A New 2*H*-Azirin-3-amine as a Synthon for α-Methyl Glutamate

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Dedicated to Professor *Peter Stanetty* on the occasion of his 60th birthday

The synthesis of a novel 2,2-disubstituted 2*H*-azirin-3-amine **10** as a building block for racemic Glu(2Me) is described. This synthon contains an ester group in the side chain. The reaction of **10** with thiobenzoic *S*-acid and the amino acid Z-Val-OH yielded the racemic monothiodiamide **17** and the dipeptide **18** as a mixture of diastereoisomers, respectively (*Scheme 2*). From **18**, each of the protecting groups was removed selectively (*Scheme 3*).

1. Introduction. – In the last few years, we have shown that 2*H*-azirin-3-amines ('3-amino-2*H*-azirines') are versatile synthons for 2,2-disubstituted glycines (α,α-disubstituted α-amino acids) in peptide synthesis. A useful method for the introduction of such amino acids into peptides is the so-called 'azirine/oxazolone method' [1], which proved to be a convenient preparative access to such peptides. This strategy has been extensively applied in the synthesis of linear oligopeptides [2–8], endothiopeptides [9–13], conformationally restricted cyclic peptides [14–17], and cyclic depsipeptides [17–26] containing 2,2-disubstituted glycines.

Recently, enantiomerically pure 2*H*-azirin-3-amines became available, such as the isovaline (Iva) synthons **1** and **2** [4][27], the Val(2Me), Leu(2Me), and the Ala(2cPent) synthons **3**, **4**, and **5** [27], the Phe(2Me) synthons **6** and **7** [27][28], as well as the synthons for Tyr(2Me) **8** and Dopa(2Me) **9** [29]. The latter two contain protected phenolic hydroxy groups, and are the first examples of enantiomerically pure building blocks with a functionalized side chain. All of these building blocks can be used for the synthesis of stereochemically pure peptides.

In the present paper, we describe the synthesis of a novel building block **10** for Glu(2Me), which contains an ester group as a new functional group in the side chain, and its applicability in the synthesis of model peptides. This racemic synthon is a first step towards the expansion of our library of enantiomerically pure 2*H*-azirin-3-amines.

2. Results.- – 2.1. *Synthesis of the 2*H-*Azirine* **10**. The 2*H*-azirin-3-amine **10**, *i.e.*, a synthon for 2-methylglutamate (Glu(2Me)), was prepared in gram quantity according to *Scheme 1*.

The synthesis started from freshly distilled 3,4,5,6-tetrahydro-2*H*-pyran-2-one (**11**), which is commercially available. Methylation of **11** in α-position to the C=O group by deprotonation with lithium diisopropylamide (LDA), followed by treatment with MeI, yielded **12**. Instead of hexamethylphosphoric triamide (HMPA), 1,3-dimethylimida-

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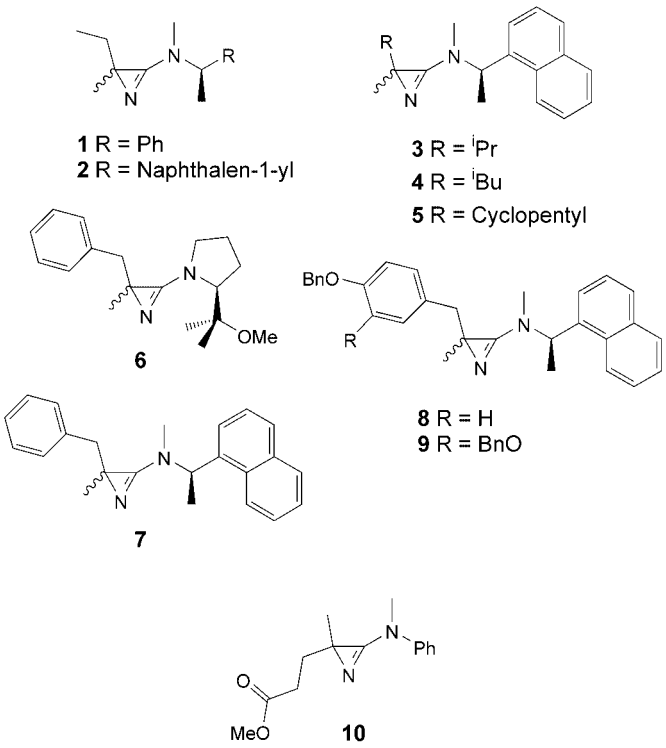


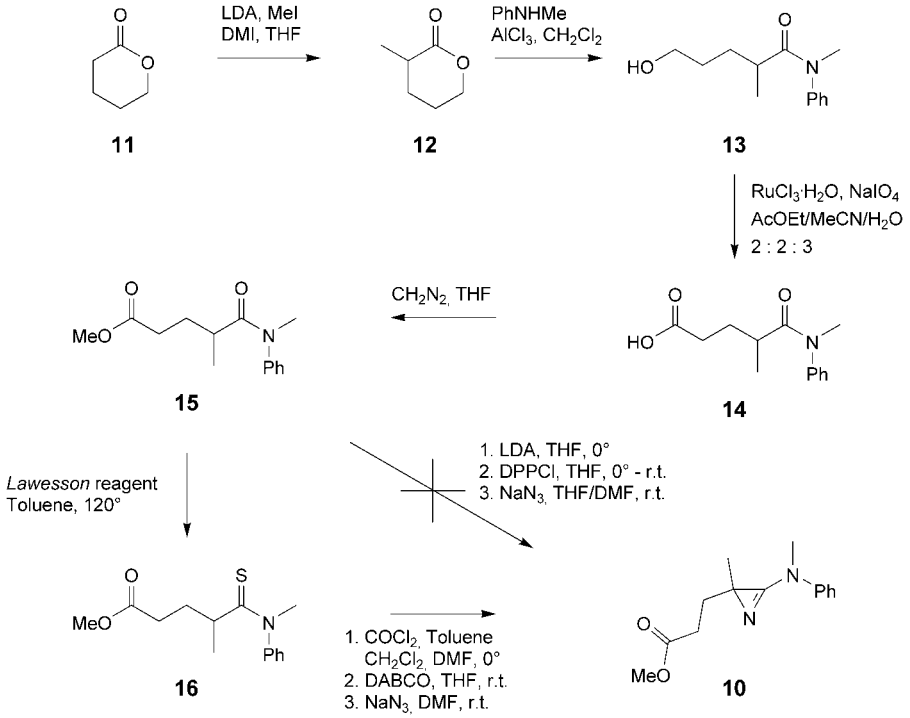
zolidin-2-one (DMI), which is of lower toxicological risk, was used as an additive [30]. Although *Li et al.* used lithiumhexamethyldisilazanide as a base for similar reactions [30], we preferred LDA in combination with DMI. Therefore, the yield (44%) was lower than reported (70%) [31].

