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Molecular Building Kit of Fused-Proline-Derived Peptide Mimetics Allowing Specific Adjustment of the Dihedral Ψ Angle

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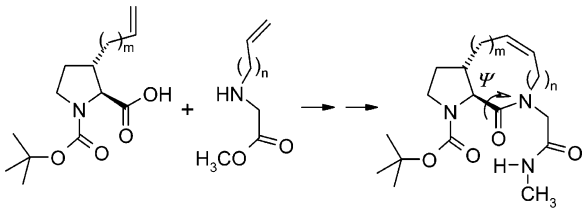

Proline-derived peptide mimetics have become an area of paramount importance in peptide and protein chemistry. Since protein crystal structures frequently display Ψ angles of 140−170° for prolyl moieties, our intention was to design a completely novel series of 2,3-fused-proline-derived lactams covering this particular conformational space. Extending our recently described toolset of spirocyclic reverse-turn mimetics, we synthesized pyrrolidinyl-fused seven-, eight-, and nine-membered unsaturated lactam model peptides taking advantage of Grubbs' ring-closing metathesis. Investigating the seven-membered lactam **3a** by means of IR and NMR spectroscopy and semiempirical molecular dynamics simulations, we could not observe a U-turn conformation; however, increasing the ring size to give eight- and nine-membered congeners revealed moderate and high type II β-turn inducing properties. Interestingly, the conformational properties of our model systems depend on both the ring size of the fused dehydro-Freidinger lactam and the position of the endocyclic double bond. Superior reverse-turn inducing properties could be observed for the fused azacyclononenone **3e**. According to diagnostic transanular NOEs, a discrete folding principle of the lactam ring strongly deviating from the regioisomeric lactams **3c**,**f** explains the conformational behavior. Hence, we were able to establish a molecular building kit that allows adjustments of a wide range of naturally occurring proline Ψ angles and thus can be exploited to probe molecular recognition and functional properties of biological systems.

Introduction

Reverse-turn motifs[1,2] are known as major recognition patterns for various target proteins and, therefore, are valuable core structures for the development of pharmaceutical drugs when starting from physiological hormones or neurotransmitters.[3] As an example, more than 100 peptide activated G-protein-coupled receptors bind ligands with U-turn type structures.[4] Drug research is focused on the design of bioisosteric scaffolds that allow a stable prearrangement of reverse-turn structures in order to enhance target binding and selectivity properties and to increase the metabolic stability of promising lead compounds.[5−7] Reverse-turn surrogates might also give rise to tailor-made

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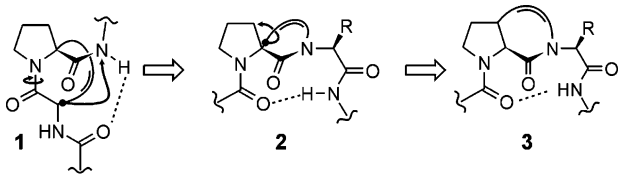


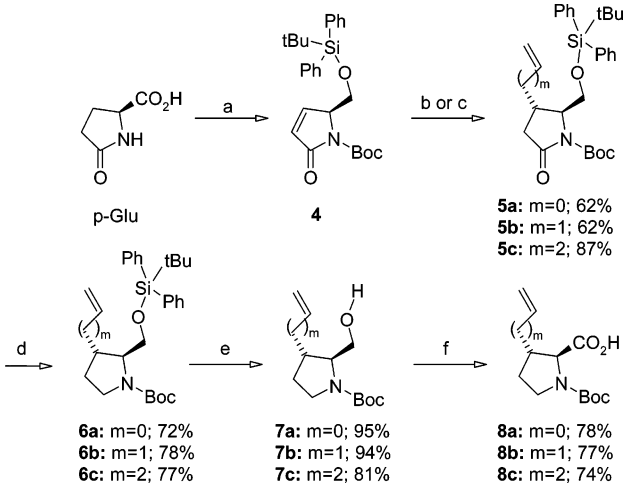
FIGURE 1. Gradual adjustment of crucial dihedral angles.

proteins displaying optimized biological properties through expressed protein ligation (EPL), which enables the semisynthetic incorporation of a limitless variety of nonproteinogenic modules into proteins of variable size, facilitating the construction of chimeric proteins.[8] As proline frequently induces a reversal in backbone conformation and is able to trigger biological signals by cis/trans isomerization,[9] it has become a subject of major interest.[10,11] By incorporating proline into position $i + 2$ of a model peptide surrogate, we were able to generate VI β-turn inducing peptide mimetics of type **1** allowing a gradual adjustment of crucial dihedral angles depending on the ring size (Figure 1).[12] To extend our synthetic approach, the proline-derived reverse-turn nucleating moiety was moved into position $i + 1$, enabling the formation of an olefin-based lactam bridge to the backbone nitrogen of Xaa_{i+2} when the molecular design of our target scaffold **3** rigidizing the backbone dihedral angles ϕ_{i+1} and ψ_{i+1} involved cis/trans isomerization and formal migration. Interestingly, the six-, seven- and eight-membered unsaturated spirocyclic lactams **2** adopted conformations almost ideally matching the prerequisites for canonical type II β-turns with Ψ_{i+1} angles between 113° and 131°.[13] Considering Ramachandran plots derived from high-resolution protein crystal structures containing proline,[14] we recognized that the largest population of proline conformers exhibited Ψ angles within a range of 140−170°. Designing a molecular building kit that facilitates a fine-tuning of the proline Ψ-angle covering this particular conformational space, we decided to formally migrate the C,C-bond connecting the lactam ring with the proline moiety from the α- into the β-position. Thus, the more coplanar orientation of a fused ring system of type **3** should result in an increase of Ψ_{i+1} when compared with the more or less perpendicular disposition of the spirocyclic molecular scaffold **2**. The ring size of the lactam and the position of the double bond within the ring should allow adjustment of the intended Ψ angle, while the calculation of the approximate values should be possible with the help of molecular dynamics (MD) simulations. We were intrigued whether the proline-derived lactams of type **3** could be assembled by peptide condensation and subsequent Grubbs' ring-closing metathesis (RCM), a concept that proved successful to generate the proline-derived lactams of type **1** and **2**.[12,13] In this article, we describe a practical synthetic approach to seven-, eight-, and nine-membered model peptide surrogates and a combination of spectroscopic investigations and semiempirical MD simulations of the conformational behavior. In order to demonstrate the general applicability of the strategy for Xaa_{i+2}, we elaborated a synthesis pathway incorporating tyrosine as a representative α-amino acid different from glycine.

Results and Discussion

Synthesis. Our plan of synthesis was based on chemoselective functionalization of pyroglutamate in position 4, followed by an effective amide coupling and Grubbs' ring-closing metathesis. Starting from pyroglutamate, the dehydrolactam **4** was synthesized in 36% overall yield and then subjected to a trans-selective, organocuprate mediated 1,4-addition (Scheme 1).[15] While lactam

SCHEME 1 [a]



[a] Reagents and conditions: (a) ref 15, 36% over five steps; (b) ref 15; (c) AllMgBr or 3-butenyl-MgBr, TMSCl, HMPA, THF, −78 °C; (d) 1. $LiAlH_4$, Et_2O, −78 °C; 2. Et_3SiH, $BF_3 \times Et_2O$, CH_2Cl_2, −86 °C to −78 °C, RP18-MPLC; (e) Bu_4NF, HOAc, THF, −14 °C to rt; (f) CrO_3, H_2SO_4, H_2O, $(CH_3)_2CO$, −14 °C to rt.

5a was readily available, acceptable yields of the allyl and homoallyl derivatives **5b** and **5c**, respectively, could only be afforded by using conditions that Bausanne et al. described for organocuprate additions to dehydropyrrolidinones.[16] Lactam reduction was performed in two steps by reaction with $LiAlH_4$ and subsequent treatment with triethylsilane/$BF_3 \times Et_2O$[17] to give the pyrrolidine derivatives **6a**−**c**. Deprotection with NBu_4F/

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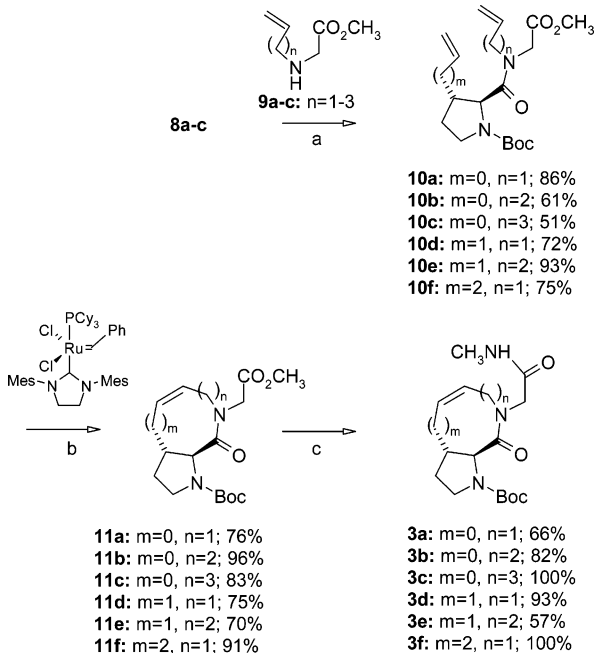
SCHEME 2 [a]



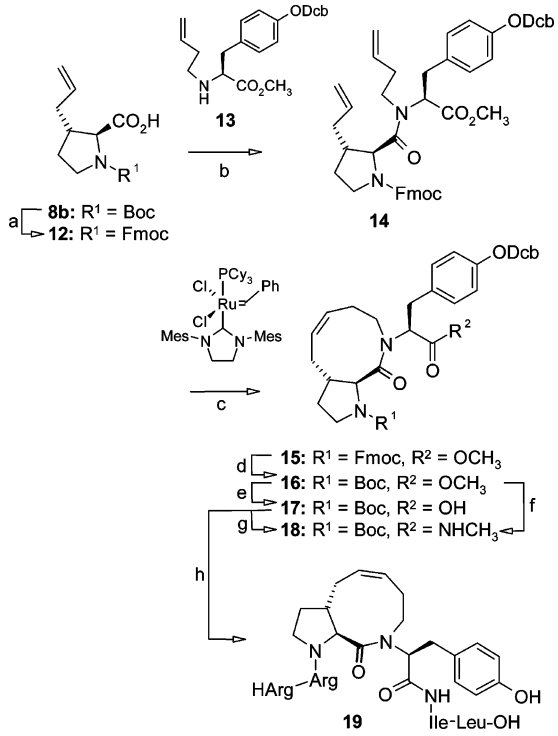
[a] Reagents and conditions: (a) HATU, HOAt, NEM, NMP, rt; (b) CH_2Cl_2, reflux; (c) H_2NMe, EtOH, rt.

HOAc furnished the prolinol derivatives **7a**−**c** in 63−67% yield over all three steps. Finally, Jones oxidation led to a formation of the C3-functionalized prolines **8a**−**c**.[18]

Amide formation between the chiral building blocks **8a**−**c** and the *N*-substituted glycine derivatives **9a**−**c**[19,20] using the coupling mixture HATU/HOAt (*O*-(7-azabenzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate/1-hydroxy-7-azabenzotriazole) allowed an efficient synthesis of the RCM precursors **10a**−**f**. Olefin metathesis employing Grubbs' catalyst of the second generation[21] to afford the seven-membered and eight-membered unsaturated bicyclic lactams **11a**,**b**,**d** readily proceeded in standard concentrations, while the nine-membered systems **11c**,**e**,**f** required high dilution or pseudo dilution to avoid cross-metathesis.[22] Finally, the model peptides **3a**−**f** were generated by aminolysis with methyl amine (Scheme 2).

To apply our methodology to a putatively bioactive peptide analogue, a conformationally restricted Pro-Tyr mimetic was synthesized and incorporated into a surrogate for the neuromodulator NT(8-13) with the sequence HArg-Arg-Pro-Tyr-Ile-Leu-OH (Scheme 3).[23] In principle, this synthesis worked

SCHEME 3 [a]



[a] Reagents and conditions: (a) 1. TFA/CH_2Cl_2 = 3:7, rt, 2. FmocOSu, $NaHCO_3$, dioxane/H_2O, rt (93%); (b) 1. $(Cl_3CO)_2CO$, 2,6-lutidine, dioxane, rt, 2. **13** (Dcb: 2,6-dichlorobenzyl), dioxane, rt (80%); (c) CH_2Cl_2, refl. (87%); (d) 1. piperidine, CH_2Cl_2, rt, 2. Boc_2O, CH_2Cl_2, rt (73%); (e) NaOH, H_2O, MeOH, THF, 0 °C (100% crude); (f) CH_3NH_2, EtOH; (g) CH_3NH_2 × HCl, PyBOP, DBU, DMF; (h) peptide synthesis: resin = Boc-Leu-PAM resin, amino acids = Boc-Ile-OH, Boc-Arg(Tos)-OH, Boc-deprotection: TFA/CH_2Cl_2/indole = 50:50:0.01, followed by DIPEA/CH_2Cl_2 = 1:9, coupling: HATU, DIPEA, NMP, rt, peptide cleavage: HF/anisole = 9:1, 0 °C.

analogously. Whereas HATU-mediated acylation failed, peptide coupling of 3-allylprolines with *N*-alkyl-substituted amino acids different from glycine was possible by employing Fmoc protection. Thus, the intermediate **8b** was converted into the congener **12** by the acidolytic cleavage subsequent reaction with FmocOSu. We took advantage of BTC (bis-trichloromethyl-carbonate)[24] that allowed a smooth and high-yielding coupling with the sterically hindered *N*-(3-butenyl)tyrosine analogue **13** (Supporting Information) to furnish the diene **14** in 80% yield. In fact, the Fmoc-protected diene showed superior properties, and the subsequent olefin metathesis resulted in 87% formation of the nine-membered lactam derivative **15**. Exchange of the Fmoc protecting group by Boc gave the carboxylic ester **16**, which was subjected to saponification and aminolysis to afford the carboxylic acid **17** and the methyl amide **18**, respectively. The amide **18** was also available by activation of the carboxylic acid **17** and coupling with methyl amine. Starting from crude carboxylic acid **17**, peptide synthesis following a well-established solid phase supported acylation−cleavage protocol[13,25] furnished the conformationally constrained peptide derivative **19**.

Conformational Investigations. To evaluate the conformational behavior of the candidate target structures **3a**−**f**, we

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(20) Compound **9c**, which was reported in Hu, Y.-J.; Roy, R. *Tetrahedron Lett.* **1999**, *40*, 3305−3308 and was conveniently synthesized as **9b** described in ref 20.

