cl (saturated) and NH_3 (300 mL, 1:1). After extraction with MTBE (2× 500 mL) the organic layer was washed with aqueous NH_4Cl (1 L) and brine (1 L), dried with $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by chromatography (SiO_2, EtOAc/cyclohexane = 1:4) (*cis*-isomer eluted first, then 1,2-product, then *trans*-isomer) to give desired *trans*-vinylpiperidine *rac*-**23** (2.7 g, 10.0 mmol, 32%) as a yellow oil. R_f = 0.56 (EtOAc/cyclohexane = 1:4). ^{1}H NMR (mixture of rotamers) (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, 13-H), 1.53–1.76 (m, 4 H, 4-H, 5-H), 2.78–3.00 (m, 2 H, 3-H, 6-H$_\beta$), 3.75 (s, 1 H, 8-H), 3.90–4.10 (m, 1 H, 6-H$_\alpha$), 4.82 (m, 1 H, 2-H), 5.11–5.19 (m, 2 H, 10-H), 5.84–5.95 (ddd, J = 17.1, 10.5, 6.3 Hz, 1 H, 9-H) ppm. ^{13}C NMR (mixture of rotamers) (75 MHz, $CDCl_3$): δ = 19.6 (C5), 25.9 (C4), 27.9 (C11), 37.9 (C3), 41.2–41.7 (C6), 52.1 (C8), 57.2–57.9 (C2), 80.0 (C12), 115.5 (C10), 138.7 (C9), 155.7 (C11), 172.0 (C7) ppm. IR: $\tilde{\nu}$ = 2975 (m), 2948 (m), 2880 (w), 1730 (s), 1696 (s), 1643 (m), 1453 (m), 1361 (s), 1336 (s), 1250 (s), 1152 (s), 1066 (s), 962 (m), 873 (m), 771 (s), 730 (w) cm^{-1}. GC–MS (EI): *m*/*z* (%) = 241 (4), 168 (19), 141 (92), 126 (46), 109 (10), 82 (44), 57 (100), 41 (53). HRMS (ESI): calcd. for $[M + Na]^+$ 292.15193; found 292.15048.

(*rac*/*trans*)-1-(*tert*-Butoxycarbonyl)-3-vinylpiperidine-2-carboxylic Acid (*rac*-6): Carboxylate *rac*-**23** (1.100 g, 4.084 mmol) was dissolved in MeOH (4.1 mL) and THF (12.3 mL). After addition of aqueous LiOH (4.1 mL, 2 N, 8.168 mmol) the mixture was stirred at 50 °C for 5 h (pH 10). After cooling to room temp the aqueous phase was washed with MTBE (5 mL) and acidified at 0 °C with HCl (10 mL, 1 N) until pH 1. After extraction with CH_2Cl_2 (5× 10 mL) the organic layer was dried with $MgSO_4$ and was concentrated under reduced pressure to give carboxylic acid *rac*-**6** (0.922 g, 3.611 mmol, 88%) as a white solid, m.p. 112 °C. R_f = 0.22 (MeOH/CH_2Cl_2 = 1:60 + 1 vol.-% AcOH). ^{1}H NMR (mixture of rotamers) (300 MHz, $CDCl_3$): δ = 1.46 (m, 10 H, 5-H$_\beta$, 12-H), 1.54–1.70 (m, 3 H, 4-H, 5-H$_\alpha$), 3.04–3.13 (m, 2 H, 3-H, 6-H$_\beta$), 3.97–4.02 (m, 1 H, 6-H$_\alpha$), 4.79–4.94 (m, 1 H, 2-H), 5.07–5.20 (m, 2 H, 9-H), 5.84–5.96 (ddd, J = 17.1, 10.5, 6.2 Hz, 1 H, 9-H) ppm. ^{13}C NMR (mixture of rotamers) (75 MHz, $CDCl_3$): δ = 19.5 (C5), 25.8 (C4), 28.3 (C12), 37.8 (C3), 40.0–42.2 (C6), 56.7–57.8 (C2), 80.4; 80.6 (C11), 115.5 (C9), 138.5 (C8), 156.1 (C10), 177.0 (C7) ppm. IR: $\tilde{\nu}$ = 3071 (w), 2969 (w), 2936 (w), 2860 (w), 1734 (m), 1692 (s), 1650 (s), 1473 (w), 1415 (m), 1391 (m), 1365 (s), 1310 (w), 1250 (m), 1140 (s), 1017 (w), 989 (w), 918 (m), 877 (m), 770 (w) cm^{-1}. HRMS (ESI): calcd. for $[M + Na]^+$ 278.13628; found 278.13529.

Di-*tert*-butyl (2*S*)-5-Formylpyrrolidine-1,2-dicarboxylate (25):[4b] To a mixture of cyanopyrrolidine **24** (for synthesis of **24** see ref.[4b]) (15.0 g, 0.051 mol) in pyridine/AcOH/H_2O (2:1:1, 210 mL) was added *Raney*-Ni (34.8 g, 50% in H_2O). Under vigorous stirring at 50 °C the mixture was saturated with H_2 under a continuous stream of gas. After 5 h at 50 °C (progress controlled by GC–MS) the reaction was diluted with H_2O (300 mL) and extracted with EtOAc (3× 300 mL). The organic layer was intensely washed with H_2O (3× 700 mL) to remove all Ni-impurities and dried with $MgSO_4$. After evaporation under reduced pressure the residue was purified by chromatography (SiO_2, EtOAc/cyclohexane = 1:6) to provide aldehyde **25** (9.2 g, 0.031 mol, 61%) as mixture of its diastereomers (*cis*/*trans* = 3:1, GC–MS) as yellow oil. R_f = 0.23 (EtOAc/cyclohexane = 1:4). ^{1}H NMR (mixture of diastereomers and rotamers) (300 MHz, $CDCl_3$): δ = 1.42–1.48 (m, 18 H, 8-H, 12-H), 2.00–2.12 (m, 4 H, 3-H, 4-H), 4.02–4.46 (m, 2 H, 2-H, 5-H), 9.55–9.67 (m, 1 H, 9-H) ppm. ^{13}C NMR (mixture of diastereomers and rotamers) (75 MHz, $CDCl_3$): δ = 24.6; 25.3; 26.3; 26.4; 28.2; 29.1; 29.3; 30.0 (C3, C4), 26.9; 28.0 (C8, C12), 60.4; 60.5; 60.6 (C5), 65.4 (C2), 80.8; 81.1; 81.3; 81.5; 81.6; 81.7 (C7, C11), 153.3; 154.0; 154.3 (C10), 171.4; 171.5; 171.6 (C10), 200.2; 201.1 (C9) ppm. IR: $\tilde{\nu}$ = 2975 (m), 2926 (w), 1733 (s), 1698 (s), 1696 (s), 1476 (m), 1453 (m), 1386 (s), 1365 (s), 1290 (m), 1253 (m), 1223 (m), 1150 (s), 1123 (s), 1090 (m), 1063 (m), 980 (m), 843 (m), 771 (m) cm^{-1}. GC–MS (EI): *m*/*z* (%) = 299 (1), 270 (9), 207 (3), 198 (2), 170 (16), 140 (6), 114 (51), 98 (17), 80 (14), 70 (38), 57 (52), 41 (100), 39 (61).

