Novel N-(2,2-Dimethyl-2H-azirin-3-yl)-L-prolinates as Aib-Pro Synthons

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The syntheses of phenacyl N-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate and allyl N-(2,2-dimethyl-2*H*-azirin-3-yl)-L-prolinate are reported. Reactions of these 2*H*-azirin-3-amine derivatives with Z-protected amino acids have shown them to be suitable synthesis for the Aib-Pro unit in peptide synthesis. After incorporation into the peptide by means of the 'azirine/oxazolone method', the C-termini of the resulting peptides were deprotected selectively with Zn in AcOH or by a mild Pd⁰-promoted procedure, respectively.

1. Introduction. – Peptides that contain α, α -disubstituted α -amino acids are of interest because the rigidity of their backbones leads to a stabilization or even a promotion of secondary structures, such as β -turns or helices [1–4]. Moreover, a group of peptide antibiotics, the 'peptaibols', contain a high proportion of α, α -disubstituted α -amino acids, in particular α -aminoisobutyric acid (Aib) [5]. A valuable and convenient method for the introduction of these sterically demanding α, α -disubstituted α -amino acids is the 'azirine/oxazolone method' [6–8]. Thus, the reaction of 2*H*-azirin-3-amines **1**, which represent the amino acid synthons, with amino or peptide acids leads to peptide amides, the terminal amide bonds of which can be hydrolyzed selectively to give the extended peptide acids. This method has been applied successfully in the introduction of a variety of α, α -disubstituted α -amino acids into peptides, and it has found application in the synthesis of some peptaibols or segments thereof [9–18].



Recently, we adapted the 'azirine/oxazolone method' to solid-phase conditions, in order to additionally profit from their benefits [19]. Moreover, it was shown that,

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also on solid phase, the method is not limited to the Aib synthon **1a**, and it was extended successfully to the 1-aminocyclopentane-1-carboxylic acid, the 4-amino-3,4,5,6-tetrahydro-2*H*-pyran-4-carboxylic acid, and the α -methylphenylalanine synthons (see **1b**-**1d**) [20].

Since the Aib-Pro motif is widespread in peptaibols – in fact, 266 out of the 309 so far known peptaibol sequences contain the Aib-Pro unit [21] – it was of great interest to introduce this unit directly. In solution-phase chemistry, the introduction of the Aib-Pro unit was accomplished with the use of dipeptide synthon **2** [22]. Unexpectedly, its use on solid phase was not successful due to the incompatibility of the linker and the strong basic media, which is required for the saponification of the Aib-Pro motif on solid phase, a 2*H*-azirin-3-amine with an easily removable carboxy-protecting group was required.

Herein, we present the synthesis, chemical characterization, and, briefly, the use in solution-phase peptide synthesis of the novel Aib-Pro synthons 3a and 3b. After introduction into the peptide, the C-termini of the resulting extended peptides can be deprotected with Zn in AcOH or by a mild Pd⁰-promoted procedure, respectively.

2. Results and Discussion. – Since the synthesis of 2H-azirin-3-amines 1 is performed under acidic conditions, the range of carboxy-protecting groups is limited to those which are base-labile, which can be removed by reduction, or which are labile towards transition-metal complexes, but feature a good stability towards acids. The (9H-fluoren-9-yl)methyl (Fm) [24] [25] and 2-[(4-nitrophenyl)sulfonyl]ethyl [26] protecting groups, which can be cleaved by treatment with secondary amines, should fulfill these prerequisites. Hence, we aimed at the synthesis of the 2H-azirin-3-amines 4a and **4b** as outlined in *Scheme 1*. After saponification of methyl prolinate **5** with LiOH and subsequent carbodiimide-induced coupling of acid 6 with the corresponding alcohols, the obtained amides **7a** and **7b** were converted to the thioamides **8a** and **8b**, respectively, by thionation with *Lawesson* reagent. A procedure slightly modified²) compared to that of Wipf [27] did not lead to the desired 2H-azirin-3-amines 4a and 4b. Consequently, we headed for 4b via the 2-[(4-nitrophenyl)sulfanyl]ethyl-protected 2Hazirin-3-amine 4c. This route comprises the 'safety catch principle', since the activation for the β -elimination is realized after the azirine synthesis by an oxidation of the sulfanyl group³). However, the synthesis of **4c** failed too.

The phenacyl (=2-oxo-2-phenylethyl) and allyl ester protecting groups, which can be removed by treatment with Zn/AcOH [28] and $[Pd(Ph_3P)_4]/PhSiH_3$ [29], respectively, were the next promising candidates for proline protection. The synthesis of the phenacyl and allyl ester-protected dipeptide synthons **3a** and **3b** started with the preparation of the esters **9a** and **9b** by alkylation of **6** with phenacyl bromide and allyl bromide, respectively (*Scheme 2*). A direct access from L-proline was accomplished for **9b**. For this purpose, L-proline was esterified with allyl alcohol and then acylated with isobutyryl (=2-methylpropanoyl) chloride. After thionation of the amides **9a**

²) To prevent an early β -elimination, EtN(i-Pr), was used instead of 1,4-diaza[2.2.2]octane (DABCO).

³) A preliminary test showed that **2** is stable under mild oxidative conditions (tetrapropylammonium perruthenate (TRAP), *N*-methylmorpholine *N*-oxide (NMO)).



a) LiOH·H₂O, THF, MeOH, H₂O, r.t. *b*) For **7a**: (9*H*-fluoren-9-yl)methanol, *N*,*N*'-dicyclohexylcarbodiimide (DCC), 4-(pyrrolidin-1-yl)pyridine (PPY), CH₂Cl₂, r.t.; for **7b**: 2-[(4-nitrophenyl)sulfonyl]ethanol, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDCI), 4-(dimethylamino)pyridine (DMAP), CH₂Cl₂, r.t.; for **7c**: 2-[(4-nitrophenyl)sulfanyl]ethanol, DCC, PPY, CH₂Cl₂, r.t. *c*) *Lawesson* reagent, PhMe, *ca.* 90°. *d*) 1. COCl₂, PhMe, CH₂Cl₂, DMF (cat.), 0°; 2. for **4a** and **4b**: EtN(i-Pr)₂, THF, r.t.; for **4c**: 1,4-diazabicyclo[2.2.2]octane (DABCO), THF, r.t., 3. NaN₃, THF (DMF), r.t.

and **9b** with *Lawesson* reagent, the synthesis of **3a** and **3b** was accomplished by consecutive treatment of the obtained thioamides **10a** and **10b**, and catalytic amounts of DMF in CH₂Cl₂ with COCl₂, evaporation of the solvent, addition of THF and 1,4-diazabicy-clo[2.2.2]octane (DABCO), filtration, and treatment with NaN₃ (*cf.* [27]). After chromatographic workup, the 2*H*-azirin-3-amines **3a** and **3b** were obtained in 58 and 62% yield, respectively, as pale yellow oils.

For a chemical characterization and for the examination of the reactivity of the novel 2H-azirin-3-amines **3a** and **3b**, they were treated with PhCOSH (*Scheme 3*). The reactions proceeded smoothly, and the thiopeptides **11** were obtained in high yield (93 and 94%, resp.). In the case of **11a**, crystals suitable for an X-ray crystal-structure determination were obtained (*Fig.*). Compound **11a** in the crystal is enantiomerically pure, and the absolute configuration of the molecule has been determined independently by the diffraction experiment. The molecule has the expected (*S*)-configuration. The amide group forms an intermolecular H-bond with the S-atom of an adjacent molecule and thereby links the molecules into extended chains, which run parallel to the [0 1 0] direction and can be described by the graph set motif [30] of C(5).



a) For **9a**: PhCOCH₂Br, Et₃N, AcOEt, r.t.; for **9b**: CH₂=CHCH₂Br, 'Aliquot 336', CH₂Cl₂, NaHCO₃, H₂O, $0^{\circ} \rightarrow$ r.t. *b*) 1. SOCl₂, allyl alcohol, $-20^{\circ} \rightarrow 65^{\circ}$; 2. isobutyryl chloride, Et₃N, AcOEt, $0^{\circ} \rightarrow$ r.t. *c*) Lawesson reagent, PhMe, *ca.* 90°. *d*) 1. COCl₂, PhMe, CH₂Cl₂, DMF (cat.), 0°; 2. DABCO, THF, r.t.; 3. NaN₃, THF, r.t.

Scheme 3



To examine the use of **3a** and **3b** in peptide synthesis, reactions with *N*-protected amino acids were performed. The Aib-Pro synthon **3a** was reacted with Z-Ile-OH and Z-Phe-OH to give the tripeptides **12a** and **13**, respectively, while the reaction of **3b** with Z-Ile-OH yielded the tripeptide **12b** (*Scheme 4*). All reactions gave the products in high purity and in very good yields (90–94%, after chromatographic workup). Then, the selective deprotection of the C-terminus of **13** was accomplished with Zn powder in AcOH, and yielded peptide acid **14**. Deprotection of the phenacyl esters with $Bu_4N^+F^-$ in DMF [32] would possibly be applicable to solid-phase conditions, which is the ultimate use of the new azirine. Therefore, **12a** and **13** were subjected to $Bu_4N^+F^-$ (3 equiv.) in DMF and THF, respectively, but in none of the experiments a peptide acid **14** or **15**, respectively, could be isolated.