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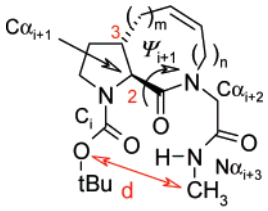
TABLE 1. Conformational Analysis of the Model Peptide Mimics 3a−f Evaluated by NMR and IR Spectroscopy and Calculated by Quantum Mechanical MD Simulations[a]



3a-f

entry	3a	3b	3c	3d	3e	3f
ring topology	$m = 0, n = 1$	$m = 0, n = 2$	$m = 0, n = 3$	$m = 1, n = 1$	$m = 1, n = 2$	$m = 2, n = 1$
lactam ring size	7	8	9	8	9	9
^{1}H NMR, δ_{NH}[b]	6.27/6.19	6.74/6.59	7.22/6.96	6.92/6.64	7.46/6.93	6.91/6.56
ratio of Boc rotamers[c]	50:50	70:30	85:15	80:20	90:10	85:15
glycine $\delta_{H\alpha}/\delta_{H\alpha'}$; $\Delta\delta_{H\alpha,H\alpha'}$[d]	4.23/3.99 0.24	4.57/3.64 0.93	4.66/3.48 1.18	4.52/3.62 0.90	4.87/3.15 1.72	4.62/3.43 1.18
IR: NH band[e]	3411, 3444	3379, (3435), (3450)	3367, (3413)	3381, (3414), (3440)	3346	3367, (3410)
Ψ_{i+1} [deg]	175.1 ± 10.5	160.8 ± 13.3	148.3 ± 16.1	159.5 ± 12.7	140.6 ± 14.2	153.3 ± 15.3
d O$_i$−C$_{i+3}$ [Å][f]	8.73 (39%) 7.44 (61%)	6.95 (57%) 8.65 (10%) 7.80 (33%)	6.26 (55%) 8.65 (45%)	6.89 (83%) 8.70 (17%)	6.55 (97%) 8.87 (3%)	6.78 (100%)
β [deg][g]	−109.3 (39%) 29.7 (61%)	25.7 (57%) −110.5 (10%) −111.2 (33%)	21.2 (55%) −118.5 (45%)	25.2 (83%) −112.8 (17%)	4.2 (97%) −130.3 (3%)	19.1 (100%)

[a] The values given are averages over 10 000 geometries extracted from a 1 ns trajectory. [b] δ_{NH} [ppm] of both Boc rotamers. [c] Boc rotamers given as the ratio of H-bonded and non-H-bonded species. [d] Data of the major rotamer are given, $c = 2$ mM, $CDCl_3$. [e] Wavenumber [cm^{-1}], $c = 2$ mM, $CHCl_3$, values in parentheses represent the weak and very weak signals of non-H-bonded species. [f] d O$_i$−C$_{i+3}$: average distance from O$_i$ to C$_{i+3}$ (distance between the *t*BuO-oxygen and the amide methyl carbon atom, representing Cα$_i$ and Cα$_{i+3}$, respectively). [g] β: virtual dihedral angle formed by the atoms C$_i$−Cα$_{i+1}$−Cα$_{i+2}$−Nα$_{i+3}$.

performed spectroscopical studies based on IR and ^{1}H NMR spectroscopy and semiempirical molecular dynamics simulations (Table 1). To exclude intermolecular interactions, spectra were recorded at 2 mM concentrations.[26]

Our initial investigations were directed to the seven-membered lactam structure **3a** when two methylamide protons, each integrating for about 0.5 H, could be observed by ^{1}H NMR (6.27 ppm/6.19 ppm), which is obviously due to the formation of an equilibrium of rotamers within the *N*-Boc moiety. According to the chemical shifts, an internal H bond seemed unlikely. This observation was corroborated by FTIR spectroscopy when NH-stretching absorptions at wave numbers of 3444 and 3411 cm^{-1} indicated the absence of internal hydrogen bonds.[27] Furthermore, difference NOE measurements did not reveal enhancement effects for the amide CH_3 or NH signals when irradiating at the Boc-protons and vice versa. Moreover, the seven-membered lactam **3a** only displayed a $\Delta\delta_{H\alpha/H\alpha'}$ value of 0.24 ppm, indicating that a reverse-turn formation was not adopted. The diagnostic value of $\Delta\delta_{H\alpha/H\alpha'}$ was recently established by Ikawa et al.,[28] when the glycine α-protons of the ring opened model peptide analogue Boc-Pro-*N*-Me-Gly-NHCH$_3$ showed highly different chemical shifts ($\Delta\delta_{H\alpha/H\alpha'}$, $CDCl_3$: 1.50 ppm). Obviously, this is due to an H-bond-mediated rigidization between the methyl amide proton and the Boc carbonyl group resulting in an anisotropic influence of the proline carbonyl onto the downfield shifted glycine α-proton. The average Ψ_{i+1} angle of the seven-membered lactam structure of **3a** was calculated to be 175.1°, far exceeding the ideal type II β-turn adjusting angle of 120°. Clustering the obtained snapshots of the molecular dynamics trajectory resulted in two main populations. Both clusters display an average distance d O$_i$−C$_{i+3}$ (representing Cα$_i$ and Cα$_{i+3}$, respectively) higher than 7 Å, which means that a U-turn formation is implausible.[29] Moreover, their variable angles β (C$_i$−Cα$_{i+1}$−Cα$_{i+2}$−N$_{i+3}$), defined by Ball[29] representing the planarity of a potential reverse-turn structure, show significant deviations from a coplanar disposition (29.7° and −109.3°).

Interestingly, both regioisomeric eight-membered lactams **3b** and **3d** exhibited an elevated tendency to adopt an internal hydrogen bond. Compared to the caprolactam **3a**, chemical shifts for the methylamide protons of **3b** [6.74 ppm (70% rotamer)/ 6.59 ppm (30% rotamer)] and **3d** [6.92 ppm (80% rotamer)/ 6.64 ppm (20% rotamer)] resonated at significantly lower field, especially for the main rotamers. Obviously, this ratio is increased in favor of the respective stronger deshielded amide proton signal by the formation of hydrogen-bonded states. The diagnostic $\Delta\delta_{H\alpha/H\alpha'}$ values of 0.93 ppm (**3b**) or 0.90 ppm (**3d**) corroborated secondary structure formation. An H-bond between the Boc C═O group and the NH could be also observed by the IR spectroscopy displaying major N−H stretching absorptions at wavenumbers of 3380 cm^{-1} for both regioisomers **3b** and **3d**. Irradiation to the Boc-CH$_3$ of **3d** caused a significant

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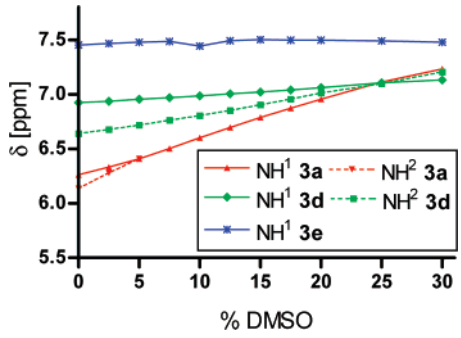

FIGURE 2. Amide proton NMR chemical shifts (δ) as a function of the percentage of DMSO-d_6 in $CDCl_3$ for the peptide mimetics **3a**,**d**,**e** (c = 2 mM); for **3e**, NH^2 could not be detected unambiguously.

difference NOE effect to the amide methyl protons, which is also observed vice versa. Independent from the position of the double bond, the eight-membered model peptides **3b** and **3d** exhibited a nearly identical conformational behavior, with the exception of **3b** populating three major conformers. Compared to the Ψ_{i+1} angle of 175.1°, indicating approximately an antiperiplanar situation for **3a**, the calculated Ψ_{i+1} angles decreased to values of 160.8° and 159.5° for **3b** and **3d**, respectively. The reduced distances d O_i-C_{i+3} (**3b**: 6.95 Å; **3d**: 6.89 Å) and pseudo-dihedral angles β (**3b**: 25.7°; **3d**: 25.2°) calculated for the major population of both conformers are also diagnostic.

Considering the nine-membered lactam systems, we noticed substantial downfield shifts for the NH protons (NH: **3c**, 7.22 ppm; **3e**, 7.46 ppm; **3f**, 6.91 ppm). It is worth mentioning that the obviously hydrogen-bonded rotamer of **3e** was populated at 90%, whereas the regioisomers **3c** and **3f** displayed an 85% preference. As expected, the IR absorption bands were in accordance with our findings when a lower wavenumber was observed for **3e** (3346 cm^{-1}) than for **3c**,**f** (each 3367 cm^{-1}). NOE investigations showed highly significant effects between the Boc-CH_3 moieties and the amide methyl group; irradiating at the NH, an enhancement of the Boc-CH_3 could also be detected.

Much attention was attracted by the nine-membered lactam series **3c**,**e**,**f** because conformational behavior significantly depended on the position of the endocyclic double bond. According to our calculations on the 'middle' double bond lactam **3e**, the major population of conformers (97%) almost ideally matched the prerequisites for a canonical reverse turn (Ψ_{i+1} = 140.6°, β = 4.2°) and, thus, could serve as a promising antiparallel pleated β-sheet nucleator whereas the double bond regioisomers **3c** and **3f** (55% and 100% of the conformers, respectively) showed higher calculated Ψ_{i+1} angles at 148.3° and 153.3° and β-values at 21.2° and 19.1°. Interestingly, the lowest d O_i-C_{i+3} value (6.26 Å) could be deduced for **3c**, although only 55% of the conformers reached this low value. To further investigate the conformational behavior dependent on the ring size, NMR spectra of the lactams **3a**, **3d**, and **3e** were measured in presence of increasing amounts of DMSO-d_6, which acts as a competitive H-bond acceptor (Figure 2). Investigating the influence on the two amide protons of the seven-membered ring system **3a**, we observed a strong downfield shift and a coalescence of the two signals at about 2.5% DMSO-d_6. This means that the amide proton was completely exposed to the H-bond-accepting solvent and therefore not integrated in a reverse-turn structure.[30] When evaluating the eight-membered system **3d**, the proton exhibiting the higher chemical shift (6.92 ppm) is moved to the downfield while displaying a minor slope compared to that of the proton of the second rotamer (6.64 ppm), which means that it is less exposed to the solvent and belongs to the H-bonded species. Interestingly, a coalescence of the two signals did not occur, obviously, since the bonded and the nonbonded forms were coexisting independent from the solvent. It is worthy of note that the nine-membered dehydro-Freidinger lactam **3e** did not reveal substantial alteration of the NH shift, thus indicating a stable intramolecular H-bond in the presence of even 30% DMSO.

Additionally, we evaluated DMSO-effected reductions of $\Delta\delta_{H\alpha/H\alpha'}$ values for **3d**,**e**. When compared to those of the ring open congener BocProN(Me)GlyNHCH$_3$[28] ([$\Delta\delta_{H\alpha,H\alpha}$ 0% DMSO-d_6] − [$\Delta\delta_{H\alpha,H\alpha}$ 30% DMSO-d_6] ≈ 0.70), addition of 30% DMSO-d_6 caused significantly less diminution for **3d** ([$\Delta\delta_{H\alpha,H\alpha}$ 0% DMSO-d_6] − [$\Delta\delta_{H\alpha,H\alpha}$ 30% DMSO-d_6] = 0.13) and **3e** ([$\Delta\delta_{H\alpha,H\alpha}$ 0% DMSO-d_6] − [$\Delta\delta_{H\alpha,H\alpha}$ 30% DMSO-d_6] = 0.33), which means that the secondary structure of Boc-Pro-*N*-Me-Gly-NHCH$_3$ is more affected by DMSO and, thus, less stable than the conformationally rigidized peptide mimetics **3d**,**e** (DMSO-d_6 titration diagram, see Supporting Information).

To comparatively investigate the structural properties of the three isomeric scaffolds **3c**,**e**,**f** and, thus, to elucidate the conformational behavior of the fused nine-membered dehydro-Freidinger lactams, we clearly assigned all proton signals (COSY, HSQC, and HMBC experiments) and performed NOE studies (difference NOE and NOESY spectra). In Figure 3, arrows are indicating the most essential diagnostic signals clearly confirming the distinctive geometry of each nine-membered ring system. For **3c**, we could observe a NOESY cross-peak from the proline Hα (H-10a) to the olefinic proton H-4 and to one H-8, which itself displayed interactions with the second olefinic proton (H-5). Moreover, the proline Hβ (H-3a) in the upper ring plane is situated close to a methylene proton at C-6. Thus, we derived a folding pattern, in which C-4, C-5, and C-8 are located below, C-6 is located above, and C-7 is approximately within the ring plane. A very similar arrangement was deduced for **3f.** We observed a cross-peak between H-10a and a respective methylene proton at C-4/C-5/C-8, whereas the olefinic carbon C-7 (cross-peak H-7/H-3a) is located slightly above the ring plane. Moreover, the second olefinic proton (H-6) is situated close to H-3a and the second methylene proton at C-4, which confirms a ring architecture analogous to that of **3c**. As we expected, a different conformational behavior can be derived for the 'middle' double bond isomer **3e**. The proximity of H-3a to the olefinic H-5 and H-10a to H-7, respectively, clearly indicates that C-5 is located above and C-7 below the ring plane, contrary to the folding of **3c** and **3f**.

Performing MD simulations of **3c**,**e**,**f**, we observed an instant lactam ring flip into one single conformation, which proved to be stable during the whole simulation time and which agreed with the structures determined experimentally. Energy-minimized structures of the conformers representing the cluster centers are shown in Figure 3. Thus, the overall similarity of the nine-membered lactams **3c** and **3f** can be explained by their closely related scaffolds evaluated experimentally and theoretically.

(30) Awasthi, S. K.; Raghothama, S.; Balaram, P. *Biochem. Biophys. Res. Commun.* **1995**, *216*, 375−381.

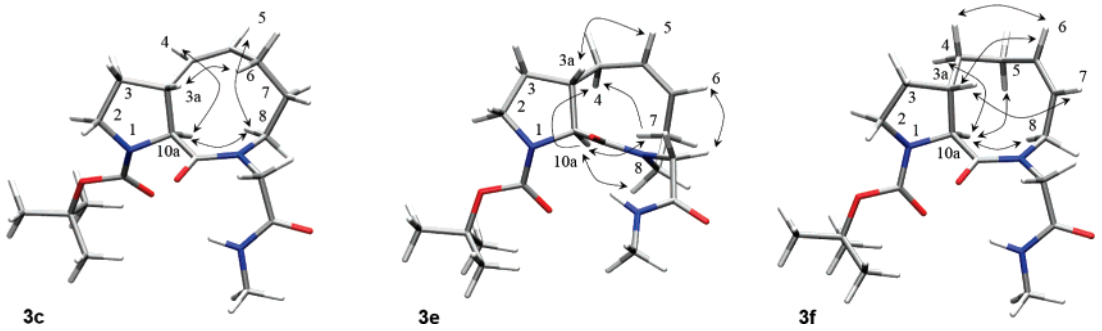

FIGURE 3. Conformers of **3c**,**e**,**f** experimentally verified by NOE investigations (single-headed arrow: difference NOE; double-headed arrow: NOESY) and theoretically calculated by energy minimization of conformations representing the cluster centers of the MD simulations.

Conclusion

In conclusion, we were able to establish a novel type of fused-proline-derived peptide mimetic scaffolds involving a newly developed EPC-synthesis of *trans*-3-alkenylprolines and the application of Grubbs' ring-closing olefin metathesis. Extended by the spirocyclic analogues that we presented very recently,[13] a fine-tuning of the proline Ψ_{i+1} angle to cover the conformational space of proline in peptides and proteins will be very helpful for future applications as molecular probes and drug candidates in chemical biology and medicinal chemistry, respectively. While the seven-membered model peptide **3a** is not able to form an internal hydrogen bond, obviously due to the conformational restriction of the proline Ψ angle in the region of 180°, the eight-membered- and nine-membered systems **3b**−**f** allow a gradual adjustment of the secondary structure. Comparing the conformational behavior of six model peptide surrogates, the nine-membered lactam derivative **3e** was evaluated as a superior type II β-turn nucleating moiety.

Experimental Section

***tert*-Butyl (4*S*,5*S*)-4-Allyl-5-(*tert*-butyldiphenylsilyloxymethyl)-2-oxopyrrolidine-1-carboxylate (5b).**[15] In a flame-dried flask, a 1 M solution of allylmagnesiumbromide in THF (6.77 mL, 6.77 mmol) was added at 0 °C to a suspension of CuI (644.4 mg, 3.384 mmol) in THF (50 mL). The mixture was then cooled to −78 °C, and then a precooled (−78 °C) solution of (*S*)-1-*tert*-butyloxycarbonyl-5-*tert*-butyldiphenylsilyloxymethyl-1,5-dihydro-2*H*-pyrrol-2-one (**4**, 509.0 mg, 1.128 mmol),[15] TMSCl (trimethylsilyl chloride, 0.285 mL, 2.256 mmol), and HMPA (hexamethyl phosphoramide, 0.408 mL, 2.256 mmol) in THF (10 mL) was added slowly. After 30 min, a saturated solution of NH_4Cl in H_2O (15 mL) was added, and the reaction mixture was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with saturated aq NH_4Cl, dried with $MgSO_4$, and evaporated. Flash chromatography (gradient petroleum ether:EtOAc 97:3 → 95:5) afforded **5b** (345.4 mg, 62%) as a colorless oil: $[\alpha]_D^{20}$ −31.1° (c = 0.942, $CHCl_3$), Lit.:[15] $[\alpha]_D^{20}$ −32.7° (c = 0.22, $CHCl_3$).