Di-*tert*-butyl (2*S*)-5-Vinylpyrrolidine-1,2-dicarboxylate (26):[4b] Under an argon atmosphere was added at room temp. KHMDS (77.8 mL, 0.051 mol, 15% in toluene) to a suspension of Ph_3PCH_3Br (18.1 g, 0.051 mol) in THF (150 mL). After stirring at room temp for 1 h the reaction mixture was cooled to –78 °C and aldehyde **25** (6.1 g, 0.020 mol) in THF (50 mL) was added. The mixture was warmed to room temp and was stirred for 2.5 h. The reaction was quenched aqueous saturated Na/K tartrate (120 mL), diluted with H_2O (80 mL) and extracted with MTBE (3× 250 mL). The organic layer was washed with brine (500 mL), dried with $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by chromatography (SiO_2, EtOAc/cyclohexane = 1:9) to give vinylproline **26** (5.4 g, 0.018 mol, 90%) as mixture of its diastereomers (*cis*/*trans* = 4:1, GC–MS) as a light yellow oil. R_f = 0.26 (EtOAc/cyclohexane = 1:9). ^{1}H NMR (mixture of diastereomers and rotamers) (300 MHz, $CDCl_3$): δ = 1.64–1.77 (m, 18 H, 8-H, 13-H), 1.84–2.17 (m, 4 H, 3-H, 4-H), 4.12–4.54 (m, 2 H, 2-H, 5-H), 5.05–5.39 (m, 2 H, 10-H), 5.71–5.93 (m, 1 H, 9-H) ppm. ^{13}C NMR (mixture of diastereomers and rotamers) (75 MHz, $CDCl_3$): δ = 28.0; 28.3 (C8, C13), 26.9; 27.3; 29.0; 30.0; 30.9; 31.5 (C3, C4), 59.4; 59.7; 60.2; 60.4; 60.6; 61.0 (C2, C5), 79.5; 79.6; 79.7; 79.9; 80.9 (C7, C12), 113.7; 113.8; 114.6; 114.9 (C10), 138.1; 138.5; 138.6; 139.2 (C9), 153.6; 153.7 (C11), 172.0; 172.1 (C6) ppm. IR: $\tilde{\nu}$ = 2974 (m), 2930 (m), 2873 (w), 1738 (s), 1693 (s), 1643 (w), 1477 (m), 1454 (m), 1384 (s), 1363 (s), 1325 (m), 1292 (m), 1254 (s), 1218 (s), 1148 (s), 1066 (m), 1024 (w), 987 (m), 957 (m), 912 (s), 874 (m), 856 (m), 843 (m), 771 (m), 686 (w) cm^{-1}. GC–MS (EI): *m*/*z* (%) = 297 (1), 196 (25), 168 (10), 140 (100), 114 (3), 96 (100), 70 (9), 79 (8), 57 (100), 41 (38), 39 (14).

***tert*-Butyl (2*S*,5*R*)-5-Vinylpyrrolidine-2-carboxylate (7):**[4b] Under an argon atmosphere vinylproline **26** (6.1 g, 0.021 mol) was dissolved in CH_2Cl_2 (75 mL). After cooling to 0 °C TMSOTf (3.74 mL, 0.021 mol) was added dropwise. Stirring was continued for 5 min and the reaction was stopped by addition of aqueous $NaHCO_3$ (20 mL) until no further gas evolution was visible. The aqueous layer was extracted with CH_2Cl_2 (5× 20 mL). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by chromatography (SiO_2, MeOH/CH_2Cl_2 = 1:25) and separated to its diastereomers to give amine **7** (1.7 g, 0.009 mol, 43%) as colorless crystals. $[\alpha]_D^{20}$ = –35.0 (c = 1.500 , $CHCl_3$) {ref.[4b] $[\alpha]_D^{20}$ = –35.1 (c = 1.475 , $CHCl_3$)}. R_f = 0.27 (MeOH/CH_2Cl_2 = 1:25). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (m, 10 H, 8-H, 4′-H), 1.88–1.97; 2.07–2.11 (2×m, 3 H, 3-H, 4-H), 2.28 (br. s, 1 H, -NH), 3.57–3.71 (m, 2 H, 2-H, 5-H), 5.03–5.23 (ddd, J = 13.7, 10.9, 0.8 Hz, 2 H, 10-H), 5.83–5.94 (ddd, J = 10.2, 9.7, 7.2 Hz, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9 (C8), 30.4; 31.9 (C3, C4), 60.7 (C2), 62.2 (C5), 81.0 (C7), 115.0 (C10), 140.1 (C9), 174.4 (C6) ppm. IR: $\tilde{\nu}$ = 3346 (w), 3286 (w), 3073 (w), 2973 (m), 2933 (m), 2866 (w), 1723 (s), 1649 (w), 1476 (w), 1453 (m), 1426 (w), 1390 (m), 1363 (s), 1280 (m), 1223

(s), 1150 (s), 1100 (s), 1033 (w), 990 (m), 913 (s), 846 (s), 756 (w) cm^{-1}. GC–MS (EI): *m*/*z* (%) = 197 (1), 114 (3), 96 (100), 79 (11), 68 (11), 57 (13), 41 (29).