Figure. ORTEP Plot [31] of the molecular structure of **11a** (50% probability ellipsoids; arbitrary numbering of atoms)

The deprotection of the C-terminus can be performed under milder conditions if synthon **3b** is used in the peptide chain extension. This was illustrated with the model peptide **12b**, in which the allyl ester group was smoothly removed by treatment with $[Pd(Ph_3P)_4]$ and PhSiH₃ in CH₂Cl₂ to give the peptide acid **15**. Moreover, these deprotecting conditions should be applicable in solid phase.

3. Conclusions. – The novel 2*H*-azirin-3-amines **3a** and **3b**, which contain a phenacyl ester and an allyl ester group, respectively, as carboxy-protecting group, have been synthesized. These azirines represent Aib-Pro synthons, and this dipeptide unit can be introduced conveniently into peptides by the 'azirine/oxazolone method'. The C-terminus of the resulting peptide esters can be deprotected under non-basic conditions, *i.e.*, by treatment with Zn/AcOH and $[Pd(Ph_3P)_4]/PhSiH_3$. The use of **3a** and **3b** as building blocks for the 'azirine/oxazolone method' in solid phase are being investigated.

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Experimental Part

1. General. – Reagents were obtained from commercial suppliers and were used without further purification. Solvents were purified by standard procedures. Compound **5** was prepared according to [22]. TLC: *Merck* TLC aluminum sheets, silica gel 60 F_{254} . Prep. TLC: *Merck* PLC plates (glass), silica gel 60 F_{254} . Column chromatography (CC): Uetikon-Chemie, silica gel C-560. M.p.: Büchi Melting Point B-450 apparatus; uncorrected. IR Spectra: Perkin-Elmer, Spectrum One FT-IR spectrophotometer; unless otherwise stated in KBr, absorptions in cm⁻¹. NMR Spectra: Bruker ARX-300, Bruker AV-600, or Bruker AV-700 instruments; in CDCl₃, δ in ppm, TMS as internal standard, coupling constants J in Hz 2D-NMR. Experiments were performed for assignment of the signals. In ¹H- and ¹³C-NMR spectra



where two conformers were observed, only the signals of the major conformer are shown. The ratio of the two conformers is given in parentheses. MS (m/z (rel.%)): *Bruker ESQUIRE-LC* quadrupole ion-trap instrument. *Abbreviations:* Aib: ' α -aminoisobutyric acid'; DABCO: 1,4-diazabicyclo[2.2.2]octane; DCC: NN-dicyclohexylcarbodiimide; DMAP: 4-(dimethylamino)pyridine; EDCI: 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride; PPY: 4-(pyrrolidin-1-yl)pyridine.

2. Synthesis of 2H-Azirin-3-amine Derivatives **3a** and **3b**. N-(2-Methyl-1-oxopropyl)-L-proline (**6**). A soln. of methyl N-(2-methyl-1-oxopropyl)-L-prolinate (**5**; 2.000 g, 10.04 mmol) and LiOH·H₂O (0.843 g, 20.11 mmol) in THF/MeOH/H₂O 3:1:1 (100 ml) was stirred at r.t. overnight. The org. solvents were removed under reduced pressure, and the residue was washed with Et₂O. At 0°, the aq. phase was acidified with 1m HCl and saturated with NaCl. After extraction with CH₂Cl₂, the combined org. layers were washed with brine, dried (MgSO₄), and concentrated *i.v.* to give **6** (1.775 g, 96%). Colorless powder. M.p. 122.6–123.7°. IR: 2969s, 2942s, 2879s, 2771m, 2606m, 1721vs, 1600vs, 1509w, 1478s, 1446vs, 1332m, 1266m, 1254s, 1228vs, 1191s, 1167m, 1154m, 1092s, 1042w, 968w, 914m, 838w, 808w, 752w. ¹H-NMR (300 MHz; conformers 95:5): 10.9–9.6 (br. s, CO₂H); 4.61–4.57 (m, CH(a)(Pro)); 3.66–3.61, 3.58–3.50 (2m, CH₂(δ)(Pro)); 2.72 (*sept.*, *J*=6.8, Me₂CH); 2.44–2.40, 2.10–1.99 (2m, CH₂(β)(Pro), CH₂(γ)(Pro)); 1.53, 1.16 (2d, *J*=6.8, 2 Me). ¹³C-NMR (75 MHz): 179.1, 172.8 (2s, 2 CO); 60.0 (d, CH(a)(Pro)); 4.76

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 $(t, CH_2(\delta)(Pro)); 32.5 (d, Me_2CH); 27.4, 24.9 (2t, CH_2(\beta)(Pro), CH_2(\gamma)(Pro)); 19.0, 18.5 (2q, 2 Me). ESI-MS (MeOH): 208 (100, [$ *M*+Na]⁺). Anal. calc. for C₉H₁₅NO₃ (185.22): C 58.36, H 8.16, N 7.56; found: C 58.51, H 8.06, N 7.77.

2-Oxo-2-phenylethyl N-(2-Methyl-1-oxopropyl)-L-prolinate (9a). A mixture of 6 (0.801 g, 4.32 mmol), Et₃N (601 µl, 4.32 mmol), and PhCOCH₂Br (0.860 g, 4.32 mmol) in AcOEt (20 ml) was stirred at r.t. overnight. The mixture was filtered, and the soln. was concentrated *i.v.* CC (SiO₂; AcOEt/hexane 6:4) yielded 9a (1.280 g, 98%). Colorless oil. IR (film): 3488*m*, 3391*w*, 3270*w*, 3063*s*, 2974*vs*, 2935*vs*, 2876*vs*, 1755*vs*, 1701*vs*, 1644*vs*, 1598*vs*, 1582*vs*, 1470*vs*, 1449*vs*, 1426*vs*, 1376*vs*, 1364*vs*, 1318*vs*, 1279*vs*, 1230*vs*, 1173*vs*, 1092*vs*, 1043*s*, 1001*vs*, 973*vs*, 953*vs*, 921*m*, 886*m*, 851*m*, 810*s*, 753*vs*, 735*vs*. ¹H-NMR (300 MHz; conformers 85:15): 7.90–7.87, 7.63–7.57, 7.52–7.45 (3*m*, 5 arom. H); 5.55, 5.21 (*AB*, *J*=16.5, CH₂CO); 4.68–4.62 (*m*, CH(*a*)(Pro)); 3.76–3.67, 3.62–3.54 (2*m*, CH₂(δ)(Pro)); 2.69 (*sept.*, *J*=6.8, Me₂CH); 2.42–2.13, 2.10–1.97 (2*m*, CH₂(β)(Pro), CH₂(γ)(Pro)); 1.15, 1.14 (2*d*, *J*=6.8, 2 Me). ¹³C-NMR (75 MHz): 192.2 (*s*, PhCO); 175.9 (*s*, CO(amide)); 171.8 (*s*, CO(ester)); 134.1 (*s*, arom. C); 133.8, 128.8, 127.6 (3*d*, 5 arom. CH); 60.0 (*t*, CH₂(γ)(Pro)); 18.7, 18.6 (2*q*, 2 Me). ESI-MS (MeOH, NaI): 326 (100, [*M*+Na]⁺). Anal. calc. for C₁₇H₂₁NO₄ (303.35): C 67.31, H 6.98, N 4.62; found: C 67.11, H 6.61, N 4.62.

Prop-2-enyl N-(*2-Methyl-1-oxopropyl*)-L-*prolinate* (**9b**). *From* **6**. A soln. of $CH_2=CHCH_2Br$ (22.8 ml, 269.50 mmol) and 'Aliquot 336' (21.6 g) in CH_2Cl_2 (75 ml) was added to a soln. of **6** (10.004 g, 54.01 mmol) and NaHCO₃ (4.539 g, 54.03 mmol) in H_2O (75 ml) at 0°. The mixture was vigorously stirred at r.t. for 3 d, then H_2O (50 ml) was added, and the suspension was extracted with CH_2Cl_2 . The combined org. layers were dried (MgSO₄) and concentrated *i.v.* CC (SiO₂, AcOEt/hexane 4:6 \rightarrow 1:1) yielded **9b** (11.328 g, 93%). Colorless liquid.

From L-*Proline.* At -20° , SOCl₂ (1.70 ml, 23.36 mmol) was added to CH₂=CHCH₂OH (12 ml, 176.45 mmol), then L-proline (2.000 g, 17.37 mmol) was added, and the mixture was slowly heated to 65° and stirred at 65° for 1 h. The mixture was concentrated *i.v.*, the residue was dissolved in AcOEt (60 ml), and Et₃N (5.05 ml, 36.23 mmol) and isobutyryl chloride (1.85 ml, 17.52 mmol) were added at 0°. The mixture was stirred at r.t. overnight, H₂O (20 ml) was added, and the mixture was extracted with AcOEt. The combined org. layers were dried (MgSO₄) and concentrated *i.v.* CC (AcOEt/hexane 1:1) yielded **9b** (3.164 g, 81%).