Hydroxy amide **13** was synthesized directly from **12** by the reaction with *N*-methylaniline in the presence of $AlCl_3$ at room temperature. Due to its carcinogenic properties, the recommended solvent, 1,2-dichlorethane [32], was replaced with CH_2Cl_2. The yield in CH_2Cl_2 (81%) is only slightly lower than in 1,2-dichlorethane (88%).

In the next step, the OH group of **13** was oxidized with ruthenium trichloride hydrate ($RuCl_3 \cdot H_2O$) and sodium metaperiodate ($NaIO_4$) to form the carboxylic acid **14**. This method, in which ruthenium tetroxide (RuO_4) is the active species [33], has the advantage that $RuCl_3 \cdot H_2O$ can be used in catalytic amounts, and the stochiometric oxidazing agent is $NaIO_4$. The task of $NaIO_4$ is to re-oxidize the reduced forms of the Ru complex to RuO_4. As a solvent, a mixture of CCl_4, MeCN, and H_2O in the ratio 2 : 2 : 3 was used [34] in a first attempt. As CCl_4 is toxic and ecologically undesirable, it was replaced with the same quantity of AcOEt [35]. As a result, the yield turned out to be lower (73%) than with CCl_4 (84%).

Methylation of **14** with CH_2N_2 gave the ester **15** in quantitative yield. The synthesis of **10** by the method of *Villalgordo* and *Heimgartner* [36][37] was unsuccessful, even though **15** is an *N*-alkyl-*N*-phenyl amide (*Scheme 1*). It is assumed that deprotonation

Scheme 1



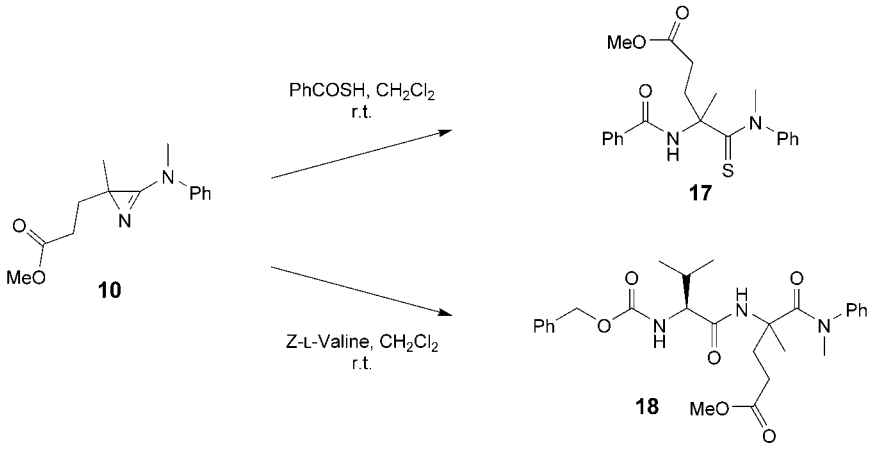
LDA = Lithium diisopropylamide; DMI = 1,3-dimethylimidazolidin-2-one;
DPPCl = diphenylphosphorochloridate; DABCO = 1,4-diazabicyclo[2.2.2]octane

occurred in α-position to the ester group instead of the α-position to the amide group. According to another well-established method, the amide **15** was first converted to the corresponding thioamide **16** with *Lawesson* reagent in toluene at 130° in 93% yield. Finally, the synthesis of **10** was achieved by consecutive treatment of **16** with 2N $COCl_2$ solution in CH_2Cl_2, deprotonation with 1,4-diazabicyclo[2.2.2]octane (DABCO) in THF, and treatment with NaN_3 in THF/DMF, in 90% yield.

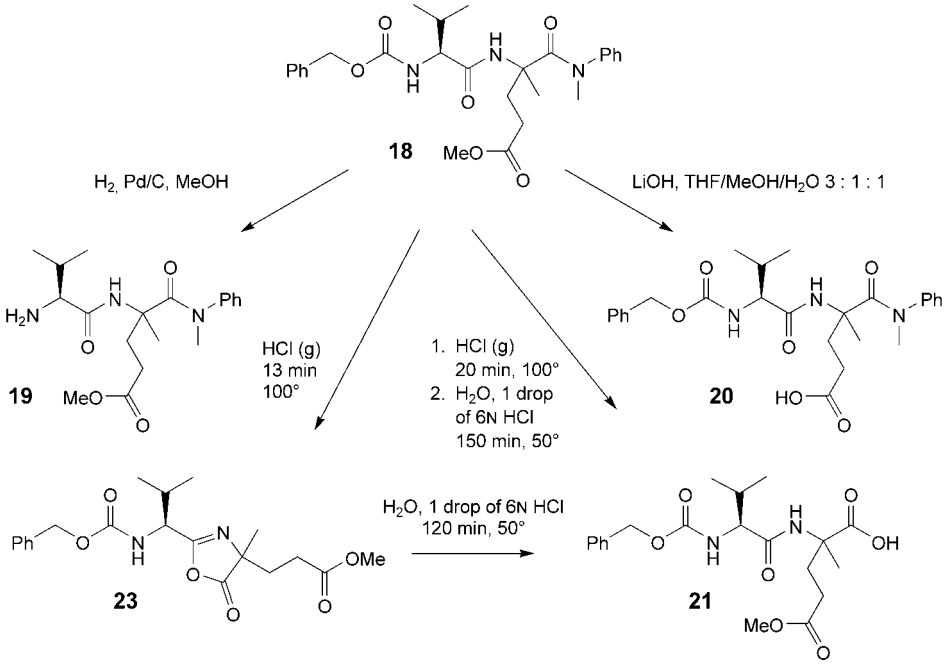
2.2. *Reactions of* **10** *with PhCOSH and Z-*L*-Valine.* To demonstrate that the new amino acid synthon **10** shows analogous chemical behavior as the already known 2*H*-azirin-3-amines (*cf.* [1]), it was reacted with PhCOSH [27–29][38][39] (*cf.* [11][12]) to give the monothiodiamide **17** in 99% yield (*Scheme 2*). The use of **10** as a synthon in peptide synthesis was shown by the reaction with Z-L-valine (*Scheme 2*), which led to the dipeptideamide **18** in 96% yield as a mixture of diastereoisomers. All attempts to separate the diastereoisomers failed.

2.3. *Selective Cleavage of the Protecting Groups in Dipeptide* **18**. With the aim of proving the usefulness of the described coupling reaction, each of the protecting groups of the dipeptide **18** was removed selectively under standard or slightly modified conditions (*Scheme 3*). For example, the Z group was removed by hydrogenolysis to give the *N*-deprotected dipeptide **19** in quantitative yield.

