Heterospirocyclic *N*-(2*H*-Azirin-3-yl)-L-prolinates: New Dipeptide Synthons

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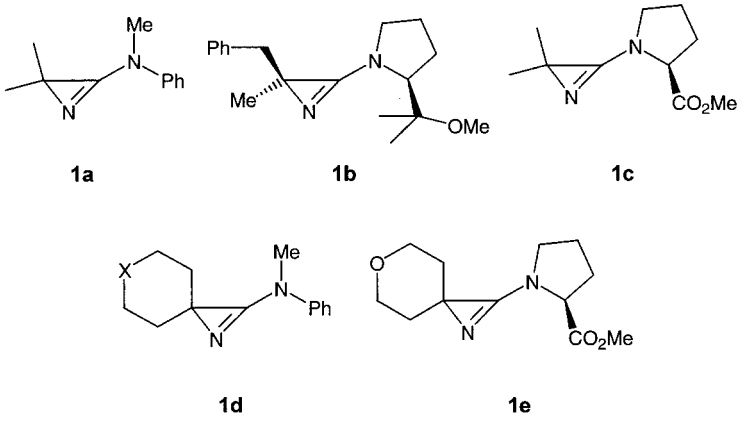
The synthesis of methyl *N*-(1-aza-6-oxaspiro[2.5]oct-1-en-2-yl)-L-prolinate (**1e**) has been performed by consecutive treatment of methyl *N*-[(tetrahydro-2*H*-pyran-4-yl)thiocarbonyl]-L-prolinate (**5**) with $COCl_2$, 1,4-diazabicyclo[2.2.2]octane (DABCO), and NaN_3 (*Scheme 1*). As the first example of a novel class of dipeptide synthons, **1e** has been shown to undergo the expected reactions with carboxylic acids and thioacids (*Scheme 2*). The successful preparation of the nonapeptide **16**, which is an analogue of the C-terminal nonapeptide of the antibiotic *Trichovirin I 1B*, proved that **1e** can be used in peptide synthesis as a dipeptide building block (*Scheme 3*). The structure of **7** has been established by X-ray crystal-structure analysis (*Figs. 1* and *2*).

1. Introduction. – Extensive studies on the use of 2*H*-azirin-3-amines (= 3-amino-2*H*-azirines) **1** proved them to be versatile synthons for α,α-disubstitued α-amino acids (2,2-disubstituted glycines) in peptide synthesis [1–8]. Thus, the reaction of peptide acids with **1a** and **1b** leads to peptide amides with a backbone extended by a 2-methylalanine (aminoisobutyric acid, Aib) and an (*S*)-2-methylphenylalanine (Phe(Me)) moiety, respectively. After the selective acid-catalyzed hydrolysis of the terminal amide bond, the extended peptide acid is obtained, which can then be used for further 'azirine coupling' or for segment condensation.

Some years ago, we designed methyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate (**1c**) as a synthon for the dipeptide unit Aib-Pro. This building block has been used to



[1]) Diploma thesis of *G.S.*, Universität Zürich, 1999.

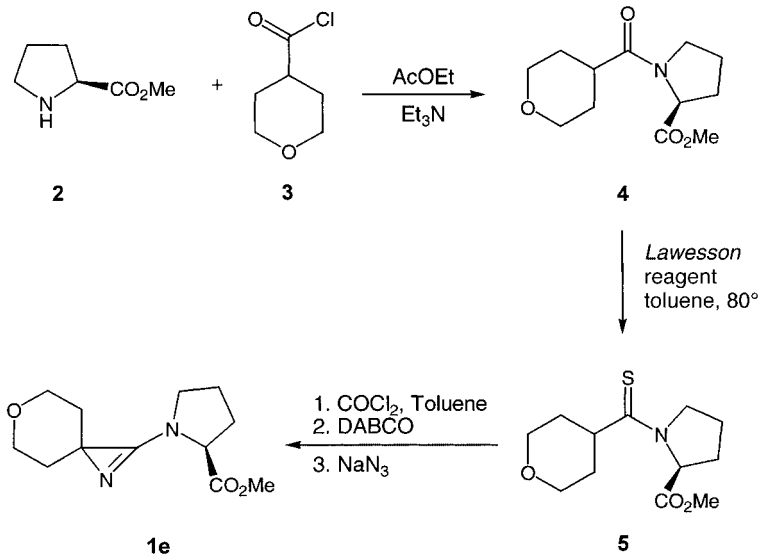
[2]) Part of the projected Ph.D. thesis of *S.A.S.*, Universität Zürich.

prepare segments of the peptaibol antibiotics *Trichovirin I 1B* and *I 4A* [9][3]) and in the synthesis of endothiopeptides with a C-terminal Aib-Pro unit [7]. Aminoazirines of type **1d** have been shown to be synthons for heterocyclic α-amino acids [12]. Incorporated in tripeptides of the type Z-Aib-Xaa-Aib-N(Ph)Me, Z-Phe-Xaa-Val-OMe, and Asp-D-Ala-Xaa-OMe, they behave like Aib and some other α,α-disubstituted α-amino acids that are known to stabilize secondary structures such as β-turns and α or 3_{10} helices (*cf.* [13–15] and refs. cit. therein)[4]).

In the present paper, we report the synthesis of methyl *N*-(1-aza-6-oxaspiro[2.5]oct-1-en-2-yl)-L-prolinate (**1e**), the first example of heterospirocyclic *N*-(2*H*-azirin-3-yl)-L-prolinates, which are expected to be new dipeptide synthons. In this novel azirine derivative, the structural elements of **1c** and **1d** are combined, and the question arose as to whether or not this sterically congested compound can be of use in peptide synthesis.

2. Results and Discussion. – The precursor for the preparation of **1e** was the thioamide **5** (*Scheme 1*). As the method of *Villalgordo* and *Heimgartner* [18], used by *Strässler* for the synthesis of **1d** [12], is limited to *N*-alkyl-*N*-phenyl amides, methyl *N*-[(tetrahydro-2*H*-pyran-4-yl)carbonyl]-L-prolinate (**4**) was converted to **5** by thionation with *Lawesson* reagent. In analogy to the procedure described in [9], consecutive treatment of a solution of the latter in CH_2Cl_2 and catalytic amounts of DMF with $COCl_2$, evaporation of the solvent, dissolution of the residue in THF, addition of 1,4-diazabicyclo[2.2.2]octane (DABCO), filtration, and reaction with NaN_3 gave azirine **1e** in 74% yield as a yellow oil.

Scheme 1

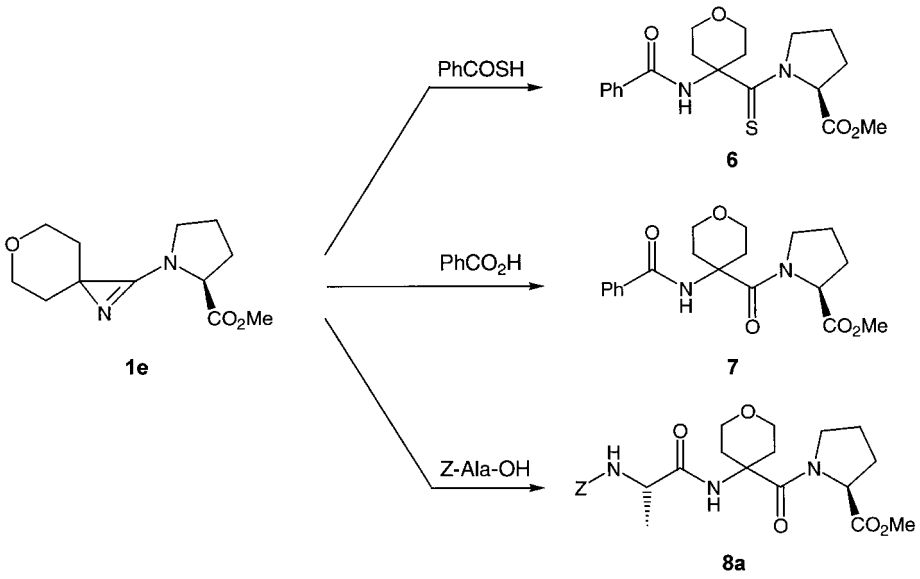


[3]) For an alternative synthesis of *Trichovirin I 4A*, see [10][11].

[4]) Other 2,2-disubstituted glycines, *e.g.*, 2,2-diethyl- and 2,2-dipropylglycine [16], as well as 2-butyl-2-ethylglycine [17], prefer planar conformations of the peptide backbone.

For the chemical characterization of **1e**, the reaction with PhCOSH acid was performed in CH_2Cl_2 at $0° \rightarrow$ room temperature. After chromatographic workup, the *N*-benzoylated endothiodipeptide **6** was obtained in 79% yield (*Scheme 2*). The analogous reaction of **1e** with PhCOOH under similar conditions proceeded more slowly and with lower yield. After chromatography, dipeptide **7** was isolated in 28% yield. Its structure was established by X-ray crystal-structure analysis (*Figs. 1* and *2*).

Scheme 2



The asymmetric unit in the structure of **7** contains one peptide and one H_2O molecule. The torsion angles ϕ(C(3)–C(2)–N(1)–C(9)) and φ(N(1)–C(2)–C(3)–N(4)) of the tetrahydro-2*H*-pyran-4-yl (Thp) residue are 52.8(3) and 39.9(4)°, respectively. They are close to the values expected for an amino acid in a β-turn of type *I* or *III*. The Thp ring adopts a chair conformation, and the pyrrolidine ring of Pro shows a half-chair conformation twisted on C(22)–C(23) (*Fig. 1*).

The amide NH forms an intermolecular H-bond with the C=O group that lies between the six- and five-membered rings of a neighboring molecule (N(1)···O(3′): 3.115(3) Å, angle: 153°). This interaction links the molecules into infinite one-dimensional chains that run parallel to the *x*-axis and have a graph set motif [20] of C(5). The H_2O molecule forms an intermolecular H-bond with each of two different molecules of **7**, thereby forming infinite one-dimensional chains of alternating peptide and H_2O molecules, which run parallel to the *z*-axis and have a graph set motif of $C_2^2(10)$. The acceptor atoms are the amide O-atom (O(9)) and the Thp O-atom (O(18)) (O···O distances in these H-bonds: 2.850(3) and 2.799(3) Å, resp., angles: 154° each). The combination of all H-bonding interactions links the peptide and H_2O molecules into infinite two-dimensional networks which lie in the *xz*-plane (*Fig. 2*).

With the aim of testing the utility of **1e** as a dipeptide synthon (Thp-Pro) in peptide synthesis, the reaction with Z-protected L-alanine (Z-Ala) was carried out in CH_2Cl_2.