Data of **9b.** Colorless liquid. IR (film): 3568w, 3479w, 3085w, 2973vs, 2935s, 2877s, 1745vs, 1650vs, 1741vs, 1426vs, 1377s, 1362s, 1318vs, 1274s, 1242s, 1177vs, 1091s, 1044m, 990s, 954m, 930s, 882w, 819w, 754m. ¹H-NMR (300 MHz; conformers 85:15): 5.97–5.84 (*m*, CH₂=CH); 5.37–5.20 (*m*, CH₂=CH); 4.68–4.60 (*m*, CH₂O); 4.53–4.48 (*m*, CH(α)(Pro)); 3.73–3.64, 3.62–3.53 (2*m*, CH₂(α)(Pro)); 2.68 (*sept.*, *J*=6.8, Me₂CH); 2.29–1.90 (*m*, CH₂(β)(Pro), CH₂(γ)(Pro)); 1.16, 1.13 (2*d*, *J*=6.8, 2 Me). ¹³C-NMR (75 MHz): 176.0 (*s*, CO(amide)); 172.3 (*s*, CO(ester)); 132.2 (*d*, CH₂=CH); 118.4 (*t*, CH₂=CH); 65.7 (*t*, CH₂O); 58.9 (*d*, CH(α)(Pro)); 46.9 (*t*, CH₂(α)(Pro)); 32.4 (*d*, Me₂CH); 29.3, 25.1 (2*t*, CH₂(β)(Pro), CH₂(γ)(Pro)); 19.0, 18.8 (2*q*, 2 Me). ESI-MS (MeOH): 298 (13, [*M*+Na+MeOH+H₂O]⁺), 248 (100, [*M*+Na]⁺). Anal. calc. for C₁₂H₁₉NO₃ (225.28): C 63.98, H 8.50, N 6.22; found: C 63.71, H 8.45, N 6.13.

2-Oxo-2-phenylethyl N-(2-Methyl-1-thioxopropyl)-L-prolinate (**10a**). A suspension of Lawesson reagent (dried *i.v.*, 444 mg, 1.10 mmol) and **9a** (600 mg, 1.98 mmol) in toluene (20 ml) was heated at 90° (oil bath) for 1 h. After cooling to r.t., the mixture was filtered, and the solvent was evaporated. CC (SiO₂; CH₂Cl₂/MeOH 200:1 \rightarrow 100:1) yielded **10a** (571 mg, 90%). Colorless solid. M.p. 83.9–84.9°. IR: 2976*m*, 2946*w*, 2928*w*, 2868*w*, 1749*v*s, 1701*v*s, 1596*m*, 1579*w*, 1468*s*, 1445*v*s, 1419*m*, 1373*m*, 1356*m*, 1345*m*, 1309*w*, 1263*m*, 1255*m*, 1237*v*s, 1192*v*s, 1173*s*, 1156*s*, 1130*m*, 1013*s*, 1000*w*, 967*m*, 910*w*, 815*w*, 757*m*, 735*w*, 690*s*. ¹H-NMR (600 MHz; conformers 87:13): 7.90–7.88, 7.65–7.59, 7.52–7.47 (3*m*, 5 arom. H); 5.54, 5.25 (*AB*, *J*=16.4, CH₂CO); 5.27–5.25 (*m*, CH(α)(Pro)); 3.97–3.93, 3.79–3.75 (2*m*, CH₂(δ)(Pro)); 3.07 (*sept.*, *J*=6.6, Me₂CH); 2.56–2.50, 2.40–2.31, 2.21–2.14 (3*m*, CH₂(β)(Pro), CH₂(γ)(Pro)); 1.26, 1.23 (2*d*, *J*=6.6, 2 Me). ¹³C-NMR (150 MHz): 209.9 (*s*, CS); 192.2 (*s*, PhCO); 170.0 (*s*, CO(ester)); 134.1 (*s*, 1 arom. C); 134.0, 128.9, 127.7 (3*d*, 5 arom. CH); 66.3 (*t*,

CH₂CO); 65.2 (*d*, CH(α)(Pro)); 50.4 (*t*, CH₂(δ)(Pro)); 38.7 (*d*, Me₂CH); 29.0, 24.7 (2*t*, CH₂(β)(Pro), CH₂(γ)(Pro)); 22.7, 22.4 (2*q*, 2 Me). ESI-MS (MeOH, NaI): 342 (100, [*M*+Na]⁺). Anal. calc. for C₁₇H₂₁NO₃S (319.42): C 63.92, H 6.63, N 4.39, S 10.04; found: C 64.07, H 6.37, N 4.30, S 10.08.

Prop-2-enyl N-(2-*Methyl-1-thioxopropyl*)-L-*prolinate* (10b). A suspension of *Lawesson* reagent (dried *i.v.*, 5.584 g, 13.81 mmol) and 9b (5.618 g, 24.94 mmol) in toluene (70 ml) was heated at 95° (oil bath) for 1 h. After cooling to r.t., the mixture was filtered, and the solvent was evaporated. CC (SiO₂; CH₂Cl₂/MeOH 400:1 → 100:1) yielded 10b (5.439 g, 90%). Pale yellow oil. IR (film): 3084w, 2973vs, 2931s, 2878s, 1742vs, 1648w, 1440vs, 1381s, 1360s, 1333vs, 1268vs, 1227vs, 1191vs, 1170vs, 1126s, 1088m, 1046m, 1016vs, 989s, 969s, 930s, 874m, 784w. ¹H-NMR (700 MHz; conformers 83:17): 5.94–5.88 (*m*, CH₂=CH); 5.37–5.23 (*m*, CH₂=CH); 5.13–5.11 (*m*, CH(α)(Pro)); 4.67–4.60 (*m*, CH₂O); 3.93–3.88, 3.78–3.74 (2*m*, CH₂(δ)(Pro)); 3.05 (*sept.*, *J*=6.6, Me₂CH); 2.30–2.25, 2.23–2.17, 2.14–2.09 (3*m*, CH₂(β)(Pro), CH₂(γ)(Pro)); 1.25, 1.24 (2*d*, *J*=6.6, 2 Me). ¹³C-NMR (175 MHz): 209.9 (*s*, CS); 170.5 (*s*, CO); 132.1 (*d*, CH₂=CH); 5.13– (*t*, CH₂=CH); 66.0 (*t*, CH₂O); 65.4 (*d*, CH(α)(Pro)); 50.4 (*t*, CH₂(δ)(Pro)); 3.89 (*d*, Me₂CH); 29.0, 24.9 (2*t*, CH₂(β)(Pro), CH₂(γ)(Pro)); 22.9, 22.5 (2*q*, 2 Me). ESI-MS (MeOH): 264 (100, [*M*+Na]⁺). Anal. calc. for C₁₂H₁₉NO₂S (241.35): C 59.72, H 7.93, N 5.80, S 13.29; found: C 59.80, H 7.65, N 5.58, S 13.07.

2-Oxo-2-phenylethyl N-(2,2-Dimethyl-2H-azirin-3-yl)-L-prolinate (3a). A soln. of COCl₂ in toluene (20%, 1.8 ml, 3.47 mmol) was added to a soln. of 10a (1.001 g, 3.13 mmol) and 3 drops of DMF in CH_2Cl_2 (10 ml) at 0°, the mixture was stirred for 30 min at 0°, and the volatiles were removed *i.v.* THF (15 ml) and DABCO (0.351 g, 3.13 mmol) were added under vigorous stirring to the residue, and the mixture was stirred at r.t. for 30 min. The solid was removed by filtration under N2 and washed with THF. To the filtrate, NaN₃ (0.617 g, 9.49 mmol) was added, and the resulting mixture was stirred at r.t. for 4 d. After addition of Et₂O, the resulting suspension was filtered over a Celite pad, and the solvent was removed *i.v.* CC (SiO₂, AcOEt/hexane 6:4, Et₃N (1%)) yielded **3a** (0.542 g, 58%). Pale yellow oil. IR (film): 3434w, 3388w, 3063w, 2976s, 2942s, 2879m, 1771vs, 1703vs, 1598m, 1581w, 1450s, 1417m, 1369s, 1345m, 1277s, 1233vs, 1174vs, 1095m, 1001w, 964s, 911w, 846w, 819w, 758m, 690s. ¹H-NMR (300 MHz): 7.91-7.88, 7.65-7.59, 7.52-7.47 (3m, 5 arom. H); 5.47-5.32 (m, CH₂CO); 4.50 (br. s, CH(a)(Pro)); 3.74-3.67, 3.62-3.54 (2m, CH₂(δ)(Pro)); 2.50-2.04 (m, CH₂(β)(Pro), CH₂(γ)(Pro)); 1.35, 1.31 (2s, 2) Me). ¹³C-NMR (75 MHz): 191.5 (s, PhCO); 171.7 (s, CO(ester)); 165.5 (s, C(3)); 134.1 (d, 1 arom. CH); 134.0 (s, 1 arom. C); 129.0, 127.7 (2d, 4 arom. CH); 66.4 (t, CH₂CO); ca. 60.9 (br. d, CH(α)(Pro)); *ca.* 46.9 (br. *t*, CH₂(δ)(Pro)); 39.2 (*s*, C(2)); 30.6 (*t*, CH₂(β)(Pro)); 25.2 (*q*, 2 Me); 24.0 (*t*, CH₂(γ)(Pro)). ESI-MS (MeOH): 323 (100, [*M*+Na]⁺). Anal. calc. for C₁₇H₂₀N₂O₃ (300.35): C 67.98, H 6.71, N 9.33; found: C 67.73, H 6.53, N 9.35.