Scheme 2



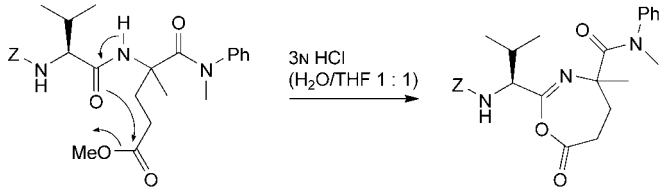
Scheme 3



Hydrolysis of the C-terminal amide group of **18** under standard conditions (3N HCl in THF/H_2O 1:1) afforded a mixture of starting material (40%), and the dipeptides **20** (27%) and **21** (14%) with a deprotected carboxy group in the side chain and main chain, respectively. As the cleavage of the methyl ester in the side chain occurs so easily, it was assumed that the reaction follows the mechanism presented in *Scheme 4:* under

the reaction conditions, the tetrahydro-1,3-oxazepin-7-one **22** could be formed instead of the oxazolone **23**. Opening of the ring of **22** with H_2O to form **20** is expected to proceed smoothly.

Scheme 4



18 **22**

Another possibility for the hydrolysis of dipeptide amides is the treatment with HCl gas in toluene, followed by hydrolysis with H_2O. Thereby, the oxazolone **23** is formed as an intermediate (*Scheme 3*). After treatment of **18** with HCl gas for 13 min in toluene at 100°, oxazolone **23** was isolated in 71% yield after CC. In addition, 22% of starting material **18** was recovered, but no acid **21** was obtained. The oxazolone **23** was not hydrolized by stirring in H_2O at room temperature overnight. Only after addition of one drop of 6N HCl and stirring at 50° for several hours, was the acid **21** obtained in 71% yield. The direct conversion of **18** to **21**, without purification of the intermediate oxazolone, gave the acid **21** in an overall yield of 70%, and 15% of the starting material **18** and 12% of the oxazolone **23** were isolated from the reaction mixture.

Finally, the selective hydrolysis of the methyl ester in **18** was achieved under standard conditions with LiOH in THF/MeOH/H_2O 3:1:1 in quantitative yield (*Scheme 3*).

3. Conclusions. – The novel racemic 2,2-disubstituted 2*H*-azirin-3-amine **10** was prepared. This new synthon for α-methylglutamate was successfully reacted with Z-protected valine and thereby incorporated into a model dipeptide. Each protecting group could be removed selectively in good-to-excellent yield. Therefore, this synthon can easily be used in peptide synthesis as a building block for Glu(2Me). The synthesis of this racemic synthon is a first step towards the corresponding enantiomerically pure 2*H*-azirin-3-amine.

We thank the analytical departments of our institute for NMR and mass spectra, and for elemental analyses. Financial support of the *Swiss National Science Foundation*, *F. Hoffmann-La Roche AG*, Basel, the *Stiftung für wissenschaftliche Forschung an der Universität Zürich*, and the *Prof. Dr. Hans E. Schmid-Stiftung* is gratefully acknowledged.

Experimental Part

1. *General.* See [27]. IR Spectra: *Perkin-Elmer* spectrometer. ^{1}H- (600 MHz) and ^{13}C-NMR (150.9 MHz) spectra: *Bruker AMX-600* instrument.

2. *Preparation of the α-Methylglutamate Synthon* **10**. 2.1. *3,4,5,6-Tetrahydro-3-methylpyran-2(2*H*)-one* (**12**). A soln. of (i-Pr)$_2$NH (15 ml, 106 mmol) in abs. THF (40 ml) was cooled to 0°; 1.6M BuLi in hexane (67 ml, 107 mmol) was added, and the mixture was stirred for 30 min, cooled to −65°, and freshly distilled *3,4,5,6-tetrahydro-2*H*-pyran-2-one* (**11**; 10.060 g, 100 mmol) was added at −65° to −60°. After stirring for 1 h, 1,3-

dimethylimidazolidin-2-one (DMI; 14 ml, 129 mmol) was added at −65°, the mixture was stirred for 20 min, and MeI (7 ml, 112 mmol) was added at −65°. After further stirring for 4 h at −65°, the reaction was terminated by addition of a very small amount of H_2O and AcOH. The org. layer was separated, and the aq. layer was extracted with AcOEt. The combined org. layers were dried (Na_2SO_4) and evaporated. CC (hexane/AcOEt 3:2) yielded 4.098 g (44%) of **12**. Colorless oil. R_f (hexane/AcOEt 3:2) 0.43. IR (neat): 2939*m*, 1738*s*, 1462*m*, 1380*m*, 1243*m*, 1156*m*, 1117*m*, 1085*m*, 1029*m*, 1014*m*, 944*w*, 905*w*, 752*w*. ^{1}H-NMR: 4.40–4.25 (*m*, CH_2O); 2.65–2.55 (*m*, MeC*H*); 2.2–2.05 (*m*, 1 H of MeCHCH_2); 1.95–1.85 (*m*, CH_2); 1.6–1.5 (*m*, 1 H of MeCHCH_2); 1.24 (*d*, *J* = 6.9, Me). ^{13}C-NMR: 175.2 (*s*, CO); 68.3 (*t*, CH_2O); 34.2 (*d*, CH); 26.7, 21.7 (2*t*, 2 CH_2); 16.3 (*q*, Me).

2.2. *5-Hydroxy-2,*N-*dimethyl*-N-*phenylpentanamide* (**13**). 2.2.1. *Procedure 1*. To a soln. of $AlCl_3$ (1.124 g, 8.43 mmol, 2 equiv.) in 1,2-dichlorethane (3 ml), *N*-methylaniline (1.75 ml, 16.1 mmol, 3.8 equiv.) was added at 15–25° (temp. control with ice bath). Thereby, the soln. turned black. Then, compound **12** (0.483 g, 4.23 mmol) in 3 ml of 1,2-dichlorethane was added at 15–25°, and the mixture was stirred for 5 h. To the grey-brown suspension, 5 ml of H_2O was added, and the mixture was stirred for 30 min. The org. layer was separated, and the aq. layer was extracted with 1,2-dichlorethane and twice with CH_2Cl_2. The combined org. layers were dried ($MgSO_4$) and evaporated. CC (hexane/AcOEt 1:1 to AcOEt) yielded 0.822 g (88%) of **13**. Slightly brown solid.