***tert*-Butyl (4*S*,5*S*)-4-(3-Butenyl)-5-(*tert*-butyldiphenylsilyloxymethyl)-2-oxopyrrolidine-1-carboxylate (5c).** The reaction was analogously performed as described for **5b**, using **4** (1000 mg, 2.206 mmol), a 0.5 M solution of 3-butenylmagnesiumbromide in THF (26.5 mL, 13.25 mmol), and CuI (1800.0 mg, 9.486 mmol) in THF (100 mL), TMSCl (0.8 mL, 7.280 mmol), and HMPA (1.1 mL, 6.323 mmol) in THF (15 mL). Flash chromatography (gradient petroleum ether:EtOAc 97:3 → 9:1) afforded **5c** (970.4 mg, 87%) as a colorless oil: $[\alpha]_D^{20}$ −28.6° (c = 1.0, $CHCl_3$); IR (film) 1789, 1752, 1712 cm^{-1}; ^1H NMR δ 1.04 (s, 9H), 1.44 (s, 9H), 1.47−1.61 (m, 2H), 2.05−2.14 (m, 2H), 2.17 (dd, J = 17.7, 2.1 Hz, 1H), 2.28−2.37 (m,1H), 2.91 (dd, J = 17.7, 8.9 Hz, 1H), 3.87 (dd, J = 12.1, 4.3 Hz, 1H), 3.85−3.87 (m, 1H), 3.87 (dd, J = 12.1, 4.6 Hz, 1H), 4.97−5.05 (m, 2H), 5.72−5.84 (m, 1H), 7.34−7.45 (m, 6H), 7.58−7.65 (m, 4H); ^{13}C NMR δ 19.2, 26.8, 28.0, 29.6, 31.0, 32.6, 34.4, 38.5, 64.3, 64.5 (conf.), 82.8 (conf.), 115.4, 127.8, 129.9, 132.7, 133.0 (conf.), 135.6, 135.5 (conf.), 137.5, 150.0; APCIMS 408 $[M - Boc + H]^+$. Anal. Calcd for $C_{30}H_{41}NO_4Si$ (507.75): C, 70.97; H, 8.14; N, 2.76. Found: C, 70.99; H, 8.19; N, 2.86.

***tert*-Butyl (2*S*,3*R*)-2-(*tert*-Butyldiphenylsilyloxymethyl)-3-vinylpyrrolidine-1-carboxylate (6a).** To a solution of (4*R*,5*S*)-1-*tert*-butyloxycarbonyl-5-(*tert*-butyldiphenylsilyloxymethyl)-4-vinylpyrrolidine-2-one (**5a**)[15] (720.0 mg, 1.546 mmol) in Et_2O (20 mL) was added a 1 M $LiAlH_4$ solution in Et_2O (1.546 mL, 1.546 mmol) at −78 °C. After 10 min, the reaction was quenched with H_2O (1 mL) and filtered through a pad of Celite. The resulting material was dried thoroughly in vacuo and then dissolved in CH_2Cl_2 (5 mL). After cooling to −78 °C, Et_3SiH (0.247 mL, 1.546 mmol) and then $BF_3 \times Et_2O$ (0.211 mL, 1.700 mmol) were added. The mixture was stirred for 30 min and then quenched with a saturated $NaHCO_3$ solution (0.5 mL). Without heating (!), the resulting mixture was concentrated to approximately 1 mL and then immediately injected into a RP18-MPLC column. Gradient elution (flow rate, 20 mL/min; MeOH:H_2O 6:4 → 8:2) and subsequent evaporation afforded the product in a quite high purity. Final purification was performed by flash chromatography (petroleum ether:EtOAc 97:3) and gave **6a** (499.7 mg, 72%) as a colorless oil: $[\alpha]_D^{20}$ −32.9° (c = 1.015, $CHCl_3$); IR (film) 1697 cm^{-1}; ^1H NMR δ 1.05 and 1.07 (2× s, 9H, 2 conf.), 1.33 (s, 6H, conf.), 1.47 (s, 4H, conf.), 1.60−1.73 (m, 1H), 1.98−2.12 (m,1H), 3.00−3.15 (m, 1H), 3.31 (ddd, J = 10.6, 7.2, 7.2 Hz, 1H), 3.53−3.77 (m, 3.6H), 4.05−4.15 (m, 0.4H, conf.), 4.96−5.04 (m, 2H), 5.72−5.88 (m, 1H), 7.34−7.45 (m, 6H), 7.63−7.74 (m, 4H); ^{13}C NMR δ 19.3, 26.8, 28.3, 28.4, 29.6, 30.6, 44.1, 44.8, 46.0, 46.7, 63.3, 63.4, 63.6, 64.3, 79.2, 80.0, 114.6, 114.9, 127.6, 127.7, 129.5, 129.6, 133.4, 133.6, 135.6, 135.7, 139.2, 139.9, 154.4; CIMS 466 $[M + H]^+$. Anal. Calcd for $C_{28}H_{39}NO_3Si$ (465.71) × H_2O: C, 69.52; H, 8.54; N, 2.90. Found: C, 69.33; H, 8.29; N, 2.91.

***tert*-Butyl (2*S*,3*S*)-3-Allyl-2-(*tert*-butyldiphenylsilyloxymethyl)-pyrrolidine-1-carboxylate (6b).** The reaction was analogously performed as described for **6a**, using **5b** (1100.0 mg, 2.234 mmol) in Et_2O (200 mL) and a 1 M $LiAlH_4$ solution in Et_2O (2.2 mL, 2.2 mmol). Further reduction: CH_2Cl_2 (5 mL), Et_3SiH (355 μL, 2.234 mmol), $BF_3 \times Et_2O$ (305 μL, 2.457 mmol). RP18-MPLC (see above) and subsequent flash chromatography (petroleum ether:EtOAc 95:5) gave **6b** (780.0 mg, 78%) as a colorless oil: $[\alpha]_D^{20}$ −17.1° (c = 0.392, $CHCl_3$); IR (film) 1696 cm^{-1}; ^1H NMR δ 1.05 and 1.06 (2× s, 9H, conf.), 1.33 and 1.46 (2× s, 9H, conf.), 1.48−1.60 (m, 1H), 1.96−2.26 (m,3H), 2.35−2.53 (m, 1H), 3.29 (ddd, J = 10.8, 8.0, 5.5 Hz, 1H), 3.43−3.95 (m, 4H), 4.97−5.10 (m, 2H), 5.69−5.85 (m, 1H), 7.33−7.45 (m, 6H), 7.64−7.70 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 18.6, 18.7, 26.5, 28.0, 28.3, 29.0, 37.5, 45.3, 62.6, 63.9, 78.2, 116.3, 127.4, 127.8, 129.1, 129.8, 132.9, 134.4, 134.9, 136.3, 136.8, 153.4; CIMS 480 $[M + H]^+$. Anal. Calcd for

$C_{29}H_{41}NO_3Si$ (479.74): C, 72.61; H, 8.61; N, 2.92. Found: C, 72.41; H, 8.65; N, 2.86.

***tert*-Butyl (2*S*,3*S*)-3-(3-Butenyl)-2-(*tert*-butyldiphenylsilyloxymethyl)pyrrolidine-1-carboxylate (6c).** The reaction was analogously performed as described for **6a**, using **5c** (110.0 mg, 0.217 mmol) in Et_2O (25 mL) and a 1 M $LiAlH_4$ solution in Et_2O (0.22 mL, 0.22 mmol) at −78 °C. Further reduction: CH_2Cl_2 (2 mL), Et_3SiH (34.4 μL, 0.217 mmol), and $BF_3 \times Et_2O$ (30 μL, 0.239 mmol). RP18-MPLC gave **6c** (81.9 mg, 77%) as a colorless oil: $[\alpha]_D^{20}$ −25.3° (c = 0.3, $CHCl_3$); IR (film) 1697 cm^{-1}; ^1H NMR δ 1.04 and 1.06 (2× s, 9H, conf.), 1.33 and 1.46 (2× s, 9H, conf.), 1.47−1.61 (m, 3H), 1.97−2.15 (m,3H), 2.30−2.67 (m, 1H, conf.), 3.27 (ddd, J = 10.6, 7.5, 6.5 Hz, 1H), 3.42−3.92 (m, 4H), 4.92−5.23 (m, 2H), 5.74−5.88 (m, 1H), 7.32−7.46 (m, 6H), 7.60−7.72 (m, 4H); ^{13}C NMR δ 19.6, 27.0, 28.7, 29.4, 32.6, 33.5, 40.8, 45.5, 46.5, 64.0, 64.4, 79.2, 79.5 (both signals only detected by HMBC), 114.9, 127.8, 128.7, 129.8, 133.8, 134.9, 135.6, 135.7, 136.6, 138.6, 154.6; EIMS 493 [M^+]. Anal. Calcd for $C_{30}H_{43}NO_3Si$ (493.77): C, 72.98; H, 8.78; N, 2.84. Found: C, 72.95; H, 8.76; N, 2.88.

***tert*-Butyl (2*S*,3*R*)-2-Hydroxymethyl-3-vinylpyrrolidine-1-carboxylate (7a).** To a solution of **6a** (178.0 mg, 0.382 mmol) in THF (25 mL) was added acetic acid (0.14 mL) at 0 °C and then a 1 M solution of Bu_4NF in THF (0.96 mL, 0.96 mmol). The mixture was allowed to warm to room temperature and was stirred for 7d, when after 4 and 5 d, respectively, another portion of Bu_4NF (each 0.382 mL, 0.382 mmol) was added. Silica gel (1 g) was added, and the solution was evaporated. Flash chromatography (gradient petroleum ether:EtOAc 95:5 → 9:1) afforded **7a** (82.5 mg, 95%) as a colorless oil: $[\alpha]_D^{20}$ −55.2° (c = 1.021, $CHCl_3$); IR (film) 3419, 1695, 1672 cm^{-1}; ^1H NMR δ 1.47 (s, 9H), 1.67 (dddd, J = 12.3, 10.5, 10.5, 8.1 Hz, 1H), 1.90−2.00 (m,1H), 2.29−2.40 (m, 1H), 3.24 (ddd, J = 10.5, 9.8, 6.6 Hz, 1H), 3.53−3.56 (m, 3H), 4.05−4.15 (m, 1H), 5.06−5.16 (m, 3H), 5.77 (ddd, J = 17.3, 10.2, 7.7 Hz, 1H); ^{13}C NMR δ 28.4, 30.6, 46.1, 46.6, 65.2, 66.0, 80.3, 116.5, 138.0, 156.8; EIMS 227 [M^+]. Anal. Calcd for $C_{12}H_{21}NO_3$ (227.31): C, 63.41; H, 9.31; N, 6.16. Found: C, 63.35; H, 9.38; N, 6.13.

***tert*-Butyl (2*S*,3*S*)-3-Allyl-2-hydroxymethylpyrrolidine-1-carboxylate (7b).**[18] The reaction was analogously performed as described for **7a**, using **6b** (643.0 mg, 1.340 mmol), THF (90 mL), acetic acid (0.47 mL), and a single addition of 1 M Bu_4NF in THF (3.36 mL, 3.36 mmol), stirring for 2 d. Flash chromatography (gradient petroleum ether:EtOAc 95:5 → 9:1) afforded **7b** (303.0 mg, 94%) as a colorless oil: $[\alpha]_D^{20}$ −18.4° (c = 0.683, $CHCl_3$), $[\alpha]_D^{20}$ −21.5° (c = 0.358, MeOH), Lit.:[18] $[\alpha]_D^{25}$ −20.5° (c = 1.5, MeOH); IR (film) 3422, 1695, 1672 cm^{-1}; ^1H NMR δ 1.47 (s, 9H), 1.76−1.87 (m, 1H), 1.88−1.99 (m, 1H), 2.03−2.13 (m, 1H), 2.24−2.35 (m, 1H), 3.19−3.29 (m, 1H), 3.50−3.65 (m, 3H), 3.67−3.77 (m, 1H), 5.02−5.11 (m, 2H), 5.70−5.82 (ddd, J = 17.3, 6.9, 3.4 Hz, 1H); EIMS 241 [M^+].

***tert*-Butyl (2*S*,3*S*)-3-(3-Butenyl)-2-hydroxymethylpyrrolidine-1-carboxylate (7c).** The reaction was analogously performed as described for **7b**, using **6c** (546.9 mg, 1.108 mmol), THF (76 mL), acetic acid (0.39 mL), and 1 M NBu_4NF in THF (2.76 mL, 2.76 mmol), stirring for 4 d. Flash chromatography (petroleum ether: EtOAc 9:1) afforded **7c** (230.1 mg, 81%) as a colorless oil: $[\alpha]_D^{20}$ −22.6° (c = 1.01, $CHCl_3$); IR (film) 3415, 1695, 1671 cm^{-1}; ^1H NMR δ 1.35−1.50 (m, 2H), 1.47 (s, 9H), 1.57−1.78 (m, 2H), 1.91−2.20 (m,3H), 3.24 (ddd, J = 10.9, 8.8, 7.0 Hz, 1H), 3.51−3.62 (m, 3H), 3.65−3.75 (m, 1H), 4.90−5.07 (m, 3H), 5.79 (m, 1H); ^{13}C NMR δ 28.6, 30.1, 32.1, 32.7, 41.3, 46.7, 66.0, 67.5, 80.5, 115.2, 138.1, 157.4; APCIMS 256 [M + H]$^+$. Anal. Calcd for $C_{12}H_{21}NO_3$ (255.36): C, 65.85; H, 9.87; N, 5.49. Found: C, 65.81; H, 9.81; N, 5.51.

(2*S*,3*R*)-*N*-(*tert*-Butyloxycarbonyl)-3-vinylproline (8a). To a solution of **7a** (284.0 mg, 1.249 mmol) in acetone (40 mL) was added a solution of CrO_3 (245.0 mg, 2.470 mmol) and H_2SO_4 (245.0 mg) in H_2O (500 μL) at −14 °C, and then the mixture was allowed to warm to room temperature. After 1 h of stirring, the solution was evaporated and H_2O (1.5 mL) was added. Subsequent extraction with EtOAc (3 × 3 mL) was performed, and the organic layer was extracted again with a saturated aq Na_2CO_3 solution (2.5 mL). The aqueous layer was adjusted to pH 2 using saturated aq citric acid and then extracted with EtOAc (3 × 5 mL). The organic layer was dried over $MgSO_4$, evaporated, and dried over P_4O_{10} to give **8a** (233.8 mg, 78%) as a colorless oil: $[\alpha]_D^{20}$ −48.6° (c = 0.683, $CHCl_3$); IR (film) 1749, 1704, 1678 cm^{-1}; ^1H NMR δ 1.42 (s, 4.5H, conf.), 1.48 (s, 4.5H, conf.),1.74−1.85 (m, 1H), 2.06−2.16 (m, 1H), 2.90−3.02 (m, 0.5H, conf.), 3.13−3.26 (m, 0.5H, conf.), 3.36−3.70 (m, 2H), 3.99 (d, J = 6.0 Hz, 0.5H, conf.), 4.13 (d, J = 4.6 Hz, 0.5H, conf.), 5.13 (d, J = 10.3 Hz, 1H), 5.18 (d, J = 17.1 Hz, 1H, conf.), 5.84 (ddd, J = 17.1, 10.3, 7.1 Hz, 1H); ^{13}C NMR δ 27.8, 28.3, 28.4, 29.7, 30.4, 37.1, 38.1, 45.5, 45.6, 46.0, 48.2, 63.8, 64.1, 80.6, 81.3, 116.1, 116.6, 136.8, 137.1, 153.7, 155.9, 175.1, 178.2; APCIMS 242 [M + H]$^+$. Anal. Calcd for $C_{12}H_{19}NO_4$ (241.29): C, 59.73; H, 7.94; N, 5.80. Found: C, 59.82; H, 7.96; N, 5.97.

