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

Hilty, Florentine M; Brun, Kathrin A; Heimgartner, Heinz

Abstract: The synthesis of a novel 2,2-disubstituted 2H-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).

DOI: https://doi.org/10.1002/hlca.200490226

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-79820
Accepted Version

Originally published at:
DOI: https://doi.org/10.1002/hlca.200490226
A New 2H-Azirin-3-amine as a Synthon for α-Methyl Glutamate

by Florentine M. Hilty¹, Kathrin A. Brun, and Heinz Heimgartner*

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich

The synthesis of a novel 2,2-disubstituted 2H-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 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 2H-azirine-3-amines (‘3-amin-2H-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 applied extensively 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, 2H-azirin-3-amines became available that are enantiomerically pure, 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 first examples of enantiomerically pure building blocks with a functionalized side chain. All these building blocks can be used for the synthesis of stereochemically pure peptides.

Formulae 1

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 2H-azirin-3-amines.

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

Scheme 1

The synthesis was started from freshly distilled tetrahydro-2H-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 HMPA, 1,3-dimethylimidazolidin-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 the combination with DMI. Therefore, the yield (44%) was lower than reported (70%) [31].

Hydroxyamide 13 was synthesized directly from 12 by the reaction with N-methylaniline in the presence of AlCl₃ at r.t. Due to its carcinogenic properties, the recommended solvent, 1,2-dichlorethane [32], was replaced by CH₂Cl₂. The yield in CH₂Cl₂ (81%) is only slightly lower than in 1,2-dichlorethane (88%).

In the next step, the hydroxy group of 13 was oxidized with ruthenium trichloride hydrate (RuCl₃·H₂O) and sodium metaperiodate (NaIO₄) to form the carboxylic acid 14. This method, in which ruthenium tetroxide (RuO₄) is the active species [33], has the advantage, that RuCl₃·H₂O can be used in catalytic amounts, and the stochiometric oxidizing agent is NaIO₄. The task of NaIO₄ is to reoxidize the reduced forms of the ruthenium complex to RuO₄. As a solvent, a mixture of CCl₄, MeCN and H₂O in the ratio 2 : 2 : 3 was used [34] in a first attempt. As CCl₄ is toxic and ecologically
undesirable, it was replaced by the same quantity of AcOEt [35]. As a result, the yield turned out to be a bit lower (73%) than with CCl4 (84%).

Methylation of 14 with CH2N2 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 occurred in α-position to the ester group instead of the α-position to the amide group. According to another well established pathway, 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 COCl2 solution in CH2Cl2, deprotonation with 1,4-diazabicyclo[2.2.2]octane (DABCO) in THF, and treatment with NaN3 in THF/DMF, in 90% yield.

2.2. Reactions of 10 with Thiobenzoic Acid and Z-L-Valine. To demonstrate that the new amino-acid synthon 10 shows analogous chemical behavior as the already known 2H-azirin-3-amines (cf. [1]), it was reacted with thiobenzoic acid [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.

Scheme 2

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 3

By using standard conditions for the hydrolysis of the C-terminal amide group (3N HCl in THF/H$_2$O 1 : 1), a mixture of starting material 18 (40%) and the dipeptides 20 (27%) and 21 (14%) with a deprotected carboxyl group in the side chain and main chain, respectively, were obtained. 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, 4H,6H-1,3-oxazepin-7-one 22 could be formed instead of the oxazolone 23. Opening of the ring of 22 with H$_2$O to form 20 is expected to proceed smoothly.

Scheme 4

Another possibility for the hydrolysis of dipeptide amides is the treatment with HCl gas in toluene, followed by hydrolysis with H$_2$O. 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$_2$O at r.t. over night. Only after addition of one drop of 6N HCl and stirring at 50° for several hours, the acid 21 was obtained in 71% yield. The direct conversion of 18 to 21, without purification of the intermediate oxazolone, gave
acid 21 in an overall yield of 70%, and 15% of starting material 18 and 12% of 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/M eOH/H2O (3 : 1 : 1) in quantitative yield (Scheme 3).