2.2.2. *Procedure 2*. To a soln. of $AlCl_3$ (1.134 g, 8.5 mmol, 2 equiv.) in CH_2Cl_2 (3 ml), *N*-methylaniline (1.75 ml, 16.1 mmol, 3.8 equiv.) was added slowly at 15–25° (temp. control with ice bath). Thereby, the soln. turned black. Compound **12** (0.489 g, 4.28 mmol) was added at 15–25°, and the mixture was stirred for 5 h. To the grey-brown suspension, 5 ml of H_2O was added, and the mixture was stirred for 30 min and passed through *Celite*. The layers were separated, and the aq. layer was extracted twice with CH_2Cl_2. The combined org. layers were dried ($MgSO_4$) and evaporated. CC (hexane/AcOEt 1:1 to AcOEt) yielded 0.785 g (81%) of **13**. Slightly brown solid. M.p. 68.9–69.5°. R_f (CH_2Cl_2/MeOH 30:1) 0.29–0.16. IR (KBr): 3383*s*, 2971*m*, 2946*m*, 2923*m*, 2864*m*, 1637*s*, 1594*s*, 1495*m*, 1465*m*, 1432*m*, 1391*m*, 1370*w*, 1331*w*, 1274*m*, 1227*w*, 1176*w*, 1116*m*, 1067*m*, 1024*w*, 986*w*, 954*w*, 909*w*, 775*m*, 701*s*. ^{1}H-NMR: 7.45–7.3 (*m*, 3 H_m, H_p); 7.2–7.15 (*m*, 2 H_o); 3.55–3.5 (*m*, CH_2OH); 3.26 (*s*, MeN); 2.45–2.35 (*m*, CH); 1.8–1.7 (*m*, 1 H of CH_2); 1.5–1.4 (*m*, CH_2); 1.4–1.3 (*m*, 1 H of CH_2); 1.04 (*d*, *J* = 6.7, Me). ^{13}C-NMR: 176.7 (*s*, CO); 144.0 (*s*, 1 arom. C); 129.7 (*d*, 2 C_m); 127.7 (*d*, 1 C_p); 127.3 (*d*, 2 C_o); 62.4 (*t*, CH_2OH); 37.3 (*q*, MeN); 36.2 (*d*, CH); 30.6, 30.3 (2*t*, 2 CH_2); 18.3 (*q*, Me). CI-MS (NH_3): 223 (15), 222 (100, $[M+1]^+$), 220 (15), 204 (7, $[M-OH]^+$). Anal. calc. for $C_{13}H_{19}NO_2$ (221.30): C 70.56, H 8.65, N 6.33; found: C 70.38, H 8.67, N 6.27.

2.3. *4-Methyl-5-[methyl(phenyl)amino]-5-oxopentanoic acid* (**14**). Compound **13** (3.21 g, 14.5 mmol) and 12.71 g (59.4 mmol, 4.1 equiv.) of $NaIO_4$ were solved in a mixture of 24 ml of MeCN, 24 ml of AcOEt, and 36 ml of H_2O. A small amount of $RuCl_3 \cdot H_2O$ was added at r.t. After 4 h, the color of the suspension changed from light yellow to brown, which indicated the end of the conversion. H_2O was added, and the aq. layer was extracted with AcOEt. The org. layers were combined, dried (Na_2SO_4), and evaporated. Recrystallization from AcOEt/hexane 1:1 yielded 2.48 (73%) of **14**. Colorless crystals. M.p. 116.1–116.7°. R_f (CH_2Cl_2/MeOH 10:1) 0.34. IR (KBr): 3445*w*, 2961*m*, 1729*s*, 1611*s*, 1586*s*, 1497*m*, 1466*m*, 1454*m*, 1401*m*, 1333*w*, 1316*w*, 1274*m*, 1260*m*, 1193*s*, 1169*m*, 1115*m*, 1095*w*, 1073*w*, 1046*w*, 1027*w*, 1002*w*, 976*w*, 912*w*, 866*w*, 796*w*, 779*m*, 754*w*, 716*w*, 703*m*. ^{1}H-NMR: 7.45–7.3 (*m*, 2 H_m, H_p); 7.2–7.15 (*m*, 2 H_o); 3.26 (*s*, MeN); 2.5–2.45 (*m*, MeC*H*); 2.35–2.2 (*m*, CH_2); 2.0–1.9 (*m*, 1 H of CH_2); 1.7–1.6 (*m*, 1 H of CH_2); 1.05 (*d*, *J* = 6.8, Me). ^{13}C-NMR: 178.2 (*s*, COO); 175.9 (*s*, CON); 143.7 (*s*, 1 arom. C); 129.7 (*d*, 2 C_m); 127.8 (*d*, 1 C_p); 127.2 (*d*, 2 C_o); 37.4 (*q*, MeN); 35.6 (*d*, CH); 31.5, 28.8 (2*t*, 2 CH_2); 17.9 (*q*, Me). CI-MS (NH_3): 237 (15), 236 (100, $[M+1]^+$). Anal. calc. for $C_{13}H_{17}NO_3$ (235.28): C 66.36, H 7.28, N 5.95; found: C 66.44, H 7.16, N 5.87.

2.4. *Methyl 4-Methyl-5-[methyl(phenyl)amino]-5-oxopentanoate* (**15**). To a soln. of **14** (2.506 g, 10.65 mmol) in abs. THF (25 ml), 40 ml of a *ca.* 4N soln. of CH_2N_2 in Et_2O (prepared according to [40]) were added at 0°, the mixture was stirred until the yellow color disappeared. After 40 min, additional CH_2N_2 soln. (10 ml) was added, and the mixture remained yellow. The ice bath was removed, and the mixture was stirred at r.t., until the yellow color disappeared again. After addition of another 4 ml of the CH_2N_2 soln., the yellow color remained at r.t. for at least 90 min. Then, the excess of CH_2N_2 was destroyed with AcOH, the solvent was evaporated, and the product was dried in high vacuum: 2.696 g (quant.) of **15**. Colorless oil. The product was used for the next step without further purification. R_f (hexane/AcOEt 2:1) 0.31. IR (neat): 2953*s*, 1738*s*, 1653*s*, 1596*s*, 1497*s*, 1436*s*, 1390*s*, 1327*s*, 1268*s*, 1170*s*, 1116*s*, 1074*m*, 1035*m*, 1002*m*, 987*m*, 918*w*, 897*w*, 842*w*, 800*w*, 776*m*, 752*m*, 703*s*. ^{1}H-NMR: 7.45–7.35 (*m*, 2 H_m, H_p); 7.2–7.15 (*m*, 2 H_o); 3.59 (*s*, MeO); 3.26 (*s*, MeN); 2.5–2.4 (*m*, CH); 2.35–2.15 (*m*, CH_2); 2.0–1.9 (*m*, 1 H of CH_2); 1.7–1.6 (*m*, 1 H of CH_2); 1.04 (*d*, *J* = 6.7, Me). ^{13}C-NMR: 175.9 (*s*, CON); 173.4 (*s*, COOMe); 143.8 (*s*, 1 arom. C); 129.7 (*d*, 2 C_m); 127.7 (*d*, 1 C_p); 127.2 (*d*, 2 C_o); 51.2 (*q*, MeO); 37.3 (*q*, MeN); 35.6 (*d*, CH); 31.6, 29.1 (2*t*, 2 CH_2); 17.9 (*q*, Me). CI-MS (NH_3):

251 (15), 250 (100, $[M+1]^+$). Anal. calc. for $C_{14}H_{19}NO_3$ (249.31): C 67.45, H 7.68, N 5.62; found: C 67.22, H 7.93, N 5.54.