(2*S*,3*S*)-3-Allyl-*N*-(*tert*-butyloxycarbonyl)proline (8b).[18] The reaction was analogously performed as described for **8a**, using **7b** (56.0 mg, 0.232 mmol) dissolved in acetone (4 mL) and a solution of CrO_3 (23.3 mg, 0.232 mmol) and H_2SO_4 (23.3 mg) in H_2O (50 μL) to give **8b** (45.4 mg, 77%) as a colorless oil: $[\alpha]_D^{20}$ −39.9° (c = 0.987, $CHCl_3$), Lit.:[18] $[\alpha]_D^{25}$ −27.5° (c = 1.0, $CHCl_3$); IR (film) 1746, 1704, 1682 cm^{-1}; ^1H NMR δ 1.42 (s, 4.5H, conf.), 1.48 (s, 4.5H, conf.), 1.60−1.70 (m, 1H), 2.06−2.18 (m,2H), 2.25−2.42 (m, 1.5H), 2.56−2.66 (m, 0.5 H), 3.37−3.55 (m, 2H), 3.89−3.94 (m, 0.5 H), 4.03−4.06 (m, 0.5H), 5.09 (d, J = 10.7 Hz, 1H), 5.10 (d, J = 17.0 Hz, 1H), 5.78 (ddd, J = 17.0, 10.7, 7.1, 5.9, 5.9 Hz, 1H); EIMS 255 [M^+].

(2*S*,3*S*)-3-(3-Butenyl)-*N*-(*tert*-butyloxycarbonyl)proline (8c). The reaction was analogously performed as described for **8a**, using **7c** (95.0 mg, 0.372 mmol) dissolved in acetone (15 mL) and a solution of CrO_3 (30.6 mg, 0.306 mmol) and H_2SO_4 (30.6 mg) in H_2O (70 μL) to give **8c** (73.8 mg, 74%) as a colorless oil: $[\alpha]_D^{20}$ −36.4° (c = 1.038, $CHCl_3$); IR (film) 1748, 1704, 1673 cm^{-1}; ^1H NMR δ 1.42 (s, 4.5H, conf.), 1.48 (s, 4.5H, conf.),1.50−1.64 (m, 2H) 1.65−1.83 (m, 1H), 2.03−2.20 (m, 3H), 2.26−2.39 (m, 0.5H, conf.), 2.41−2.54 (m, 0.5H, conf.), 3.33−3.67 (m, 2H), 3.86 (d, J = 5.7 Hz, 0.5H, conf.), 3.99 (d, J = 4.3 Hz, 0.5H, conf.), 4.99 (d, J = 10.7 Hz, 1H), 5.04 (d, J = 17.0 Hz, 1H, conf.), 5.79 (ddd, J = 17.0, 10.7, 5.9, 5.9 Hz, 1H); ^{13}C NMR δ 28.0, 28.4, 30.1, 30.2, 31.8, 31.9, 32.6, 32.7, 41.9, 44.4, 45.9, 46.1, 64.5, 64.7, 80.6, 81.3, 115.4, 137.8, 153.9, 156.2, 175.8, 179.0; EIMS 269 [M^+]. Anal. Calcd for $C_{14}H_{23}NO_4$ (269.34): C, 62.43; H, 8.61; N, 5.20. Found: C, 62.51; H, 8.59; N, 5.12.

***N*-Allyl-*N*-[(2*S*,3*R*)-*N*′-(*tert*-butyloxycarbonyl)-3-vinylprolyl]-glycine Methyl Ester (10a).** To a solution of **8a** (18.0 mg, 0.075 mmol, see Supporting Information), HATU (28.5 mg, 0.075 mmol), and HOAt (10.2 mg, 0.075 mmol) in NMP (1.2 mL) was added *N*-ethylmorpholine (18.9 μL, 0.150 mmol), and after 10 min a solution of *N*-allylglycine methyl ester (**9a**)[19] (11.5 mg, 0.090 mmol) in NMP (0.5 mL) was added. After 1 d and 2 d, respectively, portions of HATU (1 d: 5.7 mg, 0.015 mmol, 2 d: 3.0 mg, 0.008 mmol), HOAt (1 d: 2.0 mg, 0.015 mmol, 2 d: 1.0 mg, 0.008 mmol), NEM (1 d: 3.8 μL, 0.030 mmol, 2 d: 1.9 mL, 0.015 mmol), and *N*-allylglycine methyl ester (1 d: 2.3 mg, 0.018 mmol, 2 d: 1.2 mg, 0.009 mmol) were added consecutively to complete the reaction. After 3 d, 5% aq citric acid (2.5 mL) was added, and the solution was extracted with Et_2O (3 × 5 mL). The organic layer was washed with water, dried over $MgSO_4$, evaporated, and separated via flash chromatography (petroleum ether:EtOAc 2:1) to give **10a** (22.7 mg, 86%) as a colorless oil: $[\alpha]_D^{20}$ +25.8° (c = 0.842, $CHCl_3$); IR (film) 1753, 1698, 1667 cm^{-1}; ^1H NMR δ 1.42 and 1.48 (2× s, 9H, conf.), 1.68−1.77 (m, 1H), 2.15−2.16 (m, 1H), 2.89−2.99 (m, 1H), 3.45−3.67 (m, 2H), 3.57 (d, J = 17.4 Hz, 0.3H, conf.), 3.71 and 3.72 (2× s, 3H, conf.), 3.80 (d, J =

17.4 Hz, 0.7H, conf.), 3.85−4.36 (m, 2H), 4.29 (d, J = 17.4 Hz, 0.7H), 4.39 (d, J = 3.0 Hz, 0.3H, conf.), 4.50 (d, J = 3.0 Hz, 0.7H, conf.), 4.53 (d, J = 17.4 Hz, 0.3H, conf.), 5.00−5.30 (m, 4H), 5.70−5.90 (m, 2H); ^{13}C NMR (2 conf.) δ 28.4, 28.5, 29.5, 30.3, 45.6, 45.9, 46.7, 47.0, 47.2, 48.0, 51.2, 51.3, 51.9, 52.0, 61.2, 61.5, 79.5, 80.0, 115.6, 115.8, 118.5, 118.6, 132.5, 132.6, 138.4, 138.5, 153.9, 154.4, 169.6, 169.9, 172.4, 172.5; EIMS 352 [M$^+$]. Anal. Calcd for $C_{18}H_{28}N_2O_5$ (352.43): C, 61.34; H, 8.01; N, 7.95. Found: C, 61.37; H, 8.13; N, 7.81.

***N*-(3-Butenyl)-*N*-[(2*S*,3*R*)-*N*′-(*tert*-butyloxycarbonyl)-3-vinylprolyl]glycine Methyl Ester (10b).** The reaction was analogously performed as described for **10a**, using **8a** (30.0 mg, 0.124 mmol), HATU (47.3 mg, 0.124 mmol), HOAt (16.9 mg, 0.124 mmol) in NMP (1.0 mL), *N*-ethylmorpholine (30.0 μL, 0.249 mmol), and *N*-(3-butenyl)glycine methyl ester (**9b**)[19] (23.1 mg, 0.162 mmol) in NMP (0.5 mL), with 3 d of stirring without further addition of reagents. Flash chromatography (petrol ether:EtOAc 2:1) furnished **10b** (27.8 mg, 61%) as a colorless oil: $[\alpha]_D^{20}$ +40.6° (c = 0.325, $CHCl_3$); IR (film) 1753, 1699, 1664 cm^{-1}; ^{1}H NMR δ 1.42 and 1.44 (2× s, 9H, conf.), 1.66−1.78 (m, 1H), 2.12−2.50 (m, 3H), 2.80−2.98 (m, 1H), 3.26−3.70 (m, 4.4H, conf.), 3.71 and 3.72 (2× s, 3H, conf.), 3.79 (d, J = 17.0 Hz, 0.5H, conf.), 3.88−3.99 (m, 0.3H), 4.15−4.27 (m, 0.3H), 4.31 (d, J = 17.0 Hz, 0.5H, conf.), 4.36 (d, J = 2.8 Hz, 0.5H, conf.), 4.48 (d, J = 2.8 Hz, 0.5H, conf.), 4.57 (d, J = 17.0 Hz, 0.5H, conf.), 4.96−5.22 (m, 4H), 5.68−5.94 (m, 2H); ^{13}C NMR (2 conf.) δ 28.5, 28.6, 29.6, 30.5, 33.3, 33.4, 45.9, 46.1, 48.2, 48.3, 48.5, 48.6, 48.7, 51.1, 51.2, 61.3, 61.6, 79.7, 80.2, 115.7, 115.9, 117.6, 117.8, 134.1, 134.4, 138.7, 154.0, 154.6, 169.7, 170.0, 172.7; EIMS 366 [M$^+$]. Anal. Calcd for $C_{19}H_{30}N_2O_5$ (366.46): C, 62.27; H, 8.25; N, 7.64. Found: C, 62.37; H, 8.37; N, 7.47.

4*N*-[(2*S*,3*R*)-*N*′-(*tert*-Butyloxycarbonyl)-3-vinylprolyl]-*N*-(4-pentenyl)-glycine Methyl Ester (10c). The reaction was analogously performed as described for **10b**, using **8a** (130 mg, 0.539 mmol), HATU (204.8 mg, 0.539 mmol), HOAt (73.3 mg, 0.539 mmol) in NMP (2.0 mL), *N*-ethylmorpholine (137.0 μL, 1.078 mmol), and *N*-(4-pentenyl)glycine methyl ester (**9c**)[20] (118.6 mg, 0.754 mmol) in NMP (0.7 mL), with 3 d of stirring. Flash chromatography (petrol ether:EtOAc 2:1) furnished **10c** (104.3 mg, 51%) as a colorless oil: $[\alpha]_D^{20}$ +34.0° (c = 0.558, $CHCl_3$); IR (film) 1753, 1699, 1664 cm^{-1}; ^{1}H NMR δ 1.42 and 1.45 (2× s, 9H, conf.), 1.60−1.80 (m, 3H), 2.03−2.11 (m, 2H), 2.12−2.44 (m, 1H), 2.87−2.97 (m, 1H), 3.14−3.70 (m, 5.4H, conf.), 3.71 and 3.72 (2× s, 3H, conf.), 3.85−3.96 (m, 0.3H), 4.15−4.23 (m, 0.3H), 4.33 (d, J = 3.2 Hz, 0.5H, conf.), 4.34 (d, J = 17.0 Hz, 0.5H, conf.), 4.48 (d, J = 3.2 Hz, 0.5H, conf.), 4.58 (d, J = 17.0 Hz, 0.5H, conf.), 4.92−5.22 (m, 4H), 5.70−5.94 (m, 2H); ^{13}C NMR (2 conf.) δ 27.9, 28.1, 28.6, 28.7, 29.6, 30.4, 30.8, 30.9, 45.9, 46.1, 48.2, 48.5, 48.6, 52.1, 52.2, 61.4, 61.7, 79.7, 80.2, 115.7, 115.9, 116.0, 116.1, 137.0, 137.3, 138.7, 154.1, 154.6, 169.8, 170.1, 172.5, 172.6; EIMS 380 [M$^+$]. Anal. Calcd for $C_{20}H_{32}N_2O_5$ (380.48): C, 63.14; H, 8.48; N, 7.36. Found: C, 63.19; H, 8.44; N, 7.34.

***N*-Allyl-*N*-[(2*S*,3*S*)-3-allyl-*N*′-(*tert*-butyloxycarbonyl)prolyl]glycine Methyl Ester (10d).** The reaction was analogously performed as described for **10b**, using **8b** (50.0 mg, 0.196 mmol), HATU (74.5 mg, 0.196 mmol), HOAt (26.7 mg, 0.196 mmol) in NMP (1.5 mL), *N*-ethylmorpholine (49.6 μL, 0.392 mmol), and *N*-allylglycine methyl ester (**9a**)[19] (30.5 mg, 0.235 mmol) in NMP (0.7 mL), with 1 d of stirring. Flash chromatography (petrol ether:EtOAc 2:1) furnished **10d** (51.6 mg, 72%) as a colorless oil: $[\alpha]_D^{20}$ +44.7° (c = 0.692, $CHCl_3$); IR (film) 1753, 1699, 1666 cm^{-1}; ^{1}H NMR δ 1.42 and 1.45 (2× s, 9H, conf.), 1.59−1.69 (m, 1H), 2.00−2.25 (m,3H), 2.25−2.40 (m, 1H), 3.34−3.51 (m, 1.5H, conf.), 3.58 (d, J = 17.0 Hz, 0.5H, conf.), 3.61−3.69 (m, 0.5H, conf.), 3.70 and 3.71 (2× s, 3H, conf.), 3.82 (d, J = 17.0 Hz, 0.5H, conf.), 3.85−4.20 (m, 2H), 4.25 (d, J = 17.0 Hz, 0.5H), 4.33 (d, J = 1.4 Hz, 0.5H, conf.), 4.42 (d, J = 1.4 Hz, 0.5H, conf.), 4.49 (d, J = 17.0 Hz, 0.5H, conf.), 5.00−5.32 (m, 4H), 5.64−5.94 (m, 2H); ^{13}C NMR (2 conf.) δ 27.8, 28.5, 28.6, 28.8, 38.1, 38.2, 42.5, 43.5, 45.3, 45.6, 47.3, 47.4, 51.0, 51.4, 52.1, 52.2, 61.3, 61.5, 79.6, 80.0, 117.8, 117.9, 118.5, 118.6, 132.6, 132.8, 135.8, 154.4, 154.9, 169.8, 170.1, 173.0; EIMS 366 [M$^+$]. Anal. Calcd for $C_{19}H_{30}N_2O_5$ (366.46): C, 62.27; H, 8.25; N, 7.64. Found: C, 62.35; H, 8.27; N, 7.64.

***N*-[(2*S*,3*S*)-3-Allyl-*N*′-(*tert*-butyloxycarbonyl)prolyl]-*N*-(3-butenyl)-glycine Methyl Ester (10e).** The reaction was analogously performed as described for **10b**, using **8b** (50.0 mg, 0.196 mmol), HATU (74.5 mg, 0.196 mmol), HOAt (26.7 mg, 0.196 mmol) in NMP (1.9 mL), *N*-ethylmorpholine (49.6 μL, 0.392 mmol), and *N*-(3-butenyl)glycine methyl ester (**9b**, 33.7 mg, 0.235 mmol) in NMP (0.5 mL), with 1 d of stirring. Flash chromatography (petrol ether:EtOAc 2:1) furnished **10e** (69.1 mg, 93%) as a colorless oil: $[\alpha]_D^{20}$ +57.5° (c = 0.358, $CHCl_3$); IR (film) 1753, 1698, 1662 cm^{-1}; ^{1}H NMR δ 1.42 and 1.45 (2× s, 9H, conf.), 1.58−1.68 (m, 3H), 1.96−2.52 (m, 6H), 3.18−3.68 (m, 3.4H, conf.), 3.52 (d, J = 17.4 Hz, 0.5H, conf.), 3.70, 3.71, 3.75 and 3.77 (4× s, 3H, conf.), 3.76 (d, J = 17.0 Hz, 0.5H, conf.), 3.88−3.97 (m, 0.3H), 4.11−4.17 (m, 0.3H, conf.), 4.31 (d, J = 17.0 Hz, 0.5H), 4.32 (s, 0.5H, conf.), 4.42 (s, 0.5H, conf.), 4.58 (d, J = 17.4 Hz, 0.5H, conf.), 4.97−5.16 (m, 4H), 5.63−5.88 (m, 2H); ^{13}C NMR (2 maj. conf.) δ 27.8, 28.6, 28.7, 28.9, 33.2, 33.4, 38.2, 38.3, 42.5, 43.4, 45.3, 45.6, 48.2, 48.3, 48.4, 52.1, 52.2, 61.1, 61.4, 79.6, 80.0, 117.6, 117.8, 118.0, 118.1, 134.0, 134.3, 135.9, 154.5, 155.0, 169.8, 170.1, 172.9; EIMS 380 [M$^+$]. Anal. Calcd for $C_{20}H_{32}N_2O_5$ (380.48): C, 63.14; H, 8.48; N, 7.36. Found: C, 63.28; H, 8.53; N, 7.37.