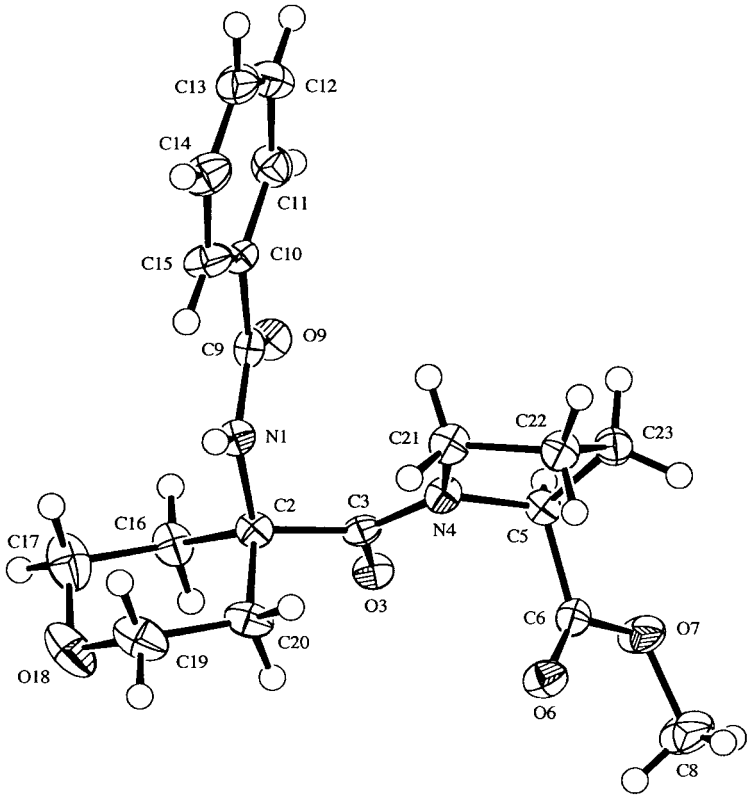


Fig. 1. *ORTEP Plot* [19] *of the molecular structure of* **7** (with 50% probability ellipsoids)

After the addition of Z-Ala-OH at 0°, the mixture was stirred overnight at room temperature. Chromatographic purification gave tripeptide Z-Ala-Thp-Pro-OMe (**8a**) in 89% yield as a colorless foam (*Scheme 2*).

The strategy for the synthesis of the nonapeptide **16**, which is an analogue of the C-terminal nonapeptide of the antibiotic peptaibol *Trichovirin I 1B* (*cf.* [9][10]), is shown in *Scheme 3*. Key steps in this synthesis are the reactions coupling Z-Val-OH and Z-Leu-OH with azirine **1e** to give the tripeptides Z-Val-Thp-Pro-OMe (**8b**) and Z-Leu-Thp-Pro-OMe (**8c**), respectively. After recrystallization, **8b** was obtained in 71% yield as pale yellow crystals, whereas **8c** was purified by column chromatography (73%; colorless foam). Saponification of **8b** and **8c** with $LiOH \cdot H_2O$ in THF/MeOH/H_2O gave the tripeptide acids **9b** and **9c** in 93 and 77% yield, respectively.

Next, the Z-protected tripeptide **9b** was reacted with 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**1a**) to give Z-Val-Thp-Pro-Aib-N(Me)Ph (**10**; 71% yield). Deprotection of the NH_2 group by catalytic hydrogenation yielded **11**, which was coupled to Z-Ser(*t*Bu)-OH with *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) in MeCN to yield 82% of Z-Ser(*t*Bu)-Val-Thp-Pro-Aib-N(Me)Ph (**12**) as a pale yellow oil. Selective hydrolysis of the C-terminal amide group

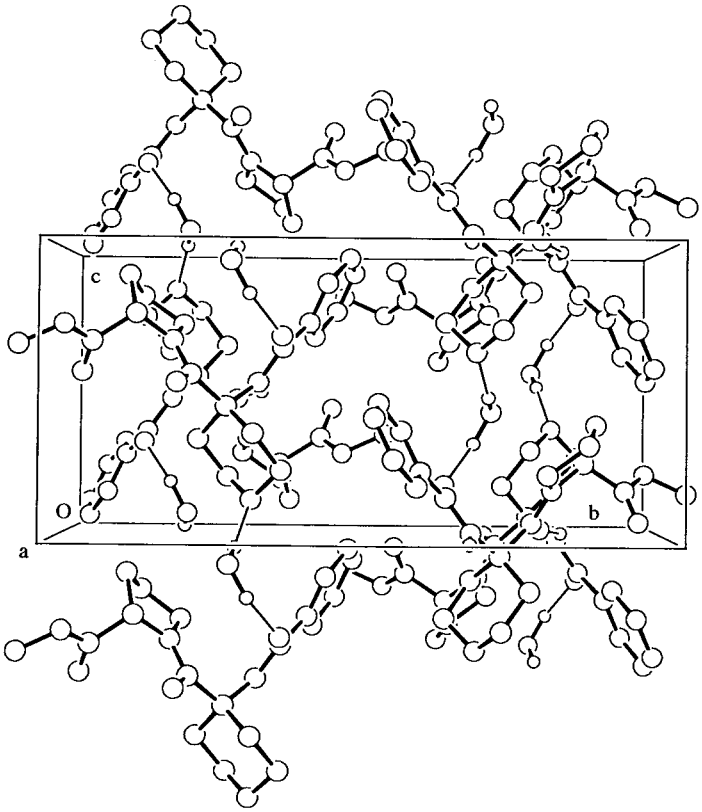


Fig. 2. *Packing diagram of dipeptide* **7**

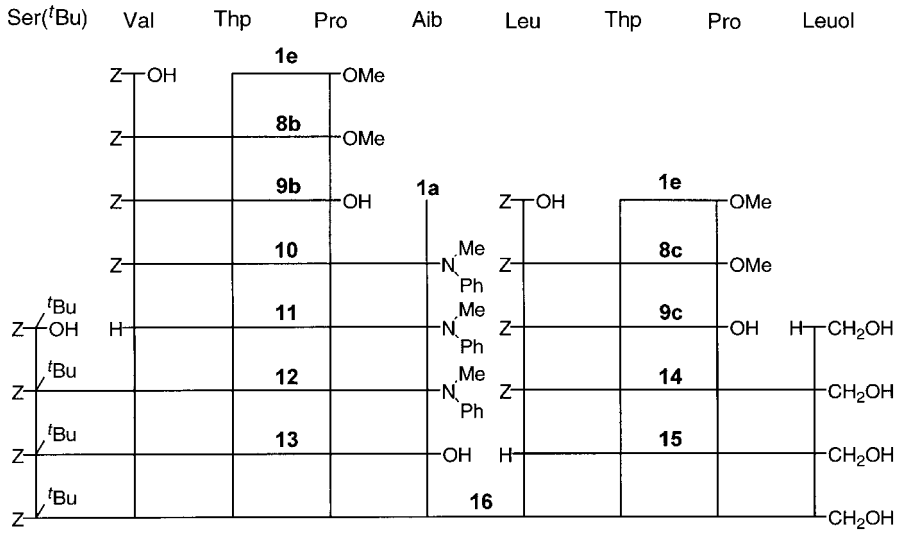
under the conditions described by *Wipf* [21] (3N HCl in THF/H_2O 1:1, room temperature) gave, after 1 h, the acid **13** in 81% yield, contaminated with 10–15% of the starting material **12**.

The synthesis of the segment H-Leu-Thp-Pro-Leuol (**15**) was performed by coupling **9c** to Leuol with HATU/HOBt/Et_3N in MeCN to give Z-Leu-Thp-Pro-Leuol (**14**) in 81% yield, which then was deprotected by catalytic hydrogenation leading to **15** in 95% yield.

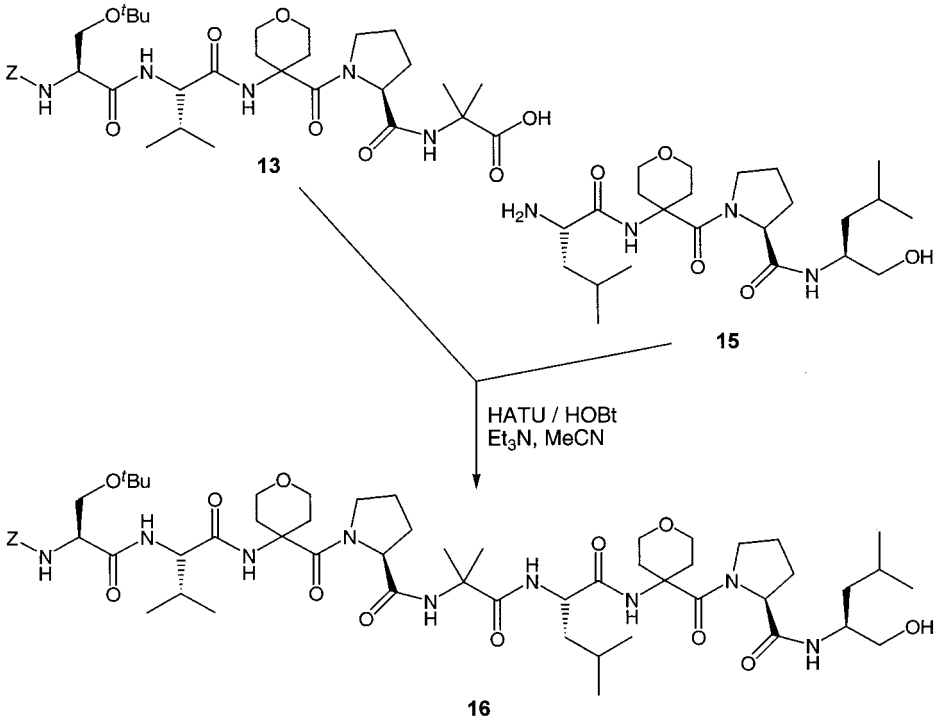
The two segments, pentapeptide **13** and tetrapeptide **15**, were coupled by the HATU/HOBt method in MeCN. The expected nonapeptide Z-Ser(^{t}Bu)-Val-Thp-Pro-Leu-Thp-Pro-Leuol (**16**; *Scheme 4*) was obtained in 73% yield as a white foam. Based on the ^{1}H- and ^{13}C-NMR spectra, there are two conformers present in $CDCl_3$ solution.