Prop-2-enyl N-(2,2-Dimethyl-2H-azirin-3-yl)-L-prolinate (3b). A soln. of COCl₂ in toluene (20%, 2.6 ml, 5.02 mmol) was added to a soln. of 10b (1.008 g, 4.14 mmol) and 3 drops of DMF in CH₂Cl₂ (10 ml) at 0° , the mixture was stirred for 30 min at 0° , and the volatiles were removed *i.v.* The residue was dissolved in THF (15 ml), DABCO (0.465 g, 4.15 mmol) was added, and the mixture was stirred at r.t. for 30 min. The solid was removed by filtration under N_2 and washed with THF. To the filtrate, NaN₃ (0.810 g, 12.46 mmol) was added, and the resulting mixture was stirred at r.t. for 4 d. After addition of Et₂O, the resulting suspension was filtered over a Celite pad, and the solvent was removed i.v. CC (SiO₂; AcOEt/hexane 6:4, Et₃N (1%)) yielded **3b** (0.575 g, 63%). Pale yellow oil. IR (film): 3458w, 3087w, 2976s, 2943s, 2879s, 1770vs, 1745vs, 1649w, 1454s, 1413m, 1368s, 1352m, 1272s, 1235s, 1177vs, 1093m, 1043w, 1015m, 987s, 933m. ¹H-NMR (300 MHz): 5.97-5.84 (m, CH₂=CH); 5.36-5.24 (m, CH₂=CH); 4.67-4.61 (m, CH₂O); 4.35–4.34 (*m*, CH(α)(Pro)); 3.70–3.52 (*m*, CH₂(δ)(Pro)); 2.39–1.99 (*m*, CH₂(β)(Pro), CH₂(γ)(Pro)); 1.32, 1.29 (2s, 2 Me). ¹³C-NMR (75 MHz): 171.6 (s, CO); 165.2 (s, C(3)); 131.4 (d, $CH_2=CH$); 118.8 (t, $CH_2=CH$); 65.8 (t, CH_2O); ca. 60.8 (br. d, $CH_2(\delta)(Pro)$); ca. 46.9 (br. t, $CH_2(\delta)(Pro)); 39.0 (s, C(2)); 30.2 (t, CH_2(\beta)(Pro)); 25.0 (q, 2 Me); 23.9 (t, CH_2(\gamma)(Pro)). ESI-MS$ (MeOH): 255 (23, $[M+H+MeOH]^+$), 245 (100, $[M+Na]^+$), 223 (29, $[M+H]^+$), 196 (25). Anal. calc. for C₁₂H₁₈N₂O₂·0.2 H₂O (225.88): C 63.81, H 8.21, N 12.40; found: C 63.85, H 8.12, N 12.32.

3. Reactions of 2H-Azirin-3-amine Derivatives **3a** and **3b** with PhCOSH. 2-Oxo-2-phenylethyl N-[2-(Benzoylamino)-2-methyl-1-thioxopropyl]-L-prolinate (**11a**). A soln. of PhCOSH (20 mg, 0.145 mmol) in CH_2Cl_2 (2 ml) was added to a soln. of **3a** (40 mg, 0.133 mmol) in CH_2Cl_2 (2.5 ml) at 0°. The mixture was stirred at r.t. overnight, the solvent was evaporated, and the crude product was purified by prep. TLC (CH₂Cl₂/MeOH 50:1, 2×dev.; CH₂Cl₂/MeOH 30:1, 1×dev.) to give **11a** (54 mg, 93%). Colorless crystals. M.p. 189.1–190.2°. IR: 3361*m*, 3301*m*, 3059*w*, 2984*m*, 2932*m*, 2881*w*, 1749vs, 1702vs, 1642vs, 1598s, 1579s, 1524vs, 1486s, 1449vs, 1419vs, 1385s, 1362s, 1341*m*, 1301s, 1288s, 1264s, 1226vs, 1186vs, 1160vs, 1092*m*, 1074*m*, 1043s, 1028*m*, 1001*m*, 965s, 911*w*, 884*w*, 803*w*, 754s, 720s, 690vs. ¹H-NMR (600 MHz): 8.51 (*s*, NH); 7.90–7.86, 7.63–7.60, 7.51–7.48, 7.45–7.43 (4*m*, 10 arom. H); 5.53, 5.27 (*AB*, *J*=16.4, CH₂CO); 5.38–5.36 (*m*, CH(*a*)(Pro)); 4.12–4.08, 3.96–3.92 (2*m*, CH₂(δ)(Pro)); 2.51–2.48, 2.39–2.31, 2.14–2.10 (3*m*, CH₂(β)(Pro), CH₂(γ)(Pro)); 1.95, 1.89 (2s, 2 Me). ¹³C-NMR (150 MHz): 205.9 (*s*, CS); 192.1 (*s*, PHCO); 169.8 (*s*, CO(ester)); 164.9 (*s*, CO(amide)); 135.0 (*s*, 1 arom. C); 134.0 (*d*, 1 arom. CH); 134.0 (*s*, 1 arom. C); 131.4, 128.9, 128.5, 127.7, 127.0 (5*d*, 9 arom. CH); 69.1 (*d*, CH(α)(Pro)); 6.3 (*t*, CH₂CO); 61.2 (*s*, C(α)(Aib)); 53.6 (*t*, CH₂(δ)(Pro)); 28.0 (*t*, CH₂(β)(Pro)); 26.0 (*t*, CH₂(γ)(Pro)); 25.8, 24.9 (2*q*, 2 Me). ESI-MS (MeOH): 461 (100, [*M*+Na]⁺). Anal. calc. for C₂₄H₂₆N₂O₄S (438.54): C 65.73, H 5.98, N 6.39, S 7.31; found: C 65.33, H 5.72, N 6.24, S 7.02. Suitable crystals for the X-ray crystal-structure determination were grown from CDCl₃/Et₂O.

Prop-2-enyl N-*[2-(Benzoylamino)-2-methyl-1-thioxopropyl]*-L-*prolinate* (**11b**). A soln. of PhCOSH (27 mg, 0.195 mmol) in CH₂Cl₂ (3 ml) was added to a soln. of **3b** (40 mg, 0.180 mmol) in CH₂Cl₂ (2 ml) at 0°. The mixture was stirred at r.t. overnight, the solvent was evaporated, and the crude product was purified by prep. TLC (CH₂Cl₂/MeOH 40 :1, Et₃N (0.5%), 2×dev.) to give **11b** (61 mg, 94%). Colorless powder. M.p. 46.5–48.0°. IR: 3303*m*, 3059*w*, 2984*m*, 2925*s*, 2880*m*, 2853*m*, 1741v*s*, 1639v*s*, 1602*m*, 1578*m*, 1530v*s*, 1488*s*, 1461*s*, 1419v*s*, 1385*s*, 1362*s*, 1340*m*, 1301*s*, 1292*s*, 1271*s*, 1245*m*, 1187v*s*, 1160v*s*, 1086*w*, 1075*w*, 1046*s*, 1028*w*, 988*m*, 969*m*, 931*m*, 885*w*, 803*w*, 717*s*, 694*m*. ¹H-NMR (300 MHz): 8.66 (br. *s*, NH); 7.89–7.85, 7.52–7.40 (2*m*, 5 arom. H); 5.99–5.86 (*m*, CH₂=CH); 5.39–5.20 (*m*, CH₂=CH, CH(α)(Pro)); 4.65–4.63 (*m*, CH₂O); 4.08–3.91 (*m*, CH₂(δ)(Pro)); 2.34–2.15, 2.10–2.00 (2*m*, CH₂(β)(Pro), CH₂(γ)(Pro)); 1.95, 1.89 (2*s*, 2 Me). ¹³C-NMR (75 MHz): 205.8 (*s*, CS); 170.0, 164.7 (2*s*, 2 CO); 135.1 (*s*, 1 arom. C); 131.7, 131.2, 128.4, 126.9 (4*d*, 5 arom. CH, CH₂=CH); 118.6 (*t*, CH₂=CH); 68.9 (*d*, CH(α)(Pro)); 25.8 (*t*, CH₂(γ)(Pro)); 25.5, 24.7 (2*q*, 2 Me(Aib)). ESI-MS (MeOH): 383 (100, [*M*+Na]⁺), 367 (17, [*M*(S → O)+Na]⁺). Anal. calc. for C₁₉H₂₄N₂O₃S (360.47): C 63.31, H 6.71, N 7.77, S 8.90; found: C 63.25, H 6.45, N 7.68, S 8.67.