***N*-Allyl-*N*-[(2*S*,3*S*)-3-(3-butenyl)-*N*′-(*tert*-butyloxycarbonyl)-prolyl]glycine Methyl Ester (10f).** The reaction was analogously performed as described for **10b**, using **8c** (60.0 mg, 0.223 mmol), HATU (84.7 mg, 0.223 mmol), HOAt (30.3 mg, 0.223 mmol) in NMP (2 mL), *N*-ethylmorpholine (57.0 μL, 0.446 mmol), and *N*-allylglycine methyl ester (**9a**, 40.3 mg, 0.312 mmol) in NMP (1.0 mL), with 1 d of stirring. Flash chromatography (petrol ether:EtOAc 2:1) furnished **10f** (63.4 mg, 75%) as a colorless oil: $[\alpha]_D^{20}$ +32.5° (c = 0.358, $CHCl_3$); IR (film) 1753, 1698, 1665 cm^{-1}; ^{1}H NMR δ 1.43 and 1.44 (2× s, 9H, conf.), 1.45−1.68 (m, 3H), 1.94−2.40 (m, 4H), 3.38−3.68 (m, 2H), 3.61 (d, J = 17.4 Hz, 0.5H, conf.), 3.70, 3.71, 3.74 and 3.76 (4× s, 3H, conf.), 3.82−3.92 (m, 0.2H), 3.87 (d, J = 17.0 Hz, 0.5H, conf.), 4.05−4.12 (m, 1.8H), 4.20 (d, J = 17.0 Hz, 0.5H), 4.26 (d, J = 2.5 Hz, 0.5H), 4.38 (d, J = 2.1 Hz, 0.5H), 4.47 (d, J = 17.4 Hz, 0.5H, conf.), 4.84−5.08 (m, 2H), 5.12−5.35 (m, 2H), 5.66−5.95 (m, 2H); ^{13}C NMR (2 maj. conf.) δ 27.7, 28.5, 28.6, 28.7, 28.8, 31.7, 31.8, 32.9, 42.6, 43.6, 45.4, 45.7, 47.3, 47.5, 51.2, 51.5, 52.1, 52.2, 62.2, 62.7, 79.6, 80.1, 115.3, 115.4, 118.6, 132.6, 132.9, 137.8, 137.9, 154.3, 154.9, 169.8, 170.0, 173.1; EIMS 380 [M$^+$]. Anal. Calcd for $C_{20}H_{32}N_2O_5$ (380.48): C, 63.14; H, 8.48; N, 7.36. Found: C, 63.02; H, 8.37; N, 7.38.

***tert*-Butyl (3a*R*,8a*S*)-7-(2-Methoxy-2-oxoethyl)-8-oxo-3,3a,6,7,8,-8a-hexahydropyrrolo[2,3-*c*]azepine-1(2*H*)-carboxylate (11a).** Diene **10a** (5.0 mg, 0.0142 mmol, see Supporting Information) was dissolved in CH_2Cl_2 (7 mL), and a solution of the Grubbs' catalyst of the second generation (**I**, 0.6 mg)[22] in CH_2Cl_2 (0.5 mL) was added. The mixture was stirred for 2 h under reflux conditions, and then silica gel (50 mg) was added. Evaporation and subsequent flash chromatography (petrol ether−EtOAc, 1:1) of the residue afforded **11a** (3.5 mg, 76%) as a colorless oil: $[\alpha]_D^{20}$ −120° (c = 0.1083, $CHCl_3$); IR (film) 1753, 1697 cm^{-1}; ^{1}H NMR δ 1.42 (s, 4.5H, *t*-Bu, first conf.), 1.47 (s, 4.5H, *t*-Bu, second conf.), 1.58−1.70 (m, 1H, H-3), 2.07 (ddd, J = 11.6, 5.8, 5.8 Hz, 1H, H-3′), 2.85−2.99 (m, 1H, H-3a), 3.39 (ddd, J = 11.6, 10.6, 5.8 Hz, 1H, H-2), 3.49 (dd, J = 18.8, 7.1 Hz, 1 H, H-6), 3.71 (s, 3H, OCH_3), 3.78 (dd, J = 10.6, 8.5 Hz, 1 H, H-2′), 3.84 (d, J = 17.4 Hz, 0.5H, NCH_2, first conf.), 4.00 (d, J = 17.4 Hz, 0.5H, NCH_2, second conf.), 4.51 (d, J = 17.4 Hz, 0.5H, NCH_2, second conf.), 4.53 and 4.56 (2× d, each J = 11.4 Hz, 1H, H-8a), 4.61−4.69 (m, 1H, H-6′), 4.68 (d, J = 17.4 Hz, 0.5H, NCH_2, first conf.), 5.63−5.72 (m, 1H,

H-4 or H-5), 5.85−5.92 (m, 1H, H-5 or H-4); ^{13}C NMR δ 28.2, 28.5 (C(CH_3)$_3$, conf.), 30.7, 31.6 (C-3, conf.), 42.0, 42.8 (C-3a, conf.), 46.5, 47.1 (C-2, conf.), 48.8 (C-6), 50.1, 50.2 (NCH_2, conf.), 52.1 (OCH_3), 60.4, 61.5 (C-8a, conf.), 79.9 (C(CH_3)$_3$), 125.0, 125.2 (C-5 or C-4, conf.), 130.4, 131.0 (C-4 or C-5, conf.), 153.8, 154.3 (COO*t*Bu, conf.), 169.8, 170.0 ($COOCH_3$, conf.), 171.5, 171.9 (C-8, conf.); EIMS 324 [M$^+$]. Anal. Calcd for $C_{16}H_{24}N_2O_5$ (324.38): C, 59.24; H, 7.46; N, 8.64. Found: C, 59.37; H, 7.55; N, 8.53.

***tert*-Butyl (3a*R*,9a*S*)-8-(2-Methoxy-2-oxoethyl)-9-oxo-2,3,-3a,6,7,8,9,9a-octahydro-1*H*-pyrrolo[2,3-*c*]azocine-1-carboxylate (11b).** Olefin metathesis was analogously performed as described for **11a**, using diene **10b** (10.0 mg, 0.0273 mmol), CH_2Cl_2 (50 mL), and catalyst **I** (1.2 mg) in CH_2Cl_2 (0.5 mL). Reaction time: 15 min, column chromatography (petrol ether−EtOAc, 2:1) afforded **11b** (8.8 mg, 96%) as a colorless oil: $[\alpha]_D^{20}$ −183.6° (c = 0.45, $CHCl_3$); IR (film) 1751, 1701, 1666 cm^{-1}; ^{1}H NMR δ 1.39 (s, 4.5H, *t*-Bu, conf.), 1.45 (s, 4.5H, *t*-Bu, conf.), 1.77 and 1.79 (2 × dddd, each: J = 12.2, 12.2, 12.2, 7.6 Hz, 1H, H-3), 2.15 (ddd, J = 12.2, 7.6, 5.2 Hz, 1H, H-3′), 2.27−2.41 (m, 1H, H-6), 2.47−2.57 (m, 0.5H, H-6′, conf.), 2.68−2.79 (m, 0.5H, H-6′, conf.), 2.95−3.15 (m, 1H, H-3a), 3.25 (dd, J = 16.3, 8.5 Hz, 0.5H, H-7, conf.), 3.28 (dd, J = 16.3, 8.5 Hz, 0.5H, H-7, conf.), 3.30 (ddd, J = 12.2, 10.8, 5.2 Hz, 1H, H-2), 3.61 (d, J = 17.0 Hz, 0.5H, NCH_2, first conf.), 3.73 (dd, J = 10.8, 7.6 Hz, 0.5H, H-2′, conf.), 3.73 and 3.74 (2 × s, 3H, OCH_3, 2 conf.), 3.78 (dd, J = 16.3, 8.5 Hz, 0.5H, H-7′), 3.79 (dd, J = 10.8, 7.6 Hz, 0.5H, H-2′, conf.), 3.87 (dd, J = 16.3, 8.5 Hz, 0.5H, H-2′, conf.), 4.09 (d, J = 17.0 Hz, 0.5 H, NCH_2, second conf.), 4.28 (d, J = 17.0 Hz, 0.5 H, NCH_2, second conf.), 4.49 (d, J = 7.5 Hz, 0.5 H, H-9a, conf.), 4.56 (d, J = 7.5 Hz, 0.5 H, H-9a, conf.), 4.73 (d, J = 17.0 Hz, 0.5 H, NCH_2, first conf.), 5.74−5.81 (m, 1H, H-4), 5.82−5.92 (m, 1H, H-5); ^{13}C NMR δ 28.2, 28.5 (C(CH_3)$_3$, conf.), 29.1, 29.4 (C-6, conf.), 33.0, 33.7 (C-3 conf.), 43.2, 44.4 (C-3a, conf.), 45.8, 46.4 (C-2, conf.), 49.5 (C-7, conf.), 49.8 (NCH_2, conf.), 50.9 (C-7, conf.), 51.6 (NCH_2, conf.), 52.1 (OCH_3), 63.7 (C-9a), 79.6 (C(CH_3)$_3$), 131.3, 132.0 (C-5, conf.), 134.5, 135.3 (C-4, conf.), 153.9, 154.3 (COO*t*Bu, conf.), 169.8, 170.2 ($COOCH_3$, conf.), 173.2, 173.7 (C-9, conf.); EIMS 338 [M$^+$]. Anal. Calcd for $C_{17}H_{26}N_2O_5$ (338.40): C, 60.34; H, 7.74; N, 8.28. Found: C, 60.36; H, 7,62; N, 8.17.

***tert*-Butyl (3a*R*,10a*S*)-9-(2-Methoxy-2-oxoethyl)-10-oxo-3,-3a,6,7,8,9,10,10a-octahydropyrrolo[2,3-*c*]azonine-1(2*H*)-carboxylate (11c).** Over a period of 30 min, a solution of diene **10c** (11.4 mg, 0.030 mmol, see Supporting Information) in CH_2Cl_2 (2 mL) and a solution of the catalyst **I** (1.0 mg) in CH_2Cl_2 (0.5 mL) were added dropwise to refluxing CH_2Cl_2 (50 mL) via separate syringes. The mixture was stirred another 4 h under reflux conditions, and then silica gel (100 mg) was added. Evaporation and subsequent flash chromatography (petrol ether−isopropanol, 99:1) of the residue afforded **11c** (8.8 mg, 83%) as a colorless oil: $[\alpha]_D^{20}$ −122.0° (c = 0.55, $CHCl_3$); IR (film) 1753, 1701, 1653 cm^{-1}; ^{1}H NMR δ 1.35−1.43 (m, 1H, H-7), 1.39 (s, 4.5H, *t*-Bu, conf.), 1.45 (s, 4.5H, *t*-Bu, conf.), 1.68−1.82 (m, 1H, H-3), 1.83−1.95 (m, 1H, H-7′), 1.96−2.05 (m, 1H, H-6), 2.06−2.14 (m, 1H, H-3′), 2.33−2.44 (m, 0.5H, H-6′, conf.), 2.59−2.70 (m, 0.5H, H-6′, conf.), 3.03−3.17 (m, 2H, H-3a, H-8), 3.39 (ddd, J = 2.2, 10.7, 5.3 Hz, 1H, H-2), 3.52 (d, J = 16.9 Hz, 0.5H, NCH_2, first conf.), 3.66 and 3.67 (2× s, 3H, OCH_3, 2 conf.), 3.68−3.80 (m, 1H, H-8′), 3.76 and 3.83 (2 × dd, each J = 10.7, 7.9 Hz, 1H, H-2′, 2 conf.), 3.99 (d, J = 16.9 Hz, 0.5 H, NCH_2, second conf.), 4.07 (d, J = 16.9 Hz, 0.5 H, NCH_2, second conf.), 4.30 (d, J = 7.5 Hz, 0.5 H, H-10a, conf.), 4.38 (d, J = 7.5 Hz, 0.5 H, H-10a, conf.), 4.47 (d, J = 16.9 Hz, 0.5 H, NCH_2, first conf.), 5.56−5.65 (m, 1H, H-5), 5.67−5.74 (m, 1H, H-4); ^{13}C NMR δ 23.1, 23.2 (C-6, conf.), 27.7, 28.3 (C-7, conf.), 28.2, 28.5 (C(CH_3)$_3$, conf.), 33.1, 33.8 (C-3), 41.2, 42.1 (C-3a, conf.), 44.7, 46.0 (C-8, conf.), 46.5, 47.0 (C-2, conf.), 47.1, 48.9 (NCH_2, conf.), 51.9, 52.0 (OCH_3, conf.), 62.2, 62.4 (C-10a, conf.), 79.5, 79.6 (C(CH_3)$_3$, conf.), 130.7, 131.0 (C-5, conf.), 134.5, 134.6 (C-4, conf.), 153.6, 154.1 (COO*t*Bu, conf.), 169.6, 170.0 ($COOCH_3$, conf.), 172.2, 173.0 (C-10, conf.); EIMS 352 [M$^+$]. Anal. Calcd for $C_{18}H_{28}N_2O_5$ (352.43): C, 61.34; H, 8.01; N, 7.95. Found: C, 61.41; H, 8.10; N, 8.03.

***tert*-Butyl (3a*S*,9a*S*)-8-(2-Methoxy-2-oxoethyl)-9-oxo-2,3,-3a,4,7,8,9,9a-octahydro-1*H*-pyrrolo[2,3-*c*]azocine-1-carboxylate (11d).** Olefin metathesis was analogously performed as described for **11a**, using diene **10d** (6.5 mg, 0.0177 mmol), CH_2Cl_2 (9 mL), and catalyst **I** (0.75 mg) in CH_2Cl_2 (0.5 mL). Reaction time: 2 h. Flash chromatography (CH_2Cl_2−MeOH, 99:1) afforded **11d** (4.5 mg, 75%) as a colorless oil: $[\alpha]_D^{20}$ −226.9° (c = 0.73, $CHCl_3$); IR (film) 1756, 1698, 1667 cm^{-1}; ^{1}H NMR δ 1.41 (s, 5.4H, *t*-Bu, first conf.), 1.46 (s, 3.6H, *t*-Bu, second conf.), 1.57−1.69 (m, 1H, H-3), 1.92−2.06 (m, 2H, H-3′/H-3a), 2.36−2.49 (m, 2H, H-4/H-4′.), 3.32 (ddd, J = 12.0, 10.7, 5.1 Hz, 1H, H-2), 3.40 and 3.46 (2 × dd, each J = 15.7, 6.8 Hz, 1H, H-7, 2 conf.), 3.69 and 3.76 (2 × dd, each J = 10.7, 7.6 Hz, 1H, H-2′, 2 conf.), 3.70 and 3.73 (2 × s, 3H, OCH_3, 2 conf.), 3.81 (d, J = 17.4 Hz, 0.6 H, NCH_2, second conf.), 3.91 (d, J = 17.0 Hz, 0.4 H, NCH_2, first conf.), 4.39 and 4.50 (2 × dd, each J = 15.7, 7.5 Hz and 15.7, 9.2 Hz, 1, H-7′, 2 conf.), 4.40 (d, J = 17.0 Hz, 0.4 H, NCH_2, first conf.), 4.57 (d, J = 17.4 Hz, 0.6 H, NCH_2, second conf.), 4.58 and 4.62 (2 × d, each J = 11.4 and 8.5 Hz, 1 H, H-9a, conf.), 5.88−6.04 (m, 2H, H-5/H-6); ^{13}C NMR δ 28.2, 28.5 (C(CH_3)$_3$, conf.), 31.9, 32.1, 33.2, 33.8 (C-3 and C-4, each 2 conf.), 42.7, 43.7, 44.0, 45.3, 46.0, 46.6 (C-2, C-3a and C-7, each 2 conf.), 47.7, 49.7 (NCH_2, conf.), 51.9, 52.0 (OCH_3, conf.), 64.2, 64.3 (C-9a, conf.), 79.5, 79.8 (C(CH_3)$_3$), 128.3, 128.8 (C-6, conf.), 133.9, 134.8 (C-5, conf.), 153.6, 154.0 (COO*t*Bu, conf.), 169.7 ($COOCH_3$, conf.), 171.3, 173.9 (C-9, conf.); EIMS 338 [M$^+$]. Anal. Calcd for $C_{17}H_{26}N_2O_5$ (338.40): C, 60.34; H, 7.74; N, 8.28. Found: C, 60.46; H, 7,81; N, 8.15.