It is worth mentioning that the acid-catalyzed hydrolysis of the pentapeptide amide **12** for 1 h gave the peptide acid **13** with the (*tert*-butoxy)-protected side chain of Ser in high yield. When the hydrolysis was performed under the same conditions, but for 48 h, Z-Ser-Val-Thp-Pro-Aib-OH (**13a**) with deprotected Ser was obtained in 80% yield. This product was coupled with **15** (HATU/HOBt) to give **16a** in 71% yield (*Scheme 5*).

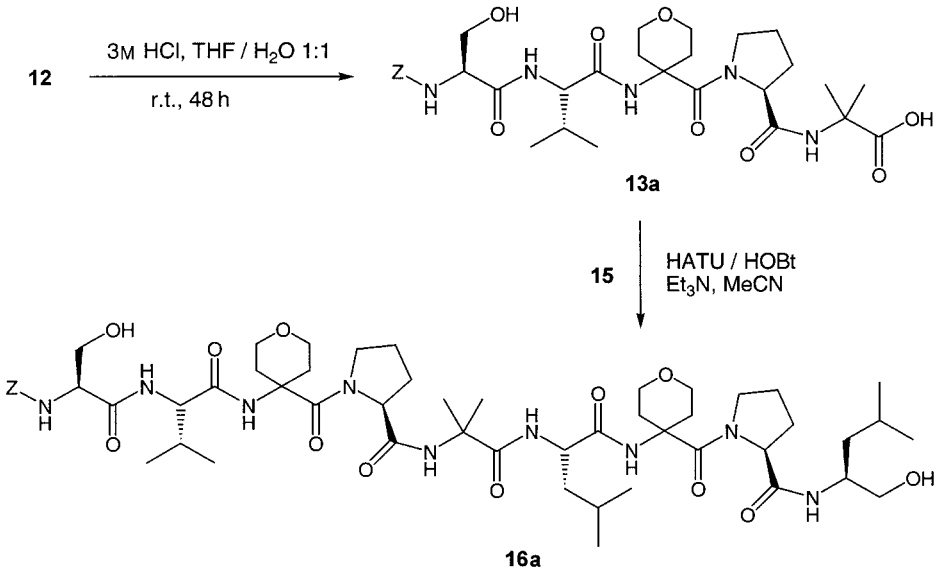
Scheme 3



Scheme 4



Scheme 5



In conclusion, the studies presented show that spirocyclic *N*-(2*H*-azirin-3-yl)prolinates of type **1e** can be prepared according to previously reported protocols. It is important to transform the *N*-acylated prolinate **4** into the corresponding thioamide **5** because of the low reactivity of **4** in the reaction with $COCl_2$ (*Scheme 1*). In the reactions with PhCOOH, PhCOSH, and *N*-protected α-amino acids, **1e** behaves like other 2*H*-azirin-3-amines (= 3-amino-2*H*-azirines) that have been extensively used as building blocks for α,α-disubstituted glycines in peptide synthesis. The novel amino-azirine **1e** has been shown to be a synthon for the dipeptide *N*-[(4-aminotetrahydro-2*H*-pyran-4-yl)carbonyl]-L-proline (Thp-Pro). As a model, the nonapeptide Z-Ser(*t*Bu)-Val-Thp-Pro-Aib-Leu-Thp-Pro-Leuol (**16**) was prepared according to a combination of the azirine/oxazolone method and segment coupling with HATU/HOBt (*Schemes 3–5*).

We thank the analytical units of our institute for spectra and analyses, and the *Swiss National Science Foundation*, the *Stiftung für wissenschaftliche Forschung an der Universität Zürich*, and *F. Hoffmann-La Roche AG*, Basel, for financial support.

Experimental Part

1. *General*. See [22]. M.p. determined on a *Büchi 510* instrument; uncorrected. Unless otherwise stated, IR spectra in KBr on a *Perkin-Elmer 1600 Series* FT-IR spectrometer, NMR spectra in $CDCl_3$ on *Bruker-ARX-300*, *DRX-500*, and *AMX-600* spectrometers (^{1}H: 300, 500, and 600 MHz; ^{13}C: 75.5, 125.8, and 150.9 MHz). Multiplicities of the C-atoms determined with DEPT technique. MS on a *Finnigan MAT SSQ-700* (EI (70 eV), CI with NH_3) and *Finnigan MAT TSQ-700* (ESI) instrument or a *Hewlett-Packard HP-5971/HP-5890 Series II* (GC/MS) combination.

2. *Synthesis of Methyl (*S*)-*N*-(1-Aza-6-oxaspiro[2.5]oct-1-en-2-yl)prolinate* (**1e**). 2.1. *Methyl (*S*)-*N*-[(Tetrahydro-2*H*-pyran-4-yl)carbonyl]prolinate* (**4**). To cooled MeOH (17 ml) was slowly added $SOCl_2$ (3.7 ml) keeping the temp. below 0°. Then, (*S*)-proline (5.42 mg, 47.0 mmol) was added, and the mixture was

heated under reflux for 1 h. Excess MeOH was evaporated, the sticky pale yellow residue was dissolved in AcOEt (17 ml), Et_3N (2.2 ml) and *tetrahydro-2*H*-pyran-4-carbonyl chloride* (**3**; 5.00 g, 33.6 mmol) [12] were added at 0°, and the mixture was heated to 55° for 2 h. After evaporation of AcOEt, the residue was dissolved in CH_2Cl_2, the soln. was washed with sat. NaCl soln., dried ($MgSO_4$), CH_2Cl_2 was evaporated, and the residue was distilled (bulb-to-bulb, 180°/$7 \cdot 10^{-2}$ mbar): 7.24 g (89%) of **4**. Pale yellow oil. IR (neat): 2955*s*, 2848*m*, 1745v*s*, 1642v*s*, 1435v*s*, 1387*m*, 1357*s*, 1311*m*, 1280*m*, 1240*m*, 1198*s*, 1175*s*, 1130*s*, 1088*s*, 1038*w*, 1015*w*, 985*m*, 959*w*, 915*w*, 886*w*, 820*w*, 779*w*. ^{1}H-NMR (600 MHz, 2D): 4.48 (*dd*, $J = 8.5$, 4.2, CH(α)(Pro)); 4.02 (*dt*, $J = 11.5$, 3.0, 2 H_{eq} of CH_2(2), CH_2(6)(Thp)); 3.75 (*s*, MeO); 3.72–3.68, 3.62–3.57 (2*m*, $CH_2(\delta)$(Pro)); 3.44 (*td*, $J = 11.6$, 3.0, 2 H_{ax} of CH_2(2), CH_2(6)(Thp)); 2.69–2.64 (*m*, CH(4)(Thp)); 2.22–2.15 (*m*, 1 H of $CH_2(\beta)$(Pro)); 2.13–2.07 (*m*, 1 H of $CH_2(\gamma)$(Pro)); 2.04–1.97 (*m*, 1 H of $CH_2(\beta)$, 1 H of $CH_2(\gamma)$(Pro)); 1.94–1.83 (*m*, 2 H_{ax} of CH_2(3), CH_2(5)(Thp)); 1.72, 1.62 (2 br. *d*, $J = 13.6$, 2 H_{eq} of CH_2(3), CH_2(5)(Thp)). ^{13}C-NMR (150.9 MHz): 173.1, 172.7 (2*s*, 2 C=O); 67.1, 66.9 (2*t*, C(2), C(6)(Thp)); 58.6 (*d*, C(α)(Pro)); 52.0 (*q*, MeO); 46.6 (*t*, C(δ)(Pro)); 39.5 (*d*, C(4)(Thp)); 28.9 (*t*, C(β)(Pro)); 28.4, 28.2 (2*t*, C(3), C(5)(Thp)); 24.8 (*t*, C(γ)(Pro)). GC/MS: Retention time (t_R) 11.9 min; 241 ($M^{+\cdot}$), 223, 213, 198, 182, 171, 152, 138, 124, 113, 96, 85, 70, 55. Anal. calc. for $C_{12}H_{19}NO_4$ (241.29): C 59.74, H 7.94, N 5.80; found: C 59.60, H 8.22, N 5.72.

2.2. *Methyl (*S*)-*N*-[(Tetrahydro-2*H*-pyran-4-yl)thiocarbonyl]prolinate* (**5**). To a soln. of **4** (6.00 g, 24.8 mmol) in abs. toluene (70 ml) was added *Lawesson* reagent (12.13 g, 30.0 mmol), and the mixture was stirred unter reflux for 2 h. After cooling to r.t., the mixture was filtered (*Celite*), the solvent evaporated, and the crude product was purified by chromatography (SiO_2; hexane/AcOEt 1:1) and distillation (bulb-to-bulb, 190°/$7 \cdot 10^{-2}$ mbar): 2.89 g (45%) of **5**. Pale yellow solid. M.p. 94–95°. IR: 2958*s*, 2922*m*, 2878*m*, 2850*m*, 2768*m*, 2700*w*, 1739v*s*, 1476v*s*, 1450v*s*, 1394*m*, 1362*m*, 1322*m*, 1239*s*, 1081*m*, 1015*m*, 985*m*, 972*m*, 925*m*, 902*m*, 874*m*, 783*s*, 748*w*. ^{1}H-NMR (300 MHz): 5.07 (*dd*, $J = 8.5$, 8.2, CH(α)(Pro)); 4.04 (*dt*, $J = 11.5$, 3.4, 2 H_{eq} of CH_2(2), CH_2(6)(Thp)); 3.96–3.82 (*m*, $CH_2(\delta)$(Pro)); 3.73 (*s*, MeO); 3.47 (*td*, $J = 11.7$, 2.0, 2 H_{ax} of CH_2(2), CH_2(6)(Thp)); 2.93 (*tt*, $J = 11.3$, 3.5, CH(4)(Thp)); 2.37–1.98 (*m*, $CH_2(\beta)$(Pro), $CH_2(\gamma)$(Pro), 2 H_{ax} of CH_2(3), CH_2(5)(Thp)); 1.72, 1.58 (2 br, *d*, $J = 13.5$, 2 H_{eq} of CH_2(3), CH_2(5)). ^{13}C-NMR (75.5 MHz): 205.6 (*s*, C=S); 170.9 (*s*, C=O); 67.4, 67.2 (2*t*, C(2), C(6)(Thp)); 65.1 (*d*, C(α)(Pro)); 52.2 (*q*, MeO); 50.1 (*t*, C(δ)(Pro)); 46.7 (*d*, C(4)(Thp)); 32.2, 31.9 (2*t*, C(3), C(5)(Thp)); 28.6 (*t*, C(β)(Pro)); 24.6 (*t*, C(γ)(Pro)). GC/MS: t_R 15.0 min; 257 ($M^{+\cdot}$), 242, 224, 214, 200, 182, 168, 154, 128, 114, 99, 85, 70, 55. Anal. calc. for $C_{12}H_{19}NO_3S$ (257.35): C 56.01, H 7.44, N 5.44, S 12.46; found: C 56.07, H 7.51, N 5.49, S 12.35.