***tert*-Butyl (2*S*,5*R*)-1-[(2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-3-(prop-1-en-1-yl)azetidine-2-carbonyl]-5-vinylpyrrolidine-2-carboxylate (27):** Under an argon atmosphere azetidinecarboxylic acid **4** (0.060 g, 0.249 mmol) and amine **7** (0.059 g, 0.298 mmol) were dissolved in MeCN (2 mL) and N,N-diisopropylethylamine (DIPEA; 0.13 mL, 0.746 mmol) was added. After the solution was cooled to 0 °C (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP; 0.143 g, 0.274 mmol) in MeCN (2 mL) was added dropwise. The mixture was stirred at room temp for 16 h and the solvent was removed under reduced pressure. The residue was dissolved in MTBE (20 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with MTBE (2× 10 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography (SiO_2, EtOAc/cyclohexane = 1:3) to give dipeptide **27** (0.081 g, 0.193 mmol, 78%) as a yellow oil. $[\alpha]_D^{20}$ = –40.3 (*c* = 0.490, $CHCl_3$). R_f = 0.19 (EtOAc/cyclohexane = 1:3). ^{1}H NMR (mixture of rotamers) (300 MHz, 288 K, $CDCl_3$): δ = 1.40–1.49 (m, 18 H, 8-H, 20-H), 1.56–1.72 (m, 3 H, 17-H), 1.81–1.93 (m, 2 H, 4-H), 2.05–2.22 (m, 2 H, 3-H), 3.19 (m, 1 H, 13-H), 3.58–3.63 (m, 1 H, 14′-H), 4.20–4.31 (m, 1 H, 14-H), 4.36–4.44 (m, 1 H, 5-H), 4.51 (dd, *J* = 19.0, 4.3 Hz, 1 H, 12-H), 4.53; 4.80 (2×m, 1 H, 2-H), 5.14; 5.40 (2×m, 2 H, 10-H), 5.49–5.57 (m, 2 H, 15-H, 16-H), 5.84–5.91 (m, 1 H, 9-H) ppm. ^{13}C NMR (mixture of rotamers) (75 MHz, 288 K, $CDCl_3$): δ = 17.8 (C17), 26.7; 27.0; 31.7; 31.8 (C3, C4), 27.9; 28.3; 31.0; 31.3 (C8, C20), 36.2; 36.6 (C13), 52.8; 54.1 (C14), 60.3 (C2), 60.8; 60.9; 61.0 (C12), 64.0; 64.2; 65.0 (C5), 79.6; 81.0; 81.2 (C7, C19), 116.6; 117.0 (C10), 127.7; 127.9; 130.0; 130.1 (C15, C16), 138.1; 138.7 (C9), 155.0; 155.8 (C18), 169.7; 169.8 (C6), 170.5; 170.9 (C11) ppm. IR: $\tilde{\nu}$ = 2973 (m), 2926 (w), 2880 (w), 1736 (m), 1700 (s), 1650 (s), 1476 (w), 1453 (m), 1423 (m), 1390 (s), 1363 (s), 1300 (m), 1253 (w), 1206 (w), 1146 (s), 1090 (w), 1033 (w), 986 (w), 963 (w), 926 (w), 863 (w), 843 (w), 770 (w) cm^{-1}. GC–MS (EI): *m*/*z* (%) = 405 (3), 364 (7), 347 (10), 308 (10), 290 (11), 263 (27), 235 (9), 219 (8), 196 (7), 180 (12), 140 (30), 96 (53), 57 (50), 41 (100). HRMS (ESI): calcd. for $[M + H]^+$ 443.2516; found 443.2514: calcd. for $[M + Na]^+$ 421.2697; found 421.2698.

Di-*tert*-butyl (2a*S*,4a*R*,7*S*,9a*S*)-9-Oxo-2,2a,4a,5,6,7,9,9a-octahydro-1*H*-azeto[3,2-*e*]pyrrolo[1,2-*a*]azepine-1,7-dicarboxylate (2c): Under an argon atmosphere dipetide **27** (0.120 g, 0.285 mmol) and Grubbs II catalyst (0.025 g, 0.029 mmol) were heated to reflux in CH_2Cl_2 (7 mL) for 24 h. Then dimethyl sulfoxide (DMSO; 0.5 mL) was added at room temp and the mixture was stirred overnight. After removal of CH_2Cl_2 under reduced pressure the crude product was purified by chromatography (SiO_2, EtOAc/cyclohexane = 1:3) to give tricyclic **2c** (0.050 g, 0.119 mmol, 46%) as a yellow oil and unreacted starting material **27** (0.046 g, 0.104 mmol, 36%). $[\alpha]_D^{20}$ = –105.2 (*c* = 0.285 , $CHCl_3$). R_f = 0.26 (EtOAc/cyclohexane = 1:1). ^{1}H NMR (mixture of rotamers) (300 MHz, $CDCl_3$): δ = 1.44 (m, 18 H, 8-H, 17-H), 1.82–1.97 (m, 1 H, 4′-H), 2.01–2.06 (m, 2 H, 3-H), 2.18–2.34 (m, 2 H, 4-H), 3.50 (m, 1 H, 11-H), 3.70 (m, 1 H, 14′-H), 3.87 (m, 1 H, 14-H), 4.59–4.65 (m, 2 H, 2-H, 5-H), 4.72 (d, *J* = 10.0 Hz, 1 H, 12-H), 5.51 (d, *J* = 10.8 Hz, 1 H, 10-H), 5.89 (dd, *J* = 10.8, 2.0 Hz, 1 H, 9-H) ppm. ^{13}C NMR (mixture of rotamers) (75 MHz, $CDCl_3$): δ = 27.1 (C4), 27.9; 28.2 (C8, C17), 33.0 (C3), 33.1 (C11), 53.3 (C14), 58.9 (C5), 59.7 (C2), 66.3 (C12), 80.5; 81.4 (C7, C16), 127.3 (C10), 129.6 (C9), 158.3 (C15), 169.3 (C13), 171.0 (C6) ppm. IR: $\tilde{\nu}$ = 2974 (m), 2929 (w), 1711 (s), 1681 (s), 1650 (s), 1477 (w), 1454 (m), 1390 (s), 1365 (s), 1318 (m), 1256 (m), 1218 (m), 1151 (s), 1075 (w), 1027 (w), 967 (w), 919 (w), 848 (w), 787 (w), 731 (m), 645 (w) cm^{-1}. HRMS (ESI): calcd. for $[M + H]^+$ 379.22275; found 379.22274: calcd. for $[M + Na]^+$ 401.20469; found 401.20461.