2.5. *Methyl 4-Methyl-5-[methyl(phenyl)amino]-5-thioxopentanoate* (**16**). To a soln. of **15** (2.599 g, 10.43 mmol) in toluene (10 ml), *Lawesson* reagent (2.57 g, 6.35 mmol, 1.2 equiv.) was added, and the mixture was stirred for 30 min at 130°. The excess of *Lawesson* reagent was precipitated with Et_2O, the precipitate was filtered over *Celite*, and the filtrate was evaporated. CC (hexane/AcOEt 4:1) yielded 2.564 g (93%) of **16**. Pale brown oil. R_f (hexane/AcOEt 4:1) 0.18. IR (neat): 2969*m*, 2930*m*, 2868*w*, 1737*s*, 1595*m*, 1493*s*, 1444*s*, 1385*s*, 1332*m*, 1269*m*, 1198*s*, 1112*m*, 1074*w*, 1037*m*, 1002*m*, 919*w*, 877*w*, 853*w*, 834*w*, 774*m*, 702*s*. ^{1}H-NMR: 7.5–7.35 (*m*, 2 H_m, H_p); 7.15–7.1 (*m*, 2 H_o): 3.71, 3.58 (2*s*, MeO, MeN); 2.8–2.7 (*m*, CH); 2.3–2.1 (*m*, 3 H of 2 CH_2); 1.8–1.55 (*m*, 1 H of 2 CH_2); 1.32 (*d*, $J=6.6$, Me). ^{13}C-NMR: 210.6 (*s*, CS); 173.3 (s, CO); 145.4 (*s*, 1 arom. C); 129.9, 128.4, 125.6 (3*d*, 5 arom. CH); 51.3 (*q*, MeO); 45.5 (*q*, MeN); 42.8 (*d*, CH); 32.7, 31.7 (2*t*, 2 CH_2); 22.0 (*q*, Me). CI-MS (NH_3): 268 (6), 267 (16), 266 (100, $[M+1]^+$). Anal. calc. for $C_{14}H_{19}NO_2S$ (265.37): C 63.36, H 7.22, N 5.28, S 12.08; found: C 63.34, H 7.20, N 5.28, S 12.11.

2.6. *Methyl 3-(3-Amino-2,*N*-dimethyl-*N*-phenyl-2*H*-azirin-2-yl)propanoate* (**10**). To a soln. of **16** (2.558 g, 9.64 mmol) and 5 drops of abs. DMF in abs. CH_2Cl_2 (12 ml) at 0°, 2N phosgene in toluene (6.5 ml, *ca.* 13 mmol, 1.3 equiv.) was added slowly, the ice bath was removed, the mixture stirred for 25 min, and the solvent evaporated. The residue was dissolved in abs. THF (12 ml), DABCO (1.096 g, 9.77 mmol) was added, and the soln. was stirred for 25 min at r.t. After filtration and addition of abs. DMF (12 ml), NaN_3 (1.256 g, 19.32 mmol, 2 equiv.) was added, the mixture was stirred for 3 d at r.t. and then filtered over *Celite*, and the filtrate was evaporated. CC (hexane/AcOEt 2:1) yielded 2.143 g (90%) of **10** as a yellow oil. In the ^{1}H- and ^{13}C-NMR spectra at 270 and 280 K, doubling of signals was observed, which almost disappeared at 300 K, and showed EXSY cross-peaks. Therefore, it is assumed that two conformers are detected at r.t. They were analyzed by HSQC and HMBC experiments at 270K. R_f (hexane/AcOEt 2:1) 0.10. IR (neat): 2950*w*, 2920*w*, 1749*s*, 1656*w*, 1600*s*, 1502*s*, 1438*m*, 1375*w*, 1347*w*, 1319*w*, 1300*m*, 1286*m*, 1228*m*, 1198*m*, 1161*m*, 1112*m*, 1086*w*, 1071*w*, 1035*w*, 987*w*, 894*w*, 841*w*, 756*m*. ^{1}H-NMR (600 MHz, 270 K): 7.60 (*d*, $J=8.1$, 2 H_o, minor conformer); 7.45–7.4 (*m*, 2 H_m); 7.2–7.1 (*m*, 1 H_p); 7.05 (*d*, $J=7.9$, 1 H_o, major conformer); 3.54 (*s*, MeO, minor conformer); 3.53 (*s*, MeO, major conformer); 3.45 (*s*, MeN, major conformer); 3.43 (*s*, MeN, minor conformer); 2.35–2.3 (*m*, 1 H of CH_2CO, minor conformer); 2.3–2.25 (*m*, 1 H of CH_2CO, minor conformer, 1 H of CH_2CO, major conformer, 1 H of $CH_2C(3)$, major conformer); 2.15–2.1 (*m*, $CH_2C(3)$, minor conformer, 1 H of CH_2CO, major conformer); 2.05–2.0 (*m*, 1 H of $CH_2C(3)$, major conformer); 1.48 (*s*, Me, major conformer); 1.43 (*s*, Me, minor conformer). ^{13}C-NMR (151 MHz, 270 K): 173.9 (*s*, CO, minor conformer); 173.6 (*s*, CO, major conformer); 166.0 (*s*, C(3), major conformer); 164.9 (*s*, C(3), minor conformer); 142.1 (*s*, 1 arom. C, minor conformer); 142.1 (*s*, 1 arom. C, major conformer); 129.6 (*d*, 2 C_m, major conformer); 129.2 (*d*, 2 C_m, minor conformer); 123.2 (*d*, 1 C_p, minor conformer); 123.1 (*d*, 1 C_p, major conformer); 116.7 (*d*, 2 C_o, minor conformer); 115.4 (*d*, 1 C_o, major conformer); 51.6 (*q*, MeO); 45.9 (*s*, C(2), major conformer); 37.7 (*q*, MeN, minor conformer); 37.1 (*s*, C(2), minor conformer); 33.5 (*q*, MeN, major conformer); 32.1 (*d*, $CH_2C(2)$, major conformer); 31.2 (*d*, $CH_2C(2)$, minor conformer); 29.9 (*d*, CH_2CO, major conformer); 29.8 (*d*, CH_2CO, minor conformer); 24.5 (*q*, Me, major conformer); 23.5 (*q*, Me, minor conformer). CI-MS (NH_3): 248 (16), 247 (100, $[M+1]^+$). Anal. calc. for $C_{14}H_{18}N_2O_2$ (246.30): C 68.27, H 7.37, N 11.37; found: C 67.99, H 7.17, N 10.99.