***tert*-Butyl (3a*S*,10a*S*)-9-(2-Methoxy-2-oxoethyl)-10-oxo-3,-3a,4,7,8,9,10,10a-octahydropyrrolo[2,3-*c*]azonine-1(2*H*)-carboxylate (11e).** Olefin metathesis was analogously performed as described for **11a**, using diene **10e** (5.0 mg, 0.0131 mmol), CH_2Cl_2 (30 mL), and catalyst **I** (0.56 mg) in CH_2Cl_2 (0.5 mL). Reaction time: 1 h. Flash chromatography (petrol ether−EtOAc, 1:1) afforded **11e** (3.2 mg, 70%) as a colorless oil: $[\alpha]_D^{20}$ −61.1° (c = 0.0917, $CHCl_3$); IR (film) 1752, 1698, 1660 cm^{-1}; ^{1}H NMR δ 1.43 (s, 9H, *t*-Bu), 1.68 (dddd, J = 11.8, 11.8, 11.8, 8.5 Hz, 1H, H-3), 1.86 and 1.87 (2× ddd, each: J = 11.8, 5.8, 5.8 Hz, 1H, H-3′), 2.20 (m, 1H, H-4), 2.50−2.61 (m, 4H, H-3a, H-4′, H-7/7′), 3.29 (m, 1H, H-8), 3.42 (ddd, J = 11.8, 10.7, 5.8 Hz, 1H, H-2), 3.57 (dd, J = 10.7, 8.2 Hz, 0.3H, H-2′ first conf.), 3.69 (dd, J = 10.7, 8.2 Hz, 0.7 H, H-2′ second conf.), 3.72 and 3.74 (2 × s, 3H, OCH_3, conf.), 3.79 (d, J = 17.0 Hz, 0.3 H, NCH_2, first conf.), 4.02 (d, J = 17.0 Hz, 0.7 H, NCH_2, second conf.), 3.89 (ddd, J = 15.9, 5.2, 5.2 Hz, 1H, H-8′), 4.13 (d, J = 17.0 Hz, 0.7 H, NCH_2, second conf.), 4.19 (d, J = 9.2 Hz, 0.7 H, H-10a, second conf.), 4.25 (d, J = 9.9 Hz, 0.3 H, H-10a first conf.), 4.48 (d, J = 17.0 Hz, 0.3 H, NCH_2, first conf.), 5.74 (ddd, J = 10.2, 9.0, 7.5 Hz, 1H, H-6), 5.84 (ddd, J = 10.2, 8.9, 8.9 Hz, 1H, H-5); ^{13}C NMR δ 26.9 (C-4 or C-7), 27.6 (C-7 or C-4), 28.3, 28.5 (C(CH_3)$_3$, conf.), 30.3 (C-3), 46.6, 47.0 (C-2, conf.), 47.7 (C-3a), 48.3 (C-8), 51.4 (NCH_2, first conf.), 52.0 (OCH_3), 52.2 (NCH_2, second conf.), 59.4, 59.8 (C-10a, conf.), 79.4, 80.0 (C(CH_3)$_3$, conf.), 128.7, 129.3 (C-6, conf.), 130.1, 130.9 (C-5, conf.), 153.6, 154.4 (COO*t*Bu, conf.), 169.8, 170.7 ($COOCH_3$, conf.), 174.1, 174.7 (C-10, conf.); EIMS 352 [M$^+$]. Anal. Calcd for $C_{18}H_{28}N_2O_5$ (352.43): C, 61.34; H, 8.01; N, 7.95. Found: C, 61.38; H, 8.04; N, 7.77.

***tert*-Butyl (3a*S*,10a*S*)-9-(2-Methoxy-2-oxoethyl)-10-oxo-3,-3a,4,5,8,9,10,10a-octahydropyrrolo[2,3-*c*]azonine-1(2*H*)-carboxylate (11f).** Olefin metathesis was analogously performed as described for **11a**, using diene **10f** (4.9 mg, 0.0129 mmol), CH_2Cl_2 (100 mL), and catalyst I (0.36 mg) in CH_2Cl_2 (0.5 mL). Reaction time: 1 h. Flash chromatography (petrol ether−EtOAc, 1:1) afforded **11f** (4.2 mg, 91%) as a colorless oil: $[\alpha]_D^{20}$ −132.3° (c = 0.30, $CHCl_3$); IR (film) 1755, 1698, 1666 cm^{-1}; ^{1}H NMR (600

MHz, protons located at the same side of the ring plane as H-3a are designated as β-protons) δ 1.43 (s, 4.5H, *t*-Bu, conf.), 1.45 (s, 4.5H, *t*-Bu, conf.), 1.49−1.57 (m, 2H, H-4β, H-3), 1.59−1.67 (m, 1H, H-4α), 2.12−2.24 (m, 2H, H-3′, H-5β), 2.45 (ddddd, J = 11.0, 11.0, 4.4, 2.1, 2.1 Hz, 0.5H, H-3a, conf.), 2.56 (ddddd, J = 11.0, 11.0, 4.4, 2.1, 2.1 Hz, 0.5H, H-3a, conf.), 2.66 and 2.68 (2 × dddd, each: J = 16.4, 12.1, 10.8, 4.9, 1H, H-5α, 2 conf.), 3.37 (dd, J = 16.5, 6.2 Hz, 0.5H, H-8β, conf.), 3.37 (dd, J = 9.0, 8.9 Hz, 0.5H, H-2, conf.), 3.42 (dd, J = 9.0, 8.9 Hz, 0.5H, H-2, conf.), 3.43 (dd, J = 16.5, 6.2 Hz, 0.5H, H-8β, conf.), 3.64 (ddd, J = 10.5, 9.0, 3.6 Hz, 0.5H, H-2′, conf.), 3.66 (d, J = 17.4 Hz, 0.5H, NCH_2, conf.), 3.71 (s, 1.5H, OCH_3, conf.), 3.72 (ddd, J = 10.5, 9.0, 3.6 Hz, 0.5H, H-2′, conf.), 3.73 (s, 1.5H, OCH_3, conf.), 3.99 (d, J = 17.0 Hz, 0.5H, NCH_2, conf.), 4.31 (d, J = 17.0 Hz, 0.5H, NCH_2, conf.), 4.64 (d, J = 17.4 Hz, 0.5H, NCH_2, conf.), 4.64 (dd, J = 16.5, 10.8 Hz, 0.5H, H-8α), 4.67 (d, J = 2.1 Hz, 0.5H, H-10a, conf.), 4.77 (d, J = 2.1 Hz, 0.5H, H-10a, conf.), 4.78 (dd, J = 16.5, 10.8 Hz, 0.5H, H-8α), 5.70 (2 × ddd, each: J = 10.8, 10.8, 4.9 Hz, 1H, H-6), 5.80 (2 × ddd, J = 10.8, 10.8, 6.2 Hz, 1H, H-7); ^{13}C NMR δ 23.8, 23.9 (C-5, conf.), 28.2, 28.4 (C(*C*H_3)$_3$, conf.), 29.7, 30.2 (C-3), 31.5, 31.7 (C-4, conf.), 39.3, 40.7 (C-3a, conf.), 45.2, 45.7 (C-8), 46.0, 46.5 (C-2, conf.), 49.2, 50.8 (NCH_2, conf.), 52.0 (OCH_3), 58.4, 58.5 (C-10a, conf.), 79.6, 79.7 (*C*(CH$_3$)$_3$, conf.), 125.2, 126.0 (C-6, conf.), 130.1, 130.7 (C-7, conf.), 154.1, 154.8 (*C*O*t*Bu, conf.), 169.8, 170.1 (*C*OOCH_3, conf.), 172.6, 173.0 (C-10, conf.); EIMS 352 [M$^+$]. Anal. Calcd for $C_{18}H_{28}N_2O_5 \times 0.5$ H_2O (352.43): C, 59.82; H, 8.09; N, 7.75. Found: C, 59.72; H, 8.06; N, 7.88.

***tert*-Butyl (3a*R*,8a*S*)-7-[2-(Methylamino)-2-oxoethyl)]-8-oxo-3,3a,6,7,8,8a-hexahydropyrrolo[2,3-*c*]azepine-1(2*H*)-carboxylate (3a).** Compounf **11a** (4.4 mg, 0.0136 mmol, see Supporting Information) was dissolved at room temperature in a solution of methyl amine in EtOH (1 mL, 8.03 M). The reaction mixture was stirred for 1 h and evaporated. The residue was purified by flash chromatography (CH_2Cl_2−MeOH 95:5) to give **3a** (2.9 mg, 66%) as a colorless oil: $[\alpha]_D^{20}$ −108.6° (c = 0.158, $CHCl_3$); IR (film) 3317, 1694, 1681, 1675 cm^{-1}; ^{1}H NMR δ 1.42 (s, 4.5H, *t*-Bu, first conf.), 1.48 (s, 4.5H, *t*-Bu, second conf.), 1.60−1.76 (m, 1H, H-3), 2.10 (ddd, J = 11.7, 5.9, 5.9 Hz, 1H, H-3′), 2.77 (d, J = 5.0 Hz, 3H, HNC*H*$_3$), 2.78−2.90 (m, 1H, H-3a), 3.36−3.48 (m, 1H, H-2), 3.60−3.74 (m, 1.5 H, H-2′/H-6), 3.79 (dd, J = 10.6, 8.5 Hz, 0.5H, H-2′), 4.01 (d, J = 15.3 Hz, 1H, NCH_2, conf.), 4.12 (d, J = 15.3 Hz, 0.5H, NCH_2, conf.), 4.21 (d, J = 15.3 Hz, 0.5H, NCH_2, conf.), 4.49−4.66 (m, H-6′/H-8a), 5.67−5.75 (m, 1H, H-5), 5.88 (ddd, J = 11.4, 2.1, 2.1 Hz, 1H, H-4), 6.22 (brs, 0.4H, *H*NCH_3, first conf.), 6.33 (brs, 0.6H, *H*NCH_3, second conf.); ^{13}C NMR δ 26.1, 26.2 (HN*C*H$_3$, conf.), 28.2, 28.4 (C(*C*H$_3$)$_3$, conf.), 30.6, 31.2 (C-3, conf.), 42.0, 42.8 (C-3a, conf.), 46.5, 47.1 (C-2, conf.), 48.7, 48.8 (C-6, conf.), 53.4, 53.5 (N*C*H$_2$, conf.), 61.2, 61.3 (C-8a, conf.), 79.9, 80.1 (*C*(CH$_3$)$_3$, conf.), 125.1, 125.4 (C-5 or C-4, conf.), 130.6, 131.0 (C-4 or C-5, conf.), 154.1, 154.8 (*C*O*t*Bu, conf.), 169.5 (*C*ONHCH$_3$), 172.0, 172.5 (C-8, conf.); APCI-MS 324 [M + 1]$^+$. Anal. Calcd for $C_{16}H_{25}N_3O_4$ (323.40): C, 59.43; H, 7.79; N, 12.99. Found: C, 59.53; H, 7.83; N, 12.83.

***tert*-Butyl (3a*R*,9a*S*)-8-[2-(Methylamino)-2-oxoethyl)]-9-oxo-2,3,3a,6,7,8,9,9a-octahydro-1*H*-pyrrolo[2,3-*c*]azocine-1-carboxylate (3b).** Aminolysis of **11b** (8.4 mg, 0.0248 mmol) was analogously performed with methyl amine in EtOH (2 mL, 8.03 M) as described for **11a**. Reaction time: 4 h. Column chromatography (CH_2Cl_2−MeOH 97:3) furnished **3b** (6.9 mg, 82%) as a colorless oil: $[\alpha]_D^{20}$ −79.3° (c = 0.442, $CHCl_3$); IR (film) 3329, 1695, 1668 cm^{-1}; ^{1}H NMR δ 1.39 (s, 2.7H, *t*-Bu, second conf.), 1.46 (s, 6.3H, *t*-Bu, first conf.), 1.79 (dddd, J = 12.4, 12.4, 12.4, 7.6 Hz, 0.3H, H-3, second conf.), 1.83 (dddd, J = 12.4, 12.4, 12.4, 7.6 Hz, 0.7H, H-3, first conf.), 2.16 (ddd, J = 12.4, 6.9, 6.3 Hz, 0.3H, H-3′, second conf.), 2.18 (ddd, J = 12.4, 6.9, 6.3 Hz, 0.7H, H-3′, first conf.), 2.29−2.50 (m, 2H, H-6/H-6′), 2.78 (d, J = 4.6 Hz, 3H, HNC*H*$_3$), 2.86−2.97 (m, 1H, H-3a), 3.29 (ddd, J = 15.9, 6.8, 2.2 Hz, 0.7H, H-7, first conf.), 3.37 (ddd, J = 12.4, 10.6, 6.9 Hz, 1H, H-2), 3.49 (ddd, J = 16.3, 6.8, 2.2 Hz, 0.3H, H-7, second conf.), 3.64 (d, J = 16.0 Hz, 0.7H, NCH_2, first conf.), 3.69 (dd, J = 10.6, 7.6 Hz, 0.7H, H-2′, first conf.), 3.72 (ddd, J = 16.2, 8.8, 2.2 Hz, 0.3H, H-7′, second conf.), 3.72 (d, J = 14.5 Hz, 0.3H, NCH_2, second conf.), 3.81 (dd, J = 10.6, 7.6 Hz, 0.3H, H-2′, second conf.), 4.29 (d, J = 14.5 Hz, 0.3 H, NCH_2, second conf.), 4.49 (d, J = 7.8 Hz, 0.3 H, H-9a, second conf.), 4.55 (d, J = 8.2 Hz, 0.7 H, H-9a, first conf.), 4.57 (d, J = 16.0 Hz, 0.7 H, NCH_2, first conf.), 5.69−5.84 (m, 1H, H-4/H-5), 6.59 (brs, 0.3H, *H*NCH_3, second conf.), 6.74 (brs, 0.7H, *H*NCH_3, first conf.); ^{13}C NMR δ 26.1, 26.2 (HN*C*H$_3$, conf.), 28.2, 28.4 (C(*C*H$_3$)$_3$, conf.), 29.5, 30.3 (C-6, conf.), 33.3, 33.5 (C-3, conf.), 43.6, 44.9 (C-3a, conf.), 45.8, 46.3 (C-2, conf.), 49.2, 49.3 (C-7, conf.), 52.7, 53.0 (N*C*H$_2$, conf.), 62.4, 63.4 (C-9a, conf.), 79.5, 80.0 (*C*(CH$_3$)$_3$, conf.), 130.5, 131.1 (C-5, conf.), 133.3, 134.4 (C-4, conf.), 154.6 (*C*O*t*Bu), 169.3 (*C*OOCH_3), 173.6, 174.6 (C-9, conf.); EIMS 337 [M$^+$]. Anal. Calcd for $C_{17}H_{27}N_3O_4$ (337.42): C, 60.51; H, 8.07; N, 12.45. Found: C, 60.48; H, 7.98; N, 12.36.