2.3. *Azirine* **1e**. In a dried two-neck round-bottom flask, a soln. of **5** (2.91 g, 12.2 mmol) in CH_2Cl_2 (15 ml) and 3 drops of DMF was cooled to 0°. After slow addition of 7.3 ml of a $COCl_2$ soln. in toluene (2M, 14.6 mmol), the mixture was stirred at r.t. for 15 min, and the solvent was evaporated. The residue was dissolved in THF (30 ml), DABCO (1.64 g, 14.6 mmol) was added, and the mixture was stirred at r.t. for 40 min. The solid was removed by filtration under Ar and washed with THF. To the pale yellow soln. was added NaN_3 (2.38 g, 36.6 mmol), the mixture was stirred at r.t. overnight, filtered through a *Celite* pad, and the solvent was evaporated. The residue was dissolved in AcOEt, the soln. was washed with sat. aq. $NaHCO_3$ and NaCl soln., the org. layer was dried ($MgSO_4$) and evaporated. Purification by CC (SiO_2; hexane/AcOEt 1:9) gave **1e**: 2.16 g (74%). Yellow oil. IR (neat): 3457*w*, 2955*m*, 2910*m*, 2849*m*, 2754*w*, 2696*w*, 2349*w*, 1773*s*, 1743*s*, 1688*m*, 1659*m*, 1565*w*, 1461*m*, 1437*m*, 1384*m*, 1349*m*, 1282*s*, 1235*s*, 1072*m*, 1029*m*, 1002*m*, 967. ^{1}H-NMR (300 MHz): 4.42–4.31 (br. *s*, CH(α)(Pro)); 3.99–3.91 (*m*, 2 H of CH_2(5), CH_2(7)(Thp)); 3.74 (*s*, MeO); 3.72–3.68 (*m*, 2 H of CH_2(5), CH_2(7)); 3.67–3.56 (*m*, $CH_2(\delta)$(Pro)); 2.38–2.02 (*m*, $CH_2(\beta)$, $CH_2(\gamma)$(Pro)); 1.91–1.85, 1.78–1.64 (*m*, 4 H of CH_2(4), CH_2(8)). ^{13}C-NMR (75.5 MHz): 164.7 (*s*, C=O); 67.4 (*t*, C(5), C(7)); 52.4 (*q*, MeO); 36.0 (*t*, C(4), C(8)); 30.2 (*t*, C(β)(Pro)); 23.9 (*t*, C(γ)(Pro)); C(α) and C(δ) of Pro could not be localized. GC/MS: t_R 11.6 min; 238 ($M^{+\cdot}$), 207, 195, 179, 168, 149, 138, 128, 110, 96, 82, 70, 53.

3. *Reactions of* **1e** *with PhCOSH*, *PhCOOH*, *and Amino Acids*. 3.1. *General Procedure 1* (*GP 1*). To a soln. of the acid (0.2–0.3 mmol) in dry CH_2Cl_2 (5 ml) at 0°, a soln. of *ca*. 0.9 mol-equiv. of **1e** in CH_2Cl_2 (5 ml) was added dropwise. The mixture was stirred at r.t. for 6–16 h, the solvent was evaporated, and the residue was purified by CC (SiO_2; AcOEt).

3.2. *Methyl (*S*)-*N*-{[4-(Benzoylamino)tetrahydro-2*H*-pyran-4-yl]thiocarbonyl}prolinate* (**6**). According to *GP 1*, PhCOSH (32 mg, 0.231 mmol) and **1e** (50 mg, 0.210 mmol), stirring for 14 h: 64 mg (79%) of **6**. Pale yellow solid. M.p. 185–187°. IR: 3369*m*, 2955*m*, 2854*m*, 1741*s*, 1646*s*, 1601*m*, 1579*w*, 1522*m*, 1488*m*, 1423*m*, 1346*m*, 1283*s*, 1248*s*, 1206*s*, 1149*s*, 1105*m*, 1077*m*, 1002*m*, 931*m*, 884*m*, 805*m*, 765*m*, 717*m*, 662*m*. ^{1}H-NMR (300 MHz): 7.81 (*d*, $J = 7.4$, 2 arom. H); 7.57–7.44 (*m*, 3 arom. H); 6.65 (br. *s*, NH); 5.19 (br. *d*, $J = 6.6$, CH(α)(Pro)); 4.14–3.93 (*m*, 2 H of CH_2(2), CH_2(6)(Thp)); 3.78–3.61 (*m*, 5 H); 3.71 (*s*, MeO); 3.06–2.95 (*m*, 1 H); 2.42–1.94 (*m*, 6 H). ^{13}C-NMR (75.5 MHz): 203.5 (*s*, C=S); 171.1 (*s*, O–C=O); 165.5 (*s*, Ph*C*=O); 133.5 (*s*, 1 arom. C); 132.0, 128.9, 126.9 (3*d*, 5 arom. CH); 68.6 (*d*, C(α)(Pro)); 64.2, 62.9 (2*t*, C(2), C(6)(Thp));

61.6 (*s*, C(4)(Thp)); 52.4 (*t*, C(δ)(Pro)); 52.1 (*q*, MeO); 35.9, 34.6, 27.4, 25.9 (4*t*, 4 CH_2). CI-MS: 378 (19), 377 (100, $[M+1]^+$), 353 (17), 346 (12), 345 (62). Anal. calc. for $C_{19}H_{24}N_2O_4S \cdot 1/2\ H_2O$ (385.48): C 59.20, H 6.28, N 7.27, S 8.32; found: C 59.22, H 6.46, N 7.21, S 8.09.

3.3. *Methyl (*S*)-*N*-{[4-(Benzoylamino)tetrahydro-2*H*-pyran-4-yl]carbonyl}prolinate* (**7**). According to *GP 1*, PhCOOH (29 mg, 0.231 mmol) and **1e** (50 mg, 0.210 mmol), stirring for 14 h: 21 mg (28%) of **7**. Colorless solid. M.p. 198–200°. IR: 3349*m*, 2958*m*, 2856*m*, 1748*s*, 1639*m*, 1617v*s*, 1579*m*, 1527*m*, 1489*m*, 1419*m*, 1360*m*, 1299*m*, 1252*m*, 1206*s*, 1163*s*, 1108*m*, 1081*m*, 940*w*, 848*m*, 806*m*, 779*w*, 720*m*, 666*w*. ^{1}H-NMR (300 MHz): 7.81–7.78 (*m*, 2 arom. H); 7.57–7.46 (*m*, 3 arom. H); 6.43 (br. *s*, NH); 4.64 (br. *s*, CH(α)(Pro)); 4.14–3.31 (*m*, 6 H); 3.72 (*s*, MeO); 2.71–2.64 (*m*, 1 H); 2.30–2.23 (*m*, 1 H); 2.12–1.76 (*m*, 6 H). ^{13}C-NMR (75.5 MHz): 173.1, 170.1 (2*s*, 2 C=O); 165.8 (*s*, Ph*C*=O); 133.5 (*s*, 1 arom. C); 132.0, 128.8, 126.8 (3*d*, 5 arom. CH); 64.5, 62.9 (2*t*, C(2), C(6)(Thp)); 60.6 (*d*, C(α)(Pro)); 56.9 (*s*, C(4)(Thp)); 52.0 (*q*, MeO); 47.6, 33.0, 32.8, 27.5, 25.7 (5*t*, 5 CH_2). ESI-MS: 399 (100, $[M+K]^+$). Anal. calc. for $C_{19}H_{24}N_2O_5 \cdot H_2O$ (360.41): C 60.30, H 6.39, N 7.40; found: C 60.20, H 6.80, N 7.26.

Suitable crystals for the X-ray crystal-structure determination were grown from DMSO.

3.4. *Methyl (*S*)-*N*-({4-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino}-1-oxopropyl)amino]tetrahydro-2*H*-pyran-4-yl}carbonyl)prolinate* (Z-Ala-Thp-Pro-OMe, **8a**). According to *GP 1*, Z-Ala (66 mg, 0.294 mmol) and **1e** (70 mg, 0.294 mmol), stirring for 6 h: 121 mg (89%) of **8a**. White foam. IR: 3341*m*, 3303*m*, 3063*m*, 2957*m*, 2878*m*, 2848*m*, 1719v*s*, 1685*s*, 1605*s*, 1541*s*, 1428*m*, 1394*m*, 1361*m*, 1298*m*, 1253*m*, 1218*m*, 1163*m*, 1143*m*, 1109*m*, 1026*m*, 988*w*, 840*w*, 782*w*, 738*m*, 697*m*. ^{1}H-NMR (300 MHz): 7.36–7.31 (*m*, 5 arom. H); 6.92 (br. *s*, NH(Thp)); 5.57 (*d*, $J=7.0$, NH(Ala)); 5.13, 5.06 (*AB*, $J=12.1$, PhCH_2); 4.55–4.51 (*m*, CH(α)(Pro)); 4.28–4.24 (*m*, CH(α)(Ala)); 3.91–3.45 (*m*, CH_2(2), CH_2(6)(Thp), CH_2(δ)(Pro)); 3.69 (*s*, MeO); 2.46–2.42 (*m*, 1 H of CH_2(3) or CH_2(5)(Thp)); 2.10–1.74 (*m*, 3 H of CH_2(3) and CH_2(5)(Thp), CH(β)(Val), CH_2(β)(Pro), CH_2(γ)(Pro)); 1.38 (*d*, $J=7.1$, Me(Ala)). ^{13}C-NMR (75.5 MHz): 173.0 (*s*, MeO*C*=O); 171.0, 169.9 (2*s*, 2 C=O); 156.3 (*s*, PhCH_2O*C*=O); 136.0 (*s*, 1 arom. C); 128.5, 128.3, 128.0 (3*d*, 5 arom. CH); 67.1 (*t*, Ph*C*H_2); 64.1, 62.7 (2*t*, CH_2(2), CH_2(6)(Thp)); 60.5 (*d*, CH(α)(Pro)); 56.5 (*s*, C(4)(Thp)); 51.9 (*q*, MeO); 50.4 (*d*, CH(α)(Ala)); 47.3 (*t*, CH_2(δ)(Pro)); 32.5, 32.2 (2*t*, CH_2(3), CH_2(5)(Thp)); 27.6 (*t*, CH_2(β)(Pro)); 25.7 (*t*, CH_2(γ)(Pro)); 17.8 (*q*, Me(Ala)). ESI-MS: 484 ($[M+Na]^+$). Anal. calc. for $C_{23}H_{31}N_3O_7 \cdot H_2O$ (461.52): C 57.61, H 6.52, N 8.76; found: C 57.27, H 6.60, N 8.62.