3. Conclusions. – The novel racemic 2,2-disubstituted 2H-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 2H-azirin-3-amine.

We thank the analytical sections 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 Spectrum one spectrometer. 1H-NMR (600 MHz) and 13C-NMR (150.9 MHz) Spectra: Bruker AMX-600 instrument.

   2. Preparation of the α-Methylglutamat-Synthon 10. 2.1. 3-Methyloxan-2-one (12). A soln. of diisopropylamine (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 tetrahydro-2H-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°, 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 H2O and AcOH. The org. layer was separated, and the aqueous layer was extracted with AcOEt. The combined org. layers were dried (Na2SO4) and evaporated. CC (hexane/AcOEt 3 : 2) yielded 4.098 g (44%) of 12 as a colorless oil. Rf (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. 1H-NMR: 4.40 – 4.25 (m, CH2O); 2.65 – 2.55 (m, MeCH); 2.2 – 2.05 (m, 1 H of MeCH2H2); 1.95 – 1.85 (m, CH2); 1.6 – 1.5 (m, 1 H of MeCH2H2); 1.24 (d, J = 6.9, Me). 13C-NMR: 175.2 (s, CO); 68.3 (t, CH2O); 34.2 (d, CH); 26.7, 21.7 (2t, 2 CH2); 16.3 (q, Me).

2.2. 5-Hydroxy-N,2-dimethyl-N-phenylpentanamide (13). – 2.2.1. Procedure A. To a soln. of AlCl3 (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° (temperature control with ice bath). Thereby, the soln. turned black. 2-M ethyloxan-2-one (12, 0.483 g, 4.23 mmol) in 3 ml 1,2-dichlorethane was added at 15-25°, and the reaction mixture was stirred for 5 h. To the grey-brown suspension, 5 ml of H2O were added, and the mixture stirred for 30 min. The org. layer was separated, and the aqueous layer was extracted with 1,2-dichlorethane and twice with CH2Cl2. The combined org. layers were dried (MgSO4), and evaporated. CC (hexane/AcOEt 1 : 1 to AcOEt) yielded 0.822 g (88%) of 13. Slightly brown solid.

2.2.2. Procedure B. To a soln. of AlCl3 (1.134 g, 8.5 mmol, 2 equiv.) in CH2Cl2 (3 ml), N-methylaniline (1.75 ml, 16.1 mmol, 3.8 equiv.) was added slowly at 15–25° (temperature control with ice bath). Thereby, the soln. turned black. 2-M ethyloxan-2-
one (12, 0.489 g, 4.28 mmol) was added at 15-25°, and the reaction mixture was stirred for 5 h. To the grey-brown suspension, 5 ml of H₂O were added, and the mixture was stirred for 30 min and passed through Celite. The layers were separated, and the aqueous layer was extracted twice with CH₂Cl₂. The combined org. layers were dried (MgSO₄) 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°. Rₓ(CH₂Cl₂/M eOH 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. ¹H-NMR: 7.45 – 7.3 (m, 3 arom. H (meta, para)); 7.2 – 7.15 (m, 2 arom. H (ortho)); 3.55 – 3.5 (m, CH₂OH); 3.26 (s, MeN); 2.45 – 2.35 (m, CH); 1.8 – 1.7 (m, 1 H of CH₂); 1.5 – 1.4 (m, CH₂); 1.4 – 1.3 (m, 1 H of CH₂); 1.04 (d, J = 6.7, Me).