3. *Reactions of the α-Methylglutamate Synthon* **10** *with PhCOSH and Z-*L*-Valine.* 3.1. *With PhCOSH. Methyl 4-Methyl-5-[methyl(phenyl)amino]-4-[(phenylcarbonyl)amino]-5-thioxopentanoate* (**17**). To PhCOSH (110 mg, 0.8 mmol), a soln. of **10** (182 mg, 0.74 mmol) in abs. CH_2Cl_2 (5 ml) was added, and the mixture was stirred for 1 h at r.t. Prep. TLC (hexane/AcOEt 1:1) gave 281 mg (99%) of **17**. Pale yellow crystals. M.p. 133.9–134.9°. R_f (hexane/AcOEt 2:1) 0.18. IR (KBr): 3444*m*, 3246*m*, 3065*m*, 3004*m*, 2956*m*, 2924*m*, 2853*w*, 1732*s*, 1641*s*, 1601*m*, 1578*m*, 1548*s*, 1490*s*, 1463*s*, 1442*m*, 1363*s*, 1330*m*, 1294*s*, 1254*m*, 1219*m*, 1196*m*, 1177*m*, 1093*s*, 1026*w*, 1006*m*, 980*m*, 934*w*, 898*w*, 857*w*, 803*w*, 773*m*, 706*s*. ^{1}H-NMR: 8.78 (br. *s*, NH); 7.8–7.75, 7.5–7.35 (2*m*, 10 arom. H); 3.76, 3.62 (2*s*, MeO, MeN); 2.95–2.9 (*m*, 1 H of 2 CH_2); 2.4–2.35 (*m*, 2 H of 2 CH_2); 2.3–2.2 (*m*, 1 H of 2 CH_2); 1.68 (*s*, Me). ^{13}C-NMR: 206.8 (*s*, CS); 173.8 (*s*, *C*OOMe); 164.6 (*s*, CON); *ca.* 147 (*s*, 1 arom. CN); 135.1 (*s*, 1 arom. C); 131.2, 129.5, 128.6, 128.3, 126.9, 126.5 (6*d*, 10 arom. CH); 65.0 (*s*, C(4)); 51.6 (*q*, MeO); the signal for MeN was not observed; 32.3, 29.3 (2*t*, 2 CH_2); 26.0 (*q*, Me). ESI-MS (MeOH, NaI): 407 (100, $[M+Na]^+$). Anal. calc. for $C_{21}H_{24}N_2O_3S$ (384.49): C 65.60, H 6.29, N 7.29, S 8.34; found: C 65.57, H 6.38, N 6.62, S 8.13.

3.2. *With Z-*L*-Valine. Methyl (*R*S)-4-[((*S*)-2-[[(Benzyloxy)carbonyl]amino]-3-methyl-1-oxobutyl)amino]-4-methyl-5-[methyl(phenyl)amino]-5-oxopentanoate* (**18**). A soln. of **10** (1.03 g, 4.18 mmol) and Z-L-valine (1.11 g, 4.42 mmol) in CH_2Cl_2 (20 ml) was stirred at r.t. for 24 h, and evaporated. CC (CH_2Cl_2/MeOH 50:1) yielded 1.99 g (96%) of **18**. Colorless foam. M.p. 103–104°. R_f (CH_2Cl_2/MeOH 50:1) 0.16. IR (KBr): 3337*m*, 2963*m*, 1733*s*, 1672*s*, 1633*s*, 1594*m*, 1495*s*, 1454*m*, 1371*m*, 1233*m*, 1110*m*, 1026*m*, 774*w*, 703*m*. ^{1}H-NMR: 7.46 (br.

s, NH of Glu(2Me), diastereoisomer B); 7.45–7.25 (*m*, 10 arom. H); 7.16 (br. *s*, NH of Glu(2Me), diastereoisomer A); 5.4–5.3 (*m*, NH of Val); 5.2–5.1 (*m*, PhC*H*$_2$O); 4.0–3.9 (*m*, CH(2) of Val, B); 3.9–3.8 (*m*, CH(2) of Val, A); 3.65 (*s*, MeO, B); 3.64 (*s*, MeO, A); 3.27 (*s*, MeN, B); 3.26 (*s*, MeN, A); 2.7–2.45 (*m*, 1 H of 2 CH$_2$); 2.45–2.15 (*m*, 2 H of 2 CH$_2$); 2.15–2.0 (*m*, CH(3) of Val); 1.95–1.8 (*m*, 1 H of 2 CH$_2$); 1.42 (*s*, Me(3) of Glu(2Me), A); 1.38 (*s*, Me(3) of Glu(2Me), B); 0.95–0.85 (*m*, 2Me(4) of Val). ^{13}C-NMR: 173.4, 171.9, 171.6, 169.2 (4*s*, *C*OOMe, 2 CON); 156.1 (*s*, OCONH); 143.6, 143.4, 136.4 (3*s*, 2 arom. C); 129.5, 128.6, 128.43, 128.37, 128.0, 127.9 (6*d*, 10 arom. CH); 66.8 (*t*, PhC*H*$_2$O); 61.8, 61.5 (2*s*, C(2) of Glu(2Me)); 60.5, 60.2 (2*d*, CH(2) of Val); 51.6, 51.5 (2*q*, MeO); 41.7, 41.6 (2*q*, MeN); 31.5, 30.8, 29.4, 29.2 (4*t*, 2 CH$_2$ of Glu(2Me)); 31.4, 31.3 (2*d*, CH(3) of Val); 23.2, 19.1, 19.0, 17.5, 17.2 (5*q*, Me(3) of Glu(2Me), 2 Me of Val). ESI-MS (MeOH, NaI): 520 (100, $[M+Na]^+$). Anal. calc. for $C_{27}H_{35}N_3O_6$ (497.58): C 65.17, H 7.09, N 8.44; found: C 65.06, H 7.15, N 8.51.