4. Synthesis of Model Peptides. 2-Oxo-2-phenylethyl N-{2-[((2\$,3\$)-2-{[(Benzyloxy)carbonyl]amino]-3-methyl-1-oxopentyl)amino]-2-methyl-1-oxopropyl]-L-prolinate (12a). A soln. of 3a (65 mg, 0.216 mmol) in CH₂Cl₂ (2.5 ml) was added to a soln. of Z-Ile-OH (57 mg, 0.215 mmol) in CH₂Cl₂ (2.5 ml) at 0°. The mixture was stirred at r.t. overnight, the solvent was evaporated, and the crude product was purified by CC (SiO₂; CH₂Cl₂/MeOH 60:1) to give 12a (105 mg, 86%). Colorless solid. M.p. 70.1-71.5°. IR: 3318s, 3064w, 3034w, 2966s, 2936m, 2877m, 1753vs, 1702vs, 1660vs, 1633vs, 1599m, 1531vs, 1468s, 1451s, 1409vs, 1378s, 1363s, 1286s, 1230vs, 1167vs, 1096m, 1042m, 1028m, 1001w, 977m, 754s, 693s. ¹H-NMR (600 MHz): 7.89-7.88, 7.62-7.59, 7.50-7.47, 7.37-7.31 (4m, 10 arom. H); 6.97 (s, NH(Aib)); 5.57, 5.21 (*AB*, J=16.4, CH₂CO); 5.41 (*d*, J=8.8, NH(Ile)); 5.12, 5.08 (*AB*, J=12.3, CH₂(carbamate)); 4.72-4.69 (*m*, CH(*a*)(Pro)); 4.00-3.97 (*m*, CH(*a*)(Ile)); 3.77-3.73, 3.57-3.54 (2*m*, CH₂(δ)(Pro)); 2.32–2.30 (m, 1 H of $CH_2(\beta)(Pro)$); 2.19–2.10 (m, 1 H of $CH_2(\beta)(Pro)$, 1 H of $CH_2(\gamma)(Pro)$); 1.90-1.88 (*m*, 1 H of CH₂(γ)(Pro)); 1.83-1.82 (*m*, CH(β)(Ile)); 1.65, 1.61 (2s, 2 Me(Aib)); 1.53-1.48, 1.16–1.11 (2*m*, CH₂(γ)(Ile)); 0.92 (*d*, J=6.8, MeCH(β)(Ile)); 0.89 (*t*, J=7.4, MeCH₂(γ)(Ile)). ¹³C-NMR (150 MHz): 192.2 (s, PhCO); 172.2 (s, CO(Aib)); 171.8 (s, CO(Pro)); 169.6 (s, CO(Ile)); 156.2 (s, CO(carbamate)); 136.3, 134.1 (2s, 2 arom. C); 134.0, 128.9, 128.5, 128.2, 128.0, 127.7 (6d, 10 arom. CH); 66.9 (t, PhCH₂); 66.2 (t, CH₂CO); 60.9 (d, CH(α)(Pro)); 59.7 (d, CH(α)(Ile)); 57.1 (s, C(a)(Aib); 48.2 (t, $CH_2(\delta)(Pro)$); 37.8 (d, $CH(\beta)(Ile)$); 27.9 (t, $CH_2(\beta)(Pro)$); 25.8 (t, $CH_2(\gamma)(Pro)$); 24.9 (t, $CH_2(\gamma)(Ile)$); 23.6, 23.2 (2q, 2 Me(Aib)); 15.4 (q, MeCH(β)(Ile)); 11.4 (q, MeCH₂(γ)(Ile)). ESI-MS (MeOH): 588 (100, $[M+Na]^+$). Anal. calc. for $C_{31}H_{39}N_3O_7$ (565.66): C 65.82, H 6.95, N 7.43; found: C 65.53, H 7.06, N 7.27.

Prop-2-enyl N-[2-[((2S,3S)-2-[(Benzyloxy)carbonyl]amino]-3-methyl-1-oxopentyl)amino]-2-methyl-1-oxopropyl]-L-prolinate (12b). A soln. of 3b (60 mg, 0.270 mmol) in CH₂Cl₂ (3 ml) was added to asoln. of Z-IIe-OH (79 mg, 0.297 mmol) in CH₂Cl₂ (2 ml) at 0°. The mixture was stirred at r.t. overnight,the solvent was evaporated, and the crude product was purified by CC (SiO₂; CH₂Cl₂/MeOH 20:1) togive 12b (123 mg, 93%). Colorless powder. M.p. 135.0–136.1°. IR: 3287s, 3256s, 3065m, 2964s, 2937m, 2876w, 1751vs, 1715vs, 1666vs, 1619vs, 1547vs, 1497m, 1453s, 1419s, 1383s, 1366m, 1355m, 1285s, 1272s, 1243vs, 1208m, 1174vs, 1162vs, 1126m, 1095w, 1047m, 1028m, 987m, 949w, 923w, 877w, 853w, 778w, 751w, 738m, 700m. ¹H-NMR (600 MHz): 7.37–7.29 (*m*, 5 arom. H); 6.97 (br. *s*, NH(Aib)); 5.94–5.87 (*m*, CH₂=CH); 5.40 (*d*, J=8.5, NH(Ile)); 5.35–5.31, 5.25–5.23 (2*m*, CH₂=CH); 5.11, 5.08 (*A*B, J=12.3, CH₂(carbamate)); 4.66–4.58 (*m*, CH₂O); 4.58–4.55 (*m*, CH(α)(Pro)); 4.00–3.97 (*m*, CH(α)(Ile)); 3.72–3.69, 3.58–3.55 (2*m*, CH₂(β)(Pro)); 2.11–2.07 (*m*, 1 H of CH₂(β)(Pro)); 2.04–1.97 (*m*, 1 H of CH₂(γ)(Pro)); 1.91–1.82 (*m*, 1 H of CH₂(β)(Pro), 1 H of CH₂(γ)(Pro), CH(β)(Ile)); 1.65, 1.62 (2*s*, 2 Me(Aib)); 1.53–1.49, 1.16–1.10 (2*m*, CH₂(γ)(Ile)); 0.92 (*d*, J=7.0, *Me*CH(β)(Ile)); 0.90 (*t*, J=7.4, *Me*CH₂(γ)(Ile)). ¹³C-NMR (150 MHz): 172.0 (*s*, CO(Aib)); 172.0 (*s*, CO(Pro)); 169.6 (*s*, CO(IIe)); 156.2 (*s*, CO(carbamate)); 136.4 (*s*, 1 arom. C); 131.9 (*d*, CH₂=CH); 128.5, 128.2, 128.0 (3*d*, 5 arom. CH); 118.5 (*t*, CH₂=CH); 66.9 (*t*, CH₂(carbamate)); 65.7 (*t*, CH₂O); 61.0 (*d*, CH(α)(Pro)); 25.8 (*t*, CH₂(γ)(Pro)); 24.9 (*t*, CH₂(γ)(Ile)); 37.8 (*d*, CH(β)(Ile)); 17.8 (*t*, CH₂(β)(Pro)); 25.8 (*t*, CH₂(γ)(Iro)); 24.9 (*t*, CH₂(γ)(Ile)); 37.8 (*d*, CH(β)(Ile)); 15.4 (*q*, *Me*CH(- β)(Ile)); 11.4 (*q*, *Me*CH₂(γ)(Ile)). ESI-MS (MeOH): 510 (100, [*M*+Na]⁺). Anal. calc. for C₂₆H₃₇N₃O₆ (487.59): C 64.05, H 7.65, N 8.62; found: C 63.89, H 7.40, N 8.58.