¹³C-NMR: 176.7 (s, CO); 144.0 (s, 1 arom. C); 129.7 (d, 2 arom. CH (meta)); 127.7 (d, 1 arom. CH (para)); 127.3 (d, 2 arom. CH (ortho)); 62.4 (t, CH₂OH); 37.3 (q, MeN); 36.2 (d, CH); 30.6, 30.3 (2t, 2 CH₂); 18.3 (q, Me). Cl-M S (NH₃): 223 (15), 222 (100, [M + 1]⁺), 204 (7, [M – OH]⁺). Anal. calc. for C₁₃H₁₉NO₂ (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-(N-methyl-N-phenylamino)-5-oxopentanoic acid (14). The hydroxyamide 13 (3.21 g, 14.5 mmol) and 12.71 g (59.4 mmol, 4.1 equiv.) of NaIO₄ were solved in a mixture of 24 ml MeCN, 24 ml AcOEt and 36 ml H₂O. A small amount of RuCl₃·H₂O 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. H₂O was added, and the aqueous layer was extracted with AcOEt. The org. layers were combined, dried (Na₂SO₄) and evaporated. Recrystallization from AcOEt/hexane 1 : 1 yielded 2.48 (73%) of 14. Colorless crystals. M.p. 116.1 – 116.7°. Rₓ(CH₂Cl₂/M eOH 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.
1316w, 1274m, 1260m, 1193s, 1169m, 1115m, 1095w, 1073w, 1046w, 1027w, 1002w, 976w, 912w, 866w, 796w, 779m, 754w, 716w, 703m. $^1$H-NMR: 7.45 – 7.3 (m, 3 arom. H (meta, para)); 7.2 – 7.15 (m, 2 arom. H (ortho)); 3.26 (s, MeN); 2.5 – 2.45 (m, MeCH); 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, CO(acid)); 175.9 (s, CO(amide)); 143.7 (s, 1 arom. C); 129.7 (d, 2 arom. CH (meta)); 127.8 (d, 1 arom. CH (para)); 127.2 (d, 2 arom. CH (ortho)); 37.4 (q, MeN); 35.6 (d, CH); 31.5, 28.8 (2t, 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-(N-methyl-N-phenylamino)-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$_2$N$_2$ in Et$_2$O (prepared according to [40]) were added at 0°, the mixture was stirred until the yellow color disappeared. After 40 min, additional CH$_2$N$_2$ 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$_2$N$_2$ soln., the yellow color remained at r.t. for at least 90 min. Then, the excess of CH$_2$N$_2$ was destroyed with AcOH, the solvent was evaporated, and the product was dried in HV: 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): 2953s, 1738s, 1653s, 1596s, 1497s, 1436s, 1390s, 1327s, 1268s, 1170s, 1116s, 1074m, 1035m, 1002m, 987m, 918w, 897w, 842w, 800w, 776m, 752m, 703s. $^1$H-NMR: 7.45 – 7.35 (m, 3 arom. H (meta, para)); 7.2 – 7.15 (m, 2 arom. H (ortho)); 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, CO(amide)); 173.4 (s, CO(ester)); 143.8 (s, arom. C); 129.7 (d, 2 arom. CH (meta)); 127.7 (d, 1 arom. CH
(para)); 127.2 (d, 2 arom. CH (ortho)); 51.2 (q, MeO); 37.3 (q, MeN); 35.6 (d, CH);
31.6, 29.1 (2t, 2 CH$_2$); 17.9 (q, Me). CI-M S (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-(N-methyl-N-phenylamino)-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 stirred for 30 min at 130°. The excess of Lawesson reagent was precipitated with Et$_2$O, the precipitate filtered over Celite, and the filtrate evaporated. CC (hexane/AcOEt 4:1) yielded 2.564 g (93%) of 16 as a 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, 1444s, 1385s, 1332m, 1269m, 1198s, 1112m, 1074w, 1037m, 1002m, 919w, 877w, 853w, 834w, 774m, 702s. $^1$H-NMR: 7.5 – 7.35 (m, 3 arom. H (meta, para)); 7.15 – 7.1 (m, 2 arom. H (ortho)); 3.71, 3.58 (2s, 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 (3d, 5 arom. CH); 51.3 (q, MeO); 45.5 (q, MeN); 42.8 (d, CH); 32.7, 31.7 (2t, 2 CH$_2$); 22.0 (q, Me). CI-M S (NH$_3$): 268 (6), 267 (16), 266 (100, [M + 1]$^+$). Anal. calc. for C$_{14}$H$_{19}$NO$_2$S (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-N,2-dimethyl-N-phenyl-2H-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$_2$Cl$_2$ (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), DABC0 (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 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-NMR and $^{13}$C-NMR-spectra at 270K and 280K, doubling of signals was observed, which almost disappeared at 300K, 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 arom. CH(ortho), minor conformer); 7.45 – 7.4 (m, 2 arom H(meta)); 7.2 – 7.1 (m, 1 arom. H(para)); 7.05 (d, $J = 7.9$, 1 arom. H(ortho), 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$_2$CO, minor conformer); 2.3 – 2.25 (m, 1 H of CH$_2$CO, minor conformer, 1 H of CH$_2$CO, major conformer, 1 H of CH$_2$C(3), major conformer); 2.15 – 2.1 (m, CH$_2$C(3), minor conformer, 1 H of CH$_2$CO, major conformer); 2.05 – 2.0 (m, 1 H of CH$_2$C(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 arom. CH(meta), major conformer); 129.2 (d, 2 arom. CH(meta), minor conformer); 123.2 (d, 1 arom. CH(para), minor conformer); 123.1 (d, 1 arom. CH(para), major conformer); 116.7 (d, 2 arom. CH(ortho), minor conformer); 115.4 (d, 1 arom. CH(ortho), major conformer); 51.6 (q, MeO); 45.9 (s, C(2), major conformer); 37.9 (q, MeN, minor conformer); 37.1 (s, C(2), minor conformer); 33.5 (q, MeN, major conformer); 32.1 (d, CH$_2$C(2), major conformer); 31.2 (d, CH$_2$C(2), minor conformer); 29.9 (d, CH$_2$CO, major conformer); 29.8 (d, CH$_2$CO,
minor conformer); 24.5 (q, Me, major conformer); 23.5 (q, Me, minor conformer). CI-MS (NH₃): 248 (16), 247 (100, [M + 1]+). Anal. calc. for C₁₄H₁₈N₂O₂ (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 Thiobenzoic Acid and Z-L-Valine. 3.1. With Thiobenzoic Acid. Methyl 4-Methyl-5-(N-methyl-N-phenylamino)-4-[(phenylcarbonyl)amino]-5-thioxopentanoate (17). To thiobenzoic acid (110 mg, 0.8 mmol), a soln. of 10 (182 mg, 0.74 mmol) in abs. CH₂Cl₂ (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°. Rf (hexane/AcOEt 2 : 1) 0.18. IR (KBr): 3444 m, 3246 m, 3065 m, 3004 m, 2956 m, 2924 m, 2853m, 1732s, 1641 s, 1601 m, 1578 m, 1548 s, 1490s, 1463s, 1442m, 1363s, 1330m, 1294s, 1254m, 1219m, 1196m, 1177m, 1093s, 1026w, 1006m, 980m, 934w, 898w, 857w, 803w, 773m, 706s. ¹H-NMR: 8.78 (br. s, NH); 7.8 – 7.75, 7.5 – 7.35 (2m, 10 arom. H); 3.76, 3.62 (2s, MeO, MeN); 2.95 – 2.9 (m, 1 H of 2 CH₂); 2.4 – 2.35 (m, 2 H of 2 CH₂); 2.3 – 2.2 (m, 1 H of 2 CH₂); 1.68 (s, Me). ¹³C-NMR: 206.8 (s, CS); 173.8 (s, CO(ester)); 164.6 (s, CO(amide)); ca. 147 (s, 1 arom. CN); 135.1 (s, 1 arom. C); 131.2, 129.5, 128.6, 128.3, 126.9, 126.5 (6d, 10 arom. CH); 65.0 (s, C(4)); 51.6 (q, MeO); the signal for MeN was not observed; 32.3, 29.3 (2t, 2 CH₂); 26.0 (q, Me). ESI-MS (MeOH, NaI): 407 (100, [M + Na]+).