***tert*-Butyl (3a*R*,10a*S*)-9-[2-(Methylamino)-2-oxoethyl)]-10-oxo-3,3a,6,7,8,9,10,10a-octahydropyrrolo[2,3-*c*]azonine-1(2*H*)-carboxylate (3c).** Aminolysis of **11c** (3.0 mg, 0.0085 mmol) was analogously performed with methyl amine in EtOH (1 mL, 8.03 M) as described for **11a**. Reaction time: 1 h. Flash chromatography (CH_2Cl_2−MeOH 95:5) gave **3c** (3.0 mg, 100%) as a colorless oil: $[\alpha]_D^{20}$ −73.7° (c = 0.45, $CHCl_3$); IR (film) 3361, 1678, 1657 cm^{-1}; ^{1}H NMR (600 MHz, protons located at the same side of the ring plane as H-3a are designated as β-protons) δ 1.35−1.43 (m, 1H, H-7α), 1.38 (s, 1.3H, *t*-Bu), 1.46 (s, 7.7H, *t*-Bu), 1.85 (dddd, J = 12.0, 12.0, 12.0, 7.8 Hz, 1H, H-3α), 1.88−1.96 (m, 1H, H-6β), 1.91−2.00 (m, 1H, H-7β), 1.88−2.05 (m, 1H, H-6α), 2.19 (ddd, J = 12.0, 7.1, 5.6 Hz, 1H, H-3β), 2.78 (d, J = 4.6 Hz, 3 H, HNC*H*$_3$), 3.07 (dddd, J = 12.0, 8.3, 7.1, 6.6 Hz, 1H, H-3α), 3.12 (ddd, J = 14.5, 2.8. 2.8 Hz, 1H, H-8β), 3.44 (ddd, J = 12.0, 10.6, 5.6 Hz, 1H, H-2), 3.48 (d, J = 16.3 Hz, 1H, NCH_2), 3.69 (dd, J = 14.5, 14.5 Hz, 1H, H-8α), 3.72 (dd, J = 10.6, 7.8 Hz, 1H, H-2′), 4.26 (d, J = 8.3 Hz, 1H, H-10a), 4.66 (d, J = 16.3 Hz, 1H, NCH_2), 5.60 (dddd, J = 10.9, 10.9, 5.7, 1.2 Hz, 1H, H-5), 5.69 (dd, J = 10.9, 6.6 Hz, 1H, H-4), 6.96 (brs, 0.15H, *H*NCH_3), 7.22 (brs, 0.85H, *H*NCH_3); ^{13}C NMR δ 23.6 (C-6), 26.4 (HN*C*H$_3$), 28.0 (C-7), 28.4 (C(*C*H$_3$)$_3$), 33.6 (C-3), 40.7 (C-3a), 45.0 (C-8), 47.0 (C-2), 49.0 (N*C*H$_2$), 62.4 (C-10a), 80.3 (*C*(CH$_3$)$_3$), 131.7 (C-5, conf.), 133.4 (C-4), 154.9 (*C*O*t*Bu), 169.0 (*C*OONHCH$_3$), 174.0 (C-10, conf.); EIMS 351 [M$^+$]. Anal. Calcd for $C_{18}H_{29}N_3O_4$ (351.45): C, 61.52; H, 8.32; N, 11.96. Found: C, 61.32; H, 8.29; N, 11.88.

***tert*-Butyl (3a*S*,9a*S*)-8-[2-(Methylamino)-2-oxoethyl)]-9-oxo-2,3,3a,4,7,8,9,9a-octahydro-1*H*-pyrrolo[2,3-*c*]azocine-1-carboxylate (3d).** Aminolysis of **11d** (4.0 mg, 0.0118 mmol) was analogously performed with methyl amine in EtOH (1 mL, 8.03 M) as described for **11a**. Reaction time: 1 h. Column chromatography (CH_2Cl_2−MeOH 97:3) gave **3d** (3.7 mg, 93%) as a colorless oil: $[\alpha]_D^{20}$ −200.9° (c = 0.492, $CHCl_3$); IR (film) 3366, 1690, 1667 cm^{-1}; ^{1}H NMR δ 1.39 (s, 1.8H, *t*-Bu, first conf.), 1.46 (s, 7.2H, *t*-Bu, second conf.), 1.61−1.75 (m, 1H, H-3), 1.90−2.05 (m, 2H, H-3′/H-3a), 2.33−2.45 (m, 2H, H-4/H-4′.), 2.75 and 2.77 (2× d, J = 4.9 and 4.7 Hz, 3H, HNC*H*$_3$, conf.), 3.38 (ddd, J = 11.7, 10.6, 5.3 Hz, 1H, H-2), 3.42 and 3.59 (2× dd, J = 15.0, 7.3 Hz and 15.7, 6.6 Hz, 1H, H-7, 2 conf.), 3.62 (d, J = 16.2 Hz, 0.8 H, NCH_2, second conf.), 3.66 and 3.79 (2× dd, each J = 10.7, 7.9 Hz, 1H, H-2′, 2 conf.), 3.97 (d, J = 14.5 Hz, 0.2 H, NCH_2, first conf.), 4.03 (d, J = 14.5 Hz, 0.2 H, NCH_2, first conf.), 4.39 and 4.48 (2× dd, J = 15.0, 9.1 Hz and 15.7, 9.2 Hz, 1, H-7′, 2 conf.), 4.52 (d, J = 16.2 Hz, 0.8 H, NCH_2, second conf.), 4.52 (d, J = 9.1 Hz, 1 H, H-9a), 5.87−6.02 (m, 2H, H-5/H-6), 6.64 (s, 0.2H, *H*NCH_3, first conf.), 6.92 (s, 0.8H, *H*NCH_3, second conf.); ^{13}C NMR δ 26.0, 26.1 (HN*C*H$_3$, conf.), 28.3, 28.4 (C(*C*H$_3$)$_3$, conf.), 31.2, 31.6, (C-4, conf.) 33.1, 33.4 (C-3, conf.), 41.4 (C-3a), 45.2, 45.6 (C-7, conf.), 46.1, 46.6 (C-2, conf.), 51.9, 52.6 (N*C*H$_2$, conf.), 64.4,

64.8 (C-9a), 79.7, 80.1 ($C(CH_3)_3$), 128.9, 129.3 (C-6, conf.), 133.6, 134.5 (C-5, conf.), 153.4, 154.4 (*C*OO*t*Bu, conf.), 169.5, 170.2 ($HNCH_3$, conf.), 172.9, 173.3 (C-9, conf.); EIMS 337 [M^+]. Anal. Calcd for $C_{17}H_{27}N_3O_4$ (337.42): C, 60.51; H, 8.07; N, 12.45. Found: C, 60.64; H, 8.05; N, 12.44.

***tert*-Butyl (3a*S*,10a*S*)-9-[2-(Methylamino)-2-oxoethyl)]-10-oxo-3,3a,4,7,8,9,10,10a-octahydropyrrolo[2,3-*c*]azonine-1(2*H*)-carboxylate (3e).** Aminolysis of **11e** (8.4 mg, 0.0238 mmol, see Supporting Information) was analogously performed with methyl amine in EtOH (2 mL, 8.03 M) as described for **11a**. Reaction time: 1 h. Flash chromatography (CH_2Cl_2−MeOH 97:3) gave **3e** (4.8 mg, 57%) as a colorless oil: $[\alpha]_D^{20}$ +20.2° (c = 0.367, $CHCl_3$); IR (film) 3350, 1661 cm^{-1}; ^1H NMR (600 MHz, protons located at the same side of the ring plane as H-3a are designated as β-protons) δ 1.38 (s, 0.9H, *t*-Bu), 1.43 (s, 8.1H, *t*-Bu), 1.69 (dddd, J = 12.0, 12.0, 12.0, 8.5 Hz, 1H, H-3α), 1.99 (ddd, J = 12.0, 5.5, 5.5 Hz, 1H, H-3β), 2.21−2.26 (m, 2H, H-4/4′), 2.36 (dddd, J = 14.3, 8.0, 7.3, 2.6 Hz, 1H, H-7β), 2.41−2.47 (m, 1H, H-3a), 2.70 (dddd, J = 14.3, 11.4, 8.7, 8.6 Hz, 1H, H-7α), 2.77 (d, J = 4.6 Hz, 3H, HNC*H*$_3$), 3.15 (d, J = 16.6 Hz, 1H, NCH_2), 3.26 (ddd, J = 15.5, 8.6, 8.0 Hz, 1H, H-8β), 3.45 (ddd, J = 12.0, 10.7, 5.5 Hz, 1H, H-2β), 3.58 (dd, J = 10.7, 8.5 Hz, 1 H, H-2α), 4.04 (ddd, J = 15.5, 8.7, 2.6 Hz, 1H, H-8α), 4.10 (d, J = 9.0 Hz, 1 H, H-10a), 4.87 (d, J = 16.6 Hz, 1 H, NCH_2'), 5.49 (ddd, J = 11.4, 10.7, 7.3 Hz, 1H, H-6), 5.83 (ddd, J = 10.7, 8.3, 8.3 Hz, 1H, H-5), 6.93 (brs, 0.1H, *H*NCH_3), 7.46 (brs, 0.9H, *H*NCH_3); ^{13}C NMR δ 26.1 ($HNCH_3$), 26.5 (C-7), 28.5 ($C(CH_3)_3$), 29.1 (C-4), 31.9 (C-3), 44.9 (C-3a), 46.7 (C-8), 46.9 (C-2), 53.5 (NCH_2), 61.5 (C-10a), 80.2 ($C(CH_3)_3$), 127.1 (C-6), 130.9 (C-5), 154.7 (*C*OO*t*Bu), 169.4 (*C*OONHCH$_3$), 174.0 (C-10); EIMS 351 [M^+]. Anal. Calcd for $C_{18}H_{29}N_3O_4$ (351.45): C, 61.52; H, 8.32; N, 11.96. Found: C, 61.50; H, 8.38; N, 11.88.

***tert*-Butyl (3a*S*,10a*S*)-9-[2-(Methylamino)-2-oxoethyl)]-10-oxo-3,3a,4,5,8,9,10,10a-octahydropyrrolo[2,3-*c*]azonine-1(2*H*)-carboxylate (3f).** Aminolysis of **11f** (2.4 mg, 0.0068 mmol) was analogously performed with methyl amine in EtOH (2 mL, 8.03 M) as described for **11a**. Reaction time: 0.5 h. Column chromatography (CH_2Cl_2−MeOH 97:3) gave **3f** (2.4 mg, 100%) as a colorless oil: $[\alpha]_D^{20}$ −46.6° (c = 0.14, $CHCl_3$); IR (film) 3338, 1668 (br) cm^{-1}; ^1H NMR (600 MHz, protons located at the same side of the ring plane as H-3a are designated as β-protons) δ 1.41 (s, 1.3H, *t*-Bu, conf.), 1.46 (s, 7.7H, *t*-Bu, conf.), 1.53 (dddd, J = 13.1, 13.1, 4.0, 4.0 Hz, 1H, H-4α), 1.58 (dddd, J = 13.1, 7.5, 5.3, 4.5 Hz, 1H, H-3α), 1.72 (dddd, J = 13.1, 13.1, 4.5, 4.5 Hz, 1H, H-4β), 2.13−2.20 (m, 1H, H-5β), 2.22 (dddd, J = 13.1, 8.5, 7.5, 7.5 Hz, 1H, H-3β), 2.38 (ddddd, J = 7.5, 4.5, 4.5, 4.0, 3.8 Hz, 1H, H-3a), 2.54−2.62 (m, 1H, H-5α), 2.78 (d, J = 4.7 Hz, 3H, HNC*H*$_3$), 3.43 (ddd, J = 10.5, 7.5, 7.5 Hz, 1H, H-2α), 3.46 (dd, J = 16.7, 4.5 Hz, 1H, H-8β), 3.51 (d, J = 16.2 Hz, 0.85H, NCH_2, conf.), 3.65 (ddd, J = 10.5, 8.5, 5.3 Hz, 0.85H, H-2β, conf.), 3.71 (d, J = 14.4 Hz, 0.15H, NCH_2, conf.), 3.73 (ddd, J = 10.5, 8.5, 4.0 Hz, 0.15H, H-2β, conf.), 4.19 (d, J = 14.4 Hz, 0.15H, NCH_2, conf.), 4.56 (dd, J = 16.1, 10.8 Hz, 1H, H-8α), 4.63 (d, J = 3.8 Hz, 1H, H-10a, conf.), 4.69 (d, J = 16.2 Hz, 0.85H, NCH_2, conf.), 4.76 (dd, J = 16.7, 8.4 Hz, 0.85H, H-8α), 5.64−5.73 (m, 1.85H, H-6/H-7), 5.82 (ddd, J = 10.6, 10.6, 5.8 Hz, 0.15H, H-7, conf.), 6.64 (brs, 0.15H, *H*NCH_3, conf.), 6.98 (brs, 0.85H, *H*NCH_3, conf.); ^{13}C NMR δ 23.8, 24.0 (C-5, conf.), 26.3 ($HNCH_3$), 28.4, 28.6 ($C(CH_3)_3$, conf.), 29.6 (C-3, conf.), 29.9 (C-4, conf.), 31.4 (C-3, conf.), 31.6 (C-4, conf.), 40.2, 41.3 (C-3a, conf.), 45.8 (C-8, conf.), 45.9 (C-2, conf.), 46.3 (C-2, conf.), 46.8 (C-8, conf.), 52.5, 53.2 (NCH_2, conf.), 59.6 (C-10a), 79.8, 80.4 ($C(CH_3)_3$, conf.), 124.9, 125.6 (C-6, conf.), 131.7, 132.2 (C-7, conf.), 153.9, 155.4 (*C*OO*t*Bu, conf.), 169.5, 170.2 (*C*OONHCH$_3$), 174.1, 174.4 (C-10); EIMS 351 [M^+]. Anal. Calcd for $C_{18}H_{29}N_3O_4$ (351.45): C, 61.52; H, 8.32; N, 11.96. Found: C, 61.32; H, 8.29; N, 11.88.