2-Oxo-2-phenylethyl N-{2-{((S)-2-{[(Benzyloxy)carbonyl]amino}-3-phenyl-1-oxopropyl)amino]-2methyl-1-oxopropyl/-L-prolinate (13). A soln. of 3a (120 mg, 0.380 mmol) in CH₂Cl₂ (3 ml) was added to a soln. of Z-Phe-OH (120 mg, 0.401 mmol) in CH₂Cl₂ (3 ml) at 0°. The mixture was stirred at r.t. overnight, the solvent was evaporated, and the crude product was purified by CC (SiO₂; CH₂Cl₂/MeOH 80:1 \rightarrow 60:1) to give **13** (213 mg, 94%). Colorless powder. M.p. 76.7–78.4°. IR: 3311s, 3062m, 3031w, 2983m, 2940m, 2880w, 1752vs, 1703vs, 1670vs, 1625vs, 1532vs, 1498s, 1469s, 1451s, 1412vs, 1377s, 1364s, 1341m, 1286s, 1232vs, 1166vs, 1097w, 1084w, 1052m, 1028m, 1001w, 977m, 913w, 848w, 752s, 698s. ¹H-NMR (600 MHz): 7.88-7.87, 7.61-7.59, 7.49-7.46, 7.37-7.20 (4m, 15 arom. H); 6.57 (s, NH(Aib)); 5.55, 5.18 (AB, J=16.5, CH₂CO); 5.39 (d, J=7.2, NH(Phe)); 5.10, 5.08 (AB, J=12.0, CH₂(carbamate)); 4.68-4.66 (*m*, CH(α)(Pro)); 4.38-4.37 (*m*, CH(α)(Phe)); 3.66-3.59, 3.46-3.42 (2*m*, CH₂(δ)(Pro)); 3.11-3.08, 3.03-3.00 (2m, CH₂(Phe)); 2.32-2.26, 2.19-2.13 (2m, CH₂(β)(Pro)); 2.10-2.06, 1.92-1.84 (2m, CH₂(γ)(Pro)); 1.50, 1.42 (2s, 2 Me(Aib)). ¹³C-NMR (150 MHz): 192.2 (s, PhCO); 171.8 (s, CO(Aib), CO(Pro)); 169.1 (s, CO(Phe)); 155.9 (s, CO(carbamate)); 136.3, 136.2, 134.1 (3s, 3 arom. C); 134.0, 129.5, 128.9, 128.7, 128.6, 128.2, 128.0, 127.7, 127.1 (9d, 15 arom. CH); 67.0 (t, $CH_2(carbamate)$; 66.1 (t, CH_2CO); 60.8 (d, $CH(\alpha)(Pro)$); 56.9 (s, $C(\alpha)(Aib)$); 56.4 (d, $CH(\alpha)(Phe)$); 48.1 (t, $CH_2(\delta)(Pro)$); 38.7 (t, $CH_2(Phe)$); 27.8 (t, $CH_2(\beta)(Pro)$); 25.8 (t, $CH_2(\gamma)(Pro)$); 23.7, 23.4 (2q, 2 Me(Aib)). ESI-MS (MeOH): 622 (100, $[M + Na]^+$). Anal. calc. for $C_{34}H_{37}N_3O_7$ (599.67): C 68.10, H 6.22, N 7.01; found: C 68.13, H 6.27, N 6.90.

N-{2-[((S)-2-{[(Benzyloxy)carbonyl]amino}-3-phenyl-1-oxopropyl)amino]-2-methyl-1-oxopropyl}-L-proline (14). Zn Powder (274 mg, 4.190 mmol) was added to a soln. of 13 (50 mg, 0.083 mmol) in AcOH (100%, 2 ml), and the mixture was stirred at r.t. for 45 min. Additional Zn powder (136 mg, 2.080 mmol) and AcOH (100%, 0.5 ml were added, and the mixture was stirred for further 45 min. The mixture was filtered, the residue was washed with AcOH, and the filtrate was concentrated under reduced pressure. Prep. TLC (CH₂Cl₂/MeOH 10:1, 2×dev.) yielded **14** (30 mg, 75%). Colorless powder. M.p. 94.4–96.3°. IR: 3305vs, 3063s, 3032s, 2984s, 2945s, 2879m, 1720vs, 1666vs, 1620vs, 1537vs, 1498vs, 1469s, 1454vs, 1419vs, 1383s, 1366s, 1341s, 1294(sh), 1245vs, 1217s, 1178s, 1152s, 1084w, 1053s, 1028m, 912w, 744s, 699vs. ¹H-NMR (600 MHz): 7.37-7.21 (m, 10 arom. H); 6.58 (br. s, NH(Aib)); 5.43 (br. s, NH(Phe)); 5.12, 5.07 (AB, J=12.1, CH₂(carbamate)); 4.57–4.54 (m, CH(α)(Pro)); 4.41 (q-like, $J\approx$ 7.4, CH(α) (Phe)); 3.39-3.35 (m, 1 H of CH₂(δ)(Pro)); 3.07-3.05 (m, CH₂(Phe)); 2.96-2.94 (m, 1 H of $CH_2(\delta)(Pro)); 2.09-1.95 \ (m, CH_2(\beta)(Pro)); 1.78-1.68 \ (m, CH_2(\gamma)(Pro)); 1.37 \ (s, 2 Me(Aib)); COOH$ could not be detected. ¹³C-NMR (150 MHz): 173.0 (s, CO(Pro)); 172.7 (s, CO(Aib)); 170.4 (s, CO(Phe)); 156.3 (s, CO(carbamate)); 136.0, 135.9 (2s, 2 arom. C); 129.5, 128.8, 128.6, 128.4, 128.1, 127.2 (6d, 10 arom. CH); 67.4 (t, CH₂(carbamate)); 61.6 (d, CH(a)(Pro)); 56.9 (s, C(a)(Aib)); 56.1 (d, $CH(\alpha)(Phe)$; 48.2 (t, $CH_2(\delta)(Pro)$); 37.4 (t, $CH_2(Phe)$); 27.3 (t, $CH_2(\beta)(Pro)$); 25.9 (t, $CH_2(\gamma)(Pro)$); 24.8, 24.3 (2q, 2 Me(Aib)). ESI-MS (MeOH): 504 (100, $[M+Na]^+$). Anal. calc. for $C_{26}H_{31}N_3O_6 \cdot H_2O_5$ (499.56): C 62.51, H 6.66, N 8.41; found: C 62.80, H 6.47, N 8.27.

 $N-{2-[((2S,3S)-2-{[(Benzyloxy)carbonyl]amino]-3-methyl-1-oxopentyl)amino]-2-methyl-1-oxopropyl]-L-proline (15). A soln. of [Pd(Ph₃P)₄] (ca. 4 mg, ca. 0.004 mmol) and PhSiH₃ (70 µl, 0.567 mmol) in$

CH₂Cl₂ (1 ml), was added to a soln. of **12b** (70 mg, 0.144 mmol) in CH₂Cl₂ (1 ml), and the mixture was stirred at r.t. under Ar and exclusion of light for 50 min. The mixture was concentrated *i.v.* and purified by prep. TLC (CH₂Cl₂/MeOH 10:1, 3×dev.) to give 15 (54 mg, 84%). Colorless powder. M.p. 101.5-103.2°. IR: 3426s, 3306vs, 3063s, 3035s, 2966vs, 2936s, 2878s, 1705vs, 1659vs, 1622vs, 1535vs, 1469s, 1454vs, 1416vs, 1384s, 1365s, 1342s, 1309s, 1288s, 1245vs, 1178s, 1128m, 1094m, 1042s, 1028m, 983w, 914w, 882w, 778w, 739m, 698s. ¹H-NMR (600 MHz): 7.34-7.31 (m, 5 arom. H); 7.10 (br. s, NH(Aib)); 5.69 (br. s, NH(Ile)); 5.11, 5.07 (AB, J = 11.8, CH₂(carbamate)); 4.55 (br. s, CH(α)(Pro)); 3.97 (br. s, CH(α)(Ile)); 3.49 (br. s, CH₂(δ)(Pro)); 2.08–1.83 (m, CH₂(β)(Pro), 1 H of CH₂(γ)(Pro), $CH(\beta)$ (Ile)); 1.75–1.67 (m, 1 H of $CH_2(\gamma)$ (Pro)); 1.53, 1.51 (2s, 2 Me(Aib)); ca. 1.50, 1.67–1.09 (2m, $CH_{2}(\gamma)(Ile)$; 0.92 (d, J=7.1, MeCH(β)(Ile)); 0.88 (t, J=7.1, MeCH_{2}(\gamma)(Ile)); COOH could not be detected. ¹³C-NMR (150 MHz): 173.9, 173.0, 171.1 (3s, 3 CO); 156.6 (s, CO(carbamate)); 136.2 (s, 1 arom. C); 128.6, 128.3, 128.0 (3d, 5 arom. CH); 67.1 (t, CH₂(carbamate)); 61.7 (d, CH(a)(Pro)); 59.8 $(d, CH(\alpha)(Ile));$ 57.0 $(s, C(\alpha)(Aib));$ 48.2 $(t, CH_2(\delta)(Pro));$ 36.8 $(d, CH(\beta)(Ile));$ 27.4 $(t, CH_2(\delta)(Pro));$ 36.8 $(d, CH(\beta)(Ile));$ 36.8 $(d, CH(\beta)$ $CH_2(\beta)(Pro)$; 25.9 (t, $CH_2(\gamma)(Pro)$); 24.8 (t, $CH_2(\gamma)(Ile)$); 24.5, 24.4 (2q, 2 Me(Aib)); 15.5 (q, $MeCH(\beta)(Ile))$; 11.2 (q, $MeCH_2(\gamma)(Ile)$). ESI-MS (MeOH): 486 (19, $[M+K]^+$), 470 (100, $[M+Na]^+$), $305 (57, [M - Pro - CO]^+)$. Anal. calc. for $C_{23}H_{33}N_3O_6 \cdot H_2O (465.54)$: C 59.34, H 7.58, N 9.03; found: C 59.46, H 7.41, N 8.69.