(2a*S*,4a*R*,7*S*,9a*S*)-1-{[(9*H*-Fluoren-9-yl)methoxy]carbonyl}-9-oxo-2,2a,4a,5,6,7,9,9a-octahydro-1*H*-azeto[3,2-*e*]pyrrolo[1,2-*a*]azepine-7-carboxylic Acid (2b): A solution of tricyclic **2c** (0.045 g, 0.119 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C and TFA (2 mL) was added dropwise. After warming to room temp stirring was continued for 1 h and the solvent was removed under reduced pressure. Aqueous, half-saturated $NaHCO_3$ (3 mL) was added (pH 8). After addition of Fmoc-Cl (0.044 g, 0.170 mmol) in THF (1.5 mL) the solution was stirred at room temp for 16 h and then diluted with CH_2Cl_2 (5 mL). The solution was acidified at 0 °C with HCl (3 mL, 1 N) to pH 1. After separation the aqueous layer was extracted with CH_2Cl_2 (2× 5 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography (SiO_2, MeOH/CH_2Cl_2 = 1:15 + 1 vol.-% AcOH) to give **2b** (0.040 g, 0.090 mmol, 76%) with slight impurities of AcOH as a white solid. $[\alpha]_D^{20}$ = –65.2 (*c* = 0.320, $CHCl_3$), m.p. 141 °C. R_f = 0.32 (MeOH/CH_2Cl_2 = 1:15 + 1 vol.-% AcOH). ^{1}H NMR (mixture of rotamers) (300 MHz, $CDCl_3$): δ = 1.86–2.01 (m, 2 H, 3′-H, 4′-H), 2.26–2.30 (m, 2 H, 3-H, 4-H), 3.53 (m, 1 H, 9-H), 3.75 (m, 1 H, 12′-H), 3.98 (m, 1 H, 12-H), 4.23 (t, *J* = 6.8 Hz, 1 H, 15-H), 4.40 (m, 2 H, 14-H), 4.55 (m, 1 H, 5-H), 4.77 (m, 2 H, 2-H, 10-H), 5.49 (d, *J* = 11.0 Hz, 1 H, 8-H), 5.89 (d, *J* = 10.8 Hz, 1 H, 7-H), 7.30 (m, 2 H, 18-H), 7.36 (m, 2 H, 19-H), 7.63 (m, 2 H, 17-H), 7.76 (m, 2 H, 20-H), 9.72 (br. s, 1 H, -COOH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.1 (C3), 33.1 (C4), 33.5 (C9), 47.0 (C15), 53.6 (C12), 60.0 (C2, C5), 66.2 (C11), 67.6 (C14), 119.8 (C20), 125.3 (C17), 127.1 (C18), 127.3 (C8), 127.7 (C19), 129.0 (C7), 141.2 (C21), 143.7 (C16), 158.8 (C13), 171.0 (C6), 174.8 (C11) ppm. IR: $\tilde{\nu}$ = 3354 (w), 3058 (w), 2950 (w), 1711 (s), 1449 (m), 1415 (m), 1319 (m), 1300 (w), 1272 (w), 1189 (m), 1130 (w), 1102 (w), 1032 (w), 969 (w), 909 (w), 759 (s), 739 (s), 620 (w) cm^{-1}. HRMS (ESI): calcd. for $[M + H]^+$ 445.17580; found 445.17582: calcd. for $[M + Na]^+$ 467.15774; found 467.15768.

***tert*-Butyl 2-[(2*S*,5*R*)-2-(*tert*-Butoxycarbonyl)-5-*trans*-vinylpyrrolidine-1-carbonyl]-3-vinylpiperidine-1-carboxylate (28):** Under an argon atmosphere piperidinecarboxylic acid *rac*-**6** (0.470 g, 1.84 mmol) and amine **7** (0.331 g, 1.68 mmol) were dissolved in MeCN (10 mL) and DIPEA (0.86 mL, 5.04 mmol) was added. After the solution was cooled to 0 °C PyBOP (1.134 g, 2.18 mmol) in MeCN (10 mL) was added dropwise. The mixture was stirred at room temp for 20 h and the solvent was removed under reduced pressure. The residue was dissolved in MTBE (50 mL) and washed with H_2O (20 mL). The aqueous layer was extracted with MTBE (3× 20 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography (SiO_2, EtOAc/cyclohexane = 1:3) to give dipeptide **28** (0.601 g, 1.38 mmol, 82%) as a yellow oil. R_f = 0.44/0.47 (diastereomers) (EtOAc/cyclohexane = 1:3). ^{1}H NMR (mixture of diastereomers and rotamers) (600 MHz, $CDCl_3$): δ = 1.35–1.48 (m, 20 H, 15-H, 8-H, 21-H), 1.48–2.22 (m, 7 H, 3-H, 4-H, 14-H, 16′-H), 2.42–3.26 (m, 1 H, 13-H), 3.36–3.98 (m, 1 H, 16-H), 4.12–4.93 (m, 3 H, 2-H, 5-H, 12-H), 4.93–5.09 (m, 2 H, 10′-H, 18-H), 5.15–5.43 (m, 1 H, 10-H), 5.65–5.97 (m, 2 H, 9-H, 17-H) ppm. ^{13}C NMR (mixture of diastereomers and rotamers) (150 MHz, $CDCl_3$): δ = 19.5; 23.6; 23.7; 25.1; 26.3; 26.7; 26.8; 29.1; 27.7; 30.2; 32.6 (C3, C4, C14, C15), 27.7; 27.8; 28.1; 28.2 (C8, C21), 37.3; 37.4; 37.8 (C13), 41.5 (C16), 52.5; 53.5; 55.8; 59.9; 60.5; 60.8; 61.4; 61.8 (C2, C5, C12), 79.4; 80.8; 81.6 (C7, C20), 114.6; 114.9;