3.5. *Methyl (*S*)-*N*-({4-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-methyl-1-oxobutyl)amino]tetrahydro-2*H*-pyran-4-yl}carbonyl)prolinate* (Z-Val-Thp-Pro-OMe, **8b**). According to *GP 1*, Z-Val (1.340 g, 5.33 mmol), **1e** (1.155 g, 4.85 mmol), 100 ml of dry CH_2Cl_2, stirring for 16 h, purification by recrystallization from Et_2O: 1.686 g (71%). Pale yellow crystals. M.p. 189–192°. IR: 3416*m*, 3284*s*, 3034*m*, 2961*m*, 2876*m*, 2843*m*, 1751*s*, 1716*s*, 1673*s*, 1619v*s*, 1542*m*, 1504*m*, 1420*m*, 1359*m*, 1285*m*, 1219*s*, 1110*m*, 1024*m*, 984*w*, 920*w*, 825*w*, 775*m*, 699*m*, 670*m*. ^{1}H-NMR (600 MHz, 2D): 7.37–7.30 (*m*, 5 arom. H); 6.55 (br. *s*, NH(Thp)); 5.49 (br. *d*, $J=8.9$, NH(Val)); 5.12, 5.06 (*AB*, $J=12.1$, PhCH_2); 4.55–4.51 (*m*, CH(α)(Pro)); 3.99–3.97 (*m*, CH(α)(Val)); 3.96–3.90, 3.78–3.61 (2*m*, CH_2(2), CH_2(6)(Thp)); 3.71 (*s*, MeO); 3.59–3.50, 3.46–3.41 (2*m*, CH_2(δ)(Pro)); 2.53 (br. *s*, 1 H of CH_2(3) or CH_2(5)(Thp)); 2.15–2.10 (*m*, 1 H of CH_2(3) or CH_2(5)(Thp)); 2.13–2.08 (*m*, CH(β)(Val)); 2.05–1.97 (*m*, 1 H of CH_2(β)(Pro)); 1.93–1.82 (*m*, 2 H of CH_2(3) and CH_2(5)(Thp)); 1.88–1.83 (*m*, 1 H of CH_2(γ)(Pro)); 1.81–1.76 (*m*, 1 H of CH_2(β)(Pro)); 1.70–1.64 (*m*, 1 H of CH_2(γ)(Pro)); 1.09–1.06 (2*d*, $J=6.8$, 2 Me). ^{13}C-NMR (150.9 MHz): 173.0 (*s*, MeO*C*=O); 170.2, 169.7 (2*s*, 2 C=O); 156.5 (*s*, PhCH_2O*C*=O); 136.0 (*s*, 1 arom. C); 128.5, 128.2, 127.8 (3*d*, 5 arom. CH); 67.0 (*t*, Ph*C*H_2); 64.4, 62.8 (2*t*, CH_2(2), CH_2(6)(Thp)); 60.4 (*d*, CH(α)(Val), CH(α)(Pro)); 56.7 (*s*, C(4)(Thp)); 51.9 (*q*, MeO); 47.3 (*t*, CH_2(δ)(Pro)); 32.7, 32.5 (2*t*, CH_2(3), CH_2(5)(Thp)); 30.6 (*d*, CH(β)(Val)); 27.6 (*t*, CH_2(β)(Pro)); 25.7 (*t*, CH_2(γ)(Pro)); 19.3, 18.0 (2*q*, 2 Me(Val)). ESI-MS: 512 (100, $[M+Na]^+$).

3.6. *Methyl (*S*)-*N*-({4-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino}-4-methyl-1-oxopentyl)amino]tetrahydro-2*H*-pyran-4-yl}carbonyl)prolinate* (Z-Leu-Thp-Pro-OMe, **8c**). According to *GP 1*, Z-Leu (0.91 g, 6.3 mmol), **1e** (1.50 g, 6.9 mmol), 100 ml of dry CH_2Cl_2, stirring for 14 h: 2.31 g (73%) of **8c**. White foam. IR: 3313*m*, 3035*m*, 2957*m*, 2871*m*, 2399*w*, 1745*s*, 1693*s*, 1664*s*, 1621*s*, 1536*s*, 1442*m*, 1409*m*, 1366*m*, 1244*m*, 1214*m*, 1162*m*, 1109*m*, 1043*m*, 843*m*, 781*m*, 740*m*, 698*m*, 613*m*. ^{1}H-NMR (300 MHz): 7.39–7.29 (*m*, 5 arom. H); 6.74, 5.38 (2 br., *s*, 2 NH); 5.13, 5.07 (*AB*, $J=12.4$, PhCH_2); 4.55–4.41 (*m*, CH(α)(Pro)); 4.21–4.13 (*m*, CH(α)(Leu)); 3.94–3.41 (*m*, CH_2(2), CH_2(6)(Thp), CH_2(δ)(Pro)); 3.70 (*s*, MeO); 2.49–1.46 (*m*, CH_2(3), CH_2(5)(Thp), CH_2(δ)(Pro), CH_2(γ)(Pro), CH_2(β)(Leu), CH(γ)(Leu)); 0.94 (*t*, $J=6.1$, 2 Me(Leu)). ^{13}C-NMR (75.5 MHz): 173.1 (*s*, MeO*C*=O); 170.8, 169.8 (2*s*, 2 C=O); 156.5 (*s*, PhCH_2O*C*=O); 135.9 (*s*, 1 arom. C); 128.5, 128.3, 128.0 (3*d*, 5 arom. CH); 67.2 (*t*, Ph*C*H_2); 64.2, 62.7 (2*t*, CH_2(2), CH_2(6)(Thp)); 60.4 (*d*, CH(α)(Pro)); 56.5 (*s*, C(4)(Thp)); 53.4 (*d*, CH(α)(Leu)); 51.9 (*q*, MeO); 47.3 (*t*, CH_2(δ)(Pro)); 40.4 (*t*, CH_2(β)(Leu)); 32.5

(*t*, CH_2(3), CH_2(5)(Thp)); 27.6 (*t*, CH_2(β)(Pro)); 25.7 (*t*, CH_2(γ)(Pro)); 24.6 (*d*, CH(γ)(Leu)); 22.7, 21.9 (2*q*, 2 Me(Leu)). ESI-MS: 526 (100, $[M+Na]^+$).

4. *Synthesis of the Nonapeptide Z-Ser(*^{t}*Bu)-Val-Thp-Pro-Aib-Leu-Thp-Pro-Leuol* (**16**). 4.1. *General Procedures. General Procedure 2* (*GP 2*). To a soln. of the Z-protected peptide methyl ester in THF/MeOH/H_2O 3:1:1 was added LiOH·H_2O (4 mol-equiv.), and the mixture was stirred at r.t. After completion of the reaction (TLC), 1M HCl was added until pH 1 was reached, and the org. solvent was evaporated. The residue was extracted with CH_2Cl_2, the org. phases were dried ($MgSO_4$), evaporated, and the residue was dried under h.v.

General Procedure 3 (*GP 3*). To a soln. of 1.1 mol-equiv. of the Z-protected amino or peptide acid in MeCN were added Et_3N (3 equiv.), 1-hydroxy-1*H*-benzotriazole (HOBt, 1 equiv.), and *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU, 1 equiv.). A soln. of the amino component (1 equiv.) in MeCN was added dropwise, and the mixture was stirred at r.t. After completion of the reaction (TLC), the solvent was evaporated, the residue dissolved in CH_2Cl_2, the soln. was washed with 1M HCl, sat. $NaHCO_3$, and NaCl soln., dried ($MgSO_4$), evaporated, and purified by CC (SiO_2).

General Procedure 4 (*GP 4*). The Z-protected peptide was dissolved in MeOH, Pd/C (10%) was added as a catalyst, and the mixture was stirred under H_2. The suspension was filtered through *Celite*, the filtrate was evaporated, and the residue was dried under h.v.

4.2. *(*S*)-*N*-({4-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-methyl-1-oxobutyl)amino]tetrahydro-2*H*-pyran-4-yl}carbonyl)proline* (Z-Val-Thp-Pro-OH, **9b**). According to *GP 2*, **8b** (1.500 g, 3.06 mmol), LiOH·H_2O (12.26 mmol), 1 h. After acidification and addition of CH_2Cl_2, **9b** precipitated. The solid was filtered, washed with cold H_2O, and dried at 60° under h.v.: 1.361 (93%) of **9b**. Colorless solid. M.p. 131–133°. IR: 3455*m*, 2954*m*, 2848*m*, 2349*w*, 1773*s*, 1743*s*, 1688*m*, 1658*m*, 1565*m*, 1535*w*, 1437*m*, 1349*m*, 1298*m*, 1235*m*, 1172*m*, 1071*m*, 1029*m*, 967*m*, 917*w*, 890*w*, 811*m*. ESI-MS: 498 (100, $[M+Na]^+$).