5. Synthesis of L-Prolinates **8a**-**8c**. (9H-Fluoren-9-yl)methyl N-(2-Methyl-1-oxopropyl)-L-prolinate (**7a**). At 0°, DCC (1.227 g, 5.95 mmol) was added to a soln. of **6** (1.000 g, 5.40 mmol), (9H-fluoren-9-yl)methanol (1.166 g, 5.94 mmol) and PPY (42 mg, 0.283 mmol) in CH₂Cl₂ (50 ml). After stirring at r.t. for 4 h, the mixture was filtered, and the solvent was evaporated. CC (SiO₂, AcOEt/hexane: 4:6 \rightarrow 6:4) yielded **7a** (1.786 g, 91%). Colorless powder. M.p. 104.4–107.3°. IR: 2971*m*, 2951*m*, 2932*m*, 2892*w*, 2873*m*, 1750*vs*, 1707*w*, 1629*vs*, 1536*w*, 1471*s*, 1446*s*, 1432*vs*, 1381*m*, 1329*s*, 1320*m*, 1270*m*, 1196*s*, 1167*vs*, 1088*m*, 1035*m*, 1024*w*, 1003*w*, 955*w*, 945*w*, 903*w*, 752*s*, 741*s*. ¹H-NMR (300 MHz; conformers 86:14): 7.78–7.73, 7.64–7.54, 7.42–7.27 (3*m*, 8 arom. H); 4.64–4.59 (*m*, CH(α)(Pro)); 4.53–4.43 (*m*, CH₂(Fm)); 4.21 (*t*, *J*=6.3, CH(Fm)); 3.52–3.46 (*m*, CH₂(δ)(Pro)); 2.60 (*sept.*, *J*=6.8, Me₂CH); 2.11–2.01, 1.91–1.65 (2*m*, CH₂(β)(Pro), CH₂(γ)(Pro)); 1.10, 1.06 (2*d*, *J*=6.8, 2 Me). ¹³C-NMR (75 MHz): 175.9, 172.4 (2*s*, 2 CO); 144.1, 143.7, 141.4, 141.4 (4*s*, 4 arom. C); 127.8, 127.2, 125.1, 125.0, 119.9 (5*d*, 8 arom. CH); 66.2 (*t*, CH₂(Fm)); 58.8 (*d*, CH(α)(Pro)); 4.71 (*d*, CH(Fm)); 46.7 (*t*, CH₂(δ)(Pro)); 32.3 (*d*, Me₂CH); 29.0, 24.7 (2*t*, CH₂(β)(Pro), CH₂(γ)(Pro)); 18.8, 18.7 (2*q*, 2 Me). ESI-MS (MeOH): 414 (19, [*M*+H+H₂O+MeOH]⁺), 386 (100, [*M*+Na]⁺).

2-[(4-Nitrophenyl)sulfonyl]ethyl N-(2-Methyl-1-oxopropyl)-L-prolinate (**7b**). A soln. of 2-[(4-nitrophenyl)sulfonyl]ethanol (433 mg, 1.873 mmol), EDCI (474 mg, 2.473 mmol), DMAP (24 mg, 0.196 mmol), and **6** (381 mg, 2.057 mmol) in CH₂Cl₂ (30 ml) was stirred under N₂ at r.t. for 1 d. Aq. AcOH (5%, *ca.* 40 ml) was added, and the mixture was extracted with CH₂Cl₂. The combined org. layers were dried (Na₂SO₄) and concentrated *i.v.* CC (SiO₂; CH₂Cl₂/MeOH 50:1) yielded **7b** (683 mg, 92%). Colorless powder. M.p. 89.8–91.9°. IR: 3463w, 3119w, 2975s, 2931m, 2879w, 1740vs, 1642vs, 1608m, 1530vs, 1467m, 1428vs, 1391m, 1351vs, 1330vs, 1312vs, 1302vs, 1270w, 1248m, 1210m, 1179vs, 1146vs, 1104m, 1089s, 1046w, 1010m, 994w, 919w, 857m, 840w, 805w, 757s, 739s, 703s. ¹H-NMR (300 MHz; conformers 96:4): 8.44–8.40, 8.20–8.15 (2m, 4 arom. H); 4.51–4.46 (m, CH₂CH₂O); 4.16–4.12 (m, CH(*α*)(Pro)); 3.67–3.49 (m, CH₂CH₂O, CH₂(*δ*)(Pro)); 2.64 (*sept.*, *J*=6.8, Me₂CH); 2.11–1.86 (m, CH₂(*β*)(Pro), CH₂(*γ*)(Pro)); 1.12, 1.10 (2d, *J*=6.8, 2 Me). ¹³C-NMR (75 MHz): 176.0 (*s*, CO(amide)); 171.8 (*s*, CO(ester)); 151.0, 144.8 (2s, 2 arom. C); 129.9, 124.6 (2d, 4 arom. CH); 58.5 (d, CH(*α*)(Pro)); 57.5 (*t*, CH₂CH₂O); 55.1 (*t*, CH₂CH₂O); 46.8 (*t*, CH(*δ*)(Pro)); 3.22 (*d*, Me₂CH); 28.8, 25.0 (2*t*, CH₂(*β*)(Pro), CH₂(*γ*)(Pro)); 18.8, 18.7 (2q, 2 Me). ESI-MS (MeOH, NaI): 421 (100, [*M*+Na]⁺).

2-[(4-Nitrophenyl)sulfanyl]ethyl N-(2-Methyl-1-oxopropyl)-L-prolinate (**7c**). At 0°, DCC (513 mg, 2.486 mmol) was added to a soln. of **6** (420 mg, 2.268 mmol), 2-[(4-nitrophenyl)sulfanyl]ethanol (470 mg, 2.359 mmol), and PPY (38 mg, 0.256 mmol) in CH₂Cl₂ (20 ml). After stirring at r.t. for 5.5 h, the mixture was filtered, and the solvent was evaporated. CC (SiO₂; AcOEt/hexane 6:4) yielded **7c** (807 mg, 97%). Yellow oil. IR (film): 3469w, 3327w, 3100m, 3069w, 2972vs, 2933vs, 2876s, 1745vs, 1643vs, 1594vs, 1578vs, 1512vs, 1471vs, 1427vs, 1381vs, 1338vs, 1322(sh), 1274vs, 1243s, 1171vs, 1090vs, 1046s, 1009s, 966m, 953m, 916w, 886w, 853vs, 742vs. ¹H-NMR (600 MHz; conformers 92:8): 8.18–8.13, 7.44–7.40 (2m, 4 arom. H); 4.45–4.43 (m, CH(α)(Pro)); 4.39–4.30 (m, CH₂CH₂O); 3.71–3.67, 3.60–3.56 (2m, 2000); 2.2000; 2.2000);

CH₂(δ)(Pro)); 3.31–3.27 (*m*, CH₂CH₂O); 2.69 (*sept.*, *J*=6.8, Me₂CH); 2.21–2.16, 2.11–2.07, 2.02–1.93 (3*m*, CH₂(β)(Pro), CH₂(γ)(Pro)); 1.16, 1.13 (2*d*, *J*=6.8, 2 Me). ¹³C-NMR (150 MHz): 176.0 (*s*, CO (amide)); 172.3 (*s*, CO(ester)); 146.0, 145.4 (2*s*, 2 arom. C); 126.7, 124.1 (2*d*, 4 arom. CH); 62.5 (*t*, CH₂CH₂O); 58.8 (*d*, CH(α)(Pro)); 46.8 (*t*, CH₂(δ)(Pro)); 32.3 (*d*, Me₂CH); 30.3 (*t*, CH₂CH₂O); 29.1 (*t*, CH₂(β)(Pro)); 25.0 (*t*, CH₂(γ)(Pro)); 18.9, 18.7 (2*q*, 2 Me). ESI-MS (CH₂Cl₂, MeOH, NaI): 389 (100, [*M*+Na]⁺).

(9H-Fluoren-9-yl)methyl N-(2-Methyl-1-thioxopropyl)-L-prolinate (**8a**). A suspension of Lawesson reagent (dried *i.v.*, 307 mg, 0.759 mmol) and **7a** (499 mg, 1.373 mmol) in toluene (15 ml) was heated at 95° (oil bath) for 1 h. After cooling to r.t., the mixture was filtered, and the solvent was evaporated. CC (SiO₂; AcOEt/hexane 2:8) yielded **8a** (369 mg, 71%). Colorless powder. M.p. 174.1–176.3°. IR: 2974*m*, 2964*m*, 2927*m*, 2873*w*, 1743*vs*, 1595*w*, 1554*w*, 1503*w*, 1461*s*, 1440*vs*, 1383*s*, 1359*m*, 1345*s*, 1336*s*, 1300*w*, 1270*s*, 1255*m*, 1229*m*, 1194*vs*, 1171*vs*, 1156*vs*, 1123*s*, 1020*m*, 1006*s*, 975*m*, 939*m*, 761*s*, 742*vs*, 716*w*. ¹H-NMR (300 MHz; conformers 88:12): 7.78–7.58, 7.42–7.27 (2*m*, 8 arom. H); 5.10–5.06 (*m*, CH(*a*)(Pro)); 4.73 (*dd*, *J*=10.8, 5.6, 1 H of CH₂(Fm)); 4.42 (*dd*, *J*=10.8, 6.4, 1 H of CH₂(Fm)); 4.24 (*t*-like, $J \approx 6.0$, CH(Fm)); 3.68–3.63 (*m*, CH₂(δ)(Pro)); 2.94 (*sept.*, *J*=6.6, Me₂CH); 2.17–2.07, 1.96–1.73 (2*m*, CH₂(β)(Pro), CH₂(γ)(Pro)); 1.21, 1.11 (2*d*, *J*=6.5, 2 Me). ¹³C-NMR (CDCl₃, 75 MHz): 209.7 (*s*, CS); 170.5 (*s*, CO); 144.0, 143.6, 141.4, 141.4 (4*s*, 4 arom. C); 127.8, 127.2, 125.2, 125.0, 119.9 (5*d*, 8 arom. H); 66.2 (*t*, CH₂(Fm)); 65.3 (*d*, CH(*a*)(Pro)); 50.1 (*t*, CH₂(δ)(Pro)); 47.1 (*d*, CH(Fm)); 3.87 (*d*, Me₂CH); 28.7, 24.5 (2*t*, CH₂(β)(Pro), CH₂(γ)(Pro)); 22.6, 22.4 (2*q*, 2 Me). ESI-MS (MeOH): 402 (100, [*M*+Na]⁺).