4. *Deprotection of Dipeptide* **18**. 4.1. *Cleavage of the Z Group. Methyl (*RS*)-4-[[(*S*)-2-Amino-3-methyl-1-oxobutyl]amino]-4-methyl-5-[methyl(phenyl)amino]-5-oxopentanoate* (**19**). A soln. of dipeptide **18** (200 mg, 0.402 mmol) and a small amount of Pd/C (10% on activated charcoal) in MeOH (10 ml) was treated with H_2 for 2.5 h at r.t. The mixture was filtered over *Celite*, and the filtrate was evaporated. Prep. TLC (CH_2Cl_2/MeOH 20:1) gave 147 mg (quant.) of **19**. Colorless, highly viscous substance. R_f (CH_2Cl_2/MeOH 10:1) 0.25. IR (neat): 3322*m*, 2959*s*, 2874*m*, 1737*s*, 1638*s*, 1594*m*, 1495*s*, 1452*m*, 1368*m*, 1271*m*, 1222*m*, 1200*s*, 1174*s*, 1110*m*, 1082*w*, 1033*w*, 995*w*, 852*w*, 777*w*, 735*w*, 706*m*. ^{1}H-NMR: 8.15, 7.80 (2 br. *s*, NH of Glu(2Me)); 7.45–7.3 (*m*, 5 arom. H); 3.68, 3.65 (2*s*, MeO); 3.28, 3.26 (2*s*, MeN); 3.11, 3.01 (2*d*, $J=4.1$ and 3.8, CH(2) of Val); 2.7–2.0 (*m*, 2 CH$_2$, CH(3) of Val); 1.95–1.9 (*m*, NH$_2$ of Val); 1.48, 1.39 (2*s*, Me(3) of Glu(2Me)); 0.96, 0.93, 0.83, 0.79 (4*d*, $J=7.0$, 7.0, 6.9, and 6.9, 2 Me(4) of Val). ^{13}C-NMR: 173.5, 173.3, 172.4, 172.2, 171.6 (5*s*, 3 CO); 144.5, 144.1 (2*s*, arom. C); 129.4, 129.3, 128.1, 128.0, 127.8, 127.7 (6*d*, 5 arom. CH); 60.9 (*s*, C(2) of Glu(2Me)); 60.33, 60.25 (2*d*, CH(2) of Val); 51.6, 51.5 (2*q*, MeO); 41.6, 41.5 (2*q*, MeN); 32.9, 31.4 (2*t*, CH$_2$); 30.8 (*d*, CH(3) of Val); 29.4, 29.1 (2*t*, CH$_2$); 23.7, 23.3, 19.5, 19.4, 16.3 (5*q*, Me(3) of Glu(2Me), 2 Me(4) of Val). ESI-MS (MeOH): 749 (23, $[2M+Na]^+$), 727 (40, $[2M+1]^+$), 402 (17, $[M+K]^+$), 386 (100, $[M+Na]^+$), 364 (46, $[M+1]^+$), 257 (24, $[M-N(Me)Ph]^+$).

4.2. *Hydrolysis of the Amide Group.* 4.2.1. *Methyl 3-[(*RS*)-2-((*S*)-1-[[(Benzyloxy)carbonyl]amino]-2-methylpropyl)-4-methyl-5-oxo-1,3-oxazol-4-yl]propanoate* (**23**). A soln. of **18** (301 mg, 0.605 mmol) in toluene (60 ml) was heated to 105°. For 13 min, HCl (g) was bubbled through the mixture. During this procedure, the temp. fell to 90–95°. The remaining HCl (g) was removed by bubbling N_2 through the soln. for 20 min. The mixture was transferred into another flask with hexane, and the crystals of *N*-methylanilide chloride precipitated were filtered (55 mg, 0.39 mmol, 64%), and the resulting soln. was evaporated. CC (hexane/AcOEt 2:1) yielded 182 mg of **23**, which still contained some AcOEt, and 67 mg of starting material **18** (22%). Calculation of the yield based on NMR integrals gave 168 mg **23** (71%) and 14 mg AcOEt. This material was hydrolized to the corresponding acid. For anal. purposes, **23** was dried in high vacuum. R_f (hexane/AcOEt 2:1) 0.17. IR (neat): 3338*m*, 3066*w*, 3035*w*, 2966*s*, 2936*m*, 2877*w*, 1823*s*, 1732*s*, 1673*s*, 1526*s*, 1453*m*, 1375*m*, 1311*s*, 1233*s*, 1177*s*, 1146*m*, 1027*m*, 966*m*, 897*s*, 775*w*, 740*w*, 699*m*. ^{1}H-NMR: 7.35–7.3 (*m*, 5 arom. H); 5.35–5.25 (*m*, NH of Val); 5.15–5.1 (*m*, PhC*H*$_2$O); 4.55–4.45 (*m*, CH(2) of Val); 3.65, 3.63 (2*s*, MeO); 2.4–2.05 (*m*, CH(3) of Val, 2 CH$_2$ of Glu(2Me)); 1.40 (br. *s*, Me(3) of Glu(2Me)); 1.02, 0.98, 0.95 (3*d*, $J=6.8$, 6.9, 6.9, 2 Me(4) of Val). ^{13}C-NMR: 179.5 (*s*, C(5)); 172.3 (*s*, *C*OOMe); 163.0 (*s*, C(2)); *ca.* 156 (*s*, OCONH); 136.0 (*s*, 1 arom. C); 128.4, 128.1, 128.0 (3*d*, 5 arom. CH); 67.6 (*s*, C(4)); 67.1 (*t*, PhC*H*$_2$O); 55.2, 54.7 (2*d*, CH(2) of Val); 51.6 (*q*, MeO); 32.3 (*t*, CH$_2$); 30.7, 30.5 (2*d*, CH(3) of Val); 28.6 (*t*, CH$_2$); 23.5, 23.3, 18.9, 18.8, 17.5, 17.1 (6*q*, Me(3) of Glu(2Me), 2 Me(4) of Val). ESI-MS (MeOH, NaI): 413 (100, $[M+Na]^+$). Anal. calc. for $C_{20}H_{26}N_2O_6$ (390.44): C 61.53, H 6.71, N 7.17; found: C 61.78, H 6.80, N 7.04.

4.2.2. *(*RS*)-2-[[(*S*)-2-[[(Benzyloxy)carbonyl]amino]-3-methyl-1-oxobutyl)amino]-5-methoxy-2-methyl-5-oxopentanoic Acid* (**21**). 4.2.2.1. *Procedure 1. From Oxazolone* **23**. A suspension of 158 mg of crude **23** (containing AcOEt, *i.e.*, 146 mg, 0.374 mmol of **23**) in 2 ml H_2O was stirred for 18 h at r.t., 2 ml of THF were added, and the suspension was stirred for 4 h at r.t. and for 1 h at 50°. As no hydrolysis was observed, one drop of 6N HCl was added. After stirring at 50° for 2 h, the hydrolysis was complete. Brine was added, and the soln. was extracted 3 × with AcOEt. The combined org. layers were dried ($MgSO_4$) and evaporated: 161 mg (quant.) of crude **21**. After Prep. TLC (CH_2Cl_2/MeOH 10:1), 109 mg (71%) of pure **21** were obtained as a colorless foam.