4.3. *2-({[(2*S*)-1-({4-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-methyl-1-oxobutyl)amino]tetrahydro-2*H*-pyran-4-yl}carbonyl)pyrrolidin-2-yl]carbonyl}amino)-2,*N*-dimethyl-*N*-phenylpropanamide* (Z-Val-Thp-Pro-Aib-N(Me)Ph, **10**). According to *GP 1*, **9b** (889 mg, 1.87 mmol), *2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine* (**1a**; 358 mg, 2.06 mmol), stirring for 24 h: 1.686 g (71%) of **10**. Colorless foam. M.p. 81–82°. ^{1}H-NMR (600 MHz, 2D): 7.48–7.30 (*m*, 10 arom. H, 2 NH); 5.81 (br. *s*, NH(Val)); 5.14, 5.08 (*AB*, *J* = 12.1, PhCH_2); 4.52–4.46 (*m*, CH(α)(Pro)); 3.95–3.89 (*m*, CH(α)(Val)); 3.79–3.73 (*m*, 3 H of CH_2(2), CH_2(6)(Thp)); 3.59–3.50, 3.46–3.39 (2*m*, CH_2(δ)(Pro)); 3.44–3.37 (*m*, 1 H of CH_2(2) or CH_2(6)(Thp)); 3.34 (*s*, MeN); 2.40–2.33 (*m*, 1 H of CH_2(3) or CH_2(5)(Thp)); 2.05–2.02 (*m*, CH(β)(Val)); 2.00–1.94 (*m*, 1 H of CH_2(3) or CH_2(5)(Thp)); 1.90–1.84 (*m*, CH_2(β)(Pro)); 1.81–1.68 (*m*, 2 H of CH_2(3), CH_2(5)(Thp)); 1.76–1.64 (*m*, CH_2(γ)(Pro)); 1.53, 1.49 (2*s*, 2 Me(Aib)); 1.02–0.90 (*m*, 2 Me(Val)). ^{13}C-NMR (150.9 MHz): 173.7, 171.2, 170.8, 169.8 (4*s*, 4 C=O); 156.6 (*s*, PhCH_2OC=O); 145.6, 136.0 (2*s*, 2 arom. C); 128.9, 128.5, 128.3, 128.0, 127.2, 126.8 (6*d*, 10 arom. CH); 67.2 (*t*, PhCH_2); 63.7, 62.7 (2*t*, CH_2(2), CH_2(6)(Thp)); 61.9 (*d*, CH(α)(Pro)); 61.0 (*d*, CH(α)(Val)); 57.1 (*s*, C(α)(Aib)); 56.8 (*s*, C(4)(Thp)); 47.7 (*t*, CH_2(δ)(Pro)); 40.3 (*q*, MeN); 31.9 (*t*, CH_2(3), CH_2(5)(Thp)); 29.6 (*d*, CH(β)(Val)); 27.8, 26.3 (2*q*, 2 Me(Aib)); 27.6 (*t*, CH_2(β)(Pro)); 25.6 (*t*, CH_2(γ)(Pro)); 19.6, 18.2 (2*q*, 2 Me(Val)). ESI-MS: 672 (100, $[M+Na]^+$). Anal. calc. for $C_{35}H_{47}N_5O_7$ (649.79): C 64.70, H 7.29, N 10.78; found: C 64.33, H 7.50, N 10.78.

4.4. *2-({[(2*S*)-1-({4-[((2*S*)-2-Amino-3-methyl-1-oxobutyl)amino]tetrahydro-2*H*-pyran-4-yl}carbonyl)pyrrolidin-2-yl]carbonyl}amino)-2,*N*-dimethyl-*N*-phenylpropanamide* (H-Val-Thp-Pro-Aib-N(Me)Ph, **11**). According to *GP 4*, **10** (700 mg, 1.079 mmol), MeOH (25 ml), Pd/C (175 mg): 521 mg (94%) of **11**. Colorless foam. M.p. 138–144°. ^{1}H-NMR (300 MHz): 8.33, 7.54 (2 br. *s*, 2 NH); 7.41–7.20 (*m*, 5 arom. H); 4.60–4.56 (*m*, CH(α)(Pro)); 3.91–3.87 (*m*, CH(α)(Val)); 3.83–3.69 (*m*, 3 H of CH_2(2), CH_2(6)(Thp)); 3.65–3.53 (*m*, CH_2(δ)(Pro)); 3.50–3.43 (*m*, 1 H of CH_2(2) or CH_2(6)(Thp)); 3.35 (*s*, MeN); 3.27 (*m*, NH_2); 2.55–2.46 (*m*, 1 H of CH_2(3) or CH_2(5)(Thp)); 2.36–2.31 (*m*, CH(β)(Val)); 2.13–1.65 (*m*, 3 H of CH_2(3), CH_2(5)(Thp), CH_2(β)(Pro), CH_2(γ)(Pro)); 1.49 (br. *s*, 2 Me(Aib)); 1.00, 0.82 (2*d*, *J* = 6.9, 2 Me(Val)). ^{13}C-NMR (75.5 MHz): 173.7, 173.6, 170.8, 170.7 (4*s*, 4 C=O); 145.8 (*s*, 1 arom. C); 128.6, 127.3, 126.6 (3*d*, 5 arom. CH); 63.9, 62.5 (2*t*, CH_2(2), CH_2(6)(Thp)); 62.1 (*d*, CH(α)(Pro)); 59.5 (*d*, CH(α)(Val)); 57.2 (*s*, C(α)(Aib)); 56.1 (*s*, C(4)(Thp)); 47.6 (*t*, CH_2(δ)(Pro)); 40.2 (*q*, MeN); 32.2, 32.0 (2*t*, CH_2(3), CH_2(5)(Thp)); 30.6 (*d*, CH(β)(Val)); 27.8 (*t*, CH_2(β)(Pro)); 26.7, 25.7 (2*q*, 2 Me(Aib)); 25.6 (*t*, CH_2(γ)(Pro)); 19.5, 15.9 (2*q*, 2 Me(Val)). ESI-MS: 538 (100, $[M+Na]^+$). Anal. calc. for $C_{27}H_{41}N_5O_5$·H_2O (515.66): C 60.77, H 7.74, N 13.12; found: C 61.09, H 8.06, N 13.01.

4.5. *2-{[((2*S*)-1-{[4-({(2*S*)-2-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-(*tert*-butoxy)-1-oxopropyl)amino]-3-methyl-1-oxobutyl}amino)tetrahydro-2*H*-pyran-4-yl]carbonyl}pyrrolidin-2-yl)carbonyl]amino}-2,*N*-dimethyl-*N*-phenylpropanamide* (Z-Ser(*^{t}*Bu)-Val-Thp-Pro-Aib-N(Me)Ph, **12**). According to *GP 2*, **11** (350 mg,

0.679 mmol), Z-Ser(ᵗBu)-OH (221 mg, 0.747 mmol), Et_3N (0.35 ml, 2.45 mmol), HOBt (92 mg, 0.679 mmol), HATU (259 mg, 0.679 mmol), MeCN (4 ml); CC (CH_2Cl_2/MeOH 9:1): 396 mg (82%) of **12**. Pale yellow oil. ^{1}H-NMR (600 MHz, 2D): 7.66 (br. *s*, NH); 7.38–7.19 (*m*, 10 arom. H); 6.86, 5.76, 5.65 (3 br. *s*, 3 NH); 5.15, 5.06 (*AB*, J = 12.2, PhCH_2); 4.51–4.47 (*m*, CH(α)(Pro)); 4.29–4.25 (*m*, CH(α)(Ser)); 4.21–4.14 (*m*, CH_2(β)(Ser)); 3.85–3.80 (*m*, CH(α)(Val)); 3.80–3.68 (*m*, CH_2(2), CH_2(6)(Thp)); 3.65 (*s*, MeN); 3.52–3.40 (*m*, CH_2(δ)(Pro)); 2.49–2.44 (*m*, 1 H of CH_2(3) or CH_2(5)(Thp)); 2.49–2.46 (*m*, CH(β)(Val)); 2.02–1.80 (*m*, 3 H of CH_2(3), CH_2(5)(Thp)); 1.90–1.75 (*m*, CH_2(β)(Pro)); 1.71–1.67 (*m*, CH_2(γ)(Pro)); 1.49, 1.45 (2*s*, 2 Me(Aib)); 1.19 (*s*, $(Me)_3$C); 0.97, 0.90 (2*d*, J = 6.6, 2 Me(Val)). ^{13}C-NMR (150.9 MHz): 173.7, 171.3, 171.0, 170.6, 170.4 (5*s*, 5 C=O); 156.8 (*s*, PhCH_2OC=O); 145.8, 135.8 (2*s*, 2 arom. C); 128.9, 128.6, 128.4, 127.7, 127.2, 126.7 (6*d*, 10 arom. CH); 74.1 (*s*, $(Me)_3C$); 67.2 (*t*, PhCH_2); 63.8, 62.7 (2*t*, CH_2(2), CH_2(6)(Thp)); 62.0 (*d*, CH(α)(Pro)); 61.1 (*d*, CH(α)(Val)); 58.6 (*d*, CH(α)(Ser)); 57.1 (*s*, C(α)(Aib)); 56.9 (*s*, C(4)(Thp)); 56.0 (*t*, CH_2(β)(Ser)); 47.8 (*t*, CH_2(δ)(Pro)); 40.2 (*q*, MeN); 31.7 (*t*, CH_2(3), CH_2(5)(Thp)); 29.3 (*d*, CH(β)(Val)); 27.8 (*t*, CH_2(β)(Pro)); 27.3 (*q*, *Me*$_3$C); 26.5 (*q*, 2 Me(Aib)); 25.7 (*t*, CH_2(γ)(Pro)); 17.4, 17.2 (2*q*, 2 Me(Val)). ESI-MS: 815 (100, $[M+Na]^+$). Anal. calc. for $C_{42}H_{60}N_6O_9 \cdot H_2O$ (792.98): C 62.20, H 7.46, N 10.36; found: C 61.91, H 7.60, N 10.24.

4.6. *2-{[((2*S*)-1-{[4-(({(2*S*)-2-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-(*tert*-butoxy)-1-oxopropyl)amino]-3-methyl-1-oxobutyl}amino)tetrahydro-2*H*-pyran-4-yl]carbonyl}pyrrolidin-2-yl)carbonyl]amino}propanoic Acid* (Z-Ser(ᵗBu)-Val-Thp-Pro-Aib-OH, **13**). To a soln. of **12** (140 mg, 0.176 mmol) in THF (1 ml) at 0°, 6M aq. HCl (1 ml) was added, and the mixture was stirred at r.t. for 1 h. Then, 4M HCl (1 ml) was added, and the mixture was extracted with CH_2Cl_2. The org. layer was dried ($MgSO_4$) and filtered, the solvent was evaporated, and the residue was dried under h.v.: 101 mg (81%) **13**. White foam. ^{1}H-NMR (300 MHz): 7.55 (br. *s*, NH); 7.29–7.19 (*m*, 5 arom. H, NH); 5.74, 5.64 (2 br. *s*, 2 NH); 5.22–5.06 (*m*, PhCH_2); 4.45 (br. *s*, CH(α)(Pro)); 4.23–4.13 (*m*, CH(α)(Ser), CH_2(β)(Ser)); 3.84–3.49 (*m*, CH(α)(Val), CH_2(2), CH_2(6)(Thp), CH_2(δ)(Pro)); 2.45–2.32 (*m*, 1 H of CH_2(3) or CH_2(5)(Thp), CH(β)(Val)); 2.08–1.63 (*m*, 3 H of CH_2(3), CH_2(5)(Thp), CH_2(β)(Pro), CH_2(γ)(Pro)); 1.48 (br. *s*, 2 Me(Aib)); 1.13 (*s*, *Me*$_3$C); 1.01–0.73 (*m*, 2 Me(Val)). ESI-MS: 726 (100, $[M+Na]^+$).