3.2. With Z-L-Valine. Methyl (RS)-4-(((S)-2-[(Benzylxoycarbonyl)amino]-3-methyl-1-oxobutyl)amino)-4-methyl-5-(N-methyl-N-phenylamino)-5-oxopentanoate (18). A soln. of 10 (1.03 g, 4.18 mmol) and Z-L-valine (1.11 g, 4.42 mmol) in CH₂Cl₂ (20 ml) was stirred at r.t. for 24 h, and evaporated. CC (CH₂Cl₂/M eOH 50 : 1) yielded 1.99 g (96%) of 18. Colorless foam. M.p. 103 – 104°. Rf (CH₂Cl₂/M eOH 50 : 1) 0.16.
IR (KBr): 3337 m, 2963 m, 1733 s, 1672 m, 1594 m, 1495 m, 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, PhCH\(_2\)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, 2 Me(4) of Val). \(^{13}\)C-NMR: 173.4, 171.9, 171.6, 169.2 (4s, CO(ester), 2 CO(amide)); 156.1 (s, CO(urethane)); 143.6, 143.4, 136.4 (3s, 2 arom. C); 129.5, 128.6, 128.4, 128.4, 128.0, 127.9 (6d, 10 arom. CH); 66.8 (t, PhCH\(_2\)O); 61.8, 61.5 (2s, C(2) of Glu(2Me)); 60.5, 60.2 (2d, CH(2) of Val); 51.6, 51.5 (2q, MeO); 41.7, 41.6 (2q, MeN); 31.5, 30.8, 29.4, 29.2 (4t, 2 CH\(_2\) of Glu(2Me)); 31.4, 31.3 (2d, CH(3) of Val); 23.2, 19.1, 19.0, 17.5, 17.2 (5q, Me(3) of Glu(2Me), 2 Me of Val). ESI-M (M eOH, Na\(^+\)): 520 (100, [M + Na\(^+\)]\(^+\)). Anal. calc. for C\(_{27}\)H\(_{35}\)N\(_3\)O\(_6\) (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-(N-methyl-N-phenylamino)-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\(_2\)Cl\(_2\)/MeOH 20 : 1) gave 147 mg (quant.) of 19. Colorless, highly viscous substance. \(R_f\) (CH\(_2\)Cl\(_2\)/MeOH 10 : 1) 0.25. IR (neat): 3322m, 2959s, 2874m, 1737s, 1638s, 1594m, 1495s, 1452m, 1368m, 1271m, 1222m, 1200s, 1174s, 1110m, 1082w, 1033w, 995w, 852w, 777w, 735w, 706m. \(^1\)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 (2s, MeO); 3.28, 3.26 (2s, MeN); 3.11, 3.01 (2d, \(J = 4.1\) and