***N*-[(2*S*,3*R*)-3-Allyl-*N*′-(9-fluorenylmethyloxycarbonyl)prolyl]-*N*-(*S*)-(3-butenyl)-*O*-(2,6-dichlorobenzyl)tyrosine Methyl Ester (14).** To a solution of (2*S*,3*S*)-3-allyl-*N*-(9-fluorenylmethyloxycarbonyl)proline (**12**, see Supporting Information, 150.0 mg, 0.397 mmol) and 2,6-lutidine in dioxane (10 mL) was added solid bis-trichloromethylcarbonate[24] (BTC, 39.3 mg, 0.132 mmol), and after 1 min (*S*)-*N*-(3-butenyl)-*O*-(2,6-dichlorobenzyl)tyrosine methyl ester (**13**, see Supporting Information, 243.4 mg, 0.596 mmol) in dioxane (2 mL) was added. After 20 min of stirring, the solvent was evaporated, and the residue was purified by flash chromatography (petrol ether:EtOAc 2:1) to furnish **14** (242.7 mg, 80%) as a colorless resin: $[\alpha]_D^{20}$ −41.1° (c = 0.583, $CHCl_3$); IR (film) 1739, 1705, 1655 cm^{-1}; ^1H NMR (2 maj. conf.) δ 1.73−1.85 (m, 1H), 2.09−2.25 (m, 3H), 2.25−2.55 (m, 2H), 2.57−2.67 (m, 0.4H), 2.78−2.88 (m, 0.6 H), 3.15−3.41 (m, 3H), 3.54−3.66 (m, 1H), 3.68 (s, 3H), 3.82−3.91 (m, 1H), 4.07−4.17 (m, 1H), 4.28−4.38 (m, 1.6H), 4.38−4.48 (m, 1.4H), 4.69−4.74 (m, 0.4H), 4.87−4.98 (m, 0.6H), 5.11−5.21 (m, 2H), 5.26 and 5.28 (2 × s, 2H), 5.51−5.64 (m, 0.4H), 5.67−5.84 (m, 1.6H), 6.95−7.01 (m, 2H), 7.10−7.19 (m, 2H), 7.25−7.46 (m, 7H) 7.55−7.70 (m, 2H), 7.75−7.81 (m, 2H); ^{13}C NMR (2 maj. conf.) δ 27.8, 29.1, 32.9, 33.0, 34.0, 34.2, 38.1, 38.3, 42.6, 43.1, 45.4, 45.6, 47.3, 47.4, 48.6, 49.0, 52.1, 52.2, 61.5, 61.8, 62.6, 62.8, 65.5, 65.6, 67.3, 67.4, 115.2, 115.3, 117.0, 117.1, 118.2, 118.3, 119.9, 125.2, 125.3, 127.0, 127.1, 1276, 127.7, 130.1, 130.2, 130.4, 132.2, 132.3, 133.9, 134.4, 135.5, 135.6, 137.0, 141.2, 141.3, 144.0, 144.2, 154.7, 154.9, 157.8, 157.9, 170.6, 171.0, 171.8, 172.3; APCIMS 767, 769 ([M + H]$^+$, main isotope peaks). Anal. Calcd for $C_{44}H_{44}Cl_2N_2O_6$ (767.75) × 3 H_2O: C, 64.31; H, 6.13; N, 3.41. Found: C, 64.70; H, 5.85; N, 3.33.

9*H*-Fluoren-9-yl (3a*S*,10a*S*,1′*S*)-9-{2-[4-(2,6-Dichlorobenzyloxy)-phenyl]-1-methoxycarbonylethyl}-10-oxo-3,3a,4,7,8,9,10,-10a-octahydropyrrolo[2,3-*c*]azonine-1(2*H*)-carboxylate (15). Olefin metathesis was analogously performed as described for **11a**, using diene **14** (183.5 mg, 0.2388 mmol), CH_2Cl_2 (180 mL), and catalyst **I** (7.0 mg) in CH_2Cl_2 (1 mL). Reaction time: 30 min. Flash chromatography (gradient petrol ether−EtOAc, 4:1 → 2:1) afforded **15** (153.7 mg, 87%) as a colorless oil: $[\alpha]_D^{20}$ −105.2° (c = 0.542, $CHCl_3$); IR (film) 1738, 1700, 1664 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.32 and 1.62 (2× dddd, each J = 13.9, 11.9, 9.8, 6.0 Hz, 1H), 1.71−1.79 (m, 1H), 1.79−1.86 (m, 0.5H), 1.87−1.95 (m, 1H), 1.95−2.03 (m, 1H), 2.08−2.19 (m, 1.5H), 2.18−2.25 (m, 0.5H), 2.43−2.49 (m, 0.5H), 2.74 (dd, J = 14.0, 7.7 Hz, 0.5H), 2.74−2.80 (m, 1.0H), 2.84 (dd, J = 13.8, 6.4 Hz, 0.5H), 3.00−3.07 (m, 0.5H), 3.03 (dd, J = 14.0, 7.7 Hz, 0.5H), 3.09−3.16 (m, 0.5H), 3.13 (dd, J = 13.8, 8.3 Hz, 0.5H), 3.24−3.29 (m, 1H), 3.42−3.46 (m, 0.5H), 3.48−3.59 (m, 2H), 3.52 and 3.55 (2× s, 3H), 3.62−3.68 (m, 0.5H), 3.76 (d, J = 9.1 Hz, 0.5H), 4.06 (dd, J = 11.1, 5.5 Hz, 0.5H), 4.16 (d, J = 9.4 Hz, 0.5H), 4.20−4.27 (m, 1.5H), 4.27−4.33 (m, 0.5H), 4.79 (dd, J = 7.7, 7.7 Hz, 0.5H), 4.85 (dd, J = 11.0, 6.0 Hz, 0.5H), 5.02 (dd, J = 8.3, 6.4 Hz, 0.5H), 5.15 and 5.14 (2× s, 2H), 5.38−5.44 (m, 0.5H), 5.44−5.50 (m, 0.5H), 5.57−5.63 (m, 0.5H), 5.66−5.72 (m, 0.5H), 6.90−6.95 (m, 2H), 7.04−7.07 (m, 1H), 7.12−7.15 (m, 1H), 7.27−7.36 (m, 2H) 7.38−7.43 (m, 2H), 7.43−7.48 (m, 1H),7.52−7.57 (m, 2.5H), 7.59−7.62 (m, 0.5H), 7.62−7.67 (m, 1H), 7.86−7.91 (m, 2H); ^{13}C NMR (2 maj. conf.) δ 27.4, 27.5, 27.7, 28.1, 30.4, 31.5, 34.7, 35.3, 43.0, 43.2, 45.8, 46,8, 47.3, 47.9, 51.9, 59.6, 59.8, 61.2, 65.5, 67.4, 115.0, 119.7, 119.9, 124.4, 125.2, 125.3, 125.6, 126.8, 127.0, 127.1, 127.3, 127.5, 127.6, 128.4, 128.5, 129.1, 129.2, 129.3, 129.6, 130.0, 130.1, 130.3, 130.5, 132.2, 132.3, 137.0, 141.3, 141.4, 143, 5, 143.9, 144.2, 144.4, 154.1, 154.7, 157.6, 157.7, 171.2, 171.4, 174.2, 174.4; APCIMS 739, 741 ([M + H]$^+$, main isotope peaks). Anal. Calcd for $C_{42}H_{40}Cl_2N_2O_6$ (739.70) × 1.7 H_2O: C, 65.49; H, 5.68; N, 3.46. Found: C, 65.44; H, 5.81; N, 3.46.

***tert*-Butyl (3a*S*,10a*S*,1′*S*)-9-{2-[4-(2,6-Dichlorobenzyloxy)-phenyl]-1-methoxycarbonylethyl}-10-oxo-3,3a,4,7,8,9,10,10a-octahydropyrrolo[2,3-*c*]azonine-1(2*H*)-carboxylate (16).** To a solution of **15** (150.6 mg, 0.204 mmol) in CH_2Cl_2 (10 mL) was added piperidine (96 μL, 1.629 mmmol). After 24 h, solid Boc_2O (444.3 mg, 2.04 mmol) was added, and the mixture was stirred for another

20 h. Thereafter, the solution was evaporated, and the residue was purified by flash chromatography (gradient petrol ether−EtOAc, 4:1 → 2:1 → 1:1) to afford **16** (92.2 mg, 73%) as a colorless oil: $[\alpha]_D^{20}$ −92.0° (c = 0.10, $CHCl_3$); IR (film) 1738, 1700, 1664 cm^{-1}; ^1H NMR (2 maj. conf.) δ 1.40 and 1.43 (2× s, 9H, *t*-Bu), 1.62 and 1.64 (2× dddd, each J = 11.5, 11.5, 11.3, 7.8 Hz, 1H, H-3), 1.86 and 1.89 (2× ddd, each: J = 11.5, 5.5, 5.5 Hz, 1H, H-3′), 2.09−2.28 (m, 3H, H-4/H-7), 2.35−2.57 (m, 2H, H-3a, H-7), 2.91 and 2.97 (2× dd, each J = 13.6, 5.1 Hz, 1H, 4-DcbOPh-CH_2), 3.22 and 3.25 (2× dd, each J = 13.6, 9.9 Hz, 1H, 4-DcbOPh-CH_2), 3.42 (ddd, J = 11.3, 10.9, 5.5 Hz, 1H, H-2), 3.54 (ddd, J = 15.5, 9.4, 5.8 Hz, 0.5H, H-8), 3.56−3.66 (m, 1H, H-8/H-8′, conf., detected with the help of HSQC), 3.60 (dd, J = 10.9, 7.8 Hz, 0.5H, H-2′ conf.), 3.62 and 3.63 (2× s, 3H, OCH_3, conf.), 3.74 (dd, J = 10.9, 7.8 Hz, 0.5 H, H-2′ conf.), 3.86 (ddd, J = 15.5, 5.2, 4.5 Hz, 0.5H, H-8′), 4.21 (d, J = 9.3 Hz, 1 H, H-10a), 5.16 and 5.22 (2× dd, each J = 9.9, 5.1, 1H, 4-DcbOPh-CH_2C*H*N), 5.23 and 5.24 (2× s, 2H, Cl_2PhCH_2), 5.52 and 5.63 (2× ddd, each J = 10.1, 10.1, 7.9 Hz, 1H, H-6 or H-5), 5.71−5.83 (m, 1H, H-5 or H-6), 6.90−6.98 (m, 2H, H-ar), 7.20−7.28 (m, 3H, H-ar), 7.32−7.38 (m, 2H, H-ar); ^{13}C NMR (2 maj. conf.) δ 27.4, 27.5, 27.7, 28.3 (C-4 and C-7), 28.5 (C(*C*H_3)$_3$, conf.), 30.4, 31.6 (C-3), 35.2, 35.4 (DcbOPh-*C*H_2), 43.7 (C-8), 45.9, 46.8, 47.1, 47.7 (C-2, C-3a), 51.8, 52.0 (OCH_3), 60.1, 60.3, 60.6, 60.8 (C-10a, DcbOPhCH_2*C*H-), 65.3 (Cl_2PhCH_2-), 79.4, 80.0 (*C*(CH_3)$_3$, conf.), 115.0, 115.2 (C−Ar), 128.5 (C−Ar), 129.1, 129.3, 129.5, 129.8 (C−Ar, C-5 or C-6), 130.3, 130.4, 130.5, 130.6 (C−Ar, C-5 or C-6), 132.2, 132.4, 137.0 (C−Ar), 153.7, 154.3 (*C*O*O*t*Bu*), 157.6, 157.8, (C−Ar), 171.2, 171.6 (*C*O*O*CH_3), 174.5, 174.6 (C-10); APCIMS 617, 619 ([M + H]$^+$, main isotope peaks). HREIMS Anal. Calcd for $C_{32}H_{38}{}^{35}Cl_2N_2O_6$: 616.2107, Found: 616.2108. Anal. Calcd for $C_{32}H_{38}Cl_2N_2O_6$ (617.57): C, 62.24; H, 6.20; N, 4.54. Found: C, 62.39; H, 6.38 (for N-determination, not sufficient material was left, but a HREIMS is given above).

Saponification of 16 To Give the Carboxylic Acid 17 and Solid Phase Supported Synthesis of Peptide 19. To a solution of **16** (46.0 mg, 0.074 mmol) in MeOH (4 mL) was added 2 N NaOH (4 mL) at 0 °C. THF (10 mL) was added to dissolve the formed precipitate. After 3 h of stirring at 0 °C, the mixture was acidified with saturated citric acid (pH 4) and 3× extracted with ethyl acetate. The organic layer was dried with $MgSO_4$ and evaporated. The residue was redissolved in CH_2Cl_2, filtered, and evaporated to afford the carboxylic acid **17** (crude: 45.1 mg, 100%) as a colorless oil. IR (film) 1734, 1691, 1653 cm^{-1}; ^1H NMR δ 1.39 and 1.43 (2× s, 9H), 1.55−1.70 (m, 2H), 1.80−1.93 (m, 2H), 1.93−2.03 (m, 1H), 2.25−2.35 (m, 1H), 2.35−2.44 (m, 1H), 3.25−3.34 (m, 0.5H), 3.34−3.47 (m, 3H), 3.53−3.59 (m, 0.5H), 3.61−3.67 (m, 0.5H), 3.67−3.73 (m, 0.5H), 3.83−3.93 (m, 0.5H), 4.05−4.15 (m, 1H), 4.23−4.32 (m, 0.5H), 4.35−4.45 (m, 0.5H), 5.23 and 5.24 (2× s, 2H), 5.44−5.53 (m, 0.5H), 5.56−5.78 (m, 2H), 6.93−7.00 (m, 2H), 7.19−7.25 (m, 3H), 7.33−7.38 (m, 2H); ^{13}C NMR (2 maj. conf.) δ 26.6, 26.8, 27.3, 28.3, 28.6, 29.4, 29.7, 34.2, 34.6, 43.7, 45.5, 46.5, 46.8, 47.2, 60.3 60.8, 65.4, 80.5, 115.3, 115.5, 128.4, 128.5, 129.5, 130.4, 130.5, 132.1, 132.3, 153.4, 154.8, 157.9, 157.3, 170.9, 173.6 (the last two signals suffered from a lack of intensity and could only be detected with the help of HMBC 2D-technique); APCIMS 603, 605 ([M + H]$^+$, main isotope peaks);

Peptide Synthesis. Commercially available PAM (4-hydroxymethylphenylacetamidomethyl polystyrene) resin preloaded with Boc-Leu was treated with TFA/CH_2Cl_2/indole (50:50:0.1; 20 min) and subsequently neutralized with 10% DIPEA in CH_2Cl_2 followed by several washes with CH_2Cl_2. Boc-Ile-OH, the crude carboxylic acid derived from **16**, and Boc-Arg(Tos)-OH were coupled according to the following procedure: HATU (3−5 equiv) and the carboxylic acids (3−5 equiv) were dissolved in NMP (least volume possible). After addition of DIPEA (6−10 equiv), the mixture was added to the resin and agitated for 8−16 h, followed by several CH_2Cl_2 washes. If possible, complete acylation was monitored with the Kaiser test. When the test indicated incomplete coupling or when Boc-Arg(Tos)-OH was coupled to the pyrrolidine moiety of the template, respectively, the procedure was repeated. After deprotection with TFA (20 min, see above), the next coupling cycle was started. Upon completion, the *N*-termini were deblocked (TFA), and the HF cleavage from the resin (HF/anisole 9:1, 2 h, 0 °C;) was performed. After evaporation of HF, the resin was washed with *tert*-butyl methyl ether and then the crude peptide was extracted with glacial acetic acid and lyophilized. Two pure isomers of the peptide **19** (ESI-MS: calcd 883 [M + H]$^+$/ 442 [M + 2H]$^{2+}$, found 883/442) were obtained by purification via preparative RP18-HPLC (gradient elution: 5−30% CH_3CN + 0.1% TFA/H_2O + 0.1% TFA in 42 min, $t_{isomer1}$ = 35.4 min, 37.4%, $t_{isomer2}$ = 39.4 min, 62.6%) using an Agilent ZORBAX 300SB-C18 PrepHT (21.2 × 250 mm, 7 μm) column. Most presumably, the alkaline ester hydrolysis of **16** was responsible for a partial epimerization of the CH-acidic tyrosine moiety, while isomerization at earlier stages of the synthesis played a minor role as described in the Supporting Information.

Molecular Dynamics Simulations. All quantum mechanical calculations were performed applying the AM1 Hamiltonian[31] implemented in the semiempirical program package VAMP 8.1.[32] The combination of classical Newtonian dynamics with quantum mechanics ensures that important effects like polarization due to intramolecular donor−acceptor interactions are taken into account. After heating the system to 400 K, sampling at constant temperature was performed for a total data acquisition time of 1 ns. The coupling constant to the external heat bath ensuring constant temperature was 40 ps, and the simulation time step of the velocity-verlet integrator was 1 fs. Translational and rotational movement of the whole molecule was removed every 100 simulation steps. Geometrical information for data averaging was extracted from the snapshots saved every 0.1 ps, generating a Cartesian coordinate trajectory with 10 000 entries in total.

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Supporting Information Available: Complete experimental procedures and characterization data for compounds **12**, **13**, and **18** and ^1H NMR spectra for compounds **5c**, **6a**−**c**, **7a**−**c**, **8a**−**c**, **10a**−**f**, **11a**−**f**, and **3a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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