4.7. *(*S*)-N-({4-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino}-4-methyl-1-oxopentyl)amino]tetrahydro-2*H*-pyran-4-yl}carbonyl)prolinate* (Z-Leu-Thp-Pro-OH, **9c**). According to *GP 2*, **8c** (1.000 g, 1.98 mmol), LiOH · H_2O (334 mg, 7.94 mmol), 1 h: 747 mg (77%) of **9c**. White foam. M.p. 90–93°. ^{1}H-NMR (300 MHz): 7.58 (br. *s*, NH); 7.36–7.29 (*m*, 5 arom. H); 6.07 (br. *s*, NH); 5.14–5.02 (*m*, PhCH_2); 4.52–4.48 (*m*, CH(α)(Pro)); 4.28–4.26 (*m*, CH(α)(Leu)); 3.90–3.44 (*m*, CH_2(2), CH_2(6)(Thp), CH_2(δ)(Pro)); 2.25–1.54 (*m*, CH_2(3), CH_2(5)(Thp), CH_2(β)(Pro), CH_2(γ)(Pro), CH_2(β)(Leu), CH(γ)(Leu)); 0.98–0.86 (*m*, 2 Me(Leu)). ^{13}C-NMR (75.5 MHz): 174.4, 172.3, 161.3 (3*s*, 3 C=O); 156.7 (*s*, PhCH_2OC=O); 136.0 (*s*, 1 arom. C); 128.4, 128.2, 127.9 (3*d*, 5 arom. CH); 67.1 (*t*, PhCH_2); 63.5, 63.1 (2*t*, CH_2(2), CH_2(6)(Thp)); 61.2 (*d*, CH(α)(Pro)); 56.5 (*s*, C(4)(Thp)); 53.5 (*d*, CH(α)(Leu)); 47.8 (*t*, CH_2(δ)(Pro)); 40.4 (*t*, CH_2(β)(Leu)); 32.0, 31.7 (2*t*, CH_2(3), CH_2(5)(Thp)); 27.3, 25.7 (2*t*, CH_2(β)(Pro), CH_2(γ)(Pro)); 24.6 (*d*, CH(γ)(Leu)); 22.7, 21.8 (2*q*, 2 Me(Leu)). ESI-MS: 512 (100, $[M+Na]^+$). Anal. calc. for $C_{25}H_{35}N_3O_7 \cdot 1/2H_2O$ (489.57): C 60.22, H 7.08, N 8.43; found: C 60.00, H 7.40, N 8.16.

4.8. *(*S*)-N-({4-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino}-4-methyl-1-oxopentyl)amino]tetrahydro-2*H*-pyran-4-yl}carbonyl)-N-[1-(hydroxymethyl)-3-methylbutyl]prolinamide* (Z-Leu-Thp-Pro-Leuol, **14**). According to *GP 3*, **9c** (400 mg, 0.817 mmol), L-Leucinol (106 mg, 0.899 mmol), Et_3N (0.35 ml, 2.45 mmol), HOBt (114 mg, 0.817 mmol), HATU (314 mg, 0.817 ml), MeCN (4 ml); CC (CH_2Cl_2/MeOH 9:1): 391 mg (81%) of **14**. Pale yellow oil. ^{1}H-NMR (600 MHz, 2D): 7.56 (br. *s*, NH(Leuol)); 7.48–7.28 (*m*, 5 arom. H); 6.99 (*d*, J = 9.3, NH(Leu)); 6.45 (br. *s*, NH(Thp)); 5.12, 5.06 (*AB*, J = 12.3, PhCH_2)); 4.32–4.29 (*m*, CH(α)(Pro)); 4.15–4.10 (*m*, CH(α)(Leu)); 4.14–4.08 (*m*, CH(α)(Leuol)); 3.84–3.79 (*m*, 1 H of CH_2(2) or CH_2(6)(Thp)); 3.77–3.67 (*m*, 2 H of CH_2(2) or CH_2(6)(Thp)); 3.55–3.45 (*m*, CH_2OH); 3.53–3.47 (*m*, 1 H of CH_2(2) or CH_2(6)(Thp)); 3.51–3.45, 3.40–3.34 (2*m*, CH_2(δ)(Pro)); 2.46–2.40 (*m*, 1 H of CH_2(3) or CH_2(5)(Thp)); 2.27–2.22 (*m*, CH(β)(Pro)); 1.90–1.76 (*m*, 3 H of CH_2(3), CH_2(5)(Thp)); 1.87–1.81 (*m*, 1 H of CH_2(γ)(Pro)); 1.72–1.67 (*m*, CH(γ)(Leuol)); 1.71–1.65 (*m*, 1 H of CH_2(γ)(Pro)); 1.65–1.58 (*m*, CH_2(β)(Leu)); 1.56–1.42 (*m*, CH(γ)(Leu)); 1.42–1.35, 1.16–1.10 (2*m*, CH_2(β)(Leuol)); 1.01–0.85 (*m*, 2 Me(Leu), 2 Me(Leuol)). ^{13}C-NMR (150.9 MHz): 173.2, 172.5, 171.9 (3*s*, 3 C=O); 156.6 (*s*, PhCH_2OC=O); 136.4 (*s*, 1 arom. C); 128.4, 128.1, 127.9 (3*d*, 5 arom. CH); 67.0 (*t*, PhCH_2); 65.4 (*t*, CH_2OH); 64.1, 62.3 (2*t*, CH_2(2), CH_2(6)(Thp)); 63.8 (*d*, CH(α)(Pro)); 56.7 (*s*, C(4)(Thp)); 54.1 (*d*, CH(α)(Leu)); 49.9 (*d*, CH(α)(Leuol)); 48.4 (*t*, CH_2(δ)(Pro)); 39.7 (*t*, CH_2(β)(Leu)); 39.2 (*t*, CH_2(β)(Leuol)); 31.9, 31.5 (2*t*, CH_2(3), CH_2(5)(Thp)); 28.8 (*t*, CH_2(β)(Pro)); 26.0 (*t*, CH_2(γ)(Pro)); 24.9 (*d*, CH(γ)(Leu)); 24.79 (*d*, CH(γ)(Leuol)); 23.1, 22.6 (2*q*, 2 Me(Leu)); 22.1, 21.7 (2*q*, 2 Me(Leuol)).

4.9. *(*S*)-*N*-({4-[((2*S*)-2-Amino-4-methyl-1-oxopentyl)amino]tetrahydro-2*H*-pyran-4-yl}carbonyl)-*N*-[1-(hydroxymethyl)-3-methylbutyl]prolinamide* (H-Leu-Thp-Pro-Leuol, **15**). According to *GP 4*, **14** (300 mg, 0.509 mmol), MeOH (15 ml), Pd/C (50 mg): 216 mg (95%) of **15**. White foam. ^{1}H-NMR (300 MHz): 8.41 (br. *s*, NH(Thp)); 7.12 (*d*, *J* = 9.1, NH(Leuol)); 4.39 – 4.34 (*m*, CH(α)(Pro)); 4.06 – 3.95 (*m*, CH(α)(Leu)); 3.84 – 3.21 (*m*, CH(α)(Leuol), CH_2(2), CH_2(6)(Thp), CH_2OH, CH_2(δ)(Pro)); 2.68 (br. *s*, NH_2); 2.47 – 2.38 (*m*, 1 H of CH_2(3) or CH_2(5)(Thp)); 2.28 – 2.22 (*m*, CH_2(β)(Pro)); 1.93 – 1.12 (*m*, 3 H of CH_2(3), CH_2(5)(Thp), CH_2(γ)(Pro), CH_2(β)(Leuol), CH(γ)(Leuol), CH_2(β)(Leu), CH(γ)(Leu)); 0.92 – 0.80 (*m*, 2 Me(Leu), 2 Me(Leuol)). ^{13}C-NMR (75.5 MHz): 175.4, 172.4, 171.8 (3*s*, 3 C=O); 65.4 (*t*, CH_2OH); 63.9, 62.3 (2*t*, CH_2(2), CH_2(6)(Thp)); 63.7 (*d*, CH(α)(Pro)); 56.2 (*s*, C(4)(Thp)); 52.9 (*d*, CH(α)(Leu)); 49.9 (*d*, CH(α)(Leuol)); 48.4 (*t*, CH_2(δ)(Pro)); 43.7 (*t*, CH_2(β)(Leu)); 39.1 (*t*, CH_2(β)(Leuol)); 31.8 (*t*, CH_2(3), CH_2(5)(Thp)); 28.8 (*d*, CH_2(β)(Pro)); 25.9 (*t*, CH_2(γ)(Pro)); 24.9, 24.7 (2*d*, CH(γ)(Leu), CH_2(γ)(Leuol)); 23.2, 23.1, 22.1, 21.3 (4*q*, 2 Me(Leu), 2 Me(Leuol)). ESI-MS: 455 (100, $[M+1]^+$).