3.8, resp., CH(2) of Val); 2.7 – 2.0 (m, 2 CH₂, CH(3) of Val); 1.95 – 1.9 (m, NH₂ of Val); 1.48, 1.39 (2s, Me(3) of Glu(2Me)); 0.96, 0.93, 0.83, 0.79 (4d, J = 7.0, 7.0, 6.9, and 6.9, resp., 2 Me(4) of Val). ¹³C-NMR: 173.5, 173.3, 172.4, 172.2, 171.6 (5s, 3 CO); 144.5, 144.1 (2s, arom. C); 129.4, 129.3, 128.1, 128.0, 127.8, 127.7 (6d, 5 arom. CH); 60.9 (s, C(2) of Glu(2Me)); 60.3, 60.3 (2d, CH(2) of Val); 51.6, 51.5 (2q, MeO); 41.6, 41.5 (2q, MeN); 32.9, 31.4 (2t, CH₂); 30.8 (d, CH(3) of Val); 29.4, 29.1 (2t, CH₂); 23.7, 23.3, 19.5, 19.4, 16.3 (5q, Me(3) of Glu(2Me), 2 Me(4) of Val). ESI-M S (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-(2-{{(S)}-1-[{(Benzyloxy carbonyl)amino]}-2-methylpropyl}-(RS)-4-methyl-5-oxo-1,3-oxazol-4-yl)propanoate (23). A soln. of dipeptide 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 temperature fell to 90 – 95°. The remaining HCl (g) was removed by bubbling N₂ through the soln. for 20 min. The mixture was transferred into another flask with hexane, and crystals of N-methylanilide chloride precipitated, were filtered (55mg, 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 analytical purposes, 23 was dried in HV. R₁ (hexane/AcOEt 2 : 1) 0.17. IR (neat): 3383m, 3066w, 3035w, 2966s, 2936m, 2877w, 1823s, 1732s, 1673s, 1526s, 1453m, 1375m, 1311s, 1233s, 1177s, 1146m, 1027m, 966m, 897s, 775w, 740w, 699m. ¹H-NMR: 7.35 – 7.3 (m, 5 arom. H); 5.35 – 5.25 (m, NH of Val); 5.15 – 5.1 (m, PhCH₂O); 4.55 – 4.45 (m, CH(2) of Val); 3.65, 3.63 (2s, MeO); 2.4 – 2.05 (m, CH(3) of Val, 2 CH₂ of Glu(2Me)); 1.40
(br. s, Me(3) of Glu(2Me)); 1.02, 0.98, 0.95 (3d, J = 6.8, 6.9, and 6.9, resp., 2 Me(4) of Val). 13C-NMR: 179.5 (s, C(5)); 172.3 (s, CO(ester)); 163.0 (s, C(2)); ca. 156 (s, CO(urethane)); 136.0 (s, 1 arom. C); 128.4, 128.1, 128.0 (3d, 5 arom. CH); 67.6 (s, C(4)); 67.1 (t, PhCH₂O); 55.2, 54.7 (2d, CH(2) of Val); 51.6 (q, Me(3)); 32.3 (t, CH₂); 30.7, 30.5 (2d, CH(3) of Val); 28.6 (t, CH₂); 23.5, 23.3, 18.8, 18.8, 17.5, 17.1 (6q, Me(3) of Glu(2Me), 2 Me(4) of Val). ESI-MS (MeOH, NaI): 413 (100, [M + Na]⁺).