4.2.2.2. *Procedure 2. From Amide* **18**. A soln. of **18** (152 mg, 0.305 mmol) in toluene (30 ml) was heated to 110°. For 20 min, HCl (g) was bubbled through the mixture. During this procedure, the temp. fell to 100–95°. The remaining HCl (g) was removed by bubbling N_2 through the soln. for 20 min. The mixture was transferred into another flask with hexane, and crystals of *N*-methylanilide chloride precipitated were filtered, and the resulting soln. was evaporated. This crude material was solved in 2 ml of THF and 2 ml of H_2O, and 1 drop of 6N HCl was added. After stirring at 50° for 2.5 h, the hydrolysis was complete. Brine was added, and the soln. was extracted 3 × with AcOEt. The combined org. layers were dried ($MgSO_4$), and evaporated. Prep. TLC

(CH_2Cl_2/MeOH 10:1) gave 87 mg (70%) of pure **21**, and a mixture of 23 mg (15%) of starting material **18** and 18 mg (12%) of oxazolone **23** (ratio determined by NMR).

4.2.2.3. *Procedure 3. Under Standard Conditions from Amide* **18**. A soln. of **18** (152 mg, 0.305 mmol) in 3N HCl (THF/H_2O 1:1, 5 ml) was stirred for 1 h at r.t. The mixture was extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated. Prep. TLC (CH_2Cl_2/MeOH 10:1) yielded 81 mg (40%) of starting material **18**, and a mixture of 53 mg (27%) of **20** and 23 mg (14%) of **21** (ratio determined by NMR).

Data of **21**. M.p. 60–62°. ^{1}H-NMR: *ca.* 8.9 (br., COOH); *ca.* 7.4 (br. *s*, NH of Glu(2Me)); 7.35–7.25 (*m*, 5 arom. H); 5.79 (*d*, $J = 8.6$, NH of Val); 5.11 (*s*, PhCH_2O); 4.15–4.1 (*m*, CH(2) of Val); 3.64, 3.62 (2*s*, MeO); 2.55–2.0 (*m*, CH(3) of Val, 2 CH_2 of Glu(2Me)); 1.59 (*s*, Me(3) of Glu(2Me)); 1.0–0.9 (*m*, 2 Me(4) of Val). ^{13}C-NMR: *ca.* 176, *ca.* 174, 171.5 (3*s*, COOH, *C*OOMe, *C*CONH); *ca.* 157 (*s*, OCONH); *ca.* 135 (*s*, 1 arom. C); 128.5, 128.2, 128.0 (3*d*, 5 arom. CH); 67.2 (*t*, Ph*C*H_2O); 60.6 (*d*, CH(2) of Val); 60.0 (*s*, C(2) of Glu(2Me)); 52.0 (*q*, MeO); 31.4 (*t*, 1 CH_2); 31.0 (*d*, CH(3) of Val); 29.3 (*t*, 1 CH_2); 22.9, 19.3, 19.1 (3*q*, Me(3) of Glu(2Me), 2 Me(4) of Val). ESI-MS (MeOH): 447 (8, $[M+K]^+$), 432 (23), 431 (100, $[M+Na]^+$). Anal. calc. for $C_{20}H_{28}N_2O_7 \cdot 0.2\ H_2O$ (412.05): C 58.30, H 6.95, N 6.80; found: C 58.26, H 6.95, N 6.69.

4.3. *Hydrolysis of the Ester Group.* 4.1.1. *(*RS*)-4-[((*S*)-2-{[(Benzyloxy)carbonyl]amino}-3-methyl-1-oxobutyl)amino]-4-methyl-5-[methyl(phenyl)amino]-5-oxopentanoic Acid* (**20**). To a soln. of **20** (213 mg, 0.428 mmol) in 6 ml of a 3:1:1 mixture of THF, MeOH, and H_2O, $LiOH \cdot H_2O$ (54.5 mg, 1.30 mmol, 3 equiv.) was added. The mixture was stirred at r.t. for 2 h, and then neutralized with 6N HCl. The aq. layer was extracted with CH_2Cl_2, and the combined org. layers were washed with 1N HCl, dried ($MgSO_4$), and evaporated: 213 mg (quant.) of **20**. Colorless solid. M.p. 80–81°. R_f (CH_2Cl_2/MeOH 10:1) 0.31. IR (KBr): 3422*s* (br.), 3065*m*, 2965*m*, 2929*m*, 1717*s*, 1633*s*, 1593*m*, 1495*s*, 1455*m*, 1388*m*, 1261*m*, 1236*m*, 1110*m*, 1085*m*, 1028*m*, 801*w*, 774*w*, 738*w*, 701*m*. ^{1}H-NMR: 7.55 (br. *s*, NH of Glu(2Me)); 7.4–7.2 (*m*, 10 arom. H); 5.7–5.6 (*m*, NH of Val); 5.15–5.1 (*m*, PhCH_2O); 3.95–3.85 (*m*, CH(2) of Val); 3.27, 3.24 (2*s*, MeN); 2.7–1.8 (*m*, CH(3) of Val, 2 CH_2 of Glu(2Me)); 1.43, 1.39 (2*s*, Me(3) of Glu(2Me)); 0.95–0.85 (*m*, 2 Me(4) of Val). ^{13}C-NMR: 176.4, *ca.* 172, *ca.* 171, 169.8 (4*s*, COOH, 2 *C*ON); 156.6, 156.5 (2*s*, OCONH); 143.4, 136.2 (2*s*, 2 arom. C); 129.6, 129.4, 128.4, 128.1, 128.0 (5*d*, 10 arom. CH); 67.0 (*t*, Ph*C*H_2O); 61.9, 61.2 (2*s*, C(2) of Glu(2Me)); 60.8, 60.2 (2*d*, CH(2) of Val); 41.7, 41.5 (2*q*, MeN); 31.4, 31.1 (2*d*, CH(3) of Val); 29.4, 28.9 (2*t*, 2 CH_2 of Glu(2Me)); 23.2, 23.1, 19.1, 17.7, 17.5 (5*q*, Me(3) of Glu(2Me), 2 Me(4) of Val). CI-MS (NH_3): 484 (12, $[M+1]^+$), 466 (9, $[M-OH]^+$), 395 (8), 394 (38), 378 (10), 377 (45, $[M-NMePh]^+$), 376 (8), 125 (8), 109 (8), 108 (100, $PhCH_2OH^{+\cdot}$). Anal. calc. for $C_{26}H_{33}N_3O_6 \cdot 0.5\ H_2O$ (501.58): C 63.40, H 6.96, N 8.53; found: C 63.33, H 6.79, N 8.29.

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