4.10. *Z-Ser*(*t*-*Bu*)-*Val-Thp-Pro-Aib-Leu-Thp-Pro-Leuol* (**16**). According to *GP 3*, **13** (78 mg, 0.110 mmol), **15** (50 mg, 0.110 mmol), Et_3N (0.05 ml, 0.330 mmol), HOBt (16 mg, 0.121 mmol), HATU (38 mg, 0.121 mmol), MeCN (2 ml); CC (AcOEt/MeOH 9 :1): 92 mg (73%) of **16**. Colorless foam. ^{1}H-NMR (500 MHz, 2D): 7.96 (br. *s*, NH(Aib)); 7.64 (br. *s*, NH(Thp)); 7.41 (*m*, NH(Val)); 7.38 – 7.29 (*m*, 5 arom. H); 7.08 – 7.02 (*m*, NH(Leuol)); 6.88 (*d*, *J* = 8.9, NH(Leu)); 5.98 (br. *s*, NH(Thp)); 5.76 (*d*, *J* = 3.9, NH(Ser)); 5.15, 5.04 (*AB*, *J* = 12.4, PhCH_2); 4.44 (*t*, *J* = 7.5, CH(α)(Pro1)); 4.41 – 4.32 (*m*, CH(α)(Leu)); 4.38 – 4.30 (*m*, CH(α)-(Val)); 4.33 – 4.27 (*m*, CH(α)(Ser)); 4.26 – 4.15 (*m*, CH(α)(Pro2)); 4.12 – 4.03 (*m*, CH(α)(Leuol)); 4.11 – 4.01 (*m*, 1 H of CH_2(2) or CH_2(6)(Thp)); 3.94 – 3.86 (*m*, 1 H of CH_2(δ)(Pro2)); 3.93 – 3.67 (*m*, 3 H of CH_2(2), CH_2(6)(Thp)); 3.84 – 3.79 (*m*, 1 H of CH_2(β)(Ser)); 3.78 – 3.67 (*m*, 1 H of CH_2OH); 3.72 – 3.59 (*m*, CH_2(δ)(Pro1)); 3.67 – 3.63 (*m*, 1 H of CH_2(β)(Ser)); 3.63 – 3.54 (*m*, 2 H of CH_2(2) or CH_2(6)(Thp)); 3.58 – 3.49 (*m*, 1 H of CH_2OH); 3.55 – 3.46 (*m*, 1 H of CH_2(δ)(Pro2)); 2.61 – 2.46 (*m*, 3 H of CH_2(3), CH_2(5)(Thp)); 2.40 – 2.33 (*m*, CH(β)(Val)); 2.35 – 2.22 (*m*, 1 H of CH_2(β)(Pro2)); 2.34 – 2.23 (*m*, 1 H of CH_2(β)(Pro1)); 2.18 – 2.10 (*m*, 1 H of CH_2(3) or CH_2(5)(Thp)); 2.05 – 1.79 (*m*, 3 H of CH_2(3), CH_2(5)(Thp)); 2.03 – 1.94 (*m*, 1 H of CH_2(γ)(Pro2)); 1.89 – 1.80 (*m*, 1 H of CH_2(γ)(Pro1)); 1.84 – 1.75 (*m*, 1 H of CH_2(β)(Pro1)); 1.80 – 1.69 (*m*, 1 H of CH_2(γ)(Pro2)); 1.78 – 1.67 (*m*, 1 H of CH_2(γ)(Pro1)); 1.78 – 1.62 (*m*, CH_2(β)(Leu)); 1.76 – 1.62 (*m*, 1 H of CH_2(β)(Pro2)); 1.73 – 1.65 (*m*, CH(γ)(Leu)); 1.66 – 1.59 (*m*, 1 H of CH_2(3) or CH_2(5)(Thp)); 1.66 – 1.57 (*m*, CH(γ)(Leuol)); 1.60 – 1.49 (*m*, 1 H of CH_2(β)(Leuol)); 1.47, 1.53 (2*s*, 2 Me(Aib)); 1.29 – 1.20 (*m*, 1 H of CH_2(β)(Leuol)); 1.20, 1.19 (2*s*, *Me*$_3$C, 2 conformers); 1.05 – 0.95 (*m*, 2 Me(Leu)); 0.98 – 0.93, 0.89 – 0.83 (2*m*, 2 Me(Val)); 0.92 – 0.85 (*m*, 2 Me(Leuol)). ^{13}C-NMR (125.8 MHz, 2 conformers): 175.7, 175.6, 174.5, 174.4, 174.0, 173.9, 172.9, 172.6, 172.2, 171.9, 171.6 (11*s*, 8 C=O); 157.6, 157.0 (2*s*, PhCH_2O*C*=O); 136.4, 136.1 (2*s*, 1 arom.. C); 129.2, 129.1, 129.0, 128.7, 128.1, 127.8 (6*d*, 5 arom. CH); 74.9, 74.5 (2*s*, Me$_3$*C*); 67.9, 67.4 (2*t*, Ph*C*H_2); 65.1 (*d*, CH(α)(Pro2)); 64.9 (*t*, CH_2(δ)(Pro2)); 64.6, 64.3, 63.3, 63.1 (4*t*, 2 CH_2(2), 2 CH_2(6)(Thp)); 64.1 (*d*, CH(α)(Pro1)); 61.7 (*t*, CH_2(δ)(Pro1)); 61.4 (*d*, CH(β)(Ser)); 59.3 (*d*, CH(α)(Val)); 57.4 (*s*, C(α)(Aib)); 57.3, 57.2 (2*s*, 2 C(4)(Thp)); 56.6 (*d*, CH(α)(Ser)); 53.0, 52.9 (2*d*, 2 CH(α)(Leu)); 50.3 (*d*, CH(α)(Leuol)); 49.0 (*t*, CH_2OH); 40.8 (*t*, CH_2(β)(Leu)); 39.7 (*t*, CH_2(β)(Leuol)); 33.1, 32.2, 31.9, 31.7 (4*t*, 2 CH_2(3), CH_2(5)(Thp)); 29.8, 29.7 (2*d*, CH(β)(Val)); 29.5 (*t*, CH_2(β)(Pro1)); 29.1 (*t*, CH_2(β)(Pro2)); 27.8 (*q*, *Me*$_3$C); 27.6, 23.6 (2*q*, 2 Me(Aib)); 26.7 (*t*, CH_2(γ)(Pro1)); 26.5 (*t*, CH_2(γ)(Pro2)); 25.3 (*d*, CH(γ)(Leuol)); 25.2 (*d*, CH(γ)(Leu)); 23.4, 22.7 (2*q*, 2 Me(Leuol)); 21.0, 19.9 (2*q*, 2 Me(Leu)); 18.0, 17.9 (2*q*, 2 Me(Val)). ESI-MS: 1163 (100, $[M+Na]^+$).

5. *Synthesis of the Nonapeptide Z-Ser-Val-Thp-Pro-Aib-Leu-Thp-Pro-Leuol* (**16a**). 5.1. *2-{[((2*S*)-1-{[4-({(2*S*)-2-[((2*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-hydroxy-1-oxopropyl)amino]-3-methyl-1-oxobutyl}amino)tetrahydro-2*H*-pyran-4-yl]carbonyl}pyrrolidin-2-yl)carbonyl]amino}propanoic Acid* (Z-Ser-Val-Thp-Pro-Aib-OH, **13a**). To a soln. of **12** (195 mg, 0.301 mmol) in THF (1 ml) at 0° was added 6M aq. HCl (1 ml), and the mixture was stirred at r.t. for 48 h. Then, 4M aq. HCl (1 ml) was added, the mixture was extracted with CH_2Cl_2, the org. phase was dried ($MgSO_4$), evaporated, and the residue was dried under h.v.: 127 mg (80%) of **13a**. Colorless foam.

5.2. *Z-Ser-Val-Thp-Pro-Aib-Leu-Thp-Pro-Leuol* (**16a**). According to *GP 3*, **13a** (85 mg, 0.131 mmol), **15** (50 mg, 0.110 mmol), Et_3N (0.05 ml, 0.330 mmol), HOBt (16 mg, 0.121 mmol), HATU (38 mg, 0.121 mmol), MeCN (2 ml); CC (AcOEt/MeOH 9 :1): 85 mg (71%) of **16a**. White foam. ^{1}H-NMR (300 MHz): 8.17 – 7.39 (br. *s*, 4 NH); 7.37 – 7.12 (*m*, 5 arom. H, NH); 6.82 (br. *s*, NH); 5.80 (br. *s*, NH); 5.13, 5.02 (*AB*, *J* = 12.6, PhCH_2); 4.51 – 4.47 (*m*, CH(α)(Pro1)); 4.44 – 3.37 (*m*, CH(α)(Leu), CH(α)(Val), CH(α)(Ser), CH(α)(Pro2), CH(α)-(Leuol), 2 CH_2(2)(Thp), 2 CH_2(6)(Thp), CH_2(δ)(Pro2), CH_2(δ)(Ser), CH_2(δ)(Pro1), CH_2OH(Leuol), 3 H of CH_2(3), CH_2(5)(Thp)); 2.42 – 1.52 (*m*, CH(β)(Val), CH_2(β)(Pro1), CH_2(β)(Pro2), 5 H of CH_2(3), CH_2(5)(Thp), CH_2(γ)(Pro1), CH_2(γ)(Pro2), CH_2(β)(Leu), CH(γ)(Leu), CH(γ)(Leuol), 1 H of

$CH_2(\beta)$(Leuol)); 1.46, 1.42 (2*s*, 2 Me(Aib)); 1.19–1.09 (*m*, 1 H of $CH_2(\beta)$(Leuol)); 0.95, 0.93 (2*s*, 2 Me(Leu)); 0.89–0.77 (*m*, 2 Me(Val), 2 Me(Leuol)). ESI-MS: 1107 (100, $[M+Na]^+$).

6. *Crystal-Structure Determination of* **7** (see *Table* and *Figs. 1* and *2*)[5]. All measurements were made on a *Rigaku AFC5R* diffractometer using graphite-monochromated MoK_α radiation (λ 0.71069 Å) and a 12-kW rotating anode generator. The $\omega/2\theta$ scan mode was employed for data collection.

The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Data collection and refinement parameters are given in the *Table*, views of the molecule and the molecular packing are shown in *Figs. 1* and *2*. The structure was solved by direct methods using SIR92 [23], which revealed the positions of all non-H-atoms. The asymmetric unit contains one peptide and one H_2O molecule. The enantiomer used in the refinement was based on the known (*S*)-configuration of L-proline. The non-H-atoms were refined anisotropically. The H-atoms of the peptide molecule were fixed in geometrically calculated positions (d(C–H) = 0.95 Å), while those of H_2O were fixed in the positions indicated by a difference-electron-density map. Each H-atom was assigned a fixed isotropic-displacement parameter with a value equal to $1.2U_{eq}$ of the atom to which it was bonded. Refinement of the structure was carried out on *F* using full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o|-|F_c|)^2$. A correction for secondary extinction was applied. Neutral-atom-scattering factors for non-H-atoms were taken from [24a] and the scattering factors for H-atoms from [25]. Anomalous dispersion effects were included in F_c [26]; the values for f' and f'' were those of [24b], and the values of the mass attenuation coefficients were those of [24c]. All calculations were performed using the *teXsan* crystallographic software package [27].

Table. *Crystallographic Data of Compound* **7**

Crystallized from	DMSO
Empirical formula	$C_{19}H_{24}N_2O_5 \cdot H_2O$
Formula weight [g mol^{-1}]	378.42
Crystal color, habit	colorless, irregular prism
Crystal dimensions [mm]	$0.40 \times 0.45 \times 0.46$
Temp. [K]	173(1)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Z	4
Reflections for cell determination	25
2θ Range for cell determination [°]	37–40
Unit-cell parameters *a* [Å]	11.628(3)
b [Å]	18.466(4)
c [Å]	8.956(3)
V [Å^3]	1923.1(7)
D_x [g cm^{-3}]	1.307
μ(MoK_α) [mm^{-1}]	0.0974
$2\theta_{(max)}$ [°]	55
Total reflections measured	2996
Symmetry independent reflections	2879
Reflections used [$I > 2\sigma(I)$]	2282
Parameters refined	245
Final *R*	0.0433
wR ($w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$)	0.0399
Goodness of fit	1.958
Secondary extinction coefficient	$5(1) \times 10^{-7}$
Final Δ_{max}/σ	0.0001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.24; −0.29

[5]) Crystallographic data (excluding structure factors) for structure **7** reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-145100. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Received July 5, 2000