A116.0 (C10, C18), 137.9; 138.2; 139.1; 139.4; 139.5 (C9, C17), 155.2 (C19), 171.1 (C6), 172.1 (C11) ppm. IR: $\tilde{\nu}$ = 3071 (w), 2962 (m), 2928 (m), 2866 (w), 1734 (s), 1680 (s), 1646 (s), 1418 (w), 1361 (s), 1340 (s), 1310 (m), 1249 (s), 1204 (m), 1147 (s), 1065 (w), 1014 (w), 990 (m), 919 (s), 871 (m), 847 (w), 766 (w), 645 (m) cm^{-1}. GC–MS (EI): *m*/*z* (%) = 434 (1), 361 (3), 305 (7), 277 (4), 210 (15), 182 (7), 154 (100), 110 (57), 57 (39), 41 (66). HRMS (ESI): calcd. for $[M + H]^+$ 435.28535; found 435.28465: calcd. for $[M + Na]^+$ 457.26729; found 457.26594.

Di-*tert*-butyl (4a*R*,6a*R*,9*S*,11a*S*)-11-Oxo-2,3,4,4a,6a,7,8,9,11,11a-decahydro-1*H*-pyrido[3,2-*e*]pyrrolo[1,2-*a*]azepine-1,9-dicarboxylate (3c) and Di-*tert*-butyl (4a*S*,6a*R*,9*S*,11a*R*)-11-Oxo-2,3,4,4a,6a,7,8,9,11,11a-decahydro-1*H*-pyrido[3,2-*e*]pyrrolo[1,2-*a*]azepine-1,9-dicarboxylate (*dia*-3c): Under an argon atmosphere dipetide **28** (0.495 g, 1.14 mmol) and Grubbs II catalyst (0.194 g, 0.23 mmol) were heated to reflux in CH_2Cl_2 (25 mL) for 48 h. Then DMSO (0.5 mL) was added at room temp and the mixture was stirred overnight. After removal of CH_2Cl_2 under reduced pressure the crude product was purified by chromatography (SiO_2, EtOAc/cyclohexane = 1:3→1:1) to give desired tricyclic **3c** (0.193 g, 0.48 mmol, 42%) and its diastereomer *dia*-**3c** (0.195 g, 0.48 mmol, 42%). **Data for 3c:** colorless crystals. $[\alpha]_D^{20}$ = –91.6 (*c* = 0.425, $CHCl_3$), m.p. 72–73 °C. R_f = 0.49 (EtOAc/cyclohexane = 1:1). ^1H NMR (mixture of rotamers, 1:1.5) (600 MHz, 248 K, $CDCl_3$): δ = 1.42–1.97 (m, 18 H, 8-H, 19-H), 1.59–1.71 (m, 1 H, 15′-H), 1.71–1.87 (m, 2 H, 14-H), 1.87–2.01 (m, 2 H, 4′-H, 15-H), 1.87–2.01 (m, 2 H, 3-H), 2.27–2.38 (m, 1 H, 4-H), 2.60 (t, *J* = 10.4 Hz, 1 H, 13-H), 3.18–3.27 (m, 1 H, 16′-H), 3.90 (dd, *J* = 13.9, 8.6 Hz, 0.6 H, 16-H^{rot1}), 3.99 (dd, *J* = 13.9, 8.1 Hz, 0.4 H, 16-H^{rot2}), 4.45 (d, *J* = 11.7 Hz, 0.4 H, 12-H^{rot2}), 4.55–4.58 (m, 0.6 H, 12-H^{rot1}), 4.58–4.59 (m, 0.4 H, 2-H^{rot2}), 4.61–4.62 (m, 1 H, 5-H), 4.67–4.70 (m, 0.6 H, 2-H^{rot1}), 5.54–5.62 (m, 2 H, 9-H, 10-H) ppm. ^{13}C NMR (mixture of rotamers, 1:1.5) (150 MHz, 248 K, $CDCl_3$): δ = 21.1; 21.5 (C15), 26.3; 26.5; 26.7 (C14), 27.2; 27.6 (C3), 27.7; 27.8; 28.1; 28.3 (C8, C19); 32.8; 32.9 (C4), 33.3; 33.5 (C13), 36.7; 38.0 (C16), 55.9; 56.3 (C2), 58.4; 59.0 (C12), 59.8; 60.0 (C5), 79.4; 79.7; 81.2; 81.4 (C7, C18), 128.2; 128.4; 132.3; 132.7 (C9, C10), 155.2; 155.8 (C17), 170.1; 170.4 (C11), 170.9; 171.2 (C6) ppm. IR: $\tilde{\nu}$ = 2970 (w), 2928 (w), 2867 (w), 1736 (m), 1697 (s), 1666 (s), 1477 (w), 1433 (m), 1409 (s), 1390 (s), 1363 (s), 1329 (w), 1283 (w), 1257 (w), 1222 (m), 1151 (s), 1129 (s), 1075 (w), 1006 (w), 947 (w), 904 (w), 851 (w), 833 (w), 770 (w) cm^{-1}. HRMS (ESI): calcd. for $[M + H]^+$ 407.25405; found 407.25432: calcd. for $[M + Na]^+$ 429.23600; found 429.23601.