4.2.2. (RS)-2-(((S)-2-[(Benzyloxycarbonyl)amino]-3-methyl-1-oxobutyl)amino)-5-methoxy-2-methyl-5-oxopentanoic Acid (21). 4.2.2.1. Procedure A. 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 H₂O 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 (MgSO₄) and evaporated: 161 mg (quant.) of crude 21. After Prep. TLC (CH₂Cl₂/MeOH 10 : 1), 109 mg (71%) of pure 21 were obtained as a colorless foam.

4.2.2.2. Procedure B. 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 temperature fell to 100 – 95°. The remaining HCl (g) was removed by bubbling N₂ 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 H₂O, 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 (MgSO₄), and evaporated. Prep. TLC (CH₂Cl₂/M eOH 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 C. Under standard conditions from amide 18. A soln. of 18 (152 mg, 0.305 mmol) in 3N HCl (THF/H₂O 1 : 1, 5 ml) was stirred for 1 h at r.t. The mixture was extracted with CH₂Cl₂, dried (MgSO₄), and evaporated. Prep. TLC (CH₂Cl₂/M eOH 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°. ¹H-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, PhCH₂O); 4.15 – 4.1 (m, CH(2) of Val); 3.64, 3.62 (2s, MeO); 2.55 – 2.0 (m, CH(3) of Val, 2 CH₂ of Glu(2Me)); 1.59 (s, Me(3) of Glu(2Me)); 1.0 – 0.9 (m, 2 Me(4) of Val). ¹³C-NMR: ca. 176, ca. 174, 171.5 (3s, CO(acid), CO(ester), CO(amide)); ca. 157 (s, CO(urethane)); ca. 135 (s, 1 arom. C); 128.5, 128.2, 128.0 (3d, 5 arom. CH); 67.2 (t, PhCH₂O); 60.6 (d, CH(2) of Val); 60.0 (s, C(2) of Glu(2Me)); 52.0 (q, MeO); 31.4 (t, 1 CH₂); 31.0 (d, CH(3) of Val); 29.3 (t, 1 CH₂); 22.9, 19.3, 19.1 (3q, 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 C₂₀H₂₈N₂O₇·0.2 H₂O (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-[(Benzylxycarbonyl)-amino]-3-methyl-1-oxobutyl]amino)-4-methyl-5-(N-methyl-N-phenylamino)-5-oxopen-tanoic 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 H₂O, LiOH·H₂O (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 aqueous layer
was extracted with CH$_2$Cl$_2$, 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$_2$Cl$_2$/MeOH 10 : 1) 0.31. IR (KBr): 3422s (broad), 3065m, 2965m, 2929m, 1717s, 1633s, 1593m, 1495s, 1455m, 1388m, 1261m, 1236m, 1110m, 1085m, 1028m, 801w, 774w, 738w, 701m. $^1$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$_2$O); 3.95 – 3.85 (m, CH(2) of Val); 3.27, 3.24 (2s, MeN); 2.7 – 1.8 (m, CH(3) of Val, 2 CH$_2$ of Glu(2Me)); 1.43, 1.39 (2s, 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 (4s, CO(acid), 2CO(amide)); 156.6, 156.5 (2s, CO(urethane)); 143.4, 136.2 (2s, 2 arom. C); 129.6, 129.4, 128.4, 128.1, 128.0 (5d, 10 arom. CH); 67.0 (t, PhCH$_2$O); 61.9, 61.2 (2s, C(2) of Glu(2Me)); 60.8, 60.2 (2d, CH(2) of Val); 41.7, 41.5 (2q, MeN); 31.4, 31.1 (2d, CH(3) of Val); 29.4, 28.9 (2t, 2 CH$_2$ of Glu(2Me)); 23.2, 23.1, 19.1, 17.7, 17.5 (5q, 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, [M – Benzyl + 2]$^+$), 378 (10), 377 (45, [M – NMePh]$^+$), 376 (8), 125 (8), 109 (8), 108 (100, PhCH$_2$OH$^+$). Anal. calc. for C$_{26}$H$_{33}$N$_3$O$_6$·0.5 H$_2$O (501.58): C 63.40, H 6.96, N 8.53; found: C 63.33, H 6.79, N 8.29.
REFERENCES


Formulae 1

1 $R = \text{Ph}$
2 $R = 1\text{-Naphth}$
3 $R = \text{iPr}$
4 $R = \text{iBu}$
5 $R = \text{cPent}$
6
7
8 $R = \text{H}$
9 $R = \text{OBn}$
Scheme 1

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

10

\[
\begin{align*}
\text{PhCOSH, CH}_2\text{Cl}_2 & \quad \text{r.t.} \\
\text{Z-L-Valine, CH}_2\text{Cl}_2 & \quad \text{r.t.}
\end{align*}
\]

17

18
Scheme 3

1. Scheme 3

2. 18

H₂, Pd/C, MeOH

LiOH, THF/MeOH/H₂O 3 : 1 : 1

19

HCl (g)
13 min
100°

20

HCl (g)
20 min, 100°
2. H₂O, 1 drop of 6N HCl
150 min, 50°

23

H₂O, 1 drop of 6N HCl
120 min, 50°

21

MeO
Scheme 4

\[
\begin{align*}
18 & \xrightarrow{3 \text{N HCl (H}_2\text{O/THF 1:1)}} 22
\end{align*}
\]