2-[(4-Nitrophenyl)sulfonyl]ethyl N-(2-Methyl-1-thioxopropyl)-L-prolinate (**8b**). A suspension of Lawesson reagent (dried *i.v.*, 374 mg, 0.925 mmol) and **7b** (662 mg, 1.662 mmol) in toluene (20 ml) was heated at 90° (oil bath) for 1 h. After cooling to r.t., the mixture was filtered, and the solvent was evaporated. CC (SiO₂; CH₂Cl₂/MeOH 70 : 1) yielded **8b** (509 mg, 74%). Yellow powder. M.p. 174.1–176.3°. IR: 3470w, 3109w, 3062w, 3033w, 2966s, 2924s, 2887m, 2864w, 1742vs, 1606m, 1524vs, 1475vs, 1458vs, 1402m, 1377s, 1350vs, 1327vs, 1303vs, 1264s, 1253s, 1226s, 1196vs, 1174vs, 1152vs, 1124s, 1106m, 1086s, 1070s, 1013s, 999m, 977m, 921w, 881w, 851s, 828w, 789w, 756vs, 738vs, 702vs. ¹H-NMR (300 MHz; conformers 95:5): 8.47–8.41, 8.20–8.14 (2m, 4 arom. H); 4.77–4.73 (m, CH(α)(Pro)); 4.61–4.44 (m, CH₂CH₂O); 4.13–3.85, 3.78–3.69 (2m, CH₂(δ)(Pro)); 3.63–3.46 (m, CH₂CH₂O); 3.02 (*sept.*, *J*=6.6, Me₂CH); 2.24–1.98 (m, CH₂(β)(Pro), CH₂(γ)(Pro)); 1.21, 1.21 (2d, *J*=6.5, 2 Me). ¹³C-NMR (75 MHz): 209.9 (*s*, CS); 169.8 (*s*, CO); 151.0, 144.8 (2s, 2 arom. C); 129.9, 124.6 (2d, 4 arom. CH); 65.0 (d, CH(α)(Pro)); 57.6 (*t*, CH₂CH₂O); 55.1 (*t*, CH₂CH₂O); 50.3 (*t*, CH₂(δ)(Pro)); 38.7 (*d*, Me₂CH); 28.5, 24.8 (2*t*, CH₂(β)(Pro), CH₂(γ)(Pro)); 22.7, 22.4 (2q, 2 Me). ESI-MS (MeOH, NaI): 437 (100, [*M*+Na]⁺), 206 (25).

2-[(4-Nitrophenyl)sulfanyl]ethyl N-(2-Methyl-1-thioxopropyl)-L-prolinate (8c). A suspension of Lawesson reagent (dried *i.v.*, 473 mg, 1.170 mmol) and 7c (773 mg, 2.110 mmol) in toluene (20 ml) was heated at 90° (oil bath) for 1 h. After cooling to r.t., the mixture was filtered, and the solvent was evaporated. CC (SiO₂; CH₂Cl₂/MeOH 300 : 1 → 100 : 1) yielded 8c (599 mg, 74%). Yellow oil. IR (film): 3098w, 3067w, 2971vs, 2929s, 2878s, 1743vs, 1594vs, 1578vs, 1513vs, 1479vs, 1462vs, 1441vs, 1381vs, 1338vs, 1300s, 1268vs, 1257vs, 1227vs, 1188vs, 1166vs, 1125s, 1090vs, 1049m, 1016vs, 970s, 922w, 912w, 877w, 853vs, 841s, 779w, 742vs. ¹H-NMR (300 MHz; conformers 93 : 7): 8.16-8.13, 7.45-7.41 (2m, 4 arom. H); 5.05-5.01 (m, CH(a)(Pro)); 4.41-4.30 (m, CH₂CH₂O); 3.91-3.89, 3.82-3.76 (2m, CH₂(δ)(Pro)); 3.31 (t, J=7.1, CH₂CH₂O); 3.06 (*sept.*, J=6.6, Me₂CH); 2.29-2.07 (m, CH₂(β)(Pro), CH₂(γ)(Pro)); 1.25, 1.25 (2d, J=6.6, 2 Me). ¹³C-NMR (75 MHz): 210.1 (*s*, CS); 170.5 (*s*, CO); 146.1, 145.6 (2s, 2 arom. C); 126.8, 124.3 (2d, 4 arom. CH); 65.4 (d, CH(a)(Pro)); 62.8 (t, CH₂CH₂O); 50.5 (t, CH₂(δ)(Pro)); 3.89 (d, Me₂CH); 30.3 (t, CH₂CH₂O); 29.0, 25.0 (2t, CH₂(β)(Pro), CH₂(γ)(Pro)); 22.9, 22.5 (2q, 2 Me). ESI-MS (MeOH, NaI): 405 (100, [M+Na]⁺).

6. X-Ray Crystal-Structure Determination of **11a** (Table and Fig.)⁴). A crystal of $C_{24}H_{26}N_2O_4S$, obtained from CDCl₃/Et₂O, was used for a low-temp. X-ray crystal-structure determination. All measure-

⁴) CCDC-602724 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Center via* http://www.ccdc.cam. ac.uk/data_request/cif.

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Table. Crystallographic Data for Compound 11a

Crystallized from	CDCl ₃ /Et ₂ O
Empirical formula	$C_{24}H_{26}N_2O_4S$
Formula weight $[g mol^{-1}]$	438.54
Crystal color, habit	colorless, needle
Crystal dimensions [mm]	$0.08 \times 0.10 \times 0.30$
Temp. [K]	160(1)
Crystal system	monoclinic
Space group	$P2_1$
Z	2
Reflections for cell determination	30655
2θ Range for cell determination [°]	4-55
Unit cell parameters a [Å]	9.2417(3)
<i>b</i> [Å]	11.1230(4)
<i>c</i> [Å]	11.4726(4)
β [°]	110.418(2)
V [Å ³]	1105.24(7)
D_x [g cm ⁻³]	1.318
$\mu(MoK_a) [mm^{-1}]$	0.180
Scan type	ϕ and ω
$2 heta_{(\max)}$ [°]	55
Transmission factors (min; max)	0.799; 0.994
Total reflections measured	24199
Symmetry independent reflections	5044
Reflections with $I > 2\sigma(I)$	4212
Reflections used in refinement	5044
Parameters refined; restraints	287; 1
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0391
$wR(F^2)$ (all data)	0.0862
Weights: $w = [\sigma^2 (F_0^2 \sigma^2) + (0.0369P)^2 + 0.2109P]^{-1}$ where $P = (F_0^2 + 2F_c^2)/3$	
Goodness-of-fit	1.030
Final Δ_{\max}/σ	0.001
$\Delta \rho$ (max; min) [e Å ⁻³]	0.19; -0.22

ments were conducted on a Nonius KappaCCD area-detector diffractometer [33] using graphite-monochromated MoK_a radiation (λ 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. The data collection and refinement parameters are given in the Table, and a view of the molecule is shown in the Figure. Data reduction was performed with HKL Denzo and Scalepack [34]. The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method [35] was applied. Equivalent reflections, other than Friedel pairs, were merged. The structure was solved by direct methods using SIR92 [36], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The amide H-atom was placed in the position indicated by a difference electron density map, and its position was allowed to refine together with an isotropic displacement parameter. All remaining H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom (1.5 U_{eq} for the Me groups). Refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w (F_o^2 - F_c^2)^2$. A correction for secondary extinction was applied. Refinement of the absolute structure parameter [37] yielded a value of -0.08(6), which confidently confirms that the refined coordinates represent the true enantiomorph. Neutral atom scattering factors for non-H atoms were taken from [38a], and the scattering factors

for H-atoms were taken from [39]. Anomalous dispersion effects were included in F_c [40]; the values for f' and f'' were those of [38b]. The values of the mass attenuation coefficients are those of [38c]. All calculations were performed using the SHELXL97 [41] program.

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