Data for *dia*-3c: Colorless crystals. $[\alpha]_D^{20}$ = –93.8 (*c* = 0.500, $CHCl_3$), m.p. 73–74 °C. R_f = 0.30 (EtOAc/cyclohexane = 1:1). ^1H NMR (mixture of rotamers, 1:1) (600 MHz, 248 K, $CDCl_3$): δ = 1.42–1.45 (m, 19 H, 15′-H, 8-H, 19-H), 1.53–1.63 (m, 1 H, 15-H), 1.91–2.13 (m, 4 H, 3′-H, 4′-H, 14-H), 2.20–2.29 (m, 1 H, 3-H), 2.29–2.35 (m, 1 H, 4-H), 2.75–2.83 (m, 2 × 0.5 H, 13′-H^{rot1}, 16′-H^{rot1}), 2.83–2.89 (m, 0.5 H, 16′-H^{rot2}), 2.89–2.99 (m, 0.5 H, 13′-H^{rot2}), 3.25 (d, *J* = 11.6 Hz, 0.5 H, 12-H^{rot2}), 3.43 (d, *J* = 11.8 Hz, 0.5 H, 12-H^{rot1}), 4.03–4.06 (m, 0.5 H, 16-H^{rot1}), 4.22–4.24 (m, 0.5 H, 16-H^{rot2}), 4.49–4.54 (m, 0.5 H, 2-H^{rot1}), 4.54–4.58 (m, 0.5 H, 2-H^{rot2}), 4.59–4.66 (m, 0.5 H, 5-H^{rot1}), 4.73–4.80 (m, 0.5 H, 5-H^{rot2}), 5.59–5.63 (m, 1 H, 10-H), 5.99–6.02 (m, 1 H, 9-H) ppm. ^{13}C NMR (mixture of rotamers, 1:1) (150 MHz, 248 K, $CDCl_3$): δ = 24.4, 25.3 (C15), 26.7; 27.1; 27.2 (C3), 27.7; 27.8; 28.2; 28.3 (C8, C19), 31.8 (C4), 32.4; 32.9 (C14), 35.6; 36.4 (C13), 49.3; 49.4 (C16), 53.2; 53.4 (C5), 61.1; 61.3 (C2), 64.8; 64.9 (C12), 79.5; 80.8; 81.0; 81.4 (C7, C18), 136.1; 136.3 (C10), 136.5; 136.6 (C9), 154.7; 155.4 (C17), 167.1; 167.4 (C11), 171.4; 172.0 (C6) ppm. IR: $\tilde{\nu}$ = 2973 (w), 2930 (w), 2874 (w), 1737 (m), 1692 (s), 1638 (s), 1477 (w), 1449 (m), 1408 (s), 1390 (s), 1364 (s), 1337 (w), 1286 (w), 1245 (m), 1219 (w), 1151 (s), 1152 (s), 1074 (w), 1039 (w), 944 (w), 903 (w), 855 (w), 829 (w), 773 (w), 755 (w), 730 (w) cm^{-1}. HRMS (ESI): calcd. for $[M + H]^+$ 407.25405; found 407.25430: calcd. for $[M + Na]^+$ 429.23600; found 429.23606.

(4a*R*,6a*R*,9*S*,11a*S*)-1-{[(9*H*-Fluoren-9-yl)methoxy]carbonyl}-11-oxo-2,3,4,4a,6a,7,8,9,11,11a-decahydro-1*H*-pyrido[3,2-*e*]pyrrolo-[1,2-*a*]azepine-9-carboxylic Acid (3b): A solution of tricyclic **3c** (0.190 g, 0.475 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C and TFA (2 mL) was added dropwise. After stirring at room temp for 1 h the solvent was removed and under reduced pressure and aqueous, half-saturated $NaHCO_3$ (5 mL) was added (pH 8). After addition of Fmoc-Cl (0.184 g, 0.713 mmol) in THF (6 mL) the solution was stirred at room temp for 16 h and then diluted with CH_2Cl_2 (25 mL). The solution was acidified at 0 °C with HCl (10 mL, 1 N) to pH 1. After separation the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by a Reveleris® flash chromatography system (SiO_2, MeOH/CH_2Cl_2 gradient: 0–20%) to give **3b** (0.181 g, 0.383 mmol, 81%) as a colorless solid. $[\alpha]_D^{20}$ = –64.7 (*c* = 0.295, $CHCl_3$), m.p. 157 °C. R_f = 0.13 (MeOH/CH_2Cl_2 = 1:15). ^1H NMR (mixture of rotamers, 1.5:1) (600 MHz, 258 K, $CDCl_3$): δ = 0.78–0.89 (m, 0.6 H, 13′-H-H^{rot1}), 1.36–1.41 (m, 0.4 H, 13′-H^{rot2}), 1.51–1.59; 1.69–2.16; 2.18–2.32 (3 × m, 7 H, 3-H, 4-H, 12-H, 13-H), 2.34–2.37 (m, 0.6 H, 11-H^{rot1}), 2.61–2.67 (m, 0.4 H, 11-H^{rot2}), 2.97–3.07 (m, 0.4 H, 14′-H^{rot2}), 2.37–3.45 (m, 0.6 H, 14′-H^{rot1}), 3.55–3.61 (m, 0.4 H, 5-H^{rot2}), 3.81–3.85 (m, 0.4 H, 10-H^{rot2}), 3.92–3.96 (m, 0.4 H, 14-H^{rot2}), 4.02–4.06 (m, 0.6 H, 14-H^{rot1}), 4.15 (m, 0.4 H, 17-H^{rot2}), 4.28–4.33 (m, 1.2 H, 16′-H^{rot1}, 17-H^{rot1}), 4.41–4.46 (m, 1 H, 2-H^{rot2}, 16-H^{rot1}), 4.56–4.58 (m, 0.4 H, 16′-H^{rot2}), 4.65 (d, *J* = 11.6 Hz, 0.6 H, 10-H^{rot1}), 4.68–4.74 (m, 0.6 H, 5-H^{rot1}), 4.76 (d, *J* = 8.6 Hz, 0.6 H, 2-H^{rot1}), 5.00–5.05 (m, 0.4 H, 16-H^{rot2}), 5.36 (m, 0.8 H, 7-H^{rot2}, 8-H^{rot2}), 5.36 (m, 1.2 H, 7-H^{rot1}, 8-H^{rot1}), 7.32–7.35 (m, 2 H, 20-H), 7.39–7.44 (m, 2 H, 20-H), 7.56–7.63 (m, 2 H, 21-H), 7.72–8.80 (m, 2 H, 19-H), 7.32–7.35 (m, 2 H, 22-H), 8.81 (br. s, 1 H, -COOH) ppm. ^{13}C NMR (mixture of rotamers, 1.5:1) (150 MHz, 258 K, $CDCl_3$): δ = 20.7, 21.5 (C13), 25.7; 25.8; 25.9; 26.2 (C3, C12), 32.8; 33.1 (C4), 32.9; 33.2 (C11), 37.1; 38.1 (C14), 46.8; 47.9 (C17), 56.2; 57.0 (C5), 58.4; 59.0 (C10), 59.9; 60.0 (C2), 62.2; 67.6 (C16), 119.6; 119.7; 119.9 (C22), 124.5; 124.8; 124.9; 125.1 (C19), 126.8; 126.9; 127.0; 127.1; 127.2; 127.5; 127.6 (C8, C20, C21), 132.2; 132.3 (C7), 141.0; 141.1; 141.2 (C23), 143.1; 143.4; 143.9; 144.4 (C18), 155.3; 156.2 (C15), 172.4; 172.8 (C9), 173.5; 173.6 (C6) ppm. IR: $\tilde{\nu}$ = 3013 (w), 2940 (w), 2866 (w), 2246 (w), 1696 (s), 1646 (s), 1446 (m), 1423 (m), 1350 (w), 1323 (w), 1280 (w), 1263 (w), 1216 (m), 1170 (m), 1126 (m), 1100 (w), 1080 (w), 1003 (w), 976 (w), 903 (s), 720 (s) cm^{-1}. HRMS (ESI): calcd. for $[M – H]^–$ 471.19145; found 471.19216.

Selective Carbamate Deprotection of the *N*-Boc-*t*Bu-carboxylate (*dia*-3c) Followed by Fmoc Protection

1-[(9*H*-Fluoren-9-yl)methyl] 9-*tert*-Butyl (4a*S*,6a*R*,9*S*,11a*R*)-11-Oxo-2,3,4,4a,6a,7,8,9,11,11a-decahydro-1*H*-pyrido[3,2-*e*]pyrrolo-[1,2-*a*]azepine-1,9-dicarboxylate (*dia*-3d): A solution of tricyclic *dia*-**3c** (0.080 g, 0.197 mmol) in CH_2Cl_2 (1 mL) was cooled to 0 °C and TFA (1 mL) was added dropwise. After stirring at 0 °C for 1 h the solvent was removed and under reduced pressure and aqueous, half-saturated $NaHCO_3$ (2 mL) was added (pH 8). After addition of Fmoc-Cl (0.076 g, 0.295 mmol) in THF (3 mL) the solution was stirred at room temp for 16 h and then diluted with CH_2Cl_2 (25 mL). The solution was acidified at 0 °C with HCl (5 mL, 1 N) to pH 1. After separation the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried with

$MgSO_4$ and concentrated under reduced pressure. The crude product was purified by a Reveleris® flash chromatography system (SiO_2, MeOH/CH_2Cl_2 gradient: 0–20%) to give *N*-Fmoc-potected *t*Bu carboxylate *dia*-**3d** (0.079 g, 0.149 mmol, 76%) as colorless crystals. $[\alpha]_D^{20}$ = –83.0 (*c* = 0.285, $CHCl_3$), m.p. 85–87 °C. R_f = 0.20 (MeOH/CH_2Cl_2 = 1:15). ^{1}H NMR (mixture of rotamers) (500 MHz, $CDCl_3$): δ = 1.07–1.38 (m, 2 H, 15-H), 1.38–1.57 (m, 10 H, 8-H, 14′-H), 1.88–2.06 (m, 3 H, 3-H, 4-H, 14-H), 2.09–2.20 (m, 1 H, 3-H), 2.21–2.33 (m, 1 H, 4-H), 2.72–2.96 (m, 2 H, 13-H, 16′-H), 3.28–3.47 (m, 1 H, 16-H), 3.89–4.05 (m, 1 H, 12-H), 4.18–4.23 (m, 1 H, 19-H), 4.34–4.44 (m, 1 H, 15′-H), 4.45–4.53 (m, 1 H, 15-H), 4.53–4.60 (m, 1 H, 2-H), 4.63–4.79 (m, 1 H, 5-H), 5.57 (m, 1 H, 10-H), 5.88–5.99 (m, 1 H, 9-H), 7.27–7.33 (m, 2 H, 22-H), 7.36–7.41 (m, 2 H, 23-H), 7.56–7.58 (m, 2 H, 21-H), 7.73–7.75 (m, 2 H, 24-H) ppm. ^{13}C NMR (mixture of rotamers) (125 MHz, $CDCl_3$): δ = 24.7; 24.9; 25.2; 25.6 (C14, C15), 27.4 (C4), 27.9 (C8), 31.9; 32.1; 32.3 (C3), 36.2 (C13), 47.2 (C19), 48.9 (C16), 53.6; 55.0 (C5), 61.5; 62.2 (C2), 66.3 (C12), 67.2; 67.3 (C18), 81.1 (C7), 119.8; 119.9 (C24), 124.8; 124.9 (C21), 127.0; 127.1 (C22), 127.6; 127.7 (C23), 135.4; 135.8 (C10), 136.6; 136.8 (C9), 141.3; 141.4 (C25), 143.4; 143.6; 143.9; 144.2 (C20); 155.9; 156.1 (C17), 167.3 (C11), 171.4; 171.5 (C6) ppm. IR: $\tilde{\nu}$ = 2969 (w), 2930 (w), 2866 (w), 1736 (m), 1697 (s), 1632 (m), 1449 (m), 1416 (s), 1364 (m), 1301 (w), 1237 (m), 1151 (s), 1122 (m), 1102 (w), 1075 (w), 944 (w), 895 (w), 759 (m), 740 (s), 620 (w) cm^{-1}. HRMS (ESI): calcd. for $[M + H]^-$ 529.26970; found 529.26963: calcd. for $[M + Na]^+$ 551.25164; found 551.25113.

(4a*S*,6a*R*,9*S*,11a*R*)-1-{[(9*H*-Fluoren-9-yl)methoxy]carbonyl}-11-oxo-2,3,4,4a,6a,7,8,9,11,11a-decahydro-1*H*-pyrido[3,2-*e*]pyrrolo-[1,2-*a*]azepine-9-carboxylic Acid (*dia*-3b): A solution of tricyclic *dia*-**3c** (0.190 g, 0.475 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C and TFA (2 mL) was added dropwise. After stirring at room temp for 1 h the solvent was removed and under reduced pressure and aqueous, half-saturated $NaHCO_3$ (5 mL) was added (pH 8). After addition of Fmoc-Cl (0.184 g, 0.713 mmol) in THF (6 mL) the solution was stirred at room temp for 16 h and then diluted with CH_2Cl_2 (25 mL). The solution was acidified at 0 °C with HCl (10 mL, 1 N) to pH 1. After separation the aqueous layer was extracted with CH_2Cl_2 (2× 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by a Reveleris® flash chromatography system (SiO_2, MeOH/CH_2Cl_2 gradient: 0–20%) to give *dia*-**3b** (0.180 g, 0.380 mmol, 80%) as a colorless solid. $[\alpha]_D^{20}$ = –29.1 (*c* = 0.375, $CHCl_3$), m.p. 131 °C. R_f = 0.14 (MeOH/CH_2Cl_2 = 1:15). ^{1}H NMR (600 MHz, 248 K, $CDCl_3$): δ = 1.12–1.30 (m, 1 H, 13′-H), 1.30–1.36 (m, 1 H, 12′-H), 1.47–1.53 (m, 1 H, 13-H), 1.94–1.99; 2.04–2.10 (2×m, 3 H, 3′-H, 4′-H, 12-H), 2.25–2.31 (m, 1 H, 3-H), 2.34–2.40 (m, 1 H, 4-H), 2.68–2.80 (m, 1 H, 11-H), 2.80–2.92 (m, 1 H, 14′-H), 3.26–3.37 (m, 1 H, 10-H), 3.91–4.01 (m, 1 H, 14-H), 4.20–4.24 (m, 1 H, 17-H), 4.35–4.40; 4.46–4.58 (2×m, 2 H, 16-H), 4.58–4.61 (m, 1 H, 5-H), 4.70–4.83 (m, 1 H, 2-H), 5.45–5.61 (m, 1 H, 8-H), 5.79–6.02 (m, 1 H, 7-H), 7.30–7.34 (m, 2 H, 20-H), 7.39–7.44 (m, 2 H, 21-H), 7.56–7.58 (m, 2 H, 19-H), 7.77–7.79 (m, 2 H, 22-H) ppm. ^{13}C NMR (150 MHz, 248 K, $CDCl_3$): δ = 24.7 (C13), 25.8 (C4), 31.6 (C12), 31.9 (C3), 35.9 (C11), 46.7; 46.8 (C17), 48.7 (C14), 54.7 (C5), 61.8 (C2), 64.8 (C10), 67.3 (C16), 119.9 (C22), 124.8 (C19), 127.0 (C21), 127.6 (C20), 135.3 (C7), 136.3 (C8), 141.1; 141.2 (C23), 143.1; 143.9 (C18), 156.1 (C15), 170.1 (C9), 172.8 (C6) ppm. IR: $\tilde{\nu}$ = 3015 (w), 2937 (w), 2866 (w), 2250 (w), 1696 (s), 1646 (s), 1443 (m), 1423 (m), 1361 (w), 1322 (w), 1280 (w), 1267 (w), 1219 (m), 1171 (m), 1128 (m), 1109 (w), 1080 (w), 1005 (w), 976 (w), 903 (s), 720 (s) cm^{-1}. HRMS (ESI): calcd. for $[M - H]^-$ 471.19145; found 471.19198.

Selective Carbamate Deprotection of (*S*)-*N*-Boc-Proline-O*t*Bu (29)

***tert*-Butyl (*S*)-Pyrrolidine-2-carboxylate (30):** A solution of *N*-Boc carboxylate **29** (for synthesis of **29** see ref.[4b]) (0.054 g, 0.200 mmol) in CH_2Cl_2 (1 mL) was cooled to 0 °C and TFA (1 mL) was added dropwise. After stirring at 0 °C for 1 h the solvent was removed and under reduced pressure and aqueous, half-saturated $NaHCO_3$ (2 mL) was added (pH 8). After separation the aqueous layer was extracted with CH_2Cl_2 (2× 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by chromatography (SiO_2, MeOH/CH_2Cl_2 = 1:30) to give free amine **30** (0.028 g, 0.164 mmol, 82%) as a colorless oil. $[\alpha]_D^{20}$ = –31.7 (*c* = 1.200, EtOH) {ref.[24] $[\alpha]_D^{20}$ = –32.0 (*c* = 1.200 , EtOH)}. R_f = 0.63 (MeOH/DCM = 1:10). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 9 H, 8-H), 1.60–1.78 (m, 3 H, 3′-H, 4-H), 1.95–2.08 (m, 1 H, 3-H), 2.30 (br. s, 1 H, -NH), 2.81–2.85 (dt, *J* = 10.2, 6.4 Hz, 1 H, 5′-H), 2.97–3.05 (dt, *J* = 10.4, 6.6 Hz, 1 H, 5-H), 3.55–3.60 (dd, *J* = 8.6, 5.2 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5 (C4), 28.0 (C8), 30.4 (C3), 47.0 (C5), 60.4 (C2), 80.9 (C7), 174.7 (C6) ppm. IR: $\tilde{\nu}$ = 3346 (w), 2972 (w), 2926 (w), 2866 (w), 1725 (s), 1476 (w), 1453 (w), 1389 (w), 1366 (m), 1226 (m), 1153 (s), 1116 (m), 846 (w), 800 (w), 743 (w) cm^{-1}.

Supporting Information (see footnote on the first page of this article): Experimental procedures, detailed correlation of NMR spectroscopic data, ^{1}H and ^{13}C NMR spectra for all new compounds.

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